# Advancing the Synthesis and Reactivity of Aza-Sulfur Functional Groups




Michael Tilby

Keble College

University of Oxford

A thesis submitted for the degree of

*Doctor of Philosophy*

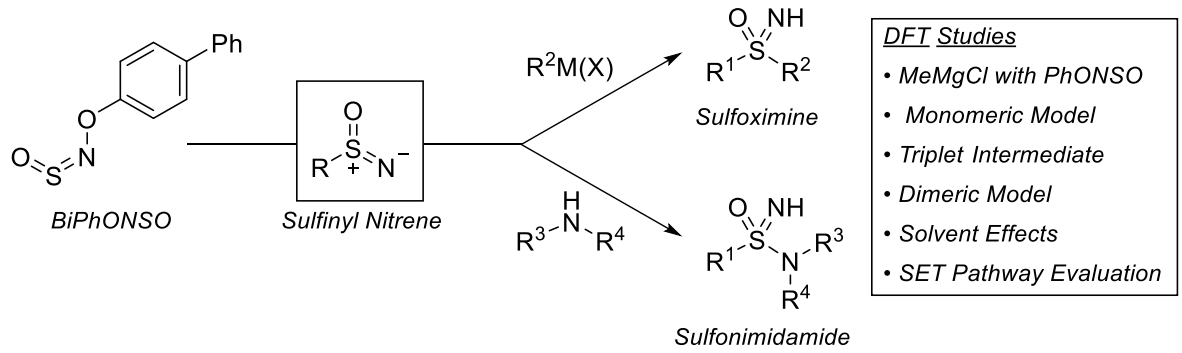
*Trinity 2021*

# Abstract

The work described herein documents several key advances in the field of aza-sulfur chemistry. Aza-sulfur chemistry encompasses a broad range of functional groups, where within this report, a particular focus has been placed on sulfoximines, sulfonimidamides and sulfonamides. In order to advance the synthesis and reactivity of these molecules a variety of projects have been undertaken, both using computational and experimental methods. On the account of these studies several key contributions to the field have been made and these will be outlined in the following chapters.

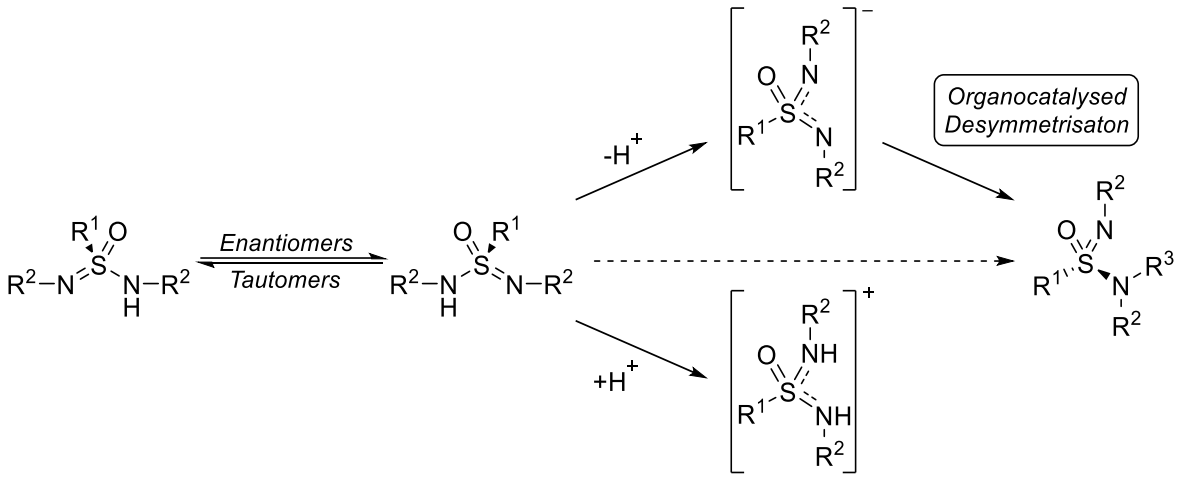
**Chapter 1** is a literature review introducing the broad variety of aza-sulfur compounds which are of interest to the community. Specifically, this literature review focuses on the methods that are currently available to synthesise sulfoximines and sulfonamidamides.

**Chapter 2** documents a density functional theory computational study on the reaction of a *N*-arylalkoxysulfinylamine linchpin with a Grignard reagent to produce sulfoximine products. In particular, this implements various models to examine each individual step, and ultimately provides support for the involvement of a key sulfinyl nitrene intermediate in this divergent sequence.

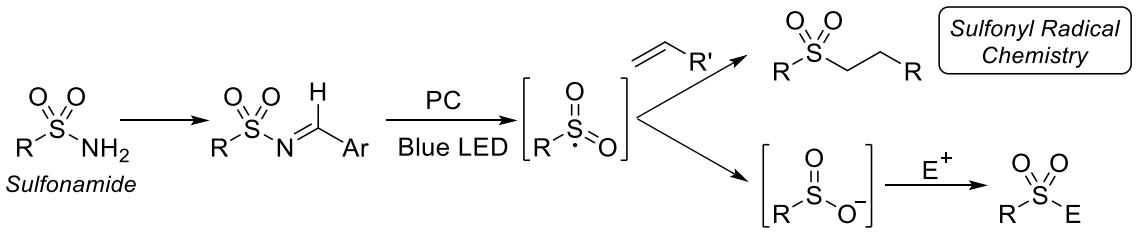



**Chapter 3** examines the current asymmetric synthesis of sulfoximines and sulfonmidamides and notes that there are only a handful of routes to enantioenriched sulfonimidamides. To address this, the work

here examines the properties of configurationally labile sulfonimidamides. In gaining a deeper understanding of these molecules an enantioselective organocatalysed alkylation reaction was developed, where this sequence utilises a key desymmetrisation step of a sulfonimidamide anion.




**Chapter 4** presents the current uses of the sulfonamide functional group and notes that these are often incorporated into commercial pharmaceuticals. Therefore, a late-stage functionalisation strategy was devised to allow primary sulfonamides to be used as synthetic handles. This methodology developed uses a photocatalytic procedure and allows access to a sulfonyl radical, hence diversifying the array of chemistries that can be accessed from sulfonamides.




**Chapter 5** discusses the conclusions of these projects and provides potential future work.

**Chapter 6** provides the experimental data and procedures used.

# Declaration

The work described in this thesis is entirely the work of the author except where specifically indicated. This thesis has not been previously submitted for a degree, diploma or any other qualification at the University of Oxford or elsewhere.

Michael Tilby

June 2021

# Acknowledgements

Firstly, I would like to thank Prof. Michael Willis. The supervision that Mike has given me over the years has been invaluable and has developed me into the chemist I am today. Since joining the MCW group as a Part II student, Mike has always believed in me and encouraged me to challenge myself as a person as well as the science. For this I am sincerely grateful, thank you.

I would like to thank everyone who has contributed academically to my DPhil. To Prof. Véronique Gouverneur, my time in the VG group on rotation was a fantastic learning experience and helped me grow in confidence. To Prof. Fernanda Duarte, you were always so positive about the computational chemistry I did and really helped me refine it, thank you for taking the time to do this. To Dr. Adrian Hall, having an industry-based perspective on my projects has provided a great deal of insight. To Dr. Carol Martínez-Lamenca, it was such valuable opportunity to come to Janssen for my industry placement, and I still miss the canteen!

One of my biggest shout outs goes to all the members of the MCW group, past and present. The Willis group has really become like a family to me, maybe a bit dysfunctional at times, nevertheless coming in everyday surrounded by these people has made my DPhil such an entertaining experience. In particular I would like to thank those members of the group who have proofread this thesis Dan, Antoine, Damien and Jonny, cheers!

A really fun part of my DPhil is all the people I've been able to directly work with on projects, each one has taught me something valuable. To Thomas (TQD), thank you for giving me the guidance in the early years of my DPhil, you truly are the 'God of synthesis'! To Loïc (LoLo), I hope Celecoxib is now one of your favourite molecules, I've appreciated your level-headed approach. To Damien, honestly jumping into these projects when I'm in full chaos mode and just going with it is pretty impressive, good luck!

To Rob, F1 really was the dream lab to start in with you looking after us kids. To Qian Wen, you were one of my first friends in the Willis group, I can't wait for my big trip to Singapore. To Rita, moaning in the break room was probably one of my favourite activities in the group. On that note, To the Chiral-HPLC, for challenging me but not enough to stop me dreaming. To Eva, you left the biggest impression on me, and I will never forget the time we had together.

To Antoine, I honestly could not have asked for a better person to have done this whole experience with. You've always supported me, cheered me on when I succeeded and picked me up when I needed it, normally both in the form of a pint! Here's a tequila shot to a lifetime of friendship and hopefully one day we'll share that bunkbed.

To Janette, you're a real inspiration, so strong and always have the ability to make me laugh, kudos for organising Wadham Ball, best night of the MCW group ever. To Xinlan, thank you for all you have done for me, your positivity and kindness, have made all the challenges so much easier, you are truly a good friend. To Ndi, for letting me talk hours to you about my Nintendo Switch. To Dan, always up for the pub, always has coffee on his desk, what more can you want? To Jonny, for being a real heartthrob and a photochem master at the same time. After being in the group for so long there are many others who have made this such a memorable experience, ZeXin, Tony, Nicoleta, Aiden, Mingyan, Terry, Ben, Callum, Alvin, Mike, Sang and Maitane to name a few.

I would also like to thank all my friends outside the lab for creating such a memorable experience. In particular those who I've lived with over the years and had such a giggle, Lucy, LVD, Dave, Dave and Ricky cheers.

I would also like to thank my family for always encouraging me to pursue my passion. Finally, I would like to thank Thomas, since starting my undergrad in Oxford you have always been by my side. I could not have done this without you and all the love you have given me. I can't wait for the next chapter to begin with you.

# Table of Contents


## Chapter 1 – Introduction 1

**1.1. Overview** 1

**1.2. Sulfoximine Synthesis** 3

1.2.1. Imination of Sulfoxides 3

1.2.2. Oxidation of Sulfilimines 10

1.2.3. Direction Oxidation from Sulfides 13

1.2.4. Nucleophilic Substitution 14

1.2.5. Direction Reactions from Sulfinamides 18

**1.3. Sulfonimidamide Synthesis** 21

1.3.1. Sulfonimidoyl Chloride Displacement 21

1.3.2. Sulfonimidoyl Fluoride Dispalcement 26

1.3.3. Sulfonimidate Ester Displacement 28

1.3.4. Miscellaneous 30

**1.4. Summary and Project Objectives** 33

## Chapter 2 – The Divergent Synthesis of Sulfoximines and Sulfonimidamides - A Computational Investigation 36

**2.1. Introduction** 36

2.1.1. Aza-Sulfur Compounds as Reactive Intermediates 37

2.1.2. Reaction Development 41

2.1.3. Mechanistic Observations 41

**2.2. Computational Model** 42

2.2.1. Model Assumptions 43

2.2.2. Functional Evaluation 44

**2.3. Monomeric Pathway** 46

2.3.1. Initial Methyl Addition 47

2.3.2. N–O Bond Fragmentation 48

2.3.3. Sulfinyl Nitrene Generation and Characterisation 49
2.3.4. The Sulfonimidate Ester Anion 53
2.3.5. Second Methyl Addition 54
**2.4. Dimeric Pathway** 58
2.4.1. Methyl Addition to PhONSO 60
2.4.2. Sulfinyl Nitrene Generation 60
2.4.3. Methyl Addition to Sulfinyl Nitrene 61
**2.5. Solvent Effects** 63
**2.6. Radical Pathway** 65
2.6.1. Radical Formation with PhONSO 65
2.6.2. Radical Formation with a Sulfinyl Nitrene 67
2.6.3. Radical Formation in the Dimeric Pathway 68
**2.7. Summary and Outlook** 70

**Chapter 3 – The Organocatalytic Enantioselective Synthesis of Sulfonimidamides** 73

**3.1. Introduction** 73
3.1.1. Contemporary Enantioselective Synthesis of Sulfoximines 73
3.1.2. Contemporary Enantioselective Synthesis of Sulfonimidamides 78
**3.2. Project Aims** 80
**3.3. Configurationally Labile Sulfonimidamides** 82
3.3.1. X-ray Crystallography 82
3.3.2. NMR Experiments 85
3.3.3. Reaction Design 90
**3.4. Reaction Optimisation** 90
3.4.1. Singly-Quaternised Catalysts 91
3.4.2. Doubly-Quaternised Catalysts 98
**3.5. Reaction Scope** 103
3.5.1. Electrophile Scope 104
3.5.2. Sulfonimidamide Scope 107

**3.6. Sulfonimidamide Configuration** 109

3.6.1. Determining the Absolute Configuration 109

3.6.2. Configuration Stress Tests 110

**3.7. Sulfonimidamide Deprotection** 111

**3.8. Summary and Outlook** 113

## Chapter 4 – Late-Stage Functionalisation of Sulfonamides *via* Photocatalysis 115

**4.1. Introduction** 115

4.1.1. Sulfonamide Synthesis 115

4.1.2. Sulfonamide Application 120

4.1.3. Late-Stage Functionalisation of Sulfonamides 122

**4.2. Project Aims** 124

**4.3. Reaction Optimisation** 127

4.3.1. Additive Effects 129

4.3.2. Catalyst Screen 132

4.3.3. Activator Screen 133

4.3.4. Solvent Screen 136

**4.4. Sulfonamide Scope** 138

4.4.1. General Sulfonamide Investigation 138

4.4.2. Medicinally Relevant Examples 140

4.4.3. Alternative Imines 143

**4.5. Radical Trap Scope** 146

4.5.1. Alkene Scope 146

4.5.2. Sulfinate Anion Generation 148

4.5.3. Electron Neutral Alkenes 150

**4.6. Mechanistic Insight** 151

4.6.1. Sulfonyl Imine Investigation 151

4.6.2. Stern-Volmer Quenching 152

4.6.3. Absorption-Emission Spectra 153

4.6.4. Cyclic Voltammetry ..... 154
4.6.5. Density Functional Theory ..... 156
4.6.6. Proposed Photocatalytic Cycle ..... 158
**4.7. Summary and Outlook** ..... 159

**Chapter 5 – Conclusions and Future Work** ..... 162

**Chapter 6 – Experimental Data and Procedures** ..... 165

**6.1. Table of Contents** ..... 165
**6.2. General Considerations** ..... 167
**6.3. Experimental Data and Procedures – Chapter 2** ..... 170
**6.4. Experimental Data and Procedures – Chapter 3** ..... 191
**6.5. Experimental Data and Procedures – Chapter 4** ..... 290

**References** ..... 371

**Appendix** ..... 385

**8.1. HPLC Data** ..... 385
**8.2. NMR Data – Chapter 3** ..... 423
**8.3. NMR Data – Chapter 4** ..... 515

# Abbreviations and Acronyms

| | |
|---|---|
| A | activator/ampere |
| Å | Angstrom |
| [α] | specific rotation |
| abs. | absorption |
| Ac | acetyl |
| app. | apparent |
| Ar | aryl |
| atm. | atmosphere |
| aq. | aqueous |
| B3LYP | Becke, 3-parameter, Lee–Yang–Parr |
| BDE | bond dissociation enthalpy |
| BINOL | 1,1′-bi-2-naphthol |
| BJD3 | D3(Becke-Johnson) dispersion |
| Bn | benzyl |
| Boc | *tert*-butyloxycarbonyl |
| bpy | 2,2′-bipyridine |
| br. | broad (spectral) |
| Bt | benzotriazolyl |
| Bu | Butyl (normal) |
| Bz | benzoyl |
| *c* | concentration |
| °C | degrees Celsius |
| *ca.* | approximately |
| CAN | ceric ammonium nitrate |
| cat. | catalyst |
| Cbz | Carbobenzyloxy |
| CC | coupled cluster |
| $cm^{-1}$ | wavenumber(s) |
| CMD | concerted metalation deprotonation |
| conc. | concentrated |
| conv. | conversion |
| CPME | cyclopentyl methyl ether |
| CSA | camphorsulfonic acid |

| | |
|---|---|
| CSD | cambridge structural database |
| Cy | cyclohexyl |
| d | doublet (spectral) |
| *d* | deuterated |
| Δ | change |
| DABSO | 1,4-diazabicyclo2.2.2octane bis(sulfur dioxide) |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCDMH | 1,3-dichloro-5,5-dimethylhydantoin |
| DCE | 1,2-dichloroethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| decomp. | decomposition |
| dF($CF_3$)ppy | 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine ligand |
| DFT | density functional theory |
| $(DHQD)_2PHAL$ | hydroquinidine 1,4-phthalazinediyl diether |
| DKR | dynamic kinetic resolution |
| DMAP | dimethylaminopyridine |
| DMC | dimethyl carbonate |
| DMF | *N,N'*-dimethylformamide |
| DMSO | dimethylsulfoxide |
| dtbpy | 4,4′-di-*tert*-butyl-2,2′-dipyridyl |
| DyKAT | dynamic kinetic asymmetric transformations |
| E | electrophile/energy/redox potential |
| *E* | entgegen |
| EDG | electron-donating group |
| *ee* | enantiomeric excess |
| *e.g.* | *exempli gratia* |
| em. | emission |
| *er* | enantiomeric ratio |
| *es* | enantiospecificity |
| ESI | electrospray ionization |
| Et | ethyl |
| equiv. | equivalent(s) |
| eV | Electron volts |
| EWG | electron-withdrawing group |

| | |
|---|---|
| FMO | frontier molecular orbital |
| FRET | Förster resonance energy transfer |
| g | gram(s)/gas |
| G | gibbs free energy |
| GGA | generalised gradient approximation |
| h | hour(s) |
| *h* | Planck's constant |
| H | enthalpy |
| HAD | hydrogen atom donor |
| HAT | hydrogen atom transfer |
| HEH | hantzsch ester |
| HetAr | hetroaromatic |
| HFIP | hexafluoro-2-propanol |
| HMDS | hexamethyldisilazane |
| HOMO | highest occupied molecular orbital |
| HRMS | high resolution mass spectroscopy |
| Hz | Hertz |
| $^{i}$Bu | *iso*-butyl |
| Im | Imination |
| $^{i}$Pr | *iso*-propyl |
| *I* | isotope spin |
| IR | infrared |
| ISC | intersystem crossing |
| *J* | coupling constant (in NMR spectroscopy) |
| K | kelvin |
| kcal | kilocalorie(s) |
| l | liquid |
| L | litre(s) |
| λ | wavelength |
| LDA | lithium diisopropylamide |
| LRMS | low resolution mass spectroscopy |
| LUMO | lowest occupied molecular orbital |
| μ | micro |
| *m* | *meta* |

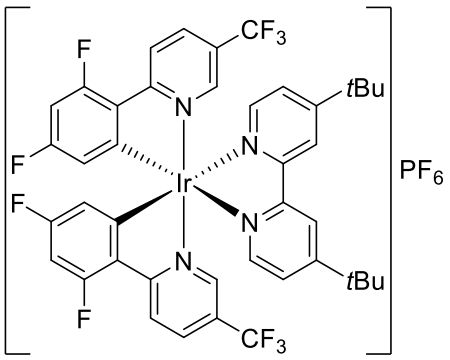
| | |
|---|---|
| m | multiplet (spectral)/milli |
| M | moles per litre/mega/generic metal |
| $M^{+/-}$ | parent molecular ion (in mass spectrometry) |
| M06 | Minnesota 06 |
| MAD | mean absolute deviation |
| Me | methyl |
| MECP | minimum energy crossing point |
| min | minute(s) |
| mol | mole(s) |
| MP | melting point |
| *m*-CPBA | *meta*-chloroperoxybenzoic acid |
| Mes | mesityl |
| Ms | methanesulfonyl- |
| MS | molecular sieves |
| MSH | O-(2,4,6-trimethylbenzenesulfonyl)hydroxylamine |
| MSO | methionine sulfoximine |
| MTBE | *tert*-butyl methyl ether |
| MVK | methyl vinyl ketone |
| *m/z* | mass-to-charge ratio (in mass spectrometry) |
| n | nano |
| N/A | not applicable |
| NCS | *N*-chlorosuccinimide |
| NBO | natural bond orbitals |
| NBS | *N*-bromosuccinimide |
| n.d. | not determined |
| NHC | *N*-heterocyclic carbene |
| NMO | *N*-methylmorpholine *N*-oxide |
| NMR | nuclear magnetic resonance |
| Ns | 4-nitrosulfonyl- |
| Nuc | nucleophile |
| *o* | *ortho* |
| $^{t}$Oct | *tert*-octyl |
| p | pentet (spectral) |
| *p* | *para* |

| | |
|---|---|
| PBE | Perdew–Burke-Ernzerhof |
| PC | photocatalyst |
| PCET | proton-coupled electron transfer |
| PES | potential energy surface |
| Ph | phenyl |
| PIDA | (diacetoxyiodo)benzene |
| PLE | pig-liver enzyme |
| PMB | *para*-methoxybenzyl |
| ppm | part(s) per million |
| ppy | 2-phenylpyridine ligand |
| Pr | propyl (normal) |
| Py | pyridine |
| q | quartet (spectral) |
| qh | quasi-harmonic |
| quant. | quantitative |
| quin | quintet (spectral) |
| (*R*) | rectus |
| *rac* | racemic |
| Red | reduction |
| $R_f$ | retention time |
| rpm | rotations per minute |
| RSM | recovered starting material |
| rt | room temperature |
| s | singlet (spectral)/second/solid |
| *s* | selectivity factor |
| S | entropy |
| (*S*) | sinister |
| sat. | saturated |
| SCE | saturated calomel electrode |
| SCRF | self-consistent reaction field |
| SET | single electron transfer |
| SMD | solvent model based on density |
| sxt | sextet |
| t | time/triplet (spectral) |

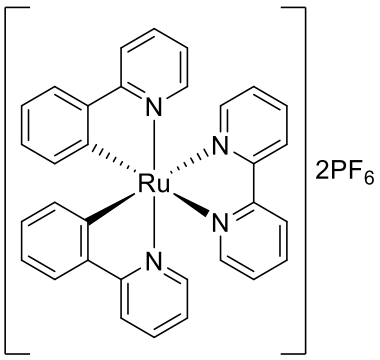
| | |
|---|---|
| τ | retention time |
| TADF | thermally activated delayed fluorescence |
| $^{t}$amyl | 2,2-dimethylbutane |
| TBAB | tetrabutylammonium bromide |
| TBDPS | *tert*-Butyldiphenylsilyl |
| TBS | *tert*-butyldimethylsilyl |
| $^{t}$Bu | *tert*-butyl |
| TC | thiophene-2-carboxylate |
| TCE | trichloroethylene |
| Tf | trifluoromethanesulfonate/triflate |
| TFA | trifluoroacetic acid |
| TMG | 1,1,3,3-tetramethylguanidine |
| THF | tetrahydrofuran |
| TIPS | triisopropylsilyl |
| TLC | thin-layer chromatography |
| TMS | trimethylsilyl |
| TPAP | tetrapropylammonium perruthenate |
| TPSS | Tao, Perdew, Staroverov, and Scuseria functional |
| tpy | terpyridine |
| Ts | 4-toluenesulfonyl- |
| TS | transition state |
| TST | transition state theory |
| Tr | trityl |
| u | unrestricted |
| V | volts |
| *v* | speed |
| vs. | versus |
| VT | variable temperature |
| *wt.* | by weight |
| X | generic atom/counterion |
| xs. | excess |
| *Z* | zusammen |
| ZPE | zero-point energy |

# Catalyst Index

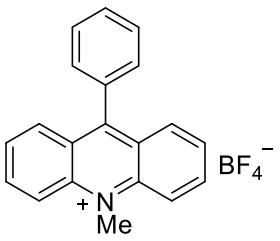
## Photocatalysts



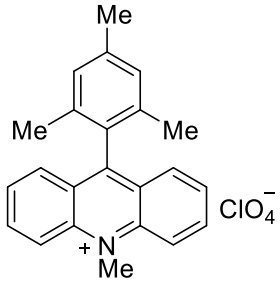

(Ir[dF(CF$_3$)ppy]$_2$(dtbpy))PF$_6$



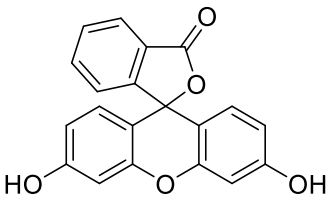

Ru(bpy)$_3$(PF$_6$)$_2$



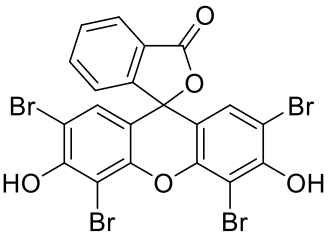

(PhAcr)BF$_4$



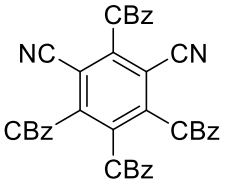

(MesAcr)ClO$_4$



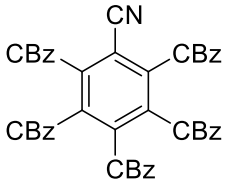

Fluorescein



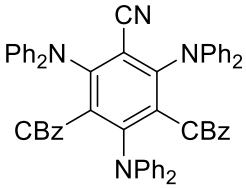

Eosin Y




4CzIPN




5CzBN




3DPA2FBN

| PC | E(PC/PC$^{\bullet-}$)[a] | E(PC$^{\bullet+}$/PC)[a] | E(PC*/PC$^{\bullet-}$)[a] | E(PC$^{\bullet+}$/PC*)[a] | $E_{0T}$[b] |
|---|---|---|---|---|---|
| (Ir[dF(CF$_3$)ppy]$_2$(dtbpy))PF$_6$ | -1.37 | +1.69 | +1.21 | -0.89 | 2.13 |
| Ru(bpy)$_3$(PF$_6$)$_2$ | -1.33 | +1.29 | +0.77 | -0.81 | 2.02 |
| (PhAcr)BF$_4$ | -0.54 | N/A | n.d. | N/A | n.d. |
| (MesAcr)ClO$_4$ | -0.82 | N/A | +1.65 | N/A | 1.94 |
| Fluorescein[c] | -1.17 | +0.87 | +0.77 | -1.07 | 1.94 |
| Eosin Y | -1.06 | +0.78 | +0.83 | -1.11 | 1.91 |
| 4CzIPN | -1.24 | +1.49 | +1.43 | -1.18 | 2.40 |
| 5CzBN | -1.52 | +1.41 | +1.31 | -1.42 | 2.77 |
| 3DPA2FBN[e] | -1.92 | +1.24 | +0.92 | -1.60 | n.d. |

All data was obtained from the literature.[1] [a] E refers to the redox potentials in V vs. SCE in MeCN. [b] $E_{0T}$ refers to the triplet energy in eV typically determined by the highest energy local maximum of phosphorescence spectrum, typically at 77 K in glassy medium (see references for details). [c] Redox potentials were obtained in MeOH. [d] Redox potentials were obtained in $CH_2Cl_2$.

# Chapter 1 – Introduction

## 1.1 Overview

Organo-sulfur containing functionalities consist of a diverse array of compounds which hold a prevalent place in chemistry; predominantly these compounds are encountered in either their sulfur(IV) or sulfur(VI) oxidation states (**Figure 1.1.**). For the sulfur(IV) compounds, arguably the most renowned is the sulfoxide, with a deal of effort devoted to their asymmetric synthesis and application.[2] In comparison the sulfoxide aza-analogues, sulfilimines, have not gained the same momentum, but have still shown promising reactivity,[3] and relevance in a biological setting.[4]

Furthermore sulfur(IV) species are shown to be universal reagents in synthesis, exemplified with the highly electrophilic sulfinyl chlorides and sulfinate esters. Which have been employed to access a range of organo-sulfur derivatives, often with these used as reactive intermediates in sequential processes.[5] In contrast the aza-derivatives of these compounds, sulfinamides, have drastically different properties, where a basic nitrogen allows them to behave as competent nucleophiles.[5b,6] This property has been monopolised on, with enantioenriched sulfinamides being used as chiral auxiliaries, with the most prominent example being the Ellman auxiliary.[7]

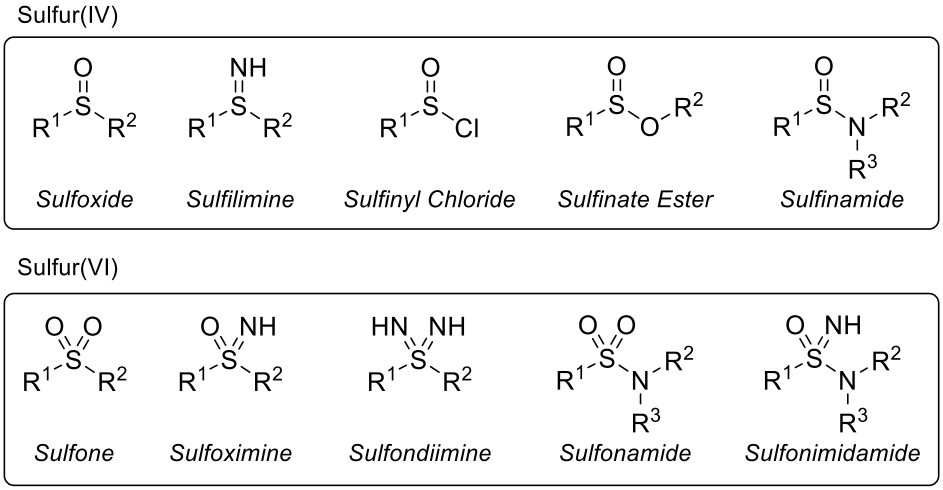



**Figure 1.1.** A selection of structures for sulfur(IV) and sulfur(VI) containing compounds.

It is common for sulfur(IV) compounds to be used as intermediates en route to sulfur(VI) species. The latter have beneficial properties including their high stability and polarity, which is especially relevant when considering their prominence as drug candidates and agrochemicals.[8] Also, sulfur(VI) compounds have a variety of synthetic applications, which is especially true for the sulfone moiety.[9] When considering the related sulfoximines and sulfondiimines, a key defining feature is that these molecules now have the possibility of a stereogenic sulfur centre, and unsurprisingly there are examples of sulfoximines having been applied as chiral ligands.[10] In contrast, sulfondiimine application is still in its infancy,[11] potentially due to there being only a few applicable routes for their synthesis.[12]

Another prominent moiety is the sulfonamide group, which has seen incorporation into multiple commercial pharmaceuticals.[13] This success has often been credited to the existence of their heteroatom rich core, which renders them with high aqueous solubility and hydrogen bonding ability.[8b] The aza-analogue, sulfonimidamides, are now inherently chiral, with an imidic nitrogen providing an opportunity to append additional substituents, allowing the fine-tuning of physiochemical properties. This has resulted in sulfonimidamides being used as bioisosteres of sulfonamides and carboxylic acids,[14] as well as their inclusion into preclinical drug candidates,[15] with cases demonstrating the importance of the sulfur's configuration on biological activity.[16]

Overall, organo-sulfur compounds have found widespread application in the field of chemistry, either as reagents, reactive intermediates, or direct incorporation into molecules of interest. However, many of the derivatives containing a nitrogen atom directly bonded to the sulfur have not been utilised to their full potential, although they can exhibit advantageous features and novel reactivity.[8c,17] In particular the limited use of the aza-sulfur(VI) class of compounds can be ascribed to the lack of efficient synthetic strategies to date, including for both racemic mixtures and enantioenriched

examples. The following chapter of this thesis will outline the current methods to synthesise key aza-sulfur compounds including sulfoximines and sulfonimidamides.

## 1.2. Sulfoximine Synthesis

The first sulfoximine to be isolated was in 1949,[18] from the action of nitrogen trichloride on proteins, producing methionine sulfoximine (MSO) as a toxic factor. Since then, a significant degree of focus has been placed on MSO's biological affects,[19] including on the role of the sulfur stereocentre's configuration on activity in select examples.[20] Since these initial reports, multiple synthetic routes to sulfoximines have been developed (**Figure 1.2.**), including *i.* imination of a sulfoxides, *ii.* oxidation of a sulfilimines, *iii.* one-pot imination and oxidation, *iv.* nucleophilic substitution of sulfonimidate esters or sulfonimidoyl halides with organometallic reagents, and *v.* reactions from sulfinamides.

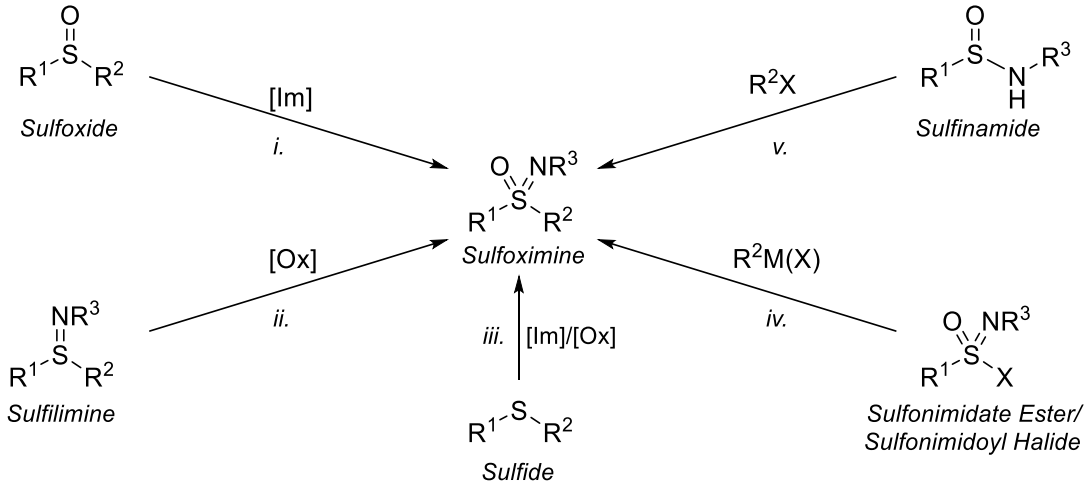
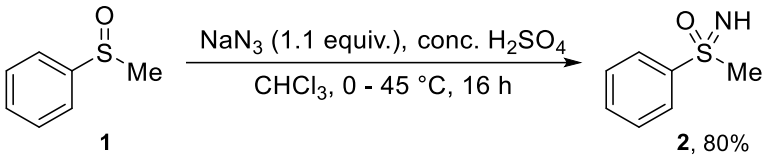



**Figure 1.2.** Common strategies used to access sulfoximines, *i.* imination *ii.* oxidation, *iii.* one-pot oxidation from a sulfide, *iv.* nucleophilic displacement and *v.* alkylation/arylation.

### 1.2.1. Imination of Sulfoxides

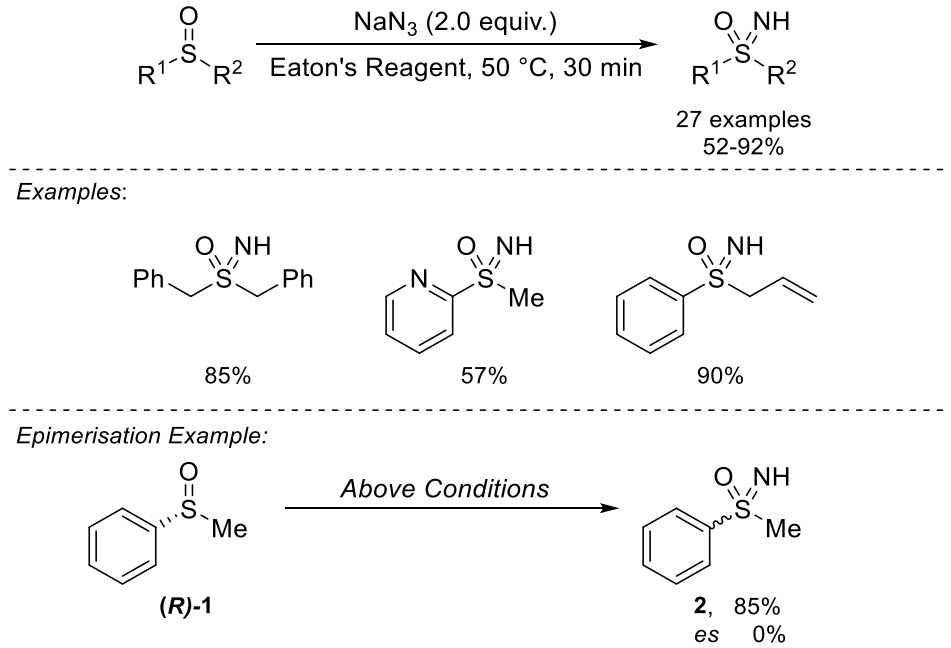
Method *i.*, imination of a sulfoxide, is the most populous method to access sulfoximines and this S–N bond construction process has been extensively reviewed.[21] The advantage of this strategy is the availability of the sulfoxide starting materials, hence practical iminations were developed soon after

the initial identification of MSO. One of the first methods reported used hydrazoic acid in the presence of sulfuric acid as catalyst.[22] The use of hydrazoic acid raised several safety concerns, due to its toxic and explosive nature, hence its generation *in situ* was deemed preferential.[23] Accordingly, the widespread use of sodium azide was alternatively developed for these reactions (**Scheme 1.1.**).[24]




**Scheme 1.1.** Example of using sodium azide with sulfuric acid to a iminate sulfoxide.[25]

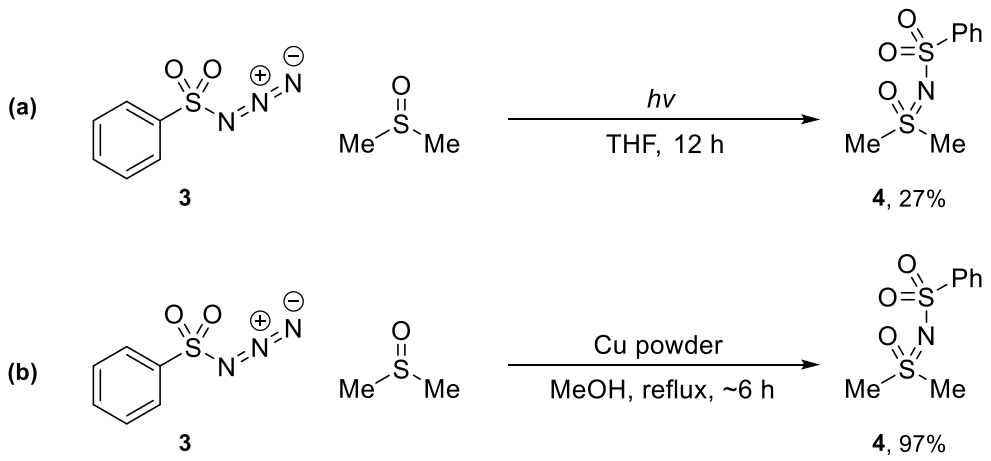
Although this route provides an atom economical procedure to access the free-sulfoximine, the presence of harsh acidic conditions limits the sulfoxide substrate pool to those containing simple aryl or methyl substituents. Consequently, sulfoxide C–S bond fission occurs when substituents such as benzyl or non-primary alkyl are present.[26] An effort has been made to circumvent this issue by using Eaton's reagent ($P_2O_5$ 7.7 *wt.* in MsOH), where this procedure has allowed the method to be extended to more complex starting materials (**Scheme 1.2.**).[27]




**Scheme 1.2.** Illustrating the use of sodium azide with Eaton's reagent to iminate a sulfoxide.

Although this reaction provides a broad scope of sulfoximines, prepared in a safe manner, the extension of this methodology to produce enantioenriched sulfoximines is still problematic. For example, the facile epimerisation of enantiopure sulfoxide starting material (***R*)-1** is observed in the reaction to sulfoximine **2** (**Scheme 1.2.**), which highlights a persisting issue with the use of acidic conditions. The need for milder conditions has therefore been heavily scrutinised, in a number of accounts.

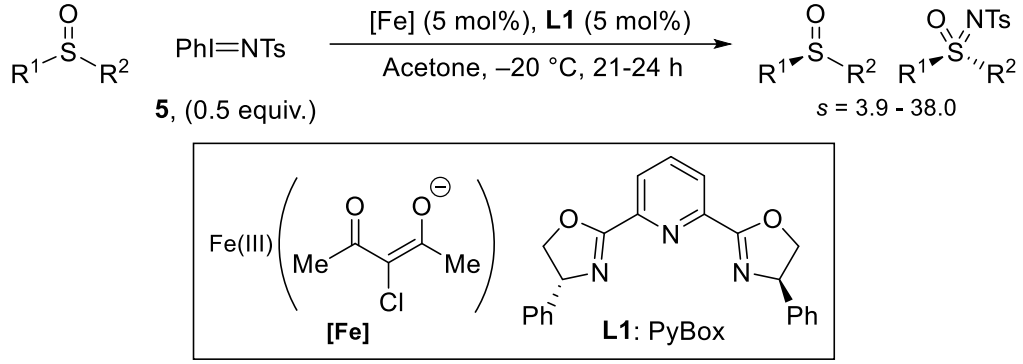
In particular, one is able to use organic azides, and to begin with, this was achieved using benzenesulfonyl azide (**3**) activated photochemically (**Scheme 1.3.a.**), albeit in low yields.[28] In a similar guise, a variety of other organic azides have been activated, photochemically or thermally, to allow nitrene addition to sulfoxides.[29]




**Scheme 1.3.** Representing the use of sulfonyl azide to iminate a simple sulfoxide, (**a**) photochemically, (**b**) thermally in the presence of a copper catalyst.

The aforementioned thermal process greatly benefitted from the use of copper powder. Not only did it drastically improved the yield of sulfoximine **4** (**Scheme 1.3.b.**),[30] but the same conditions could then be applied to optically active sulfoxides, giving chiral sulfoximines with retention of configuration.[31] This work has inevitably inspired a great deal of further developments, which utilise substoichiometric quantities of metal catalysts, with alternative nitrene sources. The breadth of research in this area has produced a variety of interesting methodologies, with one example including

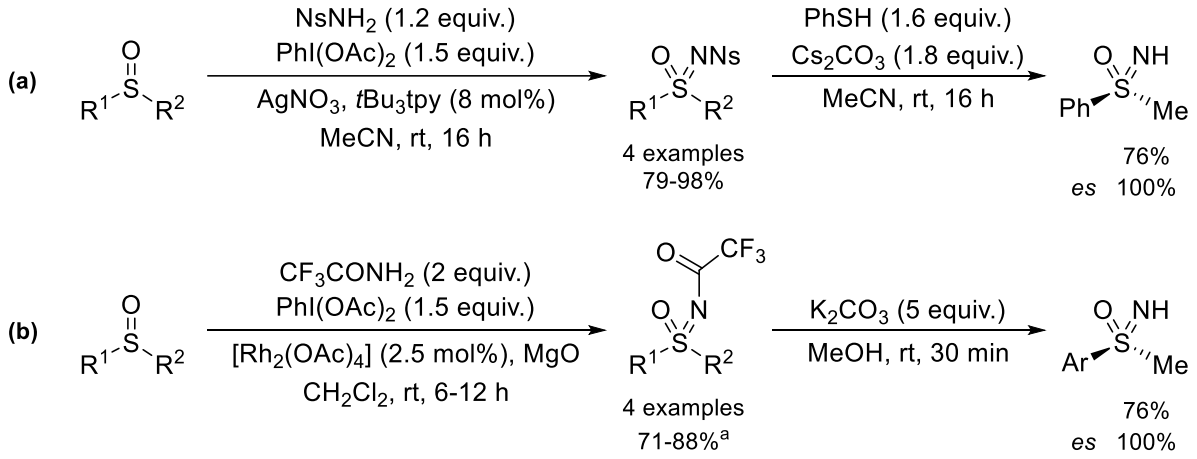
the extension of an iron-catalysed sulfoxide imination to a kinetic resolution reaction (**Scheme 1.4.**).[32] This procedure uses a readily available iodinane reagent (**5**) in combination with an iron(III) catalyst and a chiral PyBox ligand (**L1**), producing an enantioenriched sulfoxide and sulfoximine, with moderate to good selectivity factors. The advantage of this system is that it does not rely on the availability of optically active sulfoxides, hence previously difficult to access sulfoximines can potentially be obtained in high enantiomeric ratios.




**Scheme 1.4.** Showing the asymmetric synthesis of sulfoximines, with an iron-catalysed imination of a sulfoxide *via* kinetic resolution.

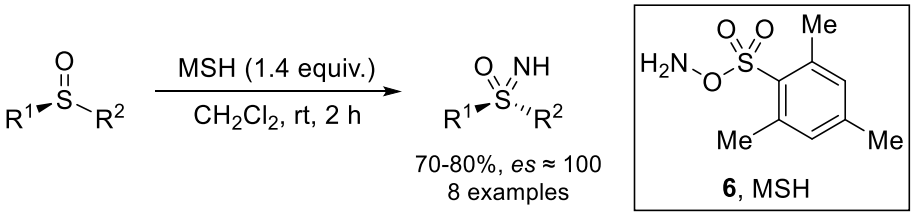
As exemplified by this case, the use of *N*-tosyl iodinane (**5**) has become commonplace for metal catalysed sulfoxide imination, however, the drawback of this is that this inevitably produces tosyl protected products. Removal of a tosyl protecting group, to generate free sulfoximines, can often be non-trivial and require harsh acidic conditions. Therefore, reactions have been developed which allow more compatible protecting groups to be incorporated onto the nitrogen. An example of this is a silver-catalysed imination, now generating an *N*-nosyl iodinane *in situ*, from the corresponding sulfonamide and phenyliodine(III) diacetate (PIDA) (**Scheme 1.5.a.**).[33] This stereospecific reaction utilises an inexpensive silver salt, followed by facile cleavage of the nosyl group in the presence of a thiol and base. The reagents used in this reaction are also translatable to a rhodium-catalysed reaction.[34] Employment of this metal broadens the reaction scope to trifluoroacetamide as the nitrene source, yielding sulfoximine products that readily deprotect under simple conditions

(**Scheme 1.5.b.**). A slight modification of these conditions (a change in equivalents and increase in temperature), allows carbamates to be used in place of trifluoroacetamide,[35] giving rise to Boc and Cbz protected sulfoximines which has provided deprotection under acid and hydrogenation conditions respectively. Overall, the development of metal-catalysed reactions has provided the opportunity for a range of protected products to be accessed, hence providing multiple options for deprotection strategies, to give the free-sulfoximines, that can also retain enantioenrichment within the products.[36]



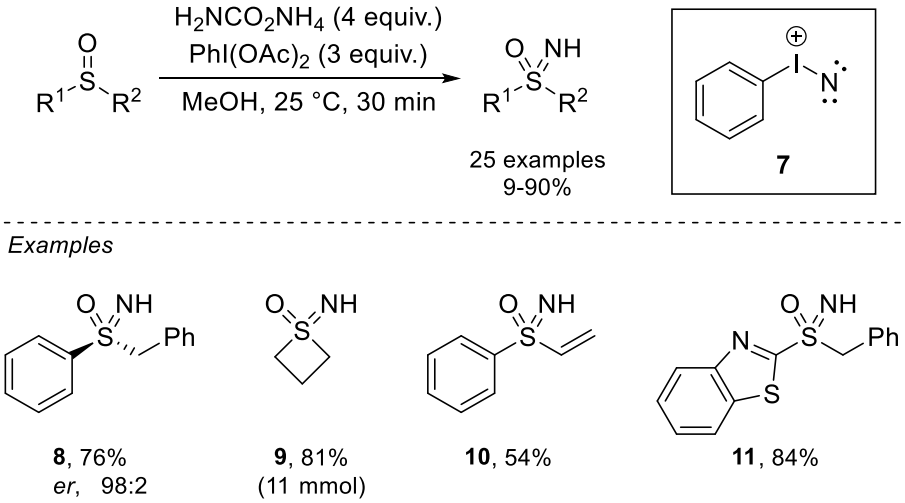

**Scheme 1.5.** Use of metal-catalysed reactions to access the free-sulfoximines, by first imination followed by deprotection (**a**) using a silver catalyst, (**b**) using a rhodium catalyst. [a]yields based on the isolation of the free-sulfoximine product, Ar = *p*-tolyl.

Regardless, of these contributions, the sole inability of the metal-catalysed method to directly access free-sulfoximines, in a single step, remains a persevering limitation. In this context, metal-free approaches have triumphed, initially with the reagent *o*-mesitylsulfonylhydroxylamine (**6**, MSH) (**Scheme 1.6.**).[37] Although this procedure has been applied in a variety of situations,[21b] MSH is a notoriously hazardous reagent,[38] hence it does not provide an operationally simple solution.



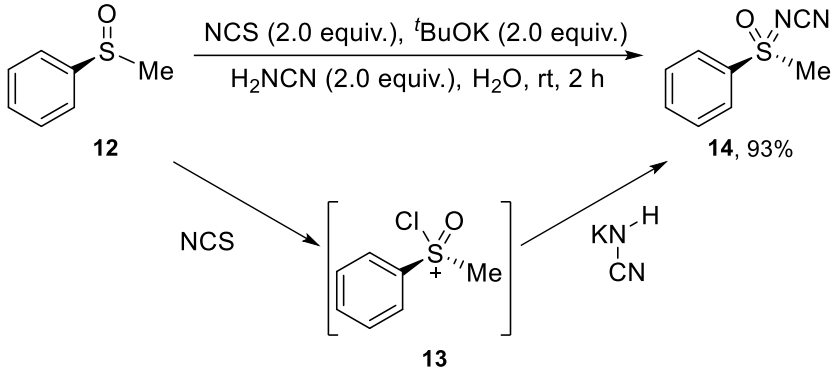

**Scheme 1.6.** Application of MSH as an imination reagent, shown to be highly stereoselective.

A handful of metal-catalysed iminations have been used in combination with alternative hydroxylamine nitrogen sources as safer strategies.[39] However, a considerable breakthrough for the direct synthesis of free-sulfoximines from sulfoxides has recently been developed by the groups of Bull and Luisi (**Scheme 1.7.**)[40] This procedure utilises the inexpensive and easy to handle ammonium carbamate as a source of ammonia, which in combination with stoichiometric hypervalent iodine oxidant is proposed to produce the key iodonitrene intermediate **7**. Fortunately, the reaction does not require the presence of a metal catalyst to generate the key reactive species **7**. Of note, species **7** was detectable by flow HRMS and $^{15}$N-labelling NMR experiments and is proposed to be capable of directly reacting with sulfoxides to eventually produce the desired sulfoximine products. This reaction provides a diverse range of products and once again is shown to result in retention of stereochemistry as seen with substrate **8**. Furthermore, when using methanol as solvent, the reaction proceeded adequately in an open-flask and could sufficiently be scaled up, as exemplified by sulfoximine **9**. The process was also adaptable to a flow-reactor by the direct use of aqueous ammonia,[41] allowing for an operationally simple method for free-sulfoximine synthesis.




**Scheme 1.7.** Direct ammonia transfer to a sulfoxide with ammonium carbonate and an iodine oxidant. Note several substrates were performed under slightly modified conditions with MeCN as solvent and alteration in stoichiometry, the most general is shown.

Many of the previous mentioned imination strategies have proven to be highly stereoselectivite when using enantioenriched sulfoxides, producing products with retention of configuration. However, Bolm and co-workers demonstrated that it was also possible for the imination to proceed with inversion of configuration (**Scheme 1.8.**).[42] For this reaction it was noted that the NCS could not be added prior to the other reagents, as this lead to sulfone products. Additionally, the strength and counter-ion of the base was crucial for reaction success. These findings along with the reaction's stereochemical outcome, allowed a mechanism to be proposed (**Scheme 1.8.**). Where initial chlorination to an unconventional oxy-chlorosulfonium (**13**) occurs,[43] followed by nucleophilic displacement with stereochemical inversion, using the deprotonated amine, to give the sulfoximine (**14**). This one-pot procedure was functional on a broad range of predominantly racemic sulfoxides, with cyanamide, to yield products with medicinal[44] and agrochemical[45] relevance. Although this particular method was limited to a single amine nucleophile, previous reports have also shown that aniline derivatives can be applied in a similar sequence.[46] It is important to emphasise that being able to employ a range of nucleophilic amines directly would have profound implications for this strategy.



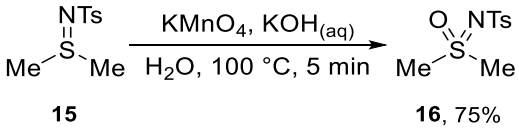

**Scheme 1.8.** Direct imination of a sulfoxide using a chlorinating agent in combination with cyanamide.

A full overview for the imination of sulfoxides shows a method that began from using harsh condition with dangerous reagents, to one which developed a diverse range of metal-catalysed processes resulting in protected sulfoximines. Modern developments have focused on producing the

highly valuable free-sulfoximines, with a metal-free approach, often *via* under-explored reactive intermediates, providing simpler protocols. Although it currently holds true for select examples only, reactions under mild conditions have the potential to be highly stereospecific, and are able to proceed with both retention or inversion of configuration.

### 1.2.2. Oxidation of Sulfilimines

The synthesis and properties of sulfilimines has been well established.[3a] This, along with an arsenal of sulfilimines being available, provides the opportunity for their oxidation to a diverse range of sulfoximines. The first reported oxidation of a sulfilimine was achieved using potassium permanganate in a basic medium (**Scheme 1.9.**),[47] on a simple *N*-tosyl sulfilimine (**15**). This reaction was also confirmed to occur with retention of stereochemistry when applied on a enantioenriched sulfilimine,[48] providing further options for the asymmetric synthesis of sulfoximines. Potassium permanganate has also been used under neutral conditions, contributing to its application to a wider range of sulfilimines, albeit with variable yields.[3a] Nonetheless, the use of the such a strong oxidant raises concerns when other sensitive functionalities are present within the starting material.

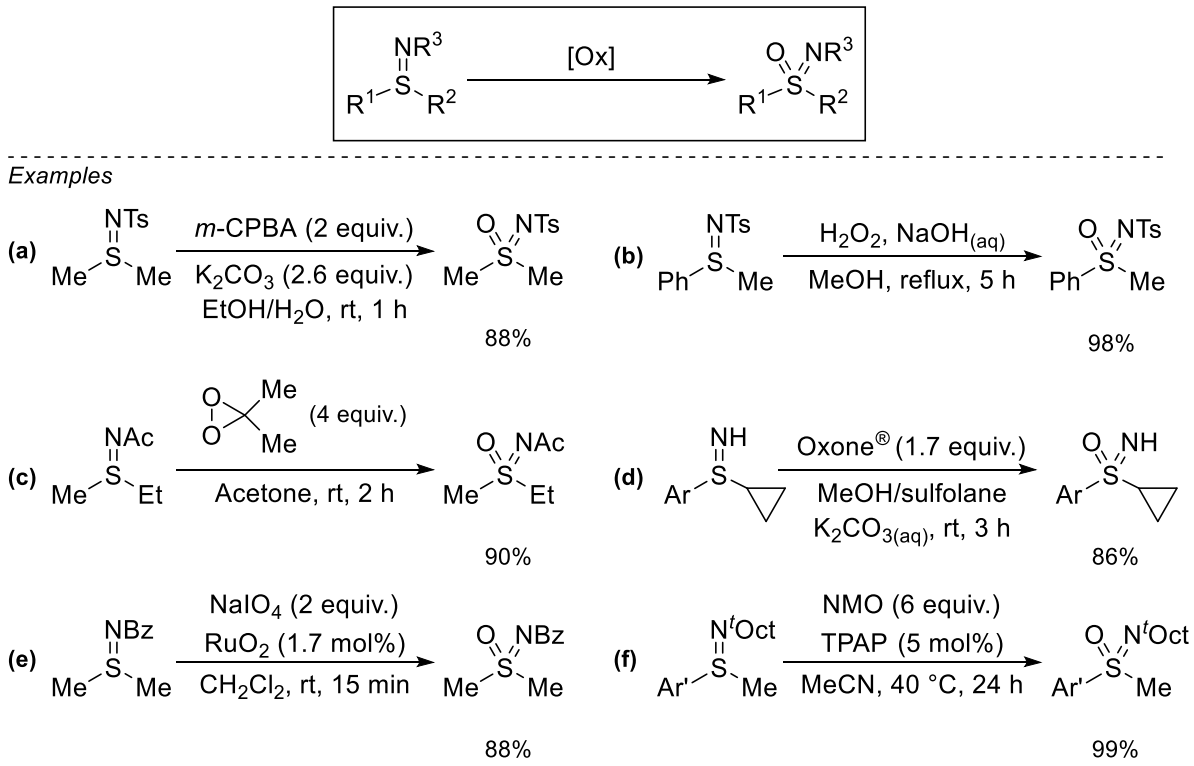



**15** **16**, 75%

**Scheme 1.9.** The first oxidation of a sulfilimine using potassium permanganate.

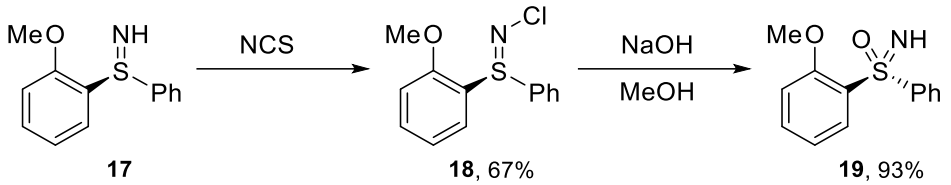
After this initial use of potassium permanganate for sulfoximine synthesis, a variety of other oxidants have been utilised in analogous procedures (**Scheme 1.10.**), including *m*-CPBA,[49] hydrogen peroxide,[50] dioxiranes,[51] oxone,[52] ruthenium tetraoxide[53] and a combination of TPAP with NMO.[12] Out of these, the most commonly applied is *m*-CPBA in the presence of a base, and this has become a reliable method with a variety of stereospecific examples.[54] Although *m*-CPBA

delivers a good general reactivity across the substrate class, better yields can be achieved on more specific examples, by using other oxidants listed.[55]




**Scheme 1.10.** Example reactions using a variety of oxidants used for sulfoximine synthesis from sulfilimines. Ar = *p*-$NO_2C_6H_4$-, Ar' = *p*-$FC_6H_4$-.

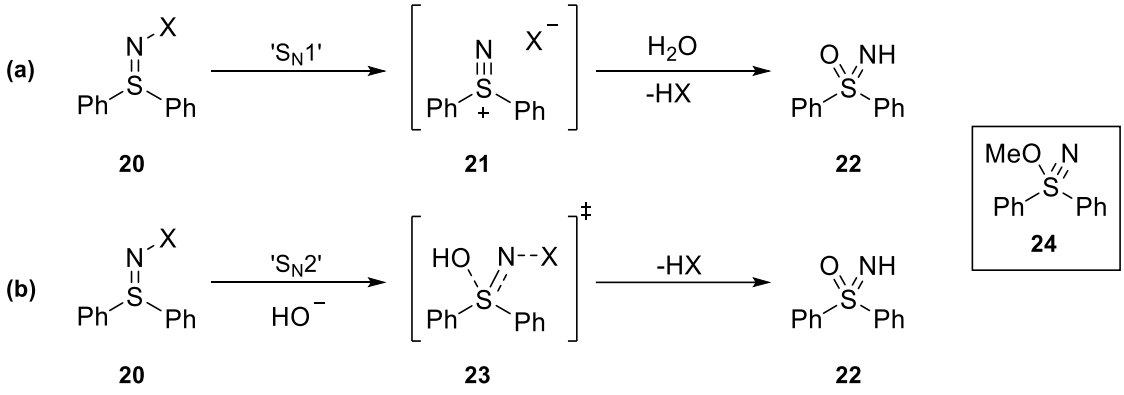
The large variety in sulfilimine oxidation strategies means that the correct oxidant can be applied depending on the nature of the substrate in hand. A less common route to sulfoximines from sulfilimines is a two-step procedure, involving a halogenation followed by hydrolysis. This process was achieved alongside the first preparation of a *N*-halosulfilimine (**18**).[56] The stereochemical outcome of this sequence has also been examined (**Scheme 1.11.**),[57] and similar to the other previous oxidation strategies, the transformation is said to proceed with a high degree of retention at sulfur. The exact consequence of the stereochemical outcome for this process has not been rationalised, and anchimeric assistance cannot be dismissed, however, the authors suggest a direct $S_N2$-like mechanism is likely for the second step.




**17** **18**, 67% **19**, 93%

**Scheme 1.11.** Conversion of a sulfilimine to a sulfoximine, with overall retention of stereochemistry at sulfur.

Further mechanistic work for the alkaline hydrolysis step has been conducted on achiral samples and kinetic data suggested two concurrent mechanisms (**Scheme 1.12.**).[58] Mechanism **(a)** is $S_N1$-like, in which N–X bond heterolysis occurs to a nitridosulfonium cation (**21**), which is then rapidly intercepted by water. Alternatively, mechanism **(b)** is $S_N2$-like, in which the halogen is displaced in a single step by a hydroxide anion, *via* the tetravalent transition state **23**. In solvolysis reactions that occur in alcoholic solvent, the $\lambda^6$-alkoxy-sulfanenitrile **24** (also referred to as a thiazyne) can be isolated.[59] These thiazyne species are considered to be key intermediate, that drive sulfoximine formation *via* alkylation of the alcoholic solvent.[60]




**20** **21** **22** **24**

**20** **23** **22**

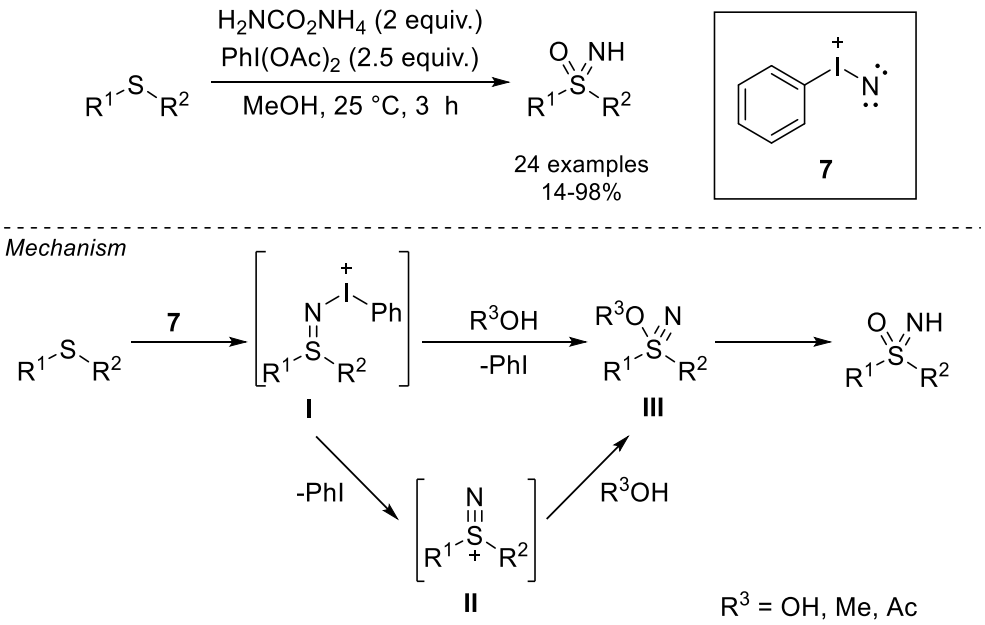
**Scheme 1.12.** Mechanistic proposals for the alkaline hydrolysis of *N*-halosulfilimines (X = Cl or Br).

The formal oxidation of a sulfilimine *via* the synthesis of *N*-halosulfilimine and subsequent hydrolysis has seen little application,[61] and currently has remained somewhat of an academic curiosity, with intriguing reactive intermediates produced.[62] In general it could be postulated that the oxidation strategies presented here would be exceedingly popular, however their uptake has not been

as common as one might expect. This trend can be ascribed to the inherent instability of the sulfilimine precursors that are required, especially when compared to alternative methods.

### 1.2.3. Direct Oxidation from Sulfides

The previous routes to sulfoximines use sulfoxides and sulfilimines as starting materials which tend to be prepared from the corresponding sulfides, therefore a more attractive route to access sulfoximines would be directly from these precursors themselves. This protocol has been established recently, building on the imination work of Bull and Luisi previously discussed (see **Scheme 1.7.**),[40] where similar conditions can be applied to a sulfide to provide sulfoximines (**Scheme 1.13.**).[63] Once again, this method provides a highly successful way to access the free-sulfoximine, whilst also delivering a concise method for $^{15}N$ incorporation. Other advantages like an extension to *S*-perfluoroalkylated derivatives[64] and a green solvents alternative, by using a recyclable oxidant in water,[65] have emphasised the power of this methodology. Mechanistic work has also been conducted on this reaction,[66,63] where it has been determined that imination precedes oxidation, likely using the reactive nitrene **7** generated *in situ*, giving the sulfilimine **I**. The fleeting intermediate **I** then draws comparison to the previous *N*-halosulfilimine method (**18**, see **Scheme 1.11.**), where similarly it is susceptible to attack from the possible nucleophiles present, such as water, methanol and acetate yielding intermediate **III**. The $\lambda^6$-alkoxy-sulfanenitrile (**III**, $R^3$ = Me) and $\lambda^6$-acetoxy-sulfanenitrile (**III**, $R^3$ = Ac) intermediates were observable by mass spectrometry and NMR experiments, and these intermediates disappear over time to give the sulfoximine product, supporting this mechanistic proposal.



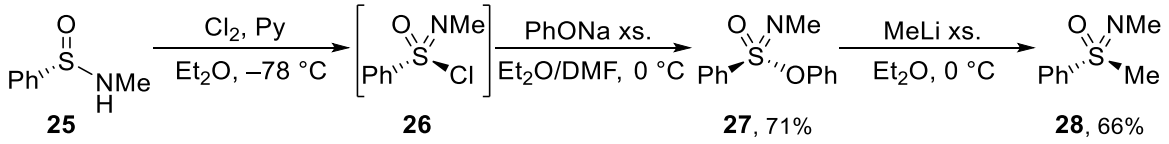

**Scheme 1.13.** Direct transfer of *-O* and *-NH* to a sulfide to synthesis the sulfoximine moiety. With the mechanistic proposal showing imination followed by oxidation.

Undoubtedly this procedure is a highly valuable contribution to the field of sulfoximine synthesis. Future reports may look to exploit the use of a prochiral, sulfide starting material, to extended this to an asymmetric reaction. However, this procedure has been applied on optically active sulfides to form diastereoisomers,[67] although from these results it is still unclear if the enantiodetermining step would be the initial imination to **I**,[68] or attack onto a possible nitridosulfonium ion (**II** to **III**). It can be expected that further exploration of these relatively underexplored reactive intermediates will have profound implications on the field of aza-sulfur compound synthesis.

### 1.2.4. Nucleophilic Substitution

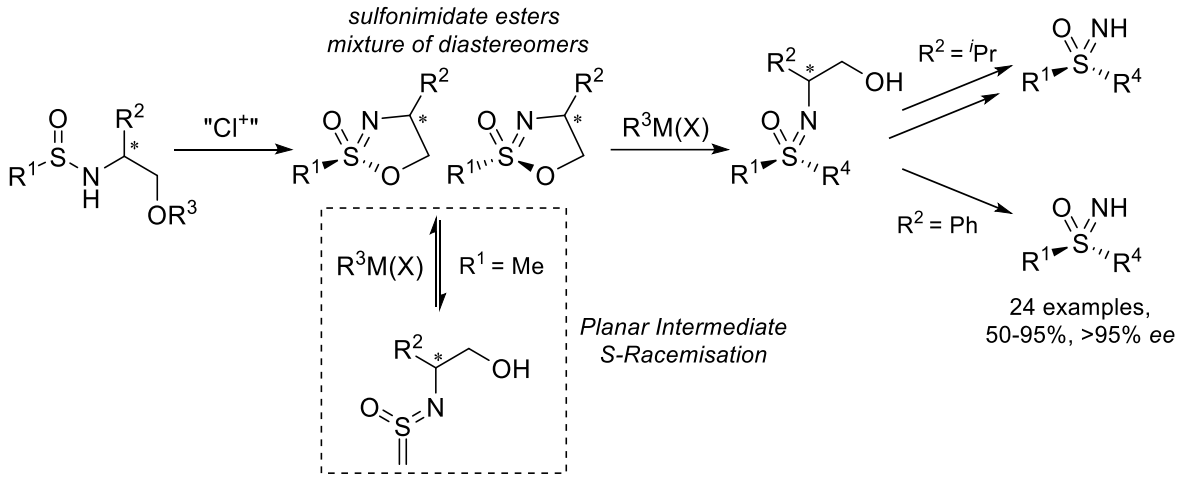
The previous routes have used redox reactions for the synthesis of the sulfoximine functional group. Redox neutral methods involving the interconversion of two different aza-sulfur(VI) functionalities have also been developed. The sulfonimidate ester has been most commonly employed in these additions, in combination with organometallic reagent, first reported in the 1970's by Johnson *et al.*, whilst examining the stereochemical course of the reaction (**Scheme 1.14.**).[69] In this

sequence, sulfinamide **25** was initially converted to sulfonimidoyl chloride **26** using chlorine gas.[70] This reaction is conducted at low temperature, in the presence of pyridine, to prevent racemisation of both starting material and product, resulting in stereochemical retention. The crude product **26**, resulting from this step, is added to sodium phenoxide in dimethylformamide. Although sulfonimidate ester **27** production was deduced to occur with stereochemical inversion, racemisation of sulfonimidoyl chloride **26** at 0 °C led to a significant loss of optical purity. Recrystallisation of sulfonimidate ester **27** was performed to obtain high enantiomeric excess before the key nucleophilic displacement, with MeLi, was conducted. This highly stereoselective reaction gave the sulfoximine with inversion.




**Scheme 1.14.** The sequence to produce sulfoximines *via* nucleophilic substitution from a sulfonimidate ester. The yield of **27** is based on the direct synthesis from **25**.

Furthermore, Johnson was able to show the generality of this final displacement step with a range of other organolithium species[71] and this has been extended to Grignard reagents,[72] albeit using excess of these species. Demonstrating the difficulty of accessing the sulfonimidate esters in high enantiomeric ratios, has led to a solution using a diastereomeric sulfonimidoyl chloride in the sequence.[72a] Where generating these intermediates *in situ* instead, then trapping with an alcohol intramolecularly to form cyclic sulfonimididate esters, has successfully led to the overall production of enriched sulfoxmines (**Scheme 1.15.**).[73]

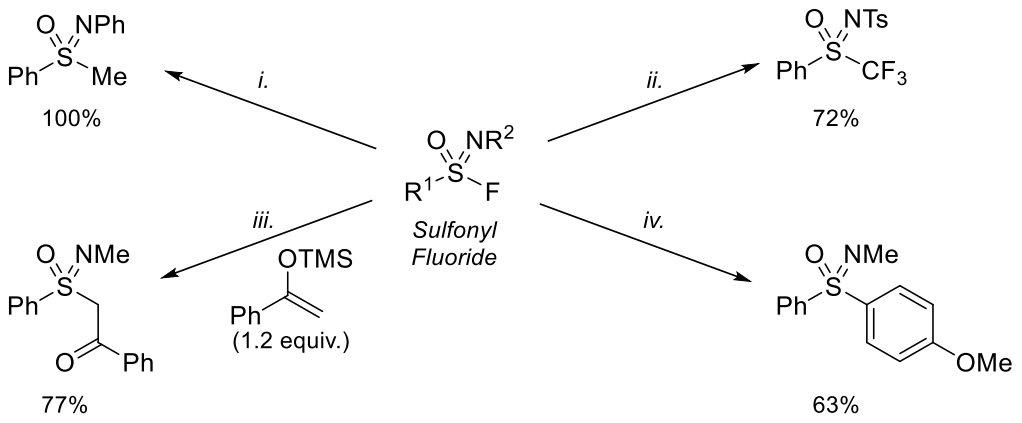



**Scheme 1.15.** Routes to enriched sulfoximines using cyclic sulfonimidate esters as key intermediates. With $R^2$ = (*R*)-Ph or (*S*)-$^i$Pr. In the case of $R^3$ = TMS a deprotection step is also required.

A variety of cyclic sulfonimidate esters diastereoisomers have been shown to be separable *via* column chromatography. The resulting enantiomers can then react with both a diverse range of organolithiums and Grignard reagents, once again requiring at least two equivalents. In addition, the appendage on the imidic site can act as an auxiliary, such as when $R^2$ = $^i$Pr and a low yielding three-step procedure from the sulfoximine was employed.[74] Whereas, when $R^2$ = Ph a direct oxidative debenzylation can be achieved to give the free-sulfoximine. Intriguingly, alkyl cyclic sulfonimididate esters ($R^1$ = alkyl) were not suitable in this sequence. For example, when $R^1$ = $^t$Bu, the reaction resulted in no desired product, as the sulfonimidate ester was considered too sterically encumbered to accept the Grignard reagent. Furthermore, when $R^1$ = Me for sulfonimidate ester, elimination to a planar achiral methylene intermediate was proposed to occur under the conditions, overall resulting in loss of stereochemical information when delivering the product.

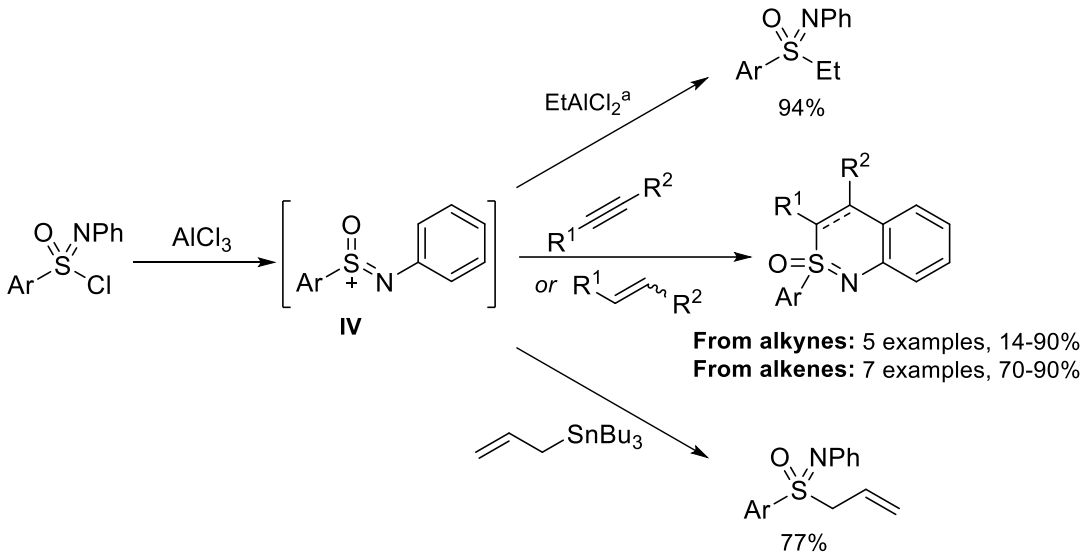
A noteworthy drawback of this strategy is the use of a multistep sequence, although more convergent routes to sulfonimididate esters are known,[73b] and have been utilised.[72b] However, one could envisage a route *via* direct displacement, with an organometallic reagent, from a sulfonimidoyl chloride. In these cases preferential reactivity at the Cl atom to give the reduced sulfinamide product

occurs.[71] In contrast, the more stable sulfonimidoyl fluorides have been shown to be able to react at sulfur when in the presence of excess organolithiums (*i.* **Scheme 1.16.**).[75] Furthermore, under specific conditions sulfonimidoyl fluorides can react with trifluoromethyl reagents (*ii.*),[76] silyl enol ethers (*iii.*)[75] and electron-rich aromatics (*iv.*).[75a]




**Scheme 1.16.** Multiple examples of sulfonimidoyl fluorides to react with nucleophiles producing a range of sulfoximines. Conditions: *i.* MeLi (2 equiv.).[75] *ii.* $TMSCF_3$ (2 equiv.).[76] *iii.* $BF_{3(g)}$ (xs.). *iv.* anisole (1 equiv.)[75] $TiCl_4$ (1.6 equiv.).[75a]

Although a variety of these reactions are not extendable to sulfonimidoyl chlorides, it has been shown that the Friedel-Craft reactivity can be achieved in moderate yields when using $FeCl_3$ as the stoichiometric catalyst.[77] This approach of activating the chloride as a leaving group with a Lewis acid has been applied to alkyl,[78] alkynyl[79] and vinyl[80] reagents for sulfoximine synthesis (**Scheme 1.17.**). The role of the aluminium reagent is hypothesised to form the highly electrophilic sulfur ion **IV**, *via* a key S–Cl bond fragmentation. When the reactive intermediate **IV** is intercepted with alkynes and alkenes, a concerted [4+2]-cycloaddition is proposed. However, when using an allyltin reagent, the stepwise addition becomes increasingly favourable due to tin's ability to stabilise β–carbocations, hence in this case the non-cyclic product was isolated. Overall, the sulfonimidoyl chloride can readily accepts carbon-based nucleophiles, but a key requirement is that these must be activated under relatively harsh conditions, which has limited this as a generally applicable route.



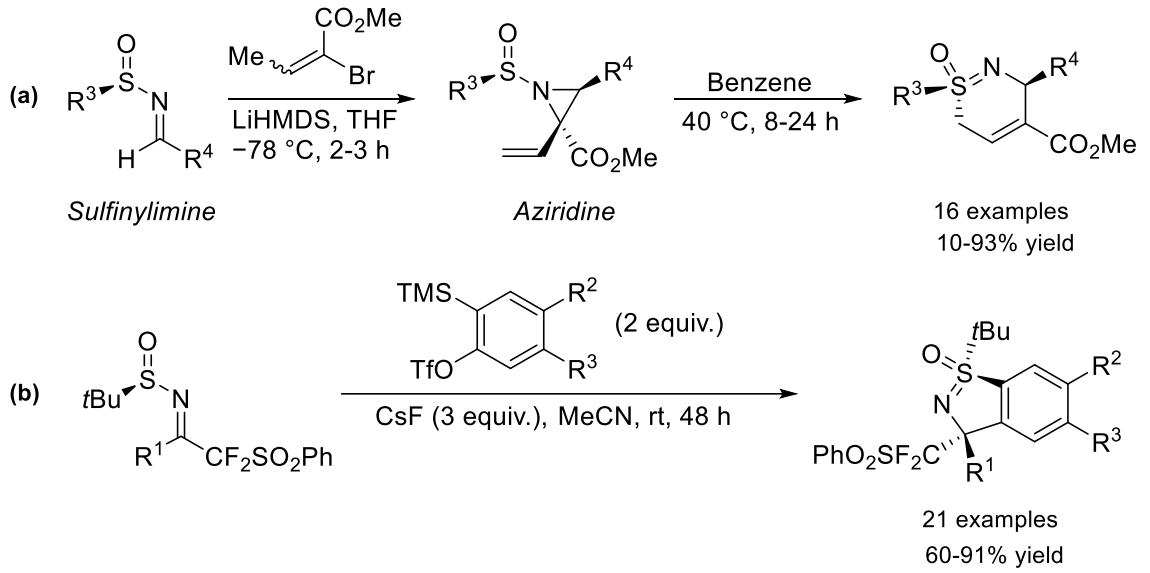

**Scheme 1.17.** Use of a lewis acid to activate sulfonimidoyl chlorides to nucleophile addition where Ar = *p*-tolyl. [a]$EtAlCl_2$ is used in place of $AlCl_3$.

Overall, these strategies demonstrate the interconversion of multiple aza-sulfur compounds to a diverse range of sulfoximines, whilst providing some insight into the stereochemical outcomes. However, the cumbersome nature of these procedures, and many requiring a large excess of reactants provides room for improvement.

### 1.2.5. Direct Reactions from Sulfinamides

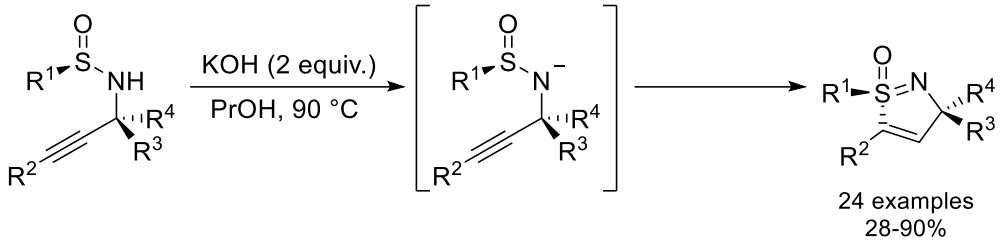
The final method to be discussed for sulfoximine synthesis is their direct generation from sulfinamide precursors, through the formation of C–S bonds with electrophiles. This strategy only started to develop in recent years, presumably due to a sulfinamide's inherent preference to react at their nitrogen atom.[5b,6] Despite this challenge, reactivity at the sulfur was first realised using sulfinylimines starting materials in pericyclic reactions (**Scheme 1.18.a.**). For example, the sulfinylimine can take advantage of the electrophilicity at the C=N bond and act as a precursor to an aziridine, which is then able to undergo a thermal 2,3-sigmatropic rearrangement to sulfoximine product, where the ester moiety is essential in modulating the correct reactivity.[81] Alternatively, an intramolecular reaction uses the sulfinylimine directly as a 1,3-dipole with an aryne in a [3 + 2]

cycloaddition reaction, to give sulfoximine (**Scheme 1.18.b.**). Once again, a key substituent, the -$CF_2SO_2Ph$, was essential in increasing electrophilicity at carbon without detriment to the sulfur lone pair nucleophilicity, additionally the -$CF_2SO_2Ph$ group provides a synthetic linchpin in the product.[82]



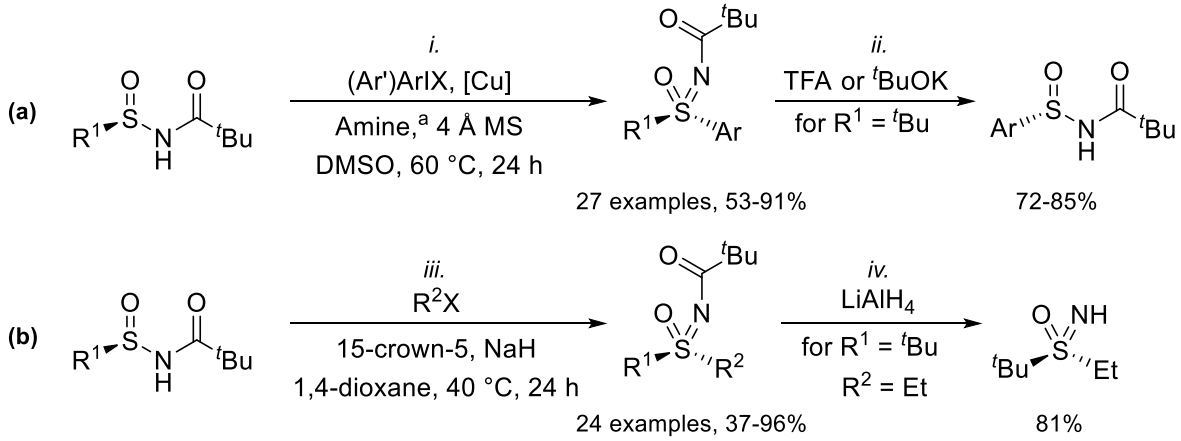

**Scheme 1.18.** Use of pericyclic reactions to modulate the reactivity of sulfinamides, giving sulfoximine products.

Although these highly stereospecific reactions showcase the ability for sulfinamides to use there sulfur lone pair to construct C–S, the reliance of pericyclic reactions creates a niche set of heterocycles. A somewhat more general strategy was initially developed by Poisson and relies on an intermolecular cyclisation,[83] where the sulfur lone pair is used in a 5-*endo-dig* reaction, which is more favourable than the possibility of using the nitrogen lone pair for a 4-*exo-dig* cyclisation. This reaction initially utilised a silver catalyst, but an analogous transformation by Maruoka noted that simply deprotonating the sulfinamide, increased the sulfur nucleophilicity, and allowed the cyclisation to be performed with a broad range of substrates (**Scheme 1.19.**).[84]




**Scheme 1.19.** A base-mediated cyclisation to give the 5-membered sulfoximine heterocycle.

Again, the requirement to form a heterocycle produces a limitation in the variation of sulfoximines produced. This however has been circumvented by the simultaneous development of an *S*-arylation[85] and *S*-alkylation[86] of sulfinamides, recently developed by Maruoka (step *i.* & *iii* respectively, **Scheme 1.20.**). By employing a pivaloyl sulfinamide, under specific conditions, reactivity could be tuned for the sulfur long pair, providing a range of sulfoximines. Furthermore, when beginning from an Ellman's auxiliary derivative ($R^1 = {}^t$Bu) the *tert*-butyl group can be deprotected under acidic or basic conditions to return a sulfinamide (step *ii*, **Scheme 1.20.a.**). Additionally, the pivaloyl protecting group can be orthogonally deprotected with $LiAlH_4$ to free-sulfoximine (step *iv*. **Scheme 1.20.b.**), allowing further derivatisation. Overall, it was shown that the aforementioned reactions were stereospecific with retention at sulfur. From this it is beneficial that the sulfinamide produced can be re-subjected to either initial reaction conditions, which allows sequential manipulation to both possible enantiomers of the sulfoximine products.




**Scheme 1.20.** Intramolecular reactions of sulfinamides to synthesis sulfoximines (**a**) arylation, (**b**) alkylation, and subsequent reactions. [a] When $R^1 = {}^t$Bu the amine is $Cy_2NMe$, whereas when $R^1$ = Ar the amine is $^i Pr_2NEt$.

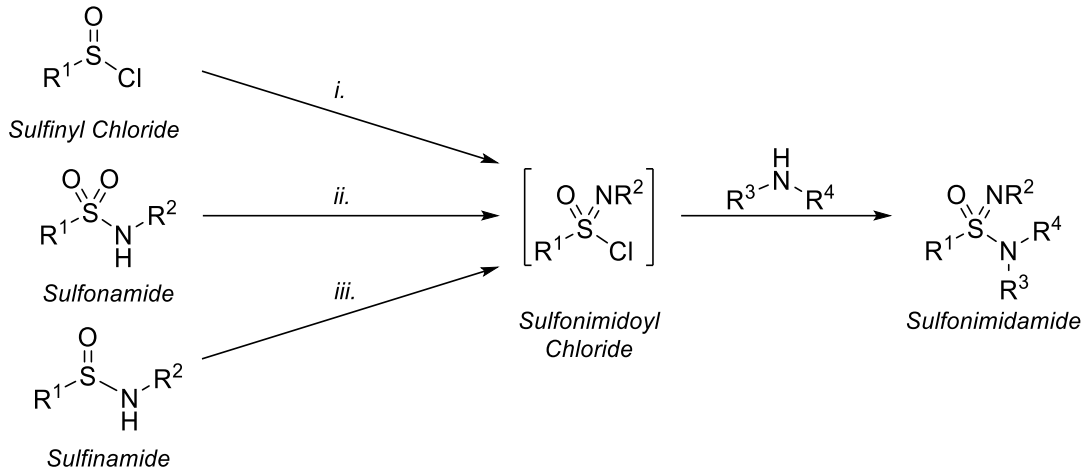
In summary, a range of methods exist to synthesise sulfoximines, using a variety of different bond construction processes that occasionally intercept underexplored intermediates. A significant limitation of many of the methods presented here is that the substrates and products are generally traced back to the use of malodorous thiols and sulfides as starting materials, which limits the possible range of sulfoximines available. Therefore, future methods should look to expand the library of available chiral sulfoximines, through circumvention of impractical precursors, and focus on the direct preparation of unsubstituted products at nitrogen, to allow for further diversification.

## 1.3. Sulfonimidamide Synthesis

The first synthesis of a sulfonimidamide actually predates the sulfoximine by approximately 20 years,[87] however, current available routes to this functional group are surprisingly diminished in comparison. Most methodologies to these functional groups are reliant on the nucleophilic displacement from a sulfonimidoyl chloride with an amine or ammonia. Reports of using alternative leaving groups, by employing sulfonimidoyl fluorides or sulfonimidate esters, are relatively scarce. Several miscellaneous methods, that directly access the sulfonimidamide from other aza-sulfur functionalities, will also be discussed in this section.

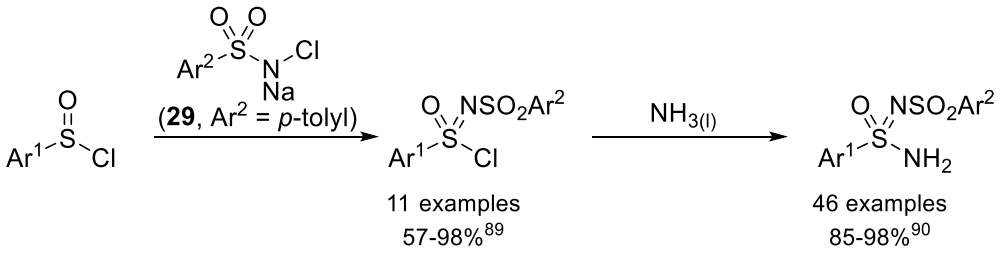
### 1.3.1. Sulfonimidoyl Chloride Displacement

As stated, routes that proceeded *via* the sulfonimidoyl chloride reaction intermediate have been the most extensively explored. Typically, the precursor to the sulfonimidoyl chloride is either a sulfinyl chloride (*i.*), sulfonamide (*ii.*) or sulfinamide (*iii.*) (**Scheme 1.21.**). The final step from the sulfonimidoyl chloride, which involves a nucleophilic displacement with an amine, predominantly occurs with inversion of stereochemistry at the sulfur centre.[69,88]



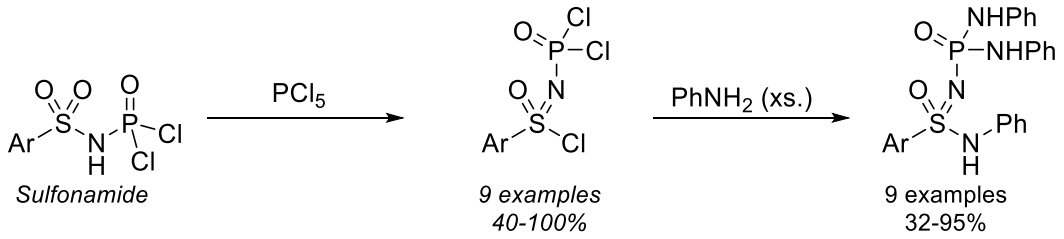

**Scheme 1.21.** The most common strategies that have been used to access sulfonimidamides from sulfonimidoyl chlorides, from (*i.*) sulfinyl chlorides (*ii.*) sulonamide and (*iii.*) sulfinamide.

The application of synthesising a sulfonimidoyl chloride from a sulfinamide was first reported in 1960 by Levchenko *et al.*,[89] using chloramine-T (**29**, $Ar^2$ = *p*-tolyl) and analogous iminating reagents. Subsequently, the sulfonimidoyl chloride could directly react with ammonia (**Scheme 1.22.**).[90] This reaction was able to produce a range of aryl-sulfonimidamides in high yield, although with little variation in imination reagents used, which practically limits this route to sulfonyl protected sulfonimidamides. Furthermore, the reaction sequence has seen relatively little modern application which is not aided by the fact that commonly available sulfinyl chlorides and appropriate iminating regents are sparse.[91] Furthermore, sulfinyl chlorides inherently have poorly defined stereochemistry,[92] meaning that these steps are not suitable for the synthesis of enantioenriched sulfonimidamides.



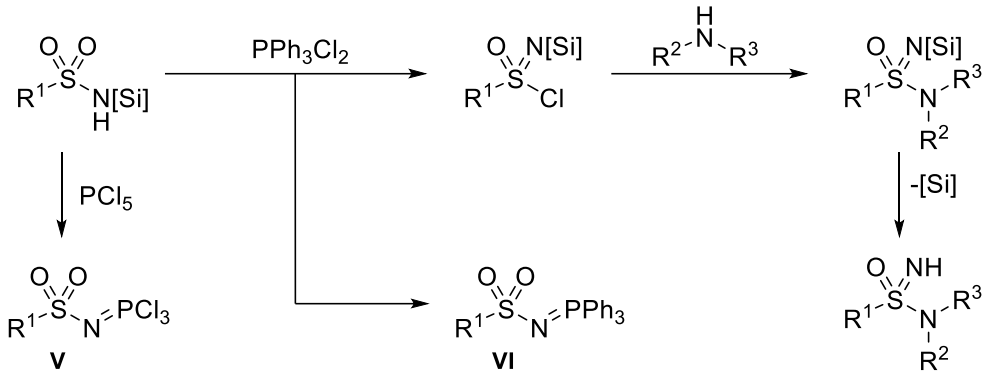

**Scheme 1.22.** Conversion of sulfinyl chlorides to sulfonimidoyl chlorides resulting in sulfonimidamides.

As the sulfonamide is already a well-established S(VI) functional group,[93] a route involving their deoxy-chlorination allows more complex sulfonimidamides to be synthesised . Developed in the early 1960's, this S(VI) interconversion pathway combined a sulfonamide starting material with phosphorus pentachloride (**Scheme 1.23.**).[94] The resulting sulfonimidoyl chloride was then shown to be reactive towards aniline, producing sulfonimidamides.[95] Overall, the first step of this process relies on phosphorus' oxophilicity, where removal of the sulfonamide oxygen is able to occur with formal substitution by chloride.



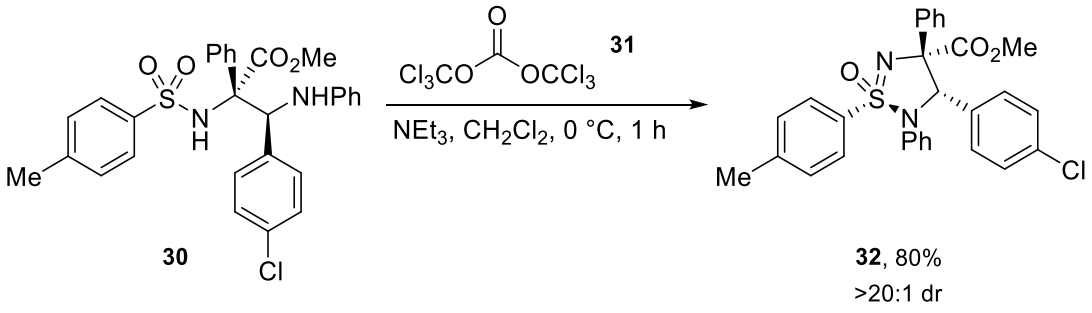

**Scheme 1.23.** Conversion of sulfonamides to sulfonimidoyl chlorides resulting in sulfonimidamides.

Modernisation of this route, to increase the generality of the scope with easier to handle starting materials, has used silyl protected sulfonamides (**Scheme 1.24.**). Where now for the TMS-protected sulfonamide a bulkier reagent, $Ph_3PCl_2$, is preferential to prevent sulfonamide iminophosphorane by-product formation (**V**).[96] When using a TBS-protecting group, the procedure could be performed in one-pot to provide a range of aryl and alkyl-substituted unprotected sulfonimidamides.[97] In these reactions, it is noteworthy that a competing unproductive process is the formation of sulfonamide **VI**, which is hypothesised to be the resulting by-product from the *in situ* deprotection of silyl-sulfonamides. Fortuitously, a bulkier TBDPS group can also be used[98] to shut down this *in situ* deprotection. Even though a prochiral starting material is used for this reaction, the synthesis of optically active sulfonimidamides has been limited to diastereomeric procedures that utilise enantiopure amines, which often result in undesirable diastereomeric ratios.[97-98]




**Scheme 1.24.** Conversion of silyl protected sulfonamides to sulfonimidoyl chlorides resulting in sulfonimidamides.

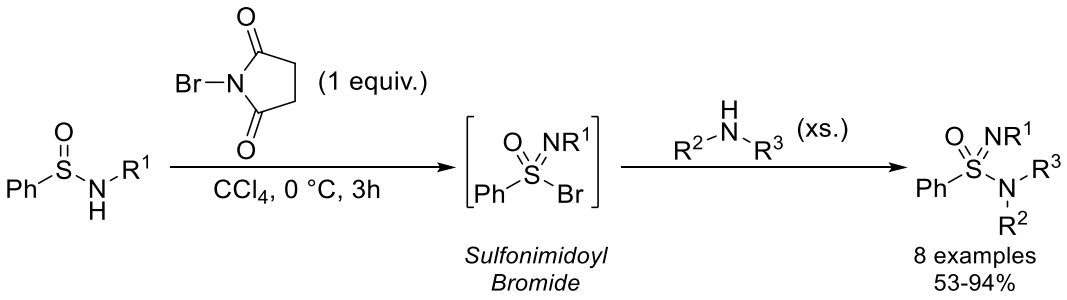
Although producing free imidic-sulfonimidamides (S=NH) is highly valuable, one can also begin with *N*-substituted sulfonamides, rather than a silyl group. This was originally shown with a very simple aryl system,[97] but a recent report has shown that a chiral alkyl amine can be used (**Scheme 1.25.**).[99] This singular example now activates the sulfonamide with triphosgene (**31**) and, by using an intramolecular reaction, the final product is obtained with a high diastereomeric ratio. These protocols have revitalised the seminal work from the 1960's and further developments may have profound implications, especially considering that a plethora of methods already exist to synthesis sulfonamides.[100]




**Scheme 1.25.** Example of direct conversion of a sulfonamide to a cyclic sulfonimidamide with high selectivity.

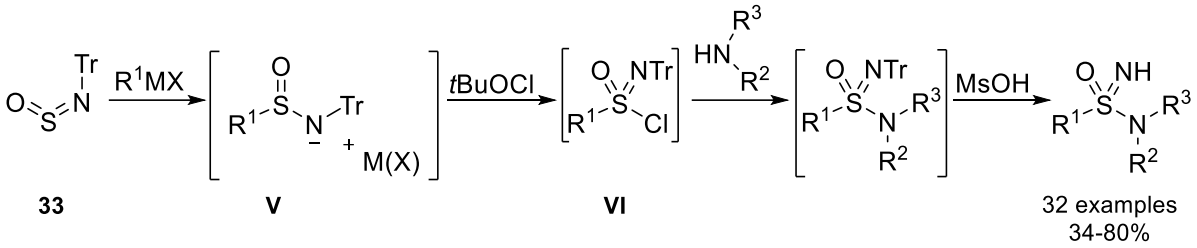
The final strategy of using sulfinamide starting materials to access sulfonimidamides is arguably the most widely used. Intriguingly, this type of sequence was originally developed by generating a sulfonimidoyl bromide, either from the addition of bromine or NBS, and intercepting the highly

unstable intermediate with an amine (**Scheme 1.26.**).[101] Due to the capricious nature of sulfonimidoyl bromides, the chloride analogues are favoured as intermediates en-route to sulfonimidamides. As previously discussed, these intermediates are accessible from the action of chlorine gas on sulfinamides (see **Scheme 1.14.**).[70] Although chlorine gas has produced a range of sulfonimidamides, the harsh conditions can be difficult to handle and when using *N*-aryl sulfinamides, and can lead to ignition if warmed above −78 °C.[91] Therefore, other oxidants have been developed including *N*-chlorobenzotriazole,[70] NCS[102] and the most popular *tert*-butyl hypochlorite.[77a] Despite this versatile selection, the reliance on a limited sulfinamide pool, keeps these methods at a disadvantage.




**Scheme 1.26.** Use of sulfinamide as a starting material to produce sulfonimidamides, *via* a sulfonimidoyl bromide.

To overcome the necessity to use sulfinamide starting materials in this strategy, recently a one-pot procedure starting from a trityl-protected *N*-sulfinylamine (**33,** TrNSO),[82] that generates the sulfonimidoyl chloride (**VI**) *in situ,* has been developed (**Scheme 1.27.**).[103] In this case, the reagent TrNSO provides a bench-stable solid which can be used in combination with a range of organometallic reagents, producing the anionic intermediate **V**. This intermediate then can undergo an analogous procedure to that previously discussed. Finally, it is worth noting that the trityl-protecting group can also be removed *in situ* under acidic conditions, meaning that this one-pot 4-step sequence expands the scope of currently available sulfonimidamides, by the simple combination of organometallics and amines with a sulfinylamine.

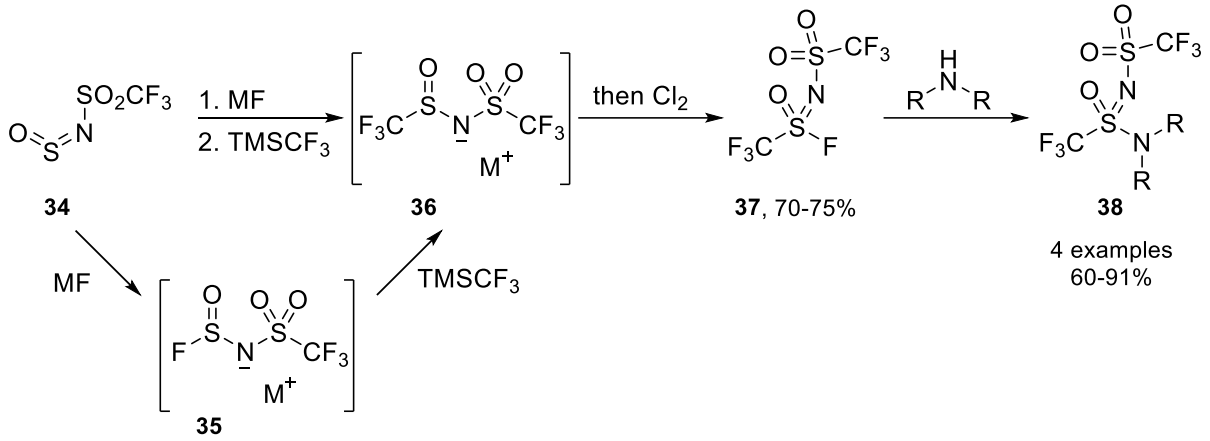



**Scheme 1.27.** Use of sulfinamide as a starting material to produce sulfonimidamides, *via* a sulfonimidoyl chloride intermediate.

Although modern developments are making the sulfonimidamide functional group much more accessible, the heavy reliance on the sulfonimidoyl chloride can be viewed as undesirable. Where these species have high instability, coupled with a tendency to racemise at elevated temperatures. Therefore, different routes *via* alternative reactive intermediates would be beneficial.

### 1.3.2. Sulfonimidoyl Fluoride Displacement

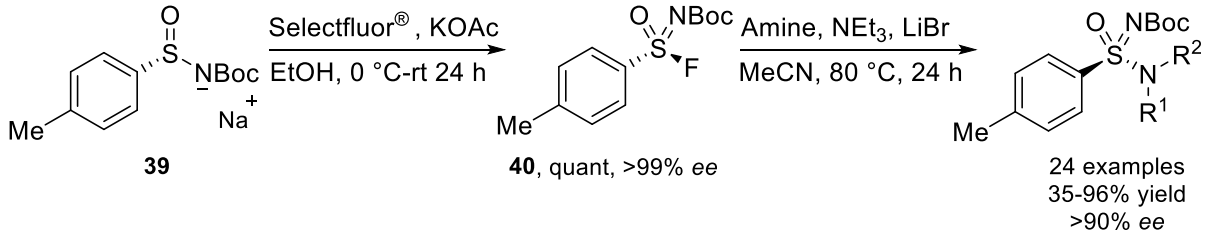
Previously the use of sulfonimidoyl bromide intermediates to synthesise sulfonimidamides was observed (see **Scheme 1.26.**). This highlights that alternative leaving groups, other than chlorine, can lead to sulfonimidamide products. Therefore, efforts towards the production of intermediates, with increased stability over the chlorides, have been conducted. The prior exploitation of sulfonimidoyl fluorides and sulfonimidate esters, as stable intermediates for sulfoximine synthesis, triggered their utility in the preparation of sulfonimidamides. Originally, sulfonimidoyl fluorides were derived from the sulfonimidoyl chlorides, *via* anionic fluoride in a halogen exchange (halex).[75a] The resulting products are less susceptible to decomposition,[104] but can still react with amines. An example using an activated species **37** involves the use of an *N*-sulfinylamine (**34**) as a starting material (**Scheme 1.28.**).[105] Here, starting material **34** is able to react with fluoride to form the intermediate **35**, which is further displaced to give sulfinamide anion **36**, this species can then be oxidatively fluorinated to **37** with a combination of chlorine gas in the presence of additional fluoride (MF).




34 36 37, 70-75% 38 35

**Scheme 1.28.** Generation of a sulfonimidoyl fluoride from a *N*-sulfinylamine, *via* fluoride addition and subsequent reaction with chlorine gas in the presence of a fluoride source.

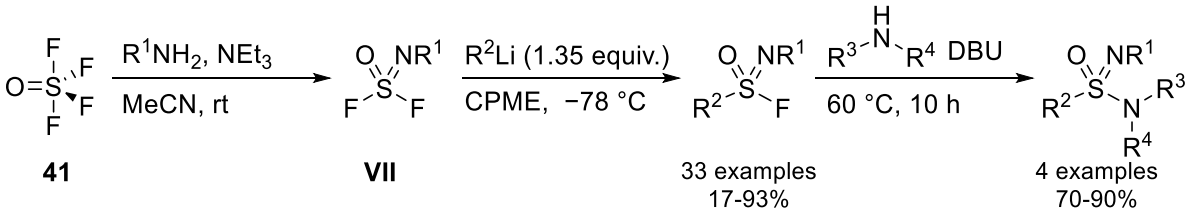
The use of a milder chlorinating reagent, in the presence of fluoride anions, has served as a successful route to sulfonimidoyl fluorides,[106] however, a more direct procedure is to use an oxidative fluorinating agent, such as Selectfluor®. With this reagent, the stereochemical outcome, within the products, has also been examined (**Scheme 1.29.**).[107] In this case, the first step occurs with retention of stereochemistry, whilst the second step occurs with inversion at sulfur. It was found that the additive LiBr was essential as a fluoride scavenger, to prevent a fluoride-assisted racemisation of the starting material **39**. This procedure also demonstrates the requirement for elevated temperatures, to accelerate fluoride displacement with an amine, which overall provides a range of sulfonimidamides. However, even though the final enantiomeric ratios are high, this procedure is limited by the diminished availability of optically pure sulfinamides.




39 40, quant, >99% *ee*

**Scheme 1.29.** Synthesis of enantioenriched sulfonimidamides using stereoselective fluorination and displacement from a sulfinamide.

Recent work by Gao *et al.* has shown that the synthesis of sulfonimidoyl fluorides does not have to involve sulfinamide starting materials (**Scheme 1.30.**).[75b] Instead this uses gaseous $SOF_4$ (**41**), generated in an autoclave, which is then reacted with an amine to generate intermediate **VII**. The reaction of S–F compounds with organometallics has been observed to be somewhat precarious,[108] however this problem was circumvented by using organolithiums at low temperature, to give sulfonimidoyl fluorides. Once again, sulfonimidamide products could be accessed at elevated temperatures, with strong base. The products could also be further functionalised with the sulfonimidoyl fluorides being converted to sulfonimidate esters and sulfoximines. Despite the method's success, having $SOF_4$ gas (**41**) as the synthetic foundation provides practical limitation for standard laboratory use.



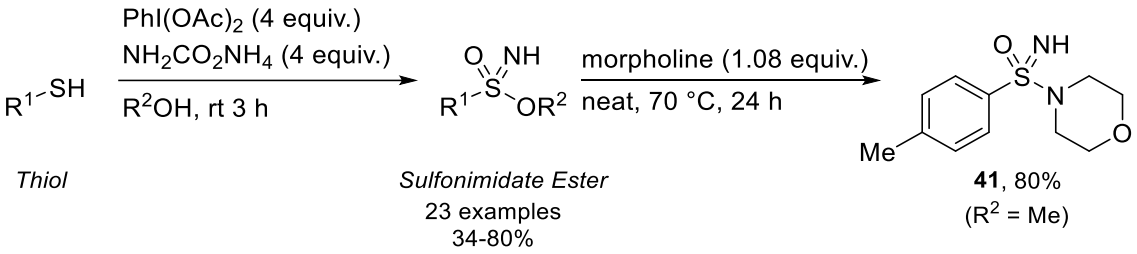

**Scheme 1.30.** Use of $SOF_4$ gas to generate a sulfonimidoyl fluoride in a stepwise procedure eventually leading to sulfonimidamide synthesis.

Although sulfonimidoyl fluorides are emerging as key intermediates for accessing both sulfoximines and sulfonimidamides, they are often synthesised through multistep sequences, or from a limited range of sulfinamides. Therefore, with only a few methodologies available for their synthesis, currently it is questionable if their increased stability offers a significant advantage over using sulfonimidoyl chlorides *in situ* under milder conditions.

### 1.3.3. Sulfonimidate Ester Displacement

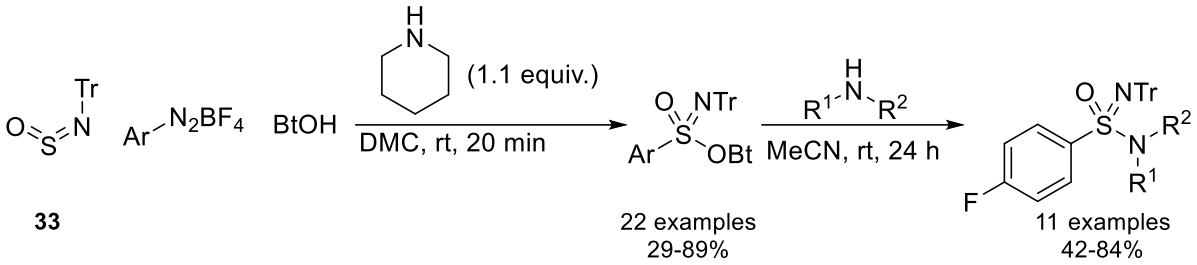
As sulfonimidate esters are well-established precursors of sulfoximines, it is unsurprising that this has been translated over to the sulfonimidamide functional group.[109] In general, one-pot strategies to

the sulfonimidate ester have been developed, offering an advantage, with respect to the ease of their synthesis, over sulfonimidoyl fluorides. For example, an extension of previous work from Bull and Luisi (see **Scheme 1.7.** & **Scheme 1.13.**), has allowed thiols to be directly converted to the imidate esters in moderate yields (**Scheme 1.31.**).[110] The high equivalents of oxidant and amine source, used in the first step, were vital to suppress sulfonamide by-product formation. In addition, several details of the mechanism were elucidated, however, it is likely that multiple pathways converge to the sulfonimidate ester product. Additionally, a singular example was shown for the synthesis to sulfonimidamide **41**.




**Scheme 1.31.** Conversion of a thiol directly to a sulfonimidate ester, which leads to sulfonimidamide **41**.

Another recent development, by the Bolm group, has shown the synthesis of sulfonimidate esters whilst avoiding the use of malodorous thiols (**Scheme 1.32.**).[111] This sulfonimidate ester formation proved very sensitive to physical parameters such as scale and order of addition. However, this was fundamentally proposed to work by the generation of an aryl radical mediated by the base and TrNSO (**33**). Therefore, TrNSO could accept a radical, which is trapped by the BtOH reagent, to give the sulfonimidate ester. In a similar guise, a recent report has also been able to add an aryl radical into *N*-sulfinylamines reagents,[112] now mediated by a copper chloride catalyst and $KHF_2$, ultimately leading to the production of sulfonimidoyl fluorides. These processes, followed by the subsequent amine addition allows a diverse range of sulfonimidamides to be synthesised with an increased functional group tolerance.



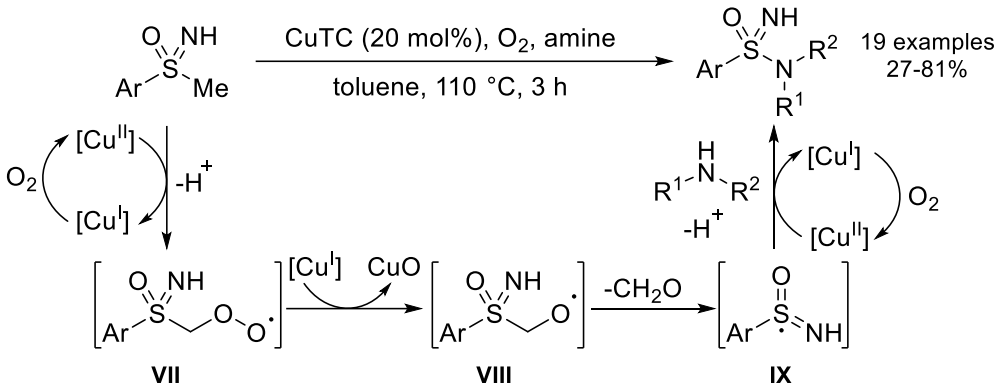

**Scheme 1.32.** Radical reaction with TrNSO to produce a sulfonimidate ester, which can be converted to sulfonimidamides.

In summary, simpler routes to sulfonimidate esters and sulfonimidoyl fluorides have started to allow a broader range of sulfonimidamides to be synthesised, and provide complementary alternatives to the previous routes, which often involve strong oxidative conditions or the use of organometallic reagents.

### 1.3.4. Miscellaneous

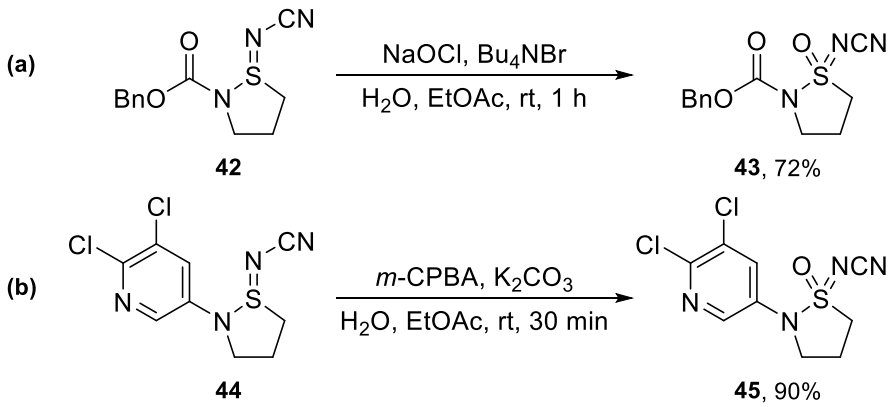
The desirability of redox neutral methods to access S(VI) compounds has led to an increasing interest in reactions which interconvert aza-sulfur species,[113] hence it is of note that sulfonimidamides can be interconverted *via* a nucleophilic displacement strategy when the nitrogen substituent is an appropriate leaving group (*e.g.* imidazole).[114] Furthermore, it has been shown that sulfoximines can be converted to sulfonimidamides. Although this nucleophilic substitution requires an activated sulfoximine,[115] therefore, a more general approach proceeds *via* a sequential de-alkylation, amine cross-coupling mediated by dioxygen and copper (**Scheme 1.33.**).[116] This was determined to be a radical mediated process, where it is hypothesised that copper coordinates to the sulfoximine, which then undergoes subsequent C–H deprotonation, single electron transfer and reaction with oxygen to form intermediate **VII**. Loss of an oxygen from intermediate **VII** gives species **VIII**, which fragments with loss of a formaldehyde group to give radical **IX**. The existence of intermediate **IX** was inferred from the trapping of formaldehyde and scrambling of stereochemistry in the reaction. This reactive intermediate was then said to undergo a copper-mediated coupling with the amine, to produce

sulfonimidamide product. Although this reaction achieves quite a feat, with moderate yields, the substrate scope is rather limited, and is only applicable to specific sulfoximines and simple cyclic amines.



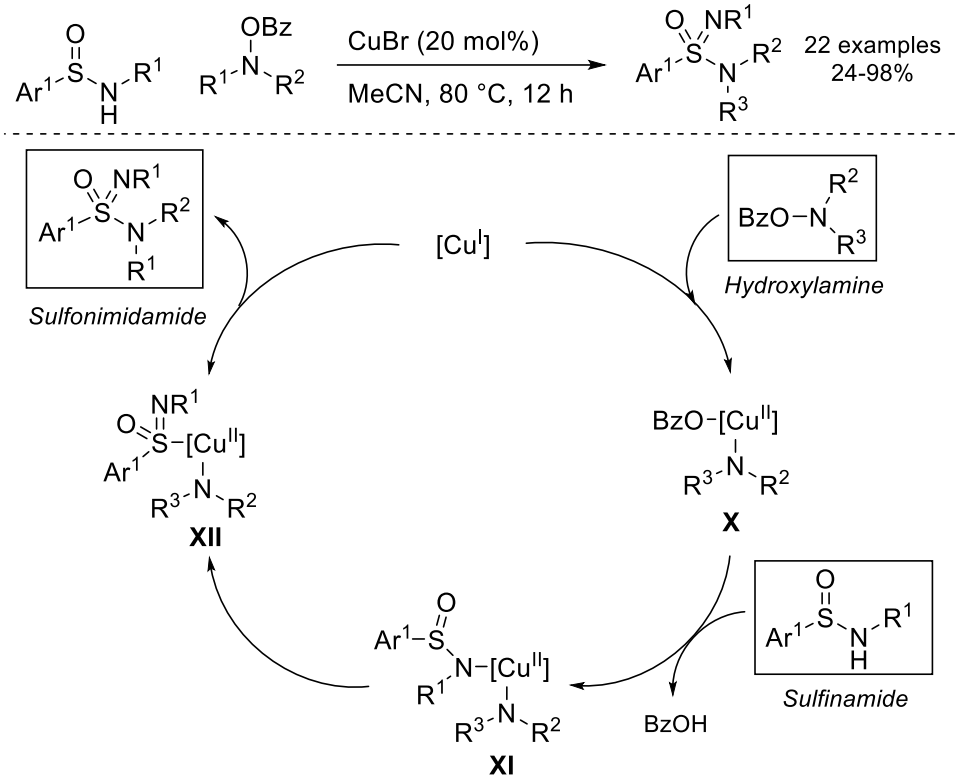

**Scheme 1.33.** Copper and oxygen mediated de-alkylation/amination of a sulfoximine to sulfonimidamide.

Another miscellaneous transformation which involves an oxidation reaction, but does not rely on a stepwise procedure or halogenation, is *via* the reaction of a sulfinamidine starting material (**42**, **Scheme 1.34.a**). In fact, the first proposed synthesis of a sulfonimidamide was *via* oxidation of a sulfinamidine with potassium permanganate,[87] this strategy has been adopted in the patent literature, albeit using milder oxidants (**Scheme 1.34.b**).[117] Although these examples provide simple procedures and show high yields on relatively complex substrates, this strategy has not been widely applicable, probably due to the current limited available routes to sulfinamidines.[118]




**Scheme 1.34.** Representative examples of direct oxidation to access sulfonimidamides.

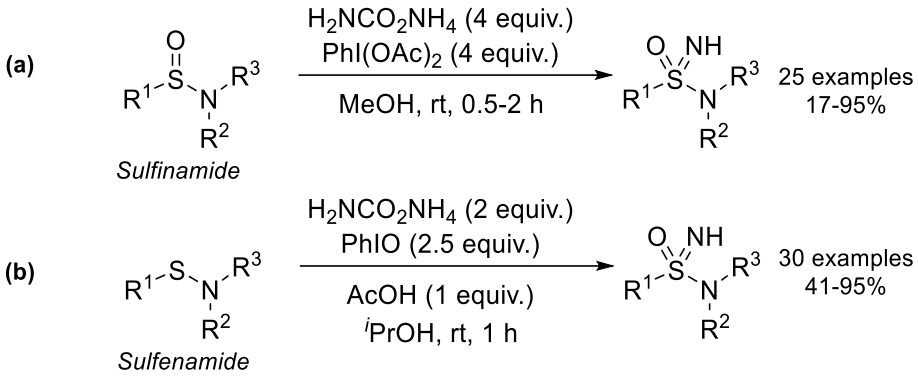
Due to the availability of sulfinamides, these have also been translated into a direct oxidation approach. An example of this is a copper mediated process (**Scheme 1.35.**).[119] In this case, a hydroxylamine undergoes oxidative addition with a copper(I) salt to produce intermediate **X**, exchange of the ester moiety with sulfinamide can eventually lead to *S*-bound **XII**, which completes the cycle *via* reductive elimination to give sulfonimidamide. Although this method demonstrates a relatively convenient synthesis of the sulfonimidamide, the strict use of an *N*-aryl sulfinamide ($R^1$ = Ar) was necessary to prevent transulfinamidation, which was proposed to occur *via* ammonia extrusion of the product when $R^1$ = H.




**Scheme 1.35.** Copper-mediated oxidation of a sulfinamide, with the hypothesised catalytic cycle.

This direct approach from a sulfinamide offers a variety of benefits over two-step procedures discussed previously. Fortuitously, a metal-free approach has also been developed, once again using the highly valuable combination of ammonium carbamate and hypervalent iodine oxidant (see **Scheme 1.7.**, **Scheme 1.13.** & **Scheme 1.31.**). This has been applied on both sulfinamides

(**Scheme 1.36.a.**)[120] and sulfenamides (**Scheme 1.36.b.**)[121] with both these reactions following similar mechanistic proposals to those discussed previously. In addition, when enantioenriched sulfinamides were employed, the reaction was shown to be stereospecific. However, it is worth noting that the reaction is only applicable when $R^2$ or $R^3 \neq H$, hence limiting the scope of available sulfonimidamides.




**Scheme 1.36.** Representative examples of direct oxidation to access sulfonimidamides.

Overall a variety of routes to sulfonimidamides exist, with most reliant on sequential oxidation then displacement reactions, from a multitude of possible intermediates. Recent publications have looked at creating more efficient processes which are operationally simple, with a few studies looking at the stereochemical outcomes. Many of the processes outlined still require the presence of an oxidant, hence, redox neutral methods, and the further development of interconverting aza-sulfur compounds may have significant impact.

## 1.4. Summary and Project Objectives

Although the synthesis of several sulfur(VI) species is now commonplace, the synthesis of sulfoximines and sulfonimidamides is still underdeveloped. While the previous discussion has presented a range of methods to synthesise both these moieties, from this analysis it is noticeable that, to date, sulfoximine synthesis is heavily reliant on the imination of sulfoxides, whilst sulfonimidamide

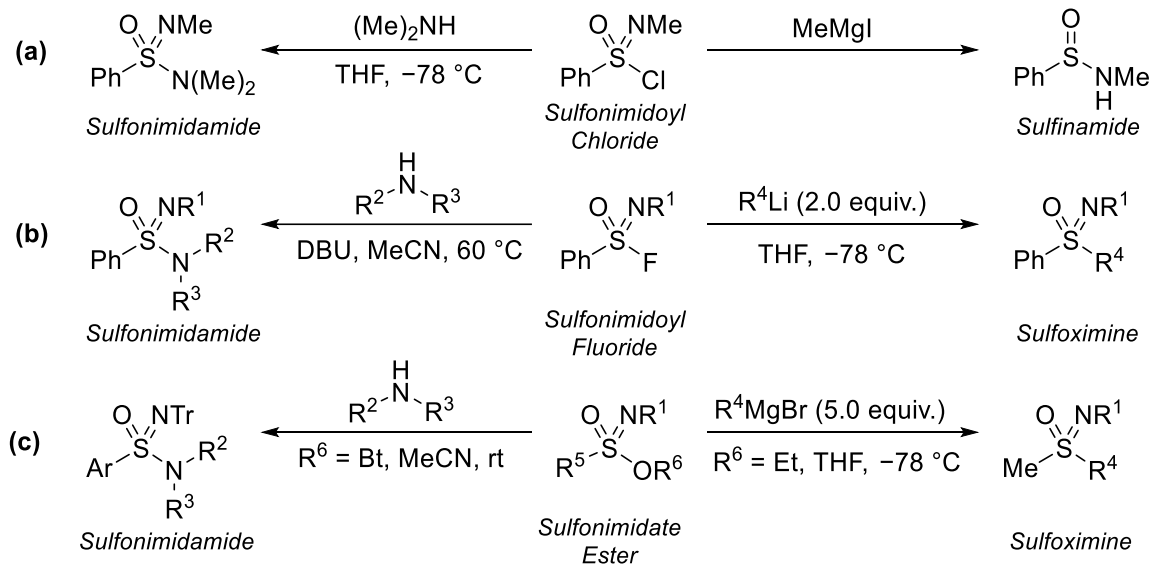
synthesis is typically limited to halogenation and subsequent displacement from sulfinamides. Although a great deal of recent efforts have attempted to diversify and develop applicable procedures to both these functional groups, most of these new routes still require malodorous and difficult to handle thiol starting materials in oxidation reactions. Furthermore, the generation of sulfoximines and sulfonimidamides with an unsubstituted nitrogen has only been observed in a handful of reports. Developing applicable routes to these species would allow further understanding of their inherent reactivity, and application in a multitude of research areas. Finally, many transformations to sulfoximines and sulfonimidamides are known to be stereoselective, however, this relies on a limited pool of chiral substrates to produce enantioenriched products, hence controlling the configuration at sulfur has not yet been mastered.

With this information in mind, a goal was to create a new synthetic strategy to access both sulfoximines and sulfonimidamides, ideally from a common intermediate, as this has been under exploited. Furthermore, by using more proficient strategies to access aza-sulfur functional groups there was the possibility to be able to explore novel reactivities of these compounds. In particular, a motivation was to exploit this in developing routes to obtain enantioenriched sulfonimidamides.

# Chapter 2 – The Divergent Synthesis of Sulfoximines and Sulfonimidamides – A Computational Investigation

## 2.1. Introduction

A divergent route to both sulfoximines and sulfonimidamides has several significant challenges, where the most prominent arises from the requirement to generate a common intermediate which readily reacts to form both of these species. For example, sulfonimidoyl chlorides will react with amines to synthesise sulfonimidamides, however, it has been reported that these intermediates will undergo a reduction reaction with organometallics to produce the corresponding sulfinamides (**Scheme 2.1.a**).[71] This reduction process can be circumvented with the use of sulfonimidoyl fluorides in combination with organolithiums at cryogenic temperatures (**Scheme 2.1.b**).[75b] In a similar guise, sulfonimidate esters have been shown to be applicable in the synthesis towards both sulfoximines and sulfonimidamides (**Scheme 2.1.c**).[72b,111,73b]

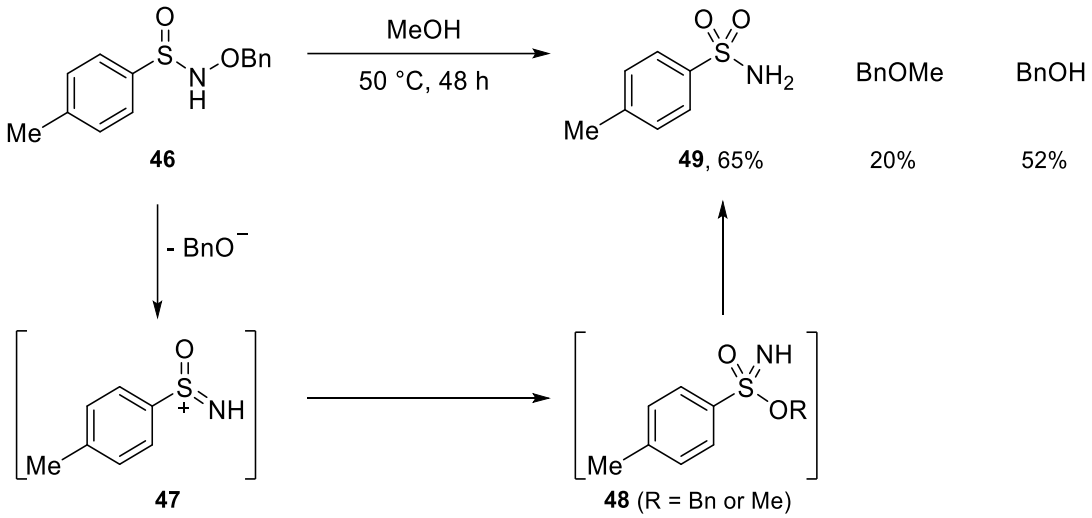



**Scheme 2.1.** Current attempts towards a divergent strategy to sulfonimidamides and sulfoximines from S(VI) intermediates.

However, there are significant drawbacks when analysing these divergent strategies such as both sulfonimidoyl fluorides and sulfonimidate esters being cumbersome to synthesis and requiring excess organometallic reagents to generate the sulfoximines. Additionally, the synthesis of sulfoximines and sulfonimidamides which are unsubstituted at their imidic nitrogen ($R^1 = H$) are becoming increasingly valued, due to the possibility for further functionalisation, hence a new divergent strategy to directly access these species is of high significance.

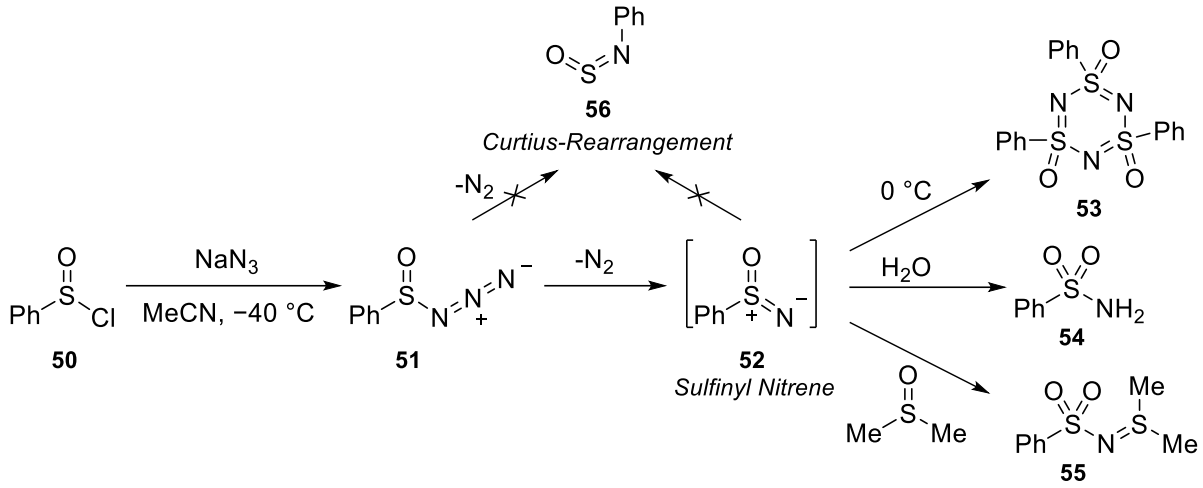
### 2.1.1. Aza-Sulfur Compounds as Reactive Intermediates

In order to develop a novel divergent synthesis to sulfoximines and sulfonimidamides, it is necessary to either use an alternative reactive intermediate or provide a simpler method for generating sulfonimidoyl fluorides or sulfonimidate esters, preferentially *in situ*. Due to this requirement, it was noted that seminal work by Maricich has previously proposed sulfonimidate esters as intermediates in the synthesis of a sulfonamide (**49**) from *N*-alkoxysulfinamides (**46**, **Scheme 2.2.**).[122] Although this sequence has limited synthetic application, due to **46** decomposing on standing at room temperature to a multitude of products. The proposed mechanism of its reaction with alcohols provides a noteworthy insight. It is speculated that the reaction is initiated by N–O bond cleavage producing a key sulfinyl nitrenium intermediate (**47**), which is then proposed to react at the sulfur centre with either the solvent or an alkoxide to give the sulfonimidate ester (**48**). This sulfonimidate ester can then function as an alkylating agent, which is a well-established process,[123] providing the final product **49**. Overall, this pioneering work indicates that it is possible to generate sulfonimidate esters *in situ* from a S(IV) precursor, however, more fundamentally this report postulates the presence of a pivotal sulfinyl nitrenium intermediate, where such underexplored species provide opportunities to explore new chemical space.




**Scheme 2.2.** Generation of a sulfonamide from an *N*-alkoxysulfinamide *via* key reactive intermediates.

Other early reports from Maricich have also focused on studying reactive S(IV) species and elucidating the role of abstruse intermediates in their reactions. For example, the synthesis, characterisation, and reactions of sulfinyl azides (**51**) has been a particular focus (**Scheme 2.3.**).[124] Initially it was demonstrated that the azide **51** can be generated from the sulfinyl chloride **50** and sodium azide, however it is commented that this reaction is rather temperamental due to reproducibility issues coupled with the spontaneous and explosive decomposition of azide **51** at ambient temperatures. Although this decomposition leads to a mixture of products it was noted that the cyclic trimer **53** was produced, indicating the presence of a sulfinyl nitrene intermediate (**52**) which is electrophilic at the sulfur centre. The electrophilicity of **52** at sulfur is further supported with their decomposition in the presence of water producing sulfonamide **54**, as well as the reaction with a sulfoxide giving a sulfilimine product **55**, rather than a sulfoximine. Furthermore, in all the reactions of **51** no Curtius rearrangement product **56** was observed, which shows these species atypical behaviour in contrast to other organic azides.[125]

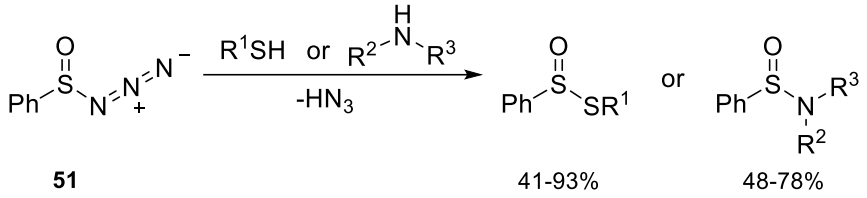



**Scheme 2.3.** Synthesis and application of sulfinyl azides *via* a key sulfinyl nitrene intermediate, which indicates reactivity at an electrophilic sulfur centre.

The presence of a sulfinyl nitrene intermediate (**52**) is based on the outcomes of the sulfinyl azides reactions as well as kinetic data.[124c] In addition, a more recent report has provided irrefutable evidence for the existence of such intermediates,[126] wherein flash vacuum pyrolysis of a sulfinyl azide and subsequent characterisation by matrix-isolation IR spectroscopy has elucidated the presence of a singlet state sulfinyl nitrene.

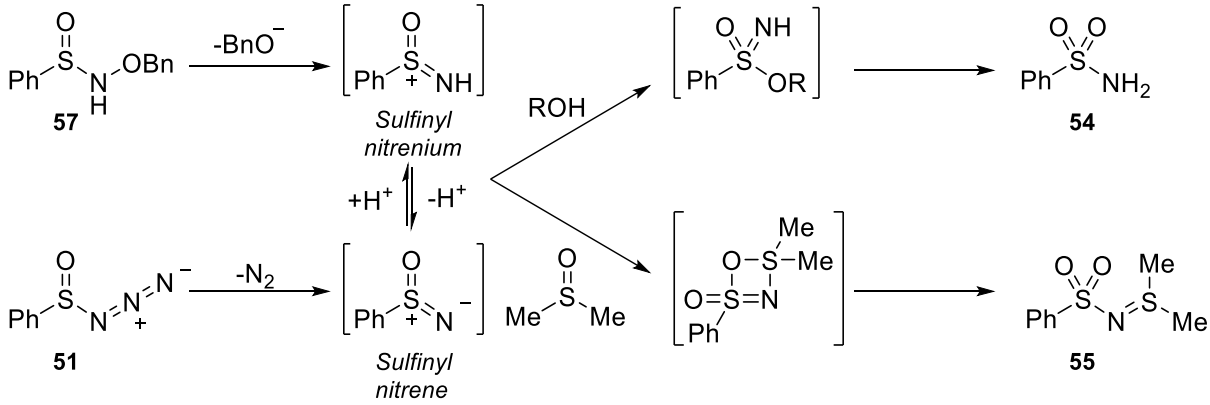
A recurring feature of the sulfinyl nitrenes is the contrasting chemistry when compared to the related sulfonyl nitrenes, which are electrophilic at nitrogen and undergo typical reactions of nitrenes such as X–H insertion (typically X = O, N or C).[127] Hence, one could envision that the presence of a sulfinyl nitrene intermediate provides a unique opportunity for atypical chemistries to be harnessed. For example, exploiting the proposed sulfur's electrophilicity in combination with carbon and nitrogen-based nucleophiles would potentially create the desired divergent route to sulfoximines and sulfonimidamides. Surprisingly, designing sulfinyl nitrenes into new methodologies has not been readily expanded on. A rationalisation for the lack of this uptake can be ascribed due to the previously observed safety concerns coupled with the irreproducibility and requirement for specialised

procedures.[128] Additionally, undesirable substitution of the -$N_3$ group, before the possibility of nitrene generation, has been reported with nucleophiles such as thiols and amines (**Scheme 2.4.**).[129]




**Scheme 2.4.** The substitution of sulfinyl azides with nucleophiles such as thiols and amines.

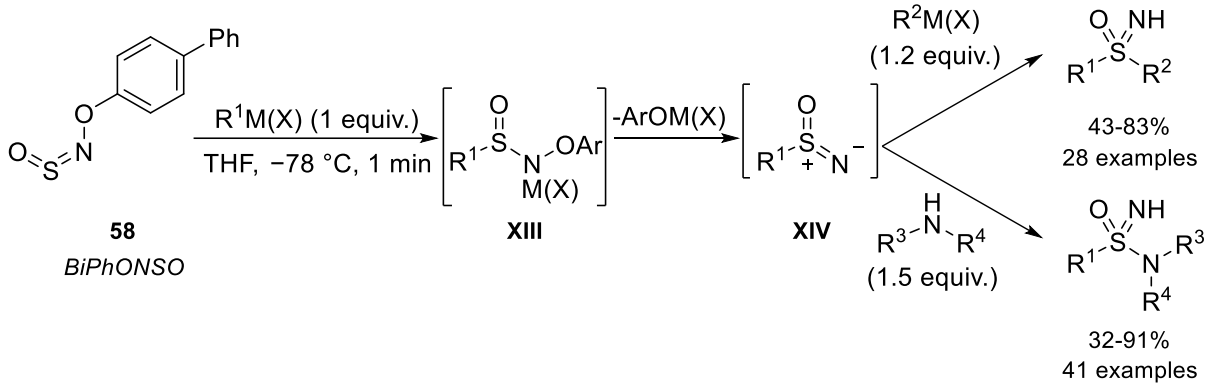
From these previous reports exploring the properties of sulfinyl azides, it appears that utilising these as sulfinyl nitrene precursors raises several serious challenges. However, preliminary work by Maricich inferred a convergence between the mechanisms of the aforementioned *N*-alkoxysulfinamides (**46**) and sulfinyl azide (**51**), in the presence of an alcohol or DMSO (**Scheme 2.5.**).[130] During these studies it was noted that both **51** and **57** provide the same sulfonamide products (**54** & **55**) when reacted with an alcohol or a sulfoxide respectively, indicating the presence of common intermediates. Therefore, implying that the *N*-alkoxysulfinamides may provide an alternative strategy to create a reaction sequence to sulfoximines and sulfonimidamides *via* sulfinyl nitrenes.




**Scheme 2.5.** Reactions which indicate that both the *N*-aryloxysulfinamides and sulfinyl azide react with alcohols or sulfoxide with a convergence in reaction mechanism.

### 2.1.2. Reaction Development

Within the Willis group the use of sulfinylamines[131] has been successful for synthesising novel aza-sulfur compounds,[103,12] and it was therefore desirable to plan a synthetic sequence which utilises a sulfinylamine reagent. Hence, Dr. Thomas Davies was able to readily synthesise a stable solid *N*-aryloxysulfinylamine, BiPhONSO (**58**, **Scheme 2.6.**),[132] where in theory, combination of this reagent with an organometallic reagent produced an *N*-aryloxysulfinamide *in situ* (**XIII**). Following on from the previous literature, this should provide a more straightforward and reliable method to generate a range of sulfinyl nitrenes (**XIV**). In practise Dr. Thomas Davies was able to produce a rapid reaction sequence (15 minutes) combining a range of organometallic species as well as amines to generate a diverse range of both unprotected sulfoximines and sulfonimidamides respectively, in good to high yields.

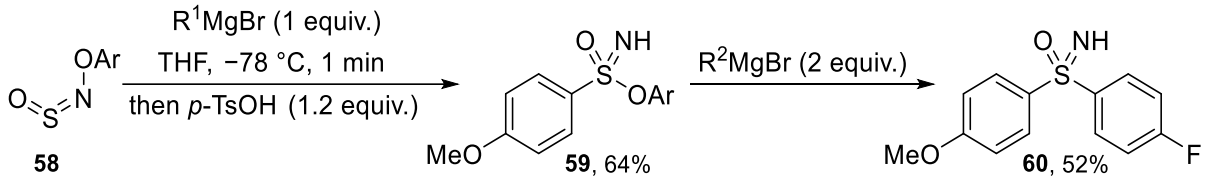



**Scheme 2.6.** Divergent synthesis of both sulfoximines and sulfonimidamides from the reagent BiPhONSO, developed by Dr. Thomas Davies. Where key *N*-aryloxysulfinamide and sulfinyl nitrene intermediates are postulated to be involved in the mechanism of this reaction sequence.

### 2.1.3. Mechanistic Observations

Alongside developing this divergent synthesis to these underexplore aza-sulfur compounds, Dr. Thomas Davies in collaboration with Jack Ren, noted several key mechanistic observations (**Scheme 2.7.**). In particular, it was noted that when using one equivalent of Grignard reagent and immediately quenching the reaction with *p*-toluenesulfonic acid, the resulting sulfonimidate ester

(**59**) was isolated. This sulfonimidate ester (**59**) could then be deprotonated with a Grignard reagent and reacted with a second equivalent to produce the previously observed sulfoximine product **60**.




**Scheme 2.7.** Key mechanistic observations realised by Dr. Thomas Davies and Jack Ren for the investigation into the mechanism of BiPhONSO (**58**) with organometallics.

These experimental observations raise several key mechanistic questions for the developed methodology. Firstly, how is this sulfonimidate ester species (**59**) produced and is it an intermediate towards sulfoximine synthesis. Secondly, is the postulated sulfinyl nitrene intermediate (**XIV**) actually involved in the reaction sequence, and if so, what role does it play and does its inherent characteristics agree with those previously observed by Maricich and others. This project aimed to provide further insight into these mechanistic questions *via* undertaking a computational investigation with Density Functional Theory (DFT)[133] applied to the reaction of organometallic reagents with BiPhONSO.

## 2.2. Computational Model

Computational chemistry, in particular DFT, has found a vital place in providing insight into a variety of chemical problems, including a wealth of reports aiding mechanistic understandings.[134] Therefore, it is somewhat surprising to note that there are comparatively few studies analysing organometallic reagents with computational methods, although such species as Grignard reagents have been known for over 100 years.[135] The minimal amount of such studies on Grignard reagents can be credited to the complexity of the problem.[136] Firstly, the ethereal solvents commonly employed in reactions are strongly associated with the magnesium centres, where magnesium can also vary in their coordination modes.[137] Secondly the presence of Schlenk equilibrium means that

multiple species,[138] as well as oligomeric states are present in solution.[139] Therefore, mechanistic complications arise as the ratio of each of these species can depend on a variety of factors, including, temperature, concentration, solvent, and the identity of the counterions.[140]

Regardless of the intricacy associated with computing Grignard reagents, several endeavours have been made to elucidate their inner workings. In particular, a significant focus has been placed on examining the Schlenk equilibrium, with the role of solvent and dimeric species being considered, using a range of *ab initio,*[141] DFT,[142a-c,141c,141d,142d] and semi-empirical methods.[143] Where a significant contribution in understanding the Schlenk equilibria has applied *ab initio* molecular dynamics simulations, complimented by DFT, to provide a better perspective on the intricate mechanism associated with the Schlenk equilibrium.[144] Despite the significant progress made, far fewer computational studies have examined the direct reactions of Grignard reagents with electrophiles.[145] These studies have exclusively focused on methyl magnesium halides in combination with simple aldehyde electrophiles. In particular, they have focused on the comparison between reactions of monomeric and dimeric magnesium species as well as on the difference between polar (nucleophilic) and radical (single electron transfer (SET))[145a,141c,146] pathways. The most current report in this field combines quantum-chemical calculations with *ab initio* molecular dynamic simulations,[146] where this work highlights the importance of the solvent and suggests that the reaction of Grignard reagents should in fact be considered as an ensemble of transformations, with simultaneous pathways potentially in operation.

### 2.2.1. Model Assumptions

Due to the aforementioned complexity of this system, it was decided to begin with a simplified, but relevant, model system for the DFT mechanistic investigation (**Figure 2.1.**). Firstly, a truncated *N*-aryloxylsulfinylamine was used, PhONSO (**61**) rather than BiPhONSO (**58**) which is expected to

have a similar geometry, electronic and steric profile, whilst reducing the computational cost. Furthermore, *N*-aryloxylsulfinylamine **61** has successfully been employed in the reactions to obtain the desired products. In this model system methyl magnesium chloride (MeMgCl) was used, due to the wealth of experimental[147] and previously outlined computational investigations into its properties. Moreover, this Grignard reagent has been employed successfully as a scope example in the reaction. Although the presence of a dimeric MeMgCl, bound with explicit ethereal solvents, may have significant implications for the mechanism, a monomeric Grignard with an implicit solvent model was first considered to gain insight. Furthermore, a polar mechanism was initially evaluated for the generation of the key sulfinyl nitrene intermediate.

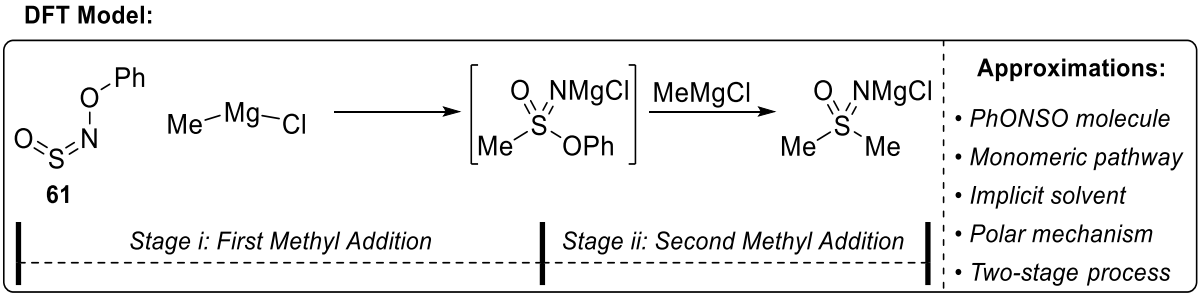



**Figure 2.1.** Proposed model for the DFT study of the addition of a Grignard reagent to a *N*-aryloxylsulfinylamine.

### 2.2.2. Functional Evaluation

Given the proposed model, an appropriate functional had to be evaluated to use in this investigation. When considering the previous DFT approaches to the Schlenk equilibrium, reactions of MeMgCl and evaluation of sulfinyl nitrenes, B3LYP[148] has proven popular. However, the shortcomings of B3LYP are well documented, especially when considering self-interaction error[149] and the poor description of long-ranged dispersion interactions.[150] Therefore, it was appropriate to assess a variety of functionals in a benchmarking study. To achieve this, several experimentally relevant magnesium diimidosulfinate (**MD**) crystal structures, that resemble potential intermediates (**MD1-MD5, Figure 2.2.**),[151] were selected from the Cambridge Structural Database (CSD).[152]

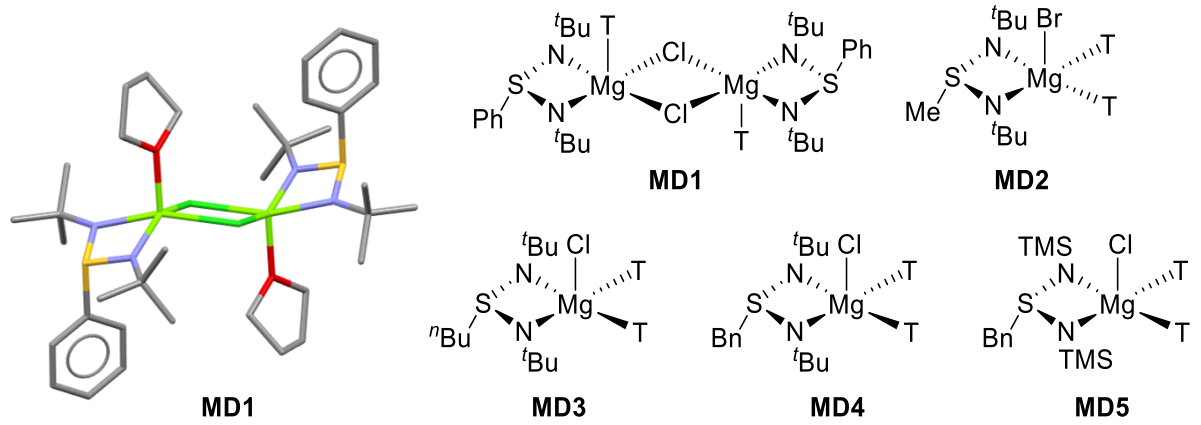
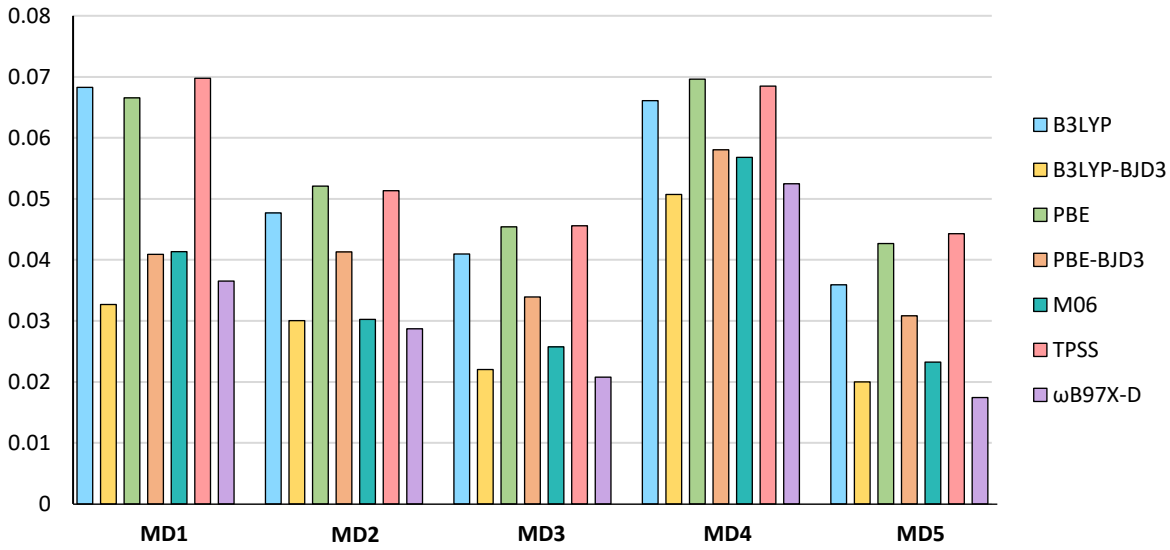



**Figure 2.2.** Selected X-ray crystal structures of magnesium diimidosulfinate complexes for structural benchmarking, where T = THF coordinated by its oxygen atom and hydrogen atoms omitted for clarity.

From these structures the geometries were re-optimised using pure (PBE[153]), hybrids (B3LYP[148] and M06[154]), range-separated (ωB97X-D[155]) and meta-GGA (TPSS[156]) functionals, as well as those including dispersion corrections with a dampening function[157] (B3LYP-BJD3 and PBE-BJD3), all with the 6-31g(d) basis set.[158] To evaluate the functionals success, the deviation in several key bond lengths were evaluated (Mg–X, X = O, N, S, Cl, Mg and S–Y, Y = C, N) as indicated by the mean absolute deviation (MAD) in Angstroms (Å) (**Graph 2.1.**).




**Graph 2.1.** Graphical representation comparing the MAD (Å) of key bond lengths for geometry optimisation of magnesium diimidosulfinate complexes with different functionals and the 6-31g(d) basis set. See section **6.3.** for details.

The results presented show a small MAD (<1 Å) for all functionals tested, indicating a good agreement between the optimised geometries and the crystal structures. However, several trends are still evident, for example B3LYP, PBE and TPSS are slightly poorer performing in all cases. Of particular note the inclusion of dispersion corrections (BJD3) increased the accuracy, especially for Mg–Mg bond distances (see section **6.3.2.**). From this data it is evident that B3LYP-BJD3 is consistently good at reproducing the bond lengths of these complexes in the solid state, hence this functional was chosen for further geometry optimisation. However, it is imperative to mention that this benchmarking may not be directly translatable to species in solution, or the most accurate functional in terms of thermochemical data. Therefore, the recent report by Eisenstein and Cascella was considered,[146] in which the bond dissociation energies are benchmarked for a methyl magnesium bond in a monomeric complex. When comparing the Coupled Cluster (CC) data[159] with the DFT functionals it is noticeable that B3LYP provides a significant under-estimation of the bond enthalpy. Therefore, for the current model system it was decided to perform single point energy calculations (SPE) with a larger basis set (6-311++g(d,p)), on the optimised geometries using the ωB97X-D functional (see section **6.3.1.**). Indeed, this functional also performed well in the structural benchmarking (**Graph 2.1.**), as well B97X[160] showing good reproducibility of the thermochemical data for Eisenstein and Cascella.[146] Furthermore, similar methodology has recently been applied by Zimmerman *et al.* to allow greater insight into long range interactions in Grignard reagents.[142d]

## 2.3. Monomeric Pathway

With an appropriate level of theory in hand, the proposed model system was investigated (**Figure 2.1.**). In order to provide a detailed investigation, the mechanism was considered in two main stages, initial generation of the sulfonimidate ester anion followed by sulfoximine production. Within the first stage it was proposed that a formal methyl anion would add to PhONSO to generate the

*N*-phenoxysulfinamide which would subsequently rearrange to the sulfonimidate ester, presumably via a sulfinyl nitrene (**XIV**, **Scheme 2.6.**).

### 2.3.1. Initial Methyl Addition

Initial geometry optimisations of the starting materials showed that MeMgCl (**M0**) adopts a bent geometry with an angle of 172°, whilst **PhONSO** preferentially had a -*Z* geometry (see section **6.3.3.**). The initial coordination of these two molecules was shown to be exergonic by -1.5 kcal mol$^{-1}$ (**M1**), however, a more favourable bidentate complex is feasible (**M2**) with a relative energy of -3.9 kcal mol$^{-1}$. From **M2**, a transition state was located (**M-TS$_{2\text{-}3}$**), corresponding to the simultaneous formation of the S–C whilst the Mg–C bond breaks. This step was shown to have a barrier height of 11.4 kcal mol$^{-1}$, which is comparable to analogous computations,[145-146] indicating a highly feasible reaction at the cryogenic temperatures employed. Furthermore, the methyl addition was observed to be highly exergonic, and hence irreversible in producing the expected *N*-phenoxysulfinamide anion (**M3$_{Cl}$**).

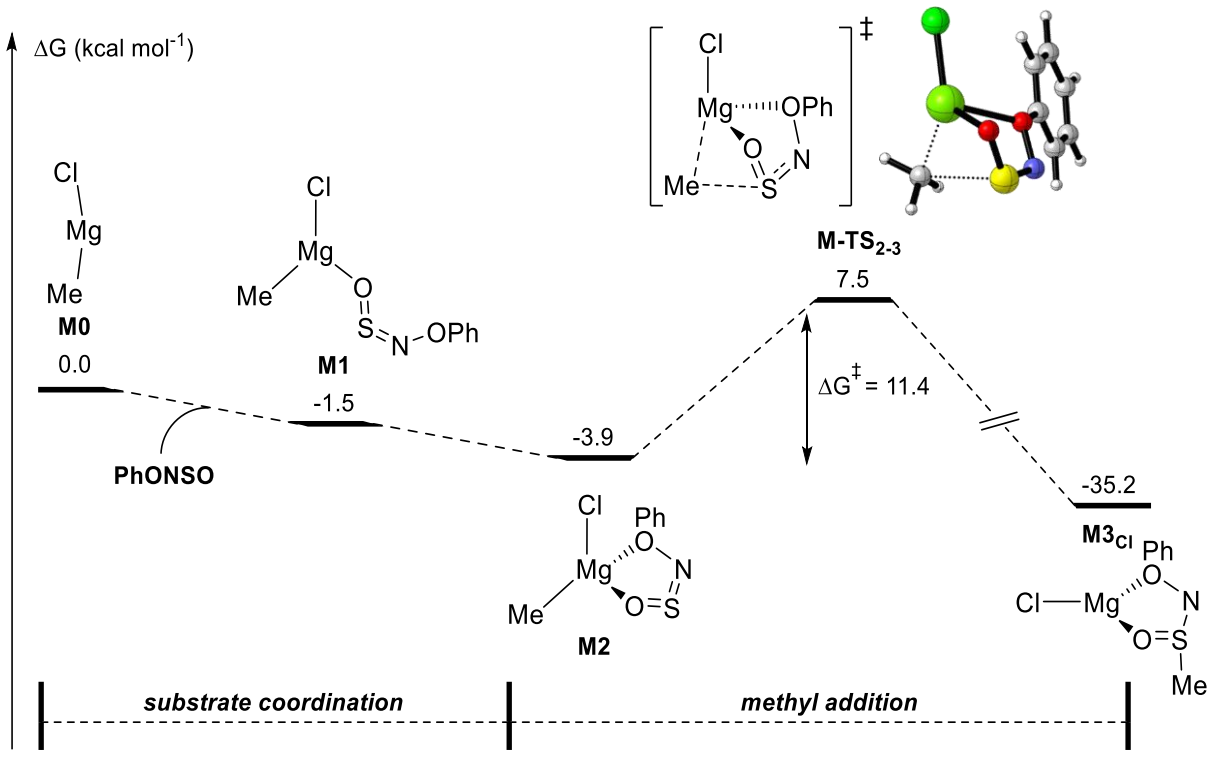
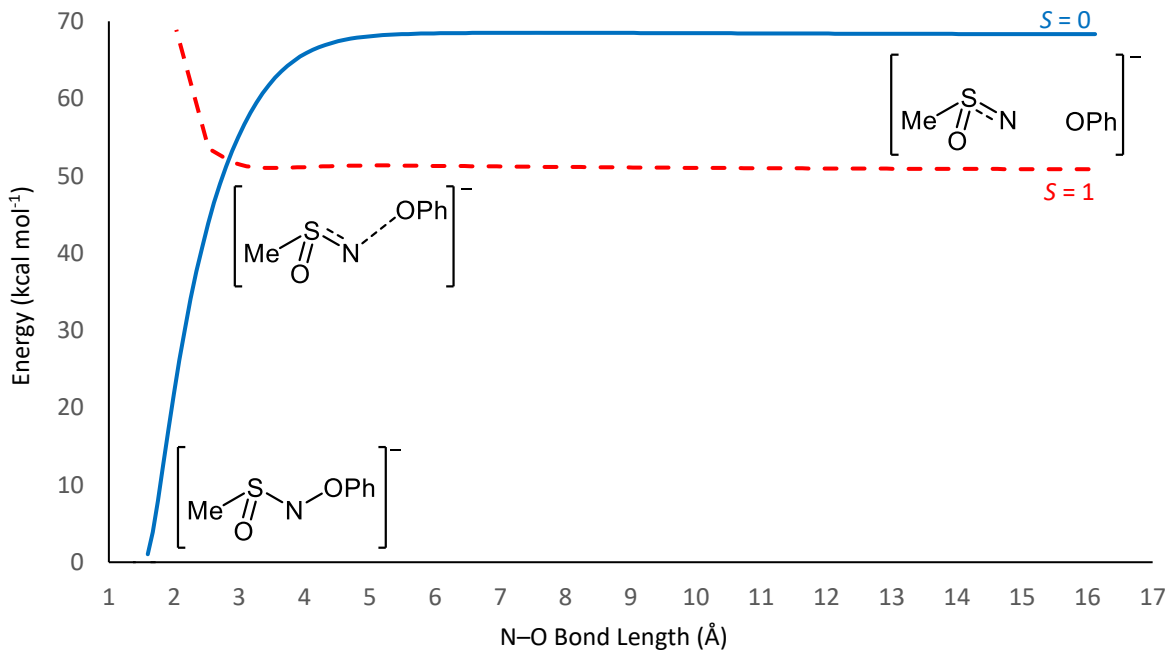



**Figure 2.3.** Energy profile diagram for the initial methyl addition into PhONSO from a monomeric magnesium complex. Energies at the SMD(THF)-ωB97X-D/6-311++g(d,p)//SMD(THF)-B3LYP-BJD3/6-31g(d) level of theory at 195 K.

### 2.3.2. N–O Bond Fragmentation

From intermediate **M3$_{Cl}$**, several possibilities were considered, for example a 1,2-shift directly to the sulfonimidate ester anion or N–O bond heterolysis to produce the sulfinyl nitrene and phenoxide anion. However, after extensive transition state searches no plausible structures were located. Therefore, to probe this in more detail, a rigid potential energy surface (PES) scan was conducted on a model sulfonimidate ester anion with no counter-ion present (**Graph 2.2.**). This analysis consisted of incrementally increasing the N–O bond length whilst keeping other geometric parameters constant. Such an approach has previously been employed for studying the formation of sulfonyl nitrene intermediates.[161]




**Graph 2.2.** Graphical plot for the rigid PES scan conducted for the *N*-phenoxylmethylsulfonamide anion. Energies at the ωB97X-D/6-31G(d) (in the gas phase at 298 K).

When considering the rigid PES scan, it is first important to note that for the singlet state ($S = 0$) a high amount of energy is required to reach a point where the interactions between nitrene and phenoxide become negligible, although, this is artificially high due to lack of re-optimisation of

geometry at each step. Regardless, this profile provides an anecdotal explanation of the challenges associated in locating a transition state for the N–O bond fission.

The final sulfinyl nitrene intermediate obtained from the rigid PES scan adopts a pyramidal conformation. In contrast, when geometry optimisation was conducted on the sulfinyl nitrene it was found that a planar conformation was preferential. The triplet state ($S = 1$) of the sulfinyl nitrene differs, and is more favourable when pyramidal, which is depicted with the lower energy pathway on the PES (**Graph 2.2**). The two surfaces obtained for the singlet and triplet states cross, and such an intersection corresponds to the most probable location for intersystem crossing (ISC), which provides the possibility for a low barrier pathway to generate the sulfinyl nitrene.

### 2.3.3. Sulfinyl Nitrene Generation and Characterisation

To find an estimate for the barrier of ISC, relating to the singlet *N*-phenoxylsulfinamide anion progressing to the triplet sulfinyl nitrene, minimum-energy crossing points (MECP) were located (**Figure 2.4.**). It should be emphasised that the energies obtained cannot directly be applied in traditional transition state theory (TST) as one must also consider the spin-hopping probability,[162] however, this still provides a qualitative estimate assuming this probability is close to one.

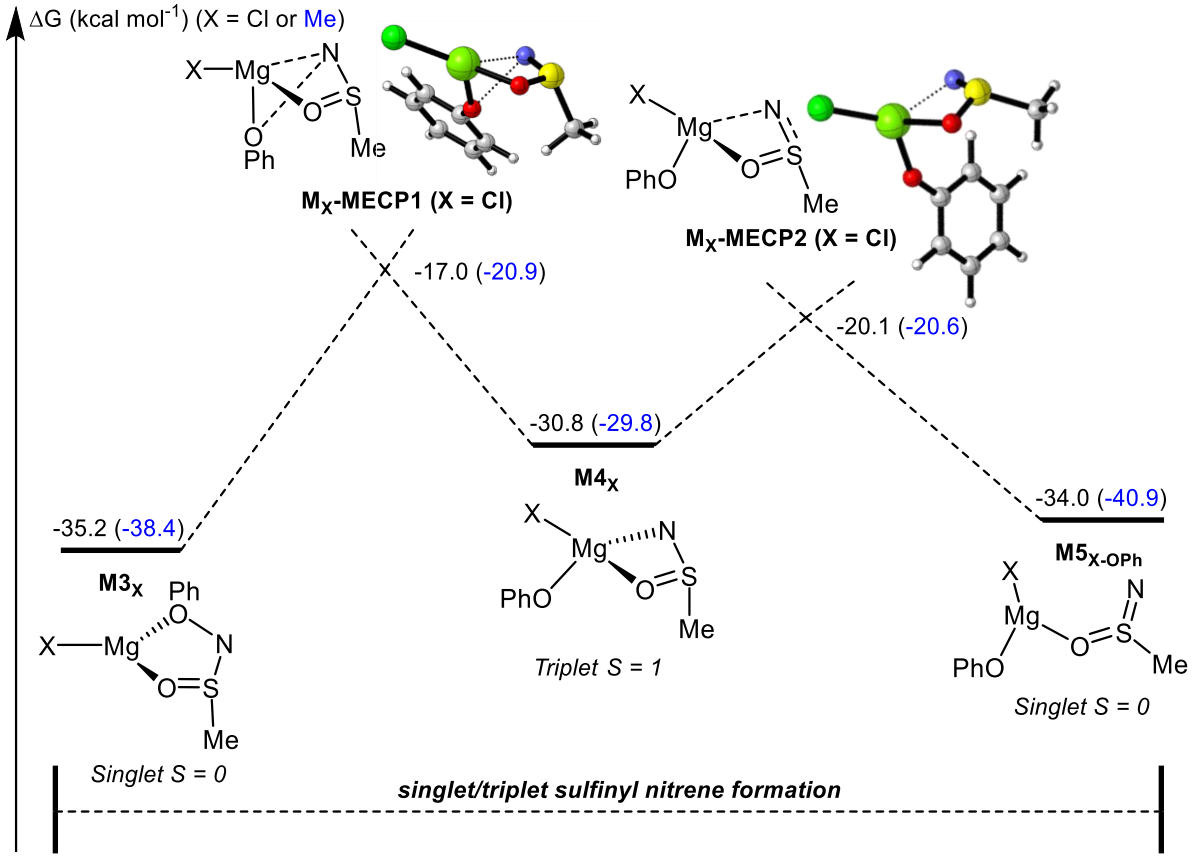



**Figure 2.4.** Energy profile diagram for the formation of the sulfinyl nitrene intermediate. Energies at the SMD(THF)-ωB97X-D/6-311++g(d,p)//SMD(THF)-B3LYP-BJD3/6-31g(d) level of theory at 195 K. Where the energies refer to those with X = Cl, and those in parentheses are X = $CH_3$, relative **PhONSO** and **$MgMe_2$.**

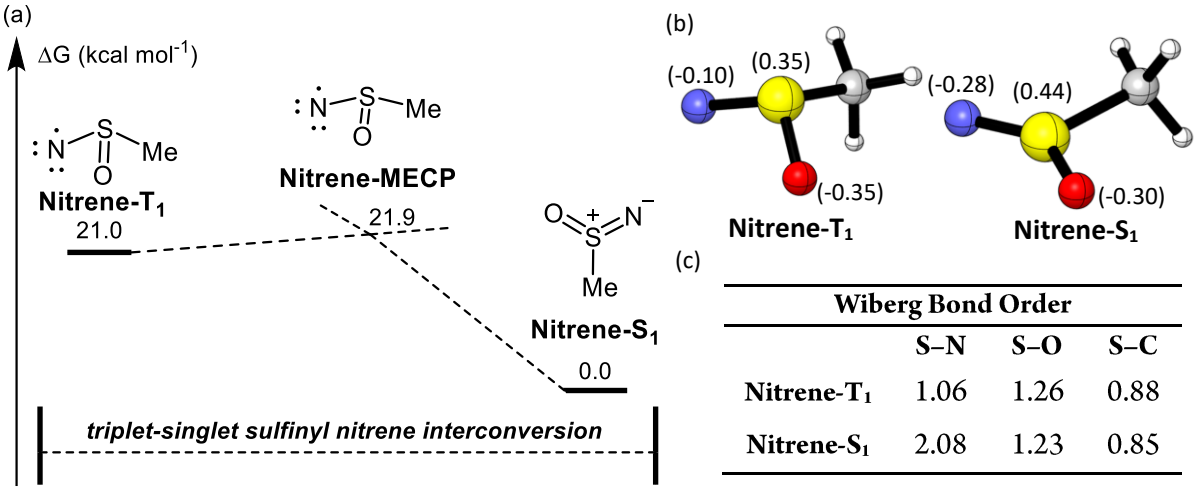
Intriguingly, the first intersection located, **$M_{Cl}$-MECP1**, was found to be relatively low in energy, 18.2 kcal $mol^{-1}$ higher than intermediate **$M3_{Cl}$** (X = Cl). Hence, it is assumed the generation of the triplet **$M4_{Cl}$** is feasible under the reaction conditions. As predicted from the previous PES, **$M_{Cl}$-MECP1** corresponds to the N–O bond cleavage (1.52 to 2.31 Å from **$M3_{Cl}$** to **$M_{Cl}$-MECP1** for X = Cl respectively), whilst the sulfur geometry retains a pyramidal structure.

Multiple possible pathways were examined from the triplet **$M4_{Cl}$**, such as the Curtius rearrangement, however, no plausible transition states were obtained, in agreement with previous observations.[126] Therefore, a second MECP (**$M_{Cl}$-MECP2**) was located which equates to the pyramidalization of triplet **$M4_{Cl}$** to planar singlet sulfinyl nitrene **$M5_{Cl\text{-}OPh}$**. Due to **$M_{Cl}$-MECP2** only

being 10.7 kcal mol$^{-1}$ higher in energy than **M4$_{Cl}$** (X = Cl) it can be assumed that this triplet is kinetically unstable and rapidly generates the more stable singlet.[126]

As multiple species are present under the Schlenk equilibria, the nature of the spectator anion (X) was also examined by considering the case when X = Me, where the most pronounced difference occurred in the energies of those resting state singlets (**M3$_X$** and **M5$_{X\text{-}OPh}$**). However, the relative differences in energies between the structures was not significantly changed (< 5 kcal mol$^{-1}$), overall indicating that the spectator ion should have little impact on generating the singlet sulfinyl nitrene **M5$_{X\text{-}OPh}$**.

These results raise the question of what role the magnesium atom plays in this intersystem crossing process and if this can be distinguished from the inherent characteristics of the sulfinyl nitrene. To probe this further, it was decided to examine the unbound sulfinyl nitrene and its MECP (**Figure 2.5.a**). These calculations showed that the singlet state (**Nitrene-S$_1$**) is lower in energy than the triplet state (**Nitrene-T$_1$**) by 21.0 kcal mol$^{-1}$. This change is credited to the role of the magnesium, which provides additional stabilisation of the electron deficient nitrogen in intermediate **M4$_X$**. Another notable difference is that **Nitrene-MECP** is much closer in energy to **Nitrene-T$_1$** (0.9 kcal mol$^{-1}$ difference) in the absence of magnesium. This suggests that **Nitrene-T$_1$** is inherently a highly unstable intermediate and on formation would likely convert to the more stable singlet instantaneously. The observation of a higher energy for **M$_X$-MECP2** in the magnesium-ligated system can be rationalised by the change in hapticity from $\eta^2$- to $\eta^1$- for triplet **M4$_X$** to singlet **M5$_{X\text{-}OPh}$**, respectively. Indeed, the Mg–N bond is cleaved during this crossing, due to the singlet stat **M5$_{X\text{-}OPh}$** being unable to have a $\eta^2$-bonding mode from increased angle strain, which overall asserts an energy penalty.




(c)

| Wiberg Bond Order | | | |
|---|---|---|---|
| | S–N | S–O | S–C |
| **Nitrene-$T_1$** | 1.06 | 1.26 | 0.88 |
| **Nitrene-$S_1$** | 2.08 | 1.23 | 0.85 |

**Figure 2.5.** (**a**) Energy profile diagram for conversion of the singlet to triplet nitrene. Energies at the ωB97X-D/6-311++g(d,p)//B3LYP-BJD3/6-31g(d) level of theory at 195 K. (**b**) Images of the singlet and triplet nitrene, denoting the Hirshfeld charges in atomic units for selected atoms shown in parenthesis. (**c**) Table showing the Wiberg bond orders for select bonds.

To gain further insight into the properties of the sulfinyl nitrene, the Hirshfeld charges[163] and Wiberg bond orders[164] were calculated at the same level of theory (**Figure 2.5.b.** & **Figure 2.5.c.** respectively). From inspection of these results, it was found that the bond order for the S–O and S–C bond in the singlet and triplet state are near identical. Whereas the bond order for the S–N bond significantly increases on traversing from the triplet to the singlet, this is also reflected in the shortening of the S–N bond length (1.69 to 1.47 Å for **Nitrene-$T_1$** to **Nitrene-$S_1$** respectively). Furthermore, examination of the Hirshfeld charge shows that, regardless of singlet or triplet state, there is little impact on the charge of the oxygen atom. In comparison, there is a notable decrease in electron density on the sulfur for **Nitrene-$S_1$**, accompanied by an increase in negative charge on the nitrogen. Due to these findings, it is appropriate to draw triplet and singlet state of the sulfinyl nitrene with the two resonance structures as depicted in **Figure 2.5.a**.

In summary, modelling of the sulfinyl nitrene in the presence or absence of magnesium resulted in several key differences, associated with the energies of the species. It can however be concluded, in both cases, that the triplet sulfinyl nitrene is likely to be a transient intermediate and readily produce

the singlet state. Additionally, several key properties of the sulfinyl nitrene can be deduced allowing one to postulate an appropriate resonance form to represent both the structure and potential chemical behaviour.

### 2.3.4. The Sulfonimidate Ester Anion

After gaining a better understanding of the generation of the sulfinyl nitrene, attention next turned to the final step of this first stage, formation of the sulfonimidate ester anion. Several sulfonimidate ester anions were computed (**M6**) and compared in energy to the sulfinyl nitrene (**M5$_{Cl\text{-}OPh}$**, **Figure 2.6.**). The sulfonimidate ester anions have an average energy of 37.4 kcal mol$^{-1}$, with the most stable species being intermediate **M6iii**, in which the phenoxide and nitrogen components are bonded to magnesium. In general, the sulfonimidate ester anions are close in energy to the singlet sulfinyl nitrene **M5$_{Cl\text{-}OPh}$**, indicating that formation of species **M8** would not create a thermodynamic sink for the reaction.

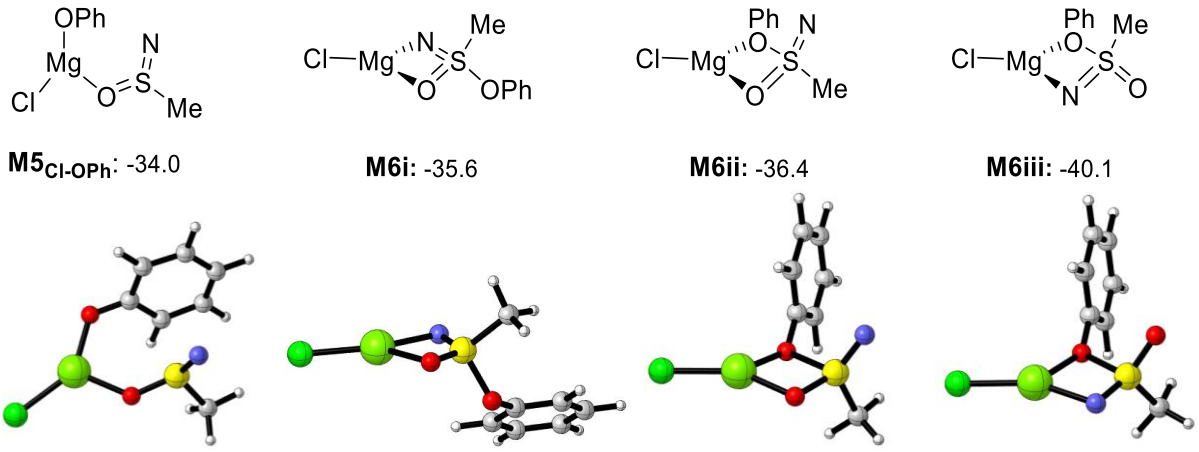
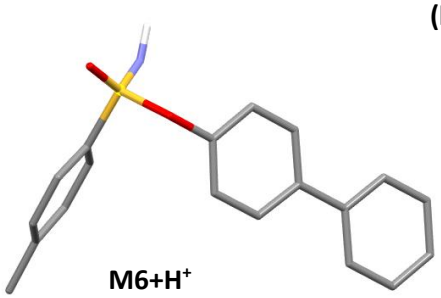



**Figure 2.6.** Calculated structures for the sulfinyl nitrene and sulfonimidate ester anion bound to magnesium chloride. Energies at the SMD(THF)-ωB97X-D/6-311++g(d,p)//SMD(THF)-B3LYP-BJD3/6-31g(d) level of theory at 195 K.

A transition state for the addition of the phenoxide component of intermediate **M5$_{Cl\text{-}OPh}$** into the sulfur centre was not located, presumably due to a relatively flat PES, indicating a low barrier process. Based on this assumption, it is proposed that the sulfinyl nitrene would be able to reversibly form the

sulfonimidate ester when deprotonated. To further assess this suggestion, key bond lengths of the computed structures of **M6** were compared to X-ray crystallographic data for sulfonimidate ester **M6+H⁺** (**Figure 2.7.**).[132]

(a)




(b)

| Key Bond Lengths (Å) | | | |
|---|---|---|---|
| | **S=O** | **S=N** | **S–OAr** |
| **M6+H⁺** | 1.41 | 1.53 | 1.65 |
| **M6i** | 1.53 | 1.49 | 1.71 |
| **M6ii** | 1.55 | 1.46 | 2.11 |
| **M6iii** | 1.47 | 1.49 | 1.95 |

**Figure 2.7.** (**a**) X-ray crystal structure of a sulfonimidate ester obtained by Dr. Thomas Davies and Jack Ren with analysis conducted by Dr. Antoine de Gombert. Non-essential hydrogen atoms have been omitted from the structure. (**b**) Table to compare several key bond lengths of **M6-H⁺** with the computed anions **M6**.

By examining the bond lengths of sulfonimidate ester **M6+H⁺** with anion **M6** it is evident that there is some variation in both the S=O and S=N bond on deprotonation. However, the most drastic change is observed with the S–OAr bond, which is significantly elongated (on average $\Delta_{S-OAr}$ = 0.27 Å). The increase of the S–OAr bond is most significant when the phenoxide is simultaneous coordinated to the magnesium (**M6ii** and **M6iii**). The weakening of this S–OAr bond upon deprotonation of the sulfonimidate ester ascertains some evidence for the reversible formation of a nitrene intermediate.

### 2.3.5. Second Methyl Addition

The results discussed so far suggest that a sulfonimidate ester is likely to be formed as a result of the addition of MeMgCl to PhONSO, *via* a sulfinyl nitrene intermediate. The subsequent addition of a second equivalent of MeMgCl to the sulfonimidate ester intermediate was next considered. Initial attempts focused on locating a transition state for the direct addition of a methyl into the sulfur of a sulfonimidate ester anion **M6** (**Figure 2.8.a**, see section **6.3.6.**). No plausible transition state was located, which is intuitive as this is effectively an attempt to combine two anionic components. As discussed previously, the sulfinyl nitrene can reversibly form from the sulfonimidate ester anion, hence

the focus was altered to examine transition states for the methyl addition directly into this sulfinyl nitrene (**Figure 2.8.b**).

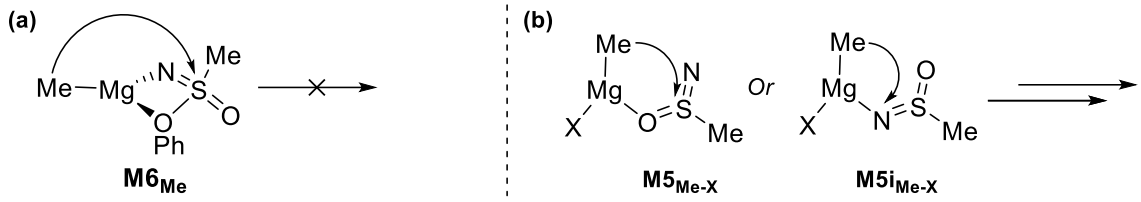



**Figure 2.8.** Representation of the transition states which were computationally explored towards the potential products of the reaction. **(a)** Direct addition from the sulfonimidate ester anion, **(b)** Addition into the sulfinyl nitrene where X = Cl or OPh.

When embarking on the exploration of the methyl addition into sulfinyl nitrenes, it was first recognised that several species would persist under equilibrium conditions. This is supported by the previous studies on solvent dynamics of Grignard reagents,[144] which indicates several low barrier kinetic profiles for the Schlenk equilibrium (typically 0.5-5.0 kcal $mol^{-1}$). Therefore, multiple anions and coordination modes were explored for the sulfinyl nitrene bound to the magnesium (see species $\mathbf{M5}_{\mathbf{Me\text{-}X}}$ and $\mathbf{M5i}_{\mathbf{Me\text{-}X}}$ of **Figure 2.8.b** for a pictorial representation). The lowest energy species was $\mathbf{M5i}_{\mathbf{Cl\text{-}OPh}}$ (see section **6.3.7.**), hence all transition state energies were considered relative to this intermediate (**Figure 2.9.**). Furthermore, within this scenario it was assumed that one can apply the Curtin-Hammett principle,[165] meaning one is concerned with the relative energy difference between transition states.

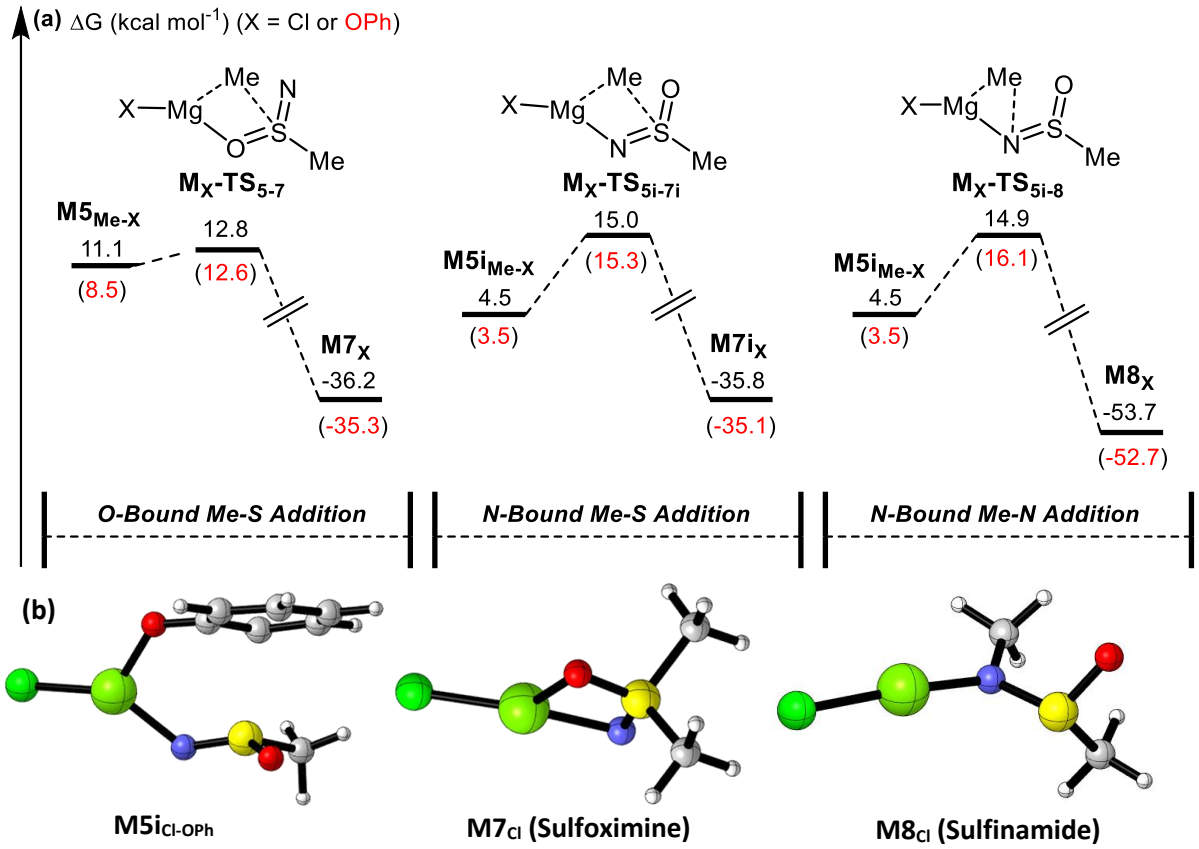


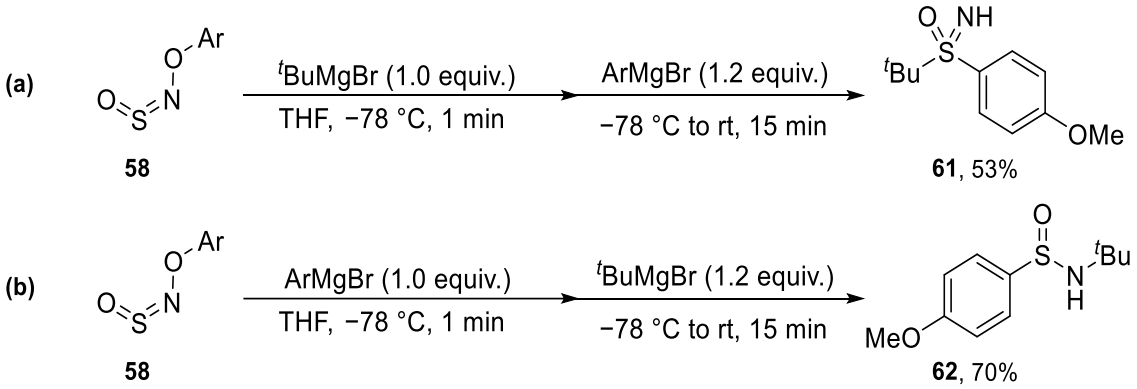

**Figure 2.9.** (a) Energy profile diagram the methyl addition to the sulfinyl nitrene. Energies at the SMD(THF)-ωB97X-D/6-311++g(d,p)//SMD(THF)-B3LYP-BJD3/6-31g(d) level of theory at 195 K, relative to intermediate **M5i$_{Cl\text{-}OPh}$** and **MeMgCl**. Energies refer to X = Cl and those in parentheses refer to X = OPh (b) Representation of several key starting materials and products along the reaction coordinates.

One key aspect when interpreting these energy profiles for the second methyl addition is that the identity of the counterion on magnesium (X) has minimal impact on the energetics, as seen by the transition states being perturbed by less than 1.5 kcal mol$^{-1}$, hence the future discussion will be limited to X = Cl. Additionally all the transition states are relatively low in energy and would allow generation of products at room temperature. Furthermore, the activation barriers relative to **M5i$_{Cl\text{-}OPh}$** are higher than the first Grignard addition (11.4 kcal mol$^{-1}$, see **Figure 2.4**), indicating that the first methyl addition will occur at a faster rate.

For the addition of the methyl to the sulfur, leading to sulfoximine anion products **M7$_{Cl}$** and **M7i$_{Cl}$**, two 4-membered ring transition states were located (**M$_{Cl}$-TS$_{5\text{-}7}$** and **M$_{Cl}$-TS$_{5i\text{-}7i}$**) with the main difference being which heteroatom is bound to magnesium. The lower energy transition state is that

with oxygen directly bonded to magnesium $\mathbf{M_{Cl}\text{-}TS_{5\text{-}7}}$ (by 2.2 kcal mol$^{-1}$). In contrast, only one 3-membered ring transition state was located for the addition of the methyl to the nitrogen atom of the sulfinyl nitrene ($\mathbf{M_{Cl}\text{-}TS_{5i\text{-}8}}$) to give sulfinamide. By applying the Curtin-Hammett principle[165] to the aforementioned transition states, one observes that the sulfoximine formation *via* transition state $\mathbf{M_X\text{-}TS_{5\text{-}7}}$ is preferential, which agrees with the experimental results and the previous statements (see section 2.1.1.) that sulfinyl nitrenes are more electrophilic at their sulfur centre.

Although, this DFT analysis on the model system indicates a preference for sulfoximine formation over sulfinamide, it is important to note that sulfinamide formation is not kinetically unfeasible. In particular, these results could readily change with perturbations in the model or even a change in Grignard reagent. Such an observation was obtained experimentally by Dr. Thomas Davies when using *tert*-butyl magnesium bromide in the reaction (**Scheme 2.8.**).




**Scheme 2.8.** Key mechanistic observations realised by Thomas Davies finding that the order of *tert*-butyl magnesium bromide addition changes the product distribution. (**a**) using *tert*-butyl magnesium bromide first, (**b**) using *tert*-butyl magnesium bromide second.

It was found that when using *tert*-butyl magnesium bromide as the first Grignard reagent the expected sulfoximine **61** was obtained (**Scheme 2.8.a.**), however, when the order was switched, sulfinamide **62** was isolated (**Scheme 2.8.b.**). Such findings provide support that the addition to the nitrogen of the sulfinyl nitrene is not a kinetically unfeasible process. Due to the complexity associated with modelling Grignard reagents, it is difficult to provide a direct rationale on the factors that control

selectivity from the model system. Formation of sulfinamide **62** with *tert*-butyl magnesium bromide is most likely due to the steric bulk of the Grignard reagent, although contributions from a radical mechanism cannot be disregarded.

## 2.4. Dimeric Pathway

The model system of using a monomeric pathway has provided a great deal of insight into the inner workings of this divergent strategy to sulfoximines, where aspects can be extrapolated to sulfonimidamides. However, as has been established in the literature, the reaction of a Grignard reagent is better thought of as an ensemble of reactions,[146] and dimeric species may play a significant contribution.[145b] Therefore, in order to consolidate the previous key findings, a dimeric pathway was also explored, considering the addition of two equivalents of methyl magnesium chloride to PhONSO (**Figure 2.10.**). Here the direct pathway to sulfoximine (**D7**) is presented for completeness, although for each step a similar approach to that formerly discussed was taken and will be mentioned when appropriate.

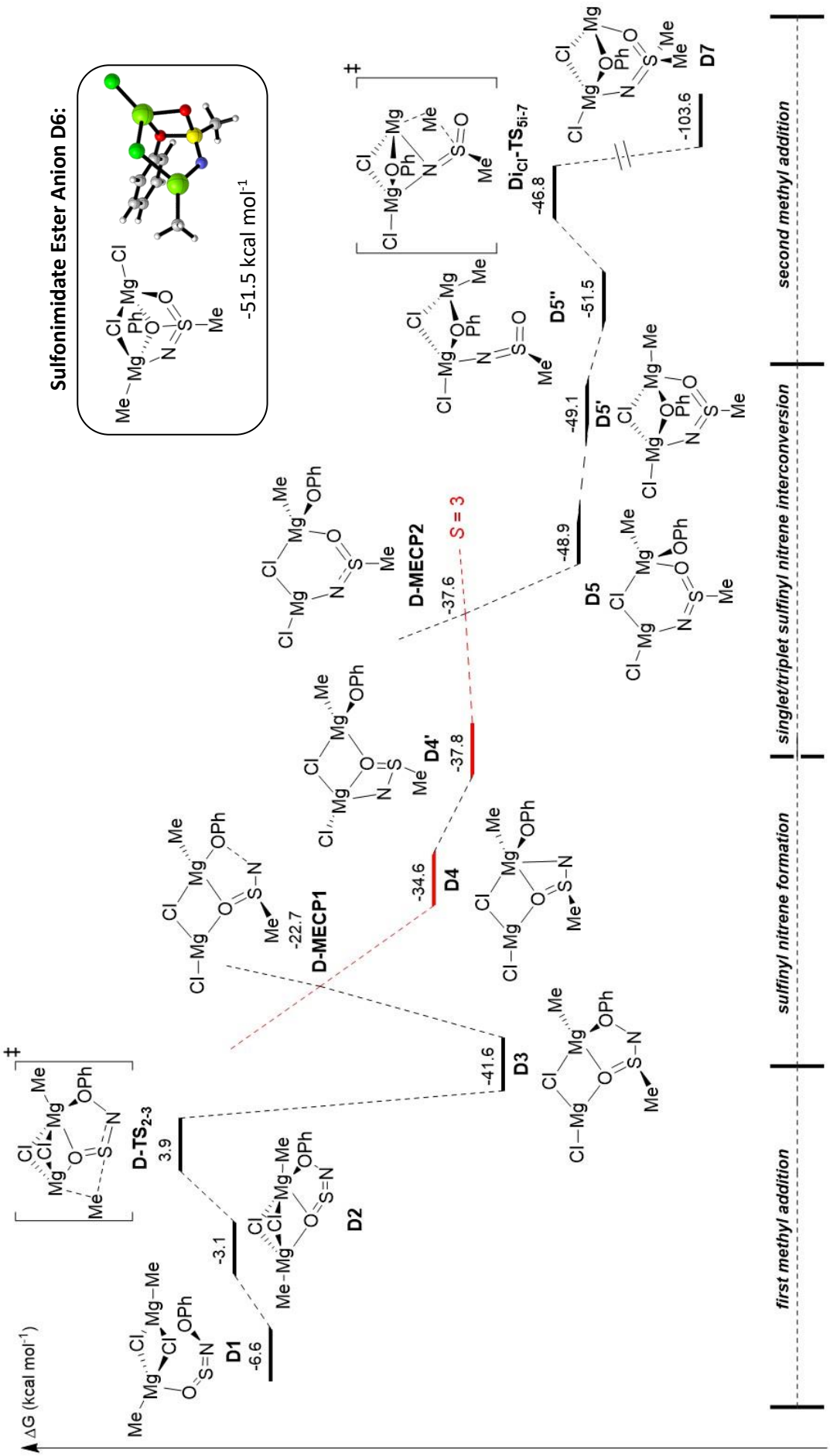



**Figure 2.10.** Energy profile diagram the reaction of methyl magnesium chloride dimer with PhONSO, ultimately leading to generation of sulfoximine product. Energies at the ωB97X-D/6-11++g(d,p)//B3LYP-BJD3/6-31g(d) level of theory at 195 K. Energies are relative to species **D0** and PhONSO.

### 2.4.1. Methyl Addition to PhONSO

The energy profile for the dimeric pathway begins with an initial exergonic substrate coordination of PhONSO to the Grignard reagent as a chloride bridged dimer,[141d] giving **D1**. A low barrier methyl addition (10.5 kcal mol$^{-1}$) *via* transition state **D-TS$_{2\text{-}3}$** is traversed, this barrier height is comparable to the monomeric pathway (11.4 kcal mol$^{-1}$, **Figure 2.3.**), multiple arrangements of bridging atoms can be considered for this step, however all resulted in similar shape energy profiles (*vida infra*). The transition state represented here (**D-TS$_{2\text{-}3}$**) involves PhONSO binding to both magnesium atoms (vicinal addition) rather than a singular magnesium (geminal addition). The difference between vicinal and geminal addition has been discussed in detail in the literature for addition into aldehydes.[146] Therefore, it is possible that a geminal addition may also be a feasible process to obtain the *N*-phenoxysulfinamide anion (**D3**), although in this case, the current pathway still provides a plausible low energy route to access intermediate **D3** and results in a reasonable coordination mode of this anion with the magnesium dimer.

### 2.4.2. Sulfinyl Nitrene Generation

After the irreversible addition producing **D3**, the N–O bond fragmentation process was examined. Once again, it was found that this is likely to occur *via* ISC to a transient triplet intermediate (**D4**), overall resulting in singlet sulfinyl nitrene formation (**D5**). Several key comparisons can be made with the monomeric pathway. Firstly, before the second ISC (*via* **D-MECP2**) the triplet sulfinyl nitrene must rearrange (**D4** to **D4'**) so the nitrogen atom is not in close proximity to the phenoxide, to enable the forward reaction. Another fundamental point arises from examining the energy difference of species **D4'** and **D-MECP2** (0.2 kcal mol$^{-1}$), this small difference now reflects the inherent properties of the free sulfinyl nitrene, that it is a short-lived intermediate (see **Figure 2.5.**).

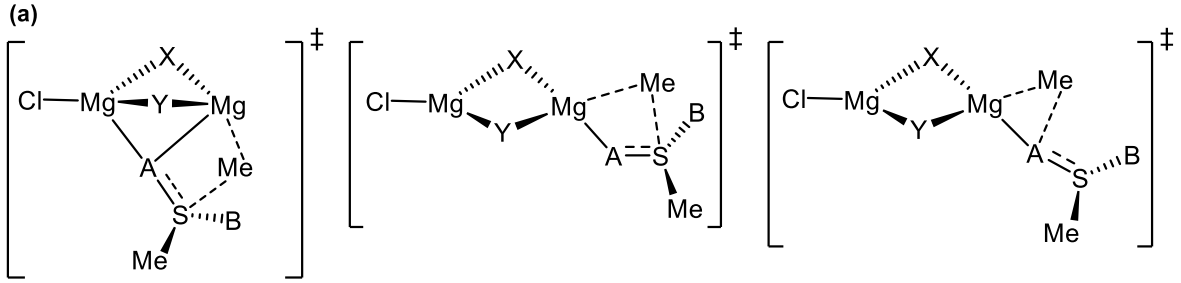
Upon generation of sulfinyl nitrene **D5**, the reaction profile depicts a direct low barrier pathway (4.7 kcal $mol^{-1}$) to provide the observed sulfoximine (**D7**). However, once again it is important to consider that multiple species may be present in equilibrium (see section **6.3.8.**). For the purpose of this discussion, the lowest energy sulfinyl nitrene (**D5''**) and sulfonimidate ester anion (**D6**) are depicted. One notable aspect is that these two species now have degenerate energies, asserting that they likely exist in a reversible equilibrium.

### 2.4.3. Methyl Addition to Sulfinyl Nitrene

For the final methyl addition into the sulfinyl nitrene, 15 transition states were evaluated, and their energies compared, of note transition states corresponding to vicinal addition into the nitrogen of the nitrene could not be located. For all the transition states evaluated it was found that the presence of both bridged chlorides produced much higher activation barriers, hence only phenoxide bridged species are presented here for clarity (see section **6.3.9.**). Therefore, three modes of action are presented (**Scheme 2.11.a.**); vicinal addition obtaining sulfoximine (**mode-i**), geminal addition obtaining sulfoximine (**mode-ii**), and geminal addition obtaining sulfinamide (**mode-iii**). For **mode-i** and **-ii** there is the possibility of the nitrogen or oxygen being bound to the magnesium. Furthermore, due to the non-symmetrical nature of the sulfinyl nitrene ligated to the magnesium-phenoxide dimer multiple isomeric transition states exist (**Scheme 2.11.b**). Within **mode-i** there was a minor energy difference when considering the respective orientation of the ligands (X, Y) and sulfinyl nitrene (A, B), as well as nitrogen bound magnesium favourable (A = N). However, **mode-ii** has a drastically different behaviour, which was ascribed to the simultaneous distortion of the magnesium dimer and 4-membered cyclic transition state. Regardless, all of **mode-ii** transition states are higher than the vicinal **Di-TS$_{5i-7}$** (4.7 kcal $mol^{-1}$ relative to **D5''**), meaning **Di-TS$_{5-7}$** is the dominant transition state to access the sulfoximine. **Mode-iii** which leads to the formation of a sulfinamide

product, has fewer transition states associated with it. With this mode, it was found that a *cis* coordination of the chloride and the oxygen is more favourable by 2.0 kcal.mol$^{-1}$ (X = Cl, B = O). Both **mode-i** and mode -**ii** have lower energy transition states than **mode-iii**, implying that the kinetic product is the sulfoximine **D7**. Considering the lowest energy transition state for sulfoximine product (**Di-TS$_{5i-7}$**) and sulfinamide (**Diii-TS$_{5i-8}$**) there is an energy difference of 7.9 kcal mol$^{-1}$, which is a much larger than the difference observed than with the monomeric pathway (*ca.* 2 kcal mol$^{-1}$, **Scheme 2.10.c**), but still provides the same selectivity.

**(a)**

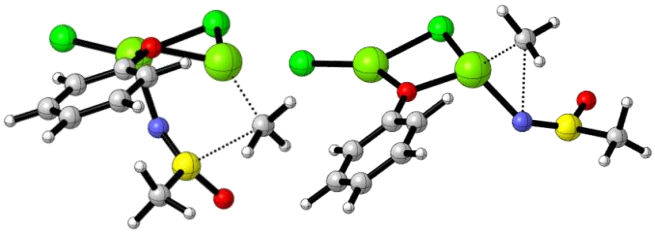



**i - Vicinal - Sulfoximine** **ii - Geminal - Sulfoximine** **iii - Geminal - Sulfinamide**

**(b)**

| Transition State Energies (kcal mol$^{-1}$) | | | |
|---|---|---|---|
| | **I** | **II** | **III** |
| **X = Cl, Y= OPh A = N, B = O** | 4.7 | 21.2 | 11.9 |
| **X = OPh, Y = Cl A = N, B = O** | 6.0 | 9.9 | 13.9 |
| **X = Cl, Y = OPh A = O, B = N** | 11.1 | 6.5 | N/A |
| **X = OPh, Y = Cl A = O, B = N** | 10.8 | 7.2 | N/A |

**(c)**



**Di-TS$_{5i-7}$** 4.7 kcal mol$^{-1}$ **Diii-TS$_{5i-8}$** 11.9 kcal mol$^{-1}$

**Figure 2.11.** **(a)** Various modelled transition states for the addition of a methyl to a sulfinyl nitrene, X, Y = Cl or OPh and A, B = N or O. **(b)** Table representing the energies of various transition states. Energies at the SMD(THF)-ωB97X-D/6-311++g(d,p)//SMD(THF)-B3LYP-BJD3/6-31g(d) level of theory at 195 K, relative to intermediate **D5**". **(c)** Pictorial representation of the two lowest energy transition states leading to sulfoximine and sulfinamide.

Gratifyingly, many of the overarching conclusions drawn from the dimeric pathway are similar to those made from the monomeric pathways. In particular, both methyl additions are low barrier processes, a transient triplet sulfinyl nitrene is a key intermediate, and the singlet sulfinyl nitrene reacts preferentially at sulfur to give sulfoximines. Therefore, exploring the dimeric model provided some

validation of the original model and supports the involvement of sulfinyl nitrene species as key intermediates.

## 2.5. Solvent Effects

Although the monomeric and dimeric models allow a range of qualitative conclusions to be made, it has previously been asserted that the inclusion of explicit solvent molecules into the model would be required to reproduce kinetic data.[145a] Therefore, to validate the previous conclusions made, it was decided to examine the effects of the coordination of THF molecules on the magnesium centre for the first methylation step.

From the previous analysis of the first methyl addition in the absence of solvent (see **Figure 2.10.** & **Figure 2.12.**), it was asserted that the highest barrier methyl addition is when the bridging methyl is *trans* to the bound PhONSO phenoxide moiety (X = Me) with an activation energy of 13.2 kcal $mol^{-1}$. In contrast, when the methyl is *cis* to -OPh (Y = Me) this is now only 0.4 kcal $mol^{-1}$ higher than the lowest energy transition state (Z = Me). With the inclusion of THF the model was complicated by the number of THF molecules included and their spatial arrangement. In order to begin the analysis, it was first decided to insert one THF molecule per magnesium atom, as previously this has been established as most energetically favourable at equilibrium,[145a,144] as well providing the best representation of the previous isolated X-ray crystal structures (**Figure 2.12.**).[151] Furthermore, this amount of THF molecules allows the magnesium coordination numbers to range between four to six, where hexavalent is the maximum coordination mode that has been observed for magnesium complexes.[166] In addition to the number of THF molecules, they can also have two possible arrangements with respect to each other, denoted *trans* or *cis*. No significant difference in energy was

observed between the *trans* and *cis* pathways, hence *trans* is presented here for simplicity (see section **6.3.10.**).

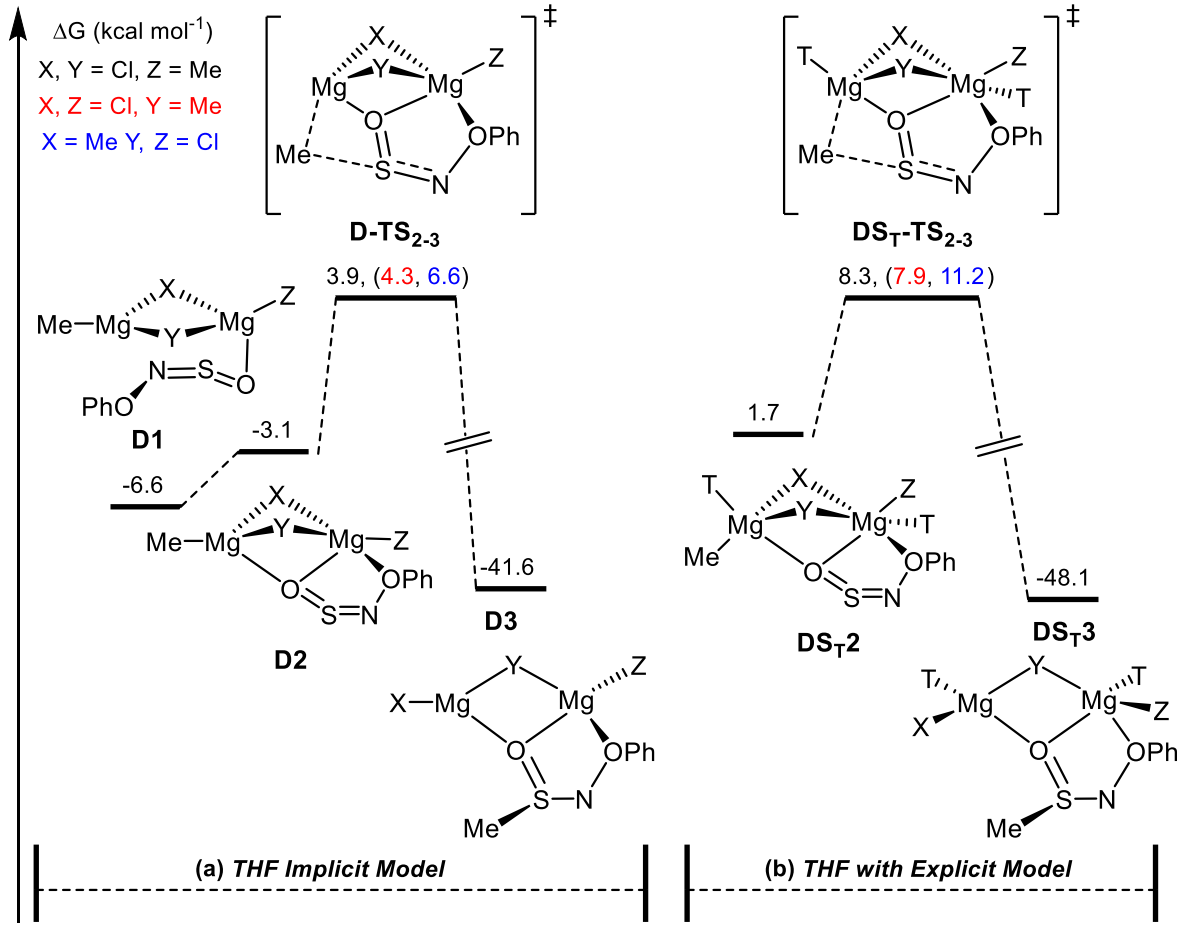



**Figure 2.12.** Energy profile examining the impact of bridging ligands on the first methyl addition, aiding the evaluation for the role of explicit solvent. Energies at the SMD(THF)-ωB97X-D/6-311++g(d,p)//SMD(THF)-B3LYP-BJD3/6-31g(d) level of theory at 195 K. Where X, Y and Z are a combination of Cl and $CH_3$ and their respective energies reported in parenthesis where appropriate. **(a)** unsolvated species, relative to **D0** and PhONSO. **(b)** Solvated species, relative to a solvated **D0** (**$DS_T$0**) and **PhONSO**

When examining the impact of THF on the first Grignard addition, one of the most drastic changes is that now the binding of PhONSO is endergonic leading directly to intermediates **$DS_T$2**. Therefore, although the transition states themselves (**$DS_T$-TS**) are higher in energy when THF is present, the activation energies are overall lowered. When examining the effects of the bridging ligands, once again it was observed that chloride bridges (Z = Me) and the methyl *cis* to -OPh (Y = Me) are comparable in energy, albeit now with the later marginally lower. Furthermore, the transition state with the methyl

*trans* to -OPh (X = Me), is on average 3.1 kcal $mol^{-1}$ higher, which is similar to that observed in the absence of THF.

Overall, it appears that the role of THF in the model does not have a significant impact on the qualitative conclusions made for the first methyl addition, and the THF main impact is to increase the activity of the intermediate producing a lower activation barrier. Direct inclusion of solvent creates a more complex model, due to multiple geometric isomers arising, hence the justification for omitting the solvent can be based on its main role being that of lowering the barrier heights without impacting the main conclusions made. Although, it is important to emphasise that to fully understand the kinetics of the system its inclusion is vital.

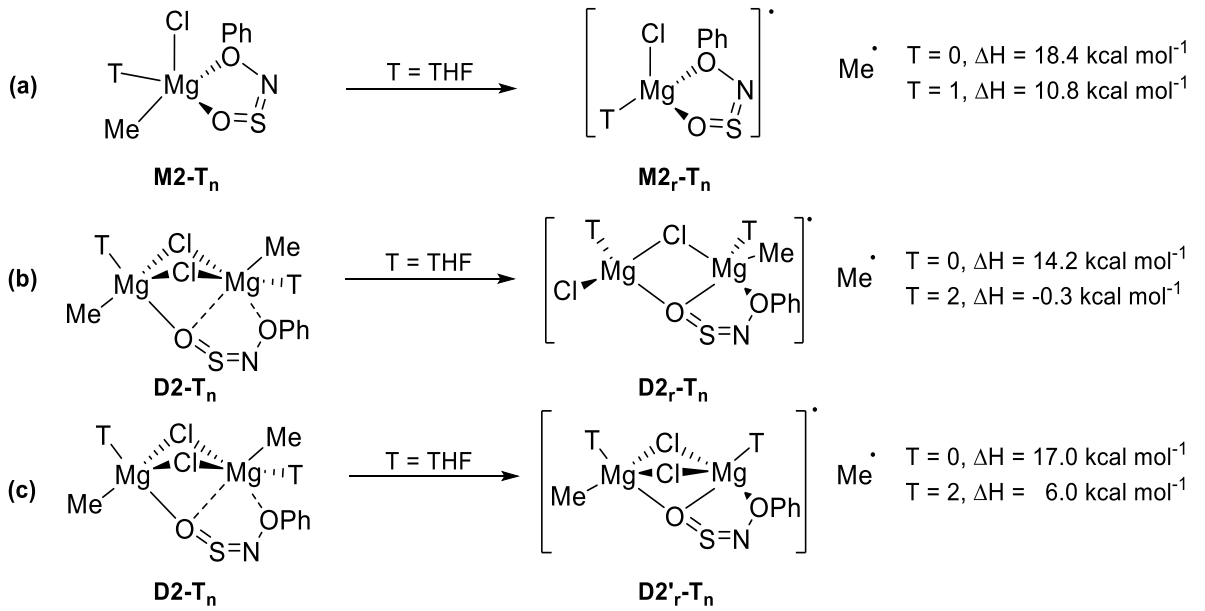
## 2.6. Radical Pathway

The previous discussion provides a plausible route to sulfoximines through a sulfinyl nitrene intermediate, using a polar mechanism. However, the existence of radical pathways in Grignard reagents has been inferred,[167] including by computational investigations showing their potential involvement *via* single electron transfer reactions.[145a,141c,146] From these analyses it has been postulated that the presence of carbon-based radicals can be promoted by substrates with low reduction potentials. Therefore, it was decided to evaluate if PhONSO and a sulfinyl nitrene would promote radical generation by examining the magnesium-carbon bond dissociation enthalpies (BDE); a similar approach has been taken by Cascella, Eisnstein and co-workers (see section **6.3.11.**).[146]

### 2.6.1. Radical Formation with PhONSO

When this computational approach was applied to the PhONSO (**Scheme 2.9.**), one of the most striking features of these results is that all the BDE are significantly low in the presence of PhONSO,

and the barrier heights for methyl radical generation are likely to be readily accessible. This observation is due to the spin density now predominantly being located on the PhONSO rather than the magnesium, which stabilises the radical. This was further exemplified with 93% of the spin density for **M2$_r$** being located on the ONSO heteroatoms (see section **6.3.12.**). Furthermore, the BDEs are now lowered by the inclusion of explicit solvent, in good agreement with observations from Cascella *et al.*[146] this effect was credited to a combination of electronic effects and the presence of THF causing less structural rearrangement to be required between intermediates. When comparing the monomeric systems (**Scheme 2.9.a.**) with the dimeric (**Scheme 2.9.b.** & **Scheme 2.9.c.**), the generation of a methyl radical from the dimeric complex is enthalpically more favourable. Within the dimeric complex, the methyl radical can either come from magnesium centre, the more favourable being from with the PhONSO directly bound *via* its terminal oxygen to magnesium, (**Scheme 2.9.b.**). In fact, for this reaction the inclusion of two explicit THF molecules implies that the generation of the radical would be spontaneous (-0.3 kcal mol$^{-1}$).

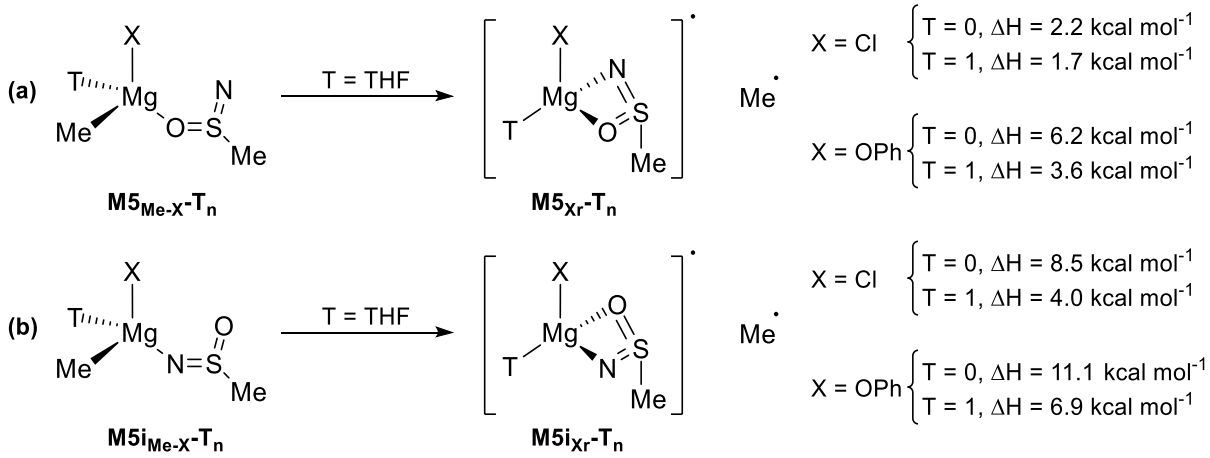



**Scheme 2.9.** Examining the bond dissociation energies for methyl magnesium chloride in THF with PhONSO coordinated. Energies at the SMD(THF)-uωB97X-D/6-311++g(d,p)//SMD(THF)-uB3LYP-BJD3/6-31g(d) level of theory at 195 K. Where T represents the amount of THF molecules which were modelled in the system, indicated by $T_n$ for the naming convention.

It should be noted that generation of the methyl radical is entropically favourable, therefore both monomeric and dimeric pathways are likely to have radical pathways at least competing with the previous outlined polar mechanism for the first methyl addition. The attention next turned to the second methyl addition involving the sulfinyl nitrene.

### 2.6.2. Radical Formation with a Sulfinyl Nitrene

The coordination of a sulfinyl nitrene species to the magnesium significantly complicates the study of the BDE of MeMgCl. Indeed, combining the different coordination modes of the sulfinyl nitrene with the different spectator ligands results in eight possibilities for the monomeric system (**Scheme 2.10.**). On average the BDEs were found to be lower than that observed with the PhONSO molecule, once again implying the feasibility of a radical pathway. Homolytic cleavage of the Mg–Me bond was calculated to be lower when the sulfinyl nitrene coordinates the Mg centre *via* its oxygen. This observation can be explained by the stability of the corresponding ground state species, as coordination of the oxygen results in the presence of an open valence nitrogen atom. The lowest energy BDE (1.7 kcal mol$^{-1}$) contains a chloride ion, when this is replaced with phenoxide the BDE increases to 3.6 kcal mol$^{-1}$, which can be ascribed to the phenoxide being a poorer electron donor.




**Scheme 2.10.** Examining the bond dissociation energies for methyl magnesium chloride in THF with the singlet sulfinyl nitrene coordinated. Energies at the SMD(THF)-uωB97X-D/6-311++g(d,p)//SMD(THF)-uB3LYP-BJD3/6-31g(d) level of theory at 195 K. Where T represents the amount of THF molecules which were modelled in the system, indicated by $T_n$ for the naming convention.

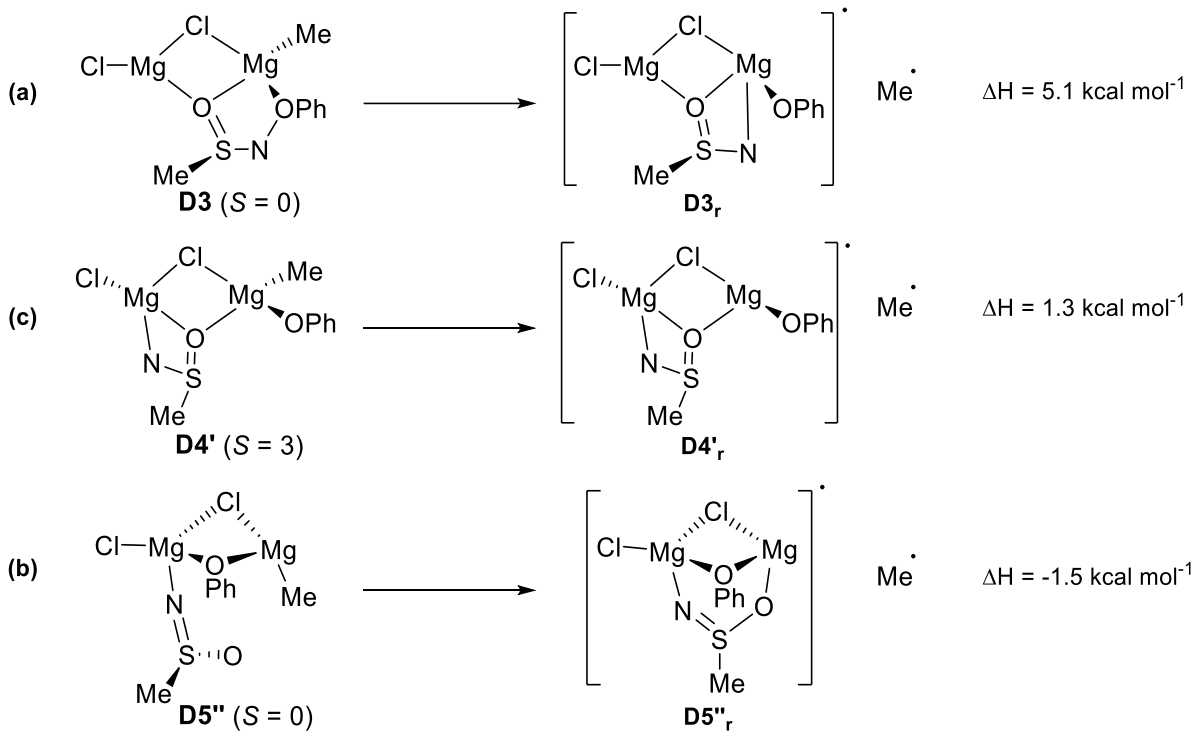
Overall, it appears that a radical pathway would also be competitive to the polar mechanism in the second methyl addition to the singlet sulfinyl nitrene. Although the triplet sulfinyl nitrene has been identified as a transient intermediate, this state is also higher in energy than the singlet ground state, hence one can envision that methyl radical generation from this intermediate would be more favourable. In fact, during the course of performing geometry optimisations on the triplet states of sulfinyl nitrenes coordinated to methyl-magnesium fragments, a significant portion of spin density was often located on said methyl (on average 49%, see section **6.3.12.**).

### 2.6.3. Radical Formation in the Dimeric Pathway

As using the dimeric model further complicates the situation, by introducing a variety of isomeric species, the plausibility of a radical pathway was simply evaluated by examining the BDEs for several low energy intermediates located along the reaction profile presented in **Figure 2.10.** (**Scheme 2.11.**). When considering the *N*-phenoxylsulfinamide anion **D3** it was seen that the generation of the methyl radical occurs simultaneously with the N–O fragmentation, with an enthalpy of 5.1 kcal $mol^{-1}$ (**Scheme 2.11.a.**). This low energy again emphasises the point that the dissociation of the N–O is not occurring *via* a heterolytic process. The next series of calculations examine the sulfinyl nitrene bound to the magnesium dimers, as a triplet (**Scheme 2.11.b.**) or as a singlet (**Scheme 2.11.c.**), again with both producing very low BDE's.

A caveat that should be pointed out when evaluating the competition between the polar and radical mechanism, is that both mechanisms appear to be providing low barrier reaction pathways, therefore the kinetics for the interchange between intermediates, assumed to be in equilibrium, may have a substantial effect. For example, with methyl magnesium chloride dimer in THF, a previous computational evaluation of the Schlenk equilibrium has estimated the activation energy for

intermediate interchange to be 4 to 13 kcal mol$^{-1}$.[144] As this value is comparable to the energies reported here it can be expected this may substantially influence which pathway dominates.

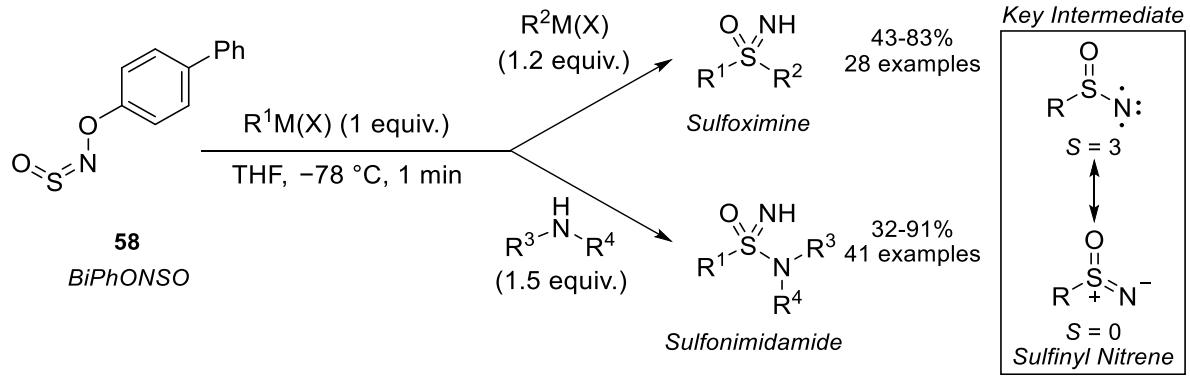



**Scheme 2.11.** Examining the bond dissociation enthalpies for intermediates along the reaction pathway for the dimeric model. Energies at the SMD(THF)-uωB97X-D/6-311++g(d,p)//SMD(THF)-uB3LYP-BJD3/6-31g(d) level of theory at 195 K.

In summary, from evaluating the BDE of the Mg–C for a range of complexes, it can be concluded that the presence of PhONSO or a sulfinyl nitrene makes the generation of radicals plausible. The consequence of these results means that a radical pathway is potentially in operation, although this will be dependent on a careful balance of factors, which are beyond the scope of this study. It should be noted that the feasibility of a radical mechanism would also be highly dependent on the nature of the Grignard reagent used. Furthermore, this does not distract from the fact that the polar mechanism presented is still a low barrier pathway and could be competitive with any radical mechanism in operation.

## 2.7. Summary and Outlook

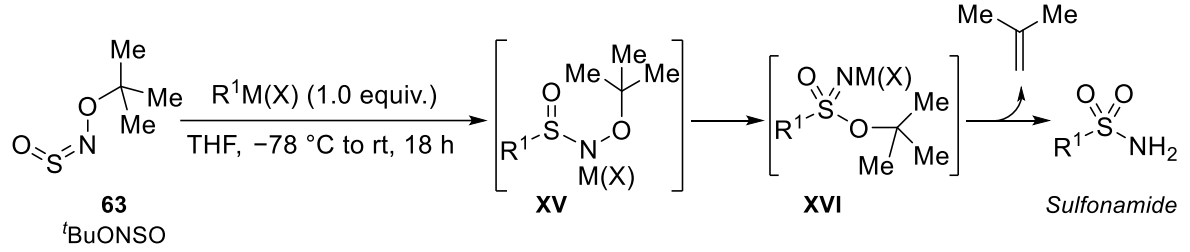
In conclusion, a divergent process was developed to access both sulfoximines and sulfonimidamides from a common stable reagent BiPhONSO (**58**, **Scheme 2.12.**). This procedure boasts several key advantages including the ease of the protocol, coupled with short reaction times, as well as the ability to use a large variety of organometallic reagents and amines. Furthermore, this produces the free-N=H-sulfoximines and sulfonimidamides which lend themselves to further functionlisation at this position.




**Scheme 2.12.** A divergent reaction to synthesis both sulfoximines and sulfonimidamides from the reagent BiPhONSO, involving a key sulfinyl nitrene intermediate.

Alongside this work, a DFT study has provided several valuable insights into the mechanism, as well as producing a rationale for the experimental observations. For example, by applying a simple monomeric model allowed the existence of the sulfinyl nitrene to be inferred. Additionally, it has been shown that the stable sulfinyl nitrene is likely produced *via* a transient triplet intermediate during a key N–O bond fission. Finally, several key characteristics of the sulfinyl nitrene have been deduced including its high electrophilicity at the sulfur atom over the nitrogen, showing the formation of the desired products. To justify the conclusions made using this model a dimeric pathway, solvent effects and the possibility of a radical mechanism were also considered.

Due to the success of this reaction, an alternative process has been developed, based now on the reagent $^{t}$BuONSO (**63**, **Scheme 2.13**).[168] When this linchpin is combined with organometallic reagents, it now produces the primary sulfonamide. From the previous studies, this can be assumed to go *via* an analogous reaction mechanism. Firstly, an *N*-alkoxysulfinamide anion is initially produced (**XV**), which can then generate sulfonimididate ester anion *in situ* (**XVI**); this intermediate will subsequently decompose to the sulfonamide product.




**Scheme 2.13.** A divergent reaction to synthesis both sulfoximines and sulfonimidamides from the reagent BiPhONSO, developed by Dr. Thomas Davies. With the sequence postulating the involvement of key *N*-alkoxysulfinamide and sulfinyl nitrene intermediates.

The computational analysis outlined here provides a suitable mechanistic rational for the sulfonamide synthesis. Furthermore, this pathway was supported by appropriate mechanistic reactions, such as $^{18}$O-labelling experiments and observing the *iso*-propene by $^{1}$H NMR experiments. Therefore, obtaining a detailed understanding of *N*-oxysulfinylamine and the potential involvement of sulfinyl nitrene reactivity, has the potential to allow for further reaction development.

Although the simple monomeric model presented provides a greater understanding of the reaction, it is important to emphasise that in reality the system is likely much more complex, and hence this model may not provide reliable information on kinetics. However, when considering other possibilities such as a dimeric system and the involvement of solvent, these point to several similar conclusions. Hence, it appears that this computational analysis shows multiple underlying chemical features associated with the reactivity of *N*-phenoxysulfinylamines, *N*-phenoxysulfinamides and sulfinyl nitrenes, which should prove useful for reaction development.

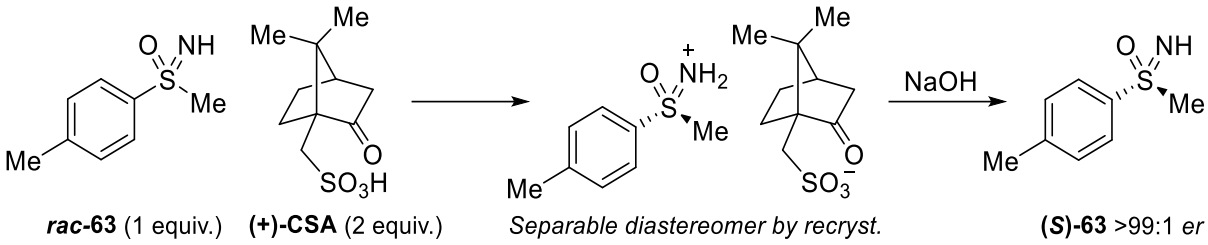
# Chapter 3 – The Organocatalytic Enantioselective Synthesis of Sulfonimidamides

## 3.1. Introduction

In the previous chapter, the application of a convenient reagent (BiPhONSO) to access free-sulfoximines and sulfonimidamides was outlined.[132] Although this methodology is highly valuable, it does not readily lend itself to the enantioselective synthesis of these aza-sulfur functional groups. As has been discussed, a handful of stereoselective transformations exist to access enantioenriched sulfoximines and sulfonimidamides *via* oxidation reactions, or nucleophilic displacements. However, many modern routes are also emerging to access these moieties, predominantly using asymmetric catalysis.

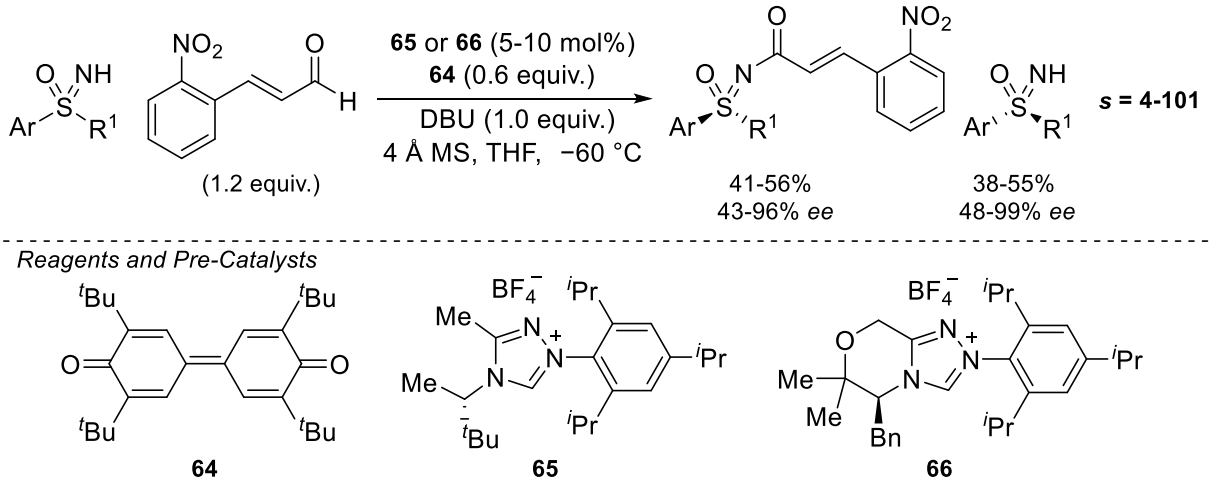
### 3.1.1. Contemporary Enantioselective Synthesis of Sulfoximines

Methods that access enantioenriched sulfoximines, which do not rely on a limited pool of sulfur-based chiral building blocks, are somewhat sparse. Even though the first such method reports date back to 1965 (**Scheme 3.1.**),[169] in which sulfoximine **63** undergoes a classical resolution with the chiral acid (+)-CSA. Either enantiomer can then be obtained *via* selective recrystallisation of one of the diastereomeric salts and subsequent deprotonation to yield enantioenriched **63**. Such a classical resolution allows high optical purity of the sulfoximine to be obtained albeit at the expense of the yield. Not only is this method laborious, the application of (+)-CSA in this process is highly substrate specific and has not successfully been applied to any other sulfoximines. However, other acids such as (+)-BINOL[170] and (+)-di-*p*-tolyl-D-tartrate[52] have been applied for specific sulfoximines.



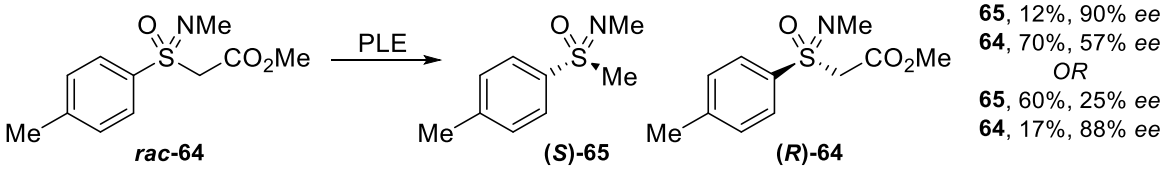

**Scheme 3.1.** Classical resolution of a sulfoximine using a chiral acid to obtain optically pure product.

One of the key underlying principles of this classical resolution is utilising the basicity of the sulfoximine's nitrogen atom. Therefore, it is unsurprising that a relatively modern method has capitalised on using the sulfoximine nitrogen's nucleophilicity in an organocatalytic kinetic resolution (**Scheme 3.2.**).[171] Bolm and co-workers were able to achieve this feat by employing an asymmetric acylation reaction catalysed by an *N*-heterocyclic carbene (NHC, generated *in situ* from **65** or **66**) in the presence of an oxidant (**64**). Therefore, one is able to obtain acylated sulfoximines in moderate yields and high enantiomeric ratios; perhaps of more significance is the recovered starting material, a free-sulfoximine, which can also be obtained in moderate to high enantiomeric excess. A beneficial feature of this reaction is that two catalysts were able to produce reactions with good to high selectivity factors, where pre-catalyst **65** could provide the free-sulfoximine with (*S*) as the major enantiomer, whilst catalyst **66** gave the opposite enantiomer, (*R*)-sulfoximine.



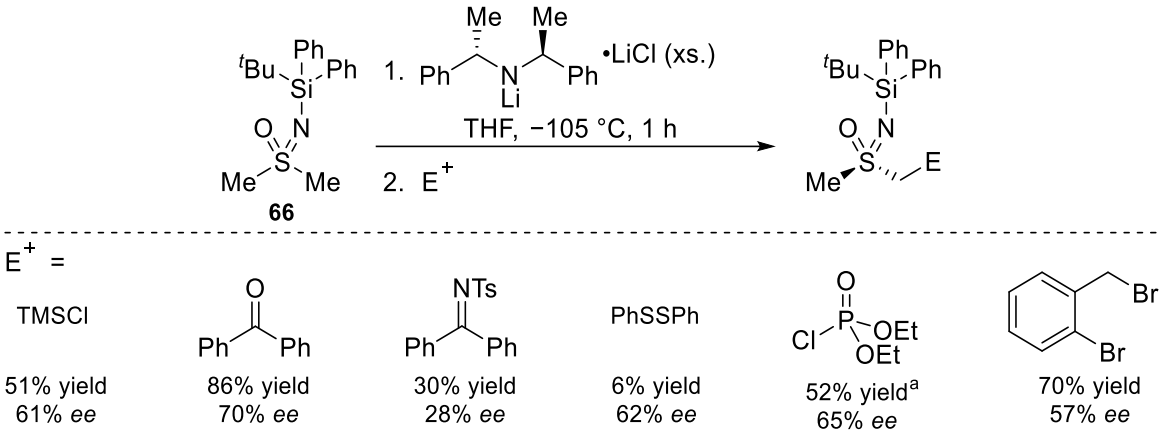

**Scheme 3.2.** *N*-heterocyclic carbene (NHC) catalysed kinetic resolution of a sulfxoimine. Where *s* refers to the selectivity factor.

There is a wealth of reactions which functionalise the unprotected sulfoximine's nitrogen atom. Therefore, one could envision multiple possible kinetic resolutions *via* asymmetric catalysis, however, this is still to be exploited fully. Instead, a greater focus has been placed on reactions which functionalise the carbon substituents of the sulfoximine to control the configuration at the sulfur centre. Seminal work in this area has performed a hydrolysis of an ester group to induce enantioenrichment of a sulfoximine, catalysed by a pig-liver esterase (PLE) enzyme (**Scheme 3.3.**).[172] The stereoselective reaction is proposed to initiate *via* hydrolysis of the ester to the carboxylate, which can then readily undergo a decarboxylation, due to formation of a relatively stable alpha-anion to the sulfoximine.[173] Although this produces the relatively simple sulfoximine **65**, obtaining high enantiomeric ratios required very low yields, limiting this kinetic resolution's impact to proof-of-concept status.




**Scheme 3.3.** Enzymatic kinetic resolution of a sulfoximine *via* a decarboxylation reaction.

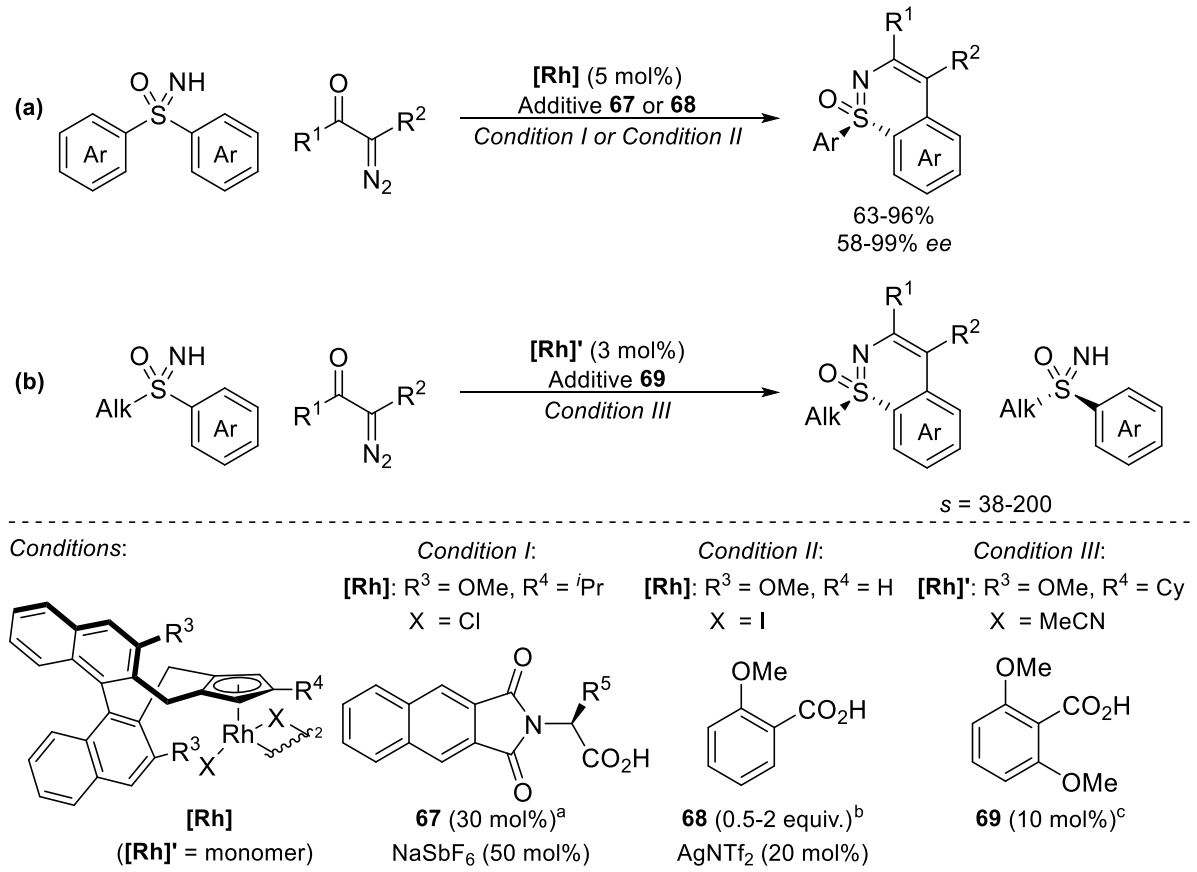
The ability to generate an anion adjacent to the sulfur of a sulfoximine creates the possibility to react these moieties with a range of electrophiles, including those which are enantiopure.[174] Furthermore, this reactivity mode creates an opportunity for a direct enantioselective synthesis of the sulfoximine, where now it is also viable to start from a prochiral sulfoximine (**66**, **Scheme 3.4.**).[175] In this scenario a stoichiometric amount of chiral lithium amide base is used to desymmetrise the starting material, which can then be trapped by a diverse range of electrophiles, with modest to good enantiomeric excess of product.




**Scheme 3.4.** Desymmetrisation of prochiral sulfoximines using a chiral base and an appropriate electrophile. [a] The yield and enantiomeric excess are based on further derivatisation reactions.

The ability to desymmetrise an achiral sulfoximine provides a powerful tool to produce these moieties in both high yield and high enantiomeric excess, especially compared to a kinetic resolution. Therefore, it is of no surprise that the most recent advances in asymmetric catalytic reactions of sulfoximines have been focused on this concept. In particular, the application of an asymmetric rhodium-catalysed annulation was converged on by both the Cramer[176] and Li,[177] using slightly different conditions (**Scheme 3.5.a.**). These reactions can generate a diverse range of cyclic enantioenriched sulfoximines incorporating multiple electrophiles. Additionally, the Li conditions could be modified (*Conditions II* with $R^3 = O^iPr$, $Ag_2SO_4$ (20 mol%), **68** (1.0 equiv.), DCE, 35 °C) to incorporate electron deficient diazo malonates ($R^1 = OR'$, $R^2 = CO_2R'$). Although this procedure is academically intriguing the usefulness of synthesising these cyclic sulfoximines is questionable.

Furthermore, Cramer and coworkers were able to show that *Conditions I* could be applied in a parallel kinetic resolution of a diaryl sulfoximine.[176] Whilst Li *et al.* were able to slightly modify their initial conditions (*Conditions III*) to apply this reaction to a kinetic resolution of aryl-alkyl sulfoximines with high selectivity factors (**Scheme 3.5.b.**).[178] This type of transformation can then be seen as more valuable due to providing enantioenriched free-sulfoximines, which can be further functionalised.




**Scheme 3.5.** The use of sulfoximines in an asymmetric rhodium-catalysed annulation. (a) A desymmetrisation process to access enantioenriched cyclic sulfoximines. (b) A kinetic resolution of a chiral sulfoximine. [a] $^{t}$BuOH, 35 °C, 30-72 h, [b] MeOH or TCE, 25-30 °C, 12-24 h, [c] MeOH, 40 °C, 12 h.

During the development of both of these asymmetric rhodium-catalysed reactions, several key observations were made. For example, solvent and the identity of the acid had a drastic effect on the stereoselectivity of the reactions. Such that if using *Conditions I* changing the solvent to HFIP causes a switch in the predominant enantiomer formed. Whilst when using *Conditions II* but using the more sterically encumbering acid **69** in the less polar solvent TCE, the major enantiomer formed is also changed. *Li et al.* was able to demonstrate this enantiodivergent behavior on a range of substrates, with a simple alternation in the achiral components of the reaction. The justification for such drastic changes in the stereochemical outcomes can be postulated by influencing the initial binding of the sulfoximine to the rhodium before the enantiodetermining concerted metalation deprotonation (CMD) step.

Recently, an analogous ruthenium-catalysed procedure has been developed for the annulation of sulfoximines.[179] This procedure now applies a chiral acid with an achiral ruthenium source, to allow annulation of sulfoxonium ylides. This reaction could be applied in a desymmetrisation, parallel kinetic resolution and kinetic resolution, providing a broad range of sulfoximines.

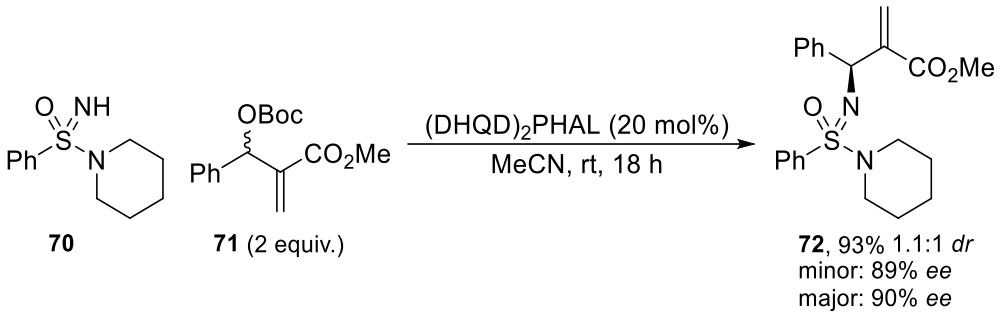
Overall, contemporary methods for the enantioselective synthesis of sulfoximines have focused on kinetic resolution reactions to obtain high optical purities, however several desymmetrisations have also been observed allowing high yields to also be obtained. It is interesting to observe that an underlying theme of these reactions is the exploitation of the sulfoximines basic nitrogen atom, either directly with its functionalization or indirectly *via* its binding to a metal catalyst. It can be expected further developments in this field will continue to use this strategy of using the sulfoximines inherent nucleophilicity of the sulfoximine nitrogen.

### 3.1.2. Contemporary Enantioselective Synthesis of Sulfonimidamides

As has previously been established there are a diminished number of routes to prepare sulfonimidamides compared to sulfoximines. Therefore, it is to be expected that there are few catalytic methods to synthesise enantioenriched sulfonimidamides. Currently, the most sophisticated methods are reliant of starting from enantiopure sulfinamide building blocks *via* stereoselective transformations (see **Scheme 1.29.**).[107]

Regardless of the limitations observed in the field for the enantioselective synthesis of sulfonimidamides, there have been a few attempts to create contemporary methods. One such endeavour has applied the reactivity of the nucleophilic nitrogen of a sulfonimidamide in an organocatalytic allylic alkylation (**Scheme 3.6.**).[180] Predominantly this Lewis base catalysed process focused on applying achiral sulfoximines in the reaction, with an emphasis on controlling the configuration of the newly formed carbon stereocentre. However, this was applied to a single example

of a racemic sulfoximine and sulfonimidamide (**70**), in a trail for a catalytic kinetic resolution. The product of the reaction **72** was obtained in high enantiomeric excess, although a near equimolar ratio of diasteromers was produced. This observation indicates an ineffective kinetic resolution, with little control of configuration at the sulfur stereocentre.

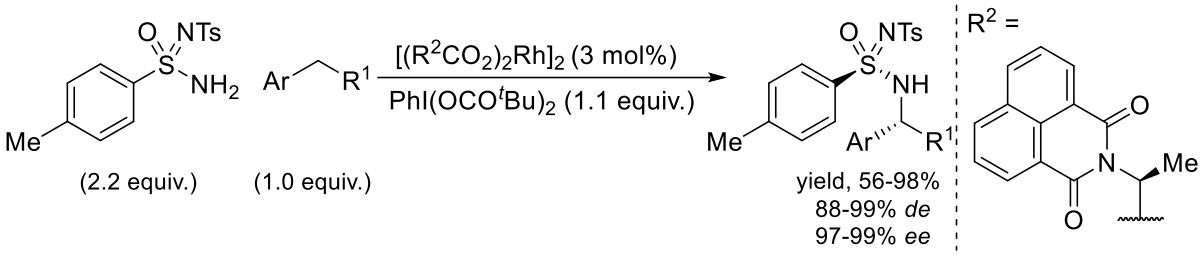



**Scheme 3.6.** Enantioselective organocatalytic allylic alkylation of a sulfonimidamide.

The reaction of sulfonimidamide **70** with the Morita-Baylis-Hillmann carbonate **71**, provides no significant advantage over a direct reaction of racemic sulfonimidamide with an enantiopure electrophile. However, a more effective method has applied a sulfonimiamide in a rhodium-catalysed C–H amination (**Scheme 3.7.**).[181] Within this report a dimeric rhodium catalyst was used, pre-formed with enantiopure amino acid derived ligands ($R^2$). This catalyst was used in combination with stoichiometric hypervalent iodine reagent, in order to generate the sulfonimidamide metallanitrene, which is then suggested to undergo a concerted C–H insertion with benzylic reagents. Previous observations had shown a strong mismatched effect between the chirality of the catalyst and the sulfonimidamide,[182] hence this reaction was readily applicable to a kinetic resolution, producing good diastereomeric and enantiomeric ratios.

Although this example of asymmetric catalysis is highly selective it was only applied to a single tosyl protected sulfonimidamide. Other carbon backbones for the sulfonimidamide gave reduced yields. Furthermore, this reaction is rather wasteful, requiring 2.2 equivalents of chiral starting material.

Which means that this methodology does not lend itself readily to re-isolation of the starting material in high optical purity.




**Scheme 3.7.** The use of a sulfonimidamide in a rhodium catalysed C–H amination, producing enantioenriched product.

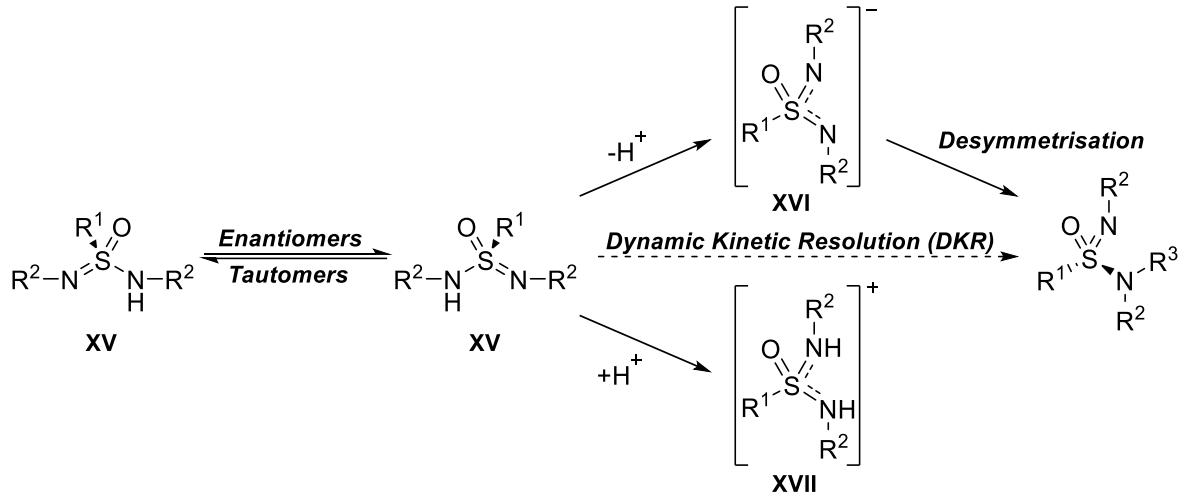
Overall, there are currently a limited number of examples which utilise the inherent nucleophilicity of a sulfonimidamide nitrogen to induce stereochemical control at the sulfur centre. These kinetic resolutions have been met with varying success, with one key limitation being the poor diversity of sulfonimidamides that have been produced, in particular these are currently restricted to simple phenyl and *p*-tolyl backbones. Furthermore, all the examples to date have required adjacent carbon stereocentres in the products; this requirement implies that there is no general catalytic transformation to directly influence the configuration of a sulfonimidamide sulfur stereocentre.

## 3.2. Project Aims

With the emerging developments in synthesis outlined, it is now rather straightforward to access free-sulfonimidamides. In addition, a great deal of effort has gone towards developing reactions which functionalise both the imidic and amidic site of sulfonimidamides.[183] Therefore, it seems appropriate that new enantioselective routes to this aza-sulfur compound continue to utilise the intrinsic reactivity of the nitrogen atom. One significant limitation of beginning from a sulfonimidamide starting material is that they are inherently chiral, and this creates a scenario in which a kinetic resolution appears to be the only suitable strategy. As has been discussed, a kinetic resolution can produce high optical purity at the expense of yield, once again limiting the synthetic application. Therefore, in the field of

asymmetric catalysis it is much more desirable to perform desymmetrisation reactions,[184] dynamic kinetic resolutions (DKR)[185] or dynamic kinetic asymmetric transformations (DyKAT),[186] as this allows both high yields and high enantiomeric excess to be obtained.

In order to devise a form of enantioselective catalysis that avoids using a kinetic resolution, it was noted that sulfonimidamides with identical substituents on their nitrogen atoms may form a privileged class of substrate (**Scheme 3.8.**). Specifically, sulfonimidamide **XV** has a unique property, in that the two enantiomers are also tautomers, and given that this tautomerisation is sufficiently facile this provides an opportunity for a catalytic DKR to be performed.




**Scheme 3.8.** Proposed nature of sulfonimidamides with two identical substituents on their nitrogen atoms, and their possible application in asymmetric catalysis.

Furthermore, there is a curiosity around the exact nature of the ionic species of sulfonimidamide **XV**. For example, it can be speculated that for the anionic (**XVI**) and cationic (**XVII**) species the S–N bonds are equivalent, hence creating symmetric ions. Given this to be the case, the symmetric ions create a scenario for an effective desymmetrisation, where the anion **XVI** could undergo a reaction at its nitrogen atom to form enantioenriched sulfonimidamide products. Therefore, this project aimed to examine this privileged class of sulfonimidamide and exploit its properties in asymmetric catalysis.

## 3.3. Configurationally Labile Sulfonimidamides

As there are limited examples of sulfonimidamides in which the two nitrogen substituents are identical,[187] little is known about their fundamental properties. In addition, only a handful of reports have examined tautomerisation of aza-sulfur compounds in general.[188,91,97,187] Hence it was decided to synthesis a sulfonimidamide of this nature and examine its possible configurational lability by examining its properties in both the solid state and solution.

### 3.3.1. X-ray Crystallography

Sulfonimidamide **73a** was readily synthesised from a sequence of reactions (see section **6.4.1.**), and subsequently crystallised from chloroform to obtain crystals suitable for X-ray crystallography (**Figure 3.1.**). On analysing the structure, it was determined that the tetrahedral sulfur centre contained two distinct sulfur nitrogen bonds. One of these bonds is best represented as a S=N double bond of length 1.508 Å, whilst the other can be described as a S–N single bond of length 1.631 Å. These bond lengths are in good agreement with the crystal structure of a fully substituted sulfonimidamide (**74a**) which is inherently chiral (with S=N as 1.510 Å and S–N as 1.637 Å). The distinguishable imidic and amidic nitrogen atoms of **73a** are further verified by one nitrogen being bound to a proton. Furthermore, the crystal was shown to be a racemate consisting of two enantiomeric sulfonimidamide units.

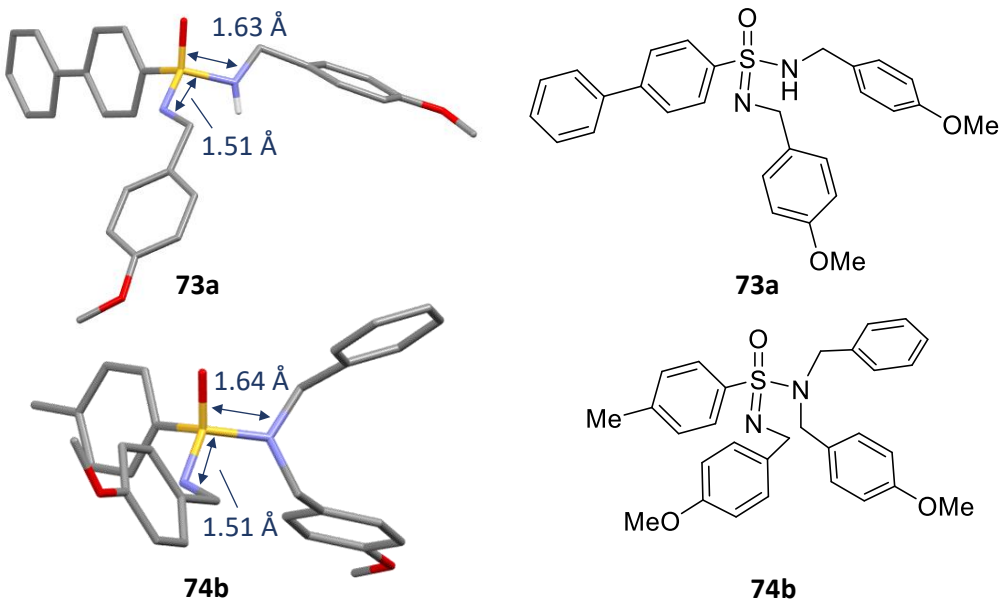



**Figure 3.1.** X-ray crystal structure of **73a** and **74b** alongside their schematic representation. The hydrogen atoms have been omitted unless they are pertinent to the discussion. X-ray crystallography interpreted by Dr. Antoine de Gombert.

From this analysis it was concluded that sulfonimidamide **73a** is a chiral molecule in the solid state. Therefore, our attention next turned to the ionic species of these sulfonimidamides. A crystal suitable for X-ray crystallography was obtained by protonation of sulfonimidamide **75** with HCl in water, which generated the cationic sulfonimidamide **75-H**$^+$ (**Figure 3.2.**). The structure was shown to contain a molecule of water and a chloride counterion, which form a hydrogen bonding network. When the sulfonimidamide unit was examined, it was noted that now both nitrogen atoms are bonded to two hydrogen atoms. Moreover, the bond lengths are 1.576 and 1.584 Å, effectively averaging to the same length of 1.58 Å. Intriguingly this distance is near the average length of the two S–N bonds for the structure of sulfonimidamide **73a** & **74b**; this therefore implies that the bonds in this cation are intermittent between a single and double bond. Although cation **75-H**$^+$ in the unit cell is not quite symmetric, due to the torsional angles, free rotation is plausible in solution, hence this molecule would be defined as achiral.

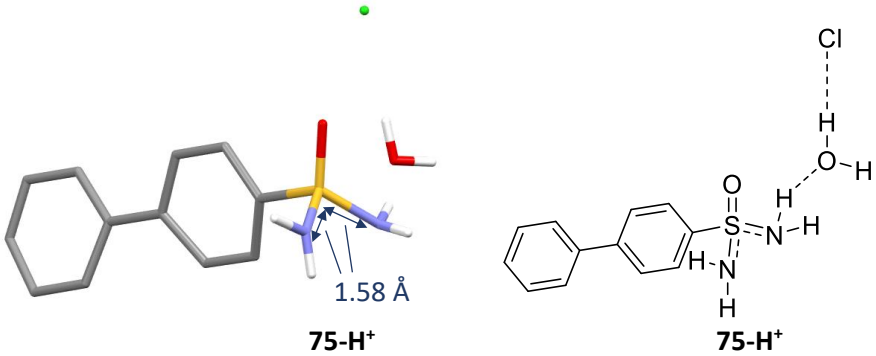
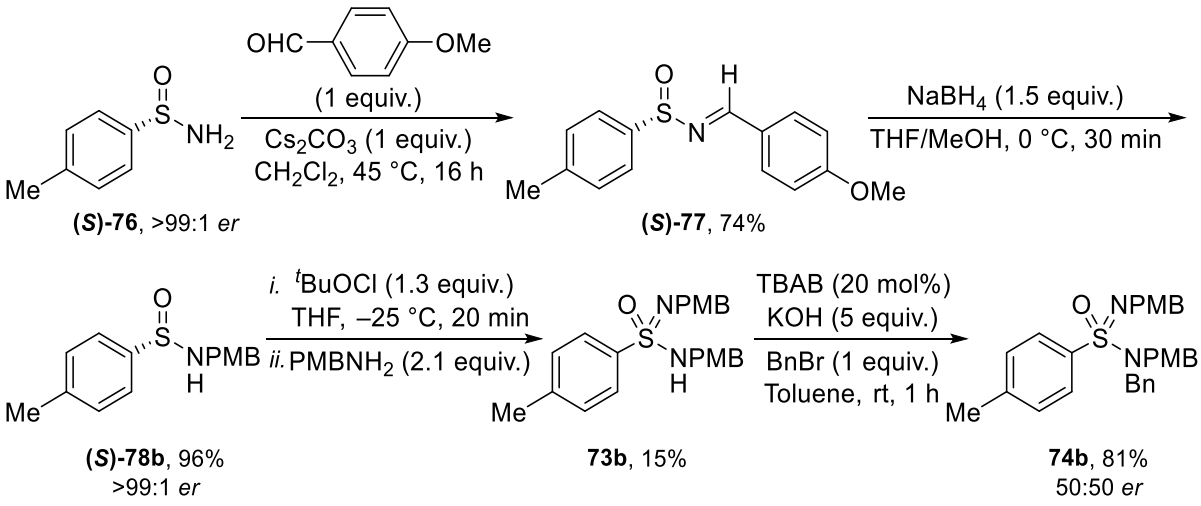



**Figure 3.2.** X-ray crystal structure of protonated **75** alongside a schematic representation. The hydrogen atoms have been omitted unless they are pertinent to the discussion. X-ray crystallography interpreted by Dr. Alasdair I. McKay.

From the analysis of sulfonimidamides in the solid state it can be proposed that the neutral species are inherently chiral, whilst for ionic sulfonimidamides the S–N bonds become equivalent, hence creating the possibility for an achiral species. Therefore, it was attempted to synthesise sulfonimidamide **73b** in its neutral form, from a known series of stereoselective transformations (**Scheme 3.9.**). The sequence began from one of the few commercially available enantiopure sulfinamides (**76**), which was derivatised into the substituted sulfinamide **78b**. From this point a chlorination was performed to the sulfonimidoyl chloride. This step is said to occur with retention of stereochemistry,[69] which was then followed by inversion *via* a nucleophilic displacement to sulfonimidamide **73b**.




**Scheme 3.9.** Reaction sequence to obtain potentially enantioenriched sulfonimidamide **73b**, *via* a series of known stereoselective transformations. With further derivation of sulfonimidamide **74b** by an alkylation.

The resulting sulfonimidamide **73b** from this sequence could not be separated *via* chiral-phase HPLC and showed no observable optical rotation. Anecdotally, these observations point to a configurationally labile sulfonimidamide, but to provide further evidence sulfonimidamide **73b** was derivatised by an alkylation reaction to sulfonimidamide **74b**, which was obtained as a racemic mixture. Therefore, this confirms that racemisation must be occurring at some point during the sequence, potentially on sulfonimidamide **73b** formation from tautomerisation, or on deprotonation of **73a** to a symmetric anion during the alkylation reaction. In order to distinguish at which stage the racemisation is occurring, it was decided to examine the dynamics of these processes more rigorously.

### 3.3.2. NMR Experiments

In order to probe the dynamics of tautomerisation a range of $^{1}H$ and $^{13}C$ NMR experiments on sulfonimidamide **73b** were conducted. Initially the $^{1}H$ spectra of **73b** in multiple deuterated solvents were obtained (**Figure 3.3.**). One of the first observations made when comparing these spectra is that the appearance in $CDCl_3$ and the non-polar solvent toluene-$d_8$ is near identical, albeit with some chemical shift altered ($H^A$ and the $CH_3$ protons). Interestingly, for both these $^{1}H$ NMR spectra the PMB groups appear to be chemically and magnetically equivalent, with singular environments for protons $H^D$ and $H^E$ as well as the diastereotopic protons of $H^C$ appearing as two discrete doublets ($J$ = 14.0 Hz). The fact that $H^C$ is a doublet implies that there is no clear coupling to the amidic proton ($H^F$), further supported by this proton not being observed in the spectrum. Overall, these results point towards tautomerisation, and hence epimerisation being rapid on the NMR timescale, in these solvents.

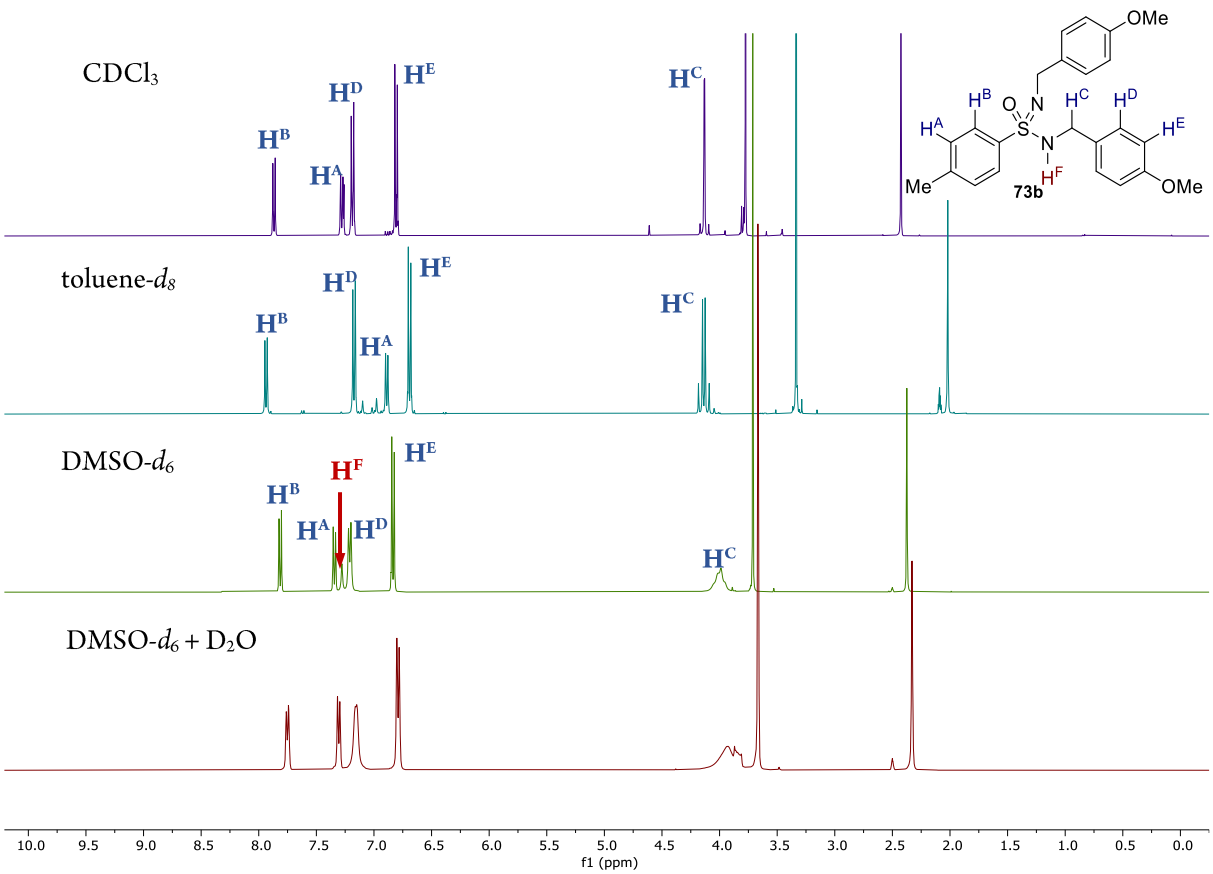



**Figure 3.3.** $^{1}$H NMR spectra of compound **73b** at 400 MHz and 295 K analysing the tautomerisation process in various solvents, with select protons of interest annotated.

DMSO-$d_6$ has previously been employed as a solvent to examine prototropic tautomerisation,[189] owning to its polar aprotic nature. When examining the $^{1}$H NMR spectrum of **73b** in DMSO-$d_6$ there are now multiple changes compared to those previously discussed. Firstly, the peaks in close proximity to the nitrogen, corresponding to $H^D$ and $H^C$, are significantly broadened, which is typical of a slowed chemical exchange process. Additionally, a broad peak at 7.28 ppm is now present, which was assigned as the amidic proton $H^F$,[97,190] which was further confirmed as an exchangeable proton by performing a '$D_2O$ shake' experiment (**Figure 3.3.**, DMSO-$d_6$ + $D_2O$). Analysis of the $^{13}$C NMR spectra in multiple solvents provided an analogous conclusion (see section **6.4.3.1.**), that in DMSO-$d_6$ tautomerisation is slowed compared to in toluene-$d_8$ and $CDCl_3$.

It was next decided to investigate whether sulfonimidamide **73a** tautomerisation persists even at lower temperatures in the non-polar solvent toluene-$d_8$. To achieve this a variable temperature (VT) $^1$H NMR spectra was obtained (**Figure 3.4**) between 23 °C and –80 °C, in regular intervals.

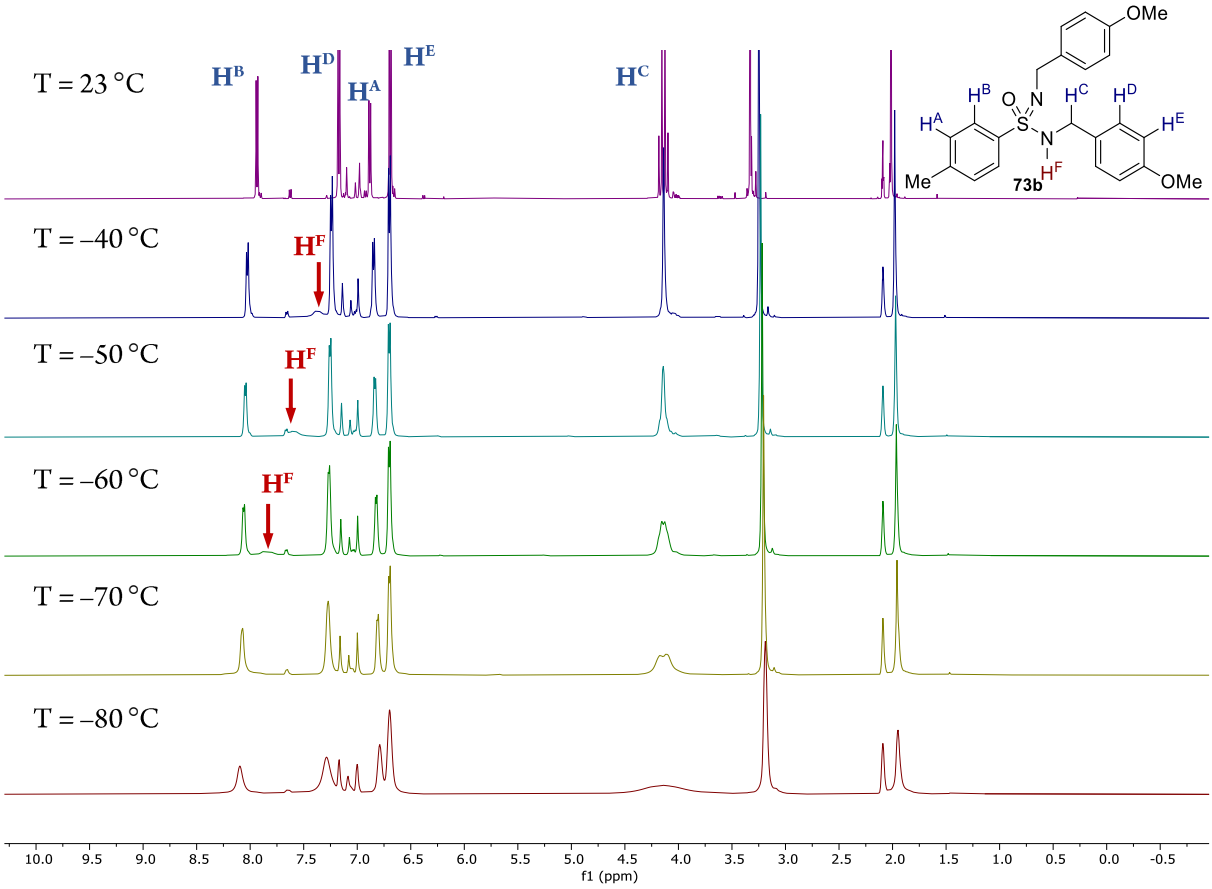



**Figure 3.4.** VT $^1$H NMR spectrum of compound **73b** at 500 MHz in toluene-$d_8$, analysing the tautomerisation process at various temperature, with select protons of interest annotated.

The first cryogenic temperature that was evaluated was –40 °C, which induced several key changes from the room temperature spectrum. For example, a broad peak at 7.37 ppm is now noticeable, which is tentatively assigned as amidic proton $H^F$. Intriguingly, the signal corresponding to $H^C$ is now an apparent singlet at 4.13 ppm, the appearance of a singlet is likely from the variation in chemical shifts with temperature. However, this has some significance as it demonstrates that there is no observable coupling between protons $H^C$ and $H^F$, allowing the conclusion to be that at –40 °C tautomerisation is still occurring, albeit at a slower rate.

Further lowering of the temperature shows that the $H^F$ peak broadens, and it shifts downfield, until at –80 °C it is no longer observable. Multiple factors could cause this broadening, including the chemical exchange process, partial averaged coupling to the $H^C$ and $^{14}N$ ($I$ = 1) and sample inhomogeneity. Next an examination of the $H^C$ protons now showed that at –60 and –70 °C these begin to again appear as two separate peaks, however, it is indistinguishable if this is from the chemical shifts of the diastereotopic protons or from chemical inequivalence from being adjacent to an amidic or imidic nitrogen. At –80 °C protons $H^C$ are exceptionally broad, especially when compared to the over environments, this could arise from multiple low intensity signals from chemically inequivalent environments.

As expected, lowering the temperature of sulfonimidamide **73a** in toluene-$d_8$ slows the rate of tautomerisation. However, it is important to emphasise that this VT $^1$H NMR experiments indicate that epimerisation would still persist down to at least –40 °C to some extent. Overall, these results show that sulfonimidamides of this nature are configurationally labile in multiple solvents and over a range of temperatures, which primes this substrate for a dynamic kinetic resolution.

One of the hypotheses made was that sulfonimidamide **73b** would form a symmetric cation and anion. In order to scrutinise this assumption, it was decided to examine the effects of acid and base on the $^1$H and $^{13}$C NMR spectra of **73a** in DMSO-$d_6$. To initiate this the base KOH and acid TFA were added to samples resulting in the following $^1$H NMR spectra (**Figure 3.5.**).

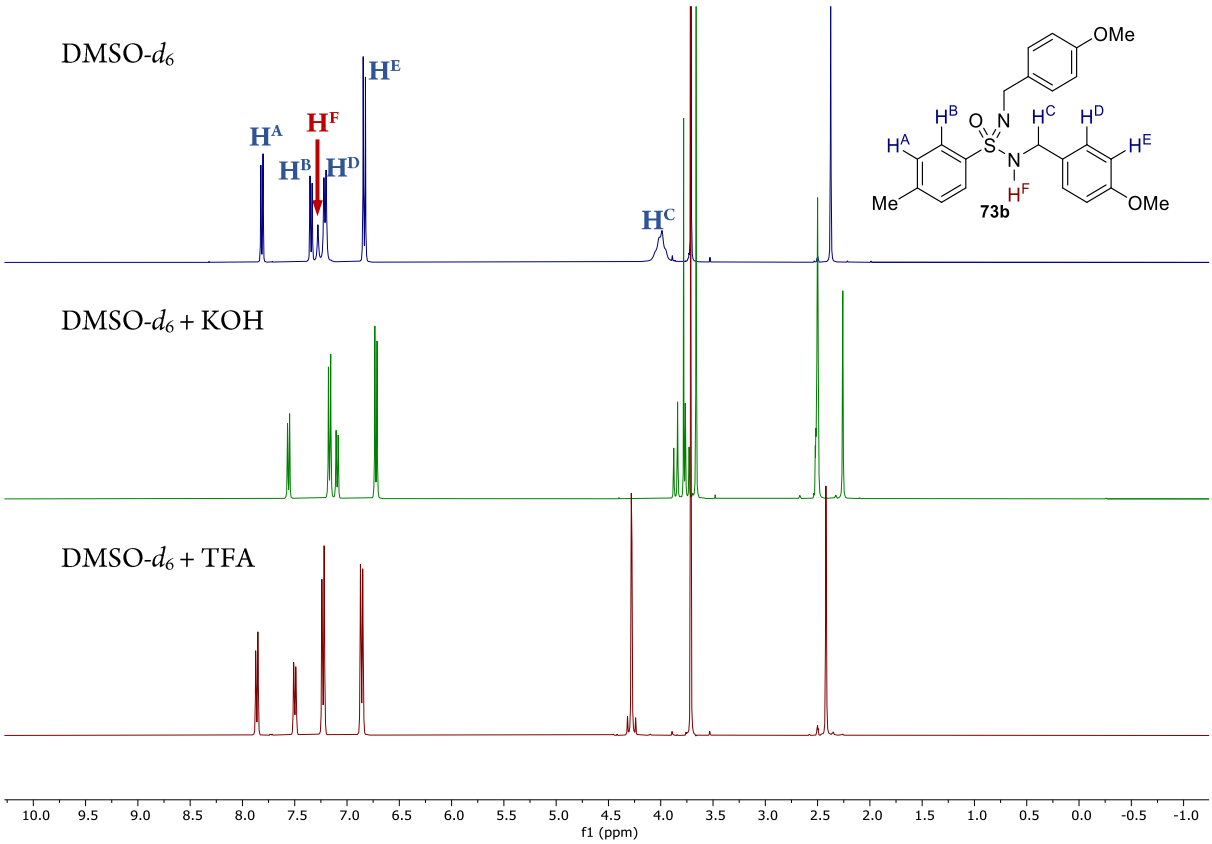



**Figure 3.5**. VT $^{1}$H NMR spectra of compound **73a** at 400 MHz in DMSO-$d_6$, with various additives added.

The presence of base causes significant alterations to the $^{1}$H NMR spectrum of sulfonimidamide **73a**, such as the disappearance of the $H^F$ proton. Another obvious change is that the diastereotopic protons $H^C$ once again become two well resolved doublets, as would be expected for chemically equivalent PMB groups. Similar observations are also seen with the addition of TFA as acid. These remarks point towards KOH and TFA accelerating the rate of tautomerisation in DMSO-$d_6$, or the formation of a symmetric anion and cation, respectively. More subtle changes include the increased shielding of environments with KOH and the deshielding of environments in TFA, which implies the formation of ionic species. Furthermore, this conclusion was corroborated by complementary observations in the $^{13}$C NMR spectra (see section **6.4.3.2.**) and the fact that KOH was shown to not alter the chemical shifts for a fully substituted sulfonimidamide (**74a**) with no acidic protons (see section **6.4.3.3.**).

Overall, sulfonimidamides with two identical substituents on their nitrogen atoms can be described as configurationally labile species, which in the presence of acid or base can form symmetrical ionic intermediates in solution. These results are profound as they provide the opportunity to desymmetrise these ions once formed, allowing methodology to be accessed to produce enantioenriched sulfonimidamides in both high yield and enantiomeric ratio.

### 3.3.3. Reaction Design

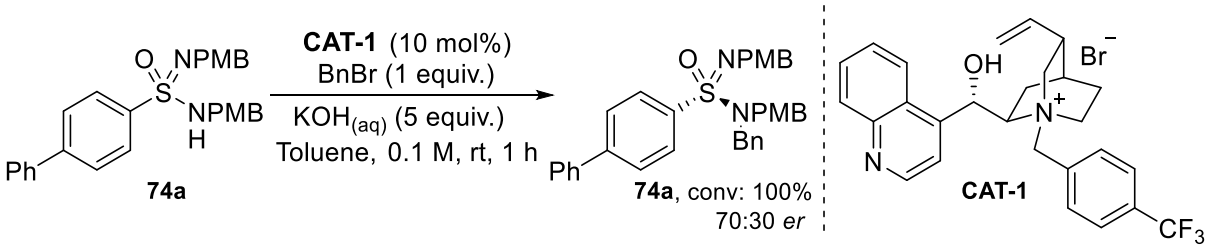
With these configurationally labile sulfonimidamides in hand, multiple types of asymmetric catalysis could have been applied to attempt achieving the overall goal. However, previously the pKa of sulfonimidamides containing electron withdrawing groups has been assessed to be in the range of 6.62 to 7.76,[14c] hence one can speculate that the formation of the symmetric anion is straightforward with the appropriate base. This knowledge, in tandem with the known reactivity of sulfonimidamides, including their basic alkylation,[183l] suggests that desymmetrising the anion, in an alkylation, is a viable reaction design to access enantioenriched sulfonimidamides.

## 3.4. Reaction Optimisation

It was decided to use asymmetric phase-transfer catalysis to desymmetrise the sulfonimidamide anion. The rationale behind using this mode of asymmetric catalysis is that it has successfully been applied to the formation of C–X bonds,[191] including C–N bonds,[192] as well as a singular example constructing a C–S bond to synthesis optically active S(IV)-sulfoxides.[193] Although phase-transfer catalysis has not been used to construct S(VI) compounds, the wealth of information known and highly modular nature of the catalysts provided an opportunity for optimisation.

### 3.4.1. Singly-Quaternised Catalysts

To initiate the optimisation, it was decided to use the cinchona alkaloid derived phase-transfer catalysts, in part due to the ease of their synthesis and highly modular nature. To begin with the commercial singly-quaternised catalyst **CAT-1** was trialed in an alkylation reaction (**Scheme 3.10.**). Pleasingly using sulfonimidamide **73a** in combination with 1 equivalent of benzyl bromide, and KOH as base produced sulfonimidamide **74a** with a low level of enantioinduction, providing proof-of-concept.

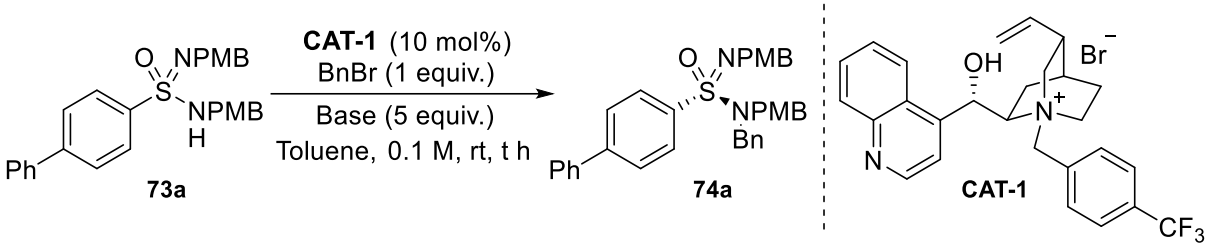



**Scheme 3.10.** Initial attempt at an asymmetric alkylation of a sulfonimidamide with a cinchona alkaloid derived catalyst. Aqueous refers to the base as a 50% *wt.* solution in water, and conversion was determined by analysis of the crude $^1$H NMR spectrum.

Encouraged by this result, the attention turned to the nature of the base, where it was found that the reaction was rather insensitive to the concentration and equivalents of aqueous KOH used. Hence, the focus was placed on the identity of the base used (**Table 3.1.**). Initially various aqueous bases were evaluated, where NaOH was shown to give a slight improvement in terms of enantioselectivity (entry 2), when compared to KOH. Whereas $K_2CO_3$ and $K_3PO_4$ were much less reactive with no significant improvement in enantiomeric ratio (entries 3-4), this reduced reactivity is ascribed to these bases lower $pK_B$ values. It was postulated that the presence of water may be problematic for the reaction, hence the reaction was tried with solid KOH (entry 5); fortuitously this solid-liquid system now retained the reactivity with a slight improvement in enantioselectivity. Due to this observation a range of other solid bases were screened, including hydroxide bases (entries 6-8), indicating that the nature of the cation can have a significant impact on reactivity, although no improvement from using

KOH was observed. A series of weak bases were also screened (entries 9-12), once again showing a significant decrease in the conversion. $K_3PO_4$ did show an increase in enantiomeric ratio (entry 10), but the conversion was too low to deem usable, in addition, the enantiomeric ratio decreased on extending the reaction time (entry 11), potentially due to competing catalyst decomposition.[194] Finally, stronger bases were evaluated (entries 13-14) although only $^t$BuOK gave a marginal improvement.

**Table 3.1.** Base screen for the asymmetric alkylation of sulfonimidamide **73b**.



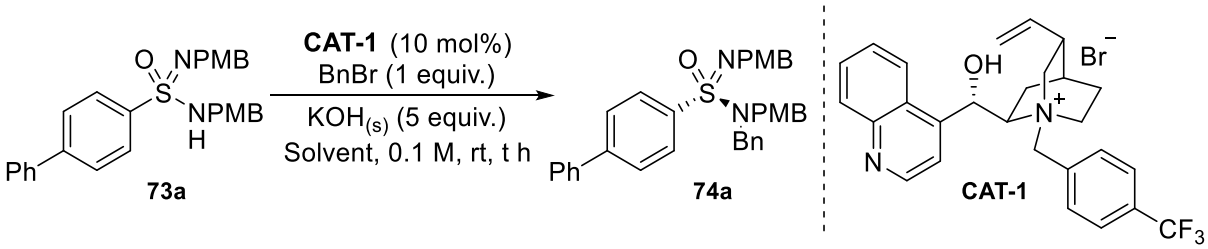

| Entry | Base | Time (h) | Conversion (%) | *er* |
|---|---|---|---|---|
| 1 | $KOH_{(aq)}$ | 1 | 100 | 70:30 |
| 2[a] | $NaOH_{(aq)}$ | 1 | 96 | 72:28 |
| 3[a] | $K_2CO_{3(aq)}$ | 16 | 22 | 71:29 |
| 4[a] | $K_3PO_{4(aq)}$ | 16 | 44 | 71:29 |
| 5 | $KOH_{(s)}$ | 1 | 100 | 72.5:27.5 |
| 6 | $NaOH_{(s)}$ | 2 | 86 | 72:28 |
| 7 | $LiOH_{(s)}$ | 16 | 0 | N/A |
| 8 | $CsOH{\cdot}OH_{2(s)}$ | 1 | 98 | 67.5:32.5 |
| 9 | $K_2CO_{3(s)}$ | 24 | 0 | N/A |
| 20 | $K_3PO_{4(s)}$ | 24 | 36 | 77.5:22.5 |
| 11 | $K_3PO_{4(s)}$ | 72 | 100 | 75:25 |
| 12 | $PhONa_{(s)}$ | 16 | 0 | N/A |
| 13 | $NaH_{(s)}$ | 24 | 68 | 66:34 |
| 14 | $^t$BuOK$_{(s)}$ | 1 | 100 | 73:27 |

Aqueous refers to the base as a 50% *wt.* solution in water, and conversions determined by analysis of crude $^1$H NMR spectra. [a] 20 mol% of **CAT-1** and a concentration of 0.5 M.

Based on the previous results solid KOH was selected as the base of choice for this asymmetric alkylation. Although toluene is a common solvent for phase-transfer catalysis, several other solvents were also evaluated (**Table 3.2.**). Solvent appeared to have a drastic effect on the enantiomeric ratio of sulfonimidamide **74a**, for example, $CH_2Cl_2$ and the ethereal solvents $Et_2O$ and MTBE gave a

reduction in the enantioselectivity (entries 2-4). An assessment of other aromatic solvents (entries 5-7) now showed that these performed similar to toluene (entry 1). Although benzene provided a marginal increase in the stereoselectivity (entry 7), this solvent was not pursued further, due to its high freezing point (6 °C), which would have caused potential issues when investigating cryogenic temperatures for the reaction.

**Table 3.2.** Solvent screen for the asymmetric alkylation of sulfonimidamide **73b**.

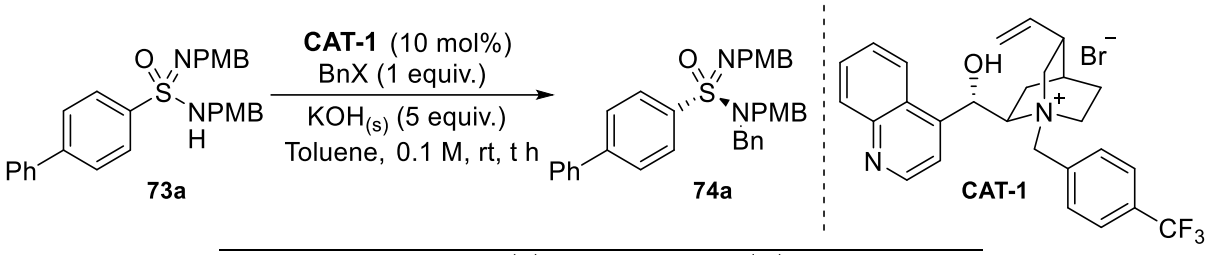



| Entry | Solvent | Time (h) | Conversion (%) | *er* |
|---|---|---|---|---|
| 1 | Toluene | 1 | 100 | 72.5:27.5 |
| 2 | $CH_2Cl_2$ | 2 | 100 | 57:43 |
| 3 | $Et_2O$ | 2 | 97 | 66:34 |
| 4 | MTBE | 1 | 97 | 68.5:31.5 |
| 5 | *m*-Xylene | 1 | 96 | 71.5:28.5 |
| 6 | Chlorobenzene | 1 | 96 | 68.5:31.5 |
| 7 | Benzene | 1 | 97 | 74:26 |

Conversions determined by analysis of crude $^1$H NMR spectra,

As the nature of the base's cation appeared to affect the reactivity, it was also questioned what effect the identity of the electrophile leaving group would have. To provide more information on leaving group effect a variety of electrophiles were screened in the reaction (**Table 3.3.**). Using electrophiles with increased leaving group ability generally retained reactivity but reduced the enantiomeric ratio (entries 2-3). In comparison, when using benzyl chloride (entry 4), the enantioselectivity increased, however this was at the detriment of the conversion, as now a rather sluggish reaction was observed.

**Table 3.3.** Electrophile screen for the asymmetric alkylation of sulfonimidamide **73b**.

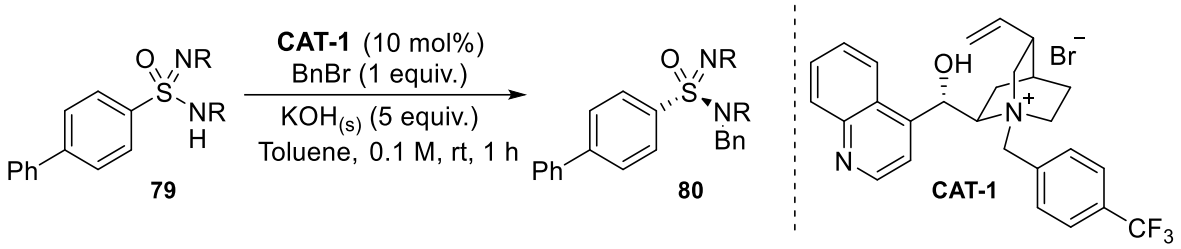


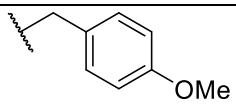
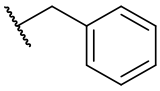
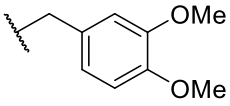
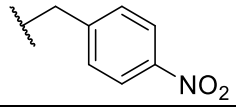

| Entry | X | Time (h) | Conversion (%) | *er* |
|---|---|---|---|---|
| 1 | Br | 1 | 100 | 72.5:27.5 |
| 2 | I | 2 | 97 | 68.5:31.5 |
| 3 | OTs | 1 | 98 | 69.5:30.5 |
| 4 | Cl | 5 | 68 | 76:24 |

Conversions determined by analysis of crude $^1$H NMR spectra.

It was postulated that the non-optimal enantiomeric ratio may be in part caused by the nature of the substituents on the configurationally labile sulfonimidamide. Although, in order for this reaction to have some synthetic utility, it is important to choose substituents which can be selectively removed after the reaction. Therefore, sulfonimidamides with various different benzyl groups (**79**) were applied in the reaction (**Table 3.4.**). Application of the electron neutral benzyl group (entry 2) decreased the enantiomeric ratio, hence a more electron rich substituent was tried (entry 3), although this also resulted in a decrease in stereoselectivity. Finally, a sulfonimidamide with the electron deficient *para*-nitro benzyl substituent was applied in the reaction, however no product was isolated due to decomposition. This decomposition can be rationalised from the benzylic protons becoming sufficiently acidic for KOH to deprotonate this position.

**Table 3.4.** Protecting group screen for the asymmetric alkylation of sulfonimidamides **76**.



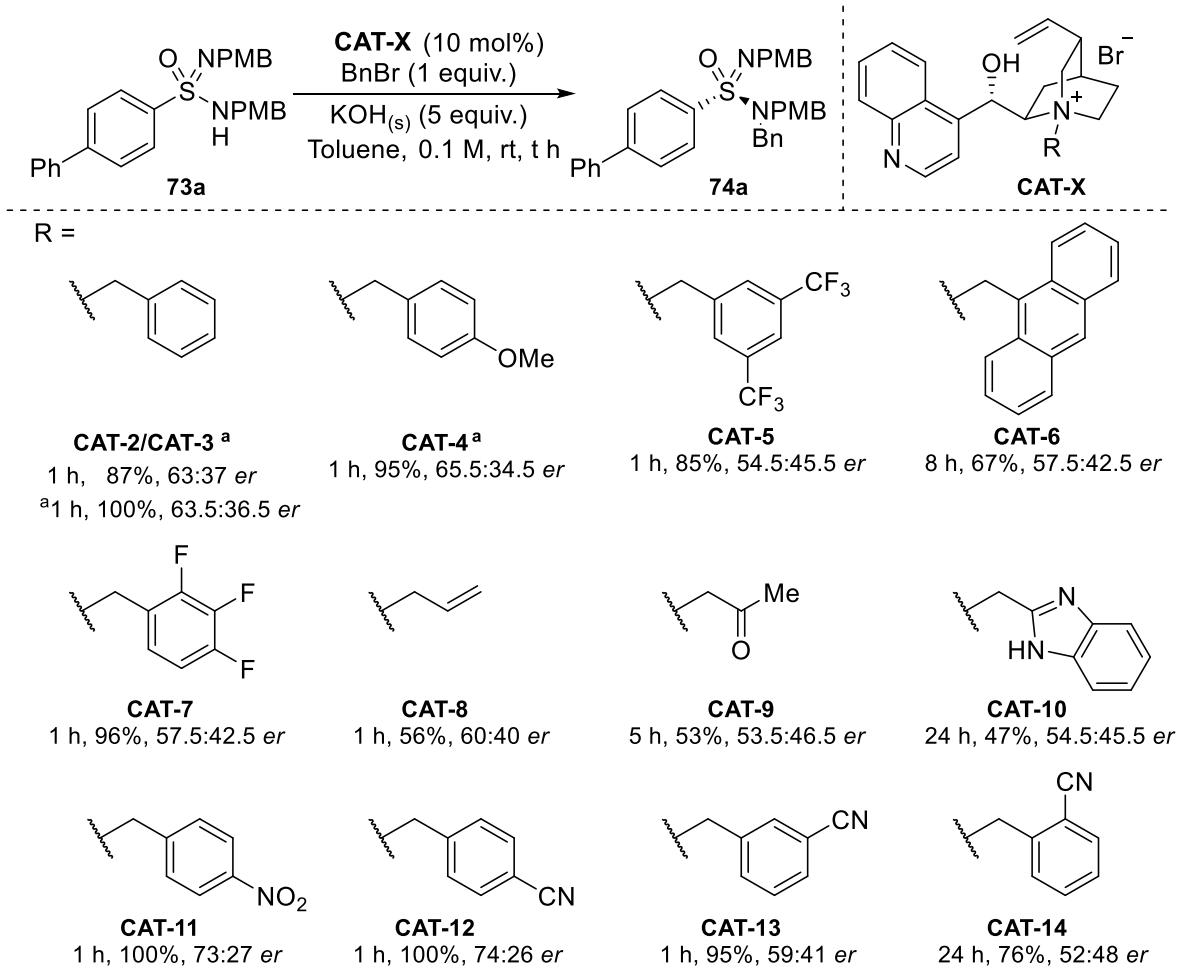

| Entry | R | Conversion (%) | *er* |
|---|---|---|---|
| 1 |  | 100 | 72.5:27.5 |
| 2[a] |  | 100 | 58:42 |
| 3[b] |  | 100 | 68:32 |
| 4[c] |  | 0 (decomp.) | N/A |

Conversions determined by analysis of crude $^1$H NMR spectra. [a] Using substrate **79a**. [b] Using substrate **79b**. [c] Using substrate **79c**.

For further screening the PMB group was used, which is also advantageous due to multiple strategies known for its removal.[195,103] Control reactions revealed that a catalyst was essential for reaction turnover, hence it is expected that the identity of the catalyst could have profound impact on the reaction outcome. To evaluate this effect a library of cinchona alkaloid derived catalysts was developed and tested (**Table 3.5.**). Initially the simple benzyl substituted catalyst (**CAT-2**) provided a lower selectivity, and this structure was then used to evaluate the effect of the anion, however, the use of **CAT-3** gave a minor improvement. Therefore, alternative catalyst structures were evaluated, including a more electron rich benzylic system (**CAT-4**) and a disubstituted-trifluoromethyl system (**CAT-5**). Although these catalysts maintained reactivity, they caused a notable drop in the enantiomeric ratio, which did show that the catalyst structure has a large influence on the success of the reaction. Due to these pronounced effects several more adventurous catalysts were screened (**CAT-6** to **CAT-10**), including multiple systems which move away from a benzylic substituent.

However, all these resulted in a reduction in the enantiomeric ratio, and many of the catalysts were found to deliver slower reactions. Therefore, the attention was again focused on benzylic substituted catalysts; pleasingly, when catalysts with an electron withdrawing group in the *para-* position were investigated (**CAT-11** & **CAT12**) the results improved. The importance of the electron withdrawing group in the *para-* position was confirmed by evaluation of **CAT13** and **CAT14**, with both causing a drastic drop in the enantiomeric ratio, and **CAT-14** also being much more sluggish. Overall, from the library of catalysts screened **CAT-12** gave excellent conversion and moderate enantioinduction. In addition, re-evaluating several of the other parameters, with this new catalyst, confirmed the conditions that were selected to be optimum.

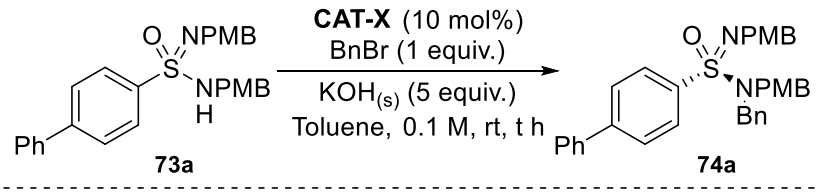
**Table 3.5.** Screen of cinchona alkaloid derived catalysts in the alkylation of **73b**.

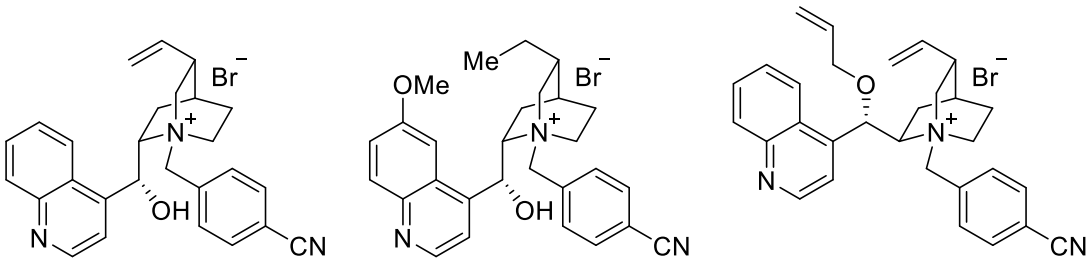



Conversions were determined by analysis of the crude $^1$H NMR spectra. [a] A chloride counter-anion is used in place of bromide.

At this point only catalysts based on the cinchonine scaffold had been tested, hence alternative scaffolds were investigated (**Table 3.6.**). As expected, the pseudo-enantiomeric catalyst derived from cinchonidine (**CAT-15**) gave the opposite enantiomer, albeit with a slight reduction in enantiomeric ratio. Whereas using a quinidine derived system (**CAT-16**) now gave an even further reduction in selectivity, which can be ascribed to the presence of the methoxy substituent. Finally, the role of the hydroxy group was evaluated (**CAT-17**), and in this case alkylating the alcohol resulted in a near racemic mixture of sulfonimidamide **74a**. Overall, this indicates that hydrogen bonding with the O–H unit is likely essential for effective enantioinduction.

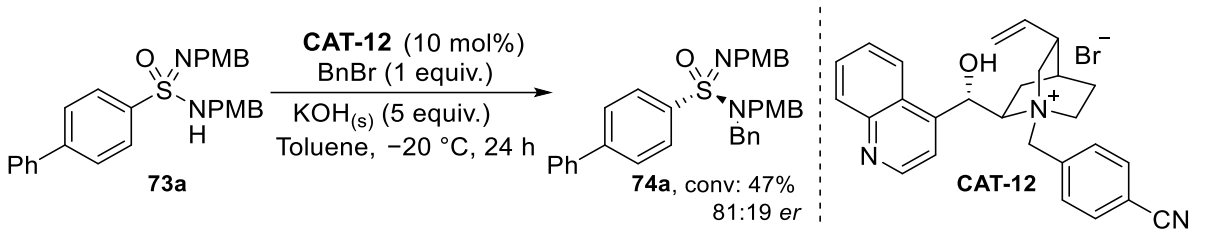
**Table 3.6.** Further evaluation of cinchona alkaloid derived catalysts in the alkylation of **73b**.




Conversions were determined by analysis of the crude $^{1}$H NMR spectra.

From the plethora of catalysts screened, **CAT-12** was identified as the optimum catalyst at room temperature. Therefore, in an attempt to improve the enantiomeric ratio to a usable value the temperature of the system was lowered to –20 °C (**Scheme 3.11.**). Disappointingly, only a slight improvement in the selectivity was observed, alongside a large decrease in the conversion, producing a non-ideal system.



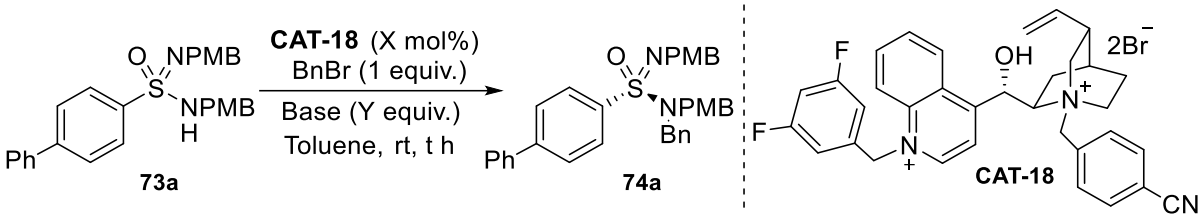

**Scheme 3.11.** Initial attempt to lower the temperature of the system at a concentration of 0.1 M, where conversions was determined by analysis of the crude $^{1}$H NMR spectrum.

Any further attempts which were made to improve the system did not come to fruition. Recently, chiral quaternary ammonium salts have been postulated to function due to a complex ensemble of H-bonding interactions with the substrate.[196] Therefore, the success of the catalyst motif screened here is likely dependent on a multitude of factors, creating a challenging optimisation. To proceed, it was decided to take an alternative approach and examine a different catalyst template altogether.

### 3.4.2. Doubly-Quaternised Catalysts

A publication of particular interest from Merck had investigated a spirocyclisation reaction,[197] in doing so they noted that doubly-quaternised cinchona alkaloid derived catalysts provided an increase in both reaction rate and enantioselectivity. Although these catalysts have seen little application outside their initial use,[198] it was postulated that their increased activity may be beneficial for developing the asymmetric alkylation of sulfonimidamides at lower temperatures. Whilst also providing an opportunity to increase the selectivity of the reaction due to the additional appendage on the catalyst allowing further fine-tuning. Hence, a doubly-quaternised catalyst (**CAT-18**) was synthesised and trialed in the reaction (**Table 3.7.**).

**Table 3.7.** Application of a doubly-quaternised catalyst for the asymmetric alkylation of sulfonimidamide **73b**.




| Entry | X (mol%) | Base | Y (equiv.) | Time (h) | Conversion (%) | *er* |
|---|---|---|---|---|---|---|
| 1 | 10 | $KOH_{(s)}$ | 5 | 7 | 61 | 68:32 |
| 2 | 1 | $KOH_{(s)}$ | 5 | 16 | 76 | 53.5:46.5 |
| 3 | 20 | $KOH_{(s)}$ | 5 | 1 | 94 | 75.5:25.5 |
| 4 | 20 | $KOH_{(aq)}$ | 5 | 24 | 100 | 66.5:33.5 |
| 5 | 20 | $NaOH_{(s)}$ | 5 | 2 | 91 | 73.5:26.5 |
| 6 | 20 | $K_2CO_3$ | 5 | 96 | 40 | 60.5:39.5 |
| 7 | 20 | $K_3PO_4$ | 5 | 24 | 44 | 72:28 |
| 8 | 20 | $KOH_{(s)}$ | 10 | 1 | 100 | 79.5:20.5 |
| 9 | 20 | $KOH_{(s)}$ | 20 | 1 | 100 | 81:19 |
| 10[a] | 20 | $KOH_{(s)}$ | 20 | 4 | 90 | 66.5:33.5 |
| 11[b] | 20 | $KOH_{(s)}$ | 20 | 1 | 95 | 71:29 |
| 12[c] | 20 | $KOH_{(s)}$ | 20 | 24 | 20 | 76:24 |

Reactions were conducted at a concentration of 0.1 M, aqueous refers to the base as a 50% *wt.* solution in water, and conversions determined by analysis of crude $^1$H NMR spectra. [a] Reaction performed with BnI, [b] Reaction performed with BnOTs, [c] Reaction performed with BnCl.

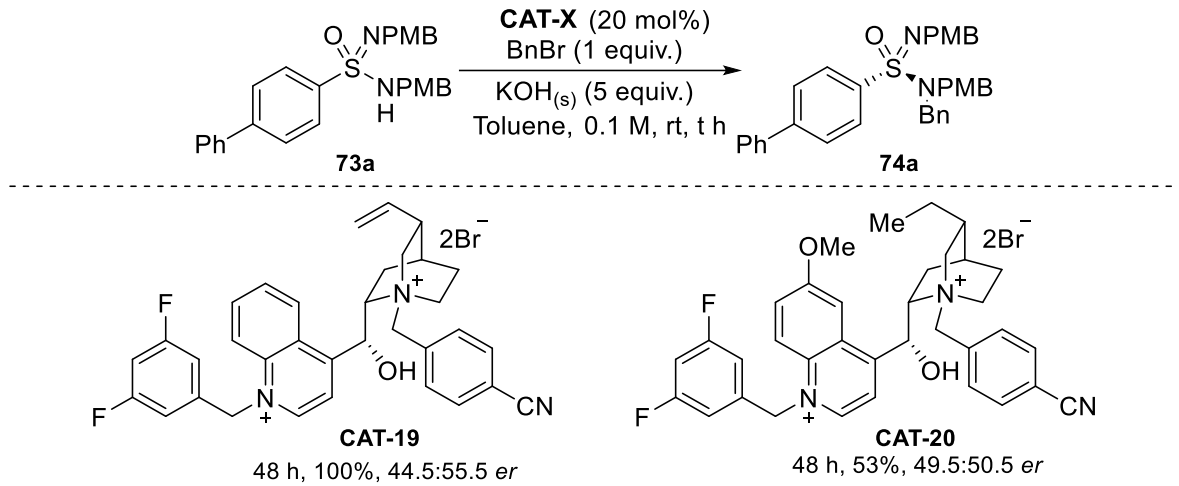
Unfortunately, **CAT-18** actually produced a slower rate of reaction and a reduced enantiomeric ratio when compared to the singly-quaternised **CAT-12** (entry 1). However, it was quickly assessed that the success of the doubly-quaternised catalyst was highly dependent on the catalyst loading. This fact was demonstrated by a decrease in **CAT-18** loading now having a detrimental impact (entry 2). Whilst increasing the loading to 20 mol% produced an improvement in the system compared to the previous results (entry 3).

As the identity of the base played an important role for the singly-quaternised catalysts this was now investigated for the doubly-quaternised template (entries 4-9). It was now observed that the use of aqueous KOH was much more detrimental to the enantioselectivity (entry 4), hence for further screening only solid bases were evaluated. Once again NaOH played a near identical role to KOH (entry 5), but now marginally lower enantiomeric ratio was observed. Also, the use of the weaker bases again proceeded at much slower rates (entry 6 & 7) now paired with reduced enantioinduction. As

the catalyst loading had such a substantial impact, the equivalents of KOH were also tested (entries 8 & 9), fortuitously increasing the equivalents of base also led to an increase in the enantiomeric ratio, obtaining a value of 81:19 with 20 equivalents of KOH (entry 9). The role of the electrophile was again evaluated (BnCl, BnI & BnCl, entries 10, 11 & 12 respectively), however BnBr was optimal.

Many of the results obtained from this optimisation can be rationalised based on previous mechanistic studies.[198b,199] In particular, doubly-quaternised catalysts require base to increase their solubility in the organic phase, however the catalysts also rapidly decompose in the presence of this base.[194,200] In the sulfonimidamide alkylation, this likely presents a scenario where KOH is required to accelerate the mass-transfer of the catalysts, whilst the increased catalyst loading is needed to suppress the prevalence of counter-productive decomposition species.

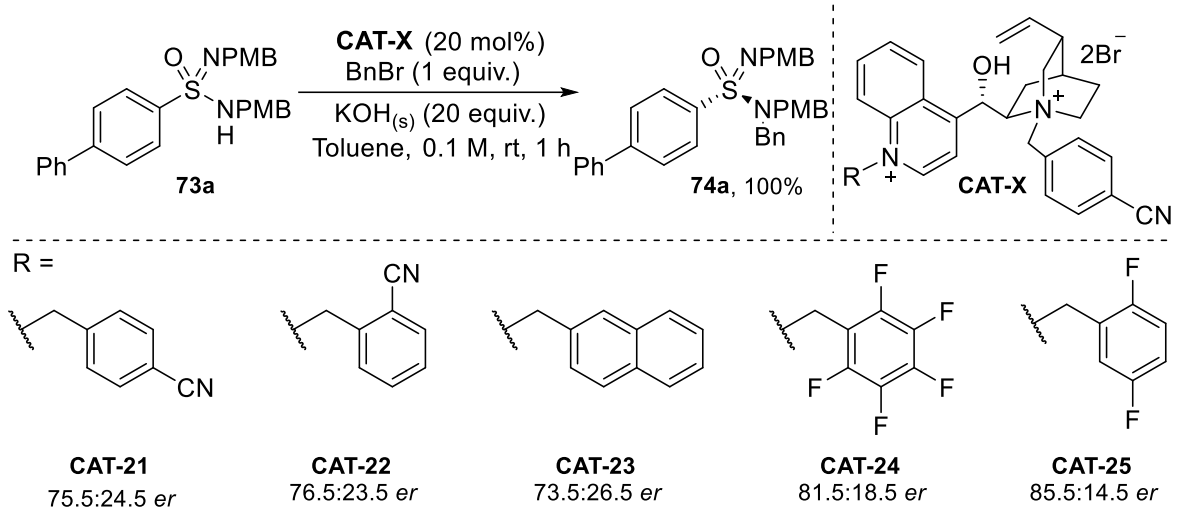
In order to compete the productive reaction with catalyst degradation, multiple variables must be balanced, including catalyst solubility and physical parameters such as agitation rate. Although the doubly-quaternised catalysts created additional challenges for optimisation, having an extra appendage on the scaffold provides an opportunity for further fine-tuning of incremental interactions which can have a substantial impact on the enantioselectivity. To begin with the role of the cinchona alkaloid scaffold was evaluated (**Scheme 3.12.**). It was now evident that the pseudo-enantiomers possess drastically different behaviour, with exceptionally slow reaction rates and producing near racemic mixtures of sulfonimidamide **74a**.




**Scheme 3.12.** Investigation into the cinchona alkaloid derived catalyst core, where conversions were determined by analysis of the crude $^{1}$H NMR spectra. Note that these catalysts were preliminarily screened with 5 equiv. of KOH.

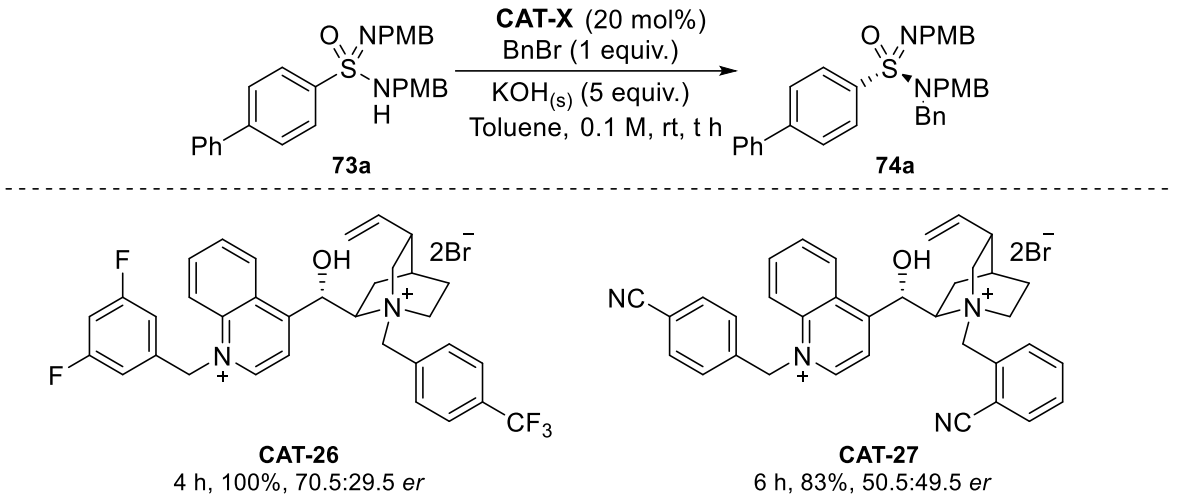
This initial screen supports the fact that the success of these catalysts can be dominated by a combination of factors including catalyst solubility and subtle catalyst-substrate interactions, generating a system which is onerous to optimise. Therefore, a library of doubly-quaternised catalysts was synthesised and tested in the asymmetric alkylation (**Table 3.8.**). Firstly, all catalysts were shown to have a high catalytic activity and produce 100% conversion in just one hour. Of the catalysts screened, many generated close selectivity to the parent catalyst (**CAT-21**, **CAT-22** & **CAT-23** compared with **CAT-12**). However, it was shown that a fluorinated aromatic ring was beneficial for the system (**CAT-24** & **CAT-25**), with **CAT-25** being a robust catalyst giving a good enantiomeric ratio of 85.5:14.5 at room temperature.

**Table 3.8.** Screen of cinchona alkaloid derived catalysts,



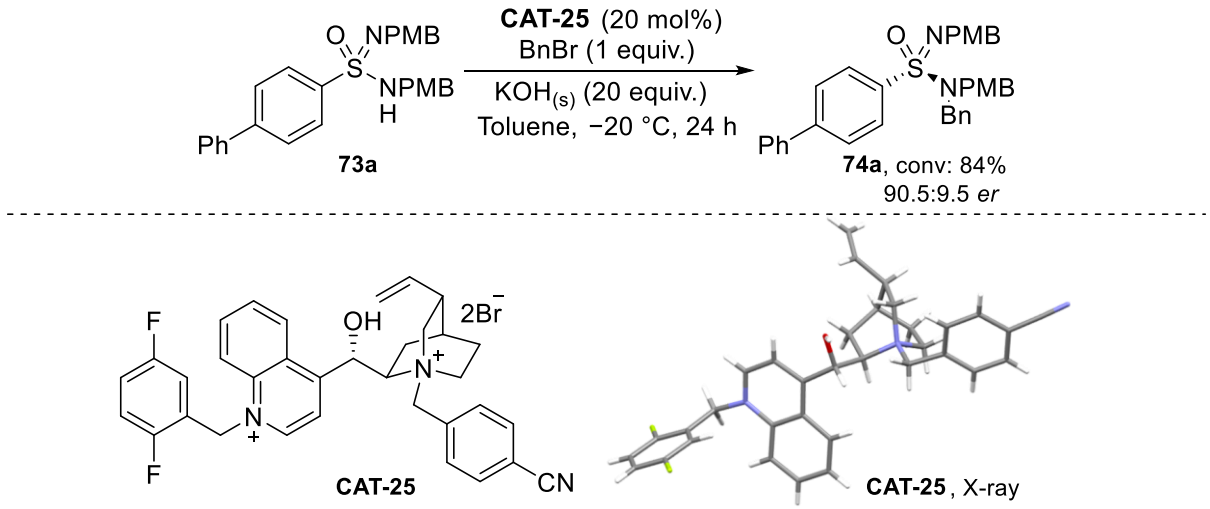

Conversions were determined by analysis of the crude $^1$H NMR spectra.

Several attempts were made to alter the core of the cinchona alkaloid, by changing the parent structure (**Scheme 3.13.**), as exemplified with the use of **CAT-26** and **CAT-27**. From both of these systems tested it can be postulated that the trends in activity and selectivity reflect that of the original singly-quaternised catalyst screen, this observation is particularly prominent with **CAT-27** which gives a near racemic mixture of sulfonimidamide **74a** (similar to **CAT-14**).




**Scheme 3.13.** Further evaluation of cinchona alkaloid derived catalysts, where conversions were determined by analysis of the crude $^1$H NMR spectra. Note that these catalysts were preliminarily screened with 5 equiv. of KOH.

Therefore, from the evaluation of a diverse library of cinchona alkaloid derived catalysts, **CAT-25** had been identified as a highly active catalyst with good enantioselectivity at room temperature, hence this system was performed at cryogenic temperatures (**Scheme 3.14.**). Gratifyingly, using this doubly-quaternised catalyst now maintained good activity at the lower temperatures whilst causing an increase to a good enantiomeric ratio.




**Scheme 3.14.** Lowering of the temperature at a concentration of 0.05 M, where conversion was determined by analysis of the crude $^1$H NMR spectrum. X-ray crystal structure was resolved by Dr. Antoine de Gombert, with the bromide counterions omitted for clarity.

Overall, after the extensive screening of conditions and catalyst, a novel methodology has been developed to construct enantioenriched sulfonimidamides. Where the success of this strategy is based on using configurationally labile sulfonimidamide starting materials, in order to desymmetrise a key anionic intermediate.

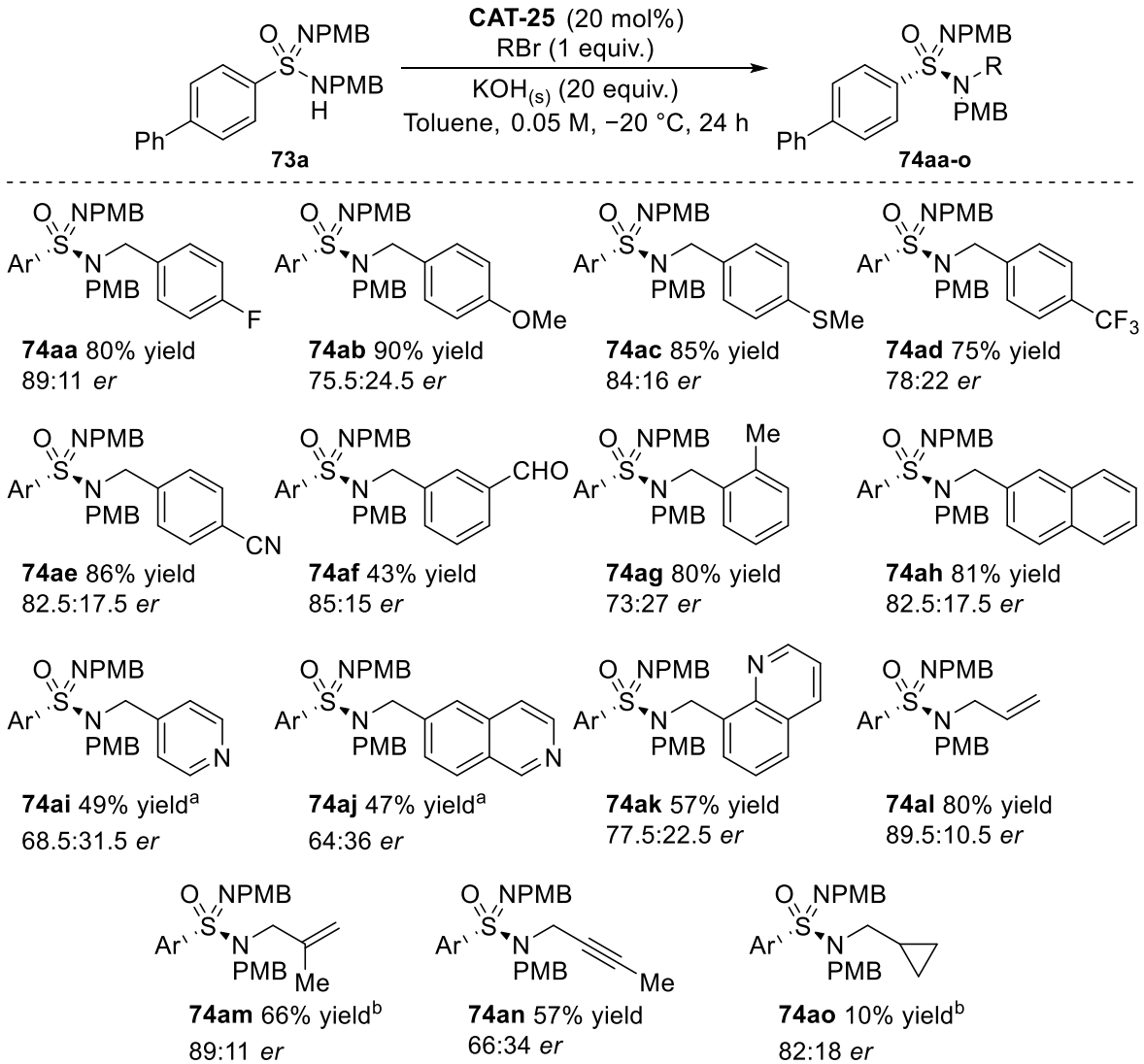
## 3.5. Reaction Scope

With a set of conditions developed for the enantioselective synthesis of sulfonimidamides, it was decided to test the applicability of this system, with respect to both the electrophile and sulfonimidamide used. In particular, a key objective in scoping this reaction was to diversify the amount of enantioenriched sulfonimidamides that are currently known.

### 3.5.1. Electrophile Scope

To initiate examining this organocatalysed enantioselective synthesis of sulfonimidamides, a range of electrophilic reagents were successfully applied under the conditions (**Table 3.9.**). In general, the reaction showed good tolerance to the electrophile used, with many cases performing near identically to the optimum result with benzyl bromide.

**Table 3.9.** Electrophile scope for the enantioselective synthesis of sulfonimidamides.

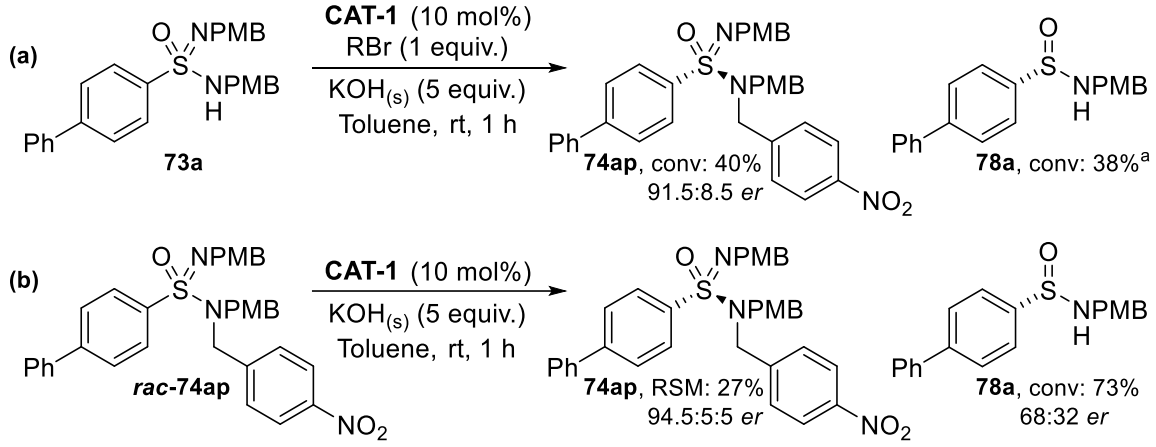



**Conditions**: The reactions were conducted on a 0.05 mmol scale with respect to **73a.** [a] Reaction used the HBr salt of the electrophile and a reaction time of 48 h. [b] Reaction time 48 h.

In particular a range of benzylic electrophiles with varying electronic properties were examined (**74aa-74af**), which produced good enantiomeric ratios. Of particular note are substrate **74ad** which provided a mixed valence sulfur sulfonimidamide, as well as species **74af** which contains an aldehyde which is potentially base sensitive. The sensitivity of the reaction to the electrophile steric hindrance was also examined with sulfonimidamide **74ag** giving a high yield but a reduction in the enantioselectivity of the reaction. Other aromatic electrophiles were also considered (**74ah-74ak**), where within this scope the naphthyl species **3ai** performed similar to the model system. As heterocycles are ubiquitous in medicinal chemistry, several sulfonimidamides containing these were synthesised, however, sulfonimidamides **74ai** and **74aj** saw a slower rate of reaction paired with a decrease in the enantiomeric ratio. However, when the hetereocycle's nitrogen was in a more sterically encumbering environment, such as with substrate **74ak**, an increase in reaction rate and optical activity was observed. It was satisfying to observe that non-aromatic electrophiles could also be employed in the reaction (**74al-74ao**), in particular an allyl electrophile performed excellently (**74al**), and even when the sterics of the system were increased (**74am**), the rate of reaction decreased but good enantiomeric ratio was maintained. These results are rather interesting as they allow a synthetic handle to be readily installed adjacent to the sulfur stereogenic centre of the sulfonimidamide. Finally, non $sp^2$-hybridised electrophiles were used, such as an alkyne (**74an**) working in the reaction, albeit with a drastic reduction in selectivity, owning to the linearity of the electrophile. Finally, the non-activated cyclopropane electrophile (**74ao**) shows a much slower reaction, however, a good level of enantioinduction was noted, which indicates that this reaction may be applicable to simple alkyl bromides given the correct catalyst selection.

One electrophile that produced anomalous results was *p*-nitrobenzyl bromide; this is best exemplified when using the singly-quaternised species **CAT-1** (**Scheme 3.15.a**). From this reaction

the isolated product (**74ap**) was observed to have an excellent enantiomeric ratio, however sulfinamide **78a** was also isolated in the course of the reaction. It was proposed that this sulfinamide was produced from the benzylic protons of sulfonimidamide **74ap** becoming sufficiently acidic to allow a deprotonation to occur. The anion generated can then undergo a β-elimination, generating the product **78a**. Intriguingly, this sequence provides the first example of a reductive cleavage for the sulfonimidamide S–N bond to produce a sulfinamide. Therefore, it was hypothesised that the high enantiomeric ratio obtained for product **74ap** was in part due to a phase-transfer catalysed kinetic resolution.




**Scheme 3.15.** Investigation into the kinetic resolution of sulfonimidamides (**a**) Using *p*-nitrobenzyl bromide as the electrophile. (**b**) Elimination of the *p*-nitrobenzyl group in the presence of catalyst and base. Reactions were at a concentration of 0.1 M, and conversions were determined by analysis of the crude $^{1}$H NMR spectra. The stereochemistry at the sulfur has been ambiguously assigned. [a] The enantiomeric ratio was not determined.

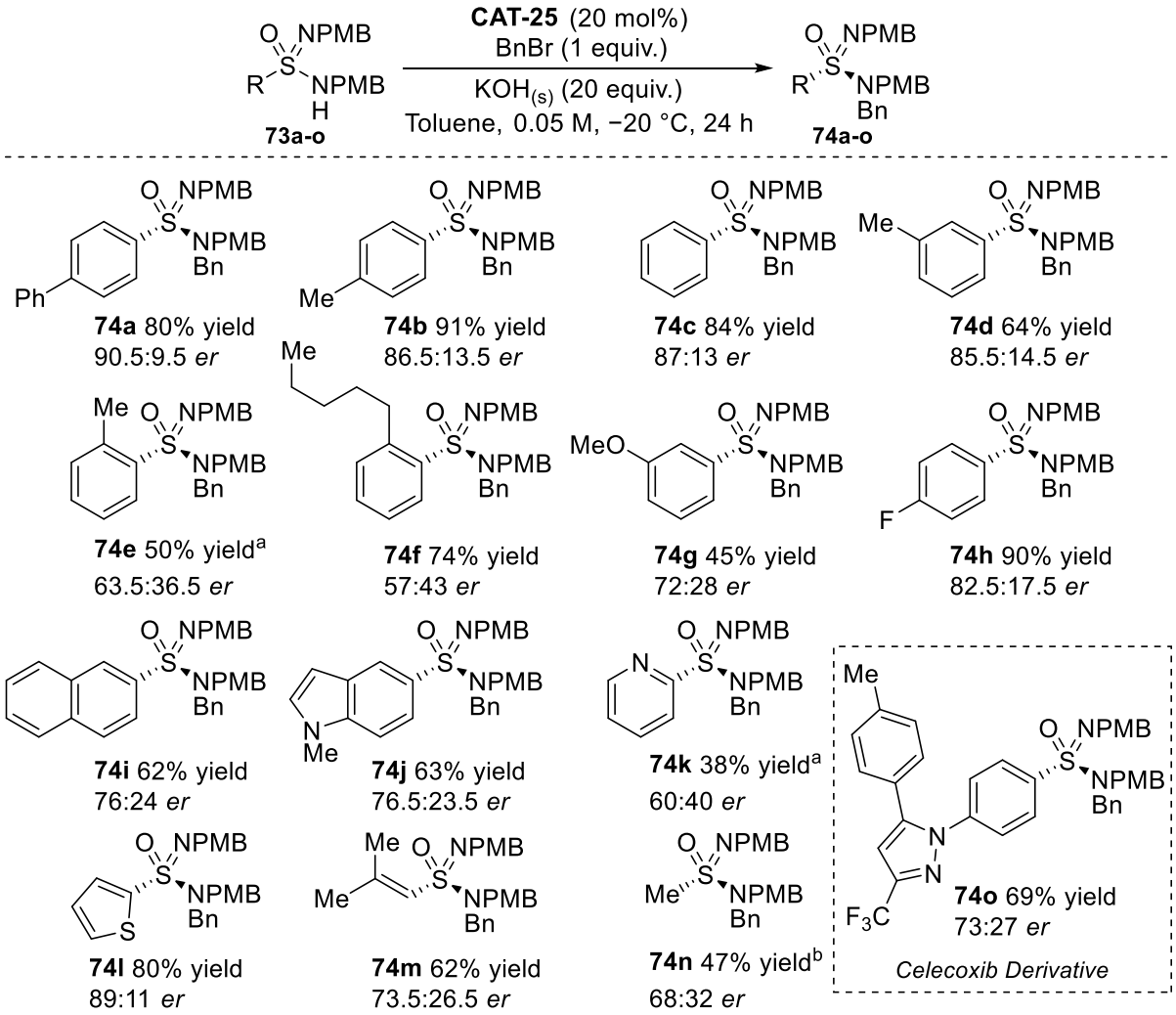
In order to test if a kinetic resolution was in operation during this sequence, a racemic mixture of sulfonimidamide **74ap** was obtained and resubjected to the reaction conditions in the absence of electrophile (**Scheme 3.15.b**). The starting material was recovered in high enantiomeric excess, and sulfinamide **78a**, was also obtained with enantioenrichment. From this a selectivity factor could be determined of $s$ = 5.2, proving the operation of a kinetic resolution. Any attempts to improve this kinetic resolution by applying alternative catalysts did not come to fruition, and of particular note, doubly-quaternised catalyst had low turnover frequencies (see section **6.4.4.**).

Overall, multiple electrophiles were well tolerated in the reaction to produce enantioenriched sulfonimidamides. Higher enantiomeric ratios could be observed when a secondary kinetic resolution was also in operation, however this is at the expense of the yield, so currently remains an academic curiosity, rather than a synthetically useful tool.

### 3.5.2. Sulfonimidamide Scope

Currently enantioenriched sulfonimidamides are heavily limited to those which have simple aryl backbones, and in particular *p*-tolyl. Hence, to expand the availability of these sulfonimidamides a diverse range of configurationally labile sulfonimidamides were applied to the reaction (**Table 3.10.**)

**Table 3.10.** Sulfonimidamide scope for the enantioselective synthesis of sulfonimidamides.




**Conditions**: The reactions were conducted on a 0.05 mmol scale with resoect to **73.** [a] Reaction time 48 h.[b] Reaction time 30 h.

As is evident from the presented scope, simple aryl backbones (**74b**-**74d**) gave marginally lower enantiomeric ratios compared to the model substrate (**74a**), indicating the substrate specificity of the system. It was observed that an *ortho*-methyl substituent dramatically decreased the enantioselectivity and yield (**3e**), however this decrease in yield was hypothesised to be from reduced solubility of the substrate. Hence an alternative *ortho*-substituted system was synthesised, which was predicted to have an increased solubility profile in toluene (**74f**), where this now increased the yield whilst providing a similar level of enantioinduction. The electronics of the sulfonimidamide were also examined as shown by sulfonimidamides **74g** and **74h**, which performed moderately well. Due to the success of the initial substate (**74a**) an alternative extended *π-system* was examined (**74i**), however, this naphthyl system caused a drastic decrease in the enantiomeric ratio. It is important to emphasise that the number of enantioenriched sulfonimidamides in the literature is extremely limited, hence optically active sulfonimidamides incorporating heterocyclic backbones are virtually non-existent. Therefore, it is quite a feat that substrate **74j** and **74k** could be synthesised with some level of enantioinduction, as well as **74l** performing near identically to the model system despite the drastically different topology. It is also worth noting that the indole substrate **74j** performs near identically to the naphthyl **74i**, and considering the similarities it can be concluded that the nitrogen heteroatom of the indole is not having a detrimental impact. Furthermore, non-aromatic backbones could be applied in this sequence such as with sulfonimidamide **74m**, where such vinyl substrates have the potential to function as chiral chemical probes. A methyl derived substrate was also used (**74n**), the fact that this shows some enantioinduction despite the methyl's small size indicates that with the correct catalyst selection this methodology could be applied to alkyl sulfonimidamides. Finally, to show the potential application for medicinal chemistry, the reaction was applied to a drug molecule derivative, Celecoxib, showing a moderate level of enantioinduction (**74o**).

Overall, analysis of the sulfonimidamide scope shows the catalyst to be rather substrate dependent. Attempts to further re-optimise specific substrates (**74i** and **74l**), carried out with Dr. Damien Dewez, proved challenging (see section **6.4.5.**), likely due to the subtle interplay of interactions which are present between the substrates and catalyst. Although this procedure proved challenging, this still provides the most accomplished methodology to access a diverse range of enantioenriched sulfonimidamides. The developed method also provides a good proof-of-concept for the strategy, in that multiple configurationally labile sulfonimidamides can be used as substrates in asymmetric catalysis.

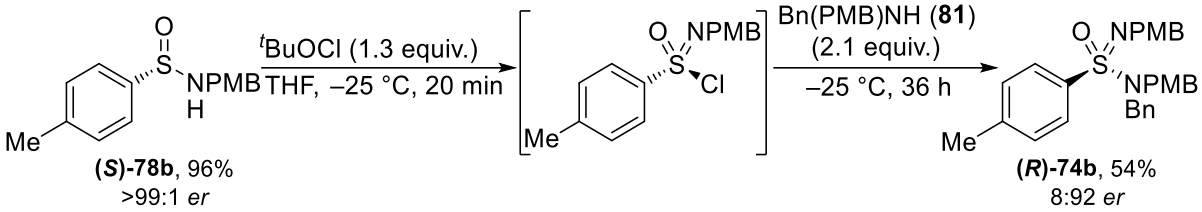
## 3.6. Sulfonimidamide Configuration

During the course of the scope many of the resulting sulfonimidamide products were found not to be crystalline, therefore the use of X-ray crystallography to assign the absolute configuration of the sulfur stereocentre was not possible. To overcome this limitation, it was decided to generate an authentic sample *via* a series of known stereoselective transformations.

### 3.6.1. Determining the Absolute Configuration

To determine the absolute configuration, the previously obtained, optically pure, sulfinamide **78b**, was subjected to a chlorination reaction (**Scheme 3.16.**), which has previously been reported to generate a sulfonimidoyl chloride with retention of stereochemistry.[69] The sulfonimidoyl chloride generated was directly reacted with the appropriate amine (**81**) *in situ*, which generated sulfonimidamide (***R***)-**74b** with overall inversion of stereochemistry.[69,201,88] During the course of this reaction it was found that it was essential to maintain the cryogenic temperature for an extended period of time, otherwise significant racemisation of the sulfonimidoyl chloride was observed. Finally, by comparison of the optical rotation and HPLC-trace of sulfonimidamide (***R***)-**74a** with that

obtained during the reaction scoping study, it could be concluded the reaction produces the (*S*)-configuration. Hence, all sulfonimidamides in the asymmetric alkylation were assigned the (*S*)-configuration by analogy.



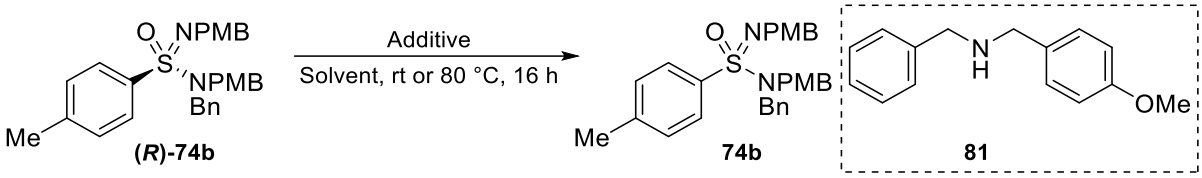

**Scheme 3.16.** Reaction sequence used to synthesise an authentic sample of **74b**, using known stereoselective reactions.

During this synthetic sequence several notable points were made, firstly, the enantiomeric ratio obtained (8:92 *er*) is comparable with several of the results from the sulfonimidamide scope. Therefore, this shows that our methodology is at least competitive with the current routes to synthesis enantioenriched sulfonimidamides and provides a more diverse range of sulfonimidamide backbones, producing the opposite enantiomer to that usually found in the literature.

### 3.6.2. Configurational Stress Tests

From the few enantioenriched sulfonimidamides that have been synthesised in the literature, a handful of reports have shown their ability to epimerise.[202,14b] Although these reports appear to be highly substrate specific, it was decided to gain a greater understanding of the configurational stability of the sulfonimidamides presented here. This investigation was achieved by subjecting sulfonimidamide **(*R*)-74b** to a range of conditions and measuring the change in enantiomeric ratio (**Table 3.11.**).

**Table 3.11. Attempts to racemise (*R*)-74a under various conditions.**




| Entry | Solvent | Temperature (°C) | Additive | *es* (%) |
|---|---|---|---|---|
| 1 | Toluene | 23 | N/A | 100 |
| 2 | Toluene | 80 | N/A | 100 |
| 3 | MeCN | 23 | N/A | 100 |
| 4 | MeCN | 80 | N/A | 100 |
| 5 | Ethanol | 23 | N/A | 100 |
| 6 | Ethanol | 80 | N/A | 100 |
| 7 | THF | 23 | N/A | 100 |
| 8 | THF | 80 | N/A | 100 |
| 9 | THF | 23 | **81** (1.1 equiv.) | 100 |
| 10 | THF | 80 | **81** (1.1 equiv.) | 100 |
| 11 | THF | 23 | $NH_3$ (xs.) | 100 |
| 12 | THF | 80 | $NH_3$ (xs.) | 100 |

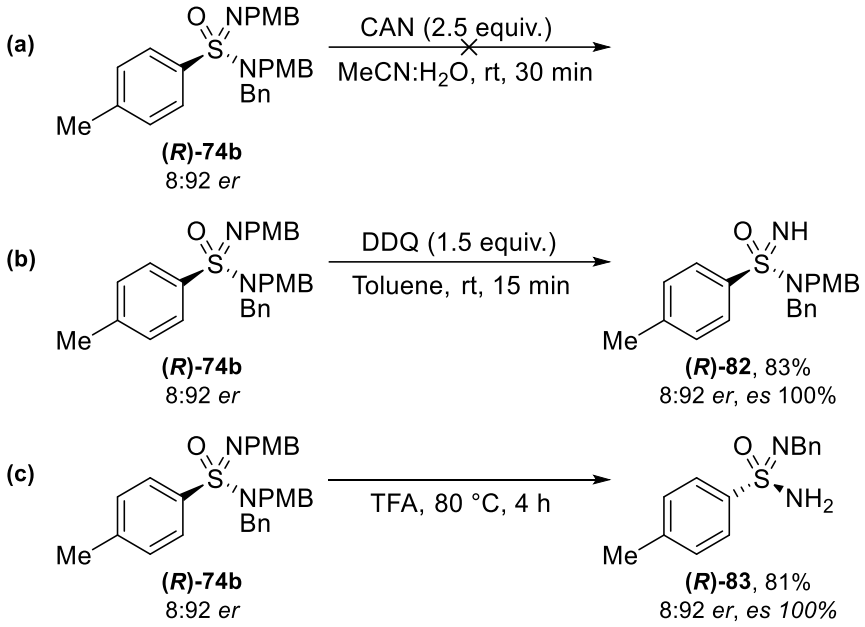
Sulfonimidamide (*ca.* 25 mg), was dissolved in solvent (0.5 mL) with the corresponding additive. *es* refers to the enantiospecificity of the process.

From these results it is evident that sulfonimidamide **74b** is configurationally stable. In particular, in a range of solvents, varying from polar protic to apolar, saw no epimerisation at the sulfur centre, even at elevated temperatures (entries 1-8). Furthermore, sulfonimidamide **(*R*)-74b** did not racemise in the presence of nucleophilic nitrogen sources such as amine **81** or ammonia. Overall, this indicates that the sulfonimidamides synthesised here are configurationally stable.

## 3.7. Sulfonimidamide Deprotection

During the course of the reaction design, the PMB groups were selected on the sulfonimidamide nitrogen atoms, so that they could effectively be removed in a later sequence, allowing access to more versatile sulfonimidamides. Multiple synthetic methods exist to remove ethereal PMB groups,[203] with the most popular being the use of CAN or DDQ. Attempting to use CAN for the deprotection of sulfonimidamide **74b** resulted in significant decomposition (**Scheme 3.17.a.**). This decomposition

is ascribed to the presence of the benzyl group which can create a reactive site under the reaction conditions.[204] Fortuitously, the use of DDQ allowed rapid and selective deprotection of the imidic PMB group (**Scheme 3.17.b**), with no effect on the stereogenic sulfur centre in sulfonimidamide **82**.




**Scheme 3.17.** Deprotection strategies for the removal of the sulfonimidamide PMB groups.

Simply using more equivalents of DDQ and extending the reaction time with sulfonimidamide **74b**, led to a complex mixture of products, rather than the desired mono-substituted product (**83**). However, it was found that both PMB groups could be removed in a single step with the use of TFA at elevated temperatures,[205] although the correct selection of time and temperature was paramount for the success of this reaction. Additionally, employing these conditions showed that the sulfur stereocentre of sulfonimidamide **74b** & **83** were resistant to epimerisation under strongly acidic conditions.

Overall, these deprotection strategies allow access to enantioenriched di- and mono- substituted sulfonimidamides (*e.g.* **82** and **83**), thus showcasing the synthetic utility of the methodology developed, and further expanding the range of optically active sulfonimidamides that are known.

## 3.8. Summary and Outlook

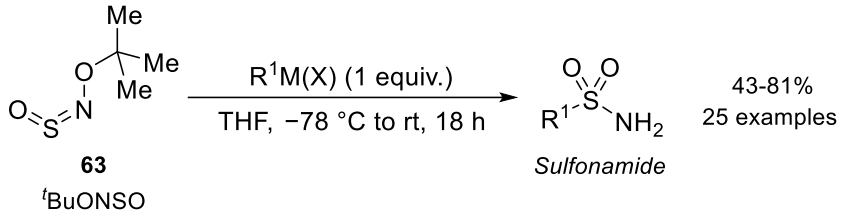
Overall, employing this organocatalytic alkylation of a sulfonimidamide has allowed a diverse range of enantioenriched sulfonimidamides to be synthesised, which were not readily accessible by previous literature methods. Furthermore, the subsequent deprotection of these configurationally stable sulfonimidamides allows an even more varied library of optically active di- and mono- substituted species to be accessed. However, it is important to realise that the current asymmetric alkylation appears to be somewhat substrate specific.

Further attempts to improve the enantioselective organocatalytic alkylation could potentially look at different catalyst motifs.[206] For example, there have been a variety of innovative variations based on the cinchona-alkaloid core, as well as new complex scaffolds developed in recent years, which may prove superior. However, a limitation in this field appears to be appropriate stereochemical models to guide catalyst design. It can be expected that this will be improved with the increasing amount of mechanistic work conducted in this area.[198b,199,196] Regardless, it appears that it will be a significant challenge to construct a clear structure-activity relationship for the enantioselectivite synthesis of sulfonimidamides *via* phase-transfer catalysis. This is in part due to the balance of subtle interactions and physical parameters that dominate this form of catalysis. Therefore, it is important to emphasise the underpinning concept that has allowed this reaction to be developed. These configurationally labile sulfonimidamides used are a privileged class of compound which should be suitable for a multitude of asymmetric catalysed processes. It should be possible to use either a dynamic kinetic resolution of the neutral sulfonimidamides or a desymmetrisation of their corresponding ions. Hence, it can be envisioned that this fundamental principle will be valuable to the further asymmetric synthesis of aza-sulfur compounds.

# Chapter 4 – Late-Stage Functionalisation of Sulfonamides *via* Photocatalysis

## 4.1. Introduction

Up to this point new methodologies for the synthesis of sulfoximines and sulfonimidamides, both racemic and enantioenriched for the later, have been discussed in detail. In particular the success of employing *N*-sulfinylamines in achieving these feats has been accentuated. A continuation for the use of *N*-sulfinylamines as a linchpin was also mentioned (**Scheme 4.1.**),[168] providing the convenient synthesis of primary sulfonamides from organometallic reagents and $^{t}$BuONSO.



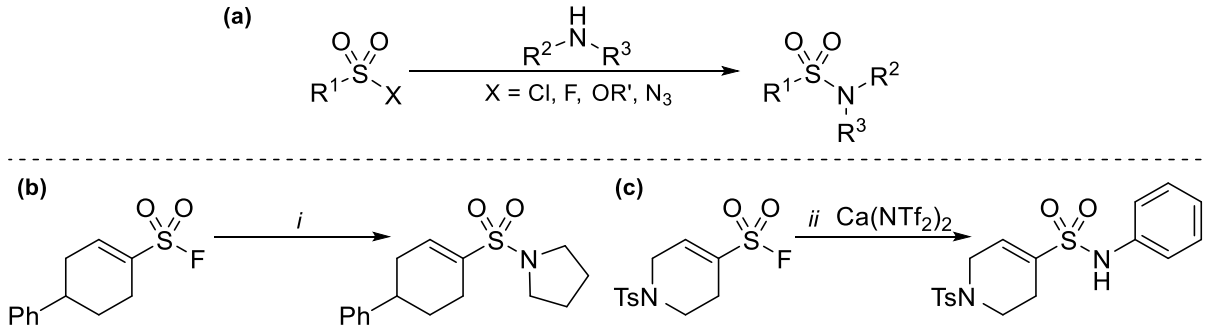

**Scheme 4.1.** The synthesis of primary sulfonamides from the reagent $^{t}$BuONSO

When considering the sulfonamide functional group, it is evident that they are a well-established class of compound, spanning a broad spectrum of applications. Therefore, significant efforts have been devoted to their synthesis. Although sulfonamides have been known for nearly 100 years,[207] novel methods to generate this moiety are still coming to fruition, as well as new functionalisation methods and applications.

### 4.1.1. Sulfonamide Synthesis

To date, the synthesis of sulfonamides has been heavily reliant on the same traditional strategy; by combining an activated sulfonyl component with an amine, often in the presence of base (**Scheme 4.2.**). Frequently, the electrophile employed is a sulfonyl chloride species (X = Cl), and the

nucleophile aryl or alkyl amines. In order to generate primary sulfonamides ($R^2 = R^3 = H$), ammonia must be used, either directly or in solution. A variety of reports have improved this sequence,[208] in particular by developing procedures which are scalable and environmentally benign,[209] as well as methods suitable for flow,[210] allowing this reaction to be applicable in an industrial setting.

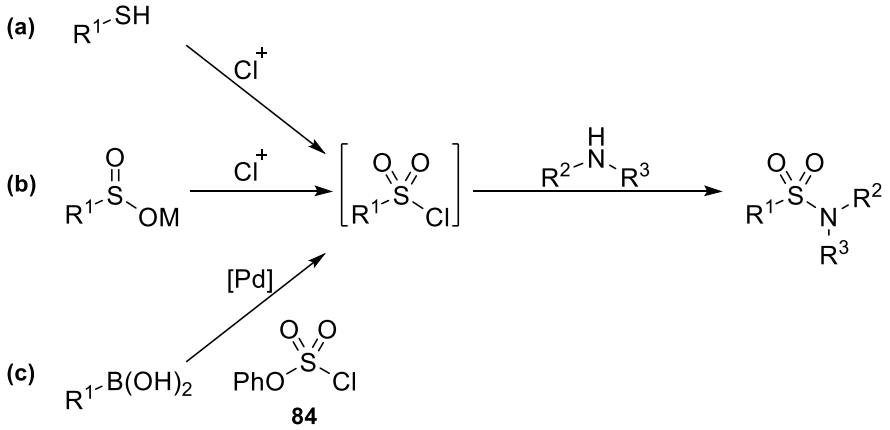



**Scheme 4.2.** The synthesis of sulfonamides using activated sulfonyl compounds as starting materials. **(a)** General method used with a range of activated sulfonyl compounds. **(b)** Use of a sulfonyl fluoride, conditions *i*: pyrrolidine (5 equiv.), MeCN, 70 °C, 3 h. **(c)** Use of a sulfonyl fluoride, conditions *ii*: Aniline (2.2 equiv.), $Ca(NTf_2)_2$ (2 equiv.), $^t$amylOH, 60 °C, 16 h.

A significant limitation of these traditional methods is the dependency on using sulfonyl chlorides, which are notoriously unsuitable due to their inherent instability and lack of availability. Therefore, recent efforts have examined the use of the more stable analogues, sulfonyl fluorides (X = F, **Scheme 4.2.a.**),[211] which have been able to demonstrate a greater functional tolerance in these reactions when compared to the chlorides (exemplified by the reactions in **Scheme 4.2.b** & **Scheme 4.2.c**).[212]

Sulfonamide synthesis is still a vibrant area of research and has been reviewed in great detail.[100,213,93] Several of the key strategies and modern methodologies will be highlighted here. As a significant issue with the traditional route is the limited availability of sulfonyl chlorides, efforts have been made to circumvent this by generating the chlorides *in situ* from more available precursors. For example, it is possible to combine thiols with an electrophilic chlorine source and subsequently displace with an amine (**Scheme 4.3.a.**). Typically, chlorine gas has been employed in this

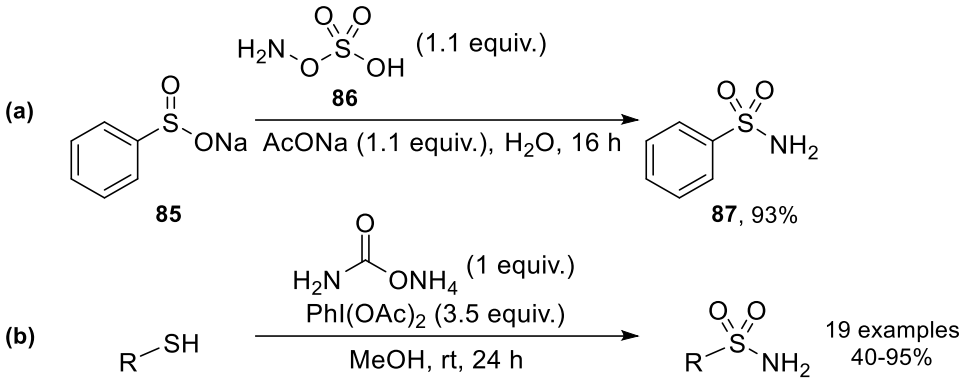
reaction,[214] however, methods using milder and more versatile oxidising agents have been explored, including sulfuryl chloride with metal nitrate,[215] sodium hypochlorite,[216] hydrogen peroxide with thionyl chloride,[217] and NCS.[218] As thiols are considered difficult to handle and malodorous, their use is often undesirable. Hence, oxidation from sulfinate salts to sulfonyl chlorides is often exploited (**Scheme 4.3.b.**). Again, a range of oxidants have been employed in this sequence, including sulfuryl chloride,[219] NCS,[220] and DCDMH.[221] A significant advantage of this methods is the diverse range of methods available to generate sulfinate salts,[222] including *via* transition metal catalysis.[223]




**Scheme 4.3.** Generation of sulfonyl chlorides *in situ* to synthesise sulfonamides. (**a**) Application of thiols *via* electrophilic chlorination. (**b**) Application of sulfinate salts *via* electrophilic chlorination. (**c**) Application of boronic esters in a palladium mediated cross-coupling.

Finally, an alternative strategy to generate sulfonyl chlorides *in situ* has emerged, using a pivotal chlorosulfate reagent (**84**) in a palladium catalysed cross-coupling with boronic acids (**Scheme 4.3.c.**).[224] This allows a diverse range of sulfonamides to be synthesised due to the increased functional group tolerance.

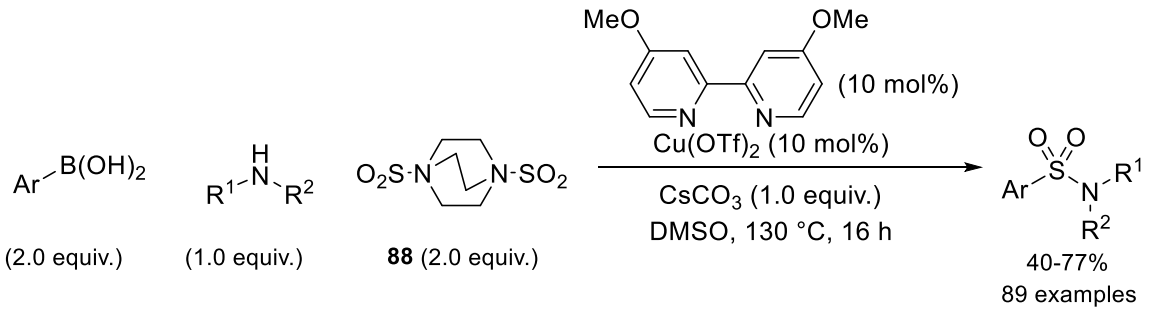
The drawback of these methods involves generating a reactive intermediate *in situ*. Therefore, umpolung strategies have also been developed in which the nitrogen component is now used as an electrophile.[225] For example, the use of hydroxylamine-*O*-sulfonic acid (**85**) in combination with a sulfinate salt (**86**, **Scheme 4.4.a.**).[225a] This provides a convenient method to access primary sulfonamides, and unsurprisingly this reaction has seen uptake in a variety of settings.




**Scheme 4.4.** Examples that utilise an umpolung strategy by employing an electrophilic nitrogen source to synthesise primary sulfonamides. (**a**) Reaction with sulfinate starting material. (**b**) Reaction with thiol starting material.

Recently, thiols have also been reacted with an electrophilic source of nitrogen to access primary sulfonamides (**Scheme 4.4.b.**).[110] This uses ammonium carbamate with a hypervalent iodine reagent to generate a nitrene source *in situ,* which allows the reaction to proceed to sulfonamides in a convenient one-pot protocol.

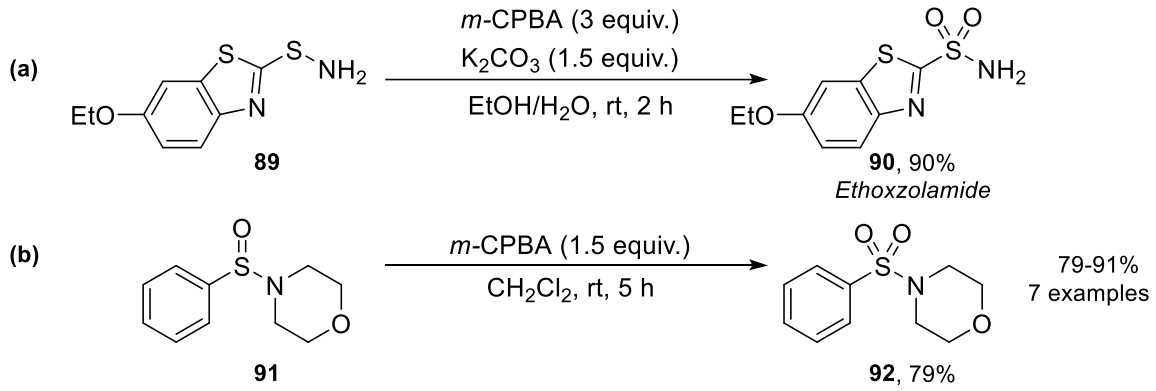
The two procedures discussed show that it is beneficial to perform reactions which do not require multi-step sequences. Therefore, a plethora of reports have focused their attention on developing methodologies to perform direct couplings,[226] and in particular using feedstock chemicals to access a broad range of sulfonamides.[227] Several methodologies have become popular in this field, including iodine mediated processes.[213a,228] However, arguably one of the most synthetically useful procedures is the copper-catalysed three-component synthesis of sulfonamides (**Scheme 4.5.**).[229] This process makes use of the $SO_2$ surrogate DABSO (**88**) with boronic acids and a diverse array of amines.




**Scheme 4.5.** Copper-catalysed synthesis of sulfonamides from readily available precursors.

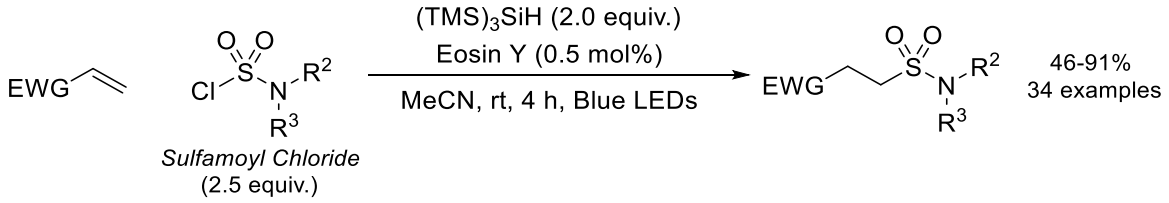
Another important direct coupling procedure is the electrochemical synthesis of sulfonamides from thiols and amines.[230] Electrochemistry is still somewhat limited for lab-based applications, but regardless, these studies show that there are multiple direct coupling strategies available to access an assortment of sulfonamides.

Although the current methods presented provide a summary of the most common methods used to synthesise sulfonamides, several miscellaneous strategies exist. For example, the direct oxidation of aza-sulfur compounds up to the S(VI) sulfonamides; in this context, sulfenamides (**89**)[231] and sulfinamides (**91**)[232] have both been used (**Scheme 4.6.**). Although this procedure is operationally simple, it is limited due to the lack of synthetic routes to the starting materials.




**Scheme 4.6.** Oxidation strategy to access sulfonamides. (**a**) From a sulfenamide. (**b**) From a sulfinamide.

Finally, an approach that is currently underdeveloped is the use of sulfamoyl precursors to generate sulfonamides.[233] A noteworthy example of this is a recent report on the hydrosulfamoylation of a sulfamoyl chloride mediated by tris(trimethylsilyl)silane ( **Scheme 4.7.**).[233h] This is able to take simple sulfamoyl chlorides and combine these with alkenes containing an electron-withdrawing group. An example of interest generated the free sulfonamide ($R^1 = R^2 = H$), in 46% yield.

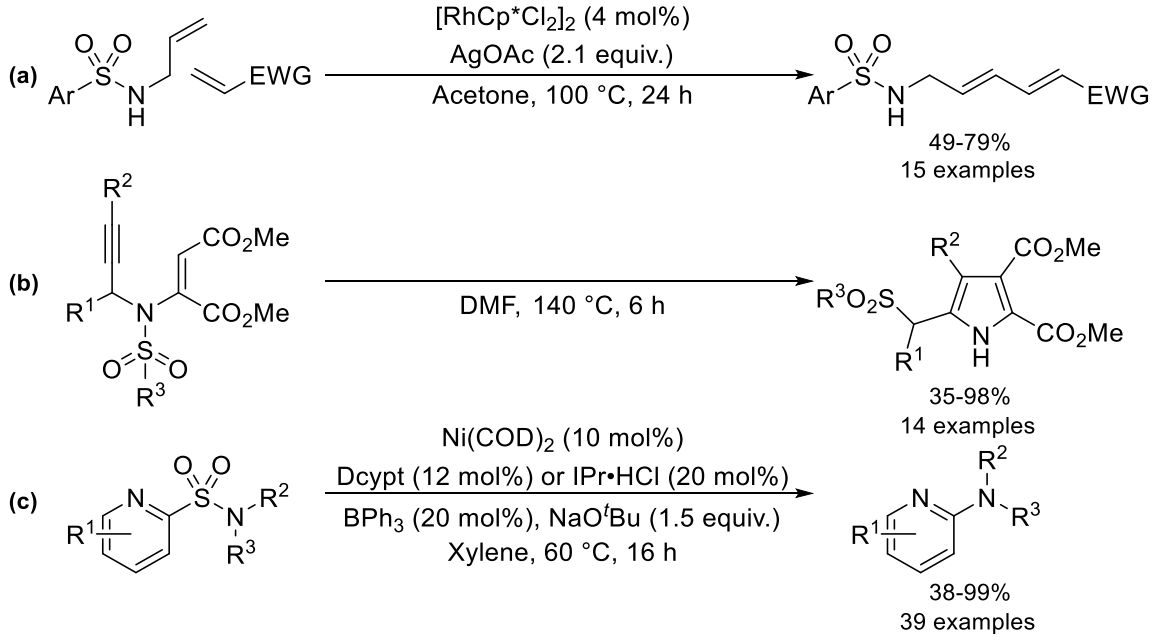



**Scheme 4.7.** Silyl-mediated hydrosulfamoylation of sulfamoyl chlorides with electron-withdrawing alkenes.

Overall, the traditional route of a nucleophilic displacement with sulfonyl chlorides to access sulfonamides is still the most popular strategy. However, a multitude of other routes are present, including several new innovative methodologies, which have diversified the available sulfonamides.

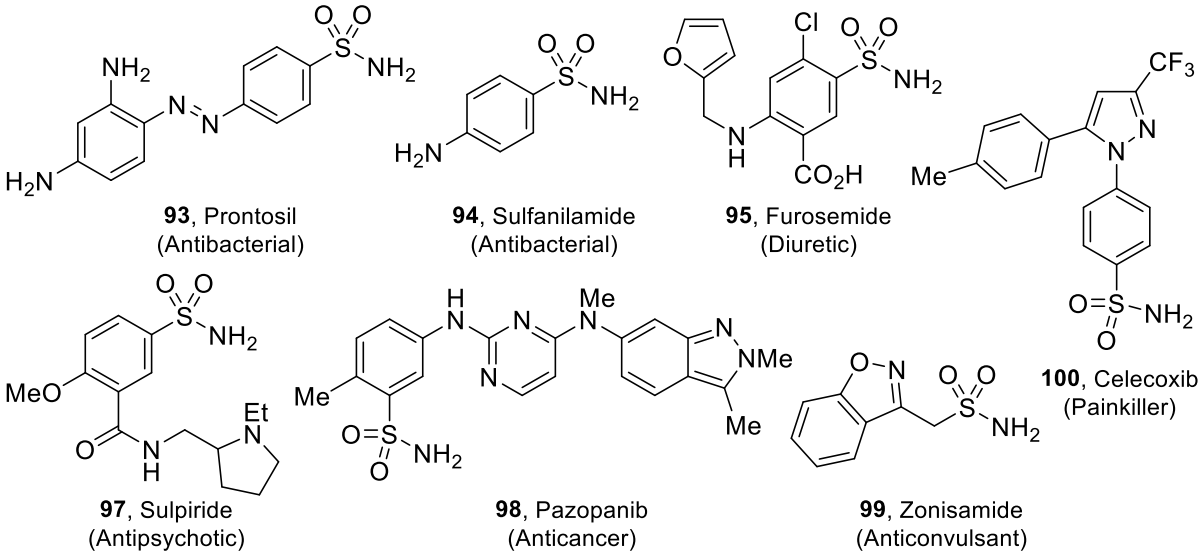
### 4.1.2. Sulfonamide Application

With many available protocols for sulfonamide synthesis, it is unsurprising that they have been used in a broad range of applications. One of the most prominent applications is as a protecting group for amines.[234] However, broader applications exist in synthesis, including as a directing group for C–H activation,[235] in rearrangement reactions,[236] and recently as an electrophilic component in a nickel-catalysed desulfitative C–N coupling.[237] (see **Scheme 4.8.** for examples).




**Scheme 4.8.** Application of sulfonamides in synthesis. (a) A Rhodium catalysed C–H activation of an alkene. (b) A Sulfonamide rearrangement to access complex hetereocycles. (c) Nickel-catalysed reaction of sulfonamides to amino pyridines.

Although the role sulfonamides have played in synthesis is considerable, they have had a much more prominent impact in a biological setting (**Scheme 4.9.**), and this has been reviewed in detail.[100,238a,13,238b,93] Currently, sulfonamides represent one of the largest biologically relevant compound libraries, which is evident from there being over 100 FDA approved drugs containing this functional group.[238b] The first sulfonamide drug dates back to the 1930's with Prontosil (**93**),[207] which coincidently was one of the first antibacterials developed. This discovery has led to a range of sulfonamide antibacterials being developed, often based on the sulfanilamide core (**94**).[239] 'Sulfa Drugs' still retain popularity today. When examining the top 200 drugs by retail sales for 2019,[240] 33% contain a sulfur atom, featuring eight sulfonamides. Therefore, it is unsurprising that sulfonamide drugs span a diverse range of disease therapies, including but not limited to; diuretics (**95**),[241] antipsychotics (**97**),[242] anticancer treatments (**98**),[243] anticonvulsants (**99**),[244] and anti-inflammatories (**100**).[245] From these representative examples, it is clear that primary sulfonamides are a recurring feature. Substituted sulfonamide drugs are also known, where varying substituents can lead to efficient structure-activity relationships being developed,[246] hence allowing improved drugs to be developed.



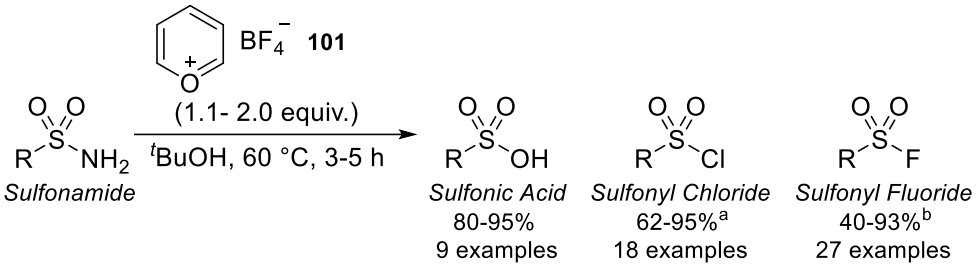

**Scheme 4.9.** Representatives of sulfonamide-based drugs, spanning multiple disease therapies.

The success of sulfonamides as a pharmacophore can be ascribed to a variety of features, including their stability, hydrolytic solubility, and multiple hydrogen bond donor and acceptor sites, allowing favourable interactions with amino acid residues and metal ions. Therefore, with the detailed knowledge of biological activity for a variety of sulfonamides and the ease of their synthesis, it is logical that they are a common functional group in drug discovery programmes.

### 4.1.3. Late-Stage Functionalisation of Sulfonamides

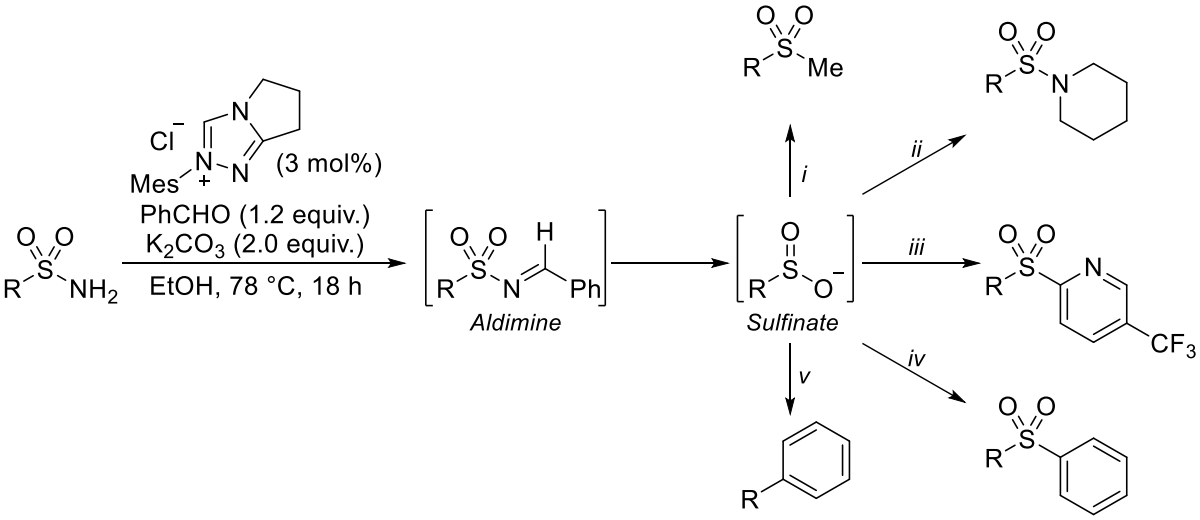
Sulfonamides are often built into drugs early on in their synthesis, and although this approach is appropriate for the synthesis of a specific drug molecules, it does not readily lend itself to drug discovery programmes. In particular, it limits developing practical structure-activity relationships and inhibits the diversification of chemical space. Therefore, late-stage functionalisation (LSF) methods of sulfonamides are desirable,[247] where such a strategy allows one to take a common functional group and convert it to a whole host of interesting moieties, hence increasing a drugs chemical complexity.

Seminal work by Cornella *et al.* has begun to change how primary sulfonamides are viewed by showing them to be useful synthetic handles (**Scheme 4.10.**).[248] A complex array of sulfonamides, including select drug molecules, were activated by a pyrylium salt (**101**) to give multiple S(VI) products. For example, sulfonyl chloride could be generated in the presence of magnesium chloride, as well as fluorides with the addition of potassium fluoride.[113c] Therefore, this reaction is able to generate electrophilic sulfonyl compounds which themselves can act as useful intermediates, for example by further reaction with amines to overall perform a formal transamination reaction.




**Scheme 4.10.** Activation of a sulfonamide with a pyrylium salt, to access sulfonic acids, sulfonyl chlorides and sulfonyl fluorides. [a] In the presence of $MgCl_2$ (2.0 equiv.), [b] Reactions run in MeCN and in the presence of $MgCl_2$ (1.5 equiv.) and KF (6.0 equiv.).

A related development in sulfonamide late-stage functionalisation has also been made by Merck (**Scheme 4.11.**).[113b] In this procedure, sulfonamides were combined with aldehydes to generate aldimines *in situ*, and the S–N bond was then reductively cleaved *via* NHC-catalysis under basic condition, providing access to the sulfinate anions. The sulfinate anion is then a useful synthon, due to the wealth of chemistries that are accessible with it. For example, Celecoxib (**100**) was subjected to this reaction, showing that the sulfonamide could be transformed into a variety of alternative functional groups (**Scheme 4.11.** conditions *i-v*).




**Scheme 4.11.** Late-stage functionalisation of a sulfonamide *via* NHC catalysis to generate a sulfinate. The sulfinate is further diversified under a variety of conditions when R = Celecoxib (**100**). Reactions: *i* Oxidative amination. *ii* Oxidative amination with an amine and iodine. *iii* $S_NAr$ procedure with a 2-chloro-pyridine. *iv* Palladium/Xantphos cross-coupling to a sulfone with phenyl iodide. *v.* Palladium/XPhos-catalysed desulfinylative cross-coupling with phenyl triflate.

Further developments of this reaction from Merck have shown its applicability to radiolabelling.[249] Additionally, a late stage functionalisation has also been developed to work on secondary sulfonamides,[113a] now *via* a chemoselective alkylation and base-mediated deprotonation. Once again, this reaction can exploit the inherent nucleophilicity of a sulfinate anion to diversify complex drug molecules.

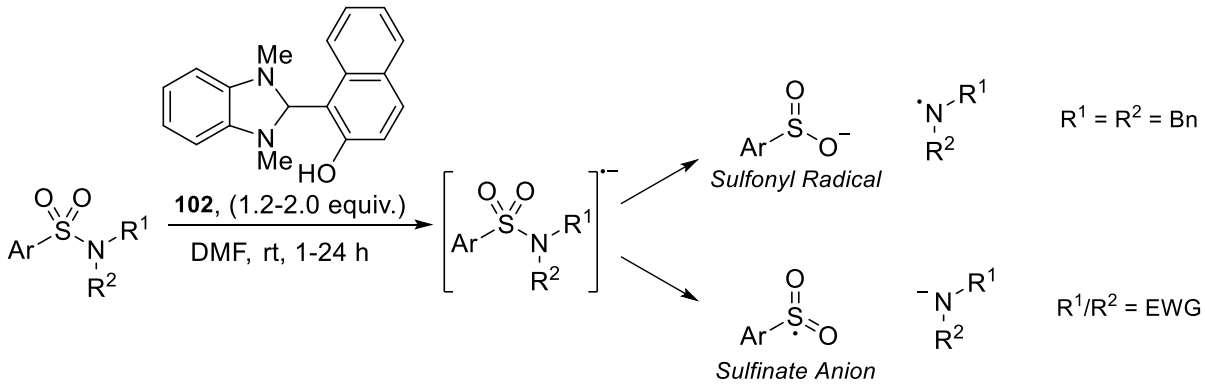
In conclusion, sulfonamide synthesis has become commonplace in organic chemistry. The ease of its synthesis has allowed the sulfonamide functional group to be installed into a range of drug molecules. However, the application of sulfonamides has been somewhat limited to their biological significance. Whereas recently, it has been demonstrated that these should in fact be seen as synthetic handles, with late-stage functionalisation reactions allowing access to new chemical space in medicinally relevant compounds.

## 4.2. Project Aims

The late-stage functionalisations of sulfonamides currently developed allows either generation of electrophilic S(VI) compounds or synthesis of a nucleophilic sulfinate anion. Although, this means a diverse array of chemistries can be accessed, it was speculated that developing a novel photocatalytic late-stage functionalisation would be highly complementary. Specifically, it would be able to exploit drastically different conditions, such as lower temperature and potentially a reduced catalyst loading. However, a more pronounced beneficial impact is the potential to access a sulfonyl radical, which would allow previously inaccessible reactivity modes to be possible.

During initiation of this project, it was noted that there are very few examples of reductively cleaving an S–N bond to generate sulfonyl radicals,[250] although this provides a route to access this reactive intermediate from a stable precursor. One of the major challenges associated with this is the low reduction potential of sulfonamides (*ca.* -2.3 V),[251] hence reductive cleavage often employs

relatively harsh conditions such as with the use of magnesium,[252] alkali metals,[253] titanium,[254] samarium iodide,[255] strong organic electron donors,[251,256] or electrochemically.[257] Although, several reports have shown that sulfonamides can be cleaved photochemically,[258] a conundrum occurs with the nature of the sulfonamide fragmentation (**Scheme 4.12.**).[258g] In this sequence, a photoinitiator (**102**) generates the radical anion, which can then fragment to produce the sulfinate anion or the sulfonyl radical. The path taken is highly dependent on the nature of the substituents on the sulfonamide, where it is proposed that at least one of the $R^1$ and $R^2$ substituents is an EWG to promote sulfonyl radical formation.

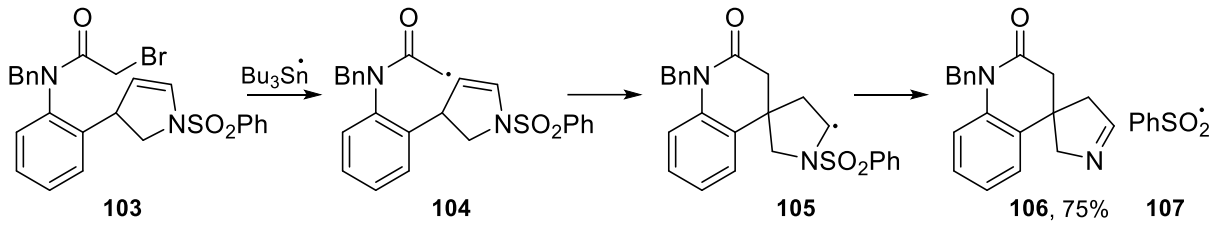



**Scheme 4.12.** Example of a photoinduced reductive cleavage of a sulfonamide S–N bond, showing the formation of two possible fragments.

The precarious nature of this fragmentation means that generation of the sulfonyl radical would be highly substrate-specific, with careful synthetic manipulations of the amino component being made to ensure the correct outcome. During the course of this project, such a process was reported,[259] in which the EWG is an amide, and the sulfonyl radical was predominantly intercepted by a radical-radical coupling with boronic acids to form aryl sulfones.

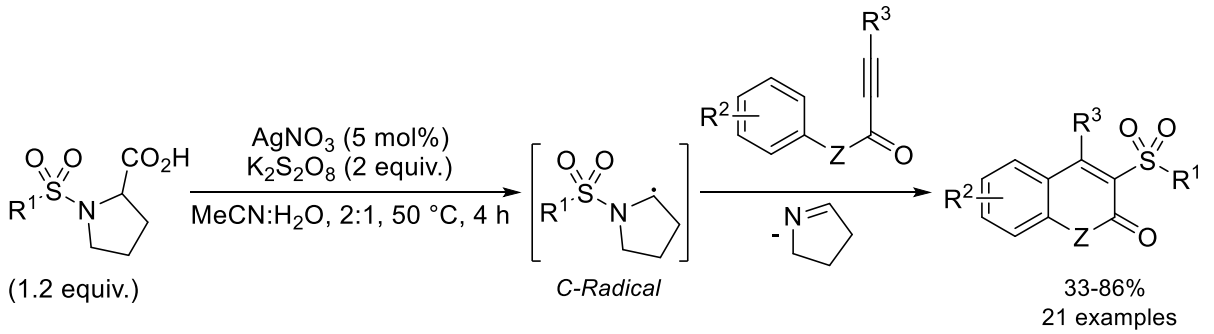
Instead, it was decided to examine methods which generate the radical in a more controlled and general fashion. Therefore, a handful of reports were noted which generate sulfonyl radicals *via* β-scission. Firstly, a few scenarios have applied this strategy in total synthesis using stoichiometric tin reductants (**Scheme 4.13.**).[260] In the sequence presented, an α-radical **105** is produced which

fragments to the imine **106** and sulfonyl radical **107**, however, the focus of this reaction was on the imine intermediates produced rather than the fate of the sulfonyl radical.




**Scheme 4.13.** Generation of a sulfonyl radical *via* a β-scission mechanism, initiated by tin.

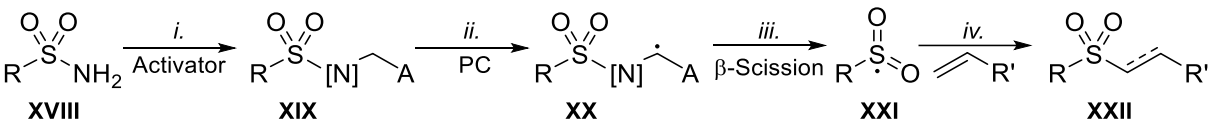
A singular example exists of utilising this β-scission procedure to make use of sulfonyl radical chemistry (**Scheme 4.14.**).[261] In this report, proline-derived sulfonamides are decarboxylated in a silver-mediated process to generate carbon-centred radical**.** This is then hypothesised to rapidly fragment and react with the alkyne, followed by a radical cascade process to product. Overall, this explicitly takes advantage of sulfonyl radical chemistry, albeit in the specific context of a cyclisation process.




**Scheme 4.14.** Application of a sulfonyl radical from a β-scission process, initiated by a silver-mediated decarboxylation.

This example provides a useful proof of concept that using a generic group on a sulfonamide can generate α-radicals. Unfortunately, this procedure is not applicable to late-stage functionalisation, due to the requirement to build specific proline-derived sulfonamides, rather than taking advantage of the ubiquitous primary sulfonamide moiety present in drug molecules. Therefore, several key objectives

were outlined for the development of a photocatalytic late-stage functionalisation of sulfonamides (**Scheme 4.15.**).




**Scheme 4.15.** Reaction design for the photocatalytic late-stage functionalisation of primary sulfonamides. *i.* Attachment of an activator to the sulfonamide. *ii.* Photocatalytic process to generate the α-radicals, with PC referring to the photocatalyst. *iii.* β-scission to the key sulfonyl radical. *iv.* Hydrosulfonylation to useful products.

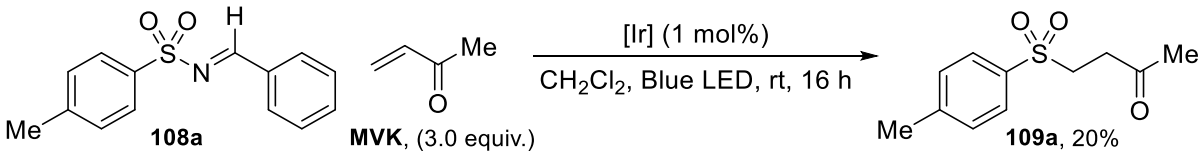
Firstly, it was suggested that we should be able to take a primary sulfonamide (**XVIII**) and easily add a suitable activator (A), preferentially *in situ* to species **XIX**. Then a choice of an appropriate photocatalytic cycle would allow straightforward generation of an α-radical (**XX**). This radical would then undergo a S–N bond fragmentation to the key sulfonyl radical (**XXI**), where multiple reaction pathways could be envisioned. Recently, several breakthroughs have been made using sulfonyl radicals in hydrosulfonylation reactions,[262] where such a reaction would provide a suitable demonstration of the applicability of this methodology.

## 4.3. Reaction Optimisation

When considering primary sulfonamides as starting materials, there are a few trivial reactions which can install a suitable activator under straightforward and mild conditions. In particular, an alkylation, or an aldehyde condensation to generate an aldimine, are deemed suitable. Due to the wealth of mild and practical literature procedures to generate aldimines,[263] these molecules were selected as the sulfonyl radical precursors. Furthermore, the generation of α-amino radicals from imines is well precedented,[264] often using a photocatalyst in a reductive quenching cycle, with the phenomenon of proton-coupled electron transfer (PCET) regularly applied to electrochemically activate the C=N bond. Many of the PCET mediated reactions employ Brønsted acid additives, however, a recent report from Rovis *et al.*[265] has shown that under basic conditions, imines are able to undergo a C–N

bond fragmentation to generate tertiary alkyl radicals, which are subsequently trapped by an alkene. Overall, there are a multitude of options to activate an imine photochemically, which provided a useful starting point.

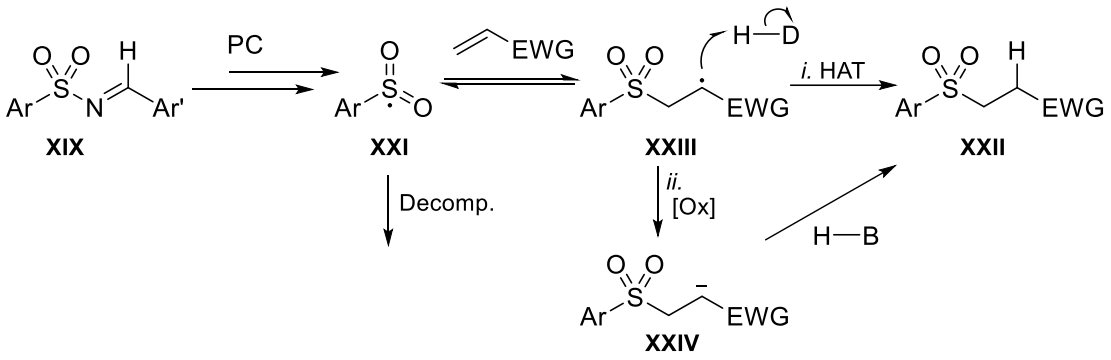
With this literature precedent in mind, initial reaction conditions were selected which aimed to react an aldimine (**108a**) with an electron deficient alkene (**MVK**), in the presence of an iridium photocatalyst and one blue LED lamp whilst cooling with a fan (**Scheme 4.16.** see section **6.5.1.3.** for images of the reaction set up). Pleasingly, this reaction produced the sulfone **109a** in a 20% isolated yield. It should be noted however, that no starting material was reisolated, and considerable decomposition was observed by $^1$H NMR spectroscopy of the crude reaction mixture. Furthermore, control reactions in the absence of catalyst and light provided recovered starting material, providing proof-of-concept for a photocatalysed process.




**Scheme 4.16.** Initial attempt towards the late-stage functionalisation of a sulfonamide, examining the ability of an aldimine to undergo an S–N cleavage to access a sulfonyl radical which is subsequently trapped by the alkene. Where [Ir] refers to $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ and at a concentration of 0.1 M.

Even without an understanding of the mechanism of radical generation, a potential pitfall of this reaction was identified. Previous experimental evidence has shown the addition of sulfonyl radicals to alkenes to be reversible (**Scheme 4.17.**).[266] To give the sulfone product from the alkyl radical intermediate **XXIII**, one potential pathway arises from an irreversible hydrogen atom transfer (HAT) (pathway *i.*). The inefficiency of this final step would cause the reverse process to regenerate the reactive sulfonyl radical, which subsequently decomposes, contributing to the low yield. Alternatively, if an oxidative quenching cycle of the photocatalyst is in operation (pathway *ii.*) then a key step may be a reduction and proton transfer, which would require an efficient redox cycle and acid to facilitate

the process. Regardless, it was determined that to improve the reaction and reduce the effect of decomposition, we would have to drive the sulfonyl radical equilibrium to sulfone.



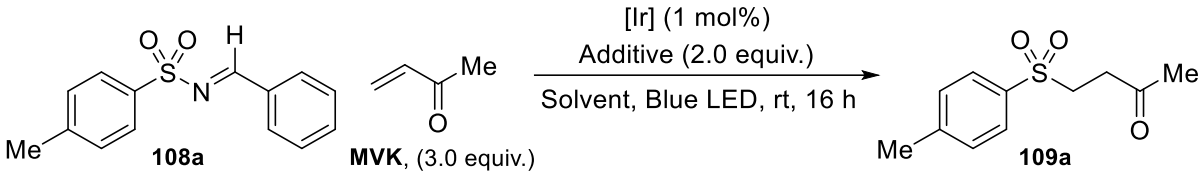

**Scheme 4.17.** Representation of the potential reaction mechanisms after sulfonyl radical generation. *i.* Represents a mechanism *via* a HAT, where D represents a generic donor molecule. *ii.* Represents a mechanism *via* a reductive quenching, where B represents a generic conjugate base.

Although at this stage several mechanistic possibilities were being considered, it was determined that use of an additive could have a profound effect on the outcome. For example, an alternative source of hydride could improve the final HAT step. Additionally, using an additive may directly influence the photoredox catalytic cycle, or contribute to a lower barrier PCET pathways.

### 4.3.1. Additive Effects

From the initial reaction trialled, it was assumed that no effective hydride source was present, due to the high bond-dissociation energy of $CH_2Cl_2$ (*ca.* 97 kcal $mol^{-1}$),[267] which would create a relatively ineffective process. In order to test this hypothesis, several other solvents were evaluated (**Table 4.1.**). Alternative solvents with similarly accessible hydrogen atoms (entries 2 & 3) performed marginally worse than the initial result (entry 1). However, when the reaction was conducted using acetonitrile as the solvent (entry 4), only trace amount of product was observed. Based on the initial hypothesis this result can be credited to acetonitrile having no available hydrogens for HAT or deprotonation, hence further depleting the yield.

**Table 4.1.** Investigation into alternative hydrogen atom sources.




| Entry | Solvent | Additive | Yield (%)[a] |
|---|---|---|---|
| 1 | $CH_2Cl_2$ | N/A | 20 |
| 2 | MeOH | N/A | 12 |
| 3 | THF | N/A | 14 |
| 4 | MeCN | N/A | 3 |
| 5 | $CH_2Cl_2$ | AcOH | 20 |
| 6 | MeCN | AcOH | 12 |

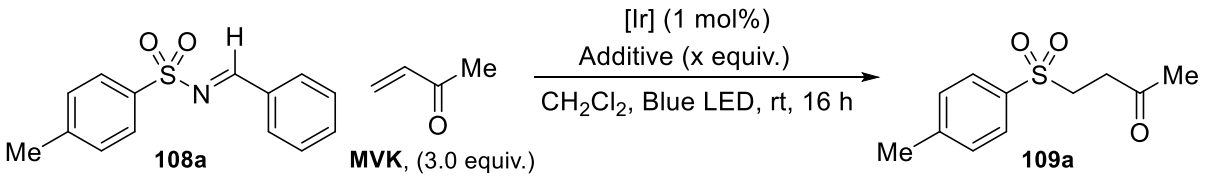
[a] Yields were determined from the $^1$H NMR spectra of the crude reaction mixture, with dimethyl sulfone as an internal standard. Where [Ir] refers to $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ and at a concentration of 0.1 M.

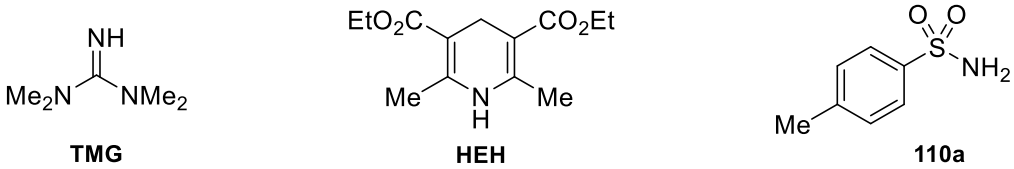
In an attempt to improve the reaction, acetic acid was used as an additive, however, when used in combination with $CH_2Cl_2$ as a solvent, no change was observed (entry 5), indicating that this is not acting as a Brønsted acid or an improved hydrogen atom donor (HAD). However, when acetic acid was used in combination with acetonitrile a 9% improvement in yield was observed (entry 6). Although, yields are lower, this result indicated that having some form of HAD in the reaction is important for the productive pathway.

In a further attempt to establish a PCET mechanism, alternative additives were screened, including those which could also perform an active role in the redox cycle (**Table 4.2.**). Once again, considerable decomposition was observed for all reactions. Initially, both inorganic (entry 1) and organic bases were tested (entries 2 & 4). Based on the work by Rovis *et al.*,[265] the idea behind this was to facilitate the C–H bond fragmentation to generate a sulfonyl radical, however, these bases reduced the yield and caused significant decomposition. Triethylamine and Hantszch ester have redox potentials of +0.69 V (vs. SCE in water),[268] +0.92 V (vs. SCE in MeCN).[269] respectively, hence they are commonly employed to reductively quench the excited state of the photocatalyst, and can play an important role in PCET with imines.[264] It was postulated that such additives may have an important

role in the reaction, however, introducing these into the system (entries 4-7) drastically reduced the yield, and sulfonamide **110a** was produced as a significant by-product. Performing the reaction with triethylamine in the absence of the iridium catalyst (entry 6) confirmed that this sulfonamide production was not a photocatalysed process.

**Table 4.2.** Screen of additives in the reaction.




| Entry | Additive | Equivalents (x) | Yield (%)[a] |
|---|---|---|---|
| 1 | $K_3PO_4$ | 1.2 | 6 |
| 2 | TMG | 1.2 | 15 |
| 3 | TMG | 0.1 | 16 |
| 4 | $N(Et)_3$ | 1.2 | 0 (35%, **110a**) |
| 5 | pyrrolidine | 1.2 | 0 (59%, **110a**) |
| 6[b] | $N(Et)_3$ | 1.2 | 0 (32%, **110a**) |
| 7 | HEH | 2.0 | 9 (43%, **110a**) |
| 8 | $(TMS)_3SiH$ | 2.0 | 40 |
| 9[c] | $(TMS)_3SiH$ | 2.0 | 38 |
| 10[d] | $(TMS)_3SiH$ | 2.0 | 37 |

[a] Yields were determined from the $^1H$ NMR spectra of the crude reaction mixture, with dimethyl sulfone as an internal standard. [b] Reaction was conducted in the absence of photocatalyst. [c] Reaction was conducted for 4 h. [d] Reaction was conducted in MeCN. Where [Ir] refers to $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ and at a concentration of 0.1 M.

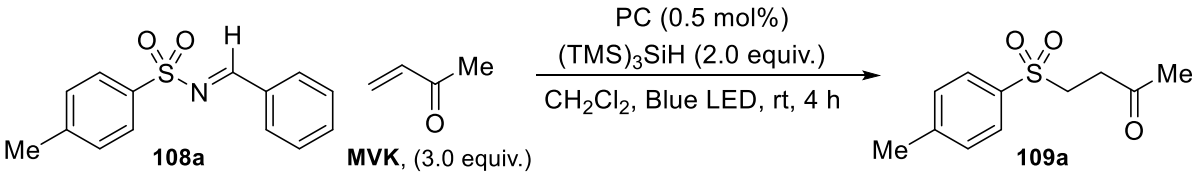
At this point in the reaction development, it appeared that attempting to encourage PCET was not having a beneficial impact. It was therefore proposed that a HAD with a better polarity match for HAT was required. In this context, $(TMS)_3SiH$ has been employed in a variety of radical based processes,[270] and furthermore has been shown to form a good polarity match in the context of hydrosulfonylation with electron-deficient alkenes.[262b] Hence, $(TMS)_3SiH$ as an additive was tested

in the reaction (entry 8). Gratifyingly, this caused a significant improvement in the yield even after four hours (entry 9), and an improved yield was also observed in acetonitrile (entry 10). Together with the previous observations, it implied that a HAD with a good polarity match is essential to drive the equilibrium of the alkene addition, thus giving the desired sulfone.

### 4.3.2. Catalyst Screen

With an appropriate additive selected, attention now turned to improving the efficiency of the photocatalytic cycle and sulfonyl radical generation. It was noted that the system is highly tuneable, as the properties of the catalyst and the sulfonamide activator can be easily varied to have a beneficial impact. Therefore, a series of photocatalysts were screened in an attempt to obtain higher yields (**Table 4.3.**).

**Table 4.3.** Screen of photocatalysts in the reaction.




| Entry | PC | Yield (%)[a] | RSM 108a (%)[a] |
|---|---|---|---|
| 1 | $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ | 31 | 13 |
| 2 | $Ru(bpy)_3(PF_6)_2$ | 0 | 100 |
| 3 | $(PhAcr)BF_4$ | 0 | 100 |
| 4 | $(MesAcr)ClO_4$ | 0 | 100 |
| 5 | Fluorescein | 0 | 100 |
| 6 | Eosin Y | 12 | 34 |
| 7 | 4CzIPN | 8 | 40 |
| 8 | 5CzBN | 54 | 0 |
| 9 | 3DPA2FBN | 18 | 64 |

[a] Yields were determined from the $^1H$ NMR spectra of the crude reaction mixture, with dimethyl sulfone as an internal standard. With reactions conducted at a concentration of 0.1 M.

Initially, reducing the catalyst loading to 0.5 mol% of iridium (entry 1) caused a minor decrease in the yield, however, now some recovered starting material was also observed. A broad spectrum of catalysts were evaluated, consisting of those with varying redox potentials and excited state

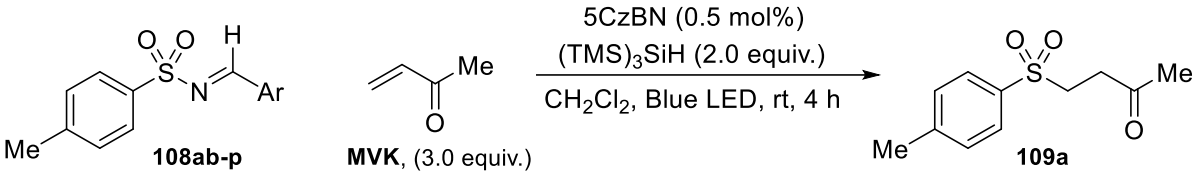
energies.[1d] The commonly employed $Ru(bpy)_3(PF_6)_2$ was shown to be ineffective (entry 2), hence organo-photocatalysts became the focus of the screen. Catalysts based on an acridinium core, which are strongly oxidizing in the excited state, gave recovered starting material (entry 3 & 4). When the organic dye molecules Fluoresein and Eosin Y were evaluated (entry 5 & 6 respectively), it was interesting to note that Fluoresein produced no product, but Eosin Y showed some catalyst turnover, with significant decomposition of the starting material. Given the similar structure of these catalysts, it implies that simple structural changes around an organic framework of an organocatalyst would have profound implications for the reaction. Therefore, it was decided to use the highly modular thermally-activated delayed fluorescence (TADF) catalysts (entries 7-10).[271] The commonly employed 4CzIPN catalyst gave traces of product, whilst showing significant decomposition (entry 7). However, when evaluating the 5CzBN catalyst, which has a lower ground state reduction potential (-1.52 V compared to -1.24 V vs. SCE in MeCN), a significant improvement in the yield was obtained (entry 8). Using a catalyst with an even lower ground state reduction potential (3DPA2FBN, entry 9), reduced the efficiency of the system. It should also be noted that extending the reaction times in the system did not appear to have a beneficial impact.

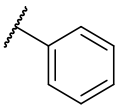
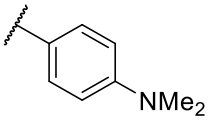
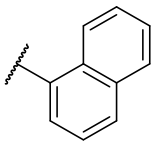
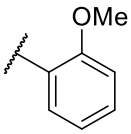
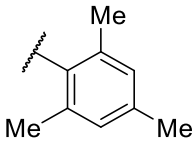
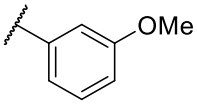
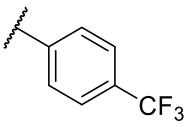
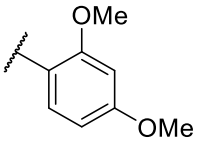
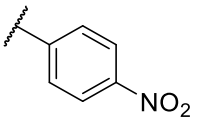
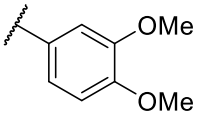
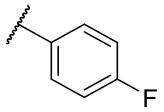
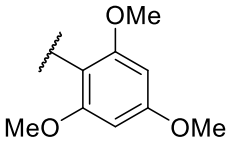
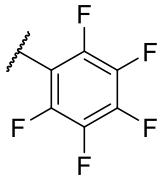
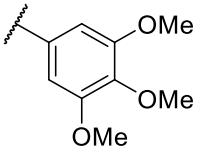
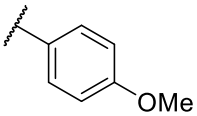
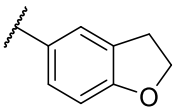
Overall, the 5CzBN catalyst provided a good yield of sulfone product. Although 5CzBN has only been applied as catalyst in known transformations for proof-of-concept,[272] it provides a variety of advantages. Primarily, as an organic molecule it has a lower cost, especially considering the low catalyst loading when compared to metal-based photocatalysts. Additionally, a wealth of physical information on this catalyst has been documented,[271] creating a tuneable system.

### 4.3.3. Activator Screen

With an appropriate catalyst selected, attention turned to the nature of the sulfonamide activator, as a range of different aldehydes can be used to generate the aldimine (**Table 4.4.**).

**Table 4.4.** Screen of aldimines in the reaction.




| Entry | Ar | Yield (%)[a] | | Entry | Ar | Yield (%)[a] | |
|---|---|---|---|---|---|---|---|
| 1 |  | 54 | | 9 |  | 0 | (100%, RSM) |
| 2 |  | 0 | (100%, RSM) | 10 |  | 54 | |
| 3 |  | 57 | | 11 |  | 63 | |
| 4 |  | 34 | | 12 |  | 55 | |
| 5 |  | 0 | (100%, RSM) | 13 |  | 28 | (43%, RSM) |
| 6 |  | 54 | | 14 |  | 44 | |
| 7 |  | 8 | | 15 |  | 23 | (31%, RSM) |
| 8 |  | 70 | (56%)[b] | 16 |  | 78 | |

[a] Yields were determined from the $^1$H NMR spectra of the crude reaction mixture, with dimethyl sulfone as an internal standard. With reactions conducted at a concentration of 0.1 M using the corresponding aldimines **108aa** to **108ap**. [b] The Reaction was conducted with the $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ catalyst for 16 h.

When the aldimine was changed from the simple phenyl substituent (entry 1) to naphthyl (entry 2), recovered starting material was obtained, likely due to the naphthyl π-system inadvertently interacts under the photochemical conditions.[273] The mesityl substrate (entry 3) performed nearly identically to the phenyl, showing that the added steric hinderance did not impact the system. Due to

these results, it was decided to perform perturbations on a simple phenyl substrate, predominantly examining electronic contributions. Therefore, electron-withdrawing groups were first considered, where *p*-ArCF$_3$ significantly reduced the yield (entry 4), and *p*-ArNO$_2$ is again assumed to quench the reaction without productive reaction occurring (entry 5). As decreasing the electron density on the aromatic ring seemed to have a negative impact, electron-donating groups were considered. Using a *p*-ArF gave a similar result to the initial phenyl (entry 6), which can be expected from its similar Hammett constant. However, increasing the amount of fluorines to the pentafluoro system caused significant decomposition (entry 7). Pleasingly the stronger electron donor *p*-ArOMe, improved the yield to 70% (entry 8), where this substrate was also superior with the previous iridium system. A further attempt to increase the electron density with *p*-ArNMe$_2$ resulted in recovered starting material (entry 9). Intriguingly this substrate has been shown to function as a photocatalyst itself,[274] hence its direct interaction with light may prevent the desired reaction. Due to this result, altering the electronics with various methoxy groups was investigated (entries 10-15). Firstly, changing the position of the methoxy appeared to reduce the yield (entries 10 & 11), although not to a level lower than the initial phenyl system. Increasing the methoxy groups on the ring provided no further improvement and appeared determinantal when a *meta*-methoxy was included (entries 13 & 15). In a final attempt to improve the yield, it was decided to reduce the conformational flexibility of the methoxy group in the optimum substrate (entry 16), which gave a marginal improvement to 78%. This increase is credited to the methoxy lone pair now being fixed in a parallel conformation to the aromatic ring, altering the electronic properties.

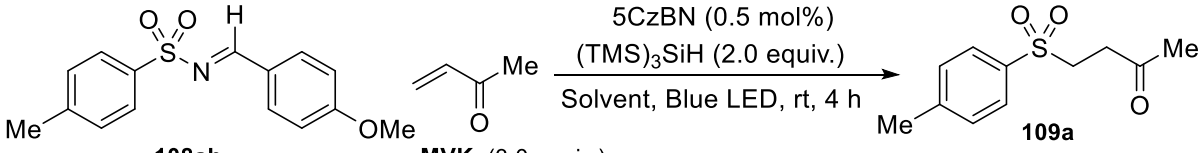
Overall, the sulfone product could now be obtained in 78% yield, with the new specialised aldimine system (entry 16). However, for further optimisation it was decided to focus on the *p*-ArOMe system

(entry 8), due to the similarity in these yields coupled with the availability of *p*-anisaldehyde, which overall created a simpler system.

### 4.3.4. Solvent Screen

With a reaction now producing good yields, one of the final parameters that was examined was the solvent (**Table 4.5.**). One of the most striking observations is that the reaction proceeded with good yields in a wide range of solvents, including solvents with drastically different properties. The most drastic decrease was seen in DMF (entry 7), lowering the yields by approximately 20% to 36%. At this stage, such an observation was a positive indication that the reaction would be generally applicable in a variety of conditions.

**Table 4.5.** Screen of solvents in the reaction.



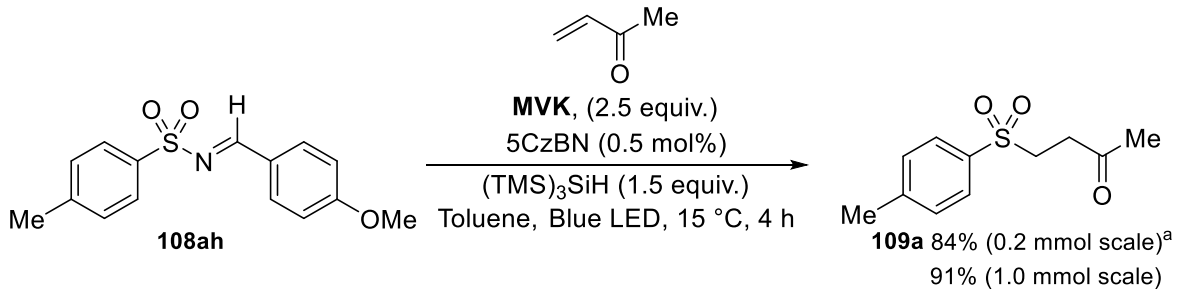

**108ah** **MVK**, (3.0 equiv.)

| Entry | Solvent | Yield (%)[a] |
|---|---|---|
| 1 | $CH_2Cl_2$ | 70 |
| 2 | $(CH_2Cl)_2$ | 62 |
| 3 | THF | 49 |
| 4 | EtOAc | 64 |
| 5 | MeOH | 61 |
| 6 | DMSO | 50 |
| 7 | DMF | 36 |
| 8 | MeCN | 56 |
| 9 | Toluene | 74 |

[a] Yields were determined from the $^1$H NMR spectra of the crude reaction mixture, with dimethyl sulfone as an internal standard. Where [Ir] refers to $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ and at a concentration of 0.1 M.

A marginal improvement was observed with toluene as solvent (entry 9); it was also noticed that when using toluene, the $^1$H NMR spectrum of the crude reaction mixture appeared to produce less decomposition, hence this was selected as the optimum solvent.

One issue which was noted during the screening of solvents, was the reproducibility of the reaction. To understand why this process occasionally gave anomalous results, the internal temperature of the system was monitored during the course of the reaction. From these experiments, it was revealed that depending on the efficiency of the fan used, the internal temperature of the reaction mixture in the vial could reach *ca.* 65 °C. Therefore, it was postulated that the reproducibility issues arose from variable temperatures, and a higher temperature could be aiding the decomposition of the sulfonyl radical, hence lowering the yield. In order to circumvent this issue, the reaction setup was changed, now using two blue LED lamps whilst cooling with a water bath. The water bath was kept at a constant temperature using a glass tempering beaker, which maintained an internal reaction temperature of 15 °C. Therefore, several minor alterations allowed a robust reaction to be developed with excellent yields (**Scheme 4.18.** see section **6.5.1.4.** for images of the reaction set ups).




**Scheme 4.18.** Optimised conditions for the photocatalytic conversion of an aldimine to a sulfone. Where the reaction was conducted at a concentration of 0.05 M. [a] An identical yield was obtained using MeCN as solvent.

Overall, a reaction had been optimised which allowed the straightforward conversion of a primary sulfonamide derivative to a sulfone. Impressively, this system was shown to be highly insensitive to both moisture and air. One of the key advantages of this procedure is that it directly intercepts sulfonyl radical chemistry and performs a reaction which would be challenging for a sulfinate salt. Furthermore, a simple reaction setup has been developed which allowed the reaction to scaled up and conducted in a round bottom flask, obtaining the product in 91% yield.

## 4.4. Sulfonamide Scope

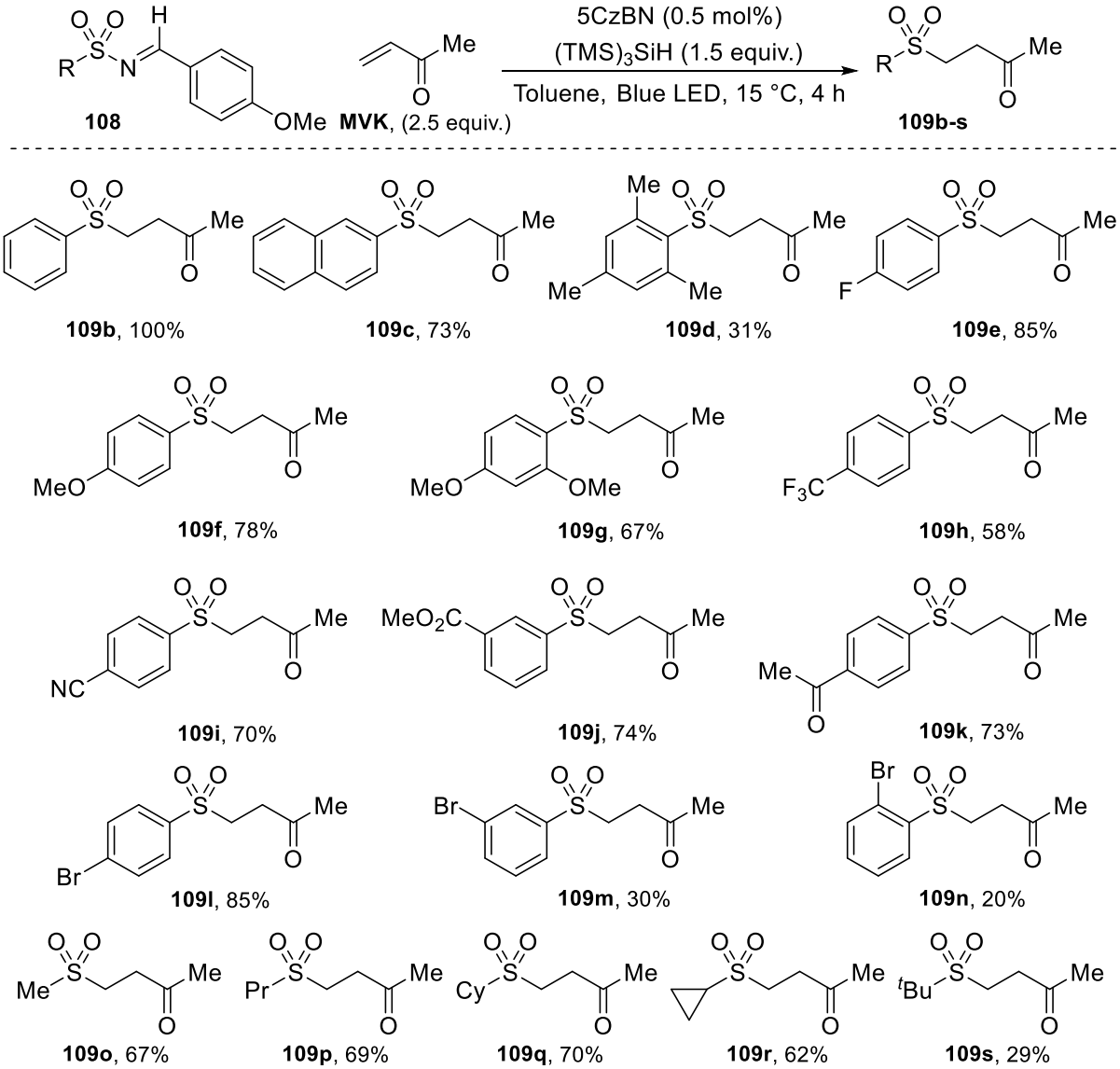
In order to test the generality of this late-stage photochemical synthesis of sulfones, it was decided to apply a variety of different sulfonamide derivatives to the optimum conditions. In particular, a focus was placed on using substrates which would be of medicinal relevance coupled with the electron deficient alkene; methyl vinyl ketone.

### 4.4.1. General Sulfonamide Investigation

Initiation of this investigation began with a variety of simple sulfonamide derivatives, which were synthesised and tested under the optimal conditions, providing 18 examples (**Table 4.6.**). The investigation began with examining simple aryl substrates close to the model system (**109b**-**109n**). Pleasingly, phenyl (**109b**) worked in quantitative yield and the naphthyl substrate (**109c**) did not provide a quench for the catalyst. The mesityl substrate gave a reduced yield of 31% (**109d**), which can be rationalised by the steric bulk around the sulfur causing a slower rate of addition into the alkene, hence leading to the decomposition pathways becoming more dominant. Next, the focus became examining the electronic properties on the aromatic ring of the sulfonamide derivatives. Electron-donating groups (**109e**-**109g**), as well as electron-withdrawing groups, both inductive and mesomeric (**109h**-**109k**), gave good to excellent yields. In particular this showed good functional group tolerance, with an ester (**109j**) and ketone (**109k**) being tolerated. Next, bromine substituents were examined (**109l**-**109n**) which provide a synthetic handle for further reactions. However, these reactions tended to produce a complex mixture of products and hence reduced yields. Although substrate **109l** was isolated in an excellent yield, presumably there is a delicate balance between potential side reactions involving the bromine substituent.[275] Finally, to broaden the scope, a range of alkyl derived substrates were examined (**109o**-**109s**). Methyl, primary and secondary substrates (**109o**, **109p** and **109q** respectively) all gave near identical yields, around 70%, showing the tolerance

of the reaction to steric changes. Additionally, the reaction was successful in the presence of a cyclopropane ring (**109r**), where no radical ring-opening was observed. Once again, increasing the sterics around the sulfur with the *tert*-butyl substrate (**109s**) also caused a reduction in yield, which draws comparisons to the previous mesityl substrate (**109d**).

**Table 4.6.** Sulfonamide scope examples.

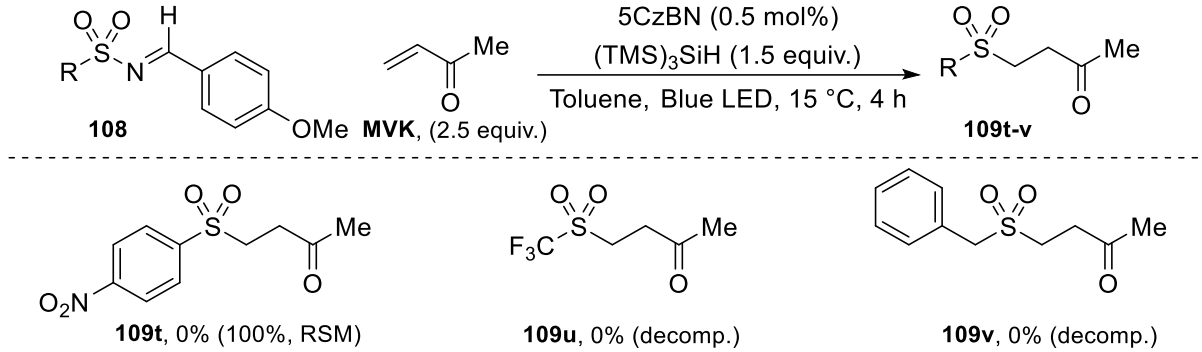



**Conditions**: The reaction was conducted on a scale of 0.2 mmol with respect to **108**, at a concentration of 0.05 M.

Although these results show that a diverse array of sulfonamides are compatible in the reaction, several sulfonamides showed no product (**Table 4.7.**). For example, when a *p*-$ArNO_2$ substrate was

used (**109t**), starting material was recovered, presumably because the sulfonamide component of the substrate quenches the excited state of the photocatalyst, rather than activating the C=N bond. Regardless, many other electron deficient sulfonamides were shown to be successful (such as *p*-ArCN **109i**). Other substrates which were unsuccessful were those which can potentially release $SO_2$ to form stable radical species (**109u** and **109v**), where these substrates only showed decomposition.

**Table 4.7.** Failed sulfonamide scope examples.



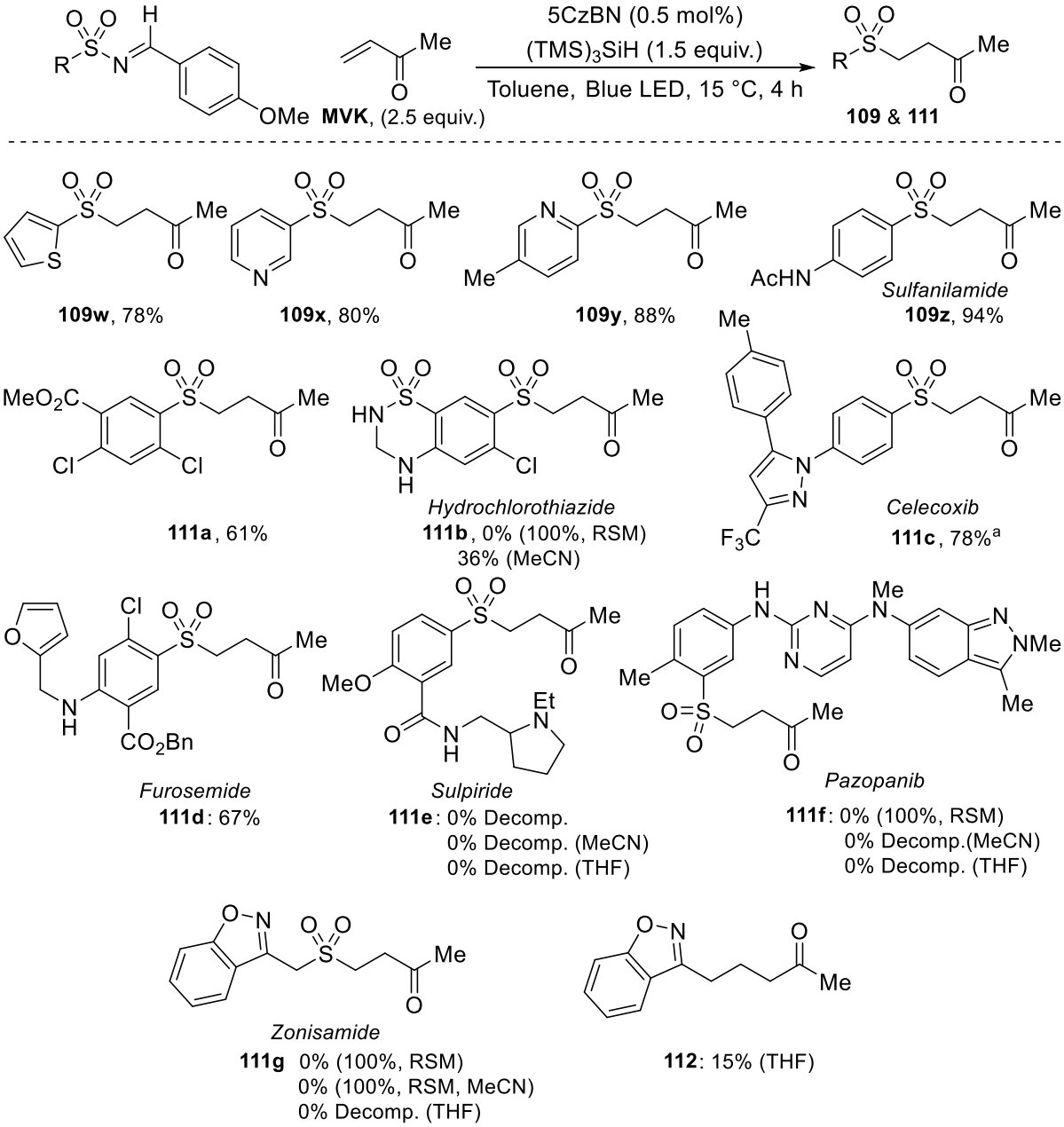

**Conditions**: The reaction was conducted on a scale of 0.2 mmol with respect to **108**, at a concentration of 0.05 M.

Therefore, it is expected that to obtain usable yields with substrates **109u** and **109v**, it would be required to increase the stability of the sulfonyl radical compared to $SO_2$ release. It should be noted that no characterisable side-products were obtained in these reactions, although this may be due to the volatility of the resulting products.

### 4.4.2. Medicinally Relevant Examples

To showcase that this methodology is suitable for late-stage functionalisation, it was decided to perform the reaction on a range of medicinally relevant fragments, as well as drug derivatives (**Table 4.8.**).

**Table 4.8.** Sulfonamide scope on heterocycles and drug derivatives.




**Conditions**: The reaction was conducted on a scale of 0.2 mmol with respect to the aldimine, at a concentration of 0.05 M, when an alternative solvent was used this is reported in parenthesis. Several examples use derivatives of the named drug molecules. [a] Reaction was conducted by Dr. Loïc Pantaine and is included for completeness.

As a variety of hetereocycles are commonly encountered in pharmaceuticals, several were tested under the optimum conditions (**109w-109y**). These substrates produced excellent yields, including a 2-pyridyl substrate (**109y**), where no $SO_2$ extrusion was observed. With these positive results, several drug derivatives were investigated. Pleasingly, a derivative of sulfanilamide (**109z**) produced a 94% yield; not only does this display the applicability for late-stage functionalisation of a drug, but this also

shows that amides are tolerated in the reaction. The substrate **11a** which is a densely functionalised sulfonamide produced a good yield, which demonstrates that chlorides can provide an alternative to the poor yields obtained with bromide substituents. Substrate **11a** is also a potential building block for carbonic anhydrase inhibitors,[276] however, the related structural drug Hydrochlorothiazide produced 0% yield when subjected to the reaction. This low yield was ascribed to the low solubility in toluene. During the optimisation, the reaction performed well in a range of solvents, hence the more polar solvent acetonitrile was used. In acetonitrile, excellent conversion was observed, but a significant amount of inseparable primary sulfonamide side-product was obtained, hence giving product **111b** in only 36% yield. It can be speculated that further screening of solvents or protection of the nitrogen heteroatoms may supress sulfonamide release from the aldimine. Regardless of the lower yield obtained for this drug, it was encouraging to see the reaction did not cause complete decomposition in the presence of nitrogen hetereoatoms. Therefore, the Celecoxib and a Furosemide derivative were trialed in the reaction (**111c** & **111d**). Both substrates produced the expected sulfone products, despite the presence of a pyrazole hetereocycle and aniline components. Due to this success, the drug Sulpiride was used (**111e**), however, even after a limited solvent screen, the reaction only led to decomposition, presumably due to the presence of the amine component which would be expected to have a low redox potential and potentially interfere with photocatalyst. Again, the drug Pazopanib (**111f**) had reduced solubility in toluene, although now changing the solvent led to decomposition, which may be from the indazole core being sensitive to photochemical conditions.[277] Finally, the drug Zonisamide (**111g**) was used, initially only recovered starting material was obtained, and this was assumed to be from the low solubility in toluene. However, when changing the solvent to acetonitrile the same result was observed, hence it was postulated that the isoxazole heterocycle may be photochemically active,[278] and thus quenching the reaction. It was expected that solvent may have a

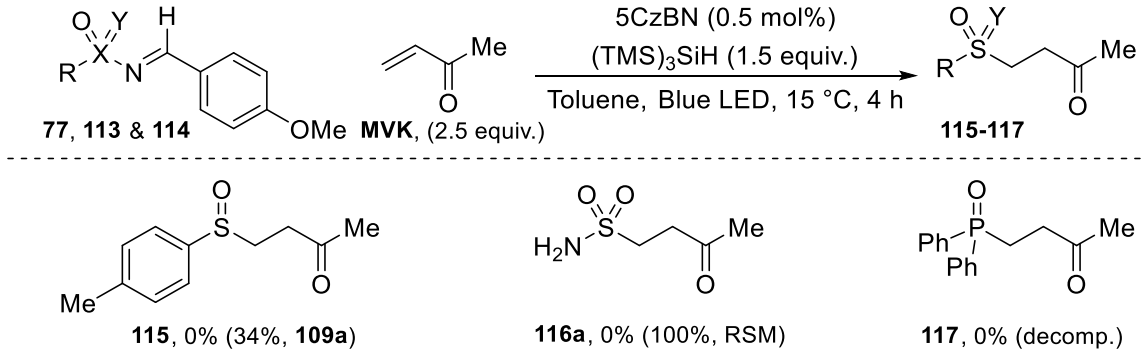
considerable impact on these undesirable interactions, hence the reaction was conducted in THF, which saw full consumption of the substrate, validating the initial hypothesis. Although considerable decomposition was observed, the product **112** was isolated, which indicates that $SO_2$ release is in operation, generating a C-based radical.

Overall, several hetereocycles and drug derivatives were successfully applied in the reaction. Although it appears that the identity of the solvent can have a profound effect on the reaction outcomes. Therefore, it is believed that many of the unsuccessful substrates presented here could potentially be improved with careful selection of conditions using the knowledge gained from the initial optimisation.

### 4.4.3. Alternative Imines

Although this project was focused on the late-stage functionalisation of sulfonamides, it was assumed that the fundamental concept would be applicable to other aldimine derivatives. Therefore, a selection of non-sulfonamide derivatives were subjected to the reaction conditions (**Table 4.9.**). Firstly, applying a sulfinamide in the reaction (**77**) resulted in the isolated of sulfone product (**109a**). This was rationalised by the productive reaction occurring, but the rapid disproportion of the radical intermediate prior to successful addition to the alkene.[279] Regardless, the activation of this substrate indicates that these conditions may be applicable to other aza-sulfur compounds. When a sulfamide was used in the reaction (**116a**), starting material was reisolated, however this is assumed to be caused by the reduced solubility of the starting material in toluene. Finally, in attempt to move away from aza-sulfur compounds, an aza-phosphorus reactant was used (**117**). Although no product was isolated from this reaction, it was encouraging to see that the starting material decomposed, implying that the photocatalyst activated the substrate, and the issue is associated with radical decomposition.

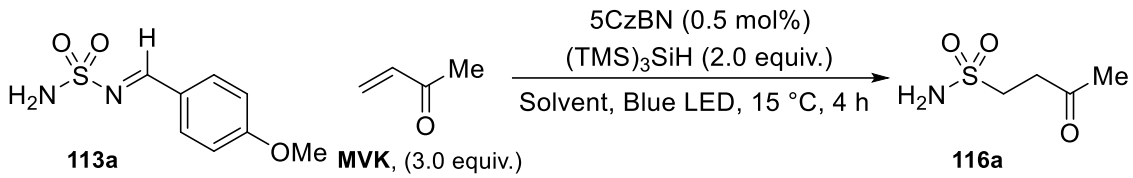
**Table 4.9.** Sulfonamide scope on heterocycles and drug derivatives.




**Conditions**: Attempt to react alternative aldimine derivatives. The reaction was conducted on a scale of 0.2 mmol with respect to the aldimine starting material, at a concentration of 0.05 M.

The results presented here show that for this reaction to be successful on other aldimines, further optimisation is likely to be required, which would be aided by a greater mechanistic understanding. Poor reactivity of the sulfamide substrate appeared to be due to poor solubility, so other conditions were screened for this reaction (**Table 4.10.**). As expected, on changing the solvent to acetonitrile (entry 2), the substrate was now consumed due to its increased solubility, however, no product was observed. When using THF, which the substrate **113a** had shown good solubility in, only trace product was obtained, and mainly starting material was recovered (entry 3). Increasing the time of the reaction did not improve the amount of desired product (entry 4). Several other solvents (entries 5-7) showed analogous results with varying levels of recovered starting material obtained, although in all cases, no decomposition was detected from analysis of the $^{1}$H NMR spectra of the crude reaction mixture. It was speculated that these results may occur due to some form of catalyst inhibition, which is solvent dependent, therefore reactions were attempted with the initial iridium catalyst (entries 8-10). Again, toluene gave recovered starting material due to solubility, but now in acetonitirile and THF, no starting material was observed, and both showed significant decomposition.

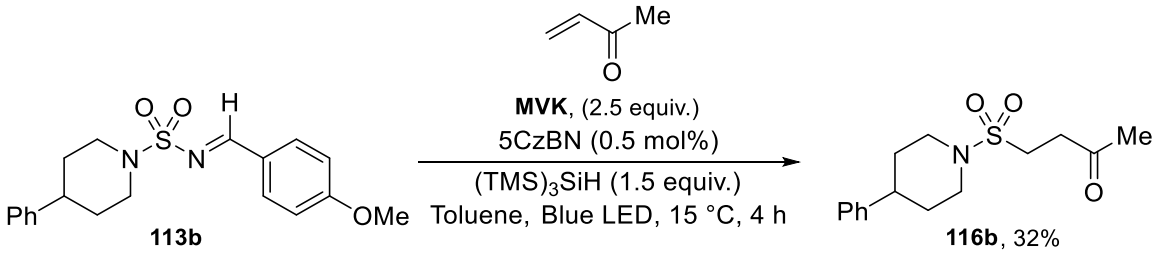
**Table 4.10.** Screen for sulfamide substrate.




| Entry | PC | Yield 116a (%)[a] | RSM 113a (%)[a] |
|---|---|---|---|
| 1 | Toluene | 0 | 100 |
| 2 | MeCN | 0 | 0 |
| 3 | THF | <5 | 73 |
| 4 | THF[b] | <5 | 56 |
| 5 | $CH_2Cl_2$ | <5 | 50 |
| 6 | Acetone | <5 | 86 |
| 7 | MeOH | <5 | 53 |
| 8 | Toluene[c] | 0 | 100 |
| 9 | MeCN[c] | <5 | 0 |
| 10[b] | THF[c] | 0 | 0 |

[a] Yields were determined from the $^1$H NMR spectra of the crude reaction mixture, with dimethyl sulfone as an internal standard. With reactions conducted at a concentration of 0.1 M. [b] Reaction conducted for 16 h. [c] $Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ was used in place of 5CzBN

Overall, these results imply that the sulfamide inhibits the 5CzBN catalyst, and therefore re-optimisation with an iridium system may be required in order to produce isolatable amounts of material. To determine whether these observations where the consequence of a free amino component in the substrate, a substituted sulfamide was tested (**Scheme 4.19.**). Pleasingly, in toluene this now provided the product in 32% isolated yield. It should be noted that considerable amounts of unsubstituted sulfamide by-product and recovered starting material were observed by analysis of the $^1$H NMR spectra of the crude reaction mixture. It is postulated that generation of sulfamide ($SO_2(NH_2)_2$) may also be occurring in the previous reactions discussed, but is challenging to detect.




**Scheme 4.19.** Subjecting a sulfamide to the reaction conditions to obtain sulfonamide product.

Overall, it appears that to obtain an improved yield of the sulfamide substrate, further optimisation is required, in particular a significant challenge appears to be balancing the correct catalyst and solvent to suppress side reactions and quenching of the catalytic cycle. With all these results combined, it appears that this photocatalytic system has the potential to be applicable to a broad range of substrates for late-stage functionalisation.

## 4.5. Radical Trap Scope

With a diverse array of primary sulfonamides applied in the reaction, we then wished to showcase the ability to exploit the varied utility of sulfonyl radical chemistry. In particular, a major goal was to show that this allows new reactivity modes. To initiate the investigation, it was chosen to explore the tolerance to various alkenes.

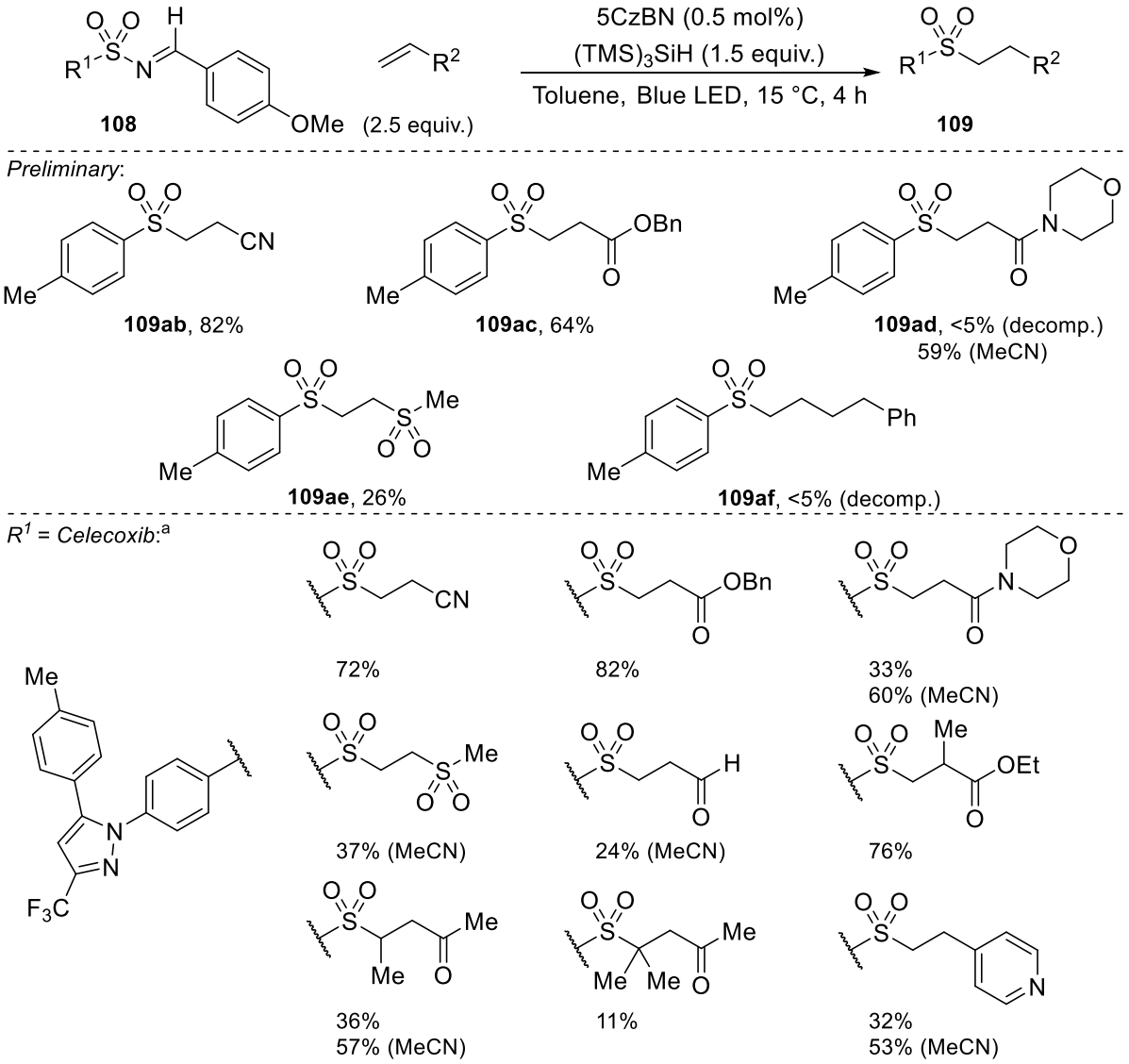
### 4.5.1. Alkene Scope

To undertake this element of the scope, several alternative alkenes to methyl vinyl ketone were paired with the optimised aldimine substrate (**Table 4.11.**). When using acrylonitrile, the reaction performed near identically to the model system (**109ab**). A good yield was observed when an ester group was in conjugation with the alkene (**109ac**). In contrast, the amide substrate (**109ad**) showed significant decomposition. The decrease in yield was assumed to be from the slower addition of the sulfonyl radical into this akene, hence producing more decomposition. To overcome this, a simple switch in solvent was trialled using acetonitrile. Pleasingly, this gave **109ad** in a 59% yield, once again emphasising the drastic impact solvent selection can have on this reaction. When a sulfone derivative was applied to the system (**109ae**), a reduced yield was observed. Previously, vinyl sulfones have been reported to undergo intramolecular photocyclisations,[280] hence it was postulated that side reactions may interfere in this case.[281] Finally, an electron neutral alkene was attempted in the reaction (**109af**),

where it appeared that the poor polarity match between the HAD ($(TMS)_3SiH$) and the resulting C-based radical caused an ineffective HAT step, hence resulting in significant decomposition.

From this preliminary scope, it was decided to show that multiple alkenes could be applied in a late-stage functionalisation setting of a known drug molecule. Dr. Loïc Pantaine was able to use Celecoxib with a range of electron withdrawing alkenes to produce a diverse array of sulfones. The results of these experiments are presented here for completeness, which shows that a variety of substrates are accessed which would be challenging for traditional sulfinate anion chemistry.

**Table 4.10.** Screen for sulfamide substrate.

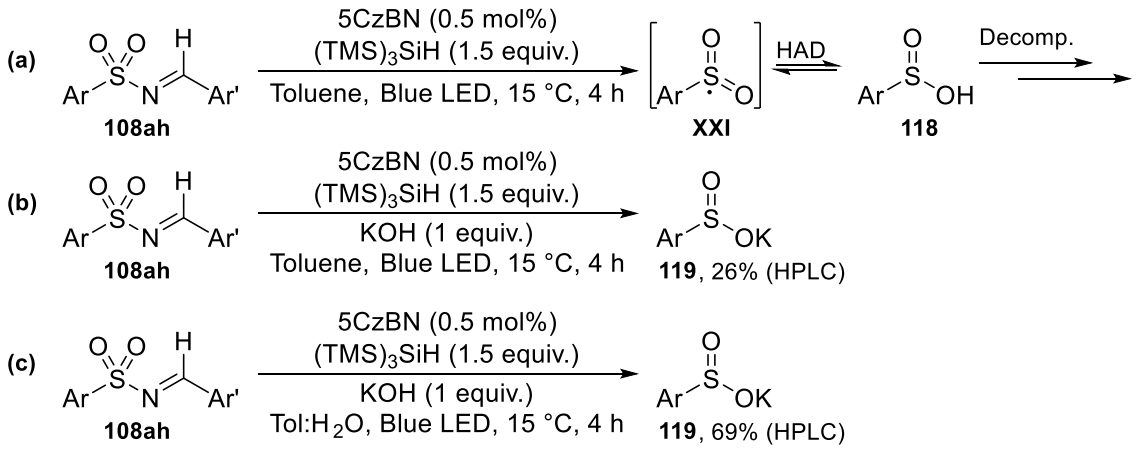



**Conditions**: The reaction was conducted on a scale of 0.2 mmol with respect to **108**, at a concentration of 0.05 M. [a] Reactions were conducted by Dr Loïc Pantaine.

Overall, a range of alkenes can be used in this reaction, although it is important to consider that sulfonyl radical longevity is important for the success of the reaction. Fortuitously, a simple change in solvent can have a profound effect in this context. It is also important to emphasise the significance of these results, in that Michael additions involving sulfinates often require forcing conditions,[282] whereas the reactivity of sulfonyl radicals provides a milder alternative.

### 4.5.2. Sulfinate Anion Generation

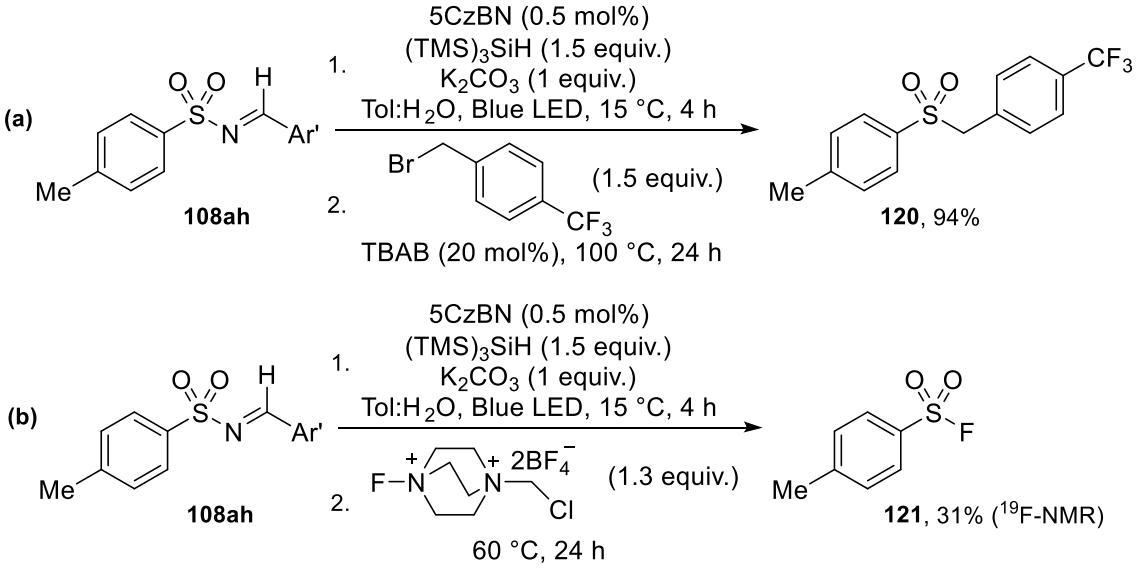
It has been established that intercepting a sulfinate anion intermediate for late-stage functionalisation allows access to a broad range of functionalities (see **Scheme 4.11.**). Therefore, it was noted that it would be extremely powerful if the photocatalytic system here could also generate a stable sulfinate anion. It was postulated that the sulfonyl radical may be able to directly react with the HAD, $(TMS)_3SiH$, to generate a sulfinic acid (**118**, **Scheme 4.20.a**),[262b] although significant decomposition was observed when this was attempted.




**Scheme 4.20.** Generation of the sulfinate anion *in situ* under photocatalytic conditions, where yields were determined by HPLC, using 1,3,5-triisopropylbenezene as an internal standard. Ar refers the *p*-PhMe and Ar' refers to *p*-PhOMe **(a)** Attempting to directly generate sulfinic acid. **(b)** Using a base to drive the equilibrium. **(c)** Changing the solvent to a toluene/water mix, in a 1:1 ratio.

This degradation may be a consequence of sulfinic acid disproportionation,[283] or may arise from the reversibility of sulfinic acid generation back to the unstable sulfonyl radical. To overcome this, we

planned to use a base to drive the equilibrium, and accordingly, addition of solid KOH to the system (**Scheme 4.20.b**) gave some desired sulfinate as analysed by HPLC. In order to further drive the equilibrium, water was used as a co-solvent (**Scheme 4.20.c.**). By effectively extracting the generated sulfinate salt into the aqueous phase, a yield of 69% (by HPLC) was obtained. In order to demonstrate this reaction's applicability, one-pot procedures were developed, using electrophiles to trap the synthesised sulfinate (**Scheme 4.21.**)



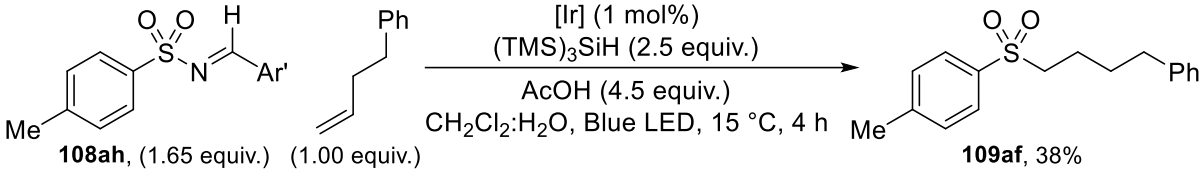

**Scheme 4.21.** Derivatisation of the sulfinate anion generated *in situ*. (**a**) Accessing a sulfone where the yield is from the isolated product. (**b**) Accessing a sulfonyl fluoride where the yield was determined by analysis of the $^{19}$F NMR spectra of the crude reaction mixture with trifluorotoluene as an internal standard.

When a one-pot procedure is used to trap the sulfinate anion using an activated bromo-benzyl electrophile, a 94% yield of the sulfone was obtained (**120**), which diversifies the number of sulfones that can be produced in this photochemical reaction. Furthermore, the $F^+$ source Selectfluor® could be used as an electrophile, although this gave the sulfonyl fluoride (**121**) in a reduced yield and proved challenging to purify. Regardless, this provides a proof-of-concept, and with further optimisation, this procedure is likely to be a useful route to access sulfonyl fluorides. This result is noteworthy, as sulfonyl fluorides are useful synthetic handles due to their electrophilicity and stability,[211] increasing the applicability of this methodology to late-stage functionalisation.

### 4.5.3. Electron Neutral Alkenes

Previously, it was demonstrated that using an electron neutral alkene in the optimised conditions led to significant decomposition (**109af**, **Table 4.10.**). In order to address this challenge, alternative HADs were examined including a thiol as a co-catalyst,[262b] however, all these attempts retained decomposition. To create a solution to this problem, a recent report on hydrosulfonation of sulfinate salts was noted.[262a] Within this report, a photocatalytic reaction of sulfinate anions with electron-neutral alkenes was conducted, using an iridium catalyst ($(IrdF(CF_3)ppy_2(dtbpy))PF_6$) in a biphasic mixture of $CH_2Cl_2$ and water in the presence of acetic acid.

Throughout the optimisation, it was shown that $(IrdF(CF_3)ppy_2(dtbpy))PF_6$ in $CH_2Cl_2$ performed as an efficient catalytic system and that acetic acid did not have a detrimental impact on the yield. Hence, it was deemed feasible that in a single step, the first catalytic cycle could generate sulfinate anion, which would then partake in a second catalytic hydrosulfonylation reaction using the same iridium catalyst (**Scheme 4.22.**).




**108ah**, (1.65 equiv.) (1.00 equiv.) **109af**, 38%

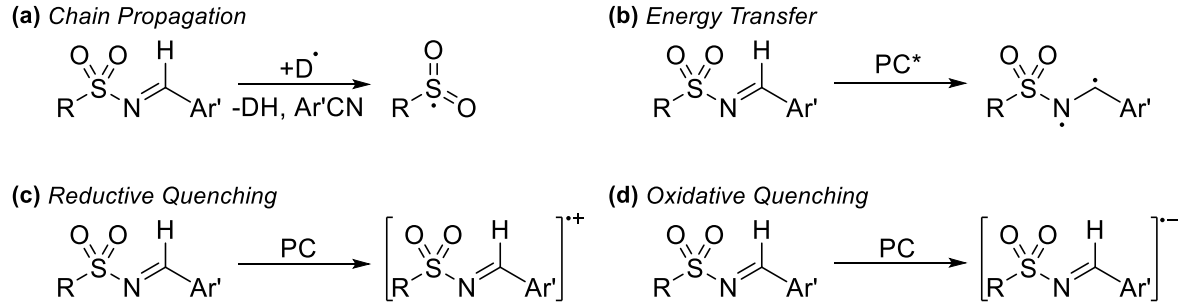
**Scheme 4.22.** Application of electron neutral alkenes in a 10:1 mixture of $CH_2Cl_2$ and $H_2O$ respectively at a concentration of 0.2 M, where Ar' refers to *p*-OMeAr and [Ir] $IrdF(CF_3)ppy_2(dtbpy))PF_6$.

Pleasingly, the desired product was now obtained in 38% isolated yield under these new conditions. During this reaction, it was also noted that applying 5CzBN as the photocatalyst led to significant decomposition, showing the specificity of the iridium system for the hydrosulfonylation step. Furthermore, with a variety of parameters changed, there is the opportunity for further optimisation to improve upon this result, but this provides a proof-of-concept that electron-neutral alkenes can be used in the reaction by exploiting sulfonyl radical chemistry.

## 4.6. Mechanistic Insight

A highly successful reaction has been developed which can take primary sulfonamides and readily convert them to an aldimine, which can then be subjected to a photocatalytic generation of a sulfonyl radical allowing diversification. From the optimisation, several mechanistic assumptions were made and appeared to allow improvement of the reaction. Therefore, to allow the opportunity to further improve refine this system, it was decided to gain a deeper mechanistic understanding.

Several mechanistic hypotheses can be postulated for the initiation of the reaction (**Scheme 4.23.**), including a chain propagation (**a**), energy transfer (**b**), reductive quenching (**c**) or oxidative quenching (**d**), which would all lead to sulfonyl radical formation.



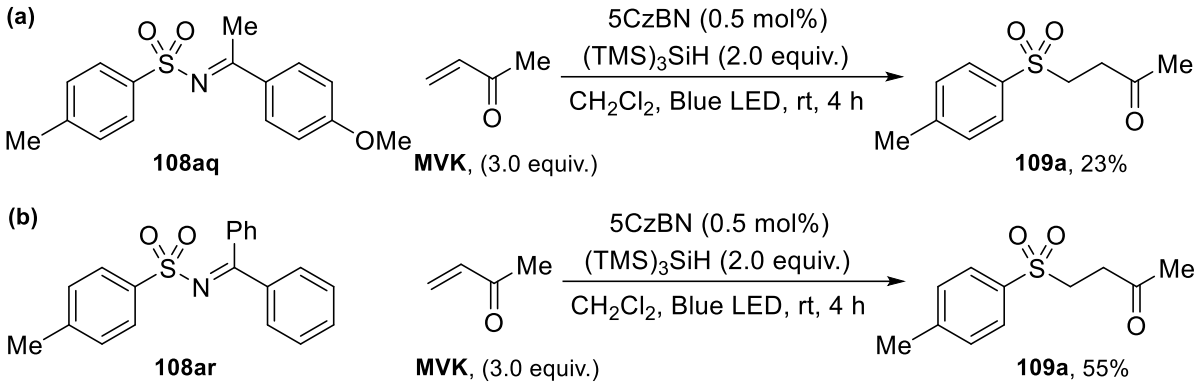

**Scheme 4.23.** Possible pathways for the initiation of the reaction to generate sulfonyl radical. (**a**) Chain propagation from a radical species. (**b**) Energy transfer from the photocatalyst. (**c**) Reductive quenching of the photocatalyst. (d) Oxidative quenching of the photocatalyst.

Although some of these mechanisms may appear more plausible than others, it was decided to attempt to obtain irrefutable evidence to dismiss certain pathways, to allow a full catalytic cycle to be proposed. Additionally, an objective was to provide a justification for some of the experimental observations.

### 4.6.1. Sulfonyl Imine Investigation

The aforementioned chain propagation mechanism is proposed to work by an initiation to generate a radical species (such as from the $(TMS)_3SiH$),[233h] which can then partake in a HAT with

the aldimine starting material, hence eliminating to the sulfonyl radical. In order to determine if such an elimination process was occurring, substituted imine derivatives were trialled in the reaction (**Scheme 4.24.**).




**Scheme 4.24.** Mechanistic studies using substituted imines in the reaction. The reactions were conducted at a concentration of 0.1 M and yields were determined by analysis of $^{1}$H NMR spectra of the crude reaction mixture. (**a**) The substrate contains a methyl group. (**b**) The substrate contains a phenyl group.

Under these conditions, the model substrate (**108ah**) gave 70% yield, whereas substituting the system with a methyl (**108aq**) caused a significant decrease in the yield. Conversely, substituting the system with a phenyl group (**108ar**) caused no significant change (compared with substrate **108a** giving 54%). What is most noteworthy about these results is that the C–H bond is not required for product generation. This gives support to a chain propagation not being in operation, as well as eliminating an analogous mechanism to that reported by Rovis *et al.*[265] with radical cation generation and subsequent deprotonation.

### 4.6.2. Stern-Volmer Quenching

In order to support the previous conclusions, it was decided to examine the emission spectra of the 5CzBN photocatalyst, in the presence of varying concentrations of the other components in the reaction. This allows one to assess which species quench the excited state of the photocatalyst, and can be represented by construction of a Stern-Volmer plot (**Figure 4.1.**, see section **6.5.2.3.**).

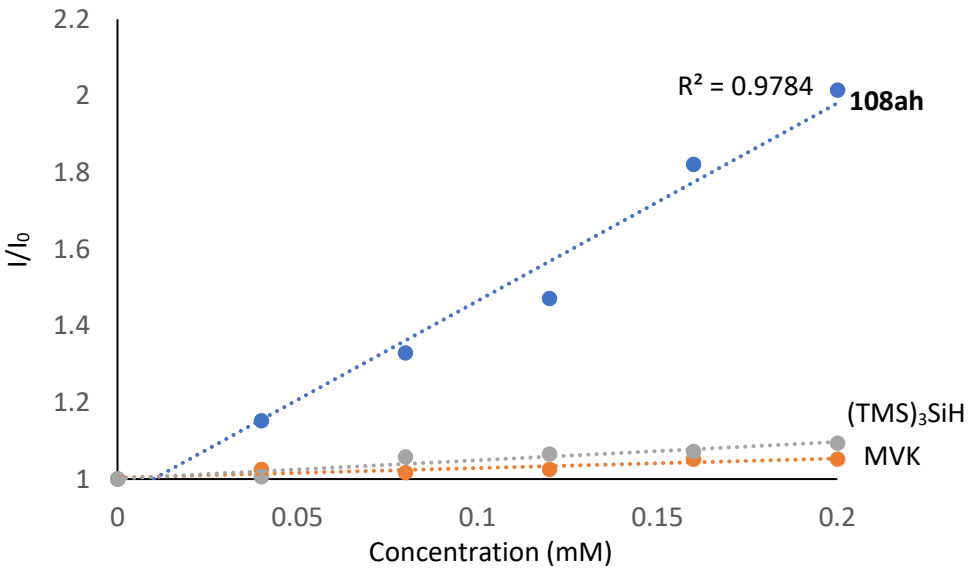



**Figure 4.1.** Stern-Volmer plot for the photocatalyst in the presence of varying concentration of aldimine **108ah**, $(TMS)_3SiH$ and methyl vinyl ketone at room temperature in toluene at $\lambda_{max}$ = 467 nm.

Analysis of the ability of $(TMS)_3SiH$ to quench the luminescence of the 5CzBN, showed that the excited state of the photocatalyst and $(TMS)_3SiH$ have minimal interaction. This provides further evidence that this species does not initiate the reaction as it is improbable that a silyl-based radical is directly generated. A similar result was observed for the interaction of the catalyst and the alkene, showing that this too is an unlikely species in aiding sulfonyl radical generation.

However, the aldimine substrate was shown to quench the photocatalyst luminescence, indicating that a direct interaction of this substrate with 5CzBN is important in the reaction. However, this data cannot distinguish if the photocatalyst excited state is being quenched by the aldimine *via* reductive or oxidative quenching, or even an energy transfer mechanism.

### 4.6.3. Absorption-Emission Spectra

When considering the remaining mechanisms, rudimentarily an energy transfer process would involve an excited state of the photocatalyst directly causing transition of the aldimine C=N bond to a diradical species.[284] If this were to occur *via* a Förster resonance energy transfer, (FRET), one would

expect significant overlap of the emission and absorption spectra of the catalyst and aldimine respectively (**Figure 4.2.**, see section **6.5.2.2.**).

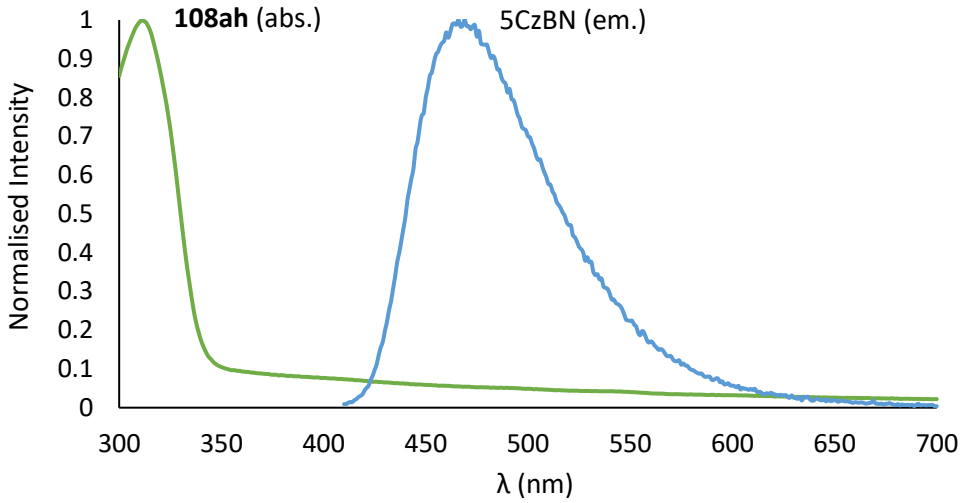



**Figure 4.2.** Normalised absorption and emission spectra of the aldimine and photocatalyst, respectively.

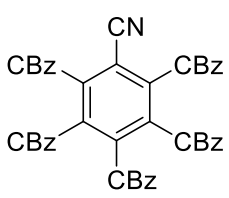
This data shows that there is minimal overlap between the emission of the photocatalyst and absorption of the aldimine substrate, therefore indicating that this type of energy transfer is likely not in operation. However, this does not eliminate the possibility of a triplet-triplet non-radiative process (Dexter electron transfer), which may be plausible considering previous photophysical characterisation of 5CzBN, and its application in this context.[285,1c] Also, the photophysical properties of similar aldimine derivatives have been characterised,[286,274] and this indicates that it is not unreasonable to assume that there are accessible triplet excited states for the imines in this reaction as well as the presence of diradical species.

### 4.6.4. Cyclic Voltammetry

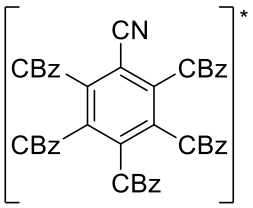
Although a triplet-triplet energy transfer could not be directly ruled out, it was decided to see if evidence could be accumulated for a photoredox process. As the redox potentials of the catalyst 5CzBN in its ground state and excited state have been determined in the literature,[1d] cyclic

voltammetry was only conducted on the model substrate (**108ah**) in acetonitrile (**Table 4.11.**, see section **6.5.3.2.** for details).

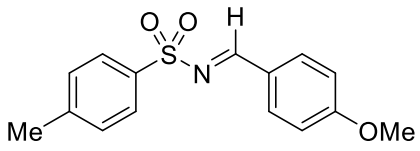
**Table 4.11.** Redox Potentials for the photocatalyst and substrate.




**5CzBN**




**5CzBN***




**108ah**

| Entry | Compound | $E_{red}(X/X^{\bullet-})$ V (vs. SCE) | $E_{ox}(X^{\bullet+}/X)$ V (vs. SCE) |
|---|---|---|---|
| 1 | **5CzBN** | -1.52 | +1.41 |
| 2 | **5CzBN*** | +1.31 | -1.42 |
| 3 | **108ah** | -1.44 | +1.98 |

Redox potentials for the photocatalyst were obtained from literature values.[1d]
Redox potentials for the substrate was obtained from cyclic voltammetry.

Both the oxidation and reduction of substrate **108ah** were irreversible processes, which suggests that further chemical processes or electron transfer events occur after the initial redox event. From the cyclic voltammetry data, one is able to abstract an oxidation potential of the aldimine, $E_{ox}$(**108ah**$^{\bullet+}$/**108ah**) = +1.98 V (vs. SCE). Compared to the photocatalyst's reduction potentials, it is unfeasible for the substrate to act as a reductant. When considering the process of an aldimine accepting an electron, a potential of $E_{red}$(**108ah**/**108ah**$^{\bullet-}$) = -1.44 V (vs. SCE) is obtained. Which is in a similar range to the oxidation potential of the excited state of the photocatalyst. This data therefore suggests that a plausible mechanism to form the sulfonyl radical from 5CzBN would be from oxidative quenching of the excited state by the aldimine to generate a radical anion. Intriguingly, only a handful of reports have invoked the involvement of such radical-anion imine derived intermediates in rationalising photocatalytic processes.[287]

Regardless, several observations still require an explanation, for example, substrates which should have higher reduction potentials (those with EWGs), performed worse during the optimisation. Also, the (Ir[dF($CF_3$)ppy]$_2$(dtbpy))$PF_6$ catalyst provided a significant yield (56%), despite the high

oxidation potential of its excited state ($E_{red}$(**5CzBN**$^{\bullet-}$/**5CzBN**$^{*}$) = -0.89 V (vs. SCE in MeCN)). Therefore, even though a photoredox process could be in operation for 5CzBN and the model substrate, this may not be general. Hence, a triplet-triplet energy transfer mechanism might be a more likely scenario, although further mechanistic evidence is required.

### 4.6.5. Density Functional Theory

Despite the wealth of experimental data obtained, several mechanistic questions were still present, one of particular interest was the role of the *para*-alkoxy substituent (*e.g.* **108ah**) in the optimised reaction. In order to provide some insight into this query, a DFT analysis was conducted on several relevant substrates. To examine trends by computational chemistry, it was decided to use B3LYP/6-31++g(d,p), as similar methodology has been applied for the analysis of aldimines in a photochemical setting.[258g,265,274]

It was deduced that the mechanism in operation involves an electron transfer between the aldimine substrate and catalyst, hence it is expected that the properties of the frontier molecular orbitals (FMOs) would have a considerable impact on the reaction outcome (**Figure 4.3.**). In general, when considering just the LUMO energies, a lower value would provide a better electron acceptor. Considering the phenyl system **108a** as a reference, substitution of the aromatic ring with EDGs raised the LUMO energy (**108ah**, **108an** & **108ai**), whilst the reverse is seen with EWGs (**108ac** & **108ad**). From these results it was expected that including EWGs should facilitate electron transfer from the photocatalyst excited state. However, this hypothesis is contrary to the experimental results where substrate **108ad** resulted in recovered starting material; therefore, to further probe this conundrum, the systems LUMOs were visually inspected.

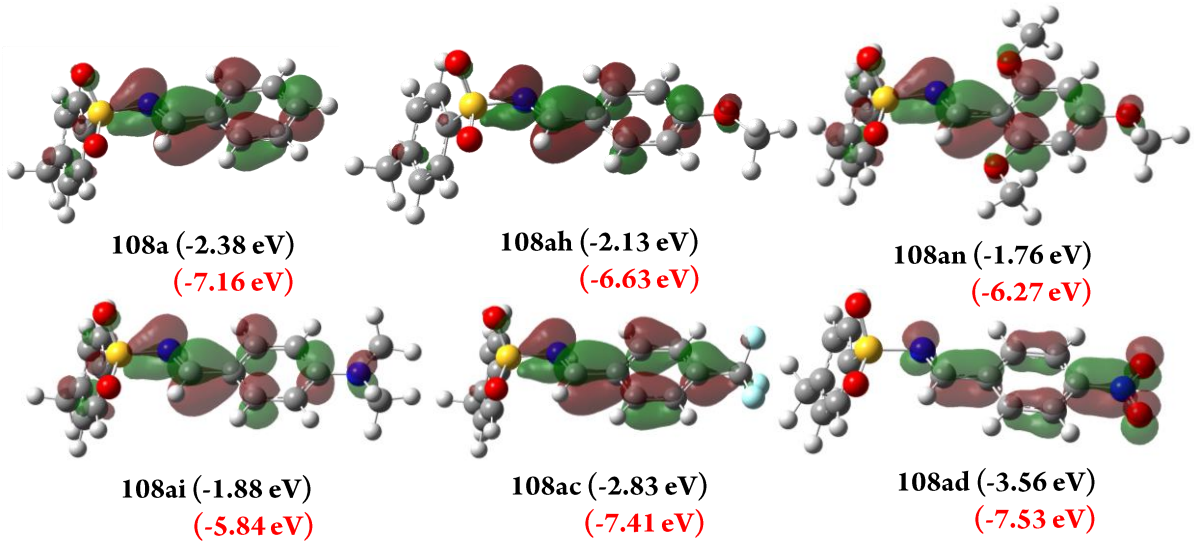



**Figure 4.3.** Images of the LUMOs for various aldimine substrates, generated with an isovalue of 0.04. Where LUMO and HOMO energies are eV, given in parenthesis, with HOMO energies in red. Geometry optimisations were conducted at the B3LYP/6-31++g(d,p) level of theory at 298 K in the gas phase.

From these images, it was determined that the sulfonyl component of the system does not considerably contribute to the LUMOs, with the density predominantly concentrated on the C=N bond and aromatic system of the aldimines. Within this series, the species containing EDGs (**108ah**,**108an** & **108ai**) appeared visually similar, with higher LUMO coefficients on the C=N bond than the aromatic system. In comparison, the phenyl substrate (**108a**) was shown to have considerable LUMO density on its phenyl ring. Therefore, it was postulated that EDGs increase the LUMO density on the C=N bond, whilst EWGs increase the LUMO density on the aromatic ring. This assumption was supported with significant LUMO coefficients observed on their aromatic system for the EWGs (**108ac** & **108ad**).

Using this analysis of the LUMOs for various aldimines, it can be postulated that in order for a successful reaction, it is beneficial to have an accessible LUMO (not too high in energy), whilst also concentrating the LUMO density on the C=N bond rather than the aryl system. Both of these conclusions provide a rationale for several of the substrates outcomes. Furthermore, given an energy

transfer mechanism, the HOMO would also have a profound effect, hence it can be rationalised that substrate **108ah** is successful due to the relatively high HOMO energy.

### 4.6.6. Proposed Photocatalytic Cycle

From all the mechanistic data that was collected, a working catalytic cycle was proposed (**Scheme 4.25.**). Firstly, the photocatalyst (PC) is excited by light to generate an excited state. This excited state then interacts with the aldimine, which at this stage is proposed to occur *via* a triplet-triplet energy transfer mechanism, however, a competing photoredox process cannot be completely ruled out. The resulting diradical then fragments to release the key sulfonyl radical, which will add to the electron-deficient alkene. The product is then obtained from an efficient hydrogen atom transfer step with a silyl reagent. Within this sequence, it is also proposed that the sulfonyl radical can be intercepted for a variety of other processes.

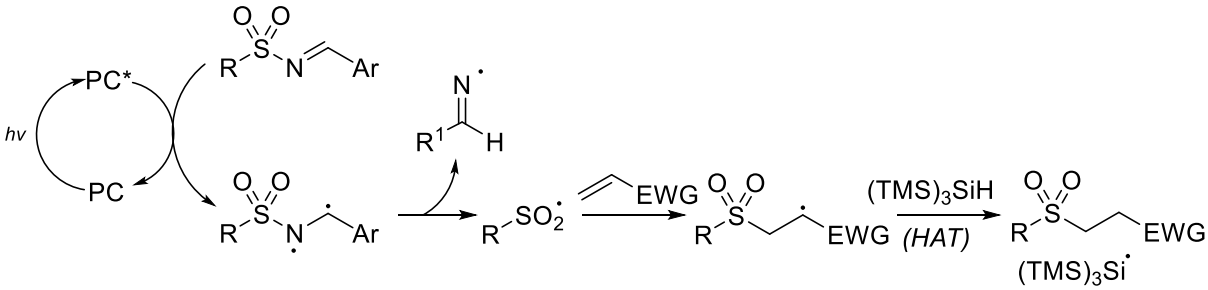
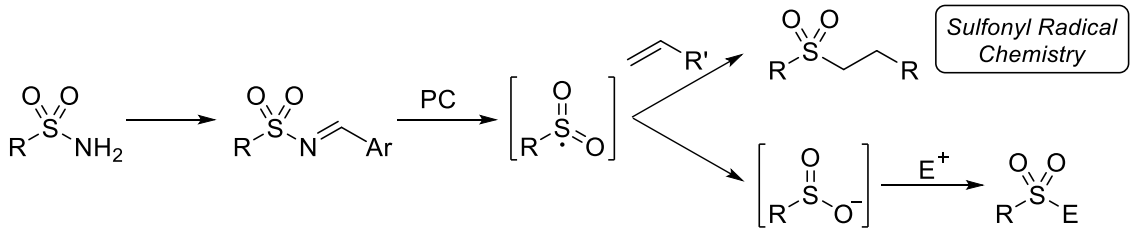



**Figure 4.25.** Proposed catalytic cycle for the hydrosulfonylation of an alkene with a aldimine, in the presence of a photocatalyst.

Although this reaction mechanism appears plausible, it should be noted that during the course of the reactions no imine derived products were obtained, therefore, it is speculated that determining the fate of the imine component and silyl species may aid further mechanism elucidation. Regardless, having a mechanistic hypothesis allows for one to begin designing and rationalising aspects of the reaction to help further improve the system.

## 4.7. Summary and Outlook

Sulfonamides are a common functional group in organic chemistry and have seen a great deal of use in drug-discovery programmes. In particular, primary sulfonamides have become a privileged class of substrate. Therefore, a method has been developed to readily take these primary sulfonamides and substitute them with an activator molecule. This activator then allows the primary sulfonamides to undergo a photocatalytic generation of a sulfonyl radical. The sulfonyl radical provides a useful synthon, as it allows new chemistry avenues to be accessed as well as generation of the sulfinate anion, overall creating a useful late-stage functionalisation strategy for sulfonamide diversification (**Scheme 4.26.**).




**Scheme 4.26.** Summary of the late-stage functionalisation of primary sulfonamides developed, using photochemistry. Where this methodology allows one to exploit sulfonyl radical chemistry as well as sulfinate anion reactivity.

During the course of the development of this reaction, several challenges were encountered, however, it can be expected that the mechanistic work obtained will be able to provide insightful solutions to improve the system. In this context, it is expected that further work to distinguish between a photoredox and photosensitisation pathway would be beneficial. Furthermore, devising a strategy for the reaction to operate under more selective conditions, or increasing the sulfonyl radical longevity to suppress detrimental decomposition, would be exceptionally useful.

Finally, with a robust system developed, there is the opportunity to create a host of new reactions that exploit sulfonyl radical chemistry from a stable precursor. Alternatively, this methodology has the potential to be applied to other aldimine derivatives, including most aza-sulfur compounds, providing

the correct conditions are ascertained. Furthermore, a reaction which would make a significant contribution to this work is the development of a one-pot procedure to directly use primary sulfonamides, similar to the previous reports that also use an aldehyde as an activator for sulfonamide derivatisation.[113b] Regardless, it should be emphasised that the current reaction developed provides a convenient late-stage functionalisation of sulfonamides and is expected to have significant industrial application.

# Chapter 5 – Conclusions and Future Work

At the beginning of this thesis a variety of aza-sulfur compounds were introduced. Several of these moieties were shown to be well established in organic chemistry, whilst others are only just emerging as compounds of interest. In particular, it was noted that the synthesis of sulfoximines and sulfonimidamides is still reliant on rather traditional methods, and this is likely impeding their potential applications. To address this issue, the Willis group has made a significant contribution by developing a divergent method to assemble both sulfoximines and sulfonimidamides from readily available organometallic species and the reagent BiPhONSO.

The work conducted in this thesis has had a significant focus on the role of sulfur based reactive intermediates. For example, computational chemistry was used as an effective tool to provide invaluable insight into the aforementioned divergent synthesis of sulfoxmines and sulfonimidamides. This DFT study has provided support for the involvement of the underexplored sulfinyl nitrene intermediate towards sulfoximines. A noteworthy benefit of this work is that by gaining a greater understanding of sulfinyl nitrenes, this allows for new chemistries to be intelligently designed. In particular it is recognised that the calculated sulfinyl nitrene is a planar intermediate, which can bind to a metal, this may therefore give rise to the possibility for asymmetric catalysis.

With the lack of synthetic routes to racemic sulfoximines and sulfonimidamides sufficiently addressed, attention turned to the enantioselective synthesis of sulfonimidamides. In order to have a useful asymmetric reaction it is desirable to use either a DKR, DyKAT or desymmetrisation process, as these allow both high yield and enantiomeric ratio to be obtained. Therefore, a strategy was devised to exploit configurationally labile sulfonimidamides in an asymmetric organocatalysed sequence. Fundamentally this worked by desymmetrising a symmetric sulfonimdamide anion. It is believed that this methodology may be able to be applied to alternative aza-sulfur compounds. However, what is

maybe more profound is that this concept of exploiting configurational lability in aza-sulfur species has not be used before, hence a diverse range of asymmetric reactions could be developed on this principle.

The final aza-sulfur compound to be discussed was sulfonamides, which have a rich history in commercial pharmaceuticals. In particular primary sulfonamides are commonly encountered in marketed drugs, however they are often viewed as terminal groups rather than synthetic handles. Therefore, a late-stage functionalisation of a primary sulfonamide derivative was developed, which allowed a sulfonyl radical to be generated. The key advantage of this strategy is that the sulfonyl radical can be used as a powerful synthon to access a diverse range of products. From the mechanism that was hypothesised, it appears that the underlying principles of the reaction could be applied to a whole host of other aza-sulfur derived compounds, even generating underexplored aza-sulfur radicals.

Although, the projects outlined in each individual chapter have the potential for future work, attention is drawn to the host of aza-sulfur compounds that have not been discussed in detail. In particular sulfondiimines and sulfonimidoyl fluorides are rapidly gaining tractions as molecules of interest, and therefore provide a great deal of opportunity. In order to further advance the field, new synthesise including asymmetric need to emerge. It can be expected that creative solution are required to develop novel methodology, and the use of underexplored reactive intermediates is likely to be vital.

# Chapter 6 – Experimental Data and Procedures

## 6.1. Table of Contents


**6.2. General Considerations** ..... **167**

**6.3. Experimental Data and Procedures – Chapter 2** ..... **170**

**6.3.1 Computational Methods** ..... **170**

**6.3.2. Benchmarking Studies – Mean Absolute Deviation** ..... **171**

**6.3.3. PhONSO Conformation** ..... **174**

**6.3.4. Rigid Potential Energy Surface Scan** ..... **175**

**6.3.5. Sulfinyl Nitrene NBO Analysis** ..... **176**

**6.3.6. Sulfonimidate Ester Anion** ..... **177**

**6.3.7. Monomeric Pathway Equilibrium** ..... **178**

**6.3.8. Dimeric Pathway Equilibrium** ..... **178**

**6.3.9. Dimeric Pathway Transition States** ..... **180**

**6.3.10. Dimeric Pathway Solvent Effects** ..... **182**

**6.3.11. Bond Dissociation Energies Model Justification** ..... **183**

**6.3.12. Mullikan's Charges and Spin Densities** ..... **184**

**6.3.13. Table of Energies** ..... **187**

**6.4. Experimental Data and Procedures – Chapter 3** ..... **191**

**6.4.1. Experimental Procedures and Characterisation** ..... **191**

**6.4.1.1. Reagent Preparation** ..... **191**

**6.4.1.2. Probing Configurational Lability** ..... **196**

**6.4.1.3. Representative Examples of Catalyst Synthesise** ..... **200**

**6.4.1.4. Synthesis of Mono-Substituted Sulfonimidamides** ..... **203**

**6.4.1.5. Synthesis of Di-Substituted *N,N'*-Sulfonimidamides** ..... **223**

**6.4.1.6. Phase-Transfer Catalysed Alkylation of Sulfonimidamides** ..... **240**

**6.4.1.7. Kinetic Resolution** ..... **275**

**6.4.1.8. Authentic Sample Synthesis** ..... **277**

**6.4.1.9. Configurational Stress Tests** ..... **278**

**6.4.1.10. Deprotections** ..... **278**

**6.4.3. NMR Experiments** 281
**6.4.3.1. Solvent Effects** 281
**6.4.3.2. Additive Effects** 282
**6.4.3.3. Substituted Sulfonimidamide** 283
**6.4.4. Kinetic Resolution** 284
**6.4.5. Further Substrate Optimisation** 285
**6.5. Experimental Data and Procedures – Chapter 4** 290
**6.5.1. Experimental Procedures and Characterisation** 290
**6.5.1.1. Precursor Preparation** 290
**6.5.1.2. Condensation Reactions** 302
**6.5.1.3. Photocatalysis Reaction Optimisation** 339
**6.5.1.4. Photocatalysis Reaction Scope** 340
**6.5.1.5. Photocatalysis Reactions Utilising the Sulfinate Anion** 361
**6.5.2. Luminescence Studies** 364
**6.5.2.1. General Considerations** 364
**6.5.2.2. Absorption and Emission Spectra** 364
**6.5.2.3. Stern-Volmer Quenching** 366
**6.5.3. Cyclic Voltammetry** 368
**6.5.3.1. General Considerations** 368
**6.5.3.2. Data Acquisition** 368
**6.5.4. Computational Details** 369

## 6.2. General Considerations

Reactions were conducted under an inert atmosphere of nitrogen, with anhydrous solvents, unless otherwise stated. Anhydrous THF, $Et_2O$, $CH_2Cl_2$, 1,4-dioxane and toluene were obtained by passing through alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system, these solvents were then degassed with nitrogen prior to use, all other solvents were purchased as anhydrous from a commercial source. All glassware was oven dried (> 80 °C) for at least 16 h prior to use and allowed to cool to room temperature under a positive pressure of nitrogen. When low temperature (< 0 °C) had to be maintained for long periods of time an Easymax 102 Advanced Thermostat system was used or a FT902 FT immersion cooler depending on the reaction in question, otherwise an ice bath or acetone/dry ice bath was used.

The reagents and catalysts *t*-butyl hypochlorite,[288] benzyl iodide,[289] benzyl tosylate[290] and photocatalysts[1d] were prepared according to the literature precedent. The reagents benzyl bromide, 4-methoxybenzaldehyde, methyl vinyl ketone and thionyl chloride were distilled under a nitrogen atmosphere prior to use and stored at −18 °C in the dark. Potassium hydroxide was ground to a fine powder with a pestle and mortar before use as a base in reactions or purchased commercial as a powder. *p*-Toluenesulfinic acid sodium salt was dried under vacuum at 100 °C for 4 h prior to use. The reagent Organometallic reagents in solution were bought from a commercial source and titrated prior to use, the volume used was then adjusted to ensure the equivalents used was constant on repeat experiments. All other reagents were purchased from Sigma-Aldrich Chemical Co. Ltd., Alfa Aesar, Acros Organic Ltd., Fluorochem Ltd., Strem Chemicals Inc. or Insight Biotechnology Ltd. and were used as supplied.

$^1$H NMR spectra were recorded on a Bruker AVIII400 (400 MHz) or AVII500 (700 MHz) spectrometer, $^{13}$C NMR were recorded on a Bruker AVIII400 (101 MHz), AVII 500 (126 MHz),

AVIII HD 500 (126 MHz) or AVIII HD 600 (151 MHz) spectrometer and $^{19}F$ NMR were recorded on a Bruker AVIII400 (377 MHz). Chemical shifts ($\delta_H$, $\delta_C$ and $\delta_F$) are quoted in ppm and relative to tetramethylsilane ($\delta_H$ = 0 ppm) and referenced to the residual solvent peaks. Coupling constants (*J*) are quoted in Hz and rounded to the nearest 0.5 Hz, with the following abbreviations used: s - singlet, br. - broad, app. - apparent, d - doublet, t - triplet, q - quartet, p - pentet, m - multiplet, dd - doublet of doublets, *etc.* Spectra assignments were determined with the use of chemical shifts, coupling constants, two-dimensional NMR spectroscopy and by comparison to spectra of other compounds.

Low resolution mass spectra were recorded on a Waters LCT Premier mass spectrometer. High resolution mass spectra were recorded by the mass spectrometry service at the Chemistry Research Laboratory, University of Oxford, using a Brüker Daltonic μTOF spectrometer (ESI). m/z values are reported in Daltons (Da) and high-resolution values are calculated to four decimal places from the molecular formula, with all found values in a tolerance of 5 ppm.

Infrared spectra (IR) were recorded using a Bruker Tensor 27 Fourier Transform spectrometer using a diamond ATR module. Absorption maximum $\nu_{max}$ are given in wavenumbers ($cm^{-1}$).
Melting points (MP) are recorded in degrees Celsius (°C) using a Leica Galen III hot-stage microscope apparatus, with the crystallisation solvent reported in parenthesis.

Thin layer chromatography (TLC) was performed on Merk aluminium silica gel 60 F254 precoated plates with visualisation under a UV lamp ($\lambda_{max}$ =254 or 365 nm) or by staining with potassium permanganate solution. The retention factors ($R_f$) are reported with the solvent system used in parenthesis. Reactions were followed by TLC when practical. Flash column chromatography (FCC) was carried out on Merk silica gel 60 (230-400 mesh) and the solvent system used reported in parenthesis, for select examples a Biotage was used for this process. Petrol refers to the fraction of light petroleum ether boiling in the range of 40-60 °C.

For reaction monitoring HPLC samples were analysed using an Ascentis® Express C18 10 cm x 4.6 mm, 2.7 μm column (cat# 53827-U). Data was processed using Chem Station for LC systems Rev.B.04.01.SP1.

Optical rotations were measured on a Schmidt Haensch UniPol L2000 polarimeter at 589 nm, 25 °C. $[\alpha]_D^{25}$ is expressed in deg $cm^3$ $g^{-1}$ $dm^{-1}$ and *c* is expressed in g 100 $cm^{-3}$. The enantiomeric ratio (*er*) was determined by chiral stationary phase HPLC in a Dionex P680 chromatogram with a Dionex UVD170U detector ($\lambda_{max}$ = 225, 250, 275 or 300 nm) using a flow rate of 1.0 mL $min^{-1}$ with either a Daicel Chiralpack AD-H, OD-H or IA-3 column. The eluent used and retention times ($\tau_{major}$ and $\tau_{minor}$) are given in parentheses. In an analogous procedure compound **74a** was also analysed on a Dionex UltiMate 3000 chromatogram and compounds **82** and **83** analysed on an Agilent 1260 Series chromatogram.

Compound names are generated by CambridgeSoft ChemBioDraw Ultra 12.0 where appropriate, whilst phase-transfer catalyst names are based on the parent alkaloid, alkylating agent and nature of the anion.

## 6.3. Experimental Data and Procedures – Chapter 2

### 6.3.1. Computational Methods

All calculations were performed using the Gaussian 16 C.01 software package.[291] Geometry optimisations and frequency calculations were obtained at the B3LYP-D3BJ/6-31G(d) level of theory.[292] Solvent effects were accounted for with the SMD implicit solvent model using parameters appropriate for tetrahydrofuran at the same level of theory.[293] Vibrational frequencies were calculated to assign stationary points as either minima or transition structures, the latter characterised by the presence of a large imaginary (negative) frequency, and to calculate the zero-point vibrational energy and thermal corrections. Single point energies were calculated on the optimised structures at the SMD(THF)-ωB97X-D/6-311++g(d,p) level of theory. Gibbs free energies were evaluated with a concentration correction, 0.15 M, in tetrahydrofuran at 195 K as well as 298 K, the relevant conditions for this reaction. In all cases, vibrational entropies were obtained using a quasi-harmonic approximation, treating vibrational modes below 100 $cm^{-1}$ as free rotors and as rigid rotors above this cut-off, as first proposed by Grimme[294] and implemented in *Goodvibes.py*[295]. All Gibbs free energy profiles presented here use the values obtained at 195 K unless otherwise stated.

The minimum-energy crossing points (MECPs) between the singlet and triplet potential-energy surfaces were located using the python script *easyMECP.py*,[296] based on a programme originally developed by Harvey et al.[297] Energies and gradients were calculated at the SMD(THF)-ωB97X-D/6-311++g(d,p) level of theory. A state-averaged vibrational analysis at the MECP was carried out with Glowacki's *glowfreq* code.[298]

A natural bond orbital (NBO) population analysis was conducted on the optimised structures at the B3LYP-D3BJ/6-311++g(d,p) level of theory unless otherwise stated. The NBO population

analysis was performed with *NBO 6.0* integrated with the Gaussian 16 programme.[2b] When appropriate the keywords Hirshfeld and Wiberg were specified.

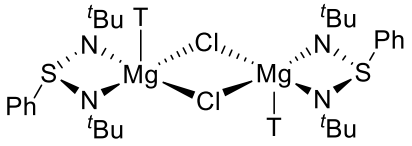
Bond dissociation enthalpies were calculated at the SMD(THF)-uωB97X-D/6-311++g(d,p)//SMD(THF)-uB3LYP-BJD3/6-31g(d) level of theory, and spin densities were analysed *via* a Mullikan population analysis.

The structures generated are visualised using the software CYLView.[299] Atom colours used are the default colour options from the software (Grey = Carbon, White = Hydrogen, Blue = Nitrogen, Red = Oxygen, Light Green = Magnesium, Yellow = Sulfur, Dark Green = Chlorine).

All coordinates are provided in an .xls document as additional information.

### 6.3.2. Benchmarking Studies – Mean Absolute Deviation

**Table 6.1.** Raw Data for MAD of **MD1**

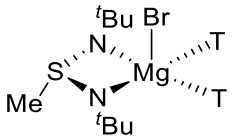



**MD1**

| **MD1** | ΔMg–X | ΔMg–O | ΔMg–N | ΔS–N | ΔS–Mg | ΔS–C | ΔMg–Mg |
|---|---|---|---|---|---|---|---|
| B3LYP | 0.069 | 0.080 | 0.046 | 0.044 | 0.048 | 0.036 | 0.154 |
| B3LYP-D3BJ | 0.034 | 0.030 | 0.020 | 0.040 | 0.026 | 0.025 | 0.054 |
| PBE | 0.060 | 0.101 | 0.051 | 0.052 | 0.056 | 0.048 | 0.098 |
| PBED3 | 0.039 | 0.079 | 0.032 | 0.049 | 0.036 | 0.039 | 0.013 |
| M06 | 0.055 | 0.070 | 0.020 | 0.032 | 0.015 | 0.022 | 0.075 |
| TPSS | 0.061 | 0.093 | 0.051 | 0.055 | 0.064 | 0.045 | 0.120 |
| ωB97X-D | 0.049 | 0.045 | 0.024 | 0.027 | 0.024 | 0.013 | 0.074 |

Comparison of DFT functional geometry optimised structure with X-ray crystallographic structure of **MD1**. Δ values are in Å and where appropriate the bond lengths are averaged, with X referring to either chlorine of bromine.

**Table 6.2.** Raw Data for MAD of **MD2**

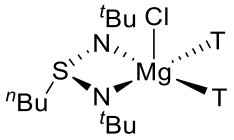



**MD2**

| **MD-2** | ΔMg–X | ΔMg–O | ΔMg–N | ΔS–N | ΔS–Mg | ΔS–C |
|---|---|---|---|---|---|---|
| B3LYP | 0.033 | 0.104 | 0.032 | 0.039 | 0.049 | 0.029 |
| B3LYP-D3BJ | 0.046 | 0.049 | 0.011 | 0.036 | 0.017 | 0.020 |
| PBE | 0.030 | 0.110 | 0.041 | 0.048 | 0.049 | 0.034 |
| PBED3 | 0.036 | 0.077 | 0.029 | 0.047 | 0.031 | 0.028 |
| M06 | 0.057 | 0.068 | 0.002 | 0.026 | 0.015 | 0.013 |
| TPSS | 0.026 | 0.098 | 0.040 | 0.052 | 0.055 | 0.038 |
| ωB97X-D | 0.046 | 0.067 | 0.017 | 0.021 | 0.017 | 0.004 |

Comparison of DFT functional geometry optimised structure with X-ray crystallographic structure of **MD2**. Δ values are in Å and where appropriate the bond lengths are averaged, with X referring to either chlorine of bromine.

**Table 6.3.** Raw Data for MAD of **MD3**

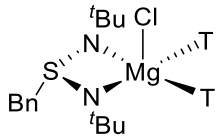



**MD3**

| **MD-3** | ΔMg–X | ΔMg–O | ΔMg–N | ΔS–N | ΔS–Mg | ΔS–C |
|---|---|---|---|---|---|---|
| B3LYP | 0.010 | 0.098 | 0.033 | 0.036 | 0.034 | 0.034 |
| B3LYP-D3BJ | 0.022 | 0.046 | 0.010 | 0.032 | 0.001 | 0.022 |
| PBE | 0.008 | 0.104 | 0.041 | 0.045 | 0.034 | 0.040 |
| PBED3 | 0.017 | 0.072 | 0.026 | 0.043 | 0.013 | 0.033 |
| M06 | 0.031 | 0.075 | 0.008 | 0.022 | 0.003 | 0.015 |
| TPSS | 0.007 | 0.094 | 0.040 | 0.049 | 0.040 | 0.043 |
| ωB97X-D | 0.025 | 0.064 | 0.010 | 0.017 | 0.004 | 0.005 |

Comparison of DFT functional geometry optimised structure with X-ray crystallographic structure of **MD3**. Δ values are in Å and where appropriate the bond lengths are averaged, with X referring to either chlorine of bromine.

**Table 6.4.** Raw Data for MAD of **MD4**

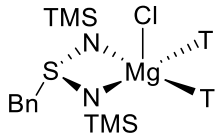



**MD4**

| **MD-4** | ΔMg–X | ΔMg–O | ΔMg–N | ΔS–N | ΔS–Mg | ΔS–C |
|---|---|---|---|---|---|---|
| B3LYP | 0.007 | 0.099 | 0.020 | 0.200 | 0.030 | 0.039 |
| B3LYP-D3BJ | 0.020 | 0.047 | 0.004 | 0.205 | 0.007 | 0.023 |
| PBE | 0.005 | 0.107 | 0.027 | 0.192 | 0.032 | 0.053 |
| PBED3 | 0.013 | 0.075 | 0.013 | 0.195 | 0.011 | 0.042 |
| M06 | 0.025 | 0.072 | 0.006 | 0.214 | 0.009 | 0.015 |
| TPSS | 0.002 | 0.097 | 0.028 | 0.189 | 0.039 | 0.056 |
| ωB97X-D | 0.018 | 0.066 | 0.001 | 0.219 | 0.008 | 0.002 |

Comparison of DFT functional geometry optimised structure with X-ray crystallographic structure of **MD4**. Δ values are in Å and where appropriate the bond lengths are averaged, with X referring to either chlorine of bromine.

**Table 6.5.** Raw Data for MAD of **MD5**




**MD5**

| **MD-5** | ΔMg–X | ΔMg–O | ΔMg–N | ΔS–N | ΔS–Mg | ΔS–C |
|---|---|---|---|---|---|---|
| B3LYP | 0.004 | 0.089 | 0.025 | 0.030 | 0.024 | 0.043 |
| B3LYP-D3BJ | 0.017 | 0.040 | 0.003 | 0.026 | 0.011 | 0.025 |
| PBE | 0.003 | 0.096 | 0.031 | 0.039 | 0.028 | 0.058 |
| PBED3 | 0.010 | 0.067 | 0.017 | 0.037 | 0.007 | 0.047 |
| M06 | 0.026 | 0.058 | 0.005 | 0.016 | 0.019 | 0.015 |
| TPSS | 0.003 | 0.090 | 0.032 | 0.041 | 0.038 | 0.062 |
| ωB97X-D | 0.014 | 0.058 | 0.010 | 0.014 | 0.006 | 0.002 |

Comparison of DFT functional geometry optimised structure with X-ray crystallographic structure of **MD5**. Δ values are in Å and where appropriate the bond lengths are averaged, with X referring to either chlorine of bromine.

### 6.3.3. PhONSO Conformation

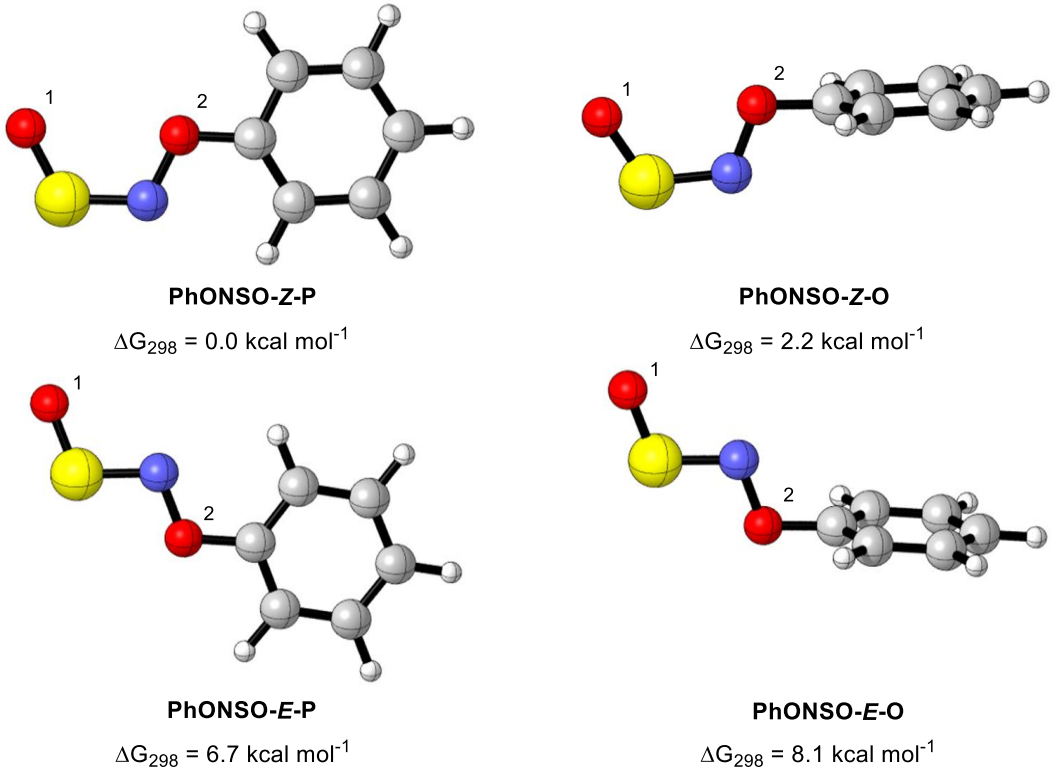



**Figure 6.1.** Examination of the conformation of PhONSO, with *Z*- (∠O-S-N-O = 0°) and *E*-isomers (∠O-S–N–O = 180°) and conformations with the phenyl orientation being on the same plane (P) or perpendicular (O) to the O-S-N-O angle, respectively. Energies at the B3LYP/6 11+g(d,p)//B3LYP/6 31g(d),SMD(THF) level of theory at 298 K.

Analysis of the various conformation of PhONSO (**Figure 6.1.**) shows that **PhONSO-*Z*-P** to be the thermodynamically most stable species, in agreement with X-ray crystallographic data.[300,132] Due to this throughout the text PhONSO refers to **PhONSO-*Z*-P**. To further understand these results a NBO analysis was conducted on the PhONSO molecules with the phenyl ring perpendicular (**Table 6.6.**).

**Table 6.6.** NBO Analysis of PhONSO

| | $n_{o1} \rightarrow$ S–N $\sigma^*$ | $n_{o1} \rightarrow$ S–N $\pi^*$ | $n_s \rightarrow$ N–$O^2$ $\sigma^*$ | $n_N \rightarrow$ S–$O^1$ $\sigma^*$ | $n_{O2} \rightarrow$ S–N $\sigma^*$ |
|---|---|---|---|---|---|
| PhONSO-*Z*-P | 66.9 | 22.1 | 6.9 | 8.1 | 34.2 |
| PhONSO-*E*-P | 64.6 | 19.1 | 0.0 | 2.7 | 31.3 |

Stabilization energies E(2) in the PhONSO molecule (in kcal $mol^{-1}$) from Second Order Perturbation Theory analysis at the SMD(THF)-B3LYP/6-31g(d) level of theory.

From this NBO analysis several key interactions appear to stabilise the **PhONSO-*Z*-P** conformation. Primarily, stabilisation by donation of the S lone pair into the N–$O^2$ σ* (6.9 vs 0.0 kcal $mol^{-1}$ in **PhONSO-*E*-P**) and the N lone pair into the S–$O^1$ σ* (8.1 vs to 2.7 kcal $mol^{-1}$). Moreover, a planar conformation of the phenyl ring relative to the O–S–N–O moiety is stabilised via delocalisation of the O lone pair within the ring. Overall, these results indicate that in the *Z*-conformation electronic delocalization into the σ* and π* orbitals outweigh any electrostatic or steric repulsion.

### 6.3.4. Rigid Potential Energy Surface Scan

The rigid PES scan was conducted with both the B3LYP and ωB97X-D functionals paired with the 6-31G(d) basis set at 298 K, which provided identical conclusions. For the calculations, the internal coordinates were specified using a Z-matrix, in which the N–O bond was scanned in increments of 0.1 Å. The final and end coordinates of the scan are provided:

| **Initial Geometry** | | | | **Final Geometry** | | | |
|---|---|---|---|---|---|---|---|
| C | 2.228854 | 1.549292 | 0.891108 | C | 10.253526 | 1.231274 | 1.061000 |
| H | 2.076214 | 1.379709 | 1.964938 | H | 9.649754 | 1.087957 | 1.966587 |
| H | 1.371251 | 2.085357 | 0.480278 | H | 9.964944 | 2.164259 | 0.573261 |
| H | 3.146879 | 2.126326 | 0.751468 | H | 11.310193 | 1.253484 | 1.340639 |
| S | 2.391077 | 0.023268 | -0.072198 | S | 10.042113 | -0.080091 | -0.171336 |
| O | 3.704192 | -0.713420 | 0.288819 | O | 10.623285 | -1.417473 | 0.349203 |
| N | 1.185908 | -0.324467 | -1.072752 | N | 9.287925 | 0.325933 | -1.528098 |
| O | 0.130559 | -1.159485 | -0.357676 | O | -6.892064 | -1.959404 | 0.058435 |
| C | -1.035701 | -0.548196 | -0.204453 | C | -7.605834 | -0.842894 | 0.023043 |
| C | -1.329517 | 0.751609 | -0.662775 | C | -7.071181 | 0.448963 | -0.153399 |
| C | -2.054458 | -1.260222 | 0.464620 | C | -9.004350 | -0.966166 | 0.169543 |
| C | -2.588133 | 1.301462 | -0.444741 | C | -7.911859 | 1.556640 | -0.170877 |
| H | -0.555213 | 1.293479 | -1.190727 | H | -6.000634 | 0.544672 | -0.282519 |
| C | -3.303152 | -0.693803 | 0.671670 | C | -9.825292 | 0.151227 | 0.148961 |
| H | -1.826304 | -2.262511 | 0.815930 | H | -9.414555 | -1.963001 | 0.304107 |
| C | -3.588743 | 0.596632 | 0.221557 | C | -9.291422 | 1.430228 | -0.019935 |
| H | -2.790188 | 2.307606 | -0.809084 | H | -7.473997 | 2.544101 | -0.309060 |
| H | -4.066230 | -1.267572 | 1.195111 | H | -10.899819 | 0.022876 | 0.268994 |
| H | -4.567909 | 1.039183 | 0.385440 | H | -9.936479 | 2.304955 | -0.035075 |

### 6.3.5. Sulfinyl Nitrene NBO Analysis

A natural bond orbital (NBO) population analysis of **Nitrene-$T_1$** and **Nitrene-$S_1$** was conducted on the optimised structures at the B3LYP/6-311++g(d,p), using both Hirshfeld and Wiberg population analysis as implemented by gaussian16. The Hirshfeld population analysis included the Charge Model 5 analysis.[301] The NBO calculation was also conducted with a smaller basis set and was shown to provide analogous results.

**Table 6.7.** Raw Data for Hirshfeld population analysis of **Nitrene-$T_1$**

| Atom | Charge | Spin Density | Dipole-$D_x$ | Dipole-$D_y$ | Dipole-$D_z$ | Charge CM5 |
|---|---|---|---|---|---|---|
| C | -0.07338 | 0.090123 | -0.02225 | -0.018227 | 0.000279 | -0.20149 |
| H | 0.059715 | 0.011491 | -0.04113 | -0.146795 | -0.05886 | 0.113407 |
| H | 0.05582 | 0.007834 | -0.11566 | 0.097498 | -0.05403 | 0.110405 |
| H | 0.058679 | 0.007818 | -0.01855 | -0.011651 | 0.160108 | 0.114211 |
| O | -0.35045 | 0.106621 | -0.14385 | 0.109022 | -0.08296 | -0.38961 |
| S | 0.347941 | 0.207901 | -0.05237 | -0.054729 | 0.095793 | 0.419711 |
| N | -0.09833 | 1.568211 | -0.01797 | -0.252995 | -0.05589 | -0.16663 |
| Total | 0.00000 | 2.00000 | -0.41176 | -0.277876 | 0.004441 | 0.00000 |

Examination of the Hirshfeld charges at the B3LYP-D3BJ/6-311++g(d,p) level of theory for **Nitrene-$T_1$,** where charges are in atomic units.

**Table 6.8.** Raw Data for Hirshfeld population analysis of **Nitrene-$S_1$**

| Atom | Charge | Spin Density | Dipole-$D_x$ | Dipole-$D_y$ | Dipole-$D_z$ | Charge CM5 |
|---|---|---|---|---|---|---|
| C | -0.05084 | 0.00000 | -0.01843 | -0.00388 | 0.000004 | -0.18050 |
| H | 0.067558 | 0.00000 | -0.07491 | 0.065005 | 0.134438 | 0.121865 |
| H | 0.064619 | 0.00000 | -0.0398 | -0.16014 | -0.000104 | 0.119262 |
| H | 0.067551 | 0.00000 | -0.07497 | 0.065185 | -0.134313 | 0.12186 |
| O | -0.30021 | 0.00000 | -0.03405 | -0.16829 | -0.000007 | -0.34251 |
| S | 0.436227 | 0.00000 | -0.19057 | 0.12268 | -0.000028 | 0.552307 |
| N | -0.28491 | 0.00000 | -0.13026 | 0.123031 | 0.000006 | -0.39229 |
| Total | 0.00000 | 0.00000 | -0.56298 | 0.043586 | -0.000004 | 0.00000 |

Examination of the Hirshfeld charges at the B3LYP-D3BJ/6-311++g(d,p) level of theory for **Nitrene-$S_1$,** where charges are in atomic units.

**Table 6.9.** Raw Data for Wiberg population analysis of **Nitrene-$T_1$**

| Atom | | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|
| 1 | C | 0.0000 | 0.9253 | 0.9275 | 0.9253 | 0.0916 | 0.8796 | 0.0305 |
| 2 | H | 0.9253 | 0.0000 | 0.0004 | 0.0003 | 0.0014 | 0.0041 | 0.0077 |
| 3 | H | 0.9275 | 0.0004 | 0.0000 | 0.0005 | 0.0132 | 0.0041 | 0.0009 |
| 4 | H | 0.9253 | 0.0003 | 0.0005 | 0.0000 | 0.0029 | 0.0110 | 0.0036 |
| 5 | O | 0.0916 | 0.0014 | 0.0132 | 0.0029 | 0.0000 | 1.2562 | 0.1667 |
| 6 | S | 0.8796 | 0.0041 | 0.0041 | 0.0110 | 1.2562 | 0.0000 | 1.0591 |
| 7 | N | 0.0305 | 0.0077 | 0.0009 | 0.0036 | 0.1667 | 1.0591 | 0.0000 |

Examination of the Wiberg bond indices at the B3LYP-D3BJ/6-311++g(d,p) level of theory for **Nitrene-$T_1$**.

**Table 6.10.** Raw Data for Wiberg population analysis of **Nitrene-$S_1$**

| Atom | | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|
| 1 | C | 0.0000 | 0.9226 | 0.9252 | 0.9226 | 0.0925 | 0.8514 | 0.1201 |
| 2 | H | 0.9226 | 0.0000 | 0.0003 | 0.0006 | 0.0023 | 0.0027 | 0.0139 |
| 3 | H | 0.9252 | 0.0003 | 0.0000 | 0.0003 | 0.0117 | 0.0032 | 0.0026 |
| 4 | H | 0.9226 | 0.0006 | 0.0003 | 0.0000 | 0.0023 | 0.0027 | 0.0139 |
| 5 | O | 0.0925 | 0.0023 | 0.0117 | 0.0023 | 0.0000 | 1.2333 | 0.4222 |
| 6 | S | 0.8514 | 0.0027 | 0.0032 | 0.0027 | 1.2333 | 0.0000 | 2.0796 |
| 7 | N | 0.1201 | 0.0139 | 0.0026 | 0.0139 | 0.4222 | 2.0796 | 0.0000 |

Examination of the Wiberg bond indices at the B3LYP-D3BJ/6-311++g(d,p) level of theory for **Nitrene-$S_1$**.

### 6.3.6. Sulfonimidate Ester Anion

Transition states were searched from three possible sulfonimidate ester anion species (**Figure 6.3.**). Although no transition states were located it was noted that the relative energies are comparable to the results obtained with the chloride counterion (see **Figure 2.6**).

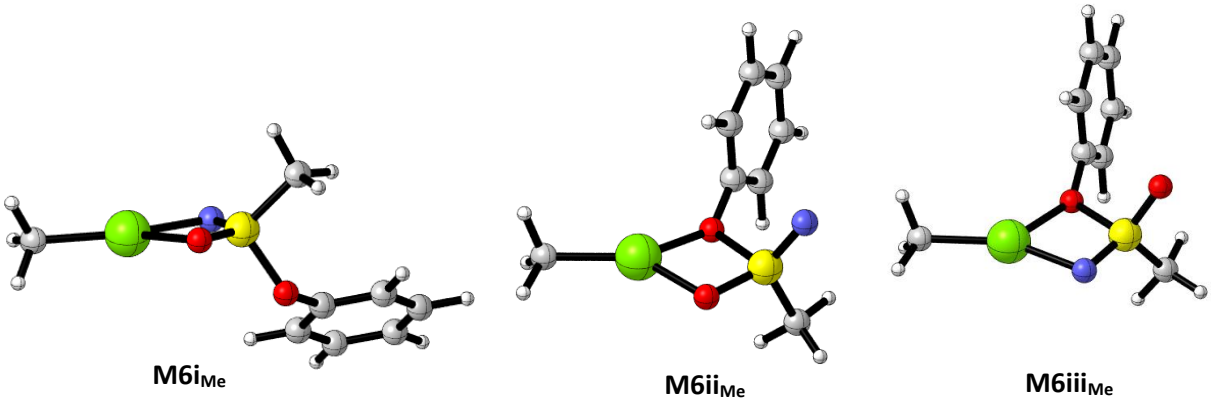



**Figure 6.2.** Calculated structures for sulfonimidate ester anion bound to magnesium methyl. Energies at the SMD(THF)-ωB97X-D/6-311++g(d,p)//SMD(THF)-B3LYP-BJD3/6-31g(d) level of theory at 195 K, relative to $MeMe_2$ and PhONSO.

### 6.3.7. Monomeric Pathway Equilibrium

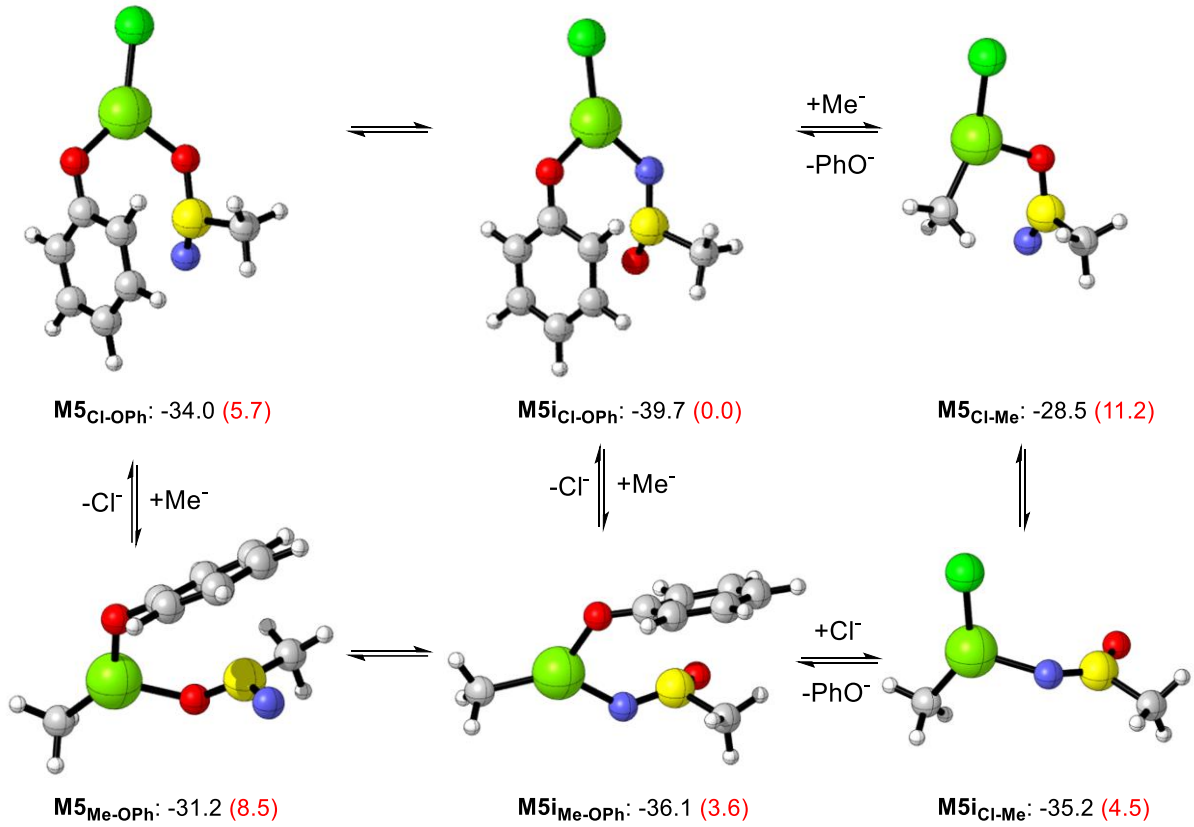



**Figure 6.3.** Intermediates in equilibrium, with the sulfinyl nitrene bound to magnesium with a range of coordinated anions. With Gibbs free energy at 195 K relative to the free **PhONSO**, **M0** and **ClMgOPh**, and **M5i**$_{\text{Cl-OPh}}$ given in parentheses. Energies at the SMD(THF)-ωB97X-D/6-311++g(d,p)//SMD(THF)-B3LYP-BJD3/6-31g(d) level of theory given in kcal mol$^{-1}$.

All sulfinyl nitrene species are assumed to be in equilibrium due to the Schlenk Equilibria and the low barrier interconversion process as determined by Cascella for MeMgCl.[144] For the discussion energies are referred to intermediate **M5i**$_{\text{Cl-OPh}}$ due to it being the most thermodynamically stable. When searching for transition states only those presented in Chapter 2 were located.

### 6.3.8. Dimeric Pathway Equilibrium

When considering the relative energy of dimeric complexes potentially in equilibrium, the methyl bridged species were not evaluated, the justification for which is based on previous work indicating that methyl bridged species are less stable.[141a,144,146] Therefore a range of alternative coordination modes and ligand arrangements were considered (**Figure 6.4.** & **Figure 6.5.**)

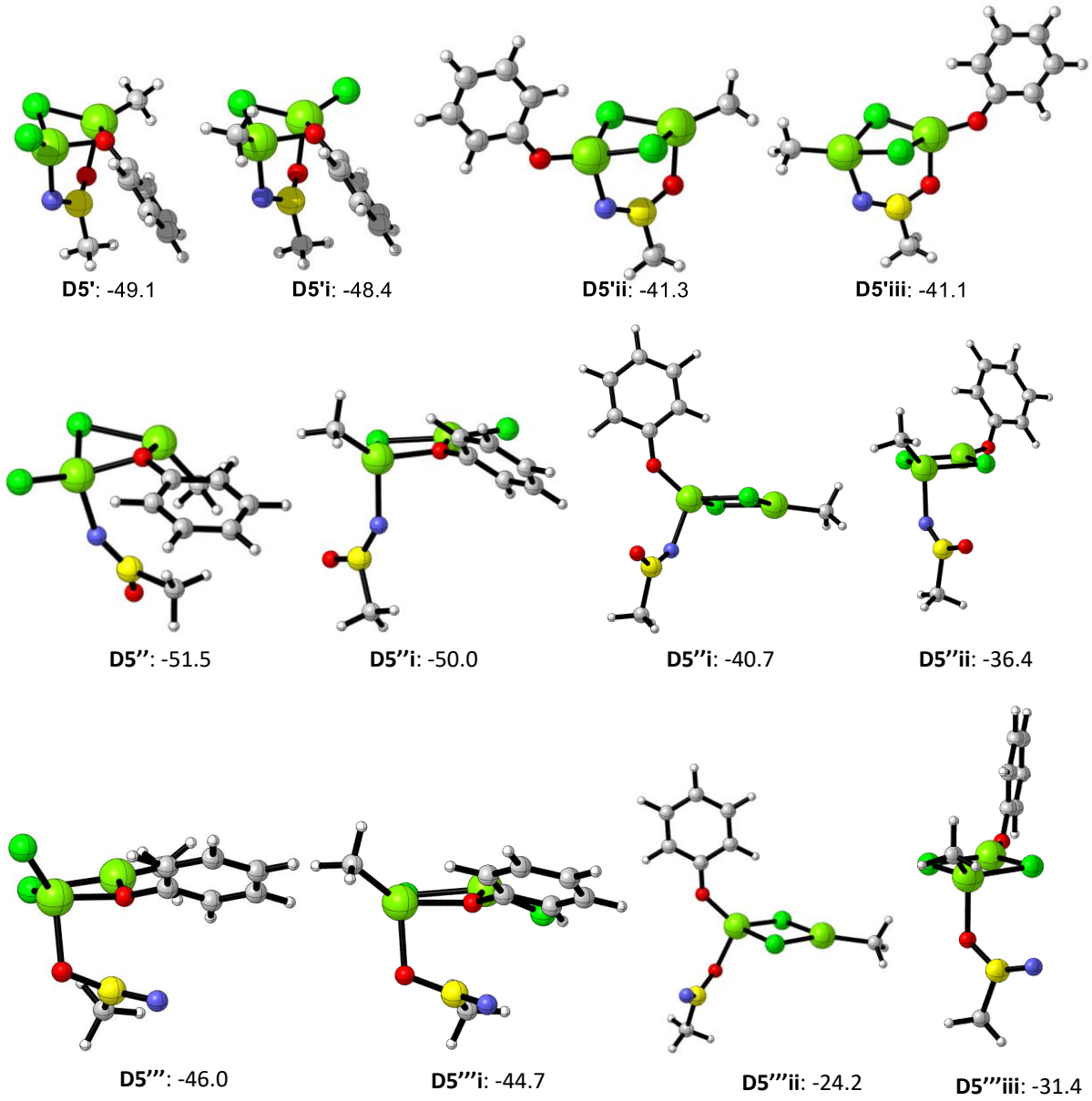



**Figure 6.4.** Various arrangements for the singlet sulfinyl nitrenes coordinated to a magnesium dimer. Energies at the SMD(THF)-ωB97X-D/6-311++g(d,p)//SMD(THF)-B3LYP-BJD3/6-31g(d) level of theory in kcal $mol^{-1}$. Energies are relative to **D0** and **PhONSO**.

A variety of arrangements were considered for the sulfinyl nitrene, including coordination to both magnesiums or a singular magnesium, as well as coordination *via* nitrogen or oxygen. The most stable sulfinyl nitrene species was **D5''**, which interestingly progresses directly to the sulfoximine product (see **Figure 2.10.**).

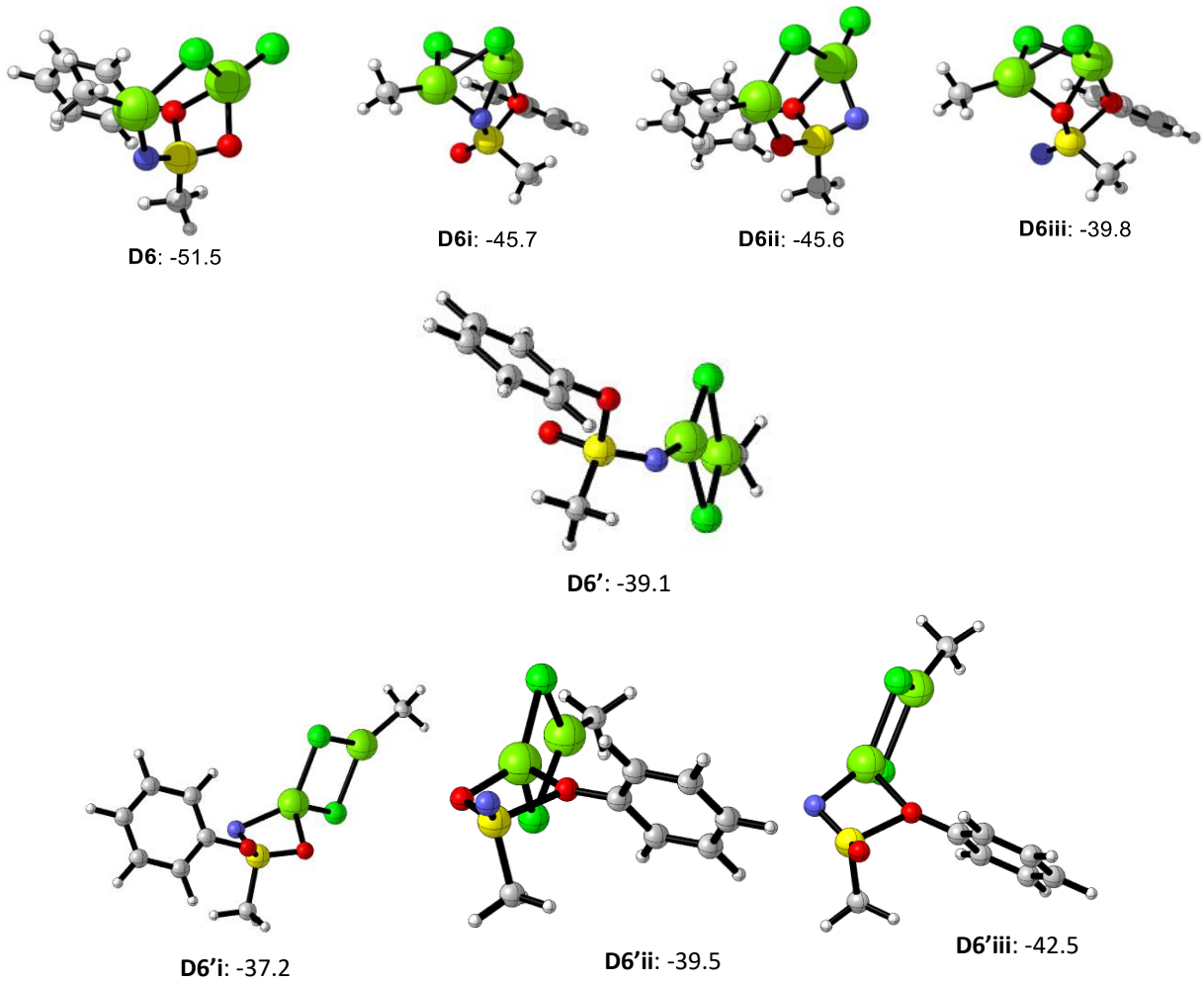



**Figure 6.5.** Various arrangements for the sulfonimidate ester anion coordinated to a magnesium dimer. Energies at the SMD(THF)-ωB97X-D/6-311++g(d,p)//SMD(THF)-B3LYP-BJD3/6-31g(d) level of theory in kcal $mol^{-1}$. Energies are relative to **D0** and **PhONSO**.

The sulfonimidate ester anion has a variety of coordination modes, although all species are shown to have comparable energies to the aforementioned sulfinyl nitrene intermediates.

### 6.3.9. Dimeric Pathway Transition States

15 transition states were located for the methyl addition to the sulfinyl nitrene (**Figure 6.7.** & **Figure 6.8.**). As can be seen the transition states involving chloride bridging dimers are much higher in energy (**Figure 6.7.**). This can be ascribed to the strain induced in these transition states compared to the lowest energy transition state (**Di-TS$_{Si-7}$**). **Figure 6.8.** provides a pictorial representation of the transition states in **Figure 2.11.**. All IRC calculations resulted in the intermediates outlined in **Figure 6.4.** and generic sulfoximine or sulfinamide anion products (**D7** and **D8** respectively).

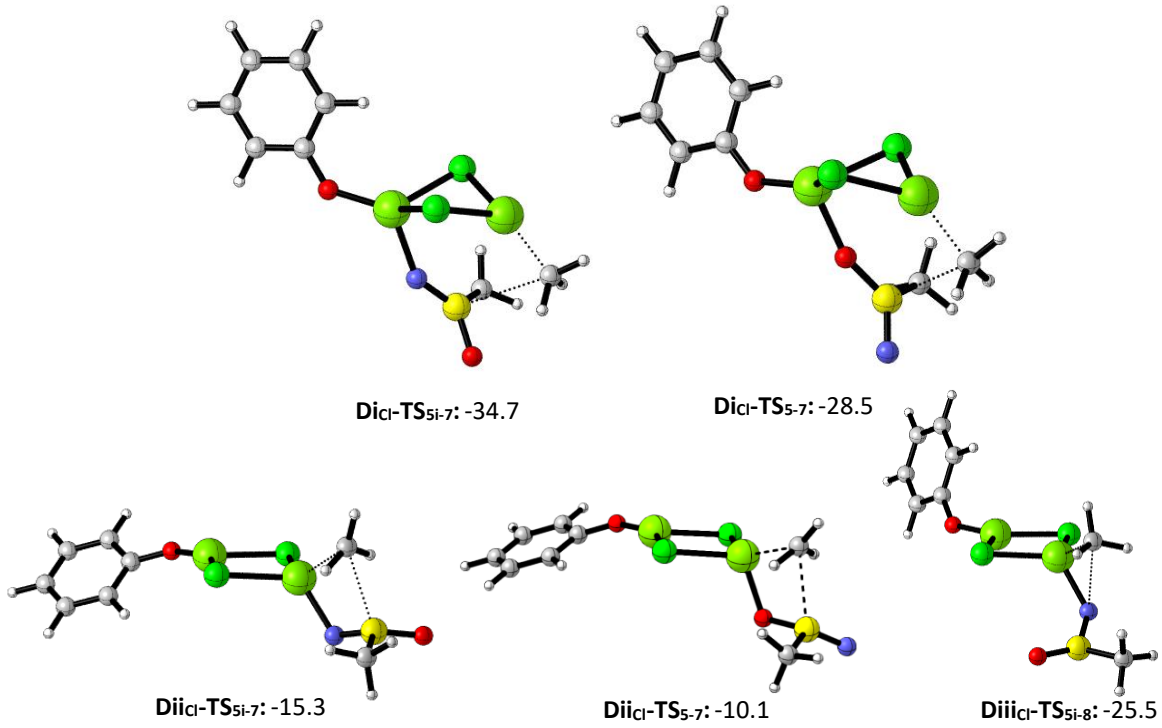



**Figure 6.7.** Various transition states for the methyl addition into the sulfinyl nitrene with bridging chloride atoms. Energies at the SMD(THF)-ωB97X-D/6-311++g(d,p)//SMD(THF)-B3LYP-BJD3/6-31g(d) level of theory in kcal mol$^{-1}$. Energies are relative to **D0** and **PhONSO**.

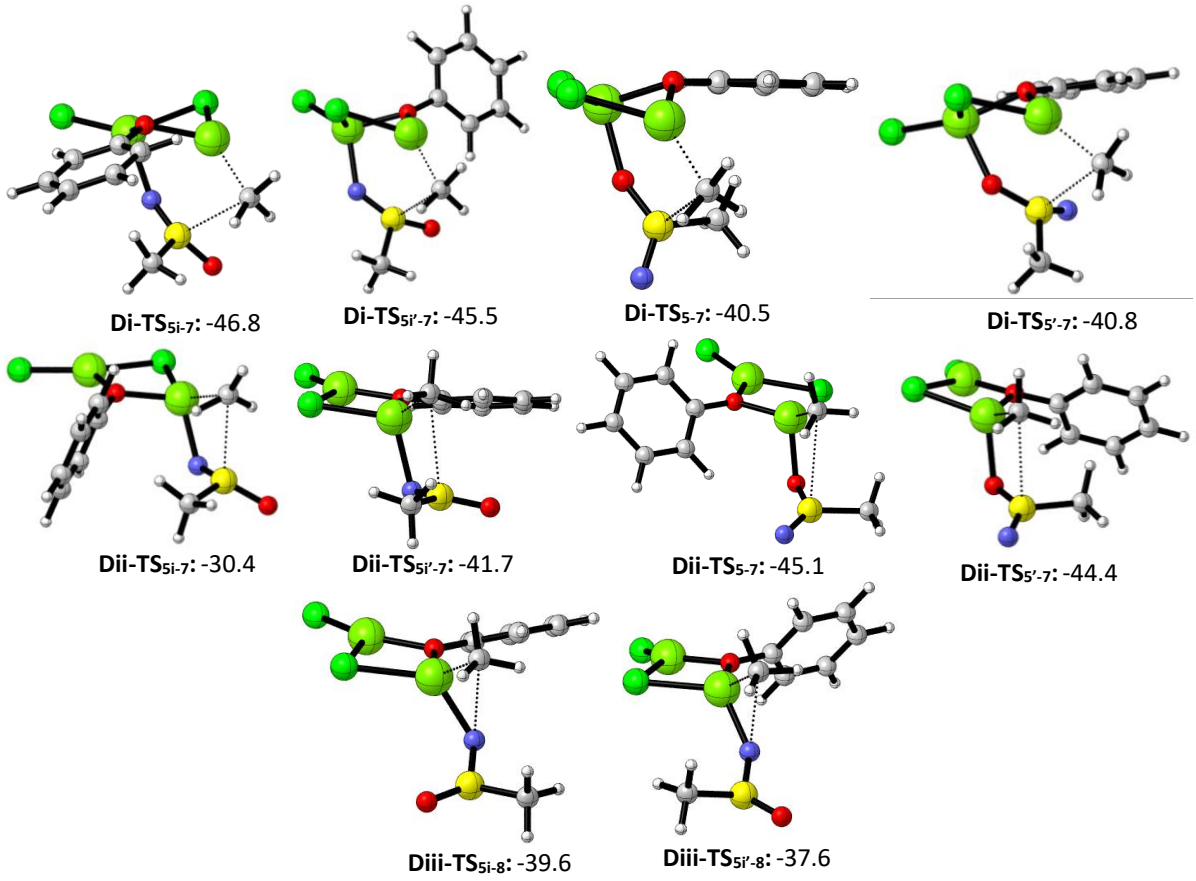



**Figure 6.8.** Various transition states for the methyl addition into the sulfinyl nitrene with a bridging phenoxide. Energies at the SMD(THF)-ωB97X-D/6-311++g(d,p)//SMD(THF)-B3LYP-BJD3/6-31g(d) level of theory in kcal mol$^{-1}$. Energies are relative to **D0** and **PhONSO**.

### 6.3.10. Dimeric Pathway Solvent Effects

As has been stated when considering implicit solvent in the first methyl addition two THF molecules can either arrange in a *trans* or *cis* conformation with respect to each other. Therefore, the energy profiles with different bridged ligands was assessed, when the THF molecules are in these two possible arrangements (**Figure 6.9.**)

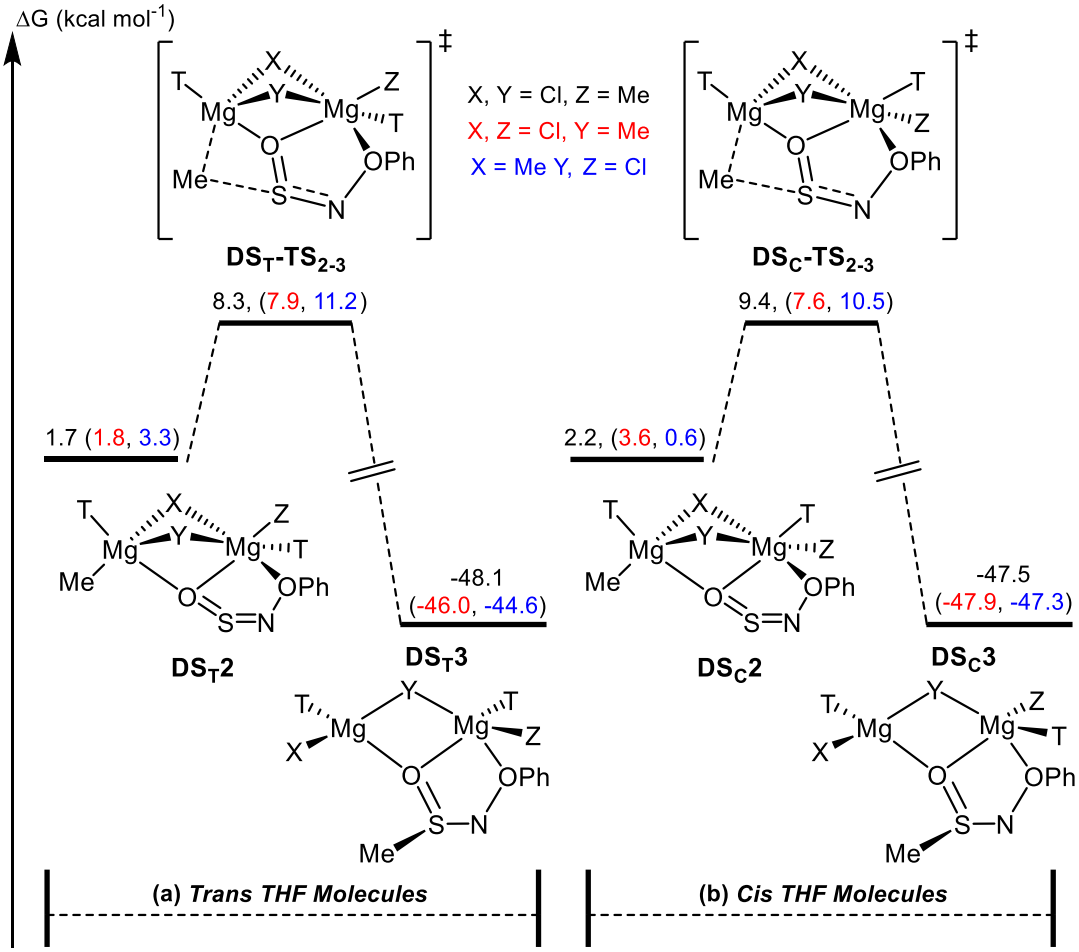


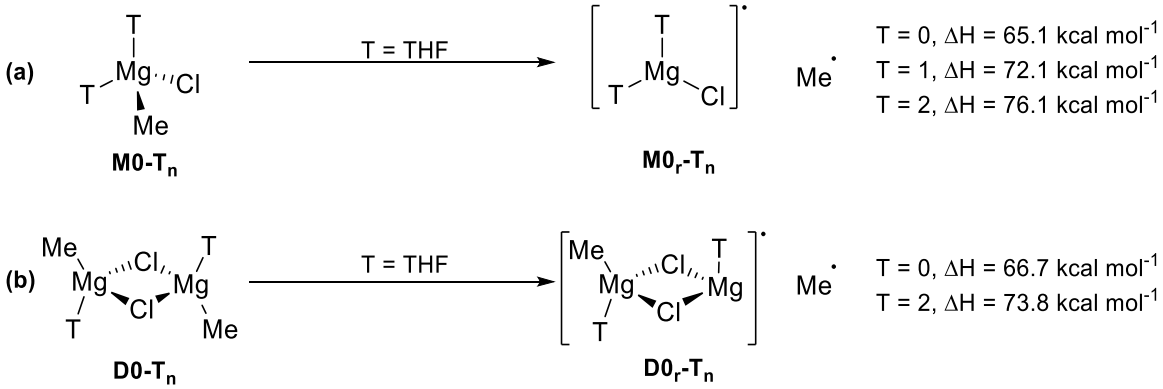

**Figure 6.9.** Energy profile examining the impact of bridging ligands on the first methyl addition, aiding the evaluation for the role of explicit solvent. Energies at the SMD(THF)-ωB97X-D/6-311++g(d,p)//SMD(THF)-B3LYP-BJD3/6-31g(d) level of theory at 195 K. Where X, Y and Z are a combination of Cl and $CH_3$ and their respective energies reported in parenthesis where appropriate. **(a)** When the THF molecules are situated *trans* to each other. **(b)** When the THF molecules are situated *cis* to each other.

Regardless of the respective orientation of the THF molecules the energy profiles produced have a similar shape. Although there some deviation between the individual species it is noticeable that the transition states show a similar trend with respect to the bridging ligands. Therefore, it is assumed that

the configuration of the THF molecules around the magnesium dimer does not have a substantial impact on the energetics, and hence provide identical conclusions.

### 6.3.11. Bond Dissociation Energies Model Justification

To determine if the methodology was appropriate to assess the plausibility of a radical pathway, the BDE of methyl magnesium chloride was first evaluated in the absence of substrate (**Scheme 6.1.**). BDE were calculated to be between 65.1 and 76.1 kcal mol$^{-1}$, and inclusion of explicit THF increased the value. This highly endothermic process for both monomer and dimer complexes is similar to experimental results obtained for BDE of MeMgBr in THF (~61 kcal mol$^{-1}$).[302] Although these values are not directly comparable, caution was taken that this method may over-approximate the energy required to form a methyl radical.



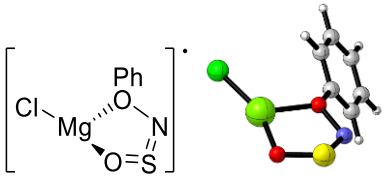

**Scheme 6.1.** Examining the bond dissociation enthalpies for methyl magnesium chloride in THF. Energies at the SMD(THF)-uωB97X-D/6-311++g(d,p)//SMD(THF)-uB3LYP-BJD3/6-31g(d) level of theory at 195 K. Where T represents the amount of THF molecules which were modelled in the system. **(a)** For a monomeric magnesium compound. **(b)** For a dimeric magnesium compound.

Therefore, it appeared that this methodology was appropriate to determine if a radical pathway was a plausible mechanism. For the calculations, the bond dissociation was proposed to occur to the most stable radical species, which may require the rearrangement of the singlet ground state to a higher energy intermediate.

### 6.3.12. Mullikan's Charges and Spin Densities

The Mullikan's charges and spin densities for each atom were determined at the SMD(THF)-uωB97X-D/6-311++g(d,p)//SMD(THF)-uB3LYP-BJD3/6-31g(d) level of theory. These indicate that the PhONSO molecules aids the low BDE by sufficient stabilisation of the resulting radical. This scenario is especially pronounced when the methyl magnesium species is in the presence of the triplet sulfinyl nitrene.

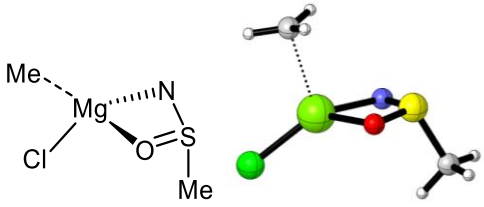
**Table 6.11.** Mullikan's Charge Spin Density for **M2$_r$**




| Number | Atom | Charge | Spin Density |
|---|---|---|---|
| 1 | Mg | 0.852164 | -0.01423 |
| 2 | Cl | -0.41035 | -0.00020 |
| 3 | O | -0.48739 | 0.083972 |
| 4 | S | 0.337794 | 0.40900 |
| 5 | N | -0.28527 | 0.476841 |
| 6 | O | -0.03029 | 0.04124 |
| 7 | C | -0.37243 | -0.0187 |
| 8 | C | 0.293831 | -0.01146 |
| 9 | C | -0.24131 | 0.033551 |
| 10 | C | -0.26954 | -0.00069 |
| 11 | H | 0.272208 | -0.00246 |
| 12 | C | -0.23915 | 0.003751 |
| 13 | H | 0.218828 | -0.00148 |
| 14 | C | -0.4362 | 0.00072 |
| 15 | H | 0.277301 | 0.000018 |
| 16 | H | 0.280576 | 0.00007 |
| 17 | H | 0.239211 | 0.000063 |

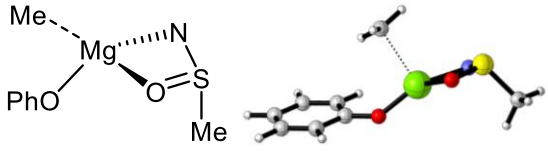
Charge and spin density for the optimised structure of **M2$_r$**

**Table 6.12. & Table 6.13.** Mullikan's Charge Spin Density for **M4$_{Clr}$** & **M4$_{OPhr}$** respectively.




| Atom | | Charge | Spin Density |
|---|---|---|---|
| 1 | Mg | 0.560556 | 0.026016 |
| 2 | C | -0.669771 | 0.111265 |
| 3 | H | 0.236490 | 0.006291 |
| 4 | H | 0.232890 | -0.002257 |
| 5 | H | 0.234343 | 0.005911 |
| 6 | O | -0.431855 | 0.012857 |
| 7 | S | 0.593603 | 0.091056 |
| 8 | N | -0.500424 | 0.851883 |
| 9 | C | -0.519534 | 0.973191 |
| 10 | H | 0.192074 | -0.029161 |
| 11 | H | 0.208226 | -0.027079 |
| 12 | H | 0.207390 | -0.027318 |
| 13 | Cl | -0.343987 | 0.007345 |

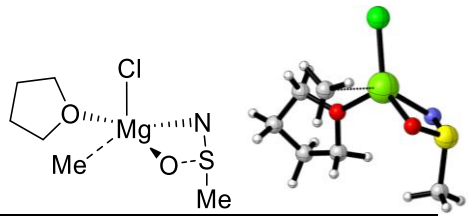
Charge and spin density for the optimised structure of **M4$_{Clr}$**




| Atom | | Charge | Spin Density |
|---|---|---|---|
| 1 | Mg | 0.580734 | 0.004081 |
| 2 | C | -0.662565 | 0.098198 |
| 3 | H | 0.235052 | 0.008948 |
| 4 | H | 0.232607 | -0.003169 |
| 5 | H | 0.235522 | 0.005076 |
| 6 | O | -0.440486 | 0.007272 |
| 7 | S | 0.848611 | 0.121441 |
| 8 | N | -0.543027 | 0.855184 |
| 9 | C | -0.491165 | 0.982645 |
| 10 | H | 0.204057 | -0.033804 |
| 11 | H | 0.224813 | -0.027178 |
| 12 | H | 0.183164 | -0.027854 |
| 13 | O | -0.356809 | 0.018955 |
| 14 | C | -0.270019 | -0.056605 |
| 15 | C | 0.075610 | 0.038546 |
| 16 | C | -0.179008 | -0.001756 |
| 17 | C | -0.221141 | 0.007931 |
| 18 | H | 0.200136 | 0.002575 |
| 19 | C | -0.305233 | -0.000916 |
| 20 | H | 0.225887 | -0.000220 |
| 21 | C | -0.491986 | 0.000399 |
| 22 | H | 0.250366 | 0.000234 |
| 23 | H | 0.245452 | 0.000154 |
| 24 | H | 0.219429 | -0.000136 |

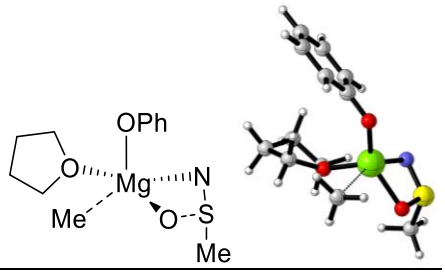
Charge and spin density for the optimised structure of **M4$_{OPhr}$**

**Table 6.14. & Table 6.15.** Mullikan's Charge Spin Density for **M4$_{Clr}$-T$_1$** & **M4$_{OPhr}$-T$_1$** respectively.




| Atom | | Charge | Spin Density |
|---|---|---|---|
| 1 | Mg | 0.257996 | 0.013147 |
| 2 | Cl | -0.308932 | 0.016017 |
| 3 | C | -0.633557 | 0.075074 |
| 4 | H | 0.219798 | 0.007272 |
| 5 | H | 0.240421 | -0.002318 |
| 6 | H | 0.226951 | 0.002394 |
| 7 | O | -0.367456 | -0.001179 |
| 8 | S | 0.697261 | 0.124252 |
| 9 | N | -0.515020 | 0.825994 |
| 10 | C | -0.547528 | 1.039049 |
| 11 | H | 0.189568 | -0.034103 |
| 12 | H | 0.216510 | -0.032088 |
| 13 | H | 0.178493 | -0.033094 |
| 14 | O | -0.020854 | -0.014645 |
| 15 | C | -0.192653 | -0.001911 |
| 16 | C | -0.310257 | 0.007813 |
| 17 | C | -0.533291 | -0.001713 |
| 18 | H | 0.225335 | -0.000733 |
| 19 | H | 0.201714 | 0.003624 |
| 20 | C | -0.572184 | 0.002693 |
| 21 | H | 0.219535 | 0.004637 |
| 22 | H | 0.279556 | -0.000832 |
| 23 | H | 0.181959 | 0.000175 |
| 24 | H | 0.240248 | 0.000215 |
| 25 | H | 0.224310 | 0.000420 |
| 26 | H | 0.202078 | -0.000162 |

Charge and spin density for the optimised structure of **M4$_{Clr}$-T$_1$**




| Atom | | Charge | Spin Density |
|---|---|---|---|
| 1 | Mg | 0.137384 | 0.004626 |
| 2 | C | -0.706746 | 0.069927 |
| 3 | H | 0.258760 | -0.000678 |
| 4 | H | 0.242957 | 0.000842 |
| 5 | H | 0.238473 | 0.004980 |
| 6 | O | -0.348901 | -0.000952 |
| 7 | S | 0.785636 | 0.097851 |
| 8 | N | -0.519031 | 0.841290 |
| 9 | C | -0.602481 | 1.045455 |
| 10 | H | 0.214758 | -0.032131 |
| 11 | H | 0.221793 | -0.035161 |
| 12 | H | 0.198848 | -0.036775 |
| 13 | O | -0.010371 | -0.006479 |
| 14 | C | 0.050951 | -0.007312 |
| 15 | C | -0.318025 | 0.028693 |
| 16 | C | -0.736397 | -0.000486 |
| 17 | H | 0.162395 | 0.007466 |
| 18 | H | 0.226097 | -0.001093 |
| 19 | C | -0.301206 | 0.003648 |
| 20 | H | 0.252488 | -0.007763 |
| 21 | H | 0.213128 | 0.003061 |
| 22 | H | 0.216820 | -0.000051 |
| 23 | H | 0.221588 | 0.000352 |
| 24 | H | 0.244335 | 0.000911 |
| 25 | H | 0.132860 | 0.000766 |
| 26 | O | -0.293176 | 0.006890 |
| 27 | C | -0.644033 | 0.000317 |
| 28 | C | -0.325419 | -0.003603 |
| 29 | C | 0.604421 | 0.017551 |
| 30 | C | -0.284761 | -0.003687 |
| 31 | H | 0.230935 | 0.000620 |
| 32 | C | -0.192597 | -0.003828 |
| 33 | H | 0.245826 | 0.000877 |
| 34 | C | -0.541688 | 0.003926 |
| 35 | H | 0.246225 | 0.000046 |
| 36 | H | 0.252654 | 0.000112 |
| 37 | H | 0.225501 | -0.000209 |

Charge and spin density for the optimised structure of **M4$_{OPhr}$-T$_1$**

### 6.3.13. Table of Energies

**Table 6.16.** Energies are provided in atumic units, with the temperature in parenthesis in Kelvin.

| Name | E | ZPE | H (-195.15) | T.qh-S (-195.15) | qh-G (-195.15) | qh-G (-298.15) |
|---|---|---|---|---|---|---|
| **M0** | -700.296116 | 0.035466 | -700.257117 | 0.018460 | -700.275577 | -700.285366 |
| **PhONSO-*Z*-P** | -834.900511 | 0.103339 | -834.792240 | 0.023655 | -834.815894 | -834.828511 |
| **M1** | -1535.210616 | 0.140045 | -1535.062014 | 0.031859 | -1535.093873 | -1535.110599 |
| **M2** | -1535.215327 | 0.140004 | -1535.067387 | 0.030236 | -1535.097623 | -1535.113646 |
| **M-TS$_{2\text{-}3}$** | -1535.198149 | 0.140435 | -1535.050114 | 0.029465 | -1535.079578 | -1535.095382 |
| **M3$_{Cl}$** | -1535.270036 | 0.144009 | -1535.118669 | 0.028940 | -1535.147609 | -1535.163212 |
| **M$_{Cl}$-MECP1** | -1535.238025 | 0.139952 | -1535.091935 | 0.026619 | -1535.118554 | -1535.133144 |
| **M4$_{Cl}$** | -1535.258802 | 0.141552 | -1535.109064 | 0.031551 | -1535.140615 | -1535.157390 |
| **M$_{Cl}$-MECP2** | -1535.239565 | 0.139790 | -1535.092235 | 0.031200 | -1535.123435 | -1535.140007 |
| **M5$_{Cl\text{-}OPh}$** | -1535.267596 | 0.143738 | -1535.116104 | 0.029555 | -1535.145660 | -1535.161641 |
| **MgMe$_2$** | -279.896946 | 0.068054 | -279.825309 | 0.018120 | -279.843428 | -279.853122 |
| **M3$_{Me}$** | -1114.875636 | 0.176964 | -1114.690691 | 0.029899 | -1114.720590 | -1114.736605 |
| **M$_{Me}$-MECP1** | -1114.839863 | 0.172907 | -1114.658600 | 0.034000 | -1114.692600 | -1114.710639 |
| **M4$_{Me}$** | -1114.857871 | 0.174086 | -1114.675211 | 0.031639 | -1114.706850 | -1114.723746 |
| **M$_{Me}$-MECP2** | -1114.840730 | 0.172273 | -1114.660779 | 0.031358 | -1114.692137 | -1114.708819 |
| **M5i$_{Me\text{-}OPh}$** | -1114.879564 | 0.177181 | -1114.694062 | 0.030370 | -1114.724433 | -1114.740740 |
| **Nitrene-T$_1$** | -567.901013 | 0.043514 | -567.854151 | 0.020703 | -567.874853 | -567.886357 |
| **Nitrene-MECP** | -567.896773 | 0.042746 | -567.850114 | 0.023280 | -567.873394 | -567.886054 |
| **Nitrene-S$_1$** | -567.937394 | 0.045749 | -567.888350 | 0.020002 | -567.908352 | -567.919406 |
| **M6i** | -1535.272253 | 0.145521 | -1535.119505 | 0.028766 | -1535.148270 | -1535.163791 |
| **M6ii** | -1535.272111 | 0.144318 | -1535.120214 | 0.029293 | -1535.149507 | -1535.165293 |
| **M6iii** | -1535.277856 | 0.144721 | -1535.125423 | 0.029923 | -1535.155346 | -1535.171352 |
| **M5i$_{Cl\text{-}OPh}$** | -1535.277668 | 0.144595 | -1535.125489 | 0.029171 | -1535.154660 | -1535.170435 |
| **M5$_{Cl\text{-}Me}$** | -1268.259438 | 0.082687 | -1268.170047 | 0.026805 | -1268.196851 | -1268.211094 |
| **M$_{Cl}$-TS$_{5\text{-}7}$** | -1268.257289 | 0.082640 | -1268.168492 | 0.025665 | -1268.194157 | -1268.207911 |
| **M7$_{Cl}$** | -1268.341786 | 0.088151 | -1268.248171 | 0.024104 | -1268.272276 | -1268.285304 |
| **M5$_{Me\text{-}OPh}$** | -1114.871247 | 0.176675 | -1114.686269 | 0.030294 | -1114.716563 | -1114.732920 |
| **M$_{OPh}$-TS$_{5\text{-}7}$** | -1114.862678 | 0.175509 | -1114.678765 | 0.031181 | -1114.709946 | -1114.726580 |
| **M7$_{OPh}$** | -1114.946541 | 0.181246 | -1114.758282 | 0.028014 | -1114.786296 | -1114.801546 |
| **M5i$_{Cl\text{-}Me}$** | -1268.269194 | 0.082561 | -1268.179544 | 0.027883 | -1268.207428 | -1268.221928 |
| **M$_{Cl}$-TS$_{5i\text{-}7i}$** | -1268.254556 | 0.083215 | -1268.165349 | 0.025282 | -1268.190631 | -1268.204257 |
| **M7i$_{Cl}$** | -1268.340733 | 0.088144 | -1268.246892 | 0.024785 | -1268.271676 | -1268.284946 |
| **M5i$_{Me\text{-}OPh}$** | -1114.879564 | 0.177181 | -1114.694062 | 0.030370 | -1114.724433 | -1114.740740 |
| **M$_{OPh}$-TS$_{5i\text{-}7i}$** | -1114.859540 | 0.176172 | -1114.675197 | 0.030440 | -1114.705637 | -1114.721952 |
| **M7i$_{OPh}$** | -1114.945133 | 0.181276 | -1114.756049 | 0.029896 | -1114.785945 | -1114.801957 |
| **M$_{Cl}$-TS$_{5i\text{-}8}$** | -1268.253445 | 0.082332 | -1268.164806 | 0.026054 | -1268.190860 | -1268.204712 |
| **M8$_{Cl}$** | -1268.368156 | 0.087461 | -1268.274620 | 0.025620 | -1268.300240 | -1268.313874 |
| **M$_{OPh}$-TS$_{5i\text{-}8}$** | -1114.857277 | 0.175507 | -1114.673405 | 0.030976 | -1114.704381 | -1114.720887 |
| **M8$_{OPh}$** | -1114.971866 | 0.180326 | -1114.783755 | 0.030201 | -1114.813956 | -1114.830079 |
| **D0** | -1400.617113 | 0.072254 | -1400.537852 | 0.027568 | -1400.565420 | -1400.580009 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **D1** | -2235.543347 | 0.176900 | -2235.355165 | 0.036732 | -2235.391897 | -2235.411404 |
| **D2** | -2235.537535 | 0.177217 | -2235.348682 | 0.037535 | -2235.386217 | -2235.406272 |
| **D-TS$_{2\text{-}3}$** | -2235.528284 | 0.177906 | -2235.339752 | 0.035415 | -2235.375167 | -2235.394373 |
| **D3** | -2235.604096 | 0.181417 | -2235.412043 | 0.035629 | -2235.447672 | -2235.468020 |
| **D-MECP1** | -2235.566976 | 0.176859 | -2235.379457 | 0.038005 | -2235.417462 | -2235.437689 |
| **D4** | -2235.588080 | 0.177895 | -2235.399042 | 0.037375 | -2235.436417 | -2235.456383 |
| **D4'** | -2235.593725 | 0.178512 | -2235.403787 | 0.037817 | -2235.441605 | -2235.461717 |
| **D-MECP2** | -2235.585493 | 0.169374 | -2235.408181 | 0.031861 | -2235.440042 | -2235.457203 |
| **D5** | -2235.617315 | 0.182548 | -2235.424269 | 0.034958 | -2235.459227 | -2235.478199 |
| **D5'** | -2235.615730 | 0.181204 | -2235.423471 | 0.036120 | -2235.459591 | -2235.478958 |
| **D5''** | -2235.619230 | 0.181329 | -2235.426624 | 0.036815 | -2235.463439 | -2235.483100 |
| **D6** | -2235.622273 | 0.182979 | -2235.429332 | 0.034034 | -2235.463365 | -2235.481863 |
| **Di-TS$_{5i\text{-}7}$** | -2235.613259 | 0.181930 | -2235.420841 | 0.035079 | -2235.455920 | -2235.474859 |
| **D7** | -2235.708490 | 0.186854 | -2235.511674 | 0.034768 | -2235.546442 | -2235.565307 |
| **Di-TS$_{5i'\text{-}7}$** | -2235.609889 | 0.181248 | -2235.417941 | 0.035873 | -2235.453814 | -2235.473138 |
| **Di-TS$_{5\text{-}7}$** | -2235.602979 | 0.181632 | -2235.410978 | 0.034829 | -2235.445807 | -2235.464727 |
| **Di-TS$_{5'\text{-}7}$** | -2235.603003 | 0.181298 | -2235.411196 | 0.035068 | -2235.446264 | -2235.465267 |
| **Dii-TS$_{5i\text{-}7}$** | -2235.587315 | 0.182249 | -2235.394733 | 0.034962 | -2235.429695 | -2235.448478 |
| **Dii-TS$_{5i'\text{-}7}$** | -2235.603226 | 0.180932 | -2235.411385 | 0.036348 | -2235.447733 | -2235.467174 |
| **Dii-TS$_{5\text{-}7}$** | -2235.608597 | 0.180502 | -2235.417293 | 0.035858 | -2235.453151 | -2235.472387 |
| **Dii-TS$_{5'\text{-}7}$** | -2235.606348 | 0.179960 | -2235.415211 | 0.036830 | -2235.452041 | -2235.471563 |
| **Diii-TS$_{5i\text{-}8}$** | -2235.599276 | 0.180325 | -2235.407973 | 0.036491 | -2235.444464 | -2235.463982 |
| **Diii-TS$_{5i'\text{-}8}$** | -2235.595011 | 0.179589 | -2235.404249 | 0.037026 | -2235.441275 | -2235.460932 |
| **D8** | -2235.713244 | 0.185926 | -2235.516633 | 0.036117 | -2235.552750 | -2235.572102 |
| **D0'** | -1400.617226 | 0.072665 | -1400.538158 | 0.026790 | -1400.564948 | -1400.579146 |
| **D1'** | -2235.543485 | 0.178273 | -2235.353908 | 0.036909 | -2235.390817 | -2235.410497 |
| **D2'** | -2235.537272 | 0.177909 | -2235.347861 | 0.037396 | -2235.385256 | -2235.405154 |
| **D-TS$_{2'\text{-}3'}$** | -2235.525762 | 0.179036 | -2235.336616 | 0.034175 | -2235.370791 | -2235.389533 |
| **D3'** | -2235.607397 | 0.181432 | -2235.415353 | 0.035448 | -2235.450801 | -2235.469762 |
| **D1''** | -2235.544994 | 0.178611 | -2235.355207 | 0.036452 | -2235.391659 | -2235.411134 |
| **D2''** | -2235.538593 | 0.177839 | -2235.349168 | 0.037806 | -2235.386974 | -2235.406992 |
| **D-TS$_{2''\text{-}3''}$** | -2235.528988 | 0.178765 | -2235.340016 | 0.034421 | -2235.374437 | -2235.393297 |
| **D3''** | -2235.606393 | 0.182464 | -2235.413630 | 0.034905 | -2235.448535 | -2235.467357 |
| **DS0** | -1865.580916 | 0.311395 | -1865.256133 | 0.041166 | -1865.297299 | -1865.318796 |
| **DS$_T$2** | -2700.493822 | 0.416176 | -2700.059523 | 0.050991 | -2700.110514 | -2700.137422 |
| **DS$_T$-TS$_{2\text{-}3}$** | -2700.485331 | 0.416765 | -2700.051558 | 0.048392 | -2700.099950 | -2700.125975 |
| **DS$_T$3** | -2700.578615 | 0.420416 | -2700.141352 | 0.048466 | -2700.189818 | -2700.215479 |
| **DS$_T$2'** | -2700.494968 | 0.416765 | -2700.060738 | 0.049639 | -2700.110378 | -2700.136686 |
| **DS$_T$-TS$_{2'\text{-}3'}$** | -2700.482711 | 0.417945 | -2700.048265 | 0.047021 | -2700.095285 | -2700.120752 |
| **DS$_T$3'** | -2700.579047 | 0.423280 | -2700.139304 | 0.047204 | -2700.186509 | -2700.211823 |
| **DS$_T$2''** | -2700.493392 | 0.417696 | -2700.058001 | 0.049955 | -2700.107955 | -2700.134448 |
| **DS$_T$-TS$_{2''\text{-}3''}$** | -2700.487268 | 0.417725 | -2700.052730 | 0.047870 | -2700.100600 | -2700.126371 |
| **DS$_T$3''** | -2700.576275 | 0.422522 | -2700.137550 | 0.046762 | -2700.184313 | -2700.209589 |
| **Me** | -39.832920 | 0.029694 | -39.800679 | 0.012695 | -39.813374 | -39.820010 |
| **M2$_r$** | -1495.348824 | 0.104867 | -1495.237414 | 0.027747 | -1495.265161 | -1495.280062 |
| **M2-T$_1$** | -1767.697616 | 0.259903 | -1767.426163 | 0.037608 | -1767.463772 | -1767.483597 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **M2$_r$-T$_1$** | -1727.842833 | 0.224924 | -1727.608239 | 0.034064 | -1727.642302 | -1727.660449 |
| **D$_{2r}$** | -2195.683633 | 0.141666 | -2195.531880 | 0.035284 | -2195.567163 | -2195.585897 |
| **D$_{2r}$-T$_2$** | -2660.657314 | 0.381584 | -2660.259371 | 0.047642 | -2660.307013 | -2660.332219 |
| **D2$_{r'}$** | -2195.678854 | 0.141446 | -2195.527362 | 0.034916 | -2195.562279 | -2195.580927 |
| **D2$_r$-T$_2$** | -2660.647333 | 0.381749 | -2660.249296 | 0.047449 | -2660.296745 | -2660.321894 |
| **M5$_{Clr}$** | -1228.418217 | 0.047485 | -1228.365889 | 0.023231 | -1228.389119 | -1228.401541 |
| **M5$_{OPhr}$** | -1075.023304 | 0.140800 | -1074.875688 | 0.028244 | -1074.903931 | -1074.919103 |
| **M5$_{Me-Cl}$-T$_1$** | -1500.743317 | 0.202191 | -1500.531166 | 0.033940 | -1500.565106 | -1500.582970 |
| **M5$_{Me-OPh}$-T$_1$** | -1347.351390 | 0.296494 | -1347.043590 | 0.036496 | -1347.080086 | -1347.099742 |
| **M5$_{Clr}$-T$_1$** | -1460.902498 | 0.167072 | -1460.727820 | 0.029786 | -1460.757606 | -1460.773456 |
| **M5$_{OPhr}$-T$_1$** | -1307.507640 | 0.260408 | -1307.237121 | 0.035329 | -1307.272451 | -1307.291220 |
| **M5i$_{Me-Cl}$-T$_1$** | -1500.747381 | 0.202576 | -1500.534915 | 0.033732 | -1500.568648 | -1500.586423 |
| **M5i$_{Me-OPh}$-T$_1$** | -1347.356933 | 0.296681 | -1347.048759 | 0.036962 | -1347.085721 | -1347.105465 |
| **D3$_r$** | -2195.756941 | 0.144550 | -2195.603192 | 0.033249 | -2195.636441 | -2195.654319 |
| **D4'$_r$** | -2195.755626 | 0.145087 | -2195.601060 | 0.033814 | -2195.634873 | -2195.653013 |
| **D5''$_r$** | -2195.782972 | 0.145711 | -2195.628326 | 0.032719 | -2195.661045 | -2195.678704 |
| **PhONSO-*Z*-O** | -834.897698 | 0.102932 | -834.790338 | 0.022599 | -834.812936 | -834.825062 |
| **PhONSO-*E*-P** | -834.890127 | 0.102675 | -834.782962 | 0.022637 | -834.805598 | -834.817815 |
| **PhONSO-*E*-O** | -834.887506 | 0.102406 | -834.780574 | 0.022742 | -834.803316 | -834.815539 |
| **M6i$_{Me}$** | -1114.877014 | 0.178199 | -1114.691422 | 0.028715 | -1114.720136 | -1114.735642 |
| **M6ii$_{Me}$** | -1114.878274 | 0.177007 | -1114.693451 | 0.029500 | -1114.722951 | -1114.738801 |
| **M6iii$_{Me}$** | -1114.882255 | 0.177673 | -1114.696267 | 0.030763 | -1114.727030 | -1114.743381 |
| **ClMgOPh** | -967.292602 | 0.095611 | -967.192078 | 0.023564 | -967.215642 | -967.228266 |
| **D5'i** | -2235.614845 | 0.181361 | -2235.422621 | 0.035813 | -2235.458434 | -2235.477809 |
| **D5'ii** | -2235.600821 | 0.179803 | -2235.409367 | 0.037819 | -2235.447186 | -2235.467287 |
| **D5'iii** | -2235.600618 | 0.179940 | -2235.409142 | 0.037664 | -2235.446806 | -2235.466921 |
| **D5''i** | -2235.614984 | 0.180119 | -2235.423577 | 0.037450 | -2235.461027 | -2235.480826 |
| **D5''ii** | -2235.598709 | 0.179702 | -2235.406884 | 0.039219 | -2235.446103 | -2235.466529 |
| **D5''iii** | -2235.592251 | 0.179729 | -2235.400612 | 0.038665 | -2235.439277 | -2235.459629 |
| **D5'''** | -2235.609764 | 0.180353 | -2235.418399 | 0.036287 | -2235.454686 | -2235.473949 |
| **D5'''i** | -2235.608215 | 0.180917 | -2235.416123 | 0.036482 | -2235.452605 | -2235.472151 |
| **D5'''ii** | -2235.572880 | 0.179597 | -2235.381394 | 0.038522 | -2235.419916 | -2235.440198 |
| **D5'''iii** | -2235.584033 | 0.179388 | -2235.392704 | 0.038707 | -2235.431412 | -2235.451753 |
| **D6i** | -2235.611406 | 0.182102 | -2235.418462 | 0.035740 | -2235.454202 | -2235.473435 |
| **D6ii** | -2235.611577 | 0.182538 | -2235.418318 | 0.035691 | -2235.454009 | -2235.473179 |
| **D6iii** | -2235.600625 | 0.180695 | -2235.409318 | 0.035452 | -2235.444769 | -2235.463922 |
| **D6'** | -2235.600389 | 0.182456 | -2235.406997 | 0.036685 | -2235.443682 | -2235.463220 |
| **D6'i** | -2235.597603 | 0.182336 | -2235.404535 | 0.036099 | -2235.440634 | -2235.459935 |
| **D6'ii** | -2235.600428 | 0.181002 | -2235.408785 | 0.035552 | -2235.444337 | -2235.463424 |
| **D6'iii** | -2235.605338 | 0.181899 | -2235.412349 | 0.036690 | -2235.449040 | -2235.468562 |
| **Di$_{Cl}$-TS$_{5i-7}$** | -2235.591914 | 0.180653 | -2235.400340 | 0.036325 | -2235.436665 | -2235.456198 |
| **Di$_{Cl}$-TS$_{5-7}$** | -2235.581508 | 0.180188 | -2235.390411 | 0.036295 | -2235.426706 | -2235.446232 |
| **Dii$_{Cl}$-TS$_{5i-7}$** | -2235.562223 | 0.181855 | -2235.369843 | 0.035824 | -2235.405668 | -2235.424888 |
| **Dii$_{Cl}$-TS$_{5-7}$** | -2235.553025 | 0.180845 | -2235.361672 | 0.035744 | -2235.397416 | -2235.416668 |
| **Diii$_{Cl}$-TS$_{5i-8}$** | -2235.575285 | 0.179397 | -2235.384602 | 0.037411 | -2235.422013 | -2235.441888 |
| **DS$_C$2** | -2700.492790 | 0.416045 | -2700.058478 | 0.051149 | -2700.109627 | -2700.136622 |
| **DS$_C$-TS$_{2-3}$** | -2700.483715 | 0.416868 | -2700.049789 | 0.048492 | -2700.098281 | -2700.124331 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **$DS_C3$** | -2700.577822 | 0.420342 | -2700.140626 | 0.048308 | -2700.188933 | -2700.214401 |
| **$DS_C2'$** | -2700.492658 | 0.417349 | -2700.057600 | 0.049782 | -2700.107382 | -2700.133847 |
| **$DS_C$-$TS_{2'-3'}$** | -2700.487546 | 0.417695 | -2700.052948 | 0.048095 | -2700.101042 | -2700.126855 |
| **$DS_C3'$** | -2700.578375 | 0.420350 | -2700.140805 | 0.048733 | -2700.189538 | -2700.215381 |
| **$DS_C2''$** | -2700.498888 | 0.418011 | -2700.063521 | 0.048715 | -2700.112236 | -2700.138329 |
| **$DS_C$-$TS_{2'-3'''}$** | -2700.482993 | 0.417722 | -2700.048552 | 0.047851 | -2700.096403 | -2700.122153 |
| **$DS_C3''$** | -2700.578958 | 0.421720 | -2700.140481 | 0.048052 | -2700.188533 | -2700.214129 |
| **$M0_r$** | -660.355720 | 0.000802 | -660.352626 | 0.014679 | -660.367305 | -660.374960 |
| **M0-$T_1$** | -932.774021 | 0.154667 | -932.613579 | 0.025149 | -932.638728 | -932.652070 |
| **$M0_r$-$T_1$** | -892.823591 | 0.120323 | -892.698061 | 0.024159 | -892.722220 | -892.734982 |
| **M0-$T_2$** | -1165.253648 | 0.274543 | -1164.969229 | 0.033780 | -1165.003009 | -1165.020706 |
| **$M0_r$-$T_2$** | -1125.295605 | 0.239859 | -1125.047291 | 0.031504 | -1125.078796 | -1125.095348 |
| **$M4_{Clr}$** | -1268.259310 | 0.080003 | -1268.172311 | 0.027935 | -1268.200246 | -1268.215027 |
| **$M4_{OPhr}$** | -1114.865772 | 0.173513 | -1114.683465 | 0.032119 | -1114.715584 | -1114.732794 |
| **$M4_{Clr}$-$T_1$** | -1500.743051 | 0.199791 | -1500.533182 | 0.034576 | -1500.567758 | -1500.586129 |
| **$M4_{OPhr}$-$T_1$** | -1347.350340 | 0.293101 | -1347.045191 | 0.039015 | -1347.084207 | -1347.105033 |

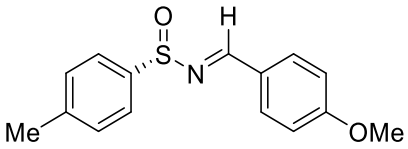
Table of energies for the computed species, given in atomic units and temperature specified. E – energy. ZPE – zero-point energy. H – enthalpy. T.qh-S – temperature times the quasi-harmoic entropy. qh-G quasi harmonic gibbs free energy, which is specified at the two relevant temperatures.

# 6.4. Experimental Data and Procedures – Chapter 3

## 6.4.1. Experimental Procedures and Characterisation

### 6.4.1.1. Reagent Preparation

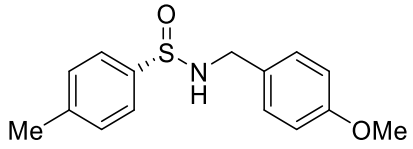
**(*S*)-4-methyl-*N*-(4-methylbenzylidene)benzenesulfinamide (77)**




Prepared according to the literature from Higashibayashi *et al.*[303] (*S*)-4-methylbenzenesulfinamide (>99:1 *er*) (2.33 g, 15 mmol, 1.0 equiv.), cesium carbonate (4.89 g, 15 mmol, 1.0 equiv.) and 4-methoxybenzaldehyde (1.83 mL, 15 mmol, 1.0 equiv.) were added to a round bottom flask equipped with a reflux condenser, and then $CH_2Cl_2$ (75 mL) was added. The reaction was then heated to 45 °C and left to stir for 16 h. The reaction mixture was then cooled to room temperature and water (50 mL) was subsequently added. The aqueous layer further extracted with $CH_2Cl_2$ (100 mL × 3). The organic extracts were combined and dried with sodium sulfate, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (Petrol:EtOAc 9:1 to 4:1), afforded the title compound (3.03 g, 74%) as a colourless solid.

**MP** (Petrol/EtOAc) 131-133 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.66 (s, 1H, NHC), 7.78 (d, *J* = 9.0 Hz, 2H, 2 × ArH), 7.62 (d, *J* = 8.0 Hz, 2H, 2 × CHArH), 7.28 (d, *J* = 8.0 Hz, 2H, 2 × CHArH), 6.92 (d, *J* = 9.0 Hz, 2H, 2 × ArH), 3.82 (s, 3H, $OCH_3$), 2.37 (s, 3H, $ArCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 163.3, 159.9, 142.3, 141.7, 131.6, 129.9, 127.1, 124.9, 114.4, 55.5, 21.5; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 296.0; $[\alpha]_D^{25}$ +33.7° (*c* = 1.0, $CHCl_3$). The spectroscopic data is in agreement with literature.[304]

**(*S*)-4-methyl-*N*-(4-methylbenzyl)benzenesulfinamide (78b)**




Prepared according to the modified procedure from Garrido-Castro *et al.*[305] Sulfinimine **(*S*)-77**, (2.46 g, 9 mmol, 1.0 equiv.) was added to a round bottom flask and dissolved in THF (45 mL) and subsequently cooled to 0 °C. To this solution was added sodium borohydride (0.51 g, 13.5 mmol 1.5 equiv.) dissolved in MeOH (13.5 mL). The reaction was left to stir for 30 min at 0 °C, then sodium bicarbonate (20 mL) was added dropwise, and the reaction extracted with $CH_2Cl_2$ × 3 (100 mL). The organic extracts were combined and dried with sodium sulfate and the solvent removed under reduced pressure affording the title compound (2.38 g, 96%) as a colourless solid. No further purification was required.

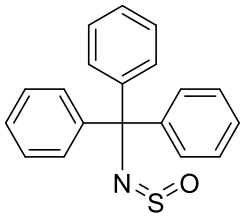
**MP** ($CH_2Cl_2$) 70-72 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.63 (d, *J* = 8.0 Hz, 2H, 2 × Ar*H*), 7.30 (d, *J* = 8.0 Hz, 2H, 2 × Ar*H*), 7.17 (d, *J* = 8.5 Hz, 2H, 2 × $CH_2$Ar*H*), 6.83 (d, *J* = 8.5 Hz, 2H, 2 × $CH_2$Ar*H*), 4.33 (br. dd, *J* = 6.5, 5.5 Hz, 1H, N*H*), 4.16 (dd, *J* = 13.0, 5.5 Hz, 1H, C$H_A$H$_B$), 3.81 (dd, *J* = 13.0, 6.5 Hz, 1H, CH$_A$$H_B$), 3.77 (s, 3H, OC$H_3$), 2.40 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.2, 141.4, 141.1, 130.0, 129.7, 129.7, 126.1, 114.1, 55.4, 44.1, 21.4; **LRMS** (ESI, *m/z*) [M+Na]$^+$ 298.0; ***er*** determined by HPLC using a Chiralpak IA-3 column (*n*-hexane:$^i$PrOH, 85:15); $\tau_{major}$ = 11.72 min, $\tau_{minor}$ = 15.29 min (>99.5:0.5 *er*); $[\alpha]_D^{25}$ +11.8° (*c* = 1.0, $CHCl_3$). The spectroscopic data is in agreement with literature.[306]

Note: To obtain a sample of the racemic material for chiral-phase HPLC analysis an alternative literature procedure was conducted.[307]

Dry *p*-toluenesulfinic acid sodium salt (1.78 g, 10.00 mmol, 1.00 equiv.) and toluene (25 mL) was added to a round bottom flask. The suspension was cooled to 0 °C and oxalyl chloride (0.89 mL, 10.52

mmol, 1.05 equiv.) was added dropwise. The reaction mixture was warmed to room temperature over 1 h to generating *p*-toluenesulfinyl chloride in situ. This solution was then added dropwise to a mixture of 4-methoxylbenzylamine (1.57 mL, 12.00 mmol, 1.20 equiv.) and triethylamine (2.10 mL, 15.00 mmol, 1.50 equiv) in toluene (7 mL) at 0 °C. After stirring for 1 h at 0 °C water (20 mL) and EtOAc (50 mL) were added to the solution, the organic layer extracted, and the aqueous phase further extracted with EtOAc × 2 (50 mL). The organic extracts were combined and washed with aqueous HCl (0.1 M), dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (Petrol:EtOAc 4:1 to 1:1), afforded the racemate of the title compound (1.80 g, 69%) as an off-white solid.

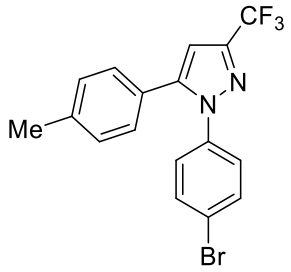
**TrNSO (33)**




Prepared according to the literature procedure Davies *et al.*[103] To a round bottom flask was added tritylamine (10.0 g, 38.6 mmol, 1.0 equiv.) which was dissolved in diethyl ether (145 mL). Triethylamine (10.76 mL, 77.1 mmol, 2.0 equiv.) was added and the reaction was cooled to 0 °C, then thionyl chloride (2.80 mL, 38.6 mmol, 1.0 equiv.) was added dropwise. The reaction was stirred at 0 °C for 2 h. Filtration through Celite® and washing with diethyl ether (200 mL), afforded TrNSO (10.3 g, 87%) as a colourless solid.

**MP** ($Et_2O$) 93-94 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.46 – 7.29 (m, 15H, Ar*H*); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 144.4, 128.7, 128.3, 127.7, 81.2; **LRMS** (ESI, *m/z*) $[M+H]^+$ 306.0 & $[M-NSO]^+$ 243.2. The spectroscopic data is in agreement with literature.[103]

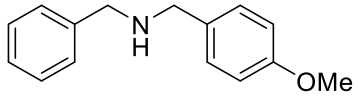
**1-(4-Bromophenyl)-5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazole (122)**




Prepared according to the literature procedure from Davies *et al.*[103] The reaction was conducted under an atmosphere of air. 4,4,4-Trifluoro-1-(*p*-tolyl)butane-1,3-dione (1.30 g, 5.65 mmol, 1.0 equiv.) was added to a 3-necked round bottom flask and dissolved in EtOH (60 mL). 4-Bromophenylhydrazine hydrochloride (1.29 g, 5.76 mmol, 1.02 equiv.) was next added. The reaction mixture was refluxed at 90 °C for 15 h. The solvent was removed under reduced pressure then diluted with EtOAc (100 mL). The solution was washed with water (50 mL), then the layers were separated, and the aqueous phase was extracted with EtOAc × 3 (100 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was dissolved in MeOH (10 mL) and heated to reflux using a heatgun, then allowed to cool to room temperature. Crystallisation was observed. The solution was cooled to 0 °C. Filtration and washing with cold MeOH (0 °C, 10 mL), afforded the title compound (1.50 g, 70%) as pale orange crystals.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.49 (d, $J$ = 9.0 Hz, 2H, 2 × Ar*H*), 7.20 (d, $J$ = 9.0 Hz, 2H, 2 × Ar*H*), 7.16 (d, $J$ = 8.5 Hz, 2H, 2 × Tol*H*), 7.10 (q, $J$ = 8.5 Hz, 2H, 2 × Tol*H*), 6.71 (s, 1H, HetAr*H*), 2.37 (s, 3H, TolC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 145.0, 143.6 (q, $^{2}J_{CF}$ = 38.0 Hz), 139.5, 138.5, 132.4, 129.7, 128.8, 127.0, 126.1, 122.3, 121.3 (q, $^{1}J_{CF}$ = 269.0 Hz), 105.8 (q, $^{3}J_{CF}$ = 1.5 Hz), 21.5; **$^{19}$F NMR** (377 MHz, $CDCl_3$) $\delta_F$ -62.26; **LRMS** (ESI, *m/z*) $[M+H]^+$ 381.0 & 383.0. The spectroscopic data is in agreement with literature.[103]

**_N_-benzyl-1-(4-methoxyphenyl)methanamine (81)**

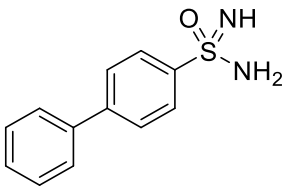



Prepared according to the literature procedure from Karanewsky *et al.*[308] Sodium triacetoxyborohydride (5.26 g, 24.5 mmol, 1.4 equiv.) was added to a round bottom flask and dissolved in dichloroethane (62.5 mL). To this suspension was added 4-methoxybenzaldehyde (2.23 mL, 17.5 mmol, 1.0 equiv.) and benzylamine (1.94 mL, 17.5 mmol, 1.0 equiv.) at room temperature and the reaction mixture was left to stir for 4 h. The reaction was quenched by the dropwise addition of sodium bicarbonate (30 mL) and the aqueous phase was extracted with $CH_2Cl_2$ × 3 (100 mL). The organic extracts were combined and dried with sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 3:7), afforded the title compound (6.60 g, 88%) as a yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.38 – 7.33 (m, 4H, 4 × Ph*H*), 7.31 – 7.24 (m, 3H, Ph*H*, 2 × *p*-OMeAr*H*), 6.89 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 3.85 – 3.79 (m, 5H, O$CH_3$, N$CH_2$), 3.77 (s, 2H, N$CH_2$), 1.74 (s, 1H, N*H*); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 158.8, 140.5, 132.5, 129.5, 128.5, 128.3, 127.1, 113.9, 55.4, 53.2, 52.7; **LRMS** (ESI, *m/z*) $[M+H]^+$ 228.2. The spectroscopic data is in agreement with literature.[309]

### 6.4.1.2. Probing Configurational Lability

### [1,1'-Biphenyl]-4-sulfonimidamide (75)

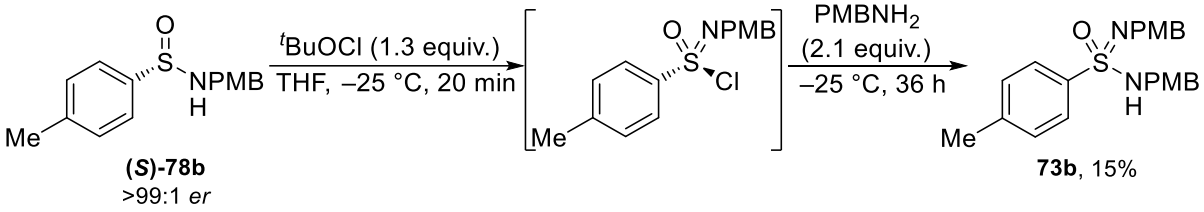



Prepared according to the modified procedure from Davies *et al.*[103] 4-Bromo-1,1'-biphenyl (4.66 g, 20.0 mmol, 1.00 equiv.) was placed in a 3-neck round bottom flask equipped with a cold trap condenser, then dissolved in THF (100 mL). The solution was cooled to −78 °C with an acetone/dry ice bath and *n*-butyllithium (8.89 mL, 2.25 M in hexanes, 1.00 equiv.) was added slowly dropwise, the reaction mixture was left to stir at −78 °C for 1 h. TrNSO (6.11 g, 20.0 mmol, 1.00 equiv.) was prepared as a solution in THF (8 mL) and added dropwise to the reaction mixture at −78 °C, then left to stir for a further 20 min. The reaction was then warmed to 0 °C with an ice bath and stirred for 10 min before addition of *t*-butyl hypochlorite (2.38 mL, 21.0 mmol, 1.05 equiv.). After this period liquid ammonia was condensed directly into the reaction medium dropwise, by passing gaseous ammonia over the cold trap condenser filled with acetone/dry ice (note: the system was opened to prevent a build-up of pressure). After 15 min the system was left to stir under a nitrogen atmosphere for 16 h. Methanesulfonic acid (13.0 mL, 200.0 mmol, 10.0 equiv.) was added at room temperature and the reaction was stirred vigorously for 15 min before dilution with EtOAc (20 mL). The solution was then washed with saturated ammonium chloride (20 mL) and the aqueous phase extracted with EtOAc (20 mL × 3). The combined organic layers were dried with sodium sulfate, filtered then concentrated under reduced pressure. Purification by flash column chromatography (Petrol:EtOAc:MeOH, 4:1:0 to 0:9:1), afforded the title compound **75**, as a brown solid. The compound was further purified by trituration with acetone, affording the title compound (1.44 g, 31%) as a colourless solid.

**MP** (Acetone) 119-121 °C; **$^1$H NMR** (400 MHz, $CD_3OD$) $\delta_H$ 8.08 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.76 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.71 – 7.58 (m, 2H, 2 × Ph*H*), 7.53 – 7.40 (m, 2H, 2 × Ph*H*), 7.43 – 7.32 (m, 1H, Ph*H*), (note: N$H_2$ & N*H* not observed); **$^1$H NMR** (400 MHz, $(CD_3)_2SO$) $\delta_H$ 7.98 (d, *J* = 8.0 Hz, 2H, 2 × Ar*H*), 7.80 (d, *J* = 8.0 Hz, 2H, 2 × Ar*H*), 7.72 (d, *J* = 7.5 Hz, 2H, 2 × Ph*H*), 7.54 – 7.46 (m, 2H, 2 × Ph*H*), 7.45 – 7.37 (m, 1H, Ph*H*), 5.96 (br. s, 3H, N$H_2$ & N*H*); **$^{13}$C NMR** (101 MHz, $CD_3OD$) $\delta_C$ 146.0, 144.9, 140.7, 130.1, 129.3, 128.3, 128.2, 128.1; **$^{13}$C NMR** (101 MHz, $(CD_3)_2SO$) $\delta_C$ 145.6, 142.6, 139.0, 129.2, 128.3, 127.1, 126.8, 126.7; **LRMS** (ESI, *m/z*) $[M+H]^+$ 233.0. The spectroscopic data is in agreement with literature.[103]

The following HCl salt of the title compound was obtained by dissolving sulfonimidamide **75** (*ca.* 10 mg) in water and adding a few drops of 1 M HCl, which subsequently crystallised allowing analysis by X-ray crystallography.

***N,N'*-bis(4-methoxybenzyl)-4-methylbenzenesulfonimidamide (73b)**




**Procedure 6.1.** Reaction sequence for the synthesis of **73b** from enantiopure starting material **(*S*)-78b.**

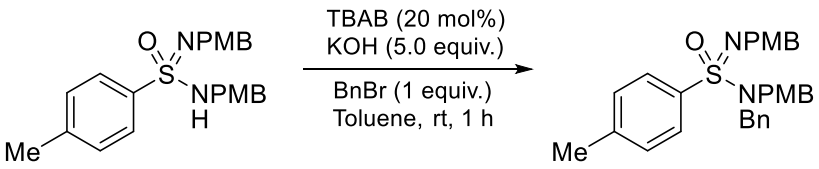
(*S*)-sulfinamide **78b** (193 mg, 0.70 mmol, 1.0 equiv.) was dissolved in THF (5.6 mL) and cooled to –25 °C using an **i**mmersion **c**ooler. To this solution, was added *t*-butyl hypochlorite (103 μL, 0.91 mmol, 1.3 equiv.) by slow dropwise addition. The reaction was stirred at –25 °C for 20 min and then 4-methoxybenzylamine (0.19 mL, 1.54 mmol, 2.2 equiv.) dissolved in THF (1.4 mL) was added. The reaction mixture was left to stir at –25 °C for 36 h, using the immersion cooler apparatus. The reaction was quenched with water (10 mL) and extracted EtOAc × 3 (25 mL), the combined organic extracts were dried with sodium sulfate and concentrated under reduced pressure. Purification by flash column

chromatography (Petrol:EtOAc, 9:1 to 1:1), afforded the title compound **73b** (41 mg, 15%) as a colourless solid.

**MP** (Pentane/EtOAc) 74-76 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.87 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.28 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.19 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 6.81 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 4.15 (d, *J* = 14.0 Hz, 2H, 2 × NC$H_AH_B$), 4.11 (d, *J* = 14.0 Hz, 2H, 2 × NC$H_AH_B$), 3.78 (s, 6H, 2 × OC$H_3$), 2.43 (s, 3H, ArC$H_3$), (note: N*H* peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 158.7, 142.7, 137.1, 131.5, 129.5, 128.9, 127.6, 113.8, 55.3, 46.3, 21.5; **LRMS** (ESI, *m/z*) $[M+H]^+$ 411.2 & $[M+Na]^+$ 433.0; **HRMS** (ESI, *m/z*) calculated for $(C_{23}H_{25}O_3N_2S)^-$ 409.1580 $[M-H]^-$, found 409.1598; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2835, 1612, 1511, 1463, 1244, 1175, 1140, 1034, 908, 814, 750, 670; **$R_f$** 0.55 (Petrol:EtOAc, 1:1).

Optical rotation measurements indicated a racemic mixture due to the small values obtained which are assumed to be within error.

**(*R*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-4-methylbenzenesulfonimidamide (74b)**




**73b**, 15% ***rac*-74b**, 81%
50:50 *er*

**Procedure 2.** Reaction for the synthesis of **74b** from the previously synthesised **73b.**

Under an atmosphere of air, the previously synthesised sulfonimidamide **73b** (34.5 mg, 0.08 mmol, 1.0 equiv.), tetrabutylammonium bromide (6.8 mg, 0.02 mmol, 0.25 equiv.), finely ground potassium hydroxide (23.6 mg, 0.4 mmol, 5.0 equiv.) and benzyl bromide (10 μL, 0.08 mmol, 1.0 equiv.) were added to a reaction vial equipped with a stirrer bar. Toluene (0.8 mL) was added, and the reaction was vigorously stirred for 1 h at room temperature, after which the reaction mixture was diluted with EtOAc (2 mL) and washed with water (1 mL). The aqueous layer further extracted with

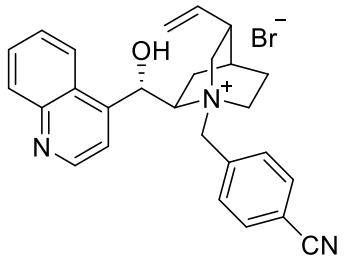
EtOAc (2 mL × 3), the organic layers were combined, then the solvent was removed under under reduced pressure. Purification by flash column chromatography (Petrol:EtOAc, 1:0 to 4:1), affording the title compound **74b** (33.3 mg, 81%) as a colourless solid.

**MP** (Petrol/EtOAc) 63-65 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.90 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.35 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.28 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.23 – 7.17 (m, 3H, 3 × $CH_2$Ph*H*), 7.05 – 6.96 (m, 2H, 2 × $CH_2$Ph*H*), 6.90 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.85 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.72 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.49 (d, *J* = 15.0 Hz, 1H, NC$H_A$$H_B$), 4.45 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.44 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.12 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.09 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.06 (d, *J* = 15.0 Hz, 1H, NC$H_A$$H_B$), 3.79 (s, 3H, OC$H_3$), 3.77 (s, 3H, OC$H_3$), 2.44 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.1, 158.4, 142.5, 138.1, 136.9, 130.3, 133.7, 129.6, 128.8, 128.7 (2 × C), 128.4, 127.6, 127.4, 113.8 (2 × C), 55.4 (2 × C), 51.0, 50.7, 45.3, 21.6; **LRMS** (ESI, *m/z*) $[M+H]^+$ 501.2 & $[M+Na]^+$ 523.1; **HRMS** (ESI, *m/z*) calculated for $(C_{30}H_{33}O_3N_2S)^+$ $[M+H]^+$ 501.2206, found 501.2202; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1612, 1512, 1463, 1246, 1176, 1141, 1035, 815, 748; **$R_f$** 0.52 (Petrol:EtOAc, 3:2).

The optical rotation measurements indicated a racemic mixture due to the small values obtained which are assumed to be within error, and analysis on chiral-phase HPLC indicated that **74a** was racemic. The title compound was crystallised in $^i$PrOH/*n*-hexane for X-ray crystallography.

### 6.4.1.3. Representative Examples of Catalyst Synthesise

**_N_-(4-cyanobenzyl)cinchoninium bromide (CAT-12)**

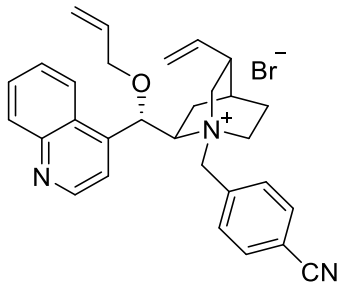



Prepared according to the modified literature procedure from Lian *et al.*[310] The reaction was conducted under an atmosphere of air. To a round bottom flask equipped with a stirrer bar and a reflux condenser added cinchonine (2.94 g, 10.0 mmol, 1.0 equiv.) THF (100 mL) and 4-(bromomethyl)benzonitrile (1.96 g, 10.0 mmol, 1.0 equiv.). The mixture was refluxed at 70 °C for 4 h then cooled to room temperature. Next $Et_2O$ (50 mL) was added, whilst stirring to give a white precipitate. The resulting suspension was filtered and washed with $Et_2O$ (200 mL). The resulting powder dried under vacuum affording the title compound (4.90 g, 100%) as a colourless solid.

**MP** ($Et_2O$) 234-236 °C (decomp.); **$^1$H NMR** (400 MHz, $(CD_3)_2SO$) $\delta_H$ 8.98 (d, $J$ = 4.5 Hz, 1H, HetAr*H*), 8.43 – 8.35 (m, 1H, Ar*H*), 8.16 – 7.93 (m, 5H, Ar*H*, 4 × *p*-CNAr*H*), 7.88 – 7.79 (m, 2H, HetAr*H*, Ar*H*), 7.75 (ddd, $J$ = 8.5, 7.0, 1.5 Hz, 1H, Ar*H*), 6.86 – 6.77 (m, 1H, O*H*), 6.54 – 6.48 (m, 1H, C*H*OH), 5.99 (ddd, $J$ = 17.5, 10.5, 7.0 Hz, 1H, $CH_2CH{=}CH_AH_B$), 5.28 (d, $J$ = 12.5 Hz, 1H, $CH_AH_B$*p*-CNAr), 5.25 – 5.18 (m, 2H, $CH_2CH{=}CH_AH_B$, $CH_2CH{=}CH_2$), 5.09 (d, $J$ = 12.5 Hz, 1H, $CH_AH_B$*p*-CNAr), 4.25 (ddd, $J$ = 12.0, 8.5, 2.5 Hz, 1H, $NCH_AH_B$), 4.11 – 4.00 (m, 1H, $NCH_AH_B$), 3.95 (app. t, $J$ = 10.0 Hz, 1H, NC*H*), 3.46 (app. t, $J$ = 11.5 Hz, 1H, $NCH_AH_B$), 2.98 (app. dt, $J$ = 12.0, 9.5 Hz, 1H, $NCH_AH_B$), 2.63 (app. q, $J$ = 8.5 Hz, 1H, C*H*CH=$CH_2$), 2.34 – 2.21 (m, 1H, $CCH_AH_B$), 1.90 – 1.81 (m, 1H, CC*H*), 1.80 – 1.70 (m, 2H, $CCH_AH_B$, $CCH_AH_B$), 1.12 – 1.00 (m, 1H, $CCH_AH_B$); **$^{13}$C NMR** (101 MHz, DMSO) $\delta_C$ 150.1, 147.6, 144.9, 137.0, 134.8, 133.3, 132.6, 129.8, 129.4, 127.3,

124.3, 123.9, 120.1, 118.3, 117.0, 112.8, 67.4, 64.6, 61.3, 56.0, 54.0, 36.7, 26.2, 23.0, 20.7; **LRMS** (ESI, *m/z*) $[M\text{-}Br]^+$ 410.2; HRMS (ESI, *m/z*) calculated for $(C_{27}H_{28}ON_3)^+$ 410.2227 $[M\text{-}Br]^+$, found 410.2224; **IR** (thin film, $\nu_{max}/cm^{-1}$) 3186, 2229, 1639, 1592, 1510, 1461, 1422, 1329, 1215, 1164, 1137, 1003, 925, 869, 837, 802, 781, 765, 632; $[\alpha]_D^{25}$ +116.8° (*c* = 1.0, MeOH).

**O-allyl-N-(4-cyanobenzyl)cinchoninium bromide (CAT-17)**

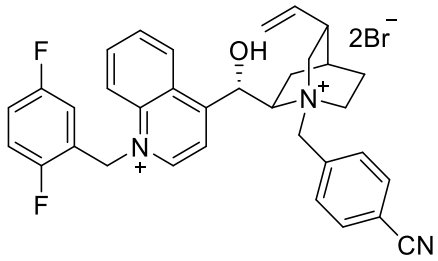



Prepared according to the modified literature procedure from Lian *et al.*[310] The reaction was conducted under an atmosphere of air. To a round bottom flask was added **CAT-12** (307 mg, 0.625 mmol, 1.0 equiv.) followed by $CH_2Cl_2$ (3 mL). To the stirred suspension was added allyl bromide (0.16 mL, 1.875 mmol, 3.0 equiv.) and aqueous potassium hydroxide (0.3 mL, 50% *wt.*) at room temperature. The reaction mixture was subsequently left to stir for 4 h. The reaction was diluted with water (1 mL) and extracted with $CH_2Cl_2$ (10 mL × 3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Recrystallisation of the residue from methanol and diethyl ether afforded the title compound (319 mg, 96%) as an off-white solid.

**MP** (MeOH/$Et_2O$) 199-201 °C (decomp.); **$^1$H NMR** (400 MHz, MeOD) $\delta_H$ 9.03 (d, *J* = 4.5 Hz, 1H, HetAr*H*), 8.55 – 8.45 (m, 1H, Ar*H*), 8.21 – 8.14 (m, 1H, Ar*H*), 8.07 (d, *J* = 8.0 Hz, 2H, 2 × *p*-CNAr*H*), 7.97 (d, *J* = 8.0 Hz, 2H, 2 × *p*-CNAr*H*), 7.95 – 7.84 (m, 3H, HetAr*H*, 2 × Ar*H*), 6.52 – 6.46 (m, 1H, C*H*OAllyl), 6.30 (app. ddt, *J* = 16.5, 10.5, 6.0 Hz, 1H, $CH_2CH{=}CH_AH_B$), 6.09 (ddd, *J* = 17.5, 10.5, 7.0 Hz, 1H, $CHCH{=}CH_AH_B$), 5.54 (app. dq, *J* = 17.5, 1.5 Hz, 1H, $CH_2CH{=}CH_AH_B$),

5.47 – 5.29 (m, 4H, CHCH=CH$_A$H$_B$, CH$_2$C*H*=CH$_2$, CHC*H*=CH$_2$, C*H*$_A$H$_B$*p*-CNAr), 4.91 (d, *J* = 12.5 Hz, 1H, CH$_A$*H*$_B$*p*-CNAr), 4.42 – 4.29 (m, 3H, C*H*$_A$H$_B$OAllyl, 2 × NC*H*$_A$H$_B$), 4.30 – 4.10 (m, 2H, CH$_A$*H*$_B$OAllyl, NC*H*), 3.72 (ddd, *J* = 12.0, 10.5, 1.5 Hz, 1H, NCH$_A$*H*$_B$), 3.18 (app. dt, *J* = 11.5, 9.0 Hz, 1H, NCH$_A$*H*$_B$), 2.81 – 2.70 (m, 1H, C*H*CH=CH$_2$), 2.69 – 2.51 (m, 1H, CC*H*$_A$H$_B$), 2.11 – 1.99 (m, 1H, CC*H*), 1.99 – 1.82 (m, 2H, CC*H*$_A$H$_B$, CCH$_A$*H*$_B$), 1.33 – 1.19 (m, 1H, CCH$_A$*H*$_B$); **$^{13}$C NMR** (101 MHz, MeOD) $\delta_C$ 150.9, 149.1, 142.7, 137.4, 136.1, 136.0, 134.6, 134.0 (2 × C), 131.4, 130.3, 129.5, 126.9, 124.8, 121.3, 119.7, 119.0, 118.1, 115.4, 71.4, 69.2, 64.1, 58.3, 56.5, 38.6, 28.3, 24.4, 22.9; **LRMS** (ESI, *m/z*) [M-Br]$^+$ 450.2; **HRMS** (ESI, *m/z*) calculated for $(C_{30}H_{32}ON_3)^+$ 450.2540 [M-Br]$^+$, found 450.2538; **IR** (thin film, $\nu_{max}$/cm$^{-1}$) 3463, 3005 2229, 2162, 1979, 1644, 1612, 1591, 1569, 1508, 1459, 1411, 1381, 1341, 1302, 1264, 1204, 1166, 1134, 1113, 1094, 1058, 1036, 998, 910, 866, 852, 836, 783, 759, 631; $[\alpha]_D^{25}$ +116.4° (*c* = 1.0, MeOH).

**_N_-(4-cyanobenzyl)-_N'_-(2,5-difluorobenzyl)cinchoninium dibromide (CAT-25)**



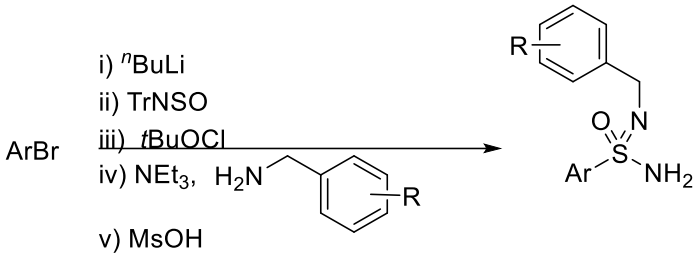

Prepared according to the modified literature procedure from Xiang *et al.*[197] **CAT-12** (2.45 g, 5.0 mmol, 1.0 equiv.) and 2,5-difluorobenzylbromide (1.29 mL, 10.0 mmol, 2.0 equiv.) in $^i$PrOH (1.2 mL) and DMF (8.3 mL) was stirred at 70 °C for 6 h. The reaction mixture was cooled and EtOAc (20 mL) added dropwise. The resulting slurry was aged for 2 h at room temperature, filtered, rinsed with EtOAc (2 × 100 mL) and dried under vacuum affording the title compound (2.79 g, 80%) as a yellow solid.

**MP** (EtOAc) 149-151 °C; **$^{1}$H NMR** (400 MHz, MeOD) $\delta_H$ 9.68 (dd, *J* = 6.5, 1.5 Hz, 1H, HetAr*H*), 8.94 (ddd, *J* = 7.5, 6.0, 1.5 Hz, 1H, Ar$_F$*H*), 8.61 (d, *J* = 6.5 Hz, 1H, HetAr*H*), 8.61 – 8.54 (m, 1H, Ar*H*), 8.30 (ddd, *J* = 9.0, 7.0, 1.5 Hz, 1H, Ar$_F$*H*), 8.23 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Ar$_F$*H*), 8.07 (d, *J* = 8.5 Hz, 2H, 2 × *p*-CNAr*H*), 7.93 (d, *J* = 8.5 Hz, 2H, 2 × *p*-CNAr*H*), 7.40 – 7.16 (m, 3H, 3 × Ar*H*), 6.99 – 6.78 (m, 1H, C*H*OH), 6.48 (s, 2H, C*H*$_2$Ar$_F$), 6.08 (ddd, *J* = 14.5, 10.5, 7.0 Hz, 1H, CH=C*H*$_A$H$_B$), 5.51 (d, *J* = 12.0 Hz, 1H, C*H*$_A$H$_B$*p*-CNAr), 5.35 – 5.25 (m, 2H, CH=CH$_A$*H*$_B$, C*H*=CH$_2$), 5.14 (d, *J* = 12.0 Hz, 1H, CH$_A$*H*$_B$*p*-CNAr), 4.43 (ddd, *J* = 12.0, 8.5, 2.5 Hz, 1H, NC*H*$_A$H$_B$), 4.33 – 4.18 (m, 2H, NC*H*, NC*H*$_A$H$_B$), 3.65 (ddd, *J* = 12.0, 10.5, 1.5 Hz, 1H, NCH$_A$*H*$_B$), 3.13 (app. dt, *J* = 11.0, 9.0 Hz, 1H, NCH$_A$*H*$_B$), 2.76 – 2.63 (m, 1H, C*H*CH=CH$_2$), 2.48 (dd, *J* = 13.5, 10.5 Hz, 1H, CC*H*$_A$H$_B$), 2.08 – 1.97 (m, 1H, CC*H*), 1.97 – 1.84 (m, 2H, CC*H*$_A$H$_B$, CCH$_A$*H*$_B$), 1.37 – 1.21 (m, 1H, CCH$_A$*H*$_B$), (note: O*H* peak not observed); **$^{13}$C NMR** (101 MHz, MeOD) $\delta_C$ 160.4, 160.3 (dd, $J_{CF}$ = 243.5, 1.5 Hz), 158.3 (dd, $J_{CF}$ = 243.5, 2.5 Hz), 150.8, 139.1, 137.4, 137.3, 136.1, 133.9 (2 × C), 132.6, 128.2, 128.1, 122.9 (dd, $J_{CF}$ = 16.5, 8.0 Hz), 122.6, 120.5, 119.4 (dd, $J_{CF}$ = 24.5, 9.0 Hz), 118.9 (dd, $J_{CF}$ = 25.5 9.0 Hz), 119.0, 118.2, 117.9 (dd, $J_{CF}$ = 26.0, 3.5 Hz). 115.5, 68.9, 67.5, 63.5, 58.4, 56.8, 56.4, 38.8, 28.3, 24.4, 22.4; **$^{19}$F NMR** (377 MHz, MeOD) $\delta_F$ -118.19 – -118.45 (m), -122.68 – -122.91 (m); **LRMS** (ESI, *m/z*) [M-H-2Br]$^+$ 536.2; **HRMS** (ESI, *m/z*) calculated for ($C_{34}H_{32}ON_3F_2$)$^+$ 536.2508 [M-H-2Br]$^+$, found 536.2507; **IR** (thin film, $\nu_{max}$/cm$^{-1}$) 3406, 2981, 2231, 1674, 1602, 1535, 1501, 1464, 1391, 1218, 1123, 1093, 1007 941, 864, 813, 757, 729, 617; $[\alpha]_D^{25}$+77.4° (*c* = 1.0, MeOH).

Compound **CAT-25** was crystallised in MeOH to obtained crystals suitable for X-ray diffraction studies.

### 6.4.1.4. Synthesis of Mono-Substituted Sulfonimidamides

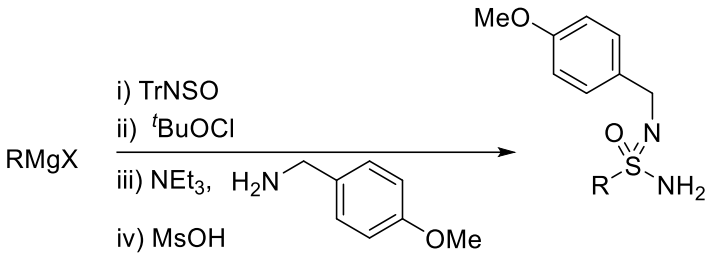
**General Procedure A.**




**General Procedure A.** General reaction sequence for the synthesis of mono-substituted sulfonimidamides from aryl bromides.

Procedure from Davies *et al.*[103] Aryl bromide (1.00 equiv.) was placed in a reaction vessel, then dissolved in THF (0.20 M). The solution was cooled to −78 °C with an acetone/dry ice bath and *n*-butyllithium (2.25 M in hexanes, 1.00 equiv.) was added slowly dropwise, the reaction mixture was left to stir at −78 °C for 1 h. TrNSO (1.00 equiv.) was prepared as a solution in THF (2.50 M) and added dropwise to the reaction mixture at −78 °C, then left to stir for a further 20 min. The reaction was then warmed to 0 °C with an ice bath and stirred for 10 min before addition of *t*-butyl hypochlorite (1.05 equiv.). After this period triethylamine (1.00 equiv.) and the corresponding amine (1.20 equiv.) were added and the reaction was left to stir for 16 h. Methanesulfonic acid (5.00-15.00 equiv.) was added at room temperature and the reaction was stirred vigorously for 15 min before dilution with $CH_2Cl_2$. The solution was then washed with a saturated aqueous solution of potassium carbonate and the aqueous phase further extracted with $CH_2Cl_2$ × 3. The combined organic layers were dried with sodium sulfate, filtered then concentrated under reduced pressure. The crude material was purified by flash column chromatography.

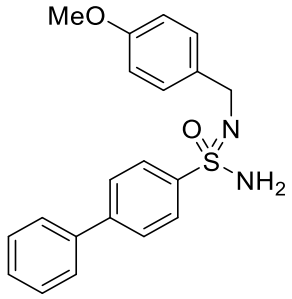
**General Procedure B**




**General Procedure B.** General reaction sequence for the synthesis of mono-substituted sulfonimidamides from Grignard reagents.

Procedure from Davies *et al.*[103] TrNSO (1.00 equiv.) was placed in a reaction vessel and dissolved in THF (0.15 M). The solution was cooled to 0 °C with an ice bath and the corresponding organometallic reagent (1.00 equiv.) was added dropwise, the reaction mixture was left to stir at the 0 °C for 5 min. *t*-Butyl hypochlorite (1.05 equiv.) was added and the mixture stirred for 15 min prior to addition of triethylamine (1.00 equiv.) and the 4-methoxybenzylamine (1.20 equiv.). The reaction mixture was stirred at room temperature for 16 h. Methanesulfonic acid (5.00-10.00 equiv.) was added and the reaction stirred vigorously for 15 min at room temperature before dilution with $CH_2Cl_2$. The solution was then washed with a saturated aqueous potassium carbonate solution, then the layers were separated and the aqueous phase was extracted with $CH_2Cl_2 \times 3$. The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography.

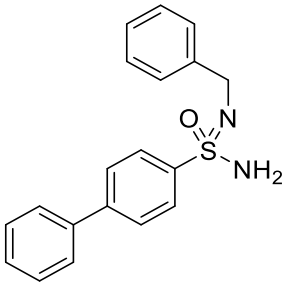
**N'-(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (123a)**




Prepared according to general procedure A, using 4-bromobiphenyl (4.662 g, 20.0 mmol, 1.00 equiv.), *n*-butyllithium (8.0 mL, 2.50 M in hexanes, 1.00 equiv.) TrNSO (6.108 g, 20.0 mmol, 1.00 equiv.), *t*-butyl hypochlorite (2.4 mL, 21.0 mmol, 1.05 equiv.), triethylamine (2.8 mL, 20.0 mmol, 1.00 equiv.), 4-methoxybenzylamine (3.1 mL, 24.0 mmol, 1.20 equiv.) and methanesulfonic acid (13.0 mL, 0.20 mol, 10.0 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:4), afforded the title compound (4.029 g, 57%) as a colourless solid.

**MP** (Petrol/EtOAc) 102-104 °C; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.92 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.58 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.57 – 7.46 (m, 2H, 2 × Ph*H*), 7.45 – 7.28 (m, 3H, 3 × Ph*H*), 7.02 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.68 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.03 (d, *J* = 13.5 Hz, 1H, NC$H_A$H$_B$), 3.93 (d, *J* = 13.5 Hz, 1H, NCH$_A$$H_B$), 3.64 (s, 3H, OC$H_3$), (note: N$H_2$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.2, 145.1, 139.8, 139.5, 129.3, 129.0, 128.9, 128.4, 127.9, 127.5, 127.3, 114.0, 55.3, 47.3; **LRMS** (ESI, *m/z*) $[M+H]^+$ 353.1; **HRMS** (ESI, *m/z*) calculated for $(C_{20}H_{21}O_2N_2S)^+$ 353.1318 $[M+H]^+$, found 353.1315; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 3271, 1612, 1513, 1248, 1177, 1134, 1006, 838, 764, 698, 664; **$R_f$** 0.31 (Petrol:EtOAc, 1:1).

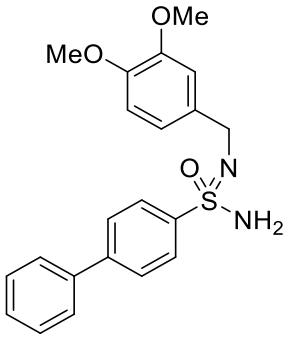
**N'-benzyl-[1,1'-biphenyl]-4-sulfonimidamide (124a)**



Prepared according to general procedure A, using 4-bromobiphenyl (233 mg, 1.0 mmol, 1.00 equiv.), *n*-butyllithium (0.46 mL, 2.18 M in hexanes, 1.00 equiv.) TrNSO (306 ,mg, 1.0 mmol, 1.00 equiv.), *t*-butyl hypochlorite (0.12 mL, 1.0 mmol, 1.05 equiv.), triethylamine (0.14 mL, 1.0 mmol, 1.00 equiv.), benzylamine (0.13 mL, 1.2 mmol, 1.20 equiv.) and methanesulfonic acid (5.0 mL, 10.0 mol, 10.0 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:4), afforded the title compound (166 mg, 52%) as a colourless solid.

**MP** (Petrol/EtOAc) 81-83 °C **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.72 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.66 – 7.61 (m, 2H, 2 × Ph*H*), 7.55 – 7.48 (m, 2H, 2 × Ph*H*), 7.48 (s, 1H, Ph*H*), 7.34 – 7.25 (m, 3H, 3 × $CH_2$Ph*H*), 7.25 – 7.21 (m, 2H, 2 × $CH_2$Ph*H*), 4.22 (d, *J* = 14.0 Hz, 1H, NC$H_A$H$_B$), 4.13 (d, *J* = 13.9 Hz, 1H, NCH$_A$$H_B$), (note: N$H_2$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 145.3, 139.7, 139.6, 137.0, 129.2, 128.8, 128.5, 128.0, 128.0, 127.9, 127.7, 127.5, 48.1; **LRMS** (ESI, *m/z*) $[M+H]^+$ 323.0 & $[M-H]^-$ 321.0; **HRMS** (ESI, *m/z*) calculated for $(C_{19}H_{19}O_2N_2S)^+$ 323.1213 $[M+H]^+$, found 323.1213; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1595, 1480, 1454, 1248, 1133, 1107, 1026, 1006, 914, 841, 763, 722, 697, 664; **R$_f$** 0.26 (Petrol:EtOAc, 4:1).

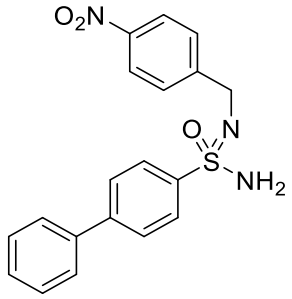
**_N_'-(3,4-dimethoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (124b)**




Prepared according to general procedure A, using 4-bromobiphenyl (466 mg, 2.0 mmol, 1.00 equiv.), *n*-butyllithium (0.92 mL, 2.18 M in hexanes, 2.00 equiv.) TrNSO (612,mg, 2.0 mmol, 1.00 equiv.), *t*-butyl hypochlorite (0.24 mL, 2.1 mmol, 1.05 equiv.), triethylamine (0.28 mL, 1.0 mmol, 1.00 equiv.), (3,4-dimethoxyphenyl)methanamine (0.34 mL, 2.4 mmol, 1.20 equiv.) and methanesulfonic acid (10.0 mL, 10.0 mol, 10.0 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:4), afforded the title compound (320 mg, 42%) as a colourless solid.

**MP** (Petrol/EtOAc) 118-120 °C; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.02 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.67 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.64 – 7.57 (m, 2H, 2 × Ph*H*), 7.53 – 7.44 (m, 2H, 2 × Ph*H*), 7.46 – 7.39 (m, 1H, Ph*H*), 6.75 – 6.66 (m, 3H, 3 × OMeAr*H*), 4.13 (d, $J$ = 14.0 Hz, 1H, NC$H_A$H$_B$), 4.04 (d, $J$ = 14.0 Hz, 1H, NCH$_A$$H_B$), 3.80 (s, 3H, OC$H_3$), 3.77 (s, 3H, OC$H_3$), (note: N$H_2$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 149.0, 148.5, 145.1, 139.9, 139.4, 129.4, 129.1, 128.5, 127.9, 127.6, 127.3, 120.3, 111.1, 111.0, 55.9, 55.8, 47.7; **LRMS** *m/z* (ESI) $[M+Na]^+$ 405.2; **HRMS** (ESI, *m/z*) calculated for $(C_{21}H_{23}O_3N_2S)^+$ 383.1424 $[M+H]^+$, found 383.1422. The spectroscopic data is in agreement with literature.[103]

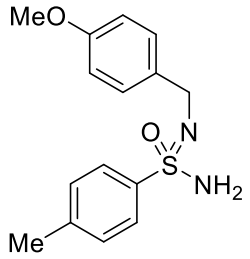
**N'-(4-nitrobenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (124c)**



Prepared according to general procedure A, using 4-bromobiphenyl (233 mg, 1.0 mmol, 1.00 equiv.), *n*-butyllithium (0.46 mL, 2.18 M in hexanes, 1.00 equiv.) TrNSO (306 ,mg, 1.0 mmol, 1.00 equiv.), *t*-butyl hypochlorite (0.12 mL, 1.0 mmol, 1.05 equiv.), triethylamine (0.14 mL, 1.0 mmol, 1.00 equiv.), (4-nitrophenyl)methanamine (226 mg, 1.2 mmol, 1.20 equiv.) and methanesulfonic acid (5.0 mL, 10.0 mol, 10.0 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:1), afforded the title compound (109 mg, 30%) as an orange solid.

**MP** (Petrol/EtOAc) 80-82 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.06 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-$NO_2$Ar*H*), 7.99 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.65 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.62 – 7.50 (m, 2H, 2 × Ph*H*), 7.50 – 7.44 (m, 2H, 2 × Ph*H*), 7.44 – 7.37 (m, 3H, 2 × *p*-$NO_2$Ar*H*, Ph*H*), 4.26 (d, $J$ = 15.5 Hz, 2H, NC$H_A$H$_B$), 4.19 (d, $J$ = 15.5 Hz, 2H, NCH$_A$$H_B$), (note: N$H_2$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 147.3, 145.6, 145.1, 139.7, 139.1, 129.2, 128.7, 128.5, 127.8, 127.8, 127.3, 123.8, 46.8; **LRMS** *m/z* (ESI) $[M+H]^+$ 368.0; **HRMS** (ESI, *m/z*) calculated for $(C_{19}H_{18}O_3N_3S)^+$ 368.1063 $[M+H]^+$, found 368.1060; **IR** ($CHCl_3$) 3275, 1597, 1518, 1345, 1254, 1109, 1007, 856, 764, 721, 664; **$R_f$** 0.43 (Petrol:EtOAc, 1:4).

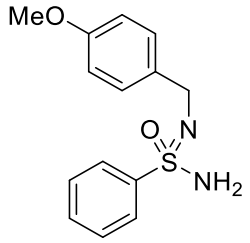
**_N'_-(4-methoxybenzyl)-4-methylbenzenesulfonimidamide (123b)**




Prepared according to general procedure A using 4-bromotoluene (1.23 mL, 10.0 mmol, 1.00 equiv.), *n*-butyllithium (4.0 mL, 2.50 M in hexanes, 1.00 equiv.) TrNSO (3.054 g, 10.0 mmol, 1.00 equiv.), *t*-butyl hypochlorite (1.2 mL, 10.5 mmol, 1.05 equiv.), triethylamine (1.4 mL, 10.0 mmol, 1.00 equiv.), 4-methoxybenzylamine (1.6 mL, 12.0 mmol, 1.20 equiv.) and methanesulfonic acid (6.5 mL, 0.1 mol, 10.00 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 4:1 to 1:4), afforded the title compound (2.766 g, 95%) as a colourless solid.

**MP** (Pentane/EtOAc) 96-98 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.86 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.29 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.09 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.79 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.05 (d, *J* = 13.5 Hz, 1H, NC$H_AH_B$), 3.95 (d, *J* = 13.5 Hz, 1H, NC$H_AH_B$), 3.77 (s, 3H, OC$H_3$), 2.43 (s, 3H, ArC$H_3$), (note: N$H_2$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.3, 143.1, 138.0, 129.7, 129.3, 129.0, 127.5, 114.2, 55.4, 47.6, 21.6; **LRMS** (ESI, *m/z*) $[M+H]^+$ 291.1; **HRMS** (ESI, *m/z*) calculated for $(C_{15}H_{17}O_2N_2S)^-$ 289.1016 $[M-H]^-$, found 289.1014; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 3009, 1613, 1514, 1456, 1251, 1177, 1099, 1041, 814, 753, 644; **$R_f$** 0.52 (Petrol:EtOAc, 1:4).

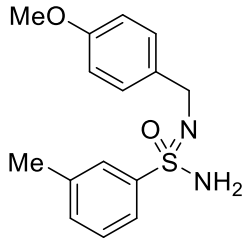
**N'-(4-methoxybenzyl)benzenesulfonimidamide (123c)**




Prepared according to general procedure A, using bromobenzene (1.07 mL, 10.0 mmol, 1.00 equiv.), *n*-butyllithium (4.0 mL, 2.50 M in hexanes, 1.00 equiv.) TrNSO (3.054 g, 10.0 mmol, 1.00 equiv.), *t*-butyl hypochlorite (1.2 mL, 10.5 mmol, 1.05 equiv.), triethylamine (1.4 mL, 10.0 mmol, 1.00 equiv.), 4-methoxybenzylamine (1.6 mL, 12.0 mmol, 1.2 equiv.) and methanesulfonic acid (6.5 mL, 0.1 mol, 10.00 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 4:1 to 1:4), afforded the title compound (1.166 g, 42%) as a colourless solid.

**MP** (Pentane/EtOAc) 64-66 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.00 – 7.95 (m, 2H, 2 × Ph*H*), 7.59 – 7.53 (m, 1H, Ph*H*), 7.52 – 7.46 (m, 2H, 2 × Ph*H*), 7.07 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.78 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.07 (d, *J* = 13.5 Hz, 1H, NC$H_A$H$_B$), 3.97 (d, *J* = 13.5 Hz, 1H, NCH$_A$$H_B$), 3.76 (s, 3H, OC$H_3$), (note: N$H_2$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.3, 141.2, 132.4, 129.3, 129.1, 129.0, 127.4, 114.2, 55.4, 47.6; **LRMS** (ESI, *m/z*) $[M+H]^+$ 277.1; **HRMS** (ESI, *m/z*) calculated for $(C_{14}H_{17}O_2N_2S)^+$ 277.1005 $[M+H]^+$, found 277.1005; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 3272, 1612, 1512, 1445, 1244, 1177, 1132, 1029, 822, 749, 689; **$R_f$** 0.46 (Petrol:EtOAc, 1:4).

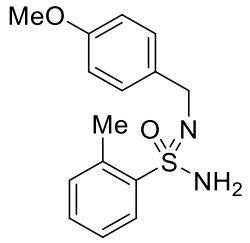
**_N'_-(4-methoxybenzyl)-3-methylbenzenesulfonimidamide (123d)**




Prepared according to general procedure A, using 3-bromotoluene (1.21 mL, 10.0 mmol, 1.00 equiv.), *n*-butyllithium (4.0 mL, 2.50 M in hexanes, 1.00 equiv.) TrNSO (3.054 g, 10.0 mmol, 1.00 equiv.), *t*-butyl hypochlorite (1.2 mL, 10.5 mmol, 1.05 equiv.), triethylamine (1.4 mL, 10.0 mmol, 1.00 equiv.), 4-methoxybenzylamine (1.6 mL, 12.0 mmol, 1.20 equiv.) and methanesulfonic acid (6.5 mL, 0.1 mol, 10.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 4:1 to 1:4), afforded the title compound (879 mg , 30%) as a colourless oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.79 – 7.74 (m, 2H, 2 × Ar*H*); 7.40 – 7.31 (m, 2H, 2 × Ar*H*), 7.08 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.77 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.06 (d, *J* = 13.5 Hz, 1H, NC$H_A$H$_B$), 3.96 (d, *J* = 13.5 Hz, 1H, NCH$_A$$H_B$), 3.76 (s, 3H, OC$H_3$), 2.40 (s, 3H, ArC$H_3$), (note: N$H_2$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.2, 140.9, 139.2, 133.1, 129.3, 129.0, 128.9, 127.8, 124.5, 114.1, 55.4, 47.5, 21.5; **LRMS** (ESI, *m/z*) $[M+H]^+$ 291.1; **HRMS** (ESI, *m/z*) calculated for $(C_{15}H_{19}O_2N_2S)^+$ 291.1162 $[M+H]^+$, found 291.1162; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2981, 1612, 1512, 1463, 1246, 1177, 1031, 898, 818, 788, 747, 688; **R$_f$** 0.53 (Petrol:EtOAc, 1:4).

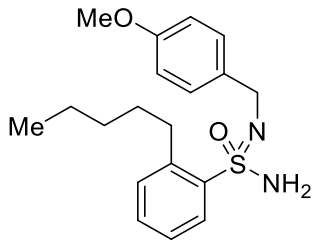
**N'-(4-methoxybenzyl)-2-methylbenzenesulfonimidamide (123e)**




Prepared according to general procedure B, using 2-methylphenylmagnesium chloride (2.10 mL, 0.78 M in THF, 1.00 equiv), TrNSO (500 mg, 1.64 mmol, 1.00 equiv.), *t*-butyl hypochlorite (0.19 mL, 1.72 mmol, 1.05 equiv.), triethylamine (0.23 mL, 1.64 mmol, 1.00 equiv.), 4-methoxybenzylamine (0.26 mL, 1.96 mmol, 1.20 equiv.) and methanesulfonic acid (0.53 mL, 8.20 mmol, 5.00 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:4), afforded the title compound (104 mg, 22%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.06 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 7.43 (app. td, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.33 – 7.25 (m, 2H, 2 × Ar*H*), 7.08 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 6.78 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 4.10 (d, *J* = 14.0 Hz, 1H, NC$H_A$H$_B$), 3.93 (d, *J* = 14.0 Hz, 1H, NCH$_A$$H_B$), 3.77 (s, 3H, OC$H_3$), 2.67 (s, 3H, ArC$H_3$), (note: N$H_2$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.2, 139.6, 137.0, 132.8, 132.2, 129.4 (2 × C), 129.1, 126.1, 114.0, 55.3, 47.0, 20.6; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 313.2; **HRMS** (ESI, *m/z*) calculated for $(C_{15}H_{19}O_2N_2S)^+$ 291.1162 $[M+H]^+$, found 291.1162; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 3282, 2933, 2836, 1612, 1512, 1459, 1245, 1179, 1031, 821, 757, 709, 682; **R$_f$** 0.50 (Petrol:EtOAc, 1:4).

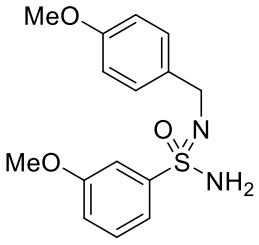
**N'-(4-methoxybenzyl)-2-pentylbenzenesulfonimidamide (123f)**




Prepared according to general procedure A, using 2-bromotoluene (0.59 mL, 4.92 mmol, 1.00 equiv), *n*-butyllithium (2.24 mL, 2.20 M in hexanes, 1.00 equiv.) TrNSO (1.500 g, 4.91 mmol, 1.00 equiv.), *t*-butyl hypochlorite (0.58 mL, 5.12 mmol, 1.05 equiv.), triethylamine (0.69 mL, 4.92 mmol, 1.00 equiv.), 4-methoxybenzylamine (0.77 mL, 5.90 mmol, 1.20 equiv.) and methanesulfonic acid (1.6 mL, 24.60 mmol, 5.00 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:4), afforded the title compound (308 mg, 18%) as a colourless oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.97 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 7.42 (app. td, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.31 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.23 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H, Ar*H*), 7.06 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.74 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.08 (d, *J* = 14.0 Hz, 1H, $NCH_AH_B$), 3.93 (d, *J* = 14.0 Hz, 1H, $NCH_AH_B$), 3.73 (s, 3H, $OCH_3$), 3.15 – 2.96 (m, 2H, $CH_3(CH_2)_3CH_2$), 1.71 – 1.56 (m, 2H, $CH_3(CH_2)_2CH_2CH_2$), 1.41 – 1.26 (m, 4H, $CH_3CH_2CH_2(CH_2)_2$, $CH_3CH_2(CH_2)_3$), 0.88 (t, *J* = 7.0 Hz, 3H, $(CH_2)_4CH_3$), (note: $NH_2$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_H$ 159.0, 142.2, 139.6, 132.0, 131.4, 129.3 (2 × C), 128.9, 125.7, 113.9, 55.2, 46.9, 32.7, 32.0, 31.0, 22.6, 14.0; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 369.2; **HRMS** (ESI, *m/z*) calculated for $(C_{19}H_{27}O_2N_2S)^+$ 347.1788 $[M+H]^+$, found 347.1784; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 2929, 2858, 1612, 1512, 1466, 1246, 1177, 1033, 821, 756; $R_f$ 0.73 (Petrol:EtOAc, 1:4).

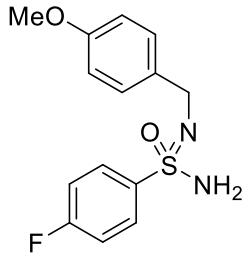
**3-methoxy-*N*'-(4-methoxybenzyl)benzenesulfonimidamide (123g)**




Prepared according to general procedure A, using 3-bromoanisole (0.42 mL, 3.28 mmol, 1.00 equiv), *n*-butyllithium (1.50 mL, 2.18 M in hexanes, 1.00 equiv.) TrNSO (1.000 g, 3.28 mmol, 1.00 equiv.), *t*-butyl hypochlorite (0.39 mL, 3.44 mmol, 1.05 equiv.), triethylamine (0.46 mL, 3.28 mmol, 1.00 equiv.), 4-methoxybenzylamine (0.51 mL, 3.94 mmol, 1.20 equiv.) and methanesulfonic acid (1.1 mL, 16.40 mmol, 5.00 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:4), afforded the title compound (447 mg, 44%) as a yellow oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.50 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, Ar*H*), 7.45 (dd, *J* = 2.5, 1.5 Hz, 1H, Ar*H*), 7.32 (app. t, *J* = 8.0 Hz, 1H, Ar*H*), 7.05 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.02 (dd, *J* = 8.0, 1.0 Hz, 1H, Ar*H*), 6.71 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.02 (d, *J* = 14.0 Hz, 1H, NC$H_A$H$_B$), 3.91 (d, *J* = 14.0 Hz, 1H, NCH$_A$$H_B$), 3.77 (s, 3H, OC$H_3$), 3.71 (s, 3H, OC$H_3$), (note: N$H_2$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.7, 158.8, 142.5, 129.8, 129.2, 129.0, 119.3, 118.4, 113.8, 111.9, 55.5, 55.1, 46.9; **LRMS** (ESI, *m/z*) [M+Na]$^+$ 329.0; **HRMS** (ESI, *m/z*) calculated for $(C_{15}H_{19}O_3N_2S)^+$ 307.1111 [M+H]$^+$, found 307.1110; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 3268, 1612, 1513, 1476, 1431, 1248, 1178, 1033, 823, 787, 685; **R$_f$** 0.48 (Petrol:EtOAc, 1:4).

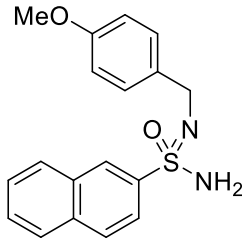
**4-fluoro-*N*'-(4-methoxybenzyl)benzenesulfonimidamide (123h)**




Prepared according to general procedure B, using 4-fluorophenylmagnesium bromide (1.84 mL, 0.89 M in THF, 1.00 equiv), TrNSO (500 mg, 1.64 mmol, 1.00 equiv.), *t*-butyl hypochlorite (0.19 mL, 1.72 mmol, 1.05 equiv.), triethylamine (0.23 mL, 1.64 mmol, 1.00 equiv.), 4-methoxybenzylamine (0.26 mL, 1.96 mmol, 1.20 equiv.) and methanesulfonic acid (0.53 mL, 8.20 mmol, 5.00 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:4), afforded the title compound (219 mg, 45%) as a colourless solid.

**MP** (Petrol/EtOAc) 76-77 °C; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.87 (dd, *J*, $J_{HF}$ = 9.0, 5.0 Hz, 2H, 2 × Ar*H*), 7.07 – 6.98 (m, 4H, 2 × Ar*H*, 2 × *p*-OMeAr*H*), 6.70 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.89 – 4.14 (br. s, 2H, N$H_2$), 3.98 (d, *J* = 14.0 Hz, 1H, NC$H_A$H$_B$), 3.88 (d, *J* = 14.0 Hz, 1H, NCH$_A$$H_B$), 3.69 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 164.6 (d, $^{1}J_{CF}$ = 253.5 Hz), 158.9, 137.3 (d, $^{4}J_{CF}$ = 3.0 Hz), 129.9 (d, $^{3}J_{CF}$ = 9.0 Hz), 129.2, 128.8, 115.8 (d, $^{2}J_{CF}$ = 22.5 Hz), 113.8, 55.2, 46.9; **$^{19}$F NMR** (377 MHz, $CDCl_3$) $\delta_F$ -106.4 – -107.0 (m); **LRMS** (ESI, *m/z*) $[M+Na]^+$ 317.0; **HRMS** (ESI, *m/z*) calculated for $(C_{14}H_{16}O_2N_2FS)^+$ 295.0911 $[M+H]^+$, found 295.0911; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 3274, 1612, 1589, 1513, 1493, 1248, 1177, 1134, 1111, 1031, 837; **$R_f$** 0.61 (Petrol:EtOAc, 1:4).

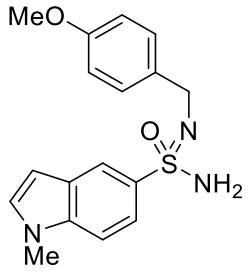
**N'-(4-methoxybenzyl)naphthalene-2-sulfonimidamide (123i)**




Prepared according to general procedure B, using 2-naphthylmagnesium bromide solution (3.09 mL, 0.53 M in THF, 1.00 equiv), TrNSO (500 mg, 1.64 mmol, 1.00 equiv.), *t*-butyl hypochlorite (0.19 mL, 1.72 mmol, 1.05 equiv.), triethylamine (0.23 mL, 1.64 mmol, 1.00 equiv.), 4-methoxybenzylamine (0.26 mL, 1.96 mmol, 1.20 equiv.) and methanesulfonic acid (0.53 mL, 8.20 mmol, 5.0 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:4), afforded the title compound (255 mg, 48%) as a brown oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.48 (d, *J* = 2.0 Hz, 1H, Ar*H*), 7.93 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar*H*), 7.89 – 7.77 (m, 3H, 3 × Ar*H*), 7.58 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Ar*H*), 7.53 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Ar*H*), 7.03 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.61 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 5.02 – 4.29 (br s, 2H, N$H_2$), 4.07 (d, *J* = 14.0 Hz, 1H, NC$H_A$H$_B$), 3.94 (d, *J* = 14.0 Hz, 1H, NCH$_A$$H_B$), 3.59 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 158.7, 138.1, 134.4, 132.0, 129.2, 129.1 (2 × C), 128.9, 128.3 (2 × C), 127.7, 127.1, 122.8, 113.6, 55.0, 46.9; **LRMS** (ESI, *m/z*) [M+Na]$^+$ 349.0; **HRMS** (ESI, *m/z*) calculated for $(C_{18}H_{19}O_2N_2S)^+$ 327.1162 [M+H]$^+$, found 327.1156; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 3270, 1612, 1587, 1512, 1462, 1246, 1177, 1111, 1074, 1030, 861, 817, 749, 646, 610; **$R_f$** 0.50 (Petrol:EtOAc, 1:4).

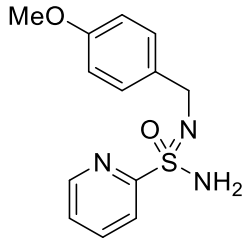
**_N'_-(4-methoxybenzyl)-1-methyl-1_H_-indole-5-sulfonimidamide (123j)**




Prepared according to general procedure A, using 5-bromo-1-methylindole (689 mg, 3.28 mmol, 1.00 equiv), *n*-butyllithium (1.54 mL, 2.14 M in hexanes, 1.00 equiv.) TrNSO (1.000 g, 3.28 mmol, 1.00 equiv.), *t*-butyl hypochlorite (0.39 mL, 3.44 mmol, 1.05 equiv.), triethylamine (0.46 mL, 3.28 mmol, 1.00 equiv.), 4-methoxybenzylamine (0.51 mL, 3.94 mmol, 1.20 equiv.) and methanesulfonic acid (1.1 mL, 16.40 mmol, 5.00 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:4), afforded the title compound (197 mg, 18%) as an orange oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.32 (dd, *J* = 2.0, 0.5 Hz, 1H, Ar*H*), 7.82 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar*H*), 7.37 (d, *J* = 8.5, Hz, 1H, Ar*H*), 7.17 (d, *J* = 3.0 Hz, 1H, HetAr*H*), 7.08 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.75 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.59 (dd, *J* = 3.0, 0.5 Hz, 1H, HetAr*H*), 4.04 (d, *J* = 13.5 Hz, 1H, NC*H*$_A$H$_B$), 3.92 (d, *J* = 13.5 Hz, 1H, NCH$_A$*H*$_B$), 3.83 (s, 3H, NC*H*$_3$), 3.73 (s, 3H OC*H*$_3$), (note: N*H*$_2$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.1, 138.3, 131.2, 131.1, 129.3, 129.2, 127.9, 121.8, 120.4, 114.0, 109.7, 102.7, 55.3, 47.5, 33.2; **LRMS** (ESI, *m/z*) $[M+H]^+$ 330.2; **HRMS** (ESI, *m/z*) calculated for $(C_{17}H_{20}O_2N_3S)^+$ 330.1271 $[M+H]^+$, found 330.1265; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2927, 1611, 1513, 1443, 1341, 1248, 1061, 1030, 806, 762, 728, 625; **R$_f$** 0.21 (Petrol:EtOAc, 1:4).

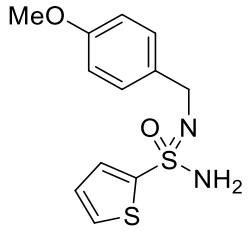
**_N'_-(4-methoxybenzyl)pyridine-2-sulfonimidamide (123k)**




Prepared according to general procedure A, using 2-bromopyridine (0.31 mL, 3.28 mmol, 1.00 equiv), *n*-butyllithium (1.51 mL, 2.18 M in hexanes, 1.00 equiv.) TrNSO (1.000 g, 3.28 mmol, 1.00 equiv.), *t*-butyl hypochlorite (0.39 mL, 3.44 mmol, 1.05 equiv.), triethylamine (0.46 mL, 3.28 mmol, 1.00 equiv.), 4-methoxybenzylamine (0.51 mL, 3.94 mmol, 1.20 equiv.) and methanesulfonic acid (1.1 mL, 16.40 mmol, 5.00 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 0:1), afforded the title compound (499 mg, 55%) as an orange solid.

**MP** (Petrol/EtOAc) 78-80 °C; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.54 (ddd, *J* = 4.5, 1.5, 1.0 Hz, 1H, Py*H*), 8.02 (app. dt, *J* = 8.0, 1.0 Hz, 1H, Py*H*), 7.78 (app. td, *J* = 8.0, 1.5 Hz, 1H, Py*H*), 7.37 (ddd, *J* = 8.0, 4.5, 1.0 Hz, 1H, Py*H*), 7.09 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.71 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.12 (d, *J* = 14.0 Hz, 1H, NC$H_A$H$_B$), 4.06 (d, *J* = 14.0 Hz, 1H, NCH$_A$$H_B$), 3.71 (s, 3H, OC$H_3$), (note: N$H_2$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 158.6, 158.1, 149.2, 137.5, 129.0, 128.9, 125.8, 122.0, 113.5, 54.9, 47.2; **LRMS** (ESI, *m/z*) [M+Na]$^+$ 300.0; **HRMS** (ESI, *m/z*) calculated for $(C_{13}H_{16}O_2N_3S)^+$ 278.0958 [M+H]$^+$, found 278.0956; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 3265, 1612, 1578, 1513, 1426, 1247, 1177, 1031, 823, 776, 750; **R$_f$** 0.25 (EtOAc).

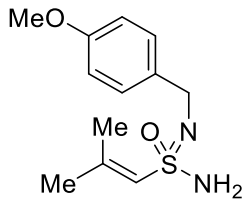
**N'-(4-methoxybenzyl)thiophene-2-sulfonimidamide (123l)**



Prepared according to general procedure B, using 2-thienylmagnesium bromide solution (3.86 mL, 0.85 M in THF, 1.00 equiv), TrNSO (1.000 g, 3.28 mmol, 1.00 equiv.), *t*-butyl hypochlorite (0.39 mL, 3.44 mmol, 1.05 equiv.), triethylamine (0.46 mL, 3.28 mmol, 1.00 equiv.), 4-methoxybenzylamine (0.51 mL, 3.94 mmol, 1.20 equiv.) and methanesulfonic acid (2.1 mL, 32.80 mmol, 10.00 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:4), afforded the title compound (211 mg, 23%) as a black oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.57 (dd, *J* = 3.5, 1.5 Hz, 1H, HetAr*H*), 7.52 (dd, *J* = 5.0, 1.5 Hz, 1H, HetAr*H*), 7.10 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.03 (dd, *J* = 5.0, 3.5 Hz, 1H, HetAr*H*), 6.78 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 4.14 (d, *J* = 13.5 Hz, 1H, NC$H_AH_B$), 4.06 (d, *J* = 13.5 Hz, 1H, NCH$_A$$H_B$), 3.75 (s, 3H, OC$H_3$), (note: N$H_2$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.2, 143.1, 132.0, 131.9, 129.3, 128.7, 127.5, 114.1, 55.4, 47.6; **LRMS** (ESI, *m/z*) $[M+H]^+$ 283.2; **HRMS** (ESI, *m/z*) calculated for $(C_{12}H_{13}N_2O_2S_2)^-$ 281.0424 $[M-H]^-$, found 281.0425; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 3277, 2837, 1611, 1512, 1405, 1247, 1177, 1029, 822, 722; **R$_f$** 0.72 (Petrol:EtOAc, 1:4).

**N'-(4-methoxybenzyl)-2-methylprop-1-ene-1-sulfonimidamide (123m)**

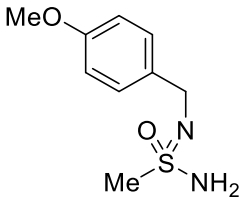


Prepared according to general procedure B, using 2-methyl-1-propenylmagnesium bromide solution (3.28 mL, 0.50 M in THF, 1.0 equiv), TrNSO (500 mg, 1.64 mmol, 1.00 equiv.), *t*-butyl

hypochlorite (0.19 mL, 1.72 mmol, 1.05 equiv.), triethylamine (0.23 mL, 1.64 mmol, 1.00 equiv.), 4-methoxybenzylamine (0.26 mL, 1.96 mmol, 1.20 equiv.) and methanesulfonic acid (0.53 mL, 8.20 mmol, 5.00 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:4), afforded the title compound (75 mg, 18%) as a colourless solid.

**MP** (Petrol/EtOAc) 72-74 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.21 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.84 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.09 (app. hept, *J* = 1.5 Hz, 1H, C=C*H*), 4.14 (d, *J* = 14.0 Hz, 1H, NC$H_AH_B$), 4.10 (d, *J* = 14.0 Hz, 1H, NC$H_AH_B$), 3.78 (s, 3H, OC$H_3$), 2.08 (d, *J* = 1.5 Hz, 3H, CC$H_3$), 1.84 (d, *J* = 1.5 Hz, 3H, CC$H_3$), (note: N$H_2$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.3, 150.9, 129.6, 129.4, 125.5, 114.2, 55.4, 47.4, 26.8, 19.0; **LRMS** (ESI, *m/z*) $[M+H]^+$ 255.1; **HRMS** (ESI, *m/z*) calculated for $(C_{12}H_{19}O_2N_2S)^+$ 255.1161 $[M+H]^+$, found 255.1161; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 2912, 2361, 1612, 1513, 1441, 1246, 1176, 1030, 821; **$R_f$** 0.15 (Petrol:EtOAc, 1:4).

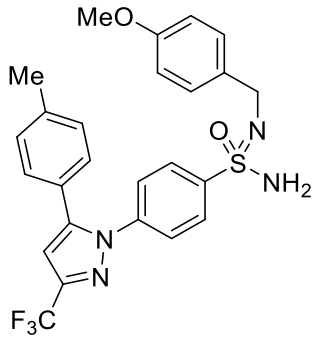
***N'*-(4-methoxybenzyl)methanesulfonimidamide (123n)**




Prepared according to general procedure B, using methyl magnesium bromide solution (1.10 mL, 3.00 M in THF, 1.00 equiv), TrNSO (1.000 g, 3.28 mmol, 1.00 equiv.), *t*-butyl hypochlorite (0.39 mL, 3.44 mmol, 1.05 equiv.), triethylamine (0.46 mL, 3.28 mmol, 1.00 equiv.), 4-methoxybenzylamine (0.53 mL, 3.94 mmol, 1.20 equiv.) and methanesulfonic acid (1.1 mL, 16.40 mmol, 5.00 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 0:1), afforded the title compound (70 mg, 10%) as a yellow solid.

**MP** (Petrol/EtOAc) 65-67 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.23 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.86 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.19 (app. s, 2H, NC$H_A$H$_B$, NCH$_A$$H_B$), 3.78 (s, 3H, OC$H_3$), 2.86 (s, 3H, SC$H_3$), (note: N$H_2$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.3, 129.6, 129.3, 114.2, 55.4, 47.5, 42.2; **LRMS** (ESI, *m/z*) $[M+H]^+$ 215.4 & $[2M+H]^+$ 429.7; **HRMS** (ESI, *m/z*) calculated for $(C_9H_{15}O_2N_2S)^+$ 215.0849 $[M+H]^+$, found 215.0851; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 3263, 1612, 1513, 1463, 1246, 1178, 1030, 820; **R$_f$** 0.12 (EtOAc).

**N'-(4-methoxybenzyl)-4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonimidamide (123o)**



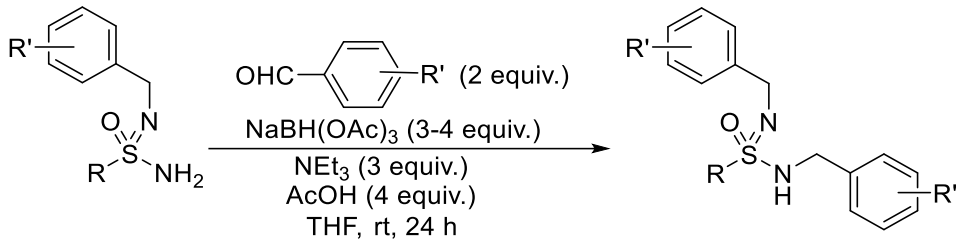

Prepared according to general procedure A, using bromide **122** (1.000 g, 2.62 mmol, 1.0 equiv), *n*-butyllithium (1.22 mL, 2.14 M in hexanes, 1.00 equiv.) TrNSO (800 mg, 2.62 mmol, 1.00 equiv.), *t*-butyl hypochlorite (0.31 mL, 2.75 mmol, 1.05 equiv.), triethylamine (0.37 mL, 2.62 mmol, 1.00 equiv.), 4-methoxybenzylamine (0.41 mL, 3.14 mmol, 1.20 equiv.) and methanesulfonic acid (2.6 mL, 39.3 mmol, 15.0 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:4), afforded the title compound (320 mg, 24%) as a colourless solid.

**MP** (Petrol/EtOAc) 94-96 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.95 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.43 (d, *J* = 8.5 Hz, 2 × 2H, Ar*H*), 7.16 (d, *J* = 8.5 Hz, 2H, 2 × Tol*H*), 7.10 (d, *J* = 8.5 Hz, 2H, 2 × Tol*H*), 7.06 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.79 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.74 (s, 1H, HetAr*H*), 4.06 (d, *J* = 13.5 Hz, 1H, NC$H_A$H$_B$), 3.97 (d, *J* = 13.5 Hz, 1H, NCH$_A$$H_B$), 3.76 (s, 3H,

OC$H_3$), 2.37 (s, 3H TolC$H_3$), (note: N$H_2$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.5, 145.4, 144.2 (q, $^2J_{CF}$ = 39.0 Hz), 142.4, 140.6, 139.9, 129.9, 129.6, 129.3, 128.9, 128.5, 127.2 (q, $^1J_{CF}$ = 266.5 Hz), 125.6, 114.3 (2 × C), 106.3 (q, $^3J_{CF}$ = 1.5 Hz), 55.4, 47.7, 21.5; **$^{19}$F NMR** (377 MHz, $CDCl_3$) $\delta_F$ -62.4 (s); **LRMS** (ESI, *m/z*) $[M+Na]^+$ 523.2; **HRMS** (ESI, *m/z*) calculated for $(C_{25}H_{24}O_2N_4F_3S)^+$ 501.1567 $[M+H]^+$, found 501.1554; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 3265, 1613, 1514, 1471, 1374, 1237, 1161, 1134, 1033, 976, 826, 757; **$R_f$** 0.79 (Petrol:EtOAc, 1:4).

### 6.4.1.5. Synthesis of Di-Substituted *N,N'*-Sulfonimidamides

**General Procedure C**

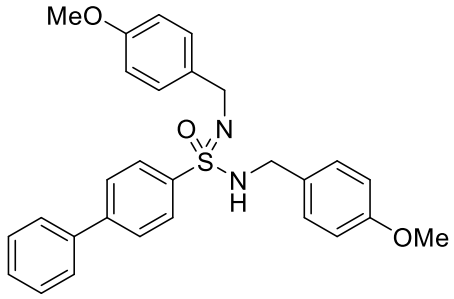



**General Procedure C.** General reaction sequence for the synthesis of di-substituted *N,N'*-sulfonimidamides using a one-pot reductive amination process.

Modified procedure from Abdel-Magid *et al.*[311] Sulfonimidamide (1.0 equiv.), aldehyde (2.0 equiv.), and $NaBH(OAc)_3$ (3.0 equiv.) were added to a reaction vessel equipped with a stirrer bar and dissolved in THF (0.4 M) followed by the addition of triethylamine (3.0 equiv.). This solution was treated dropwise with acetic acid (4.0 equiv.) at room temperature and left to stir at this temperature for 24 h, then the reaction mixture was quenched by the dropwise addition of saturated aqueous $NaHCO_3$ solution and extracted with $CH_2Cl_2$ × 3, the combined organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography.

Note: If after 24 h the reaction has not gone to full conversion as indicated by TLC, an additional equivalent of $NaBH(OAc)_3$ can be added and left to stir for an addition 6 h.

**N,N'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (73a)**

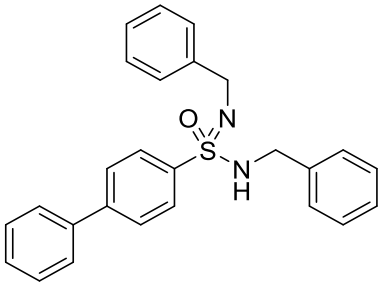



Prepared according to general procedure C, using sulfonimidamide **123a** (5.000 g, 14.2 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (3.46 mL, 28.4 mmol, 2.0 equiv.), $NaBH(OAc)_3$ (9.029 g, 42.6 mmol, 3.0 equiv.), triethylamine (5.94 mL, 42.6 mmol, 3.0 equiv.) and acetic acid (3.25 mL, 56.8 mmol, 4.0 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:1) followed by crystallisation (petrol/$Et_2O$), afforded the title compound (5.342 g, 80%) as a colourless solid.

**MP** (Petrol/$Et_2O$) 68-70 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.02 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.67 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.64 – 7.58 (m, 2H, 2 × Ph*H*), 7.53 – 7.45 (m, 2H, 2 × Ph*H*), 7.45 – 7.36 (m, 1H, Ph*H*), 7.21 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 6.81 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 4.20 (d, *J* = 14.0 Hz, 2H, 2 × NC$H_A$H$_B$), 4.16 (d, *J* = 14.0 Hz, 2H, 2 × NCH$_A$$H_B$), 3.77 (s, 6H, 2 × OC$H_3$), (note: N*H* peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 158.9, 145.0, 139.7, 138.9, 131.6, 129.1, 129.0, 128.4, 128.2, 127.6, 127.3, 114.0, 55.4, 46.4; **LRMS** (ESI, *m/z*) $[M+H]^+$ 473.2; **HRMS** (ESI, *m/z*) calculated for $(C_{28}H_{29}O_3N_2S)^+$ 473.1893 $[M+H]^+$, found 473.1887; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 3263, 3032, 2933, 2835, 1611, 1511, 1245, 1140, 1034, 820, 763, 675, 636; **$R_f$** 0.25 (Petrol:EtOAc, 4:1).

Compound **73a** was crystallised in $CHCl_3$ to obtained crystals suitable for X-ray diffraction studies.

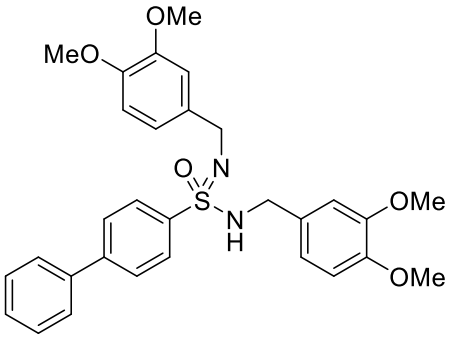
**_N,N'_-dibenzyl-[1,1'-biphenyl]-4-sulfonimidamide (79a)**



Prepared according to general procedure C, using sulfonimidamide **124a** (65 mg, 0.2 mmol, 1.0 equiv.), benzaldehyde (41 μL, 0.4 mmol, 2.0 equiv.), $NaBH(OAc)_3$ (127 mg, 0.3 mmol, 3.0 equiv.), triethylamine (0.08 mL, 0.3 mmol, 3.0 equiv.) and acetic acid (46 μL, 0.4 mmol, 4.0 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:1), afforded the title compound (36 mg, 44%) as a colourless solid.

**MP** (Petrol/EtOAc) 120-122 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.71 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.65 – 7.59 (m, 2H, 2 × Ph*H*), 7.54 – 7.47 (m, 2H, 2 × Ph*H*), 7.47 – 7.38 (m, 1H, Ph*H*), 7.26 – 7.17 (m, 5H, 6 × $CH_2$Ph*H*), 7.12 – 7.04 (m, 4H, 4 × $CH_2$Ph*H*), 4.38 (app. s, 4H, 2 × NC*H*$_2$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 150.3, 145.6, 139.5, 137.8, 136.7, 135.8, 129.2, 128.8, 128.6 (2 × C), 127.8, 127.5, 50.7; **LRMS** (ESI, *m/z*) $[M+H]^+$ 435.2: **HRMS** (ESI, *m/z*) calculated for $(C_{26}H_{24}N_2ONaS)^+$ 435.1503 $[M+Na]^+$, found 435.1503; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1595, 1495, 1481, 1455, 1337, 1205, 1158, 1098, 1053, 1029, 1007, 894, 843, 787, 762, 729, 697, 668, 609; **$R_f$** 0.38 (Petrol:EtOAc, 4:1).

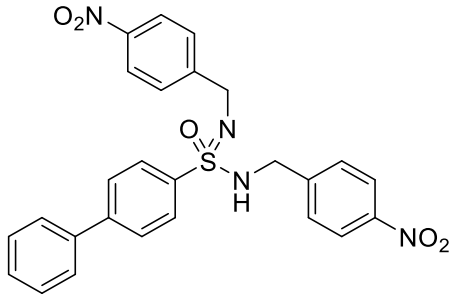
**_N,N'_-bis(3,4-dimethoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (79b)**




Prepared according to general procedure C, using sulfonimidamide **124b** (231 mg, 0.6 mmol, 1.0 equiv.), 3,4-dimethoxybenzaldehyde (201 mg,1.2 mmol, 2.0 equiv.), $NaBH(OAc)_3$ (381 mg, 1.8 mmol, 3.0 equiv.), triethylamine (0.25 mL, 1.8 mmol, 3.0 equiv.) and acetic acid (0.14 mL, 2.4 mmol, 4.0 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:1), afforded the title compound (230 mg, 72%) as a colourless solid.

**MP** (Petrol/EtOAc) 71-73 °C; **$^1$H NMR** (400 MHz,) $\delta_H$ 8.03 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.68 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.64 – 7.56 (m, 2H, 2 × Ph*H*), 7.53 – 7.43 (m, 2H, 2 × Ph*H*), 7.46 – 7.37 (m, 1H, Ph*H*), 6.85 – 6.78 (m, 4H 4 × OMeAr*H*), 6.75 (d, *J* = 8.5 Hz, 2H, 2 × OMeAr*H*), 4.21 (d, *J* = 14.0 Hz, NC$H_A$H$_B$), 4.17 (d, *J* = 14.0 Hz, NCH$_A$$H_B$), 3.83 (s, 6H, 2 × OC$H_3$), 3.80 (s, 6H, 2 × OC$H_3$), (note: N*H* peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 149.0, 148.2, 145.1, 139.5, 138.9, 131.9, 129.2, 128.5, 128.2, 127.6, 127.4, 119.9, 111.0 (2 × C), 55.9, 46.8; **LRMS** *m/z* (ESI) $[M+H]^+$ 533.2 & $[M+Na]^+$ 555.2; **HRMS** (ESI, *m/z*) calculated for $(C_{30}H_{33}O_5N_2S)^+$ 533.2105 $[M+H]^+$, found 533.2099; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2835, 2360, 1593, 1463, 1418, 1357, 1259, 1234, 1192, 1155, 1137, 1094, 1027, 1008, 943, 844, 807, 762, 722, 698, 676, 666; **$R_f$** 0.60 (Petrol:EtOAc, 1:1).

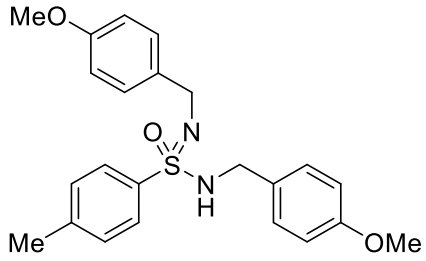
**_N,N'_-bis(4-nitrobenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (79c)**



Prepared according to general procedure C, using sulfonimidamide **124c** (92 mg, 0.25 mmol, 1.0 equiv.), 4-nitrobenzaldehyde (76 mg, 0.50 mmol, 2.0 equiv.), $NaBH(OAc)_3$ (159 mg, 0.75 mmol, 3.0 equiv.), triethylamine (0.11 mL, 0.75 mmol, 3.0 equiv.) and acetic acid (0.06 mL, 1.0 mmol, 4.0 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:4), afforded the title compound (74 mg, 59%) as a colourless solid.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.15 (d, *J* = 9.0 Hz, 4H, 4 × *p*-$NO_2$Ar*H*), 8.04 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.73 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.65 – 7.56 (m, 2H, 2 × Ph*H*), 7.56 – 7.36 (m, 7H, 3 × Ph*H* & 4 × *p*-$NO_2$Ar*H*), 4.41 (d, *J* = 15.5 Hz, 2H, NC$H_AH_B$), 4.32 (d, *J* = 15.5 Hz, 2H, NC$H_AH_B$), (note: N*H* peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 147.3, 146.7, 146.0, 139.3, 138.0, 129.3, 128.8, 128.3, 128.0, 128.0, 127.4, 123.9, 46.4; **LRMS** *m/z* (ESI) $[M+H]^+$ 503.2 & $[M-H]^-$ 501.1; **HRMS** (ESI, *m/z*) calculated for $(C_{26}H_{23}O_5N_4S)^+$ 503.1384 $[M+H]^+$, found 503.1380; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 3298, 2924, 2852, 1600, 1517, 1344, 1284, 1148, 912, 843, 764, 737, 696; **$R_f$** 0.57 (Petrol:EtOAc. 1:1).

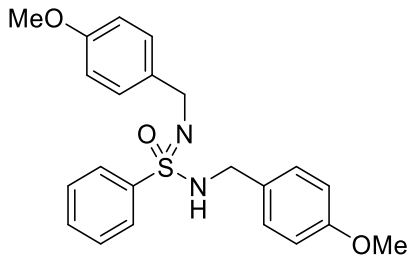
**N,N'-bis(4-methoxybenzyl)-4-methylbenzenesulfonimidamide (73b)**




Prepared according to general procedure C, using sulfonimidamide **123b** (581 mg, 2.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.49 mL, 4.0 mmol, 2.0 equiv.), $NaBH(OAc)_3$ (1.272 g, 6.0 mmol, 3.0 equiv.), triethylamine (0.84 mL, 6.0 mmol, 3.0 equiv.) and acetic acid (0.46 mL, 8.0 mmol, 4.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 4:1 to 1:1), afforded the title compound (484 mg, 59%) as a colourless solid.

The spectroscopic data was in agreement with the previously synthesised compound (see **Section 6.4.1.2.**)

**N,N'-bis(4-methoxybenzyl)benzenesulfonimidamide (73c)**

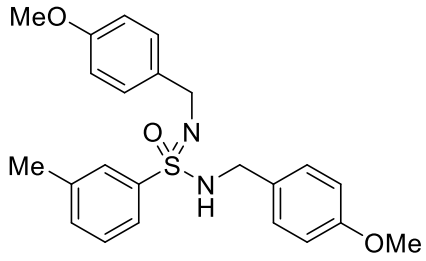



Prepared according to general procedure C, using sulfonimidamide **123c** (553 mg, 2.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.49 mL, 4.0 mmol, 2.0 equiv.), $NaBH(OAc)_3$ (1.272 g, 6.0 mmol, 3.0 equiv.), triethylamine (0.84 mL, 6.0 mmol, 3.0 equiv.) and acetic acid (0.46 mL, 8.0 mmol, 4.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 4:1 to 1:1), afforded the title compound (523 mg, 66%) as a colourless solid.

**MP** (Pentane/EtOAc) 47-49 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.00 – 7.96 (m, 2H, 2 × Ph*H*), 7.57 – 7.51 (m, 1H, Ph*H*), 7.50 – 7.45 (m, 2H, 2 × Ph*H*), 7.18 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*),

6.80 (d, $J$ = 8.5 Hz, 4H, 4 × $p$-OMeAr$H$), 4.16 (d, $J$ = 14.0 Hz, 2H, 2 × NC$H_A$H$_B$), 4.12 (d, $J$ = 14.0 Hz, 2H, 2 × NCH$_A$$H_B$), 3.77 (s, 6H, 2 × OC$H_3$), (note: N$H$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 158.8, 140.3, 132.1, 131.5, 129.0, 127.6, 113.9, 55.4, 46.4; **LRMS** (ESI, $m/z$) $[M+Na]^+$ 419.2; **HRMS** (ESI, $m/z$) calculated for $(C_{22}H_{25}O_3N_2S)^+$ 397.1580 $[M+H]^+$, found 398.1579; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2836, 1612, 1512, 1445, 1246, 1175, 1142, 1034, 820, 750, 689; **$R_f$** 0.48 (Petrol:EtOAc, 3:2).

***N,N'*-bis(4-methoxybenzyl)-3-methylbenzenesulfonimidamide (73d)**

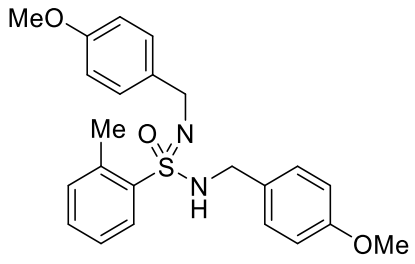



Prepared according to general procedure C, using sulfonimidamide **123d** (581 mg, 2.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.49 mL, 4.0 mmol, 2.0 equiv.), $NaBH(OAc)_3$ (1.272 g, 6.0 mmol, 3.0 equiv.), triethylamine (0.84 mL, 6.0 mmol, 3.0 equiv.) and acetic acid (0.46 mL, 8.0 mmol, 4.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 4:1 to 1:1), afforded the title compound (558 mg, 68%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.82 – 7.76 (m, 2H, 2 × Ar$H$), 7.41 – 7.32 (m, 2H, 2 × Ar$H$), 7.18 (d, $J$ = 8.5 Hz, 4H, 4 × $p$-OMeAr$H$), 6.81 (d, $J$ = 8.5 Hz, 4H, 4 × $p$-OMeAr$H$), 4.16 (d, $J$ = 14.0 Hz, 2H, 2 × NC$H_A$H$_B$), 4.12 (d, $J$ = 14.0 Hz, 2H, 2 × NCH$_A$$H_B$), 3.77 (s, 6H, 2 × OC$H_3$), 2.40 (s, 3H, ArC$H_3$), (note: N$H$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 158.8, 140.0, 139.1, 132.9, 131.6, 129.0, 128.8, 128.0, 124.7, 113.9, 55.4, 46.4, 21.5; **LRMS** (ESI, $m/z$) $[M+H]^+$ 411.2 & $[M+Na]^+$ 433.2; **HRMS** (ESI, $m/z$) calculated for $(C_{23}H_{27}O_3N_2S)^+$ 411.1737 $[M+H]^+$, found

411.1735; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 2835, 1612, 1511, 1463, 1245, 1175, 1139, 1034, 819, 748, 688; $\mathbf{R_f}$ 0.54 (Petrol:EtOAc, 1:1).

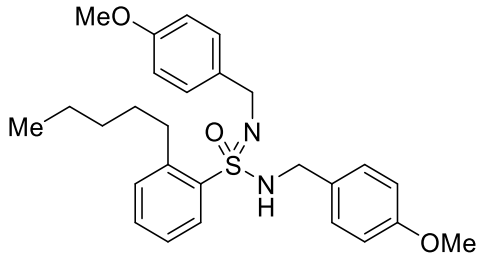
***N,N'*-bis(4-methoxybenzyl)-2-methylbenzenesulfonimidamide (73e)**




Prepared according to general procedure C, using sulfonimidamide **123e** (88 mg, 0.30 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (73 μL, 0.60 mmol, 2.0 equiv.), $NaBH(OAc)_3$ (191 mg, 0.90 mmol, 3.0 equiv.), triethylamine (0.13 mL, 0.90 mmol, 3.0 equiv.) and acetic acid (0.07 mL, 1.20 mmol, 4.0 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:1), afforded the title compound (70 mg, 56%) as a colourless solid.

**MP** (Petrol/EtOAc) 51-53 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.09 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 7.43 (app. td, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.34 – 7.25 (m, 2H, 2 × Ar*H*), 7.18 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 6.81 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 4.16 (d, *J* = 14.0 Hz, 2H, 2 × NC$H_A$$H_B$), 4.11 (d, *J* = 14.0 Hz, 2H, 2 × NC$H_A$$H_B$), 3.79 (s, 6H, 2 × OC$H_3$), 2.63 (s, 3H, ArC$H_3$), (note: N*H* peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 158.7, 138.2, 137.3, 132.7, 132.1, 131.6, 129.9, 129.1, 126.1, 113.9, 55.4, 46.5, 20.6; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 433.2; **HRMS** (ESI, *m/z*) calculated for $(C_{23}H_{27}O_3N_2S)^+$ 411.1748 $[M+H]^+$, found 411.1751; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 2931, 2835, 1612, 1586, 1512, 1462, 1245, 1175, 1146, 1063, 1034, 818, 755, 709; $\mathbf{R_f}$ 0.61 (Petrol:EtOAc, 1:1).

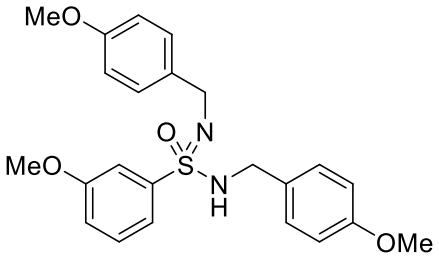
**N,N'-bis(4-methoxybenzyl)-2-pentylbenzenesulfonimidamide (73f)**




Prepared according to general procedure C, using sulfonimidamide **123f** (156 mg, 0.45 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.11 mL, 0.90 mmol, 2.0 equiv.), $NaBH(OAc)_3$ (286 mg, 1.35 mmol, 3.0 equiv.), triethylamine (0.19 mL, 1.35 mmol, 3.0 equiv.) and acetic acid (0.10 mL, 1.80 mmol, 4.0 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:1), afforded the title compound (74 mg, 35%) as a colourless solid.

**MP** (Petrol/EtOAc) 113-115 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.01 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.53 (app. t, *J* = 7.5 Hz, 1H, Ar*H*), 7.38 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.33 – 7.17 (m, 5H, Ar*H*, 4 × *p*-OMeAr*H*), 6.81 (d, *J* = 8.0 Hz, 4H, 4 × *p*-OMeAr*H*), 4.32 (d, *J* = 14.5 Hz, 2H, 2 × $NCH_AH_B$), 4.22 (d, *J* = 14.5 Hz, 2H, $NCH_AH_B$), 3.79 (s, 6H, 2 × $OCH_3$), 3.01 – 2.78 (m, 2H, $CH_3(CH_2)_3CH_2$), 1.56 (app. p, *J* = 7.0 Hz, 2H, $CH_3(CH_2)_2CH_2CH_2$), 1.37 – 1.17 (m, 4H, $CH_3CH_2CH_2(CH_2)_2$, $CH_3CH_2(CH_2)_3$), 0.98 – 0.76 (m, 3H, $(CH_2)_4CH_3$), (note: N*H* peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.5, 145.7, 135.2, 132.4 (2 × C), 132.2, 130.2, 127.8, 126.7, 114.1, 55.4, 45.7, 33.0, 32.0, 31.0, 22.5, 14.2; **LRMS** (ESI, *m/z*) $[M+H]^+$ 467.2 & $[M+Na]^+$ 489.2; **HRMS** (ESI, *m/z*) calculated for $(C_{27}H_{35}O_3N_2S)^+$ 467.2363 $[M+H]^+$, found 467.2356; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 2931, 2631, 1613, 1514, 1441, 1251, 1178, 1034, 887, 819, 756; **$R_f$** 0.83 (Petrol:EtOAc, 1:1).

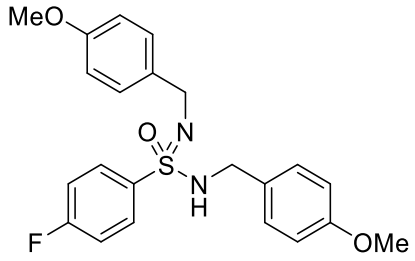
**3-methoxy-*N*,*N*'-bis(4-methoxybenzyl)benzenesulfonimidamide (73g)**




Prepared according to general procedure C, using sulfonimidamide **123g** (116 mg, 0.38 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (93 μL, 0.76 mmol, 2.0 equiv.), $NaBH(OAc)_3$ (242 mg, 1.14 mmol, 3.0 equiv.), triethylamine (0.16 mL, 1.14 mmol, 3.0 equiv.) and acetic acid (0.09 mL, 1.52 mmol, 4.0 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:1), afforded the title compound (99 mg, 61%) as a pale yellow solid.

**MP** (Petrol/EtOAc) 53-55 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.56 (ddd, *J* = 8.0, 1.5, 1.0 Hz, 1H, Ar*H*), 7.49 (dd, *J* = 2.5, 1.5 Hz, 1H, Ar*H*), 7.39 (app. t, *J* = 8.0 Hz, 1H, Ar*H*), 7.18 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 7.07 (ddd, *J* = 8.5, 2.5, 1.0 Hz, 1H, Ar*H*), 6.81 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 4.15 (s, 4H, 2 × NC$H_AH_B$, 2 × NC$H_AH_B$), 3.83 (s, 3H, OC$H_3$), 3.77 (s, 6H, 2 × OC$H_3$), (note: N*H* peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 160.0, 158.8, 141.4, 131.5, 130.0, 129.0, 119.9, 118.5, 113.9, 112.5, 55.7, 55.4, 46.4; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 449.2; **HRMS** (ESI, *m/z*) calculated for $(C_{23}H_{27}O_4N_2S)^+$ 427.1686 $[M+H]^+$, found 427.1683; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 3269, 2836, 1611, 1597, 1512, 1477, 1246, 1176, 1139, 992, 787, 748, 685; **$R_f$** 0.50 (Petrol:EtOAc, 1:1).

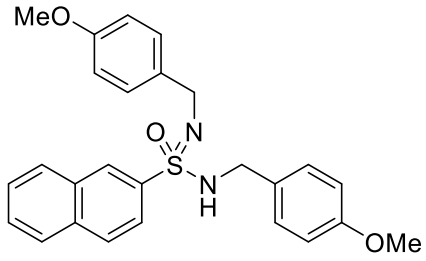
**4-fluoro-*N*,*N*'-bis(4-methoxybenzyl)benzenesulfonimidamide (73h)**




Prepared according to general procedure C, using sulfonimidamide **123h** (112 mg, 0.38 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (93 μL, 0.76 mmol, 2.0 equiv.), $NaBH(OAc)_3$ (242 mg, 1.14 mmol, 3.0 equiv.), triethylamine (0.16 mL, 1.14 mmol, 3.0 equiv.) and acetic acid (0.09 mL, 1.52 mmol, 4.0 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:1) followed by crystallisation (petrol/$Et_2O$), afforded the title compound (87 mg, 55%) as a colourless solid.

**MP** (Petrol/$Et_2O$) 78-80 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.96 (dd, *J*, $J_{HF}$ = 8.5, 5.0 Hz, 2H, 2 × Ar*H*), 7.16 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 7.11 (app. t, *J*, $J_{HF}$ = 8.5 Hz, 2H, 2 × Ar*H*), 6.81 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 4.14 (d, *J* = 14.0 Hz, 2H, 2 × NC$H_AH_B$), 4.10 (d, *J* = 14.0 Hz, 2H, 2 × NC$H_AH_B$), 3.77 (s, 6H, 2 × OC$H_3$), (note: N*H* peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 164.9 (d, $^1J_{CF}$ = 253.5 Hz), 158.9, 136.4 (d, $^4J_{CF}$ = 3.0 Hz), 131.3, 130.3 (d, $^3J_{CF}$ = 9.0 Hz), 129.0, 116.0 (d, $^2J_{CF}$ = 22.4 Hz), 114.0, 55.4, 46.4; **$^{19}$F NMR** (377 MHz, $CDCl_3$) $\delta_F$ -106.66 – -107.02 (m); **LRMS** (ESI, *m/z*) $[M+Na]^+$ 437.2; **HRMS** (ESI, *m/z*) calculated for $(C_{22}H_{24}O_3N_2FS)^+$ 415.1486 $[M+H]^+$, found 415.1480; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2981, 1612, 1588, 1512, 1492, 1463, 1246, 1175, 1141, 1034, 836, 751; **$R_f$** 0.65 (Petrol:EtOAc, 1:1).

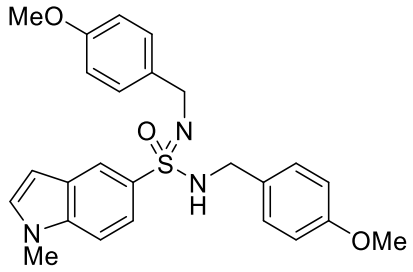
**_N,N'_-bis(4-methoxybenzyl)naphthalene-2-sulfonimidamide (73i)**




Prepared according to general procedure C, using sulfonimidamide **123i** (147 mg, 0.45 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.11 mL, 0.90 mmol, 2.0 equiv.), $NaBH(OAc)_3$ (286 mg, 1.35 mmol, 3.0 equiv.), triethylamine (0.19 mL, 1.35 mmol, 3.0 equiv.) and acetic acid (0.13 mL, 2.25 mmol, 4.0 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:1), afforded the title compound (105 mg, 52%) as a yellow solid.

**MP** (Petrol/EtOAc) 57-59 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.53 (d, $J$ = 2.0 Hz, 1H, Ar*H*), 7.97 – 7.86 (m, 4H, 4 × Ar*H*), 7.67 – 7.54 (m, 2H, 2 × Ar*H*), 7.19 (d, $J$ = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 6.77 (d, $J$ = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 5.30 (br. s, 1H, N*H*), 4.16 (app. s, 4H, 2 × $NCH_AH_B$, 2 × $NCH_AH_B$), 3.73 (s, 6H, 2 × $OCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 158.7, 137.0, 134.6, 132.3, 131.5, 129.3, 129.2, 129.0, 128.9, 128.5, 127.9, 127.3, 123.2, 113.8, 55.3, 46.3; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 469.2; **HRMS** (ESI, *m/z*) calculated for $(C_{26}H_{27}O_3N_2S)^+$ 447.1737 $[M+H]^+$, found 447.1732; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2835, 1611, 1586, 1511, 1463, 1244, 1175, 1143, 1126, 1034, 862, 816, 749, 665, 640; **$R_f$** 0.61 (Petrol:EtOAc, 1:1).

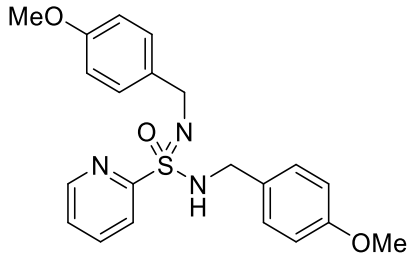
**_N,N'_-bis(4-methoxybenzyl)-1-methyl-1H-indole-5-sulfonimidamide (73j)**




Prepared according to general procedure C, using sulfonimidamide **123j** (148 mg, 0.45 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.11 mL, 0.90 mmol, 2.0 equiv.), $NaBH(OAc)_3$ (286 mg, 1.35 mmol, 3.0 equiv.), triethylamine (0.19 mL, 1.35 mmol, 3.0 equiv.) and acetic acid (0.10 mL, 1.80 mmol, 4.0 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:4), afforded the title compound (132 mg, 65%) as a yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.35 (dd, $J$ = 2.0, 0.5 Hz, 1H, Ar*H*), 7.83 (dd, $J$ = 8.5, 2.0 Hz, 1H, Ar*H*), 7.35 (d, $J$ = 8.5, Hz, 1H, Ar*H*), 7.21 (d, $J$ = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 7.16 (d, $J$ = 3.0 Hz, 1H, HetAr*H*), 6.79 (d, $J$ = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 6.59 (dd, $J$ = 3.0, 0.5 Hz, 1H, HetAr*H*), 4.87 (br. s, 1H, N*H*), 4.13 (app. s, 4H, 2 × $NCH_AH_B$, 2 × $NCH_AH_B$), 3.81 (s, 3H, $NCH_3$), 3.75 (s, 6H, 2 × $OCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 158.6, 138.2, 131.9, 130.9, 130.2, 129.0, 127.9, 122.0, 120.6, 113.7, 109.5, 102.6, 55.3, 46.4, 33.1; **LRMS** (ESI, *m/z*) $[M+H]^+$ 450.2 & $[M+Na]^+$ 472.2; **HRMS** (ESI, *m/z*) calculated for $(C_{25}H_{28}O_3N_3S)^+$ 450.1846 $[M+H]^+$, found 450.1838; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2835, 1611, 1511, 1442, 1341, 1245, 1175, 1136, 1105, 1034, 818, 760, 726, 649, 622; **$R_f$** 0.19 (Petrol:EtOAc, 1:1).

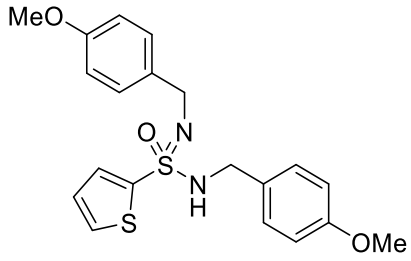
**_N,N'_-bis(4-methoxybenzyl)naphthalene-2-sulfonimidamide (73k)**




Prepared according to general procedure C, using sulfonimidamide **123k** (105 mg, 0.38 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (93 μL, 0.76 mmol, 2.0 equiv.), $NaBH(OAc)_3$ (236 mg, 1.14 mmol, 3.0 equiv.), triethylamine (0.16 mL, 1.14 mmol, 3.0 equiv.) and acetic acid (0.09 mL, 1.52 mmol, 4.0 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 4:1 to 1:4), afforded the title compound (128 mg, 85%) as an off-white solid.

**MP** (Petrol/EtOAc) 69-71 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.64 (ddd, *J* = 4.5, 2.0, 1.0 Hz, 1H, Py*H*), 8.16 (app. dt, *J* = 7.5, 1.0 Hz, 1H, Py*H*), 7.84 (app. td, *J* = 7.5, 2.0 Hz, 1H, Py*H*), 7.42 (ddd, *J* = 7.5, 4.5, 1.0 Hz, 1H, Py*H*), 7.22 (d, *J* = 8.5 Hz, 4H 4 × *p*-OMeAr*H*), 6.81 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 4.27 (d, *J* = 14.0 Hz, 2H, 2 × NC$H_A$H$_B$), 4.18 (d, *J* = 14.0 Hz, 2H, 2 × NCH$_A$$H_B$), 3.77 (s, 6H, 2 × OC$H_3$), (note: N*H* peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 158.8, 157.8, 149.6, 137.9, 131.5, 129.1, 126.1, 123.2, 113.9, 55.4, 46.6; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 420.2; **HRMS** (ESI, *m/z*) calculated for $(C_{21}H_{24}O_3N_3S)^+$ 398.1533 $[M+H]^+$, found 398.1528; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 3252, 2836, 1612, 1578, 1511, 1453, 1425, 1245, 1173, 1117, 992, 819, 775, 753, 607; **$R_f$** 0.18 (Petrol:EtOAc, 1:1).

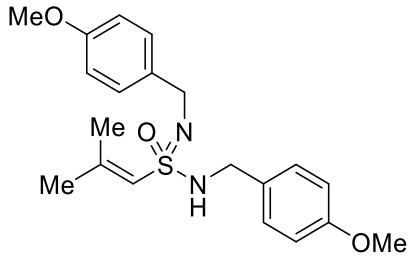
**N,N'-bis(4-methoxybenzyl)thiophene-2-sulfonimidamide (73l)**




Prepared according to general procedure C, using sulfonimidamide **123l** (113 mg, 0.40 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (98 μL, 0.80 mmol, 2.0 equiv.), $NaBH(OAc)_3$ (254 mg, 1.20 mmol, 3.0 equiv.), triethylamine (0.17 mL, 1.20 mmol, 3.0 equiv.) and acetic acid (0.09 mL, 1.60 mmol, 4.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 4:1 to 1:1), afforded the title compound (56 mg, 35%) as a yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.57 (dd, *J* = 3.5, 1.5 Hz, 1H, HetAr*H*), 7.54 (dd, *J* = 5.0, 1.5 Hz, 1H, HetAr*H*), 7.19 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 7.07 (dd, *J* = 5.0, 3.5 Hz, 1H, HetAr*H*), 6.82 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 4.19 (app. s, 4H, 2 × NC$H_A$H$_B$, 2 × NCH$_A$$H_B$), 3.78 (s, 6H, 2 × OC$H_3$), (note: N*H* peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 158.9, 142.0, 132.0, 131.7, 131.2, 129.0, 127.6, 114.0, 55.4, 46.7; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 403.1; **HRMS** (ESI, *m/z*) calculated for $(C_{20}H_{23}O_3N_2S_2)^+$ 403.1145 $[M+Na]^+$, found 403.1146; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 3262, 2836, 1612, 1512, 1463, 1246, 1176, 1143, 1033, 819, 722; **R$_f$** 0.46 (Petrol:EtOAc, 1:1).

**N,N'-bis(4-methoxybenzyl)-2-methylprop-1-ene-1-sulfonimidamide (73m)**

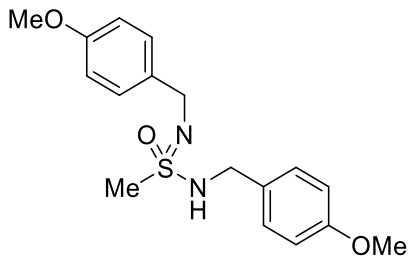



Prepared according to general procedure C, using sulfonimidamide **123m** (64 mg, 0.25 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (61 μL, 0.50 mmol, 2.0 equiv.), $NaBH(OAc)_3$ (159 mg,

0.75 mmol, 3.0 equiv.), triethylamine (0.10 mL, 0.75 mmol, 3.0 equiv.) and acetic acid (0.06 mL, 1.00 mmol, 4.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 1:1), afforded the title compound (48 mg, 51%) as a colourless solid.

**MP** (Pentane/EtOAc) 67-69 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.24 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 6.84 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 6.11 (app. hept, *J* = 1.5 Hz, 1H, C=C*H*), 4.18 (d, *J* = 14.0 Hz, 2H, 2 × NC$H_A$H$_B$), 4.09 (d, *J* = 14.0 Hz, 2H, 2 × NCH$_A$$H_B$), 3.78 (s, 6H, 2 × OC$H_3$), 2.08 (d, *J* = 1.5 Hz, 3H, CC$H_3$), 1.84 (d, *J* = 1.5 Hz, 3H, CC$H_3$), (note: N*H* peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 155.9, 150.6, 131.8, 129.2, 125.3, 114.0, 55.4, 46.2, 26.7, 19.1; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 397.2; **HRMS** (ESI, *m/z*) calculated for $(C_{20}H_{27}O_3N_2S)^+$ 375.1737 $[M+H]^+$, found 375.1736; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2836, 1612, 1511, 1441, 1245, 1174, 1128., 1034 878, 819, 618; **R$_f$** 0.20 (Petrol:EtOAc, 4:1).

***N,N'*-bis(4-methoxybenzyl)methanesulfonimidamide (73n)**

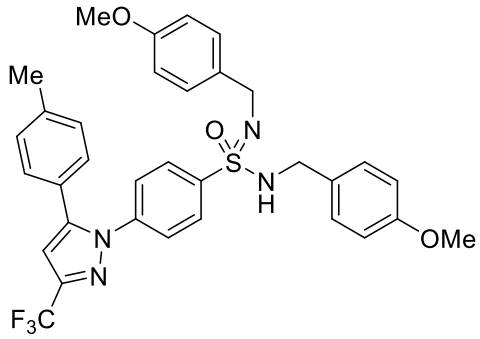



Prepared according to general procedure C, using sulfonimidamide **123n** (54 mg, 0.25 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (61 µL, 0.50 mmol, 2.0 equiv.), $NaBH(OAc)_3$ (159 mg, 0.75 mmol, 3.0 equiv.), triethylamine (0.10 mL, 0.75 mmol, 3.0 equiv.) and acetic acid (0.06 mL, 1.00 mmol, 4.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 1:4), afforded the title compound (58 mg, 69%) as a yellow solid.

**MP** (Pentane/EtOAc) 74-76 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.17 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 6.78 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 4.13 (d, *J* = 14.0 Hz, 2H, 2 × NCH$_A$$H_B$),

4.04 (d, $J$ = 14.0 Hz, 2H, 2 × NCH$_A$H$_B$), 3.72 (s, 6H, 2 × OC$H_3$), 2.84 (s, 3H, SC$H_3$), (note: N$H$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.6, 131.7, 129.1, 114.1, 55.4, 46.4, 42.6; **LRMS** (ESI, $m/z$) $[M+H]^+$ 335.1; **HRMS** (ESI, $m/z$) calculated for $(C_{17}H_{23}O_3N_2S)^+$ 335.1424 $[M+H]^+$, found 335.1422; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2836, 1612, 1512, 1463, 1246, 1176, 1135, 1033, 819; **R$_f$** 0.21 (Petrol:EtOAc, 1:4).

***N,N'*-bis(4-methoxybenzyl)-4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonimidamide (73o)**



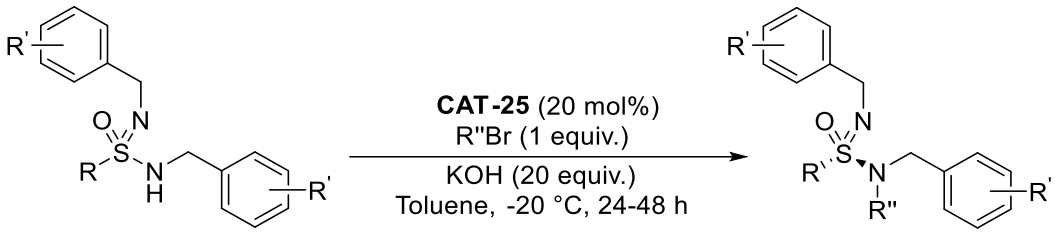

Prepared according to general procedure C, using sulfonimidamide **123o** (200 mg, 0.40 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (98 μL, 0.80 mmol, 2.0 equiv.), $NaBH(OAc)_3$ (254 mg, 1.20 mmol, 3.0 equiv.), triethylamine (0.17 mL, 1.20 mmol, 3.0 equiv.) and acetic acid (0.09 mL, 1.60 mmol, 4.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 4:1 to 1:1), afforded the title compound (127 mg, 51%) as a colourless solid.

**MP** (Petrol/EtOAc) 51-53 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.94 (d, $J$ = 8.5 Hz, 2H, 2 × Ar$H$), 7.41 (d, $J$ = 8.5 Hz, 2H, 2 × Ar$H$), 7.21 – 7.13 (m, 6H, 2 × Tol$H$, 4 × $p$-OMeAr$H$), 7.10 (d, $J$ = 8.0 Hz, 2H, 2 × Tol$H$), 6.81 (d, $J$ = 8.5 Hz, 4H, 4 × $p$-OMeAr$H$), 6.74 (s, 1H, HetAr$H$), 4.16 (d, $J$ = 14.0 Hz, 2H, 2 × NC$H_A$H$_B$), 4.10 (d, $J$ = 14.0 Hz, 2H, 2 × NCH$_A$$H_B$) 3.77 (s, 6H, 2 × OC$H_3$), 2.37 (s, 3H, TolC$H_3$), (note: N$H$ peak not observed); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.0, 145.3, 144.1 (q, $^2J_{CF}$ = 38.5 Hz), 142.1, 139.9, 139.8, 131.1, 129.8, 129.0, 128.8, 128.6, 125.9, 125.5, 121.3 (q,

$^{1}J_{CF}$ = 269.0 Hz), 14.0, 106.3 (q, $^{3}J_{CF}$ = 2.0 Hz), 55.4, 46.4, 21.4; **$^{19}$F NMR** (377 MHz, $CDCl_3$) $\delta_F$ -62.36; **LRMS** (ESI, *m/z*) $[M+H]^+$ 621.2; **HRMS** (ESI, *m/z*) calculated for $(C_{33}H_{32}O_3N_4F_3S)^+$ 621.2142 $[M+H]^+$, found 621.2141; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 2837, 1612, 1512, 1471, 1374, 1238, 1135, 1035, 976, 812, 761, 640; **$R_f$** 0.74 (Petrol:EtOAc, 1:1).

### 6.4.1.6. Phase-Transfer Catalysed Alkylation of Sulfonimidamides

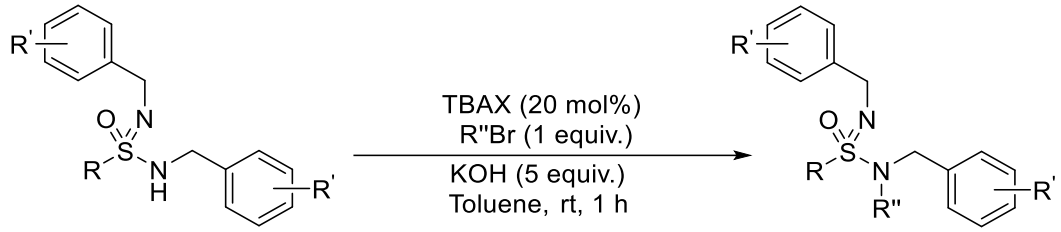
**General Procedure D**




**General Procedure D.** General reaction for the asymmetric phase-transfer catalysed alkylation of sulfonimidamides.

Under an atmosphere of air, sulfonimidamide (0.05 mmol, 1.0 equiv.), phase-transfer catalyst **CAT-25** (7.0 mg, 0.01 mmol, 0.2 equiv.), finely ground potassium hydroxide (56 mg, 1.00 mmol, 20.0 equiv.) and electrophile (0.05 mmol, 1.0 equiv.) were added to a screw-cap vial equipped with a stirrer bar. Toluene (1.0 mL, 0.05 M) was added to the vial and was cooled to −20 °C in an Easymax 102 Advanced Thermostat system then stirred at 1000 rpm for 24-48 h, after which the reaction mixture was diluted with EtOAc and washed with water. The aqueous layer further extracted with EtOAc (2 mL × 3), the organic layers were combined, then the solvent was removed under reduced pressure and the crude material was purified by flash column chromatography.

Note: To obtain samples of the racemic material for chiral-phase HPLC analysis the reaction was conducted with the alterations as below:



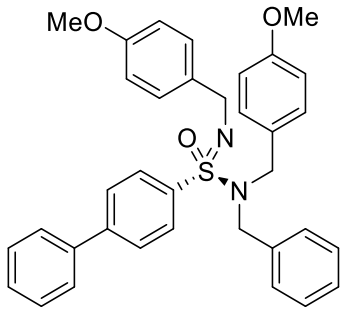

**General Procedure D'.** General reaction for the phase-transfer catalysed alkylation of sulfonimidamides, obtaining racemic product.

Under an atmosphere of air, sulfonimidamide (1.0 equiv.), tetrabutylammonium bromide or tetrabutylammonium hydrogensulfate (0.25 equiv.), finely ground potassium hydroxide (5.0 equiv.) and electrophile (1.0-2.0 equiv.) were added to a reaction vial equipped with a stirrer bar. Toluene (0.1 M) was added and the reaction was vigorously stirred for 1 h at room temperature, after which the reaction mixture was diluted with EtOAc and washed with water. The aqueous layer was further extracted with EtOAc × 3, the organic layers were combined, then the solvent was removed under reduced pressure and the crude material was purified by flash column chromatography.

Note: Reactions were either conducted on a 0.05 or 0.10 mmol scale with respect to the sulfonimidamide and typically used 1.0 equiv. of electrophile unless otherwise stated.

Note: Reactions for the optimisation were conducted under analogous procedures to those outlined above, changing the conditions as stated.

**(*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74a)**

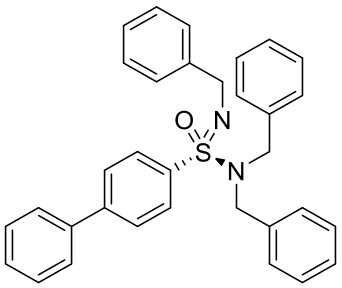


Prepared according to general procedure D, using sulfonimidamide **73a** (23.6 mg, 0.05 mmol, 1.0 equiv.) and benzyl bromide (6 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column

chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (22.5 mg, 80%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.07 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.69 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.55 – 7.46 (m, 2H, 2 × Ph*H*), 7.55 – 7.47 (m, 2H, 2 × Ph*H*), 7.46 – 7.40 (m, 1H, Ph*H*), 7.38 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.26 – 7.17 (m, 3H, 3 × $CH_2$Ph*H*), 7.09 – 6.98 (m, 2H, 2 × $CH_2$Ph*H*), 6.93 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.87 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.73 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.57 (d, $J$ = 15.0 Hz, 1H, NC$H_A$H$_B$), 4.52 (d, $J$ = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.50 (d, $J$ = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.15 (d, $J$ = 14.5 Hz, 1H, NCH$_A$$H_B$), 4.14 (d, $J$ = 15.0 Hz, 1H, NCH$_A$$H_B$), 4.10 (d, $J$ = 14.5 Hz, 1H, NCH$_A$$H_B$), 3.80 (s, 3H, OC$H_3$), 3.76 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.1, 158.4, 144.8, 139.9, 139.8, 136.8, 133.7, 130.3, 128.1, 128.8, 128.7, 128.6, 128.4 (2 × C), 128.0, 127.6, 127.5, 127.4, 113.8, 113.8, 55.4 (2 × C), 51.0, 50.6, 45.3; **HRMS** (ESI, *m/z*) calculated for $(C_{35}H_{35}O_3N_2S)^+$ 563.2363 $[M+H]^+$, found 563.2361; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 3030, 2909, 2835, 2361, 1611, 1511, 1245, 1145, 1007, 894, 817, 763, 728, 697, 671; ***er*** determined by HPLC using a Chiralpak IA-3 column (*n*-hexane:$^i$PrOH, 70:30); $\tau_{major}$ = 19.52 min, $\tau_{minor}$ = 37.62 min (90.5:9.5 *er*); $[\alpha]_D^{25}$ −1.1° (*c* = 0.75, $CHCl_3$); $\mathbf{R_f}$ 0.38 (Petrol:EtOAc, 4:1).

**(S)-*N,N,N'*-tribenzyl-[1,1'-biphenyl]-4-sulfonimidamide (80a)**

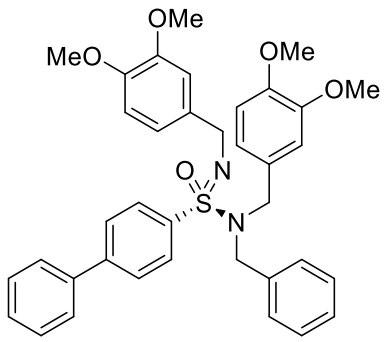



Prepared according to a modified general procedure D, using sulfonimidamide **79a** (20.6 mg, 0.05 mmol, 1.0 equiv.) and benzyl bromide (6 μL, 0.05 mmol, 1.0 equiv.), potassium hydroxide (14.0 mg,

0.25 mmol, 5.0 equiv.), **CAT-1** (2.7 mg, 10 mol%) and toluene (0.5 mL) at room temperature. The title compound was analysed without further purification (see appendix).

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.07 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.69 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.66 – 7.57 (m, 2H, 2 × Ph*H*), 7.54 – 7.47 (m, 2H, 2 × Ph*H*), 7.47 – 7.39 (m, 3H, 2 × $CH_2$Ph*H*, Ph*H*), 7.35 – 7.29 (m, 2H, 2 × $CH_2$Ph*H*), 7.25 – 7.15 (m, 7H, 7 × $CH_2$Ph*H*), 7.06 – 6.98 (m, 4H, 4 × $CH_2$Ph*H*), 4.57 (d, $J$ = 15.0 Hz, 2H, 2 × NC$H_A$$H_B$), 4.55 (d, $J$ = 14.5 Hz, 1H, NC$H_A$$H_B$) 4.20 (d, $J$ = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.15 (d, $J$ = 15.0, Hz, 2H, 2 × NC$H_A$$H_B$); **LRMS** (ESI, *m/z*) [M+Na]$^+$ 525.2; ***er*** determined by HPLC using a Chiralpak IA-3 column (*n*-hexane:$^i$PrOH, 70:30); $\tau_{major}$ = 21.73 min, $\tau_{minor}$ = 36.01 min (58:42 *er*).

**(*S*)-*N*-benzyl-*N*,*N*'-bis(3,4-dimethoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (80b)**

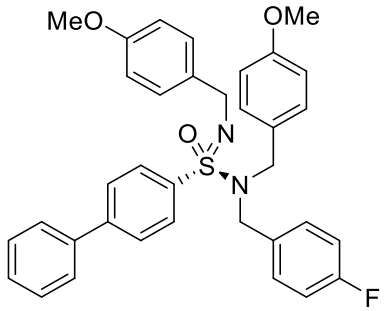



Prepared according to a modified general procedure D, using sulfonimidamide **79b** (20.6 mg, 0.05 mmol, 1.0 equiv.) and benzyl bromide (6 μL, 0.05 mmol, 1.0 equiv.), potassium hydroxide (14.0 mg, 0.25 mmol, 5.0 equiv.), **CAT-1** (2.7 mg, 10 mol%) and toluene (0.5 mL) at room temperature. Purification by flash column chromatography (Petrol:EtOAc, 1:0 to 4:1), afforded the title compound (20. mg, 64%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.09 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.71 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.66 – 7.58 (m, 2H, 2 × Ph*H*), 7.55 – 7.46 (m, 2H, 2 × Ph*H*), 7.46 – 7.40 (m, 1H, Ph*H*), 7.25 – 7.20 (m, 3H, 3 × $CH_2$Ph*H*), 7.11 – 7.06 (m, 2H, 3 × $CH_2$Ph*H*), 7.02 (d, $J$ = 2.0 Hz, 1H, OMeAr*H*), 6.96

(dd, *J* = 8.0, 2.0 Hz, 1H, OMeAr*H*), 6.81 (d, *J* = 8.0 Hz, 1H, OMeAr*H*), 6.68 (d, *J* = 8.0 Hz, 1H, OMeAr*H*), 6.54 (dd, *J* = 8.0, 2.0 Hz, 1H, OMeAr*H*), 6.45 (d, *J* = 2.0 Hz, 1H, OMeAr*H*), 4.60 (d, *J* = 15.0 Hz, 1H, NC$H_A$H$_B$), 4.52 (d, *J* = 15.0 Hz, 1H, NC$H_A$H$_B$), 4.49 (d, *J* = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.14 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 4.13 (d, *J* = 15.0 Hz, 1H, NCH$_A$$H_B$), 4.11 (d, *J* = 15.0 Hz, 1H, NCH$_A$$H_B$), 3.86 (app. d, *J* = 1.0 Hz, 6H, 2 × OC$H_3$), 3.83 (s, 3H, OC$H_3$), 3.57 (s, 3H OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 148.9, 148.5, 147.8, 144.9, 139.9, 139.6, 136.9, 134.1, 129.2, 128.9, 128.8, 128.5, 128.0, 127.7, 127.6, 127.4, 121.4, 119.5, 111.7, 111.1 (2 × C), 110.7, 56.1, 56.0, 55.9, 55.7, 51.0 (2 × C), 45.7; **LRMS** (ESI, *m/z*) [M+Na]$^+$ 645.2; **HRMS** (ESI, *m/z*) calculated for ($C_{37}H_{39}O_5N_2S$)$^+$ 623.2574 [M+H]$^+$, found 623.2569; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1593, 1514, 1463, 1419, 1261, 1235, 1157, 1138, 1028, 894, 847, 808, 766, 726, 699, 672; ***er*** determined by HPLC using a Chiralpak OD-H column (*n*-hexane: $^i$PrOH, 80:20); $\tau_{minor}$ = 32.55 min, $\tau_{major}$ = 39.58 min (32:68 *er*); **$R_f$** 0.33 (Petrol:EtOAc, 1:1).

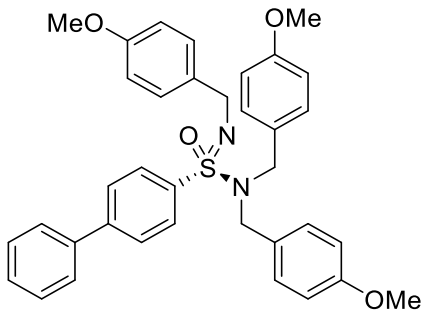
**(*S*)-*N*-(4-fluorobenzyl)-*N,N'*-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74aa)**




Prepared according to general procedure D, using sulfonimidamide **73a** (23.6 mg, 0.05 mmol, 1.0 equiv.) and 4-fluorobenzyl bromide (6 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (23.2 mg, 80%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.05 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.70 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.66 – 7.60 (m, 2H, 2 × Ph*H*), 7.55 – 7.46 (m, 2H, 2 × Ph*H*), 7.50 – 7.39 (m, 1H, Ph*H*), 7.37 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.99 (dd, *J*, $J_{HF}$ = 8.5, 5.5 Hz, 2H, 2 × *p*-FAr*H*), 6.94 – 6.82 (m, 6H, 2 × *p*-FAr*H*, 4 × *p*-OMeAr*H*), 6.72 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.51 (d, *J* = 15.0 Hz, 1H, NC$H_AH_B$), 4.48 (d, *J* = 14.5 Hz, 1H, NC$H_AH_B$), 4.46 (d, *J* = 14.5 Hz, 1H, NC$H_AH_B$), 4.15 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 4.10 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 4.08 (d, *J* = 15.0 Hz, 1H, NCH$_A$$H_B$), 3.79 (s, 3H, OC$H_3$), 3.76 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 162.2 (d, $^1J_{CF}$ = 246.0 Hz), 159.2, 158.5, 144.9, 139.7, 139.6, 133.6, 132.7 (d, $^4J_{CF}$ = 3.5 Hz), 130.5 (d, $^3J_{CF}$ = 8.0 Hz), 130.2, 129.2, 128.7, 128.5, 128.4, 128.0, 127.6, 127.4, 115.3 (d, $^2J_{CF}$ = 21.5 Hz), 113.9, 113.8, 55.4 (2 × C), 50.9, 50.4, 45.3; **$^{19}$F NMR** (377 MHz, $CDCl_3$) $\delta_F$ -114.92 – -115.34 (m); **LRMS** (ESI, *m/z*) $[M+H]^+$ 581.2; **HRMS** (ESI, *m/z*) calculated for $(C_{35}H_{34}O_3N_2FS)^+$ 581.2269 $[M+H]^+$, found 581.2264; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1611, 1510, 1246, 1146, 1036, 905, 821, 760, 731, 697, 670; ***er*** determined by HPLC using a Chiralpak IA-3 column (*n*-hexane:$^i$PrOH, 80:20); $\tau_{major}$ = 25.28 min, $\tau_{minor}$ = 37.19 min (89:11 *er*); $[\alpha]_D^{25}$ –2.0° (*c* = 0.75, $CHCl_3$); **$R_f$** 0.45 (Petrol:EtOAc, 4:1).

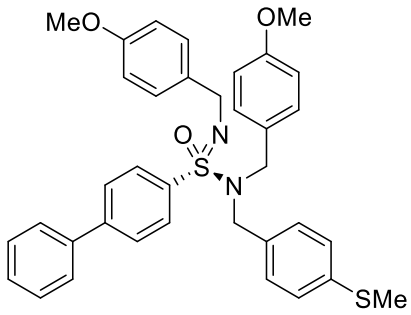
**(*S*)-*N*,*N*,*N*'-tris(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ab)**




Prepared according to general procedure D, using sulfonimidamide **73a** (23.6 mg, 0.05 mmol, 1.0 equiv.) and 4-methoxybenzyl bromide (7 µL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (26.7 mg, 90%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.06 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.69 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.67 – 7.59 (m, 2H, 2 × Ph*H*), 7.55 – 7.45 (m, 2H, 2 × Ph*H*), 7.46 – 7.40 (m, 1H, Ph*H*), 7.38 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.94 (d, *J* = 8.5 Hz, 4H, 4 × *p*-OMeAr*H*), 6.87 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.74 (d, *J* = 8.7 Hz, 4H, 4 × *p*-OMeAr*H*), 4.50 (d, *J* = 15.0 Hz, 2H, 2 × NC$H_A$$H_B$), 4.48 (d, *J* = 14.5 Hz, 1H, 2 × NC$H_A$$H_B$), 4.14 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.07 (d, *J* = 15.0 Hz, 2H, 2 × NC$H_A$$H_B$), 3.80 (s, 3H, OC$H_3$), 3.77 (s, 6H, 2 × OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.0, 158.4, 144.7, 139.9, 139.8, 133.7, 130.2, 129.1, 128.7 (2 × C), 128.4, 128.0, 127.5, 127.4, 113.8, 113.7, 55.4 (2 × C), 50.2, 45.2; **LRMS** (ESI, *m/z*) $[M+H]^+$ 593.2 & $[M+Na]^+$ 615.2; **HRMS** (ESI, *m/z*) calculated for $(C_{36}H_{37}O_4N_2S)^+$ 593.2469 $[M+H]^+$, found 593.2466; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2908, 1611, 1510, 1462, 1279, 1243, 1142, 1007, 898, 817, 760, 729, 697, 670; ***er*** determined by HPLC using a Chiralpak IA-3 column (*n*-hexane: $^i$PrOH, 70:30); $\tau_{major}$ = 23.73 min, $\tau_{minor}$ = 33.77 min (75.5:24.5 *er*); $[\alpha]_D^{25}$ +5.4° (*c* = 0.75, $CHCl_3$); **$R_f$** 0.28 (Petrol:EtOAc, 4:1).

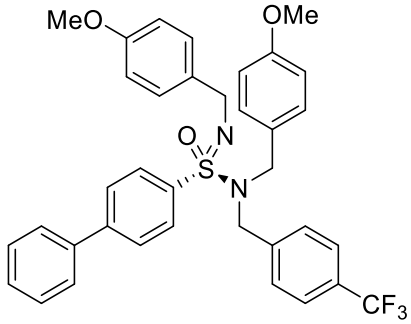
**(*S*)-*N*,*N*'-bis(4-methoxybenzyl)-*N*-(4-(methylthio)benzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ac)**




Prepared according to general procedure D, using sulfonimidamide **73a** (23.6 mg, 0.05 mmol, 1.0 equiv.) and 4-(methylthio)benzyl bromide (10.9 mg, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (25.9 mg, 85%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.05 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.68 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.65 – 7.61 (m, 2H, 2 × Ph*H*), 7.53 – 7.47 (m, 2H, 2 × Ph*H*), 7.46 – 7.39 (m, 1H, Ph*H*), 7.36 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.08 (d, *J* = 8.5 Hz, 2H, 2 × *p*-SMeAr*H*), 6.93 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.92 (d, *J* = 8.5 Hz, 2H, 2 × *p*-SMeAr*H*), 6.86 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.72 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.50 (d, *J* = 15.0 Hz, 1H, NC$H_A$H$_B$), 4.49 (d, *J* = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.48 (d, *J* = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.14 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 4.08 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 4.07 (d, *J* = 15.0 Hz, 1H, NCH$_A$$H_B$), 3.79 (s, 3H, OC$H_3$), 3.76 (s, 3H, OC$H_3$), 2.44 (s, 3H, SC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.1, 158.5, 144.8, 139.8 (2 ×C), 137.6, 133.7 (2 × C), 130.2, 129.4, 129.2, 128.7, 128.5, 128.4, 128.0, 127.6, 127.4, 126.6, 113.9, 113.8, 55.4 (2 × C), 50.7, 50.5, 45.3, 16.0; **LRMS** (ESI, *m/z*) [M+H]$^+$ 609.2; **HRMS** (ESI, *m/z*) calculated for $(C_{36}H_{37}O_3N_2S_2)^+$ 609.2240 [M+H]$^+$, found 609.2234; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1611, 1511, 1441, 1277, 1246, 1146, 1035, 903, 818, 763, 733, 698, 671; ***er*** determined by HPLC using a Chiralpak OD-H column (*n*-hexane:$^i$PrOH, 80:20); $\tau_{major}$ = 15.68 min, $\tau_{minor}$ = 19.53 min (84:16 *er*); $[\alpha]_D^{25}$ +4.4° (*c* = 0.75, $CHCl_3$); **R$_f$** 0.39 (Petrol:EtOAc, 4:1).

**(*S*)-*N*,*N*'-bis(4-methoxybenzyl)-*N*-(4-(trifluoromethyl)benzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ad)**

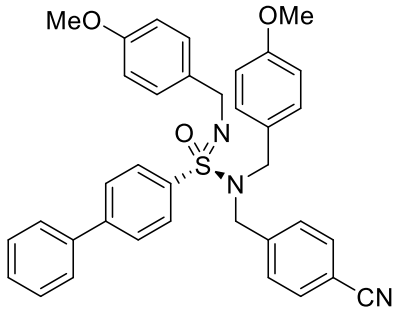



Prepared according to general procedure D, using sulfonimidamide **73a** (23.6 mg, 0.05 mmol, 1.0 equiv.) and 4-(trifluoromethyl)benzyl bromide (8 μL, 0.05 mmol, 1.0 equiv.). Purification by flash

column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (23.7 mg, 75%) as a colourless oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.07 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.72 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.67 – 7.61 (m, 2H, 2 × Ph*H*), 7.55 – 7.48 (m, 2H, 2 × Ph*H*), 7.47 – 7.41 (m, 3H, Ph*H*, 2 × *p*-$CF_3$Ar*H*), 7.38 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.14 (d, $J$ = 8.0 Hz, 2H, 2 × *p*-$CF_3$Ar*H*), 6.90 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.87 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.70 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.58 (d, $J$ = 15.0 Hz, 1H, NC$H_A$$H_B$), 4.53 (d, $J$ = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.44 (d, $J$ = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.20 (d, $J$ = 15.0 Hz, 1H), 4.16 (d, $J$ = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.14 (d, $J$ = 14.5 Hz, 1H, NC$H_A$$H_B$), 3.80 (s, 3H, OC$H_3$), 3.75 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.2, 158.5, 145.0, 141.4, 139.6, 139.0, 133.4, 130.3, 129.5 (d, $^{2}J_{CF}$ = 32.5 Hz) 129.2, 128.8, 128.6, 128.5, 128.0, 127.7, 127.4, 125.3 (q, $^{3}J_{CF}$ = 4.0 Hz), 124.2 (d, $^{1}J_{CF}$ = 272.0 Hz), 114.4, 113.9, 113.8, 55.4, 55.3, 51.7, 50.9, 45.2; **$^{19}$F NMR** (377 MHz, $CDCl_3$) $\delta_F$ -62.42; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 653.2; **HRMS** (ESI, *m/z*) calculated for $(C_{36}H_{34}O_3N_2F_3S)^+$ 631.2237 $[M+H]^+$, found 631.2229; **IR** ($CHCl_3$, $\nu_{max}$/$cm^{-1}$) 2837, 1612, 1511, 1479, 1464, 1324, 1245, 1122, 1066, 1035, 902, 777, 736, 698, 671, 631; ***er*** determined by HPLC using a Chiralpak OD-H column (*n*-hexane: $^{i}$PrOH, 80:20); $\tau_{major}$ = 11.39 min, $\tau_{minor}$ = 14.61 min (78:22 *er*); $[\alpha]_D^{25}$ +3.3° (*c* = 0.75, $CHCl_3$); $\mathbf{R_f}$ 0.57 (Petrol:EtOAc, 4:1).

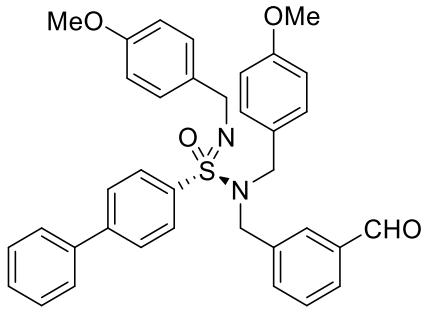
**(*S*)-*N*-(4-cyanobenzyl)-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ae)**




Prepared according to general procedure D, using sulfonimidamide **73a** (23.6 mg, 0.05 mmol, 1.0 equiv.) and 4-(bromomethyl)benzonitrile (9.8 mg, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (25.3 mg, 86%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.06 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.73 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.66 – 7.61 (m, 2H, 2 × Ph*H*), 7.56 – 7.46 (m, 2H, Ph*H*), 7.50 – 7.39 (m, 3H, Ph*H*, 2 × *p*-CNAr*H*), 7.36 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.13 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-CNAr*H*), 6.92 – 6.81 (m, 4H, 4 × *p*-OMeAr*H*), 6.69 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeArH), 4.55 (d, $J$ = 15.5 Hz, 1H, NC$H_A$H$_B$), 4.51 (d, $J$ = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.37 (d, $J$ = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.20 (d, $J$ = 14.5 Hz, 1H, NCH$_A$$H_B$), 4.19 (d, $J$ = 14.5 Hz, 1H, NCH$_A$$H_B$) 4.11 (d, $J$ = 15.5 Hz, 1H, NCH$_A$$H_B$), 3.79 (s, 3H, OC$H_3$), 3.75 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.4, 158.5, 145.2, 143.1, 139.5, 138.7, 133.3, 132.1, 130.3, 129.2, 129.0, 128.6 (2 × C), 128.0, 127.8, 127.7, 127.4, 118.8, 113.9, 113.8, 111.1, 55.4 (2 × C), 52.2, 51.2, 45.3; **LRMS** (ESI, *m/z*) [M+H]$^+$588.2 & [M+Na]$^+$610.2; **HRMS** (ESI, *m/z*) calculated for $(C_{36}H_{34}O_3N_3S)^+$ 588.2326 [M+H]$^+$, found 588.2311; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2836, 2228, 1610, 1511, 1479, 1463, 1245, 1146, 1034, 902, 819, 762, 725, 698, 671; ***er*** determined by HPLC using a Chiralpak OD-H column (*n*-hexane: $^i$PrOH, 80:20); $\tau_{major}$ = 26.19 min, $\tau_{minor}$ = 32.39 min (82.5:17.5 *er*); $[\alpha]_D^{25}$ +8.4° ($c$ = 0.75, $CHCl_3$); **R$_f$** 0.22 (Petrol:EtOAc, 4:1).

**(*S*)-*N*-(3-formylbenzyl)-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74af)**

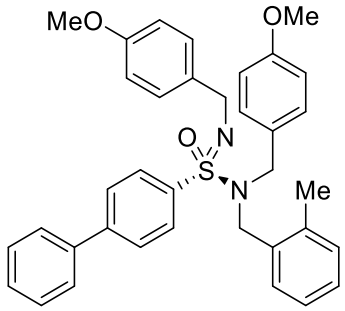



Prepared according to general procedure D, using sulfonimidamide 73**a** (23.6 mg, 0.05 mmol, 1.0 equiv.) and 3-(bromomethyl)benzaldehyde (10.0 mg, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (12.7 mg, 43%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.82 (s, 1H, C*H*O), 8.07 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.71 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*) , 7.69 – 7.67 (m, 1H, $CH_2$Ar*H*), 7.66 – 7.58 (m, 2H, 2 × Ph*H*), 7.54 – 7.47 (m, 2H, 2 × Ph*H*), 7.46 – 7.40 (m, 1H, Ph*H*) 7.40 – 7.36 (m, 2H, 2 × $CH_2$Ar*H*), 7.36 – 7.30 (m, 3H, $CH_2$Ar*H*, 2 × *p*-OMeAr*H*) , 6.92 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.86 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.70 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.58 (d, *J* = 15.0 Hz, 1H, NC$H_A$$H_B$), 4.51 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.44 (d, *J* = 15.0 Hz, 1H, NC$H_A$$H_B$), 4.19 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.16 (d, *J* = 15.0 Hz, 2H, 2 × NC$H_A$$H_B$), 3.79 (s, 3H, OC$H_3$), 3.74 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 192.1, 159.3, 158.6, 145.1, 139.7, 139.1, 138.5, 136.5, 134.7, 133.5, 130.3, 129.9, 129.2, 129.1, 128.7, 128.6, 128.5, 128.2, 128.0, 127.7, 127.5, 114.0, 113.8, 55.5, 55.4, 51.8, 50.9, 45.3; **LRMS** (ESI, *m/z*) $[M+H]^+$ 591.2; **HRMS** (ESI, *m/z*) calculated for $(C_{36}H_{35}O_4N_2S)^+$ 591.2312 $[M+H]^+$, found 591.2307; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2850, 1699, 1611, 1512, 1453, 1280, 1247, 1145, 1035, 908, 816, 759, 731, 670; ***er*** determined by HPLC using a Chiralpak IA-3 column

(*n*-hexane:$^{i}$PrOH, 70:30); $\tau_{major}$ = 30.92 min, $\tau_{minor}$ = 47.55 min (85:15 *er*); $[\alpha]_D^{25}$ -1.5° (*c* = 0.75, $CHCl_3$); $\mathbf{R_f}$ 0.34 (Petrol :EtOAc 4:1).

**(*S*)-*N*,*N*'-bis(4-methoxybenzyl)-*N*-(2-methylbenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ag)**

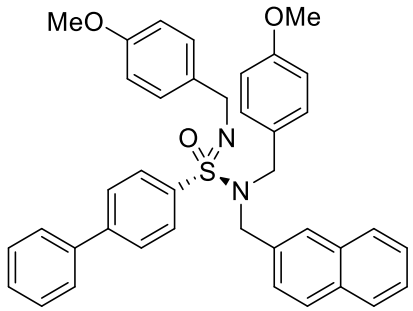



Prepared according to general procedure D, using sulfonimidamide **73a** (23.6 mg, 0.05 mmol, 1.0 equiv.) and 2-methylbenzyl bromide (7 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (23.1 mg, 80%) as a colourless oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.06 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.69 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.65 – 7.60 (m, 2H, 2 × Ph*H*), 7.54 – 7.46 (m, 2H, 2 × Ph*H*), 7.46 – 7.38 (m, 1H Ph*H*), 7.34 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.15 – 7.06 (m, 1H, $CH_2$Ar*H*), 7.07 – 7.01 (m, 3H, 3 × $CH_2$Ar*H*) 6.85 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.81 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.66 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.55 (d, *J* = 15.5 Hz, 1H, NC$H_A$$H_B$), 4.50 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.47 (d, *J* = 15.0 Hz, 1H, NC$H_A$$H_B$), 4.17 (d, *J* = 15.5 Hz, 1H, NC$H_A$$H_B$), 4.16 (d, *J* = 15.0 Hz, 1H, NC$H_A$$H_B$), 4.12 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 3.79 (s, 3H, OC$H_3$), 3.73 (s, 3H, OC$H_3$), 2.09 (s, 3H, CC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.0, 158.4, 144.8, 139.8, 139.2, 136.5, 134.6, 133.8, 130.5, 130.2, 129.2, 128.7 (2 × C), 128.5, 128.4, 128.1, 127.6, 127.4, 127.3, 126.0, 113.8, 113.7, 55.4 (2 × C), 51.0 49.1, 45.4, 19.3; **LRMS** (ESI, *m/z*) $[M+H]^+$ 577.2; **HRMS** (ESI, *m/z*) calculated for $(C_{29}H_{31}O_3N_2S)^+$ 577.2495 $[M+H]^+$, found 577.2518; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1612, 1511, 1462, 1279,

1245, 1147, 1035, 901, 818, 762, 698, 671; **er** determined by HPLC using a Chiralpak IA-3 column (*n*-hexane:$^{i}$PrOH, 80:20); $\tau_{major}$ = 25.25 min, $\tau_{minor}$ = 30.69 min (73:27 *er*); $[\alpha]_D^{25}$ +25.7° (*c* = 0.75, $CHCl_3$); $\mathbf{R_f}$ 0.51 (Petrol:EtOAc, 4:1).

**(*S*)-*N*,*N*'-bis(4-methoxybenzyl)-*N*-(naphthalen-2-ylmethyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ah)**

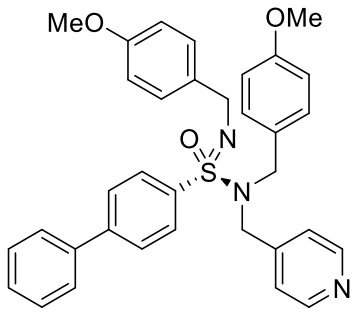



Prepared according to general procedure D, using sulfonimidamide **73a** (23.6 mg, 0.05 mmol, 1.0 equiv.) and 2-(bromomethyl)naphthalene (11.1 mg, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (24.8 mg, 81%) as a colourless oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.09 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.82 – 7.75 (m, 1H, $CH_2$Ar*H*), 7.72 – 7.65 (m, 3H, $CH_2$Ar*H*, 3 × Ar*H*), 7.65 – 7.57 (m, 3H, $CH_2$Ar*H*, 2 × Ph*H*), 7.54 – 7.47 (m, 2H, 2 × Ph*H*), 7.47 – 7.41 (m, 2H, $CH_2$Ar*H*, Ph*H*), 7.37 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.31 (d, *J* = 2.0 Hz, 1H, $CH_2$Ar*H*), 7.16 (dd, *J* = 8.5, 2.0 Hz, 1H, $CH_2$Ar*H*), 6.94 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.85 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.71 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.72 (d, *J* = 15.0 Hz, 1H, NC$H_A$H$_B$), 4.56 (d, *J* = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.53 (d, *J* = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.28 (d, *J* = 15.0 Hz, 1H, NCH$_A$$H_B$), 4.19 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 4.12 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 3.78 (s, 3H, OC$H_3$), 3.73 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.1, 158.5, 144.9, 140.0, 139.8, 134.2, 133.7, 133.3, 132.8, 130.3, 129.2, 128.7, 128.6, 128.4, 128.2, 128.0, 127.9, 127.7 (2 × C), 127.6, 127.5, 126.7, 126.2, 126.0, 113.9, 113.8, 55.5, 55.4, 51.1,

50.7, 45.3; **LRMS** (ESI, *m/z*) [M+H]$^+$ 613.2; **HRMS** (ESI, *m/z*) calculated for $(C_{39}H_{37}O_3N_2S)^+$ 613.2519 [M+H]$^+$, found 613.2514; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1611, 1511, 1463, 1246, 1145, 1035, 909, 818, 760, 730, 699, 671; ***er*** determined by HPLC using a Chiralpak IA-3 column (*n*-hexane: $^i$PrOH, 70:30); $\tau_{major}$ = 20.24 min, $\tau_{major}$ = 33.09 min (81:19 *er*); $[\alpha]_D^{25}$ +2.8° (*c* = 0.75, $CHCl_3$); $\mathbf{R_f}$ 0.45 (Petrol:EtOAc, 4:1).

**(*S*)-*N*,*N*'-bis(4-methoxybenzyl)-*N*-(pyridin-4-ylmethyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ai)**

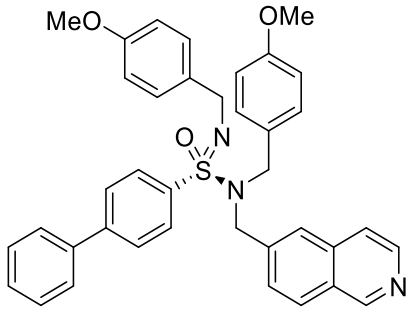



Prepared according to general procedure D, using sulfonimidamide **73a** (23.6 mg, 0.05 mmol, 1.0 equiv.) and 4-(bromomethyl)pyridine hydrobromide (12.6 mg, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 1:1), afforded the title compound (13.8 mg, 49%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.41 (d, *J* = 6.0 Hz, 2H, 2 × $CH_2$Py*H*), 8.05 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.71 (d, *J* = 8.5 Hz, 1H, 2 × Ar*H*), 7.66 – 7.59 (m, 2H, 2 × Ph*H*), 7.53 – 7.47 (m, 2H, 2 × Ph*H*), 7.46 – 7.40 (m, 1H, Ph*H*), 7.36 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.93 (d, *J* = 6.0 Hz, 1H, 2 × $CH_2$Py*H*), 6.89 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*) , 6.86 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.70 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.52 (d, *J* = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.50 (d, *J* = 16.0 Hz, 1H, NC$H_A$H$_B$), 4.41 (d, *J* = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.20 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 4.18 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 4.08 (d, *J* = 16.0 Hz, 1H, NCH$_A$$H_B$), 3.79 (s, 3H, OC$H_3$), 3.74 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.4, 158.6, 149.8, 146.6, 145.2, 139.6, 138.9, 133.4, 130.4,

129.2, 128.6, 128.6, 128.0, 127.8 (2 × C), 127.5, 123.2, 114.0, 113.9, 55.5, 55.4, 52.0, 50.4, 45.3; **LRMS** (ESI, *m/z*) $[M+H]^+$ 564.2 & $[M+Na]^+$ 586.2; **HRMS** (ESI, *m/z*) calculated for $(C_{34}H_{34}O_3N_3S)^+$ 564.2315 $[M+H]^+$, found 564.2310; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1611, 1511, 1454, 1424, 1246, 1164, 1117, 1035, 896, 817, 752, 703; ***er*** determined by HPLC using a Chiralpak OD-H column (*n*-hexane:$^i$PrOH, 80:20); $\tau_{minor}$ = 32.54 min, $\tau_{major}$ = 42.57 min (68.5:31.5 *er*); $[\alpha]_D^{25}$ +2.7° (*c* = 0.75, $CHCl_3$); $\mathbf{R_f}$ 0.42 (Petrol:EtOAc, 3:2).

**(*S*)-*N*-(isoquinolin-6-ylmethyl)-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74aj)**

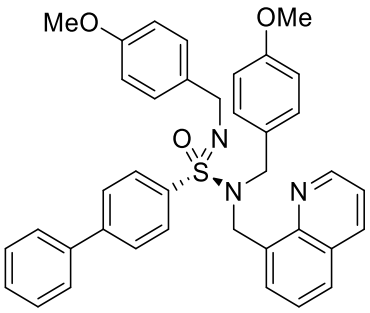



Prepared according to general procedure D, using sulfonimidamide **73a** (23.6 mg, 0.05 mmol, 1.0 equiv.) and 6-(bromomethyl)quinoline hydrobromide (15.1 mg, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 1:1), afforded the title compound (14.4 mg, 47%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.18 (s, 1H, HetAr*H*), 8.46 (d, *J* = 6.0 Hz, 1H, HetAr*H*), 8.09 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.80 (d, *J* = 8.5 Hz, 1H, $CH_2$Ar*H*), 7.70 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.66 – 7.58 (m, 2H, 2 × Ph*H*), 7.54 – 7.48 (m, 2H, 2 × Ph*H*), 7.46 – 7.42 (m, 1H, PhH), 7.40 (d, *J* = 6.0 Hz, 1H, HetAr*H*), 7.36 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.32 (dd, *J* = 8.5, 1.5 Hz, 1H, $CH_2$Ar*H*), 7.28 (app. s, 1H, $CH_2$Ar*H*), 6.91 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.85 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.67 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.71 (d, *J* = 15.5 Hz, 1H, NC$H_A$H$_B$), 4.53 (d, *J* = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.50 (d, *J* = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.28 (d, *J* = 15.5 Hz, 1H,

$NCH_AH_B$), 4.21 (d, $J$ = 14.5 Hz, 1H, $NCH_AH_B$), 4.18 (d, $J$ = 14.5 Hz, 1H, $NCH_AH_B$), 3.78 (s, 3H, $OCH_3$), 3.70 (s, 3H, $OCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.3, 158.5, 152.3, 145.1, 143.4, 139.8, 139.6, 139.3, 135.7, 133.5, 130.4, 129.2, 128.7, 128.6, 128.2 (2 × C), 128.1, 127.9, 127.8, 127.7, 127.5, 125.8, 120.4, 113.9, 113.8, 55.4 (2 × C), 51.6, 51.4, 45.3; **LRMS** (ESI, *m/z*) $[M+H]^+$ 614.2; **HRMS** (ESI, *m/z*) calculated for $(C_{36}H_{36}O_3N_3S)^+$ 614.2472 $[M+H]^+$, found 614.2465; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 2981, 2920, 1611, 1511, 1462, 1382, 1247, 1149, 1035, 96, 910, 818, 763, 725, 699, 672; ***er*** determined by HPLC using a Chiralpak IA-3 column (*n*-hexane: $^i$PrOH, 80:20); $\tau_{minor}$ = 59.05 min, $\tau_{major}$ = 70.71 min (36:64 *er*); $[\alpha]_D^{25}$ +0.4° (*c* = 0.75, $CHCl_3$); $R_f$ 0.37 (Petrol:EtOAc, 1:1).

**(*S*)-*N*,*N*'-bis(4-methoxybenzyl)-*N*-(quinolin-8-ylmethyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ak)**

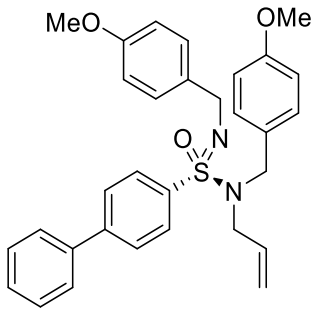



Prepared according to general procedure D, using sulfonimidamide **73a** (23.6 mg, 0.05 mmol, 1.0 equiv.) and 8-(bromomethyl)quinoline (11.1 mg, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 1:1), afforded the title compound (17.5 mg, 57%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.81 (dd, $J$ = 4.0, 2.0 Hz, 1H, HetAr*H*), 8.07 (dd, $J$ = 8.5, 2.0 Hz, 1H, HetAr*H*), 8.00 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.70 (dd, $J$ = 7.0, 1.5 Hz, 1H, $CH_2$Ar*H*), 7.63 (dd, $J$ = 8.0, 1.5 Hz, 1H, $CH_2$Ar*H*), 7.61 – 7.57 (m, 4H, 2 × Ar*H*, 2 × Ph*H*), 7.52 – 7.46 (m, 2H, 2 × Ph*H*), 7.45 – 7.40 (m, 1H, Ph*H*), 7.40 – 7.32 (m, 4H, $CH_2$Ar*H*, HetAr*H*, 2 × *p*-OMeAr*H*), 6.98 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.83 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.56 (d, $J$ = 8.5 Hz, 2H,

2 × *p*-OMeAr*H*), 5.17 (d, *J* = 16.5 Hz, 1H, NC*H*$_A$H$_B$), 5.09 (d, *J* = 16.5 Hz, 1H, NCH$_A$*H*$_B$), 4.58 (d, *J* = 14.5 Hz, 1H, NC*H*$_A$H$_B$), 4.53 (d, *J* = 14.5 Hz, 1H, NC*H*$_A$H$_B$), 4.45 (d, *J* = 14.5 Hz, 1H, NCH$_A$*H*$_B$), 4.28 (d, *J* = 14.5 Hz, 1H, NCH$_A$*H*$_B$), 3.78 (s, 3H, OC*H*$_3$), 3.67 (s, 3H, OC*H*$_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 158.9, 158.4, 149.2, 146.4, 144.6, 140.0, 139.3, 136.3, 135.7, 133.9, 130.4, 129.4, 129.1, 129.0, 128.7, 128.3, 128.2, 128.1, 127.5, 127.4, 127.1, 126.3, 121.0, 113.7, 113.5, 55.4, 55.3, 52.9, 47.6, 45.5; **LRMS** (ESI, *m/z*) $[M+H]^+$ 614.2; **HRMS** (ESI, *m/z*) calculated for $(C_{32}H_{35}O_3N_2S)^+$ 614.2472 $[M+H]^+$, found 614.2464; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2980, 1611, 1511, 1463, 1245, 1147, 1035, 895, 822, 763, 699, 671; ***er*** determined by HPLC using a Chiralpak IA-3 column (*n*-hexane: $^i$PrOH, 80:20); $\tau_{major}$ = 48.27 min, $\tau_{minor}$ = 56.80 min (77.5:22.5 *er*); $[\alpha]_D^{25}$ +0.1° (*c* = 0.75, $CHCl_3$); **R$_f$** 0.32 (Petrol:EtOAc, 4:1).

**(*S*)-*N*-allyl-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamidede (74al)**

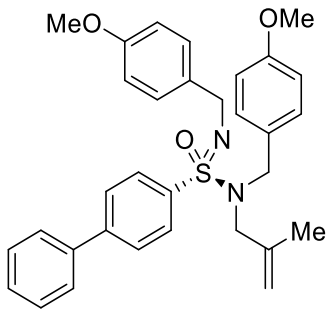



Prepared according to general procedure D, using sulfonimidamide **73a** (23.6 mg, 0.05 mmol, 1.0 equiv.) and allyl bromide (4 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (20.5 mg, 80%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.07 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.71 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.67 – 7.59 (m, 2H, 2 × Ph*H*), 7.53 – 7.45 (m, 2H, 2 × Ph*H*), 7.45 – 7.42 (m, 1H), 7.40 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.18 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.88 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.84 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 5.40 (dddd, *J* = 17.0, 10.0, 7.0, 6.0 Hz, 1H,

C*H*=CH$_2$), 5.03 (app. dq, *J* = 10.0, 1.5 Hz, 1H, CH=C*H*$_A$H$_B$), 4.99 (app. dq, *J* = 17.0, 1.5 Hz, 1H, CH=CH$_A$*H*$_B$), 4.51 (d, *J* = 14.5 Hz, 2H, 2 × NC*H*$_A$H$_B$), 4.23 (d, *J* = 14.5 Hz, 1H, NCH$_A$*H*$_B$), 4.20 (d, *J* = 14.5 Hz, 1H, NCH$_A$*H*$_B$), 3.86 – 3.77 (m, 7H, NC*H*$_A$H$_B$, 2 × OC*H*$_3$), 3.71 (dd, *J* = 15.5, 7.0 Hz, 1H, NCH$_A$*H*$_B$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.1, 158.4, 144.7, 139.6, 139.4, 133.7, 133.0, 130.1, 129.1, 128.9, 128.7, 128.4, 128.0, 127.51, 127.4, 119.1, 113.9, 113.7, 55.4 (2 × C), 50.3, 50.0, 45.1; **LRMS** (ESI, *m/z*) $[M+H]^+$ 513.2 & $[M+Na]^+$ 535.2; **HRMS** (ESI, *m/z*) calculated for $(C_{31}H_{33}O_3N_2S)^+$ 513.2206 $[M+H]^+$, found 513.2197; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2835, 1611, 1510, 1479, 1441, 1242.22, 1143, 1107, 1007, 816, 762, 733, 698, 673; ***er*** determined by HPLC using a Chiralpak IA-3 column (*n*-hexane: $^i$PrOH, 85:15); $\tau_{major}$ = 25.91 min, $\tau_{minor}$ = 29.00 min (89.5:10.5 *er*); $[\alpha]_D^{25}$ −1.2° (*c* = 0.75, $CHCl_3$); **R$_f$** 0.50 (Petrol:EtOAc, 4:1).

**(*S*)-*N*,*N*'-bis(4-methoxybenzyl)-*N*-(2-methylallyl)-[1,1'-biphenyl]-4-sulfonimidamide (74am)**

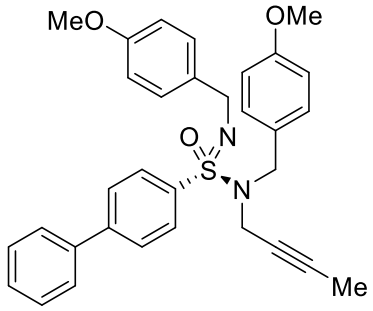



Prepared according to general procedure D, using sulfonimidamide **73a** (23.6 mg, 0.05 mmol, 1.0 equiv.) and 3-bromo-2-methylprop-1-ene (5 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (17.4 mg, 66%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.01 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.66 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.63 – 7.57 (m, 2H, 2 × Ph*H*), 7.52 – 7.45 (m, 2H, 2 × Ph*H*), 7.44 – 7.39 (m, 1H, PhH), 7.37 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.09 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.87 (d, *J* = 8.5 Hz, 2H,

2 × *p*-OMeAr*H*), 6.75 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.82 (app. q, *J* = 1.0 Hz, 1H, CMe=C$H_A$H$_B$), 4.75 (app. q, *J* = 1.0 Hz, 1H, CMe=CH$_A$$H_B$), 4.51 (d, *J* = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.46 (d, *J* = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.16 (d, *J* = 14.5 Hz, 1H, , NCH$_A$$H_B$), 4.12 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 3.82 – 3.74 (m, 7H, NC$H_A$H$_B$, 2 × OC$H_3$), 3.64 (d, *J* = 15.0 Hz, 1H, NCH$_A$$H_B$) 1.50 (app. t, *J* = 1.5 Hz, 3H, CC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.1, 158.4, 144.7, 141.1, 139.8, 139.6, 133.8, 130.6, 129.1, 129.0, 128.7, 128.4, 128.0, 127.4, 127.4, 114.4, 113.8, 113.7, 55.5, 55.4, 53.9, 50.9, 45.2, 20.4; **LRMS** (ESI, *m/z*) $[M+H]^+$ 527.2; **HRMS** (ESI, *m/z*) calculated for $(C_{32}H_{35}O_3N_2S)^+$ 527.2363 $[M+H]^+$, found 527.2360; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1612, 1511, 1442, 1280, 1246, 1146, 1035, 905, 818, 761, 697; ***er*** determined by HPLC using a Chiralpak AD-H column (*n*-hexane:$^i$PrOH, 80:20); $\tau_{minor}$ = 31.24 min, $\tau_{major}$ = 36.46 min (11:89 *er*); $[\alpha]_D^{25}$ −15.6° (*c* = 0.75, $CHCl_3$); **$R_f$** 0.75 (Petrol:EtOAc, 4:1).

**(*S*)-*N*-(but-2-yn-1-yl)-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74an)**

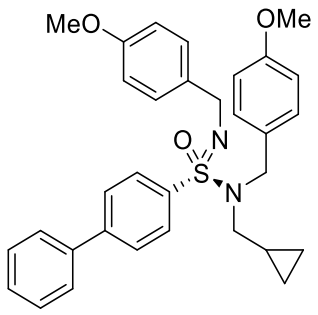



Prepared according to general procedure D, using sulfonimidamide **73a** (23.6 mg, 0.05 mmol, 1.0 equiv.) and 1-bromo-2-butyne (4 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (15.0 mg, 57%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.11 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.70 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.66 – 7.58 (m, 2H, 2 × Ph*H*), 7.51 – 7.45 (m, 2H, 2 × Ph*H*), 7.44 – 7.37 (m, 3H, Ph*H*, 2 × *p*-OMeAr*H*), 7.24 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.86 (app. dd, *J* = 9.0, 2.5 Hz, 4H,

4 × *p*-OMeAr*H*), 4.52 (d, *J* = 14.5 Hz, 1H, NC*H*$_A$H$_B$), 4.36 (d, *J* = 13.5 Hz, 1H, NC*H*$_A$H$_B$), 4.31 (d, *J* = 13.5 Hz, 1H, NCH$_A$*H*$_B$), 4.30 (d, *J* = 14.5 Hz, 1H, NCH$_A$*H*$_B$), 3.88 – 3.72 (m, 8H, NC*H*$_A$H$_B$, NCH$_A$*H*$_B$, 2 × OC*H*$_3$), 1.48 (app. t, *J* = 2.5 Hz, 3H, CC*H*$_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.4, 158.5, 144.9, 139.9, 137.7 (2 × C), 130.2, 129.2, 128.8 (2 × C), 128.4, 128.3, 127.4, 127.1, 114.1, 113.8, 81.7, 72.3, 55.4 (2 × C), 50.0, 45.1, 36.6, 3.4; **LRMS** (ESI, *m/z*) $[M+H]^+$ 525.2; **HRMS** (ESI, *m/z*) calculated for $(C_{32}H_{33}O_3N_2S)^+$ 525.2206 $[M+H]^+$, found 525.2199; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1612, 1512, 1464, 1247, 1146, 1036, 907, 818, 758, 731, 698, 670; ***er*** determined by HPLC using a Chiralpak IA-3 column (*n*-hexane:$^i$PrOH, 80:20); $\tau_{major}$ = 18.30 min, $\tau_{minor}$ = 22.08 min (66:34 *er*); $[\alpha]_D^{25}$ +0.1° (*c* = 0.75, $CHCl_3$); **R$_f$** 0.63 (Petrol:EtOAc. 4:1).

**(*S*)-*N*-(cyclopropylmethyl)-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ao)**

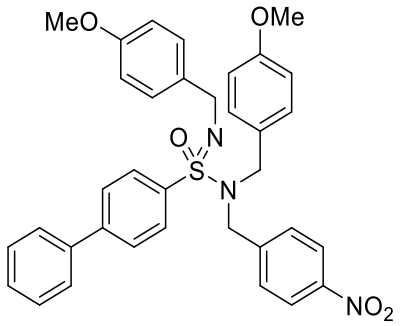



Prepared according to general procedure D, using sulfonimidamide **73a** (23.6 mg, 0.05 mmol, 1.0 equiv.) and (bromomethyl)cyclopropane (5 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (2.6 mg, 10%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.06 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.69 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.65 – 7.58 (m, 2H, 2 × Ph*H*), 7.51 – 7.45 (m, 2H, 2H, 2 × Ph*H*), 7.44 – 7.36 (m, 3H, Ph*H*, 2 × *p*-OMeAr*H*), 7.18 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.87 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.82 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.56 (d, *J* = 15.0 Hz, 1H, NC*H*$_A$H$_B$), 4.52 (d, *J* = 14.5 Hz,

1H, NC$H_A$H$_B$), 4.39 (d, $J$ = 15.0 Hz, 1H, NCH$_A$$H_B$), 4.24 (d, $J$ = 14.5 Hz, 1H, NCH$_A$$H_B$), 3.79 (s, 3H, OC$H_3$), 3.78 (s, 3H, OC$H_3$), 3.09 (dd, $J$ = 14.5, 6.5 Hz, 1H, NC$H_A$H$_B$), 2.97 (dd, $J$ = 14.5, 7.0 Hz, 1H, NCH$_A$$H_B$), 0.68 – 0.54 (m, 1H, (CH$_2$)$_2$C$H$), 0.39 – 0.23 (m, 2H, 2 × CHC$H_A$H$_B$), -0.03 – -0.12 (m, 2H, 2 × CHCH$_A$$H_B$); **$^{13}$C NMR** (101 MHz, CDCl$_3$) $\delta_C$ 159.0, 158.4, 144.6, 139.8, 139.5, 133.9, 129.6, 129.5, 129.1, 128.7, 128.4, 128.0, 127.5, 127.4, 113.9, 113.8, 55.5, 55.4, 52.3, 51.2, 45.2, 9.3, 4.6, 3.8; **LRMS** (ESI, *m/z*) [M+H]$^+$ 527.2 & [M+Na]$^+$ 549.2; **HRMS** (ESI, *m/z*) calculated for (C$_{32}$H$_{35}$O$_3$N$_2$S)$^+$ 527.2363 [M+H]$^+$, found 527.2360; **IR** (CHCl$_3$, $\nu_{max}$/cm$^{-1}$) 2925, 1741, 1612, 1512, 1462, 1380, 1245, 1149, 953, 907, 817, 762, 729, 670, 619; ***er*** determined by HPLC using a Chiralpak IA-3 column (*n*-hexane:$^i$PrOH, 80:20); $\tau_{major}$ = 21.97 min, $\tau_{minor}$ = 27.96 min (82:18 *er*); [$\alpha$]$_D^{25}$ +4.4° (*c* = 0.75, CHCl$_3$); **R$_f$** 0.69 (Petrol:EtOAc 4:1).

***N,N'*-bis(4-methoxybenzyl)-N-(4-nitrobenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ap)**

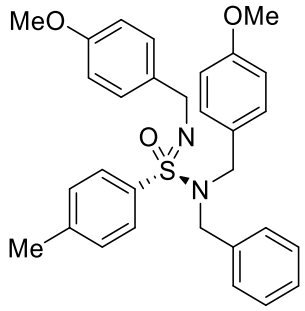



Prepared according to a modified general procedure D', using sulfonimidamide **79b** (47.3 mg, 0.100 mmol, 1.0 equiv.), tetrabutylammonium hydrogen sulfate (48.5 mg, 0.025 mmol, 0.25 equiv.) 1-(bromomethyl)-4-nitrobenzene (43 mg, 0.200 mmol, 2.0 equiv.), potassium hydroxide (28.0 mg, 0.500 mmol, 5.0 equiv.). Purification by flash column chromatography (Petrol:EtOAc, 1:0 to 1:1), afforded the title compound (49.7 mg, 82%) as a yellow oil.

**$^1$H NMR** (400 MHz, CDCl$_3$) $\delta_H$ 8.07 (d, $J$ = 8.5 Hz, 2H, 2 × p-NO$_2$ArH), 8.02 (d, $J$ = 8.5 Hz, 2H, 2 × Ar$H$), 7.73 (d, $J$ = 8.5 Hz, 2H, 2 × Ar$H$), 7.67 – 7.60 (m, 2H, 2 × Ph$H$), 7.55 – 7.47 (m, 2H, 2 × Ph$H$), 7.47 – 7.41 (m, 1H, Ph$H$), 7.35 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr$H$), 7.17 (d, $J$ = 8.5 Hz,

2H, 2 × *p*-OMeAr*H*), 6.90 – 6.84 (m, 4H, 2 × p-$NO_2$Ar*H*, 2 × *p*-OMeAr*H*), 6.68 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.58 (d, *J* = 15.5 Hz, 1H), 4.51 (d, *J* = 14.5 Hz, 1H), 4.36 (d, *J* = 14.5 Hz, 1H), 4.22 (d, *J* = 3.5 Hz, 1H), 4.19 (d, *J* = 3.5 Hz, 1H), 4.14 (d, *J* = 15.5 Hz, 1H), 3.79 (s, 3H, OC$H_3$), 3.73 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.4, 159.3, 158.4, 147.1, 145.2, 145.2, 139.4, 138.4, 133.1, 130.3, 129.1, 129.0, 128.5, 127.9, 127.7, 127.6, 127.3, 123.4, 113.9, 113.7, 55.3, 52.2, 50.9, 45.2; **LRMS** *m/z* (ESI) $[M+H]^+$ 609.0; **HRMS** (ESI, *m/z*) calculated for $(C_{35}H_{34}N_3O_5S)^+$ 608.2214 $[M+H]^+$, found 608.2210; I**R** ($CHCl_3$, $\nu_{max}$/$cm^{-1}$) 1609, 1512, 1343, 1244, 1174, 1144, 1108, 1033, 902, 841, 760, 670; 645.

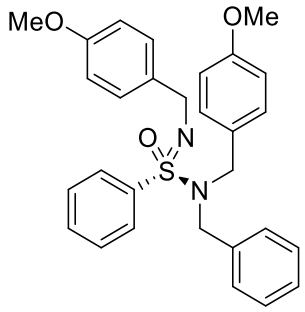
**(*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-4-methylbenzenesulfonimidamide (74b)**




Prepared according to general procedure D, using sulfonimidamide **73b** (20.5 mg, 0.05 mmol, 1.0 equiv.) and benzyl bromide (6 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (22.8 mg, 91%) as a colourless solid.

***er*** determined by HPLC using a Chiralpak OD-H column (*n*-hexane: $^i$PrOH, 80:20); $\tau_{minor}$ = 7.37 min, $\tau_{major}$ = 10.05 min (13.5:86.5 *er*); $[\alpha]_D^{25}$ −1.0° (*c* = 0.75, $CHCl_3$). The spectroscopic data was in agreement with the previously synthesised compound (see Section **6.4.1.2**).

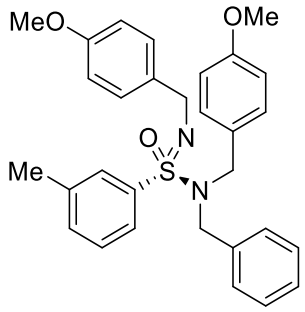
**(*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)benzenesulfonimidamide (74c)**




Prepared according to general procedure D, using sulfonimidamide **73c** (19.8 mg, 0.05 mmol, 1.0 equiv.) and benzyl bromide (6 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (20.2 mg, 83%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.98 (m, 2H, 2 × Ph*H*), 7.58 – 7.52 (m, 1H, Ph*H*), 7.52 – 7.44 (m, 2H, 2 × Ph*H*), 7.34 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.23 – 7.16 (m, 3H, 3 × $CH_2$Ph*H*), 7.02 – 6.95 (m, 2H, 2 × $CH_2$Ph*H*), 6.87 (d, *J* = 8.5 Hz, 2H 2 × *p*-OMeAr*H*), 6.85 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.71 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.52 (d, *J* = 15.0 Hz, 1H, NC$H_AH_B$), 4.48 (d, *J* = 14.5 Hz, 1H, NC$H_AH_B$), 4.46 (d, *J* = 14.5 Hz, 1H, NC$H_AH_B$), 4.11 (d, *J* = 14.5 Hz, 1H, NC$H_AH_B$), 4.07 (d, *J* = 15.0 Hz, 1H, NC$H_AH_B$), 4.04 (d, *J* = 14.5 Hz, 1H, NC$H_AH_B$), 3.79 (s, 3H, OC$H_3$), 3.77 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 159.1, 158.4, 141.3, 136.8, 133.7, 131.9, 130.3, 129.0, 128.8, 128.7, 128.5, 128.5, 127.5 (2 × C), 113.8 (2 × C), 55.4 (2 × C), 50.8, 50.5, 45.2; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 509.2; **HRMS** (ESI, *m/z*) calculated for $(C_{29}H_{31}O_3N_2S)^+$ 487.2050 $[M+H]^+$, found 487.2048; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2920, 1612, 1511, 1445, 1279, 1246, 1146, 1034, 894, 817, 736, 690; ***er*** determined by HPLC using a Chiralpak OD-H column (*n*-hexane: $^i$PrOH, 80:20); $\tau_{minor}$ = 7.72 min, $\tau_{minor}$ = 9.09 min (13:87 *er*); $[\boldsymbol{\alpha}]_D^{25}$ −1.5° (*c* = 0.75, $CHCl_3$); $\mathbf{R_f}$ 0.57 (Petrol:EtOAc, 4:1).

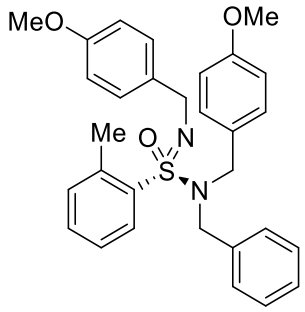
**(*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-3-methylbenzenesulfonimidamide (74d)**




Prepared according to general procedure D, using sulfonimidamide **73d** (20.5 mg, 0.05 mmol, 1.0 equiv.) and benzyl bromide (6 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (16.0 mg, 64%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.86 – 7.77 (m, 1H, Ar*H*), 7.80 – 7.74 (m, 1H, Ar*H*), 7.41 – 7.30 (m, 4H, 2 × Ar*H*, 2 × *p*-OMeAr*H*), 7.24 – 7.16 (m, 3H, 3 × $CH_2$Ph*H*), 7.05 – 6.96 (m, 2H, 2 × $CH_2$Ph*H*), 6.89 (d, *J* = 8.7 Hz, 2H, 2 × *p*-OMeAr*H*), 6.85 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.72 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.50 (d, *J* = 15.0 Hz, 1H, NC$H_A$H$_B$), 4.46 (d, *J* = 14.5 Hz, 2H, NC$H_A$H$_B$), 4.45 (d, *J* = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.11 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 4.09 (d, *J* = 15.0 Hz, 1H, NCH$_A$$H_B$), 4.05 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 3.79 (s, 3H, OC$H_3$), 3.77 (s, 3H, OC$H_3$), 2.39 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.1, 158.4, 140.9, 139.0, 136.9, 133.8, 132.7, 130.3, 128.8, 128.7, 128.6, 128.4, 127.8, 127.5, 124.7, 113.8 (2 × C), 55.4 (2 × C), 50.9, 50.6, 45.3, 21.6; **LRMS** (ESI, *m/z*) $[M+H]^+$ 501.2 & $[M+Na]^+$ 523.2; **HRMS** (ESI, *m/z*) calculated for $(C_{30}H_{33}O_3N_2S)^+$ $[M+H]^+$ 501.2206, found 501.2204; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1745, 1612, 1512, 1457, 1370, 1245, 1041, 910, 732; ***er*** determined by HPLC using a Chiralpak IA-3 column (*n*-hexane:$^i$PrOH, 80:20); $\tau_{major}$ = 10.13 min, $\tau_{minor}$ = 13.22 min (85.5:14.5 er); $[\alpha]_D^{25}$ –1.9° (*c* = 0.75, $CHCl_3$); **R$_f$** 0.52 (Petrol:EtOAc, 4:1).

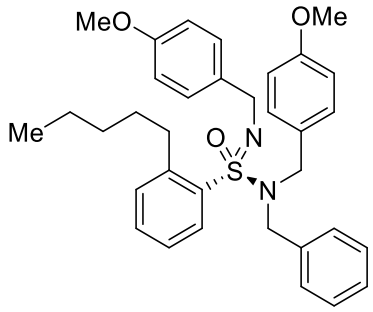
**(*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-2-methylbenzenesulfonimidamide (74e)**




Prepared according to general procedure D, using sulfonimidamide **73e** (20.5 mg, 0.05 mmol, 1.0 equiv.) and benzyl bromide (6 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (12.5 mg, 50%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.06 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 7.40 (app. td, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.33 – 7.18 (m, 7H, 2 × Ar*H*, 3 × $CH_2$Ph*H*, 2 × *p*-OMeAr*H*), 7.12 – 7.04 (m, 2H, 2 × $CH_2$Ph*H*), 6.96 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.82 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.78 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.50 (d, *J* = 15.0 Hz, 1H, NC$H_A$H$_B$), 4.46 (d, *J* = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.32 (d, *J* = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.23 (d, *J* = 15.0 Hz, 1H, NCH$_A$$H_B$), 4.17 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 4.02 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 3.79 (s, 3H, OC$H_3$), 3.78 (s, 3H, OC$H_3$), 2.65 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.2, 158.4, 139.9, 138.0, 136.8, 133.9, 133.0, 131.9, 130.6, 130.1, 129.1, 128.7, 128.6, 128.5, 127.7, 126.0, 113.9, 113.7, 55.4 (2 × C), 49.8, 49.4, 45.9, 21.1; **LRMS** (ESI, *m/z*) $[M+H]^+$ 501.2; **HRMS** (ESI, *m/z*) calculated for $(C_{30}H_{33}O_3N_2S)^+$ 501.2206 $[M+H]^+$, found 501.2209; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2911, 1611, 1511, 1456, 1246, 1175, 1150, 1129, 1036, 893, 817, 757, 731, 702; ***er*** determined by HPLC using a Chiralpak OD-H column (*n*-hexane: $^i$PrOH, 85:15); flow rate 1.0 mL/min; $\tau_{minor}$ = 6.75 min, $\tau_{minor}$ = 8.31 min (36.5:63.5 *er*); $[\alpha]_D^{25}$ +4.0° (*c* = 0.75, $CHCl_3$); $\mathbf{R_f}$ 0.39 (Petrol:EtOAc, 4:1).

**(*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-2-pentylbenzenesulfonimidamide (74f)**

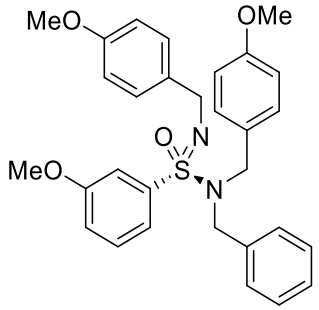



Prepared according to general procedure D, using sulfonimidamide **73f** (23.3 mg, 0.05 mmol, 1.0 equiv.) and benzyl bromide (6 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (20.6 mg, 74%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.91 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 7.42 (app. td, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.36 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.30 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.28 – 7.24 (m, 3H, 3 × $CH_2$Ph*H*), 7.17 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H, Ar*H*), 7.14 – 7.08 (m, 2H, $CH_2$Ph*H*), 7.00 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.83 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.78 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.53 (d, *J* = 15.0 Hz, 1H, NC*H*$_A$H$_B$), 4.49 (d, *J* = 14.5 Hz, 1H, NC*H*$_A$H$_B$), 4.38 (d, *J* = 14.0 Hz, 1H, NC*H*$_A$H$_B$), 4.26 (d, *J* = 15.0 Hz, 1H, NCH$_A$*H*$_B$), 4.21 (d, *J* = 14.5 Hz, 1H, NC*H*$_A$*H*$_B$), 4.04 (d, *J* = 14.0 Hz, 1H, NCH$_A$*H*$_B$), 3.79 (s, 3H, OC*H*$_3$), 3.78 (s, 3H, OC*H*$_3$), 3.16 – 2.98 (m, 2H, $CH_3(CH_2)_3CH_2$), 1.76 – 1.55 (m, 2H, $CH_3(CH_2)_2CH_2CH_2$), 1.38 – 1.20 (m, 4H, $CH_3CH_2CH_2(CH_2)_2$, $CH_3CH_2(CH_2)_3$), 0.87 (t, *J* = 7.0 Hz, 3H, $(CH_2)_4CH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.2, 158.4, 143.0, 139.7, 136.7, 133.9, 131.8, (2 × C), 130.7, 129.5, 129.1, 128.9, 128.5 (2 × C), 127.6, 125.6, 113.9, 113.7, 55.4, 50.1, 49.7, 46.1, 33.1, 32.5, 31.1, 22.7, 14.4, 14.2; **LRMS** (ESI, *m/z*) $[M+H]^+$ 557.2 & $[M+Na]^+$ 579.2; **HRMS** (ESI, *m/z*) calculated for $(C_{34}H_{41}O_3N_2S)^+$ 557.2832 $[M+H]^+$, found 557.2829; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2929, 1612, 1511, 1456, 1248, 1175, 1037, 892, 818, 757, 732, 701; ***er*** determined by HPLC using a Chiralpak OD-H column (*n*-hexane:$^i$PrOH, 97:3);

$\tau_{minor}$ = 8.65 min, $\tau_{minor}$ = 10.10 min (43:57 *er*); $[\alpha]_D^{25}$ +2.8° (*c* = 0.75, $CHCl_3$); $R_f$ 0.54 (Petrol:EtOAc, 4:1).

**(*S*)-*N*-benzyl-3-methoxy-*N*,*N*'-bis(4-methoxybenzyl)benzenesulfonimidamide (74g)**

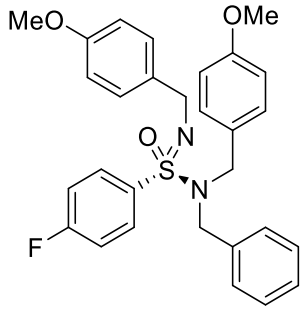



Prepared according to general procedure D, using sulfonimidamide **73g** (21.3 mg, 0.05 mmol, 1.0 equiv.) and benzyl bromide (6 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (11.6 mg, 45%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.59 (ddd, *J* = 8.0, 1.5, 1.0 Hz, 1H, Ar*H*), 7.51 (dd, *J* = 2.5, 1.5 Hz, 1H, Ar*H*), 7.39 (app. t, *J* = 8.0 Hz, 1H, Ar*H*), 7.34 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.23 – 7.18 (m, 3H, $CH_2$Ph*H*), 7.07 (ddd, *J* = 8.5, 2.5, 1.0 Hz, 1H, Ar*H*), 7.02 – 6.97 (m, 2H, $CH_2$Ph*H*), 6.89 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.84 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.72 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.51 (d, *J* = 15.0 Hz, 1H, NC$H_A$$H_B$), 4.46 (d, *J* = 15.0 Hz, 1H, NC$H_A$$H_B$), 4.45 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.11 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.09 (d, *J* = 15.0 Hz, 1H, NC$H_A$$H_B$), 4.05 (d, *J* = 15.0 Hz, 1H, NC$H_A$$H_B$), 3.82 (s, 3H, OC$H_3$), 3.78 (s, 3H, OC$H_3$), 3.77 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_H$ 159.9, 159.1, 158.4, 142.3, 136.8, 133.7, 130.3, 130.0, 128.8, 128.7, 128.5 (2 × C), 127.5, 119.8, 118.2, 113.8, 113.7, 112.4, 55.8, 55.4 (2 × C), 50.9, 50.5, 45.3; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 539.2; **HRMS** (ESI, *m/z*) calculated for $(C_{30}H_{33}O_4N_2S)^+$ 517.2156 $[M+H]^+$, found 517.2152; **IR** ($CHCl_3$, $\nu_{max}$/$cm^{-1}$) 2933, 2836, 1712, 1612, 1512, 1482, 1395, 1246, 1177, 1143, 992, 894, 817, 748, 700; ***er*** determined by HPLC using a Chiralpak OD-H column (*n*-hexane:$^i$PrOH,

95:5); $\tau_{minor}$ = 19.34 min, $\tau_{major}$ = 22.71 min (28:72 *er*); $[\alpha]_D^{25}$ +4.6° (*c* = 0.75, $CHCl_3$); $\mathbf{R_f}$ 0.24 (Petrol:EtOAc, 4:1).

**(*S*)-*N*-benzyl-4-fluoro-*N*,*N*'-bis(4-methoxybenzyl)benzenesulfonimidamide (74h)**

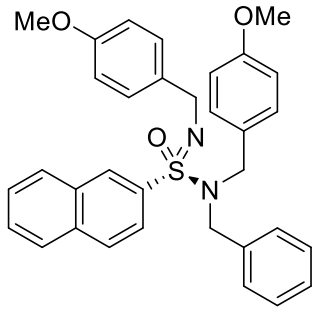



Prepared according to general procedure D, using sulfonimidamide **73h** (20.7 mg, 0.05 mmol, 1.0 equiv.) and benzyl bromide (6 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (22.7 mg, 90%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.98 (dd, *J*, $J_{HF}$ = 9.0, 5.0 Hz, 2 × Ar*H*), 7.32 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.25 – 7.19 (m, 3H, 3 × $CH_2$Ph*H*), 7.13 (app. t, *J*, $J_{HF}$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.05 – 6.96 (m, 2H, 2 × $CH_2$Ph*H*), 6.90 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.84 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.73 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.50 (d, *J* = 15.0 Hz, 1H, NC$H_A$$H_B$), 4.46 (d, *J* = 15.5 Hz, 1H, NC$H_A$$H_B$), 4.43 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.07 (app. t, *J* = 14.0 Hz, 3H, 3 × NC$H_A$$H_B$), 3.78 (s, 3H, OC$H_3$), 3.77 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 164.8 (d, $^1J_{CF}$ = 253.5 Hz), 159.2, 158.5, 137.4 (d, $^4J_{CF}$ = 3.0 Hz), 136.6, 133.5, 130.2, 130.1 (d, $^3J_{CF}$ = 9.0 Hz), 128.8, 128.7, 128.5, 128.3, 127.6, 116.0 (d, $^2J_{CF}$ = 22.5 Hz), 113.9, 113.8, 55.4 (2 × C), 50.8, 50.5, 45.3; **$^{19}$F NMR** (377 MHz, $CDCl_3$) $\delta_F$ -107.20 – -107.38 (m); **LRMS** (ESI, *m/z*) $[M+Na]^+$ 527.2; **HRMS** (ESI, *m/z*) calculated for $(C_{29}H_{30}O_3N_2FS)^+$ 505.1956 $[M+H]^+$, found 505.1955; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1612, 1588, 1511, 1492, 1456, 1277, 1246, 1144, 1035, 894, 818, 751, 699; ***er*** determined

by HPLC using a Chiralpak AD-H column (*n*-hexane:$^{i}$PrOH, 85:15); $\tau_{minor}$ = 21.36 min, $\tau_{major}$ = 34.89 min (82.5:17.5 *er*); $[\alpha]_D^{25}$ −1.9° (*c* = 0.75, $CHCl_3$); $\mathbf{R_f}$ 0.57 (Petrol:EtOAc, 4:1).

**(*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)naphthalene-2-sulfonimidamide (74i)**

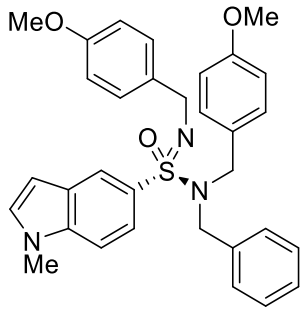



Prepared according to general procedure D, using sulfonimidamide **73i** (22.3 mg, 0.05 mmol, 1.0 equiv.) and benzyl bromide (6 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (16.6 mg, 62%) as a yellow oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.51 (d, *J* = 1.5 Hz, 1H, Ar*H*), 7.99 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar*H*), 7.96 – 7.87 (m, 3H, 3 × Ar*H*), 7.67 – 7.53 (m, 2H, 2 × Ar*H*), 7.38 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.23 – 7.11 (m, 3H, 3 × $CH_2$Ph*H*), 7.08 – 6.99 (m, 2H, 2 × $CH_2$Ph*H*), 6.91 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.86 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.67 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.55 (d, *J* = 15.0 Hz, 1H, NC$H_A$H$_B$), 4.51 (d, *J* = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.50 (d, *J* = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.18 (app. d, *J* = 14.5 Hz, 2H, 2 × NC$H_A$H$_B$), 4.14 (d, *J* = 15.0 Hz, 1H, NCH$_A$H$_B$), 3.79 (s, 3H, OC$H_3$), 3.73 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.1, 158.5, 138.1, 136.8, 134.6, 133.7, 132.5, 130.3, 129.4, 129.0, 128.8, 128.7, 128.5 (2 × C), 128.4 (2 × C), 127.9, 127.5, 127.28, 123.5, 113.8 (2 × C), 55.4, 55.3, 51.1, 50.7, 45.4; **LRMS** (ESI, *m/z*) $[M+H]^+$ 537.2 & $[M+Na]^+$ 559.2; **HRMS** (ESI, *m/z*) calculated for $(C_{33}H_{33}O_3N_2S)^+$ 537.2206 $[M+H]^+$, found 537.2211; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2835, 1611, 1586, 1511, 1455, 1279, 1246, 1175, 1147, 1128, 1035, 895, 816, 749, 699, 660;

***er*** determined by HPLC using a Chiralpak IA-3 column (*n*-hexane: $^{i}$PrOH, 70:30); $\tau_{major}$ = 18.87 min, $\tau_{minor}$ = 20.61 min (76:24 *er*); $[\alpha]_D^{25}$ −2.0° (*c* = 0.75, $CHCl_3$); $\mathbf{R_f}$ 0.29 (Petrol:EtOAc, 4:1).

**(*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-1-methyl-1H-indole-5-sulfonimidamide (74j)**

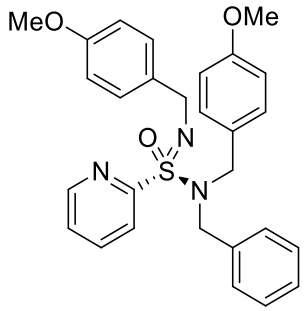



Prepared according to general procedure D, using sulfonimidamide **73j** (22.5 mg, 0.05 mmol, 1.0 equiv.) and benzyl bromide (6 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 1:1), afforded the title compound (17.0 mg, 62%) as a yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.34 (dd, *J* = 2.0, 0.5 Hz, 1H, Ar*H*), 7.87 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar*H*), 7.38 (app. d, *J* = 8.5 Hz, 3H, Ar*H*, 2 × *p*-OMeAr*H*), 7.22 – 7.10 (m, 4H, HetAr*H*, 3 × $CH_2$Ph*H*), 7.05 – 6.97 (m, 2H, 2 × $CH_2$Ph*H*), 6.89 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.85 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.67 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.60 (dd, *J* = 3.0, 0.5 Hz, 1H, HetAr*H*), 4.49 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.48 (d, *J* = 15.0 Hz, 1H, NC$H_A$$H_B$), 4.42 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.15 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 4.12 (d, *J* = 15.0 Hz, 1H, NCH$_A$$H_B$), 4.09 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 3.86 (s, 3H, NC$H_3$), 3.79 (s, 3H, OC$H_3$), 3.74 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 158.9, 158.3, 138.2, 137.4, 134.2, 131.3, 130.9, 130.3, 129.1, 128.9, 128.7, 128.3, 128.0, 127.3, 121.8, 120.9, 113.7 (2 × C), 109.4, 102.9, 55.4 (2 × C), 51.4, 51.0, 45.5, 33.3; **LRMS** (ESI, *m/z*) $[M+H]^+$ 540.2; **HRMS** (ESI, *m/z*) calculated for $(C_{32}H_{34}O_3N_3S)^+$ 540.2315 $[M+H]^+$, found 540.2311; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2835, 1611, 1586, 1511, 1455, 1340, 1275, 1245, 1205, 1175, 1141, 1106, 1035, 894, 816, 762, 726, 701, 645; ***er*** determined by HPLC using a Chiralpak

OD-H column (*n*-hexane: $^{i}$PrOH, 80:20); $\tau_{minor}$ = 18.88 min, $\tau_{major}$ = 26.08 min (23.5:76.5 *er*); $[\alpha]_D^{25}$ +3.7° (*c* = 0.75, $CHCl_3$); $\mathbf{R_f}$ 0.54 (Petrol:EtOAc, 1:1).

**(*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)pyridine-2-sulfonimidamide (74k)**

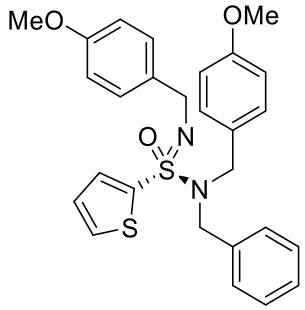



Prepared according to general procedure D, using sulfonimidamide **73k** (19.9 mg, 0.05 mmol, 1.0 equiv.) and benzyl bromide (6 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 1:1), afforded the title compound (9.3 mg, 38%) as a yellow oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.60 (ddd, *J* = 4.5, 1.5, 1.0 Hz, 1H, Py*H*), 8.19 (app. dt, *J* = 7.5, 1.0 Hz, 1H, Py*H*), 7.80 (app. td, *J* = 7.5, 1.5 Hz, 1H, Py*H*), 7.39 (ddd, *J* = 7.5, 4.5, 1.0 Hz, 1H, Py*H*), 7.36 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.28 – 7.16 (m, 3H, 3 × $CH_2$Ph*H*), 7.10 – 7.05 (m, 2H, 2 × $CH_2$Ph*H*), 6.96 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.85 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.71 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.72 (d, *J* = 15.5 Hz, 1H), 4.65 (d, *J* = 15.0 Hz, 1H, NC$H_A$$H_B$), 4.54 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.25 (d, *J* = 15.5 Hz, 1H, NC$H_A$$H_B$), 4.20 (d, *J* = 15.0 Hz, 1H, NCH$_A$$H_B$), 4.15 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 3.79 (s, 3H, OC$H_3$), 3.76 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.4, 159.0, 158.4, 149.5, 137.6, 136.9, 133.6, 130.3, 128.8 (2 × C), 128.7, 128.4, 127.4, 125.8, 123.3, 113.8, 113.7, 55.4 (2 × C), 51.5, 51.1, 45.1; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 510.2; **HRMS** (ESI, *m/z*) calculated for $(C_{28}H_{30}O_3N_3S)^+$ 488.2002 $[M+H]^+$, found 488.2002; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2836, 1611, 1511, 1454, 1424, 1278, 1246, 1172, 1117, 1083, 1035, 896, 817, 768, 703, 637; ***er*** determined by HPLC using a Chiralpak OD-H column (*n*-hexane: $^{i}$PrOH, 85:15); $\tau_{minor}$

= 12.75 min, $\tau_{major}$ = 16.41 min (40:60 *er*); $[\alpha]_D^{25}$ −4.6° (*c* = 0.75, $CHCl_3$); $\mathbf{R_f}$ 0.39 (Petrol:EtOAc, 1:1).

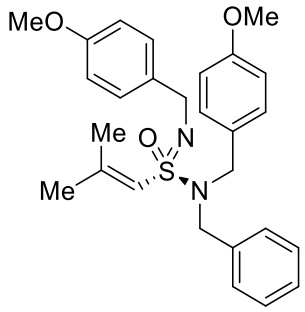
**(*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)thiophene-2-sulfonimidamide (74l)**




Prepared according to general procedure D, using sulfonimidamide **2m** (20.1 mg, 0.05 mmol, 1.0 equiv.) and benzyl bromide (6 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (19.7 mg, 80%) as a pale yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.54 – 7.47 (m, 2H, 2 × HetAr*H*), 7.33 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.29 – 7.17 (m, 3H, 3 × $CH_2$Ph*H*), 7.11 – 7.00 (m, 3H, HetAr*H*, 2 × $CH_2$Ph*H*), 6.93 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.84 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.74 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.50 (d, *J* = 15.0 Hz, 1H), 4.46 (d, *J* = 15.0 Hz, 1H, NC$H_A$$H_B$), 4.41 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.18 (d, *J* = 15.0 Hz, 1H, NC$H_A$$H_B$), 4.15 (d, *J* = 15.0 Hz, 1H, NC$H_A$$H_B$), 4.12 (d, *J* = 14.5 Hz, 1H, NC$H_A$$H_B$), 3.78 (s, 3H, OC$H_3$), 3.77 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.1, 158.4, 142.6, 136.6, 133.4, 131.4, 130.7, 130.3, 128.8, 128.5 (2 × C), 128.3, 127.6, 127.5, 113.9, 113.8, 55.4 (2 × C), 51.1, 50.8, 45.6; **LRMS** (ESI, *m/z*) $[M+H]^+$ 493.2; **HRMS** (ESI, *m/z*) calculated for $(C_{27}H_{29}O_3N_2S_2)^+$ 493.1590 $[M+H]^+$, found 493.1611; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1612, 1512, 1455, 1281, 1247, 1147, 1035, 908, 817, 731, 667, 620; ***er*** determined by HPLC using a Chiralpak OD-H column (*n*-hexane:$^i$PrOH, 80:20); $\tau_{minor}$ = 9.82 min, $\tau_{major}$ = 11.72 min (11:89 *er*); $[\alpha]_D^{25}$ −10.8° (c = 0.5, $CHCl_3$); $\mathbf{R_f}$ 0.40 (Petrol:EtOAc, 4:1).

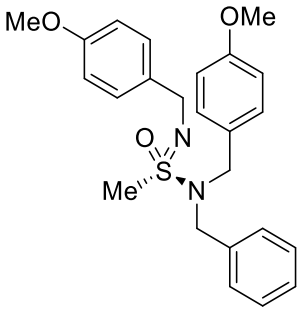
**(*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-2-methylprop-1-ene-1-sulfonimidamide (74m)**




Prepared according to general procedure D, using sulfonimidamide **73m** (18.7 mg, 0.05 mmol, 1.0 equiv.) and benzyl bromide (6 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 1:1), afforded the title compound (14.4 mg, 62%) as a colourless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.36 – 7.26 (m, 7H, 2 × *p*-OMeAr*H*, 5 × $CH_2$Ph*H*), 7.18 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.84 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.82 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 5.99 (app. p, *J* = 1.5 Hz, 1H, C=C*H*), 4.42 (d, *J* = 14.5 Hz, 1H, NC$H_AH_B$), 4.38 (d, *J* = 14.0 Hz, 1H, NC$H_AH_B$), 4.35 (d, *J* = 14.0 Hz, 1H, NC$H_AH_B$), 4.20 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 4.17 (d, *J* = 14.0 Hz, 1H, NCH$_A$$H_B$), 3.95 (d, *J* = 14.5 Hz, 1H, NCH$_A$$H_B$), 3.81 (s, 3H, OC$H_3$), 3.77 (s, 3H, OC$H_3$), 2.14 (d, *J* = 1.5 Hz, 3H, CC$H_3$), 1.80 (d, *J* = 1.5 Hz, 3H, CC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.2, 158.4, 149.6, 136.9, 133.8, 130.6, 129.0 (2 × C), 128.7, 128.6, 127.7, 125.4, 113.9, 113.8, 55.4 (2 × C), 50.2, 49.9, 45.3, 26.8, 19.6; **LRMS** (ESI, *m/z*) $[M+H]^+$ 465.2; **HRMS** (ESI, *m/z*) calculated for $(C_{27}H_{33}O_3N_2S)^+$ 465.2182 $[M+H]^+$, found 465.2192; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1611, 1511, 1441, 1244, 1174, 1131, 1035, 894, 817, 751, 703, 614; ***er*** determined by HPLC using a Chiralpak IA-3 column (*n*-hexane:$^i$PrOH, 80:20); $\tau_{major}$ = 9.31 min, $\tau_{minor}$ = 12.31 min (73.5:26.5 *er*); $[\alpha]_D^{25}$ +8.5° (*c* = 0.75, $CHCl_3$); **$R_f$** 0.19 (Petrol:EtOAc, 4:1).

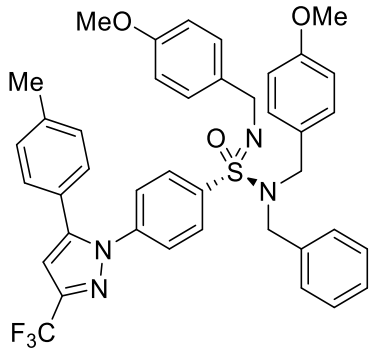
**(*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)methanesulfonimidamide (74n)**




Prepared according to general procedure D, using sulfonimidamide **73n** (16.7 mg, 0.05 mmol, 1.0 equiv.) and benzyl bromide (6 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 1:1), afforded the title compound (10.0 mg, 47%) as a pale yellow oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.40 – 7.31 (m, 5H, 5 × $CH_2PhH$), 7.29 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.25 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.88 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.83 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.40 – 4.28 (m, 5H, 3 × $NCH_AH_B$, 2 × $NCH_AH_B$), 4.00 (d, $J$ = 14.0 Hz, 1H, $NCH_AH_B$), 3.82 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 2.77 (s, 3H, $SCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.4, 158.5, 136.4, 133.6, 130.5, 129.0 (2 × C), 128.9, 128.1, 127.9, 114.2, 113.9, 55.4 (2 × C), 50.2, 49.8, 45.3, 41.1; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 447.2; **HRMS** (ESI, *m/z*) calculated for $(C_{24}H_{29}O_3N_2S)^+$ 425.1893 $[M+H]^+$, found 425.1898; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1727, 1611, 1512, 1457, 1247, 1178, 1136, 1080, 1035, 972, 893, 817, 750, 703; ***er*** determined by HPLC using a Chiralpak IA-3 column (*n*-hexane:$^i$PrOH, 80:20); $\tau_{minor}$ = 10.69 min, $\tau_{major}$ = 15.14 min (32:68 *er)*; $[\alpha]_D^{25}$ −8.7° (*c* = 0.5, $CHCl_3$); $\mathbf{R_f}$ 0.27 (Petrol:EtOAc, 4:1).

**(*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonimidamide (74o)**



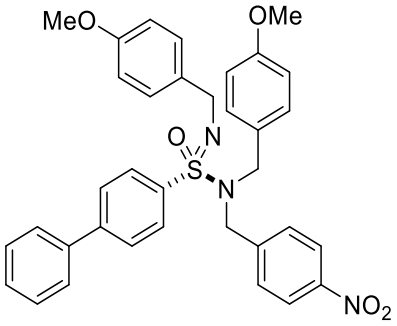

Prepared according to general procedure D, using sulfonimidamide **73o** (31.0 mg, 0.05 mmol, 1.0 equiv.) and benzyl bromide (6 μL, 0.05 mmol, 1.0 equiv.). Purification by flash column chromatography (Pentane:EtOAc, 1:0 to 4:1), afforded the title compound (24.5 mg, 69%) as a colourless oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.96 (d, $J$ = 9.0 Hz, 2H, 2 × Ar*H*), 7.41 (d, $J$ = 9.0 Hz, 2H, 2 × Ar*H*), 7.32 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.27 – 7.20 (m, 3H, 3 × $CH_2$Ph*H*), 7.15 (d, $J$ = 8.5 Hz, 2H, 2 × Tol*H*), 7.10 (d, $J$ = 8.5 Hz, 2H, 2 × Tol*H*), 7.07 – 6.99 (m, 2H, 2 × $CH_2$Ph*H*), 6.90 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.85 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.74 (s, 1H, HetAr*H*), 6.73 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.48 (d, $J$ = 15.0 Hz, 1H, NC$H_A$H$_B$), 4.45 (d, $J$ = 14.5 Hz, 1H, NC$H_A$H$_B$), 4.41 (d, $J$ = 15.0 Hz, 1H, NC$H_A$H$_B$), 4.07 (app. t, $J$ = 15.0 Hz, 3H, 3 × NCH$_A$$H_B$), 3.79 (s, 3H, OC$H_3$), 3.76 (s, 3H, OC$H_3$), 2.37 (s, 3H, TolC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.2, 158.5, 145.3, 144.1 (q, $^{2}J_{CF}$ = 38.5 Hz), 141.9, 140.5, 139.8, 136.5, 133.3, 130.3, 129.9, 128.8 (2 × C), 128.7, 128.6, 128.5, 128.1, 127.7, 126.0, 125.4, 121.3 (q, $^{1}J_{CF}$ = 269.0 Hz), 113.9, 113.8, 106.3 (q, $^{3}J_{CF}$ = 2.5 Hz), 55.4 (2 × C), 51.1, 50.7, 45.2, 21.5; **$^{19}$F NMR** (377 MHz, $CDCl_3$) $\delta_F$ -62.36; **HRMS** (ESI, *m/z*) calculated for $(C_{40}H_{38}O_3N_4F_3S)^+$ 711.2611 $[M+H]^+$, found 711.2606; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1612, 1511, 1471, 1373, 1237, 1136, 1036, 975, 894, 812, 771, 630; ***er*** determined by HPLC using a

Chiralpak IA-3 column (*n*-hexane:$^{i}$PrOH, 80:20); $\tau_{major}$ = 15.14 min, $\tau_{minor}$ = 22.93 min (73.5:26.5 *er*); $[\alpha]_D^{25}$ −12.7° (c = 0.75, $CHCl_3$); $\mathbf{R_f}$ 0.52 (Petrol:EtOAc, 4:1).

**6.4.1.7. Kinetic Resolution**

***N,N'*-bis(4-methoxybenzyl)-N-(4-nitrobenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ap)**

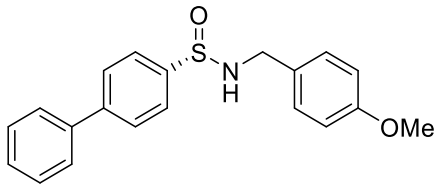



Prepared according to a modified general procedure D, using sulfonimidamide **73a** (20.6 mg, 0.05 mmol, 1.0 equiv.) and 1-(bromomethyl)-4-nitrobenzene (10.8 mg, 0.05 mmol, 1.0 equiv.), potassium hydroxide (14.0 mg, 0.25 mmol, 5.0 equiv.), **CAT-1** (2.7 mg, 10 mol%) and toluene (0.5 mL) at room temperature for 30 min. Purification by flash column chromatography (Petrol:EtOAc, 1:0 to 1:1), afforded the title compound (2.6 mg, 10%) as a yellow oil.

For the kinetic resolution procedure, a modified general procedure D was followed. With racemic sulfonimidamide 74**ap** (30.4 mg, 0.05 mmol, 1.0 equiv.), potassium hydroxide (14.0 mg, 0.25 mmol, 5.0 equiv.), **CAT-1** (2.7 mg, 10 mol%), and toluene (0.5 mL), in the absence of electrophile at room temperature for 1 h. Purification by flash column chromatography (Petrol:EtOAc, 1:0 to 4:1), afforded the title compound (27% conversion from $^{1}$H NMR spectrum) as a yellow oil. The spectroscopic data was in agreement with the previously synthesised compound (see **Section 6.4.1.2.**).

***er*** determined by HPLC using a Chiralpak OD-H column (*n*-hexane:$^{i}$PrOH, 80:20); $\tau_{major}$ = 28.99 min, $\tau_{minor}$ = 37.47 min (73.5:26.5 *er*).

***N*-(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfinamide (78a)**




Prepared according to a modified general procedure D, using sulfonimidamide **73a** (20.6 mg, 0.05 mmol, 1.0 equiv.) and 1-(bromomethyl)-4-nitrobenzene (10.8 mg, 0.05 mmol, 1.0 equiv.), potassium hydroxide (14.0 mg, 0.25 mmol, 5.0 equiv.), **CAT-1** (2.7 mg, 10 mol%) and toluene (0.5 mL) at room temperature for 30 min. Purification by flash column chromatography (Petrol:EtOAc, 1:0 to 4:1), afforded the title compound (38% conversion from $^{1}$H NMR spectrum) as a colourless solid.

For the kinetic resolution procedure, a modified general procedure D was followed. With racemic sulfonimidamide 74**ap** (30.4 mg, 0.05 mmol, 1.0 equiv.), potassium hydroxide (14.0 mg, 0.25 mmol, 5.0 equiv.), **CAT-1** (2.7 mg, 10 mol%), and toluene (0.5 mL), in the absence of electrophile at room temperature for 1 h. Purification by flash column chromatography (Petrol:EtOAc, 1:0 to 4:1), afforded the title compound (73% conversion from $^{1}$H NMR spectrum) as a colourless solid.

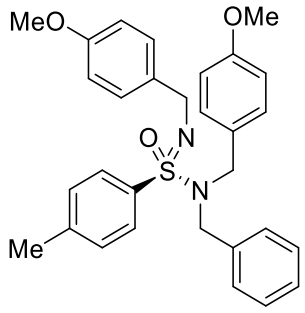
Note: The racemic product was obtained in an analogous procedure using racemic **73a** on a 0.1 mmol scale obtaining the title compound (13.4 mg, 40%) as a colourless solid.

**MP** (Petrol/EtOAc) 112-114 °C; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.83 (d, $J$ = 8.5 Hz, 2H, 2 × ArH), 7.73 (d, $J$ = 8.5 Hz, 2H, 2 × ArH), 7.65 – 7.57 (m, 2H, 2 × PhH), 7.53 – 7.42 (m, 2H, 2 × PhH), 7.43 – 7.37 (m, 1H, PhH), 7.21 (d, $J$ = 8.5 Hz, 2H, 2 × p-OMeArH), 6.85 (d, $J$ = 8.5 Hz, 2H, 2 × p-OMeArH), 4.35 (br. dd, $J$ = 7.0, 5.0 Hz, 1H, N*H*), 4.23 (dd, $J$ = 13.0, 5.0 Hz, 1H, NC$H_A$H$_B$), 3.89 (dd, $J$ = 13.0, 7.0 Hz, 1H, NC$H_A$H$_B$), 3.78 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.3, 144.1, 142.8, 134.0, 129.8, 129.1, 128.2, 127.8, 127.4, 126.7, 114.2, 113.9, 55.4, 44.3; **LRMS** *m/z* (ESI)

$[M+H]^+$ 372.2; **HRMS** (ESI, *m/z*) calculated for $(C_{20}H_{20}O_2NS)^+$ 338.1209 $[M+H]^+$, found 338.1208; **IR** ($CHCl_3$) 1612, 1513, 1480, 1303, 1249, 1177, 1089, 1033, 829, 763, 655; ***er*** determined by HPLC using a Chiralpak OD-H column (*n*-hexane:$^i$PrOH, 80:20); $\tau_{major}$ = 12.71 min, $\tau_{minor}$ = 14.55 min (68:32 *er*); $\mathbf{R_f}$ 0.13 (Petrol:EtOAc, 4:1).

### 6.4.1.8. Authentic Sample Synthesis

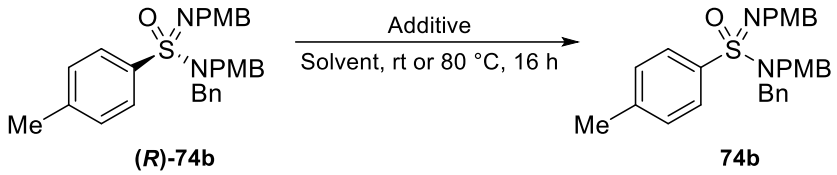
### (*R*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-4-methylbenzenesulfonimidamide (74b)




Prepared according to the modified procedure from Worch *et al.*[88] (*S*)-sulfinamide **78b** (606 mg, 2.20 mmol, 1.0 equiv.) was dissolved in THF (18 mL) and cooled to –25 °C using an **i**mmersion **c**ooler. To this solution, was added *t*-butyl hypochlorite (0.32 mL, 2.86 mmol, 1.3 equiv.) by slow dropwise addition. The reaction was stirred at –25 °C for 20 min and then *N*-benzyl-1-(4-methoxyphenyl)methanamine **81** (1.05 g, 4.84 mmol, 2.2 equiv.) dissolved in THF (4.4 mL) was added. The reaction mixture was left to stir at –25 °C for 36 h, using the immersion cooler apparatus. The reaction was quenched with water (10 mL) and extracted EtOAc × 3 (50 mL), the combined organic extracts were dried with sodium sulfate and the solvent removed under reduced pressure. Purification by flash column chromatography (Petrol:EtOAc, 9:1 to 4:1), afforded the title compound (597 mg, 54%) as a colourless solid.

***er*** determined by HPLC using a Chiralpak OD-H column (*n*-hexane:$^i$PrOH, 80:20); $\tau_{major}$ = 7.37 min, $\tau_{minor}$ = 10.05 min (92:8 *er*); $[\boldsymbol{\alpha}]_D^{25}$ +2.9° (*c* = 0.75, $CHCl_3$). The spectroscopic data was in agreement with the previously synthesised compound (see **Section 6.4.1.2.**).

### 6.4.1.9. Configurational Stress Tests

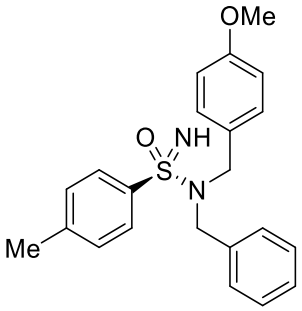



(*R*)-74b 74b

Sulfonimidamide **(*R*)-74b** of known enantioenrichment (ca. 10 mg, 37:63 *er*) was subjected to multiple stress tests by placing it in a given solvent (0.5 mL) at either room temperature or 80 °C in a sealed microwave vial. After a period of 16 h the reactions were cooled to room temperature and the solvent removed under reduced pressure, the crude mixture was directly dissolved in $^{i}$PrOH and analysed by chiral-phase HPLC, to obtain the enantiospecificity (*es*).

### 6.4.1.10. Deprotections

**(*R*)-*N*-benzyl-*N*-(4-methoxybenzyl)-4-methylbenzenesulfonimidamide (82)**



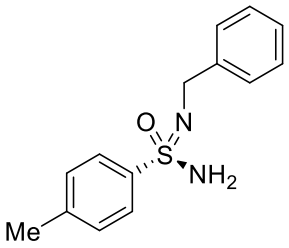

Sulfonimidamide **(*R*)-74b** (50.1 mg, 0.10 mmol, 1.0 equiv.), was added to a reaction vial and dissolved in toluene (1 mL). To this solution, was added DDQ (34.1 mg, 0.15 mmol, 1.5 equiv.) and the reaction was left to stir at room temperature for 15 min. After this time period, the crude mixture was directly purified by flash column chromatography (Petrol:EtOAc, 9:1 to 1:1), affording the title compound (31.5 mg, 83%) as a yellow oil.

Note: To obtain a sample of the racemic material for chiral-phase HPLC analysis the reaction was conducted with the racemic starting material under identical conditions.

Note: Reactions were also attempted with the reagent CAN (ceric ammonium nitrate), according to the literature procedure,[103] but resulted in decomposition.

**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 2H, 2 × Ar*H*), 7.30 (d, *J* = 8.0 Hz, 2H, 2 × Ar*H*), 7.24 – 7.18 (m, 3H, 3 × $CH_2$Ph*H*), 7.10 – 7.01 (m, 2H, 2 × $CH_2$Ph*H*), 6.95 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 6.73 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.30 (app. d, *J* = 14.0 Hz, 4H, 2 × NC$H_AH_B$), 3.76 (s, 3H, OC$H_3$), 2.44 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 159.2, 143.2, 137.6, 136.8, 130.0, 129.7 (2 × C), 128.5 (2 × C), 127.7, 127.6, 113.9, 55.4, 51.7, 51.4, 21.6; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 403.2; **HRMS** (ESI, *m/z*) calculated for $(C_{22}H_{25}O_2N_2S)^+$ 381.1631 $[M+H]^+$, found 381.1632; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$). 3287, 2918, 1611, 1586, 1512, 1494, 1455, 1367, 1303, 1248, 1176, 1133, 1110, 1074, 1031, 982, 938, 914, 893, 816, 765, 732, 698, 643; ***er*** determined by HPLC using a Chiralpak IA-3 column (*n*-hexane: $^i$PrOH, 85:15); $\tau_{minor}$ = 31.11 min, $\tau_{major}$ = 32.91 min (8:92 *er*); $[\alpha]_D^{25}$ −33.8° (*c* = 0.75, $CHCl_3$); $R_f$ 0.50 (Petrol:EtOAc, 1:1).

**(*R*)-*N'*-benzyl-4-methylbenzenesulfonimidamide (83)**




Sulfonimidamide **(*R*)-74b** (50.1 mg, 0.10 mmol, 1.0 equiv.), was added to a microwave vial and sealed with a microwave vial cap. The sulfonimidamide **(*R*)-74b** was then dissolved in TFA (1 mL) and heated to 80 °C. The reaction was left to stir for 3.5 h, after which it was quenched by the dropwise addition of saturated aqueous sodium carbonate solution until effervescence stopped. The reaction was extracted with $CH_2Cl_2$ × 3 (10 mL) and the combined organic extracts were dried with sodium sulfate. Then the solvent removed under reduced pressure. Purification by flash column

chromatography (Petrol:EtOAc, 4:1 to 1:4), afforded the title compound (21.2 mg, 81%) as a yellow oil.

Note: To obtain a sample of the racemic material for chiral-phase HPLC analysis the reaction was conducted with the racemic starting material under identical conditions.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.79 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.35 – 7.26 (m, 3H, 3 × $CH_2$Ph*H*), 7.25 – 7.13 (m, 4H, 2 × Ar*H*, 2 × $CH_2$Ph*H*), 5.97 (br. s, 2H, N$H_2$), 4.19 (d, $J$ = 14.5 Hz, 1H, NC$H_A$$H_B$), 4.10 (d, $J$ = 14.5 Hz, 1H, NC$H_A$$H_B$), 2.43 (s, 3H ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 145.5, 135.8, 130.2, 128.8, 128.1 (3 × C), 128.0, 46.6, 21.7; **LRMS** (ESI, *m/z*) $[M+H]^+$ 261.0 & $[M+Na]^+$ 283.0; **HRMS** (ESI, *m/z*) calculated for $(C_{14}H_{17}ON_2S)^+$ 261.1056 $[M+H]^+$, found 261.1056; **IR** ($CHCl_3$, $\nu_{max}$/$cm^{-1}$), 3257, 2922, 1598, 1495, 1454, 1361, 1247, 1183, 1131, 1103, 1064, 1026, 1012, 814, 735, 698, 646; ***er*** determined by HPLC using a Chiralpak IA-3 column (*n*-hexane: $^i$PrOH, 85:15); $\tau_{major}$ = 14.91 min, $\tau_{minor}$ = 17.74 min (92:8 *er*); $[\boldsymbol{\alpha}]_D^{25}$ −21.2° (*c* = 0.75, $CHCl_3$); $\mathbf{R_f}$ 0.21 (Petrol:EtOAc, 1:1).

### 6.4.2. X-ray Crystallography

X-Ray Crystallography: Single crystal X-ray diffraction data were collected using Agilent SuperNova diffractometer (Cu Kα radiation, λ = 1.54180 Å), a Rigaku XtaLAB Mini II, diffractometer (Mo Kα radiation, λ = 0.71073 Å) or a Rigaku XtaLAB Synergy diffractometer and data was refined using SHELXT by either Dr Antoine de Gomber & Dr Alasdair Mckay (University of Oxford). The following .cif files can be located in the additional information.

### 6.4.3. NMR Experiments

#### 6.4.3.1. Solvent Effects

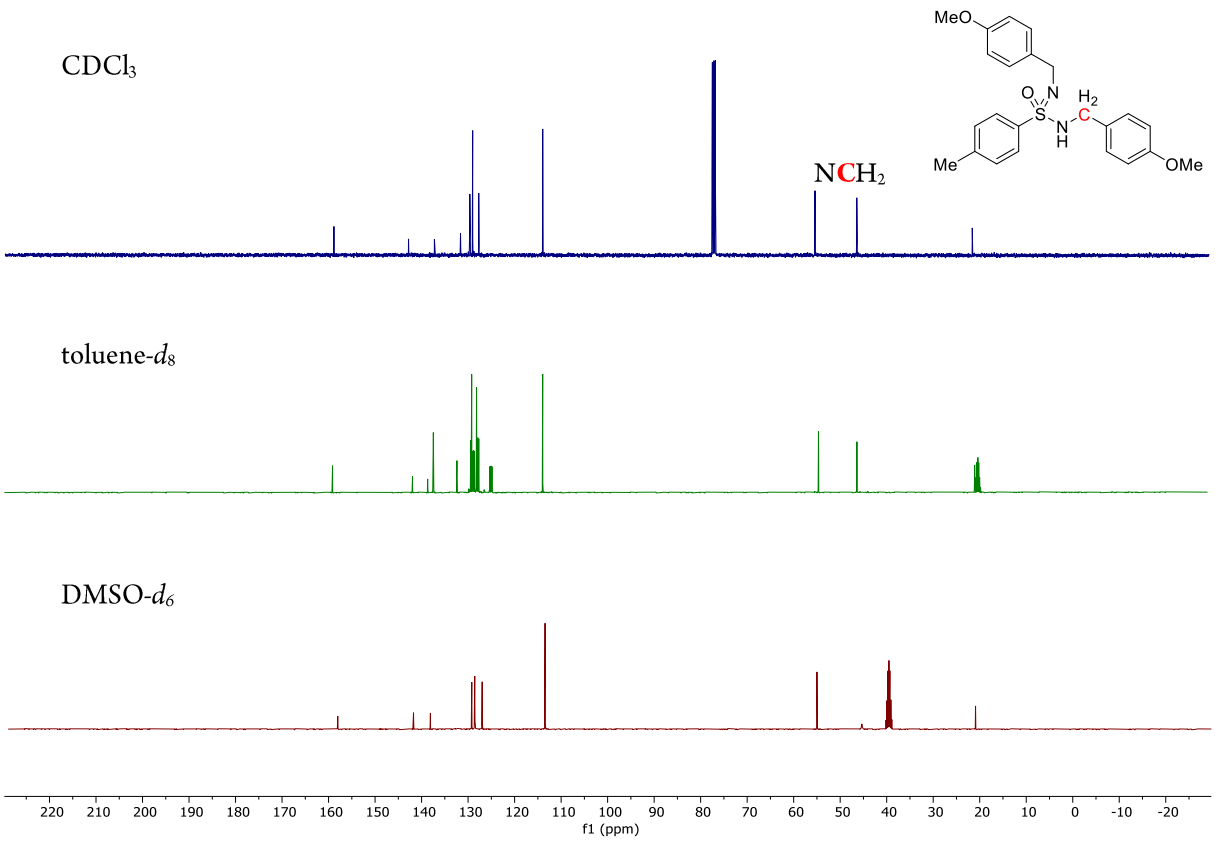



**Figure 6.10.** $^{13}C$ NMR spectra of compound **73b** at 101 MHz and 295 K analysing the tautomerization process in various solvents.

The $^{13}C$ NMR spectra in $CDCl_3$ and toluene-$d_8$ appear near identical, however several key changes occur in DMSO-$d_6$. In particular significant broadening of the peak at 45.3 ppm arises, indicating that this carbon environment consists of multiple peaks involved in a chemical exchange process. Also, the aromatic region only shows 7 clean signals which may arise from broadening of an aromatic quaternary centre.

### 6.4.3.2. Additive Effects

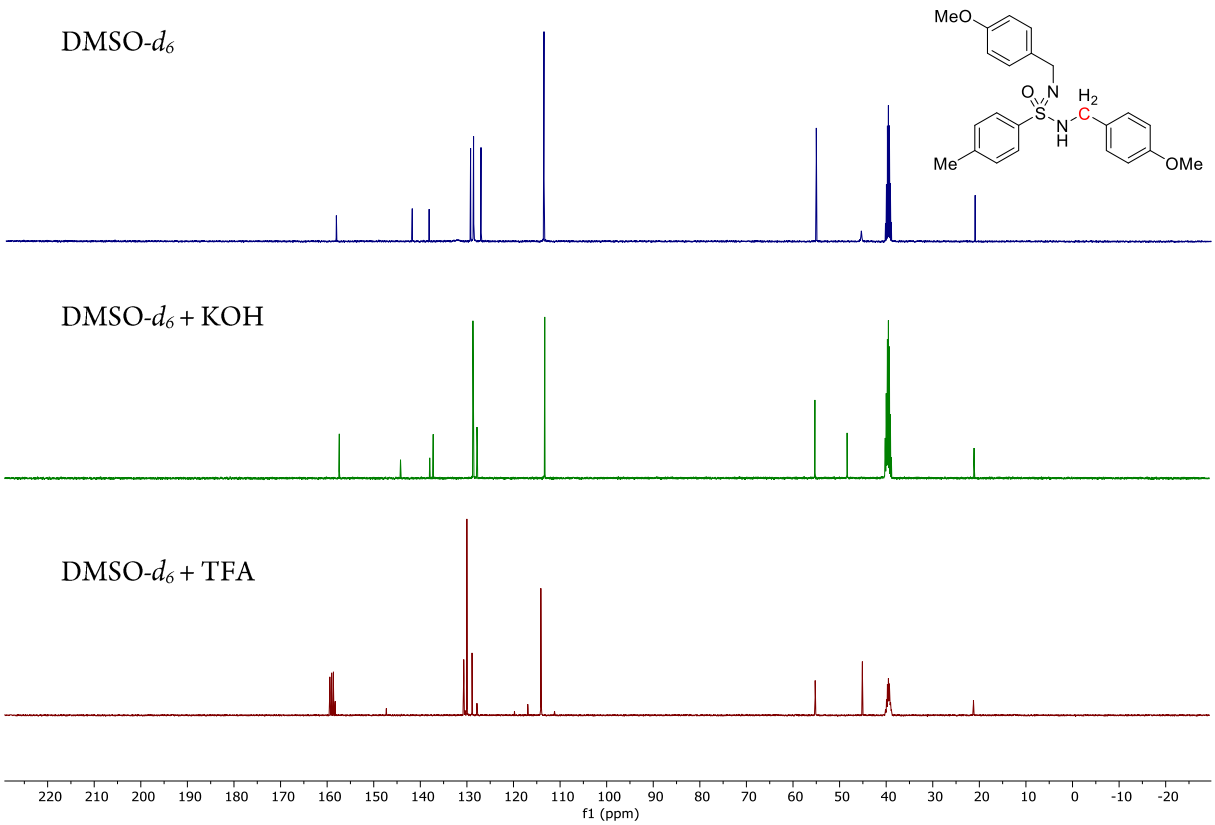



**Figure 6.11.** $^{13}$C NMR spectra of compound **73b** at 101 MHz and 295 K analysing the tautomerization process in the presence of additives.

Significant chemical shift difference can be observed on addition of KOH and, which is ascribed to be from the formation of the symmetric sulfonimidamide ions. Of particular note is the aromatic region in TFA, including a quaternary centre that is shifted downfield to 147.3 ppm, such a drastic change allows one to conclude that the protonated sulfonimidamide is a significant component of the sample.

Another key observation is based on the previously discussed methylene signal. One the addition of acid or base the intensity of this signal increases once again implying the involvement of a symmetric species.

### 6.4.3.3. Substituted Sulfonimidamide

In order to test if these observations in the $^{1}H$ & $^{13}C$ NMR spectrum were an artificial property from the sulfonimidamide substrate, several analogous experiments were conducted on a fully substituted sulfonimidamide (**74b**, **Figure 6.10.** & **Figure 6.11.**)

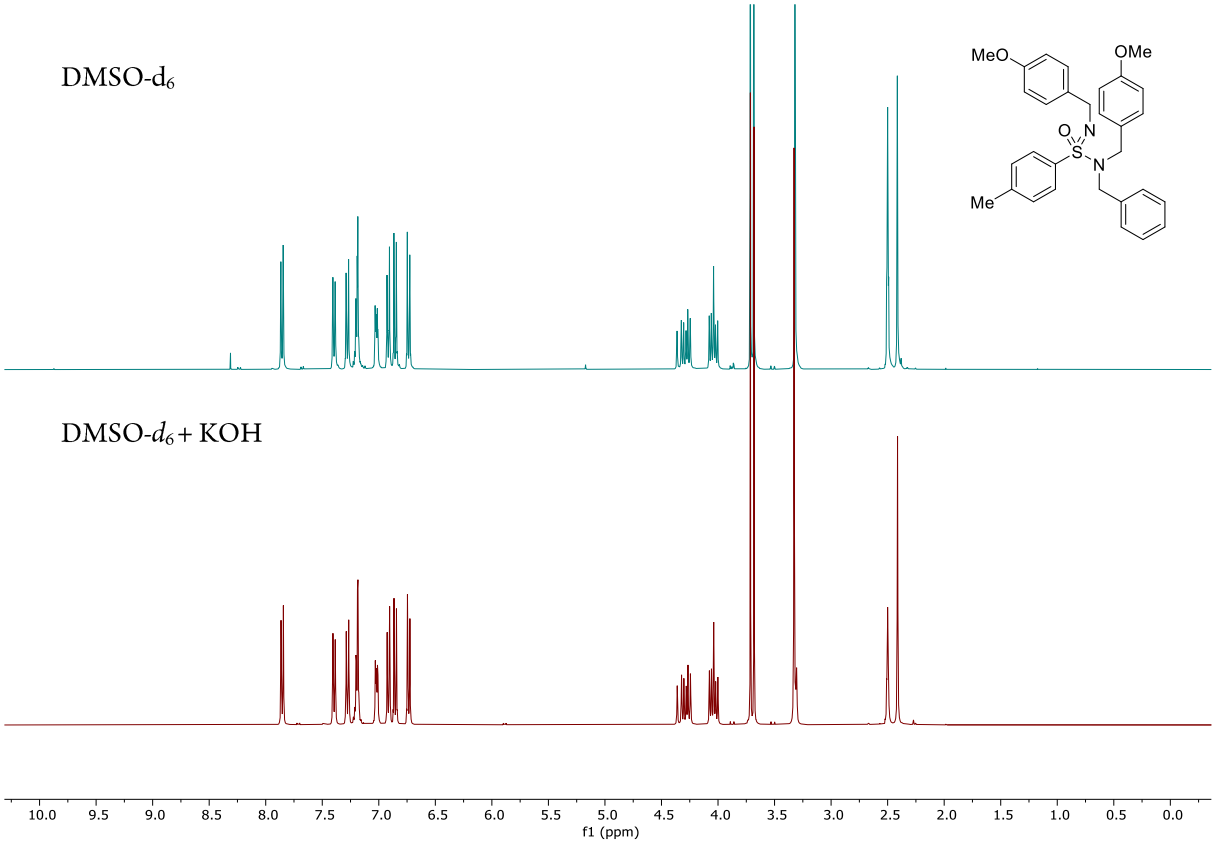



**Figure 6.12.** $^{1}H$ NMR spectrum of compound **74b** at 400 MHz and 295 K analysing the effect of KOH as an additive.

Comparison of the $^{1}H$ NMR spectrum of **74b** under neutral and basic conditions in DMSO-$d_6$ showed no significant change in the chemical shifts or coupling constants of any of the protons. This result indicates that the presence of KOH does not significantly impact the $^{1}H$ NMR spectra of **74b** and the previous changes seen for **73b** arise due to deprotonation.

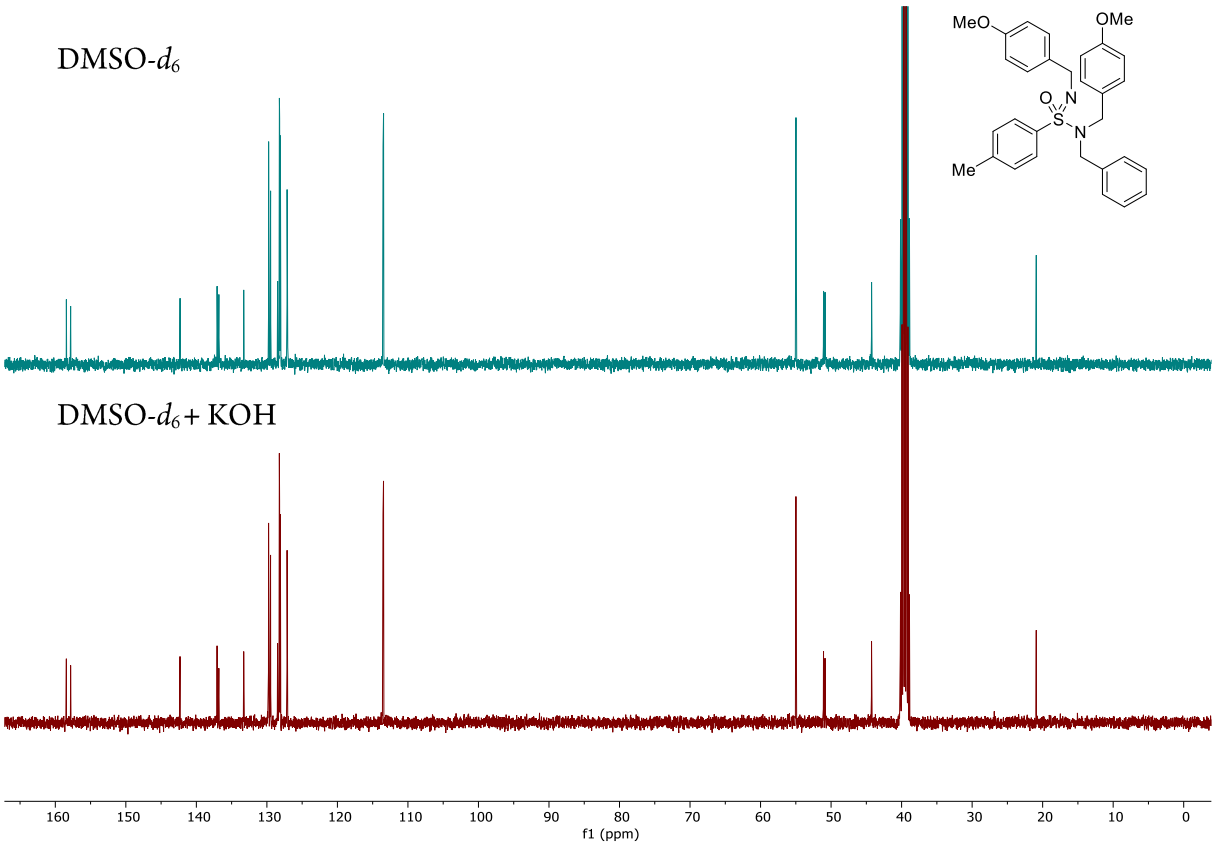


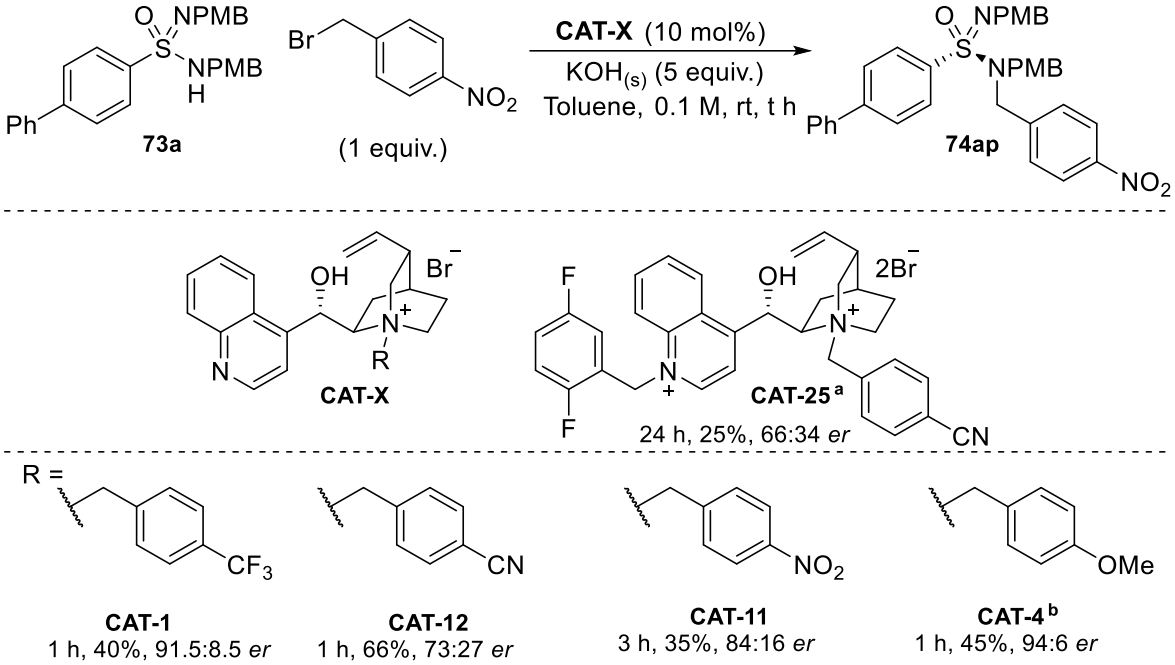

**Figure 6.13.** $^{13}$C NMR spectrum of compound **74b** at 101 MHz and 295 K analysing the effect of KOH as an additive.

The comparison of the $^{13}$C NMR spectrum in DMSO-$d_6$ under neutral and basic conditions for **74b** gave an analogous conclusion to that previously discussed, with no significant change in any of the carbon chemical shifts. This observation supports the previous conclusions.

### 6.4.4. Kinetic Resolution

In an attempt to improve the previously discussed tandem kinetic resolution procedure (see section **3.5.1.**) a small selection of alternative phase-transfer catalysts was employed in the reaction (**Table 6.17.**).

**Table 6.17.** Attempts to improve the tandem kinetic resolution.

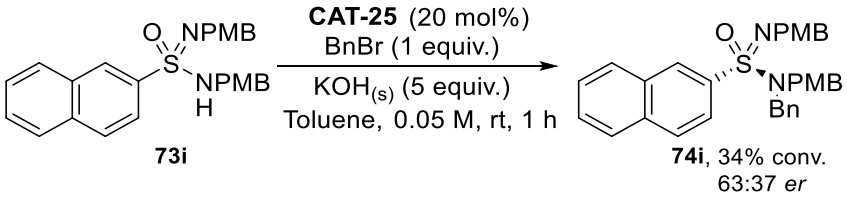



[a] reaction was conducted at –20 °C with 20 mol% of **CAT-25**, 20 equiv. of base and at concentration of 0.05 M. [b] The catalyst has a chloride counterion rather than bromide.

The catalysts screened in this reaction produced varied results. Firstly, the optimum singly-quaternised catalyst (**CAT-12**), now produced the lowest enantiomeric ratio, additionally in this reaction none of the sulfinamide product (**78a**) indicating that no kinetic resolution is in progress. Other singly-quaternised catalysts performed better, with the best result obtained with **CAT-4** which also gave sulfinamide **78a** in 28% conversion and 57:43 *er*. Finally, examining the optimum catalyst **CAT-25** gave a poor result, again indicating that little kinetic resolution is likely in operation. Overall, this procedure appears to be highly convolute, hence was not probed further.

### 6.4.5. Further Substrate Optimisation

Due to the optimised reaction appearing to be highly substrate specific, it was decided to attempt to improve the enantiomeric ratio another substrate by alteration of the catalyst. To do this the naphthyl derived system was investigated (**73i**), first examining the effectiveness of the optimised catalyst at room temperature (**Scheme 6.2.**) This optimisation was done in collaboration with Dr. Damien Dewez.



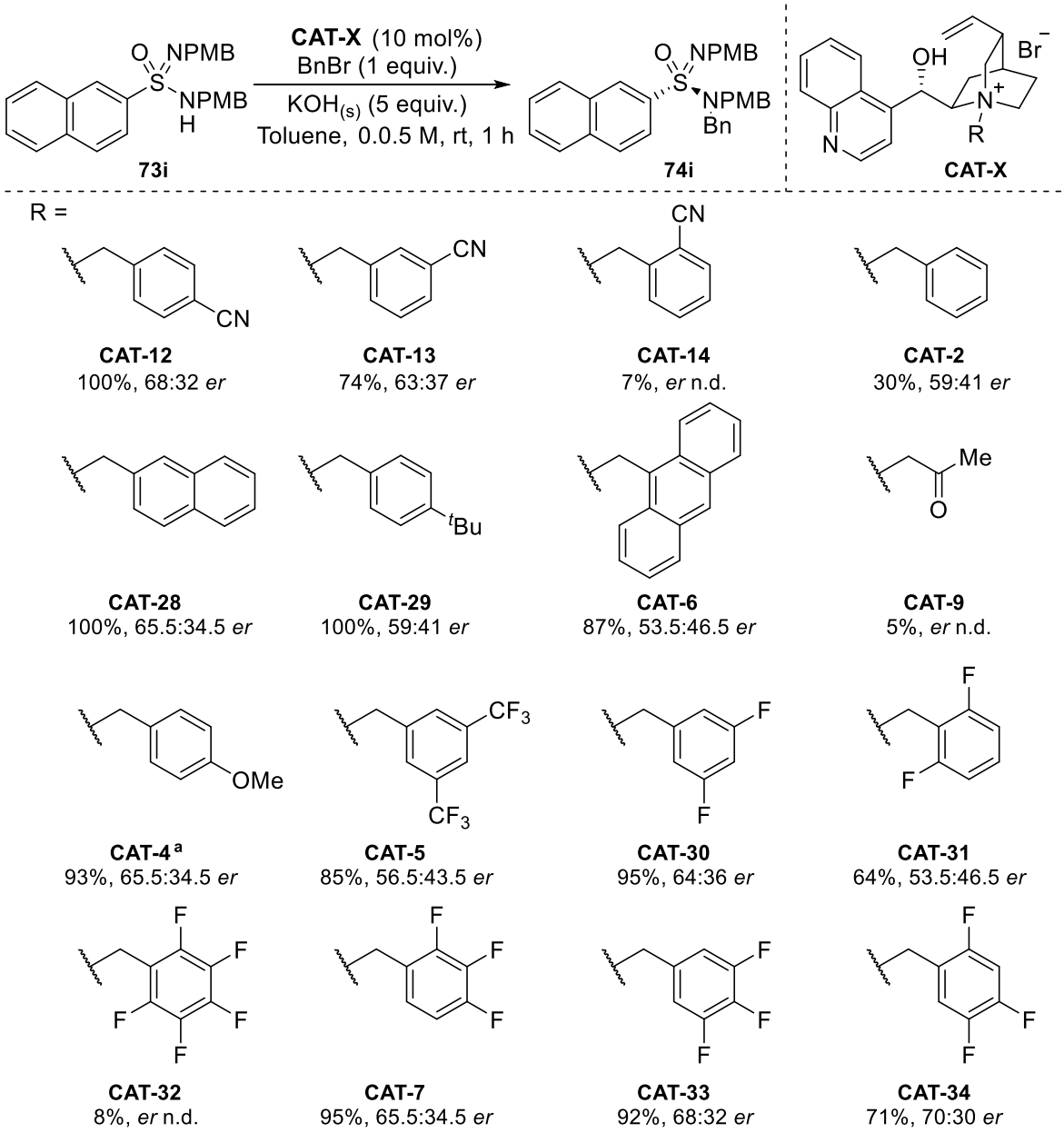

**Scheme 6.2.** Examination of the optimum catalyst with an alternative substrate, where conversion was determined by analysis of the crude $^1$H NMR spectrum.

Interestingly substrate **73i** showed a drastically different behaviour to the model substrate (see **Table 3.8.**). Previously all the doubly-quaternised catalysts showed excellent activity and good level of enantioinduction, whereas this reaction was now very sluggish and gave a lower enantiomeric ratio than that which was observed with the singly-quaternised system. It was postulated that this may be a consequence of the *para*-cyano substituent of the catalyst not being optimum, hence other catalysts with similar scaffolds were investigated (**Table 6.18.**).

As can be seen a broad range of catalysts were screened. The naphthyl system appeared to behave very differently from the previously discussed biphenyl system. This is exemplified with the simple benzyl catalyst (**CAT-2**) now producing a near racemic mixture. Therefore, several drastic changes were made on the catalyst in an attempt to improve the selectivity, with several depicted in the optimisation table. Ultimately it was discovered that fluorine substituents on the aryl system appeared to have a beneficial effect especially when they appear to break the symmetry of the aryl system. Overall, this led to catalyst **PTC-34** producing moderate enantioselectivity, it should be noted that this is relatively close to the enatiomeric ratio obtained under the previous optimised conditions (76:24 *er*).

Another point of interest is that when **PTC-34** was used on the model substrate (**73a**) the product (**74a**) was obtained in good conversion but reduced enantiomeric ration (65.5:34.5) compared to **CAT-12** (74:26 *er*).

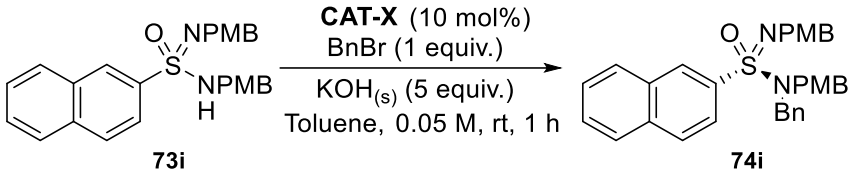
**Table 6.18.** Screen of cinchona alkaloid derived catalysts,



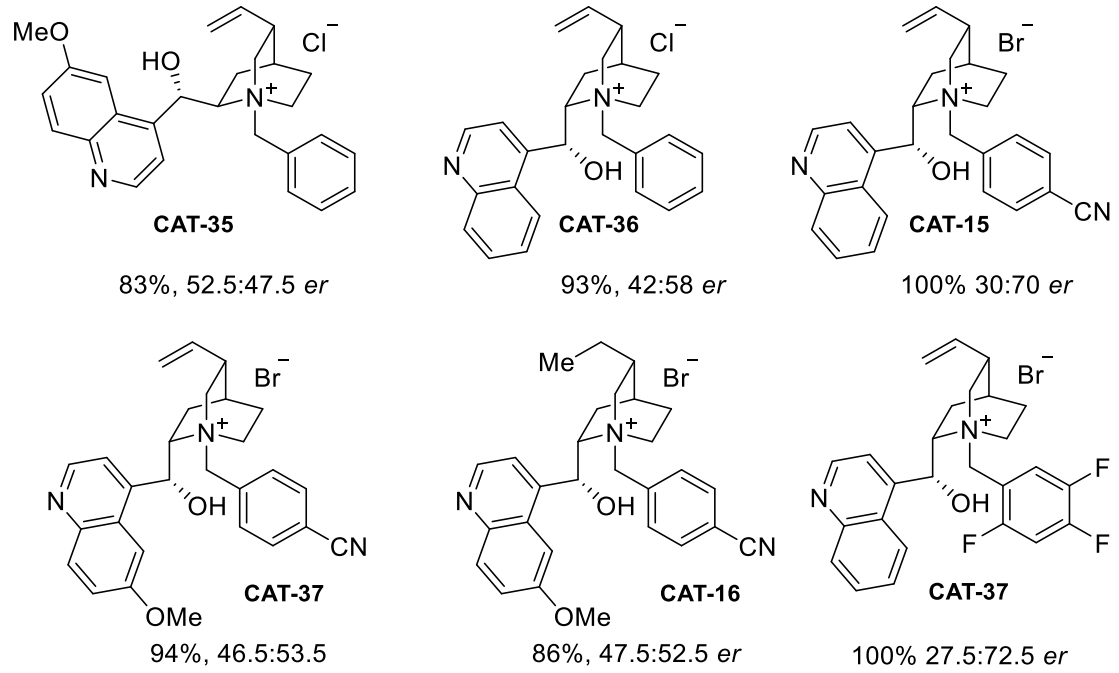

Conversions were determined by analysis of the crude $^1$H NMR spectra. [a] The catalyst has a chloride counterion rather than bromide.

Once again it was decided to examine the impact of the scaffold, by using alternatives to the cinchonine derivatives. Therefore, quinine type catalysts and the corresponding pseudo-enantiomers were evaluated (**Table 6.19**).

**Table 6.19.** Screen of catalysts, with a different scaffold.



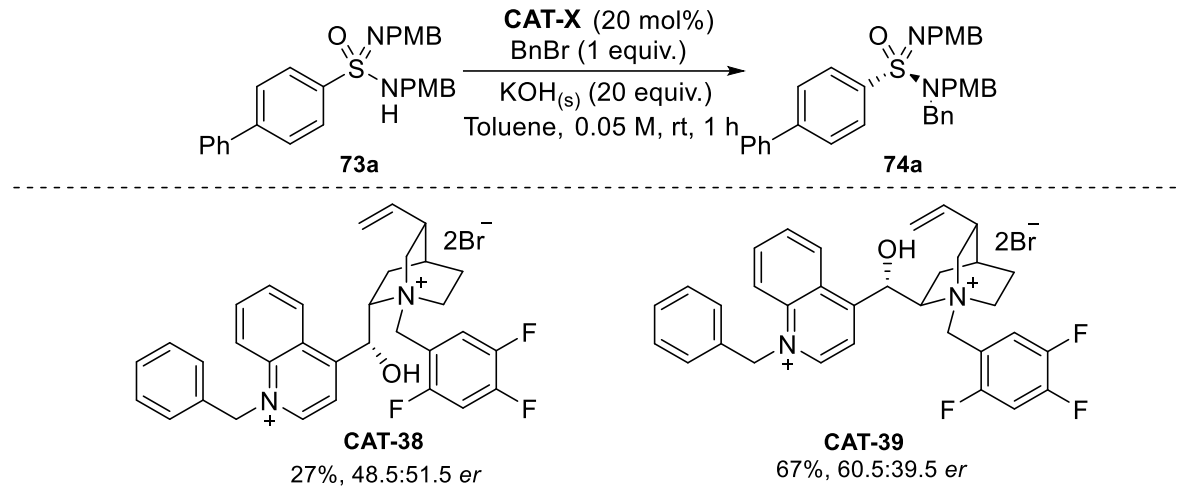

73i 74i




Conversions were determined by analysis of the crude $^1$H NMR spectra. [a] The catalyst has a chloride counterion rather than bromide.

Interestingly the pseudo-enantiomer now appeared to be more selective in the reaction, which was not observed with the original biphenyl. However, it is important to note that the electronic effects to the catalyst appeared to have the same impact as previously discussed. Overall, this led to the optimum catalyst being **CAT-37**. Again, this catalyst was used in combination with substrate **73a**, surprisingly this now proceeded to full conversion but gave a racemic mixture. Such a result exemplified how these catalysts are highly sensitive to minuscule interactions around the scaffold, which can produce drastically different results.

With this new optimum catalyst in hand, doubly-quaternised systems were synthesised from it, and applied in the reaction (**Scheme 6.3.**). To initiate this investigation both pseudo-enantiomers were examined.




**Scheme 6.3.** Investigation into the cinchona alkaloid derived catalyst core which are doubly quaternised, where conversions were determined by analysis of the crude $^{1}$H NMR spectra.

However, both catalysts still showed a reduced rate of reaction, and a decline in the enantiomeric ratio, especially in the case with **CAT-38**. Several further catalysts were synthesised using different appendages, even though all showed a diminished result when compared to the singly-quaternised system. Additionally, multiple attempts were made to improve the system by altering the conditions, such as changing the identity of the base, but nothing came to fruition.

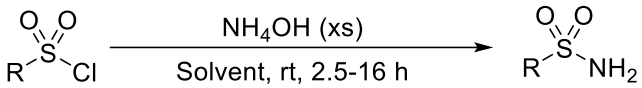
The celecoxib derived substrate (**73o**) was also re-optimised, but this demonstrated very similar behaviour to the naphthyl system discussed. Overall, these results indicate that this appears to be highly substate specific and the system appears to be very delicate. Further work should endeavour to identify and understand the interactions which govern selectivity in these cinchona alkaloid-based catalysts. Alternatively, several other phase-transfer scaffolds have become popular, and these should also be considered.

# 6.5. Experimental Data and Procedures – Chapter 4

## 6.5.1. Experimental Procedures and Characterisation

### 6.5.1.1. Precursor Preparation

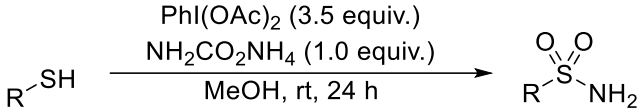
**General Procedure E**




**General Procedure E**: Nucleophilic displacement reaction of a sulfonyl chloride with ammonia.

Modified procedure from Mallinger *et al.*[312] Under an atmosphere of air sulfonyl chloride was added to a reaction round bottom flask then dissolved in an appropriate solvent (0.75-0.30 M). To this solution was added ammonium hydroxide in excess by slow dropwise addition. The reaction mixture was stirred at room temperature until completion as determined by TLC and then the solvent was removed under reduced pressure. The reaction mixture was diluted with EtOAc, and water was added. The two layers were separated, and the aqueous layer was extracted with EtOAc × 3. The combined organic layers were dried over $Na_2SO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by washing with *n*-hexane and $Et_2O$.

**General Procedure F**

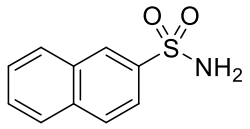



**General Procedure F**: Oxidation of a thiol to a primary sulfonamide in one-pot.

Modified procedure from Tota *et al.*[110] Under an atmosphere of air, thiol (1.0 equiv.) was added to a round bottom flask and dissolved in MeOH (0.2 M). To this solution was added ammonium carbamate (1.0 equiv.) and [(diacetoxy)iodo]benzene (3.5 equiv.) (2.5 mL). The reaction mixture

was stirred at room temperature for 24 h until and then the solvent was removed under reduced pressure. The crude material was directly purified by flash column chromatography.

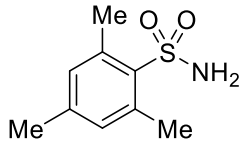
**Naphthalene-2-sulfonamide (110c)**



Prepared according to general procedure E, using naphthalene-2-sulfonyl chloride (907 mg, 4.0 mmol), THF (13.0 mL) and ammonium hydroxide (8.7 mL), with stirring for 2.5 h, affording the title compound (647 mg, 78%) as a pale pink solid.

**MP** (*n*-hexane/$Et_2O$) 207-209 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2CO$) $\delta_H$ 8.47 (d, *J* = 2.0 Hz, 1H, Ar*H*), 8.14 – 8.06 (m, 2H, 2 × Ar*H*), 8.06 – 7.98 (m, 1H, Ar*H*), 7.95 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar*H*), 7.73 – 7.61 (m, 2H, 2 × Ar*H*), 6.66 (br. s, 2H, $SO_2NH_2$); **$^{13}$C NMR** (101 MHz, $(CD_3)_2CO$) $\delta_C$ 142.2, 135.5, 133.2, 130.0 (2 × C), 129.3, 128.8, 128.3, 127.3, 123.2; **LRMS** (ESI, *m/z*) $[M-H]^-$ 206.0 & $[M+Na]^+$ 230.0. The spectroscopic data is in agreement with literature.[313]

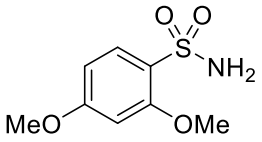
**2,4,6-Trimethylbenzenesulfonamide (110d)**



Prepared according to general procedure E, using 2,4,6-trimethylbenzenesulfonyl chloride (875 mg, 4.0 mmol), THF (13.0 mL) and ammonium hydroxide (8.7 mL), with stirring for 2.5 h, affording the title compound (717 mg, 90%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 129-131 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2CO$) $\delta_H$ 7.00 (s, 1H, Ar*H*), 6.43 (br. s, 2H, $SO_2NH_2$), 2.62 (s, 6H, 2 × Ar$CH_3$), 2.28 (s, 3H, Ar$CH_3$); **$^{13}$C NMR** (101 MHz, $(CD_3)_2CO$) $\delta_C$ 142.1, 139.1, 138.7, 132.5, 23.1, 20.9; **LRMS** (ESI, *m/z*) $[M-H]^-$ 198.1 & $[M+Na]^+$ 222.0. The spectroscopic data is in agreement with literature.[314]

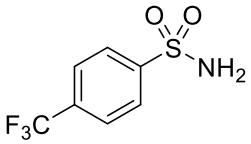
**2,4-Dimethoxybenzenesulfonamide (110g)**



Prepared according to general procedure E, using 2,4-dimethoxybenzenesulfonyl chloride (947 mg, 4.0 mmol), THF (13.0 mL) and ammonium hydroxide (8.7 mL), with stirring for 2.5 h, affording the title compound (337 mg, 39%) as a pink solid.

**MP** (*n*-hexane/$Et_2O$) 148-150 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2CO$) $\delta_H$ 7.72 (d, *J* = 8.5 Hz, 1H, Ar*H*), 6.71 (d, *J* = 2.5 Hz, 1H, Ar*H*), 6.60 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar*H*), 6.14 (br. s, 2H, $SO_2NH_2$), 3.97 (s, 3H, $OCH_3$), 3.88 (s, 3H, $OCH_3$); **$^{13}$C NMR** (101 MHz, $(CD_3)_2CO$) $\delta_C$ 165.2, 158.7, 130.3, 125.1, 105.2, 99.9, 56.6, 56.1; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 240.0; **HRMS** (ESI, *m/z*) calculated for $(C_8H_{12}NO_4S)^+$ 218.0482 $[M+H]^+$, found 218.0484; **IR** (thin film, $\nu_{max}/cm^{-1}$) 3382, 3271, 1601, 1574, 1490, 1464, 1434, 1413, 1299, 1212, 1163, 1079, 1018, 920, 895, 866, 834, 808, 720; **$R_f$** 0.13 (*n*-hexane:EtOAc, 1:1).

**4-(Trifluoromethyl)benzenesulfonamide (110h)**

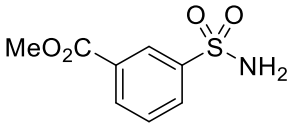


Prepared according to general procedure E, using 4-(trifluoromethyl)benzenesulfonyl chloride (978 mg, 4.0 mmol), THF (13.0 mL) and ammonium hydroxide (8.7 mL), with stirring for 2.5 h, affording the title compound (720 mg, 80%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 162-164 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2CO$) $\delta_H$ 8.14 (d, *J* = 8.0 Hz, 2H, 2 × Ar*H*), 7.95 (d, *J* = 8.0 Hz, 2H, 2 × Ar*H*), 6.87 (br. s, 2H, $SO_2NH_2$); **$^{13}$C NMR** (101 MHz, $(CD_3)_2CO$) $\delta_C$ 148.8, 133.7 (q, *J* = 32.5 Hz), 127.8, 127.0 (q, *J* = 4.0 Hz), 124.61 (q, *J* = 272.0 Hz);

**$^{19}$F NMR** (377 MHz, $(CD_3)_2CO$) $\delta_F$ -58.31 (s); **LRMS** (ESI, *m/z*) $[M-H]^-$ 224.0. The spectroscopic data is in agreement with literature.[314]

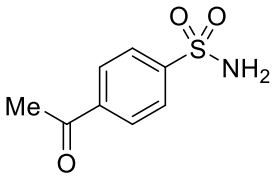
**Methyl 3-sulfamoylbenzoate (110j)**




Prepared according to general procedure E, using methyl 3-(chlorosulfonyl)benzoate (409 mg, 1.74 mmol), THF (6.0 mL) and ammonium hydroxide (3.8 mL), with stirring for 2.5 h, affording the title compound (232 mg, 62%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 119-121 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2CO$) $\delta_H$ 8.49 (app. td, *J* = 2.0, 0.5 Hz, 1H, Ar*H*), 8.20 (ddd, *J* = 8.0, 1.5, 1.0 Hz, 1H, Ar*H*), 8.14 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar*H*), 7.73 (app. td, *J* = 8.0, 0.5 Hz, 1H, Ar*H*), 6.77 (br. s, 2H, $SO_2NH_2$), 3.94 (s, 3H, $CO_2CH_3$); **$^{13}$C NMR** (101 MHz, $(CD_3)_2CO$) $\delta_C$ 166.1, 145.7, 133.3, 131.9, 131.1, 130.4, 127.7, 52.8; **LRMS** (ESI, *m/z*) $[M-H]^-$ 214.0 & $[M+Na]^+$ 238.0. The spectroscopic data is in agreement with literature.[314]

**4-Acetylbenzenesulfonamide (110k)**

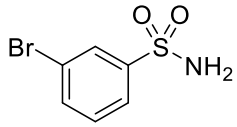



Prepared according to general procedure E, using 4-acetylbenzenesulfonyl chloride (875 mg, 4.0 mmol), THF (13.0 mL) and ammonium hydroxide (8.7 mL), with stirring for 2.5 h, affording the title compound (494 mg, 62%) as a pale-yellow solid.

**MP** (*n*-hexane/$Et_2O$) 166-168 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2CO$) $\delta_H$ 8.14 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 8.02 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 6.83 (br. s, 2H $SO_2NH_2$), 2.64 (s, 3H, $COCH_3$); **$^{13}$C NMR**

(101 MHz, $(CD_3)_2CO$) $\delta_C$ 197.3, 148.5, 140.4, 129.5, 127.0, 26.9; **LRMS** (ESI, *m/z*) $[M-H]^-$ 198.0 & $[M+Na]^+$ 222.0. The spectroscopic data is in agreement with literature.[314]

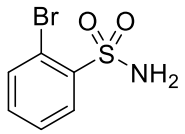
**3-Bromobenzenesulfonamide (110m)**



Prepared according to general procedure F, using 3-bromobenzenethiol (0.41 mL, 4.0 mmol), ammonium carbamate (384 mg, 4.0 mmol) and [(diacetoxy)iodo]benzene (4.51 g, 14.0 mmol). Purification by flash column chromatography (*n*-hexane:EtOAc, 1:9 to 1:1), afforded the title compound (547 mg, 58%) as a colourless solid.

**MP** (*n*-hexane/EtOAc) 140-142 °C; **$^1$H NMR** (400 MHz, MeOD) $\delta_H$ 8.06 (t, *J* = 2.0 Hz, 1H, Ar*H*), 7.88 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar*H*), 7.76 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar*H*), 7.48 (t, *J* = 8.0 Hz, 1H, Ar*H*), (note: $SO_2NH_2$ peak not observed); **$^{13}$C NMR** (101 MHz, MeOD) $\delta_C$ 147.0, 136.1, 131.9, 130.0, 125.9, 123.5; **LRMS (ESI, *m/z*)** $[M-H]^-$ 233.9, 235.9; **HRMS** (ESI, *m/z*) calculated for $(C_6H_5{}^{79}BrNO_2S)^-$ & $(C_6H_5{}^{81}BrNO_2S)^-$ 233.9230 & 235.9209 $[M-H]^-$, found 233.9224 & 235.9201 respectively; **IR** (thin film, $\nu_{max}$/cm$^{-1}$) 3330, 3243, 1571, 1463, 1418, 1326, 1297, 1162, 1069, 995, 879, 848, 786, 675 656. **$R_f$** 0.65 (*n*-hexane:EtOAc, 1:1).

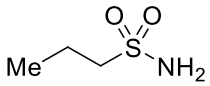
**2-Bromobenzenesulfonamide (110n)**



Prepared according to general procedure E, using 2-bromobenzenesulfonyl chloride (1.02 g, 4.0 mmol), THF (13.0 mL) and ammonium hydroxide (8.7 mL), with stirring for 2.5 h, affording the title compound (708 mg, 75%) as a colourless solid.

**MP** (*n*-hexane/EtOAc) 184-186 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2CO$) $\delta_H$ 8.12 (dd, *J* = 7.5, 2.0 Hz, 1H, Ar*H*), 7.83 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.57 (app. td, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.52 (app. td, *J* = 7.5, 2.0 Hz, 1H, Ar*H*), 6.73 (br. s, 2H, $SO_2NH_2$); **$^{13}$C NMR** (101 MHz, $(CD_3)_2CO$) $\delta_C$ 143.7, 135.9, 134.2, 130.5, 128.8, 120.2; **LRMS** (ESI, *m/z*) $[M-H]^-$ 233.9, 235.9. The spectroscopic data is in agreement with literature.[110]

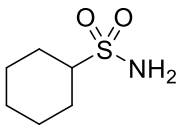
**Propane-1-sulfonamide (110p)**




Prepared according to general procedure E, using propanesulfonyl chloride (1.01 g, 10.0 mmol), MeOH (7.5 mL) and ammonium hydroxide (37.0 mL), with stirring for 16 h, affording the title compound (160 mg, 13%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 48-50 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2SO$) $\delta_H$ 6.72 (br. s, 2H, $SO_2NH_2$), 2.98 – 2.88 (m, 2H, $CH_3CH_2CH_2S$), 1.80 – 1.61 (m, 2H, $CH_3CH_2CH_2$), 0.97 (t, *J* = 7.5 Hz, 3H, $CH_3CH_2$); **$^{13}$C NMR** (101 MHz, $(CD_3)_2SO$) $\delta_C$ 56.2, 17.2, 12.8; **LRMS** (ESI, *m/z*) $[M-H]^-$ 122.1; **HRMS** (ESI, *m/z*) calculated for $(C_3H_8NO_2S)^-$ 122.0281 $[M-H]^-$, found 122.0275; **IR** (thin film, $\nu_{max}/cm^{-1}$) 3340, 3254, 2965, 1664, 1540, 1460, 1308, 1288, 1135, 1039, 907, 885, 785, 692; **$R_f$** 0.27 (*n*-hexane:EtOAc, 1:1).

**Cyclo*n*-hexane**sulfonamide (110q)**

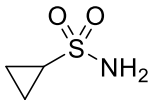



Prepared according to general procedure F, using cyclo*n*-hexanethiol (0.61 mL, 5.0 mmol), ammonium carbamate (480 mg, 5.0 mmol) and [(diacetoxy)iodo]benzene (5.64 g, 17.5 mmol).

Purification by flash column chromatography (*n*-hexane:EtOAc, 1:1 to 1:9), afforded the title compound (654 mg, 80%) as a white waxy solid.

**MP** (*n*-hexane/EtOAc) 82-84 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 4.72 (br. s, 2H, $SO_2NH_2$), 2.91 (tt, *J* = 12.0, 3.5 Hz, 1H, Cy*H*), 2.23 (app. dq, *J* = 12.0, 1.5 Hz, 2H, 2 × Cy*H*), 1.90 (app. dq, *J* = 13.0, 3.5 Hz, 2H, 2 × Cy*H*), 1.72 (app. dq, *J* = 12.0, 1.5 Hz, 1H, Cy*H*), 1.49 (app. qd, *J* = 12.0, 3.5 Hz, 2H, 2 × Cy*H*), 1.30 (app. qt, *J* = 12.0, 3.0 Hz, 1H, 2 × Cy*H*), 1.19 (app. qt, *J* = 13.0, 3.0 Hz, 1H, Cy*H*); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 62.9, 26.7, 25.2 (2 × C); **HRMS** (ESI, *m/z*) calculated for $(C_6H_{12}NO_2S)^-$ 162.0594 $[M-H]^-$, found 162.0585. The spectroscopic data is in agreement with literature.[110]

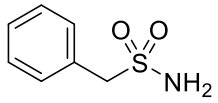
**Cyclopropanesulfonamide (110r)**



Prepared according to general procedure E, using cyclopropylsulfonyl chloride (1.01 mL, 10.0 mmol), MeOH (7.5 mL) and ammonium hydroxide (37.0 mL), with stirring for 16 h, affording the title compound (516 mg, 43%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 96-98 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2CO$) $\delta_H$ 6.09 (br. s, 2H, $SO_2NH_2$), 2.57 (tt, *J* = 8.0, 5.0 Hz, 1H, $(CH_2)_2CH$), 1.06 – 0.87 (m, 4H, $(CH_2)_2CH$); **$^{13}$C NMR** (101 MHz, $(CD_3)_2CO$) $\delta_C$ 32.8, 5.6; **LRMS** (ESI, *m/z*) $[M-H]^-$ 120.0. The spectroscopic data is in agreement with literature.[168]

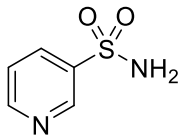
**Phenylmethanesulfonamide (110v)**



Prepared according to general procedure E, using benzylsulfonyl chloride (763 mg, 4.0 mmol), THF (13.0 mL) and ammonium hydroxide (8.7 mL), with stirring for 2.5 h, affording the title compound (462 mg, 67%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 88-90 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.47 – 7.35 (m, 5H, Ph*H*), 4.59 (s, 2H, PhC$H_2$), 4.32 (br. s, 2H, $SO_2NH_2$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 130.9, 129.5, 129.1 (2 × C), 61.2; **LRMS (ESI, *m/z*)** $[M\text{-}H]^-$ 171.0. The spectroscopic data is in agreement with literature.[168]

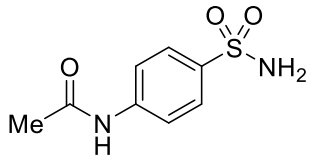
**Pyridine-3-sulfonamide (110x)**



Prepared according to general procedure E, using pyridine-3-sulfonyl chloride (763 mg, 4.0 mmol), THF (13.0 mL) and ammonium hydroxide (8.7 mL), with stirring for 2.5 h, affording the title compound (410 mg, 65%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 94-96 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2CO$) $\delta_H$ 9.05 (dd, *J* = 2.5, 1.0 Hz, 1H, Py*H*), 8.78 (dd, *J* = 5.0, 1.5 Hz, 1H, Py*H*), 8.24 (ddd, *J* = 8.0, 2.5, 1.5 Hz, 1H, Py*H*), 7.59 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H, Py*H*), 6.91 (br. s, 2H, $SO_2NH_2$); **$^{13}$C NMR** (101 MHz, $(CD_3)_2CO$) $\delta_C$ 153.3, 147.7, 141.1, 134.5, 124.5; **LRMS** (ESI, *m/z*) $[M\text{-}H]^-$ 157.0 & $[M+H]^+$ 159.0. The spectroscopic data is in agreement with literature.[315]

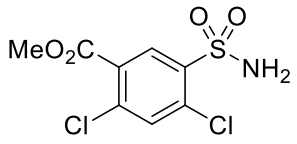
**_N_-(4-sulfamoylphenyl)acetamide (110z)**



Prepared according to general procedure E, using 4-acetamidobenzenesulfonyl chloride (1.87 mg, 8.0 mmol), THF (26.0 mL) and ammonium hydroxide (17.4 mL), with stirring for 2.5 h, affording the title compound (536 mg, 31%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 206-208 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2SO$) $\delta_H$ 10.26 (br. s, 1H, CONH), 7.75 (d, $J$ = 9.5 Hz, 2H, 2 × ArH), 7.72 (d, $J$ = 9.5 Hz, 1H, 2 × ArH), 7.22 (br. s, 2H, $SO_2NH_2$), 2.08 (s, 3H, $NHCOCH_3$); **$^{13}$C NMR** (101 MHz, $(CD_3)_2SO$) $\delta_C$ 168.9, 142.2, 138.1, 126.7, 118.4, 24.1; **LRMS** (ESI, *m/z*) $[M-H]^-$ 213.0, $[M+H]^+$ 215.0 & $[M+Na]^+$ 237.0. The spectroscopic data is in agreement with literature.[316]

**Methyl 2,4-dichloro-5-sulfamoylbenzoate (125a)**

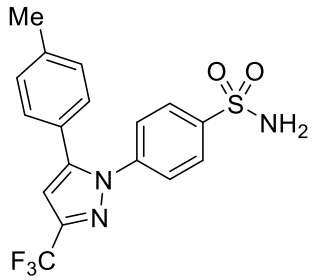


Prepared according to the modified procedure from Matulis *et al.*[317] Under an atmosphere of air 2,4-dichloro-5-sulfamoylbenzoic acid (1.35 g, 5.0 mmol) were added to a round bottom flask equipped with a reflux condenser and dissolved in MeOH (50.0 mL). The solution was refluxed at 65 °C with concentrated $H_2SO_4$ (0.5 mL) for 16 h. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. Purification by recrystallisation from MeOH, affording the title compound (1.01 g, 71%) as a colourless solid.

**MP** (MeOH) 186-188 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2SO$) $\delta_H$ 8.39 (s, 1H, ArH), 8.01 (s, 1H, ArH), 7.85 (br. s, 2H, $SO_2NH_2$), 3.90 (s, 3H, $CO_2CH_3$); **$^{13}$C NMR** (101 MHz, $(CD_3)_2SO$) $\delta_C$ 163.7,

140.1, 136.3, 134.6, 133.6, 131.3, 128.4, 53.1; **LRMS** (ESI, *m/z*) $[M-H]^-$ 281.9; **HRMS** (ESI, *m/z*) calculated for $(C_8H_6{}^{35}Cl_2NO_4S)^-$ 281.9400 $[M-H]^-$, found 281.9399; **IR** (thin film, $\nu_{max}/cm^{-1}$) 3350, 3247, 1721, 1562, 1430, 1358, 1293, 1257, 1171, 1074, 975, 920, 779, 688, 610; $\mathbf{R_f}$ 0.38 (*n*-hexane:EtOAc, 1:1).

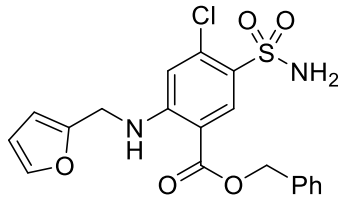
**4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide (100)**




Prepared according to the modified procedure from Lil *et al.*[318] Under an atmosphere of air 4,4,4-trifluoro-1-(p-tolyl)butane-1,3-dione, (2.21 g, 20.3 mmol, 1.0 equiv.) and (5.00 g, 22.4 mmol, 1.1 equiv.) 4-hydrazinylbenzen-sulfonamide hydrochloride were added to a round bottom flask equipped with a reflux condenser and dissolved in in EtOH (50 mL). The resulting suspension was refluxed for 20 h, then cooled to room temperature and the solvent removed under reduced pressure. The residue was dissolved in EtOAc (50 mL), washed with water (2 x 50 mL) and brine (50 mL). The organic phase was dried over $Na_2SO_4$, filtrated, and concentrated under reduced pressure. Purification by recrystallisation from *n*-hexane, affording the title compound (5.97 g, 77%) as a colourless solid.

**MP** (*n*-hexane) 145-147 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2CO$) $\delta_H$ 7.96 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.56 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 7.24 (app. s, 4H, 4 × Tol*H*), 6.99 (s, 1H, HetAr*H*), 6.75 (br. s, 2H, $SO_2NH_2$), 2.35 (s, 3H, $ArCH_3$); **$^{13}$C NMR** (101 MHz, $(CD_3)_2CO$) $\delta_C$ 146.4, 144.8, 143.9 (q, $J$ = 38.0 Hz), 142.8, 140.3, 130.3, 129.8, 128.0, 126.8, 126.6, 122.4 (q, $J$ = 268.0 Hz), 106.7 (q, $J$ = 2.0 Hz), 21.2; **$^{19}$F NMR** (377 MHz, $(CD_3)_2CO$) $\delta_F$ -62.77 (s); **LRMS** (ESI, *m/z*) $[M-H]^-$ 380.0, $[M+H]^+$ 382.0 & $[M+Na]^+$ 404.0. The spectroscopic data is in agreement with literature.[318]

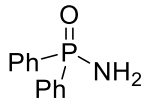
**Benzyl 4-chloro-2-((furan-2-ylmethyl)amino)-5-sulfamoylbenzoate (125d)**



Prepared according to the modified procedure from Lil *et al.*[113c] Under an atmosphere furosemide **95** (2.00 g, 6.00 mmol, 1.00 equiv.) was added to a round bottom flask equipped with a reflux condenser and dissolved in DMF (40 mL). To this solution was added of benzyl chloride (0.65 mL, 5.72 mmol, 0.95 equiv.) and $Et_3N$ (0.88 mL, 6.32 mmol, 1.05 equiv.) The mixture was stirred at 80 °C for 12 h and allowed to cool to room temperature. The mixture was diluted with $CH_2Cl_2$ (80 mL) and washed with $H_2O$ (80 mL), sat. $NH_4Cl$ (80 mL), then dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (*n*-hexane:EtOAc, 1:4 to 2:3) afforded the title compound (2.08 g, 86%) as an off-white solid.

**MP** (*n*-hexane/EtOAc) 90-92 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2SO$) $\delta_H$ 8.55 – 8.50 (m, 2H, Ar*H*, $CH_2NHAr$), 7.62 (d, *J* = 2.0 Hz, 1H, HetAr*H*), 7.47 – 7.33 (m, 7H, $SO_2NH_2$, 5 × Ph*H*), 7.14 (s, 1H, Ar*H*), 6.43 (dd, *J* = 3.5, 2.0 Hz, 1H, HetAr*H*), 6.40 (d, *J* = 3.5 Hz, 1H, HetAr*H*), 5.37 (s, 2H, $CO_2CH_2Ph$), 4.62 (d, *J* = 6.0 Hz, 2H, HetAr$CH_2$NH); **$^{13}$C NMR** (101 MHz, $(CD_3)_2SO$) $\delta_C$ 166.3, 152.3, 151.2, 142.8, 136.9, 135.9, 133.0, 128.6, 128.3, 128.1, 127.2, 114.0, 110.6, 107.8, 107.2, 66.3, 39.3; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 443.0. The spectroscopic data is in agreement with literature.[113c]

***P,P*-diphenylphosphinic amide (126)**



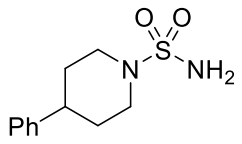
Prepared according to the modified procedure from Jennings *et al.*[319] Diphenylphosphinic acid (897 mg, 4.11 mmol, 1.0 equiv.) was added to a round bottom flask and dissolved in toluene (10 mL).

Thionyl chloride (0.6 mL, 8.22 mmol, 2.0 equiv.) was added by slow dropwise addition. The resulting suspension was stirred at 80 °C for 3 h. After cooling to room temperature, the solvent and excess thionyl chloride were removed under reduced pressure. The residue was re-dissolved in toluene (25 mL) and evaporated to give the corresponding phosphinic chloride, which was used in the next step without further purification.

The phosphinic chloride was dissolved in THF (11 mL), followed by the slow dropwise addition of aqueous ammonium hydroxide (0.56 mL). The resulting suspension was filtered, and the filtrate was washed with water (10 mL) and extracted with $CH_2Cl_2$ (10 mL). The solvent was removed under reduced pressure, affording the title compound 466.7 mg (467 mg, 52%) as a colourless solid.

**MP** ($CH_2Cl_2$) 148-150 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.94 – 7.83 (m, 4H, 4 × Ph*H*), 7.51 – 7.43 (m, 2H, 2 × Ph*H*), 7.44 – 7.35 (m, 4H, 4 × Ph*H*), 3.34 (s, 3H, N*H*$_2$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 133.5 (d, $J$ = 130.0 Hz), 131.9 (d, $J$ = 3.5 Hz), 131.9 (d, $J$ = 9.5 Hz), 128.6 (d, $J$ = 12.5 Hz); **$^{31}$P NMR** (162 MHz, $CDCl_3$) $\delta_P$ 22.43 (s); **LRMS** (ESI, *m/z*) $[M+H]^+$ 218.0 & $[M+Na]^+$ 240.0. The spectroscopic data is in agreement with literature.[320]

**4-Phenylpiperidine-1-sulfonamide (127)**



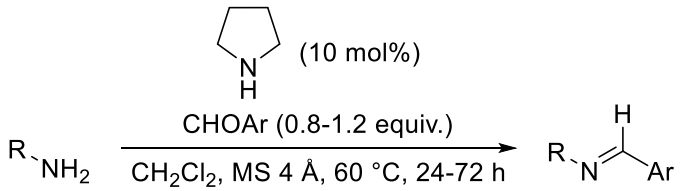

Prepared according to the modified procedure from Jennings *et al.*[321] Under and atmosphere of air, 4-phenylpiperidine amine (645 mg, 4.0 mmol, 1.0 equiv.) and sulfamide (422 mg, 4.4 mmol, 1.1 equiv.) were added to a round bottom flask equipped with a reflux condenser and dissolved in in 1,4-dioxane (30 mL). The resulting suspension was refluxed at 100 °C for 2 h and then cooled to room temperature, and the solvent removed under reduced pressure. Purification by flash column

chromatography (Petrol:EtOAc, 1:4) afforded the title compound (359 mg, 75%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 160-162 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2CO$) $\delta_H$ 7.36 – 7.25 (m, 4H, 4 × Ph*H*), 7.24 – 7.16 (m, 1H, Ph*H*), 3.74 (app. ddt, *J* = 11.5, 4.0, 2.0 Hz, 2H, 2 × NC$H_A$$H_B$$CH_2$) 2.75 (app. td, *J* = 12.0, 2.0 Hz, 2H, 2 × NC$H_A$$H_B$$CH_2$), 2.64 (tt, *J* = 12.0, 4.0 Hz, 1H, PhC*H*$(CH_2)_2$), 1.96 – 1.86 (m, 2H, 2 × $NCH_2$C$H_A$$H_B$), 1.78 (app. qd, *J* = 13.0, 4.0 Hz, 2H, 2 × $NCH_2CH_A$$H_B$). (Note: $SO_2NH_2$ peak not observed); **$^{13}$C NMR** (101 MHz, $(CD_3)_2CO$) $\delta_C$ 146.4, 129.1, 127.4, 126.9, 47.5, 42.4, 33.1: **LRMS** (ESI, *m/z*) $[M-H]^-$ 239.0; **HRMS** (ESI, *m/z*) calculated for $(C_{11}H_{15}N_2O_2S)^-$ 239.0860 $[M-H]^-$, found 239.0859; **IR** (thin film, $\nu_{max}$/$cm^{-1}$) 3370, 3274, 2160, 2029, 1543.23 1468, 1358, 1248, 1166, 1094, 934, 883, 765, 722, 701, 641; **$R_f$** 0.47 (*n*-hexane:EtOAc, 1:1).

### 6.5.1.2. Condensation Reactions

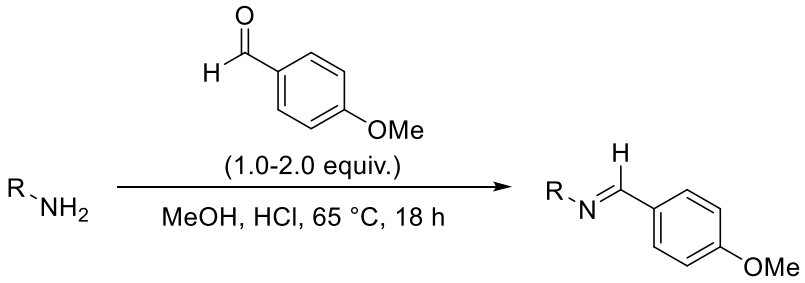
**General Procedure G**




**General Procedure G**: Aldehyde and an amino reagent condensation utilising pyrrolidine as a catalyst.

Modified procedure from Morales *et al.*[263h] The amino compound (1.0 equiv.) and 4 Å molecular sieves (1g mmol$^{-1}$) were added to an appropriate reaction vessel and $CH_2Cl_2$ (0.32 M) was added. The corresponding aldehyde (0.8-1.2 equiv.) and pyrrolidine (10 mol%) were added and the resulting suspension was refluxed at 60 °C, either with a reflux condenser equipped or in a sealed vial. The reaction was stirred for 24-72 h and cooled to room temperature, then filtered through a short pad of Celite®, whilst washing with $CH_2Cl_2$. The solvent was removed from the filtrate under reduced pressure and the crude product was purified by crystallisation in $Et_2O$ and washing with *n*-hexane.

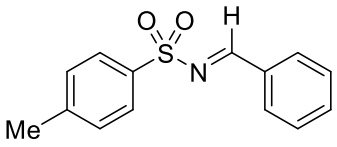
**General Procedure H**




**General Procedure H**: 4-methoxylbenzaldehyde and an amino reagent condensation utilising HCl as a catalyst.

Modified procedure from Pansare *et al.*[322] Under an atmosphere of air the amino compound (1.0 equiv.) was added to a round bottom flask equipped with a reflux condenser and MeOH (1.0-0.7 M) was added. 4-Methoxybenzaldehyde (1.0-2.0 equiv.) and conc. HCl (20%) were added and the resulting suspension was refluxed at 65 °C for 18 h, then the reaction was cooled to room temperature and the solvent removed under reduced pressure. The crude product was purified by washing with an appropriate solvent.

***N*-benzylidene-4-methylbenzenesulfonamide (108a)**

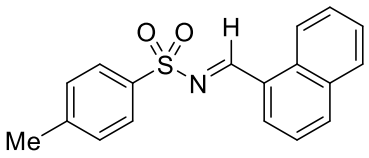



Prepared according to general procedure G, using 4-methylbenzenesulfonamide (1.71 g, 10.0 mmol, 1.0 equiv.), benzaldehyde (1.22 mL, 12.0 mmol, 1.2 equiv.) and pyrrolidine (83 μL, 1.0 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (1.74 g, 67%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 99-101 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.03 (s, 1H, N*H*C), 7.97 – 7.83 (m, 4H, 2 × *p*-MeAr*H*, 2 × Ph*H*), 7.65 – 7.55 (m, 1H, Ph*H*), 7.52 – 7.43 (m, 2H, 2 × Ph*H*), 7.34 (d, *J* = 8.0 Hz, 2H 2 × *p*-MeAr*H*), 2.43 (s, 3H, Ar$CH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 170.2, 144.7,

135.2, 135.0, 132.5, 131.4, 129.9, 129.2, 128.2, 21.7; **LRMS** (ESI, *m/z*) $[M+H]^+$ 260.0 & $[M+Na]^+$ 282.0. The spectroscopic data is in agreement with literature.[323]

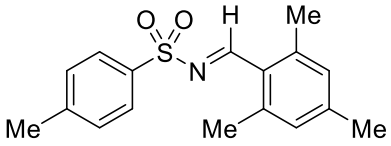
**4-Methyl-*N*-(naphthalen-1-ylmethylene)benzenesulfonamide (108ab)**



Prepared according to general procedure G, using 4-methylbenzenesulfonamide (171 mg, 1.0 mmol, 1.0 equiv.), 1-naphthaldehyde (0.16 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (211 mg, 68%) as a pale-yellow solid.

**MP** (*n*-hexane/$Et_2O$) 120-122 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.61 (s, 1H, N*H*C), 8.98 (app. dq, *J* = 8.5, 1.0 Hz, 1H, Ar*H*), 8.14 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 8.09 (app. dt, *J* = 8.5, 1.0 Hz, 1H, Ar*H*), 7.95 (d, *J* = 8.5 Hz, 2H, 2 × *p*-MeAr*H*), 7.91 (dd, *J* = 8.0, 0.5 Hz, 1H, Ar*H*), 7.67 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, Ar*H*), 7.62 – 7.55 (m, 2H, 2 × Ar*H*), 7.35 (d, *J* = 8.5 Hz, 2H, 2 × *p*-MeAr*H*), 2.43 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 169.9, 144.6, 136.2, 135.6, 135.3, 133.9, 132.0, 130.0, 129.2, 129.0, 128.2, 127.8, 127.1, 125.2, 124.4, 21.8; **LRMS** (ESI, *m/z*) $[M+H]^+$ 310.0 & $[M+Na]^+$ 332.0. The spectroscopic data is in agreement with literature.[324]

**4-methyl-*N*-(2,4,6-trimethylbenzylidene)benzenesulfonamide (108ac)**

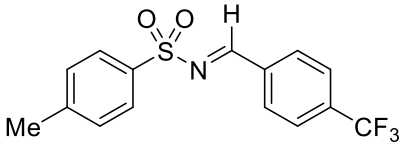


Prepared according to general procedure G, using 4-methylbenzenesulfonamide (171 mg, 1.0 mmol, 1.0 equiv.), 2,4,6-trimethylbenzaldehyde (0.18 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine

(9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (216 mg, 72%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 84-86 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.50 (s, 1H, N*H*C), 7.88 (d, *J* = 8.5 Hz, 2H, 2 × *p*-MeAr*H*), 7.33 (d, *J* = 8.5 Hz, 2H, 2 × *p*-MeAr*H*), 6.92 (s, 2H, 2 × Ar*H*), 2.53 (s, 6H, 2 × ArC$H_3$), 2.44 (s, 3H, CC$H_3$), 2.31 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 169.2, 144.7, 144.3, 143.1, 130.8, 129.8, 128.0, 126.6, 126.3, 21.9, 21.8, 21.7; **LRMS** (ESI, *m/z*) $[M+H]^+$ 302.0 & $[M+Na]^+$ 324.0; **HRMS** (ESI, *m/z*) calculated for $(C_{17}H_{20}NO_2S)^+$ 302.1209 $[M+H]^+$, found 302.1209; **IR** ($CHCl_3$, $\nu_{max}$/$cm^{-1}$) 1589, 1555, 1304, 1088, 1035, 831, 815, 772, 724, 705, 635; **$R_f$** 0.75 (*n*-hexane:EtOAc, 3:2).

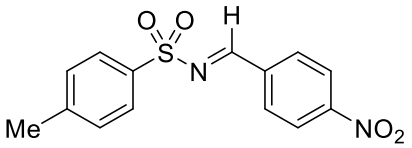
**4-methyl-*N*-(4-(trifluoromethyl)benzylidene)benzenesulfonamide (108ad)**




Prepared according to general procedure G, using 4-methylbenzenesulfonamide (171 mg, 1.0 mmol, 1.0 equiv.), 4-(trifluoromethyl)benzaldehyde (0.16 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (232 mg, 71%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 146-148 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.07 (s, 1H, N*H*C), 8.03 (d, *J* = 8.0 Hz, 2H, 2 × *p*-$CF_3$Ar*H*), 7.89 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 7.72 (d, *J* = 8.0 Hz, 2H, 2 × *p*-$CF_3$Ar*H*), 7.35 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 2.42 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 168.5, 145.1, 135.4, 135.7 (q, *J* = 33.0 Hz), 134.5, 131.4, 130.0, 128.3 126.1 (q, *J* = 4.0 Hz), 123.4 (q, *J* = 273.0 Hz), 21.7; **$^{19}$F NMR** (377 MHz, $CDCl_3$) $\delta_F$ -63.28 (s); **LRMS** (ESI, *m/z*) $[M+Na]^+$ 350.0. The spectroscopic data is in agreement with literature.[323]

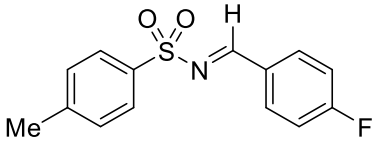
**4-methyl-*N*-(4-nitrobenzylidene)benzenesulfonamide (108ae)**



Prepared according to general procedure G, using 4-methylbenzenesulfonamide (188 mg, 1.1 mmol, 1.1 equiv.), 4-nitrobenzaldehyde (94 mg, 1.0 mmol, 1.0 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (193 mg, 63%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 185-187 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.10 (s, 1H, N*H*C), 8.32 (d, *J* = 9.0 Hz, 2H, 2 × *p*-$NO_2$Ar*H*), 8.11 (d, *J* = 9.0 Hz, 2H, 2 × *p*-$NO_2$Ar*H*), 7.90 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 7.38 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 2.46 (s, 3H, Ar$CH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 167.5, 151.3, 145.5, 137.6, 134.3, 132.0, 130.2, 128.5, 124.3, 21.9; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 327.0. The spectroscopic data is in agreement with literature.[323]

***N*-(4-fluorobenzylidene)-4-methylbenzenesulfonamide (108af)**

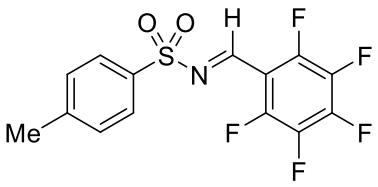


Prepared according to general procedure G, using 4-methylbenzenesulfonamide (171 mg, 1.0 mmol, 1.0 equiv.), 4-fluorobenzaldehyde (0.13 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (92 mg, 33%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 98-100 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.00 (s, 1H, N*H*C), 8.00 – 7.91 (m, 2H, 2 × *p*-FAr*H*), 7.88 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 7.35 (d, *J* = 8.0 Hz, 1H, 2 × *p*-MeAr*H*), 7.23 – 7.13 (m, 2H, 2 × *p*-FAr*H*), 2.44 (s, 3H, Ar$CH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 168.7, 167.0

(d, $^{1}J_{CF}$ = 258.5 Hz), 144.8, 135.2, 133.9 (d, $^{3}J_{CF}$ = 10.0 Hz), 130.0, 128.9 (d, $^{4}J_{CF}$ = 3.0 Hz), 128.2, 116.8 (d, $^{2}J_{CF}$ = 22.5 Hz), 21.8; **$^{19}$F NMR** (377 MHz, $CDCl_3$) $\delta_F$ -101.08 (tt, *J* = 8.5, 5.5 Hz); **LRMS** (ESI, *m/z*) [M+Na]$^+$ 300.0. The spectroscopic data is in agreement with literature.[323]

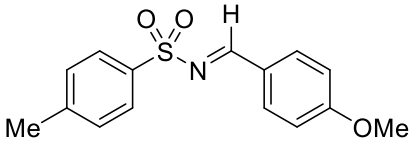
**4-methyl-*N*-((perfluorophenyl)methylene)benzenesulfonamide (108ag)**




Prepared according to general procedure G, using 4-methylbenzenesulfonamide (171 mg, 1.0 mmol, 1.0 equiv.), 2,3,4,5,6-pentafluorobenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (79 mg, 23%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 127-129 °C; **$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.19 (s, 1H, N*H*C), 7.87 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 7.36 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 2.45 (s, 3H, ArC$H_3$). **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 158.7, 149.9 – 145.8 (m) 147.2 – 142.7 (m), 145.6, 140.3 – 135.7 (m), 134.0, 130.1, 128.5, 108.6 – 108.0 (m), 21.8. **$^{19}$F NMR** (377 MHz, $CDCl_3$) $\delta_F$ -135.68 – -136.29 (m), -141.57 – -144.61 (m), -159.04 – -161.46 (m). **LRMS** (ESI, *m/z*) [M+K]$^+$ 388.0. The spectroscopic data is in agreement with literature.[325]

***N*-(4-methoxybenzylidene)-4-methylbenzenesulfonamide (108ah)**

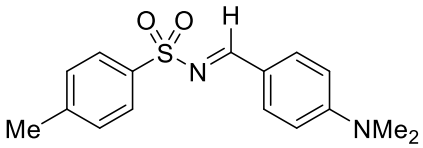



Prepared according to general procedure G, using 4-methylbenzenesulfonamide (5.14 g, 30.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (3.65 mL, 36.0 mmol, 1.2 equiv.) and pyrrolidine

(0.25 mL, 3.0 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (6.85 g, 79%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 116-118 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.93 (s, 1H, N*H*C), 7.91 – 7.82 (m, 4H, 2 × *p*-OMeAr*H*, 2 × *p*-MeAr*H*), 7.32 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 6.95 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.87 (s, 3H, OC$H_3$), 2.41 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 169.3, 165.4, 144.4, 135.8, 133.8, 129.8, 128.0, 125.3, 114.8, 55.8, 21.7; **LRMS** (ESI, *m/z*) $[M+H]^+$ 290.0 & $[M+Na]^+$ 312.0. The spectroscopic data is in agreement with literature.[323]

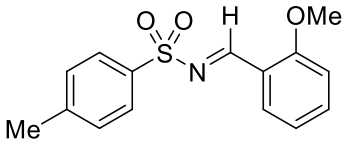
***N*-(4-(dimethylamino)benzylidene)-4-methylbenzenesulfonamide (108ai)**




Prepared according to general procedure G, using 4-methylbenzenesulfonamide (171 mg, 1.0 mmol, 1.0 equiv.), 4-(dimethylamino)benzaldehyde (0.13 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 µL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (232 mg, 77%) as a bright yellow solid.

**MP** (*n*-hexane/$Et_2O$) 165-167 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.80 (s, 1H, N*H*C), 7.85 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 7.76 (d, *J* = 9.0 Hz, 2H, 2 × *p*-$NMe_2$Ar*H*), 7.29 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 6.64 (d, *J* = 9.0 Hz, 2H, 2 × *p*-$NMe_2$Ar*H*), 3.08 (s, 6H, N($CH_3$)$_2$), 2.40 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 169.1, 155.0, 143.6, 137.0, 134.1, 129.7, 127.7, 119.9, 111.4, 40.2, 21.7; **LRMS** (ESI, *m/z*) $[M+H]^+$ 303.0 & $[M+Na]^+$ 325.0. The spectroscopic data is in agreement with literature.[274]

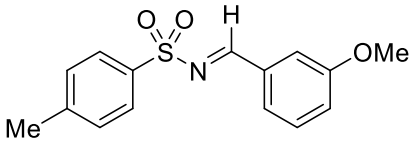
**N-(2-methoxybenzylidene)-4-methylbenzenesulfonamide (108aj)**




Prepared according to general procedure G, using 4-methylbenzenesulfonamide (171 mg, 1.0 mmol, 1.0 equiv.), 2-methoxybenzaldehyde (0.14 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (150 mg, 52%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 97-99 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.55 (s, 1H, N*H*C), 8.05 (dd, *J* = 8.0, 2.0 Hz, 1H, *o*-OMeAr*H*), 7.88 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 7.55 (ddd, *J* = 9.0, 7.5, 2.0 Hz, 1H, *o*-OMeAr*H*), 7.32 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 7.02 – 6.92 (m, 2H, 2 × *o*-OMeAr*H*), 3.92 (s, 3H, OC$H_3$), 2.42 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 166.5, 161.9, 144.4, 137.0, 135.9, 129.8, 129.5, 128.1, 121.1, 121.0, 111.6, 55.9, 21.8; **LRMS** (ESI, *m/z*) $[M+H]^+$ 290.0 & $[M+Na]^+$ 312.0. The spectroscopic data is in agreement with literature.[323]

**N-(3-methoxybenzylidene)-4-methylbenzenesulfonamide (108ak)**

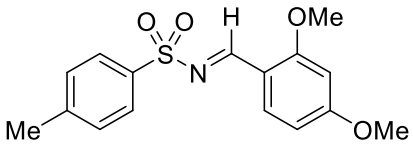



Prepared according to general procedure G, using 4-methylbenzenesulfonamide (171 mg, 1.0 mmol, 1.0 equiv.), 3-methoxybenzaldehyde (0.14 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h. Purification by flash column chromatography (*n*-hexane:EtOAc, 1:0 to 1:4), afforded the title compound (170 mg, 59%) as a yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.88 (s, 1H, N*H*C), 7.78 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 7.38 – 7.32 (m, 2H, 2 × *m*-OMeAr*H*), 7.37 (app. t, *J* = 8.0 Hz, 1H, *m*-OMeAr*H*), 7.24 (d, *J* = 8.0 Hz, 2H,

2 × *p*-MeAr*H*), 7.05 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, *m*-OMeAr*H*), 3.72 (s, 3H, OC$H_3$), 2.33 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 170.3, 160.2, 144.8, 135.3, 133.8, 130.2, 130.0, 128.3, 125.5, 122.3, 113.5, 55.7, 21.8; **LRMS** (ESI, *m/z*) $[M+H]^+$ 290.0 & $[M+Na]^+$ 312.0. The spectroscopic data is in agreement with literature.[323]

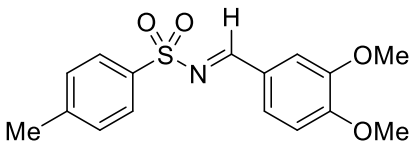
**N-(2,4-dimethoxybenzylidene)-4-methylbenzenesulfonamide (108al)**




Prepared according to general procedure G, using 4-methylbenzenesulfonamide (171 mg, 1.0 mmol, 1.0 equiv.), 2,4-dimethoxybenzaldehyde (0.18 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (264 mg, 83%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 141-143 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.41 (s, 1H, N*H*C), 8.03 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.86 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 7.30 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 6.51 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar*H*), 6.40 (d, *J* = 2.5 Hz, 1H, Ar*H*), 3.89 (s, 3H, OC$H_3$), 3.87 (s, 3H, OC$H_3$), 2.41 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 167.5, 165.6, 163.8, 144.0, 136.5, 131.6, 129.7, 127.9, 114.5, 106.9, 97.7, 55.9 (2 × C), 21.7; **LRMS** (ESI, *m/z*) $[M+H]^+$ 320.0. The spectroscopic data is in agreement with literature.[326]

**N-(2,4-dimethoxybenzylidene)-4-methylbenzenesulfonamide (108am)**

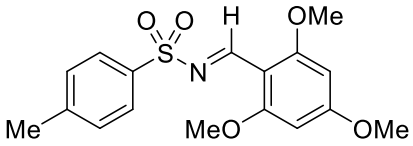



Prepared according to general procedure G, using 4-methylbenzenesulfonamide (171 mg, 1.0 mmol, 1.0 equiv.), 3,4-dimethoxybenzaldehyde (0.18 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine

(9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (147 mg, 46%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 96-98 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.91 (s, 1H, N*H*C), 7.88 (d, *J* = 8.5 Hz, 2H, 2 × *p*-MeAr*H*), 7.51 (d, *J* = 2.0 Hz, 1H, Ar*H*), 7.43 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar*H*), 7.34 (d, *J* = 7.7 Hz, 2H, 2 × *p*-MeAr*H*), 6.93 (d, *J* = 8.5 Hz, 1H, Ar*H*), 3.96 (s, 3H, OC$H_3$), 3.91 (s, 3H, OC$H_3$), 2.43 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 169.6, 155.4, 149.8, 144.4, 135.8, 129.9, 129.3, 128.1, 125.7, 110.7, 110.4, 56.4, 56.2, 21.8; **LRMS** (ESI, *m/z*) $[M+H]^+$ 320.0. The spectroscopic data is in agreement with literature.[324]

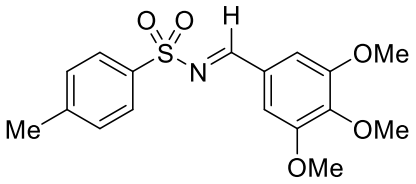
**4-methyl-*N*-(2,4,6-trimethoxybenzylidene)benzenesulfonamide (108an)**




Prepared according to general procedure G, using 4-methylbenzenesulfonamide (171 mg, 1.0 mmol, 1.0 equiv.), 2,4,6-trimethoxybenzaldehyde (235 mg, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (246 mg, 71%) as an off-white solid.

**MP** (*n*-hexane/$Et_2O$) 146-148 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.43 (s, 1H, N*H*C), 7.86 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 7.28 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 6.04 (s, 2H, 2 × Ar*H*), 3.86 (s, 3H, OC$H_3$), 3.85 (s, 6H, OC$H_3$), 2.40 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_H$ 167.6, 164.5 (2 × C), 143.4, 137.2, 129.6, 127.8, 104.5, 90.6, 56.2, 55.8, 21.7; **LRMS** (ESI, *m/z*) $[M+H]^+$ 350.0 & $[M+Na]^+$ 372.0. The spectroscopic data is in agreement with literature.[263i]

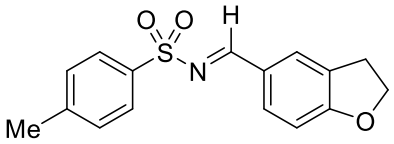
**4-methyl-*N*-(3,4,5-trimethoxybenzylidene)benzenesulfonamide (108ao)**



Prepared according to general procedure G, using 4-methylbenzenesulfonamide (171 mg, 1.0 mmol, 1.0 equiv.), 3,4,5-trimethoxybenzaldehyde (235 mg, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (192 mg, 55%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 105-107 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.91 (s, 1H, NHC), 7.87 (d, $J$ = 8.0 Hz, 2H, 2 × *p*-MeArH), 7.34 (d, $J$ = 8.0 Hz, 2H, 2 × *p*-MeArH), 7.16 (s, 2H, 2 × ArH), 3.93 (s, 3H, $OCH_3$), 3.89 (s, 6H, 2 × $OCH_3$), 2.43 (s, 3H, $ArCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 169.9, 153.6, 144.6, 144.4, 135.5, 129.9, 128.2, 127.5, 108.7, 61.2, 56.5, 21.8; **LRMS** (ESI, *m/z*) $[M+H]^+$ 372.0; **HRMS** (ESI, *m/z*) calculated for $(C_{17}H_{20}NO_5S)^+$ 350.1057 $[M+H]^+$, found 350.1053; **IR** ($CHCl_3$, $\nu_{max}$/$cm^{-1}$) 1598, 1569, 1501, 1457, 1418, 1369, 1317, 1237, 1185, 1157, 1127, 1089, 1002, 826, 782, 697, 666, 619; **$R_f$** 0.33 (*n*-hexane:EtOAc, 3:2).

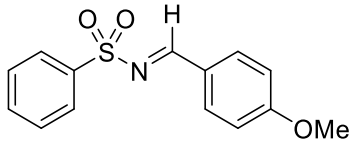
***N*-((2,3-dihydrobenzofuran-5-yl)methylene)-4-methylbenzenesulfonamide (108ap)**



Prepared according to general procedure G, using 4-methylbenzenesulfonamide (342 mg, 2.0 mmol, 1.0 equiv.), 2,3-dihydrobenzofuran-5-carbaldehyde (0.32 mL, 2.4 mmol, 1.2 equiv.) and pyrrolidine (18 μL, 0.2 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (360 mg, 60%) as a pale-yellow solid.

**MP** (*n*-hexane/$Et_2O$) 116-118 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.90 (s, 1H, N*H*C), 7.86 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 7.84 (app. q, *J* = 1.5 Hz, 1H, Ar*H*), 7.67 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar*H*), 7.32 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 6.84 (d, *J* = 8.5 Hz, 1H, Ar*H*), 4.68 (t, *J* = 9.0 Hz, 2H, OC$H_2$), 3.23 (td, *J* = 8.0, 1.5 Hz, 2H, ArC$H_2$), 2.42 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 169.4, 166.6, 144.3, 136.1, 135.0, 129.8, 129.1, 128.0, 127.6, 125.6, 110.2, 72.8, 28.8, 21.8; **LRMS** (ESI, *m/z*) $[M+H]^+$ 302.0 & $[M+Na]^+$ 324.0; **HRMS** (ESI, *m/z*) calculated for $(C_{16}H_{16}NO_3S)^+$ 302.0845 $[M+H]^+$, found 302.0841; **IR** ($CHCl_3$, $\nu_{max}$/$cm^{-1}$) 1563, 1492, 1446, 1317, 1253, 1154, 1087, 1019, 981, 936, 834, 804, 765, 706, 674; **$R_f$** 0.38 (*n*-hexane:EtOAc, 3:2).

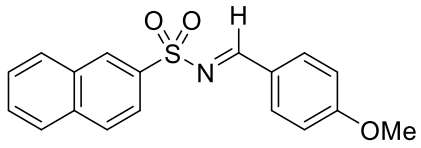
***N*-(4-methoxybenzylidene)benzenesulfonamide (108b)**




Prepared according to general procedure G, using benzenesulfonamide (157 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (142 mg, 52%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 102-104 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.97 (s, 1H, N*H*C), 8.03 – 7.96 (m, 2H, 2 × Ph*H*), 7.89 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.65 – 7.57 (m, 1H, Ph*H*), 7.57 – 7.49 (m, 2H, 2 × Ph*H*), 6.97 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.88 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 169.8, 165.5, 139.0, 134.0, 133.4, 129.2, 128.0, 125.3, 114.9, 55.8; **LRMS** (ESI, *m/z*) $[M+H]^+$ 276.0 & $[M+Na]^+$ 298.0. The spectroscopic data is in agreement with literature.[327]

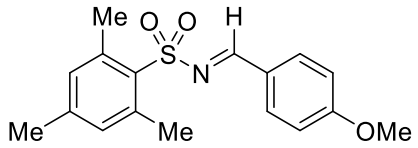
***N*-(4-methoxybenzylidene)naphthalene-2-sulfonamide (108c)**




Prepared according to general procedure G, using naphthalene-2-sulfonamide (**110c**) (207 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 µL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (255 mg, 78%) as a pale-yellow solid.

**MP** (*n*-hexane/$Et_2O$) 98-100 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.02 (s, 1H, N*H*C), 8.59 (s, 1H, Ar*H*), 8.02 – 7.93 (m, 3H, Ar*H*), 7.93 – 7.87 (m, 3H, 2 × *p*-OMeAr*H*, Ar*H*), 7.69 – 7.56 (m, 2H, 2 × Ar*H*), 6.96 (d, $J$ = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.88 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 169.7, 165.5, 135.8, 135.3, 134.0, 132.3, 129.5, 129.5 (2 × C), 129.2, 128.1, 127.7, 125.4, 123.1, 114.9, 55.8; **LRMS** (ESI, *m/z*) $[M+H]^+$ 326.0 & $[M+Na]^+$ 348.0. The spectroscopic data is in agreement with literature.[273]

***N*-(4-methoxybenzylidene)-2,4,6-trimethylbenzenesulfonamide (108d)**

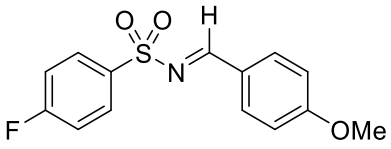



Prepared according to general procedure G, using 2,4,6-trimethylbenzenesulfonamide (**110d**) (200 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 µL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (245 mg, 76%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 112-114 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.94 (s, 1H, N*H*C), 7.87 (d, $J$ = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.00 – 6.93 (m, 4H, 2 × *p*-OMeAr*H*, 2 × Ar*H*), 3.88 (s, 3H, OC$H_3$),

2.70 (s, 6H, 2 × ArC$H_3$), 2.30 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 168.1, 165.2, 143.1, 140.2, 133.7, 132.8, 132.0, 125.6, 114.8, 55.8, 23.2, 21.2; **LRMS** (ESI, *m/z*) $[M+H]^+$ 318.0 & $[M+Na]^+$ 340.0; **HRMS** (ESI, *m/z*) calculated for $(C_{17}H_{20}NO_3S)^+$ 318.1158 $[M+H]^+$, found 318.1156; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1588, 1561, 1512, 1425, 1314, 1260, 1150, 1056, 1025, 836, 800, 761, 666; **$R_f$** 0.69 (*n*-hexane:EtOAc, 3:2).

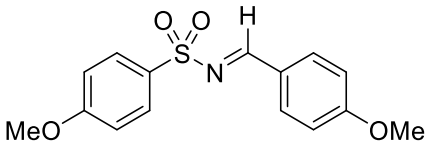
**4-Fluoro-*N*-(4-methoxybenzylidene)benzenesulfonamide (108e)**




Prepared according to general procedure G, using 4-fluorobenzenesulfonamide (1.75 g, 10.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (1.5 mL, 12.0 mmol, 1.2 equiv.) and pyrrolidine (82 μL, 1.0 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (2.05 g, 70%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 108-110 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.96 (s, 1H, NC*H*), 8.06 – 7.96 (m, 2H, 2 × *p*-FAr*H*), 7.89 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.25 – 7.16 (m, 2H, 2 × *p*-FAr*H*), 6.98 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.89 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 169.8, 165.7 (d, $^1J_{CF}$ = 255.5 Hz), 165.7, 135.1 (d, $^4J_{CF}$ = 2.5 Hz), 134.0, 130.8 (d, $^3J_{CF}$ = 9.5 Hz), 125.2, 116.5 (d, $^2J_{CF}$ = 22.7 Hz), 114.9, 55.9; **$^{19}$F NMR** (377 MHz, $CDCl_3$) $\delta_F$ -104.24 (tt, *J* = 8.5, 5.5 Hz); **LRMS** (ESI, *m/z*) $[M+Na]^+$ 316.0; **HRMS** (ESI, *m/z*) calculated for $(C_{14}H_{13}FNO_3S)^+$ 294.0595 $[M+H]^+$, found 294.0593; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1587, 1557, 1512, 1494, 1426, 1367, 1291, 1261, 1151, 1086, 1023, 834 802, 764, 675; **$R_f$** 0.30 (*n*-hexane:EtOAc, 3:2).

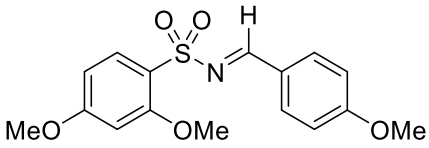
**4-Methoxy-*N*-(4-methoxybenzylidene)benzenesulfonamide (108f)**




Prepared according to general procedure G, using 4-methoxybenzenesulfonamide (187 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (171 mg, 56%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 83-85 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.91 (s, 1H, N*H*C), 7.92 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.87 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 6.99 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 6.96 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.87 (s, 3H, OC$H_3$), 3.86 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 168.8, 165.3, 163.6, 133.8, 130.3, 130.2, 125.4, 114.8, 114.5, 55.8 (2× C); **LRMS** (ESI, *m/z*) $[M+H]^+$ 306.0; **HRMS** (ESI, *m/z*) calculated for $(C_{15}H_{16}NO_4S)^+$ 306.0795 $[M+H]^+$, found 306.0791; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1592, 1561, 1513, 1499, 1318, 1259, 1150, 1090, 1023, 835, 810, 762, 674; **$R_f$** 0.25 (*n*-hexane:EtOAc, 3:2).

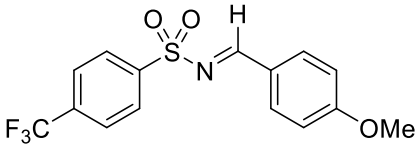
**2,4-Dimethoxy-*N*-(4-methoxybenzylidene)benzenesulfonamide (108g)**




Prepared according to general procedure G, using 2,4-dimethoxybenzenesulfonamide (**110g**) (217 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (207 mg, 62%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 136-138 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.99 (s, 1H, N*H*C), 8.01 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.89 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 6.97 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 6.58 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.43 (d, *J* = 2.5 Hz, 1H, Ar*H*), 3.87 (s, 3H, OC$H_3$), 3.84 (s, 3H, OC$H_3$), 3.77 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 171.3, 165.7, 165.2, 158.7, 133.7, 132.5, 125.6, 118.2, 114.8, 104.9, 99.5, 56.2, 55.9, 55.8; **LRMS** (ESI, *m/z*) $[M+H]^+$ 336.0 & $[M+Na]^+$ 358.0; **HRMS** (ESI, *m/z*) calculated for $(C_{16}H_{18}NO_5S)^+$ 336.0900 $[M+H]^+$, found 336.0896; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1590, 1561, 1513, 1464, 1424, 1306, 1259, 1214, 1159, 1139, 1074, 1023, 873, 836, 806, 764, 676, 611; **$R_f$** 0.38 (*n*-hexane:EtOAc, 2:3).

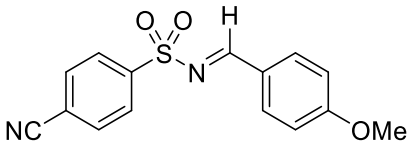
***N*-(4-methoxybenzylidene)-4-(trifluoromethyl)benzenesulfonamide (108h)**




Prepared according to general procedure G, using 4-(trifluoromethyl)benzenesulfonamide (**110h**) (225 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (148 mg, 43%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 119-121 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.00 (s, 1H, N*H*C), 8.13 (d, *J* = 8.5 Hz, 2H, 2 × *p*-$CF_3$Ar*H*), 7.91 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.80 (d, *J* = 8.5 Hz, 2H, 2 × *p*-$CF_3$Ar*H*), 6.99 (d, *J* = 9.0 Hz, 2H. 2 × *p*-OMeAr*H*), 3.90 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 170.8, 166.0, 142.7, 135.0 (d, $^2J_{CF}$ = 33.0 Hz), 134.3, 128.5, 126.3 (q, $^3J_{CF}$ = 4.0 Hz), 125.1, 123.3 (d, $^1J_{CF}$ = 273.0 Hz), 115.0, 55.9; **$^{19}$F NMR** (377 MHz, $CDCl_3$) $\delta_F$ -63.18 (s); **LRMS** (ESI, *m/z*) $[M+H]^+$ 344.0 & $[M+Na]^+$ 336.0; **HRMS** (ESI, *m/z*) calculated for $(C_{15}H_{13}F_3NO_3S)^+$ 344.0563 $[M+H]^+$, found 344.0558; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1589, 1557, 1513, 1426, 1405, 1321, 1264, 1158, 1108, 1062, 1020, 837, 809, 764, 712, 622; **$R_f$** 0.42 (*n*-hexane:EtOAc, 3:2).

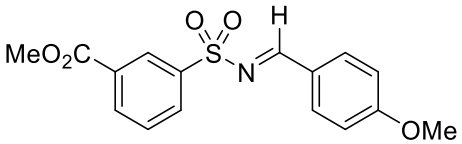
**4-Cyano-*N*-(4-methoxybenzylidene)benzenesulfonamide (108i)**



Prepared according to general procedure G, using 4-cyanobenzenesulfonamide (182 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (163 mg, 54%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 142-144 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.00 (s, 1H, N*H*C), 8.11 (d, *J* = 8.5 Hz, 2H, 2 × *p*-CNAr*H*), 7.91 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.83 (d, *J* = 8.5 Hz, 2H, 2 × *p*-CNAr*H*), 6.99 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.90 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 171.2, 166.1, 143.5, 134.4, 133.0, 128.6, 125.0, 117.4, 117.1, 115.1, 55.9; **LRMS** (ESI, *m/z*) $[M+H]^+$ 301.0 & $[M+Na]^+$ 323.0; **HRMS** (ESI, *m/z*) calculated for $(C_{15}H_{13}N_2O_3S)^+$ 301.0641 $[M+H]^+$, found 301.0643; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1587, 1556, 1513, 1462, 1321, 1264, 1154, 1087, 1021, 837, 813, 763, 650; **$R_f$** 0.20 (*n*-hexane:EtOAc, 3:2).

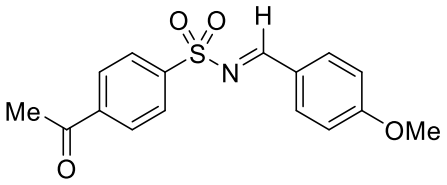
**Methyl 3-(*N*-(4-methoxybenzylidene)sulfamoyl)benzoate (108j)**



Prepared according to general procedure G, using methyl 3-sulfamoylbenzoate (124 mg, 0.6 mmol, 1.2 equiv.), 4-methoxybenzaldehyde (0.60 mL, 0.5 mmol, 1.0 equiv.) and pyrrolidine (5 μL, 0.05 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (40 mg, 24%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 108-110 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.00 (s, 1H, N*H*C), 8.64 (app. td, *J* = 2.0, 0.5 Hz, 1H, Ar*H*), 8.27 (app. dt, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 8.19 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar*H*), 7.90 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.63 (app. td, *J* = 8.0, 0.5 Hz, 1H, Ar*H*), 6.98 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.95 (s, 3H, $CO_2CH_3$), 3.89 (s, 3H, $OCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 170.4, 165.8, 165.6, 139.8, 134.3, 134.1, 132.0, 131.5, 129.5, 129.1, 125.2, 114.9, 55.9, 52.7; **LRMS** (ESI, *m/z*) $[M+H]^+$ 334.0 & $[M+Na]^+$ 356.0; **HRMS** (ESI, *m/z*) calculated for $(C_{16}H_{16}NO_5S)^+$ $[M+H]^+$, 334.0744 found 334.0743; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1727, 1589, 1561, 1513, 1426, 1305, 1266, 1156, 1123, 1023, 839, 807, 773, 753, 611; **$R_f$** 0.43 (*n*-hexane:EtOAc, 3:2).

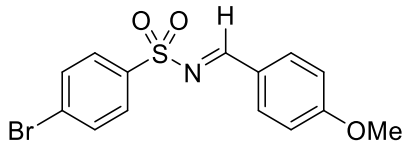
**4-Acetyl-*N*-(4-methoxybenzylidene)benzenesulfonamide (108k)**




Prepared according to general procedure G, 4-acetylbenzenesulfonamide (**110k**) (239 mg, 1.2 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.12 mL, 1.0 mmol, 1.0 equiv.) and pyrrolidine (9 µL, 0.1 mmol, 0.1 equiv.) with stirring for 48 h. Purification by flash column chromatography (*n*-hexane:EtOAc, 1:0 to 1:4), afforded the title compound (86 mg, 27%) as a yellow solid.

**MP** (*n*-hexane/EtOAc) 109-111 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.00 (s, 1H, N*H*C), 8.09 (app. s, 4H, 4 × Ar*H*), 7.90 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 6.98 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.89 (s, 3H, $OCH_3$), 2.65 (s, 3H, $COCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 196.9, 170.6, 165.9, 143.0, 140.6, 134.2, 129.0, 128.3, 125.2, 115.0, 55.9, 27.0; **LRMS** (ESI, *m/z*) $[M+H]^+$ 318.0 & $[M+Na]^+$ 340.0; **HRMS** (ESI, *m/z*) calculated for $(C_{16}H_{16}NO_4S)^+$ 318.0795 $[M+H]^+$, found 318.0796; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1689, 1588, 1557, 1513, 1361, 1319, 1260, 1155, 1090, 1022, 808, 778, 756, 647; **$R_f$** 0.16 (*n*-hexane:EtOAc, 3:2).

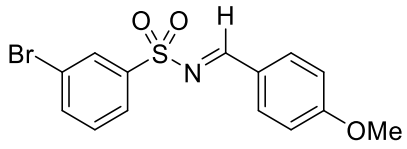
**4-Bromo-*N*-(4-methoxybenzylidene)benzenesulfonamide (108l)**




Prepared according to general procedure G, using 4-bromobenzenesulfonamide (**110l**) (236 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 µL, 0.05 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (233 mg, 66%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 115-117 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.96 (s, 1H, NC*H*), 7.89 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.86 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 7.67 (d, *J* = 8.5 Hz, 2H, 2 × Ar*H*), 6.98 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.89 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 170.1, 165.8, 138.1, 134.1, 132.5, 129.5, 128.6, 125.2, 114.9, 55.9; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 376.0, 378.0. The spectroscopic data is in agreement with literature.[328]

**3-Bromo-*N*-(4-methoxybenzylidene)benzenesulfonamide (108m)**

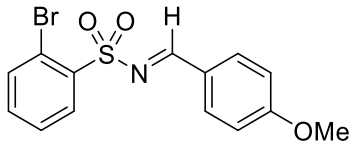



Prepared according to general procedure G, using 3-bromobenzenesulfonamide (**110m**) (236 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 µL, 0.05 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (55 mg, 16%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 79-81 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.97 (s, 1H, NC*H*), 8.13 (app. t, *J* = 2.0 Hz, 1H, Ar*H*), 7.97 – 7.85 (m, 3H, Ar*H*, 2 × *p*-OMeAr*H*), 7.73 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar*H*), 7.41 (app. t, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.90 (s, 3H, OC$H_3$);

**$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 170.5, 165.8, 140.9, 136.4, 134.2, 130.9, 130.7, 126.5, 125.2, 123.1, 115.0, 55.9; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 375.9, 377.9; **HRMS** (ESI, *m/z*) calculated for $(C_{14}H_{13}{}^{79}BrNO_3S)^+$ & $(C_{14}H_{13}{}^{81}BrNO_3S)^+$ 353.9794 & 355.9773 $[M+H]^+$, found 353.9792 & 355.9771 respectively; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1589, 1557, 1513, 1461, 1426, 1320, 1264, 1156, 1099, 1023, 873,, 837, 782, 753, 678, 658, 611; **R$_f$** 0.62 (*n*-hexane:EtOAc, 3:2).

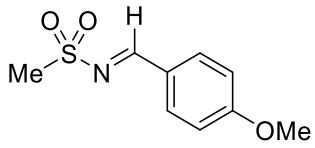
**2-Bromo-*N*-(4-methoxybenzylidene)benzenesulfonamide (108n)**




Prepared according to general procedure G, using 2-bromobenzenesulfonamide (**110n**) (236 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.05 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (113 mg, 32%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 102-104 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.13 (s, 1H, NC*H*), 8.33 (dd, *J* = 8.0, 2.0 Hz, 1H Ar*H*), 7.93 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.70 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 7.52 (app. td, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.43 (app. td, *J* = 7.5, 2.0 Hz, 1H, Ar*H*), 6.99 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.89 (s, 3H, OC*H*$_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 172.6, 165.8, 137.9, 135.4, 134.4, 134.2, 131.6, 128.0, 125.2, 121.2, 115.0, 55.9; **LRMS** (ESI, *m/z*) $[M+H]^+$ 354.0, 356.0 & $[M+Na]^+$ 376.0, 378.0; **HRMS** (ESI, *m/z*) calculated for $(C_{14}H_{13}BrNO_3S)^+$ 353.9794, 355.9773 $[M+H]^+$, found 353.9792, 355.9771; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1589, 1558, 1513, 1426, 1319, 1264, 1157, 1125, 1101, 1026, 837, 809, 770, 734, 607; **R$_f$** 0.60 (*n*-hexane:EtOAc, 3:2).

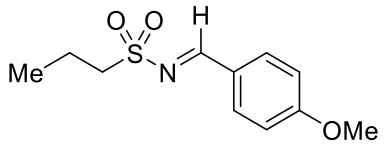
**N-(4-methoxybenzylidene)methanesulfonamide (108o)**




Prepared according to general procedure G, using methanesulfonamide (95 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.05 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (67 mg, 31%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 78-80 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.93 (s, 1H, N*H*C), 7.92 (d, $J$ = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.01 (d, $J$ = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.91 (s, 3H, OC$H_3$), 3.11 (s, 3H, $SO_2CH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 170.6, 165.6, 133.9, 125.1, 114.9, 55.9, 40.6; **LRMS** (ESI, *m/z*) $[M+H]^+$ 214.0 & $[M+Na]^+$ 236.0; **HRMS** (ESI, *m/z*) calculated for $(C_9H_{12}NO_3S)^+$ 214.0532 $[M+H]^+$, found 214.0533; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1593, 1566, 1514, 1426, 1306, 1261, 1139, 1022, 965, 810, 783, 741; **$R_f$** 0.16 (*n*-hexane:EtOAc, 3:2).

**N-(4-methoxybenzylidene)propane-1-sulfonamide (108p)**

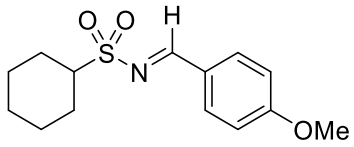



Prepared according to general procedure G, using propane-1-sulfonamide (**110p**) (123 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.0 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 48 h. Purification by flash column chromatography (*n*-hexane:EtOAc, 1:0 to 1:4), afforded the title compound (167 mg, 69%) as a pale-yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.87 (s, 1H, N*H*C), 7.87 (d, $J$ = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 6.97 (d, $J$ = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.86 (s, 3H, OC$H_3$), 3.19 – 3.08 (m, 2H, $SO_2CH_2$), 1.94 – 1.77

(m, 2H, $CH_2CH_2CH_3$), 1.04 (t, $J$ = 7.5 Hz, 3H, $(CH_2)_2CH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 170.9, 165.4, 133.7, 125.1, 114.8, 55.7, 54.3, 16.9, 13.0; **LRMS** (ESI, *m/z*) $[M+H]^+$ 242.2 & $[M+Na]^+$ 264.0; **HRMS** (ESI, *m/z*) calculated for $(C_{11}H_{16}NO_3S)^+$ 242.0845 $[M+H]^+$, found 242.0845; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1591, 1564, 1513, 1426, 1313, 1260, 1169, 1135, 1023, 766; **$R_f$** 0.32 (*n*-hexane:EtOAc, 3:2).

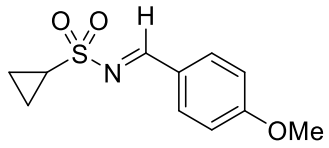
***N*-(4-methoxybenzylidene)cyclo*n*-hexanesulfonamide (108q)**




Prepared according to general procedure G, using cyclo*n*-hexanesulfonamide (**110q**) (392 mg, 2.4 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.38 mL, 2.9 mmol, 1.2 equiv.) and pyrrolidine (18 μL, 0.2 mmol, 0.1 equiv.) with stirring for 48 h, affording the title compound (211 mg, 31%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 88-90 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.93 (s, 1H, N*H*C), 7.92 (d, $J$ = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.00 (d, $J$ = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.91 (s, 3H, $OCH_3$), 3.06 (tt, $J$ = 12.0, 3.5 Hz, 1H, Cy*H*), 2.23 (ddd, $J$ = 12.0, 4.0, 2.0 Hz, 2H, 2 × Cy*H*), 1.90 (app. dq, $J$ = 13.0, 3.0 Hz, 2H, 2 × Cy*H*), 1.76 – 1.66 (m, 1H, Cy*H*), 1.56 (app. qd, $J$ = 12.0, 3.5 Hz, 2H, 2 × Cy*H*), 1.36 – 1.13 (m, 3H, 3 × Cy*H*); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 171.5, 165.4, 133.7, 125.4, 114.7, 60.9, 55.8, 26.8, 26.1, 25.3; **LRMS** (ESI, *m/z*) $[M+H]^+$ 304.0; **HRMS** (ESI, *m/z*) calculated for $(C_{14}H_{20}NO_3S)^+$ 282.1158 $[M+H]^+$, found 282.1157; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 2936, 2857, 1591, 1564, 1513, 1453, 1425, 1307, 1261, 1169, 1138, 1023, 827, 802, 776, 750, 622; **$R_f$** 0.68 (*n*-hexane:EtOAc, 3:2).

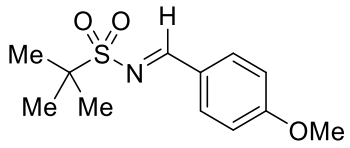
***N*-(4-methoxybenzylidene)cyclopropanesulfonamide (108r)**



Prepared according to general procedure G, using cyclopropanesulfonamide (**110r**) (217 mg, 2.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.30 mL, 2.4 mmol, 1.2 equiv.) and pyrrolidine (18 μL, 0.2 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (199 mg, 41%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 79-81 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.85 (s, 1H, N*H*C), 7.91 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 6.99 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.89 (s, 3H, O$CH_3$), 2.57 (tt, *J* = 8.0, 4.5 Hz, 1H, $(CH_2)_2CH$), 1.36 – 1.23 (m, 2H, $(CH_AH_B)_2CH$), 1.15 – 0.99 (m, 2H, $(CH_AH_B)_2CH$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 170.1, 165.4, 133.7, 125.2, 114.8, 55.8, 29.7, 6.0; **LRMS** (ESI, *m/z*) $[M+H]^+$ 240.0 & $[M+Na]^+$ 262.0; **HRMS** (ESI, *m/z*) calculated for $(C_{11}H_{14}NO_3S)^+$ 240.0689 $[M+H]^+$, found 240.0688; **IR** ($CHCl_3$, $\nu_{max}$/$cm^{-1}$) 1589, 1561, 1513, 1425, 1319, 1298, 1260, 1169, 1137, 1023, 887, 806, 768, 705; **$R_f$** 0.26 (*n*-hexane:EtOAc, 3:2).

***N*-(4-methoxybenzylidene)-2-methylpropane-2-sulfonamide (108s)**

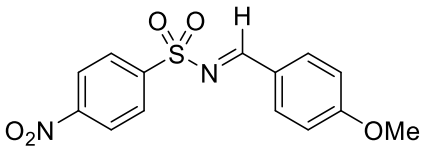


Prepared according to general procedure G, using *tert*-butylsulfonamide (137 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (145 mg, 57%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 74-76 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.88 (s, 1H, N*H*C), 7.88 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 6.96 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.85 (s, 3H, O$CH_3$), 1.43

(s, 9H, C($CH_3$)$_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 171.8, 165.3, 133.5, 125.3, 114.8, 58.2, 55.7, 24.1; **LRMS** (ESI, *m/z*) [M+Na]$^+$ 278.0. The spectroscopic data is in agreement with literature.[329]

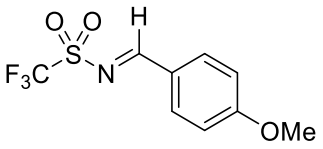
**_N_-(4-methoxybenzylidene)-4-nitrobenzenesulfonamide (108t)**



Prepared according to general procedure G, using 4-nitrobenzenesulfonamide (202 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (156 mg, 49%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 153-155 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.02 (s, 1H, N*H*C), 8.37 (d, *J* = 9.0 Hz, 2H, 2 × *p*-$NO_2$Ar*H*), 8.19 (d, *J* = 9.0 Hz, 2H, 2 × *p*-$NO_2$Ar*H*), 7.91 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 6.99 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.90 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 171.3, 166.2, 150.6, 145.0, 134.4, 129.3, 125.0, 124.4, 115.1, 55.9; **LRMS** (ESI, *m/z*) [M+Na]$^+$ 343.0. The spectroscopic data is in agreement with literature.[330]

**1,1,1-Trifluoro-_N_-(4-methoxybenzylidene)methanesulfonamide (108u)**

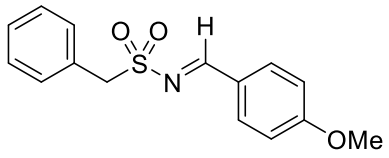


Prepared according to general procedure G, using trifluoromethanesulfonamide (358 mg, 2.4 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.24 mL, 2.0 mmol, 1.0 equiv.) and pyrrolidine (18 μL, 0.2 mmol, 0.1 equiv.) with stirring for 48 h, affording the title compound (229 mg, 50%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 62-64 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.02 (s, 1H, N*H*C), 8.02 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.06 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.95 (s, 3H, OC$H_3$);

**$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 178.4, 167.8, 135.8, 124.6, 119.40 (q, $^1J_{CF}$ = 321.5 Hz), 115.5, 56.1; **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta_F$ -77.01 (s). The spectroscopic data is in agreement with literature.[331]

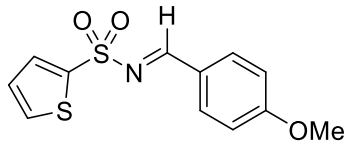
***N*-(4-methoxybenzylidene)-1-phenylmethanesulfonamide (108v)**




Prepared according to general procedure G, using phenylmethanesulfonamide (205 mg, 1.2 mmol, 1.2 equiv.), 4-methoxybenzaldehyde (0.12 mL, 1.0 mmol, 1.0 equiv.) and pyrrolidine (9 µL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (180 mg, 59%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 113-115 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.60 (s, 1H, N*H*C), 7.83 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeArH), 7.44 – 7.28 (m, 5H, 5 × Ph*H*), 6.98 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 4.43 (s, 2H, PhC$H_2$), 3.89 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 172.3, 165.6, 133.8, 131.1, 128.9, 128.8, 128.5, 125.0, 114.9, 58.8, 55.8; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 312.0; **HRMS** (ESI, *m/z*) calculated for $(C_{15}H_{16}NO_3S)^+$ 290.0845 $[M+H]^+$, found 290.0841; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1590, 1562, 1513, 1426, 1315, 1262, 1169, 1145, 1126, 1022, 883, 812, 765, 698, 625, 607; **$R_f$** 0.60 (*n*-hexane:EtOAc, 3:2).

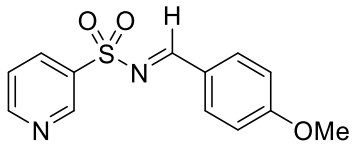
***N*-(4-methoxybenzylidene)thiophene-2-sulfonamide (108w)**




Prepared according to general procedure G, using thiophene-2-sulfonamide (163 mg, 1.0 mmol, 1.2 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.0 mmol, 1.0 equiv.) and pyrrolidine (9 µL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (171 mg, 61%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 94-96 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.91 (s, 1H, N*H*C), 7.90 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.76 (dd, *J* = 4.0, 1.5 Hz, 1H, HetAr*H*), 7.67 (dd, *J* = 5.0, 1.5 Hz, 1H, HetAr*H*), 7.12 (dd, *J* = 5.0, 4.0 Hz, 1H, HetAr*H*), 6.98 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.89 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 169.5, 165.7, 139.4, 134.1, 133.7, 133.6, 127.7, 125.1, 114.9, 55.9; **LRMS** (ESI, *m/z*) $[M+H]^+$ 282.0 & $[M+Na]^+$ 304.0. The spectroscopic data is in agreement with literature.[332]

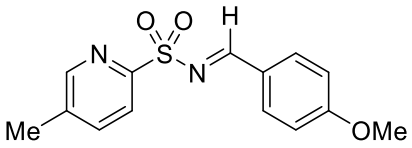
***N*-(4-methoxybenzylidene)pyridine-3-sulfonamide (108x)**




Prepared according to general procedure G, using pyridine-3-sulfonamide (**110x**) (285 mg, 1.8 mmol, 1.2 equiv.), 4-methoxybenzaldehyde (0.18 mL, 1.5 mmol, 1.0 equiv.) and pyrrolidine (14 μL, 0.2 mmol, 0.2 equiv.) with stirring for 48 h, affording the title compound (211 mg, 51%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 140-142 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.20 (d, *J* = 2.0 Hz, 1H, Py*H*), 9.01 (s, 1H, N*H*C), 8.83 (dd, *J* = 4.5, 2.0 Hz, 1H, Py*H*), 8.28 (app. dt, *J* = 8.0, 2.0 Hz, 1H, Py*H*), 7.91 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.48 (dd, *J* = 8.0, 4.5 Hz, 1H, Py*H*), 6.99 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.90 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 170.8, 166.0, 153.8, 148.8, 136.0, 135.6, 134.3, 125.0, 123.8, 115.0, 55.9; **LRMS** (ESI, *m/z*) $[M+H]^+$ 277.0 & $[M+Na]^+$ 299.0; **HRMS** (ESI, *m/z*) calculated for $(C_{13}H_{13}N_2O_3S)^+$ 277.0641 $[M+H]^+$, found 277.0639; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1589, 1558, 1513, 1426, 1317, 1264, 1160, 1103, 1021, 874, 838, 805, 738, 701, 625, 609; **$R_f$** 0.34 (*n*-hexane:EtOAc, 2:3).

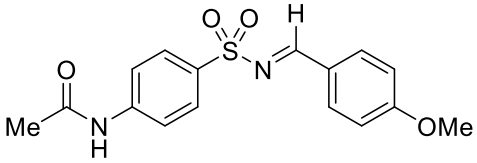
**N-(4-methoxybenzylidene)-5-methylpyridine-2-sulfonamide (108y)**



Prepared according to general procedure G, using 5-methylpyridine-2-sulfonamide (172 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (202 mg, 69%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 134-136 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.13 (s, 1H, N*H*C), 8.52 (app. dt, *J* = 2.0, 1.0 Hz, 1H, HetAr*H*), 8.11 (dd, *J* = 8.0, 1.0 Hz, 1H, HetAr*H*), 7.92 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.73 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, HetAr*H*), 6.97 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.89 (s, 3H, OC$H_3$), 2.43 (app. t, *J* = 1.0 Hz, 3H, HetArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 172.8, 165.7, 153.7, 151.0, 138.2, 137.9, 134.3, 125.4, 123.1, 114.9, 55.9, 18.7; **LRMS** (ESI, *m/z*) $[M+H]^+$ 291.1 & $[M+Na]^+$ 313.1; **HRMS** (ESI, *m/z*) calculated for $(C_{14}H_{15}N_2O_3S)^+$ 291.0798 $[M+H]^+$, found 291.0797; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1590, 1557, 1513, 1426, 1318, 1264, 1163, 1100, 1025, 831, 802, 765, 671; **$R_f$** 0.19 (*n*-hexane:EtOAc, 3:2).

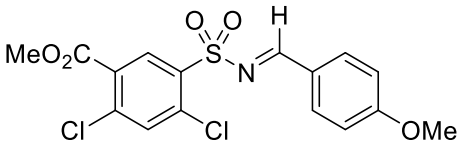
**N-(4-(N-(4-methoxybenzylidene)sulfamoyl)phenyl)acetamide (108z)**



Prepared according to general procedure G, using *N*-(4-sulfamoylphenyl)acetamide (214 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (115 mg, 36%) as an off-white solid.

**MP** (*n*-hexane/$Et_2O$) 166-168 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2SO$) $\delta_H$ 10.40 (br. s, 1H, CON*H*Ar), 9.00 (s, 1H, N*H*C), 7.99 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.86 (d, *J* = 9.5 Hz, 2H, 2 × Ar*H*), 7.82 (d, *J* = 9.5 Hz, 2H, 2 × Ar*H*), 7.10 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.86 (s, 3H, OC$H_3$), 2.09 (s, 3H, COC$H_3$); **$^{13}$C NMR** (101 MHz, $(CD_3)_2SO$) $\delta_C$ 169.9, 169.1, 165.0, 143.9, 133.7, 131.6, 128.7, 124.9, 118.8, 114.9, 55.8, 24.2; **LRMS** (ESI, *m/z*) $[M+H]^+$ 333.0 & $[M+Na]^+$ 355.0; **HRMS** (ESI, *m/z*) calculated for $(C_{16}H_{17}N_2O_4S)^+$ 333.0904 $[M+H]^+$, found 333.0900; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 3340, 1680. 1590, 1531, 1319, 1262, 1152, 1023, 836, 805, 767, 639, 624; **$R_f$** 0.16 (*n*-hexane:EtOAc, 2:3).

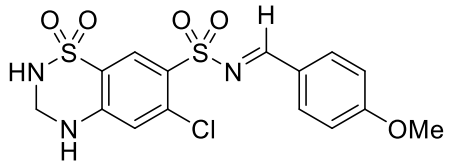
**Methyl 2,4-dichloro-5-(*N*-(4-methoxybenzylidene)sulfamoyl)benzoate (128a)**




Prepared according to general procedure G, using 2,4-dichloro-5-sulfamoylphenyl acetate (**125a**) (682 mg, 2.4 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.38 mL, 2.9 mmol, 1.2 equiv.) and pyrrolidine (18 μL, 0.2 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (648 mg, 67%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 148-150 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.08 (s, 1H, N*H*C), 8.75 (s, 1H, Ar*H*), 7.92 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.61 (s, 1H, Ar*H*), 6.99 (d, *J* = 8.9 Hz, 2H, 2 × *p*-OMeAr*H*), 3.96 (s, 3H, $CO_2CH_3$), 3.90 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 173.0, 166.2, 163.8, 139.9, 136.6, 135.2, 134.5, 134.1, 128.9, 125.0, 115.1, 114.4, 55.9, 53.1; **LRMS** (ESI, *m/z*) $[M+H]^+$ 402.0, 404.0; **HRMS** (ESI, *m/z*) calculated for $(C_{16}H_{14}{}^{35}Cl_2NO_5S)^+$ 401.9964 $[M+H]^+$, found 401.9960; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1736, 1584, 1554, 1512, 1427, 1290, 1255, 1156, 1075, 1022, 893, 838, 808, 765, 686 654, 621; **$R_f$** 0.60 (*n*-hexane:EtOAc, 3:2).

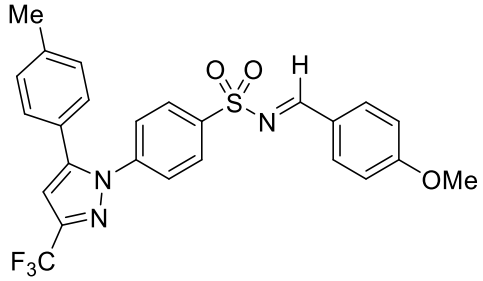
**6-Chloro-N-(4-methoxybenzylidene)-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazine-7-sulfonamide 1,1-dioxide (128b)**




Prepared according to general procedure H, using hydrochlorothiazide (595 mg, 2.0 mmol, 1.0 equiv.), MeOH (3 mL), 4-methoxybenzaldehyde (0.48 mL, 4.0 mmol, 2.0 equiv.) and conc. HCl (2 μL), Purification by washing with MeOH (10 mL) then $CH_2Cl_2$ (10 mL) afforded the title compound (125 mg, 30%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 192-194 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2SO$) $\delta_H$ 9.10 (s, 1H, N*H*C), 8.32 (br. t, *J* = 3.0 Hz, 1H, $SO_2NH$), 8.11 (s, 1H, Ar*H*), 8.05 (m, 3H, ArN*H*, 2 × *p*-OMeAr*H*), 7.12 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 7.00 (s, 1H, Ar*H*), 4.77 (s, 2H, $(NH)_2CH_2$), 3.88 (s, 3H, $OCH_3$); **$^{13}$C NMR** (101 MHz, $(CD_3)_2SO$) $\delta_C$ 172.0, 165.3, 148.0, 135.1, 134.1, 127.5, 124.7, 121.2, 119.0, 117.4, 115.0, 55.9, 54.4; **LRMS** (ESI, *m/z*) $[M+H]^+$ 416.1 & $[M+Na]^+$ 438.1; **HRMS** (ESI, *m/z*) calculated for $(C_{15}H_{15}ClN_3O_5S_2)^+$ 416.0136, 418.0105 $[M+H]^+$, found 416.0136, 418.0104; **IR** (thin film, $\nu_{max}/cm^{-1}$) 3411, 3304, 1597, 1585, 1546, 15089, 1456, 1427, 1368, 1335, 1309, 1293, 1267, 1165, 1151, 1109, 1055, 1022, 915, 867, 837, 806, 770, 729, 710, 686, 608; **$R_f$** 0.24 (MeOH:EtOAc, 1:9).

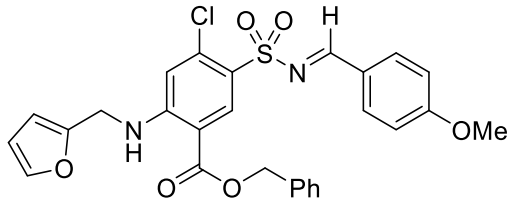
**_N_-(4-methoxybenzylidene)-4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide (128c)**




Prepared according to general procedure G, using celecoxib (**100**) (5.00 g, 13.1 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (1.91 mL, 15.7 mmol, 1.2 equiv.) and pyrrolidine (0.11 mL, 1.3 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (4.73 g, 72%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 114-116 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.94 (s, 1H, NHC), 7.97 (d, $J$ = 9.0 Hz, 2H, 2 × ArH), 7.87 (d, $J$ = 9.0 Hz, 2H, 2 × *p*-OMeArH), 7.48 (d, $J$ = 9.0 Hz, 2H, 2 × ArH), 7.16 (d, $J$ = 8.0 Hz, 2H, 2 × *p*-TolH), 7.11 (d, $J$ = 8.0 Hz, 2H, 2 × *p*-TolH), 6.97 (d, $J$ = 9.0 Hz, 2H, 2 × *p*-OMeArH), 6.72 (s, 1H, HetArH), 3.87 (s, 3H, $OCH_3$), 2.36 (s, 3H, $ArCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 170.2, 165.7, 145.3, 144.1 (q, $^2J_{CF}$ = 38.5 Hz), 143.0, 139.8, 138.3, 134.0, 129.8, 128.9, 128.8, 125.7, 125.4, 125.0, 121.1 (q, $^1J_{CF}$ = 269.5 Hz) 114.9, 106.4 (q, $^3J_{CF}$ = 2.0 Hz), 55.8, 21.3; **$^{19}$F NMR** (377 MHz, $CDCl_3$) $\delta_F$ -62.38 (s); **LRMS** (ESI, *m/z*) $[M+H]^+$ 500.0; **HRMS** (ESI, *m/z*) calculated for $(C_{25}H_{21}F_3N_3O_3S)^+$ 500.1250 $[M+H]^+$, found 500.1247; **IR** ($CHCl_3$, $\nu_{max}$/$cm^{-1}$) 1593, 1561, 1513, 1472, 1426, 1372, 1322, 1267, 1237, 1157, 1091, 975, 838, 808, 774, 638; **$R_f$** 0.25 (*n*-hexane:EtOAc, 3:2).

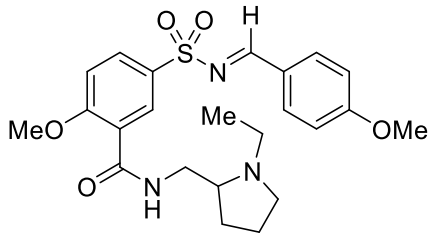
**Benzyl 4-chloro-2-((furan-2-ylmethyl)amino)-5-(*N*-(4-methoxybenzylidene)sulfamoyl)benzoate (128d)**




Prepared according to general procedure G, using sulfonamide **125d** (421 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 µL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (373 mg, 69%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 121-123 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.03 (s, 1H, N*H*C), 8.85 (s, 1H, Ar*H*), 8.72 (t, *J* = 5.5 Hz, 1H, $CH_2$N*H*Ar), 7.91 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.47 – 7.30 (m, 6H, 5 × Ph*H*, HetAr*H*), 6.98 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 6.83 (s, 1H, Ar*H*), 6.33 (dd, *J* = 3.5, 2.0 Hz, 1H, HetAr*H*), 6.26 (dd, *J* = 3.5, 1.0 Hz, 1H, Het*A*rH), 5.34 (s, 2H, $CO_2CH_2$Ph), 4.42 (d, *J* = 5.5 Hz, 2H, HetArC$H_2$Ar), 3.89 (s, 3H, O$CH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 171.2, 167.0, 165.5, 153.7, 150.2, 142.7, 138.8, 136.1, 135.6, 133.9, 128.8, 128.5, 128.3, 125.3, 121.7, 114.8, 113.7, 110.6, 108.8, 107.9, 66.9, 55.8, 40.3; **LRMS** (ESI, *m/z*) $[M+H]^+$ 539.2; **HRMS** (ESI, *m/z*) calculated for $(C_{27}H_{24}{}^{35}ClN_2O_6S)^+$ 539.1038 $[M+H]^+$, found 539.1036; **IR** ($CHCl_3$, $\nu_{max}$/$cm^{-1}$) 3327, 1686, 1590, 1562, 1512, 1426, 1310, 1263, 1228, 1158, 1124, 873, 834, 806, 763; **$R_f$** 0.45 (*n*-hexane:EtOAc, 3:2).

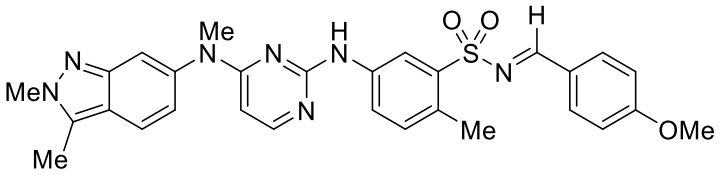
**N-((1-ethylpyrrolidin-2-yl)methyl)-2-methoxy-5-(N-(4-methoxybenzylidene)sulfamoyl)benzamide (128e)**




Prepared according to general procedure G, using sulpiride (**97**) (1.02 g, 3.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.38 mL, 3.6 mmol, 1.2 equiv.) and pyrrolidine (21 μL, 0.3 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (975 mg, 71%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 97-99 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.96 (s, 1H, NHC), 8.73 (d, *J* = 2.5 Hz, 1H, ArH), 8.23 (br. s, 1H, CONH), 8.11 (dd, *J* = 8.5, 2.5 Hz, 1H, ArH), 7.87 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeArH), 7.10 (d, *J* = 8.5 Hz, 1H, ArH), 6.95 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeArH), 4.02 (s, 3H, $OCH_3$), 3.88 (s, 3H, $OCH_3$), 3.72 (ddd, *J* = 13.5, 7.0, 3.0 Hz, 1H, $CONHCH_AH_B$), 3.31 (app. d, *J* = 13.5 Hz, 1H, $CONHCH_AH_B$), 3.21 (app. s, 1H, $EtNCH_AH_B$), 2.84 (dq, *J* = 14.5, 7.0 Hz, 1H, $NCH_AH_BCH_3$), 2.66 (app. s, 1H, $NHCH_2CHNEt$), 2.32 – 2.12 (m, 2H, $NCH_AH_BCH_3$, $EtNCH_AH_B$), 1.96 – 1.83 (m, 1H, $EtNCHCH_AH_B$), 1.75 – 1.67 (m, 2H, $EtNCH_2CH_2$), 1.61 (app. dt, *J* = 12.0, 6.5 Hz, 1H, $EtNCHCH_AH_B$), 1.12 (t, *J* = 7.0 Hz, 3H, $NCH_2CH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 169.7, 165.4, 163.8, 161.0, 134.0, 132.6, 132.5, 131.6, 125.3, 123.2, 114.8, 111.9, 62.3, 56.5, 55.8, 53.8, 48.1, 41.5, 28.5, 23.1, 14.3; **LRMS** (ESI, *m/z*) $[M+H]^+$ 460.2; **HRMS** (ESI, *m/z*) calculated for $(C_{23}H_{30}N_3O_5S)^+$ 460.1901 $[M+H]^+$, found 460.1897; **IR** ($CHCl_3$, $\nu_{max}$/$cm^{-1}$) 2969, 2802, 1649, 1595, 1559, 1513, 1483, 1319, 1262, 1168, 1123, 1085, 1019, 836, 812, 764, 692, 658; **$R_f$** 0.05 (MeOH:EtOAc, 1:9).

**5-((4-((2,3-dimethyl-2*H*-indazol-6-yl)(methyl)amino)pyrimidin-2-yl)amino)-*N*-(4-methoxybenzylidene)-2-methylbenzenesulfonamidemethanesulfonamide (128f)**



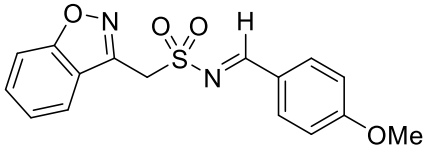

Initially the free base was prepared according to the modified procedure from Rendell *et al.*[333] Under an atmosphere of air, pazopanib (**98**) HCl salt (1.0 g, 1.69 mmol) was added to a round bottom flask, and MeOH (9.0 mL) was added. The suspension was stirred at room temperature and sodium carbonate (10 mL, 10% aq. solution) was added by slow dropwise addition. Stirring was continued for 5 h before the solid was filtered and dried under reduced pressure, affording pazopanib (902 mg, 97%), which was used in the next step without further purification.

The title compound was then prepared according to general procedure G, using pazopanib (**98**) (474 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 μL, 0.1 mmol, 0.1 equiv.) with stirring for 72 h, affording the title compound (274 mg, 46%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 46-48 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2SO$) $\delta_H$ 9.53 (br. s, 1H, ArN*H*), 9.06 (s, 1H, N*H*C), 8.77 (d, *J* = 2.5 Hz, 1H, Ar*H*), 8.03 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.83 (d, *J* = 6.0 Hz, 1H, Py*H*), 7.79 – 7.69 (m, 2H, Ar*H*, HetAr*H*), 7.45 (dd, *J* = 4.0, 2.0 Hz, 1H, HetAr*H*), 7.23 (d, *J* = 5.0 Hz, 1H, Ar*H*), 7.12 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 6.88 (dd, *J* = 8.5, 2.0 Hz, 1H, HetAr*H*), 5.76 (d, *J* = 6.0 Hz, 1H, Py*H*), 4.06 (s, 3H, HetArNC$H_3$), 3.86 (s, 3H, OC$H_3$), 3.51 (s, 3H, NC$H_3$), 2.62 (s, 3H, HetArC$H_3$), 2.50 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $(CD_3)_2SO$) $\delta_C$ 170.1, 165.1, 162.4, 159.1, 155.5, 155.2, 147.0, 141.8, 139.7, 136.5, 133.8, 132.6, 132.2, 128.5, 124.8, 121.9, 121.5, 119.6, 118.1, 115.0, 114.0, 96.9, 55.8, 38.0, 37.5, 19.2, 9.4; **LRMS** (ESI, *m/z*) $[M+H]^+$ 556.2;

**HRMS** (ESI, *m/z*) calculated for $(C_{29}H_{30}N_7O_3S)^+$ 556.2125 $[M+H]^+$, found 556.2121; **IR** (thin film, $\nu_{max}/cm^{-1}$) 1588, 1553, 1511, 1421, 1402, 1361, 1310, 1261, 1232, 1137, 1055, 1024, 978, 946, 871, 833, 800, 764, 703, 672, 619; $\mathbf{R_f}$ 0.49 (MeOH:EtOAc, 1:9).

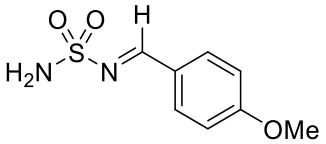
**1-(Benzo[d]isoxazol-3-yl)-N-(4-methoxybenzylidene)methanesulfonamide (128g)**




Prepared according to general procedure G, using zonisamide (**99**) (212 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 µL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (229 mg, 69%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 150-152 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.75 (s, 1H, N*H*C), 7.92 (app. dt, *J* = 8.0, 1.0 Hz, 1H, Ar*H*), 7.84 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.62 – 7.51 (m, 2H, 2 × Ar*H*), 7.33 (ddd, *J* = 8.0, 6.0, 2.0 Hz, 1H, Ar*H*), 6.98 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 4.89 (s, 2H, HetArC$H_2SO_2$), 3.90 (s, 3H, OC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 172.8, 166.1, 163.9, 149.1, 134.3, 130.5, 124.8, 124.3, 122.6, 120.9, 115.0, 110.1, 55.9, 49.7; **LRMS** (ESI, *m/z*) $[M+H]^+$ 331.1 & $[M+Na]^+$ 353.1; **HRMS** (ESI, *m/z*) calculated for $(C_{16}H_{14}N_2NaO_4S)^+$ 353.0566 $[M+Na]^+$, found 353.0566; **IR** (thin film, $\nu_{max}/cm^{-1}$) 1602, 1564, 1514, 1428, 1380, 1316, 1265, 1182, 1147, 1135, 1024, 864, 831, 748; $\mathbf{R_f}$ 0.40 (*n*-hexane:EtOAc, 3:2).

**4-methoxybenzylidenesulfamide (113a)**

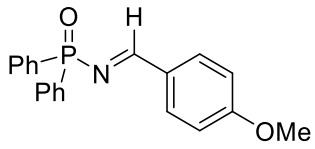



Prepared according to general procedure H, using sulfamide (1.0 mg, 10.4 mmol, 1.0 equiv.), MeOH (10 mL), 4-methoxybenzaldehyde (1.27 mL, 10.4 mmol, 2.0 equiv.) and conc. HCl (10 µL).

Purification by washing with water (10 mL) then $CH_2Cl_2$ (10 mL) afforded the title compound (1.96 g, 88%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 167-169 °C; **$^1$H NMR** (400 MHz, $(CD_3)_2CO$) $\delta_H$ 8.85 (s, 1H, NHC), 7.96 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.12 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 6.45 (br. s, 2H, $SO_2NH_2$), 3.92 (s, 3H, $OCH_3$); **$^{13}$C NMR** (101 MHz, $(CD_3)_2CO$) $\delta_C$ 167.2, 165.6, 133.6, 126.6, 115.6, 56.2; **LRMS** (ESI, *m/z*) $[M-H]^-$ 213.0, $[M+H]^+$ 215.0 & $[M+Na]^+$ 237.0.; **HRMS** (ESI, *m/z*) calculated for $(C_8H_{11}N_2O_3S)^+$ 215.0485 $[M+H]^+$, found 215.0486; **IR** (thin film, $\nu_{max}/cm^{-1}$) 3283, 1583, 1566, 1512, 1462, 1421, 1336, 1316, 1267, 1146, 1030, 877, 832, 764, 607; **$R_f$** 0.59 (*n*-hexane:EtOAc, 2:3).

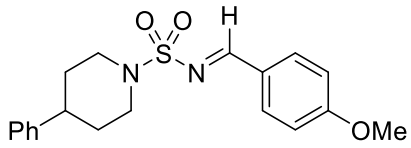
***N*-(4-methoxybenzylidene)-*P*,*P*-diphenylphosphinic amide (114)**




Prepared according to general procedure G, using *P*,*P*-diphenylphosphinic amide (**126**) (217 mg, 1.0 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.15 mL, 1.2 mmol, 1.2 equiv.) and pyrrolidine (9 µL, 0.1 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (176 mg, 52%) as a pale-yellow solid.

**MP** (*n*-hexane/$Et_2O$) 96-98 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.23 (d, *J* = 32.0 Hz, 1H, NHC), 8.00 – 7.79 (m, 6H, 4 × Ph*H*, 2 × *p*-OMeAr*H*), 7.54 – 7.37 (m, 6H, 6 × Ph*H*), 6.99 (d, *J* = 8.5 Hz, 2H, 2 × *p*-OMeAr*H*), 3.88 (s, 3H, $OCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$, 172.8 (d, *J* = 7.5 Hz), 164.3, 133.6 (d, *J* = 127.0 Hz), 132.5, 131.8 (d, *J* = 2.5 Hz), 131.7 (d, *J* = 9.0 Hz), 129.3 (d, *J* = 25.5 Hz), 128.6 (d, *J* = 12.5 Hz), 114.5, 55.7; **$^{31}$P NMR** (162 MHz, $CDCl_3$) $\delta_P$ 24.71 (s); **LRMS** (ESI, *m/z*) $[M+H]^+$ 336.0.

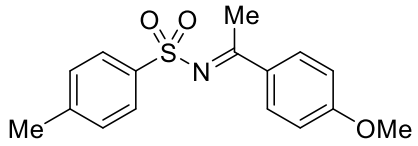
***N*-(4-methoxybenzylidene)-4-phenylpiperidine-1-sulfonamide (113b)**




Prepared according to general procedure G, using 4-phenylpiperidine-1-sulfonamide (**127**) (120 mg, 0.50 mmol, 1.0 equiv.), 4-methoxybenzaldehyde (0.08 mL, 0.65 mmol, 1.2 equiv.) and pyrrolidine (5 μL, 0.05 mmol, 0.1 equiv.) with stirring for 24 h, affording the title compound (136 mg, 76%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 130-132 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.84 (s, 1H, N*H*C), 7.92 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.34 – 7.27 (m, 2H, 2 × Ph*H*), 7.25 – 7.15 (m, 3H, 3 × Ph*H*), 7.02 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 4.02 – 3.92 (m, 2H, 2 × NC$H_A$$H_B$$CH_2$), 3.91 (s, 3H, OC$H_3$), 2.91 – 2.80 (m, 2H, 2 × NCH$_A$$H_B$$CH_2$), 2.58 (tt, *J* = 10.5, 5.5 Hz, 1H, PhC*H*$(CH_2)_2$), 1.96 – 1.80 (m, 4H, 2 × $NCH_2CH_2$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 169.6, 165.1, 145.2, 133.4, 128.7, 126.9, 126.7, 125.5, 114.9, 55.8, 47.4, 42.1, 32.6; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 381.2; **HRMS** (ESI, *m/z*) calculated for $(C_{19}H_{23}N_2O_3S)^+$ 359.1424 $[M+H]^+$, found 359.1420; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1595, 1566, 1513, 1350, 1262, 1155, 1114, 1055, 1023, 937, 873, 806, 766, 701; **$R_f$** 0.33 (*n*-hexane:EtOAc, 3:2).

***N*-(1-(4-methoxyphenyl)ethylidene)-4-methylbenzenesulfonamide (108aq)**

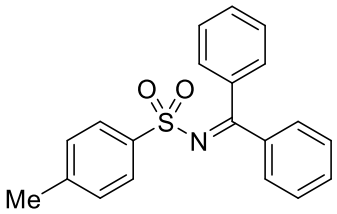



Prepared according to the modified procedure from Cui *et al.*[334] 4-methylbenzenesulfonamide (86 mg, 0.50 mmol), $(PPh_3)AuCl$ (5 mg, 0.01 mmol), and AgOTf (10 mg, 0.04 mmol) were added to a reaction vial and subsequently sealed. Toluene (2 mL), and 1-ethynyl-4-methoxybenzene (0.2 mL, 1.5 mmol) were added and the resulting mixture was heated to 100 °C stirred and stirred for 9 h. The

solution was the cooled to room temperature and quenched with saturated. aqueous $NaHCO_3$ (2 mL). The aqueous phase was removed and further extracted with EtOAc (5 mL × 3), the combined organic extracts were dried over $Na_2SO_4$, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (Petrol:EtOAc, 5:1), afforded the title compound (147 mg, 97%) as a brown oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.96 – 7.86 (m, 4H, 2 × *p*-MeAr*H*, 2 × *p*-OMeAr*H*), 7.33 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 6.88 (d, *J* = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.84 (s, 3H, OC$H_3$), 2.94 (s, 3H, CC$H_3$), 2.43 (s, 3H, ArC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 178.8, 164.0, 143.4, 139.2, 130.8, 130.0, 129.5, 127.1, 114.0, 55.6, 21.7, 20.8; **LRMS** (ESI, *m/z*) $[M-H]^-$ 302.0, $[M+H]^+$ 304.0 & $[M+Na]^+$ 326.0. The spectroscopic data is in agreement with literature.[334]

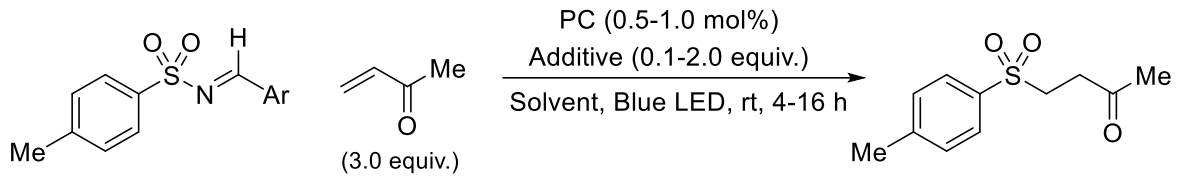
**N-(diphenylmethylene)-4-methylbenzenesulfonamide (108ar)**




Prepared according to the modified procedure from Hayashi *et al.*[335] Tosyl chloride (381 mg, 2.1 mmol, 1.05 equiv.) was added to a reaction vial and dissolved in toluene (1 mL). The solution was cooled to 0 °C and benzophenone imine (335 μL, 2 mmol, 1.0 equiv.) added by dropwise addition. The reaction mixture was heated to 90 °C and stirred for 2 h, then cooled to room temperature, before the addition of saturated ammonium chloride solution (1 mL) was added to the flask. The mixture was extracted with $CH_2Cl_2$ (2 mL × 3), and the solvent removed from the combined organic extracts under reduced pressure. Purification by flash column chromatography (Petrol:EtOAc, 9:1 to 1:1), afforded the title compound (204 mg, 30%) as a colourless solid.

**MP** (*n*-hexane/$Et_2O$) 80-82 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.84 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 7.62 – 7.49 (m, 6H, Ph*H*), 7.48 – 7.34 (m, 4H, Ph*H*), 7.29 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 2.43 (s, 3H, Ar$CH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 178.9, 143.4, 138.7, 132.5, 130.2, 129.5, 128.4, 128.2 (br.), 127.5, 21.7; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 358.0. The spectroscopic data is in agreement with literature.[336]

### 6.5.1.3. Photocatalysis Reaction Optimisation




**Scheme 6.4.** Photocatalytic reaction of an aldimine to a sulfone, for reaction optimisation.

Reactions for optimisation were conducted as followed; aldimine (0.10 mmol, 1.0 equiv.), photocatalyst (0.5-1.0 mol%), additive (when solid) and internal standard (dimethyl sulfone) were added to a 1.8 mL screw capped vial equipped with a rubber septum. The vial was evacuated and back filled with nitrogen three times, followed by the addition of additive (when liquid), methyl vinyl ketone (25 μL, 0.3 mmol, 3.0 equiv.) and solvent (1 mL). The vial was then placed in an EvoluChem™ PhotoRedOx Box device and irradiated with EvoluChem™ 450 nm LED spotlight (**Figure 6.14.**). After the given amount of time the reaction was diluted with $CHCl_3$ (2 mL), and the solvent removed under reduced pressure, followed by analysis of the crude $^1$H NMR spectra.

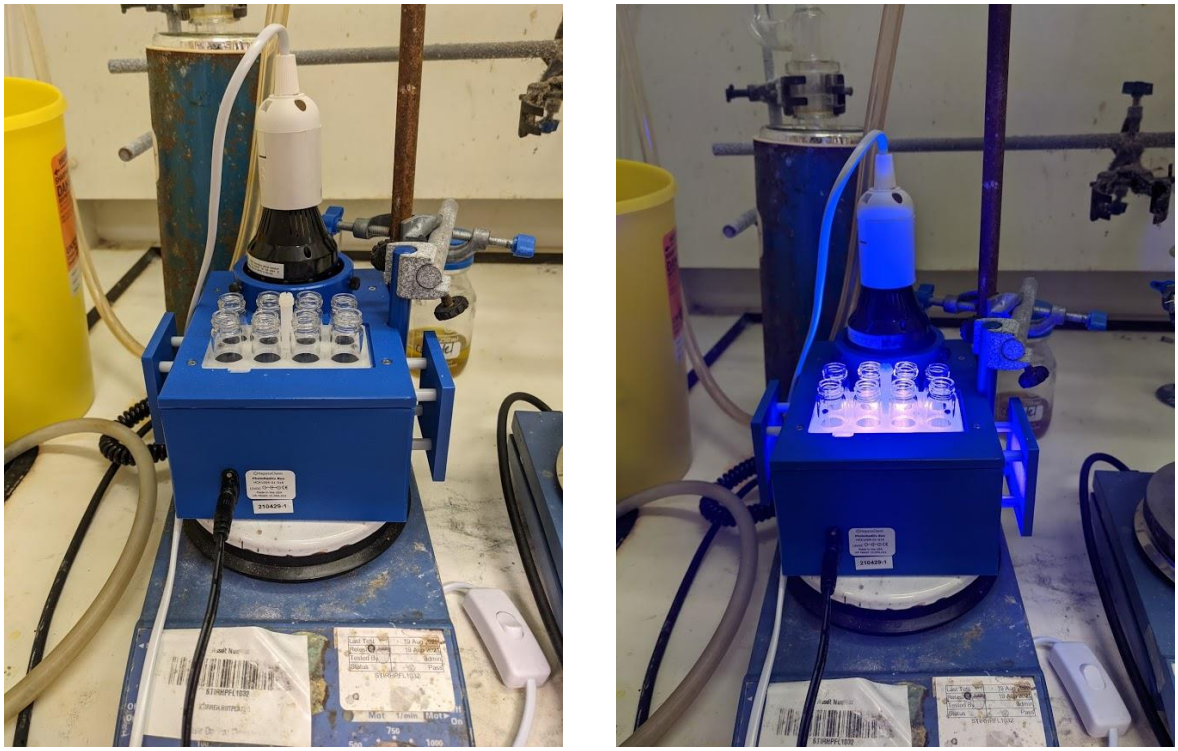


**Figure 6.14.** Photochemistry reaction set up for optimisation, using a EvoluChem™ PhotoRedOx Box. The image on the left shows the light off, and on the right light on.

### 6.5.1.4. Photocatalysis Reaction Scope

**General Procedure I**




**General Procedure I**: Photocatalytic hydrosulfonylation reaction of an aldimine.

Reactions for the scope were conducted as followed; aldimine (0.2 mmol, 0.1 equiv.) and 5CzBN (0.9 mg 0.5 mol%) were added to an 8.0 mL screw capped vial equipped with a rubber septum. The vial was evacuated and back filled with nitrogen three times, followed by the addition of tris(trimethylsilyl)silane (93 µL, 0.3 mmol, 1.5 equiv.), methyl vinyl ketone (42 µL, 0.5 mmol, 2.5 equiv.) and toluene (4 mL, 0.05 M). The vial was then placed in a glass tempering beaker connected to a flow of water, the vial was subsequently submerged in water and irradiated with two

EvoluChem™ 450 nm LED spotlights (**Figure 6.15.**). After 4 h the reaction was diluted with $CHCl_3$ (4 mL), and the solvent removed under reduced pressure, followed by purification by flash column chromatography.

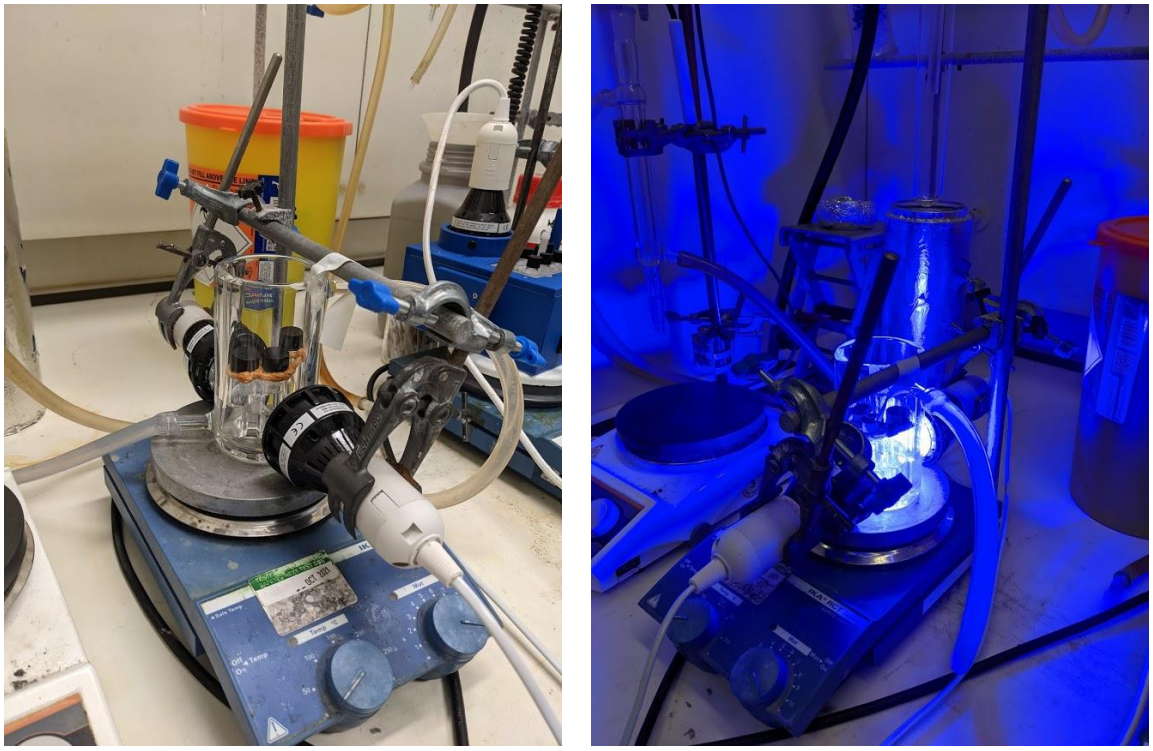
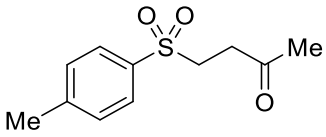


**Figure 6.15.** Photochemistry reaction set up for the scope, using a EvoluChem™ 450 nm LED spotlights and a tempering beaker. The image on the left shows the lights off, and on the right lights on, both with the vials submerged in water.

**4-Tosylbutan-2-one (109a)**



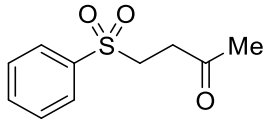

Prepared according to general procedure H, using aldimine **108ah** (58 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (38 mg, 84%) as a brown solid.

**MP** (*n*-hexane/EtOAc) 63-65 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.74 (d, $J$ = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 7.33 (d, $J$ = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 3.32 (t, $J$ = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.87 (t, $J$ = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.41 (s, 3H, $ArCH_3$), 2.13 (s, 3H $COCH_3$); **$^{13}$C NMR** (101 MHz,

$CDCl_3$) $\delta_H$ 203.8, 145.0, 136.0, 130.0, 128.0, 50.6, 36.0, 29.9, 21.6; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 249.0. The spectroscopic data is in agreement with literature.[337]

The reaction scale up was performed using a modified general procedure H, using **108ah** (289 mg, 1.0 mmol, 1.0 equiv.), 5CzBN (4.6 mg, 0.5 mol%), tris(trimethylsilyl)silane (0.42 mL, 1.5 mmol, 1.5 equiv.), methyl vinyl ketone (0.21 mL, 2.5 mmol, 2.5 equiv.) and toluene (20 mL), using a round bottom flask in place of a vial. Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (206 mg, 91%) as a brown solid.

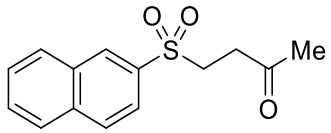
**4-(Phenylsulfonyl)butan-2-one (109b)**




Prepared according to general procedure H, using aldimine **108b** (55 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (43 mg, 100%) as an orange solid.

**MP** (*n*-hexane/EtOAc) 68-70 °C' **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.93 – 7.87 (m, 2H, 2 × Ph*H*), 7.70 – 7.63 (m, 1H, Ph*H*), 7.61 – 7.53 (m, 2H, 2 × Ph*H*), 3.37 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.92 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.17 (s, 3H, $COCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 203.8, 139.1, 134.1, 129.5, 128.1, 50.7, 36.0, 30.0; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 255.1. The spectroscopic data is in agreement with literature.[338]

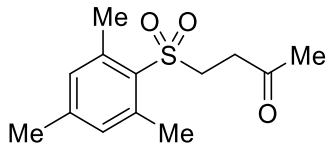
**4-(Naphthalen-2-ylsulfonyl)butan-2-one (109c)**



Prepared according to general procedure H, using aldimine **108c** (65 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (38 mg, 73%) as an off-white solid.

**MP** (*n*-hexane /EtOAc) 114-116 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.48 (d, *J* = 2.0 Hz, 1H, Ar*H*), 8.05 – 7.97 (m, 2H, 2 × Ar*H*), 7.94 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 7.86 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar*H*), 7.69 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H, Ar*H*), 7.64 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H, Ar*H*), 3.46 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.95 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.16 (s, 3H, $COCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 203.8, 135.9, 135.5, 132.3, 130.0 (2 × C), 129.9, 129.6, 128.2, 128.0, 122.6, 50.7, 36.1, 30.0; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 285.1; **HRMS** (ESI, *m/z*) calculated for $(C_{14}H_{15}O_3S)^+$ 263.0736 $[M+H]^+$, found 263.0738; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1719, 1347, 1309, 1245, 1149, 1125, 1074, 820, 752, 638; **$R_f$** 0.22 (*n*-hexane:EtOAc, 3:2).

**4-(Mesitylsulfonyl)butan-2-one (109d)**

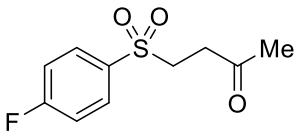


Prepared according to general procedure H, using aldimine **108d** (64 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (16 mg, 31%) as an orange solid.

**MP** (*n*-hexane/EtOAc) 53-55 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 6.97 (s, 2H, 2 × Ar*H*), 3.36 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.97 (t, *J* = 7.5, Hz, 2H, $CH_2CH_2CO$), 2.64 (s, 6H, 2 × Ar$CH_3$), 2.31

(s, 3H, ArC$H_3$), 2.20 (s, 3H, COC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 204.3, 143.7, 140.2, 133.0, 132.5, 50.4, 35.2, 30.1, 23.0, 21.1; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 277.1; **HRMS** (ESI, *m/z*) calculated for $(C_{13}H_{18}NaO_3S)^+$ 277.0869 $[M+Na]^+$, found 277.0869; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1720, 1603, 1452, 1416, 1309, 1246, 1146, 838, 771, 657; **$R_f$** 0.37 (*n*-hexane:EtOAc, 3:2).

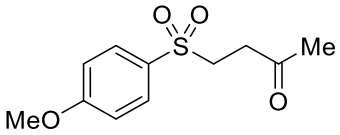
**4-((4-Fluorophenyl)sulfonyl)butan-2-one (109e)**




Prepared according to general procedure H, using aldimine **108e** (59 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (39 mg, 85%) as an off-white solid.

**MP** (*n*-hexane/EtOAc) 76-78 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.97 – 7.86 (m, 2H, 2 × *p*-FAr*H*), 7.29 – 7.19 (m, 2H, 2 × *p*-FAr*H*), 3.36 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.93 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.18 (s, 3H, COC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 203.7, 166.1 (d, *J* = 257.0 Hz), 135.2 (d, *J* = 3.5 Hz), 131.0 (d, *J* = 9.5 Hz), 116.9 (d, *J* = 22.5 Hz), 50.8, 35.9, 30.0; **$^{19}$F NMR** (377 MHz, $CDCl_3$) $\delta_F$ -102.98 (tt, *J* = 8.5, 5.0 Hz); **LRMS** (ESI, *m/z*) $[M+Na]^+$ 253.0; **HRMS** (ESI, *m/z*) calculated for $(C_{10}H_{11}FNaO_3S)^+$ 253.0305 $[M+Na]^+$, found 253.0306; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1720, 1591, 1494, 1407, 1317, 1291, 1236, 1148, 1087, 842, 772; **$R_f$** 0.19 (*n*-hexane:EtOAc, 3:2).

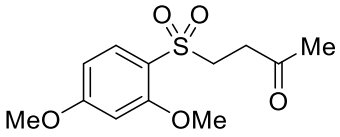
**4-((4-Methoxyphenyl)sulfonyl)butan-2-one (109f)**



Prepared according to general procedure H, using aldimine **108f** (61 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (38 mg, 78%) as a yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.81 (d, $J$ = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 7.01 (d, $J$ = 9.0 Hz, 2H, 2 × *p*-OMeAr*H*), 3.88 (s, 3H, OC$H_3$), 3.33 (t, $J$ = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.90 (t, $J$ = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.17 (s, 3H, COC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 204.0, 164.0, 130.6, 130.3, 114.7, 55.8, 51.0, 36.2, 30.00; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 265.1; **HRMS** (ESI, *m/z*) calculated for $(C_{11}H_{15}O_4S)^+$ 243.0686 $[M+H]^+$, found 243.0688; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1719, 1596, 1499, 1317, 1298, 1262, 1144, 1089, 1023, 838, 805, 770, 733, 704, 667; **$R_f$** 0.13 (*n*-hexane:EtOAc, 3:2).

**4-((2,4-Dimethoxyphenyl)sulfonyl)butan-2-one (109g)**

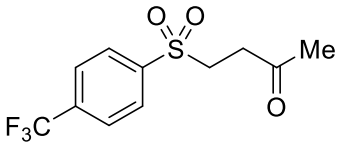


Prepared according to general procedure H, using aldimine **108g** (67 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (37 mg, 67%) as a yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.84 (d, $J$ = 9.0 Hz, 1H, Ar*H*), 6.56 (dd, $J$ = 9.0, 2.5 Hz, 1H, Ar*H*), 6.51 (d, $J$ = 2.5 Hz, 1H, Ar*H*), 3.94 (s, 3H, OC$H_3$), 3.86 (s, 3H, OC$H_3$), 3.56 (t, $J$ = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.89 (t, $J$ = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.15 (s, 3H, COC$H_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 204.4, 165.9, 159.2, 132.4, 119.0, 104.9, 99.6, 56.4, 55.9, 49.0, 36.1, 30.1; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 295.1; **HRMS** (ESI, *m/z*) calculated for $(C_{12}H_{16}NaO_5S)^+$ 295.0611 $[M+Na]^+$, found

295.0612.; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1719, 1597, 1576, 1468, 1439, 1416, 1364, 1302, 1214, 1165, 1126, 1073, 1022, 838 773; $\mathbf{R_f}$ 0.38 (*n*-hexane:EtOAc, 1:4).

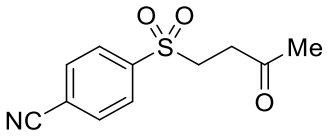
**4-((4-(Trifluoromethyl)phenyl)sulfonyl)butan-2-one (109h)**



Prepared according to general procedure H, using aldimine **108h** (69 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (33 mg, 58%) as an off-white solid.

**MP** (*n*-hexane/EtOAc) 115-117 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.05 (d, *J* = 8.0 Hz, 2H, 2 × *p*-$CF_3$Ar*H*), 7.85 (d, *J* = 8.0 Hz, 2H, 2 × *p*-$CF_3$Ar*H*), 3.41 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.95 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.20 (s, 3H, $COCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 203.4, 142.7, 135.8 (q, *J* = 33.5 Hz), 128.8, 126.7 (q, *J* = 3.5 Hz), 123.2 (q, *J* = 273.5 Hz), 50.6, 35.7, 30.0; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 303.1; **HRMS** (ESI, *m/z*) calculated for $(C_{11}H_{11}F_3NaO_3S)^+$ 303.0273 $[M+Na]^+$, found 303.0275; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1714, 1408, 1328, 1269, 1246, 1149, 1127, 1107, 1091, 1065, 1021, 842, 790, 765, 712, 620; $\mathbf{R_f}$ 0.46 (*n*-hexane:EtOAc, 3:2).

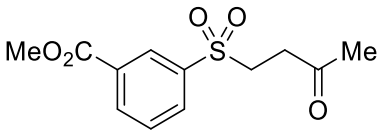
**4-((3-Oxobutyl)sulfonyl)benzonitrile (109i)**



Prepared according to general procedure H, using aldimine **108i** (60 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 1:1), afforded the title compound (33 mg, 70%) as an off-white solid.

**MP** (*n*-hexane/EtOAc) 118-120 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.03 (d, *J* = 8.5 Hz, 2H, 2 × *p*-CNAr*H*), 7.88 (d, *J* = 8.5 Hz, 2H, 2 × *p*-CNAr*H*), 3.40 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.95 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.19 (s, 3H, $COCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 203.3, 143.4, 133.3, 128.9, 117.9, 117.1, 50.6, 35.6, 30.0; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 260.0; **HRMS** (ESI, *m/z*) calculated for $(C_{11}H_{11}NNaO_3S)^+$ 260.0352 $[M+Na]^+$, found 260.0353; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1709, 1409, 1365, 1326, 1269, 1245, 1168, 1145, 1085, 1022, 841, 802, 761, 642; **$R_f$** 0.13 (*n*-hexane:EtOAc, 3:2).

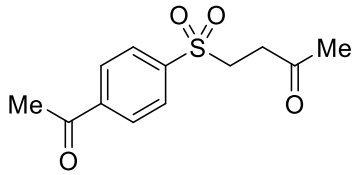
**Methyl 3-((3-oxobutyl)sulfonyl)benzoate (109j)**




Prepared according to general procedure H, using aldimine **108j** (67 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 1:1), afforded the title compound (40 mg, 74%) as an off-white solid.

**MP** (*n*-hexane/EtOAc) 65-67 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.56 (app. td, *J* = 1.5, 0.5 Hz, 1 Hz), 8.33 (app. dt, *J* = 8.0, 1.5 Hz, 1H), 8.09 (ddd, *J* = 8.0, 2.0, 1.5 Hz, 1H), 7.68 (app. td, *J* = 8.0, 0.5 Hz, 1H), 3.97 (s, 3H, $CO_2CH_3$), 3.41 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.95 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.19 (s, 3H, $COCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 203.6, 165.3, 139.9, 135.0, 132.1, 131.9, 129.9, 129.3, 52.8, 50.7, 35.8, 30.0; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 293.1; **HRMS** (ESI, *m/z*) calculated for $(C_{12}H_{14}NaO_5S)^+$ 293.0454 $[M+Na]^+$, found 293.0454; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1723, 1439, 1304, 1270, 1151, 1122, 752; **$R_f$** 0.18 (*n*-hexane:EtOAc, 3:2).

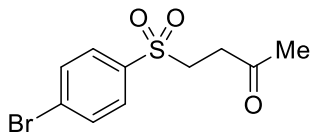
**4-((4-Acetylphenyl)sulfonyl)butan-2-one (109k)**



Prepared according to general procedure H, using aldimine **108k** (64 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 1:1), afforded the title compound (37 mg, 73%) as a colourless solid.

**MP** (*n*-hexane/EtOAc) 110-112 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.12 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 8.01 (d, $J$ = 8.5 Hz, 2H, 2 × Ar*H*), 3.40 (t, $J$ = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.94 (t, $J$ = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.66 (s, 3H, $COCH_3$), 2.19 (s, 3H, $COCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 203.5, 196.7, 142.9, 141.2, 129.3, 128.5, 50.6, 35.8, 30.0, 27.; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 277.1; **HRMS** (ESI, *m/z*) calculated for $(C_{12}H_{14}NaO_4S)^+$ 277.0505 $[M+Na]^+$, found 277.0506; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1719, 1690, 1398, 1361, 1317, 1297, 1262, 1152, 1014, 732, 641; **$R_f$** 0.14 (*n*-hexane:EtOAc, 3:2).

**4-((4-Bromophenyl)sulfonyl)butan-2-one (109l)**

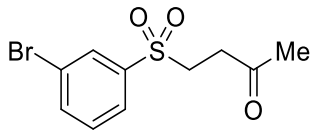


Prepared according to general procedure H, using aldimine **108l** (71 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (50 mg, 85%) as an off-white solid.

**MP** (*n*-hexane/EtOAc) 99-101 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.76 (d, $J$ = 9.0 Hz, 2H, 2 × *p*-BrAr*H*), 7.72 (d, $J$ = 9.0 Hz, 2H, 2 × *p*-BrAr*H*), 3.37 (t, $J$ = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.93 (t, $J$ = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.18 (s, 3H, $COCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 203.6, 138.2,

132.9, 129.7, 128.1, 50.7, 35.9, 30.0; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 313.0, 315.0; **HRMS** (ESI, *m/z*) calculated for $(C_{10}H_{11}{}^{79}BrNaO_3S)^+$ 312.9504 & $(C_{10}H_{11}{}^{81}BrNaO_3S)^+$ 312.9483 $[M+Na]^+$, found 312.9506 & 312.9484 respectively; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1719, 1575, 1390, 1363, 1315, 1275, 1244, 1150, 1086, 1067, 1010, 836, 774; $\mathbf{R_f}$ 0.24 (*n*-hexane:EtOAc, 3:2).

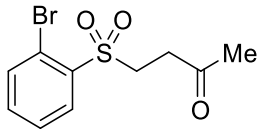
**4-((3-Bromophenyl)sulfonyl)butan-2-one (109m)**




Prepared according to general procedure H, using aldimine **108m** (71 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (18 mg, 30%) as a colourless solid.

**MP** (*n*-hexane/EtOAc) 51-53 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.05 (app. t, *J* = 2.0 Hz, 1H, Ar*H*), 7.84 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar*H*), 7.80 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar*H*), 7.48 (app. t, *J* = 8.0 Hz, 1H, Ar*H*), 3.39 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.95 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.20 (s, 3H, $COCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 203.5, 141.1, 137.2, 131.1, 131.1, 126.7, 123.6, 50.8, 35.8, 30.0; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 313.0, 315; **HRMS** (ESI, *m/z*) calculated for $(C_{10}H_{11}{}^{79}BrNaO_3S)^+$ 312.9504, & 314.9485 $(C_{10}H_{11}{}^{81}BrNaO_3S)^+$ $[M+Na]^+$, found 312.9506, & 314.9483 respectively; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 2928, 1721, 1462, 1413, 1364, 1317, 1295, 1242, 1152, 1099, 782; $\mathbf{R_f}$ 0.45 (*n*-hexane:EtOAc, 3:2).

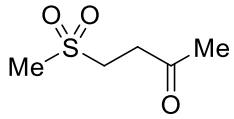
**4-((2-Bromophenyl)sulfonyl)butan-2-one (109n)**



Prepared according to general procedure H, using aldimine **108n** (71 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (12 mg, 20%) as a colourless solid.

**MP** (*n*-hexane/EtOAc) 68-70 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.97 – 7.88 (m, 2H, 2 × *o*-BrAr*H*), 7.72 – 7.63 (m, 1H, BrAr*H*), 7.63 – 7.52 (m, 2H, 2 × *o*-BrAr*H*), 3.38 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.94 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.18 (s, 3H, $COCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 203.8, 139.2, 134.1, 129.6 (2 × C), 128.1 (2 × C), 50.7, 36.0, 30.0; **LRMS** (ESI, *m/z*) $[M+K]^+$ 329.0, 331.0; **HRMS** (ESI, *m/z*) calculated for $(C_{10}H_{11}{}^{79}BrNaO_3S)^+$ 312.9504 & $(C_{10}H_{11}{}^{79}BrNaO_3S)^+$ 314.9485 $[M+Na]^+$, found 312.9505 & 314.9485 respectively; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1720, 1447, 1416, 1364, 1307, 1150, 1087, 753, 690, 619; **$R_f$** 0.29 (*n*-hexane:EtOAc, 3:2).

**4-(Methylsulfonyl)butan-2-one (109o)**

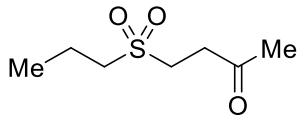


Prepared according to general procedure H, using aldimine **108o** (43 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (20 mg, 67%) as a colourless solid.

**MP** (*n*-hexane/EtOAc) 88-90 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 3.31 (td, *J* = 7.0, 0.5 Hz, 2H, $SO_2CH_2CH_2$), 3.02 (t, *J* = 7.0 Hz, 2H, $CH_2CH_2CO$), 2.93 (t, 3H, *J* = 0.5 Hz $SO_2CH_3$), 2.24 (s, 3H, $COCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 204.1, 49.0, 41.8, 35.7, 30.0; **LRMS** (ESI, *m/z*) $[M+Na]^+$

272.9; **HRMS** (ESI, *m/z*) calculated for $(C_5H_{10}NaO_3S)^+$ 173.0243 $[M+Na]^+$, found 173.0245; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1716, 1291, 1261, 1120, 774; $\mathbf{R_f}$ 0.24 (*n*-hexane:EtOAc, 1:4).

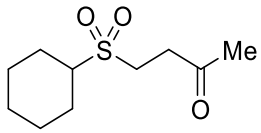
**4-(Propylsulfonyl)butan-2-one (109p)**



Prepared according to general procedure H, using aldimine **108p** (48 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (25 mg, 69%) as an off-white solid.

**MP** (*n*-hexane/EtOAc) 53-55 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 3.24 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2CO$), 3.01 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.99 – 2.92 (m, 2H, $SO_2CH_2CH_2CH_3$), 2.24 (s, 3H, $COCH_3$), 1.96 – 1.82 (m, 2H, $CH_2CH_2CH_3$), 1.09 (t, *J* = 7.5 Hz, 3H, $CH_2CH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 204.3, 55.7, 47.0, 35.2, 30.0, 16.0, 13.3; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 201.1. The spectroscopic data is in agreement with literature.[339]

**4-(Cyclohexylsulfonyl)butan-2-one (109q)**

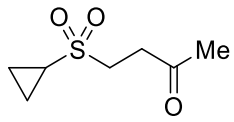


Prepared according to general procedure H, using aldimine **108q** (56 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (31 mg, 70%) as a colourless solid.

**MP** (*n*-hexane/EtOAc) 68-70 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 3.18 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 3.00 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.83 (tt, *J* = 12.5, 3.5 Hz, 1H, Cy*H*), 2.24 (s, 3H, $COCH_3$), 2.22 – 2.14 (m, 2H, 2 × Cy*H*), 1.99 – 1.87 (m, 2H, 2 × Cy*H*), 1.73 (dtt, *J* = 11.0, 3.5, 1.5 Hz, 1H, Cy*H*), 1.53 (app. qd, *J* = 12.5, 3.5 Hz, 2H, 2 × Cy*H*), 1.37 – 1.14 (m, 3H, 3 × Cy*H*); **$^{13}$C NMR**

(101 MHz, $CDCl_3$) $\delta_C$ 204.5, 62.0, 43.6, 34.5, 30.1, 26.7, 25.3, 25.2 (2 × C); **LRMS** (ESI, *m/z*) $[M+Na]^+$ 241.1; **HRMS** (ESI, *m/z*) calculated for $(C_{10}H_{18}NaO_3S)^+$ 241.0869 $[M+Na]^+$, found 241.0870; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 2938, 2859, 1719, 1453, 1415, 1362, 1301, 1263, 1124, 612; $\mathbf{R_f}$ 0.26 (*n*-hexane:EtOAc, 3:2).

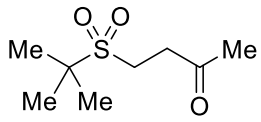
**4-(Cyclopropylsulfonyl)butan-2-one (109r)**




Prepared according to general procedure H, using aldimine **108r** (48 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (22 mg, 62%) as a brown oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 3.34 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 3.02 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.40 (tt, *J* = 8.0, 4.5 Hz, 1H, $SO_2CH(CH_2)_2$), 2.24 (s, 3H, $COCH_3$), 1.31 – 1.15 (m, 2H, $CH(CH_AH_B)_2$), 1.12 – 0.98 (m, 2H, $CH(CH_AH_B)_2$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 204.2, 48.1, 35.5, 30.1, 30.0, 5.0; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 199.1; **HRMS** (ESI, *m/z*) calculated for $(C_7H_{12}NaO_3S)^+$ 199.0399 $[M+Na]^+$, found 199.0402; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1719, 1420, 1317, 1296, 1125, 1044, 889, 834; $\mathbf{R_f}$ 0.16 (*n*-hexane:EtOAc, 3:2).

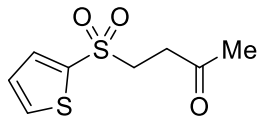
**4-(Tert-butylsulfonyl)butan-2-one (109s)**




Prepared according to general procedure H, using aldimine **108s** (51 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (11 mg, 29%) as an orange oil.

**MP** (*n*-hexane/EtOAc) 50-52 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 3.21 (t, *J* = 7.5, Hz, 2H, $SO_2CH_2CH_2$), 3.03 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.25 (s, 3H, $COCH_3$), 1.43 (s, 9H, $C(CH_3)_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 204.8, 59.2, 41.1, 40.2, 34.1, 23.5; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 215.1; **HRMS** (ESI, *m/z*) calculated for $(C_8H_{17}O_3S)^+$ 193.0893 $[M+H]^+$, found 193.0896; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1720, 1298, 1268, 1114, 756; **$R_f$** 0.14 (*n*-hexane:EtOAc, 3:2).

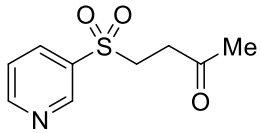
**4-(Thiophen-2-ylsulfonyl)butan-2-one (109w)**




Prepared according to general procedure H, using aldimine **108w** (56 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (34 mg, 78%) as a brown oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.73 (dd, *J* = 5.0, 1.5 Hz, 1H, HetAr*H*), 7.69 (dd, *J* = 4.0, 1.5 Hz, 1H, HetAr*H*), 7.17 (dd, *J* = 5.0, 4.0 Hz, 1H, HetAr*H*), 3.49 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.97 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.19 (s, 3H, $COCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 203.6, 140.0, 134.4, 134.4, 128.2, 52.2, 36.5, 30.0; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 241.0; **HRMS** (ESI, *m/z*) calculated for $(C_8H_{10}NaO_3S_2)^+$ 240.9964 $[M+Na]^+$, found 240.9964; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1719, 1507, 1403, 1344, 1314, 1228, 1133, 1091, 1069, 1017, 856, 772, 730, 666; **$R_f$** 0.19 (*n*-hexane:EtOAc, 3:2).

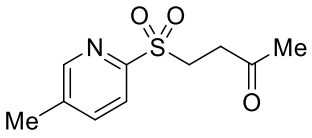
**4-(Pyridin-3-ylsulfonyl)butan-2-one (109x)**




Prepared according to general procedure H, using aldimine **108x** (55 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 1:4), afforded the title compound (34 mg, 80%) as a brown solid.

**MP** (*n*-hexane/EtOAc) 42-44 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 9.11 (dd, *J* = 2.5, 1.0 Hz, 1H, Py*H*), 8.90 (dd, *J* = 5.0, 1.5 Hz, 1H, Py*H*), 8.19 (ddd, *J* = 8.0, 2.5, 1.5 Hz, 1H, Py*H*), 7.53 (ddd, *J* = 8.0, 5.0, 1.0 Hz, 1H, Py*H*), 3.43 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.97 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.19 (s, 3H, $COCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 203.4, 154.7, 149.2, 135.9, 135.7, 124.1, 51.1, 35.7, 30.0; **LRMS** (ESI, *m/z*) $[M+H]^+$ 214.1; **HRMS** (ESI, *m/z*) calculated for $(C_9H_{11}NNaO_3S)^+$ 236.0352 $[M+Na]^+$, found 236.0354; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1719, 1575, 1417, 1313, 1121, 1103, 967, 839, 777, 703, 622; **$R_f$** 0.33 (EtOAc).

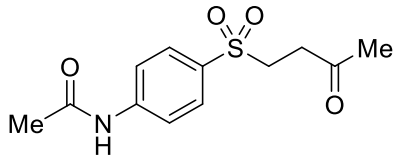
**4-((5-Methylpyridin-2-yl)sulfonyl)butan-2-one (109y)**




Prepared according to general procedure H, using aldimine **108y** (58 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 1:1), afforded the title compound (58 mg, 69%) as an off-white solid.

**MP** (*n*-hexane/EtOAc) 130-132 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.54 (dt, *J* = 2.5, 1.0 Hz, 1H, HetAr*H*), 7.95 (dd, *J* = 8.0, 1.0 Hz, 1H, HetAr*H*), 7.74 (ddq, *J* = 8.0, 2.5, 1.0 Hz, 1H, HetAr*H*), 3.61 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 3.00 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.45 (d, *J* = 1.0 Hz, 3H $ArCH_3$), 2.18 (s, 3H, $COCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 203.9, 154.6, 150.9, 138.49, 138.5, 121.9, 47.1, 36.0, 30.0, 18.7; **LRMS** (ESI, *m/z*) $[M+H]^+$ 228.1 & $[M+Na]^+$ 250.1; **HRMS** (ESI, *m/z*) calculated for $(C_{10}H_{13}NNaO_3S)^+$ 250.0508 $[M+Na]^+$, found 250.0508; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1719, 1311, 1159, 1100, 1027, 902, 839, 770, 664; **$R_f$** 0.32 (*n*-hexane:EtOAc, 1:4).

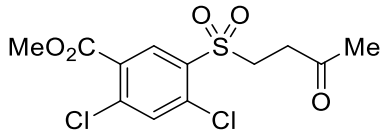
**N-(4-((3-oxobutyl)sulfonyl)phenyl)acetamide (109z)**



Prepared according to general procedure H, using aldimine **108z** (67 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 1:4), afforded the title compound (50 mg, 93%) as an off-white solid.

**MP** (*n*-hexane/EtOAc) 129-131 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.12 (s, 1H, ArN*H*CO), 7.78 (d, *J* = 9.0 Hz, 2H, 2 × Ar*H*), 7.71 (d, *J* = 9.0 Hz, 2H, 2 × Ar*H*), 3.38 (d, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.90 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.19 (s, 3H, $CH_2COCH_3$), 2.17 (s, 3H, $NHCOCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 204.0, 169.2, 143.5, 133.2, 129.3, 119.7, 50.8, 36.2, 30.0, 24.8; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 292.1; **HRMS** (ESI, *m/z*) calculated for $(C_{12}H_{15}NNaO_4S)^+$ 292.0614 $[M+Na]^+$, found 292.0615; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1701, 1591, 1531, 1402, 1370, 1319, 1263, 1137, 1089, 1034, 841, 753; **$R_f$** 0.53 (EtOAc).

**Methyl 2,4-dichloro-5-((3-oxobutyl)sulfonyl)benzoate (111a)**

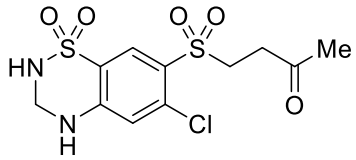


Prepared according to general procedure H, using aldimine **128a** (80 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 1:1), afforded the title compound (41 mg, 61%) as a colourless solid.

**MP** (*n*-hexane/EtOAc) 125-127 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 8.54 (s, 1H, Ar*H*), 7.69 (s, 1H, Ar*H*), 3.96 (s, 3H, $CO_2CH_3$), 3.66 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.95 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.19 (s, 3H, $COCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 203.3, 163.7, 140.8, 136.6,

135.5, 134.4, 129.2, 53.2, 49.1, 35.6, 30.0; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 361.0, 363.0; **HRMS** (ESI, *m/z*) calculated for $(C_{12}H_{12}{}^{35}Cl_2NaO_5S)^+$ 360.9675 $[M+Na]^+$, found 360.9676; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1737, 1721, 1583, 1540, 1435, 1319, 1290, 1256, 1153, 1116, 1075, 971, 891, 839; $\mathbf{R_f}$ 0.57 (*n*-hexane:EtOAc, 3:2).

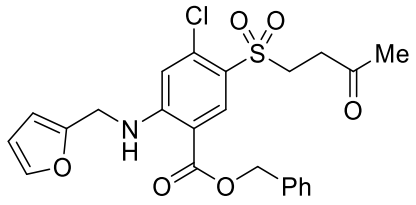
**4-((6-Chloro-1,1-dioxido-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazin-7-yl)sulfonyl)butan-2-one (111b)**




Prepared according to a modified general procedure H, using aldimine **128b** (80 mg, 0.2 mmol, 1.0 equiv.) and acetonitrile as solvent. Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 1:1), afforded the title compound (25 mg) as a colourless solid, in 52% purity (36%), (see appendix).

**MP** (*n*-hexane/EtOAc) 117-119 °C; **$^1$H NMR** (400 MHz, MeOD) $\delta_H$ 8.12 (s, 1H, Ar*H*), 6.97 (s, 1H, Ar*H*), 4.80 (s, 2H $(NH)_2CH_2$), 3.64 (t, *J* = 7.0 Hz, 2H, $SO_2CH_2CH_2$), 2.91 (t, *J* = 7.0 Hz, 2H, $CH_2CH_2CO$), 2.13 (s, 3H, $COCH_3$); **$^{13}$C NMR** (101 MHz, MeOD) $\delta_C$ 206.3, 149.8, 137.7, 130.2, 123.9, 121.0, 118.5, 56.0, 50.3, 36.8, 29.7; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 375.0; **HRMS** (ESI, *m/z*) calculated for $(C_{11}H_{13}ClN_2NaO_5S_2)^+$ 374.9847, 376.9815 $[M+Na]^+$, found 374.9846, 376.9811; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1596, 1552, 1514, 1457, 1412, 1367, 1322, 1238, 1156, 1113, 1055, 1026, 920, 856, 732, 675, 642; $\mathbf{R_f}$ 0.61 (EtOAc).

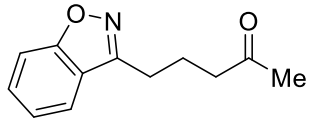
**Benzyl 4-chloro-2-((furan-2-ylmethyl)amino)-5-((3-oxobutyl)sulfonyl)benzoate (111d)**



Prepared according to general procedure H, using aldimine **128d** (108 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (64 mg, 67%) as a colourless solid.

**MP** (*n*-hexane/EtOAc) 97-99 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.75 (t, *J* = 5.5 Hz, 1H, $CH_2NHAr$), 8.63 (s, 1H, Ar*H*), 7.46 – 7.31 (m, 6H 5 × Ph*H*, HetAr*H*), 6.89 (s, 1H, Ar*H*), 6.35 (dd, *J* = 3.5, 2.0 Hz, 1H, HetAr*H*), 6.28 (dd, *J* = 3.5, 1.0 Hz, 1H, HetAr*H*), 5.33 (s, 3H, $CO_2CH_2Ph$), 4.44 (d, *J* = 5.5 Hz, 2H, $HetArCH_2NH$), 3.59 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.93 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.17 (s, 3H $COCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 204.0, 166.9, 153.9, 150.0, 142.8, 138.8, 136.3, 135.6, 128.8, 128.6, 128.4, 122.1, 114.0, 110.7, 108.8, 108.1, 67.0, 49.5, 40.4, 35.9, 30.0; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 498.1, 500.1; **HRMS** (ESI, *m/z*) calculated for $(C_{23}H_{22}ClNNaO_6S)^+$ 498.0749, 500.0721 $[M+Na]^+$, found 498.0746, 500.0713; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 3334, 1719, 1689, 1593, 1570, 1313, 1279, 1258, 1229, 1151, 838, 749, 699; **$R_f$** 0.40 (*n*-hexane:EtOAc, 3:2).

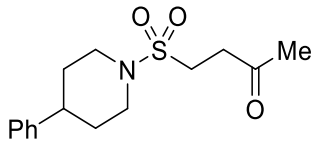
**5-(Benzo[*d*]isoxazol-3-yl)pentan-2-one (112)**



Prepared according to a modified general procedure H, using aldimine **128g** (66 mg, 0.2 mmol, 1.0 equiv.) and THF as solvent. Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1), afforded the title compound (6 mg, 15%) as a colourless solid.

**MP** (n-hexane/EtOAc) 47-49 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.70 (dt, *J* = 8.0, 1.0 Hz, 1H, Ar*H*), 7.60 – 7.50 (m, 2H, 2 × Ar*H*), 7.31 (ddd, *J* = 8.0, 5.5, 2.5 Hz, 1H, Ar*H*), 3.02 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.59 (t, *J* = 7.0 Hz, 2H, $ArCH_2CH_2$), 2.22 – 2.08 (m, 7H, $CH_2(CH_2)_2CH_2$, $COCH_3$); **$^{13}$C NMR** (151 MHz, $CDCl_3$) $\delta_C$ 208.1, 163.2, 158.1, 130.0, 123.4, 121.7, 121.5, 110.1, 42.6, 30.2, 24.6, 21.5; **LRMS** (ESI, *m/z*) $[M+H]^+$ 204.1 & $[M+Na]^+$ 226.1; **HRMS** (ESI, *m/z*) calculated for $(C_{12}H_{14}NO_2)^+$ 204.1019 $[M+H]^+$, found 204.1021; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1714, 1610, 1521, 1440, 1357, 1237, 1159, 894, 838, 753, 618, 609; **$R_f$** 0.67 (n-hexane:EtOAc, 3:2).

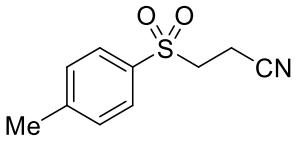
**4-((4-Phenylpiperidin-1-yl)sulfonyl)butan-2-one (116b)**




Prepared according to a modified general procedure H, using aldimine **113b** (72 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 1:1) and subsequent washing with $Et_2O$, afforded the title compound (19 mg, 32%) as a colourless solid.

**MP** (*n*-hexane/EtOAc) 75-78 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.36 – 7.29 (m, 2H, 2 × Ph*H*), 7.25 – 7.18 (m, 3H, 3 × Ph*H*), 3.91 (app. dp, *J* = 12.0, 2.0 Hz, 2H, 2 × $NCH_AH_BCH_2$), 3.21 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 3.00 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO$), 2.87 (app. td, *J* = 12.0, 2.5 Hz, 2H, 2 × $NCH_AH_BCH_2$), 2.62 (tt, *J* = 12.0, 3.6 Hz, 1H, $PhCH(CH_2)_2$), 2.25 (s, 3H, $COCH_3$), 1.99 – 1.89 (m, 2H, 2 × $NCH_2CH_AH_B$), 1.80 (app. qd, *J* = 13.0, 4.0 Hz, 2H, 2 × $NCH_2CH_AH_B$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 204.7, 144.9, 128.8, 126.9, 126.8, 46.6, 43.4, 42.2, 36.8, 33.1, 30.1; **LRMS** (ESI, *m/z*) $[M+H]^+$ 296.2 & $[M+Na]^+$ 318.2.; **HRMS** (ESI, *m/z*) calculated for $(C_{15}H_{21}NNaO_3S)^+$ 318.1134 $[M+Na]^+$, found 318.1136; **IR** ($CHCl_3$, $\nu_{max}$/cm$^{-1}$) 1710, 1326, 1248, 1151, 1054, 939, 837, 760, 702, 640; **$R_f$** 0.19 (*n*-hexane:EtOAc, 3:2).

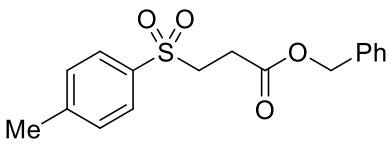
**3-Tosylpropanenitrile (109ab)**




Prepared according to general procedure H, using aldimine **108ah** (34 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (34 mg, 82%) as an off-white solid.

**MP** (*n*-hexane/EtOAc) 80-82 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.80 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 7.41 (d, *J* = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 3.36 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.79 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CN$), 2.47 (s, 3H, $ArCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 146.1, 134.6, 130.5, 128.4, 116.2, 51.3, 21.8, 12.2; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 232.1. The spectroscopic data is in agreement with literature.[340]

**Benzyl 3-tosylpropanoate (109ac)**

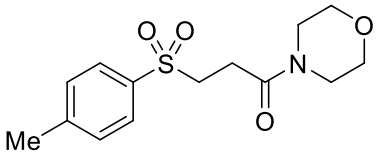



Prepared according to general procedure H, using aldimine **108ah** (34 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (41 mg, 64%) as a colourless solid.

**MP** (*n*-hexane/EtOAc) 70-72 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.78 (d, *J* = 8.5 Hz, 2H, 2 × *p*-MeAr*H*), 7.41 – 7.27 (m, 7H, 2 × *p*-MeAr*H*, 5 × Ph*H*), 5.07 (s, 2H, $CO_2CH_2Ph$), 3.42 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2CH_2$), 2.78 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CO_2Bn$), 2.45 (s, 3H, $ArCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 170.0, 145.2, 135.6, 135.3, 130.2, 128.8, 128.7, 128.5, 128.3, 67.3, 51.6, 28.1, 21.8; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 341.1; **HRMS** (ESI, *m/z*) calculated for

$(C_{17}H_{18}NaO_4S)^+$ 341.0818 $[M+Na]^+$, found 341.0818; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1737, 1597, 1455, 1317, 1289, 1176, 1149, 1088, 817, 736, 699; $\mathbf{R_f}$ 0.57 (*n*-hexane:EtOAc, 3:2).

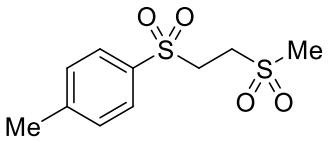
**1-Morpholino-3-tosylpropan-1-one (109ad)**




Prepared according to a modified general procedure H, using aldimine **108ah** (34 mg, 0.2 mmol, 1.0 equiv.) and acetonitrile as solvent. Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 1:1), afforded the title compound (39 mg, 65%) as a yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.78 (d, $J$ = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 7.35 (d, $J$ = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 3.70 – 3.60 (m, 5H, $SO_2CH_2CH_2$, 2 × $NCH_AH_B$, $NCH_AH_B$), 3.58 – 3.51 (m, 2H, 2 × $OCH_AH_B$), 3.48 – 3.39 (m, 3H, 2 × $OCH_AH_B$, $NCH_AH_B$), 2.78 (t, $J$ = 7.5 Hz, 2H, $CH_2CH_2CON$), 2.44 (s, 3H, $ArCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 167.6, 145.1, 136.2, 130.1, 128.1, 66.8, 66.5, 52.1, 45.9, 42.3, 26.0, 21.8; **LRMS** (ESI, *m/z*) $[M+H]^+$ 298.1; **HRMS** (ESI, *m/z*) calculated for $(C_{14}H_{20}NO_4S)^+$ 298.1108 $[M+H]^+$, found 298.1109; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1647, 1512, 1440, 1303, 1246, 1150, 1116, 1088, 1069, 959, 836, 745; $\mathbf{R_f}$ 0.66 (*n*-hexane:EtOAc, 3:2).

**1-Methyl-4-((2-(methylsulfonyl)ethyl)sulfonyl)benzene (109ae)**

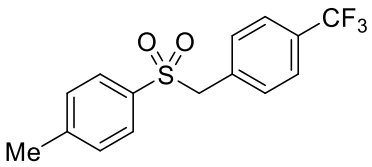



Prepared according to general procedure H, using aldimine **108ah** (34 mg, 0.2 mmol, 1.0 equiv.). Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1 to 3:2), afforded the title compound (19 mg, 36%) as a colourless solid.

**MP** (*n*-hexane/EtOAc) 53-55 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.80 (d, *J* = 8.5 Hz, 2H, 2 × *p*-MeAr*H*), 7.40 (d, *J* = 8.5 Hz, 2H, 2 × *p*-MeAr*H*), 3.57 – 3.49 (m, 2H, $ArSO_2CH_2CH_2$), 3.45 – 3.37 (m, 2H, $CH_3SO_2CH_2CH_2$), 2.99 (s, 3H, $SO_2CH_3$), 2.47 (s, 3H, $ArCH_3$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 146.0, 135.2, 130.5, 128.2, 49.2, 48.1, 41.6, 21.9; **LRMS** (ESI, *m/z*) $[M+Na]^+$ 285.1; **HRMS** (ESI, *m/z*) calculated for $(C_{10}H_{14}NaO_4S_2)^+$ 285.0226 $[M+Na]^+$, found 285.0226; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1298, 1151, 1131, 1086, 821, 774, 731, 657; **$R_f$** 0.17 (*n*-hexane:EtOAc, 3:2).

### 6.5.1.5. Photocatalysis Reactions Utilising the Sulfinate Anions

### 1-Methyl-4-((4-(trifluoromethyl)benzyl)sulfonyl)benzene (120)

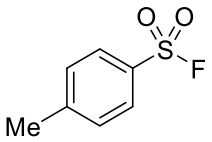



Aldimine **180ah** (34 mg, 0.2 mmol, 1.0 equiv.), potassium carbonate (28 mg, 0.2 mmol, 1.0 equiv.) and 5CzBN (0.9 mg 0.5 mol%) were added to an 8.0 mL microwave vial equipped with a rubber septum. The vial was evacuated and back filled with nitrogen three times, followed by the addition of tris(trimethylsilyl)silane (93 μL, 0.3 mmol, 1.5 equiv.), toluene (1.0 mL) and water (1.0 mL). The vial was then placed in a glass tempering beaker connected to a flow of water, the vial was subsequently submerged in water and irradiated with two EvoluChem™ 450 nm LED spotlights (**Figure 6.15.**). After 4 h the reaction was removed from the reactor and 1-(bromomethyl)-4-(trifluoromethyl)benzene (72 mg, 0.3 mmol, 1.5 equiv.) and TBAB (13 mg, 20 mol%), were added. The reaction was sealed with a cap then heated to 100 °C and stirred for 24 h. The reaction was cooled to room temperature then diluted with EtOAc (2 mL), and the aqueous phase removed. The aqueous phase was further extracted with EtOAc (2 mL × 3), and the organic extracts combined, dried with

sodium sulfate, filtered, and the solvent removed under reduced pressure. Purification by flash column chromatography (*n*-hexane:EtOAc, 4:1), afforded the title compound (59 mg, 94%) as a yellow solid.

**MP** (*n*-hexane /EtOAc) 213-215 °C; **$^{1}$H NMR** (400 MHz, $(CD_3)_2SO$) $\delta_H$ 7.69 (d, $J$ = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 7.61 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-$CF_3$Ar*H*), 7.41 (d, $J$ = 8.0 Hz, 2H, 2 × *p*-MeAr*H*), 7.39 (d, $J$ = 8.5 Hz, 2H, 2 × *p*-$CF_3$Ar*H*), 4.80 (s, 2H, $SO_2CH_2Ar$), 2.40 (s, 3H, $ArCH_3$); **$^{13}$C NMR** (101 MHz, $(CD_3)_2SO$) $\delta_C$ 144.5, 135.4, 133.6 (d, $J$ = 1.5 Hz), 131.8, 129.7, 128.8 (d, $J$ = 32.0 Hz), 128.0, 125.1 (d, $J$ = 4,0 Hz), 124.1 (d, $J$ = 272.0 Hz), 60.1, 21.1; **$^{19}$F NMR** (377 MHz, $(CD_3)_2SO$) $\delta_F$ -61.07 (s); **LRMS** (ESI, *m/z*) $[M+Na]^+$ 337.0. The spectroscopic data is in agreement with literature.[341]

**1-Methyl-4-((4-(trifluoromethyl)benzyl)sulfonyl)benzene (121)**

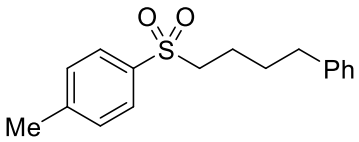



Aldimine **180ah** (34 mg, 0.2 mmol, 1.0 equiv.), potassium carbonate (28 mg, 0.20 mmol, 1.0 equiv.) and 5CzBN (0.9 mg 0.5 mol%) were added to an 8.0 mL microwave vial equipped with a rubber septum. The vial was evacuated and back filled with nitrogen three times, followed by the addition of tris(trimethylsilyl)silane (93 μL, 0.30 mmol, 1.5 equiv.), toluene (1.0 mL) and water (1.0 mL). The vial was then placed in a glass tempering beaker connected to a flow of water, the vial was subsequently submerged in water and irradiated with two EvoluChem™ 450 nm LED spotlights (**Figure 6.15.**). After 4 h the reaction was removed from the reactor and selectfluor® (92 mg, 0.26 mmol, 1.3 equiv.) was added. The reaction was sealed with a cap then heated to 60 °C and stirred for 24 h. The reaction was cooled to room temperature then diluted with EtOAc (2 mL), and the aqueous phase removed. The aqueous phase was further extracted with EtOAc (2 mL × 3), and the organic extracts combined, dried with sodium sulfate, filtered, and the solvent removed under reduced

pressure. Purification by flash column chromatography (*n*-hexane:EtOAc, 9:1), afforded the title compound as an impure colourless oil (see appendix). The yield (37%) was determined by analysis of the $^{19}$F NMR spectra of the crude reaction mixture with trifluorotoluene as an internal standard.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.90 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 2.49 (s, 3H); **$^{19}$F NMR** (376 MHz, $CDCl_3$) $\delta_F$ 66.24 (s). The spectroscopic data is in agreement with literature,[342] and was confirmed by doping with an authentic commercial sample.

**1-Methyl-4-((4-phenylbutyl)sulfonyl)benzene (109af)**




Aldimine **180ah** (96 mg, 0.33 mmol, 1.65 equiv.) and $[Ir[dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2.0 mg 1.0 mol%) were added to an 8.0 mL screw capped vial equipped with a rubber septum. The vial was evacuated and back filled with nitrogen three times, followed by the addition of tris(trimethylsilyl)silane (154 μL, 0.50 mmol, 2.50 equiv.), 4-phenyl-1-butene (30 μL, 0.90 mmol, 1.0 equiv.) and $CH_2Cl_2$ (1.0 mL) and water (0.1 mL). To this mixture was added acetic acid (52 μL, 0.20 mmol, 4.50 equiv.), then the vial was then placed in a glass tempering beaker connected to a flow of water, the vial was subsequently submerged in water and irradiated with two EvoluChem™ 450 nm LED spotlights (**Figure 6.15.**). After 4 h the reaction was diluted with EtOAc (2 mL), and the aqueous phase removed. The aqueous phase was further extracted with EtOAc (2 mL × 3), and the organic extracts combined, dried with sodium sulfate, filtered, and the solvent removed under reduced pressure. Purification by flash column chromatography (*n*-hexane:EtOAc, 3:2), afforded the title compound (26.9 mg, 81% purity, 38%) as a pale-yellow oil.

**$^{1}$H NMR** (400 MHz, $CDCl_3$) $\delta_H$ 7.76 (d, *J* = 8.5 Hz, 2H, 2 × *p*-MeAr*H*), 7.35 (d, *J* = 8.5 Hz, 2H, 2 × *p*-MeAr*H*), 7.28 – 7.22 (m, 2H, 2 × Ph*H*), 7.20 – 7.14 (m, 1H, Ph*H*), 7.12 – 7.06 (m, 2H,

2 × PhH), 3.07 (t, *J* = 7.5 Hz, 2H, $SO_2CH_2(CH_2)_3Ph$), 2.58 (t, *J* = 7.5 Hz, 2H $PhCH_2(CH_2)_3SO_2$), 2.45 (s, 3H, $ArCH_3$), 1.89 – 1.55 (m, 4H, $SO_2CH_2(CH_2)_2CH_2Ph$); **$^{13}$C NMR** (101 MHz, $CDCl_3$) $\delta_C$ 144.7, 141.4, 136.4, 130.0, 128.5, 128.4, 128.2, 126.1, 56.3, 35.4, 30.1, 22.5, 21.7; **LRMS** (ESI, *m/z*) $[M+H]^+$ 289.2 & $[M+Na]^+$ 311.1; **HRMS** (ESI, *m/z*) calculated for $(C_{17}H_{20}NaO_2S)^+$ 311.1076 $[M+Na]^+$, found 311.1075; **IR** ($CHCl_3$, $\nu_{max}/cm^{-1}$) 1598, 1496, 1454, 1405, 1316, 1300, 1145, 1087, 1032, 817, 735, 700, 666, 630; **$R_f$** 0.67 (*n*-hexane:EtOAc, 3:2).

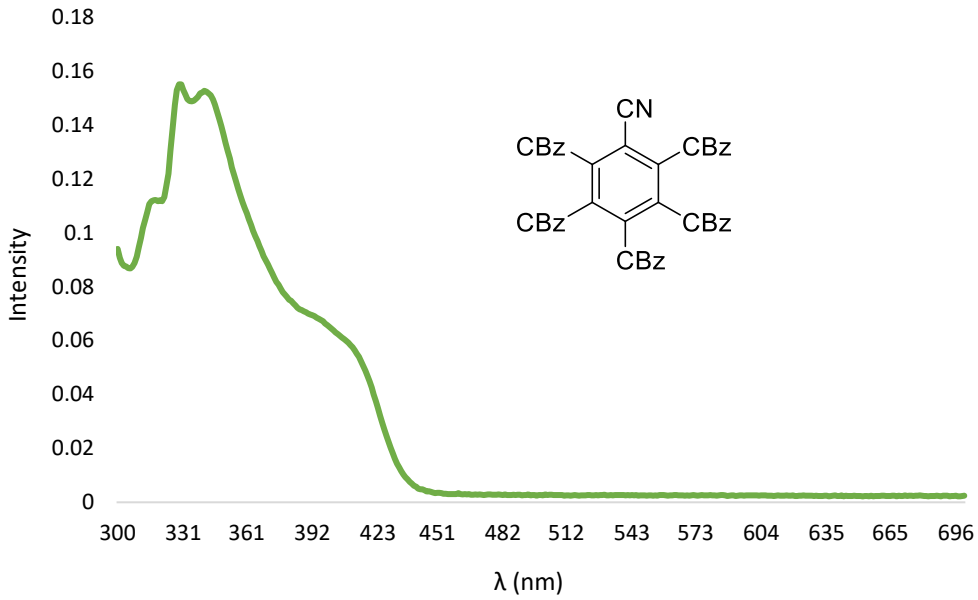
### 6.5.2. Luminescence Studies

#### 6.5.2.1. General Considerations

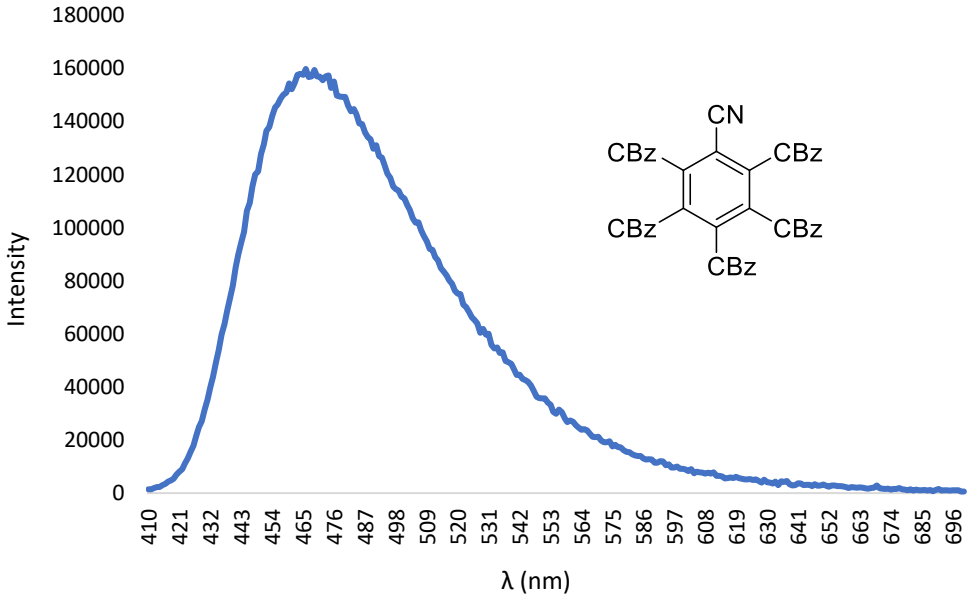
All spectroscopic measurements were conducted in HPLC grade toluene solvents using quartz cuvettes (10 mm path length, Starna Scientific Ltd, UK) under an atmosphere of nitrogen. UV-vis absorption spectra were acquired on a Perkin Elmer Lambda 20 spectrometer at 298 K, with temperature control by a PTP-1 Peltier unit from Perkin Elmer. Fluorescence spectra were acquired at 298 K using an Edinburgh Instruments FS5 spectrofluorometer operating Fluoracle® software, and equipped with a xenon arc lamp (providing 230–1000 nm excitation range), a thermostatic sample holder (SC-20) and an R13456 PMT detector (200–950 nm spectral coverage, Hamamatsu).

#### 6.5.2.2. Absorption and Emission Spectra

Although the absorption and emission spectra for the catalyst 5CzBN has already been reported,[285] this was repeated here (**Graph 6.1.** & **Graph 6.2.**). Initially the absorption spectrum was obtained and the emission spectrum acquired by using an appropriate wavelength of light.

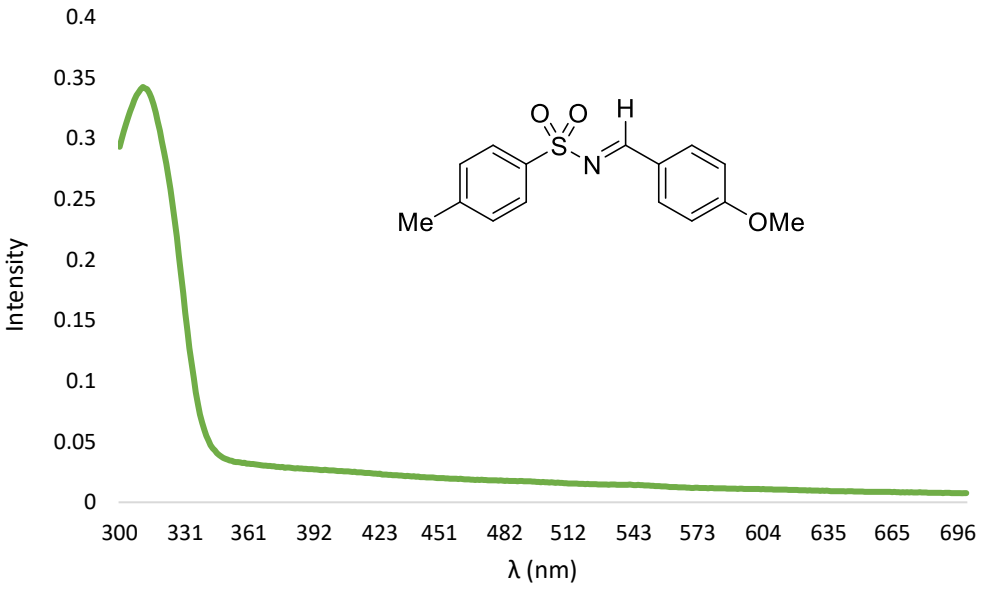



**Graph 6.1.** Absorption spectrum for 5CzBN between 300 and 700 nm.

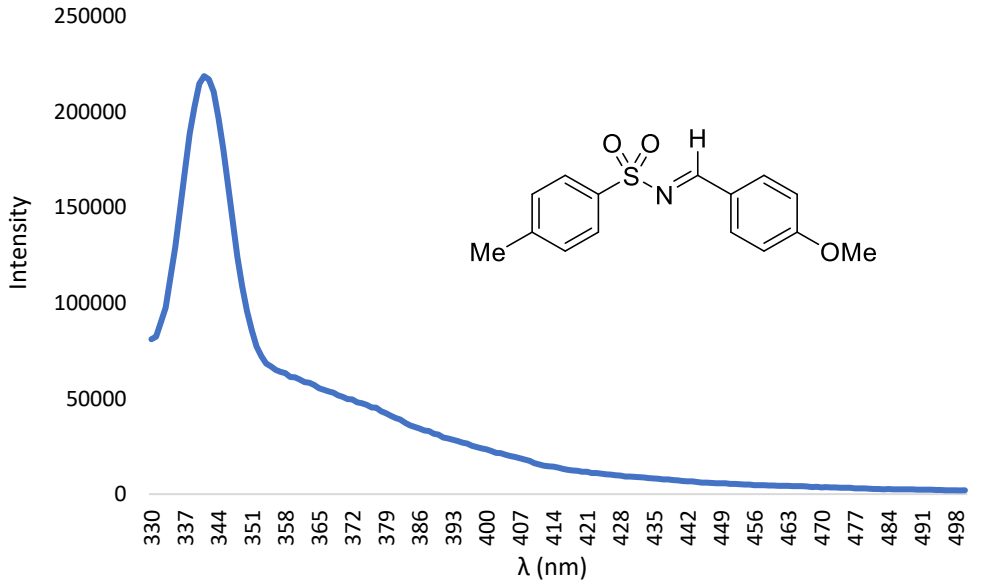



**Graph 6.2.** Emission spectrum for 5CzBN between 410 and 700 nm, using excitation at 400 nm.

These spectra were in good agreement with previous literature. Interestingly, this shows that the photocatalysts is likely just in range of the light used in the reaction, allowing it to proceed. The absorption and emission spectra of the optimum substrate (**108ah**) was obtained in ana analogous manor (**Graph 6.3.** & **Graph 6.4.**).




**Graph 6.3.** Absorption spectrum for **108ah** between 300 and 700 nm.




**Graph 6.4.** Emission spectrum for **108ah** between 330 and 500 nm, using excitation at 310 nm.

The imine was shown to absorb at *ca.* 310 nm and gave a weak fluorescence spectrum. These results are similar to the previous photophysical characterisation of imines.[274]

### 6.5.2.3. Stern-Volmer Quenching

Fluorescence quenching of 5CzBN was investigated by measuring the emission spectrum of 5CzBN in the presence of the reaction components at varying concentrations A solution of 5CzBN

(0.01 mM) was treated with (0.04-0.80 mM) of either aldimine **108ah**, methyl vinyl ketone or (TMS)3SiH in toluene. The samples were irradiated at 400 nm and luminescence was measured over a range of 410 – 700 nm (at $\lambda_{max}$ = 467 nm), (**Table 6.20.** & **Figure 6.16.**).

**Table 6.20.** Fluorescence quenching of catalyst 5CzBN

| *c* (mM) | **108ah** | MVK | $(TMS)_3SiH$ |
|---|---|---|---|
| 0 | 1.00 | 1.00 | 1.00 |
| 0.04 | 1.15 | 1.03 | 1.01 |
| 0.08 | 1.33 | 1.02 | 1.06 |
| 0.12 | 1.47 | 1.03 | 1.06 |
| 0.16 | 1.82 | 1.05 | 1.07 |
| 0.2 | 2.02 | 1.05 | 1.09 |
| 0.4 | 2.49 | 1.08 | 1.12 |
| 0.8 | 3.09 | 1.15 | 1.15 |

The values for each concentration correspond to the normalised intensity ($I/I_0$) examined at λmax = 467 nm.

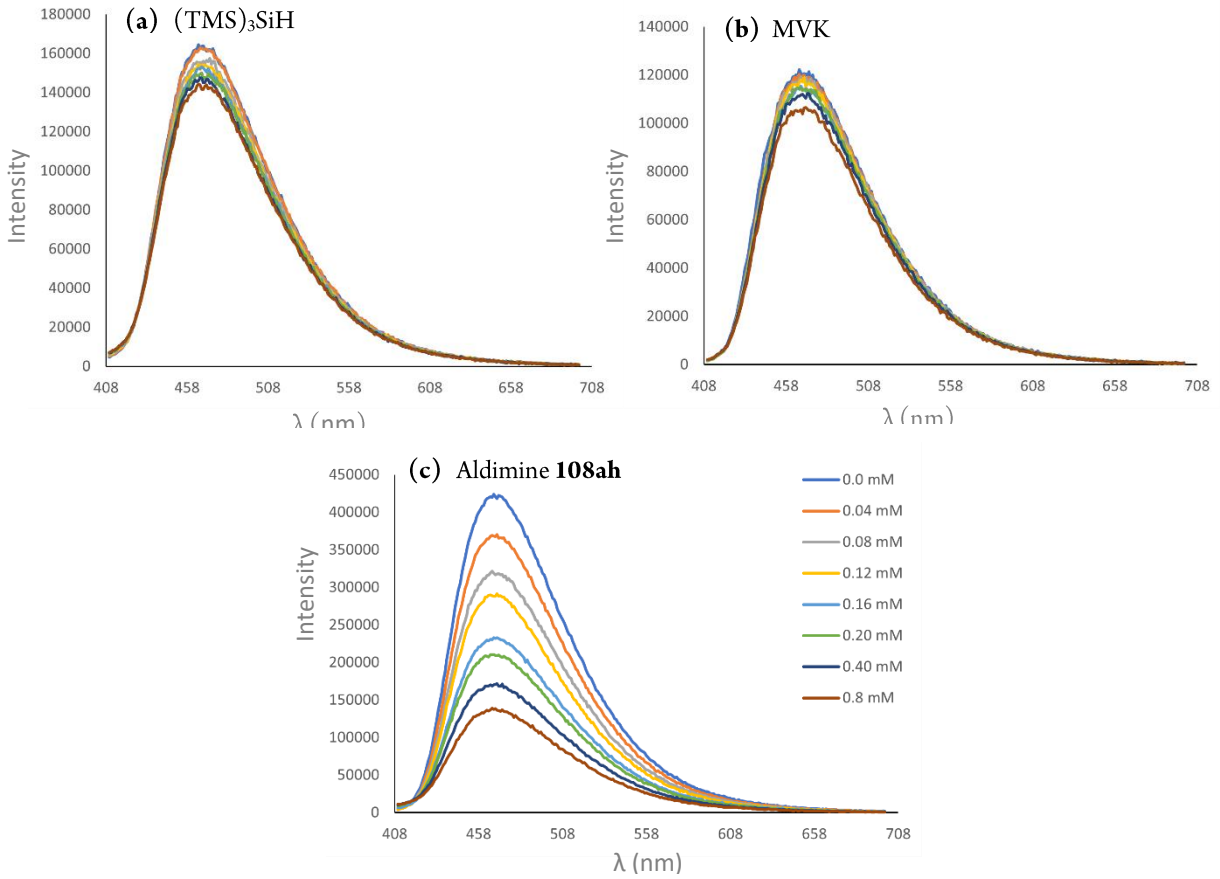



**Figure 6.16.** Fluorescence quenching of the catalyst 5CzBN in the presence of different components in the reaction at varying concentrations in toluene at room temperature. **(a)** In the presence of $(TMS)_3SiH$. **(b)** In the presence of methyl vinyl ketone. **(c)** In the presence of the model aldimine substrate.

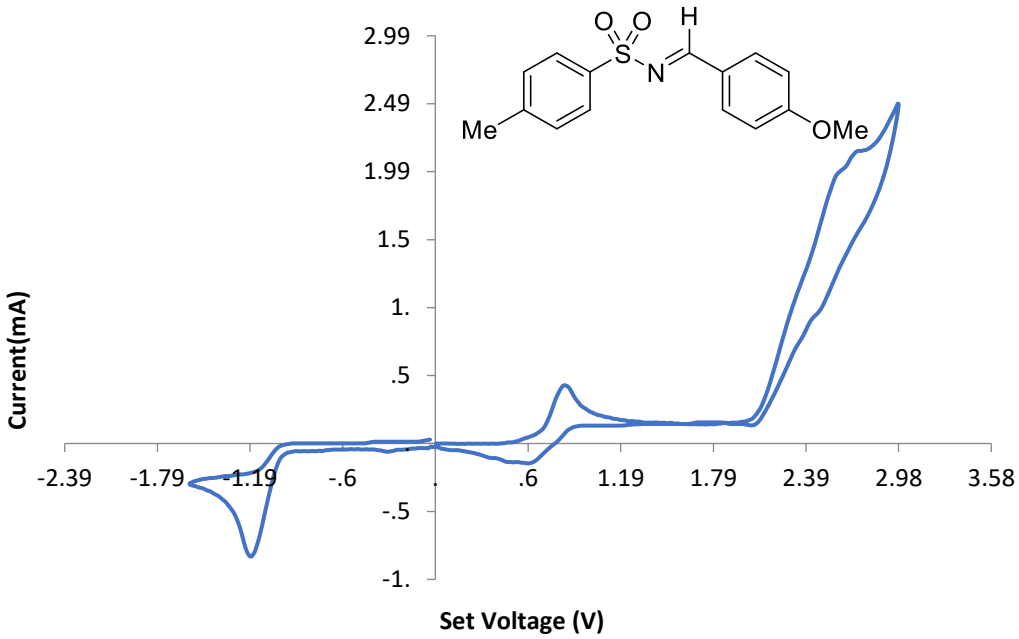
### 6.5.3. Cyclic Voltammetry

#### 6.5.3.1. General Considerations

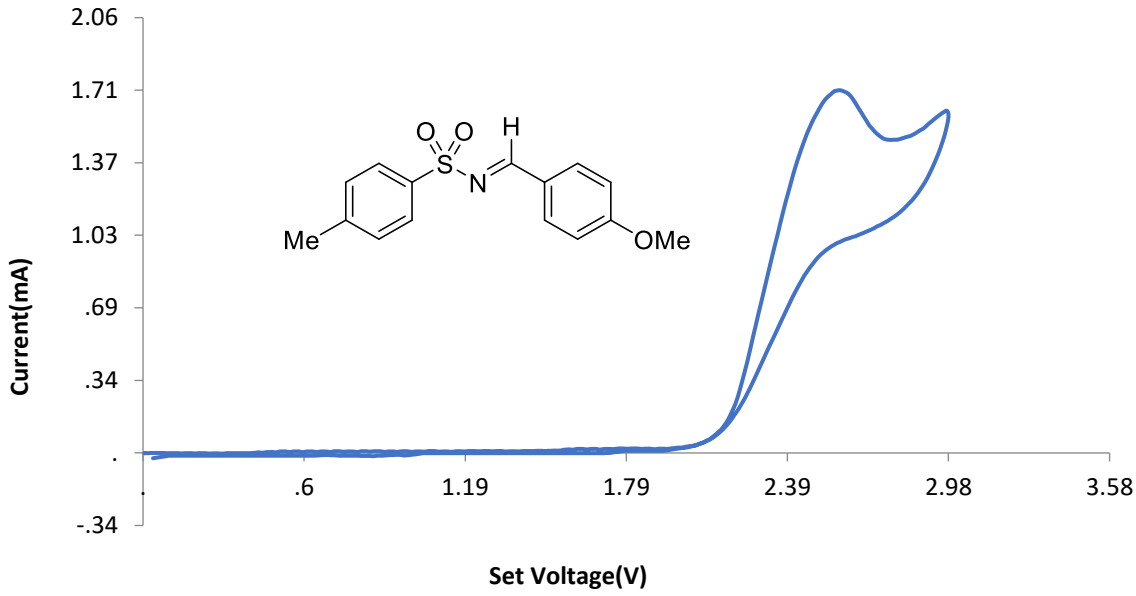
Cyclic voltammetry measurements were made using an IKA ElectroSyn setup. The voltammetric cell consisted of a glassy carbon electrode, a Pt wire counter electrode, and $Ag/AgNO_3$ (0.01 M in acetonitrile) reference electrode. The measurements were carried out under a nitrogen atmosphere using a solution of sample with a concentration of 1.0 mM in acetonitrile containing tetrabutylammonium perchlorate ($n$-$Bu_4N{\cdot}ClO_4$) as a supporting electrolyte (0.10 M). The scan rate was 100 mV $s^{-1}$. Voltammograms were calibrated with ferrocene (0.40 V vs SCE) as an internal reference. The reported potentials were taken at the half-height of the cathodic peaks ($E_{p/2}$) of the compounds since all redox processes were irreversible.

#### 6.5.3.2. Data Acquisition

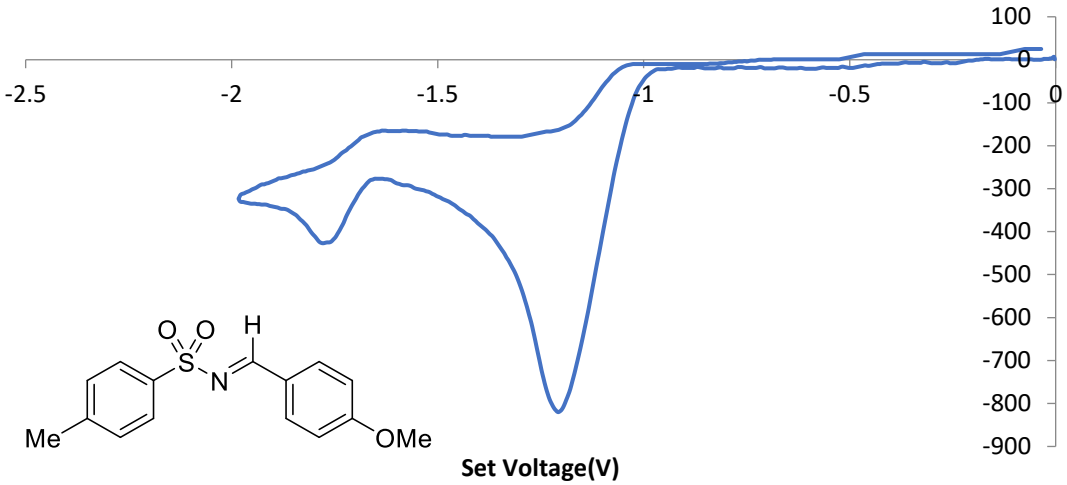
Initially both oxidation and reduction were examined in the presence of ferrocene for **180ah** (**Graph 6.5.**), the sample was the scanned examining the oxidation (**Graph 6.6.**) and reduction process (**Graph 6.7.**).




**Graph 6.5.** Cyclic voltammetry of **180ah** scanning for both oxidation and reduction in the presence of ferrocene.




**Graph 6.6.** Cyclic voltammetry of **180ah** scanning to obtain the oxidation potential.




**Graph 6.7.** Cyclic voltammetry of **180ah** scanning to obtain the reduction potential.

### 6.5.4. Computational Details

All calculations were performed using the Gaussian 16 C.01 software package.[291] Geometry optimisations and frequency calculations were obtained at the B3LYP/6-31++g(d,p) level of theory in the gas phase at 298.15 K.[292a] Vibrational frequencies were calculated to confirm the species as stationary points. Images of the FMOs were generated with the Cubegen utility and visualised with GaussView, these used an isovalue of 0.04. All coordinates are provided in an .xls document as additional information.

# References


[1] a) H. Nakanotani; K. Masui; J. Nishide; T. Shibata; C. Adachi, *Sci. Rep.* **2013**, *3*, 2127; b) N. A. Romero; D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075; c) H. Noda; H. Nakanotani; C. Adachi, *Sci. Adv.* **2018**, *4*, eaao6910; d) E. Speckmeier; T. G. Fischer; K. Zeitler, *J. Am. Chem. Soc.* **2018**, *140*, 15353; e) M. Teders; C. Henkel; L. Anhäuser; F. Strieth-Kalthoff; A. Gómez-Suárez; R. Kleinmans; A. Kahnt; A. Rentmeister; D. Guldi; F. Glorius, *Nat. Chem.* **2018**, *10*, 981; f) P. Lundberg; Y. Tsuchiya; E. M. Lindh; S. Tang; C. Adachi; L. Edman, *Nat. Commun.* **2019**, *10*, 5307.

[2] a) I. Fernández; N. Khiar, *Chem. Rev.* **2003**, *103*, 3651; b) J. Legros; J. R. Dehli; C. Bolm, *Adv. Synth. Catal.* **2005**, *347*, 19; c) E. Wojaczyńska; J. Wojaczyński, *Chem. Rev.* **2010**, *110*, 4303; d) J. Han; V. A. Soloshonok; K. D. Klika; J. Drabowicz; A. Wzorek, *Chem. Soc. Rev.* **2018**, *47*, 1307.

[3] a) T. L. Gilchrist; C. J. Moody, *Chem. Rev.* **1977**, *77*, 409; b) N. Furukawa; S. Oae, *Ind. Eng. Chem. Prod. Res. Dev.* **1981**, *20*, 260; c) I. V. Koval, *Sulfur Rep.* **1993**, *14*, 149.

[4] a) R. Vanacore; A.-J. L. Ham; M. Voehler; C. R. Sanders; T. P. Conrads; T. D. Veenstra; K. B. Sharpless; P. E. Dawson; B. G. Hudson, *Science* **2009**, *325*, 1230; b) S. J. Weiss, *Nat. Chem. Biol.* **2012**, *8*, 740; c) S. Lin; X. Yang; S. Jia; A. M. Weeks; M. Hornsby; P. S. Lee; R. V. Nichiporuk; A. T. Iavarone; J. A. Wells; F. D. Toste; C. J. Chang, *Science* **2017**, *355*, 597; d) F. Xiong; L. Lu; T.-Y. Sun; Q. Wu; D. Yan; Y. Chen; X. Zhang; W. Wei; Y. Lu; W.-Y. Sun; J. J. Li; J. Zhao, *Nat. Commun.* **2017**, *8*, 15912.

[5] a) M. Furukawa; T. Okawara, *Synthesis* **1976**, *1976*, 339; b) B. J. Backes; D. R. Dragoli; J. A. Ellman, *J. Org. Chem.* **1999**, *64*, 5472; c) R. Kawęcki, *Tetrahedron: Asymmetry* **1999**, *10*, 4183; d) R.-H. Zhu; X.-X. Shi, *Tetrahedron: Asymmetry* **2011**, *22*, 387; e) X.-B. Li; Z.-F. Xu; L.-J. Liu; J.-T. Liu, *Eur. J. Org. Chem.* **2014**, *2014*, 1182; f) J. Wei; Z. Sun, *Org. Lett.* **2015**, *17*, 5396; g) D. C. Lenstra; V. Vedovato; E. Ferrer Flegeau; J. Maydom; M. C. Willis, *Org. Lett.* **2016**, *18*, 2086; h) P. K. T. Lo; G. A. Oliver; M. C. Willis, *J. Org. Chem.* **2020**, *85*, 5753.

[6] X. Sun; X. Tu; C. Dai; X. Zhang; B. Zhang; Q. Zeng, *J. Org. Chem.* **2012**, *77*, 4454.

[7] a) J. A. Ellman; T. D. Owens; T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984; b) M. T. Robak; M. A. Herbage; J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600.

[8] a) U. Lücking, *Angew. Chem. Int. Ed.* **2013**, *52*, 9399; b) A. Ajeet; A. K. Mishra; A. Kumar, *Am. J. Pharmacol. Sci.* **2015**, *3*, 18; c) G. C. Nandi; P. I. Arvidsson, *Adv. Synth. Catal.* **2018**, *360*, 2976.

[9] B. M. Trost; C. A. Kalnmals, *Chem. Eur. J.* **2019**, *25*, 11193.

[10] O. Hiroaki; B. Carsten, *Chem. Lett.* **2004**, *33*, 482.

[11] U. Lücking, *Org. Chem. Front.* **2019**, *6*, 1319.

[12] Z.-X. Zhang; T. Q. Davies; M. C. Willis, *J. Am. Chem. Soc.* **2019**, *141*, 13022.

[13] S. Apaydın; M. Török, *Bioorg. Med. Chem. Lett.* **2019**, *29*, 2042.

[14] a) N. Pemberton; H. Graden; E. Evertsson; E. Bratt; M. Lepistö; P. Johannesson; P. H. Svensson, *ACS Med. Chem. Lett.* **2012**, *3*, 574; b) F. Sehgelmeble; J. Janson; C. Ray; S. Rosqvist; S. Gustavsson; L. I. Nilsson; A. Minidis; J. Holenz; D. Rotticci; J. Lundkvist; P. I. Arvidsson, *ChemMedChem* **2012**, *7*, 396; c) S. R. Borhade; R. Svensson; P. Brandt; P. Artursson; P. I. Arvidsson; A. Sandström, *ChemMedChem* **2015**, *10*, 455.

[15] P. K. Chinthakindi; T. Naicker; N. Thota; T. Govender; H. G. Kruger; P. I. Arvidsson, *Angew. Chem. Int. Ed.* **2017**, *56*, 4100.

[16] a) W. Guba; W. Haap; A. Kuglstatter; J.-U. Peters; U. Obst Sander; C. Schnider; R. Wermuth; T. Woltering, WO2015091595A1, **2015**; b) L. Anselm; B. Bartels; C. Dolente; W. Guba; W. Haap; J.-U. Peters; T. Woltering; U. Obst Sander; M. Rogers-Evans, WO2016023927A1, **2016**; c) B. Bartels; C. Dolente; W. Guba; W. Haap; A. Kuglstatter; U. Obst Sander; J.-U. Peters; M. Rogers-Evans; T. Woltering; C. Schnider; R. Wermuth, WO2016012422A1, **2016**; d) C. McBride; L. L. Trzoss; A. Boloor; N. Sokolo-VA; R. M. Pastor; S. T. Staben; C. Stivala; M. Volgraf; S. M. Bronner, WO2020018975A1, **2020**.

[17] P. Mäder; L. Kattner, *J. Med. Chem.* **2020**, *63*, 14243.

[18] H. R. Bentley; E. E. McDermott; J. Pace; J. K. Whitehead; T. Moran, *Nature* **1949**, *163*, 675.
[19] W. S. A. Brusilow; T. J. Peters, *Expert Opin. Ther.* **2017**, *21*, 461.
[20] a) W. B. Rowe; A. Meister, *Proc. Natl. Acad. Sci. USA* **1970**, *66*, 500; b) F. C. Wedler; Y. Sugiyama; K. E. Fisher, *Biochemistry* **1982**, *21*, 2168.
[21] a) V. Bizet; R. Kowalczyk; C. Bolm, *Chem. Soc. Rev.* **2014**, *43*, 2426; b) V. Bizet; C. M. M. Hendriks; C. Bolm, *Chem. Soc. Rev.* **2015**, *44*, 3378; c) J. A. Bull; L. Degennaro; R. Luisi, *Synlett* **2017**, *28*, 2525; d) E. Wojaczyńska; J. Wojaczyński, *Chem. Rev.* **2020**, *120*, 4578.
[22] a) H. R. Bentley; E. E. McDermott; J. K. Whitehead; E. C. Dodds, *Proc. R. Soc. London, Ser. B* **1951**, *138*, 265; b) F. Misani; T. W. Fair; L. Reiner, *J. Am. Chem. Soc.* **1951**, *73*, 459.
[23] B. Gutmann; P. Elsner; A. O'Kearney-McMullan; W. Goundry; D. M. Roberge; C. O. Kappe, *Org. Process Res. Dev.* **2015**, *19*, 1062.
[24] C. R. Johnson; E. R. Janiga, *J. Am. Chem. Soc.* **1973**, *95*, 7692.
[25] M. D. Tzirakis; M. N. Alberti; M. Orfanopoulos, *Org. Lett.* **2011**, *13*, 3364.
[26] M. Reggelin; C. Zur, *Synthesis* **2000**, *2000*, 1.
[27] J. Wang; J. Zhang; K. Miao; H. Yun; H. C. Shen; W. Zhao; C. Liang, *Tetrahedron Lett.* **2017**, *58*, 333.
[28] L. Horner; A. Christmann, *Chem. Ber.* **1963**, *96*, 388.
[29] a) V. J. Bauer; W. J. Fanshawe; S. R. Safir, *J. Org. Chem.* **1966**, *31*, 3440; b) P. Robson; P. R. H. Speakman, *J. Chem. Soc. B* **1968**, 463; c) R. E. Banks; A. Prakash, *J. Chem. Soc., Perkin Trans. 1* **1974**, 1365; d) G. W. Kirby; J. W. M. Mackinnon; R. P. Sharma, *Tetrahedron Lett.* **1977**, *18*, 215; e) R. E. Banks; A. Prakash; N. D. Venayak, *J. Fluorine Chem.* **1980**, *16*, 325; f) G. W. Kirby; H. McGuigan; J. W. M. Mackinnon; D. McLean; R. P. Sharma, *J. Chem. Soc., Perkin Trans. 1* **1985**, 1437.
[30] a) H. Kwart; A. A. Kahn, *J. Am. Chem. Soc.* **1967**, *89*, 1950; b) H. Kwart; A. A. Khan, *J. Am. Chem. Soc.* **1967**, *89*, 1951.
[31] a) C. R. Johnson; C. W. Schroeck, *J. Am. Chem. Soc.* **1968**, *90*, 6852; b) D. R. Rayner; D. M. Von Schriltz; J. Day; D. J. Cram, *J. Am. Chem. Soc.* **1968**, *90*, 2721; c) M. A. Sabol; R. W. Davenport; K. K. Andersen, *Tetrahedron Lett.* **1968**, *9*, 2159; d) D. J. Cram; J. Day; D. R. Rayner; D. M. Von Schriltz; D. J. Duchamp; D. C. Garwood, *J. Am. Chem. Soc.* **1970**, *92*, 7369; e) C. R. Johnson; R. A. Kirchhoff; R. J. Reischer; G. F. Katekar, *J. Am. Chem. Soc.* **1973**, *95*, 4287; f) F. G. Yamagishi; D. R. Rayner; E. T. Zwicker; D. J. Cram, *J. Am. Chem. Soc.* **1973**, *95*, 1916; g) S. Jugé; G. Meyer, *Tetrahedron* **1980**, *36*, 959; h) S. S. Taj; R. Soman, *Tetrahedron: Asymmetry* **1994**, *5*, 1513; i) S. S. Taj; A. C. Shah; D. Lee; G. Newton; R. Soman, *Tetrahedron: Asymmetry* **1995**, *6*, 1731.
[32] J. Wang; M. Frings; C. Bolm, *Chem. Eur. J.* **2014**, *20*, 966.
[33] G. Y. Cho; C. Bolm, *Org. Lett.* **2005**, *7*, 4983.
[34] H. Okamura; C. Bolm, *Org. Lett.* **2004**, *6*, 1305.
[35] M. Zenzola; R. Doran; R. Luisi; J. A. Bull, *J. Org. Chem.* **2015**, *80*, 6391.
[36] C. Lai; G. Mathieu; L. P. Gabrielli Tabarez; H. Lebel, *Chem. Eur. J.* **2019**, *25*, 9423.
[37] a) Y. Tamura; K. Sumoto; J. Minamikawa; M. Ikeda, *Tetrahedron Lett.* **1972**, *13*, 4137; b) C. R. Johnson; R. A. Kirchhoff; H. G. Corkins, *J. Org. Chem.* **1974**, *39*, 2458.
[38] J. Mendiola; J. A. Rincón; C. Mateos; J. F. Soriano; Ó. de Frutos; J. K. Niemeier; E. M. Davis, *Org. Process Res. Dev.* **2009**, *13*, 263.
[39] a) J. Miao; N. G. J. Richards; H. Ge, *Chem. Commun.* **2014**, *50*, 9687; b) H. Yu; Z. Li; C. Bolm, *Angew. Chem. Int. Ed.* **2018**, *57*, 324.
[40] M. Zenzola; R. Doran; L. Degennaro; R. Luisi; J. A. Bull, *Angew. Chem. Int. Ed.* **2016**, *55*, 7203.
[41] L. Degennaro; A. Tota; S. De Angelis; M. Andresini; C. Cardellicchio; M. A. Capozzi; G. Romanazzi; R. Luisi, *Eur. J. Org. Chem.* **2017**, *2017*, 6486.
[42] C. A. Dannenberg; L. Fritze; F. Krauskopf; C. Bolm, *Org. Biomol. Chem.* **2017**, *15*, 1086.
[43] M. Cinquini; S. Colonna; F. Montanari, *ChemComm.* **1970**, 1441.
[44] S. J. Park; H. Baars; S. Mersmann; H. Buschmann; J. M. Baron; P. M. Amann; K. Czaja; H. Hollert; K. Bluhm; R. Redelstein; C. Bolm, *ChemMedChem* **2013**, *8*, 217.

[45] a) J. M. Babcock; C. B. Gerwick; J. X. Huang; M. R. Loso; G. Nakamura; S. P. Nolting; R. B. Rogers; T. C. Sparks; J. Thomas; G. B. Watson; Y. Zhu, *Pest Manag. Sci.* **2011**, *67*, 328; b) G. B. Watson; M. R. Loso; J. M. Babcock; J. M. Hasler; T. J. Letherer; C. D. Young; Y. Zhu; J. E. Casida; T. C. Sparks, *Insect Biochem. Mol. Biol.* **2011**, *41*, 432; c) Y. Zhu; M. R. Loso; G. B. Watson; T. C. Sparks; R. B. Rogers; J. X. Huang; B. C. Gerwick; J. M. Babcock; D. Kelley; V. B. Hegde; B. M. Nugent; J. M. Renga; I. Denholm; K. Gorman; G. J. DeBoer; J. Hasler; T. Meade; J. D. Thomas, *J. Agric. Food. Chem.* **2011**, *59*, 2950; d) K. E. Arndt; D. C. Bland; N. M. Irvine; S. L. Powers; T. P. Martin; J. R. McConnell; D. E. Podhorez; J. M. Renga; R. Ross; G. A. Roth; B. D. Scherzer; T. W. Toyzan, *Org. Process Res. Dev.* **2015**, *19*, 454.

[46] P. K. Claus; W. Rieder; P. Hofbauer; E. Vilsmaier, *Tetrahedron* **1975**, *31*, 505.

[47] H. R. Bentley; J. K. Whitehead, *J. Chem. Soc.* **1950**, 2081.

[48] A. Kjaer; O. Malver, *Tetrahedron Lett.* **1982**, *23*, 2687.

[49] S.-L. Huang; D. Swern, *J. Org. Chem.* **1979**, *44*, 2510.

[50] C. R. Johnson; R. A. Kirchhoff, *J. Org. Chem.* **1979**, *44*, 2280.

[51] N. Gaggero; L. D'Accolti; S. Colonna; R. Curci, *Tetrahedron Lett.* **1997**, *38*, 5559.

[52] J. Gries; J. Krüger, *Synlett* **2014**, *25*, 1831.

[53] H. S. Veale; J. Levin; D. Swern, *Tetrahedron Lett.* **1978**, *19*, 503.

[54] a) F. Collet; R. H. Dodd; P. Dauban, *Org. Lett.* **2008**, *10*, 5473; b) Y. Brussaard; F. Olbrich; E. Schaumann, *Inorg. Chem.* **2013**, *52*, 13160; c) J. Wang; M. Frings; C. Bolm, *Angew. Chem. Int. Ed.* **2013**, *52*, 8661; d) H. Marzag; M. Schuler; A. Tatibouët; V. Reboul, *Eur. J. Org. Chem.* **2017**, *2017*, 896.

[55] H. Lebel; H. Piras, *J. Org. Chem.* **2015**, *80*, 3572.

[56] N. Furukawa; T. Yoshimura; S. Oae, *Tetrahedron Lett.* **1973**, *14*, 2113.

[57] A. Takeshi; Y. Toshiaki; F. Naomichi; O. Shigeru, *Chem. Lett.* **1978**, *7*, 417.

[58] Y. Toshiaki; T. Eiichi; K. Hiroshi; F. Hiroshi; S. Choichiro, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1764.

[59] T. Yoshimura; E. Tsukurimichi; H. Kita; H. Fujii; C. Shimasaki, *Tetrahedron Lett.* **1989**, *30*, 6339.

[60] Y. Toshiaki; T. Eiichi; S. Yasuhisa; K. Hiroshi; S. Choichiro; H. Kiyoshi, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3176.

[61] N. Furukawa; K. Akutagawa; T. Yoshimura; S. Oae, *Synthesis* **1982**, *1982*, 77.

[62] T. Yoshimura; H. Kita; K. Takeuchi; E. Takata; K. Hasegawa; C. Shimasaki; E. Tsukurimichi, *Chem. Lett.* **1992**, *21*, 1433.

[63] A. Tota; M. Zenzola; S. J. Chawner; S. S. John-Campbell; C. Carlucci; G. Romanazzi; L. Degennaro; J. A. Bull; R. Luisi, *Chem. Commun.* **2017**, *53*, 348.

[64] S. Chaabouni; J.-F. Lohier; A.-L. Barthelemy; T. Glachet; E. Anselmi; G. Dagousset; P. Diter; B. Pégot; E. Magnier; V. Reboul, *Chem. Eur. J.* **2018**, *24*, 17006.

[65] G. Zhang; H. Tan; W. Chen; H. C. Shen; Y. Lu; C. Zheng; H. Xu, *ChemSusChem* **2020**, *13*, 922.

[66] J.-F. Lohier; T. Glachet; H. Marzag; A.-C. Gaumont; V. Reboul, *Chem. Commun.* **2017**, *53*, 2064.

[67] A. Tota; C. Carlucci; L. Pisano; G. Cutolo; G. J. Clarkson; G. Romanazzi; L. Degennaro; J. A. Bull; P. Rollin; R. Luisi, *Org. Biomol. Chem.* **2020**, *18*, 3893.

[68] a) S. Cassel; I. Plessis; H. P. Wessel; P. Rollin, *Tetrahedron Lett.* **1998**, *39*, 8097; b) F. Chéry; S. Cassel; H. P. Wessel; P. Rollin, *Eur. J. Org. Chem.* **2002**, *2002*, 171.

[69] E. U. Jonsson; C. R. Johnson, *J. Am. Chem. Soc.* **1971**, *93*, 5308.

[70] E. U. Jonsson; C. C. Bacon; C. R. Johnson, *J. Am. Chem. Soc.* **1971**, *93*, 5306.

[71] C. R. Johnson; E. U. Jonsson; A. Wambsgans, *J. Org. Chem.* **1979**, *44*, 2061.

[72] a) M. R. Jones; D. J. Cram, *J. Am. Chem. Soc.* **1974**, *96*, 2183; b) P. M. Matos; W. Lewis; J. C. Moore; R. A. Stockman, *Org. Lett.* **2018**, *20*, 3674.

[73] a) M. Reggelin; H. Weinberger, *Tetrahedron Lett.* **1992**, *33*, 6959; b) P. M. Matos; R. A. Stockman, *Org. Biomol. Chem.* **2020**, *18*, 6429; c) P. Mendonça Matos; W. Lewis; S. P. Argent; J. C. Moore; R. A. Stockman, *Org. Lett.* **2020**, *22*, 2776.

[74] M. Reggelin; C. Mehler; J. P. Kaiser, *Synlett* **2012**, *23*, 1095.

[75] a) C. R. Johnson; K. G. Bis; J. H. Cantillo; N. A. Meanwell; M. F. D. Reinhard; J. R. Zeller; G. P. Vonk, *J. Org. Chem.* **1983**, *48*, 1; b) B. Gao; S. Li; P. Wu; J. E. Moses; K. B. Sharpless, *Angew. Chem. Int. Ed.* **2018**, *57*, 1939.
[76] a) R. Y. Garlyauskajte; S. V. Sereda; L. M. Yagupolskii, *Tetrahedron* **1994**, *50*, 6891; b) R. Kowalczyk; A. J. F. Edmunds; R. G. Hall; C. Bolm, *Org. Lett.* **2011**, *13*, 768.
[77] a) C. R. Johnson; A. Wambsgans, *J. Org. Chem.* **1979**, *44*, 2278; b) Y. Furusho; Y. Okada; T. Takata, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2827.
[78] M. Harmata, *Tetrahedron Lett.* **1989**, *30*, 437.
[79] M. Harmata; E. O. Schlemper, *Tetrahedron Lett.* **1987**, *28*, 5997.
[80] a) M. Harmata; R. J. Claassen, *Tetrahedron Lett.* **1991**, *32*, 6497; b) M. Harmata; R. J. Claassen; C. L. Barnes, *J. Org. Chem.* **1991**, *56*, 5059.
[81] E. Leemans; F. Colpaert; S. Mangelinckx; S. De Brabandere; B. Denolf; N. De Kimpe, *Synlett* **2011**, 674.
[82] J. Rong; C. Ni; Y. Gu; J. Hu, *Helv. Chim. Acta* **2021**, *104*, e2100019.
[83] P. Cividino; C. Verrier; C. Philouze; S. Carret; J.-F. Poisson, *Adv. Synth. Catal.* **2019**, *361*, 1236.
[84] Y. Aota; Y. Maeda; T. Kano; K. Maruoka, *Chem. Eur. J.* **2019**, *25*, 15755.
[85] Y. Aota; T. Kano; K. Maruoka, *J. Am. Chem. Soc.* **2019**, *141*, 19263.
[86] Y. Aota; T. Kano; K. Maruoka, *Angew. Chem. Int. Ed.* **2019**, *58*, 17661.
[87] S. G. Clarke; J. Kenyon; H. Phillips, *J. Chem. Soc.* **1930**, 1225.
[88] C. Worch; I. Atodiresei; G. Raabe; C. Bolm, *Chem. Eur. J.* **2010**, *16*, 677.
[89] E. S. Levchenko; N. Y. Derkach; A. V. Kirsanov, *Zh. Obs. Khim.* **1960**, *20*, 1971.
[90] E. S. Levchenko; N. Y. Derkach; A. V. Kirsanov, *Zh. Obs. Khim.* **1962**, *32*, 1208.
[91] C. R. Johnson; E. U. Jonsson; C. C. Bacon, *J. Org. Chem.* **1979**, *44*, 2055.
[92] N. Khiar; C. S. Araújo; F. Alcudia; I. Fernández, *J. Org. Chem.* **2002**, *67*, 345.
[93] S. Mondal; S. Malakar, *Tetrahedron* **2020**, *76*, 131662.
[94] E. S. Levchenko; A. V. Kirsanov, *Zh. Obs. Khim.* **1960**, *30*, 1553.
[95] E. S. Levchenko; S. I. E.; A. V. Kirsanov, *Zh. Obs. Khim.* **1960**, *30*, 1941.
[96] A. K. Roy, *J. Am. Chem. Soc.* **1993**, *115*, 2598.
[97] Y. Chen; J. Gibson, *RSC Adv.* **2015**, *5*, 4171.
[98] P. K. Chinthakindi; A. Benediktsdottir; A. Ibrahim; A. Wared; C.-J. Aurell; A. Pettersen; E. Zamaratski; P. I. Arvidsson; Y. Chen; A. Sandström, *Eur. J. Org. Chem.* **2019**, *2019*, 1045.
[99] S. Yu; X. Fu; G. Liu; H. Qui; W. Hu, *Chinese J. Org. Chem.* **2018**, *76*, 895.
[100] M. Feng; B. Tang; S. H. Liang; X. Jiang, *Curr. Top. Med. Chem.* **2016**, *16*, 1200.
[101] H. Takei; I. Watanabe; T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1965**, *38*, 1989.
[102] O. García Mancheño; C. Bolm, *Beilstein J. Org. Chem.* **2007**, *3*, 25.
[103] T. Q. Davies; A. Hall; M. C. Willis, *Angew. Chem. Int. Ed.* **2017**, *56*, 14937.
[104] C. Gnamm; A. Jeanguenat; A. C. Dutton; C. Grimm; D. P. Kloer; A. J. Crossthwaite, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3800.
[105] R. Y. Garlyauskayte; A. V. Bezdudny; C. Michot; M. Armand; Y. L. Yagupolskii; L. M. Yagupolskii, *J. Chem. Soc., Perkin Trans. 1* **2002**, 1887.
[106] C. S. Richards-Taylor; C. Martínez-Lamenca; J. E. Leenaerts; A. A. Trabanco; D. Oehlrich, *J. Org. Chem.* **2017**, *82*, 9898.
[107] S. Greed; E. L. Briggs; F. I. M. Idiris; A. J. P. White; U. Lücking; J. A. Bull, *Chem. Eur. J.* **2020**, *26*, 12533.
[108] a) W. C. Smith; C. W. Tullock; R. D. Smith; V. A. Engelhardt, *J. Am. Chem. Soc.* **1960**, *82*, 551; b) Y. Shirota; T. Nagai; N. Tokura, *Tetrahedron* **1967**, *23*, 639.
[109] M. Wright; C. Martínez-Lamenca; J. E. Leenaerts; P. E. Brennan; A. A. Trabanco; D. Oehlrich, *J. Org. Chem.* **2018**, *83*, 9510.
[110] A. Tota; S. St John-Campbell; E. L. Briggs; G. O. Estévez; M. Afonso; L. Degennaro; R. Luisi; J. A. Bull, *Org. Lett.* **2018**, *20*, 2599.
[111] M. Bremerich; C. M. Conrads; T. Langletz; C. Bolm, *Angew. Chem. Int. Ed.* **2019**, *58*, 19014.
[112] Y. Liu; Q. Pan; X. Hu; Y. Guo; Q.-Y. Chen; C. Liu, *Org. Lett.* **2021**.

[113] a) P. S. Fier; S. Kim; K. M. Maloney, *J. Am. Chem. Soc.* **2019**, *141*, 18416; b) P. S. Fier; K. M. Maloney, *J. Am. Chem. Soc.* **2019**, *141*, 1441; c) M. Pérez-Palau; J. Cornella, *Eur. J. Org. Chem.* **2020**, *2020*, 2497.
[114] S. V. Zasukha; V. M. Timoshenko; A. A. Tolmachev; V. O. Pivnytska; O. Gavrylenko; S. Zhersh; Y. Shermolovich; O. O. Grygorenko, *Chem. Eur. J.* **2019**, *25*, 6928.
[115] N. V. Kondratenko; V. I. Popov; R. O. A.; I. e. N. V.; L. M. Yagupolskii, *Zh. Obs. Khim.* **1986**, *22*, 1716.
[116] J. Wen; H. Cheng; S. Dong; C. Bolm, *Chem. Eur. J.* **2016**, *22*, 5547.
[117] R. Paulini; D. Breuninger; W. Von Deyn; H. M. M. Bastiaans; C. Beyer; D. D. Anspaugh; H. Oloumi-Sadeghi, W0 2009/156336 A1, **2009**.
[118] M. Andresini; M. Spennacchio; G. Romanazzi; F. Ciriaco; G. Clarkson; L. Degennaro; R. Luisi, *Org. Lett.* **2020**, *22*, 7129.
[119] H. Yu; Z. Li; C. Bolm, *Angew. Chem. Int. Ed.* **2018**, *57*, 15602.
[120] F. Izzo; M. Schäfer; R. Stockman; U. Lücking, *Chem. Eur. J.* **2017**, *23*, 15189.
[121] E. L. Briggs; A. Tota; M. Colella; L. Degennaro; R. Luisi; J. A. Bull, *Angew. Chem. Int. Ed.* **2019**, *58*, 14303.
[122] T. J. Maricich; R. A. Jourdenais; T. A. Albright, *J. Am. Chem. Soc.* **1973**, *95*, 5831.
[123] T. J. Maricich; M. J. Allan; B. S. Kislin; A. I. T. Chen; F.-C. Meng; C. Bradford; N.-C. Kuan; J. Wood; O. Aisagbonhi; A. Poste; D. Wride; S. Kim; T. Santos; M. Fimbres; D. Choi; H. Elia; J. Kaladjian; A. Abou-Zahr; A. Mejia, *Synthesis* **2013**, *45*, 3361.
[124] a) T. J. Maricich, *J. Am. Chem. Soc.* **1968**, *90*, 7179; b) T. J. Maricich; V. L. Hoffman, *J. Am. Chem. Soc.* **1974**, *96*, 7770; c) T. J. Maricich; C. N. Angeletakis; R. Mjanger, *J. Org. Chem.* **1984**, *49*, 1928.
[125] H. Tanimoto; K. Kakiuchi, *Nat. Prod. Comm.* **2013**, *8*, 1021.
[126] Z. Wu; D. Li; H. Li; B. Zhu; H. Sun; J. S. Francisco; X. Zeng, *Angew. Chem. Int. Ed.* **2016**, *55*, 1507.
[127] T. Shingaki; M. Inagaki; N. Torimoto; M. Takebayashi, *Chem. Lett.* **1972**, *1*, 1181.
[128] A. V. Gontcharov; H. Liu; K. B. Sharpless, *Org. Lett.* **1999**, *1*, 783.
[129] T. J. Maricich; C. N. Angeletakis, *J. Org. Chem.* **1984**, *49*, 1931.
[130] T. J. Maricich; S. Madhusoodanan; C. A. Kapfer, *Tetrahedron Lett.* **1977**, *18*, 983.
[131] T. Q. Davies; M. C. Willis, *Chem. Eur. J.* **2021**, *n/a*.
[132] T. Q. Davies; M. J. Tilby; J. Ren; N. A. Parker; D. Skolc; A. Hall; F. Duarte; M. C. Willis, *J. Am. Chem. Soc.* **2020**, *142*, 15445.
[133] W. Kohn; A. D. Becke; R. G. Parr, *J. Phys. Chem.* **1996**, *100*, 12974.
[134] N. Mardirossian; M. Head-Gordon, *Mol. Phys.* **2017**, *115*, 2315.
[135] V. C. Grignard, *Compt. Rend. Hebd. Seances Acad. Sci.* **1900**, *130*, 1322.
[136] D. Seyferth, *Organometallics* **2009**, *28*, 1598.
[137] a) L. J. Guggenberger; R. E. Rundle, *J. Am. Chem. Soc.* **1968**, *90*, 5375; b) M. Vallino, *J. Organomet. Chem.* **1969**, *20*, 1.
[138] W. Schlenk; W. Schlenk jun, *Ber. Dtsch. Chem. Ges.* **1929**, *62*, 920.
[139] F. W. Walker; E. C. Ashby, *J. Am. Chem. Soc.* **1969**, *91*, 3845.
[140] E. C. Ashby, *Pure Appl. Chem.* **1980**, *52*, 545.
[141] a) J. Axten; J. Troy; P. Jiang; M. Trachtman; C. W. Bock, *Struct. Chem.* **1994**, *5*, 99; b) T. Mori; S. Kato, *Chem. Phys. Lett.* **2007**, *437*, 159; c) A. M. Henriques; A. G. H. Barbosa, *J. Phys. Chem. A* **2011**, *115*, 12259; d) H. Lioe; J. M. White; R. A. J. O'Hair, *J. Mol. Model.* **2011**, *17*, 1325.
[142] a) A. W. Ehlers; G. P. M. van Klink; M. J. van Eis; F. Bickelhaupt; P. H. J. Nederkoorn; K. Lammertsma, *J. Mol. Model.* **2000**, *6*, 186; b) J. Tammiku; P. Burk; A. Tuulmets, *J. Phys. Chem. A* **2001**, *105*, 8554; c) J. Tammiku-Taul; P. Burk; A. Tuulmets, *J. Phys. Chem. A* **2004**, *108*, 133; d) E. R. Curtis; M. D. Hannigan; A. K. Vitek; P. M. Zimmerman, *J. Phys. Chem. A* **2020**, *124*, 1480.
[143] a) K. Ohkubo; F. Watanabe, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2867; b) H. Kato; S. Tsuruya, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1001.
[144] R. M. Peltzer; O. Eisenstein; A. Nova; M. Cascella, *J. Phys. Chem. B* **2017**, *121*, 4226.
[145] a) S. Yamazaki; S. Yamabe, *J. Org. Chem.* **2002**, *67*, 9346; b) T. Mori; S. Kato, *J. Phys. Chem. A* **2009**, *113*, 6158.

[146] R. M. Peltzer; J. Gauss; O. Eisenstein; M. Cascella, *J. Am. Chem. Soc.* **2020**, *142*, 2984.
[147] S. Sakamoto; T. Imamoto; K. Yamaguchi, *Org. Lett.* **2001**, *3*, 1793.
[148] a) S. H. Vosko; L. Wilk; M. Nusair, *Can. J. Phys.* **1980**, *58*, 1200; b) C. Lee; W. Yang; R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785; c) P. J. Stephens; F. J. Devlin; C. F. Chabalowski; M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623.
[149] J. L. Bao; L. Gagliardi; D. G. Truhlar, *J. Phys. Chem. Lett.* **2018**, *9*, 2353.
[150] H. Kruse; L. Goerigk; S. Grimme, *J. Org. Chem.* **2012**, *77*, 10824.
[151] T. Schulz; S. Deuerlein; D. Stalke, *Eur. J. Inorg. Chem.* **2010**, *2010*, 2178.
[152] C. R. Groom; I. J. Bruno; M. P. Lightfoot; S. C. Ward, *Acta Crystallogr., Sect. B* **2016**, *72*, 171.
[153] J. P. Perdew; K. Burke; M. Ernzerhof, *Phys. Rev. Lett.* **1996**, *77*, 3865.
[154] Y. Zhao; D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215.
[155] J.-D. Chai; M. Head-Gordon, *PCCP* **2008**, *10*, 6615.
[156] J. Tao; J. P. Perdew; V. N. Staroverov; G. E. Scuseria, *Phys. Rev. Lett.* **2003**, *91*, 146401.
[157] S. Grimme; S. Ehrlich; L. Goerigk, *J. Comput. Chem.* **2011**, *32*, 1456.
[158] V. A. Rassolov; M. A. Ratner; J. A. Pople; P. C. Redfern; L. A. Curtiss, *J. Comput. Chem.* **2001**, *22*, 976.
[159] J. T. Margraf; A. Perera; J. J. Lutz; R. J. Bartlett, *J. Chem. Phys.* **2017**, *147*, 184101.
[160] J.-D. Chai; M. Head-Gordon, *J. Chem. Phys.* **2008**, *128*, 084106.
[161] B. A. Shainyan; A. V. Kuzmin, *J. Phys. Org. Chem.* **2014**, *27*, 156.
[162] J. N. Harvey, *PCCP* **2007**, *9*, 331.
[163] F. L. Hirshfeld, *Theor. Chim. Acta* **1977**, *44*, 129.
[164] K. B. Wiberg, *Tetrahedron* **1968**, *24*, 1083.
[165] S. Chakraborty; C. Saha, *Resonance* **2016**, *21*, 151.
[166] S. Pirinen; I. O. Koshevoy; P. Denifl; T. T. Pakkanen, *Organometallics* **2013**, *32*, 4208.
[167] a) C. Blomberg; H. S. Mosher, *J. Organomet. Chem.* **1968**, *13*, 519; b) C. Blomberg; R. M. Salinger; H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2385; c) C. Blomberg; H. H. Grootveld; T. H. Gerner; F. Bickelhaupt, *J. Organomet. Chem.* **1970**, *24*, 549; d) E. C. Ashby; I. G. Lopp; J. D. Buhler, *J. Am. Chem. Soc.* **1975**, *97*, 1964; e) E. C. Ashby, **1980**, *52*, 545; f) E. C. Ashby; J. R. Bowers, *J. Am. Chem. Soc.* **1981**, *103*, 2242; g) T. Lund; M. L. Pedersen; L. A. Frandsen, *Tetrahedron Lett.* **1994**, *35*, 9225; h) J. J. Gajewski; W. Bocian; N. J. Harris; L. P. Olson; J. P. Gajewski, *J. Am. Chem. Soc.* **1999**, *121*, 326; i) R. W. Hoffmann; B. Hölzer, *Chem. Commun.* **2001**, 491.
[168] T. Q. Davies; M. J. Tilby; D. Skolc; A. Hall; M. C. Willis, *Org. Lett.* **2020**, *22*, 9495.
[169] a) R. Fusco; F. Tericoni, *Chim. Ind. (Milan)* **1965**, *47*, 61; b) C. R. Johnson; C. W. Schroeck, *J. Am. Chem. Soc.* **1973**, *95*, 7418; c) C. R. Johnson; C. W. Schroeck; J. R. Shanklin, *J. Am. Chem. Soc.* **1973**, *95*, 7424; d) C. S. Shiner; A. H. Berks, *J. Org. Chem.* **1988**, *53*, 5542; e) J. Brandt; H.-J. Gais, *Tetrahedron: Asymmetry* **1997**, *8*, 909.
[170] M. Koji; T. Fumio, *Chem. Lett.* **1988**, *17*, 1997.
[171] S. Dong; M. Frings; H. Cheng; J. Wen; D. Zhang; G. Raabe; C. Bolm, *J. Am. Chem. Soc.* **2016**, *138*, 2166.
[172] P. Kielbasinski, *Pol. J. Chem.* **1999**, *73*, 735.
[173] F. G. Bordwell; J. C. Branca; C. R. Johnson; N. R. Vanier, *J. Org. Chem.* **1980**, *45*, 3884.
[174] a) M. Kahraman; G. H. Posner; S. Uttam, **2003**; b) M. Kahraman; S. Sinishtaj; P. M. Dolan; T. W. Kensler; S. Peleg; U. Saha; S. S. Chuang; G. Bernstein; B. Korczak; G. H. Posner, *J. Med. Chem.* **2004**, *47*, 6854.
[175] a) M. J. McGrath; C. Bolm, *Beilstein J. Org. Chem.* **2007**, *3*, 33; b) A. G. Pandey; M. J. McGrath; O. García Mancheño; C. Bolm, *Synthesis* **2011**, *2011*, 3827.
[176] Y. Sun; N. Cramer, *Angew. Chem. Int. Ed.* **2018**, *57*, 15539.
[177] B. Shen; B. Wan; X. Li, *Angew. Chem. Int. Ed.* **2018**, *57*, 15534.
[178] M. Brauns; N. Cramer, *Angew. Chem. Int. Ed.* **2019**, *58*, 8902.
[179] T. Zhou; P.-F. Qian; J.-Y. Li; Y.-B. Zhou; H.-C. Li; H.-Y. Chen; B.-F. Shi, *J. Am. Chem. Soc.* **2021**, *143*, 6810.
[180] Z. Li; M. Frings; H. Yu; G. Raabe; C. Bolm, *Org. Lett.* **2018**, *20*, 7367.

[181] C. Liang; F. Collet; F. Robert-Peillard; P. Müller; R. H. Dodd; P. Dauban, *J. Am. Chem. Soc.* **2008**, *130*, 343.
[182] C. Liang; F. Robert-Peillard; C. Fruit; P. Müller; R. H. Dodd; P. Dauban, *Angew. Chem. Int. Ed.* **2006**, *45*, 4641.
[183] a) P. H. Di Chenna; F. Robert-Peillard; P. Dauban; R. H. Dodd, *Org. Lett.* **2004**, *6*, 4503; b) M. Funes Maldonado; F. Sehgelmeble; F. Bjarnemark; M. Svensson; J. Åhman; P. I. Arvidsson, *Tetrahedron* **2012**, *68*, 7456; c) Á. Beltrán; C. Lescot; M. Mar Díaz-Requejo; P. J. Pérez; P. Dauban, *Tetrahedron* **2013**, *69*, 4488; d) S. R. Borhade; A. Sandström; P. I. Arvidsson, *Org. Lett.* **2013**, *15*, 1056; e) S. R. K. Battula; G. V. Subbareddy; I. E. Chakravarthy, *Tetrahedron Lett.* **2014**, *55*, 517; f) G. C. Nandi; S. R. Kota; T. Naicker; T. Govender; H. G. Kruger; P. I. Arvidsson, *Eur. J. Org. Chem.* **2015**, 2861; g) G. C. Nandi; S. R. Kota; P. B. Wakchaure; P. K. Chinthakindi; T. Govender; H. G. Kruger; T. Naicker; P. I. Arvidsson, *RSC Adv.* **2015**, *5*, 62084; h) P. B. Wakchaure; S. R. Borhade; A. Sandström; P. I. Arvidsson, *Eur. J. Org. Chem.* **2015**, 213; i) Y. Chen, *Synthesis* **2016**, *48*, 1019; j) G. C. Nandi, *Eur. J. Org. Chem.* **2017**, *2017*, 6633; k) G. C. Nandi; C. Raju, *Org. Biomol. Chem.* **2017**, *15*, 2234; l) F. Izzo; M. Schäfer; P. Lienau; U. Ganzer; R. Stockman; U. Lücking, *Chem. Eur. J.* **2018**, *24*, 9295; m) A.-K. Bachon; A. Hermann; C. Bolm, *Chem. Eur. J.* **2019**, *25*, 5889; n) N. Thota; P. Makam; K. K. Rajbongshi; S. Nagiah; N. S. Abdul; A. A. Chuturgoon; A. Kaushik; G. Lamichhane; A. M. Somboro; H. G. Kruger; T. Govender; T. Naicker; P. I. Arvidsson, *ACS Med. Chem. Lett.* **2019**, *10*, 1457; o) A. Wimmer; B. König, *Org. Lett.* **2019**, *21*, 2740.
[184] a) M. C. Willis, *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765; b) A. Borissov; T. Q. Davies; S. R. Ellis; T. A. Fleming; M. S. W. Richardson; D. J. Dixon, *Chem. Soc. Rev.* **2016**, *45*, 5474; c) X.-P. Zeng; Z.-Y. Cao; Y.-H. Wang; F. Zhou; J. Zhou, *Chem. Rev.* **2016**, *116*, 7330.
[185] a) R. Noyori; M. Tokunaga; M. Kitamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36; b) H. Pellissier, *Tetrahedron* **2003**, *59*, 8291.
[186] K. Faber, *Chem. Eur. J.* **2001**, *7*, 5004.
[187] Y. Chen; J. Söderlund; G. Grönberg; A. Pettersen; C.-J. Aurell, *Eur. J. Org. Chem.* **2019**, *2019*, 4731.
[188] O. J. Scherer; R. Schmitt, *J. Organomet. Chem.* **1969**, *16*, P11.
[189] C. I. Nieto; P. Cabildo; M. Á. García; R. M. Claramunt; I. Alkorta; J. Elguero, *Beilstein J. Org. Chem.* **2014**, *10*, 1620.
[190] P. K. Chinthakindi; A. Benediktsdottir; P. I. Arvidsson; Y. Chen; A. Sandström, *Eur. J. Org. Chem.* **2020**, 3796.
[191] a) S. Shirakawa; K. Maruoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 4312; b) R. J. Armstrong; M. D. Smith, *Angew. Chem. Int. Ed.* **2014**, *53*, 12822; c) J. D. Jolliffe; R. J. Armstrong; M. D. Smith, *Nat. Chem.* **2017**, *9*, 558.
[192] a) J. Ren; X. Ban; X. Zhang; S. M. Tan; R. Lee; C.-H. Tan, *Angew. Chem. Int. Ed., n/a*; b) M. Bandini; A. Bottoni; A. Eichholzer; G. P. Miscione; M. Stenta, *Chem. Eur. J.* **2010**, *16*, 12462; c) K. Tomooka; K. Uehara; R. Nishikawa; M. Suzuki; K. Igawa, *J. Am. Chem. Soc.* **2010**, *132*, 9232; d) L. Wang; S. Shirakawa; K. Maruoka, *Angew. Chem. Int. Ed.* **2011**, *50*, 5327; e) S. Shirakawa; K. Liu; K. Maruoka, *J. Am. Chem. Soc.* **2012**, *134*, 916; f) M. Weiß; S. Borchert; E. Rémond; S. Jugé; H. Gröger, *Heteroat. Chem* **2012**, *23*, 202; g) X. Zhang; J. Ren; S. M. Tan; D. Tan; R. Lee; C.-H. Tan, *Science* **2019**, *363*, 400.
[193] a) F. Gelat; J. Jayashankaran; J.-F. Lohier; A.-C. Gaumont; S. Perrio, *Org. Lett.* **2011**, *13*, 3170; b) F. Gelat; A.-C. Gaumont; S. Perrio, *Journal of Sulfur Chemistry* **2013**, *34*, 596; c) L. Zong; X. Ban; C. W. Kee; C.-H. Tan, *Angew. Chem. Int. Ed.* **2014**, *53*, 11849.
[194] D. E. Patterson; S. Xie; L. A. Jones; M. H. Osterhout; C. G. Henry; T. D. Roper, *Org. Process Res. Dev.* **2007**, *11*, 624.
[195] a) S. G. Davies; O. Ichihara, *Tetrahedron Lett.* **1998**, *39*, 6045; b) A. L. Williams; S. R. Dandepally; S. V. Kotturi, *Molecular Diversity* **2010**, *14*, 697; c) N. Iqbal; E. J. Cho, *Adv. Synth. Catal.* **2015**, *357*, 2187.
[196] M. F. A. Adamo; G. Bencivenni; D. S. Illera; M. Moccia; K. N. Houk; J. A. Izzo; J. Novacek; P. Grieco; M. J. Vetticatt; M. Waser, *Chem. Eur. J.* **2021**, *n/a*.
[197] B. Xiang; K. M. Belyk; R. A. Reamer; N. Yasuda, *Angew. Chem. Int. Ed.* **2014**, *53*, 8375.

[198] a) M. Luzung; G. Humphrey; Ba Xiang; K. M Belyk; M. S Dalby; W. Schwab; B. Klenke; T. Moody; G. Brown, WO2015088931 (A1) **2015**; b) G. R. Humphrey; S. M. Dalby; T. Andreani; B. Xiang; M. R. Luzung; Z. J. Song; M. Shevlin; M. Christensen; K. M. Belyk; D. M. Tschaen, *Org. Process Res. Dev.* **2016**, *20*, 1097.
[199] a) C. Q. He; A. Simon; Y.-h. Lam; A. P. J. Brunskill; N. Yasuda; J. Tan; A. M. Hyde; E. C. Sherer; K. N. Houk, *J. Org. Chem.* **2017**, *82*, 8645; b) J. A. Daponte; Y. Guo; R. T. Ruck; J. E. Hein, *ACS Catal.* **2019**, *9*, 11484.
[200] R.-S. Yang; H. Sheng; K. W. Lexa; E. C. Sherer; L.-K. Zhang; B. Xiang; R. Helmy; B. Mao, *J. Am. Soc. Mass. Spectrom.* **2017**, *28*, 452.
[201] M. Steurer; C. Bolm, *J. Org. Chem.* **2010**, *75*, 3301.
[202] R. Kluge; H. Hocke; M. Schulz; F. Schilke, *Phosphorus, Sulfur, and Silicon and the Related Elements* **1999**, *149*, 179.
[203] a) M. Schelhaas; H. Waldmann, *Angew. Chem. Int. Ed.* **1996**, *35*, 2056; b) K. T. Howard; J. D. Chisholm, *Org. Prep. Proced. Int.* **2016**, *48*, 1.
[204] S. D. Bull; S. G. Davies; G. Fenton; A. W. Mulvaney; R. S. Prasad; A. D. Smith, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3765.
[205] F. Robert-Peillard; P. H. Di Chenna; C. Liang; C. Lescot; F. Collet; R. H. Dodd; P. Dauban, *Tetrahedron: Asymmetry* **2010**, *21*, 1447.
[206] a) J. Schörgenhumer; M. Tiffner; M. Waser, *Beilstein J. Org. Chem.* **2017**, *13*, 1753; b) N. Patel; R. Sood; P. V. Bharatam, *Chem. Rev.* **2018**, *118*, 8770.
[207] R. Bentley, *J. Ind. Microbiol. Biotechnol.* **2009**, *36*, 775.
[208] J.-G. Kim; D. O. Jang, *Synlett* **2007**, *2007*, 2501.
[209] S. Mondal, *Synth. Commun.* **2021**, *51*, 1023.
[210] A. Gioiello; E. Rosatelli; M. Teofrasti; P. Filipponi; R. Pellicciari, *ACS Comb. Sci.* **2013**, *15*, 235.
[211] a) A. V. Bogolubsky; Y. S. Moroz; P. K. Mykhailiuk; S. E. Pipko; A. I. Konovets; I. V. Sadkova; A. Tolmachev, *ACS Comb. Sci.* **2014**, *16*, 192; b) P. Mukherjee; C. P. Woroch; L. Cleary; M. Rusznak; R. W. Franzese; M. R. Reese; J. W. Tucker; J. M. Humphrey; S. M. Etuk; S. C. Kwan; C. W. am Ende; N. D. Ball, *Org. Lett.* **2018**, *20*, 3943.
[212] T. S.-B. Lou; S. W. Bagley; M. C. Willis, *Angew. Chem. Int. Ed.* **2019**, *58*, 18859.
[213] a) O. M. Mulina; A. I. Ilovaisky; A. O. Terent'ev, *Eur. J. Org. Chem.* **2018**, *2018*, 4648; b) T. C. Das; S. A. Quadri; M. Farooqui, *Chem. Bio. Interface* **2018**, *8*, 194.
[214] I. B. Douglass; T. B. Johnson, *J. Am. Chem. Soc.* **1938**, *60*, 1486.
[215] Y. J. Park; H. H. Shin; Y. H. Kim, *Chem. Lett.* **1992**, *21*, 1483.
[216] S. W. Wright; K. N. Hallstrom, *J. Org. Chem.* **2006**, *71*, 1080.
[217] K. Bahrami; M. M. Khodaei; M. Soheilizad, *J. Org. Chem.* **2009**, *74*, 9287.
[218] H. Veisi; R. Ghorbani-Vaghei; S. Hemmati; J. Mahmoodi, *Synlett* **2011**, *2011*, 2315.
[219] a) R. Pandya; T. Murashima; L. Tedeschi; A. G. M. Barrett, *J. Org. Chem.* **2003**, *68*, 8274; b) H. Woolven; C. González-Rodríguez; I. Marco; A. L. Thompson; M. C. Willis, *Org. Lett.* **2011**, *13*, 4876.
[220] M. Furukawa; M. Nishikawa; Y. Inaba; Y. Noguchi; T. Okawara; T. Hitoshi, *Chem. Pharm. Bull.* **1981**, *29*, 623.
[221] A. Shavnya; S. B. Coffey; K. D. Hesp; S. C. Ross; A. S. Tsai, *Org. Lett.* **2016**, *18*, 5848.
[222] a) S. Liang; K. Hofman; M. Friedrich; G. Manolikakes, *Eur. J. Org. Chem.* **2020**, *2020*, 4664; b) R. J. Reddy; A. H. Kumari, *RSC Adv.* **2021**, *11*, 9130.
[223] a) E. J. Emmett; B. R. Hayter; M. C. Willis, *Angew. Chem. Int. Ed.* **2014**, *53*, 10204; b) M. W. Johnson; S. W. Bagley; N. P. Mankad; R. G. Bergman; V. Mascitti; F. D. Toste, *Angew. Chem. Int. Ed.* **2014**, *53*, 4404; c) Y. Chen; M. C. Willis, *Chem. Sci.* **2017**, *8*, 3249; d) P. K. T. Lo; Y. Chen; M. C. Willis, *ACS Catal.* **2019**, *9*, 10668.
[224] J. R. DeBergh; N. Niljianskul; S. L. Buchwald, *J. Am. Chem. Soc.* **2013**, *135*, 10638.
[225] a) S. L. Graham; T. H. Scholz, *Synthesis* **1986**, *1986*, 1031; b) W. Y. Chan; C. Berthelette, *Tetrahedron Lett.* **2002**, *43*, 4537; c) A. S. Deeming; C. J. Russell; M. C. Willis, *Angew. Chem. Int. Ed.* **2015**, *54*, 1168.

[226] a) S.-Y. Moon; J. Nam; K. Rathwell; W.-S. Kim, *Org. Lett.* **2014**, *16*, 338; b) A. S. Tsai; J. M. Curto; B. N. Rocke; A.-M. R. Dechert-Schmitt; G. K. Ingle; V. Mascitti, *Org. Lett.* **2016**, *18*, 508; c) B. Du; Y. Wang; W. Sha; P. Qian; H. Mei; J. Han; Y. Pan, *Asian Journal of Organic Chemistry* **2017**, *6*, 153; d) F. Zhang; D. Zheng; L. Lai; J. Cheng; J. Sun; J. Wu, *Org. Lett.* **2018**, *20*, 1167; e) S. Chung; J. Kim, *Tetrahedron Lett.* **2019**, *60*, 792.

[227] a) B. Nguyen; E. J. Emmett; M. C. Willis, *J. Am. Chem. Soc.* **2010**, *132*, 16372; b) S. Ye; J. Wu, *Chem. Commun.* **2012**, *48*, 7753; c) S. Ye; J. Wu, *Chem. Commun.* **2012**, *48*, 10037; d) X. Tang; L. Huang; C. Qi; X. Wu; W. Wu; H. Jiang, *Chem. Commun.* **2013**, *49*, 6102; e) X. Wang; L. Xue; Z. Wang, *Org. Lett.* **2014**, *16*, 4056; f) D. Zheng; Y. An; Z. Li; J. Wu, *Angew. Chem. Int. Ed.* **2014**, *53*, 2451; g) W. Zhang; J. Xie; B. Rao; M. Luo, *J. Org. Chem.* **2015**, *80*, 3504; h) B. Yang; C. Lian; G. Yue; D. Liu; L. Wei; Y. Ding; X. Zheng; K. Lu; D. Qiu; X. Zhao, *Org. Biomol. Chem.* **2018**, *16*, 8150; i) V. T. Nguyen; G. C. Haug; V. D. Nguyen; N. T. H. Vuong; H. D. Arman; O. V. Larionov, *Chem. Sci.* **2021**, *12*, 6429.

[228] a) J. Chen; X. Han; L. Mei; J. Liu; K. Du; T. Cao; Q. Li, *RSC Adv.* **2019**, *9*, 31212; b) H. Jiang; X. Tang; Z. Xu; H. Wang; K. Han; X. Yang; Y. Zhou; Y.-L. Feng; X.-Y. Yu; Q. Gui, *Org. Biomol. Chem.* **2019**, *17*, 2715; c) D. L. Poeira; J. Macara; H. Faustino; J. A. S. Coelho; P. M. P. Gois; M. M. B. Marques, *Eur. J. Org. Chem.* **2019**, *2019*, 2695.

[229] Y. Chen; P. R. D. Murray; A. T. Davies; M. C. Willis, *J. Am. Chem. Soc.* **2018**, *140*, 8781.

[230] G. Laudadio; E. Barmpoutsis; C. Schotten; L. Struik; S. Govaerts; D. L. Browne; T. Noël, *J. Am. Chem. Soc.* **2019**, *141*, 5664.

[231] R. D. Larsen; F. E. Roberts, *Synth. Commun.* **1986**, *16*, 899.

[232] Q. Wang; X.-Y. Tang; M. Shi, *Angew. Chem. Int. Ed.* **2016**, *55*, 10811.

[233] a) M. S. Kharasch; R. A. Mosher, *J. Org. Chem.* **1952**, *17*, 453; b) P. Bougeard; M. D. Johnson, *J. Organomet. Chem.* **1981**, *206*, 221; c) M. Arnswald; W. P. Neumann, *Chem. Ber.* **1991**, *124*, 1997; d) C. G. Frost; J. P. Hartley; D. Griffin, *Synlett* **2002**, *2002*, 1928; e) F. Montermini; E. Lacôte; M. Malacria, *Org. Lett.* **2004**, *6*, 921; f) J. M. Young; A. G. Lee; R. Y. Chandrasekaran; J. W. Tucker, *J. Org. Chem.* **2015**, *80*, 8417; g) Q. Luo; R. Mao; Y. Zhu; Y. Wang, *J. Org. Chem.* **2019**, *84*, 13897; h) S. M. Hell; C. F. Meyer; G. Laudadio; A. Misale; M. C. Willis; T. Noël; A. A. Trabanco; V. Gouverneur, *J. Am. Chem. Soc.* **2020**, *142*, 720.

[234] E. H. Gold; E. Babad, *J. Org. Chem.* **1972**, *37*, 2208.

[235] a) H.-X. Dai; A. F. Stepan; M. S. Plummer; Y.-H. Zhang; J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7222; b) S. Hu; D. Wang; J. Liu; X. Li, *Org. Biomol. Chem.* **2013**, *11*, 2761; c) W. Xie; J. Yang; B. Wang; B. Li, *J. Org. Chem.* **2014**, *79*, 8278; d) W. J. Kerr; M. Reid; T. Tuttle, *ACS Catal.* **2015**, *5*, 402.

[236] a) K. A. DeKorver; W. L. Johnson; Y. Zhang; R. P. Hsung; H. Dai; J. Deng; A. G. Lohse; Y.-S. Zhang, *J. Org. Chem.* **2011**, *76*, 5092; b) X. Xin; D. Wang; X. Li; B. Wan, *Angew. Chem. Int. Ed.* **2012**, *51*, 1693; c) Y. Zhu; W.-T. Lu; H.-C. Sun; Z.-P. Zhan, *Org. Lett.* **2013**, *15*, 4146; d) H. Tanimoto; K. Yokoyama; Y. Mizutani; T. Shitaoka; T. Morimoto; Y. Nishiyama; K. Kakiuchi, *J. Org. Chem.* **2016**, *81*, 559; e) G. Di Mauro; B. Maryasin; D. Kaiser; S. Shaaban; L. González; N. Maulide, *Org. Lett.* **2017**, *19*, 3815; f) K. Watanabe; K. Moriyama, *J. Org. Chem.* **2020**, *85*, 5683.

[237] J. Liu; X. Jia; X. Chen; H. Sun; Y. Li; S. Kramer; Z. Lian, *J. Org. Chem.* **2020**, *85*, 5702.

[238] a) C. T. Supuran, *Molecules* **2017**, *22*; b) C. Zhao; K. P. Rakesh; L. Ravidar; W.-Y. Fang; H.-L. Qin, *Eur. J. Med. Chem.* **2019**, *162*, 679.

[239] X.-L. Wang; K. Wan; C.-H. Zhou, *Eur. J. Med. Chem.* **2010**, *45*, 4631.

[240] N. A. McGrath; M. Brichacek; J. T. Njardarson, *J. Chem. Educ.* **2010**, *87*, 1348.

[241] V. V. Avidon; M. G. Pleshakov, *Pharm. Chem. J.* **1969**, *3*, 144.

[242] D. Kim; W. Kim; S. Jeong; D. Kim; J.-W. Yoo; Y. Jung, *Drug Deliv. Transl. Res.* **2019**, *9*, 334.

[243] A. M. Pick; K. K. Nystrom, *Clin. Ther.* **2012**, *34*, 511.

[244] N. D. Grover; R. P. Limaye; D. V. Gokhale; T. R. Patil, *Indian J. Pharmacol* **2013**, *45*, 547.

[245] P. L. McCormack, *Drugs* **2011**, *71*, 2457.

[246] a) A. Vedani; E. F. Meyer, *J. Pharm. Sci.* **1984**, *73*, 352; b) J. K. Modak; Y. C. Liu; C. T. Supuran; A. Roujeinikova, *J. Med. Chem.* **2016**, *59*, 11098; c) F. Naaz; R. Srivastava; A. Singh; N. Singh; R. Verma; V. K. Singh; R. K. Singh, *Biorg. Med. Chem.* **2018**, *26*, 3414.
[247] T. Cernak; K. D. Dykstra; S. Tyagarajan; P. Vachal; S. W. Krska, *Chem. Soc. Rev.* **2016**, *45*, 546.
[248] A. Gómez-Palomino; J. Cornella, *Angew. Chem. Int. Ed.* **2019**, *58*, 18235.
[249] S. W. Reilly; F. Bennett; P. S. Fier; S. Ren; N. A. Strotman, *Chem. Eur. J.* **2020**, *26*, 4251.
[250] D.-Q. Dong; Q.-Q. Han; S.-H. Yang; J.-C. Song; N. Li; Z.-L. Wang; X.-M. Xu, *ChemistrySelect* **2020**, *5*, 13103.
[251] F. Schoenebeck; J. A. Murphy; S.-z. Zhou; Y. Uenoyama; Y. Miclo; T. Tuttle, *J. Am. Chem. Soc.* **2007**, *129*, 13368.
[252] B. Nyasse; L. Grehn; U. Ragnarsson, *Chem. Commun.* **1997**, 1017.
[253] a) S. Ji; L. B. Gortler; A. Waring; A. J. Battisti; S. Bank; W. D. Closson; P. A. Wriede, *J. Am. Chem. Soc.* **1967**, *89*, 5311; b) R. C. Roemmele; H. Rapoport, *J. Org. Chem.* **1988**, *53*, 2367; c) E. Alonso; D. J. Ramón; M. Yus, *Tetrahedron* **1997**, *53*, 14355; d) P. Nandi; M. Y. Redko; K. Petersen; J. L. Dye; M. Lefenfeld; P. F. Vogt; J. E. Jackson, *Org. Lett.* **2008**, *10*, 5441; e) M. Carraro; L. Pisano; U. Azzena, *Synthesis* **2017**, *49*, 1931.
[254] a) E. Vellemäe; O. Lebedev; U. Mäeorg, *Tetrahedron Lett.* **2008**, *49*, 1373; b) N. Shohji; T. Kawaji; S. Okamoto, *Org. Lett.* **2011**, *13*, 2626.
[255] a) E. Vedejs; S. Lin, *J. Org. Chem.* **1994**, *59*, 1602; b) H. Knowles; A. F. Parsons; R. M. Pettifer, *Synlett* **1997**, *1997*, 271; c) T. Ankner; G. Hilmersson, *Org. Lett.* **2009**, *11*, 503.
[256] S. S. Hanson; E. Doni; K. T. Traboulsee; G. Coulthard; J. A. Murphy; C. A. Dyker, *Angew. Chem. Int. Ed.* **2015**, *54*, 11236.
[257] a) E. R. Civitello; H. Rapoport, *J. Org. Chem.* **1992**, *57*, 834; b) V. Coeffard; C. Thobie-Gautier; I. Beaudet; E. Le Grognec; J.-P. Quintard, *Eur. J. Org. Chem.* **2008**, *2008*, 383; c) H. Senboku; K. Nakahara; T. Fukuhara; S. Hara, *Tetrahedron Lett.* **2010**, *51*, 435; d) P. Viaud; V. Coeffard; C. Thobie-Gautier; I. Beaudet; N. Galland; J.-P. Quintard; E. Le Grognec, *Org. Lett.* **2012**, *14*, 942.
[258] a) T. Hamada; A. Nishida; O. Yonemitsu, *J. Am. Chem. Soc.* **1986**, *108*, 140; b) Q. Liu; Z. Liu; Y.-L. Zhou; W. Zhang; L. Yang; Z.-L. Liu; W. Yu, *Synlett* **2005**, *2005*, 2510; c) X. Hong; J. M. Mejía-Oneto; S. France; A. Padwa, *Tetrahedron Lett.* **2006**, *47*, 2409; d) J. Xuan; B.-J. Li; Z.-J. Feng; G.-D. Sun; H.-H. Ma; Z.-W. Yuan; J.-R. Chen; L.-Q. Lu; W.-J. Xiao, *Chem. Asian J.* **2013**, *8*, 1090; e) S. O'Sullivan; E. Doni; T. Tuttle; J. A. Murphy, *Angew. Chem. Int. Ed.* **2014**, *53*, 474; f) E. Hasegawa; N. Izumiya; T. Miura; T. Ikoma; H. Iwamoto; S.-y. Takizawa; S. Murata, *J. Org. Chem.* **2018**, *83*, 3921; g) E. Hasegawa; Y. Nagakura; N. Izumiya; K. Matsumoto; T. Tanaka; T. Miura; T. Ikoma; H. Iwamoto; K. Wakamatsu, *J. Org. Chem.* **2018**, *83*, 10813; h) E. Hasegawa; T. Tanaka; N. Izumiya; T. Kiuchi; Y. Ooe; H. Iwamoto; S.-y. Takizawa; S. Murata, *J. Org. Chem.* **2020**, *85*, 4344; i) M. D. Heredia; W. D. Guerra; S. M. Barolo; S. J. Fornasier; R. A. Rossi; M. E. Budén, *J. Org. Chem.* **2020**, *85*, 13481; j) C. J. Hunter; M. J. Boyd; G. D. May; R. Fimognari, *J. Org. Chem.* **2020**, *85*, 8732; k) I. A. MacKenzie; L. Wang; N. P. R. Onuska; O. F. Williams; K. Begam; A. M. Moran; B. D. Dunietz; D. A. Nicewicz, *Nature* **2020**, *580*, 76.
[259] Y. Luo; H. Ding; J.-S. Zhen; X. Du; X.-H. Xu; H. Yuan; Y.-H. Li; W.-Y. Qi; B.-Z. Liu; S.-M. Lu; C. Xue; Q. Ding, *Chem. Sci.* **2021**.
[260] H. Zhang; E. B. Hay; S. J. Geib; D. P. Curran, *J. Am. Chem. Soc.* **2013**, *135*, 16610.
[261] K. S. Kanyiva; D. Hamada; S. Makino; H. Takano; T. Shibata, *Eur. J. Org. Chem.* **2018**, *2018*, 5905.
[262] a) J.-J. Wang; W. Yu, *Org. Lett.* **2019**, *21*, 9236; b) S. M. Hell; C. F. Meyer; A. Misale; J. B. I. Sap; K. E. Christensen; M. C. Willis; A. A. Trabanco; V. Gouverneur, *Angew. Chem. Int. Ed.* **2020**, *59*, 11620.
[263] a) J. H. Wynne; S. E. Price; J. R. Rorer; W. M. Stalick, *Synth. Commun.* **2003**, *33*, 341; b) Z. Li; X. Ren; P. Wei; H. Wan; Y. Shi; P. Ouyang, *Green Chemistry* **2006**, *8*, 433; c) Z. Li; X. Ren; Y. Shi; P. Ouyang, *Synth. Commun.* **2007**, *37*, 713; d) R. Fan; D. Pu; F. Wen; Y. Ye; X. Wang, *J. Org. Chem.* **2008**, *73*, 3623; e) K. Wang; Z. Xing; Y. Ma; Q. Wang, *Catal. Lett.* **2008**, *123*, 129; f) X.-F. Wu; C. Vovard-Le Bray; L. Bechki; C. Darcel, *Tetrahedron* **2009**, *65*, 7380; g) M. A. Zolfigol; A. Khazaei; A. R. Moosavi-Zare; A. Zare, *J. Iran. Chem. Soc.* **2010**, *7*, 646; h) S. Morales; F. G. Guijarro; J. L. García Ruano; M. B. Cid, *J. Am.*

*Chem. Soc.* **2014**, *136*, 1082; i) J. T. Reeves; M. D. Visco; M. A. Marsini; N. Grinberg; C. A. Busacca; A. E. Mattson; C. H. Senanayake, *Org. Lett.* **2015**, *17*, 2442; j) M. D. Hopkins; Z. C. Brandeburg; A. J. Hanson; A. A. Lamar, *Molecules* **2018**, *23*; k) C. Verrier; S. Carret; J.-F. Poisson, *ACS Sustain. Chem. Eng.* **2018**, *6*, 8563; l) A. Ashouri; S. Samadi; B. Nasiri; Z. Bahrami, *Compt. Rend. Chim.* **2019**, *22*, 549; m) A. S. Hanan; E.-S. Mahmoud; S. Abdel-Ghany, *Lett. Org. Chem.* **2019**, *16*, 584.

[264] J. A. Leitch; T. Rossolini; T. Rogova; J. A. P. Maitland; D. J. Dixon, *ACS Catal.* **2020**, *10*, 2009.

[265] M. A. Ashley; T. Rovis, *J. Am. Chem. Soc.* **2020**, *142*, 18310.

[266] C. Chatgilialoglu; O. Mozziconacci; M. Tamba; K. Bobrowski; G. Kciuk; M. P. Bertrand; S. Gastaldi; V. I. Timokhin, *J. Phys. Chem. A* **2012**, *116*, 7623.

[267] Y. Tian; Z.-Q. Liu, *RSC Adv.* **2014**, *4*, 64855.

[268] Y. L. Chow; W. C. Danen; S. F. Nelsen; D. H. Rosenblatt, *Chem. Rev.* **1978**, *78*, 243.

[269] K. Cao; S. M. Tan; R. Lee; S. Yang; H. Jia; X. Zhao; B. Qiao; Z. Jiang, *J. Am. Chem. Soc.* **2019**, *141*, 5437.

[270] C. Chatgilialoglu; C. Ferreri; Y. Landais; V. I. Timokhin, *Chem. Rev.* **2018**, *118*, 6516.

[271] M. A. Bryden; E. Zysman-Colman, *Chem. Soc. Rev.* **2021**.

[272] J. Lu; B. Pattengale; Q. Liu; S. Yang; W. Shi; S. Li; J. Huang; J. Zhang, *J. Am. Chem. Soc.* **2018**, *140*, 13719.

[273] R. Sakamoto; T. Inada; S. Sakurai; K. Maruoka, *Org. Lett.* **2016**, *18*, 6252.

[274] D. Uraguchi; Y. Tsuchiya; T. Ohtani; T. Enomoto; S. Masaoka; D. Yokogawa; T. Ooi, *Angew. Chem. Int. Ed.* **2020**, *59*, 3665.

[275] C. Chatgilialoglu; J. Lalevée, *Molecules* **2012**, *17*.

[276] J. Sławiński; A. Pogorzelska; B. Żołnowska; K. Brożewicz; D. Vullo; C. T. Supuran, *Eur. J. Med. Chem.* **2014**, *82*, 47.

[277] J. P. Ferris; K. V. Prabhu; R. L. Strong, *J. Am. Chem. Soc.* **1975**, *97*, 2835.

[278] T. Morita; S. Fuse; H. Nakamura, *Org. Lett.* **2020**, *22*, 3460.

[279] F. Freeman; M. C. Keindl, *Sulfur Rep.* **1985**, *4*, 231.

[280] C. Li; P. L. Fuchs, *Tetrahedron Lett.* **1993**, *34*, 1855.

[281] Q.-A. Wu; F. Chen; C.-C. Ren; X.-F. Liu; H. Chen; L.-X. Xu; X.-C. Yu; S.-P. Luo, *Org. Biomol. Chem.* **2020**, *18*, 3707.

[282] G. M. Schaaf; S. Mukherjee; A. G. Waterson, *Tetrahedron Lett.* **2009**, *50*, 1928.

[283] J. L. Kice; K. W. Bowers, *J. Am. Chem. Soc.* **1962**, *84*, 605.

[284] F. Strieth-Kalthoff; M. J. James; M. Teders; L. Pitzer; F. Glorius, *Chem. Soc. Rev.* **2018**, *47*, 7190.

[285] T. Hosokai; H. Matsuzaki; H. Nakanotani; K. Tokumaru; T. Tsutsui; A. Furube; K. Nasu; H. Nomura; M. Yahiro; C. Adachi, *Sci. Adv.* **2017**, *3*, e1603282.

[286] D. Staveness; J. L. Collins Iii; R. C. McAtee; C. R. J. Stephenson, *Angew. Chem. Int. Ed.* **2019**, *58*, 19000.

[287] a) D. Uraguchi; N. Kinoshita; T. Kizu; T. Ooi, *J. Am. Chem. Soc.* **2015**, *137*, 13768; b) N. R. Patel; C. B. Kelly; A. P. Siegenfeld; G. A. Molander, *ACS Catal.* **2017**, *7*, 1766; c) X. Fan; X. Gong; M. Ma; R. Wang; P. J. Walsh, *Nat. Commun.* **2018**, *9*, 4936; d) J. Guo; Q.-L. Wu; Y. Xie; J. Weng; G. Lu, *J. Org. Chem.* **2018**, *83*, 12559.

[288] Y. Liu; Z. Wang; B. Guo; Q. Cai, *Tetrahedron Lett.* **2016**, *57*, 2379.

[289] C. T. Hoang; F. Bouillère; S. Johannesen; A. Zulauf; C. Panel; A. Pouilhès; D. Gori; V. Alezra; C. Kouklovsky, *J. Org. Chem.* **2009**, *74*, 4177.

[290] F. Kazemi; A. R. Massah; M. Javaherian, *Tetrahedron* **2007**, *63*, 5083.

[291] M. J. Frisch; G. W. Trucks; H. B. Schlegel; G. E. Scuseria; M. A. Robb; J. R. Cheeseman; G. Scalmani; V. Barone; G. A. Petersson; H. Nakatsuji; X. Li; M. Caricato; A. V. Marenich; J. Bloino; B. G. Janesko; R. Gomperts; B. Mennucci; H. P. Hratchian; J. V. Ortiz; A. F. Izmaylov; J. L. Sonnenberg; Williams; F. Ding; F. Lipparini; F. Egidi; J. Goings; B. Peng; A. Petrone; T. Henderson; D. Ranasinghe; V. G. Zakrzewski; J. Gao; N. Rega; G. Zheng; W. Liang; M. Hada; M. Ehara; K. Toyota; R. Fukuda; J. Hasegawa; M. Ishida; T. Nakajima; Y. Honda; O. Kitao; H. Nakai; T. Vreven; K. Throssell; J. A. Montgomery Jr.; J. E. Peralta; F. Ogliaro; M. J. Bearpark; J. J. Heyd; E. N. Brothers; K. N. Kudin; V. N. Staroverov; T. A. Keith; R. Kobayashi; J. Normand; K. Raghavachari; A. P. Rendell; J. C. Burant; S. S.

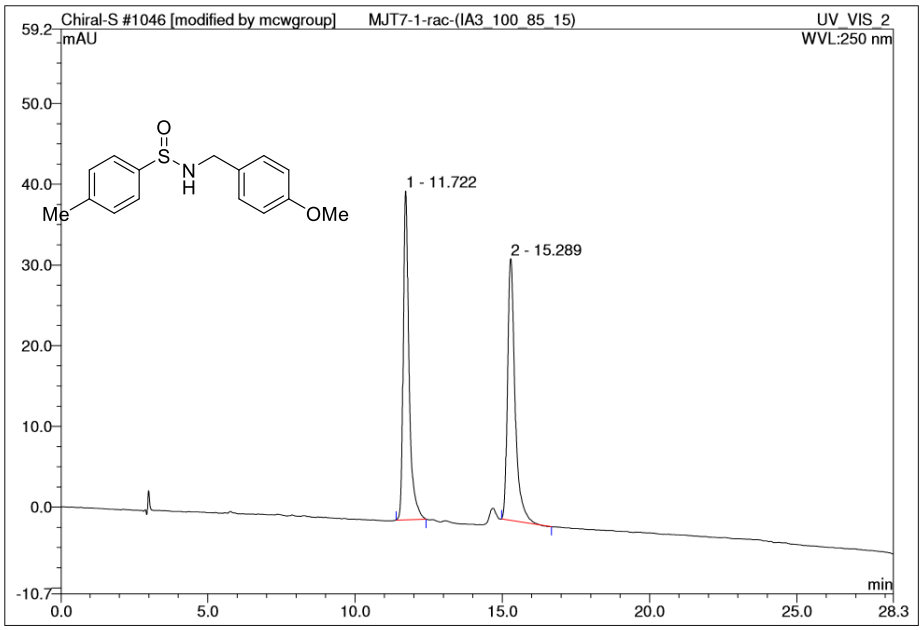
Iyengar; J. Tomasi; M. Cossi; J. M. Millam; M. Klene; C. Adamo; R. Cammi; J. W. Ochterski; R. L. Martin; K. Morokuma; O. Farkas; J. B. Foresman; D. J. Fox, Wallingford, CT, **2016**.
[292] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648; b) S. Grimme; J. Antony; S. Ehrlich; H. Krieg, *J. Chem. Phys.* **2010**, *132*, 154104.
[293] A. V. Marenich; C. J. Cramer; D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378.
[294] S. Grimme, *Chem. Eur. J.* **2012**, *18*, 9955.
[295] J. R.-G. Paton Lab, JingTao Chen, & IFunes. , **(2019, July 23).**
[296] J. Rodríguez-Guerra.
[297] J. N. Harvey; M. Aschi; H. Schwarz; W. Koch, *Theor. Chem. Acc.* **1998**, *99*, 95.
[298] K. L. Gannon; M. A. Blitz; C.-H. Liang; M. J. Pilling; P. W. Seakins; D. R. Glowacki; J. N. Harvey, *Faraday Discuss.* **2010**, *147*, 173.
[299] C. Y. Legault.
[300] K. O. Christe; M. Gerken; R. Haiges; S. Schneider; T. Schroer; F. S. Tham; A. Vij, *Solid State Sciences* **2002**, *4*, 1529.
[301] A. V. Marenich; S. V. Jerome; C. J. Cramer; D. G. Truhlar, *Journal of Chemical Theory and Computation* **2012**, *8*, 527.
[302] T. Holm, *Journal of the Chemical Society, Perkin Transactions 2* **1981**, 464.
[303] S. Higashibayashi; H. Tohmiya; T. Mori; K. Hashimoto; M. Nakata, *Synlett* **2004**, *2004*, 457.
[304] F. A. Davis; Y. Zhang; Y. Andemichael; T. Fang; D. L. Fanelli; H. Zhang, *The Journal of Organic Chemistry* **1999**, *64*, 1403.
[305] A. F. Garrido-Castro; N. Salaverri; M. C. Maestro; J. Alemán, *Org. Lett.* **2019**, *21*, 5295.
[306] G.-J. Li; Y.-L. Pan; Y.-L. Liu; H.-F. Xu; J.-Z. Chen, *Tetrahedron Lett.* **2019**, *60*, 151260.
[307] M. Revés; T. Achard; J. Solà; A. Riera; X. Verdaguer, *The Journal of Organic Chemistry* **2008**, *73*, 7080.
[308] D. S. Karanewsky; J. R. Fotsing; C. Tachdjian; M. Arellano, US9247759, B2, **2016**.
[309] P. R. Likhar; R. Arundhathi; M. L. Kantam; P. S. Prathima, *Eur. J. Org. Chem.* **2009**, *2009*, 5383.
[310] M. Lian; Z. Li; J. Du; Q. Meng; Z. Gao, **2010**, *2010*, 6525.
[311] A. F. Abdel-Magid; K. G. Carson; B. D. Harris; C. A. Maryanoff; R. D. Shah, *The Journal of Organic Chemistry* **1996**, *61*, 3849.
[312] A. Mallinger; K. Schiemann; C. Rink; F. Stieber; M. Calderini; S. Crumpler; M. Stubbs; O. Adeniji-Popoola; O. Poeschke; M. Busch; P. Czodrowski; D. Musil; D. Schwarz; M.-J. Ortiz-Ruiz; R. Schneider; C. Thai; M. Valenti; A. de Haven Brandon; R. Burke; P. Workman; T. Dale; D. Wienke; P. A. Clarke; C. Esdar; F. I. Raynaud; S. A. Eccles; F. Rohdich; J. Blagg, *J. Med. Chem.* **2016**, *59*, 1078.
[313] E. Hayashi; Y. Yamaguchi; Y. Kita; K. Kamata; M. Hara, *Chem. Commun.* **2020**, *56*, 2095.
[314] M. Wang; Q. Fan; X. Jiang, *Green Chemistry* **2018**, *20*, 5469.
[315] U. Galli; O. Mesenzani; C. Coppo; G. Sorba; P. L. Canonico; G. C. Tron; A. A. Genazzani, *Eur. J. Med. Chem.* **2012**, *55*, 58.
[316] F. Wang; H. Liu; H. Fu; Y. Jiang; Y. Zhao, *Adv. Synth. Catal.* **2009**, *351*, 246.
[317] D. Matulis; E. Čapkauskaite; A. Zaksauskas; V. Morkunaite, WO2017017505 (A1), **2017**.
[318] A. Lill; K. Scholich; H. Stark, *Tetrahedron Lett.* **2013**, *54*, 6682.
[319] W. B. Jennings; C. J. Lovely, *Tetrahedron* **1991**, *47*, 5561.
[320] B. Wahl; A. Cabré; S. Woodward; W. Lewis, *Tetrahedron Lett.* **2014**, *55*, 5829.
[321] D. F. McComsey; V. L. Smith-Swintosky; M. H. Parker; D. E. Brenneman; E. Malatynska; H. S. White; B. D. Klein; K. S. Wilcox; M. E. Milewski; M. Herb; M. F. A. Finley; Y. Liu; M. L. Lubin; N. Qin; A. B. Reitz; B. E. Maryanoff, *J. Med. Chem.* **2013**, *56*, 9019.
[322] S. V. Pansare; M. G. Malusare, *Tetrahedron Lett.* **1996**, *37*, 2859.
[323] D. Stead, *Tetrahedron Lett.* **2020**, *61*, 152325.
[324] D. Huang; X. Wang; X. Wang; W. Chen; X. Wang; Y. Hu, *Org. Lett.* **2016**, *18*, 604.
[325] S. Cinar; B. Temelli; C. Unaleroglu, *Tetrahedron Lett.* **2014**, *55*, 544.
[326] B. M. Trost; S. M. Silverman, *J. Am. Chem. Soc.* **2012**, *134*, 4941.
[327] M. C. Kohler; J. M. Yost; M. R. Garnsey; D. M. Coltart, *Org. Lett.* **2010**, *12*, 3376.

[328] M. Rueping; N. Tolstoluzhsky, *Org. Lett.* **2011**, *13*, 1095.
[329] J. C. Lanter; H. Chen; X. Zhang; Z. Sui, *Org. Lett.* **2005**, *7*, 5905.
[330] Y.-X. Jia; J.-H. Xie; H.-F. Duan; L.-X. Wang; Q.-L. Zhou, *Org. Lett.* **2006**, *8*, 1621.
[331] E. C. Lee; B. L. Hodous; E. Bergin; C. Shih; G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 11586.
[332] A. S. González; R. G. Arrayás; J. C. Carretero, *Org. Lett.* **2006**, *8*, 2977.
[333] J. Rendell; A. Kwokal, WO2011069053 (A1), **2011**.
[334] D.-M. Cui; J.-Z. Zheng; L.-Y. Yang; C. Zhang, *Synlett* **2010**, *2010*, 809.
[335] S. Hayashi; H. Yorimitsu; K. Oshima, *Angew. Chem. Int. Ed.* **2009**, *48*, 7224.
[336] O. Pablo; J. F. Collados; S. R. Harutyunyan, *Eur. J. Org. Chem.* **2016**, *2016*, 1247.
[337] M. Vellakkaran; M. M. S. Andappan; K. Nagaiah; J. B. Nanubolu, *Eur. J. Org. Chem.* **2016**, *2016*, 3575.
[338] X. Marset; G. Guillena; D. J. Ramón, *Chem. Eur. J.* **2017**, *23*, 10522.
[339] W. Keim; J. Herwig; G. Pelzer, *J. Org. Chem.* **1997**, *62*, 422.
[340] W. Li; L. Gao; W. Zhuge; X. Sun; G. Zheng, *Org. Biomol. Chem.* **2017**, *15*, 7819.
[341] H. Zhu; Y. Zhang; Y. Liu; L. Yang; Z. Xie; G. Jiang; Z.-G. Le, *Tetrahedron Lett.* **2020**, *61*, 151975.
[342] H. Zhang; Y. Zhou; P. Tian; C. Jiang, *Org. Lett.* **2019**, *21*, 1921.

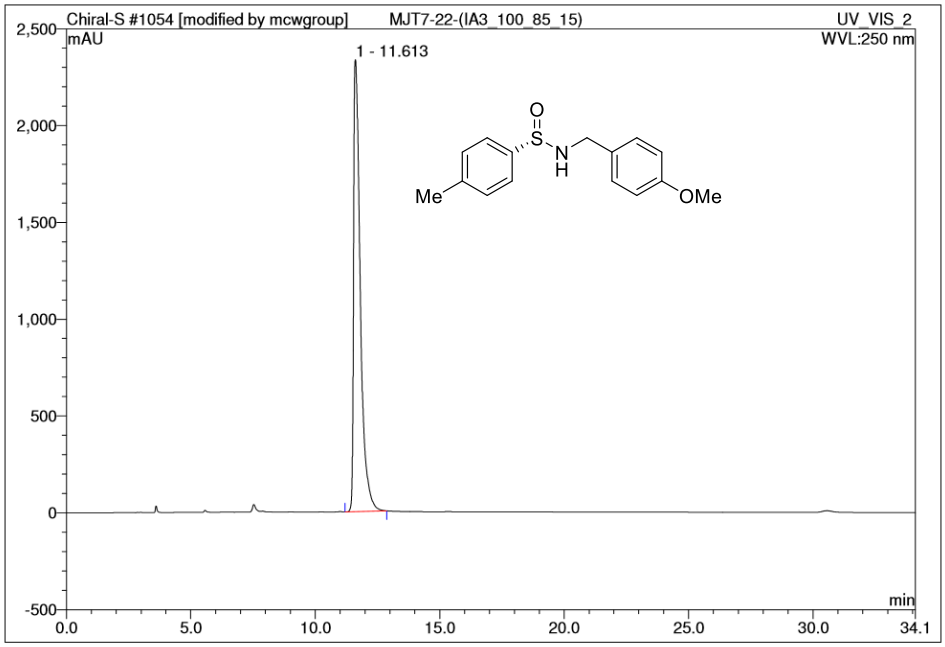
# Appendix

## 8.1. HPLC Data

### 4-methyl-*N*-(4-methylbenzyl)benzenesulfinamide (78b)

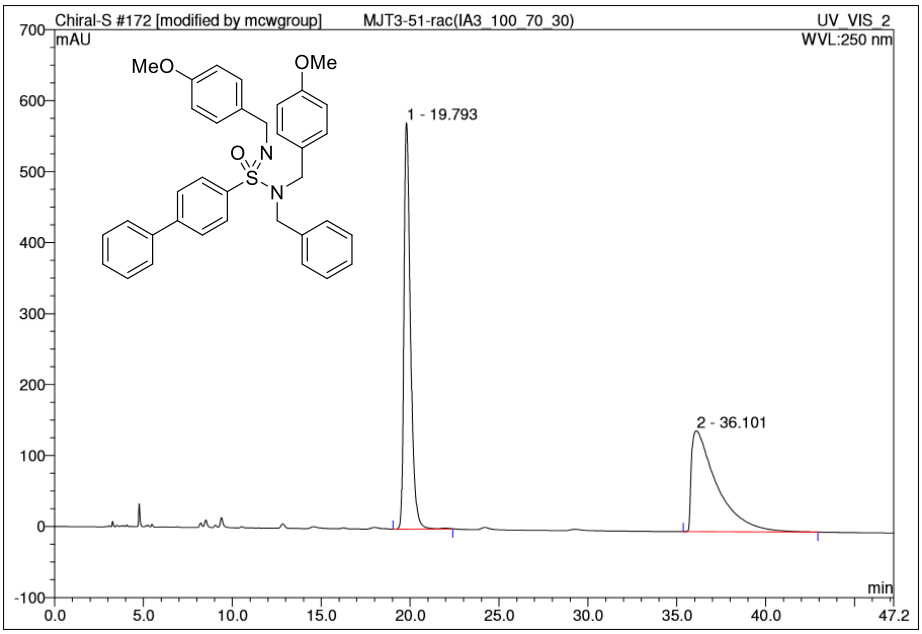



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 11.72 | n.a. | 40.752 | 9.300 | 49.36 | n.a. | BMB* |
| 2 | 15.29 | n.a. | 32.415 | 9.543 | 50.64 | n.a. | BMB* |
| **Total:** | | | 73.167 | 18.843 | 100.00 | 0.000 | |

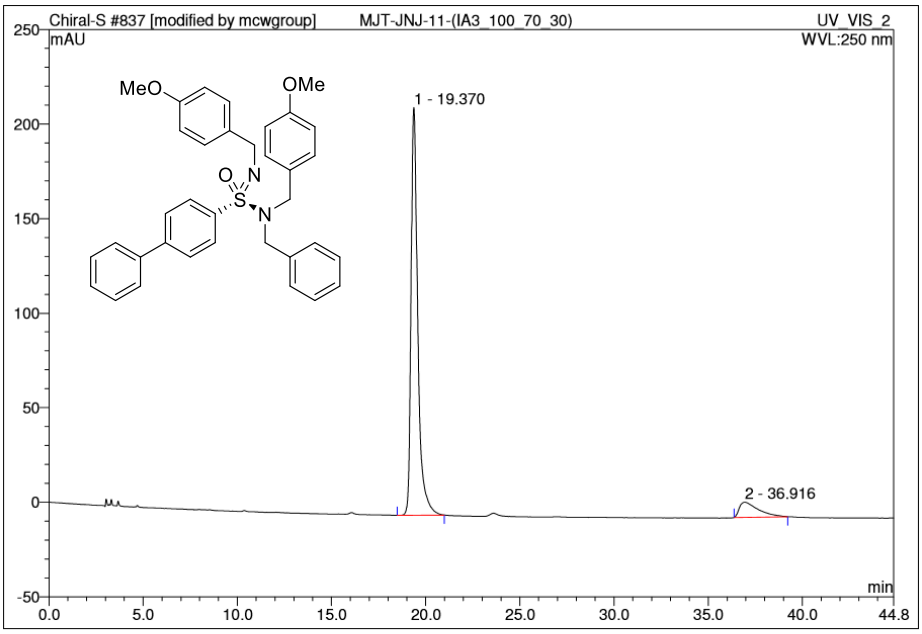



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 11.61 | n.a. | 2333.485 | 733.057 | 100.00 | n.a. | BMB* |
| **Total:** | | | 2333.485 | 733.057 | 100.00 | 0.000 | |

## *N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74a)

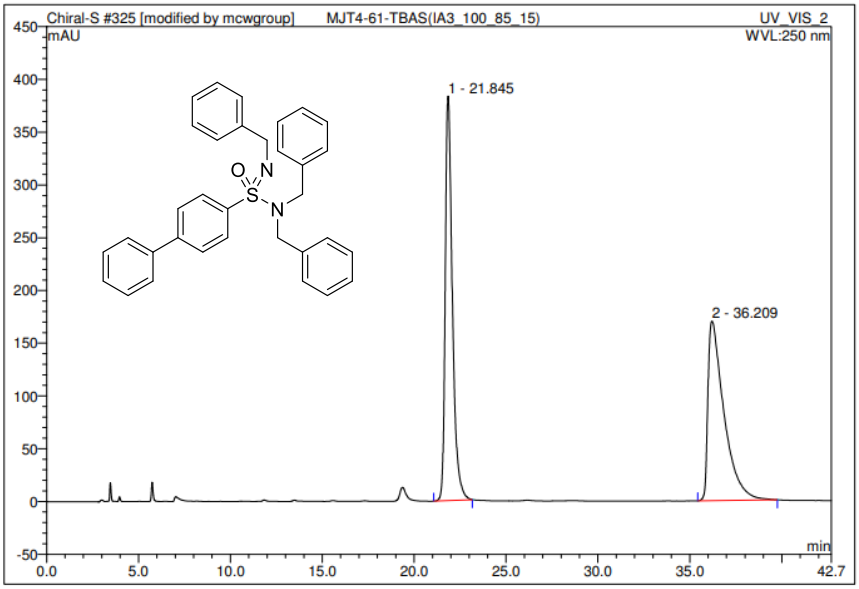



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 19.79 | n.a. | 572.290 | 243.177 | 50.76 | n.a. | BMB* |
| 2 | 36.10 | n.a. | 141.996 | 235.876 | 49.24 | n.a. | BMB* |
| **Total:** | | | 714.286 | 479.053 | 100.00 | 0.000 | |

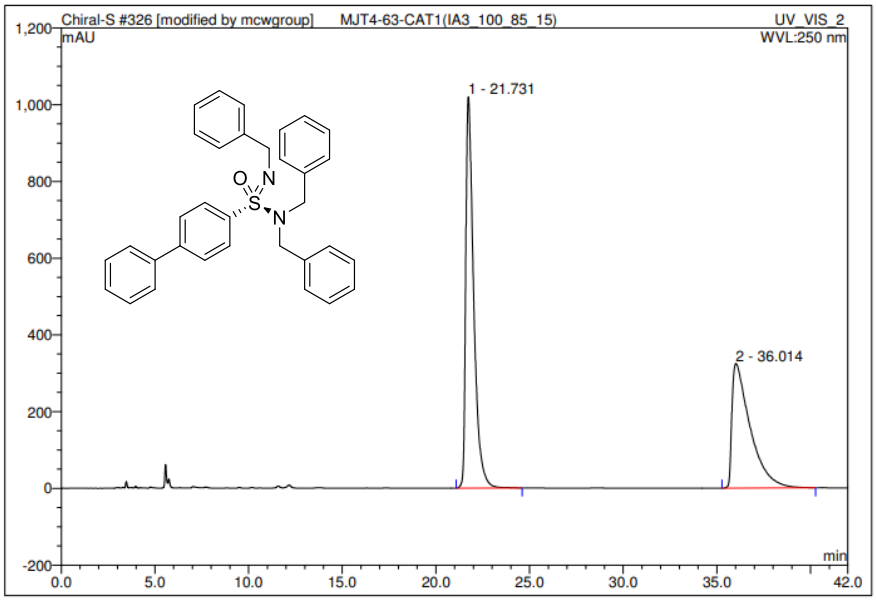



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 19.37 | n.a. | 215.670 | 89.525 | 90.54 | n.a. | BMB* |
| 2 | 36.92 | n.a. | 7.975 | 9.356 | 9.46 | n.a. | BMB* |
| **Total:** | | | 223.645 | 98.881 | 100.00 | 0.000 | |

## *N,N,N'*-tribenzyl-[1,1'-biphenyl]-4-sulfonimidamide (80a)

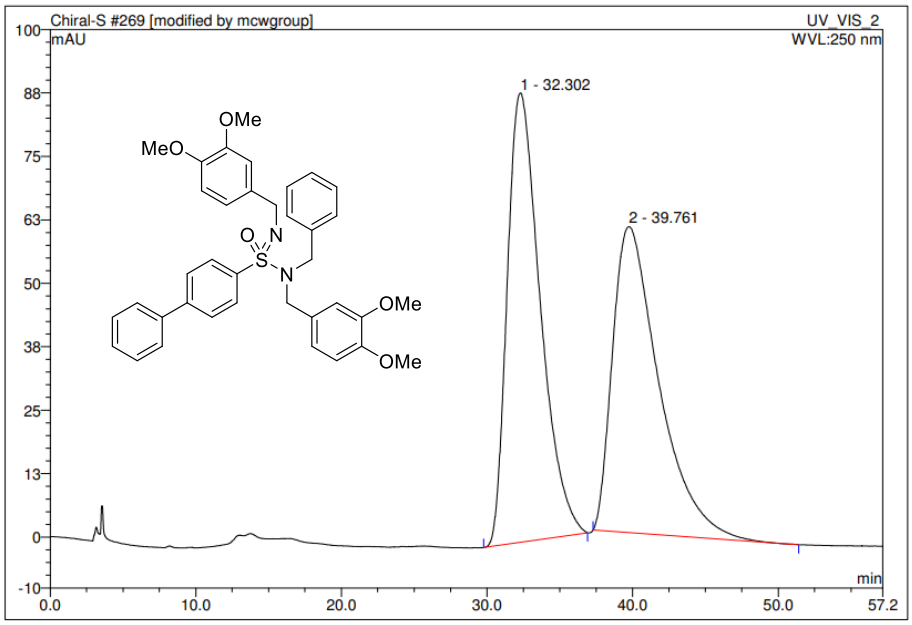



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 21.85 | n.a. | 383.506 | 172.961 | 50.07 | n.a. | BMB* |
| 2 | 36.21 | n.a. | 170.049 | 172.473 | 49.93 | n.a. | BMB* |
| **Total:** | | | 553.555 | 345.434 | 100.00 | 0.000 | |

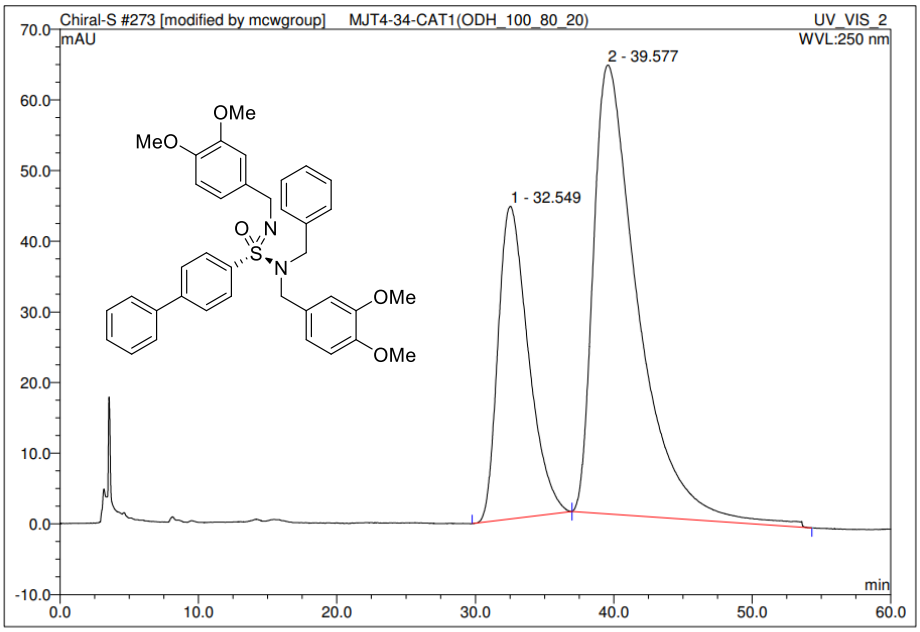



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 21.73 | n.a. | 1019.725 | 500.225 | 57.73 | n.a. | BMB* |
| 2 | 36.01 | n.a. | 324.043 | 366.255 | 42.27 | n.a. | BMB* |
| **Total:** | | | 1343.768 | 866.480 | 100.00 | 0.000 | |

## (*N*-benzyl-*N*,*N*'-bis(3,4-dimethoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (80b)

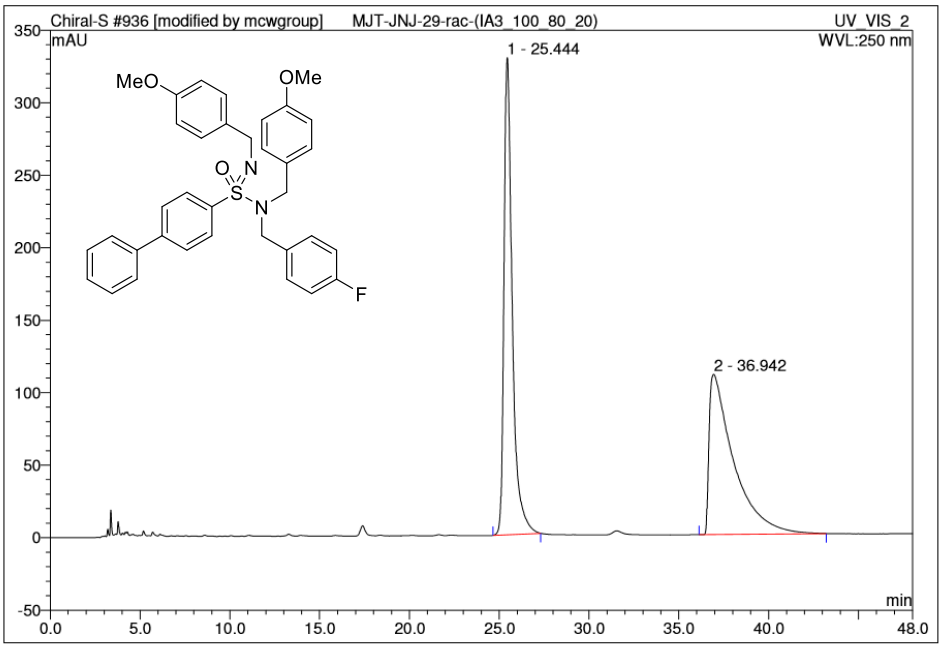



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 32.30 | n.a. | 88.507 | 232.581 | 51.17 | n.a. | BMB* |
| 2 | 39.76 | n.a. | 60.263 | 221.902 | 48.83 | n.a. | BMB* |
| **Total:** | | | 148.770 | 454.483 | 100.00 | 0.000 | |

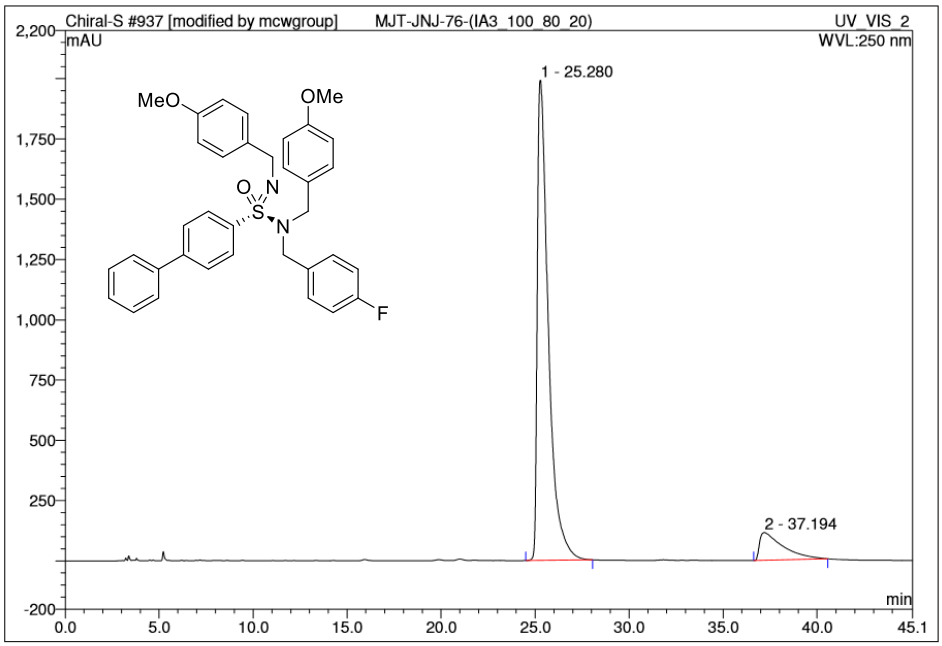



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 32.55 | n.a. | 44.263 | 112.134 | 32.12 | n.a. | BMb* |
| 2 | 39.58 | n.a. | 63.530 | 236.988 | 67.88 | n.a. | bMB* |
| **Total:** | | | 107.794 | 349.121 | 100.00 | 0.000 | |

## *N*-(4-fluorobenzyl)-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74aa)

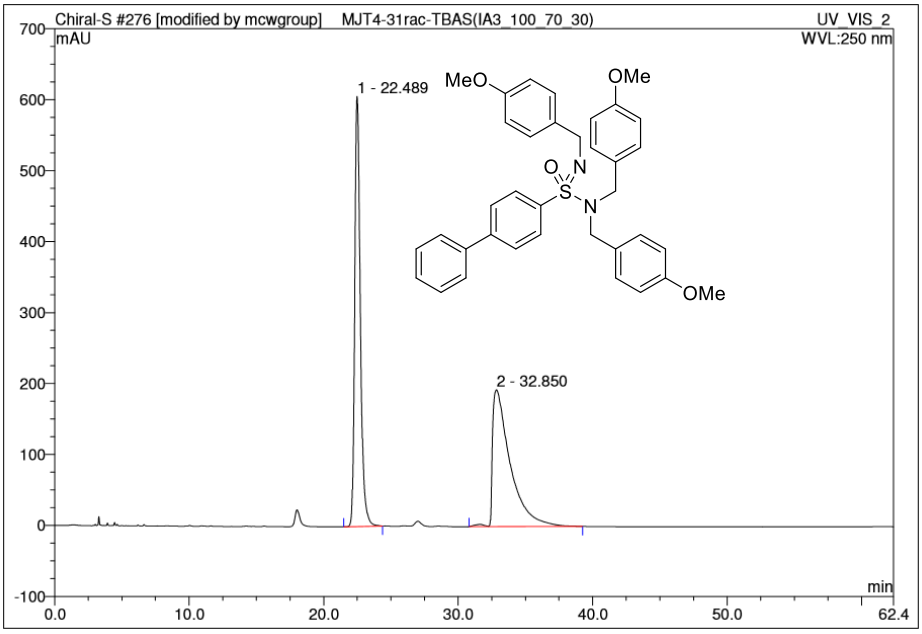



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 25.44 | n.a. | 329.122 | 176.327 | 50.29 | n.a. | BMB* |
| 2 | 36.94 | n.a. | 110.482 | 174.317 | 49.71 | n.a. | BMB* |
| **Total:** | | | 439.604 | 350.644 | 100.00 | 0.000 | |

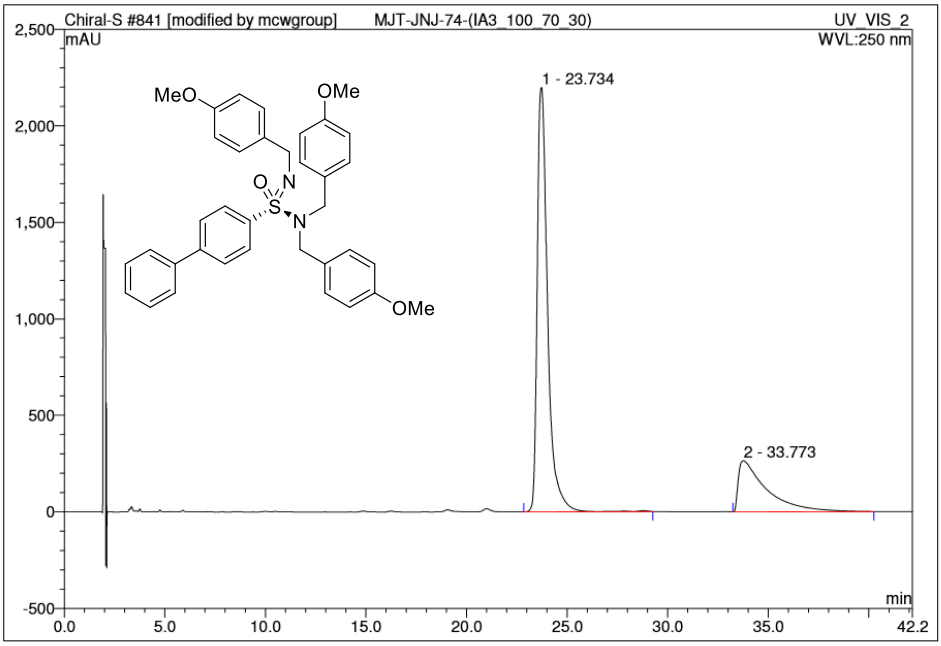



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 25.28 | n.a. | 1991.140 | 1357.768 | 89.15 | n.a. | BMB* |
| 2 | 37.19 | n.a. | 114.795 | 165.245 | 10.85 | n.a. | BMB* |
| **Total:** | | | 2105.934 | 1523.014 | 100.00 | 0.000 | |

## *N,N,N'*-tris(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ab)

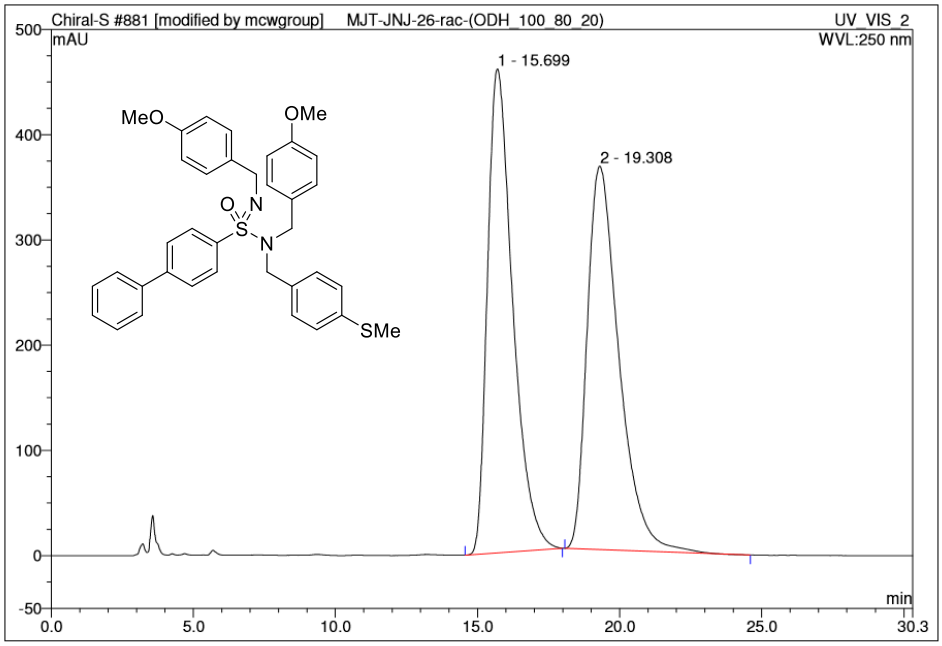



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 22.49 | n.a. | 606.256 | 293.481 | 49.97 | n.a. | BMB* |
| 2 | 32.85 | n.a. | 192.621 | 293.819 | 50.03 | n.a. | BMB* |
| **Total:** | | | 798.878 | 587.300 | 100.00 | 0.000 | |

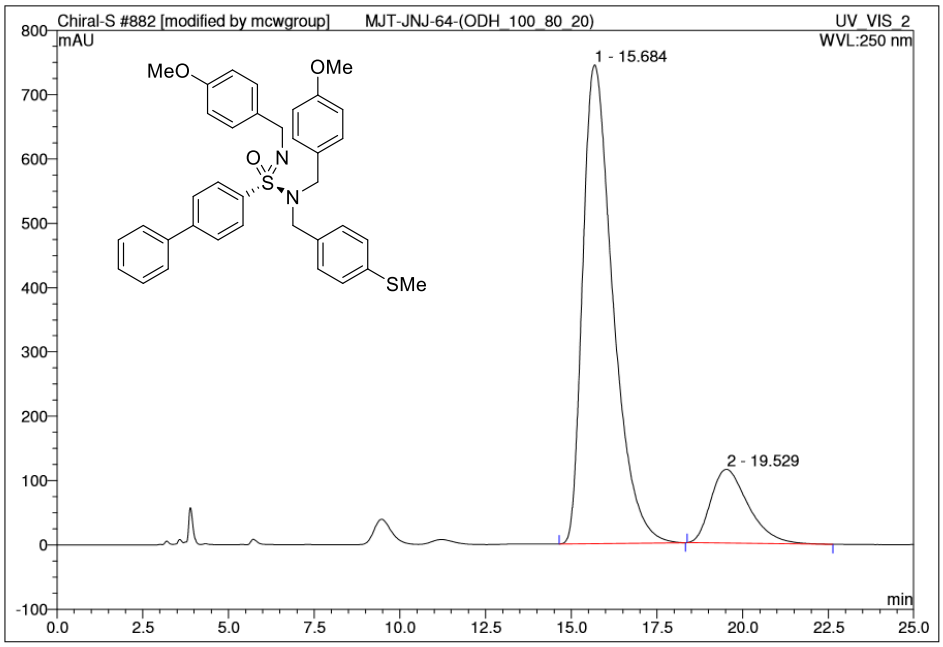



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 23.73 | n.a. | 2198.735 | 1314.113 | 75.49 | n.a. | BMB* |
| 2 | 33.77 | n.a. | 263.863 | 426.751 | 24.51 | n.a. | BMB* |
| **Total:** | | | 2462.599 | 1740.864 | 100.00 | 0.000 | |

## *N,N'*-bis(4-methoxybenzyl)-N-(4-(methylthio)benzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ac)

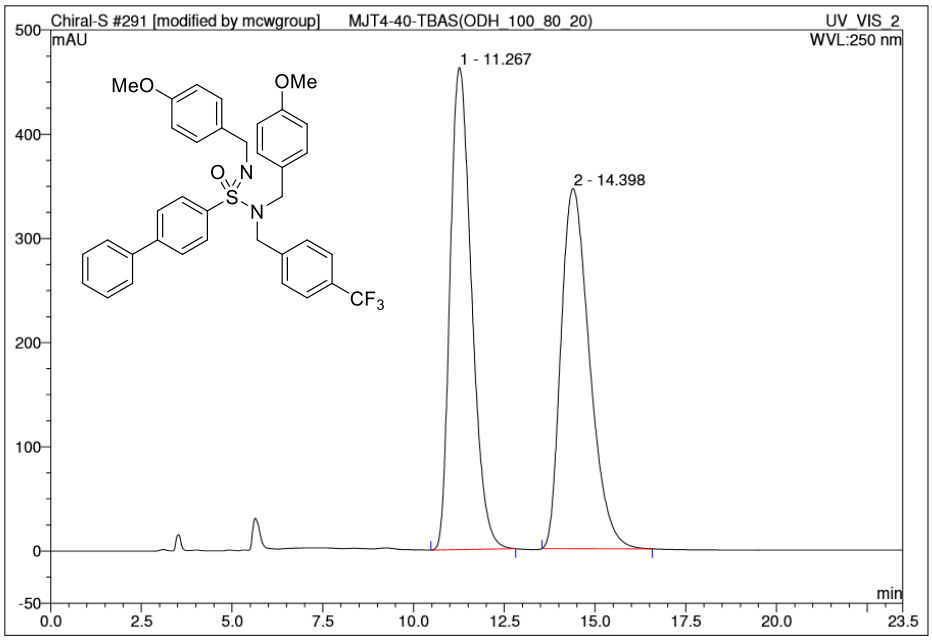



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 15.70 | n.a. | 459.736 | 474.044 | 50.08 | n.a. | BMB* |
| 2 | 19.31 | n.a. | 364.278 | 472.583 | 49.92 | n.a. | BMB* |
| **Total:** | | | 824.014 | 946.627 | 100.00 | 0.000 | |

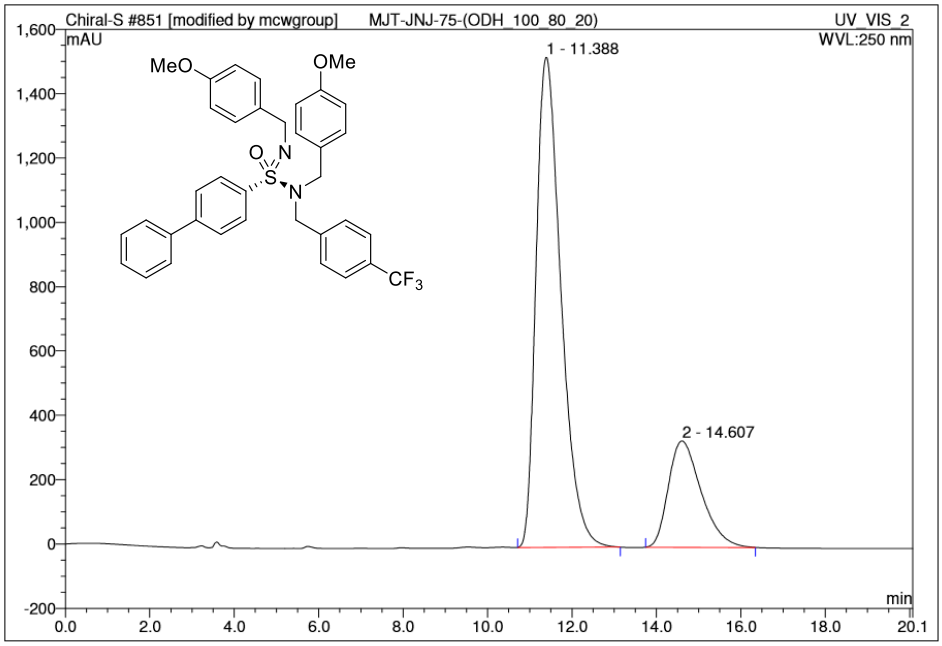



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 15.68 | n.a. | 744.251 | 759.847 | 83.96 | n.a. | BMB* |
| 2 | 19.53 | n.a. | 114.489 | 145.178 | 16.04 | n.a. | BMB* |
| **Total:** | | | 858.740 | 905.025 | 100.00 | 0.000 | |

## *N,N'*-bis(4-methoxybenzyl)-*N*-(4-(trifluoromethyl)benzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ad)

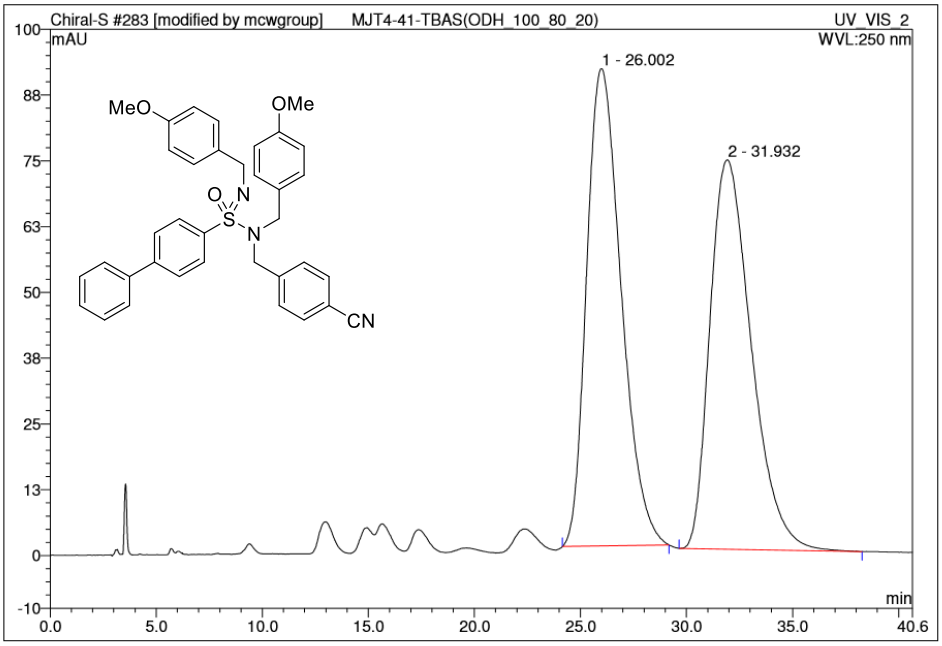



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 11.27 | n.a. | 462.499 | 316.548 | 50.12 | n.a. | BMB* |
| 2 | 14.40 | n.a. | 345.710 | 315.037 | 49.88 | n.a. | BMB* |
| **Total:** | | | 808.209 | 631.584 | 100.00 | 0.000 | |

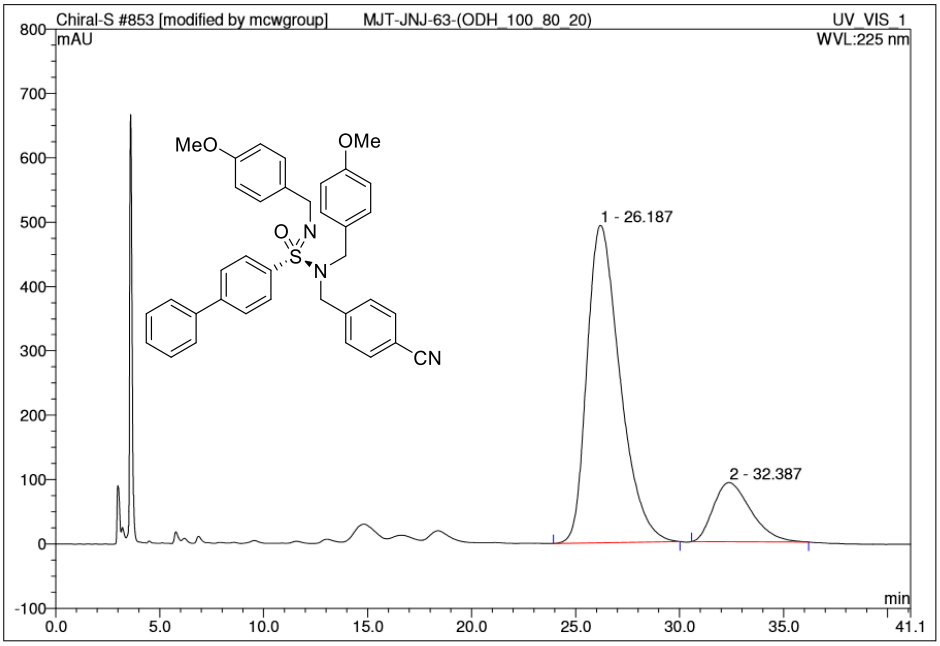



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 11.39 | n.a. | 1523.296 | 1041.714 | 77.79 | n.a. | BMB* |
| 2 | 14.61 | n.a. | 330.300 | 297.397 | 22.21 | n.a. | BMB* |
| **Total:** | | | 1853.595 | 1339.111 | 100.00 | 0.000 | |

## *N*-(4-cyanobenzyl)-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ae)

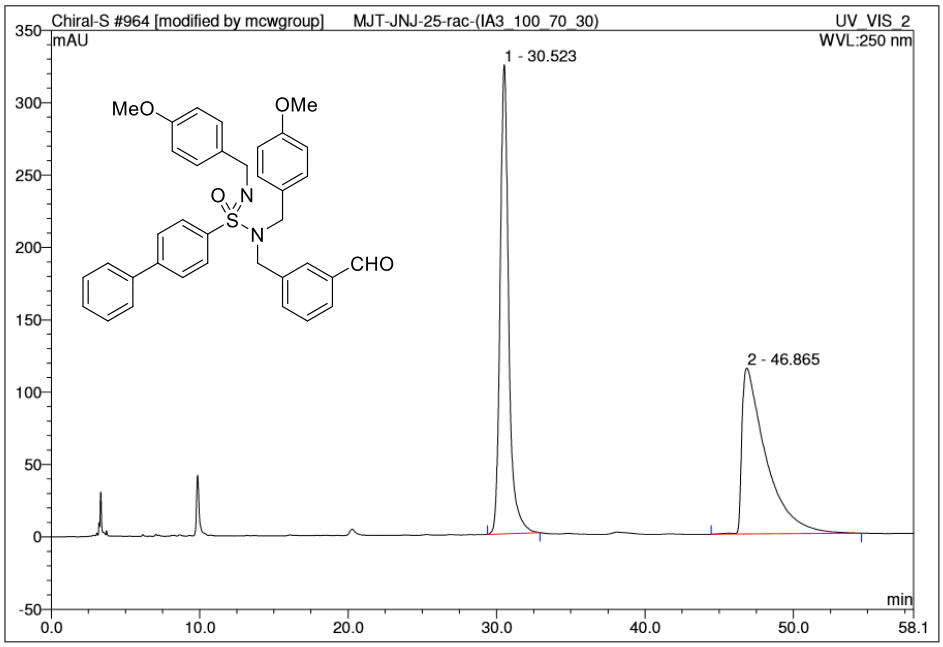



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 26.00 | n.a. | 90.675 | 170.835 | 50.54 | n.a. | BMB* |
| 2 | 31.93 | n.a. | 74.005 | 167.171 | 49.46 | n.a. | BMB* |
| **Total:** | | | 164.681 | 338.006 | 100.00 | 0.000 | |

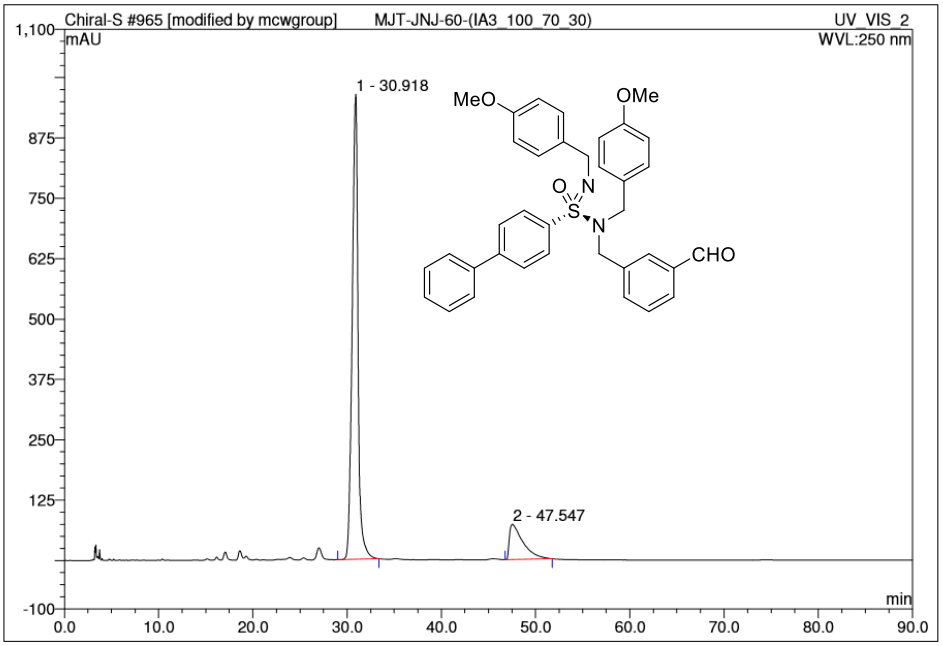



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 26.19 | n.a. | 493.187 | 908.533 | 82.53 | n.a. | BMB* |
| 2 | 32.39 | n.a. | 91.877 | 192.265 | 17.47 | n.a. | BMB* |
| **Total:** | | | 585.065 | 1100.798 | 100.00 | 0.000 | |

## *N*-(3-formylbenzyl)-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74af)

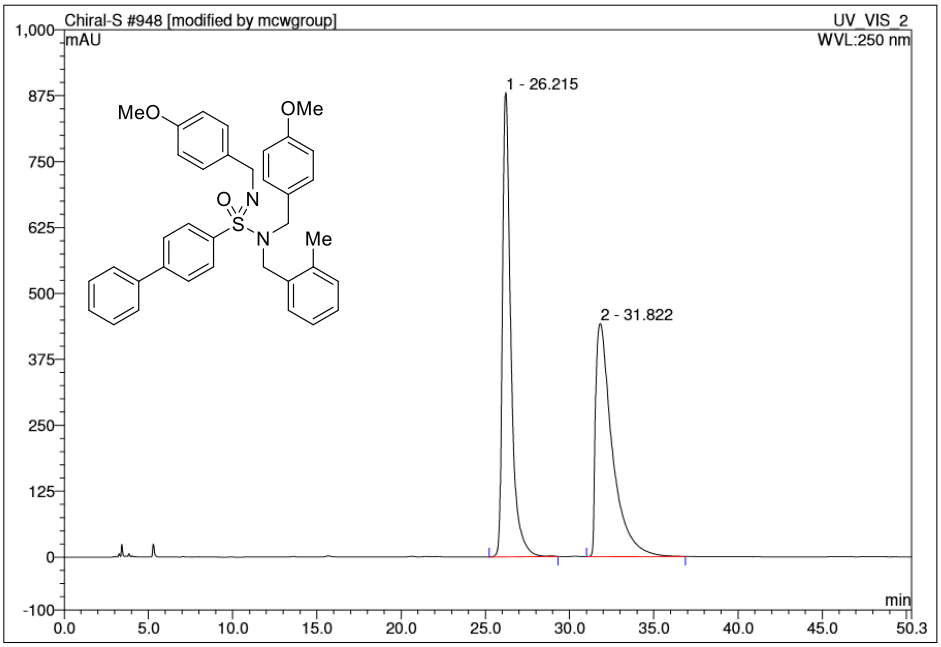



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 30.52 | n.a. | 324.102 | 216.727 | 50.19 | n.a. | BMB* |
| 2 | 46.87 | n.a. | 114.588 | 215.109 | 49.81 | n.a. | BMB* |
| **Total:** | | | 438.690 | 431.836 | 100.00 | 0.000 | |

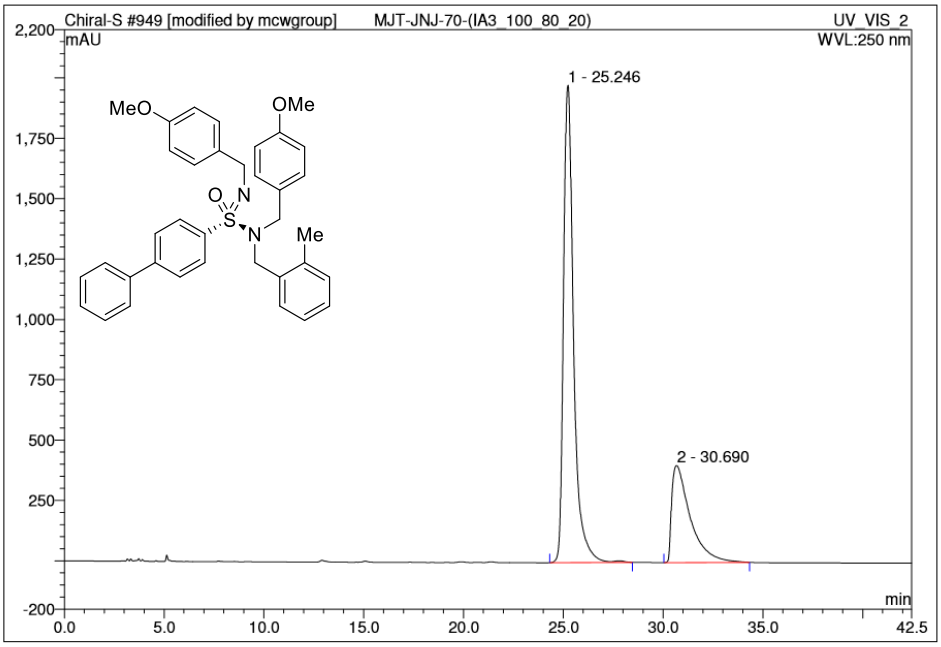



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 30.92 | n.a. | 962.843 | 689.726 | 84.98 | n.a. | BMB* |
| 2 | 47.55 | n.a. | 73.020 | 121.881 | 15.02 | n.a. | BMB* |
| **Total:** | | | 1035.863 | 811.607 | 100.00 | 0.000 | |

## *N,N'*-bis(4-methoxybenzyl)-*N*-(2-methylbenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ag)

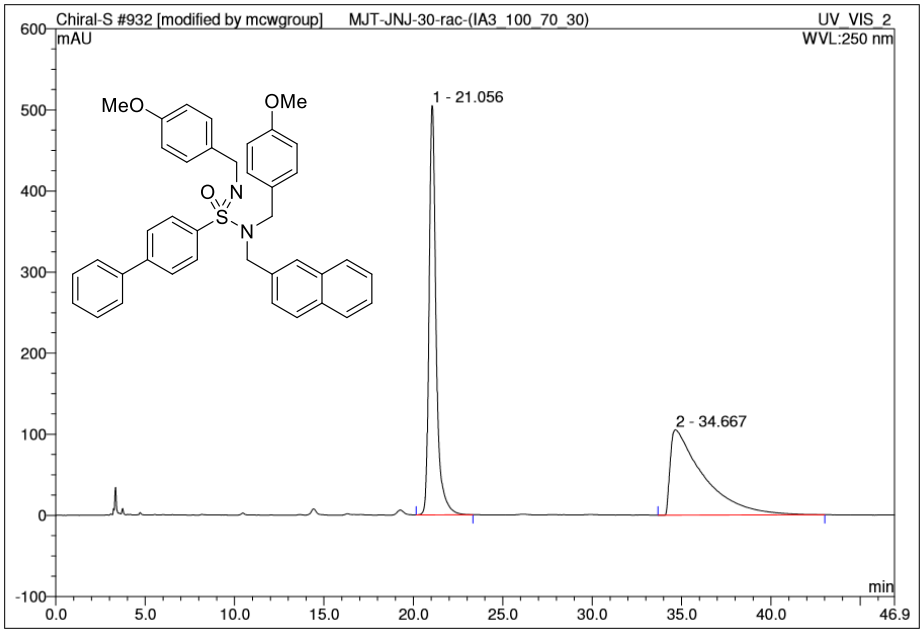



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 26.21 | n.a. | 879.997 | 511.549 | 50.20 | n.a. | BMB* |
| 2 | 31.82 | n.a. | 442.158 | 507.503 | 49.80 | n.a. | BMB* |
| **Total:** | | | 1322.155 | 1019.052 | 100.00 | 0.000 | |

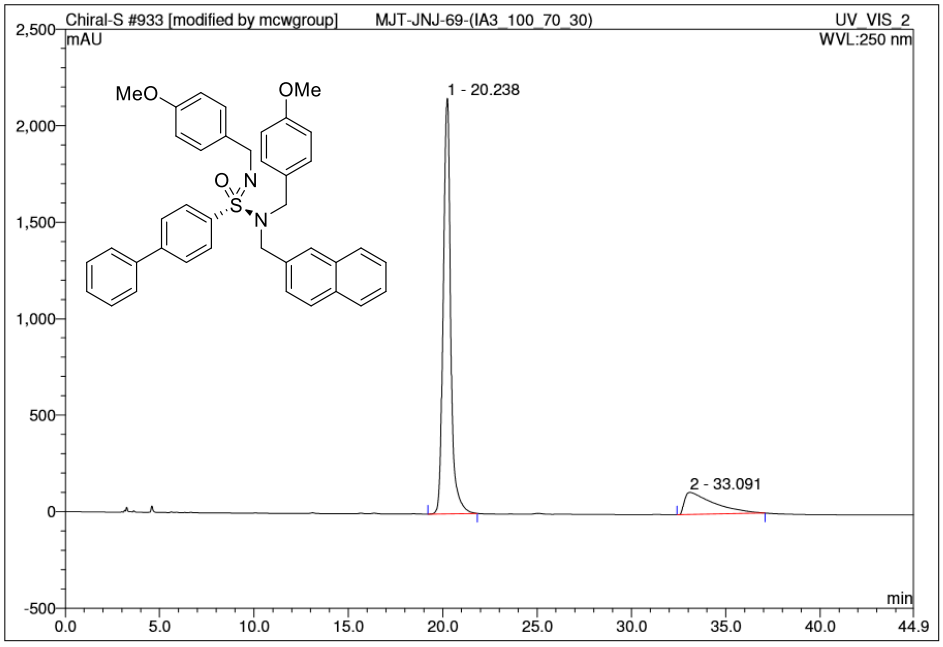



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 25.25 | n.a. | 1977.005 | 1159.470 | 72.84 | n.a. | BMB* |
| 2 | 30.69 | n.a. | 401.712 | 432.421 | 27.16 | n.a. | BMB* |
| **Total:** | | | 2378.716 | 1591.890 | 100.00 | 0.000 | |

## *N,N'*-bis(4-methoxybenzyl)-*N*-(naphthalen-2-ylmethyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ah)

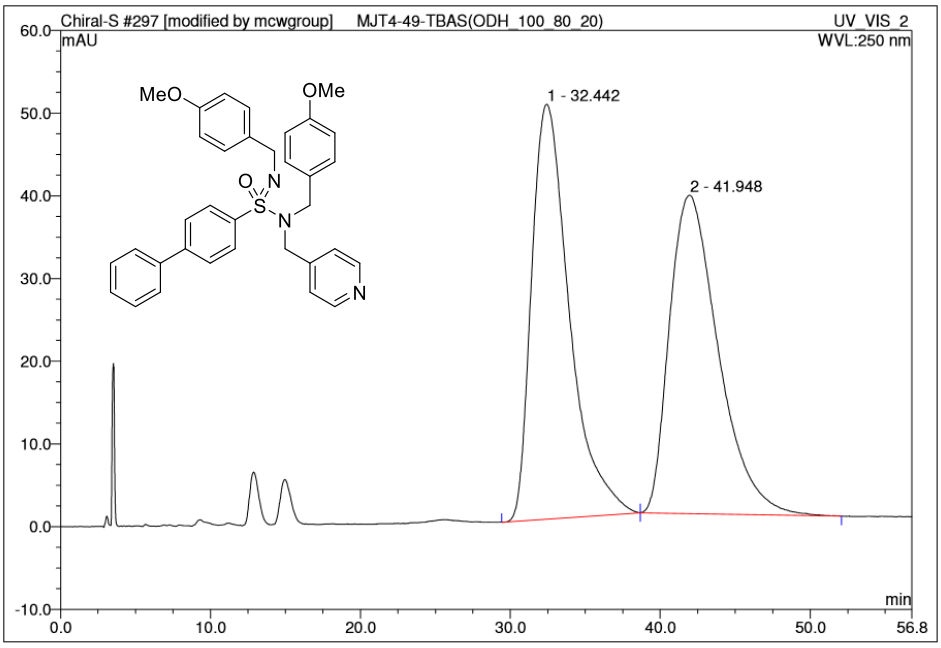



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 21.06 | n.a. | 504.827 | 229.397 | 50.39 | n.a. | BMB* |
| 2 | 34.67 | n.a. | 105.147 | 225.875 | 49.61 | n.a. | BMB* |
| **Total:** | | | 609.974 | 455.273 | 100.00 | 0.000 | |

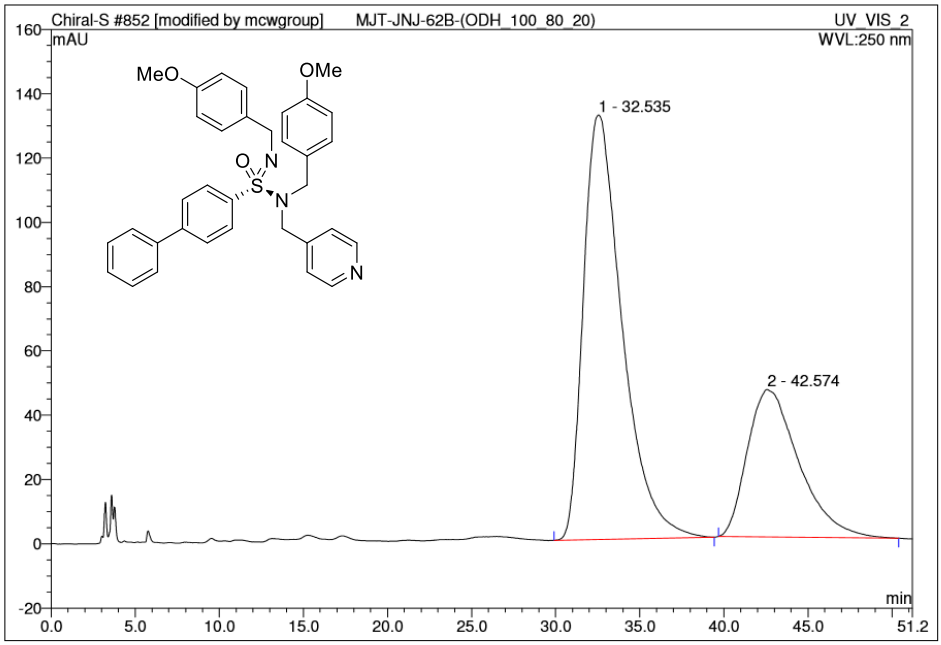



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 20.24 | n.a. | 2153.249 | 979.978 | 82.65 | n.a. | BMB* |
| 2 | 33.09 | n.a. | 114.338 | 205.728 | 17.35 | n.a. | BMB* |
| **Total:** | | | 2267.587 | 1185.707 | 100.00 | 0.000 | |

## *N*,*N*'-bis(4-methoxybenzyl)-*N*-(pyridin-4-ylmethyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ai)

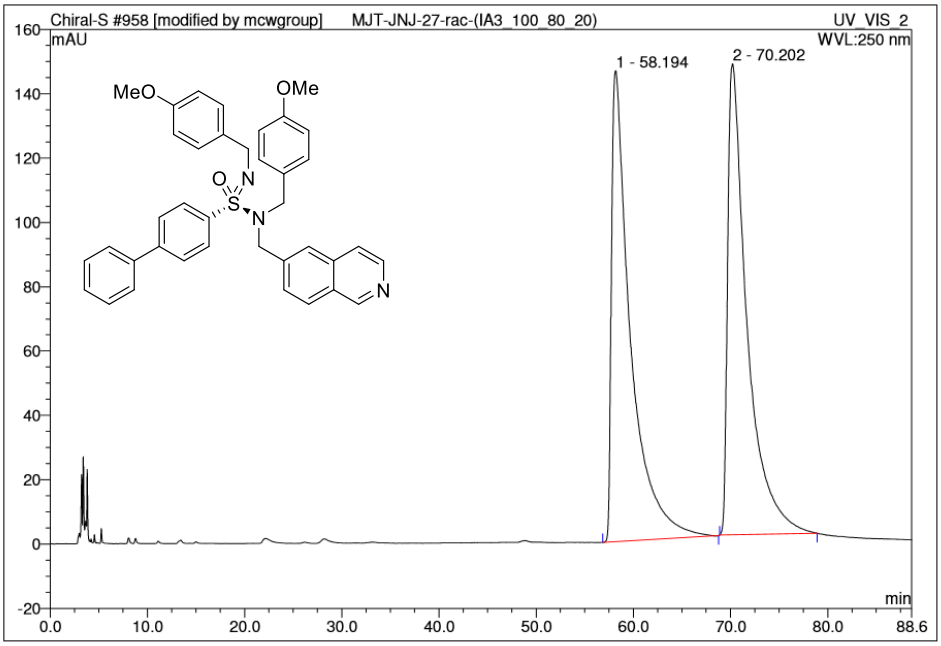



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 32.44 | n.a. | 50.166 | 146.349 | 50.16 | n.a. | BMb* |
| 2 | 41.95 | n.a. | 38.494 | 145.423 | 49.84 | n.a. | bMB* |
| **Total:** | | | 88.660 | 291.772 | 100.00 | 0.000 | |

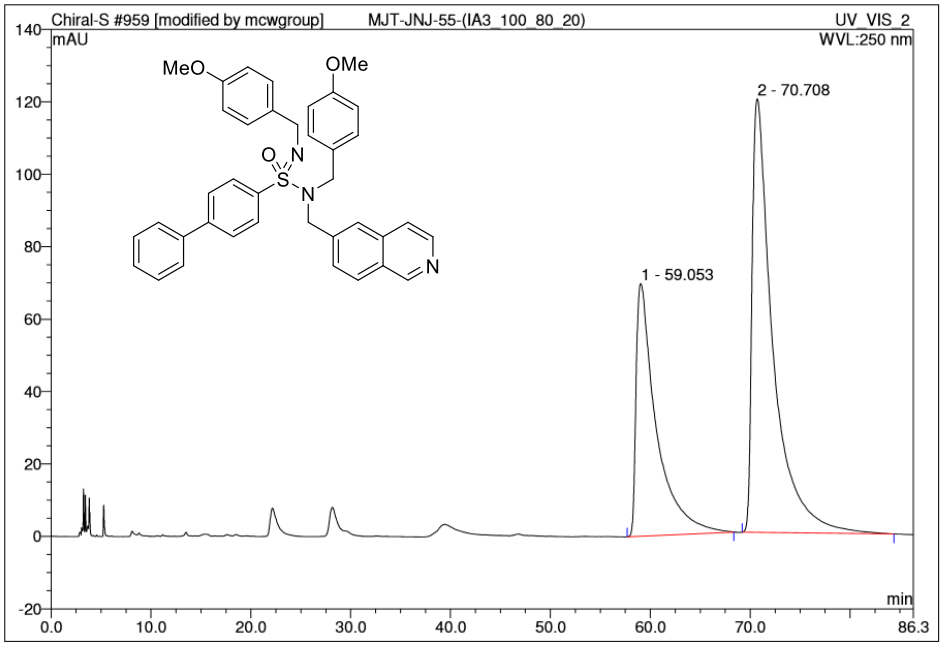



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 32.54 | n.a. | 132.052 | 352.250 | 68.42 | n.a. | BMB* |
| 2 | 42.57 | n.a. | 45.825 | 162.595 | 31.58 | n.a. | BMB* |
| **Total:** | | | 177.876 | 514.845 | 100.00 | 0.000 | |

## *N*-(isoquinolin-6-ylmethyl)-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74aj)

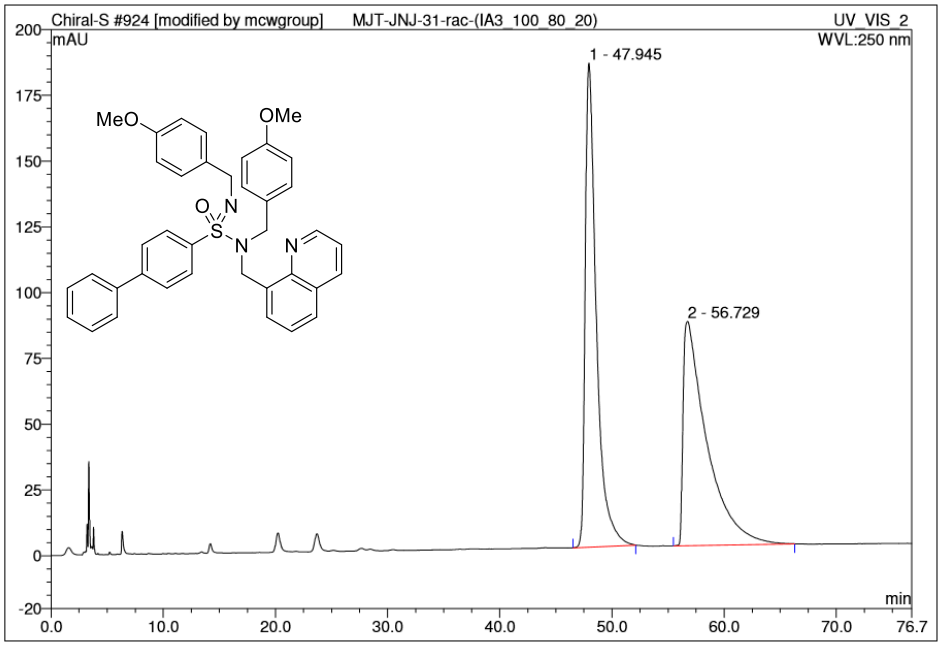



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 58.19 | n.a. | 146.392 | 331.286 | 49.53 | n.a. | BMB* |
| 2 | 70.20 | n.a. | 146.454 | 337.537 | 50.47 | n.a. | BMB* |
| **Total:** | | | 292.845 | 668.823 | 100.00 | 0.000 | |

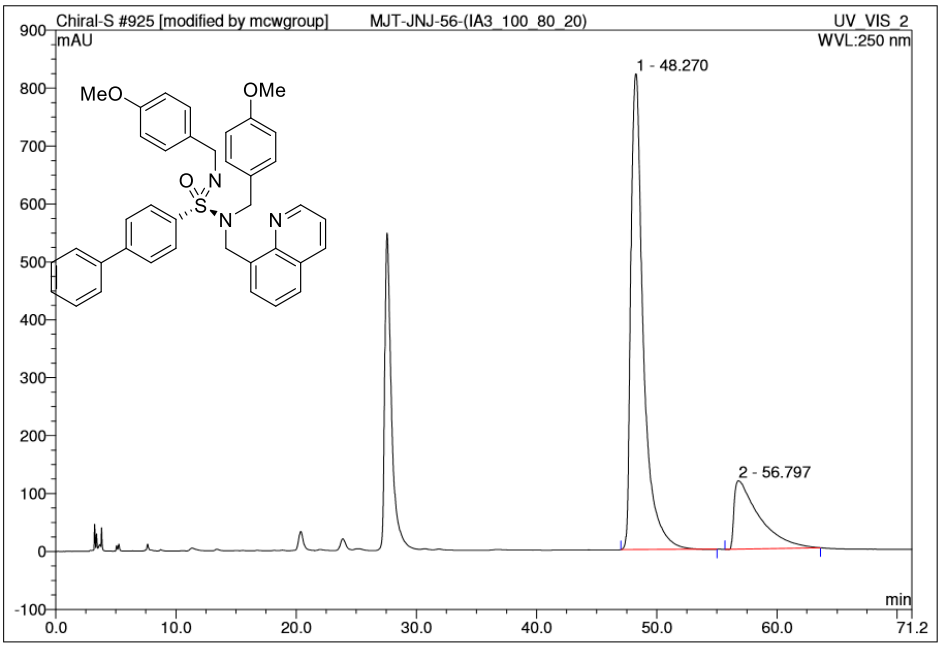



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 59.05 | n.a. | 69.790 | 163.146 | 36.12 | n.a. | BMB* |
| 2 | 70.71 | n.a. | 119.693 | 288.498 | 63.88 | n.a. | BMB* |
| **Total:** | | | 189.483 | 451.644 | 100.00 | 0.000 | |

## *N,N'*-bis(4-methoxybenzyl)-*N*-(quinolin-8-ylmethyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ak)

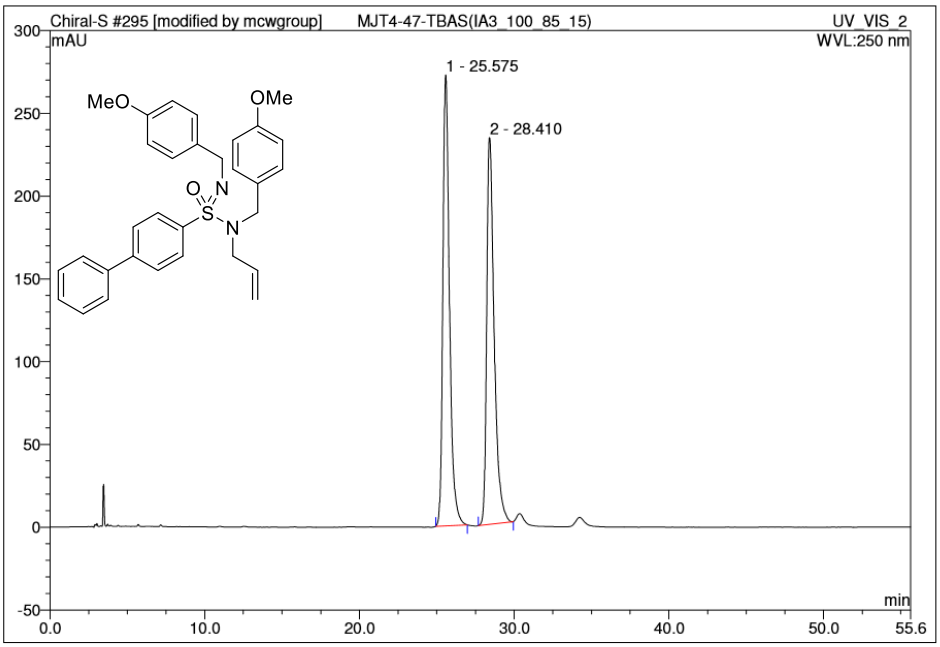



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 47.94 | n.a. | 183.989 | 210.730 | 50.33 | n.a. | BMB* |
| 2 | 56.73 | n.a. | 85.295 | 208.003 | 49.67 | n.a. | BMB* |
| **Total:** | | | 269.284 | 418.733 | 100.00 | 0.000 | |

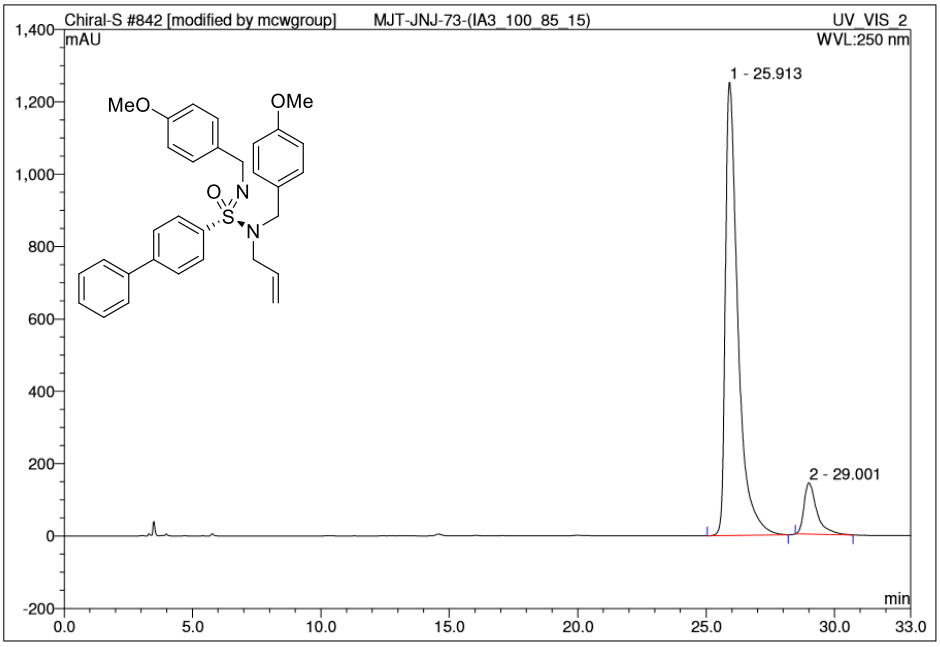



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 48.27 | n.a. | 821.468 | 987.687 | 77.61 | n.a. | BMB* |
| 2 | 56.80 | n.a. | 118.087 | 285.013 | 22.39 | n.a. | BMB* |
| **Total:** | | | 939.556 | 1272.700 | 100.00 | 0.000 | |

## *N*-allyl-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamidede (74al)

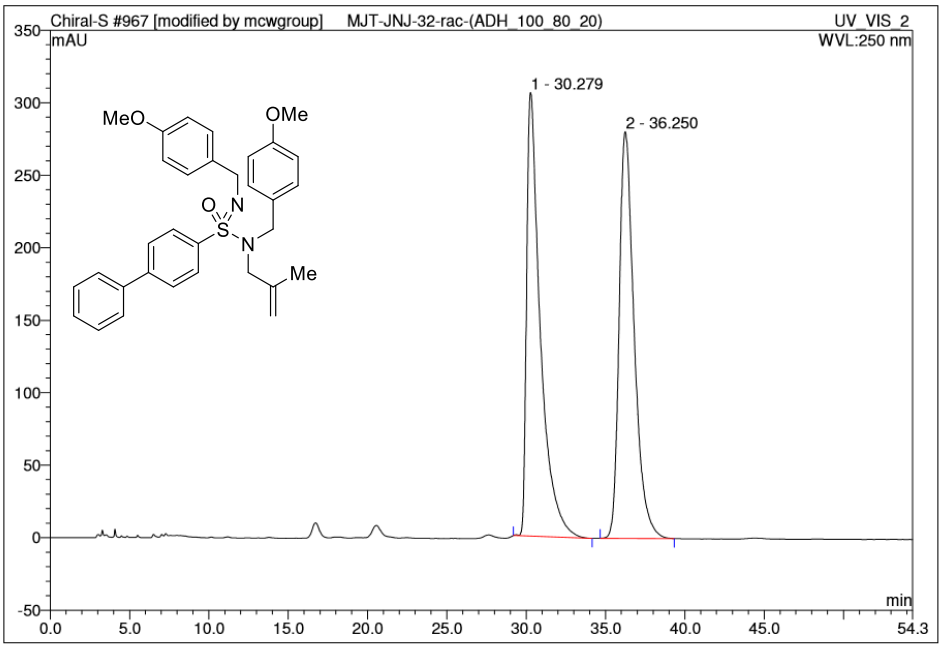



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 25.58 | n.a. | 272.347 | 134.489 | 50.73 | n.a. | BMB* |
| 2 | 28.41 | n.a. | 233.636 | 130.644 | 49.27 | n.a. | BMB* |
| **Total:** | | | 505.982 | 265.134 | 100.00 | 0.000 | |

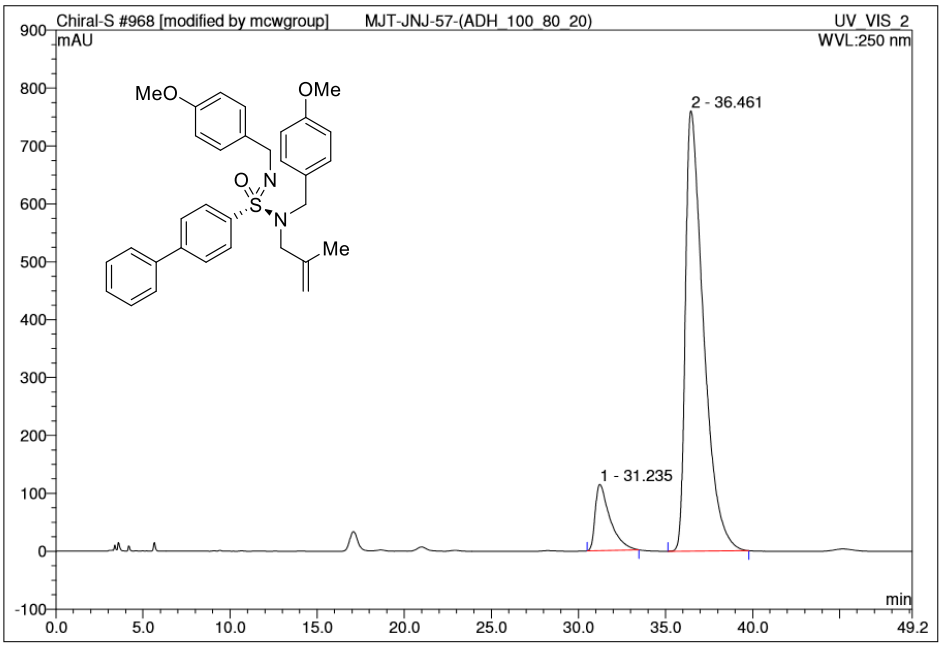



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 25.91 | n.a. | 1252.286 | 707.992 | 89.65 | n.a. | BMB* |
| 2 | 29.00 | n.a. | 141.525 | 81.756 | 10.35 | n.a. | BMB* |
| **Total:** | | | 1393.810 | 789.748 | 100.00 | 0.000 | |

## *N,N'*-bis(4-methoxybenzyl)-*N*-(2-methylallyl)-[1,1'-biphenyl]-4-sulfonimidamide (74am)

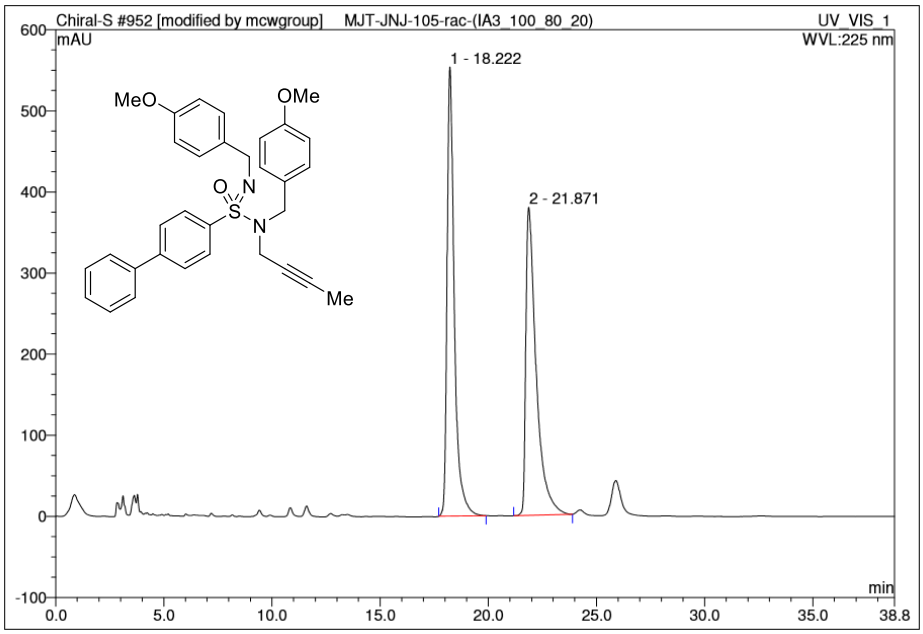



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 30.28 | n.a. | 305.982 | 305.429 | 49.79 | n.a. | BMB* |
| 2 | 36.25 | n.a. | 280.572 | 308.014 | 50.21 | n.a. | BMB* |
| **Total:** | | | 586.554 | 613.443 | 100.00 | 0.000 | |

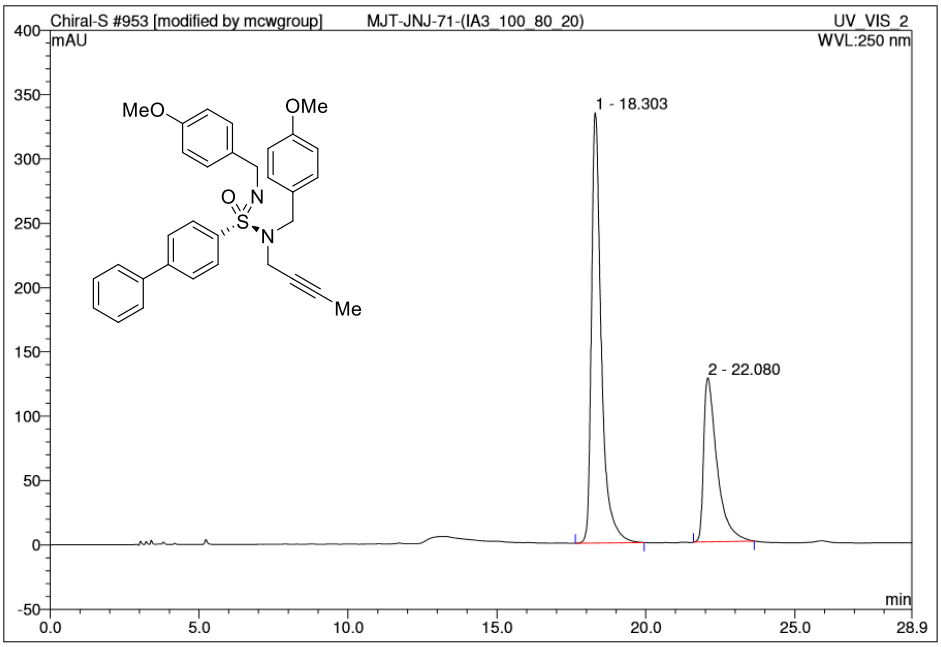



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 31.24 | n.a. | 114.388 | 112.602 | 10.96 | n.a. | BMB* |
| 2 | 36.46 | n.a. | 760.676 | 914.906 | 89.04 | n.a. | BMB* |
| **Total:** | | | 875.063 | 1027.508 | 100.00 | 0.000 | |

## *N*-(but-2-yn-1-yl)-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide ( 74an)

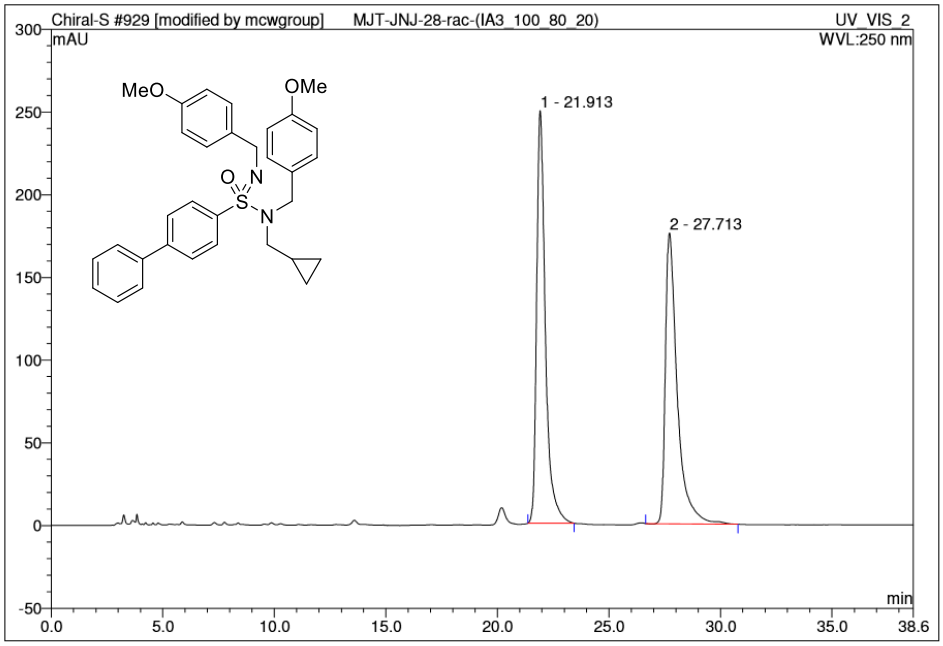



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 18.22 | n.a. | 553.749 | 213.602 | 50.39 | n.a. | BMB* |
| 2 | 21.87 | n.a. | 380.007 | 210.267 | 49.61 | n.a. | BMB* |
| Total: | | | 933.756 | 423.869 | 100.00 | 0.000 | |

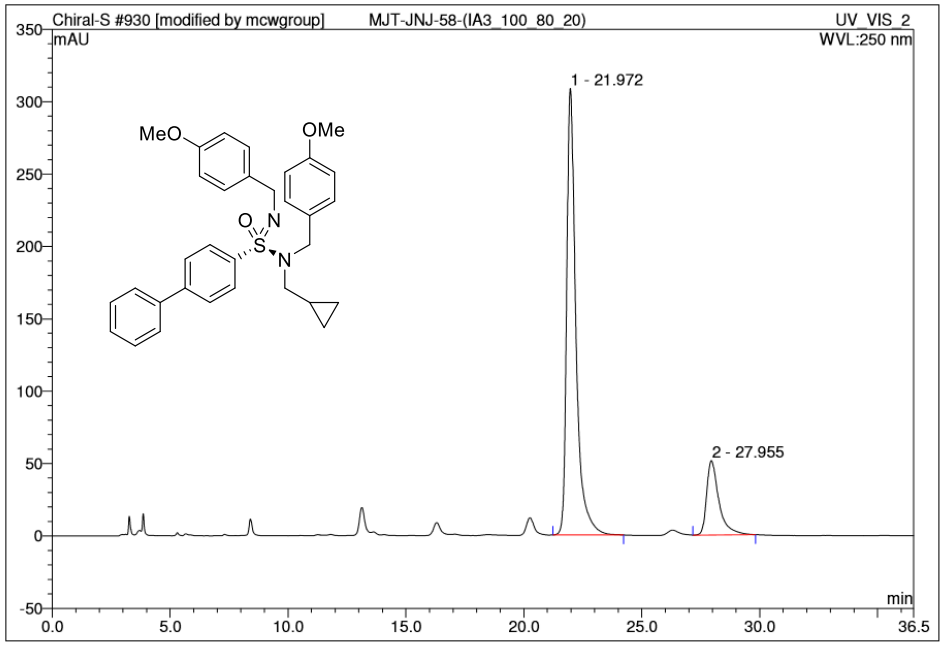



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 18.30 | n.a. | 334.510 | 128.212 | 65.84 | n.a. | BMB* |
| 2 | 22.08 | n.a. | 127.473 | 66.525 | 34.16 | n.a. | BMB* |
| Total: | | | 461.983 | 194.737 | 100.00 | 0.000 | |

## *N*-(cyclopropylmethyl)-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ao)

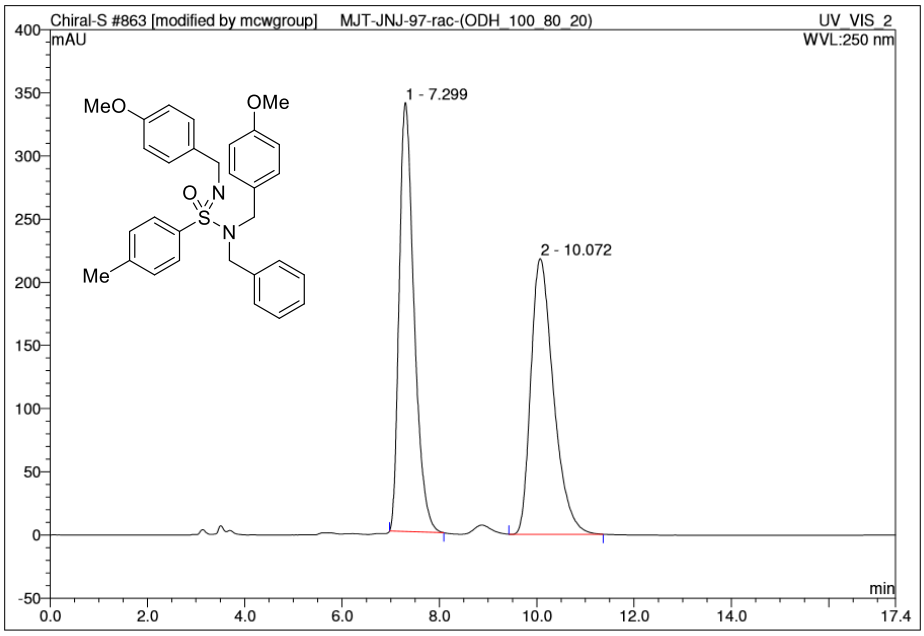



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 21.91 | n.a. | 249.459 | 112.649 | 50.98 | n.a. | BMB* |
| 2 | 27.71 | n.a. | 175.858 | 108.301 | 49.02 | n.a. | BMB* |
| **Total:** | | | 425.317 | 220.951 | 100.00 | 0.000 | |

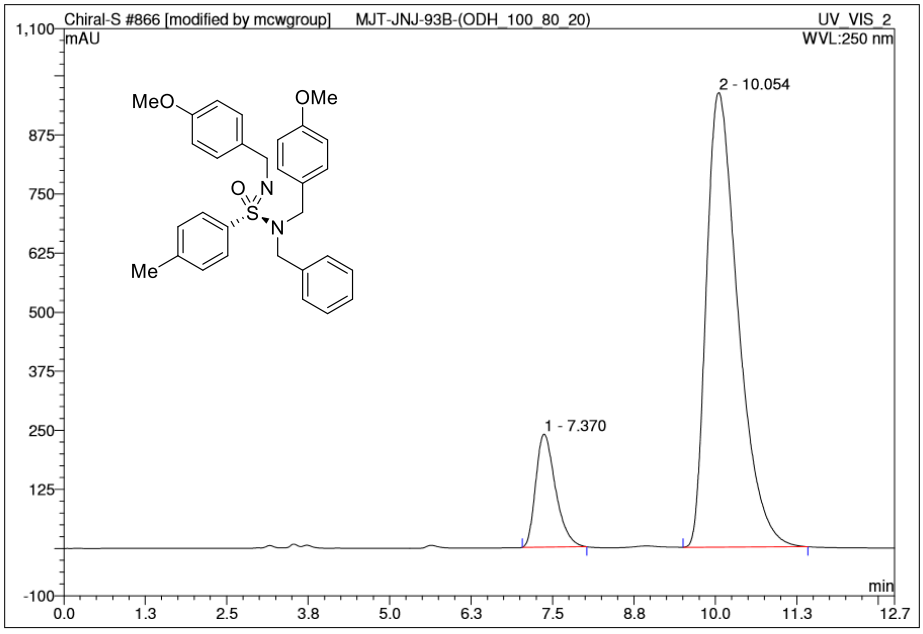



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 21.97 | n.a. | 308.450 | 140.247 | 81.90 | n.a. | BMB* |
| 2 | 27.95 | n.a. | 51.322 | 30.994 | 18.10 | n.a. | BMB* |
| **Total:** | | | 359.773 | 171.241 | 100.00 | 0.000 | |

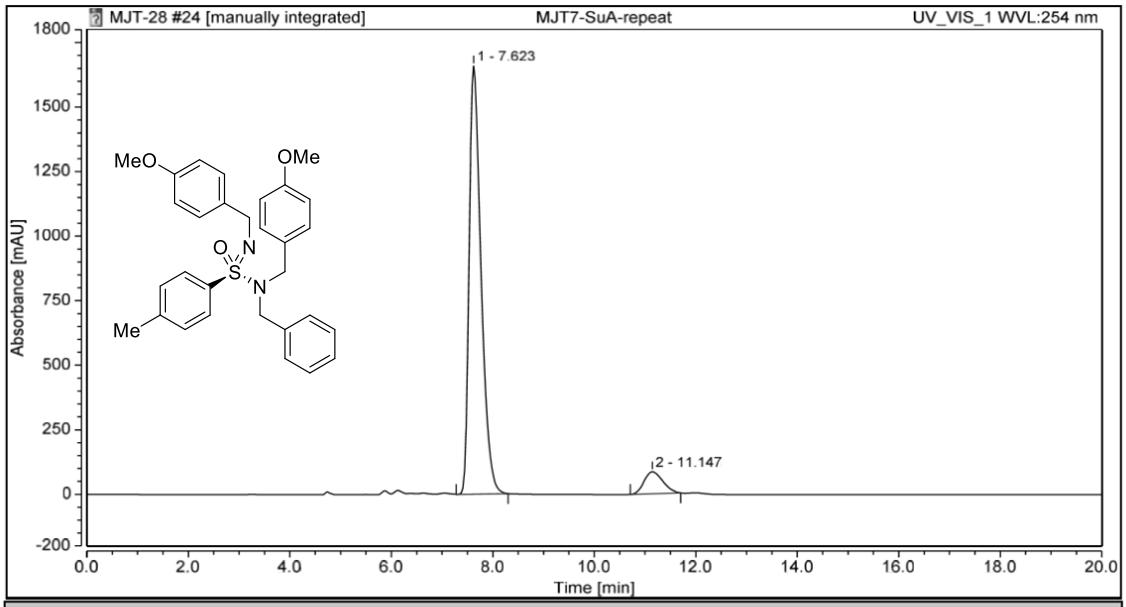
## *N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-4-methylbenzenesulfonimidamide (74b)




| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 7.30 | n.a. | 339.601 | 119.879 | 50.40 | n.a. | BMB* |
| 2 | 10.07 | n.a. | 218.286 | 117.970 | 49.60 | n.a. | BMB* |
| **Total:** | | | 557.887 | 237.849 | 100.00 | 0.000 | |




| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 7.37 | n.a. | 238.990 | 84.136 | 13.44 | n.a. | BMB* |
| 2 | 10.05 | n.a. | 961.662 | 541.867 | 86.56 | n.a. | BMB* |
| **Total:** | | | 1200.652 | 626.003 | 100.00 | 0.000 | |

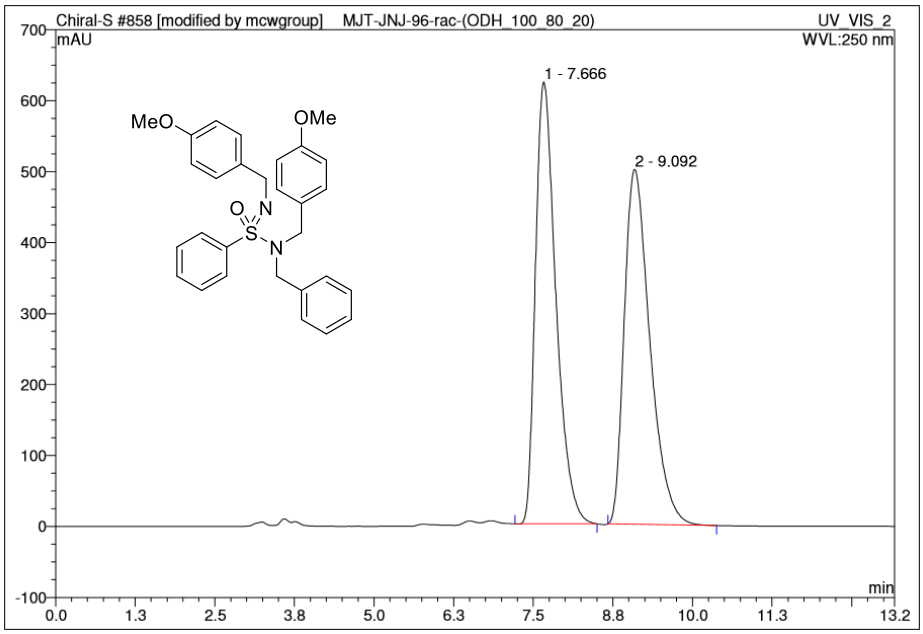



**Integration Results**

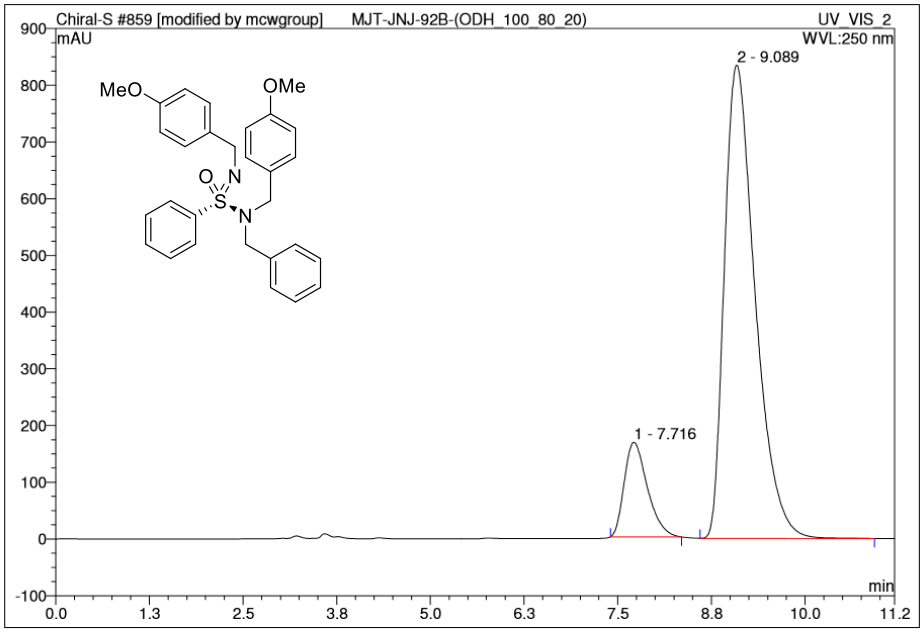
| No. | Peak Name | Retention Time min | Area mAU*min | Height mAU | Relative Area % |
|---|---|---|---|---|---|
| 1 | | 7.623 | 450.911 | 1658.573 | 92.53 |
| 2 | | 11.147 | 36.397 | 85.003 | 7.47 |
| **Total:** | | | **487.309** | **1743.576** | **100.00** |

*HPLC trace for the authentic sample synthesis.

## *N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)benzenesulfonimidamide (74c)

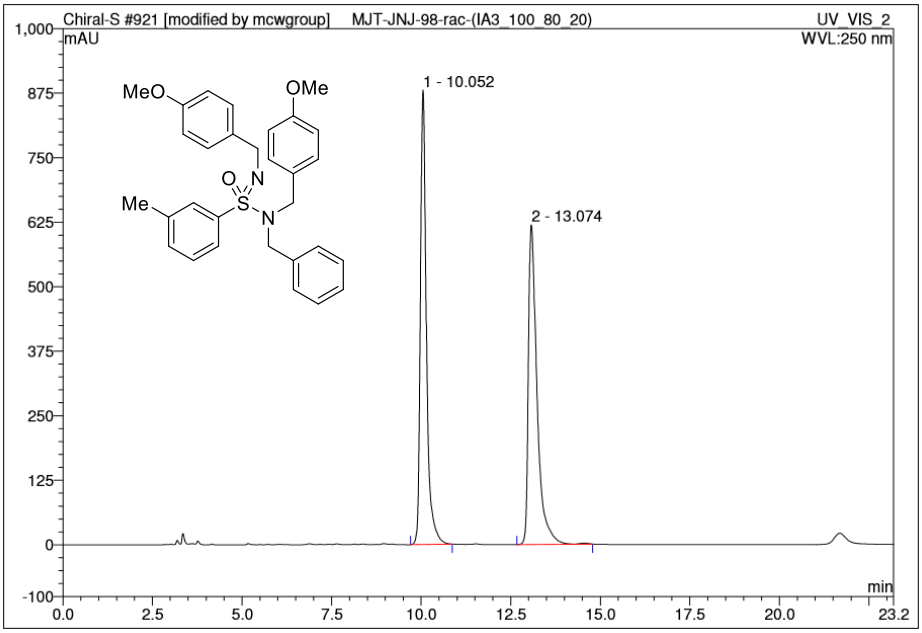



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 7.67 | n.a. | 622.473 | 231.759 | 49.92 | n.a. | BMB* |
| 2 | 9.09 | n.a. | 499.903 | 232.537 | 50.08 | n.a. | BMB* |
| **Total:** | | | 1122.375 | 464.296 | 100.00 | 0.000 | |

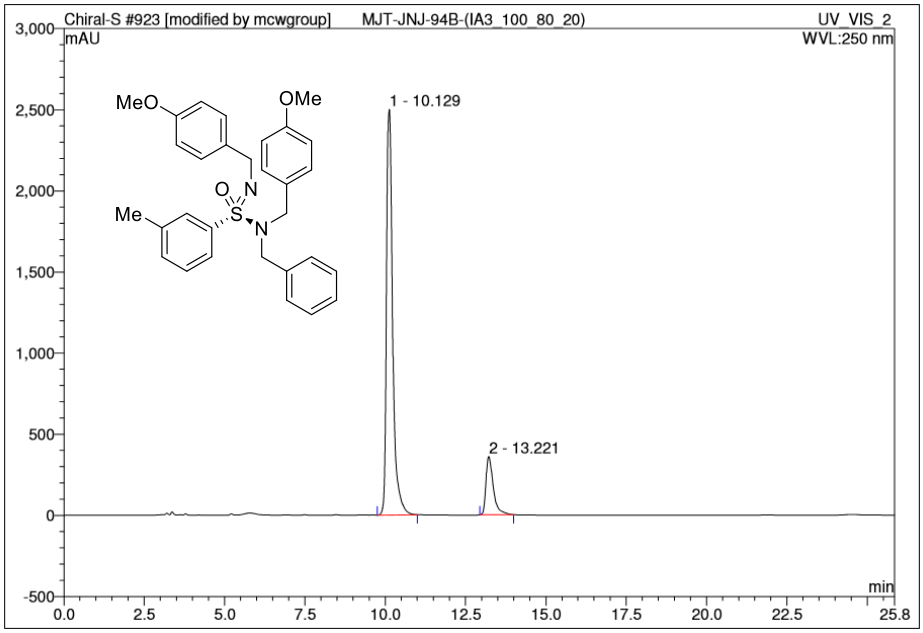



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 7.72 | n.a. | 166.751 | 59.683 | 13.10 | n.a. | BMB* |
| 2 | 9.09 | n.a. | 834.213 | 395.942 | 86.90 | n.a. | BMB* |
| **Total:** | | | 1000.964 | 455.625 | 100.00 | 0.000 | |

## *N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-3-methylbenzenesulfonimidamide (74d)

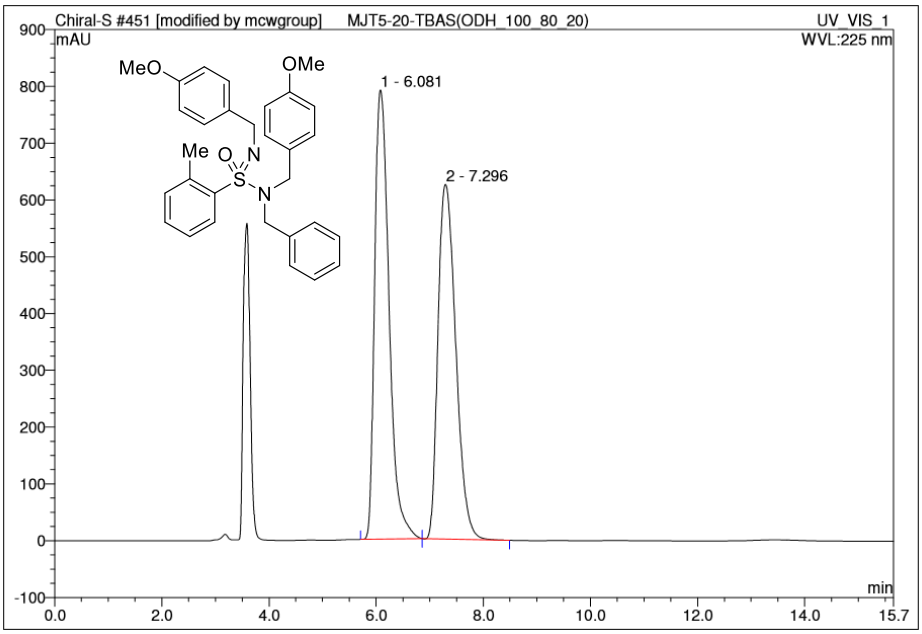



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 10.05 | n.a. | 879.899 | 172.167 | 49.75 | n.a. | BMB* |
| 2 | 13.07 | n.a. | 619.476 | 173.908 | 50.25 | n.a. | BMB* |
| **Total:** | | | 1499.375 | 346.074 | 100.00 | 0.000 | |

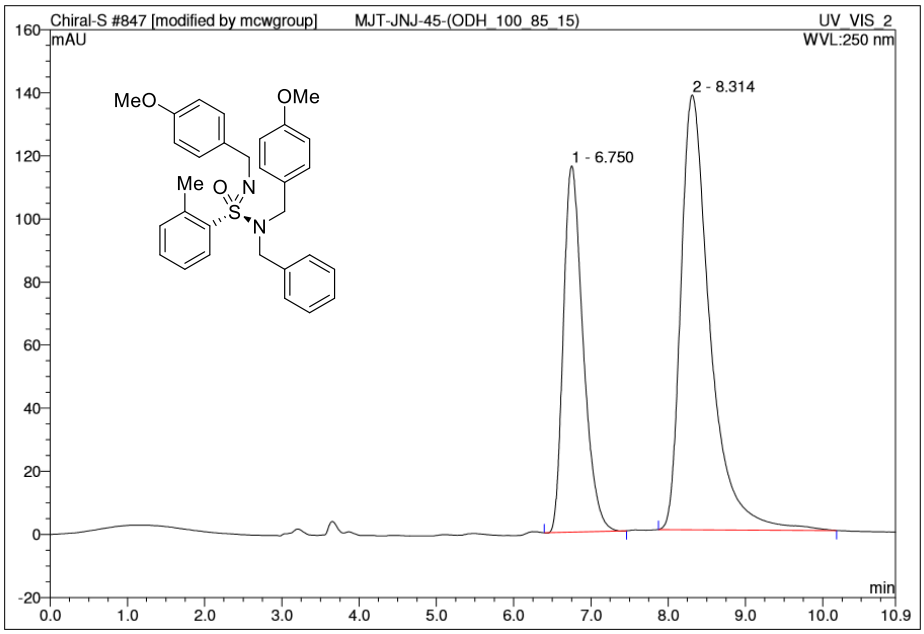



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 10.13 | n.a. | 2500.101 | 558.419 | 85.49 | n.a. | BMB* |
| 2 | 13.22 | n.a. | 359.050 | 94.812 | 14.51 | n.a. | BMB* |
| **Total:** | | | 2859.152 | 653.231 | 100.00 | 0.000 | |

## *N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-2-methylbenzenesulfonimidamide (74e)

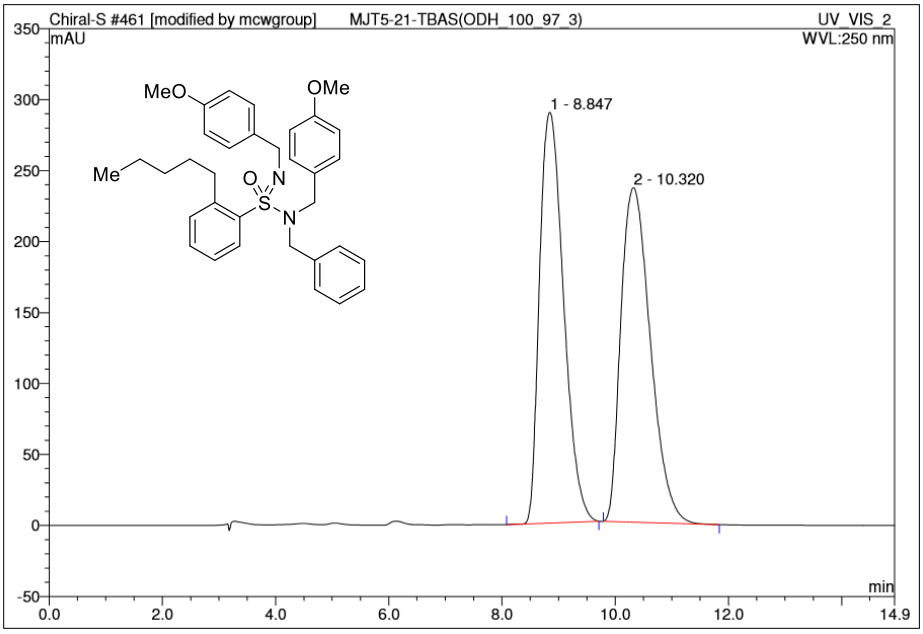



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 6.08 | n.a. | 791.043 | 246.467 | 50.71 | n.a. | BMb* |
| 2 | 7.30 | n.a. | 624.559 | 239.536 | 49.29 | n.a. | bMB* |
| **Total:** | | | 1415.602 | 486.004 | 100.00 | 0.000 | |

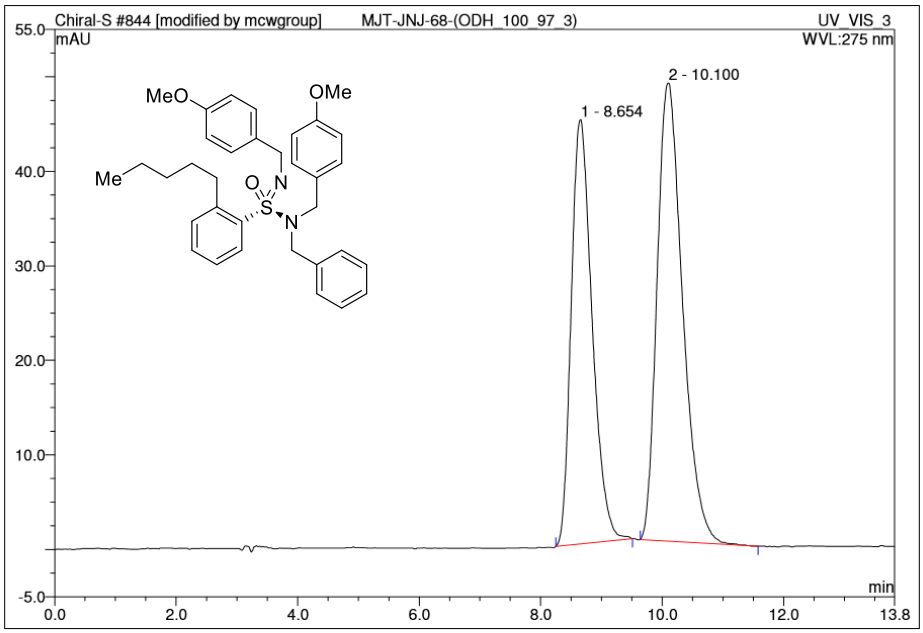



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 6.75 | n.a. | 116.161 | 34.326 | 36.33 | n.a. | BMB* |
| 2 | 8.31 | n.a. | 137.800 | 60.169 | 63.67 | n.a. | BMB* |
| **Total:** | | | 253.961 | 94.495 | 100.00 | 0.000 | |

## *N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-2-pentylbenzenesulfonimidamide (74f)

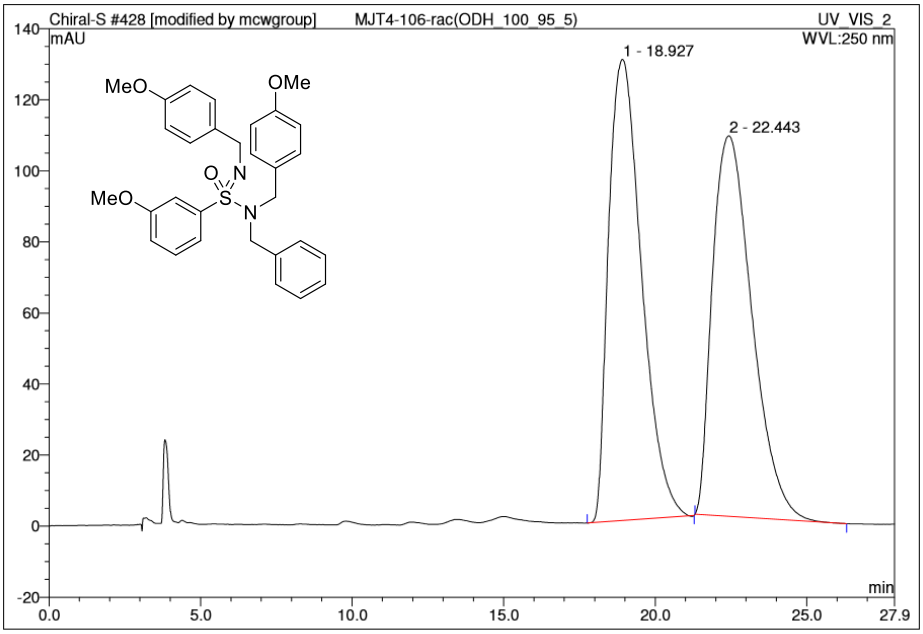



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 8.85 | n.a. | 289.273 | 142.149 | 50.00 | n.a. | BMB* |
| 2 | 10.32 | n.a. | 235.532 | 142.152 | 50.00 | n.a. | BMB* |
| **Total:** | | | 524.805 | 284.301 | 100.00 | 0.000 | |

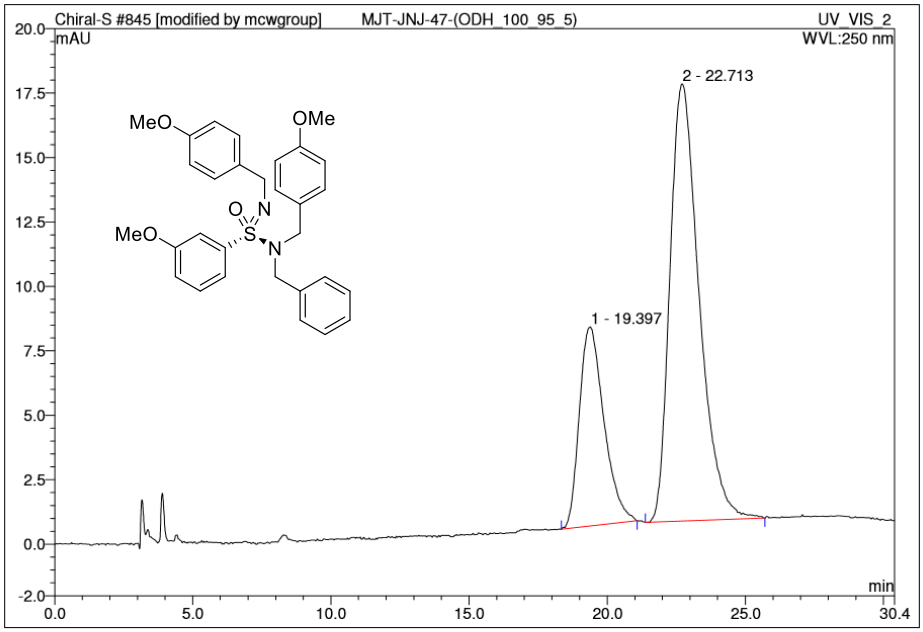



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 8.65 | n.a. | 44.864 | 17.863 | 43.14 | n.a. | BMB* |
| 2 | 10.10 | n.a. | 48.460 | 23.540 | 56.86 | n.a. | BMB* |
| **Total:** | | | 93.324 | 41.402 | 100.00 | 0.000 | |

## *N*-benzyl-3-methoxy-*N*,*N*'-bis(4-methoxybenzyl)benzenesulfonimidamide (74g)

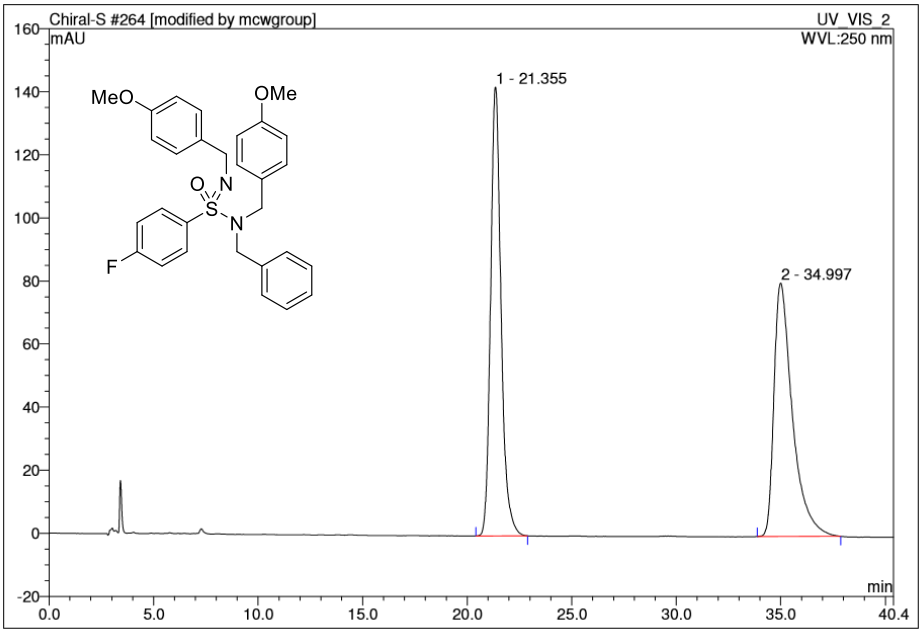



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 18.93 | n.a. | 129.770 | 163.508 | 50.20 | n.a. | BMB* |
| 2 | 22.44 | n.a. | 107.119 | 162.178 | 49.80 | n.a. | BMB* |
| **Total:** | | | 236.889 | 325.686 | 100.00 | 0.000 | |

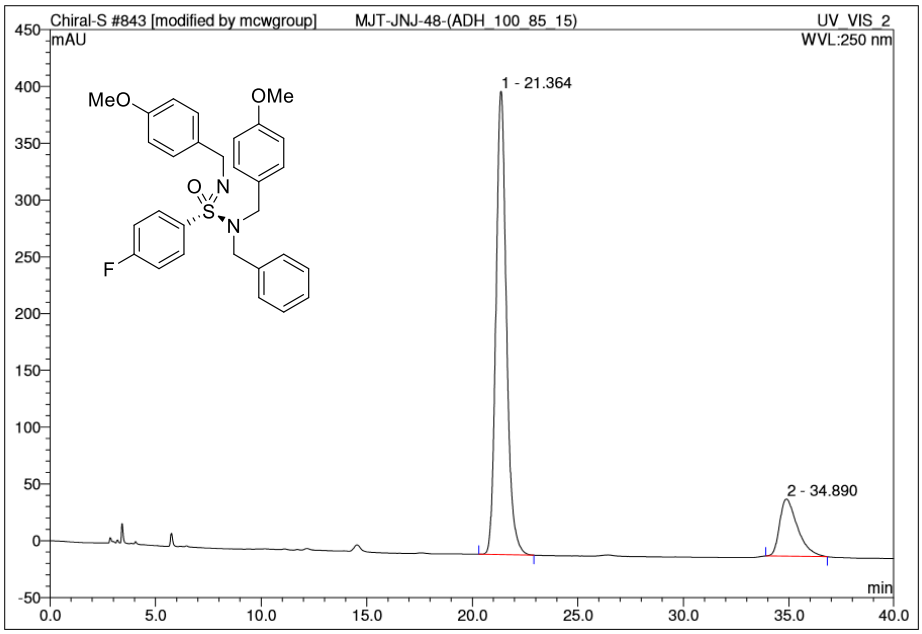



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 19.40 | n.a. | 7.712 | 7.982 | 27.78 | n.a. | BMB* |
| 2 | 22.71 | n.a. | 16.951 | 20.748 | 72.22 | n.a. | BMB* |
| **Total:** | | | 24.663 | 28.730 | 100.00 | 0.000 | |

## *N*-benzyl-4-fluoro-*N*,*N*'-bis(4-methoxybenzyl)benzenesulfonimidamide (74h)

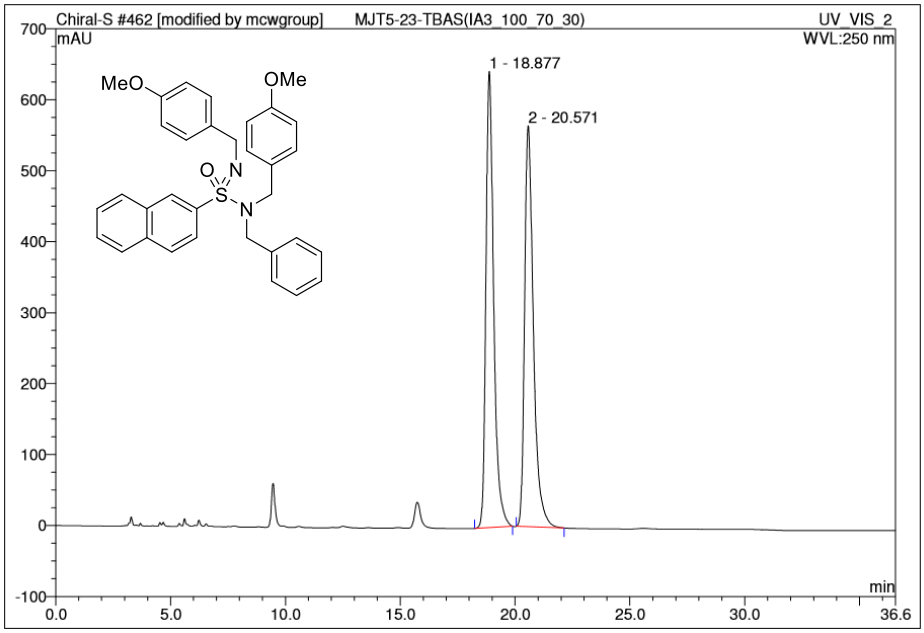



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 21.35 | n.a. | 142.353 | 82.458 | 50.16 | n.a. | BMB* |
| 2 | 35.00 | n.a. | 80.373 | 81.936 | 49.84 | n.a. | BMB* |
| **Total:** | | | 222.726 | 164.394 | 100.00 | 0.000 | |

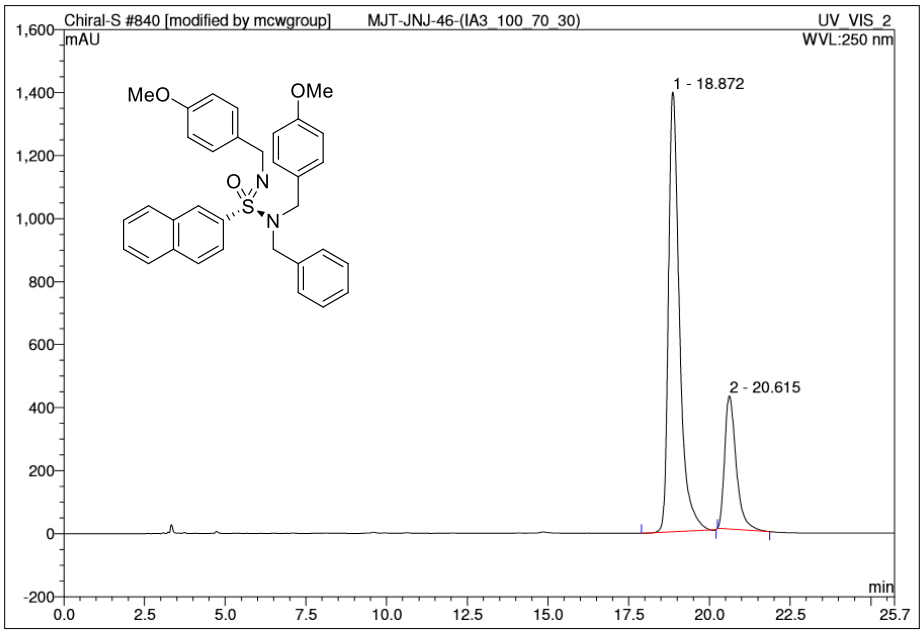



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 21.36 | n.a. | 408.063 | 234.807 | 82.65 | n.a. | BMB* |
| 2 | 34.89 | n.a. | 50.189 | 49.291 | 17.35 | n.a. | BMB* |
| **Total:** | | | 458.253 | 284.098 | 100.00 | 0.000 | |

## *N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)naphthalene-2-sulfonimidamide (74i)

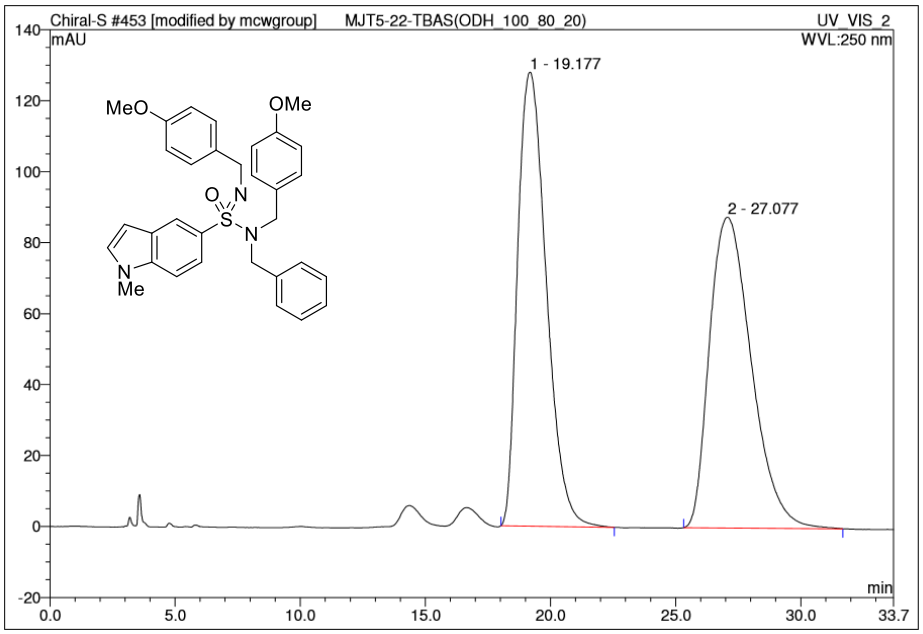



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 18.88 | n.a. | 642.736 | 251.611 | 50.12 | n.a. | BMB* |
| 2 | 20.57 | n.a. | 564.813 | 250.363 | 49.88 | n.a. | BMB* |
| **Total:** | | | 1207.549 | 501.974 | 100.00 | 0.000 | |

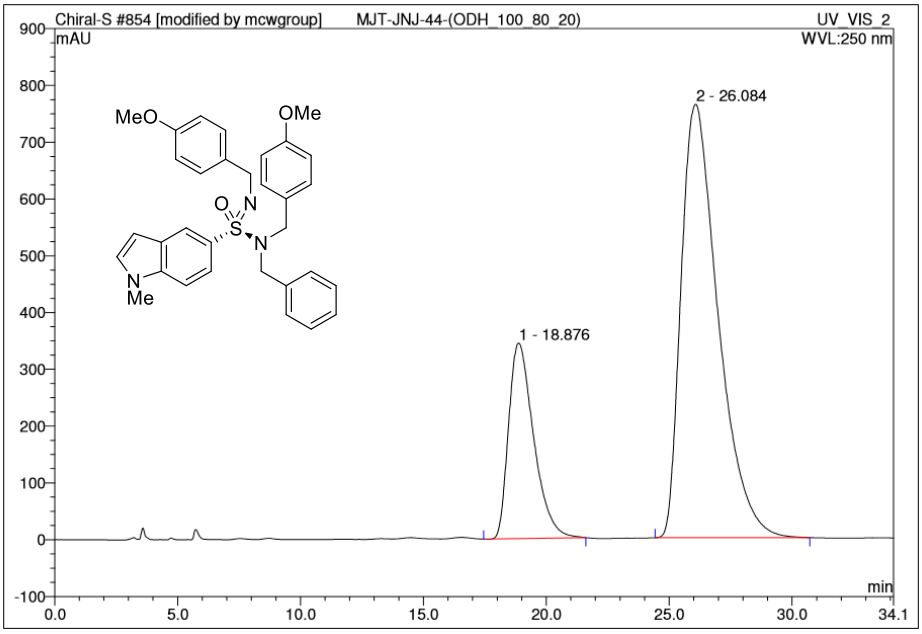



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 18.87 | n.a. | 1395.436 | 550.868 | 75.93 | n.a. | BMB* |
| 2 | 20.61 | n.a. | 421.826 | 174.585 | 24.07 | n.a. | BMB* |
| **Total:** | | | 1817.262 | 725.454 | 100.00 | 0.000 | |

## *N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-1-methyl-1H-indole-5-sulfonimidamide (74j)

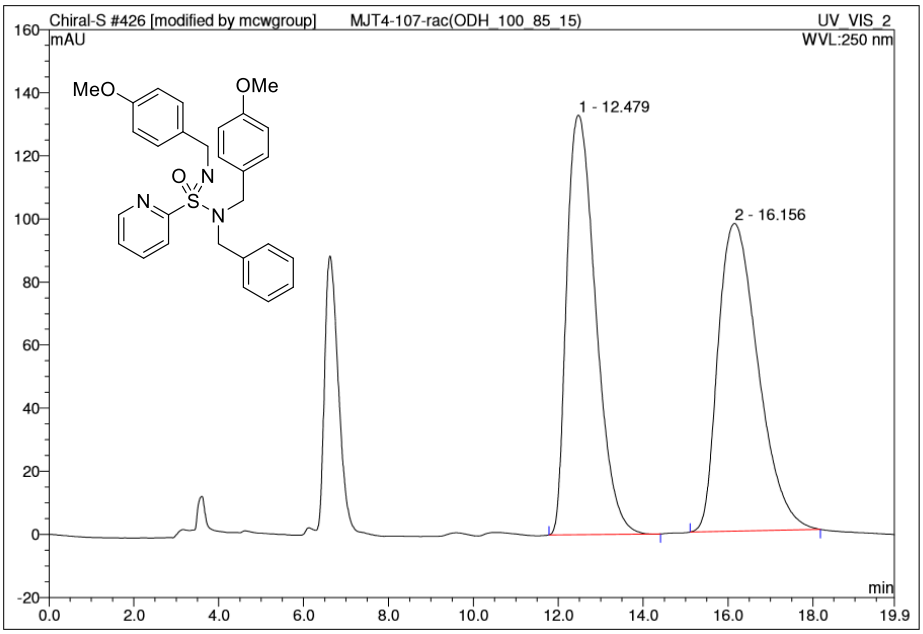



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 19.18 | n.a. | 127.884 | 169.637 | 49.97 | n.a. | BMB* |
| 2 | 27.08 | n.a. | 87.586 | 169.862 | 50.03 | n.a. | BMB* |
| **Total:** | | | 215.470 | 339.498 | 100.00 | 0.000 | |

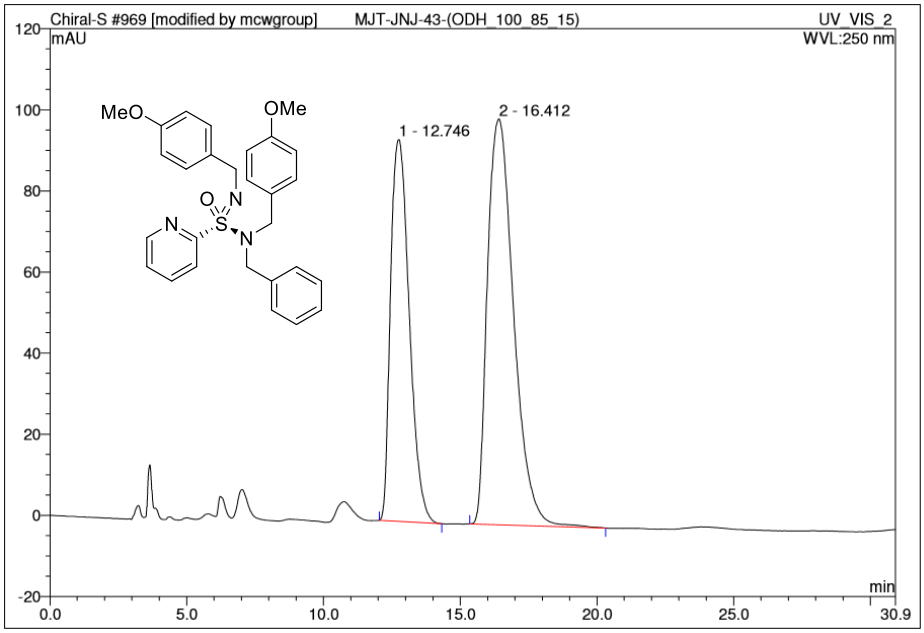



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 18.88 | n.a. | 344.269 | 406.886 | 23.41 | n.a. | BMB* |
| 2 | 26.08 | n.a. | 763.306 | 1331.148 | 76.59 | n.a. | BMB* |
| **Total:** | | | 1107.575 | 1738.034 | 100.00 | 0.000 | |

## *N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)pyridine-2-sulfonimidamide (74k)

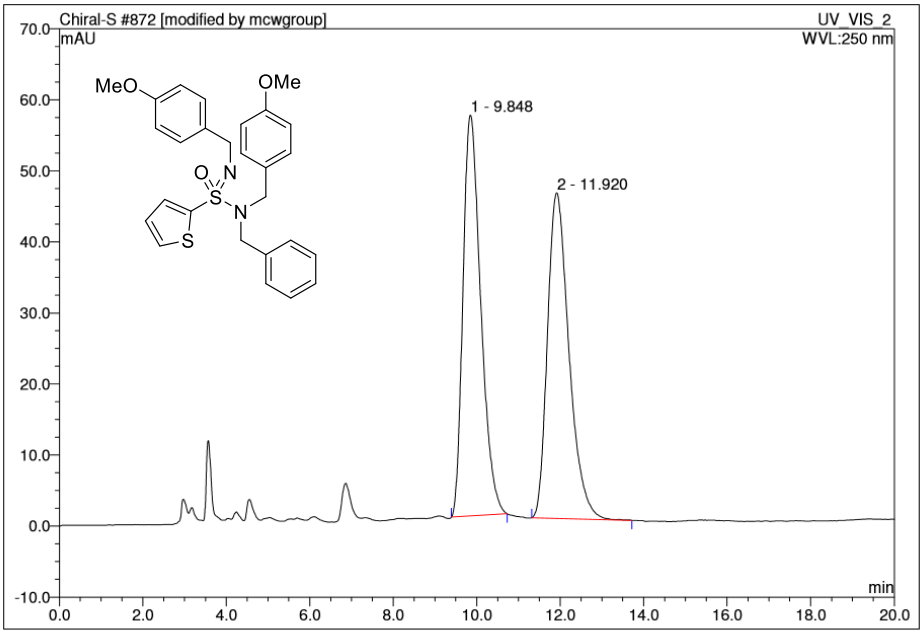



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 12.48 | n.a. | 132.991 | 105.226 | 49.65 | n.a. | BMB* |
| 2 | 16.16 | n.a. | 97.620 | 106.719 | 50.35 | n.a. | BMB* |
| **Total:** | | | 230.610 | 211.944 | 100.00 | 0.000 | |

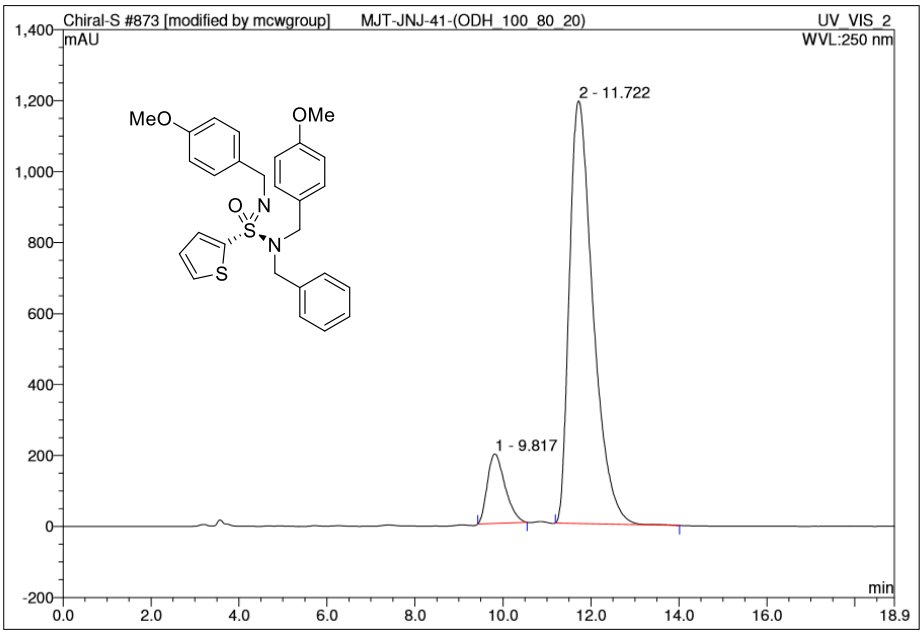



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 12.75 | n.a. | 94.166 | 74.512 | 40.19 | n.a. | BMB* |
| 2 | 16.41 | n.a. | 100.093 | 110.900 | 59.81 | n.a. | BMB* |
| **Total:** | | | 194.260 | 185.412 | 100.00 | 0.000 | |

## *N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)thiophene-2-sulfonimidamide (74l)

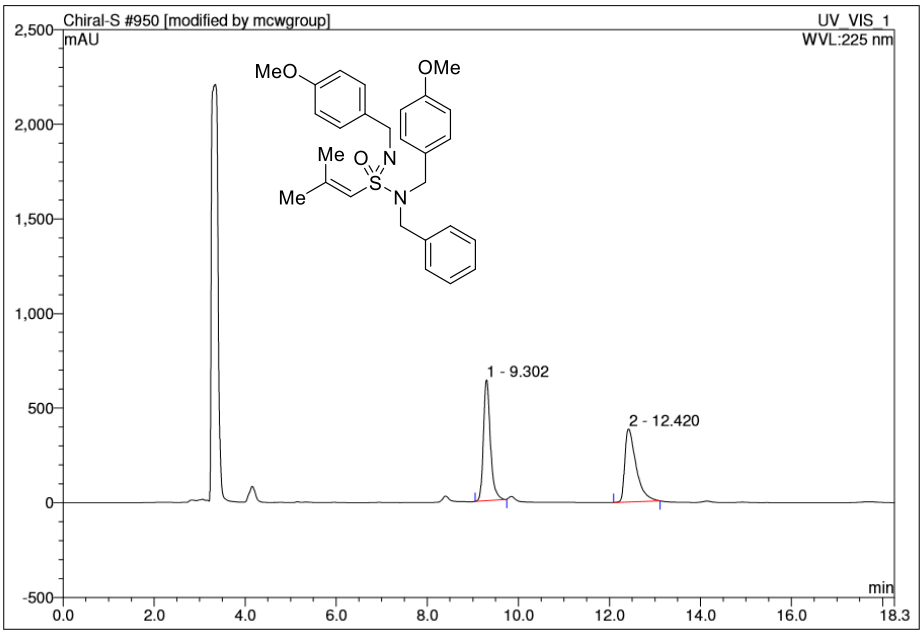



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 9.85 | n.a. | 56.407 | 27.792 | 50.45 | n.a. | BMB* |
| 2 | 11.92 | n.a. | 45.814 | 27.298 | 49.55 | n.a. | BMB* |
| **Total:** | | | 102.221 | 55.090 | 100.00 | 0.000 | |

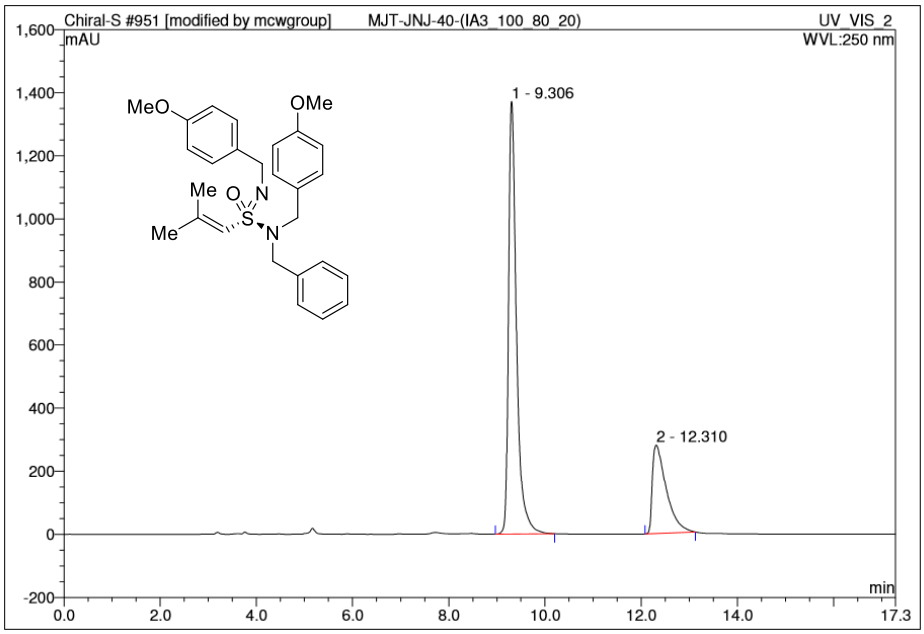



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 9.82 | n.a. | 195.506 | 90.943 | 10.92 | n.a. | BMB* |
| 2 | 11.72 | n.a. | 1190.596 | 741.725 | 89.08 | n.a. | BMB* |
| **Total:** | | | 1386.101 | 832.668 | 100.00 | 0.000 | |

## *N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-2-methylprop-1-ene-1-sulfonimidamide (74m)

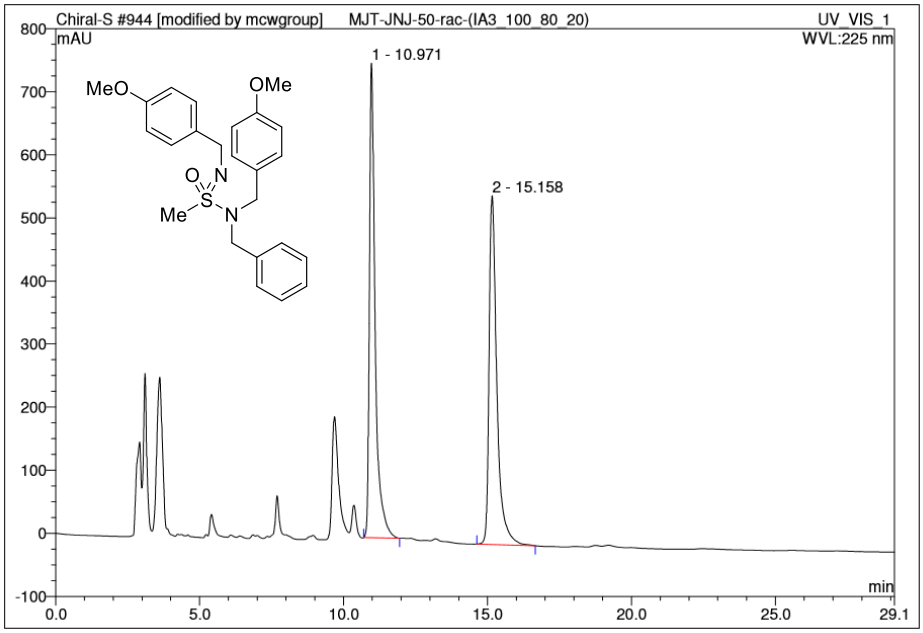



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 9.30 | n.a. | 637.643 | 112.341 | 50.39 | n.a. | BMB* |
| 2 | 12.42 | n.a. | 385.143 | 110.621 | 49.61 | n.a. | BMB* |
| **Total:** | | | 1022.786 | 222.962 | 100.00 | 0.000 | |

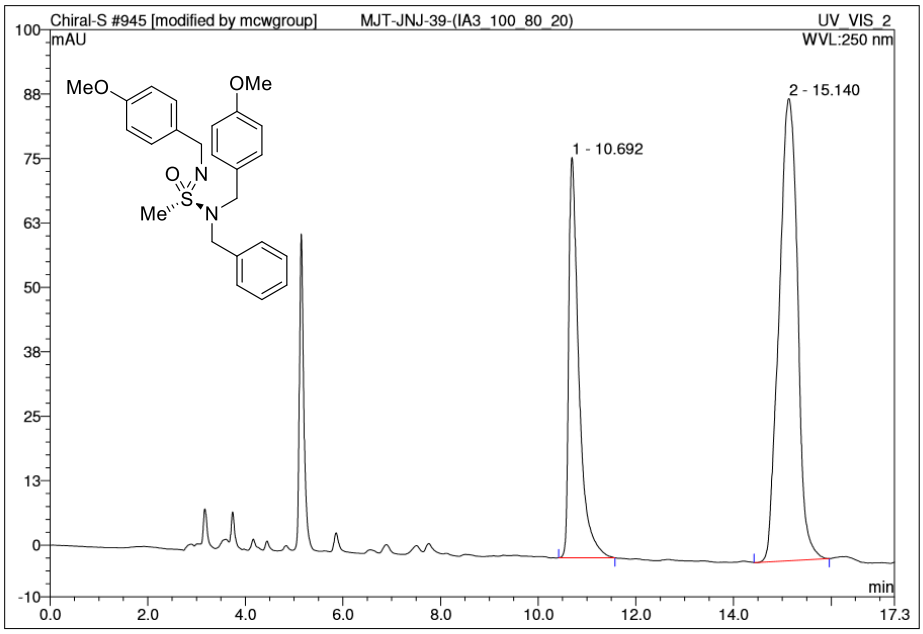



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 9.31 | n.a. | 1371.234 | 262.603 | 73.56 | n.a. | BMB* |
| 2 | 12.31 | n.a. | 280.444 | 94.409 | 26.44 | n.a. | BMB* |
| **Total:** | | | 1651.678 | 357.012 | 100.00 | 0.000 | |

## *N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)methanesulfonimidamide (74n)

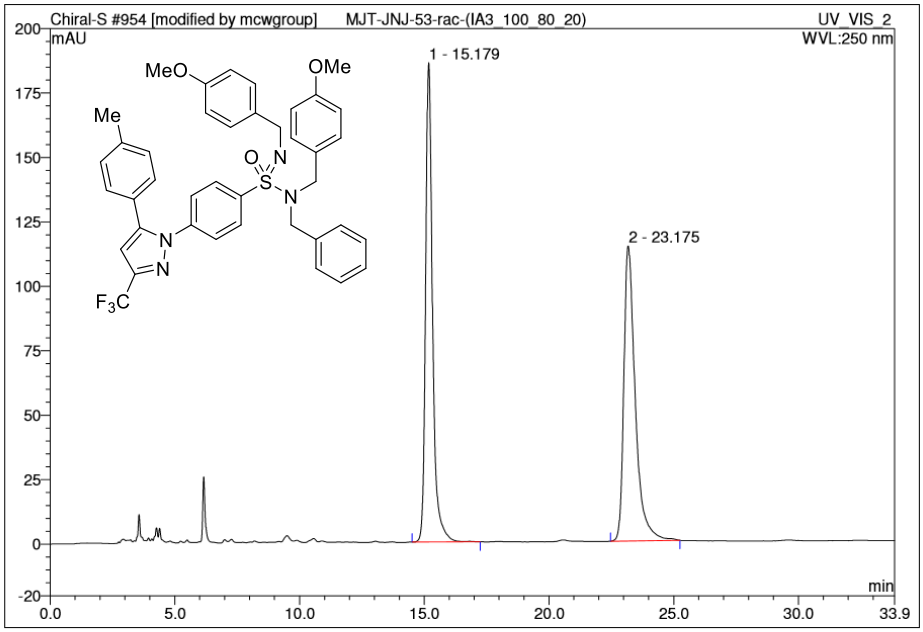



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 10.97 | n.a. | 752.505 | 175.470 | 50.35 | n.a. | BMB* |
| 2 | 15.16 | n.a. | 552.989 | 173.030 | 49.65 | n.a. | BMB* |
| **Total:** | | | 1305.494 | 348.500 | 100.00 | 0.000 | |

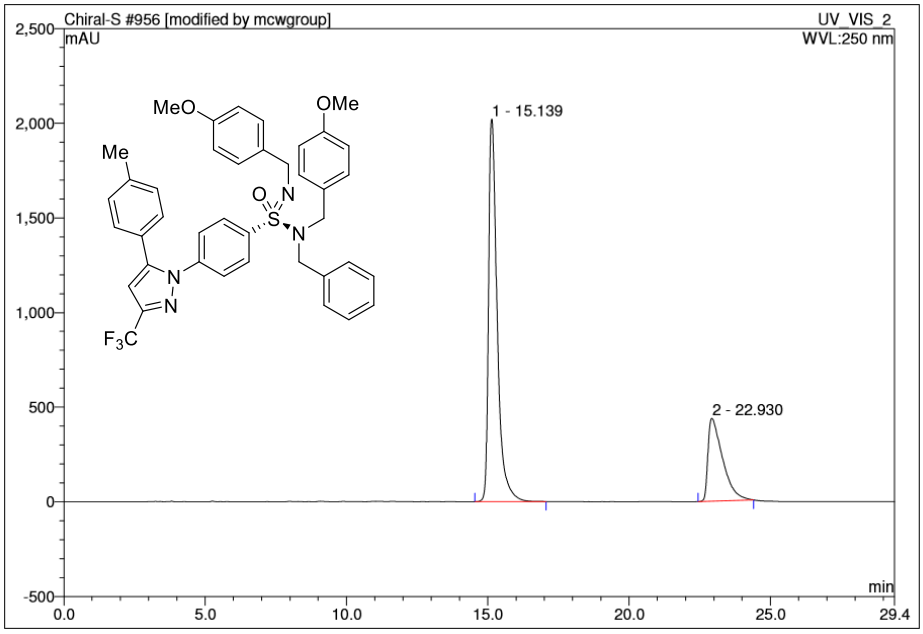



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 10.69 | n.a. | 77.707 | 18.695 | 32.17 | n.a. | BMB* |
| 2 | 15.14 | n.a. | 89.646 | 39.421 | 67.83 | n.a. | BMB* |
| **Total:** | | | 167.353 | 58.115 | 100.00 | 0.000 | |

## *N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonimidamide (74o)

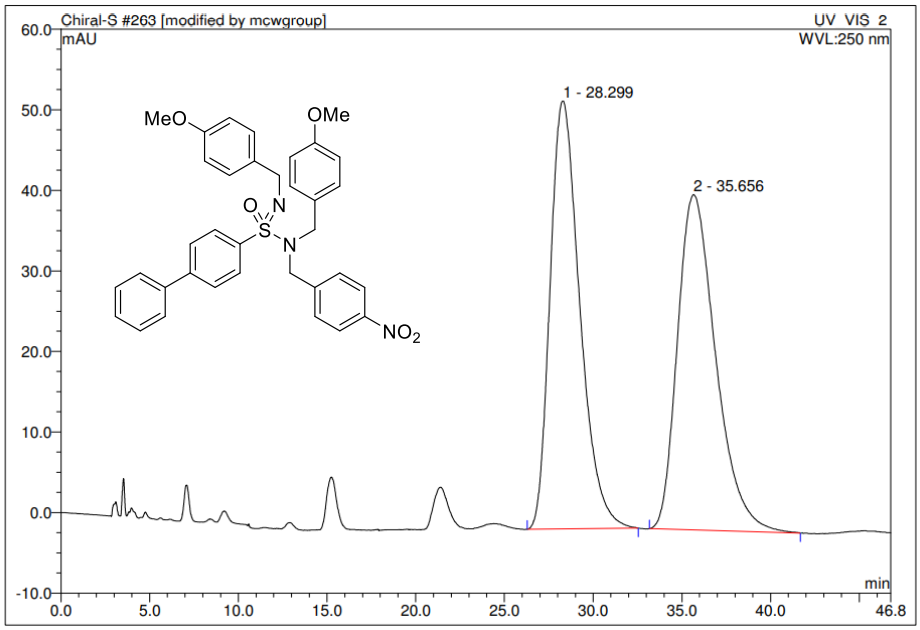



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 15.18 | n.a. | 185.951 | 60.557 | 49.90 | n.a. | BMB* |
| 2 | 23.18 | n.a. | 114.516 | 60.795 | 50.10 | n.a. | BMB* |
| **Total:** | | | 300.467 | 121.352 | 100.00 | 0.000 | |

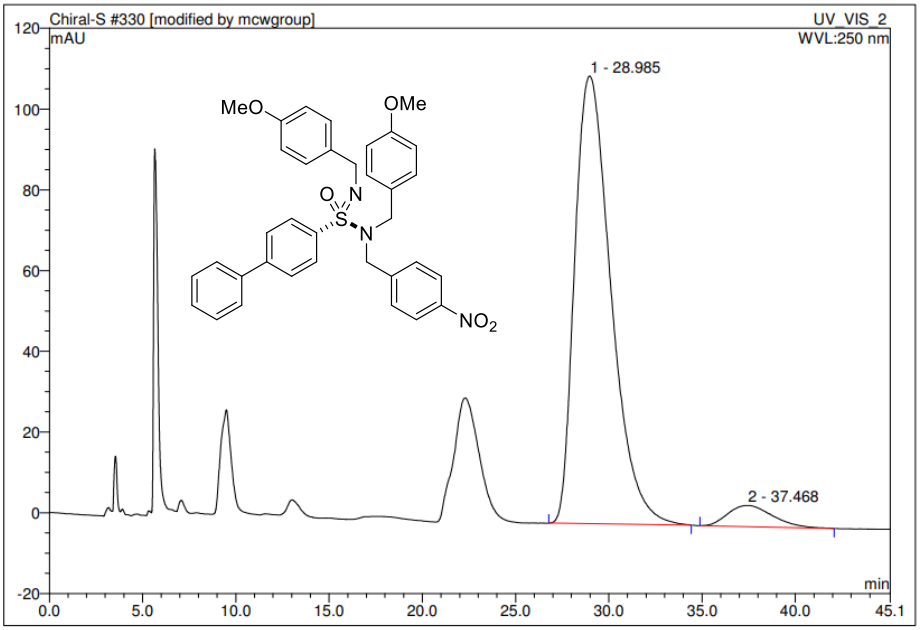



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 15.14 | n.a. | 2021.099 | 716.712 | 73.20 | n.a. | BMB* |
| 2 | 22.93 | n.a. | 437.543 | 262.455 | 26.80 | n.a. | BMB* |
| **Total:** | | | 2458.642 | 979.167 | 100.00 | 0.000 | |

## *N,N'*-bis(4-methoxybenzyl)-N-(4-nitrobenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ap)

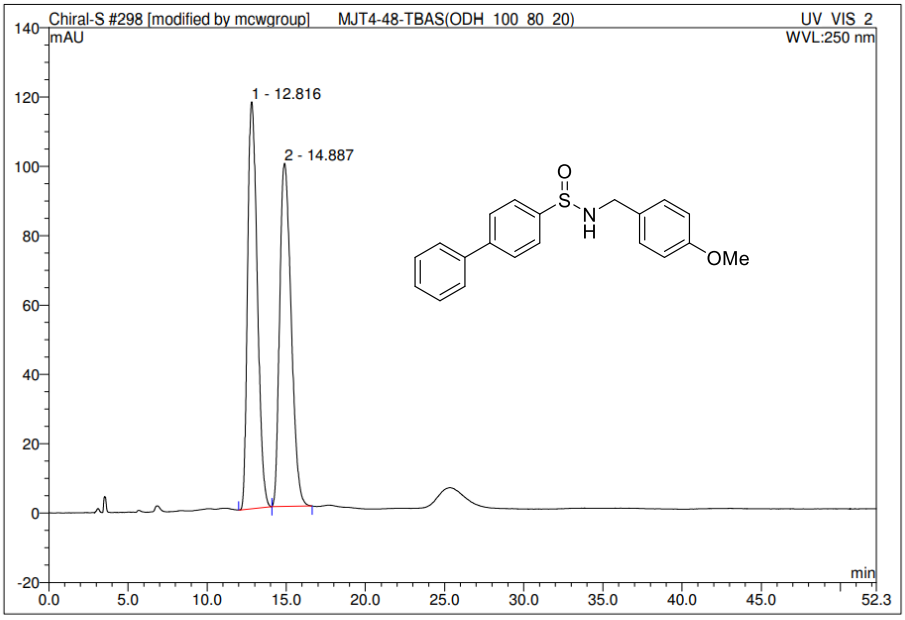



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 28.30 | n.a. | 53.096 | 103.042 | 49.83 | n.a. | BMB* |
| 2 | 35.66 | n.a. | 41.619 | 103.732 | 50.17 | n.a. | BMB* |
| **Total:** | | | 94.715 | 206.774 | 100.00 | 0.000 | |

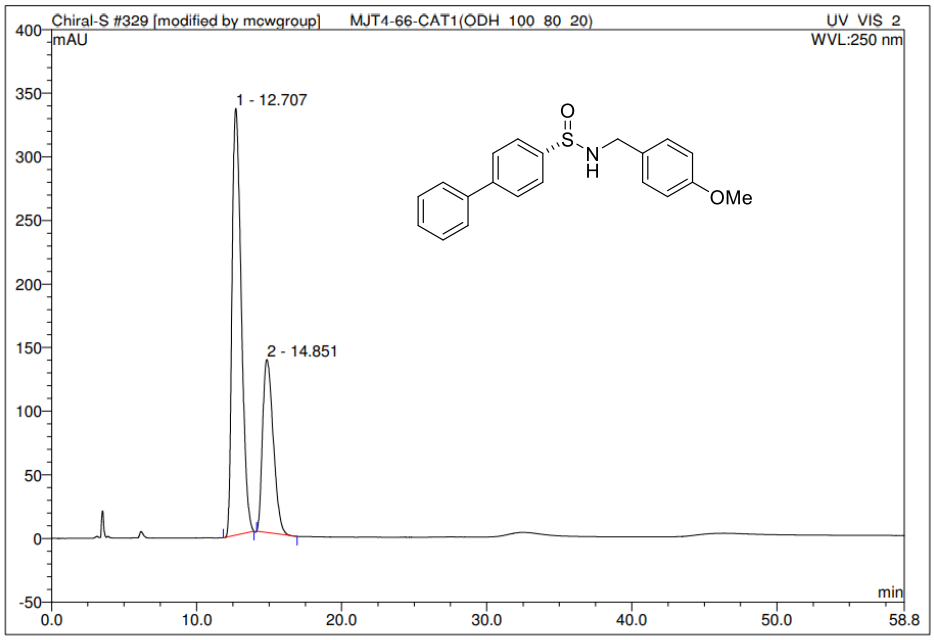



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 28.99 | n.a. | 110.888 | 249.680 | 94.46 | n.a. | BMB* |
| 2 | 37.47 | n.a. | 5.259 | 14.636 | 5.54 | n.a. | BMB* |
| **Total:** | | | 116.147 | 264.316 | 100.00 | 0.000 | |

## *N*-(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfinamide (78a)

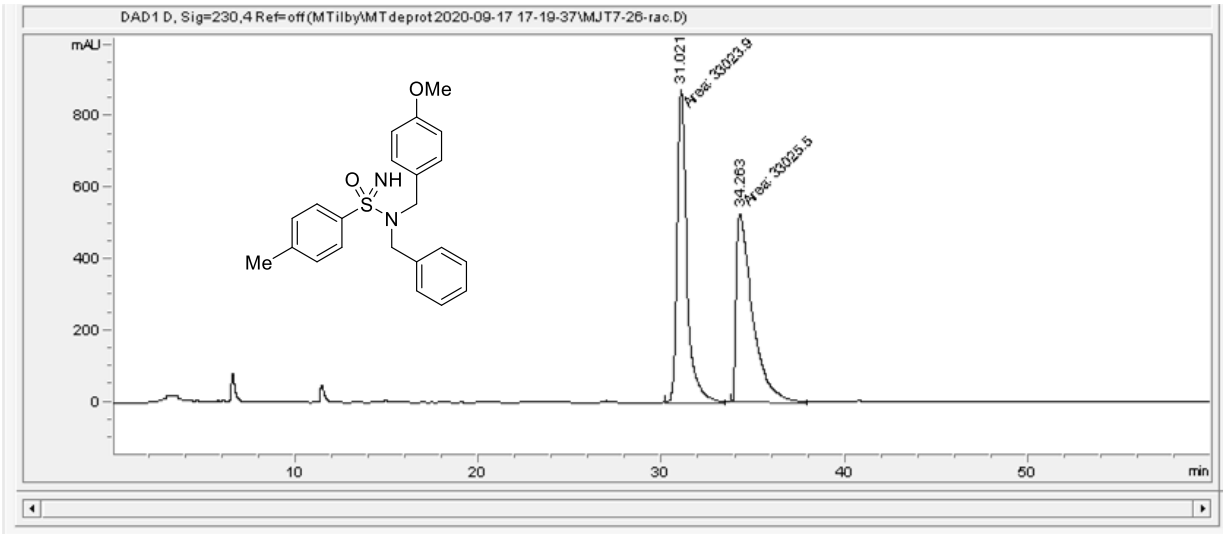



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 12.82 | n.a. | 117.380 | 83.443 | 50.09 | n.a. | BMb* |
| 2 | 14.89 | n.a. | 98.973 | 83.145 | 49.91 | n.a. | bMB* |
| **Total:** | | | 216.354 | 166.588 | 100.00 | 0.000 | |

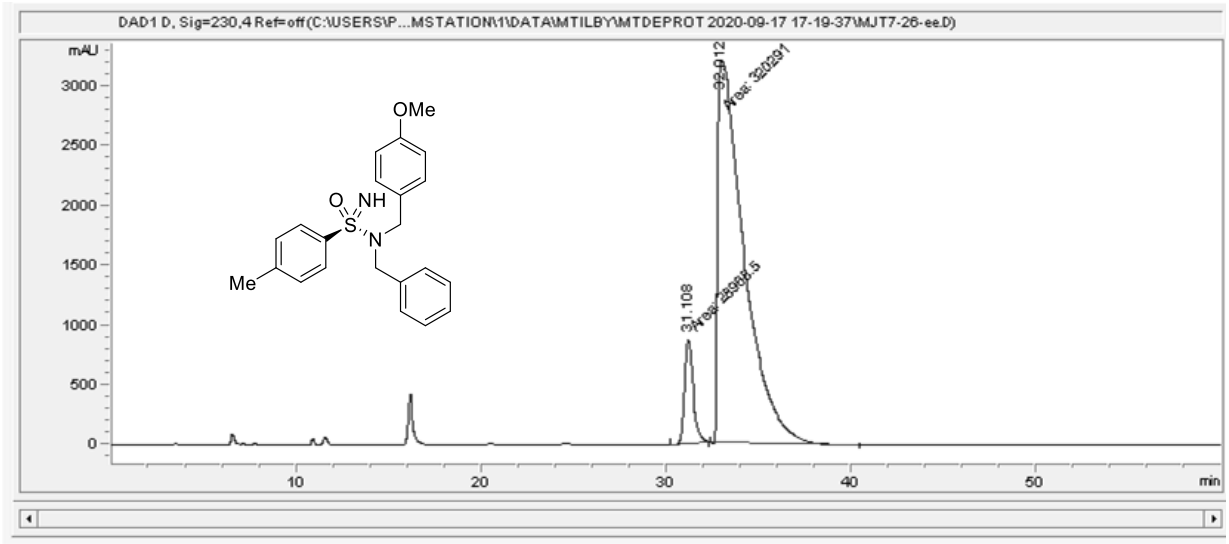



| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|---|---|---|---|---|---|---|---|
| 1 | 12.71 | n.a. | 335.462 | 246.728 | 68.05 | n.a. | BMB* |
| 2 | 14.85 | n.a. | 135.934 | 115.842 | 31.95 | n.a. | BMB* |
| **Total:** | | | 471.396 | 362.570 | 100.00 | 0.000 | |

## *N*-benzyl-*N*-(4-methoxybenzyl)-4-methylbenzenesulfonimidamide (82)

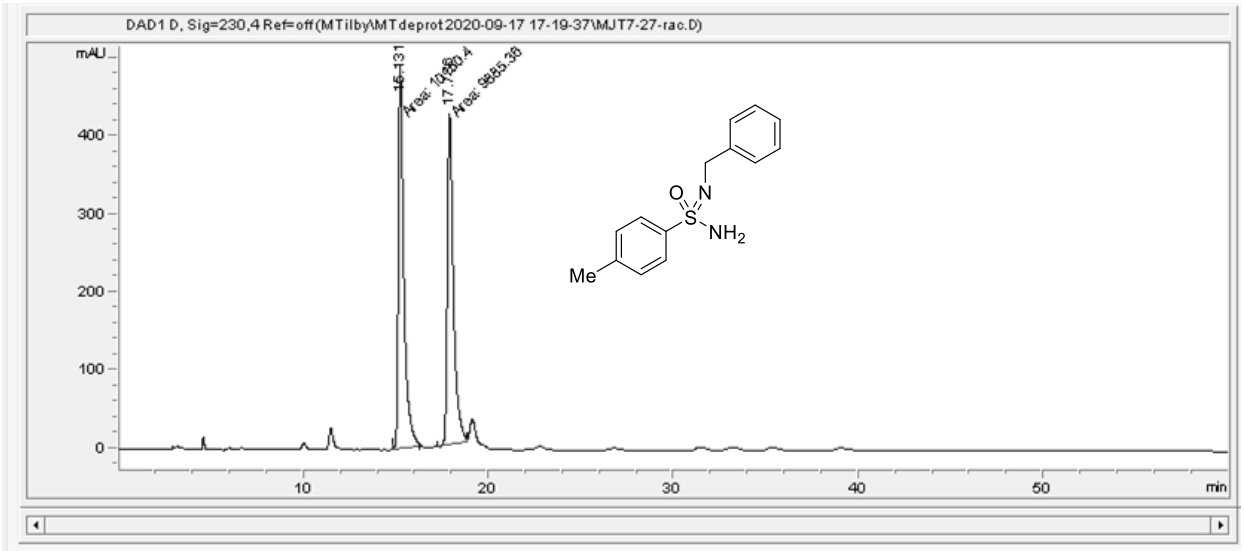



| # | Time | Type | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|---|
| 1 | 31.021 | MM | 33023.9 | 879 | 0.6262 | 49.999 | 0.565 |
| 2 | 34.263 | MM | 33025.5 | 528 | 1.0424 | 50.001 | 0.254 |

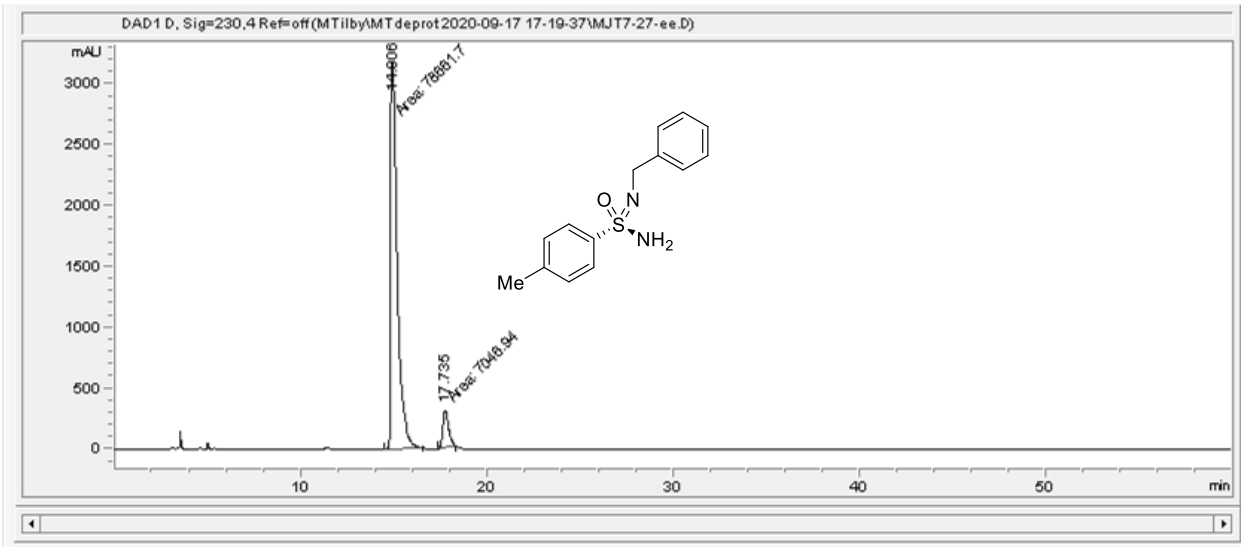



| # | Time | Type | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|---|
| 1 | 31.108 | MM | 28968.5 | 877.6 | 0.5502 | 8.294 | 0.643 |
| 2 | 32.912 | MM | 320291.5 | 3191.6 | 1.6726 | 91.706 | 0.155 |

## *N'*-benzyl-4-methylbenzenesulfonimidamide (83)



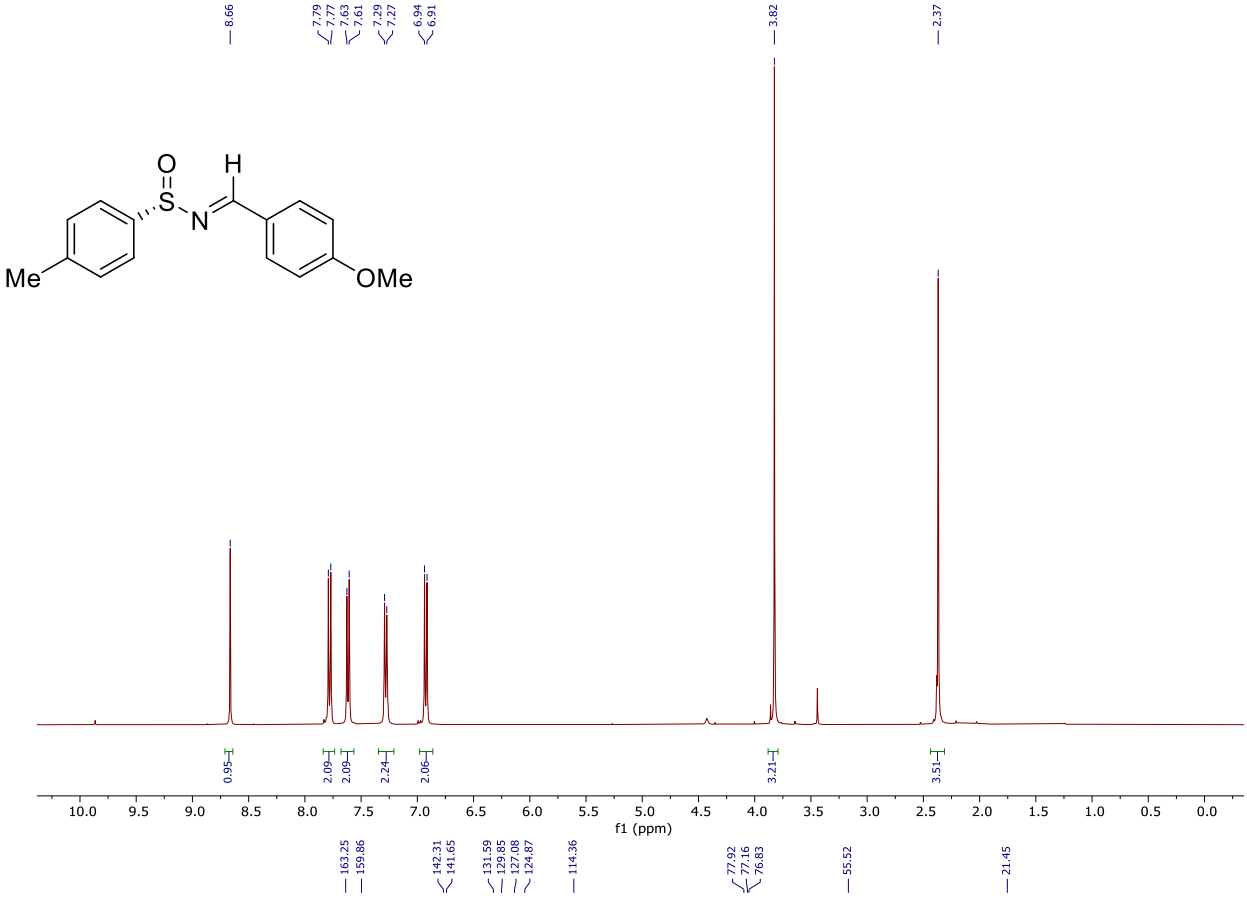

| # | Time | Type | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|---|
| 1 | 15.131 | MM | 10150.4 | 491.6 | 0.3441 | 50.661 | 0.489 |
| 2 | 17.786 | MM | 9885.4 | 426.4 | 0.3863 | 49.339 | 0.549 |

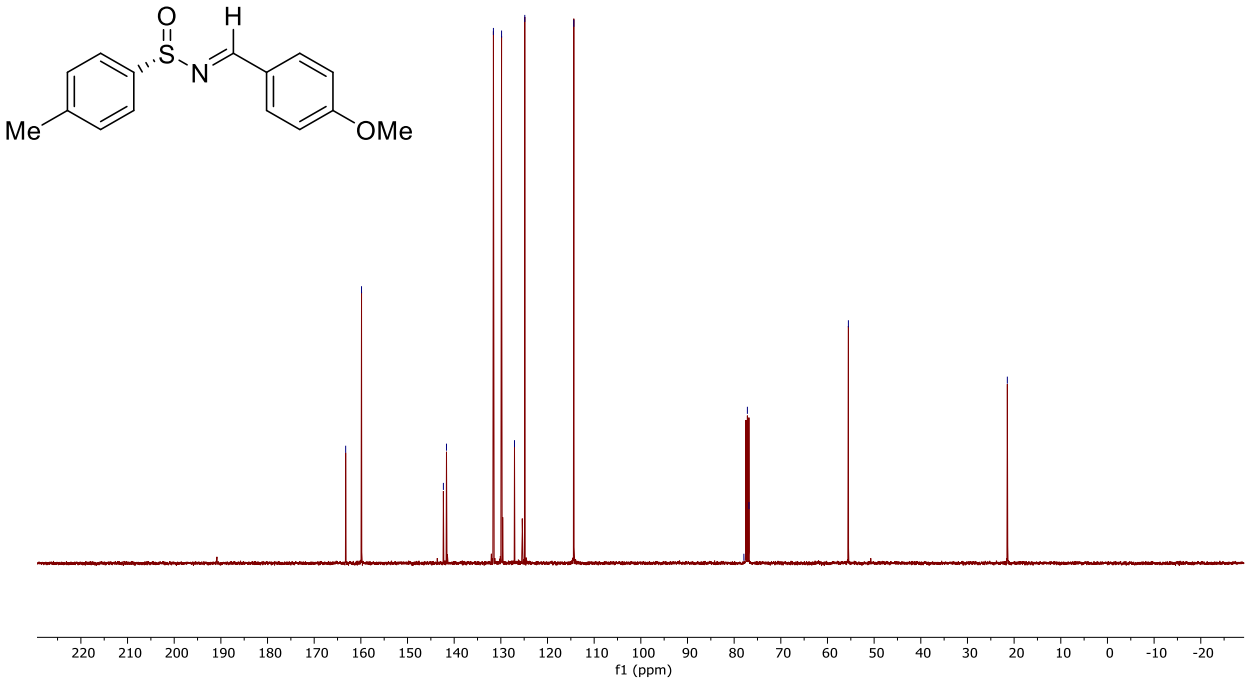



| # | Time | Type | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|---|
| 1 | 14.906 | MM | 78661.7 | 3177.6 | 0.4126 | 91.778 | 0.37 |
| 2 | 17.735 | MM | 7046.9 | 320.3 | 0.3667 | 8.222 | 0.601 |

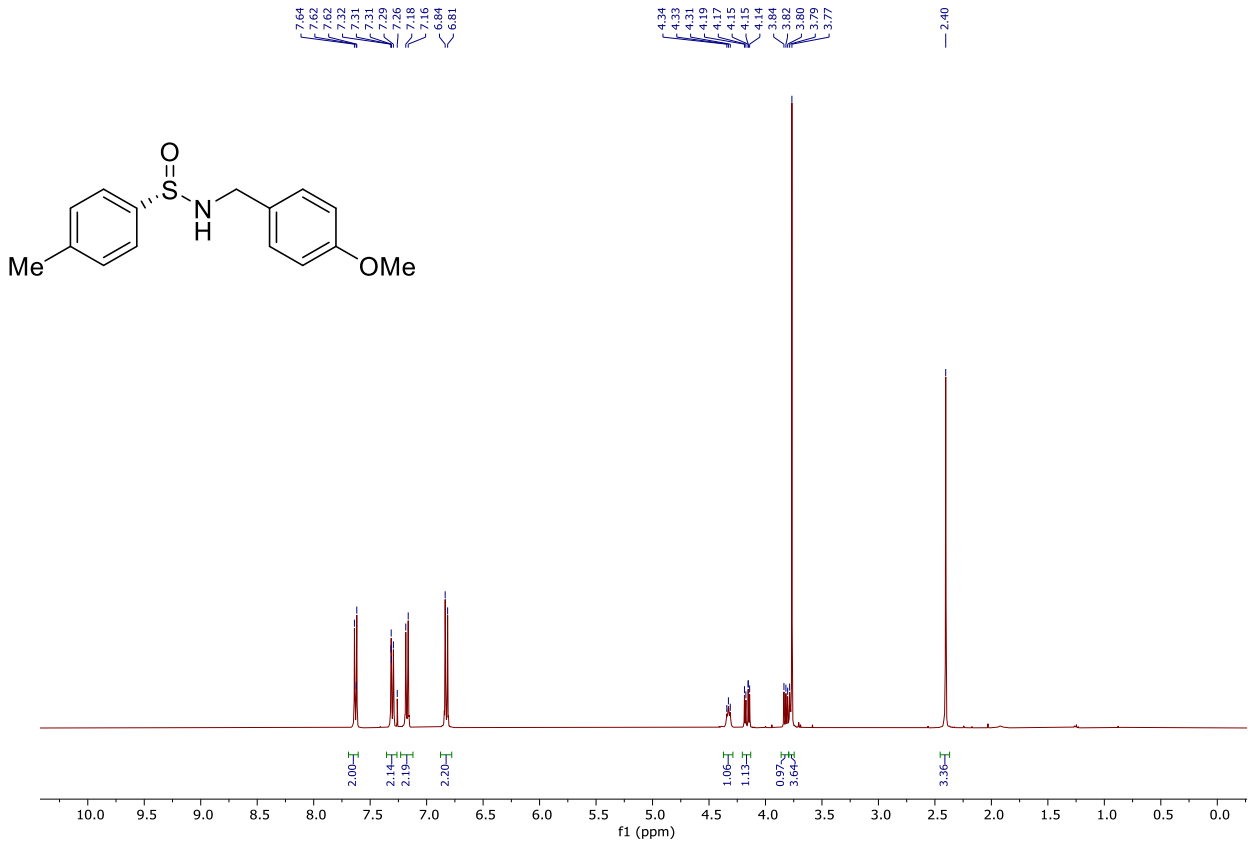
## 8.2. NMR Spectra – Chapter 3

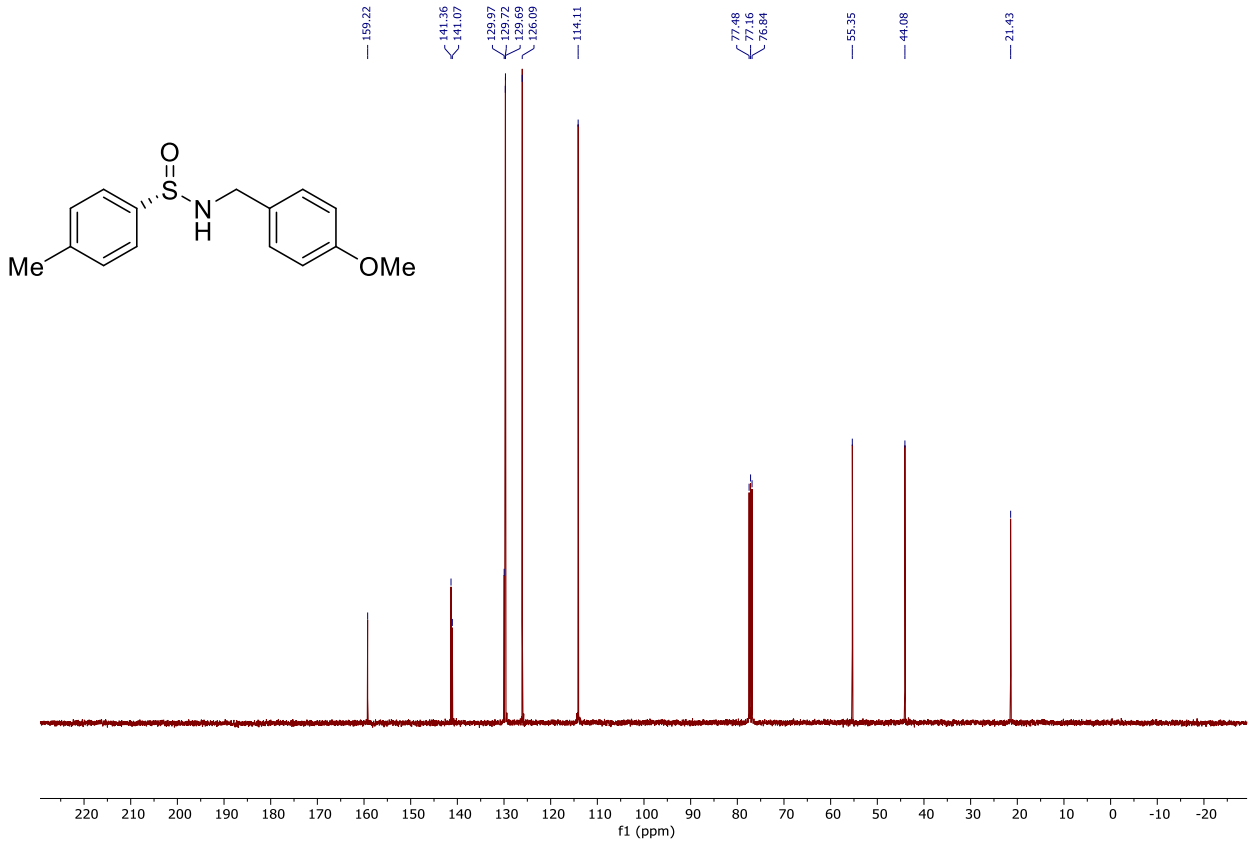
### (*S*)-4-methyl-*N*-(4-methylbenzylidene)benzenesulfinamide (77)



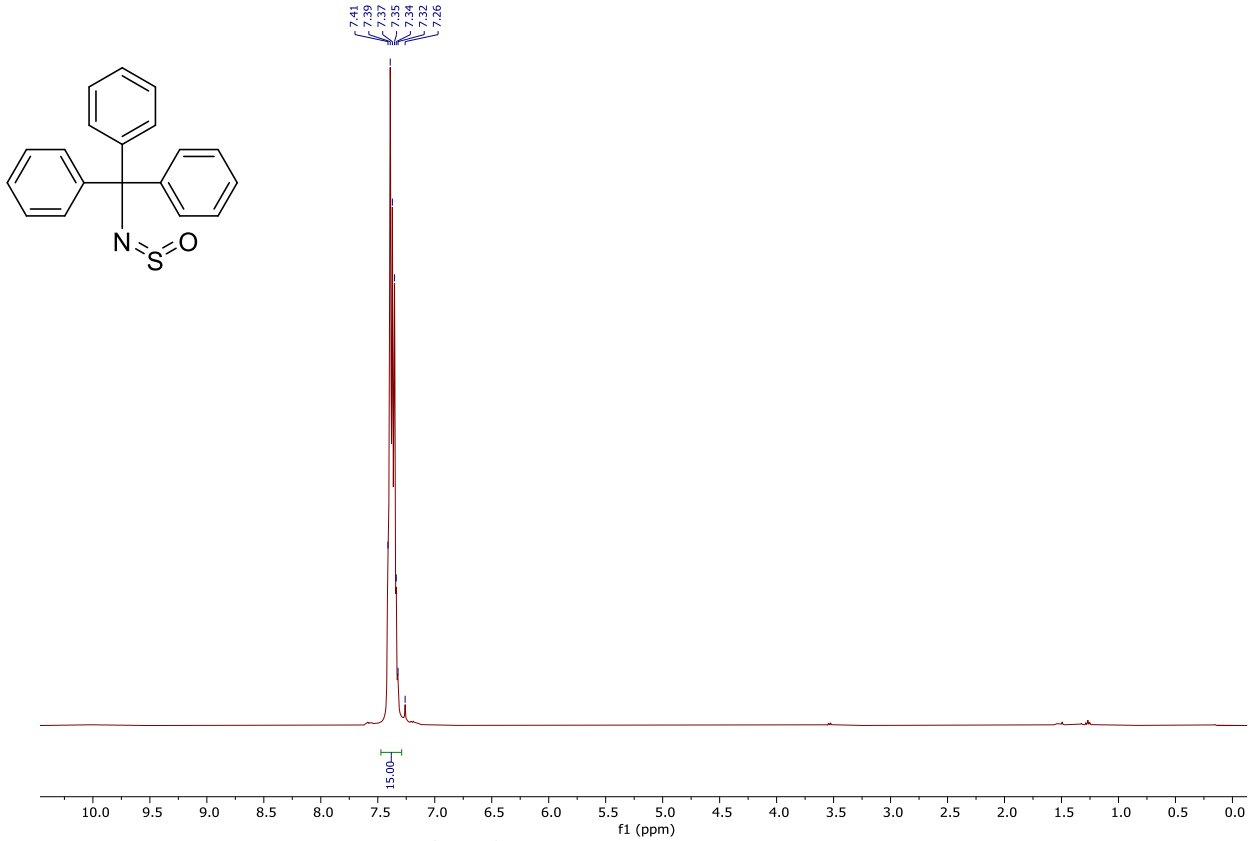



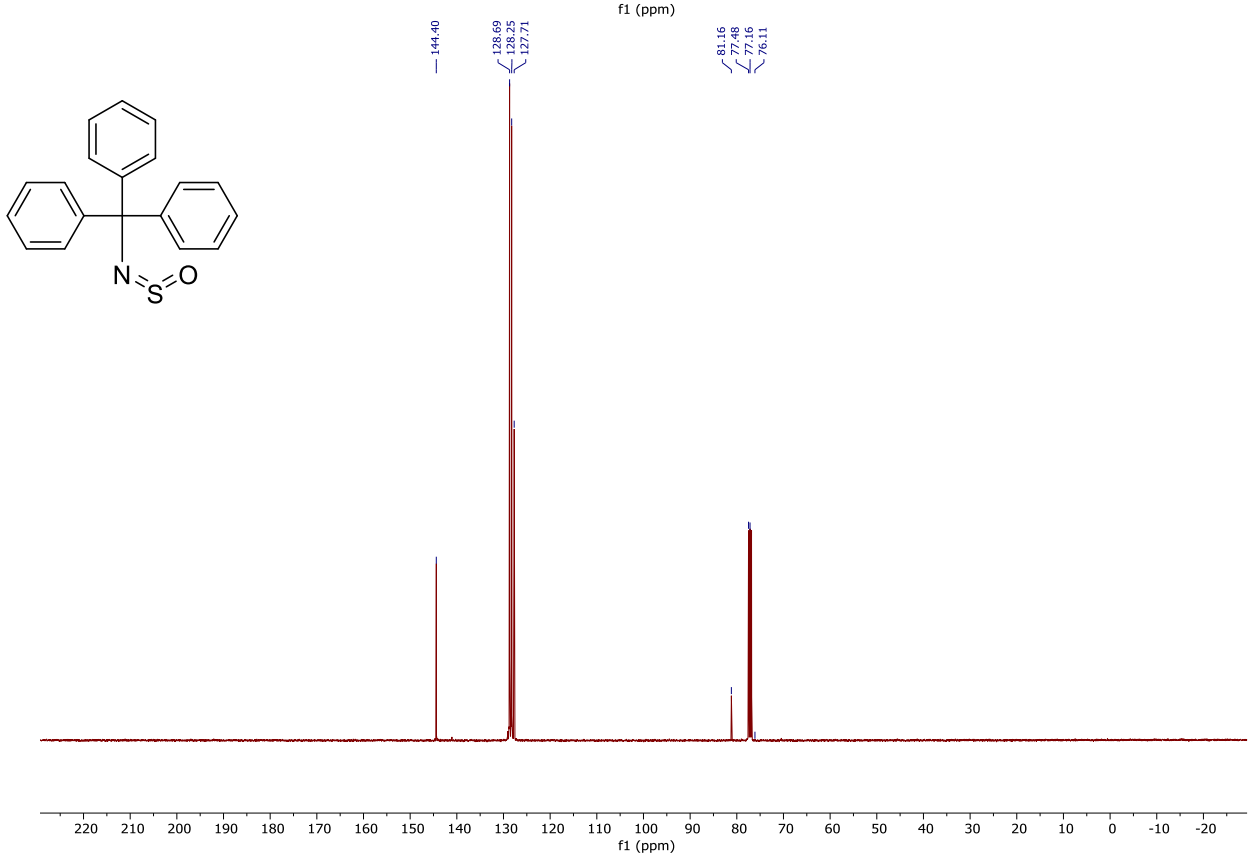
## (*S*)-4-methyl-*N*-(4-methylbenzyl)benzenesulfinamide (78b)



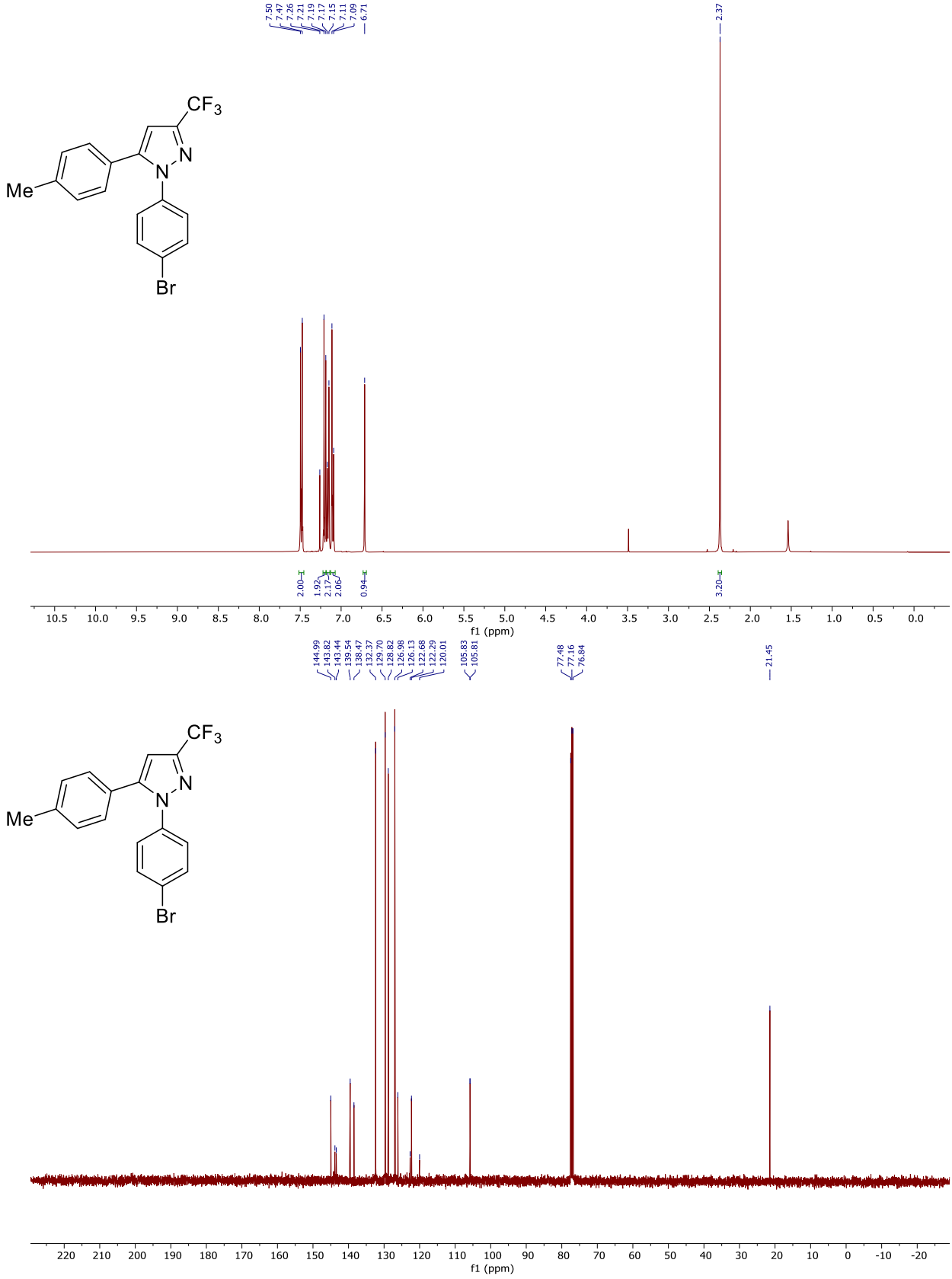



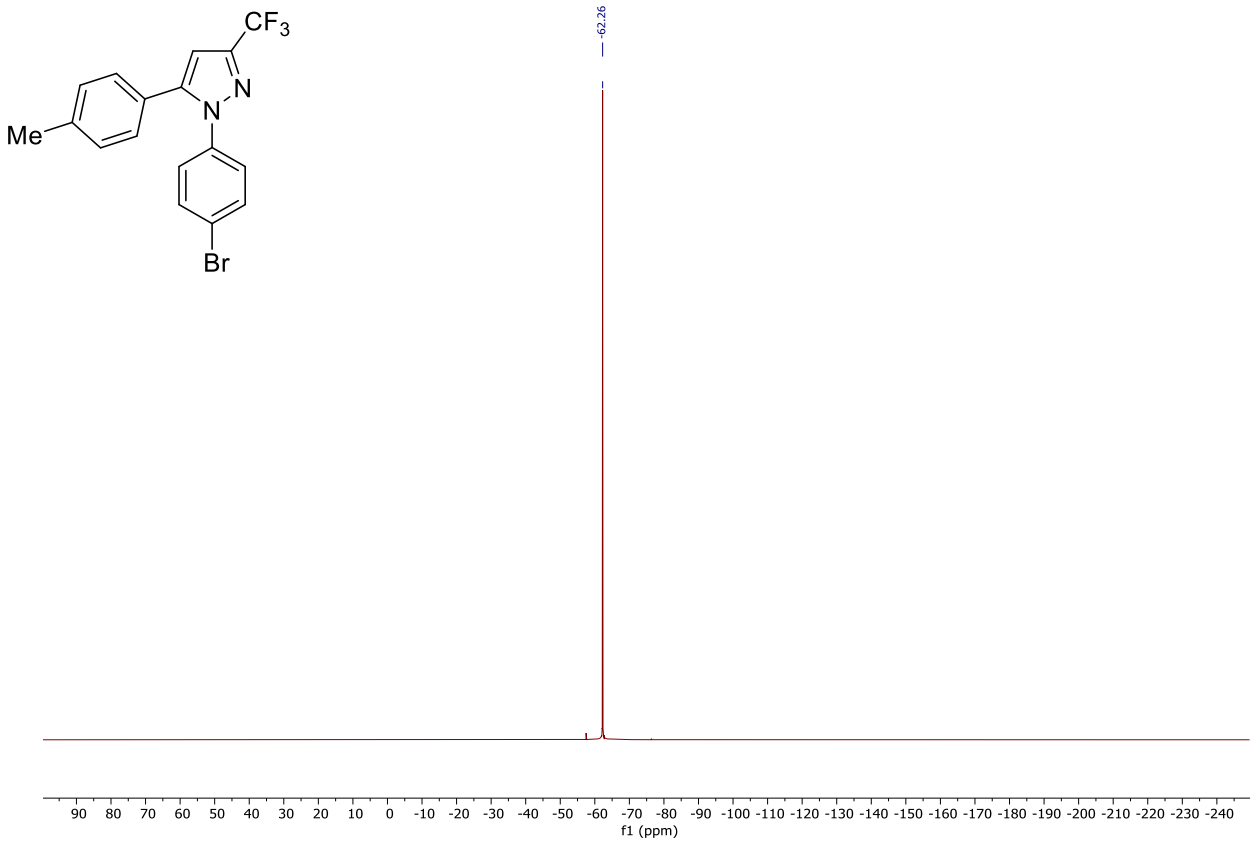
**TrNSO (33)**


7.41
7.39
7.37
7.35
7.34
7.32
7.26
15.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

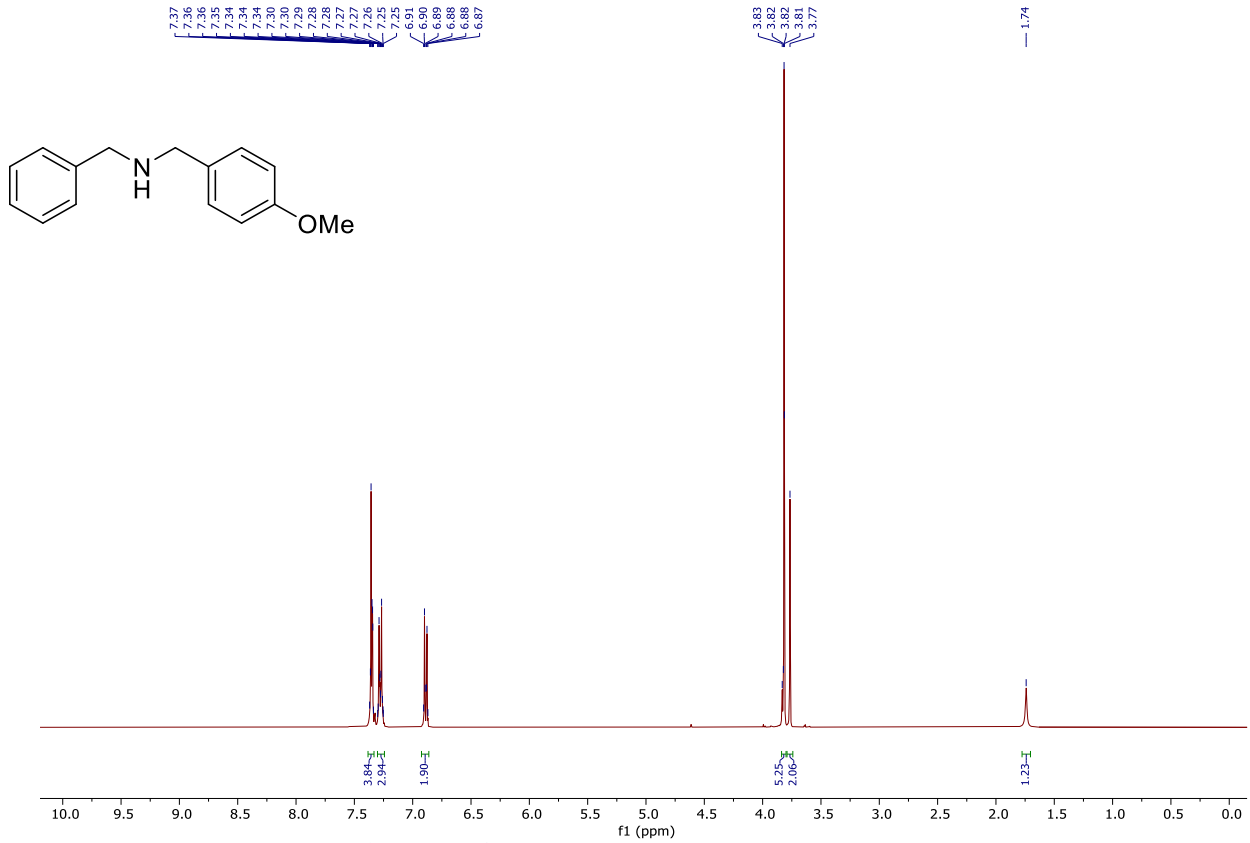

144.40
128.69
128.25
127.71
81.16
77.48
77.16
76.11
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

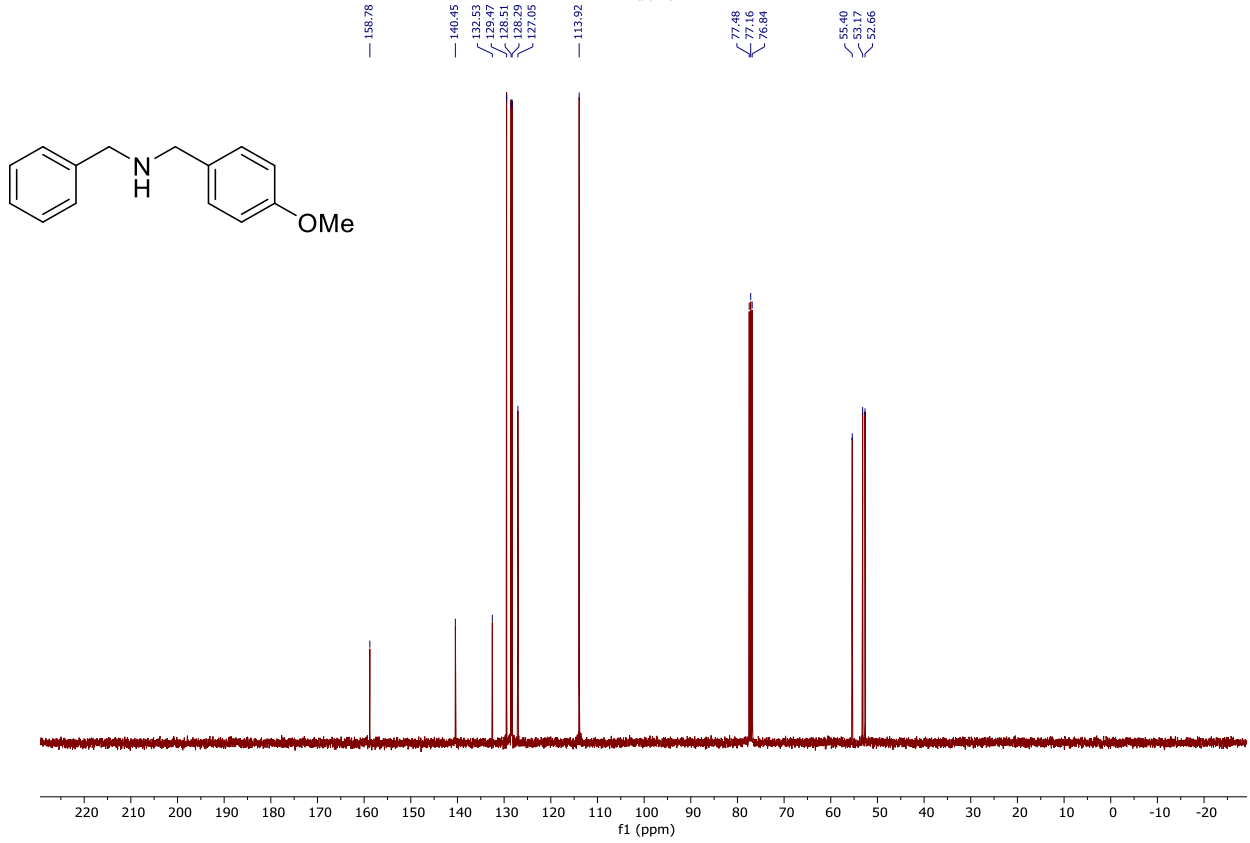
**1-(4-Bromophenyl)-5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazole (122)**



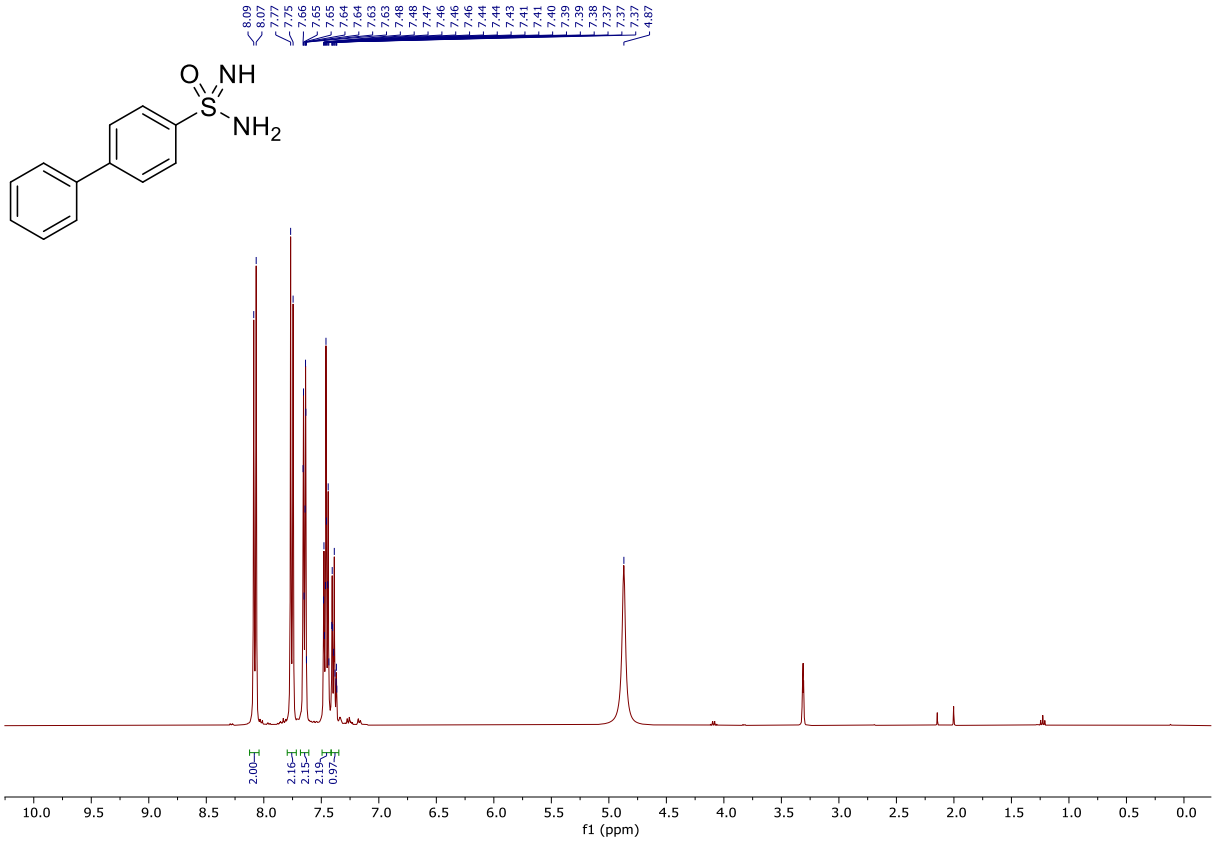

CF3
N
N
Me
Br
-62.26
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

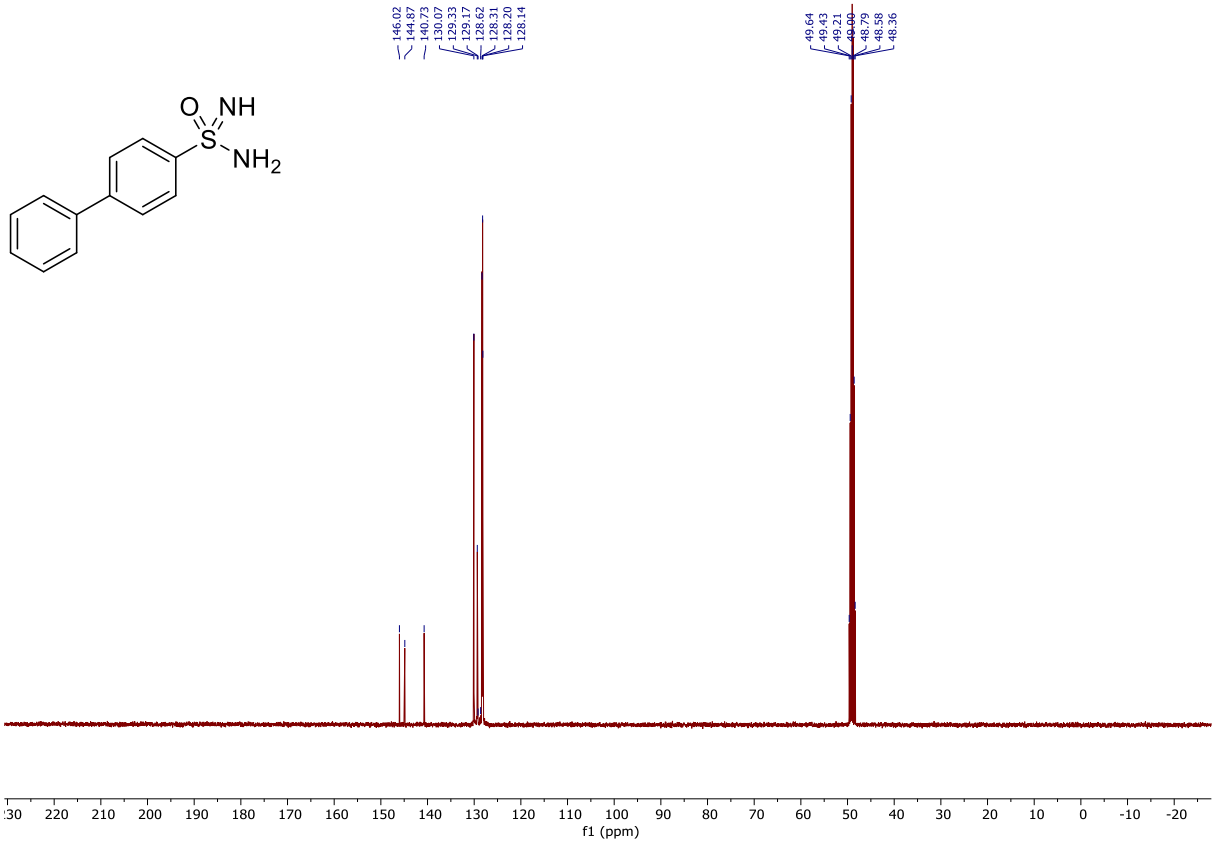
## *N*-benzyl-1-(4-methoxyphenyl)methanamine (81)

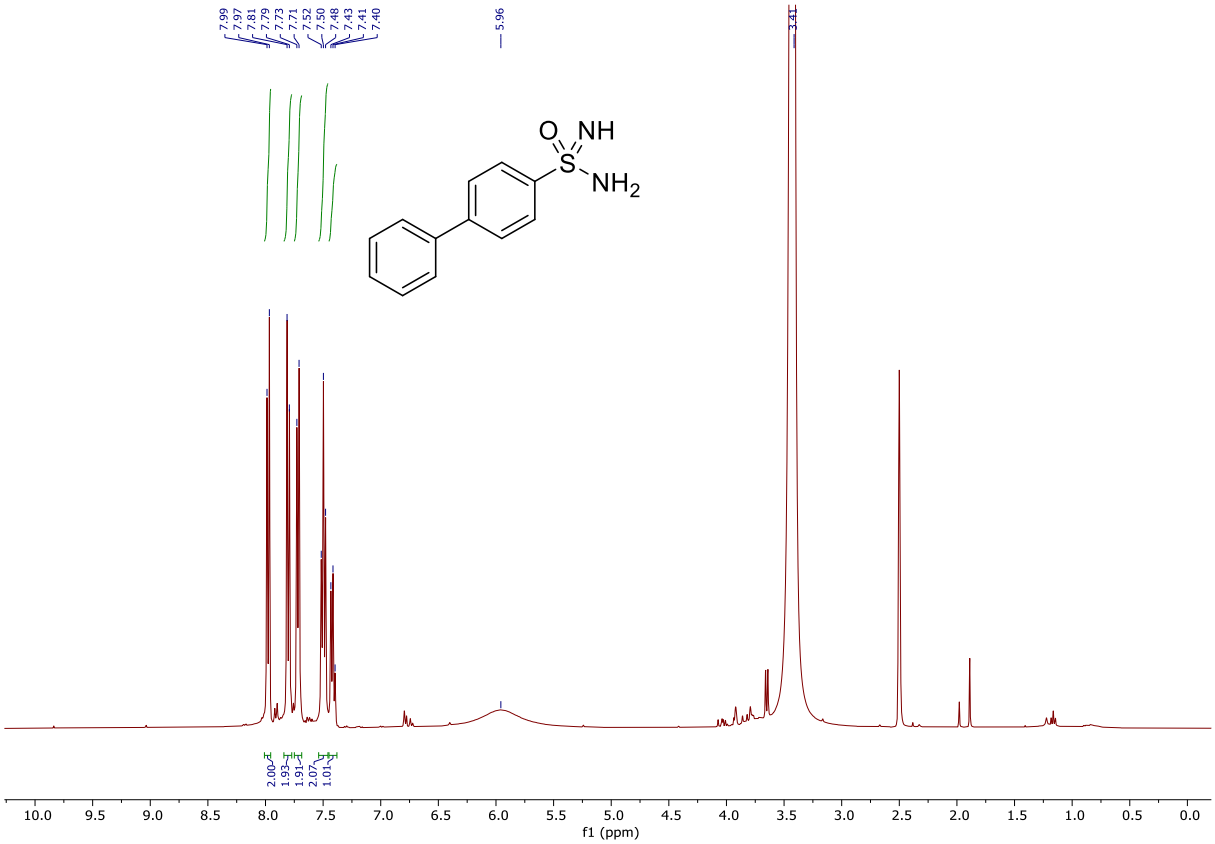


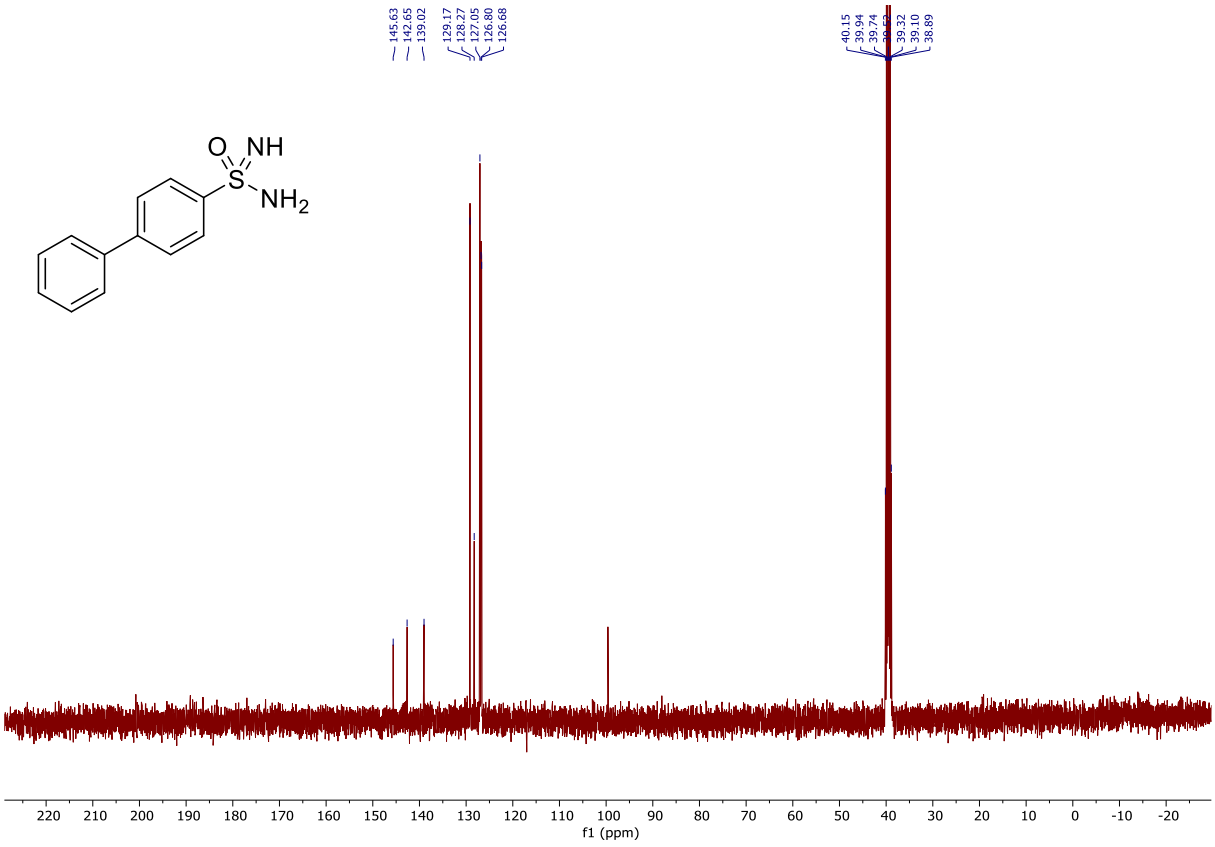



## [1,1'-biphenyl]-4-sulfonimidamide (75)

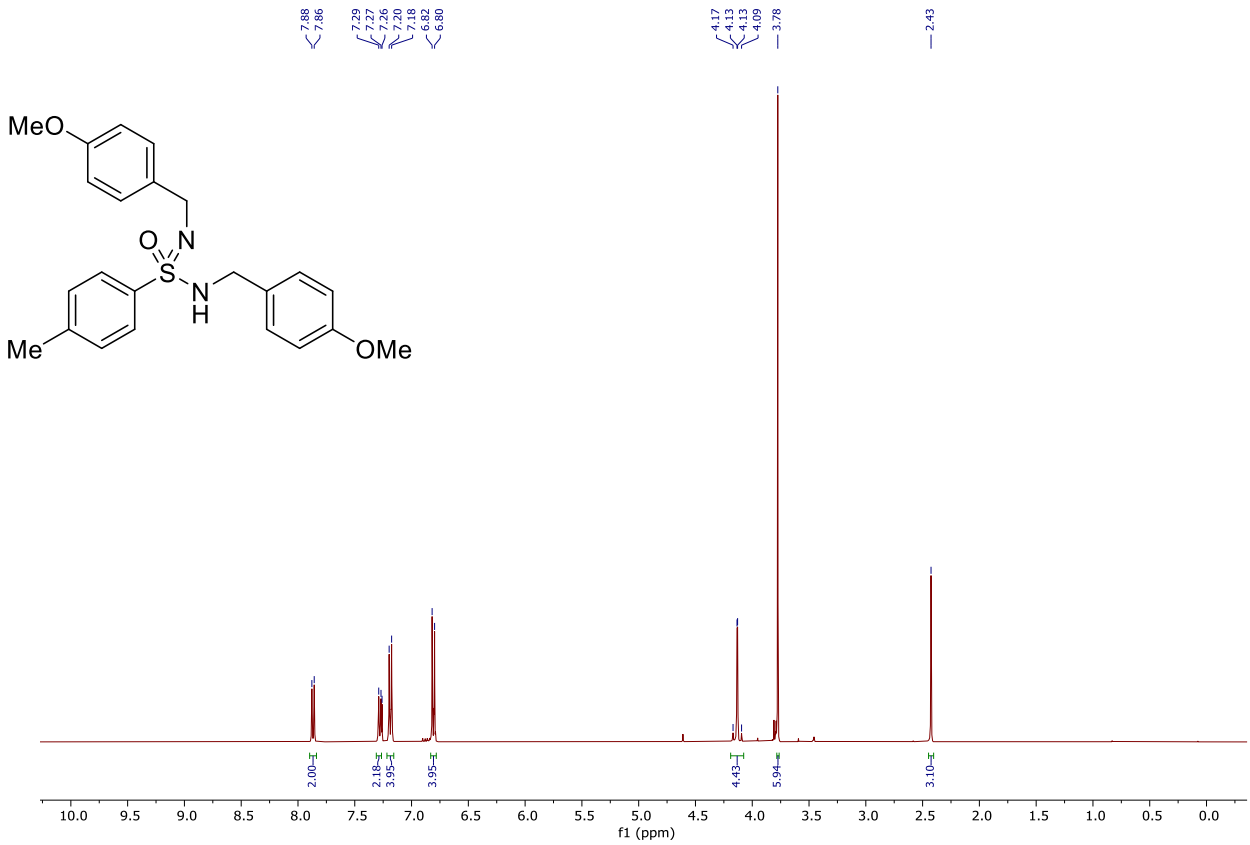


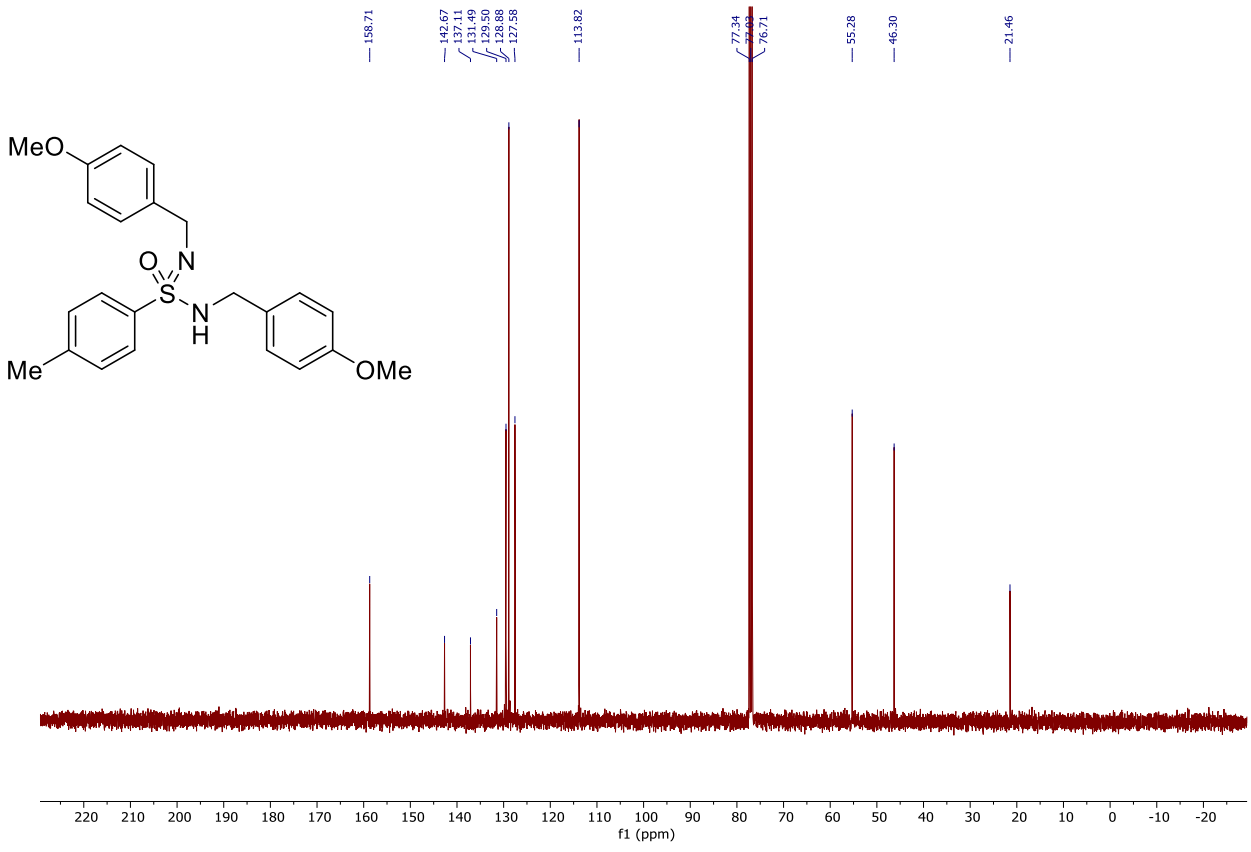




7.99
7.97
7.81
7.79
7.73
7.71
7.52
7.50
7.48
7.43
7.41
7.40
5.96
3.41
O
NH
S
NH2
2.00
1.93
1.91
2.07
1.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

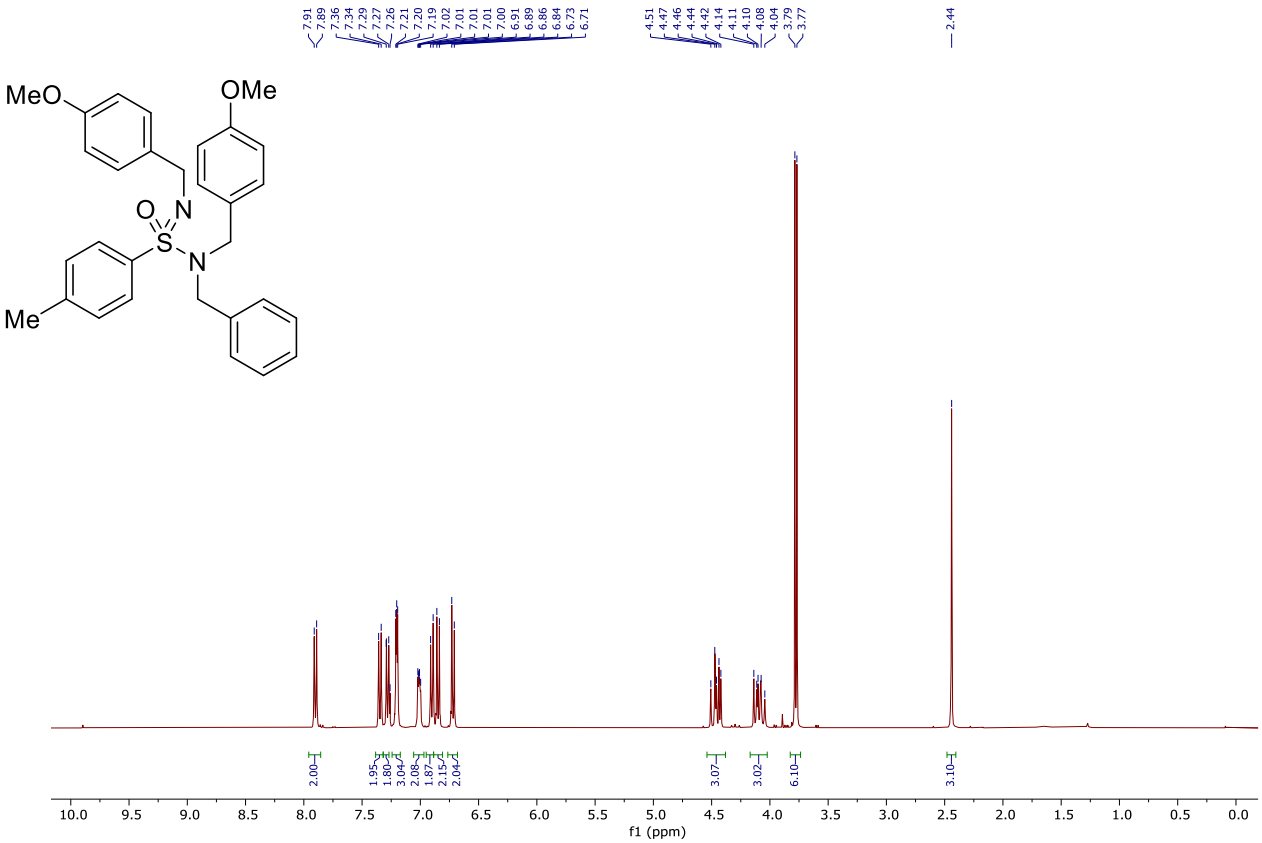

145.63
142.65
139.02
129.17
128.27
127.05
126.80
126.68
40.15
39.94
39.74
39.32
39.10
38.89
O
NH
S
NH2
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

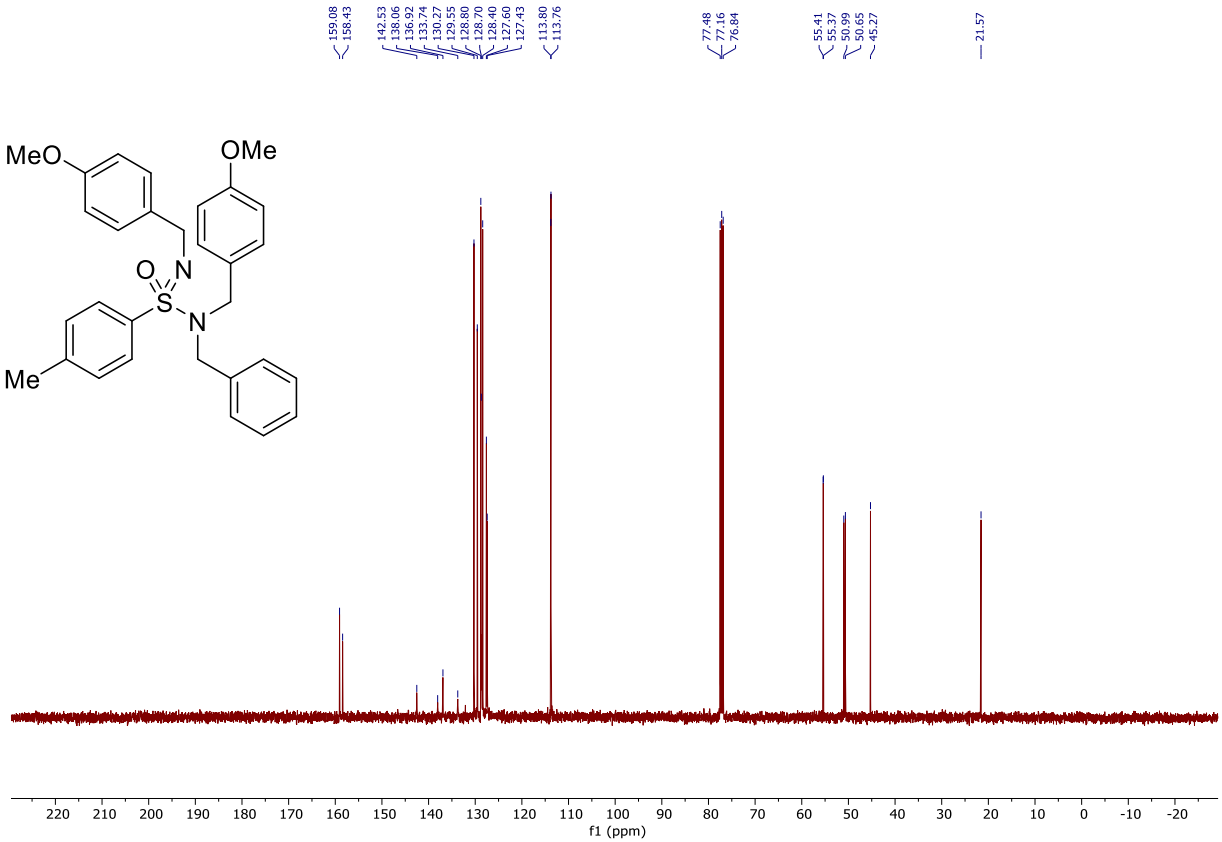
**N,N'-bis(4-methoxybenzyl)-4-methylbenzenesulfonimidamide (73b)**



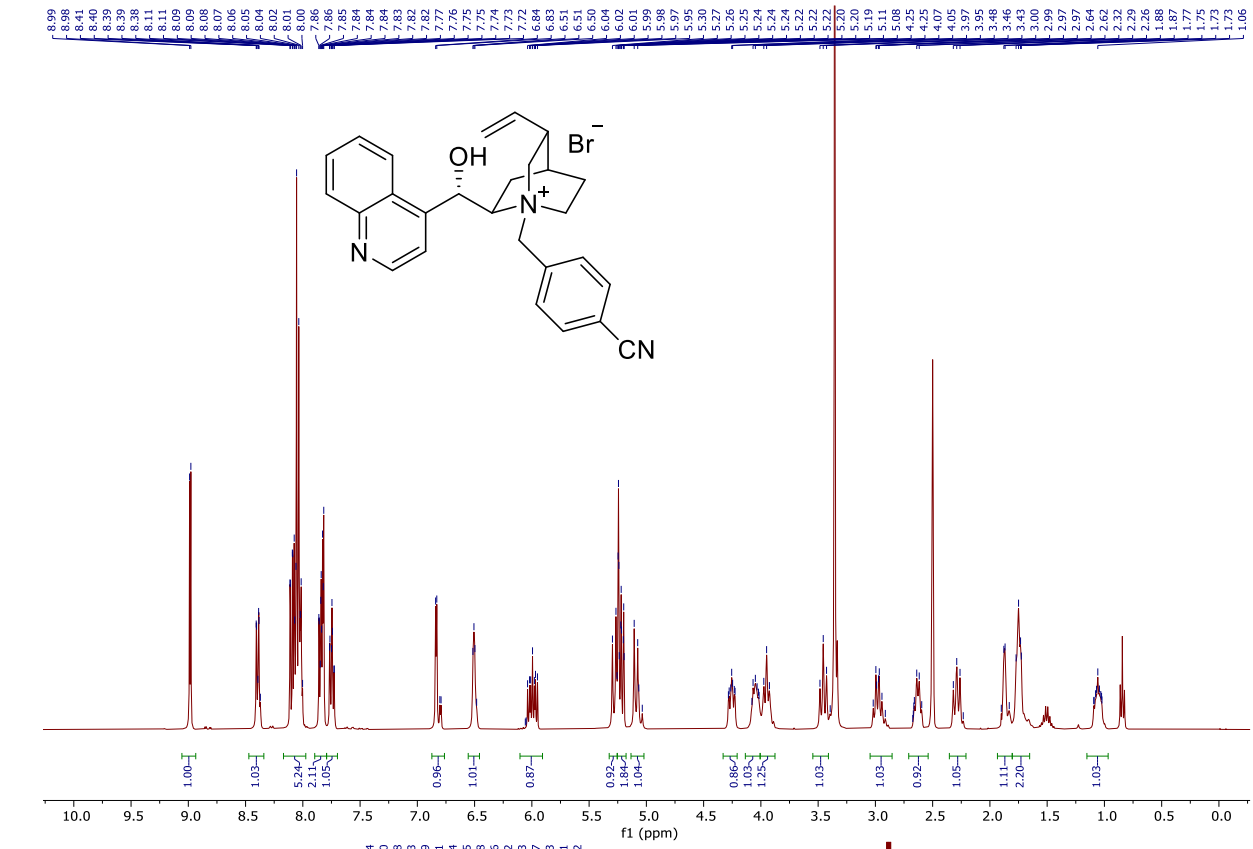



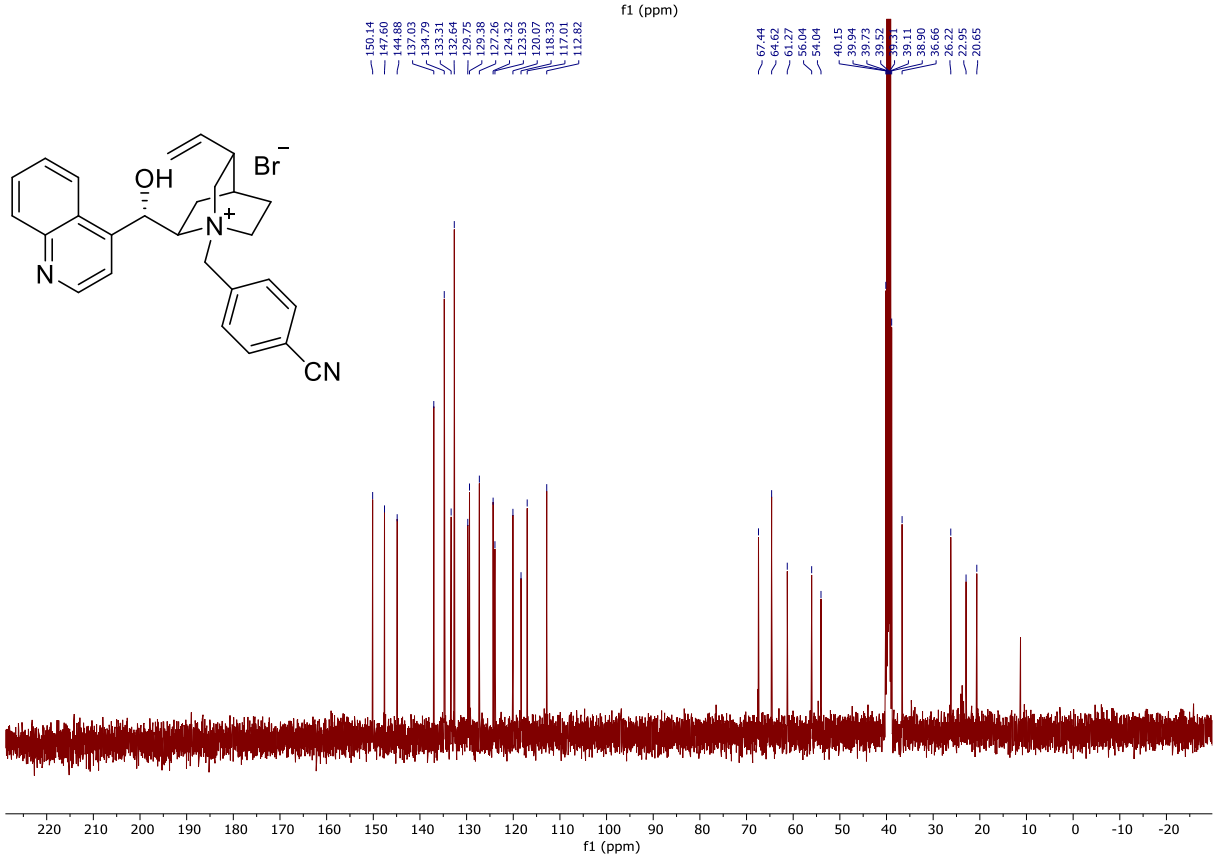
**N-benzyl-N,N'-bis(4-methoxybenzyl)-4-methylbenzenesulfonimidamide (74b)**



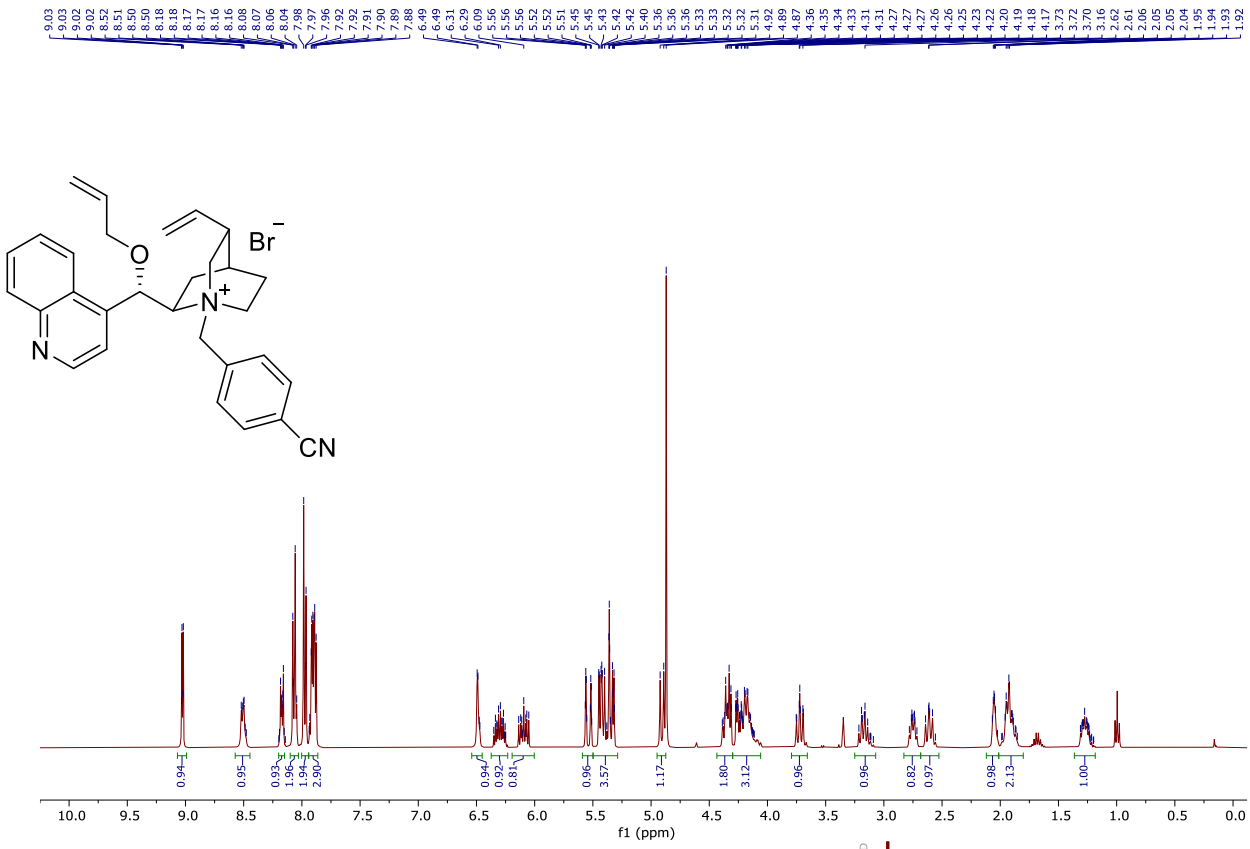



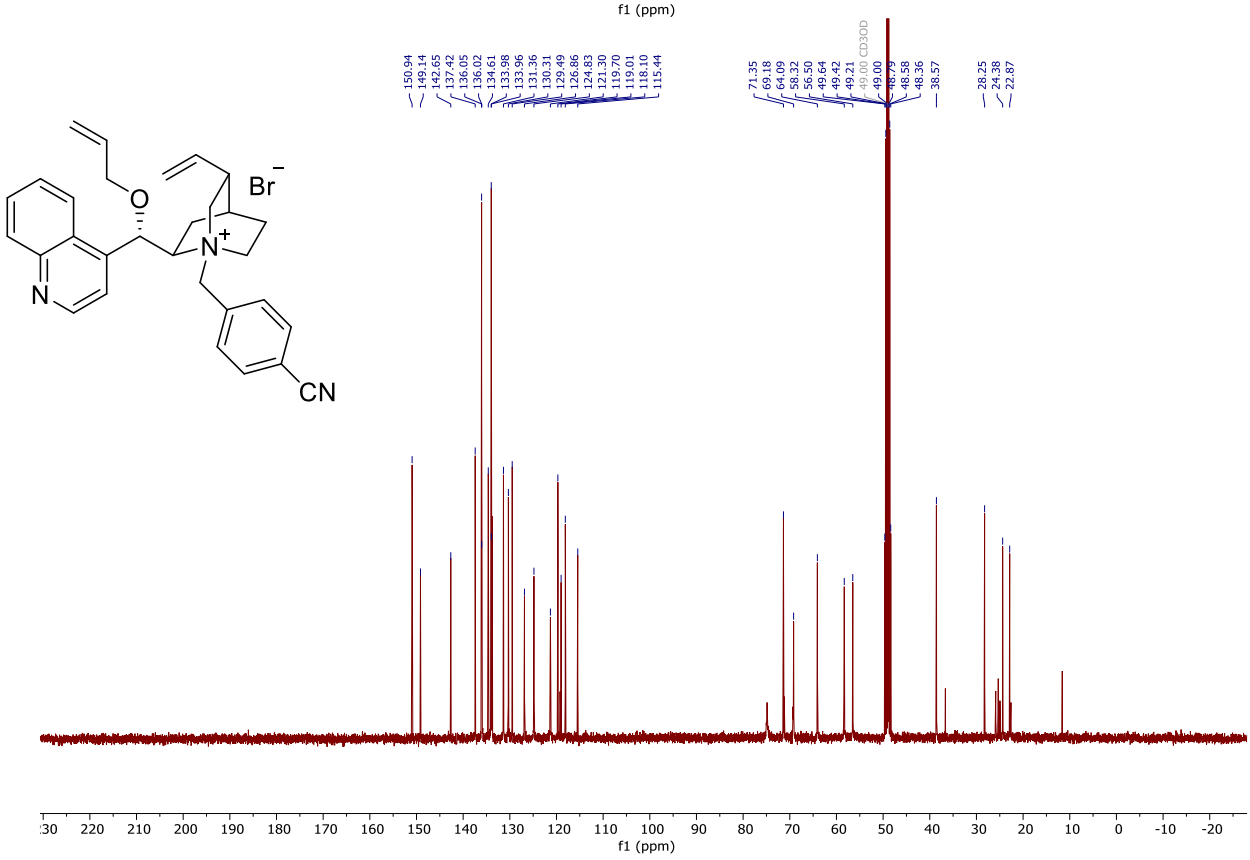
## *N*-(4-cyanobenzyl)cinchoninium bromide (CAT-12)



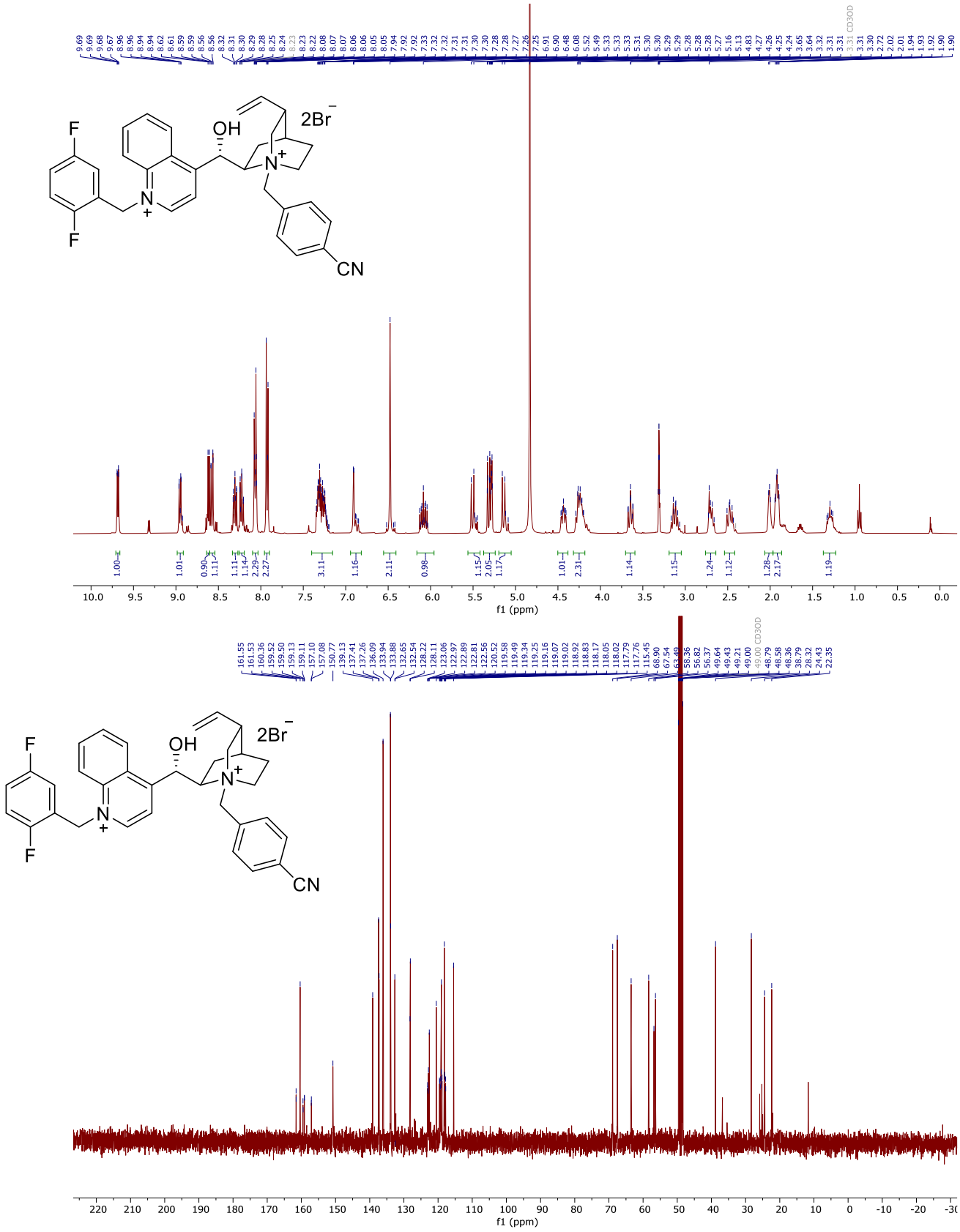



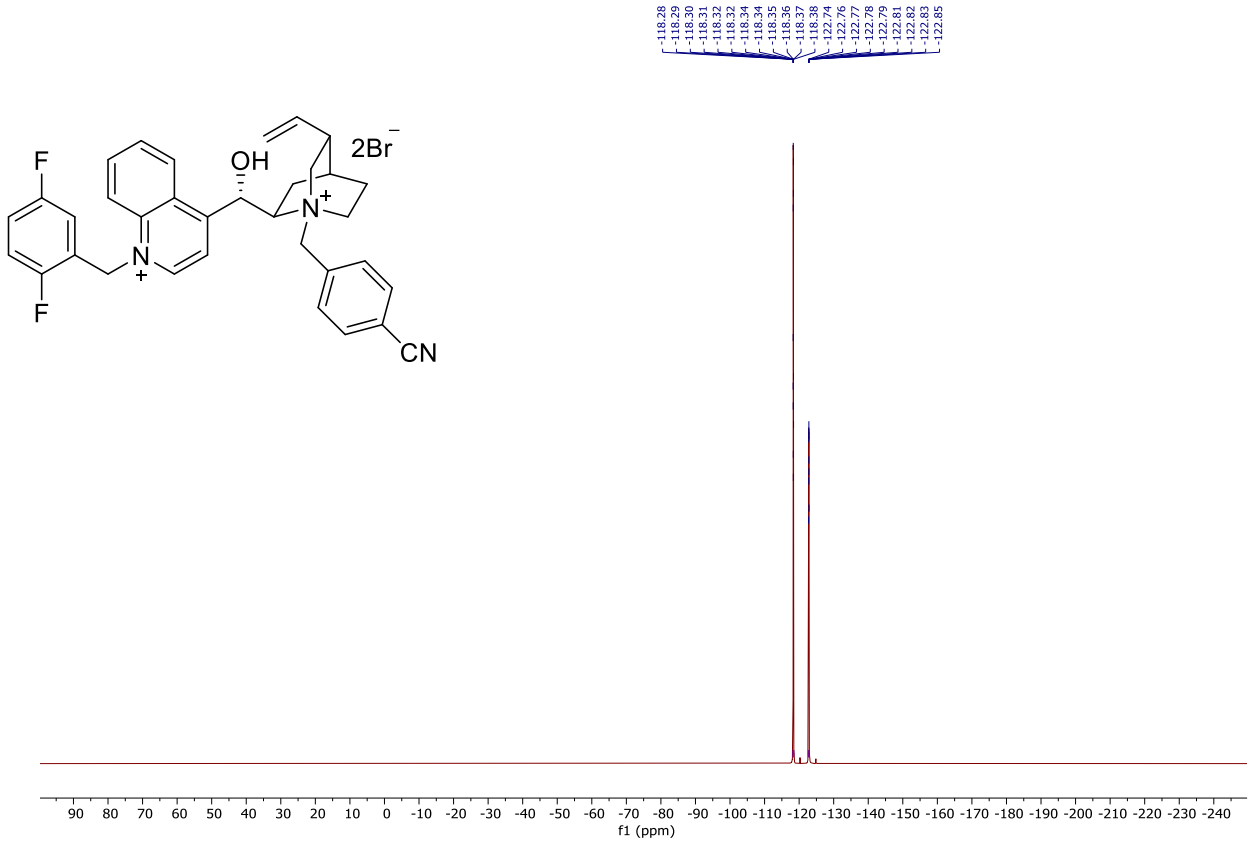
## *O*-allyl-*N*-(4-cyanobenzyl)cinchoninium bromide (CAT-17)



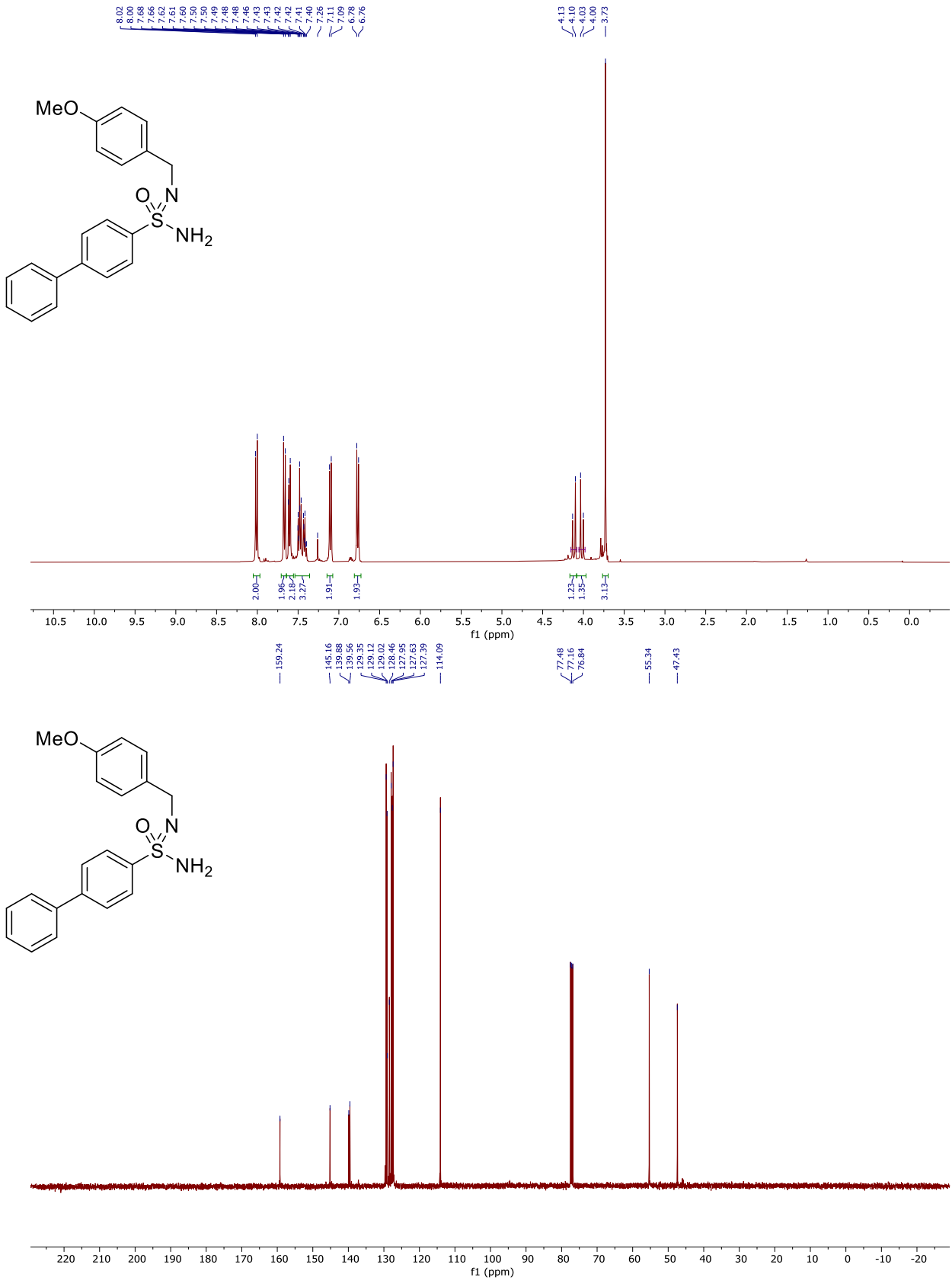



## *N*-(4-cyanobenzyl)-*N'*-(2,5-difluorobenzyl)cinchoninium dibromide (CAT-25)

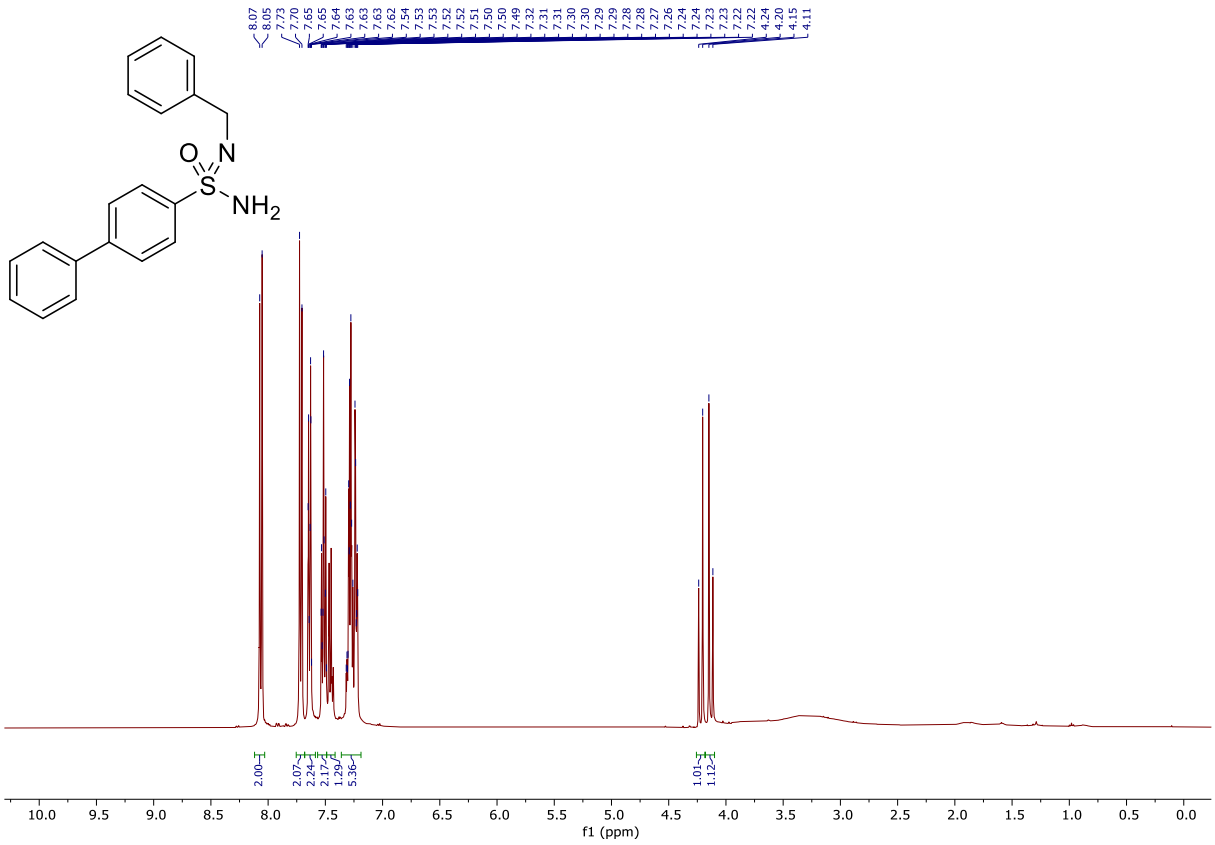


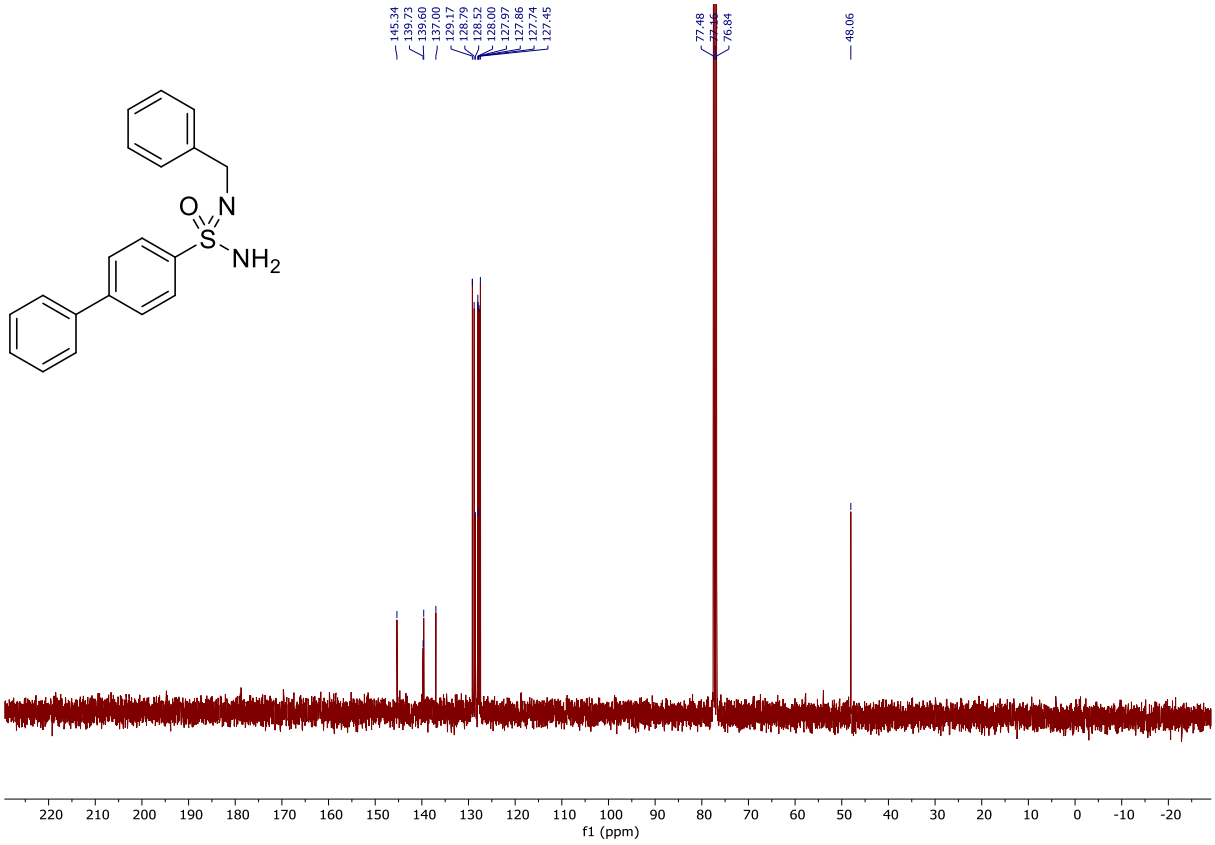

-118.28
-118.29
-118.30
-118.31
-118.32
-118.32
-118.34
-118.34
-118.35
-118.36
-118.37
-118.38
-122.74
-122.76
-122.77
-122.78
-122.79
-122.81
-122.82
-122.83
-122.85
F
OH
2Br⁻
N
N
F
CN
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

## *N*'-(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (123a)

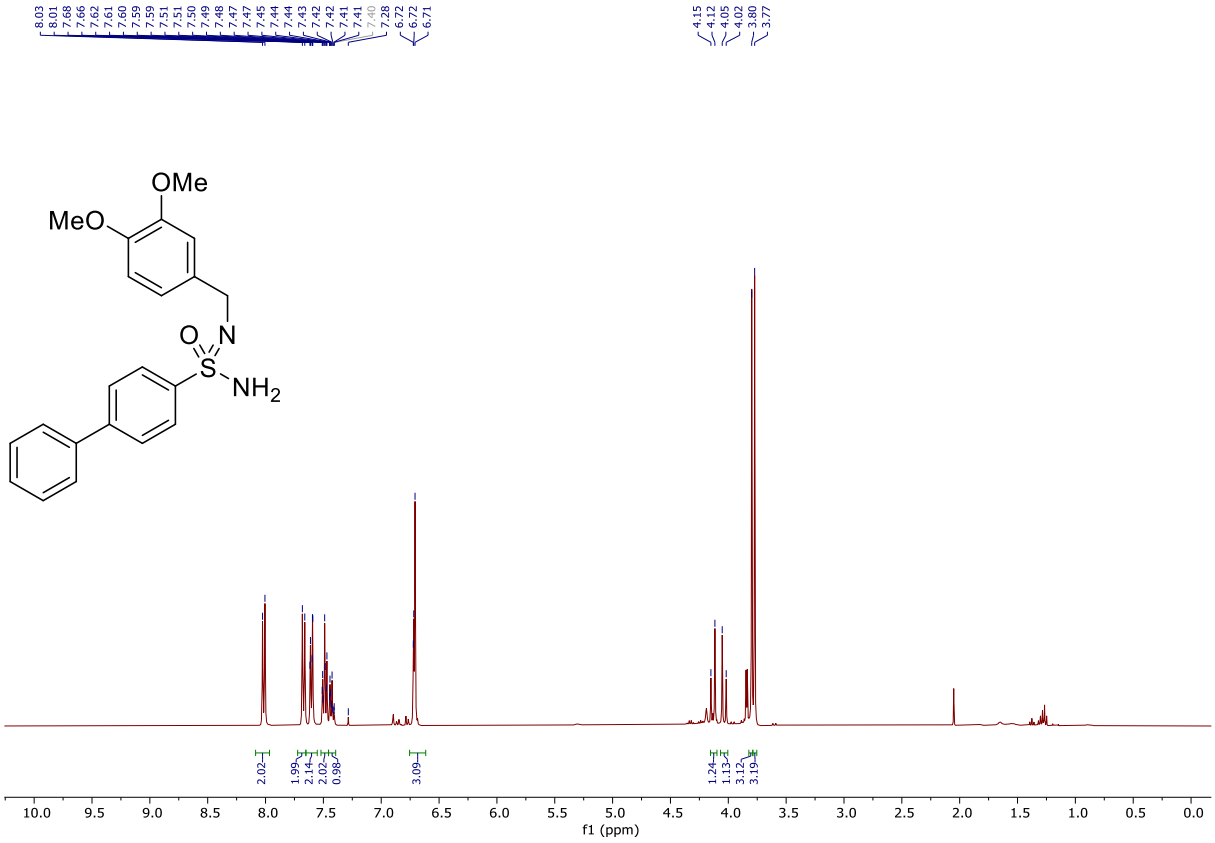


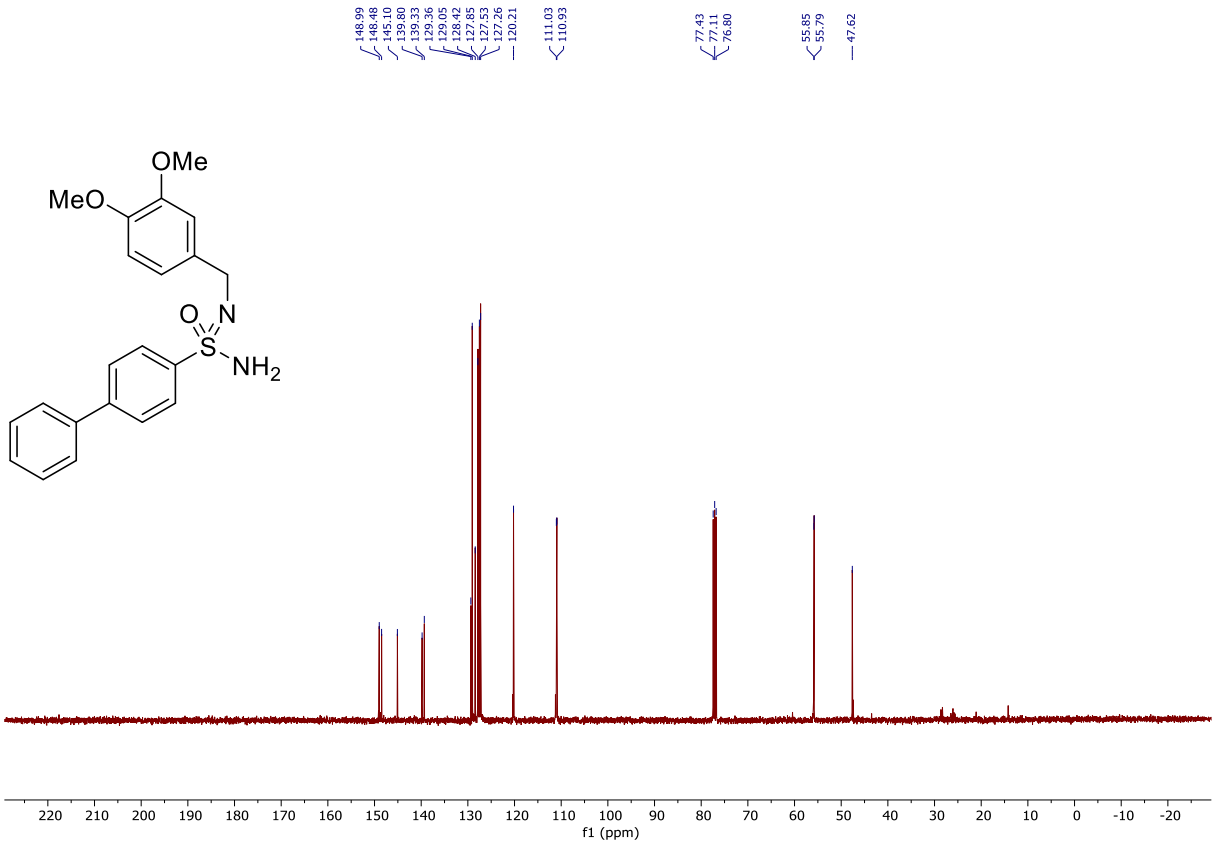
## *N*'-benzyl-[1,1'-biphenyl]-4-sulfonimidamide (124a)



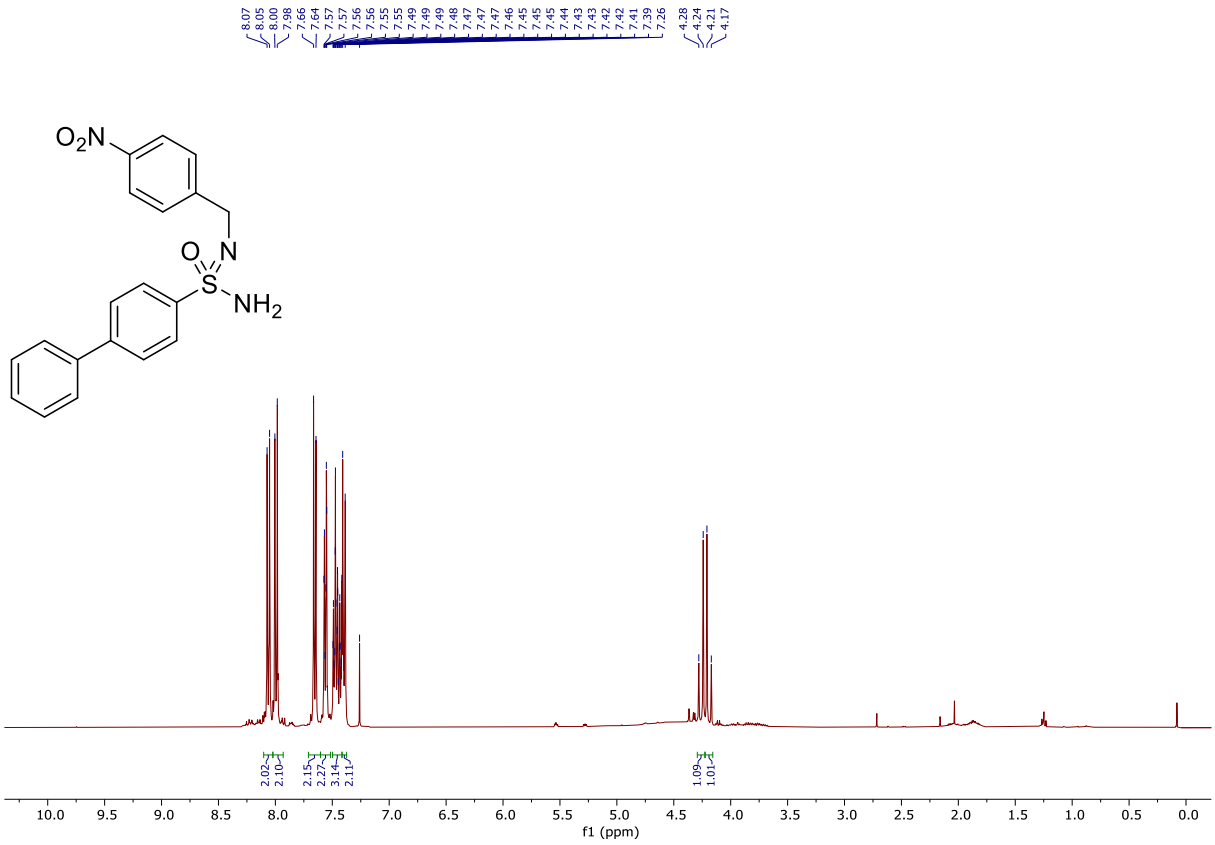



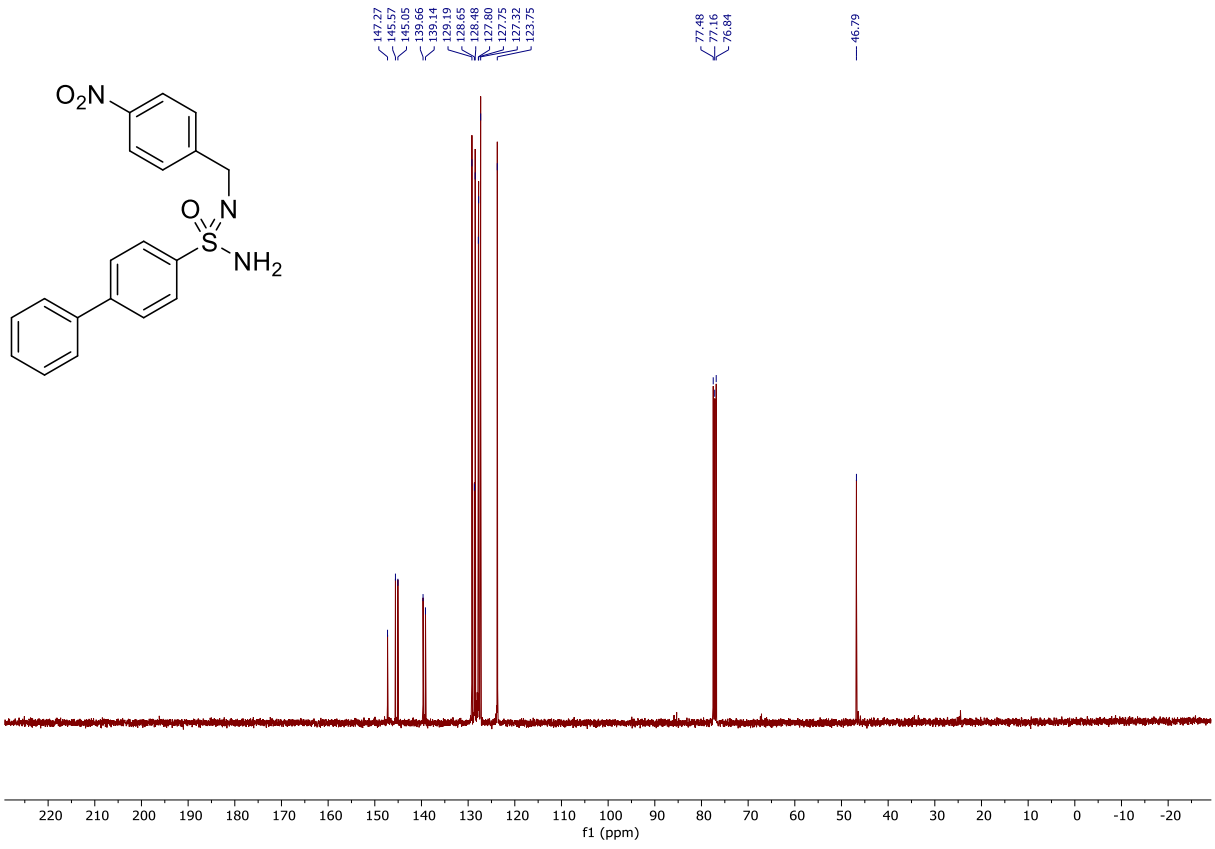
## *N*'-(3,4-dimethoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (124b)



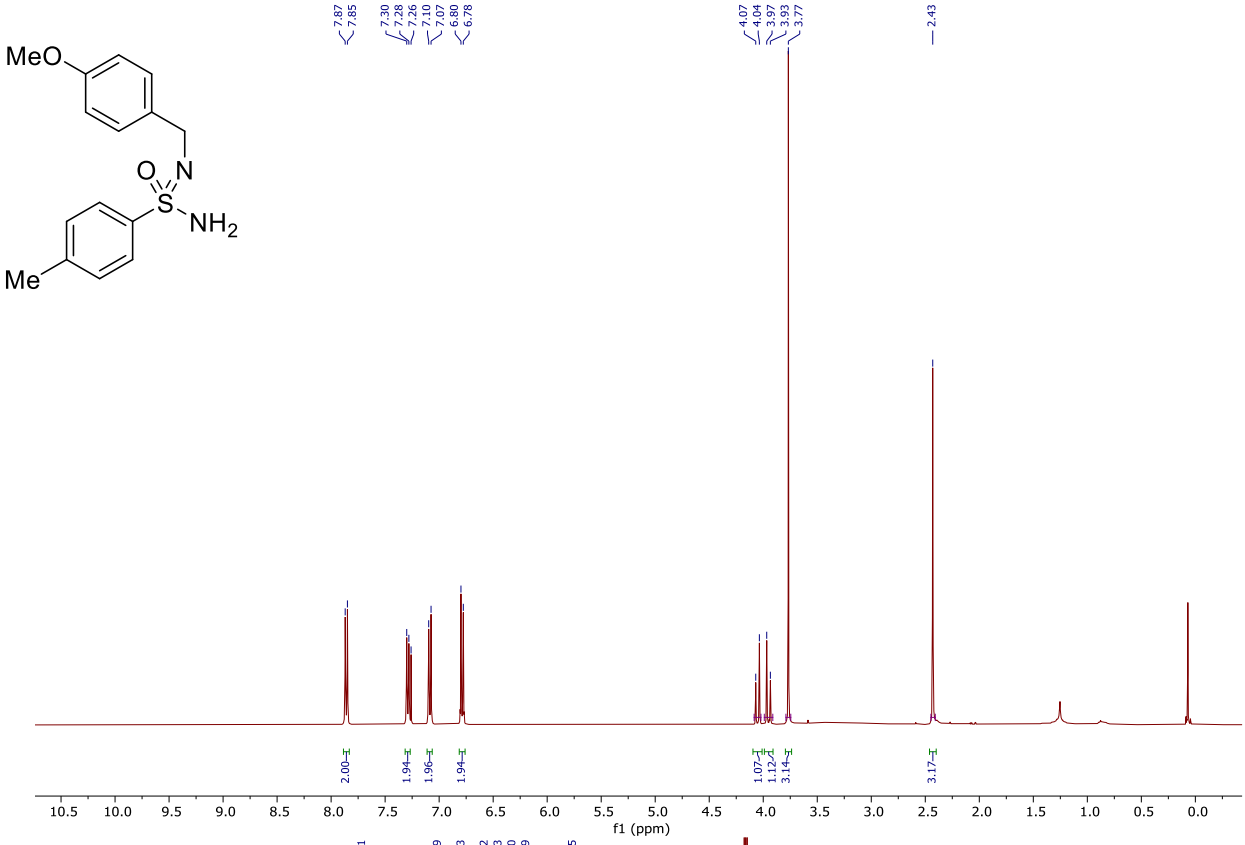



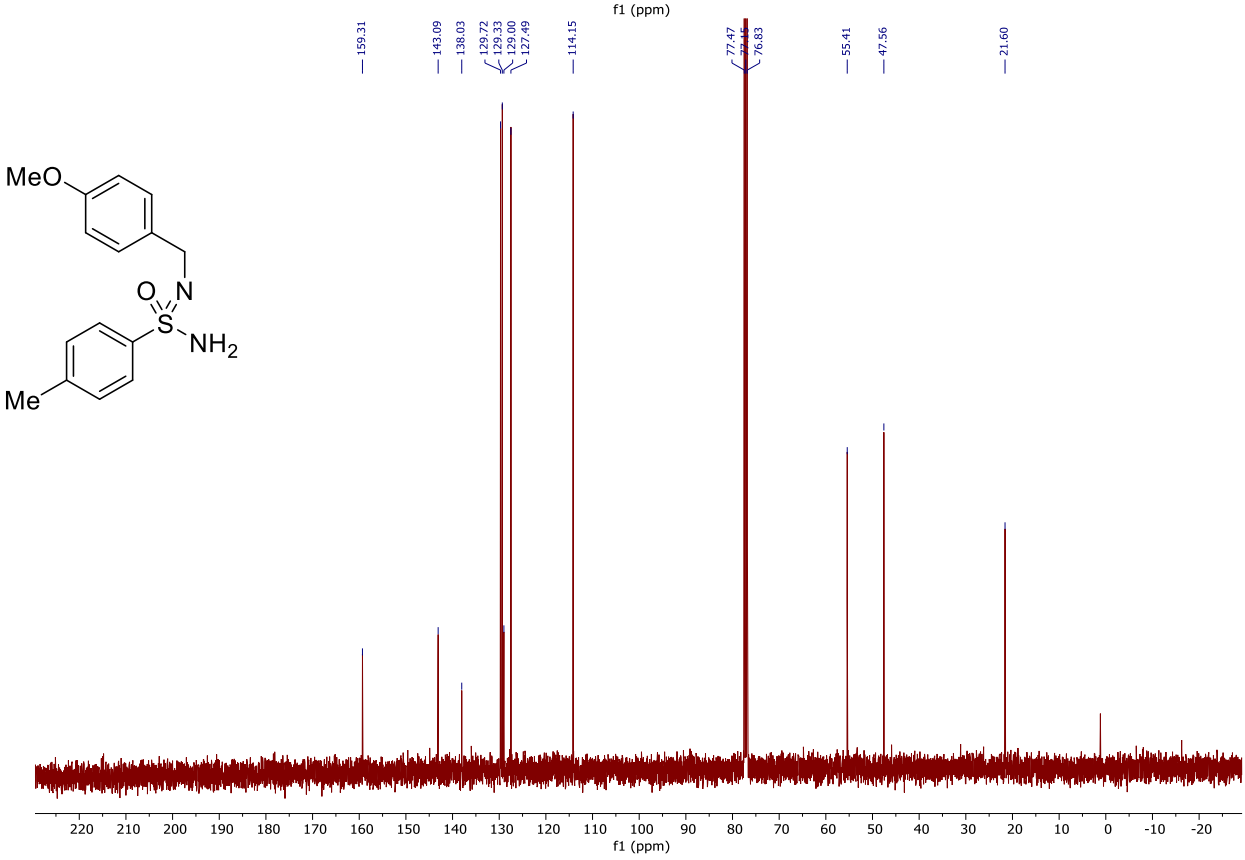
## *N*'-(4-nitrobenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (124c)



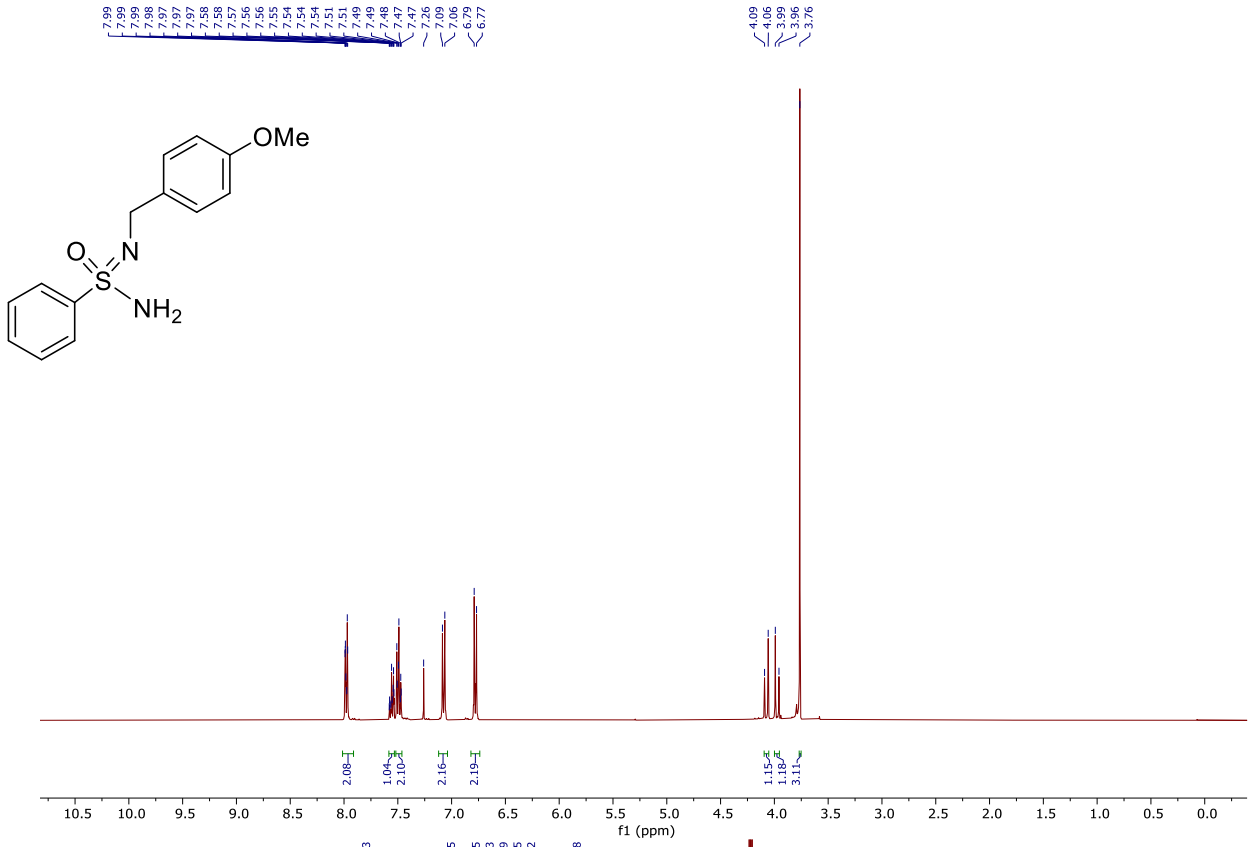



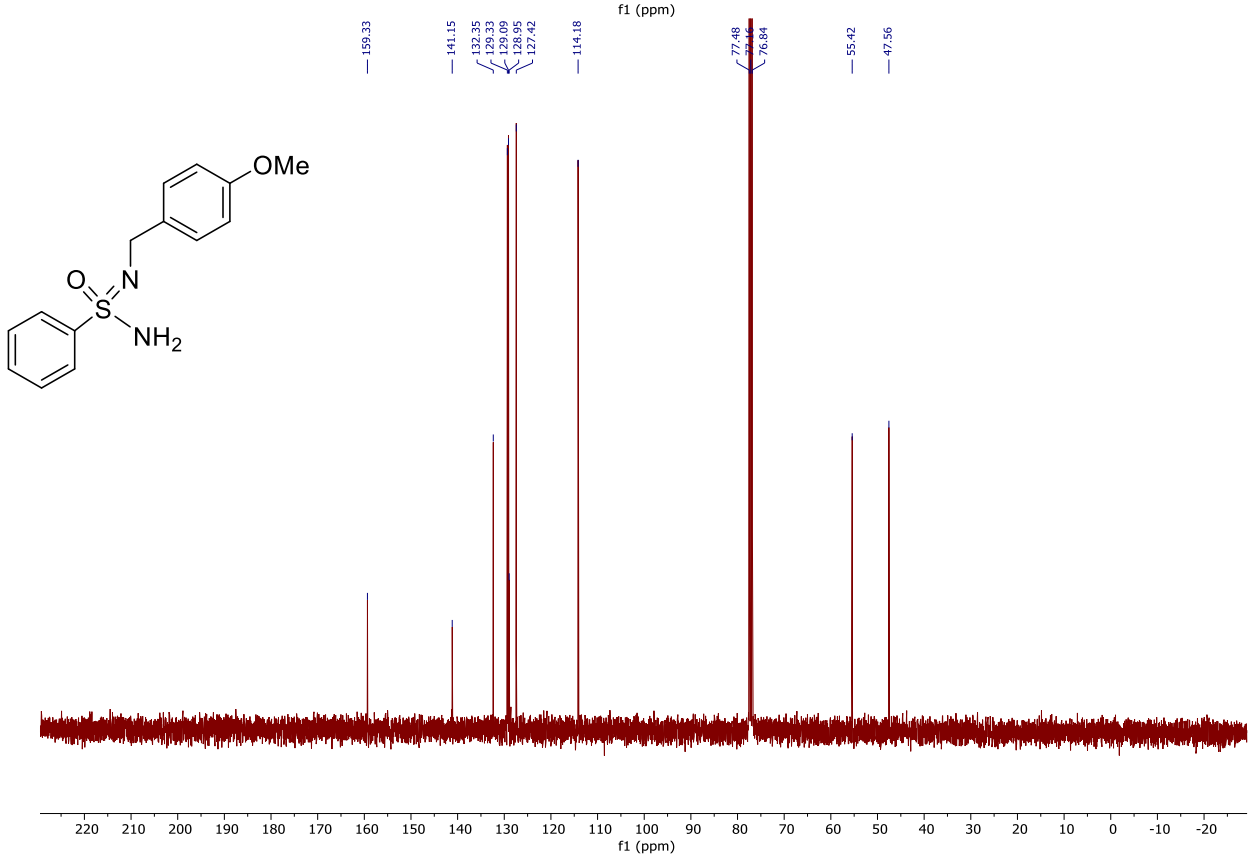
## *N'*-(4-methoxybenzyl)-4-methylbenzenesulfonimidamide (123b)



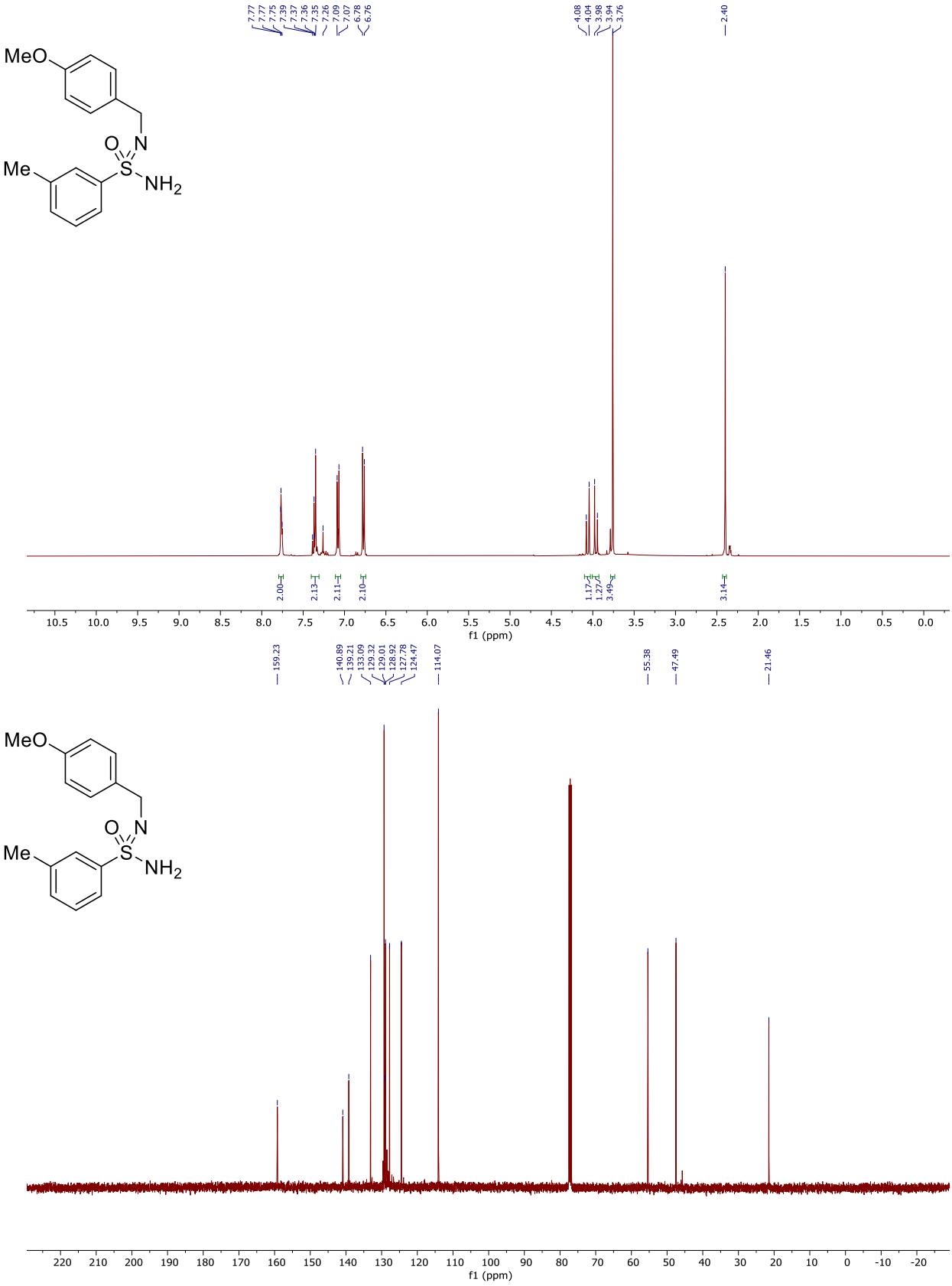



## *N*'-(4-methoxybenzyl)benzenesulfonimidamide (123c)

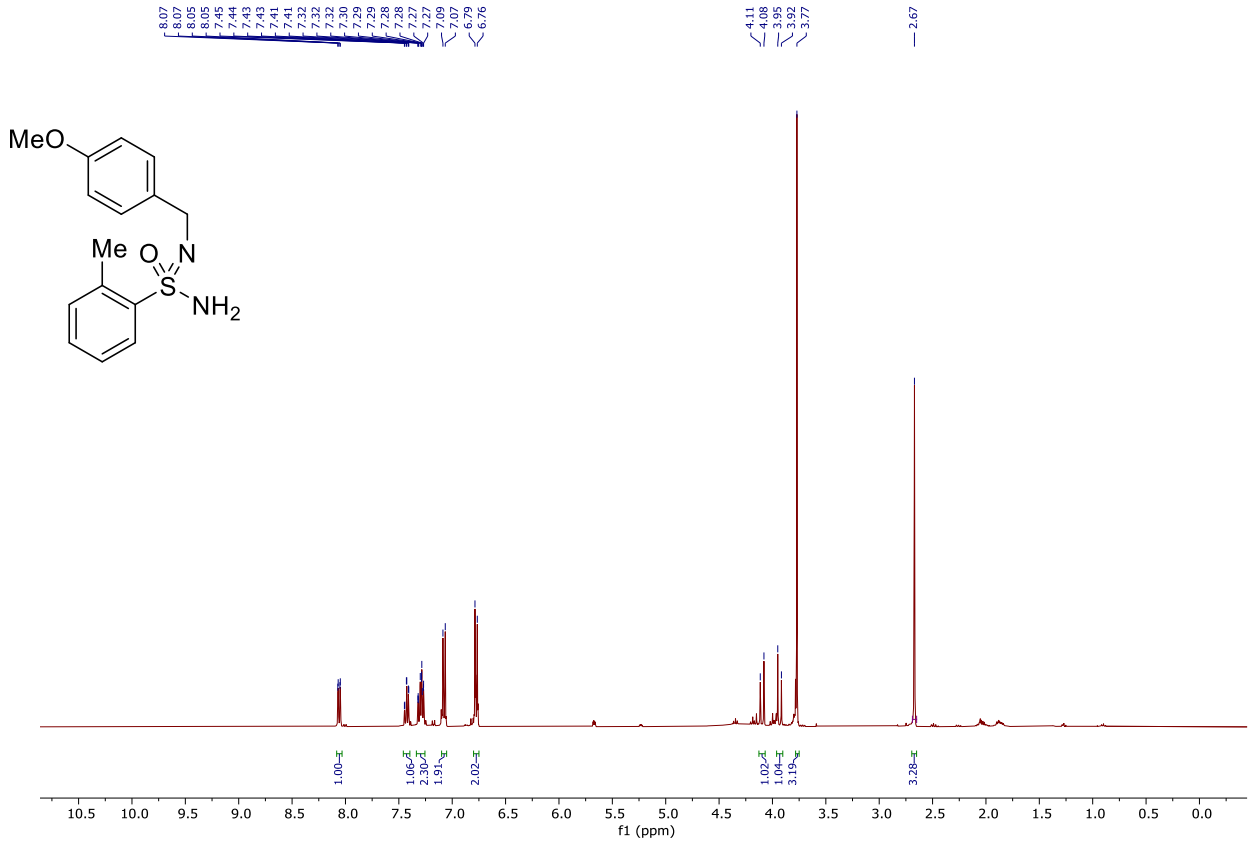


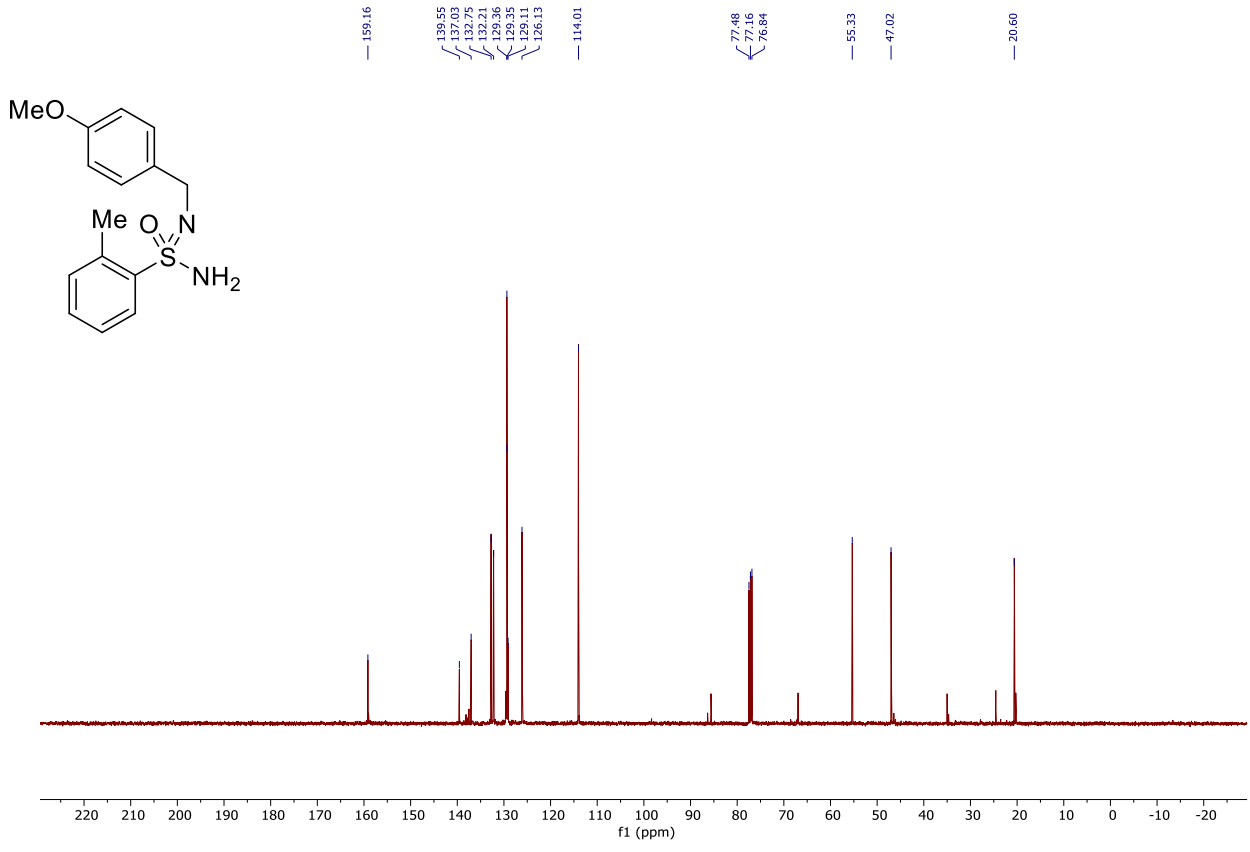



## *N*′-(4-methoxybenzyl)-3-methylbenzenesulfonimidamide (123d)

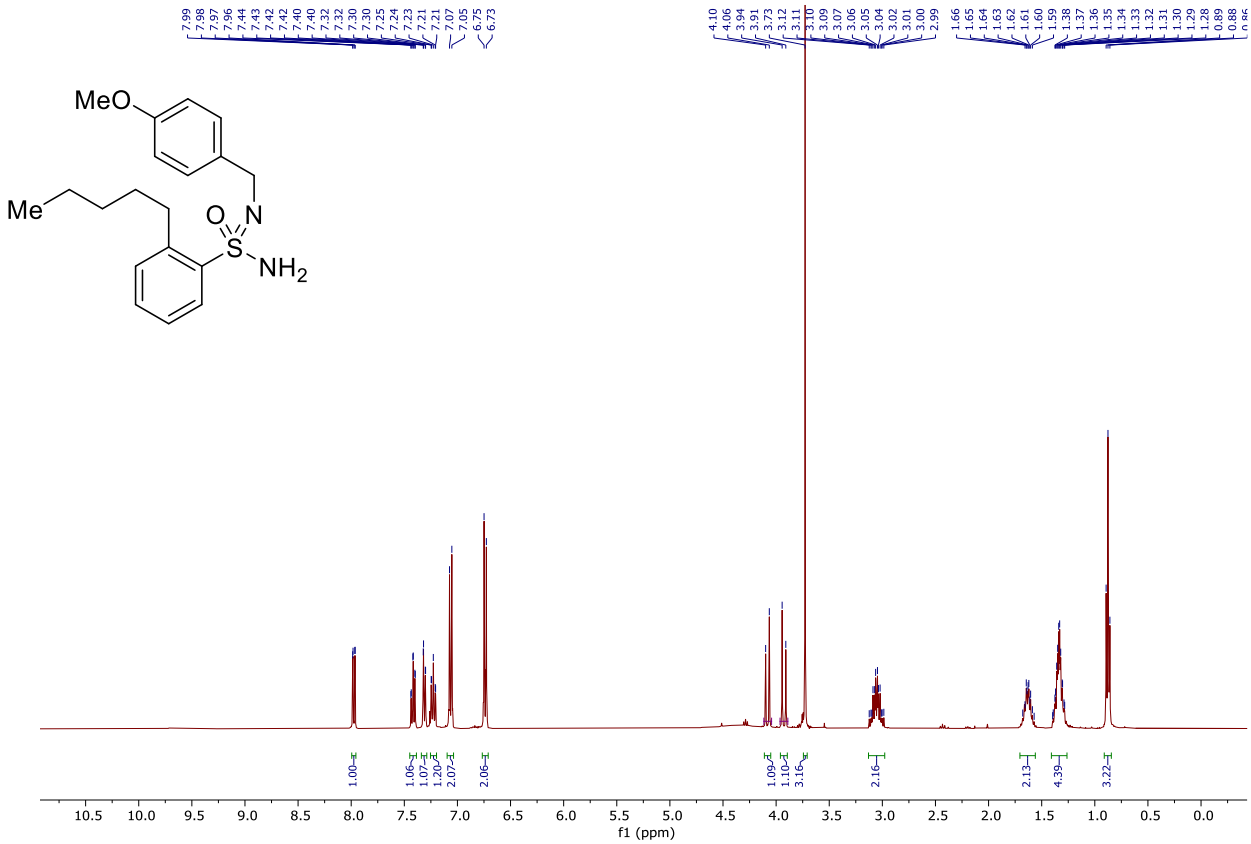


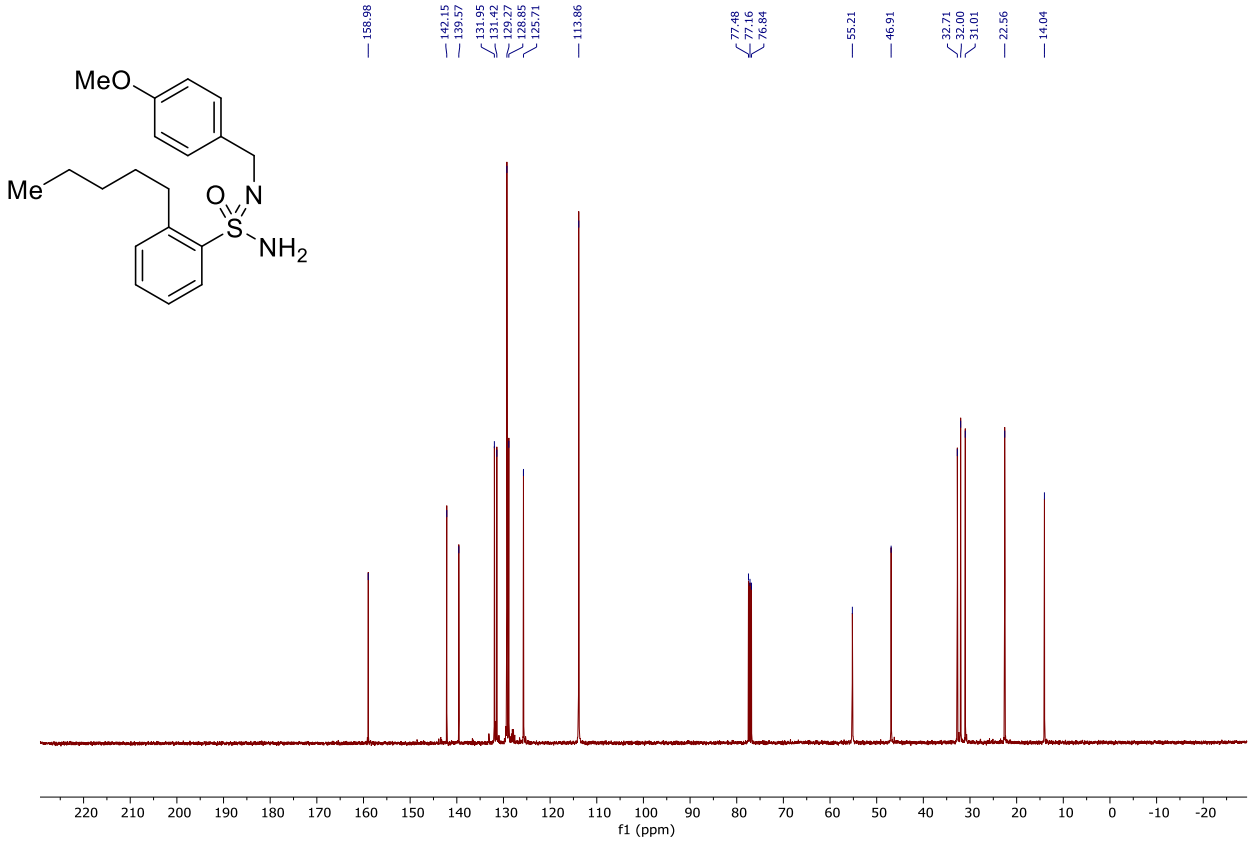
## *N*'-(4-methoxybenzyl)-2-methylbenzenesulfonimidamide (123e)



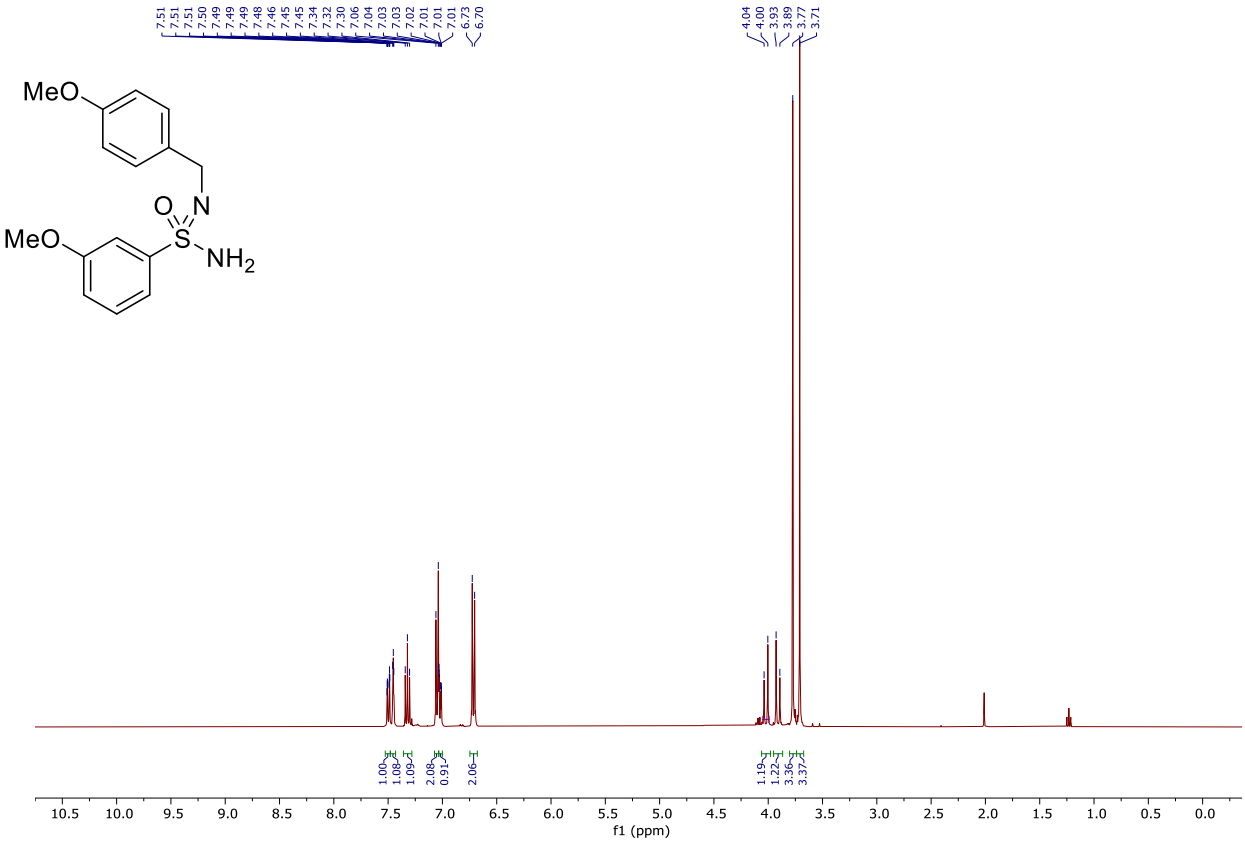



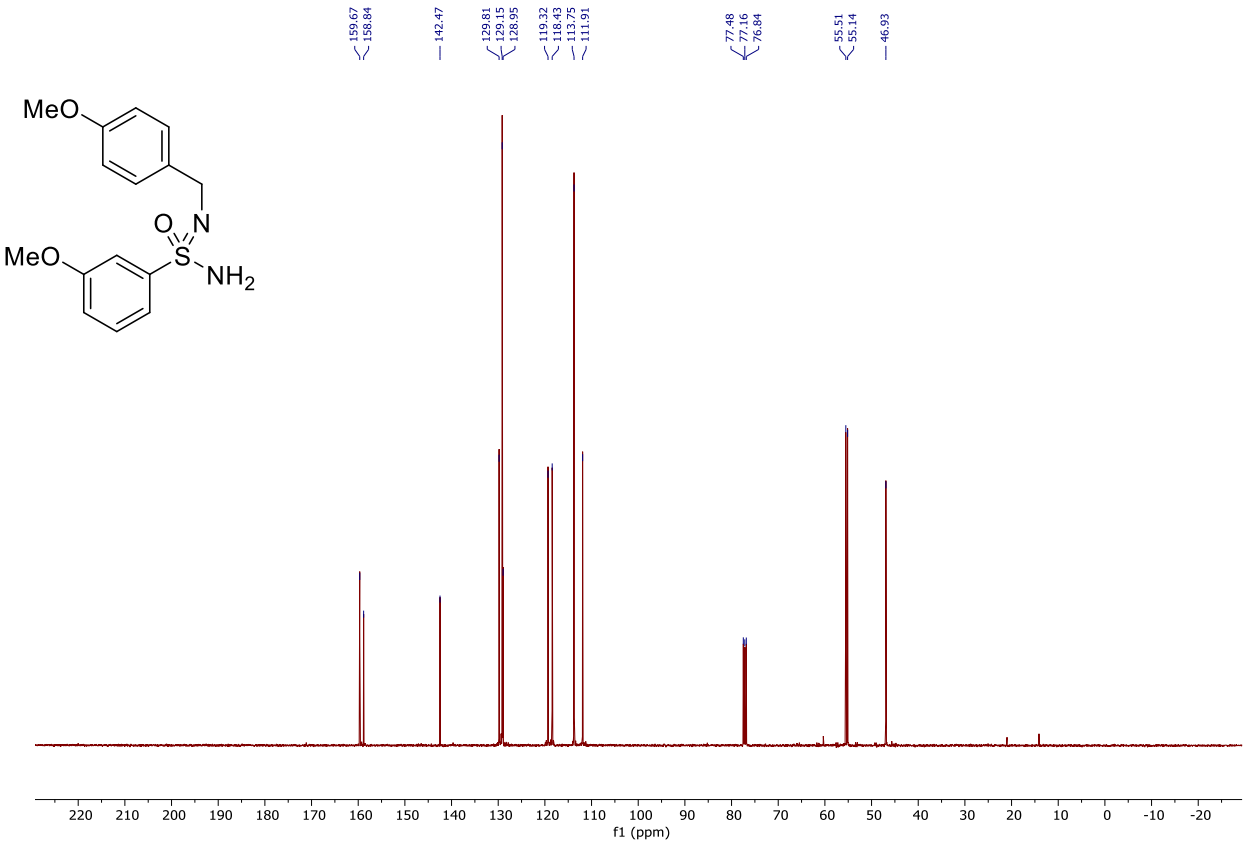
## *N*'-(4-methoxybenzyl)-2-pentylbenzenesulfonimidamide (123f)



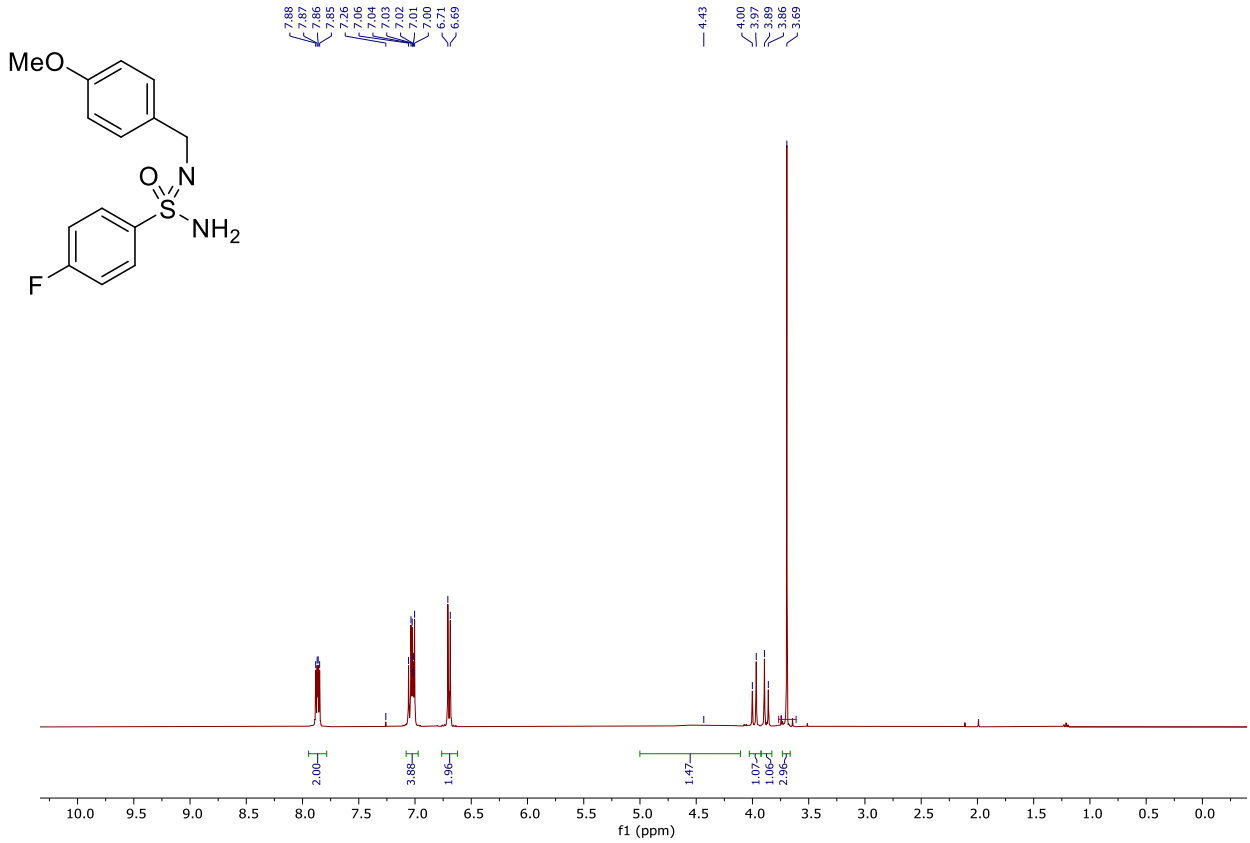



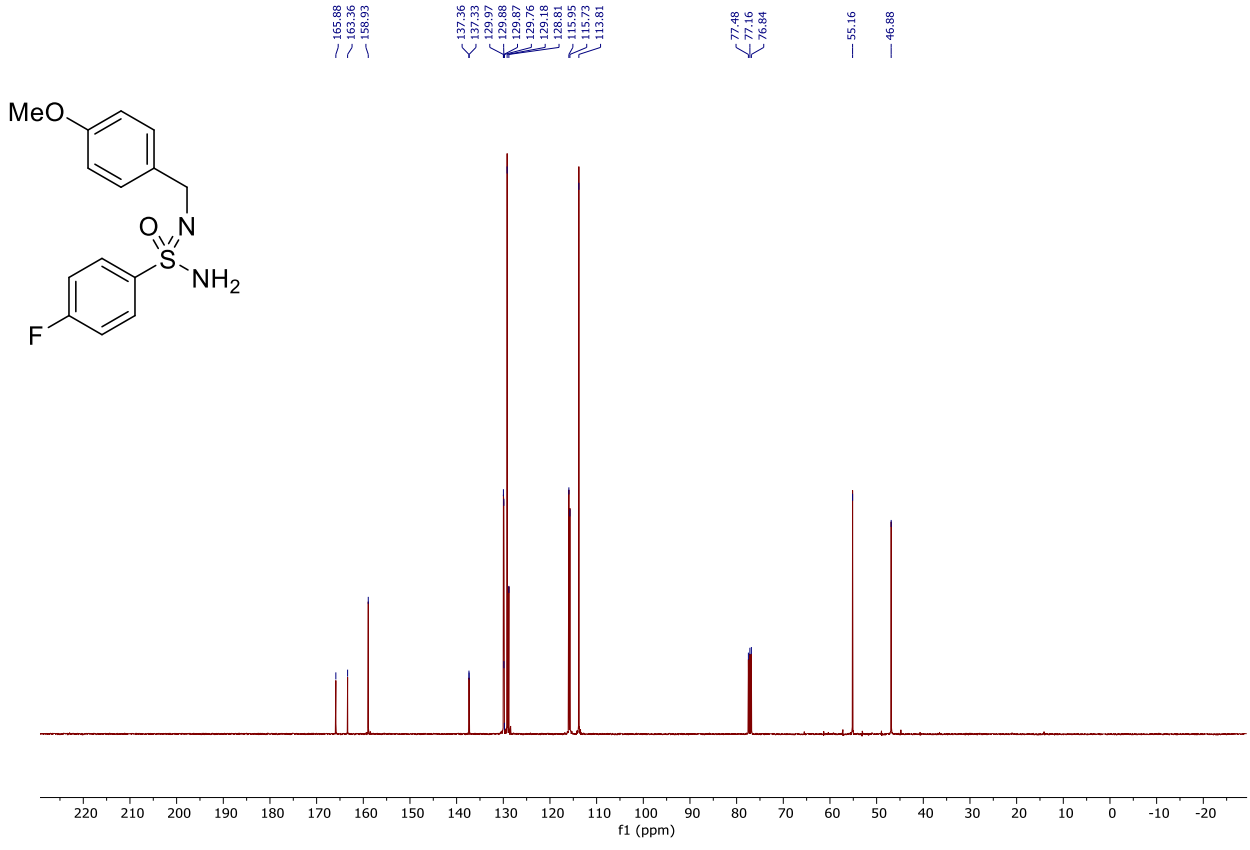
**3-methoxy-*N*'-(4-methoxybenzyl)benzenesulfonimidamide (123g)**

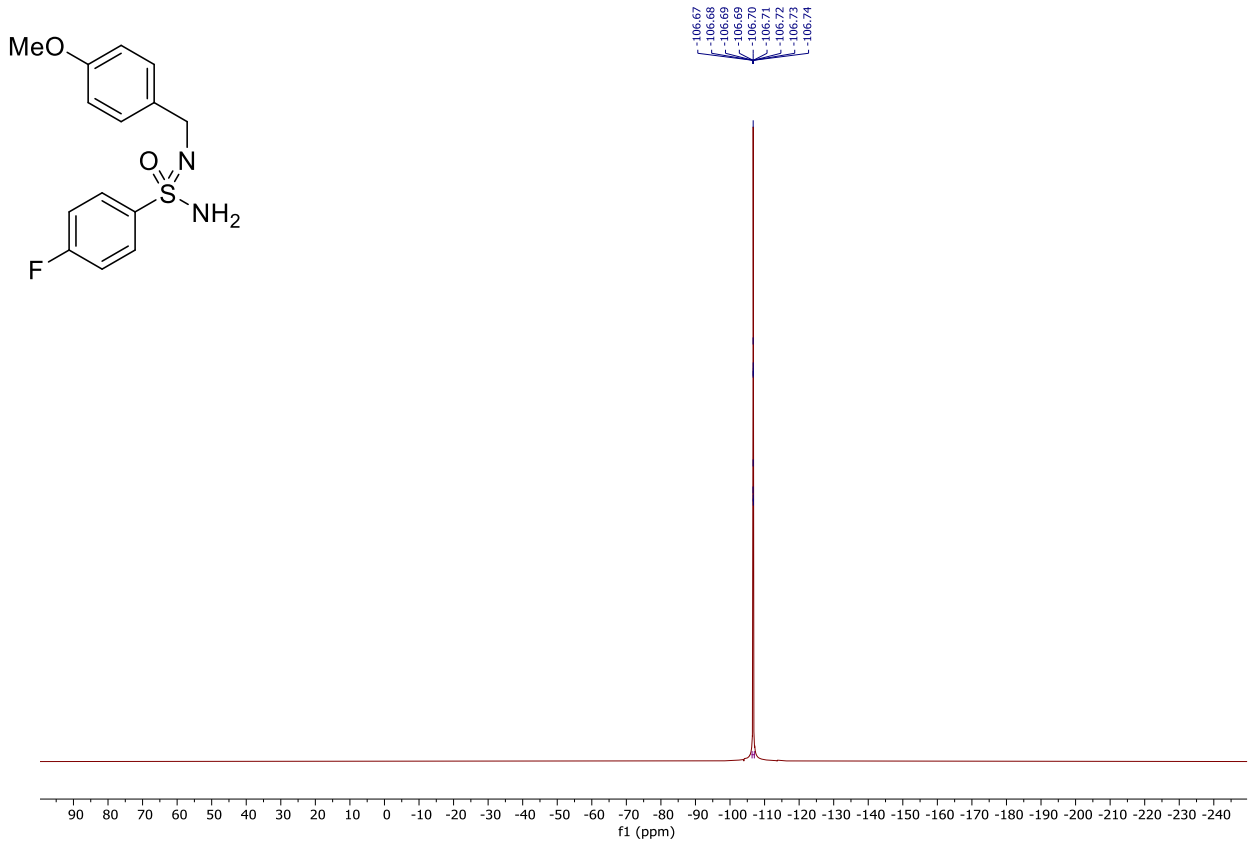


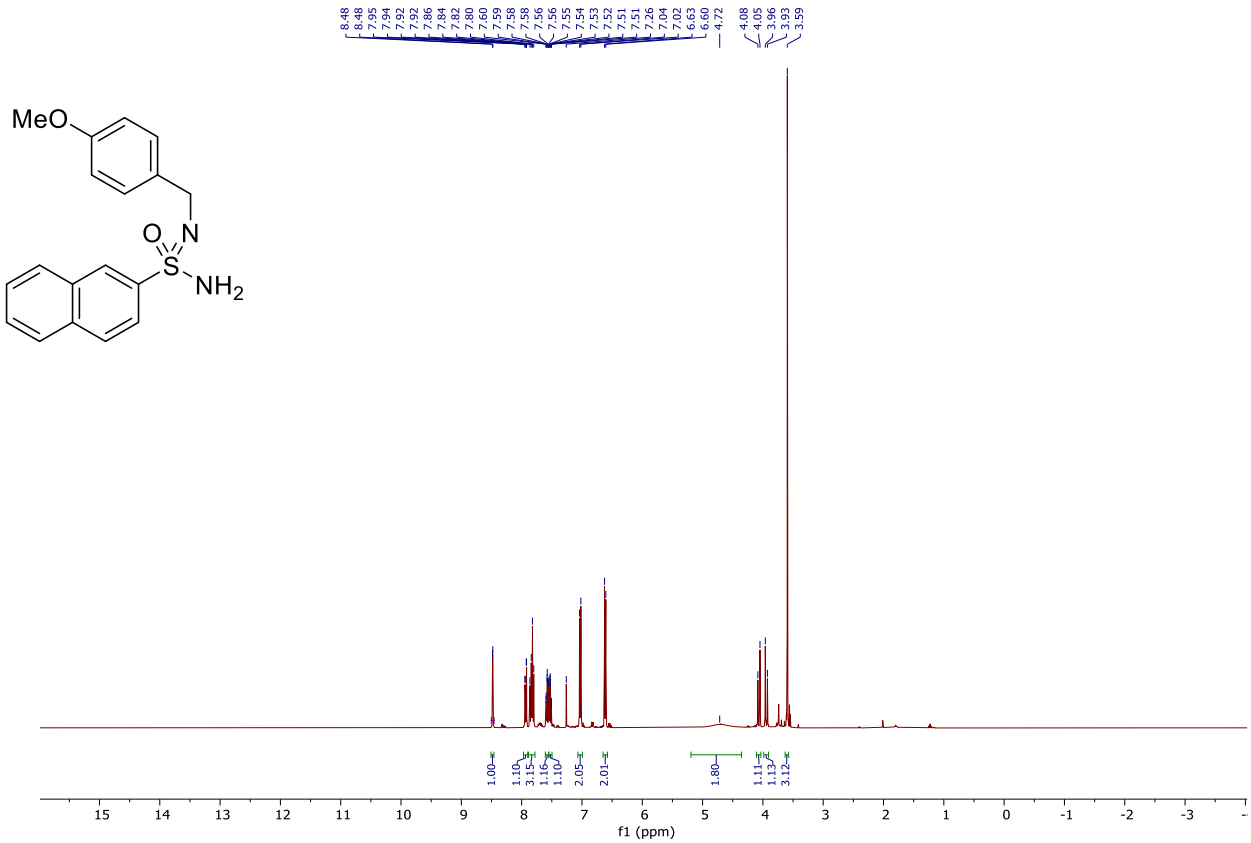
**4-fluoro-*N*'-(4-methoxybenzyl)benzenesulfonimidamide (123h)**

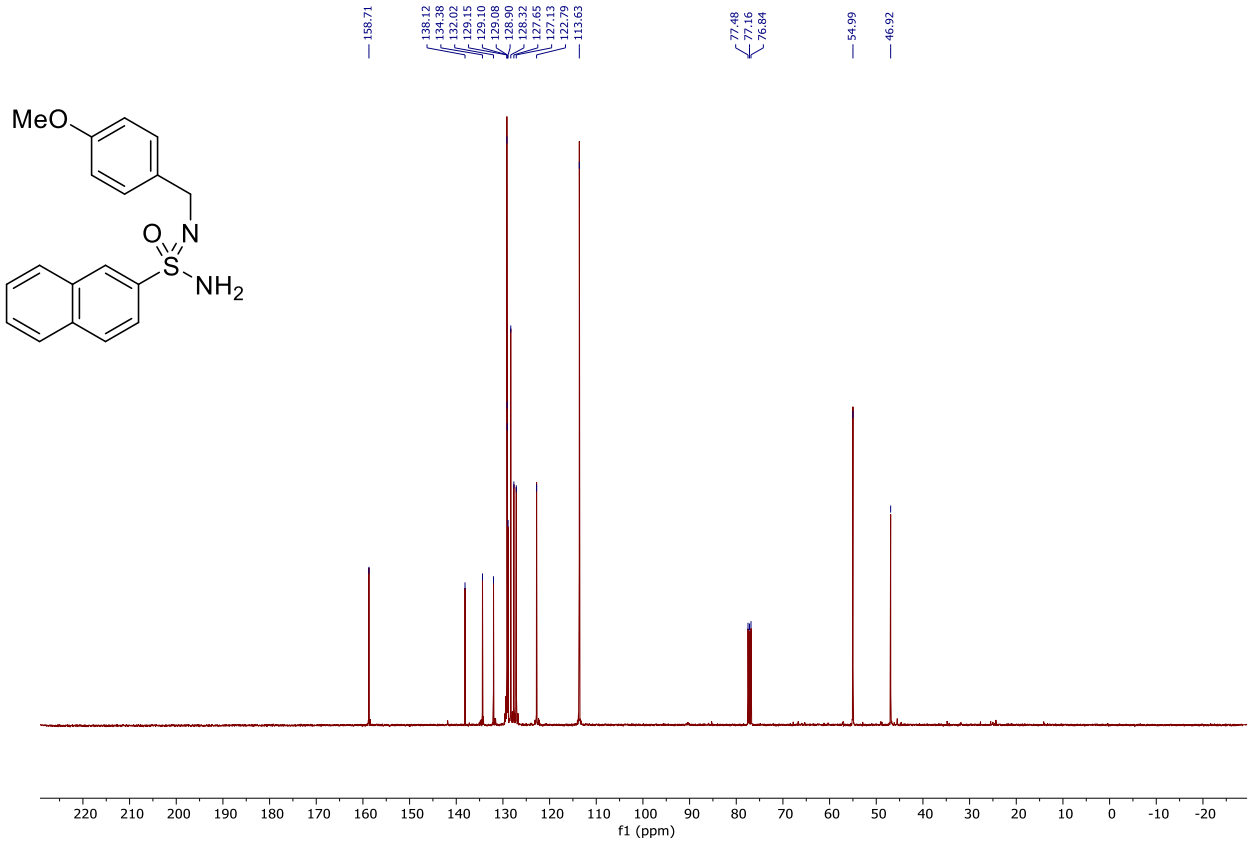


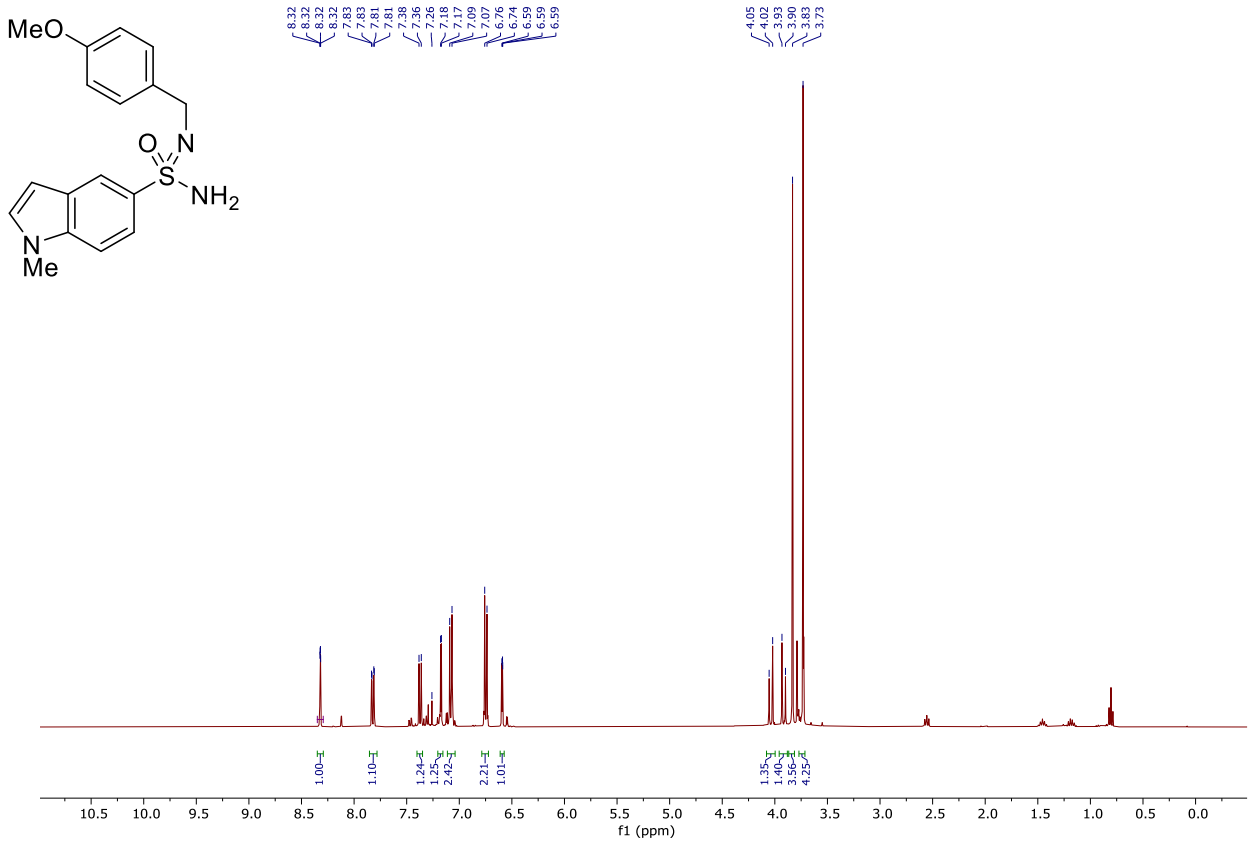

MeO
O
N
S
NH2
F
-106.67
-106.68
-106.69
-106.69
-106.70
-106.71
-106.72
-106.73
-106.74
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

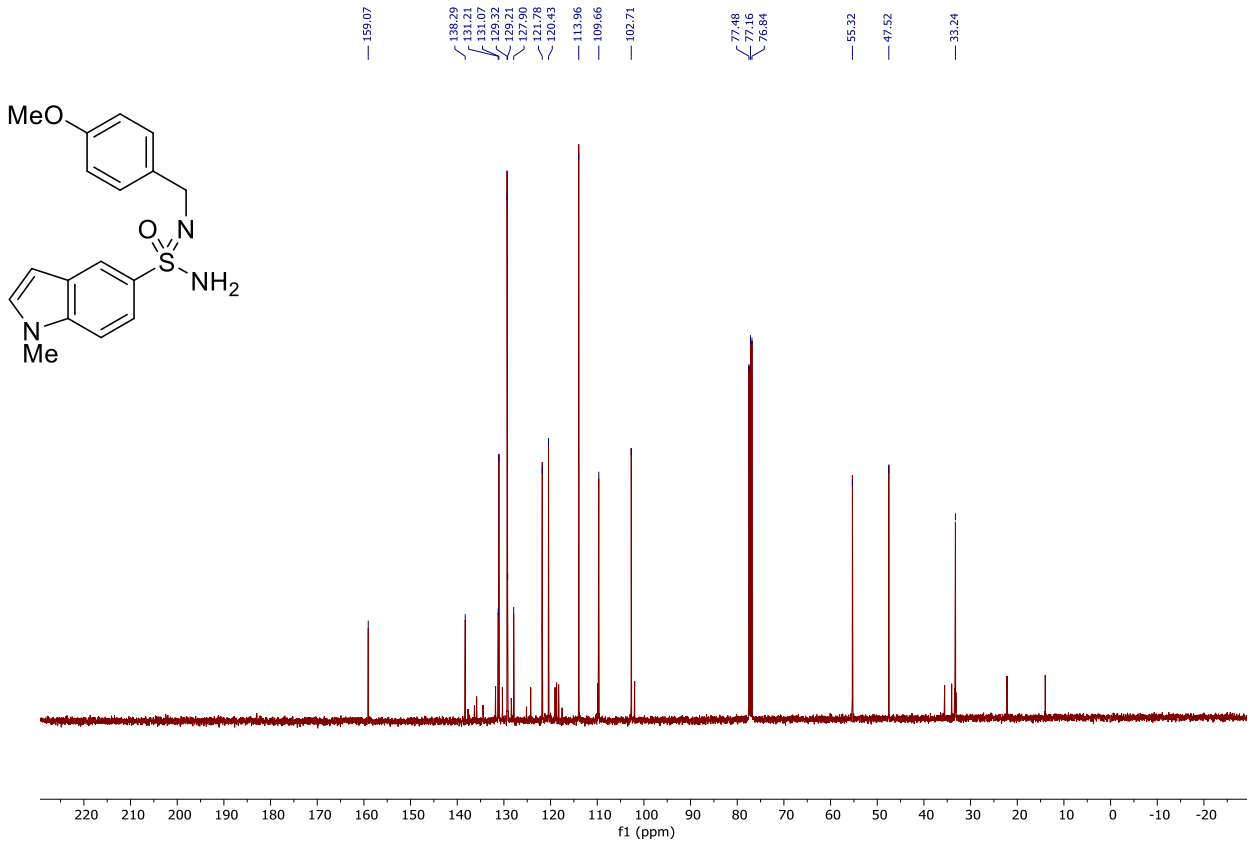
## *N*'-(4-methoxybenzyl)naphthalene-2-sulfonimidamide (123i)



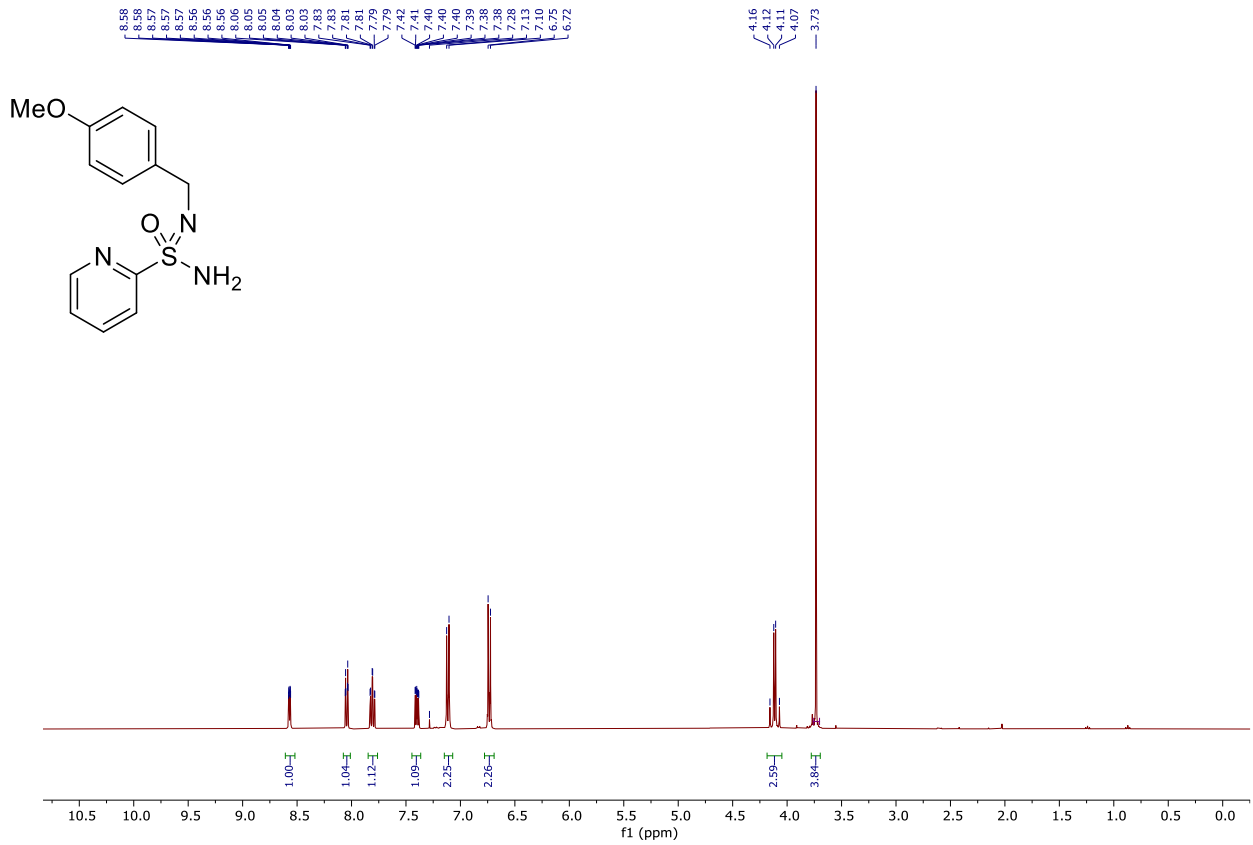



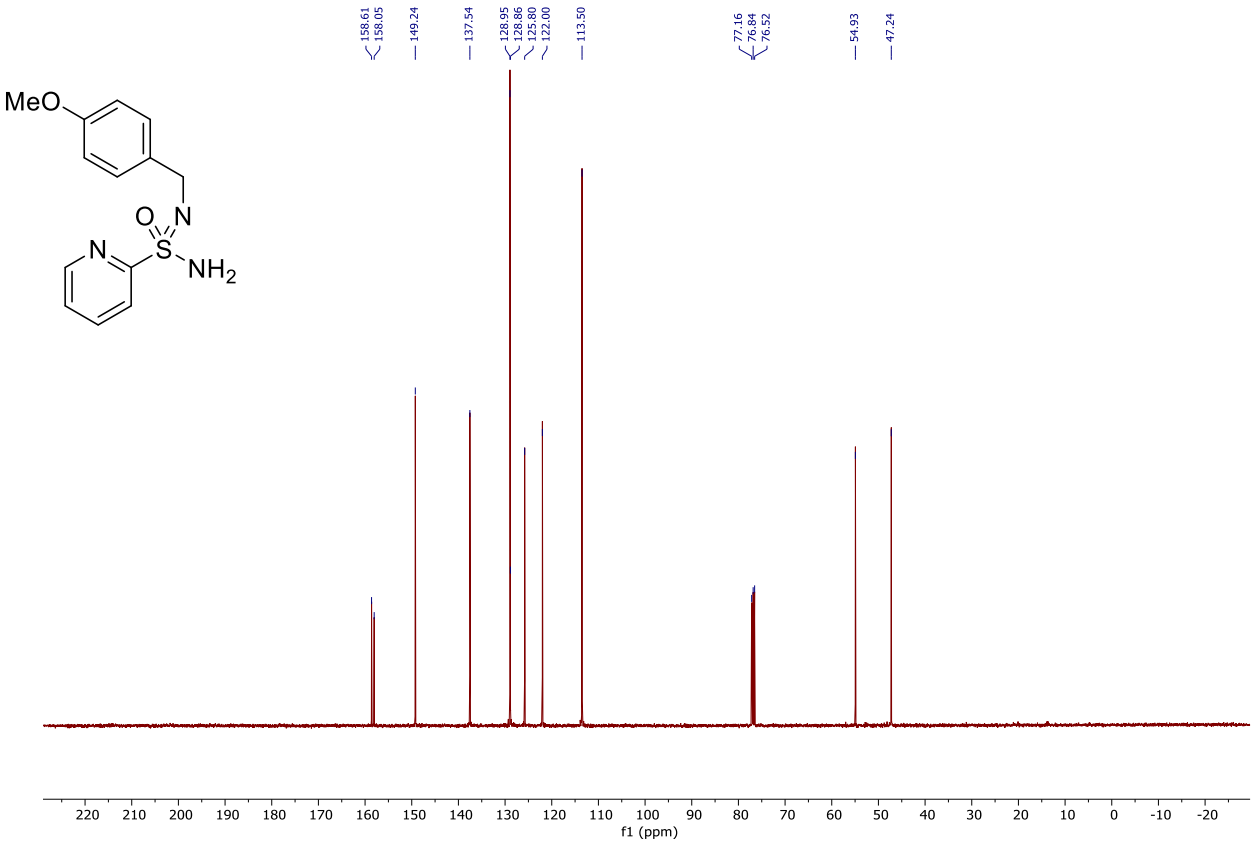
## *N'*-(4-methoxybenzyl)-1-methyl-1*H*-indole-5-sulfonimidamide (123j)



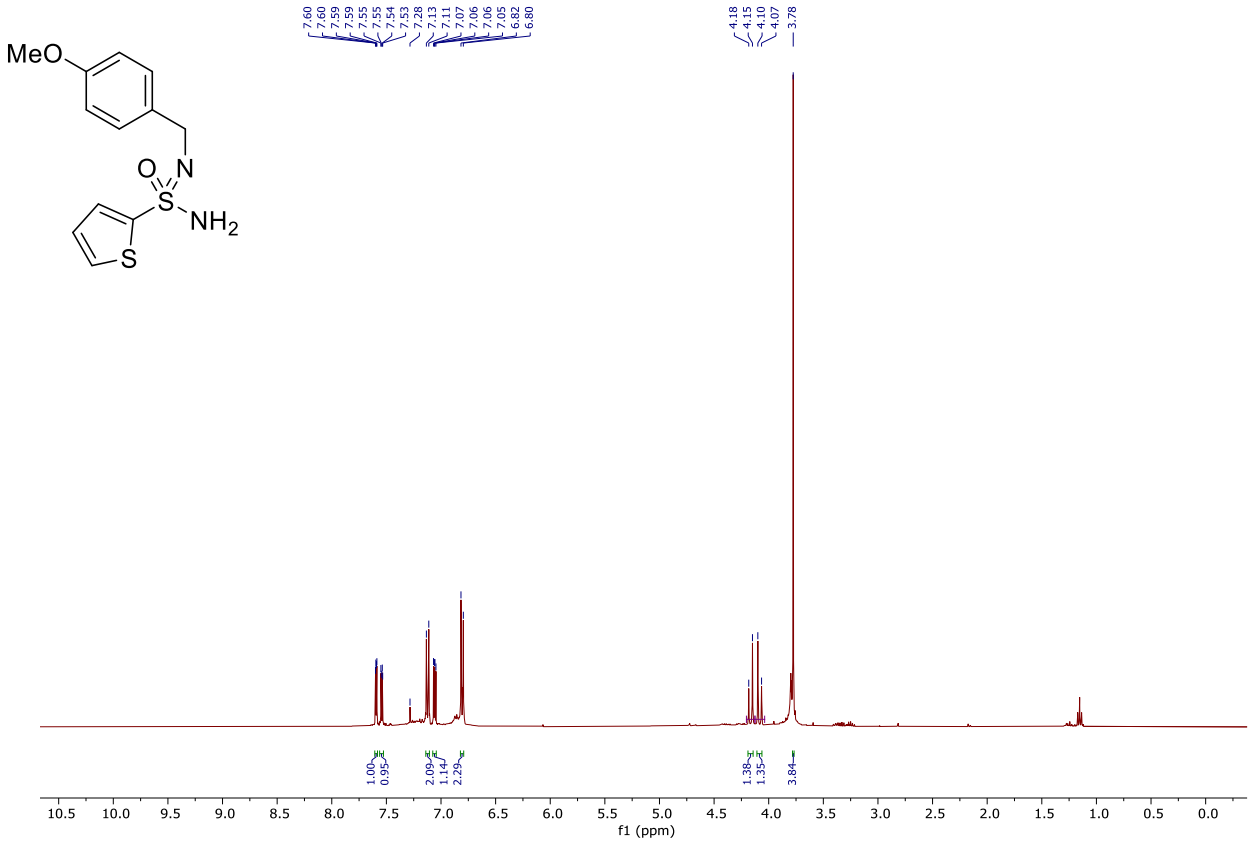



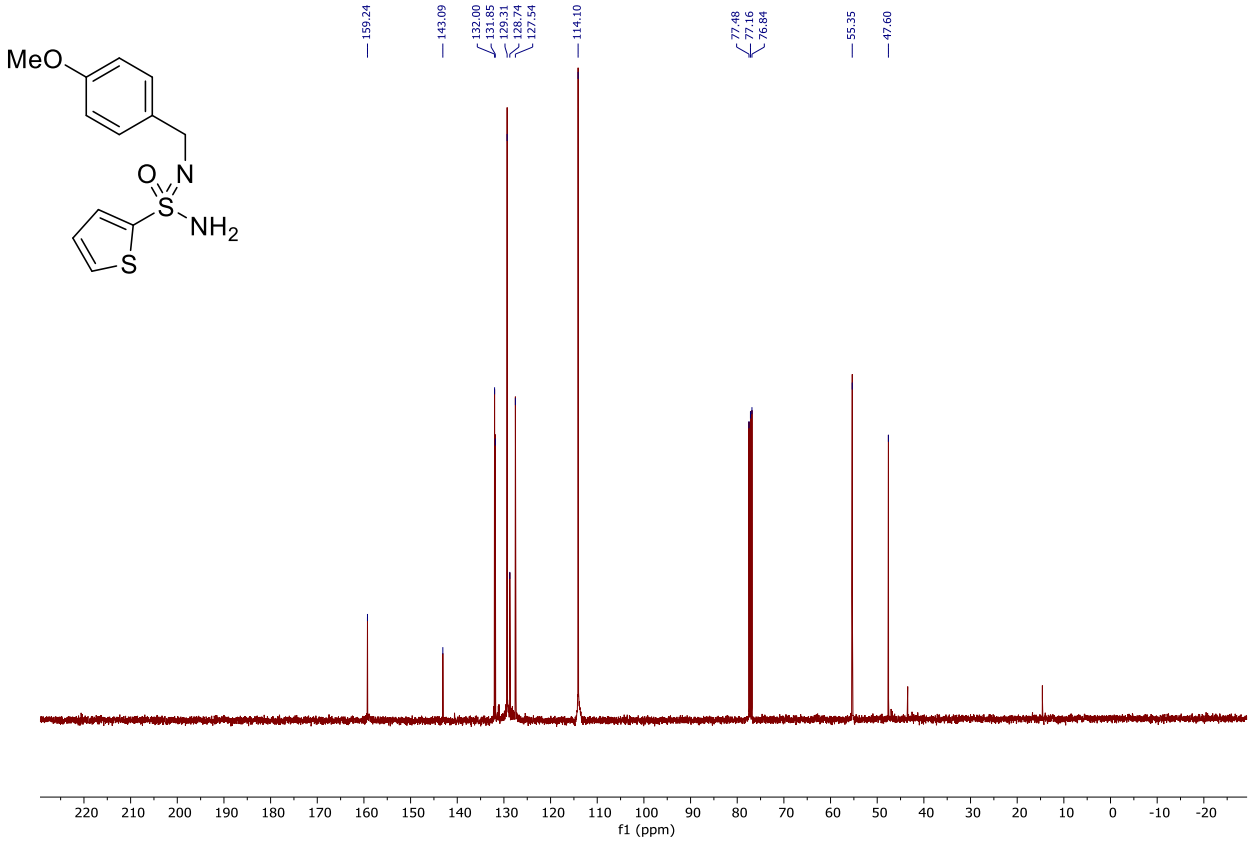
## *N*'-(4-methoxybenzyl)pyridine-2-sulfonimidamide (123k)



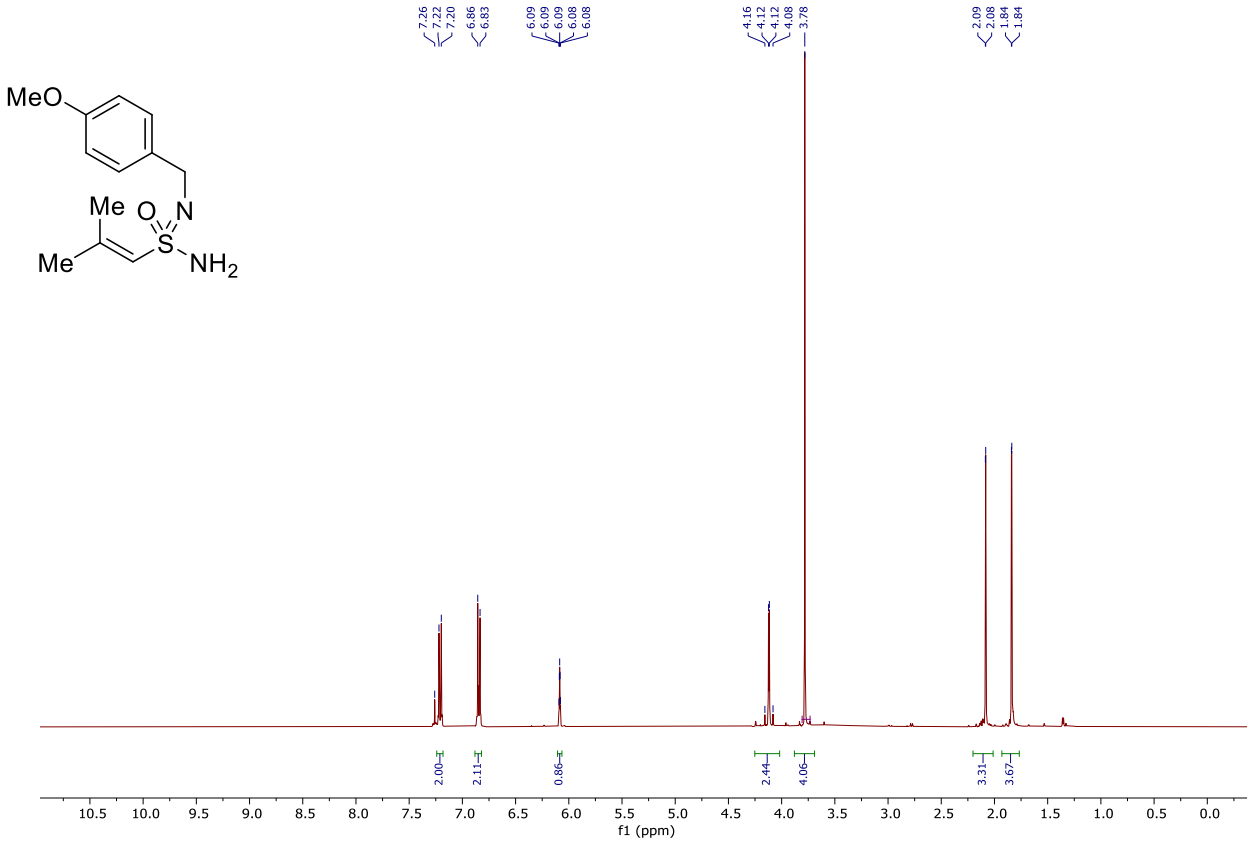



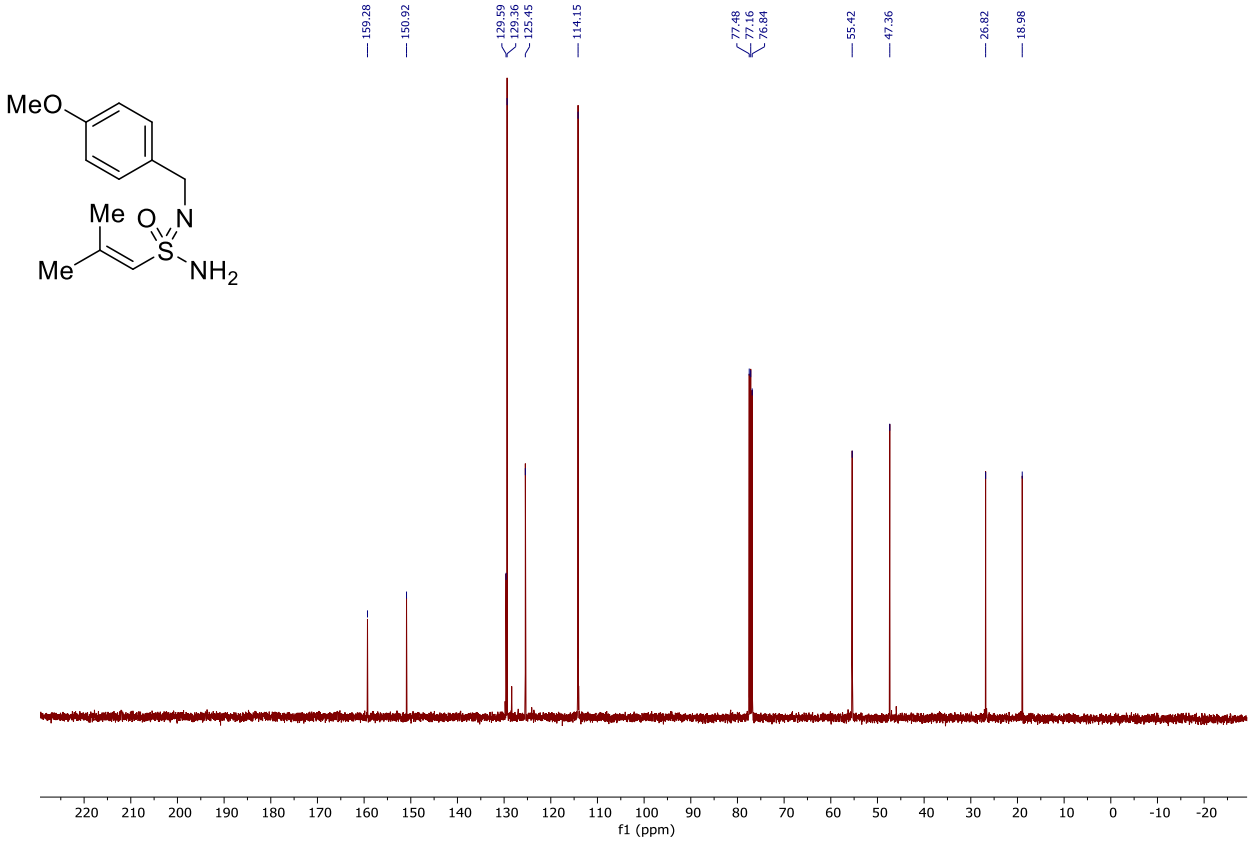
## *N*'-(4-methoxybenzyl)thiophene-2-sulfonimidamide (123l)



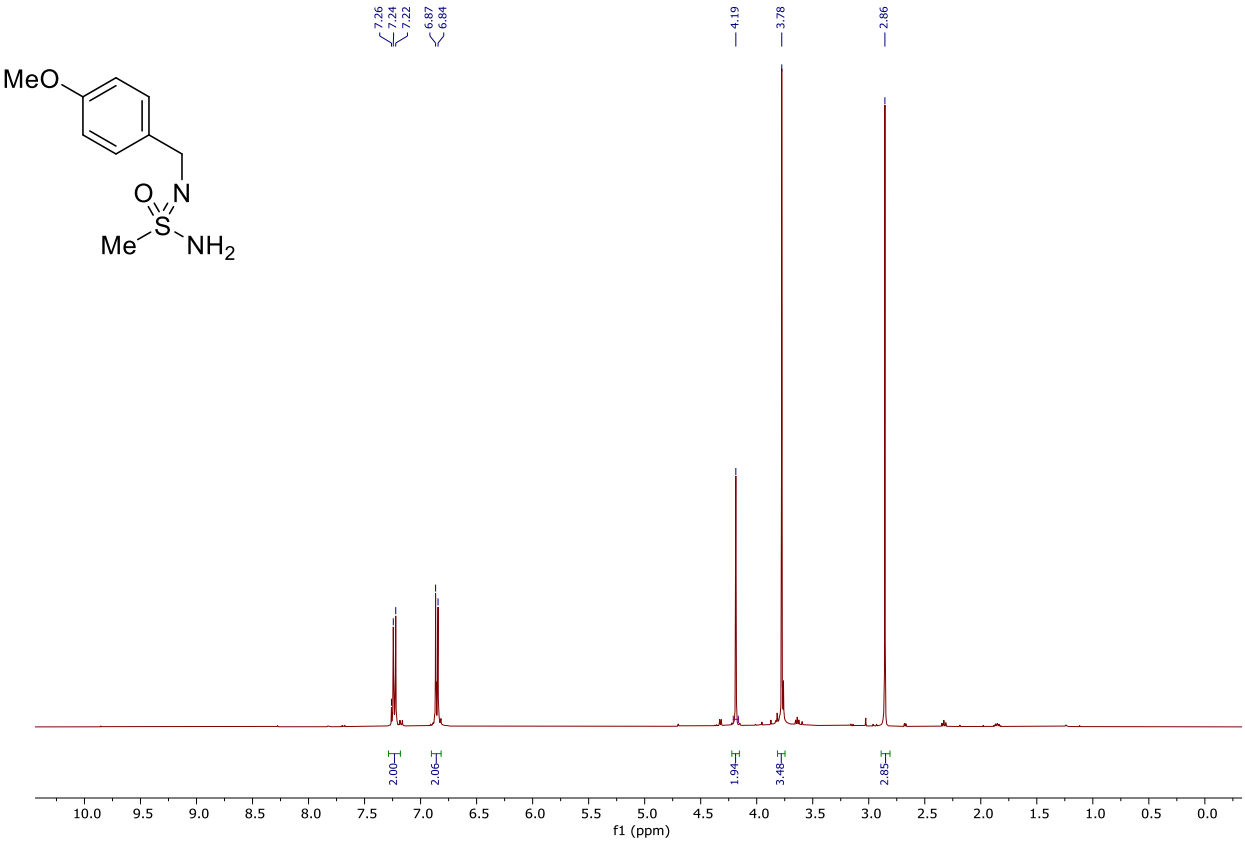



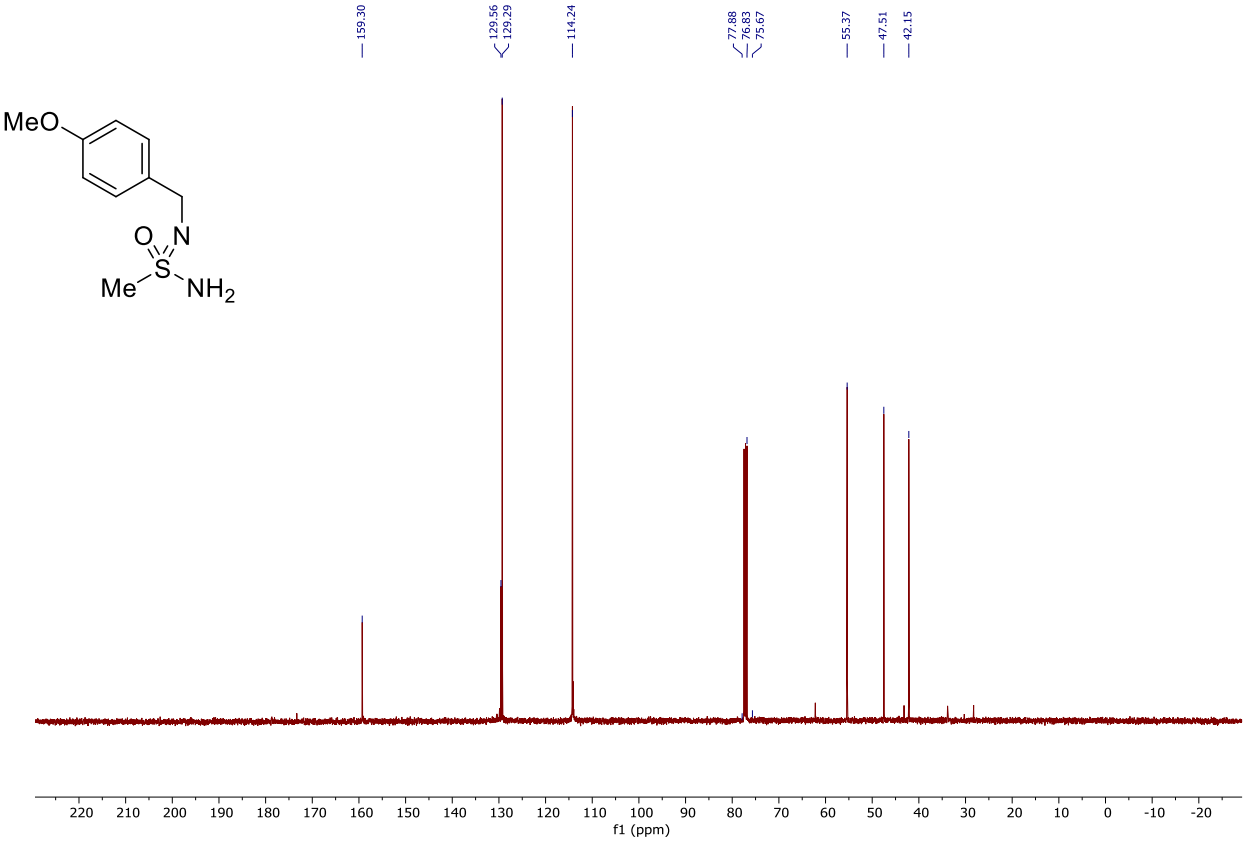
## *N*'-(4-methoxybenzyl)-2-methylprop-1-ene-1-sulfonimidamide (123m)



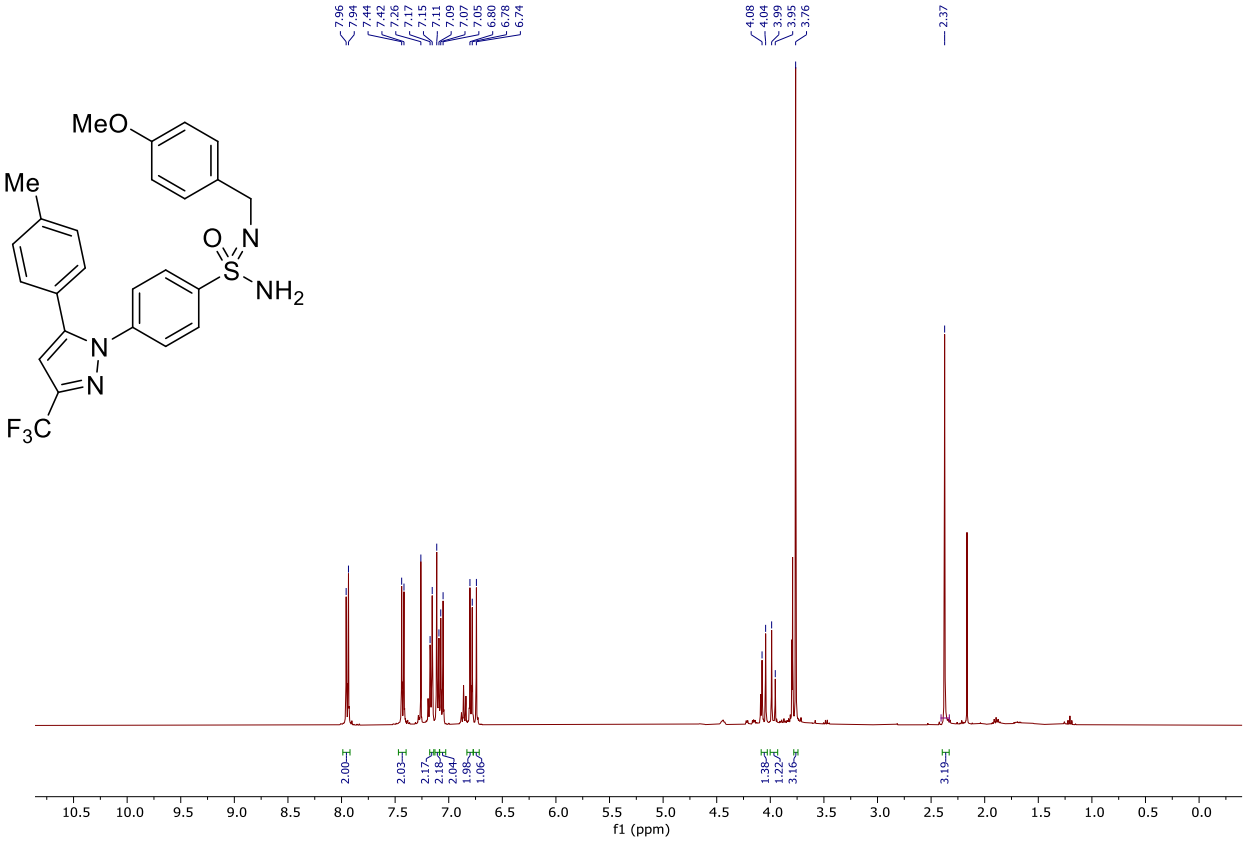



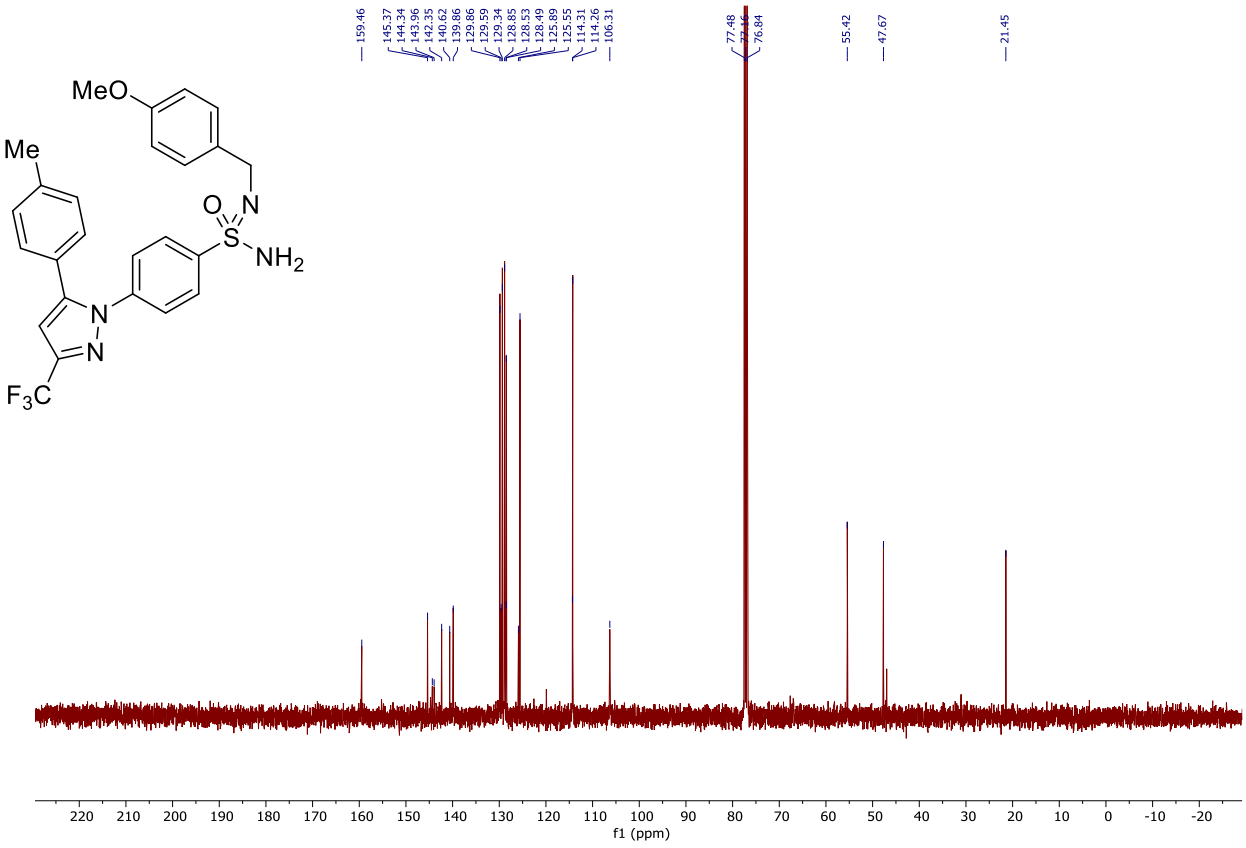
## *N'*-(4-methoxybenzyl)methanesulfonimidamide (123n)

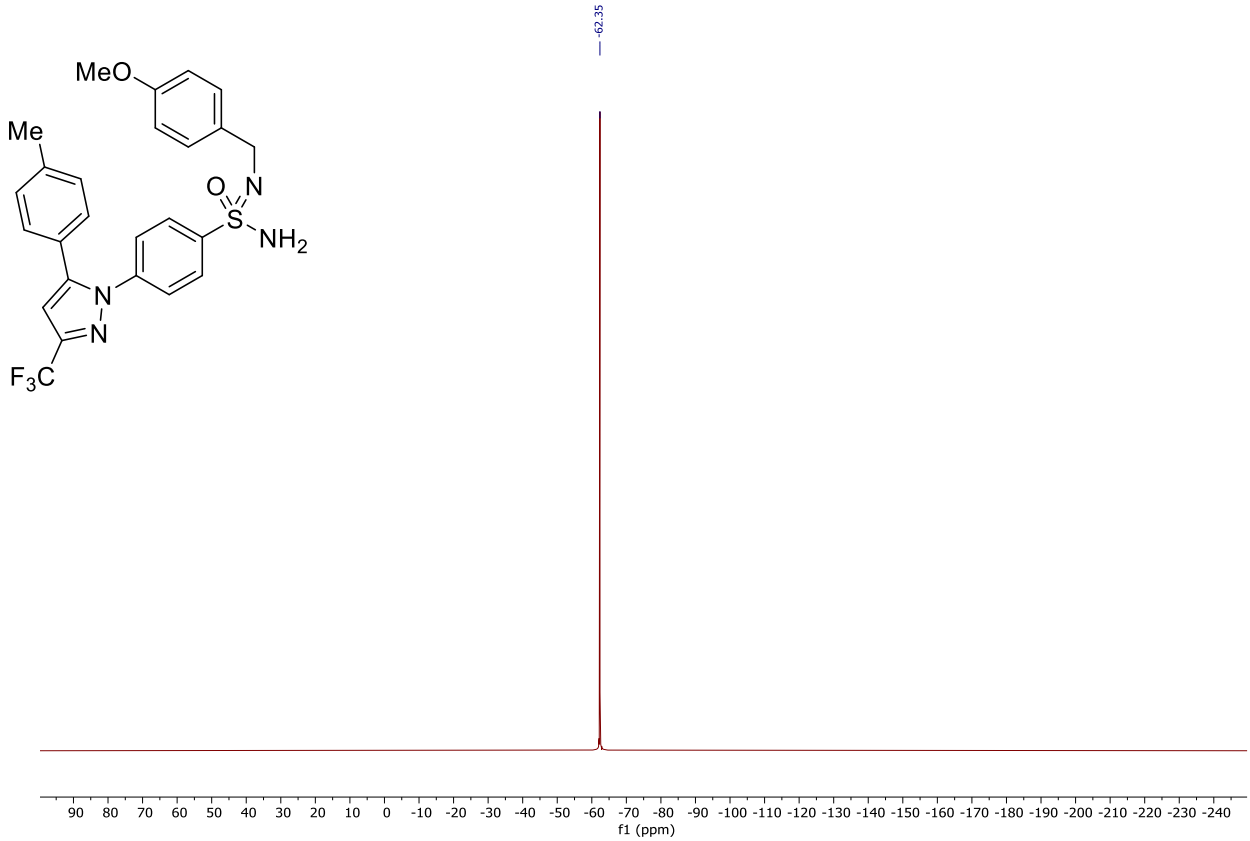


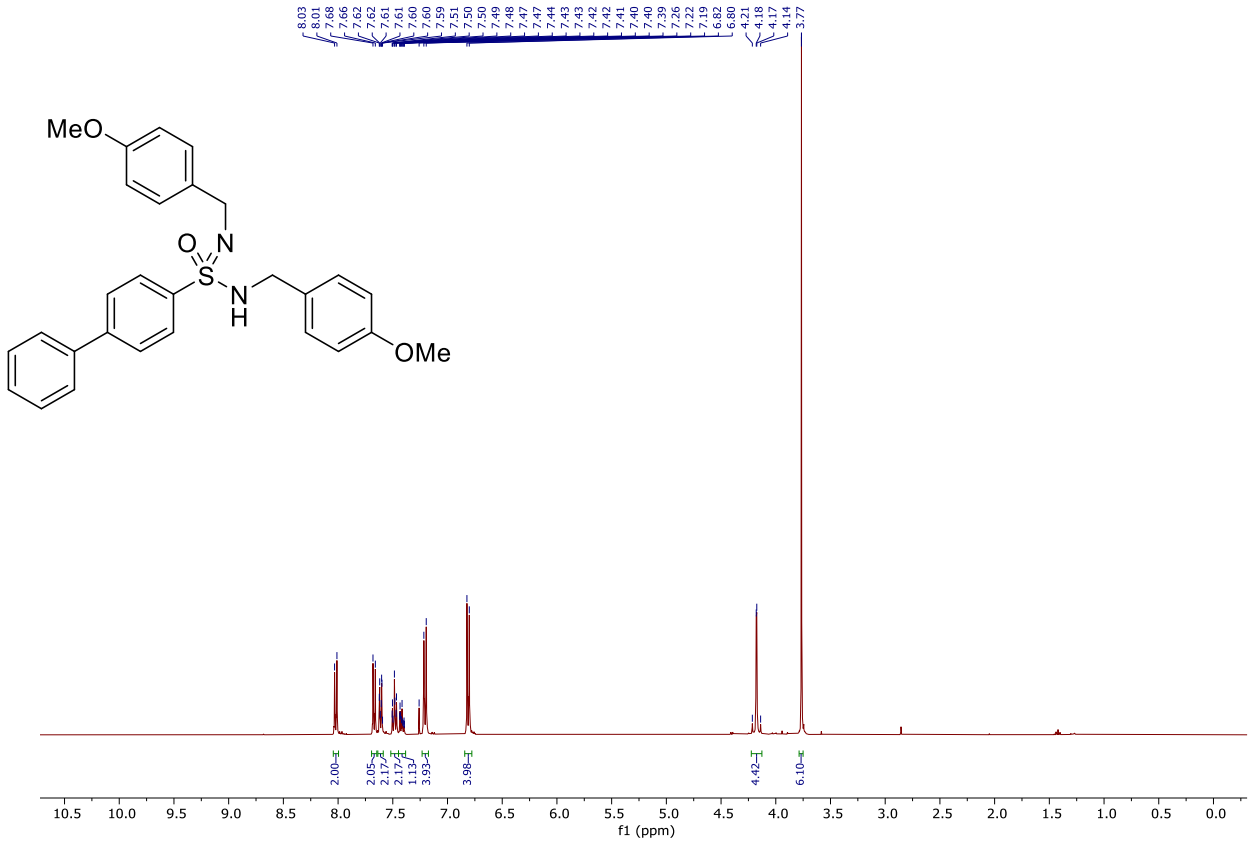
**N'-(4-methoxybenzyl)-4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonimidamide (123o)**

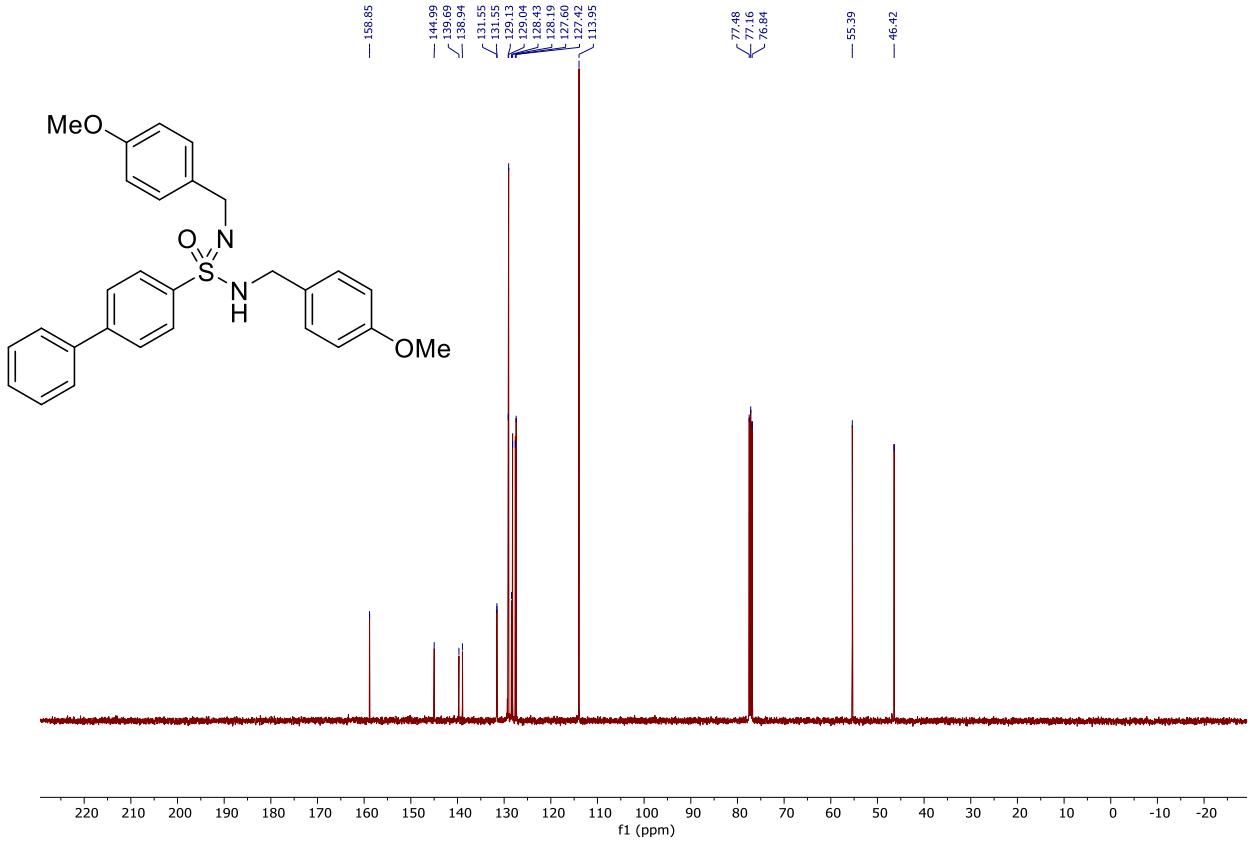


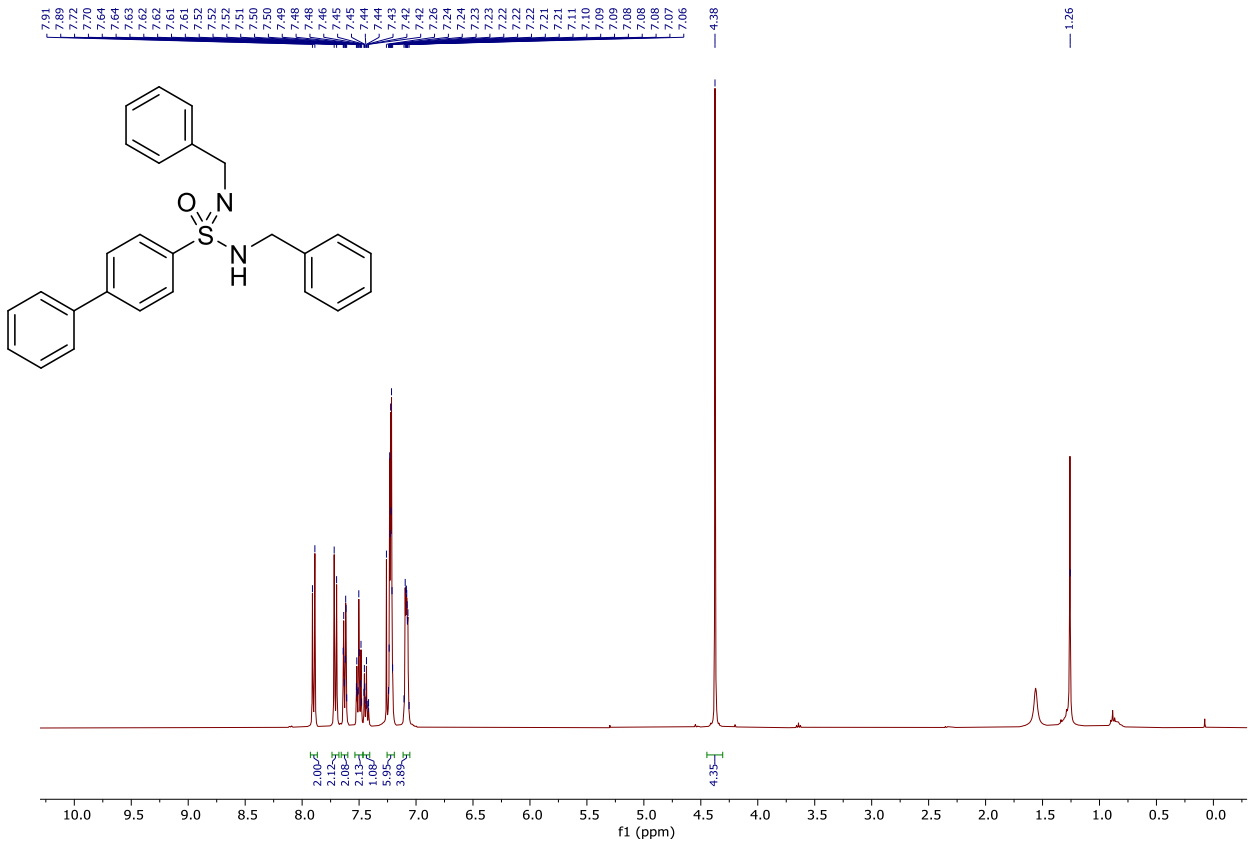

MeO
Me
O
N
S
NH2
N
N
F3C
-62.35
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

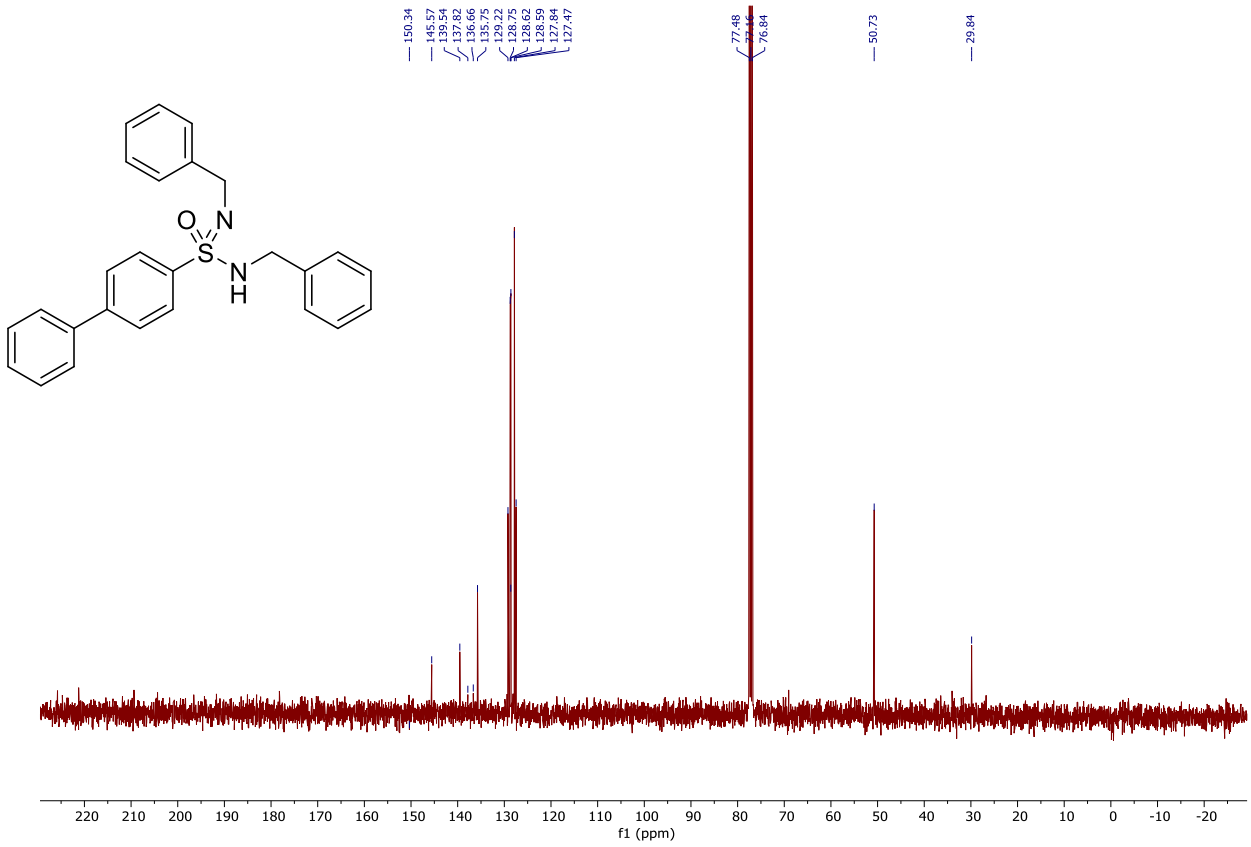
**N,N'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74a)**



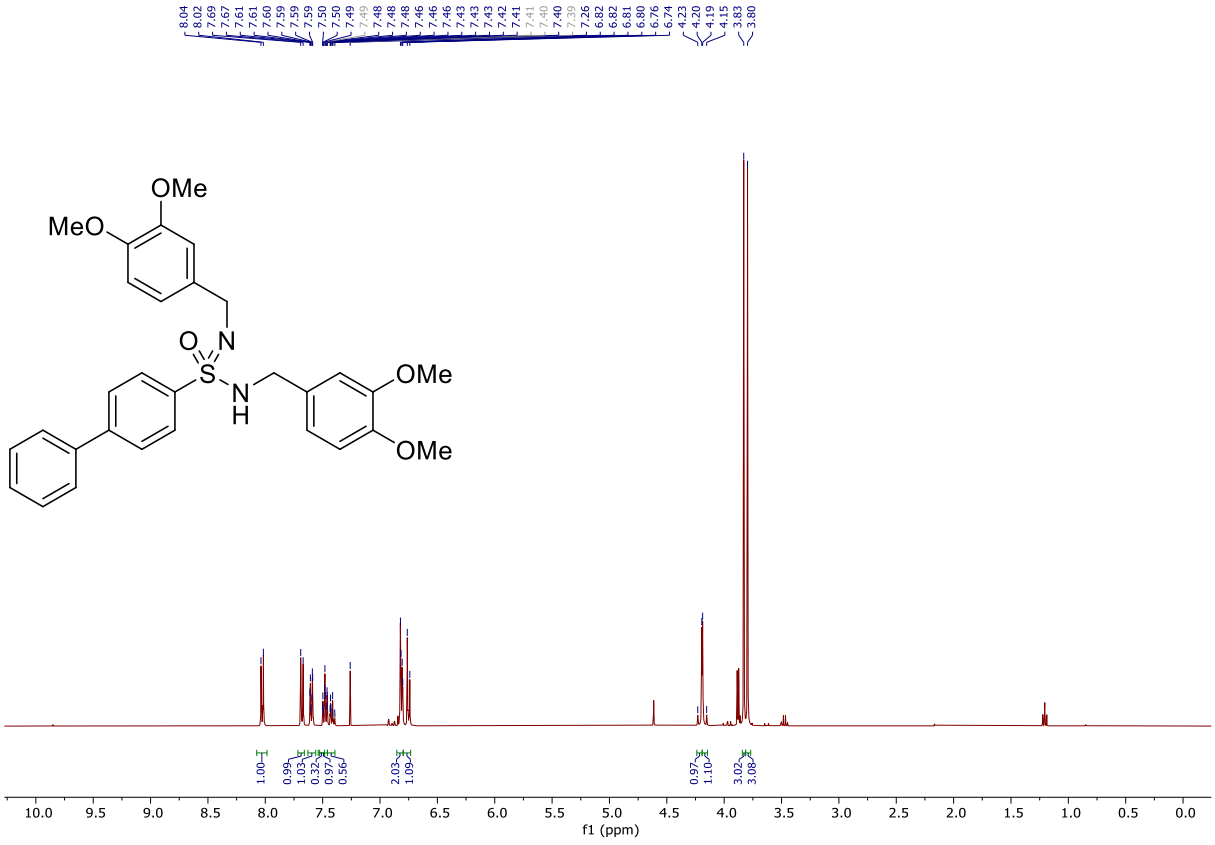



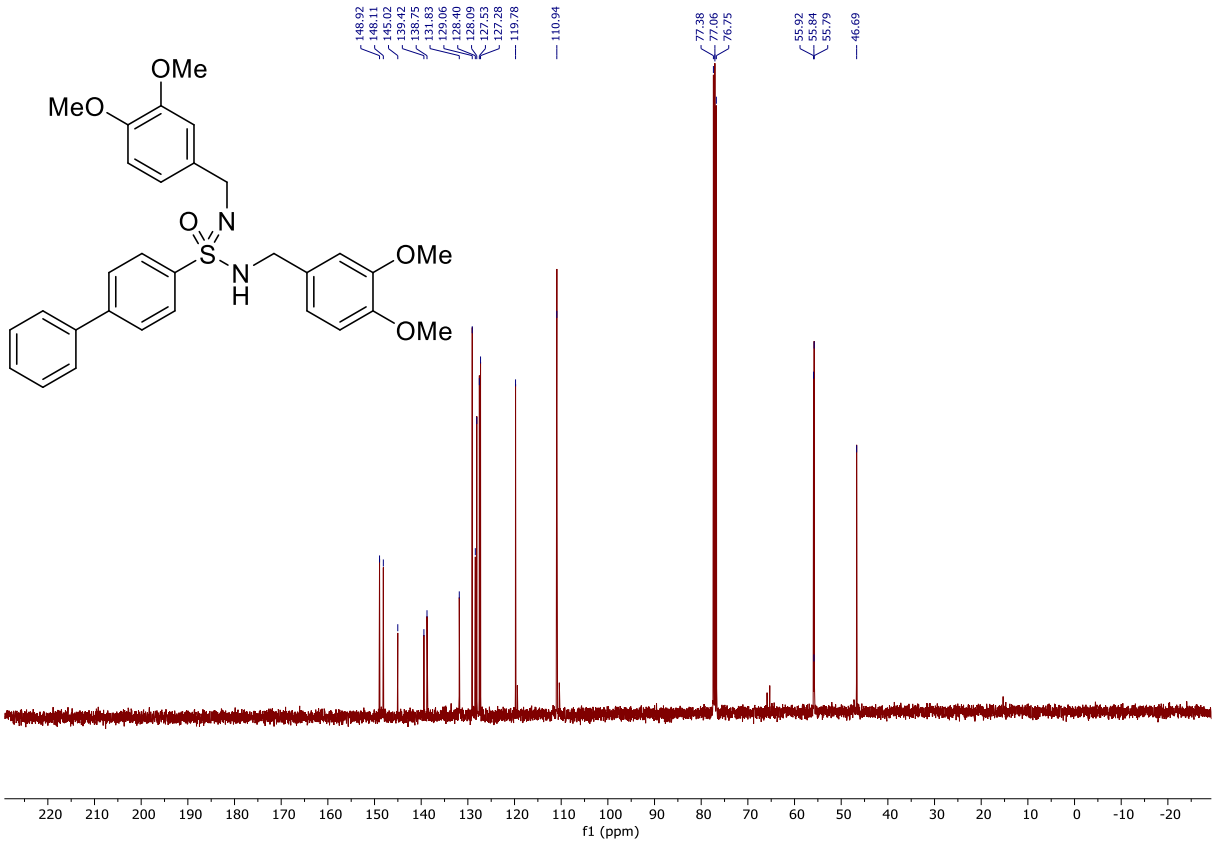
## *N,N'*-dibenzyl-[1,1'-biphenyl]-4-sulfonimidamide (79a)



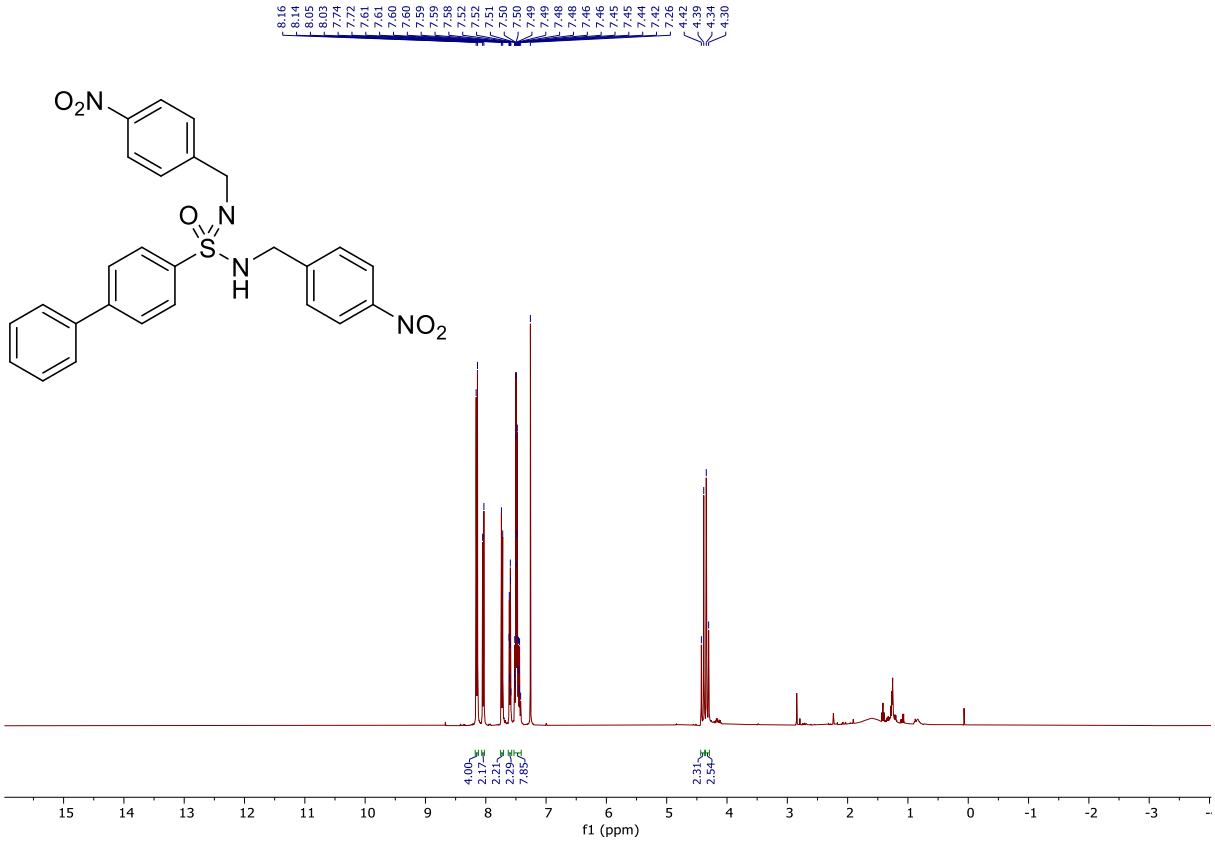



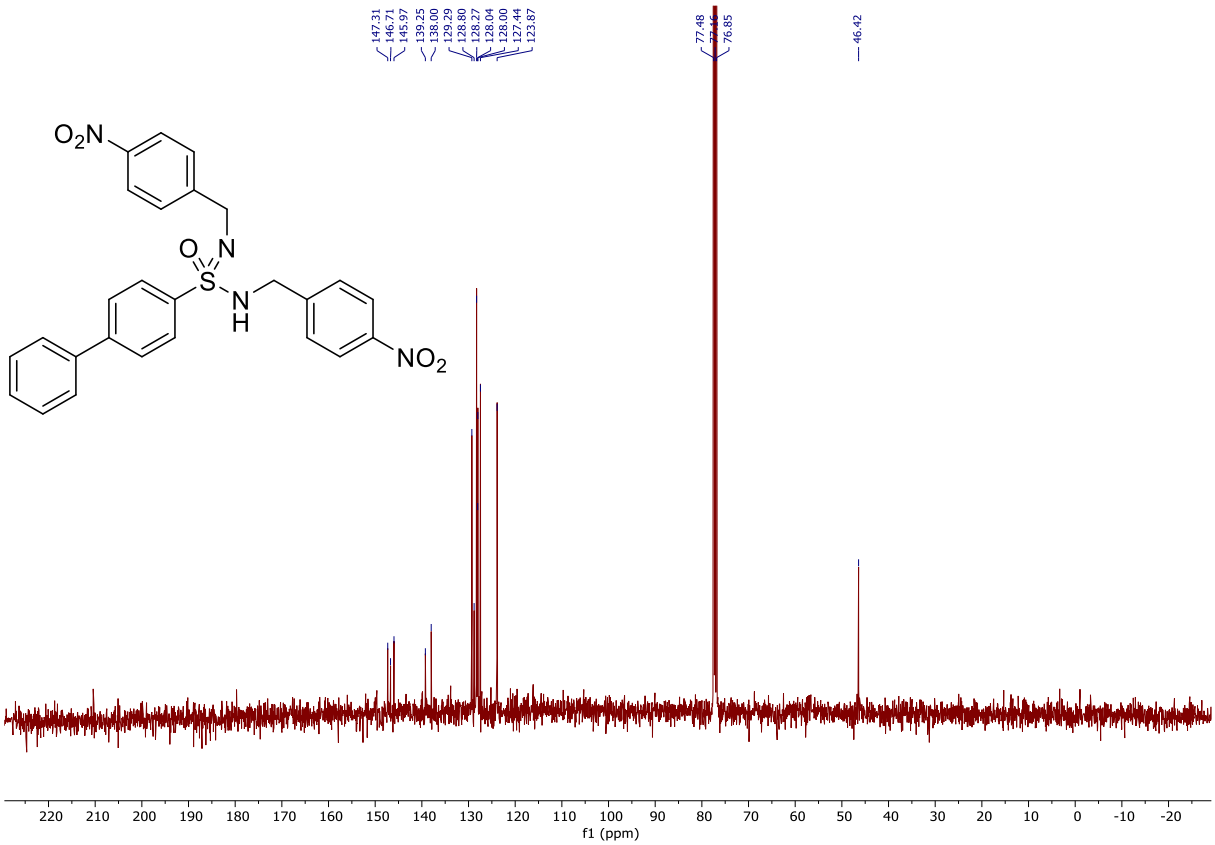
## *N,N'*-bis(3,4-dimethoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (79b)



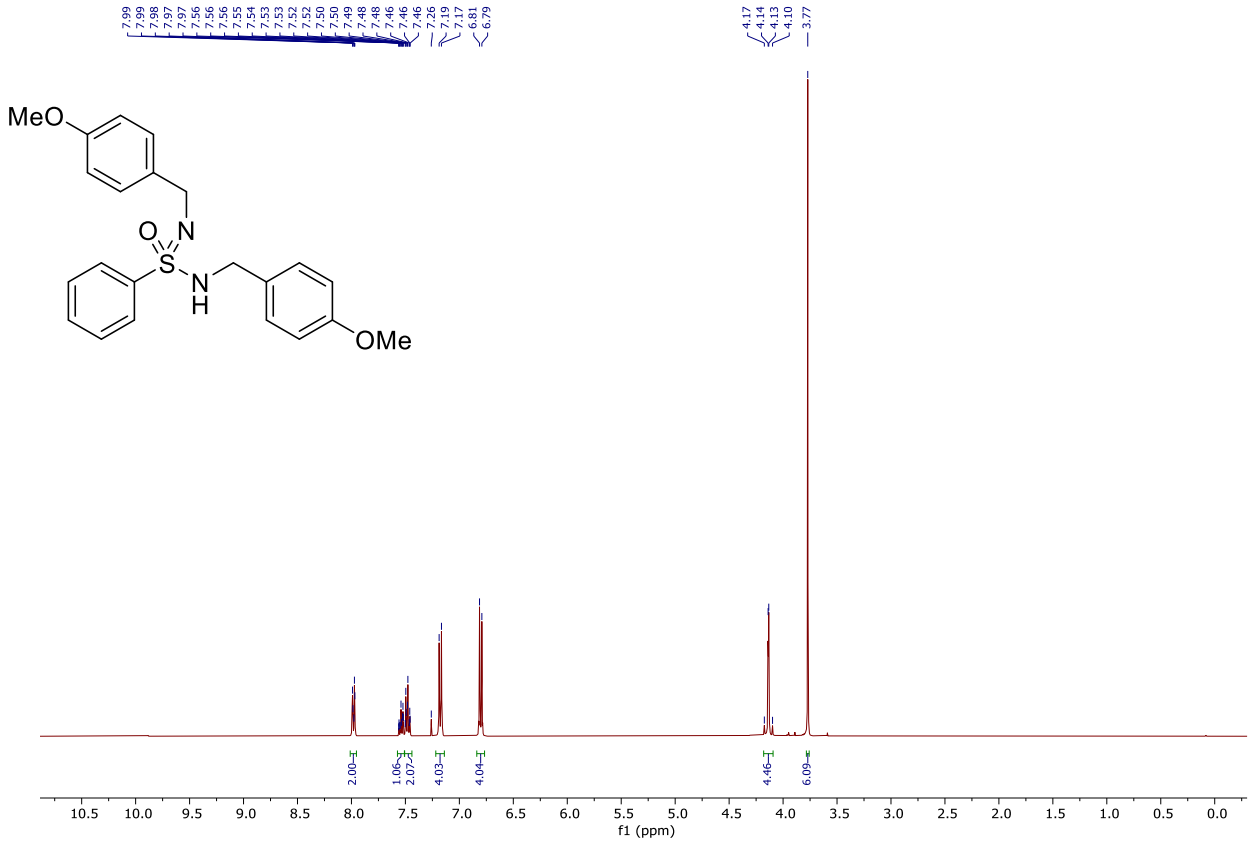



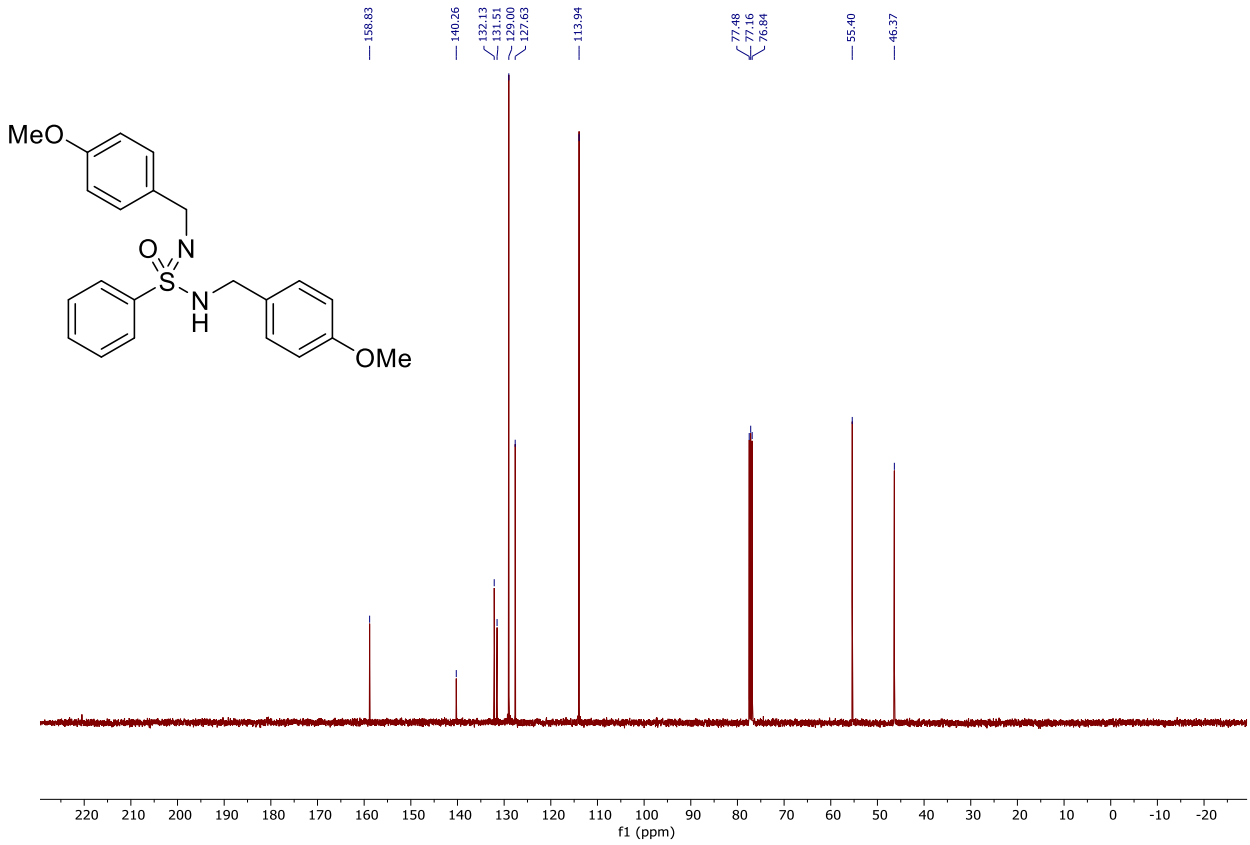
**N,N'-bis(4-nitrobenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (79c)**



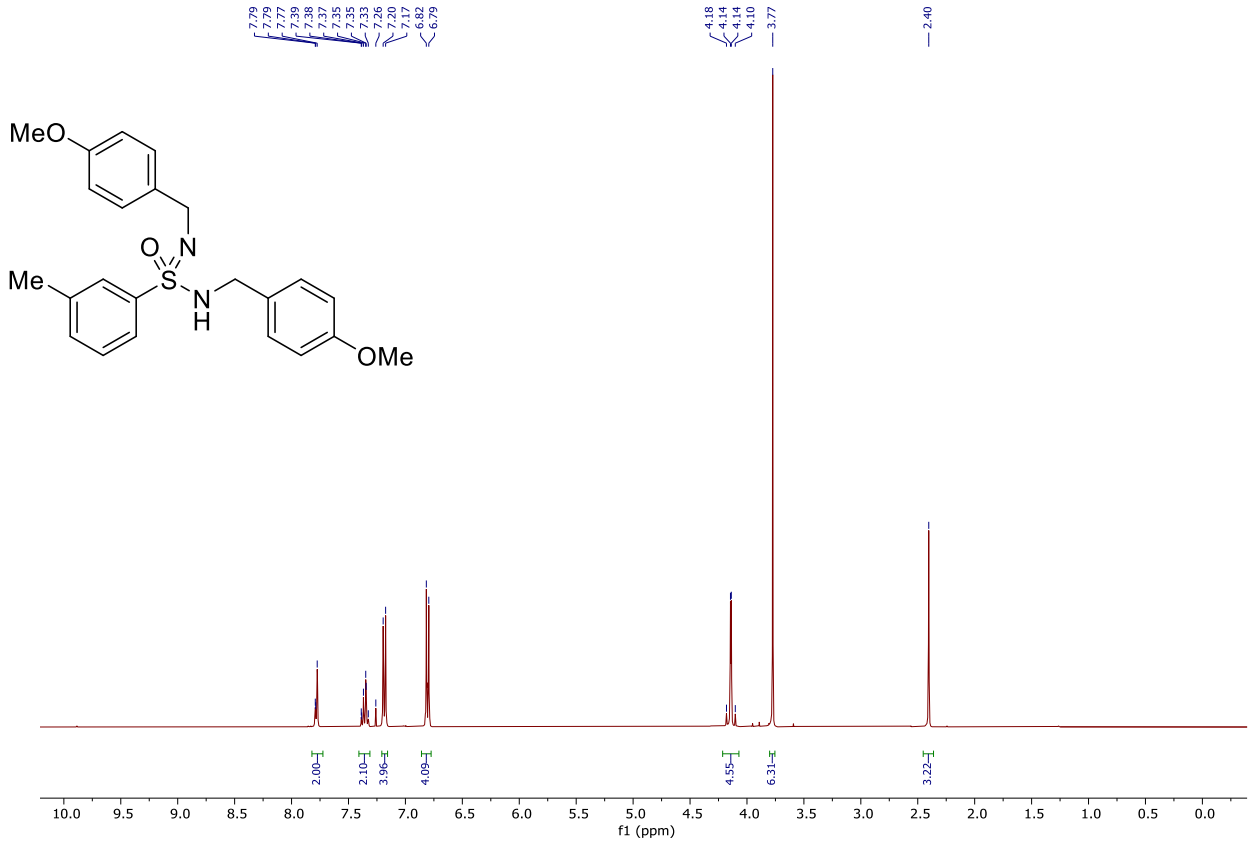



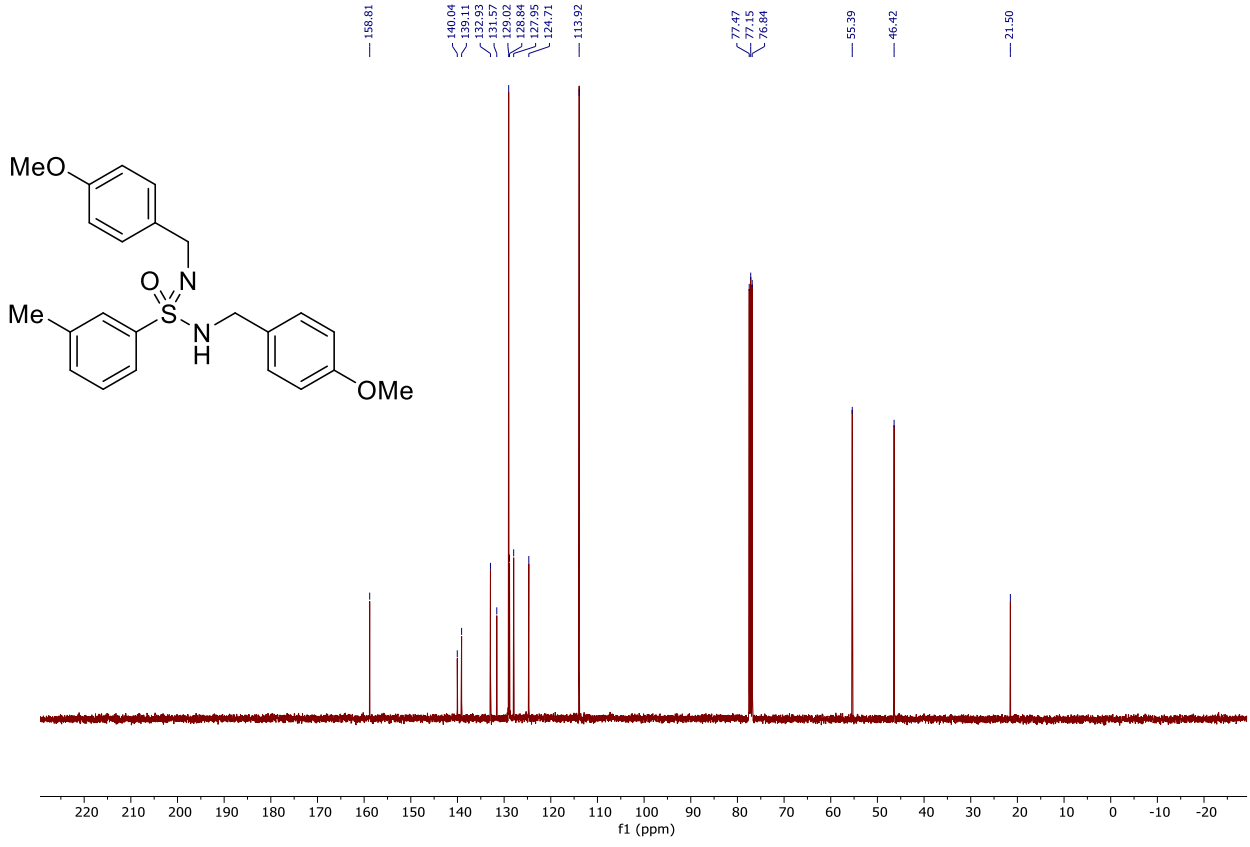
## *N,N'*-bis(4-methoxybenzyl)benzenesulfonimidamide (73c)



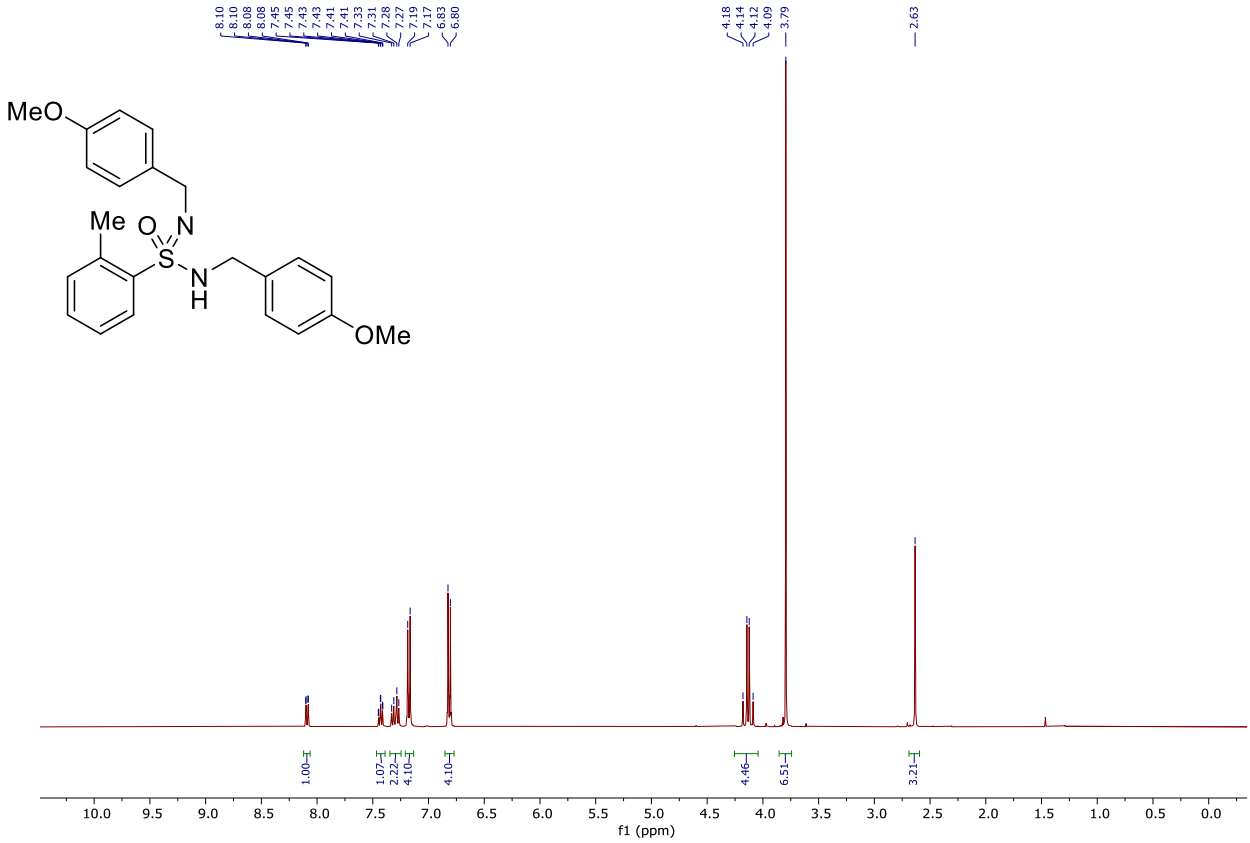



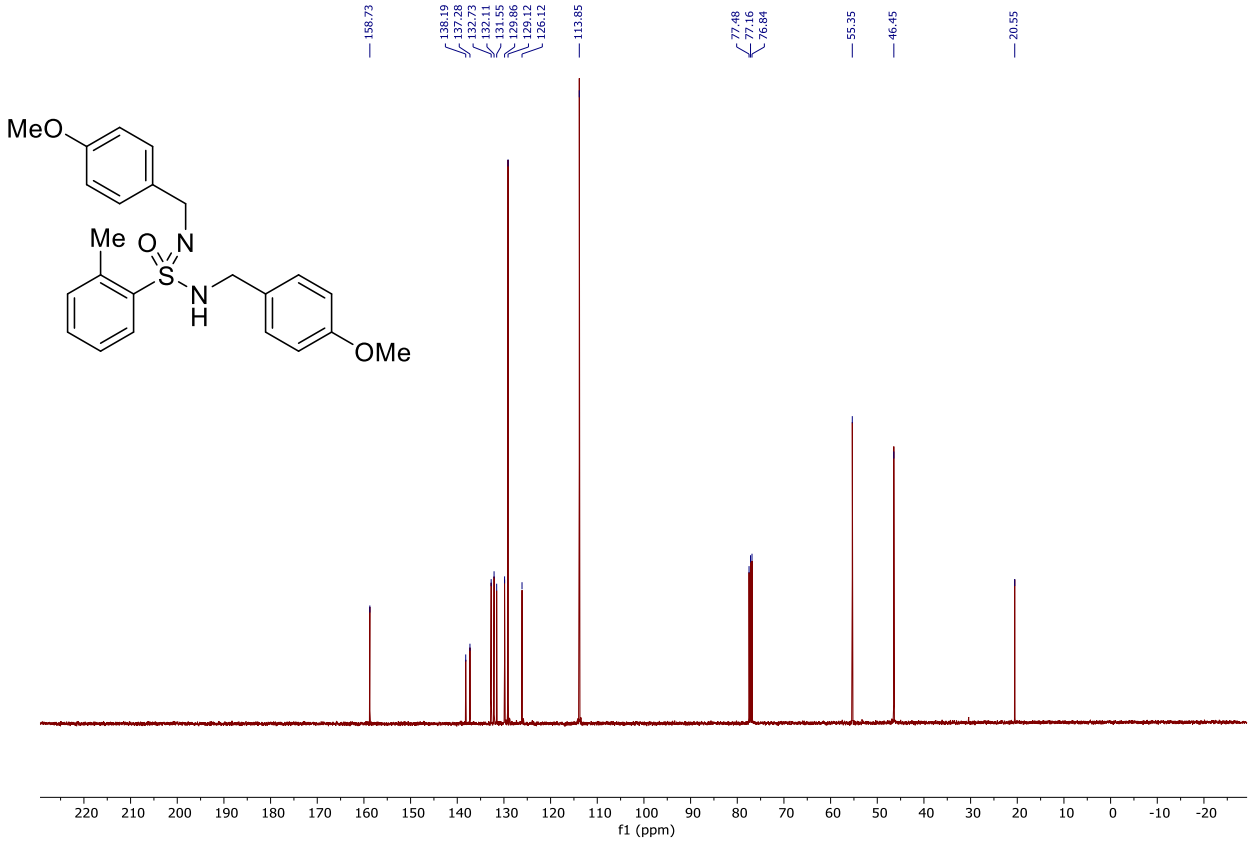
**N,N'-bis(4-methoxybenzyl)-3-methylbenzenesulfonimidamide (73d)**



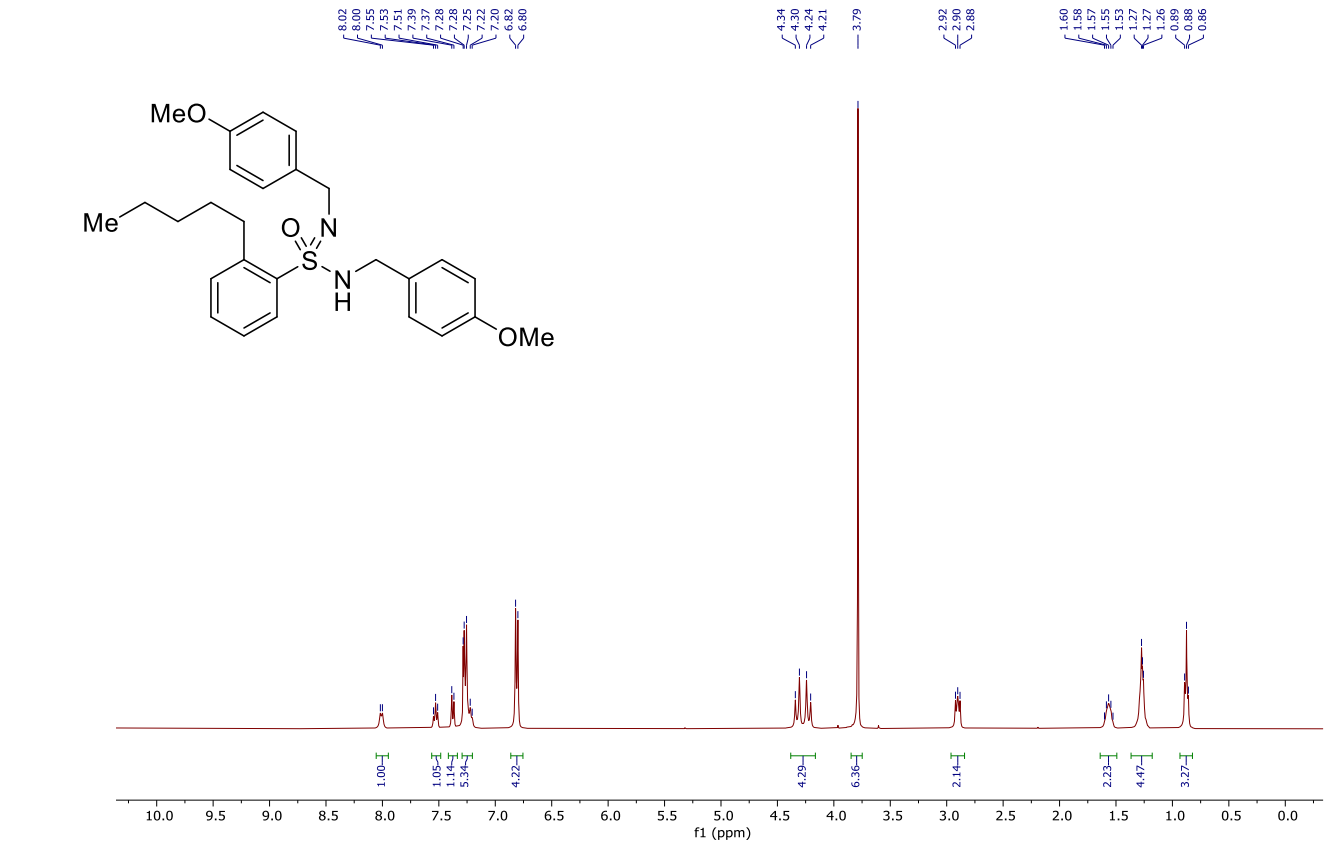



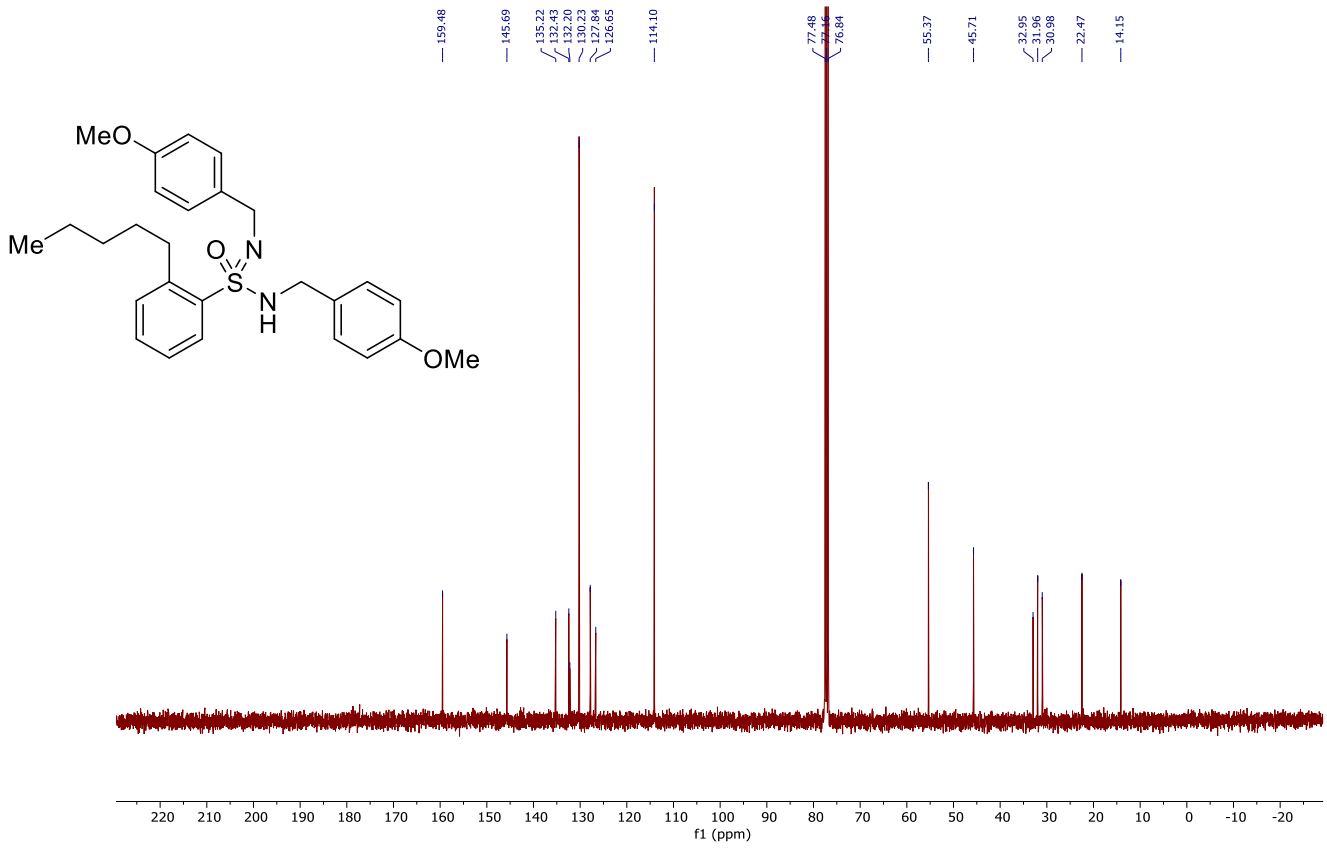
## *N,N'*-bis(4-methoxybenzyl)-2-methylbenzenesulfonimidamide (73e)



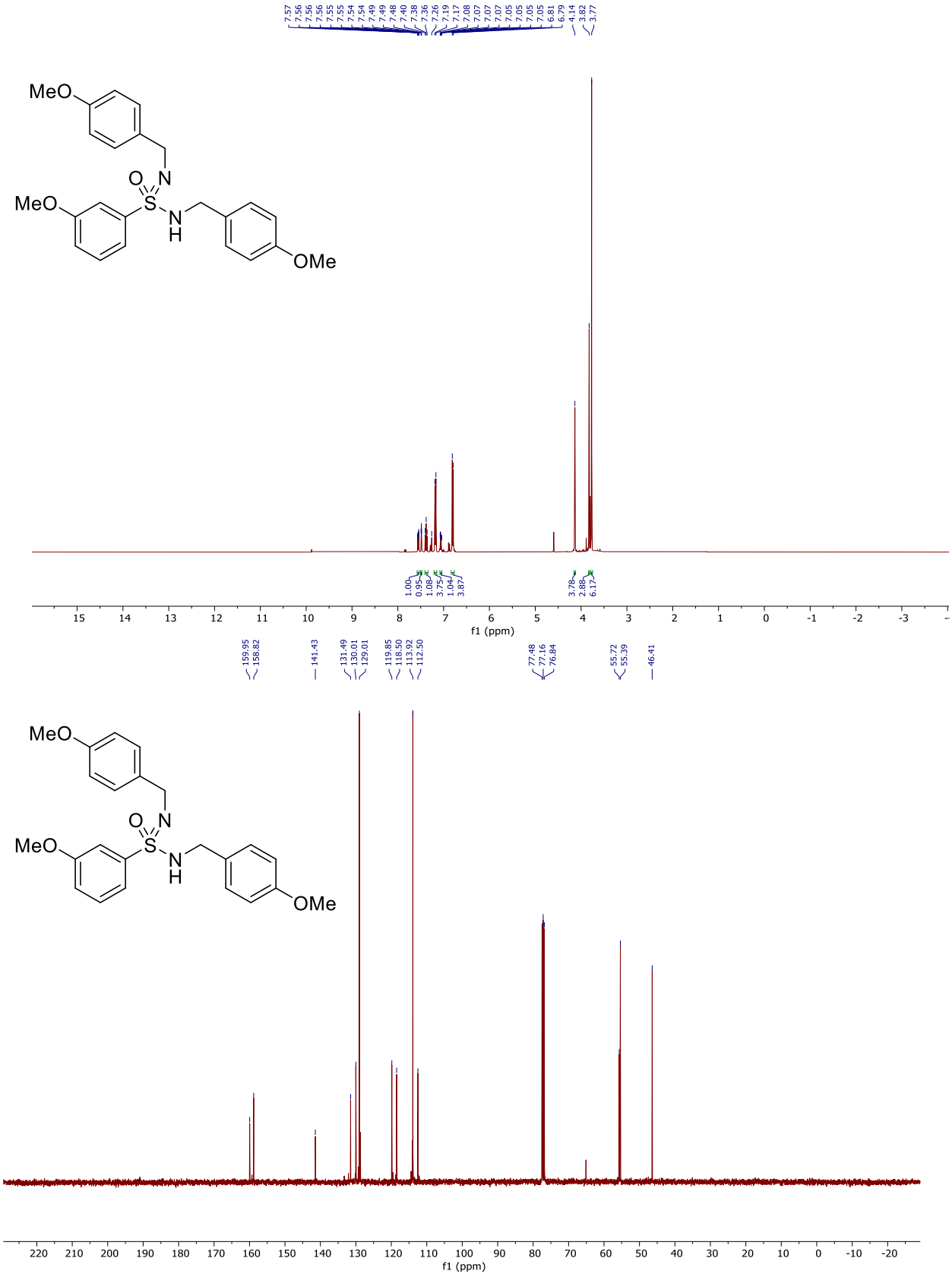



## *N*,N'-bis(4-methoxybenzyl)-2-pentylbenzenesulfonimidamide (73f)

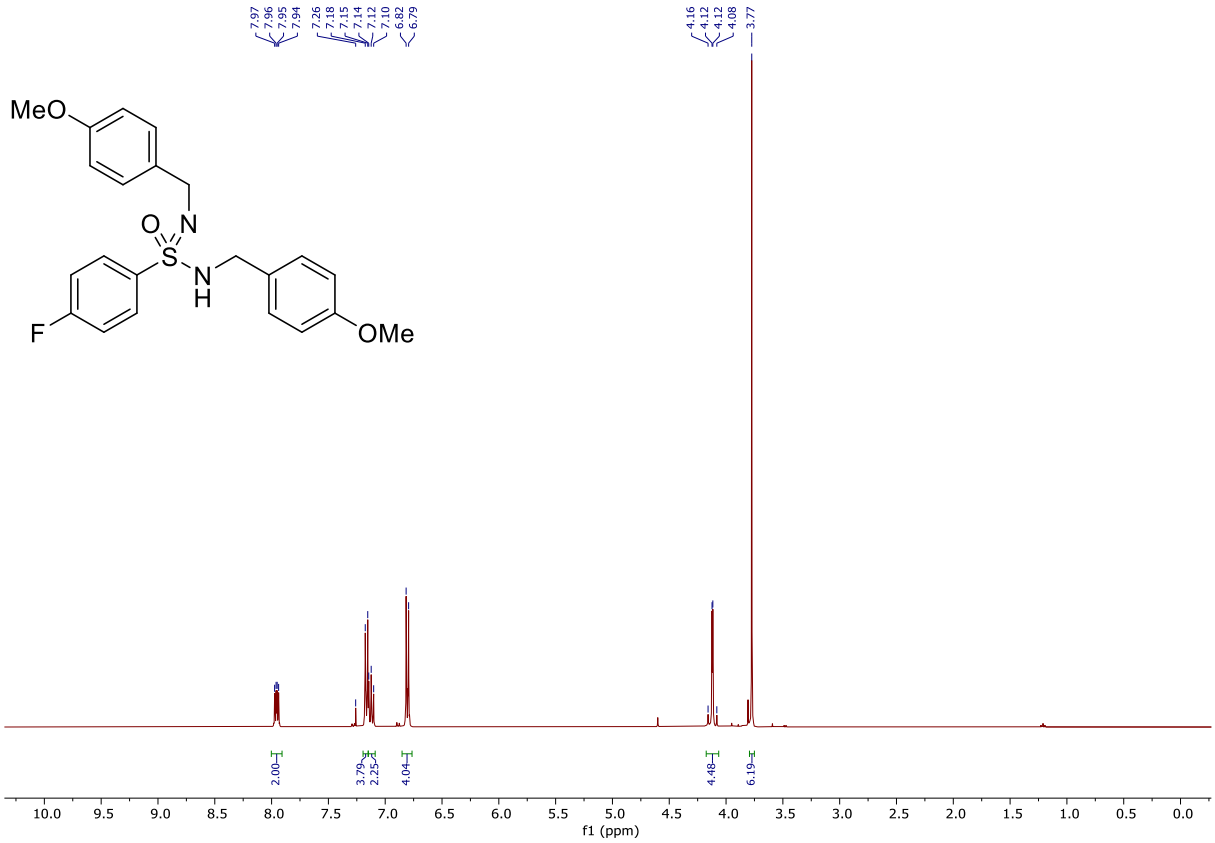


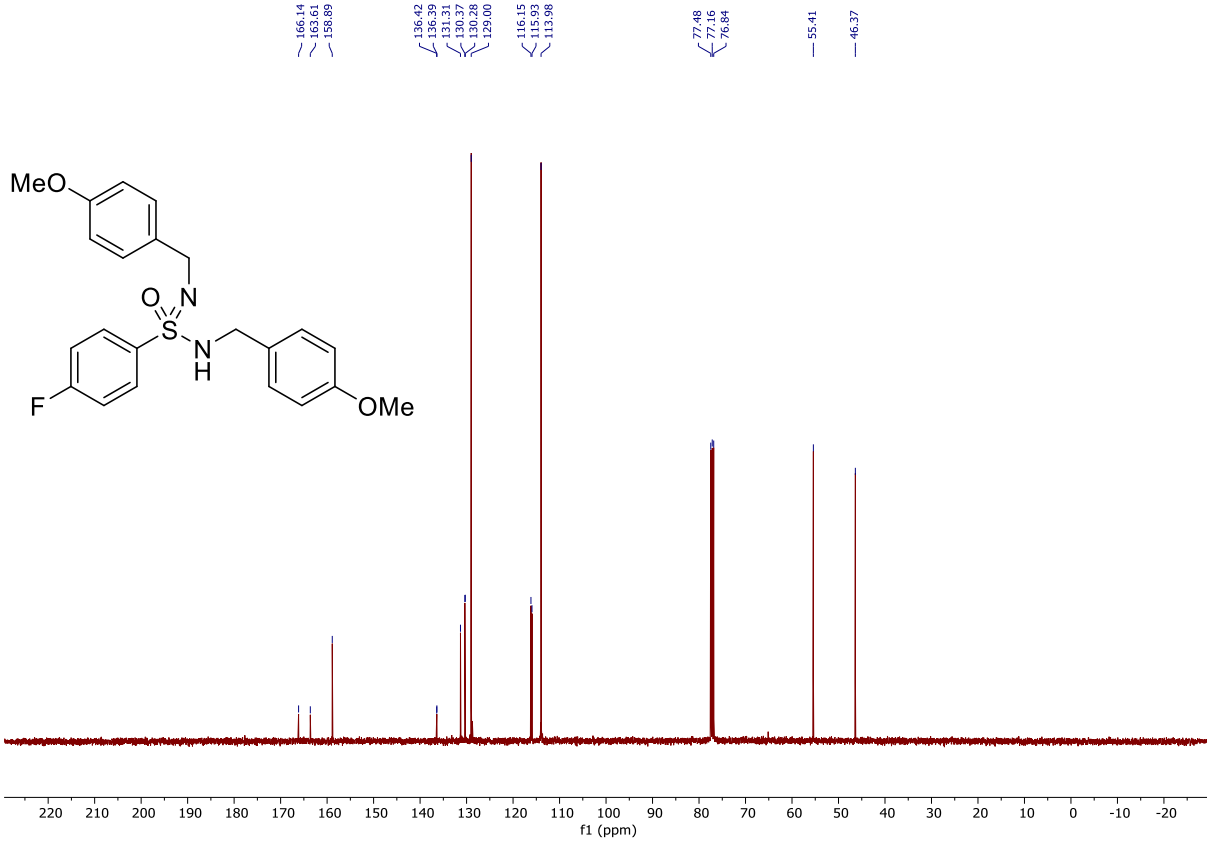



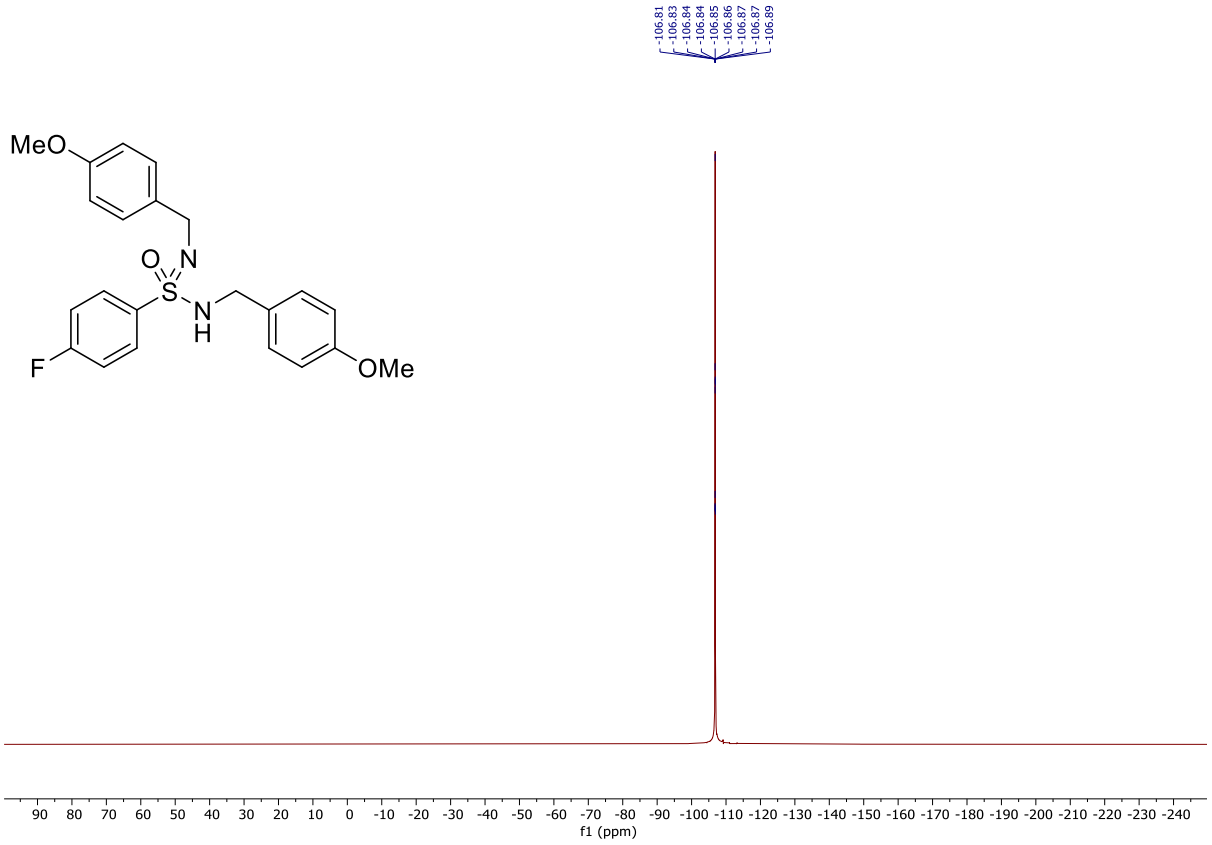
## 3-methoxy-*N*,*N*'-bis(4-methoxybenzyl)benzenesulfonimidamide (73g)



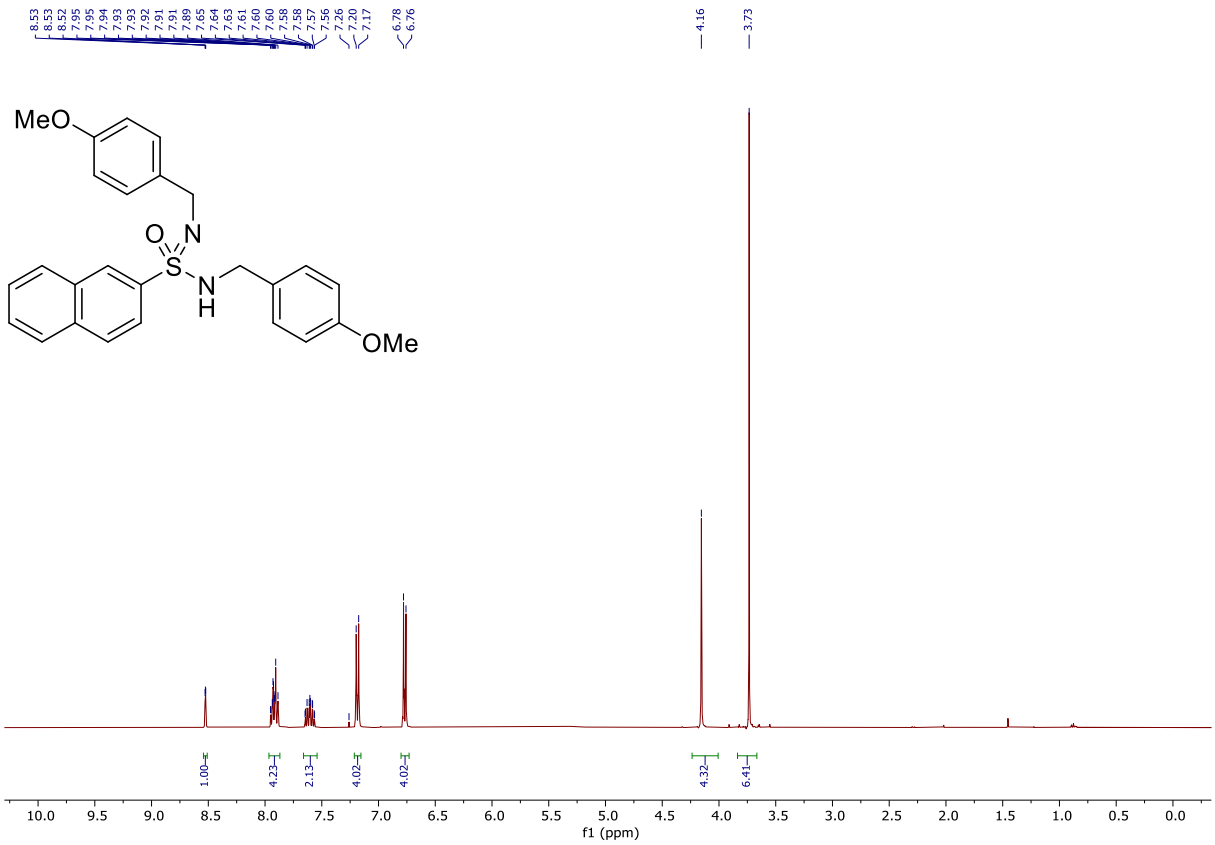
**4-fluoro-*N*,*N*'-bis(4-methoxybenzyl)benzenesulfonimidamide (73h)**

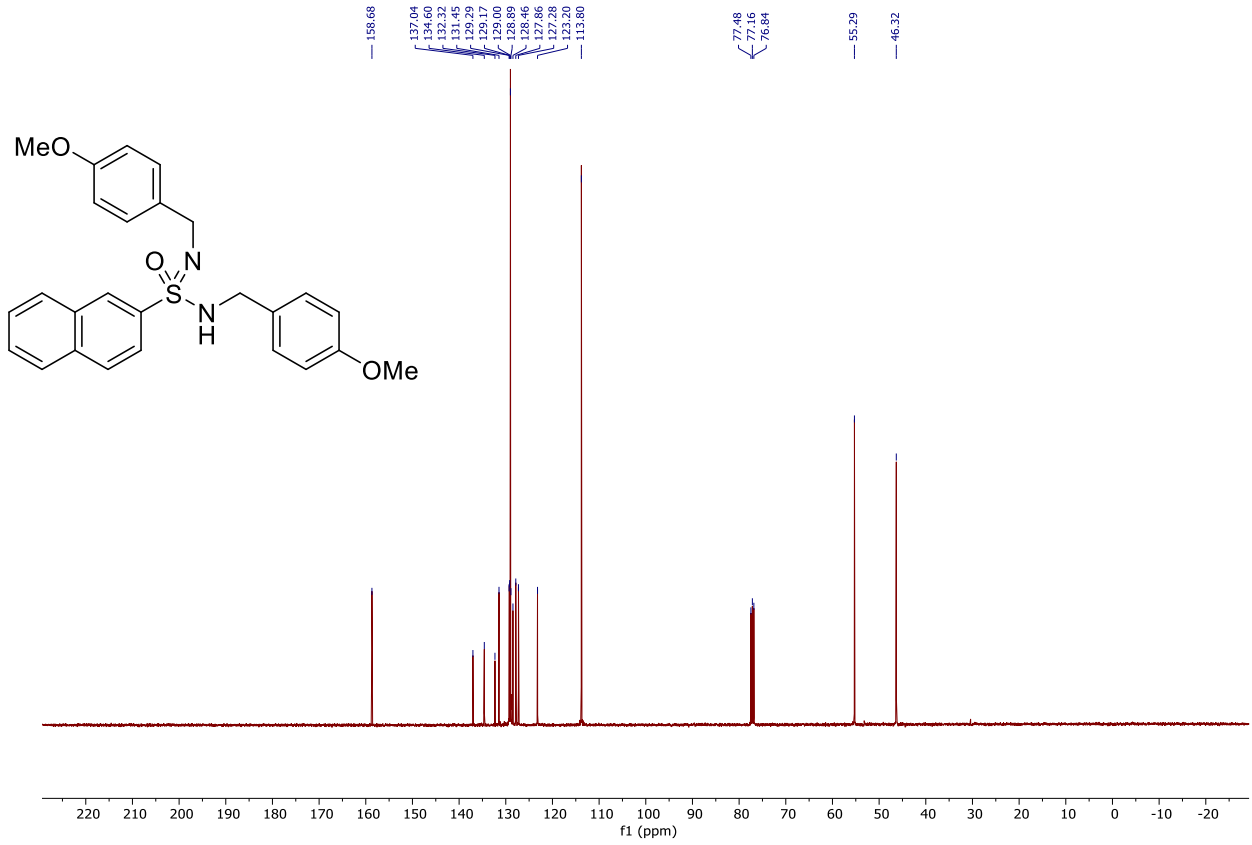


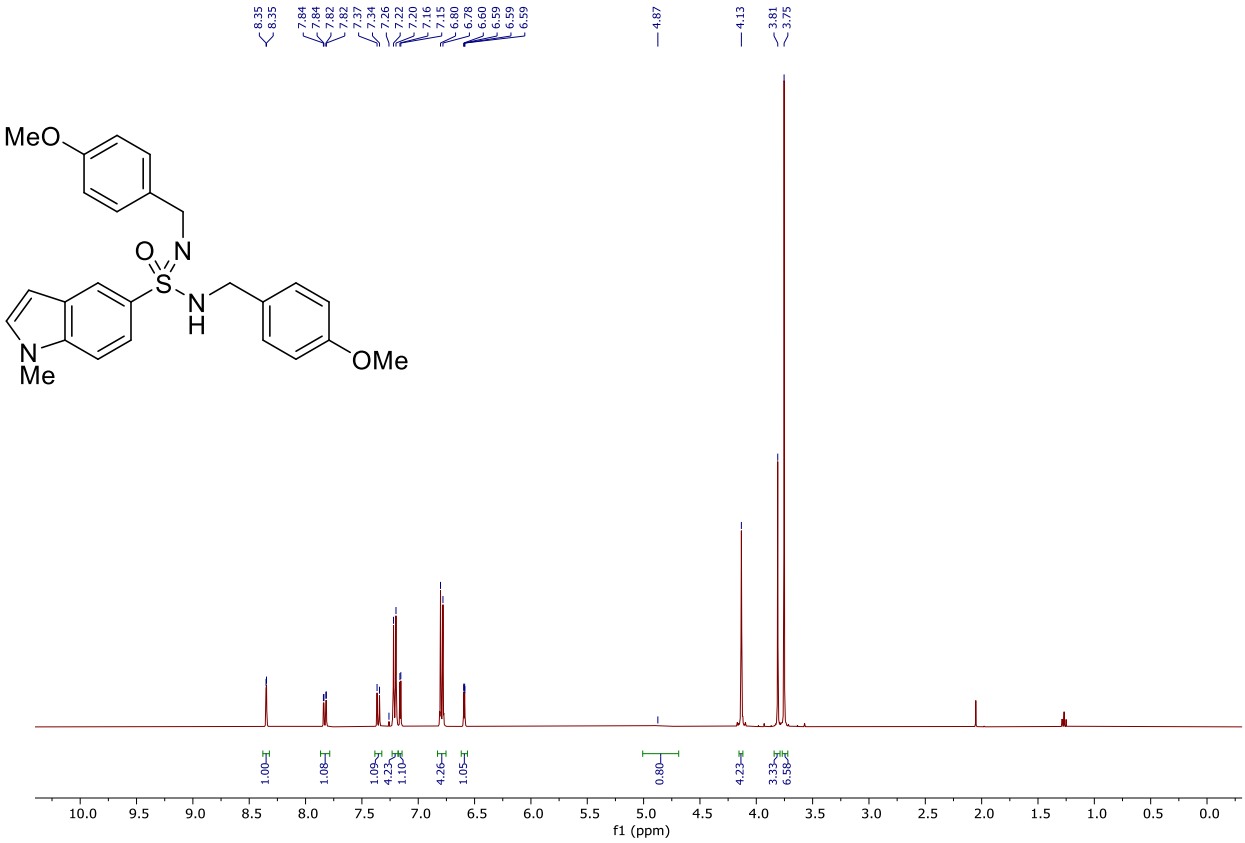

-106.81
-106.83
-106.84
-106.84
-106.85
-106.86
-106.87
-106.87
-106.89
MeO
O
N
S
N
H
F
OMe
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

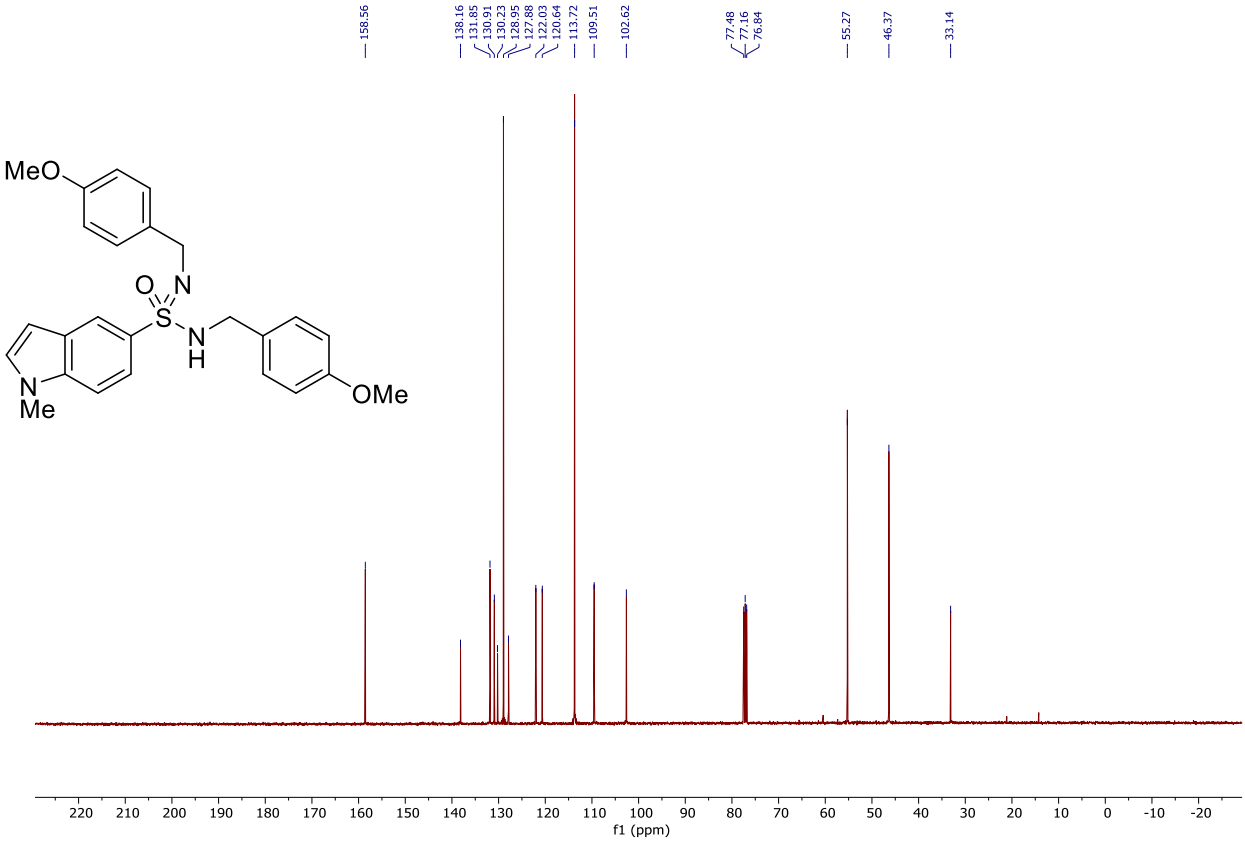
## *N,N'*-bis(4-methoxybenzyl)naphthalene-2-sulfonimidamide (73i)



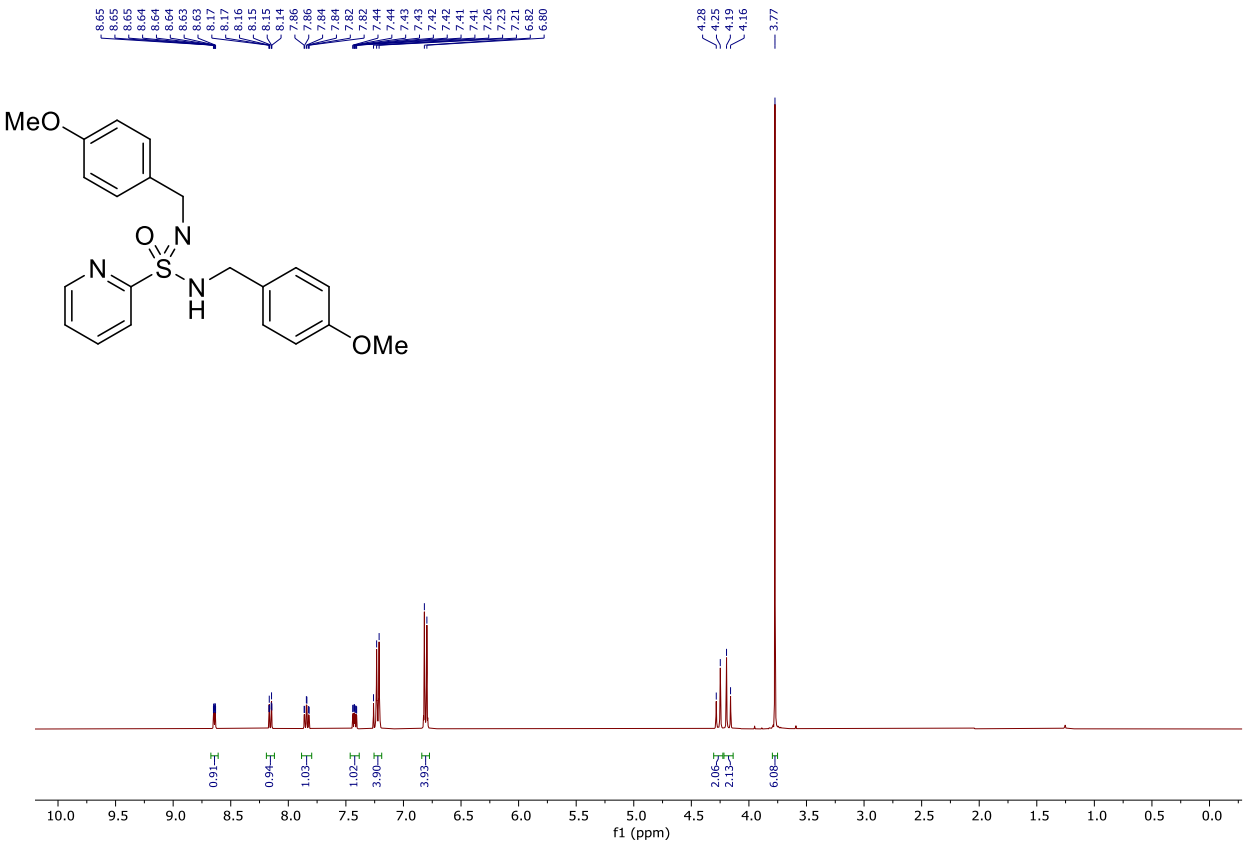



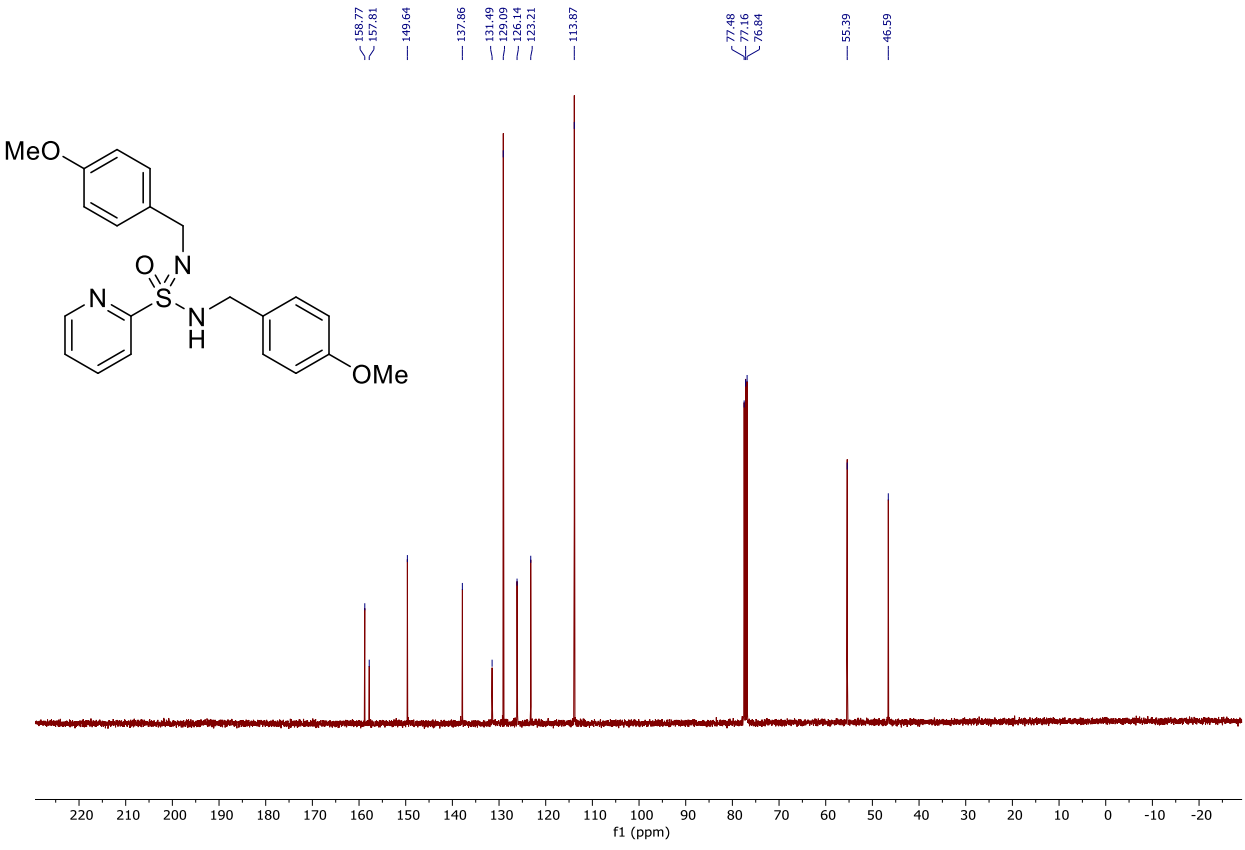
**N,N'-bis(4-methoxybenzyl)-1-methyl-1H-indole-5-sulfonimidamide (73j)**



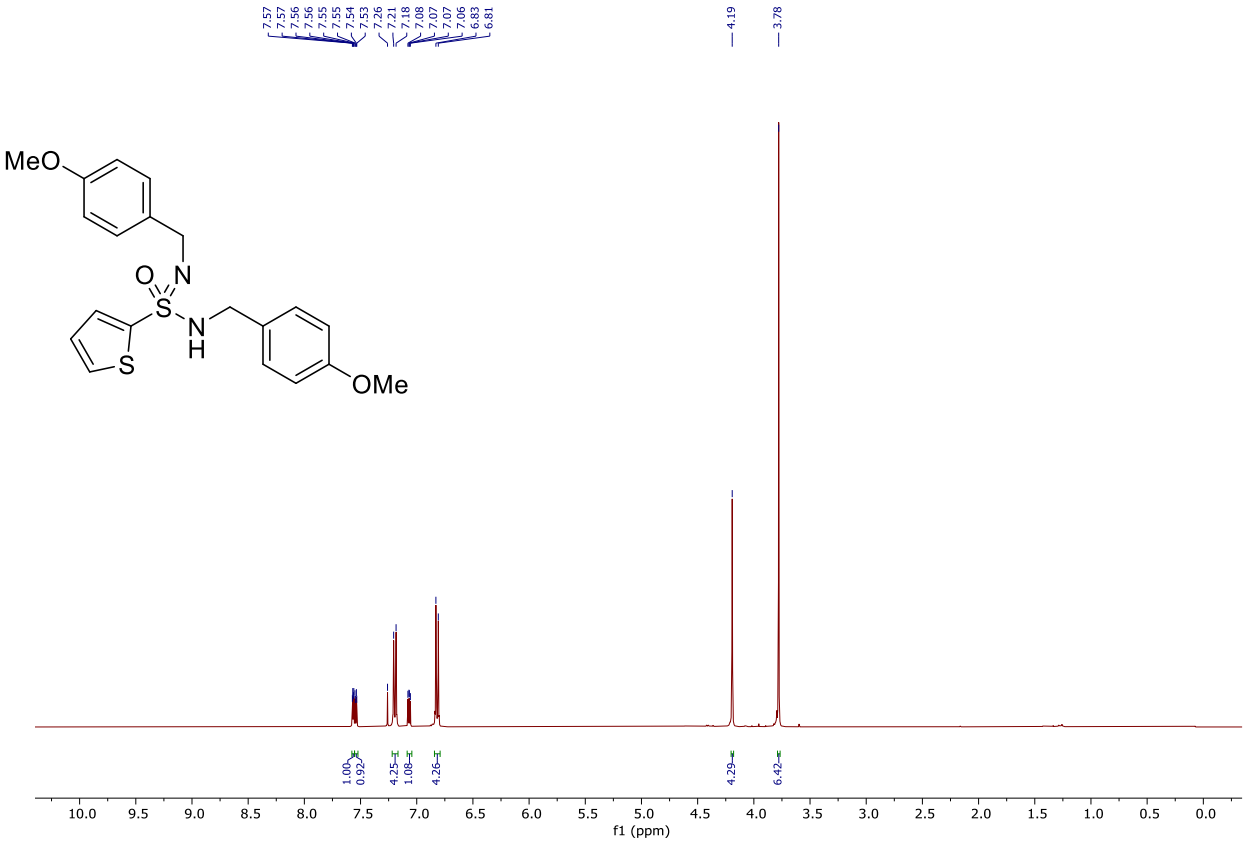



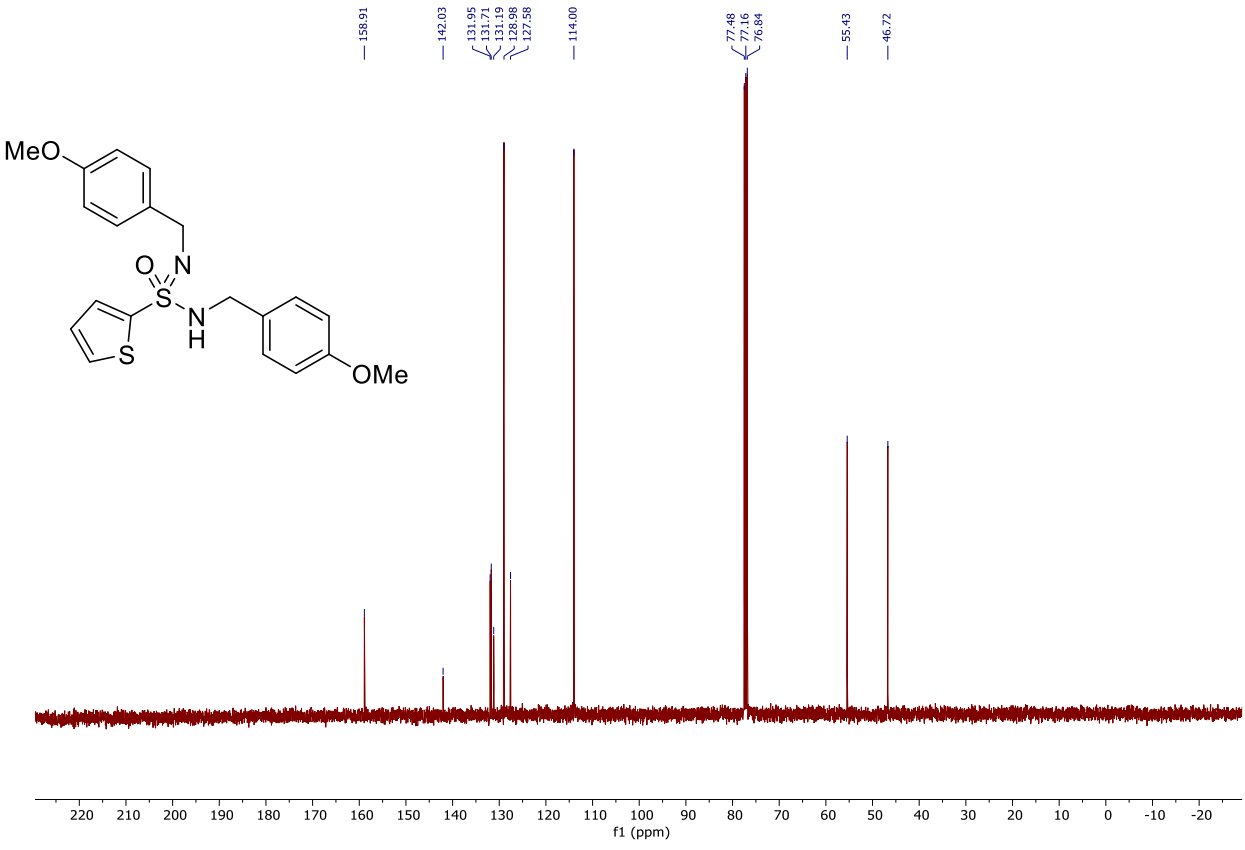
## *N,N'*-bis(4-methoxybenzyl)naphthalene-2-sulfonimidamide (73k)



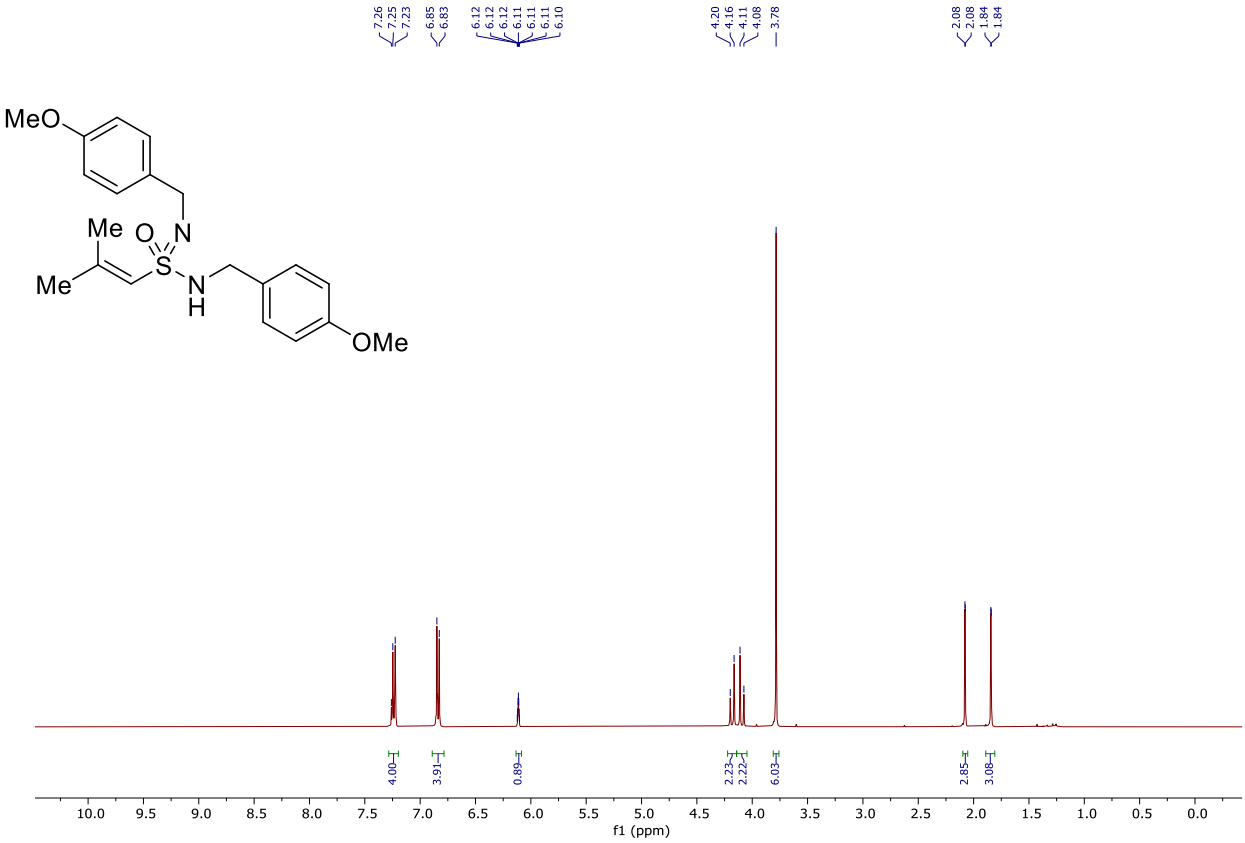



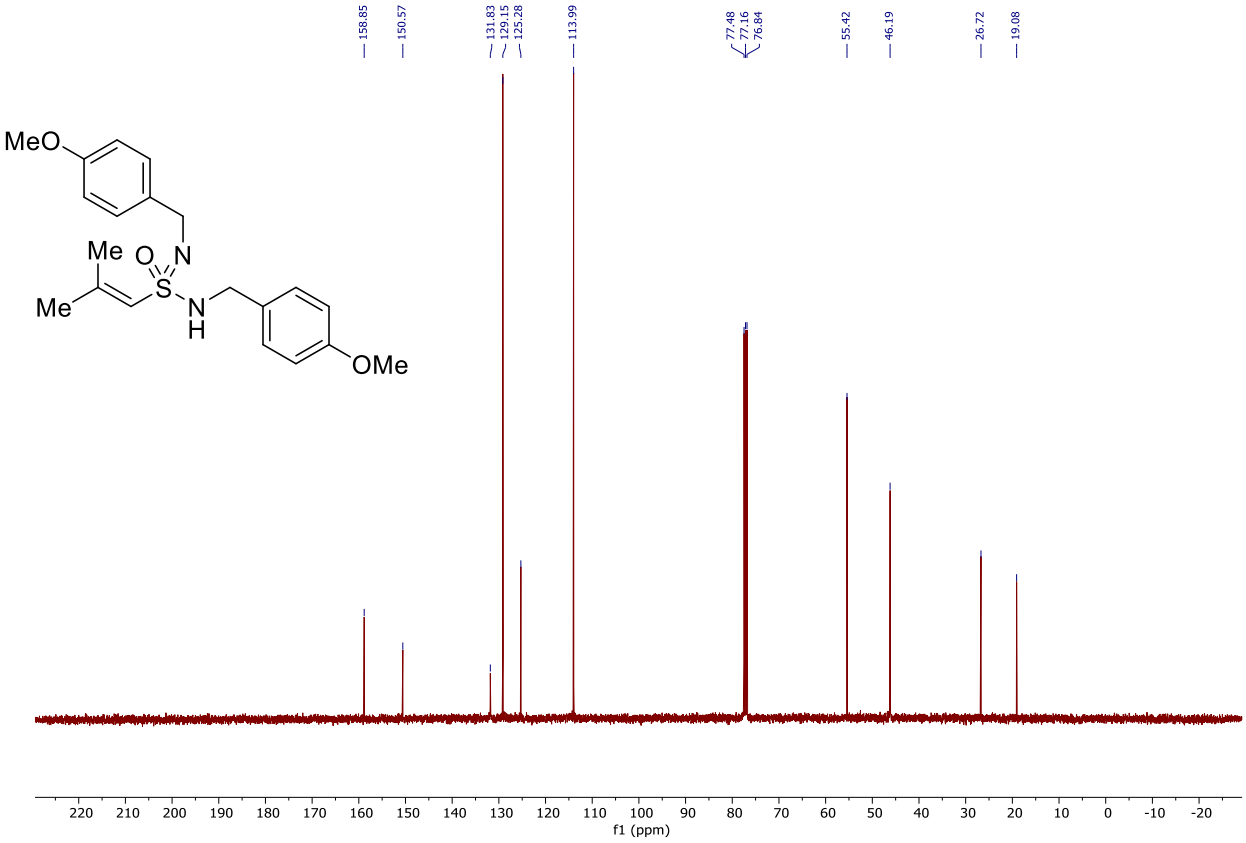
## *N,N'*-bis(4-methoxybenzyl)thiophene-2-sulfonimidamide (73l)



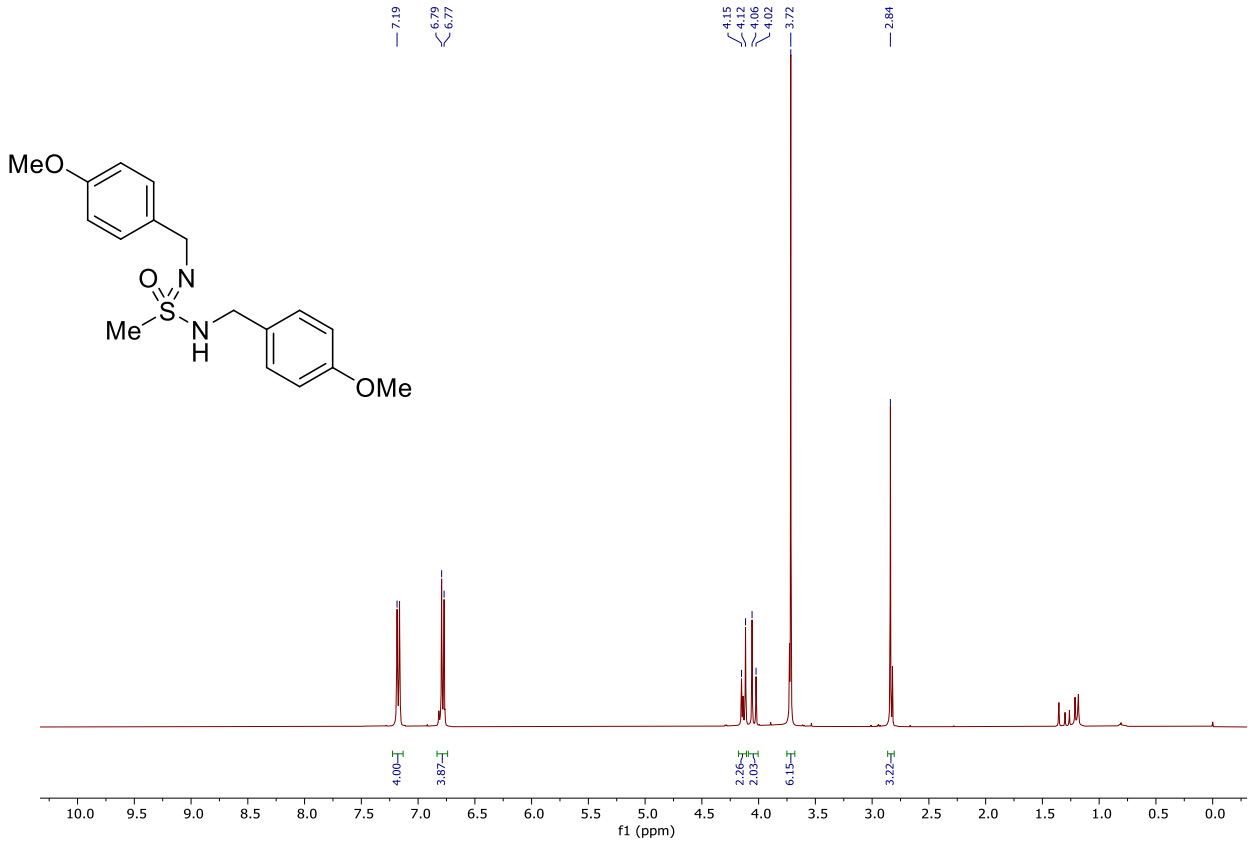



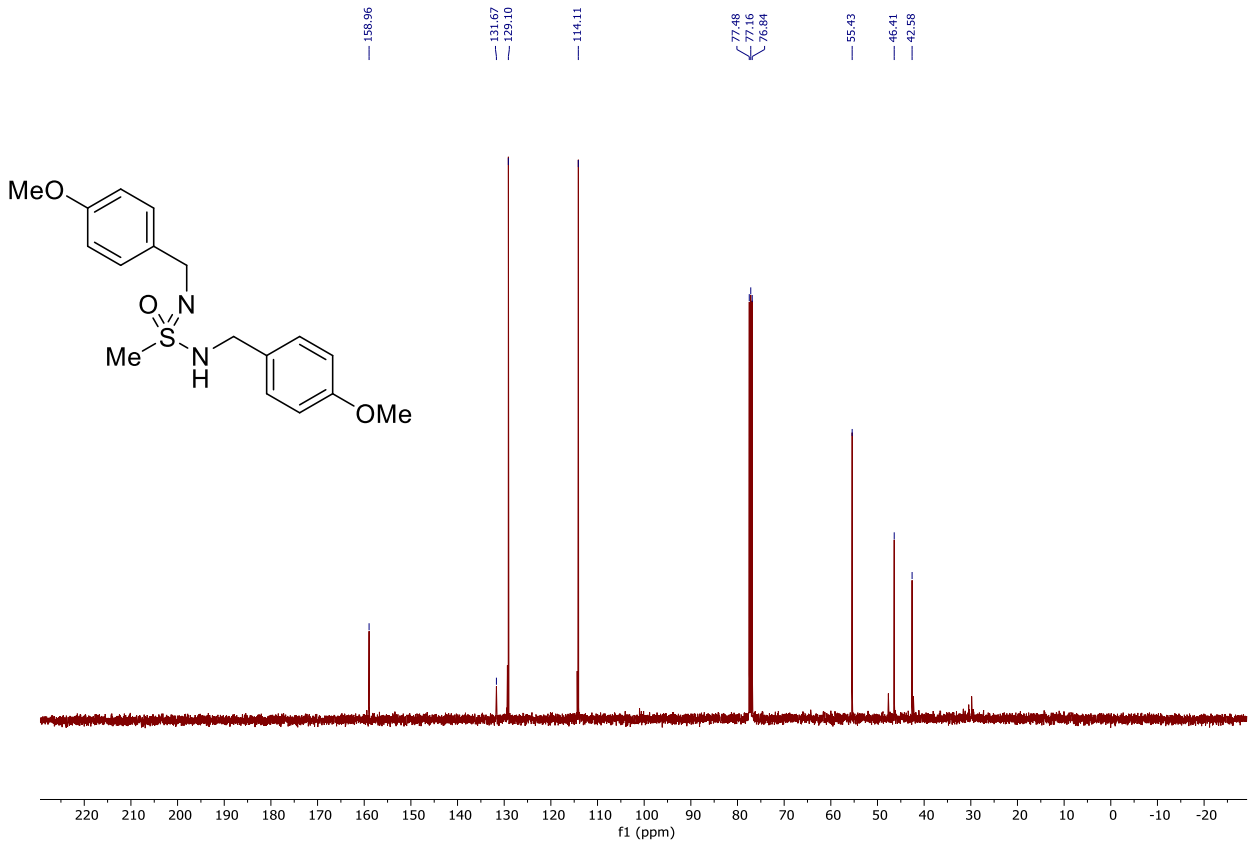
**N,N'-bis(4-methoxybenzyl)-2-methylprop-1-ene-1-sulfonimidamide (73m)**



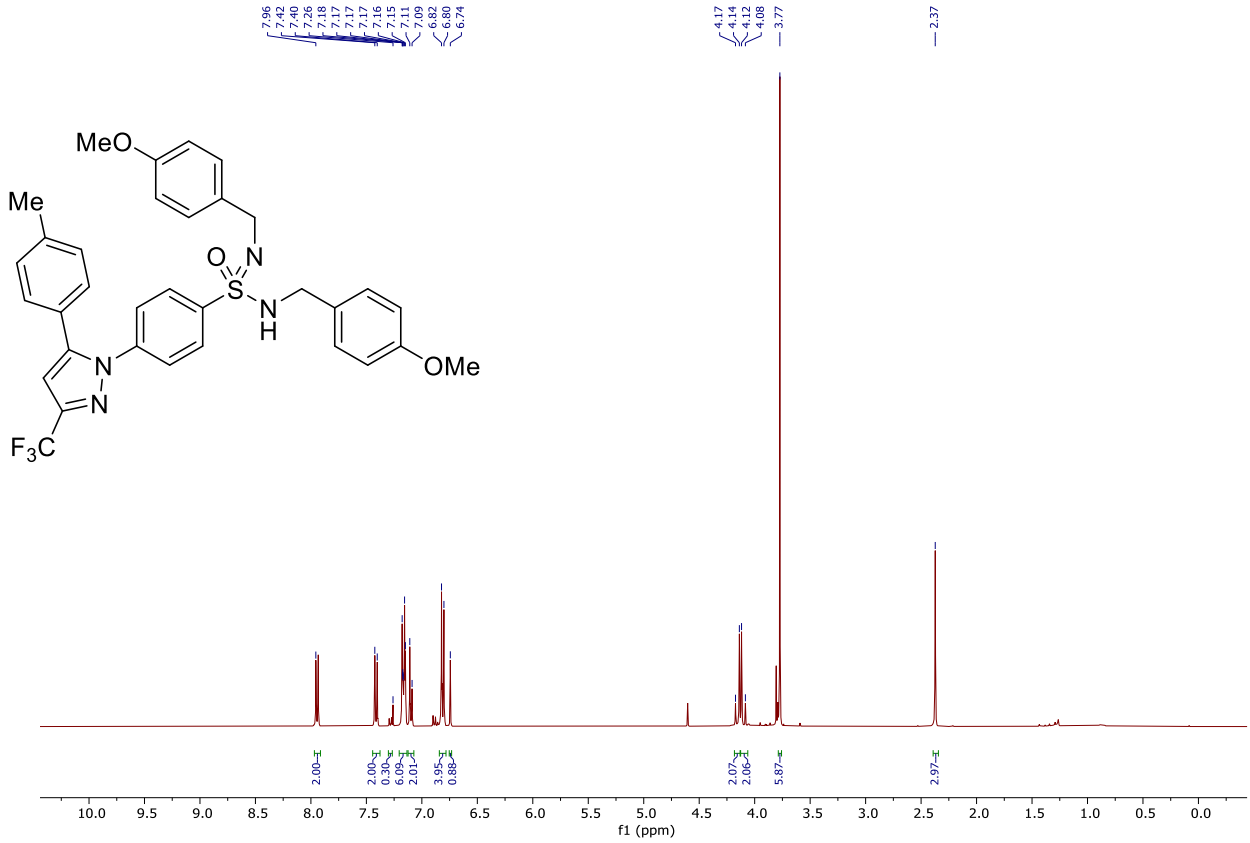



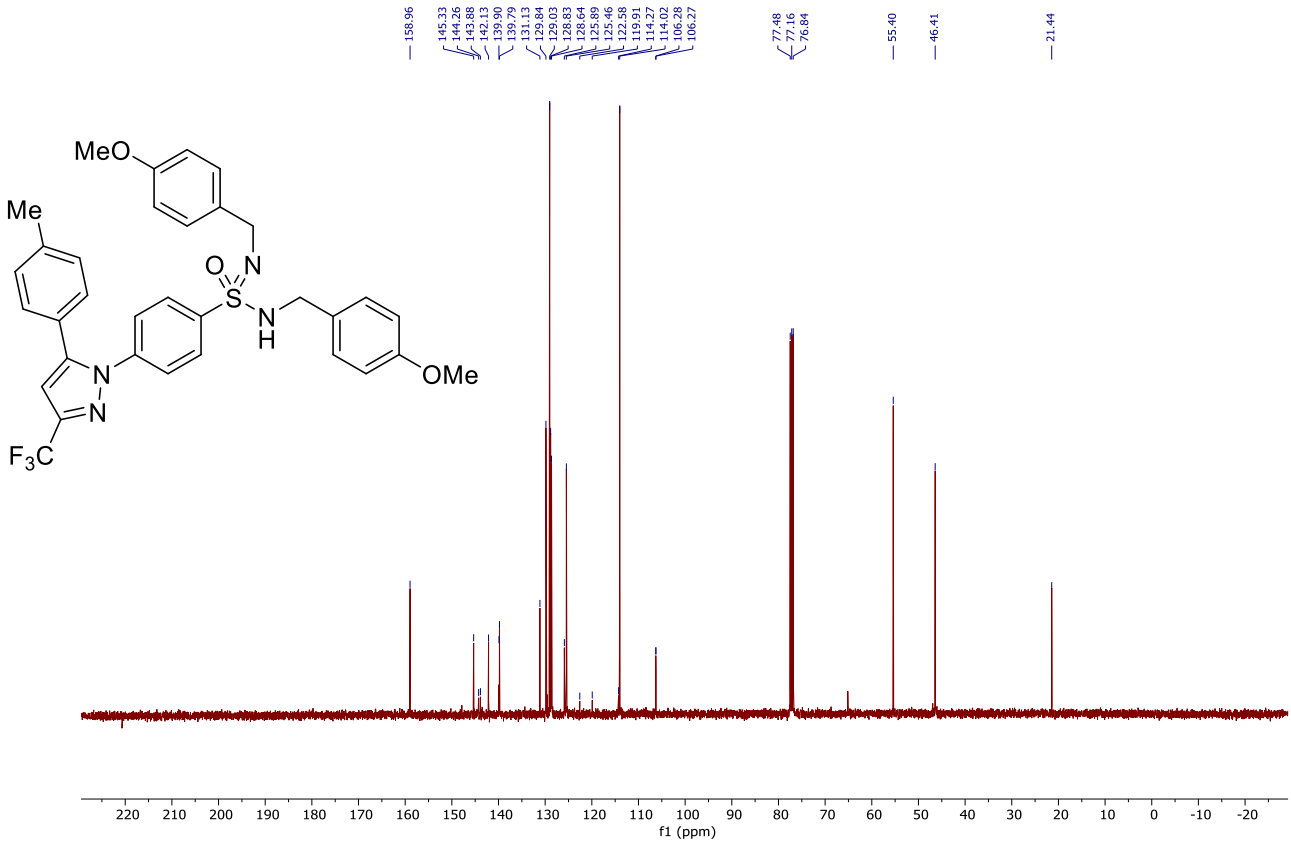
**N,N'-bis(4-methoxybenzyl)methanesulfonimidamide (73n)**

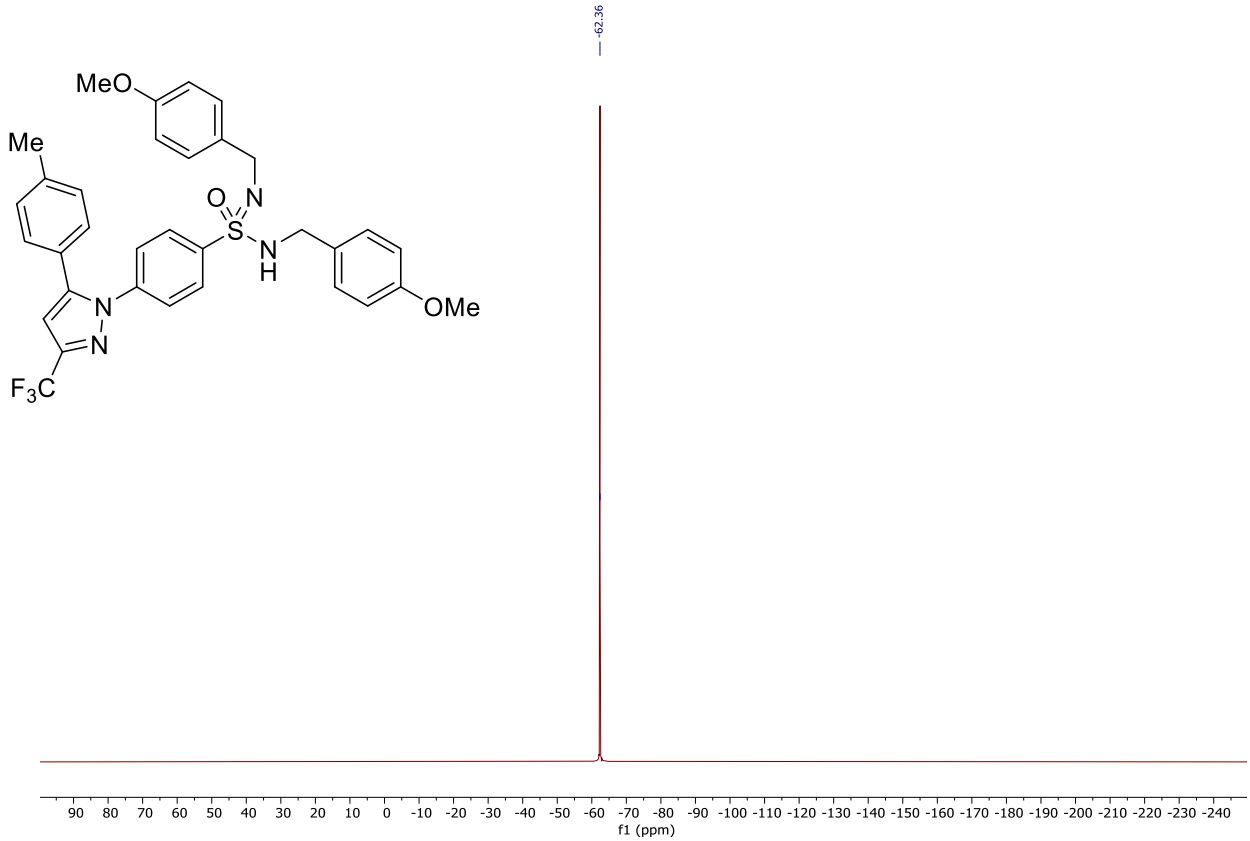


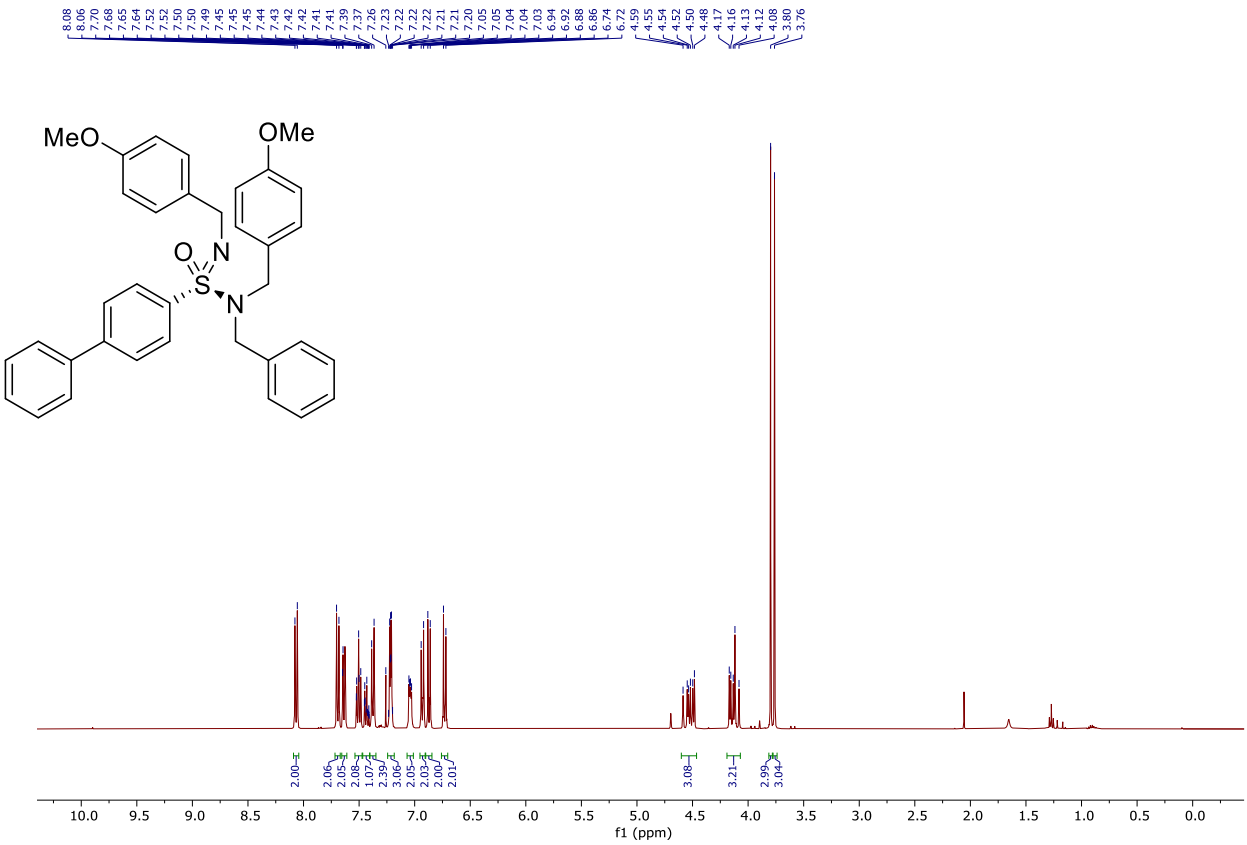
**N,N'-bis(4-methoxybenzyl)-4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonimidamide (73o)**

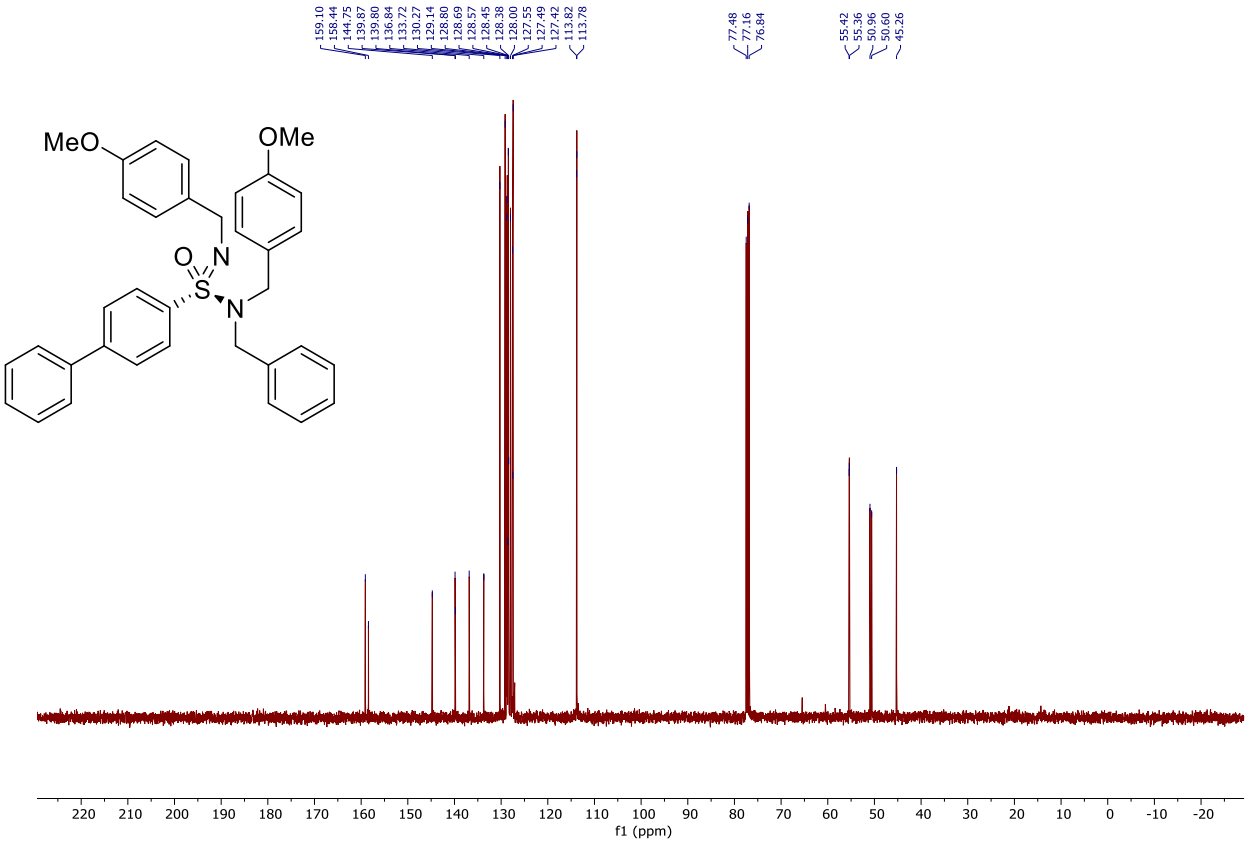


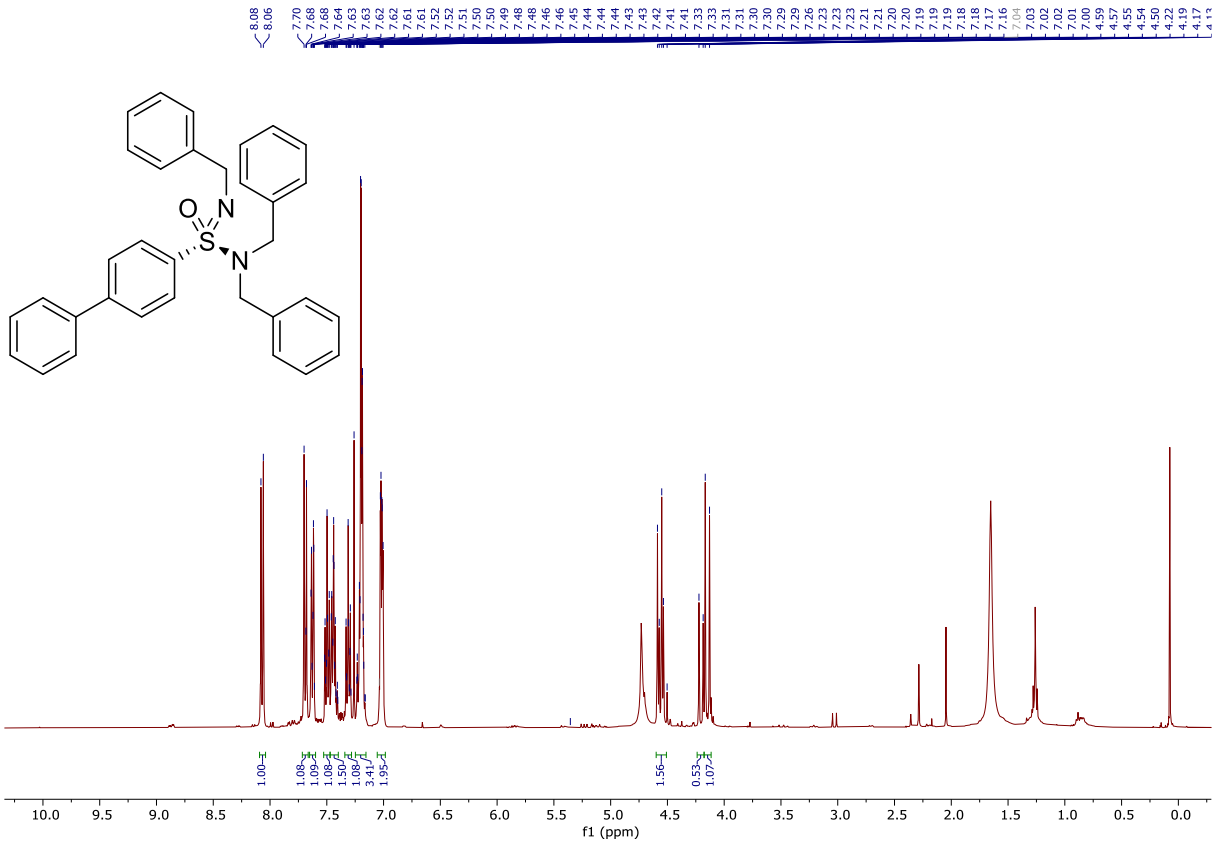

-62.36
MeO
Me
O
N
S
N
H
OMe
N
N
F3C
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

## (*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74a)



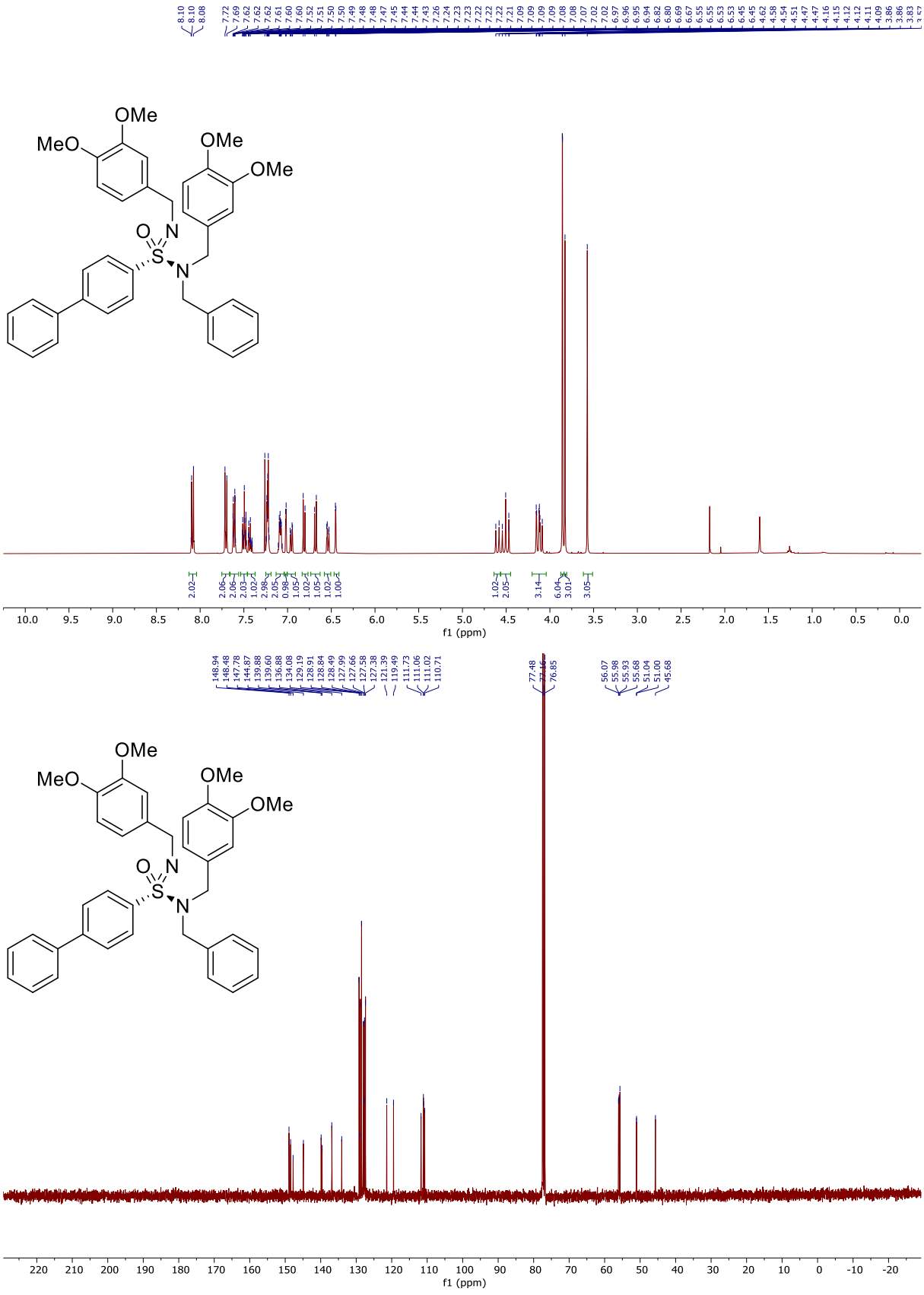



**(S)-*N,N,N'*-tribenzyl-[1,1'-biphenyl]-4-sulfonimidamide (80a)**

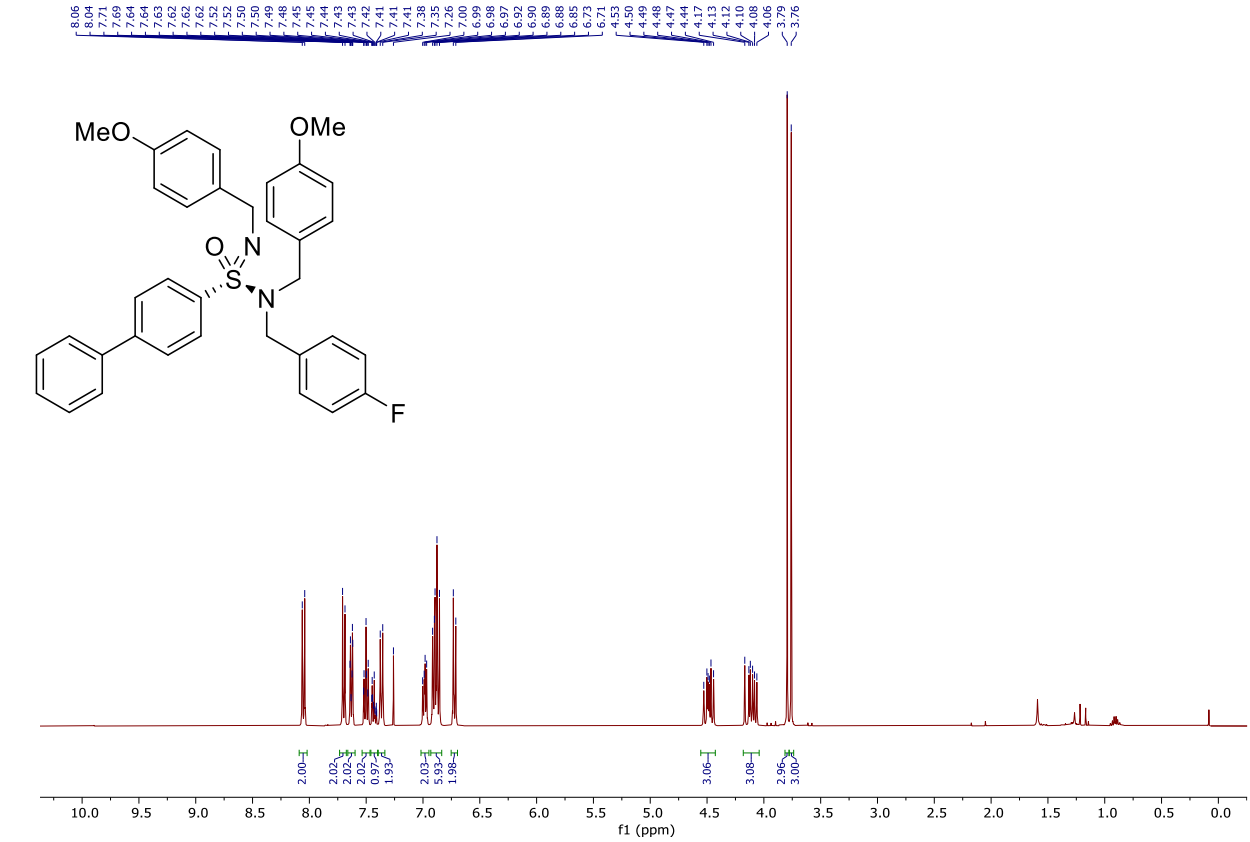


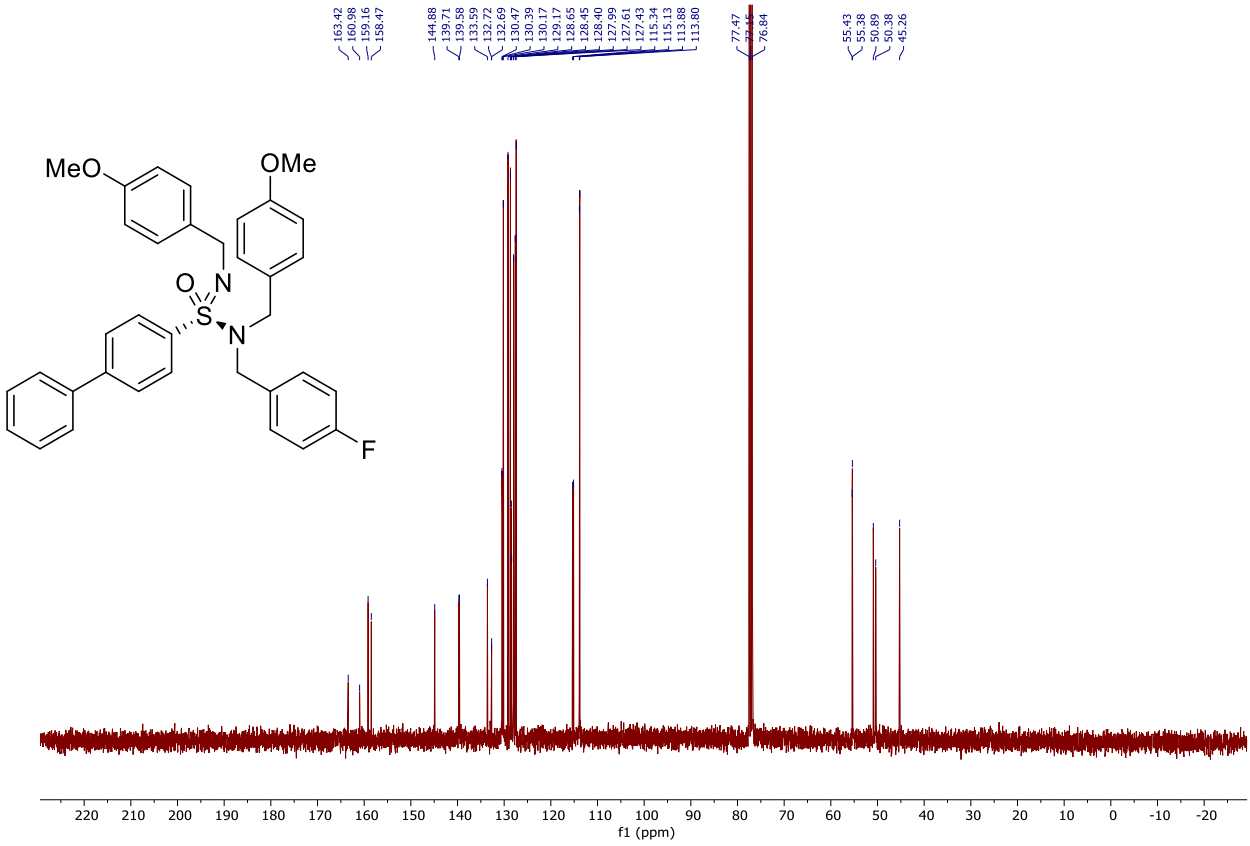

*Crude $^{1}$H NMR spectrum of compound **80a**.

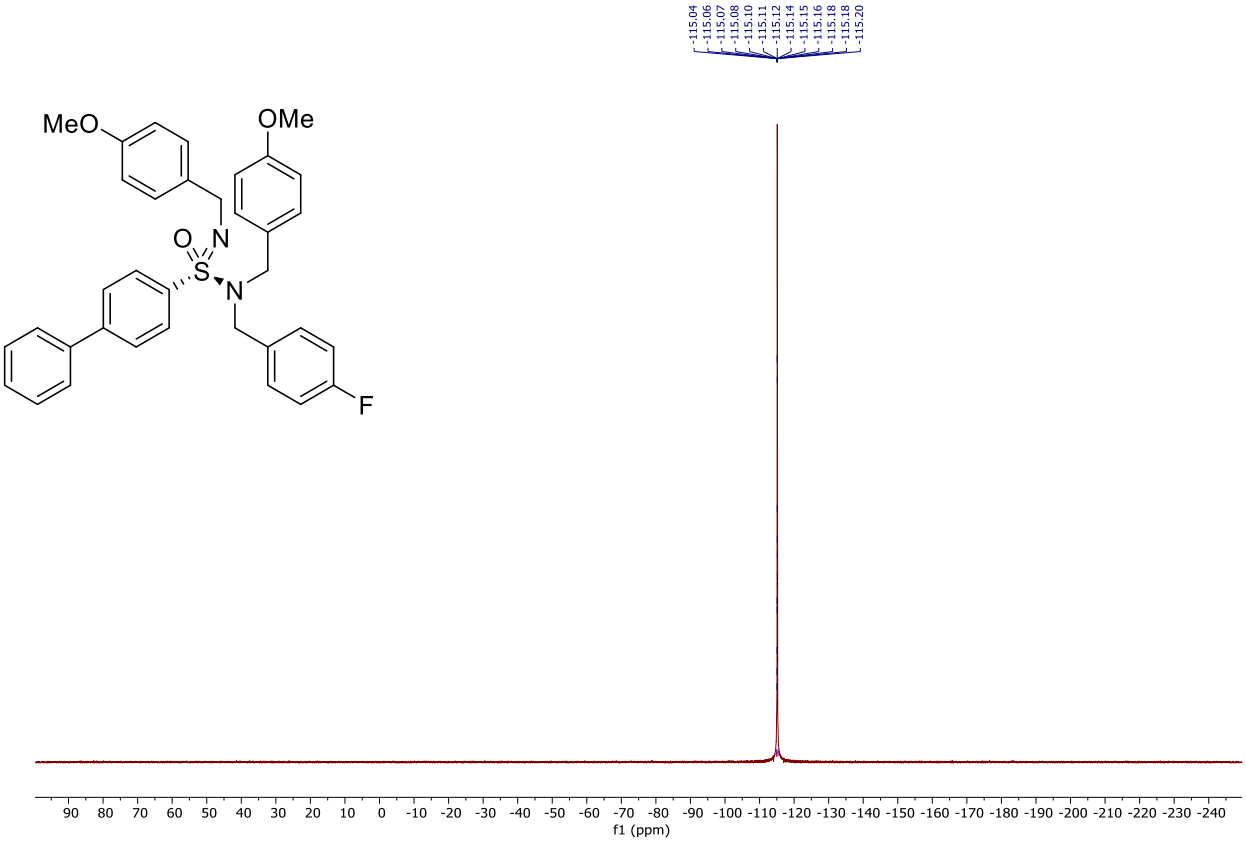
## (*S*)-*N*-benzyl-*N*,*N*'-bis(3,4-dimethoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (80b)



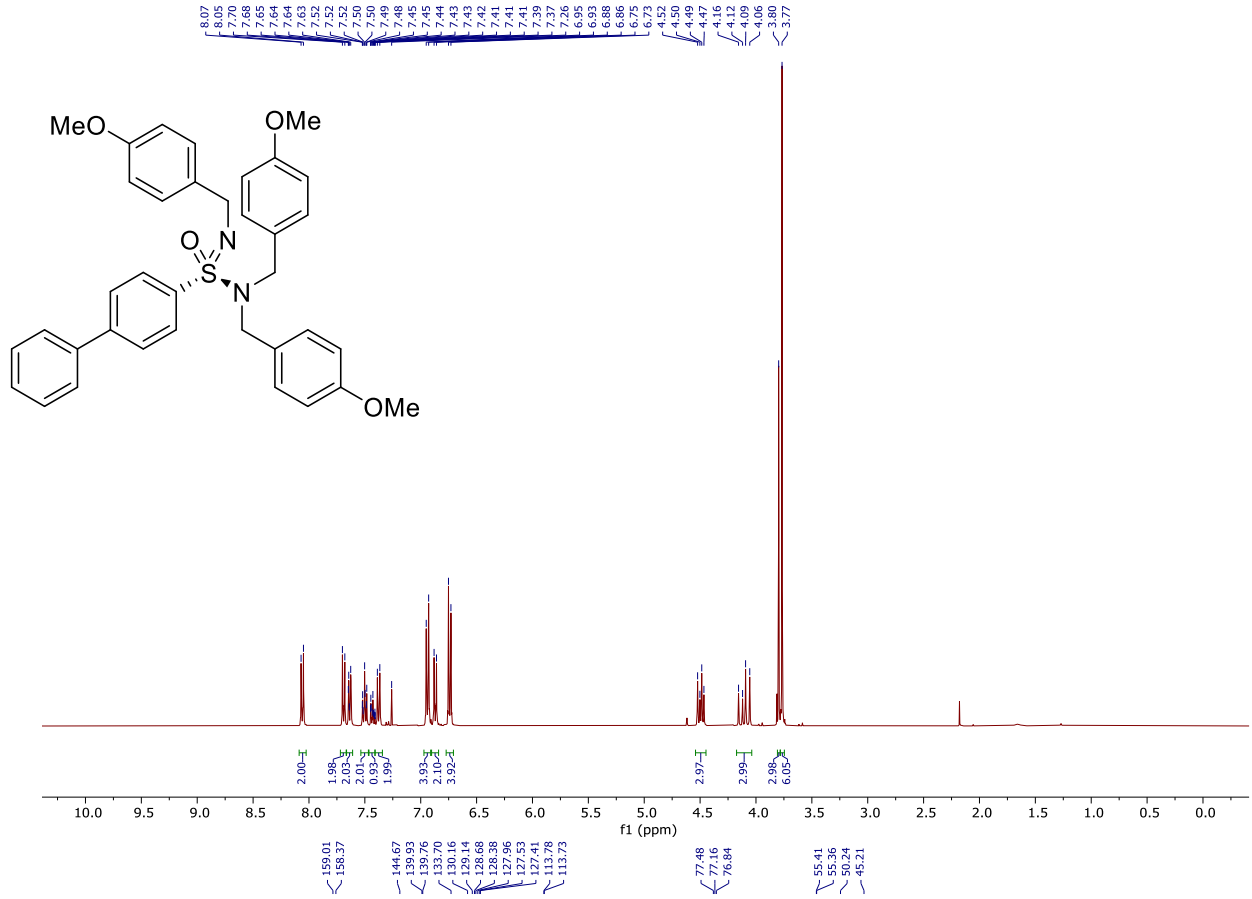
**(*S*)-*N*-(4-fluorobenzyl)-*N*,*N*′-bis(4-methoxybenzyl)-[1,1′-biphenyl]-4-sulfonimidamide (74aa)**

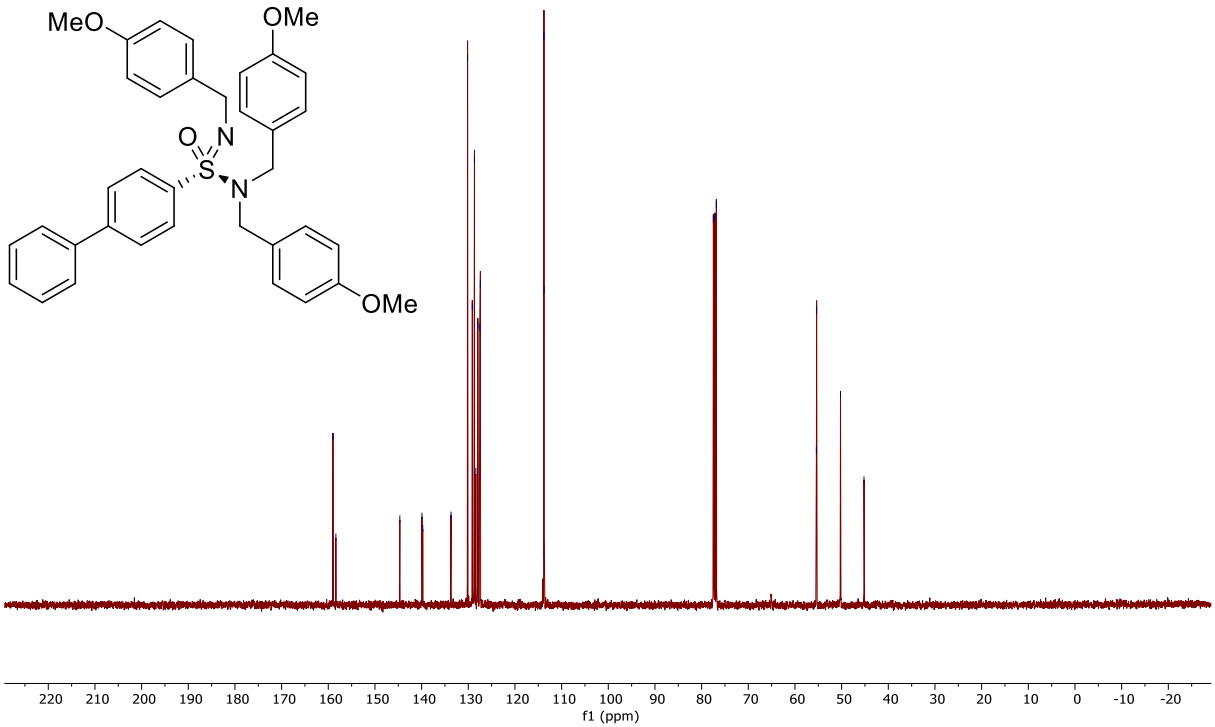


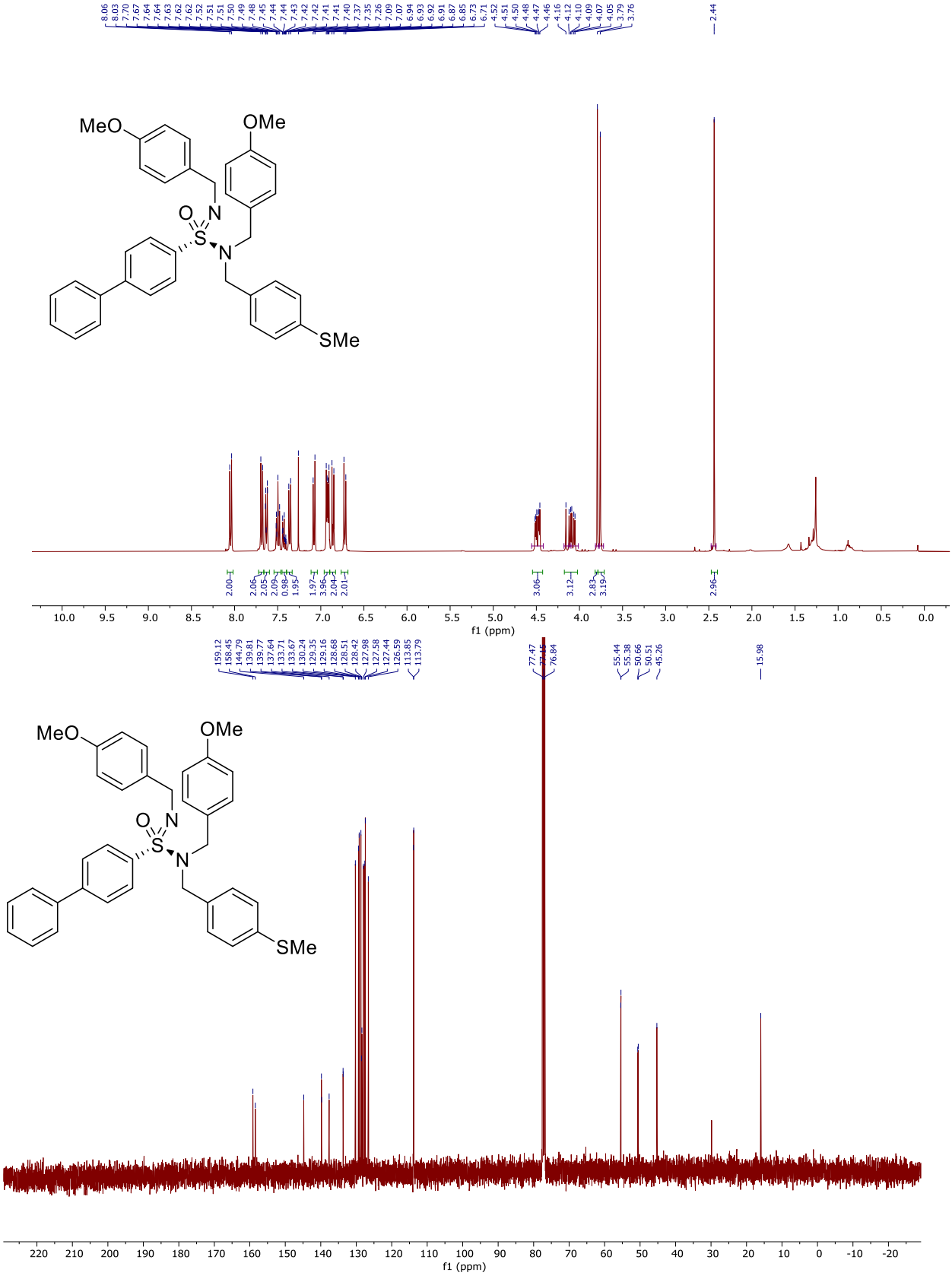

-115.04
-115.06
-115.07
-115.08
-115.10
-115.11
-115.12
-115.14
-115.15
-115.16
-115.18
-115.18
-115.20
MeO
OMe
O
N
S
N
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

**(*S*)-*N*,*N*,*N*'-tris(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ab)**

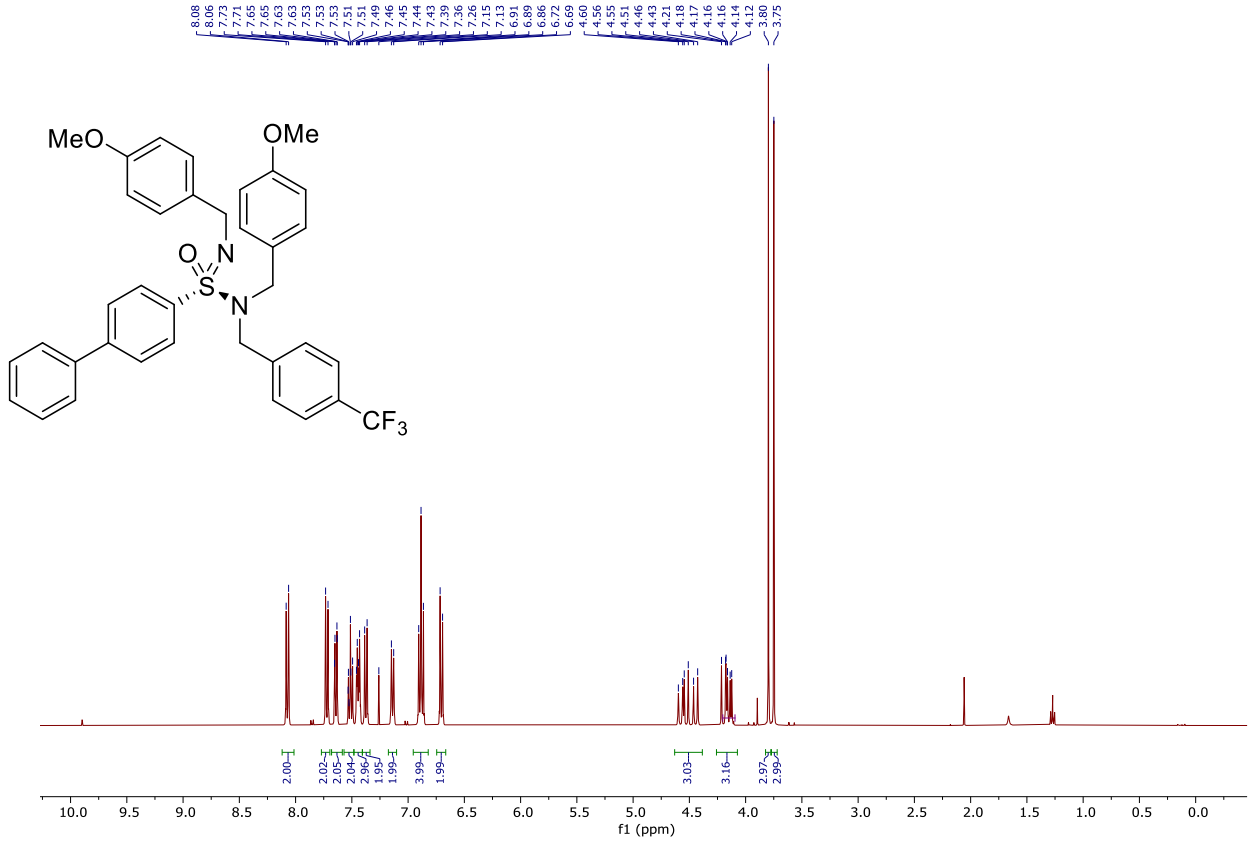


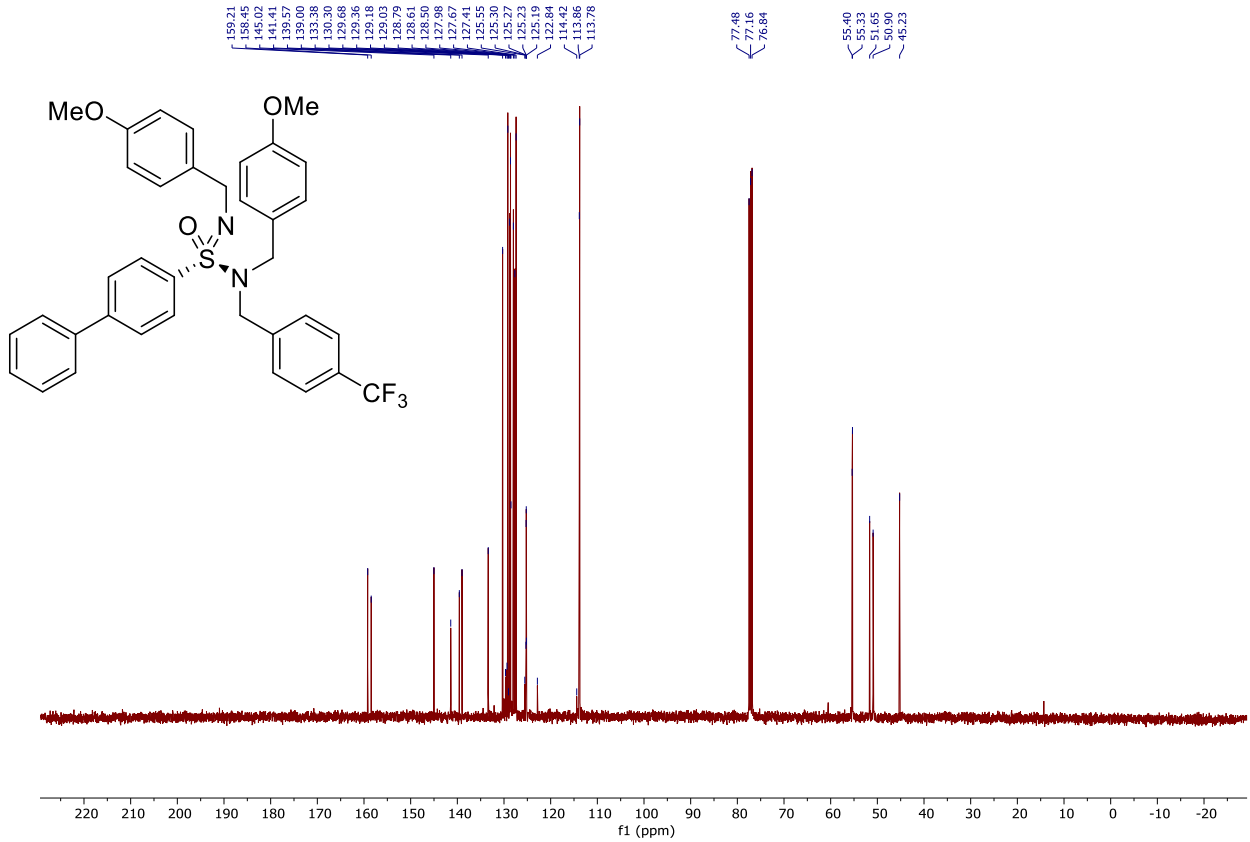



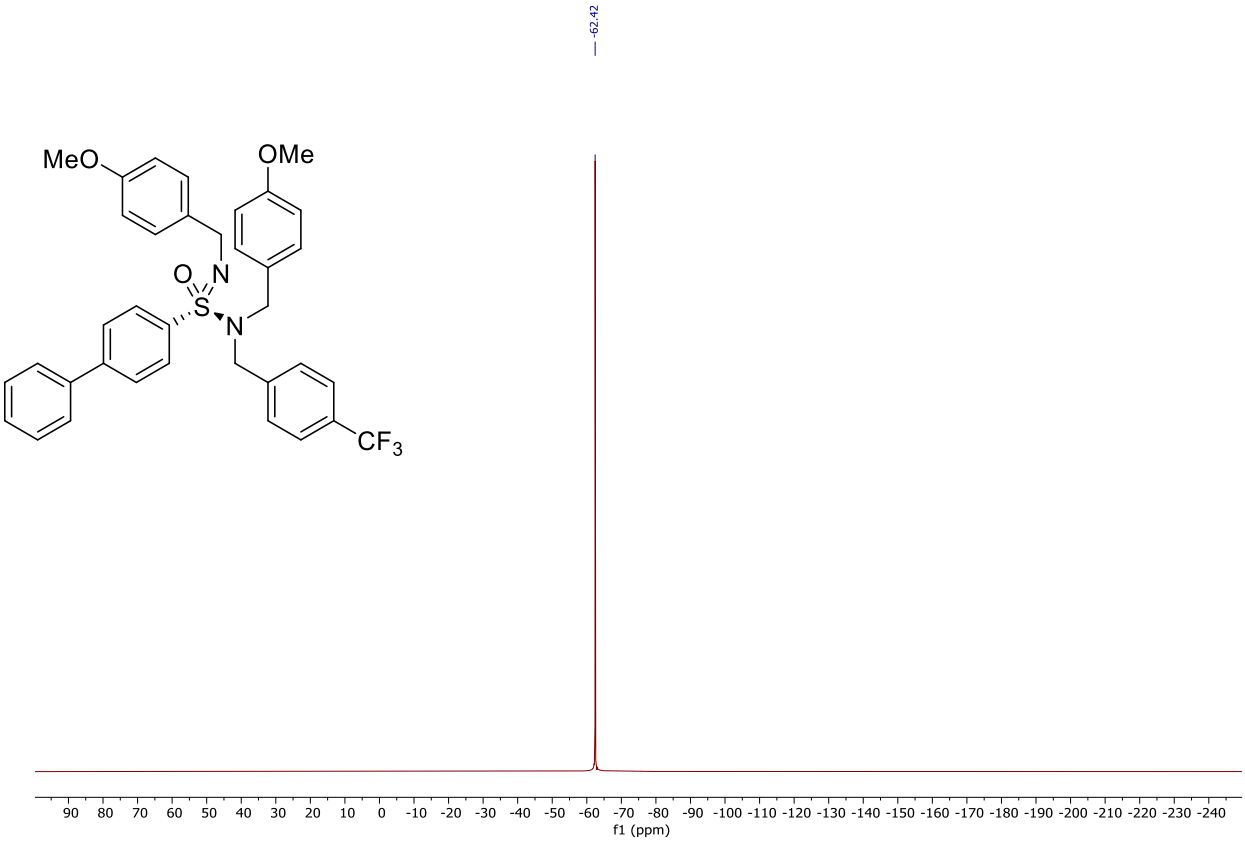
**(*S*)-*N*,*N*'-bis(4-methoxybenzyl)-*N*-(4-(methylthio)benzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ac)**



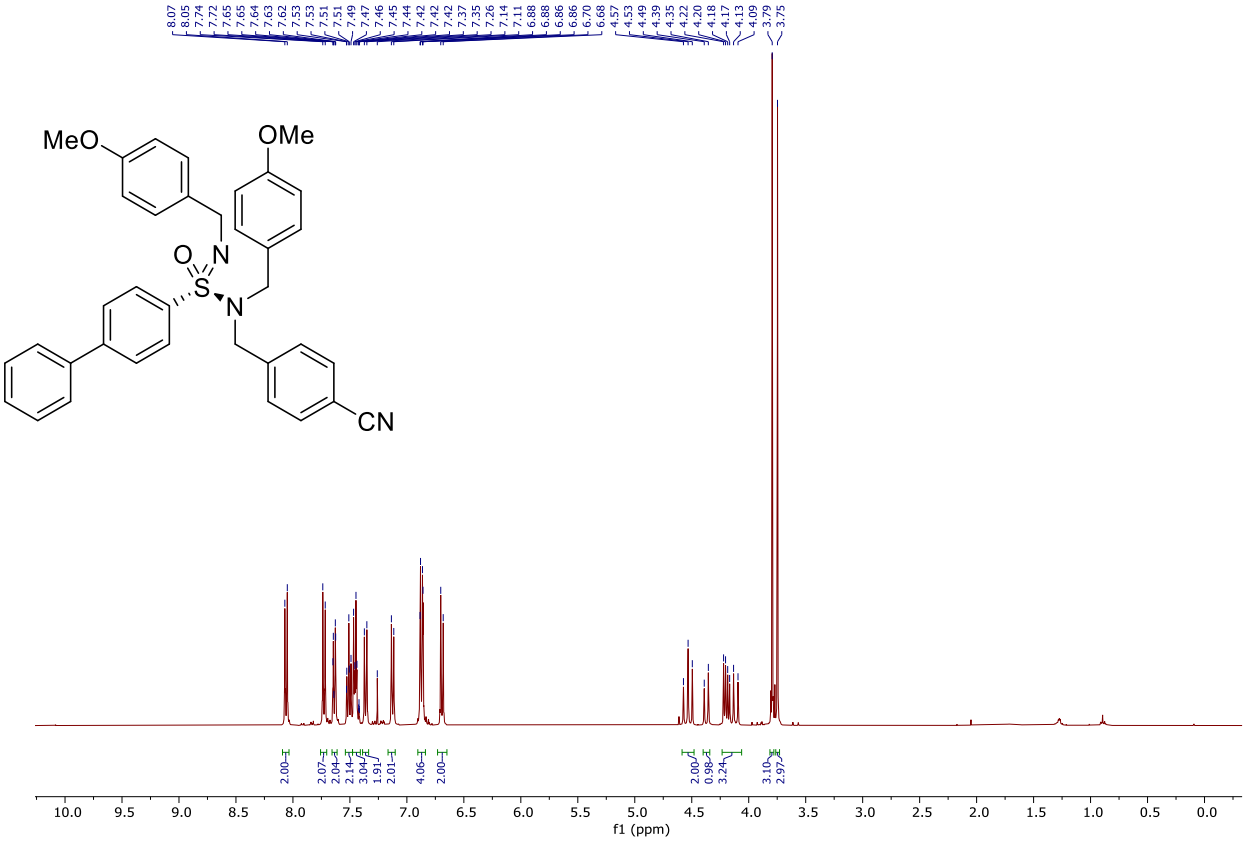
**(*S*)-*N*,*N*'-bis(4-methoxybenzyl)-*N*-(4-(trifluoromethyl)benzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ad)**

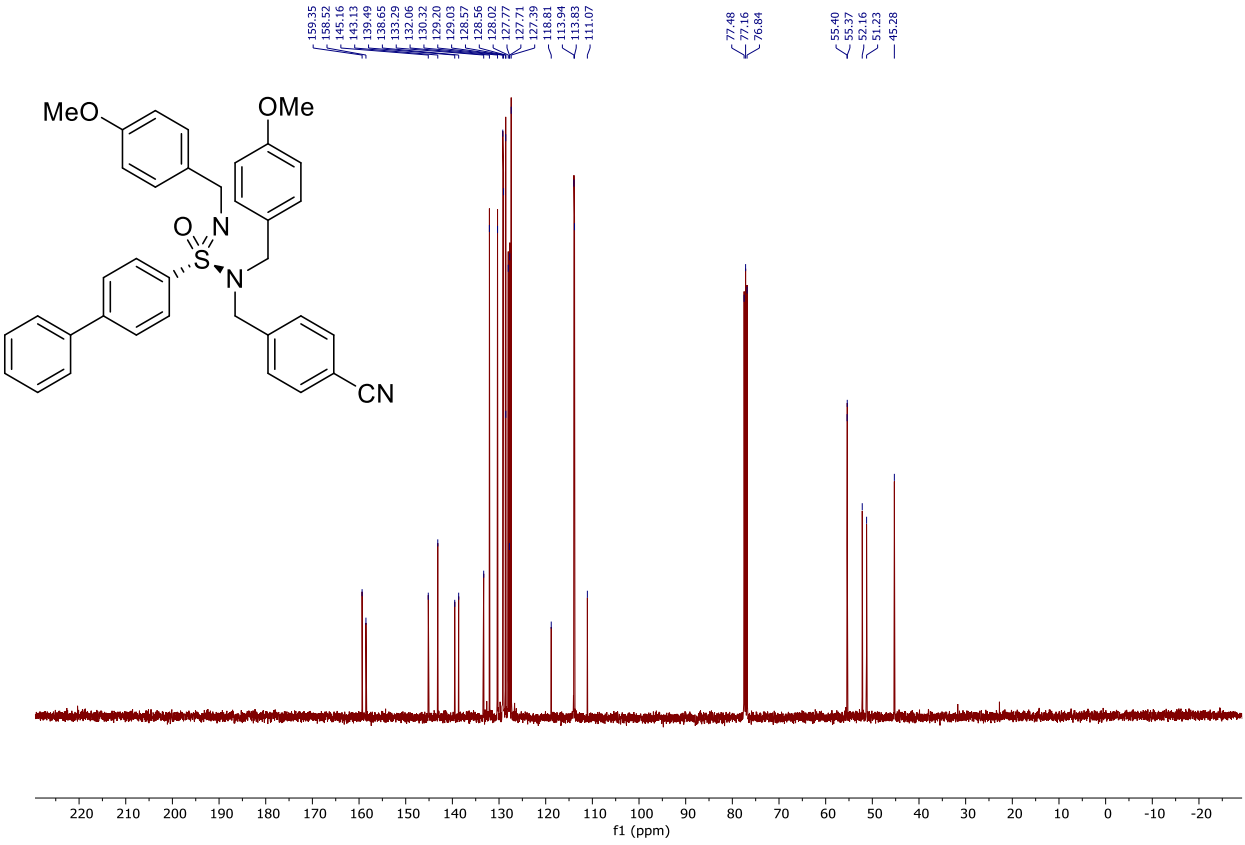


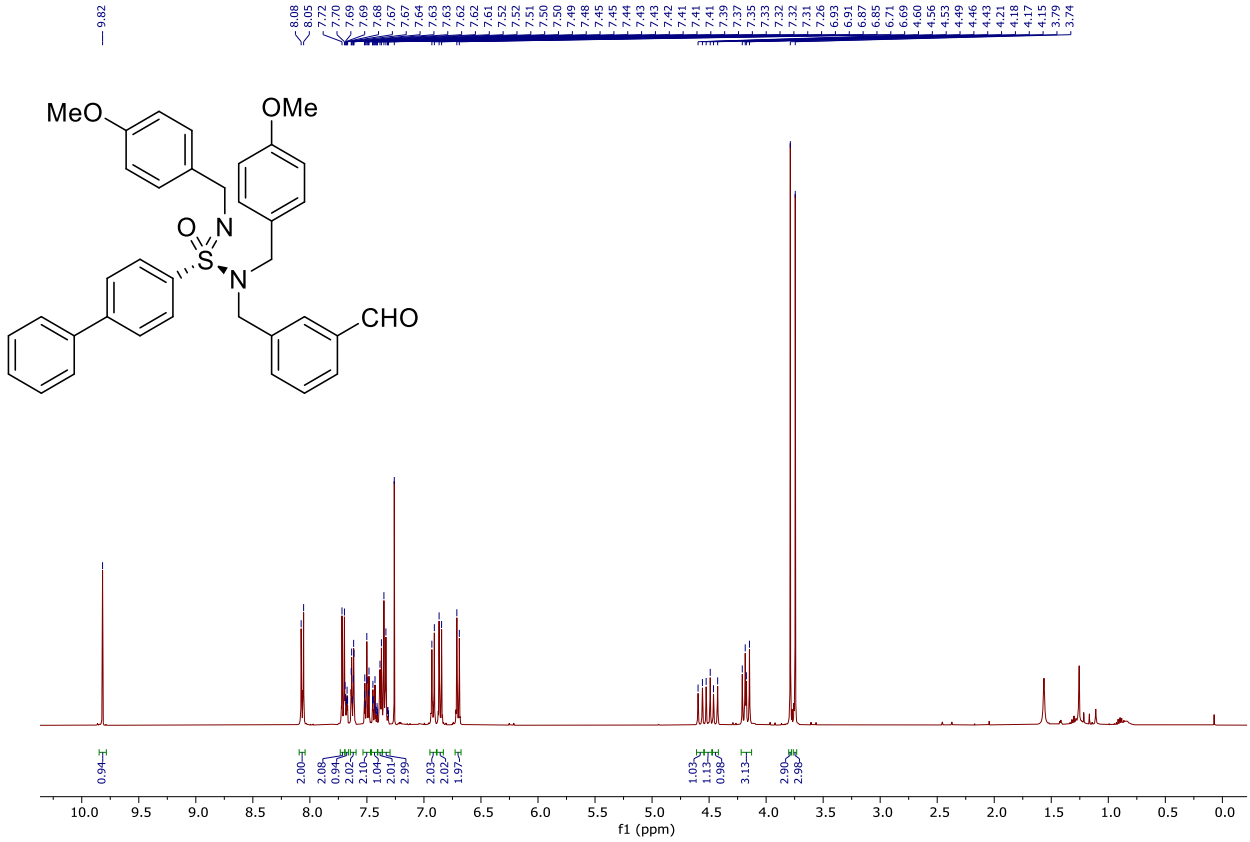

-62.42
MeO
OMe
O
N
S
N
CF3
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

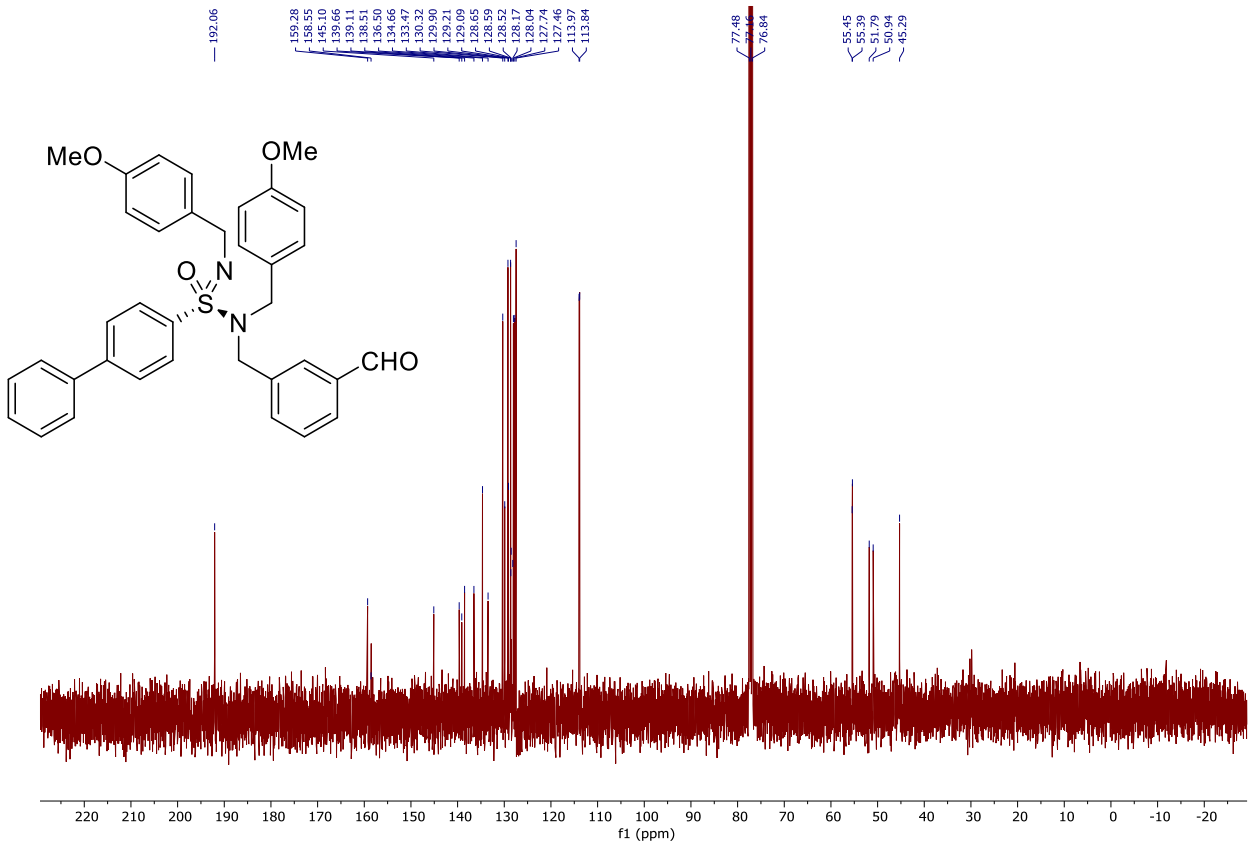
**(*S*)-*N*-(4-cyanobenzyl)-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ae)**



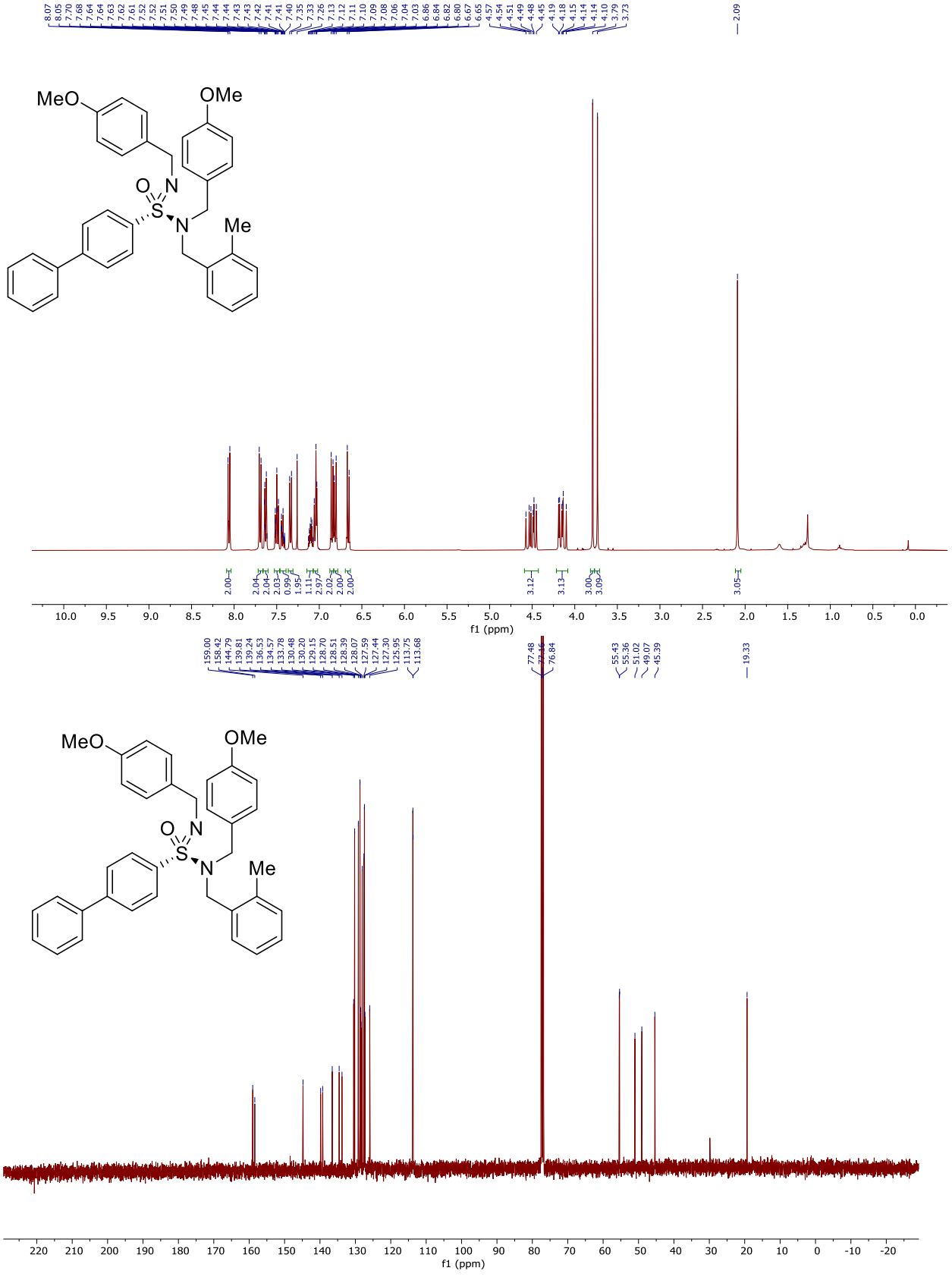



**(*S*)-*N*-(3-formylbenzyl)-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74af)**

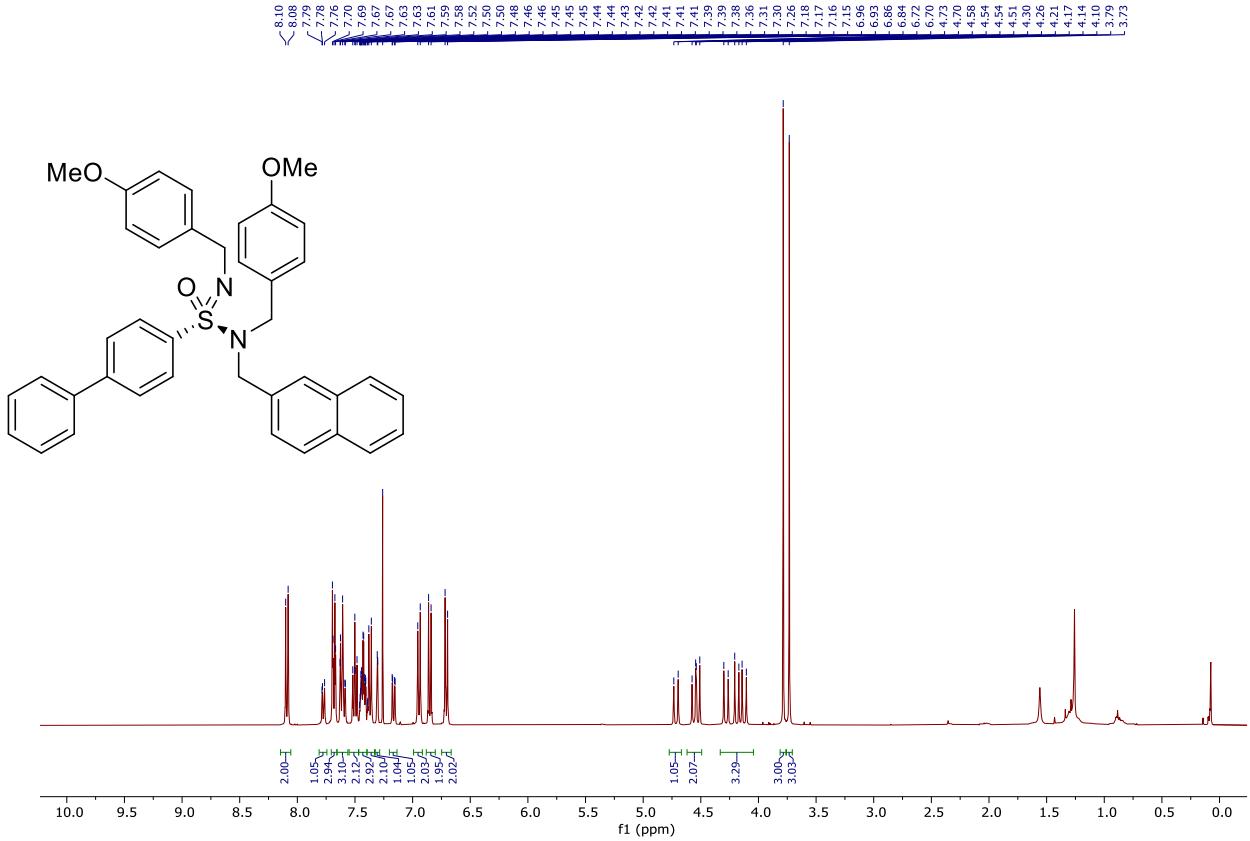


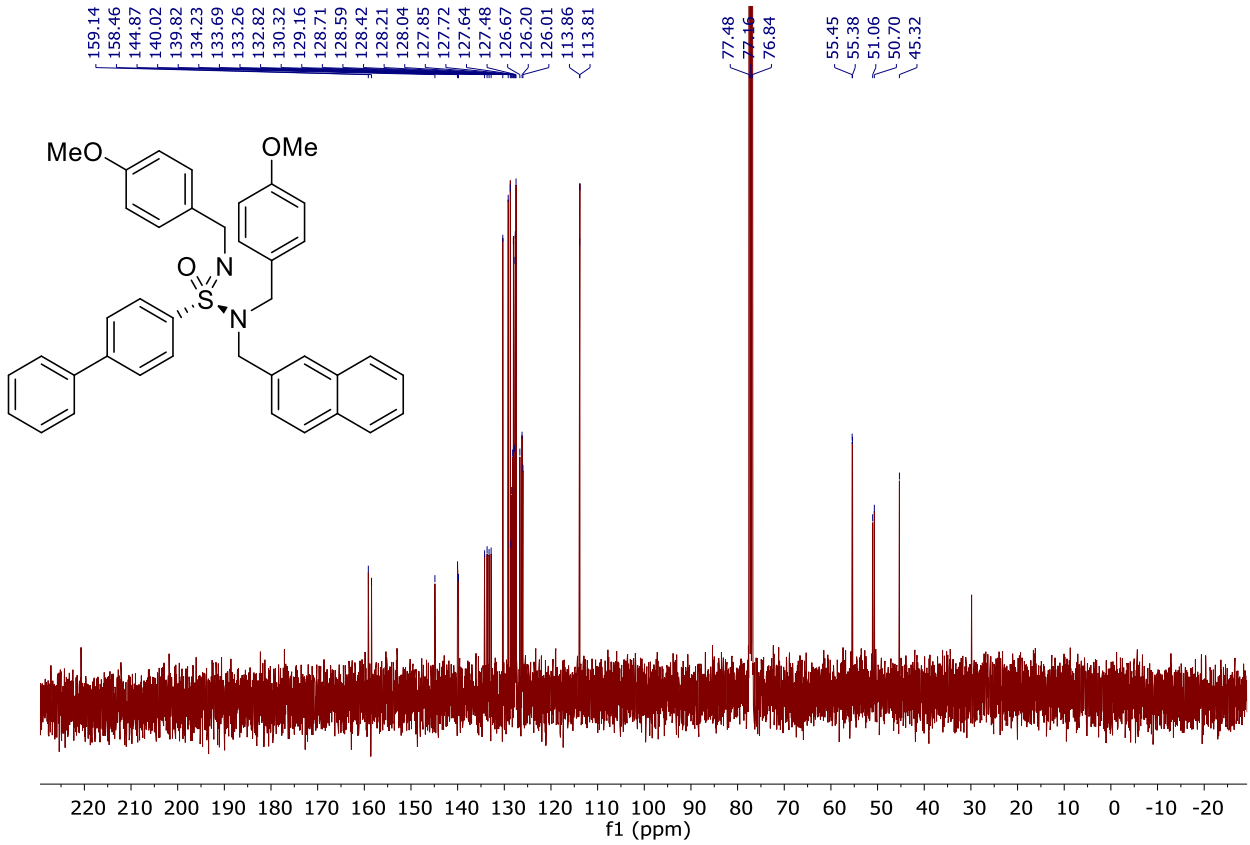



**(*S*)-*N*,*N*'-bis(4-methoxybenzyl)-*N*-(2-methylbenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ag)**

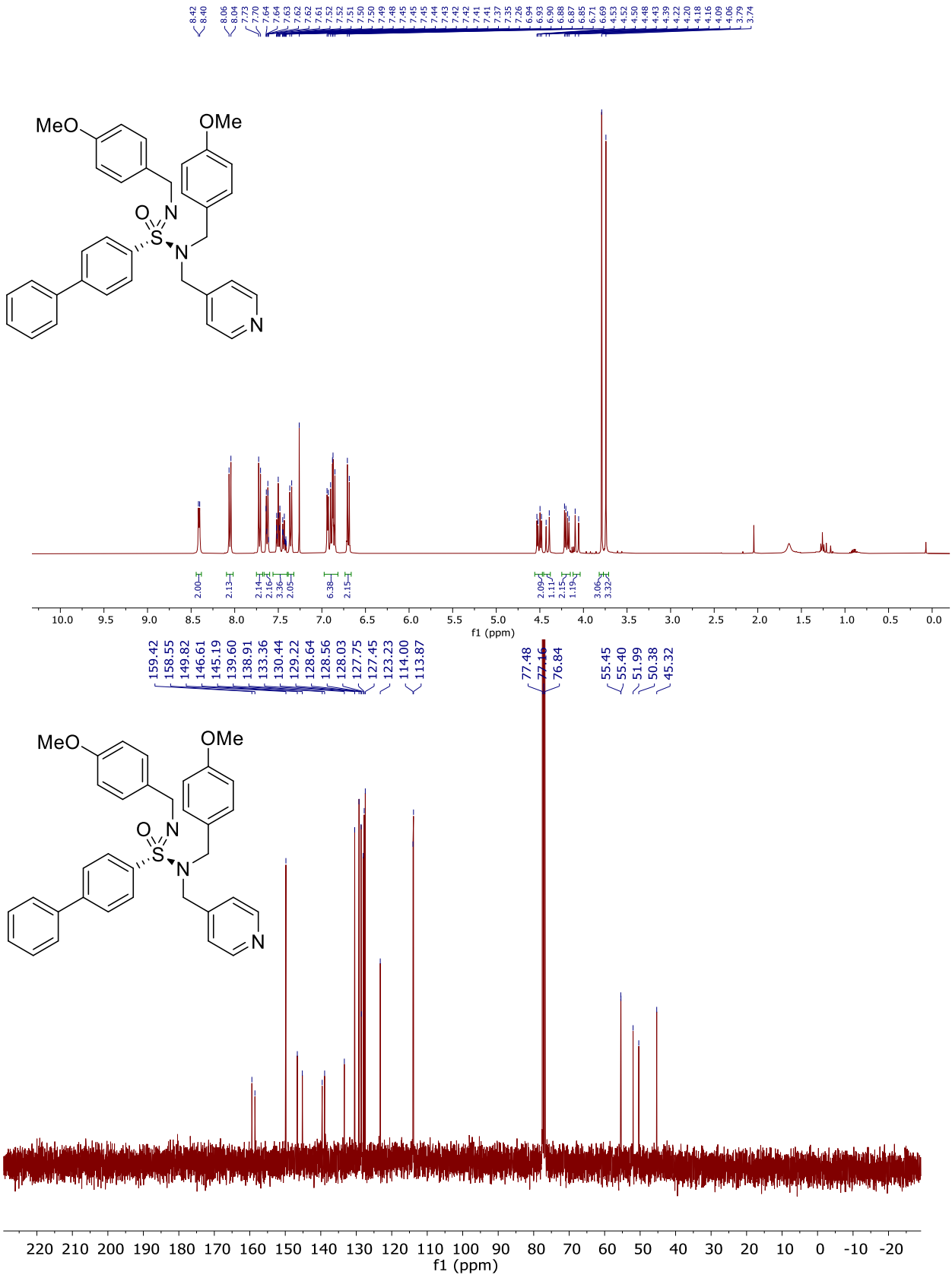


**(*S*)-*N*,*N*'-bis(4-methoxybenzyl)-*N*-(naphthalen-2-ylmethyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ah)**

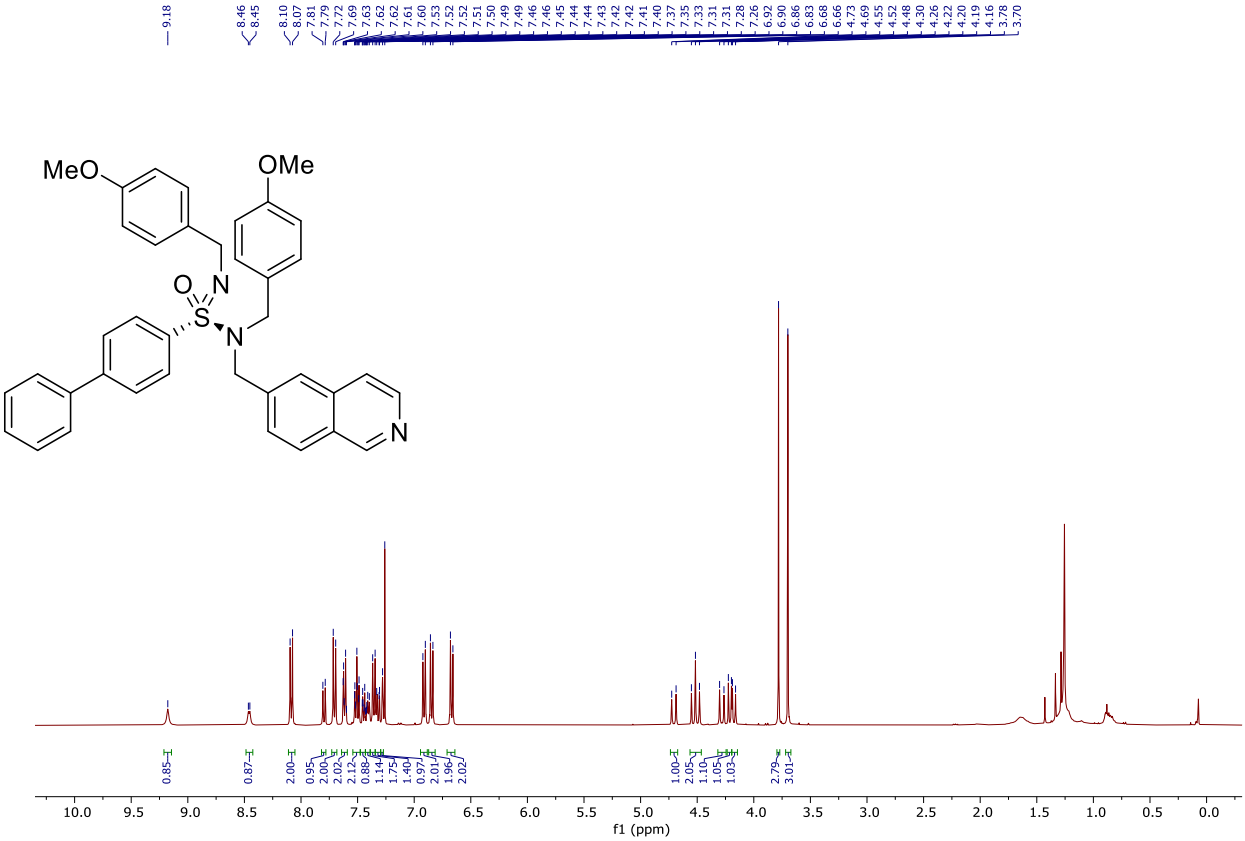


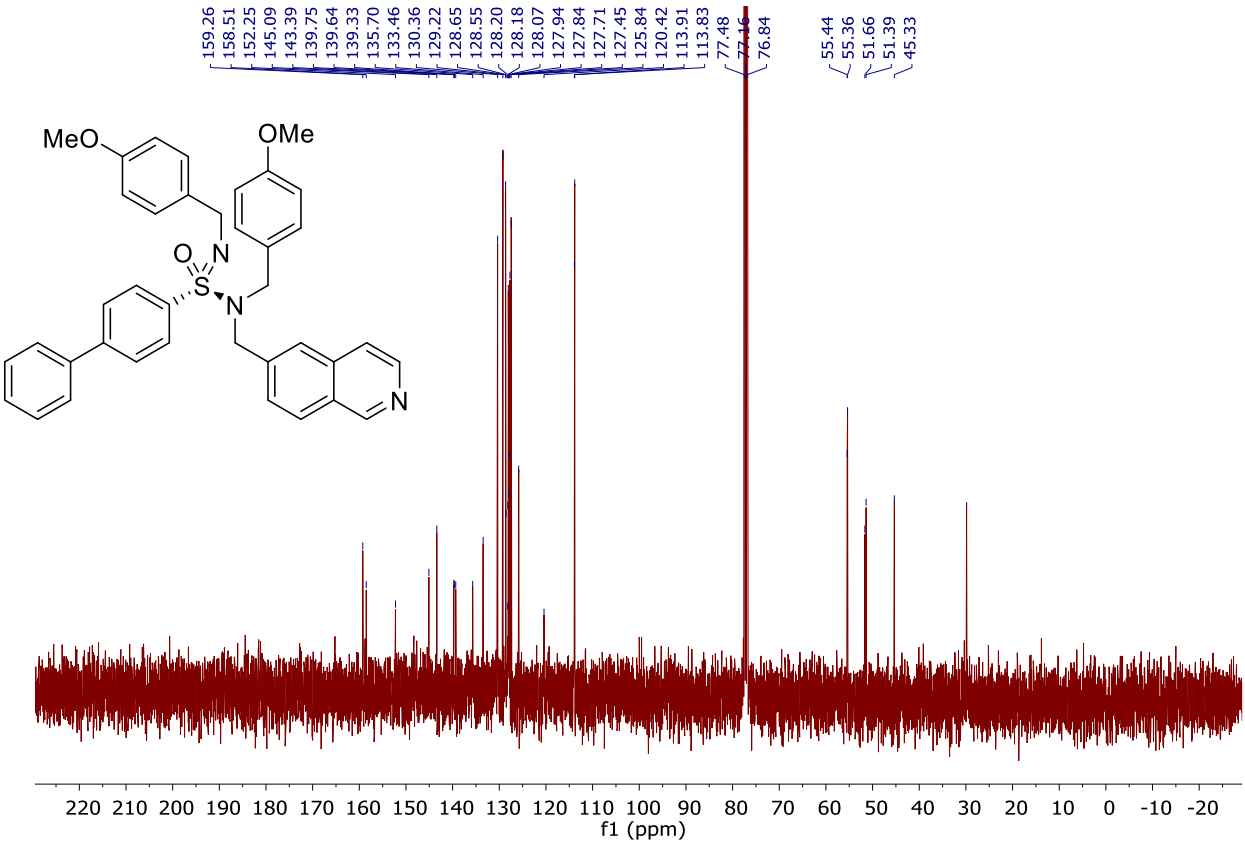



**(*S*)-*N*,*N*'-bis(4-methoxybenzyl)-*N*-(pyridin-4-ylmethyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ai)**

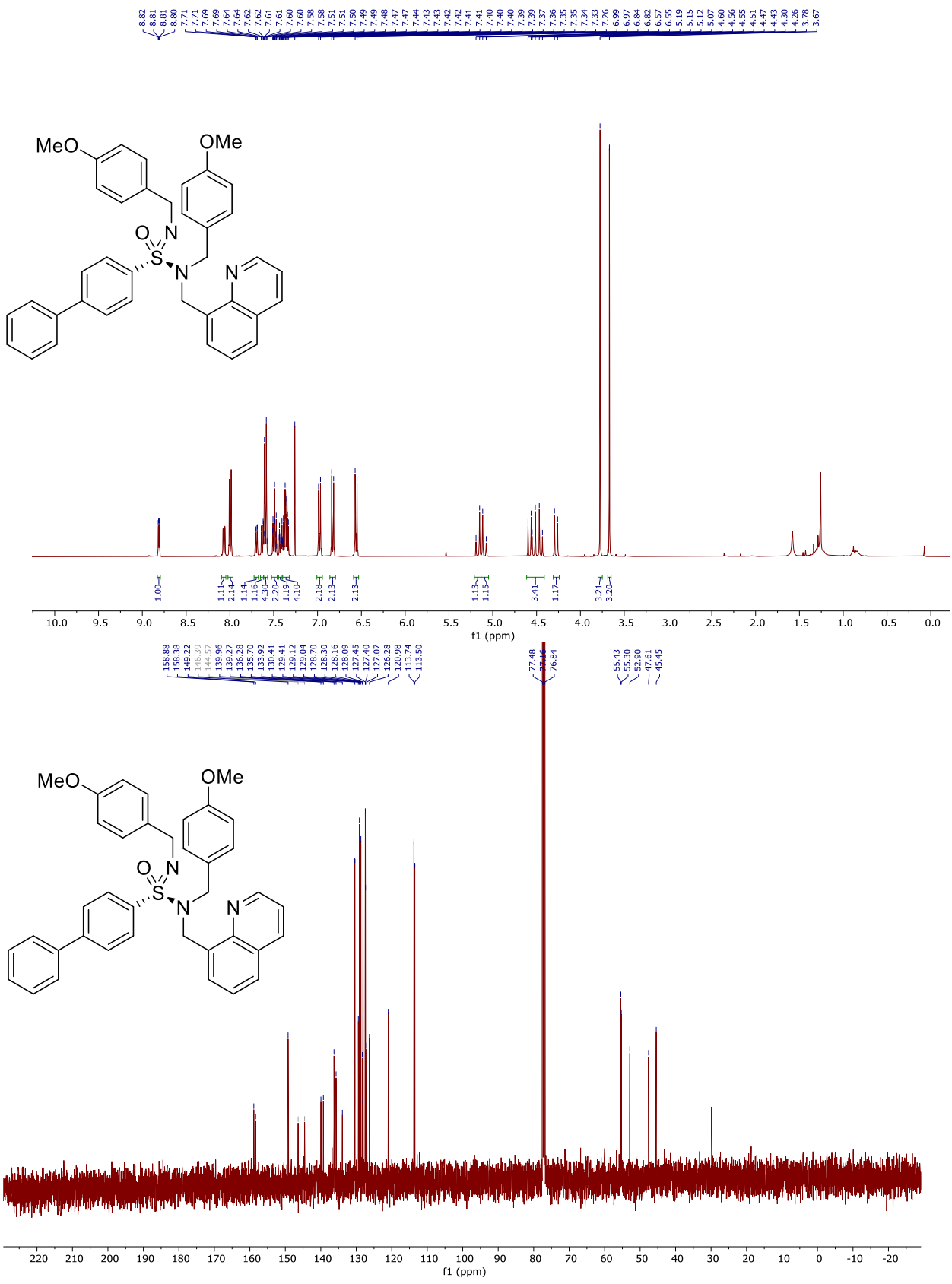


**(*S*)-*N*-(isoquinolin-6-ylmethyl)-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74aj)**

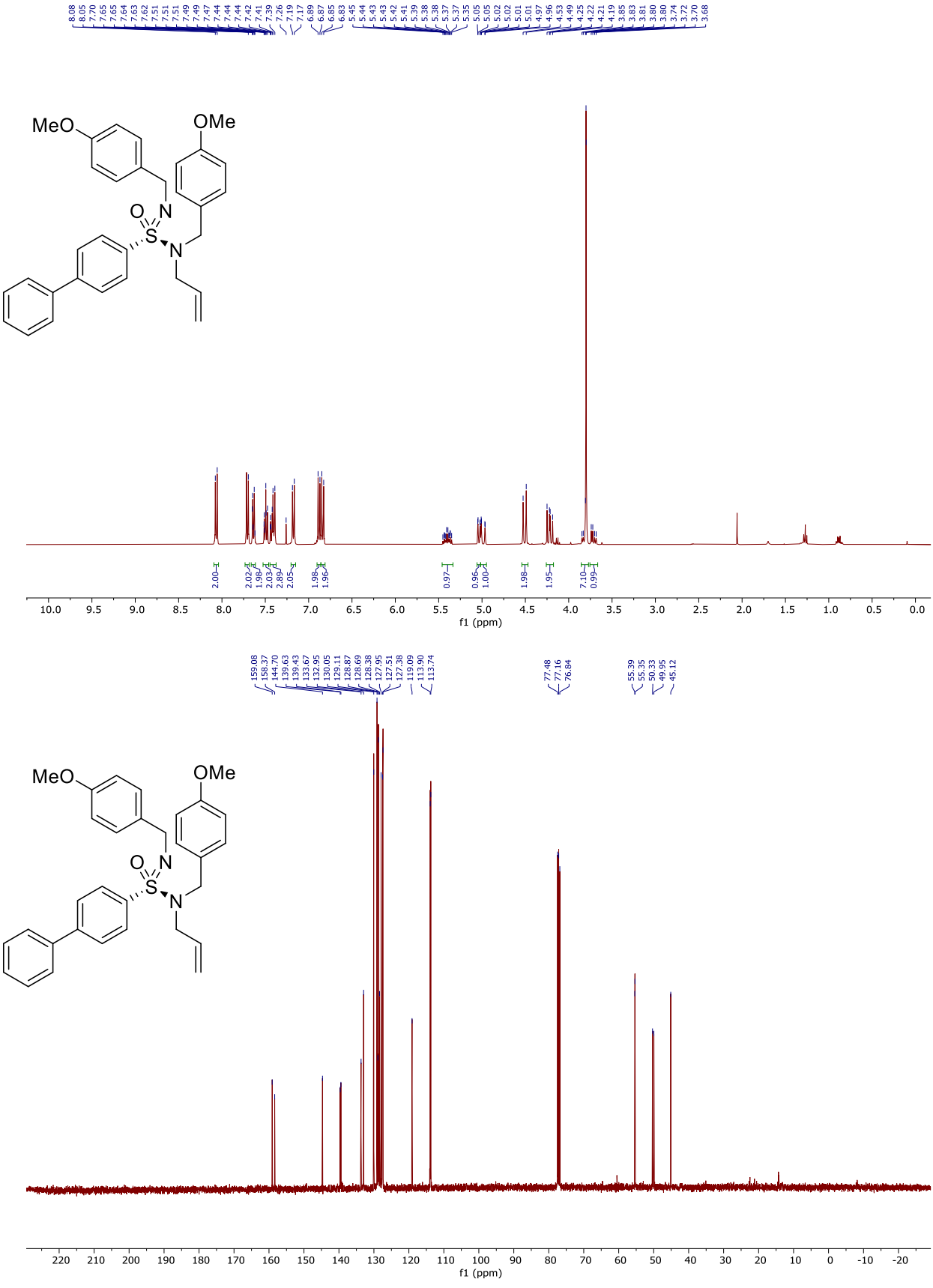


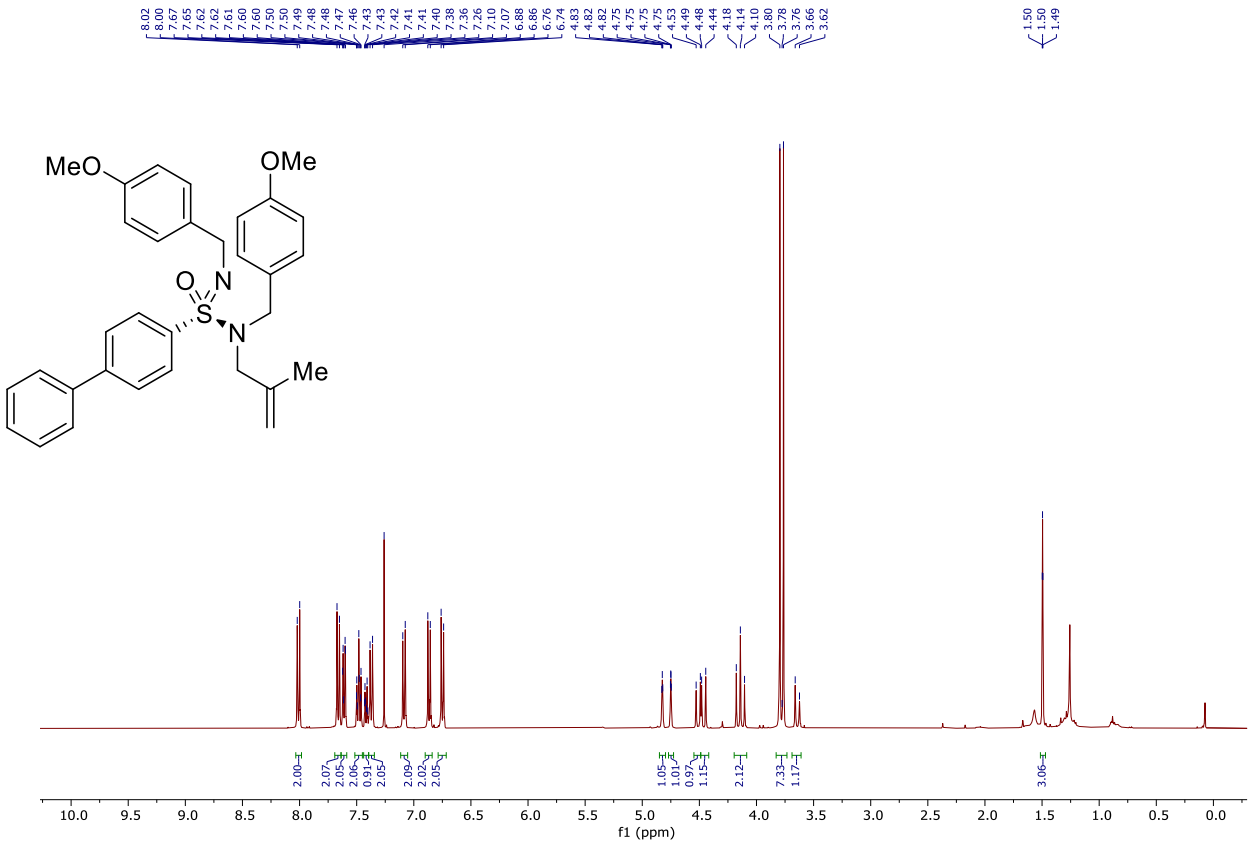
**(*S*)-*N*,*N*'-bis(4-methoxybenzyl)-*N*-(quinolin-8-ylmethyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ak)**

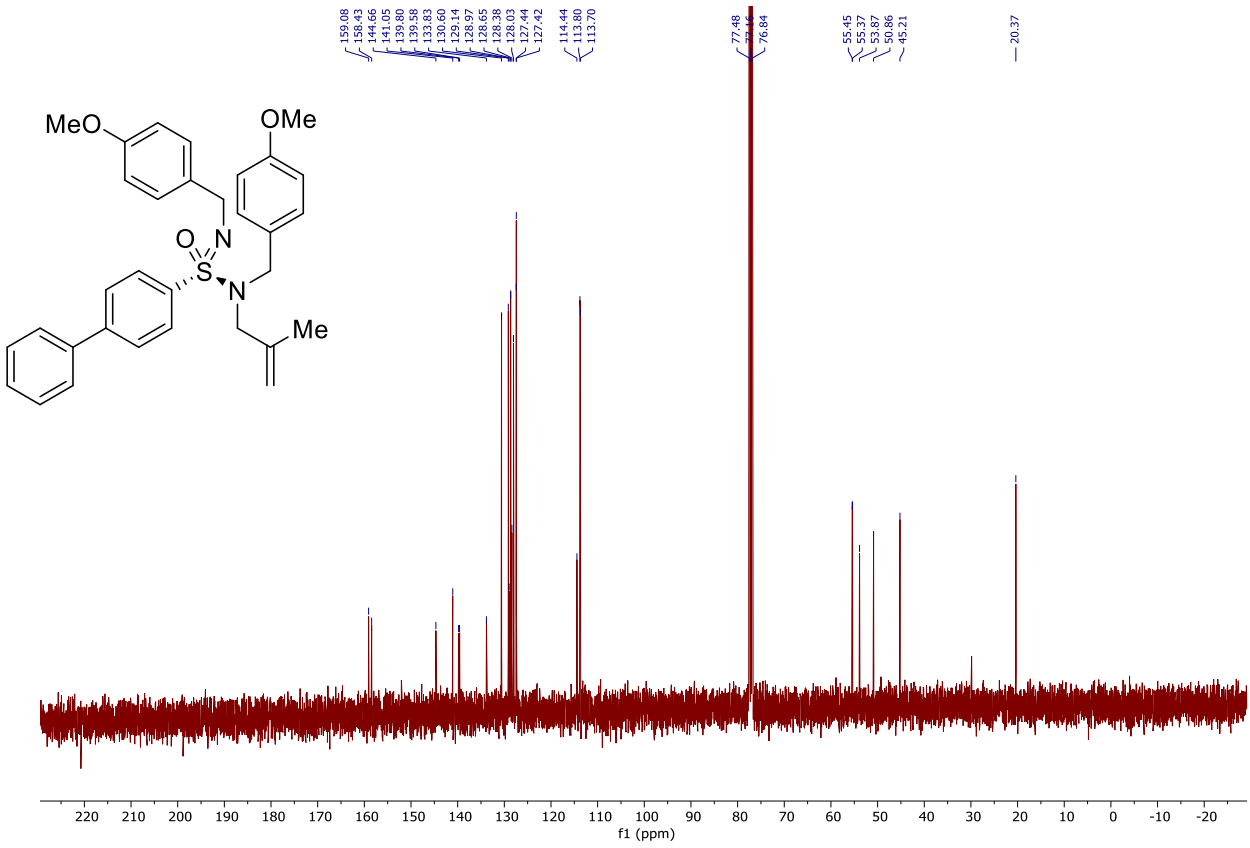


**(*S*)-*N*-allyl-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamidede (74al)**

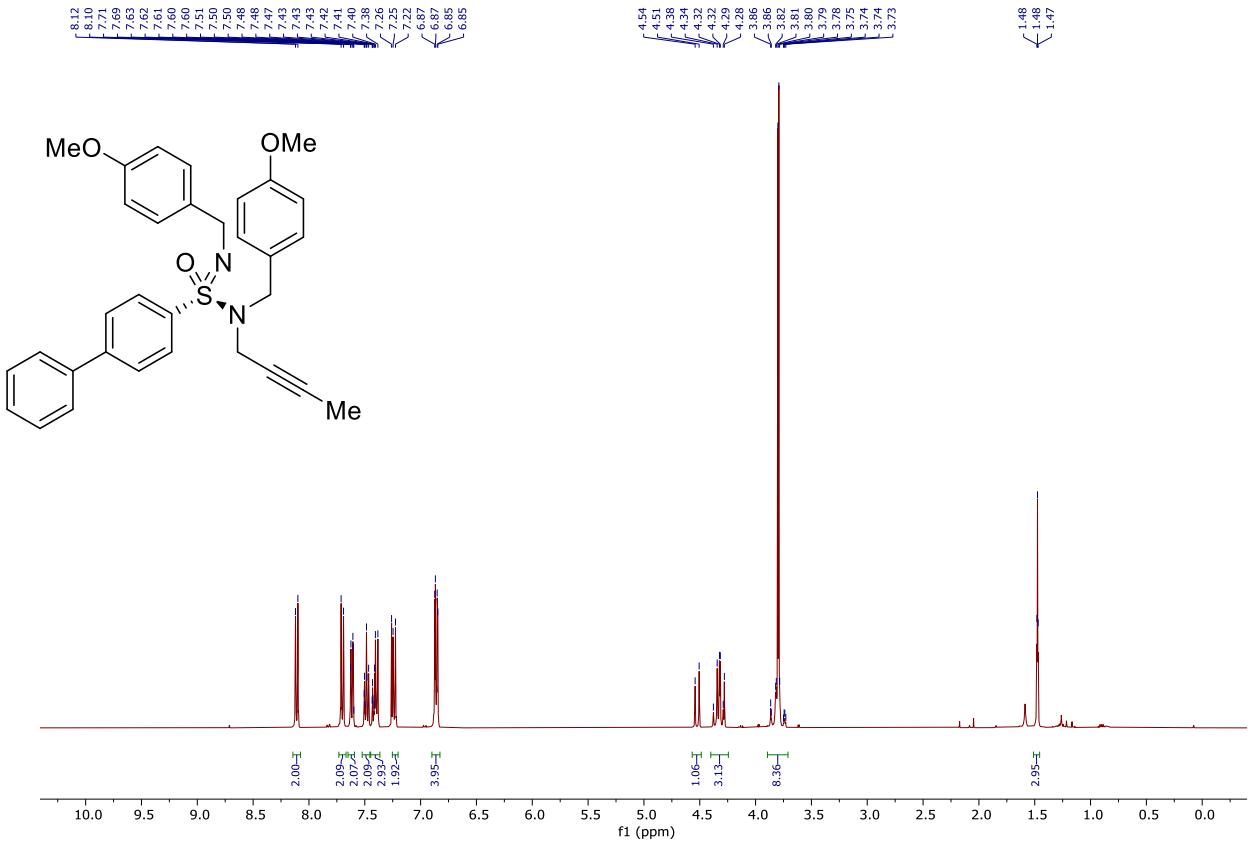


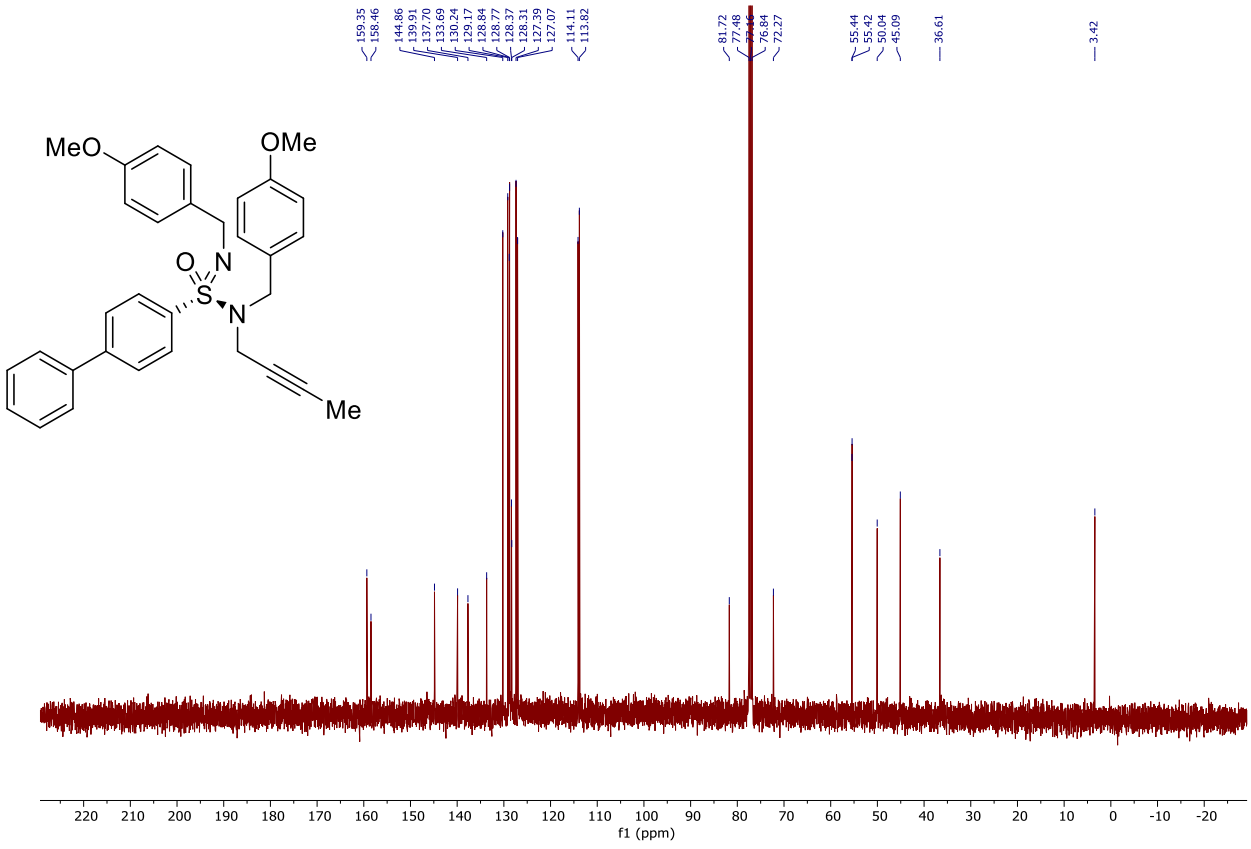
**(*S*)-*N*,*N*'-bis(4-methoxybenzyl)-*N*-(2-methylallyl)-[1,1'-biphenyl]-4-sulfonimidamide (74am)**



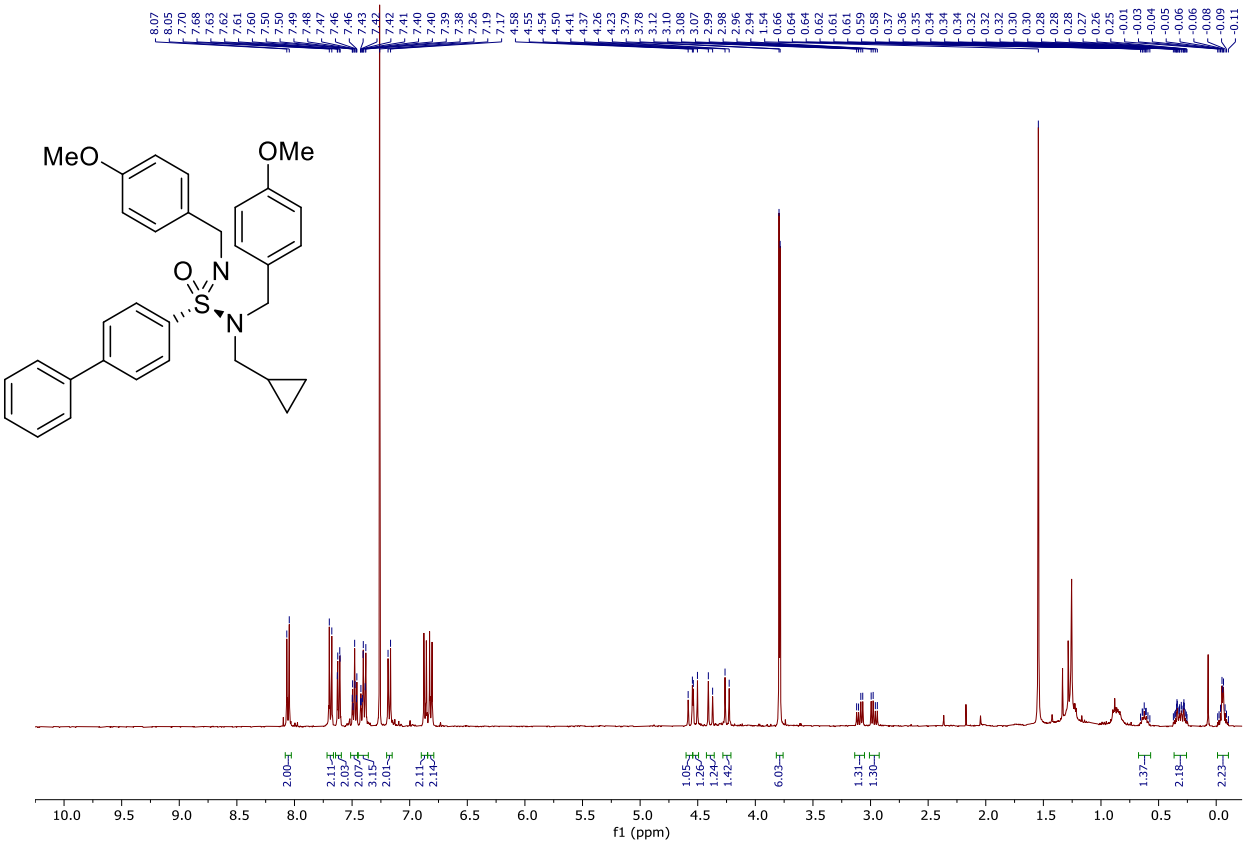



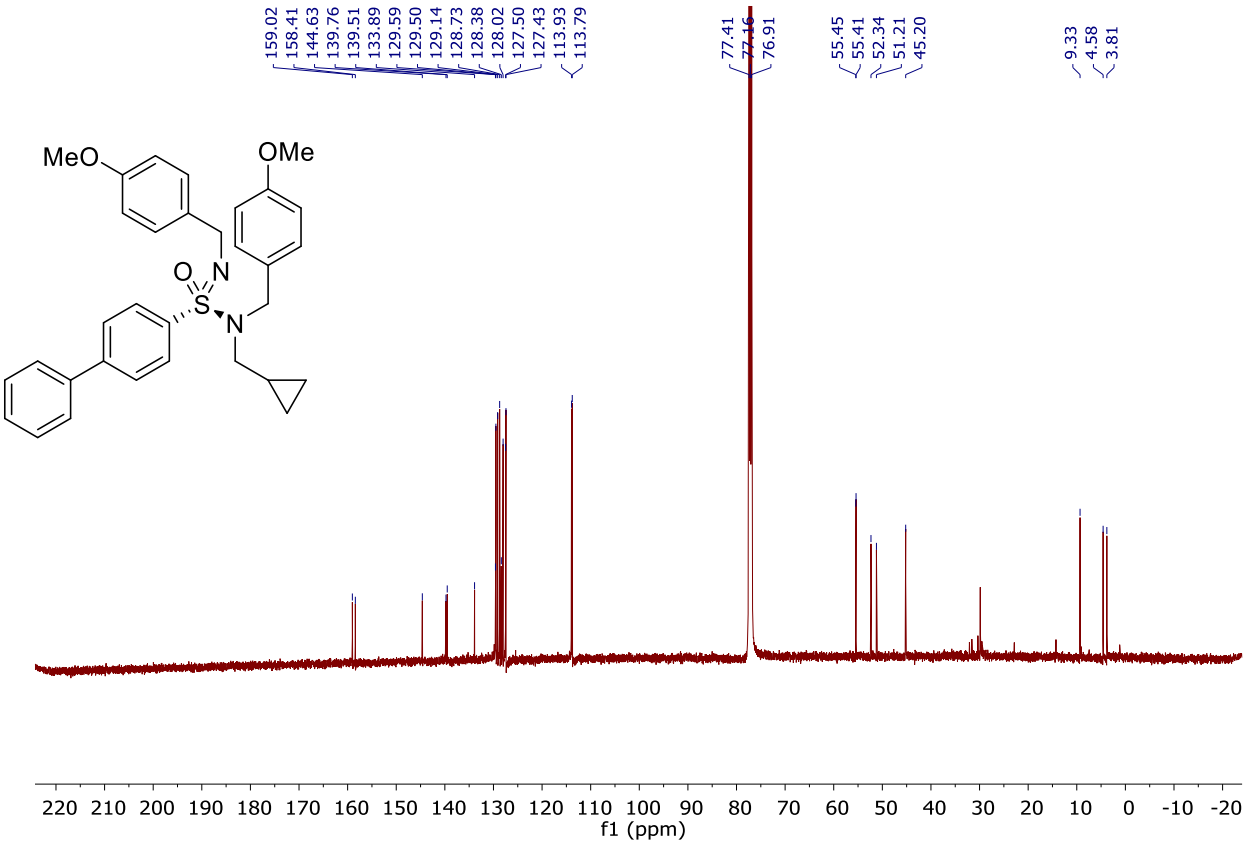
**(*S*)-*N*-(but-2-yn-1-yl)-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74an)**



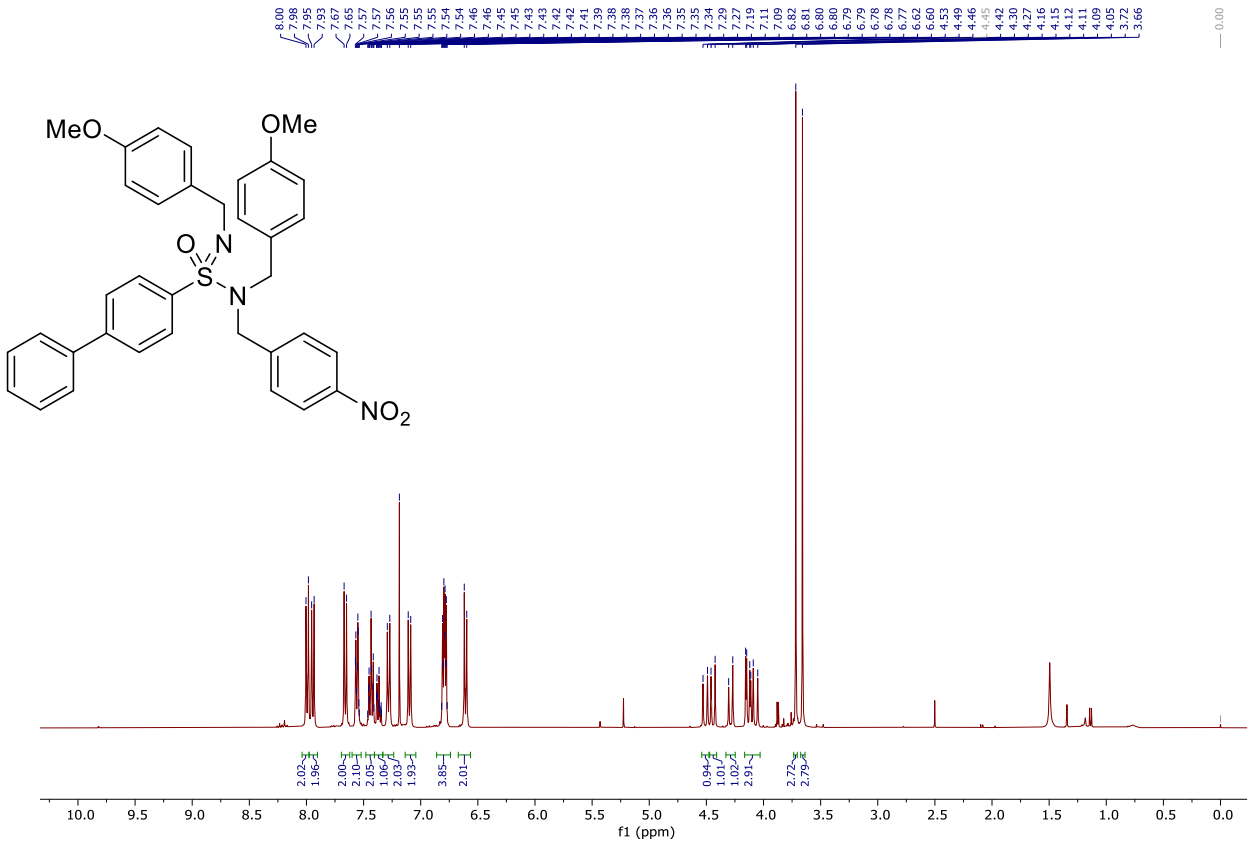



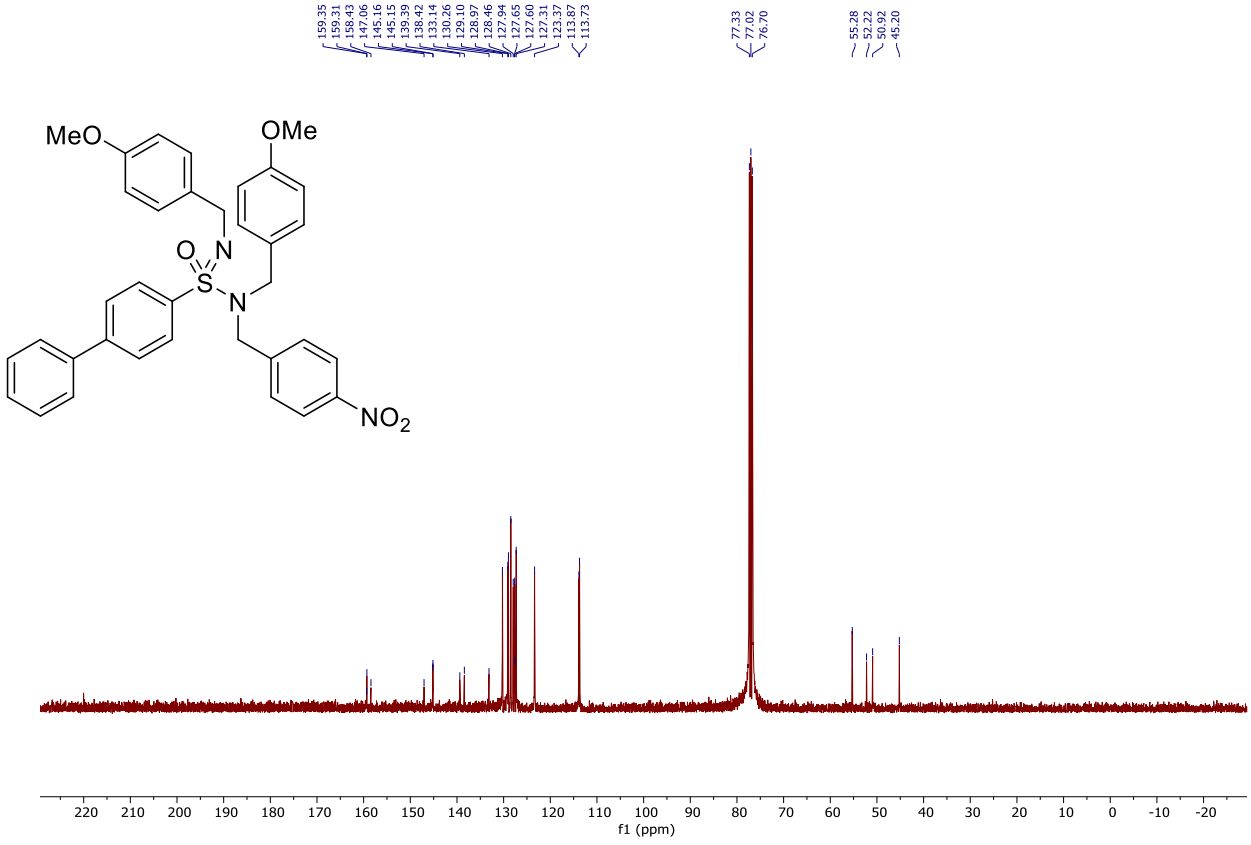
**(*S*)-*N*-(cyclopropylmethyl)-*N*,*N*'-bis(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ao)**



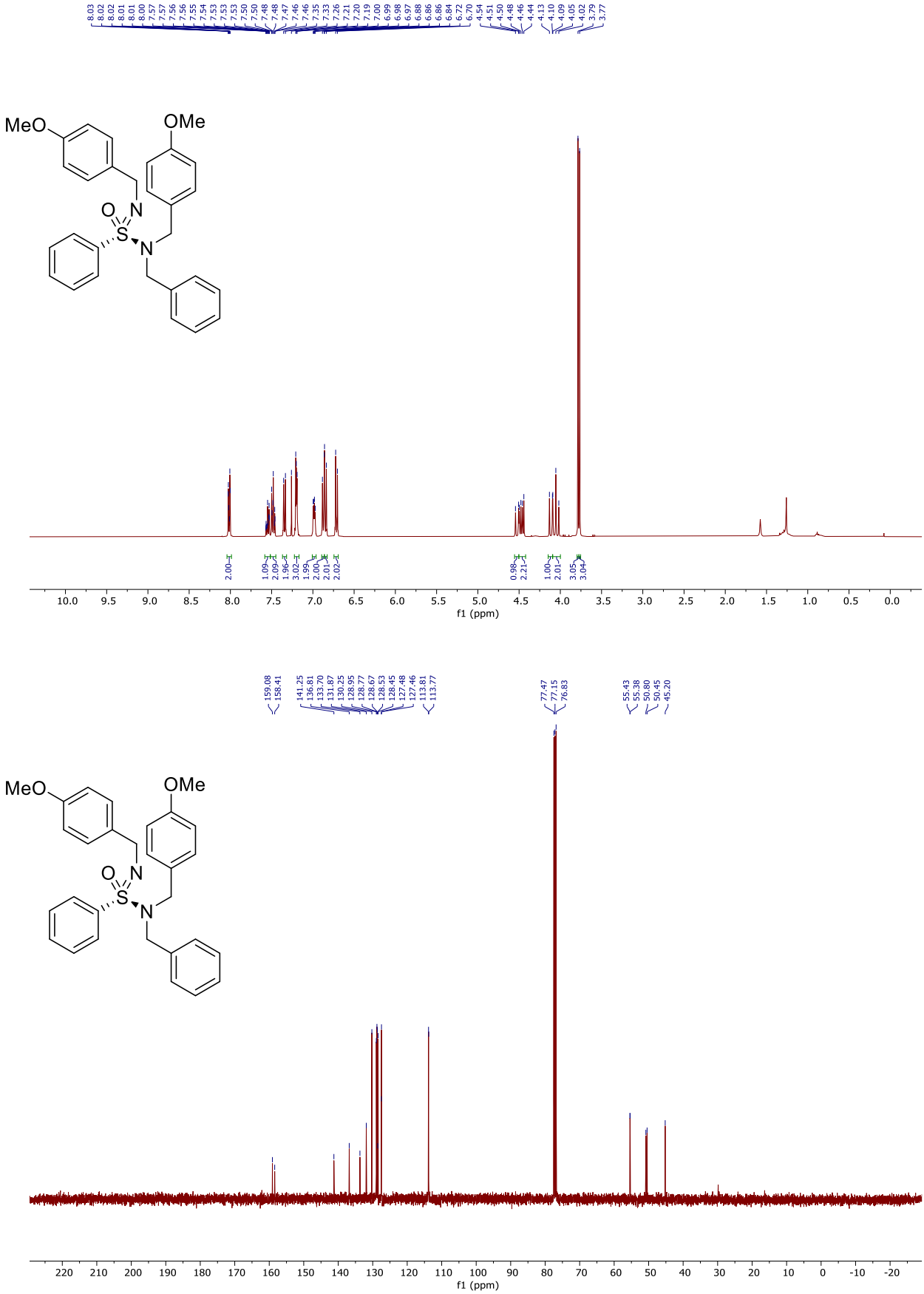



**N,N'-bis(4-methoxybenzyl)-N-(4-nitrobenzyl)-[1,1'-biphenyl]-4-sulfonimidamide (74ap)**

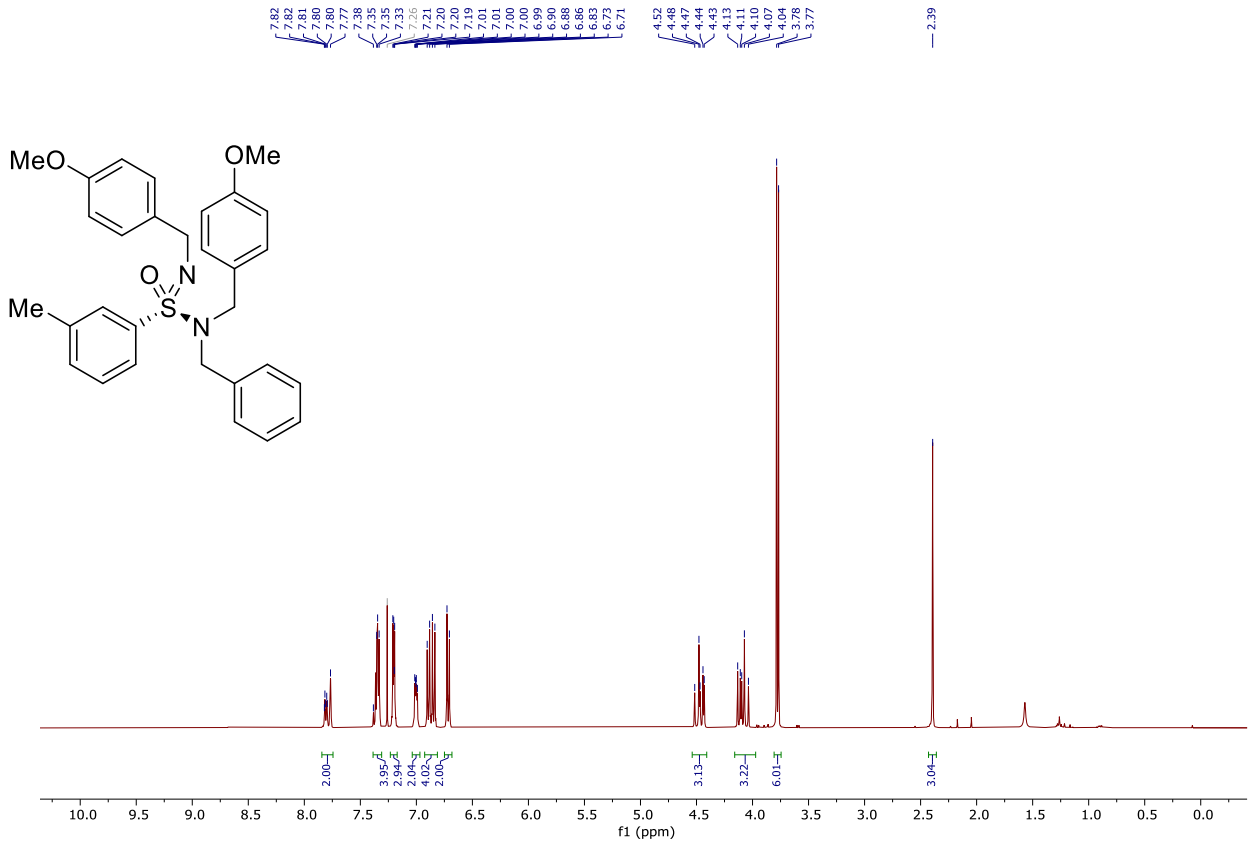


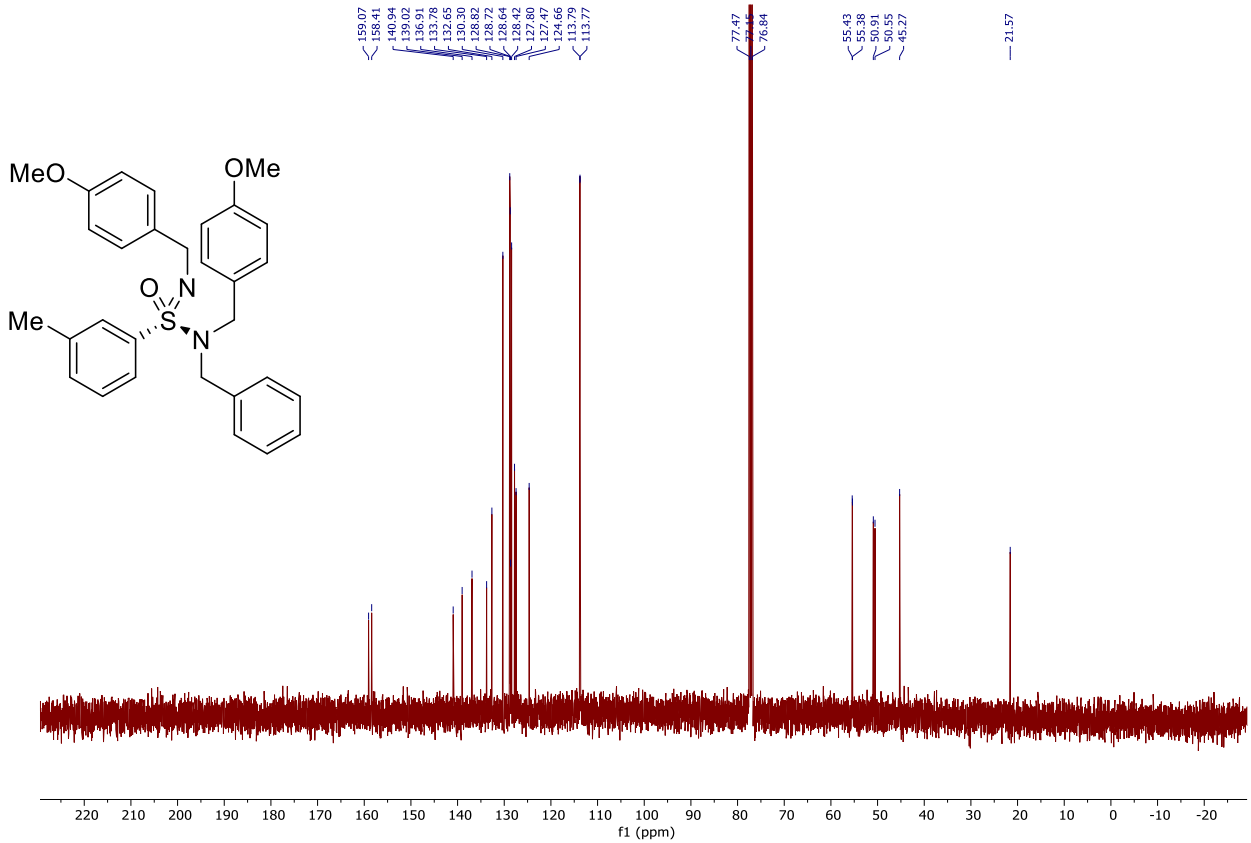



## (*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)benzenesulfonimidamide 74c)

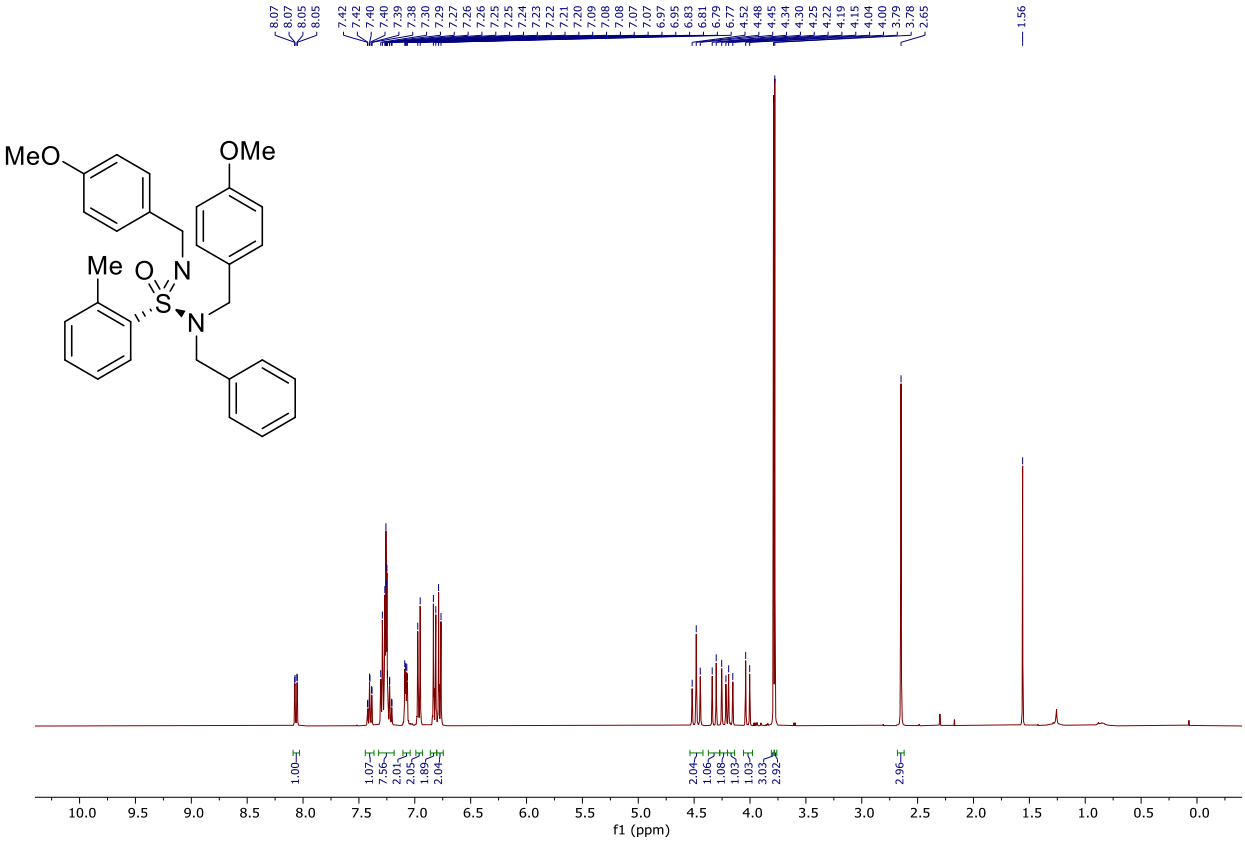


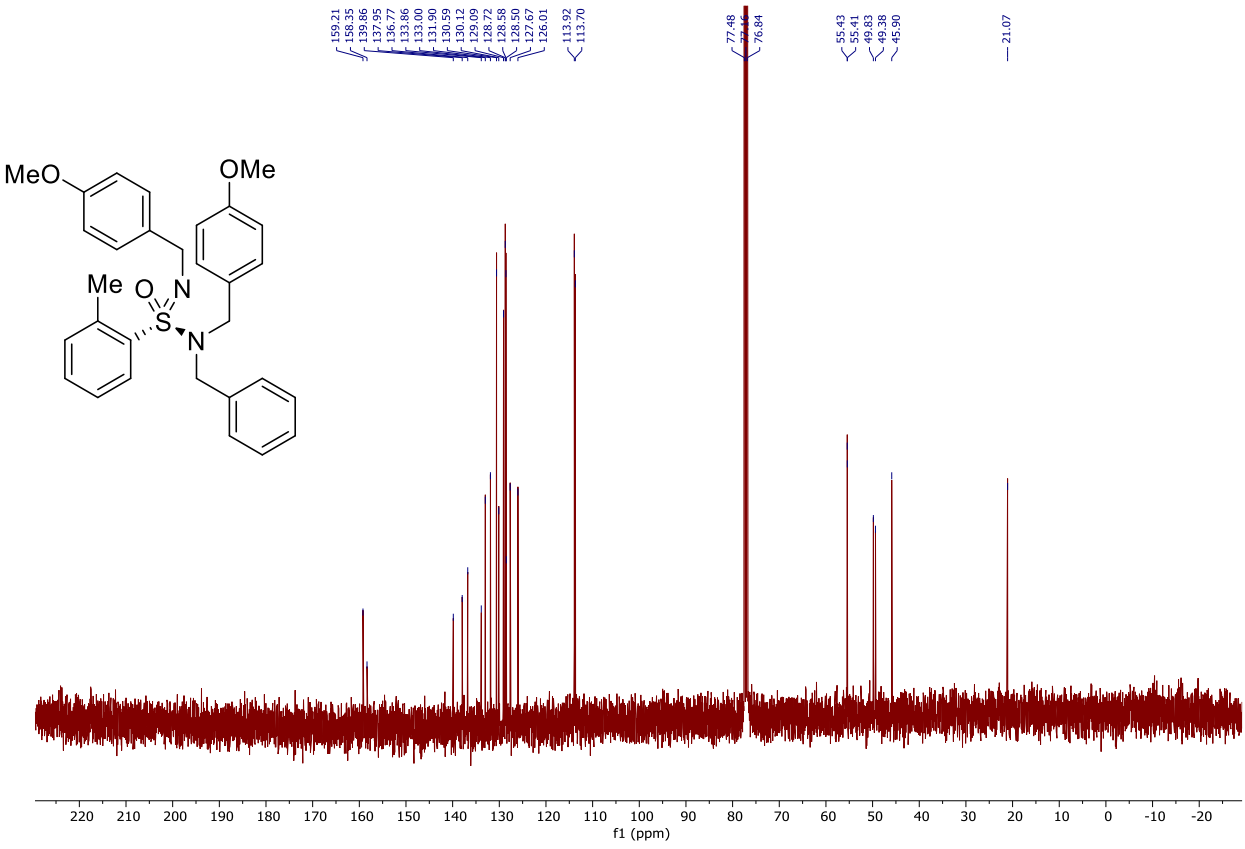
## (*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-3-methylbenzenesulfonimidamide (74d)



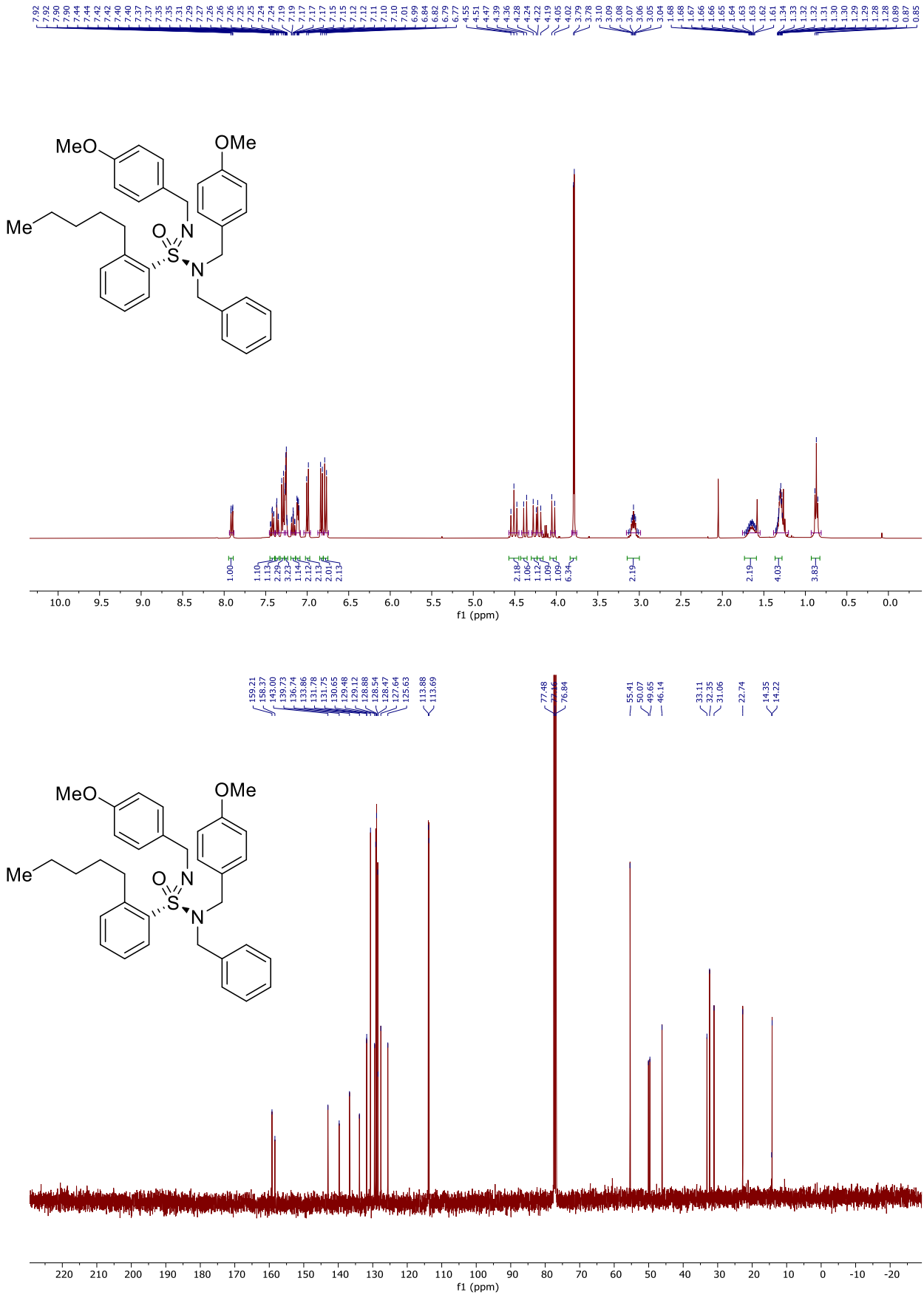



## (*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-2-methylbenzenesulfonimidamide (74e)

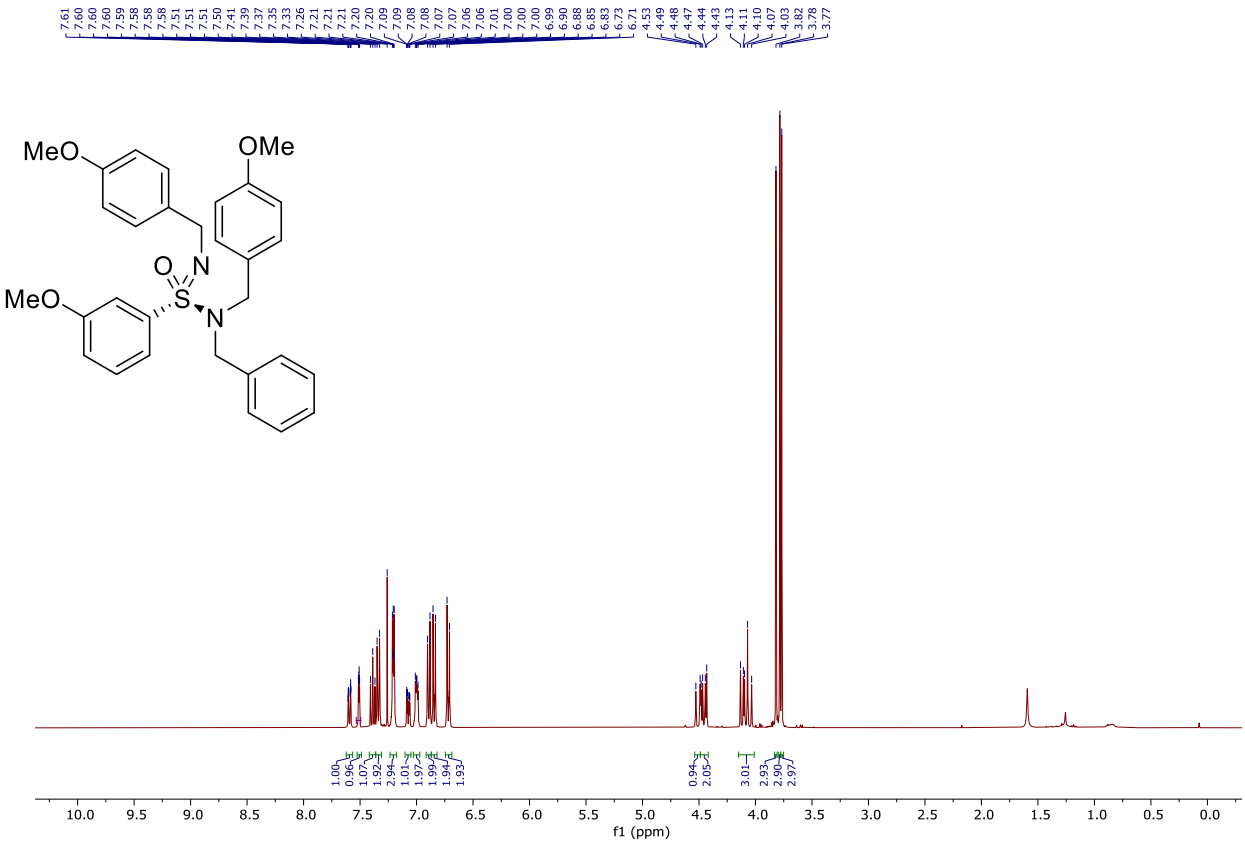


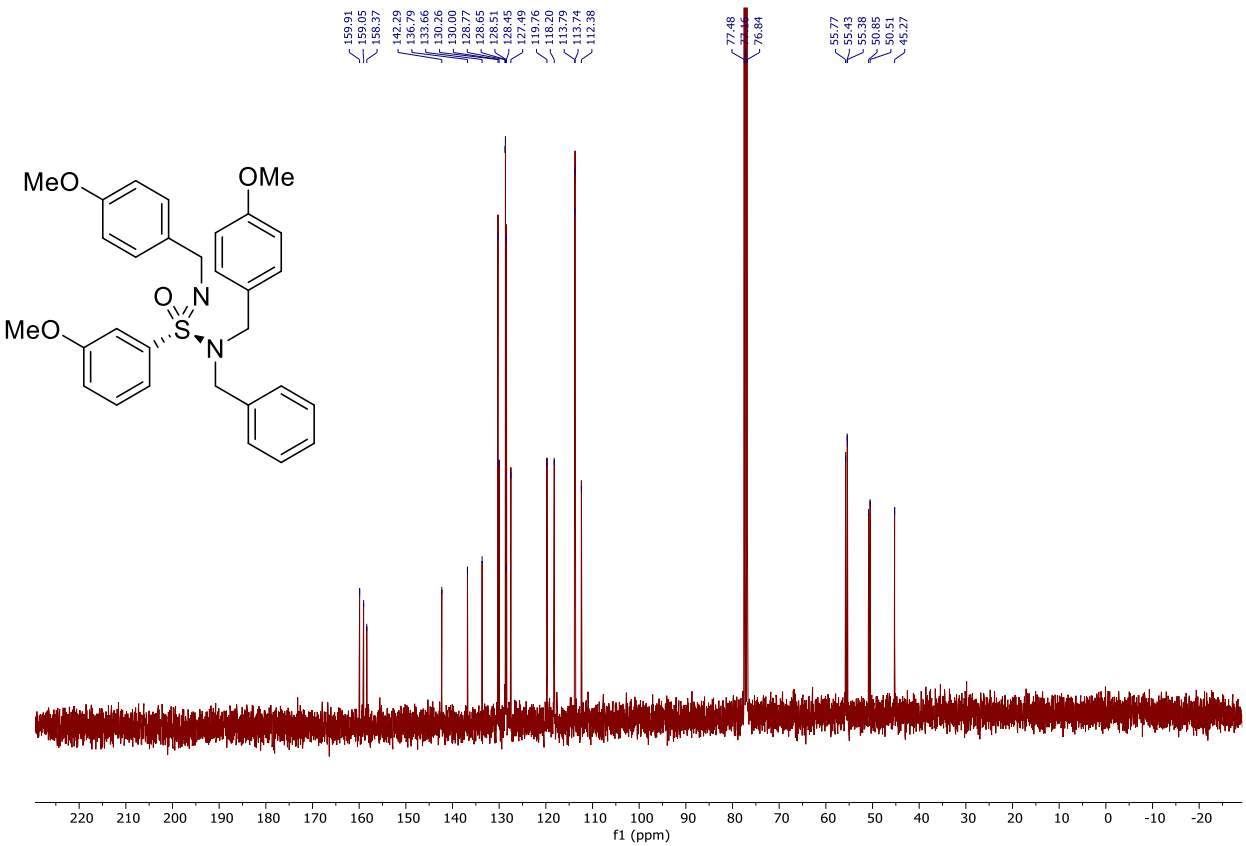



## (*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-2-pentylbenzenesulfonimidamide (74f)

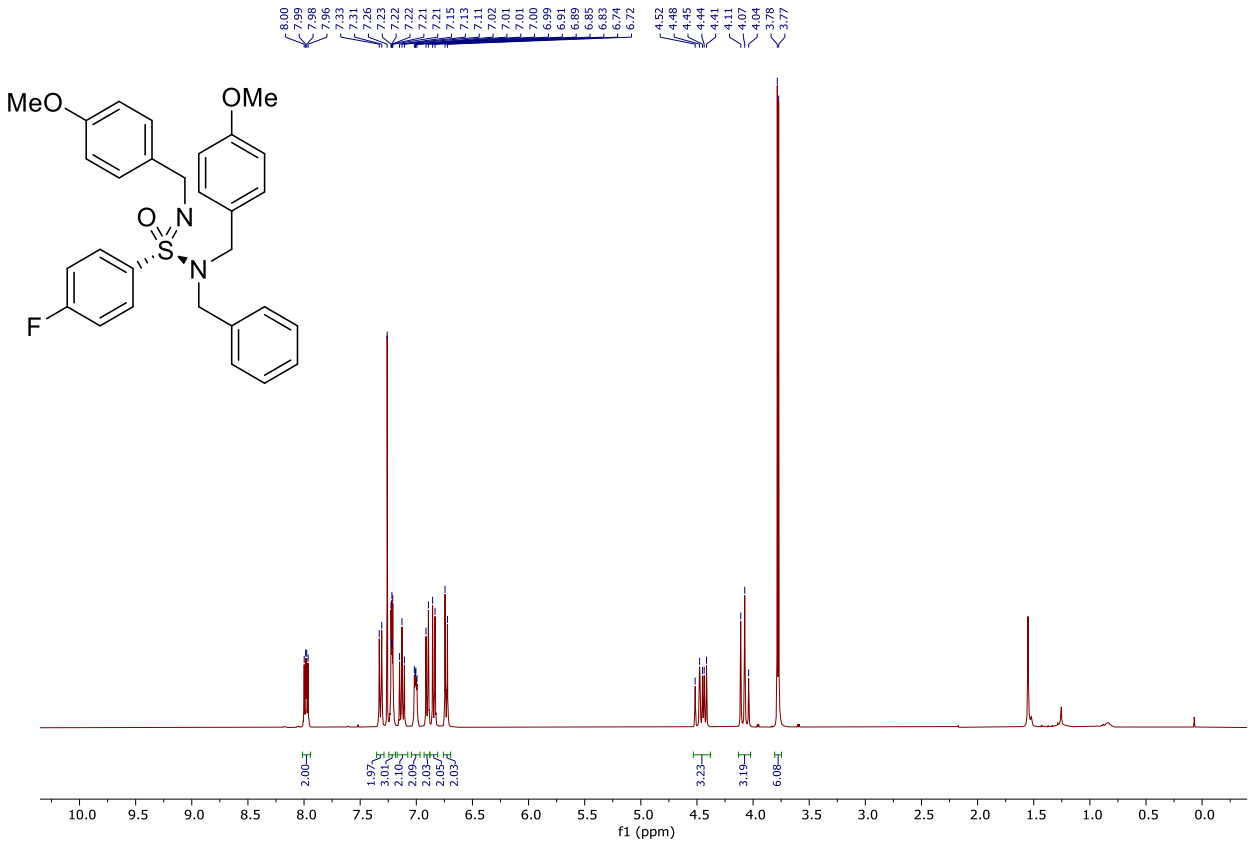


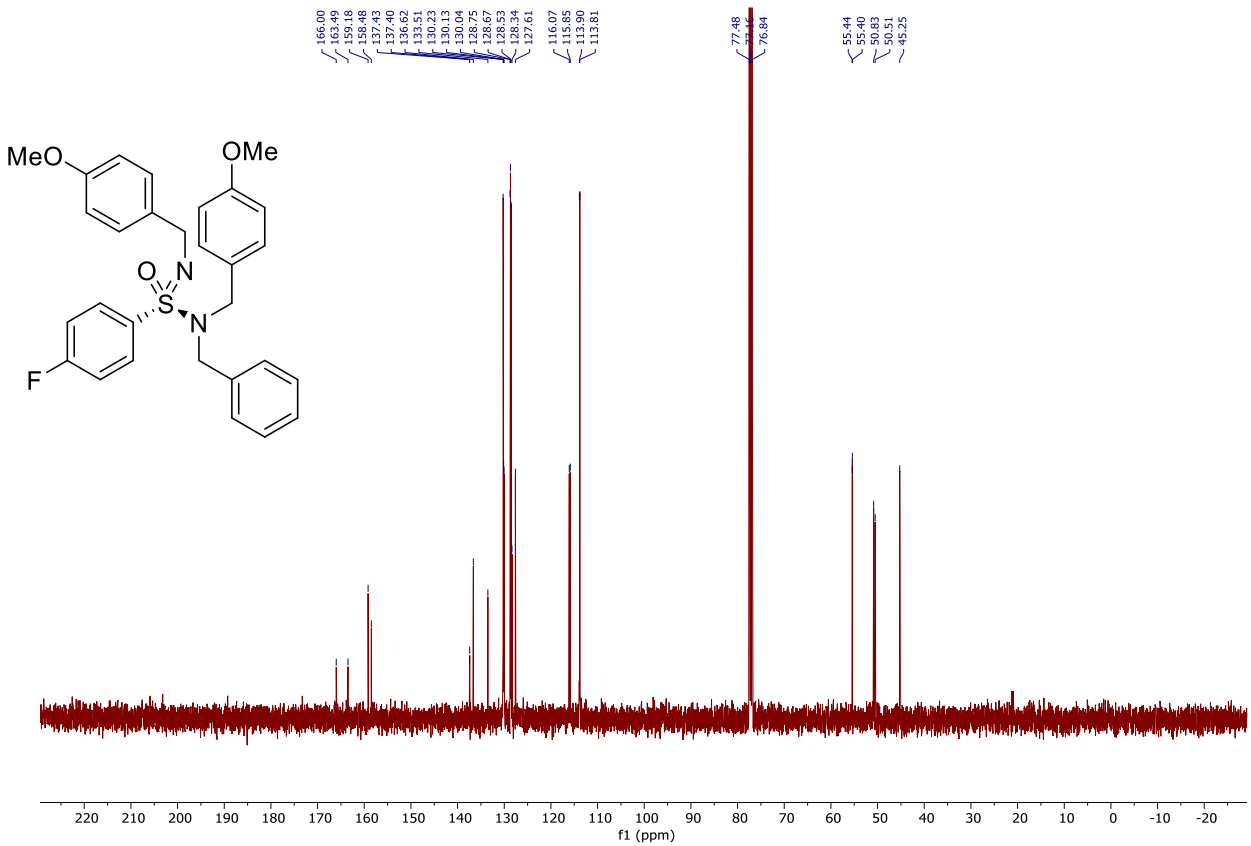
## (*S*)-*N*-benzyl-3-methoxy-*N*,*N*′-bis(4-methoxybenzyl)benzenesulfonimidamide (74g)

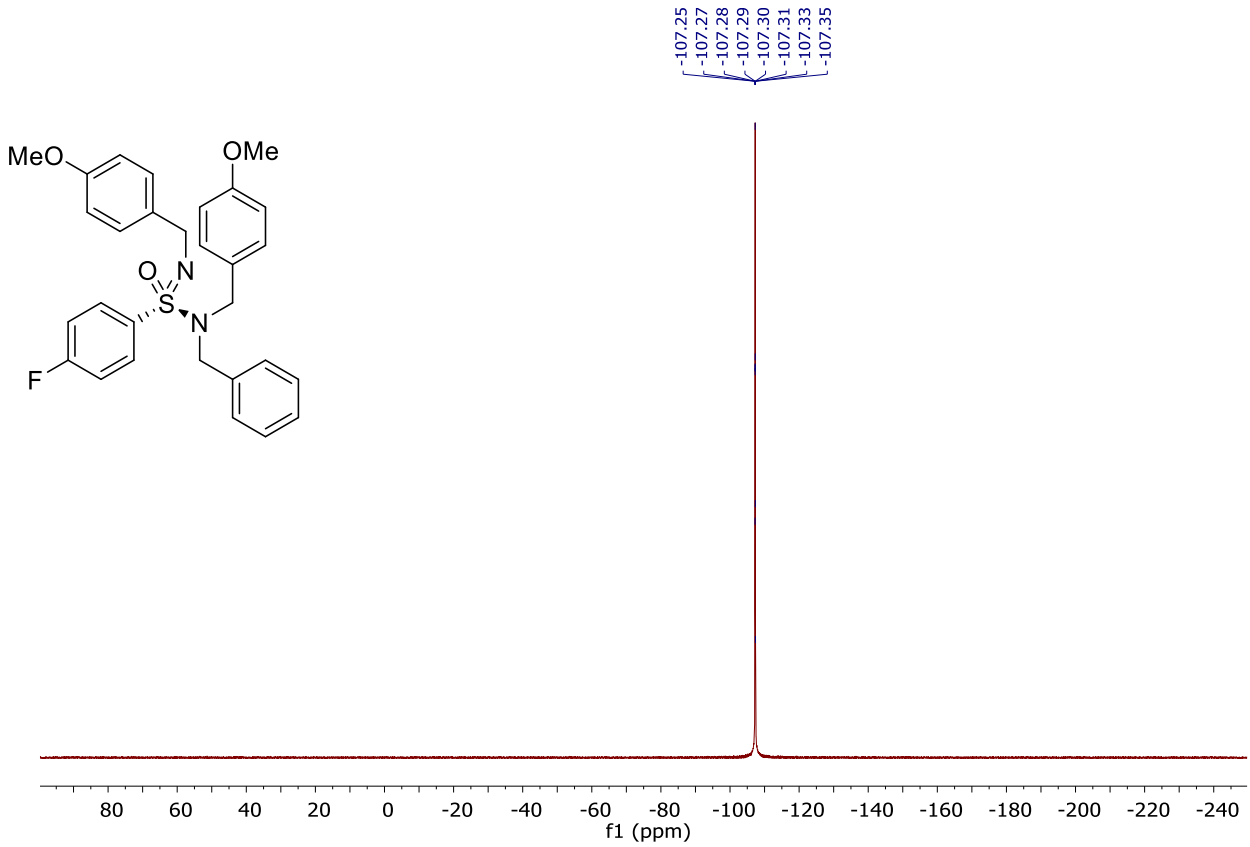


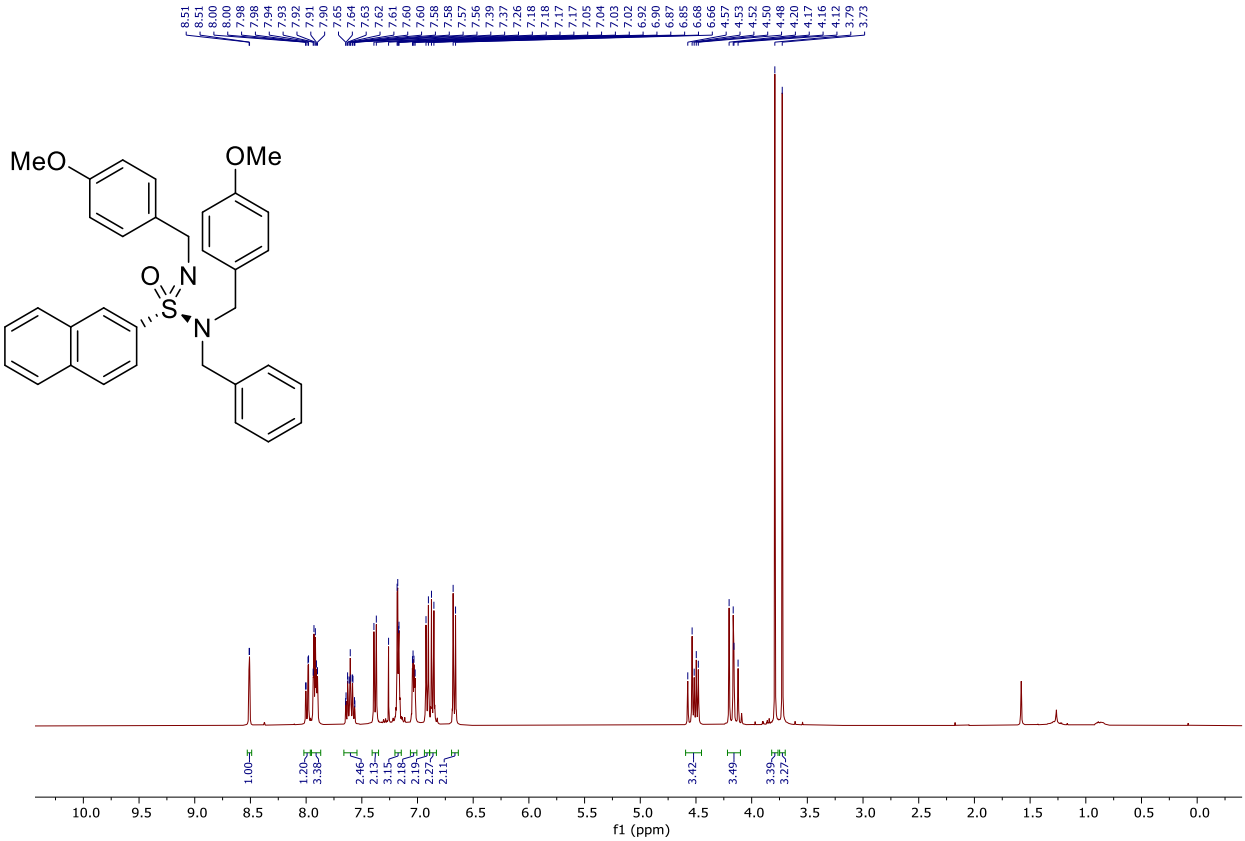
## (*S*)-*N*-benzyl-4-fluoro-*N*,*N*'-bis(4-methoxybenzyl)benzenesulfonimidamide (74h)

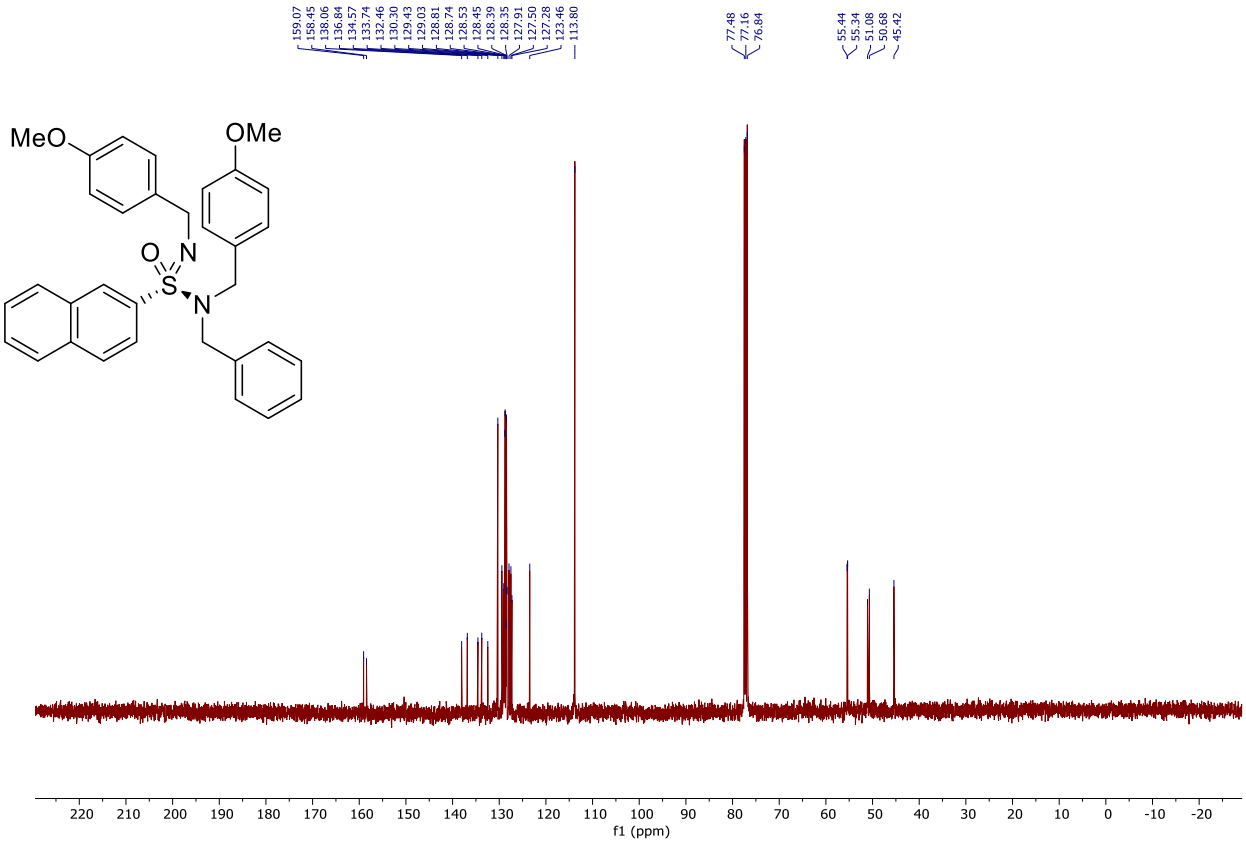


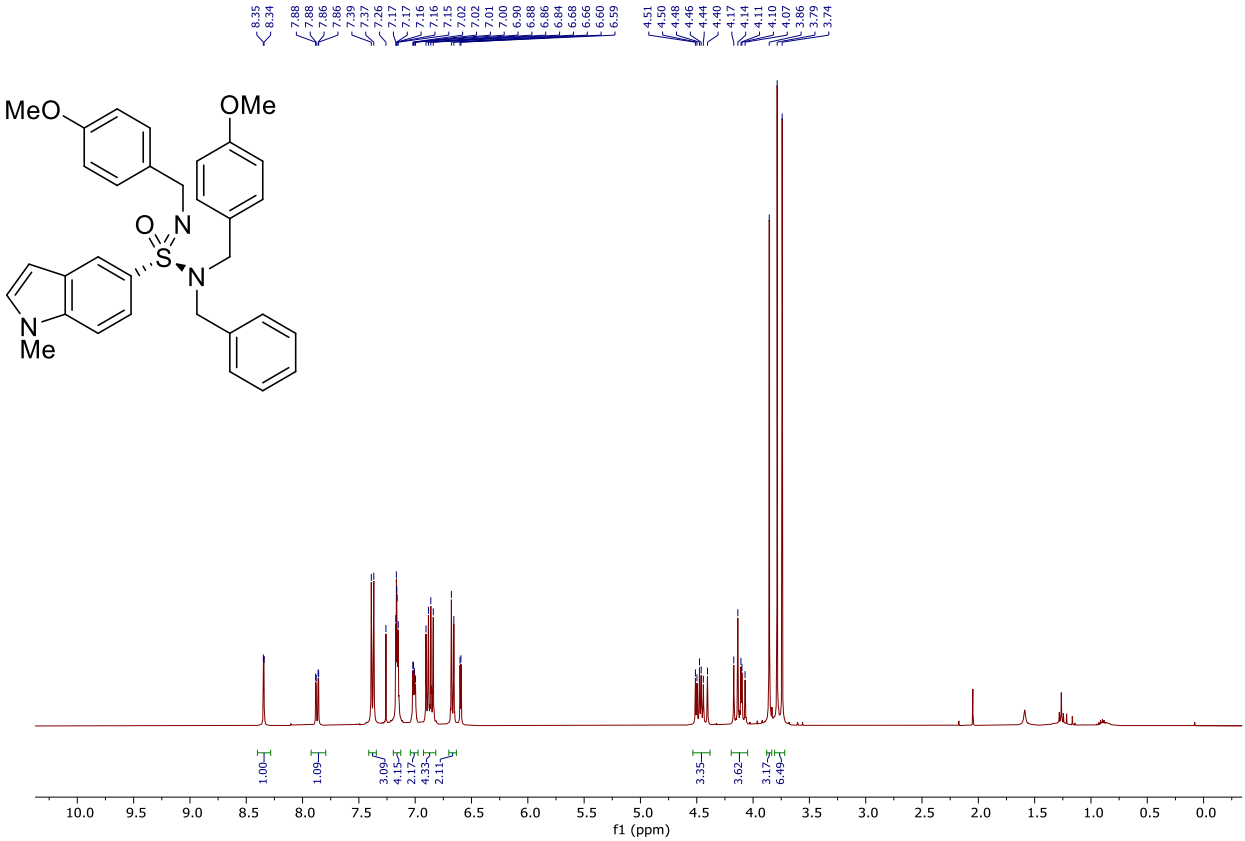

-107.25
-107.27
-107.28
-107.29
-107.30
-107.31
-107.33
-107.35
MeO
OMe
O
N
S
N
F
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

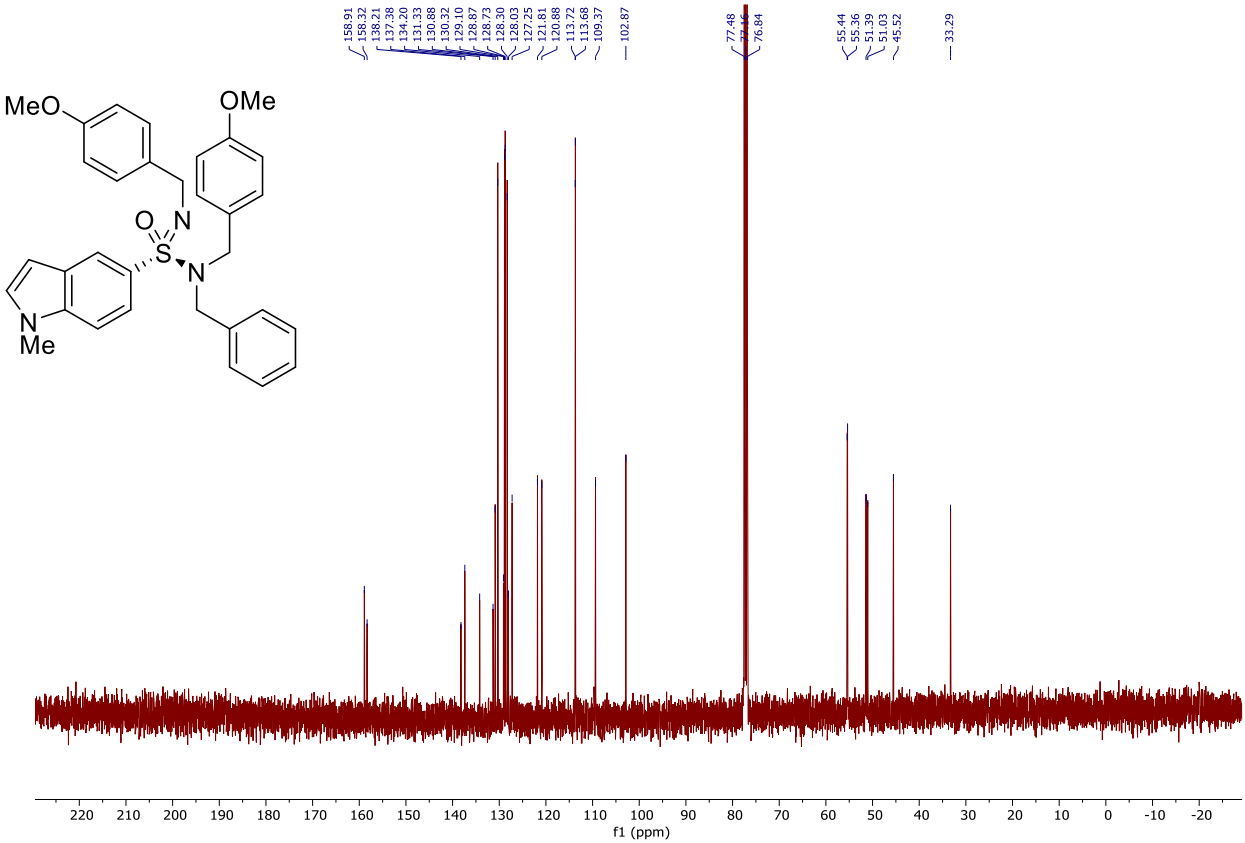
## (*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)naphthalene-2-sulfonimidamide (74i)



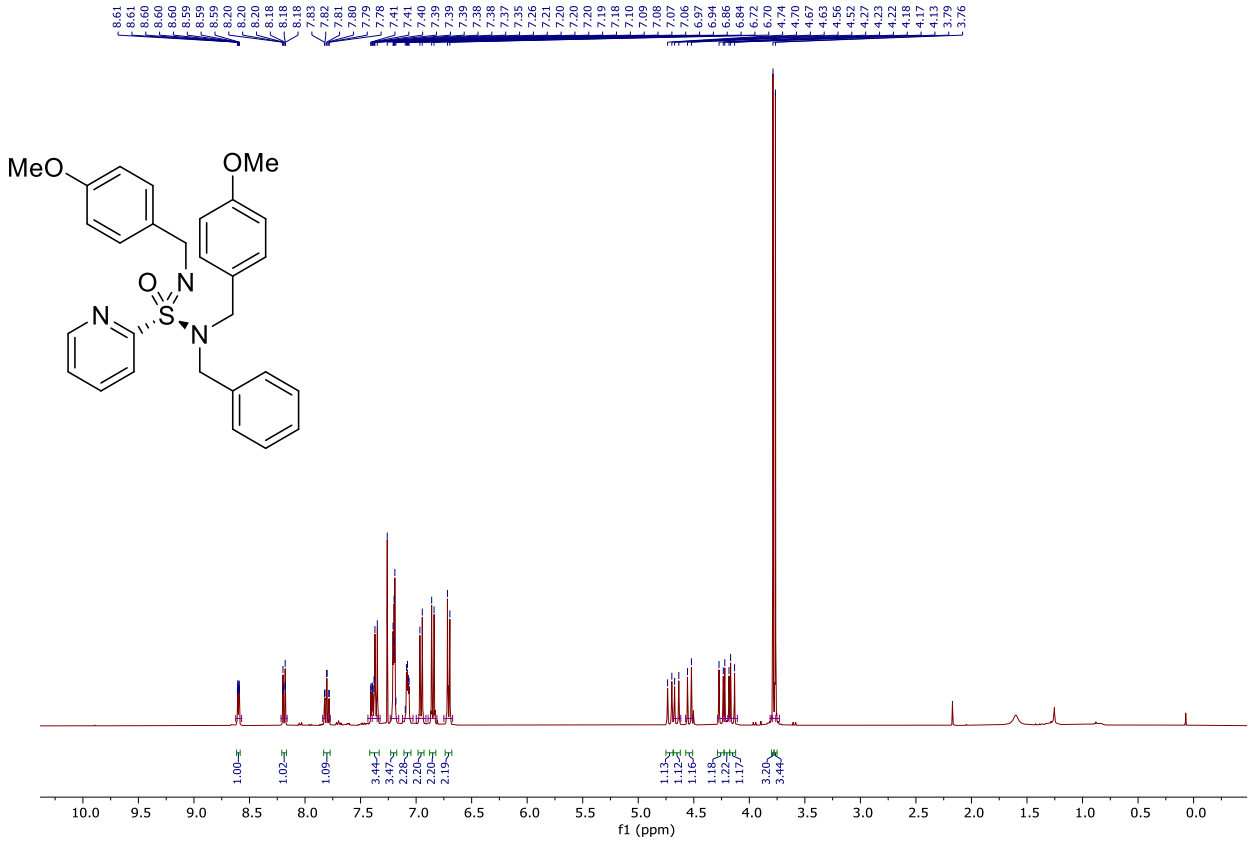



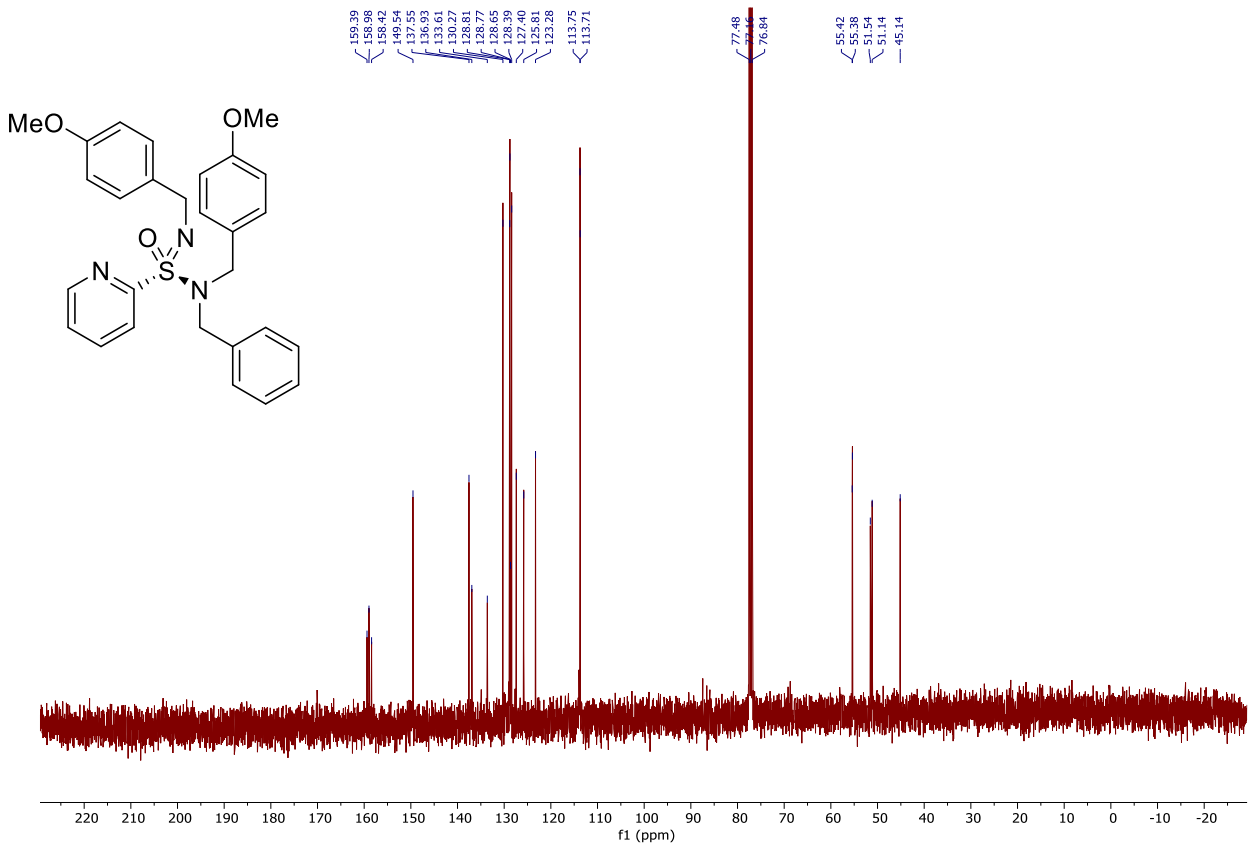
## (*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-1-methyl-1H-indole-5-sulfonimidamide (74j)



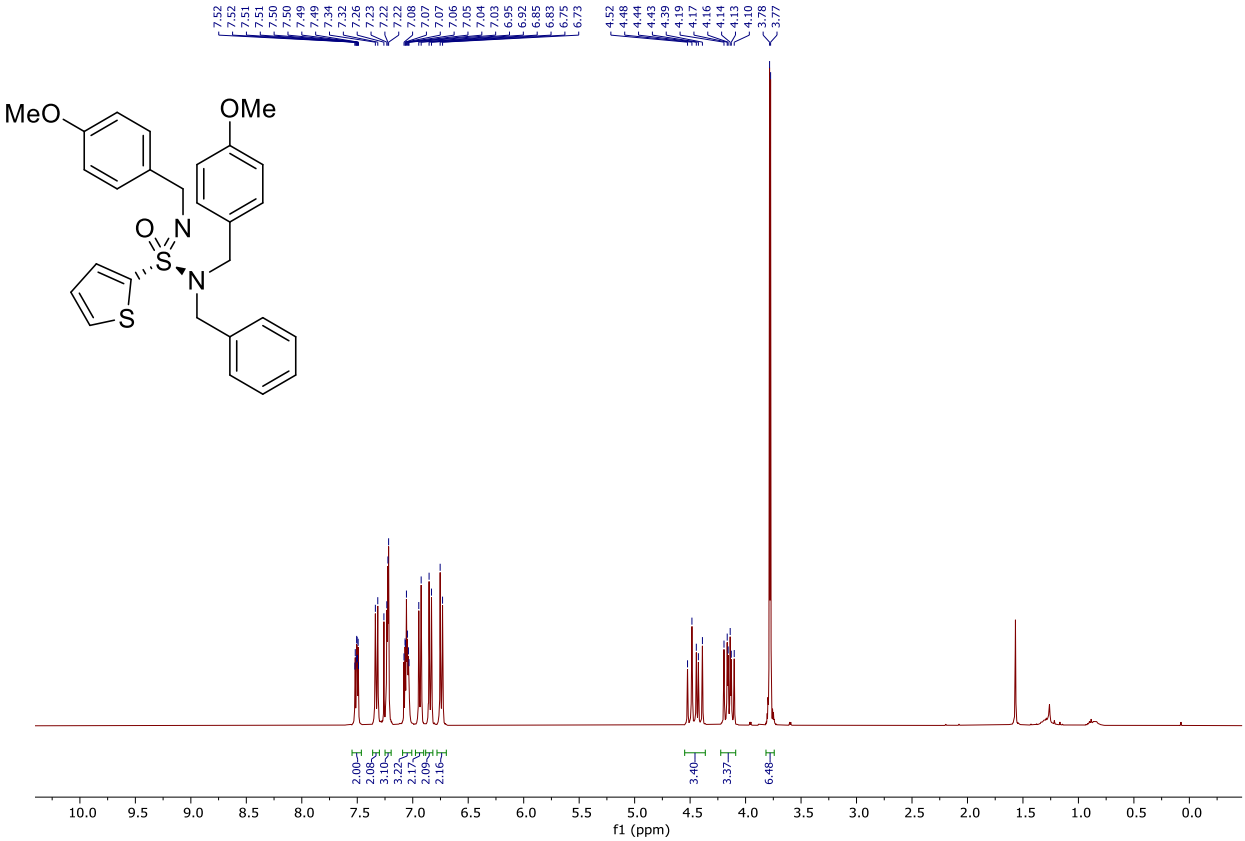



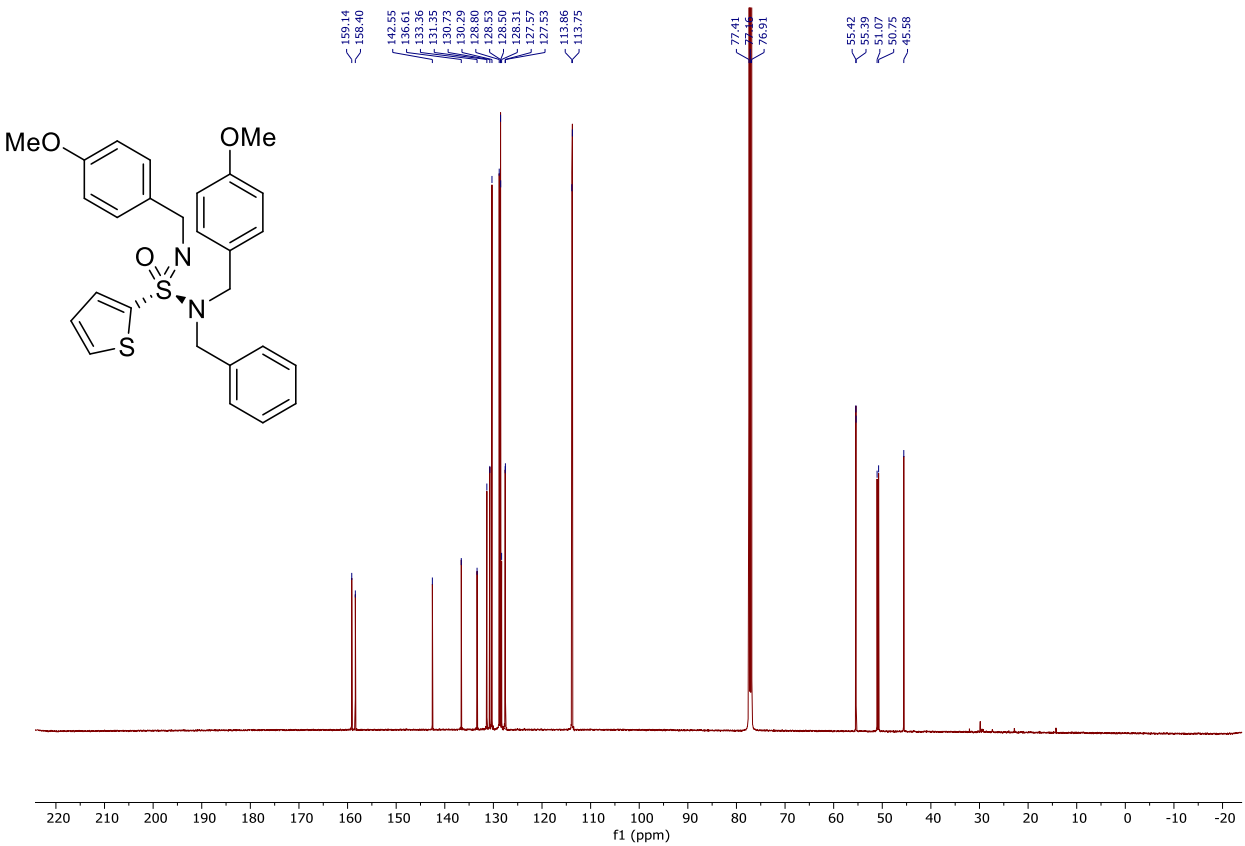
## (*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)pyridine-2-sulfonimidamide (74k)



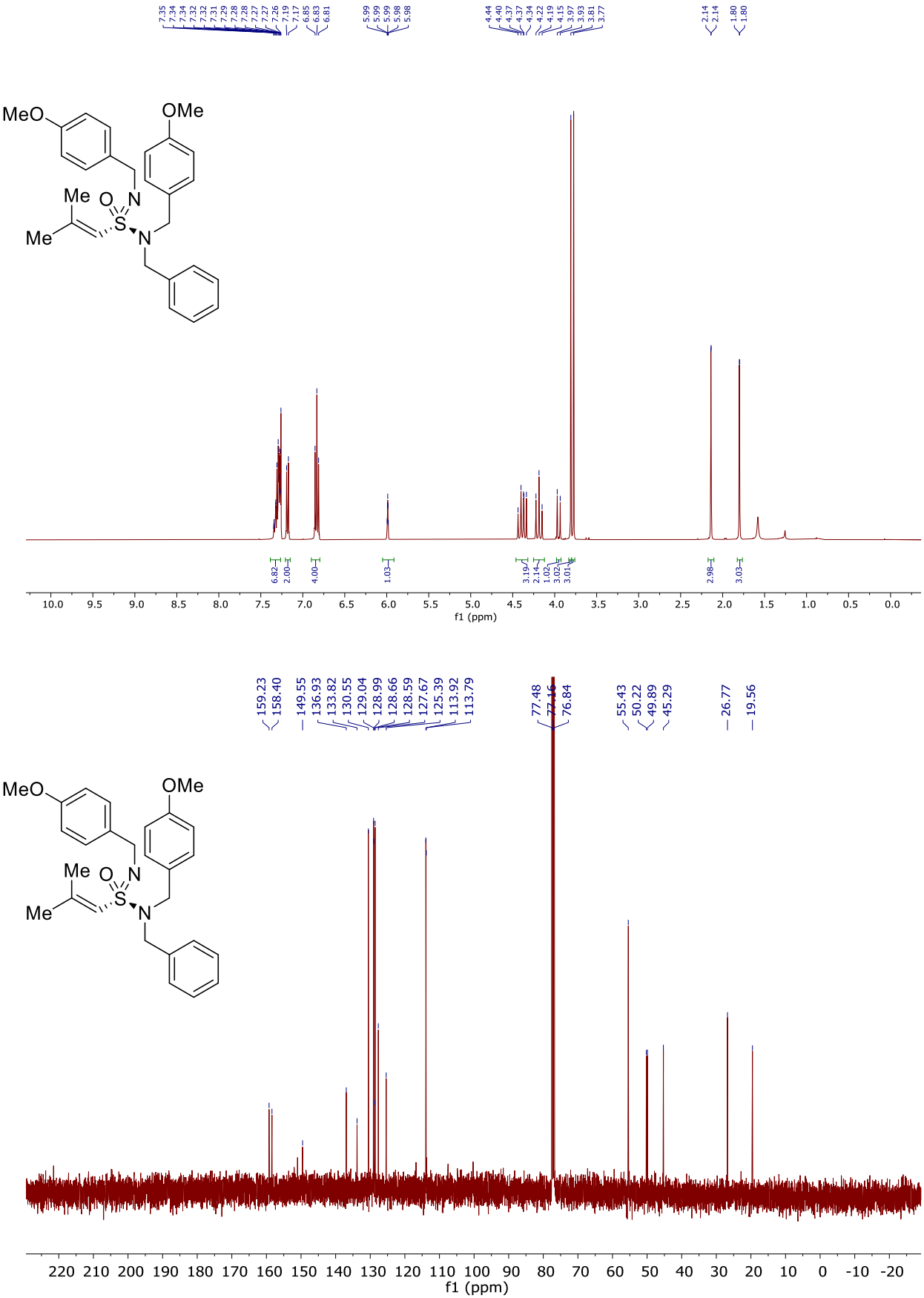



## (*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)thiophene-2-sulfonimidamide (74l)

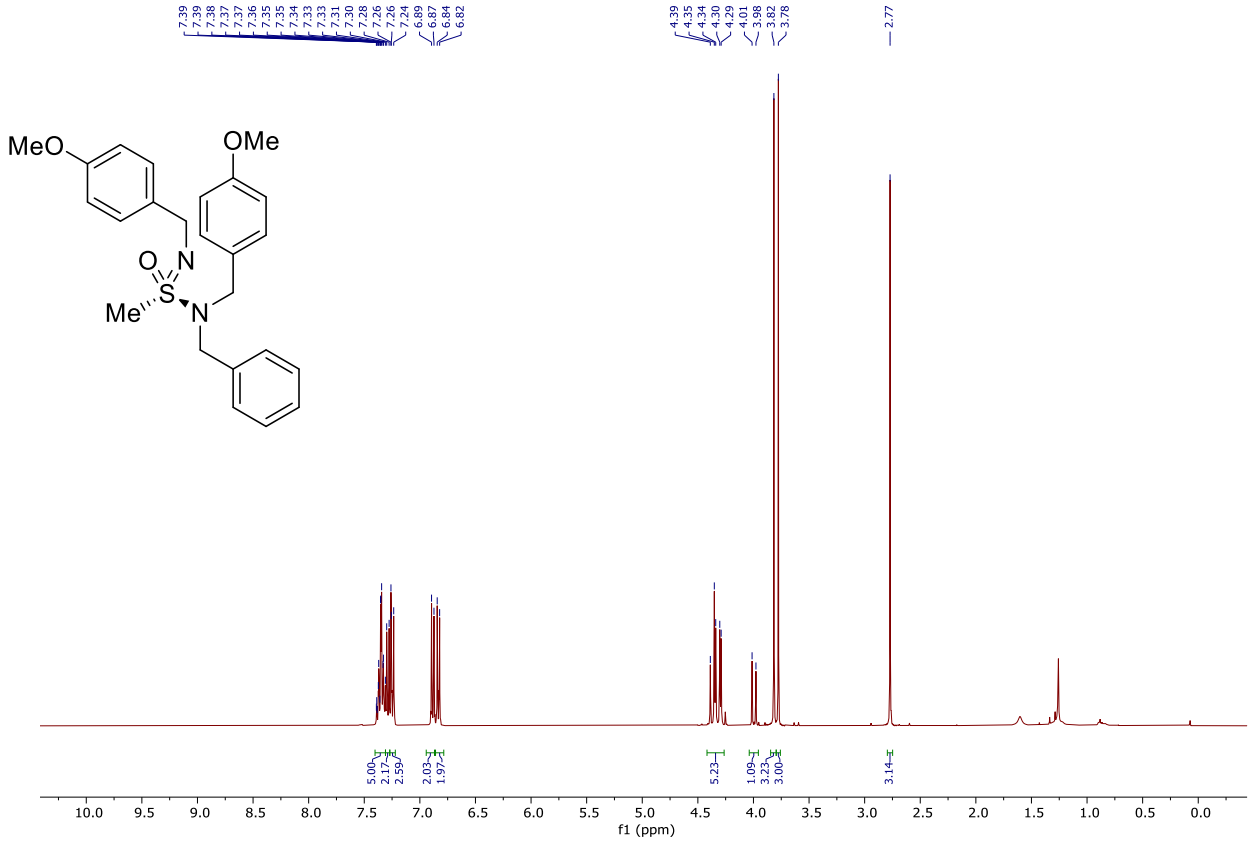


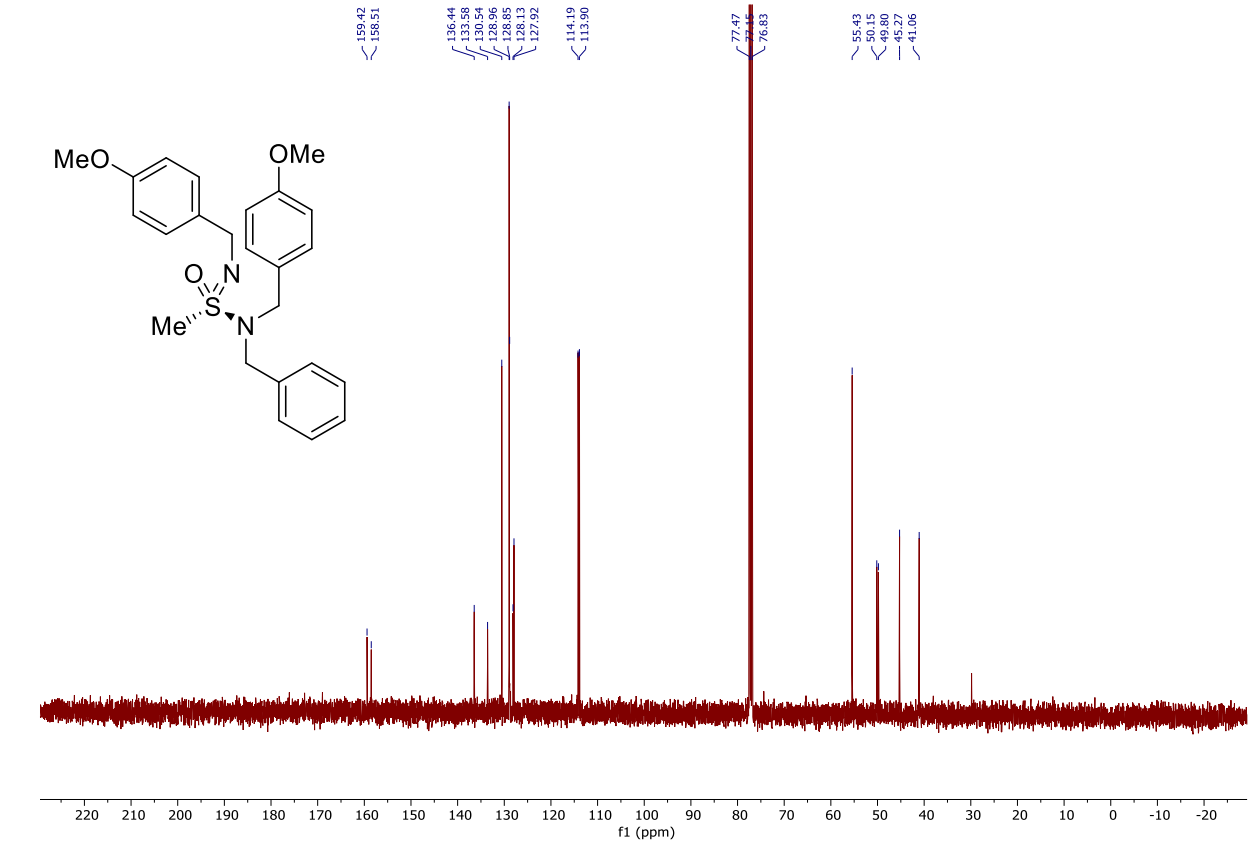



**(*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-2-methylprop-1-ene-1-sulfonimidamide (74m)**

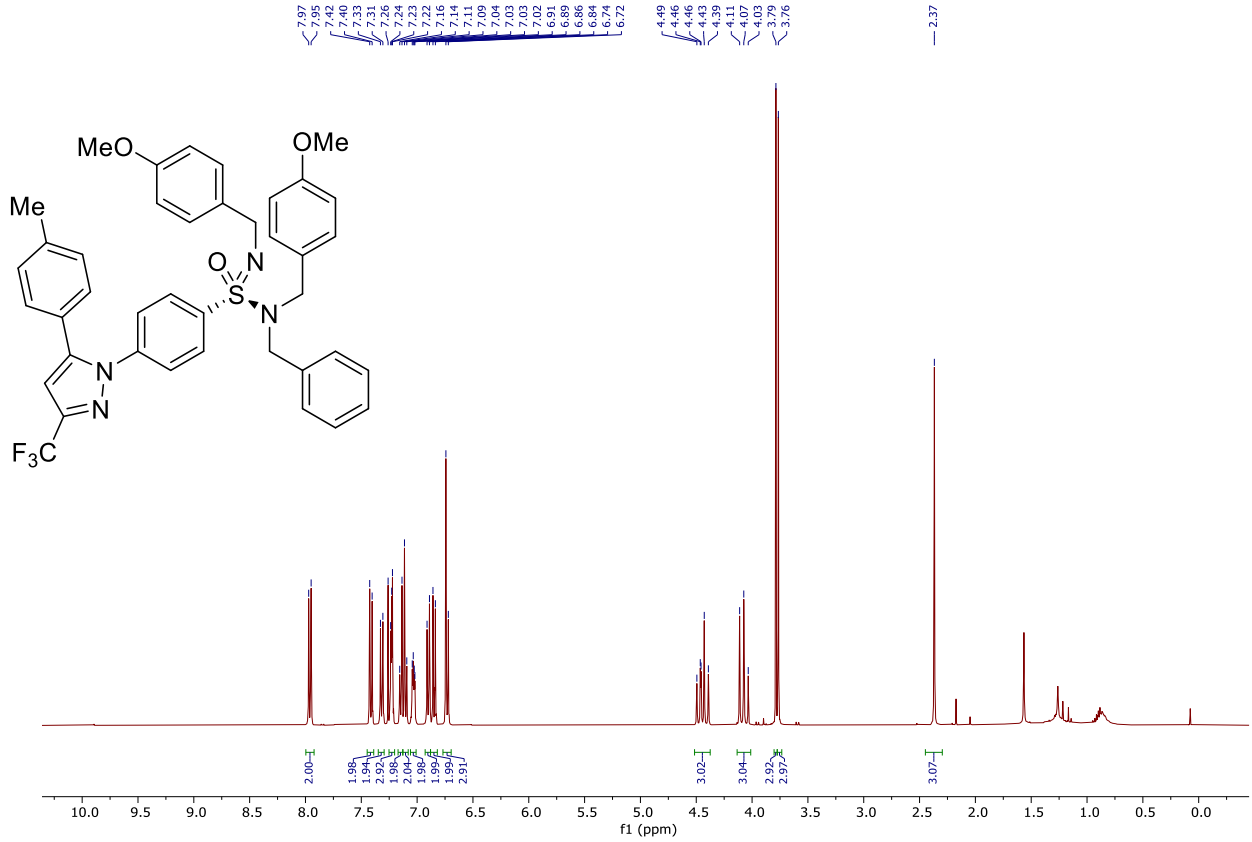


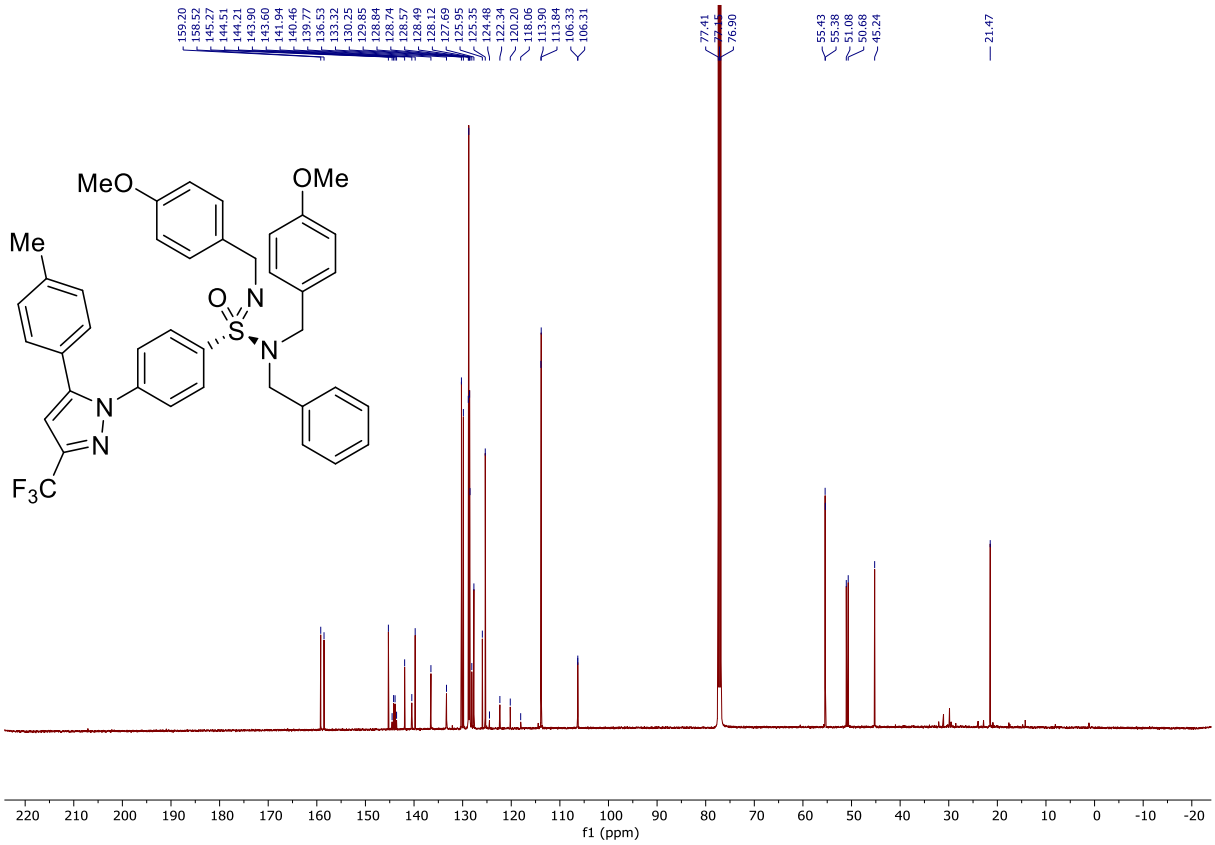
## (*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)methanesulfonimidamide (74n)

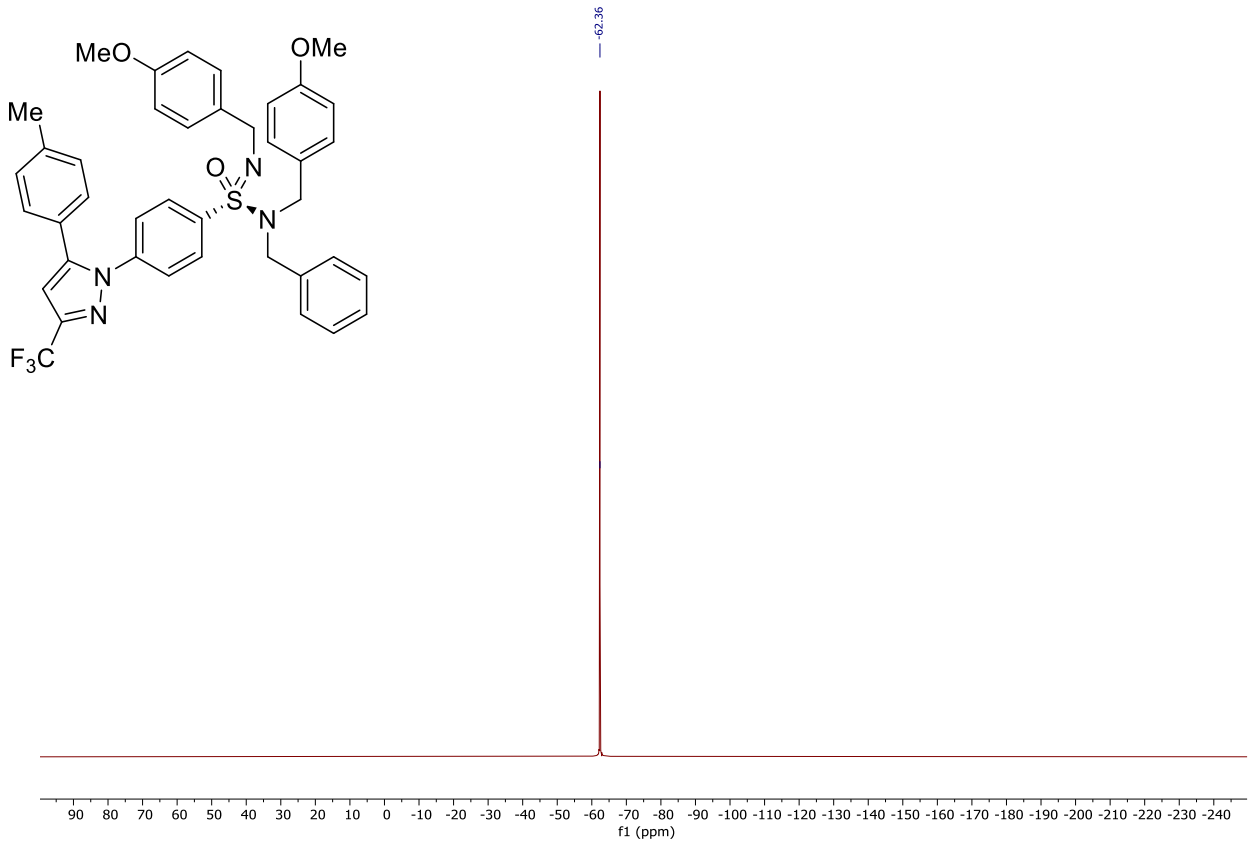


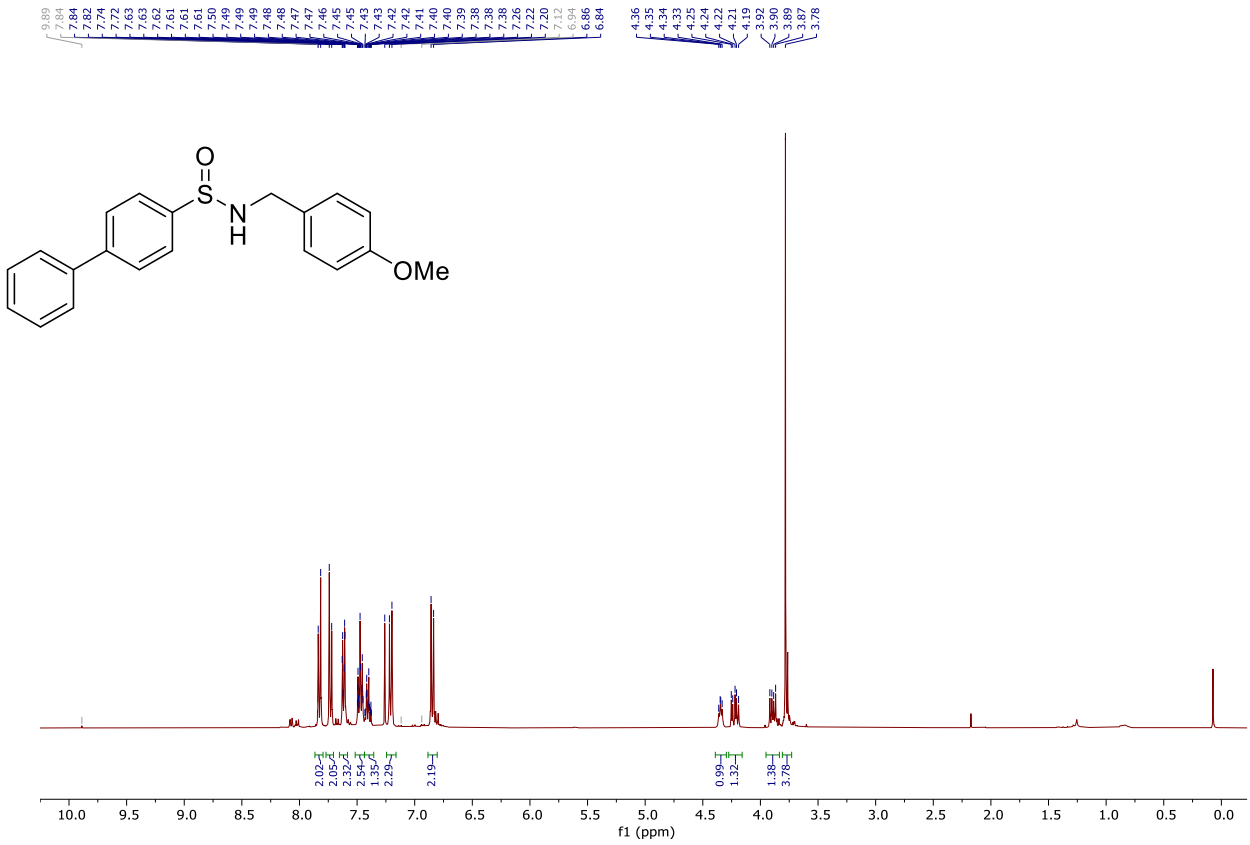
**(*S*)-*N*-benzyl-*N*,*N*'-bis(4-methoxybenzyl)-4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonimidamide (74o)**

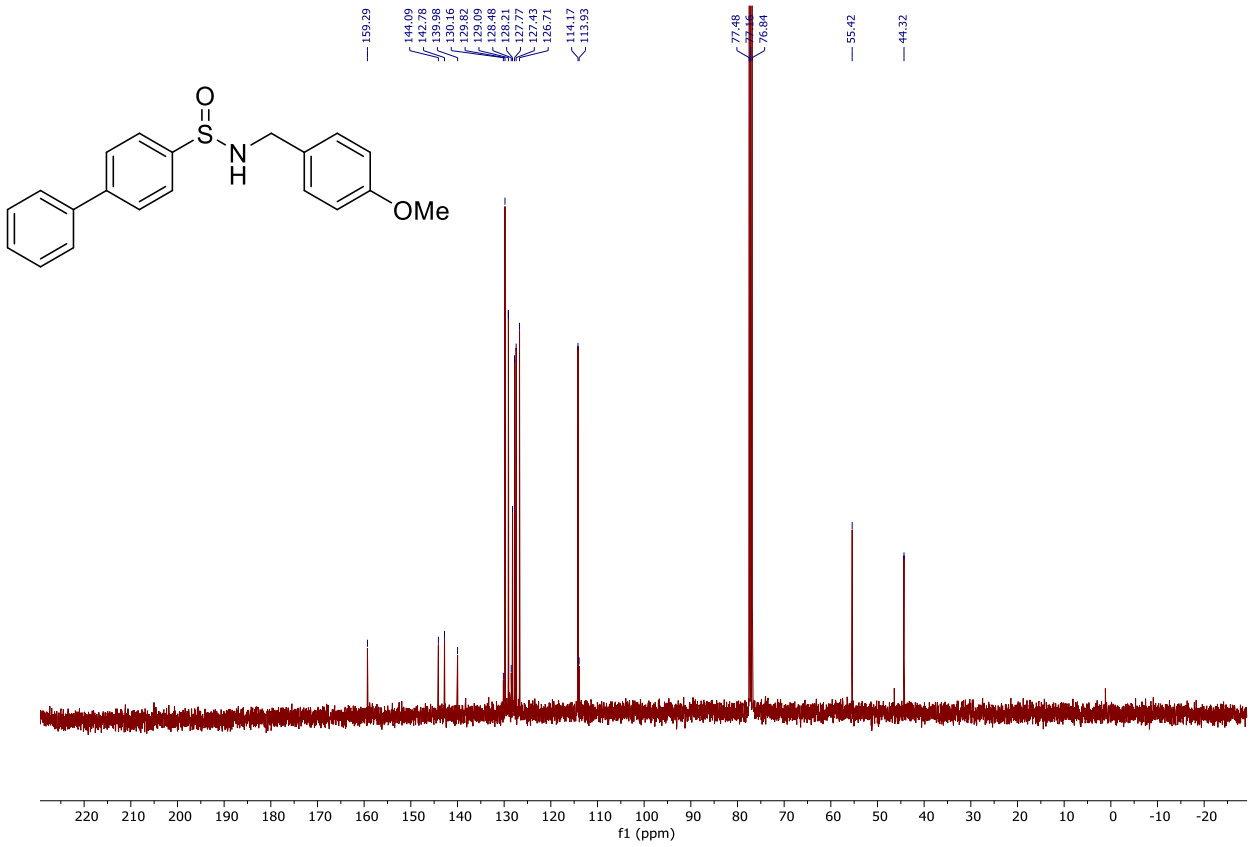


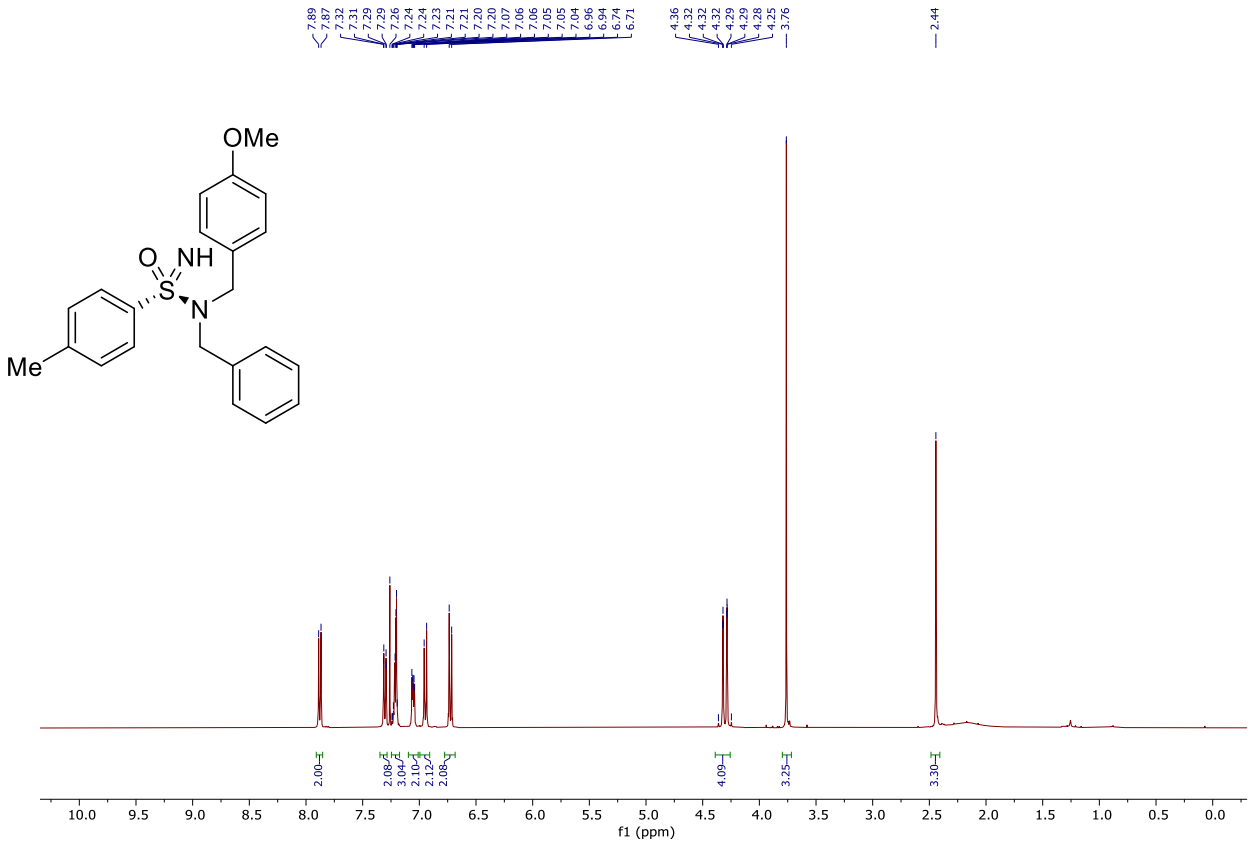

MeO
OMe
Me
O
N
S
N
N
N
F3C
-62.36
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

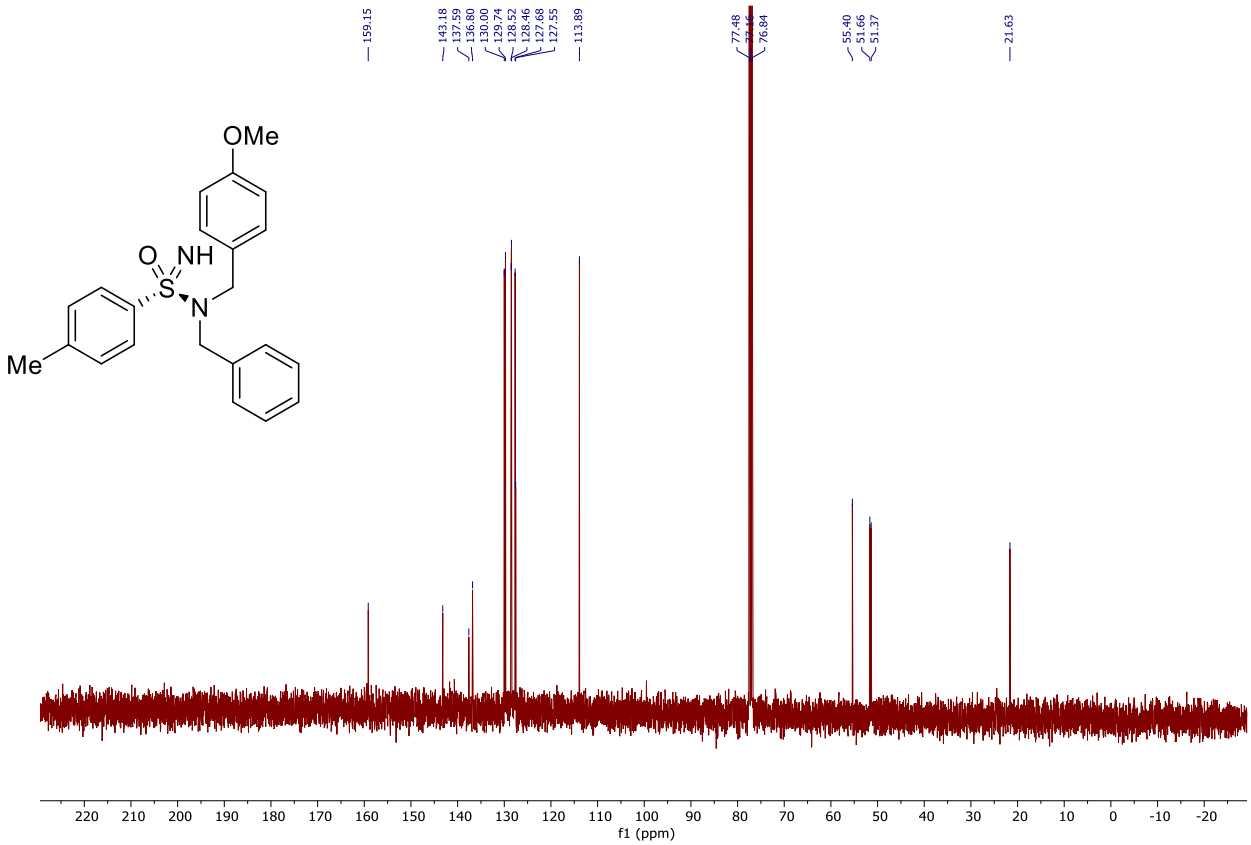
## *N*-(4-methoxybenzyl)-[1,1'-biphenyl]-4-sulfinamide (78a)



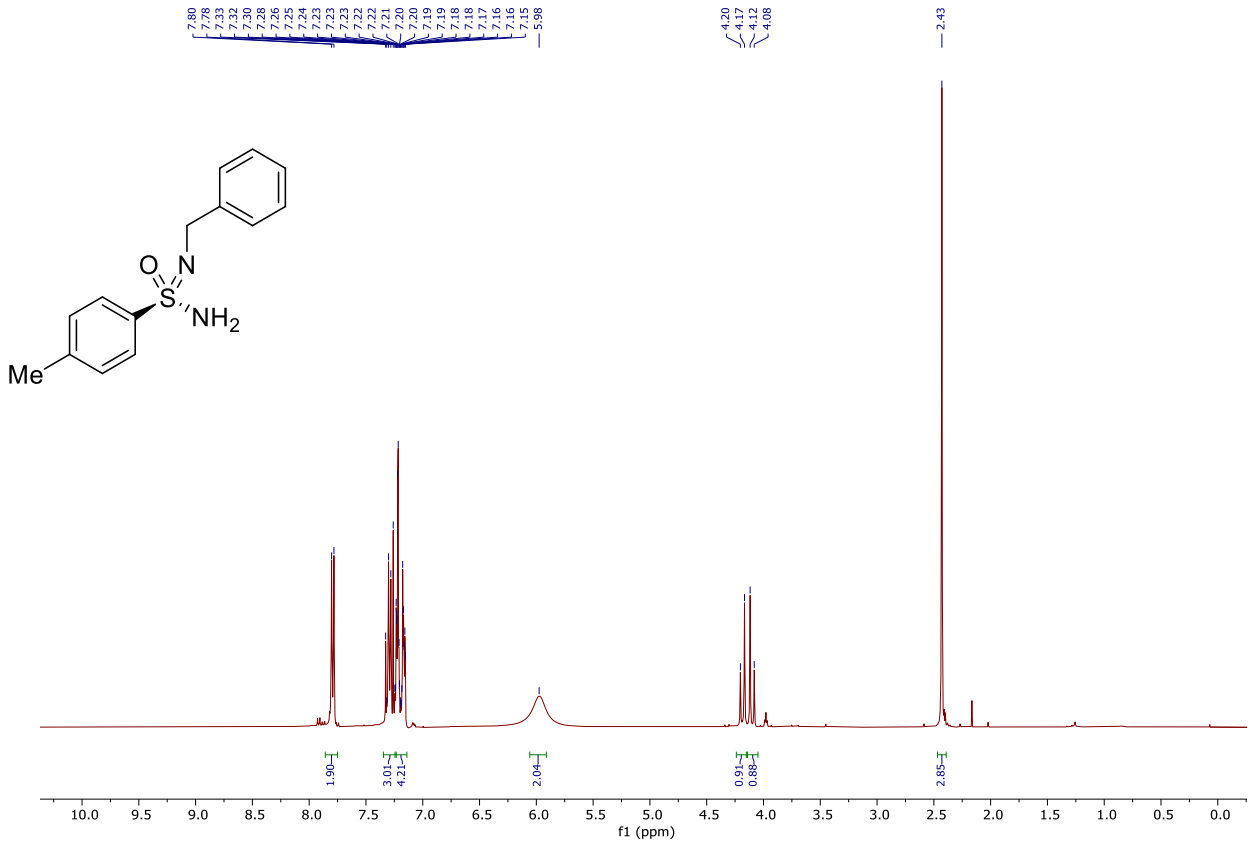



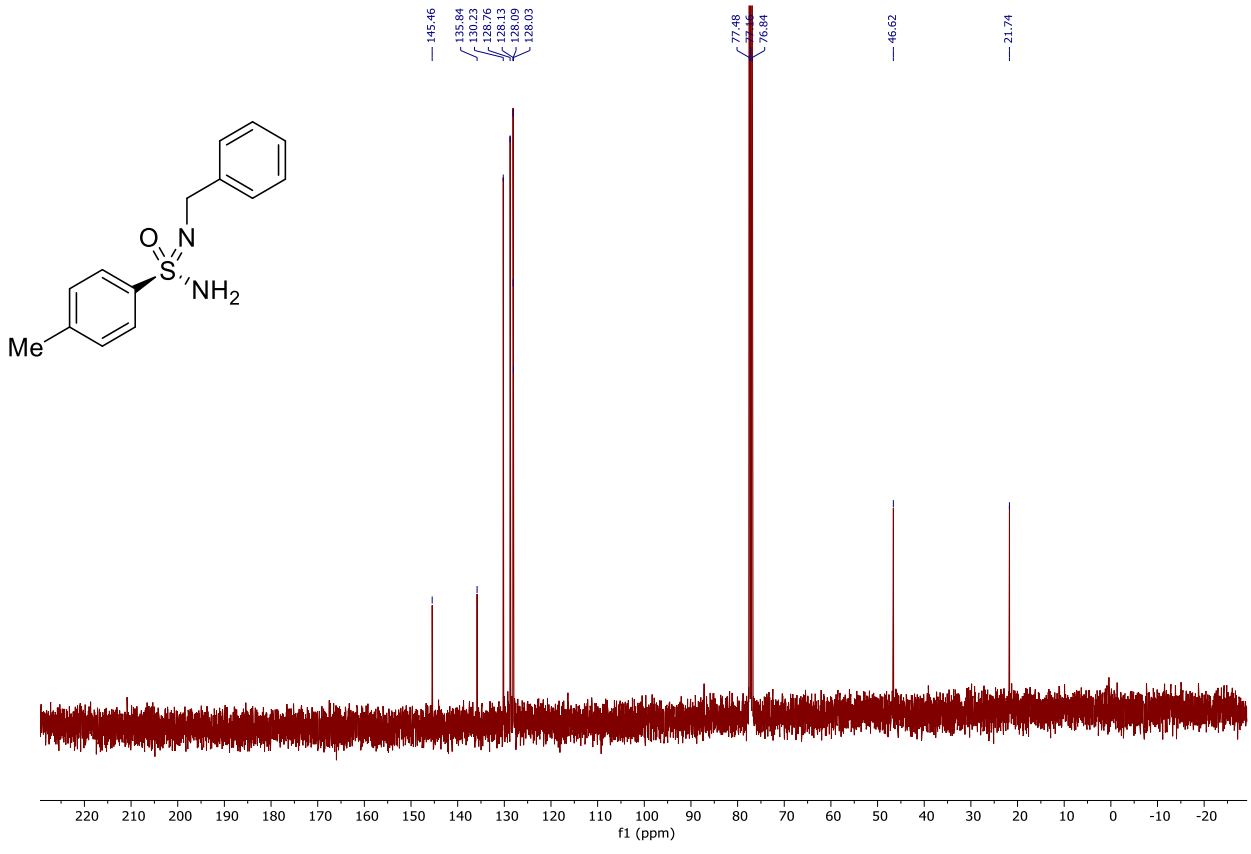
## (*R*)-*N*-benzyl-*N*-(4-methoxybenzyl)-4-methylbenzenesulfonimidamide (82)



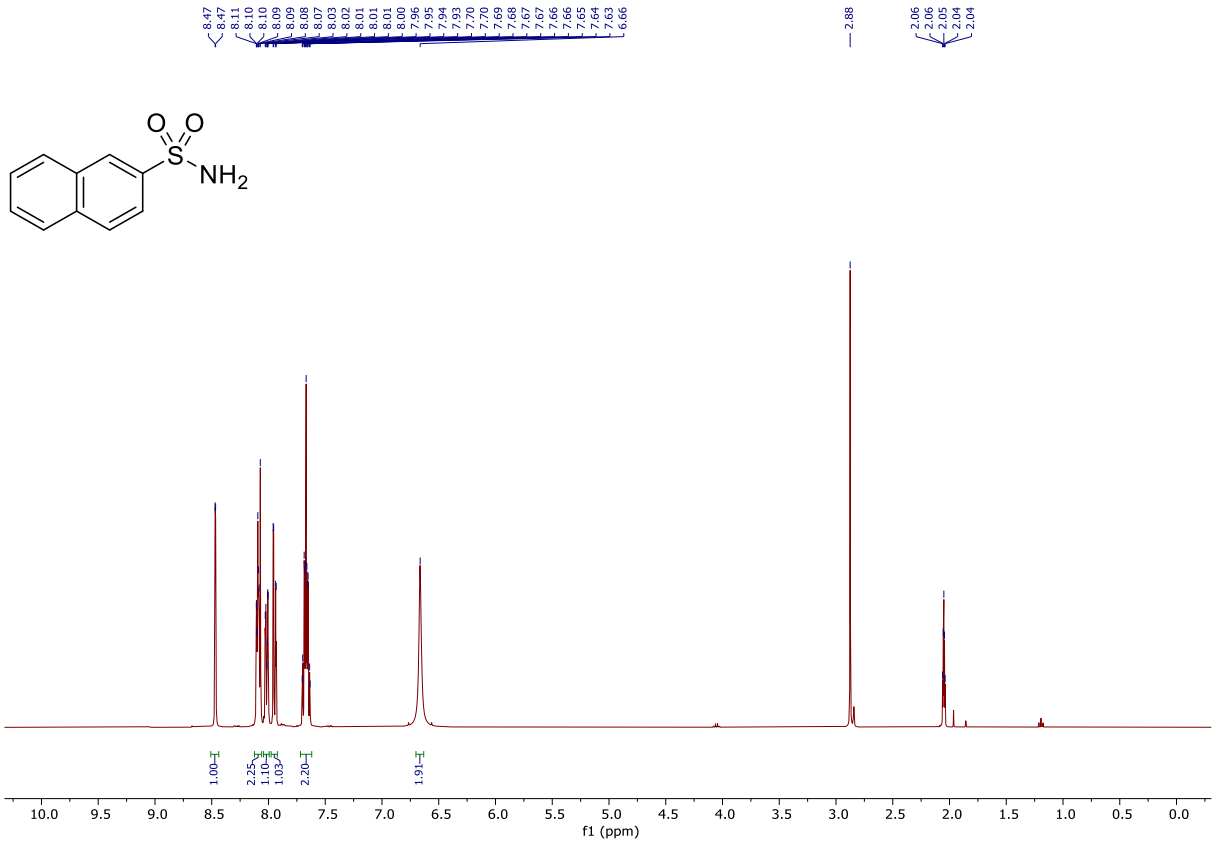
## (*R*)-*N'*-benzyl-4-methylbenzenesulfonimidamide (83)

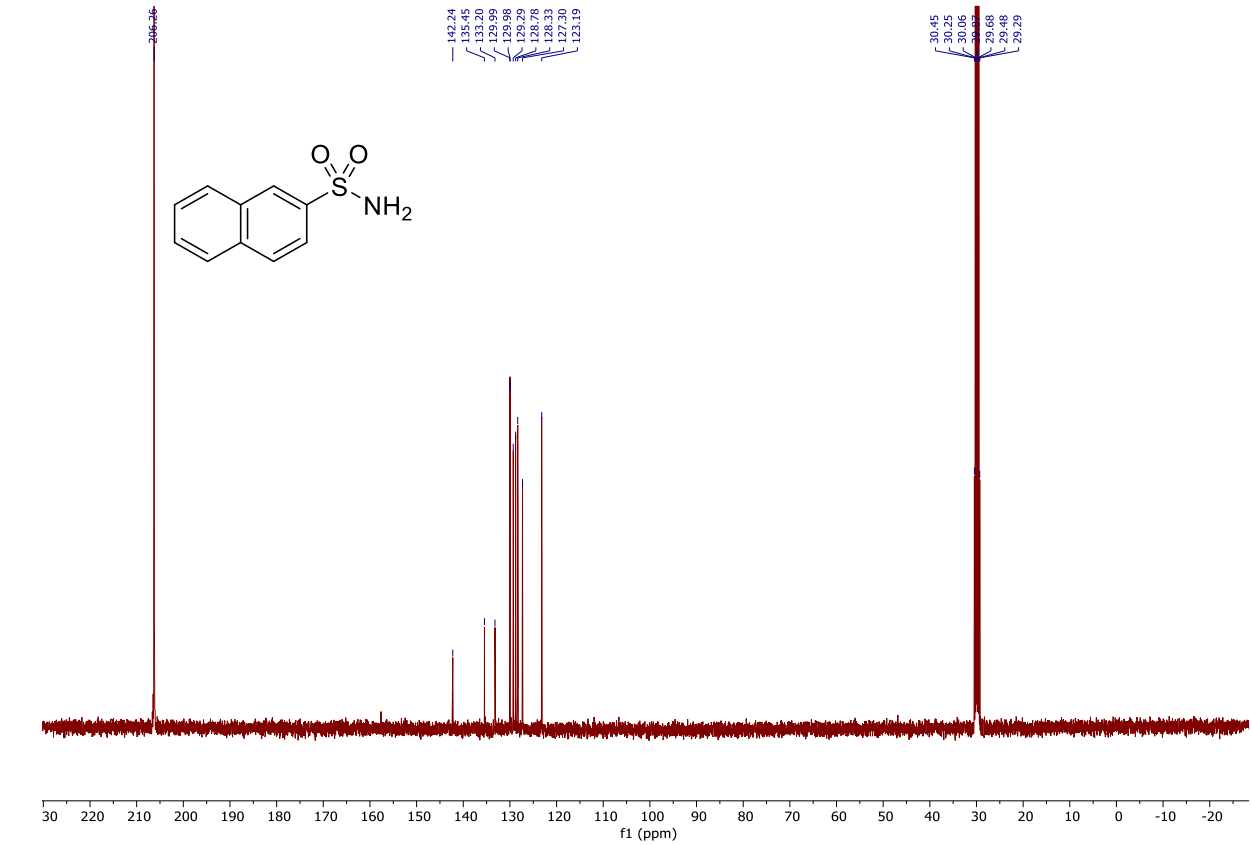


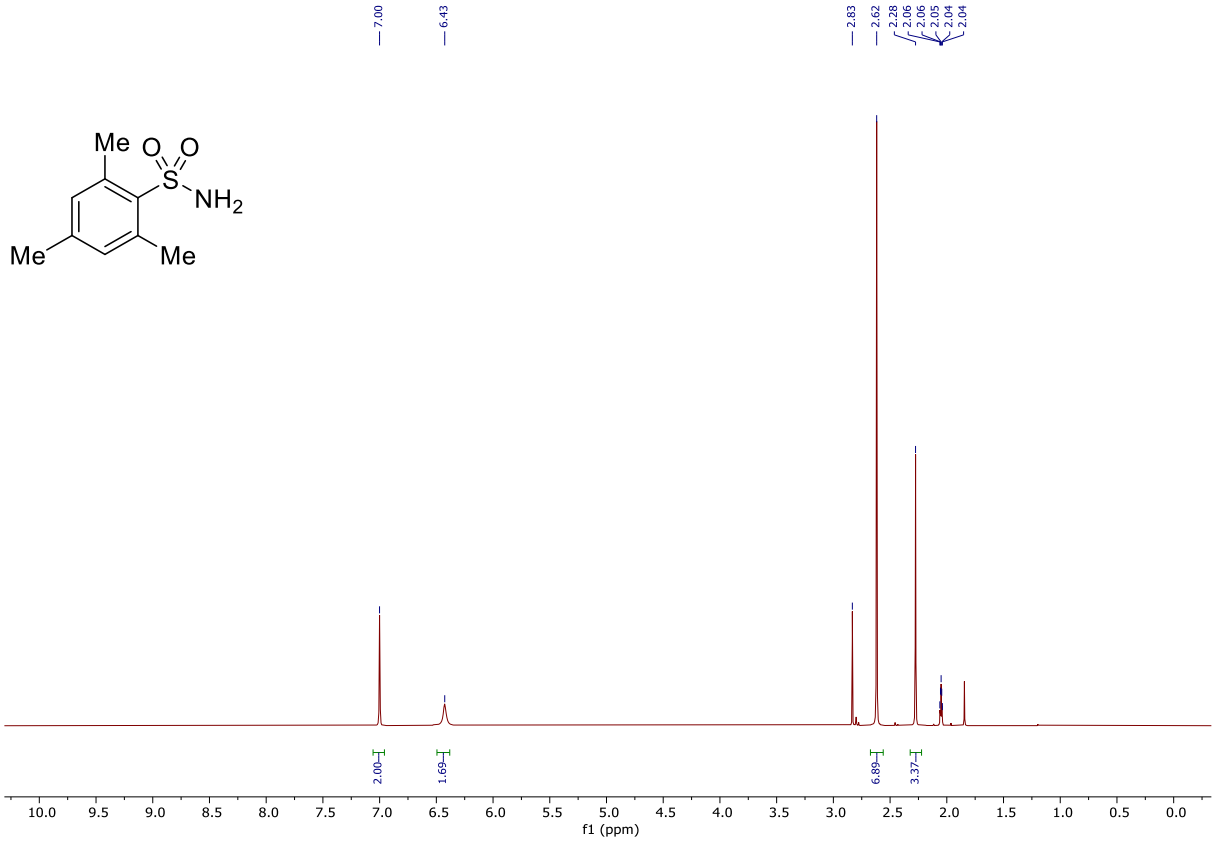
# 8.3. NMR Spectra – Chapter 4

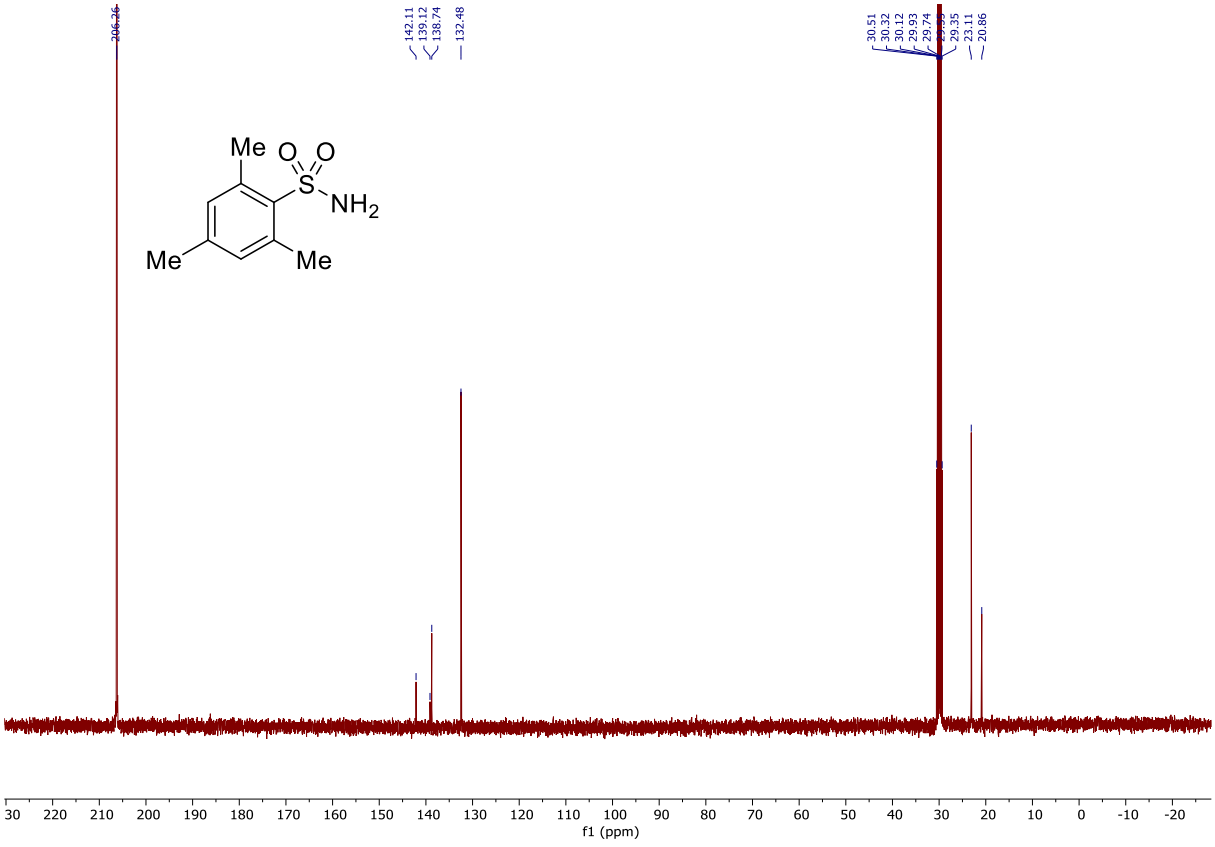
## Naphthalene-2-sulfonamide (110c)



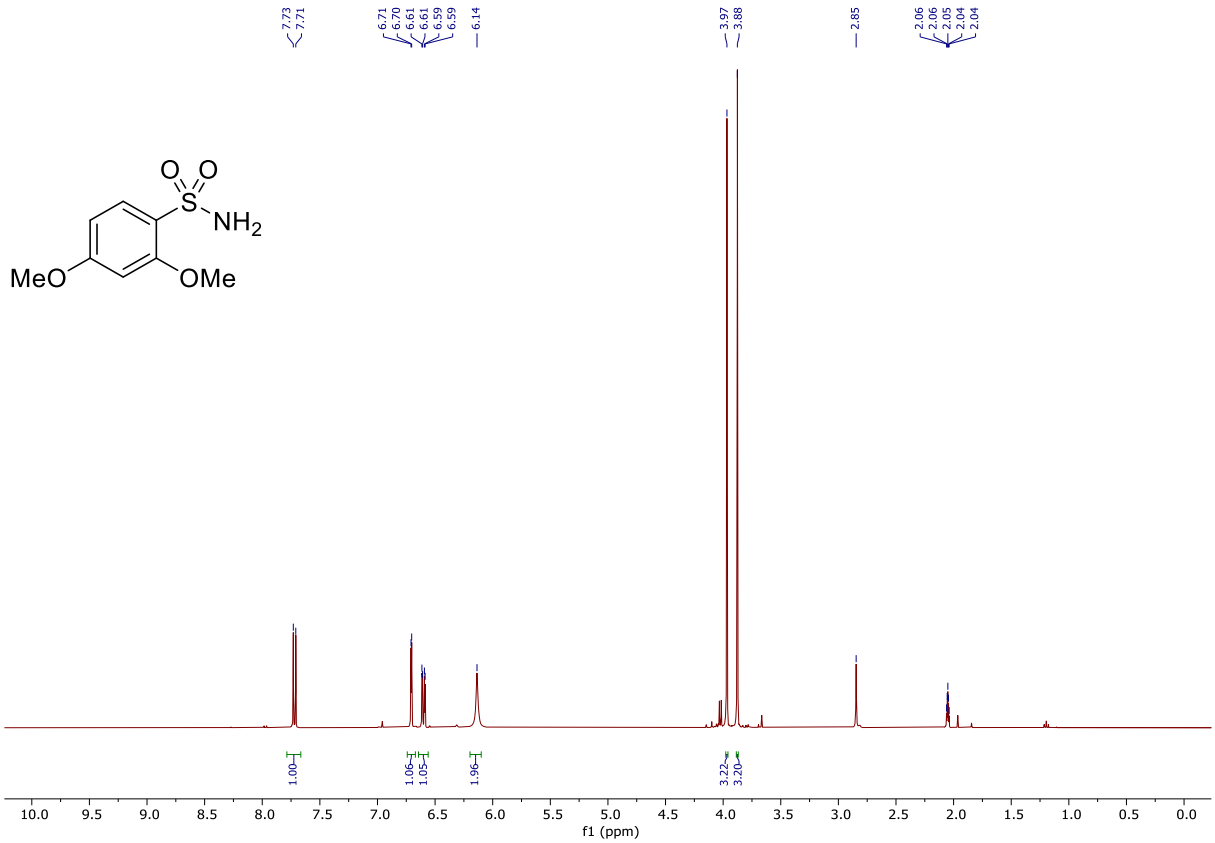



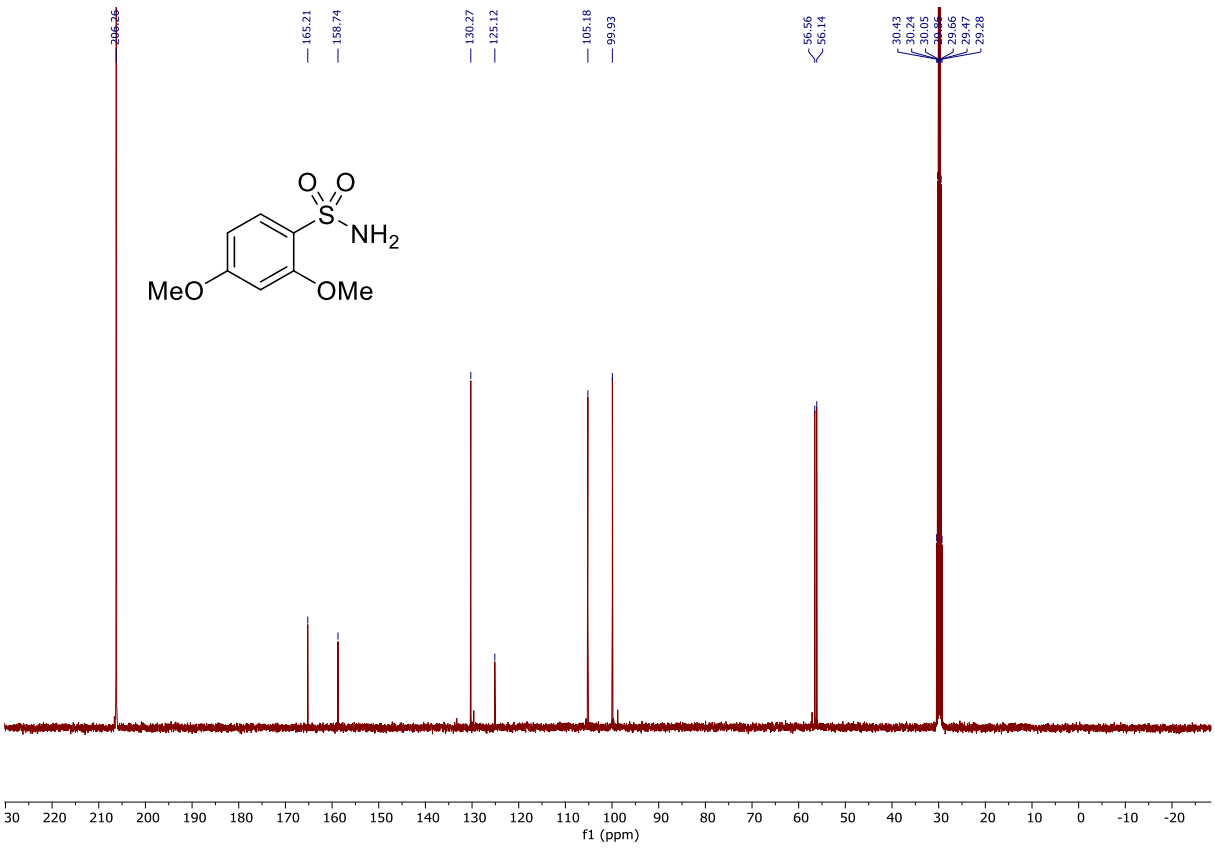
## 2,4,6-Trimethylbenzenesulfonamide (110d)



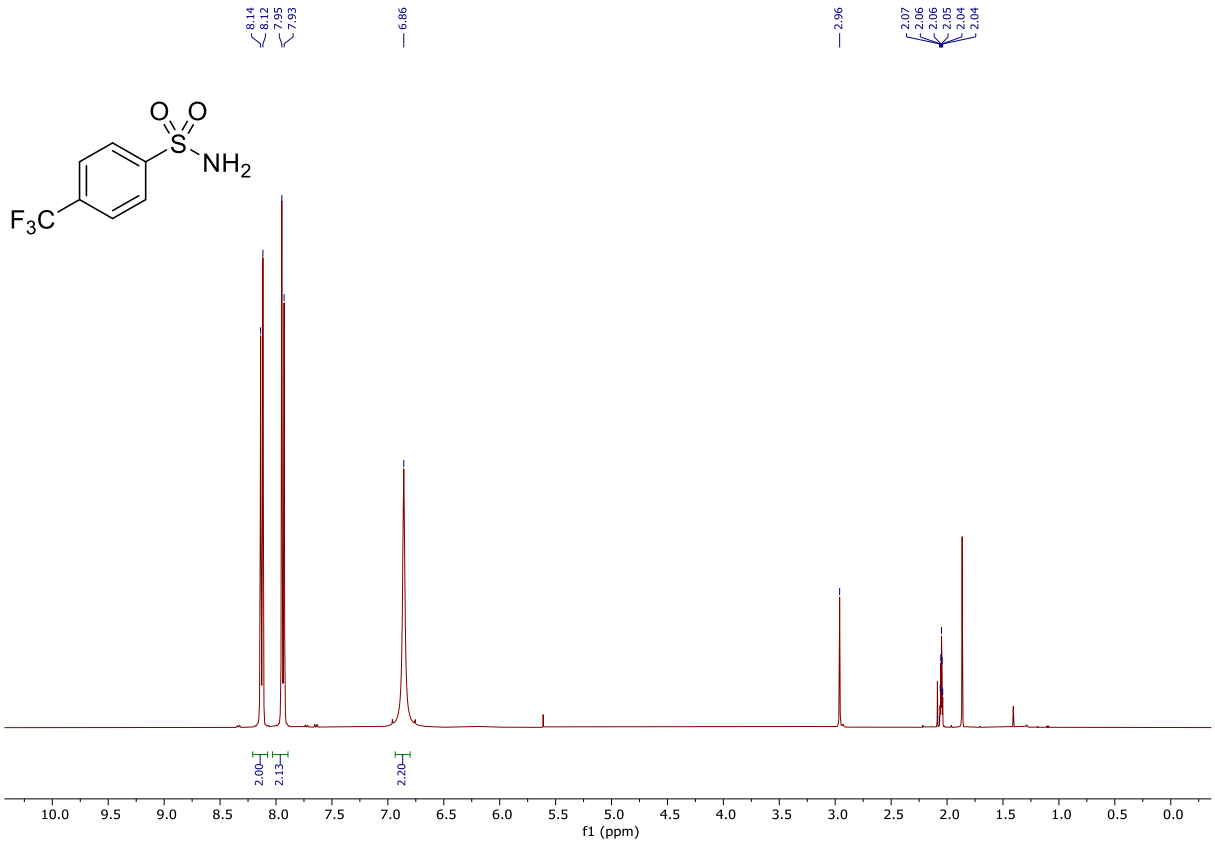



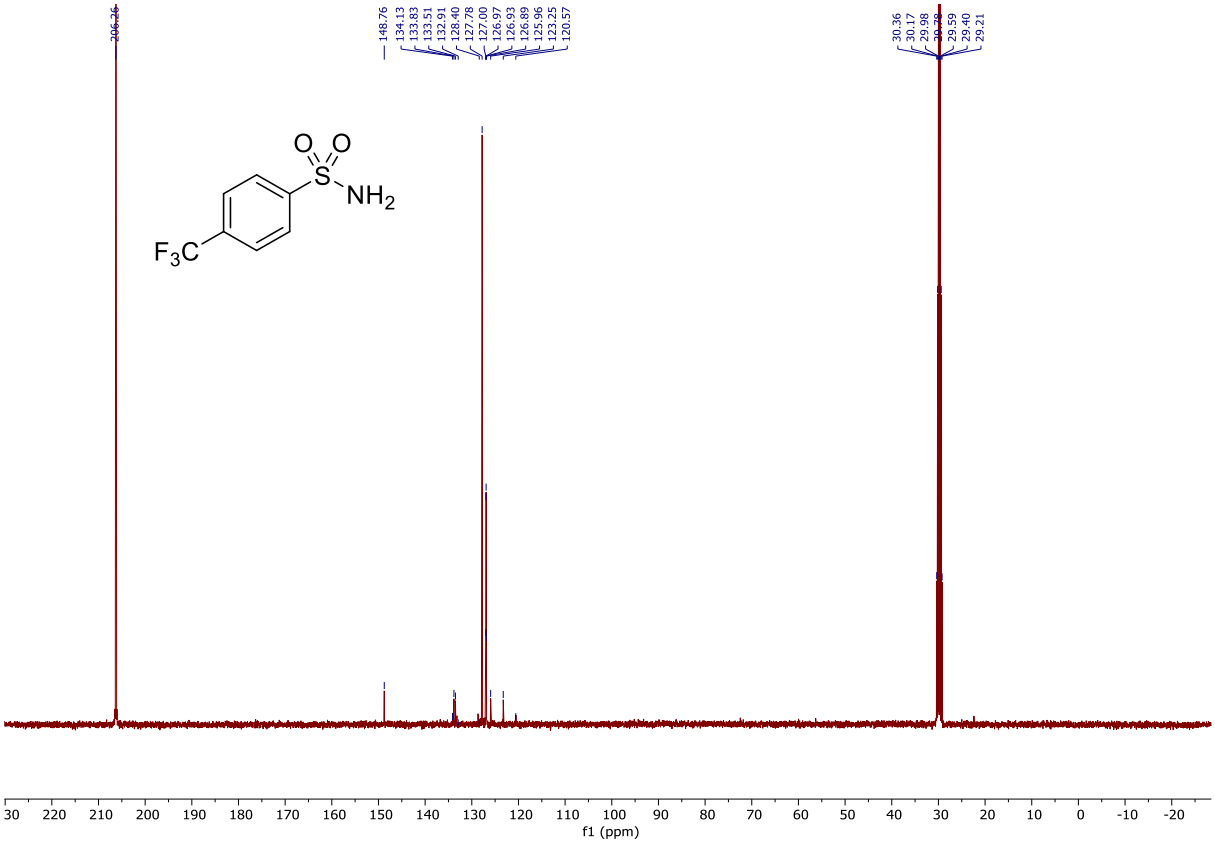
## 2,4-Dimethoxybenzenesulfonamide (110g)

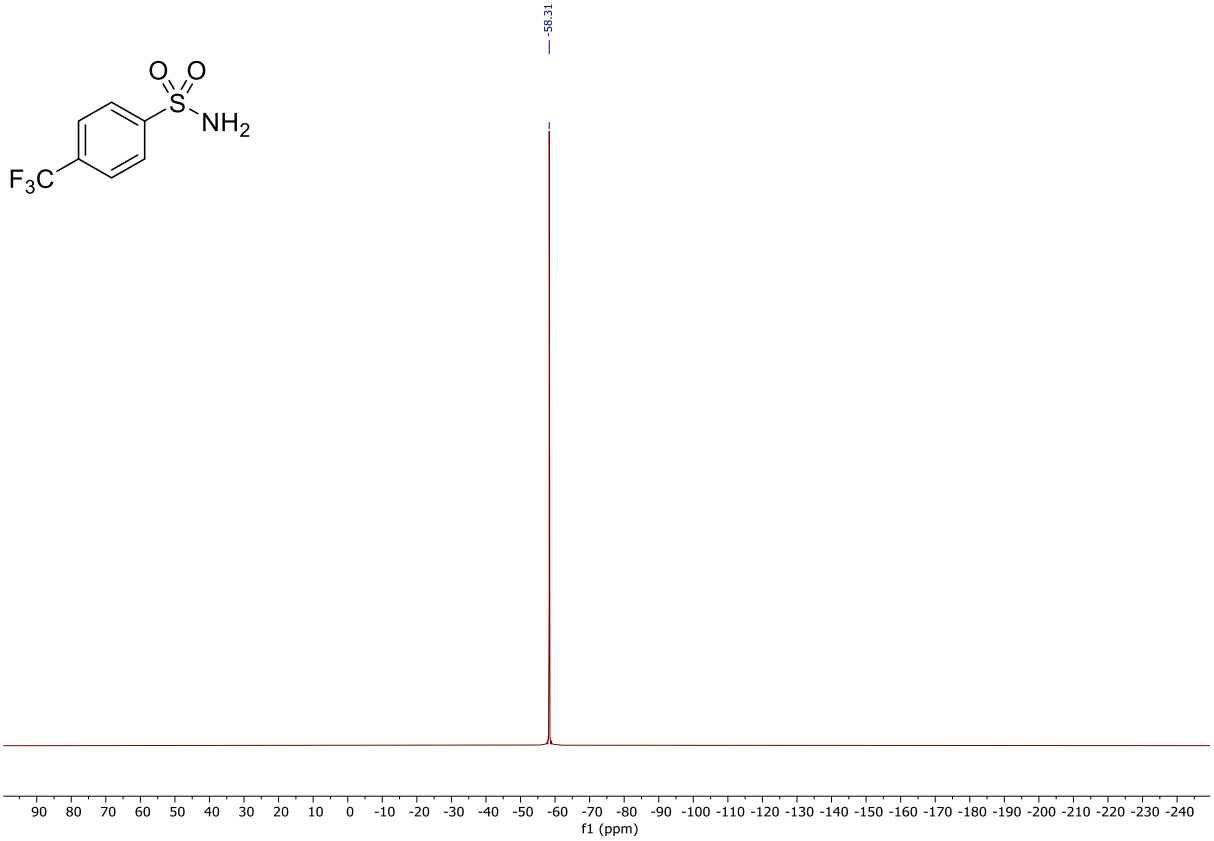


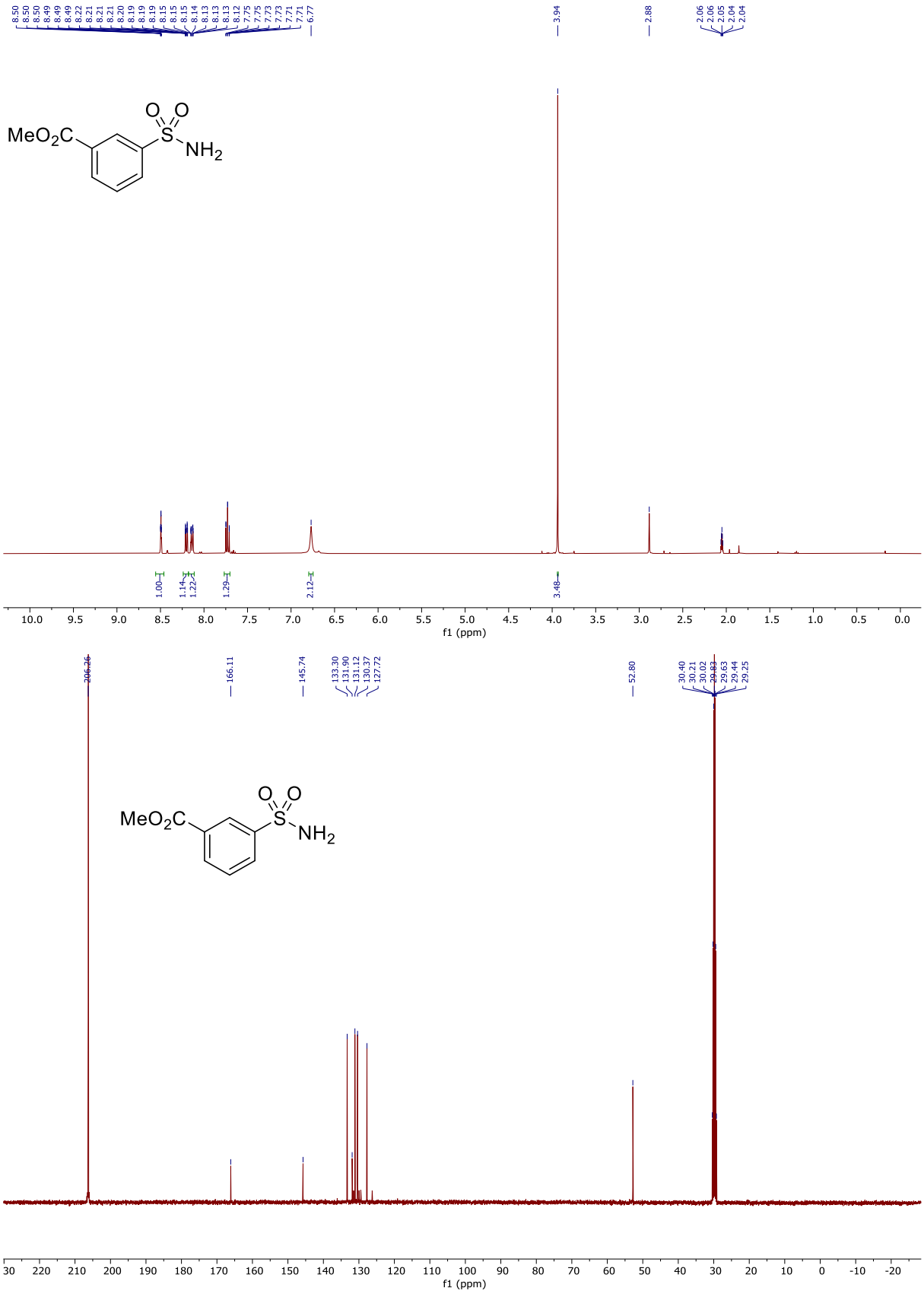
## 4-(Trifluoromethyl)benzenesulfonamide (110h)



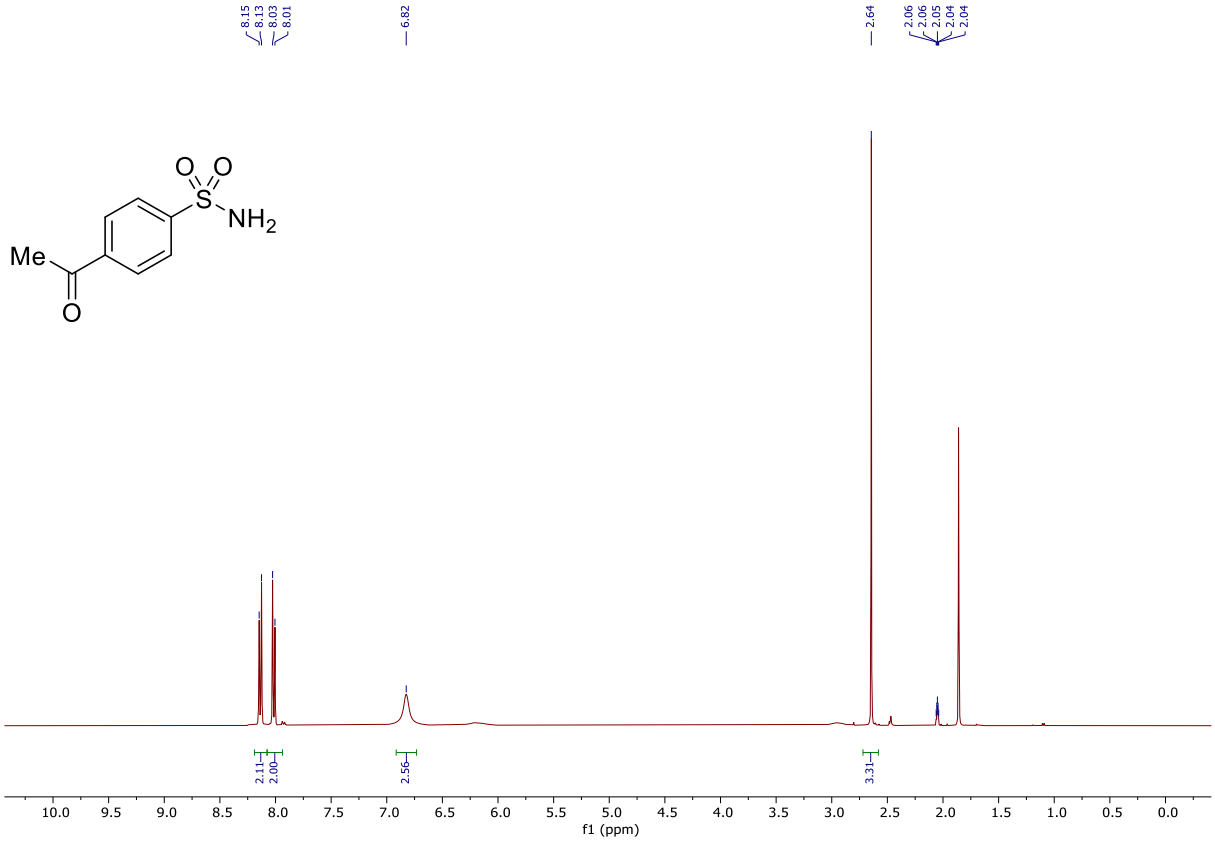



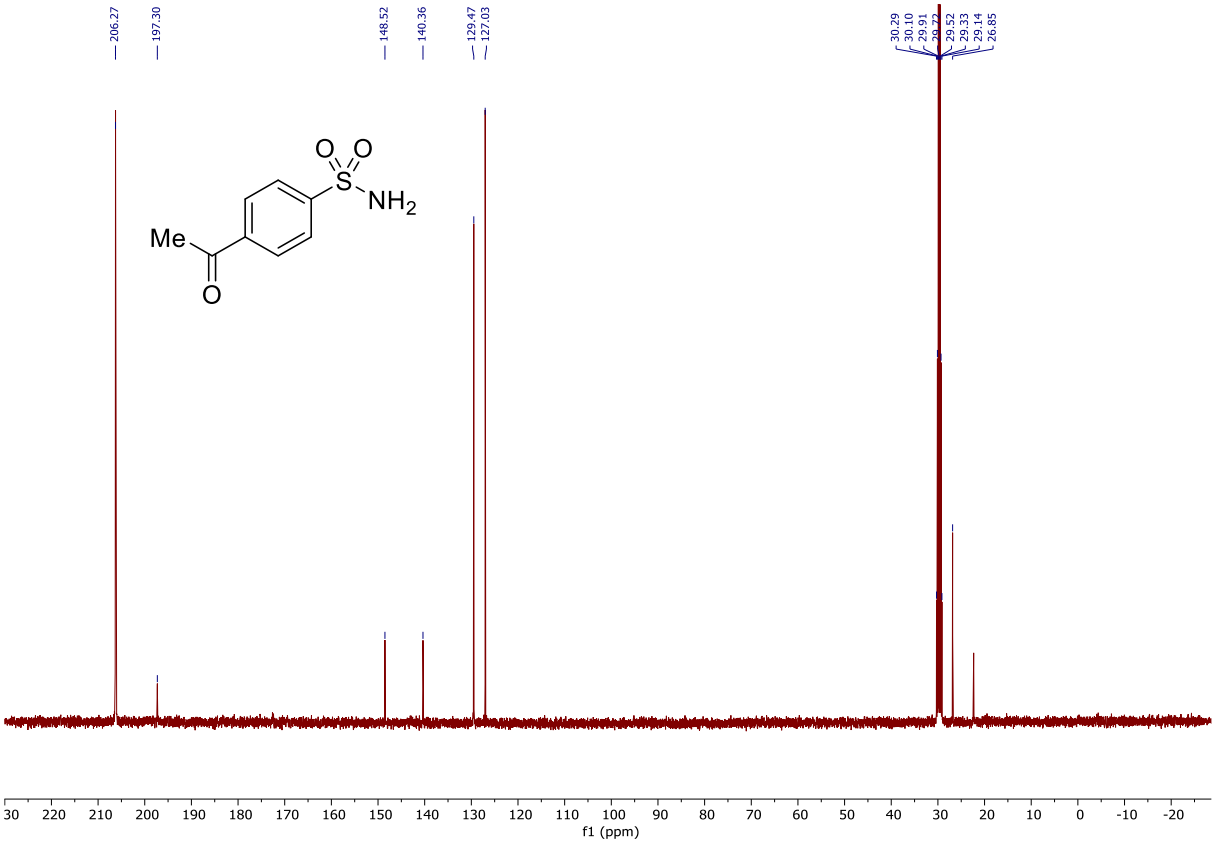

-58.31
O
O
S
NH2
F3C
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

## Methyl 3-sulfamoylbenzoate (110j)

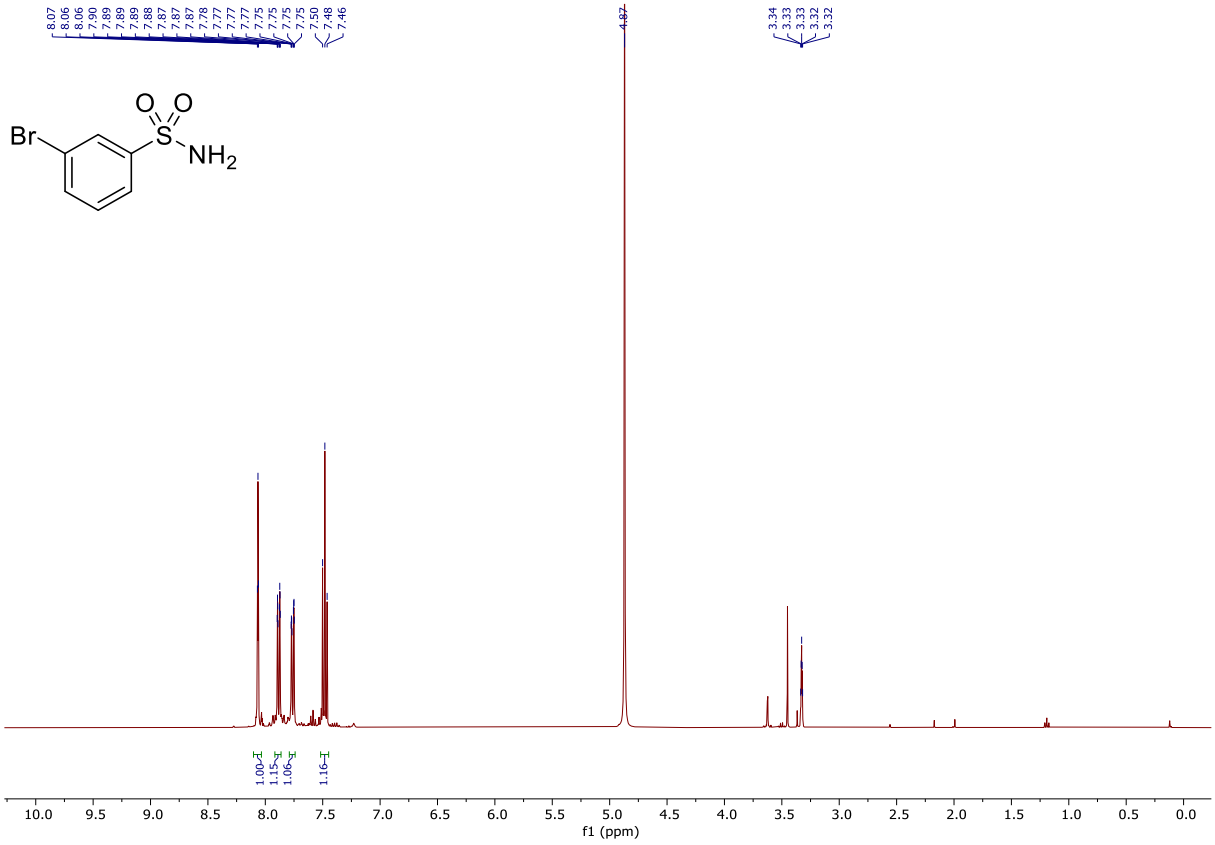


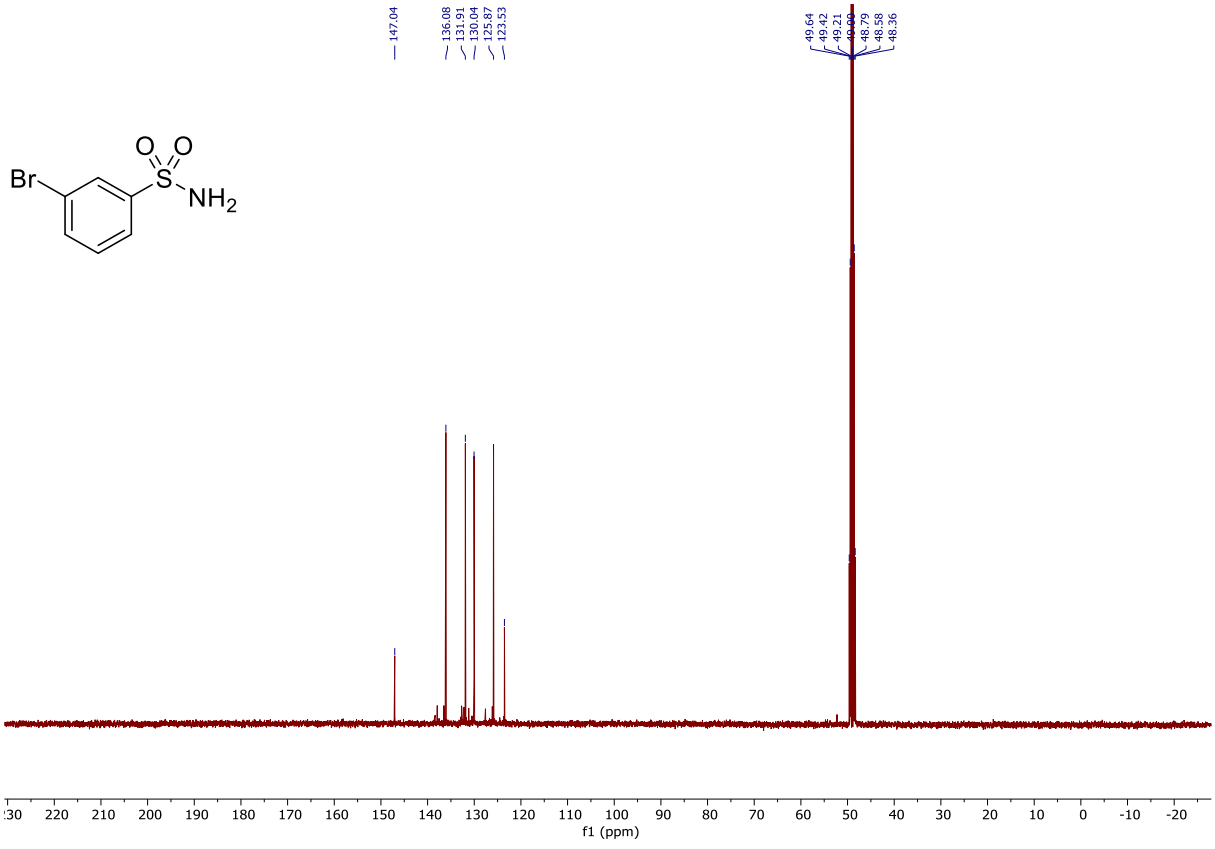
## 4-Acetylbenzenesulfonamide (110k)



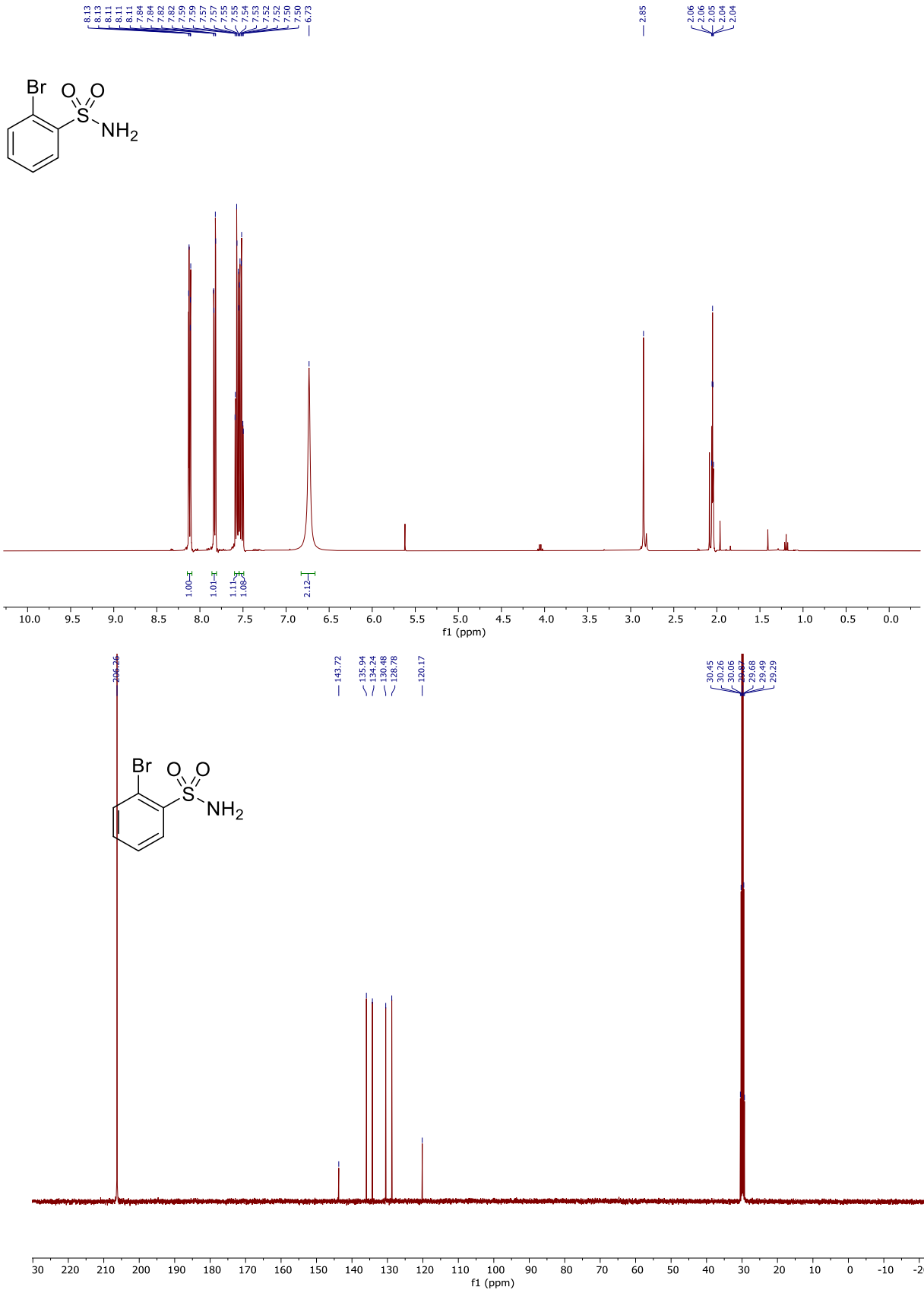



## 3-Bromobenzenesulfonamide (110m)

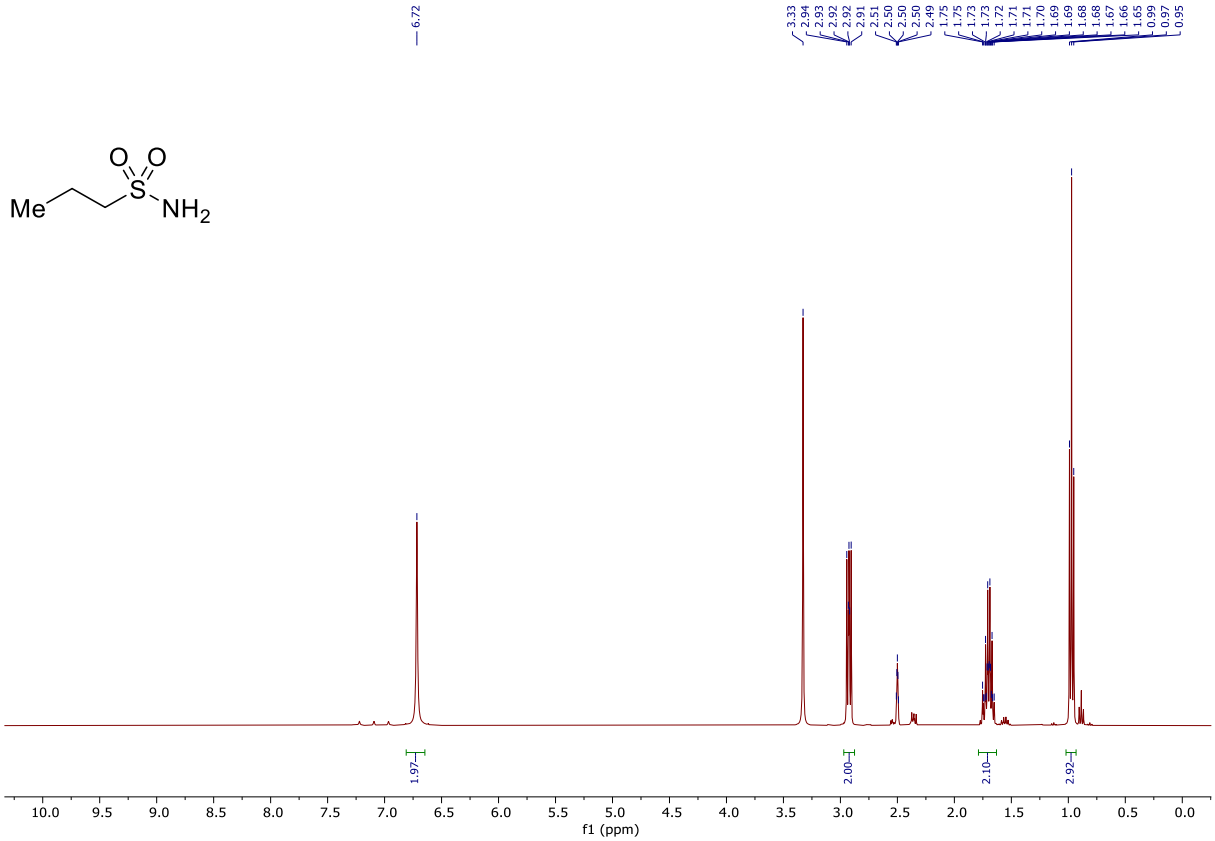


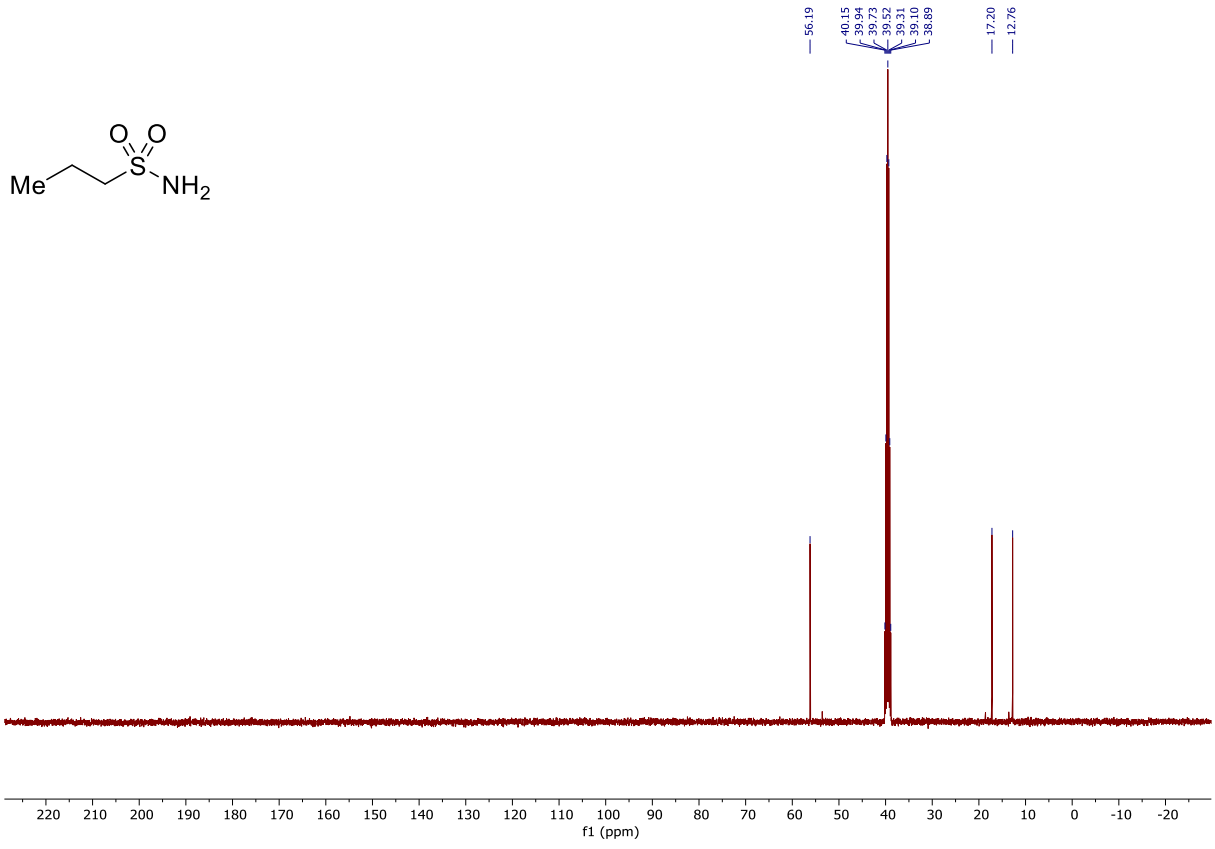



## 2-Bromobenzenesulfonamide (110n)

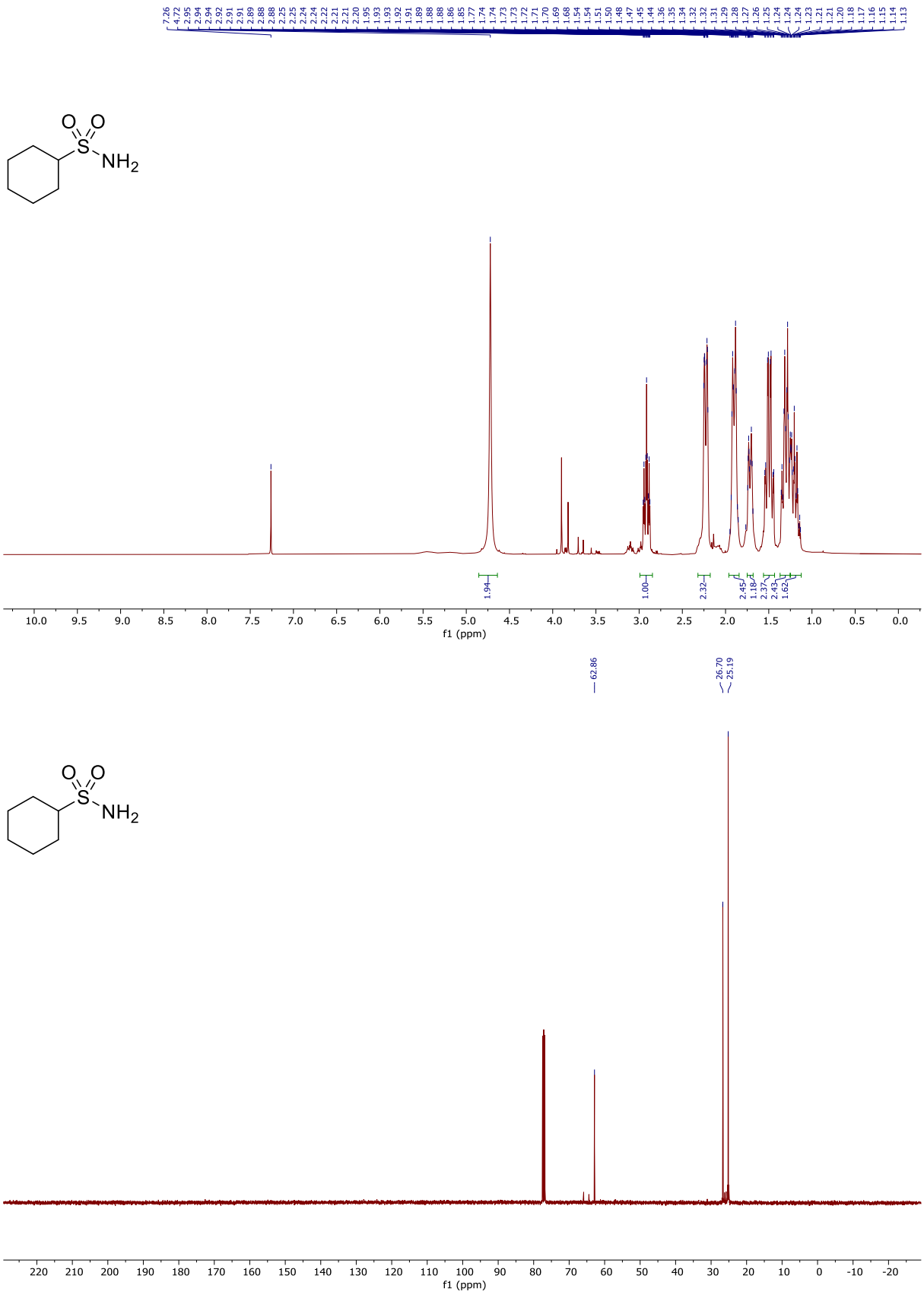


**Propane-1-sulfonamide (110p)**

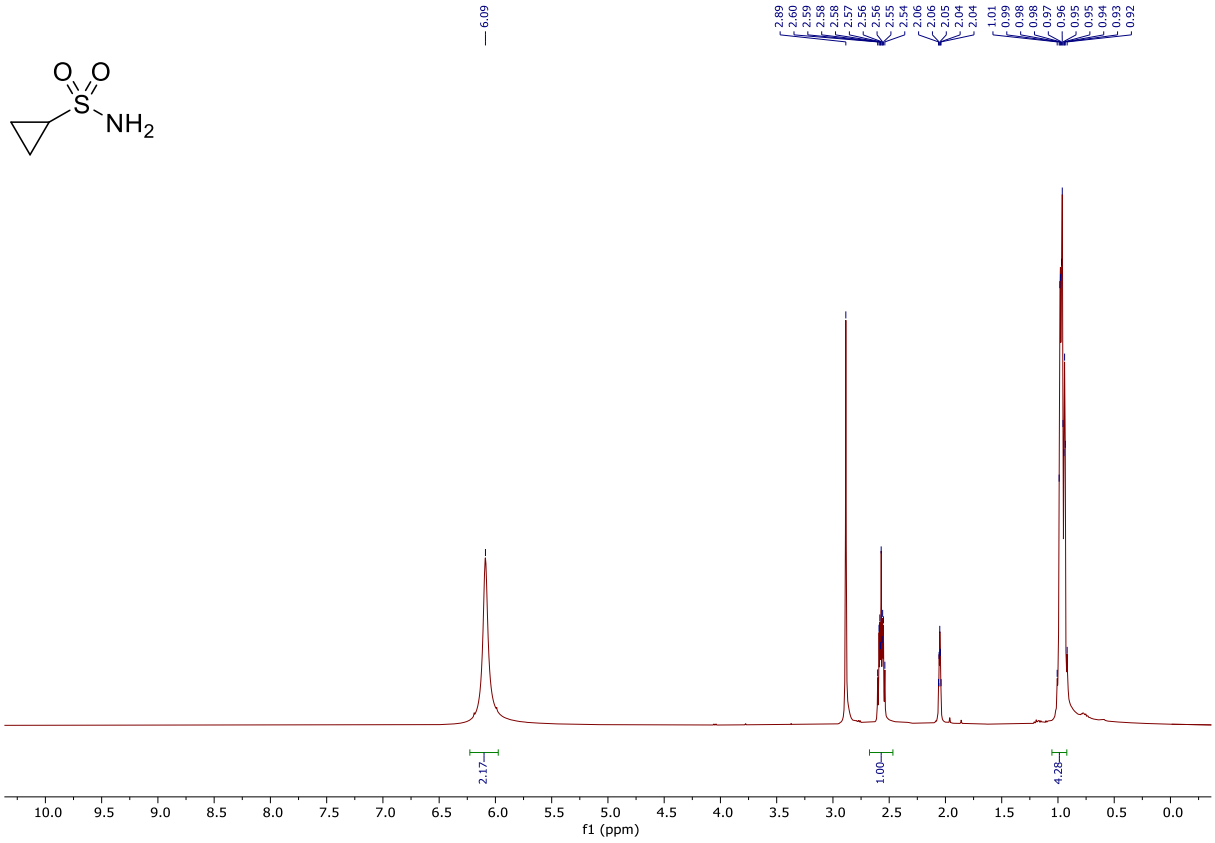


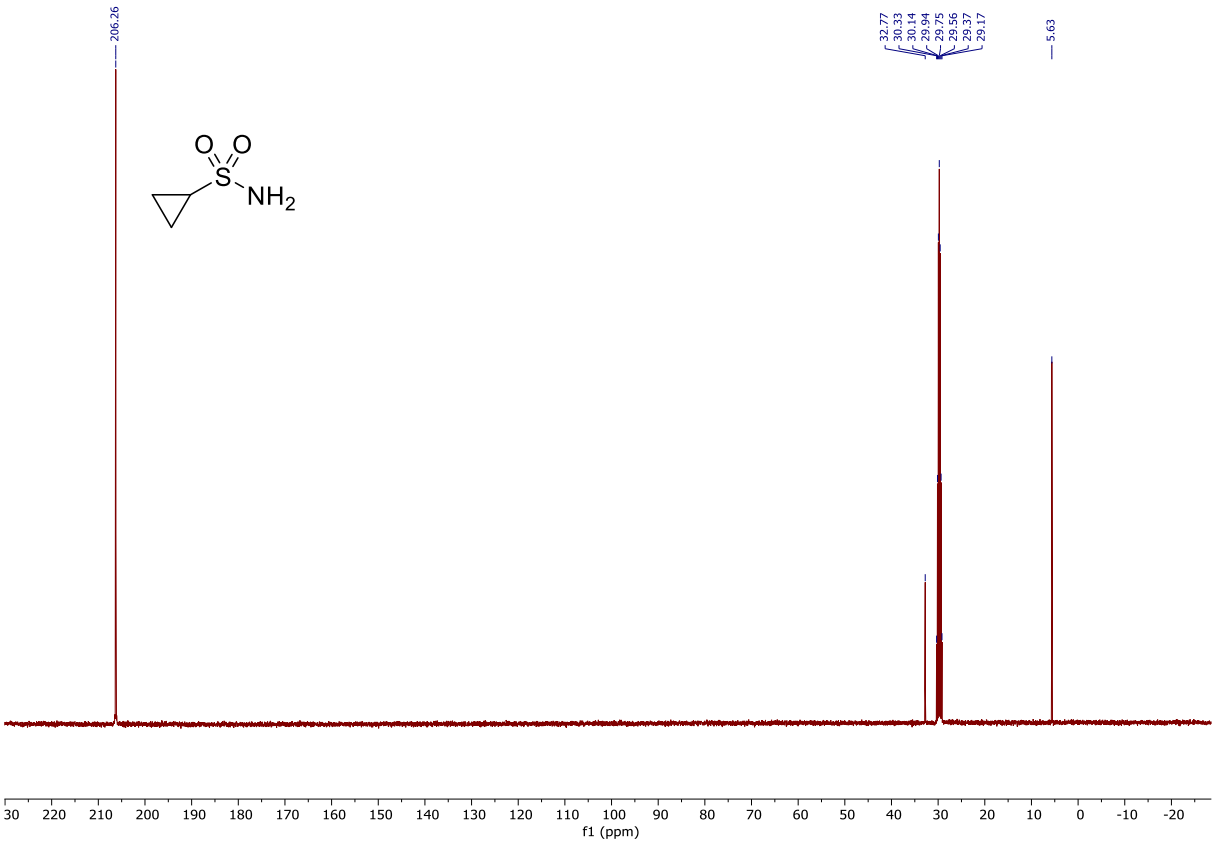



## Cyclohexanesulfonamide (110q)

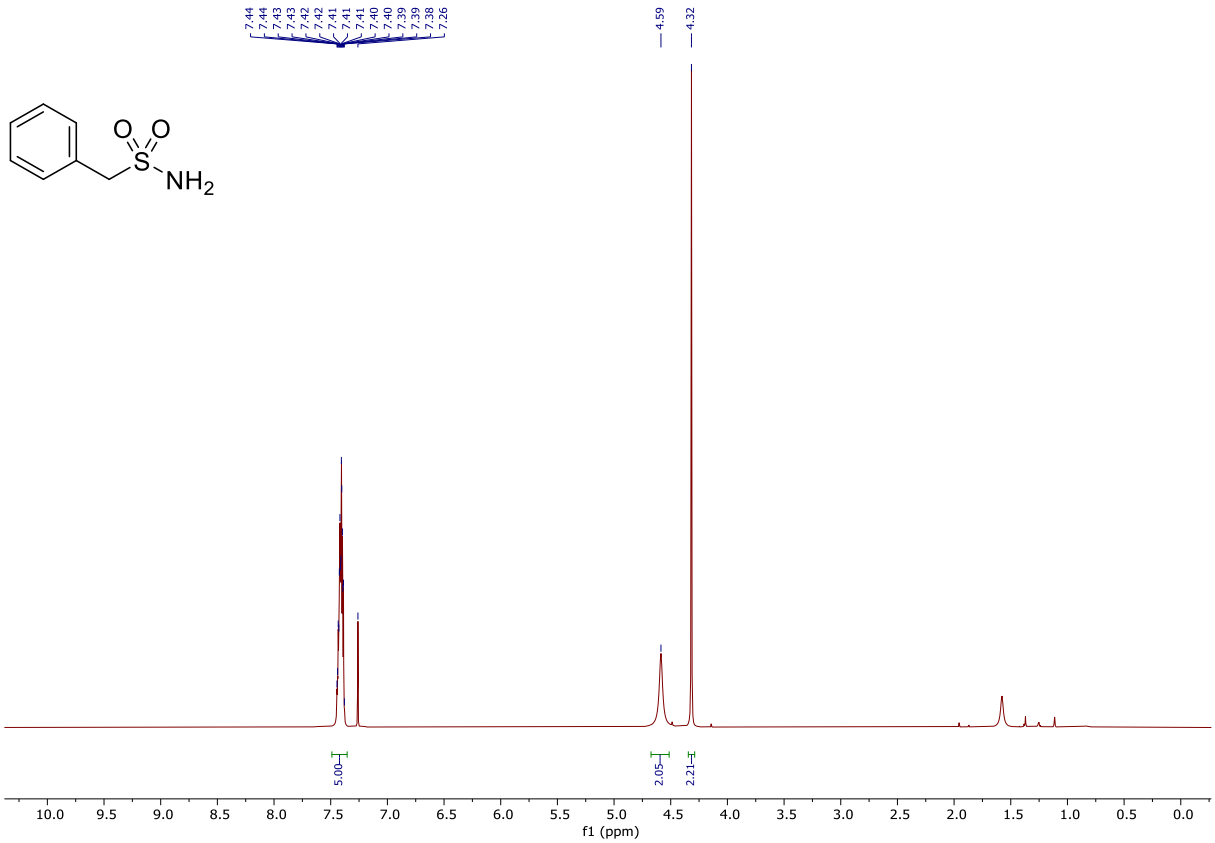


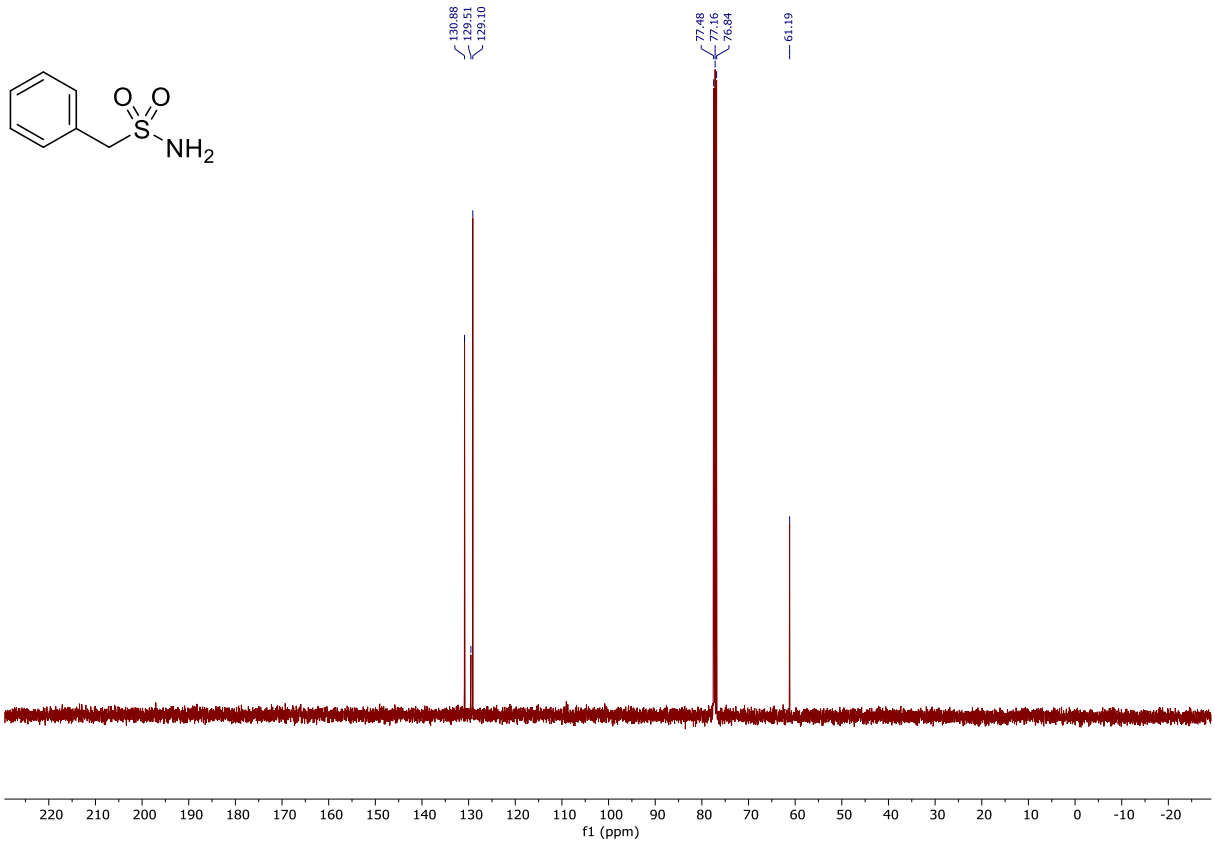
## Cyclopropanesulfonamide (110r)



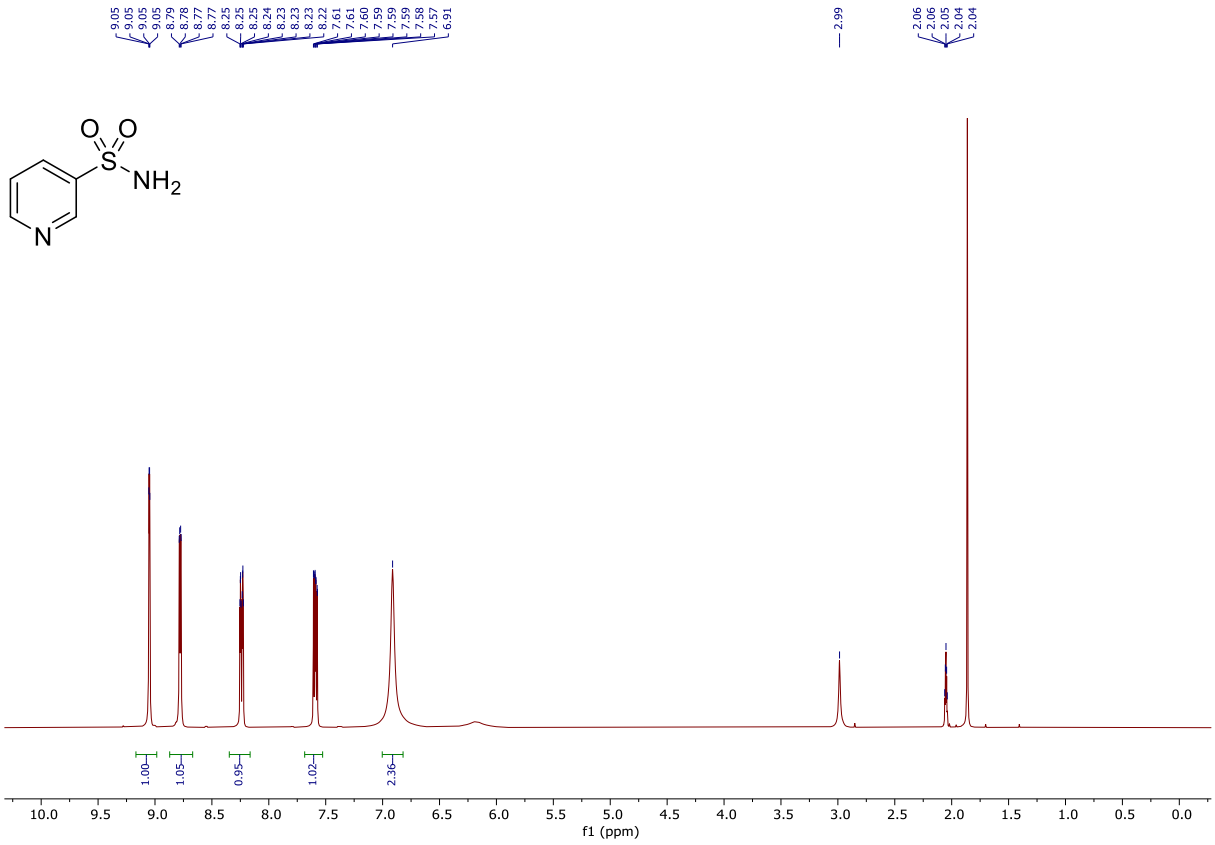



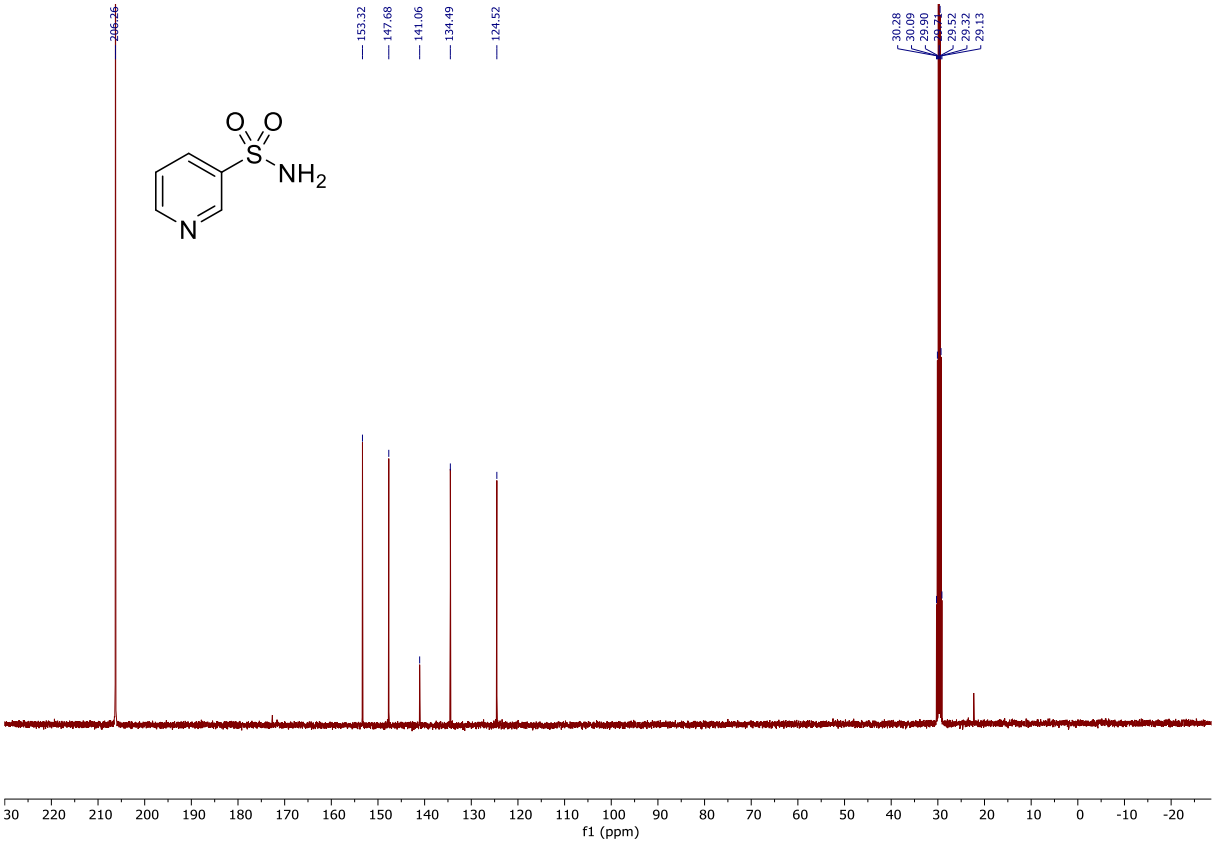
**Phenylmethanesulfonamide (110v)**



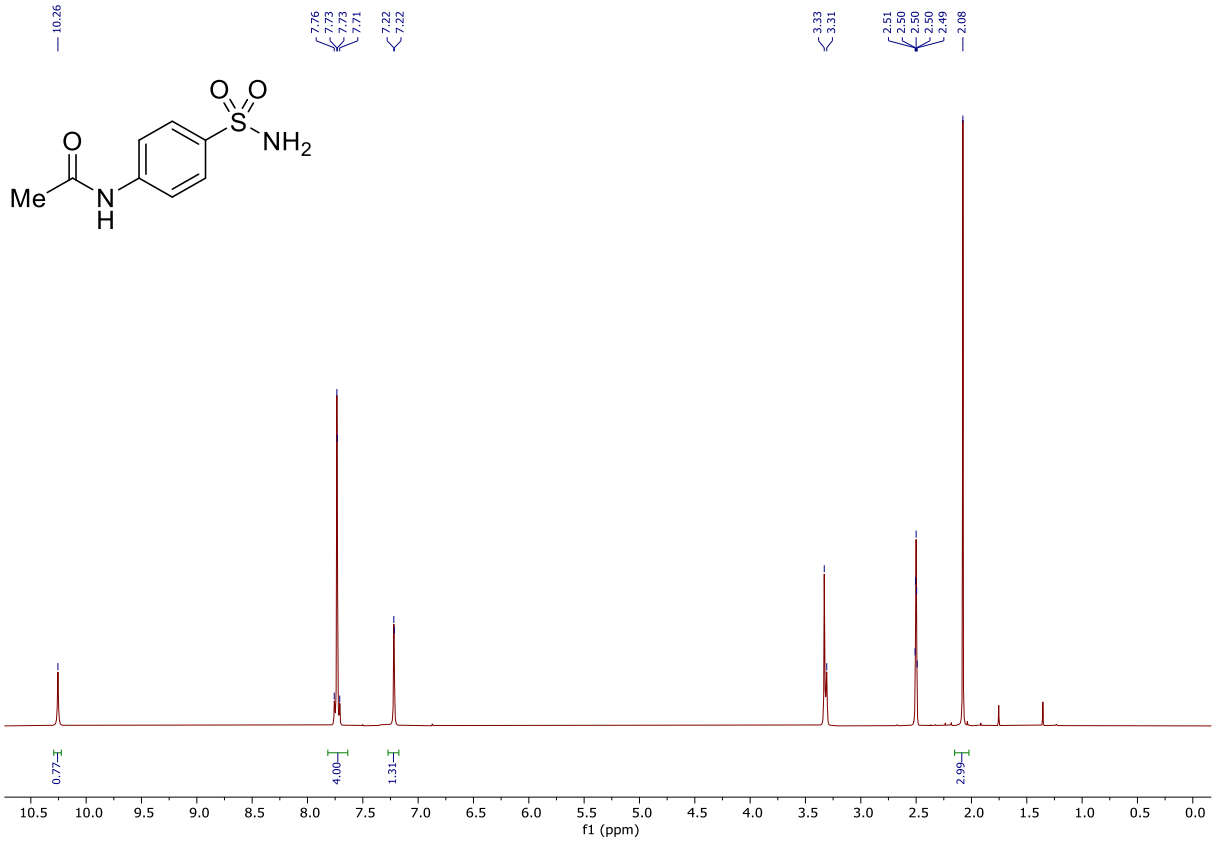



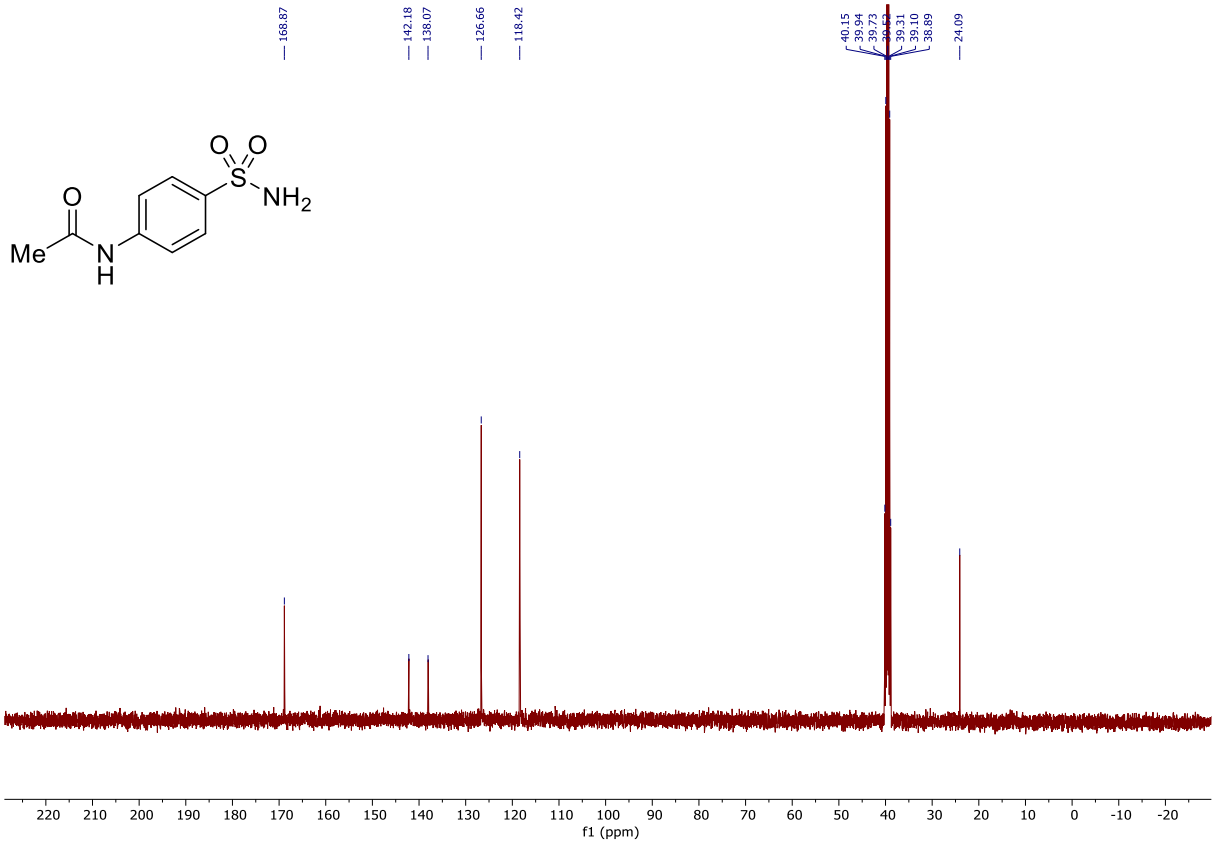
## Pyridine-3-sulfonamide (110x)



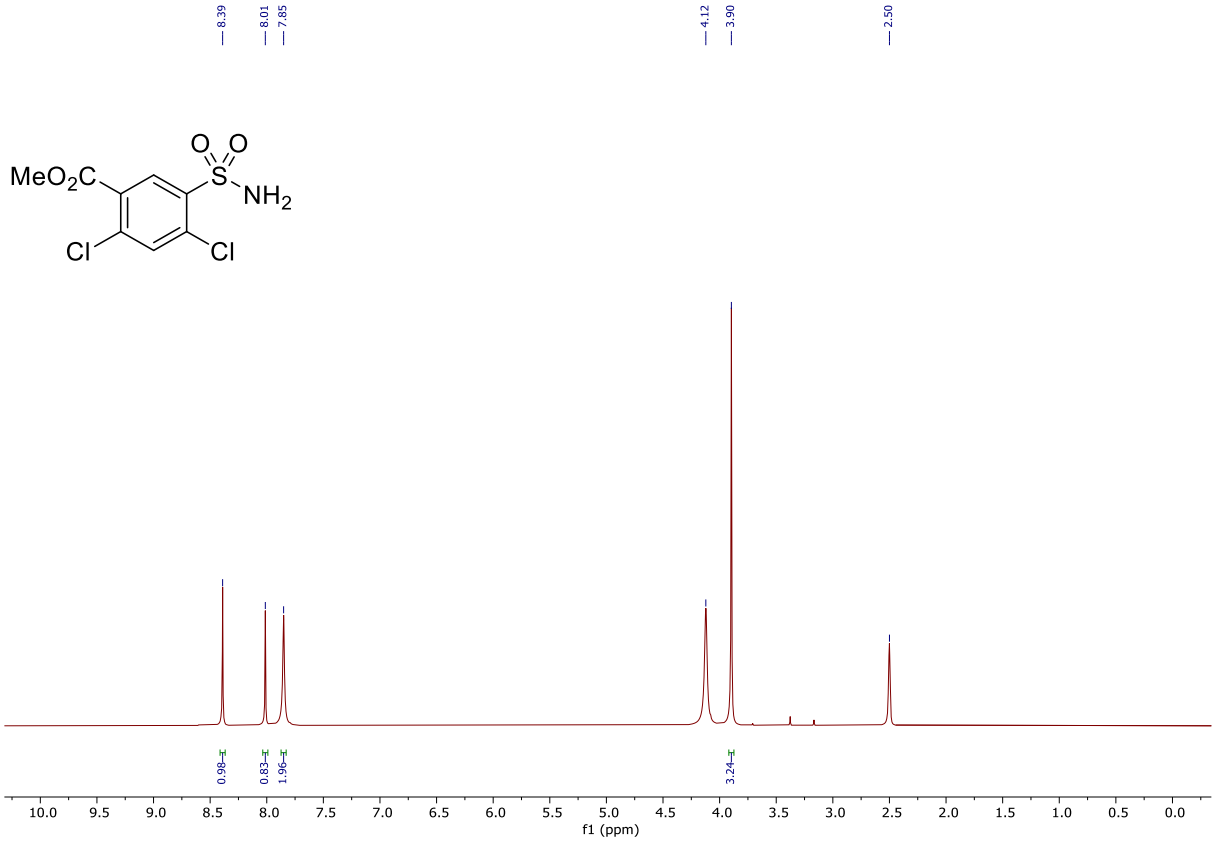



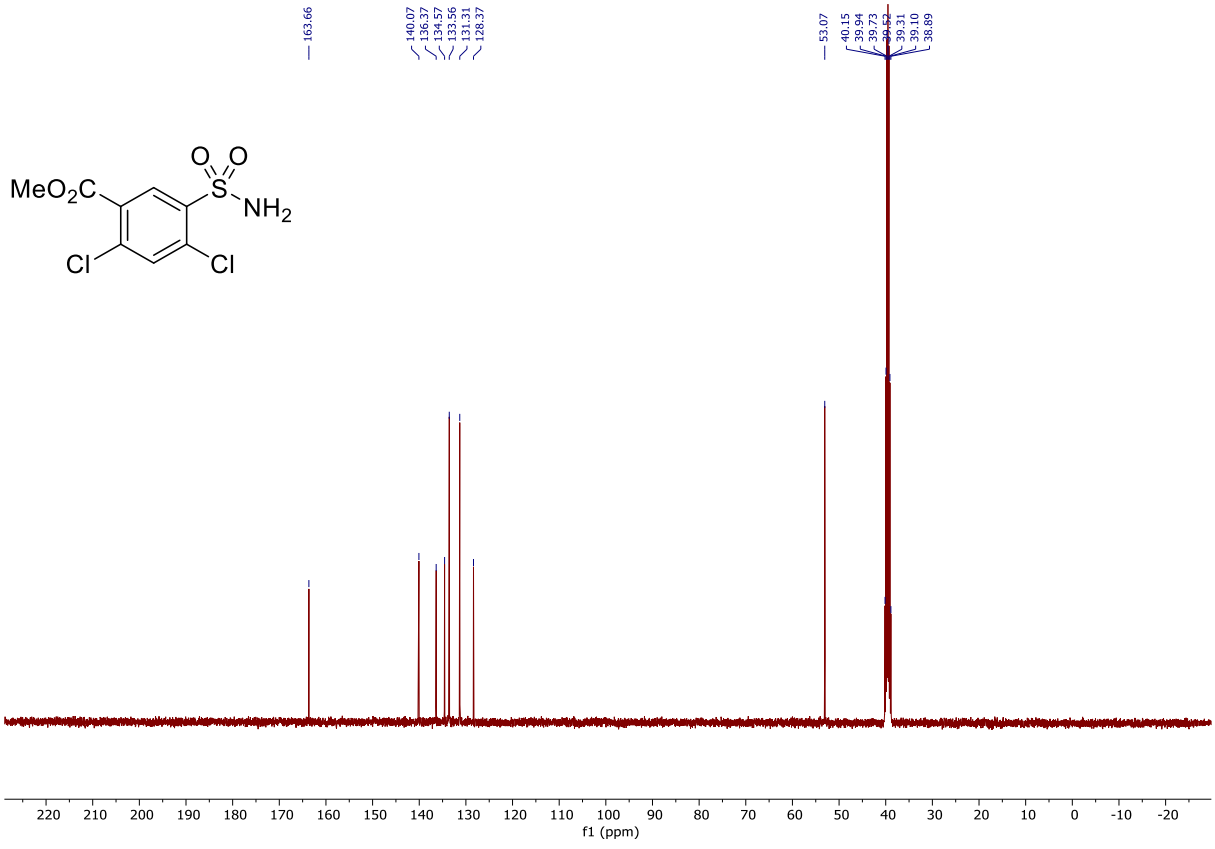
## *N*-(4-sulfamoylphenyl)acetamide (110z)



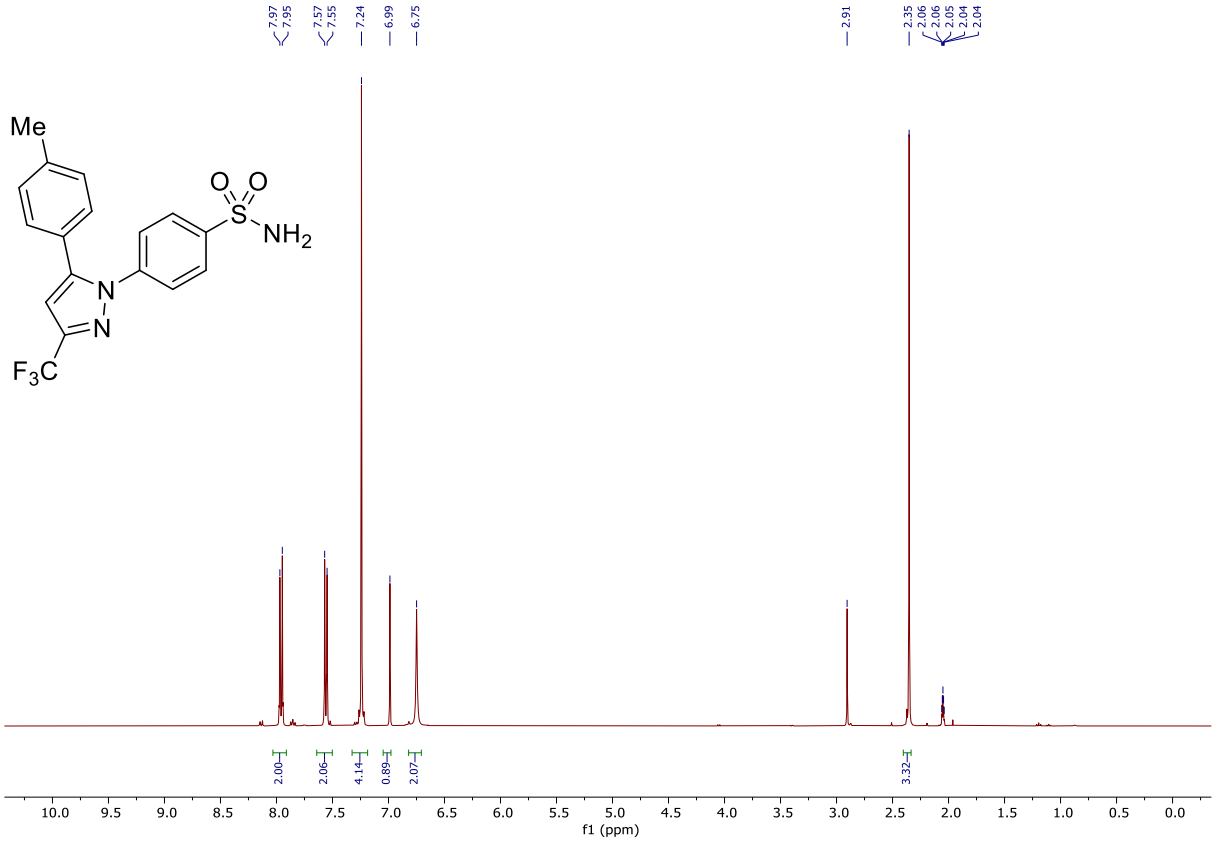



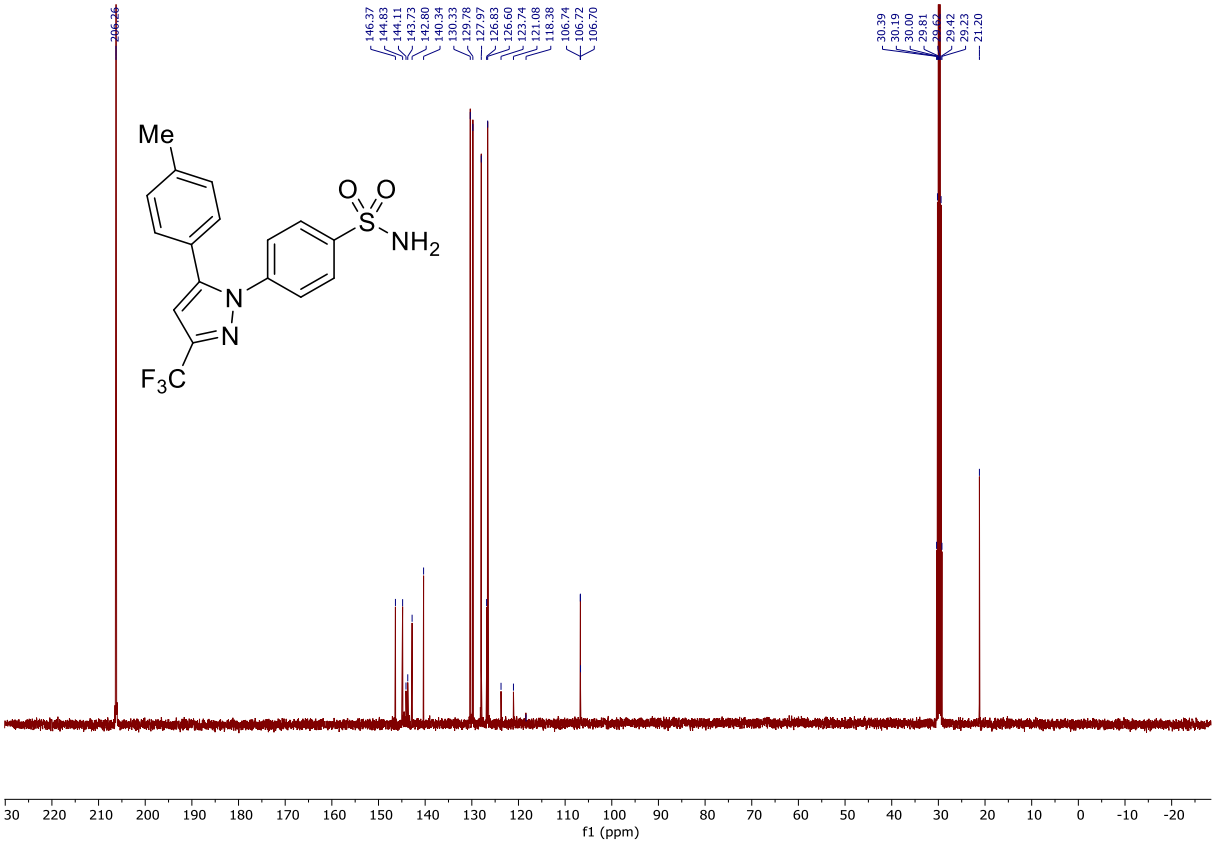
## Methyl 2,4-dichloro-5-sulfamoylbenzoate (125a)

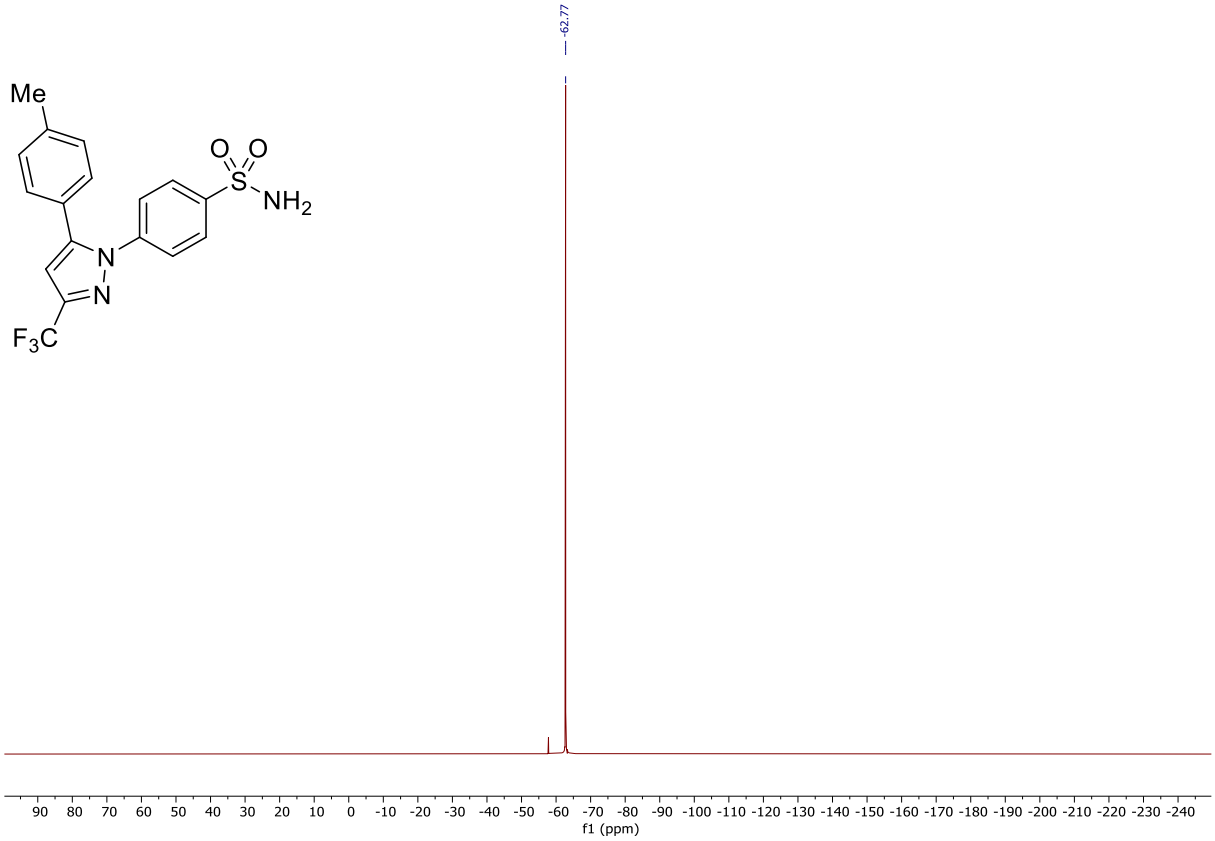


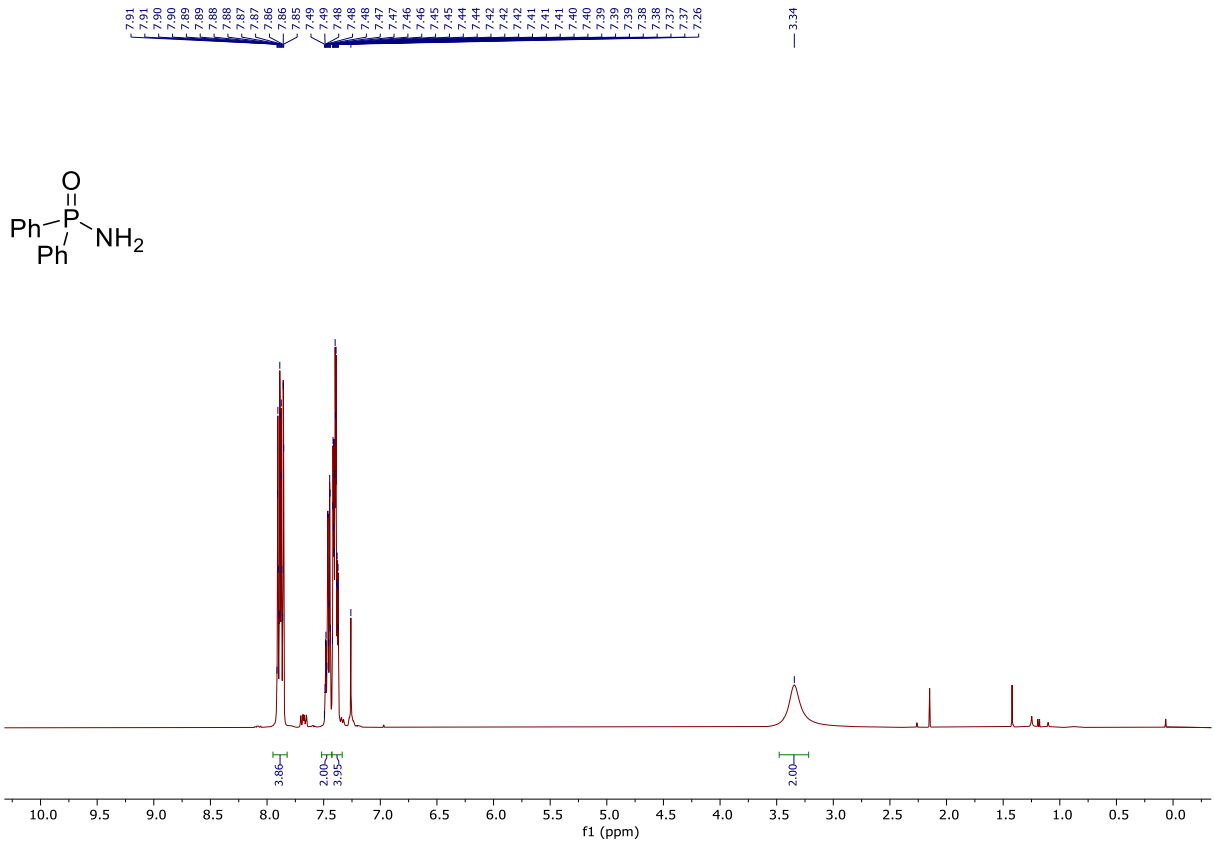
**4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide (100)**

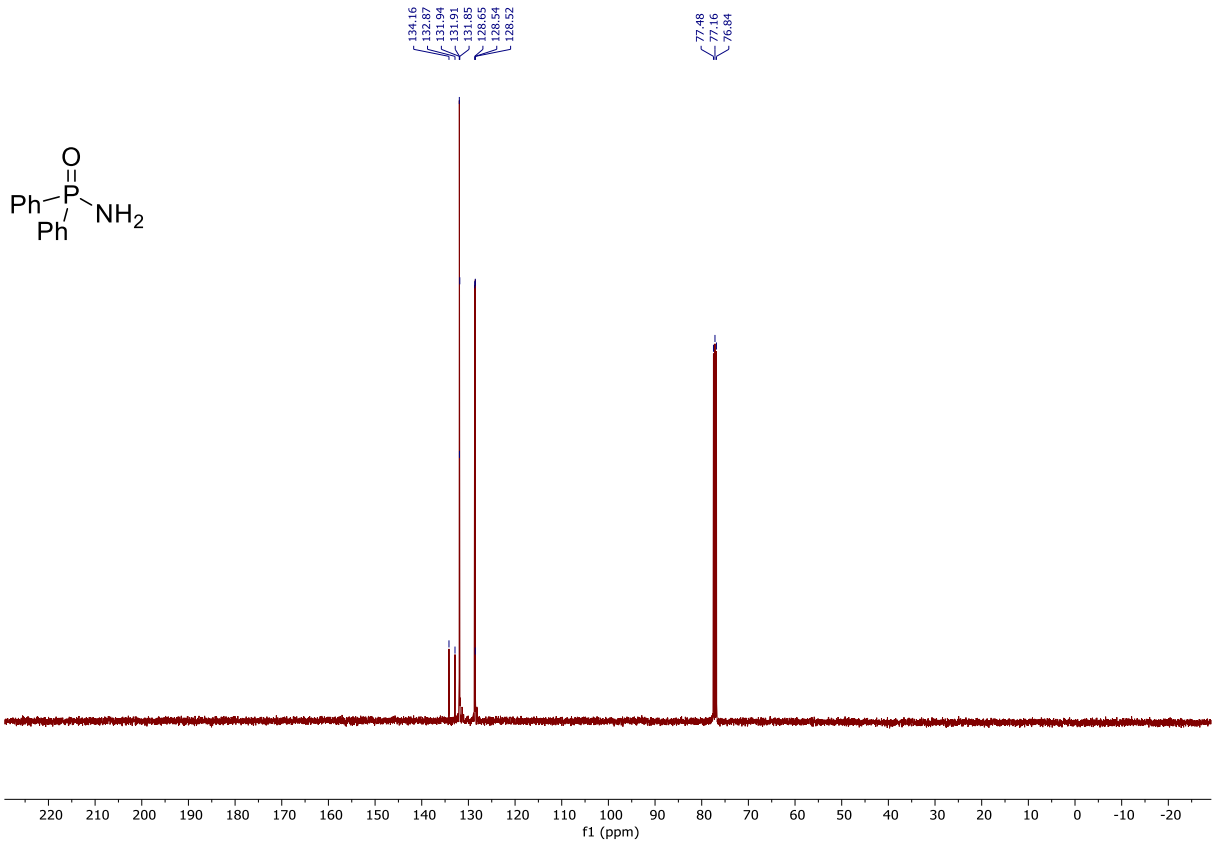


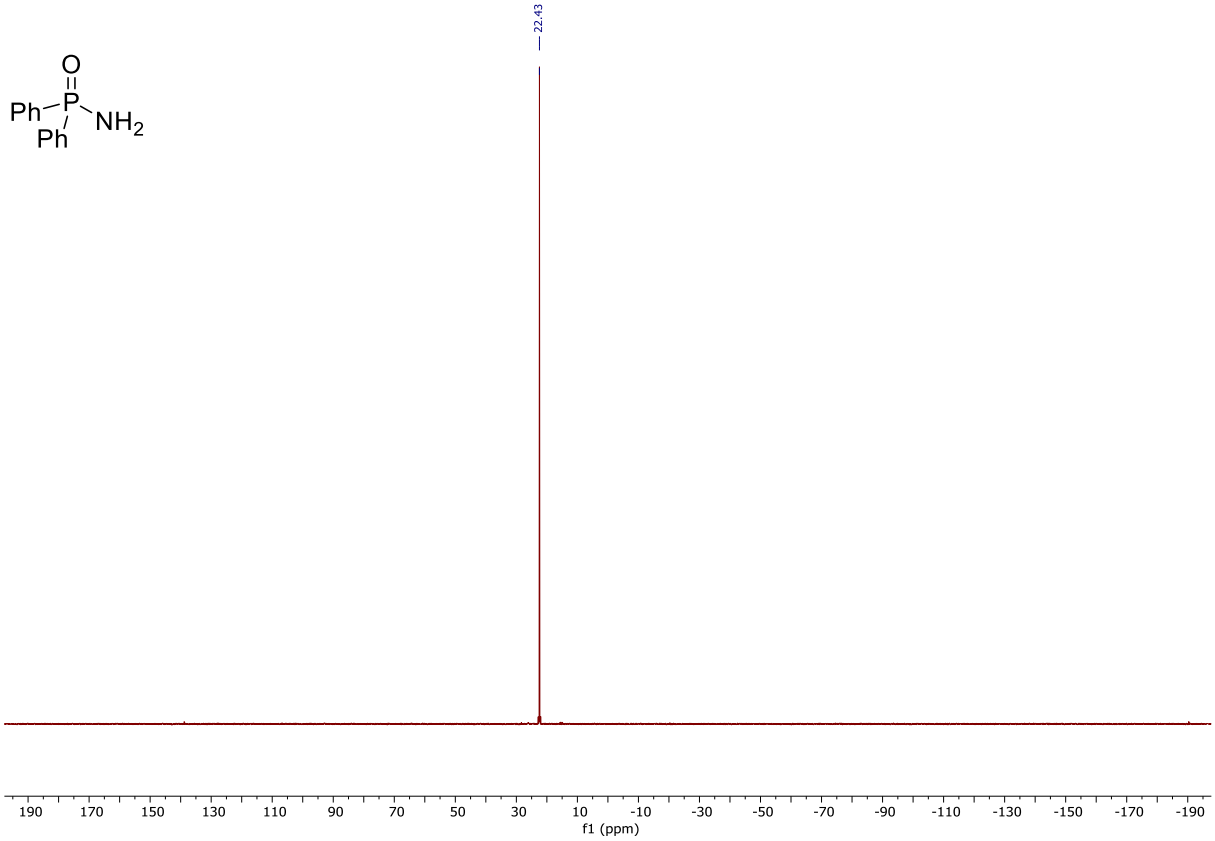




Me
O
O
S
NH2
N
N
F3C
-62.77
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

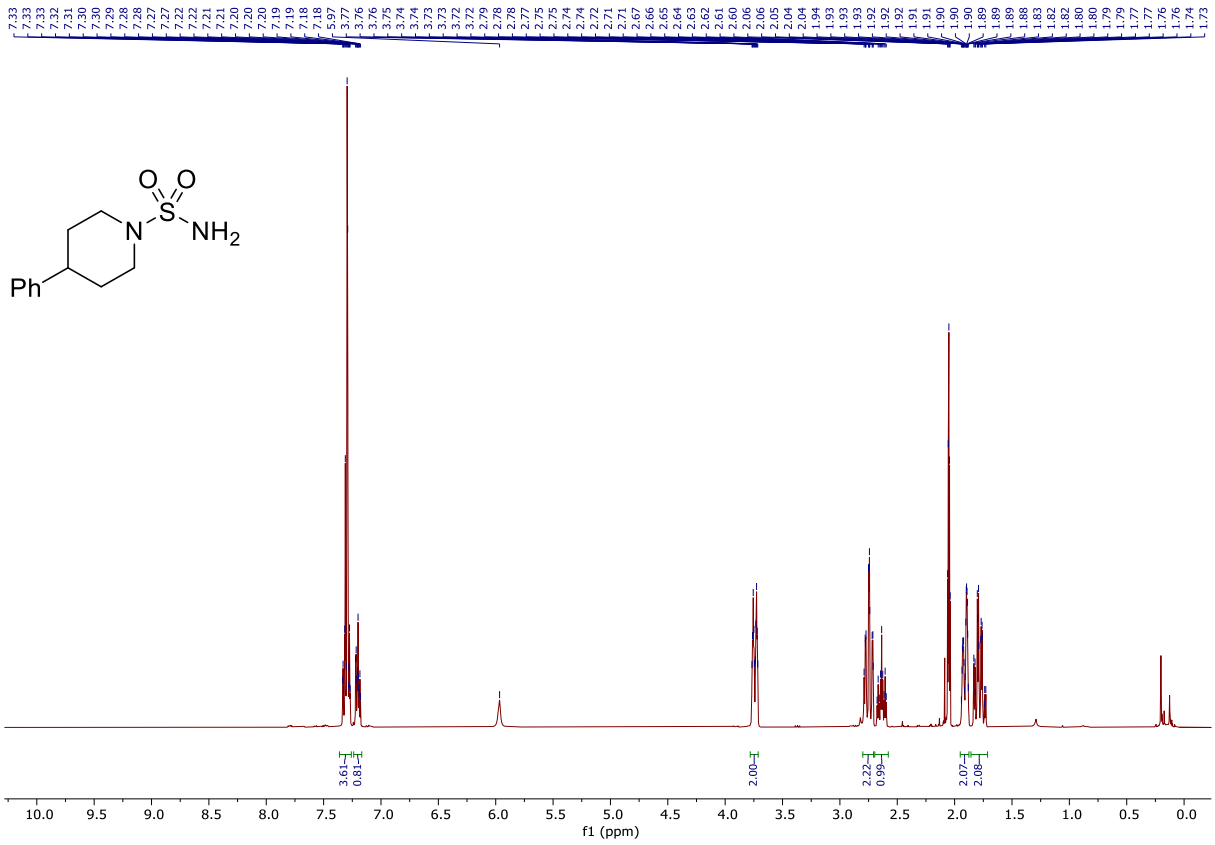
## *P,P*-diphenylphosphinic amide (126)

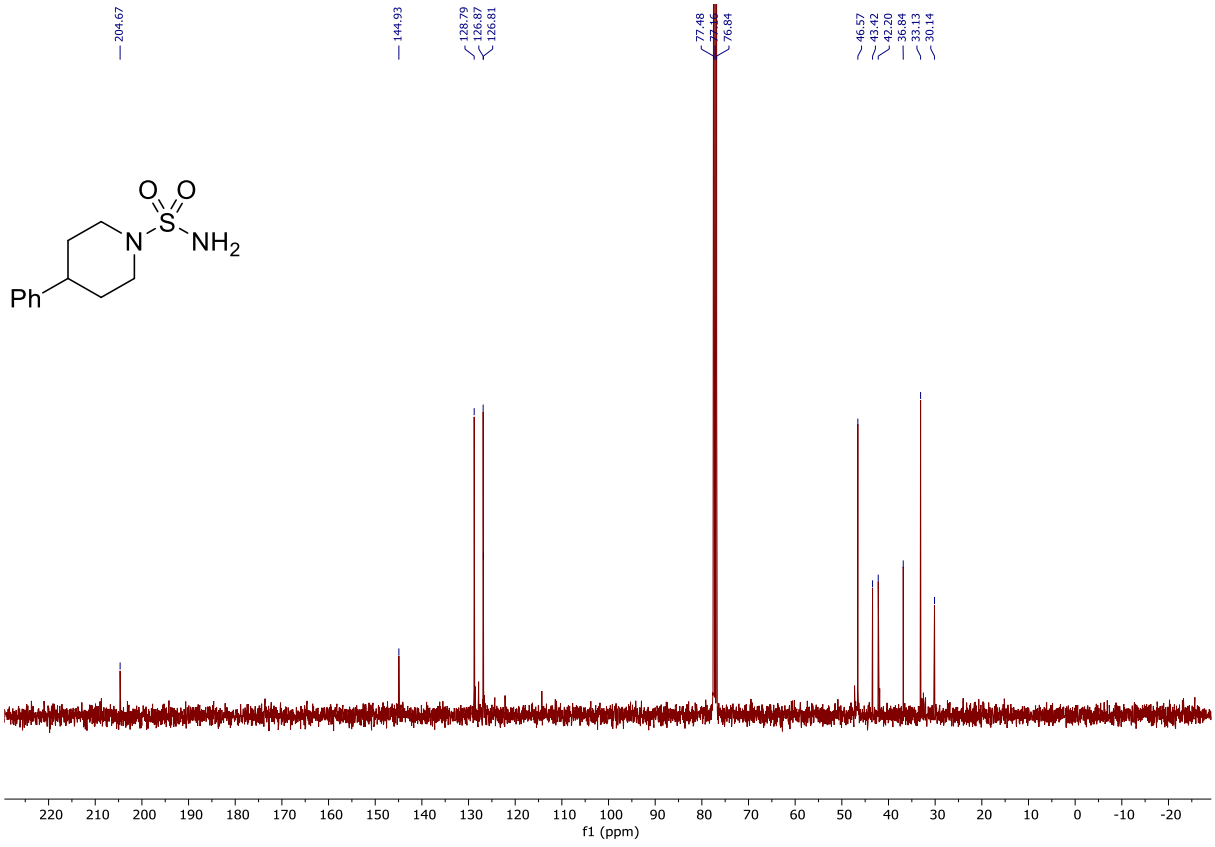


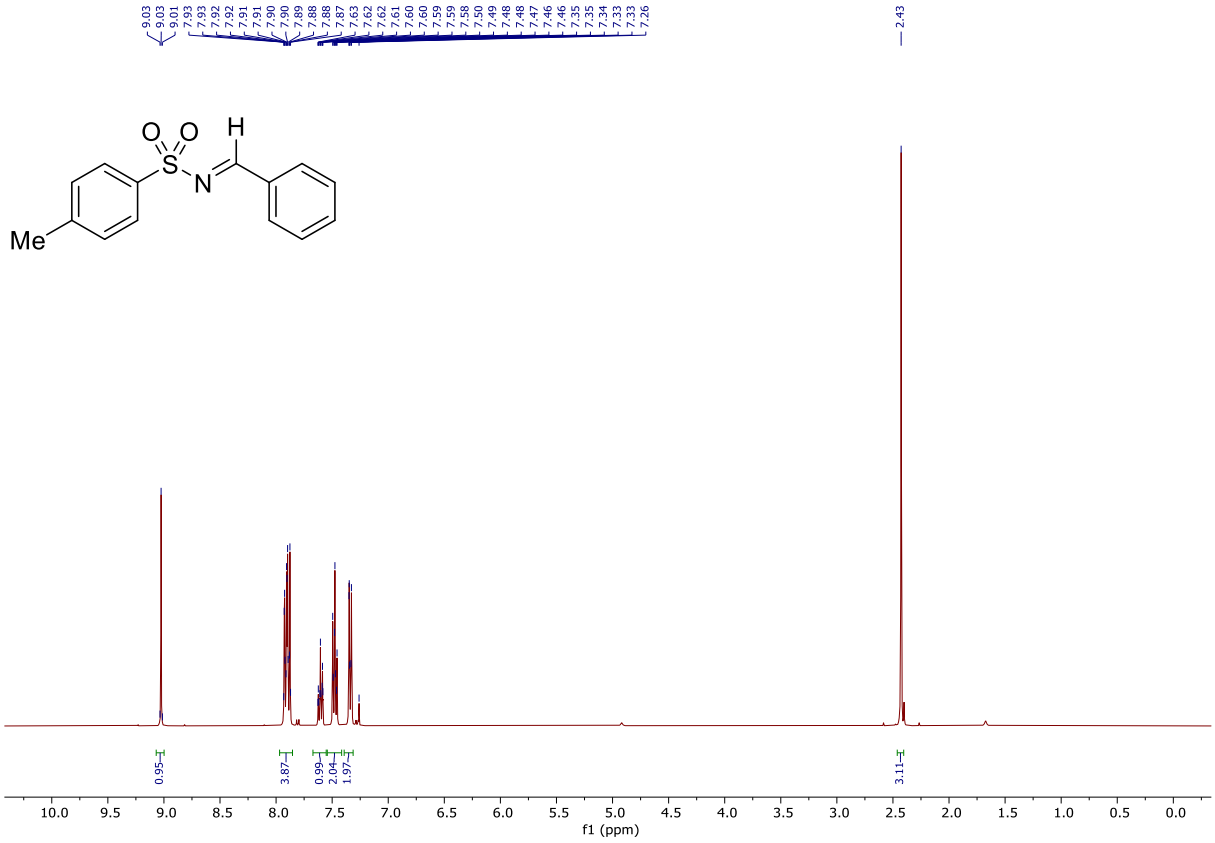

O
Ph
P
NH2
Ph
22.43
190
170
150
130
110
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
f1 (ppm)

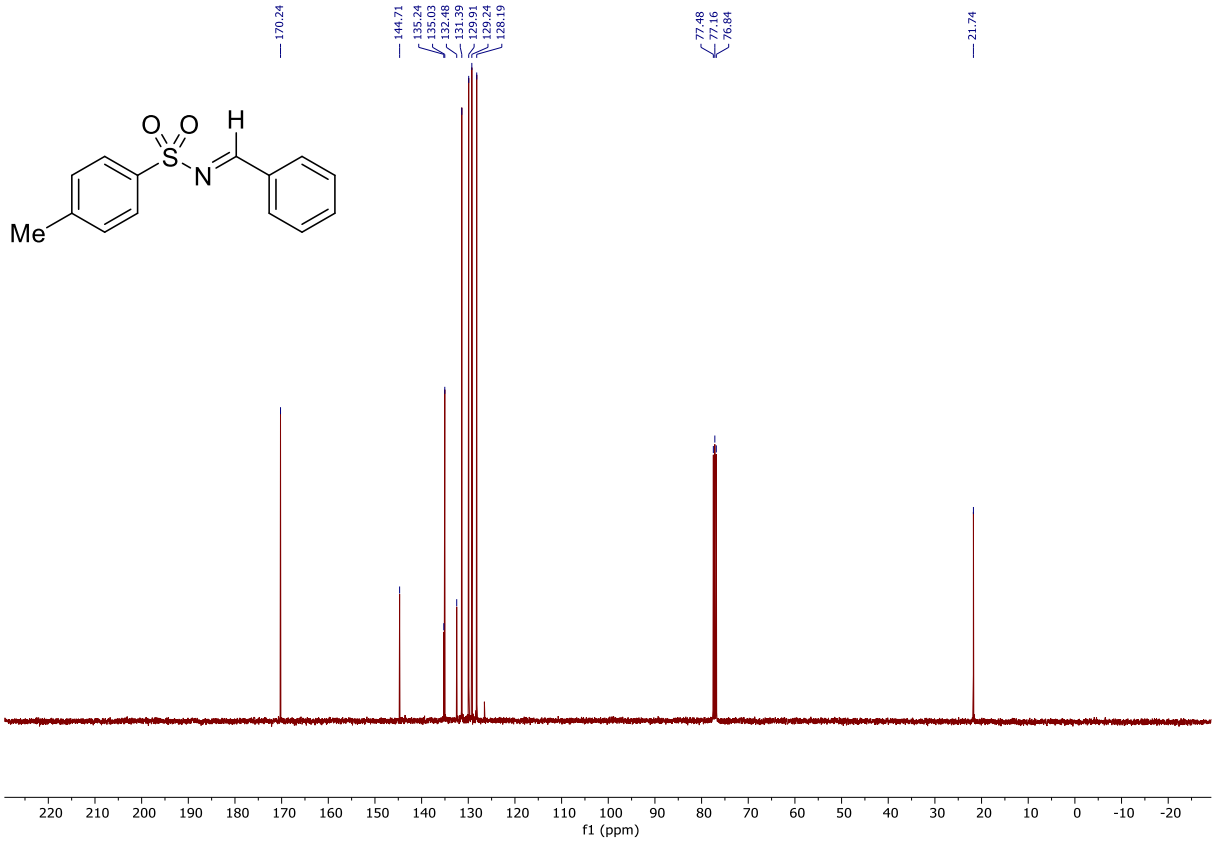
## 4-Phenylpiperidine-1-sulfonamide (127)



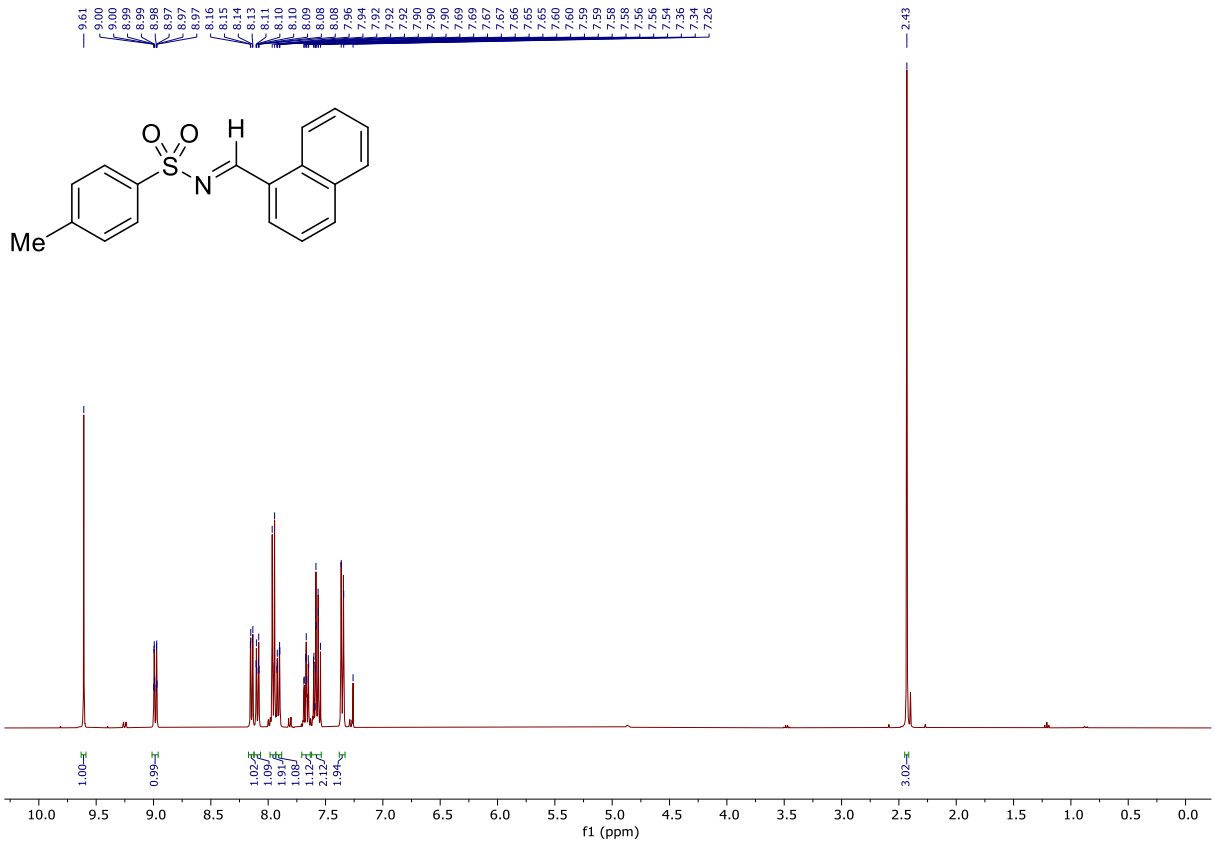



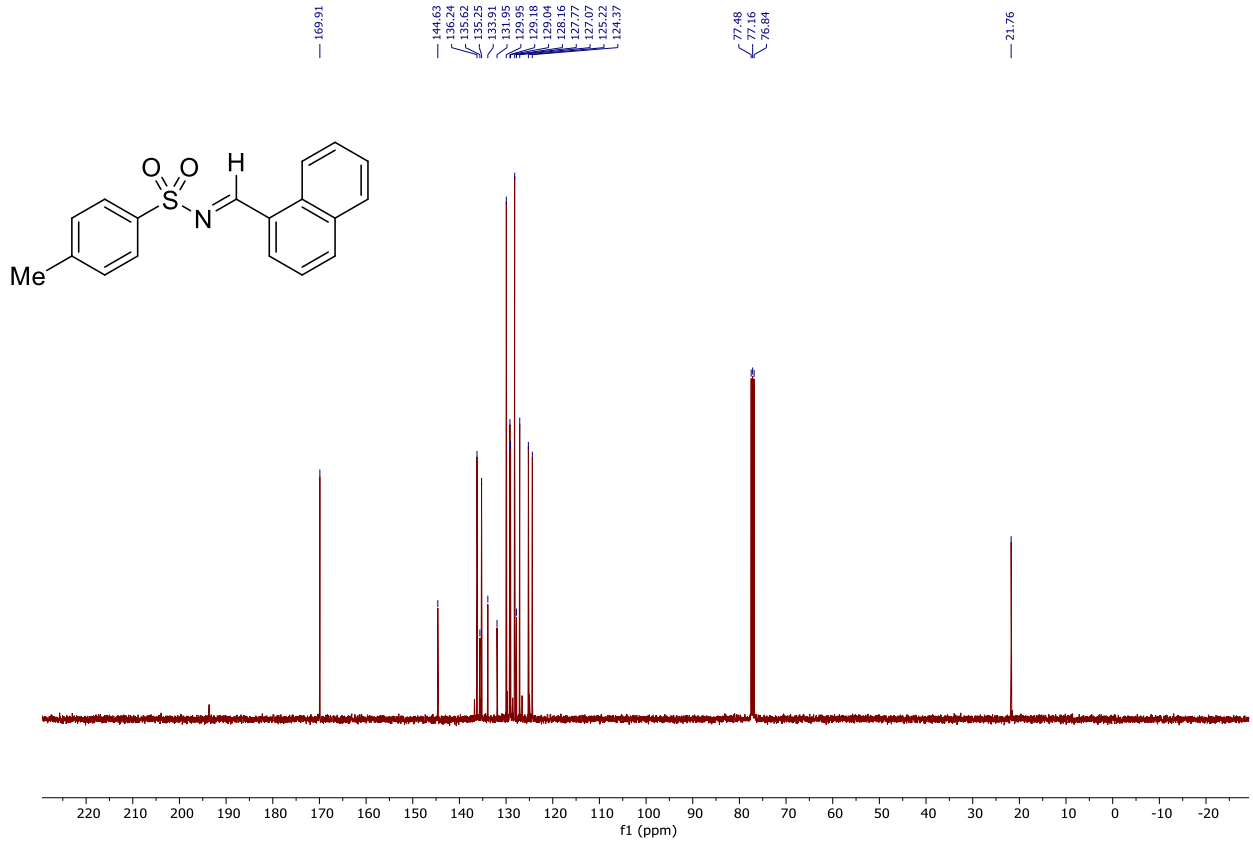
## *N*-benzylidene-4-methylbenzenesulfonamide (108a)



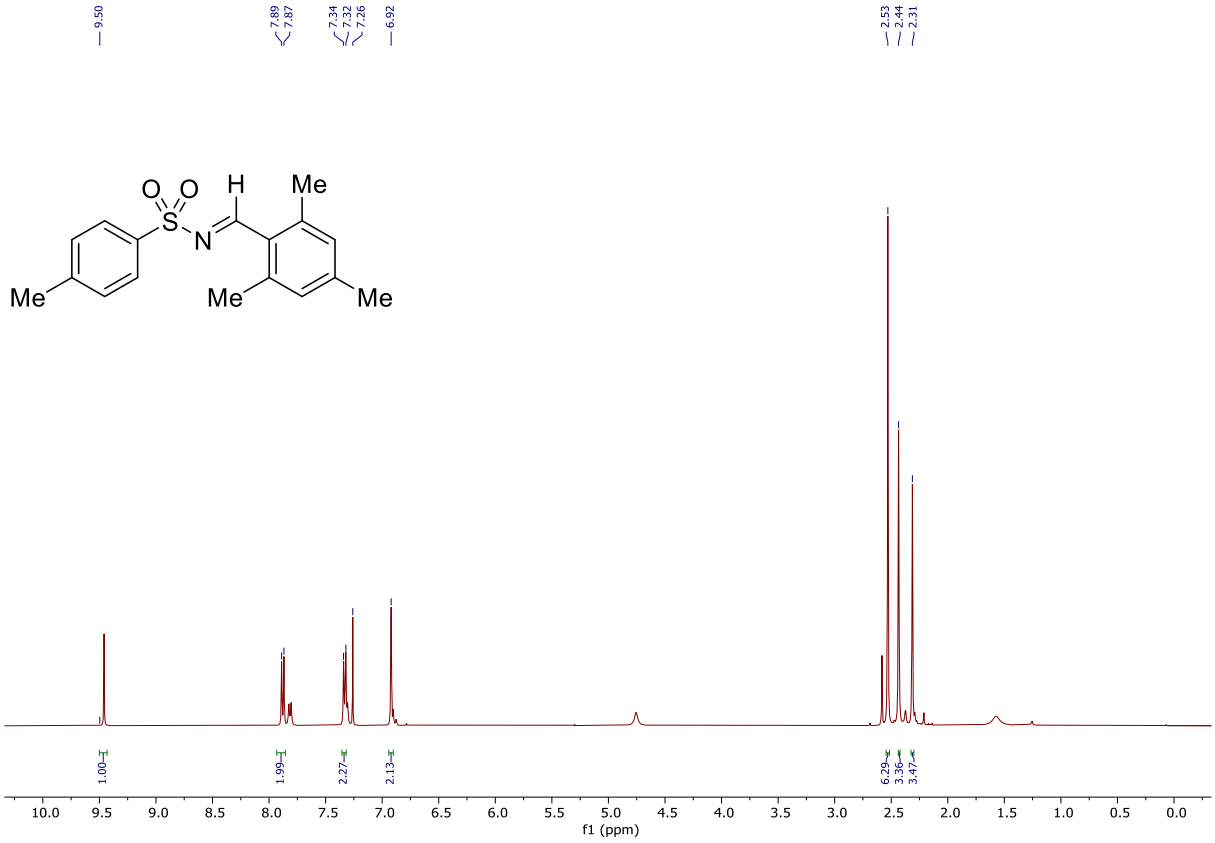



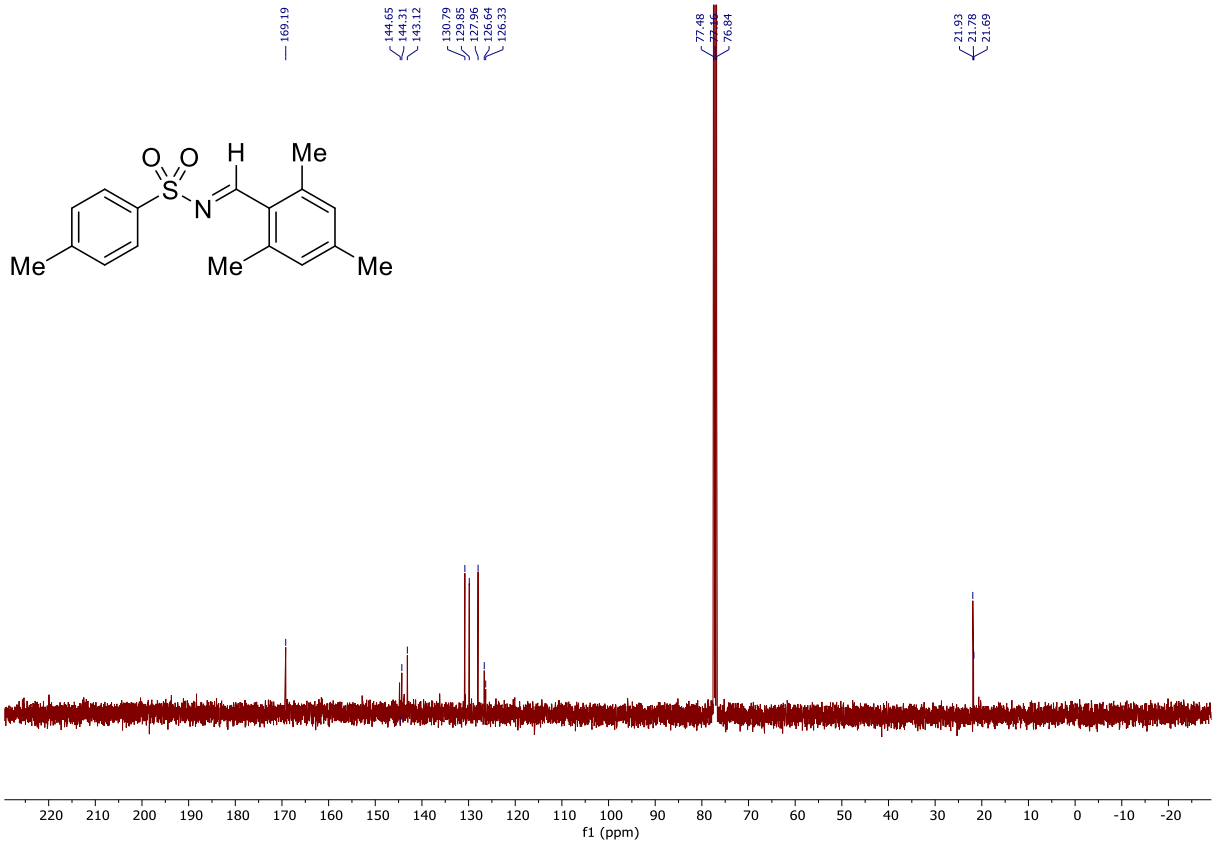
## 4-Methyl-*N*-(naphthalen-1-ylmethylene)benzenesulfonamide (108ab)



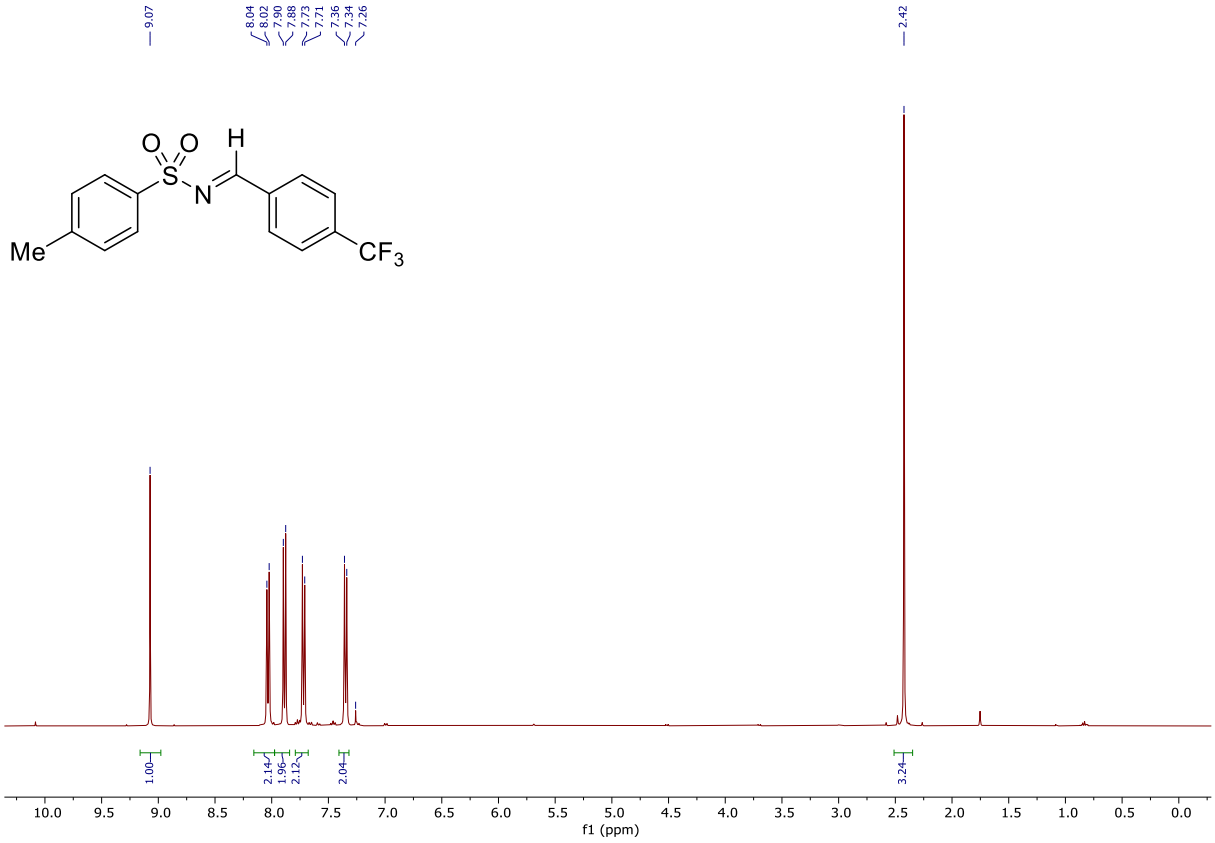



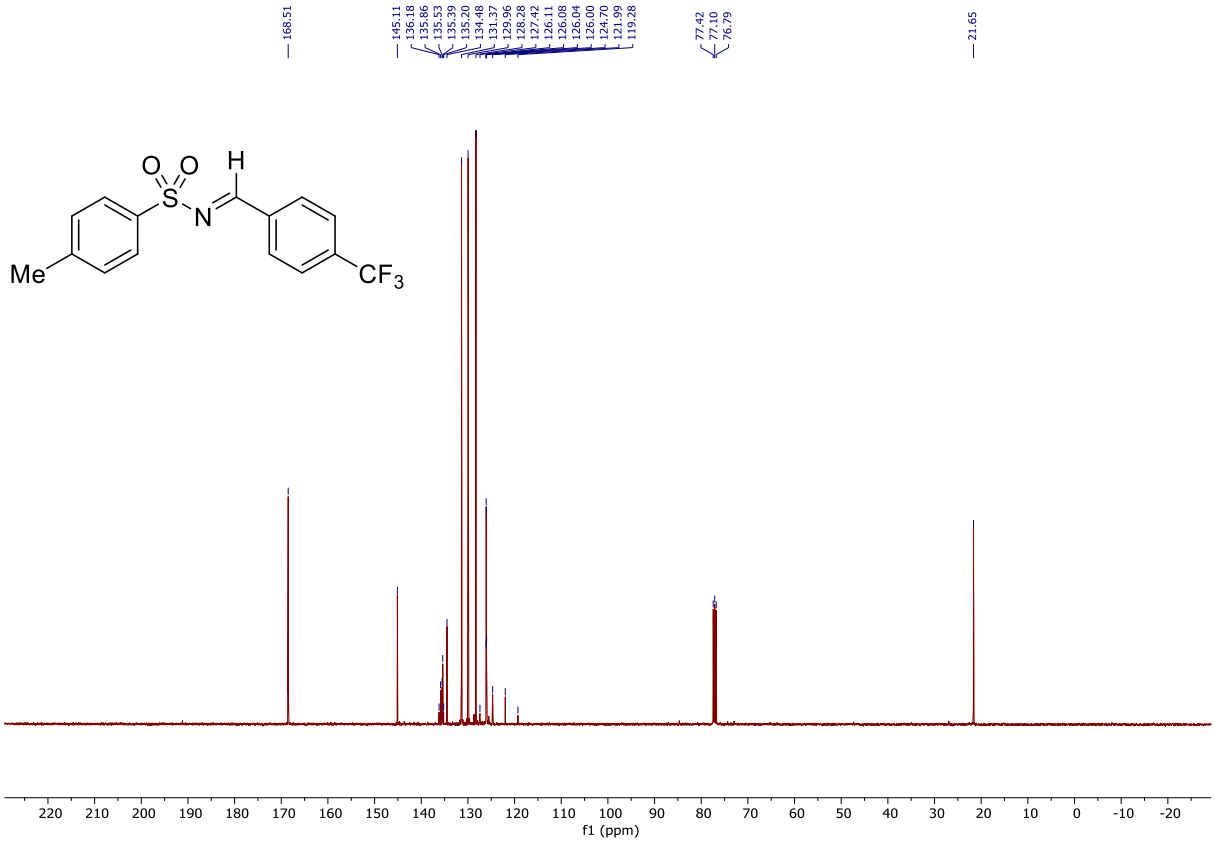
## 4-methyl-*N*-(2,4,6-trimethylbenzylidene)benzenesulfonamide (108ac)

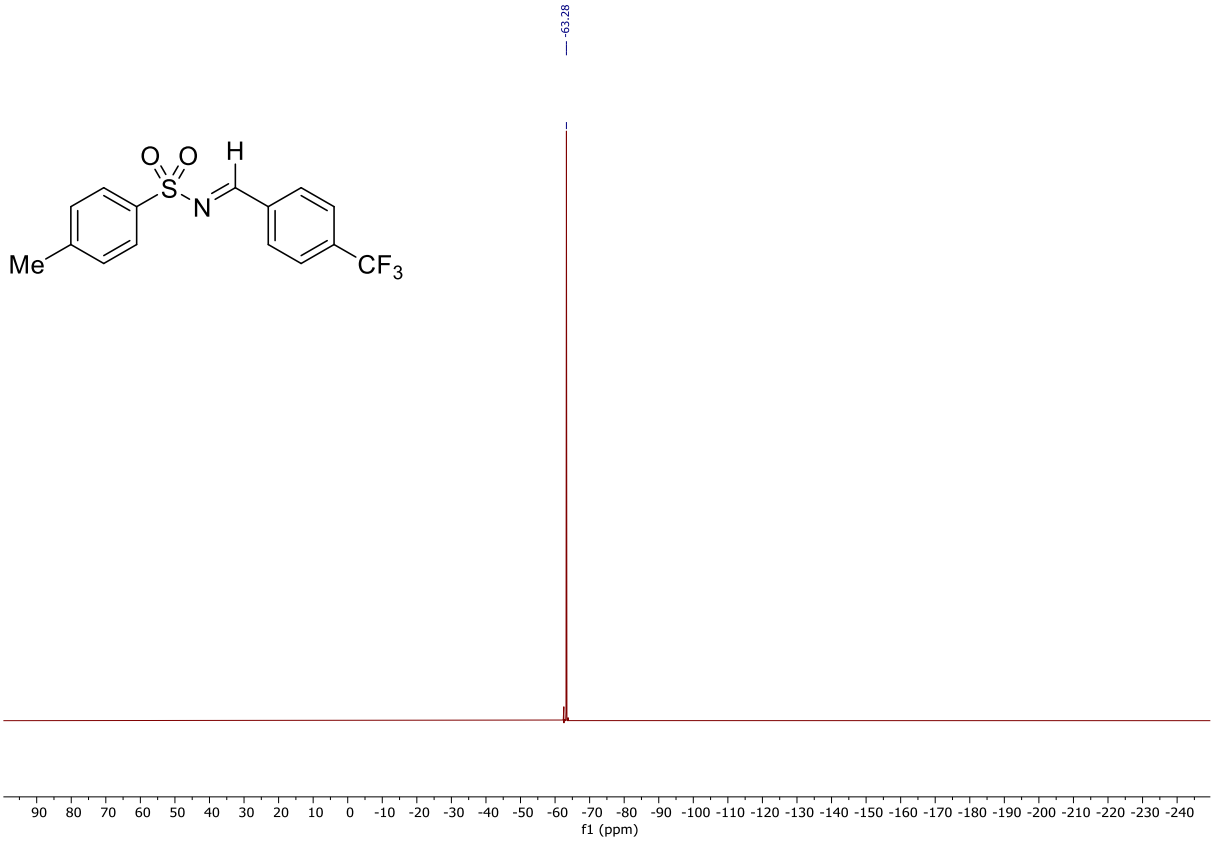


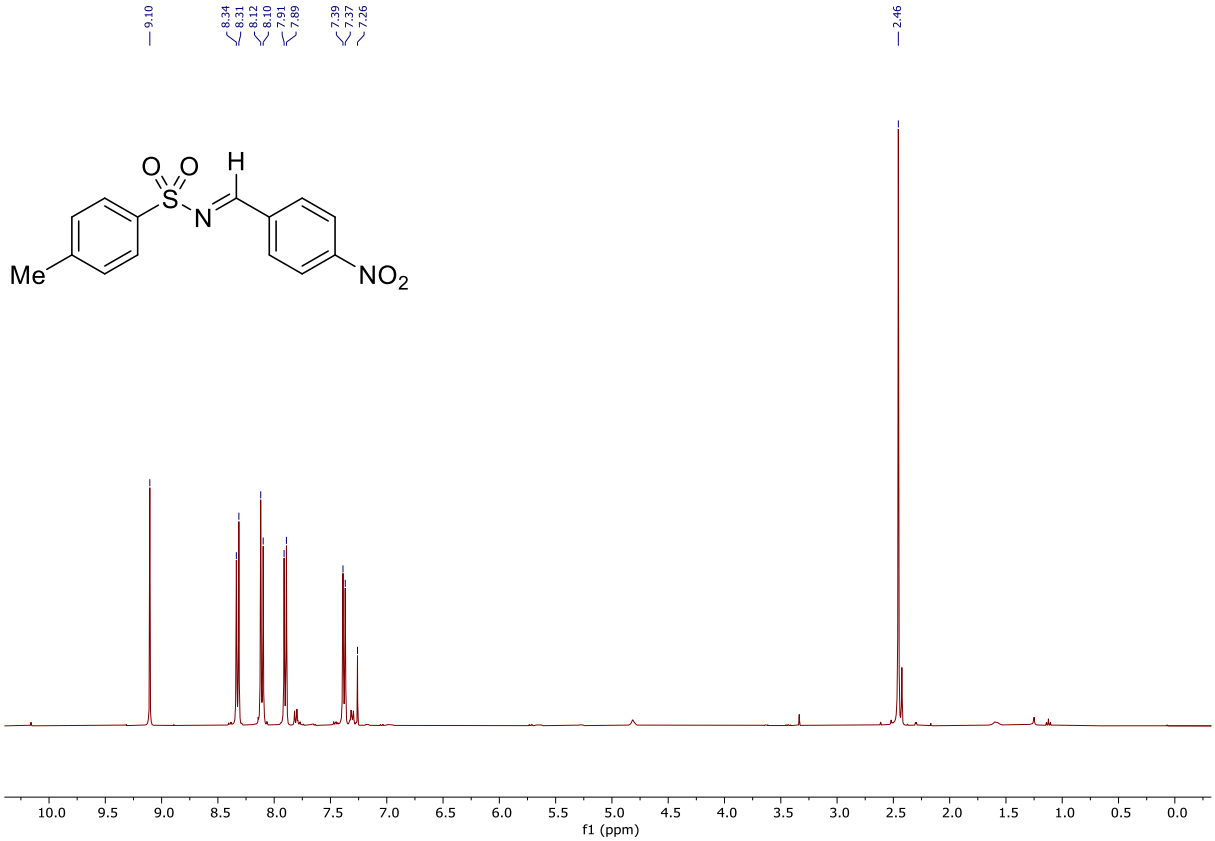
**4-methyl-*N*-(4-(trifluoromethyl)benzylidene)benzenesulfonamide (108ad)**

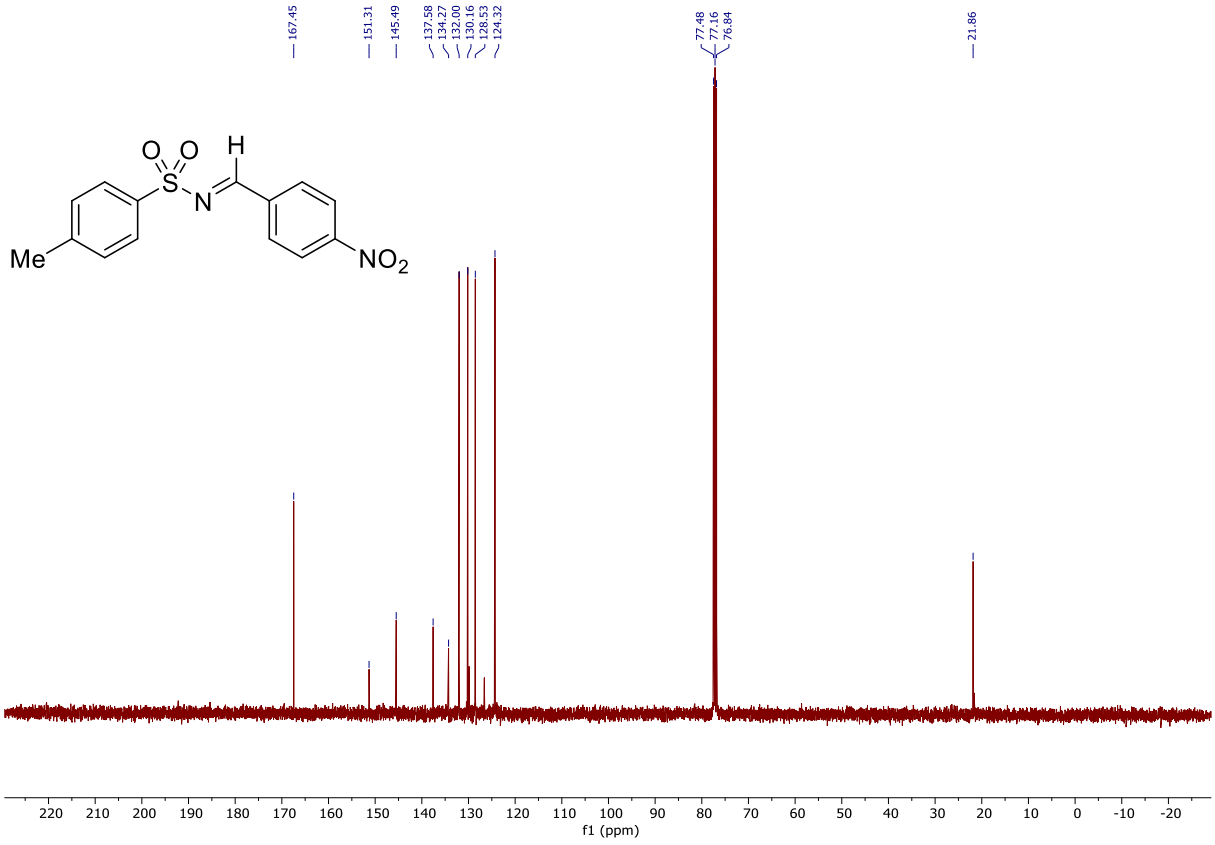


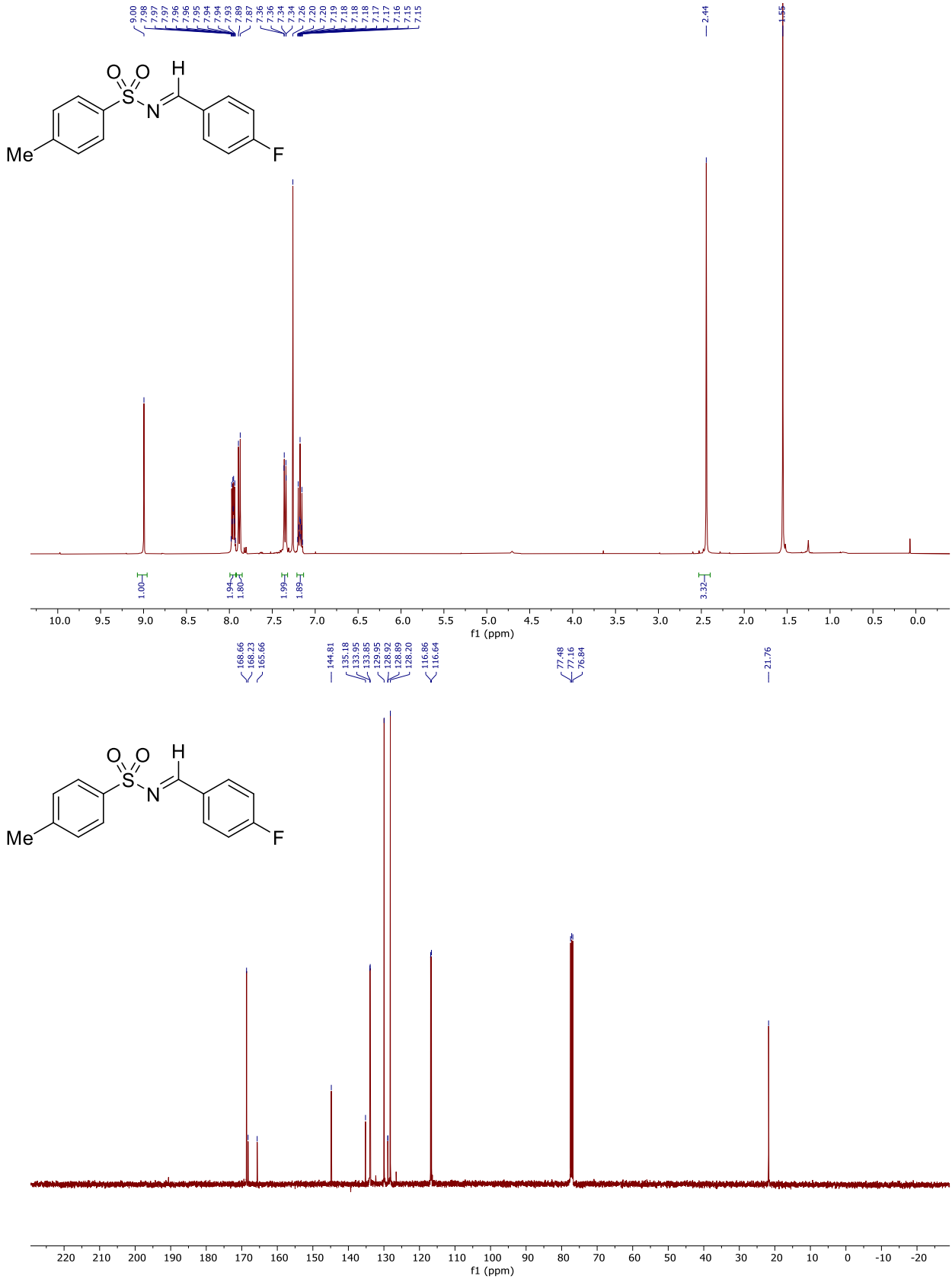

-63.28
O
O
H
S
N
Me
CF3
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

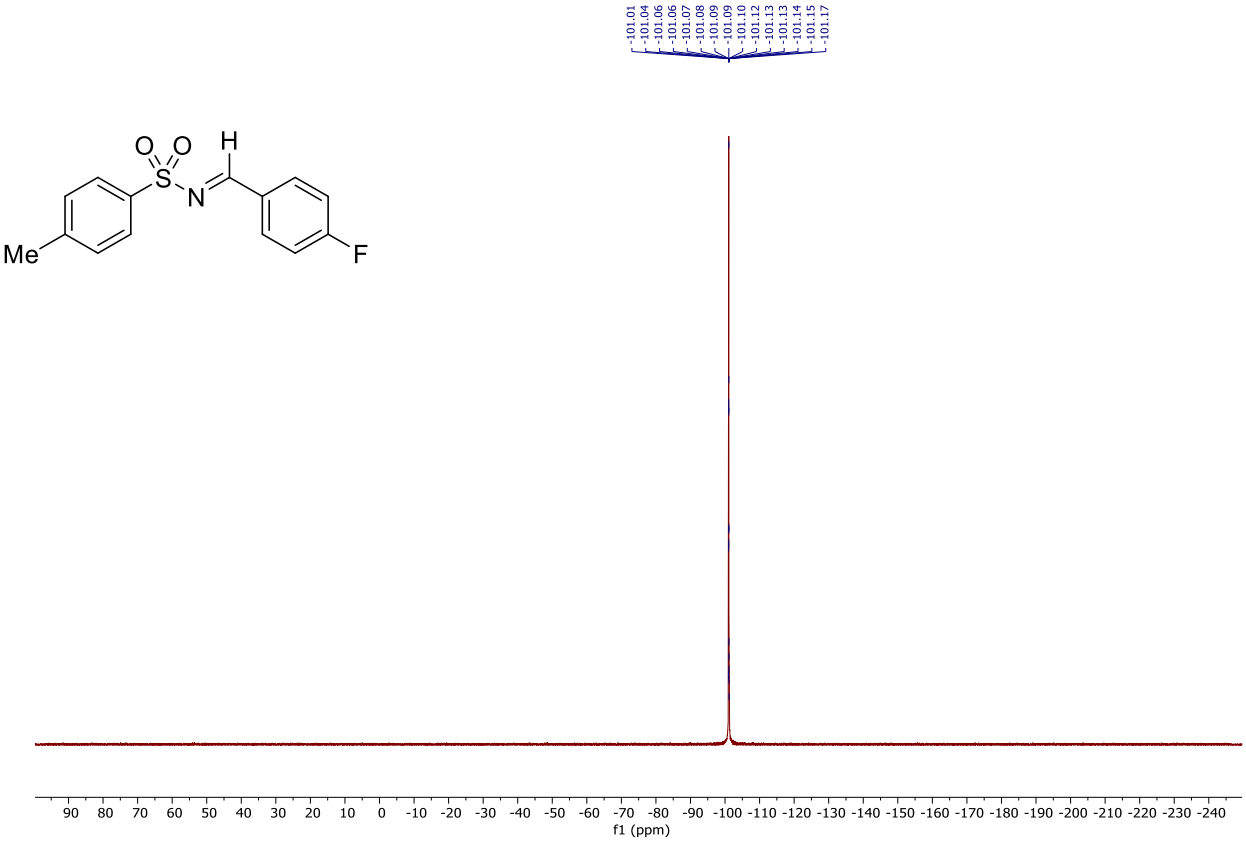
**4-methyl-*N*-(4-nitrobenzylidene)benzenesulfonamide (108ae)**



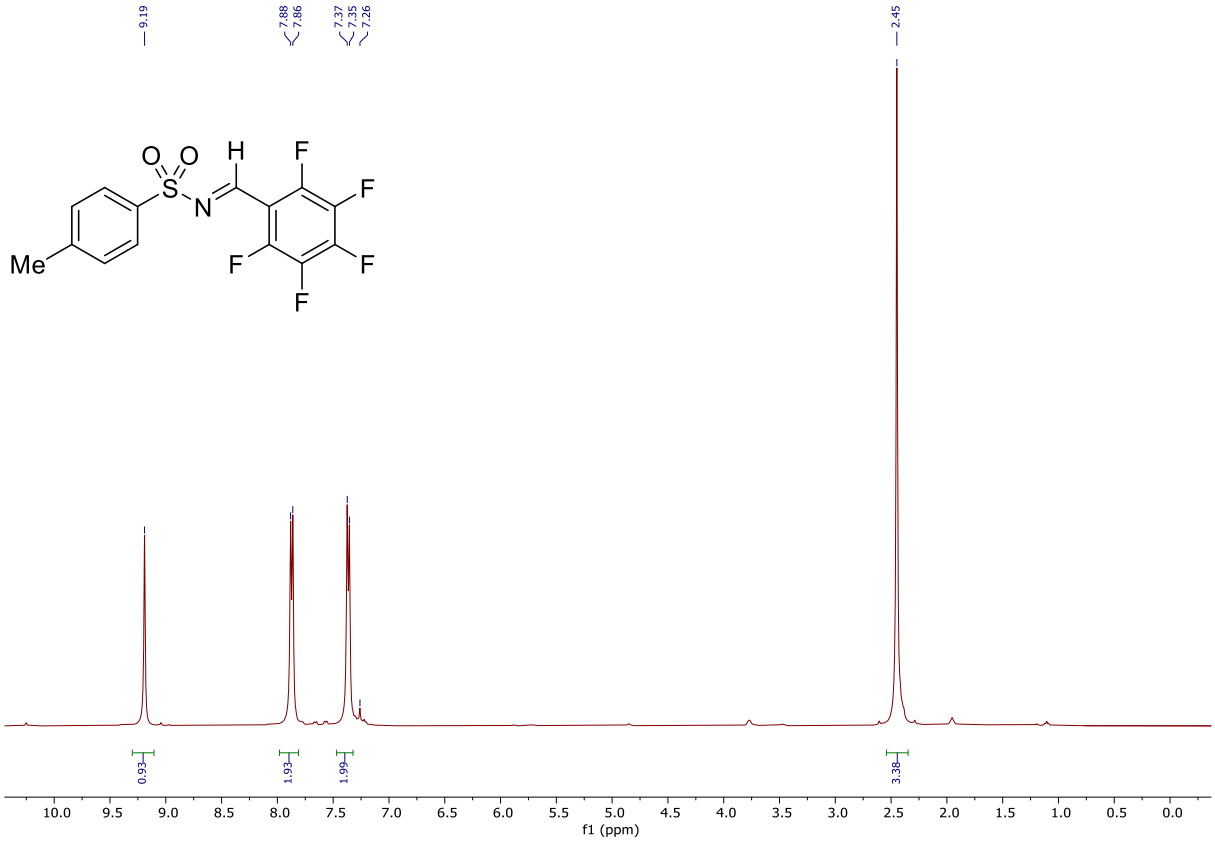



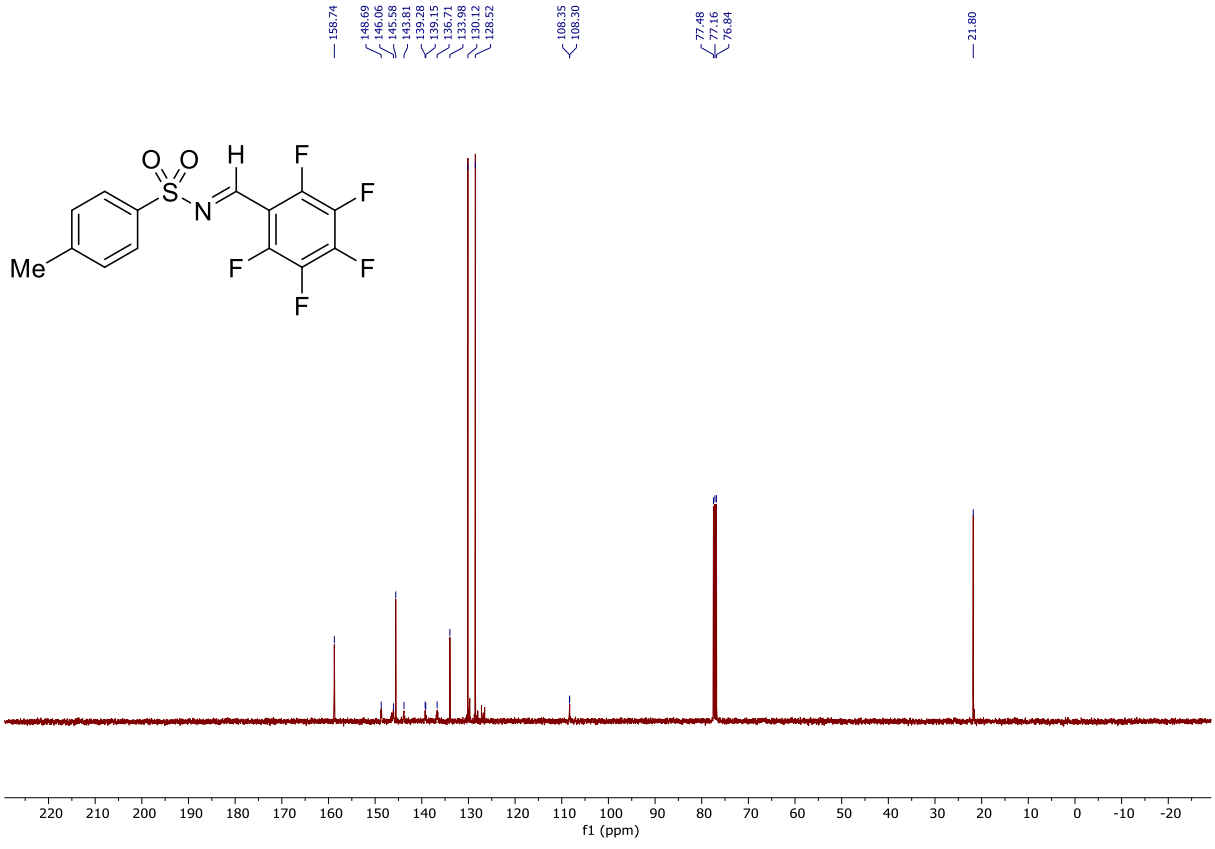
## *N*-(4-fluorobenzylidene)-4-methylbenzenesulfonamide (108af)

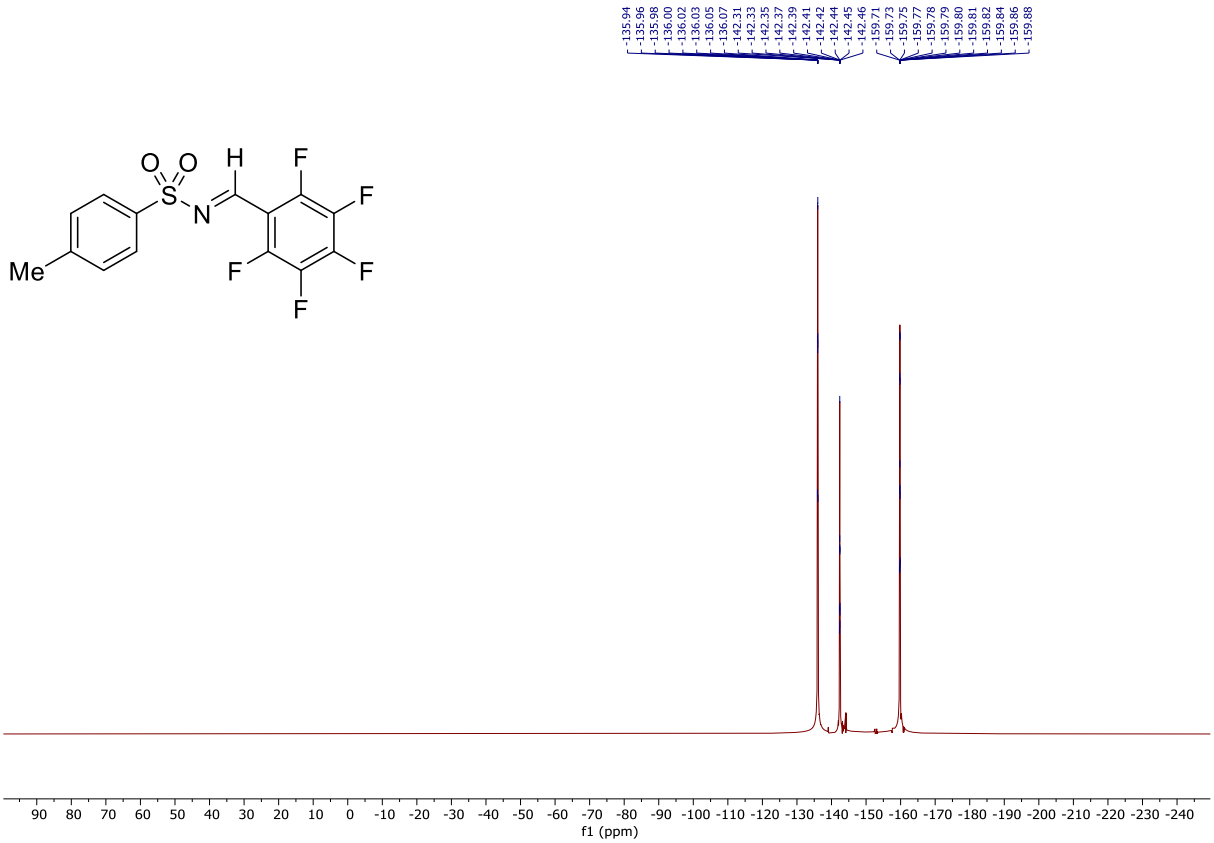



-101.01
-101.04
-101.06
-101.06
-101.07
-101.08
-101.09
-101.09
-101.10
-101.12
-101.13
-101.13
-101.14
-101.15
-101.17
O
O
S
N
H
Me
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

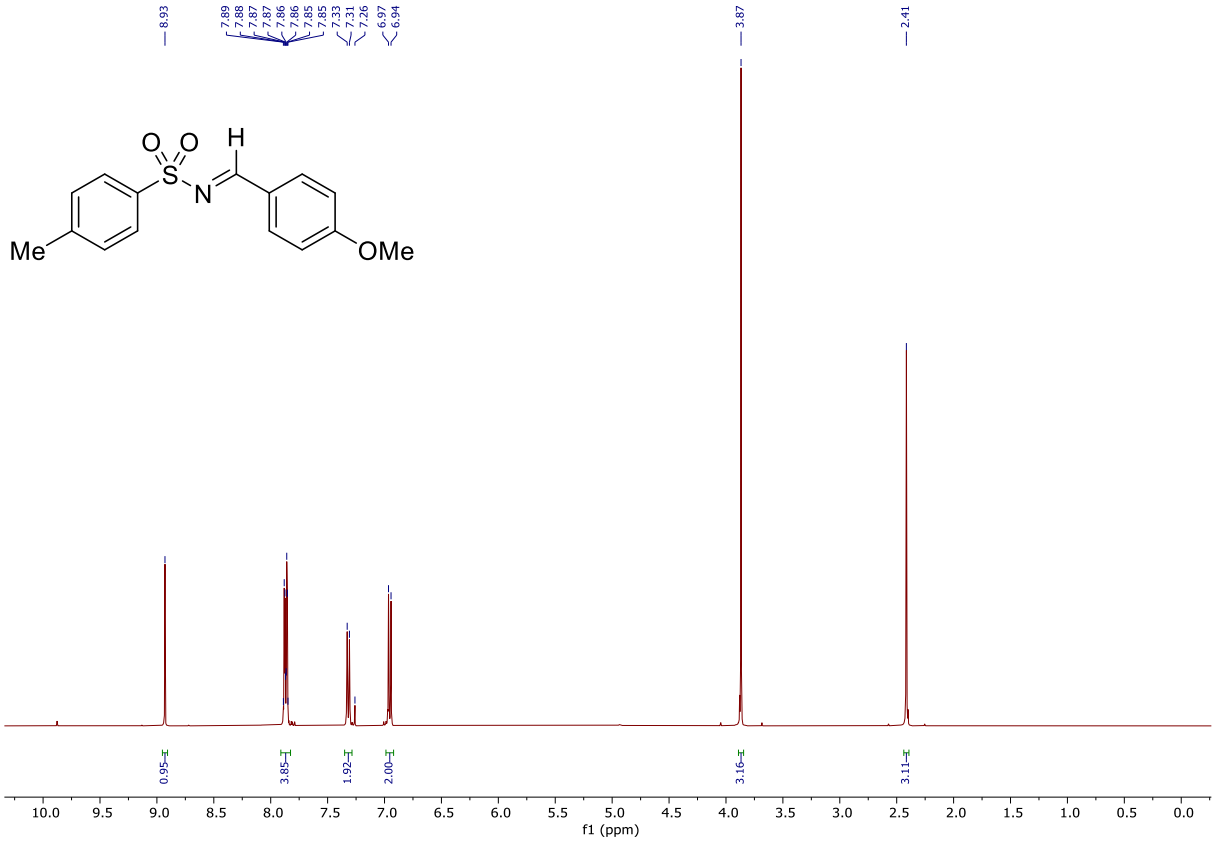
**4-methyl-*N*-((perfluorophenyl)methylene)benzenesulfonamide (108ag)**

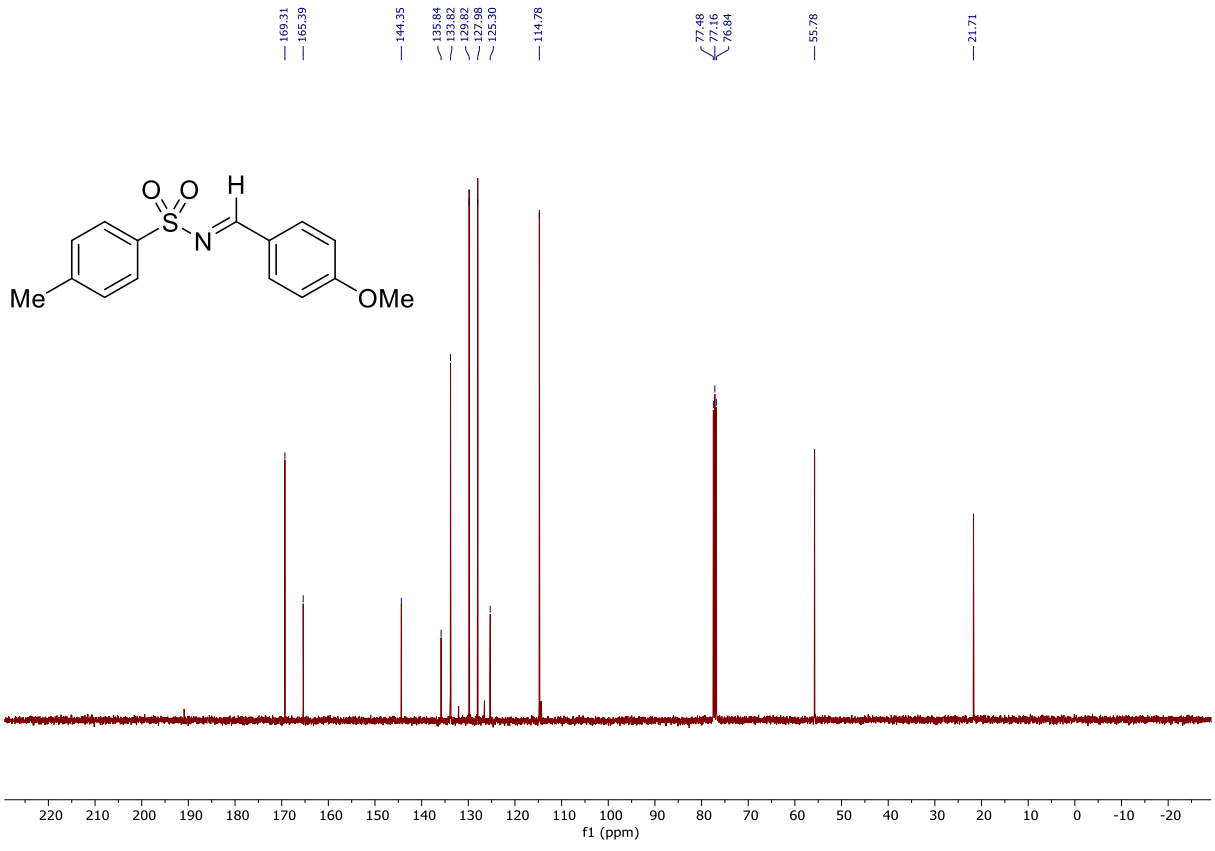


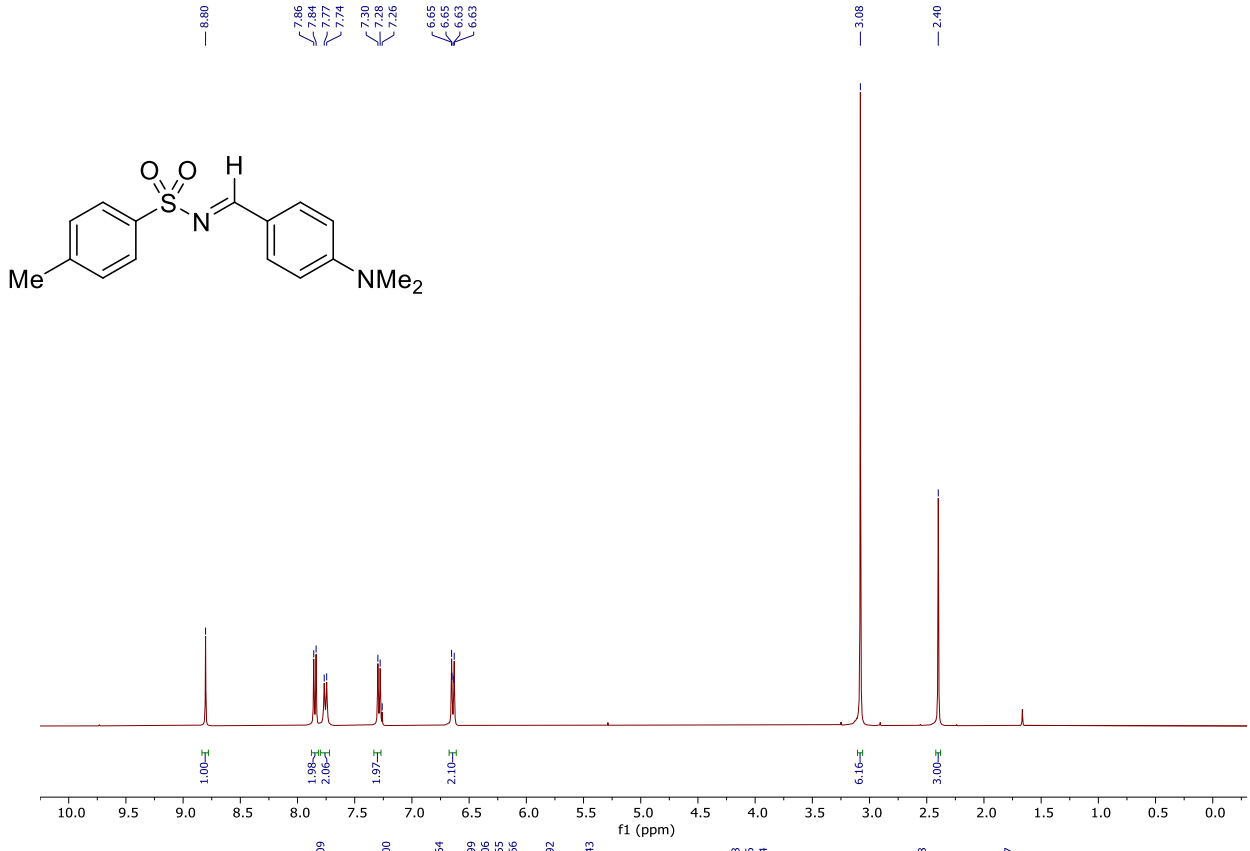

-135.94
-135.96
-135.98
-136.00
-136.02
-136.03
-136.05
-136.07
-142.31
-142.33
-142.35
-142.37
-142.39
-142.41
-142.42
-142.44
-142.45
-142.46
-159.71
-159.73
-159.75
-159.77
-159.78
-159.79
-159.80
-159.81
-159.82
-159.84
-159.86
-159.88
O
O
S
N
H
F
F
F
F
F
Me
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

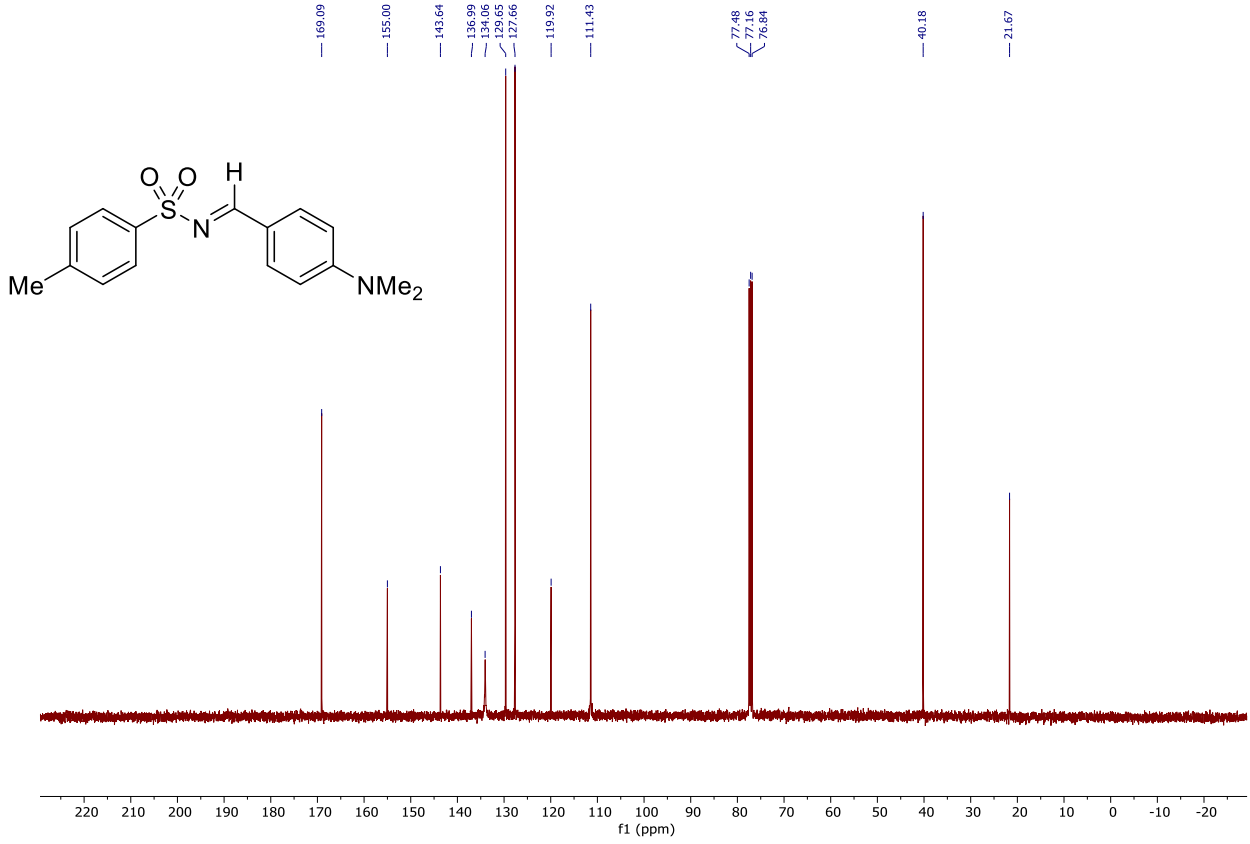
## *N*-(4-methoxybenzylidene)-4-methylbenzenesulfonamide (108ah)



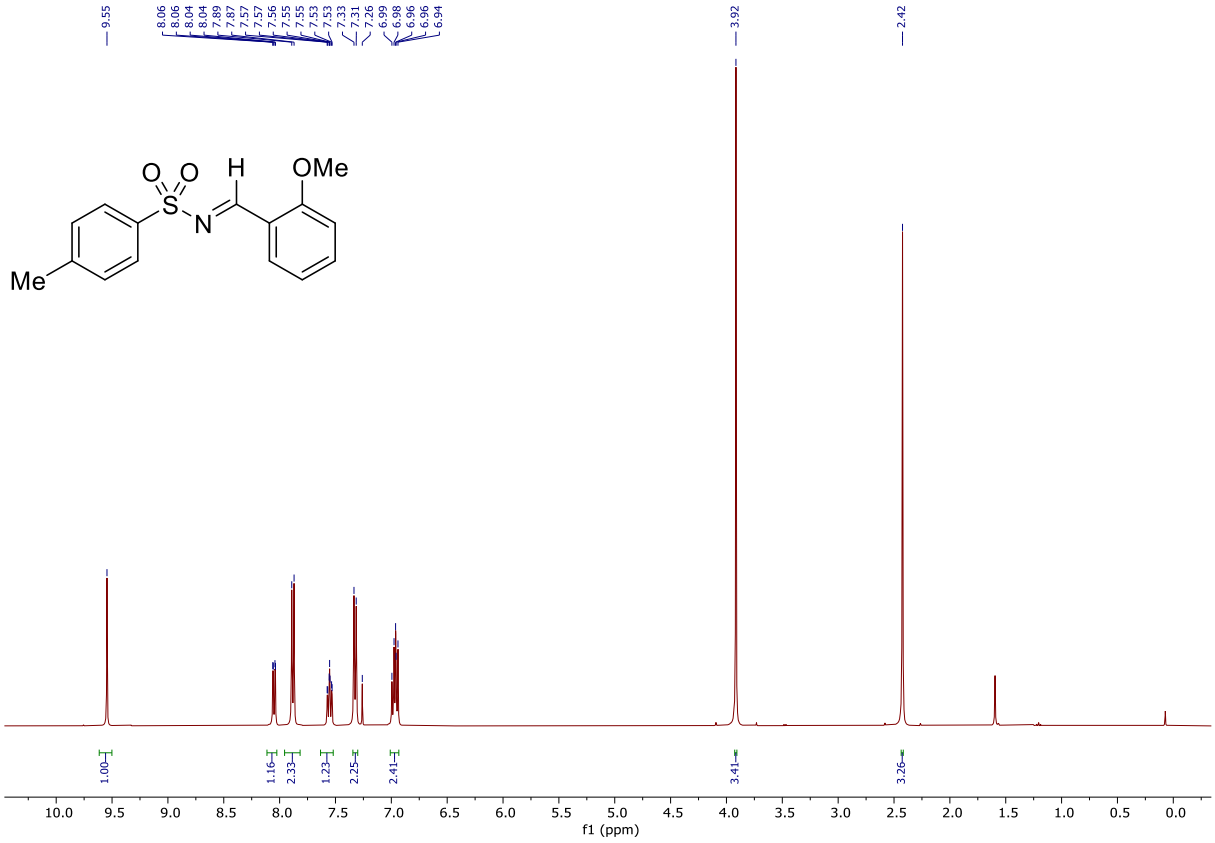



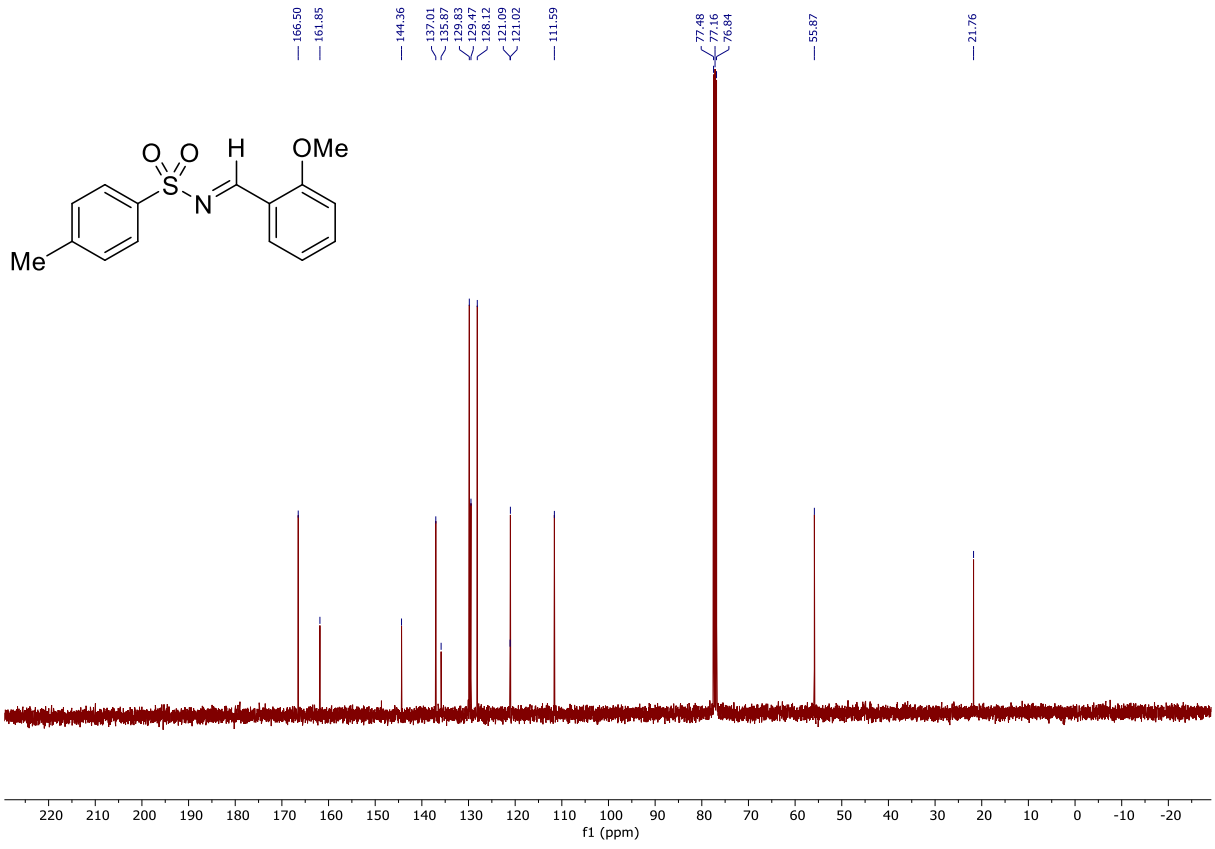
## *N*-(4-(dimethylamino)benzylidene)-4-methylbenzenesulfonamide (108ai)



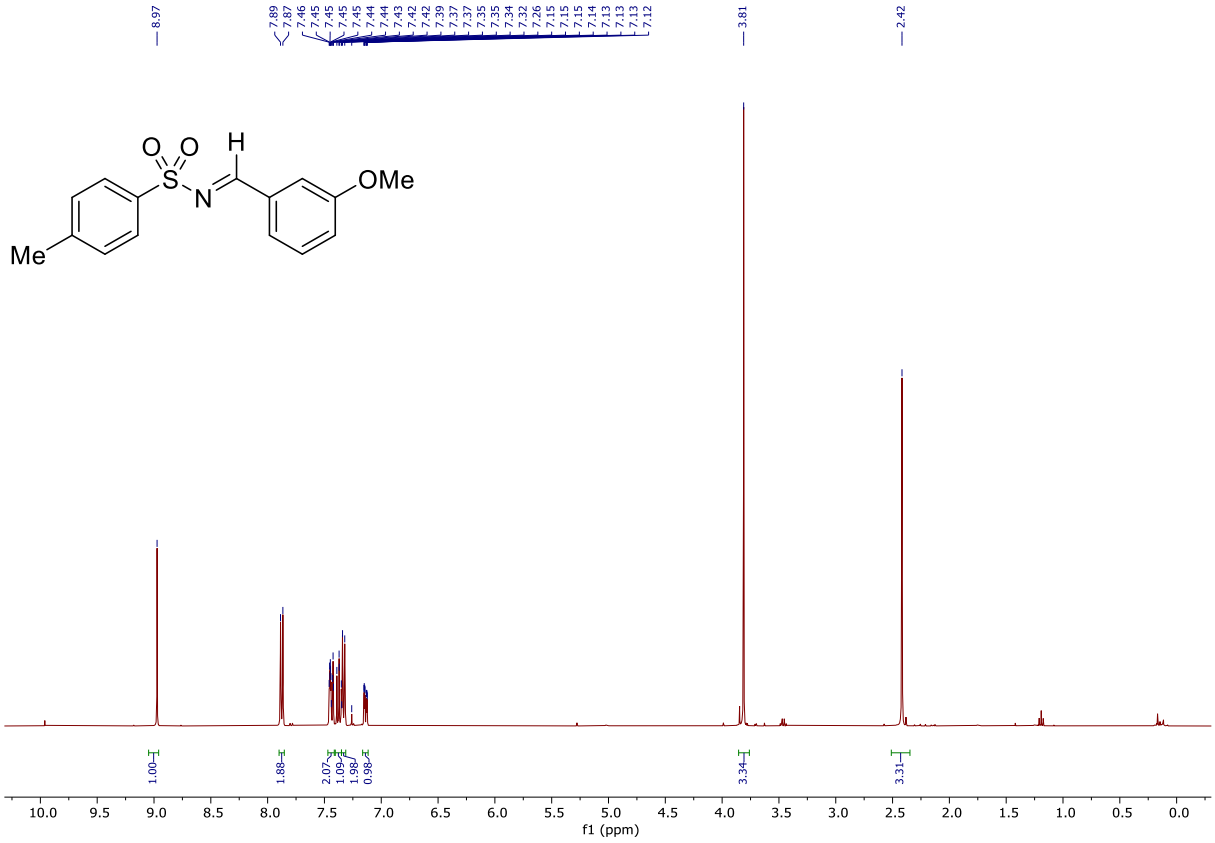



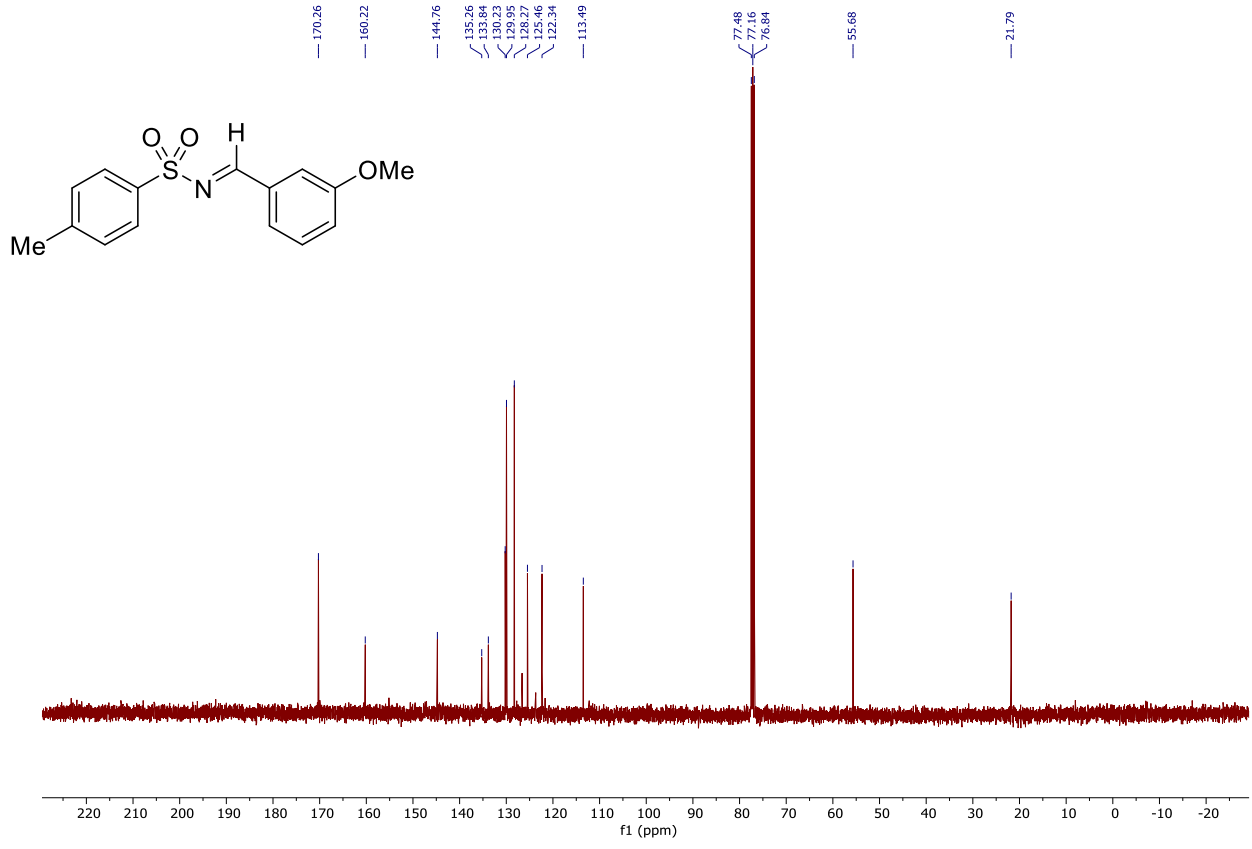
## *N*-(2-methoxybenzylidene)-4-methylbenzenesulfonamide (108aj)



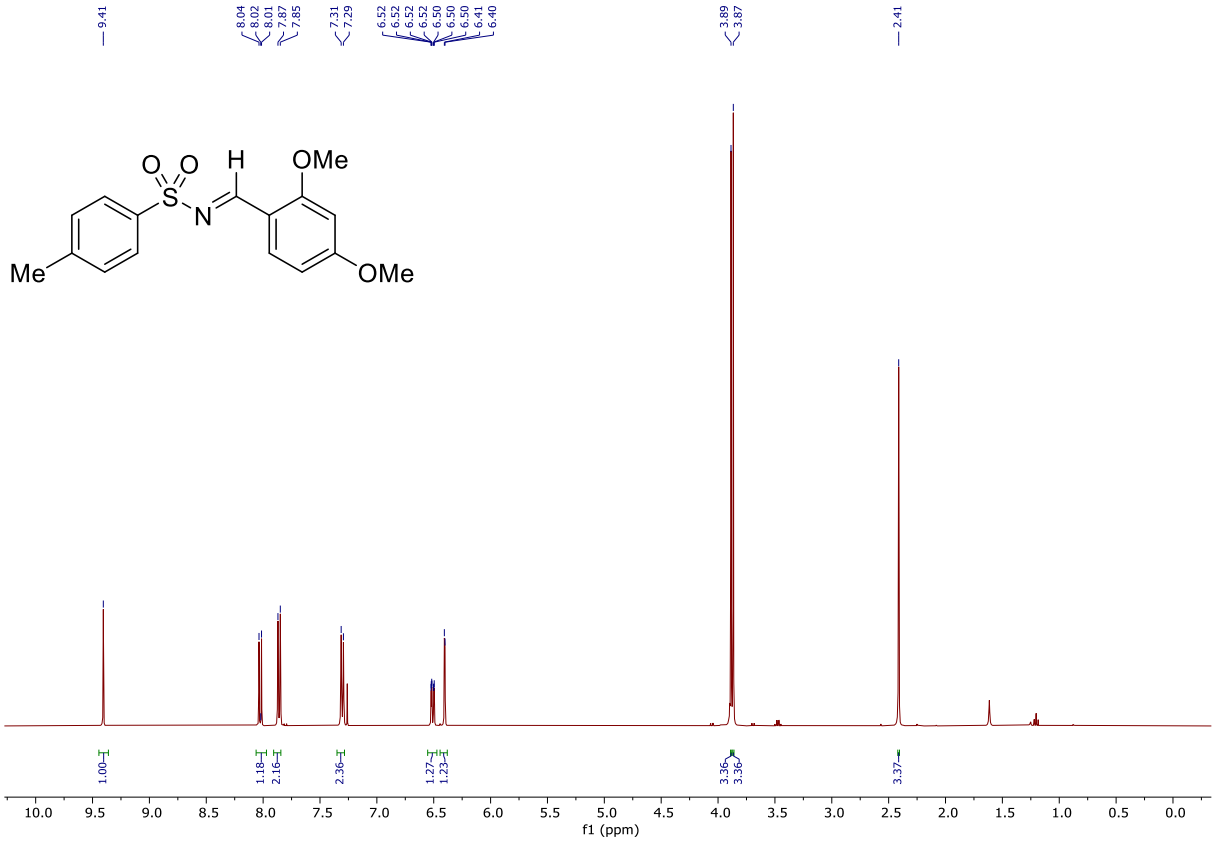



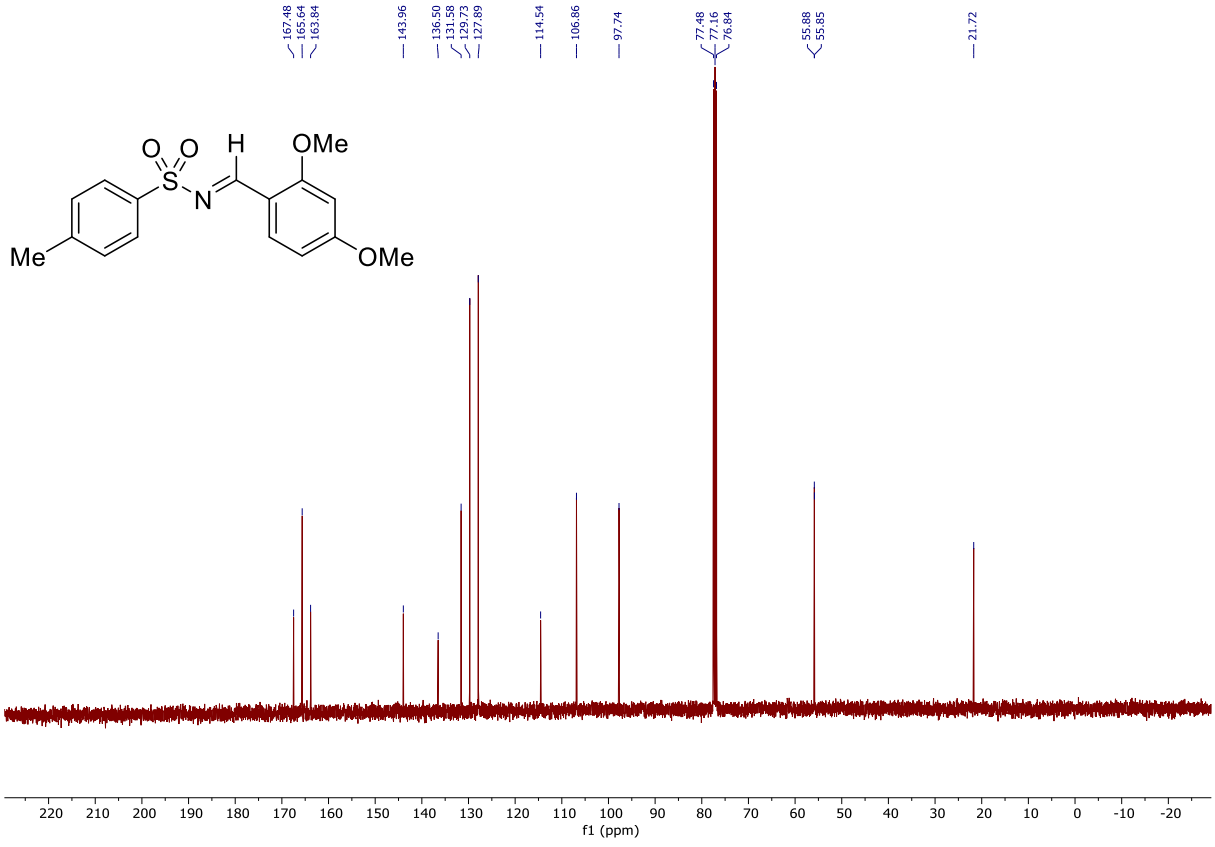
## *N*-(3-methoxybenzylidene)-4-methylbenzenesulfonamide (108ak)



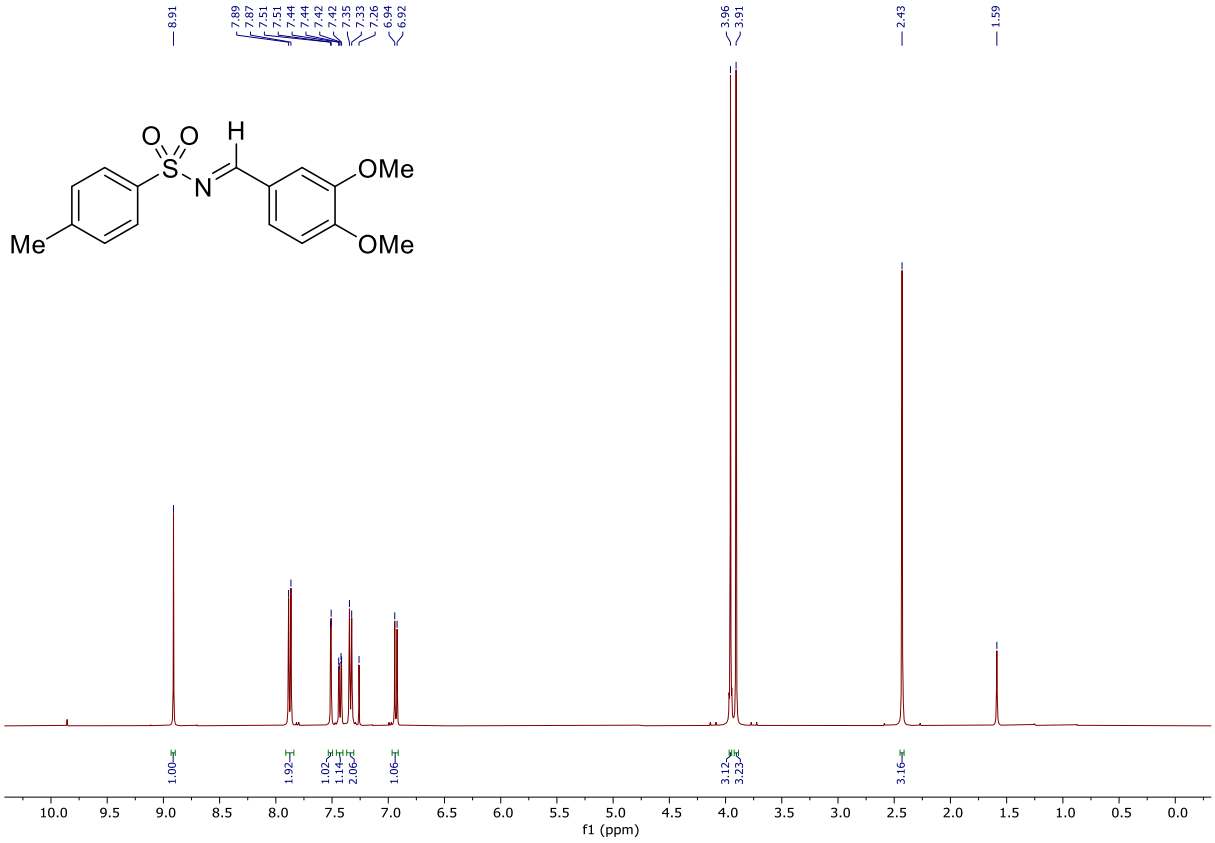



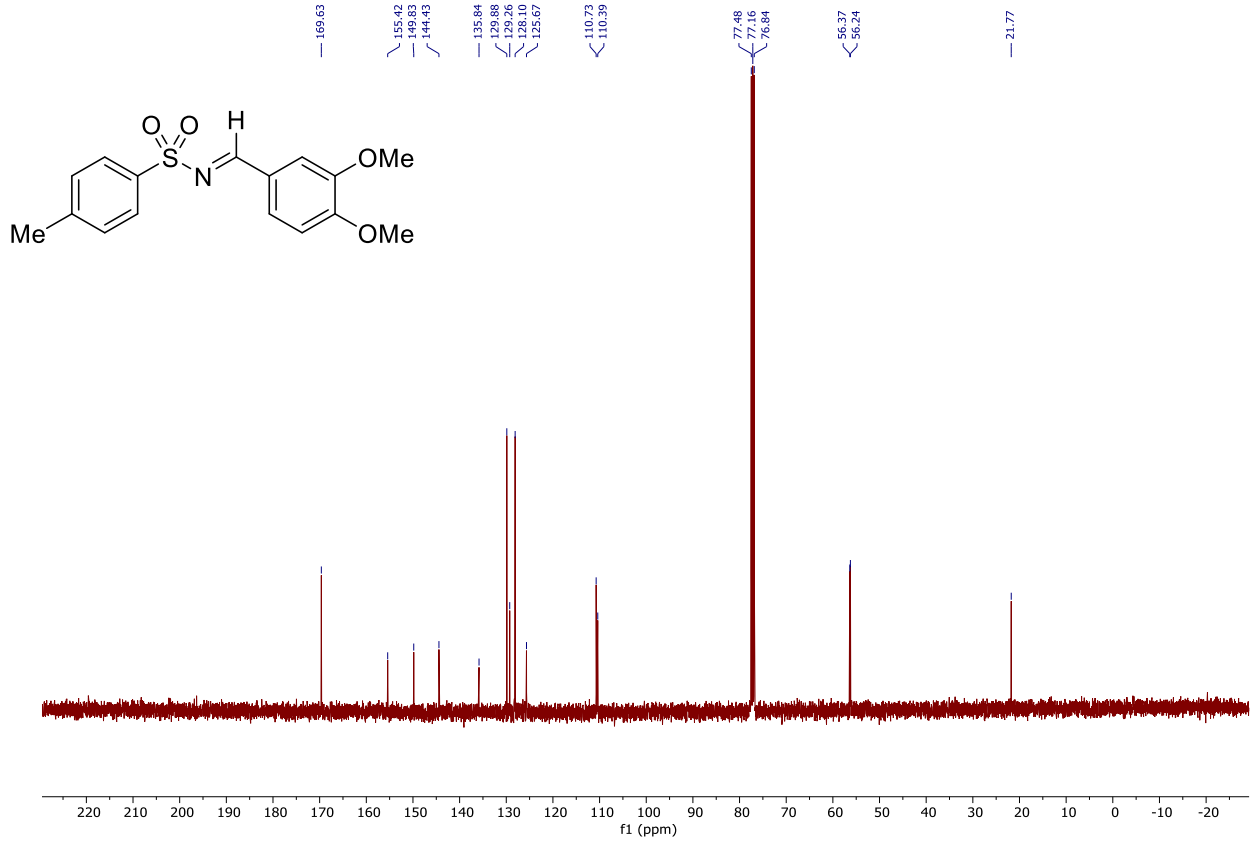
## *N*-(2,4-dimethoxybenzylidene)-4-methylbenzenesulfonamide (108al)



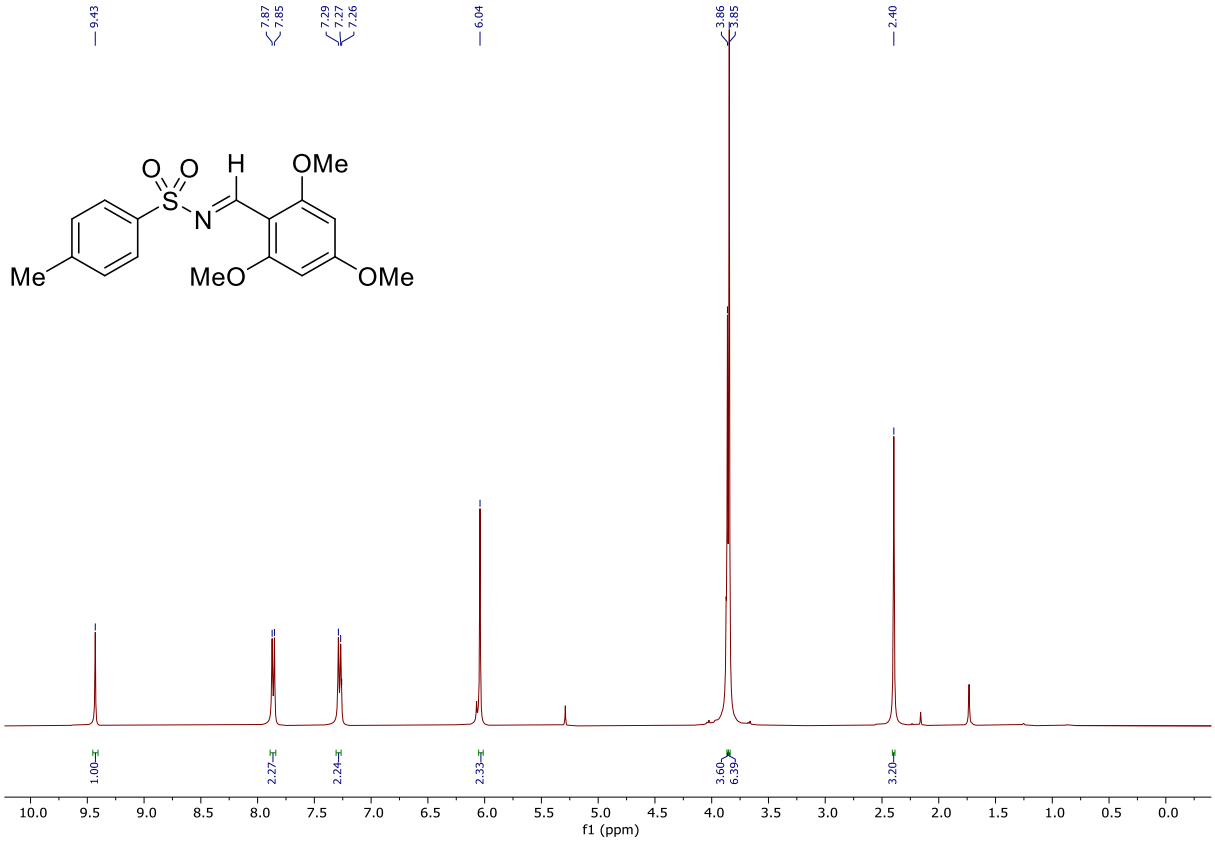



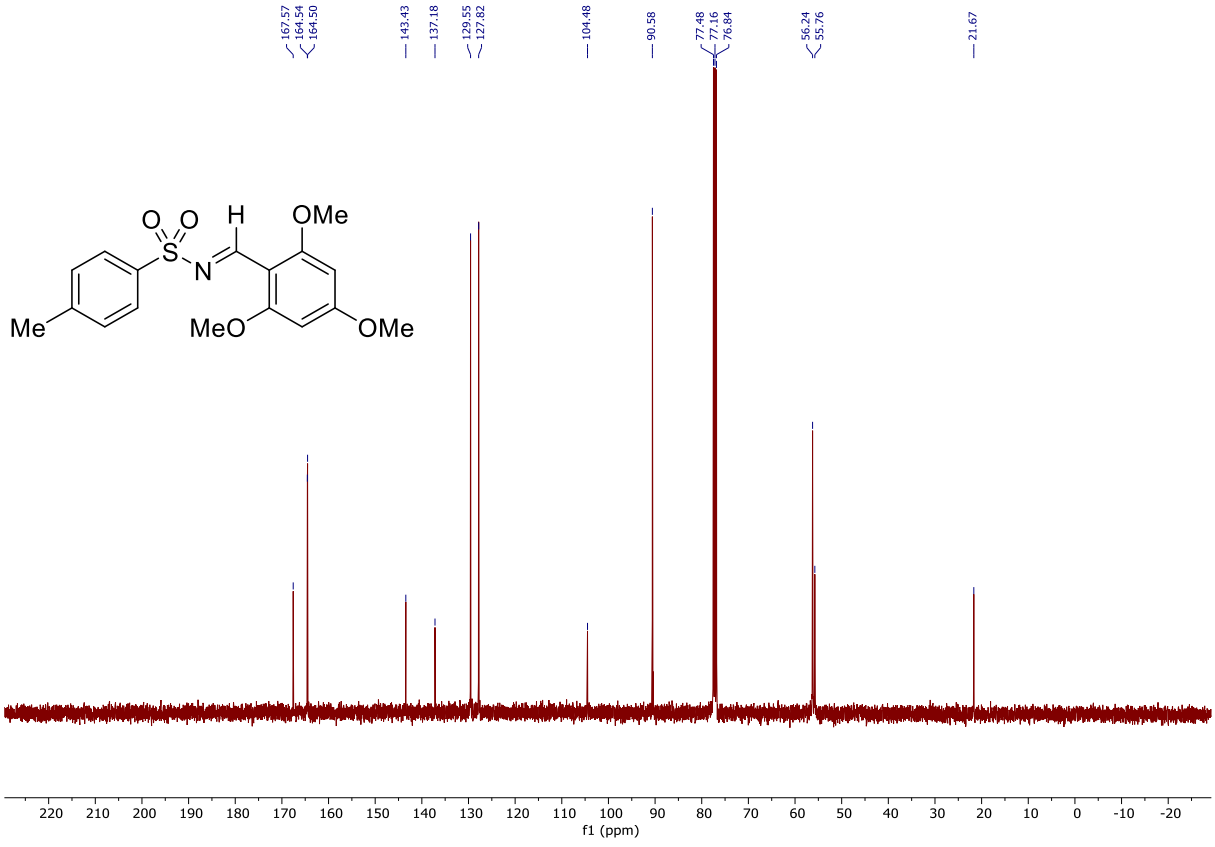
## *N*-(2,4-dimethoxybenzylidene)-4-methylbenzenesulfonamide (108am)



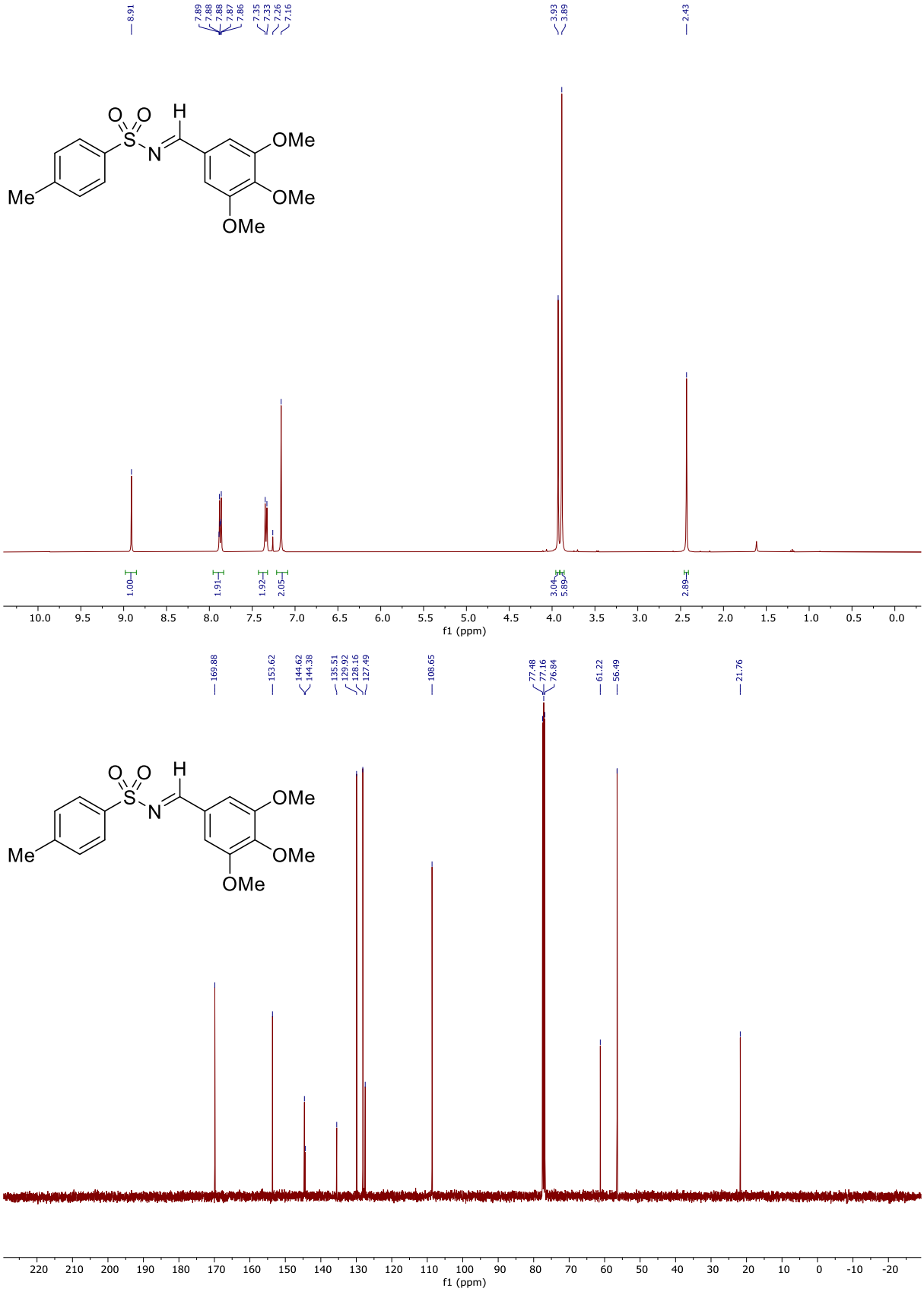



## 4-Methyl-*N*-(2,4,6-trimethoxybenzylidene)benzenesulfonamide (108an)

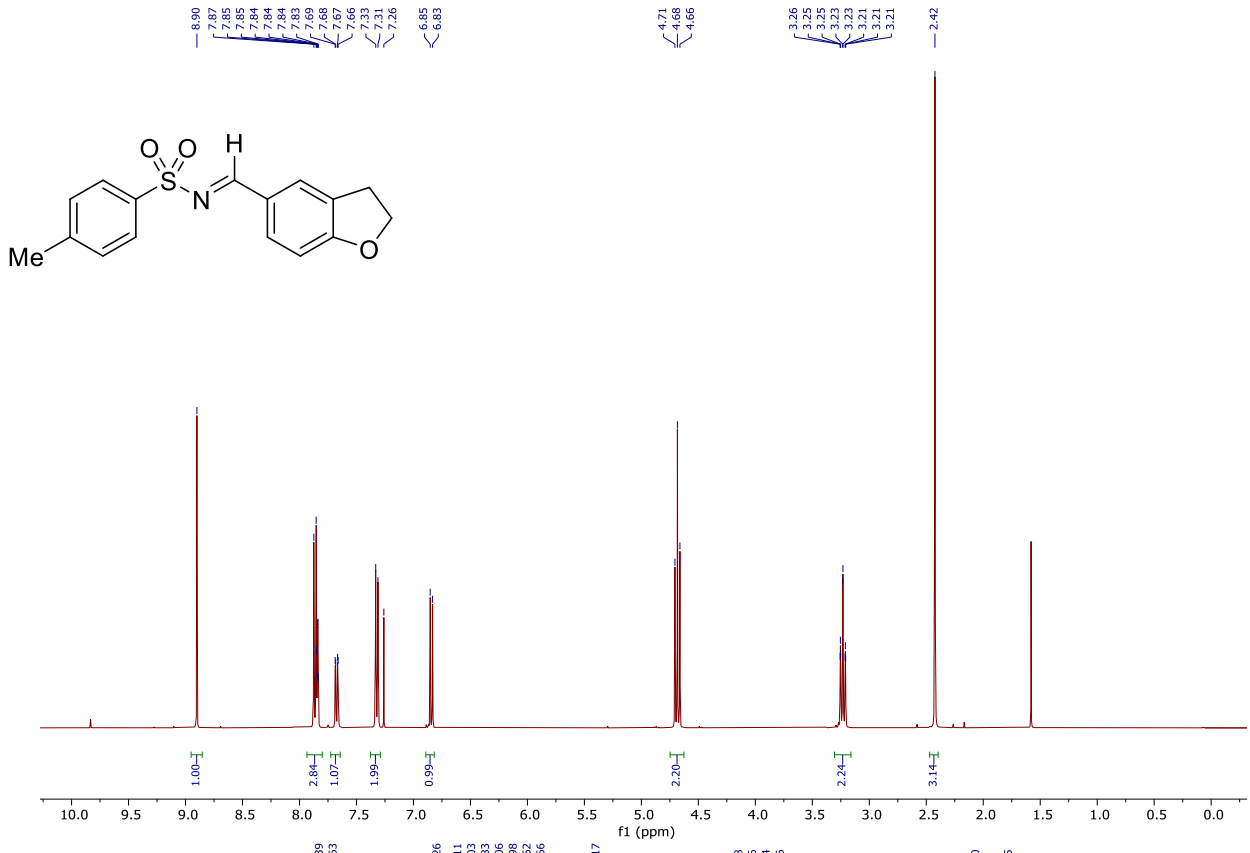


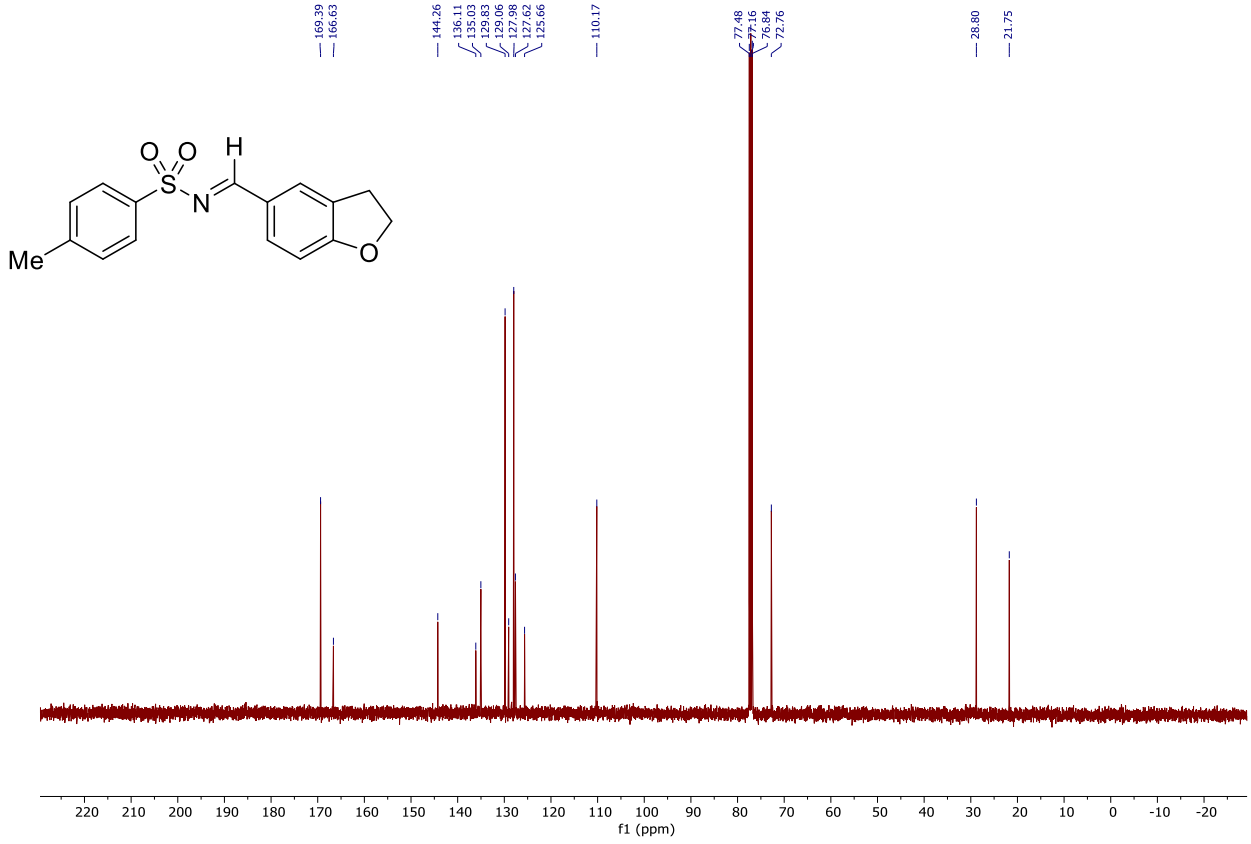



## 4-Methyl-*N*-(3,4,5-trimethoxybenzylidene)benzenesulfonamide (108ao)

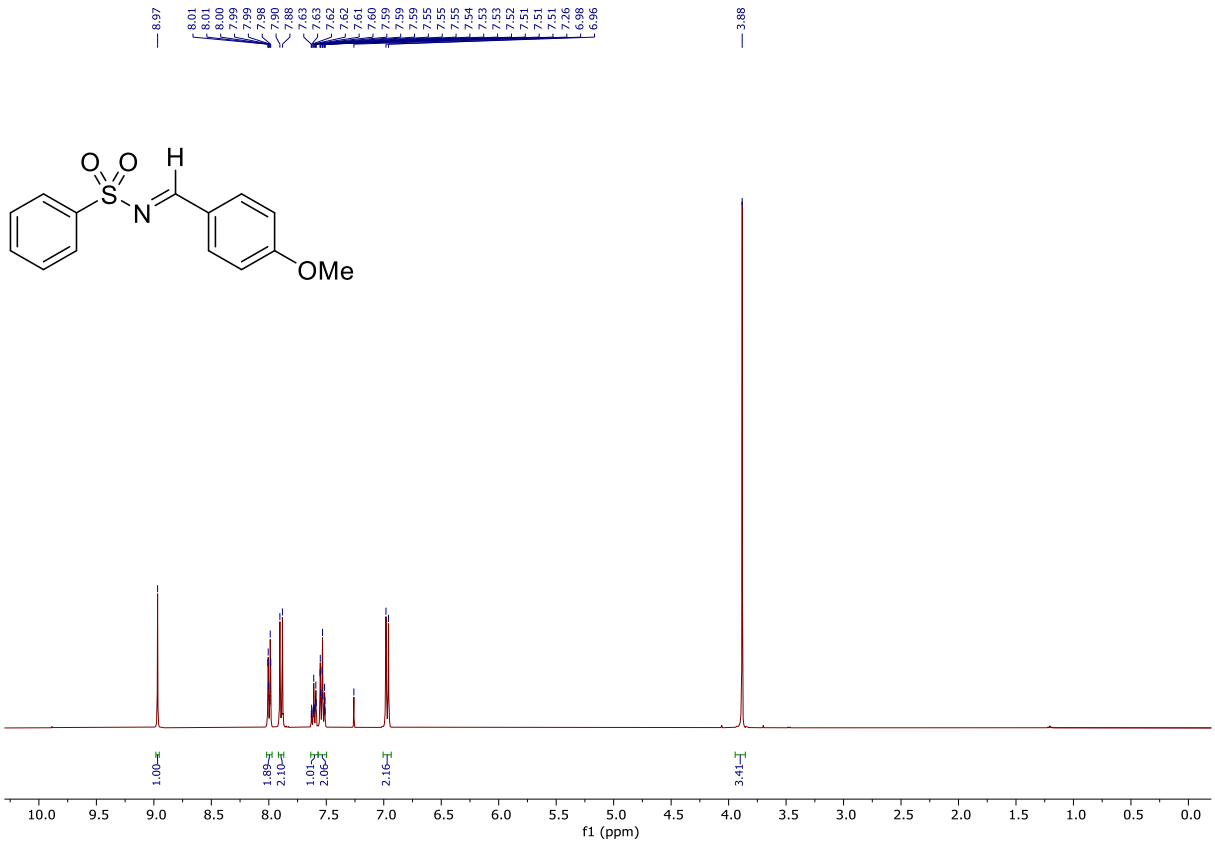


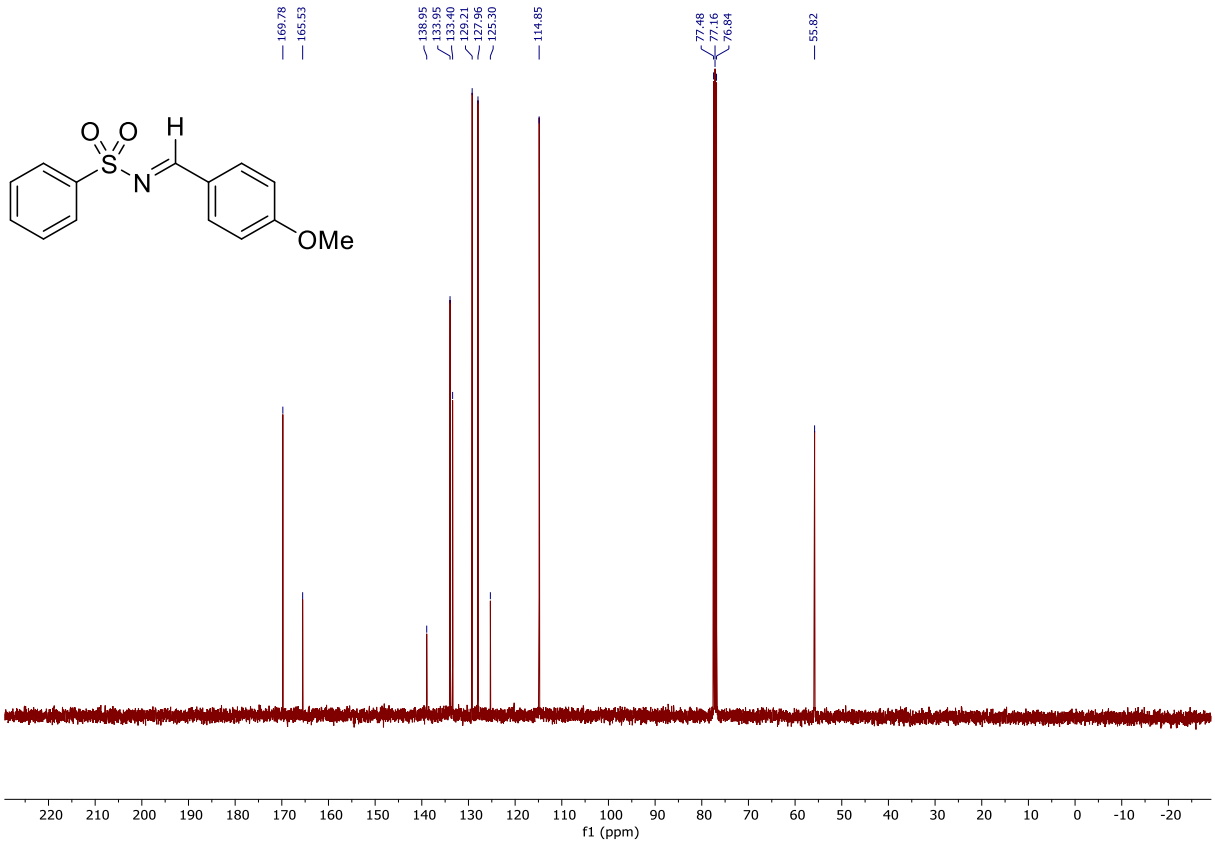
**N-((2,3-dihydrobenzofuran-5-yl)methylene)-4-methylbenzenesulfonamide (108ap)**



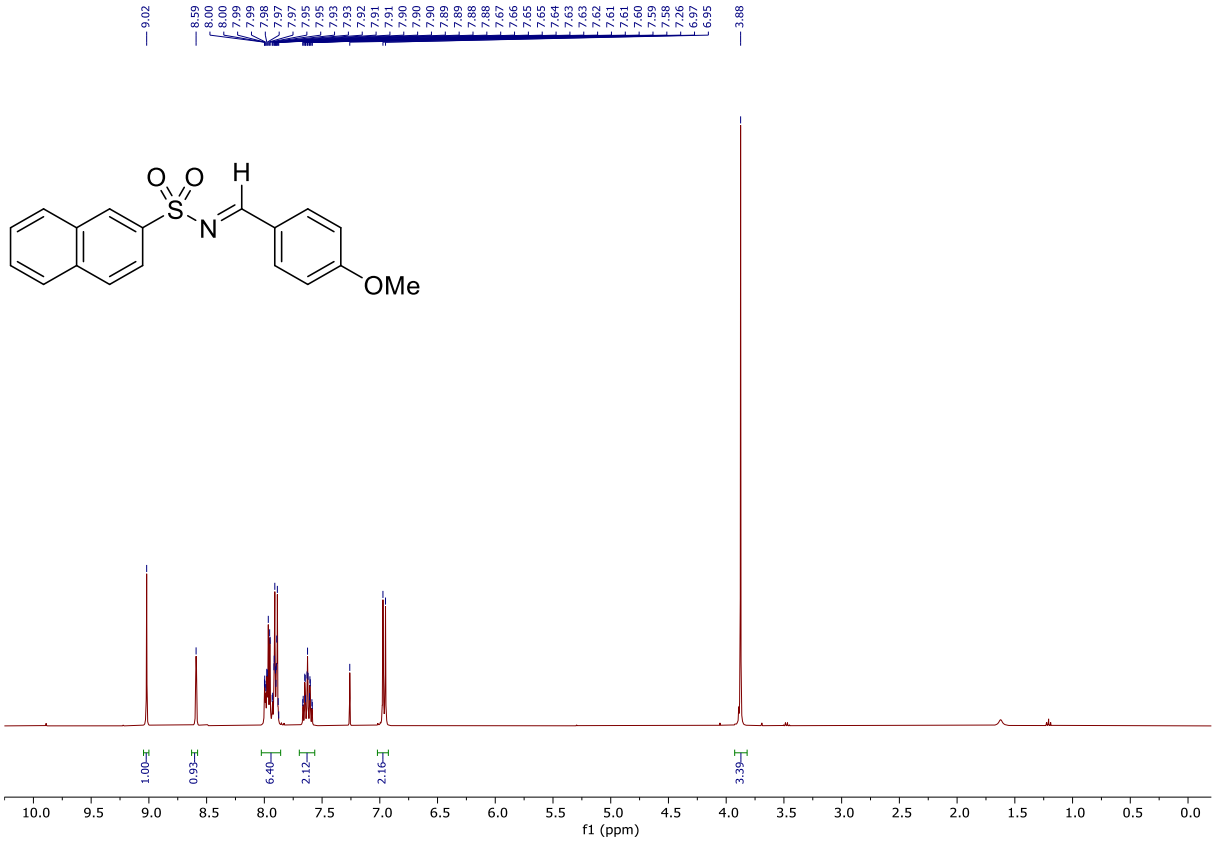



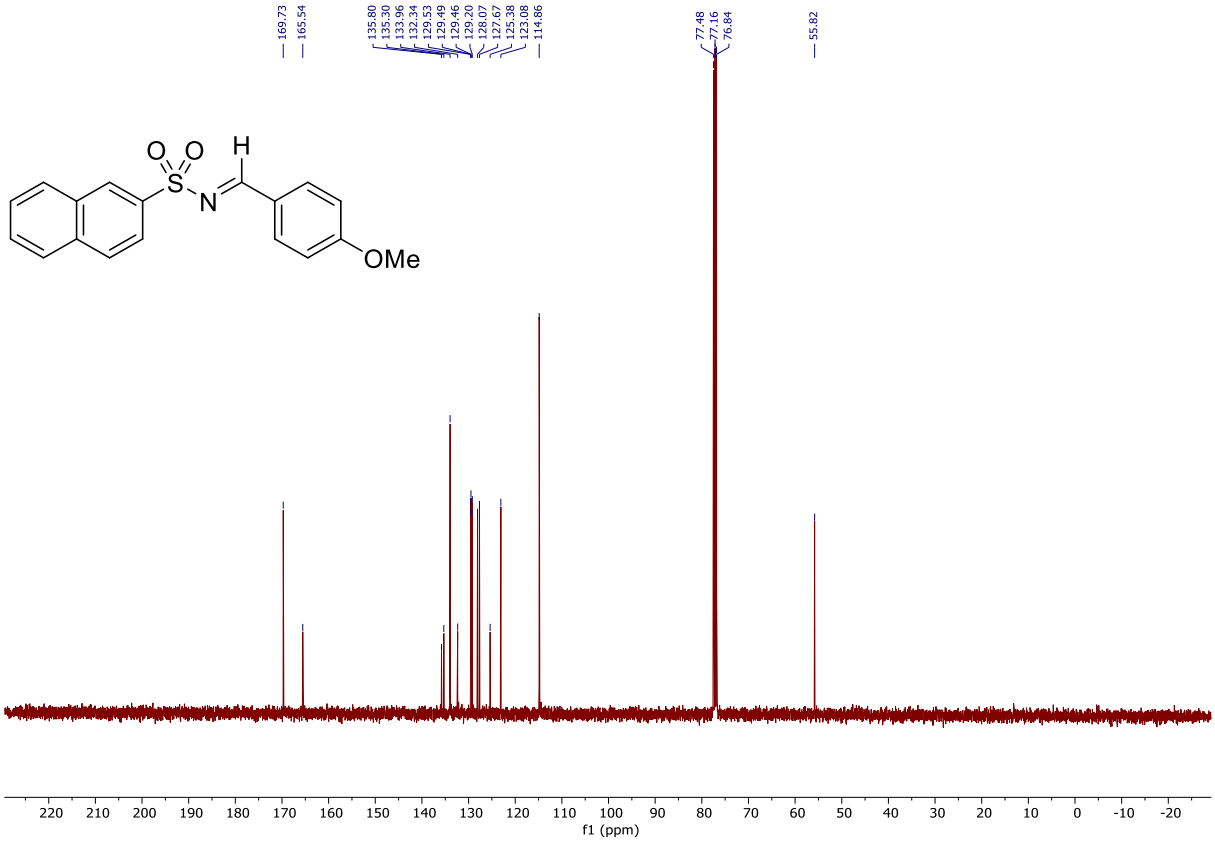
## *N*-(4-methoxybenzylidene)benzenesulfonamide (108b)



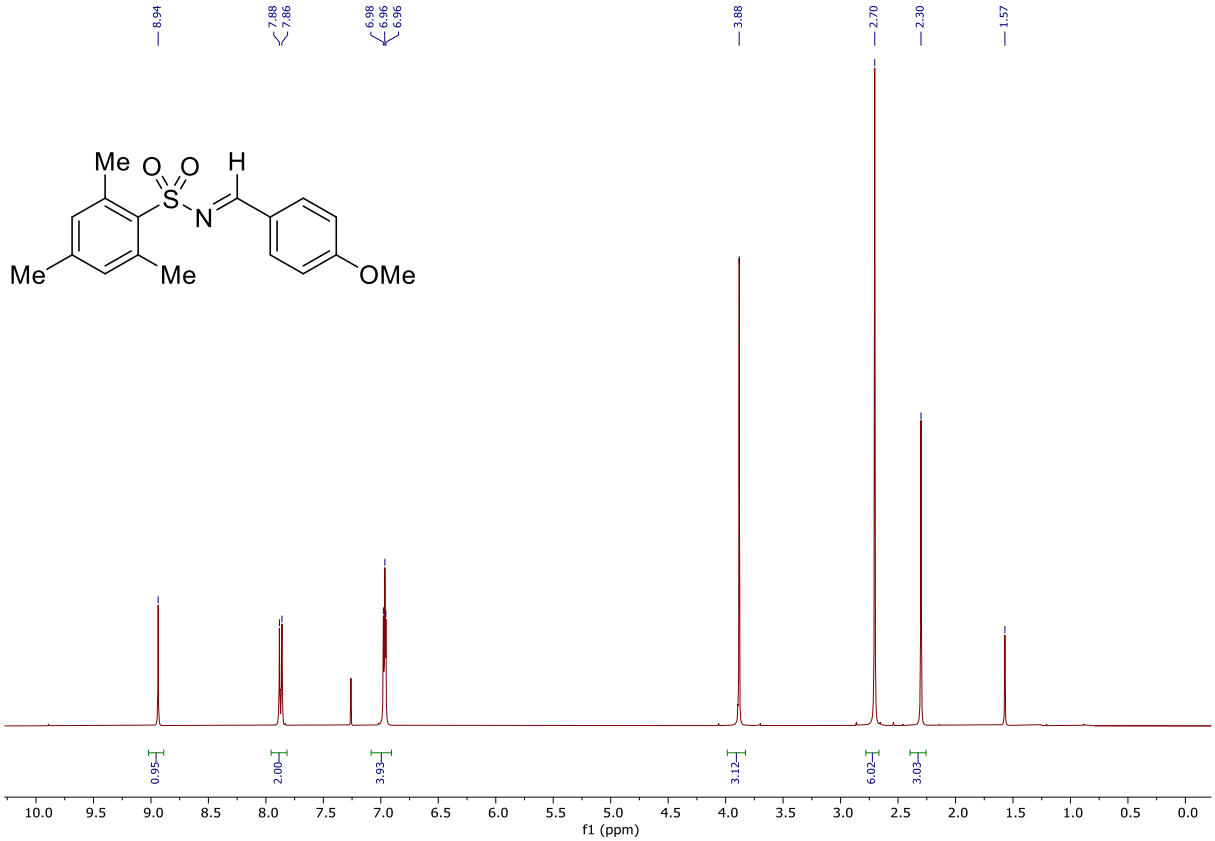



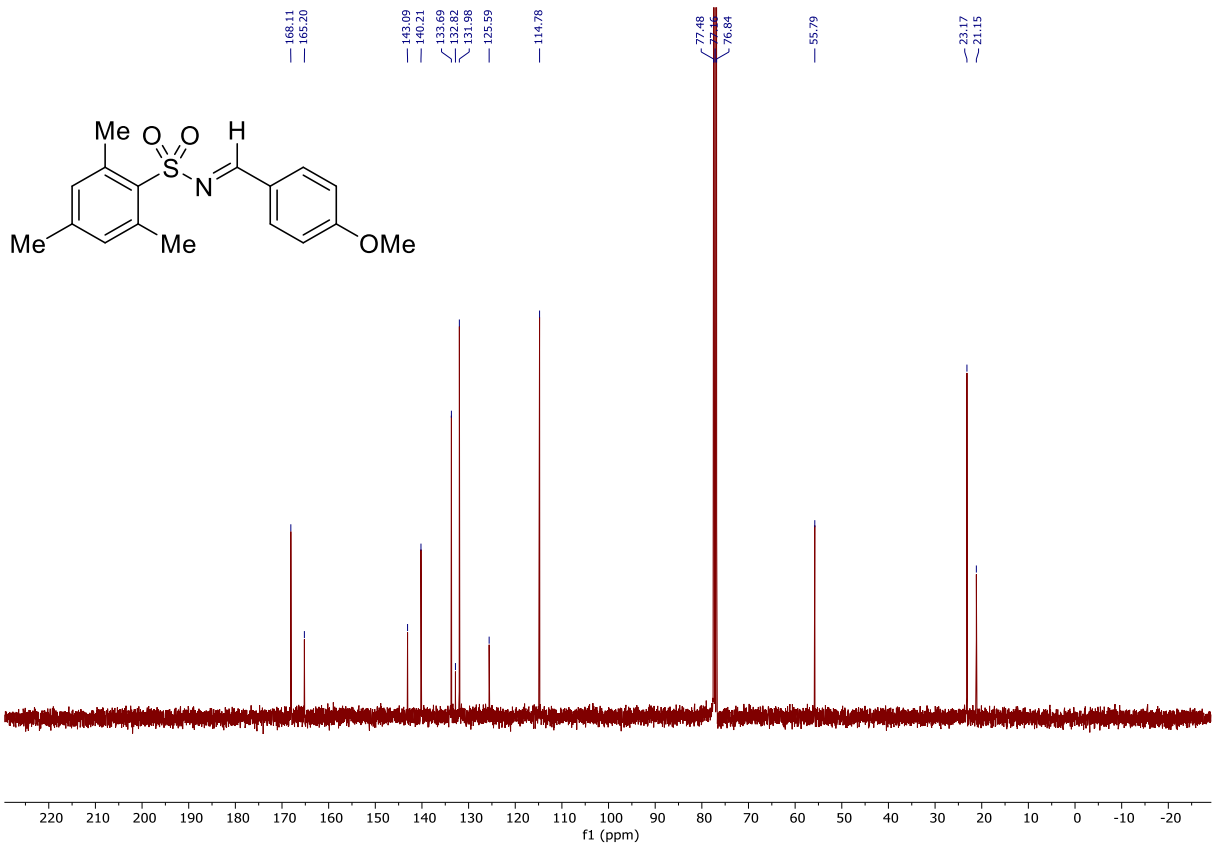
## *N*-(4-methoxybenzylidene)naphthalene-2-sulfonamide (108c)



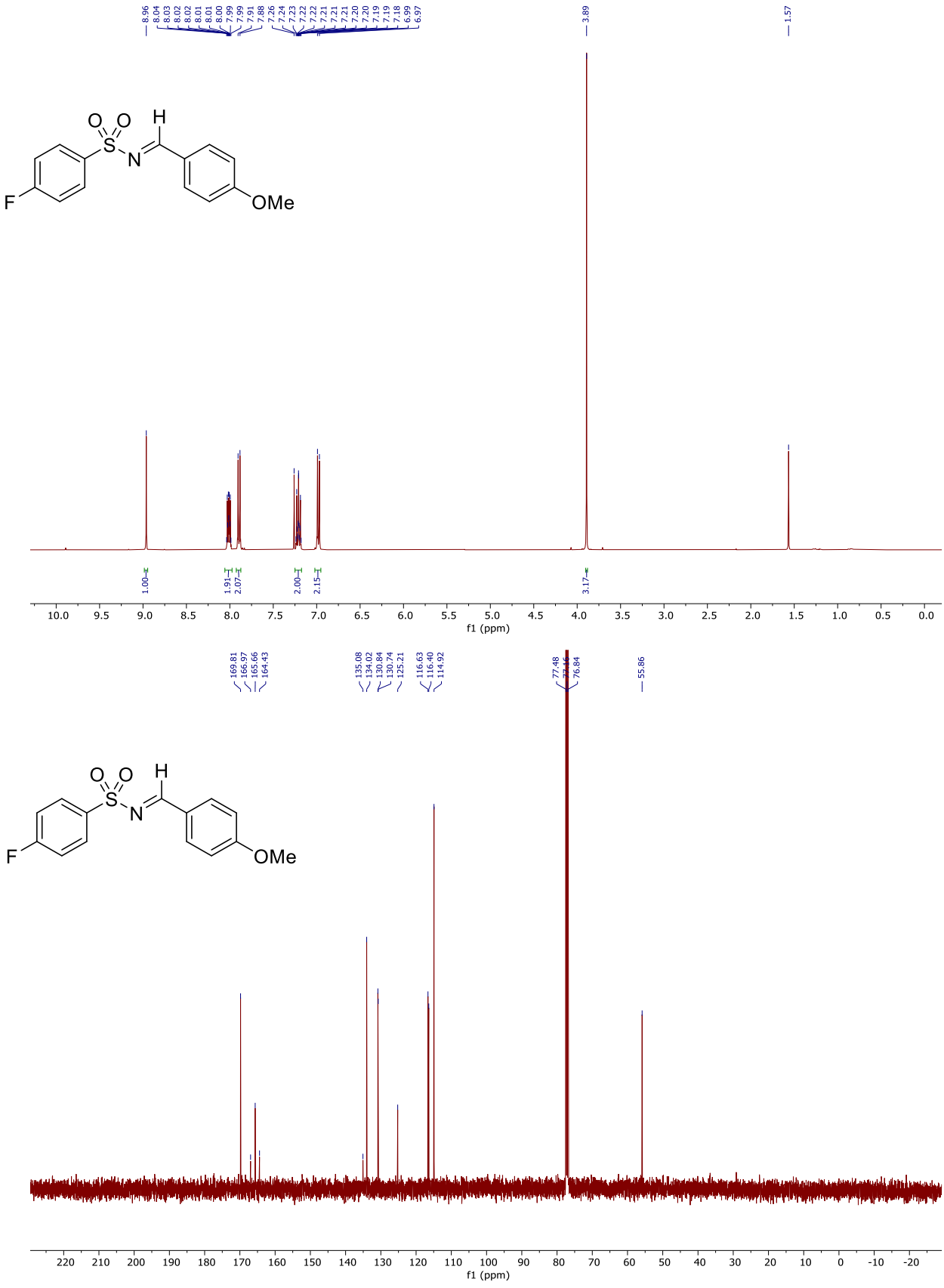



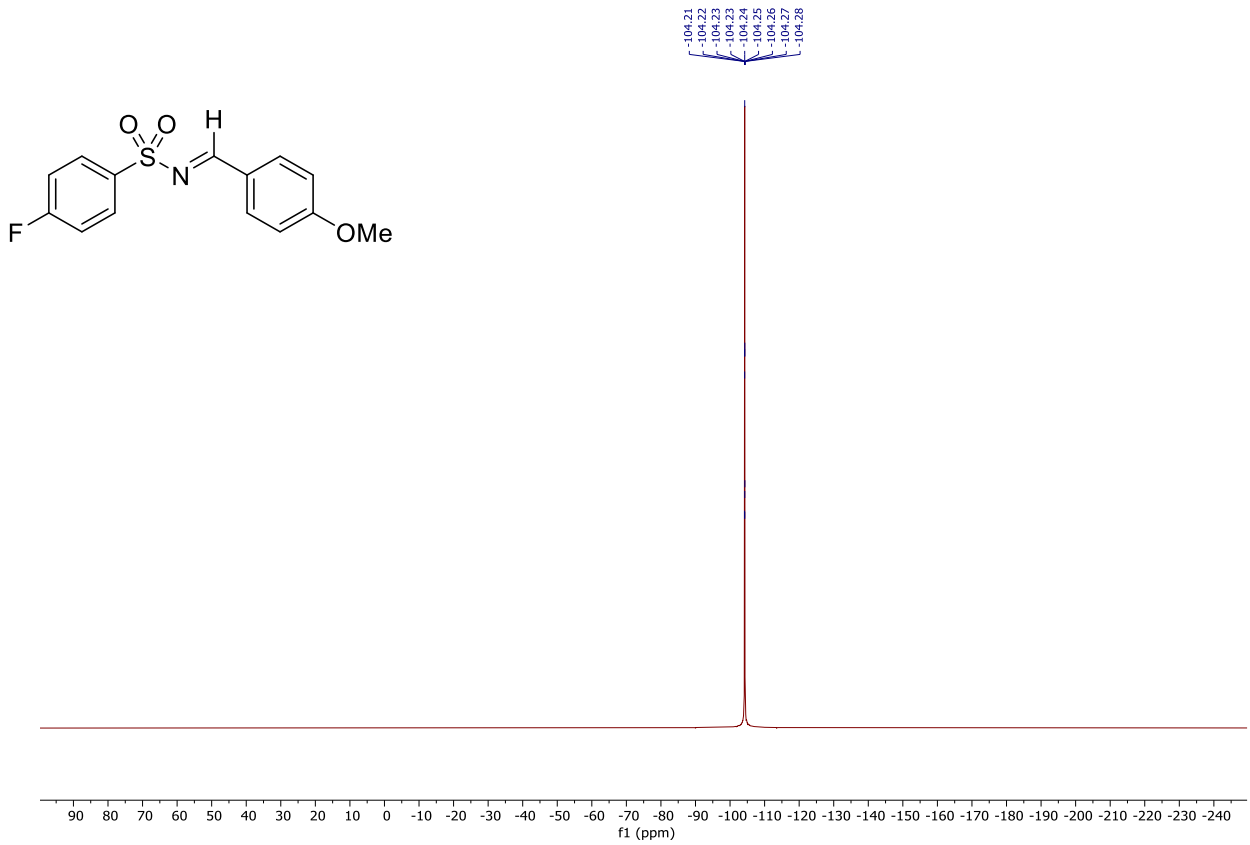
## *N*-(4-methoxybenzylidene)-2,4,6-trimethylbenzenesulfonamide (108d)



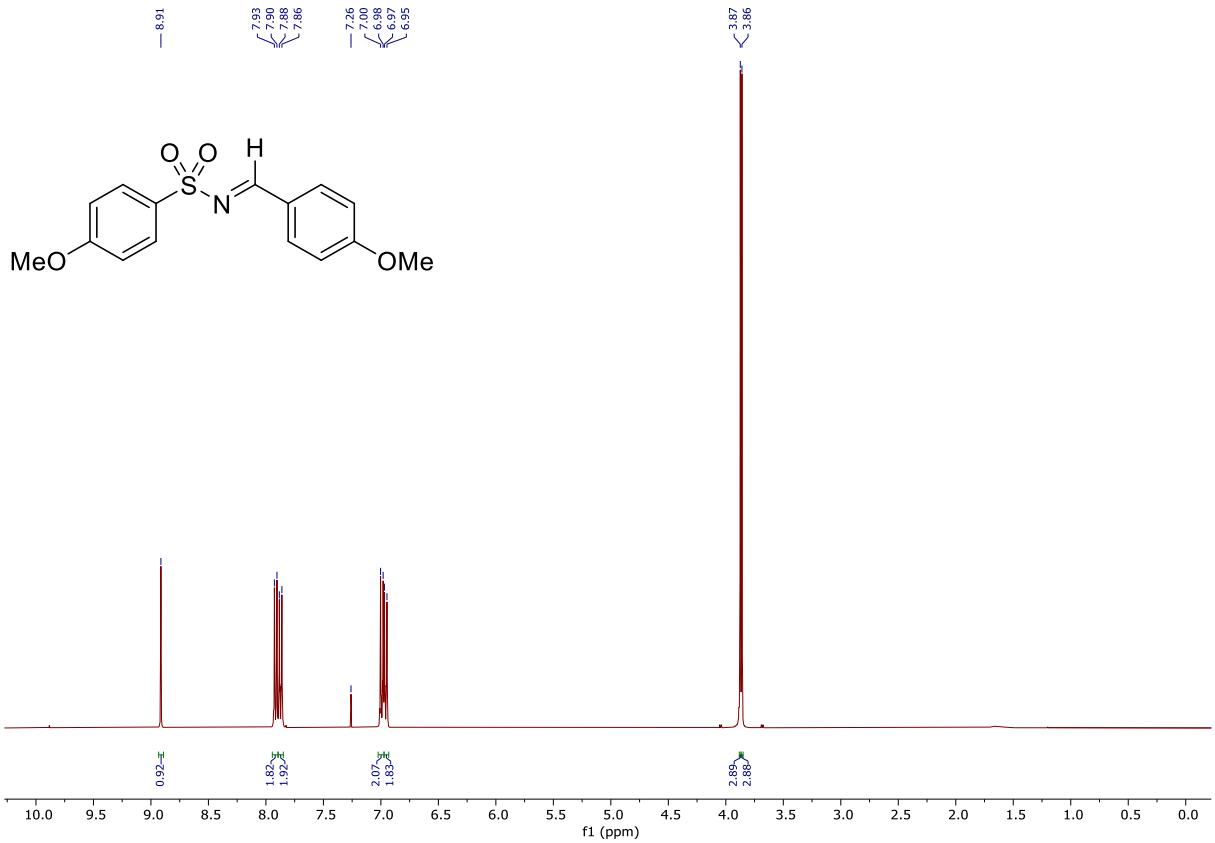



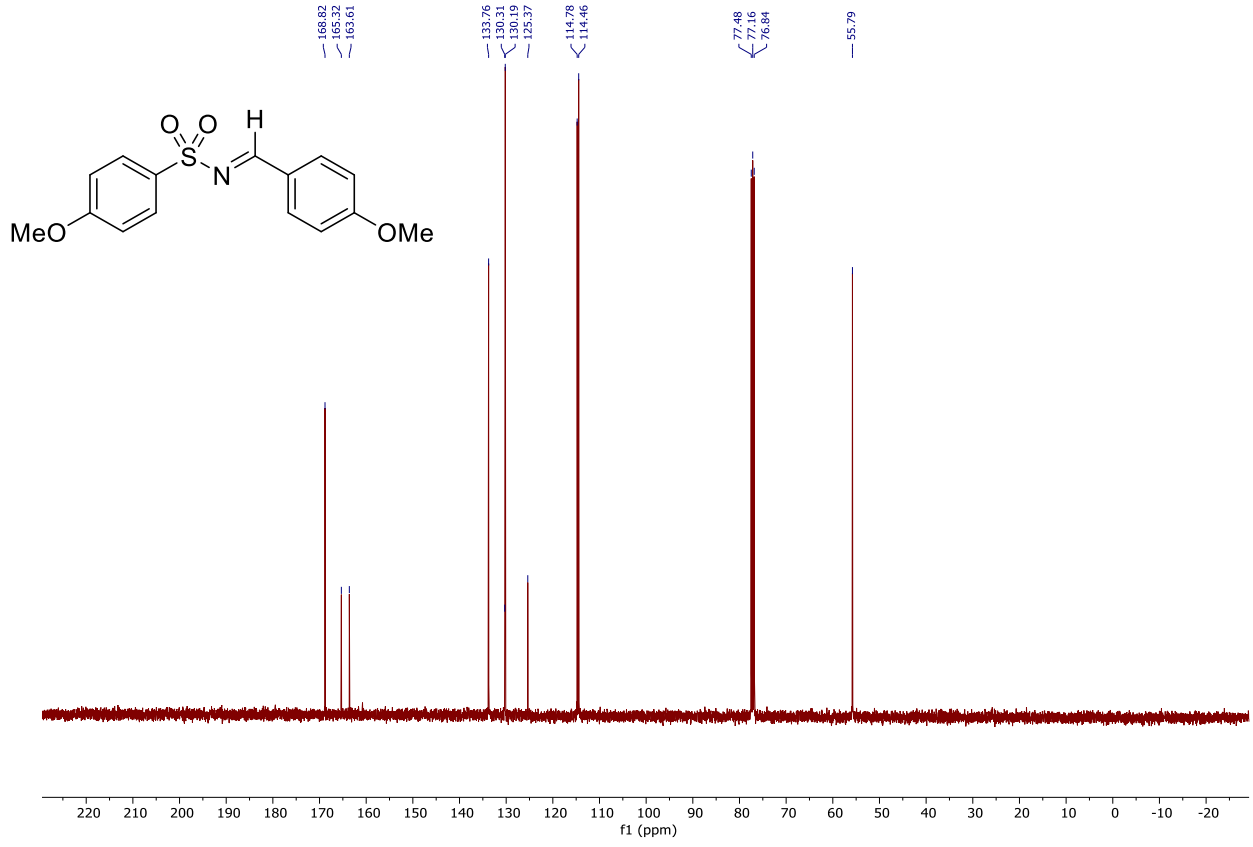
## 4-Fluoro-*N*-(4-methoxybenzylidene)benzenesulfonamide (108e)



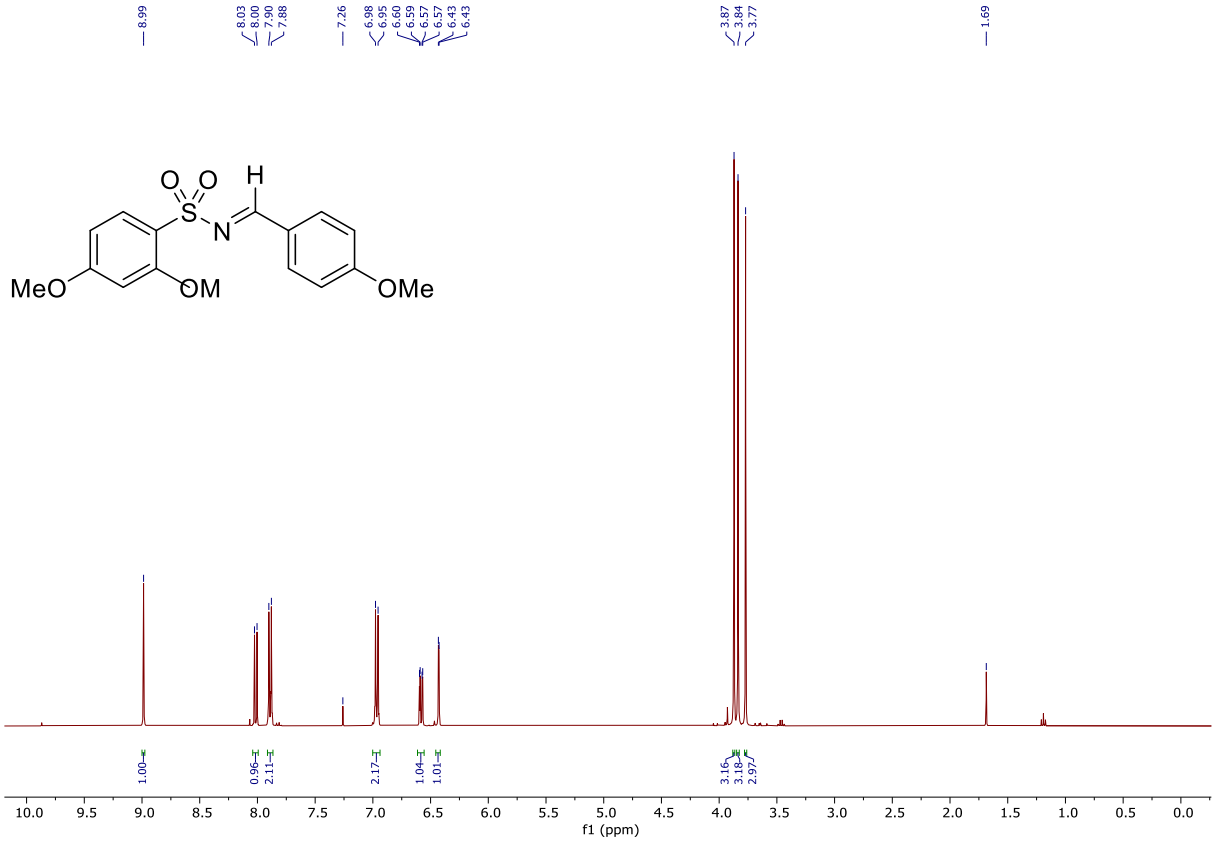

-104.21
-104.22
-104.23
-104.23
-104.24
-104.25
-104.26
-104.27
-104.28
O
O
H
S
N
F
OMe
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

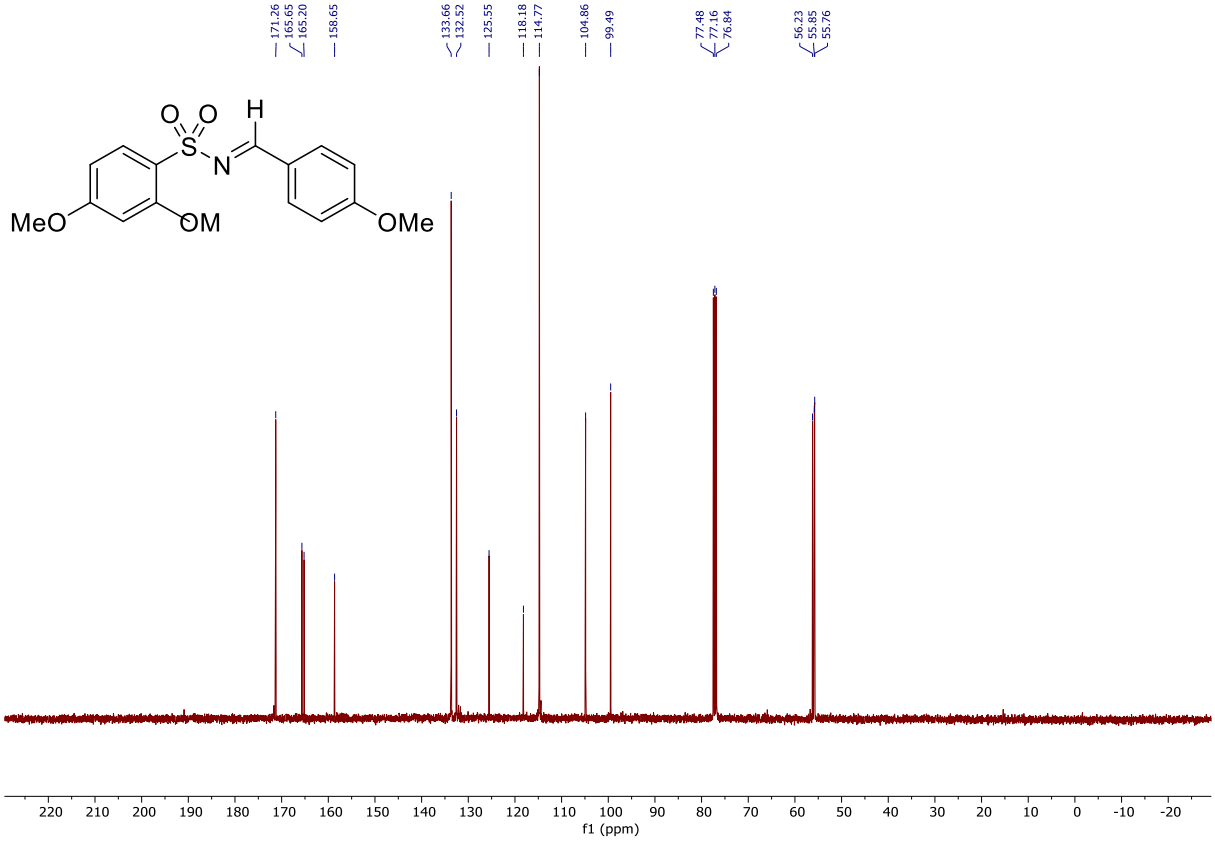
## 4-Methoxy-*N*-(4-methoxybenzylidene)benzenesulfonamide (108f)



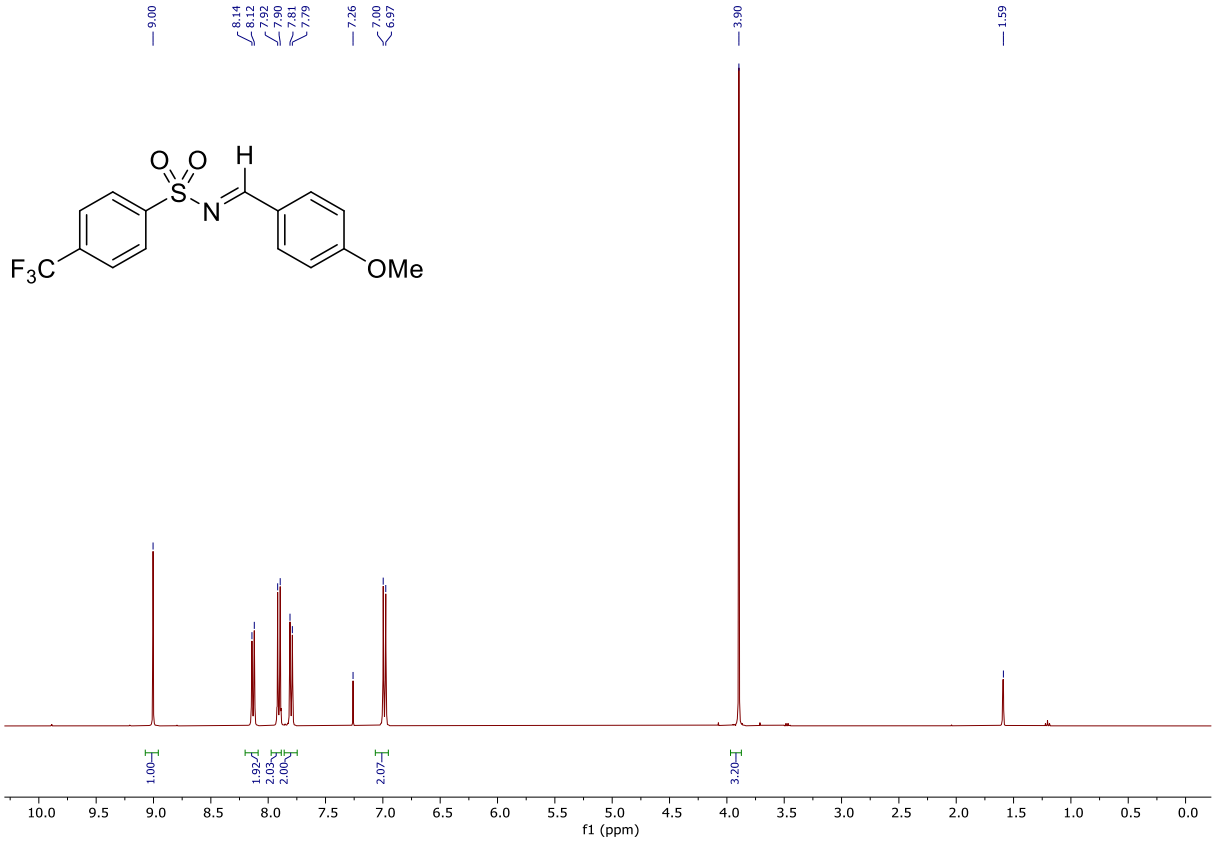



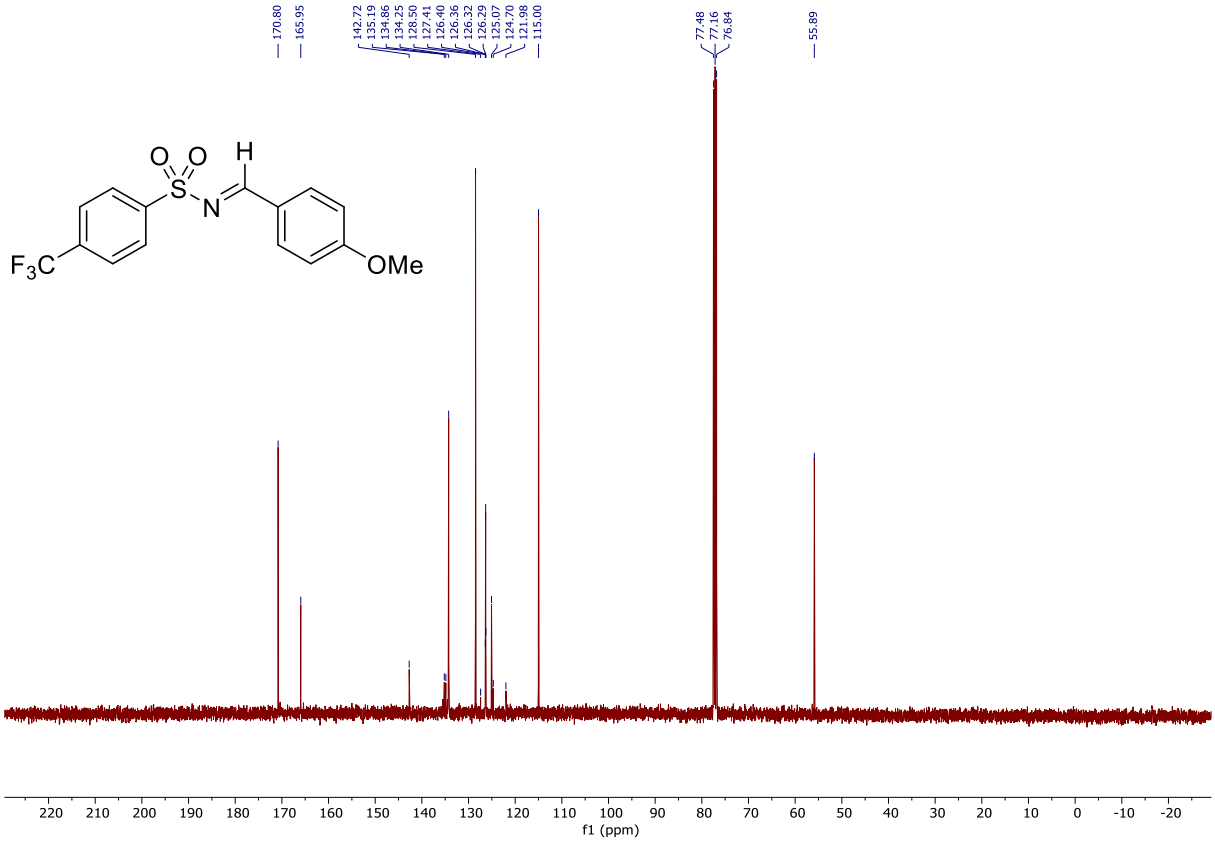
## 2,4-Dimethoxy-*N*-(4-methoxybenzylidene)benzenesulfonamide (108g)

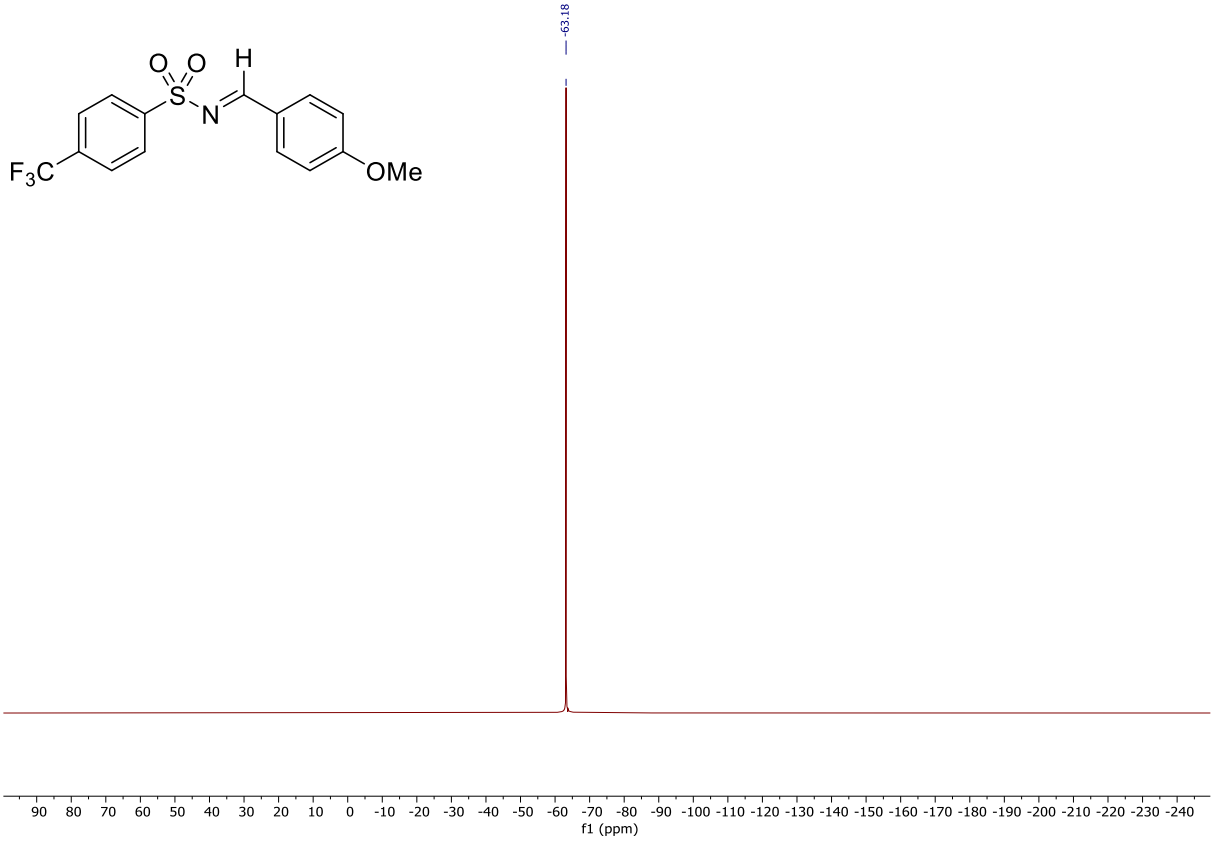


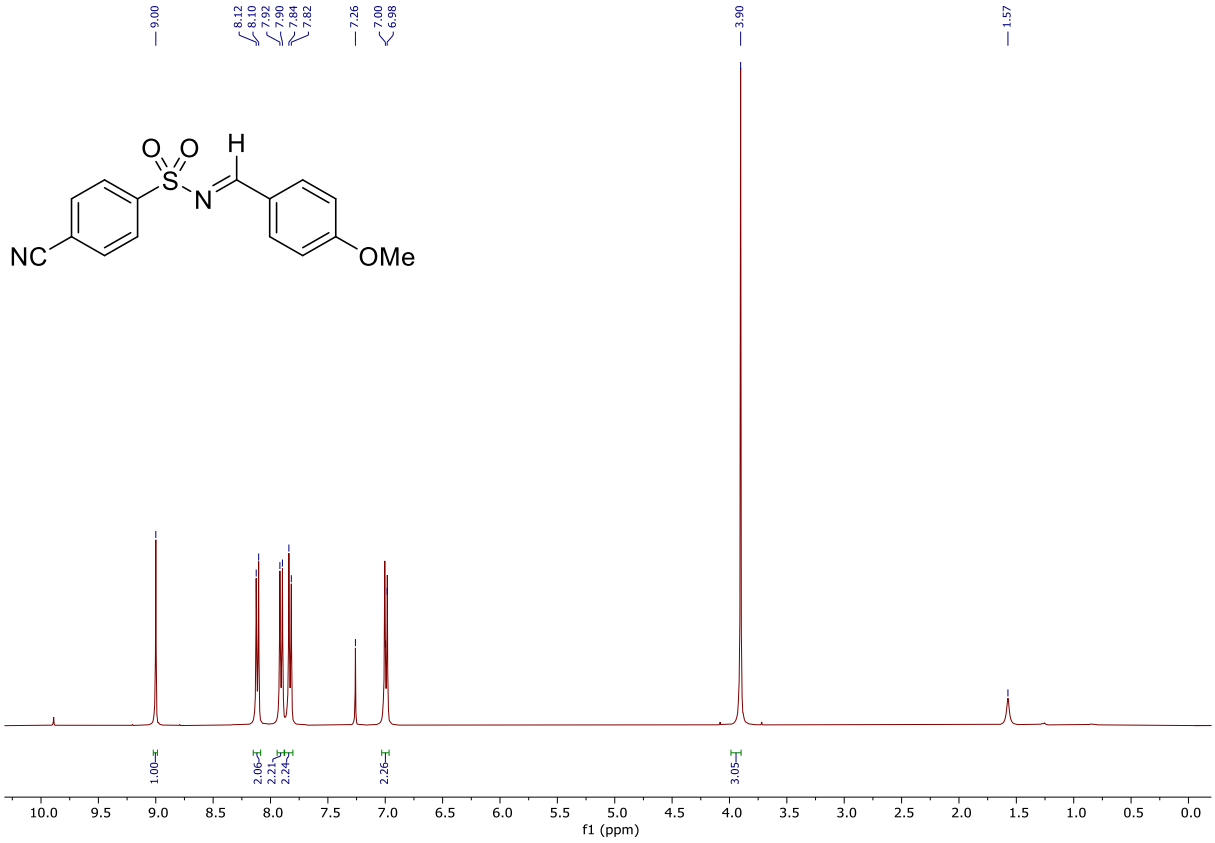
## *N*-(4-methoxybenzylidene)-4-(trifluoromethyl)benzenesulfonamide (108h)

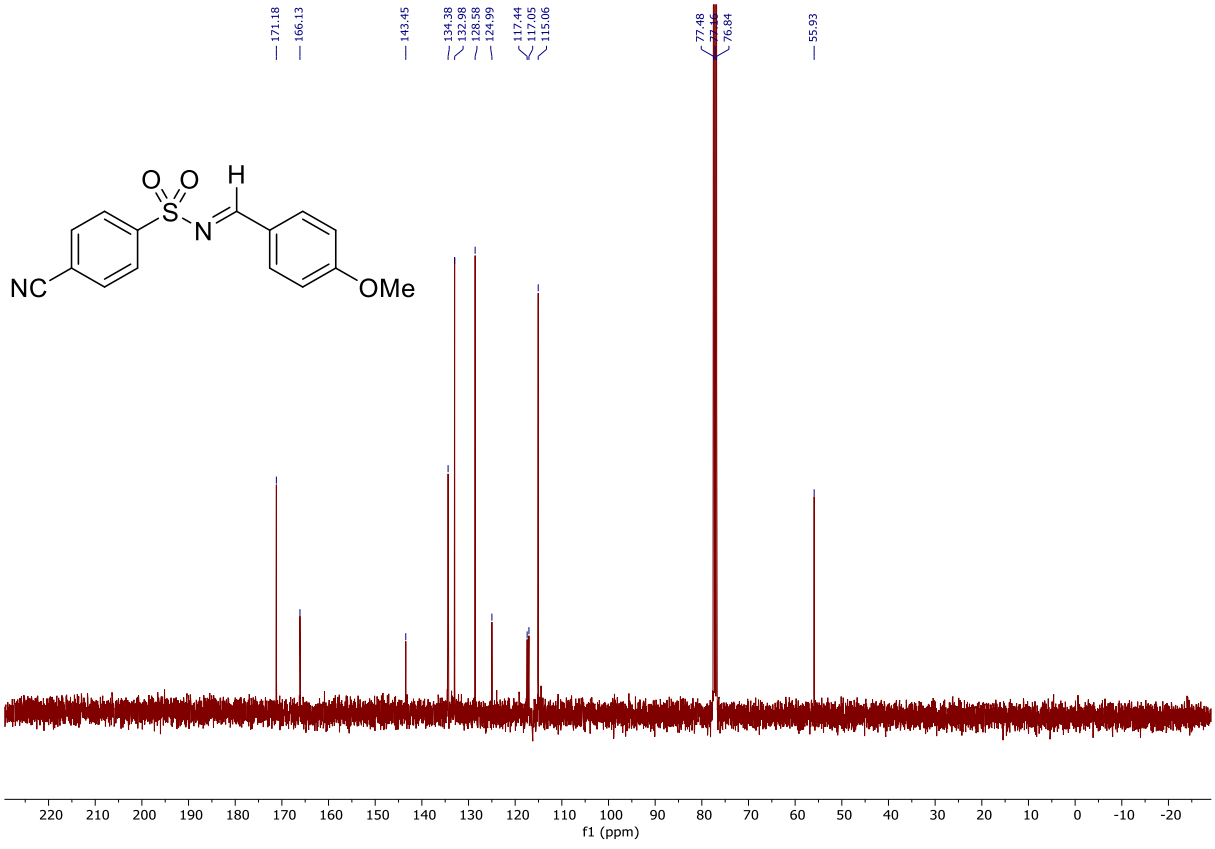


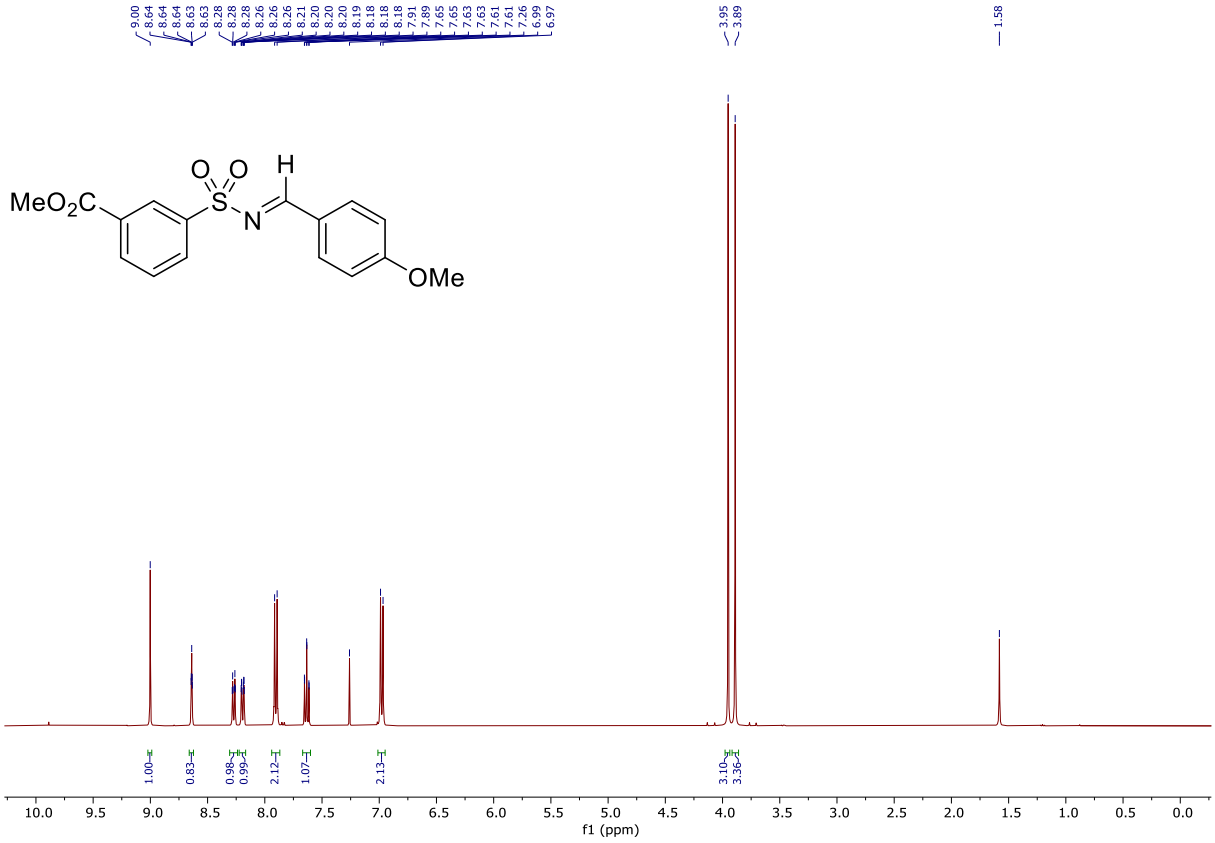

O
O
H
S
N
F3C
OMe
-63.18
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

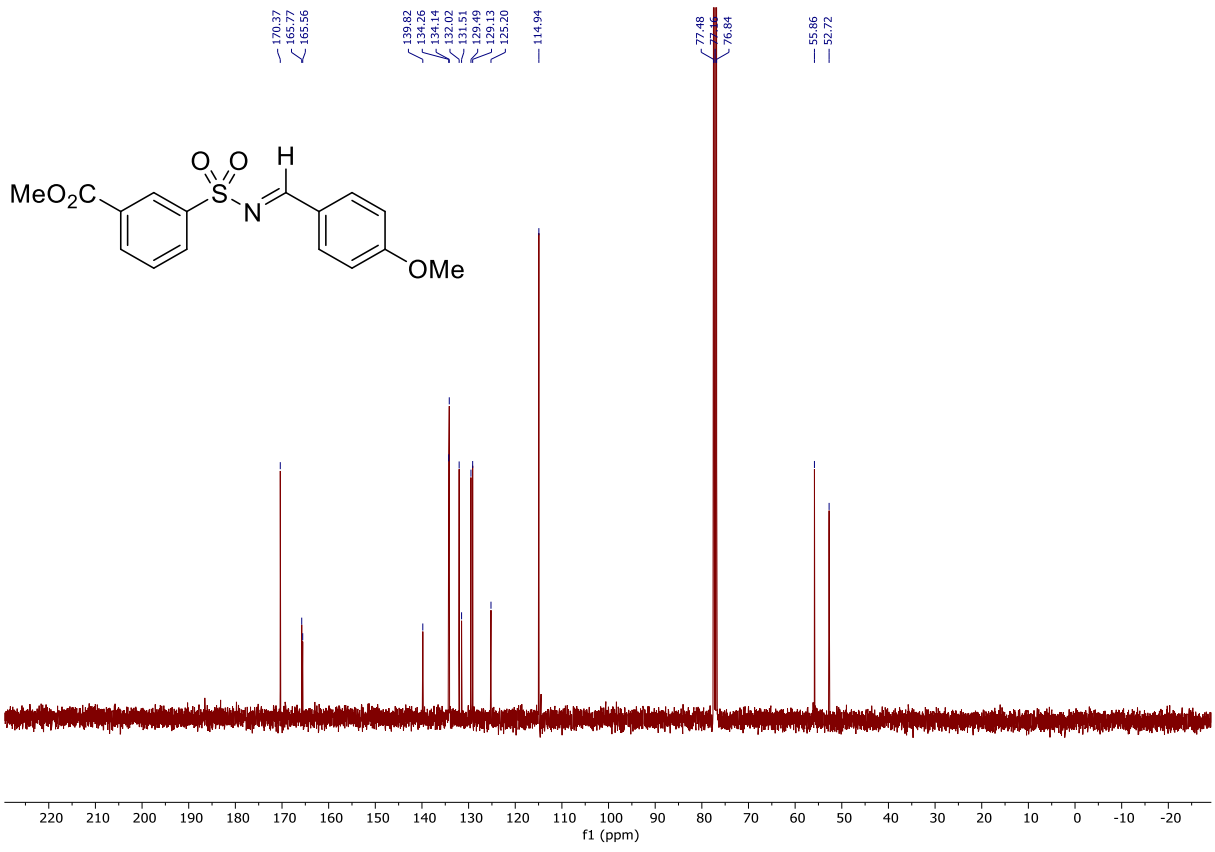
## 4-Cyano-*N*-(4-methoxybenzylidene)benzenesulfonamide (108i)



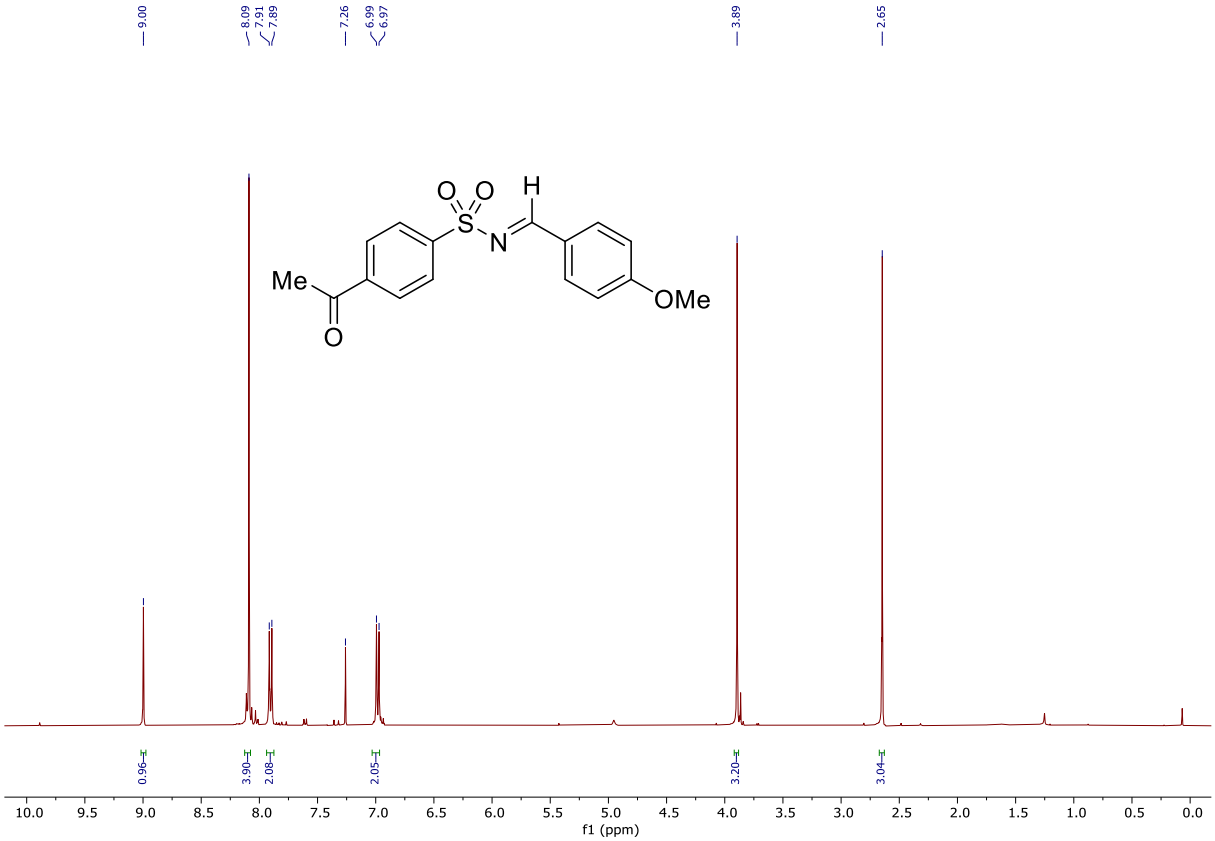



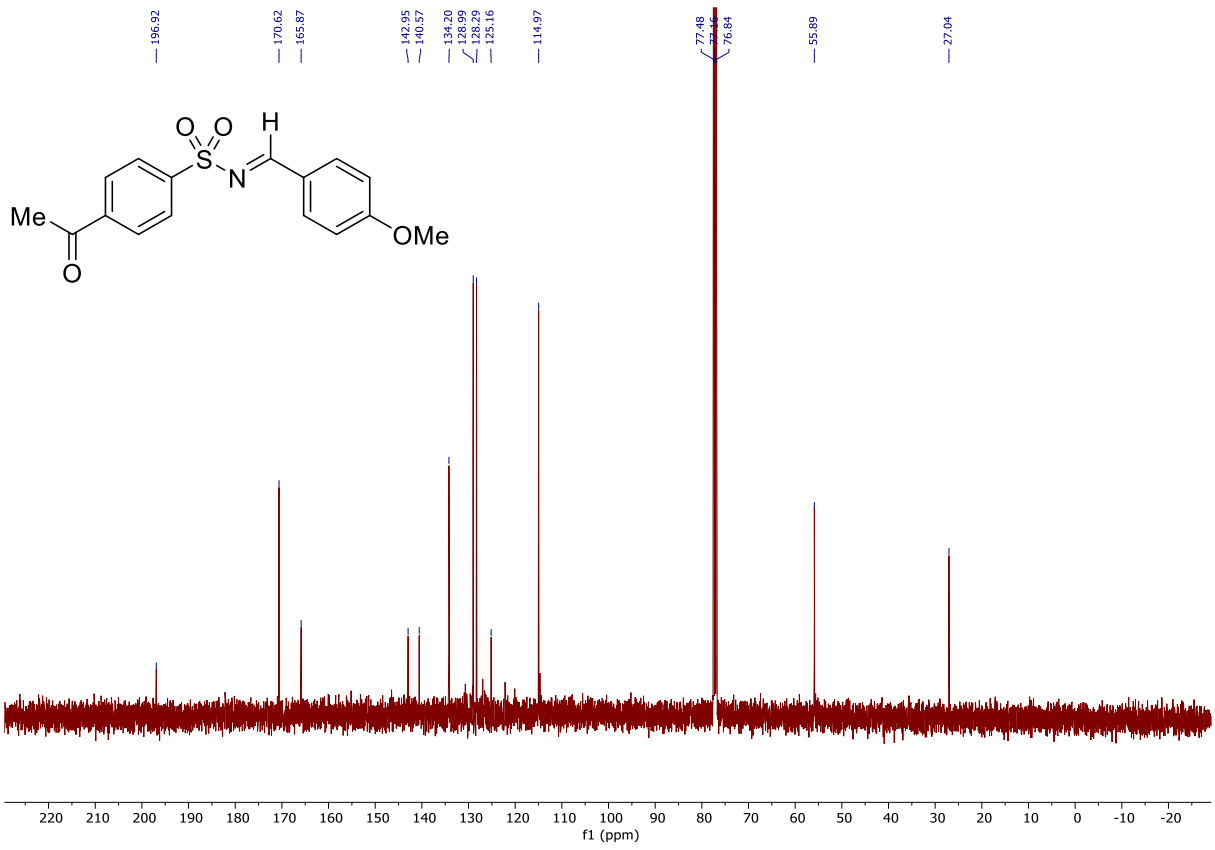
## Methyl 3-(*N*-(4-methoxybenzylidene)sulfamoyl)benzoate (108j)



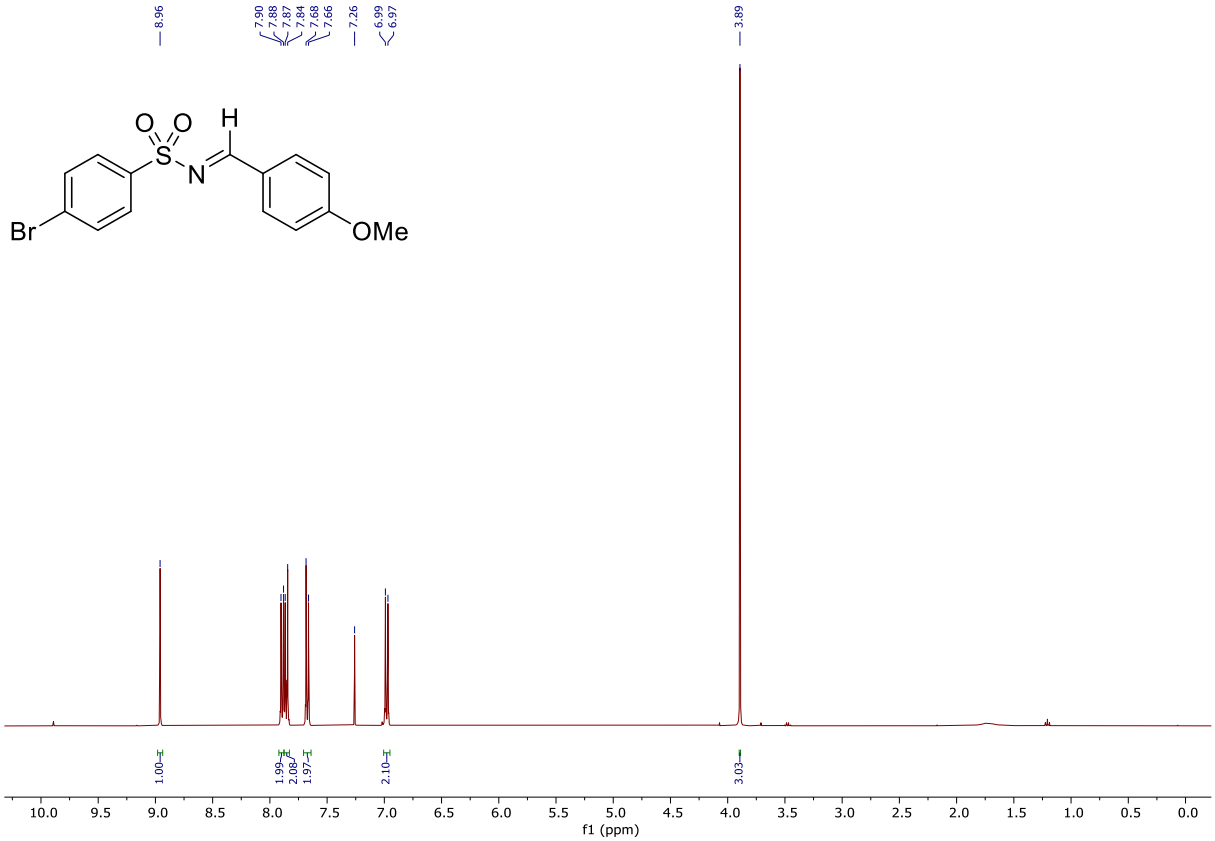



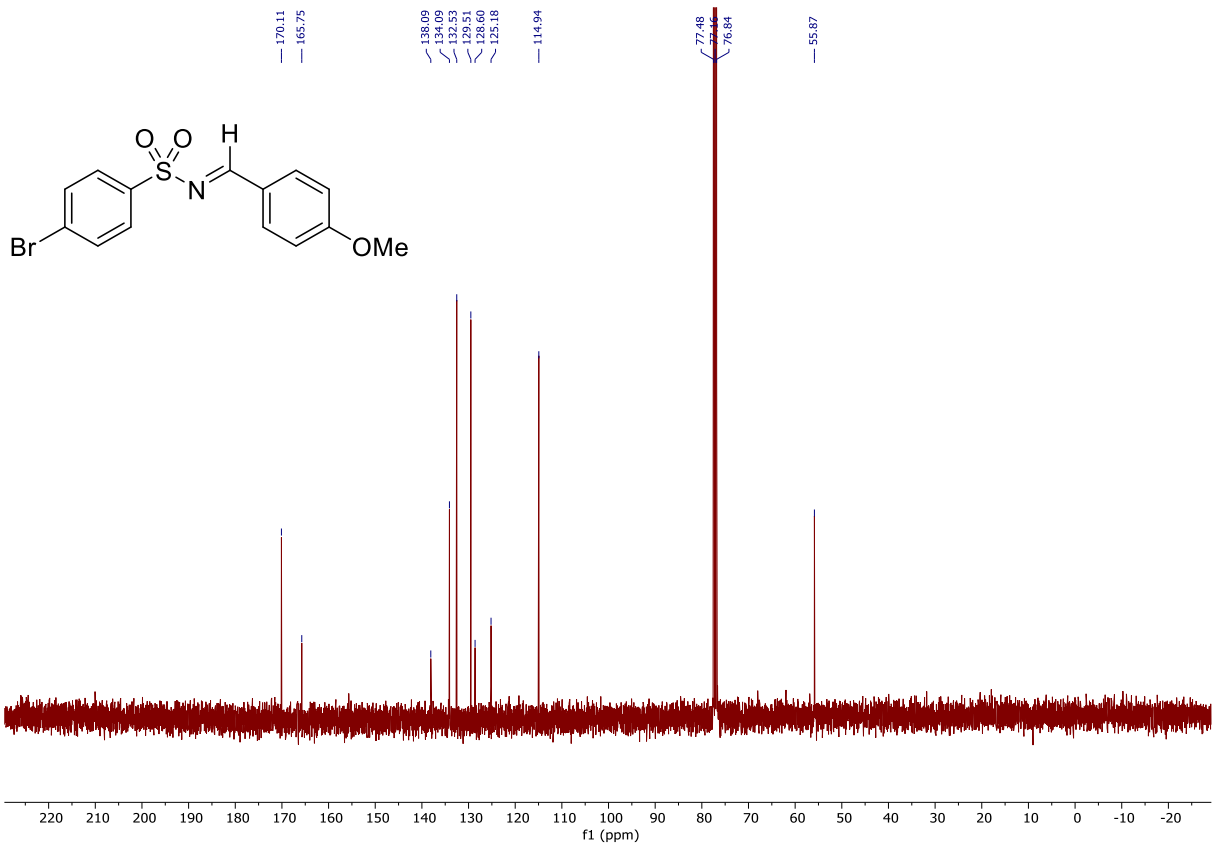
## 4-Acetyl-*N*-(4-methoxybenzylidene)benzenesulfonamide (108k)



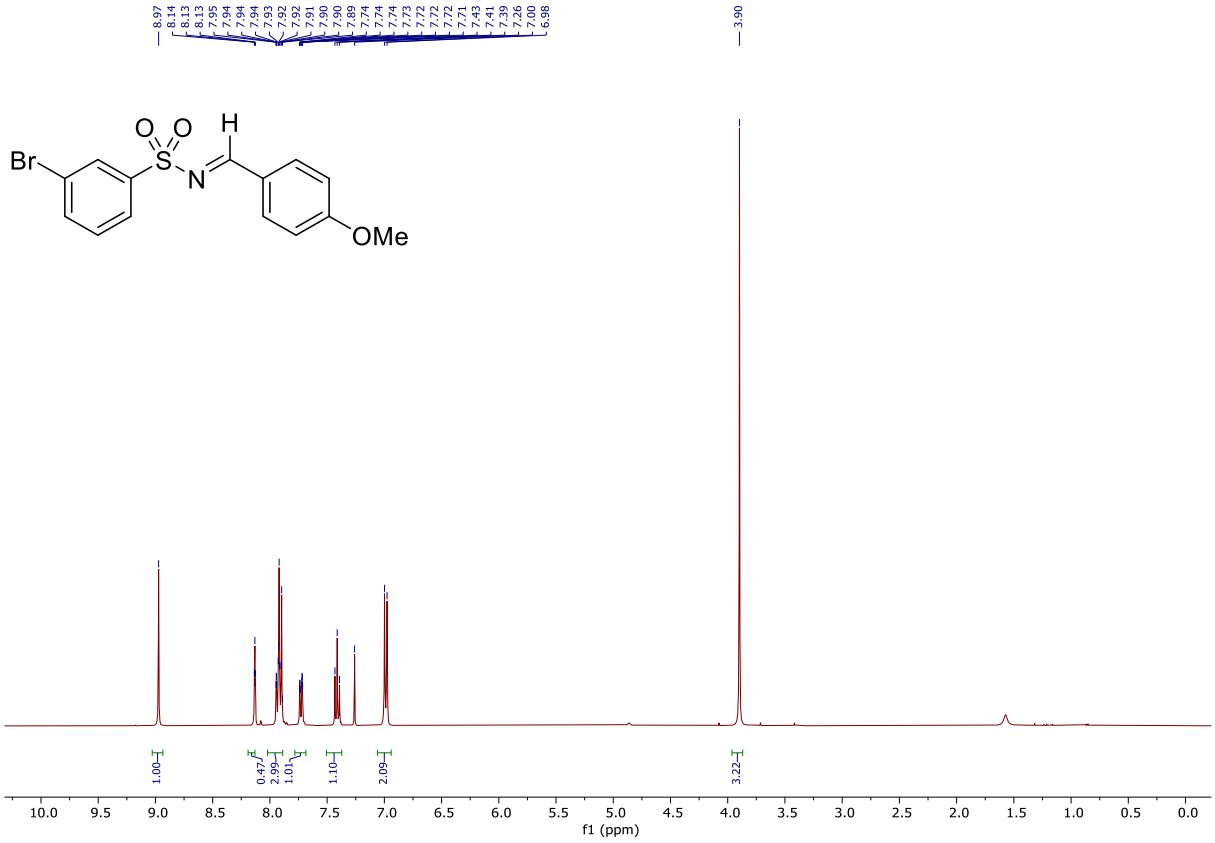



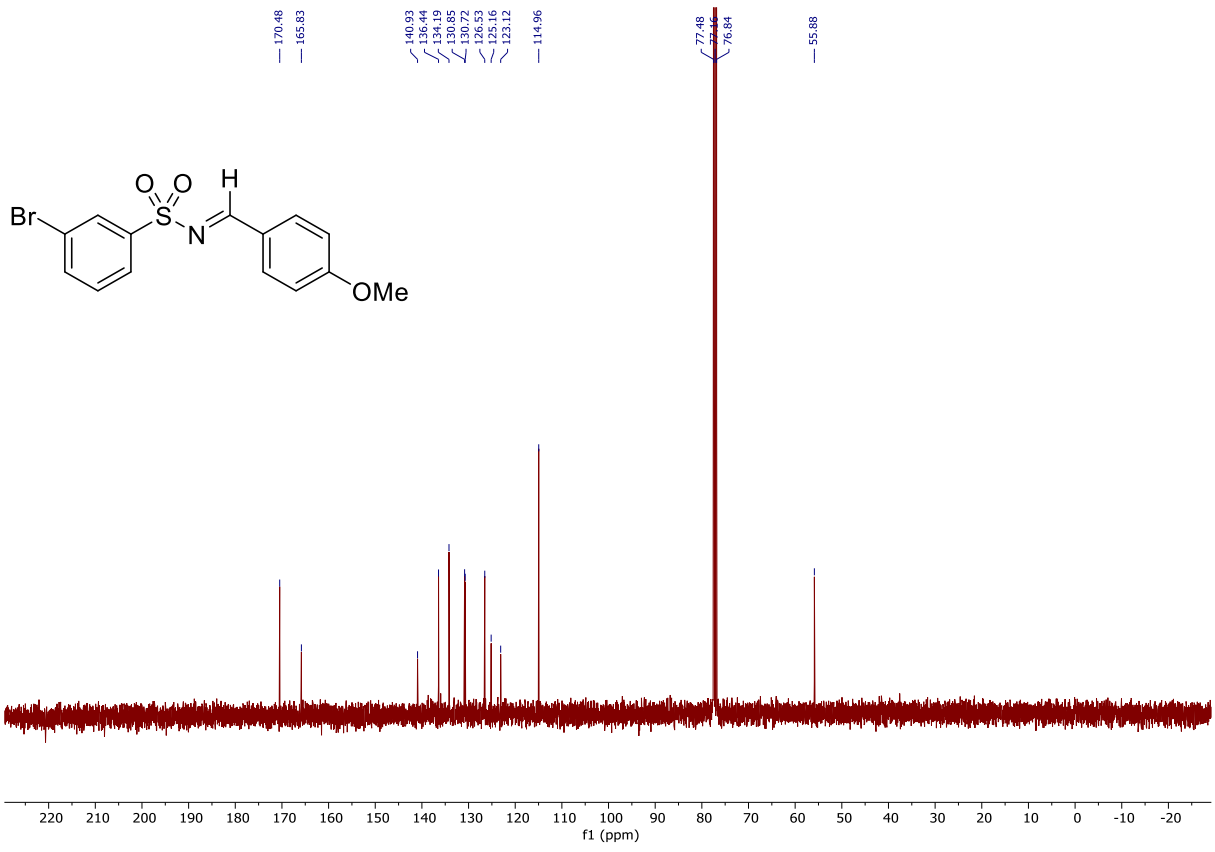
## 4-Bromo-*N*-(4-methoxybenzylidene)benzenesulfonamide (108l)



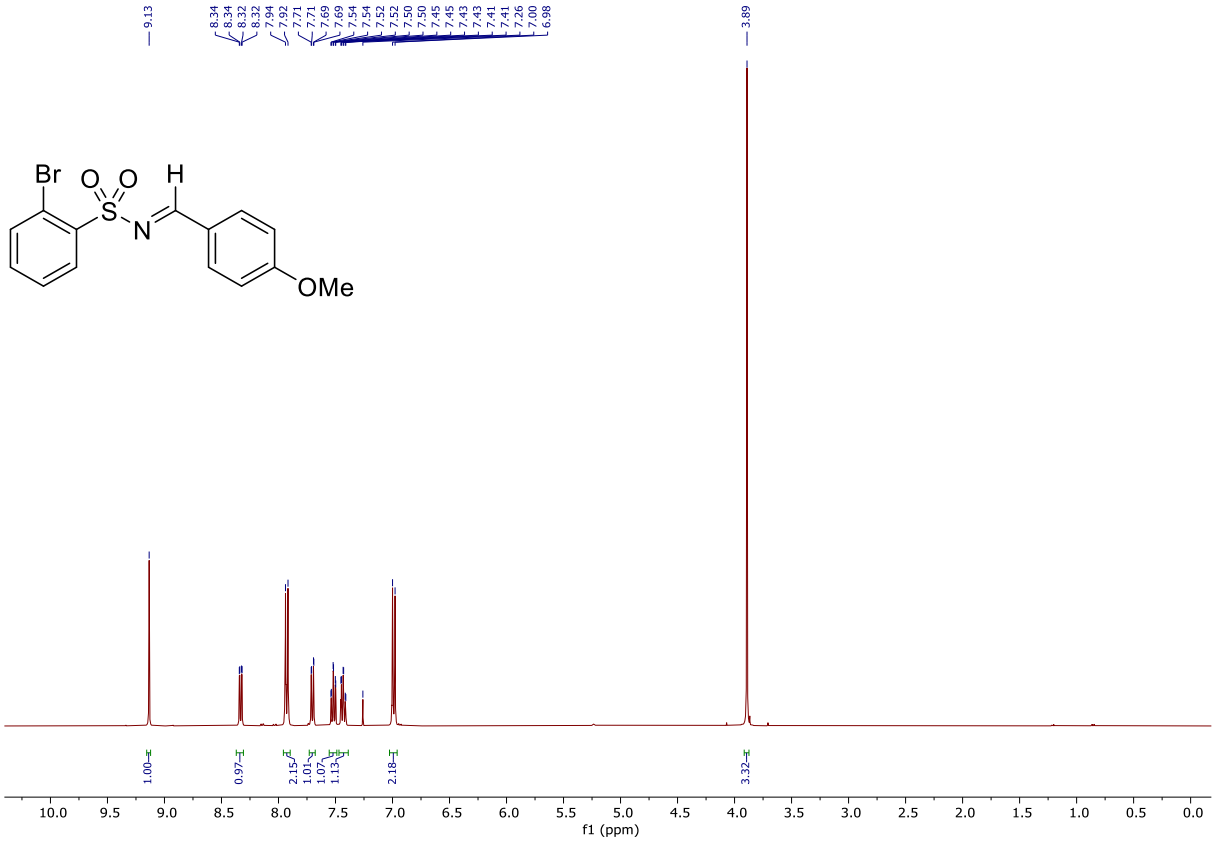



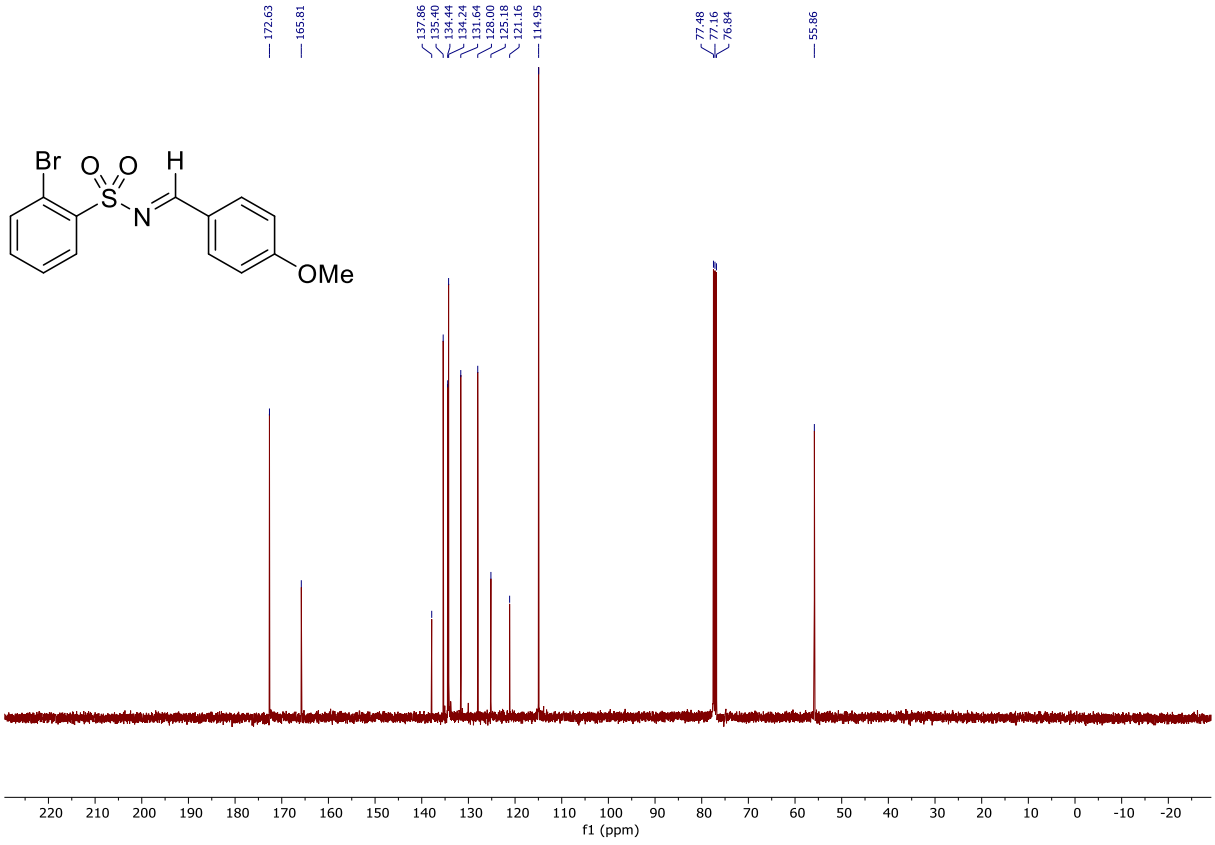
## 3-Bromo-*N*-(4-methoxybenzylidene)benzenesulfonamide (108m)



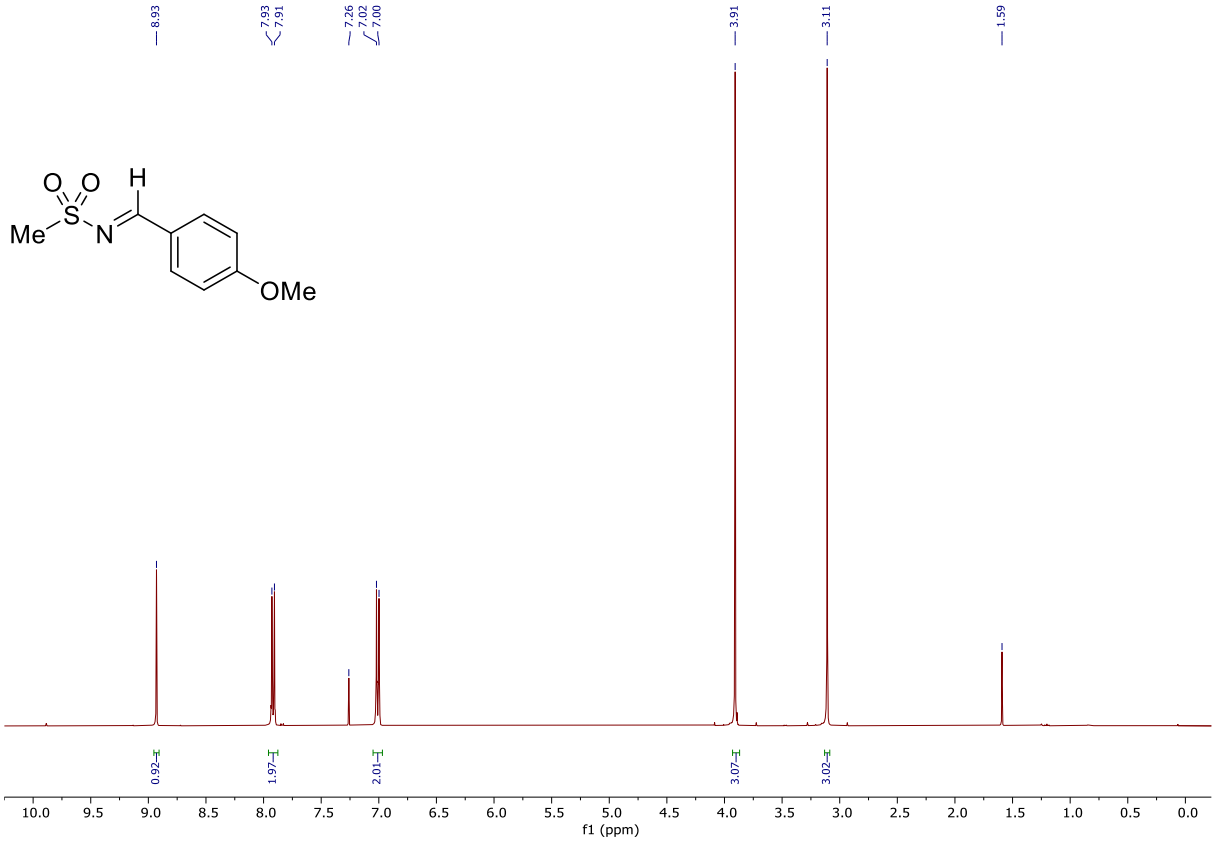



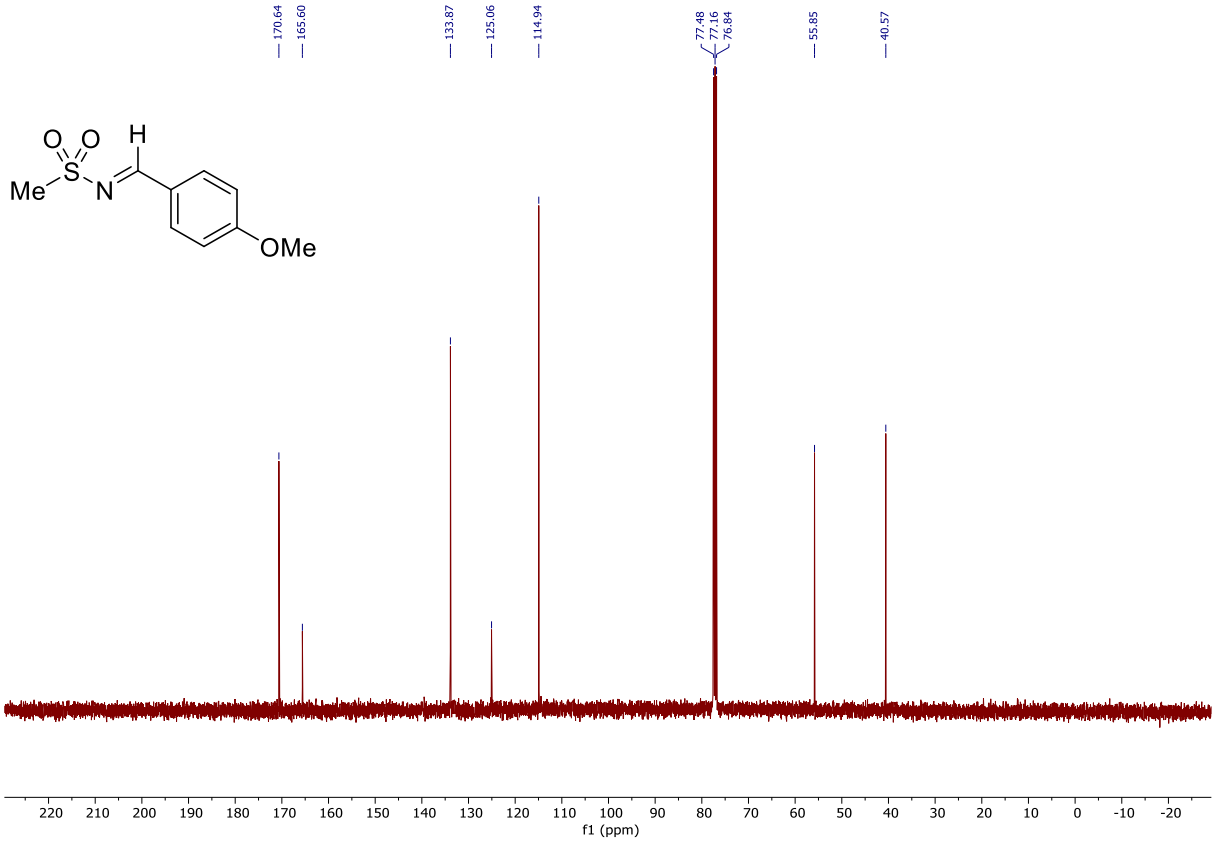
## 2-Bromo-*N*-(4-methoxybenzylidene)benzenesulfonamide (108n)



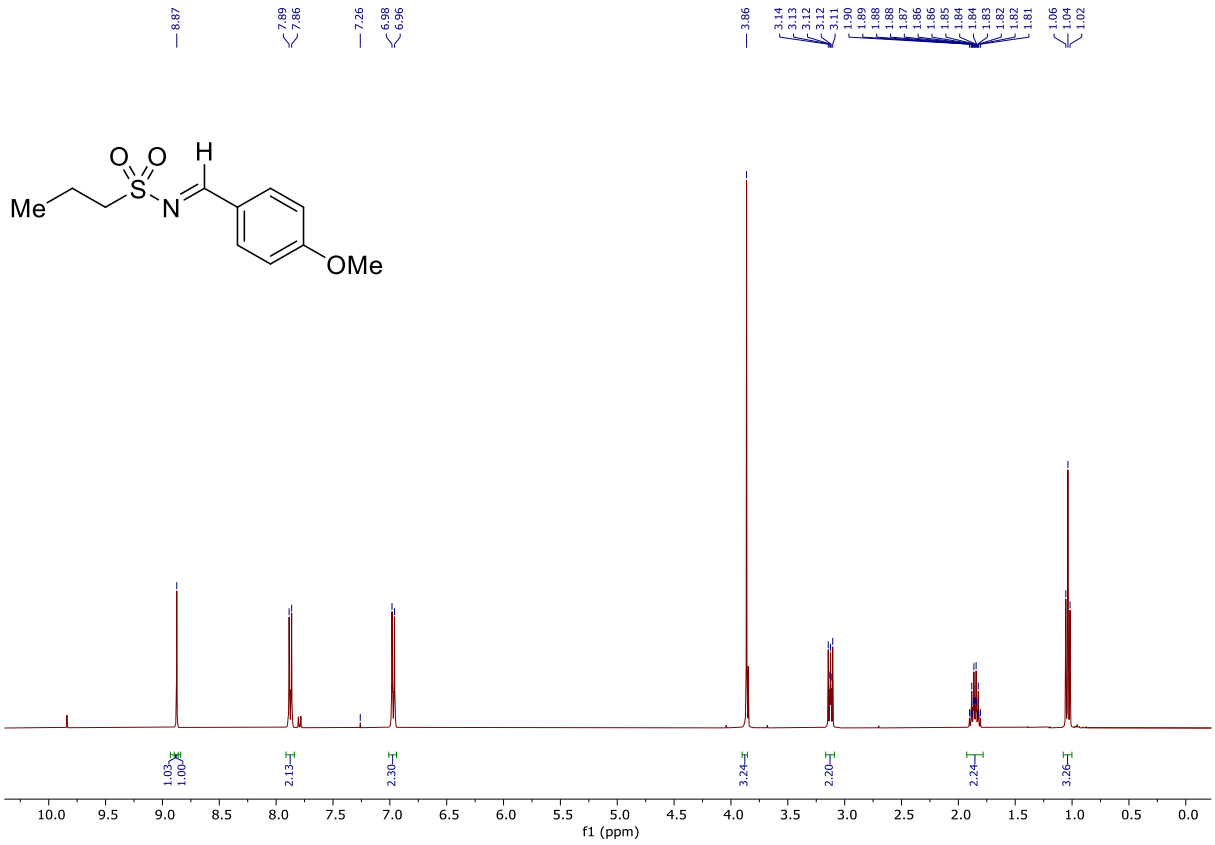



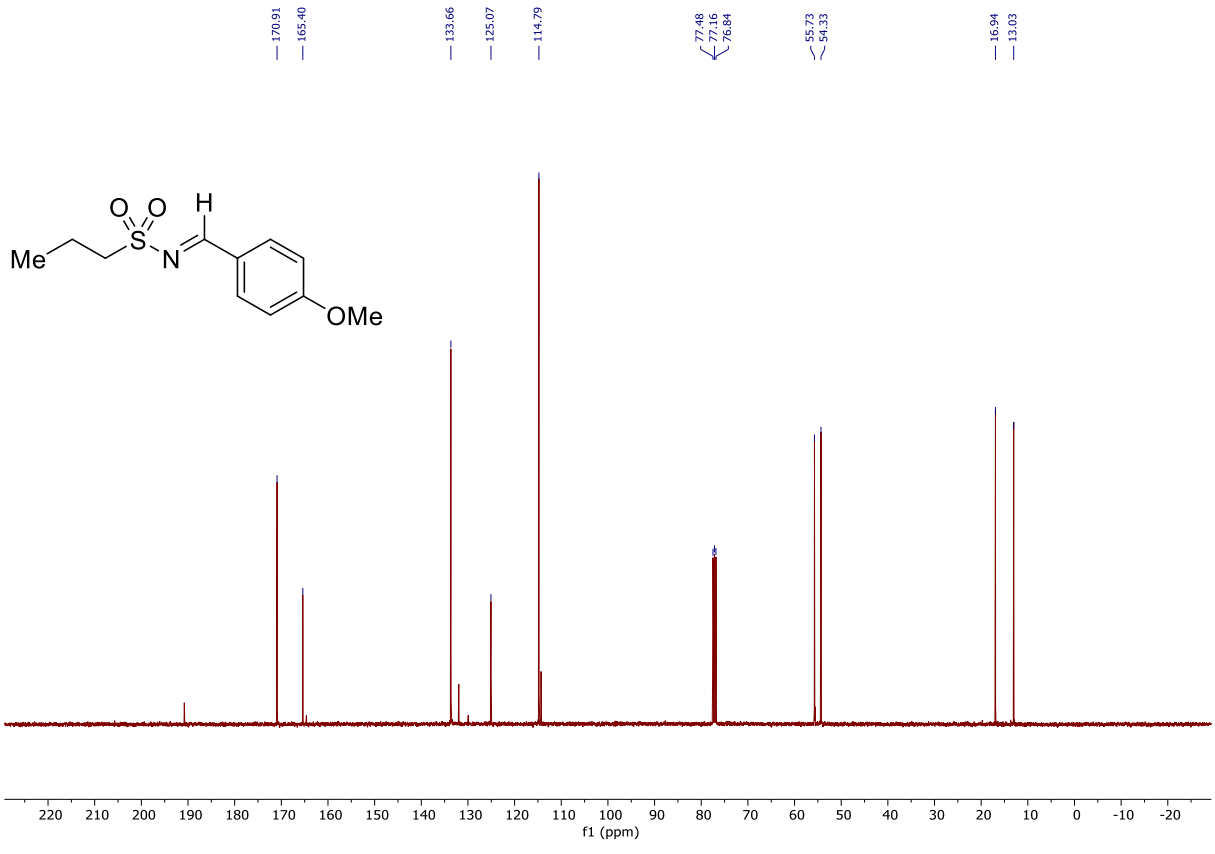
## *N*-(4-methoxybenzylidene)methanesulfonamide (108o)



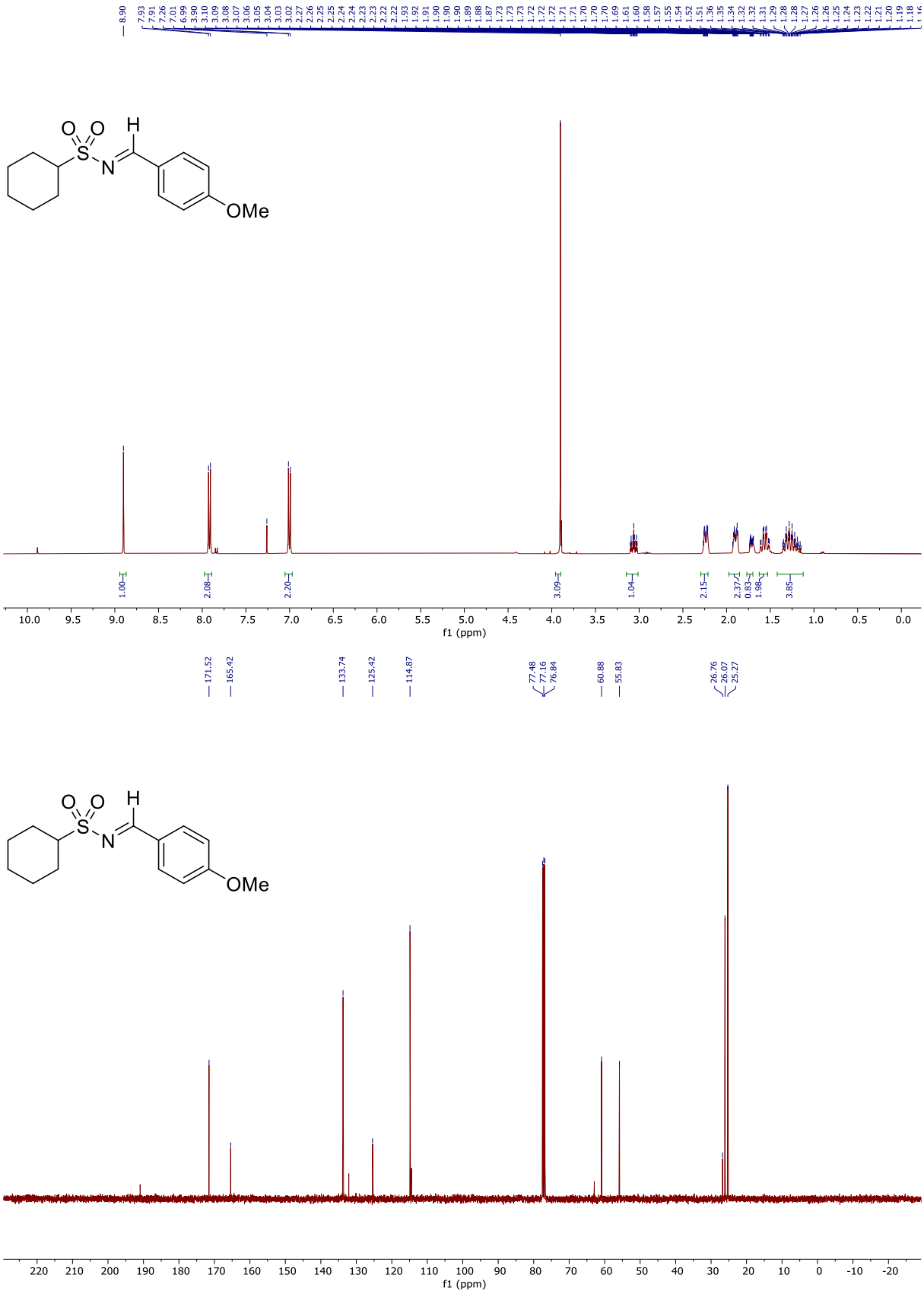



## *N*-(4-methoxybenzylidene)propane-1-sulfonamide (108p)

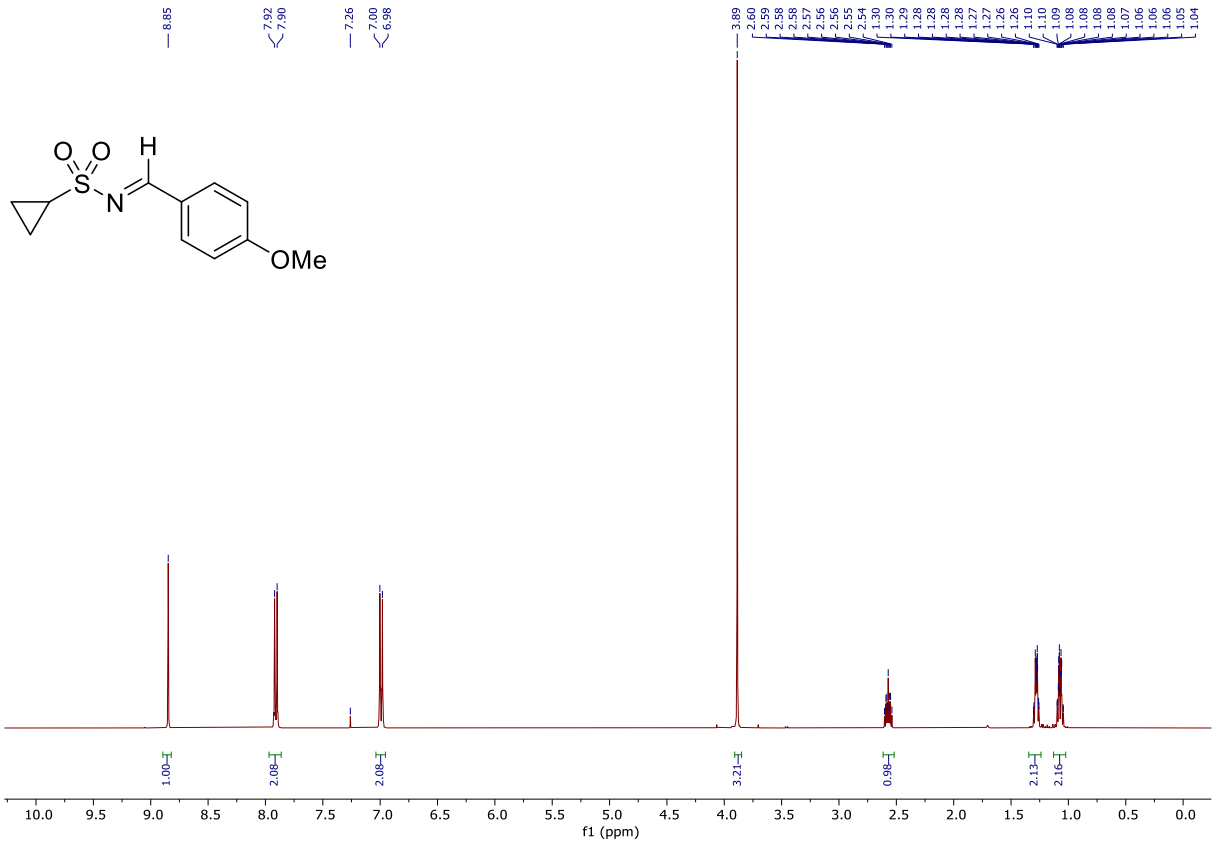


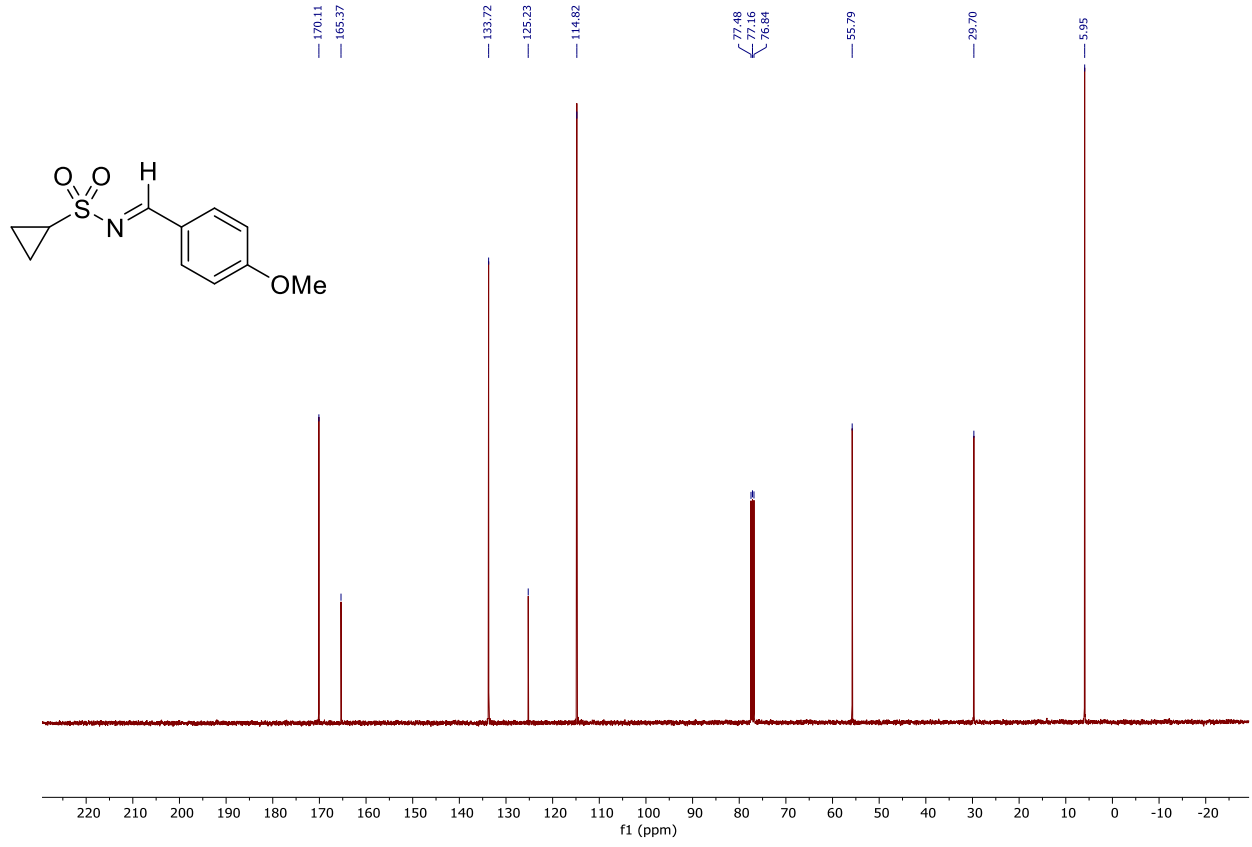



## *N*-(4-methoxybenzylidene)cyclohexanesulfonamide (108q)

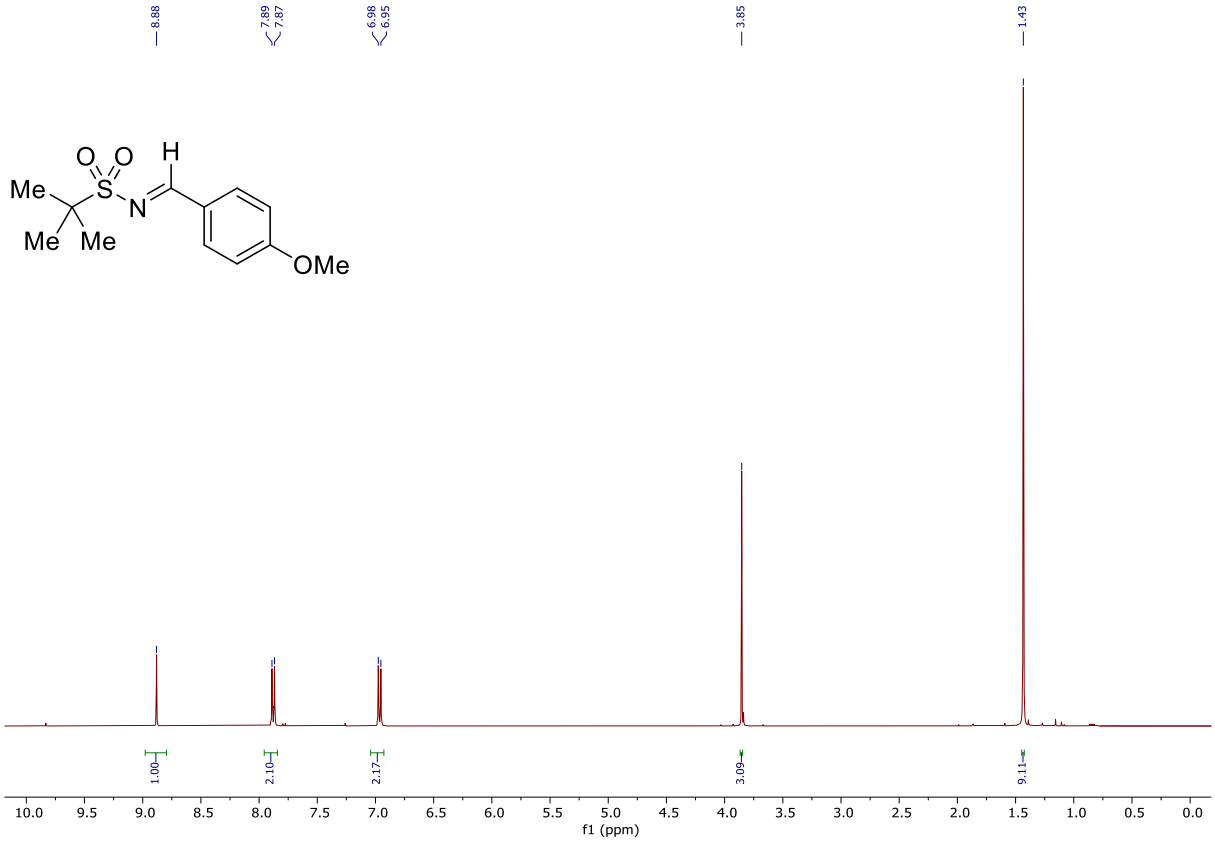


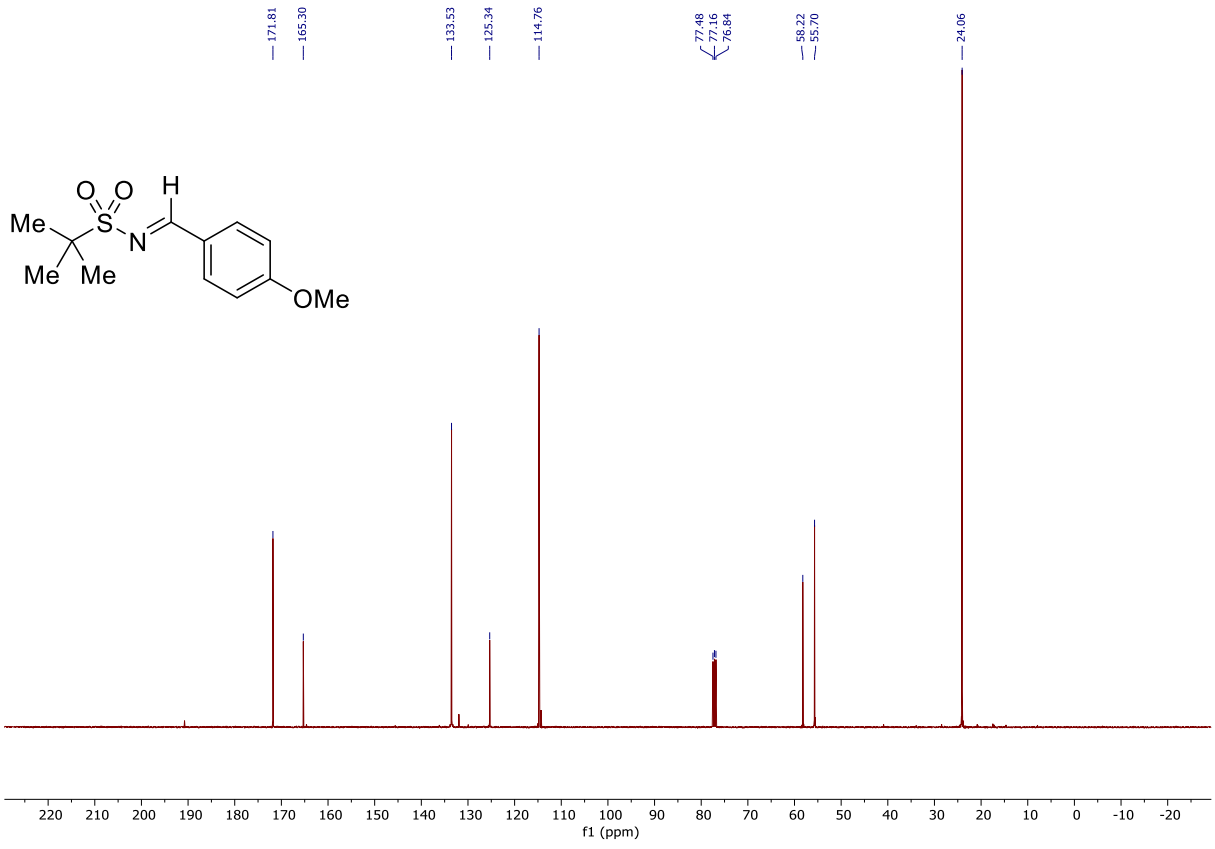
## *N*-(4-methoxybenzylidene)cyclopropanesulfonamide (108r)



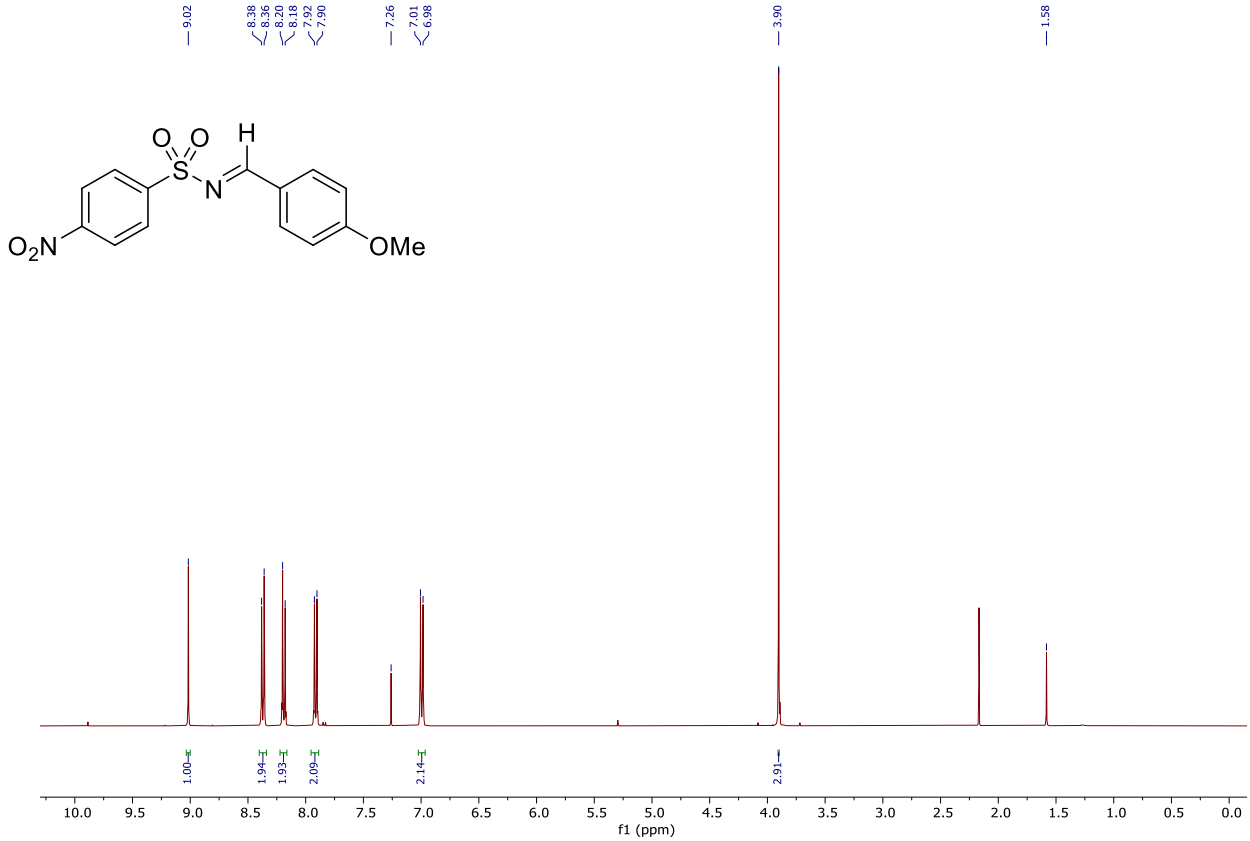



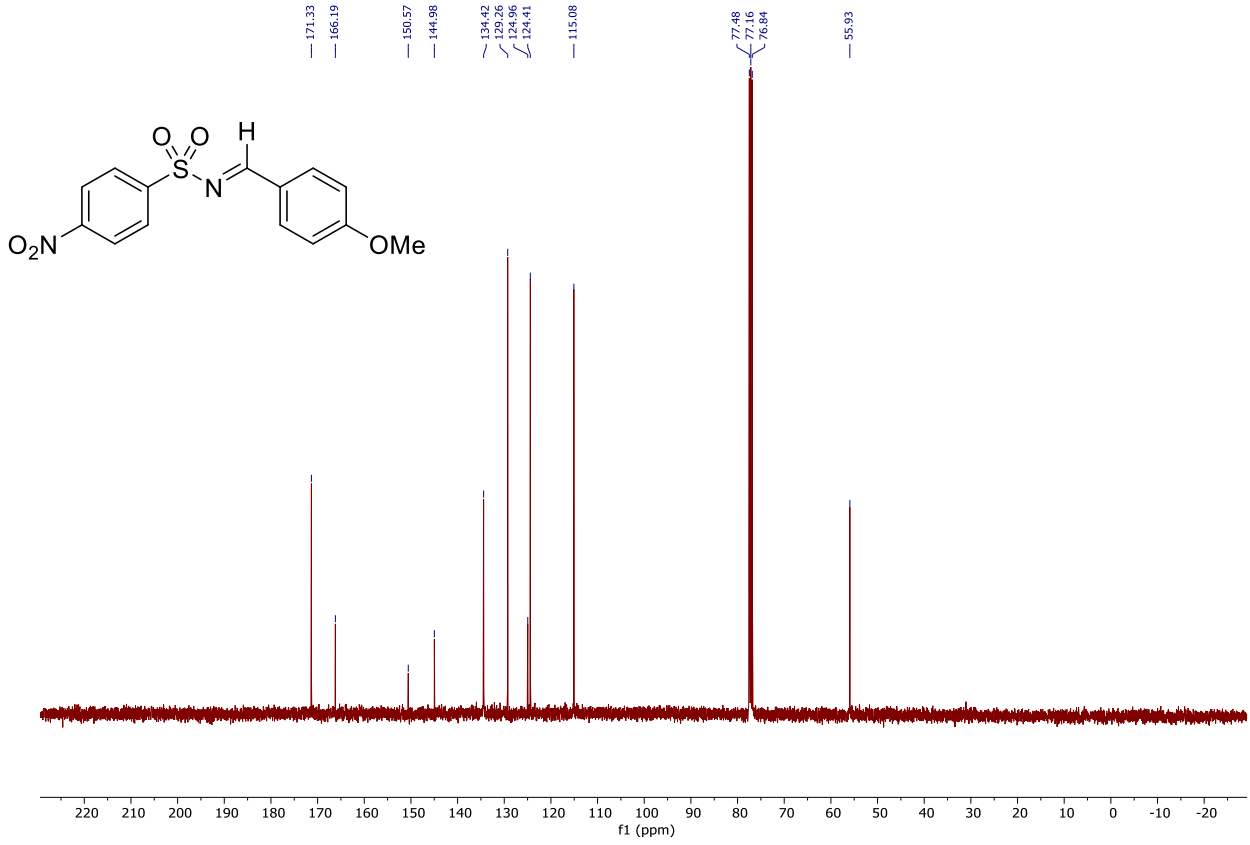
## *N*-(4-methoxybenzylidene)-2-methylpropane-2-sulfonamide (108s)



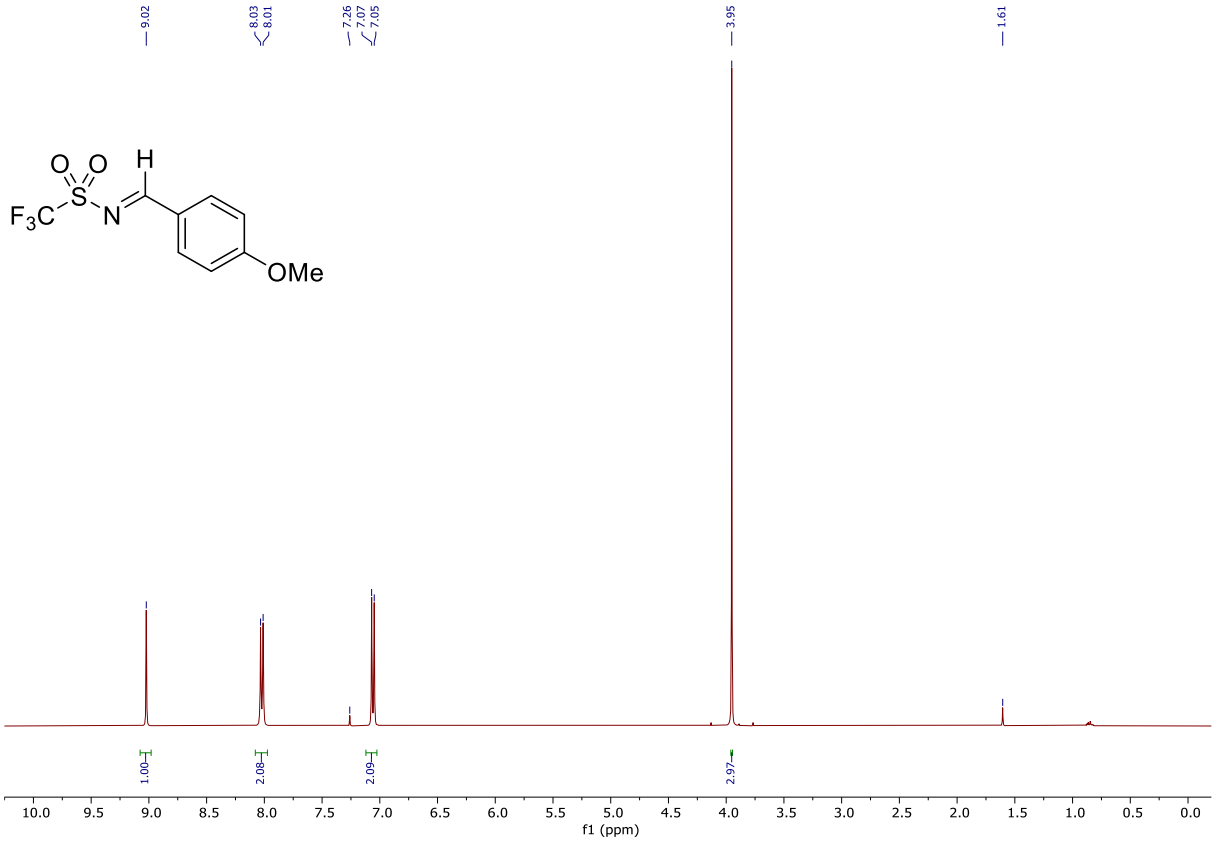



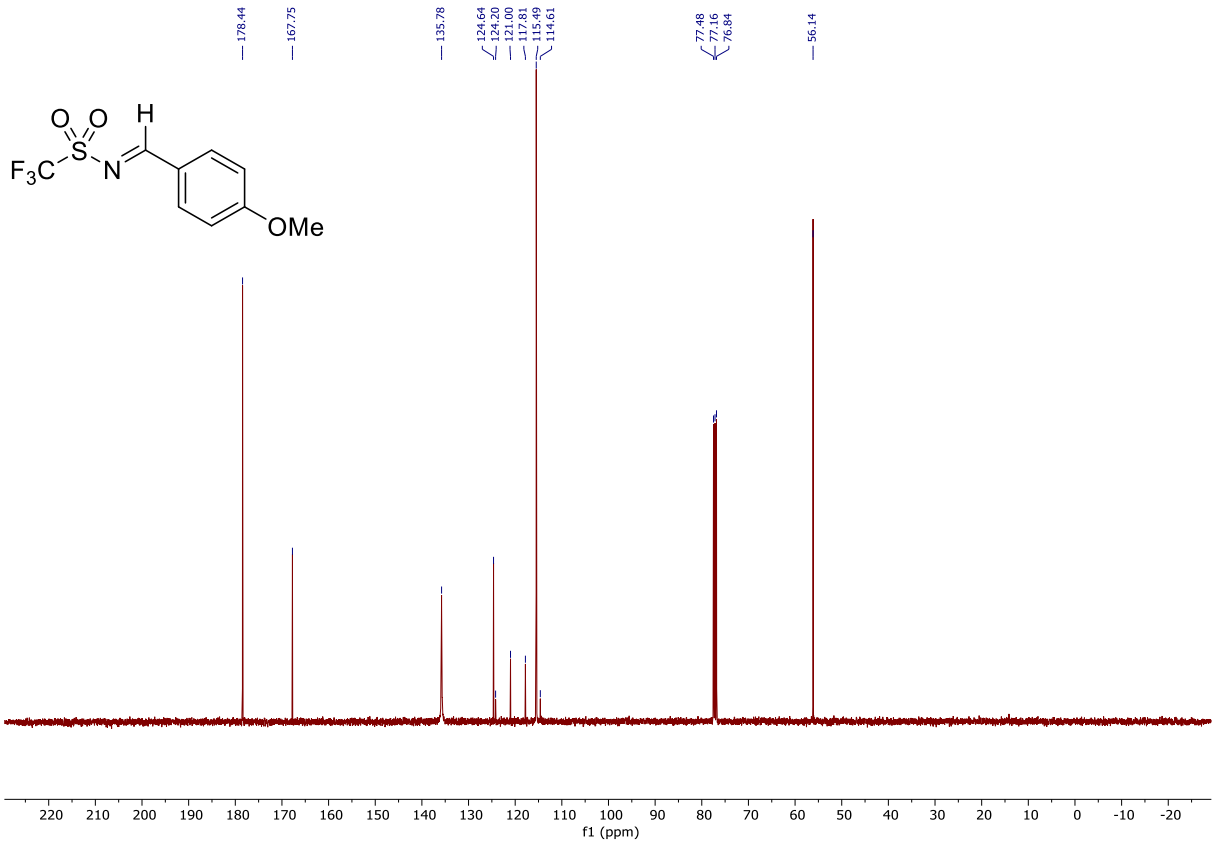
## *N*-(4-methoxybenzylidene)-4-nitrobenzenesulfonamide (108t)

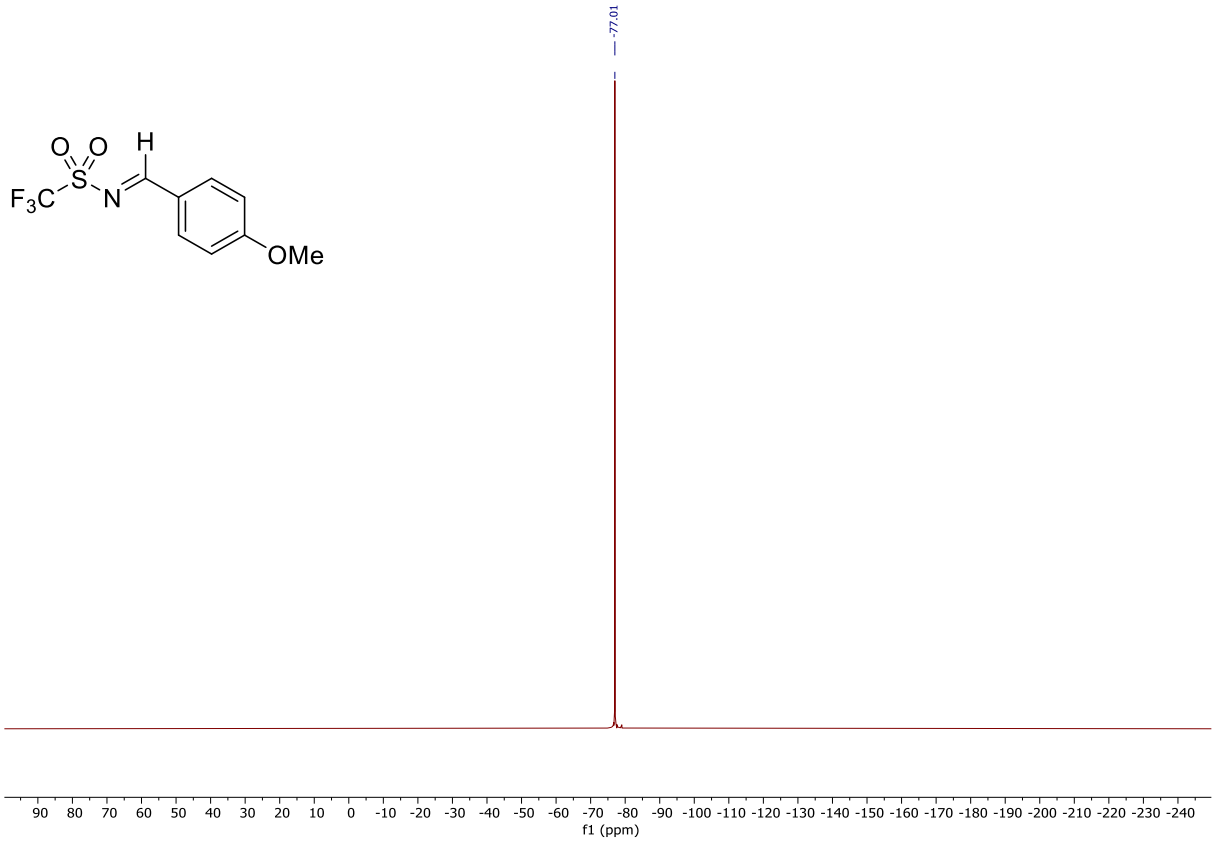


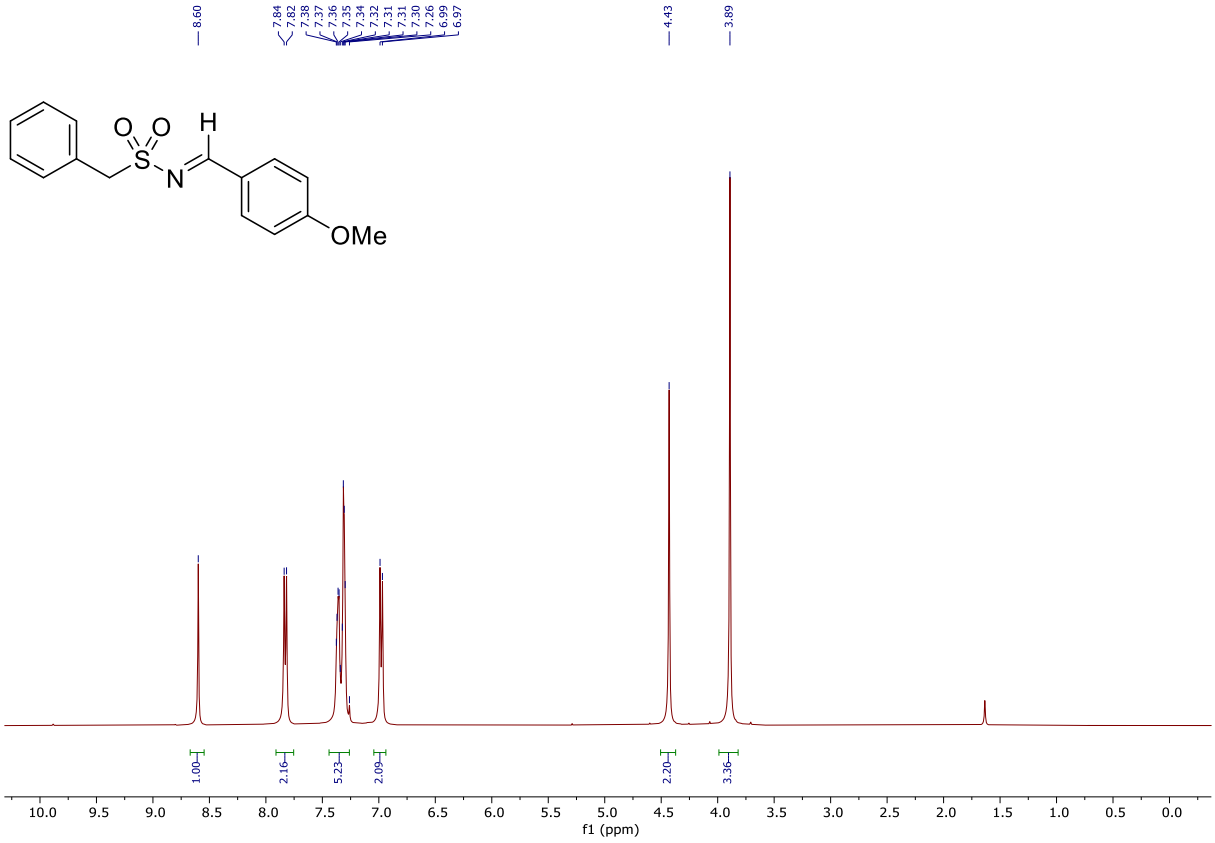
## 1,1,1-Trifluoro-*N*-(4-methoxybenzylidene)methanesulfonamide (108u)

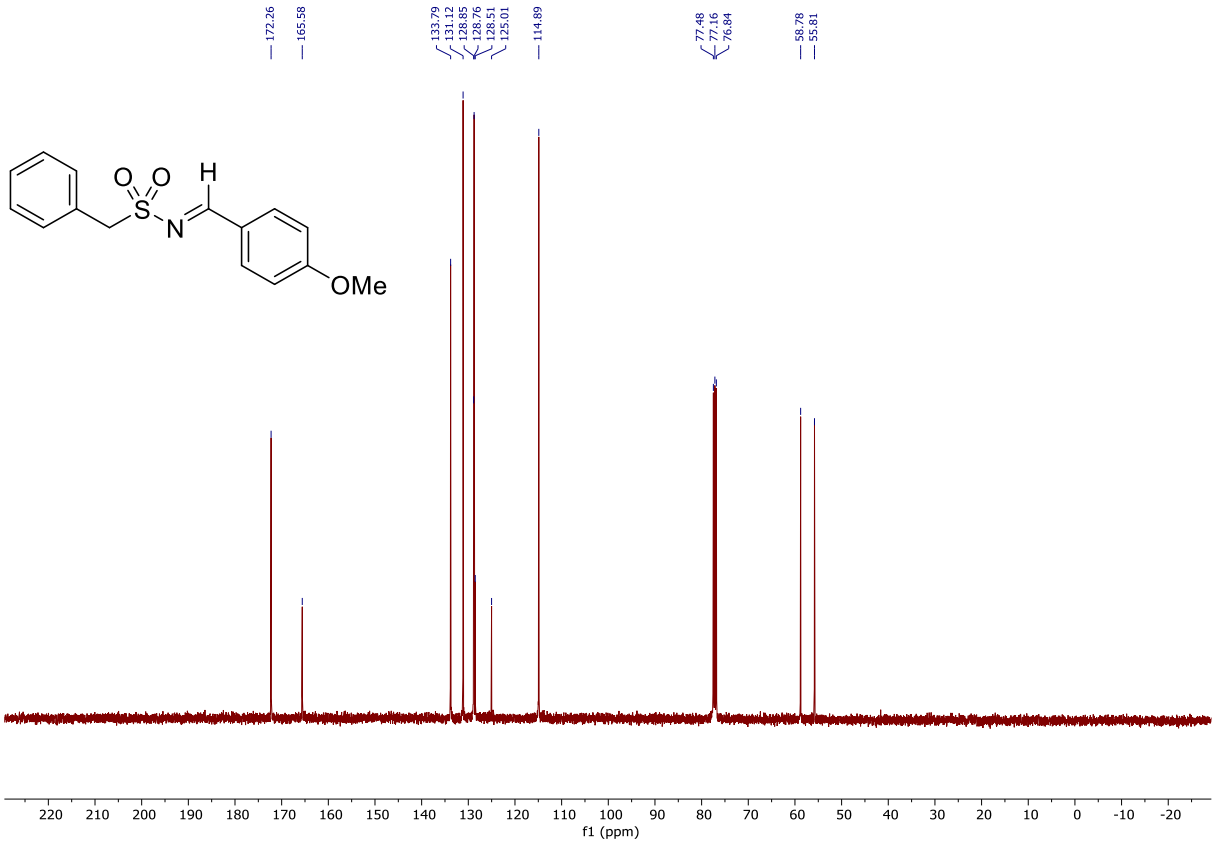


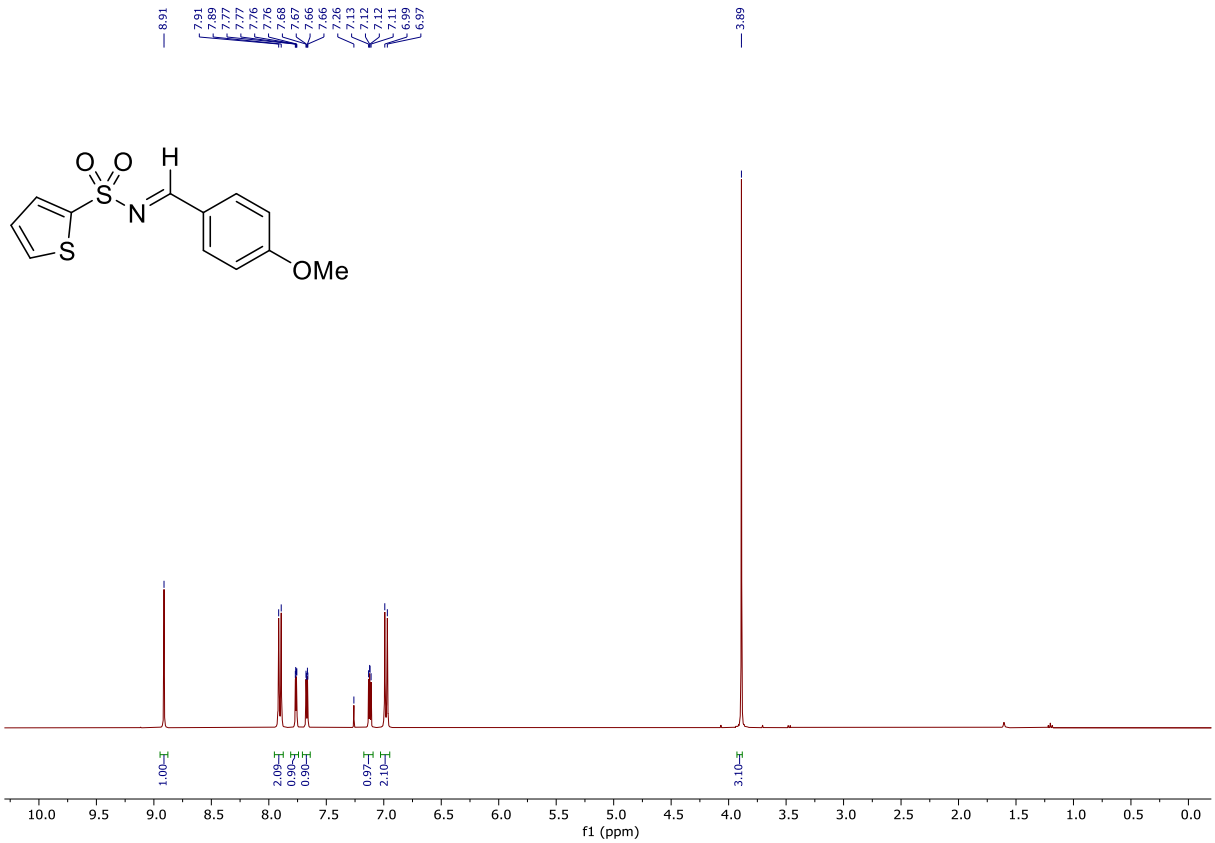

-77.01
O
O
H
S
F3C
N
OMe
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

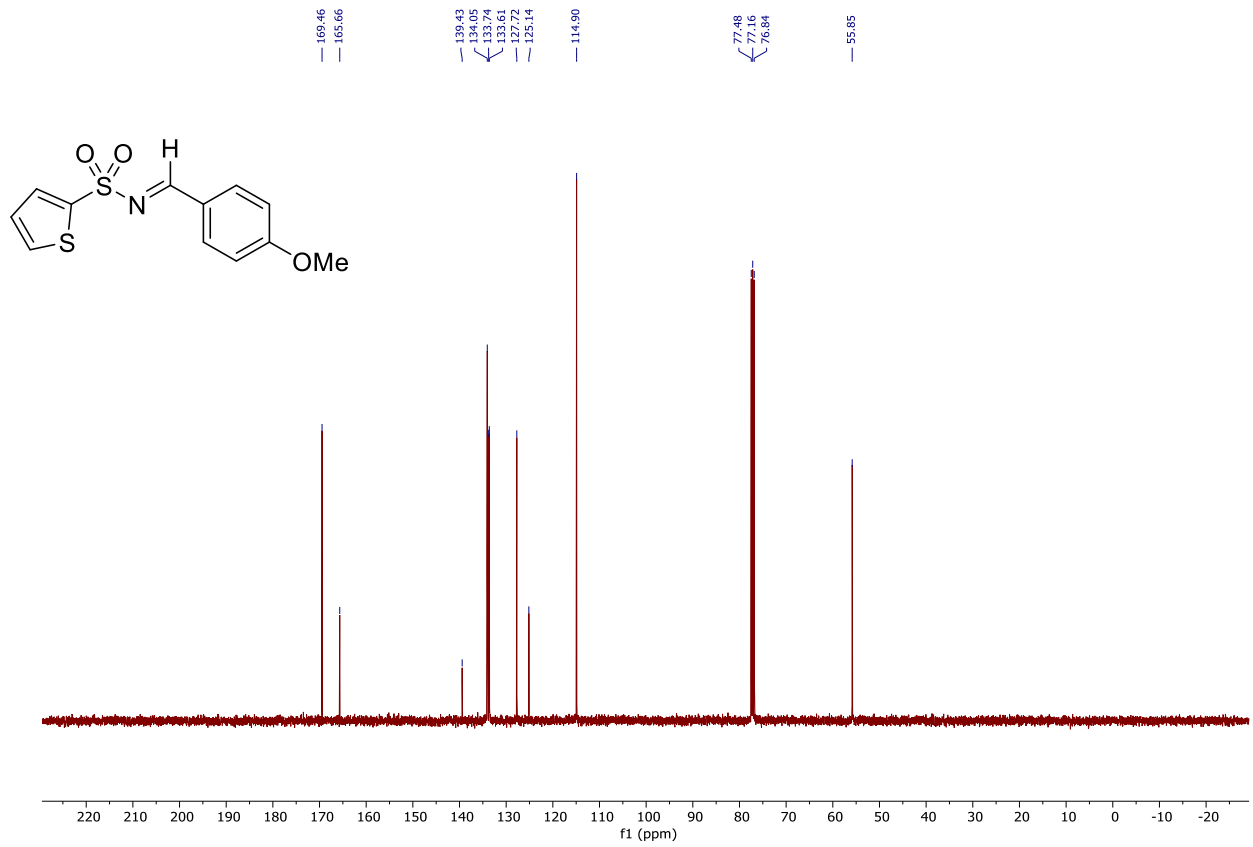
**Phenylmethanesulfonamide (108v)**



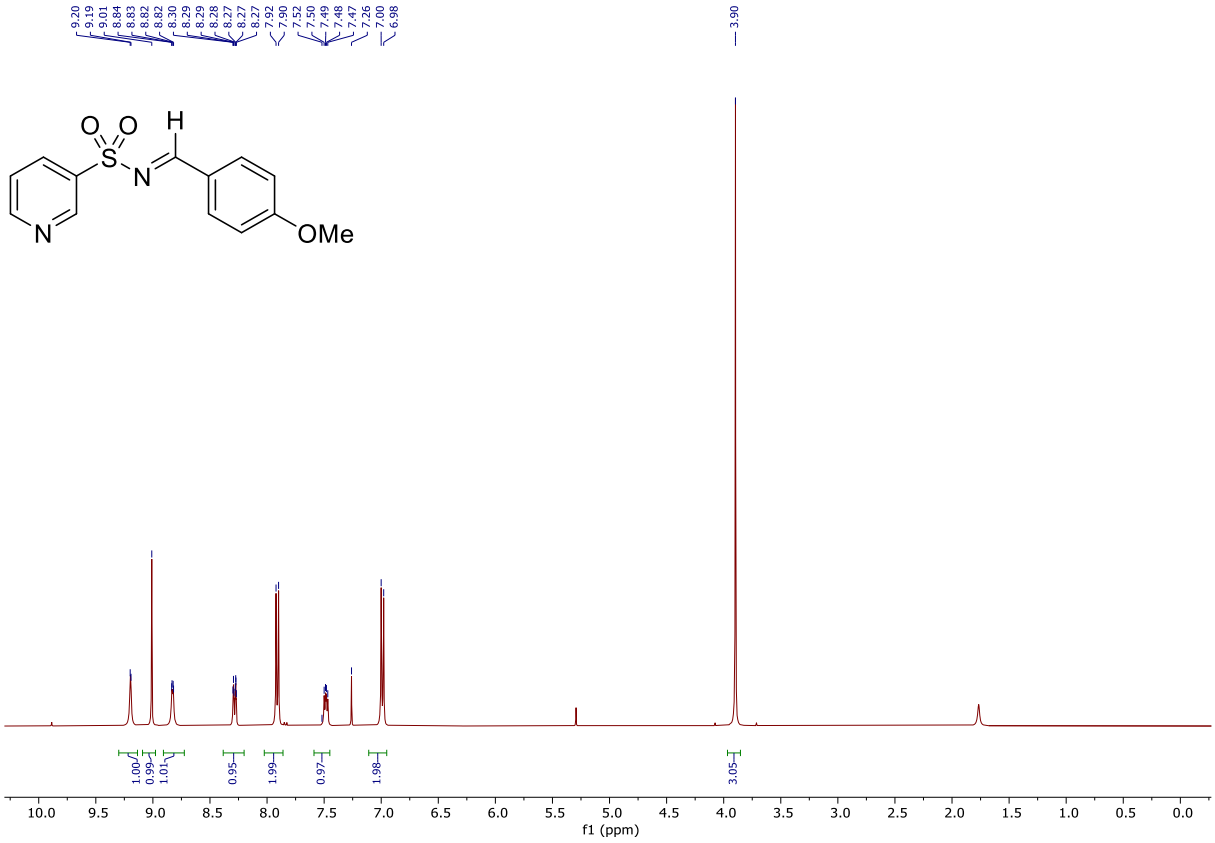



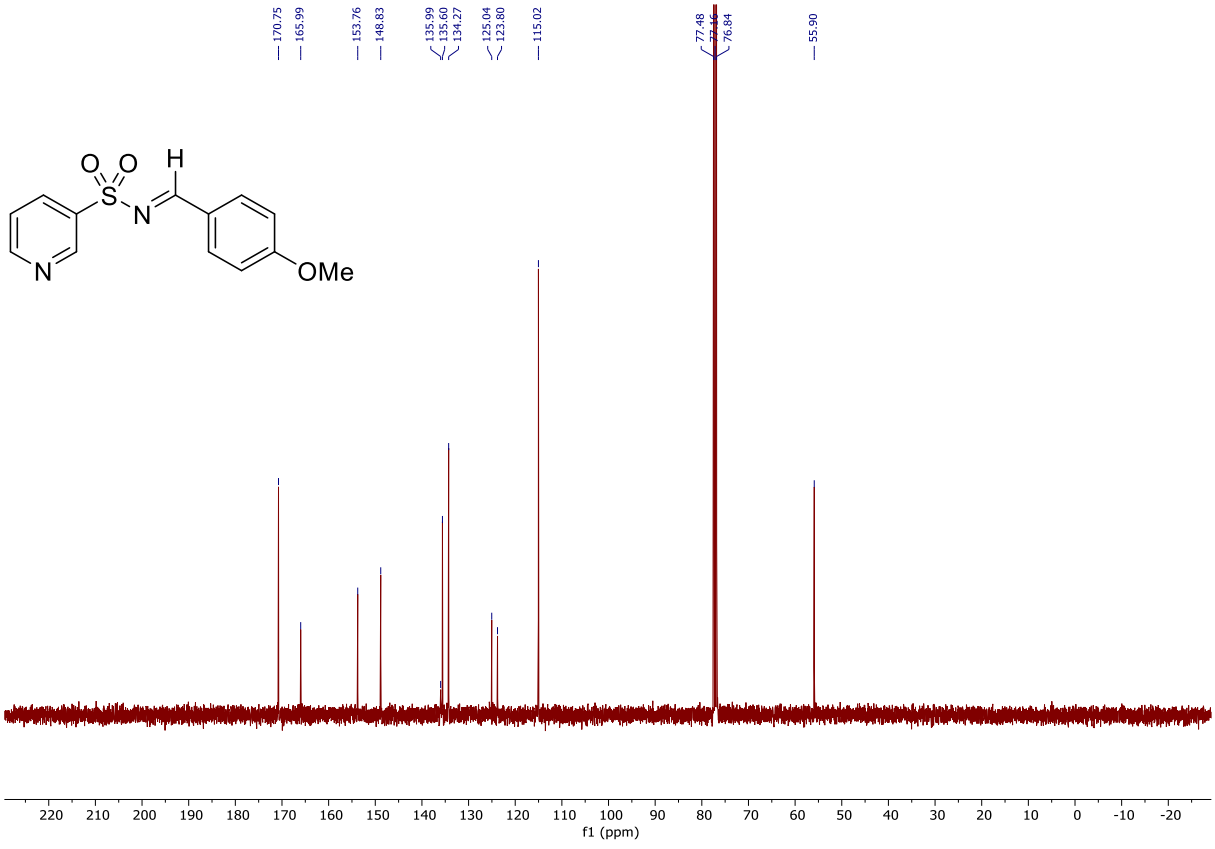
## *N*-(4-methoxybenzylidene)thiophene-2-sulfonamide (108w)



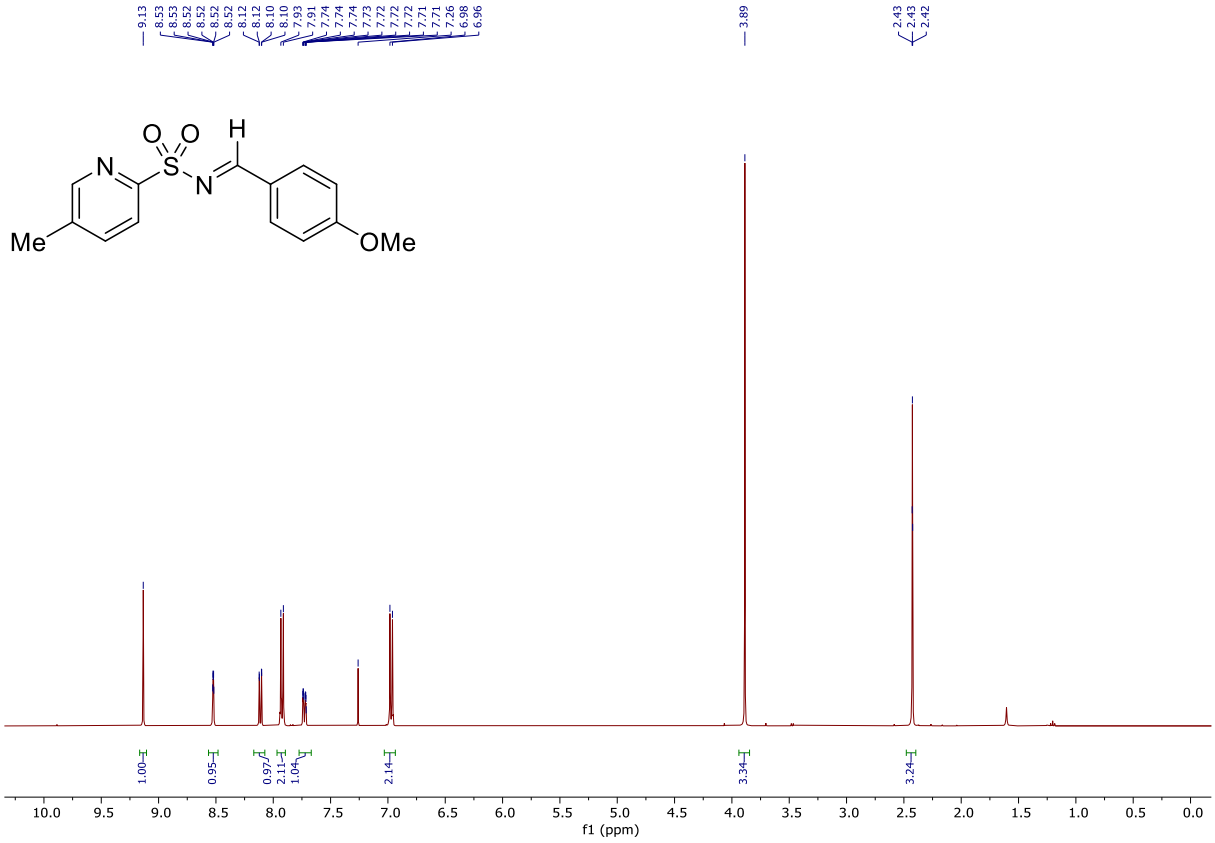



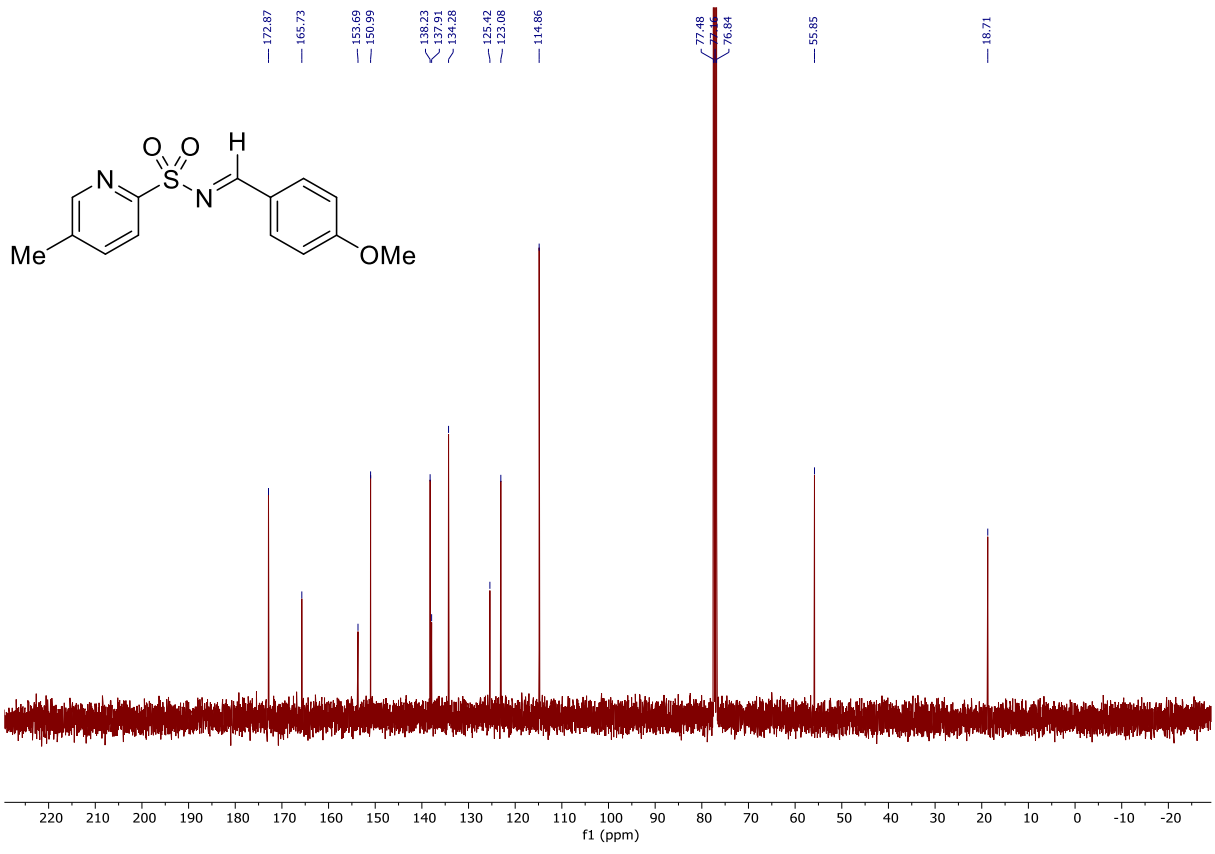
## *N*-(4-methoxybenzylidene)pyridine-3-sulfonamide (108x)



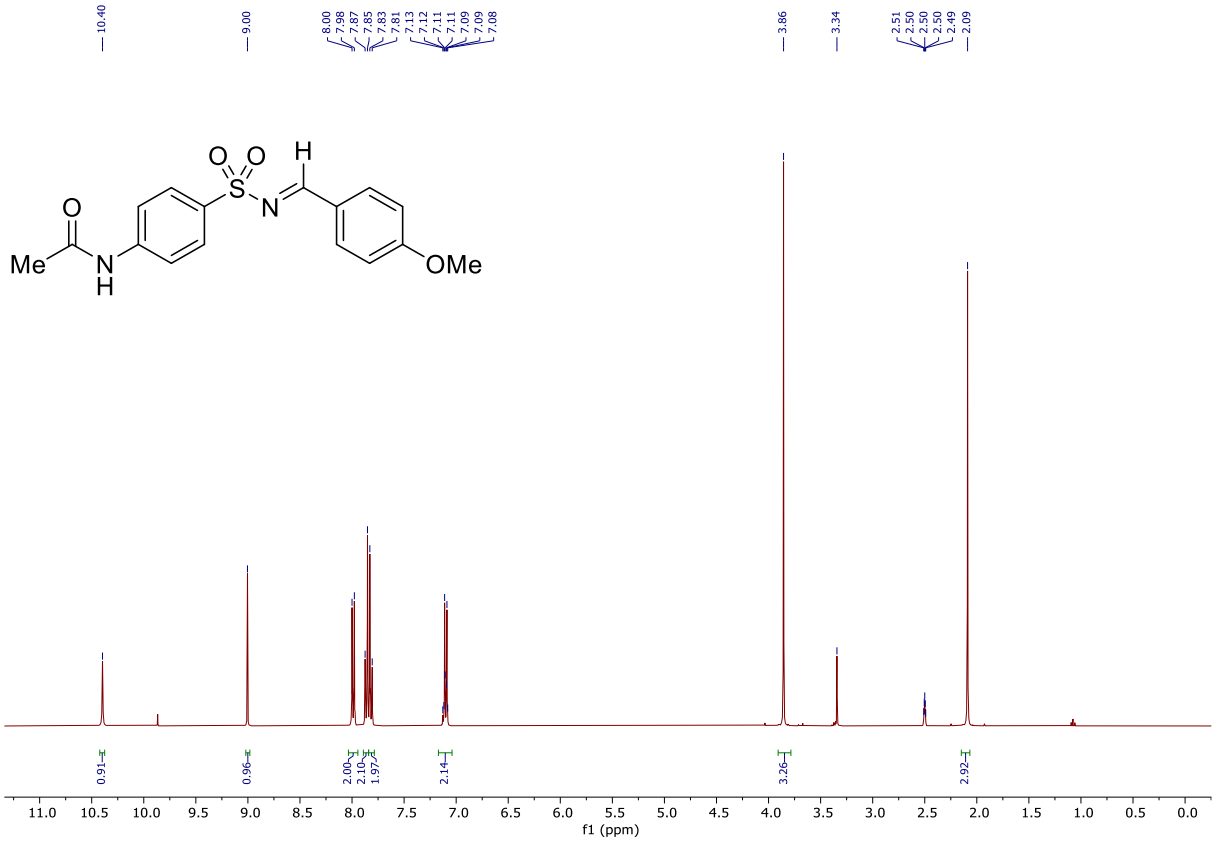



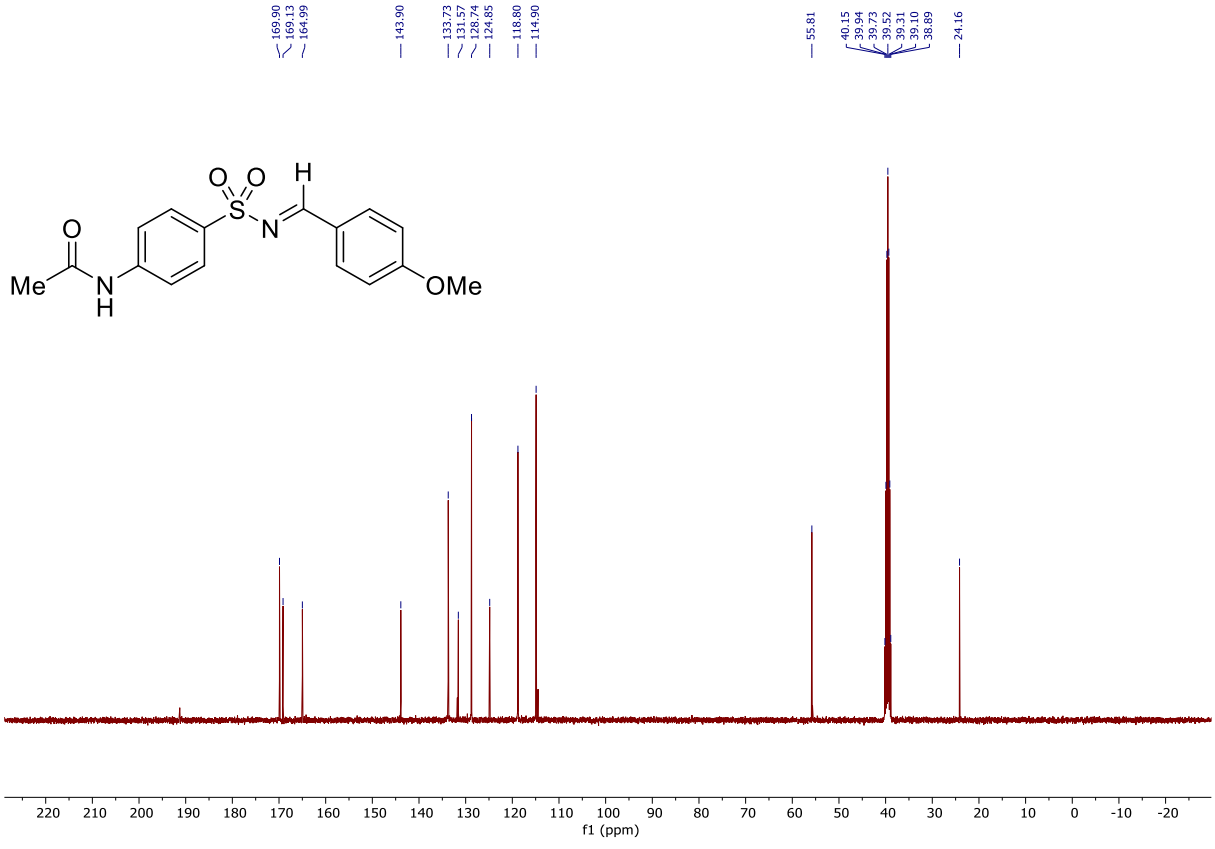
## *N*-(4-methoxybenzylidene)-5-methylpyridine-2-sulfonamide (108y)



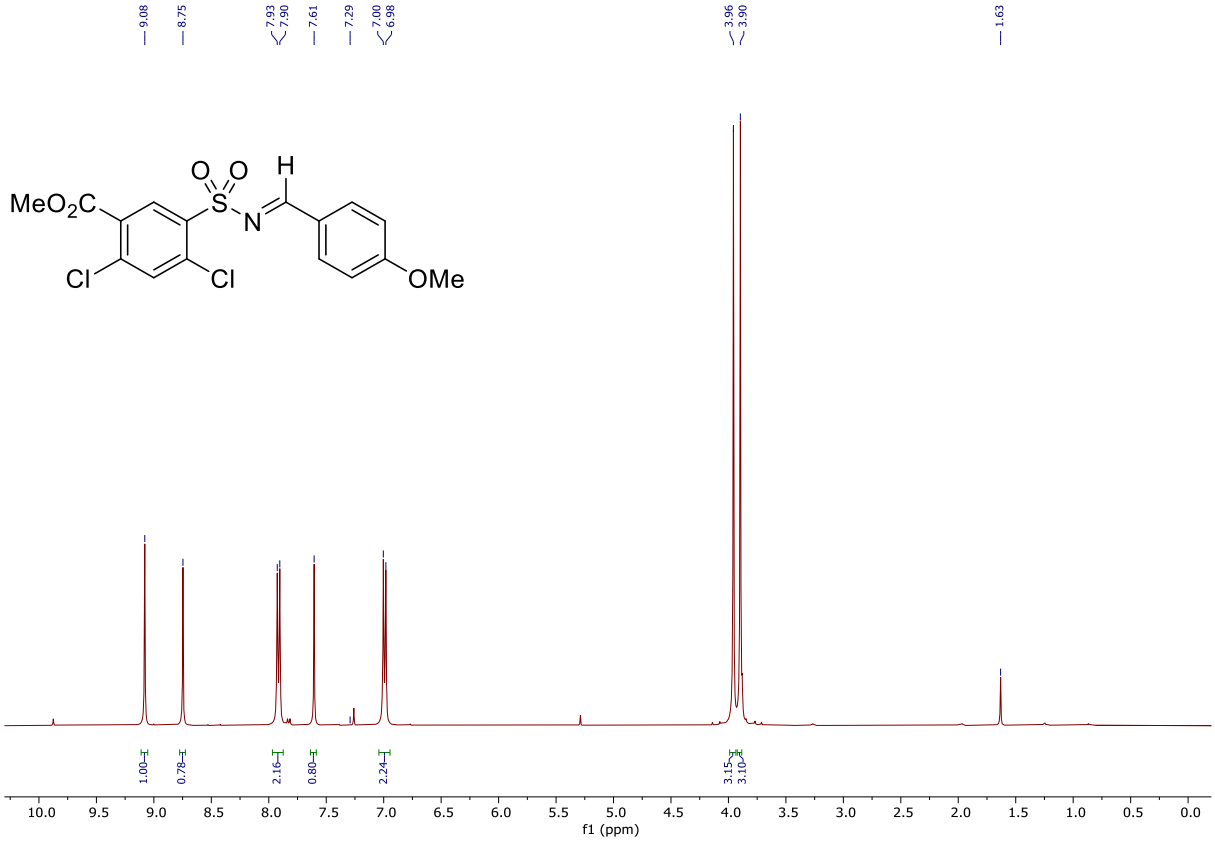



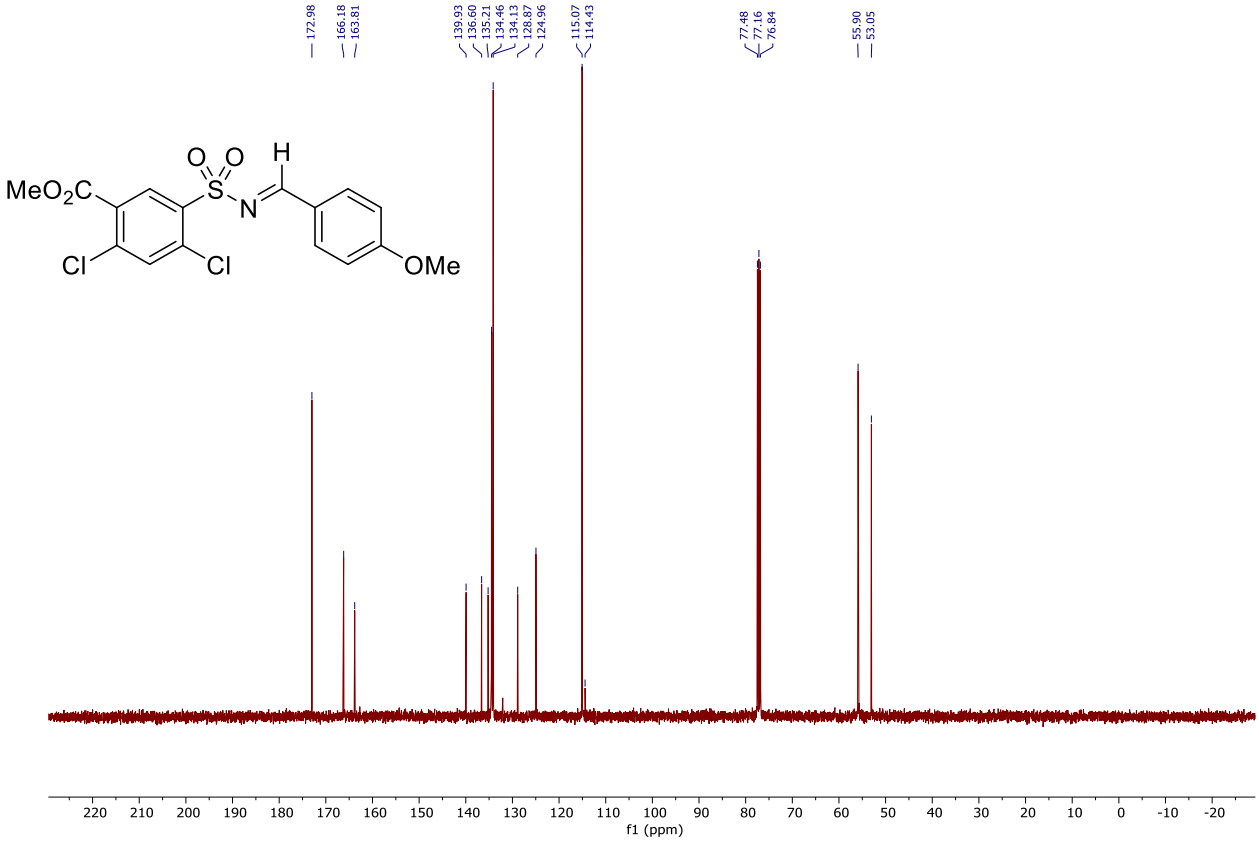
## *N*-(4-(N-(4-methoxybenzylidene)sulfamoyl)phenyl)acetamide (108z)



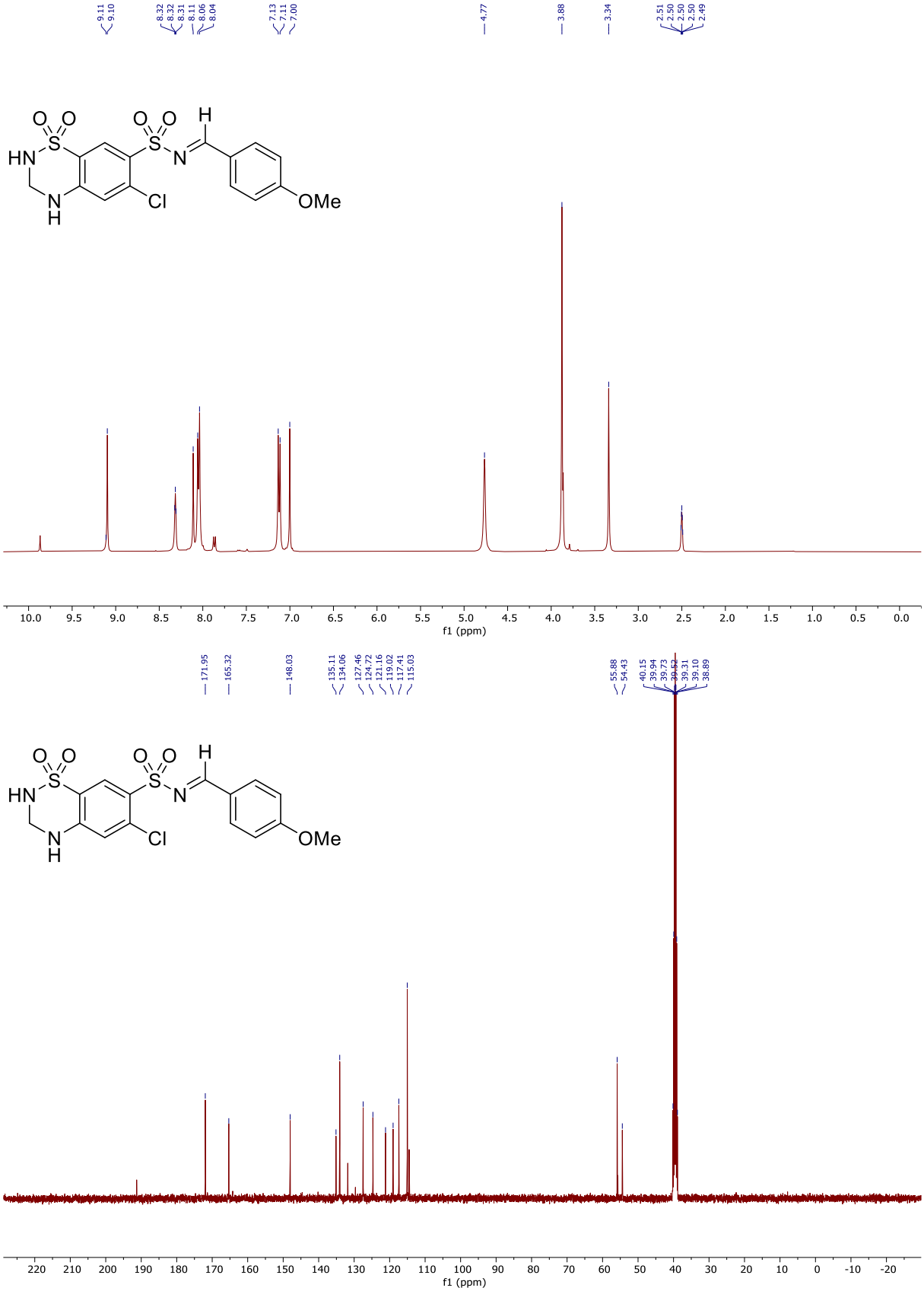



**Methyl 2,4-dichloro-5-(N-(4-methoxybenzylidene)sulfamoyl)benzoate (128a)**

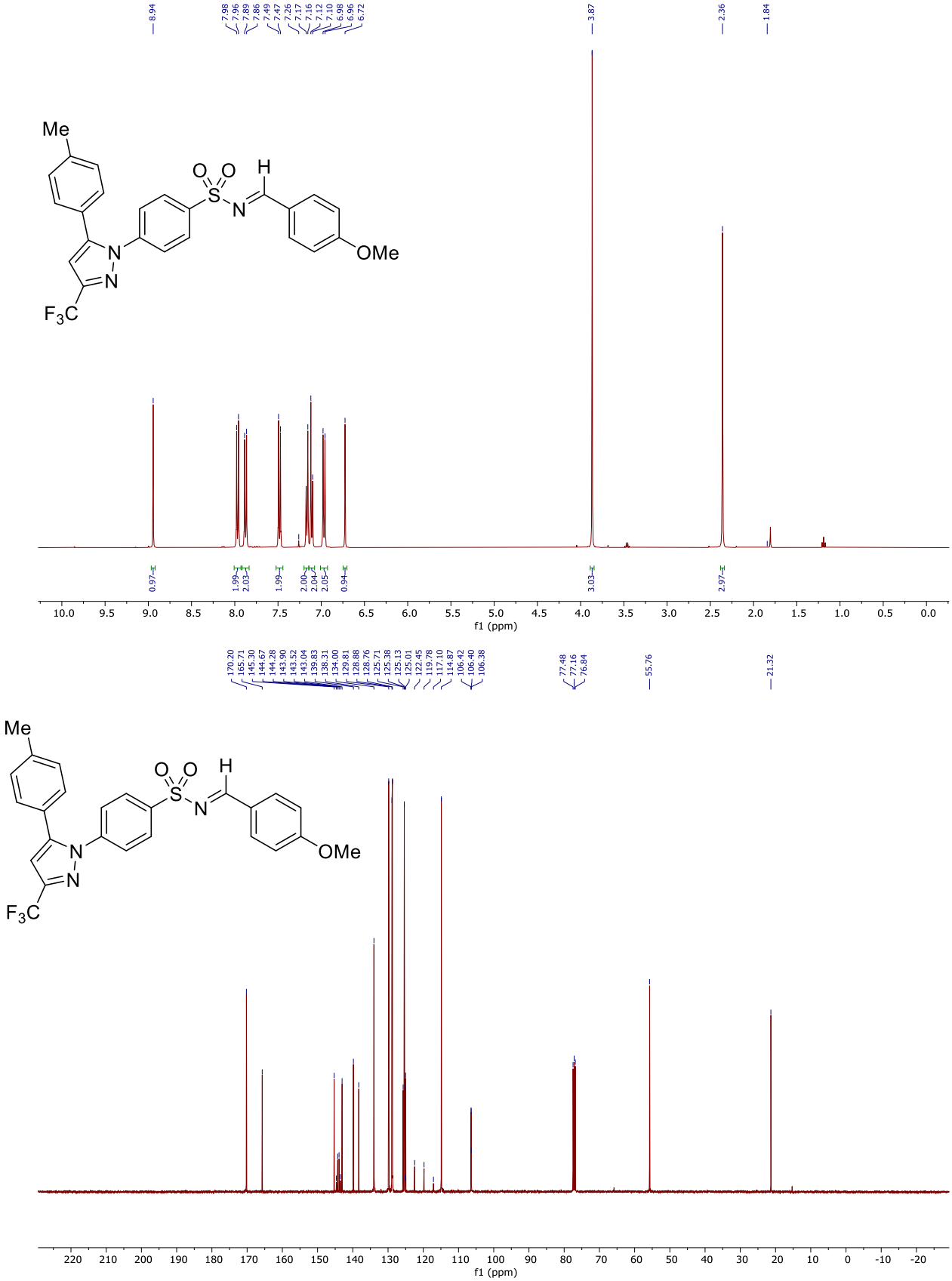


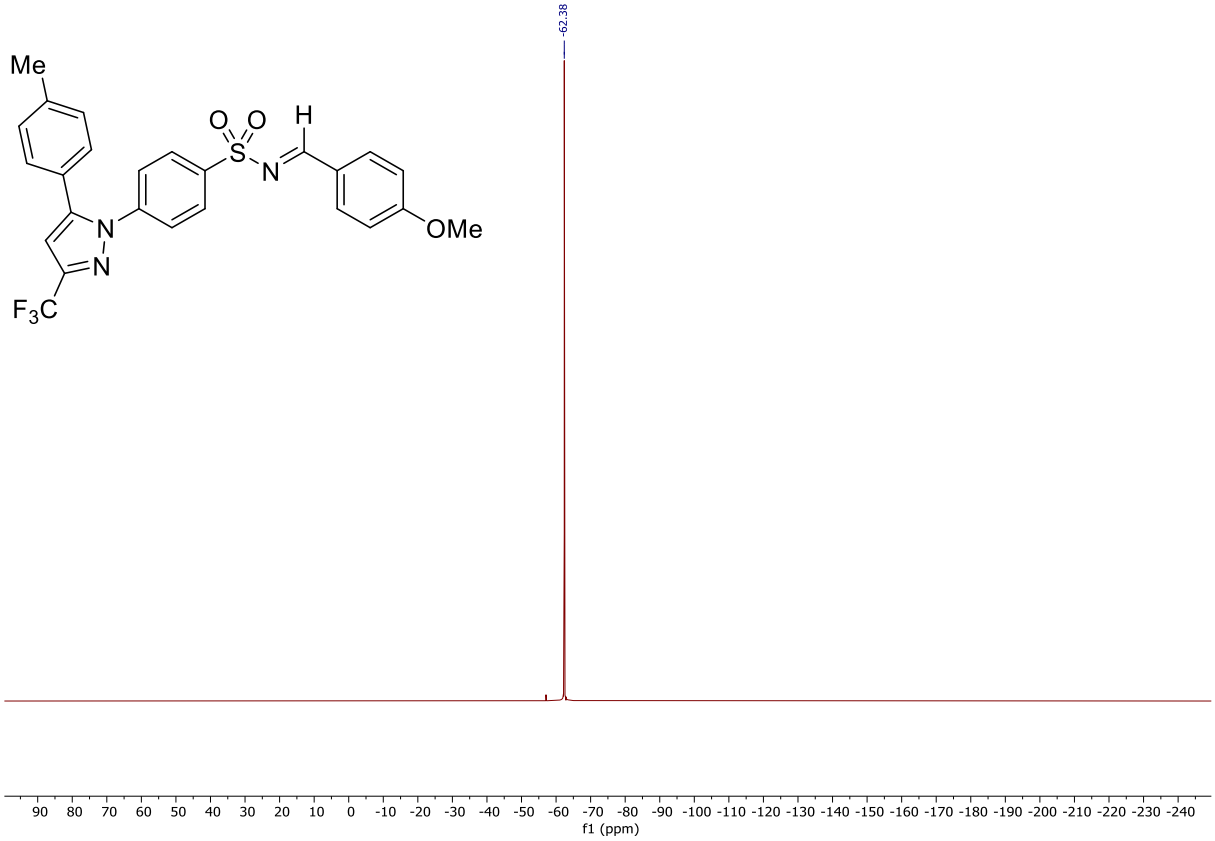



**6-Chloro-*N*-(4-methoxybenzylidene)-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazine-7-sulfonamide 1,1-dioxide (128b)**

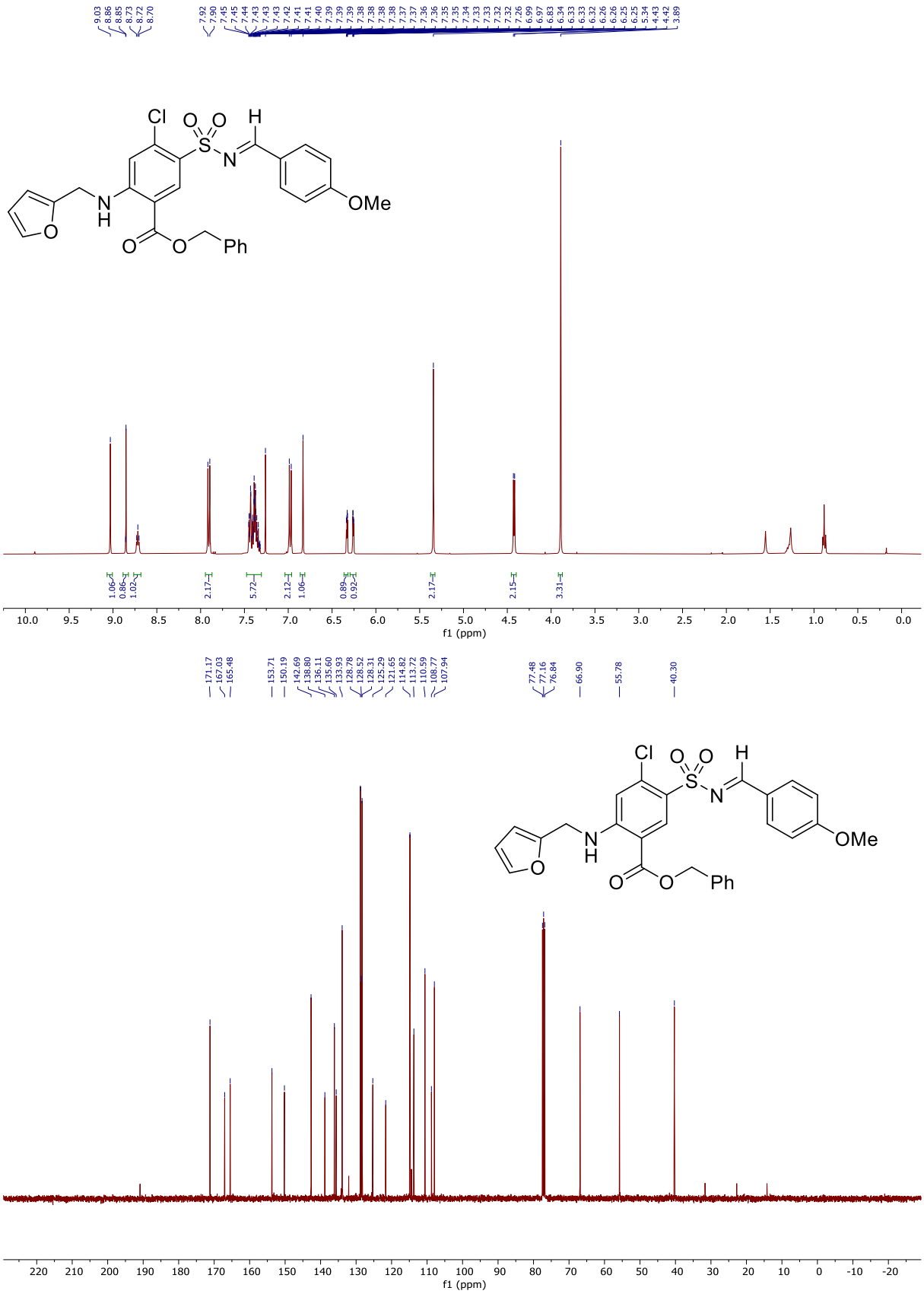


**N-(4-methoxybenzylidene)-4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide (128c)**

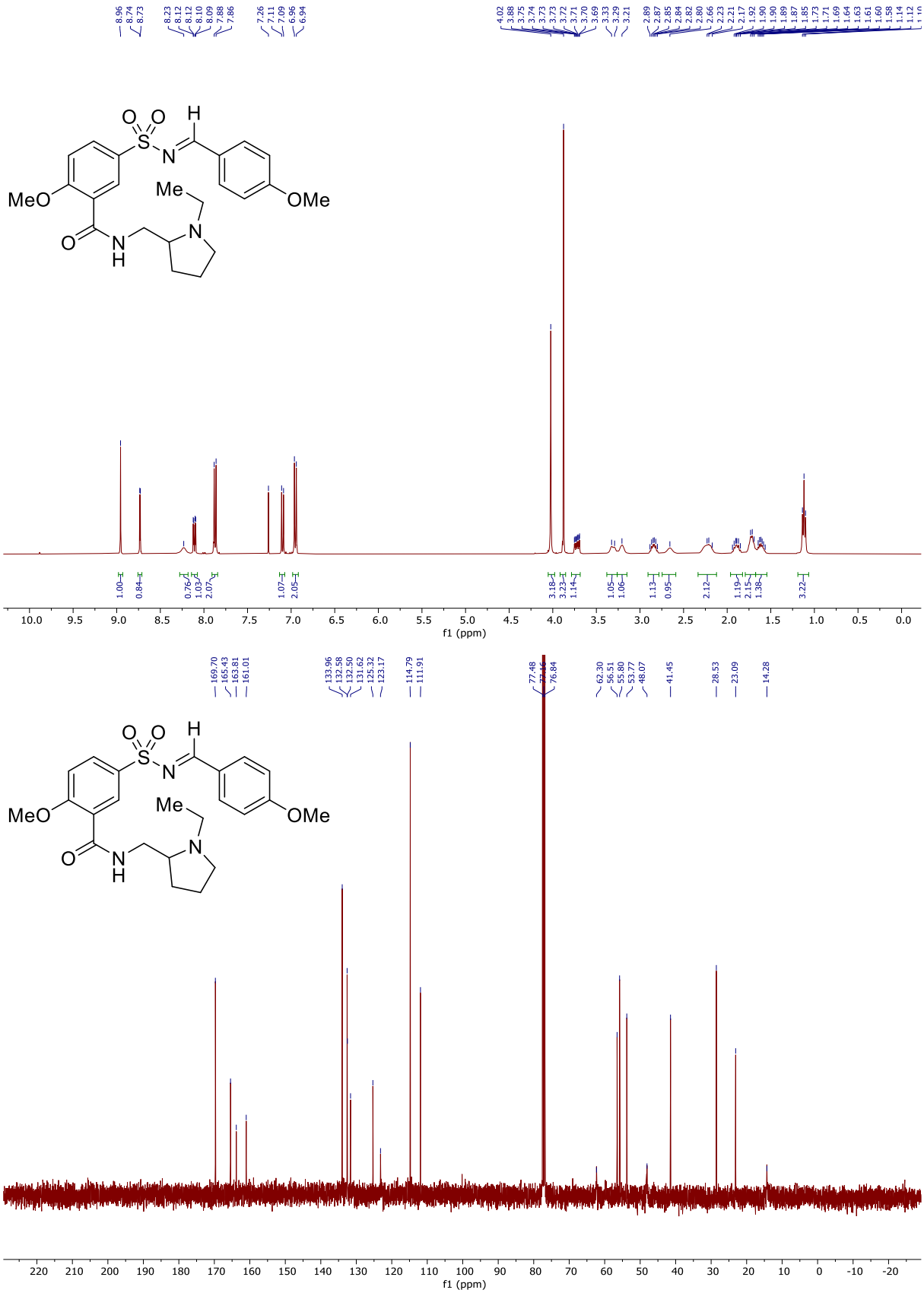



-62.38
Me
O
O
S
N
H
OMe
N
N
F3C
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

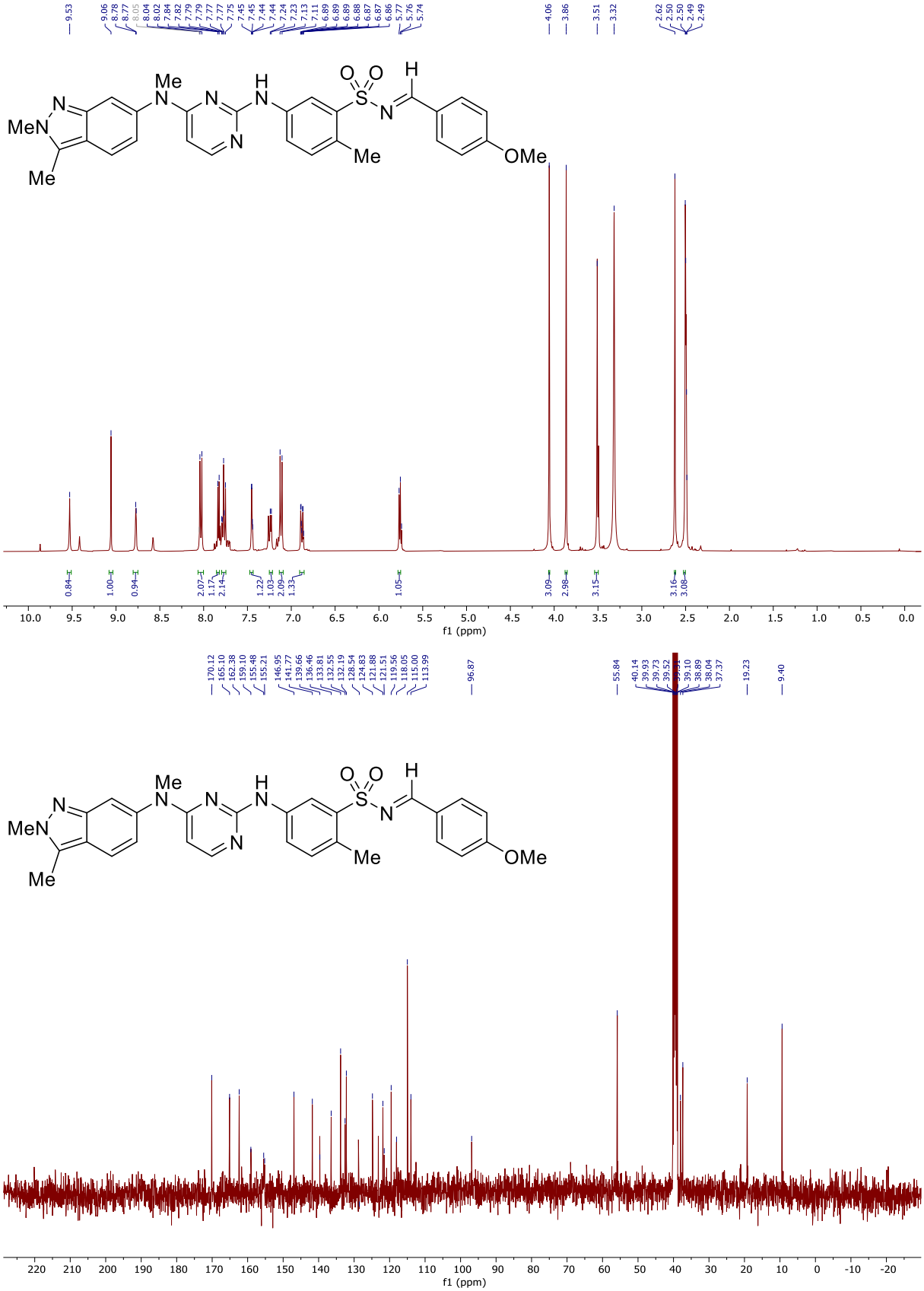
**Benzyl (4-chloro-2-(furan-2-ylmethyl)-5-(*N*-(4-methoxybenzylidene)sulfamoyl)benzoate (128d)**



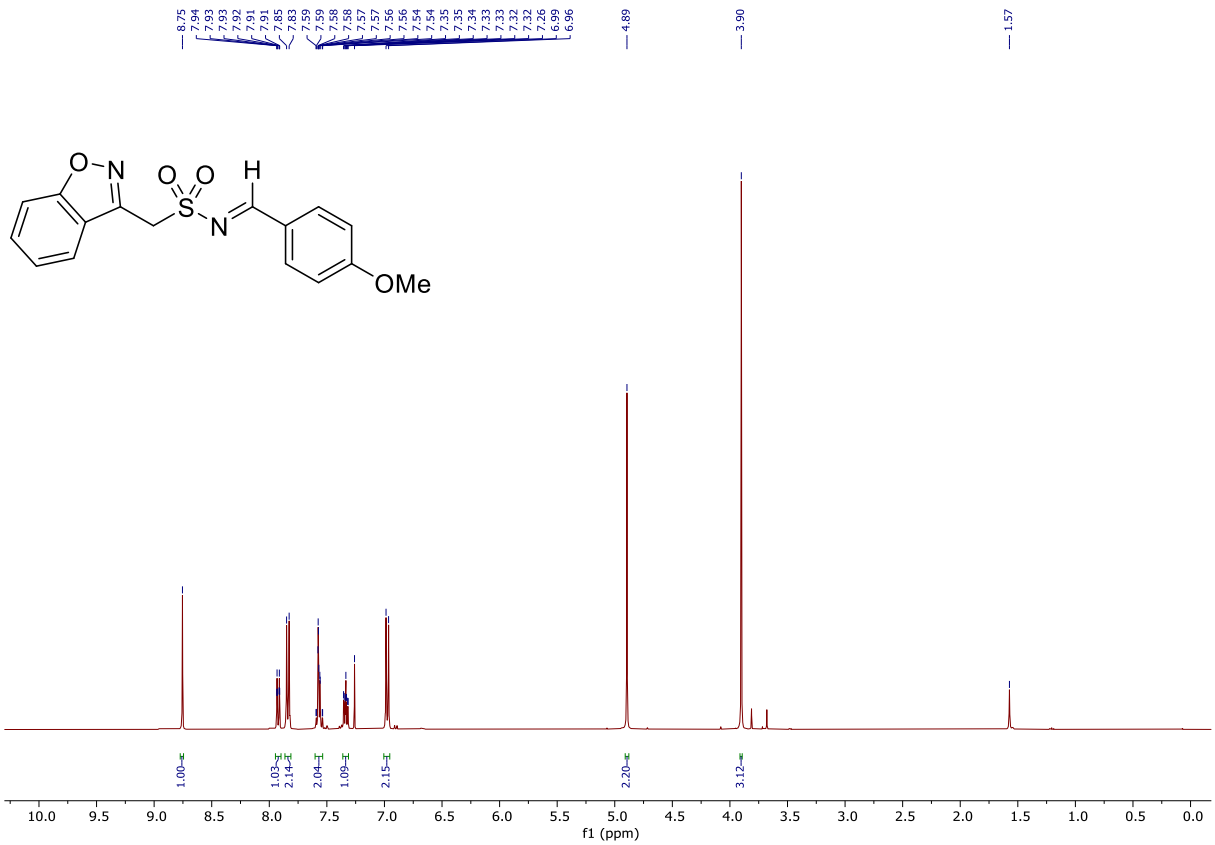
**N-((1-ethylpyrrolidin-2-yl)methyl)-2-methoxy-5-(N-(4-methoxybenzylidene)sulfamoyl)benzamide (128e)**

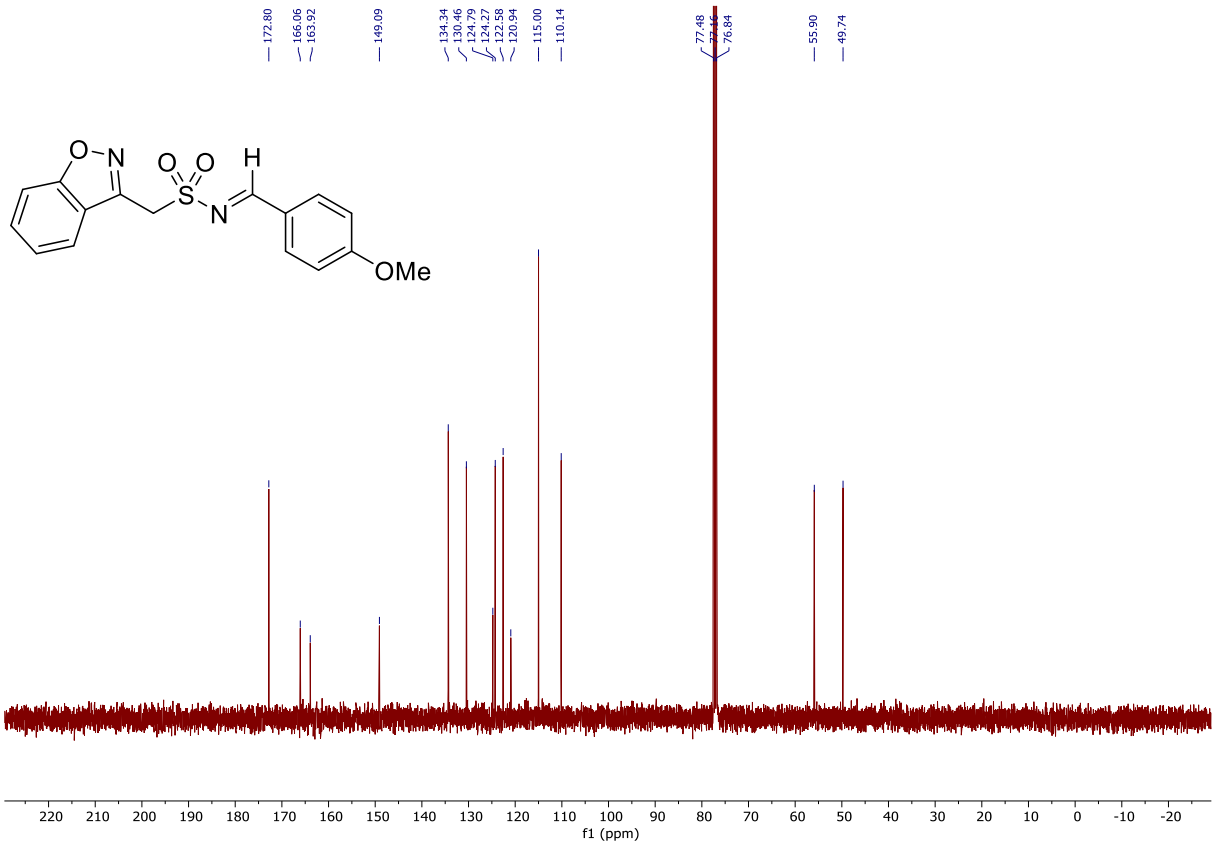


**5-((4-((2,3-dimethyl-2*H*-indazol-6-yl)(methyl)amino)pyrimidin-2-yl)amino)-*N*-(4-methoxybenzylidene)-2-methylbenzenesulfonamidemethanesulfonamide (128f)**

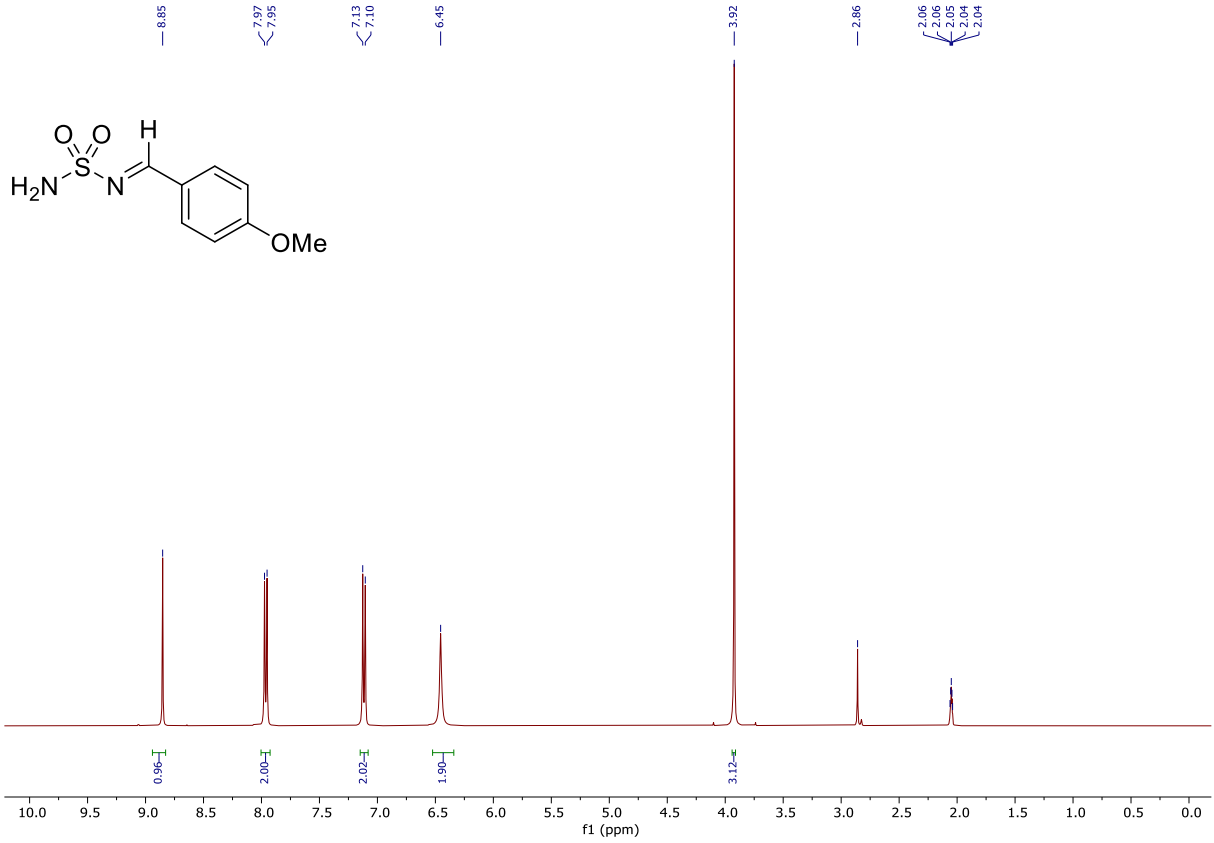


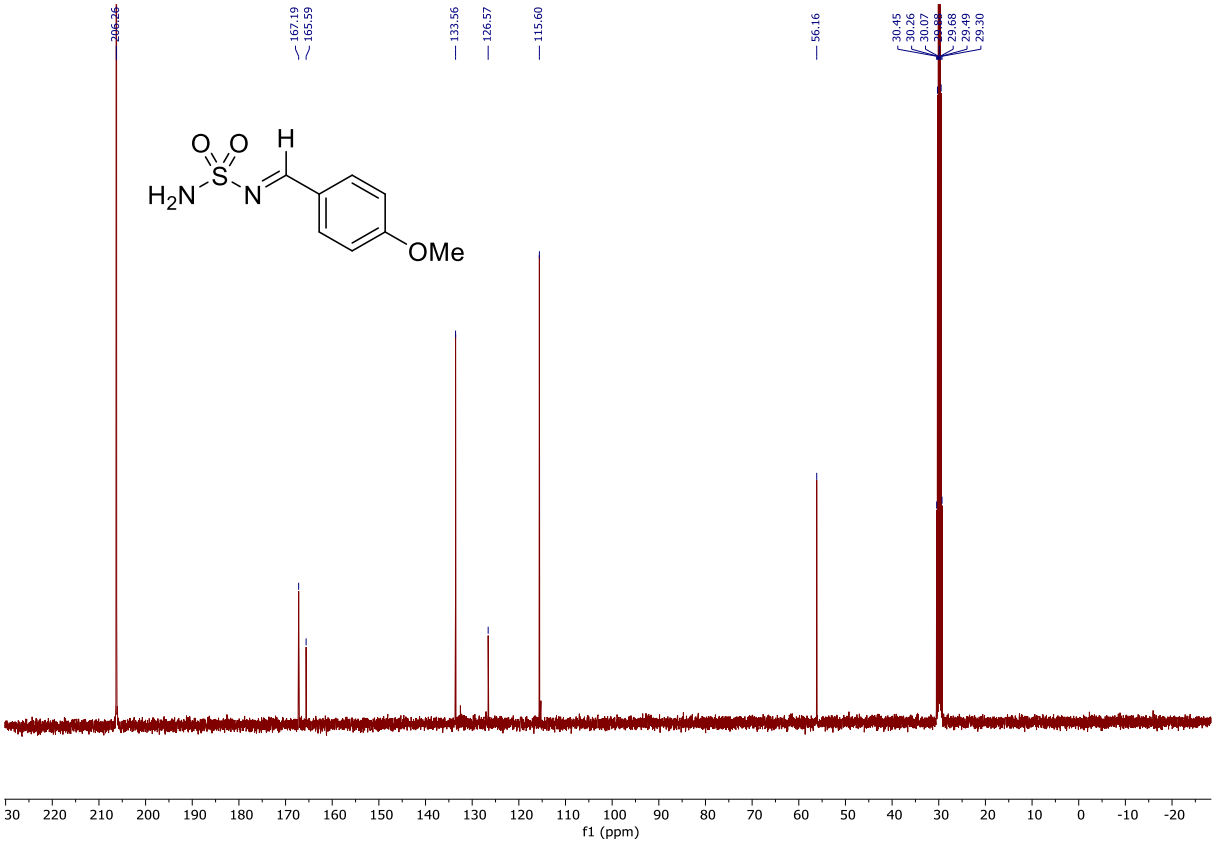
## 1-(Benzo[d]isoxazol-3-yl)-N-(4-methoxybenzylidene)methanesulfonamide (128g)



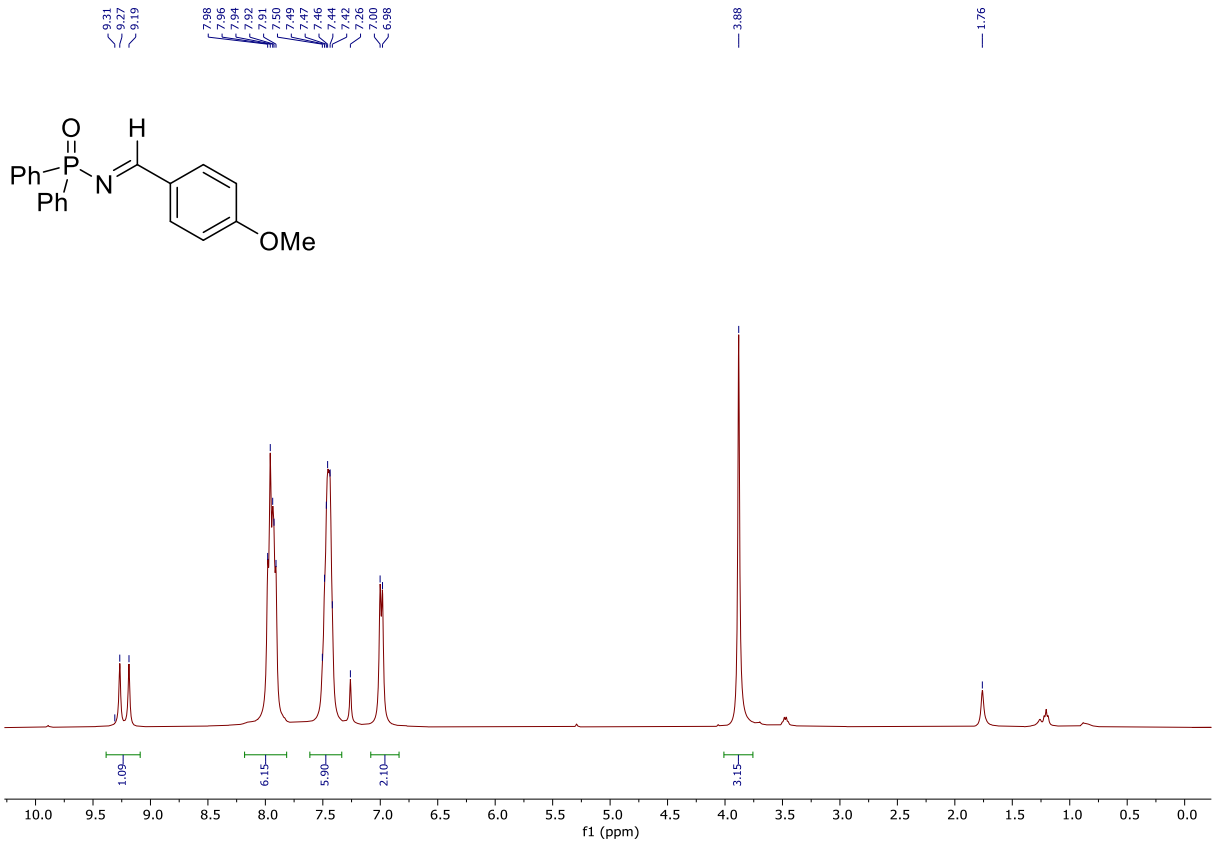



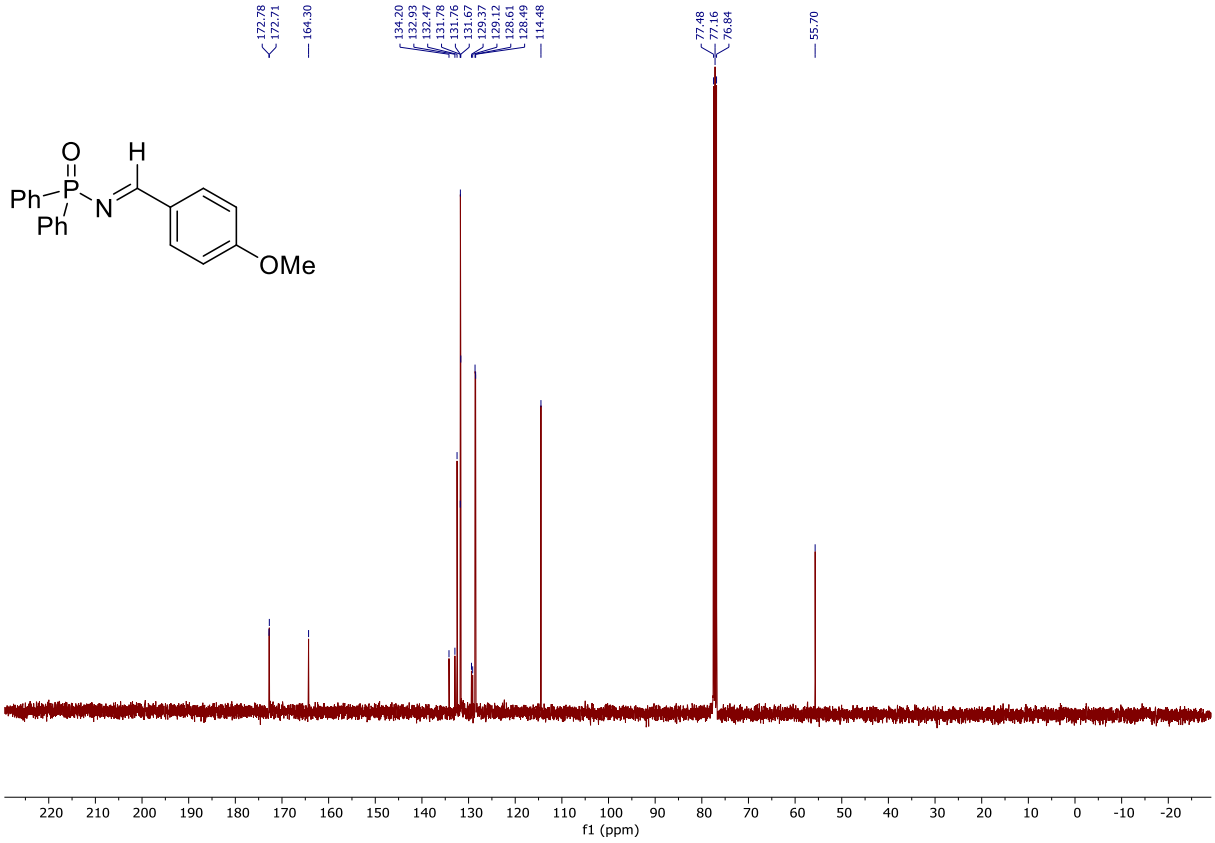
**4-methoxybenzylidenesulfamide (113a)**

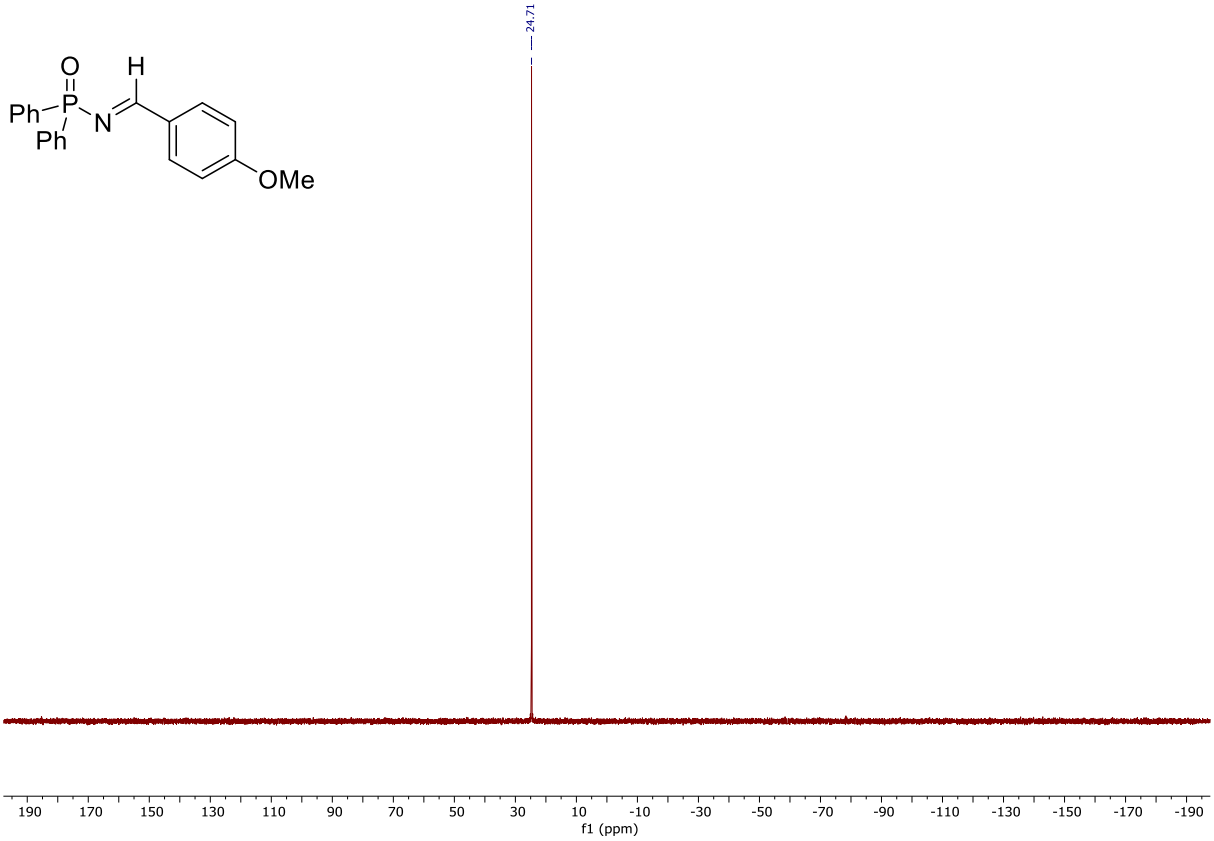


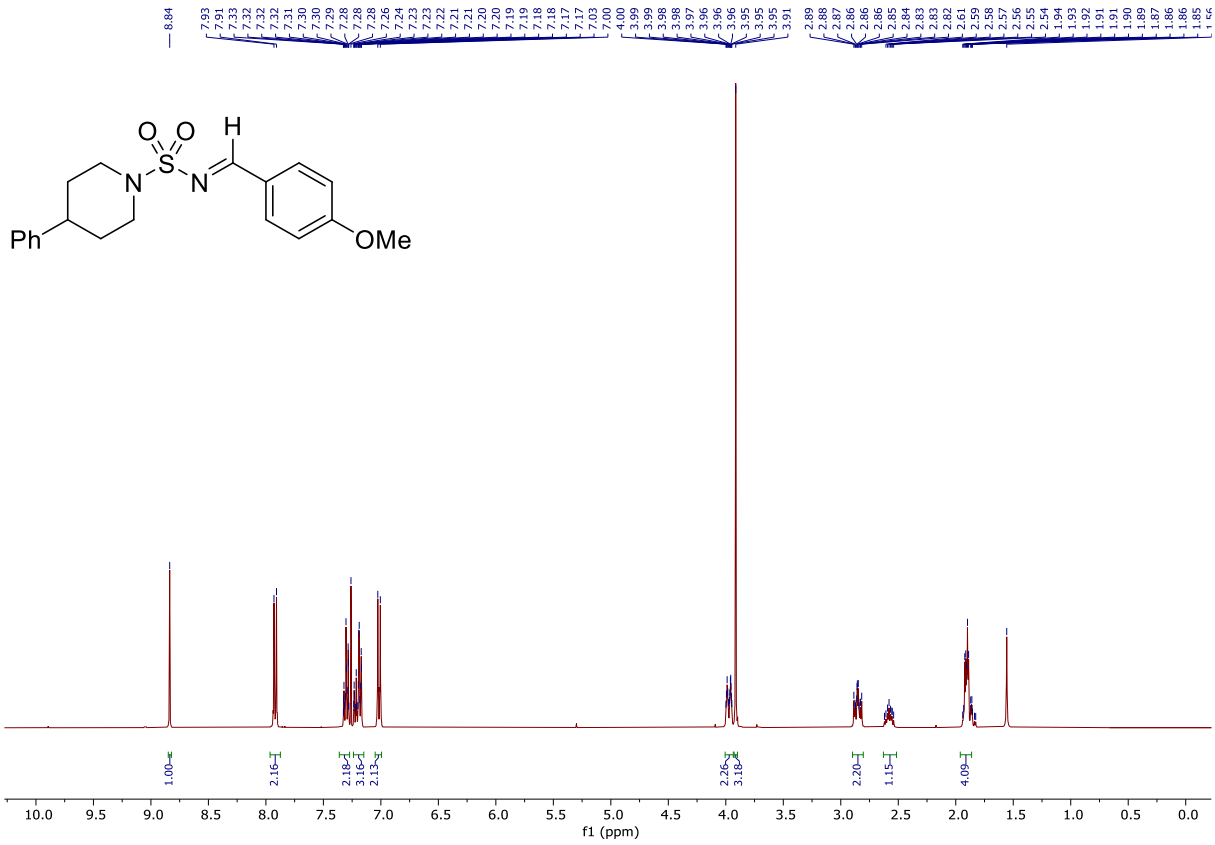
## *N*-(4-methoxybenzylidene)-*P*,*P*-diphenylphosphinic amide (114)

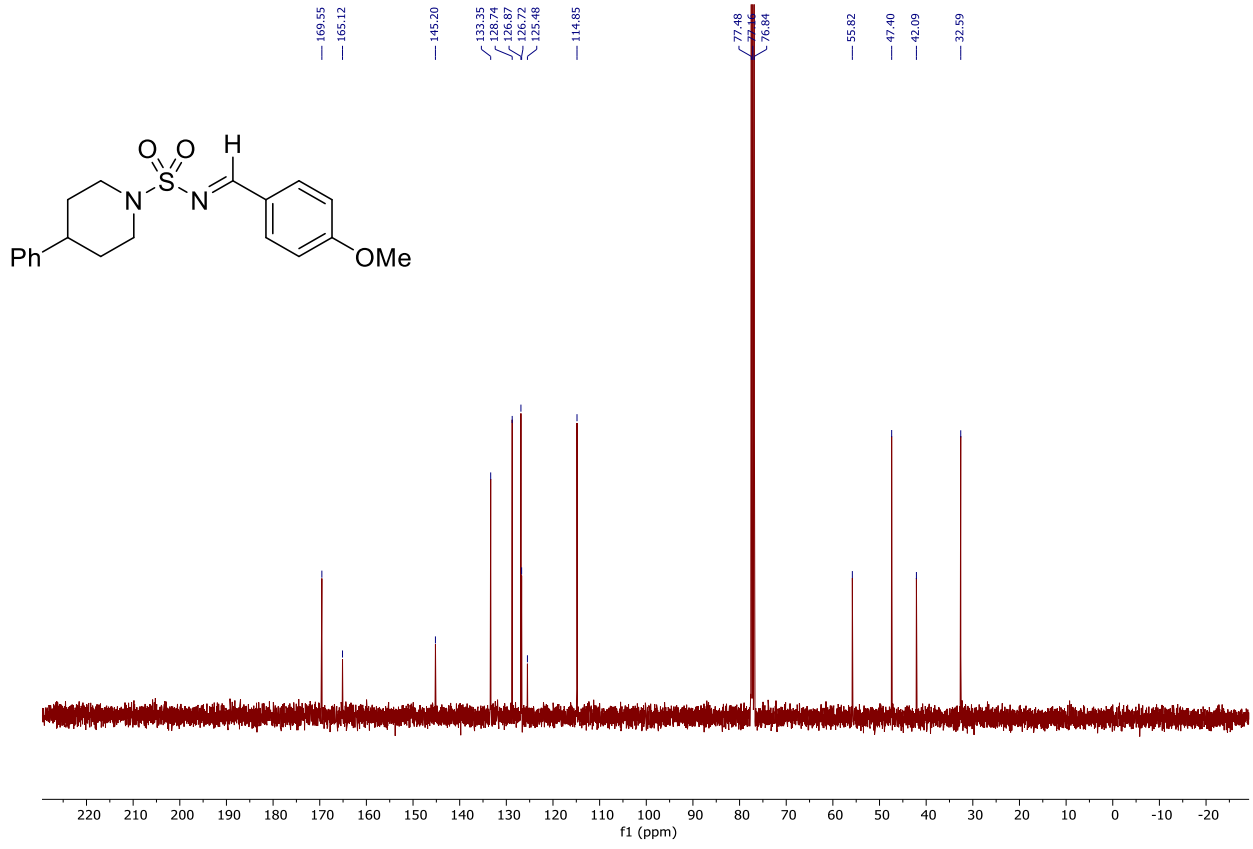


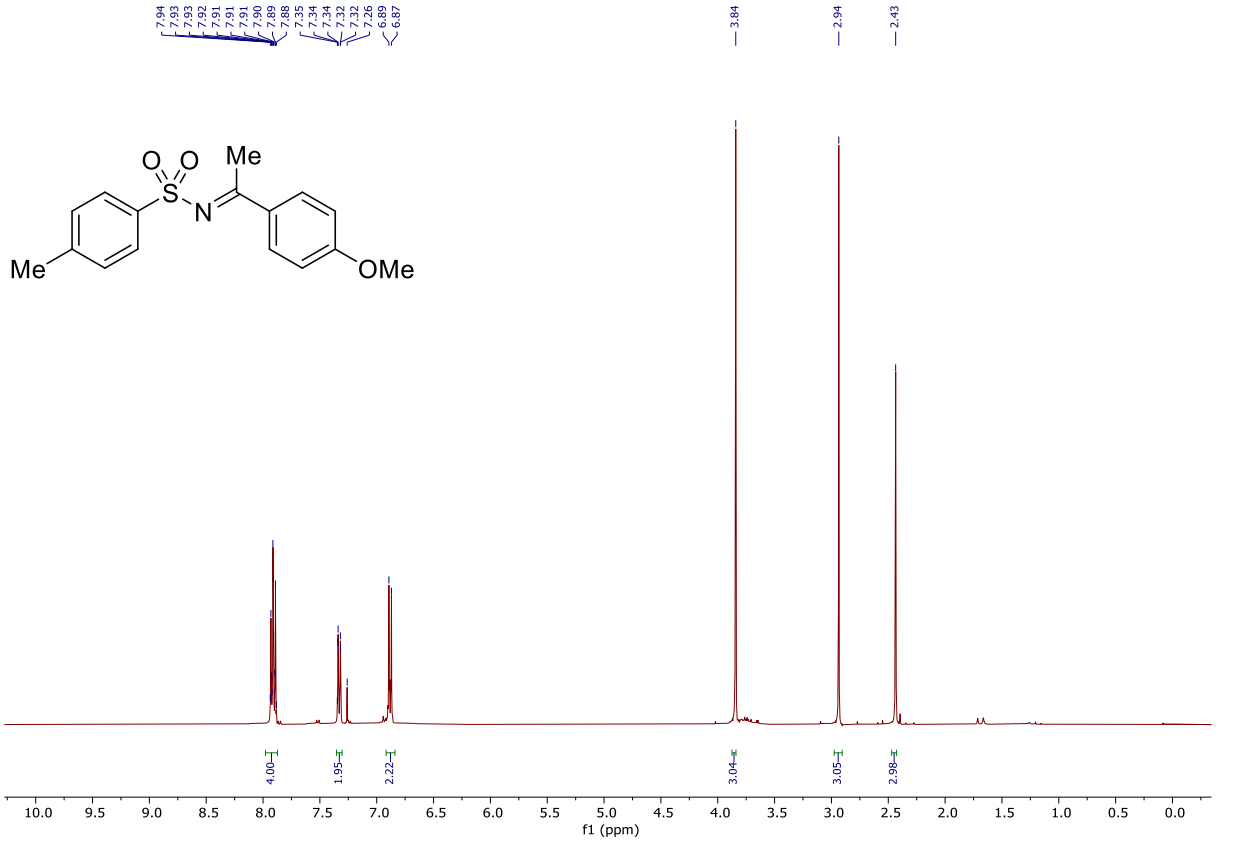

O
H
Ph
P
N
Ph
OMe
24.71
190
170
150
130
110
90
70
50
30
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
f1 (ppm)

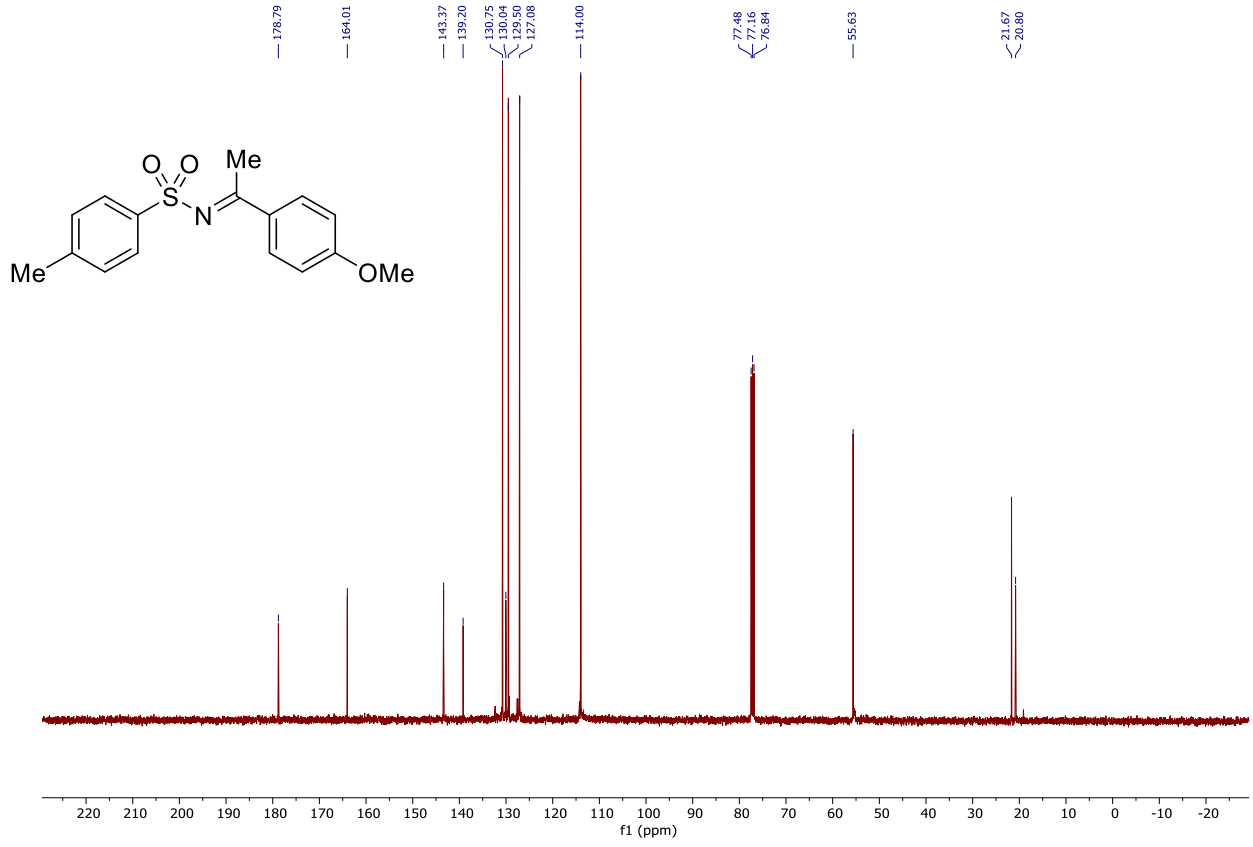
## *N*-(4-methoxybenzylidene)-4-phenylpiperidine-1-sulfonamide (113b)



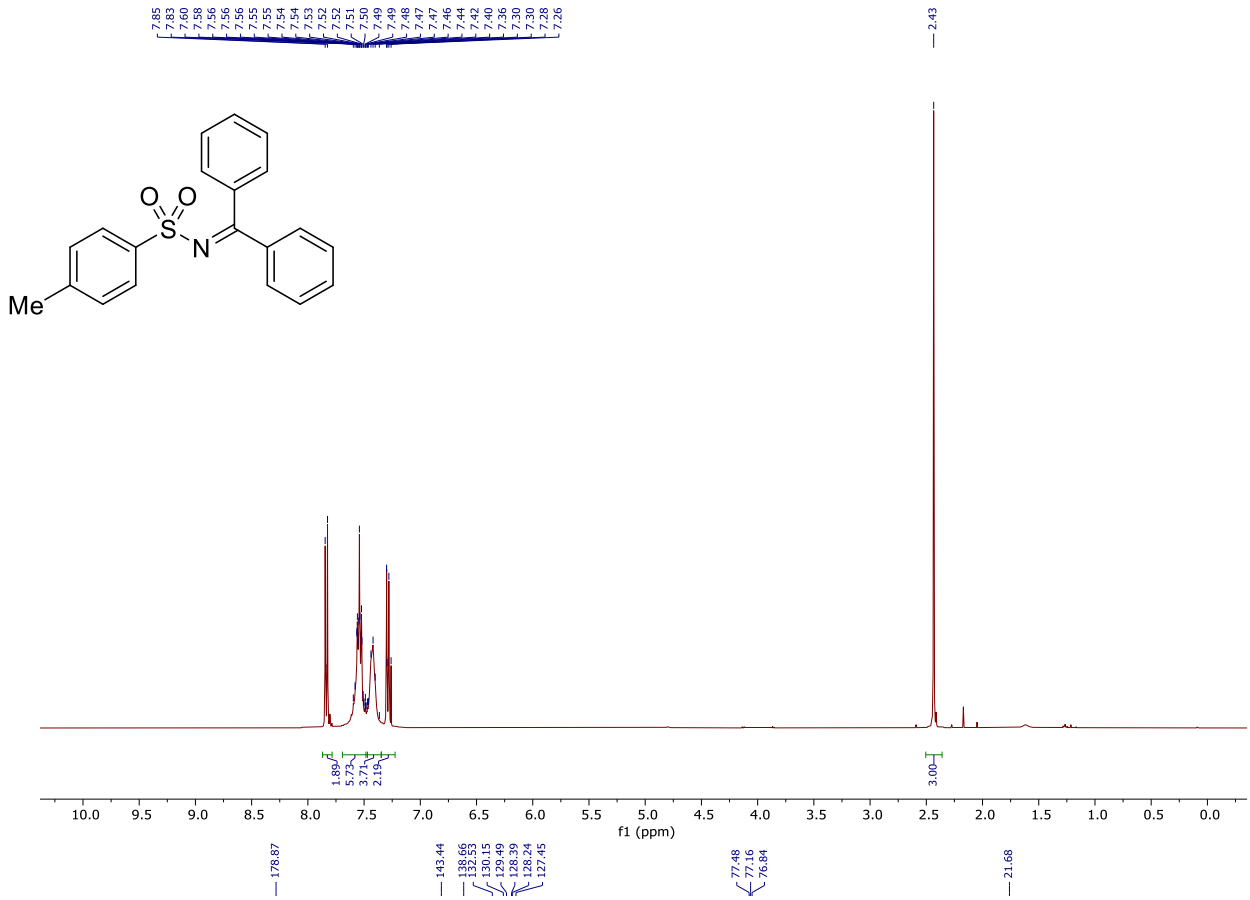



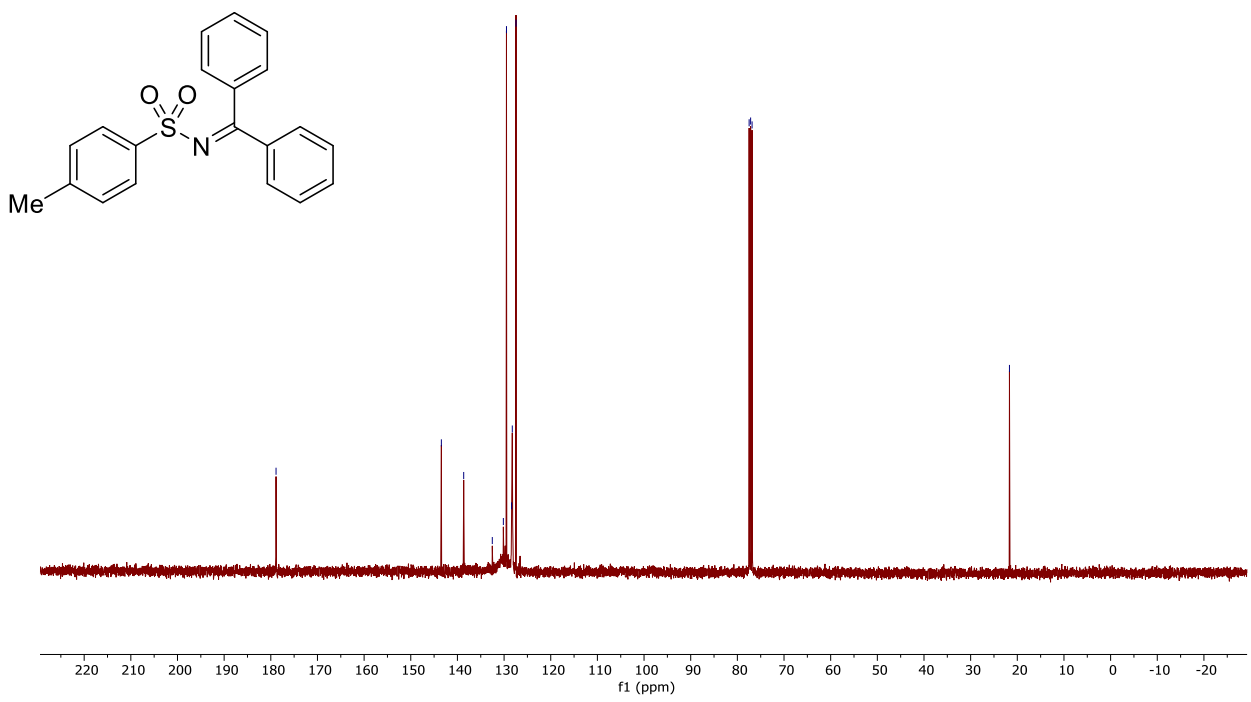
## *N*-(1-(4-methoxyphenyl)ethylidene)-4-methylbenzenesulfonamide (108aq)



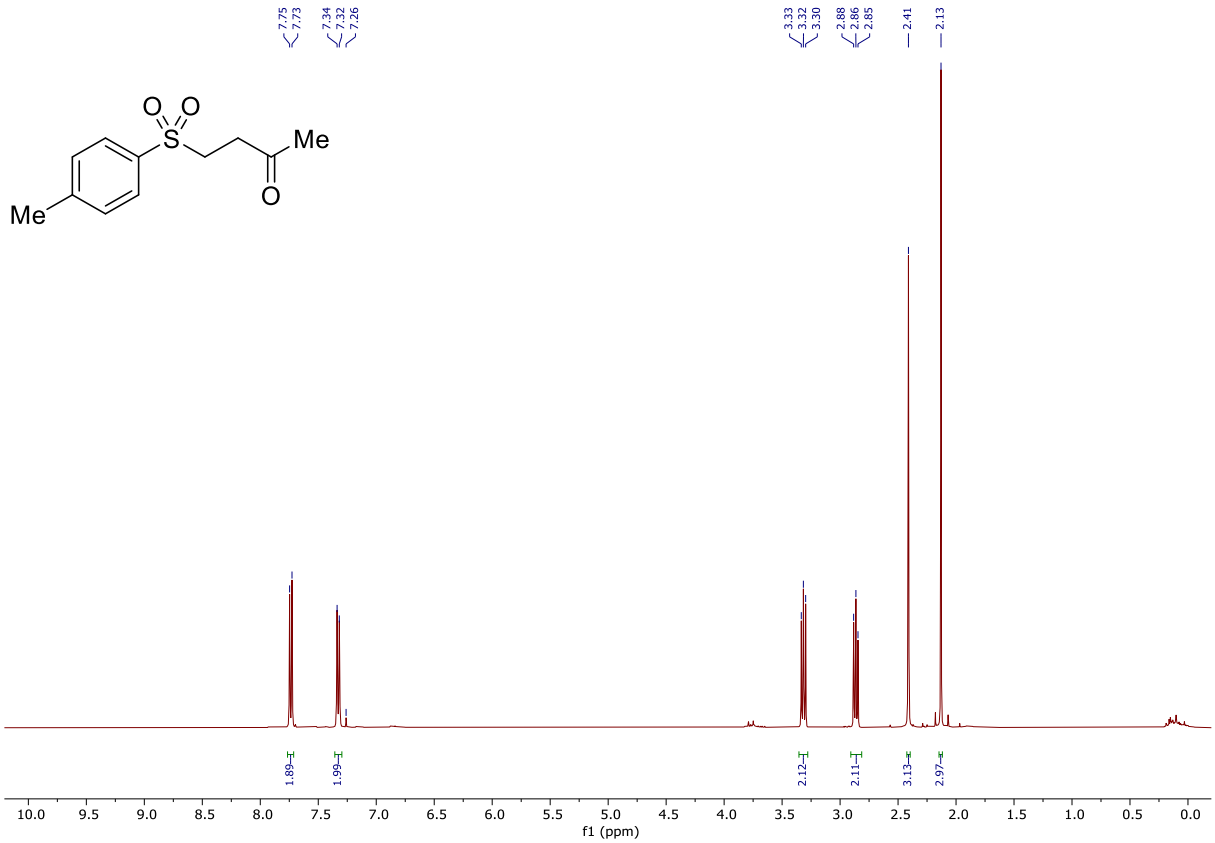



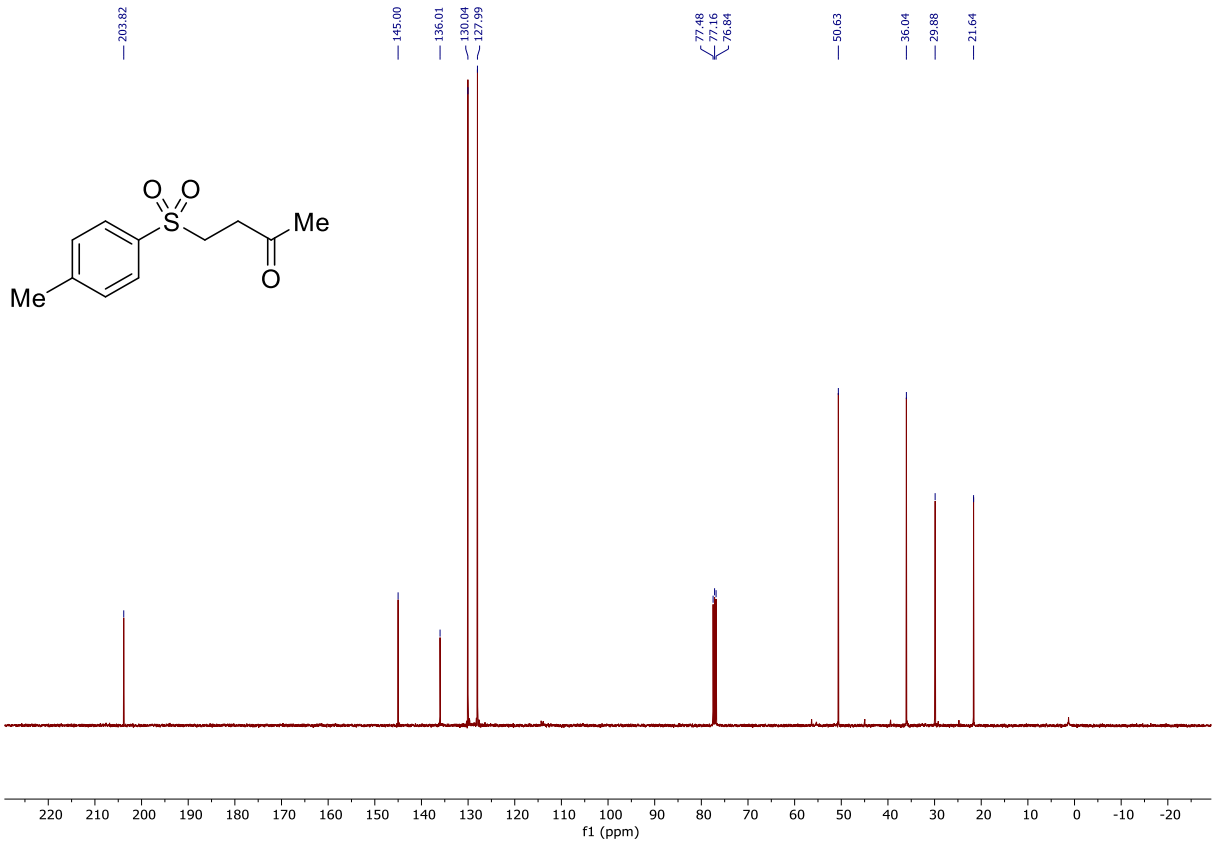
## *N*-(diphenylmethylene)-4-methylbenzenesulfonamide (108ar)



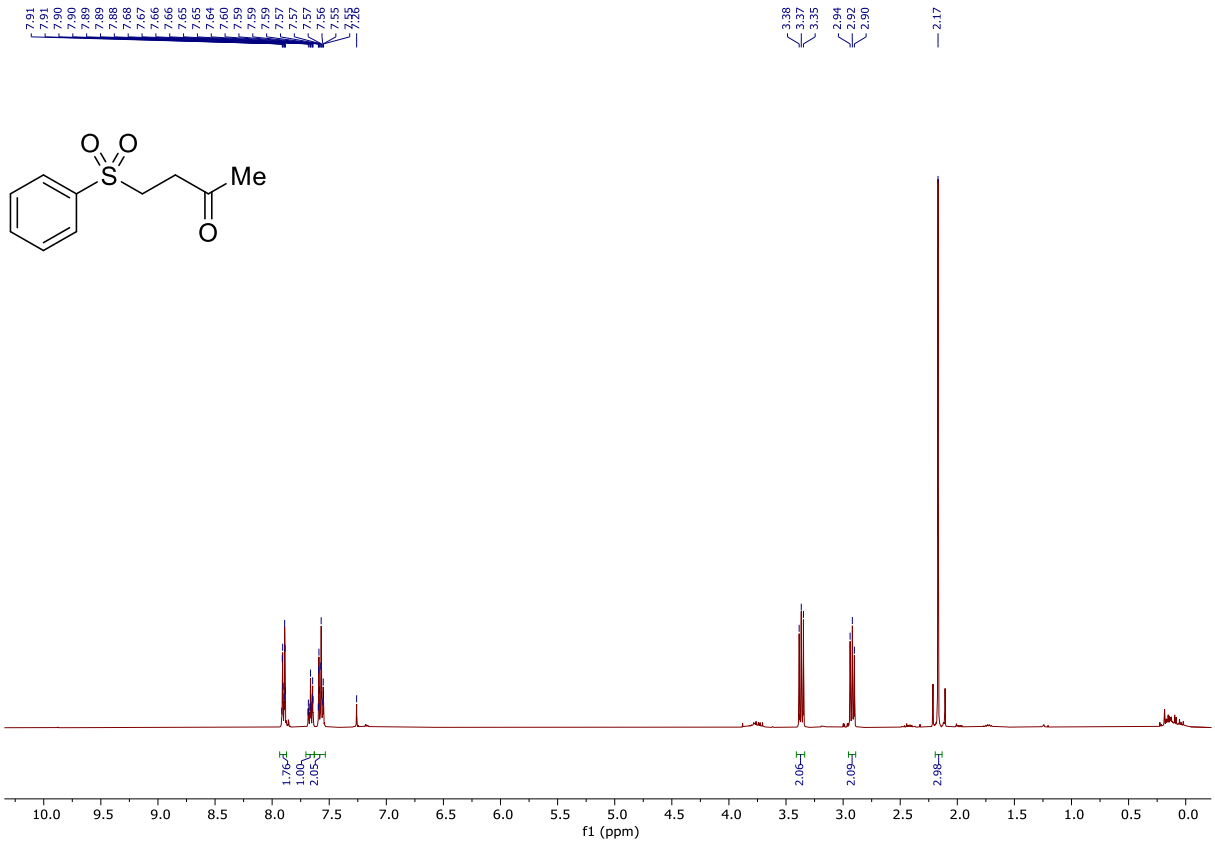



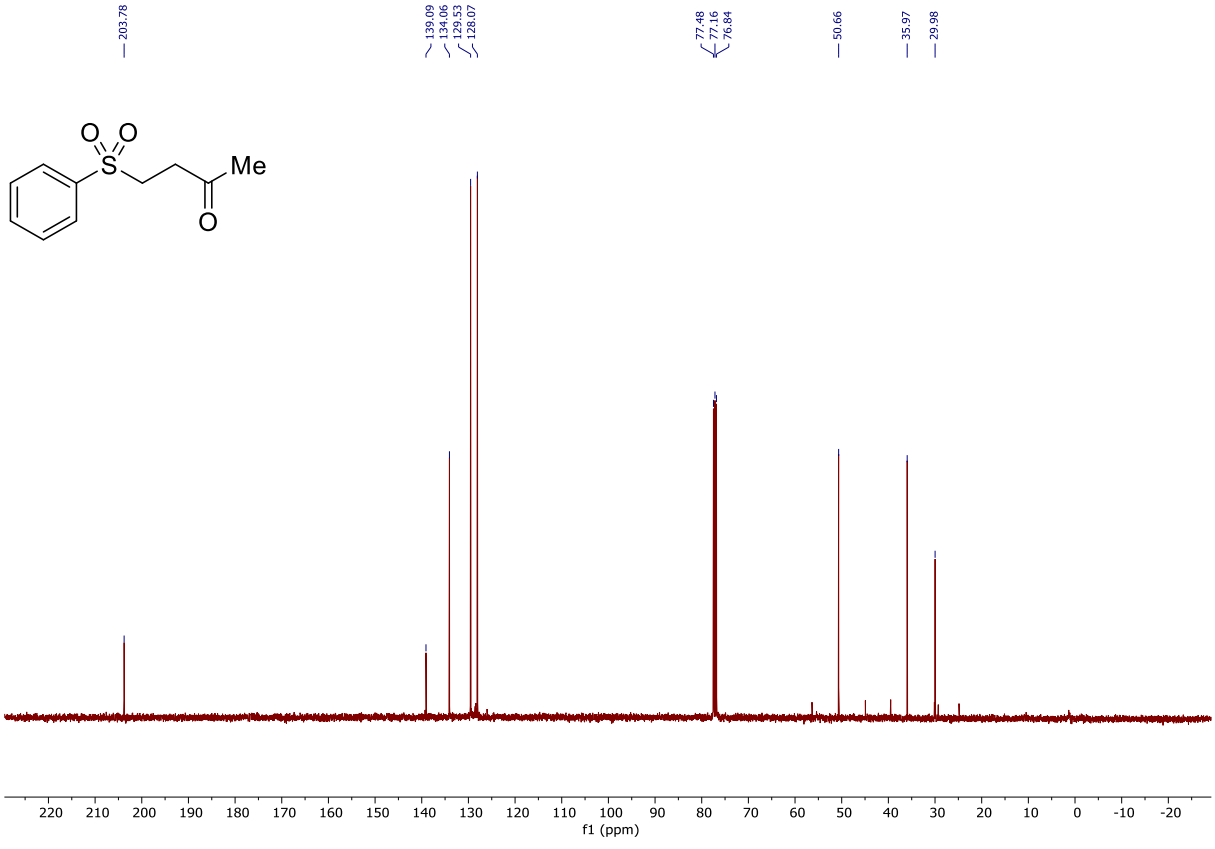
## 4-Tosylbutan-2-one (109a)



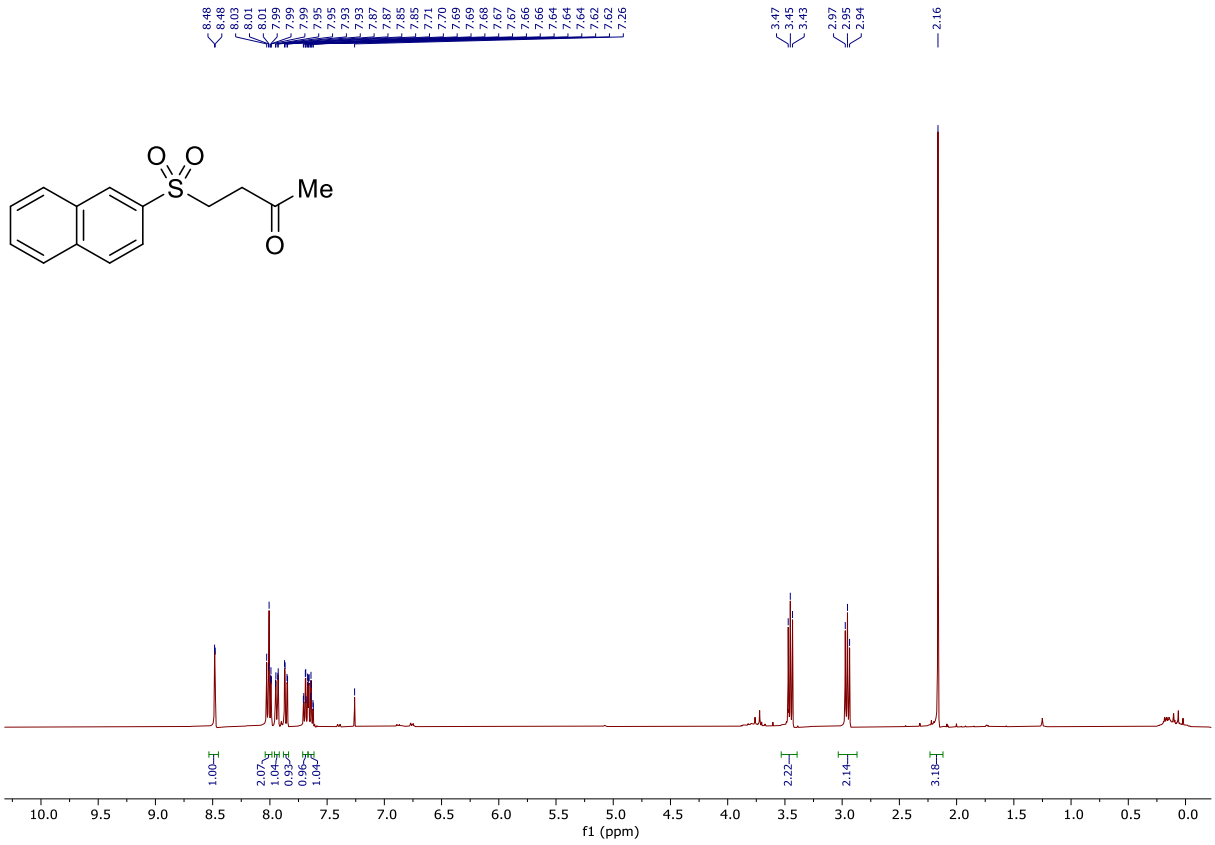



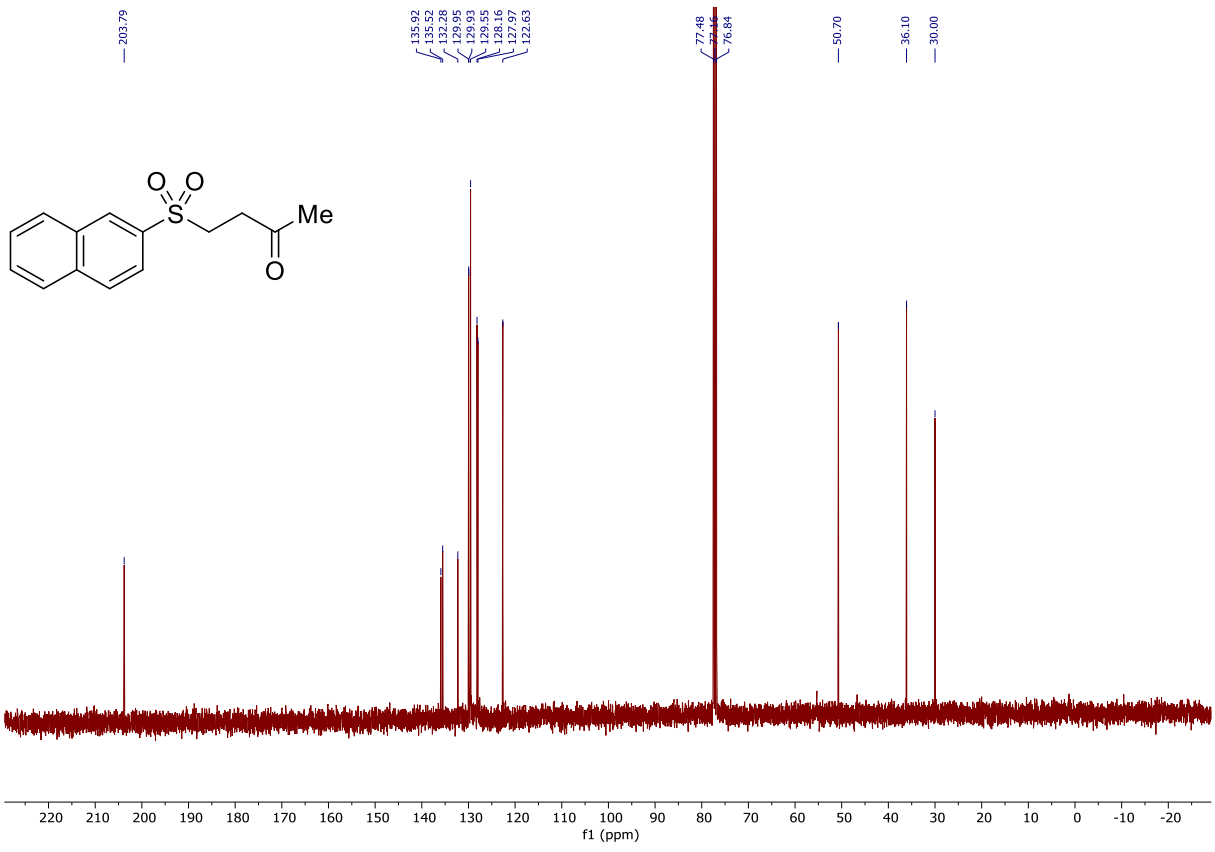
## 4-(Phenylsulfonyl)butan-2-one (109b)



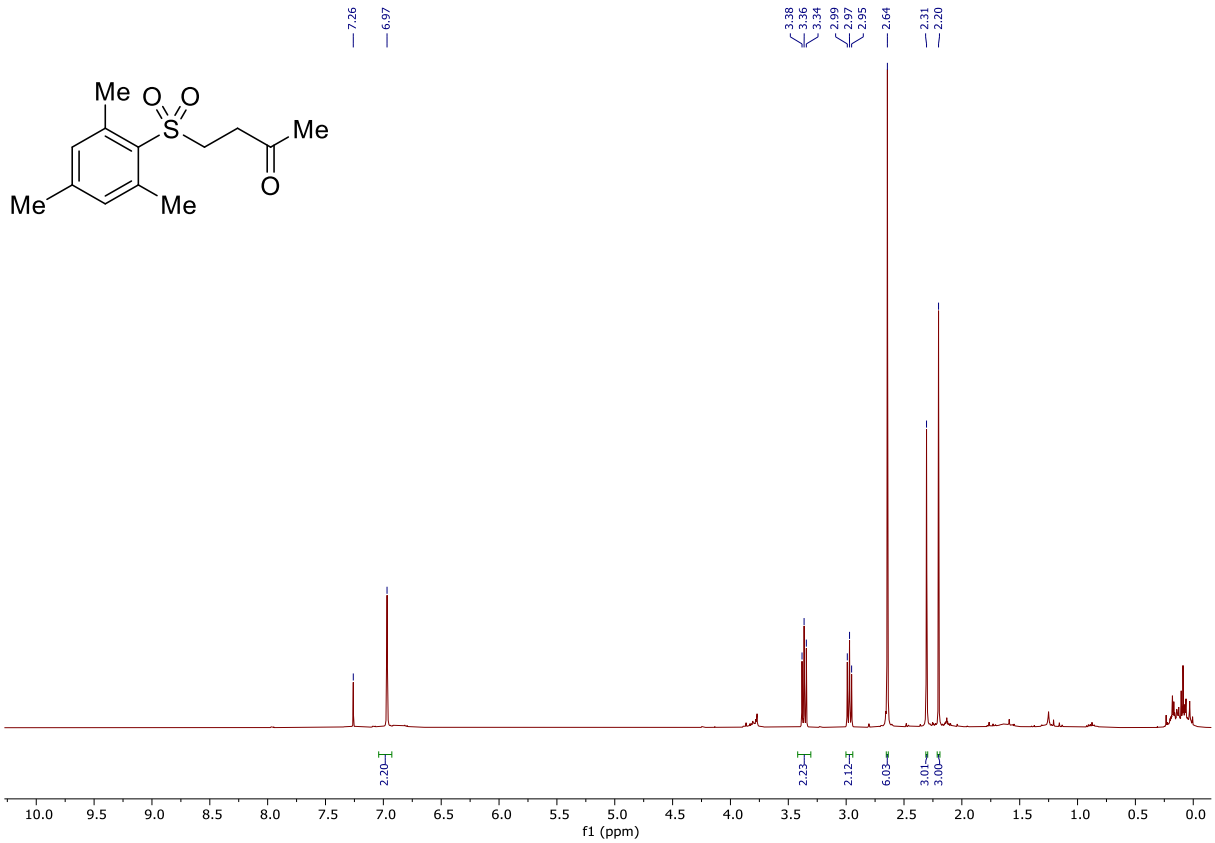



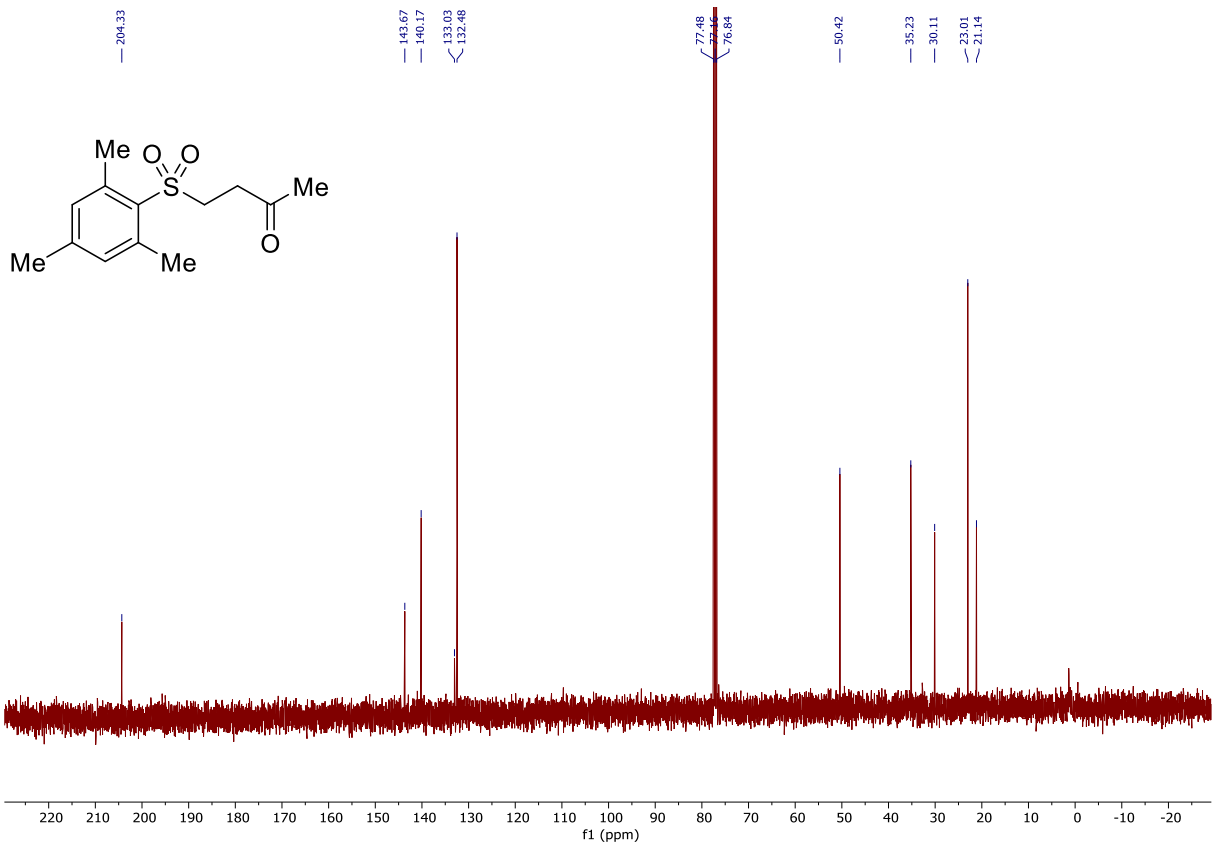
## 4-(Naphthalen-2-ylsulfonyl)butan-2-one (109c)



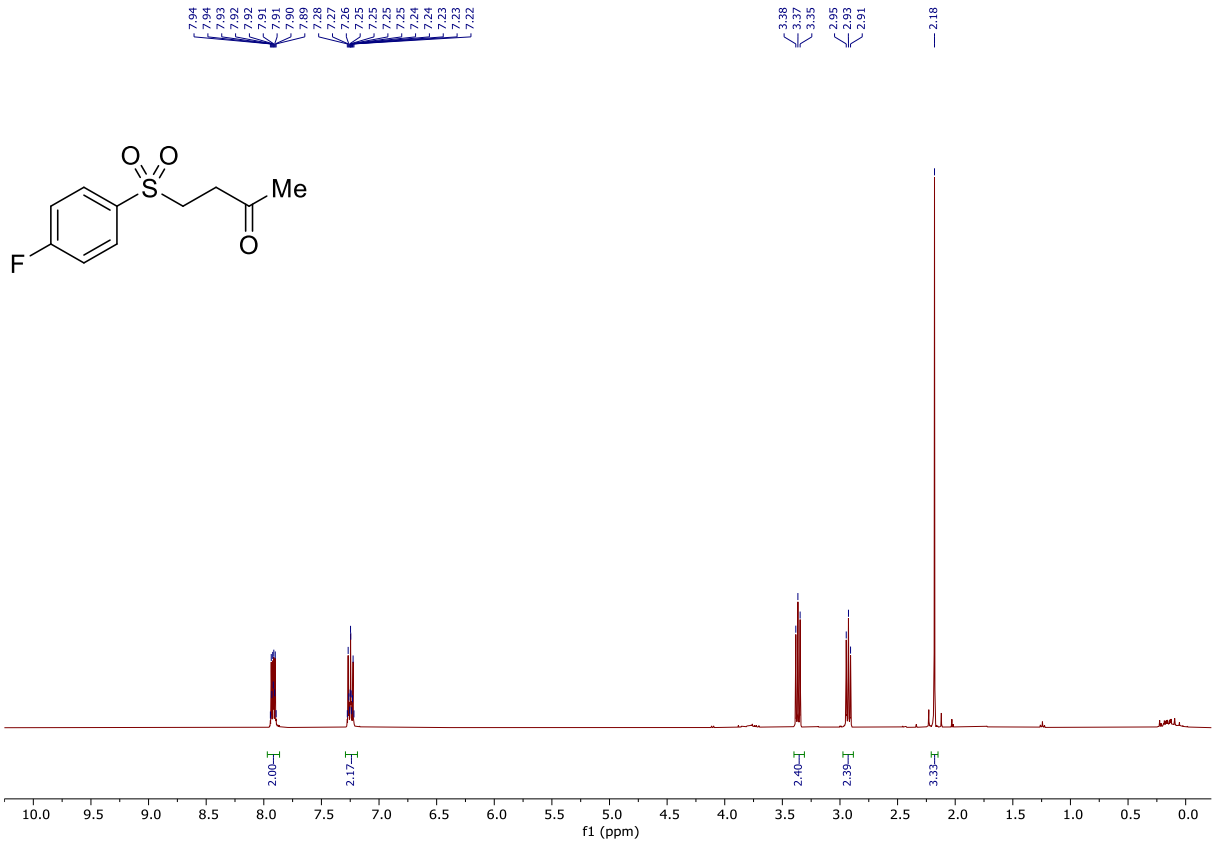



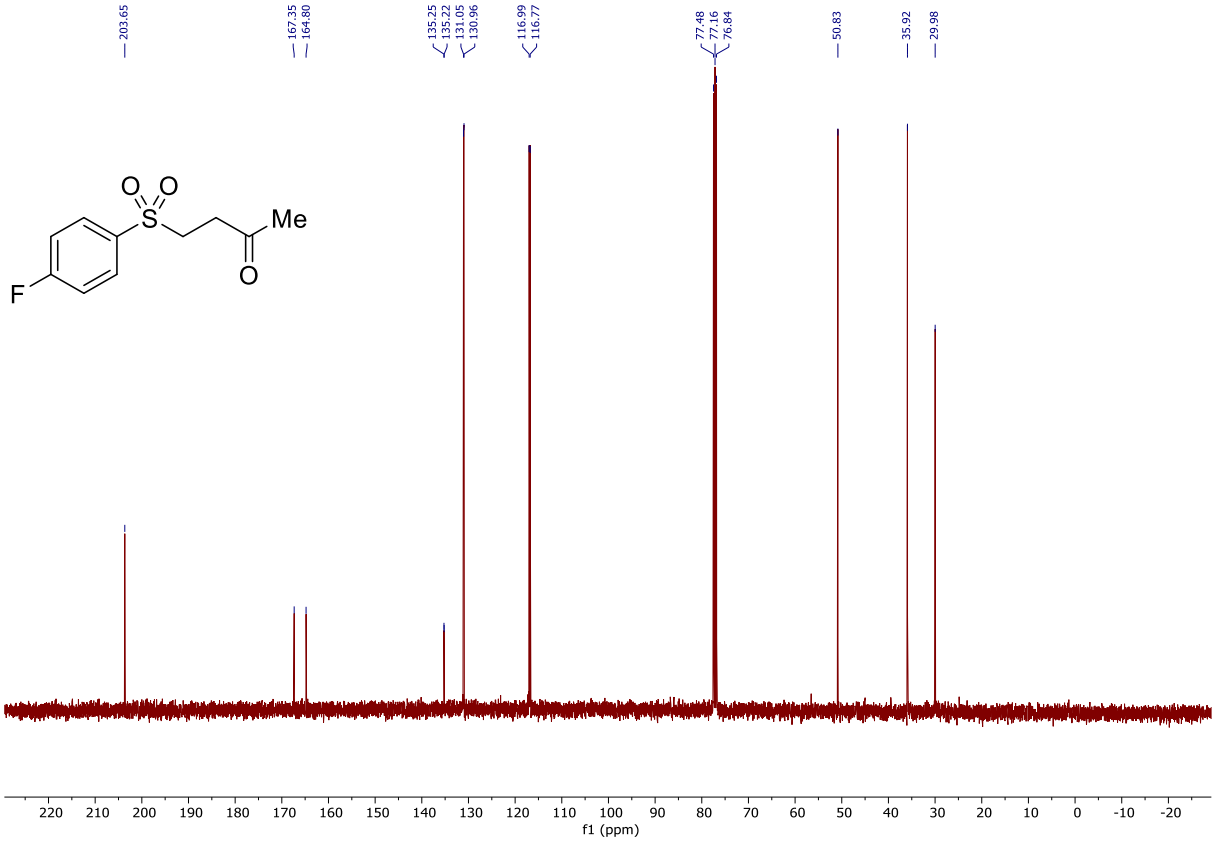
## 4-(Mesitylsulfonyl)butan-2-one (109d)

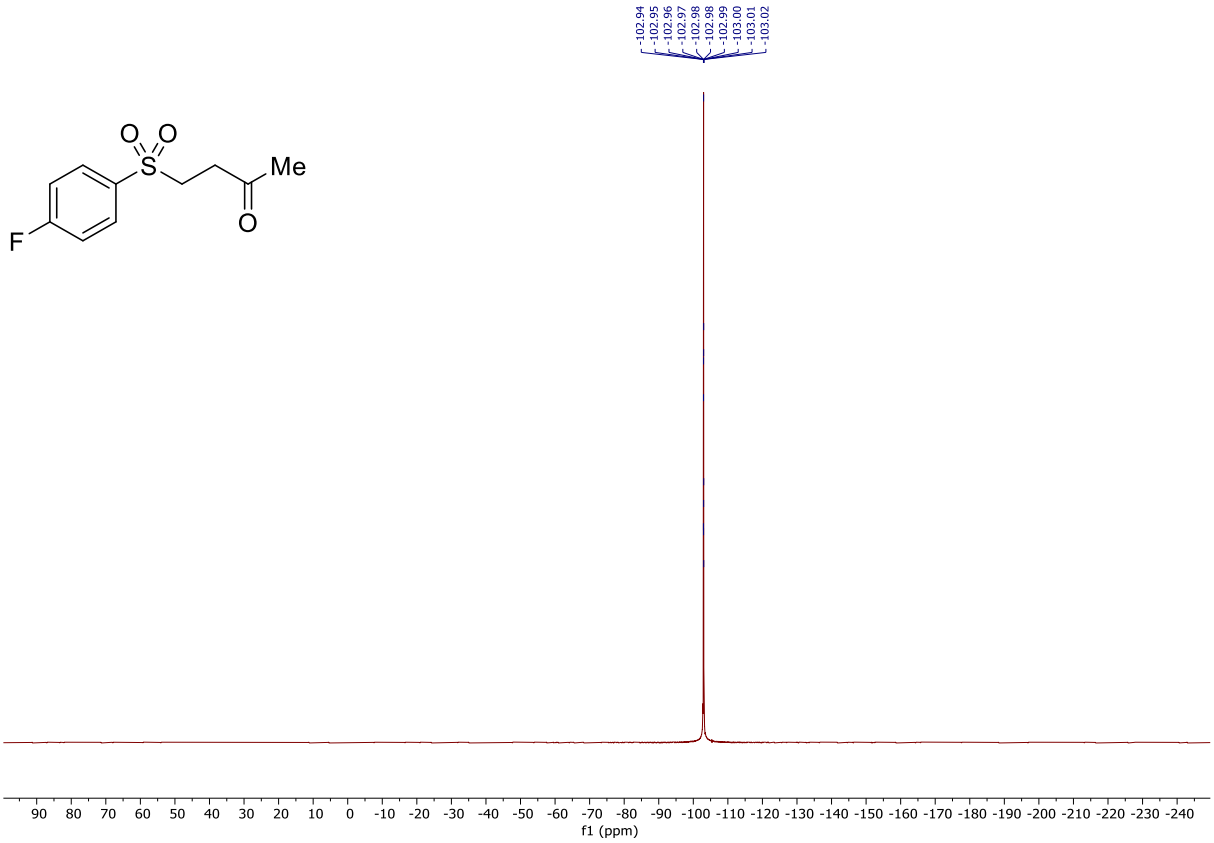


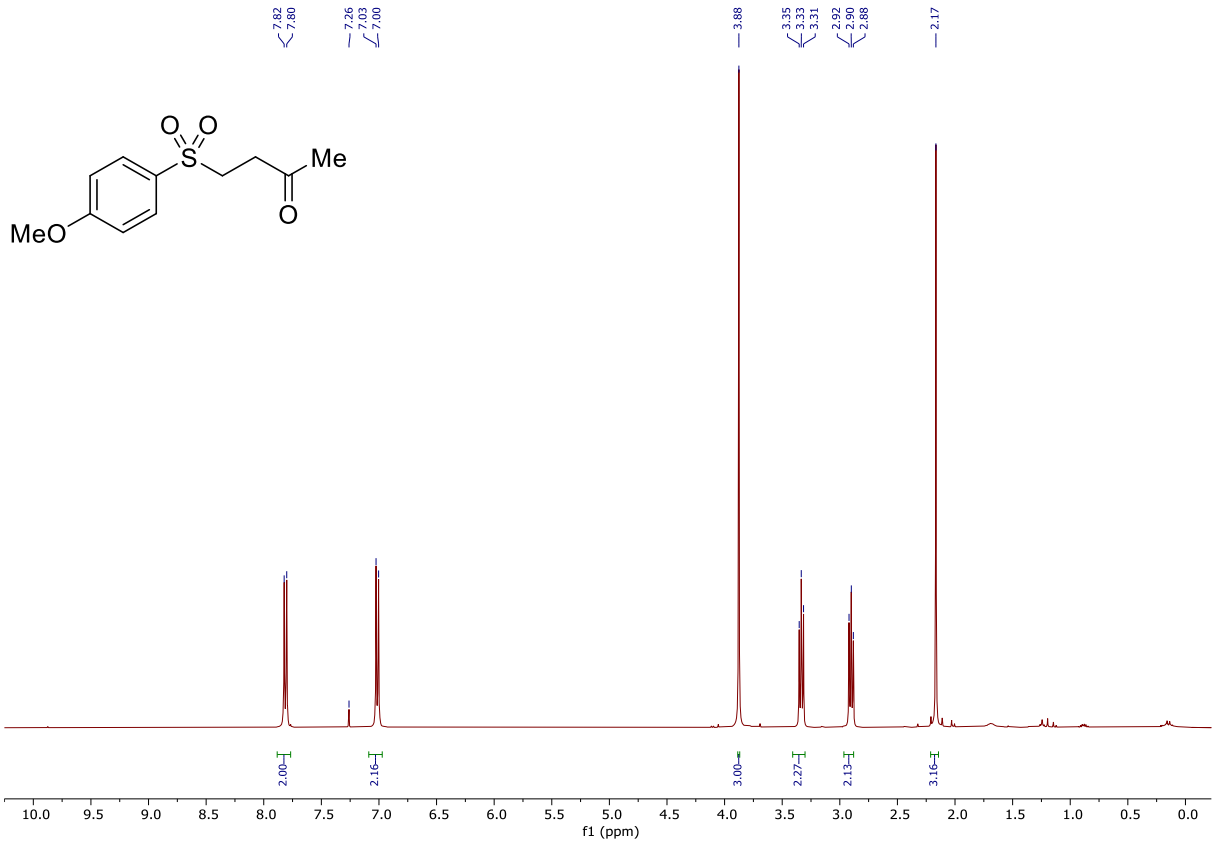
## 4-((4-Fluorophenyl)sulfonyl)butan-2-one (109e)

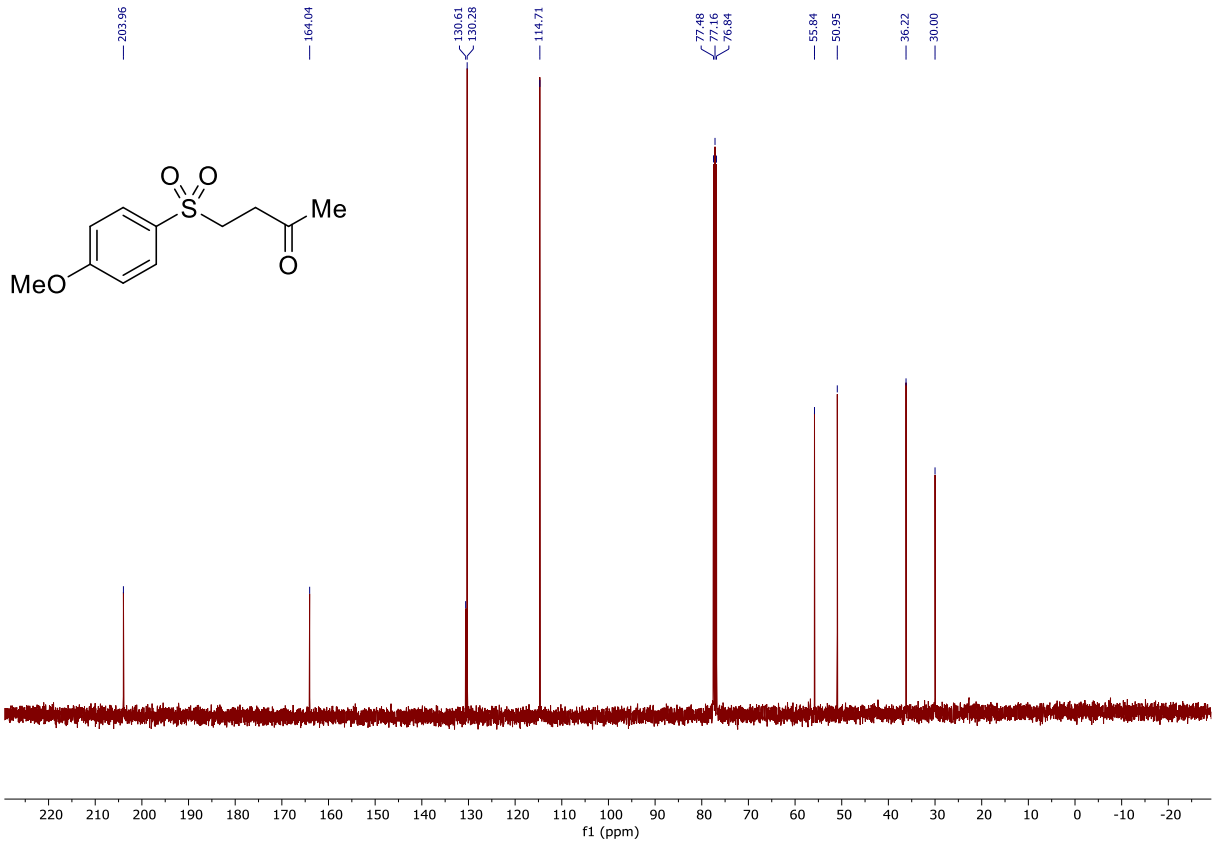


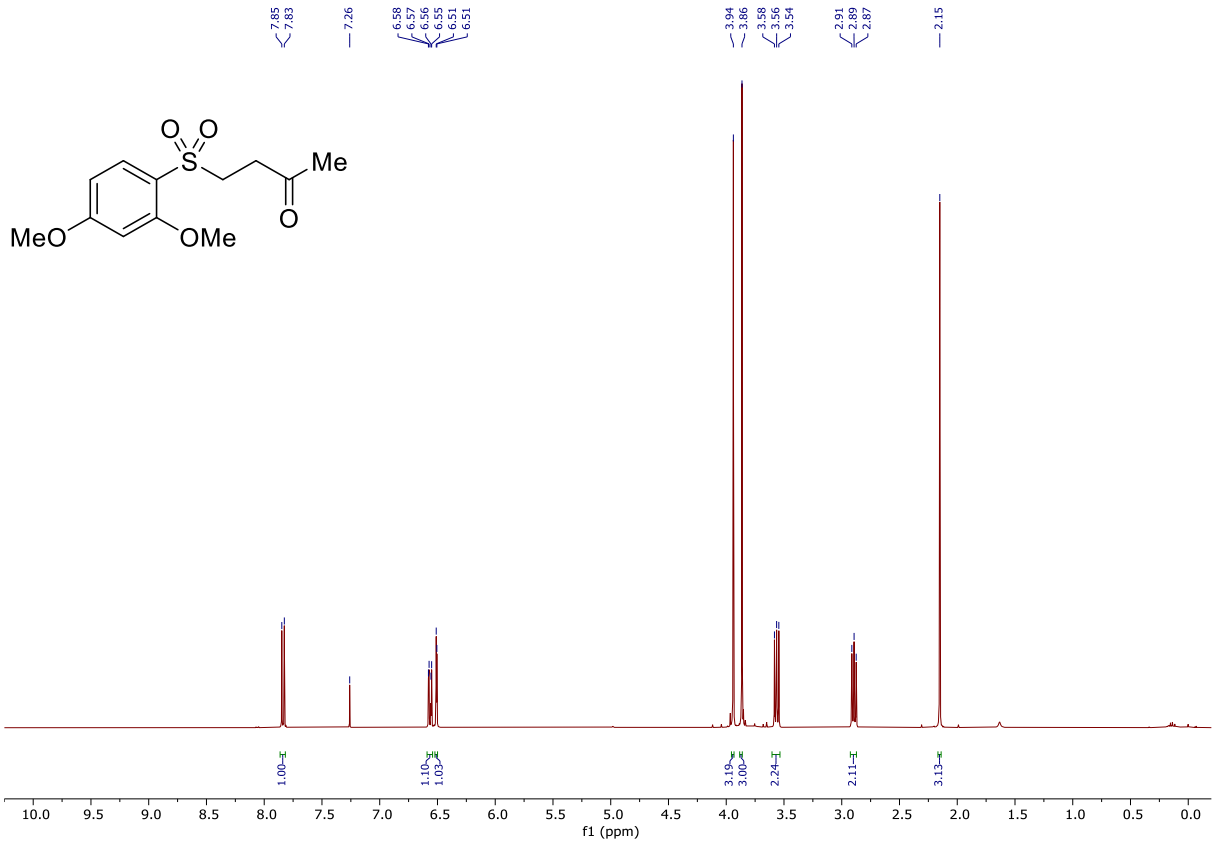

-102.94
-102.95
-102.96
-102.97
-102.98
-102.98
-102.99
-103.00
-103.01
-103.02
O
O
S
Me
O
F
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

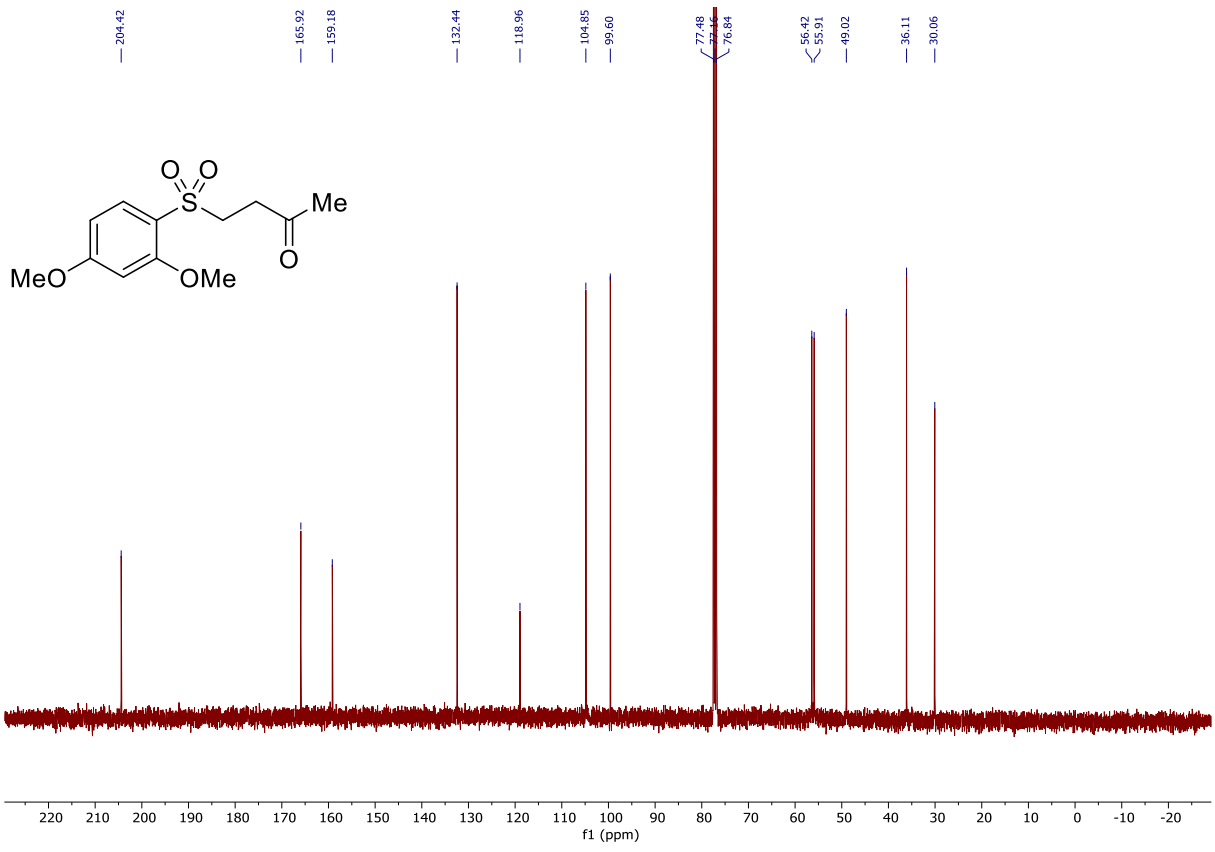
## 4-((4-Methoxyphenyl)sulfonyl)butan-2-one (109f)



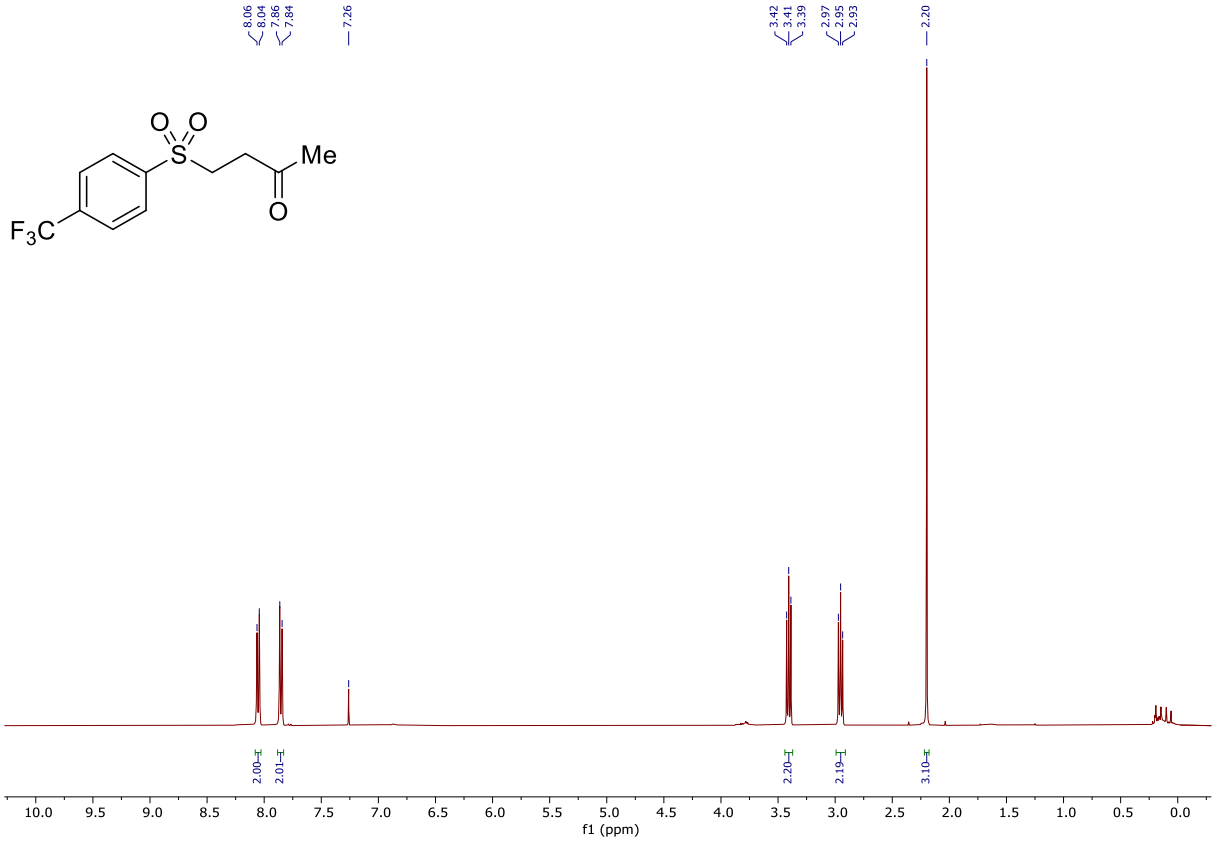



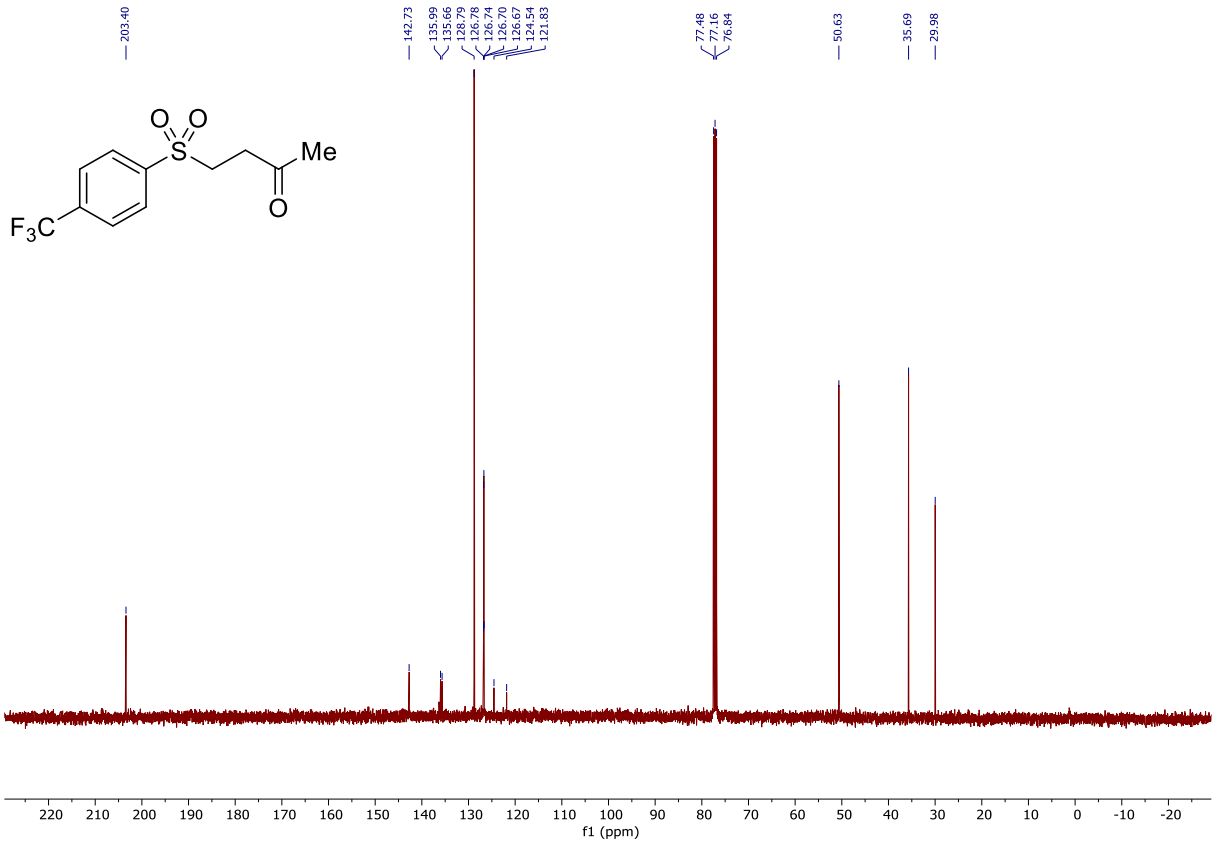
## 4-((2,4-Dimethoxyphenyl)sulfonyl)butan-2-one (109g)

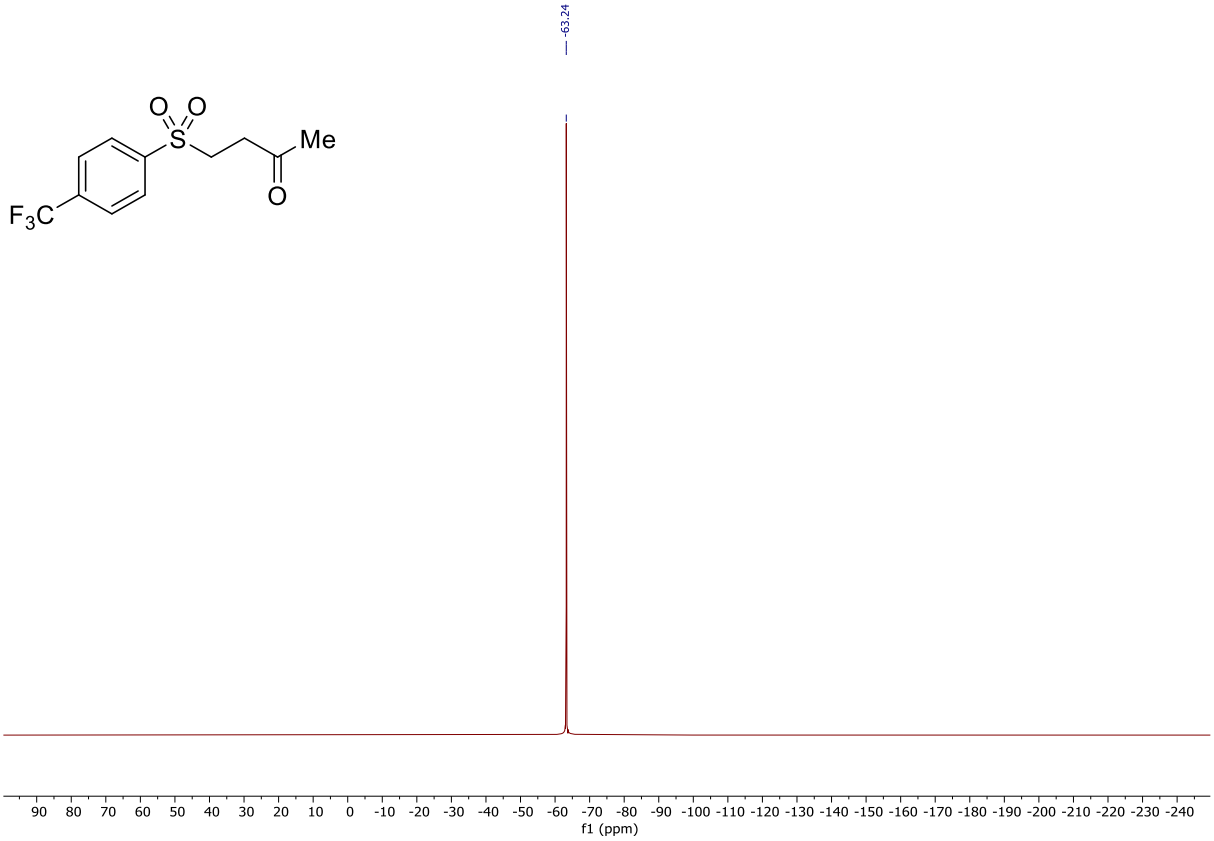


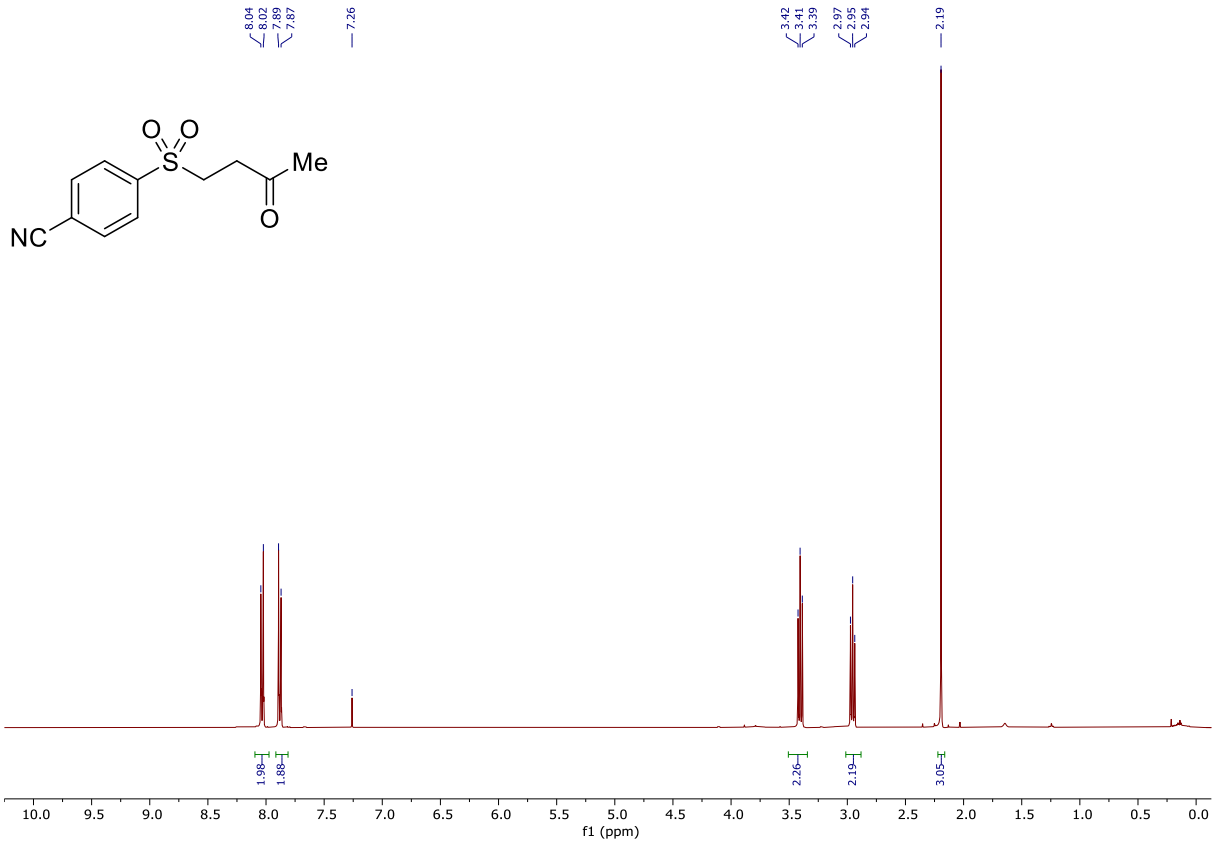
## 4-((4-(Trifluoromethyl)phenyl)sulfonyl)butan-2-one (109h)

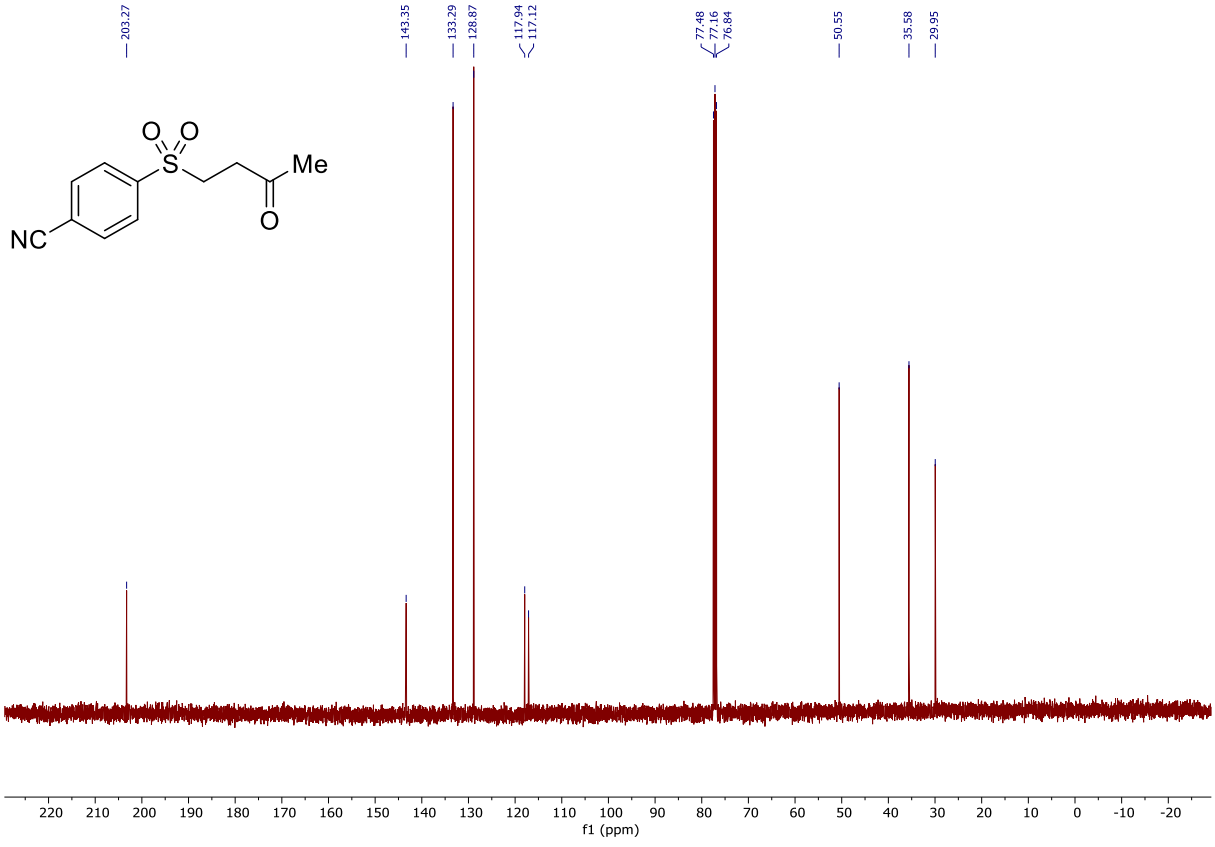


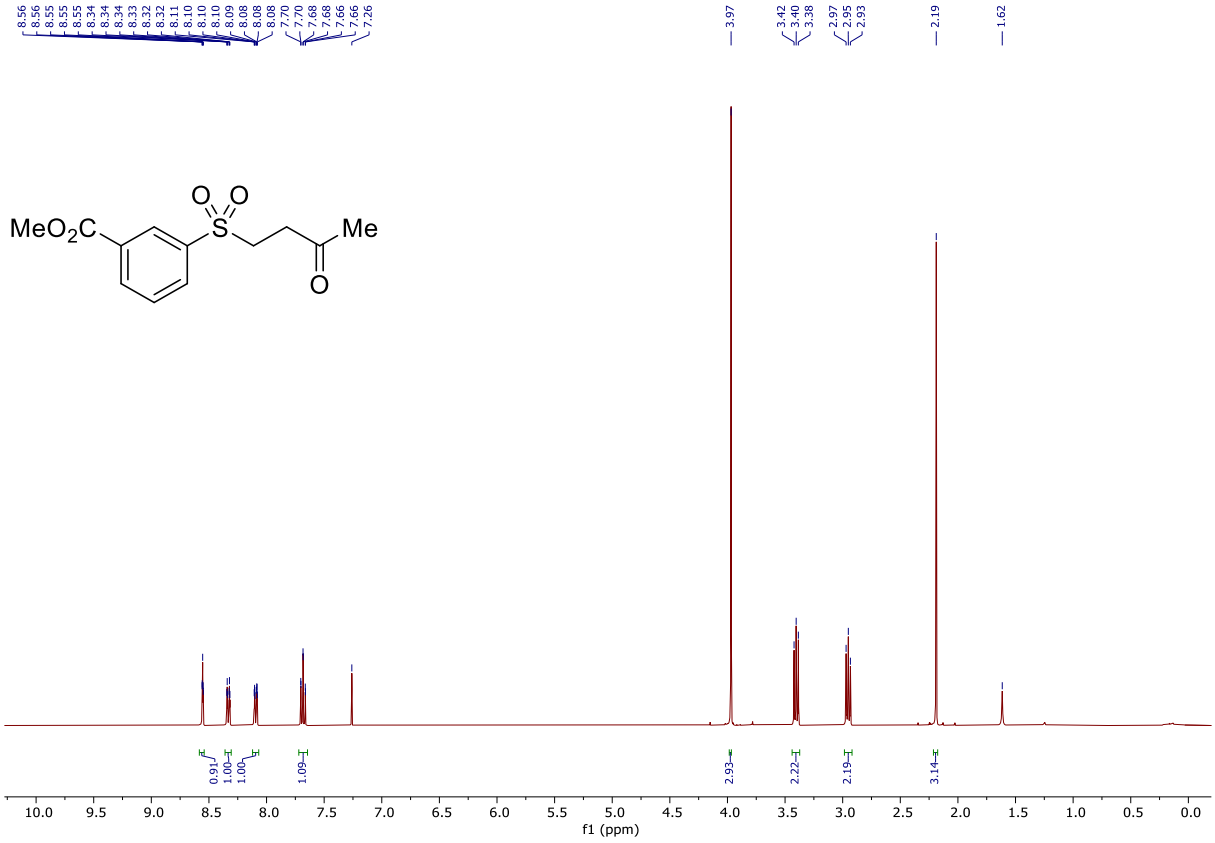

-63.24
O
O
S
Me
O
F3C
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

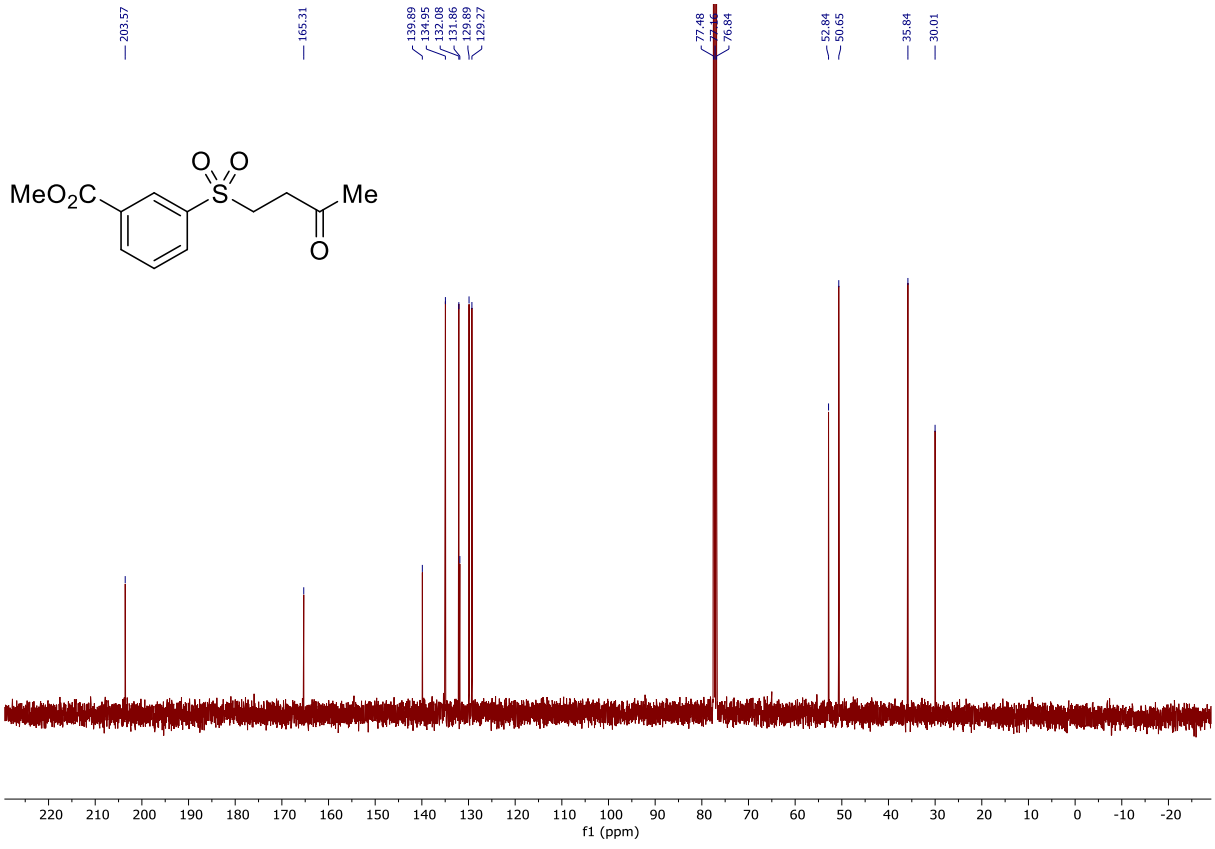
## 4-((3-Oxobutyl)sulfonyl)benzonitrile (109i)



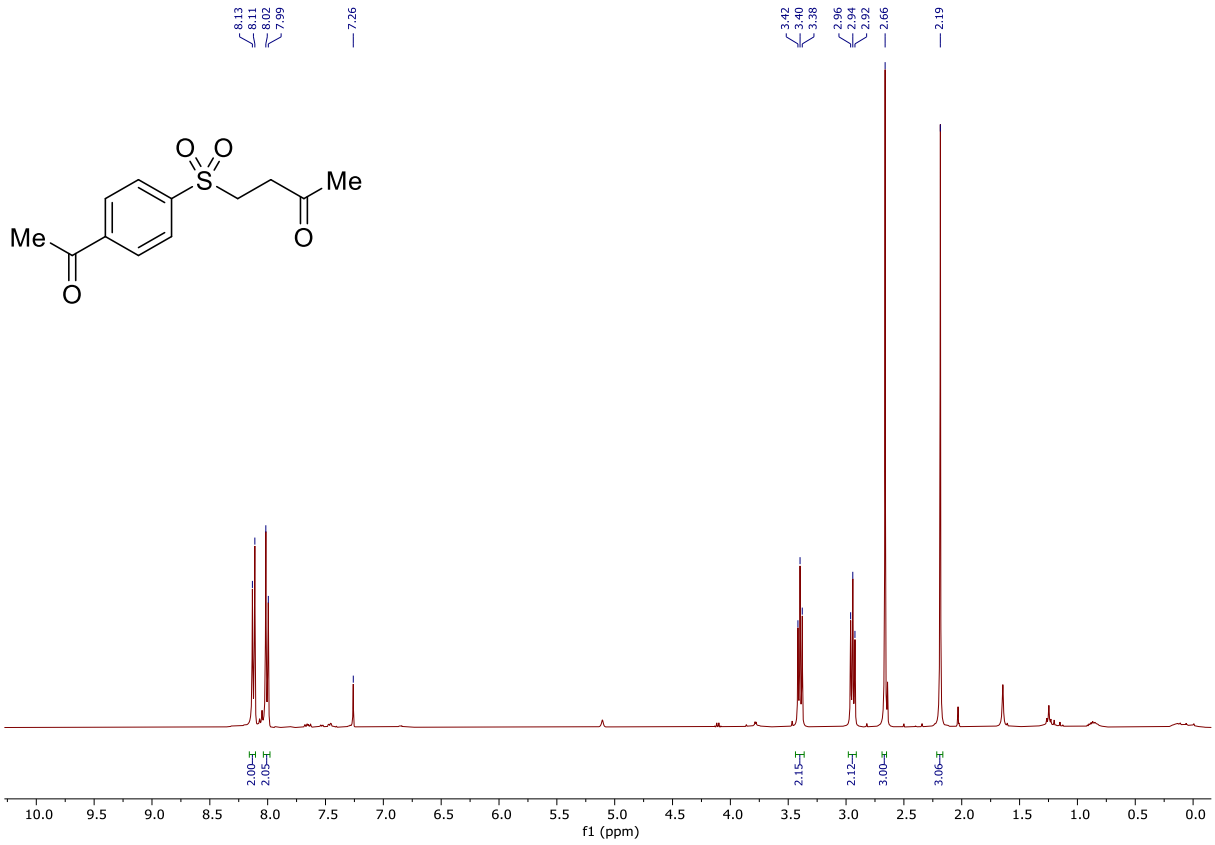



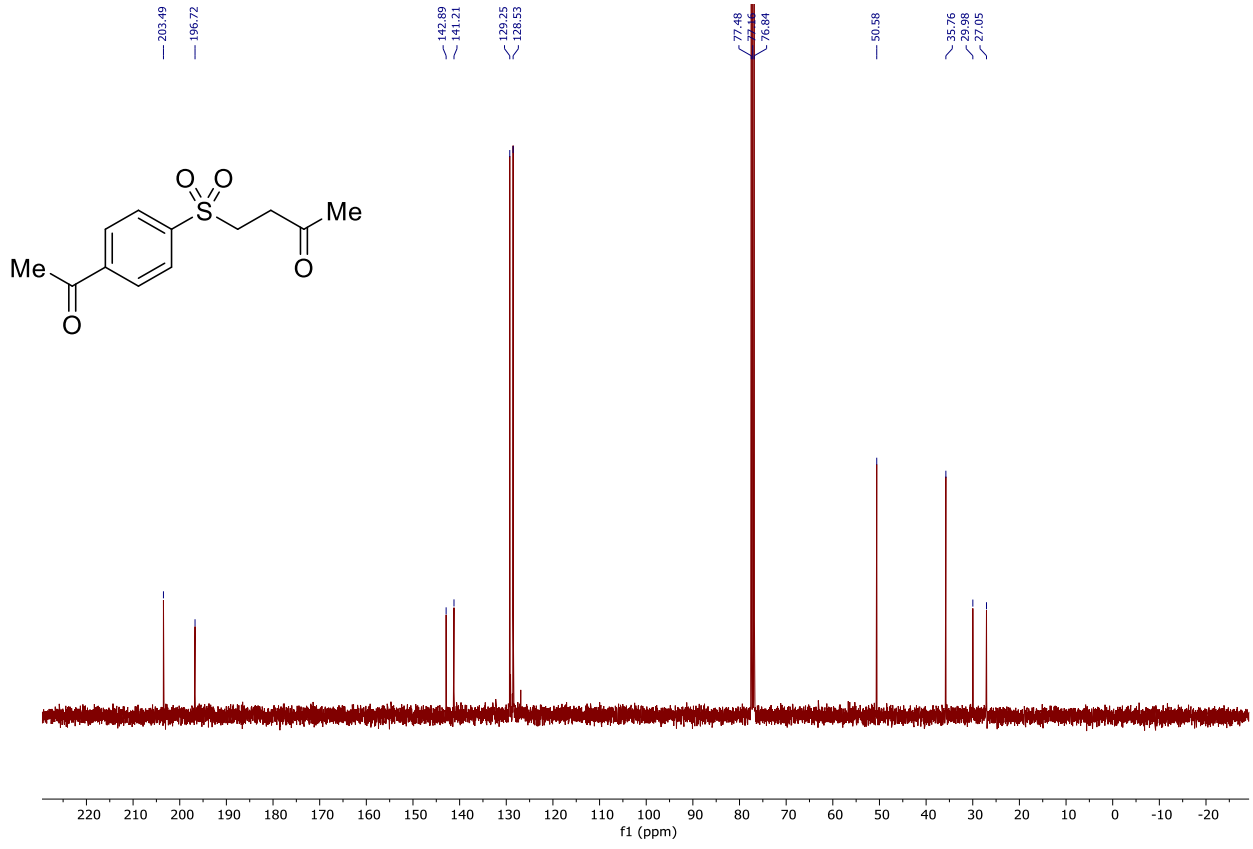
## Methyl 3-((3-oxobutyl)sulfonyl)benzoate (109j)



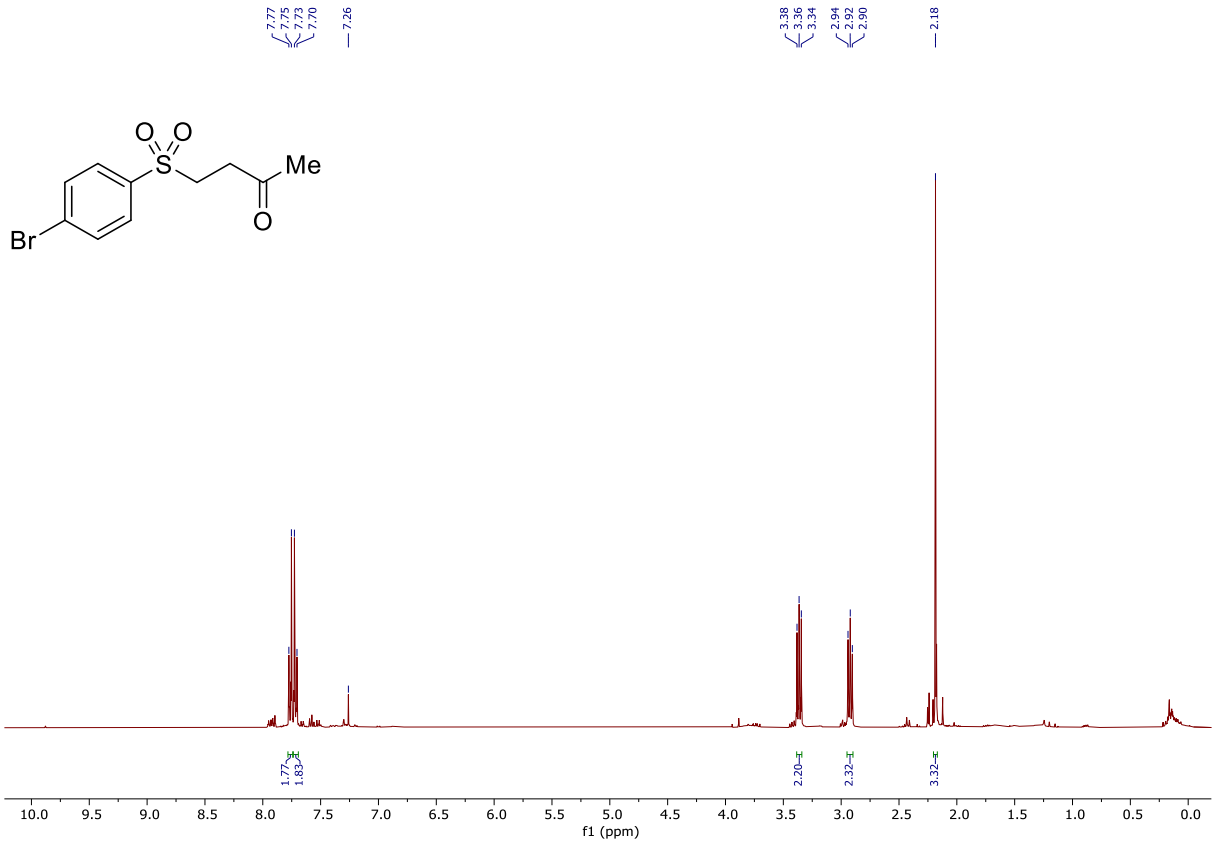



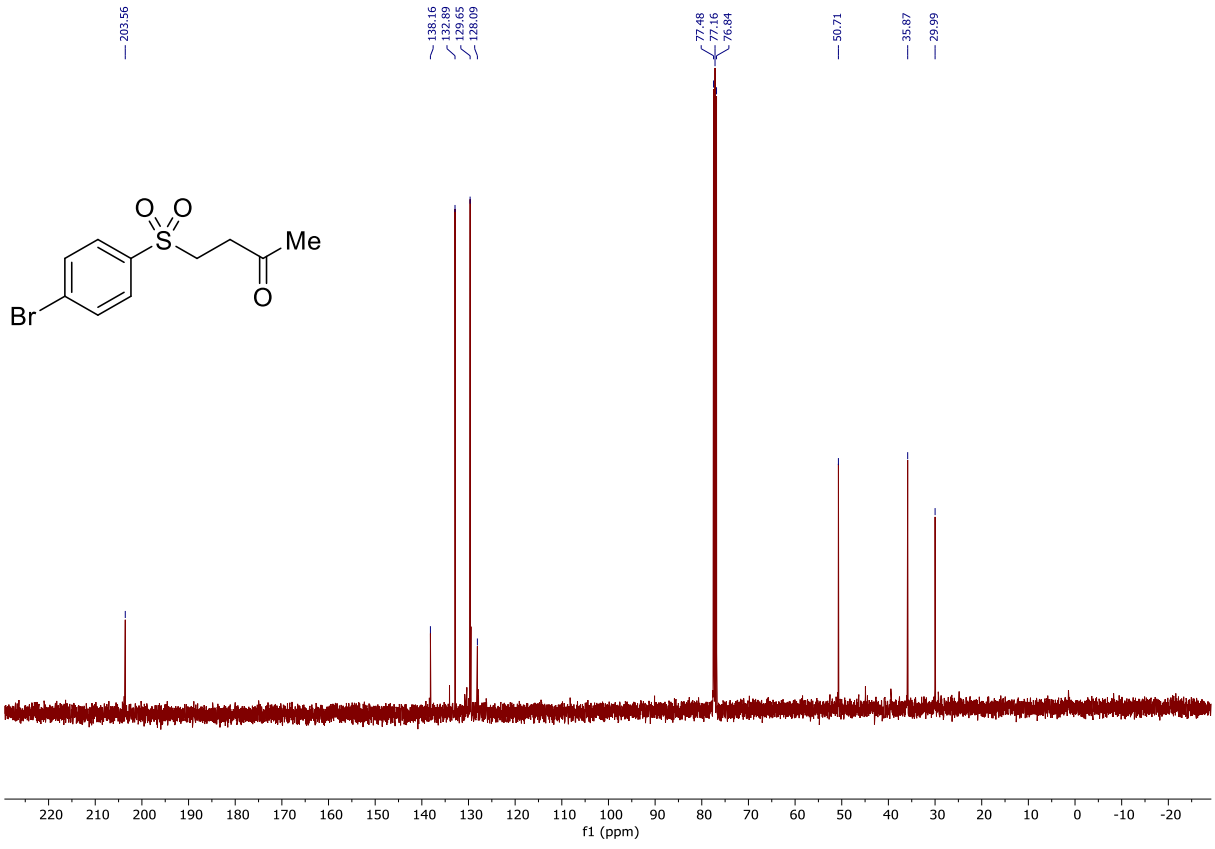
## 4-((4-Acetylphenyl)sulfonyl)butan-2-one (109k)



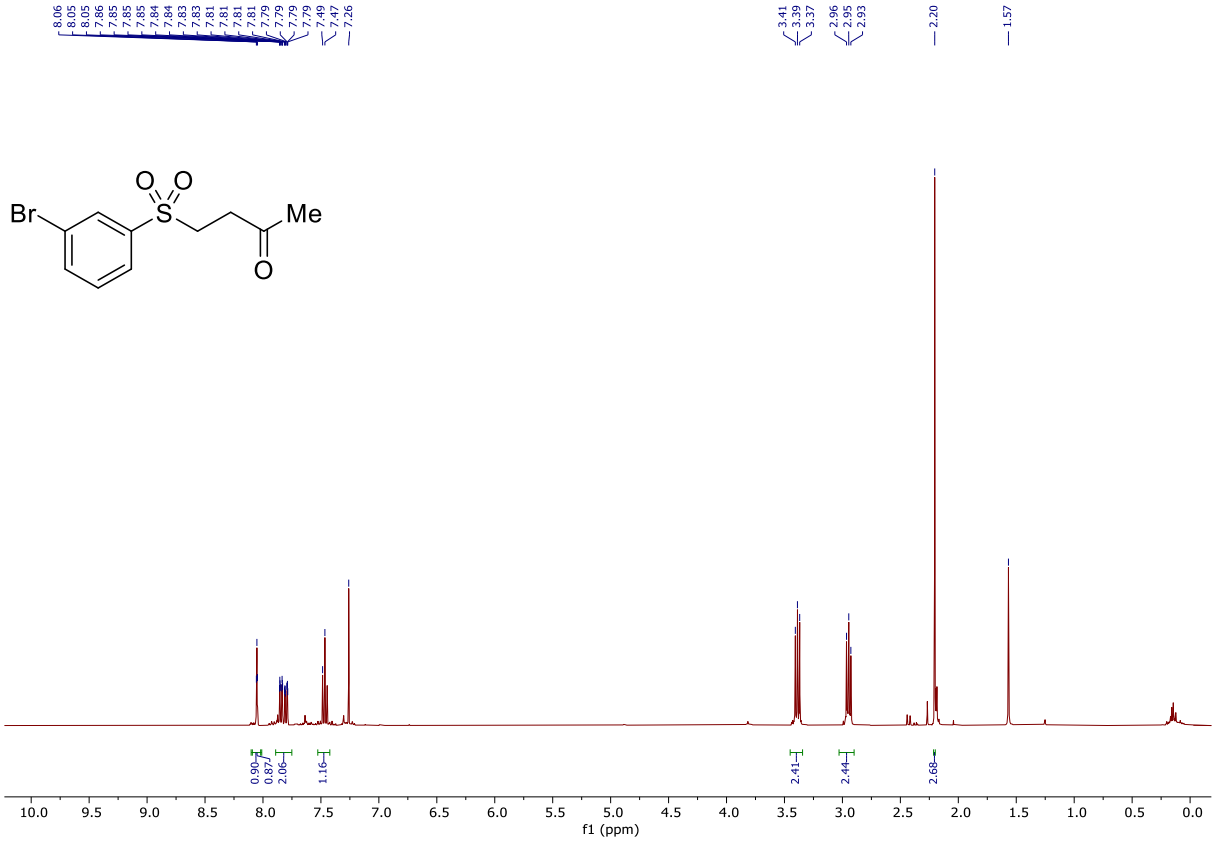



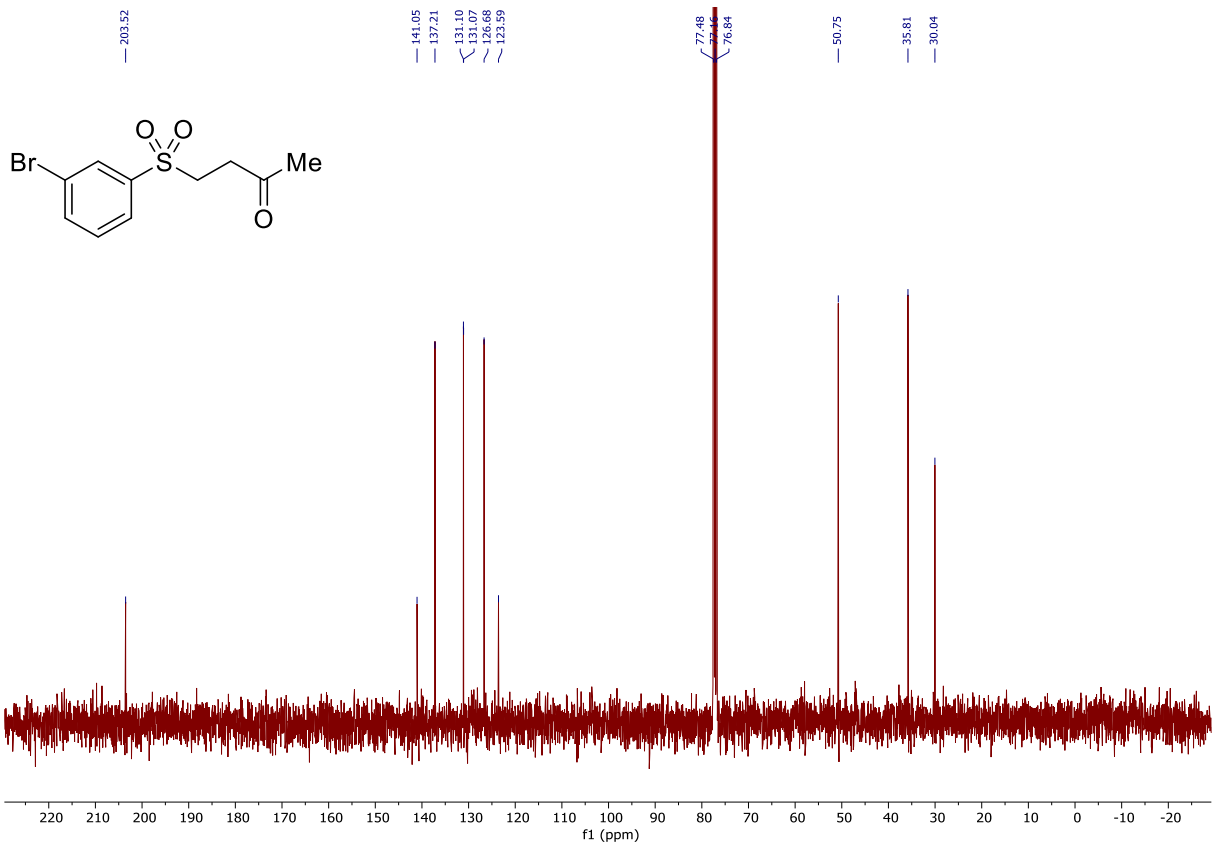
## 4-((4-Bromophenyl)sulfonyl)butan-2-one (109l)



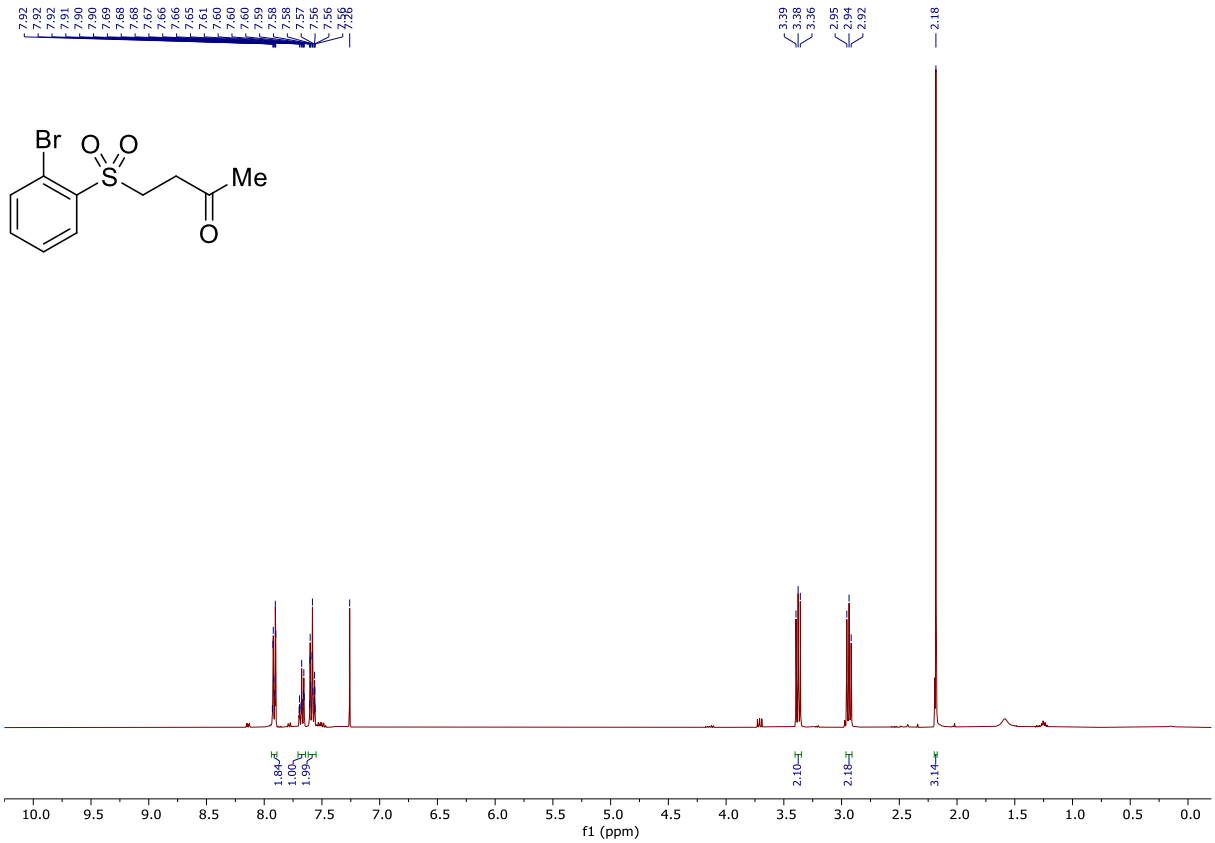



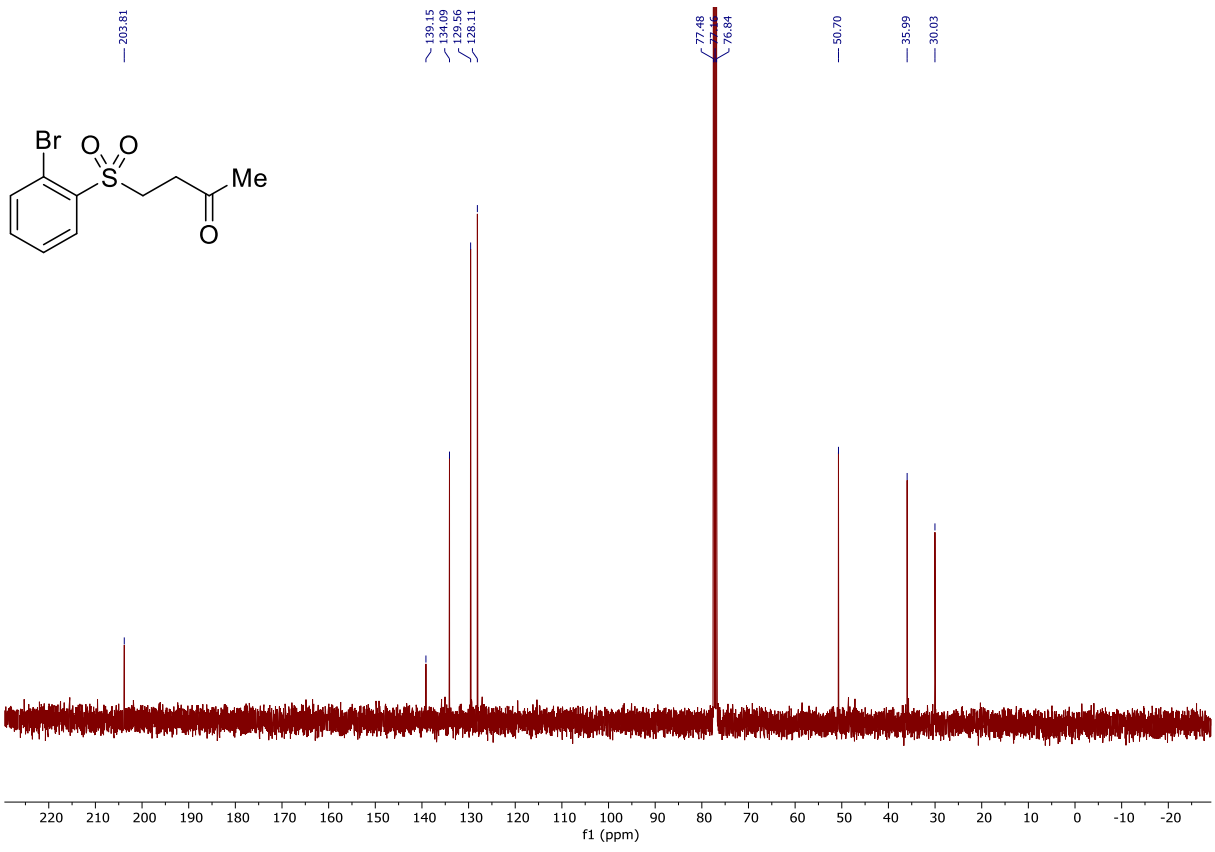
## 4-((3-Bromophenyl)sulfonyl)butan-2-one (109m)



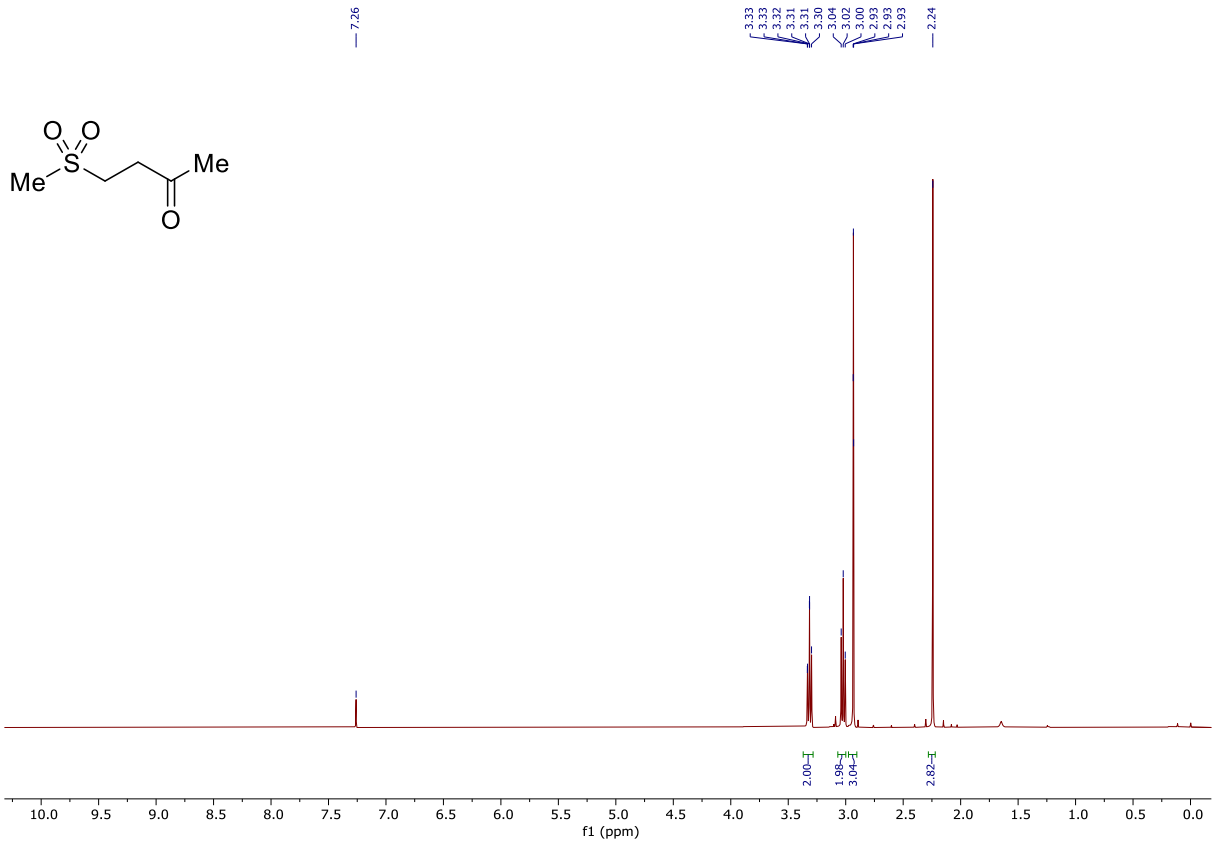



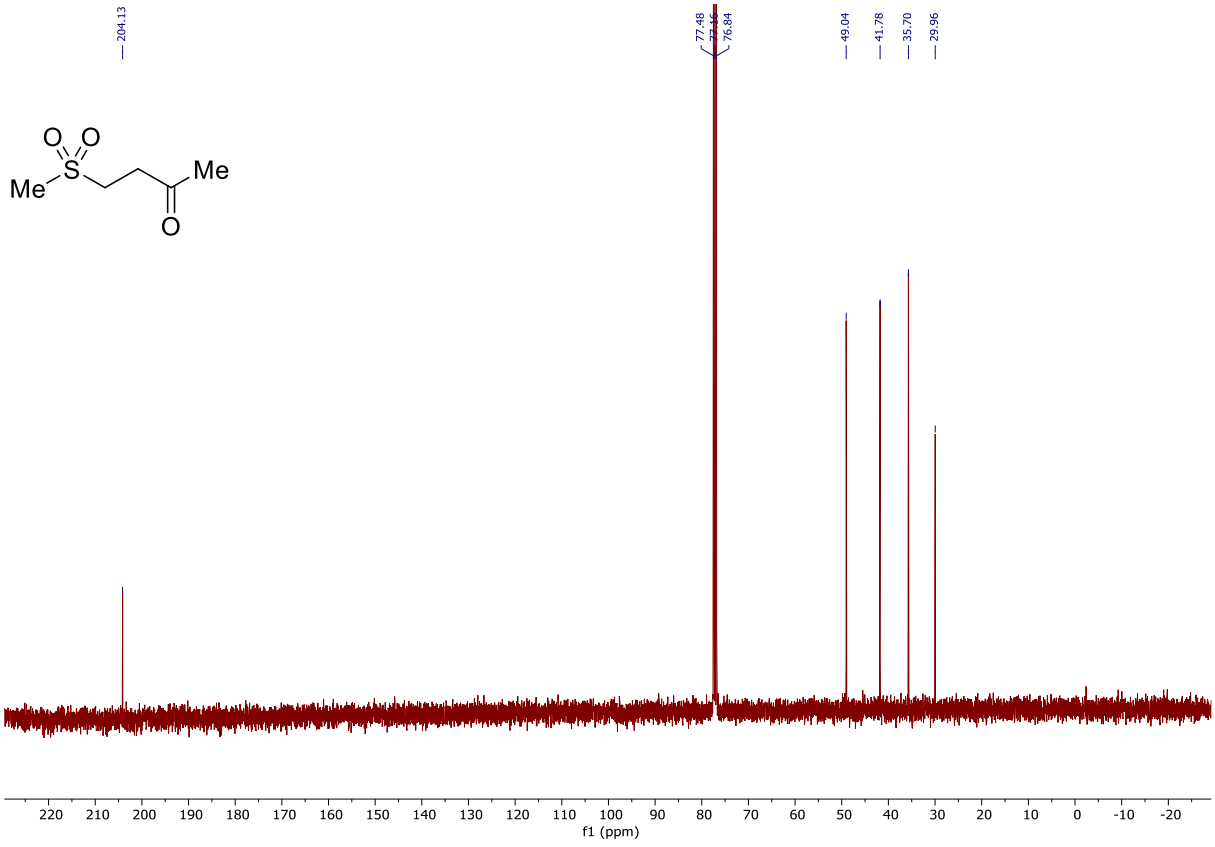
## 4-((2-Bromophenyl)sulfonyl)butan-2-one (MJT8-109n)



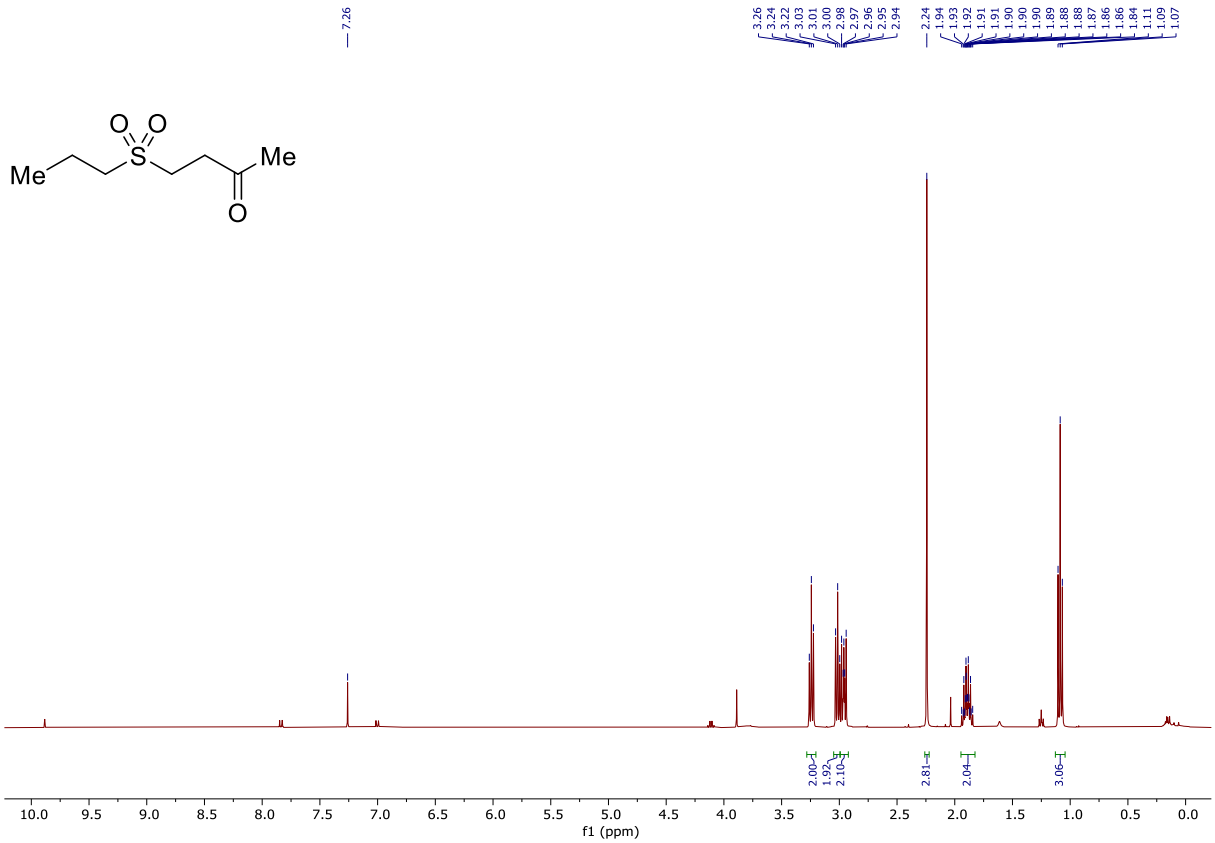



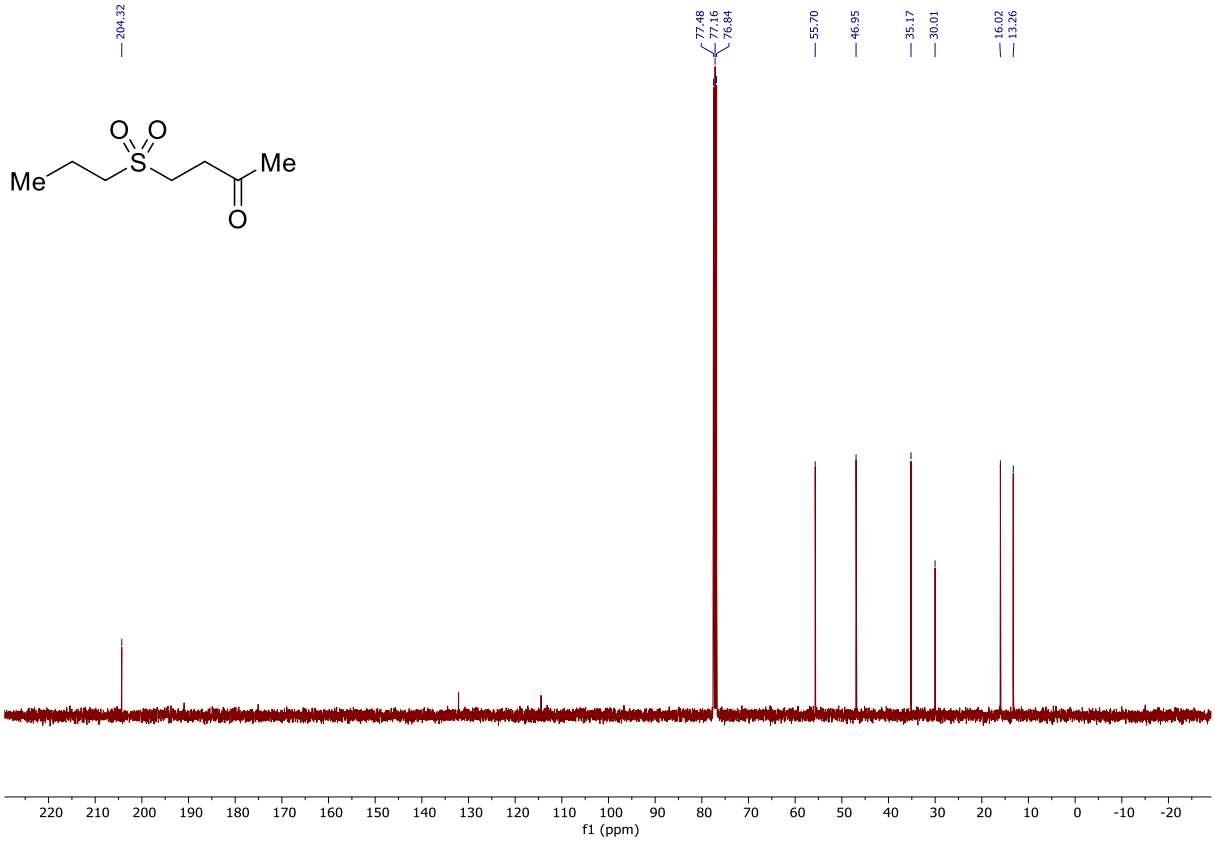
## 4-(Methylsulfonyl)butan-2-one (109o)



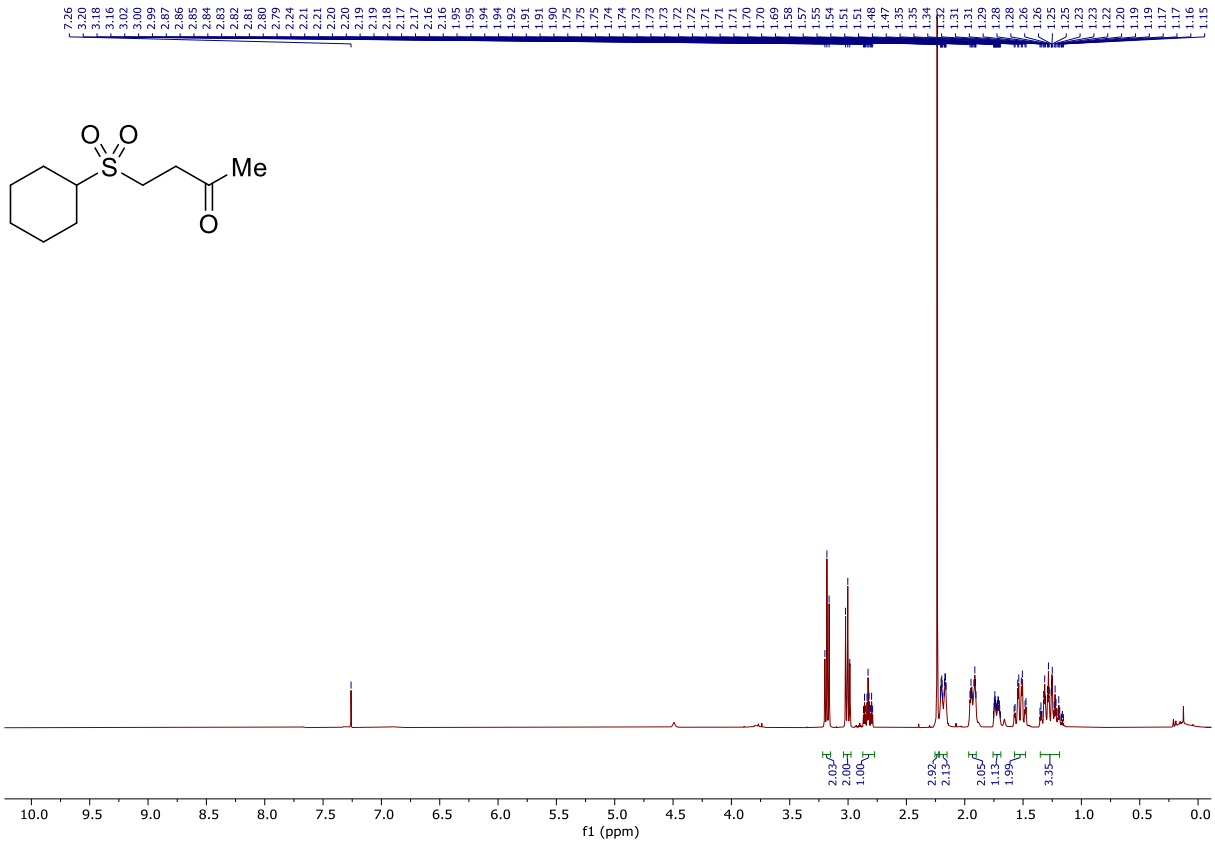



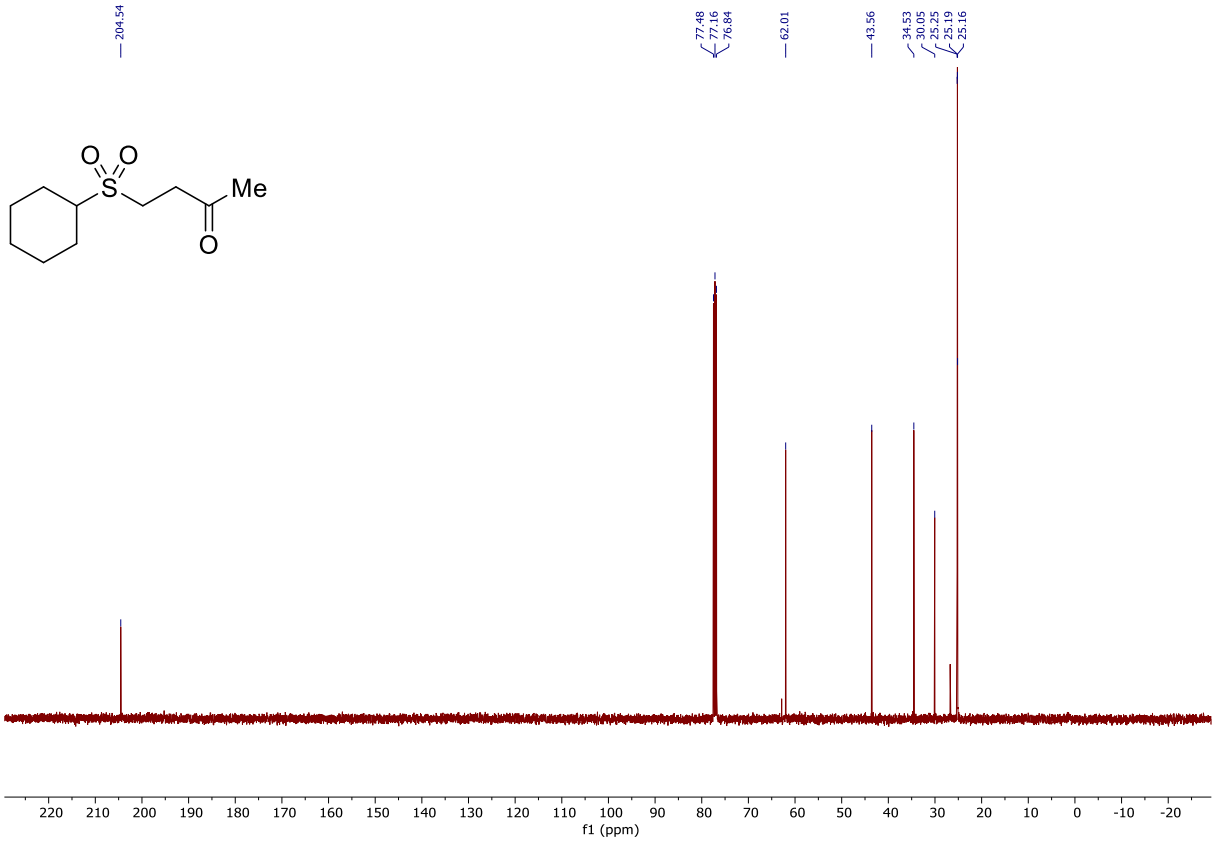
## 4-(Propylsulfonyl)butan-2-one (109p)



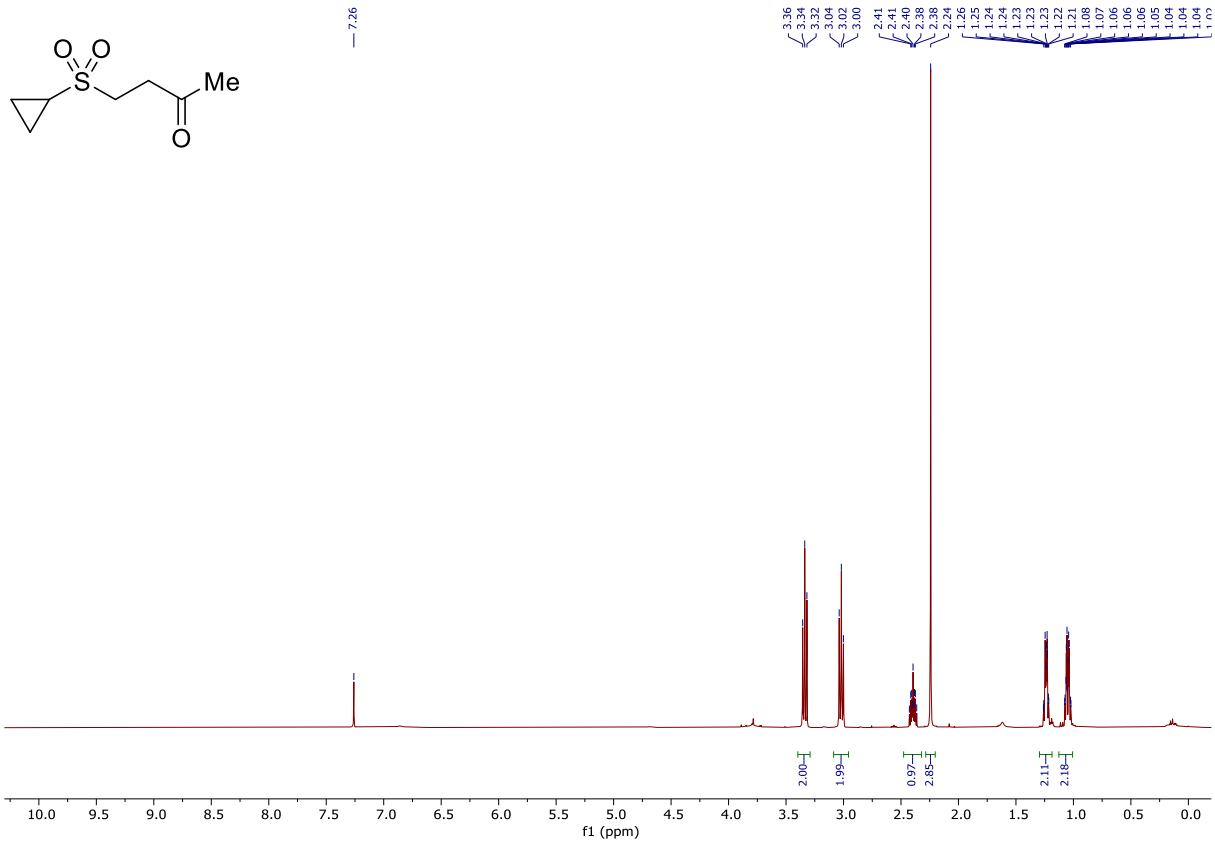



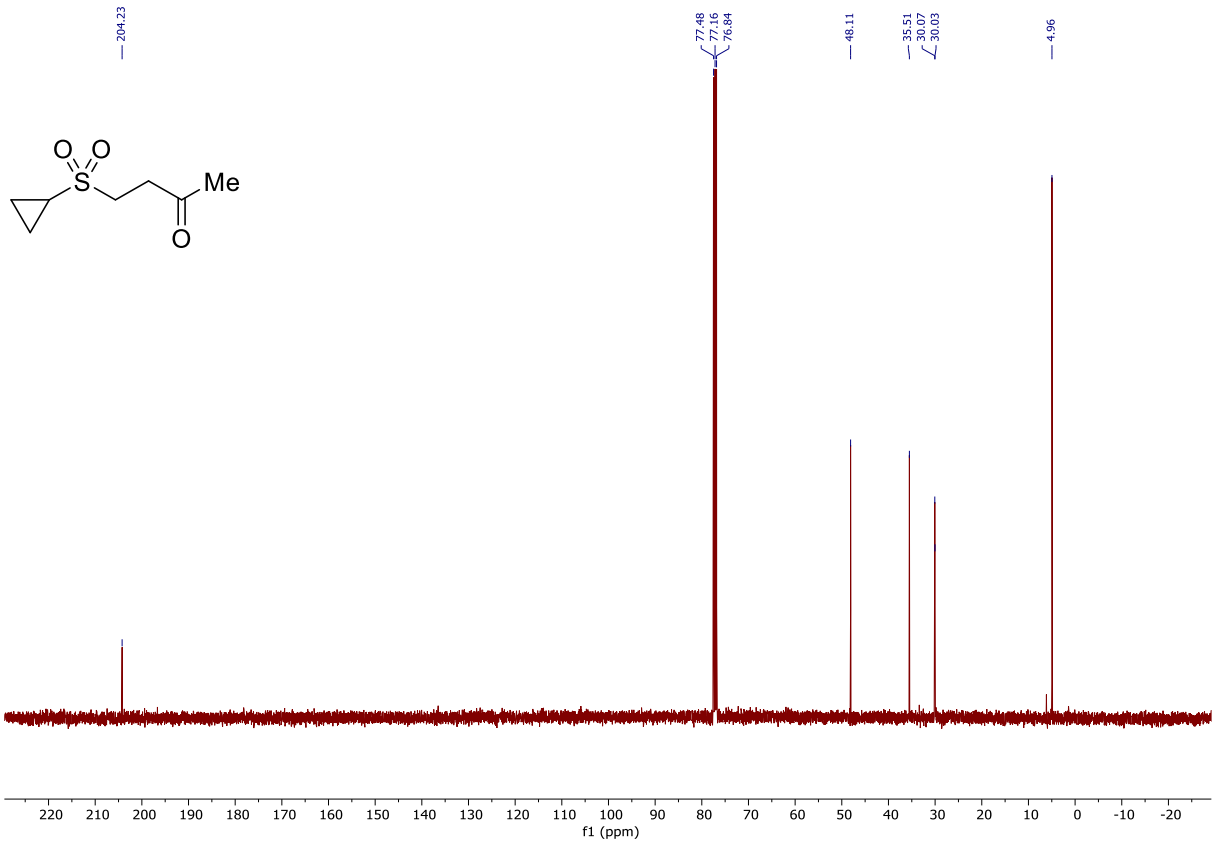
## 4-(Cyclohexylsulfonyl)butan-2-one (109q)



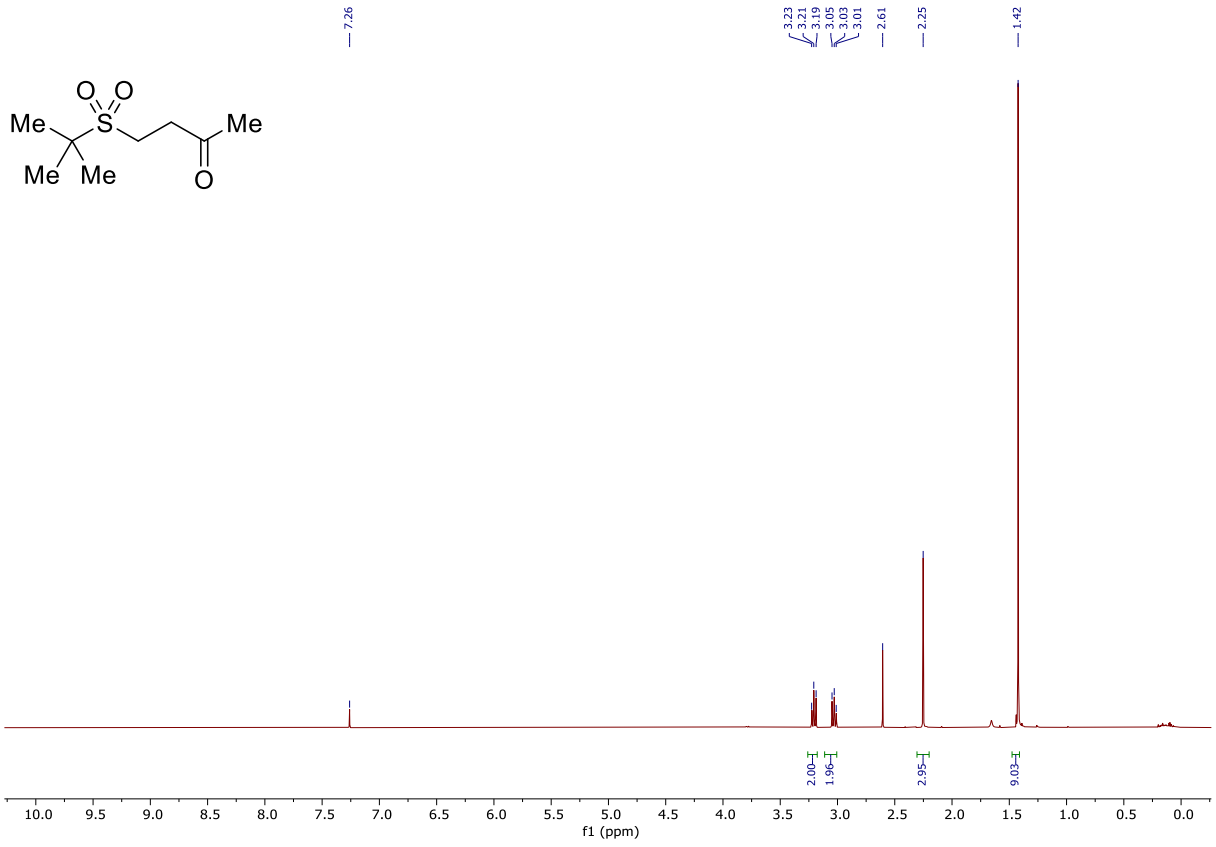



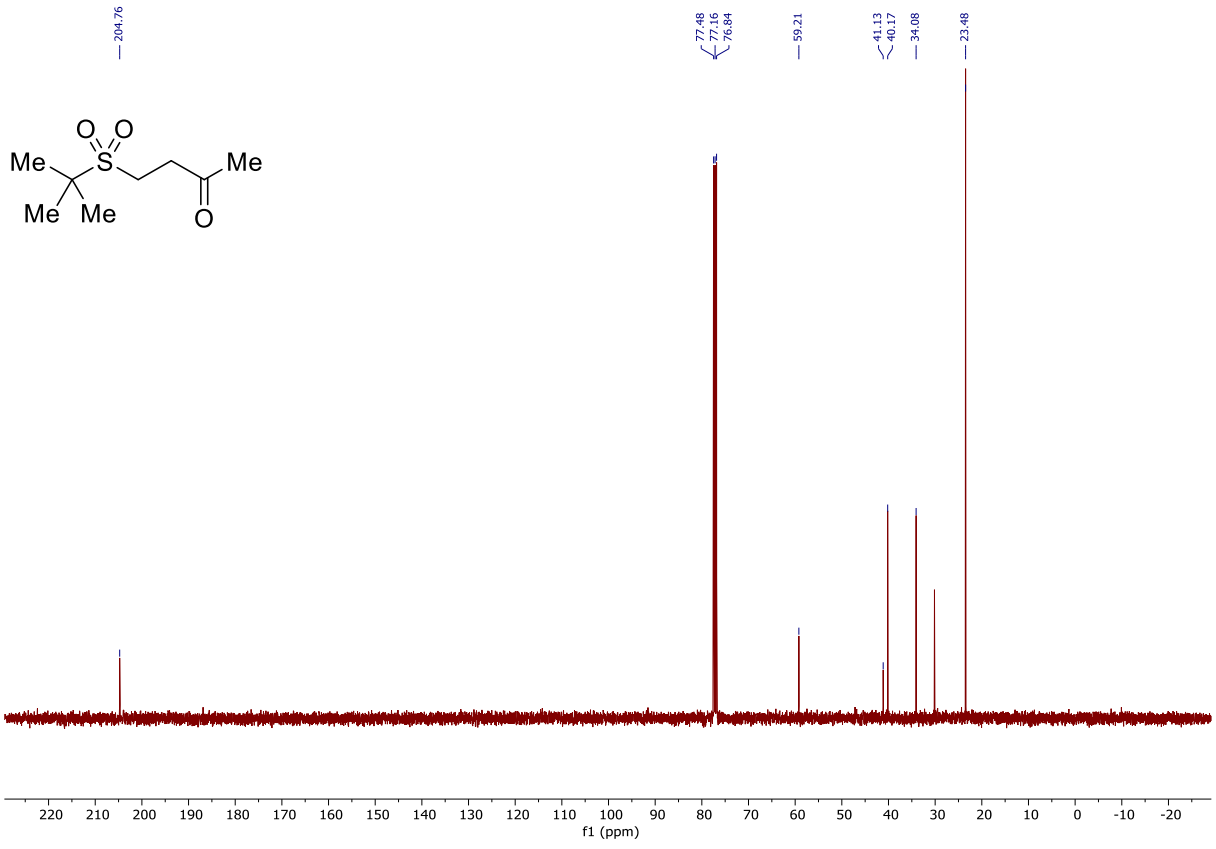
## 4-(Cyclopropylsulfonyl)butan-2-one (109r)



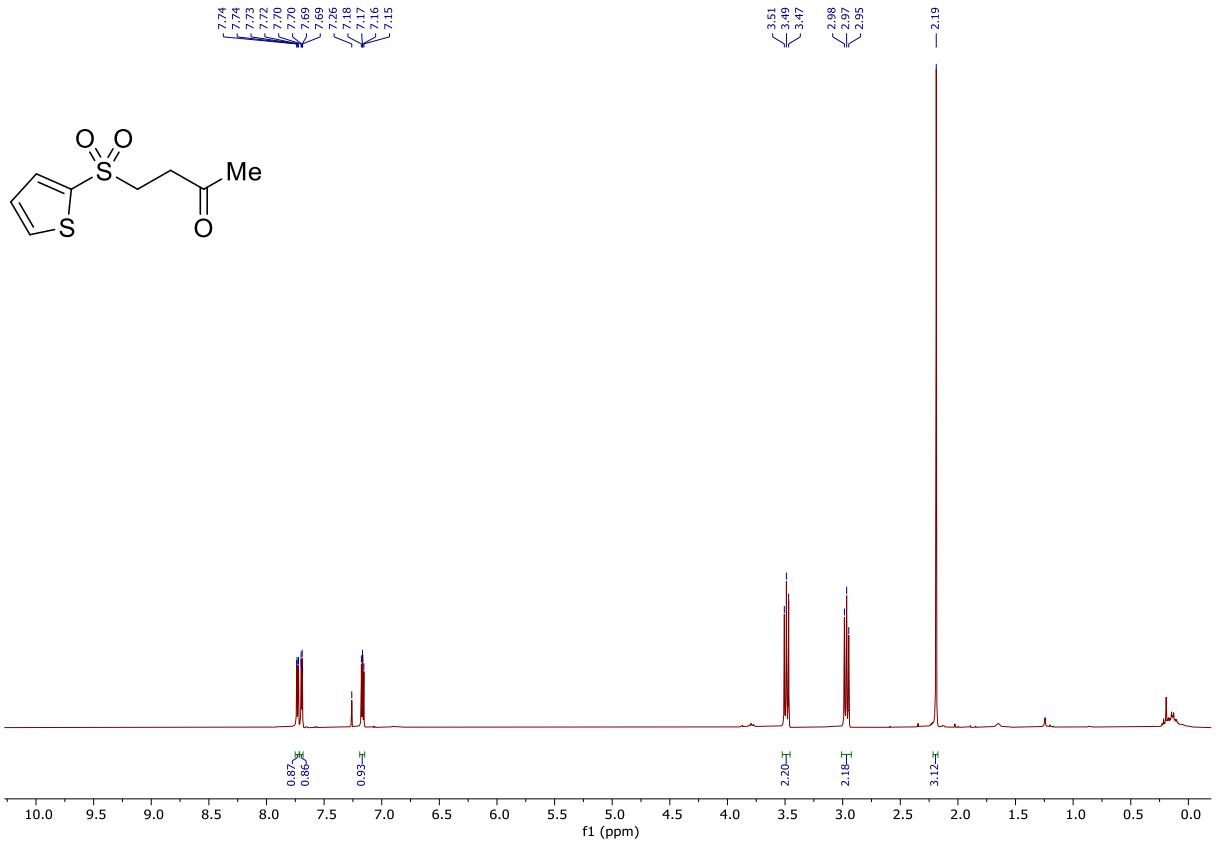



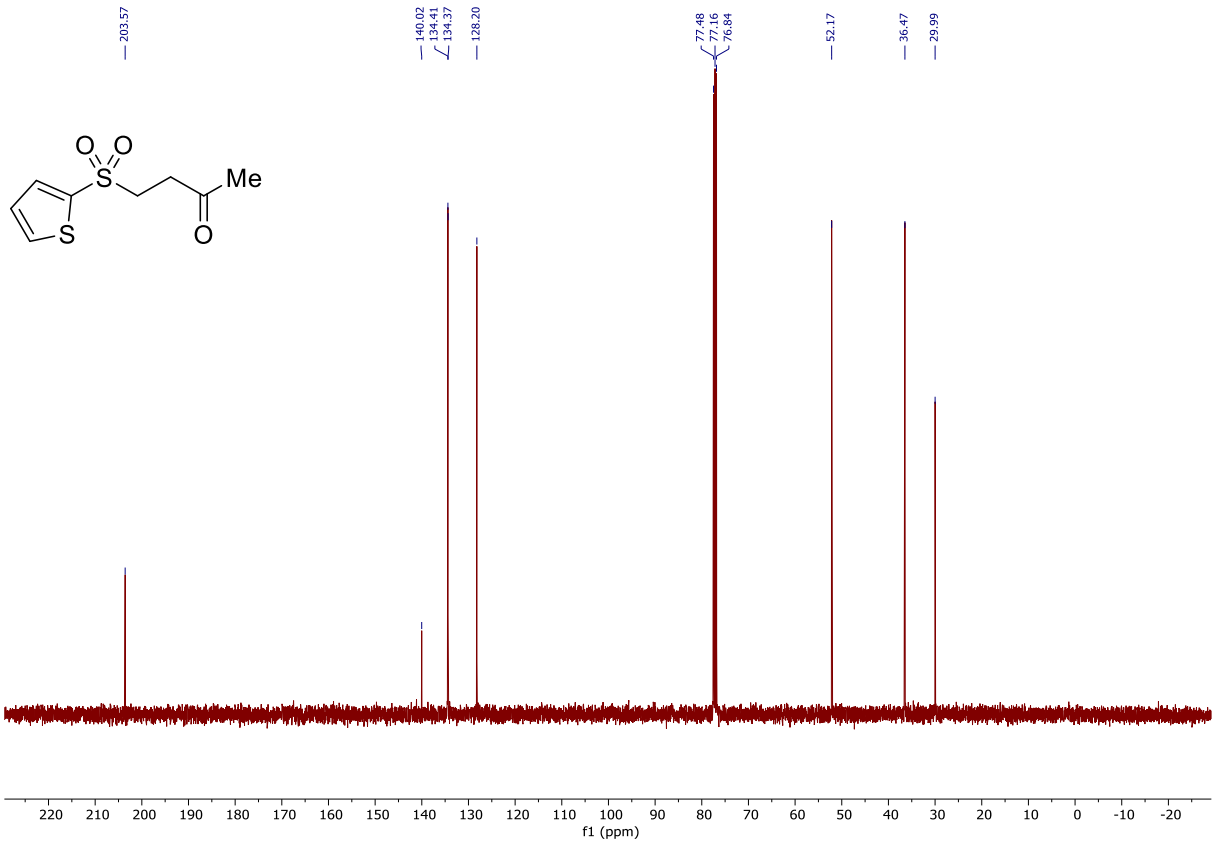
## 4-(Tert-butylsulfonyl)butan-2-one (109s)



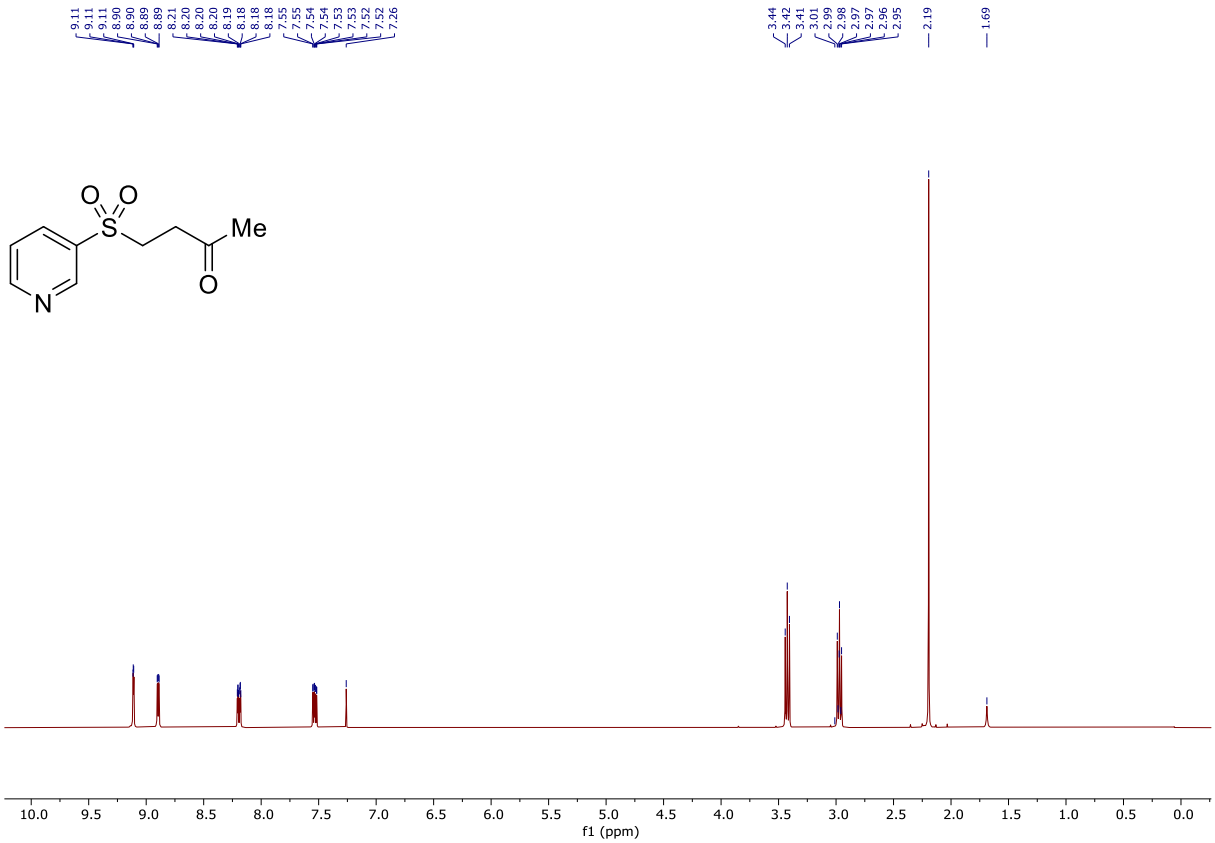



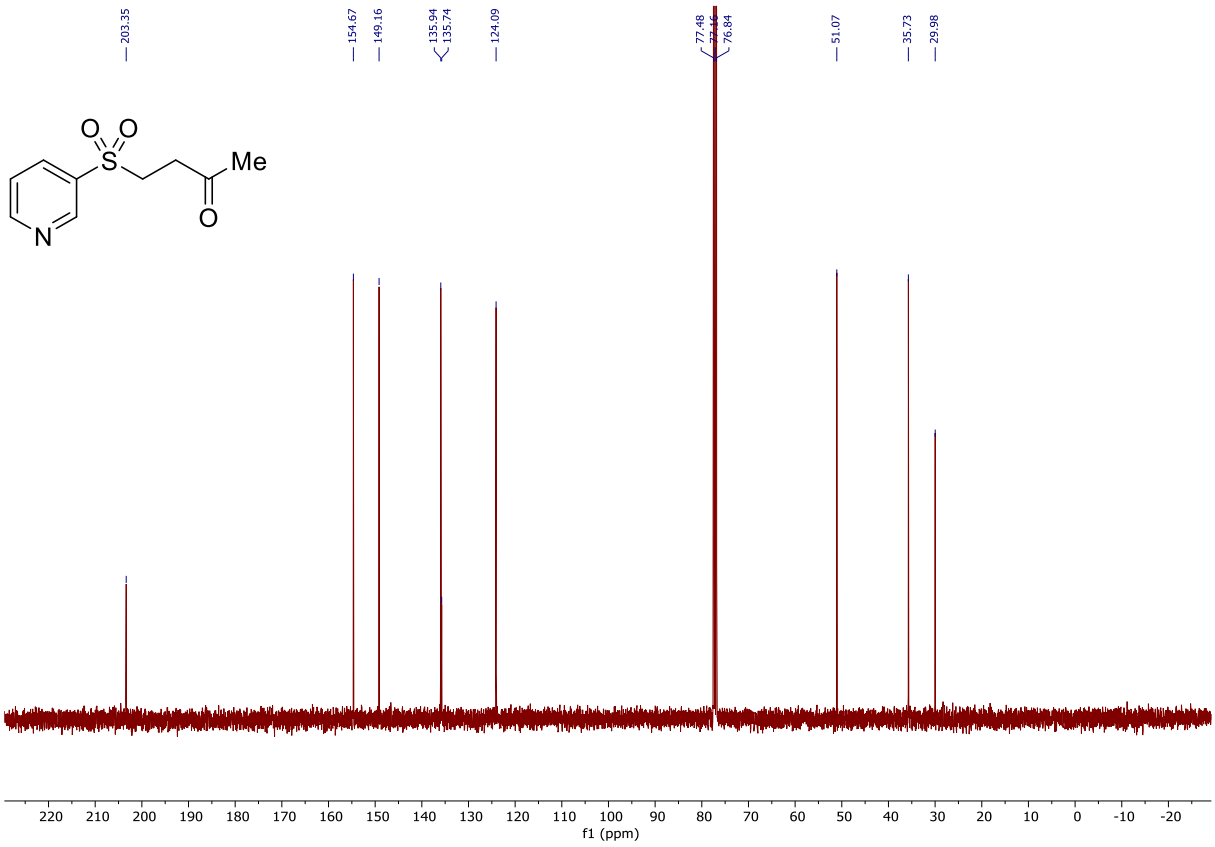
## 4-(Thiophen-2-ylsulfonyl)butan-2-one (109w)



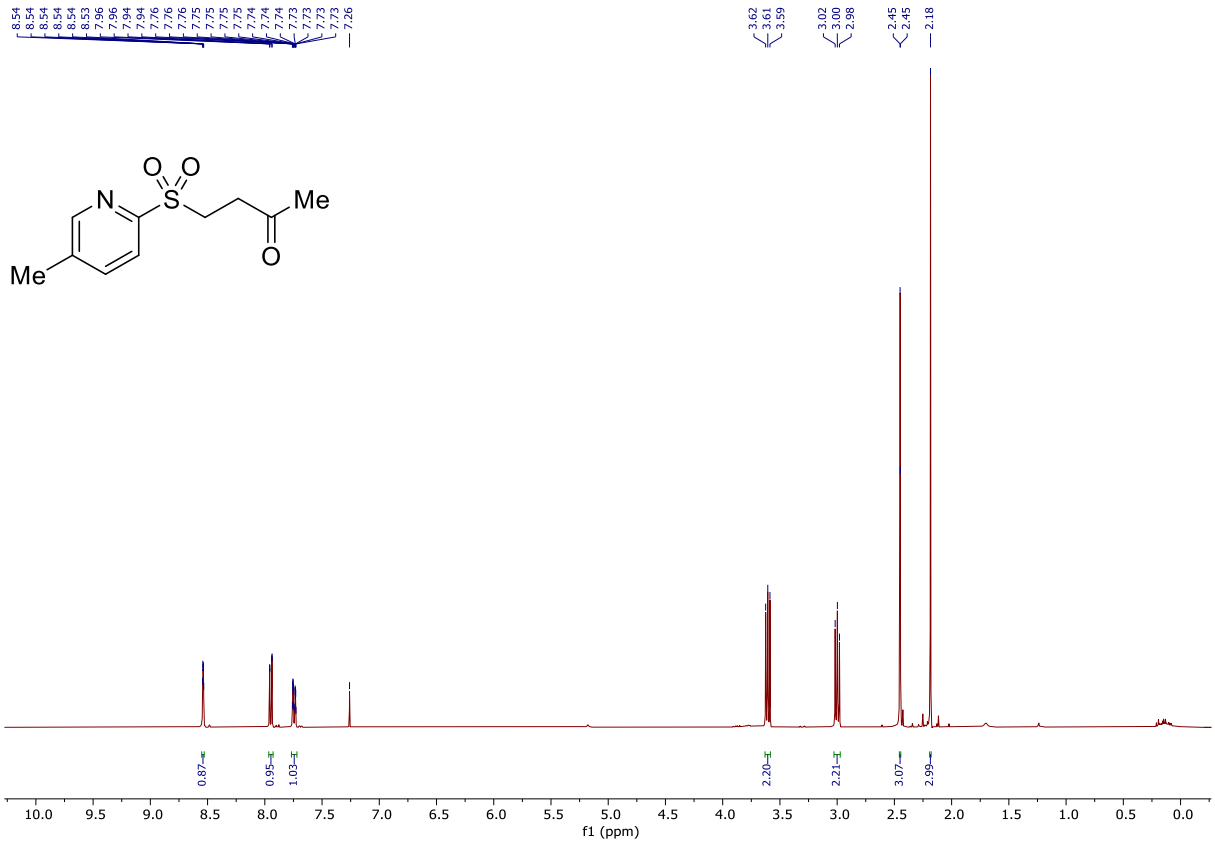



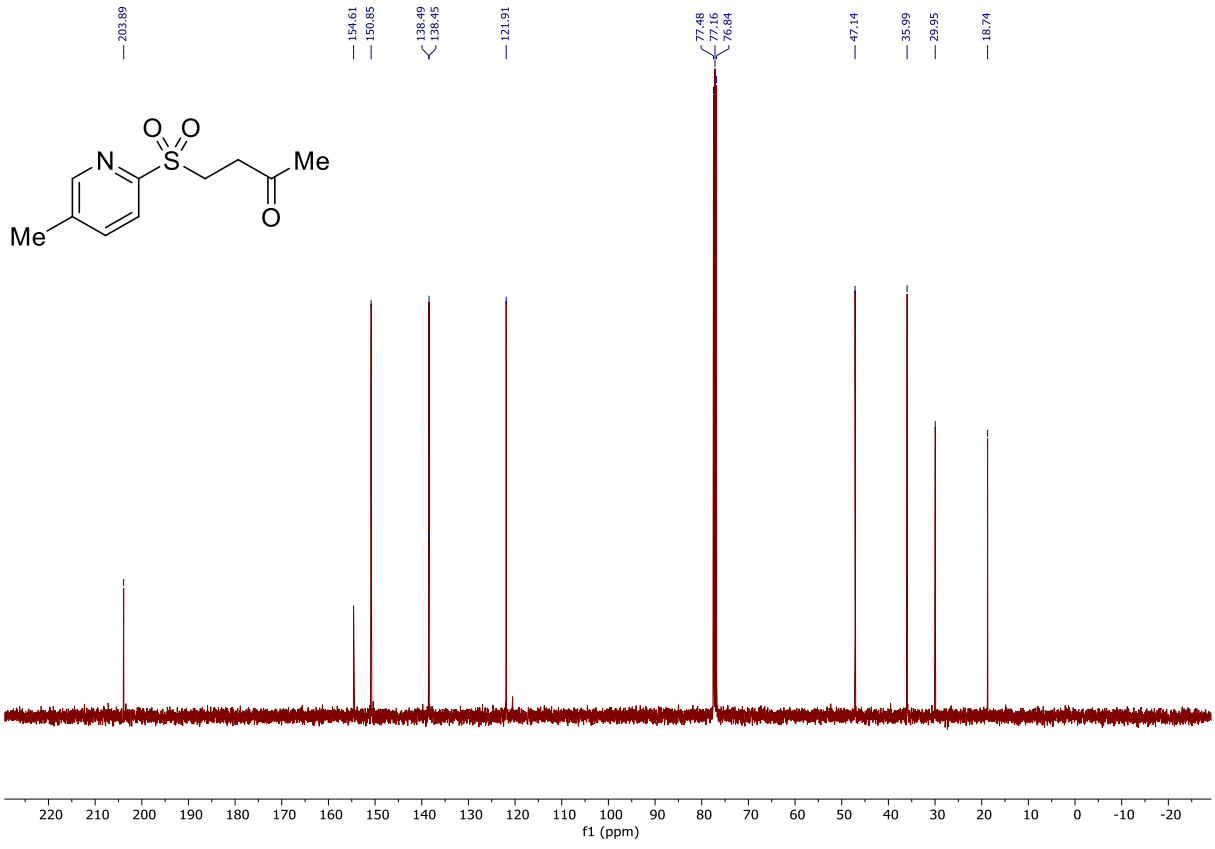
## 4-(Pyridin-3-ylsulfonyl)butan-2-one (109x)



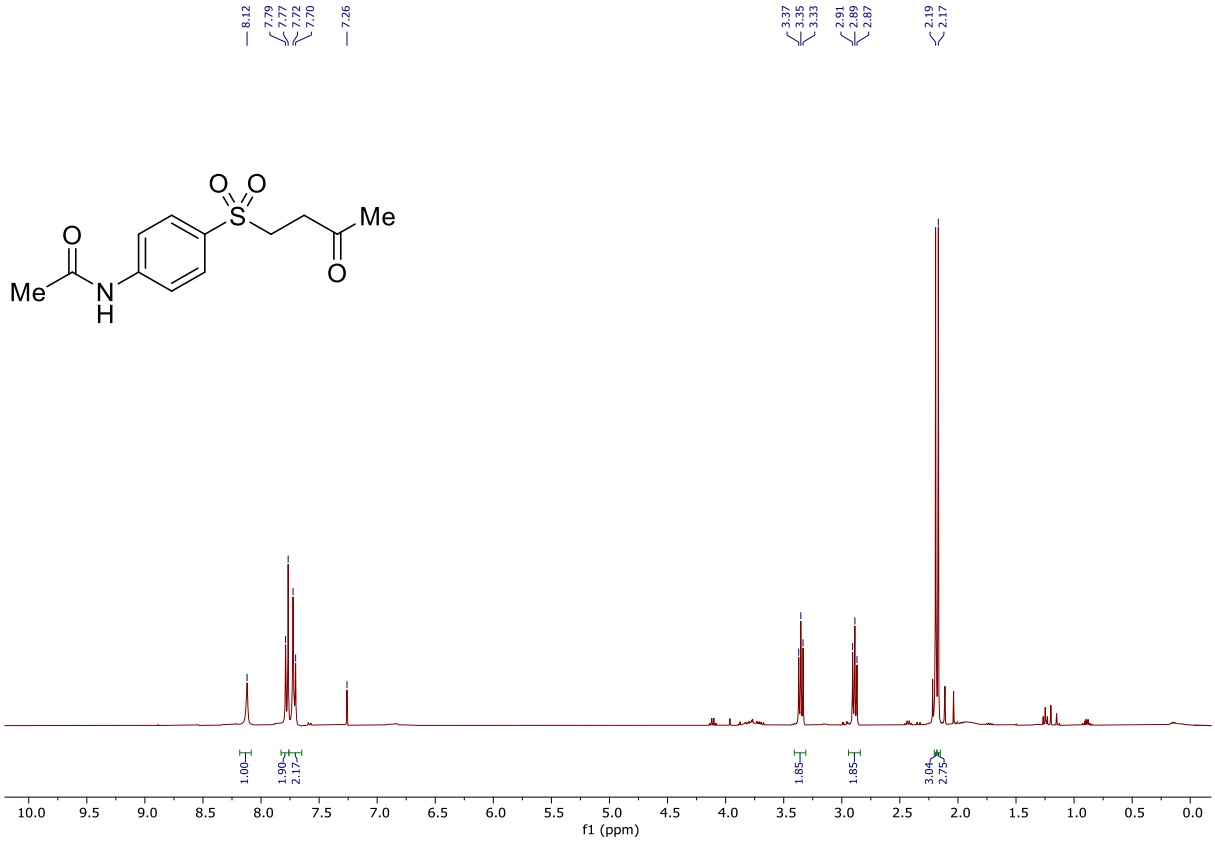



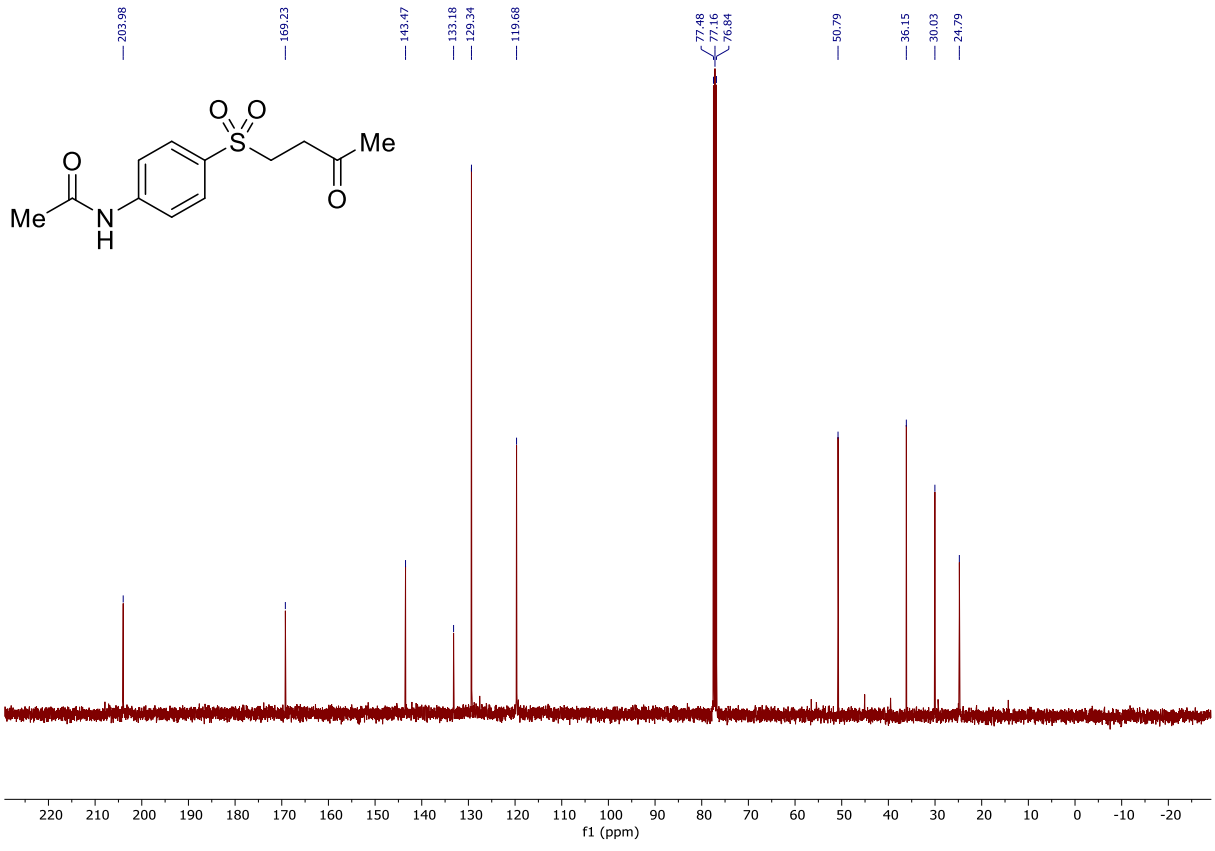
## 4-((5-Methylpyridin-2-yl)sulfonyl)butan-2-one (109y)



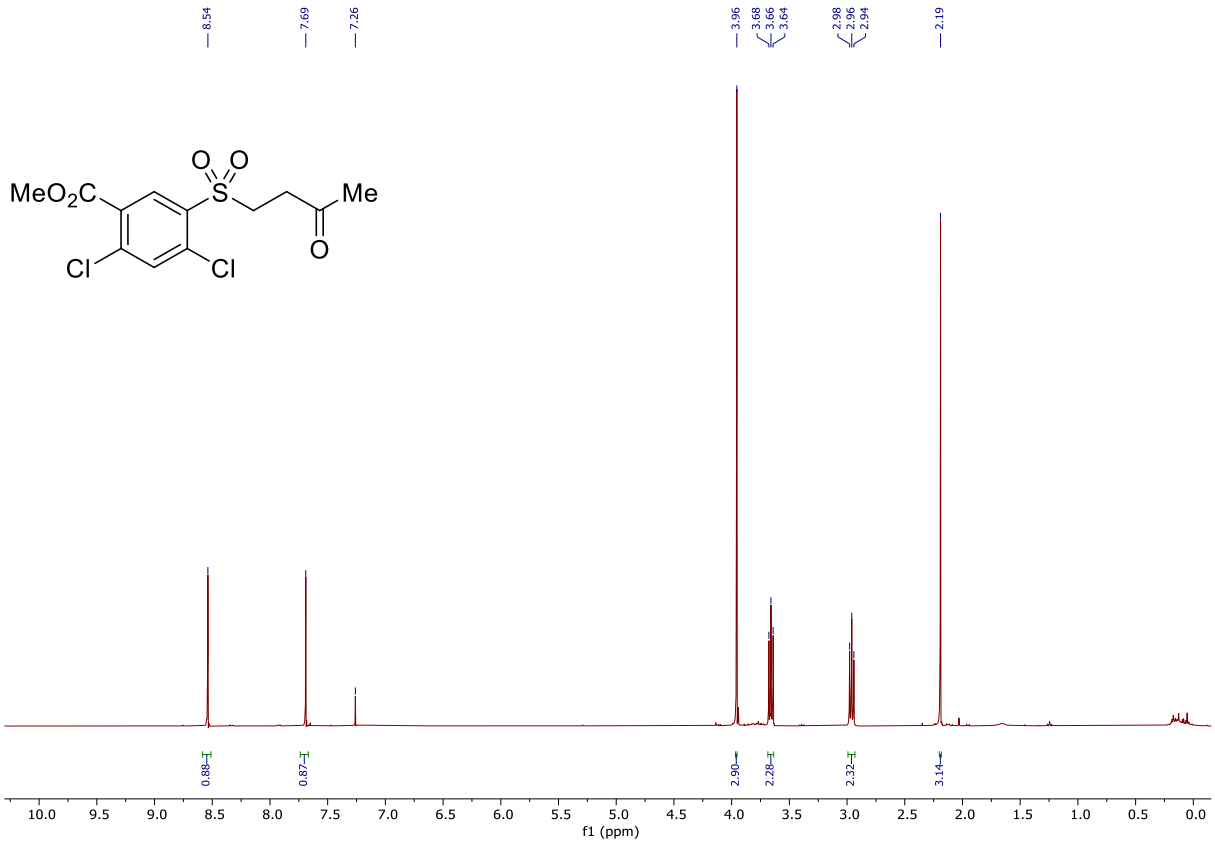



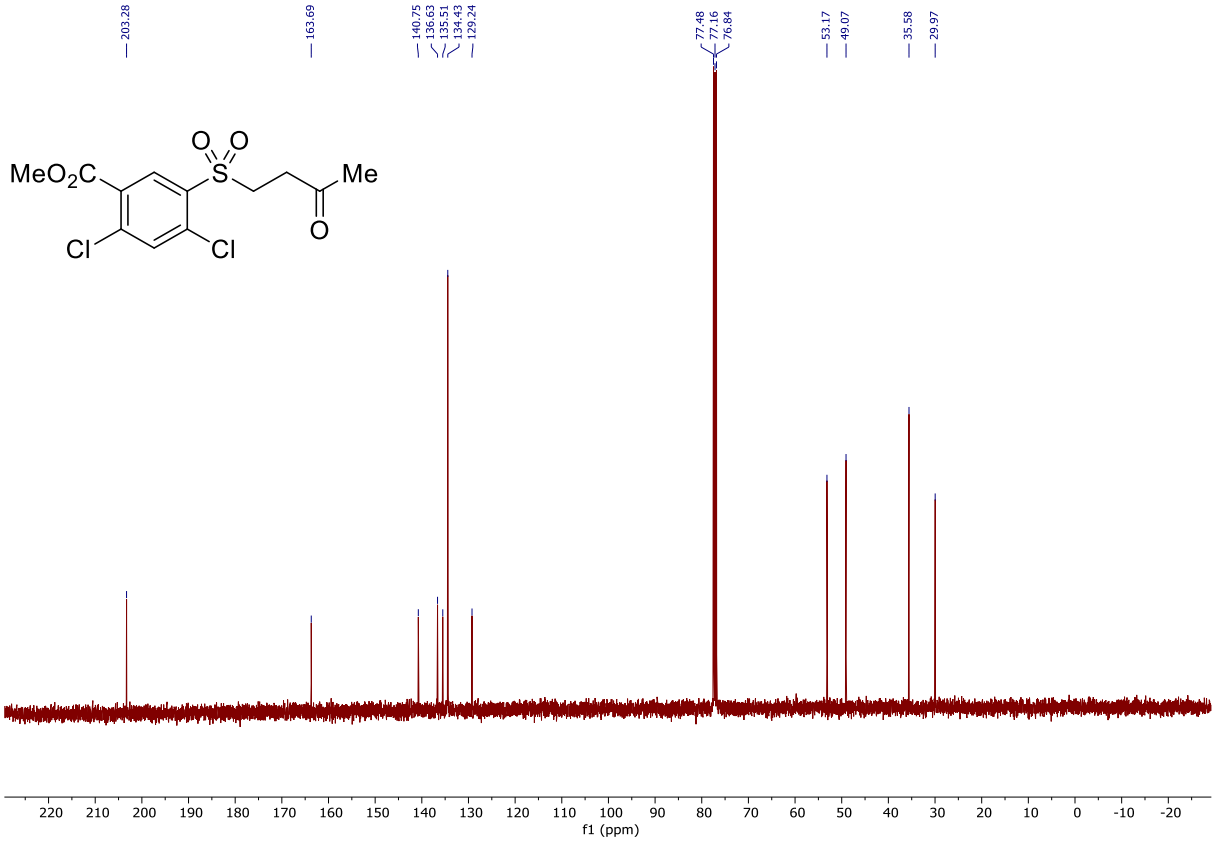
## *N*-(4-((3-oxobutyl)sulfonyl)phenyl)acetamide (109z)



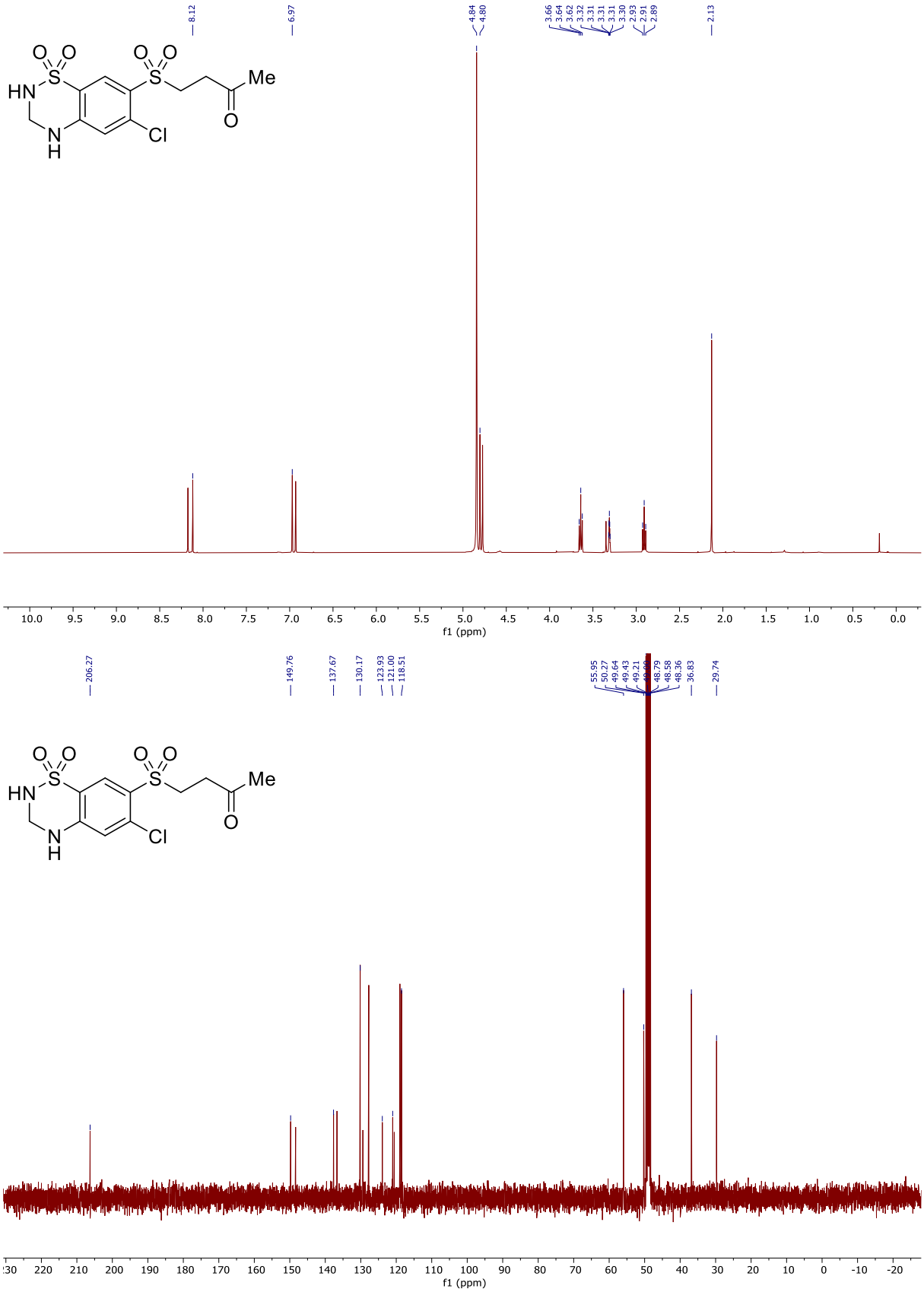



**Methyl 2,4-dichloro-5-((3-oxobutyl)sulfonyl)benzoate (111a)**



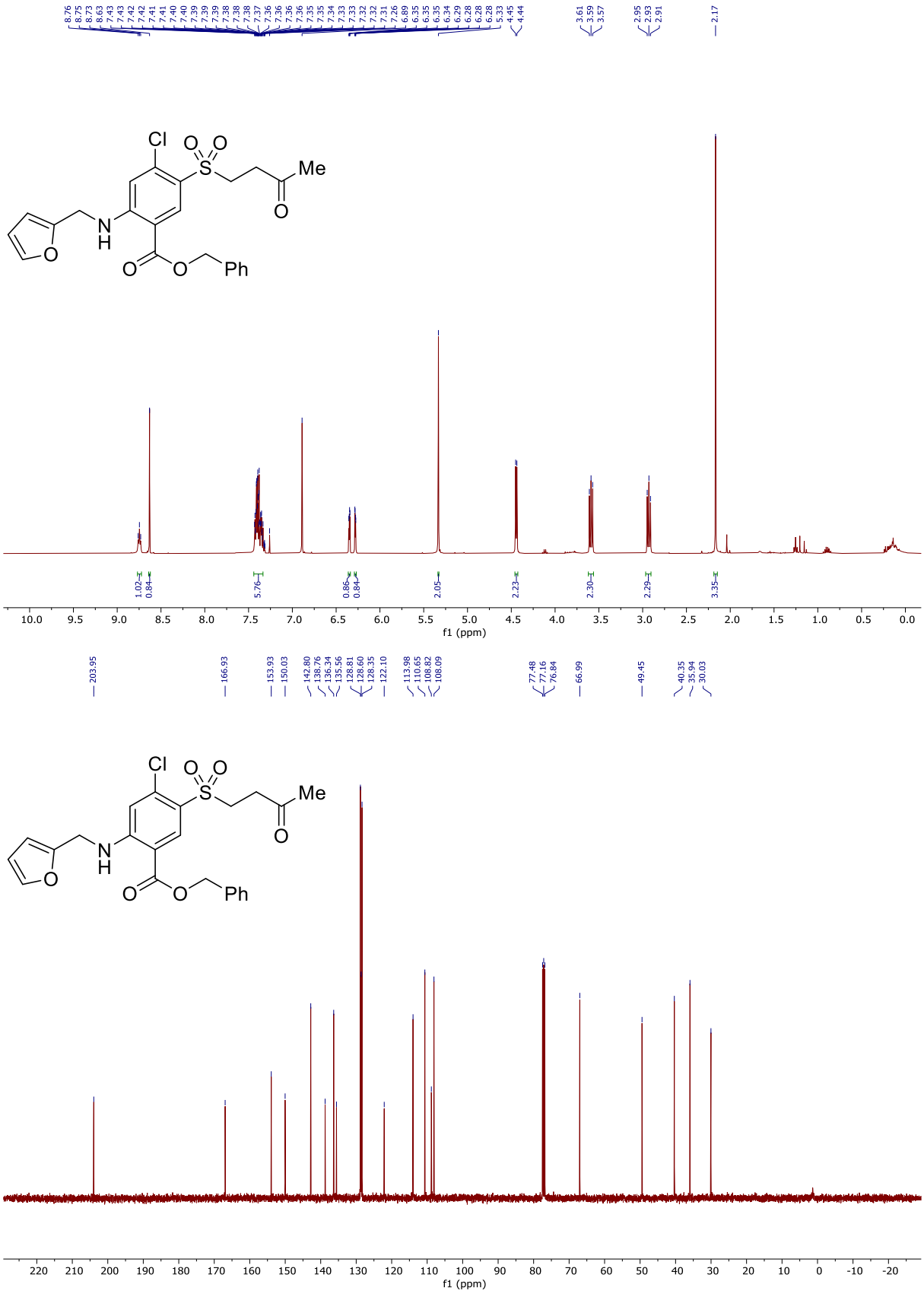



**4-((6-Chloro-1,1-dioxido-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazin-7-yl)sulfonyl)butan-2-one (111b)**

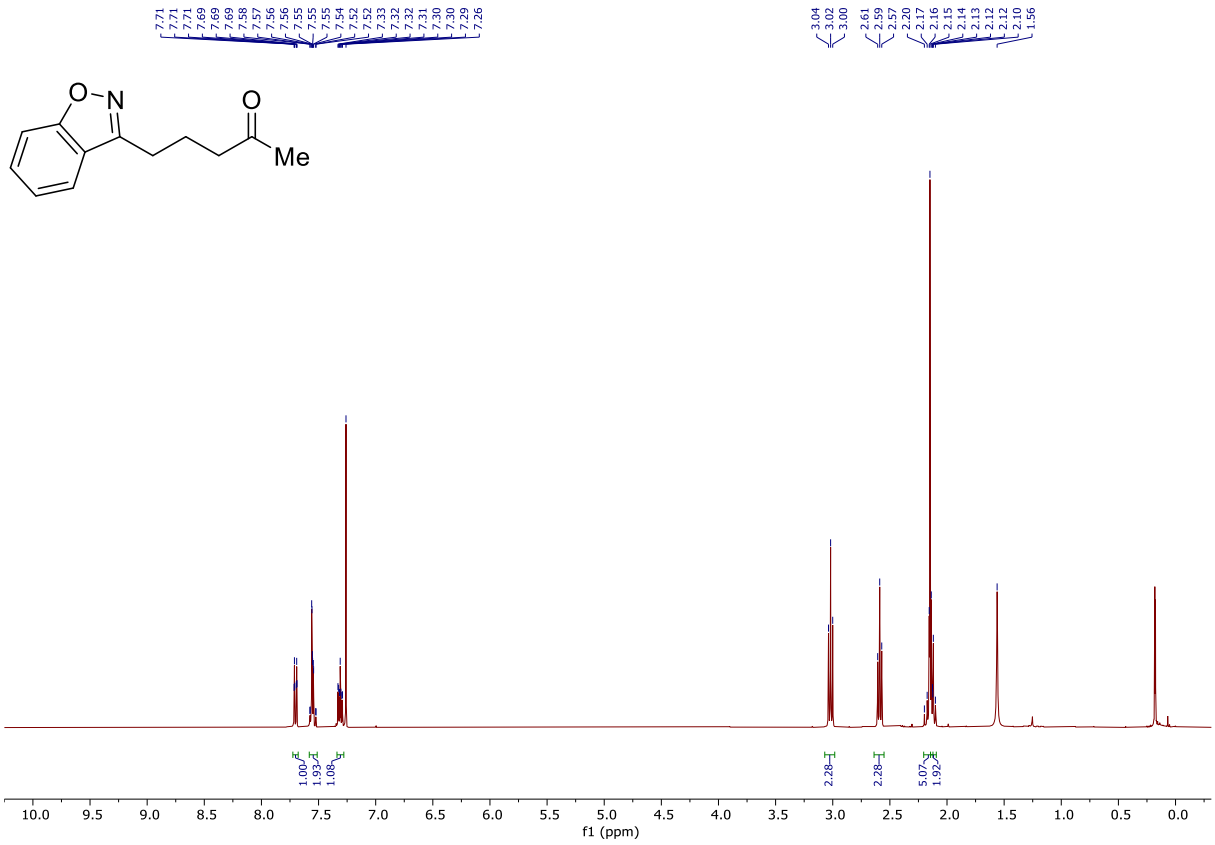


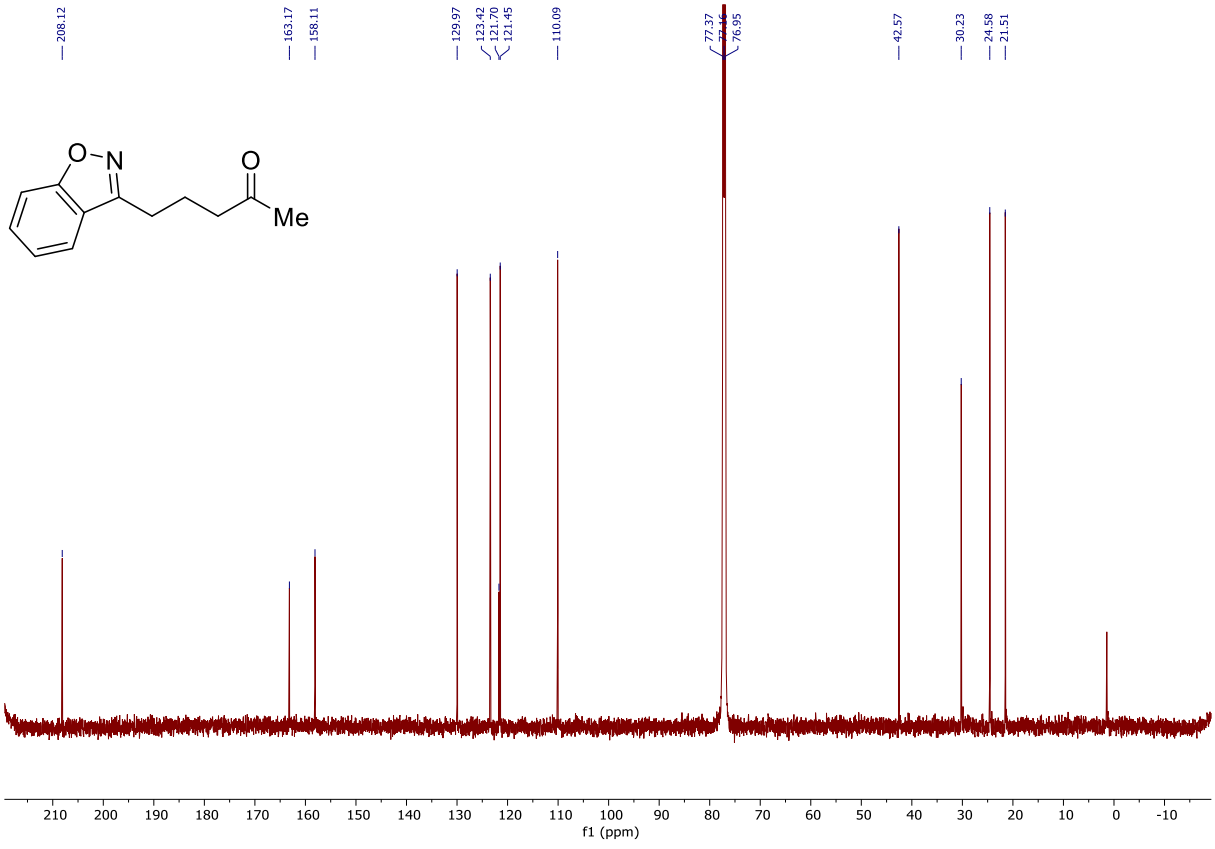

*52% purity due to the presensce of sulfonamide.

**Benzyl 4-chloro-2-((furan-2-ylmethyl)amino)-5-((3-oxobutyl)sulfonyl)benzoate (111d)**

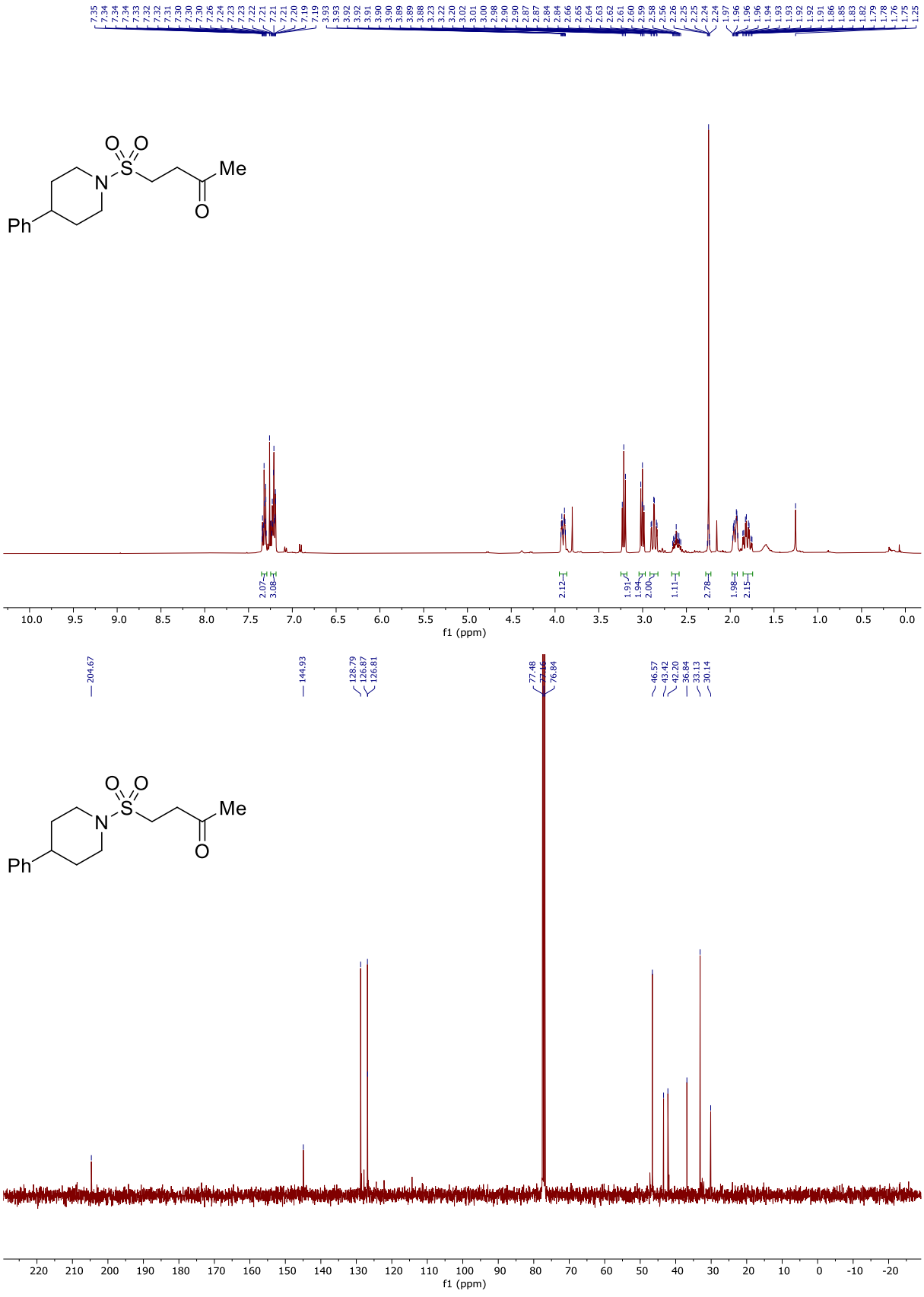


## 5-(Benzo[*d*]isoxazol-3-yl)pentan-2-one (112)

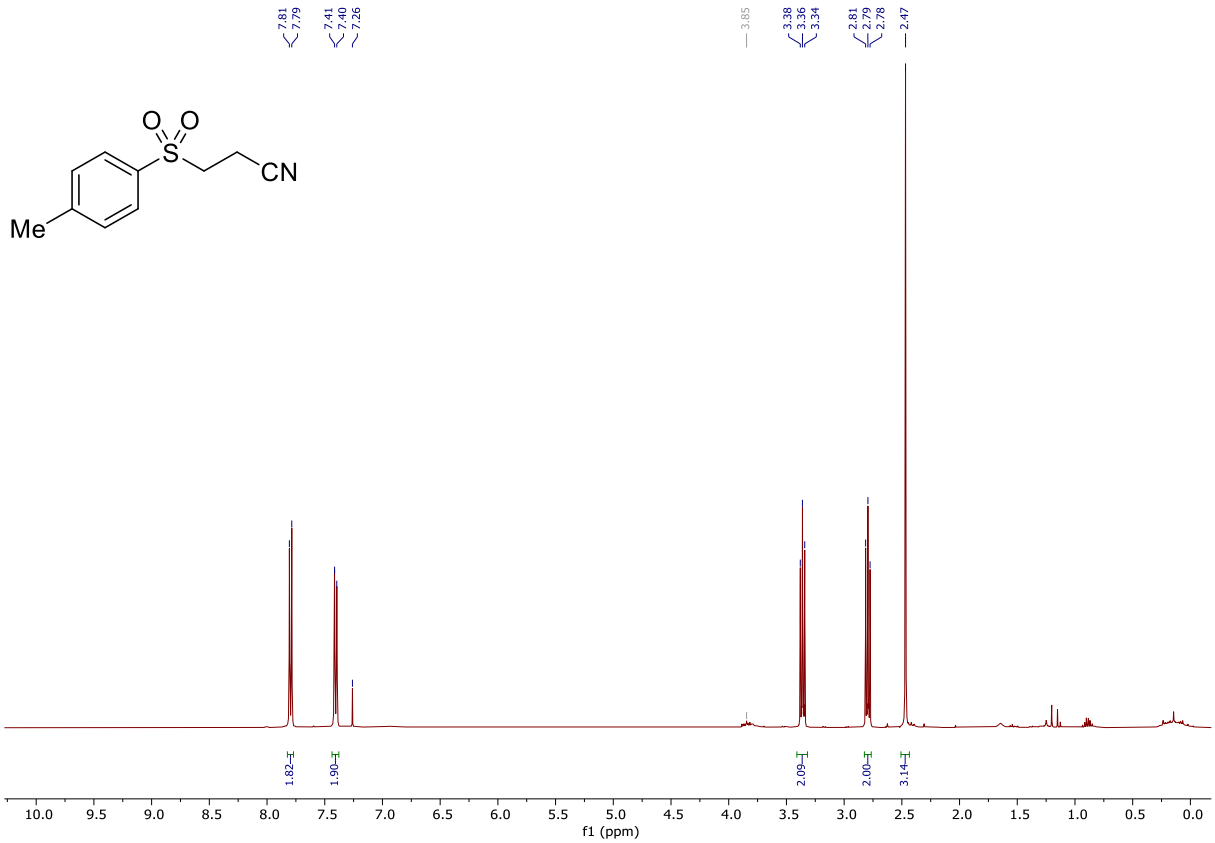


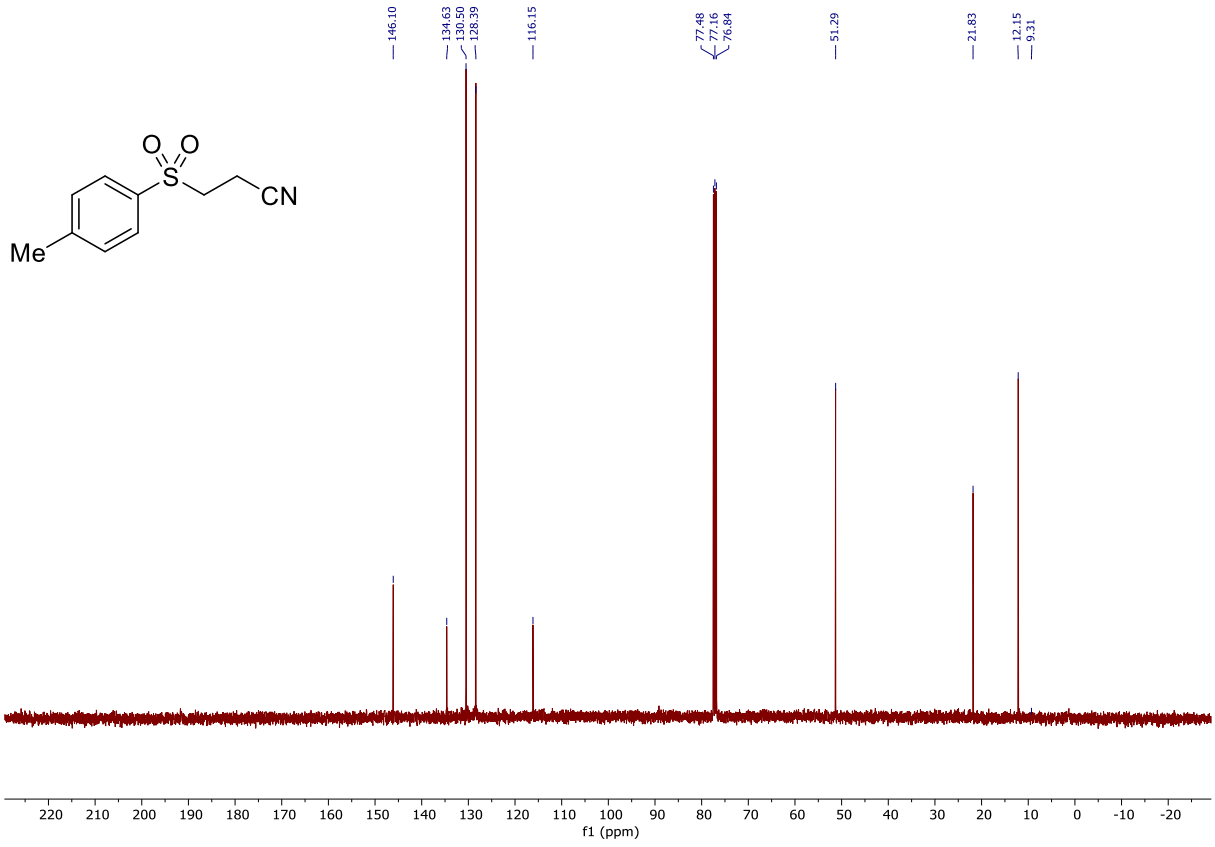



## 4-((4-Phenylpiperidin-1-yl)sulfonyl)butan-2-one (116b)

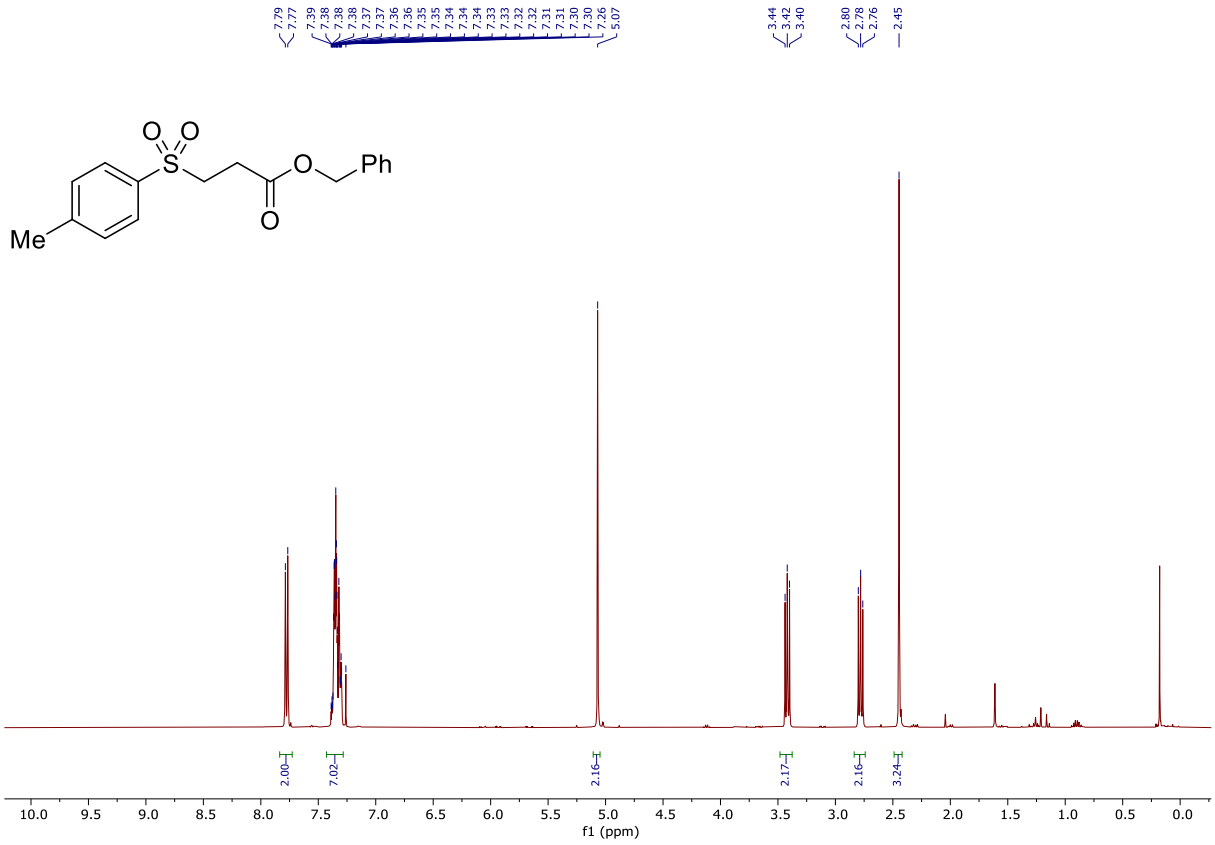


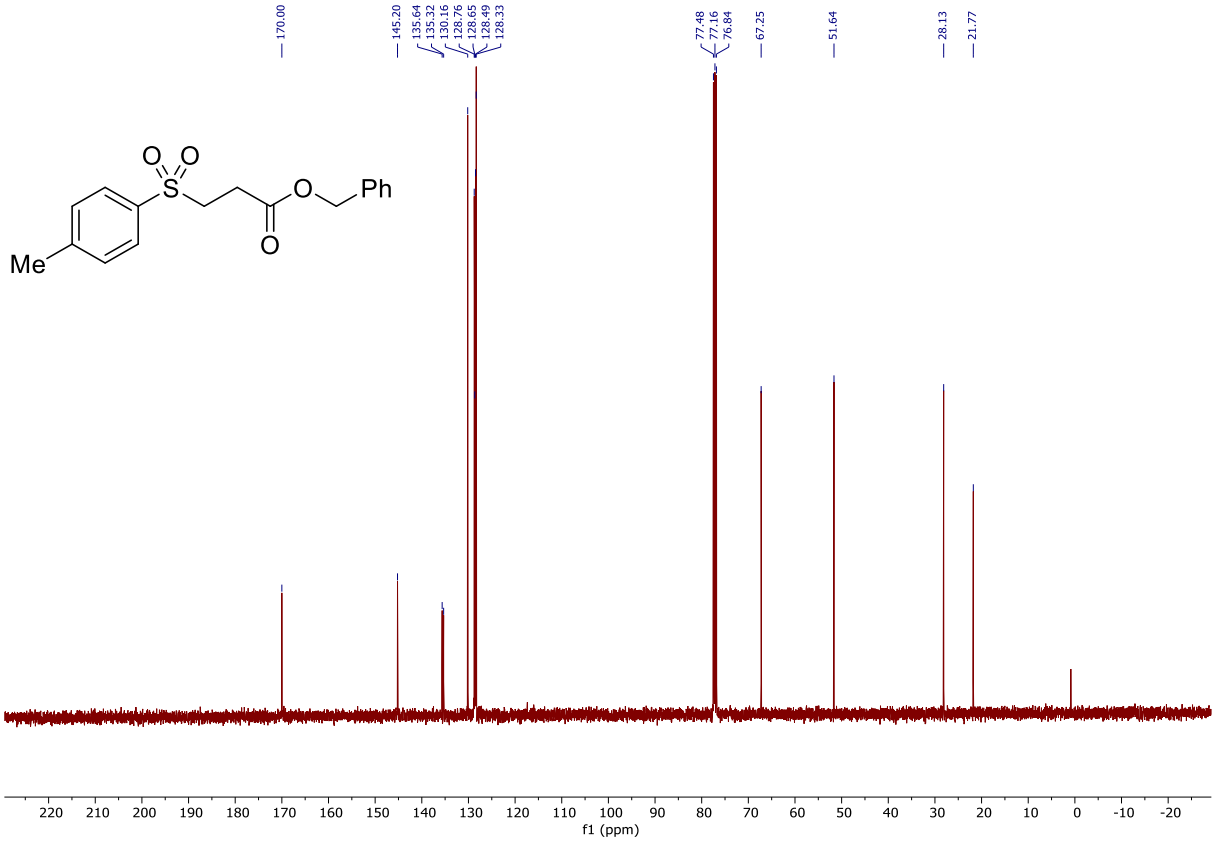
## 3-Tosylpropanenitrile (109ab)



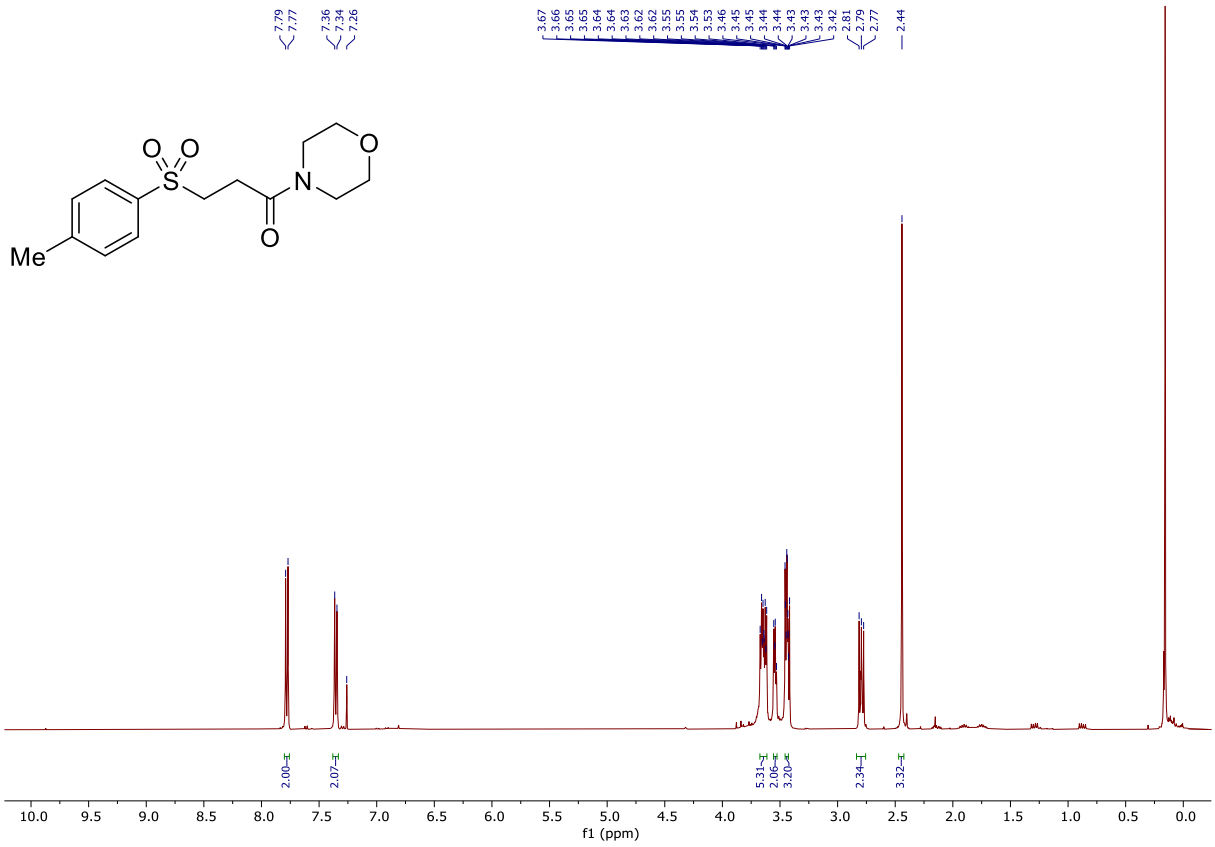



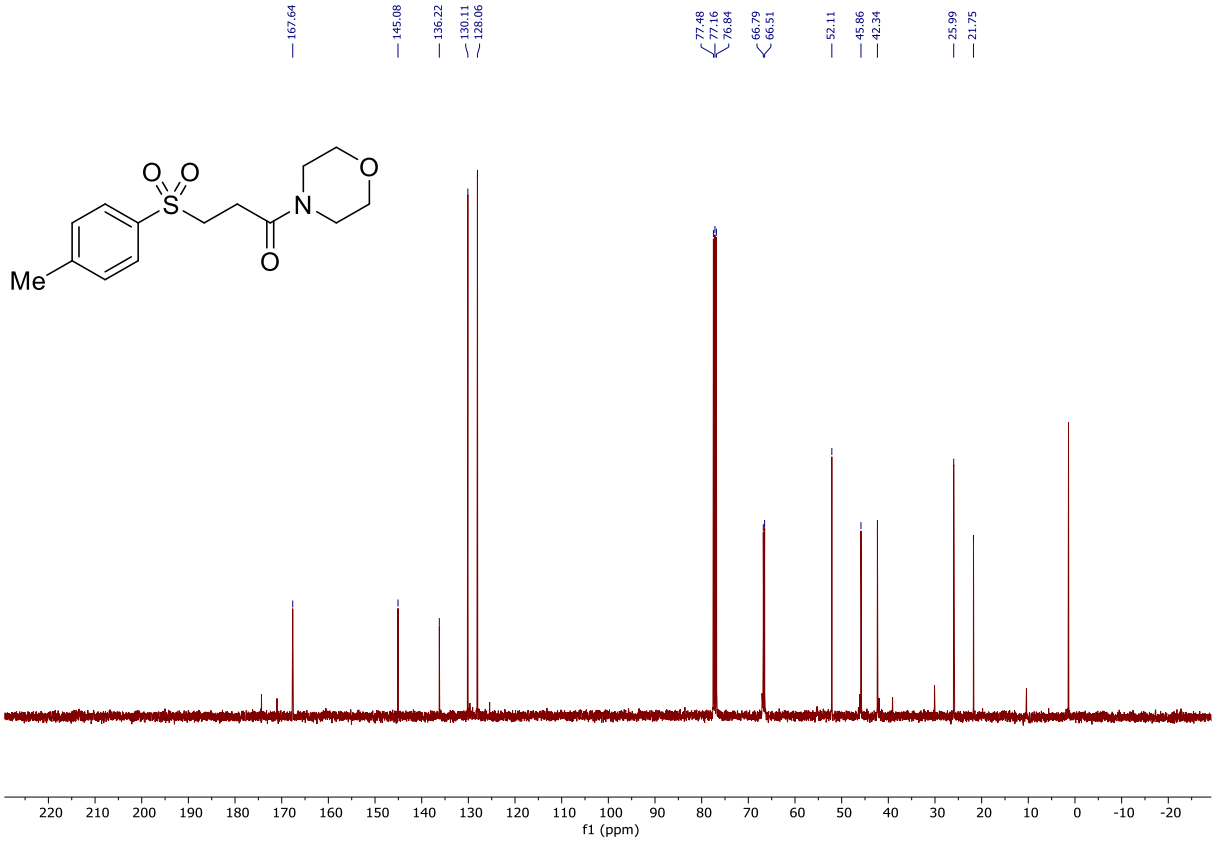
## Benzyl 3-tosylpropanoate (109ac)



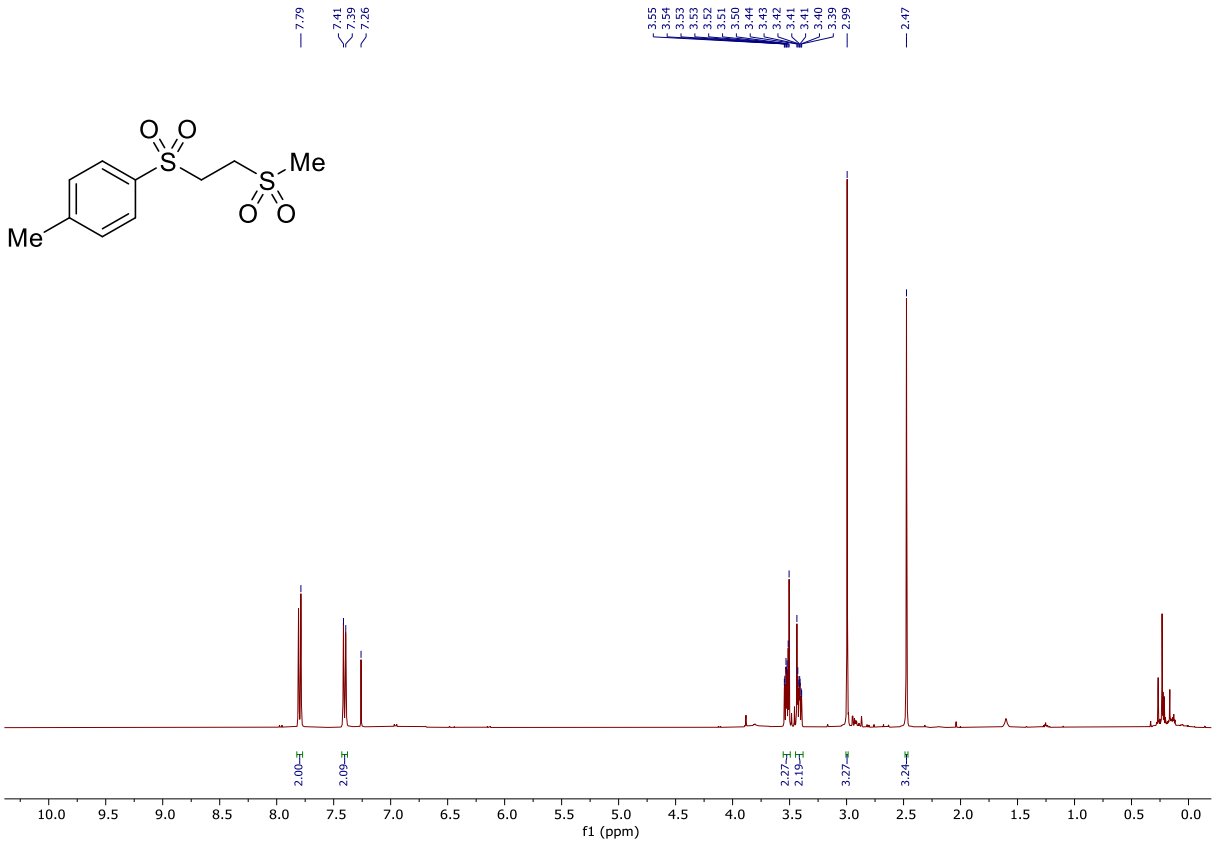



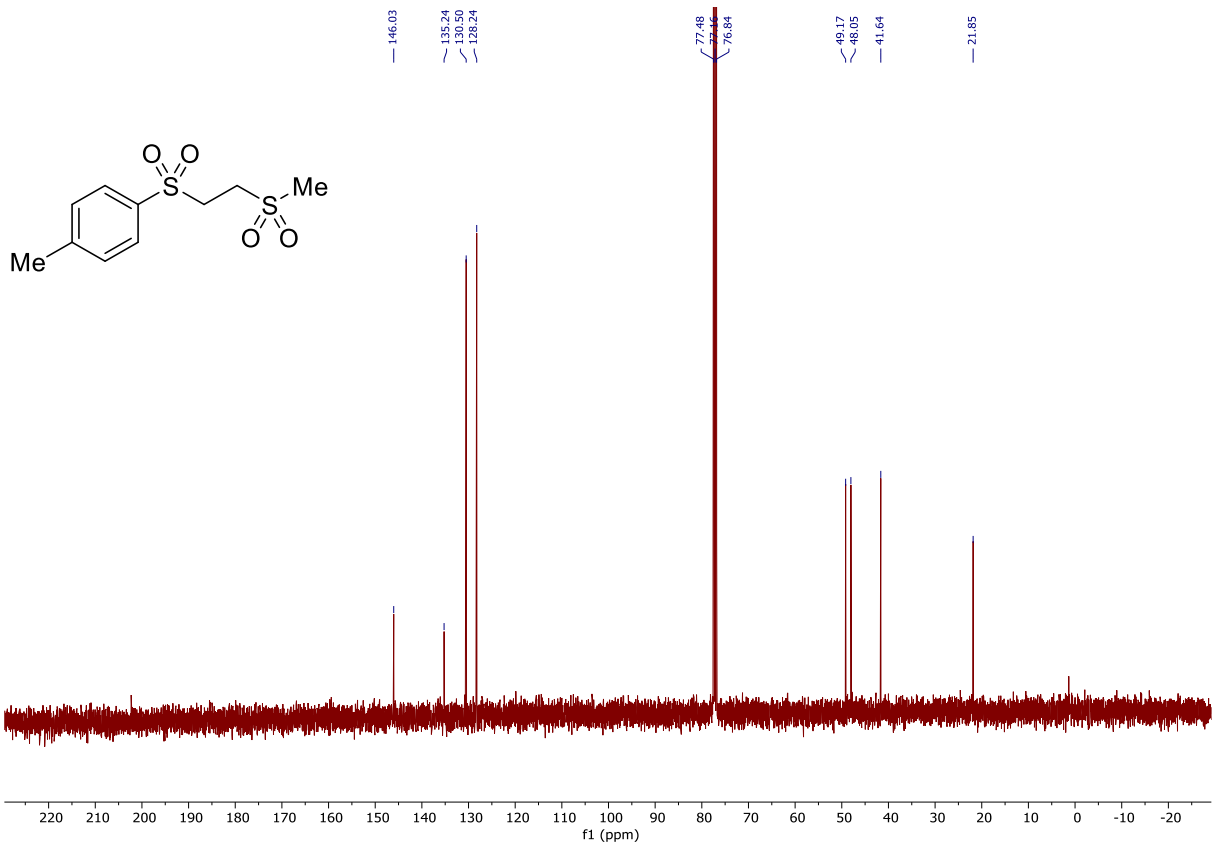
## 1-Morpholino-3-tosylpropan-1-one (109ad)



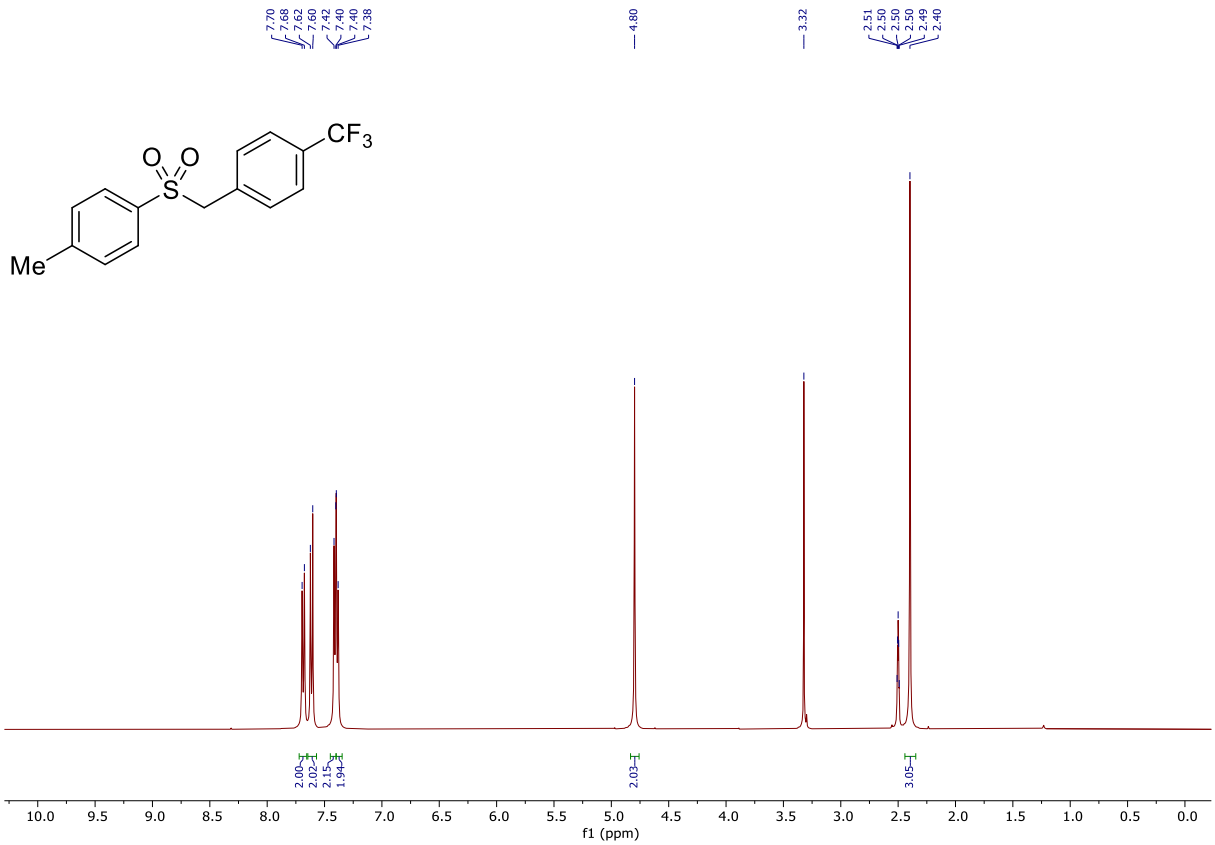



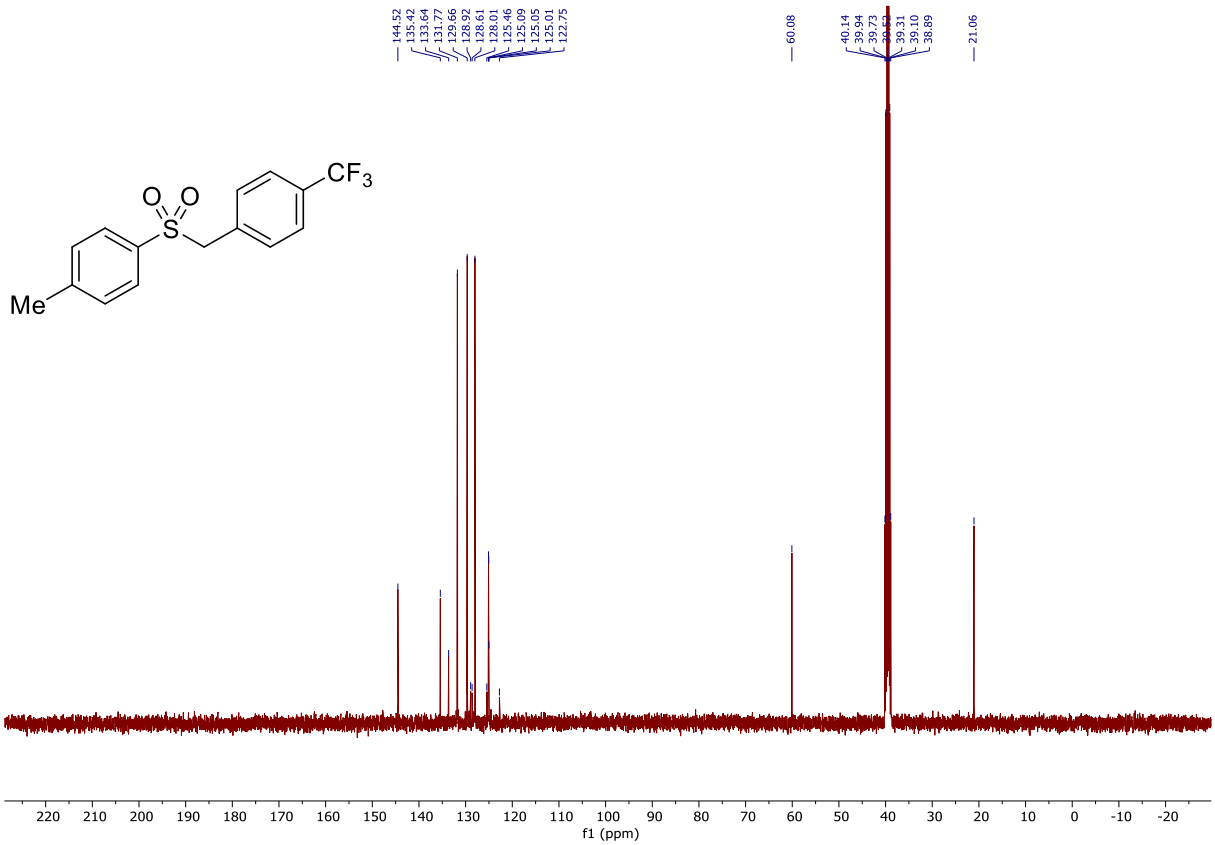
## 1-Methyl-4-((2-(methylsulfonyl)ethyl)sulfonyl)benzene (109ae)

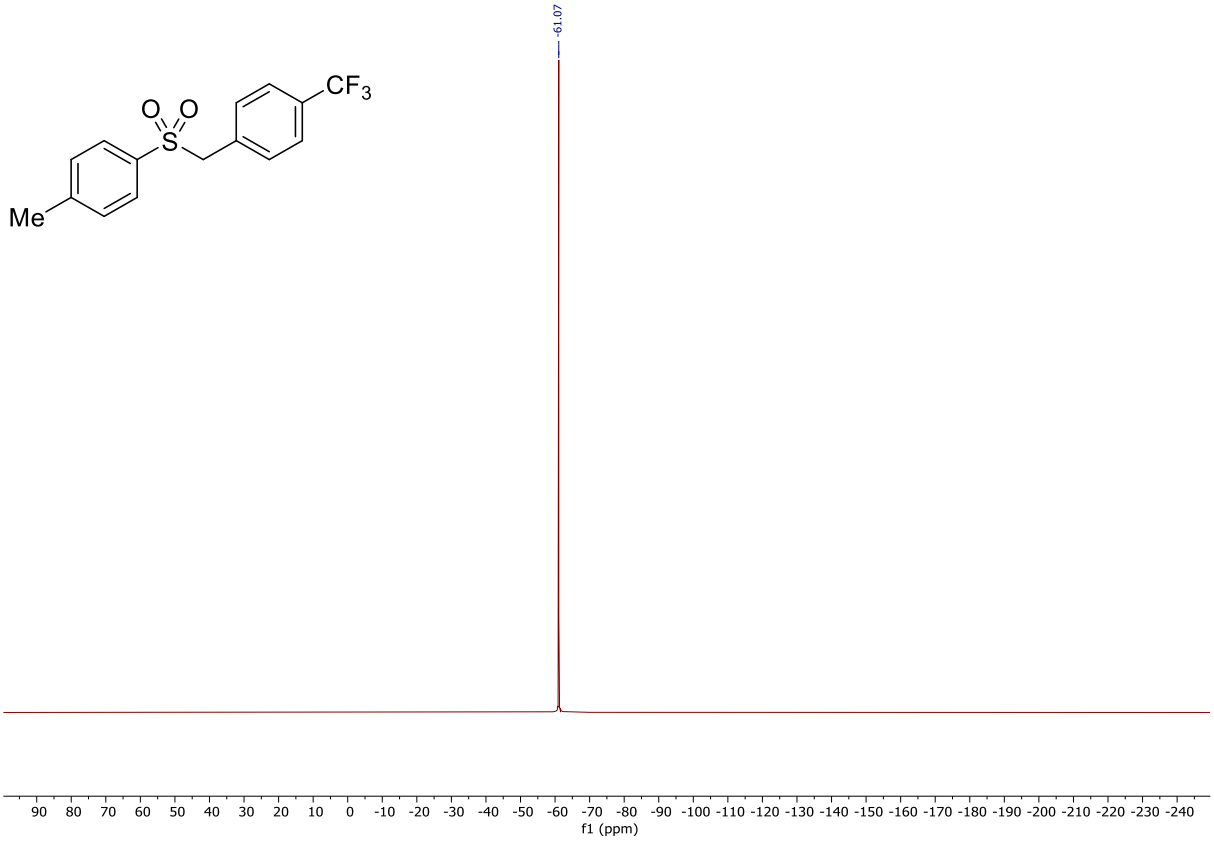


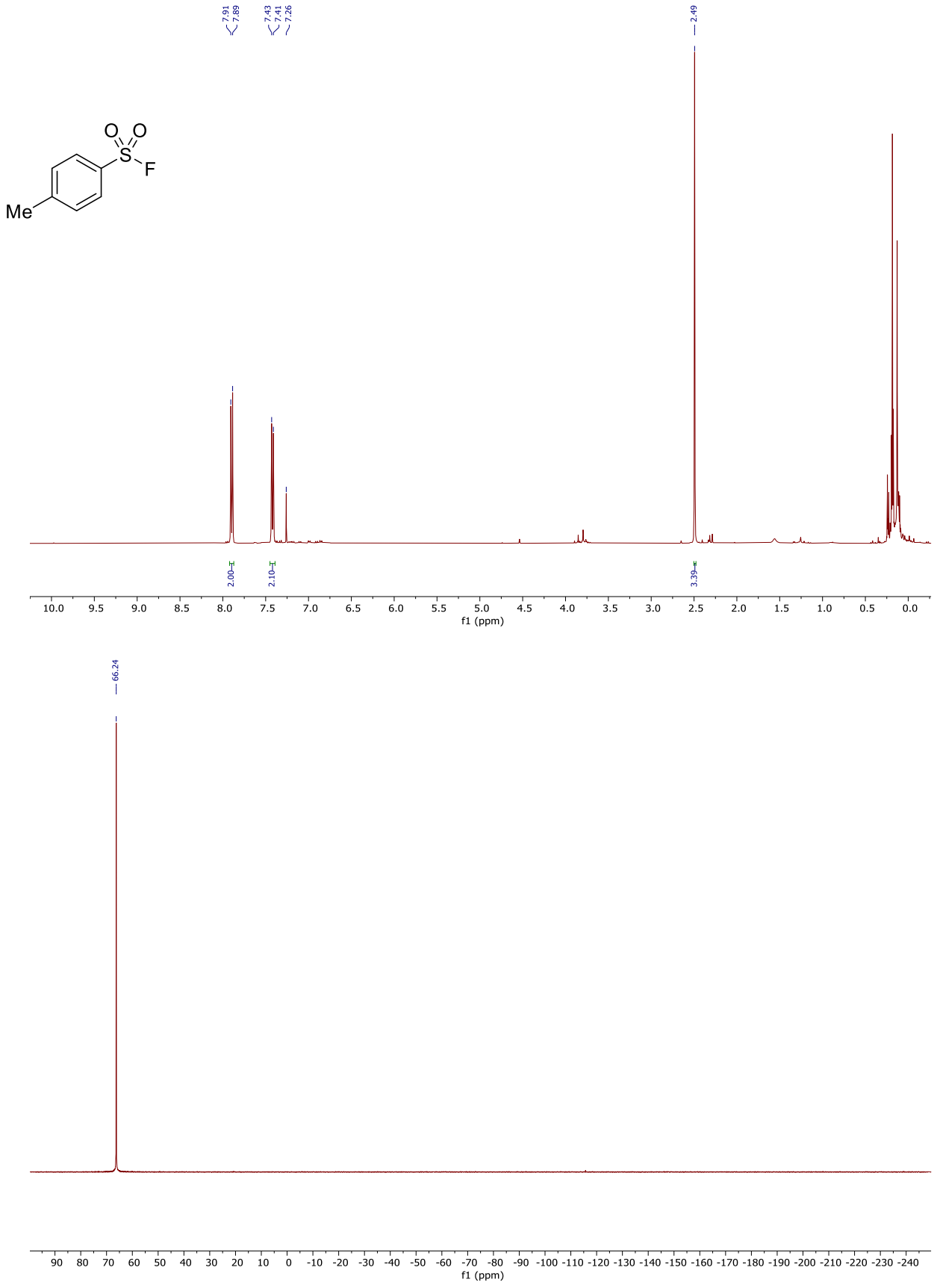
## 1-Methyl-4-((4-(trifluoromethyl)benzyl)sulfonyl)benzene (120)



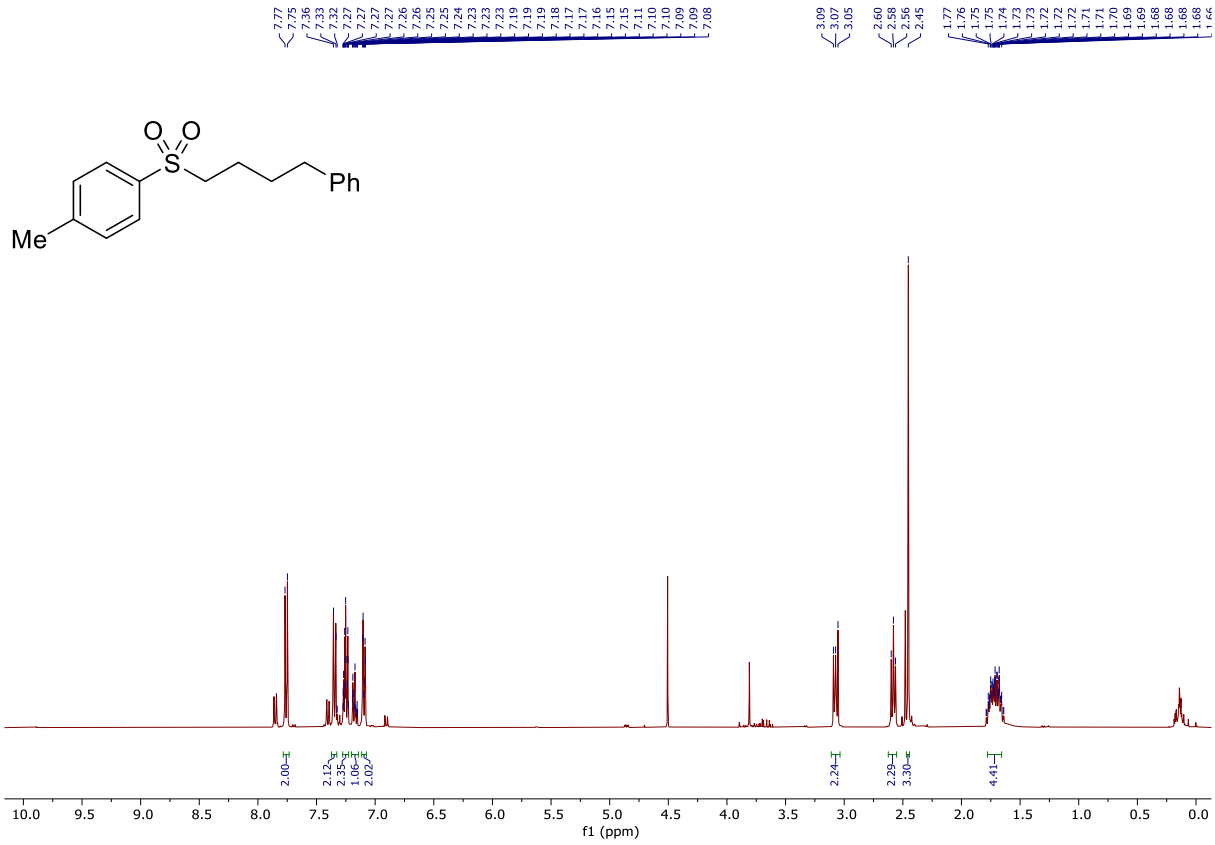

-61.07
CF3
O
O
S
Me
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

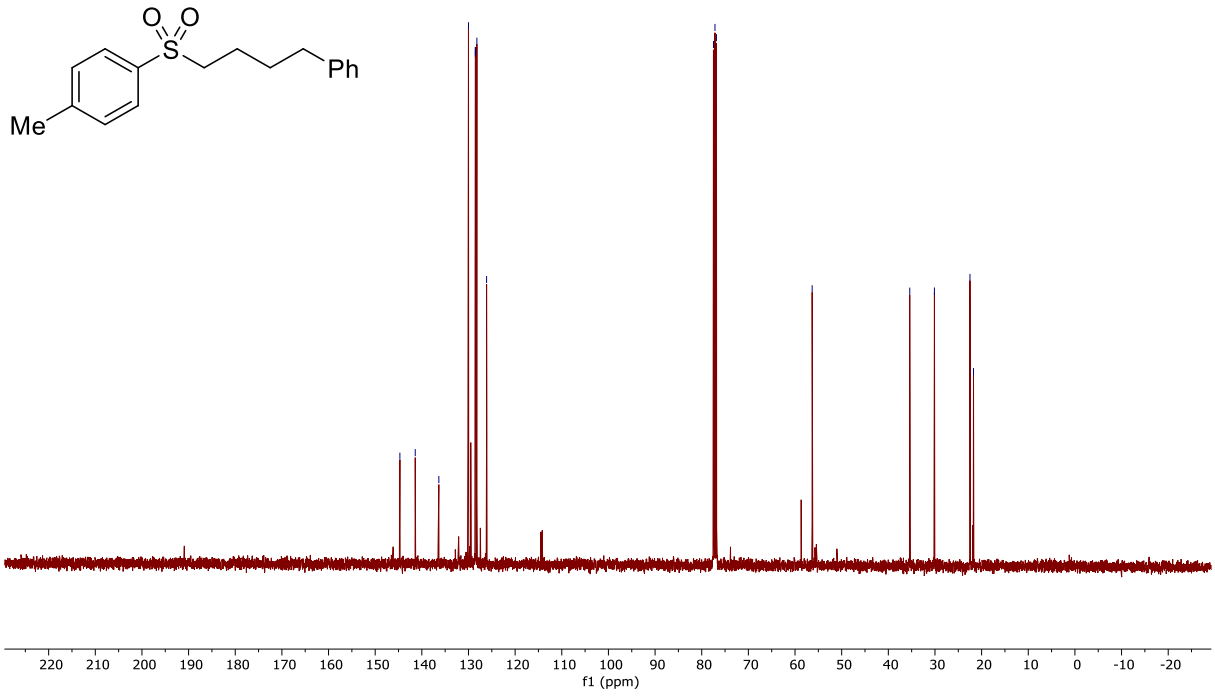
**1-Methyl-4-((4-(trifluoromethyl)benzyl)sulfonyl)benzene (121)**




*Contains silyl derived impurities.

## 1-Methyl-4-((4-phenylbutyl)sulfonyl)benzene (109af)




*81% pure.