Exploiting Sulfinylamines In Synthesis

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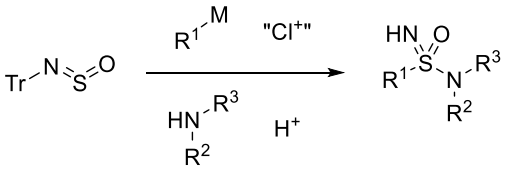
Doctor of Philosophy in Organic Chemistry

Abstract

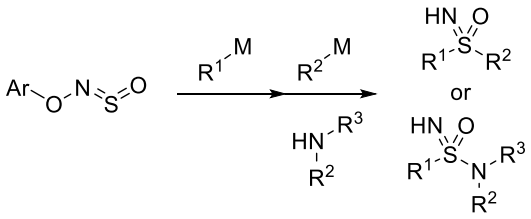
In the following thesis, new methodologies which exploit sulfinylamine reagents to enable one-pot syntheses of a range of nitrogen-containing sulfur(VI) functional groups are documented. The union of sulfinylamines with widely available organometallic reagents and amines allows the rapid construction of complex, medicinally relevant sulfoximine, sulfonimidamide and primary sulfonamide products.

Chapter 1 is a literature review covering the properties, applications and synthesis of sulfonimidamides and sulfoximines.

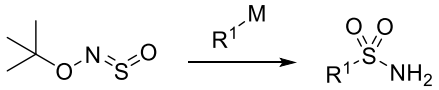
Chapter 2 describes the development of a new strategy for the preparation of sulfonimidamides. A remarkably stable sulfinylamine reagent, *N*-sulfinyltritylamine (TrNSO), is identified and used in a one-pot, three component synthesis of N-H sulfonimidamides. Analogues of the anti-arthritis drug Celecoxib are prepared using the method and subjected to biological assays by collaborators at UCB Biopharma.



Chapter 3 documents the discovery of a new class of sulfinylamines, *O*-aryl-*N*-sulfinylhydroxylamines, that enable the preparation of sulfoximines by the sequential addition of two Grignard reagents, or sulfonimidamides by the sequential addition of a Grignard reagent and an amine. Two possible mechanistic pathways are discussed and evaluated.



Chapter 4 details the serendipitous discovery of a one-pot synthesis of primary sulfonamides from the novel reagent *O*-*tert*-butyl-*N*-sulfinylhydroxylamine. Preliminary mechanistic studies are presented.



Chapter 5 discusses the conclusion of the research and the potential for future work.

Chapter 6 presents the experimental data.

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.

Thomas Davies

October 2018

Acknowledgements

Firstly, I would like to thank Prof. Michael Willis. I couldn't have asked for a better supervisor or a more exciting and intellectually stimulating project. His constant support, enthusiasm and guidance, not only for my DPhil work but my career in general, have been invaluable and are sincerely appreciated. Thank you.

I thank Dr Adrian Hall for being such an enthusiastic industrial supervisor and especially for being so welcoming during my placement - it's been fantastic working with you. Special thanks also go to David Skolc, for making the atmosphere in the lab so enjoyable and always being willing to help, as well as Pierre Burssens and everyone else at UCB for being so friendly.

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I would also like to thank my parents and my brother for always being there for me – it means so much. Ecem, your love and all the amazing times we've spent together have kept me going. This thesis would not have been possible without all of you.

Table of Contents

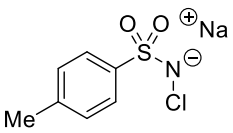
Abbreviations and Acronyms

aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bz	benzoyl
Bu	butyl
CAN	ceric ammonium nitrate
cat.	catalyst *or* catalytic
CPME	cyclopentyl methyl ether
CSA	camphorsulfonic acid
Cy	cyclohexyl
decomp.	decomposition
dioxane	1,4-dioxane
DMB	3,4-dimethoxybenzyl
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPH	2,4-dinitrophenylhydroxylamine
EI	electron impact
equiv.	equivalents
ESI	electrospray ionisation
FT	Fourier Transform
h	hour(s)
Het	heteroaryl
HMDS	hexamethyldisilazane
HRMS	high resolution mass spectrometry
Hz	Hertz
MSH	*O*-mesitylenesulfonylhydroxylamine
i	iso

IR	infrared
J	coupling constant
L	ligand *or* litre
LRMS	low resolution mass spectrometry
M	metal *or* molar
M	milli *or* multiplet
m	*meta*
mCPBA	3-chloroperoxybenzoic acid
MSH	*O*-Mesitylenesulfonylhydroxylamine
NCS	*N*-chlorosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
Nuc	nucleophile
o	*ortho*
[O]	oxidant
p	*para*
PG	protecting group
Ph	phenyl
ppm	parts per million
quant.	quantitative
R	generic group/substituent
rt	room temperature
s	secondary
sat.	saturated
t	tertiary
t-BuOCl	*tert*-butyl hypochlorite
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBS	*tert*-butyldimethylsilyl
temp.	temperature
Tf	trifluoromethanesulfonyl

TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	tolyl
Tr	trityl, triphenylmethyl
Ts	4-toluenesulfonyl
UV	ultraviolet
wt	weight
X	(pseudo)halide (unless stated otherwise)
µ	micro
v	frequency

Ligands and Chemical Structures



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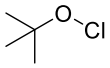

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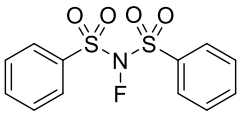

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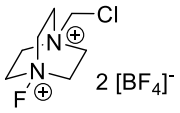

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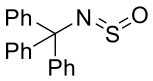
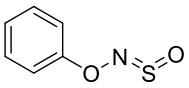
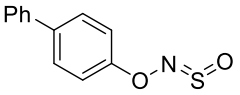


TrNSO



PhONSO



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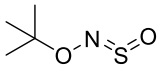
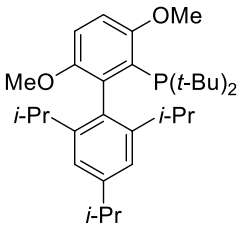


t-BuONSO



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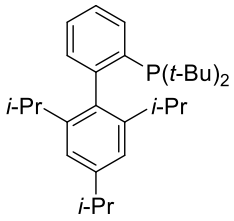

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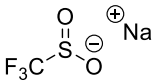
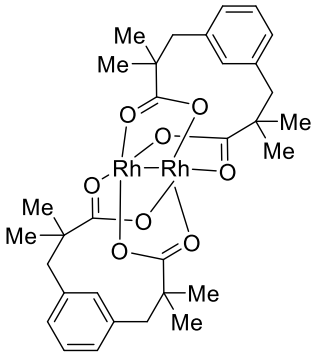


Langlois' reagent



$Rh_2(esp)_2$

Chapter 1 – Introduction

1.1 Properties and Applications of Sulfonimidamides and Sulfoximines

Sulfonimidamides **1** and sulfoximines **2** are conceptually derived from sulfonamides and sulfones, respectively, by the substitution of one oxygen for an imine nitrogen (**Figure 1.1**).[1-3] This seemingly small modification has a profound influence on the chemistry and properties of these molecules; perhaps most notably, it renders the sulfur atom stereogenic (when $R^1 \neq R^2$ for **2**). Compared to their sulfonyl congeners, these sulfonimidoyl compounds also possess an additional functional handle and further opportunities for directed hydrogen bonding.

Replacement of oxygen by nitrogen also dramatically alters the reactivity of these compounds. Both sulfonimidamides and sulfoximines are weak bases and nucleophiles, unlike their oxygenated analogues, and their N-H protons can be removed by strong bases. The ability to vary the substituent on nitrogen also enables the tuning of various properties, such as the pK_a of sulfonimidamide N-H protons. Indeed, *N*-acyl sulfonimidamides are acids and have been investigated as carboxylic acid bioisosteres.[4] Furthermore, the acidity of sulfoximine α-hydrogens can be modulated by at least 9 pK_a units (32 for R^3 = Me, 23 for R^3 = Ts).[2]

Sulfonimidamides **1** Sulfoximines **2**

Figure 1.1 Structure of sulfonimidamides and sulfoximines

The synthetic potential of these properties has not gone unnoticed by chemists. Sulfoximines have been exploited as chiral ligands[5] and organocatalysts (**Figure 1.2a**).[6] Various functionalisations both on nitrogen (including alkylation,[7] arylation,[8] acylation,[9] alkenylation,[10] alkynylation[11] and trifluoromethylation[12]) (**Figure 1.2b**) and carbon (e.g. α-arylation,[13] C-H functionalisation *via* metal catalysis,[14] including annulation processes,[15] and directed *ortho*-lithiation[16]) (**Figure 1.2c**) have been reported. The nucleophilicity of the sulfoximine nitrogen has been leveraged for the synthesis of activated *N*,*N*-dimethylsulfoximinium methylene,[17] trifluoromethyl[18] and difluoromethyl[19] transfer reagents. In addition, by judicious choice of N-substituent, neutral electrophilic[20] and nucleophilic[21] difluoromethylation reagents, as well as a nucleophilic monofluoromethylation[22] reagent, can be prepared (**Figure 1.2d**).

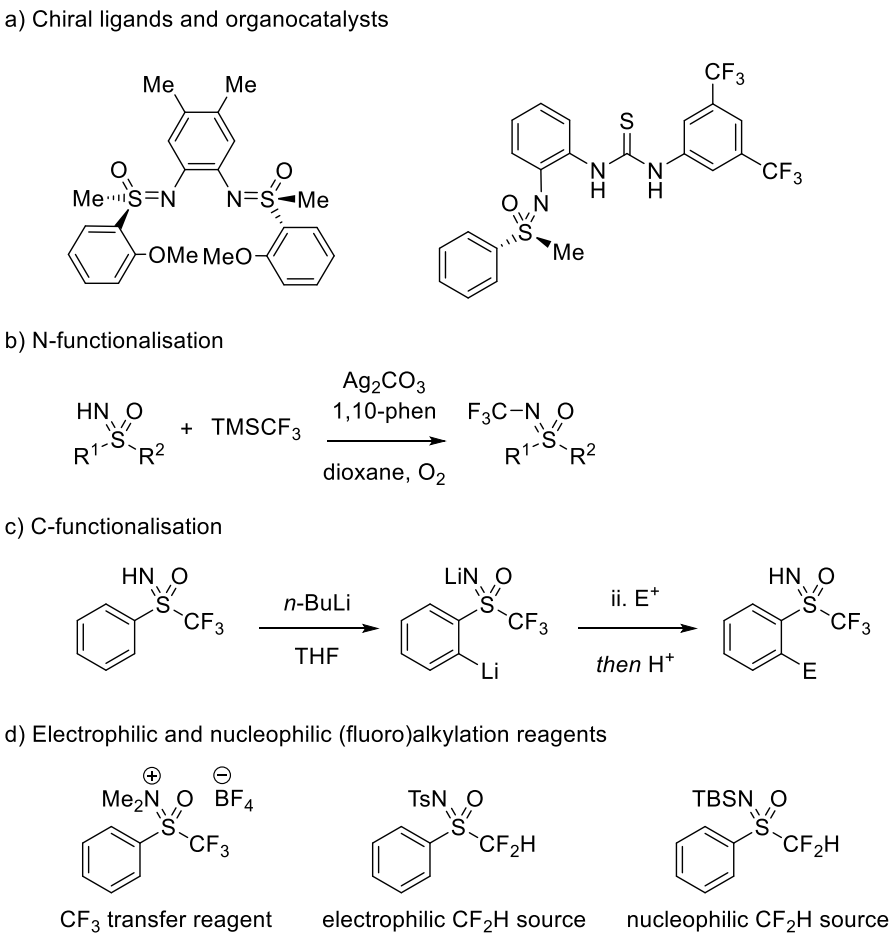


Figure 1.2. Synthetic applications of sulfoximines

Synthetic applications of sulfonimidamides have been not been so widely explored, likely due to lower awareness of this functional group and a paucity of methods for their synthesis. Despite this, they arguably possess greater potential as ligands[23] and organocatalysts[24] (**Figure 1.3a**) than sulfoximines due to their greater tunability and larger number of hydrogen bond donors. In addition, many of the N-functionalisation reactions mentioned above for sulfoximines are also possible using sulfonimidamides (including alkylation,[7] arylation,[25] acylation,[26] alkenylation[27] and alkynylation[28]) (**Figure 1.3b**). Deprotonation of the α-position of *N*,*N*,*N*'-trisubstituted sulfonimidamides and reaction of the resulting anion with electrophiles has also been shown (**Figure 1.3c**).[29] Their most notable synthetic application thus far is perhaps as chiral nitrene sources for diastereoselective aziridination,[30] sulfide imination[31] and C-H amination (**Figure 1.3d**).[32]

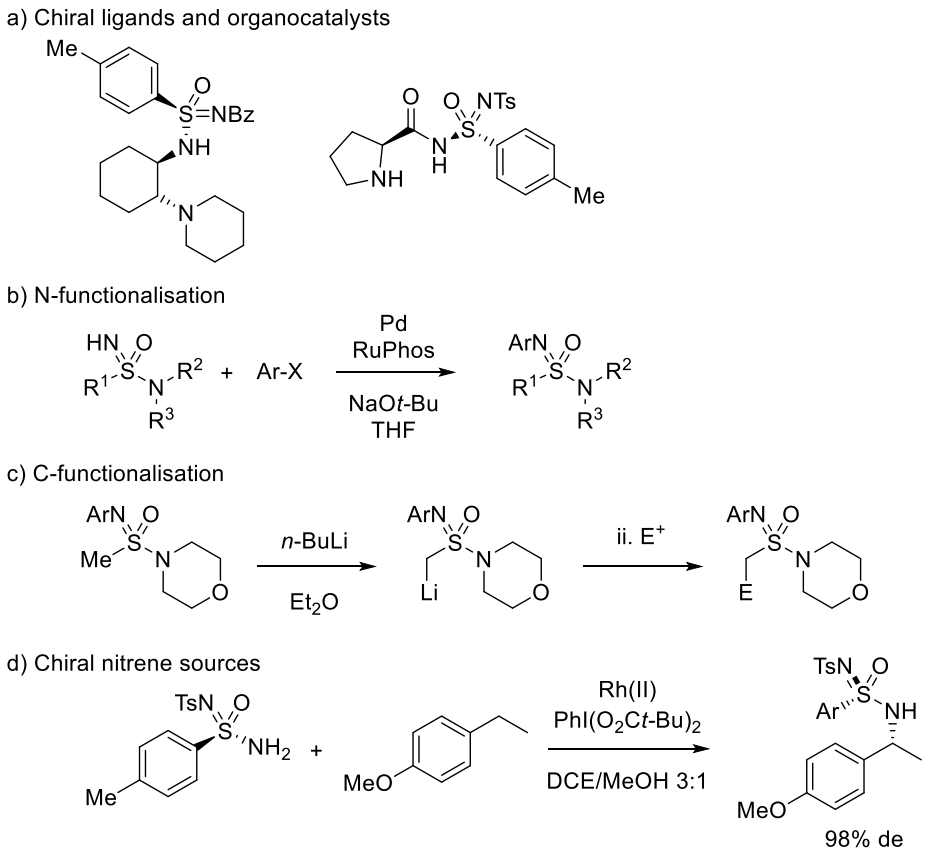


Figure 1.3. Synthetic applications of sulfonimidamides

Sulfoximines and sulfonimidamides share several properties that make them well-suited for applications in drug and agrochemical discovery. Both functional groups are stable and polar with a three-dimensional (tetrahedral) shape, offering myriad possibilities for structural diversification.[33] Although there is a lack of data on the physicochemical properties of sulfonimidamides, it has been noted that they typically exhibit lower lipophilicity and higher aqueous solubility and metabolic stability relative to analogous sulfonamides.[1] Sulfoximines have been reported to exhibit higher stability, comparable lipophilicity and improved aqueous solubility compared to sulfones.[3] Sulfoximines are present in marketed agrochemicals (Sulfoxaflor, Dow)[34] and anticancer compounds currently in clinical trials (Roniciclib, Bayer[35] and AZD6738, AstraZeneca[36]).

In contrast, there are no sulfonimidamides in clinical trials to the best of our knowledge, but they have been reported in preclinical studies as anti-tumour agents,[37] analogues for the transition state of aspartic acid and metallo-proteases,[38] γ-secretase inhibitors (acting as sulfonamide bioisosteres),[39] among others.[1] Notably, an analogue of the sulfonamide-containing anti-tumour agent Tasisulam has shown promising anti-proliferative activity against melanoma cell lines.[40] Although medicinal chemists have apparently been sceptical of sulfoximines and sulfonimidamides due to their unusual structure and concerns over their stability, a recent review stated that they “do not exhibit any intrinsic flaw but significantly enrich the toolbox of medicinal chemists”.[33]

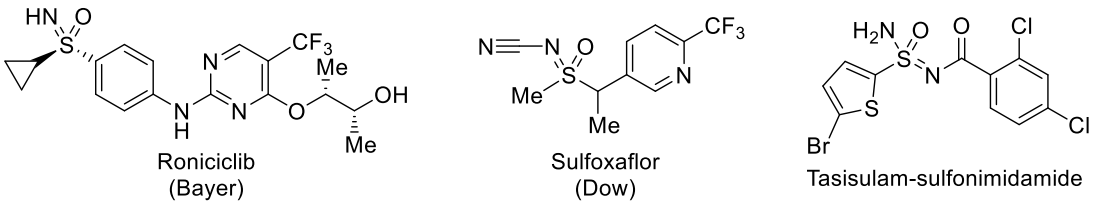


Figure 1.4. Bioactive sulfoximines and sulfonimidamides

1.2 Synthesis of Sulfonimidamides

Although widely reported to have been first prepared by the group of Levchenko, the earliest synthesis of a sulfonimidamide in fact appears to have been conducted by Clarke, Kenyon and Phillips at Battersea Polytechnic in 1930.[41] The action of potassium permanganate on the sodium salt of the unusual aza-sulfinamide **3** (itself derived by the reaction of ethanethiol with Chloramine T) afforded sulfonimidamide **4** (**Figure 1.5**). The limitations of the harsh conditions are readily apparent from the oxidation of the methyl groups of the tosyl protecting groups to carboxylic acids.

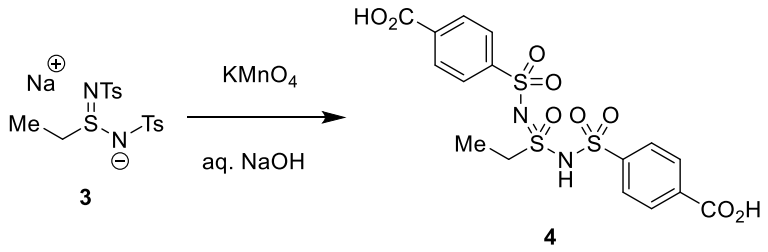


Figure 1.5. The first synthesis of a sulfonimidamide, *via* oxidation of aza-sulfinamide **3**.

In 1962, Levchenko and co-workers described a more general synthesis of sulfonimidamides *via* the reaction of *N*-arenesulfonyl sulfonimidoyl chlorides with amines (**Figure 1.6**).[42] At this time, sulfonimidoyl chlorides were typically derived from the reaction of highly sensitive sulfinyl chlorides with chloroamides such as Chloramine T.[43] The synthesis of *N*-alkyl or *N*-aryl sulfonimidoyl chlorides is challenging using this approach due to the instability of the relevant chloroamines. Nevertheless, the nucleophilic substitution of sulfonimidoyl chlorides by amines has become by far the most common method for the preparation of sulfonimidamides.

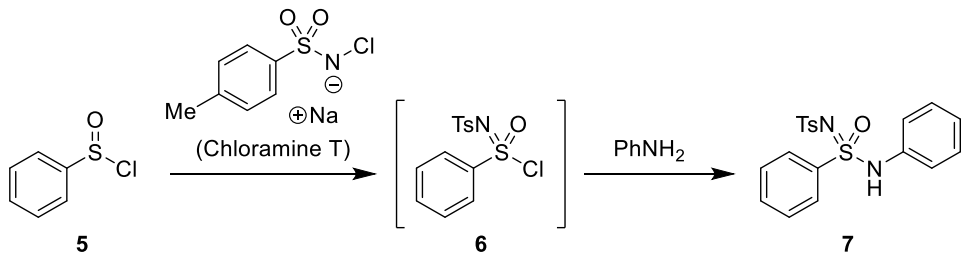


Figure 1.6. Levchenko's synthesis of sulfonimidamides from sulfonimidoyl chlorides **6**

The synthesis of sulfonimidamides from sulfinamides **8** *via in-situ* generated sulfonimidoyl bromides **9** was reported in 1965 by Takei, Watanabe and Mukaiyama (**Figure 1.7**).[44] Bromine, *N*-bromosuccinimide and *N*-bromophthalimide were all found to be suitable oxidants, although NBS provided the highest yields. The sulfonimidoyl bromides were reported to be unstable, as they could not be isolated and lower yields were obtained if the amine was added several hours after the oxidant.

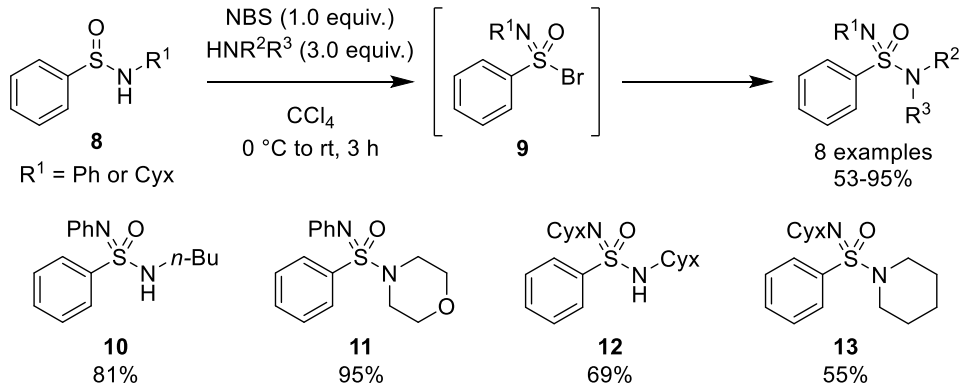


Figure 1.7. Synthesis of sulfonimidamides from transient sulfonimidoyl bromides

The group of Carl Johnson has reported several methodologies for the synthesis of sulfonimidoyl chlorides in the 1970s, with a few examples of their subsequent transformation into sulfonimidamides (**Figure 1.8**). Most notably, the electrophilic chlorinating reagent *tert*-butyl hypochlorite (*t*-BuOCl) was found to cleanly effect the oxidation of *N*-methyl and *N*-phenyl sulfinamides (**14** and **17**) to sulfonimidoyl chlorides (**15** and **18**) at room temperature.[45] Following a solvent swap to diethyl ether, addition

of an amine provided sulfonimidamides (**16** and **19**) in good yields. Chlorine gas and *N*-chlorobenzotriazole have also been used as oxidants;[46] however, the use of chlorine with *N*-aryl sulfinamides has been reported to result occasionally in violent over-chlorination of the activated aromatic ring.[47] A sulfonimidamide analogue of the sulfonamide antibiotic Sulfanilamide was prepared from a sulfonimidoyl chloride using these methods. In principle, enantioenriched sulfonimidamides, which are generally configurationally stable,[39] may be prepared from chiral sulfinamides using this method. Electrophilic chlorination has been shown to proceed with retention of configuration.[48] In reality, however, the configurational instability of sulfonimidoyl chlorides makes this challenging, and they are more commonly prepared *via* separation of diastereomers as discussed later (section 2.3).

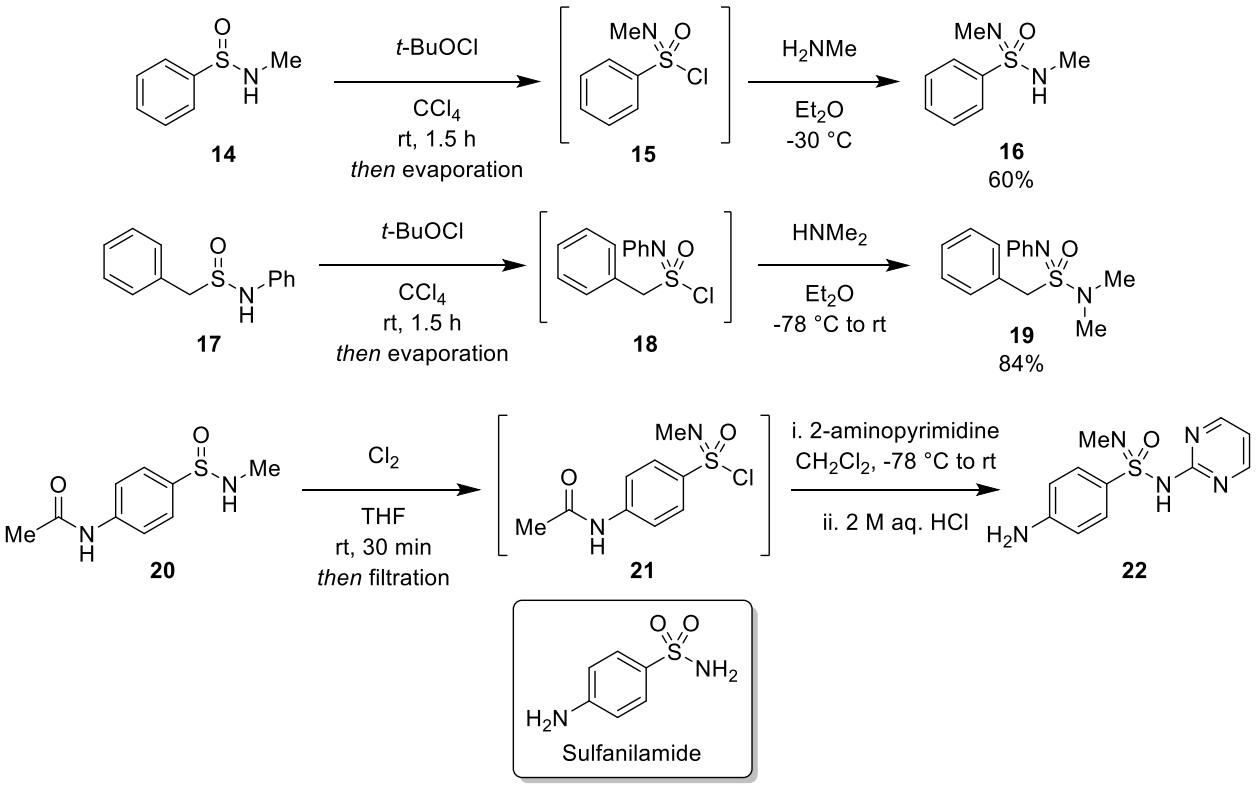


Figure 1.8. Johnson's synthesis of sulfonimidamides from sulfonimidoyl chlorides

In 1994, Yagupolskii and co-workers reported the synthesis of *N*-triflyl sulfonimidamides.[49] Due to the exceptional electron-withdrawing nature of the SO_2CF_3 group, sulfonimidoyl chlorides did not undergo substitution at sulfur, instead preferring to act as a source of "Cl^+". The analogous sulfonimidoyl fluorides did, however, provide the desired product upon reaction with ammonia and subsequent acidification with H_2SO_4 (**Figure 1.9a**). In a follow-up paper in 2002, *S*-trifluoromethyl-*N*-triflyl sulfonimidamides were prepared using a similar method (**Figure 1.9b**).[50]

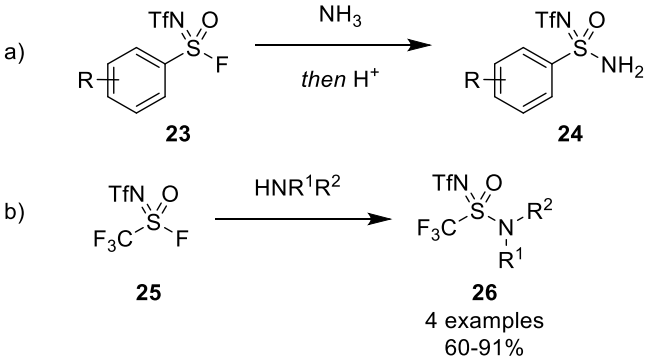


Figure 1.9. Yagupolskii's synthesis of highly electron-deficient sulfonimidamides

In 2007, the Bolm group reported the synthesis of sulfonimidamides from sulfinamides using the common electrophilic chlorinating agent, *N*-chlorosuccinimide (NCS) (**Figure 1.10**).[51] Yields were generally high, although only 10 examples were shown and all contained a simple 4-tolyl group on sulfur. The *N*-benzoyl group could be cleaved under harsh acidic conditions for the tosyl-substituted sulfonimidamide **30**, but only sulfinamide **33** was obtained from **32** due to loss of the dimethylamino group.

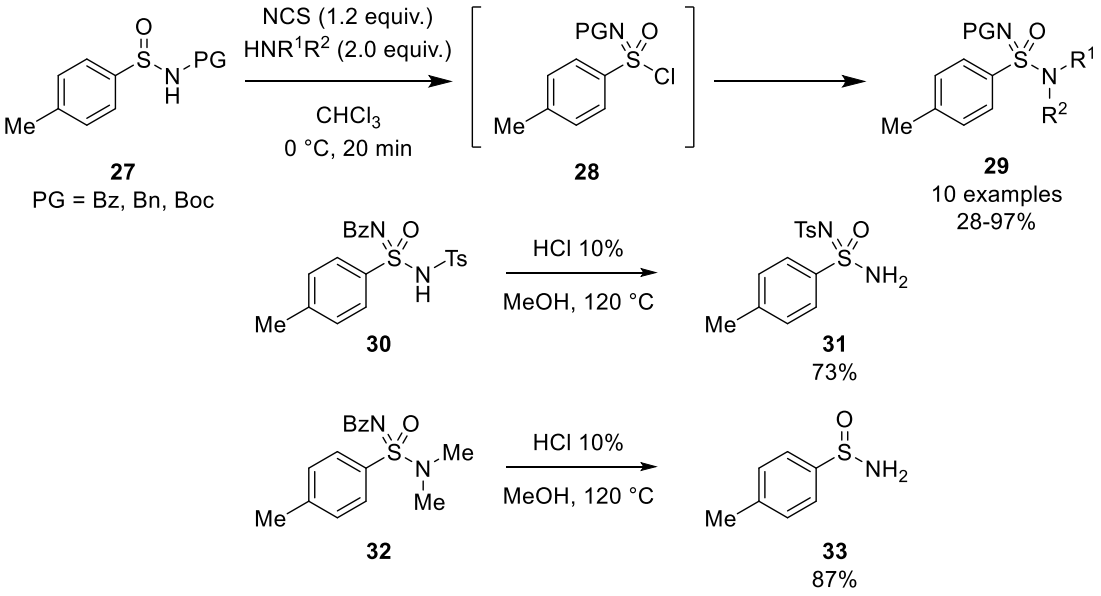


Figure 1.10. Oxidative chlorination of sulfinamides using NCS and subsequent reaction with amines

In 2015, Chen and Gibson from AstraZeneca reported a synthesis of sulfonimidamides from sulfonamides **34** *via* deoxychlorination (**Figure 1.11**).[52] Formation of sulfonimidoyl chlorides **35** was achieved by reaction with triphenyldichlorophosphorane (Ph_3PCl_2), a reagent previously employed by Roy and co-workers to prepare sulfonimidate esters.[53] This deoxygenative chlorination strategy was first employed by Levchenko and Kirsanov.[54] The authors state that N-protection with a TBS group was necessary to avoid reaction of the sulfonimidamide products with the intermediate sulfonimidoyl chloride. The silyl group could be retained or removed with acid, allowing access to rare unsubstituted sulfonimidamides such as **38**. Lower yields were obtained when the starting sulfonamide contained an *N*-aryl group (**41**).

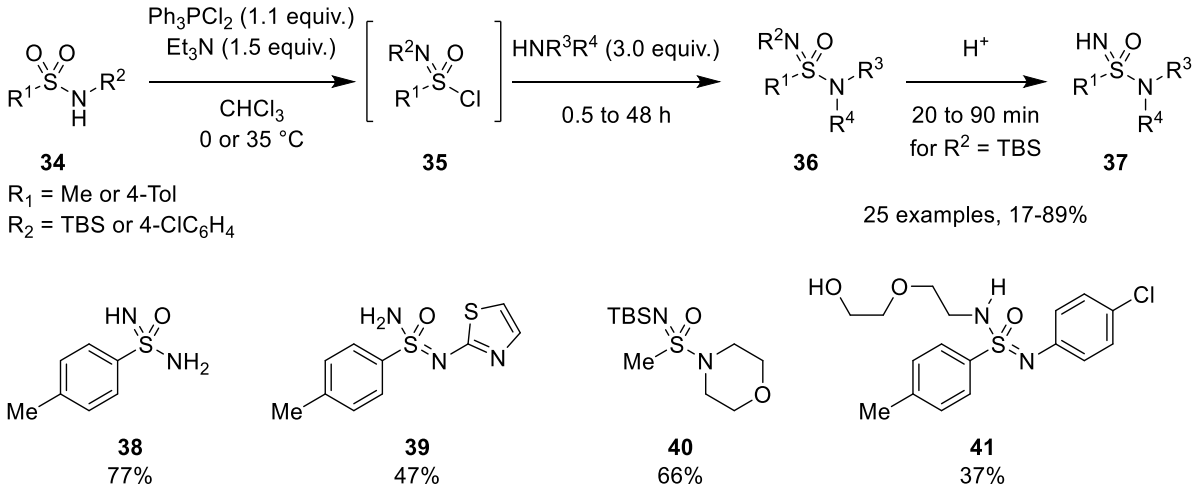


Figure 1.11. Deoxychlorination of sulfonamides **34** to sulfonimidoyl chlorides *en route* to sulfonimidamides

An alternative strategy for the preparation of sulfonimidamides was reported by Bolm and co-workers in 2016. In the presence of oxygen and a copper catalyst, *S*-aryl-*S*-methyl sulfoximines **42** undergo C-S bond cleavage and can combine with secondary cyclic amines to form sulfonimidamides in moderate yields (**Figure 1.12**).[55] The methyl group is postulated to undergo deprotonation and single electron transfer to CuTC; the resulting carbon-centred radical then attacks dioxygen to give a peroxy radical. Subsequent O-O bond cleavage and expulsion of formaldehyde results in a sulfur-centred radical which combines with the amine to give the sulfonimidamide. Although interesting from a mechanistic perspective, the general utility of the method is clearly limited by the high amine loading and low availability of sulfoximines.

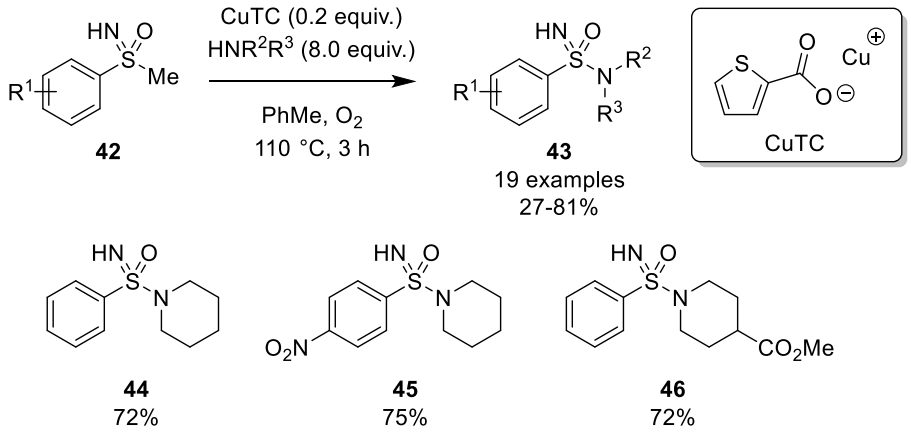


Figure 1.12. Copper-catalysed conversion of sulfoximines to sulfonimidamides

A convenient synthesis of *S*-trifluoromethyl sulfonimidamides **49** was reported by Oehlrich and co-workers in 2017 (**Figure 1.13**).[56] Trifluoromethane sulfinamides **47** were prepared in a single step from the Langlois reagent, phosphorus oxychloride and amines. These were then converted to sulfonimidoyl fluorides **48** using *N*-chlorosuccinimide and TBAF, and subsequent combination with an excess of amine provided the desired sulfonimidamides. It is interesting to note that oxidative chlorination of trifluoromethane sulfinamides was previously reported to be unsuccessful by Bolm and co-workers.[57] The authors of the current study observe that oxidation did not occur in the absence of the fluoride source. It therefore seems likely that the sulfinamide is deprotonated by fluoride before reaction with NCS.

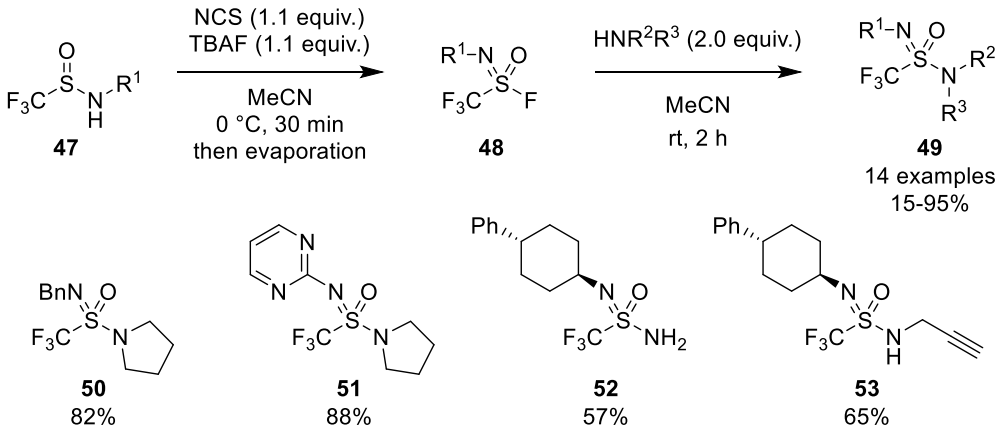


Figure 1.13. Synthesis of trifluoromethyl sulfonimidamides from trifluoromethanesulfinamides.

An oxidative route to sulfonimidamides was reported by Stockman and Lücking in 2017.[58] Simply applying the Bull conditions for sulfoxide imination[59] to sulfinamides **54** resulted in the desired NH transfer in generally moderate to high yields (**Figure 1.14**). The reaction was however limited to tertiary sulfinamides; reaction of primary or secondary sulfinamides resulted mainly in the formation of the methyl sulfonimidate ester **56**. Sulfonimidamide **44** and its sulfonamide analogue were subjected to hydrolytic and metabolic stability tests. The sulfonimidamide was found to be hydrolytically stable at physiologically relevant pH values and showed generally high metabolic stability, overall performing better than its oxygenated congener. In addition, it had a lower logD of 1.9 compared to 2.6 for the sulfonamide; this is significant as lower lipophilicity is thought by many medicinal chemists to correlate with "drug-likeness" and greater success rates in drug clinical trials.[60]

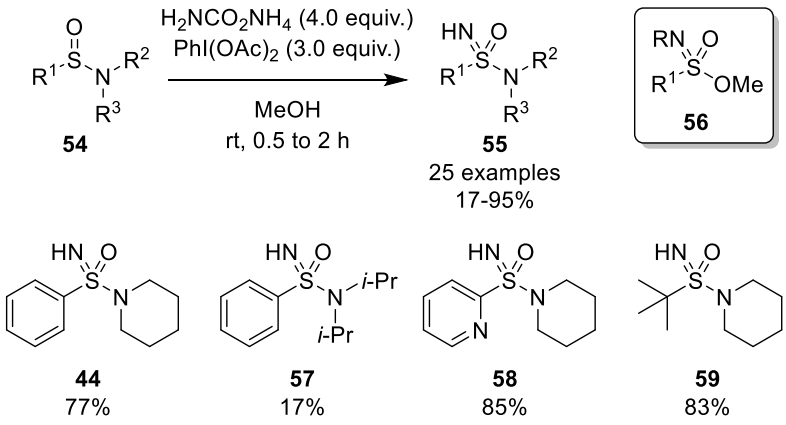


Figure 1.14. Synthesis of sulfonimidamides from tertiary sulfinamides **54** *via* direct NH transfer.

In 2017, Sharpless and co-workers reported a novel synthesis of sulfonimidoyl fluorides **62** from the reaction of organolithium reagents with iminosulfur oxydifluorides **61** (**Figure 1.15**).[61] Four sulfonimidamides were prepared *via* this approach. DBU was employed as a Lewis base additive for the addition of pyrrolidine at 60 °C. For the electron-deficient primary amines shown, prior deprotonation with *n*-butyllithium at -70

°C before reaction with the sulfonimidoyl fluoride at 0 °C was necessary. This “SuFEx” (sulfur fluoride exchange) strategy is severely limited by the use of SOF_4 as a starting material: thionyl tetrafluoride **60** is a gas which is not commercially available, and therefore must be synthesised using specialist equipment from sulfur tetrafluoride, dioxygen and 20 mol% nitrogen dioxide at 238 °C.

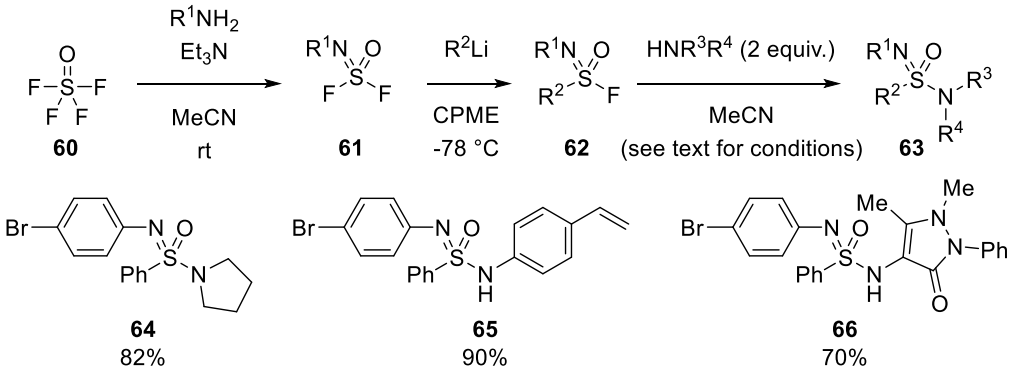


Figure 1.15. Sharpless’s “SuFEx” synthesis of sulfonimidoyl fluorides **62** from the gas thionyl tetrafluoride **60** and their subsequent transformation into sulfonimidamides **63**

1.3 Synthesis of Sulfoximines

The following sections will briefly describe the methods for preparing sulfoximines. There are three principle strategies: imination of a sulfoxide, oxidation of a sulfilimine, or attack of a carbon nucleophile on a sulfonimidoyl halide or sulfonimidate ester (**Figure 1.16**).

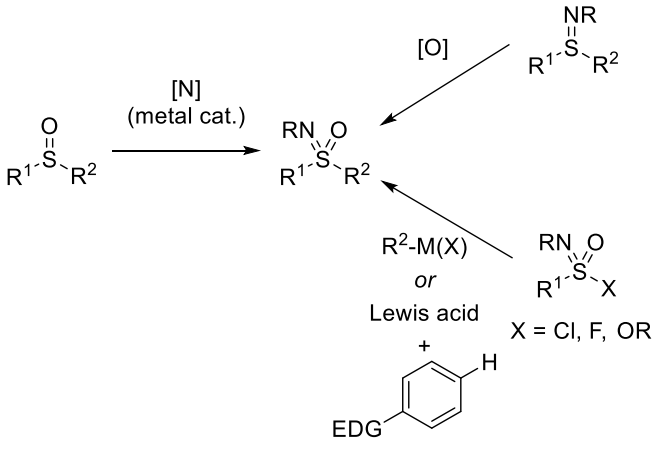


Figure 1.16 Strategies for the preparation of sulfoximines

1.3.1 Imination of Sulfoxides

The reaction of sulfoxides with nitrenes or nitrene equivalents, usually mediated by a metal catalyst, is by far the most widely used method for the synthesis of sulfoximines, due to the relative ease of accessibility of sulfoxides. Many metals and nitrogen sources have been discovered to enable this transformation; this section will focus on the most synthetically useful reactions, with a particular emphasis on recent advances which enable the direct synthesis of *N*-H sulfoximines under mild conditions.

The original conditions for the imination of sulfoxides involved the use of sodium azide and sulfuric acid, forming toxic and explosive hydrazoic acid (HN_3) *in situ* (**Figure 1.17**).[62] These conditions have largely been superseded by other methods, although a recent application to flow chemistry has reduced the safety risks associated with this procedure.[63] However, erosion of stereochemistry at the sulfur centre appears to be unavoidable under the harsh acidic conditions. *O*-Mesitylenesulfonylhydroxylamine (MSH) can be used to iminate sulfoxides[64] with retention of configuration.[65] However, MSH is highly explosive and its use is usually avoided where possible.

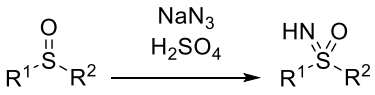


Figure 1.17. Classic sulfoximine synthesis using hydrazoic acid formed *in situ*

In 2004, the Bolm group reported a mild and general imination of sulfoxides, which remained the method of choice for sulfoximine synthesis for over a decade.[66] The combination of trifluoroacetamide or sulfonamides with a base and iodobenzene diacetate results in the formation of an iminoiodane. In the presence of a rhodium(II) catalyst, nitrogen is transferred to sulfoxides to form sulfoximines in high yields (**Figure 1.18**). Deprotection of the trifluoroacetyl group is facile under basic conditions to

access N-H sulfoximines. The imination was shown to be stereospecific, occurring with retention of configuration.

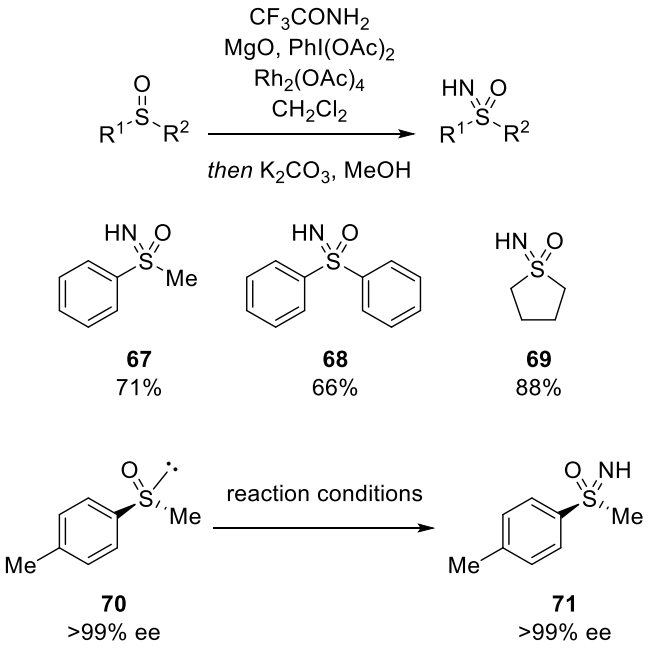


Figure 1.18. Bolm's rhodium-catalysed sulfoxide imination

The first transition metal-catalysed direct synthesis of unprotected sulfoximines from sulfoxides was reported in 2014 by Miao, Richards and Ge using $Rh_2(esp)_2$ and *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) (**Figure 1.19**).[67] A wide substrate scope was demonstrated with generally high yields, though limitations include low yields for *ortho*-substituted aryl rings (**73**) and a large excess of the iminating reagent.

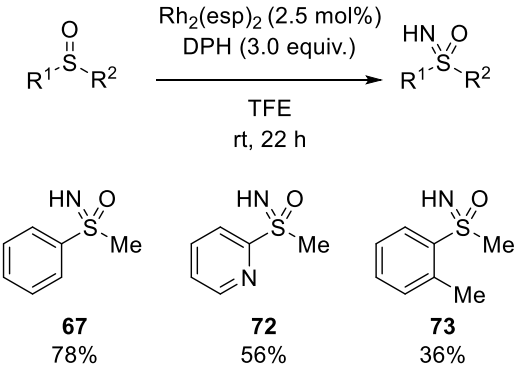


Figure 1.19. Richards and Ge's direct *N*-H sulfoximine synthesis

A significant advance was reported by Luisi and Bull in 2016.[59] Direct, metal-free NH transfer to sulfoxides to afford sulfoximines was achieved simply by combining iodobenzene diacetate and ammonium carbamate (**Figure 1.20**). A large substrate scope was performed, demonstrating the success of the method on sulfoxides substituted with alkyl and aryl groups, a vinyl group, and even a protected amino acid. Lower yields were generally obtained when electron-withdrawing groups were attached to sulfur (**78**). Flow mass spectrometry indicated iminoiodane **79** and iodonitrene **80** as possible electrophilic intermediates. The same team then reported that the reaction is also successful with sulfides as the substrate.[68] Similar reactions have been published by the groups of Li[69] and Reboul.[70]

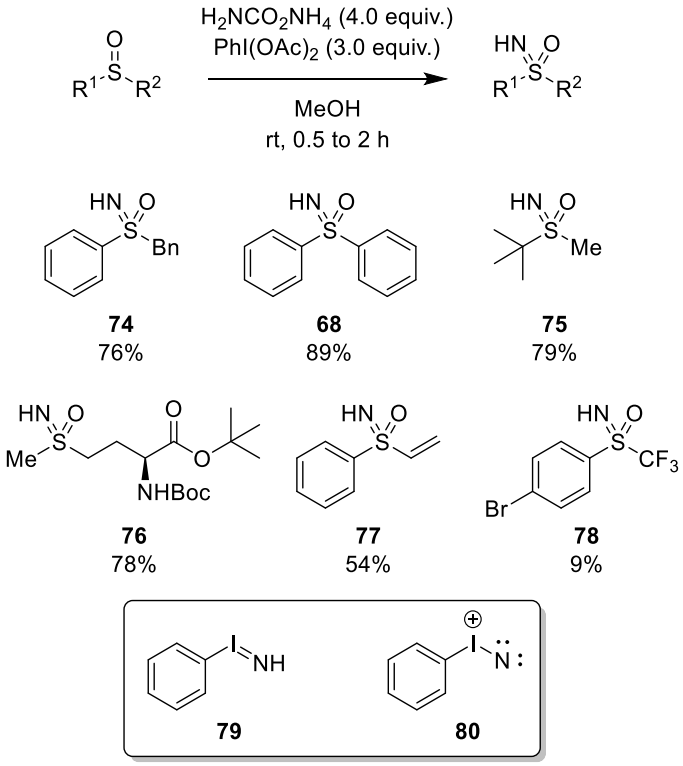


Figure 1.20. Luisi and Bull's metal-free *N*-H sulfoximine synthesis using a convenient source of NH_3

Bolm and co-workers reported an iron-catalysed direct imination of sulfoxides using hydroxylammonium salt **81** as the nitrogen source (**Figure 1.21**).[71] Yields were good across a range of substrates, with impressive tolerance of *ortho*-substituted aromatics

such as **82**. However, the hydroxylamine reagent is used in excess and must be synthesised *via* a two-step procedure.[72]

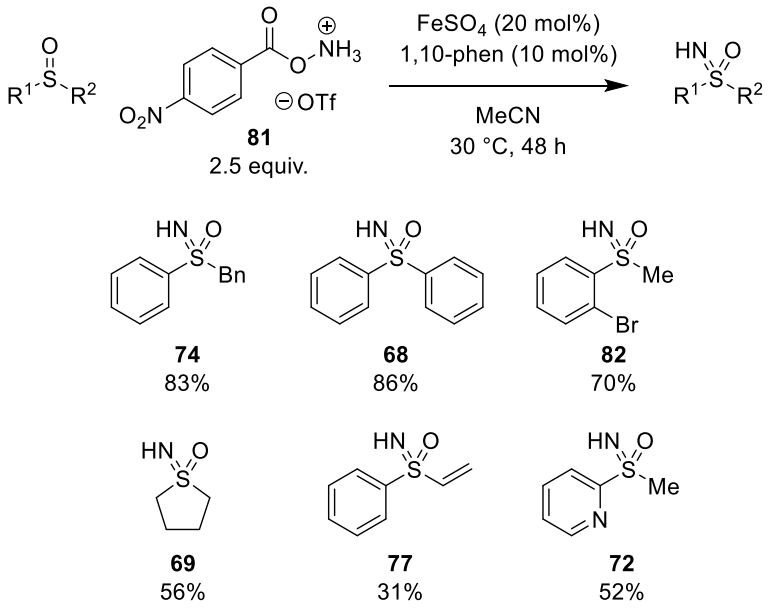


Figure 1.21. Bolm's iron-catalysed direct *N*-H sulfoximine synthesis

1.3.2 Oxidation of Sulfilimines

This approach is typically less favoured due to the chemical instability of sulfilimines with respect to hydrolysis[73] and the paucity of methods for their synthesis relative to sulfoxides, and will therefore not be covered in detail here. Nevertheless, it is interesting to note that the first deliberate preparation of a sulfoximine was achieved in 1950 by the oxidation of tosyl-protected sulfilimine **83** with potassium permanganate (**Figure 1.22**).[74]

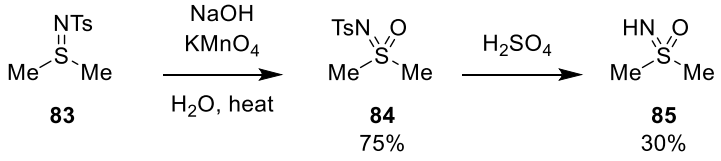


Figure 1.22. Bentley and Whitehead's sulfoximine synthesis *via* sulfilimine oxidation

1.3.3 Reactions of Sulfonimidoyl Electrophiles with Carbon Nucleophiles

The final method is conceptually attractive due to the possibility of rapidly synthesising analogues by reacting various carbon nucleophiles with a sulfur(VI) electrophile. However, in practice this approach is problematic due to the sensitivity of electrophiles such as sulfonimidoyl chlorides and their propensity to undergo reduction to sulfinamides. Upon their reaction with common organometallic nucleophiles such as organolithium and Grignard reagents, attack takes place at chlorine instead of sulfur. This has led to the development of alternative electrophiles which are more difficult to reduce, such as the analogous aryl esters and fluorides. However, even with these compounds, an excess of the nucleophile is usually required to achieve often moderate yields.

Carl Johnson and co-workers reported the reaction of sulfonimidate esters **86** with organolithium reagents to afford sulfoximines **87** in 1979 (**Figure 1.23**).[48] The esters were derived by the reaction of sulfonimidoyl chlorides with sodium phenoxide. The reaction proved sensitive to the steric bulk around sulfur; the best results were obtained with small alkyl nucleophiles when R^1 = Me. The use of aryllithium reagents was not shown and, surprisingly, starting materials were recovered when the reaction was attempted with Grignard reagents. It is worth noting that substitution at tetracoordinate sulfur(VI) electrophiles, such as the reaction of sulfonimidoyl chlorides with amines or sulfonimidate esters with methyllithium, was shown in this paper to proceed with inversion of configuration. In accordance with this stereochemical outcome, most studies on the mechanism of nucleophilic substitution at sulfur(VI) suggest a concerted bimolecular displacement (S_N2) pathway.[75]

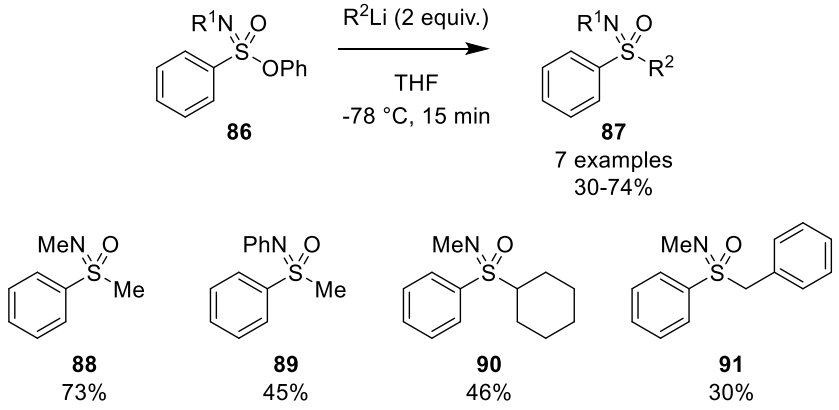


Figure 1.23. Johnson's synthesis of sulfoximines from sulfonimidate esters

The first synthesis of sulfonimidoyl fluorides **92** was reported by Johnson in 1983 (**Figure 1.24**).[76] The combination of sulfonimidoyl chlorides with NaF, KF or TBAF gave the desired fluorides in high yield. These were found to react well with methyl- and *n*-butyllithium, but phenyllithium and Grignard reagents gave mixtures of sulfoximines and sulfinamides. Compound **95**, containing an α-methylbenzyl substituent on nitrogen, was obtained as a 1.3:1 mixture of diastereomers.

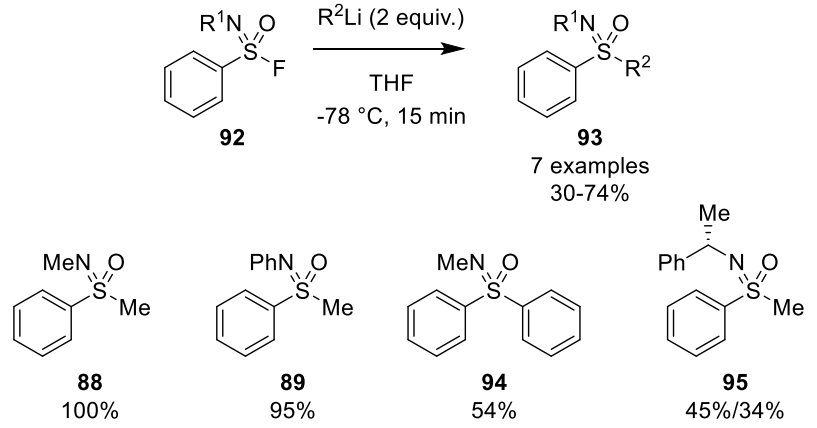


Figure 1.24. Johnson's synthesis of sulfoximines from sulfonimidoyl fluorides

In 1989, Harmata reported an unusual synthesis of sulfoximines from reaction of *N*-aryl and *N*-benzyl sulfonimidoyl chlorides with ethylaluminium dichloride (**Figure**

1.25).[77] The author proposed that the reaction proceeds by abstraction of chloride and subsequent ethyl transfer, although no mechanistic studies were described.

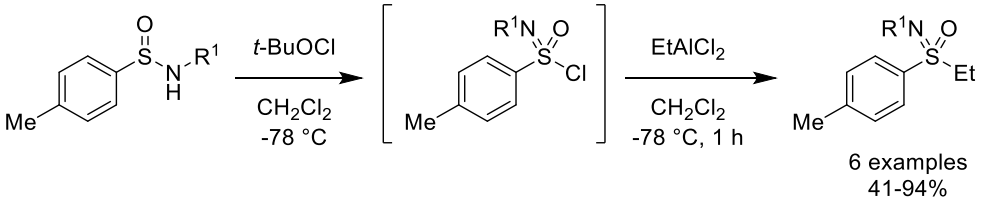


Figure 1.25. Harmata's synthesis of *S*-ethyl sulfoximines

One example of an *S*-trifluoromethyl sulfoximine was reported by Yagupolskii and co-workers in 1994.[49] Tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) was employed as an anhydrous fluoride source to activate $TMSCF_3$, generating the CF_3 anion, which reacted with the sulfonimidoyl fluoride **96** in 70% yield (**Figure 1.26**). This result would later serve as the inspiration for Bolm's general synthesis of trifluoromethyl sulfoximines.[57]

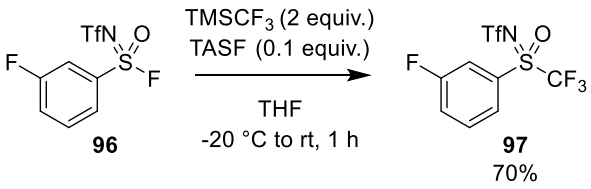


Figure 1.26. Yagupolskii's synthesis of a trifluoromethyl sulfoximine

In 2000, Takata and co-workers described the synthesis of sulfoximines from sulfonimidoyl chlorides *via* a Friedel-Crafts reaction. Use of the appropriate nucleophilic arene as solvent in the presence of stoichiometric $FeCl_3$ was required to obtain the best yields (**Figure 1.27**).[78] Yields dropped precipitously when the strong electron-donating 4-methoxy group was present on either the sulfonimidoyl chloride or nucleophile component (**100** and **101**). Unsurprisingly, no substrates containing electron-withdrawing groups were reported.

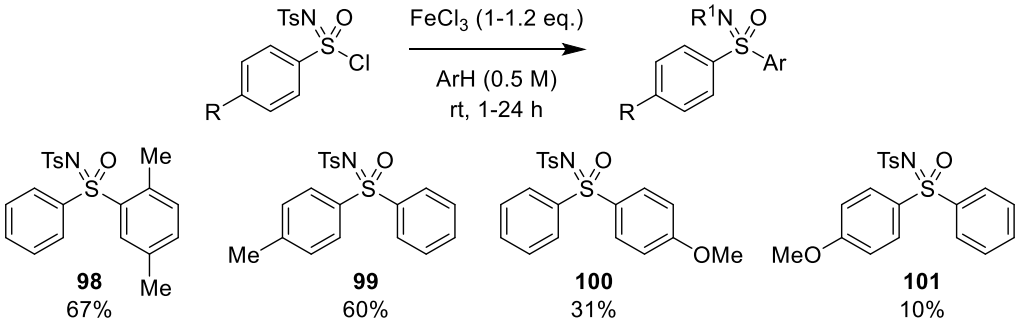


Figure 1.27. Takata's Friedel-Crafts synthesis of diaryl sulfoximines

In 2010, Bolm and co-workers reported the preparation of *S*-trifluoromethyl sulfoximines from sulfonimidoyl fluorides.[57] Using $TMSCF_3$ and TBAF as a convenient source of the trifluoromethanide ion, displacement of fluoride occurred in good yields (**Figure 1.28**). The use of sulfonimidoyl chlorides did not give any product. This example demonstrates the utility of accessing sulfoximines *via* sulfonimidoyl compounds, since trifluoromethyl derivatives are difficult to access using conventional sulfoxide imination chemistry due to the strong electron-withdrawing influence of the CF_3 group.

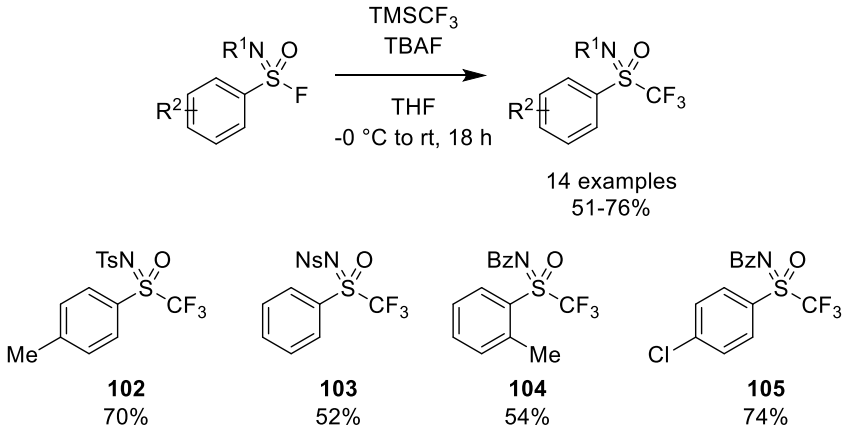


Figure 1.28. Bolm's preparation of trifluoromethyl sulfoximines from sulfonimidoyl fluorides

Sharpless and co-workers have also synthesised sulfoximines from sulfonimidoyl fluorides (**Figure 1.29**),[61] using very similar conditions to Johnson.[76] Importantly, several examples containing a deprotectable *para*-methoxybenzyl group on nitrogen

were shown (**106**-**108**), potentially allowing access to N-H sulfoximines. Curiously, although Johnson reported that *tert*-butyllithium failed to react with *N*-(4-chlorophenyl)-benzenesulfonimidoyl fluoride, an excellent yield was obtained (**109**) with *N*-phenyl benzenesulfonimidoyl fluoride. Substitution with less reactive Grignard or organozinc reagents was not shown.

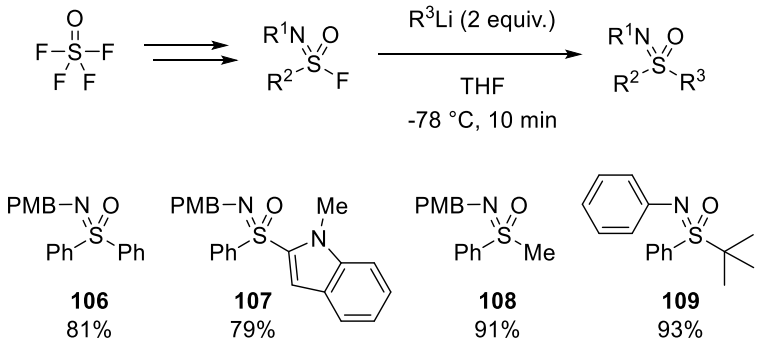


Figure 1.29. Sharpless's synthesis of sulfoximines

1.4 Research Aims

Although the methods described in the preceding literature review allow access to a range of sulfoximines and sulfonimidamides, even the most widely applicable methods require several steps from commercial materials, typically thiols. In addition, most involve sequential oxidations and, particularly in the case of sulfonimidamides, moisture-sensitive intermediates. These factors undoubtedly limit the usage of these molecules in medicinal chemistry and agrochemistry. Underpinning the work detailed in this thesis was our vision that the development of appropriate sulfinylamine (R-N=S=O) reagents could streamline their synthesis, resulting in one-pot syntheses from readily available starting materials (**Figure 1.30**).

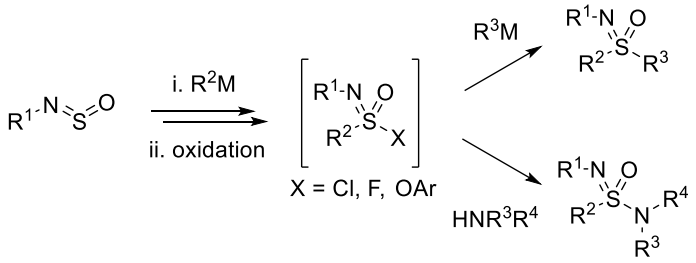


Figure 1.30. Our strategy for sulfoximine and sulfonimidamide synthesis

The following chapter will describe our work to identify a moisture-stable sulfinylamine which could be leveraged for a concise and broadly applicable one-pot synthesis of unprotected sulfonimidamides.

Chapter 2 – A One-pot Sulfonimidamide Synthesis

2.1 Sulfinylamines

Sulfinylamines **110** are the monoaza analogues of sulfur dioxide. They are typically prepared by the reaction of primary amines with thionyl chloride and were first synthesised in 1878,[79] although their structure was not assigned until 1890.[80] Their central tetravalent sulfur atom is electrophilic and can undergo reaction with a range of nucleophiles, as exemplified by the tendency of many sulfinylamines to hydrolyse in moist air, giving the parent amine and the toxic gas SO_2.[81] This characteristic often makes them challenging to purify and use in reactions. Their reaction with alcohols (providing the parent amines *via* double addition), primary amines (to prepare other sulfinylamines by transsulfinylation), and Grignard reagents (to form sulfinamides)[82] have all been described. Other applications have rarely been explored; the most common is perhaps the use of *N*-aryl,[83] *N*-sulfonyl (**111**)[81] and carbamate[84] derivatives as dienophiles in Diels-Alder reactions (**Figure 2.1**).

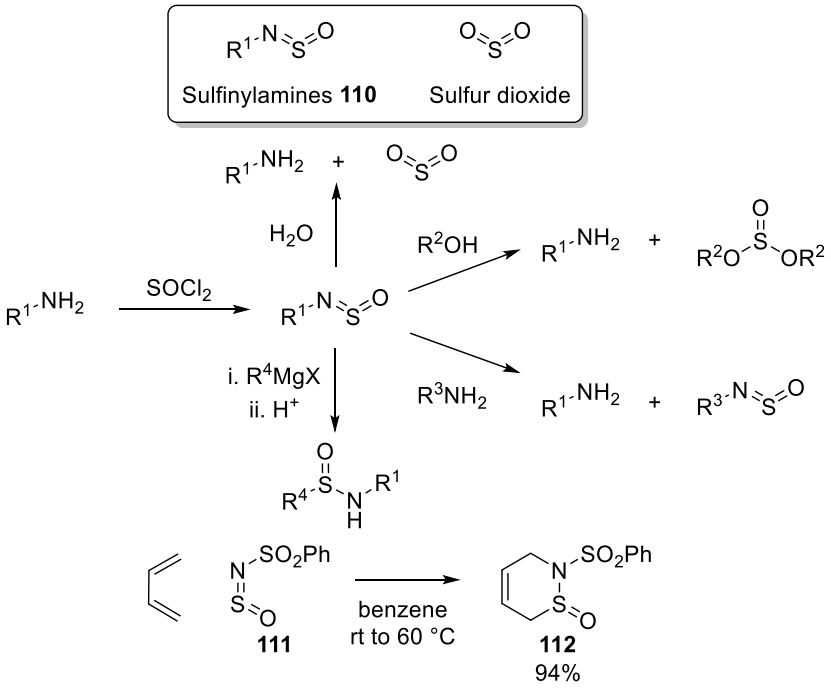


Figure 2.1. Synthesis and applications of sulfinylamines

2.2 Origin of Project and Synthesis of Sulfinylamines

Despite the reported instability of sulfinylamines, we were struck by their untapped potential for the preparation of nitrogen-containing sulfur(VI) compounds. Considering their ability to react with Grignard reagents to form sulfinamides, and the well-known oxidation of sulfinamides to sulfonimidoyl chlorides, we believed that they could enable a concise synthesis of sulfoximines and sulfonimidamides (**Figure 2.2**). We were particularly interested in the synthesis of N-H sulfoximines and sulfonimidamides, as these are perhaps the most medicinally relevant derivatives, and in addition can be converted to a wide range of N-substituted products (see section 1.1). Use of the parent thionylimine HNSO was thought unfeasible as it is a gas at standard temperature and pressure, and polymerises to polythionylimide $(HNSO)_n$ when condensed to a liquid at temperatures above -70 °C.[85] We therefore considered that a sulfinylamine with an appropriate protecting group R^1 on nitrogen would be more practical. Crucially, we wished to conduct all four steps in a single pot to result in a rapid, user-friendly process for preparing sulfoximines and sulfonimidamides.

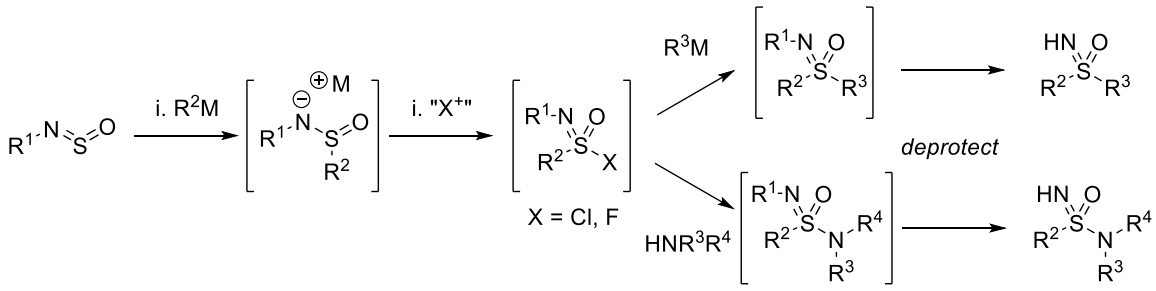


Figure 2.2. Our strategy for one-pot sulfoximine and sulfonimidamide syntheses

Our investigations therefore began with the synthesis of some known sulfinylamines. Preparation of the tosyl derivative **114** was attempted by the reaction of 4-toluenesulfonamide **113** with neat, refluxing thionyl chloride (**Figure 2.3**).[86] However, the product could not be obtained in pure form due to its low hydrolytic stability.

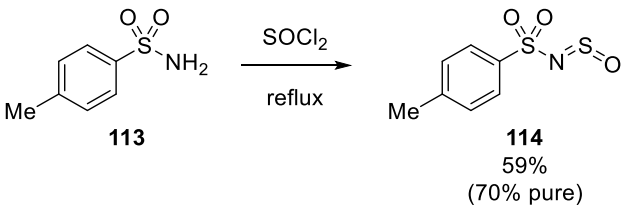


Figure 2.3. Failed synthesis of *N*-sulfinyl-4-toluenesulfonamide

The *N*-Boc derivative **116**[87] was obtained pure using strict air- and moisture-free conditions, with reaction and purification (by filter cannula) conducted in Schlenk flasks. (**Figure 2.4**) The product was stable under nitrogen but immediate hydrolysis occurred upon exposure to moist air, and it was judged impractical for further use.

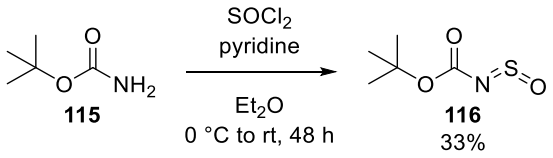


Figure 2.4. Preparation of *N*-sulfinyl-*tert*-butyl carbamate

N-Sulfinylcyclohexylamine **118** was prepared according to a literature procedure[81] and obtained pure following distillation, in low yield due to hydrolysis during filtration of the amine hydrochloride salt formed during the reaction (**Figure 2.5**). However, despite storage in a Schlenk flask under an inert atmosphere, the product decomposed upon standing at room temperature. The inherent instability of *N*-alkyl sulfinylamines has been noted by Kresze and co-workers.[81] We speculated that this may be due to the formation of an oligomeric or polymeric species, as in the parent thionylimine, by intermolecular attack of the nucleophilic nitrogen at sulfur.

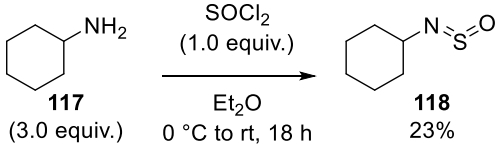


Figure 2.5. Preparation of *N*-sulfinylcyclohexylamine

In contrast, a range of *N*-aryl sulfinylamines were prepared and found to exhibit good stability, presumably due to resonance stabilisation of the N=S bond with the aromatic ring (**Figure 2.6**). They could be manipulated in air for short periods with no decomposition and, when stored at -20 °C, hydrolysis was typically only observed after several weeks. Furthermore, those with *ortho*-substituents (**124** and **125**) were less sensitive to moisture, despite the N=S=O moiety likely being twisted out of conjugation with the ring. This led us to consider that a sulfinylamine with an extremely bulky group on nitrogen may be stable to moisture. The use of *N*-aryl sulfinylamines for the one-pot synthesis of sulfoximines and sulfonimidamides was not pursued due to the difficulty of deprotecting aryl groups.

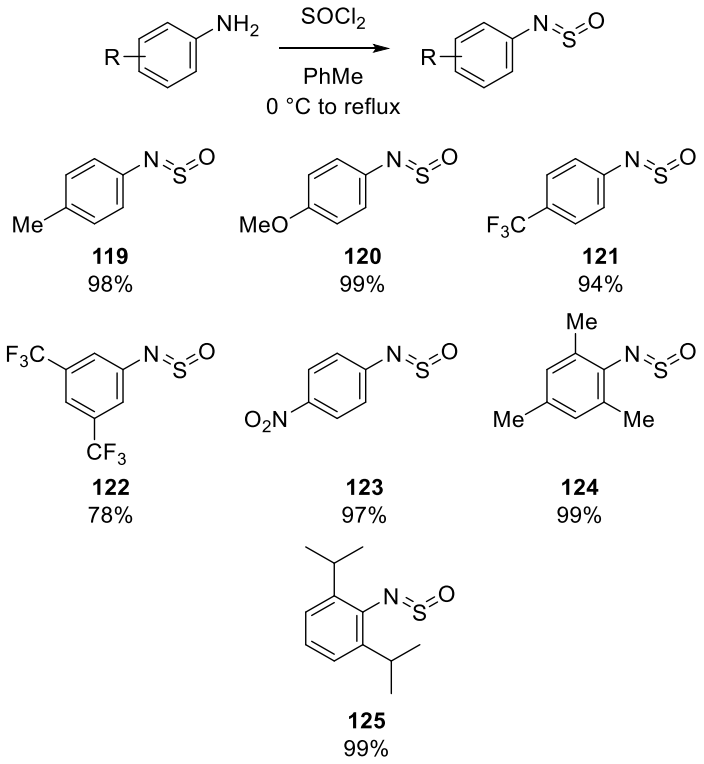


Figure 2.6. Preparation of *N*-sulfinylanilines

In particular, we speculated that a sulfinylamine with a triphenylmethyl (trityl) group could both be stable and potentially allow access to N-H sulfoximines and sulfonimidamides *via* acidic deprotection. To our delight, the reaction of commercially

available tritylamine **126** with $SOCl_2$ gave a moisture-insensitive white solid, *N*-sulfinyltritylamine (TrNSO) **127**, which was obtained pure after filtration through Celite (**Figure 2.7**). The compound could be stored at -20 °C for several months without observable decomposition and was prepared in an excellent 98% yield on 10 gram scale. It was discovered afterwards that *N*-sulfinyltritylamine had previously been prepared, though its synthesis was carried out in a glovebox and involved a complex procedure which included cooling to -196 °C. Furthermore, no reactions of the product were reported; only its spectroscopic properties were investigated.[88] A crystal structure of the compound was obtained from crystals grown by slow evaporation in *n*-hexane.

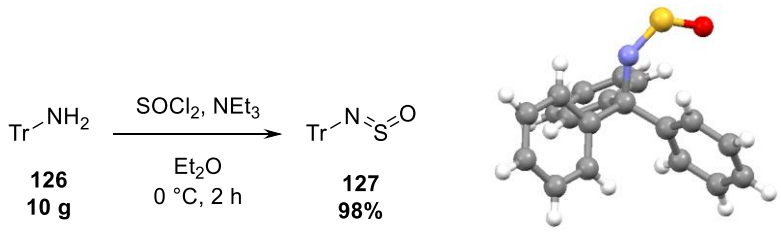


Figure 2.7. Preparation and crystal structure of *N*-sulfinyltritylamine, TrNSO. Tr = Ph_3C

With a stable sulfinylamine in hand, we decided to investigate its application to the synthesis of sulfonimidoyl fluorides. As described in chapter 1, these molecules are typically prepared from the analogous chloride by exchange with nucleophilic fluoride. However, we hoped to achieve their synthesis in a one-pot fashion from TrNSO, *via* an intermediate sulfinamide, using an electrophilic source of fluorine. To the best of our knowledge, only one example of this type of transformation has been published, on unusual cyclic sulfinyl amidines **128** (**Figure 2.8**).[89] The absence of other electrophilic fluorinations of sulfinamides in the literature suggests that this is likely not a general reaction. However, we believed that an anionic sulfinamide, which would be

formed from the reaction of a sulfinylamine with a Grignard reagent, would prove more amenable to oxidation.

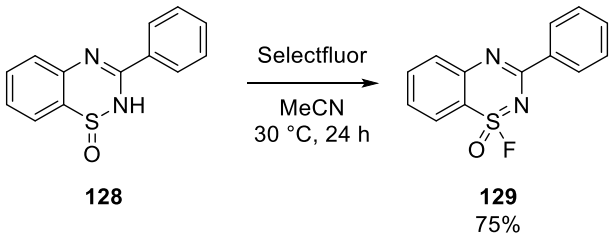


Figure 2.8. Direct electrophilic fluorination of sulfinyl amidine **128** by Shermolovich and co-workers

Despite the bulk of the trityl group, reaction of TrNSO with 4-fluorophenylmagnesium bromide proceeded to full conversion to sulfinamide intermediate **130** within 5 minutes at 0 °C (**Figure 2.9**). ^{19}F NMR analysis of an aliquot taken from the reaction showed a peak at -109.5 ppm, indicative of the expected aryl fluoride signal. Upon addition of *N*-fluorobenzenesulfonimide (NFSI), new peaks appeared at -103.3 and +92.1 ppm. The latter is diagnostic of a fluorine attached to a strongly electron-withdrawing group and corresponded well with reported ^{19}F NMR chemical shifts for sulfonimidoyl fluorides.[61] The reaction went to completion after 5 hours at 0 °C, with 1.1 equivalents of NFSI proving optimal. Strict maintenance of a low temperature and inert atmosphere proved crucial to obtaining the best results, as the reactivity stalled when the reaction was allowed to warm or was exposed to air. As no reactivity with NFSI was observed in separate experiments with neutral sulfinamides, this was thought to be due to protonation of the intermediate by adventitious water. The product **131** was isolated in 62% yield after column chromatography. The use of alternative fluorinating agents such as *N*-fluoropyridinium salts or Selectfluor did not result in the formation of sulfonimidoyl fluoride; the failure of Selectfluor is likely due to its insolubility in THF.

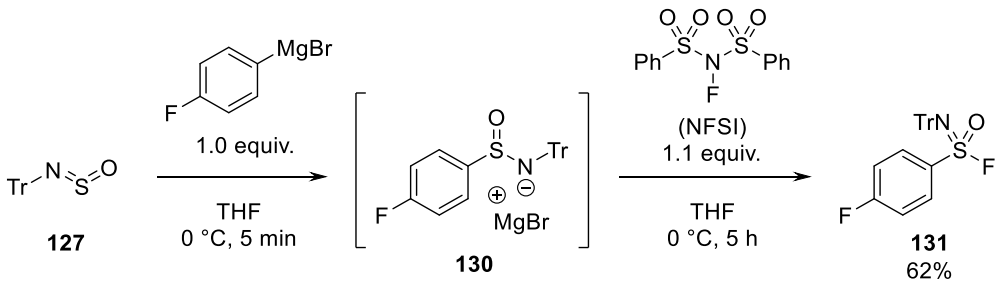


Figure 2.9. One-pot sulfonimidoyl fluoride synthesis from TrNSO, a Grignard reagent and NFSI

The proposed structure of **131** was proven beyond doubt by obtaining a crystal suitable for X-ray analysis *via* slow evaporation in $CDCl_3$ in an NMR tube (**Figure 2.10**).

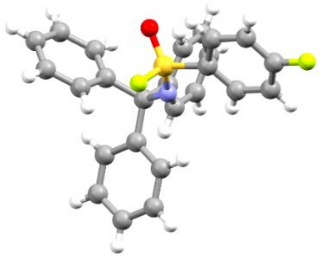
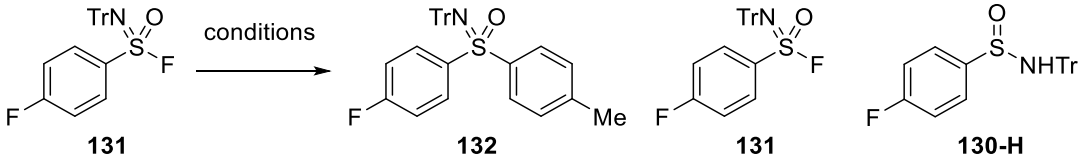


Figure 2.10. X-ray crystal structure of sulfonimidoyl fluoride **131**

We were keen to investigate the reactivity of *N*-trityl sulfonimidoyl fluoride **131** with Grignard reagents (**Table 2.1**). However, to our dismay, the desired sulfoximine product **132** was never observed in these reactions, despite variation of solvent, temperature and the addition of Lewis acidic or basic additives. In all cases, the starting material was either returned unchanged or reduced to the sulfinamide **130-H**, presumably *via* attack at fluorine, as 4-fluorotoluene and 1,4-difluorobenzene could be observed by ^{19}F NMR spectroscopy of the crude reaction mixture when the appropriate Grignard reagents were used. Full conversion of the starting material was only observed when a large excess of the Grignard reagent was used at 80 °C (**Entry 7**).

Table 2.1. Reaction of sulfonimidoyl fluoride **131** with Grignard reagents



131 **132** **131** **130-H**

Entry[a]	Nucleophile	Time	Solvent	Temp.	Additive	Ratio[b]
1	4-TolMgBr (1.1 eq)	3 h	dioxane	rt	-	0:1:0
2	4-TolMgBr (1.1 eq)	3 h	Et_2O	0 °C	-	0:1:0
3	4-TolMgBr (1.1 eq)	3 h	Et_2O	rt	-	0:1:0
4	4-TolMgBr (1.1 eq)	3 h	THF	0 °C	-	0:1:0
5	4-TolMgBr (1.1 eq)	3 h	THF	rt	-	0:1:0
6	4-TolMgBr (1.1 eq)	3 h	THF	50 °C	-	0:5:1
7	4-TolMgBr (4.0 eq)	5 h	dioxane	80 °C	-	0:0:1
8	4-TolMgBr (1.1 eq)	22 h	THF	rt	-	0:5:1
8	4-TolMgBr (1.1 eq)	22 h	THF	rt	$Sc(OTf)_3$ (0.1 eq)	0:1:0
9	4-TolMgBr (4.0 eq)	18 h	THF	rt	$In(OTf)_3$ (0.1 eq)	0:5:1
10	4-TolMgBr (4.0 eq)	18 h	THF	rt	LiCl (1.0 eq)	0:5:1
11	4-TolMgBr (4.0 eq)	5 h	THF	rt	DMAP (1.1 eq)	0:5:1
12	4-FC_6H_4MgBr (1.1 eq)	3 h	THF	rt	-	0:1:0
13	*n*-BuMgCl (1.1 eq)	3 h	THF	rt	-	0:1:0
14	*n*-BuMgCl (4.0 eq)	22 h	THF	rt	-	0:1:0
15	*n*-BuMgCl (4.0 eq)	5 h	THF	80 °C	-	0:3:1

a. Reaction conditions: sulfonimidoyl fluoride (0.024 mmol, 1.0 equiv.), nucleophile, additive, solvent (0.12 M). b. Determined by ^{19}F NMR spectrum of crude reaction mixture.

This surprising lack of reactivity led us to reconsider the use of sulfonimidoyl fluorides.

Although sulfonimidoyl chlorides are known to be reduced by organometallic nucleophiles,[90] we decided to prepare a trityl sulfonimidoyl chloride to investigate any differences in reactivity. Pleasingly, the reaction of sulfinamide intermediate **130** with a slight excess (1.05 equiv.) of the readily available chlorinating agent *tert*-butyl hypochlorite (*t*-BuOCl)[91] gave full conversion to sulfonimidoyl chloride **133** in less than 15 minutes, as judged by TLC and ^{19}F NMR analysis (**Figure 2.11**). The use of 1.5

equivalents of *N*-chlorosuccinimide gave incomplete conversion even after 5 hours. In stark contrast to their fluoride analogues, complete consumption of the sulfonimidoyl chlorides and conversion to the sulfinamide **130-H**, among other unidentified by-products, was observed rapidly at room temperature after addition of a Grignard reagent (**Figure 2.11**). The requirement for temperatures above 50 °C to fully react sulfonimidoyl fluoride **131** with organometallic nucleophiles is therefore surprising and suggests the sulfur-fluorine bond in **131** is very strong and that the sulfur atom is extremely difficult to access. By way of comparison, Johnson reported the substitution of *N*-alkyl and *N*-aryl sulfonimidoyl fluorides to sulfoximines with organolithium reagents in just 15 minutes at -78 °C,[76] while sulfonyl fluorides are competent in reactions with Grignard reagents at 0 °C, albeit requiring often long reaction times.[92] The switch of one oxygen atom to a less electronegative nitrogen presumably decreases the electrophilicity of the sulfonimidoyl fluoride. Combined with the extreme steric bulk of the trityl group, this may explain, at least in part, the inability of Grignard reagents to react at sulfur with compound **131**.

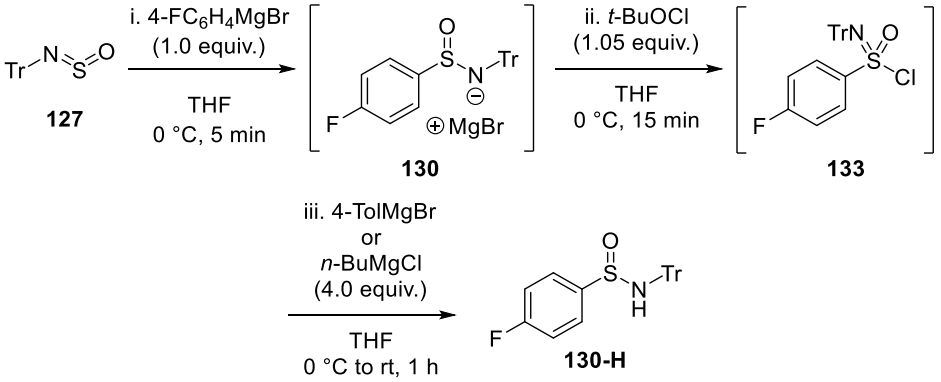


Figure 2.11. Generation of sulfonimidoyl chloride **133** and its reduction by Grignard reagents

Considering these results, we decided against pursuing further a synthesis of sulfoximines from TrNSO. A masters student in the group, Julian Greb, investigated the synthesis and reactivity of less bulky TrNSO analogues (**134** and **135**). Promising

initial results were obtained for the reaction of sulfonimidoyl fluorides **136** and **137** with methyllithium to form sulfoximines **138** and **139**. However, the substitution of even one phenyl group for methyl resulted in a marked decrease in stability of the sulfinylamine (**Figure 2.12**). The full results are presented in his thesis.[93]

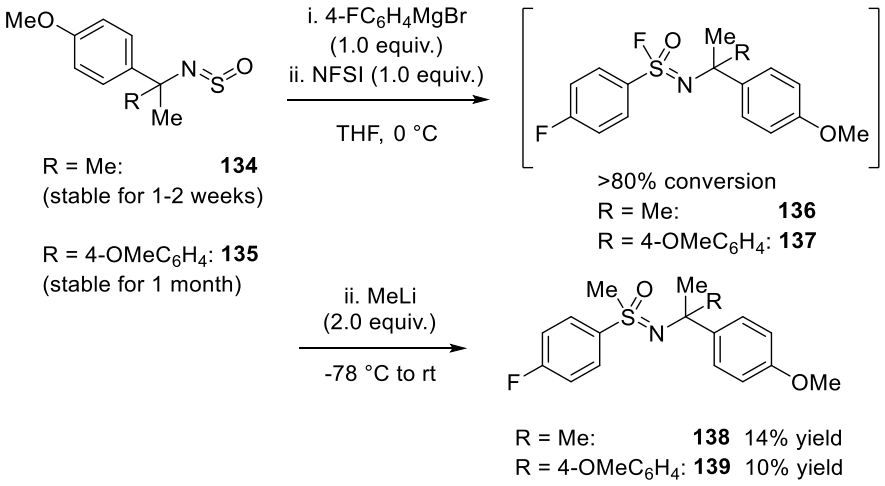


Figure 2.12. One-pot sulfoximine syntheses from less hindered TrNSO analogues **134** and **135** by Julian Greb

2.3 One-pot Synthesis of Sulfonimidamides from TrNSO

As discussed in Chapter 1, sulfonimidoyl chlorides are commonly used as precursors to sulfonimidamides. We therefore decided to test the reactivity of amines with our *in situ*-generated *N*-trityl sulfonimidoyl chlorides. We were pleased to find that amines reacted smoothly despite the bulk of the trityl group, forming the desired sulfonimidamide after stirring overnight at room temperature (**Figure 2.13**). Methanesulfonic acid (MsOH) proved optimal for removing the trityl group, with full conversion observed in just 15 minutes, whereas the use of trifluoroacetic acid gave incomplete conversion. Following the one-pot, four-step process, the unprotected sulfonimidamide **141a** was isolated in 70% yield.

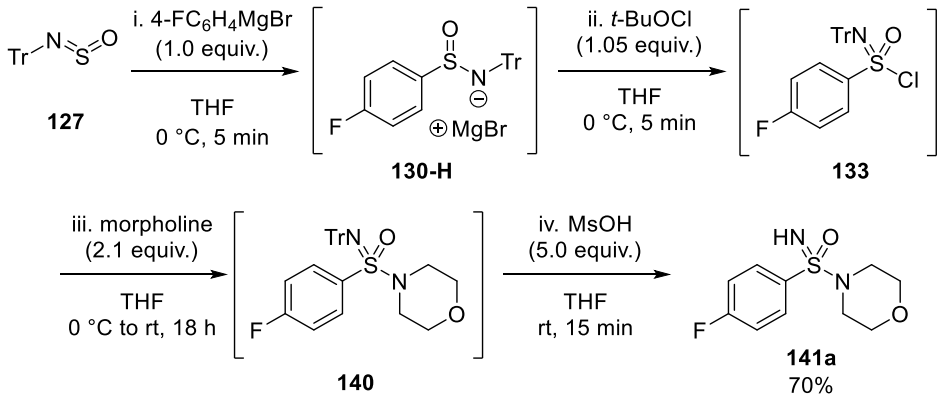


Figure 2.13. One-pot sulfonimidamide synthesis from TrNSO **127**

With a convenient method for sulfonimidamide synthesis in hand, we decided to vary the amine component to investigate the scope of the reaction (**Figure 2.14**).

Cyclic and non-cyclic secondary amines both provided sulfonimidamides in high yields (**141a** to **141e**). The presence of a second basic nitrogen did not affect the reaction (**141c**). Primary amines also reacted well, giving products with a double bond to the more substituted nitrogen as judged by ^{1}H NMR analysis in $CDCl_3$. We were pleased to note that reaction with 3,4-dimethoxybenzylamine proceeded with equally high efficiency on gram scale (**141h**). Use of chiral α-methylbenzylamine resulted in the formation of two separable diastereomers, providing access to enantioenriched sulfonimidamides **141k** and **141l**.

Aniline nucleophiles proved problematic. Products derived from electron-neutral (**141n**) and electron-poor anilines (see section 2.4) showed some acid sensitivity, while a more electron-rich derivative (**141o**) gave a lower yield, seemingly due to competing reduction of the sulfonimidoyl chloride intermediate by the amine. It is interesting to note that in the case of the 4-methoxy derivative **141o**, a ^{1}H NMR spectrum taken in acetone-d_6 showed two separate singlets for the NH protons, suggestive of the tautomer shown with the double bond out of conjugation. Although

solubility was low in $CDCl_3$, and a satisfactory spectrum was therefore not obtained, a broad singlet with an integration of 2 appeared to be present when using this solvent, suggesting the alternative structure. This indicates that sulfonimidamide tautomerisation is solvent-dependent. Finally, the drug molecule Amoxapine was reacted in good yield (**141p**).

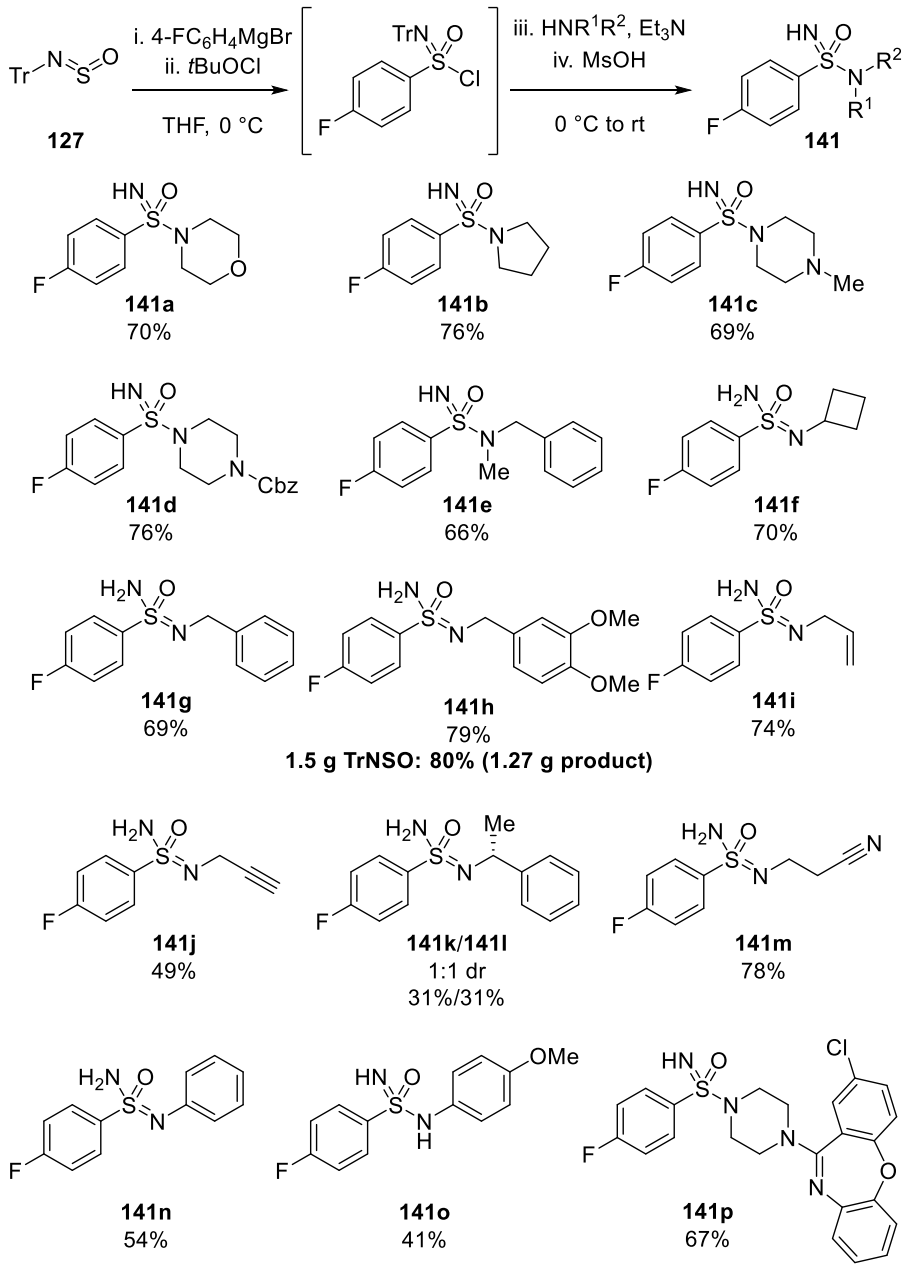


Figure 2.14. Scope of amine nucleophiles

We then turned to variation of the organometallic nucleophile, keeping 1-Cbz-piperazine constant as the amine nucleophile to provide potentially pharmaceutically relevant building blocks (**Figure 2.15**).

Electron-rich (**141q** and **141r**) and electron-poor (**141s**) aryl Grignard reagents were competent in the reaction, and only small decreases in yield were observed for *meta*-(**141t**) and even *ortho*-substituted aryls (**141u**). The latter is particularly surprising considering the extreme steric hindrance around the sulfur atom.

Nitrogen-containing heteroaromatics, particularly pyridines, are ubiquitous in drug molecules, yet many synthetic methods fail in the presence of basic nitrogens. We were keen to show that our method could tolerate such functionality. Organolithium reagents formed from the combination of *n*-butyllithium with 5-bromo-1-methylindole and 5-bromo-2-methoxy-pyridine, provided compounds **141v** and **141w** in high yields. 2- And 3-pyridyl Grignard reagents were prepared from the corresponding bromides using isopropylmagnesium chloride lithium chloride complex[94] and reacted with TrNSO to afford sulfonimidamides **141x** and **141y** in moderate yields.

The use of alkyl organomagnesium reagents gave slightly lower yields, though the success of the medicinally relevant methyl and cyclopropyl nucleophiles was gratifying (**141aa** and **141ac**). An alkenyl Grignard reagent gave a poor yield, possibly due to Michael acceptor reactivity of the product **141ae**.

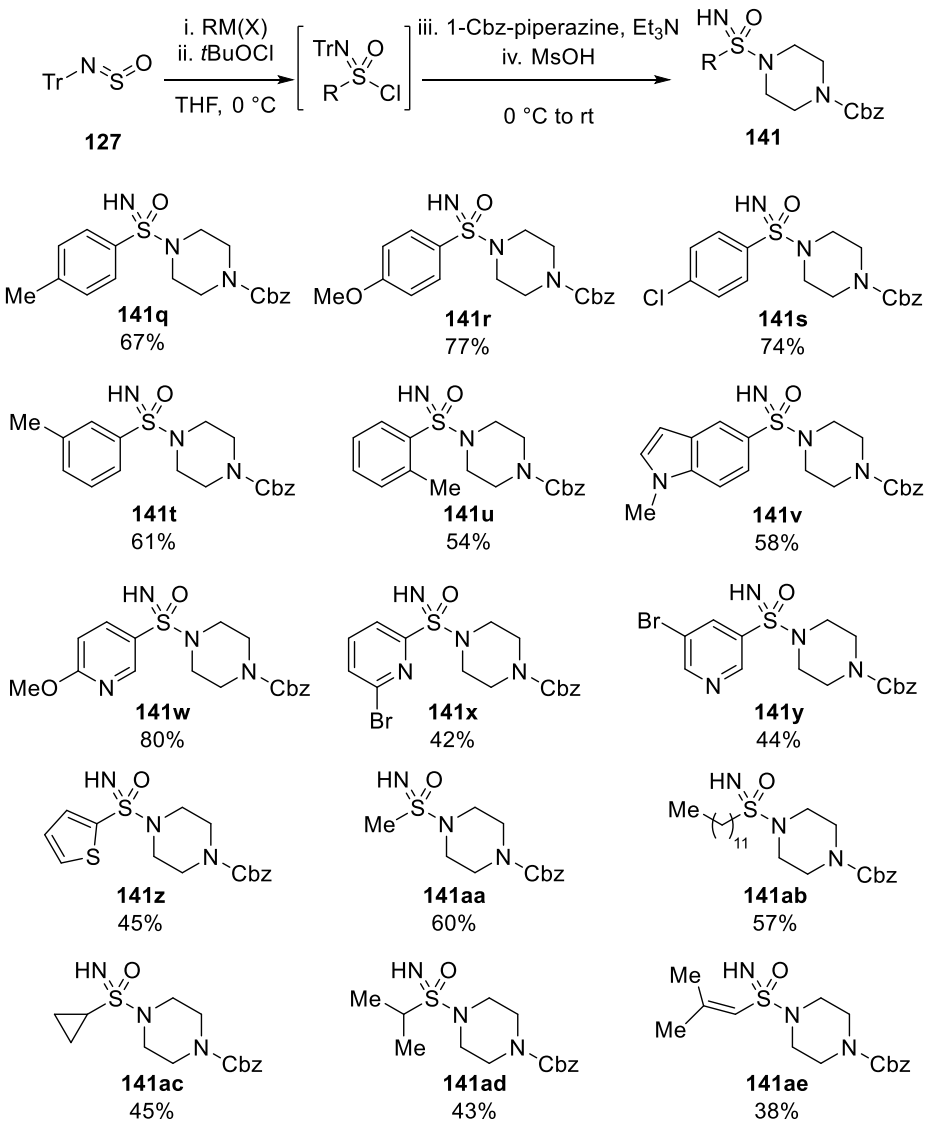


Figure 2.15. Scope of organometallic nucleophiles

2.4 Low Yielding and Unsuccessful Reactions

Although a range of amines and organometallic reagents performed well in the reaction, there were some limitations to the method (**Figure 2.16**). Use of bulky amines and alkyl Grignard reagents were particularly problematic. *tert*-Butylamine gave a low yield (**141af**), while no product could be isolated when cyclohexylmagnesium bromide (**141ah**) or diisopropylamine (**141ag**) were used as the first or second nucleophile, respectively. In addition, several attempts using benzylmagnesium bromide failed and *tert*-butylmagnesium chloride gave a high yield of sulfinamide **142**.

Sulfonimidamides derived from electron-deficient anilines such as 4-(trifluoromethyl)aniline and 4-bromoaniline appeared to be formed in the reaction but could not be isolated in pure form, likely due to decomposition under the acidic deprotection conditions or on silica. As noted before, *N*-aryl sulfonimidamides are acid-sensitive, a trait which is seemingly exacerbated by the presence of electron-withdrawing groups. No product was detected using 3-aminopyridine or (*O*-benzyl)hydroxylamine. To our surprise, only 1-Cbz-piperazine was isolated when propynylmagnesium bromide was used, indicating that alkynyl nucleophiles are not compatible with the reaction.

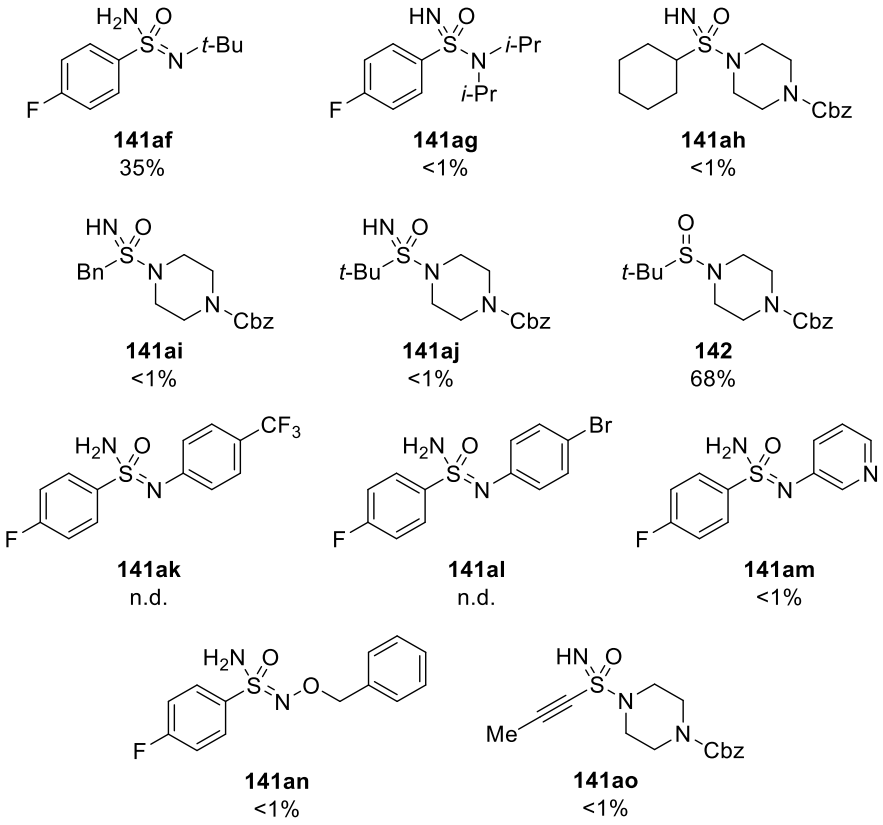


Figure 2.16. Limitations of the one-pot reaction

2.5 Preparation of the Parent Sulfonimidamide

We were also interested in synthesising the N-unsubstituted, or parent, sulfonimidamide. However, we were surprised to find that ammonia, the smallest amine nucleophile, performed poorly in the reaction, giving low yields of the desired parent sulfonimidamide **143** (**Figure 2.17**). The use of alternative ammonia sources, including hexamethyldisilazane, ammonium formate, benzophenone imine and tritylamine were all also unsuccessful.

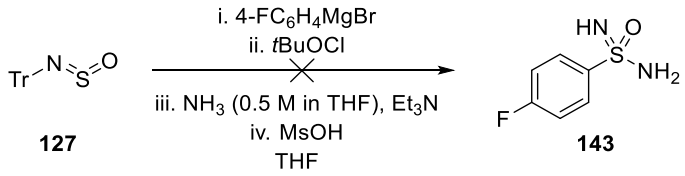


Figure 2.17. Attempted one-pot parent sulfonimidamide synthesis from TrNSO and ammonia

Due to these failures, we decided to target a two-step route to parent sulfonimidamides. In particular, we believed a 3,4-dimethoxybenzyl group (see compound **141h**) could provide the solution. The use of catalytic hydrogenation conditions for deprotection returned only starting material even at elevated temperatures. However, we were encouraged to see that full deprotection occurred when the strong single electron oxidants DDQ and cerium ammonium nitrate (CAN) were used. Curiously, although formation of the 3,4-dimethoxybenzaldehyde by-product was always seen by TLC and ^{1}H NMR spectroscopy, the desired sulfonimidamide product proved difficult to observe and isolate. After some experimentation, this was found to be due to several factors. The parent sulfonimidamide was surprisingly water-soluble and almost completely insoluble in many common organic solvents, including $CDCl_3$, making its extraction from the

aqueous layer and observation by NMR spectroscopy challenging. In addition, its extreme polarity complicated purification by column chromatography.

We decided to switch to a more lipophilic biphenyl substituent in the hope that this would simplify purification. The DMB-protected sulfonimidamide **144** was synthesised under standard conditions *via* lithiation of 4-bromobiphenyl with *n*-butyllithium and addition of the generated organometallic species to TrNSO. Following CAN deprotection, we were delighted to isolate the parent sulfonimidamide **145** in an excellent 89% yield after column chromatography (**Figure 2.18**).

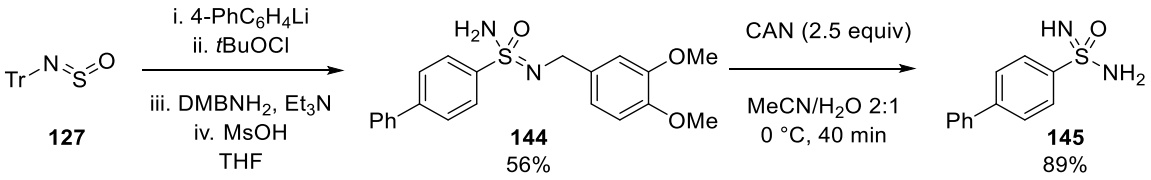


Figure 2.18. Oxidative DMB deprotection to access the parent sulfonimidamide **145**. DMB = 3,4-dimethoxybenzyl

2.6 Drug Analogue Synthesis

To demonstrate the applicability of our method to medicinal chemistry, we wished to prepare complex, drug-like molecules and test their biological activity and physicochemical properties. We identified the sulfonamide-containing painkiller Celecoxib as an ideal target structure for preparing sulfonimidamide analogues.

Aryl bromide **146** could be accessed in one step from commercial materials, and lithium-halogen exchange with *n*-butyllithium to provide our desired nucleophile **147** was found to be straightforward. We were pleased to see that sulfonimidamides **148a**-**148c** could be synthesised, albeit in low-to-moderate yields, under the standard reaction conditions (**Figure 2.19**). Further functionalisation on these complex scaffolds was possible; morpholino derivative **148a** could be both alkylated (**148d**) and

arylated[25] (**148e**) in high yields. In addition, the DMB group could be cleaved from analogue **148c** in 85% yield using the previously developed oxidative deprotection conditions to deliver the direct sulfonimidamide analogue of Celecoxib (**148f**).

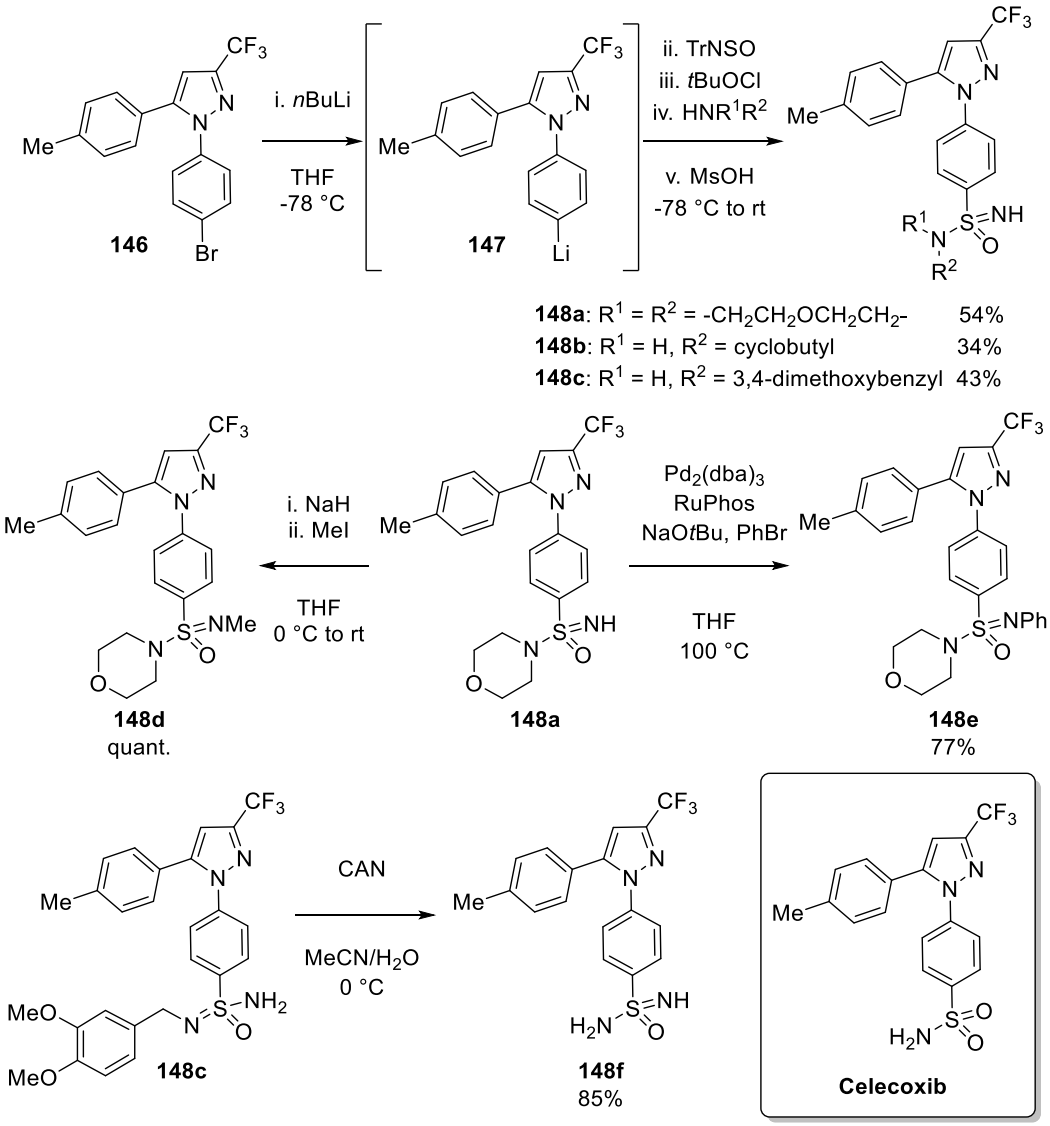


Figure 2.19. Synthesis of sulfonimidamide-containing Celecoxib analogues

Our collaborators at UCB Biopharma in Braine, Belgium then compared compounds **148f**, **148a** and **148b** to the original drug molecule in various biological and physicochemical assays. The data are presented in **Table 2.2**.

Table 2.2. Summary of data for Celecoxib *versus* compounds **148f**, **148a** and **148b**.

Compound	COX-2 pIC_{50}	HT logD[a]	HLM CL_{int}[b]	HLM E_h[c]	RLM CL_{int}[b]	RLM E_h
Celecoxib	7.33	3.6	16.1	0.439	11.2	0.223
148f	5.46	3.0	4.84	0.19	8.21	0.174
148a	< 5 (42%@10 uM)	3.7	404	0.951	114	0.745
148b	<5 (39% @ 10 uM)	4.3	95	0.822	50	0.561

[a] High Throughput (HT) logD. [b] Intrinsic clearance (CL_{int}) measured in human or rat liver microsomes (HLM or RLM respectively), in µL/min/mg protein. [c] Calculated hepatic extraction ratio, based on the assumption F_u (fraction unbound) = 1 for all compounds.

Unsurprisingly, inhibition of the COX-2 enzyme dropped relative to Celecoxib for all tested sulfonimidamides. However, the parent sulfonimidamide **148f** still showed significant activity (~100-fold drop in potency), had a lower logD, and even showed improvements in metabolic stability, displaying lower clearance in human and rat liver microsomes and lower hepatic extractions ratios than Celecoxib. A sharp drop-off in activity and metabolic stability was noted for N-substituted compounds **148a** and **148b**.

It is worth noting that sulfonimidamide analogues were not included in the patent for Celecoxib.[95] Switching from a sulfonamide to a sulfonimidamide could therefore be a generally useful strategy for “patent-busting” in medicinal chemistry and agrochemistry.

The reduced bioactivity of the sulfonimidamide analogues can be rationalised by studying the crystal structure of Celecoxib bound to mouse COX-2 (**Figure 2.20**). The sulfonyl oxygens function as hydrogen bond acceptors, making favourable interactions with nearby phenylalanine and arginine moieties. In the sulfonimidamide **148f**, one acceptor (O) is substituted for a donor (NH), resulting in the loss of a hydrogen bond. However, the hydrogen bond between the sulfonamide NH_2 and a backbone carbonyl

would still be present in **148f**. It is also evident that the environment around the sulfonamide group in the active site is sterically constrained, and that additional substitution on nitrogen is unlikely to be tolerated, as demonstrated by **148a** and **148b** (see **Table 2.2**).

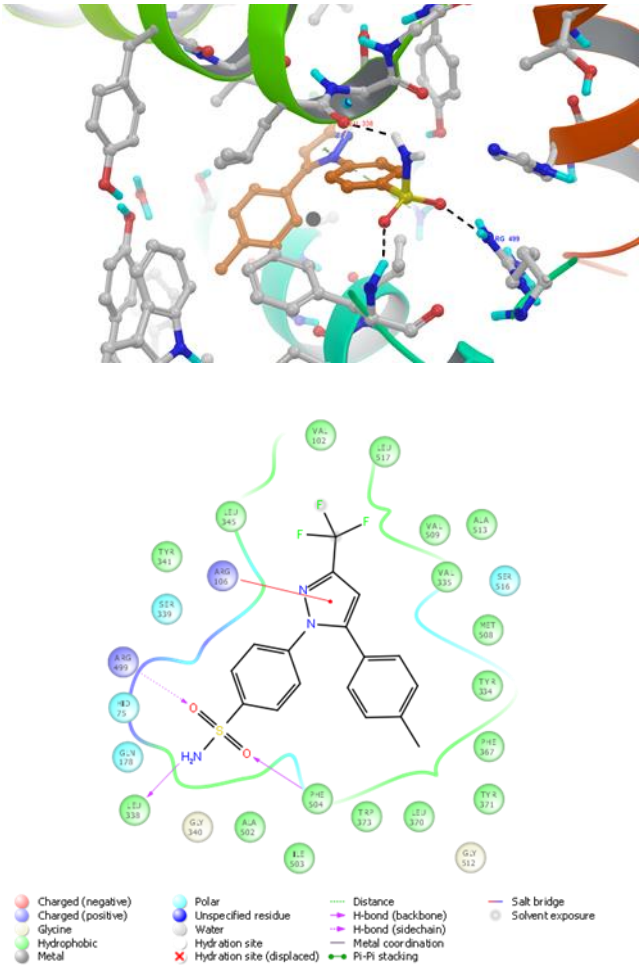


Figure 2.20. Depiction of Celecoxib bound to mouse COX-2 (PDB: 3LN1), hydrogen bonds denoted by dashed lines. Generated using Maestro Elements 2.5 (Schrödinger), Release 2016-1. Graphic created by Adrian Hall (UCB)

2.7 Summary

We have developed a one-pot, three-component synthesis of sulfonimidamides from a stable and readily available sulfinylamine reagent, TrNSO (**127**). The developed reaction displayed a broad substrate scope of organometallic and amine nucleophiles, enabling the preparation of a range of medicinally relevant structures. In contrast to previous sulfonimidamide syntheses, which typically require at least four steps, substituents on both sulfur and nitrogen can be easily varied. This was exemplified by the facile preparation of several analogues of the drug Celecoxib, one of which was found to show significant biological activity and improvements in logD and metabolic stability.

Unfortunately, the synthesis of sulfoximines has not been possible from TrNSO thus far. This is believed to be due to the large steric bulk of the trityl group preventing the attack of organometallic reagents at sulfur in sulfonimidoyl fluorides. The next chapter will focus on our efforts to circumvent this issue and deliver a one-pot preparation of sulfoximines from novel sulfinylhydroxylamine reagents.

Finally, we would like to note that our sulfinylamine reagent TrNSO has been commercialised by Tokyo Chemical Industries (Catalogue number T3773).

Chapter 3 – Sulfinylhydroxylamines – New Reagents for Sulfoximine and Sulfonimidamide Synthesis

3.1 Introduction

Sulfonimidoyl fluorides have often been employed as precursors to sulfoximines, usually *via* nucleophilic substitution by highly reactive organolithium reagents. However, the use of the more stable and easily prepared Grignard reagents results in a mixture of sulfoximine and the undesired reduction product sulfinamide (**Figure 3.1**), the latter derived by attack at fluorine.[76] Furthermore, our strategy of stabilising sulfinylamines by using a bulky trityl substituent on nitrogen led to low reactivity and exclusive formation of sulfinamide in reactions with the related sulfonimidoyl fluorides (see Chapter 2). Therefore, although sulfonimidoyl fluorides are less likely to undergo reduction than their chloride counterparts, it is clearly still a significant and problematic side reaction.

Considering these facts, we decided a different approach was necessary to achieve an efficient synthesis of sulfoximines. We were particularly interested in the use of *O*-aryl sulfonimidate esters; although these species had been reported by Johnson to react only with organolithiums and not Grignard reagents,[48] no reduction to sulfinamide was noted. The use of *O*-alkyl sulfonimidate esters was thought to be less likely to succeed due to the possibility of attack at carbon, in analogy with the well-known alkylating agents dimethyl sulfate and methyl triflate. A recent report from Stockman and co-workers describing the use of *O*-ethyl sulfonimidate esters as sulfoximine precursors appears to validate this concern, considering the relatively low yields of product reported and the requirement for small methyl or cyclopropyl substituents on sulfur.[96]

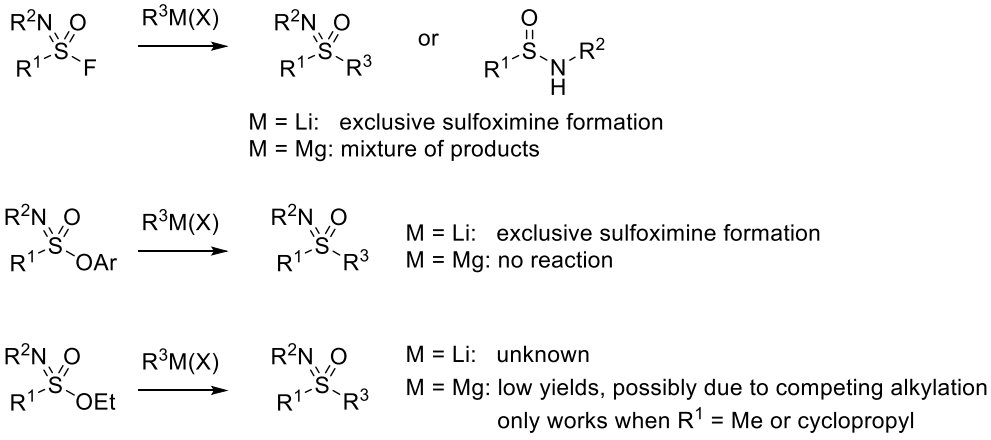


Figure 3.1. Limitations of sulfonimidoyl electrophiles as sulfoximine precursors

Sulfonimidate esters are typically prepared by the substitution of sulfonimidoyl chlorides with alcohols.[48] However, we suspected this would be challenging in the presence of a bulky group on nitrogen. Oxidation of sulfinamides to sulfonimidate esters using iodine(III) reagents and alcohols is also possible, but these methods fail in the case of phenols.[97]

We were therefore keen to develop a new method for their synthesis, and were inspired by a study on the mechanism of the oxidation of sulfinamides to sulfonimidoyl chlorides (**Figure 3.2**).[98] Reggelin and Junker obtained ^{1}H NMR data which appeared to suggest the intermediacy of an *N*-chlorosulfinamide species **149**, which then undergoes a rapid 1,2-shift from nitrogen to sulfur. Their assignment was made on the basis of the disappearance of the N-H signal in their intermediate, suggestive of N-chlorination rather than S-chlorination. This rearrangement process would presumably be thermodynamically driven by the formation of an S=N double bond.

The same driving force could in theory also enable the rearrangement of an *N*-aryloxysulfinamide **151**. We speculated that the combination of an *O*-aryl-*N*-hydroxysulfinylamine **150** with an organometallic reagent would lead to the formation of an electrophilic sulfonimidate ester **152**, which could then react further to form

diverse sulfur(VI) products, including sulfoximines and sulfonimidamides *via* the reaction of a second organometallic reagent or amine, respectively.

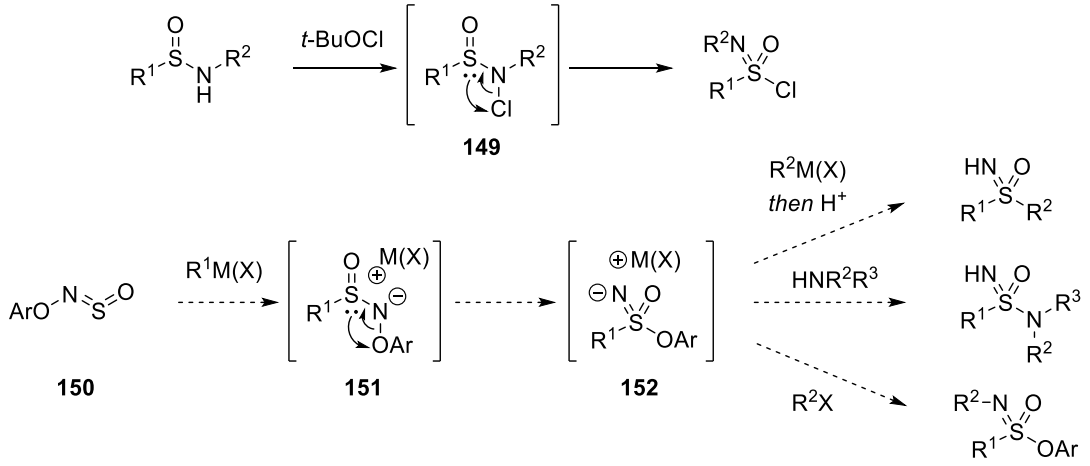


Figure 3.2. Reported rearrangement of *N*-chlorosulfinamides to sulfonimidoyl chlorides; sulfinylhydroxylamines as sulfur(VI) compound precursors *via* a related mechanism?

We therefore set out to prepare *O*-phenyl-*N*-sulfinylhydroxylamine **154** to determine its reactivity and stability. Although such molecules have not been previously synthesised, we were encouraged by the report of Michaelis in 1893 that the related *O*-benzyl-*N*-sulfinylhydroxylamine **156** could be prepared and displayed high resistance to moisture.[99] We synthesised the benzyl derivative according to our own procedure from commercially available *O*-benzylhydroxylamine **155** and confirmed its stability (**Figure 3.3**).

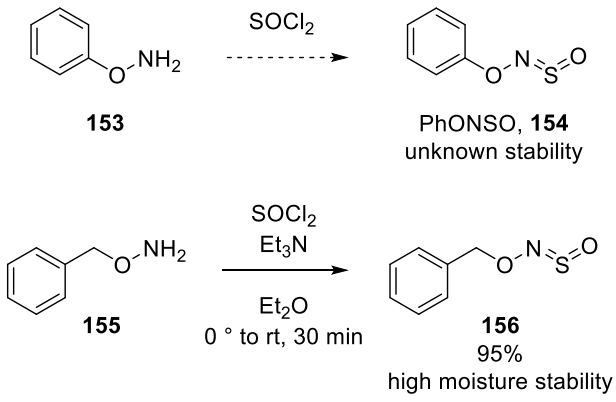


Figure 3.3. Our previously unprepared target, PhONSO **154**, and known *O*-benzyl-*N*-sulfinylhydroxylamine **156**, confirmed to be insensitive to moisture

O-Arylhydroxylamines are principally prepared *via* electrophilic amination of phenols,[100] nucleophilic aromatic substitution (S_NAr) of an electron-deficient arene with a hydroxylamine equivalent (**157** or **158**),[101] or transition metal-catalysed cross-coupling of an aryl halide or boronic acid with a hydroxylamine equivalent (**Figure 3.4**). The former approach suffers from low yields, a lack of generality due to dependence on the pK_a of the phenoxide anion and the use of explosive amination reagents such as MSH. The latter two are limited by the need for pre-functionalisation and/or activation of the aromatic ring, as well as the requirement for relatively low reaction temperatures to avoid undesired N-O bond thermolysis[102] or insertion of palladium(0).[103] Nevertheless, several metal-catalysed methods have been published, using both copper[104] and palladium.[105]

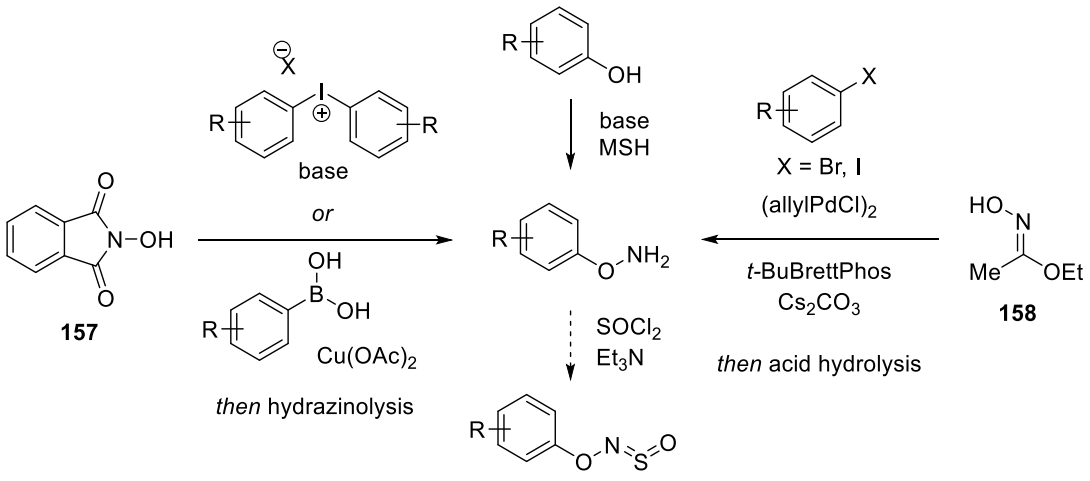


Figure 3.4. Common methods to prepare *O*-arylhydroxylamines

3.2 Synthesis and Applications of *O*-Aryl-*N*-Sulfinylhydroxylamines

We decided that the reaction of commercially available diphenyliodonium chloride with *N*-hydroxyphthalimide **157** and subsequent hydrazinolysis of product **159** was the most convenient route to the targeted *O*-phenylhydroxylamine **153**, and indeed the reactions proceeded smoothly according to literature procedures (**Figure 3.5**).[106] We were pleased to find that our previously employed sulfinylation conditions were

compatible with hydroxylamine **153**, giving *O*-phenyl-*N*-sulfinylhydroxylamine (PhONSO) **154** in excellent yield. To our delight, no hydrolysis was observed by ^{1}H NMR spectroscopy despite the filtration through Celite and solvent evaporation being conducted in air.

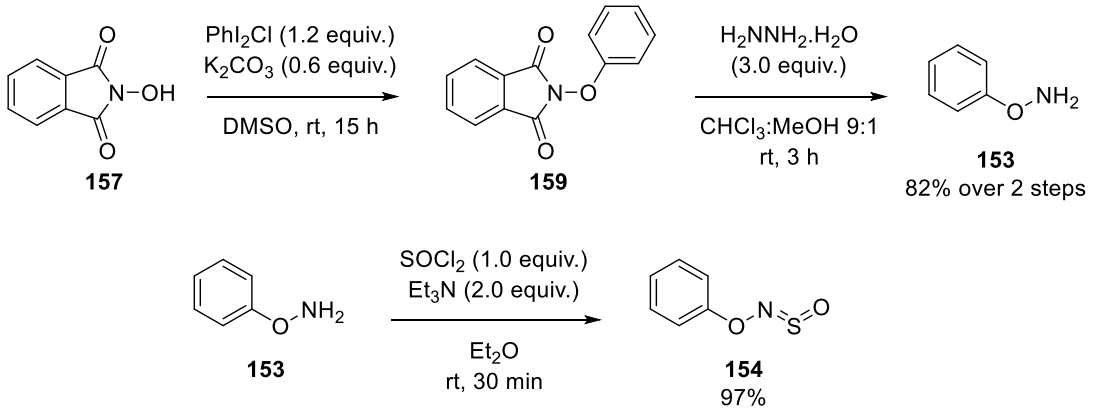


Figure 3.5. Three step synthesis of PhONSO **154**

With sulfinylhydroxylamine reagent **154** in hand, we wished to probe whether our hypothesised rearrangement was feasible. We chose to attempt the preparation of known sulfonimidamide **141a**. We suspected that anionic intermediate **152** (**Figure 3.2**) may self-condense,[53] and that this could be prevented by adding a Brønsted acid to the reaction to protonate the intermediate. Indeed, when we added 4-fluorophenylmagnesium bromide to a solution of PhONSO in THF, prior to sequential addition of an excess of morpholine and one equivalent of camphorsulfonic acid (CSA), the desired product was isolated in 47% yield (59% ^{19}F NMR yield) (**Figure 3.6**). Surprisingly, if the acid was added first, the isolated yield dropped to 38%.

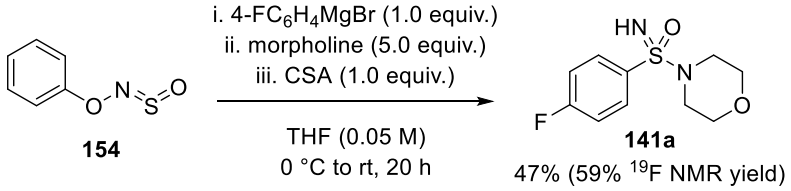
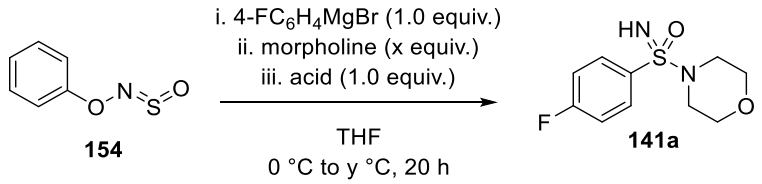


Figure 3.6. One-pot synthesis of sulfonimidamide **141a** from PhONSO

We then set out to optimise this promising result. We were pleased to find that stirring at 66 °C after the final addition resulted in an increased NMR yield of 72%, with the product isolated in a good 63% yield (entry 4). Changing the acid additive to benzoic acid (BzOH) or even omitting acid completely did not affect the yield relative to our original result when an excess (2 or 5 equiv.) of morpholine was used (entries 5 and 6). However, when only 1 equiv. of amine was used, the NMR yield dropped to 40% (entry 8), although interestingly this did appear to be attenuated somewhat by the presence of acid (entry 9).

Table 3.1. Optimisation of the one-pot sulfonimidamide synthesis from PhONSO



Entry[a]	morpholine (x equiv.)	temp. (y °C)	acid	^{19}F NMR yield (isolated)
1	5	23	CSA	59% (47%)
2	5	0	CSA	59%
3	5	40	CSA	66%
4	5	66	CSA	72% (63%)
5	5	23	BzOH	58%
6	5	23	-	58%
7	2	66	-	60%
8	1	66	-	40%
9	1	66	BzOH	51%

a. Reaction conditions: PhONSO (0.15 mmol, 1.0 equiv.), 4-FC_6H_4MgBr (1.0 equiv.), morpholine (x equiv.), additive, THF (0.05 M). b. Determined by ^{19}F NMR spectrum of crude reaction mixture.

Unfortunately, further attempts to optimise the reaction, varying solvent and concentration, acid, and temperature all resulted in lower yields. This raised our suspicions and we attempted to repeat our previous results with different batches of PhONSO. Several experiments failed to provide any product, even though the reagent

appeared to be pure as judged by ^{1}H NMR spectroscopy. This apparent instability and lack of reproducibility led us to abandon PhONSO as a reagent, which as a foul-smelling oil was in any case unpleasant and inconvenient to use. We considered that a solid sulfinylhydroxylamine may show greater stability and also improve ease of handling. In addition, increasing molecular weight would lower the volatility of the reagent and its precursors, simplifying their isolation.

We decided that this would also be a good opportunity to study the effect of electronic and steric factors on the stability and reactivity of *O*-aryl-*N*-sulfinylhydroxylamines. We wished to avoid electrophilic or easily reduced groups such as carbonyl or nitro functionalities in case of undesired reactivity with amines and Grignard reagents. To this end, we targeted compounds **160** to **165** (**Figure 3.7**). 4-(Trifluoromethanesulfonyl)phenyl derivative **160** would allow us to determine if a weaker N-O bond may promote the rearrangement. The biphenyl compound BiPhONSO **161** should be electronically similar to PhONSO, but was judged more likely to be solid due to the rigidity of the biaryl linkage. *ortho*-Substituted reagents **162** and **163** would test the influence of steric hindrance upon the reaction, while the *para*-methoxy and -dimethylamino derivatives **164** and **165** would help gauge if a more electron-rich aryl ring may help stabilise the reagent.

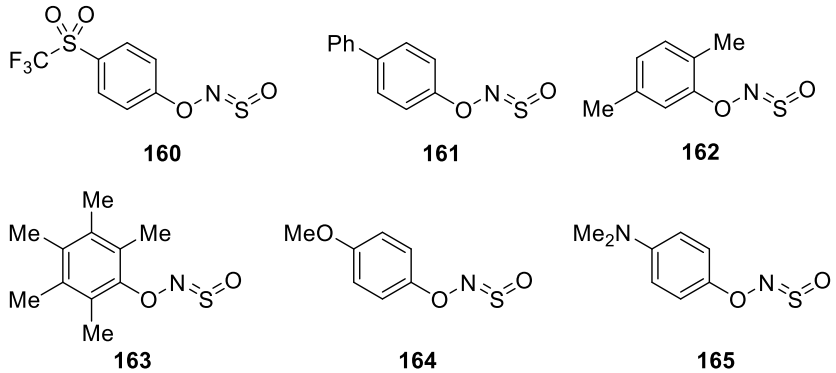


Figure 3.7. Targeted *O*-aryl-*N*-sulfinylhydroxylamine reagents **160**-**165**

We chose Buchwald's palladium-catalysed cross-coupling of ethyl acetohydroximate **158** with aryl halides and subsequent acid hydrolysis to prepare an array of *O*-arylhydroxylamines (**Figure 3.8**).[105] Electron-withdrawing and relatively electron-neutral substrates **167** to **169** were prepared in straightforward fashion, although the volatility of the precursor to **169** resulted in a low yield for the first step. Pentamethylphenyl derivative **170** could not be synthesised, presumably due to the aryl bromide being too sterically crowded to achieve oxidative addition of palladium(0) into the carbon-halogen bond. More surprising was the failure of 4-methoxy and 4-(dimethylamino)phenyl halides to provide any product, even when increased temperatures or palladium loadings were used. Indeed, the only electron-donating group reported in the *para*-position in the original paper is *tert*-butyl, suggesting that the concomitant increase in strength of the C-X bond significantly disfavours oxidative addition.

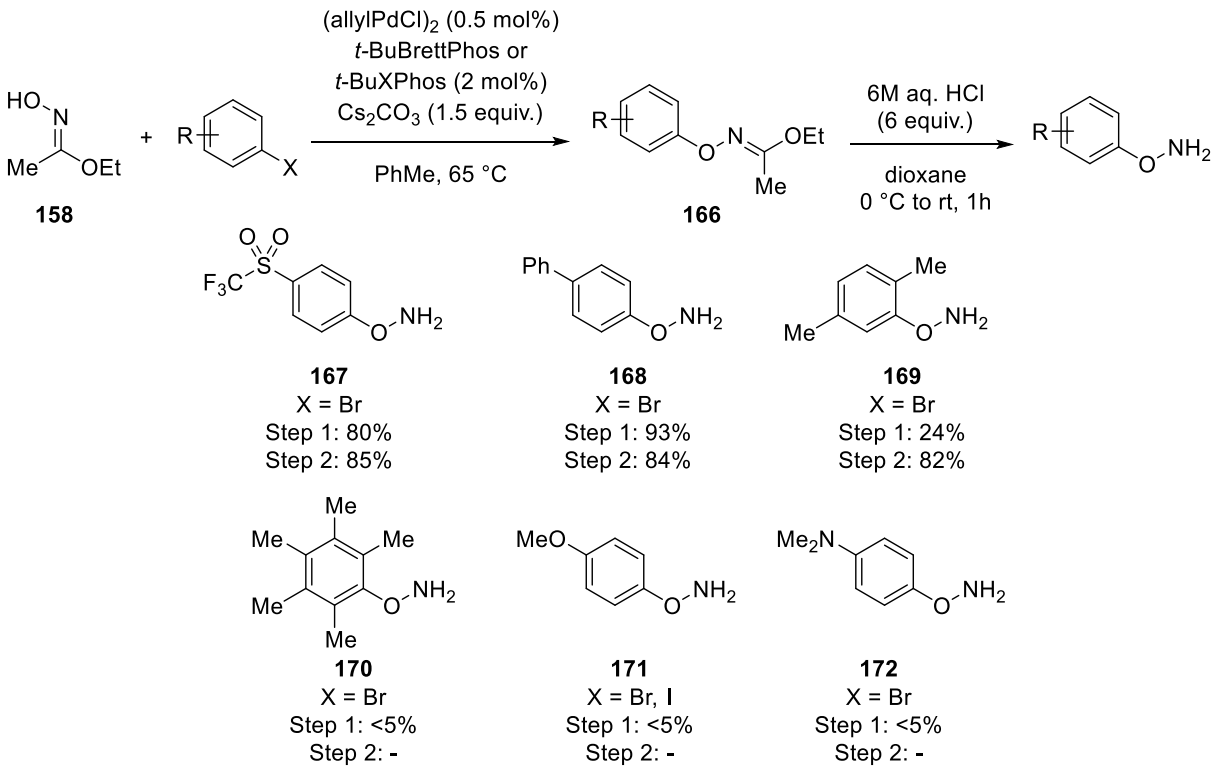


Figure 3.8. Palladium-catalysed synthesis of *O*-arylhydroxylamines using Buchwald's procedure

We were particularly interested in the 4-methoxyphenyl derivative **171** and decided to try and pursue its synthesis by other means (**Figure 3.9**). Compound **173** had previously been prepared in low yield by a Chan-Lam reaction.[104] Frustratingly, this proved difficult to reproduce, especially on gram scale. Nevertheless, some impure material could be obtained, and this was subjected to standard hydrazinolysis conditions. We were excited to observe the apparent formation of the desired compound in the ^{1}H NMR spectrum of the crude mixture, yet all attempts to purify it, including silica gel chromatography and vacuum distillation, resulted only in decomposition. The main product identified after chromatography was 4-methoxyphenol **174**, generated *via* cleavage of the O-N bond. Indeed, contrary to our expectations, it seemed that the presence of an electron-donating group destabilised the hydroxylamine.

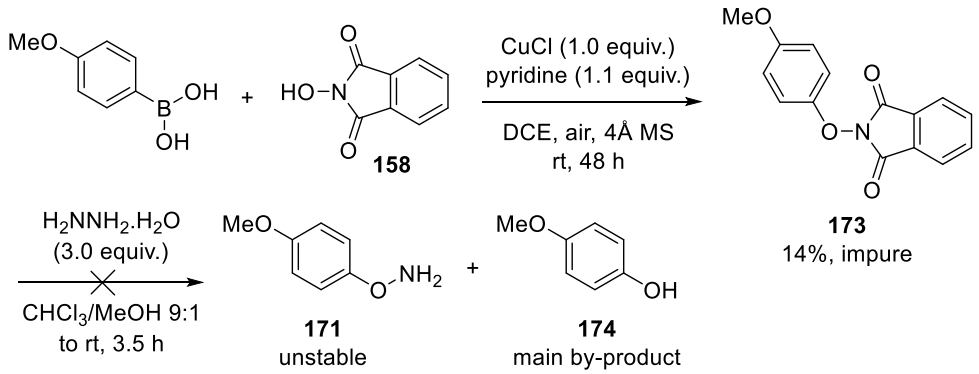


Figure 3.9. Failed synthesis of *O*-(4-methoxyphenyl)hydroxylamine **171**

This may be explained by a study of acid-catalysed amino-migrations of *O*-arylhydroxylamines reported by Endo in 1992 (**Figure 3.10a**).[107] The formation of phenols was observed, and, although the mechanism of this precise transformation was not explained, N-O bond cleavage was reported to proceed by protonation and the formation of a phenoxenium ion **175**. In the presence of a 4-methoxy group, which would impart significant stabilisation to intermediate **175** (**Figure 3.10b**), the barrier to this pathway may be lowered enough that the compound decomposes when exposed

to silica or elevated temperatures. This instability may explain why, although *O*-(4-methoxyphenyl)hydroxylamine[108] and its hydrochloride salt[109] have been reported in the literature, they have never been characterised.

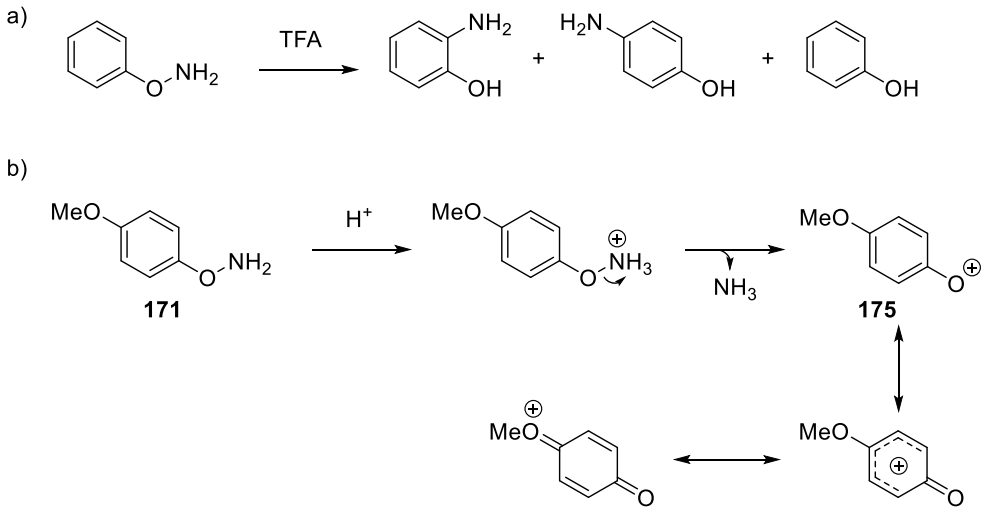


Figure 3.10. a) Acid-catalysed amine migration and phenol side-product reported by Endo; b) Reported mechanism of N-O bond cleavage would be promoted by a 4-methoxy substituent[107]

We therefore returned to the *O*-arylhydroxylamines **167** to **169** that we had managed to prepare previously. In each case, their transformation to the desired sulfinylamine proceeded smoothly, although a lower yield was again obtained for the 2,5-dimethyl derivative **162**, probably again due to volatility (**Figure 3.11**). Reagents **160** and **161** were solids and all showed good moisture stability.

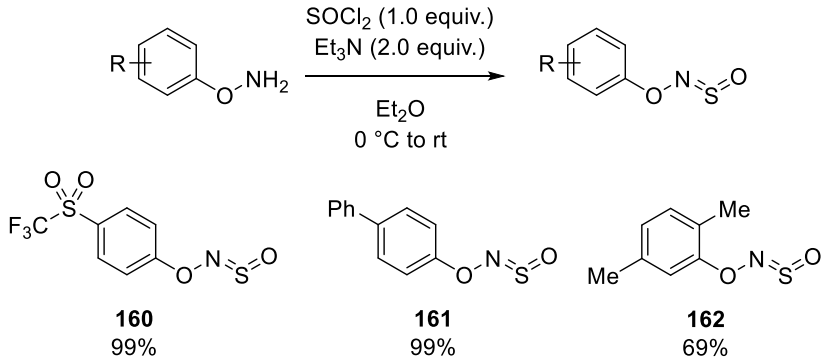


Figure 3.11. Synthesis of *O*-aryl-*N*-sulfinylhydroxylamine reagents **160** to **162**

We attempted to prepare sulfonimidamide **141a** from the 4-(trifluoromethylsulfonyl)phenyl derivative **160** using conditions previously developed for PhONSO (**Figure 3.12**). We were interested to find that only a trace of sulfonimidamide could be detected in the ^{19}F NMR spectrum of the crude mixture, but around 20% of the apparent symmetrical sulfoximine **176** (identified by ^{1}H NMR spectroscopy and mass spectrometry) had formed. This suggested that the presence of a strong electron-withdrawing group did indeed promote the rearrangement, such that it proceeded even before the addition of Grignard reagent was complete. Encouraged by the formation of a sulfoximine, and supposing that lowering the reaction temperature should allow better control over the process, we added 4-fluorophenylmagnesium bromide and 4-tolylmagnesium bromide to reagent **160** sequentially at -78 °C. An inseparable mixture of sulfoximines **176** to **178** was isolated in around 30% yield.

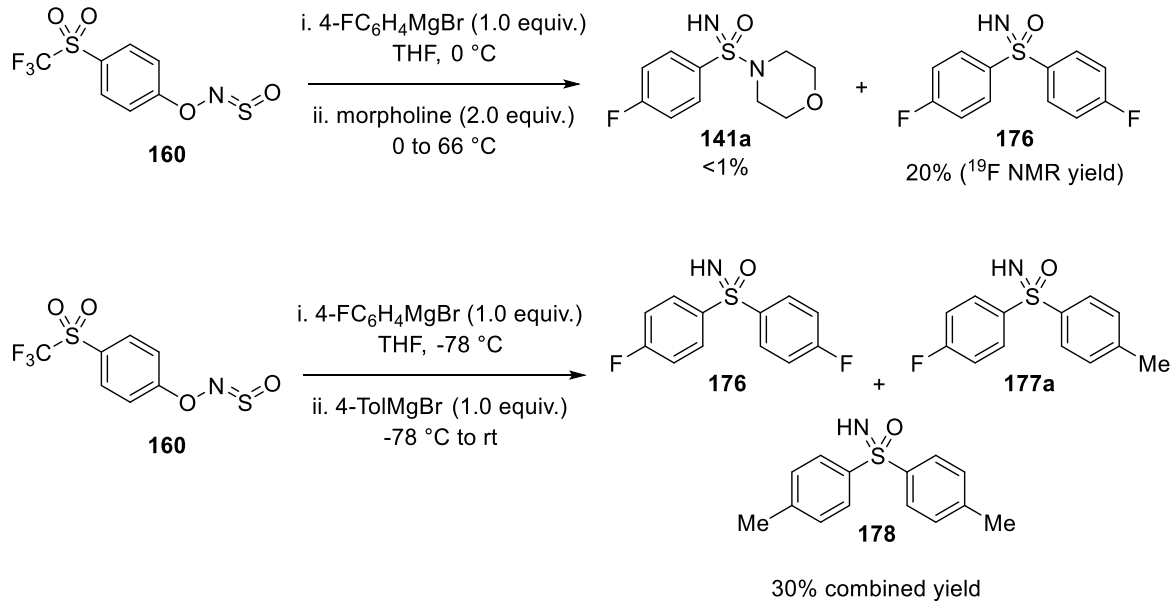


Figure 3.12. Unselective synthesis of sulfoximines from sulfinylamine reagent **160**

Despite the low selectivity with reagent **160**, we were encouraged that the rearrangement appeared to proceed at lower temperatures and we suspected that a

more electron-rich reagent may deliver a more selective system. While *ortho*-substituted sulfinylhydroxylamine **162** gave only a 16% yield of product **177a** by ^{19}F NMR spectroscopy, the undesired symmetrical sulfoximines **176** and **178** were not observed (**Figure 3.13**). Further studies were not conducted with this reagent due to its volatility, and in addition we were concerned that it may show similar reproducibility issues to PhONSO, since it was also an oil.

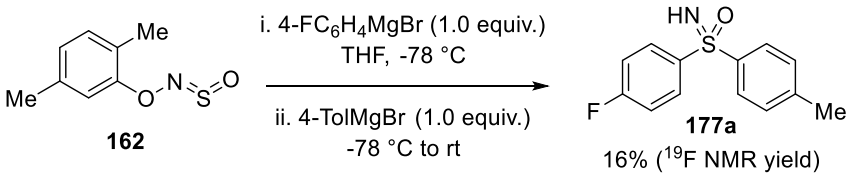


Figure 3.13. Low yielding synthesis of sulfoximine **177a** from sulfinylamine reagent **162**

We then turned to BiPhONSO **161**. We were delighted to obtain a 64% yield of compound **177a** by ^{19}F NMR spectroscopy when two Grignard reagents were added sequentially at -78 °C (**Figure 3.14**). The desired product was isolated in 53% yield but was contaminated by 15% of the symmetrical sulfoximine **176**. The 4-phenylphenol by-product **179** was also obtained in a high 78% yield. We were surprised that when the second Grignard reagent was added after 20 minutes, none of the desired product was seen in the ^{1}H or ^{19}F NMR spectra of the crude mixture. This suggested that a reactive intermediate was formed and could decompose even at -78 °C.

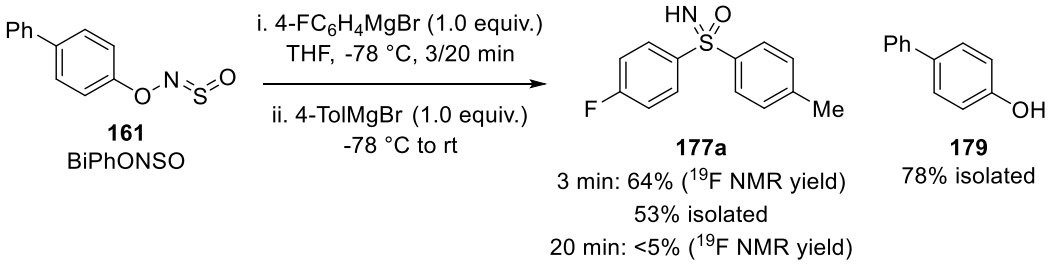


Figure 3.14. Synthesis of sulfoximine **177a** from BiPhONSO **161**

Our initial attempts to optimise or even reproduce the result in **Figure 3.14** failed; control of temperature proved to be the crucial factor. When the reaction vial was left

in the dry-ice acetone bath after the second addition and warmed to room temperature slowly, no sulfoximine product was observed. In contrast, when the vial was removed immediately after the second addition, the previous yield of 53% was reproduced. To our delight, when the vial was removed immediately and then quickly warmed to room temperature by immersion in a water bath, a 72% yield was obtained. Furthermore, by adding a slight excess (1.2 equivalents) of the second Grignard reagent one minute after the initial addition, the desired product **177a** was isolated in an excellent 83% yield and the symmetrical sulfoximine **176** was not observed (**Figure 3.15**). An identical yield was achieved when the reaction mixture was stirred for just 15 minutes and purified directly by column chromatography, maximising ease of use.

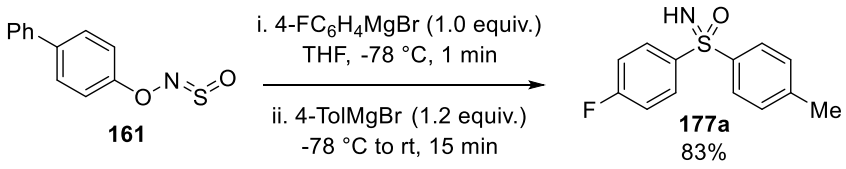


Figure 3.15. Optimised conditions for the synthesis of sulfoximine **177a** from BiPhONSO

With the optimised conditions determined, we required large quantities of BiPhONSO to conduct the substrate scope. Hydroxylamine **168** could be prepared in 82% yield over two steps (one purification) on gram scale from 4-bromobiphenyl using Buchwald's palladium-catalysed cross-coupling conditions (**Figure 3.16**).[105] However, due its sensitivity to air (and possibly light), exacerbated by acidic conditions, several precautions were taken to obtain the highest yields. Exclusion of oxygen during the acid hydrolysis step was crucial. Performing column chromatography quickly in a darkened fume hood was found to be the most reliable method for purification; attempted recrystallisation of the neutral hydroxylamine or its HCl salt seemed to result mainly in decomposition. The pure product, which was initially a white solid, visibly darkened to a light brown colour when left to stand at room

temperature. Another complicating factor was decomposition in $CDCl_3$; clean spectra were only obtained when benzene-d_6 was instead used as the NMR solvent. Nevertheless, using the optimised protocol, hydroxylamine **168** could be reproducibly prepared in excellent purity, and sulfinylation proceeded smoothly on gram scale to afford BiPhONSO in 97% yield.

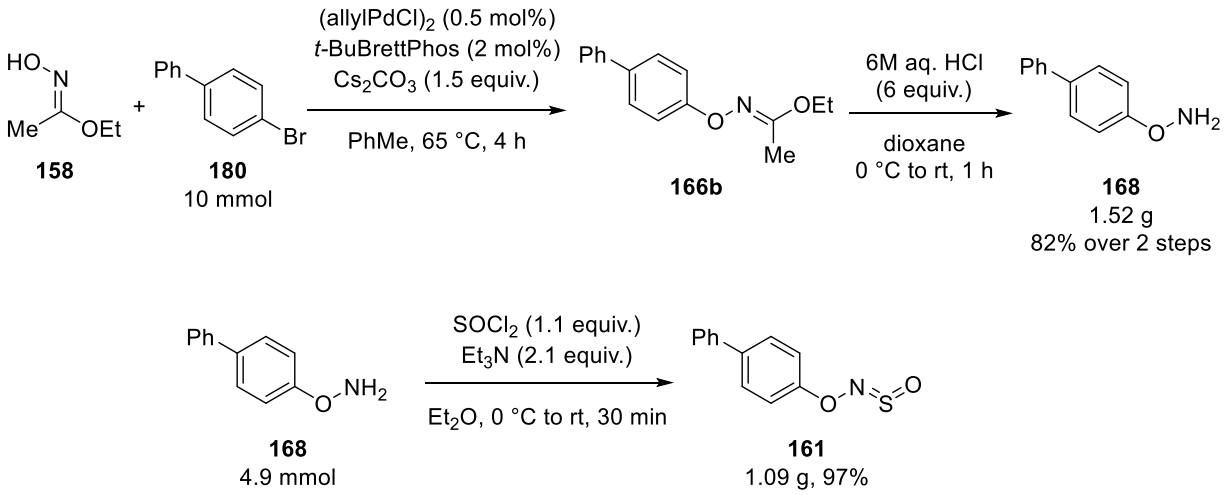


Figure 3.16. Optimised three step synthesis of BiPhONSO **161**

With large quantities of BiPhONSO in hand, we examined the scope of Grignard reagents that could be employed (**Figure 3.17**). Both electron-withdrawing (**177a** and **177g**) and -donating (**177c** and **177d**) substituents could be tolerated, and the reaction could incorporate a remarkable degree of steric hindrance with only minor reductions in yield (**177e** and **177f**). Indeed, to the best of our knowledge, **177f** is the first reported example of a sulfoximine featuring two *ortho*-substituted aryl groups connected to sulfur, suggesting that our reaction may represent an improvement over existing oxidative methodologies for sterically crowded substrates. The synthesis of *S*-alkyl-*S*-aryl and *S*,*S*-dialkyl sulfoximines was also possible in good yields (**177h** and **177i**). Sulfoximines containing a methyl group are perhaps the most medicinally relevant derivatives, and so we prepared a range of substituted *S*-aryl-*S*-methyl derivatives (**177j** to **177m**).

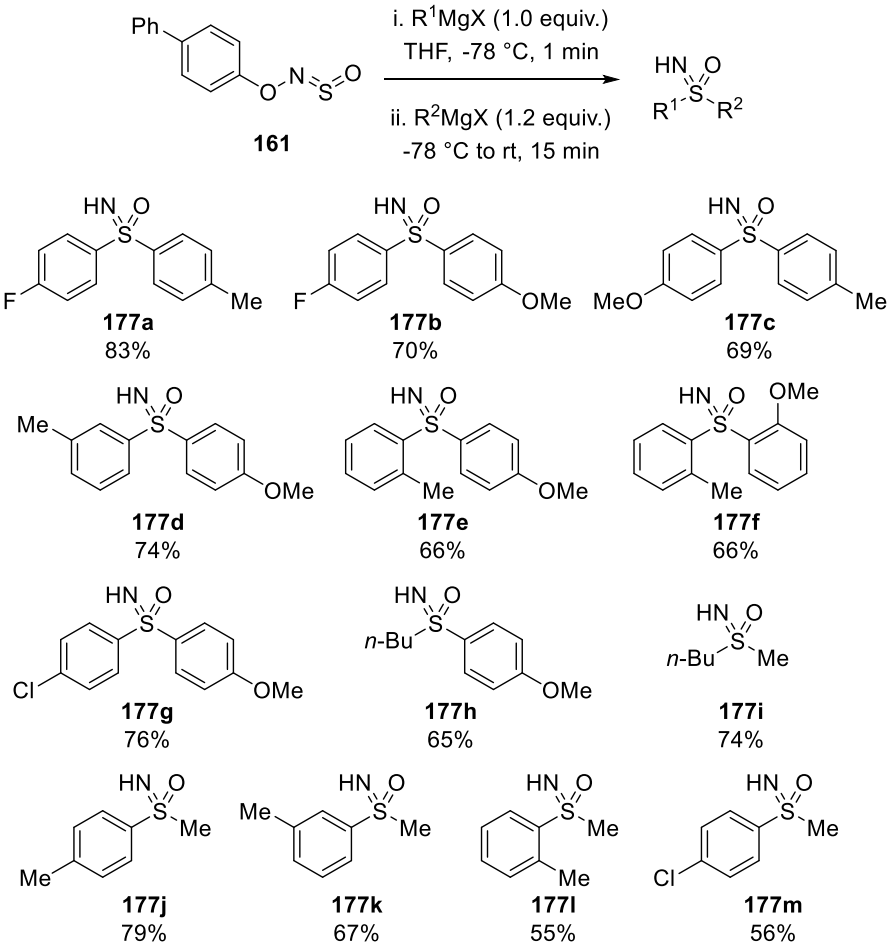


Figure 3.17. Scope of sulfoximines

We were pleased to find that simply using an excess (1.5 equivalents) of an amine in place of the second Grignard reagent proved optimal for the synthesis of sulfonimidamides. The scope with respect to the initial organometallic component, keeping morpholine constant as the amine nucleophile, is shown in **Figure 3.18**. High yields were obtained regardless of the electronic or steric properties of aryl Grignard reagents. An *n*-butyl derivative **180g**, using the less polar 1-Cbz-piperazine as the amine to aid isolation, gave a lower but still acceptable 57% yield.

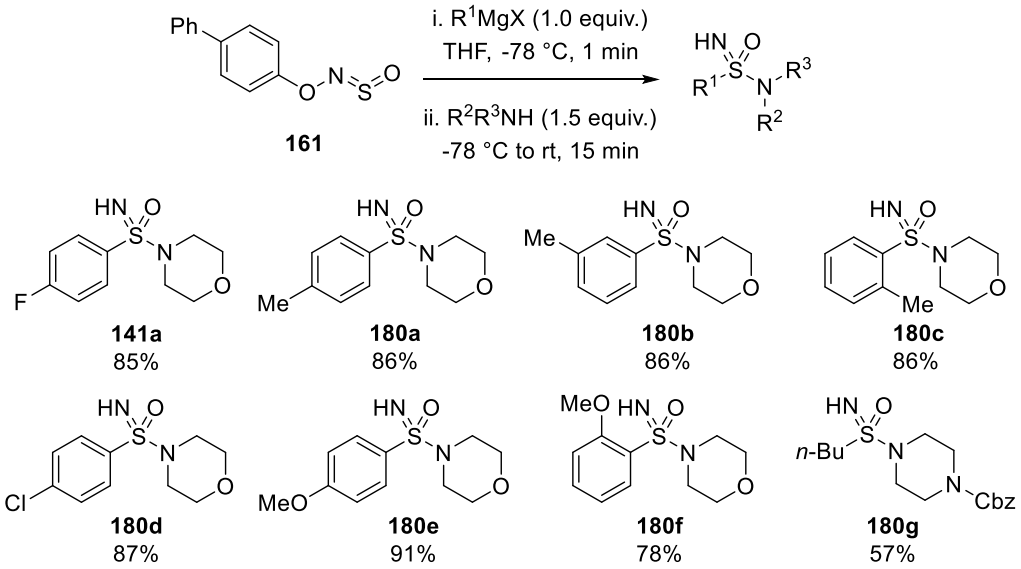


Figure 3.18. Sulfonimidamide organometallic scope

Keeping 4-fluorophenylmagnesium bromide constant as the initial nucleophile, we then varied the amine component (**Figure 3.19**). Several cyclic secondary amines proved to be excellent substrates, with 80% being the lowest yield obtained. Some bulkier noncyclic secondary amines gave only slightly decreased yields (**180j** and **180k**); however, a clear steric limit was breached with *N*-*tert*-butylmethylamine and *N*,*N*-diisopropylamine, as none of the desired product could be isolated from these reactions. Primary amines, including an aniline (**180o**), were also competent nucleophiles, although isolated yields were generally lower than for secondary amines. Some amines with more sensitive functional groups, including a terminal alkyne (**141j**), ketal (**180p**) and ethyl ester (**180q**) performed well in the reaction. It is worth pointing out the improved performance of propargylamine relative to our original reaction with TrNSO (66% vs 49%), and the ability to incorporate an acid-sensitive group (**180p**) which likely would not survive our trityl deprotection step.

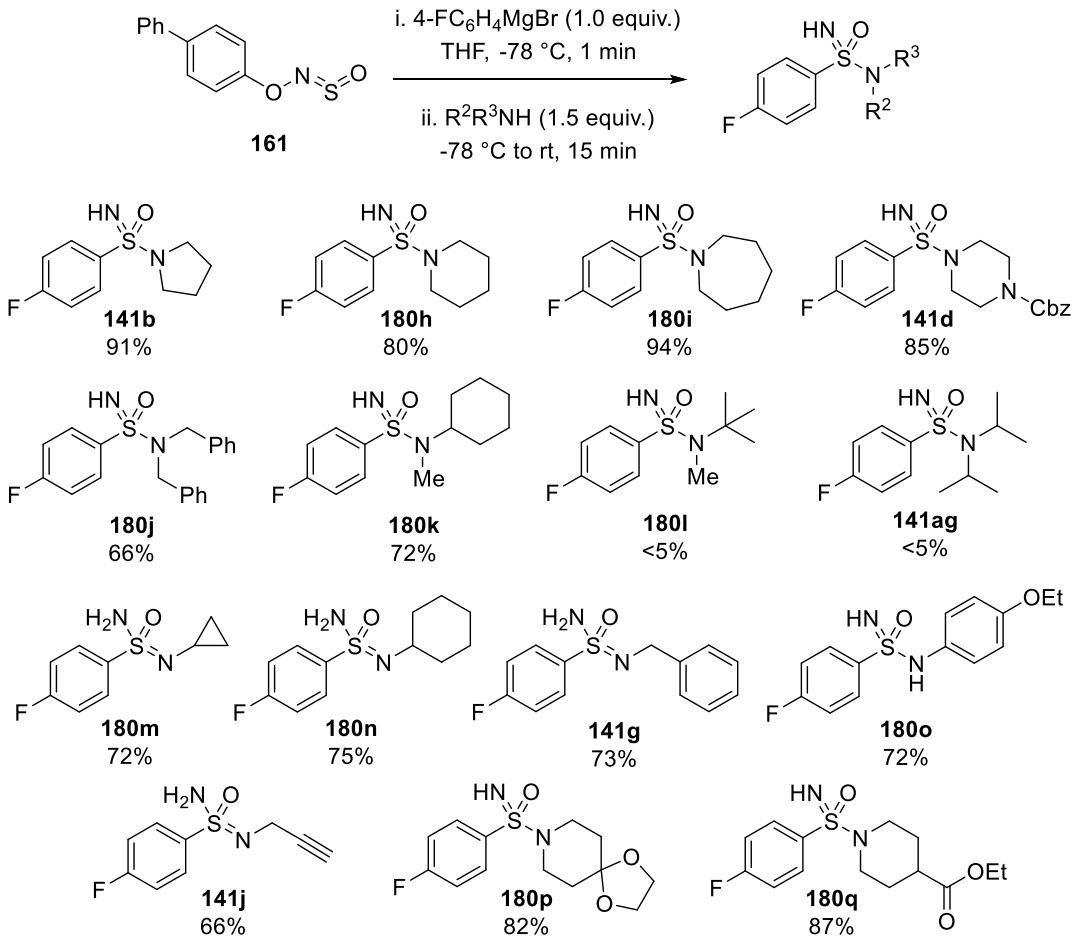


Figure 3.19. Sulfonimidamide amine scope

Further studies on the scope of our two reactions must be done to show that medicinally and synthetically relevant motifs such as nitrogen heterocycles, alkenes and alkynes can be incorporated as part of the Grignard reagent. It would also be interesting to determine whether functionalities with acidic protons (amides, alcohols, carboxylic acids) can be tolerated on the amine component, or whether protonation of the sulfinamide intermediate **151** (**Figure 3.2**) may occur and inhibit the reaction.

3.3 Mechanistic Discussion

The mechanistic hypothesis which led us to the discovery that *O*-arylsulfinylhydroxyamines **150** are useful reagents for the synthesis of sulfoximines and sulfonimidamides hinges upon a concerted 1,2-shift of an oxygen substituent from

nitrogen to sulfur, transforming an aryloxysulfinamide **151** into a sulfonimidate ester **152**. We rationalised this by invoking the thermodynamic driving force of the formation of a sulfur-nitrogen double bond. However, we must also consider the possibility of N-O bond heterolysis, which would form a phenoxide anion, which would stabilise the negative charge significantly more than a sulfinamide, and an electrophilic sulfinylnitrene (which can be represented by at least three plausible tautomeric forms **181a**-**181c**) (**Figure 3.20**). This bond cleavage may be assisted by involvement of the sulfur atom's lone pair of electrons. In either case, an electrophilic species is formed which could react further with a Grignard reagent or amine to form sulfoximines or sulfonimidamides. Indeed, it is possible that even if a sulfinylnitrene is formed, it would then react with the phenoxide anion to result in the same sulfonimidate ester intermediate as the concerted pathway.

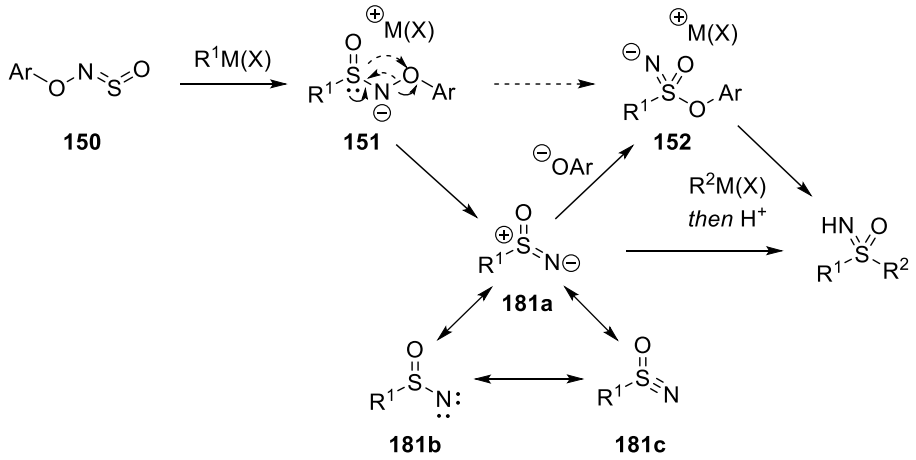


Figure 3.20. Two possible mechanistic pathways for the formation of sulfoximines from *O*-aryl-*N*-sulfinylhydroxylamines **150**; either *via* concerted 1,2-shift to form a sulfonimidate ester **152** (dashed arrow), or heterolytic N-O bond cleavage to form a sulfinylnitrene **181** and phenoxide anion (solid arrow). Both should react with a Grignard reagent to give a sulfoximine

Sulfinylnitrenes are known species and have previously been generated from sulfinyl azides (themselves formed by the reaction of sulfinyl chlorides with sodium azide).[110] Sulfinylnitrenes have been found to behave very differently to other nitrenes, which

are typically electrophilic at nitrogen. Rather than inserting into C-H bonds, or forming aziridines when reacted with double bonds, their main mode of reactivity is through nucleophilic addition to sulfur, forming *N*-sulfonylsulfilimines **186** rather than the expected sulfoximine **185** when reacted with DMSO (**Figure 3.21**).[111] For this reason, tautomer **181a** may be the most useful representation of this species. Little research has been conducted into sulfinyl azides since the original reports by Maricich, perhaps due to their reported instability at temperatures higher than -20 °C and explosive decomposition when rapidly warmed to room temperature.[110]

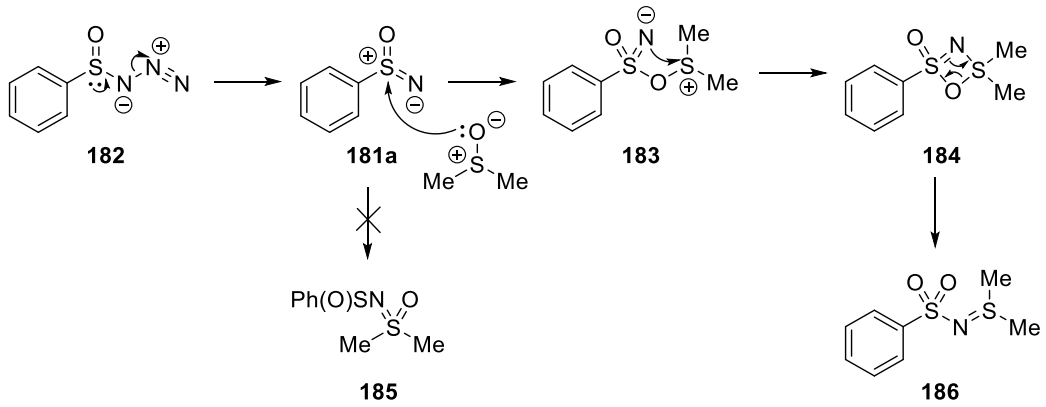


Figure 3.21. Sulfinyl azides **182** spontaneously evolve nitrogen to form sulfinylnitrenes, which react with sulfoxides to form *N*-sulfonylsulfilimines **186** rather than the expected sulfoximines **185**

Intriguingly, and of particular relevance to our research, Maricich also invoked a (protonated) sulfinylnitrene intermediate (**188**) to explain the reactivity of *N*-alkoxysulfinamides **187** (prepared from the addition of *O*-alkylhydroxylamines to sulfinyl chlorides). *N*-Alkoxysulfinamides were found to convert to primary sulfonamides **190** *via* an intermediate sulfonimidate ester (**189**) and subsequent C-alkylation by the methanol solvent (**Figure 3.22**).[112] At first glance this could plausibly be explained by a concerted 1,2-shift mechanism. However, cross-over experiments and a subsequent discovery that *N*-alkoxysulfinamides can give rise to the same *N*-sulfonylsulfilimine products (**186**) as sulfinyl azides in the presence of DMSO lend

weight to the N-O bond heterolysis mechanism. In addition, sulfinyl azides react with alcohols in a similar way to *N*-alkoxysulfinamides, further suggesting both species undergo a transformation to the same or similar intermediate.[113]

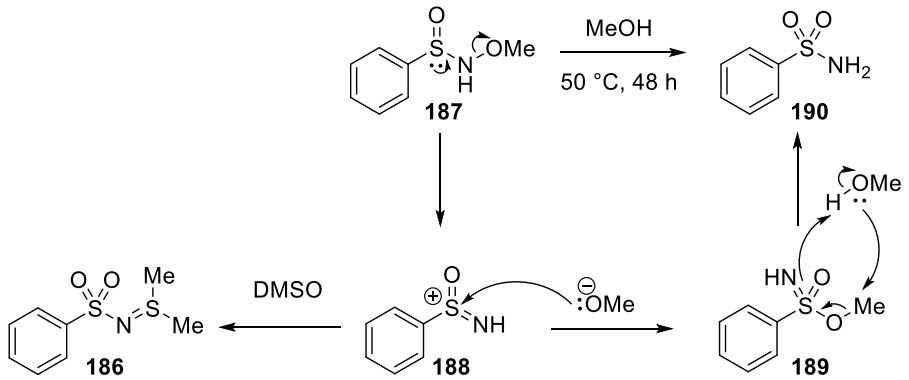


Figure 3.22. *N*-Alkoxysulfinamides have been reported by Maricich to undergo N-O bond heterolysis to form sulfinylnitrenium ions and react to form the same products as sulfinyl azides

While the reaction reported by Maricich uses different substrates and occurs under drastically different conditions to our process, it is possible that our *O*-arylhydroxysulfinamides also undergo N-O bond cleavage. Indeed, considering the improved leaving group ability of a phenoxide anion compared to an alkoxide, and the formation of a neutral sulfinylnitrene as opposed to a sulfinylnitrenium cation, it is plausible that such a process would be dramatically accelerated and even occur at cryogenic temperatures. Nevertheless, computational studies will likely be required to determine the true pathway.

3.4 Summary

In summary, we have developed an unprecedented one-pot synthesis of both sulfoximines and sulfonimidamides from previously unknown *O*-aryl-*N*-sulfinylhydroxylamine reagents. Various aryl and alkyl Grignard reagents can be added sequentially to BiPhONSO (**161**) to afford sulfoximines in good yields, and a

remarkable degree of steric hindrance can be tolerated. Sulfonimidamides derived from primary and secondary amines and anilines were also obtained in high yields, although less nucleophilic bulky amines such as diisopropylamine failed to add. Further reactions will focus on the use of heterocyclic organometallic reagents to demonstrate that our methodology can rapidly deliver truly druglike molecules which would otherwise require multistep syntheses.

Two main mechanistic pathways have been put forward to explain this transformation. Our initial hypothesis involved a concerted 1,2-shift of a phenoxy substituent from nitrogen to sulfur to convert a hydroxysulfinamide, generated *in situ* by the addition of a Grignard reagent to BiPhONSO, to a sulfonimidate ester. However, literature precedent suggests that N-O bond heterolysis may occur to form a sulfinylnitrene species. In either case, an electrophilic intermediate is formed which may react with a second organometallic reagent or amine. Computational studies will be required to determine which pathway is favoured.

During the course of the research described in this chapter, we also investigated the synthesis and reactivity of *O*-*tert*-butyl-*N*-sulfinylhydroxylamine (*t*-BuONSO). To our surprise, after addition of an initial organometallic reagent, *t*-BuONSO did not react with a second nucleophile, but instead afforded primary sulfonamides *via* an unknown mechanism. The following chapter will be an account of the serendipitous discovery and scope of this reaction.

Chapter 4 – A Serendipitous Synthesis of Primary Sulfonamides

4.1 Introduction

Primary sulfonamides **190** are present in a wide range of drugs and other biologically active molecules,[114] including one of the first modern antibiotics (Sulfanilamide) and common therapeutics for the treatment of high blood pressure (Hydrochlorothiazide) and oedema (Furosemide) (**Figure 4.1a**).[115] Despite their ubiquity, they can be difficult to synthesise using existing methods. They are often prepared *via* the reaction of ammonia with sulfonyl chlorides **191** (**Figure 4.1b**). However, sulfonyl chlorides are moisture-sensitive compounds which are typically installed by electrophilic aromatic substitution under harsh conditions using chlorosulfonic acid.[116] This limits functional group compatibility and the arene substitution patterns which can be achieved; indeed, all of the drug molecules shown in **Figure 4.1a** feature the sulfonamide in the *para*-position relative to a strongly electron-donating amine. Furthermore, if the use of gaseous ammonia is to be avoided, an ammonia surrogate must be employed, necessitating an extra deprotection step.

Primary sulfonamides may also be prepared directly from sulfinate salts **192** with an electrophilic amine source such as hydroxylamine-*O*-sulfonic acid.[117] However, sulfinates are generally not commercially available and can be difficult to prepare. Our own group has recently reported a significant advance in the synthesis of sulfonamides from the SO_2 surrogate DABSO, boronic acids and amines.[118] Unfortunately, ammonia could not be used in this system. A recent contribution from the Bull group demonstrated that primary sulfonamides could be prepared directly from thiols.[119] However, thiols are typically malodorous and not always commercially available, and

are hence not ideal starting materials. There is therefore a clear need for improved procedures to prepare these molecules. A simple, one-pot process to install primary sulfonamides from common feedstock chemicals such as aryl and alkyl halides would undoubtedly find use in drug and agrochemical discovery.

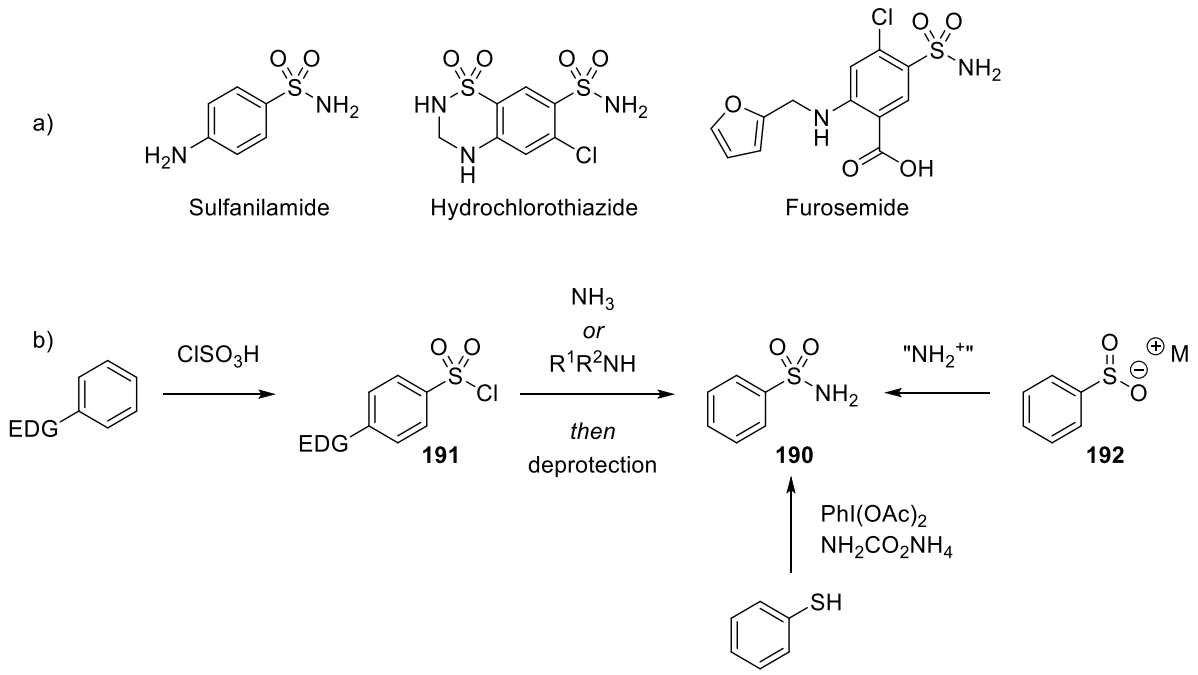


Figure 4.1. a) Primary sulfonamide-containing drugs. b) Common methods for their preparation

4.2 Results and Discussion

During the course of our investigation into a one-pot synthesis of sulfoximines, we decided to investigate the synthesis and reactivity of *O*-*tert*-alkyl substituted sulfinylhydroxylamines. In particular, we were interested in *O*-trityl- and *O*-*tert*-butyl-*N*-sulfinylhydroxylamine. We speculated that the former could be a conveniently accessible solid reagent with similar reactivity to the more synthetically challenging *O*-arylsulfinylhydroxylamines. For the latter, we were intrigued by what effect the poor leaving group ability of the *tert*-butoxide anion might have on our hypothesised rearrangement (or fragmentation) process. We considered that this process would be

significantly slowed and that this may result in higher yields or allow the use of non-cryogenic temperatures.

O-Tritylhydroxylamine **193** is commercially available (Aldrich 358894) or can be made in two steps from trityl chloride (**Figure 4.2**).[120] Its reaction with thionyl chloride proceeded in moderate yield to give the sulfinylhydroxylamine TrONSO **194** as an off-white solid. A few attempts to grow a crystal suitable for X-ray diffraction failed; upon heating, solutions of TrONSO decomposed and became a distinctive orange colour, potentially due to the formation of the trityl cation and a relatively stabilised "ONSO" anion. Due to the disappointing reactivity we will describe in this section, our efforts to obtain a crystal structure were not pursued further.

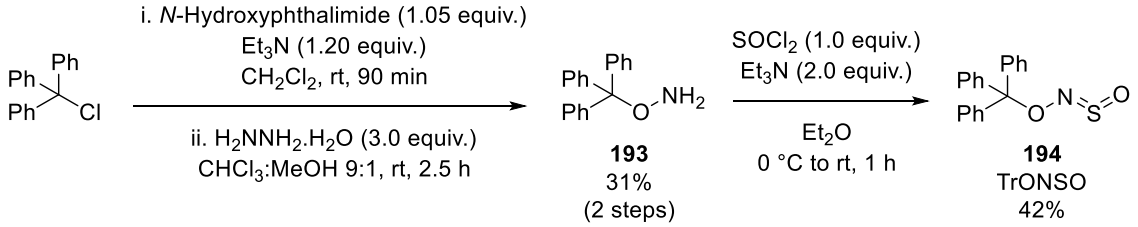


Figure 4.2. Synthesis of *O*-tritylsulfinylhydroxylamine, TrONSO

We first attempted to prepare a sulfonimidamide from TrONSO. Our initial attempt using conditions similar to the optimised BiPhONSO reaction (see chapter 3) with three equivalents of morpholine gave an encouraging 41% yield (**Figure 4.3**). However, brief attempts to increase this by using five equivalents of morpholine, or a reduced amine loading with addition of an acid, gave disappointing yields.

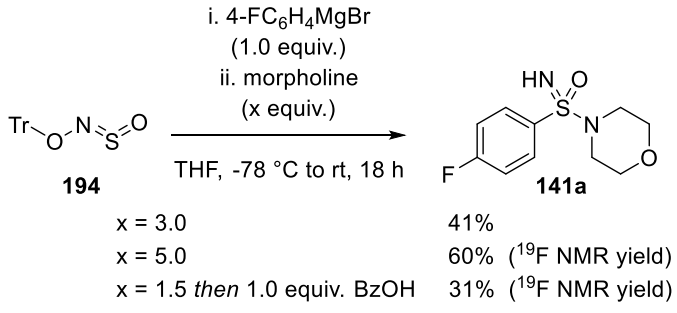


Figure 4.3. Sulfonimidamide synthesis from TrONSO **193**

We then attempted to prepare a sulfoximine from TrONSO. However, only an unselective mixture of sulfoximines was formed in very low yield (**Figure 4.4**). In the absence of a second nucleophile, the main product identified by ^{1}H and ^{19}F NMR spectroscopy was sulfonamide **195a** in a low 18% yield.

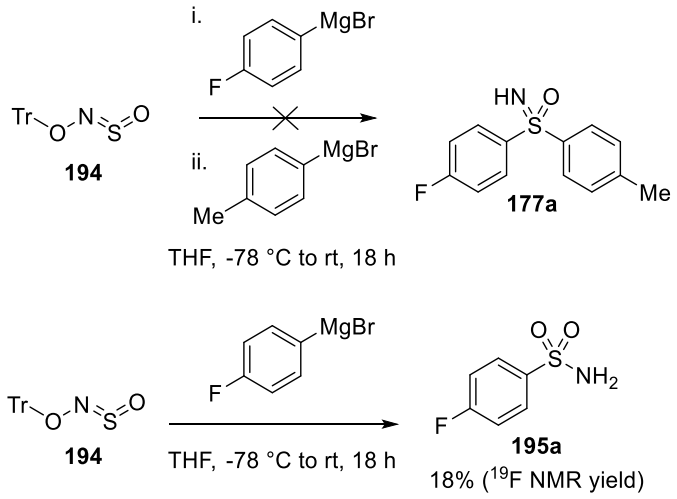


Figure 4.4. Failed sulfoximine synthesis from TrONSO; low yield of sulfonamide **195a** in the absence of a second nucleophile

Due to the poor reactivity exhibited by TrONSO, we decided to focus our efforts on preparing *O-tert*-butylsulfinylhydroxylamine (*t*-BuONSO) **197**. *O-tert*-Butylhydroxylamine is commercially available as the hydrochloride salt **196** (Aldrich B5765). Sulfinylation was possible by changing the solvent to dichloromethane (due to low solubility of **196** in diethyl ether) and using three equivalents of triethylamine (**Figure 4.5**). A moderate yield was obtained due to the volatility of the product, though the reaction could be carried out on 200 mmol scale and in total 15 grams of the product, a clear nonviscous liquid, were obtained.

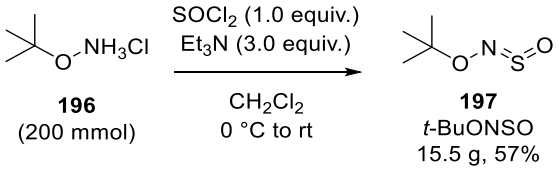


Figure 4.5. Synthesis of *O-tert*-butylsulfinylhydroxylamine, TrONSO

When *t*-BuONSO **197** was subjected to our previously developed conditions, involving addition of the organometallic reagent and amine in quick succession at -78 °C, only a very low yield of the desired sulfonimidamide product was determined by ^{19}F NMR spectroscopy. In addition, no trace of sulfoximine could be observed when using a Grignard reagent as the second nucleophile. We noted that in each reaction a large amount of an insoluble (in $CDCl_3$) by-product was present. To our surprise, this was identified as the primary sulfonamide **195a**. Repeating the reaction without the addition of a second nucleophile provided the sulfonamide in an excellent 80% yield following column chromatography (**Figure 4.6**). A brief evaluation of conditions varying temperature and Grignard reagent stoichiometry showed the robustness of the reaction and confirmed that the original result was optimal.

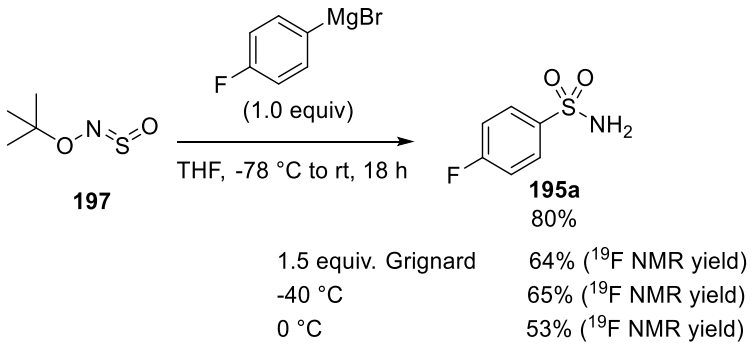


Figure 4.6. Serendipitous primary sulfonamide synthesis from *t*-BuONSO **197**

We then conducted a substrate scope to determine the limitations of the reaction (**Figure 4.7**). Primary sulfonamides with *para*-, *meta*- and *ortho*-methyl substituents could be prepared in good yields. Electron-withdrawing chloro and electron-donating methoxy groups were also tolerated. An alkyl example, *n*-butanesulfonamide **195g**, was obtained in a low 34% yield using *n*-butyllithium. The use of a less reactive alkyl Grignard reagent may provide a higher yield, but this remains to be investigated.

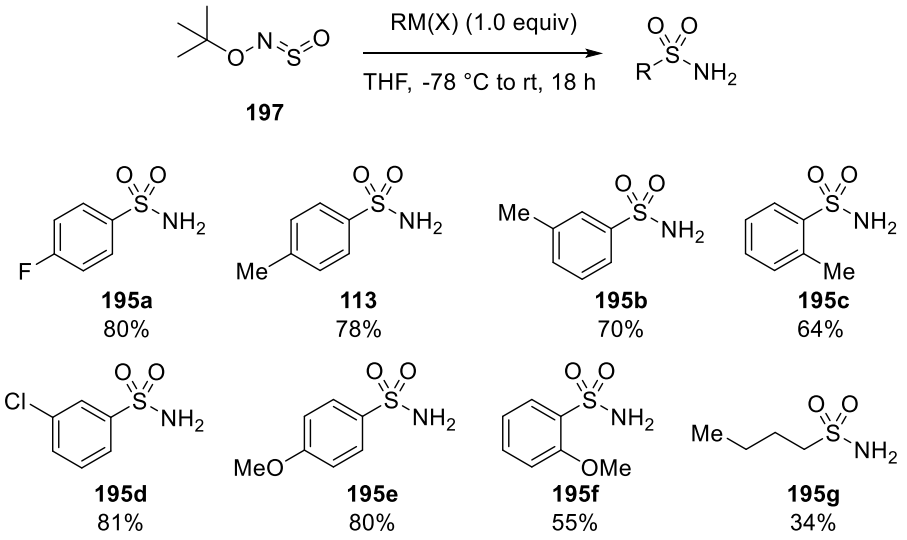


Figure 4.7. Scope of the one-pot primary sulfonamide synthesis

4.3 Mechanistic Discussion

The isolation of primary sulfonamides from the reaction of organometallic reagents with *t*-BuONSO was unexpected and the possible mechanistic pathways deserve some discussion. The initial reaction intermediate, *N*-*tert*-butoxy-4-fluorobenzenesulfinamide **198-H**, was formed by quenching with aqueous ammonium chloride at -78 °C shortly after Grignard addition and isolated in high purity following aqueous work-up (**Figure 4.8**). When **198-H** was dissolved in DMSO-d_6 in the presence of an internal standard (4-(trifluoromethyl)phenol) and left to stand at room temperature, it was found to convert to the primary sulfonamide at a rate of approximately 8% per week. *tert*-Butanol appeared to be formed during this process. The raw data is presented in full in chapter 6 (**page 163**).

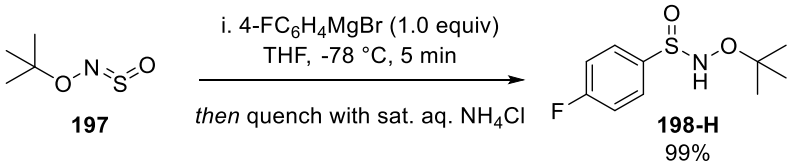


Figure 4.8. Isolation of the *tert*-butoxysulfinamide intermediate **198**

Several mechanistic hypotheses are depicted in **Figure 4.9**. The difference in reaction rate for the anionic versus neutral sulfinamide intermediate is striking and may hint at heterolysis of the N-O bond as the first step; under the standard reaction conditions a neutral sulfinylnitrene **181a** would be formed, as opposed to a less stable cationic species for the neutral sulfinamide. The sulfinylnitrene could then react with adventitious water to directly form the primary sulfonamide **195a** or, more likely, be attacked by *tert*-butoxide to give the sulfonimidate ester intermediate **199**. Alternatively, a concerted rearrangement process to give sulfonimidate ester intermediate **199** directly. In either case, the lack of reactivity with second nucleophiles such as Grignard reagents and amines may be explained by the enhanced stability and low electrophilicity of ester **199**. As the *tert*-butoxide anion is a significantly poorer leaving group than a phenoxide, it is likely that this would not eliminate to form the more electrophilic sulfinylnitrene **181a**. However, such a sulfonimidate ester would presumably be stable enough to isolate, yet we have not thus far observed it in any reactions or the aforementioned ^{1}H NMR experiment.

The source of the second sulfonyl oxygen is unclear. It seems most likely that it originates from reagent **197** or water. The reaction is conducted under an inert atmosphere in anhydrous solvent, so it is unlikely that hydrolysis of the transient sulfinylnitrene intermediate **181a** provides a full explanation for the reactivity, although small quantities of magnesium hydroxides are likely present in the solution of the Grignard reagent. Loss of a relatively stabilised cation is another possibility and could indicate why only *t*-BuONSO (and TrONSO), but not the *O*-arylsulfinylhydroxylamine reagents, form primary sulfonamides. This transformation seems energetically unfavourable, however, as it would result in a dianionic sulfonamide intermediate. For

t-BuONSO, a concerted mechanism which expels isobutylene as shown in **Figure 4.9** may be more plausible.

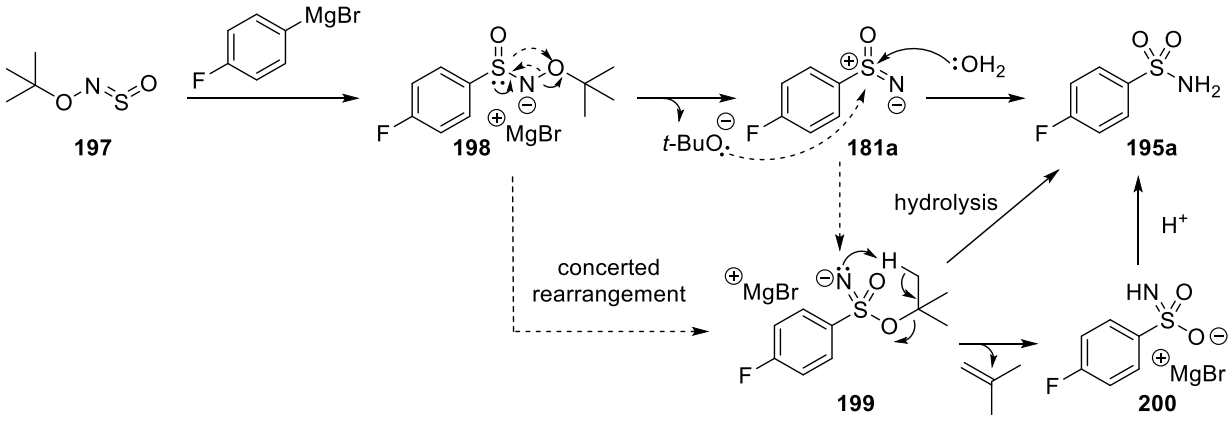


Figure 4.9. Possible mechanistic pathways for the formation of primary sulfonamide **195a** from *t*-BuONSO **197**

We hoped to probe the mechanism by the addition of heavy water ($^{18}OH_2$) to the reaction following addition of the Grignard reagent (**Figure 4.10**). However, this appeared to shut down reactivity. When the reaction was heated to 50 °C for two days, sulfonamide **195a** was formed and around 25% incorporation of oxygen-18 was seen by LCMS. The requirement for higher temperatures suggested the intermediate was protonated, slowing down the rearrangement process. We therefore reran the experiment with an excess of the organometallic reagent in the hope that this would restore reactivity. In this case however, no incorporation of oxygen-18 was found after stirring overnight at room temperature or several days at 50 °C. Although they are by no means definitive and more work is required, these experiments may suggest that water is not the source of the second oxygen under our optimised reaction conditions.

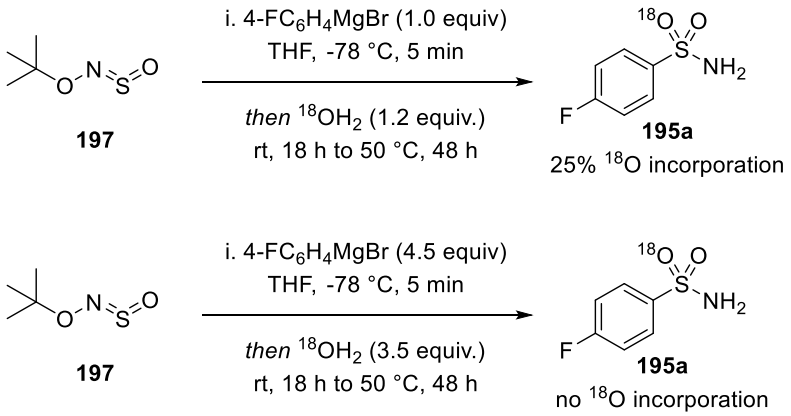


Figure 4.10. Addition of oxygen-18 labelled water retards reactivity and results in low or no isotopic enrichment

The use of oxygen-18 labelled *t*-BuONSO could provide an answer to this mechanistic puzzle. If the isotopically enriched oxygen is retained in the product, this would point to a mechanism involving loss of isobutylene or a *tert*-butyl cation. However, if it is present in the *tert*-butanol by-product and not the sulfonamide, the second sulfonyl oxygen must presumably arise from water. Due to time constraints, the preparation of an isotopically enriched reagent has not yet been attempted. However, a plausible synthesis is outlined in **Figure 4.11**. The reaction of commercially available oxygen-18 labelled acetone (Aldrich 609897) with methylmagnesium bromide would give *tert*-butanol. *tert*-Butanol is then known to react with ethyl azidoformate **201** to give ethyl *N*-*tert*-butoxycarbamate **202**, which can be hydrolysed to the desired product **196**.[121] ^{18}*O*-*tert*-butylhydroxylamine hydrochloride **196** could then be sulfinylated under the standard conditions to access the desired *t*-Bu^{18}ONSO reagent **197**.

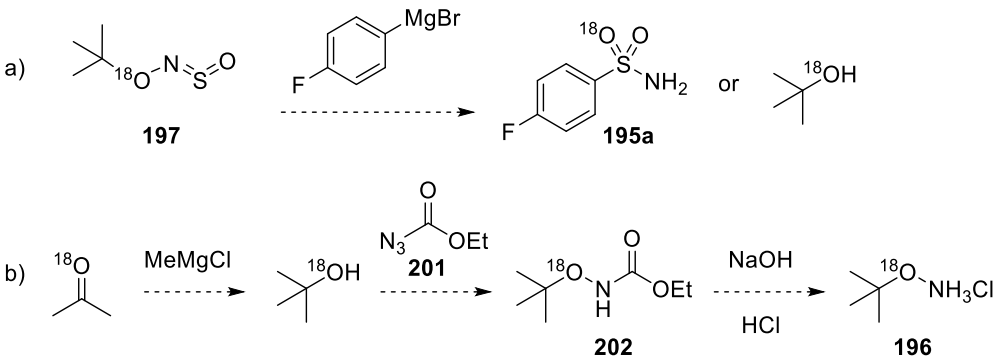


Figure 4.11. a) Use of oxygen-18 labelled *t*-BuONSO could provide strong mechanistic evidence. b) A potential route to the isotopically enriched reagent *t*-BuONSO precursor **196**

4.4 Summary

In summary, a convenient one-pot synthesis of medicinally relevant but difficult-to-access primary sulfonamides has been developed. The transformation was unexpectedly enabled by the novel sulfinylamine reagent *O*-*tert*-butyl-*N*-sulfinylhydroxylamine (*t*-BuONSO) **197**. A range of aryl bromides can be converted to primary sulfonamides in high yields. However, the *n*-butyl derivative **195g** was obtained in low yield, and work remains to be done to improve the synthesis of alkyl sulfonamides and extend the scope to include heteroaryl, alkenyl and alkynyl organometallic reagents.

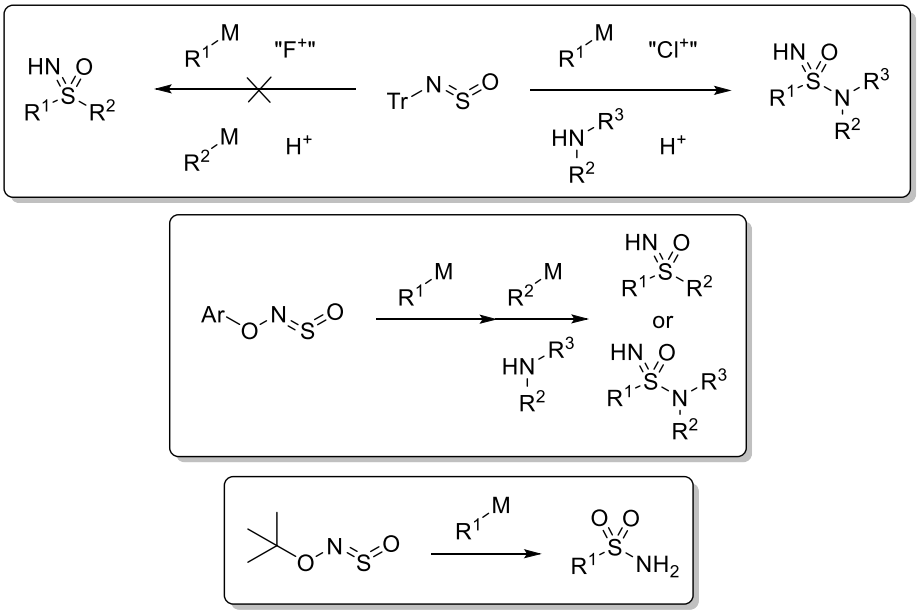
The mechanism of the transformation, including whether the second sulfonyl oxygen originates from adventitious water or the reagent itself, is currently unclear. Experiments involving the addition of $^{18}OH_2$ to the reaction mixture were inconclusive, but the synthesis of an oxygen-18 labelled version of *t*-BuONSO could provide vital clues. A combination of experimental and computational evidence will probably be required to fully elucidate the true mechanistic pathway.

Chapter 5 – Conclusions and Future Work

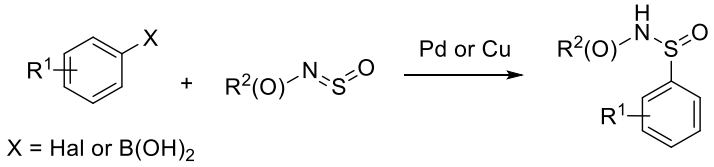
The work described in this thesis demonstrates that sulfinylamines, first discovered in the 19th century but virtually absent from the scientific literature since the 1960s, are versatile reagents for the synthesis of nitrogen-containing sulfur(VI) compounds. Though most previously synthesised members of this class of molecules are highly moisture-sensitive, judicious choice of the substituent on nitrogen can give rise to reagents exhibiting remarkable stability and reactivity.

Our initial work in this area resulted in a one-pot synthesis of sulfonimidamides from the sulfinylamine TrNSO, organometallic reagents and amines. This discovery has transformed the synthesis of these pharmaceutically relevant molecules, which were previously only available through tedious multistep procedures. The extreme steric hindrance of the trityl group conferred excellent moisture stability, but prevented the synthesis of sulfoximines from TrNSO, despite our development of a one-pot synthesis of sulfonimidoyl fluorides.

The design of a novel class of sulfinylamine, *O*-aryl-*N*-sulfinylhydroxylamines, provided a solution to this problem. Sulfoximines and sulfonimidamides could be prepared simply by the sequential addition of two organometallic reagents or one organometallic reagent and an amine, respectively, to our BiPhONSO reagent. Moreover, a serendipitous synthesis of primary sulfonamides was developed from *O*-*tert*-butyl-*N*-sulfinylhydroxylamine (*t*-BuONSO). Future work in the group will focus on elucidating the mechanism of these transformations through computation and experiment. The identification of reaction intermediates, perhaps through low temperature NMR studies or *in-situ* IR monitoring, could point the way to novel transformations.



More generally, the use of palladium or other metals to enable the catalytic addition of common feedstocks such as aryl halides or boronic acids to sulfinylamines would be a crucial contribution to this emerging field. This would avoid the use of highly reactive and pyrophoric pre-formed organometallic reagents and improve functional group tolerance, expanding the range of sulfur(VI) compounds which could be formed.



There is also a pressing need for catalytic enantioselective methods to unleash the full potential of sulfoximines and sulfonimidamides in medicinal chemistry. This could perhaps be achieved by the use of chiral ligands in a metal-catalysed process, or *via* chiral phase transfer catalysis.

Finally, to the best of our knowledge, there are no examples reported of the addition of radical species to sulfinylamines. With the relatively recent development of mild methods to prepare organic radicals, such as photoredox catalysis, it can be expected that exciting new reactivity modes of sulfinylamines are awaiting discovery.

Chapter 6 – Experimental Data and Procedures

6.1 General Considerations

Reactions were performed under inert nitrogen atmosphere with anhydrous solvent unless otherwise stated. All glassware was oven dried at >100 °C and allowed to cool to room temperature under positive pressure of nitrogen. Reactions were monitored by TLC until deemed complete using aluminium backed silica plates. Plates were visualized under ultraviolet light (254 nm) and/or staining with $KMnO_4$ or ninhydrin.

Reagents were purchased from Sigma-Aldrich Chemical Co. Ltd., Alfa Aesar, Acros Organics Ltd., Fluorochem Ltd. or Strem Chemicals Inc. and were used as supplied. *tert*-Butyl hypochlorite was prepared according to the Mintz-Walling procedure.[91] Grignard reagents were titrated against iodine using Knochel's method,[94] or using salicylaldehyde phenylhydrazone.[122] Flash chromatography was carried out using matrix 60 silica. 'Petrol' refers to the fraction of light petroleum ether boiling in the range 40–60 °C.

^{1}H-NMR spectra were obtained on a Bruker AVIII400 (400 MHz) spectrometer using the residual solvent as an internal standard. ^{13}C-NMR spectra were obtained on a Bruker AVIII400 (100 MHz) using the residual solvent as an internal standard. ^{19}F-NMR spectra were obtained on a Bruker AVIII400 (376 MHz) spectrometer. Chemical shifts (δ) were reported in parts per million (ppm) with the multiplicities of the spectra reported as following: s, singlet; d, doublet; t, triplet; q, quartet; pent., pentet; m, multiplet; app., apparent; br. broad. Coupling constants (*J*) were given in Hertz (Hz) and rounded to the nearest 0.5 Hz.

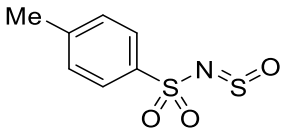
Low resolution ESI mass spectra were recorded on a Waters LCT Premier spectrometer. High resolution mass spectrometry measurements were recorded on a Bruker Daltronics MicroTOF (ESI) spectrometer or on a Micromass LCT (FI) spectrometer by the internal service at Chemistry Research Laboratory, University of Oxford. Samples for mass spectra were prepared as 1 mg/mL solution in MeCN (LRMS, HRMS-ESI) or submitted neat (HRMS-EI/HRMS-CI).

Infrared spectra were recorded as thin films on a Bruker Tensor 27 FT-IR spectrometer. Melting points were determined using a Stuart Scientific Melting Point Apparatus SMP1.

6.2 Chapter 2 Data

6.2.1 Synthesis of Sulfinylamines

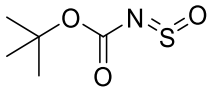
_N_-Sulfinyl-4-toluenesulfonamide 114



4-Toluenesulfonamide (2.00 g, 11.68 mmol, 1.0 equiv.) was added to a round-bottom flask equipped with reflux condenser. Thionyl chloride (10 mL) was added and the mixture stirred at reflux for 24 h. The reaction was allowed to warm to room temperature and excess thionyl chloride was removed under reduced pressure. The crude mixture was distilled (0.14 mbar, 130 °C) to afford sulfinylamine **114** as a yellow solid (1.50 g, 59%, 70% pure as determined by ^{1}H NMR spectroscopy). The ^{1}H NMR data obtained was consistent with the literature.[86]

δ_H (400 MHz, $CDCl_3$) 7.95 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.40 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 2.48 (s, 3H, C*H*$_3$).

_N_-Sulfinyl-*tert*-butyl carbamate 116 (*Liebigs Ann. Chem.* **1971**, *746*, 28-31)

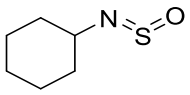


tert-Butyl carbamate (1.5 g, 12.80 mmol, 1.0 equiv.) was dissolved in diethyl ether (30 mL) in a Schlenk flask. Thionyl chloride (1.0 mL, 13.78 mmol, (1.05 equiv.) was added and the solution was cooled to 0 °C. Pyridine (2.2 mL, 27.31 mmol, 2.1 equiv.) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 48 h. Precipitated pyridine hydrochloride was removed by filter cannula. Remaining

solvent and thionyl chloride were removed under high vacuum to give sulfinylamine **116** as a yellow liquid (700 mg, 33%).

δ_H (400 MHz, $CDCl_3$) 1.54 (s, 9H, *t*-Bu-*H*).

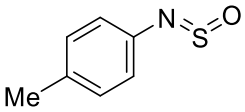
_N_-Sulfinylcyclohexylamine 118 [81]



Cyclohexylamine (10.4 mL, 90.50 mmol, 3.0 equiv.) was dissolved in diethyl ether (70 mL). The solution was cooled to 0 °C and thionyl chloride (2.20 mL, 30.32 mmol, 1 equiv.) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 18 h. The reaction was filtered. Remaining solvent and thionyl chloride were removed under reduced pressure. The residue was purified by distillation to give sulfinylamine **118** as a colourless liquid (1.03 g, 23%).

δ_H (400 MHz, $CDCl_3$) 4.66 (app. td, 1H, *J* = 9.5, 5.0 Hz, C*H*-NSO), 1.88-1.70 (m, 4H, Alk-*H*), 1.66-1.21 (m, 6H, Alk-*H*); δ_C (100 MHz, $CDCl_3$) 57.9, 33.6, 25.4, 24.2.

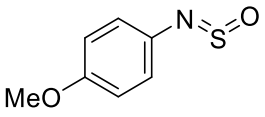
_N_-Sulfinyl-*para*-toluidine 119



para-Toluidine (3.0 g, 28.00 mmol, 1.0 equiv.) was dissolved in toluene (54 mL). The solution was cooled to 0 °C and thionyl chloride (2.44 mL, 33.60 mmol, 1.2 equiv.) was added dropwise. The reaction was allowed to warm to rt and stirred for 2 h, before refluxing for 8 h. Remaining solvent and thionyl chloride were removed under reduced pressure to give sulfinylamine **119** as a yellow oil (4.22 g, 98%). The experimental data was consistent with the literature.[123]

ν_{max} (neat, cm^{-1}) 1321, 1269, 1167, 1124, 1106, 1065, 1014, 847, 655; δ_H (400 MHz, $CDCl_3$) 7.79 (d, 2H, *J* = 8.0 Hz, Ar-*H*), 7.21 (d, 2H, *J* = 8.0 Hz, Ar-*H*), 2.39 (s, 3H, CH_3); HRMS (EI^+, *m*/*z*) calculated for $(C_7H_7ONS)^+$ 152.0243 $[M]^+$, found 152.0243.

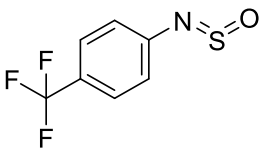
_N_-Sulfinyl-*para*-anisidine 120



para-Anisidine (1.50 g, 12.18 mmol, 1.0 equiv.) was dissolved in toluene (27 mL). The solution was cooled to 0 °C and thionyl chloride (1.06 mL, 14.62 mmol, 1.2 equiv.) was added dropwise. The reaction was allowed to warm to rt and stirred for 2 h, before refluxing for 5 h. Remaining solvent and thionyl chloride were removed under reduced pressure to give sulfinylamine **120** as a dark brown oil (2.10 g, quant.). The data was consistent with the literature.[124]

ν_{max} (neat, cm^{-1}) 1592, 1498, 1306, 1289, 1251, 1175, 1140, 1108, 1035, 1016, 834, 694; δ_H (400 MHz, $CDCl_3$) 7.91 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 6.89 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 3.85 (s, 3H, OCH_3); δ_C (100 MHz, $CDCl_3$) 161.0, 137.4, 129.6, 114.2, 55.6; HRMS (EI^+, *m*/*z*) calculated for $(C_7H_7O_2NS)^+$ 169.0192 $[M]^+$, found 169.0199.

_N_-Sulfinyl-4-(trifluoromethyl)aniline 121

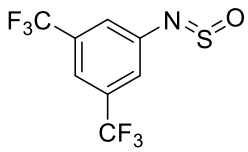


4-(Trifluoromethyl)aniline (1.50 g, 9.56 mmol, 1.0 equiv.) was dissolved in toluene (27 mL). The solution was cooled to 0 °C and thionyl chloride (0.83 mL, 11.47 mmol, 1.2 equiv.) was added dropwise. The reaction was allowed to warm to rt and stirred for 2

h, before refluxing for 5 h. Remaining solvent and thionyl chloride were removed under reduced pressure to give sulfinylamine **121** as a yellow liquid (1.87 g, 94%).

ν_{max} (neat, cm^{-1}) 1613, 1413, 1321, 1289, 1167, 1124, 1106, 1065, 1034, 1014, 847, 655; δ_H (400 MHz, $CDCl_3$) 7.91 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.69 (d, 2H, *J* = 8.5 Hz, Ar-*H*), δ_C (100 MHz, $CDCl_3$) 144.4 (d, $^5J_{CF}$ = 1.5 Hz), 131.6 (q, $^2J_{CF}$ = 33.0 Hz), 126.9, 126.5 (q, $^3J_{CF}$ = 4.0 Hz), 123.5 (q, $^1J_{CF}$ = 272.5 Hz); δ_F (376 MHz, $CDCl_3$) -63.0 (s, 3F, CF_3); HRMS (EI^+, *m*/*z*) calculated for $(C_7H_4F_3ONS)^+$ 206.9960 $[M]^+$, found 209.9964.

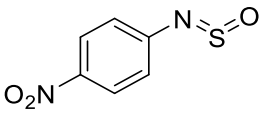
_N_-Sulfinyl-3,5-bis(trifluoromethyl)aniline 122



3,5-Bis(trifluoromethyl)aniline (680 µL, 4.35 mmol, 1.0 equiv.) was dissolved in toluene (10 mL). The solution was cooled to 0 °C and thionyl chloride (380 µL, 5.23 mmol, 1.2 equiv.) was added dropwise. The reaction was stirred at reflux for 3 h, then at rt for 16 h. Remaining solvent and thionyl chloride were removed under reduced pressure to give sulfinylamine **122** as a yellow liquid (937 mg, 78%).

ν_{max} (neat, cm^{-1}) 1461, 1372, 1273, 1167, 1128, 1062, 900, 858, 845, 724, 696, 683; δ_H (400 MHz, $CDCl_3$) 8.17 (s, 2H, Ar-*H*), 7.81 (s, 1H, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 142.7, 133.2 (q, $_2J_{CF}$ = 34.2 Hz), 126.8 (q, $^3J_{CF}$ = 4.1 Hz), 123.5 (hept, $^3J_{CF}$ = 4.0 Hz), 122.8 (q, $^1J_{CF}$ = 273.0 Hz); δ_F (376 MHz, $CDCl_3$) -63.3 (Ar-CF_3); HRMS (EI^+, *m*/*z*) calculated for $(C_8H_3F_6NOS)^+$ 274.9840 $[M]^+$, found 274.9839.

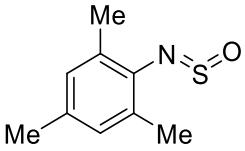
***N*-Sulfinyl-4-nitroaniline 123**



4-Nitroaniline (1.00 g, 7.24 mmol, 1.0 equiv.) was dissolved in toluene (10 mL). The solution was cooled to 0 °C and thionyl chloride (630 µL, 8.69 mmol, 1.2 equiv.) was added dropwise. The reaction was stirred at reflux for 4 h. Remaining solvent and thionyl chloride were removed under reduced pressure to give sulfinylamine **123** as a brown solid (1.29 g, 97%). The data was consistent with the literature.[124]

ν_{max} (neat, cm^{-1}) 3734, 1743, 1511, 1285, 1227, 1109, 1035, 886, 752; δ_H (400 MHz, $CDCl_3$) 8.29 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.92 (d, 2H, *J* = 8.5 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 147.4, 146.2, 127.3, 125.0; HRMS (EI^+, *m*/*z*) calculated for $(C_6H_4N_2O_3S)^+$ 183.9937 $[M]^+$, found 183.9939.

***N*-Sulfinylmesidine 124**

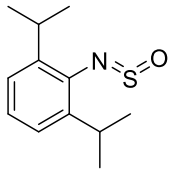


Mesidine (1.00 mL, 7.12 mmol, 1.0 equiv.) was dissolved in toluene (10 mL). The solution was cooled to 0 °C and thionyl chloride (620 µL, 8.54 mmol, 1.2 equiv.) was added dropwise. The reaction was stirred at reflux for 3.5 h. Remaining solvent and thionyl chloride were removed under reduced pressure to give sulfinylamine **124** as a brown liquid (1.31 g, quant.). The data was consistent with the literature.[125]

ν_{max} (neat, cm^{-1}) 2918, 1607, 1470, 1273, 1185, 1148, 852, 734; δ_H (400 MHz, $CDCl_3$) 6.81 (s, 2H, Ar-*H*), 2.17 (s, 3H, Ar-CH_3), 2.14 (s, 6H, Ar-CH_3); δ_C (100 MHz, $CDCl_3$)

138.2, 137.4, 130.0, 128.9, 21.0, 19.7; HRMS (EI$^+$, *m*/*z*) calculated for $(C_9H_{11}NOS)^+$ 181.0561 $[M]^+$, found 181.0560.

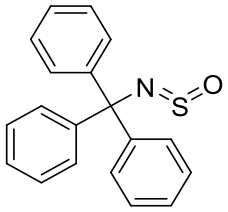
_N_-Sulfinyl-2,6-diisopropylaniline 125



2,6-Diisopropylaniline (1.00 mL, 5.30 mmol, 1.0 equiv.) was dissolved in toluene (10 mL). The solution was cooled to 0 °C and thionyl chloride (460 µL, 6.36 mmol, 1.2 equiv.) was added dropwise. The reaction was stirred at reflux for 4 h. Remaining solvent and thionyl chloride were removed under reduced pressure to give sulfinylamine **125** as a brown liquid (1.27 g, quant.). The data was consistent with the literature.[126]

ν_{max} (neat, cm^{-1}) 2964, 2871, 1462, 1281, 1171, 751; δ_H (400 MHz, $CDCl_3$) 7.19-7.10 (m, 3H, Ar-*H*), 2.93 (hept, 1H, *J* = 7.0 Hz, Ar-C*H*), 1.15 (d, 12H, *J* = 7.0 Hz, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 138.8, 137.5, 127.4, 123.5, 30.0, 23.2; HRMS (EI$^+$, *m*/*z*) calculated for $(C_{12}H_{17}NOS)^+$ 223.1031 $[M]^+$, found 223.1027.

_N_-Sulfinyltriphenylmethylamine, TrNSO 127 [88]



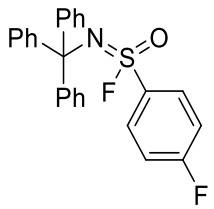
Tritylamine (10.0 g, 38.56 mmol, 1.0 equiv.) was dissolved in anhydrous diethyl ether (145 mL) in an oven-dried 250 mL 3 necked round bottom flask. Triethylamine (10.8 mL, 77.12 mmol, 2.0 equiv.) was added and the reaction was cooled to 0 °C. Thionyl

chloride (2.80 mL, 38.56 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 afforded TrNSO **127** as a white solid (11.59 g, 98%).

mp 93-95 °C; ν_{max} (neat, cm^{-1}) 3060, 1491, 1446, 1265, 750, 699; δ_H (400 MHz, $CDCl_3$) 7.36-7.25 (m, 15H, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 144.5, 128.8, 128.3, 127.8, 81.3; HRMS (EI^+, *m*/*z*) calculated for $(C_{19}H_{15}NOS)^+$ 305.0874 $[M]^+$, found 305.0879.

6.2.2 Synthesis of Sulfonimidoyl Fluoride **131**

4-Fluoro-*N*-tritylbenzenesulfonimidoyl fluoride 131



TrNSO (50.0 mg, 0.164 mmol, 1.0 equiv.) was added to an oven-dried reaction tube and dissolved in THF (1 mL). The reaction was cooled to 0 °C. 4-Fluorophenylmagnesium bromide (256 µL, 0.164 mmol, 0.64 M in THF) was added dropwise and the mixture stirred at the same temperature for 20 min. NFSI (51.6 mg, 0.180 mmol, 1.1 equiv.) was added and the mixture stirred for 2 h. The solution was quenched with water, then the layers were separated and the aqueous phase was extracted with ethyl acetate × 3. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacu*o. Purification by flash chromatography (SiO_2, 5:1 petrol/ethyl acetate afforded sulfonimidoyl fluoride **131** as an off-white solid (43 mg, 62%).

R_f = 0.43 (petrol/ethyl acetate 5:1); mp 172-174 °C; ν_{max} (neat, cm^{-1}) 3060, 1591, 1491, 1446, 1362, 1216, 1155, 699; δ_H (400 MHz, $CDCl_3$) 8.10-8.04 (m, 2H, Ar_F-*H*), 7.39-

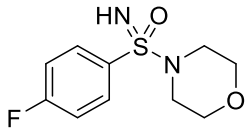
7.33 (m, 6H, Ar-*H*), 7.27-7.15 (m, 11H, Ar_F-*H*/Ar-*H*); δ_C (126 MHz, $CDCl_3$) 165.9 (d, $^1J_{CF}$ = 256.5 Hz), 146.2 (d, $^4J_{CF}$ = 4.0 Hz), 134.2 (dd, $^2J_{CF}$ /$^4J_{CF}$ = 30.5, 3.0 Hz), 130.4 (d, $^3J_{CF}$ = 9.5 Hz), 128.9, 128.0, 127.3 116.6 (d, $^2J_{CF}$ = 23.0 Hz), 74.3 (d, $^3J_{CF}$ = 4.5 Hz); δ_F (376 MHz, $CDCl_3$) 92.1 (s, S-F), -103.3 (app. td, *J* = 7.9, 4.0 Hz, Ar-F); HRMS (EI$^+$, *m*/*z*) calculated for $(C_{25}H_{19}F_2NOS)^+$ 419.1155 $[M]^+$, found 419.1154.

6.2.3 Synthesis of Sulfonimidamides

General Procedure A for Sulfonimidamide Synthesis

TrNSO (50.0 mg, 0.164 mmol, 1.0 equiv.) was added to an oven-dried reaction tube and dissolved in THF (1 mL). The reaction was cooled to 0 °C. The corresponding organometallic reagent (0.164 mmol, 1.0 equiv.) was added dropwise and the mixture stirred at the same temperature for 5 min. *tert*-Butyl hypochlorite (19.5 µL, 0.172 mmol, 1.05 equiv.) was added in a darkened fume hood and the mixture stirred for 15 min prior to addition of triethylamine (23 µL, 0.164 mmol, 1.0 equiv.) and the corresponding amine (1.0-1.2 equiv.). The reaction mixture was stirred at room temperature for 16 h. Methanesulfonic acid (53 µL, 0.819 mmol, 5.0 equiv.) was added and the reaction stirred vigorously for 15 min at room temperature before dilution with CH_2Cl_2. The solution was washed with saturated aqueous sodium bicarbonate solution, then the layers were separated and the aqueous phase was extracted with CH_2Cl_2 × 3. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by silica gel flash chromatography afforded the desired sulfonimidamide.

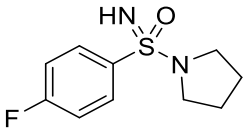
4-(4-Fluorophenylsulfonimidoyl)morpholine 141a



TrNSO (50.0 mg, 0.164 mmol, 1.0 equiv.) was added to an oven-dried reaction tube and dissolved in THF (1 mL). The reaction was cooled to 0 °C. 4-Fluorophenylmagnesium bromide (178 µL, 0.164 mmol, 0.92 M in THF, 1.0 equiv.) was added dropwise and the mixture stirred at the same temperature for 5 min. *tert*-Butyl hypochlorite (19.5 µL, 0.172 mmol, 1.05 equiv.) was added and the mixture stirred for 15 min, before addition of morpholine (30 µL, 0.344 mmol, 2.1 equiv.). The reaction mixture was stirred at room temperature for 22 h. Methanesulfonic acid (53 µL, 0.819 mmol, 5.0 equiv.) was added and the reaction stirred vigorously for 1 h at room temperature before dilution with CH_2Cl_2. The solution was washed with saturated aqueous sodium bicarbonate solution, then the layers were separated and the aqueous phase was extracted with CH_2Cl_2 × 3. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:2) afforded sulfonimidamide **141a** as a white solid (28 mg, 70 % yield).

mp 123-125 °C; ν_{max} (neat, cm^{-1}) 3271, 2856, 1590, 1490, 1258, 1113, 931, 714; δ_H (400 MHz, $CDCl_3$) 7.91-7.84 (m, 2H, Ar-*H*), 7.23-7.16 (m, 2H, Ar-*H*), 3.73-3.69 (m, 4H, OCH_2), 3.00-2.94 (m, 4H, NCH_2), 2.56 (br. s, 1H, N-*H*); δ_C (100 MHz, $CDCl_3$) 165.2 (d, $^1J_{CF}$ = 255.0 Hz), 131.0 (d, $^4J_{CF}$ = 3.0 Hz), 130.8 (d, $^3J_{CF}$ = 9.0 Hz), 116.1 (d, $^2J_{CF}$ = 22.5 Hz), 66.4, 47.1; δ_F (376 MHz, $CDCl_3$) -105.7 (app. td, *J* = 8.3, 4.6 Hz, Ar-F); LRMS *m*/*z* (ESI^+) $[M+H]^+$ 245.0; HRMS (ESI^+, *m*/*z*) calculated for $(C_{10}H_{13}FN_2O_2S)^+$ 245.07545 $[M+H]^+$, found 245.07560.

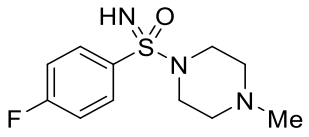
1-(4-Fluorophenylsulfonimidoyl)pyrrolidine 141b



Prepared according to general procedure A using 4-fluorophenylmagnesium bromide (178 µL, 0.164 mmol, 0.92 M in THF, 1.0 equiv.) and pyrrolidine (16 µL, 0.196 mmol, 1.2 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:2) afforded sulfonimidamide **141b** as a white solid (28 mg, 76% yield).

mp 78-80 °C; ν_{max} (neat, cm^{-1}) 3279, 2973, 2878, 1589, 1490, 1256, 999; δ_H (400 MHz, $CDCl_3$) 8.01-7.94 (m, 2H, Ar-*H*), 7.21-7.14 (m, 2H, Ar-*H*), 3.25-3.10 (m, 4H, NC*H*$_2$), 2.73 (br. s, 1H, N-*H*), 1.76-1.65 (m, 4H, NCH_2CH_2); δ_C (100 MHz, $CDCl_3$) 165.1 (d, $^1J_{CF}$ = 254.0 Hz), 133.3 (d, $^4J_{CF}$ = 3.0 Hz), 130.6 (d, $^3J_{CF}$ = 9.0 Hz), 116.0 (d, $^2J_{CF}$ = 22.5 Hz), 48.8, 25.4; δ_F (376 MHz, $CDCl_3$) -106.7 (app. ddd, *J* = 13.3, 8.6, 5.2 Hz, Ar-F); LRMS *m/z* (ESI^+) $[M+H]^+$ 229.0; HRMS (ESI^+, *m/z*) calculated for $(C_{10}H_{14}FN_2OS)^+$ 229.08054, found 229.08050.

1-(4-Fluorophenylsulfonimidoyl)-4-methylpiperazine 141c

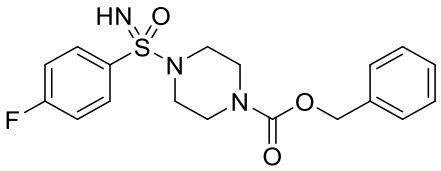


Prepared according to general procedure A using 4-fluorophenylmagnesium bromide (178 µL, 0.164 mmol, 0.92 M in THF, 1.0 equiv.) and 1-methyl-piperazine (22 µL, 0.196 mmol, 1.2 equiv.). Purification by flash chromatography (SiO_2, ethyl acetate/methanol, 1:0 to 9:1) afforded sulfonimidamide **141c** as a light yellow oil (29 mg, 69% yield).

ν_{max} (neat, cm^{-1}) 2849, 2800, 1589, 1491, 1134, 926, 716; δ_H (400 MHz, $CDCl_3$) 7.90-7.83 (m, 2H, Ar-*H*), 7.19-7.13 (m, 2H, Ar-*H*), 3.00 (app. br. s, 4H, NC*H*$_2$), 2.59 (br. s,

1H, N*H*), 2.43 (app. t, 4H, *J* = 4.5 Hz, MeNC*H*$_2$), 2.26 (s, 3H, NC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 165.2 (d, $^1J_{CF}$ = 254.5 Hz), 131.3 (d, $^4J_{CF}$ = 3.0 Hz), 130.9 (d, $^3J_{CF}$ = 9.0 Hz), 116.1 (d, $^2J_{CF}$ = 22.5 Hz), 54.5, 47.0, 45.7; δ_F (376 MHz, $CDCl_3$) -106.2 (tt, *J* = 8.1, 5.1 Hz, Ar-F); LRMS *m*/*z* (ESI^+) $[M+H]^+$ 258.1; HRMS (ESI^+, *m*/*z*) calculated for $(C_{11}H_{17}FN_3OS)^+$ 258.10709 $[M+H]^+$, found 258.10727.

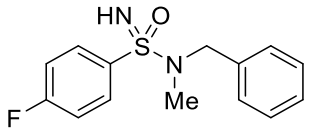
Benzyl 4-(4-fluorophenylsulfonimidoyl)piperazine-1-carboxylate 141d



Prepared according to general procedure A using 4-fluorophenylmagnesium bromide (178 µL, 0.164 mmol, 0.92 M in THF, 1.0 equiv.) and benzyl piperazine-1-carboxylate (32 µL, 0.164 mmol, 1.0 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:2) afforded sulfonimidamide **141d** as an off-white solid (47 mg, 76% yield).

mp 146-147 °C; ν_{max} (neat, cm^{-1}) 3271, 2856, 1590, 1490, 1258, 1113, 931, 714; δ_H (400 MHz, $CDCl_3$) 7.86 (dd, 2H, *J* = 9.0, 5.0 Hz, Ar$_F$-*H*), 7.36-7.26 (m, 5H, Ar-*H*), 7.18 (app. t, 2H, *J* = 8.5 Hz, Ar$_F$-*H*), 5.06 (s, 2H, OC*H*$_2$), 3.55 (app. br. s, 4H, C(O)NC*H*$_2$), 2.96 (app. br. s, 4H, SNC*H*$_2$), 2.61 (br. s, 1H, N-*H*); δ_C (100 MHz, $CDCl_3$) 165.3 (d, $^1J_{CF}$ = 255.0 Hz), 154.9, 136.3, 131.4 (d, $^4J_{CF}$ = 3.0 Hz), 130.8 (d, $^3J_{CF}$ = 9.0 Hz), 128.6, 128.3, 128.1, 116.3 (d, $^2J_{CF}$ = 22.5 Hz), 67.6, 46.9, 43.6; δ_F (376 MHz, $CDCl_3$) -105.7 (app. td, *J* = 8.3, 4.6 Hz, Ar-F); HRMS (ESI^+, *m*/*z*) calculated for $(C_{18}H_{20}FN_3O_3S)^+$ 378.1282 $[M+H]^+$, found 378.1284.

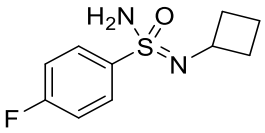
N-Benzyl-4-fluoro-*N*-methylbenzenesulfonimidamide 141e



Prepared according to general procedure A using 4-fluorophenylmagnesium bromide 4-fluorophenylmagnesium bromide (256 µL, 0.164 mmol, 0.64 M in THF, 1.0 equiv.) and *N*-benzylmethylamine (25 µL, 0.196 mmol, 1.2 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 6:1 to 3:1 to 2:1) afforded sulfonimidamide **141e** as a brown oil (30 mg, 66% yield).

ν_{max} (neat, cm^{-1}) 3281, 2969, 1589, 1491, 1256, 1228, 1135, 979, 928, 901, 838, 719, 695; δ_H (400 MHz, $CDCl_3$) 8.02-7.97 (m, 2H, Ar_F-*H*), 7.38-7.19 (m, 7H, Ar_F-*H*/Ar-*H*), 4.15 (s, 2H, NC*H*$_2$Ph), 2.63 (bs, 1H, N*H*), 2.61 (s, 3H, NC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 165.1 (d, $^1J_{CF}$ = 254.0 Hz), 136.4, 133.3 (d, $^4J_{CF}$ = 3.0 Hz), 130.5 (d, $^3J_{CF}$ = 9.0 Hz), 128.8, 128.4, 127.9, 116.2 (d, $^2J_{CF}$ = 22.5 Hz), 55.2, 35.7; δ_F (376 MHz, $CDCl_3$) -106.4 (app. ddd, *J* = 13.4, 8.3, 5.1 Hz, Ar-F); HRMS (CI^+ (NH_3), m/z) calculated for $(C_{14}H_{15}FN_2OS)^+$ 279.0962 $[M+H]^+$, found 279.0960.

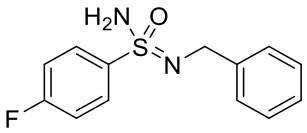
N-Cyclobutyl-4-fluorobenzenesulfonimidamide 141f



Prepared according to general procedure A using 4-fluorophenylmagnesium bromide (178 µL, 0.164 mmol, 0.92 M in THF, 1.0 equiv.) and cyclobutylamine (17 µL, 0.196 mmol, 1.2 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:2) afforded sulfonimidamide **141f** as a yellow oil (26 mg, 70% yield).

ν_{max} (neat, cm^{-1}) 3258, 2943, 2866, 1591, 1492, 1235, 1008, 838; δ_H (400 MHz, $CDCl_3$) 8.02-7.96 (m, 2H, Ar-*H*), 7.13 (app. t, 2H, *J* = 8.5 Hz, Ar-*H*), 5.00-3.28 (br. s, 2H, NH_2), 3.76 (pent., 1H, *J* = 8.0 Hz, NC*H*), 2.13-1.92 (m, 2H, Alk-C*H*), 1.81-1.44 (m, 4H, Alk-C*H*); δ_C (100 MHz, $CDCl_3$) 165.0 (d, $^1J_{CF}$ = 254.0 Hz), 138.3 (d, $^4J_{CF}$ = 3.0 Hz), 130.0 (d, $^3J_{CF}$ = 9.0 Hz), 116.1 (d, $^2J_{CF}$ = 22.5 Hz), 48.6, 31.9, 31.9, 15.1; δ_F (376 MHz, $CDCl_3$) -106.7 (app. td, *J* = 8.4, 4.2 Hz, Ar-F); LRMS *m/z* (ESI^+) $[M+H]^+$ 229.0; HRMS (ESI^+, *m*/*z*) calculated for $(C_{10}H_{14}FN_2OS)^+$ 229.08054 $[M+H]^+$, found 229.08071.

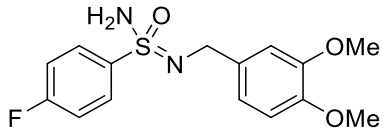
N'-Benzyl-4-fluorobenzenesulfonimidamide 141g



Prepared according to general procedure A using 4-fluorophenylmagnesium bromide (178 µL, 0.164 mmol, 0.92 M in THF, 1.0 equiv.) and benzylamine (21.5 µL, 0.196 mmol, 1.2 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 4:1 to 1:1) afforded sulfonimidamide **141g** as a light yellow oil (30 mg, 69% yield).

ν_{max} (neat, cm^{-1}) 3263, 2853, 1591, 1493, 1232, 1021, 838; δ_H (400 MHz, $CDCl_3$) 7.95 (dd, 2H, *J* = 8.5, 5.0 Hz, Ar_F-*H*), 7.29-7.21 (m, 3H, Ar-*H*), 7.19-7.08 (m, 4H, Ar-*H*), 4.65-3.48 (br. s, 2H, NH_2), 4.13 (d, 1H, *J* = 14.0 Hz, NCH_aH_b), 4.03 (d, 1H, *J* = 14.0 Hz, NCH_aH_b); δ_C (100 MHz, $CDCl_3$) 165.0 (d, $^1J_{CF}$ = 254.0 Hz), 137.2 (d, $^4J_{CF}$ = 2.0 Hz), 136.8, 131.1 (d, $^3J_{CF}$ = 9.5 Hz), 128.8, 127.9, 127.9, 116.2 (d, $^2J_{CF}$ = 22.5 Hz), 47.8; δ_F (376 MHz, $CDCl_3$) -106.4 (app. ddd, *J* = 13.3, 7.2, 4.2 Hz, Ar-F); LRMS *m/z* (ESI^+) $[M+H]^+$ 265.0; HRMS (ESI^+, *m*/*z*) calculated for $(C_{13}H_{14}FN_2OS)^+$ 265.08054 $[M+H]^+$, found 265.08057.

***N*'-(3,4-Dimethoxybenzyl)-4-fluorobenzenesulfonimidamide 141h**

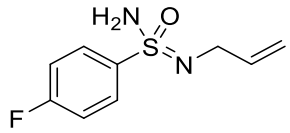


TrNSO (1.50 g, 4.91 mmol, 1.0 equiv.) was added to an oven-dried 100 mL round bottom flask and dissolved in THF (30 mL). The reaction was cooled to 0 °C. 4-Fluorophenylmagnesium bromide (7.68 mL, 4.91 mmol, 0.64 M in THF, 1.0 equiv.) was added dropwise and the mixture stirred at the same temperature for 5 min. *tert*-Butyl hypochlorite (580 µL, 5.16 mmol, 1.05 equiv.) was added in a darkened fume hood and the mixture stirred for 15 min prior to addition of triethylamine (690 µL, 4.91 mmol, 1.0 equiv.) and 3,4-dimethoxybenzylamine (740 µL, 4.91 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature for 16 h. Methanesulfonic acid (1.60 mL, 24.6 mmol, 5.0 equiv.) was added and the reaction stirred vigorously for 15 min at room temperature before dilution with CH_2Cl_2. The solution was washed with saturated aqueous sodium bicarbonate solution, then the layers were separated and the aqueous phase was extracted with CH_2Cl_2 × 3. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:5) afforded sulfonimidamide **141h** as a clear oil (1.27 g, 80% yield).

ν_{max} (neat, cm^{-1}) 3272, 2937, 2837, 1590, 1514, 1231, 1136, 1024, 837, 730; δ_H (400 MHz, $CDCl_3$) 7.89 (d, 2H, *J* = 8.5, 5.0 Hz, Ar_F-*H*), 7.06 (app. t, 2H, *J* = 8.5 Hz, Ar_F-*H*), 6.68-6.58 (m, 3H, Ar-*H*), 4.47-4.05 (br. s, 2H, NH_2), 4.01 (d, 1H, *J* = 14.0 Hz, NC$H_a$$H_b$), 3.90 (d, 1H, *J* = 14.0 Hz, NC$H_a$$H_b$) 3.77 (s, 3H, ArOC$H_3$), 3.73 (s, 3H, ArOC$H_3$); δ_C (100 MHz, $CDCl_3$) 164.8 (d, $^1J_{CF}$ = 254.0 Hz), 148.9, 148.5, 137.3 (d, $^4J_{CF}$ = 3.0 Hz), 130.0 (d, $^3J_{CF}$ = 9.0 Hz), 129.2, 120.2, 116.0 (d, $^2J_{CF}$ = 22.5 Hz), 111.0, 110.9, 55.9,

55.8, 47.4; δ_F (376 MHz, $CDCl_3$) -106.5 (app. ddd, *J* = 13.5, 8.7, 5.2 Hz, Ar-F); LRMS *m/z* (ESI^-) $(M-H)^-$ 323.0; HRMS (ESI^+, *m/z*) calculated for $(C_{15}H_{18}FN_2O_3S)^+$ 325.10168 $[M+H]^+$, found 325.10167.

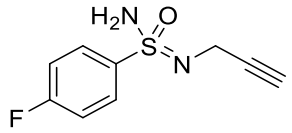
***N'*-Allyl-4-fluorobenzenesulfonimidamide 141i**



Prepared according to general procedure A using 4-fluorophenylmagnesium bromide (195 µL, 0.164 mmol, 0.84 M in THF, 1.0 equiv.) and allylamine (15.0 µL, 0.196 mmol, 1.2 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:2) afforded sulfonimidamide **7i** as a light yellow oil (26 mg, 74% yield).

ν_{max} (neat, cm^{-1}) 3267, 2852, 1591, 1492, 1214, 1010, 839; δ_H (400 MHz, $CDCl_3$) 8.02-7.96 (m, 2H, Ar-*H*), 7.19-7.12 (m, 2H, Ar-*H*), 5.68 (ddt, 1H, *J* = 17.0, 10.0, 6.0 Hz, C*H*=CH_aH_b), 5.13 (app. dq, 1H, *J* = 17.0, 1.5 Hz, CH=C*H*$_a$$H_b$), 5.05 (app. dq, 1H, J = 10.0, 1.0 Hz, CH=CH_aH_b), 4.36-3.65 (br. s, 2H, N*H*$_2$), 3.61-3.48 (m, 2H, NC*H*$_2$); δ_C (100 MHz, $CDCl_3$) 164.9 (d, $^1J_{CF}$ = 254.0 Hz), 137.2 (d, $^4J_{CF}$ = 3.0 Hz), 133.4, 130.0 (d, $^3J_{CF}$ = 9.5 Hz), 117.4, 116.1 (d, $^2J_{CF}$ = 22.5 Hz), 46.2; δ_F (376 MHz, $CDCl_3$) -106.4 (tt, *J* = 8.2, 5.1 Hz, Ar-F); LRMS *m/z* (ESI^+) $[M+H]^+$ 215.0; HRMS (ESI^+, *m/z*) calculated for $(C_9H_{12}FN_2OS)^+$ 215.06489 $[M+H]^+$, found 215.06488.

4-Fluoro-*N*'-(prop-2-yn-1-yl)benzenesulfonimidamide 141j

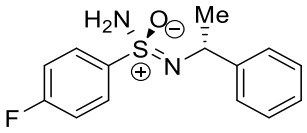


Prepared according to general procedure A using 4-fluorophenylmagnesium bromide (195 µL, 0.164 mmol, 0.84 M in THF, 1.0 equiv.) and propargylamine (12.5 µL, 0.196 mmol, 1.2 equiv.). Note: amine step stirred at rt for 21 h. Purification by flash chromatography (SiO_2, hexane/ethyl acetate, 3:1 to 1:1 to 1:2) afforded sulfonimidamide **141j** as a light yellow oil (17 mg, 49% yield).

ν_{max} (neat, cm^{-1}) 3287, 2852, 1590, 1493, 1231, 1012, 838; δ_H (400 MHz, $CDCl_3$) 8.05-7.99 (m, 2H, Ar-*H*), 7.20-7.13 (m, 2H, Ar-*H*), 3.98-3.43 (br. s, 2H, NH_2), 3.81 (d, 2H, *J* = 2.5 Hz, NCH_2), 2.06 (t, 1H, *J* = 2.5 Hz, C≡C*H*); δ_C (100 MHz, $CDCl_3$) 165.3 (d, $^1J_{CF}$ = 254.5 Hz), 136.6 (d, $^4J_{CF}$ = 3.0 Hz), 130.5 (d, $^3J_{CF}$ = 9.5 Hz), 116.5 (d, $^2J_{CF}$ = 23.0 Hz), 78.8, 72.8, 33.5; δ_F (376 MHz, $CDCl_3$) -106.0 (tt, *J* = 8.1, 5.0 Hz, Ar-F); LRMS *m/z* (ESI$^+$) $[M+H]^+$ 213.0; HRMS (ESI$^+$, *m/z*) calculated for $(C_9H_{10}FN_2OS)^+$ 213.04924 $[M+H]^+$, found 213.04931.

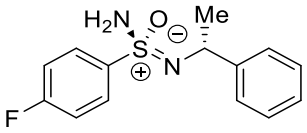
The following two compounds were prepared according to general procedure A using 4-fluorophenylmagnesium bromide (195 µL, 0.164 mmol, 0.84 M in THF, 1.0 equiv.) and (*R*)-(+)-α-methylbenzylamine (25 µL, 0.196 mmol, 1.2 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 2:1 to 3:2) afforded sulfonimidamide **141k** as an off-white solid (14 mg, 31% yield) and sulfonimidamide **141l** as a light yellow oil (14 mg, 31% yield).

(*R*)-4-Fluoro-*N*'-((*R*)-1-phenylethyl)benzenesulfonimidamide 141k (Sulfur stereochemistry not known)



mp 127-128 °C; ν_{max} (neat, cm^{-1}) 3253, 2855, 1591, 1492, 1233, 1017, 839, 701; δ_H (400 MHz, $CDCl_3$) 7.89-7.83 (m, 2H, Ar-*H*), 7.23-7.16 (m, 3H, Ar-*H*), 7.12-7.08 (m, 2H, Ar-*H*), 7.05-6.99 (m, 2H, Ar-*H*), 4.79-3.37 (br. s, 2H, NH_2), 4.47 (q, 1H, *J* = 7.0 Hz, NC*H*), 1.36 (d, 3H, *J* = 7.0 Hz, NCHCH_3); δ_C (100 MHz, $CDCl_3$) 164.8 (d, $^1J_{CF}$ = 254.0 Hz), 142.7, 138.0 (d, $^4J_{CF}$ = 3.0 Hz), 130.1 (d, $^3J_{CF}$ = 9.0 Hz), 128.7, 127.5, 126.1, 115.9 (d, $^2J_{CF}$ = 22.5 Hz), 54.1, 23.9; δ_F (376 MHz, $CDCl_3$) -106.9 (tt, *J* = 8.2, 5.1 Hz, Ar-F); HRMS (ESI$^+$, *m*/*z*) calculated for $(C_{14}H_{16}FN_2OS)^+$ 279.09619 $[M+H]^+$, found 279.09619; $[\alpha]_D^{26}$: +57.0, c = 1.

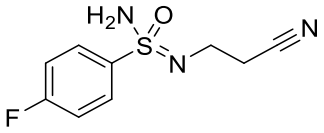
(*S*)-4-Fluoro-*N*'-((*R*)-1-phenylethyl)benzenesulfonimidamide 141l (Sulfur stereochemistry not known)



ν_{max} (neat, cm^{-1}) 3259, 2853, 1592, 1493, 1234, 1017, 838, 702; δ_H (400 MHz, $CDCl_3$) 7.82-7.77 (m, 2H, Ar-*H*), 7.19-7.13 (m, 3H, Ar-*H*), 7.07-7.03 (m, 2H, Ar-*H*), 7.01-6.95 (m, 2H, Ar-*H*), 4.80-3.40 (br. s, 2H, NH_2), 4.42 (q, 1H, *J* = 7.0 Hz, NC*H*), 1.41 (d, 3H, *J* = 7.0 Hz, NCHCH_3); δ_C (100 MHz, $CDCl_3$) 164.7 (d, $^1J_{CF}$ = 253.5 Hz), 142.6, 137.8 (d, $^4J_{CF}$ = 3.0 Hz), 130.0 (d, $^3J_{CF}$ = 9.5 Hz), 128.6, 127.5, 126.2, 115.8 (d, $^2J_{CF}$ = 22.5 Hz), 54.3, 24.1; δ_F (376 MHz, $CDCl_3$) -107.0 (tt, *J* = 8.4, 5.2 Hz, Ar-F); HRMS (ESI$^+$,

m/*z*) calculated for $(C_{14}H_{16}FN_2OS)^+$ 279.09619 $[M+H]^+$, found 279.09616; $[\alpha]_D^{26}$: +76.0, c = 1.

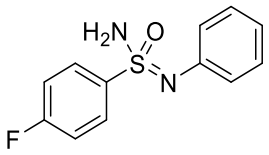
_N_'-(2-Cyanoethyl)-4-fluorobenzenesulfonimidamide 141m



Prepared according to general procedure A using 4-fluorophenylmagnesium bromide (195 µL, 0.164 mmol, 0.84 M in THF, 1.0 equiv.) and 3-aminopropionitrile (14.5 µl, 0.196 mmol, 1.2 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 1:1 to 1:5) afforded sulfonimidamide **7m** as a light yellow oil (29 mg, 78% yield).

ν_{max} (neat, cm^{-1}) 3264, 2922, 2853, 2253, 1590, 1491, 1233, 1094, 1004, 838; δ_H (400 MHz, $CDCl_3$) 8.01 (dd, 2H, *J* = 8.5, 5.0 Hz, Ar-*H*), 7.20 (app. t, 2H, *J* = 8.5 Hz, Ar-*H*), 4.35-3.46 (br. s, 2H, N*H*$_2$), 3.33-3.18 (m, 2H, SNC*H*$_2$), 2.65-2.49 (m, 2H, NCC*H*$_2$); δ_C (100 MHz, $CDCl_3$) 165.2 (d, $^1J_{CF}$ = 255.0 Hz), 137.3 (d, $^4J_{CF}$ = 3.0 Hz), 130.0 (d, $^3J_{CF}$ = 9.5 Hz), 118.1, 116.5 (d, $^2J_{CF}$ = 22.5 Hz), 39.4, 19.9; δ_F (376 MHz, $CDCl_3$) -105.4 (m, Ar-F); LRMS *m*/*z* (ESI^+) $[M+H]^+$ 228.0; HRMS (ESI^+, *m*/*z*) calculated for $(C_9H_{11}FN_3OS)^+$ 228.06029 $[M+H]^+$, found 228.06014.

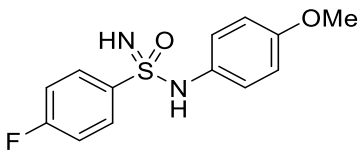
4-Fluoro-*N*'-phenylbenzenesulfonimidamide 141n



Prepared according to general procedure A using 4-fluorophenylmagnesium bromide (195 µL, 0.164 mmol, 0.84 M in THF, 1.0 equiv.) and aniline (18.0 µL, 0.196 mmol, 1.2 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 3:2) afforded sulfonimidamide **141n** as a light yellow solid (22 mg, 54% yield).

mp 145-147 °C; ν_{max} (neat, cm^{-1}) 3362, 1591, 1491, 1196, 840, 694; δ_H (500 MHz, Acetone-d_6) 8.12-8.06 (m, 2H, Ar_F-*H*), 7.33-7.27 (m, 2H, Ar_F-*H*), 7.17-7.12 (m, 2H, Ar-*H*), 7.11-7.08 (m, 2H, Ar-*H*), 6.88 (tt, 1H, *J* = 7.0, 1.5 Hz, Ar-*H*), 6.75-6.11 (br. s, 2H, N*H*$_2$); δ_C (125 MHz, Acetone-d_6) 164.4 (d, $^1J_{CF}$ = 250.5 Hz), 144.4, 140.3, 129.8 (d, $^3J_{CF}$ = 9.5 Hz), 128.6, 123.1, 121.4, 115.6 (d, $^2J_{CF}$ = 23.0 Hz); δ_F (376 MHz, Acetone-d_6) -109.6 (tt, *J* = 8.7, 5.2 Hz, Ar-F); LRMS *m/z* (ESI^-) (M-*H*)$^-$ 249.1; HRMS (ESI^-, *m*/*z*) calculated for $(C_{12}H_{10}FN_2OS)^-$ 249.05034 $[M+H]^+$, found 249.05037.

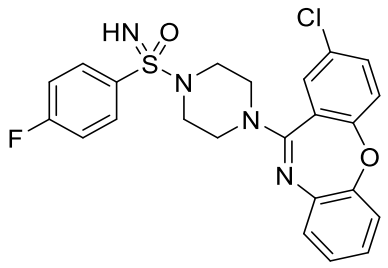
4-Fluoro-N'-(4-methoxyphenyl)benzenesulfonimidamide 141o



Prepared according to general procedure A using 4-fluorophenylmagnesium bromide (195 µL, 0.164 mmol, 0.84 M in THF, 1.0 equiv.) and *p*-anisidine (20 mg, 0.196 mmol, 1.2 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 5:1 to 3:1 to 1:1) afforded sulfonimidamide **141o** as a brown solid (19 mg, 41% yield).

mp 133-135 °C; ν_{max} (neat, cm^{-1}) 3364, 1592, 1493, 1229, 1192, 1029, 829; δ_H (400 MHz, Acetone-d_6) 8.07-8.00 (m, 2H, Ar_F-*H*), 7.32-7.24 (m, 2H, Ar_F-*H*), 7.02 (d, 2H, *J* = 9.0 Hz, Ar-*H*), 6.74 (d, 2H, *J* = 9.0 Hz, Ar-*H*), 6.52-6.00 (br. s, 1H, N-*H*), 3.70 (s, 3H, ArOCH_3), 3.12-2.65 (br. s, 1H, N-*H*); δ_C (100 MHz, Acetone-d_6) 165.3 (d, $^1J_{CF}$ = 250.0 Hz), 156.2, 140.8, 131.0 (d, $^4J_{CF}$ = 3.0 Hz), 130.8 (d, $^3J_{CF}$ = 9.5 Hz), 125.3, 116.3 (d, $^2J_{CF}$ = 22.5 Hz), 114.7, 55.5; δ_F (376 MHz, Acetone-d_6) -109.8 (m, Ar-F); LRMS *m/z* (ESI$^-$) $(M\text{-}H)^+$ 279.0; HRMS (ESI$^-$, *m/z*) calculated for $(C_{13}H_{12}N_2O_2S)^-$ 279.06090 [M-H]$^-$, found 279.06055.

2-Chloro-11-(4-(4-fluorophenylsulfonimidoyl)piperazin-1-yl)dibenzo[*b*,*f*][1,4]oxazepane 141p

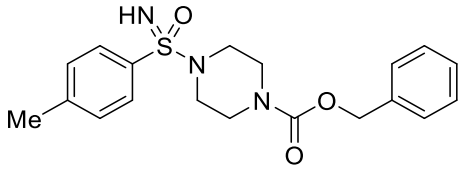


Prepared according to general procedure A using 4-fluorophenylmagnesium bromide (224 µL, 0.164 mmol, 0.73 M in THF, 1.0 equiv.) and Amoxapine (52 mg, 0.164 mmol, 1.0 equiv.). Purification by flash chromatography (SiO_2, hexane/ethyl acetate, 5:1 to 5:2 to 3:2) afforded sulfonimidamide **141p** as an off-white solid (52 mg, 67% yield).

mp 147-149 °C; ν_{max} (neat, cm^{-1}) 3285, 2924, 1588, 1216, 1135, 936, 688; δ_H (400 MHz, CD_3CN) 7.92-7.86 (m, 2H, Ar-*H*), 7.45 (dd, 1H, *J* = 8.5, 2.5 Hz, Ar-*H*), 7.32-7.21 (m, 4H, Ar-*H*), 7.13-6.96 (m, 4H, Ar-*H*), 3.50 (app. br. s, 4H, NCH_2), 3.15 (br. s, 1H, N-*H*), 3.03 (app. br. s, 4H, NCH_2); δ_C (100 MHz, CD_3CN) 165.9 (d, $^1J_{CF}$ = 251.0 Hz), 160.1, 159.5, 152.6, 140.9, 133.9, 133.4 (d, $^4J_{CF}$ = 3.0 Hz), 131.9 (d, $^3J_{CF}$ = 9.5 Hz), 131.1, 129.8, 127.6, 126.8, 125.7, 125.5, 123.6, 121.1, 116.8 (d, $^2J_{CF}$ = 23.0 Hz), 47.8,

47.5; δ_F (376 MHz, CD_3CN) -108.7 (tt, *J* = 8.6, 5.3 Hz, Ar-F); HRMS (ESI^+, *m*/*z*) calculated for $(C_{23}H_{21}{}^{35}ClFN_4O_2S)^+$ 471.10523 $[M+H]^+$, found 471.10464.

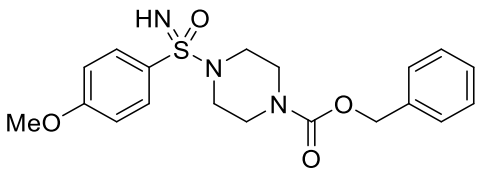
Benzyl 4-(4-methylphenylsulfonimidoyl)piperazine-1-carboxylate 141q



Prepared according to general procedure A using 4-methylphenylmagnesium bromide (180 µL, 0.164 mmol, 0.91 M in THF, 1.0 equiv.) and benzyl piperazine-1-carboxylate (32 µL, 0.164 mmol, 1.0 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:2) afforded sulfonimidamide **141q** as an off-white solid (41 mg, 67% yield).

mp 121-122 °C; ν_{max} (neat, cm^{-1}) 2849, 1695, 1429, 1241, 1125, 915, 750, 700; δ_H (400 MHz, $CDCl_3$) 7.72 (d, 2H, *J* = 8.0 Hz, Tol-*H*), 7.36-7.26 (m, 7H, Tol-*H*/Ph-*H*), 5.05 (s, 2H, OC*H*$_2$Ph), 3.54 (app. br. s, 4H, C(O)NC*H*$_2$), 2.95 (app. br. s, 4H, SNC*H*$_2$), 2.56 (br. s, 1H, N-*H*), 2.41 (s, 3H, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 154.9, 143.5, 136.3, 132.3, 129.6, 128.6, 128.2, 128.1, 128.1, 67.5, 46.9, 43.6, 21.6; LRMS *m/z* (ESI^+) $[M+H]^+$ 374.2; HRMS (ESI^+, *m*/*z*) calculated for $(C_{19}H_{24}N_3O_3S)^+$ 374.15329 $[M+H]^+$, found 374.15350.

Benzyl 4-(4-methoxyphenylsulfonimidoyl)piperazine-1-carboxylate 141r

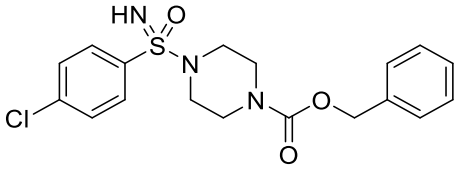


Prepared according to general procedure A using 4-methoxyphenylmagnesium bromide (409 µL, 0.164 mmol, 0.40 M in THF, 1.0 equiv.) and benzyl piperazine-1-

carboxylate (32 μL, 0.164 mmol, 1.0 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:3) afforded sulfonimidamide **141r** as a light yellow oil (49 mg, 77% yield), which crystallised to an off-white solid on standing.

mp 131-133 °C; ν_{max} (neat, cm^{-1}) 2844, 1695, 1429, 1242, 1127, 915, 750, 700; δ_H (400 MHz, $CDCl_3$) 7.77 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.35-7.27 (m, 5H, Ph-*H*), 6.97 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 5.05 (s, 2H, OC*H*$_2$Ph), 3.85 (s, 3H, OC*H*$_3$), 3.54 (app. br. s, 4H, C(O)NC*H*$_2$), 2.95 (app. br. s, 4H, SNC*H*$_2$), 2.54 (br. s, 1H, N*H*); δ_C (100 MHz, $CDCl_3$) 163.0, 154.9, 136.3, 130.2, 128.6, 128.2, 128.1, 126.8, 114.2, 67.5, 55.7, 46.9, 43.6; LRMS *m/z* (ESI^+) $[M+H]^+$ 390.2; HRMS (ESI^+, *m/z*) calculated for $(C_{19}H_{24}N_3O_4S)^+$ 390.14820 $[M+H]^+$, found 390.14802.

Benzyl 4-(4-chlorophenylsulfonimidoyl)piperazine-1-carboxylate 141s

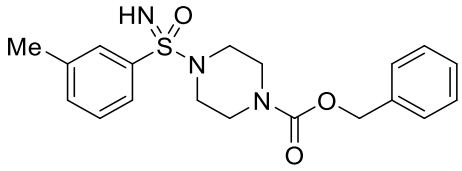


Prepared according to general procedure A using 4-chlorophenylmagnesium bromide (218 μL, 0.164 mmol, 0.75 M in MeTHF, 1.0 equiv.) and benzyl piperazine-1-carboxylate (32 μL, 0.164 mmol, 1.0 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:1 to 1:2) afforded sulfonimidamide **141s** as a yellow oil (51 mg, 74% yield).

ν_{max} (neat, cm^{-1}) 3265, 2852, 1694, 1429, 1242, 1126, 1089, 911, 729, 698; δ_H (400 MHz, $CDCl_3$) 7.80-7.75 (m, 2H, Ar-*H*), 7.50-7.46 (m, 2H, Ar-*H*), 7.34-7.27 (m, 5H, Ph-*H*), 5.06 (s, 2H, OC*H*$_2$Ph), 3.55 (app. br. s, 4H, C(O)NC*H*$_2$), 2.96 (app. br. s, 4H, SNC*H*$_2$), 2.78-2.41 (br. s, 1H, N-*H*); δ_C (100 MHz, $CDCl_3$) 154.8, 139.4, 136.2, 133.9, 129.5, 129.3, 128.6, 128.3, 128.1, 67.6, 46.9, 43.6; LRMS *m/z* (ESI^+) $(^{35}M+Na)^+$ 416.0;

HRMS (ESI$^+$, *m*/*z*) calculated for $(C_{18}H_{21}N_3O_3{}^{35}ClS)^+$ 394.09867 $[^{35}M+H]^+$, found 394.09845.

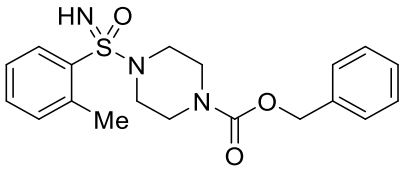
Benzyl 4-(3-methylphenylsulfonimidoyl)piperazine-1-carboxylate 141t



Prepared according to general procedure A using 3-methylphenylmagnesium bromide (260 µL, 0.164 mmol, 0.63 M in THF, 1.0 equiv.) and benzyl piperazine-1-carboxylate (32 µL, 0.164 mmol, 1.0 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:2) afforded sulfonimidamide **141t** as a colourless oil (37 mg, 61% yield).

ν_{max} (neat, cm^{-1}) 3266, 2850, 1697, 1429, 1242, 1126, 918, 708; δ_H (400 MHz, $CDCl_3$) 7.67-7.61 (m, 2H, Tol-*H*), 7.43-7.26 (m, 7H, Tol-*H*/Ph-*H*), 5.06 (s, 2H, OC*H*$_2$Ph), 3.55 (app. br. s, 4H, C(O)NC*H*$_2$), 2.97 (app. br. s, 4H, SNC*H*$_2$), 2.57 (br. s, 1H, N-*H*), 2.42 (s, 3H, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 154.9, 139.2, 136.3, 135.1, 133.6, 128.9, 128.6, 128.3, 128.3, 128.1, 125.2, 67.5, 46.9, 43.7, 21.5; HRMS (CI$^+$ (NH_3), *m*/*z*) calculated for $(C_{19}H_{24}N_3O_3S)^+$ 374.1533 $[M+H]^+$, found 374.1535.

Benzyl 4-(2-methylphenylsulfonimidoyl)piperazine-1-carboxylate 141u

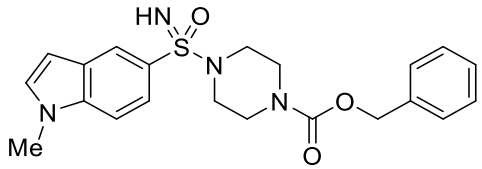


Prepared according to general procedure A using 2-methylphenylmagnesium bromide (268 µL, 0.164 mmol, 0.61 M in THF, 1.0 equiv.) and benzyl piperazine-1-carboxylate (32 µL, 0.164 mmol, 1.0 equiv.). Purification by flash chromatography (SiO_2,

petrol/ethyl acetate, 3:1 to 1:1) afforded sulfonimidamide **141u** as a colourless oil (33 mg, 54% yield).

ν_{max} (neat, cm^{-1}) 3267, 2858, 1694, 1428, 1241, 1125, 913, 729, 698; δ_H (400 MHz, $CDCl_3$) 7.94 (dd, 1H, *J* = 8.5, 1.5 Hz, Tol-*H*), 7.43 (td, 1H, *J* = 7.5, 1.5 Hz, Tol-*H*), 7.38-7.27 (m, 7H, Tol-*H*/Ph-*H*), 5.10 (s, 2H, OCH_2Ph), 3.55 (app dt, *J* = 6.5, 3.0 Hz, 4H, C(O)NCH_2), 3.15 (app. br. s, 4H, SNCH_2), 2.73 (br. s, 1H, N-*H*), 2.69 (s, 3H, CH_3); δ_C (100 MHz, $CDCl_3$) 155.0, 138.2, 136.5, 136.4, 133.3, 132.7, 130.1, 128.6, 128.3, 128.1, 126.2, 67.6, 45.9, 43.9, 21.5; LRMS *m/z* (ESI^+) $[M+H]^+$ 374.0; HRMS (ESI^+, *m/z*) calculated for $(C_{19}H_{24}N_3O_3S)^+$ 374.15329 $[M+H]^+$, found 374.15283.

Benzyl 4-(1-methyl-1*H*-indole-5-sulfonimidoyl)piperazine-1-carboxylate 141v

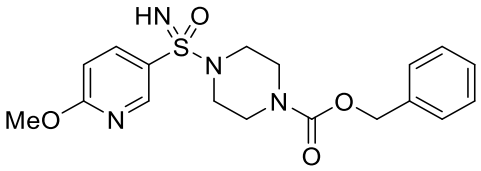


n-Butyllithium (80 µL, 0.164 mmol, 2.25 M in hexanes, 1.1 equiv.) was added to an oven-dried reaction tube. The reaction was cooled to -78 °C. 5-Bromo-1-methyl-1*H*-indole (34.5 mg, 0.164 mmol, 1.0 equiv.) was added dropwise as a solution in THF (400 µL) and stirred for 2 h. TrNSO (60.0 mg, 0.196 mmol, 1.2 equiv.) was added dropwise as a solution in THF (400 µL) and stirred at -78 °C for 25 mins before being placed in an ice bath at 0 °C. After stirring for a further 10 mins, *tert*-butyl hypochlorite (19.5 µL, 0.172 mmol, 1.05 equiv.) was added and the mixture stirred for 15 min, before addition of triethylamine (23 µl, 0.164 mmol, 1.0 equiv.) and benzyl piperazine-1-carboxylate (38 µL, 0.196 mmol, 1.2 equiv.). The reaction mixture was stirred at room temperature for 16 h. Methanesulfonic acid (53 µL, 0.819 mmol, 5.0 equiv.) was added and the reaction stirred vigorously for 15 min at room temperature before

dilution with CH_2Cl_2. The solution was extracted with saturated aqueous sodium bicarbonate solution, then the layers were separated and the aqueous phase was extracted with CH_2Cl_2 × 3. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 1:1 to 1:3 to 1:5) afforded sulfonimidamide **141v** as a light yellow oil (39 mg, 58% yield).

ν_{max} (neat, cm^{-1}) 3252, 2855, 1695, 1424, 1242, 1126, 916, 695; δ_H (400 MHz, $CDCl_3$) 8.18 (d, 1H, *J* = 2.0 Hz, HetAr-*H*), 7.69 (dd, 2H, *J* = 8.0, 2.0 Hz, HetAr-*H*), 7.38 (d, 1H, *J* = 9.0 Hz, HetAr-*H*), 7.32-7.24 (m, 5H, Ar-*H*), 7.18 (d, 1H, *J* = 3.0 Hz, HetAr-*H*), 6.60 (d, 1H, *J* = 3.0 Hz, HetAr-*H*), 5.02 (s, 2H, OC*H*$_2$Ph), 3.83 (s, 3H, NC*H*$_3$), 3.54 (app. br. s, 4H, C(O)NC*H*$_2$), 2.97 (app. br. s, 4H, SNC*H*$_2$), 2.58 (br. s, 1H, N-*H*); δ_C (100 MHz, $CDCl_3$) 154.8, 138.5, 136.3, 131.2, 128.6, 128.2, 128.1, 128.0, 125.6, 122.3, 121.1, 109.4, 102.8, 67.4, 47.0, 43.6, 33.3; HRMS (ESI$^+$, *m*/*z*) calculated for $(C_{21}H_{25}N_4O_3S)^+$ 413.16419 $[M+H]^+$, found 413.16418.

Benzyl 4-(6-methoxypyridine-3-sulfonimidoyl)piperazine-1-carboxylate 141w

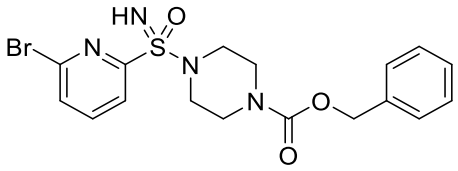


5-Bromo-2-methoxypyridine (21.0 µL, 0.164 mmol, 1.0 equiv.) and THF (800 µL) were added to an oven-dried reaction tube. The reaction was cooled to -78 °C. *n*-Butyllithium (73 µL, 0.164 mmol, 2.25 M in hexanes, 1.0 equiv.) was added dropwise and the mixture stirred at the same temperature for 40 min. TrNSO (60.0 mg, 0.196 mmol, 1.2 equiv.) was added dropwise as a solution in THF (400 µL) and stirred at -

78 °C for 25 mins before being placed in an ice bath at 0 °C. After stirring for a further 5 mins, *tert*-butyl hypochlorite (19.5 µL, 0.172 mmol, 1.05 equiv.) was added and the mixture stirred for 20 min, before addition of triethylamine (23 µl, 0.164 mmol, 1.0 equiv.) and benzyl piperazine-1-carboxylate (38 µL, 0.196 mmol, 1.2 equiv.). The reaction mixture was stirred at room temperature for 16 h. Methanesulfonic acid (53 µL, 0.819 mmol, 5.0 equiv.) was added and the reaction stirred vigorously for 15 min at room temperature before dilution with CH_2Cl_2. The solution was extracted with saturated aqueous sodium bicarbonate solution, then the layers were separated and the aqueous phase was extracted with CH_2Cl_2 × 3. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 1:1 to 1:4) afforded sulfonimidamide **141w** as a light yellow oil (51 mg, 80% yield).

ν_{max} (neat, cm^{-1}) 3264, 2850, 1696, 1580, 1479, 1428, 1242, 1123, 914, 704; δ_H (400 MHz, $CDCl_3$) 8.63 (d, 1H, *J* = 2.5 Hz, HetAr-*H*), 7.94 (dd, 1H, *J* = 9.0, 2.5 Hz, HetAr-*H*), 7.36-7.27 (m, 5H, Ar-*H*), 6.80 (dd, 1H, *J* = 9.0 Hz, HetAr-*H*), 5.06 (s, 2H, OC*H*$_2$Ph), 3.99 (s, 3H, OC*H*$_3$), 3.56 (app. br. s, 4H, C(O)NC*H*$_2$), 2.98 (app. br. s, 4H, SNC*H*$_2$), 2.65 (br. s, 1H, N-*H*); δ_C (100 MHz, $CDCl_3$) 166.6, 154.8, 148.2, 138.3, 136.2, 128.6, 128.3, 128.1, 124.7, 111.2, 67.5, 54.4, 46.8, 43.6; LRMS *m/z* (ESI^+) $[M+H]^+$ 391.2; HRMS (ESI^+, *m*/*z*) calculated for $(C_{18}H_{23}N_4O_4S)^+$ 391.14345 $[M+H]^+$, found 391.14188.

Benzyl 4-(6-bromopyridine-2-sulfonimidoyl)piperazine-1-carboxylate 141x

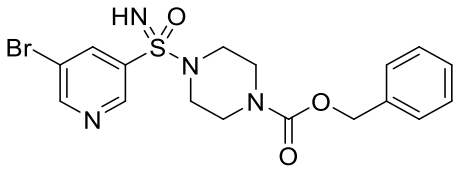


Isopropylmagnesium chloride lithium chloride complex (215 µL, 0.164 mmol, 0.77 M in THF, 1.0 equiv.) was added to an oven-dried reaction tube. The reaction was cooled to 0 °C. 2,6-Dibromopyridine (38.8 mg, 0.164 mmol, 1.0 equiv.) in THF (400 µL) was added dropwise then allowed to warm to rt and stirred for 3 h. TrNSO (60.0 mg, 0.196 mmol, 1.2 equiv.) was added dropwise as a solution in THF (400 µL) at 0 °C and stirred for 15 min before addition of *tert*-butyl hypochlorite (19.5 µL, 0.172 mmol, 1.05 equiv.). The mixture was stirred for 15 min at 0 °C, then triethylamine (23 µl, 0.164 mmol, 1.0 equiv.) and benzyl piperazine-1-carboxylate (38 µL, 0.196 mmol, 1.2 equiv.) were added. The reaction mixture was stirred at room temperature for 16 h. Methanesulfonic acid (53 µL, 0.819 mmol, 5.0 equiv.) was added and the reaction stirred vigorously for 15 min at room temperature before dilution with CH_2Cl_2. The solution was extracted with saturated aqueous sodium bicarbonate solution, then the layers were separated and the aqueous phase was extracted with CH_2Cl_2 × 3. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 1:1 to 1:4) afforded sulfonimidamide **141x** as a light yellow oil (31 mg, 42% yield).

ν_{max} (neat, cm^{-1}) 3267, 2922, 1694, 1423, 1242, 1124, 918, 697; δ_H (400 MHz, $CDCl_3$) 7.99 (dd, 1H, *J* = 7.5, 1.0 Hz, HetAr-*H*), 7.73 (t, 1H, *J* = 8.0 Hz, HetAr-*H*), 7.63 (dd, 1H, *J* = 8.0, 1.0 Hz, HetAr-*H*), 7.38-7.28 (m, 5H, Ar-*H*), 5.12 (s, 2H, OC*H*$_2$Ph), 3.58 (app. br. s, 4H, C(O)NC*H*$_2$), 3.35 (app. qq, 4H, *J* = 10.5, 5.0 Hz, SNC*H*$_2$), 2.88 (br. s, 1H, N-*H*); δ_C (100 MHz, $CDCl_3$) 157.5, 155.0, 141.8, 140.0, 136.3, 131.2, 128.6, 128.2, 128.1,

121.8, 67.5, 47.2, 43.9; HRMS (ESI$^+$, *m*/*z*) calculated for ($C_{17}H_{20}N_4O_3{}^{79}BrS$)$^+$ 439.04340 [M+H]$^+$, found 439.04333.

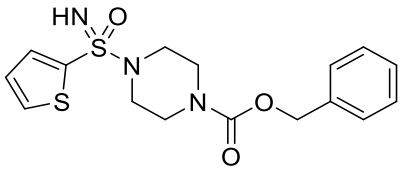
Benzyl 4-(5-bromopyridine-3-sulfonimidoyl)piperazine-1-carboxylate 141y



3,5-Dibromopyridine (38.8 mg, 0.164 mmol, 1.0 equiv.) was added to an oven-dried reaction tube and dissolved in THF (400 µL). The reaction was cooled to 0 °C. Isopropylmagnesium chloride lithium chloride complex (165 µL, 0.164 mmol, 1.04 M in THF, 1.0 equiv.) was added dropwise and stirred for 1 h 40 mins. TrNSO (60.0 mg, 0.196 mmol, 1.2 equiv.) was added dropwise as a solution in THF (500 µL) at 0 °C and stirred for 10 min before addition of *tert*-butyl hypochlorite (19.5 µL, 0.172 mmol, 1.05 equiv.). The mixture was stirred for 15 min at 0 °C, then triethylamine (23 µl, 0.164 mmol, 1.0 equiv.) and benzyl piperazine-1-carboxylate (38 µL, 0.196 mmol, 1.2 equiv.) were added. The reaction mixture was stirred at room temperature for 16 h. Methanesulfonic acid (53 µL, 0.819 mmol, 5.0 equiv.) was added and the reaction stirred vigorously for 15 min at room temperature before dilution with CH_2Cl_2. The solution was extracted with saturated aqueous sodium bicarbonate solution, then the layers were separated and the aqueous phase was extracted with CH_2Cl_2 × 3. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 1:1 to 2:5) afforded sulfonimidamide **141y** as a light yellow oil (32 mg, 44% yield).

ν_{max} (neat, cm^{-1}) 3252, 2855, 1695, 1424, 1242, 1126, 916, 695; δ_H (400 MHz, $CDCl_3$) 8.96 (d, 1H, *J* = 2.0 Hz, HetAr-*H*), 8.86 (d, 2H, *J* = 2.0 Hz, HetAr-*H*), 8.28 (t, 1H, *J* = 2.0 Hz, HetAr-*H*), 7.37-7.27 (m, 5H, Ar-*H*), 5.07 (s, 2H, OCH_2Ph), 3.59 (app. br. s, 4H, C(O)NCH_2), 3.04 (app. br. s, 4H, SNCH_2), 2.75 (br. s, 1H, N-*H*); δ_C (100 MHz, $CDCl_3$) 154.8, 154.5, 146.8, 138.0, 136.2, 133.7, 128.7, 128.4, 128.2, 121.1, 67.7, 46.9, 43.6; HRMS (ESI$^+$, *m*/*z*) calculated for $(C_{17}H_{20}N_4O_3{}^{79}BrS)^+$ 439.04340 $[M+H]^+$, found 439.04349.

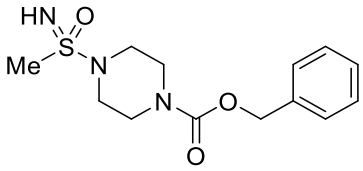
Benzyl 4-(thiophene-2-sulfonimidoyl)piperazine-1-carboxylate 141z



Prepared according to general procedure A using 2-thienylmagnesium bromide (221 µL, 0.164 mmol, 0.74 M in THF, 1.0 equiv.) and benzyl piperazine-1-carboxylate (32 µL, 0.164 mmol, 1.0 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 2:3) afforded sulfonimidamide **141z** as an orange oil (27 mg, 45% yield).

ν_{max} (neat, cm^{-1}) 3264, 2850, 1693, 1429, 1242, 1125, 915, 726, 700; δ_H (400 MHz, $CDCl_3$) 7.59 (dd, 1H, *J* = 5.0, 1.5 Hz, HetAr-*H*), 7.51 (dd, 1H, *J* = 4.0, 1.5 Hz, HetAr-*H*), 7.37-7.28 (m, 5H, Ar-*H*), 7.12 (dd, 1H, *J* = 5.0, 4.0 Hz, HetAr-*H*), 5.08 (s, 2H, OCH_2Ph), 3.63-3.56 (m, 4H, C(O)NCH_2), 3.06 (app. br s, 4H, SNCH_2), 2.76 (br s, 1H, N-*H*); δ_C (100 MHz, $CDCl_3$) 154.9, 136.8, 136.3, 132.6, 132.6, 128.6, 128.3, 128.2, 127.9, 67.6, 46.9, 43.6; HRMS (CI$^+$ (NH_3), *m*/*z*) calculated for $(C_{16}H_{19}N_3O_3S_2)^+$ 366.0941 $[M+H]^+$, found 366.0946.

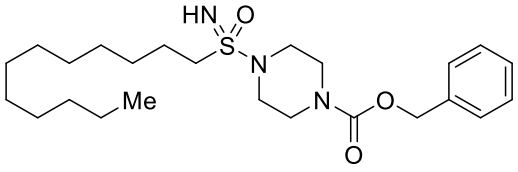
Benzyl 4-(*S*-methylsulfonimidoyl)piperazine-1-carboxylate 141aa



Prepared according to general procedure A using methylmagnesium bromide (55 µL, 0.164 mmol, 2.96 M in Et_2O, 1.0 equiv.) and benzyl piperazine-1-carboxylate (32 µL, 0.164 mmol, 1.0 equiv.). Note: extracted with CH_2Cl_2 × 5. Purification by flash chromatography (SiO_2, petrol/ethyl acetate/methanol, 3:1:0 to 0:1:0 to 0:97:3) afforded sulfonimidamide **141aa** as an off-white solid (29 mg, 60% yield).

mp 110-112 °C; ν_{max} (neat, cm^{-1}) 2934, 1686, 1428, 1239, 1127, 919, 757, 693; δ_H (400 MHz, $CDCl_3$) 7.40-7.29 (m, 5H, Ar-*H*), 5.14 (s, 2H, OC*H*$_2$Ph), 3.59 (app. br. s, 4H, C(O)NC*H*$_2$), 3.20 (app. br. s, 4H, SNC*H*$_2$), 2.78 (s, 3H, C*H*$_3$), 2.17 (br. s, 1H, N-*H*); δ_C (100 MHz, $CDCl_3$) 155.0, 136.3, 128.7, 128.4, 128.2, 67.6, 46.8, 43.9, 34.8; LRMS *m/z* (ESI^+) $[M+H]^+$ 298.0; HRMS (ESI^+, *m/z*) calculated for $(C_{13}H_{20}N_3O_3S)^+$ 298.12199 $[M+H]^+$, found 298.12216.

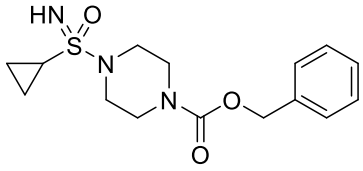
Benzyl 4-(dodecylsulfonimidoyl)piperazine-1-carboxylate 141ab



Prepared according to general procedure A using *n*-dodecylmagnesium chloride (290 µL, 0.164 mmol, 0.57 M in Et_2O, 1.0 equiv.) and benzyl piperazine-1-carboxylate (32 µL, 0.164 mmol, 1.0 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:1 to 0:1) afforded sulfonimidamide **141ab** as an off-white solid (42 mg, 57% yield).

mp 78-80 °C; ν_{max} (neat, cm^{-1}) 3271, 2922, 2852, 1701, 1460, 1428, 1281, 941, 698; δ_H (400 MHz, $CDCl_3$) 7.39-7.29 (m, 5H, Ar-*H*), 5.13 (s, 2H, OC*H*$_2$Ph), 3.56 (app. br. s, 4H, C(O)NC*H*$_2$), 3.24 (app. br. s, 4H, SNC*H*$_2$), 2.94 (ddd, 1H, *J* = 14.0, 10.0, 6.0 Hz, SC*H*$_a$H$_b$), 2.77 (ddd, 1H, *J* = 14.0, 10.0, 6.0 Hz, SCH$_a$*H*$_b$), 2.14 (br. s, 1H, N-*H*), 1.89-1.75 (m, 2H, SCH$_2$C*H*$_2$), 1.37 (pent., 2H, *J* = 7.0 Hz, SCH$_2$CH$_2$C*H*$_2$), 1.31-1.19 (m, 16H, Alk-*H*), 0.90-0.83 (m, 3H, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 155.1, 136.4, 128.7, 128.3, 128.2, 67.6, 49.2, 46.5, 44.2, 32.0, 29.7, 29.6, 29.4, 29.2, 28.6, 23.5, 22.8, 14.2 (3 Carbons missing due to overlap); LRMS *m*/*z* (ESI^+) $[M+H]^+$ 452.2; HRMS (ESI^+, *m*/*z*) calculated for $(C_{24}H_{42}N_3O_3S)^+$ 452.29414 $[M+H]^+$, found 452.29319.

Benzyl 4-(cyclopropanesulfonimidoyl)piperazine-1-carboxylate 141ac

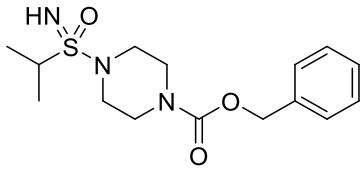


Prepared according to general procedure A using cyclopropylmagnesium bromide (260 µL, 0.164 mmol, 0.63 M in THF, 1.0 equiv.) and benzyl piperazine-1-carboxylate (32 µL, 0.164 mmol, 1.0 equiv.). Note: 1.00 equiv. lithium chloride (330 µL, 0.164 mmol, 0.5 M in THF) added before Grignard reagent. Purification by flash chromatography (SiO_2, ethyl acetate/methanol, 1:0 to 95:5) afforded sulfonimidamide **141ac** as an orange oil (24 mg, 45% yield).

ν_{max} (neat, cm^{-1}) 2921, 2852, 1695, 1461, 1240, 1123, 912, 698; δ_H (400 MHz, $CDCl_3$) 7.40-7.30 (m, 5H, Ar-*H*), 5.16-5.11 (m, 2H, OC*H*$_2$Ph), 3.63-3.50 (m, 4H, C(O)NC*H*$_2$), 3.36-3.23 (m, 4H, SNC*H*$_2$), 2.29 (tt, 1H, *J* = 8.0, 5.0 Hz, SC*H*), 2.16 (br. s, 1H, N-*H*), 1.22-1.12 (m, 2H, SCHC*H*$_2$), 1.01-0.91 (m, 2H, SCHC*H*$_2$); δ_C (100 MHz, $CDCl_3$) 155.1,

136.4, 128.7, 128.4, 128.2, 67.6, 46.9, 44.1, 25.9, 4.4, 4.3; LRMS *m/z* (ESI^+) $[M+H]^+$ 324.2; HRMS (ESI^+, *m*/*z*) calculated for $(C_{15}H_{22}N_3O_3S)^+$ 324.13764 $[M+H]^+$, found 324.13733.

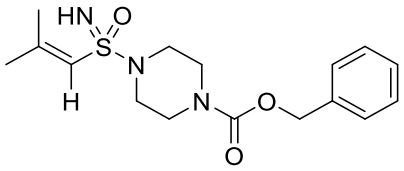
Benzyl 4-(propan-2-ylsulfonimidoyl)piperazine-1-carboxylate 141ad



Prepared according to general procedure A using isopropylmagnesium chloride lithium chloride complex (132 µL, 0.164 mmol, 1.24 M in THF, 1.0 equiv.) and benzyl piperazine-1-carboxylate (32 µL, 0.164 mmol, 1.0 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate/methanol, 3:1:0 to 0:97:3) afforded sulfonimidamide **141ad** as a light yellow oil (23 mg, 43% yield).

ν_{max} (neat, cm^{-1}) 3271, 2922, 1696, 1428, 1239, 1128, 943, 702; δ_H (400 MHz, $CDCl_3$) 7.44-7.28 (m, 5H, Ar-*H*), 5.13 (s, 2H, OC*H*$_2$Ph), 3.52 (app. br. s, 4H, C(O)NC*H*$_2$), 3.35 (app. br. s, 4H, SNC*H*$_2$), 3.22 (hept, 1H, *J* = 6.5 Hz, SC*H*), 2.12 (br. s, 1H, N-*H*), 1.37 (dd, 3H, *J* = 7.0 Hz, SCHC*H*$_3$), 1.32 (dd, 3H, *J* = 7.0 Hz, SCHC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 155.1, 136.4, 128.7, 128.3, 128.2, 67.6, 54.0, 46.8, 44.7, 17.7, 17.1; LRMS *m/z* (ESI^+) $[M+H]^+$ 326.2; HRMS (ESI^+, *m*/*z*) calculated for $(C_{15}H_{24}N_3O_3S)^+$ 326.15329 $[M+H]^+$, found 326.15317.

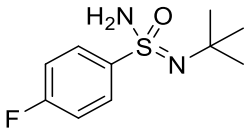
Benzyl 4-(2-methylprop-1-en-1-ylsulfonimidoyl)piperazine-1-carboxylate 141ae



Prepared according to general procedure A using 2-methyl-1-propenylmagnesium bromide (496 µL, 0.164 mmol, 0.33 M in THF, 1.0 equiv.) and benzyl piperazine-1-carboxylate (32 µL, 0.164 mmol, 1.0 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 2:3) afforded sulfonimidamide **141ae** as a light yellow oil (21 mg, 38% yield).

ν_{max} (neat, cm^{-1}) 3270, 2917, 2851, 1696, 1428, 1240, 1124, 915, 731, 698; δ_H (400 MHz, $CDCl_3$) 7.39-7.29 (m, 5H, Ar-*H*), 5.92 (app. br. pent., 1H, *J* = 1.5 Hz, SC*H*), 5.13 (s, 2H, OCH_2Ph), 3.63-3.51 (m, 4H, NCH_2), 3.15 (app. br s, 4H, NCH_2), 2.33 (br s, 1H, N-*H*), 2.15 (d, 3H, *J* = 1.0 Hz, CH_3), 1.92 (d, 3H, *J* = 1.0 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 155.0, 153.8, 136.3, 128.6, 128.2, 128.1, 119.1, 67.5, 46.5, 43.8, 27.3, 19.3; LRMS *m/z* (ESI^+) $[M+Na]^+$ 360.2; HRMS (ESI^+, *m/z*) calculated for $(C_{16}H_{24}N_3O_3S)^+$ 338.15329 $[M+H]^+$, found 338.15320.

***N*'-(*tert*-Butyl)-4-fluorobenzenesulfonimidamide 141af**

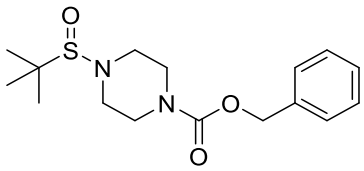


TrNSO (50.0 mg, 0.164 mmol) was added to an oven dried reaction tube under N_2 and dissolved in THF (1 ml). The reaction was cooled to 0 °C. 4-Fluorophenylmagnesium bromide (0.64 M in THF, 256 µl, 0.164 mmol) was added drop-wise and the mixture stirred at the same temperature for 5 min. *tert*-Butyl hypochlorite (19.5 µl, 0.172 mmol)

was added and the mixture stirred for 15 min, before addition of triethylamine (23 µl, 0.164 mmol) and *tert*-butylamine (21 µl, 0.196 mmol). The reaction mixture was stirred at room temperature for 16 h. Methanesulfonic acid (53 µl, 0.819 mmol) was added and the reaction stirred vigorously for 15 min at room temperature before dilution with CH_2Cl_2. The solution was extracted with saturated aqueous sodium bicarbonate solution, then the layers were separated and the aqueous phase was extracted with 3x CH_2Cl_2. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Purification by flash chromatography (SiO_2, petroleum ether (40-60)/ethyl acetate, 3:1 to 1:2) afforded sulfonimidamide **141af** as an off-white solid (13 mg, 35% yield).

R_f = 0.10 (petroleum ether/ethyl acetate 1:2); mp 100-102 °C; ν_{max} (neat, cm^{-1}) 3253, 2974, 1590, 1491, 1523, 1223, 1126, 1010, 972, 837; δ_H (400 MHz, $CDCl_3$) 8.02-7.97 (m, 2H, Ar-H), 7.16-7.10 (m, 2H, Ar-H), 4.96-2.58 (br s, 2H, N-H), 1.18 (s, 9H, N-C(C*H*$_3$)); δ_C (100 MHz, $CDCl_3$) 164.7 (d, $^1J_{CF}$ = 253.5 Hz), 141.0 (d, $^4J_{CF}$ = 3.0 Hz), 129.9 (d, $^3J_{CF}$ = 9.0 Hz), 116.0 (d, $^2J_{CF}$ = 22.5 Hz), 54.9, 30.3; δ_F (376 MHz, $CDCl_3$) -107.4 (tt, *J* = 8.6, 5.0 Hz, Ar-F); *m*/*z* (ESI^-) $(M-H)^-$ 229.1; HRMS (ESI^+, *m*/*z*) calculated for $(C_{10}H_{16}N_2OS)^+$ 231.09619, found 231.09628.

Benzyl 4-(tert-butylsulfinyl)piperazine-1-carboxylate 142

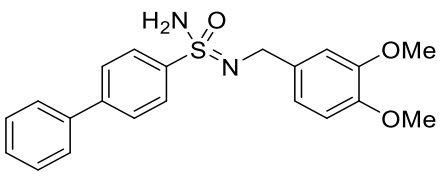


TrNSO (50.0 mg, 0.164 mmol) was added to an oven dried reaction tube under N_2 and dissolved in THF (1 ml). The reaction was cooled to 0 °C. *tert*-Butylmagnesium chloride (0.78 M in THF, 210 µl, 0.164 mmol) was added drop-wise and the mixture

stirred at the same temperature for 5 min. *tert*-Butyl hypochlorite (19.5 µl, 0.172 mmol) was added and the mixture stirred for 15 min, before addition of triethylamine (23 µl, 0.164 mmol) and 1-Z-piperazine (32 µl, 0.164 mmol). The reaction mixture was stirred at room temperature for 16 h. Methanesulfonic acid (53 µl, 0.819 mmol) was added and the reaction stirred vigorously for 15 min at room temperature before dilution with CH_2Cl_2. The solution was extracted with saturated aqueous sodium bicarbonate solution, then the layers were separated and the aqueous phase was extracted with 3x CH_2Cl_2. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Purification by flash chromatography (SiO_2, petroleum ether (40-60)/ethyl acetate, 3:1 to 1:1 to 1:2) afforded sulfinamide **142** as a colourless oil (36 mg, 68% yield).

R_f = 0.24 (petroleum ether 40-60/ethyl acetate 1:2); ν_{max} (neat, cm^{-1}) 2919, 1699, 1426, 1240, 1124, 1075, 915, 699; δ_H (400 MHz, $CDCl_3$) 7.38-7.27 (m, 5H, Ar-*H*), 5.12 (s, 2H, OCH_2Ph), 3.54 (app. t, 4H, *J* = 5.0 Hz, $SNCH_2$), 3.21-3.00 (m, 4H, $C(O)NCH_2$), 1.16 (s, 9H, *t*-Bu-*H*); δ_C (100 MHz, $CDCl_3$) 155.2, 136.5, 128.6, 128.2, 128.0, 67.4, 58.8, 46.7, 44.3, 23.0; *m*/*z* (ESI^+) $(M+H)^+$ 325.2; HRMS (CI^+ (NH_3), *m*/*z*) calculated for $(C_{16}H_{25}N_2O_3S)^+$ 325.1580, found 325.1584.

_N_'-(3,4-dimethoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide 144

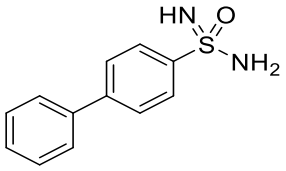


4-Bromobiphenyl (233 mg, 1.00 mmol, 1.0 equiv.) was added to an oven-dried reaction tube and dissolved in THF (5.0 mL). The reaction was cooled to -78 °C. *n*-Butyllithium (444 µL, 1.00 mmol, 2.25 M in hexanes, 1.0 equiv.) was added dropwise and the

mixture stirred at the same temperature for 1 h. TrNSO (306.0 mg, 1.00 mmol, 1.0 equiv.) was added dropwise as a solution in THF (400 µL) and stirred at -78 °C for 20 mins before being placed in an ice bath at 0 °C. After stirring for a further 10 mins, *tert*-butyl hypochlorite (120.0 µL, 1.05 mmol, 1.05 equiv.) was added and the mixture stirred for 20 min, before addition of triethylamine (139 µL, 1.00 mmol, 1.0 equiv.) and 3,4-dimethoxybenzylamine (181 µL, 1.20 mmol, 1.2 equiv.). The reaction mixture was stirred at room temperature for 16 h. Methanesulfonic acid (650 µL, 10.0 mmol, 10.0 equiv.) was added and the reaction stirred vigorously for 15 min at room temperature before dilution with CH_2Cl_2. The solution was extracted with saturated aqueous sodium bicarbonate solution, then the layers were separated and the aqueous phase was extracted with CH_2Cl_2 × 3. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 1:1 to 1:4) afforded sulfonimidamide **144** as a white solid (216 mg, 56% yield).

mp 157-159 °C; ν_{max} (neat, cm^{-1}) 3285, 3080, 1517, 1238, 1074, 1020, 768; δ_H (400 MHz, $CDCl_3$) 8.04-8.00 (m, 2H, Ar-*H*), 7.70-7.65 (m, 2H, Ar-*H*), 7.61-7.57 (m, 2H, Ph-*H*), 7.50-7.45 (m, 2H, Ph-*H*), 7.44-7.38 (m, 1H, Ph-*H*), 6.70 (app. s, 3H, Ar_{OMe}-*H*), 4.13 (d, 1H, *J* = 13.5 Hz, NC$H_a$$H_b$), 4.03 (d, 1H, *J* = 13.5 Hz, NC$H_a$$H_b$), 3.80 (s, 3H, OC$H_3$), 3.77 (s, 3H, OC$H_3$) (Note: NH_2 not observed); δ_C (100 MHz, $CDCl_3$) 149.2, 148.7, 145.3, 139.9, 139.5, 129.4, 129.2, 128.5, 128.0, 127.7, 127.4, 120.3, 111.1, 111.1, 56.0, 55.9, 47.8; LRMS *m*/*z* (ESI^+) $[M-H]^+$ 381.1; HRMS (ESI^+, *m*/*z*) calculated for $(C_{21}H_{23}N_2O_3S)^+$ 383.14239, found 383.14224.

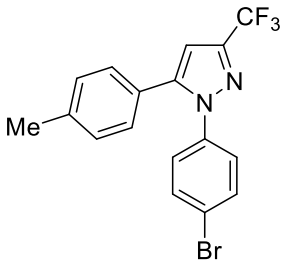
[1,1'-Biphenyl]-4-sulfonimidamide 145



N'-(3,4-dimethoxybenzyl)-[1,1'-biphenyl]-4-sulfonimidamide **144** (50 mg, 0.13 mmol, 1.0 equiv.) was added to a reaction tube and dissolved in acetonitrile (1.3 mL). Water (650 µL) was added and the reaction cooled to 0 °C. Ceric ammonium nitrate (179 mg, 0.327 mmol, 2.5 equiv.) was added and the reaction stirred for 40 min. The reaction mixture was diluted with water and extracted with ethyl acetate × 3. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, hexane/ethyl acetate/methanol 1:6:0 to 0:1:0 to 0:96:4 to 0:90:10) afforded sulfonimidamide **145** as a brown solid (27 mg, 89% yield).

mp 152-154 °C (decomp.); ν_{max} (neat, cm^{-1}) 3270, 3183, 3034, 1479, 1397, 1236, 1105, 996, 758; δ_H (400 MHz, DMSO-d_6) 7.98 (d, 2H, J = 8.5 Hz, Ar-*H*), 7.81 (d, 2H, J = 8.5 Hz, Ar-*H*), 7.74-7.70 (m, 2H, Ph-*H*), 7.52-7.47 (m, 2H, Ph-*H*), 7.44-7.40 (m, 1H, Ph-*H*), 6.38-5.82 (br. s, 3H, N*H*$_2$/N-*H*); δ_C (100 MHz, DMSO-d_6) 146.1, 143.0, 139.4, 129.5, 128.6, 127.4, 127.2, 127.0; HRMS (ESI^+, *m*/*z*) calculated for $(C_{12}H_{13}N_2OS)^+$ 233.07431 $[M+H]^+$, found 233.07436.

1-(4-Bromophenyl)-5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazole 146



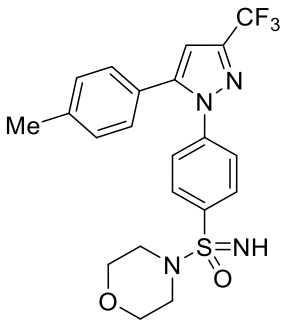
Note: procedure adapted from Uddin *et al*. Bioorg. Med. Chem. 2003, 11, 5273[127]

4,4,4-Trifluoro-1-(*p*-tolyl)butane-1,3-dione (1.300 g, 5.648 mmol, 1.0 equiv.) was added to a 100 mL 3-necked round bottom flask and dissolved in ethanol (60 mL). 4-Bromophenylhydrazine hydrochloride (1.287 g, 5.760 mmol, 1.02 equiv.) was added. The reaction mixture was refluxed at 90 °C for 15 h. The solvent was removed *in vacuo* before dilution with ethyl acetate. The solution was washed with water, then the layers were separated and the aqueous phase was extracted with ethyl acetate × 3. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was dissolved in methanol 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 (0 °C) methanol afforded desired aryl bromide **146** as pale orange crystals (1.539 g, 72% yield).

mp 125-127 °C; ν_{max} (neat, cm^{-1}) 1492, 1470, 1232, 1155, 1127, 1098, 972, 801; δ_H (400 MHz, $CDCl_3$) 7.49 (d, 2H, *J* = 9.0 Hz, Ar-*H*), 7.20 (d, 2H, *J* = 9.0 Hz, Ar-*H*), 7.16 (d, 2H, *J* = 8.0 Hz, Tol-*H*), 7.10 (d, 2H, *J* = 8.0 Hz, Tol-*H*), 6.72 (s, 1H, HetAr-*H*), 2.37 (s, 3H, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 145.0, 143.6 (q, $^2J_{CF}$ = 38.5 Hz), 139.5, 138.4, 132.4, 129.7, 128.8, 127.0, 126.1, 122.3, 121.3 (q, $^1J_{CF}$ = 269.0 Hz) 105.8 (app. d, $^3J_{CF}$ = 6.0 Hz), 21.4; δ_F (376 MHz, $CDCl_3$) -62.3 (s, Ar-CF_3); LRMS *m*/*z* (ESI^+) $[M+H]^+$ 381.0;

HRMS (ESI$^+$, *m*/*z*) calculated for ($C_{17}H_{13}N_2{}^{79}BrF_3$)$^+$ 381.02087 [M+H]$^+$, found 381.02081.

4-(4-(5-(*p*-Tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenylsulfonimidoyl)morpholine 148a

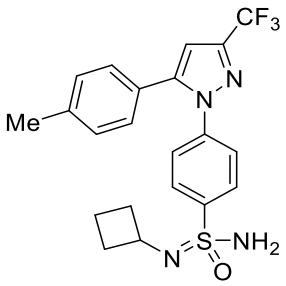


Aryl bromide **146** (152.2 mg, 0.400 mmol, 1.0 equiv.) was added to an oven-dried 10 ml round bottom flask and dissolved in THF (4 mL). The reaction was cooled to -78 °C. *n*-Butyllithium (182 µL, 0.400 mmol, 1.0 equiv.) was added dropwise and the mixture stirred for 1 h. TrNSO (122.2 mg, 0.400 mmol, 1.0 equiv.) was added dropwise as a solution in THF (2 mL) and the mixture stirred at -78 °C for 25 min before being placed in an ice bath at 0 °C and stirred for a further 5 min. *tert*-Butyl hypochlorite (47.5 µL, 0.420 mmol, 1.05 equiv.) was added. The mixture was stirred for 15 min at 0 °C. Morpholine (104 µL, 1.200 mmol, 3.0 equiv.) was added and the mixture was stirred at rt for 16 h. Methanesulfonic acid (390 µL, 6.000 mmol, 15.0 equiv.) was added and the mixture was stirred vigorously for 20 min before dilution with CH_2Cl_2. The solution was washed with saturated aqueous sodium bicarbonate solution, then the layers were separated and the aqueous phase was extracted with CH_2Cl_2 × 3. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/ethyl acetate 2:1 to 1:1) afforded

sulfonimidamide **148a** as a light yellow oil, which crystallised upon standing to a white solid (98 mg, 54% yield).

mp 86-88 °C; ν_{max} (neat, cm^{-1}) 3271, 2857, 1595, 1261, 1236, 1133, 1112, 973, 930; δ_H (400 MHz, $CDCl_3$) 7.85 (d, 2H, *J* = 9.0 Hz, Ar-*H*), 7.48 (d, 2H, *J* = 9.0 Hz, Ar-*H*), 7.15 (d, 2H, *J* = 8.0 Hz, Tol-*H*), 7.08 (d, 2H, *J* = 8.0 Hz, Tol-*H*), 6.74 (s, 1H, HetAr-*H*), 3.72-3.66 (m, 4H, OCH_2), 2.98-2.92 (m, 4H, NCH_2), 2.60 (br. s, 1H, N-*H*), 2.36 (s, 3H, CH_3); δ_C (100 MHz, $CDCl_3$) 145.3, 144.1 (q, $^2J_{CF}$ = 38.5 Hz), 142.6, 139.8, 134.6, 129.8, 129.2, 128.8, 125.7, 125.4, 121.1 (q, $^1J_{CF}$ = 269.0 Hz), 106.3, 66.5, 47.2, 21.4; δ_F (376 MHz, $CDCl_3$) -62.4 (s, Ar-CF_3); LRMS *m*/*z* (ESI^+) $[M+H]^+$ 451.0; HRMS (ESI^+, *m*/*z*) calculated for $(C_{21}H_{22}N_4O_2F_3S)^+$ 451.14101 $[M+H]^+$, found 451.14093.

_N_'-Cyclobutyl-4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonimidamide 148b

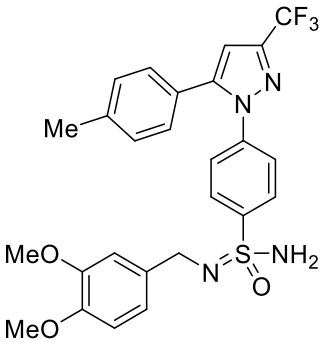


Aryl bromide **146** (152.2 mg, 0.400 mmol, 1.0 equiv.) was added to an oven-dried 10 ml round bottom flask and dissolved in THF (4 mL). The reaction was cooled to -78 °C. *n*-Butyllithium (182 µL, 0.400 mmol, 1.0 equiv.) was added dropwise and the mixture stirred for 1 h. TrNSO (122.2 mg, 0.400 mmol, 1.0 equiv.) was added dropwise as a solution in THF (2 mL) and the mixture stirred at -78 °C for 25 min before being placed in an ice bath at 0 °C and stirred for a further 5 min. *tert*-Butyl hypochlorite (47.5

μL, 0.420 mmol, 1.05 equiv.) was added. The mixture was stirred for 15 min at 0 °C. Cyclobutylamine (103 μL, 1.200 mmol, 3.0 equiv.) was added and the mixture was stirred at rt for 16 h. Methanesulfonic acid (260 μL, 6.000 mmol, 10.0 equiv.) was added and the mixture was stirred vigorously for 35 min before dilution with CH_2Cl_2. The solution was washed with saturated aqueous sodium bicarbonate solution, then the layers were separated and the aqueous phase was extracted with CH_2Cl_2 × 3. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/ethyl acetate 3:1 to 2:1 to 1:1) afforded sulfonimidamide **148b** as a white solid (59 mg, 34% yield).

mp 83-85 °C; ν_{max} (neat, cm^{-1}) 3253, 2977, 1595, 1237, 1161, 1132, 973; δ_H (400 MHz, $CDCl_3$) 7.97 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.42 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.14 (d, 2H, *J* = 8.0 Hz, Tol-*H*), 7.07 (d, 2H, *J* = 8.0 Hz, Tol-*H*), 6.73 (s, 1H, HetAr-*H*), 3.78 (pent., 1H, *J* = 8.0 Hz, NC*H*), 2.36 (s, 3H, Tol-CH_3), 2.14-1.91 (m, 2H, Alk-*H*), 1.79-1.46 (m, 4H, Alk-*H*) (Note: NH_2 peak not observed); δ_C (100 MHz, $CDCl_3$) 145.3, 144.1 (q, $^2J_{CF}$ = 38.5 Hz), 142.2, 141.7, 139.8, 129.8, 128.8, 128.4, 125.8, 125.6, 121.2 (q, $^1J_{CF}$ = 269.5 Hz), 106.2, 48.7, 32.0, 21.4, 15.1; δ_F (376 MHz, $CDCl_3$) -62.4 (s, Ar-CF_3); LRMS *m*/*z* (ESI^+) $[M-H]^-$ 433.1; HRMS (ESI^-, *m*/*z*) calculated for $(C_{21}H_{20}N_4OF_3S)^-$ 433.13044 $[M-H]^-$, found 433.13129.

_N_'-(3,4-Dimethoxybenzyl)-4-(5-(_p_-tolyl)-3-(trifluoromethyl)-1_H_-pyrazol-1-yl)benzenesulfonimidamide 148c

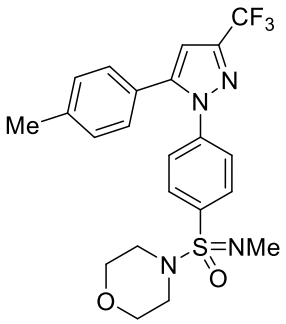


Aryl bromide **146** (152.2 mg, 0.400 mmol, 1.0 equiv.) was added to an oven-dried 10 ml round bottom flask and dissolved in THF (4 mL). The reaction was cooled to -78 °C. *n*-Butyllithium (182 µL, 0.400 mmol, 1.0 equiv.) was added dropwise and the mixture stirred for 1 h. TrNSO (122.2 mg, 0.400 mmol, 1.0 equiv.) was added dropwise as a solution in THF (2 mL) and the mixture stirred at -78 °C for 25 min before being placed in an ice bath at 0 °C and stirred for a further 5 min. *tert*-Butyl hypochlorite (47.5 µL, 0.420 mmol, 1.05 equiv.) was added. The mixture was stirred for 15 min at 0 °C. Cyclobutylamine (103 µL, 1.200 mmol, 3.0 equiv.) was added and the mixture was stirred at rt for 16 h. Methanesulfonic acid (260 µL, 6.000 mmol, 10.0 equiv.) was added and the mixture was stirred vigorously for 35 min before dilution with CH_2Cl_2. The solution was washed with saturated aqueous sodium bicarbonate solution, then the layers were separated and the aqueous phase was extracted with CH_2Cl_2 × 3. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/ethyl acetate 3:1 to 3:2 to 1:2) afforded sulfonimidamide **148c** as a yellow solid (91 mg, 44% yield).

mp 155-157 °C; ν_{max} (neat, cm^{-1}) 3276, 1593, 1515, 1233, 1132, 1022, 972, 802; δ_H (400 MHz, $CDCl_3$) 7.95 (d, 2H, *J* = 9.0 Hz, Ar-*H*), 7.43 (d, 2H, *J* = 9.0 Hz, Ar-*H*), 7.16

(d, 2H, *J* = 8.0 Hz, Tol-*H*), 7.10 (d, 2H, *J* = 8.0 Hz, Tol-*H*), 6.75-6.73 (m, 4H, Ar_{OMe}-*H*/HetAr-*H*), 4.05 (d, 1H, *J* = 13.5 Hz, NC*H*$_a$H$_b$), 3.95 (d, 1H, *J* = 13.5 Hz, NCH$_a$*H*$_b$), 3.82 (s, 3H, OC*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 2.37 (s, 3H, Tol-C*H*$_3$) (Note: NH_2 peak not observed); δ_C (100 MHz, $CDCl_3$) 149.2, 148.8, 145.3, 144.1 (q, $^2J_{CF}$ = 38.5 Hz), 142.4, 140.4, 139.8, 129.8, 128.9, 128.8, 128.5, 125.8, 125.6, 121.2 (q, $^1J_{CF}$ = 269.0 Hz), 120.3, 111.1, 111.1, 106.3, 56.0, 56.0, 48.0, 21.4; δ_F (376 MHz, $CDCl_3$) -62.4 (s, Ar-CF_3); LRMS *m*/*z* (ESI$^+$) [M-H]$^-$ 529.0; HRMS (ESI$^-$, *m*/*z*) calculated for $(C_{26}H_{26}N_4O_3F_3S)^+$ 531.16722 [M+H]$^+$, found 531.16699.

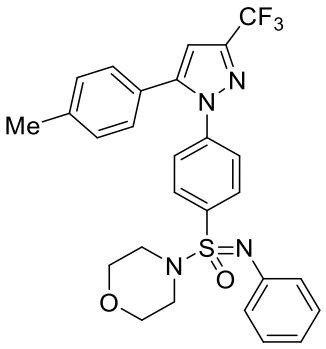
4-(*N*-Methyl-4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenylsulfonimidoyl)morpholine 148d



Sulfonimidamide **148a** (25.0 mg, 0.0555 mmol, 1.0 equiv.) was dissolved in THF (500 µL) and the reaction mixture was cooled to 0 °C. Sodium hydride (60% mineral oil) (6.5 mg, 0.167 mmol, 3.0 equiv.) was added and the reaction mixture stirred for 1 h. Methyl iodide (35.5 µL, 0.555 mmol, 10.0 equiv.) was added. The reaction mixture was stirred for 22 h before dilution with CH_2Cl_2. The solution was washed with water, then the layers were separated and the aqueous phase was extracted with CH_2Cl_2 × 3. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 1:0 to 3:1) afforded sulfonimidamide **148d** as a white solid (26 mg, quant. yield).

mp 159-161 °C; ν_{max} (neat, cm^{-1}) 2855, 1472, 1280, 1200, 1124, 932, 764; δ_H (400 MHz, $CDCl_3$) 7.84 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.46 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.15 (d, 2H, *J* = 8.0 Hz, Tol-*H*), 7.06 (d, 2H, *J* = 8.0 Hz, Tol-*H*), 6.73 (s, 1H, HetAr-*H*), 3.71 (app. t, 4H, *J* = 4.5 Hz, OCH_2), 2.94 (app. dt, 2H, *J* = 12.0, 4.5 Hz, NCH_2), 2.89-2.83 (m, 5H, NCH_2, NCH_3), 2.36 (s, 3H, Tol-CH_3); δ_C (125 MHz, $CDCl_3$) 145.4, 144.2 (q, $^2J_{CF}$ = 38.5 Hz), 142.5, 139.8, 134.8, 129.8, 128.9, 128.8, 125.8, 125.5, 121.2 (q, $^1J_{CF}$ = 269.0 Hz), 106.3, 66.5, 46.9, 28.0, 21.4; δ_F (376 MHz, $CDCl_3$) -62.4 (s, Ar-CF_3); LRMS *m*/*z* (ESI^+) $[M+H]^+$ 465.2; HRMS (ESI^+, *m*/*z*) calculated for $(C_{22}H_{24}N_4O_2F_3S)^+$ 465.15666 $[M+H]^+$, found 465.15619.

4-(*N*-Phenyl-4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenylsulfonimidoyl)morpholine 148e

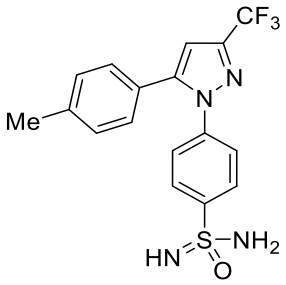


Sulfonimidamide **148a** (10.0 mg, 0.0222 mmol, 1.0 equiv.), sodium *tert*-butoxide (2.6 mg, 0.0266 mmol, 1.2 equiv.), $Pd_2(dba)_3$ (1.0 mg, 0.00111 mmol, 0.05 equiv.) and RuPhos (1.2 mg, 0.00266 mmol, 0.12 equiv.) were added to an oven-dried reaction tube. The tube was sealed with a crimp cap. THF (300 µL) and bromobenzene (3.5 µL, 0.0333 mmol, 1.5 equiv.) were added through the septum. The reaction mixture was placed in a pre-heated oil bath at 100 °C and stirred for 3 h. The solution was diluted with water and extracted with ethyl acetate × 3. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash

chromatography (SiO_2, petrol/ethyl acetate, 1:0 to 9:1 to 5:1) afforded sulfonimidamide **148e** as a white solid (9 mg, 77%).

mp 93-95 °C; ν_{max} (neat, cm^{-1}) 2921, 2854, 1596, 1490, 1313, 1233, 1111, 931; δ_H (400 MHz, $CDCl_3$) 7.97 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.52 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.28-7.20 (m, 4H, Ph-*H*), 7.17 (d, 2H, *J* = 8.0 Hz, Tol-*H*), 7.11 (d, 2H, *J* = 8.0 Hz, Tol-*H*), 7.00 (tt, 1H, *J* = 7.0, 2.0 Hz, Ph-*H*), 6.76 (s, 1H, HetAr-*H*), 3.61 (app. qdd, 4H, *J* = 11.5, 6.0, 3.5 Hz, OCH_2), 3.04 (ddd, 2H, *J* = 12.0, 6.0, 3.5 Hz, NCH_2), 2.96 (ddd, 2H, *J* = 11.5, 6.0, 3.5 Hz, NCH_2), 2.38 (s, 3H, CH_3); δ_C (125 MHz, $CDCl_3$) 145.4, 144.3 (q, $^2J_{CF}$ = 38.5 Hz), 142.9, 142.7, 140.0, 135.0, 129.9, 129.3, 129.1, 128.9, 125.8, 125.6, 123.8, 122.6, 121.2 (q, $^2J_{CF}$ = 269.0 Hz), 106.4, 66.3, 46.8, 21.5; δ_F (376 MHz, $CDCl_3$) -62.4 (s, Ar-CF_3); HRMS (ESI$^+$, *m*/*z*) calculated for $(C_{27}H_{26}N_4O_2F_3S)^+$ 527.17231 $[M+H]^+$, found 527.17194.

4-(5-(*p*-Tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonimidamide 148f



Sulfonimidamide **148c** (28 mg, 0.053 mmol, 1.0 equiv.) was added to a reaction tube and dissolved in acetonitrile (650 µL). Water (325 µL) was added and the reaction cooled to 0 °C. Ceric ammonium nitrate (72 mg, 0.132 mmol, 2.5 equiv.) was added and the reaction stirred for 15 min. The reaction mixture was diluted with water and extracted with ethyl acetate × 3. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2,

hexane/ethyl acetate 1:1 to 1:3) afforded sulfonimidamide **148f** as a light brown solid (17 mg, 85% yield).

mp 157-159 °C; ν_{max} (neat, cm^{-1}) 3300, 1470, 1236, 1162, 1134, 973; δ_H (400 MHz, $CDCl_3$) 8.02-7.98 (m, 2H, Ar-*H*), 7.46-7.41 (m, 2H, Ar-*H*), 7.16 (d, 2H, *J* = 8.0 Hz, Tol-*H*), 7.10 (d, 2H, *J* = 8.0 Hz, Tol-*H*), 6.73 (s, 1H, HetAr-*H*), 4.84-4.01 (br. s, 3H, N-*H*), 2.37 (s, 3H, Tol-C*H*$_3$); δ_C (126 MHz, $CDCl_3$) 145.3, 144.1 (q, $^2J_{CF}$ = 38.5 Hz), 143.5, 142.4, 139.9, 129.9, 128.9, 127.7, 125.9, 125.5, 121.2 (q, $^1J_{CF}$ = 269.0 Hz), 106.4, 21.5; δ_F (376 MHz, $CDCl_3$) -62.4 (s, Ar-CF_3); LRMS *m*/*z* (ESI^+) $[M+H]^+$ 381.0; HRMS (ESI^+, *m*/*z*) calculated for $(C_{17}H_{16}N_4OF_3S)^+$ 381.09914 $[M+H]^+$, found 381.09915.

6.2.4 Biological Assay Details

High-Throughput $LogD_{7.4}$ ($HTLogD_{7.4}$) carried out in a 96 deep well plate format. All pipetting carried out on a Hamilton Star liquid handing robot. Analysis carried out on a reverse phase Agilent 1290 - 6120 LC-MS system using Chemstation software. Assay measures LogD7.4 values from –1.5 to 5 (compound dependant). All compounds measured in duplicate.

20 µL 10 mM DMSO stock solution of compound added to deep well plate. 200 µL octanol and 180 µL 150mM phosphate buffer pH 7.4 (both phases pre-saturated) added to deep well plate. Deep well plate is shaken for 90 mins at RT then centrifuged for 10 minutes at 4000 rpm. Octanol and aqueous phases are separated and transferred to LC analysis plate. The concentration of sample in each phase is determined by measuring UV peak areas at either 254 nm, 280 nm or 230 nm. Ratio of concentration (peak area) used to calculate $HTLogD_{7.4}$ value.

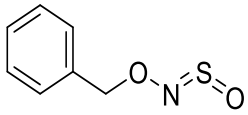
6.3 Chapter 3 Data

6.3.1 Synthesis of Sulfinylhydroxylamines

General Procedure B for Sulfinylhydroxylamine Synthesis

The corresponding hydroxylamine (1.0 equiv.) was added to a reaction flask and dissolved in diethyl ether. Triethylamine (2.0 equiv.) was added and the reaction mixture was cooled to 0 °C. $SOCl_2$ (1.0 equiv.) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. Filtration through Celite (washed with diethyl ether) and evaporation of solvent *in vacuo* afforded the desired sulfinylhydroxylamine.

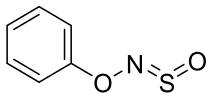
***O*-Benzyl-*N*-sulfinylhydroxylamine 156**



Prepared according to general procedure B using *O*-benzylhydroxylamine **155** (350 µL, 2.98 mmol), diethyl ether (15 mL), triethylamine (832 µL, 5.97 mmol) and $SOCl_2$ (216 µL, 2.98 mmol) to afford BnONSO **156** as a light yellow oil (481 mg, 95%).

ν_{max} (neat, cm^{-1}) 2981, 1455, 1201, 946, 914, 754, 697; δ_H (400 MHz, $CDCl_3$) 7.41 (s, 5H, Ar-*H*), 5.30 (s, 2H, C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 134.3, 129.4, 129.4, 128.8, 81.4; Compound could not be observed by ESI or EI mass spectrometry.

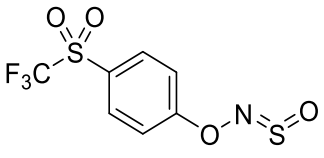
_O_-Phenyl-_N_-sulfinylhydroxylamine 154



Prepared according to general procedure B using *O*-phenylhydroxylamine **153** (400 mg, 3.67 mmol), diethyl ether (16 mL), triethylamine (1.02 mL, 5.97 mmol) and $SOCl_2$ (266 µL, 2.98 mmol) to afford PhONSO **156** as a brown oil (552 mg, 97%).

ν_{max} (neat, cm^{-1}) 1589, 1486, 1459, 1212, 1186, 1153, 1026, 898, 751; δ_H (400 MHz, $CDCl_3$) 7.42-7.36 (m, 2H, Ar-*H*), 7.31-7.25 (m, 2H, Ar-*H*), 7.22 (m, 1H, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 158.5, 129.8, 125.2, 114.5**;** HRMS (EI^+, m/z) calculated for $(C_6H_5NO_2S)^+$ 155.0040 $[M]^+$, found 155.0036.

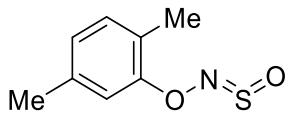
_O_-(4-(Trifluoromethanesulfonyl)phenyl-_N_-sulfinylhydroxylamine 160



Prepared according to general procedure B using *O*-(4-(trifluoromethanesulfonyl)phenylhydroxylamine **167** (150 mg, 0.622 mmol), diethyl ether (3.1 mL), triethylamine (173 µL, 1.24 mmol) and $SOCl_2$ (45 µL, 0.622 mmol) to afford sulfinylhydroxylamine **160** as a yellow solid (552 mg, 97%).

mp 87-89 °C; ν_{max} (neat, cm^{-1}) 1579, 1485, 1361, 1197, 1137, 1070, 1023, 841; δ_H (400 MHz, $CDCl_3$) 8.10 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.56 (d, 2H, *J* = 8.5 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 163.2, 133.6, 127.2, 119.8 (q, $^1J_{CF}$ = 325.5 Hz), 115.7; δ_F (376 MHz, $CDCl_3$) -78.4 (s, CF_3); HRMS (EI^+, m/z) calculated for $(C_7H_4F_3NO_4S_2)^+$ 286.9528, found 286.9534.

_O_-2,5-dimethylphenyl-_N_-sulfinylhydroxylamine 162

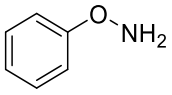


Prepared according to general procedure B using 2,5-dimethylphenylhydroxylamine **169** (198 mg, 1.44 mmol), diethyl ether (7.2 mL), triethylamine (402 µL, 2.89 mmol) and $SOCl_2$ (45 µL, 1.44 mmol) to afford sulfinylhydroxylamine **162** as a brown oil (243 mg, 69%).

ν_{max} (neat, cm^{-1}) 2924, 1581, 1506, 1241, 1205, 1100, 1022, 900, 809; δ_H (400 MHz, $CDCl_3$) 7.15-7.06 (m, 2H, Ar-*H*), 6.91 (d, 2H, *J* = 7.5 Hz, Ar-*H*), 2.35 (s, 3H, Ar-C*H*$_3$), 2.32 (s, 3H, Ar-C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 156.6, 137.4, 131.2, 125.9, 122.2, 115.5, 21.3, 15.2; HRMS (EI$^+$, m/z) calculated for $(C_8H_9NO_2S)^+$ 183.0349, found 183.0347.

6.3.2 Synthesis of Sulfinylhydroxylamine Precursors

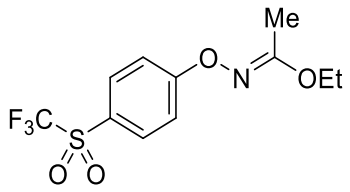
O-Phenylhydroxylamine 153



Prepared according to literature procedure[106] to give the desired hydroxylamine **153** as an orange oil (898 mg, 77% yield). The data matched the literature.[104]

δ_H (400 MHz, $CDCl_3$) 7.33-7.27 (m, 2H, Ar-*H*), 7.18-7.12 (m, 2H, Ar-*H*), 6.99-6.93 (m, 1H, Ar-*H*), 5.84 (br. s, 2H, NH_2); δ_C (100 MHz, $CDCl_3$) 161.3, 129.3, 121.2, 113.2; LRMS *m/z* (ESI$^+$) $[M+H]^+$ 110.0.

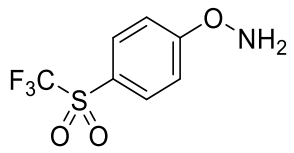
Ethyl *N*-(4-((trifluoromethyl)sulfonyl)phenoxy)acetimidate 166a



1-Bromo-4-[(trifluoromethyl)sulfonyl]benzene (289 mg, 1.00 mmol, 1.0 equiv.), $(allylPdCl)_2$ (1.9 mg, 0.005 mmol, 0.5 mol%), *t*-BuBrettPhos (9.7 mg, 0.02 mmol, 2 mol%) and Cs_2CO_3 (490 mg, 1.50 mmol, 1.5 equiv.) were added to an oven-dried reaction flask. The flask was evacuated and back-filled with nitrogen three times. Toluene (2.0 mL, 0.5 M) and ethyl acetohydroximate (125 µL, 1.25 mmol, 1.25 equiv.) were added. The flask was placed in a pre-heated oil bath at 65 °C and stirred for 7 hours. The reaction mixture was diluted with ethyl acetate and filtered through a short pad of silica. The crude mixture was purified by flash chromatography (SiO_2, petrol/dichloromethane, 9:1 to 3:1) to afford compound **166a** as a white solid (248 mg, 80% yield.

mp 83-85 °C, ν_{max} (neat, cm^{-1}) 3030, 2979, 1900, 1644, 1604, 1481, 1375, 1315, 1235, 1050, 977, 835, 758, 694; δ_H (400 MHz, $CDCl_3$) 7.94 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.37 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 4.21 (q, 2H, *J* = 7.0 Hz, OCH_2), 2.16 (s, 3H, $C(N)CH_3$), 1.38 (t, 3H, *J* = 7.0 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 167.6, 166.2, 133.1, 122.2, 120.1 (q, $^1J_{CF}$ = 325.5 Hz), 115.1, 63.6, 14.8, 14.4; δ_F (376 MHz, $CDCl_3$) -78.9 (s, CF_3); HRMS (ESI^+, m/z) calculated for $(C_{11}H_{13}NO_4S)^+$ 312.05119, found 312.05075.

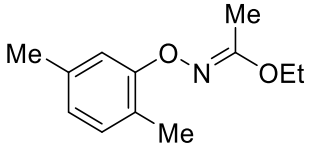
_O_-(4-((Trifluoromethyl)sulfonyl)phenyl)hydroxylamine 167



Compound **166a** (623 mg, 2.00 mmol, 1.0 equiv.) was added to a reaction flask and dissolved in degassed, anhydrous dioxane (4 mL). The flask was cooled to 0 °C and 6 M aqueous HCl (2 mL, 12.00 mmol, 6 equiv.) was added dropwise. The solution was stirred at 0 °C for 5 min and then taken out of the ice bath and stirred for 2.5 hours. The reaction mixture was diluted with diethyl ether and transferred to a separating funnel. The organic layer was washed with 1 M aqueous NaOH and brine, then dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, *n*-hexane/ethyl acetate 1:1 to 2:3) to give hydroxylamine **167** as a white solid (410 mg, 85% yield).

mp 81-83°C; ν_{max} (neat, cm^{-1}) 1608, 1587, 1538, 1183, 1126, 1072, 843, 681; δ_H (400 MHz, $CDCl_3$) 7.93 (app. dd, 2H, *J* = 9.0 Hz, 2.0 Hz, Ar-*H*), 7.39 (app. dd, 2H, *J* = 9.0 Hz, 2.0 Hz, Ar-*H*), 6.09 (br. s, 2H, ON*H*$_2$); δ_C (100 MHz, $CDCl_3$) 168.1, 133.1, 122.3, 120.0 (q, $^1J_{CF}$ = 325.5 Hz), 114.6; δ_F (376 MHz, $CDCl_3$) -78.9 (s, CF_3); HRMS (APCI$^-$, m/z) calculated for $(C_7H_5NO_3S)^+$ 239.99477, found 239.99420.

Ethyl (*E*)-*N*-(2,5-dimethylphenoxy)acetimidate 166c

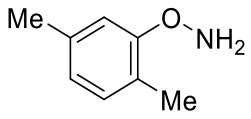


2-Bromo-*p*-xylene (412 µL, 3.00 mmol, 1.0 equiv.), $(allylPdCl)_2$ (5.5 mg, 0.015 mmol, 0.5 mol%), *t*-BuXPhos (25.5 mg, 0.06 mmol, 2 mol%) and Cs_2CO_3 (1.47 g, 4.50 mmol,

1.5 equiv.) were added to an oven-dried reaction flask. The flask was evacuated and back-filled with nitrogen three times. Toluene (6.0 mL, 0.5 M) and ethyl acetohydroximate (375 µL, 1.25 mmol, 1.25 equiv.) were added. The flask was placed in a pre-heated oil bath at 65 °C and stirred for 3 hours. The reaction mixture was diluted with ethyl acetate and filtered through a short pad of silica. The crude mixture was purified by flash chromatography (SiO_2, petrol/dichloromethane, 20:1 to 6:1) to afford compound **166c** as a colourless oil (150 mg, 24% yield). The data matched the literature.[105]

ν_{max} (neat, cm^{-1}) 2980, 2924, 1649, 1613, 1503, 1376, 1309, 1120, 982, 802; δ_H (400 MHz, $CDCl_3$) 7.12 (s, 1H, Ar-*H*), 6.99 (d, 2H, *J* = 7.5 Hz, Ar-*H*), 6.68 (d, 2H, *J* = 7.5 Hz, Ar-*H*), 4.22 (q, 2H, *J* = 7.0 Hz, OC*H*$_2$), 2.31 (s, 3H, Ar-C*H*$_3$), 2.20 (s, 3H, Ar-C*H*$_3$), 2.13 (s, 3H, C(N)C*H*$_3$), 1.36 (t, 3H, *J* = 7.0 Hz, OCH_2CH_3); LRMS *m*/*z* (ESI^+) $[M+H]^+$ 208.2.

_O_-(2,5-dimethylphenyl)hydroxylamine 169

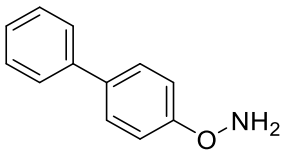


Compound **166c** (414 mg, 2.00 mmol, 1.0 equiv.) was added to a reaction flask and dissolved in degassed, anhydrous dioxane (4 mL). The flask was cooled to 0 °C and 6 M aqueous HCl (2 mL, 12.00 mmol, 6 equiv.) was added dropwise. The solution was stirred at 0 °C for 5 min and then taken out of the ice bath and stirred for 1 hour. The reaction mixture was diluted with diethyl ether and transferred to a separating funnel. The organic layer was washed with 1 M aqueous NaOH and brine, then dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, pentane/diethyl ether 19:1 to 4:1) to give hydroxylamine **169** as a brown oil (225 mg, 82% yield). The data was consistent with the literature.[105]

ν_{max} (neat, cm^{-1}) 3318, 2922, 1618, 1583, 1502, 1415, 1261, 1187, 1102, 993, 937, 866, 805; δ_H (400 MHz, $CDCl_3$) 7.24 (s, 1H, Ar-*H*), 6.97 (d, 2H, *J* = 7.5 Hz, Ar-*H*), 6.68 (d, 2H, *J* = 7.5 Hz, Ar-*H*), 5.82 (br. s, 2H, N*H*$_2$), 2.34 (s, 3H, Ar-C*H*$_3$), 2.15 (s, 3H, Ar-C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 159.0, 136.8, 130.3, 121.4, 121.0, 112.4, 21.5, 15.6; LRMS *m*/*z* (ESI^+) $[M+H]^+$ 138.0.

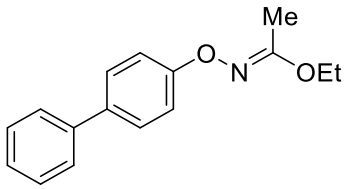
6.3.3 Gram Scale Preparation of BiPhONSO

_O_-([1,1'-Biphenyl]-4-yl)hydroxylamine 168



4-Bromobiphenyl (2.33 g, 10.00 mmol, 1.0 equiv.), $(allylPdCl)_2$ (18.5 mg, 0.050 mmol, 0.5 mol%), *t*-BuBrettPhos (97.0 mg, 0.200 mmol, 2 mol%) and Cs_2CO_3 (4.89 g, 15.00 mmol, 1.5 equiv.) were added to an oven-dried reaction flask. The flask was evacuated and back-filled with nitrogen three times. Toluene (20 mL, 0.5 M) and ethyl acetohydroximate (1.25 mL, 12.50 mmol, 1.25 equiv.) were added. The flask was placed in a pre-heated oil bath at 65 °C and stirred for 4 hours. The reaction mixture was diluted with ethyl acetate and filtered through a short pad of silica. ^{1}H NMR spectroscopy showed full conversion to product and some remaining solvent and ethyl acetohydroximate. The crude mixture can be purified by flash chromatography (SiO_2, petrol/dichloromethane 14:1 to 2:1) at this stage to give the intermediate **166b** as a white solid, but this is not necessary.

Ethyl *N*-([1,1'-biphenyl]-4-yloxy)acetimidate 166b



mp 58-60 °C; ν_{max} (neat, cm^{-1}) 3030, 2978, 1900, 1645, 1604, 1480, 1375, 1315, 1235, 977, 834, 757, 693; δ_H (400 MHz, $CDCl_3$) 7.56 (d, 2H, *J* = 7.5 Hz, Ph-*H*), 7.52 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.42 (t, 2H, *J* = 7.5 Hz, Ph-*H*), 7.30 (t, 1H, *J* = 7.5 Hz, Ph-*H*), 7.21 (d, 2H, *J* = 8.6 Hz, Ar-*H*), 4.22 (q, 2H, *J* = 7.0 Hz, OCH_2), 2.14 (s, 3H, $C(N)CH_3$), 1.37 (t, 3H, *J* = 7.0 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 165.9, 159.5, 141.1, 134.4, 128.8, 128.0, 126.9, 126.7, 114.3, 63.1, 14.5, 14.4; LRMS *m*/*z* (ESI^+) $[M+H]^+$ 256.1; HRMS (ESI^+, m/z) calculated for $(C_{16}H_{18}NO_2)^+$ 256.13321, found 256.13315.

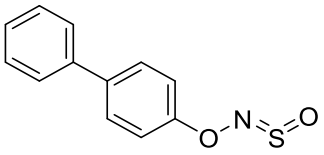
The flask containing the crude product was evacuated and back-filled with nitrogen three times. The crude mixture was dissolved in degassed, anhydrous dioxane and placed in an ice bath at 0 °C. 6 M aqueous HCl was added dropwise. The solution was stirred at 0 °C for 5 min and then taken out of the ice bath and stirred for 1 hour. The reaction mixture was diluted with diethyl ether and transferred to a separating funnel. The organic layer was washed with 1 M aqueous NaOH and brine, then dried over sodium sulfate, filtered and concentrated *in vacuo*. ^1H NMR spectroscopy showed product and remaining dioxane, with small impurities.

The crude product was purified by flash chromatography (SiO_2, *n*-hexane/ethyl acetate 4:1) to give hydroxylamine **168** as a white solid (1.52 g, 82% yield).

mp 116-118 °C; ν_{max} (neat, cm^{-1}) 3317, 3034, 1603, 1479, 1242, 1123, 903, 832, 757, 687; δ_H (400 MHz, $CDCl_3$) 7.57 (d, 2H, *J* = 7.5 Hz, Ph-*H*), 7.53 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.42 (t, 2H, *J* = 7.5 Hz, Ph-*H*), 7.31 (t, 1H, *J* = 7.5 Hz, Ph-*H*), 7.22 (d, 2H, *J* = 8.5

Hz, Ar-*H*), 5.90 (br. s, 2H, ONH_2); δ_C (100 MHz, $CDCl_3$) 161.0, 141.0, 134.4, 128.8, 128.1, 126.9, 126.8, 113.6; HRMS (APCI$^+$, m/z) calculated for $(C_{12}H_{12}NO)^+$ 186.09134, found 186.09123.

BiPhONSO 161



O-([1,1'-Biphenyl]-4-yl)hydroxylamine was added to a reaction flask, dissolved in degassed anhydrous diethyl ether and placed in an ice bath at °C. Triethylamine (2.1 equiv.) was added. Thionyl chloride (1.1 equiv.) was added dropwise. The reaction was stirred at 0 ° for 20 min, then taken out of the ice bath and stirred for a further 15 min. The reaction mixture was filtered through Celite (washed with diethyl ether). The solvent was evaporated *in vacuo* to afford BiPhONSO **161** as a gold solid (1.09 g, 97% yield). Note: DSC tests have shown that BiPhONSO begins to decompose above 90 °C and is a potential detonating agent. Although no explosions have occurred, caution is advised if heating the material.

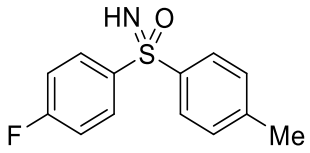
mp 112-114 °C; ν_{max} (neat, cm^{-1}) 1597, 1481, 1207, 1154, 1027, 899, 835, 755, 686; δ_H (400 MHz, $CDCl_3$) 7.63-7.59 (m, 2H, Ar-*H*), 7.58-7.55 (m, 2H, Ar-*H*), 7.47-742 (m, 2H, Ar-*H*), 7.38-7.33 (m, 3H, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 158.2, 140.1, 138.4, 129.0, 128.5, 127.6, 127.1, 114.9; HRMS (EI$^+$, m/z) calculated for $(C_{12}H_9NO_2S)^+$ 231.0349, found 231.0350.

6.3.4 Synthesis of Sulfoximines

General Procedure C for Sulfoximine and Sulfonimidamide Synthesis

BiPhONSO (34.7 mg, 0.15 mmol, 1.0 equiv.) was added to a reaction tube and dissolved in THF (1 mL). The solution was cooled to -78 °C. The first organometallic reagent (1.0 equiv.) was added over 30 seconds. The second organometallic reagent (1.2 equiv.) or the amine (1.5 equiv.) was added 1 min later. The reaction was immediately warmed to room temperature by being placed in a water bath and stirred for 15 min. The reaction mixture was then quenched with 2-propanol and purified directly by column chromatography to afford the desired sulfoximine or sulfonimidamide.

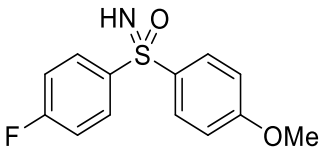
(4-Fluorophenyl)(imino)(*p*-tolyl)- λ^6-sulfanone 177a



Prepared according to general procedure C using 4-fluorophenylmagnesium bromide (172 µL, 0.15 mmol, 0.87 M in THF, 1.0 equiv.) and 4-methylphenylmagnesium bromide (188 µL, 0.18 mmol, 0.96 M in THF, 1.2 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 4:1 to 2:1) afforded sulfoximine **177a** as a light yellow oil (31 mg, 83% yield).

ν_{max} (neat, cm^{-1}) 3269, 2924, 1589, 1489, 1226, 1093, 976, 812, 662; δ_H (400 MHz, $CDCl_3$) 8.05-8.00 (m, 2H, Ar_F-*H*), 7.89 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.27 (d, 2H, *J* = 8.5 Hz, Ar-*H*), 7.15-7.08 (m, 2H, Ar_F-*H*), 3.18 (br. s, 1H, N-*H*), 2.37 (s, 3H, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 165.2 (d, $^1J_{CF}$ = 255.0 Hz), 143.7, 140.4, 139.7 (d, $^4J_{CF}$ = 2.5 Hz), 130.7 (d, $^3J_{CF}$ = 9.5 Hz), 130.0, 128.0, 116.4 (d, $^2J_{CF}$ = 22.5 Hz), 21.6; δ_F (376 MHz, $CDCl_3$) -106.1 (tt, *J* = 8.2, 5.1 Hz, Ar-F); LRMS *m/z* (ESI$^+$) $[M+H]^+$ 250.0; HRMS (ESI$^+$, m/z) calculated for $[C_{13}H_{13}FNO_2S]^+$ 250.06964, found 250.06964.

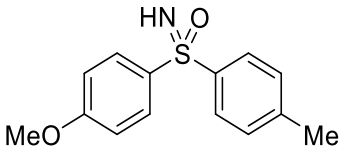
(4-Fluorophenyl)(imino)(4-methoxyphenyl)- λ⁶-sulfanone 177b



Prepared according to general procedure C using 4-fluorophenylmagnesium bromide (172 µL, 0.15 mmol, 0.87 M in THF, 1.0 equiv.) and 4-methoxyphenylmagnesium bromide (375 µL, 0.18 mmol, 0.48 M in THF, 1.2 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 2:1 to 3:2) afforded sulfoximine **177b** as a light yellow oil (28 mg, 70% yield).

ν_{max} (neat, cm^{-1}) 3271, 2942, 1589, 1490, 1257, 1225, 1093, 977, 833, 731, 666; δ_H (400 MHz, $CDCl_3$) 8.04-7.99 (m, 2H, Ar_F-*H*), 7.93 (d, 2H, *J* = 9.0 Hz, Ar-*H*), 7.15-7.08 (m, 2H, Ar_F-*H*), 6.93 (d, 2H, *J* = 9.0 Hz, Ar-*H*), 3.82 (s, 3H, OC*H*$_3$), 3.00 (br. s, 1H, N-*H*); δ_C (100 MHz, $CDCl_3$) 165.1 (d, $^1J_{CF}$ = 254.0 Hz), 163.2, 140.2 (d, $^4J_{CF}$ = 3.0 Hz), 134.9, 130.5 (d, $^3J_{CF}$ = 9.5 Hz), 130.1, 116.3 (d, $^2J_{CF}$ = 22.5 Hz), 114.5, 55.7; δ_F (376 MHz, $CDCl_3$) -106.4 (tt, *J* = 8.1, 5.0 Hz, Ar-F); LRMS *m/z* (ESI^+) $[M+H]^+$ 266.0; HRMS (ESI^+, m/z) calculated for $[C_{13}H_{13}FNO_2S]^+$ 266.06455, found 266.06458.

(4-Methoxyphenyl)(imino)(*p*-tolyl)- λ⁶-sulfanone 177c

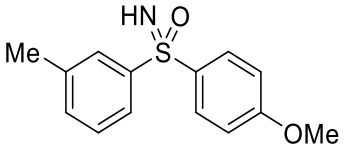


Prepared according to general procedure C using 4-methoxyphenylmagnesium bromide (313 µL, 0.15 mmol, 0.48 M in THF, 1.0 equiv.) and 4-methylphenylmagnesium bromide (188 µL, 0.18 mmol, 0.96 M in THF, 1.2 equiv.).

Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 3:2 to 11:9) afforded sulfoximine **177c** as a colourless oil (27 mg, 69% yield).

ν_{max} (neat, cm^{-1}) 3270, 2919, 2847, 1593, 1494, 1257, 1226, 1129, 1096, 980, 665; δ_H (400 MHz, $CDCl_3$) 7.95 (d, 2H, *J* = 9.0 Hz, Ar_{OMe}-*H*), 7.88 (d, 2H, *J* = 8.0 Hz, Ar-*H*), 7.24 (d, 2H, *J* = 8.0 Hz, Ar-*H*), 6.92 (d, 2H, *J* = 9.0 Hz, Ar_{OMe}-*H*), 3.81 (s, 3H, OCH_3), 2.80 (br. s, 1H, N-*H*), 2.36 (s, 3H, Ar-CH_3); δ_C (100 MHz, $CDCl_3$) 163.0, 143.2, 141.3, 135.3, 130.1, 129.8, 127.8, 114.4, 55.7, 21.5; LRMS *m/z* (ESI^+) $[M+H]^+$ 262.0; HRMS (ESI^+, m/z) calculated for $[C_{14}H_{16}NO_2S]^+$ 262.08963, found 262.08945.

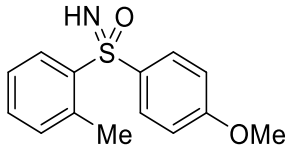
(*m*-Tolyl)(imino)(4-methoxyphenyl)- λ⁶-sulfanone 177d



Prepared according to general procedure C using 3-methylphenylmagnesium bromide (188 µL, 0.15 mmol, 0.80 M in THF, 1.0 equiv.) and 4-methoxyphenylmagnesium bromide (313 µL, 0.18 mmol, 0.48 M in THF, 1.2 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 4:1 to 5:2 to 1:1) afforded sulfoximine **177d** as a colourless oil (29 mg, 74% yield).

ν_{max} (neat, cm^{-1}) 3271, 2923, 2840, 1592, 1493, 1256, 1225, 1092, 973, 833, 689; δ_H (400 MHz, $CDCl_3$) 7.98-7.93 (m, 2H, Ar_{OMe}-*H*), 7.82-7.78 (m, 2H, Ar-*H*), 7.35-7.27 (m, 2H, Ar-*H*), 6.95-6.90 (m, 2H, Ar_{OMe}-*H*), 3.81 (s, 3H, OCH_3), 3.05 (br. s, 1H, N-*H*), 2.37 (s, 3H, Ar-CH_3); δ_C (100 MHz, $CDCl_3$) 163.0, 144.0, 139.4, 135.0, 133.2, 130.2, 129.0, 128.0, 124.8, 114.4, 55.7, 21.4; LRMS *m/z* (ESI^+) $[M+H]^+$ 262.0; HRMS (ESI^+, m/z) calculated for $[C_{14}H_{16}NO_2S]^+$ 262.08963, found 262.08966.

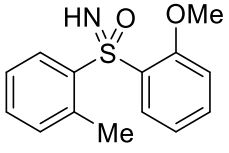
(*o*-Tolyl)(imino)((4-methoxyphenyl)- λ⁶-sulfanone 177e



Prepared according to general procedure C using 2-methylphenylmagnesium bromide (205 µL, 0.15 mmol, 0.73 M in THF, 1.0 equiv.) and 4-methoxyphenylmagnesium bromide (313 µL, 0.18 mmol, 0.48 M in THF, 1.2 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 4:1 to 5:2 to 3:2) afforded sulfoximine **177e** as a colourless oil (26 mg, 66% yield).

ν_{max} (neat, cm^{-1}) 3272, 2929, 1593, 1495, 1461, 1257, 1223, 1123, 974, 835, 762; δ_H (400 MHz, $CDCl_3$) 8.18 (dd, 1H, *J* = 8.0, 1.5 Hz, Ar-*H*), 7.84-7.78 (m, 2H, Ar_{OMe}-*H*), 7.34 (app. td, 1H, *J* = 7.5, 1.6 Hz, Ar-*H*), 7.30-7.24 (m, 1H, Ar-*H*), 7.14-7.10 (m, 1H, Ar-*H*), 6.89-6.84 (m, 2H, Ar_{OMe}-*H*), 3.76 (s, 3H, OC*H*$_3$), 2.94 (br. s, 1H, N-*H*), 2.40 (s, 3H, Ar-C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 162.9, 141.8, 137.8, 133.9, 132.9, 132.7, 130.3, 129.1, 126.4, 114.2, 55.7, 20.6; LRMS *m/z* (ESI^+) $[M+H]^+$ 262.0; HRMS (ESI^+, m/z) calculated for $[C_{14}H_{16}NO_2S]^+$ 262.08963, found 262.08972.

(*o*-Tolyl)(imino)((2-methoxyphenyl)- λ⁶-sulfanone 177f

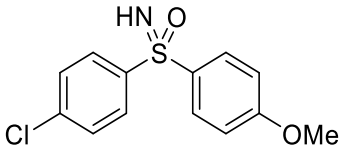


Prepared according to general procedure C using 2-methylphenylmagnesium bromide (205 µL, 0.15 mmol, 0.73 M in THF, 1.0 equiv.) and 2-methoxyphenylmagnesium bromide (175 µL, 0.18 mmol, 1.03 M in THF, 1.2 equiv.). Purification by flash

chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 2:1 to 1:1 to 1:2) afforded sulfoximine **177f** as an off-white solid (26 mg, 66% yield).

ν_{max} (neat, cm^{-1}) 3271, 2935, 2842, 1589, 1477, 1279, 1223, 971, 759; mp 134-136 °C; δ_H (400 MHz, $CDCl_3$) 8.30 (dd, 1H, *J* = 8.0, 1.5 Hz, Ar-*H*), 8.08 (dd, 1H, *J* = 8.0, 1.5 Hz, Ar-*H*), 7.50 (ddd, 1H, *J* = 8.5, 7.5, 1.5 Hz, Ar-*H*), 7.42 (td, 1H, *J* = 7.5, 1.5 Hz, Ar-*H*), 7.36 (dddd, 1H, *J* = 8.0, 7.5, 1.5, 0.5 Hz, Ar-*H*), 7.17 (ddt, 1H, *J* = 7.5, 1.5, 0.5 Hz, Ar-*H*), 7.09 (ddd, 1H, 8.5, 7.5, 1.0 Hz, Ar-*H*), 6.89 (dd, 1H, *J* = 8.5, 1.0 Hz, Ar-*H*), 3.62 (s, 3H, OC*H*$_3$), 3.28 (br. s, 1H, N-*H*), 2.34 (s, 3H, Ar-C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 156.8, 140.9, 137.6, 134.6, 132.6, 132.3, 130.7, 130.3, 129.6, 125.8, 120.5, 112.9, 56.0, 20.5; LRMS *m/z* (ESI^+) $[M+H]^+$ 262.0; HRMS (ESI^+, m/z) calculated for $[C_{14}H_{16}NO_2S]^+$ 262.08963, found 262.08981.

(4-Chlorophenyl)(imino)(4-methoxyphenyl)- λ^6-sulfanone 177g

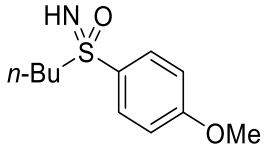


Prepared according to general procedure C using 4-chlorophenylmagnesium bromide (181 µL, 0.15 mmol, 0.83 M in THF, 1.0 equiv.) and 4-methoxyphenylmagnesium bromide (375 µL, 0.18 mmol, 0.48 M in THF, 1.2 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 2:1 to 1:1) afforded sulfoximine **177g** as a colourless oil (32 mg, 76% yield).

ν_{max} (neat, cm^{-1}) 3093, 2924, 1577, 1224, 1084, 966, 747; δ_H (400 MHz, $CDCl_3$) 7.96-7.90 (m, 4H, Ar$_{Cl}$/Ar$_{OMe}$-*H*), 7.43-7.38 (m, 2H, Ar$_{Cl}$-*H*), 6.95-6.91 (m, 2H, Ar$_{OMe}$-*H*), 3.82 (s, 3H, OC*H*$_3$), 3.04 (br. s, 1H, N-*H*); δ_C (100 MHz, $CDCl_3$) 163.2, 142.7, 139.0, 134.4,

130.2, 129.4, 129.2, 114.6, 55.7; LRMS *m/z* (ESI$^+$) $[M+H]^+$ 282.0; HRMS (ESI$^+$, m/z) calculated for $[C_{13}H_{13}{}^{35}ClNO_2S]^+$ 282.03500, found 282.03505.

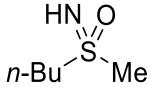
_n_-Butyl(imino)(4-methoxyphenyl)- λ^6-sulfanone 177h



Prepared according to general procedure C using *n*-butylmagnesium chloride (82 µL, 0.15 mmol, 1.84 M in THF, 1.0 equiv.) and 4-methoxyphenylmagnesium bromide (375 µL, 0.18 mmol, 0.48 M in THF, 1.2 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 2:1 to 1:1) afforded sulfoximine **177h** as a colourless oil (22 mg, 65% yield).

ν_{max} (neat, cm^{-1}) 3270, 2961, 1593, 1493, 1256, 1213, 1102, 1016, 978, 835; δ_H (400 MHz, $CDCl_3$) 7.88-7.84 (m, 2H, Ar-*H*), 7.00-6.96 (m, 2H, Ar-*H*), 3.86 (s, 3H, OC*H*$_3$), 3.12-3.06 (m, 2H, SC*H*$_2$), 2.54 (br. s, 1H, N-*H*), 1.75-1.54 (m, 2H, SCH$_2$C*H*$_2$), 1.33 (app. hept., 2H, *J* = 7.5 Hz, SCH$_2$CH$_2$C*H*$_2$), 0.85 (t, 3H, *J* = 7.5 Hz, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 163.3, 133.4, 130.6, 114.4, 57.7, 55.7, 25.3, 21.6, 13.7; LRMS *m/z* (ESI$^+$) $[M+H]^+$ 228.0; HRMS (ESI$^+$, m/z) calculated for $[C_{11}H_{18}NO_2S]^+$ 228.10528, found 228.10507.

_n_-Butyl(imino)methyl- λ^6-sulfanone 177i

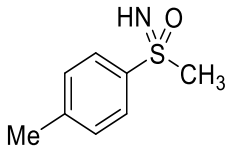


Prepared according to general procedure C using *n*-butylmagnesium chloride (82 µL, 0.15 mmol, 1.84 M in THF, 1.0 equiv.) and methylmagnesium bromide (60 µL, 0.18 mmol, 3.00 M in THF, 1.2 equiv.). Purification by flash chromatography (SiO_2, ethyl

acetate/methanol, 1:0 to 95:5 to 9:1) afforded sulfoximine **177i** as a colourless oil (15 mg, 74% yield).

ν_{max} (neat, cm^{-1}) 3271, 2962, 2935, 2874, 1650, 1210, 1019, 800; δ_H (400 MHz, $CDCl_3$) 3.10-3.04 (m, 2H, SC*H*$_2$), 2.96 (s, 3H, SC*H*$_3$), 1.87-1.77 (m, 2H, SCH_2CH_2), 1.47 (app. dq, 2H, *J* = 15.0, 7.5 Hz, $SCH_2CH_2CH_2$), 0.95 (t, 3H, *J* = 7.5 Hz, Alk-C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 57.0, 42.9, 25.1, 21.8, 13.7; LRMS *m/z* (ESI^+) $[M+H]^+$ 136.0; HRMS (ESI^+, m/z) calculated for $[C_5H_{14}NOS]^+$ 136.07906, found 136.07911.

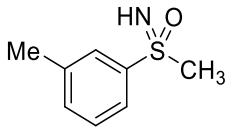
(Imino)methyl(*p*-tolyl)- λ^6-sulfanone 177j



Prepared according to general procedure C using 4-methylphenylmagnesium bromide (160 µL, 0.15 mmol, 0.94 M in THF, 1.0 equiv.) and methylmagnesium bromide (60 µL, 0.18 mmol, 3.00 M in THF, 1.2 equiv.). Purification by flash chromatography (SiO_2, ethyl acetate/methanol, 1:0 to 95:5) afforded sulfoximine **177j** as a light yellow oil (20 mg, 79% yield). The data was consistent with the literature.[59]

δ_H (400 MHz, $CDCl_3$) 7.87 (d, 2H, *J* = 8.0 Hz, Ar-*H*), 7.33 (d, 2H, *J* = 8.0 Hz, Ar-*H*), 3.21 (br.s, 1H, N-*H*), 3.08 (s, 3H, SC*H*$_3$), 2.43 (3H, s, Ar-C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 144.1, 140.6, 130.0, 127.8, 46.3, 21.6; LRMS *m/z* (ESI^+) $[M+H]^+$ 170.0.

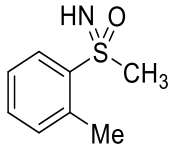
(Imino)methyl(*m*-tolyl)- λ^6-sulfanone 177k



Prepared according to general procedure C using 3-methylphenylmagnesium bromide (188 µL, 0.15 mmol, 0.80 M in THF, 1.0 equiv.) and methylmagnesium bromide (60 µL, 0.18 mmol, 3.00 M in THF, 1.2 equiv.). Purification by flash chromatography (SiO_2, ethyl acetate/methanol, 1:0 to 95:5) afforded sulfoximine **177k** as a colourless oil (17 mg, 67% yield). The data was consistent with the literature.[67]

δ_H (400 MHz, $CDCl_3$) 7.84-7.76 (m, 2H, Ar-*H*), 7.45-7.37 (m, 2H, Ar-*H*), 3.08 (s, 3H, SC*H*$_3$), 2.60 (br.s, 1H, N-*H*), 2.43 (3H, s, Ar-C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 143.5, 139.6, 133.9, 129.2, 128.1, 124.8, 46.3, 21.4; LRMS *m/z* (ESI^+) $[M+H]^+$ 170.0.

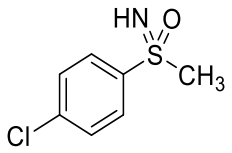
(Imino)methyl(*o*-tolyl)- λ^6-sulfanone 177l



Prepared according to general procedure C using 2-methylphenylmagnesium bromide (205 µL, 0.15 mmol, 0.73 M in THF, 1.0 equiv.) and methylmagnesium bromide (60 µL, 0.18 mmol, 3.00 M in THF, 1.2 equiv.). Purification by flash chromatography (SiO_2, ethyl acetate/methanol, 1:0 to 98:2) afforded sulfoximine **177l** as a colourless oil (14 mg, 55% yield). The data was consistent with the literature.[67]

δ_H (400 MHz, $CDCl_3$) 8.09 (dd, 1H, *J* = 8.0, 1.5 Hz, Ar-*H*), 7.47 (td, 2H, *J* = 7.5, 1.5 Hz, Ar-*H*), 7.38-7.30 (m, 2H, Ar-*H*), 3.12 (s, 3H, SC*H*$_3$), 2.75 (s, 3H, Ar-C*H*$_3$), 2.62 (br.s, 1H, N-*H*); δ_C (100 MHz, $CDCl_3$) 141.8, 137.6, 133.1, 133.0, 129.4, 126.8; LRMS m/z (ESI^+) $[M+H]^+$ 170.0.

(*p*-Chlorophenyl)(imino)methyl- λ⁶-sulfanone 177m

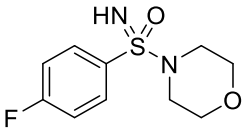


Prepared according to general procedure C using 4-chlorophenylmagnesium bromide (181 µL, 0.15 mmol, 0.83 M in THF, 1.0 equiv.) and methylmagnesium bromide (60 µL, 0.18 mmol, 3.00 M in THF, 1.2 equiv.). Purification by flash chromatography (SiO_2, ethyl acetate/methanol, 1:0 to 95:5) afforded sulfoximine **177j** as a light yellow oil (16 mg, 56% yield). The data was consistent with the literature.[67]

δ_H (400 MHz, $CDCl_3$) 7.96-7.92 (m, 2H, Ar-*H*), 7.54-7.50 (m, 2H, Ar-*H*), 3.10 (s, 3H, C*H*$_3$), 2.82 (br.s, 1H, N-*H*); δ_C (100 MHz, $CDCl_3$) 142.1, 139.9, 129.7, 129.4, 46.3; HRMS (ESI$^+$, m/z) calculated for $[C_7H_9{}^{35}ClNOS]^+$ 190.00879, found 190.00896.

6.3.5 Synthesis of Sulfonimidamides

4-(4-Fluorophenylsulfonimidoyl)morpholine 141a



Prepared according to general procedure C using 4-fluorophenylmagnesium bromide (172 µL, 0.15 mmol, 0.87 M in THF, 1.0 equiv.) and morpholine (20 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:2) afforded sulfonimidamide **141a** as a colourless oil (31 mg, 85% yield). The data matched material obtained from our previous synthesis (see section 6.2.3).

4-(4-Methylphenylsulfonimidoyl)morpholine 180a

Prepared according to general procedure C using 4-methylphenylmagnesium bromide (156 µL, 0.15 mmol, 0.96 M in THF, 1.0 equiv.) and morpholine (20 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:1 to 1:3) afforded sulfonimidamide **180a** as a white solid (31 mg, 86% yield). The data was consistent with the literature.[52]

ν_{max} (neat, cm^{-1}) 3271, 2854, 1597, 1452, 1254, 1111, 927, 771; δ_H (400 MHz, $CDCl_3$) 7.76-7.72 (m, 2H, Ar-*H*), 7.33-7.29 (m, 2H, Ar-*H*), 3.72-3.67 (m, 4H, OC*H*$_2$), 2.99-2.94 (m, 4H, NC*H*$_2$), 2.51 (br.s, 1H, N-*H*), 2.42 (3H, s, Ar-C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 143.5, 132.2, 129.6, 128.3, 66.6, 47.2, 21.6; LRMS *m/z* (ESI^+) $[M+H]^+$ 241.0; HRMS (ESI^+, m/z) calculated for $[C_{11}H_{17}N_2O_2S]^+$ 241.10053, found 241.10054.

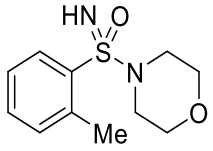
4-(3-Methylphenylsulfonimidoyl)morpholine 180b

Prepared according to general procedure C using 3-methylphenylmagnesium bromide (188 µL, 0.15 mmol, 0.80 M in THF, 1.0 equiv.) and morpholine (20 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:1 to 1:3) afforded sulfonimidamide **180b** as a colourless oil (31 mg, 86% yield).

ν_{max} (neat, cm^{-1}) 3269, 2854, 1453, 1255, 1112, 928, 714; δ_H (400 MHz, $CDCl_3$) 7.67-7.62 (m, 2H, Ar-*H*), 7.42-7.35 (m, 2H, Ar-*H*), 3.71-3.67 (m, 4H, OC*H*$_2$), 2.99-2.94 (m, 4H, NC*H*$_2$), 2.54 (br. s, 1H, N-*H*), 2.41 (s, 3H, Ar-C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 139.1,

135.0, 133.5, 128.8, 128.5, 125.4, 66.6, 47.2, 21.5; LRMS *m/z* (ESI^+) $[M+H]^+$ 241.0; HRMS (ESI^+, m/z) calculated for $[C_{11}H_{17}N_2O_2S]^+$ 241.10053, found 241.10060.

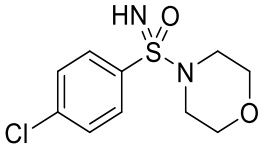
4-(2-Methylphenylsulfonimidoyl)morpholine 180c



Prepared according to general procedure C using 2-methylphenylmagnesium bromide (205 µL, 0.15 mmol, 0.73 M in THF, 1.0 equiv.) and morpholine (20 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:1 to 1:2) afforded sulfonimidamide **180c** as a colourless oil (31 mg, 86% yield).

ν_{max} (neat, cm^{-1}) 3268, 2919, 2855, 1454, 1254, 1111, 1070, 927, 712; δ_H (400 MHz, $CDCl_3$) 7.96 (dd, 1H, *J* = 8.5, 1.5 Hz, Ar-*H*), 7.42 (td, 1H, *J* = 7.5, 1.5 Hz, Ar-*H*), 7.31-7.26 (m, 2H, Ar-*H*), 3.72-3.65 (m, 4H, OCH_2), 3.18-3.07 (m, 4H, NCH_2), 2.70 (s, 3H, Ar-CH_3); δ_C (100 MHz, $CDCl_3$) 138.3, 136.4, 133.2, 132.6, 130.2, 126.1, 66.7, 46.1, 21.5; LRMS *m/z* (ESI^+) $[M+H]^+$ 241.0; HRMS (ESI^+, m/z) calculated for $[C_{11}H_{17}N_2O_2S]^+$ 241.10053, found 241.10062.

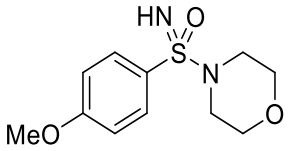
4-(4-Chlorophenylsulfonimidoyl)morpholine 180d



Prepared according to general procedure C using 4-chlorophenylmagnesium bromide (181 µL, 0.15 mmol, 0.83 M in THF, 1.0 equiv.) and morpholine (20 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 2:1 to 1:2) afforded sulfonimidamide **180d** as a colourless oil (34 mg, 87% yield).

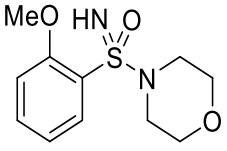
ν_{max} (neat, cm^{-1}) 3218, 2969, 2859, 1577, 1251, 1110, 1005, 927, 830, 752; δ_H (400 MHz, $CDCl_3$) 7.82-7.78 (m, 2H, Ar-*H*), 7.51-7.47 (m, 2H, Ar-*H*), 3.72-3.68 (m, 4H, OC*H*$_2$), 2.99-2.94 (m, 4H, NC*H*$_2$), 2.58 (br.s, 1H, N-*H*); δ_C (100 MHz, $CDCl_3$) 139.3, 133.7, 129.7, 129.3, 66.5, 47.2; LRMS *m/z* (ESI^+) $[M+H]^+$ 261.0; HRMS (ESI^+, m/z) calculated for $[C_{10}H_{14}{}^{35}ClN_2O_2S]^+$ 261.04590, found 261.04596.

4-(4-Methoxyphenylsulfonimidoyl)morpholine 180e



Prepared according to general procedure C using 4-methoxyphenylmagnesium bromide (313 µL, 0.15 mmol, 0.48 M in THF, 1.0 equiv.) and morpholine (20 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 1:1 to 1:3 to 1:4) afforded sulfonimidamide **180e** as a colourless oil (35 mg, 91% yield). ν_{max} (neat, cm^{-1}) 3272, 2849, 1594, 1495, 1252, 1111, 927, 713; δ_H (400 MHz, $CDCl_3$) 7.81-7.76 (m, 2H, Ar-*H*), 7.00-6.95 (m, 2H, Ar-*H*), 3.85 (s, 3H, ArOC*H*$_3$), 3.71-3.67 (m, 4H, OC*H*$_2$), 2.97-2.93 (m, 4H, NC*H*$_2$), 2.49 (br. s, 1H, N-*H*); δ_C (100 MHz, $CDCl_3$) 163.1, 130.4, 126.7, 114.1, 66.6, 55.7, 47.2; LRMS *m/z* (ESI^+) $[M+H]^+$ 257.0; HRMS (ESI^+, m/z) calculated for $[C_{11}H_{17}N_2O_3S]^+$ 257.09544, found 257.09525.

4-(2-Methoxyphenylsulfonimidoyl)morpholine 180f

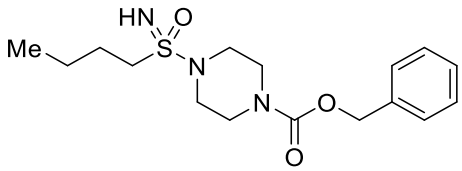


Prepared according to general procedure C using 2-methoxyphenylmagnesium bromide (146 µL, 0.15 mmol, 1.03 M in THF, 1.0 equiv.) and morpholine (20 µL, 0.225

mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 1:9 to 0:1) afforded sulfonimidamide **180f** as a colourless oil (35 mg, 91% yield).

ν_{max} (neat, cm^{-1}) 3349, 2854, 1586, 1477, 1278, 1255, 1109, 1012, 936, 761, 710; δ_H (400 MHz, $CDCl_3$) 7.92 (dd, 1H, *J* = 8.0, 1.5 Hz, Ar-*H*), 7.50 (ddd, 1H, *J* = 8.5, 7.5, 2.0 Hz, Ar-*H*), 7.07-7.00 (m, 2H, Ar-*H*), 3.92 (s, 3H, OC*H*$_3$), 3.74-3.63 (m, 4H, OC*H*$_2$), 3.22 (br. s, 1H, N-*H*), 3.19-3.09 (m, 4H, NC*H*$_2$); δ_C (100 MHz, $CDCl_3$) 156.4, 134.2, 131.2, 126.6, 120.7, 112.2, 66.9, 56.0, 46.6; LRMS *m/z* (ESI^+) $[M+H]^+$ 257.0; HRMS (ESI^+, m/z) calculated for $[C_{11}H_{17}N_2O_3S]^+$ 257.09544, found 257.09528.

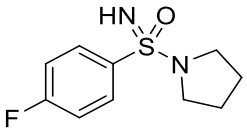
Benzyl 4-(butylsulfonimidoyl)piperazine-1-carboxylate 180g



Prepared according to general procedure C using *n*-butylmagnesium chloride (82 µL, 0.15 mmol, 1.84 M in THF, 1.0 equiv.) and 1-Cbz-piperazine (43.4 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 1:3 to 0:1) afforded sulfonimidamide **180g** as a colourless oil (29 mg, 57% yield).

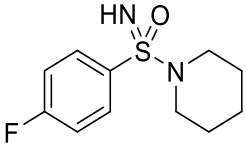
R_f = 0.35 (ethyl acetate); ν_{max} (neat, cm^{-1}) 3297, 2873, 1695, 1466, 1242, 1125, 918, 733, 696; δ_H (400 MHz, $CDCl_3$) 7.41-7.29 (m, 5H, Ar-H), 5.14 (s, 2H, OCH_2Ph), 3.57 (bs, 4H, SNC*H*$_2$), 3.26 (bs, 4H, C(O)NC*H*$_2$), 3.00-2.90 (m, 1H, S-CH_2), 2.85-2.73 (m, 1H, S-CH_2), 2.12 (bs, 1H, NH), 1.89-1.76 (m, 2H, S-CH_2C*H*$_2$), 1.43 (app hex, 2H, *J* = 7.5 Hz, S-CH_2CH_2C*H*$_2$), 0.94 (t, 3H, *J* = 7.5 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 155.1 (N*C*O_2), 136.4 (Ar-C), 128.7 (Ar-C), 128.4 (Ar-C), 128.2 (Ar-C), 67.6 (NCO_2*C*H_2Ph), 49.0 (S-*C*H_2), 46.5 (N-*C*H_2), 44.2 (N-*C*H_2), 25.5 (S-CH_2*C*H_2), 21.9 (S-CH_2CH_2*C*H_2), 13.7 (CH_3); *m/z* (ESI^+) $(M+Na)^+$ 362.0; HRMS (ESI^+, *m/z*) calculated for $(C_{16}H_{26}N_3O_3S)^+$ 340.16894, found 340.16864.

1-(4-Fluorophenylsulfonimidoyl)pyrrolidine 141b



Prepared according to general procedure C using 4-fluorophenylmagnesium bromide (172 µL, 0.15 mmol, 0.87 M in THF, 1.0 equiv.) and piperidine (19 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:2) afforded sulfonimidamide **141b** as a white solid (31 mg, 91% yield). The data matched material obtained from our previous synthesis (see section 6.2.3).

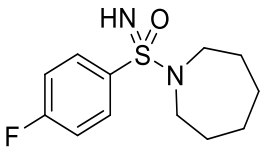
1-(4-Fluorophenylsulfonimidoyl)piperidine 180h



Prepared according to general procedure C using 4-fluorophenylmagnesium bromide (172 µL, 0.15 mmol, 0.87 M in THF, 1.0 equiv.) and piperidine (18.5 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1) afforded sulfonimidamide **180h** as a colourless oil (29 mg, 80% yield).

ν_{max} (neat, cm^{-1}) 3280, 2938, 2852, 1589, 1490, 1253, 1132, 981, 914, 839, 702; δ_H (400 MHz, $CDCl_3$) 7.91-7.85 (m, 2H, Ar-*H*), 7.20-7.13 (m, 2H, Ar-*H*), 2.99-2.94 (m, 4H, NC*H*$_2$), 2.44 (br. s, 1H, N-*H*), 1.64-1.57 (m, 4H, NCH_2CH_2), 1.41-1.34 (m, 2H, $NCH_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 165.1 (d, $^1J_{CF}$ = 253.5 Hz), 132.5 (d, $^4J_{CF}$ = 3.0 Hz), 130.7 (d, $^3J_{CF}$ = 9.0 Hz), 115.9 (d, $^2J_{CF}$ = 22.5 Hz), 48.1, 25.7, 23.7; δ_F (376 MHz, $CDCl_3$) -106.8 (tt, *J* = 8.3, 5.2 Hz, Ar-F); LRMS *m/z* (ESI^+) $[M+H]^+$ 243.0; HRMS (ESI^+, m/z) calculated for $[C_{11}H_{16}FNO_2S]^+$ 243.09619, found 243.09624.

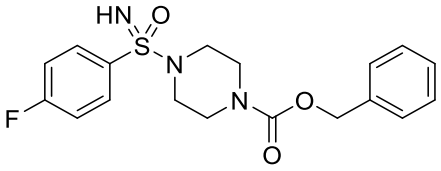
1-(4-Fluorophenylsulfonimidoyl)azepane 180i



Prepared according to general procedure C using 4-fluorophenylmagnesium bromide (172 µL, 0.15 mmol, 0.87 M in THF, 1.0 equiv.) and azepane (25.5 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 5:1 to 4:1 to 3:1) afforded sulfonimidamide **180i** as a colourless oil (36 mg, 94% yield).

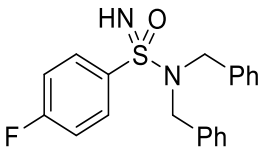
ν_{max} (neat, cm^{-1}) 3277, 2927, 2855, 1590, 1490, 1250, 1130, 840, 684; δ_H (400 MHz, $CDCl_3$) 7.94-7.88 (m, 2H, Ar-*H*), 7.17-7.10 (m, 2H, Ar-*H*), 3.25 (t, 4H, *J* = 6.0 Hz, N-C*H*$_2$), 2.46 (br. s, 1H, N-*H*), 1.74-1.66 (m, 4H, Alk-*H*), 1.59-1.51 (m, 4H, Alk-*H*); δ_C (100 MHz, $CDCl_3$) 164.8 (d, $^1J_{CF}$ = 253.5 Hz), 136.0 (d, $^4J_{CF}$ = 3.5 Hz), 129.8 (d, $^3J_{CF}$ = 9.0 Hz), 116.0 (d, $^2J_{CF}$ = 22.5 Hz), 49.3, 29.5, 26.9; δ_F (376 MHz, $CDCl_3$) -107.3 (tt, *J* = 8.2, 5.1 Hz, Ar-F); LRMS *m/z* (ESI^+) $[M+H]^+$ 257.1; HRMS (ESI^+, m/z) calculated for $[C_{12}H_{18}FN_2OS]^+$ 257.11184, found 257.11165.

Benzyl 4-(4-fluorophenylsulfonimidoyl)piperazine-1-carboxylate 141d



Prepared according to general procedure C using 4-fluorophenylmagnesium bromide (172 µL, 0.15 mmol, 0.87 M in THF, 1.0 equiv.) and 1-Cbz-piperazine (43.5 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 5:1 to 4:1 to 3:1) afforded sulfonimidamide **141d** as a colourless oil (46 mg, 85% yield). The data matched material obtained from our previous synthesis (see section 6.2.3).

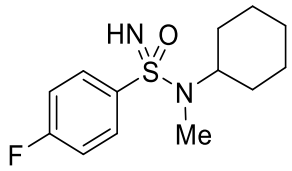
***N,N*-Dibenzyl-4-fluorobenzenesulfonimidamide 180j**



Prepared according to general procedure C using 4-fluorophenylmagnesium bromide (172 µL, 0.15 mmol, 0.87 M in THF, 1.0 equiv.) and dibenzylamine (43.5 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 6:1) afforded sulfonimidamide **180j** as a colourless oil (35 mg, 66% yield).

ν_{max} (neat, cm^{-1}) 3320, 3064, 3031, 2920, 1590, 1491, 1254, 1232, 1131, 929, 889, 837, 745, 698; δ_H (400 MHz, $CDCl_3$) 8.00-7.94 (m, 2H, Ar_F-*H*), 7.24-7.20 (m, 6H, Ar-*H*), 7.18-7.12 (m, 2H, Ar_F-*H*), 7.08-7.02 (m, 4H, Ar-*H*), 4.37 (s, 4H, N-CH_2), 2.67 (br. s, 1H, N-*H*); δ_C (100 MHz, $CDCl_3$) 164.9 (d, $^1J_{CF}$ = 254.0 Hz), 137.2 (d, $^4J_{CF}$ = 3.0 Hz), 136.5, 130.1 (d, $^3J_{CF}$ = 9.0 Hz), 128.6, 128.4, 127.7, 116.1 (d, $^2J_{CF}$ = 22.5 Hz), 51.9; δ_F (376 MHz, $CDCl_3$) -106.7 (tt, *J* = 8.2, 5.1 Hz, Ar-F); LRMS *m/z* (ESI^+) $[M+H]^+$ 355.2; HRMS (ESI^+, m/z) calculated for $[C_{20}H_{20}FN_2OS]^+$ 355.12749, found 355.12723.

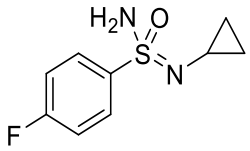
***N*-Cyclohexyl-4-fluoro-*N*-methylbenzenesulfonimidamide 180k**



Prepared according to general procedure C using 4-fluorophenylmagnesium bromide (172 µL, 0.15 mmol, 0.87 M in THF, 1.0 equiv.) and *N*-methylcyclohexylamine (29.5 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 5:1 to 4:1 to 7:2) afforded sulfonimidamide **180k** as a colourless oil (29 mg, 72% yield).

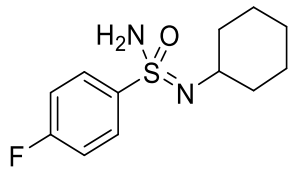
ν_{max} (neat, cm^{-1}) 3280, 2930, 2856, 1590, 1490, 1247, 1131, 996, 946, 840, 749; δ_H (400 MHz, $CDCl_3$) 7.96-7.91 (m, 2H, Ar-*H*), 7.17-7.10 (m, 2H, Ar-*H*), 3.86 (app. ddq, 1H, *J* = 11.5, 7.5, 4.0 Hz, N-C*H*), 2.73 (s, 3H, N-CH_3), 2.42 (br. s, 1H, N-*H*), 1.74-1.64 (m, 2H, Alk-*H*), 1.62-1.55 (m, 1H, Alk-*H*), 1.41-1.19 (m, 7H, Alk-*H*), 1.03-0.91 (m, 1H, Alk-*H*); δ_C (100 MHz, $CDCl_3$) 164.2 (d, $^1J_{CF}$ = 253.0 Hz), 137.0 (d, $^4J_{CF}$ = 3.0 Hz), 129.8 (d, $^3J_{CF}$ = 9.0 Hz), 116.0 (d, $^2J_{CF}$ = 22.5 Hz), 57.4, 30.6, 30.6, 29.6, 26.0, 25.9, 25.5; δ_F (376 MHz, $CDCl_3$) -107.2 (tt, *J* = 8.3, 5.2 Hz, Ar-F); LRMS *m/z* (ESI^+) $[M+H]^+$ 271.0; HRMS (ESI^+, m/z) calculated for $[C_{13}H_{20}FN_2OS]^+$ 271.12749, found 271.12735.

N'-Cyclopropyl-4-fluorobenzenesulfonimidamide 180m



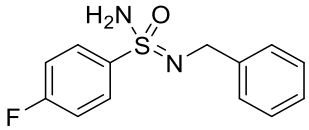
Prepared according to general procedure C using 4-fluorophenylmagnesium bromide (172 µL, 0.15 mmol, 0.87 M in THF, 1.0 equiv.) and cyclopropylamine (15.5 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:1 to 2:3) afforded sulfonimidamide **180m** as a colourless oil (23 mg, 72% yield). ν_{max} (neat, cm^{-1}) 3264, 3103, 1590, 1491, 1231, 1101, 1005, 836; δ_H (400 MHz, $CDCl_3$) 8.05-7.99 (m, 2H, Ar-*H*), 7.20-7.13 (m, 2H, Ar-*H*), 4.02 (br. s, 2H, NH_2), 2.23-2.17 (m, 1H, N-C*H*), 0.62-0.49 (m, 3H, N-CH-CH_2), 0.47-0.40 (m, 1H, N-CH-CH_2); δ_C (100 MHz, $CDCl_3$) 165.1 (d, $^1J_{CF}$ = 254.0 Hz), 137.2 (d, $^4J_{CF}$ = 3.0 Hz), 130.4 (d, $^3J_{CF}$ = 9.0 Hz), 116.1 (d, $^2J_{CF}$ = 22.5 Hz), 25.0, 6.2, 6.1; δ_F (376 MHz, $CDCl_3$) -106.4 (tt, *J* = 8.3, 5.2 Hz, Ar-F); LRMS *m/z* (ESI^+) $[M+H]^+$ 215.0; HRMS (ESI^+, m/z) calculated for $[C_9H_{12}FN_2OS]^+$ 215.06489, found 215.06474.

N'-Cyclohexyl-4-fluorobenzenesulfonimidamide 180n



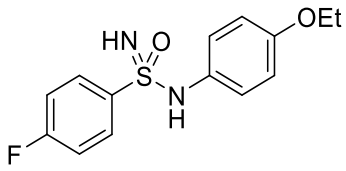
Prepared according to general procedure C using 4-fluorophenylmagnesium bromide (172 µL, 0.15 mmol, 0.87 M in THF, 1.0 equiv.) and cyclohexylamine (26.0 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:1 to 1:2) afforded sulfonimidamide **180n** as a colourless oil (29 mg, 75% yield). ν_{max} (neat, cm^{-1}) 3257, 2930, 2855, 1591, 1491, 1227, 1009, 837; δ_H (400 MHz, $CDCl_3$) 8.03-7.97 (m, 2H, Ar-*H*), 7.18-7.11 (m, 2H, Ar-*H*), 3.37 (br. s, 1H, N-*H*), 3.10 (tt, 1H, *J* = 10.5, 4.0 Hz, N-C*H*), 1.78-1.70 (m, 1H, Alk-*H*), 1.67-1.55 (m, 3H, Alk-*H*), 1.54-1.46 (m, 1H, Alk-*H*), 1.28-1.00 (m, 6H, Alk-*H*); δ_C (100 MHz, $CDCl_3$) 164.9 (d, $^1J_{CF}$ = 253.5 Hz), 139.1 (d, $^4J_{CF}$ = 3.0 Hz), 129.9 (d, $^3J_{CF}$ = 9.0 Hz), 116.1 (d, $^2J_{CF}$ = 22.5 Hz), 53.1, 34.3, 34.2, 25.3, 24.9, 24.9; δ_F (376 MHz, $CDCl_3$) -106.9 (tt, *J* = 8.4, 5.2 Hz, Ar-F); LRMS *m/z* (ESI^+) $[M+H]^+$ 257.0; HRMS (ESI^+, m/z) calculated for $[C_{12}H_{18}FN_2OS]^+$ 257.11184, found 257.11151.

N'-Benzyl-4-fluorobenzenesulfonimidamide 141g



Prepared according to general procedure C using 4-fluorophenylmagnesium bromide (172 µL, 0.15 mmol, 0.87 M in THF, 1.0 equiv.) and benzylamine (24.5 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 2:1 to 11:9) afforded sulfonimidamide **141g** as a colourless oil (29 mg, 73% yield). The data matched material obtained from our previous synthesis (see section 6.2.3).

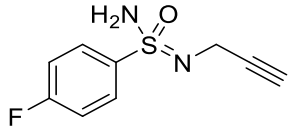
_N_-(4-ethoxyphenyl)-4-fluorobenzenesulfonimidamide 180o



Prepared according to general procedure C using 4-fluorophenylmagnesium bromide (172 µL, 0.15 mmol, 0.87 M in THF, 1.0 equiv.) and *p*-phenetidine (29.0 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 4:1 to 3:1 to 7:3 to 2:1) afforded sulfonimidamide **180o** as a light brown solid (29 mg, 73% yield).

mp 120-122 °C; ν_{max} (neat, cm^{-1}) 3250, 2981, 2926, 1590, 1501, 1229, 1047, 835; δ_H (400 MHz, $CDCl_3$) 8.06-8.00 (m, 2H, Ar_F-*H*), 7.31-7.24 (m, 2H, Ar_F-*H*), 7.03-6.98 (m, 2H, Ar-*H*), 6.75-6.70 (m, 2H, Ar-*H*), 6.27 (br. s, 1H, N-*H*), 3.94 (q, 2H, *J* = 7.0 Hz, OC*H*$_2$), 2.85 (br. s, 1H, N-*H*), 1.31 (t, 3H, *J* = 7.0 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 165.3 (d, $^1J_{CF}$ = 250.5 Hz), 155.6, 140.8, 131.0 (d, $^4J_{CF}$ = 3.0 Hz), 130.8 (d, $^3J_{CF}$ = 9.5 Hz), 125.4, 116.3 (d, $^2J_{CF}$ = 22.5 Hz), 115.4, 64.0, 15.2; δ_F (376 MHz, $CDCl_3$) -109.9 (tt, *J* = 9.0, 4.4 Hz, Ar-F); HRMS (ESI$^+$, m/z) calculated for $[C_{14}H_{16}FN_2O_2S]^+$ 295.09110, found 295.09128.

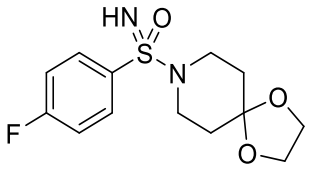
4-Fluoro-_N_'-(prop-2-yn-1-yl)benzenesulfonimidamide 141j



Prepared according to general procedure C using 4-fluorophenylmagnesium bromide (172 µL, 0.15 mmol, 0.87 M in THF, 1.0 equiv.) and propargylamine (14.5 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1

to 1:1 to 1:2) afforded sulfonimidamide **141j** as a colourless oil (21 mg, 66% yield). The data matched material obtained from our previous synthesis (see section 6.2.3).

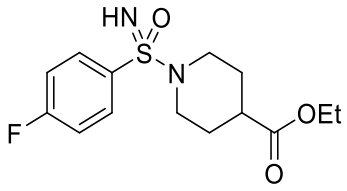
8-(4-Fluorophenylsulfonimidoyl)-1,4-dioxa-8-azaspiro[4.5]decane 180p



Prepared according to general procedure C using 4-fluorophenylmagnesium bromide (172 µL, 0.15 mmol, 0.87 M in THF, 1.0 equiv.) and 1,4-dioxa-8-azaspiro[4.5]decane (29.0 µL, 0.225 mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 1:1 to 1:2) afforded sulfonimidamide **180p** as a colourless oil (37 mg, 82% yield).

ν_{max} (neat, cm^{-1}) 3222, 2966, 2857, 1589, 1490, 1256, 1223, 1141, 1038, 933, 840, 708; δ_H (400 MHz, $CDCl_3$) 7.91-7.85 (m, 2H, Ar-*H*), 7.20-7.12 (m, 2H, Ar-*H*), 3.87 (s, 4H, OCH_2), 3.13 (app. t, 4H, *J* = 5.5 Hz, NCH_2), 2.53 (br. s, 1H, N-*H*), 1.77-1.72 (m, 4H, NCH_2CH_2); δ_C (100 MHz, $CDCl_3$) 165.1 (d, $^1J_{CF}$ = 254.0 Hz), 132.5 (d, $^4J_{CF}$ = 3.0 Hz), 130.6 (d, $^3J_{CF}$ = 9.0 Hz), 116.1 (d, $^2J_{CF}$ = 22.5 Hz), 106.2, 64.5, 45.6, 34.8; δ_F (376 MHz, $CDCl_3$) -106.4 (m, Ar-F); LRMS *m/z* (ESI^+) $[M+H]^+$ 301.0; HRMS (ESI^+, m/z) calculated for $[C_{13}H_{18}FN_2O_3S]^+$ 301.10167, found 301.10159.

Ethyl 1-(4-fluorophenylsulfonimidoyl)piperidine-4-carboxylate 180q



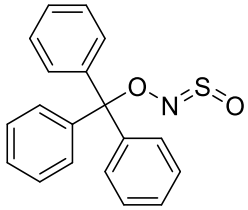
Prepared according to general procedure C using 4-fluorophenylmagnesium bromide (172 µL, 0.15 mmol, 0.87 M in THF, 1.0 equiv.) and ethyl isonipecotate (34.5 µL, 0.225

mmol, 1.5 equiv.). Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 2:1 to 1:1) afforded sulfonimidamide **180q** as a colourless oil (41 mg, 87% yield). ν_{max} (neat, cm^{-1}) 3284, 2980, 2838, 1725, 1589, 1490, 1254, 1135, 1038, 918, 840, 699; δ_H (400 MHz, $CDCl_3$) 7.90-7.84 (m, 2H, Ar-*H*), 7.20-7.12 (m, 2H, Ar-*H*), 4.08 (q, 2H, *J* = 7.0 Hz, OC*H*$_2$), 3.68 (dtd, 2H, *J* = 10.5, 4.0, 2.0 Hz, Alk-*H*), 2.51 (br. s, 1H, N-*H*), 2.37 (dddd, 2H, *J* = 12.0, 11.0, 3.0, 1.5 Hz, Alk-*H*), 2.19 (tt, 1H, *J* = 10.5, 4.0 Hz, C(O)C*H*), 1.93 (dddd, 2H, *J* = 14.5, 7.0, 3.5, 2.0 Hz, Alk-*H*), 1.76 (dtdd, 2H, *J* = 12.5, 11.0, 4.0, 2.0 Hz, Alk-*H*), 1.19 (t, 3H, *J* = 7.0 Hz, Alk-*H*); δ_C (100 MHz, $CDCl_3$) 174.0, 165.1 (d, $^1J_{CF}$ = 254.0 Hz), 132.3 (d, $^4J_{CF}$ = 3.0 Hz), 130.6 (d, $^3J_{CF}$ = 9.0 Hz), 116.0 (d, $^2J_{CF}$ = 22.5 Hz), 60.7, 46.6, 46.4, 40.2, 28.0, 28.0, 14.2; δ_F (376 MHz, $CDCl_3$) -106.4 (tt, *J* = 8.3, 5.2 Hz, Ar-F); LRMS *m/z* (ESI^+) $[M+H]^+$ 315.0; HRMS (ESI^+, m/z) calculated for $[C_{14}H_{20}FN_2O_3S]^+$ 315.11732, found 315.11703.

6.4 Chapter 4 Data

6.4.1 Synthesis of TrONSO

_O_-Trityl-_N_-sulfinylhydroxylamine, TrONSO, 194

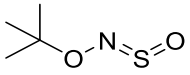


_O_-Tritylhydroxylamine **193** (1.90 g, 6.90 mmol, 1.0 equiv.) was dissolved in diethyl ether (34.5 mL) and triethylamine (1.94 mL, 13.8 mmol, 2.0 equiv.) was added. The reaction was cooled to 0 °C. Thionyl chloride (0.50 mL, 6.90 mmol, 1.0 equiv.) was added and the reaction mixture was stirred at 0 °C for 1 hour before filtration through Celite. The solvent was evaporated under reduced pressure to give TrONSO **194** as an off-white solid (964 mg, 43%).

ν_{max} (neat, cm^{-1}) 1601, 1445, 1192, 1026, 879, 761, 697, 634; mp 139-141 °C (decomp.); δ_H (400 MHz, $CDCl_3$) 7.38-7.28 (m, 15H, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 141.9, 129.2, 128.3, 128.1, 97.6; The compound could not be identified by ESI, EI or CI mass spectrometry.

6.4.2 Synthesis of *t*-BuONSO

O-tert-butyl-_N_-sulfinylhydroxylamine 197



O-tert-Butylhydroxylamine hydrochloride (25.37 g, 200.0 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (800 mL) and cooled to 0 °C. Triethylamine (84.0 mL, 600.0 mmol, 3.0 equiv.) was added and a white solid precipitated. Thionyl chloride (14.6 mL, 200.0

mmol, 1.0 equiv.) was added over 5 min. The reaction was stirred at 0 °C for 10 min and then taken out of the ice bath and stirred for 1 hour. The reaction mixture was diluted with diethyl ether, filtered through Celite and the solvent evaporated under reduced pressure. The crude mixture was purified by distillation (75 °C, 40 mbar) to afford *t*-BuONSO **197** as a colourless liquid (15.52 g, 57% yield).

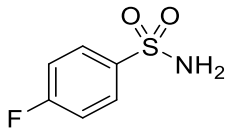
ν_{max} (neat, cm^{-1}) 2983, 1370, 1200, 1013, 893, 853; δ_H (400 MHz, $CDCl_3$) 1.41 (s, 9H, *t*-Bu-*H*); δ_C (100 MHz, $CDCl_3$) 87.9, 27.0. The compound could not be identified by ESI, EI or CI mass spectrometry.

6.4.3 Synthesis of Primary Sulfonamides

General Procedure D for Primary Sulfonamide Synthesis

O-tert-Butyl-*N*-sulfinylhydroxylamine **197** (40.5 mg, 0.30 mmol, 1.0 equiv.) was dissolved in THF (1.2 mL) and cooled to -78 °C. The corresponding organometallic reagent was added and the reaction was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was purified directly by flash chromatography to afford the desired primary sulfonamide.

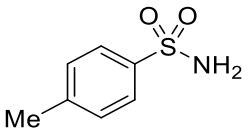
4-Fluorobenzenesulfonamide 195a



Prepared according to general procedure D using 4-fluorophenylmagnesium bromide (340 µL, 0.30 mmol, 0.88 M in THF, 1.0 equiv.) Purification by flash chromatography (SiO_2, heptane/ethyl acetate, gradient 9:1 to 0:1) afforded sulfonamide **195a** as a white solid (42 mg, 80% yield). The data was consistent with the literature.[119]

δ_H (400 MHz, Acetone-d_6) 8.01 (dd, 2H, *J* = 8.5, 5.0 Hz, Ar-*H*), 7.36 (app. t, 2H, *J* = 8.5 Hz, Ar-*H*), 6.69 (br. s, 2H, NH_2); δ_C (100 MHz, Acetone-d_6) 165.3 (d, $^1J_{CF}$ = 251.0 Hz), 141.3 (d, $^4J_{CF}$ = 3.0 Hz), 129.8 (d, $^3J_{CF}$ = 9.5 Hz), 116.6 (d, $^2J_{CF}$ = 23.0 Hz); δ_F (376 MHz, Acetone-d_6) -109.1 (app. ddd, *J* = 14.0, 9.0, 5.3 Hz, Ar-F); LRMS *m/z* (ESI^-) $[M-H]^-$ 174.0.

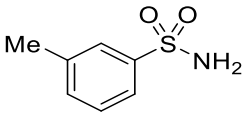
4-Toluenesulfonamide 113



Prepared according to general procedure D using 4-methylphenylmagnesium bromide (320 µL, 0.30 mmol, 0.95 M in THF, 1.0 equiv.) Purification by flash chromatography (SiO_2, heptane/ethyl acetate, gradient 9:1 to 1:2) afforded sulfonamide **113** as a white solid (41 mg, 78% yield). The data was consistent with a commercial sample.

δ_H (400 MHz, DMSO-d_6) 7.70 (d, 2H, *J* = 8.0 Hz, Ar-*H*), 7.36 (d, 2H, *J* = 8.0 Hz, Ar-*H*), 7.25 (br. s, 2H, N*H*$_2$), 2.37 (s, 3H, CH_3). LRMS *m/z* (ESI^-) $[M-H]^-$ 170.0.

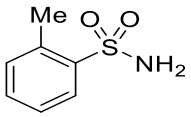
3-Methylbenzenesulfonamide 195b



Prepared according to general procedure D using 3-methylphenylmagnesium bromide (380 µL, 0.30 mmol, 0.80 M in THF, 1.0 equiv.) Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 2:1) afforded sulfonamide **195b** as a white solid (36 mg, 70% yield). The data was consistent with the literature.[119]

δ_H (400 MHz, MeOH-d_4) 7.73 (s, 1H, Ar-*H*), 7.71-7.67 (m, 1H, Ar-*H*), 7.44-7.38 (m, 2H, Ar-*H*), 4.81 (s, 2H, NH_2), 2.42 (s, 3H, Ar-CH_3); δ_C (100 MHz, MeOH-d_4) 144.9, 140.4, 133.8, 129.9, 127.4, 124.2, 21.3; LRMS *m/z* (ESI^-) $[M-H]^-$ 170.0.

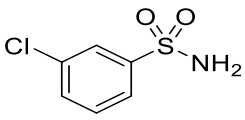
2-Methylbenzenesulfonamide 195c



Prepared according to general procedure D using 2-methylphenylmagnesium bromide (380 µL, 0.30 mmol, 0.80 M in THF, 1.0 equiv.) Purification by flash chromatography (SiO_2, gradient heptane/ethyl acetate, 9:1 to 0:1) afforded sulfonamide **195c** as a white solid (33 mg, 70% yield). The data was consistent with the literature.[119]

δ_H (400 MHz, $CDCl_3$) 8.02 (dd, 1H, *J* = 8.5, 1.5 Hz, Ar-*H*), 7.47 (td, 1H, *J* = 7.5, 1.5 Hz, Ar-*H*), 7.35-7.29 (m, 2H, Ar-*H*), 4.80 (br. s, 2H, NH_2), 2.69 (s, 3H, Ar-CH_3); δ_C (100 MHz, $CDCl_3$) 139.9, 136.9, 133.0, 132.6, 128.3, 126.4, 20.5; LRMS *m/z* (ESI^-) $[M-H]^-$ 170.0.

3-Chlorobenzenesulfonamide 195d

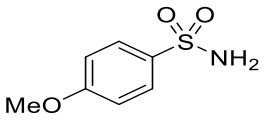


Prepared according to general procedure D using 3-chlorophenylmagnesium bromide (380 µL, 0.30 mmol, 0.80 M in THF, 1.0 equiv.) Purification by flash chromatography (SiO_2, gradient heptane/ethyl acetate, 9:1 to 0:1) afforded sulfonamide **195d** as a white solid (47 mg, 81% yield). The data was consistent with the literature.[119]

δ_H (400 MHz, $CDCl_3$) 7.93 (t, 1H, *J* = 2.0 Hz, Ar-*H*), 7.82 (dt, 1H, *J* = 8.0, 1.0 Hz, Ar-*H*), 7.57 (ddd, 1H, *J* = 8.0, 2.0, 1.0 Hz, Ar-*H*), 7.47 (t, 1H, *J* = 8.0 Hz, Ar-*H*), 4.89 (br.

s, 2H, N*H*$_2$); δ_C (100 MHz, $CDCl_3$) 143.7, 135.5, 133.1, 130.6, 126.9, 124.7; LRMS *m/z* (ESI^-) $[M-H]^-$ 190.0.

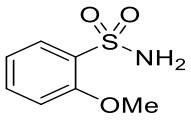
4-Methoxybenzenesulfonamide 195e



Prepared according to general procedure D using 4-methoxyphenylmagnesium bromide (625 µL, 0.30 mmol, 0.48 M in THF, 1.0 equiv.) Purification by flash chromatography (SiO_2, petrol/ethyl acetate, 3:1 to 2:1 to 1:1) afforded sulfonamide **195e** as a white solid (45 mg, 80% yield). The data was consistent with the literature.[119]

δ_H (400 MHz, MeOH-*d*$_4$) 7.85-7.80 (m, 2H, Ar-*H*), 7.06-7.01 (m, 2H, Ar-*H*), 4.80 (s, 2H, N*H*$_2$), 3.86 (s, 3H, OC*H*$_3$); δ_C (100 MHz, MeOH-*d*$_4$) 164.0, 136.7, 129.2, 115.0, 56.1; LRMS *m/z* (ESI^-) $[M-H]^-$ 186.0.

2-Methoxybenzenesulfonamide 195f

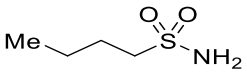


Prepared according to general procedure D using 2-methoxyphenylmagnesium bromide (291 µL, 0.30 mmol, 1.03 M in THF, 1.0 equiv.) Purification by flash chromatography (SiO_2, petrol/ethyl acetate, to 2:1 to 2:3) afforded sulfonamide **195f** as a white solid (31 mg, 55% yield). The data was consistent with the literature.[119]

mp 172-174 °C; δ_H (400 MHz, MeOH-*d*$_4$) 7.84 (dd, 1H, *J* = 8.0, 2.0 Hz, Ar-*H*), 7.57 (ddd, 1H, *J* = 8.5, 7.5, 1.5 Hz, Ar-*H*), 7.19 (dd, 1H, *J* = 8.5, 1.0 Hz, Ar-*H*), 7.06 (app.

td, 1H, *J* = 7.6, 1.0 Hz, Ar-*H*), 4.80 (s, 2H, N*H*$_2$), 3.98 (s, 3H, OC*H*$_3$); δ_C (100 MHz, MeOH-*d*$_4$) 157.9, 135.3, 132.0, 129.1, 121.2, 113.5, 56.6.

***n*-Butanesulfonamide 195g**

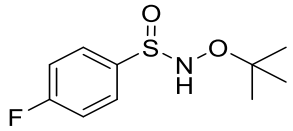


Prepared according to general procedure D using *n*-butyllithium (130 µL, 0.30 mmol, 2.33 M in THF, 1.0 equiv.) Purification by flash chromatography (SiO_2, gradient heptane/ethyl acetate, 9:1 to 1:2) afforded sulfonamide **195g** as a white solid (14 mg, 34% yield). The data was consistent with the literature.[128]

mp 46-48 °C; δ_H (400 MHz, $CDCl_3$) 4.87 (br. s, 2H, N*H*$_2$), 3.15-3.09 (m, 2H, SC*H*$_2$), 1.83 (tt, 2H, *J* = 8.0, 6.5 Hz, SCH_2CH_2), 1.47 (app. hept., 2H, *J* = 7.5 Hz, $SCH_2CH_2CH_2$), 0.96 (t, 3H, *J* = 7.5 Hz, C*H*$_3$).

6.4.4 Mechanistic Studies

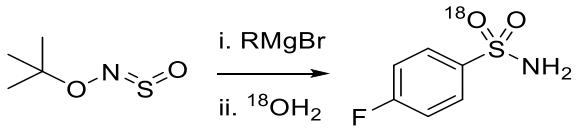
***N-tert*-butoxy-4-fluorobenzenesulfinamide 198-H**



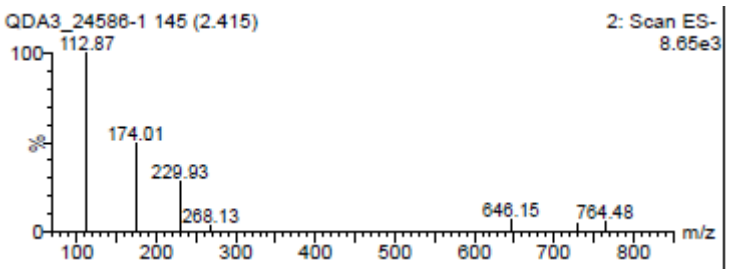
O-tert-Butyl-*N*-sulfinylhydroxylamine **197** (41.5 mg, 0.31 mmol, 1.0 equiv.) was dissolved in THF (6.1 mL) and cooled to -78 °C. 4-Fluorophenylmagnesium bromide (350 µL, 0.31 mmol, 0.88 M in THF, 1.0 equiv.) was added and the reaction mixture was stirred for 5 min before being quenched with sat. aq. ammonium chloride solution. The aqueous mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to give *N-tert*-butoxy-4-fluorobenzenesulfinamide **198-H** as a white solid (73 mg, quant.).

ν_{max} (neat, cm^{-1}) 3093, 2983, 1585, 1493, 1214, 1091, 1061, 1036, 841, 688; δ_H (400 MHz, $CDCl_3$) 7.77-7.72 (m, 2H, Ar-*H*), 7.21 (t, 2H, *J* = 8.5 Hz, Ar-*H*), 6.48 (s, 1H, N-*H*), 1.24 (s, 9H, *t*-Bu-*H*); δ_C (100 MHz, $CDCl_3$) 165.0 (d, $^1J_{CF}$ = 252.5 Hz), 136.9 (d, $^4J_{CF}$ = 3.0 Hz), 128.1 (d, $^3J_{CF}$ = 9.0 Hz), 116.4 (d, $^2J_{CF}$ = 22.5 Hz), 80.9, 26.7; δ_F (376 MHz, $CDCl_3$) -107.5 (td, *J* = 8.5, 4.3 Hz, Ar-F); LRMS *m/z* (ESI^-) $[M-H]^-$ 230.0; HRMS (ESI^+, m/z) calculated for $[C_{10}H_{15}FNO_2S]^+$ 232.08020, found 232.08034.

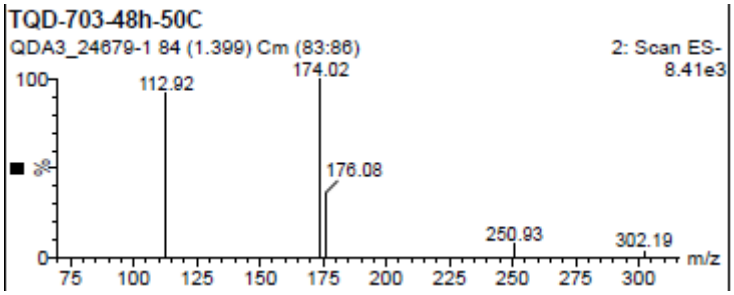
18-Oxygen Labelling Experiment



O-tert-Butyl-*N*-sulfinylhydroxylamine **197** (43.0 mg, 0.32 mmol, 1.0 equiv.) was dissolved in THF (6.3 mL) and cooled to -78 °C. 4-Fluorophenylmagnesium bromide (360 µL, 0.32 mmol, 0.88 M in THF, 1.0 equiv.) was added and the reaction mixture was stirred for 5 min before the addition of $^{18}OH_2$ (7 µL, 0.38 mmol, 1.2 equiv.) The reaction mixture was allowed to warm to room temperature and stirred overnight. No 18-oxygen incorporation was detected by LCMS. The reaction mixture was stirred at 50 °C for 48 h. 25% 18-Oxygen incorporation (m/z = 176.08) was detected by LCMS**.**



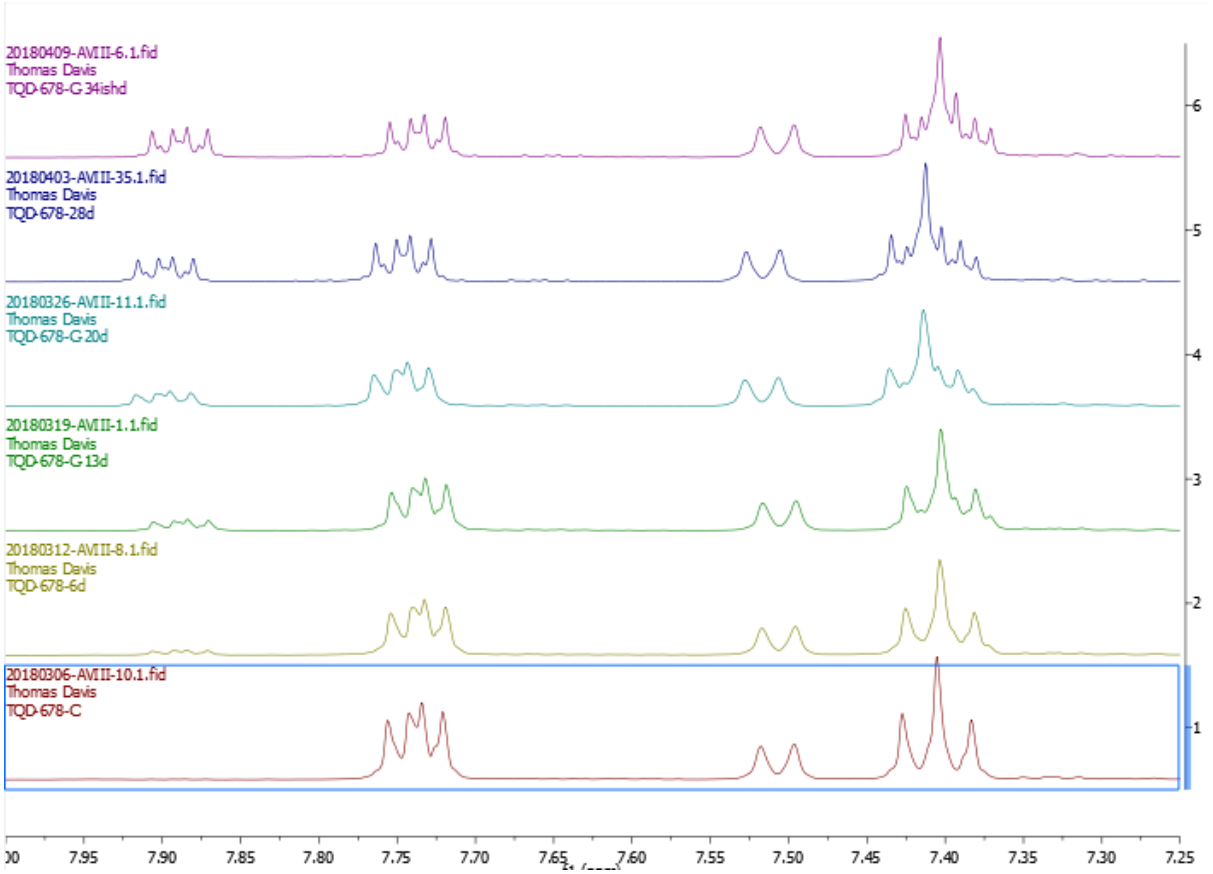
No 18-oxygen incorporation after stirring at rt



25% 18-oxygen incorporation after stirring at 50 °C

Conversion of *tert*-butoxysulfinamide 198-H to sulfonamide 195a

Sulfinamide **198-H** (multiplet at 7.74 ppm) was dissolved in DMSO-d_6 with 0.33 equiv. of 4-(trifluoromethyl)phenol (doublet at 7.51 ppm) as an internal standard. 4-Fluorobenzenesulfonamide (multiplet at 7.89 ppm) and a signal that appears to correspond to *tert*-butanol (singlet at 1.11 ppm) were formed over the course of several weeks. The initial spectrum was taken immediately after purification, and each subsequent one was recorded at intervals of one week.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TQD-678-G 34ishd
20180403-AVIII-35.1.fid
Thomas Davis
TQD-678-28d
20180326-AVIII-11.1.fid
Thomas Davis
TQD-678-G 20d
20180319-AVIII-1.1.fid
Thomas Davis
TQD-678-G 13d
20180312-AVIII-8.1.fid
Thomas Davis
TQD-678-6d
20180306-AVIII-10.1.fid
Thomas Davis
TQD-678-C
6
5
4
3
2
1
7.95
7.90
7.85
7.80
7.75
7.70
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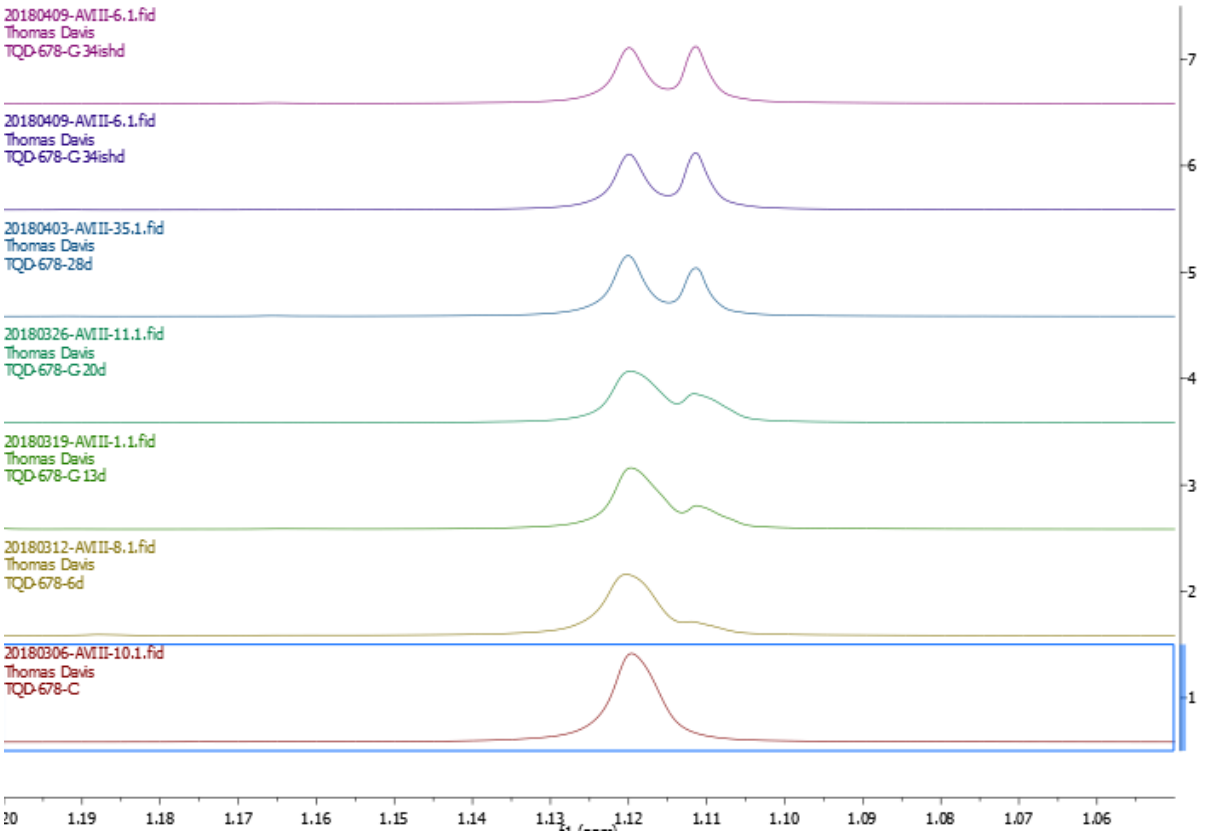
7.60
7.55
7.50
7.45
7.40
7.35
7.30
7.25

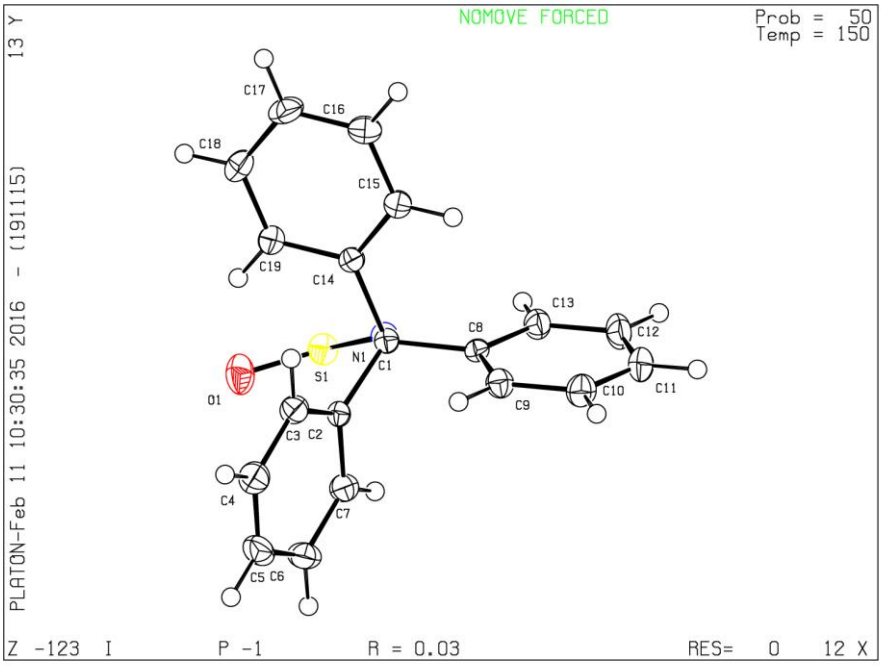

20180409-AVIII-6.1.fid
Thomas Davis
TQD-678-G 34ishd
20180409-AVIII-6.1.fid
Thomas Davis
TQD-678-G 34ishd
20180403-AVIII-35.1.fid
Thomas Davis
TQD-678-28d
20180326-AVIII-11.1.fid
Thomas Davis
TQD-678-G 20d
20180319-AVIII-1.1.fid
Thomas Davis
TQD-678-G 13d
20180312-AVIII-8.1.fid
Thomas Davis
TQD-678-6d
20180306-AVIII-10.1.fid
Thomas Davis
TQD-678-C
7
6
5
4
3
2
1
1.19
1.18
1.17
1.16
1.15
1.14
1.13
1.12
1.11
1.10
1.09
1.08
1.07
1.06

6.5 Crystallographic Data

Dr Mark Chadwick (Andrew Weller group, University of Oxford) is gratefully acknowledged for obtaining the following X-ray crystal structures.

N-Sulfinyltriphenylmethylamine, TrNSO 127

Crystals obtained *via* slow evaporation of TrNSO in *n*-hexane.

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Bond precision: C-C = 0.0020 A Wavelength=1.54180
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alpha=93.575(7) beta=101.315(7) gamma=118.022(9)
Temperature: 150 K
Calculated Reported
Volume 768.67(14) 768.66(14)
Space group P -1 P -1
Hall group -P 1 -P 1
Moiety formula C19 H15 N O S C19 H15 N1 O1 S1
Sum formula C19 H15 N O S C19 H15 N1 O1 S1
Mr 305.38 305.40
Dx,g cm-3 1.319 1.319
Z 2 2
Mu (mm-1) 1.864 1.864
F000 320.0 320.0
F000' 321.47
h,k,lmax 11,11,13 11,11,13
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Nref 3234 3175
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Tmin' 0.830
Correction method= # Reported T Limits: Tmin=0.660 Tmax=0.910
AbsCorr = MULTI-SCAN
Data completeness= 0.982 Theta(max)= 76.477
R(reflections)= 0.0319( 2928) wR2(reflections)= 0.0846( 3164)
S = 0.971 Npar= 200
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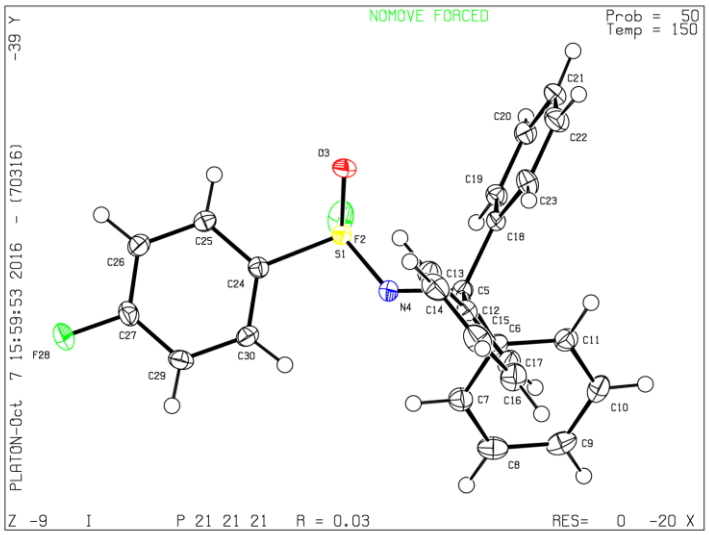
NumberLabel	Charge	SybylType	Xfrac + ESD	Yfrac + ESD	Zfrac + ESD	Symm. op.
1 C1	0	C.3	0.56764(15)	0.20512(14)	0.70454(11)	x,y,z
2 C2	0	C.2	0.61579(15)	0.36793(14)	0.78982(11)	x,y,z
3 C3	0	C.2	0.75553(17)	0.43693(16)	0.89707(12)	x,y,z
4 C4	0	C.2	0.79209(18)	0.58086(18)	0.97610(13)	x,y,z
5 C5	0	C.2	0.6896(2)	0.65560(17)	0.94916(14)	x,y,z
6 C6	0	C.2	0.5480(2)	0.58536(18)	0.84390(14)	x,y,z
7 C7	0	C.2	0.51142(17)	0.44238(16)	0.76489(13)	x,y,z
8 C8	0	C.2	0.41119(15)	0.05603(15)	0.73492(12)	x,y,z
9 C9	0	C.2	0.39698(17)	0.04800(16)	0.85828(12)	x,y,z
10 C10	0	C.2	0.25722(19)	-0.08811(18)	0.88536(13)	x,y,z
11 C11	0	C.2	0.13012(19)	-0.21822(17)	0.78982(15)	x,y,z
12 C12	0	C.2	0.14375(19)	-0.21137(17)	0.66720(15)	x,y,z
13 C13	0	C.2	0.28318(17)	-0.07540(16)	0.63946(13)	x,y,z
14 C14	0	C.2	0.72484(15)	0.17522(15)	0.71362(11)	x,y,z
15 C15	0	C.2	0.72137(17)	0.03057(17)	0.74731(13)	x,y,z
16 C16	0	C.2	0.86348(19)	0.00491(18)	0.74833(15)	x,y,z
17 C17	0	C.2	1.00898(18)	0.12273(19)	0.71477(14)	x,y,z

18	C18	0	C.2	1.01456(17)	0.26865(18)	0.68248(13)	x,y,z
19	C19	0	C.2	0.87408(16)	0.29524(16)	0.68215(12)	x,y,z
20	S1	0	S.3	0.55910(4)	0.33502(4)	0.48460(3)	x,y,z
21	O1	0	O.2	0.70217(14)	0.50702(13)	0.52868(11)	x,y,z
22	N1	0	N.2	0.50770(14)	0.20890(13)	0.57013(10)	x,y,z
23	H31	0	H	0.8277	0.3845	0.9158	x,y,z
24	H41	0	H	0.8880	0.6252	1.0538	x,y,z
25	H51	0	H	0.7156	0.7544	1.0039	x,y,z
26	H61	0	H	0.4752	0.6355	0.8254	x,y,z
27	H71	0	H	0.4147	0.3952	0.6912	x,y,z
28	H91	0	H	0.4843	0.1385	0.9243	x,y,z
29	H101	0	H	0.2483	-0.0924	0.9717	x,y,z
30	H111	0	H	0.0335	-0.3127	0.8087	x,y,z
31	H121	0	H	0.0580	-0.3005	0.6011	x,y,z
32	H131	0	H	0.2902	-0.0715	0.5535	x,y,z
33	H151	0	H	0.6205	-0.0526	0.7710	x,y,z
34	H161	0	H	0.8586	-0.0969	0.7719	x,y,z
35	H171	0	H	1.1056	0.1037	0.7138	x,y,z
36	H181	0	H	1.1147	0.3521	0.6599	x,y,z
37	H191	0	H	0.8803	0.3971	0.6600	x,y,z

4-Fluoro-*N*-tritylbenzenesulfonimidoyl fluoride 131

Crystals obtained *via* slow evaporation of fluoride **131** from $CDCl_3$ in an NMR tube.

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alpha=90 beta=90 gamma=90
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Calculated Reported
Volume 1969.91(6) 1969.91(6)
Space group P 21 21 21 P 21 21 21
Hall group P 2ac 2ab P 2ac 2ab
Moiety formula C25 H19 F2 N O S C25 H19 F2 N1 O1 S1
Sum formula C25 H19 F2 N O S C25 H19 F2 N1 O1 S1
Mr 419.47 419.49
Dx,g cm-3 1.414 1.414
Z 4 4
Mu (mm-1) 1.767 1.767
F000 872.0 872.0
F000' 875.94
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Nref 4056[ 2341] 3363
Tmin,Tmax 0.809,0.838 0.540,0.840
Tmin' 0.702
Correction method= # Reported T Limits: Tmin=0.540 Tmax=0.840
AbsCorr = MULTI-SCAN
Data completeness= 1.44/0.83 Theta(max)= 75.200
R(reflections)= 0.0326( 3186) wR2(reflections)= 0.0914( 3345)
S = 0.912 Npar= 272
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1	S1	0	S.3	0.06836(7)	0.56902(5)	0.55301(2)	x,y,z
2	F2	0	F	0.20901(19)	0.56043(16)	0.50197(6)	x,y,z
3	O3	0	O.2	0.0456(2)	0.69511(13)	0.55891(8)	x,y,z
4	N4	0	N.2	0.1229(3)	0.48657(16)	0.59727(7)	x,y,z
5	C5	0	C.3	0.2483(3)	0.50359(19)	0.64542(8)	x,y,z
6	C6	0	C.2	0.3794(3)	0.39540(19)	0.64665(8)	x,y,z
7	C7	0	C.2	0.3302(3)	0.2869(2)	0.62358(10)	x,y,z
8	C8	0	C.2	0.4498(4)	0.1902(2)	0.62615(10)	x,y,z
9	C9	0	C.2	0.6186(4)	0.1998(2)	0.65233(10)	x,y,z
10	C10	0	C.2	0.6687(3)	0.3074(2)	0.67617(9)	x,y,z
11	C11	0	C.2	0.5498(3)	0.40443(19)	0.67312(9)	x,y,z
12	C12	0	C.2	0.1213(3)	0.50526(19)	0.69664(9)	x,y,z
13	C13	0	C.2	-0.0271(3)	0.5855(2)	0.69819(10)	x,y,z
14	C14	0	C.2	-0.1368(3)	0.5944(2)	0.74471(10)	x,y,z
15	C15	0	C.2	-0.1044(4)	0.5215(2)	0.78994(10)	x,y,z
16	C16	0	C.2	0.0379(3)	0.4407(2)	0.78826(10)	x,y,z
17	C17	0	C.2	0.1518(3)	0.4326(2)	0.74213(9)	x,y,z
18	C18	0	C.2	0.3633(3)	0.61829(18)	0.64101(9)	x,y,z
19	C19	0	C.2	0.4860(3)	0.6308(2)	0.59711(9)	x,y,z
20	C20	0	C.2	0.5925(3)	0.7322(2)	0.59081(9)	x,y,z
21	C21	0	C.2	0.5784(4)	0.82452(19)	0.62902(10)	x,y,z
22	C22	0	C.2	0.4617(4)	0.8119(2)	0.67362(10)	x,y,z
23	C23	0	C.2	0.3541(3)	0.7098(2)	0.67996(9)	x,y,z

24	C24	0	C.3	-0.1258(3)	0.50727(19)	0.52014(9)	x,y,z
25	C25	0	C.2	-0.2124(3)	0.5765(2)	0.48001(8)	x,y,z
26	C26	0	C.2	-0.3665(3)	0.53094(19)	0.45364(9)	x,y,z
27	C27	0	C.2	-0.4277(3)	0.4192(2)	0.46796(9)	x,y,z
28	F28	0	F	-0.5771(2)	0.37508(13)	0.44125(6)	x,y,z
29	C29	0	C.2	-0.3448(3)	0.35032(19)	0.50789(9)	x,y,z
30	C30	0	C.2	-0.1904(3)	0.39562(19)	0.53468(9)	x,y,z
31	H71	0	H	0.2131	0.2794	0.6060	x,y,z
32	H81	0	H	0.4145	0.1164	0.6089	x,y,z
33	H91	0	H	0.7011	0.1344	0.6541	x,y,z
34	H101	0	H	0.7832	0.3165	0.6942	x,y,z
35	H111	0	H	0.5833	0.4781	0.6892	x,y,z
36	H131	0	H	-0.0508	0.6346	0.6669	x,y,z
37	H141	0	H	-0.2365	0.6493	0.7454	x,y,z
38	H151	0	H	-0.1757	0.5277	0.8215	x,y,z
39	H161	0	H	0.0594	0.3883	0.8186	x,y,z
40	H171	0	H	0.2518	0.3792	0.7420	x,y,z
41	H191	0	H	0.4957	0.5666	0.5710	x,y,z
42	H201	0	H	0.6760	0.7391	0.5611	x,y,z
43	H211	0	H	0.6474	0.8950	0.6238	x,y,z
44	H221	0	H	0.4546	0.8736	0.7011	x,y,z
45	H231	0	H	0.2739	0.7008	0.7109	x,y,z
46	H251	0	H	-0.1653	0.6528	0.4714	x,y,z

47	H261	0	H	-0.4282	0.5761	0.4260	x,y,z
48	H291	0	H	-0.3928	0.2758	0.5171	x,y,z
49	H301	0	H	-0.1280	0.3531	0.5618	x,y,z

References

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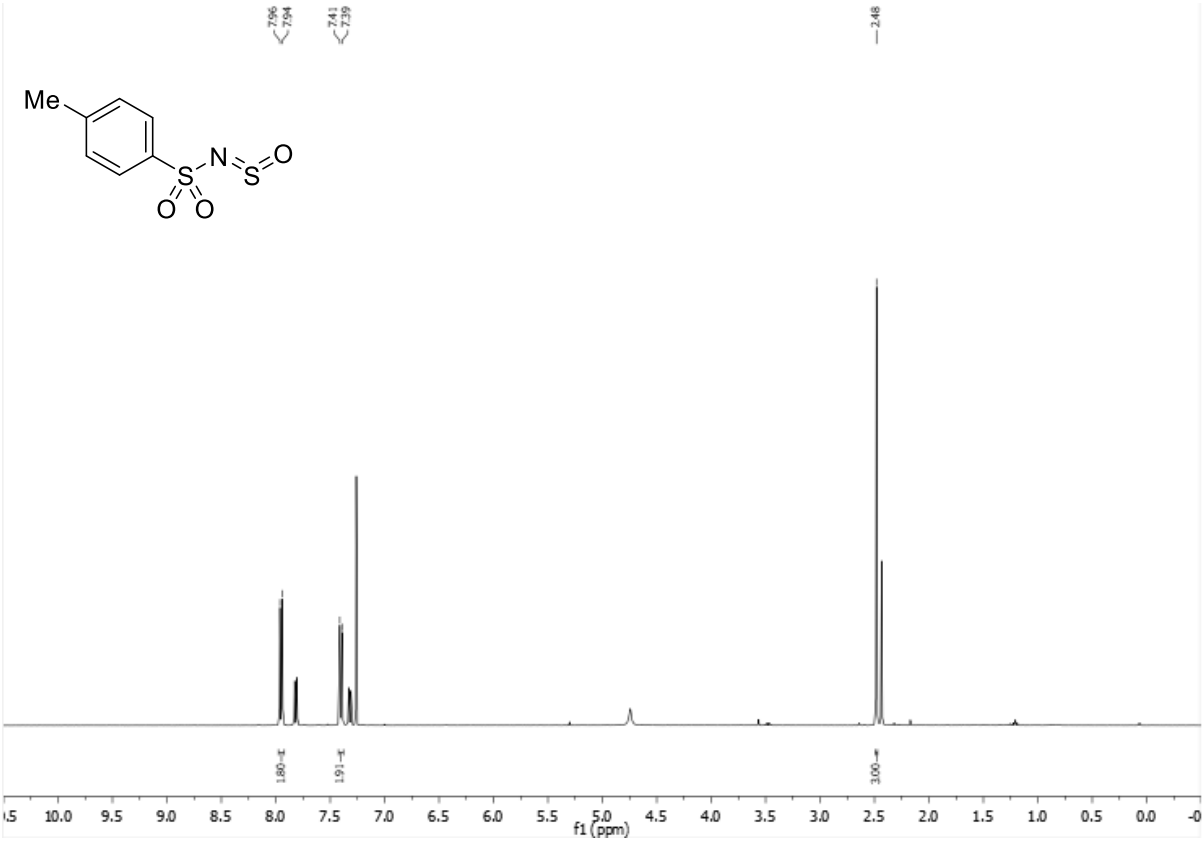
Spectra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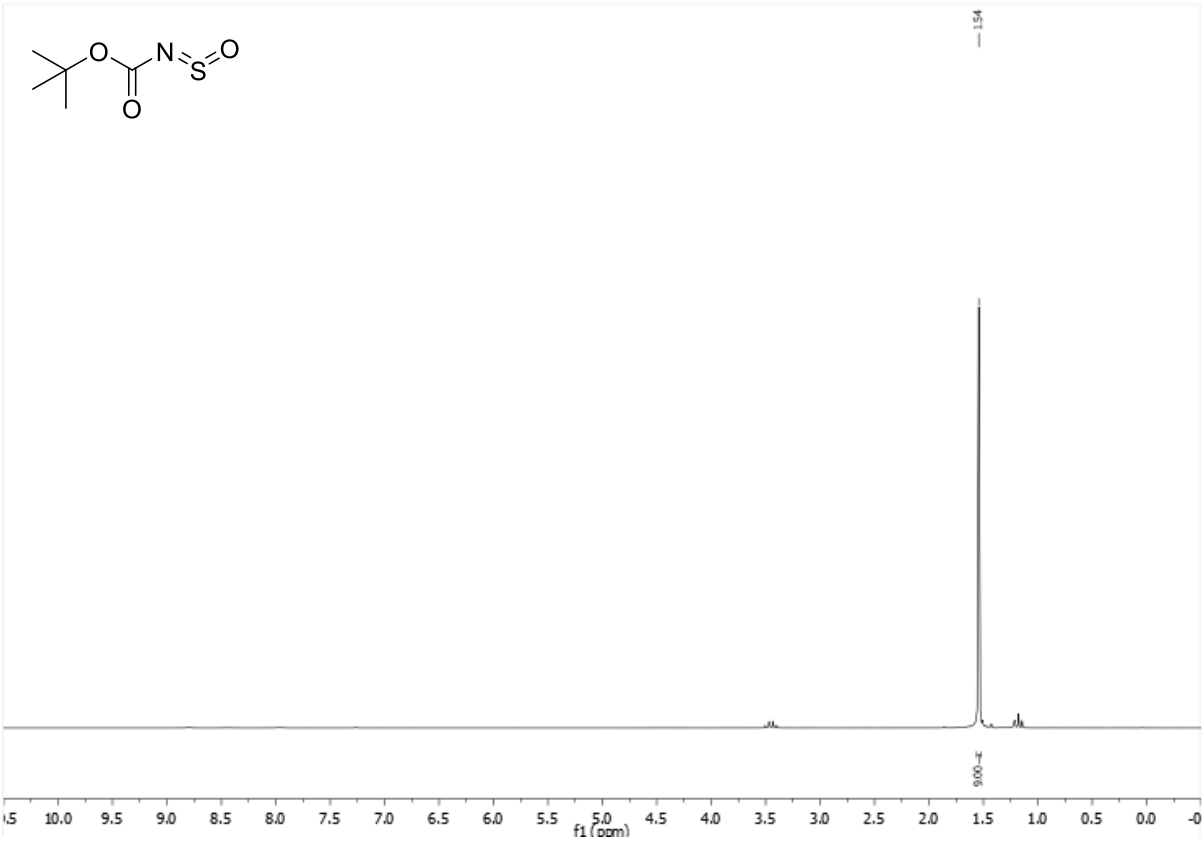
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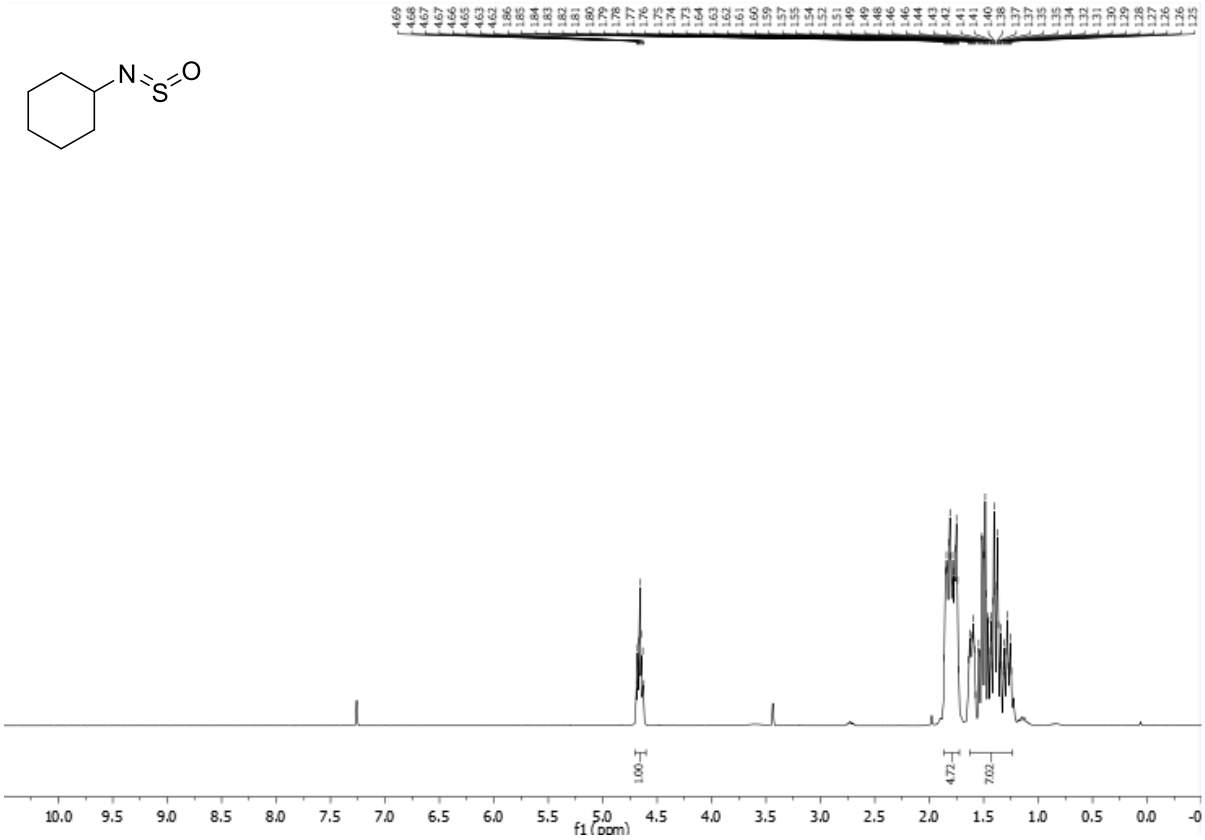
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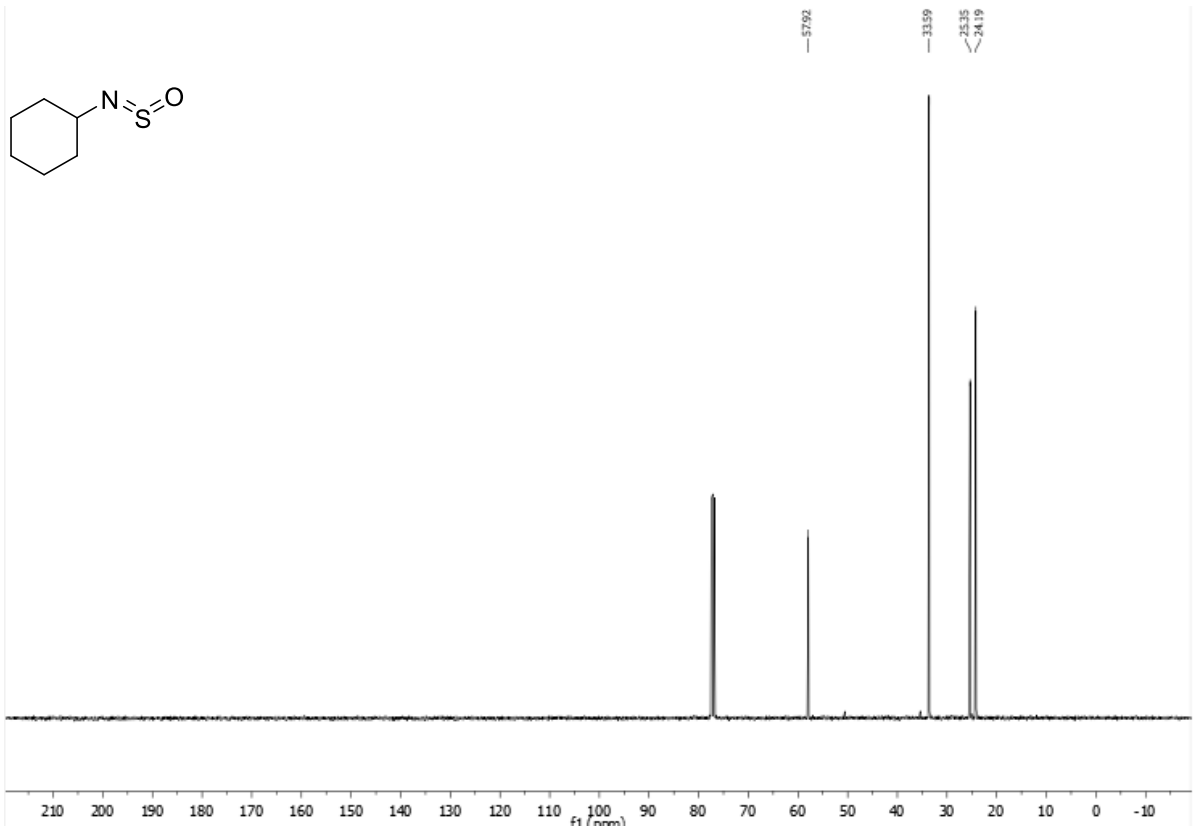
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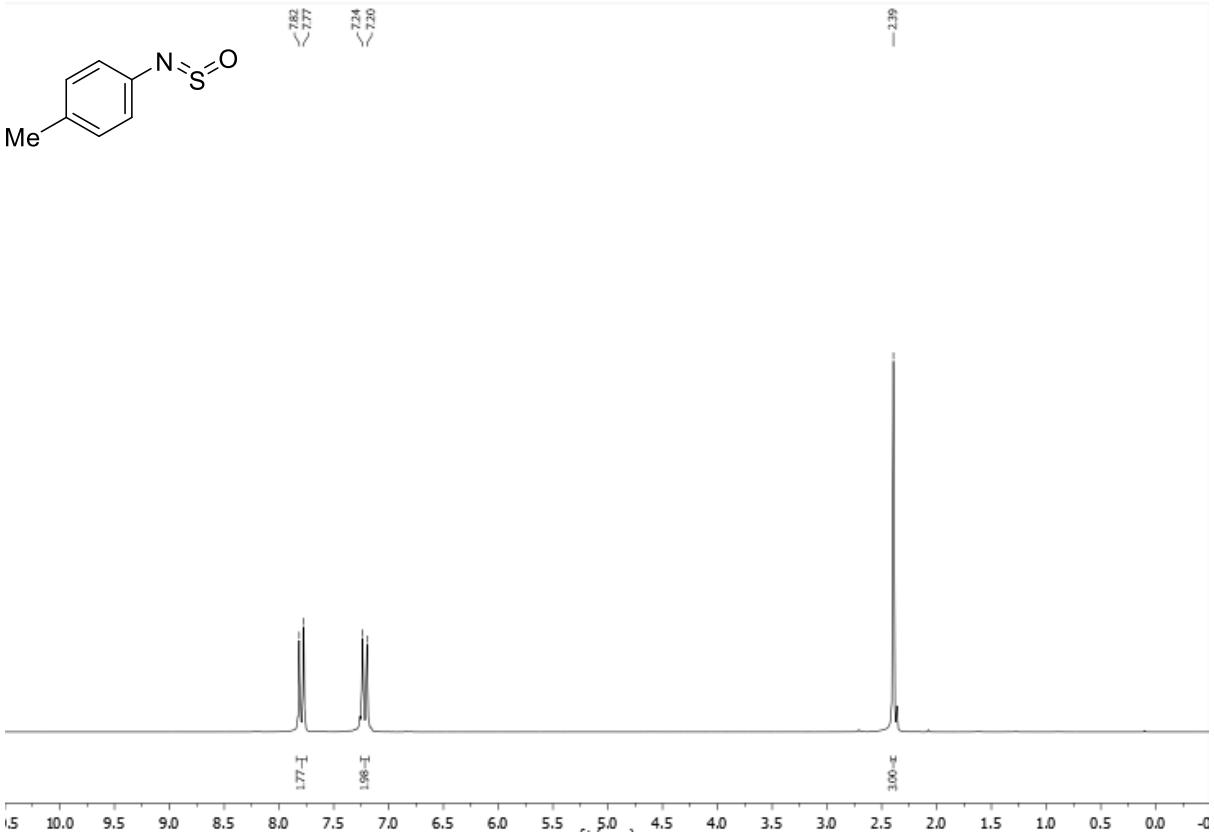
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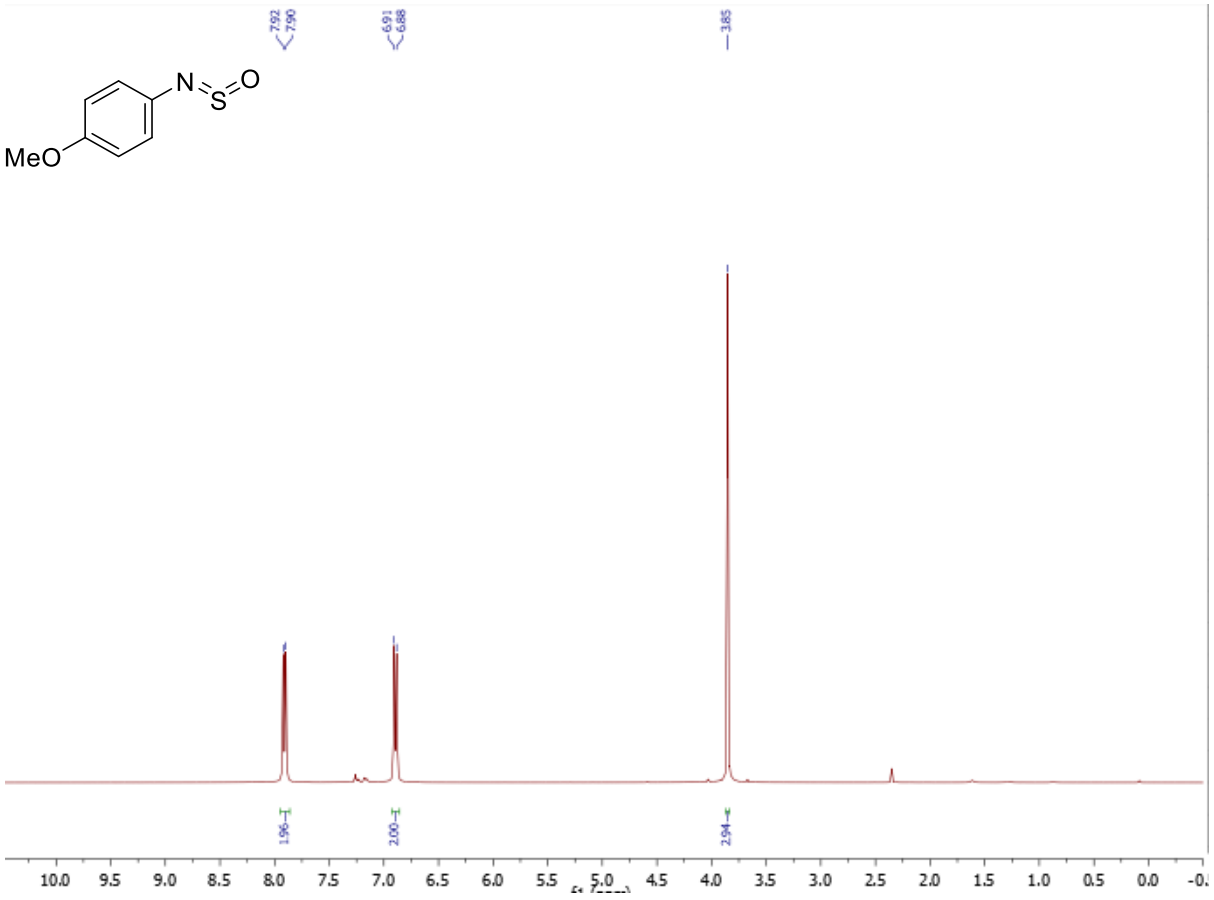
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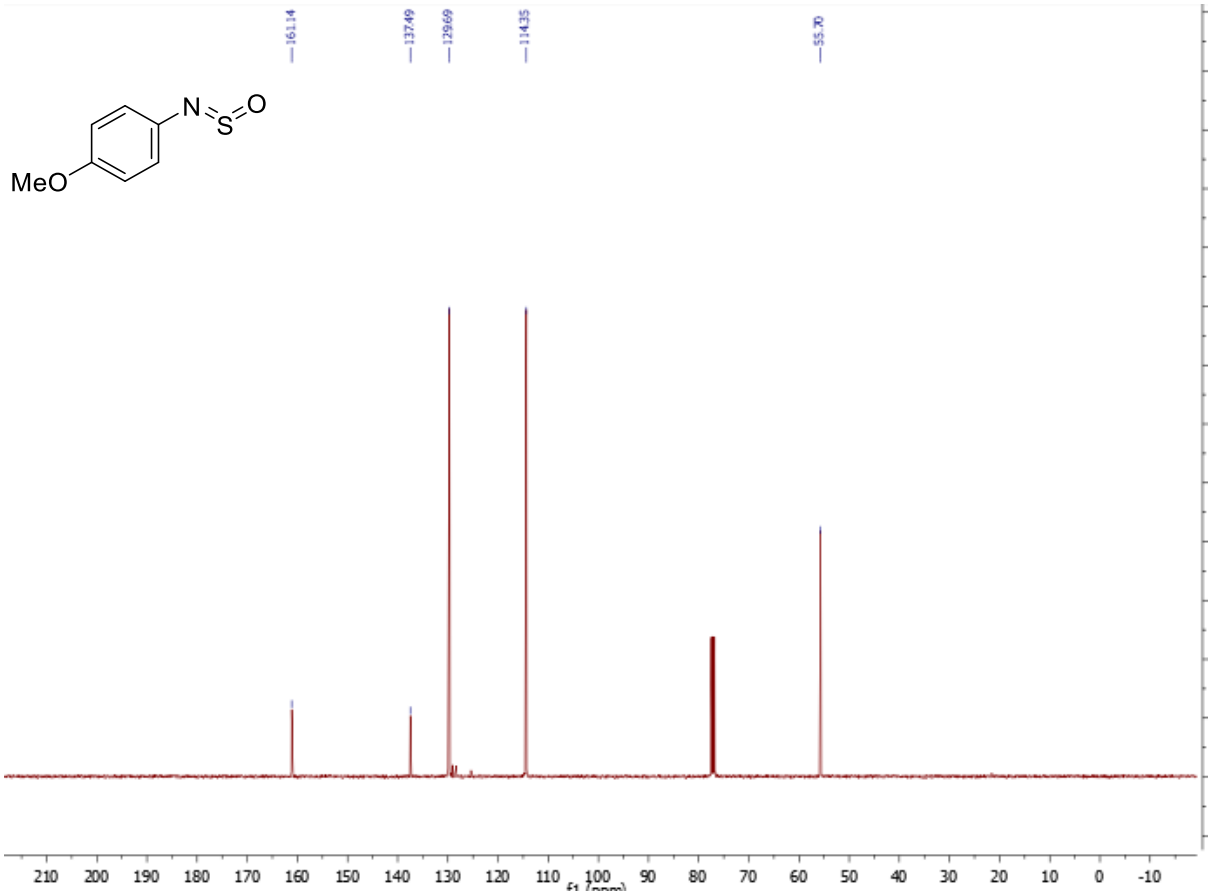
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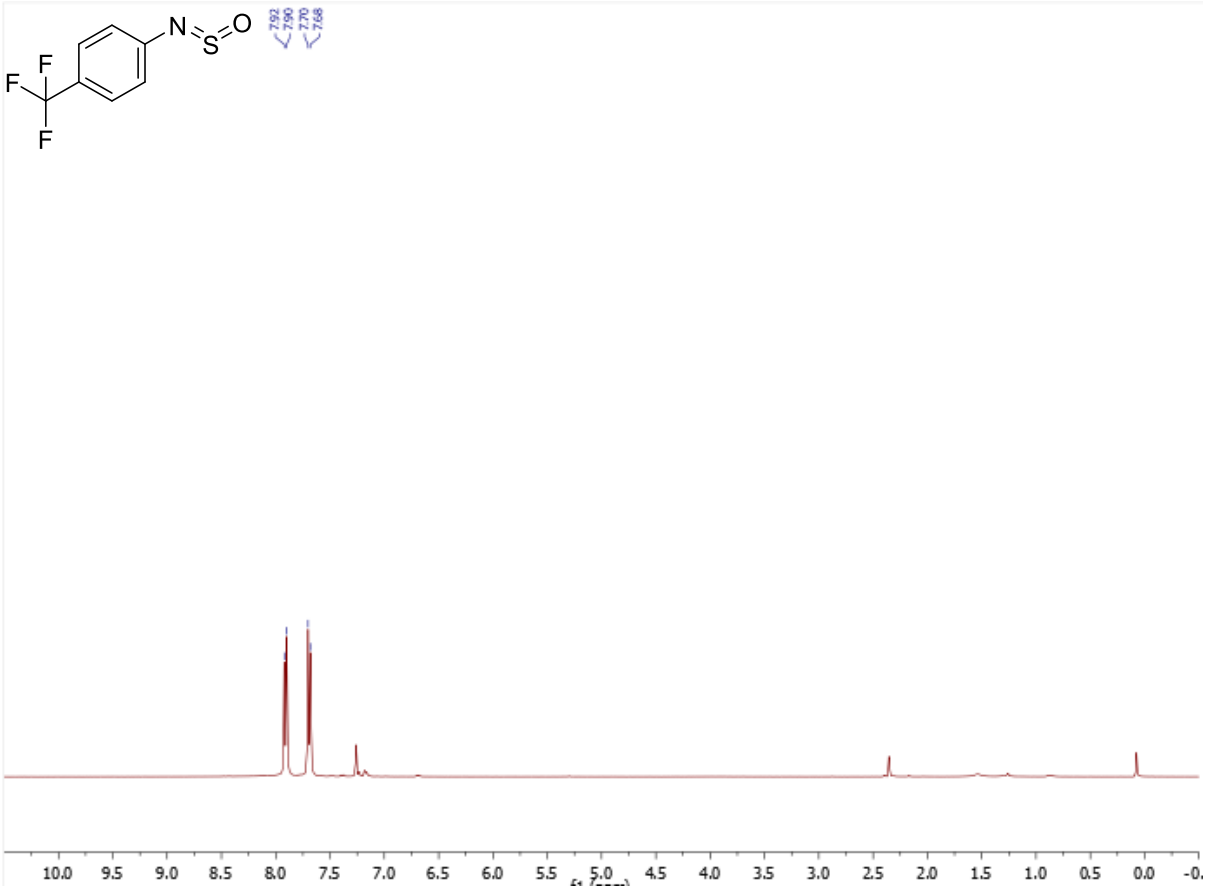
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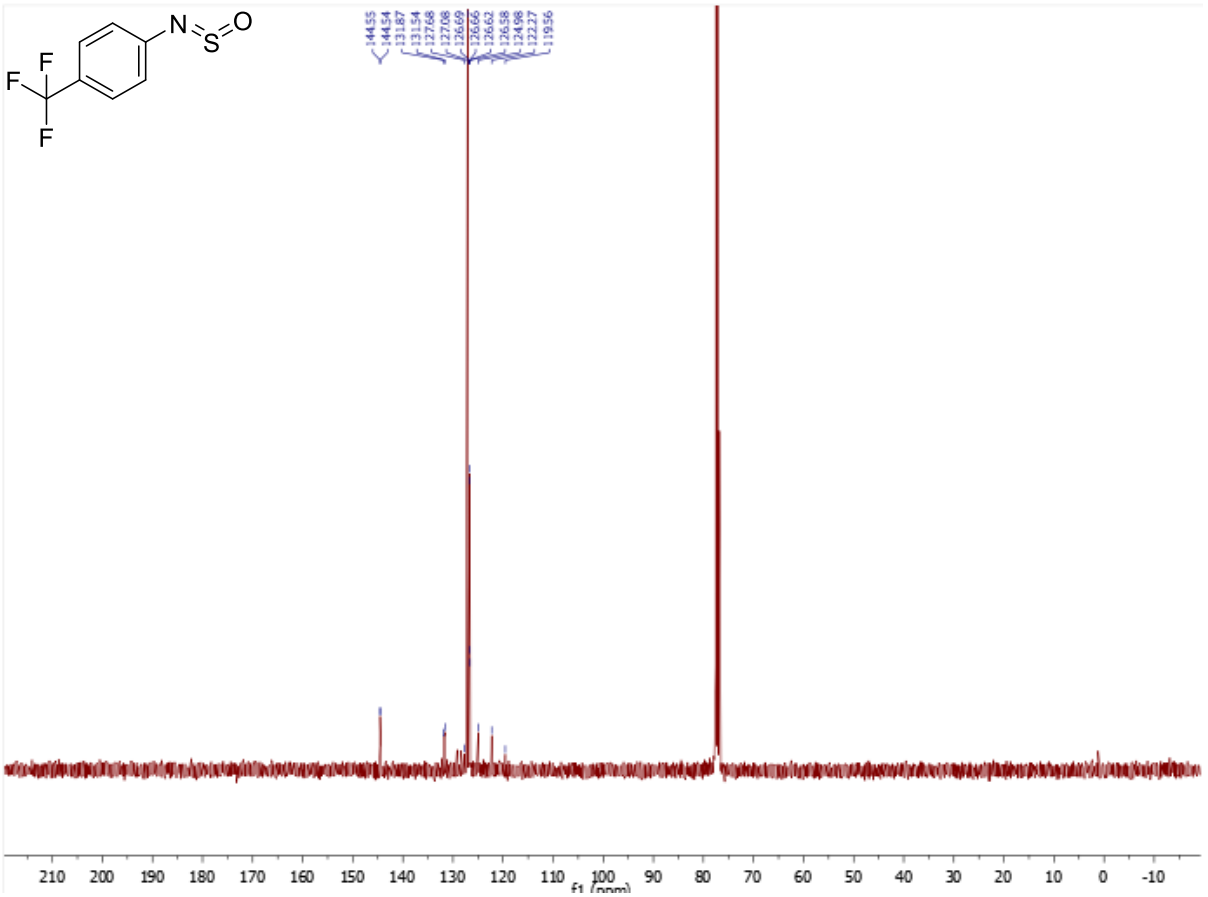
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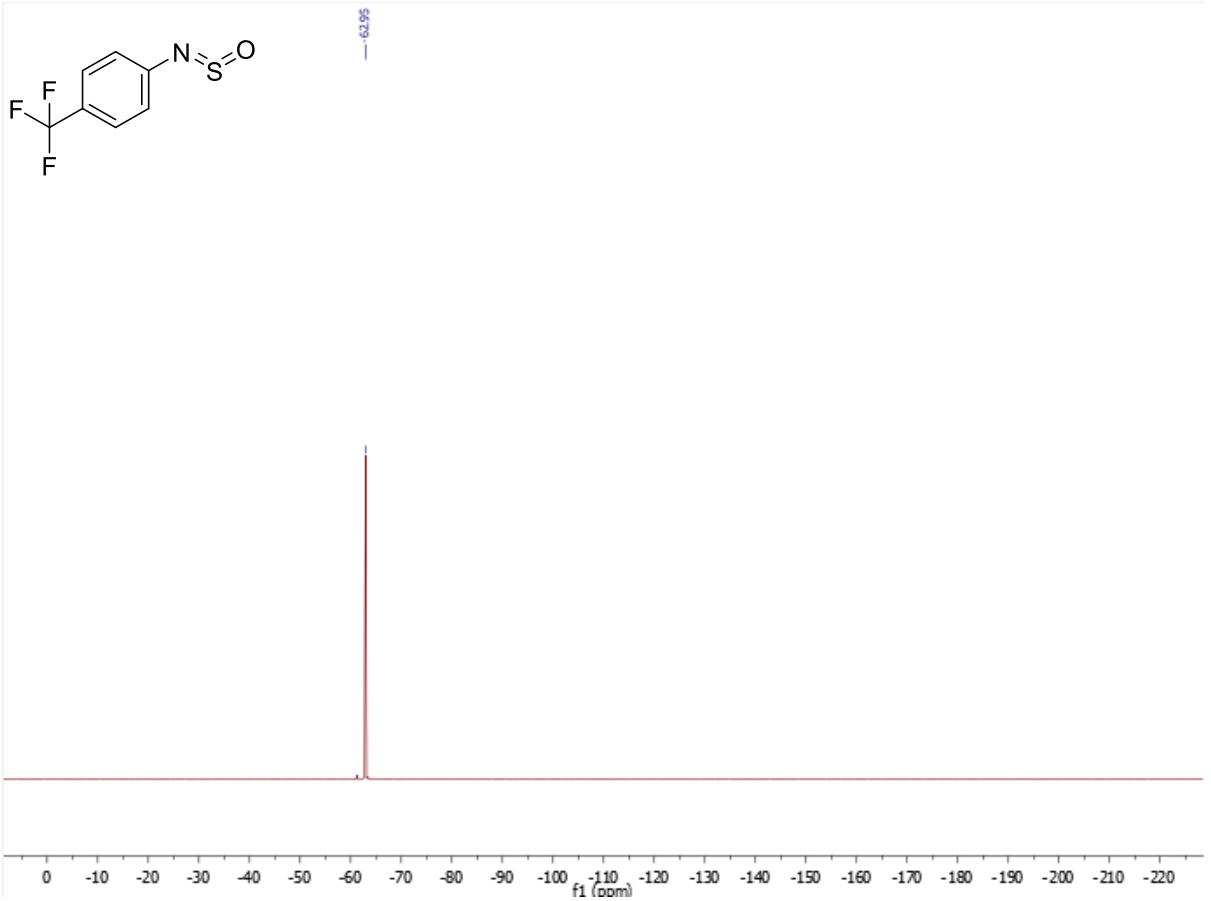
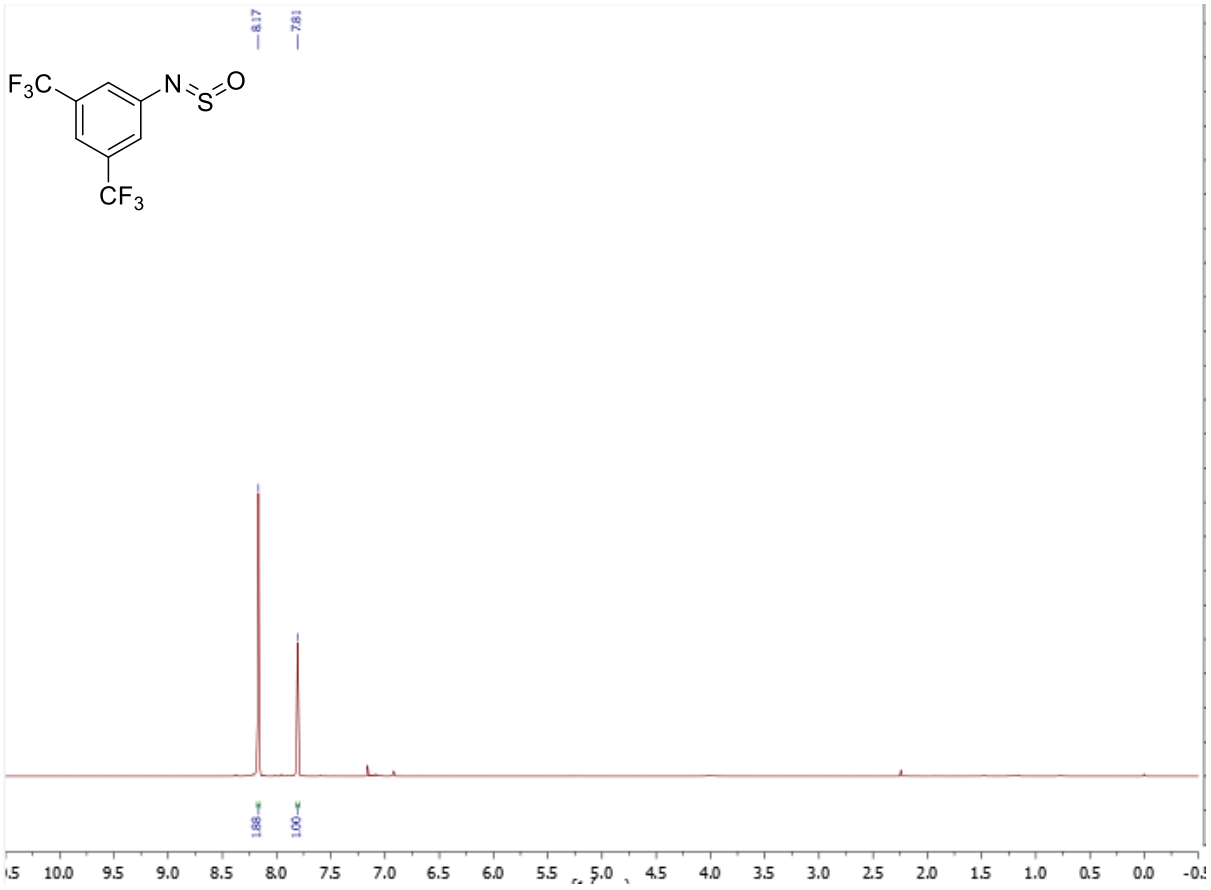
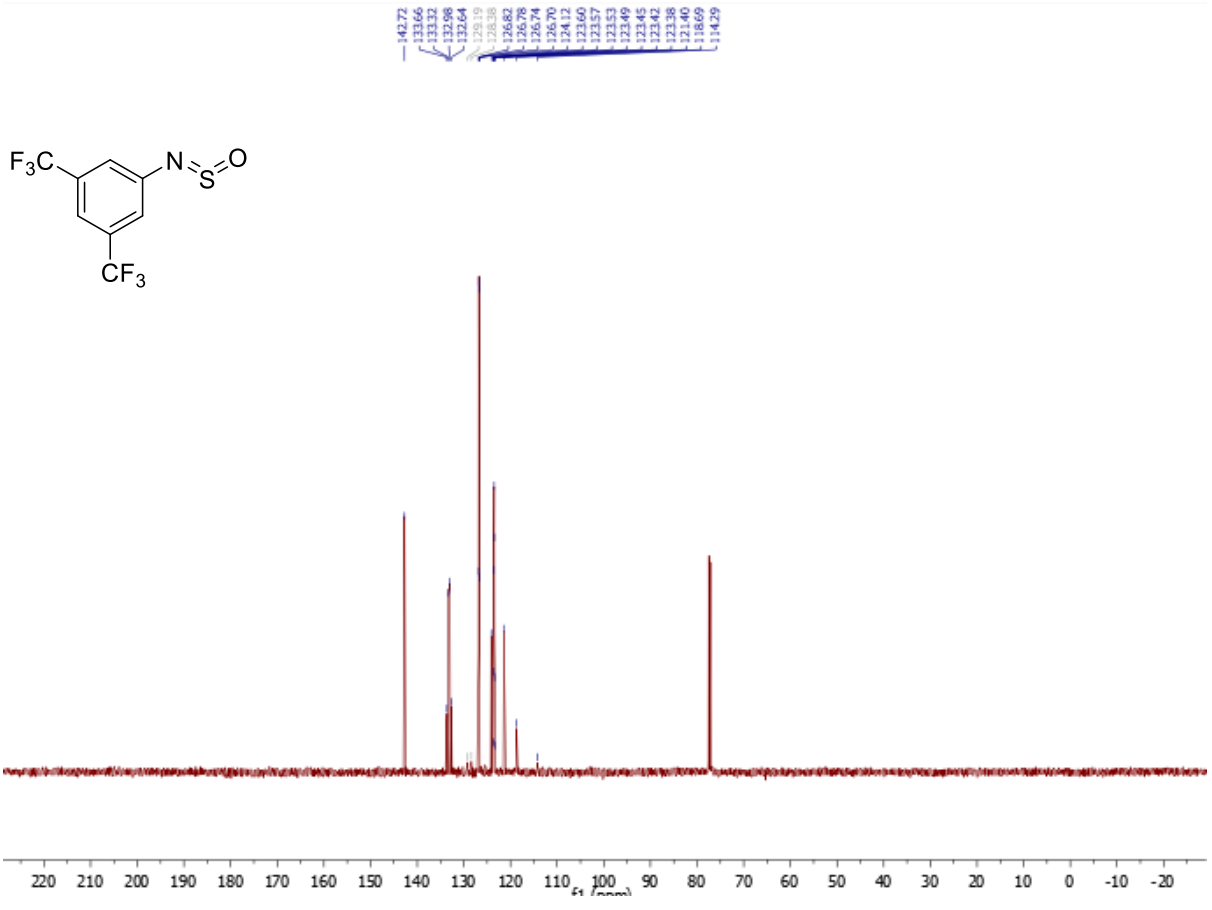
f1 (ppm)


-62.95
F
F
F
N
S
O
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)


8.17
7.81
F3C
N
S
O
CF3
1.88
1.00
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


142.72
133.66
133.32
132.98
132.64
129.19
128.38
126.82
126.78
126.74
126.70
124.12
123.60
123.57
123.53
123.49
123.45
123.42
123.38
121.40
118.69
114.29
F3C
N
S
O
CF3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
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50
40
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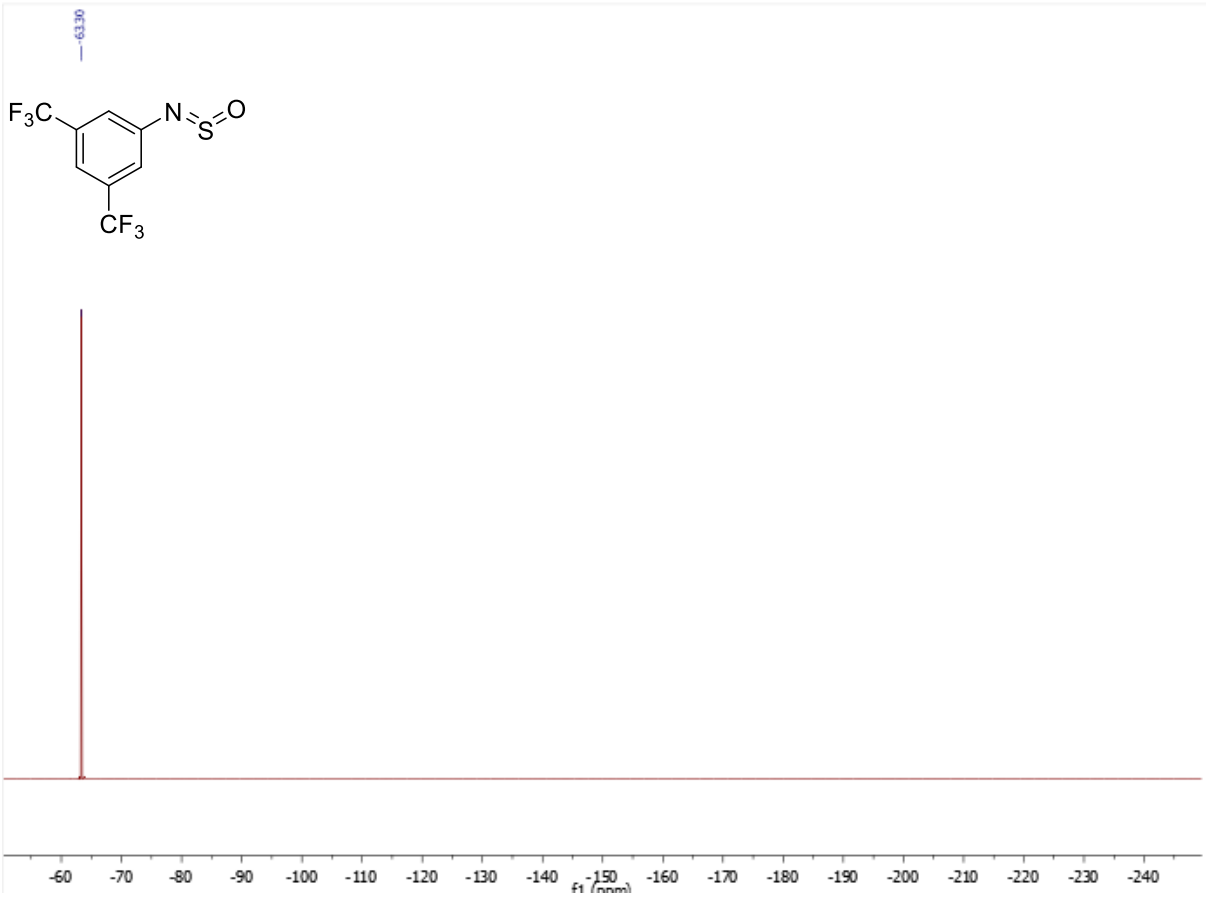
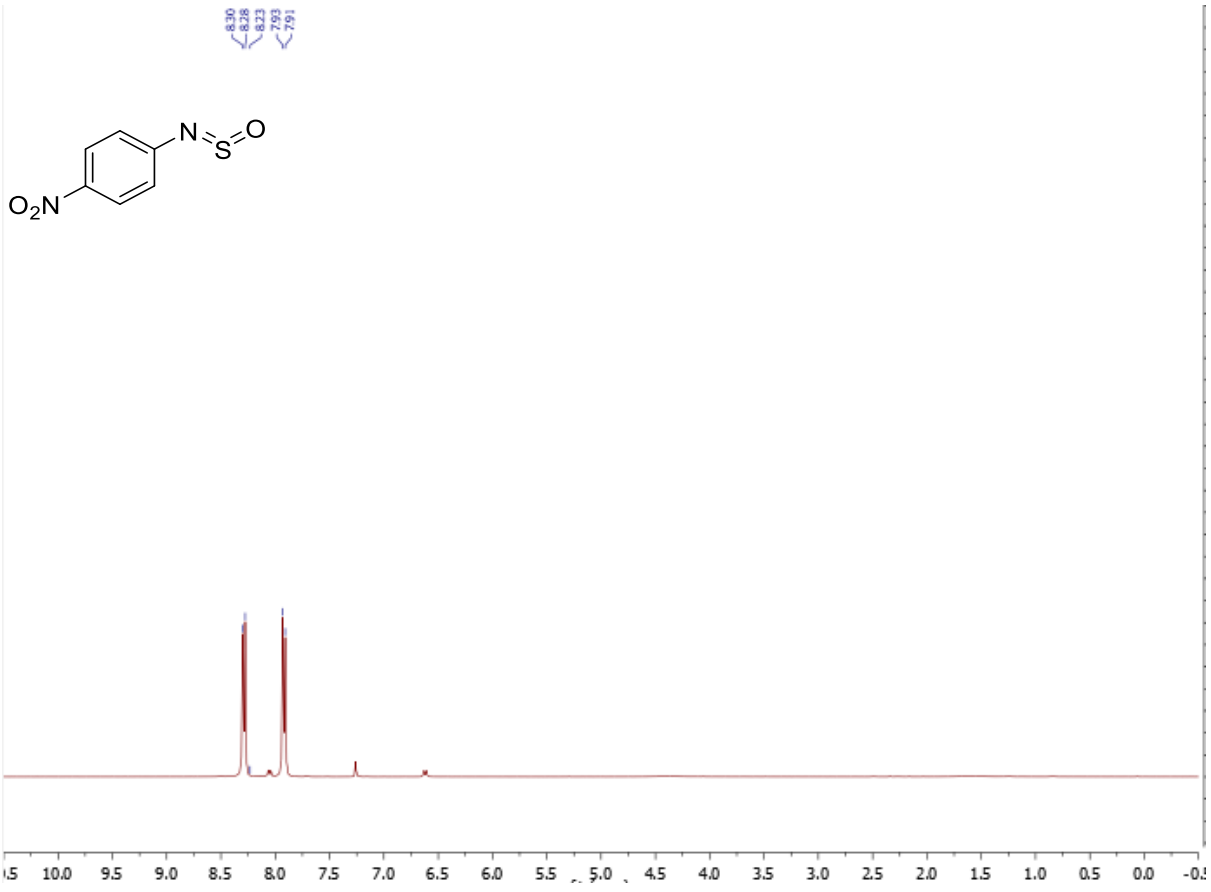
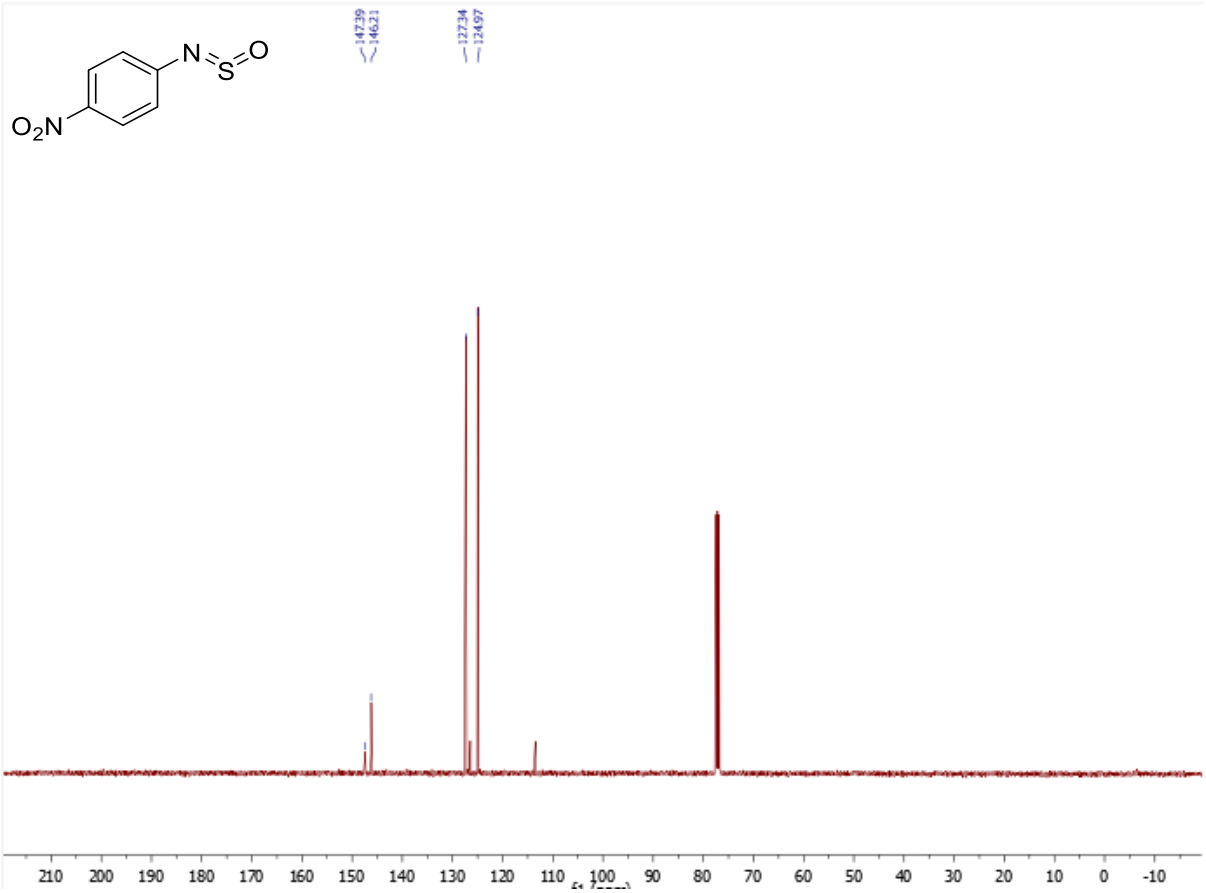
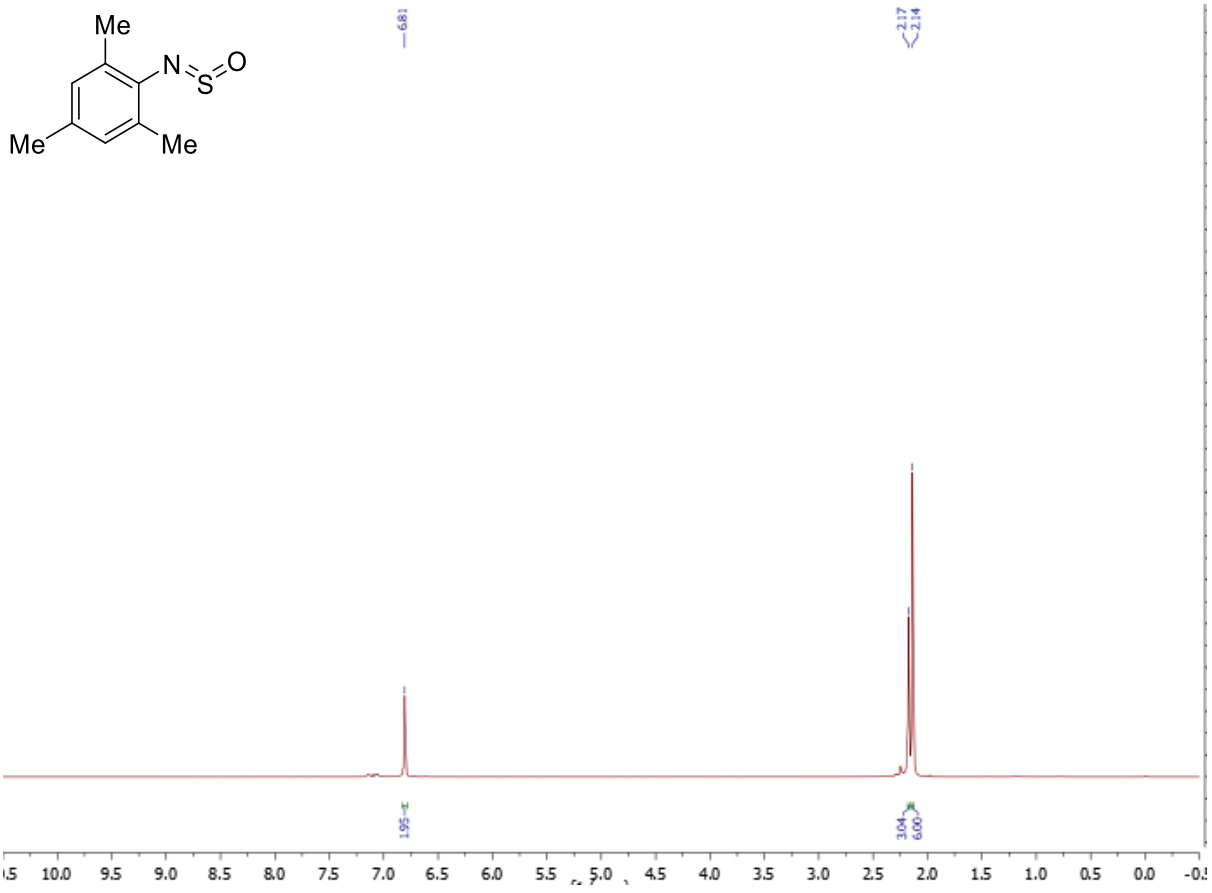
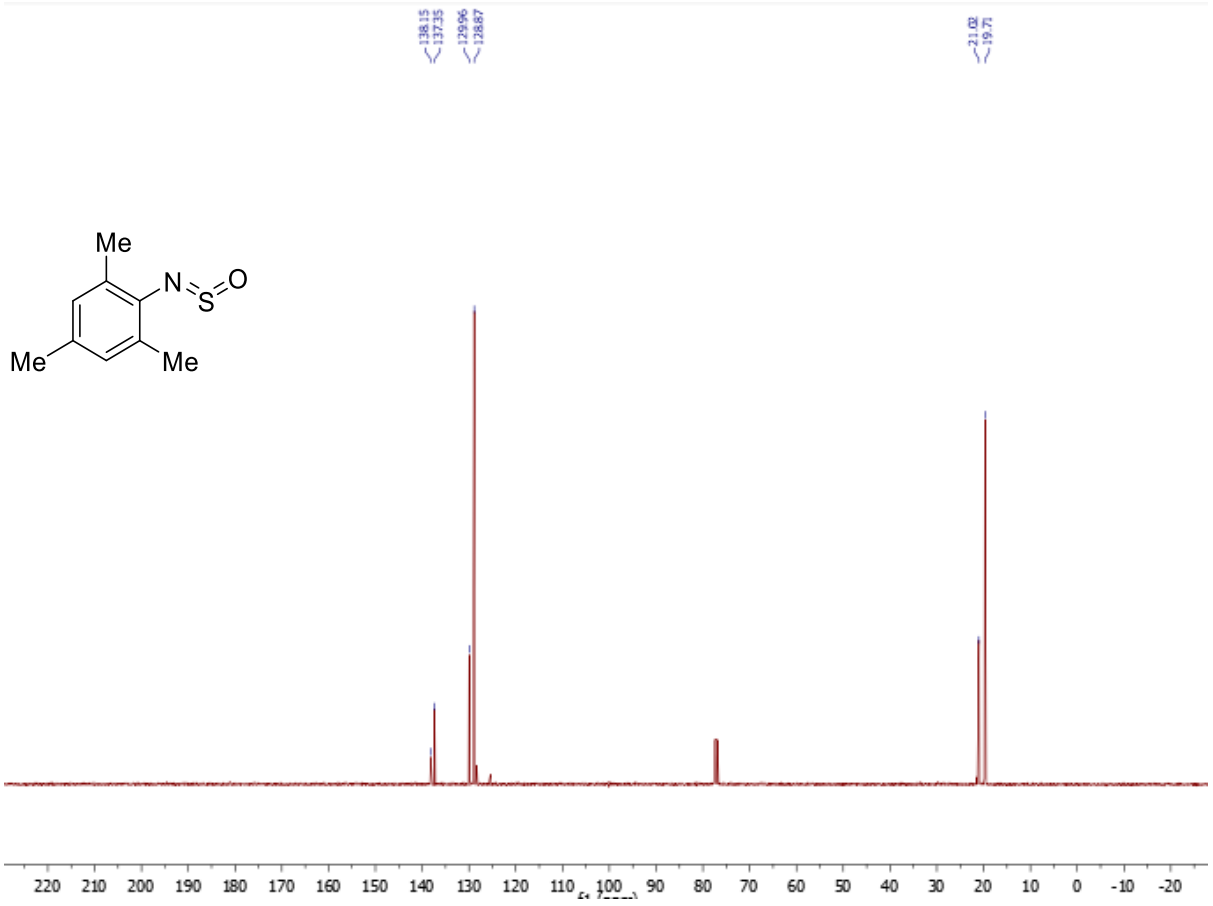
10
0
-10
-20

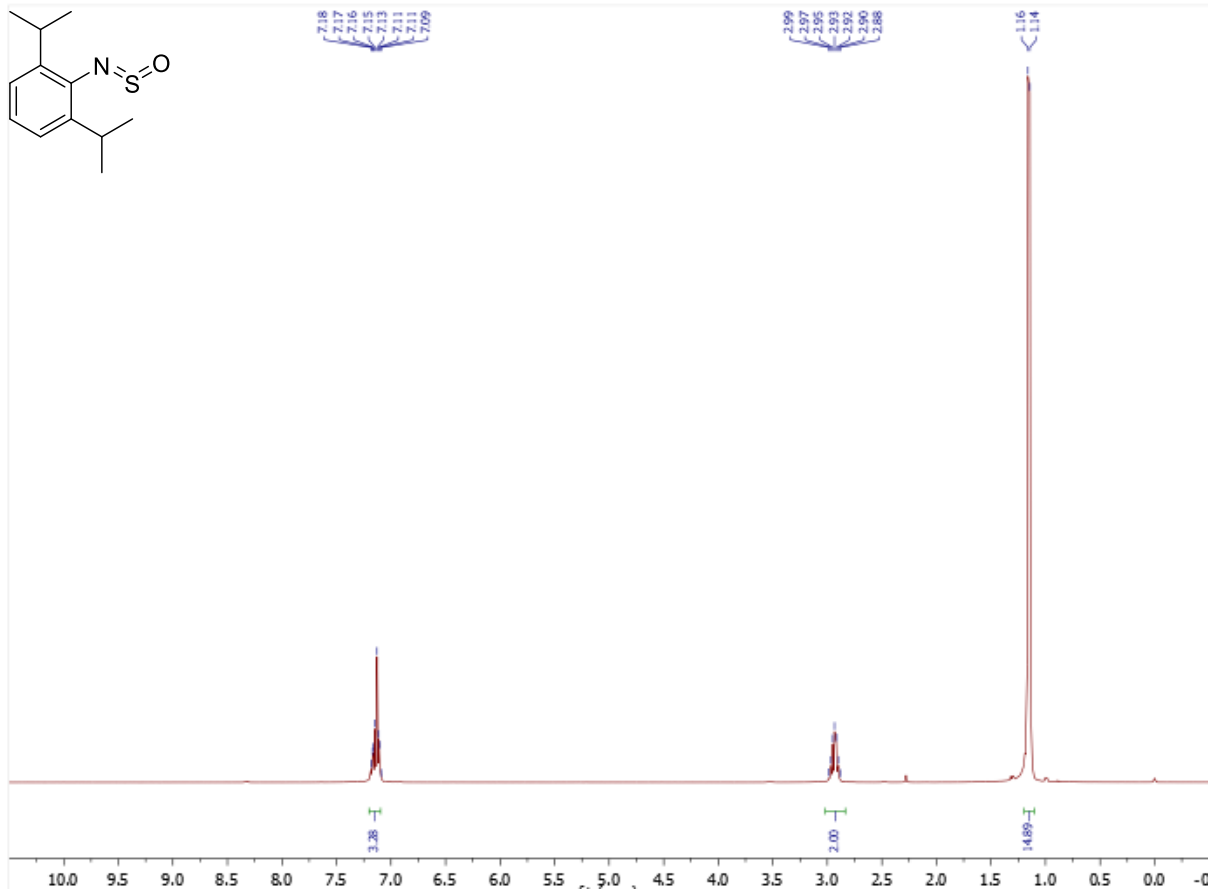

-63.30
F3C
N
S
O
CF3
-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

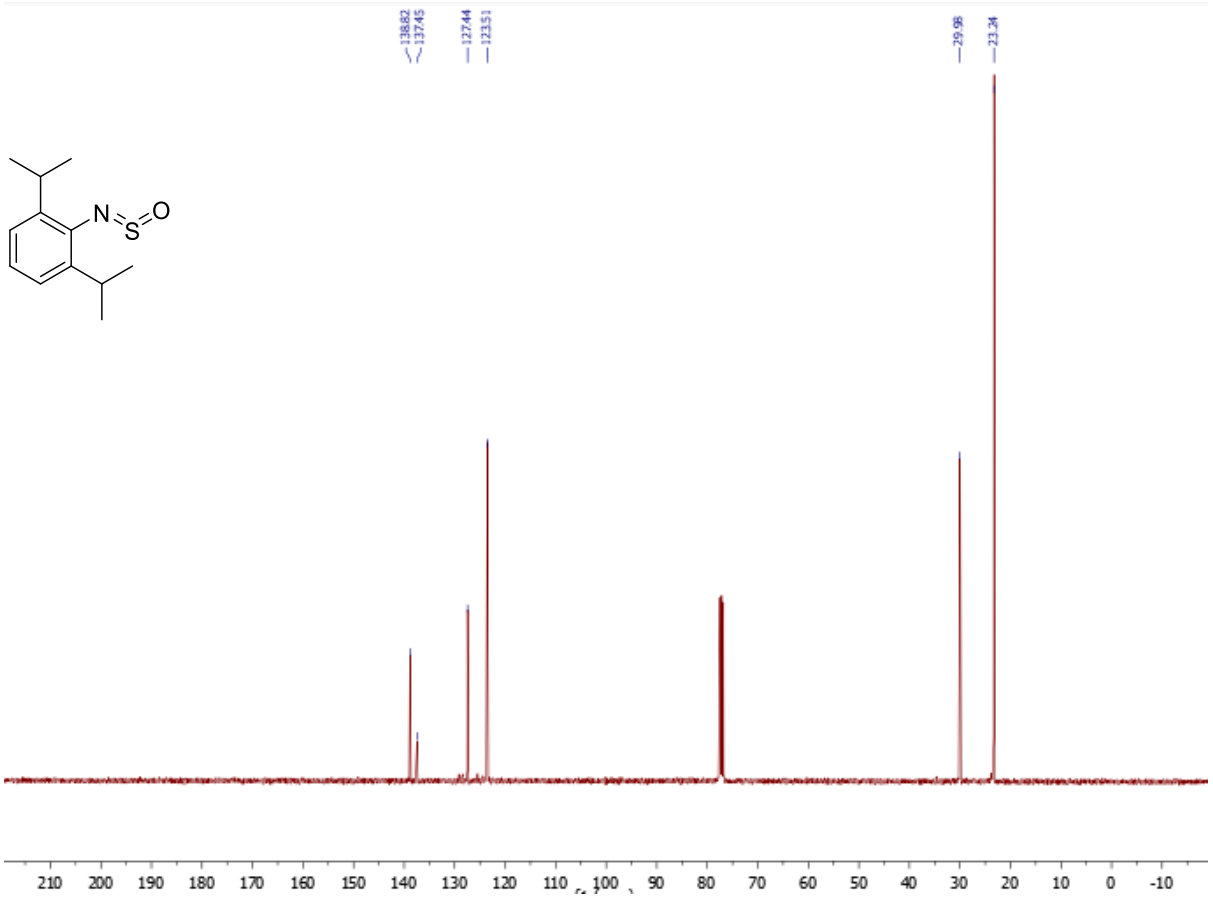

8.30
8.28
8.23
7.93
7.91
N
S
O
O2N
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

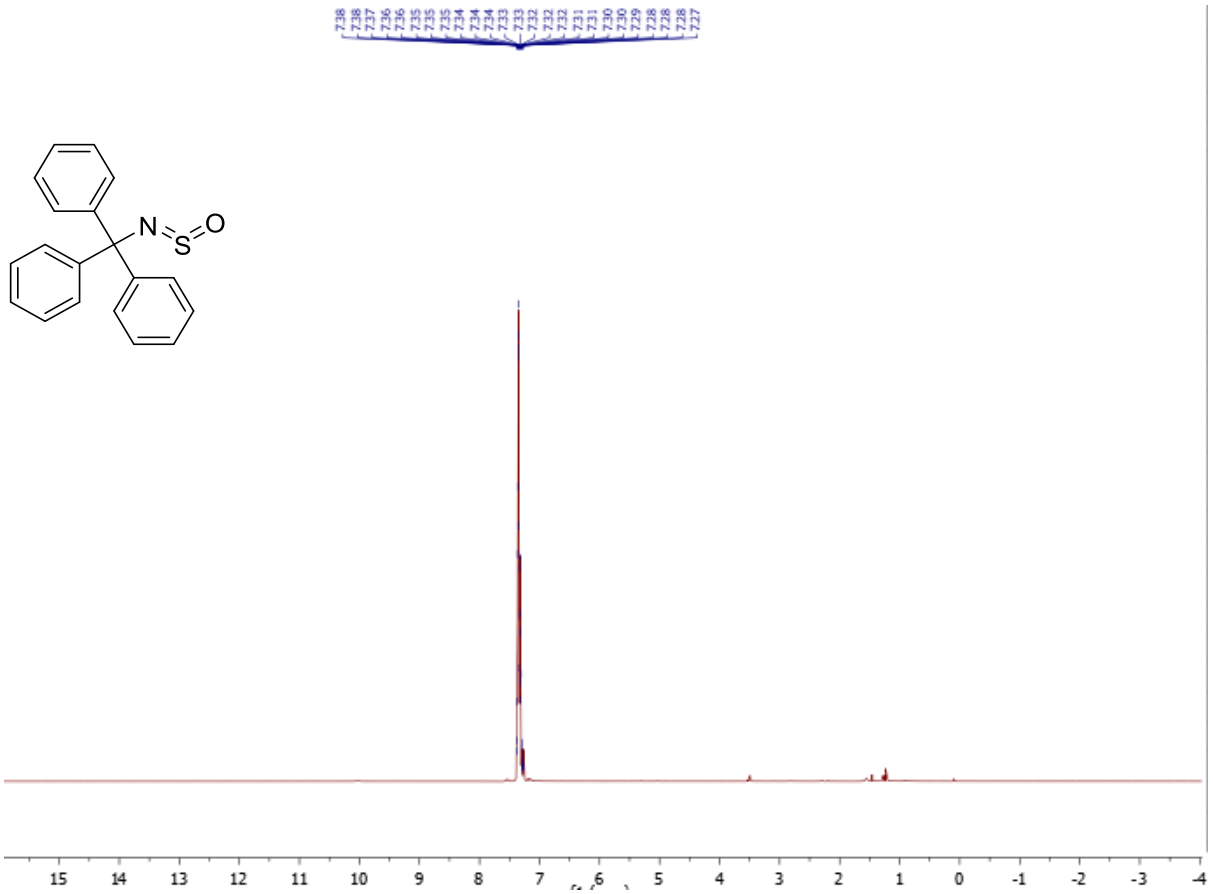

147.39
146.21
127.34
124.97
O2N
N
S
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

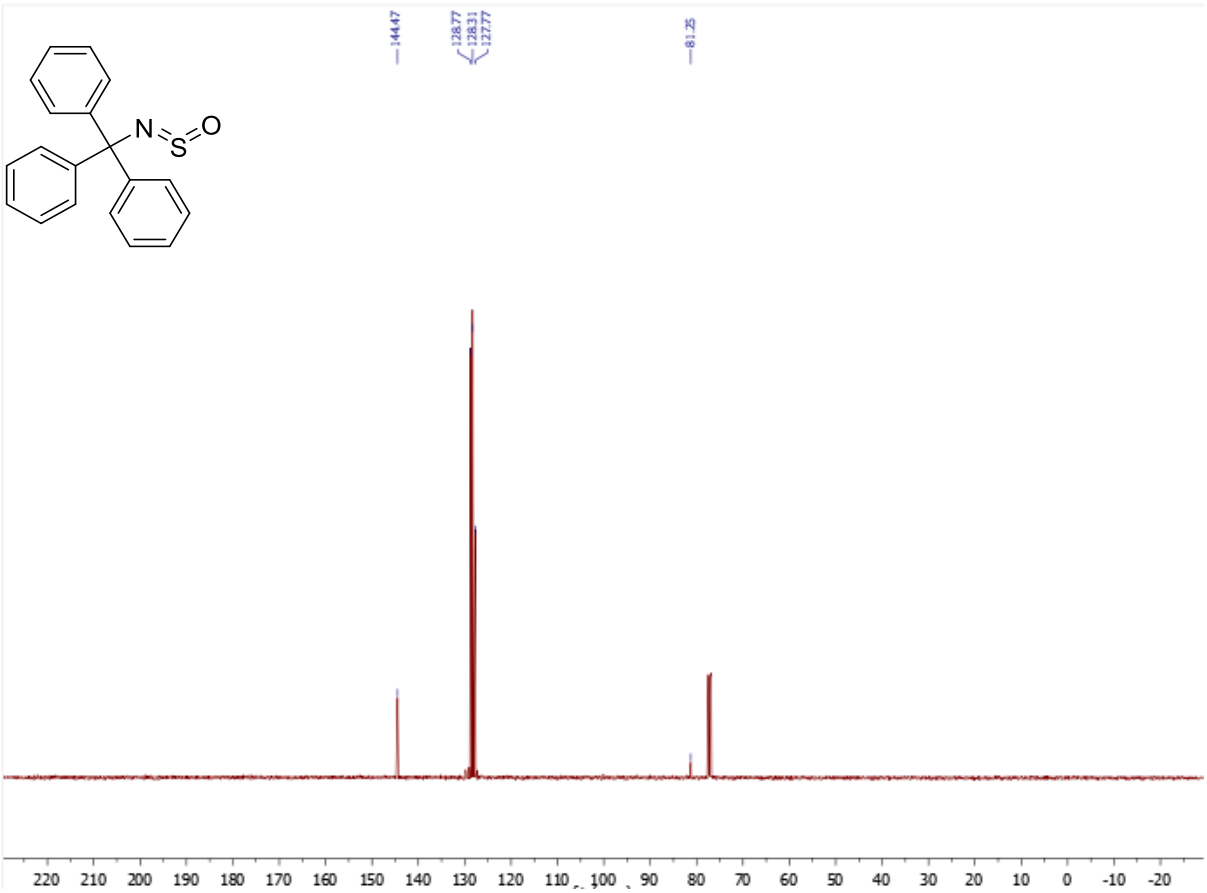

Me
N
S
O
Me
Me
6.81
2.17
2.14
1.95
3.04
6.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

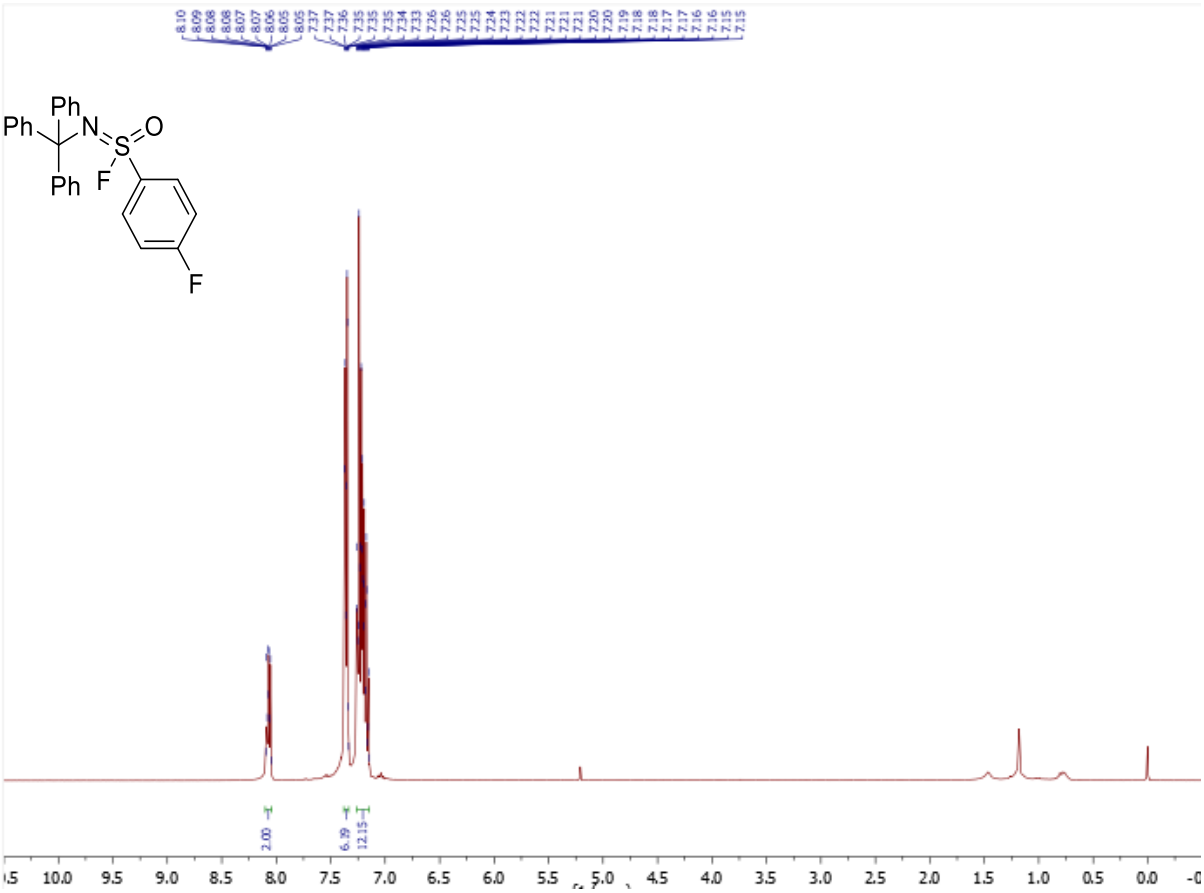

Me
N
S
O
Me
Me

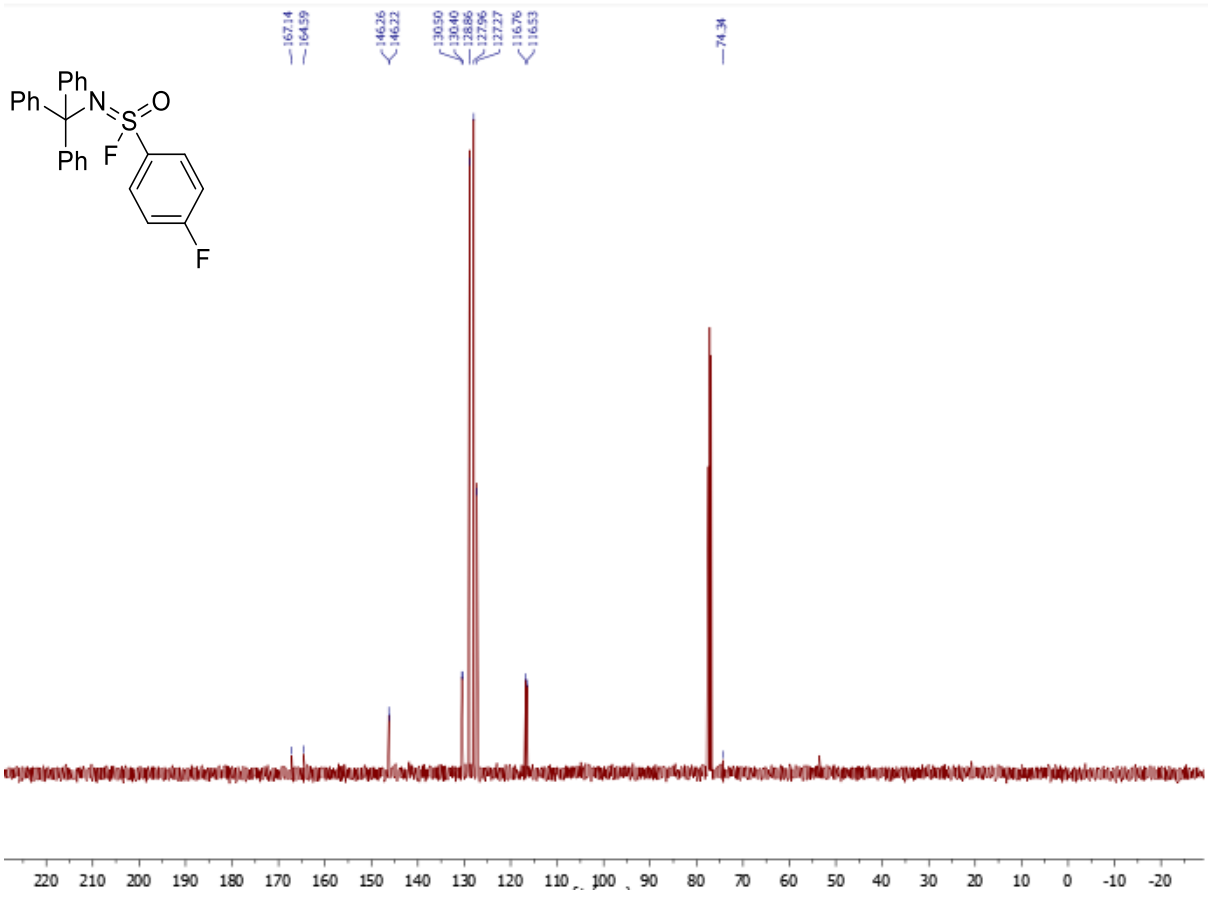

N
S
O

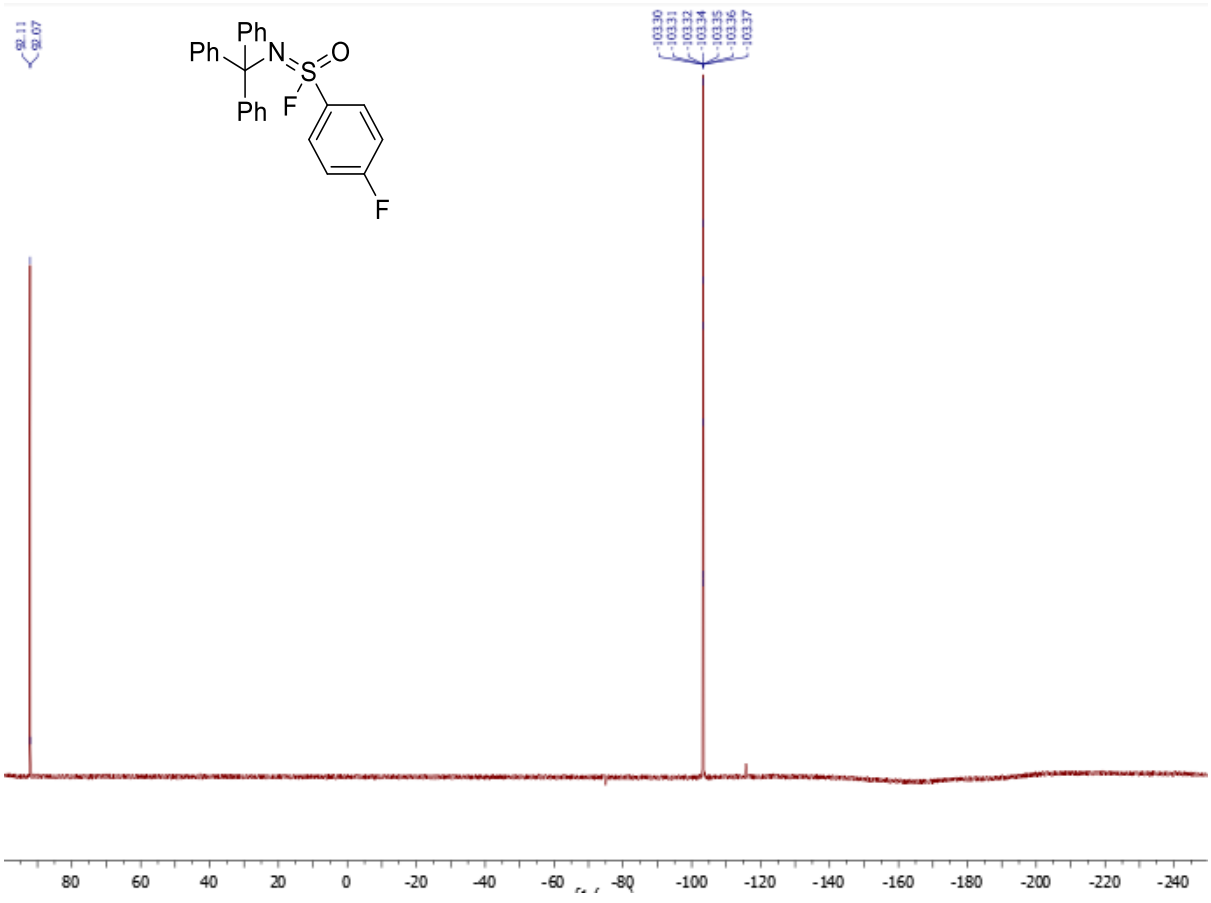

138.62
137.45
127.44
123.51
29.98
23.24
N
S
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

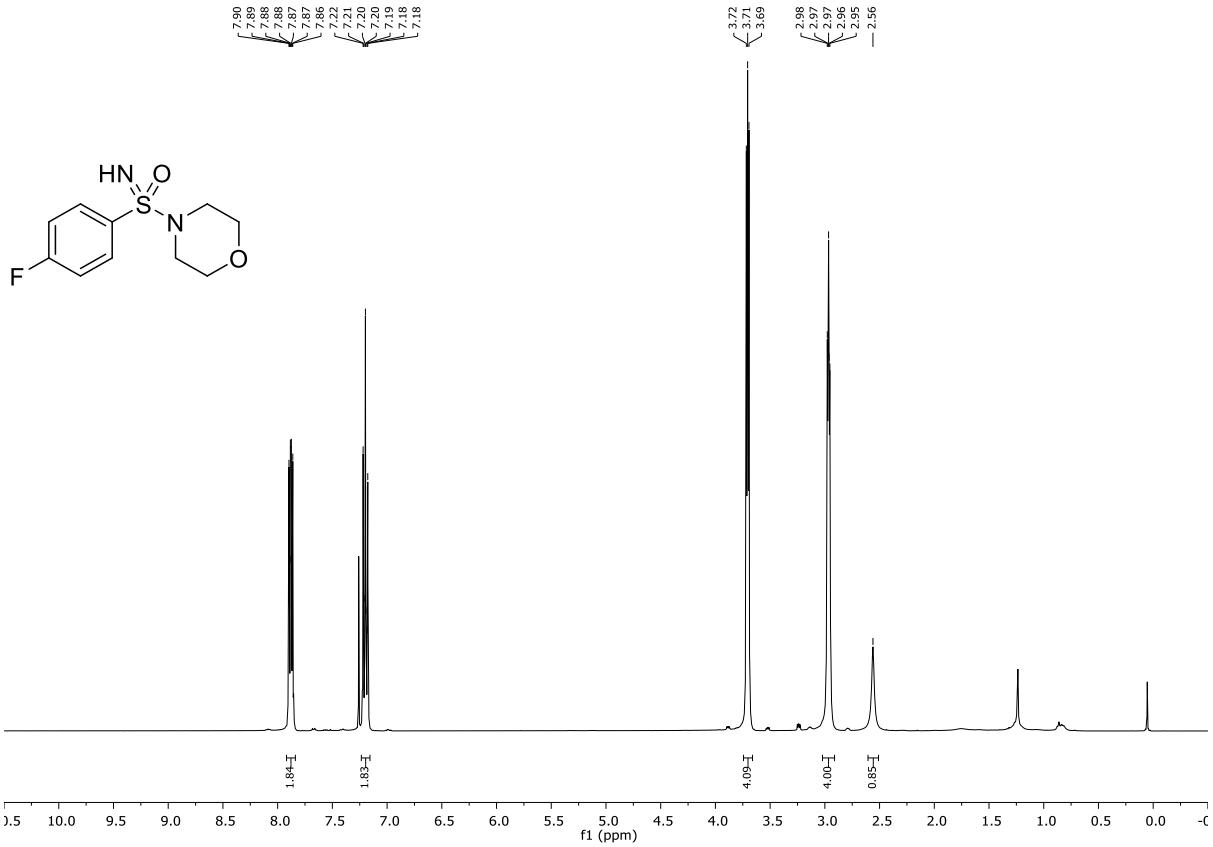

N
S
O
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4

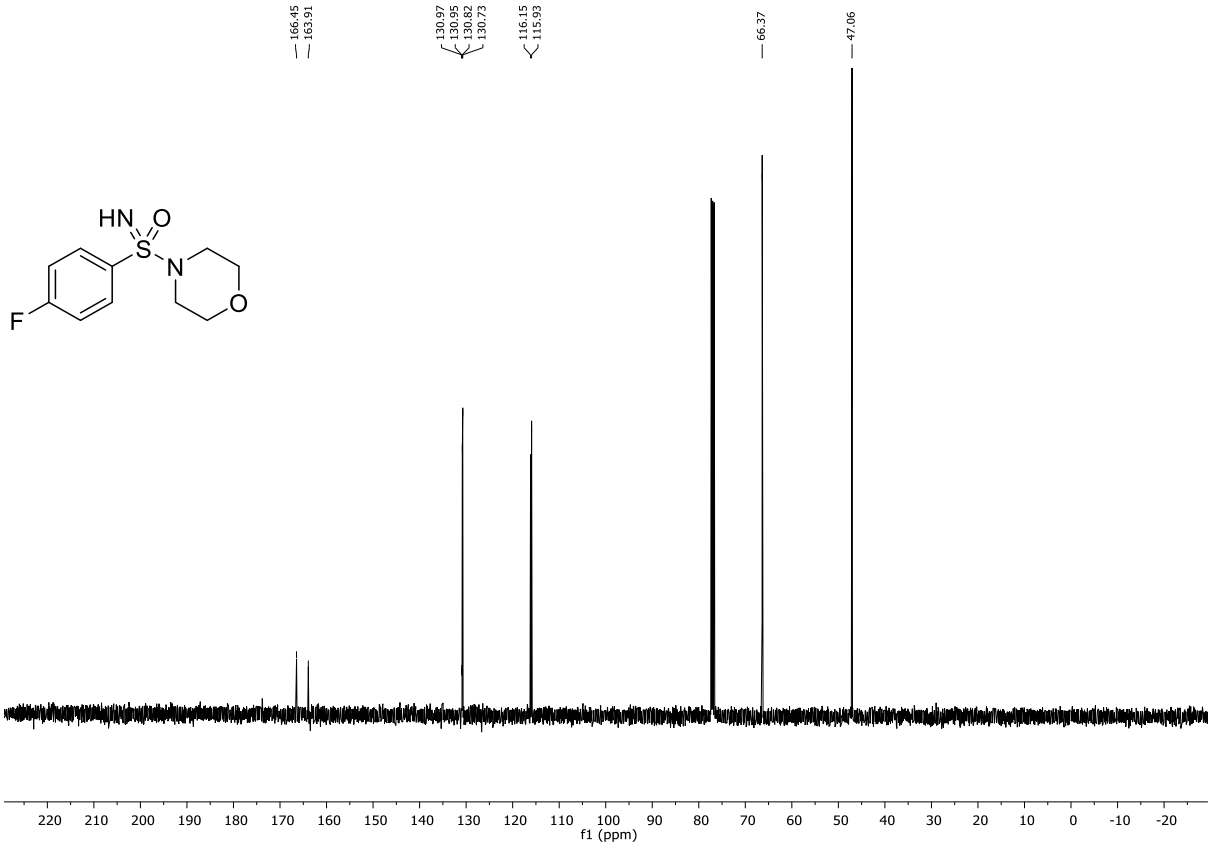

144.47
128.77
128.31
127.77
81.25
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

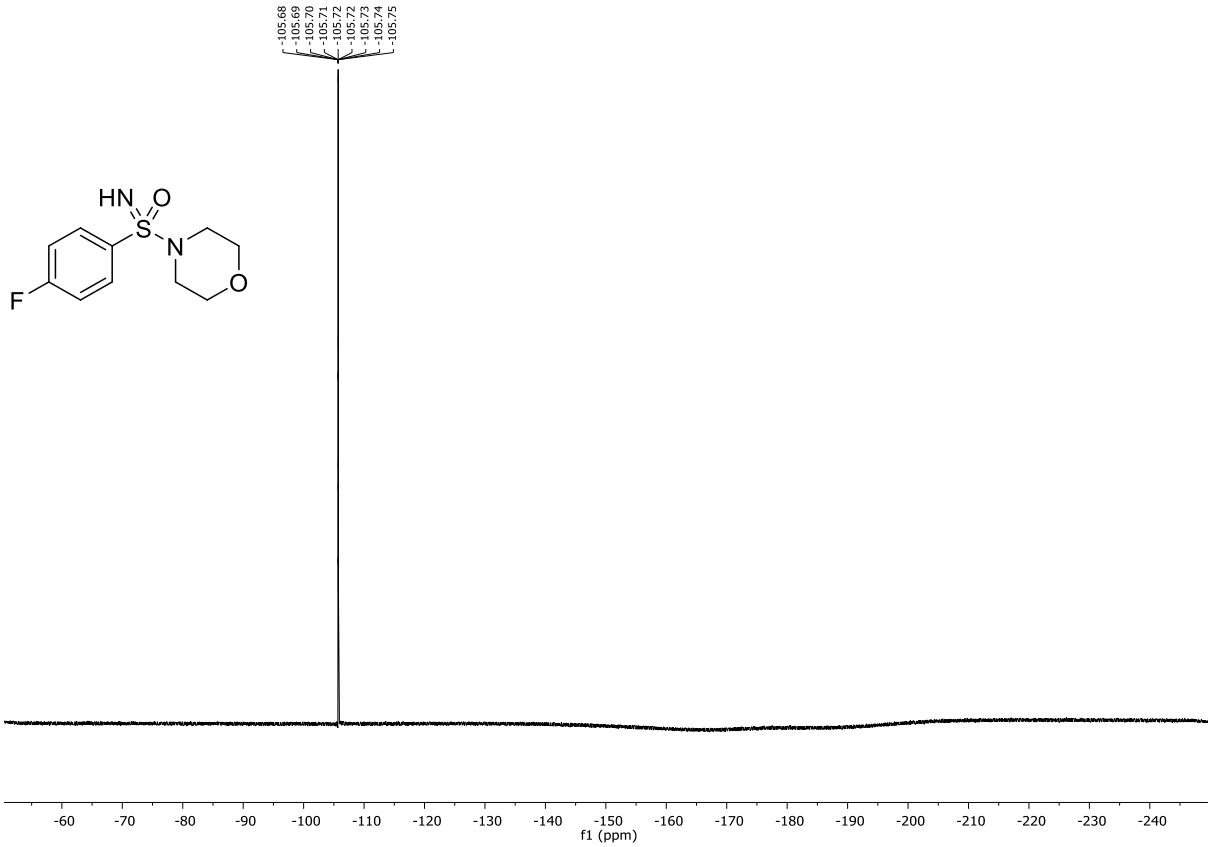

Ph
Ph
Ph
N
S
O
F
F
2.00
6.39
12.15
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


Ph
Ph
N
S
O
F
Ph
F
167.14
164.59
146.26
146.22
130.50
130.40
128.86
127.96
127.27
116.76
116.53
74.34
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


Ph
Ph
N
S
O
F
Ph
F
91.11
91.07
-103.30
-103.31
-103.32
-103.34
-103.35
-103.36
-103.37
80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240


7.90
7.89
7.88
7.88
7.87
7.87
7.86
7.22
7.21
7.20
7.20
7.19
7.18
7.18
3.72
3.71
3.69
2.98
2.97
2.97
2.96
2.95
2.56
HN
O
S
N
O
F
1.84
1.83
4.09
4.00
0.85
f1 (ppm)


166.45
163.91
130.97
130.95
130.82
130.73
116.15
115.93
66.37
47.06
HN
O
S
N
O
F
f1 (ppm)


-105.68
-105.69
-105.70
-105.71
-105.72
-105.72
-105.73
-105.74
-105.75
HN
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O
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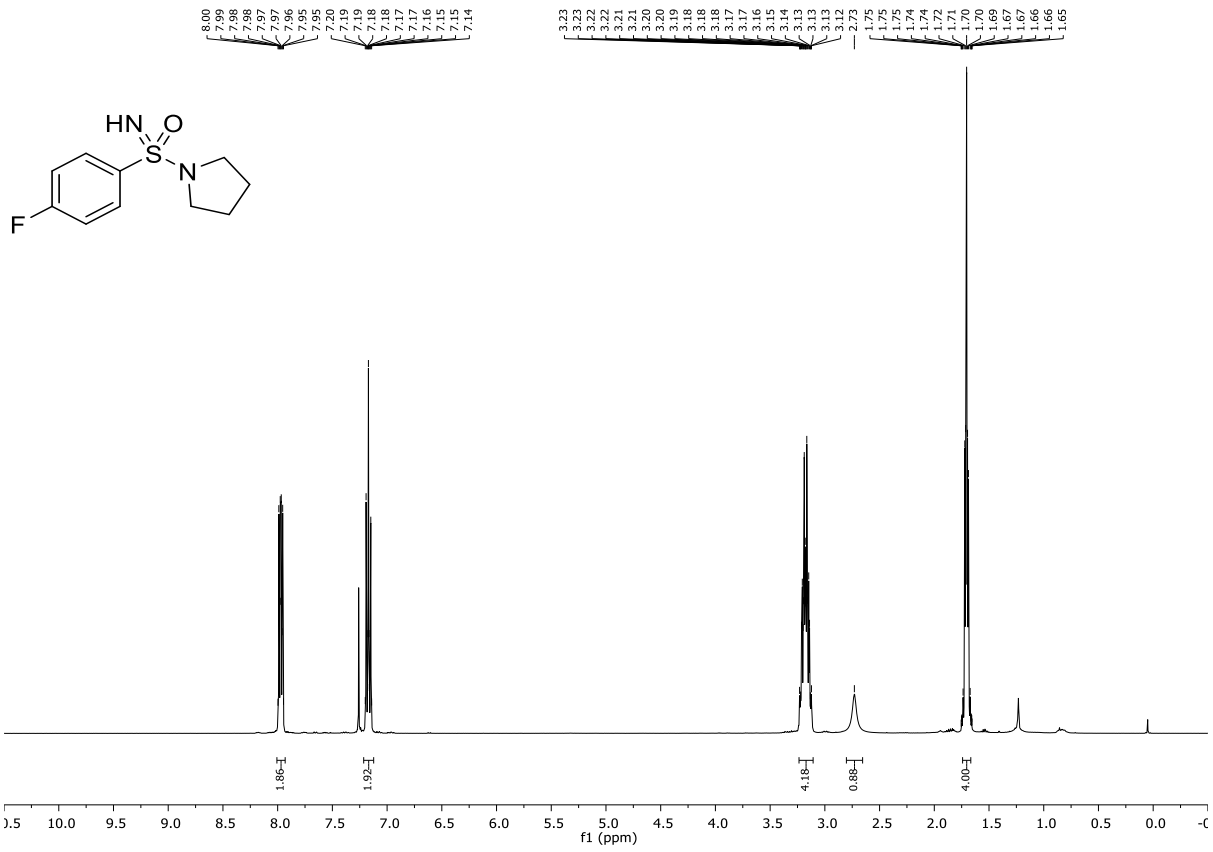
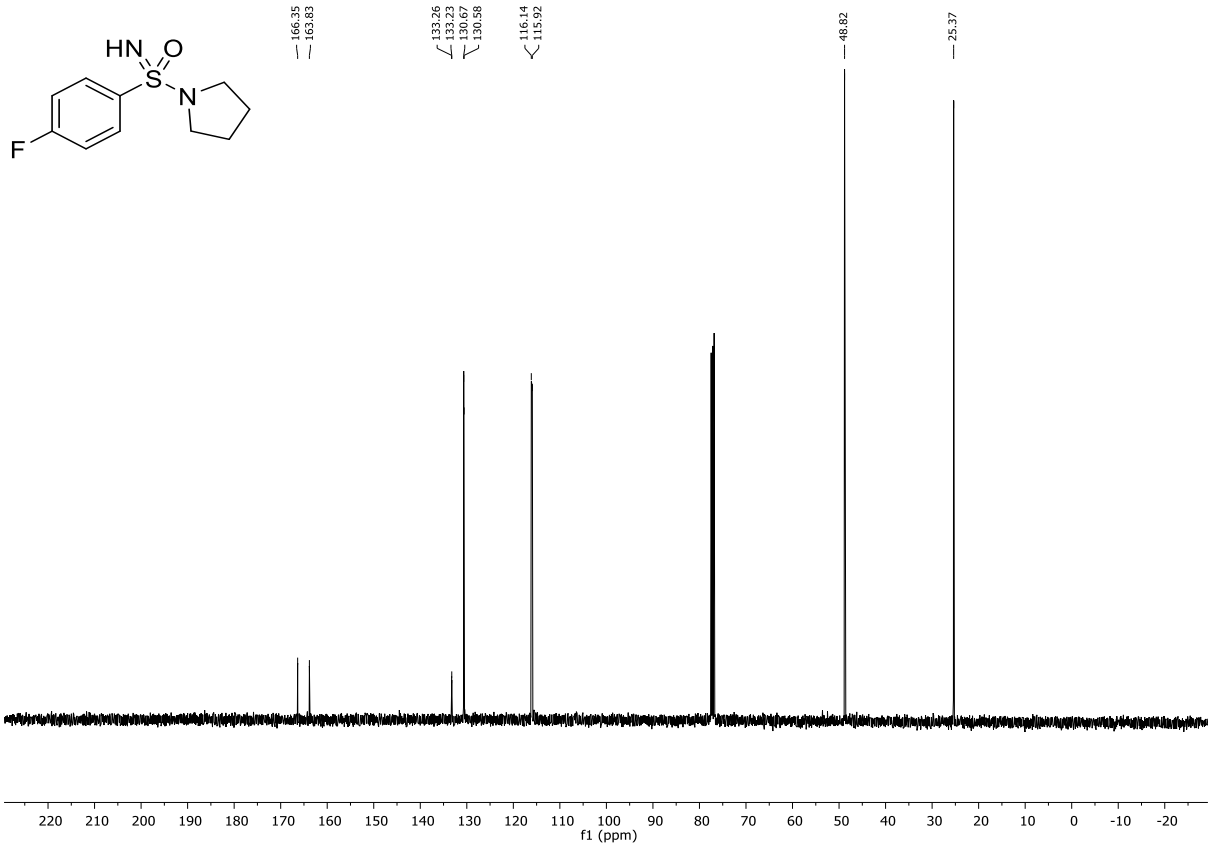
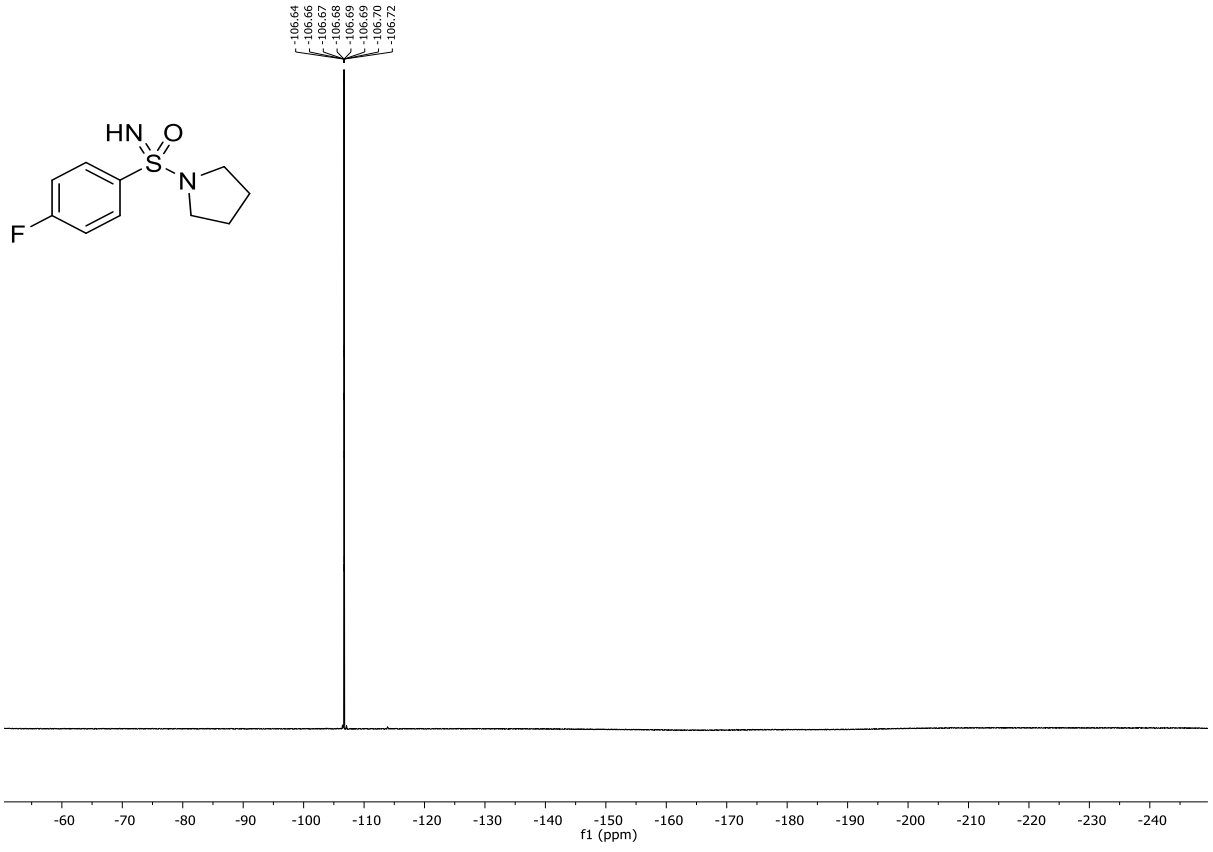
f1 (ppm)


8.00
7.99
7.98
7.98
7.97
7.97
7.96
7.95
7.95
7.20
7.19
7.19
7.18
7.18
7.17
7.17
7.16
7.15
7.15
7.14
3.23
3.23
3.22
3.22
3.21
3.21
3.20
3.20
3.19
3.18
3.18
3.18
3.17
3.17
3.16
3.15
3.14
3.13
3.13
3.13
3.12
2.73
1.75
1.75
1.75
1.74
1.74
1.72
1.71
1.70
1.70
1.69
1.67
1.67
1.66
1.66
1.65
HN
O
S
N
F
1.86
1.92
4.18
0.88
4.00
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)


HN
O
S
N
F
166.35
163.83
133.26
133.23
130.67
130.58
116.14
115.92
48.82
25.37
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)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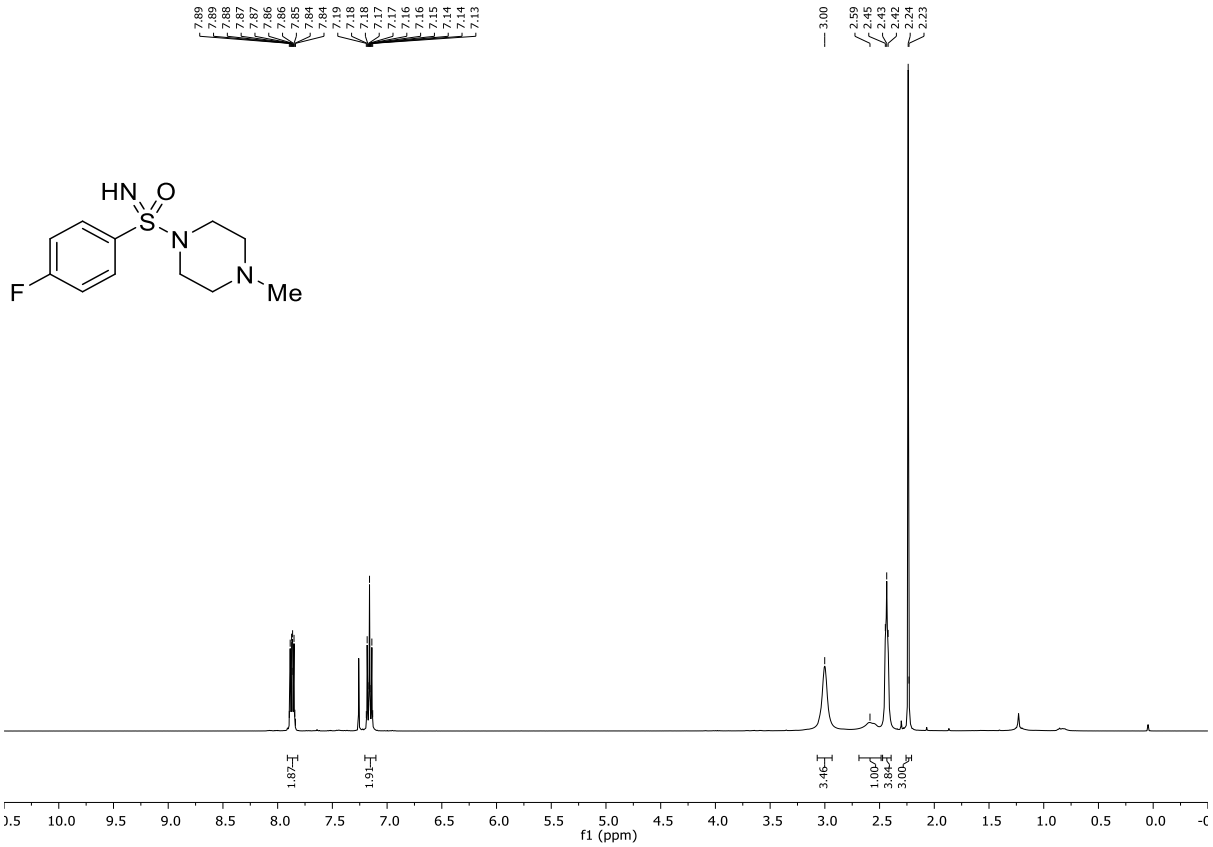
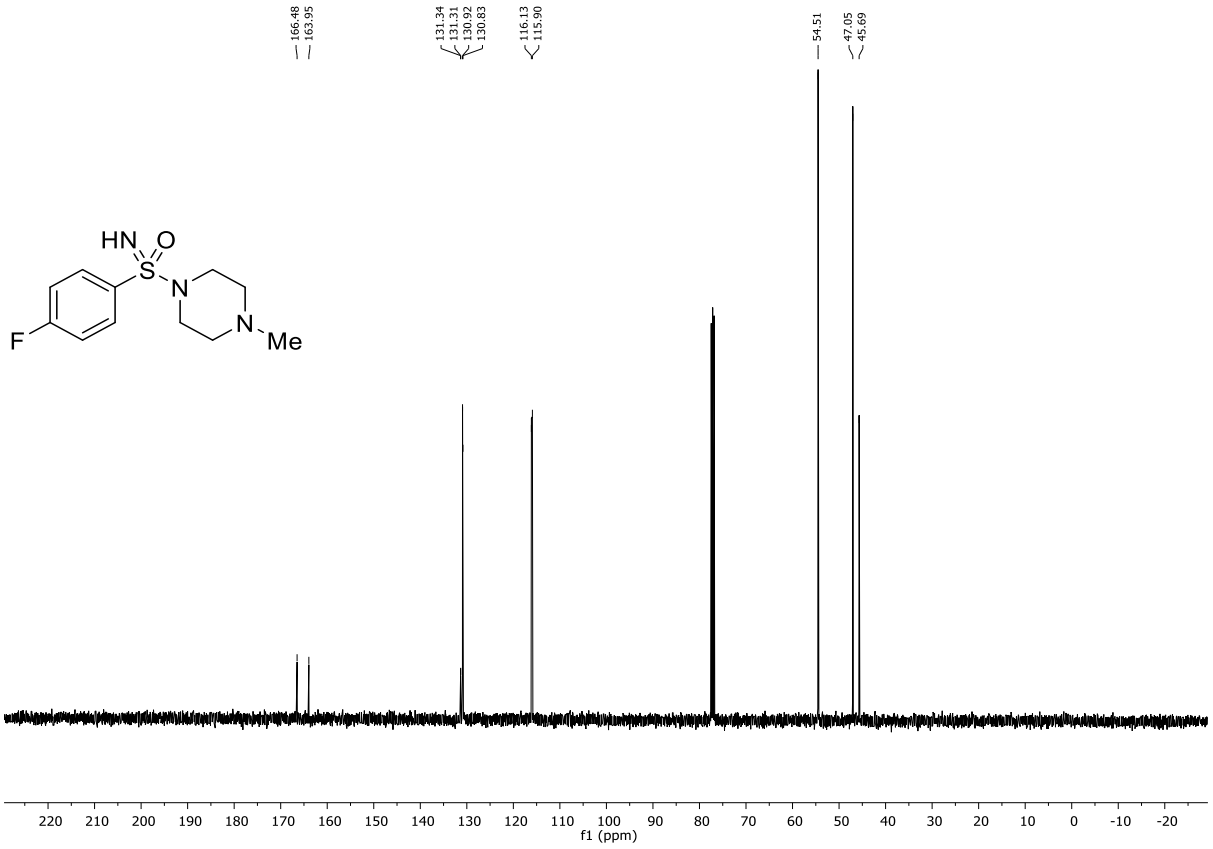
-106.66
-106.67
-106.68
-106.69
-106.69
-106.70
-106.72
HN
O
S
N
F
-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)


7.89
7.89
7.88
7.87
7.87
7.86
7.86
7.85
7.84
7.84
7.19
7.18
7.18
7.17
7.17
7.16
7.16
7.15
7.14
7.14
7.13
3.00
2.59
2.45
2.43
2.42
2.24
2.23
HN
O
S
N
N
Me
F
1.87
1.91
3.46
1.00
3.84
3.00
f1 (ppm)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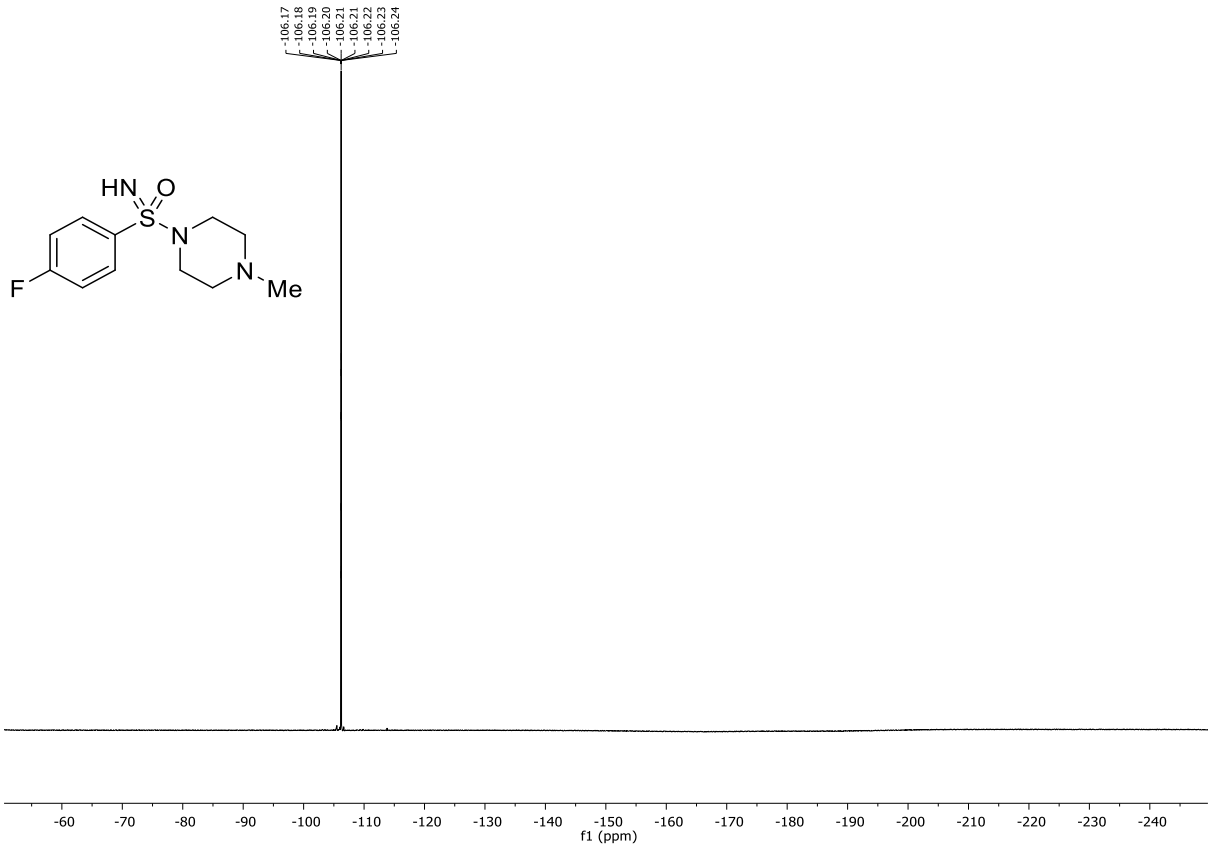
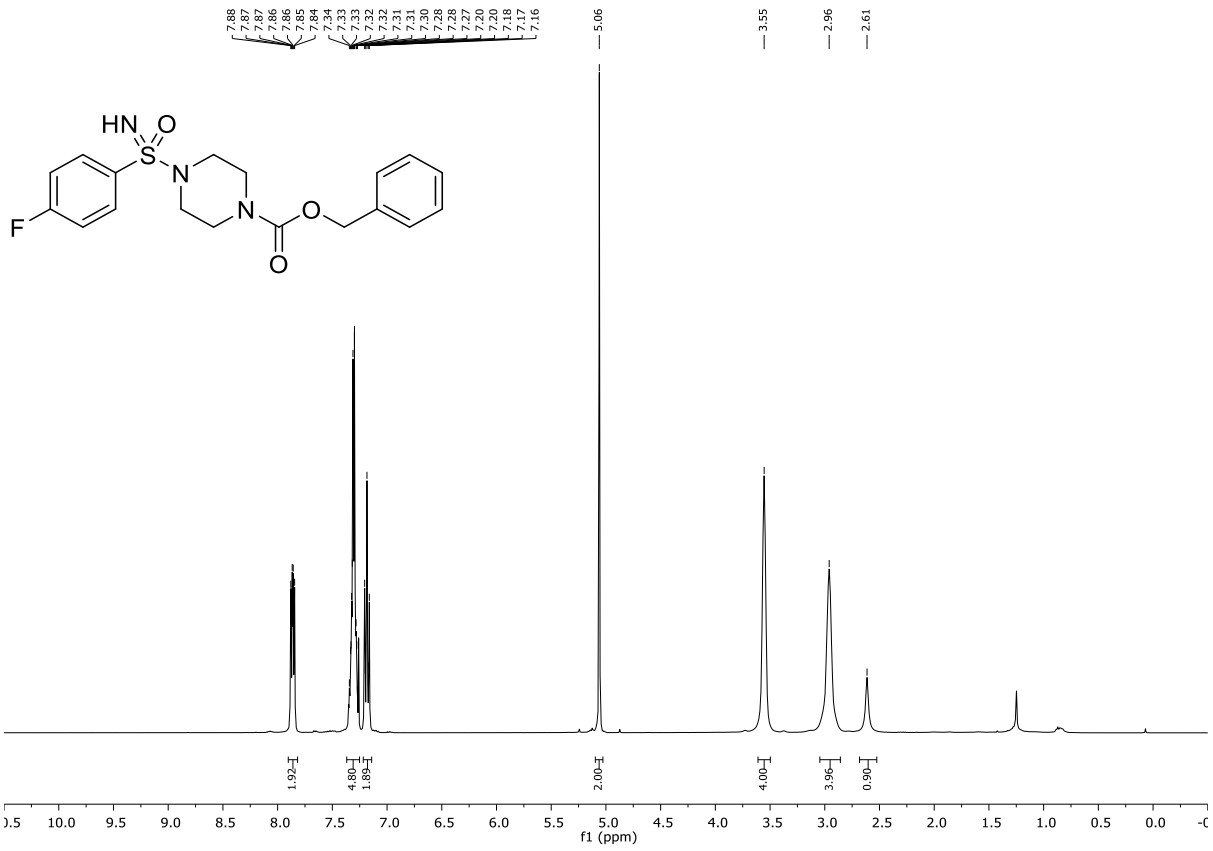
163.95
131.34
131.31
130.92
130.83
116.13
115.90
54.51
47.05
45.69
HN
O
S
N
N
Me
F
f1 (ppm)


-106.17
-106.18
-106.19
-106.20
-106.21
-106.21
-106.22
-106.23
-106.24
HN
O
S
N
N
Me
F
-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)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7.87
7.87
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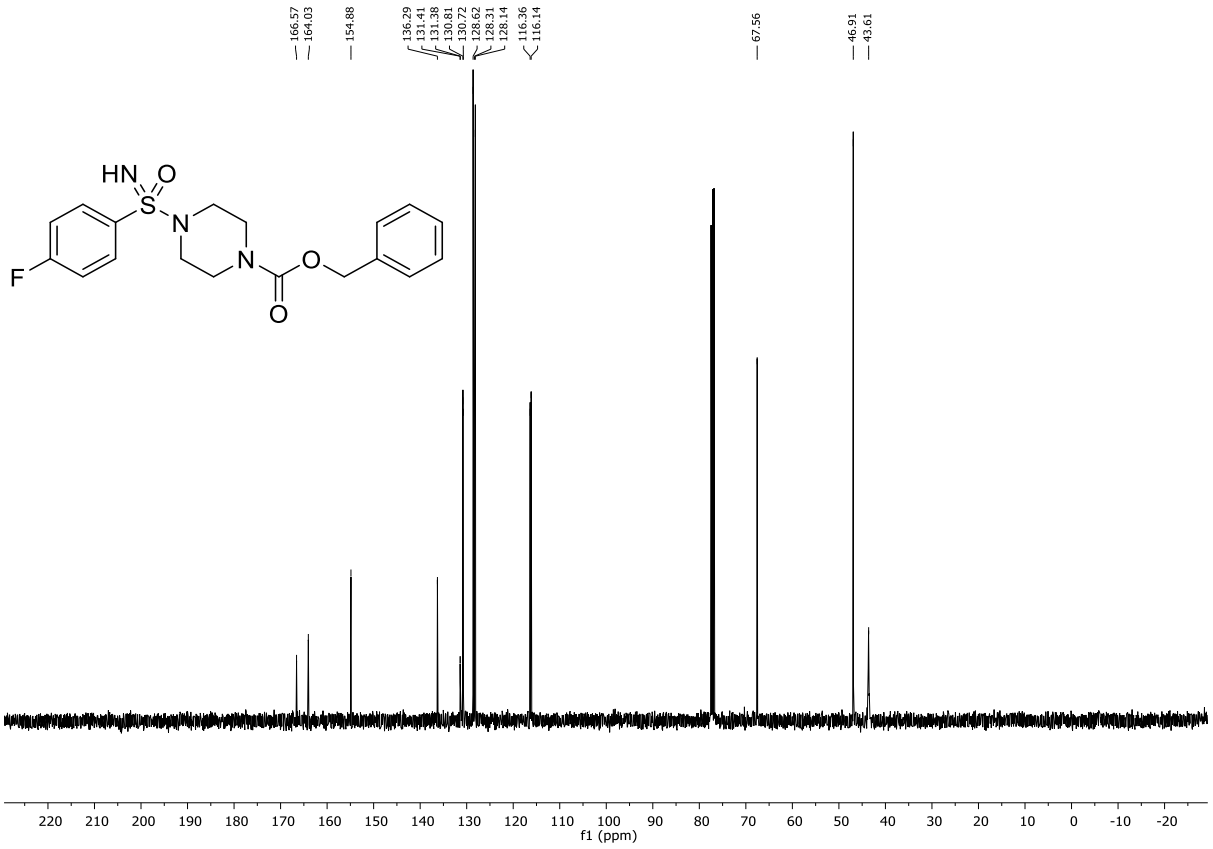
7.86
7.85
7.84
7.34
7.33
7.33
7.32
7.32
7.31
7.31
7.30
7.28
7.28
7.27
7.20
7.20
7.18
7.17
7.16
5.06
3.55
2.96
2.61
HN
O
S
N
N
O
O
F
1.92
4.80
1.89
2.00
4.00
3.96
0.90
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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154.88
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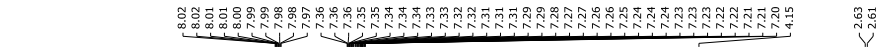
131.41
131.38
130.81
130.72
128.62
128.31
128.14
116.36
116.14
67.56
46.91
43.61
HN
O
S
N
N
O
F
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


-105.56
-105.57
-105.58
-105.59
-105.61
-105.62
-105.63
HN
O
S
N
N
O
F
O
-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)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8.02
8.01
8.01
8.00
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7.99
7.98
7.98
7.97
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7.35
7.35
7.34
7.34
7.34
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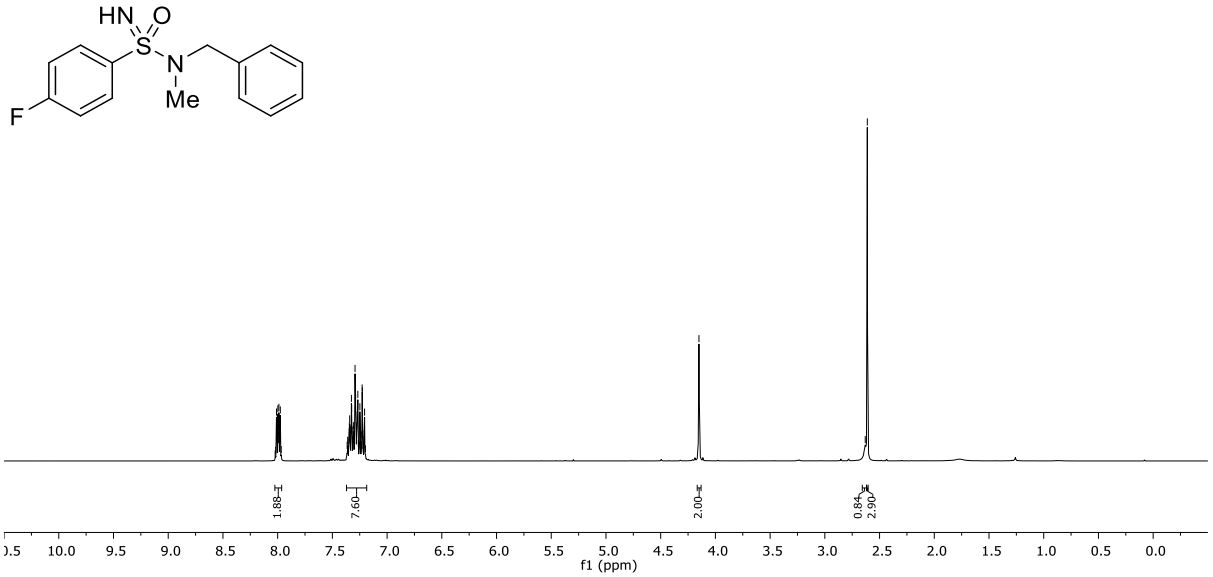
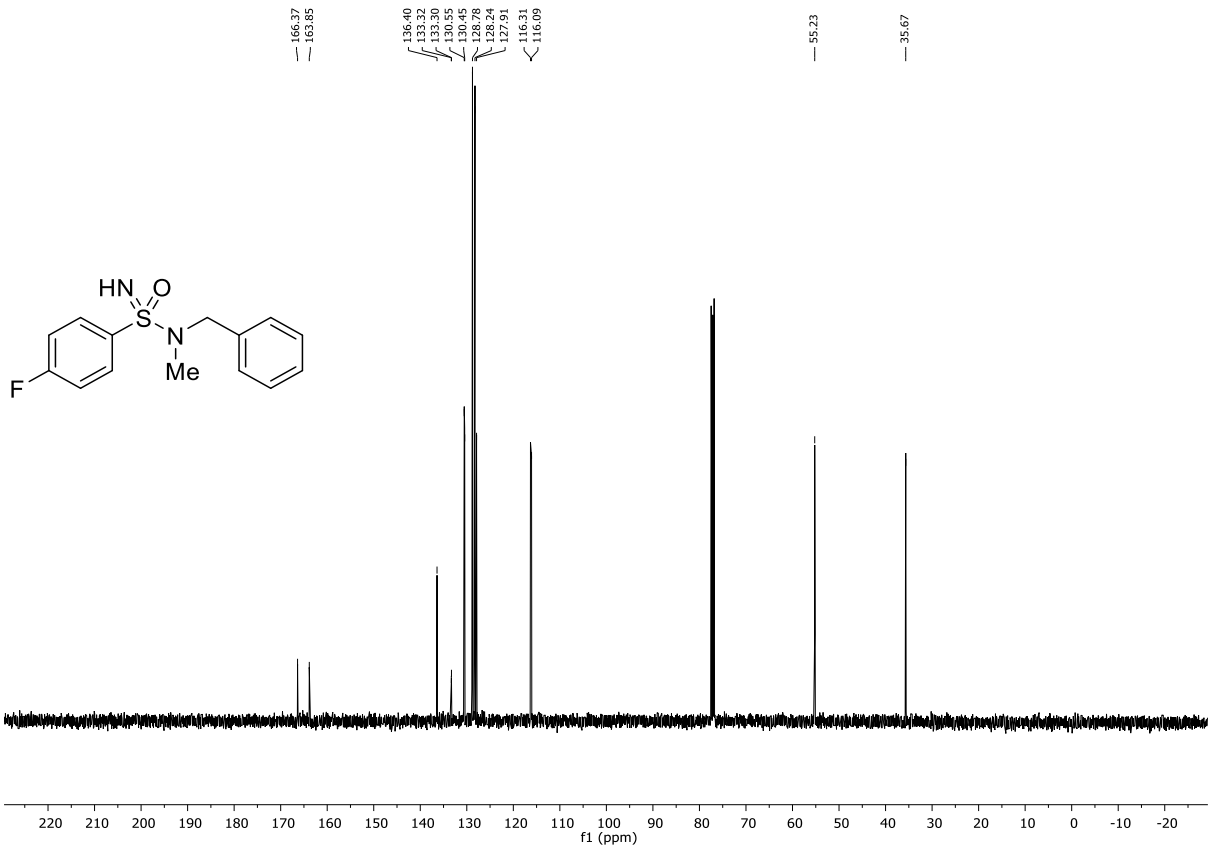
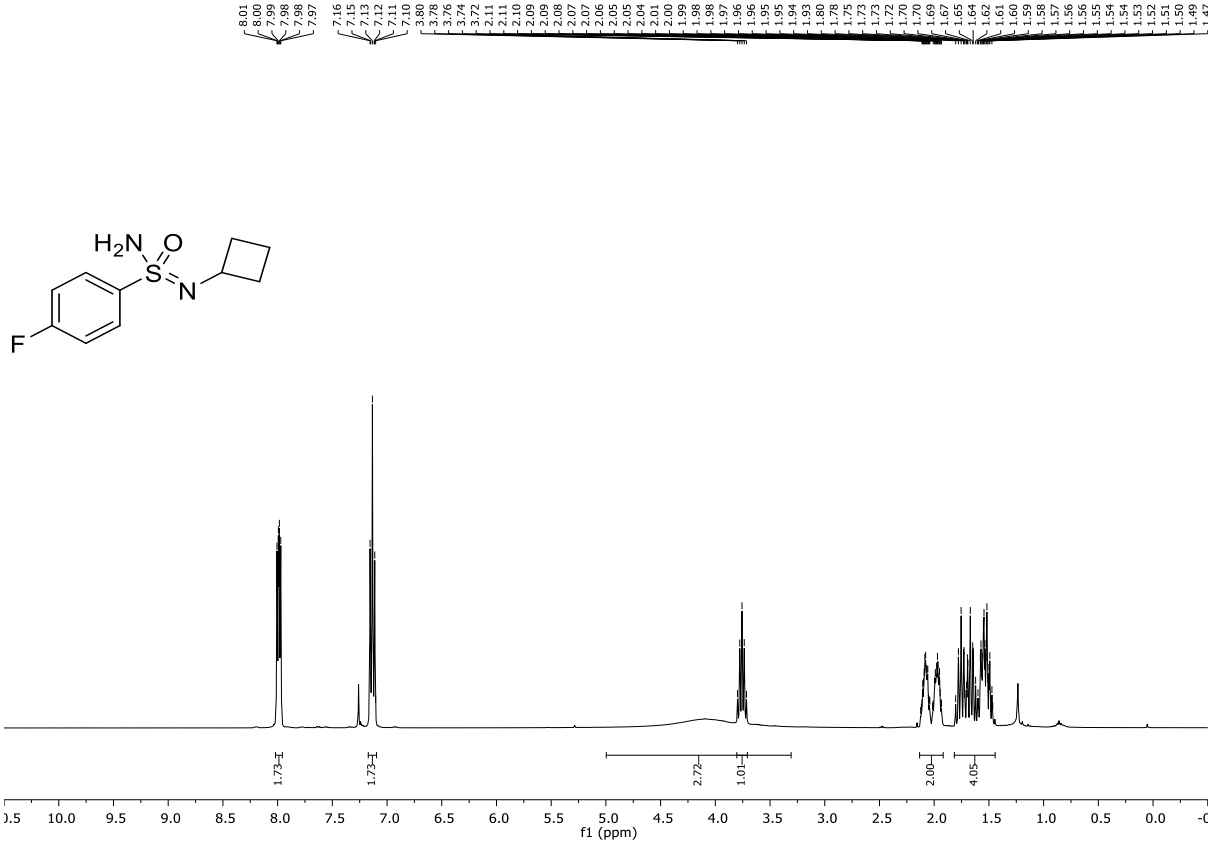
7.21
7.20
4.15
2.63
2.61


HN
O
S
N
Me
F
1.88
7.60
2.00
0.84
2.90
f1 (ppm)


166.37
163.85
136.40
133.32
133.30
130.55
130.45
128.78
128.24
127.91
116.31
116.09
55.23
35.67
HN
O
S
N
Me
F
f1 (ppm)


-106.35
-106.37
-106.37
-106.39
-106.40
-106.41
-106.42
HN
O
S
N
Me
F
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
-240
f1 (ppm)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O
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N
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1.73
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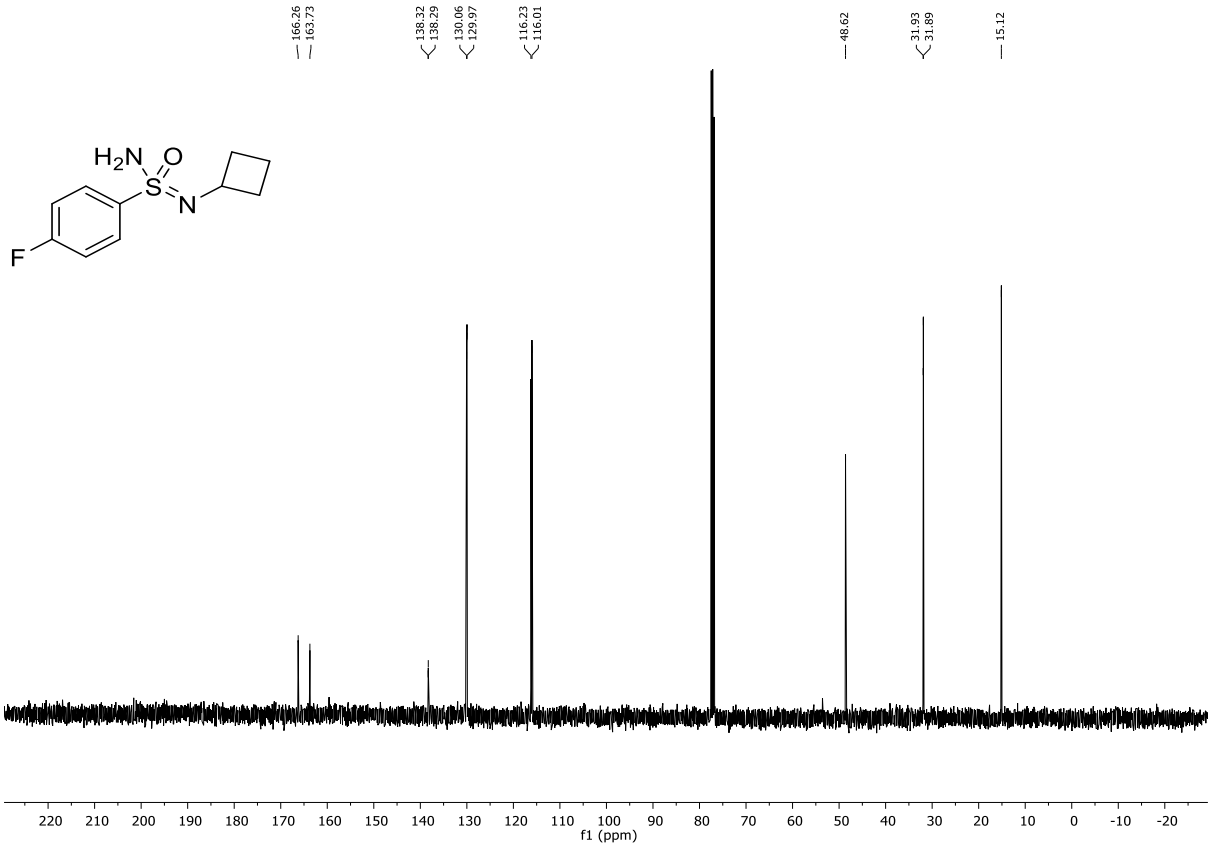
2.00
4.05
f1 (ppm)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116.01
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31.93
31.89
15.12
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O
S
N
F
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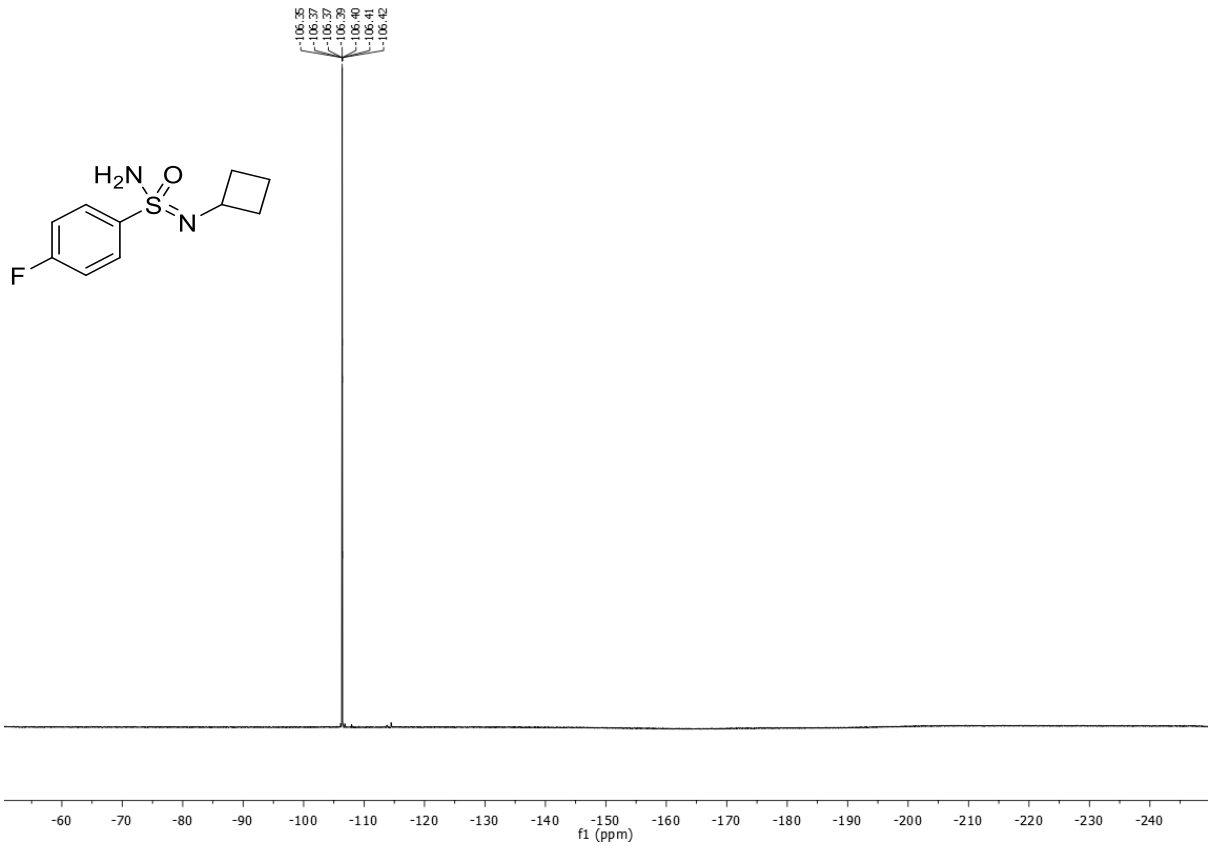
f1 (ppm)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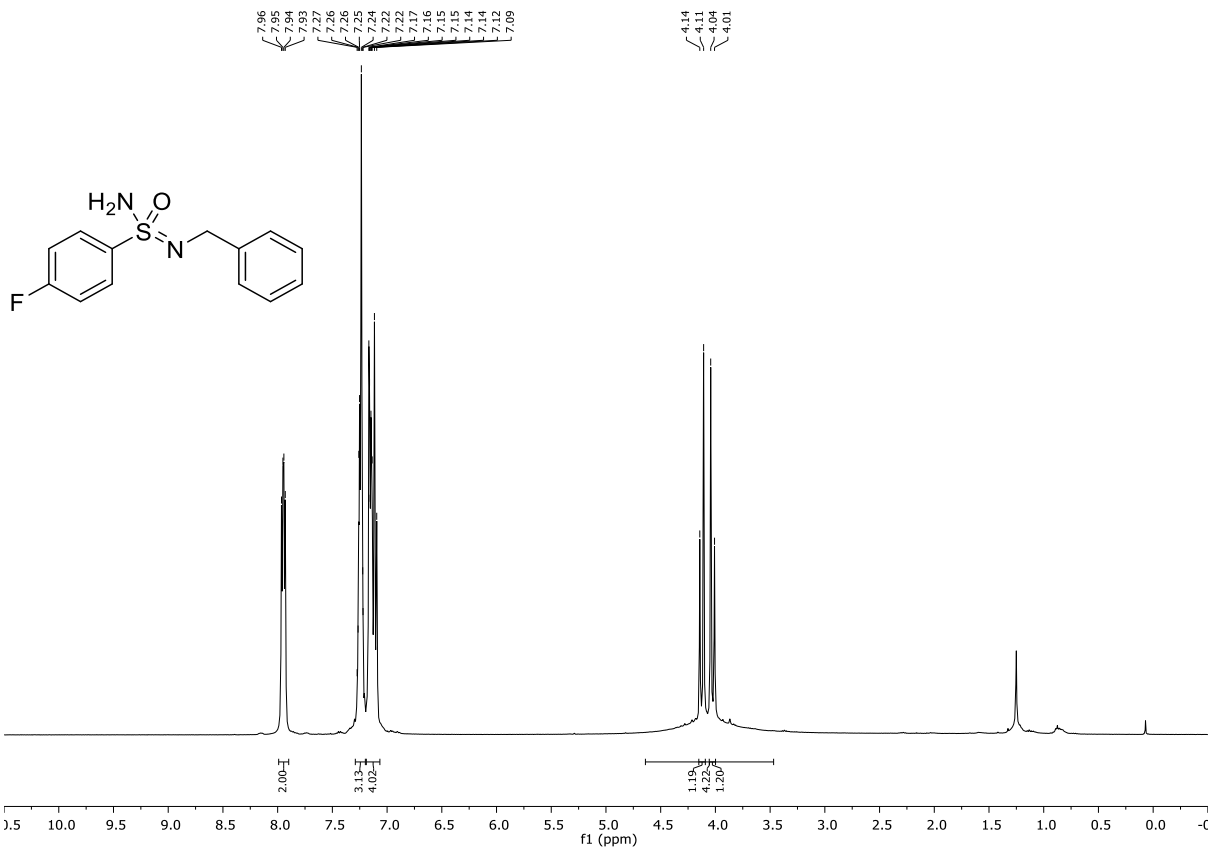
106.41
106.42
H2N
O
S
N
F
-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)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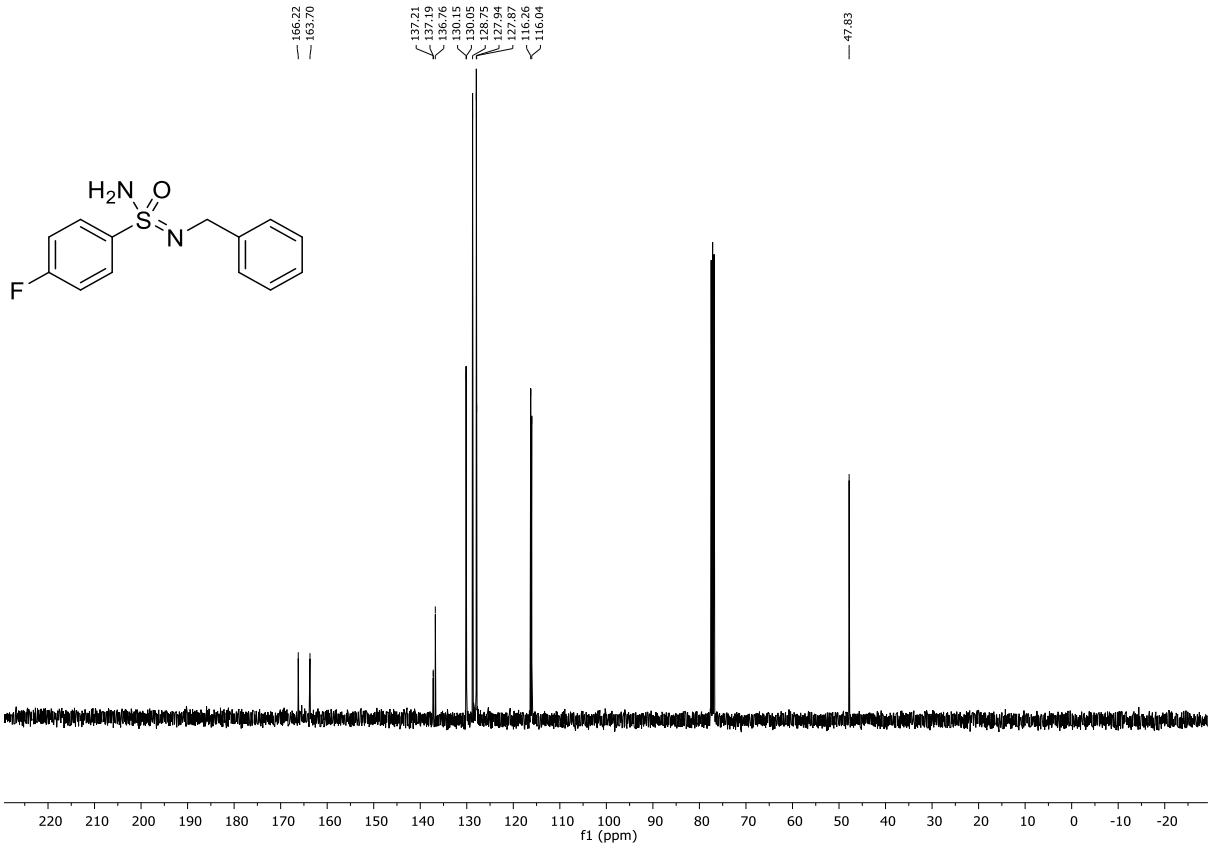
7.24
7.22
7.17
7.16
7.15
7.15
7.14
7.12
7.09
4.14
4.11
4.04
4.01
H2N
O
S
N
F
2.00
3.13
4.02
1.19
4.22
1.20
f1 (ppm)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163.70
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130.15
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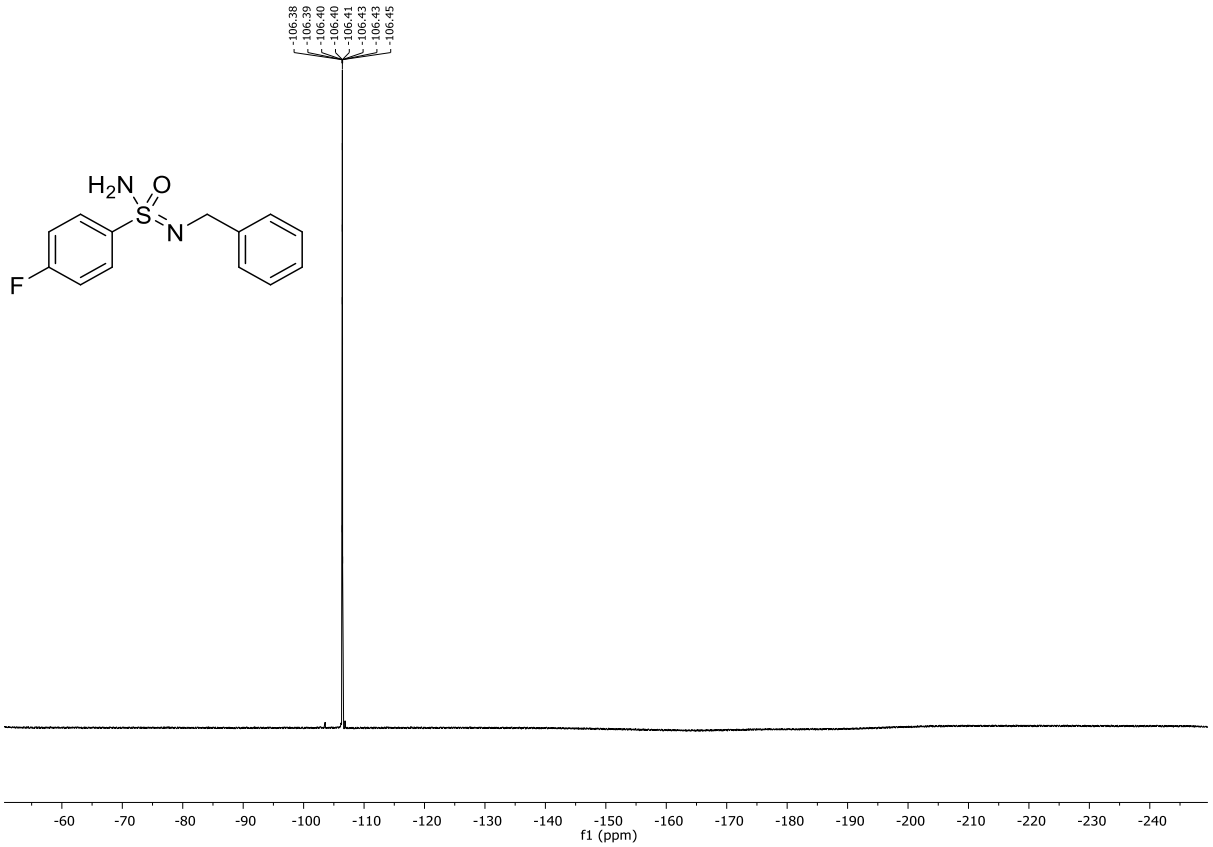
127.84
127.97
116.26
116.04
47.83
H2N
O
S
N
F
f1 (ppm)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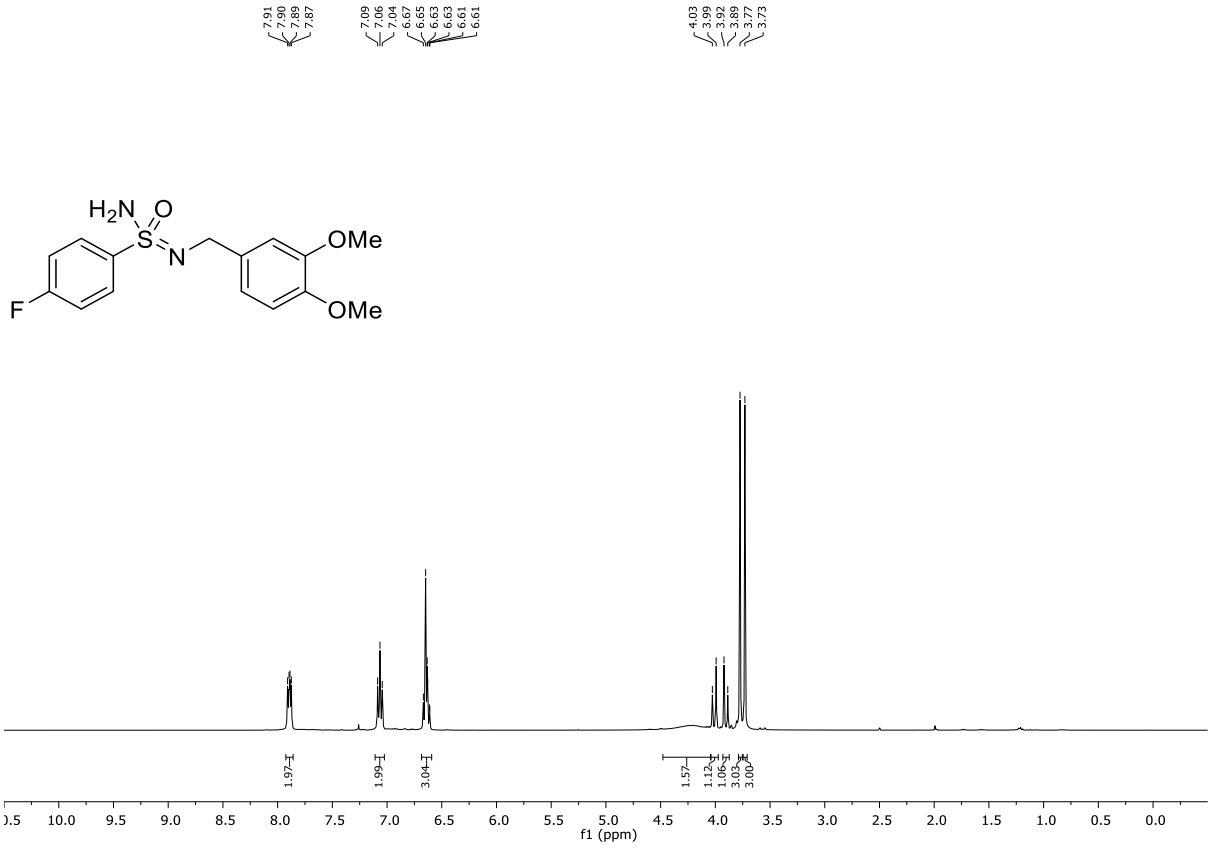
-106.41
-106.43
-106.43
-106.45
H2N
O
S
N
F
-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)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7.06
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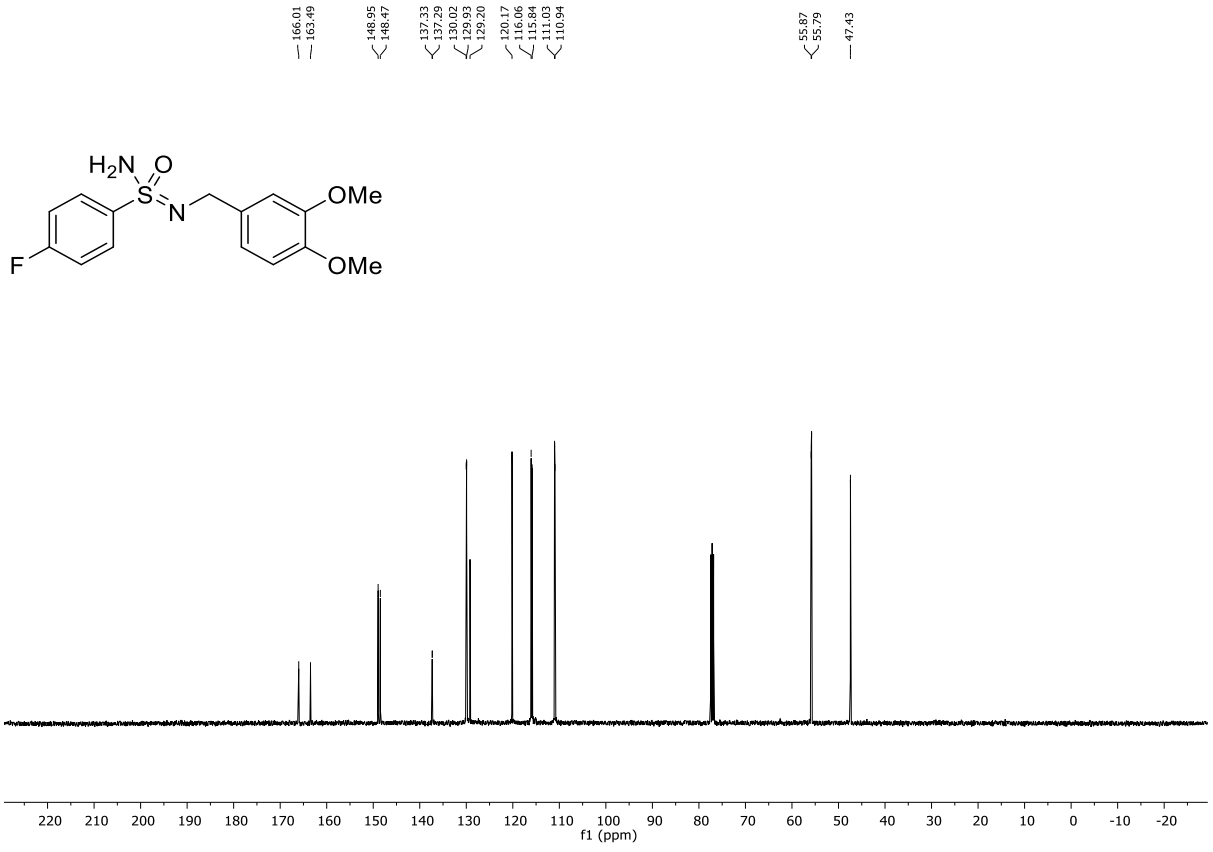
6.67
6.65
6.63
6.63
6.61
6.61
4.03
3.99
3.92
3.89
3.77
3.73
H2N
O
S
N
OMe
OMe
F
1.97
1.99
3.04
1.57
1.12
1.06
1.04
3.00
f1 (ppm)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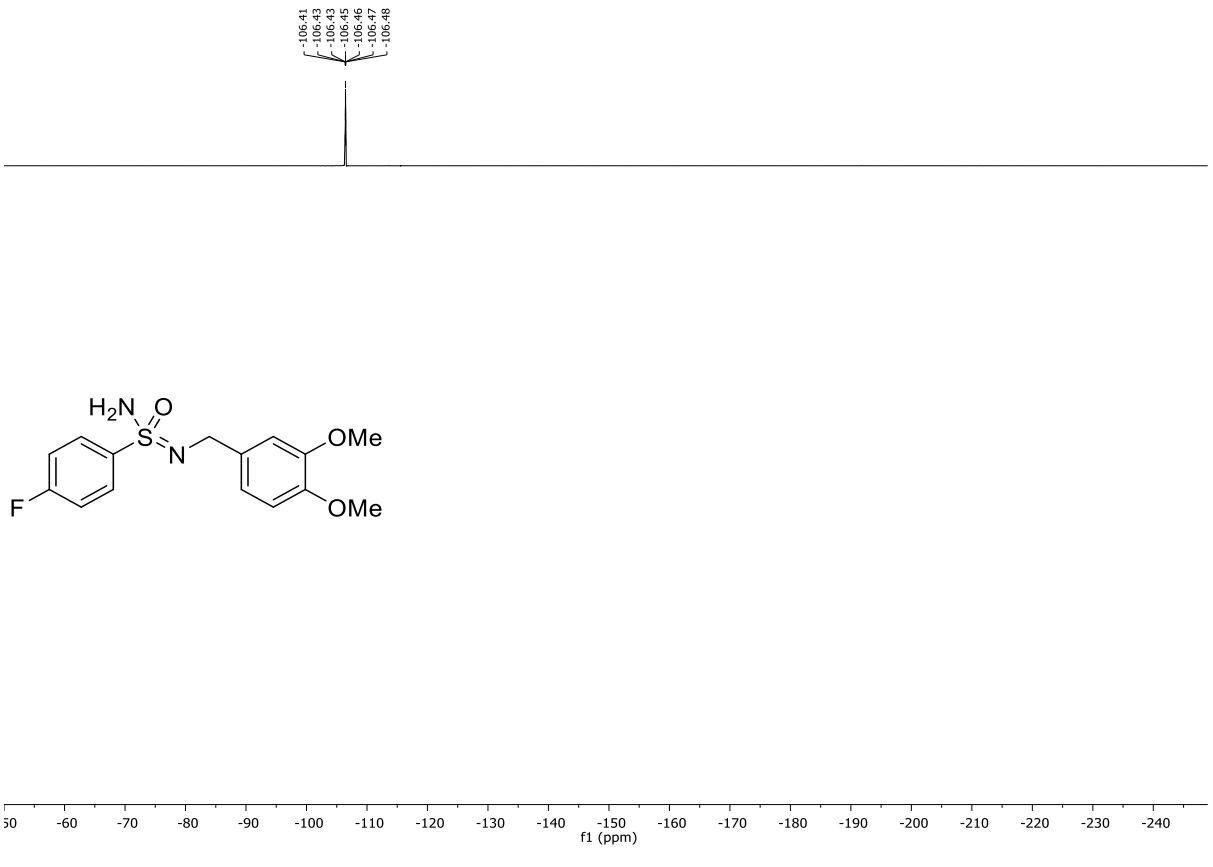
137.29
130.02
129.93
129.20
120.17
116.06
115.84
111.03
110.94
55.87
55.79
47.43
H2N
O
S
N
OMe
OMe
F
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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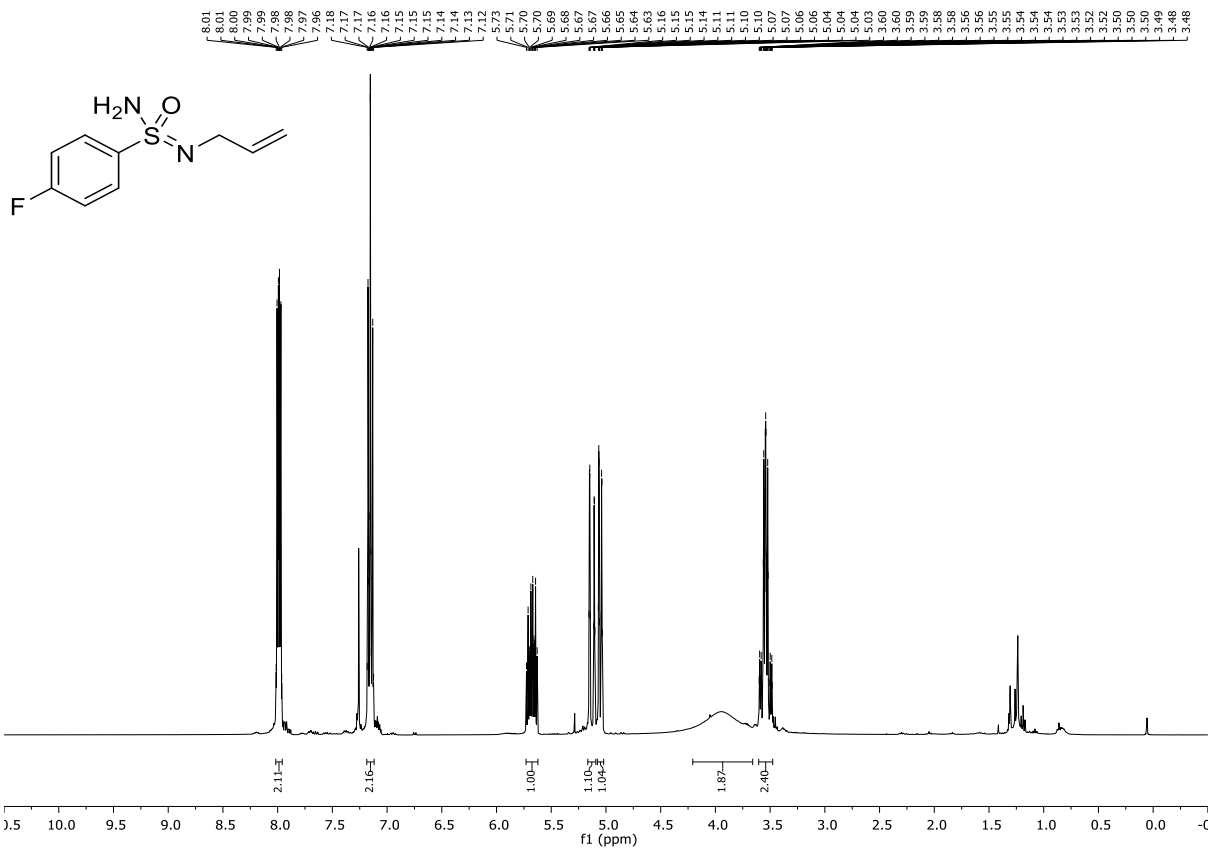
-106.43
-106.43
-106.43
-106.45
-106.46
-106.47
-106.48
H2N
O
S
N
OMe
OMe
F
-50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)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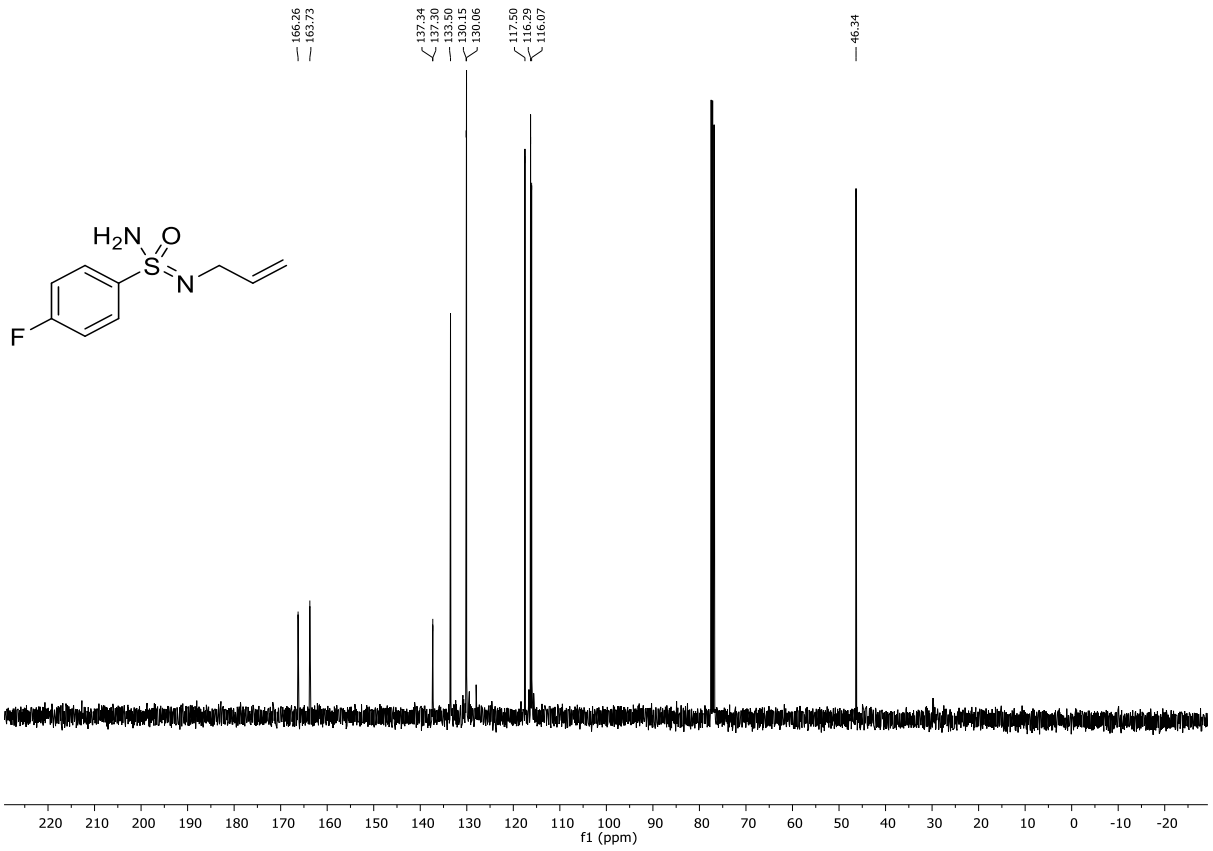
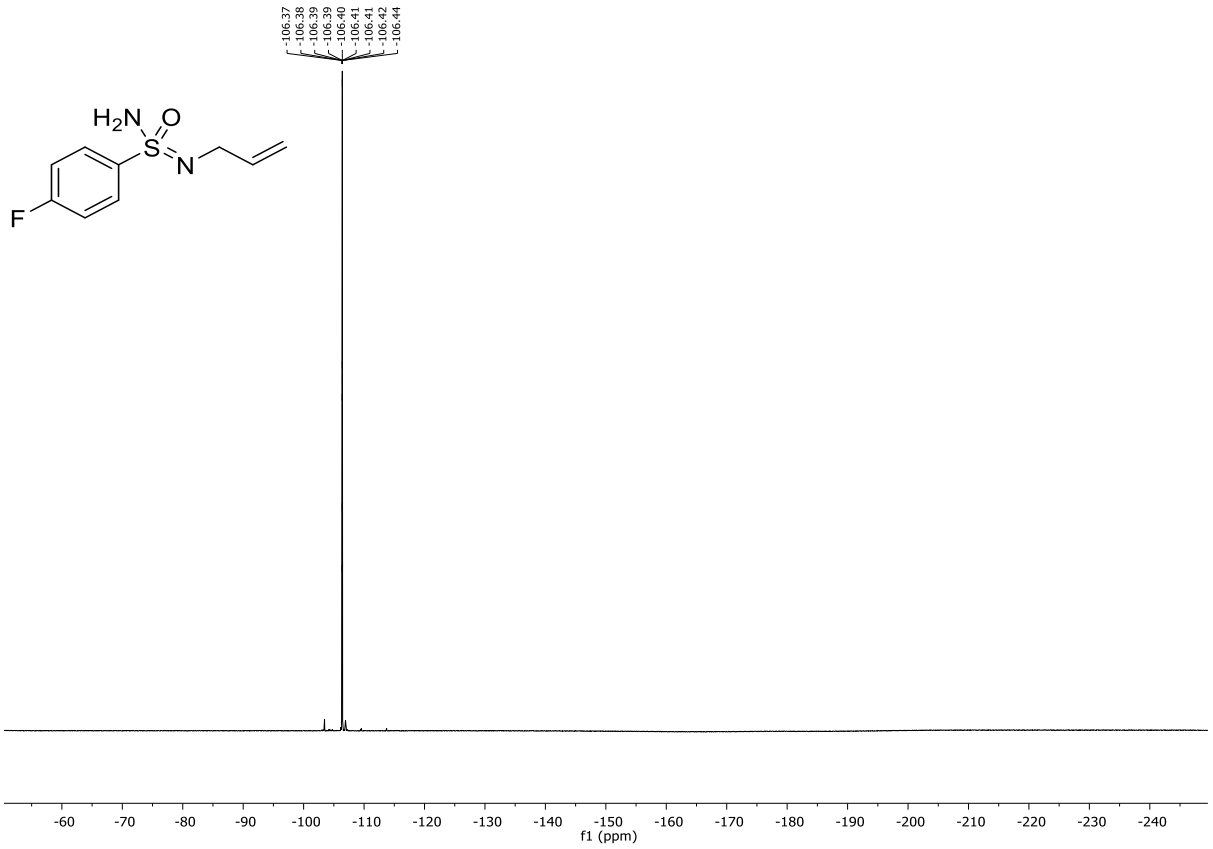
H2N O S N F
2.11 2.16 1.00 1.10 1.04 1.87 2.40
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


166.26 163.73 137.34 137.30 133.50 130.15 130.06 117.50 116.29 116.07 46.34
H2N O S N F
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)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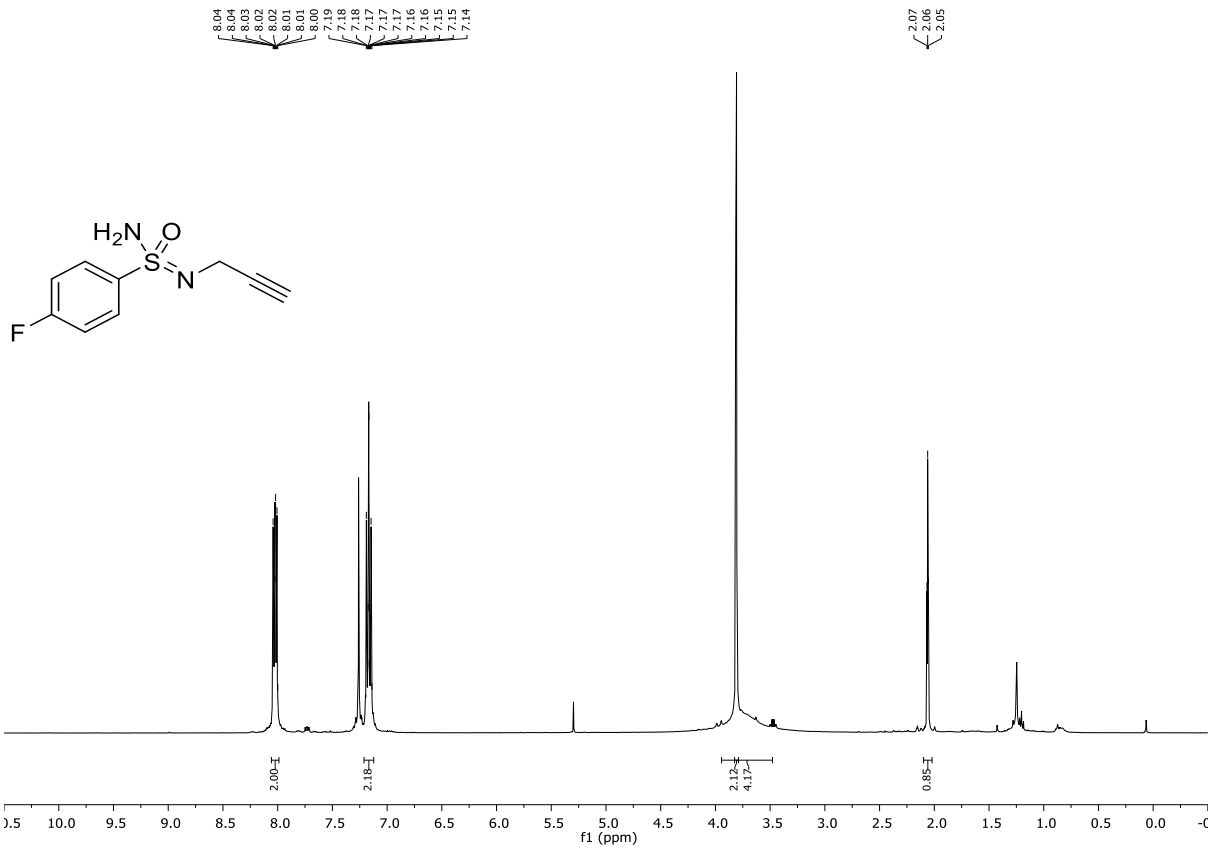
-106.38
-106.39
-106.39
-106.40
-106.41
-106.41
-106.42
-106.44
H2N
O
S
N
F
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
-240
f1 (ppm)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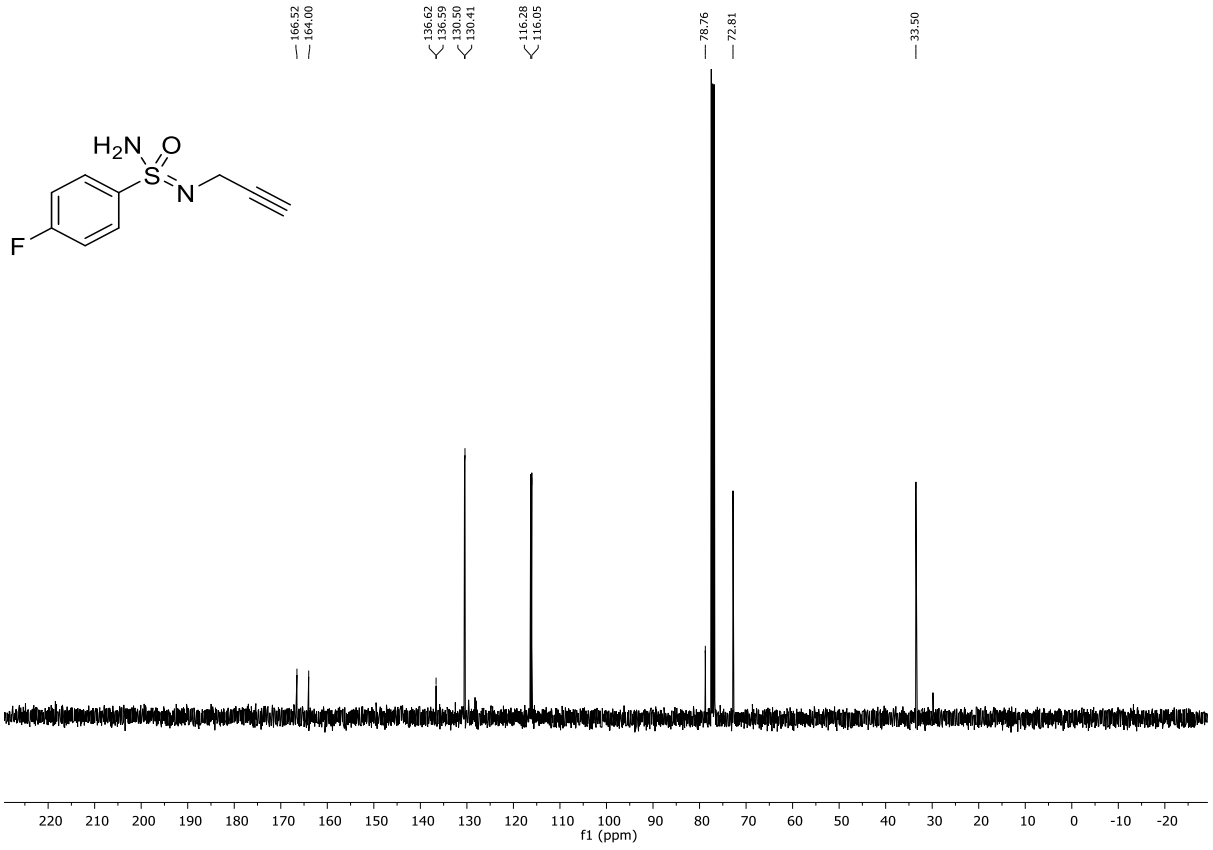
8.04
8.03
8.02
8.02
8.01
8.01
8.00
7.19
7.18
7.18
7.17
7.17
7.17
7.16
7.16
7.15
7.15
7.14
2.07
2.06
2.05
H2N
O
S
N
F
2.00
2.18
2.12
4.17
0.85
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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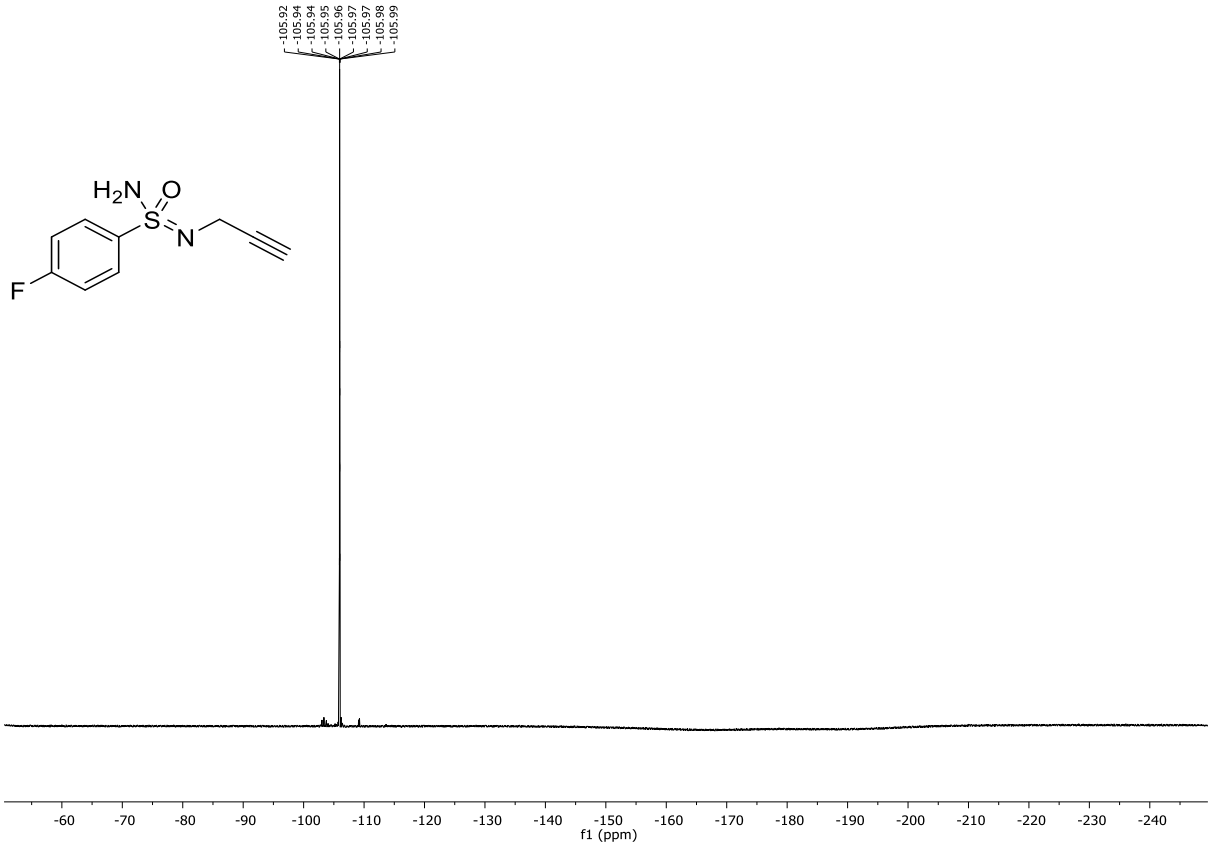
130.50
130.41
116.28
116.05
78.76
72.81
33.50
H2N
O
S
N
F
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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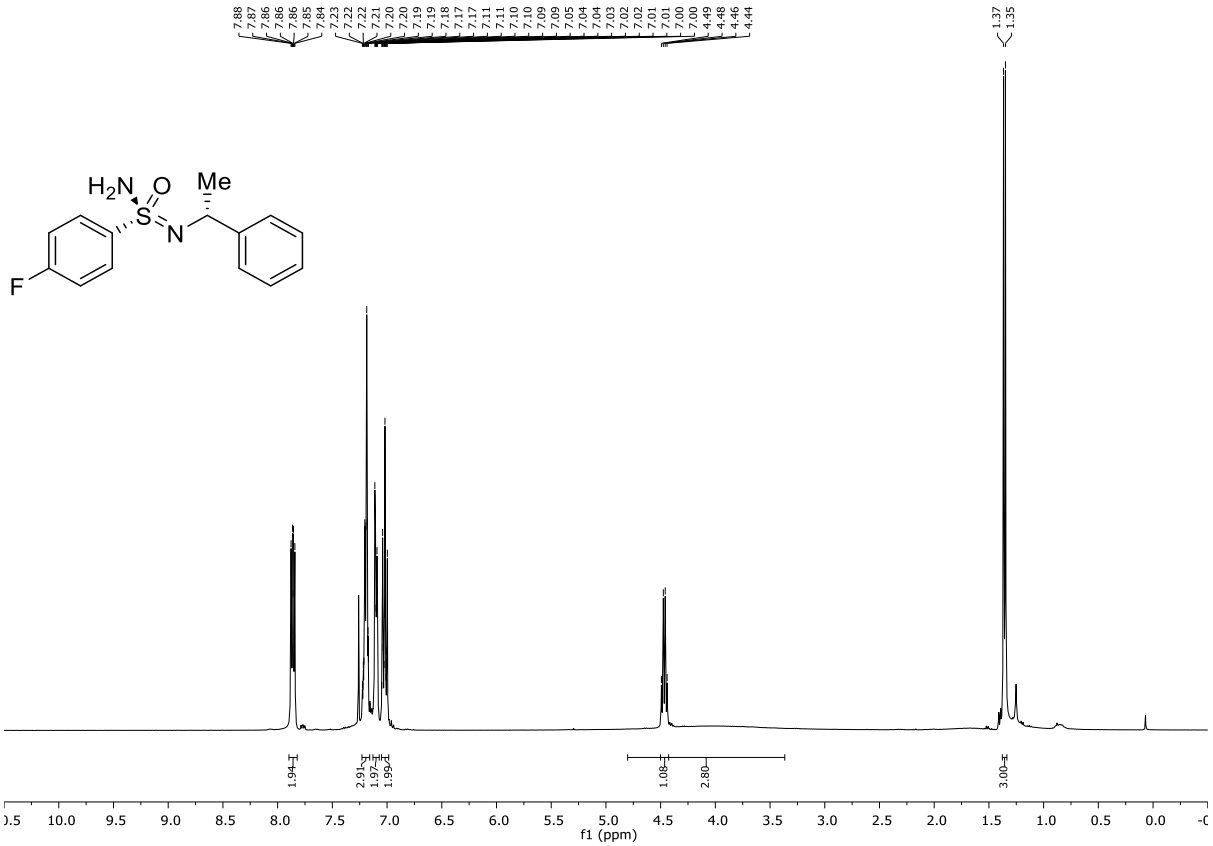
-105.94
-105.95
-105.96
-105.97
-105.97
-105.98
-105.99
H2N
O
S
N
F
-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)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7.23
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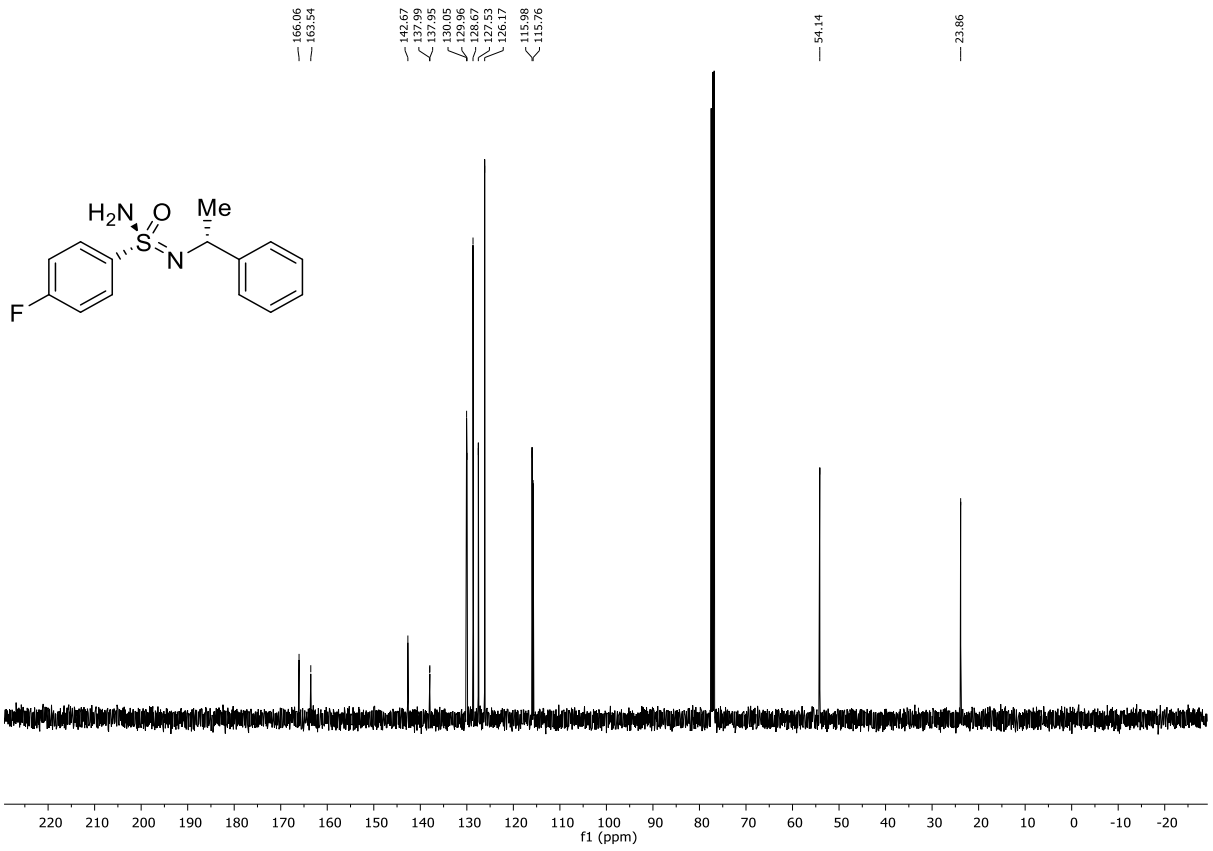
7.22
7.21
7.20
7.20
7.19
7.19
7.18
7.17
7.17
7.11
7.11
7.10
7.10
7.09
7.09
7.05
7.04
7.04
7.03
7.02
7.02
7.01
7.01
7.00
7.00
4.49
4.48
4.46
4.44
1.37
1.35
H2N
O
Me
S
N
F
1.94
2.91
1.97
1.99
1.08
2.80
3.00
f1 (ppm)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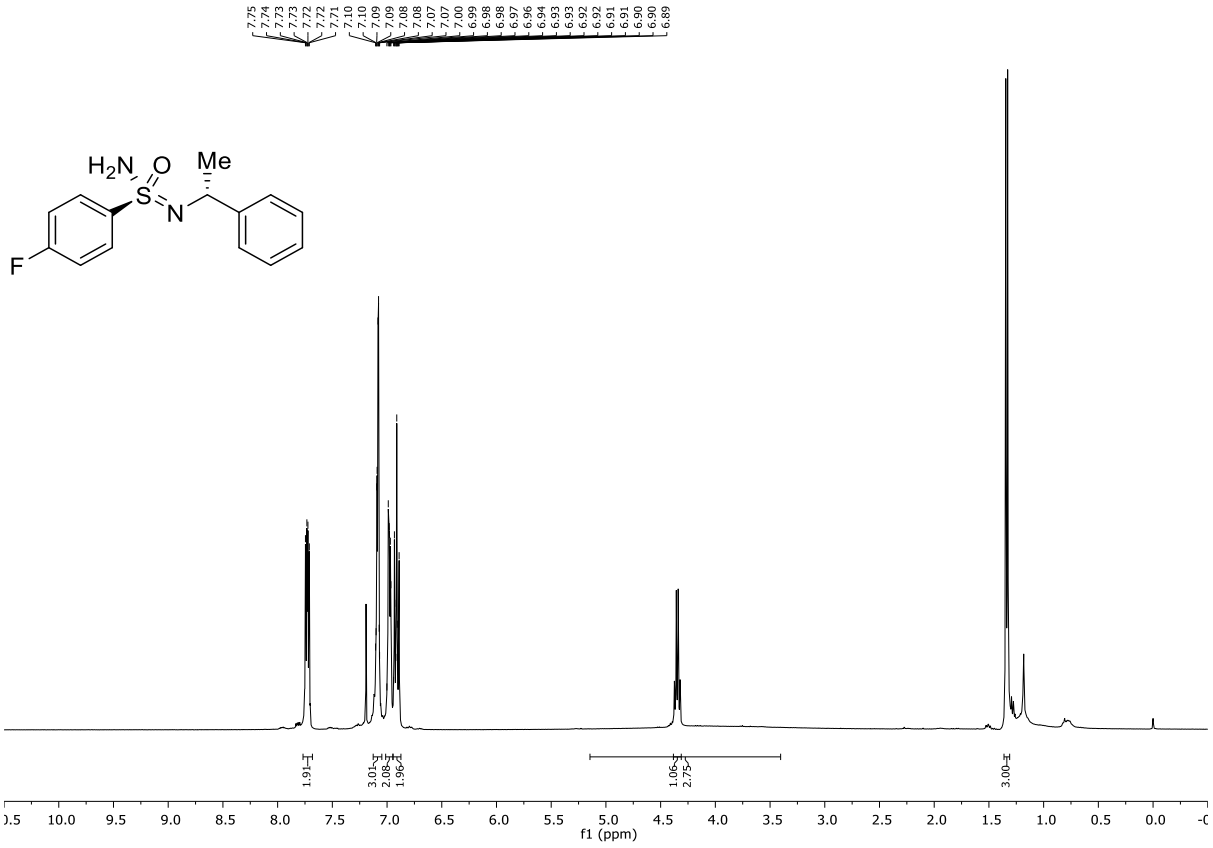
137.95
130.05
129.96
128.67
127.53
126.17
115.98
115.76
54.14
23.86
H2N
O
Me
S
N
F
f1 (ppm)


-106.84
-106.85
-106.86
-106.88
-106.88
-106.89
-106.90
-106.91
H2N
O
S
N
Me
F
-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)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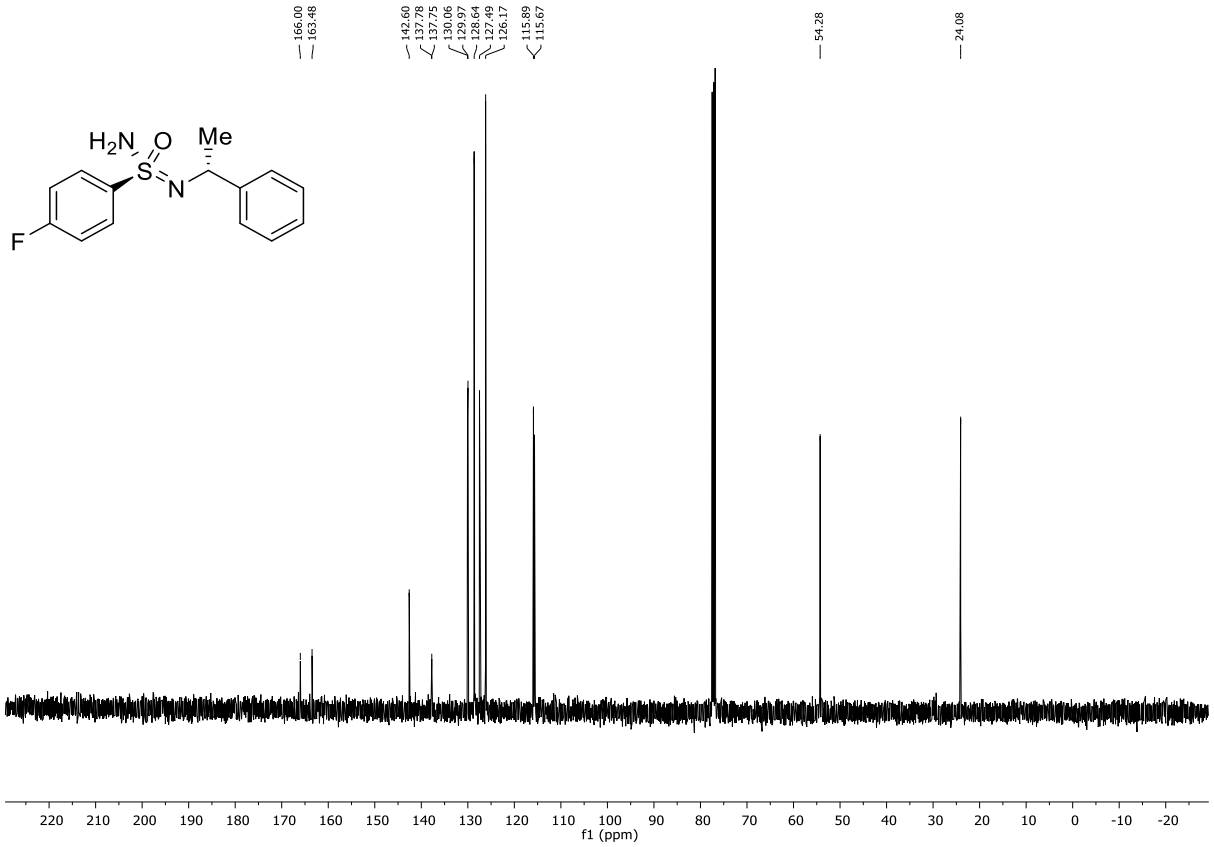
7.09
7.08
7.08
7.07
7.07
7.00
6.99
6.98
6.98
6.97
6.96
6.94
6.93
6.93
6.92
6.92
6.91
6.91
6.90
6.90
6.89
H2N
O
S
N
Me
F
1.91
3.01
2.08
1.96
1.06
2.75
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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163.48
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137.78
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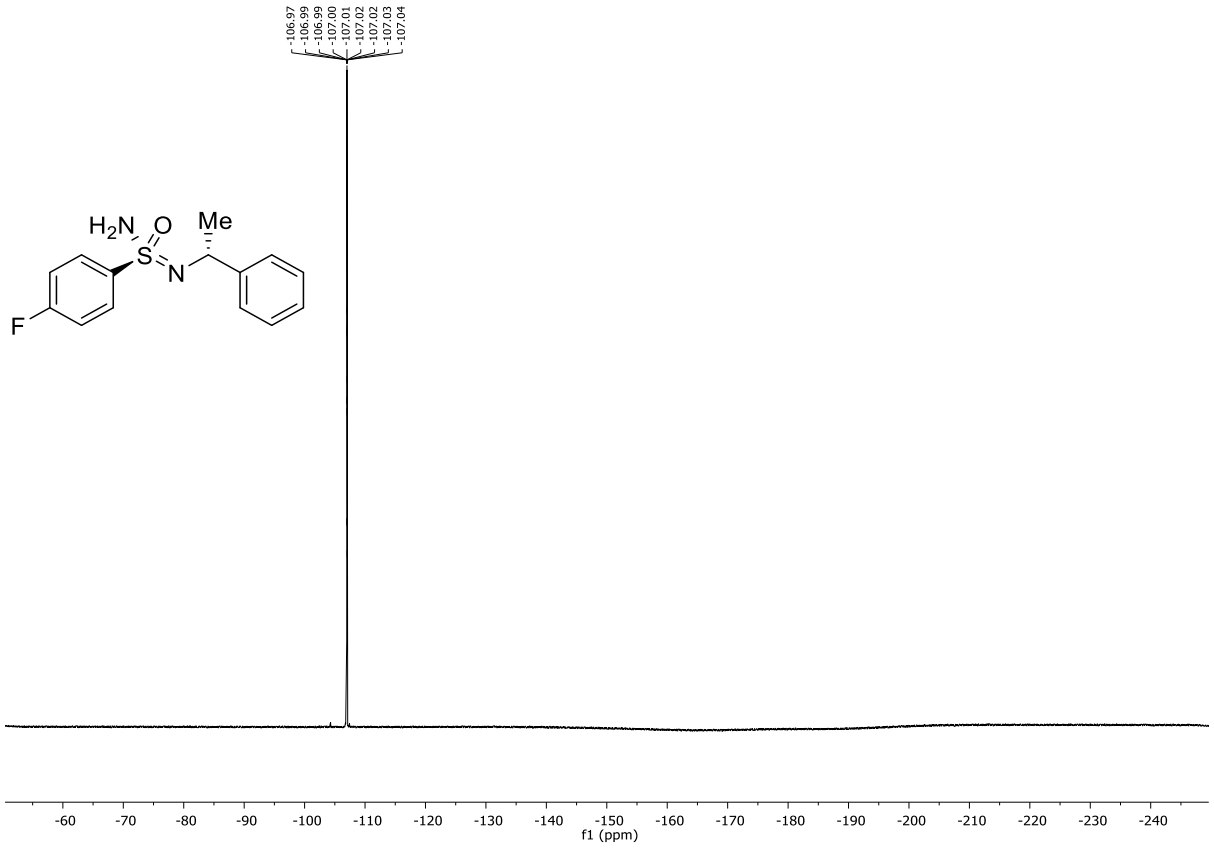
130.06
129.97
128.64
127.49
126.17
115.89
115.67
54.28
24.08
H2N
O
S
N
Me
F
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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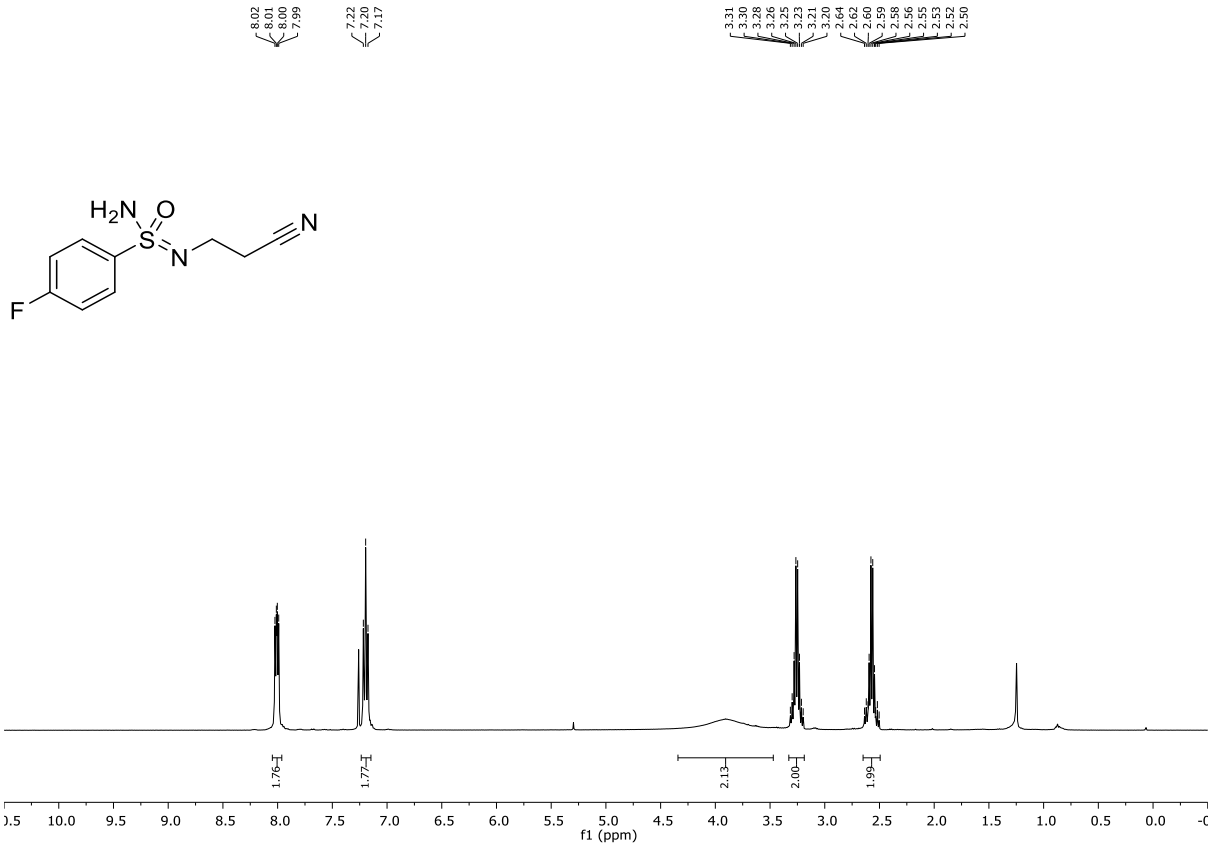
-106.99
-106.99
-107.00
-107.01
-107.02
-107.02
-107.03
-107.04
H2N
O
S
N
Me
F
-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)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8.00
7.99
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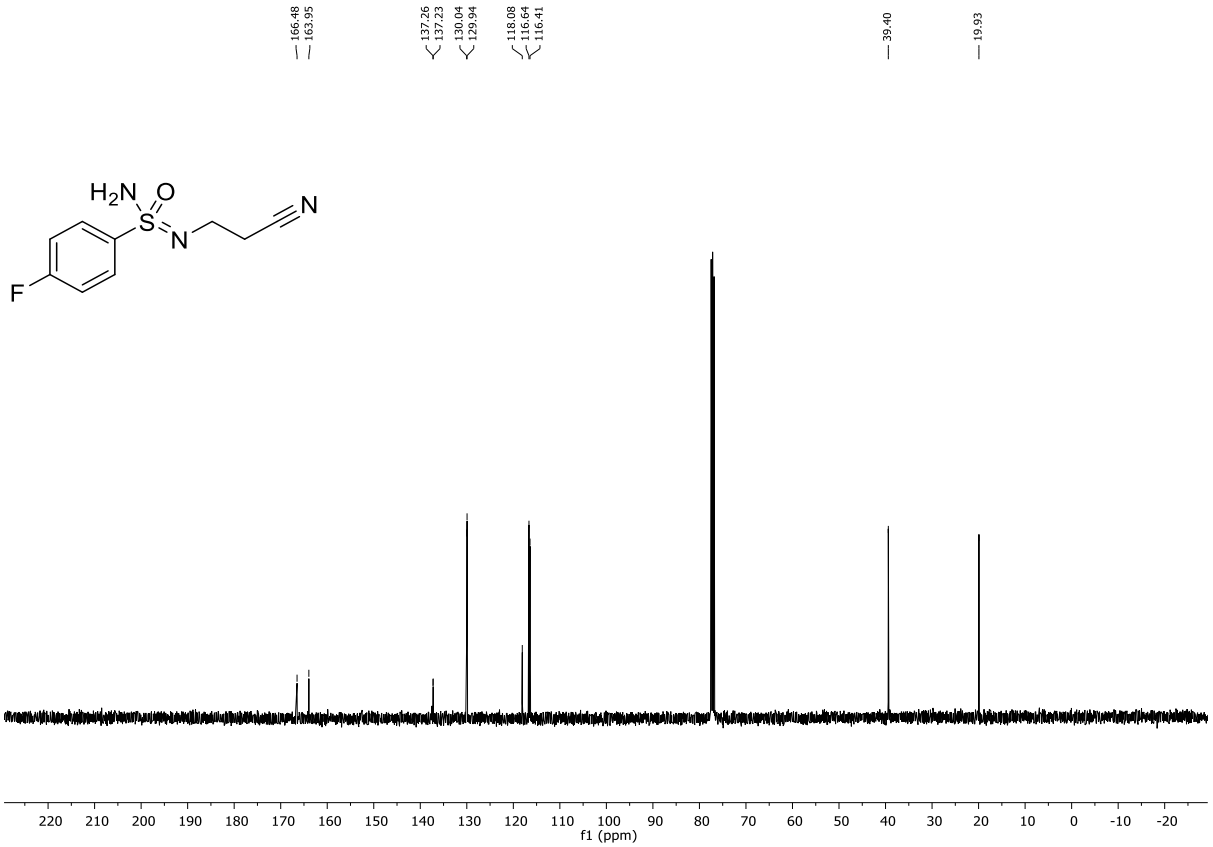
7.20
7.17
3.31
3.30
3.28
3.26
3.25
3.23
3.21
3.20
2.64
2.62
2.60
2.59
2.58
2.56
2.55
2.53
2.52
2.50
H2N
O
S
N
N
F
1.76
1.77
2.13
2.00
1.99
f1 (ppm)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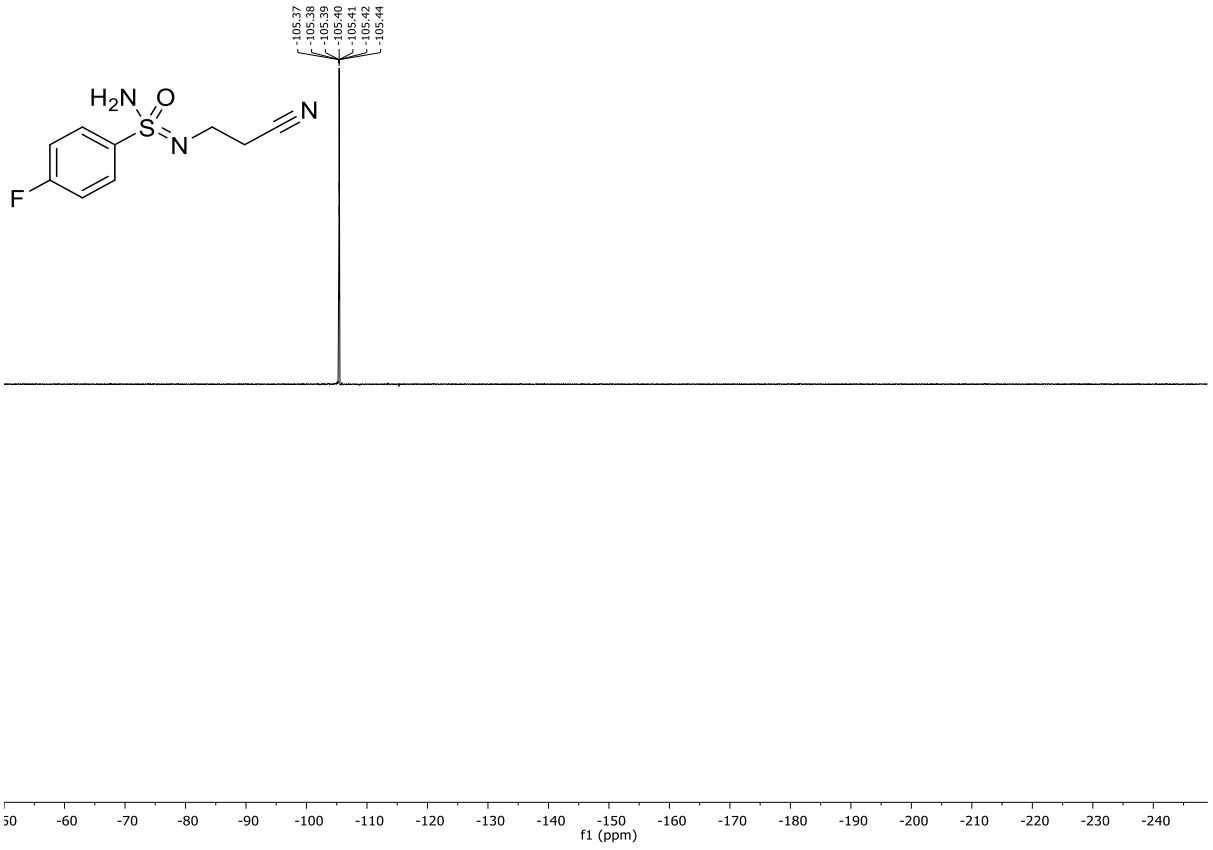
163.95
137.26
137.23
130.04
129.94
118.08
116.64
116.41
39.40
19.93
H2N
O
S
N
N
F
f1 (ppm)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-105.38
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-105.41
-105.42
-105.44
H2N
O
S
N
N
F
-50
-60
-70
-80
-90
-100
-110
-120
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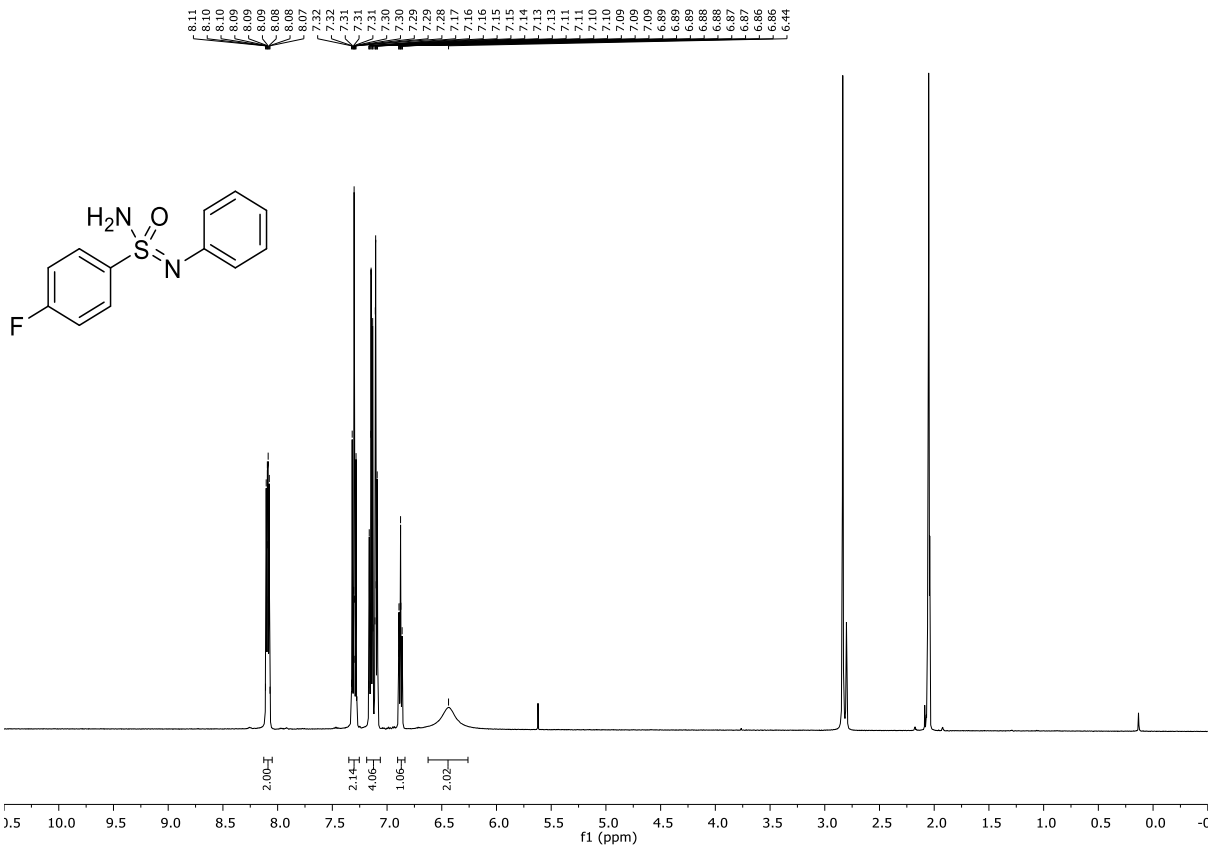
-150
-160
-170
-180
-190
-200
-210
-220
-230
-240
f1 (ppm)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8.10
8.09
8.09
8.09
8.08
8.08
8.07
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7.32
7.31
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7.31
7.30
7.30
7.29
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7.28
7.17
7.16
7.16
7.15
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7.14
7.13
7.11
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7.10
7.09
7.09
7.09
6.89
6.89
6.89
6.88
6.88
6.87
6.87
6.86
6.86
6.44
H2N
O
S
N
F
2.00
2.14
4.06
1.06
2.02
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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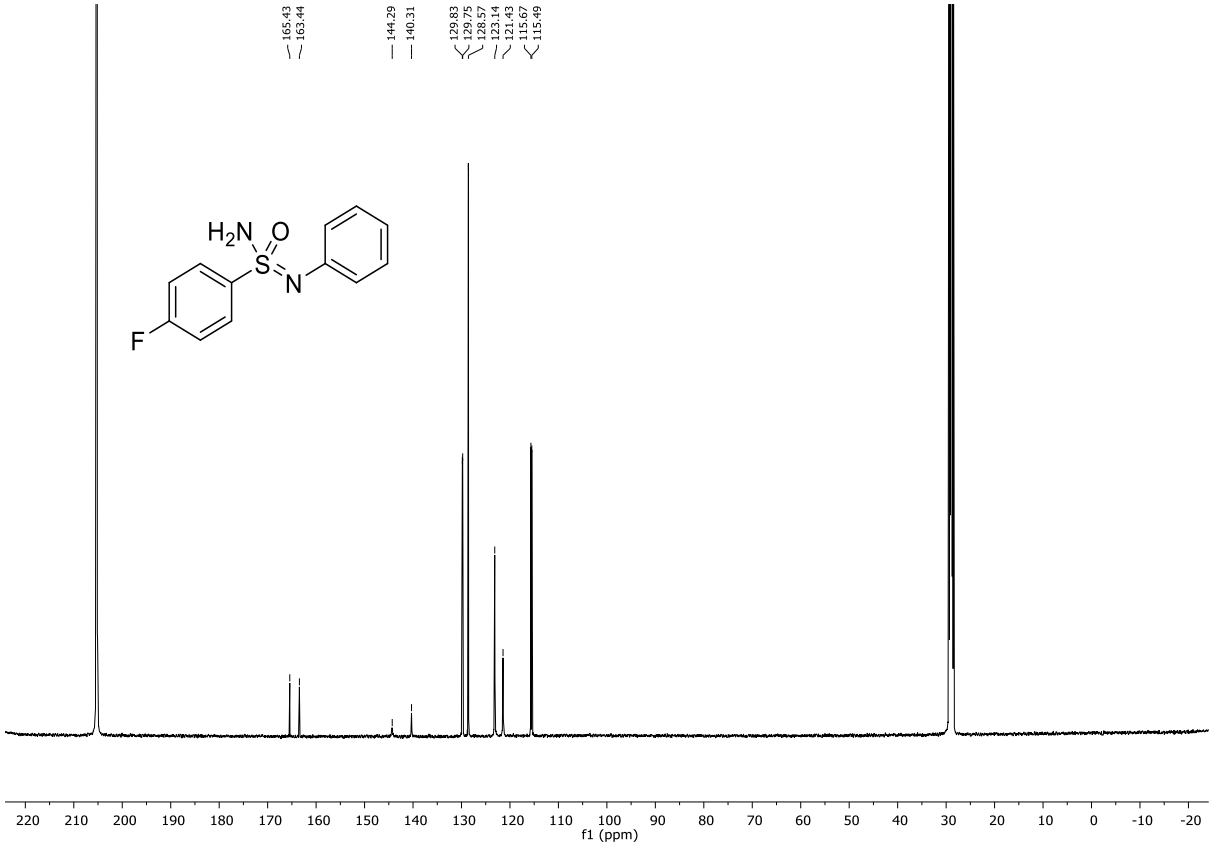
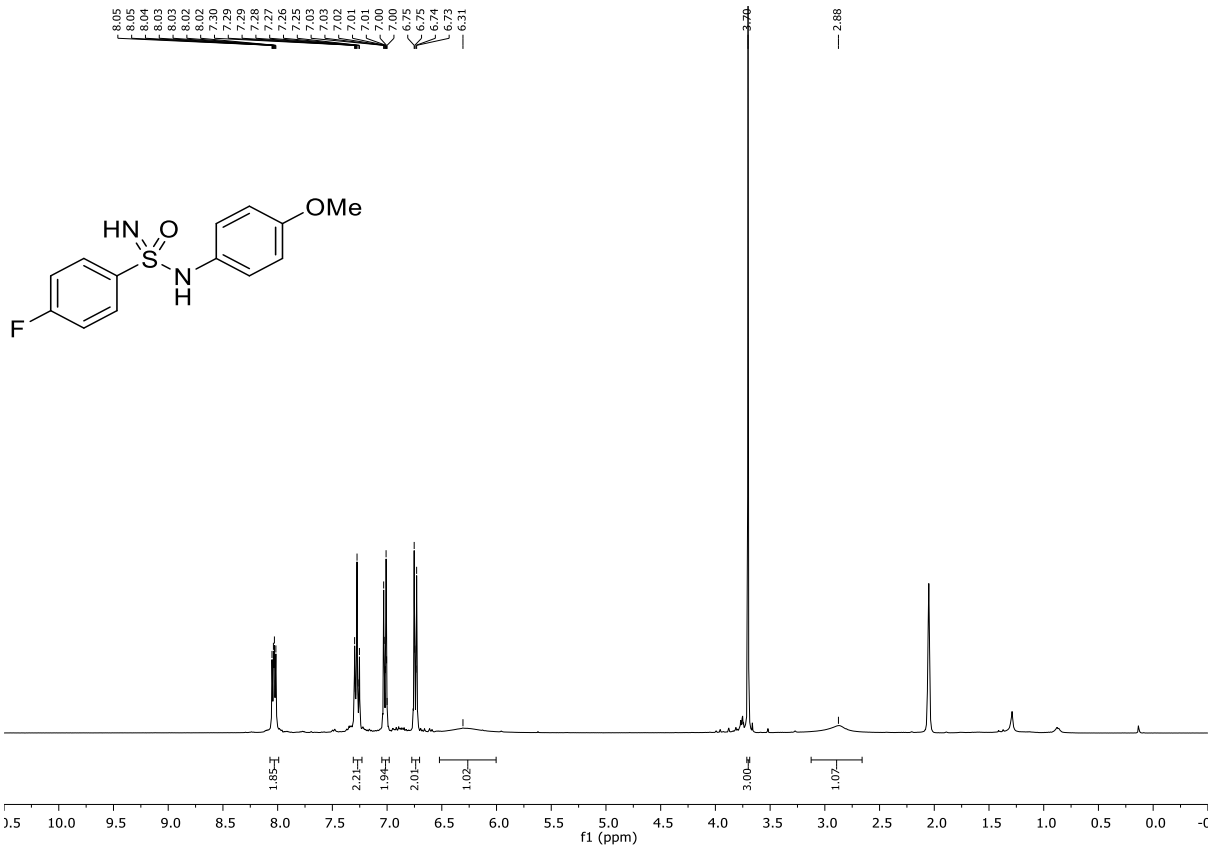
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


165.43
163.44
144.29
140.31
129.83
129.75
128.57
123.14
121.43
115.67
115.49
H2N
O
S
N
F
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)


-109.59
-109.60
-109.61
-109.61
-109.62
-109.63
-109.64
-109.65
-109.66
H2N
O
S
N
F
-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)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8.05
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7.29
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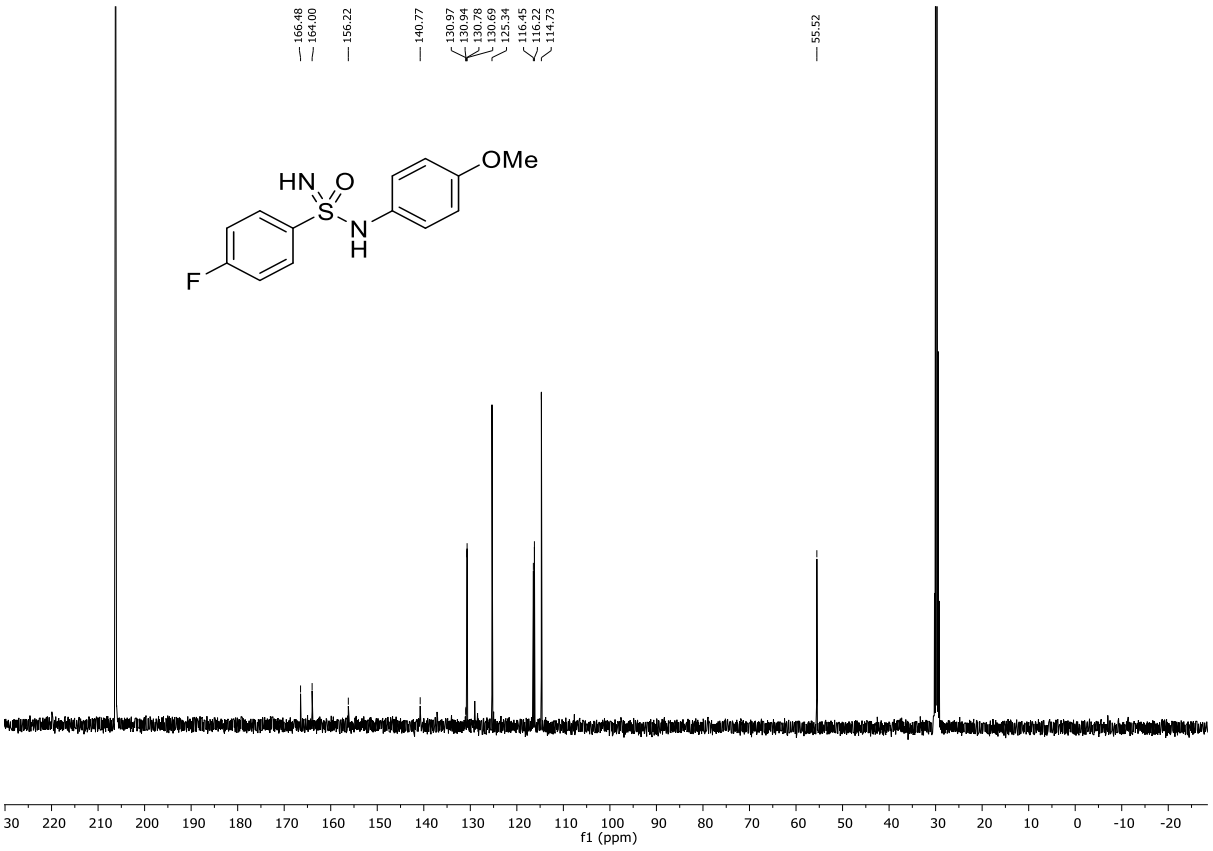
7.26
7.25
7.03
7.03
7.02
7.01
7.01
7.00
7.00
6.75
6.75
6.74
6.73
6.31
3.70
2.88
HN
O
S
N
H
F
OMe
1.85
2.21
1.94
2.01
1.02
3.00
1.07
f1 (ppm)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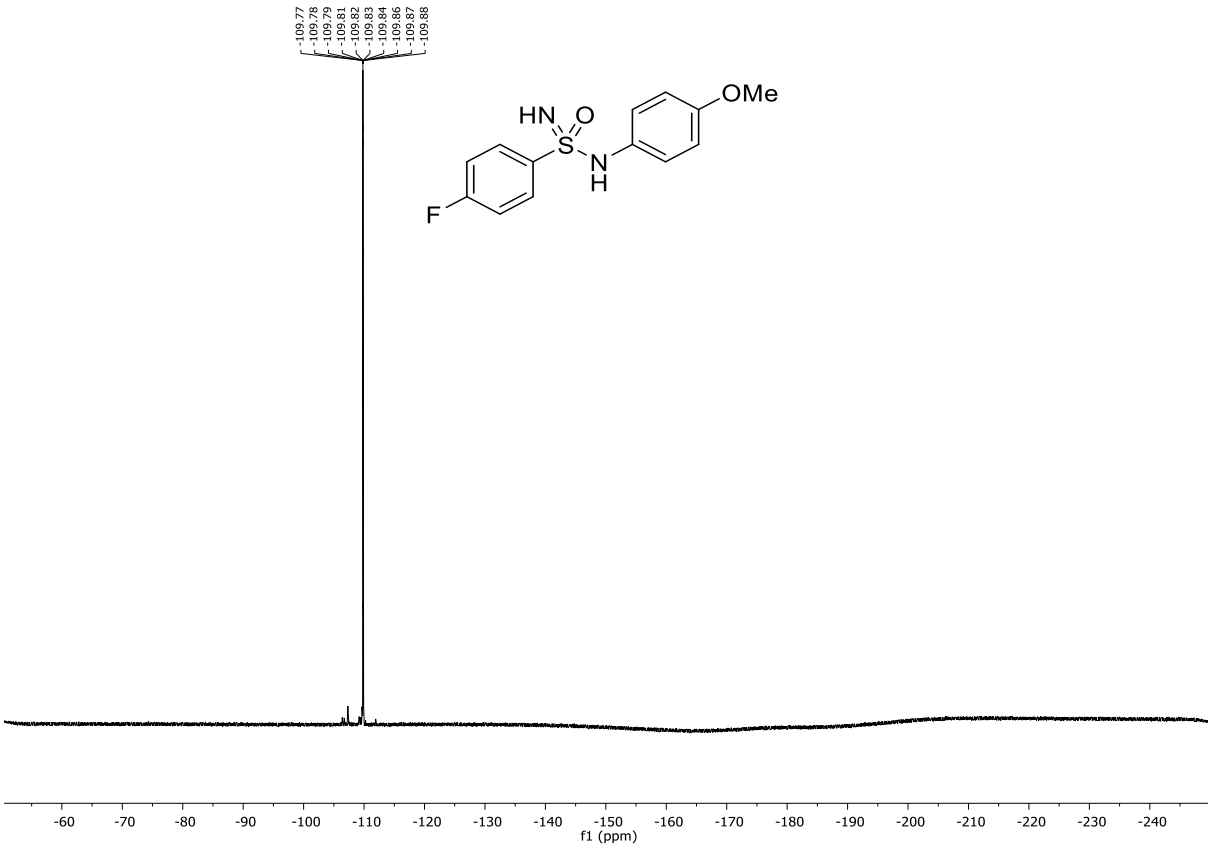
116.22
114.73
55.52
HN
O
S
N
H
F
OMe
f1 (ppm)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-109.84
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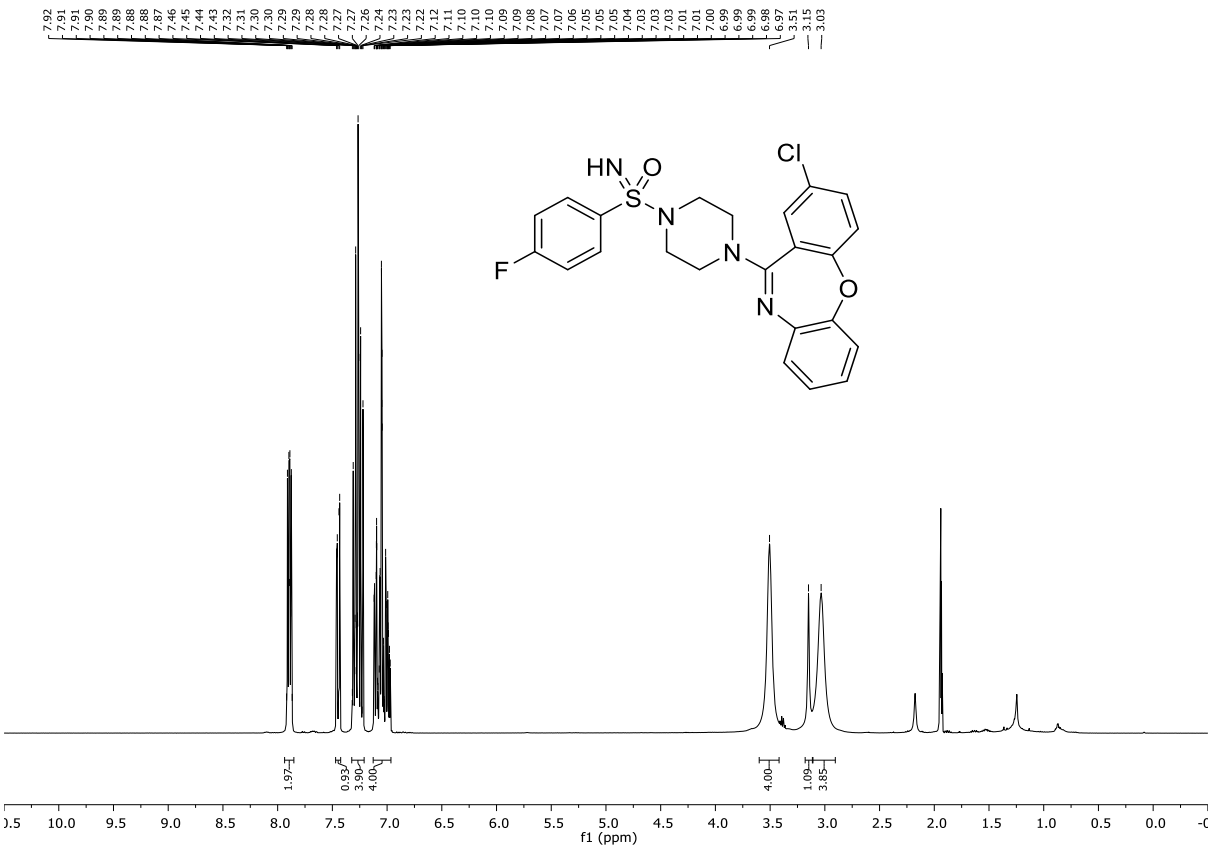
-109.87
-109.88
HN
O
S
N
H
OMe
F
-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)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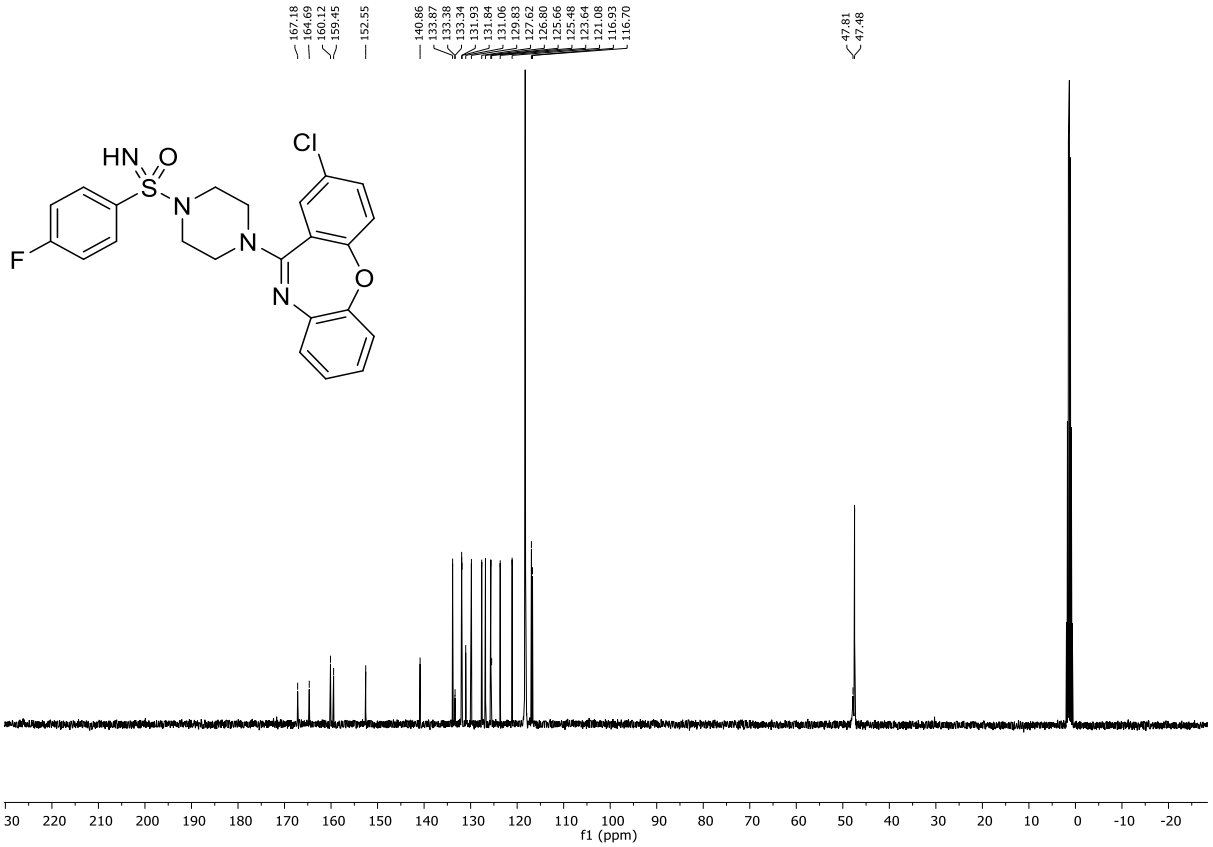
HN
O
S
N
N
N
O
F
Cl
1.97
0.93
3.90
4.00
4.00
1.09
3.85
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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126.80
125.66
125.48
123.64
121.08
116.93
116.70
47.81
47.48
HN
O
S
N
N
Cl
F
N
O
f1 (ppm)


-108.67
-108.68
-108.69
-108.69
-108.70
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-108.73
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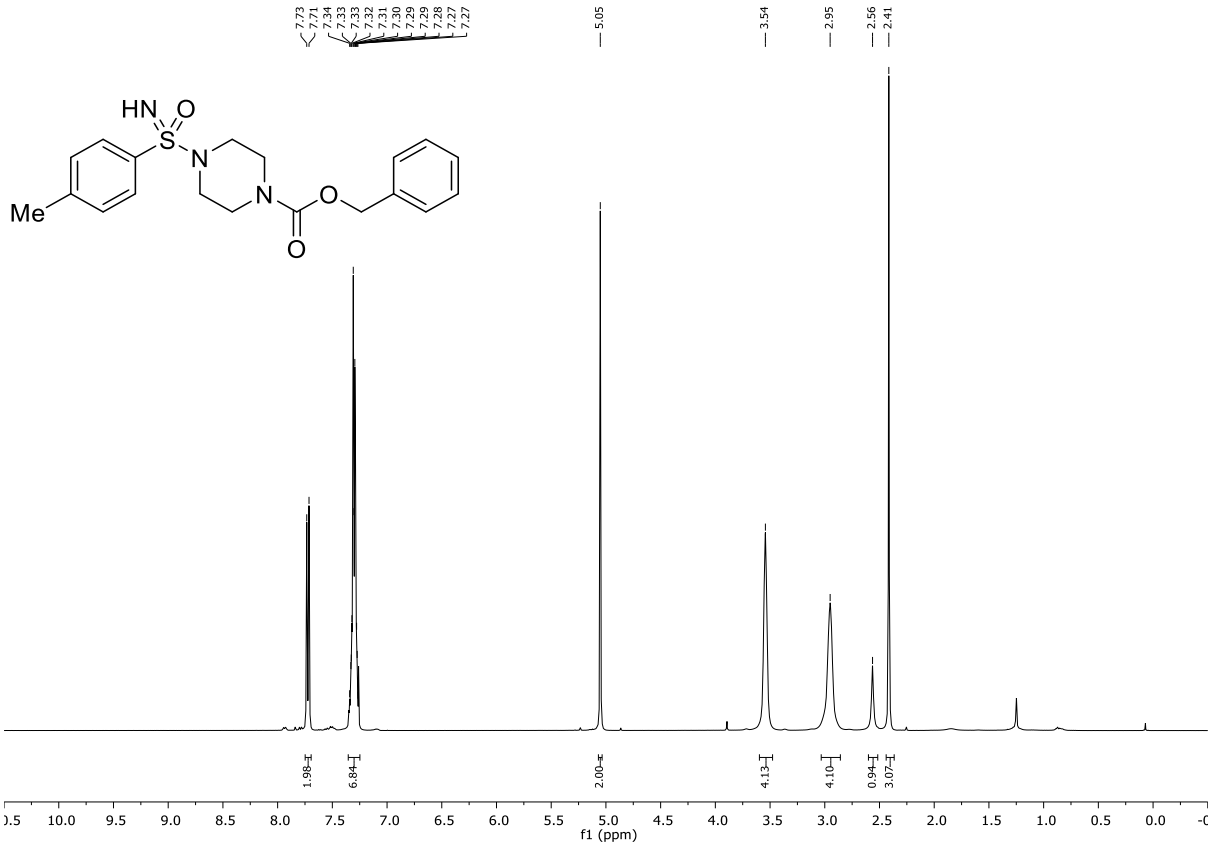
HN
O
S
N
N
Cl
F
N
O
f1 (ppm)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7.28
7.27
7.27
5.05
3.54
2.95
2.56
2.41
HN
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Me
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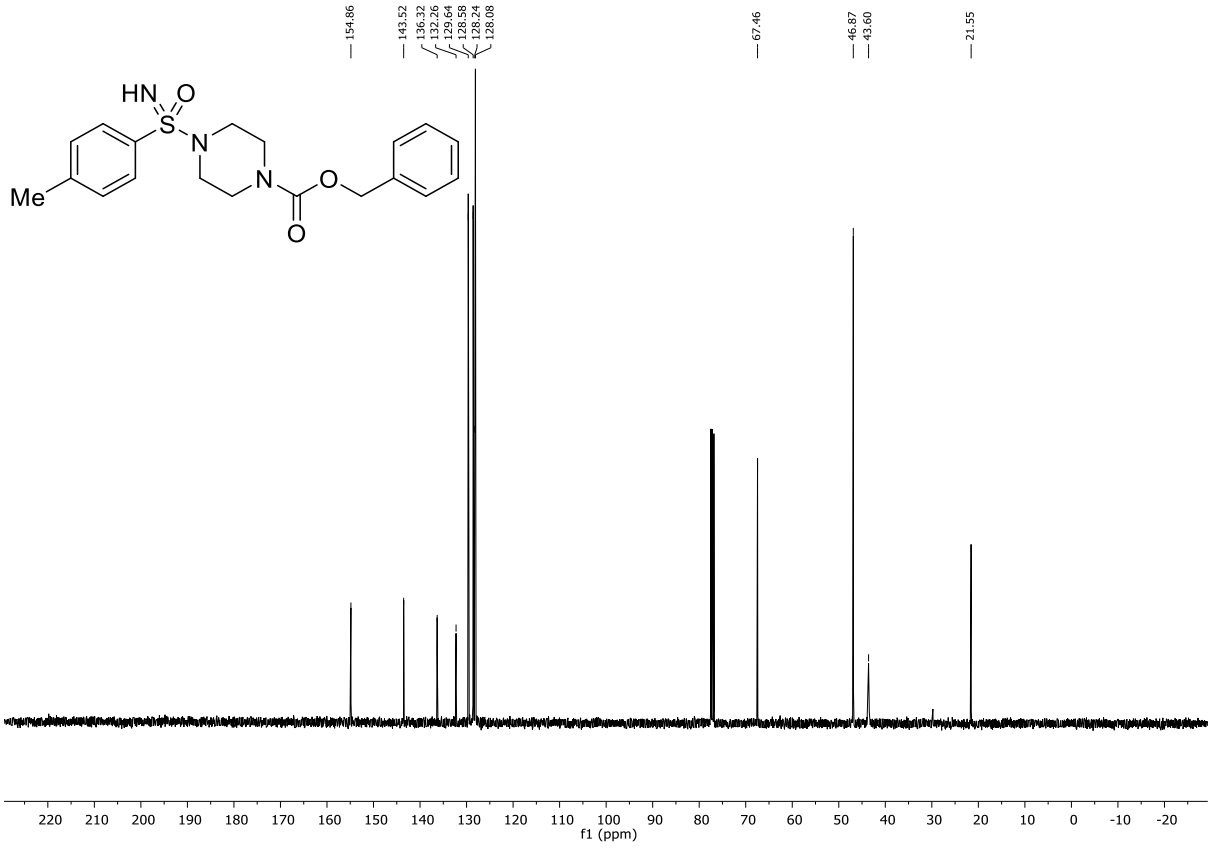
6.84
2.00
4.13
4.10
0.94
3.07
f1 (ppm)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143.52
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132.26
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128.58
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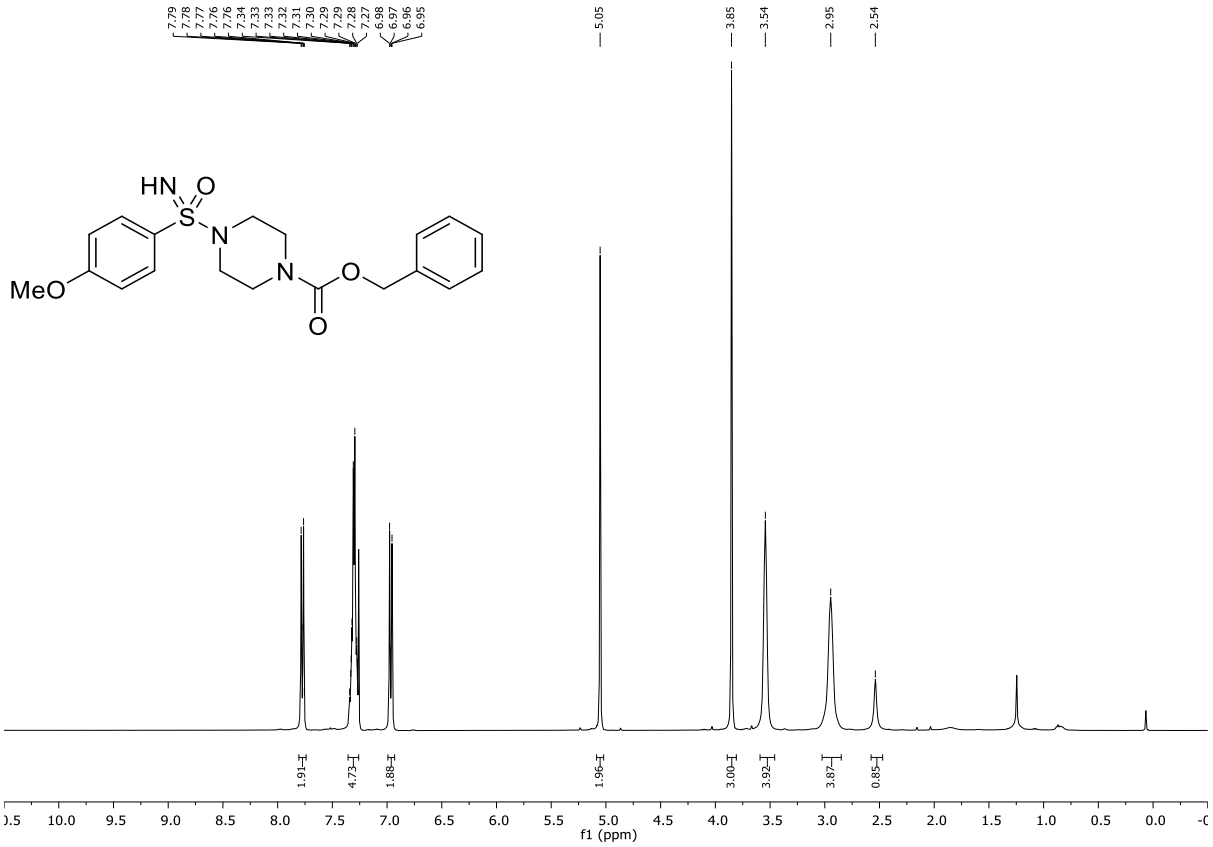
128.08
67.46
46.87
43.60
21.55
HN
O
S
N
N
O
O
Me
f1 (ppm)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7.33
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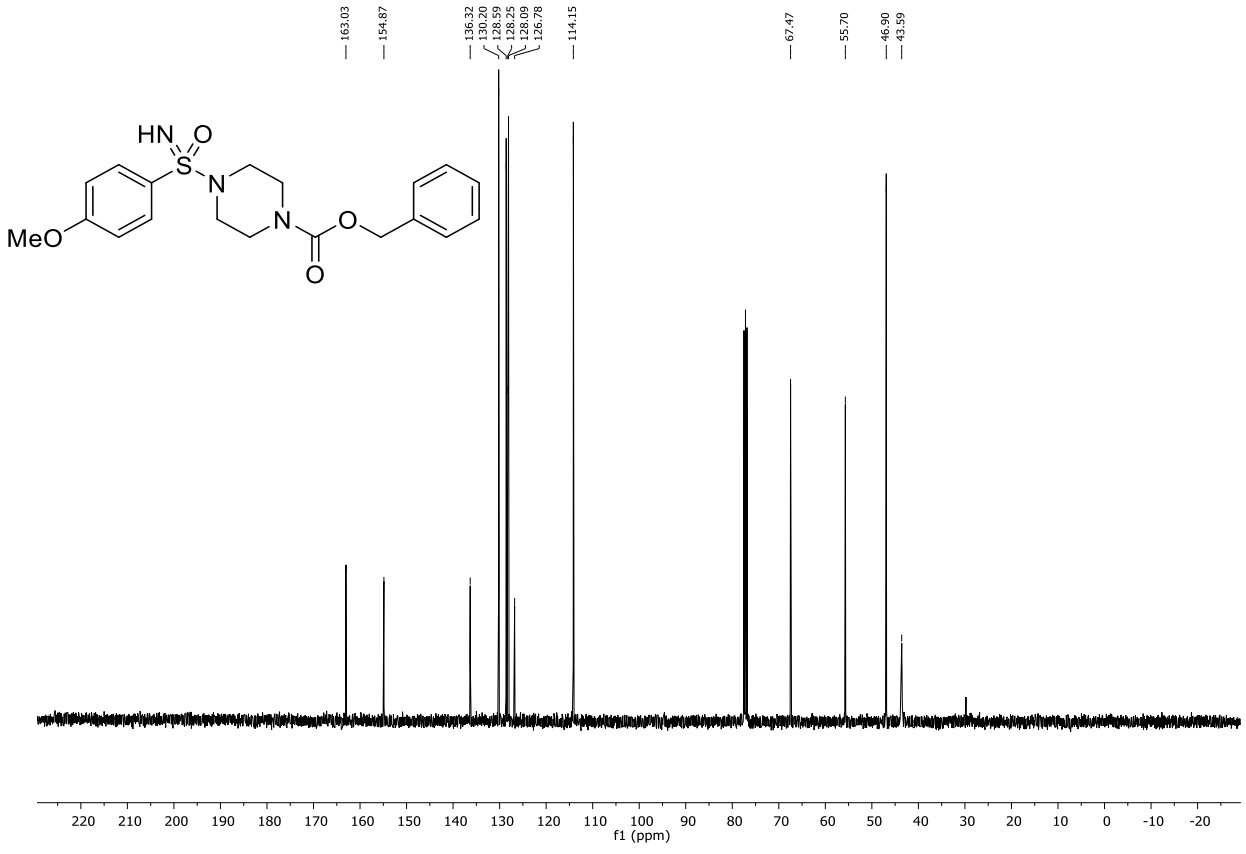
7.31
7.30
7.29
7.29
7.28
7.27
6.98
6.97
6.96
6.95
5.05
3.85
3.54
2.95
2.54
HN
O
S
N
N
O
MeO
O
1.91
4.73
1.88
1.96
3.00
3.92
3.87
0.85
f1 (ppm)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128.09
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55.70
46.90
43.59
HN
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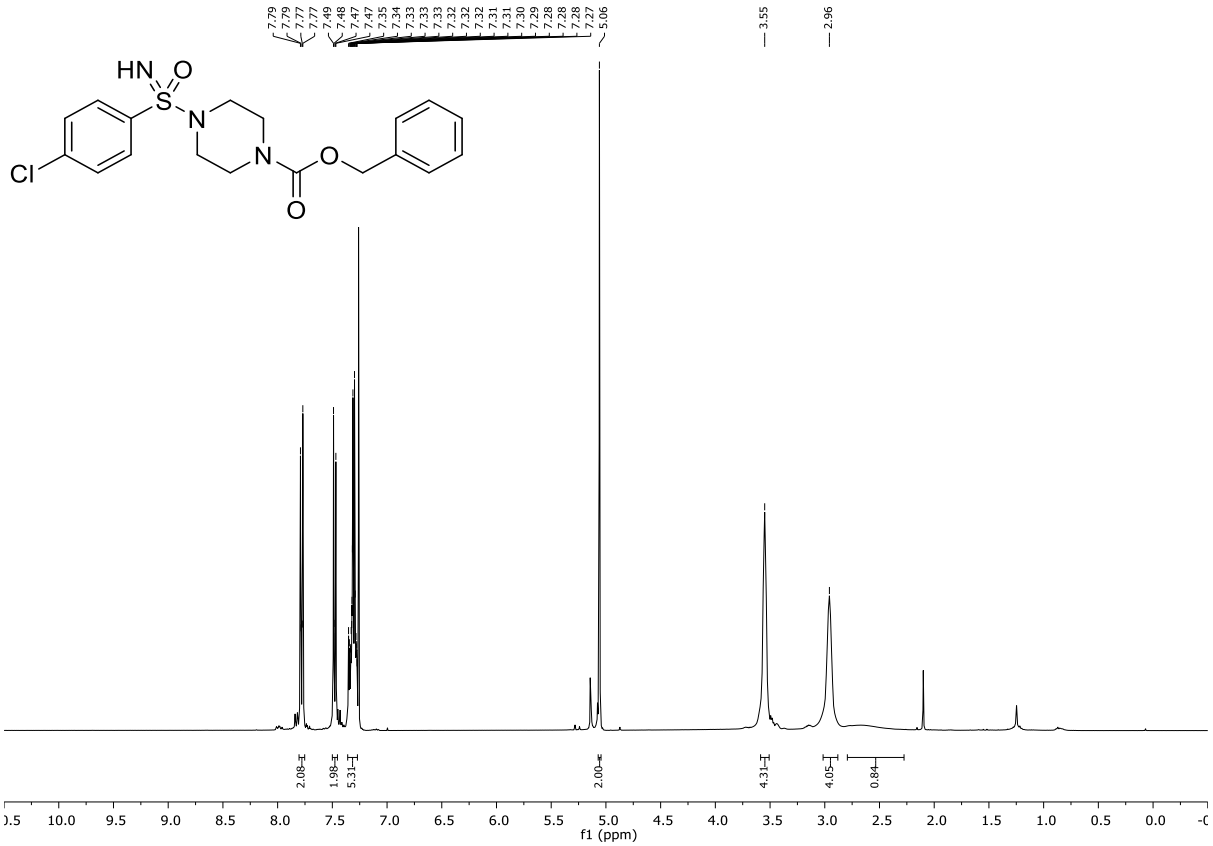
S
N
N
O
MeO
O
f1 (ppm)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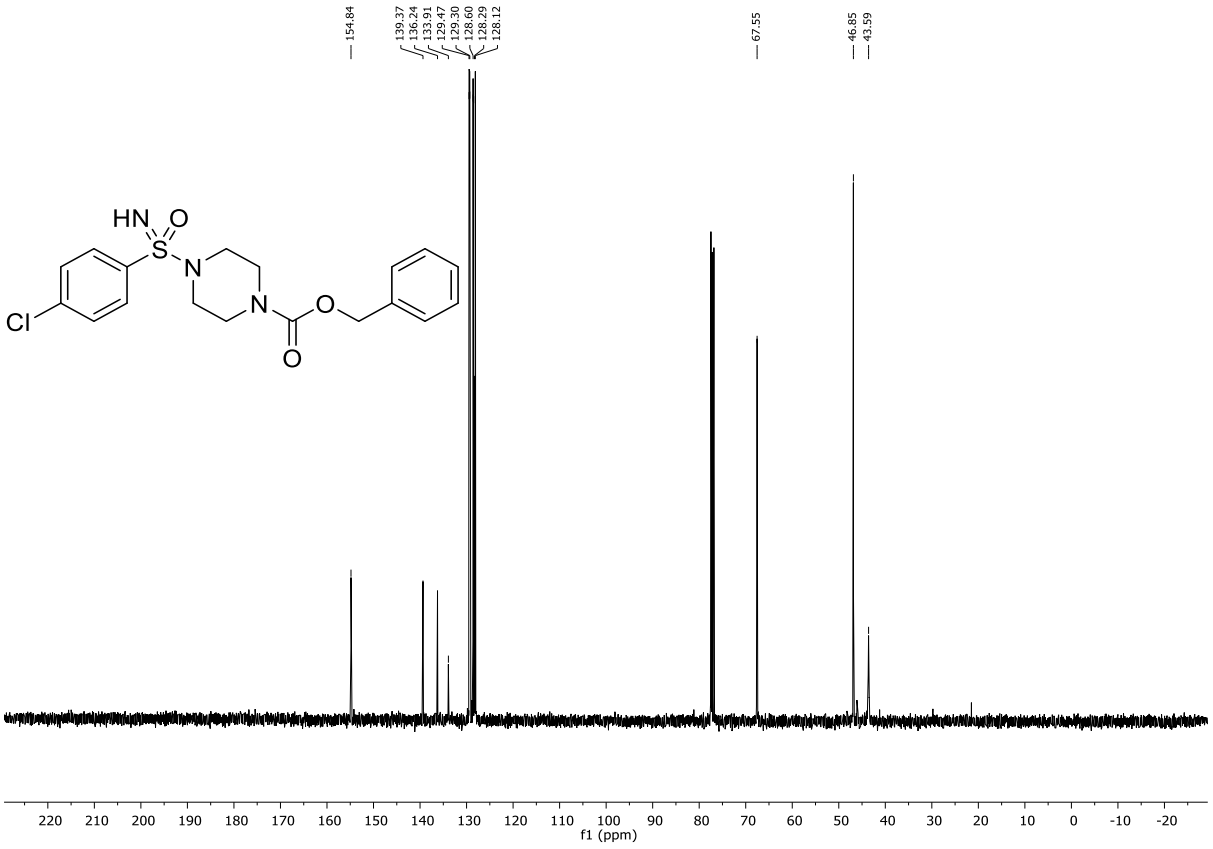
7.47
7.47
7.35
7.34
7.33
7.33
7.32
7.32
7.31
7.30
7.29
7.28
7.28
7.27
5.06
3.55
2.96
HN
O
S
N
N
O
Cl
O
2.08
1.98
5.31
2.00
4.31
4.05
0.84
f1 (ppm)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139.37
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129.30
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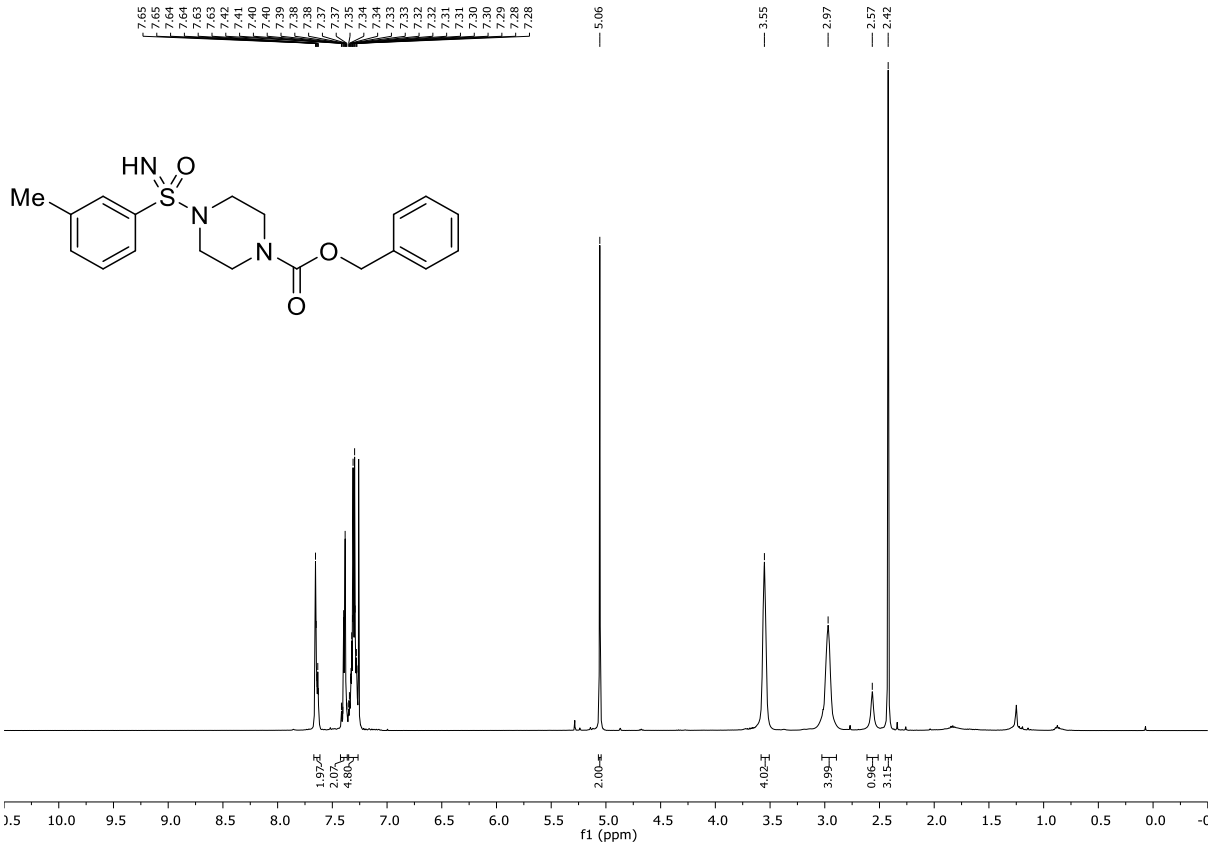
67.55
46.85
43.59
HN
O
S
N
N
O
Cl
O
f1 (ppm)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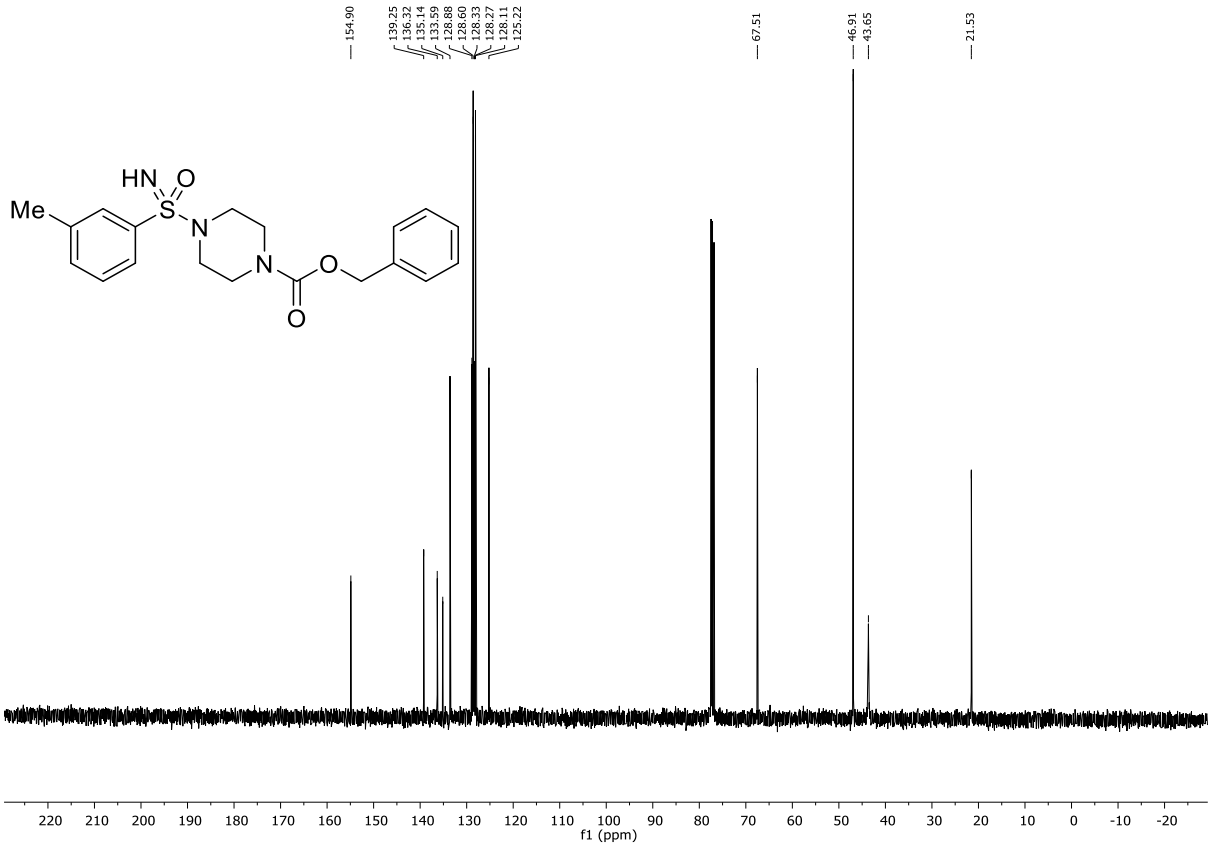
5.06
3.55
2.97
2.57
2.42
HN
O
S
N
Me
N
O
O
1.97
2.07
4.80
2.00
4.02
3.99
0.96
3.15
f1 (ppm)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128.33
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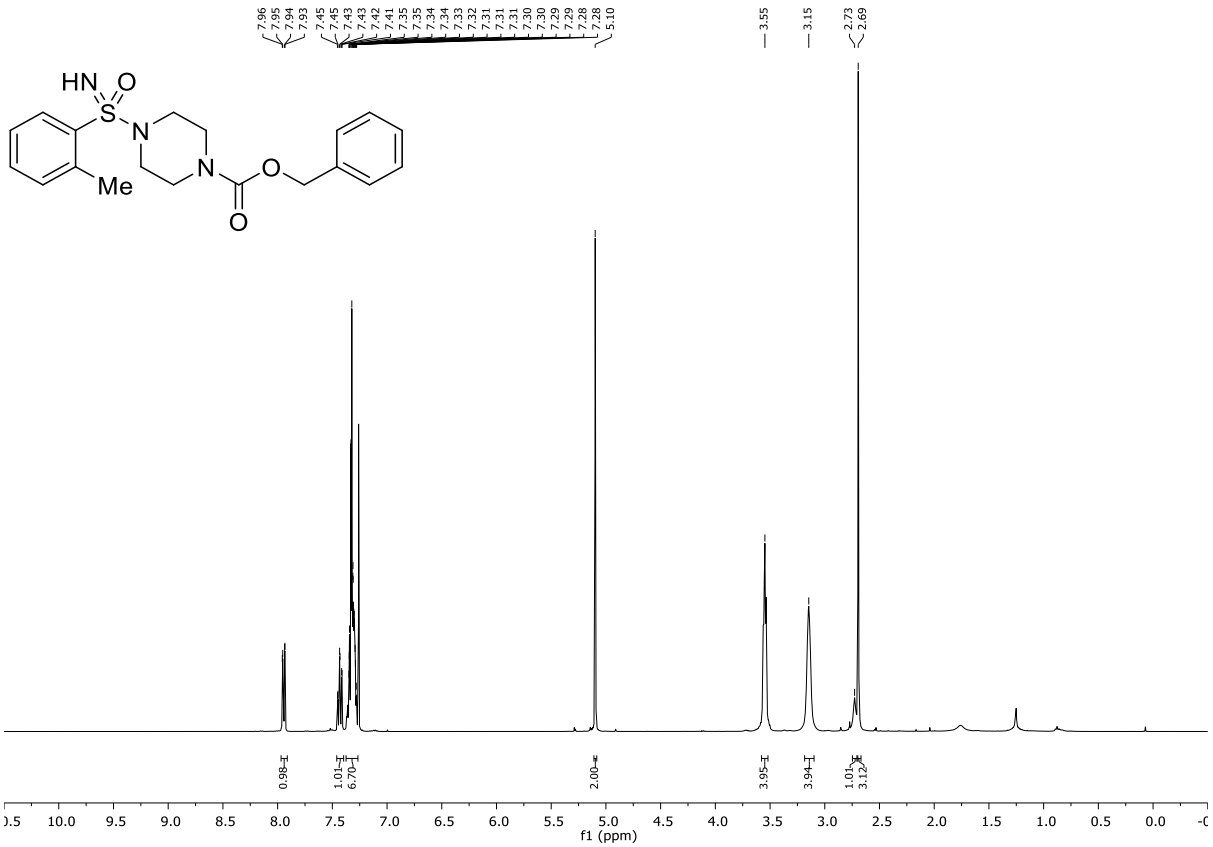
46.91
43.65
21.53
HN
O
S
N
Me
N
O
O
f1 (ppm)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7.45
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7.42
7.41
7.35
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7.29
7.28
7.28
5.10
3.55
3.15
2.73
2.69
HN
O
S
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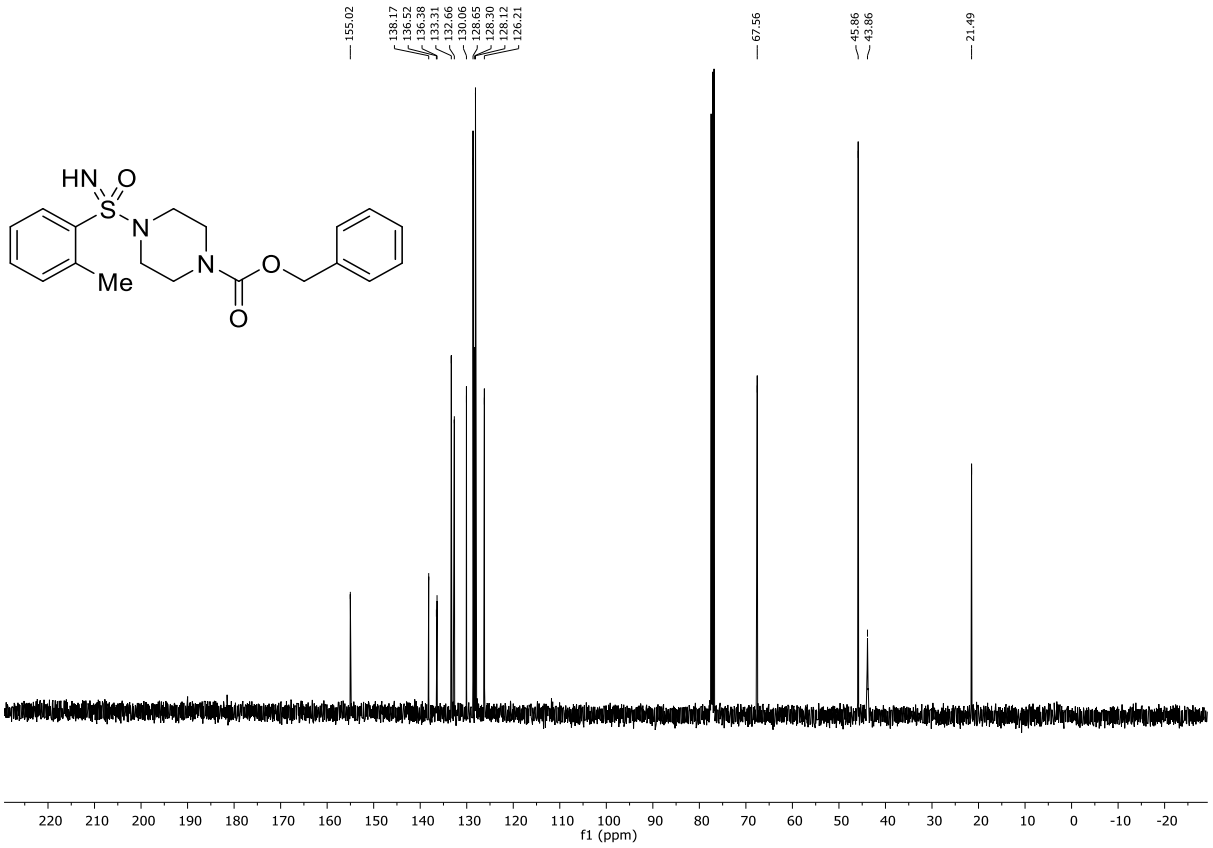
6.70
2.00
3.95
3.94
1.01
3.12
f1 (ppm)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133.31
132.66
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128.65
128.30
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21.49
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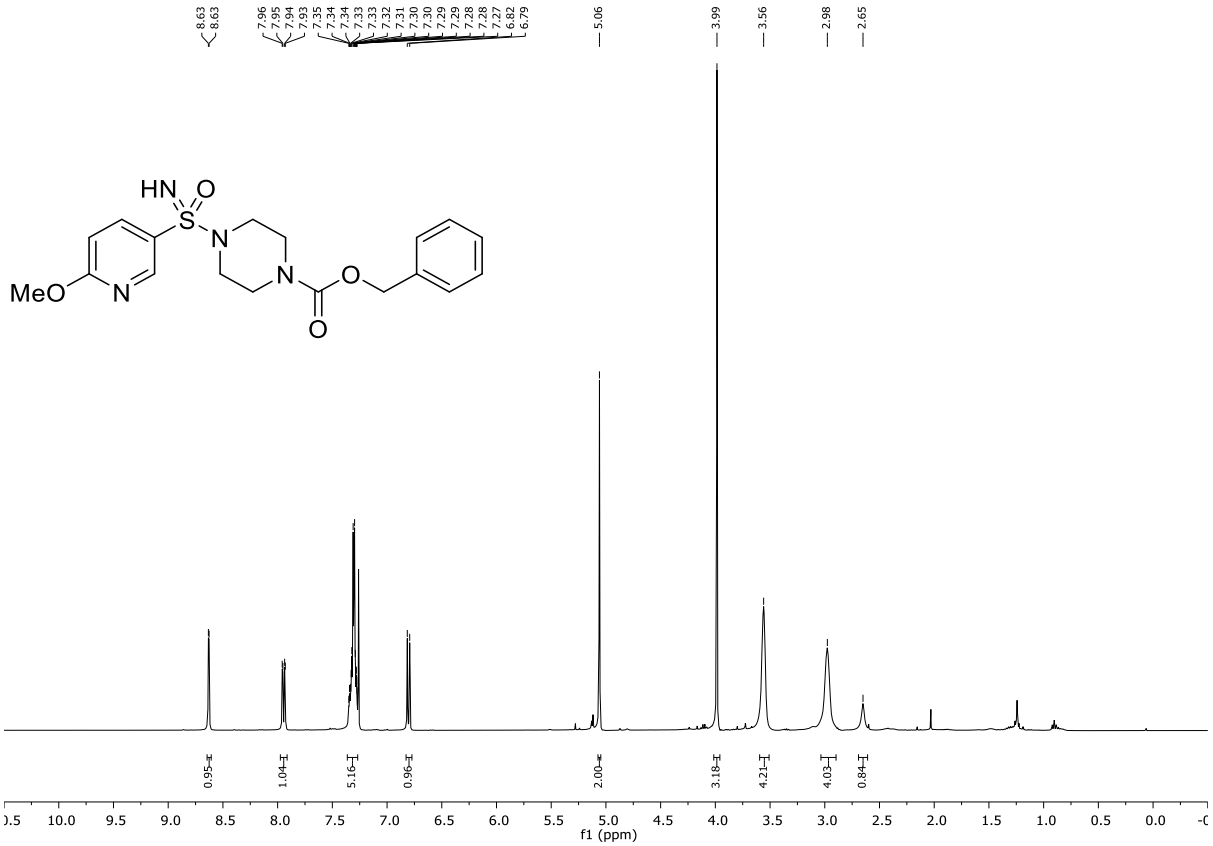
S
N
N
O
Me
O
f1 (ppm)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7.94
7.93
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7.34
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7.33
7.32
7.31
7.30
7.29
7.29
7.28
7.28
7.27
6.82
6.79
5.06
3.99
3.56
2.98
2.65
HN
O
S
N
N
O
MeO
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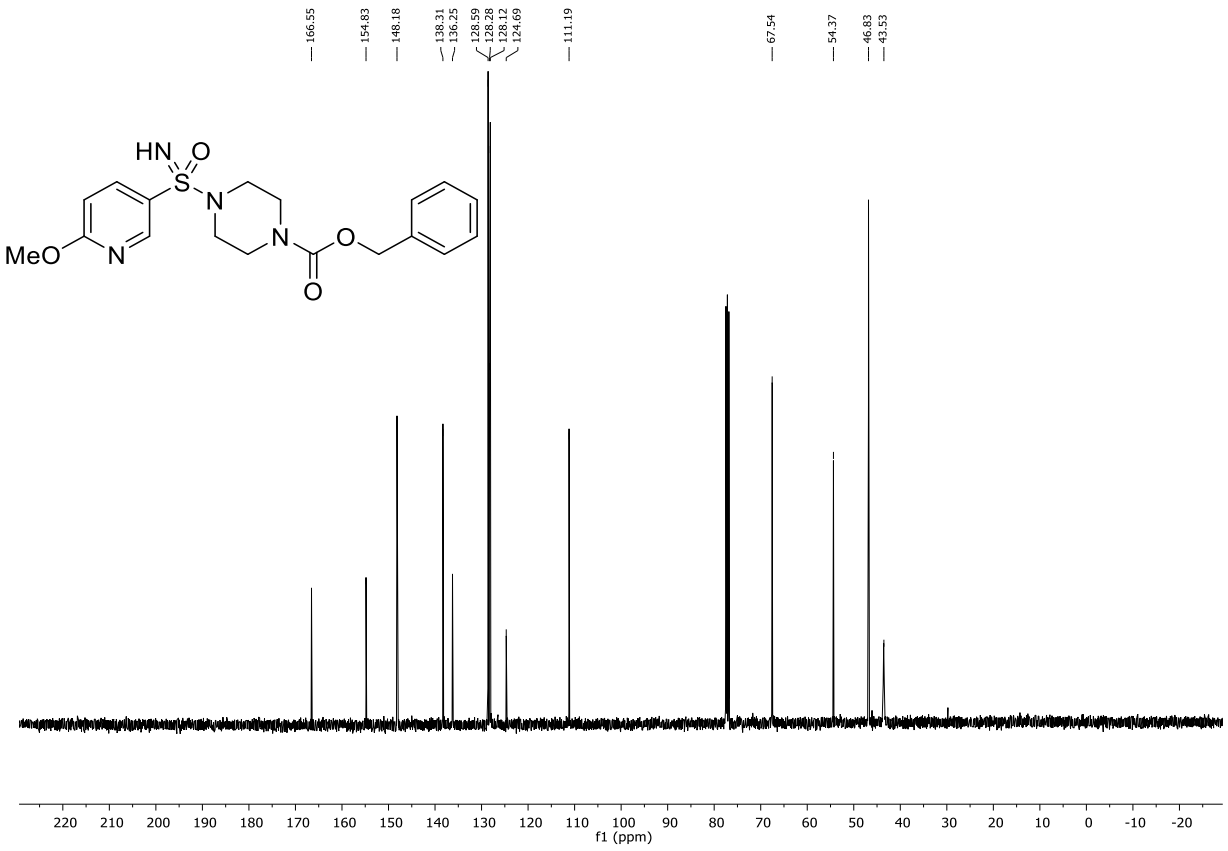
4.21
4.03
0.84
f1 (ppm)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46.83
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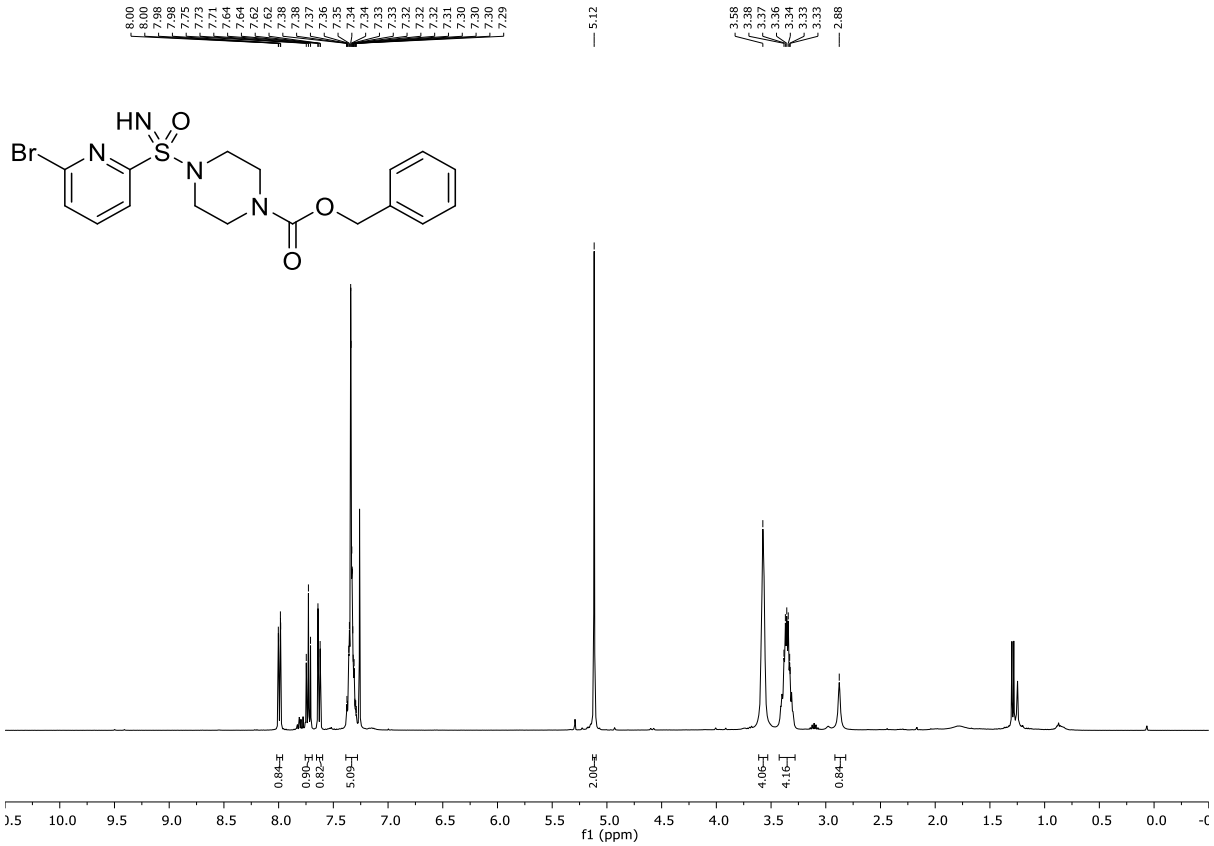
S
N
N
O
MeO
N
O
f1 (ppm)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7.38
7.37
7.36
7.35
7.34
7.34
7.33
7.33
7.32
7.32
7.32
7.31
7.30
7.30
7.30
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3.58
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3.37
3.36
3.34
3.33
3.33
2.88
HN
O
Br
N
S
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4.06
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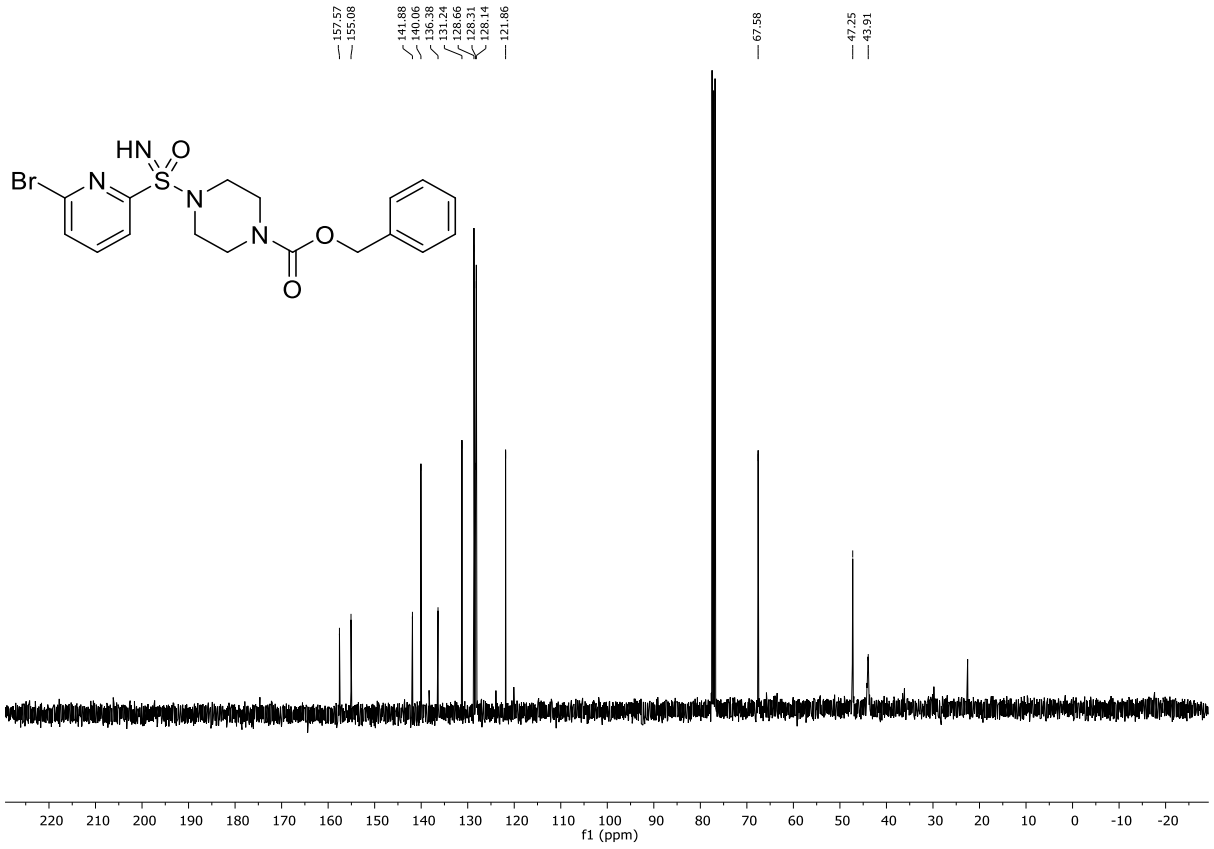
f1 (ppm)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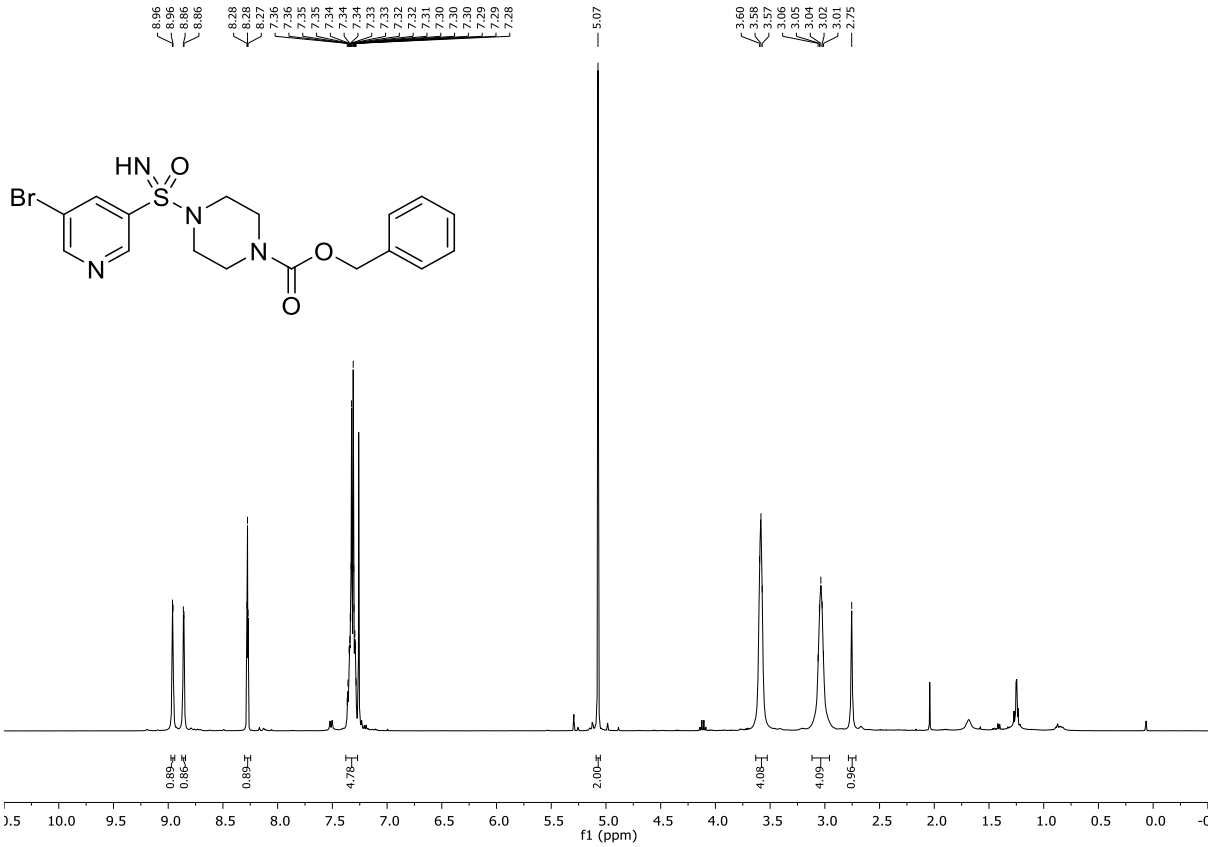
Br
N
S
N
N
O
O
f1 (ppm)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3.58
3.57
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3.05
3.04
3.02
3.01
2.75
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O
Br
S
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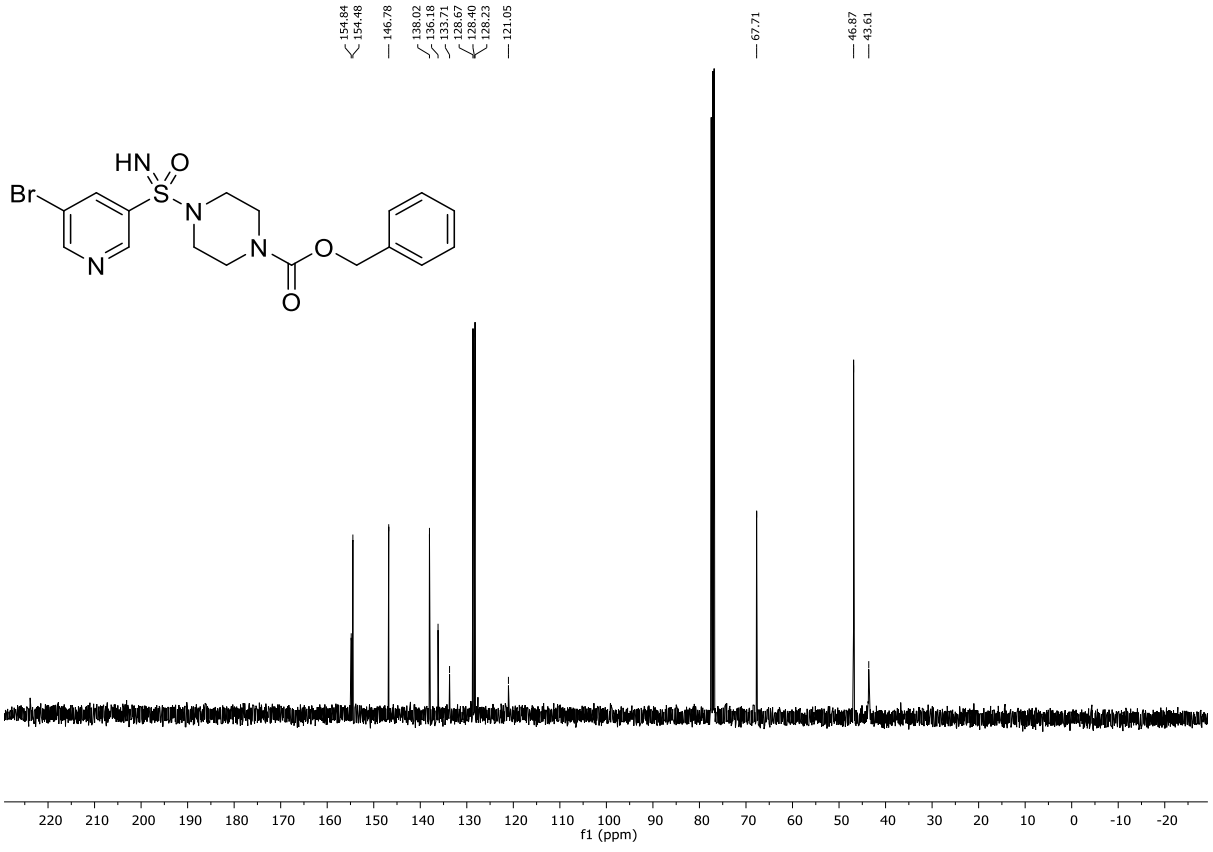
f1 (ppm)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Br
S
N
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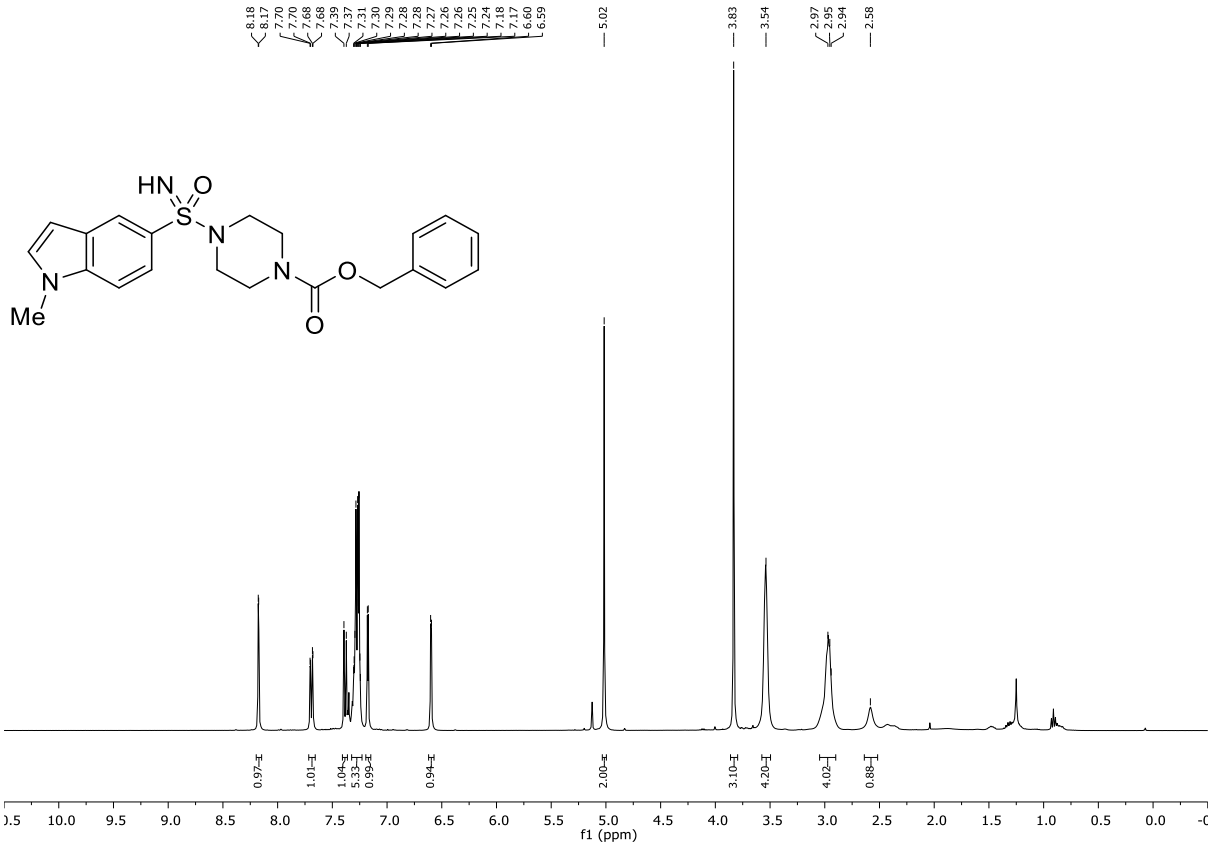
N
O
O
f1 (ppm)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7.26
7.25
7.24
7.18
7.17
6.60
6.59
5.02
3.83
3.54
2.97
2.95
2.94
2.58
HN
O
S
N
N
O
N
Me
O
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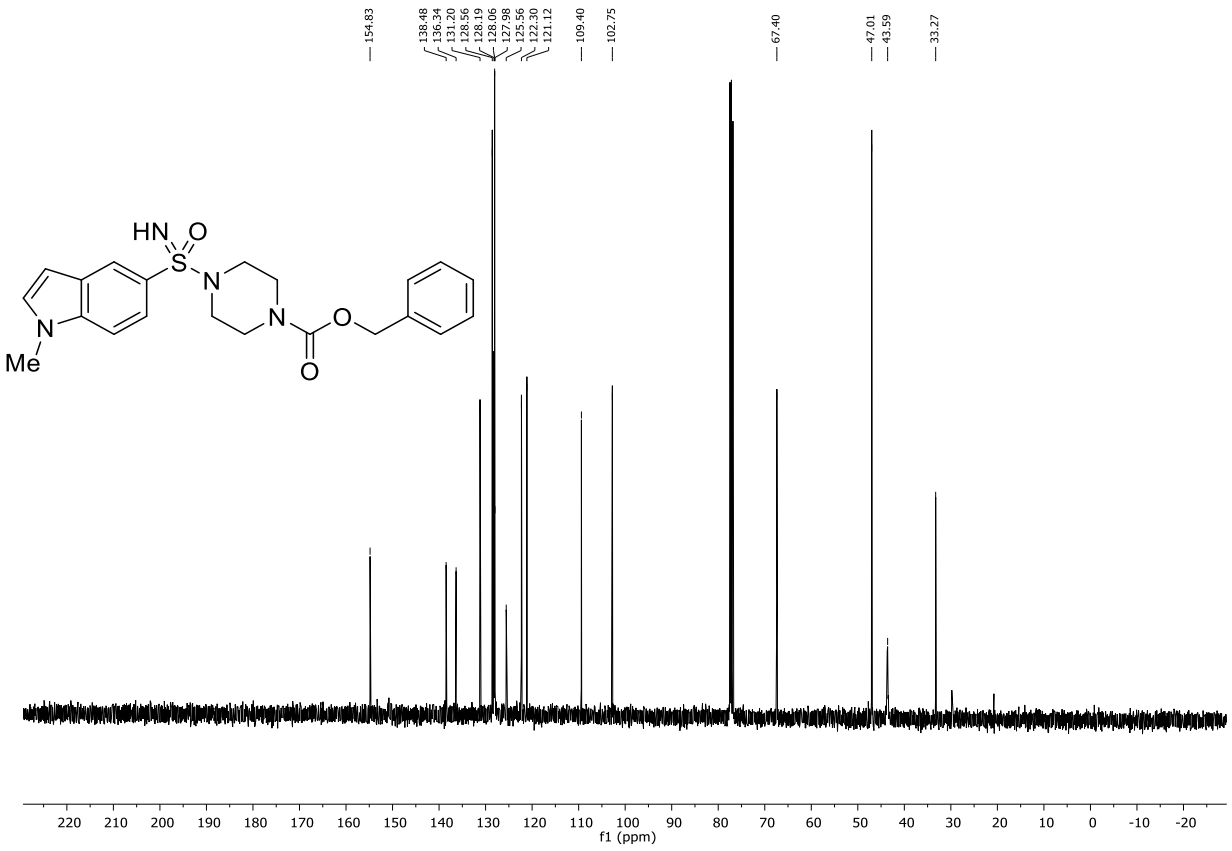
5.33
0.99
0.94
2.00
3.10
4.20
4.02
0.88
f1 (ppm)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128.19
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127.98
125.56
122.30
121.12
109.40
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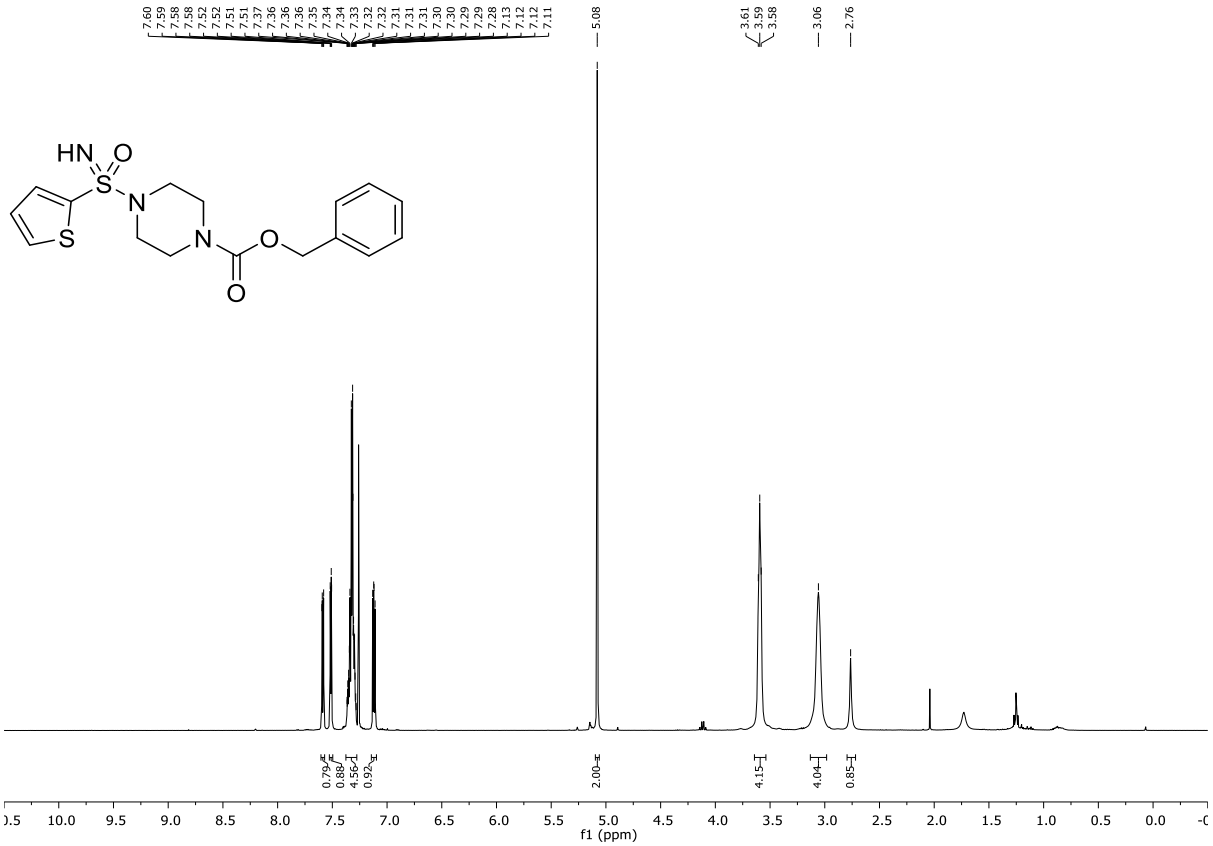
67.40
47.01
43.59
33.27
HN
O
S
N
N
O
N
Me
O
f1 (ppm)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7.12
7.11
5.08
3.61
3.59
3.58
3.06
2.76
HN
O
S
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0.88
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4.15
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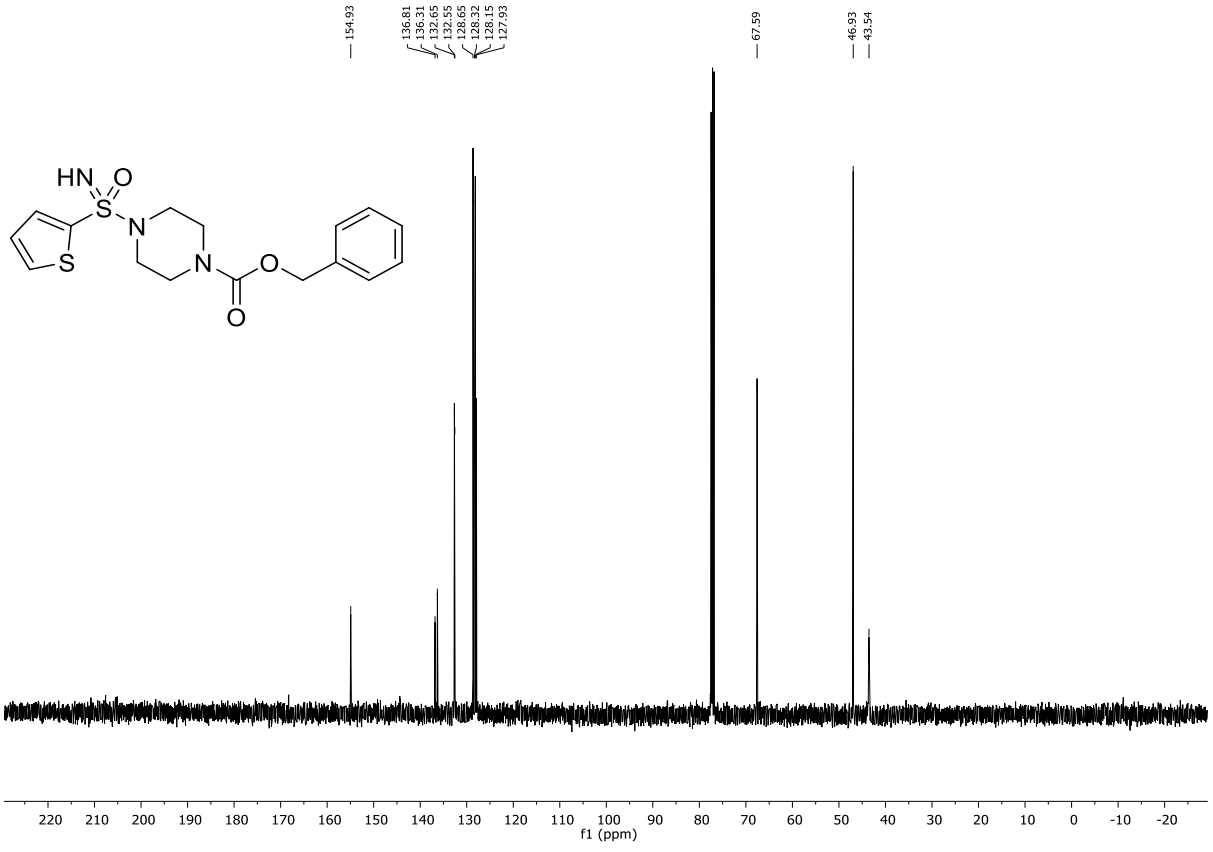
0.85
f1 (ppm)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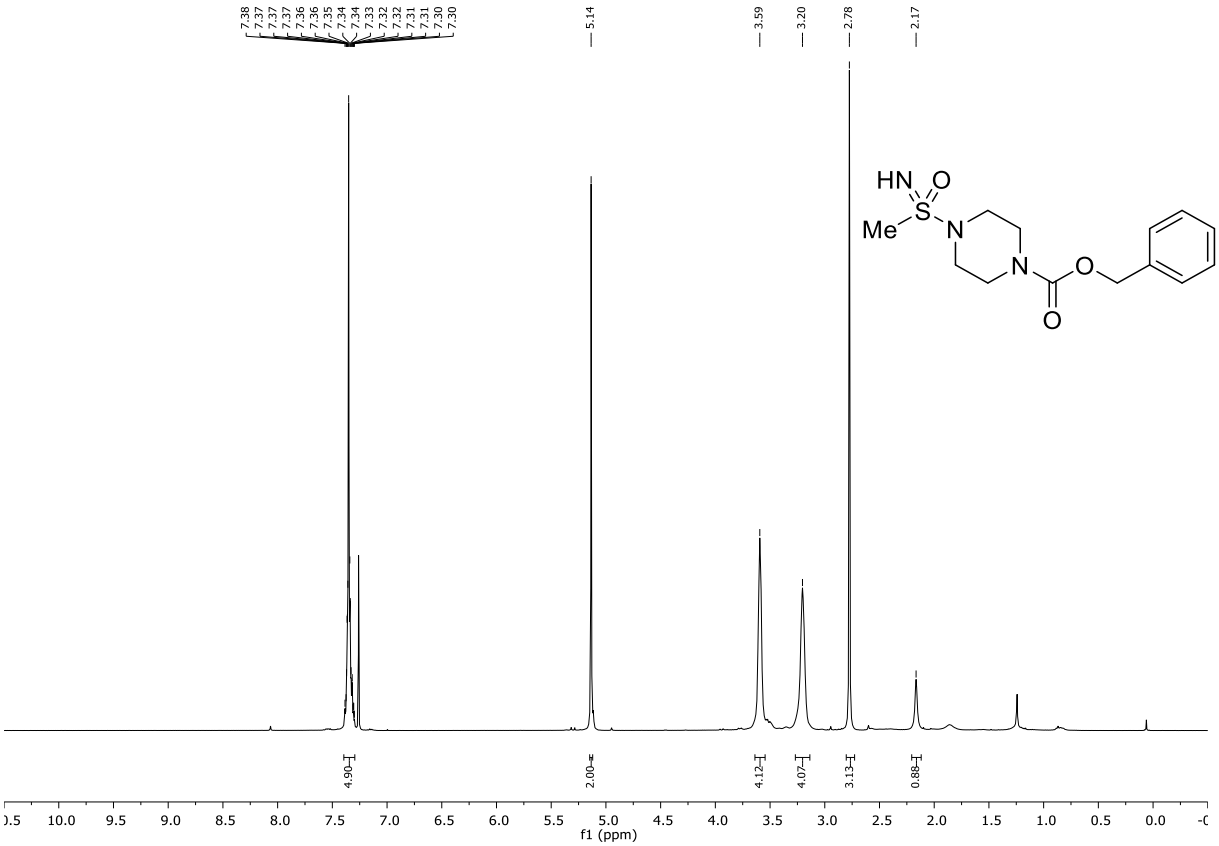
67.59
46.93
43.54
HN
O
S
N
S
N
O
O
f1 (ppm)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7.37
7.37
7.37
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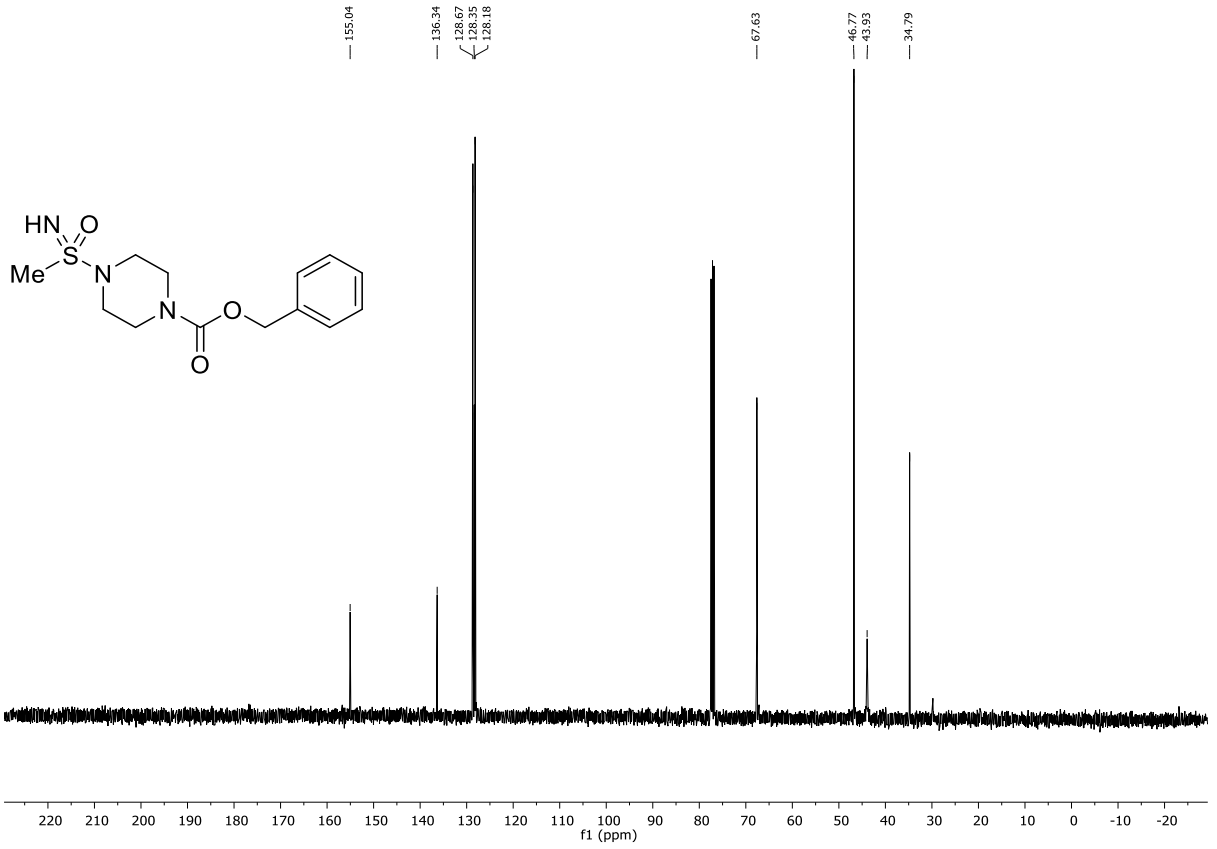
7.35
7.34
7.34
7.33
7.32
7.32
7.31
7.31
7.30
7.30
5.14
3.59
3.20
2.78
2.17
HN
O
S
Me
N
N
O
O
4.90
2.00
4.12
4.07
3.13
0.88
f1 (ppm)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136.34
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128.18
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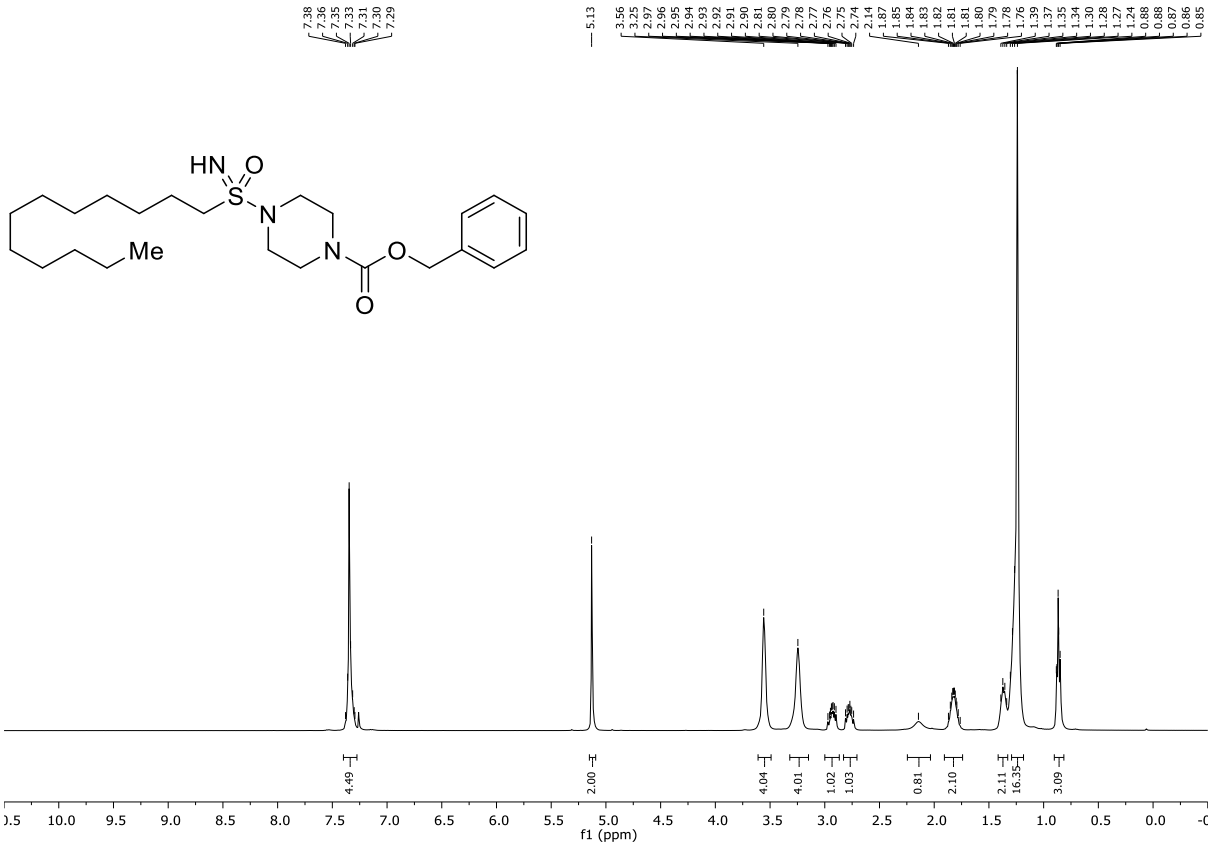
43.93
34.79
HN
O
S
Me
N
N
O
O
f1 (ppm)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O
S
N
N
O
O
Me
7.38
7.36
7.35
7.33
7.31
7.30
7.29
5.13
4.49
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4.01
1.02
1.03
0.81
2.10
2.11
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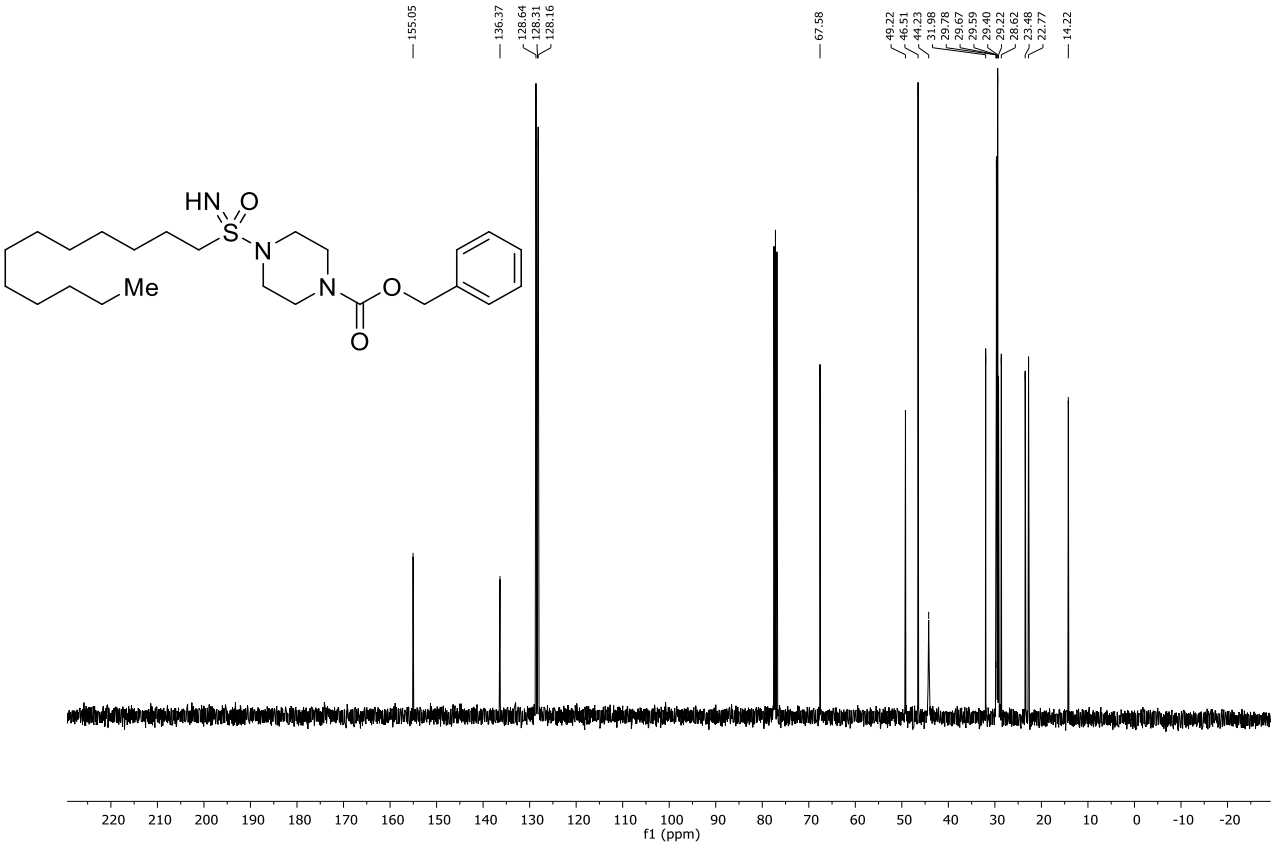
3.09
f1 (ppm)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N
O
O
Me
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128.16
67.58
49.22
46.51
44.23
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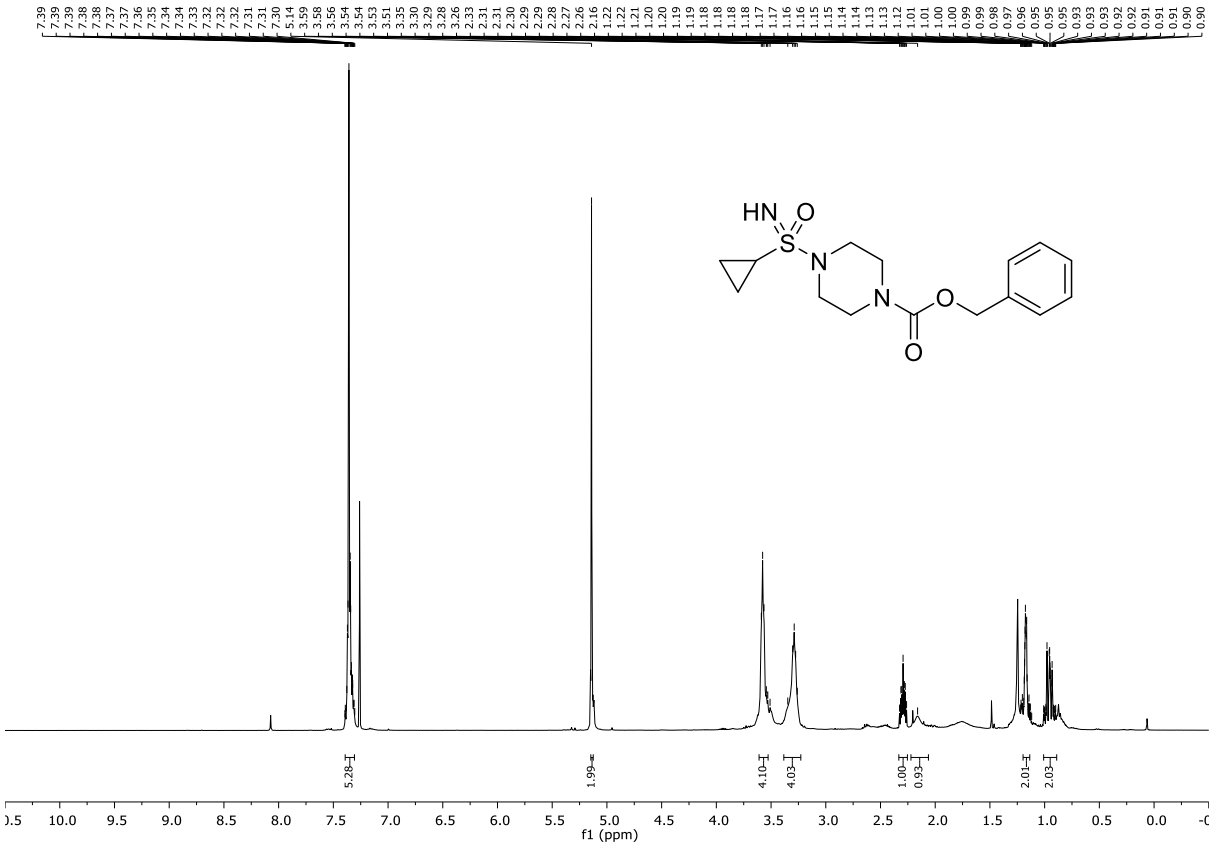
29.67
29.59
29.40
29.22
28.62
23.48
22.77
14.22
f1 (ppm)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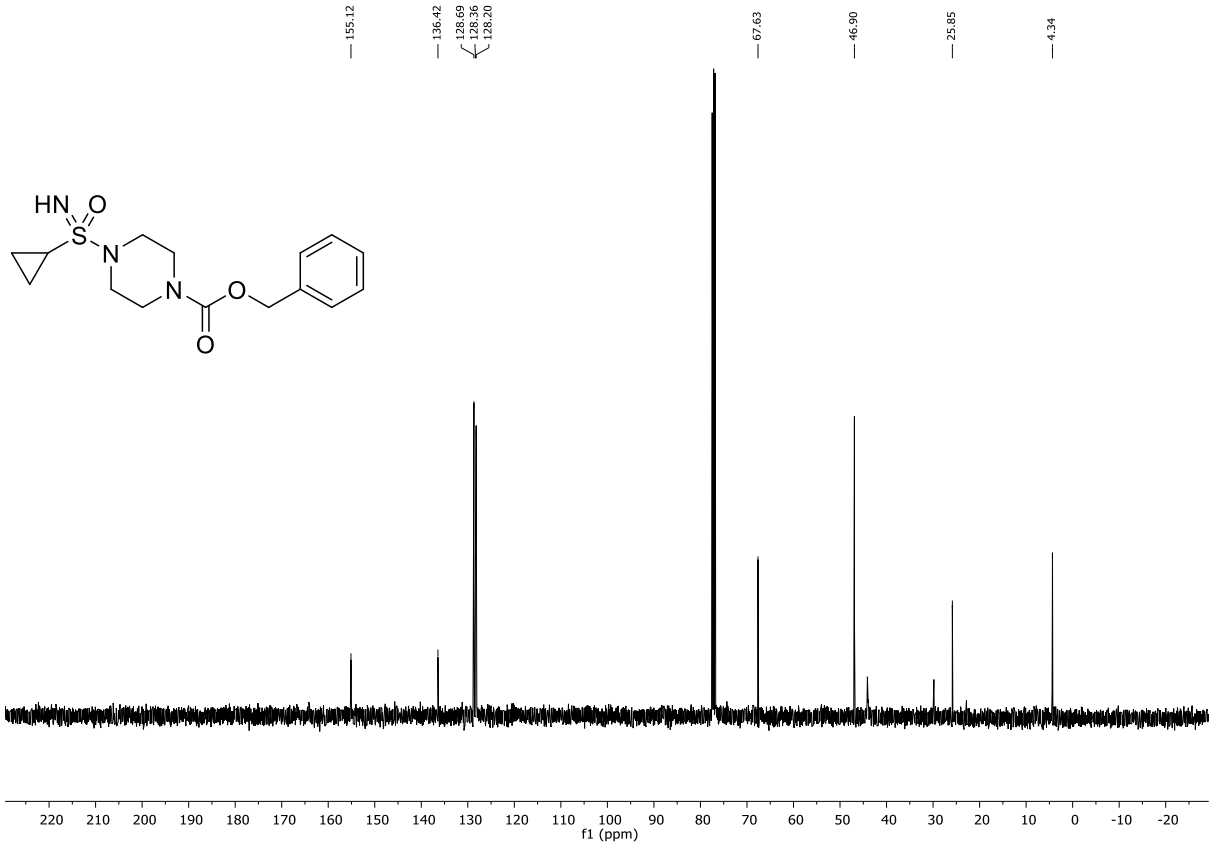
O
S
N
N
O
O
f1 (ppm)


155.12
136.42
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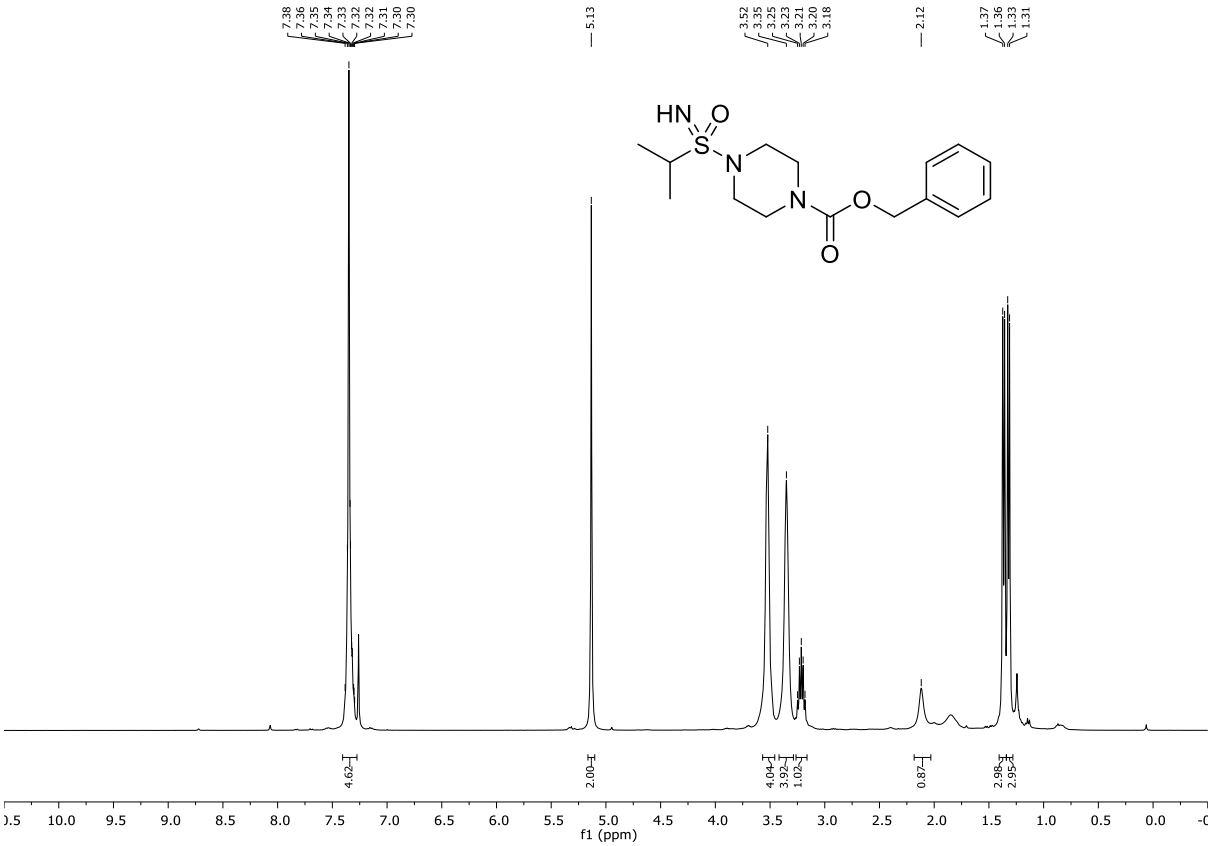
25.85
4.34
HN
O
S
N
N
O
O
f1 (ppm)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7.35
7.34
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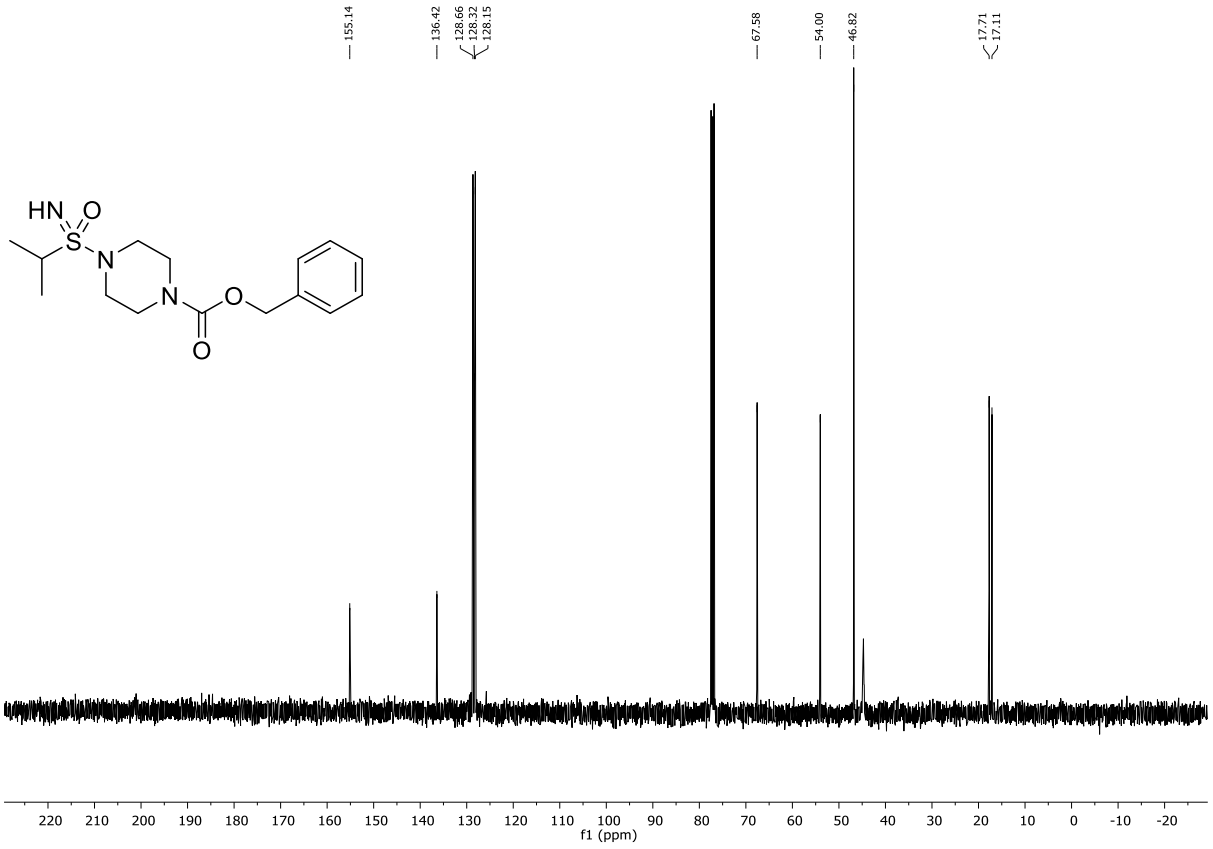
7.31
7.30
7.30
5.13
3.52
3.35
3.25
3.23
3.21
3.20
3.18
2.12
1.37
1.36
1.33
1.31
HN
O
S
N
N
O
O
4.62
2.00
4.04
3.92
1.02
0.87
2.98
2.95
f1 (ppm)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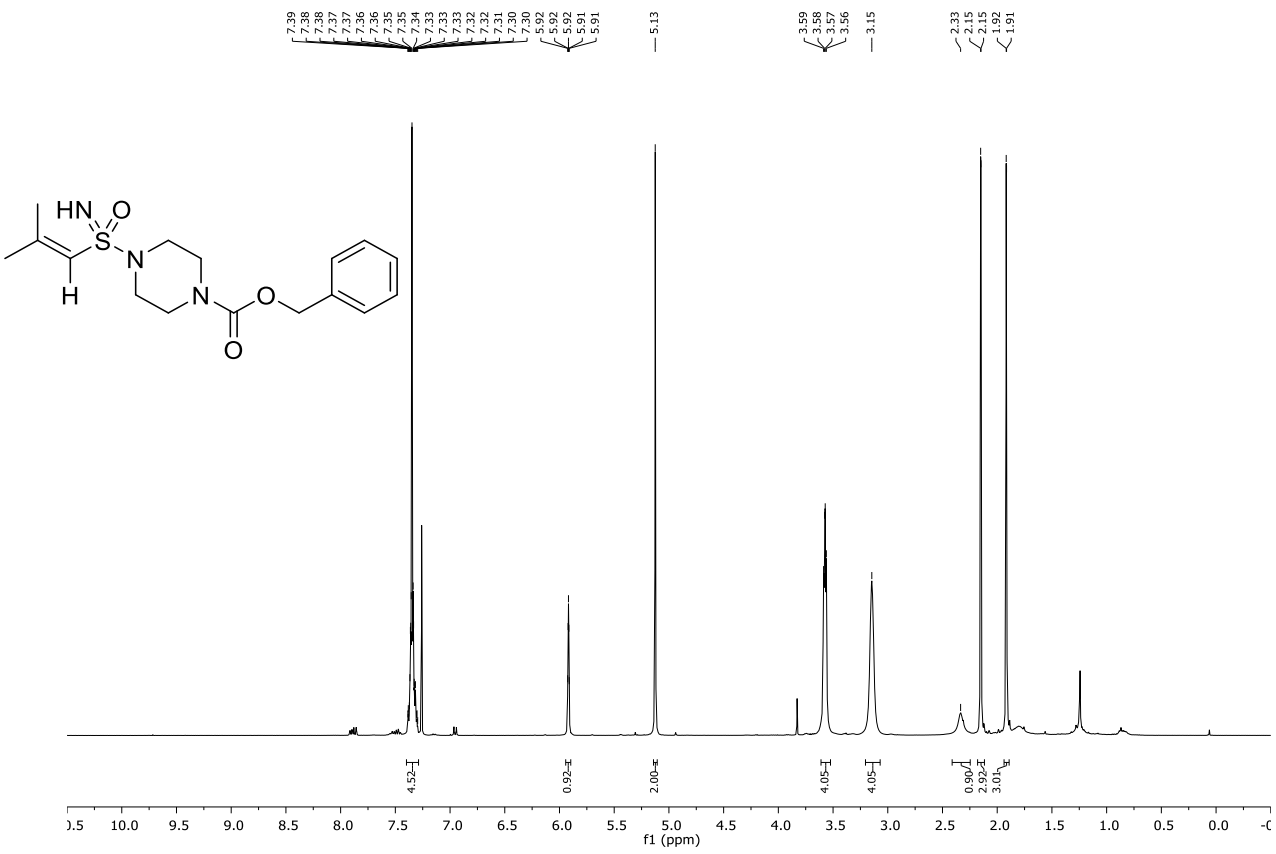
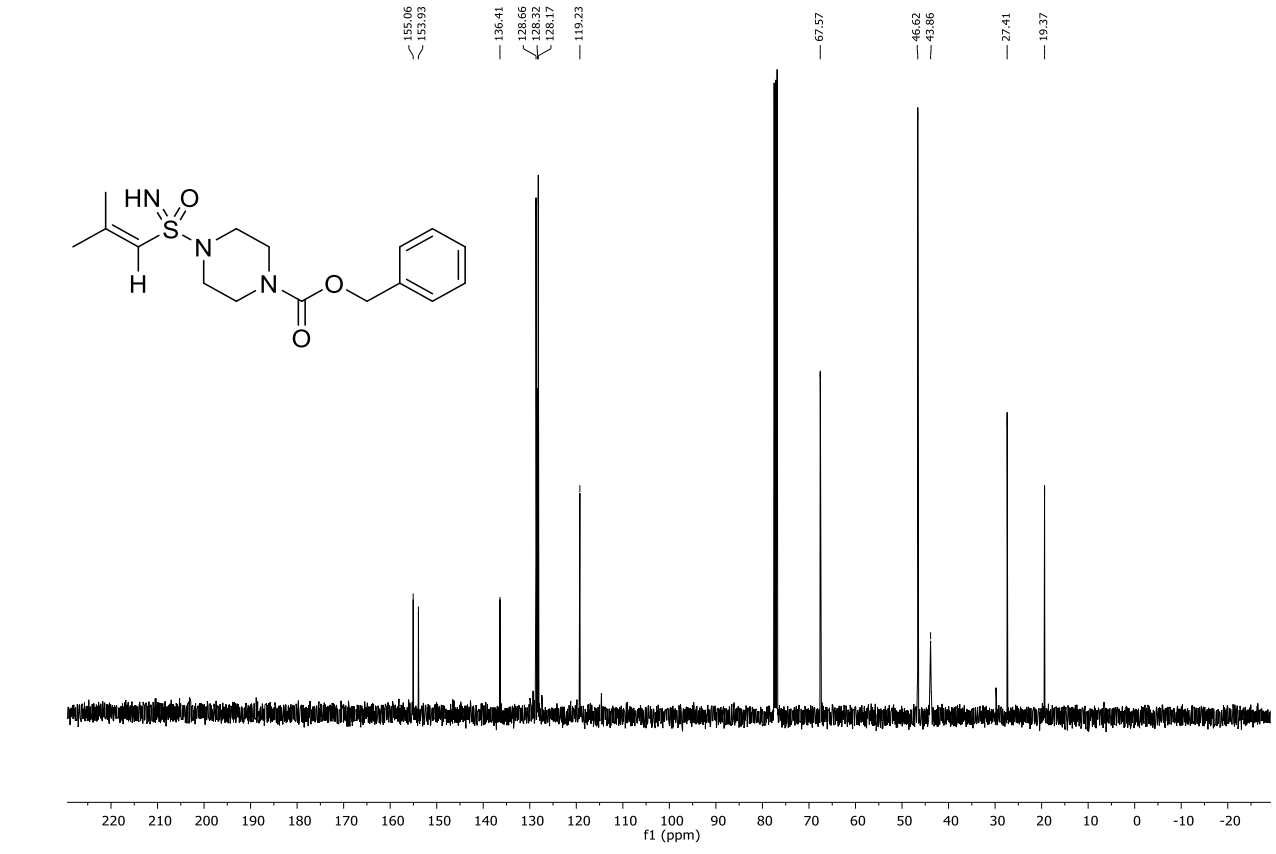
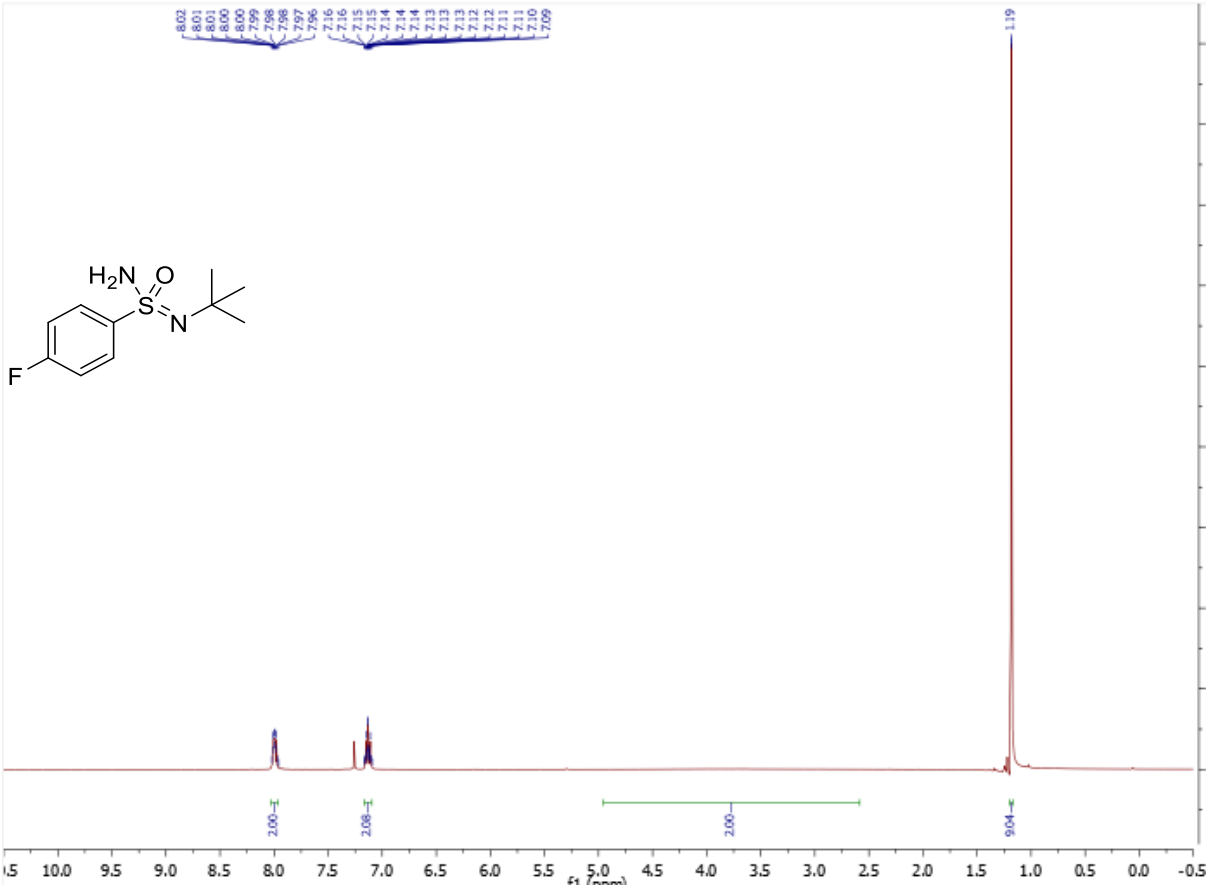
17.71
17.11
HN
O
S
N
N
O
O
f1 (ppm)


HN
O
S
N
H
N
O
O
f1 (ppm)


HN
O
S
N
H
N
O
O
f1 (ppm)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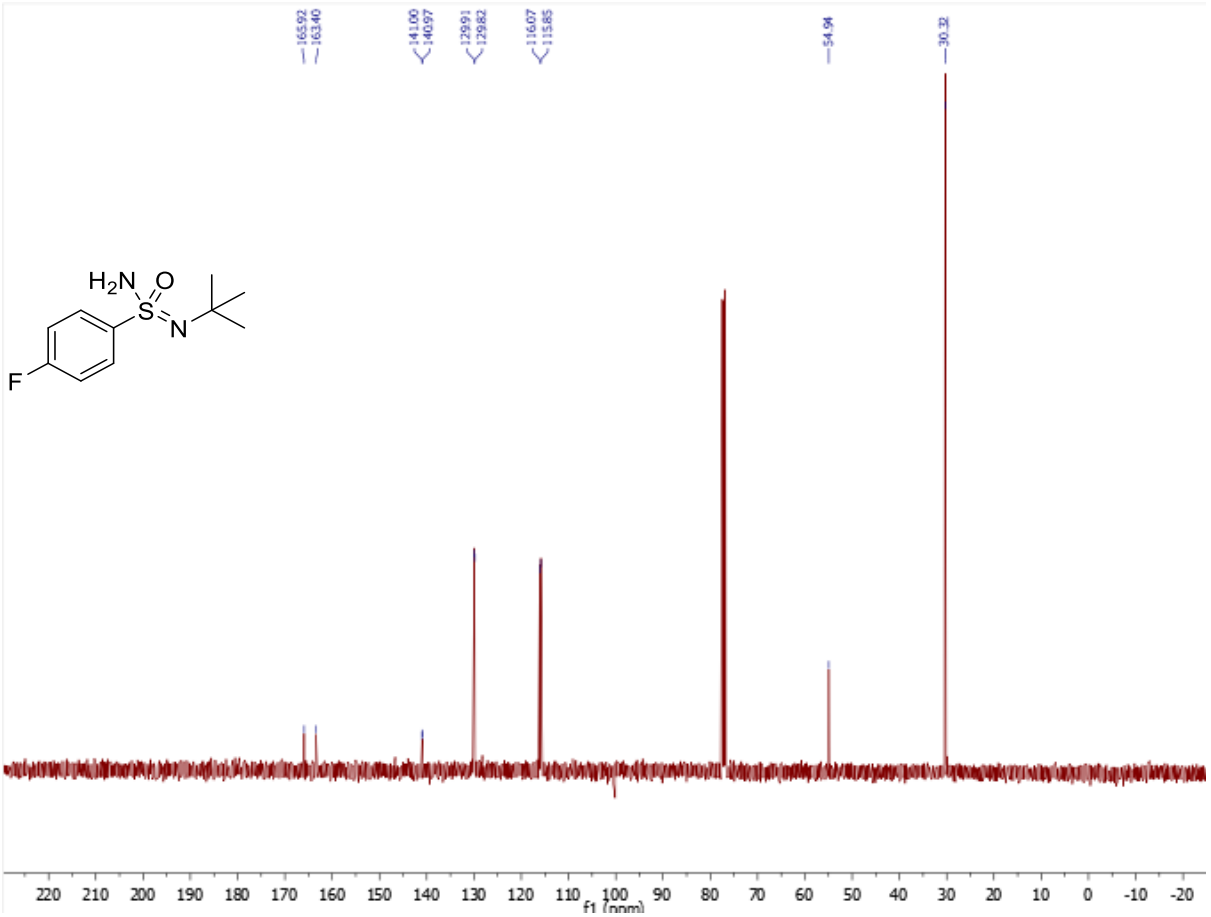
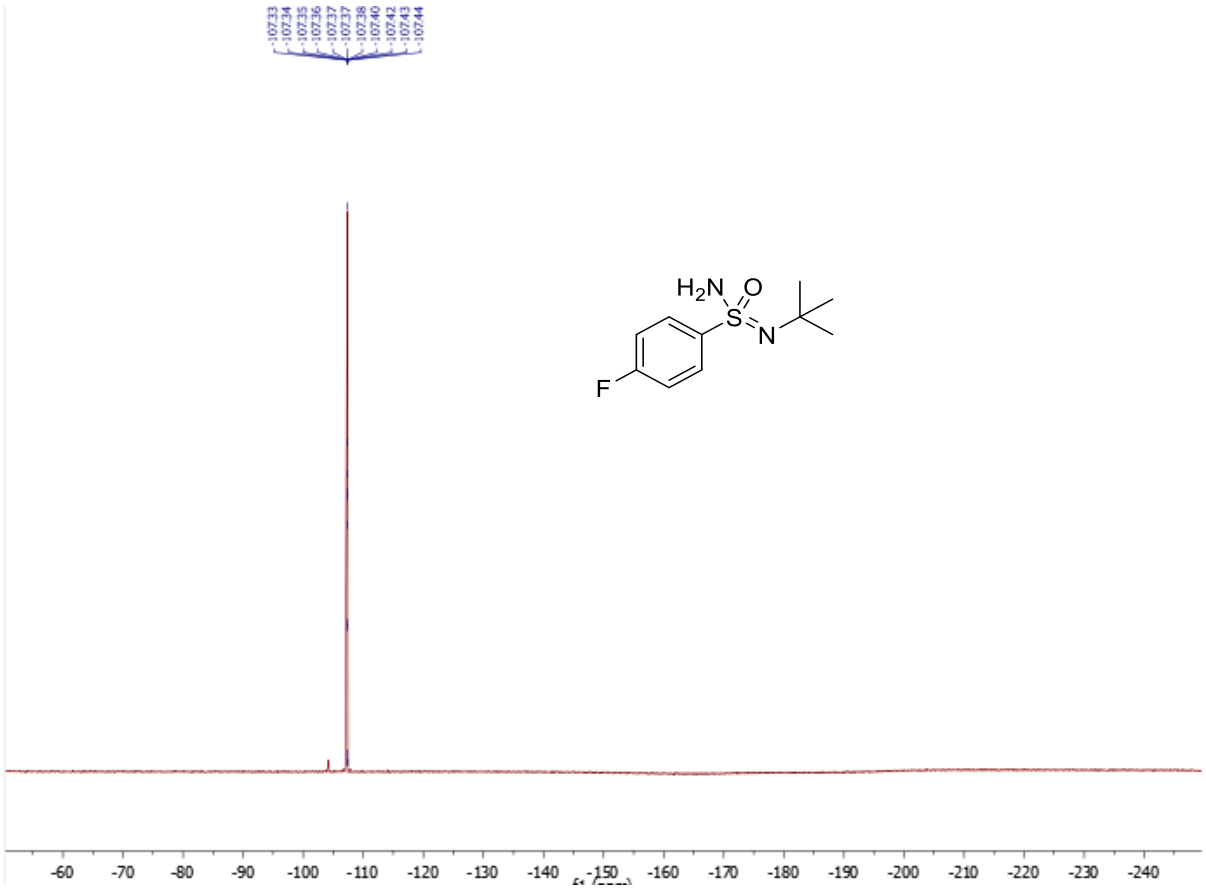
8.01
8.01
8.00
8.00
7.99
7.98
7.98
7.97
7.96
7.16
7.16
7.15
7.15
7.14
7.14
7.14
7.13
7.13
7.13
7.12
7.12
7.11
7.11
7.10
7.09
1.19
2.00
2.08
2.00
9.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
H2N
O
S
N
F


165.92
163.40
141.00
140.97
129.91
129.82
116.07
115.85
54.94
30.32
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)
H2N
O
S
N
F


-10733
-10734
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-10736
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-10737
-10738
-10740
-10742
-10743
-10744
H2N
O
S
N
F
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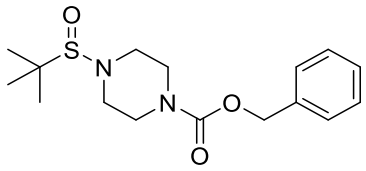
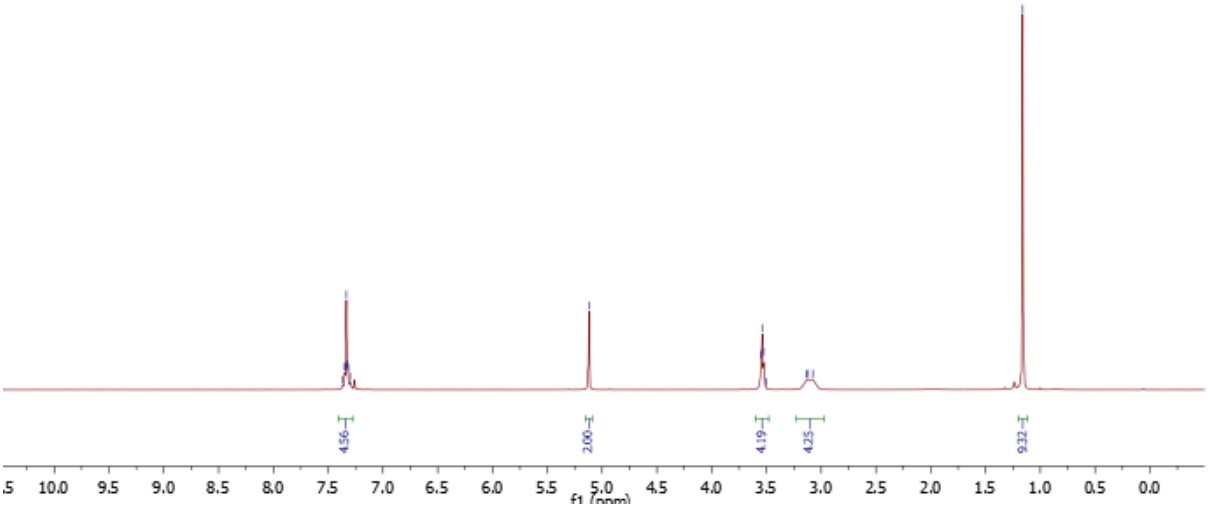
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
-240


7.37
7.35
7.35
7.33
7.32
7.32
7.30
5.12
3.55
3.54
3.53
3.50
3.13
3.12
3.08
1.16


O
S
N
N
O
O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2.00
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10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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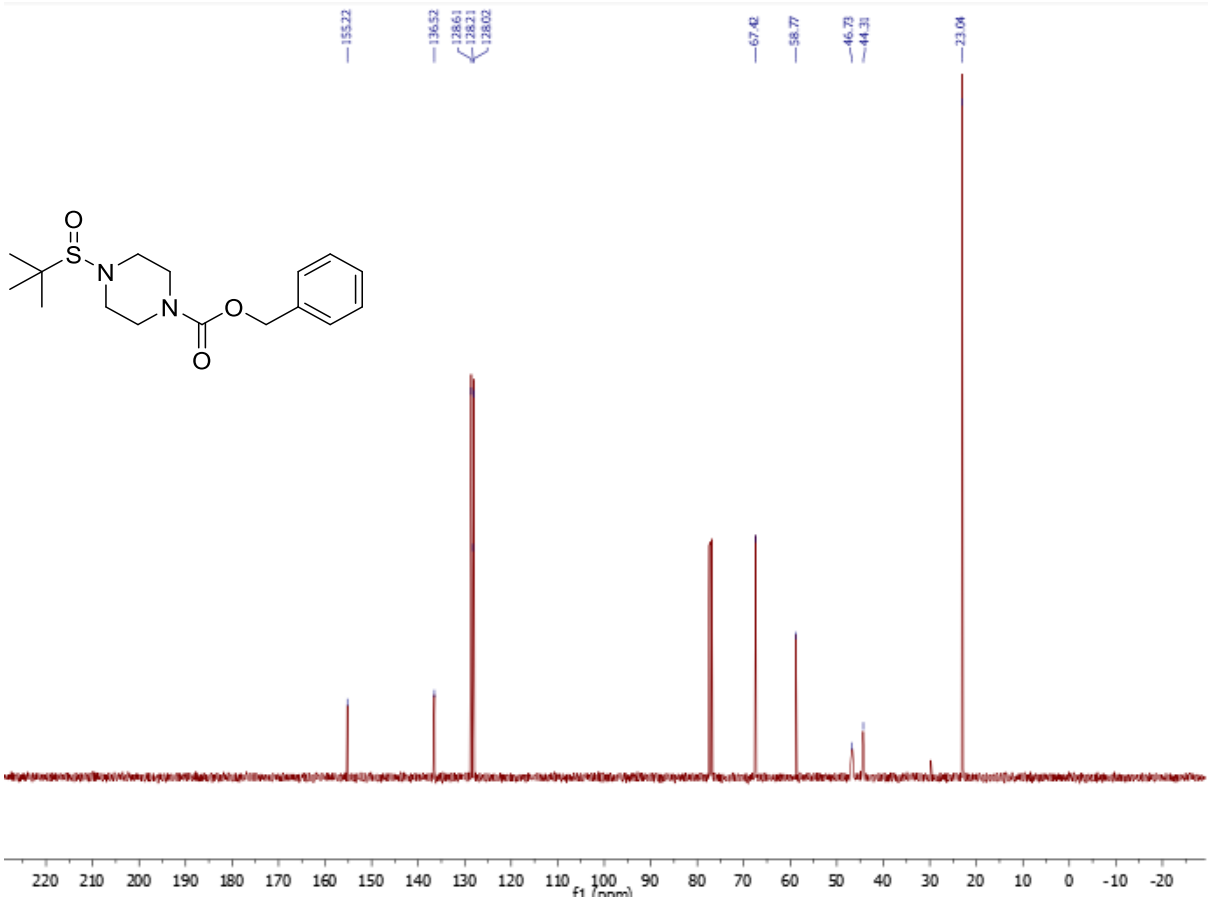
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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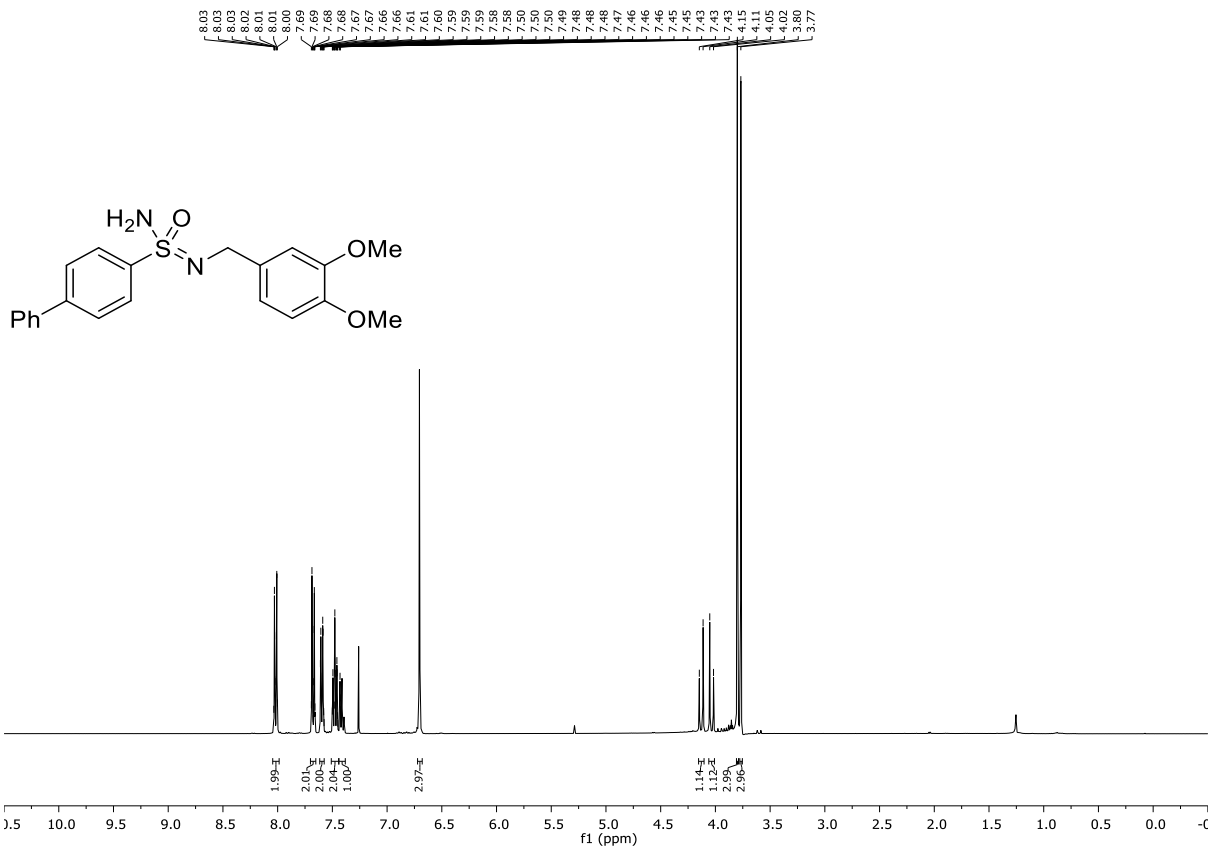
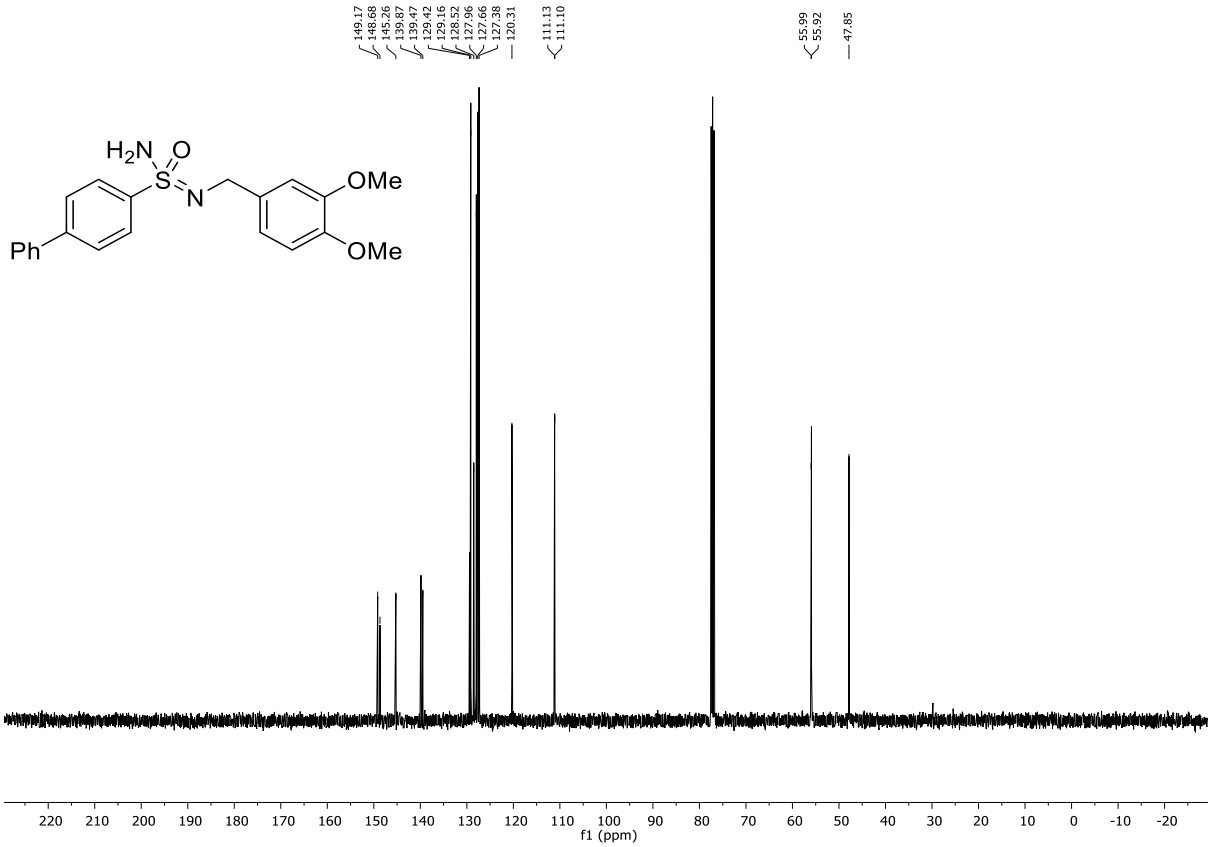
67.42
58.77
46.73
44.31
23.04
f1 (ppm)


8.03
8.03
8.03
8.02
8.01
8.01
8.00
7.69
7.69
7.68
7.68
7.67
7.67
7.66
7.66
7.61
7.61
7.60
7.59
7.59
7.59
7.58
7.58
7.50
7.50
7.49
7.48
7.48
7.48
7.47
7.46
7.46
7.46
7.45
7.45
7.43
7.43
7.43
4.15
4.11
4.05
4.02
3.80
3.77
1.99
2.01
2.00
2.04
1.00
2.97
1.14
1.12
2.99
2.96
f1 (ppm)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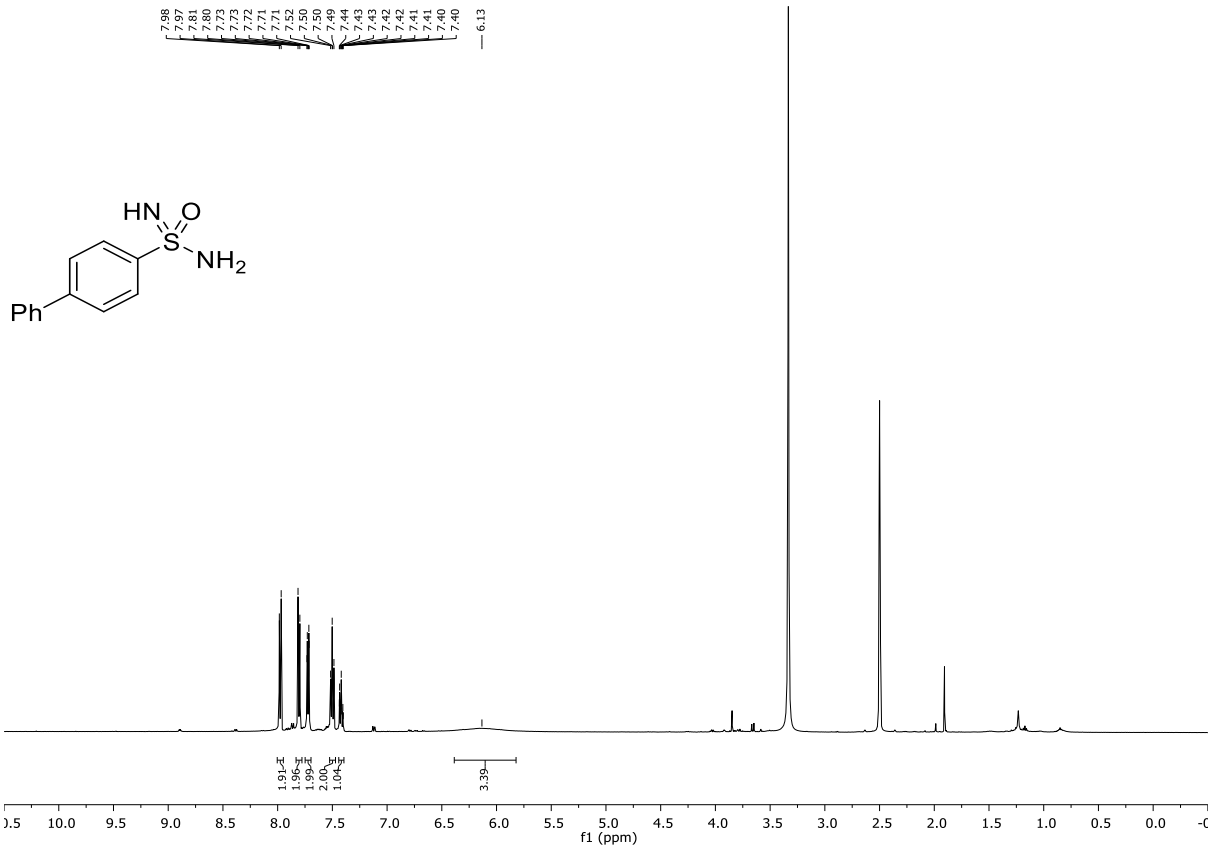
148.68
146.26
145.87
139.47
129.42
129.16
128.52
127.96
127.66
127.38
120.31
111.13
111.10
55.99
55.92
47.85
H2N
O
S
N
OMe
OMe
Ph
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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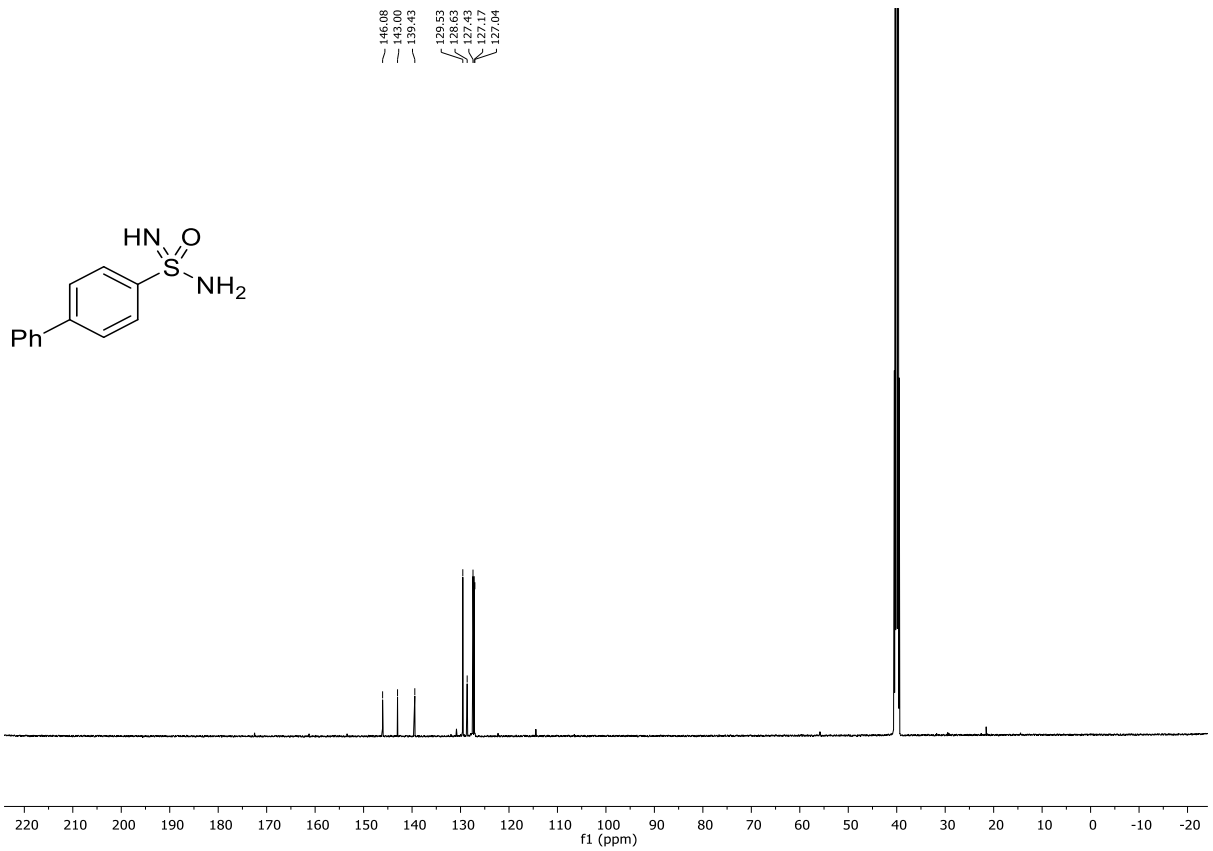
7.97
7.81
7.80
7.73
7.73
7.72
7.71
7.71
7.52
7.50
7.50
7.49
7.44
7.43
7.43
7.42
7.42
7.41
7.41
7.40
7.40
6.13
HN
O
S
NH2
Ph
1.91
1.96
1.99
2.00
1.04
3.39
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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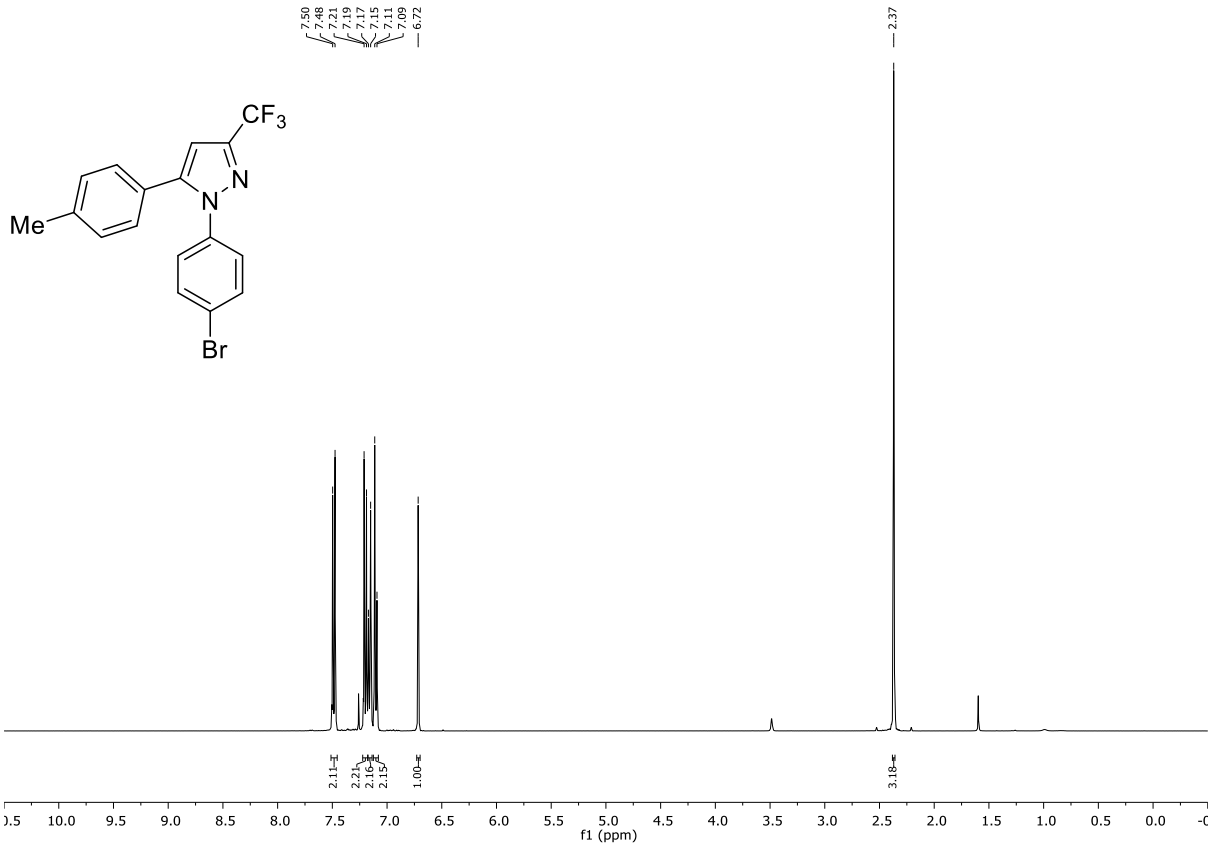
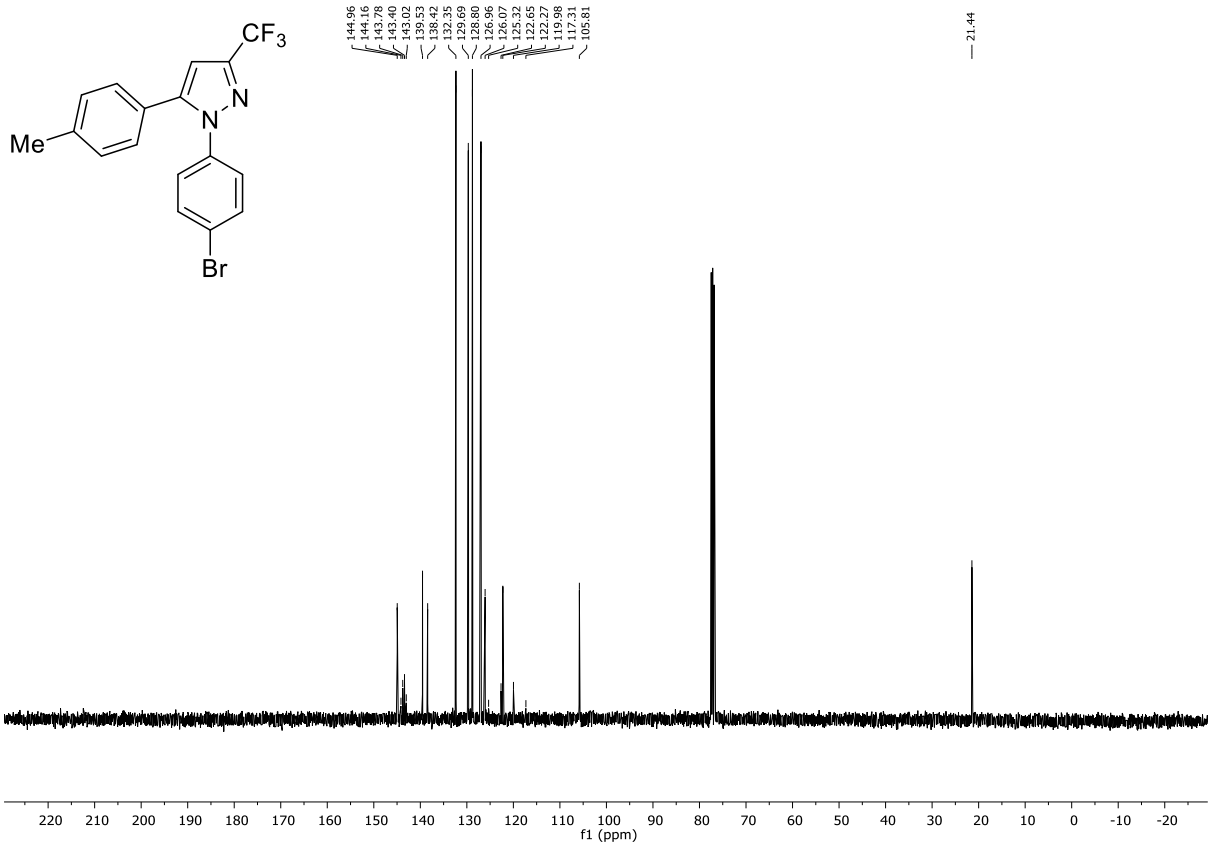
143.00
139.43
129.53
128.63
127.43
127.17
127.04
HN
O
S
NH2
Ph
f1 (ppm)


7.50
7.48
7.21
7.19
7.17
7.15
7.11
7.09
6.72
2.37
CF3
N
N
Me
Br
2.11
2.21
2.16
2.15
1.00
3.18
f1 (ppm)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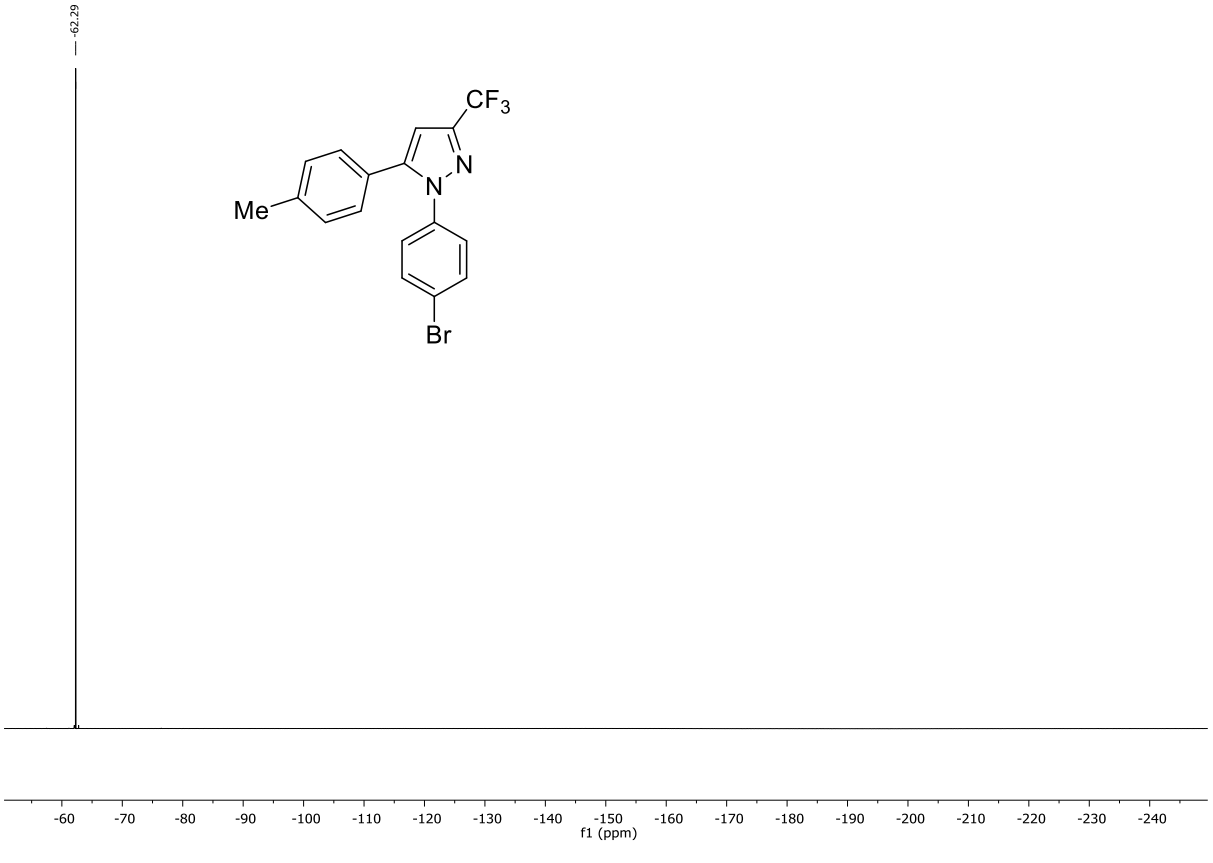
138.42
132.35
129.69
128.80
126.96
126.07
125.32
122.65
122.27
119.98
117.31
105.81
21.44
CF3
N
N
Me
Br
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


-62.29
CF3
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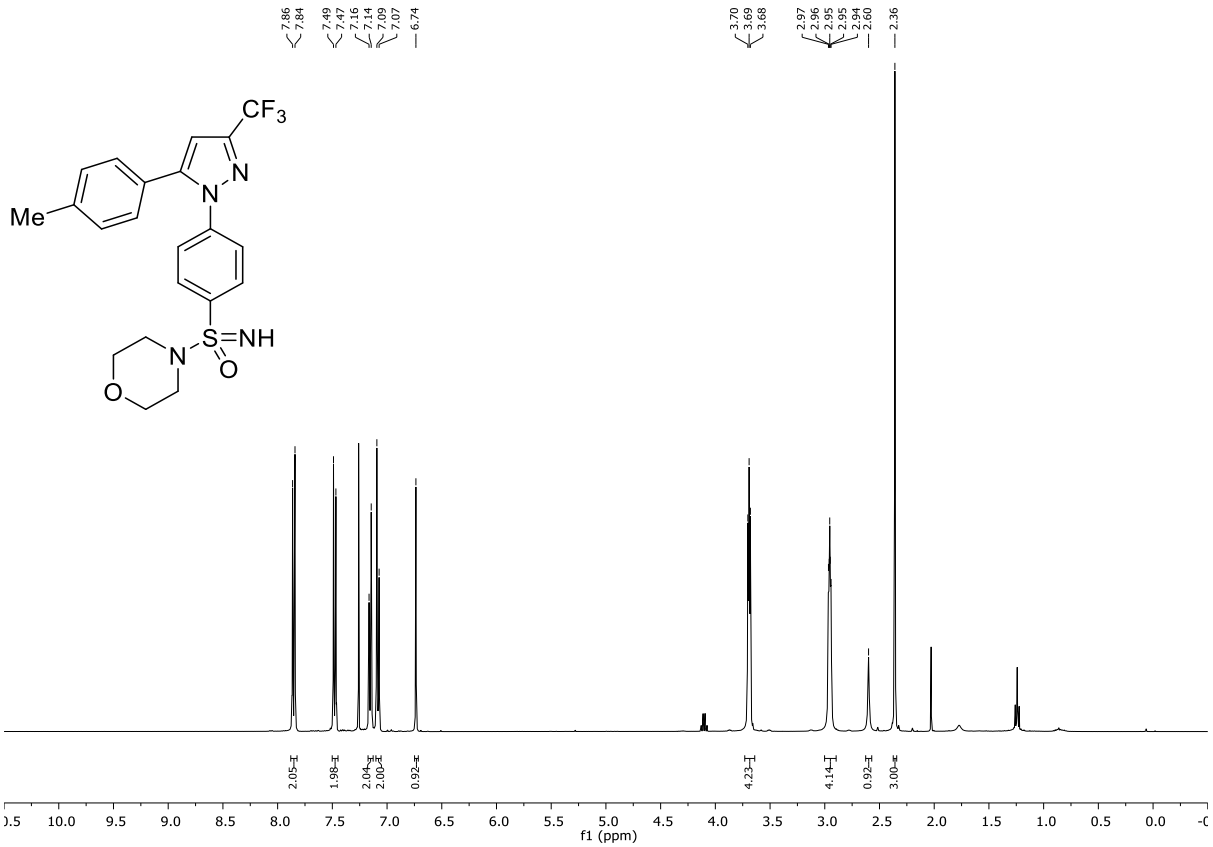
N
Me
Br
-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)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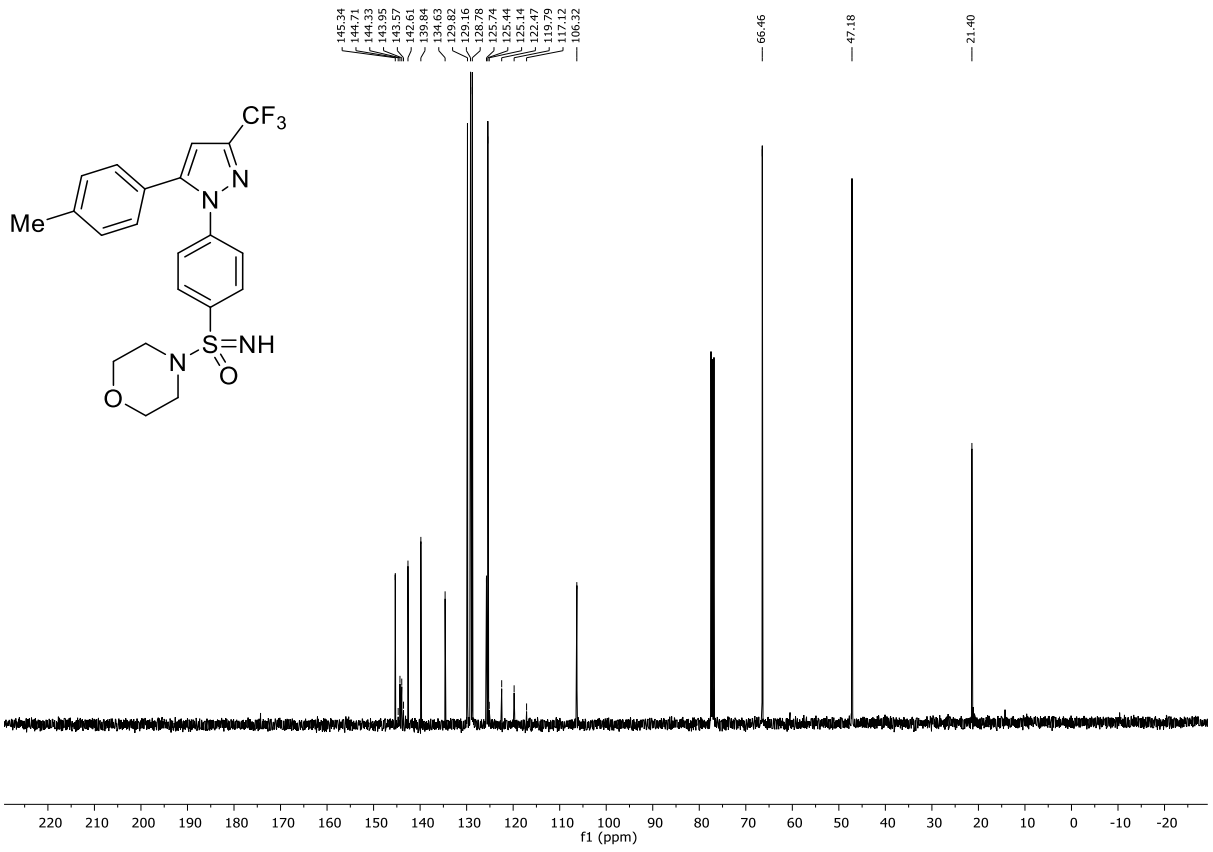
7.47
7.16
7.14
7.09
7.07
6.74
3.70
3.69
3.68
2.97
2.96
2.95
2.95
2.94
2.60
2.36
CF3
N
N
Me
S=NH
N
O
O
2.05
1.98
2.04
2.00
0.92
4.23
4.14
0.92
3.00
f1 (ppm)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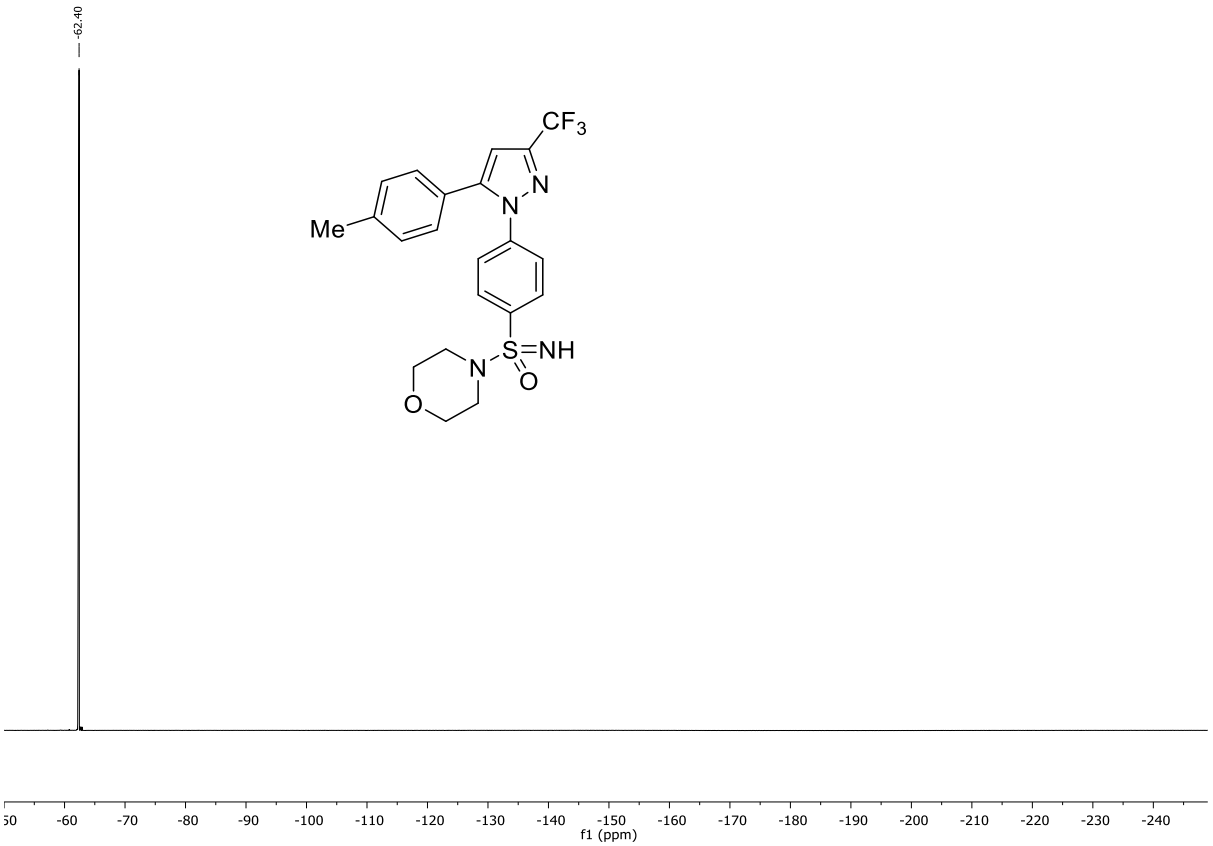
142.61
139.84
134.63
129.82
129.16
128.78
125.74
125.44
125.14
122.47
119.79
117.12
106.32
66.46
47.18
21.40
CF3
N
N
Me
S=NH
N
O
O
f1 (ppm)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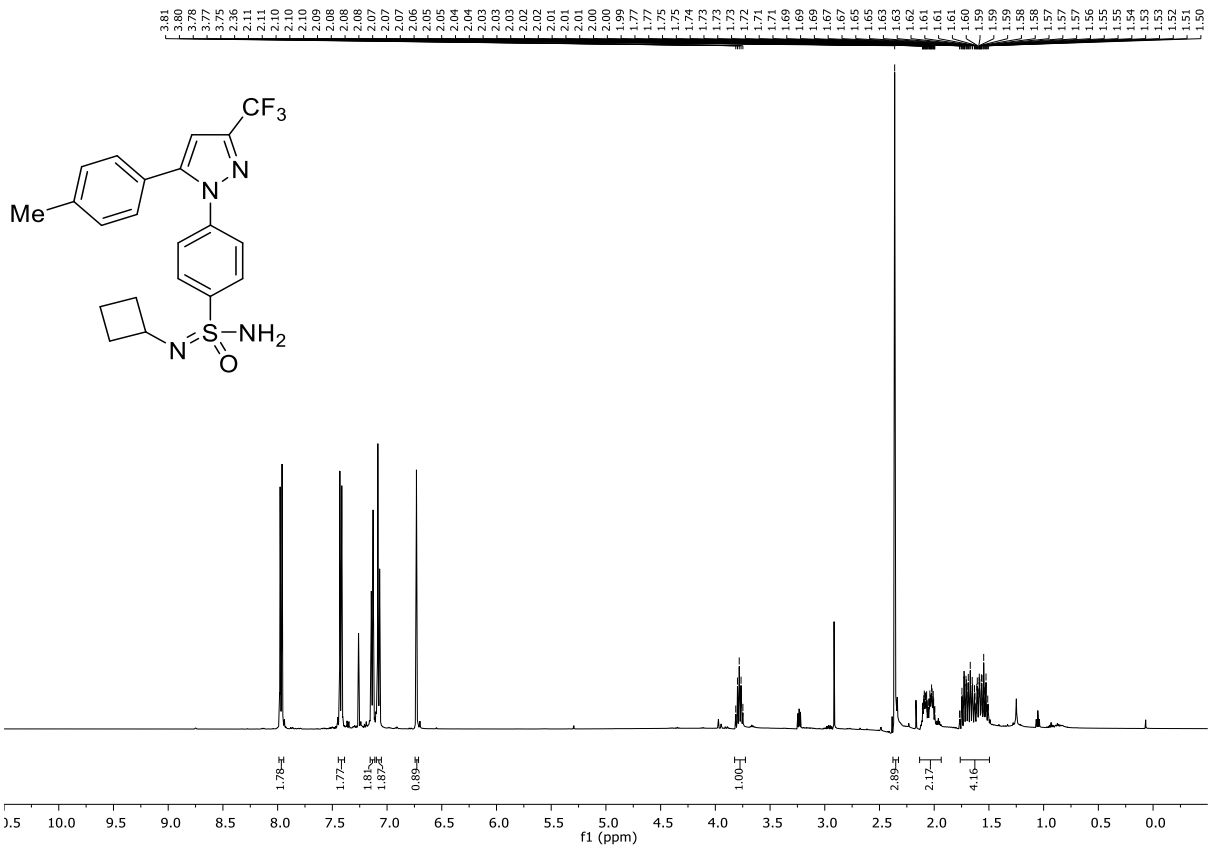
N
Me
N
S=NH
O
O
f1 (ppm)


CF3
N
N
Me
N
S—NH2
O
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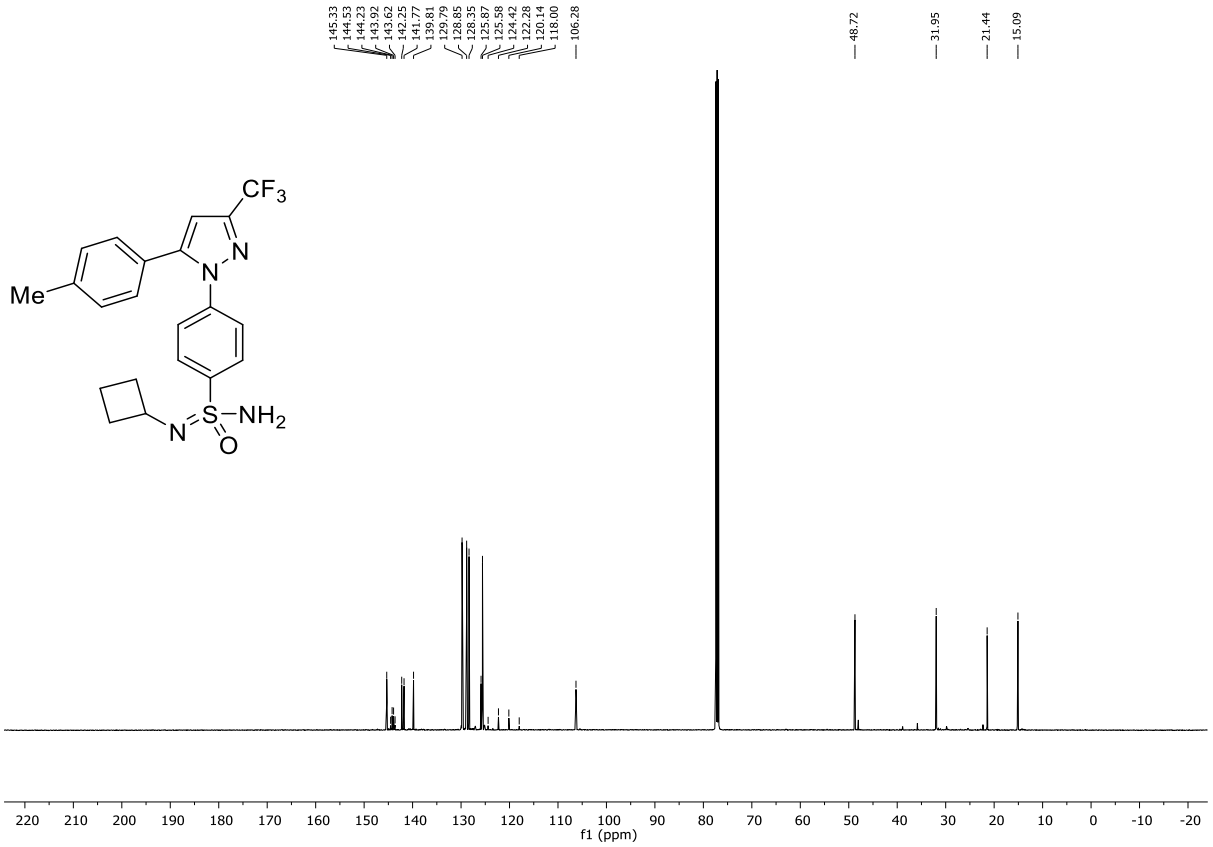
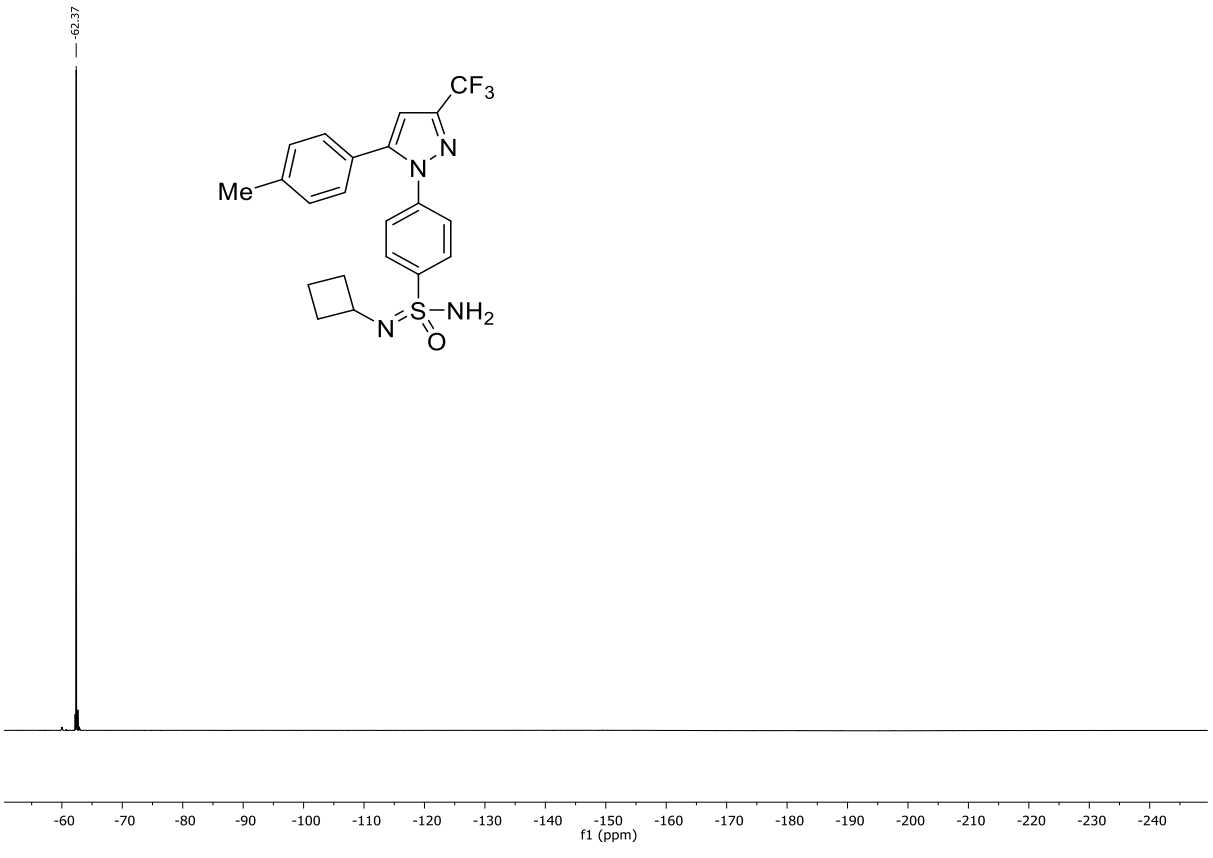
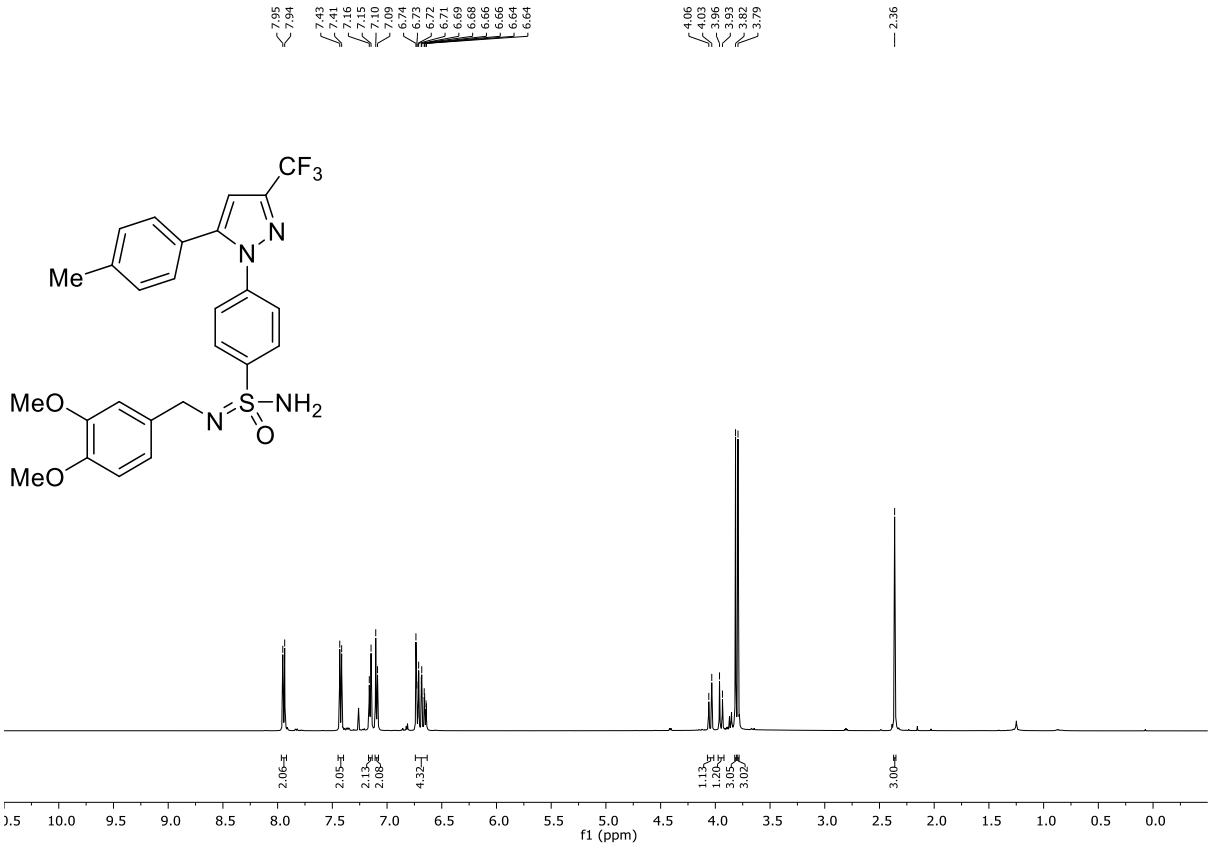
1.77
1.81
1.87
0.89
1.00
2.89
2.17
4.16
f1 (ppm)


145.33
144.53
144.23
143.92
143.62
142.25
141.77
139.81
129.79
128.85
128.35
125.87
125.58
124.42
122.28
120.14
118.00
106.28
48.72
31.95
21.44
15.09
CF3
N
N
Me
N
S
NH2
O
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)


-62.37
CF3
N
N
Me
N
S
NH2
O
-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)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7.43
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7.15
7.10
7.09
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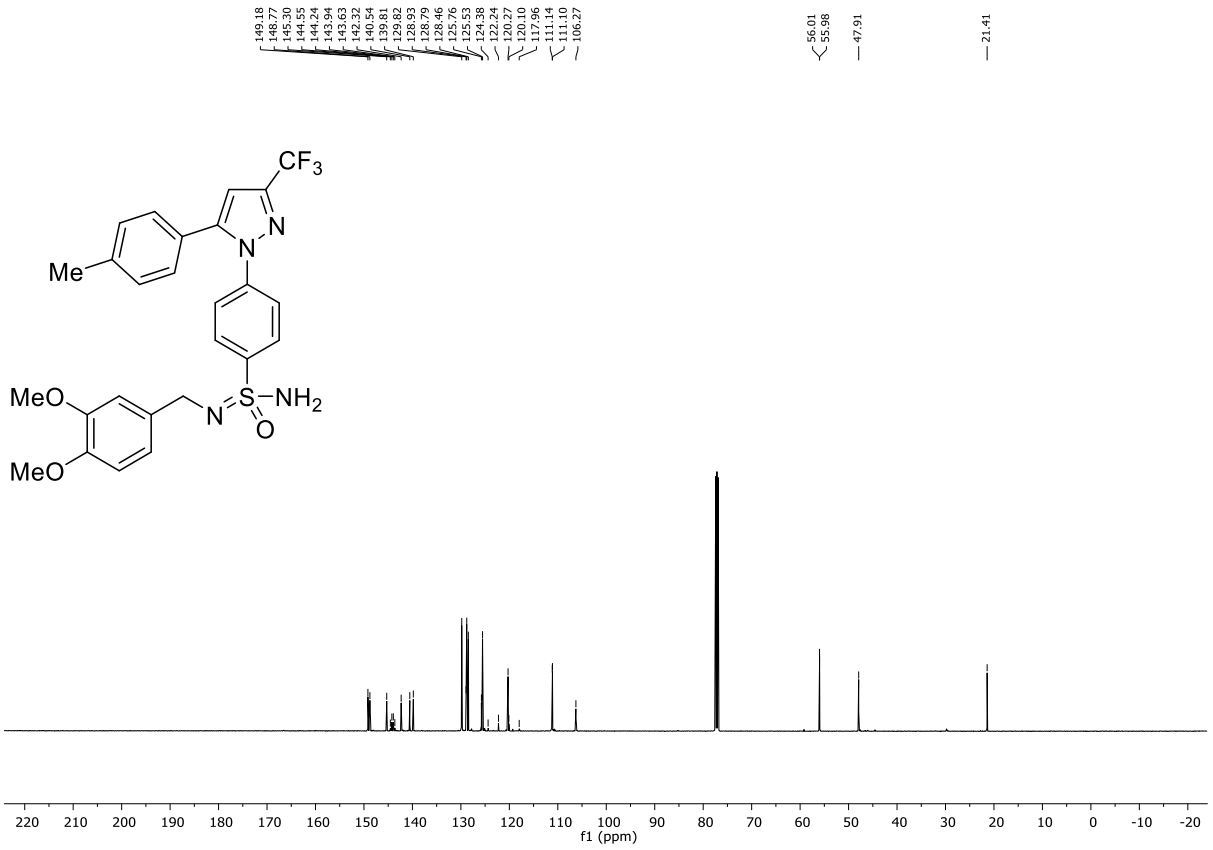
6.73
6.72
6.71
6.69
6.68
6.66
6.66
6.64
6.64
4.06
4.03
3.96
3.93
3.82
3.79
2.36
CF3
N
N
Me
MeO
MeO
S
NH2
O
N
2.06
2.05
2.13
2.08
4.32
1.13
1.20
3.05
3.02
3.00
f1 (ppm)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148.77
145.30
144.55
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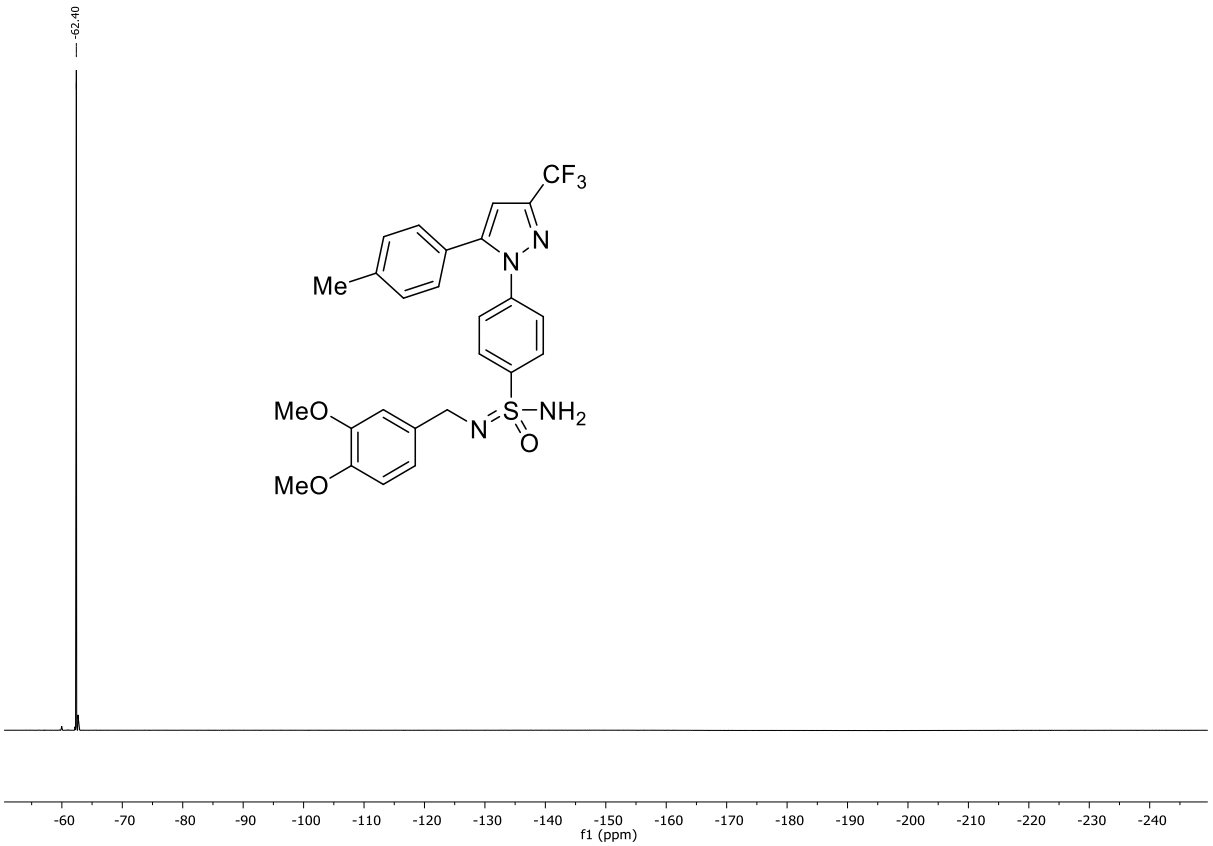
143.94
143.63
142.32
140.54
139.81
129.82
128.93
128.79
128.46
125.76
125.53
124.38
122.24
120.27
120.10
117.96
111.14
111.10
106.27
56.01
55.98
47.91
21.41
CF3
N
N
Me
MeO
MeO
S
NH2
O
N
f1 (ppm)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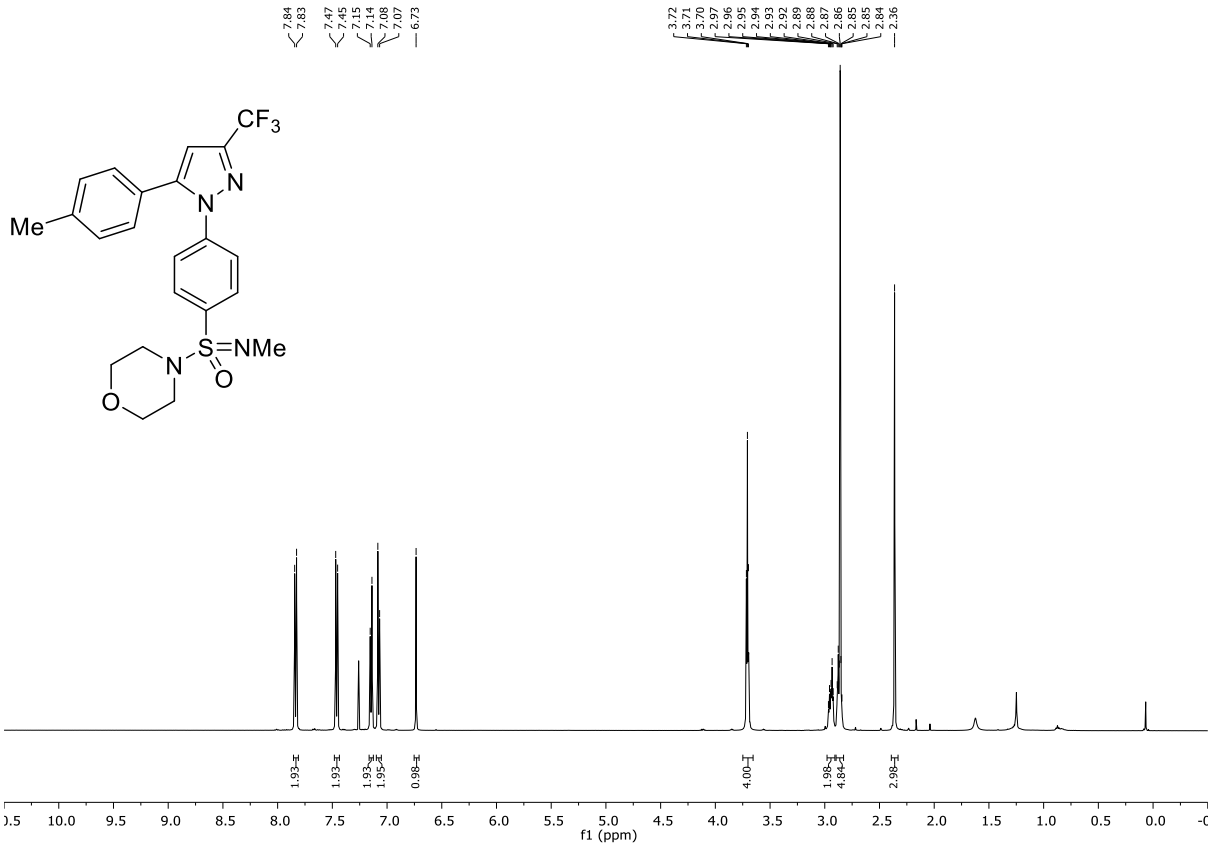
N
Me
MeO
MeO
N
S
NH2
O
-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)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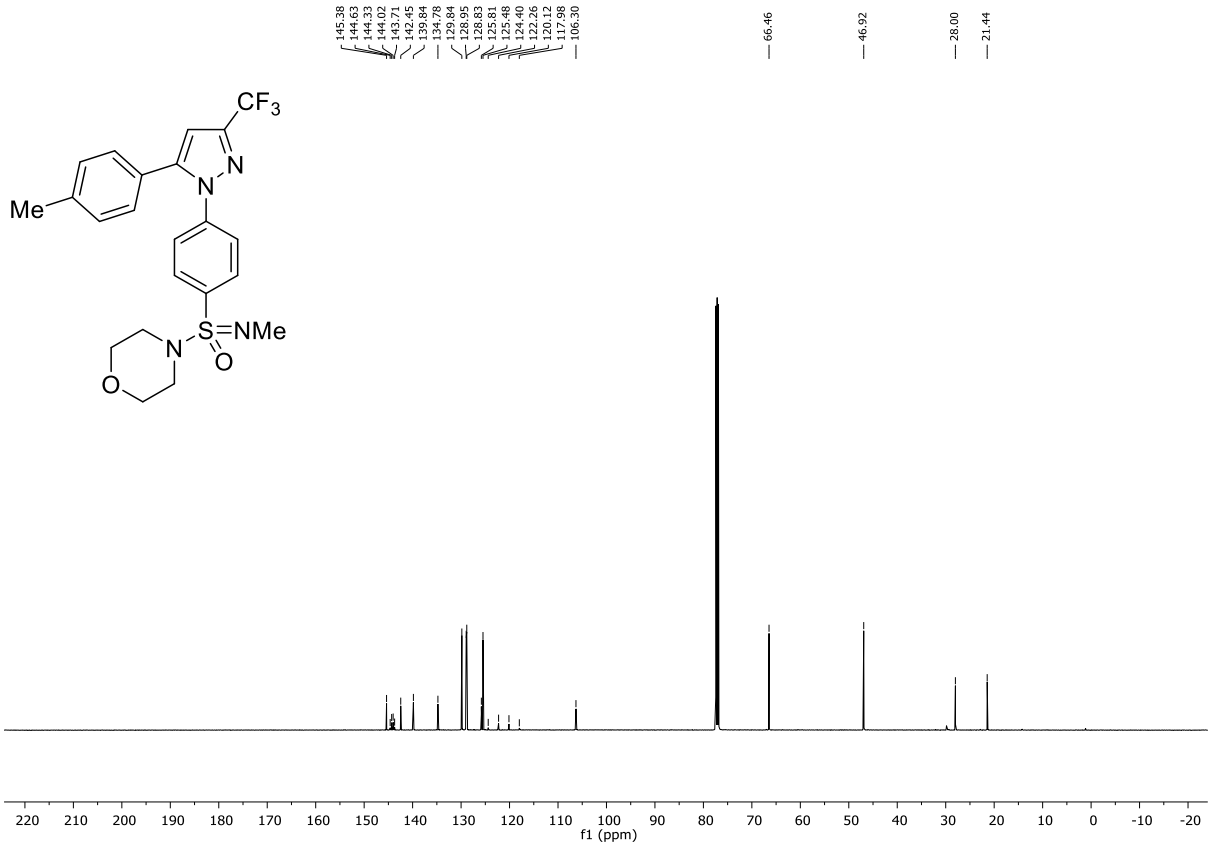
7.83
7.47
7.45
7.15
7.14
7.08
7.07
6.73
3.72
3.71
3.70
2.97
2.96
2.95
2.94
2.93
2.92
2.89
2.88
2.87
2.86
2.85
2.85
2.84
2.36
CF3
N
N
Me
N
S
NMe
O
O
1.93
1.93
1.93
1.95
0.98
4.00
1.98
4.84
2.98
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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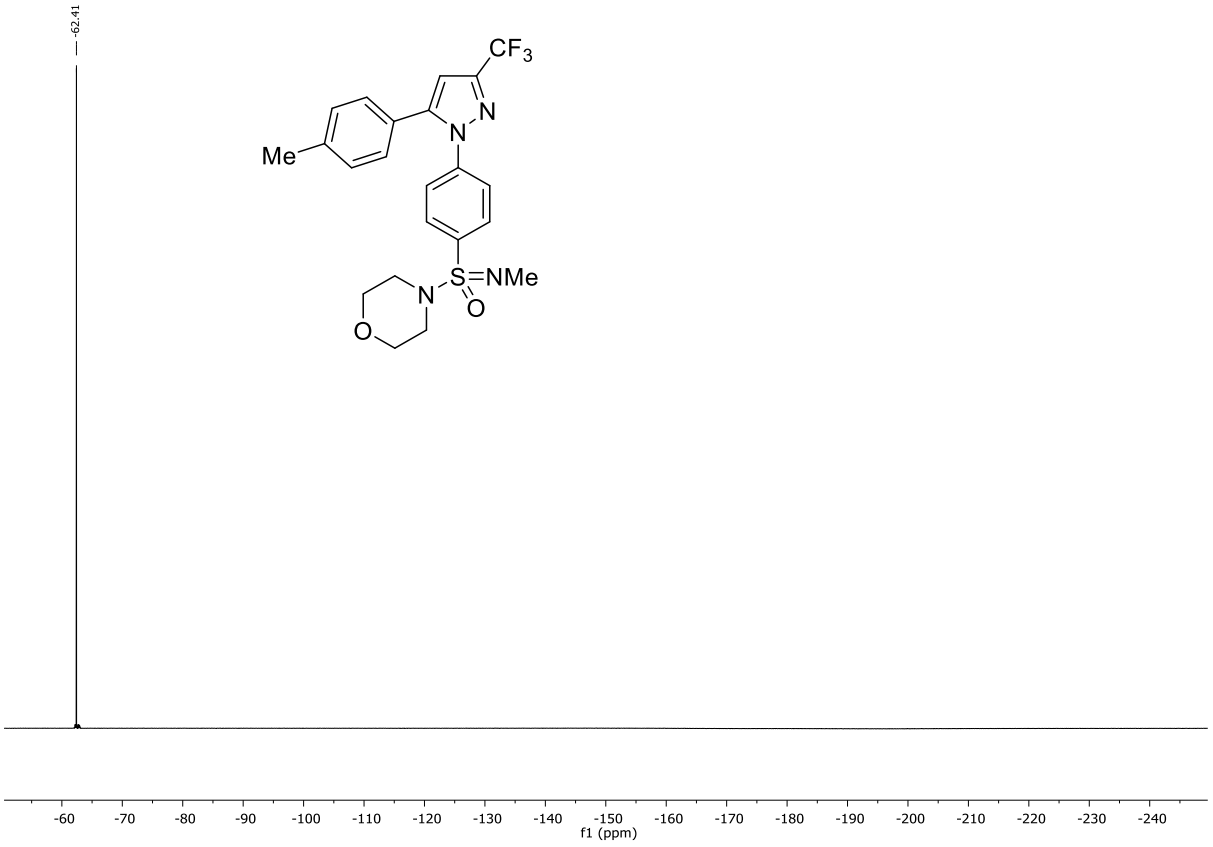
144.63
144.33
144.02
143.71
142.45
139.84
134.78
129.84
128.95
128.83
125.81
125.48
124.40
122.26
120.12
117.98
106.30
66.46
46.92
28.00
21.44
CF3
N
N
Me
S=NMe
N
O
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)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CF3
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N
Me
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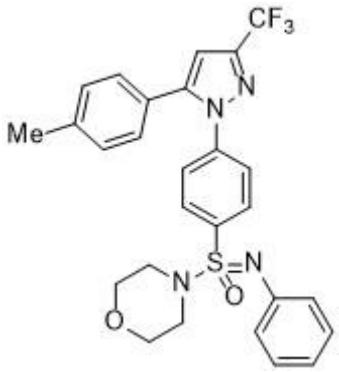
O
O
-60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)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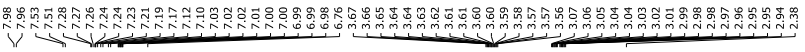
Me
N
N
S
N
O
N
O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7.96
7.53
7.51
7.28
7.27
7.26
7.24
7.24
7.23
7.21
7.19
7.17
7.12
7.10
7.03
7.02
7.02
7.01
7.00
7.00
6.99
6.99
6.98
6.76
3.67
3.66
3.65
3.64
3.64
3.63
3.62
3.61
3.61
3.60
3.60
3.59
3.58
3.57
3.57
3.56
3.07
3.06
3.05
3.04
3.04
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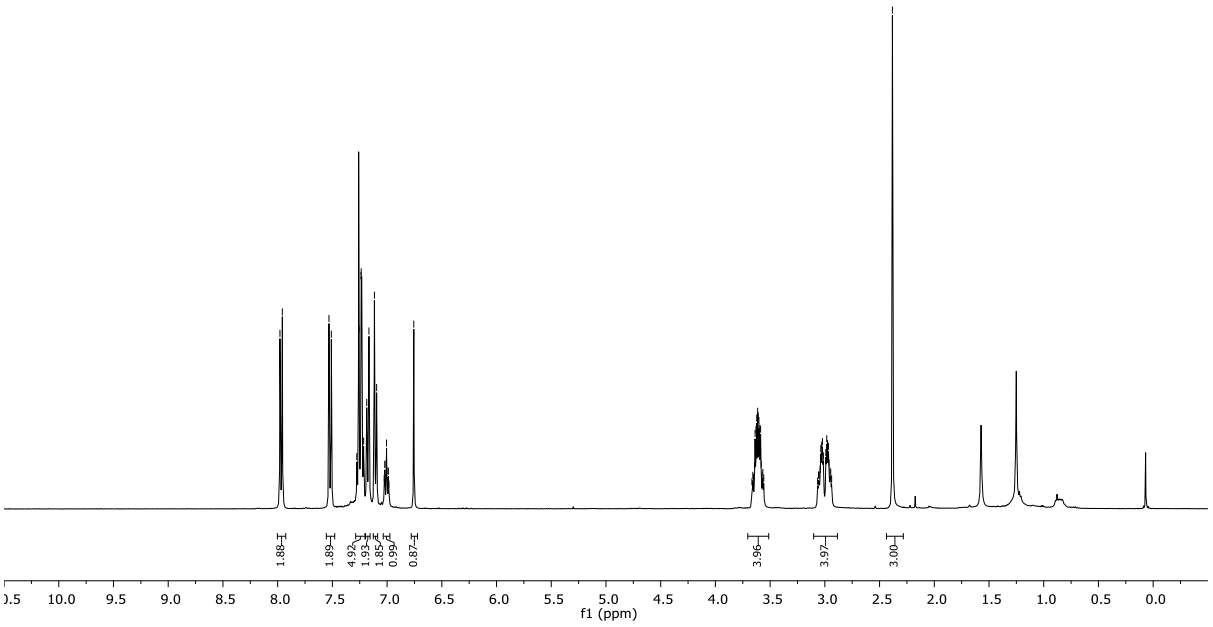
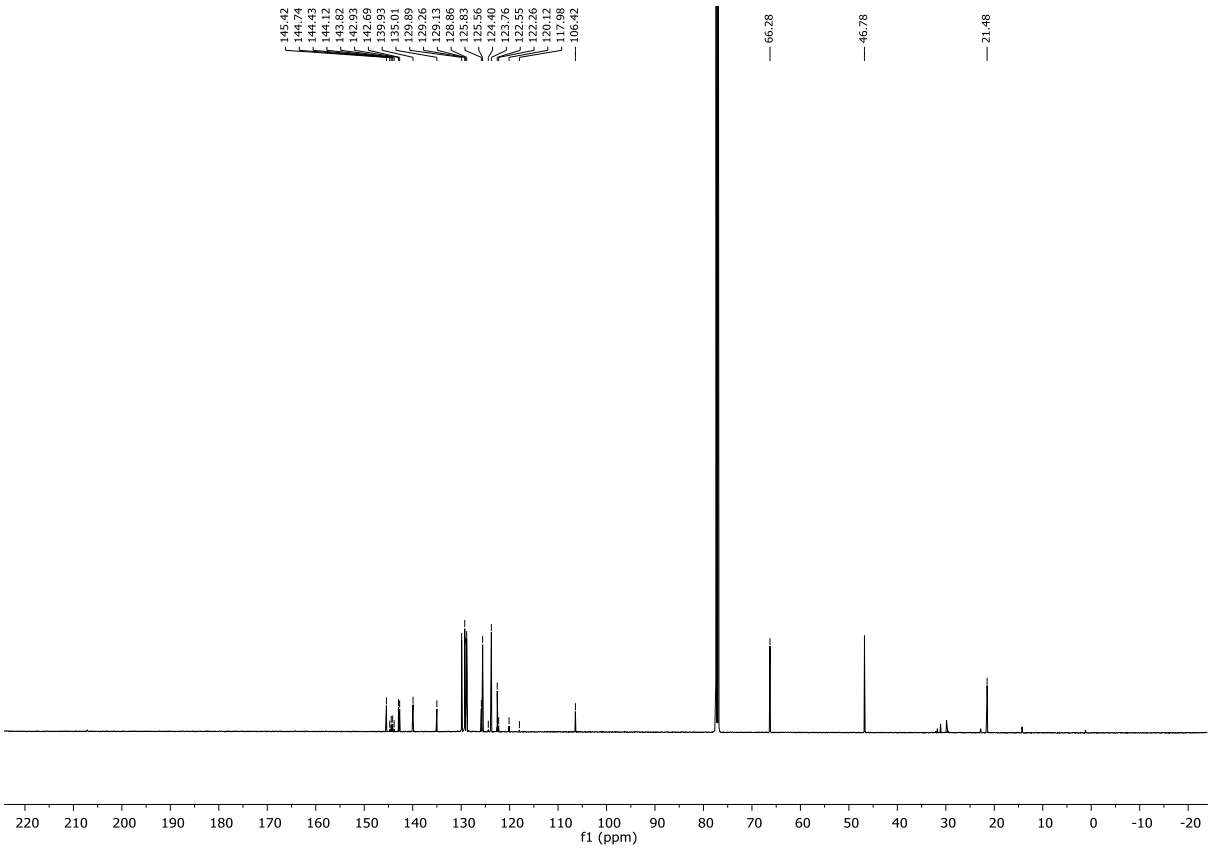
2.97
2.96
2.95
2.95
2.94
2.38


1.88
1.89
4.92
1.93
1.85
0.99
0.87
3.96
3.97
3.00
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)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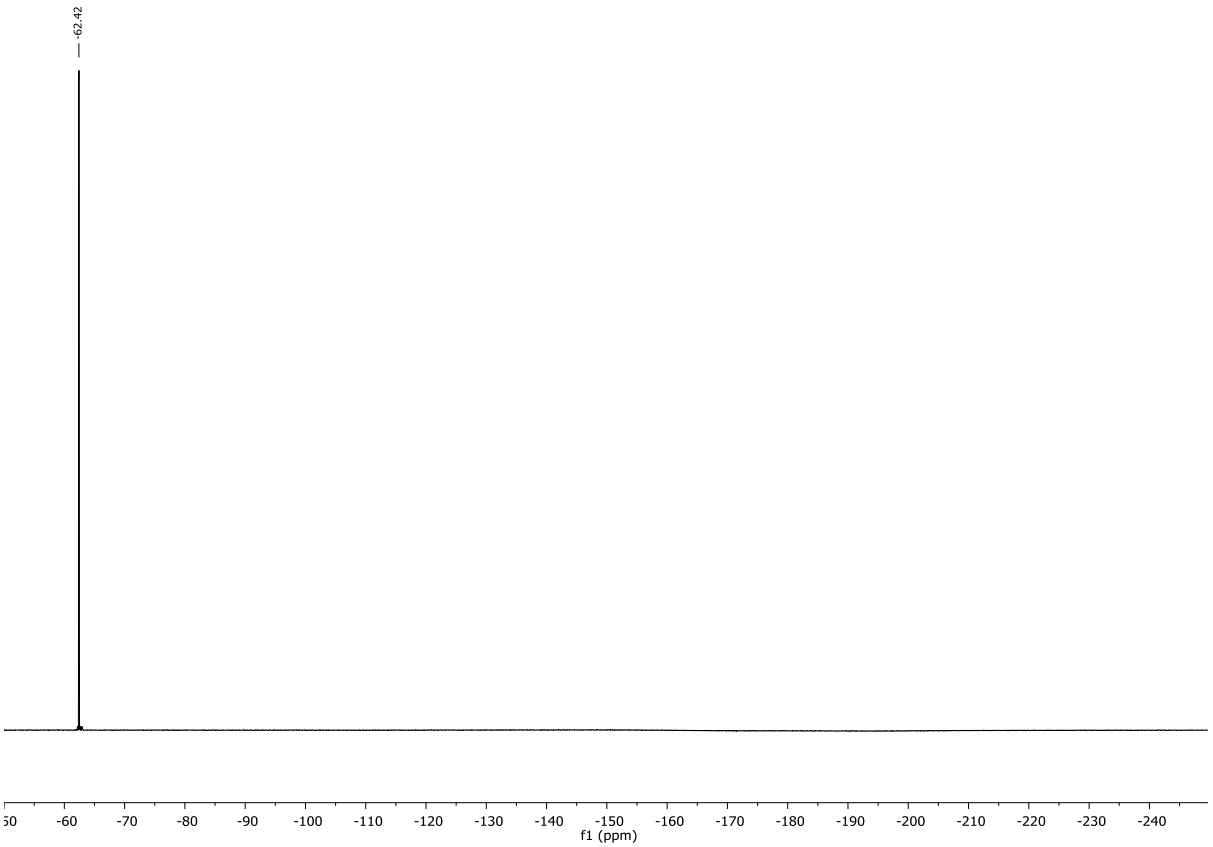
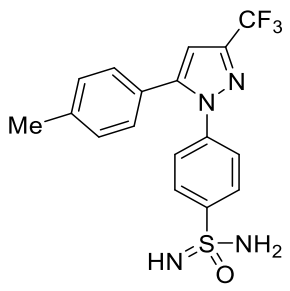
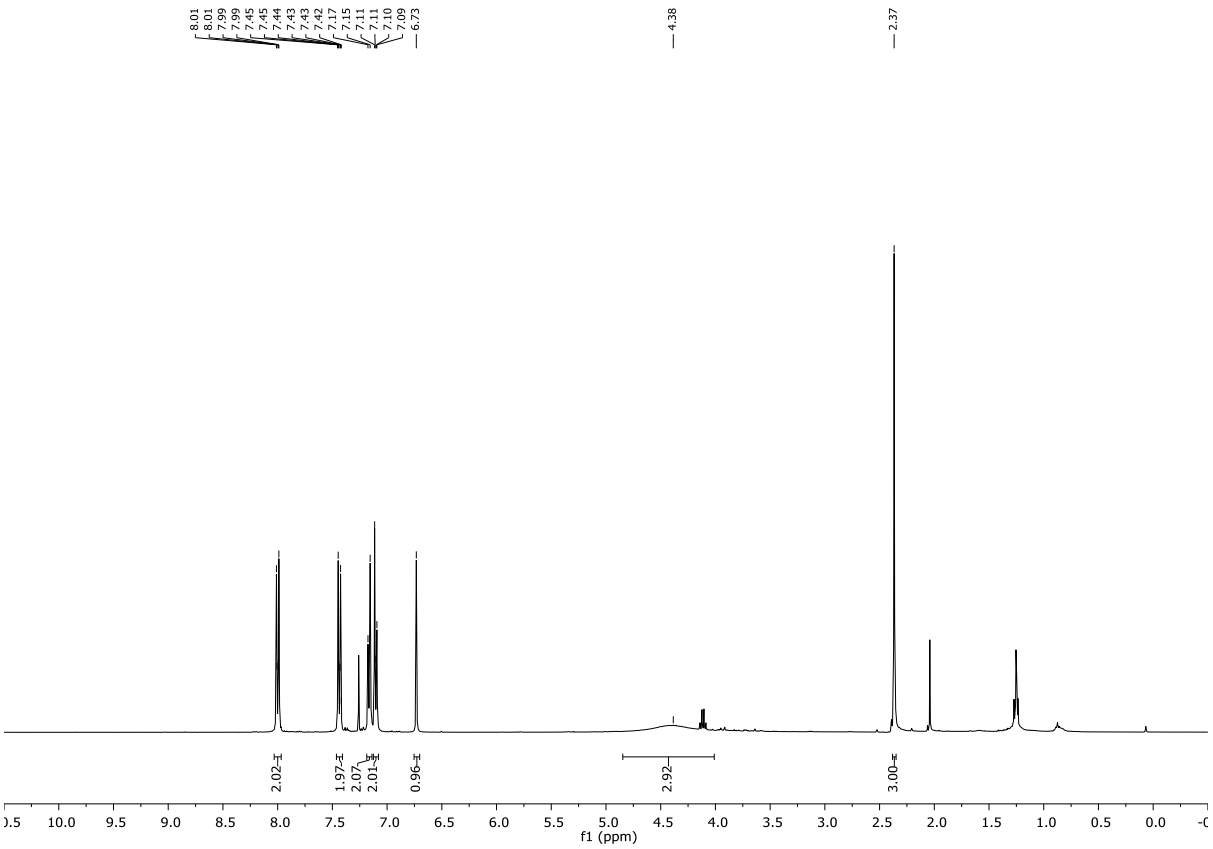
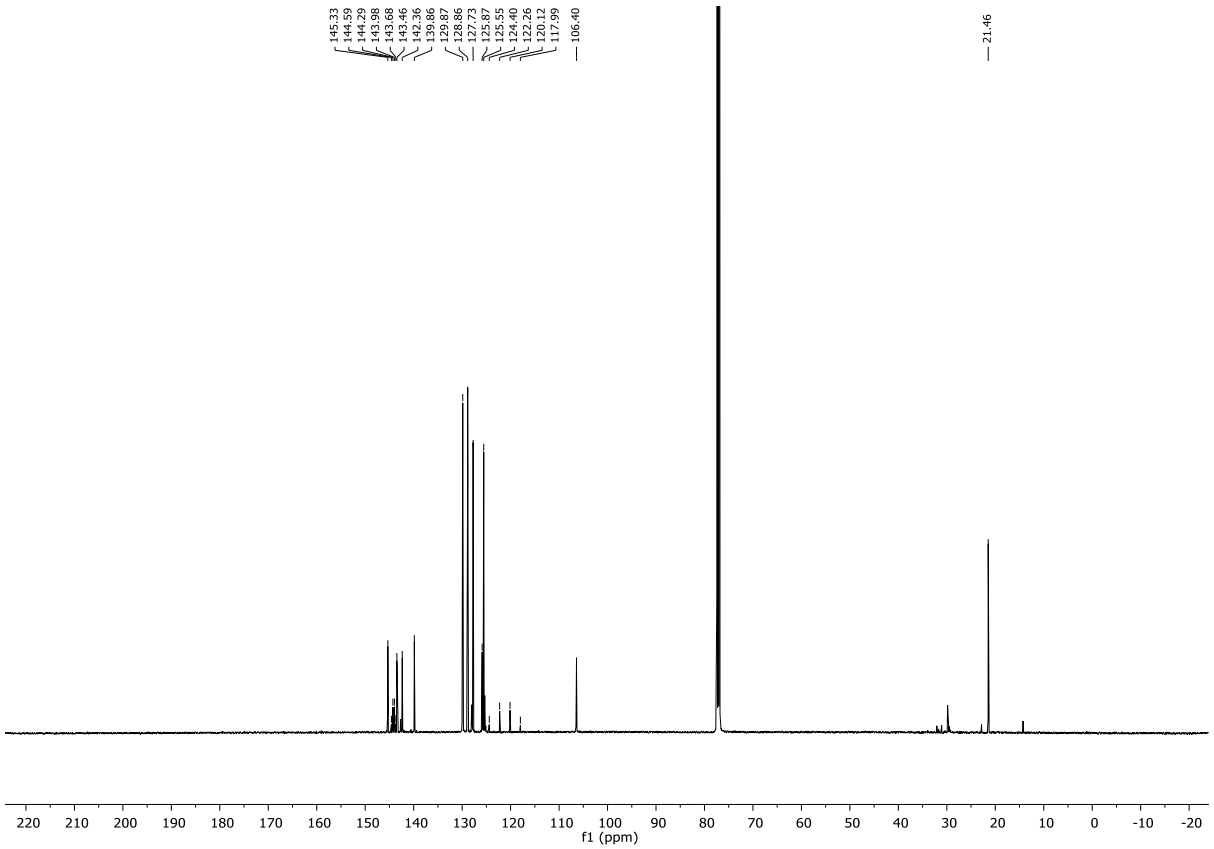
143.82
142.93
142.69
139.93
135.01
129.89
129.26
129.13
128.86
125.83
125.56
124.40
123.76
122.55
122.26
120.12
117.98
106.42
66.28
46.78
21.48
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


-62.42
-50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)


CF3
N
N
Me
HN
S
NH2
O


8.01
8.01
7.99
7.99
7.45
7.45
7.44
7.43
7.43
7.42
7.17
7.15
7.11
7.11
7.10
7.09
6.73
4.38
2.37
2.02
1.97
2.07
2.01
0.96
2.92
3.00
f1 (ppm)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144.59
144.29
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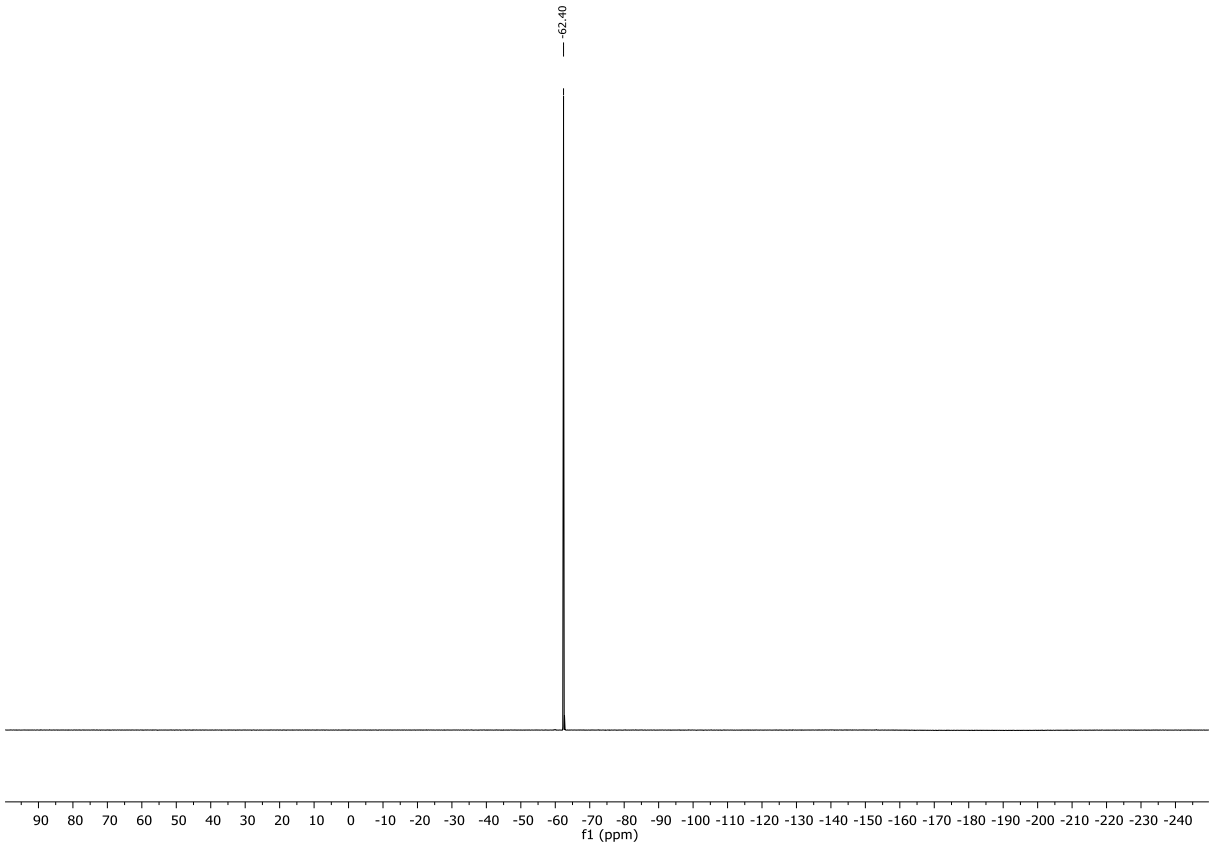
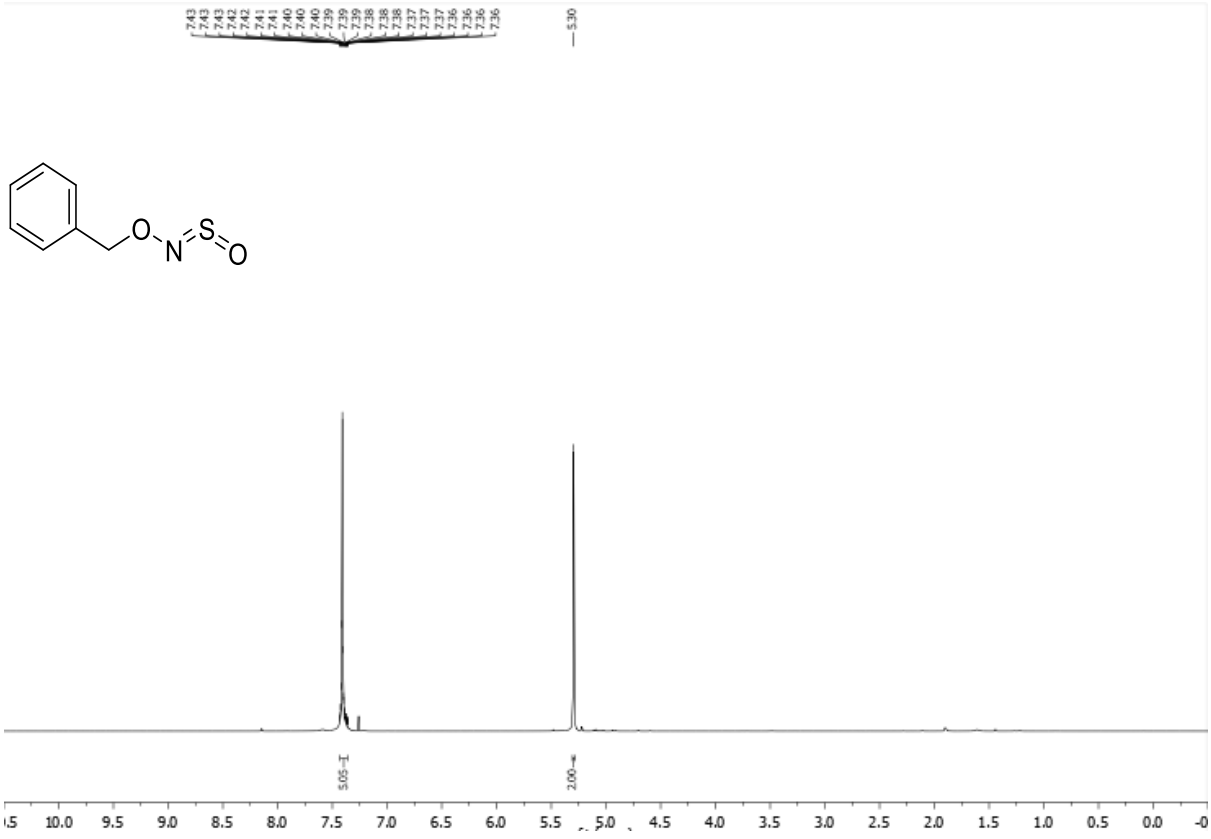
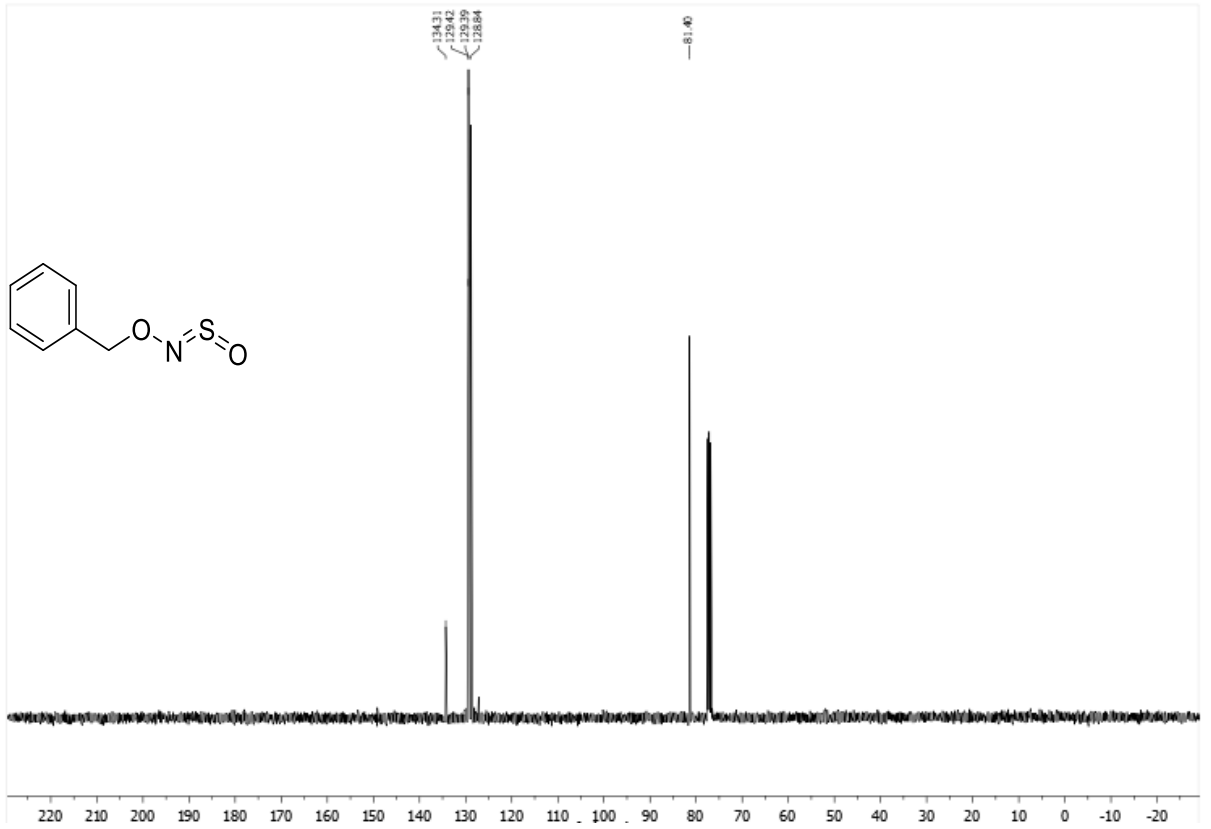
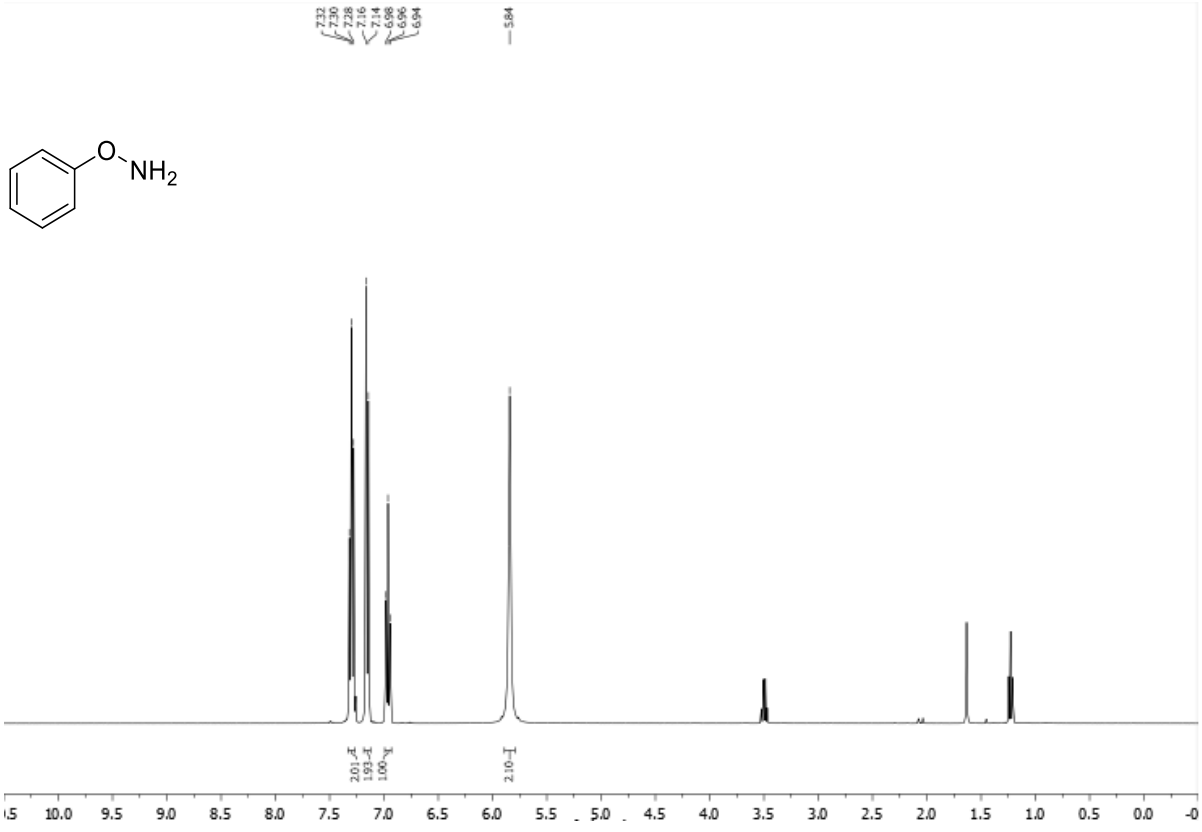
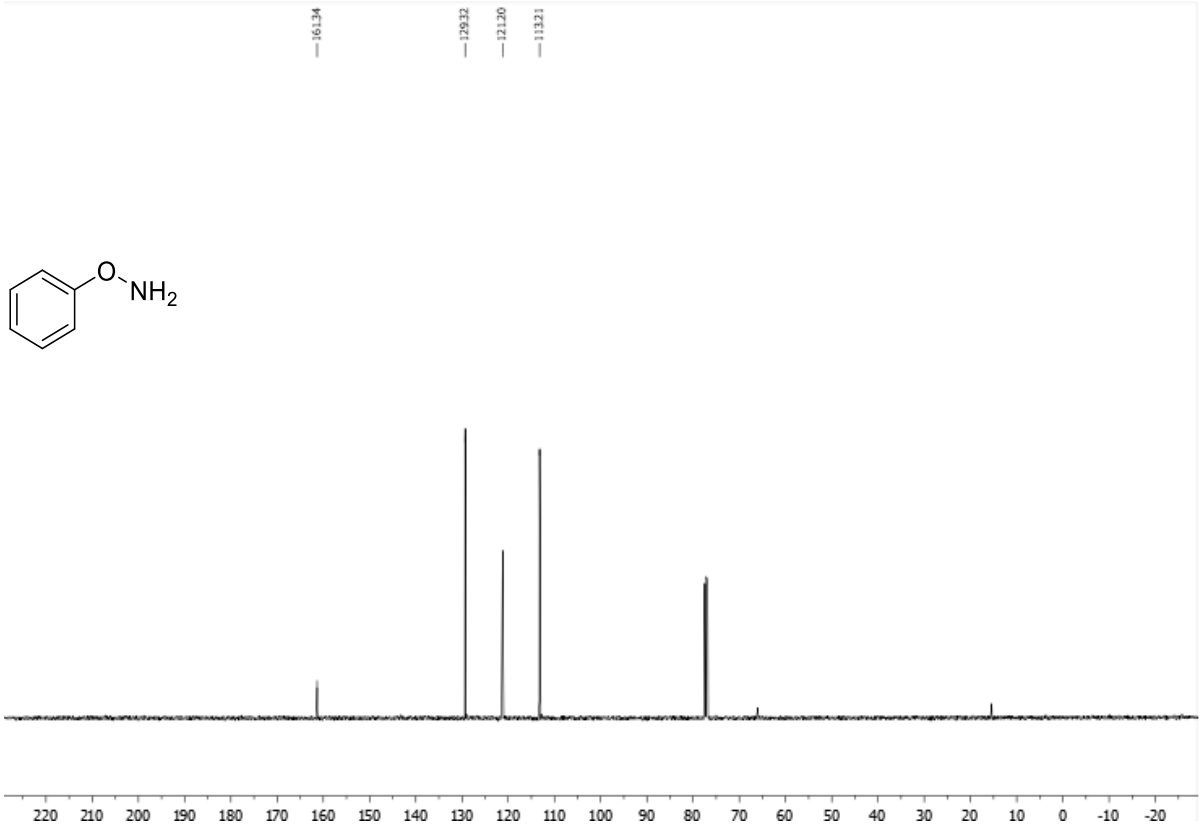
143.68
143.46
142.36
139.86
129.87
128.86
127.73
125.87
125.55
124.40
122.26
120.12
117.99
106.40
21.46
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


-62.40
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)






7.32
7.30
7.28
7.16
7.14
6.98
6.96
6.94
5.84
O
NH2
2.01
1.93
1.00
2.10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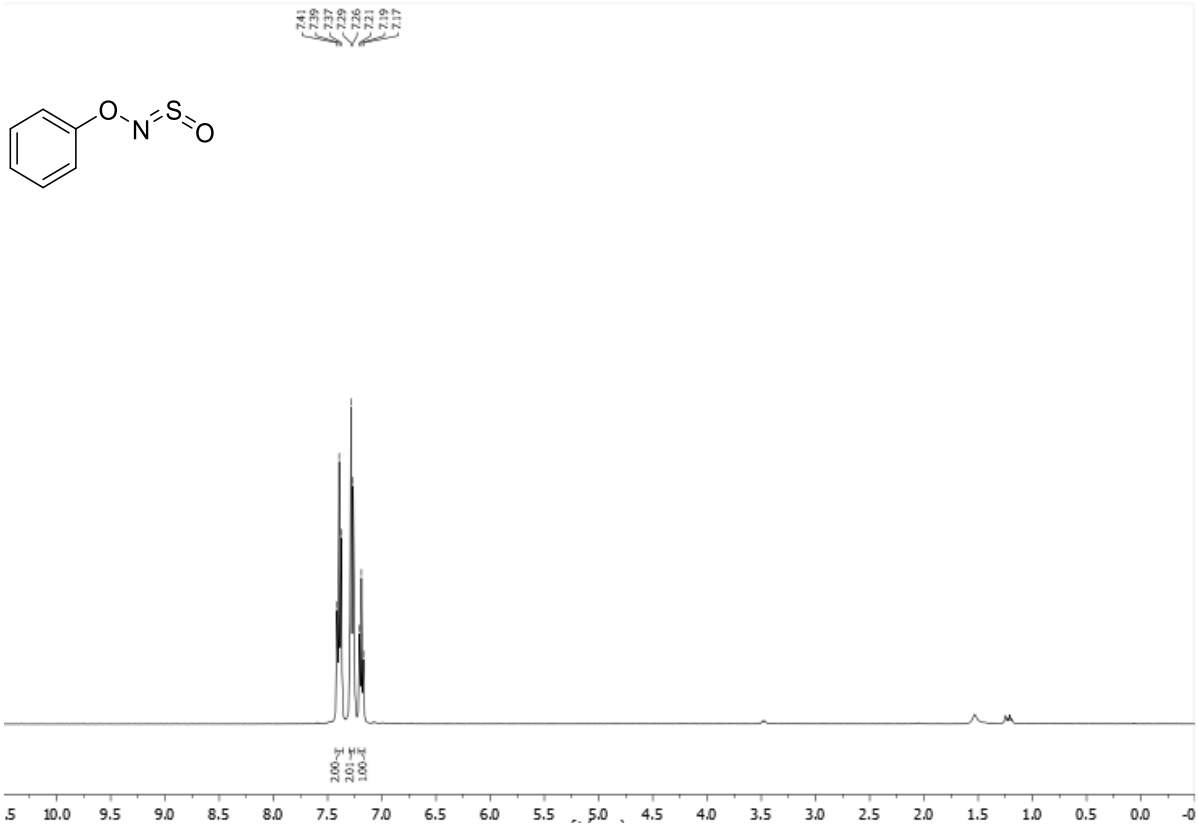
129.32
121.20
113.21
O
NH2


7.41
7.39
7.37
7.29
7.26
7.21
7.19
7.17
O
N
S
O
2.00
2.01
1.00
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
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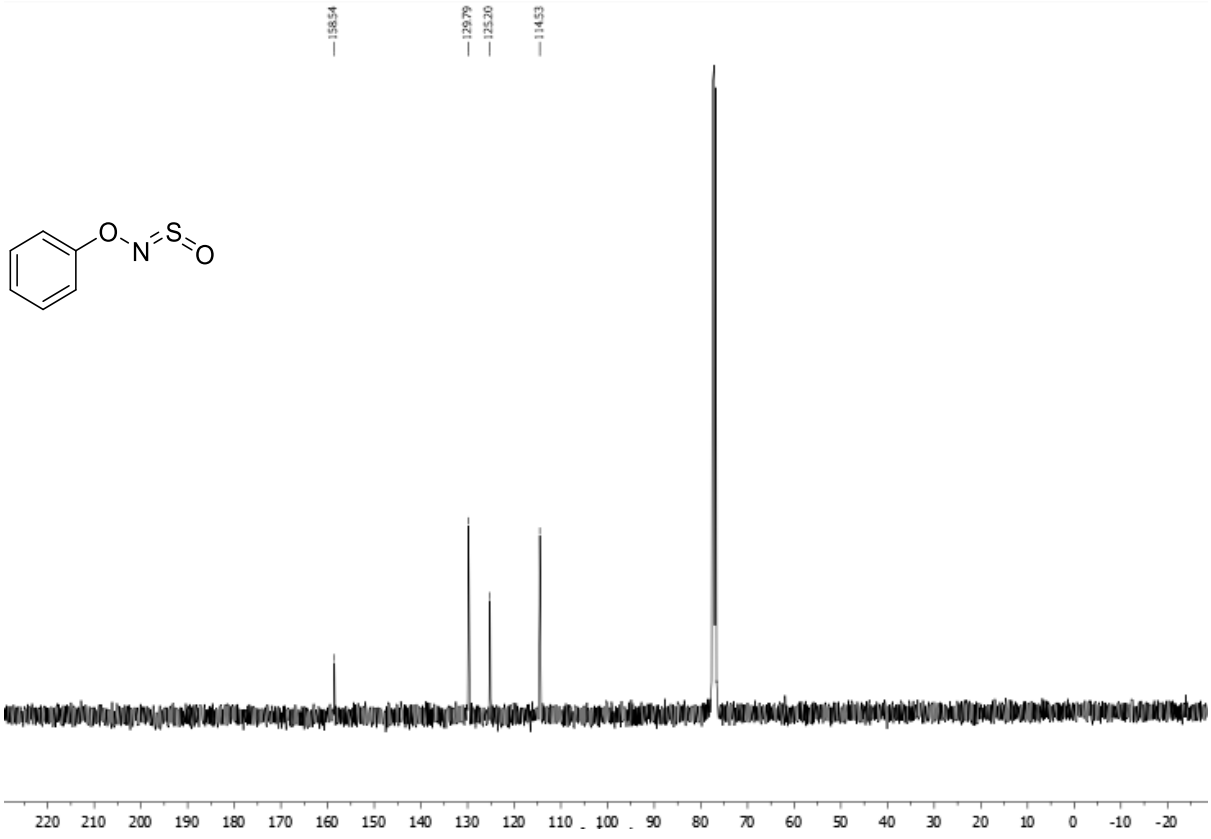
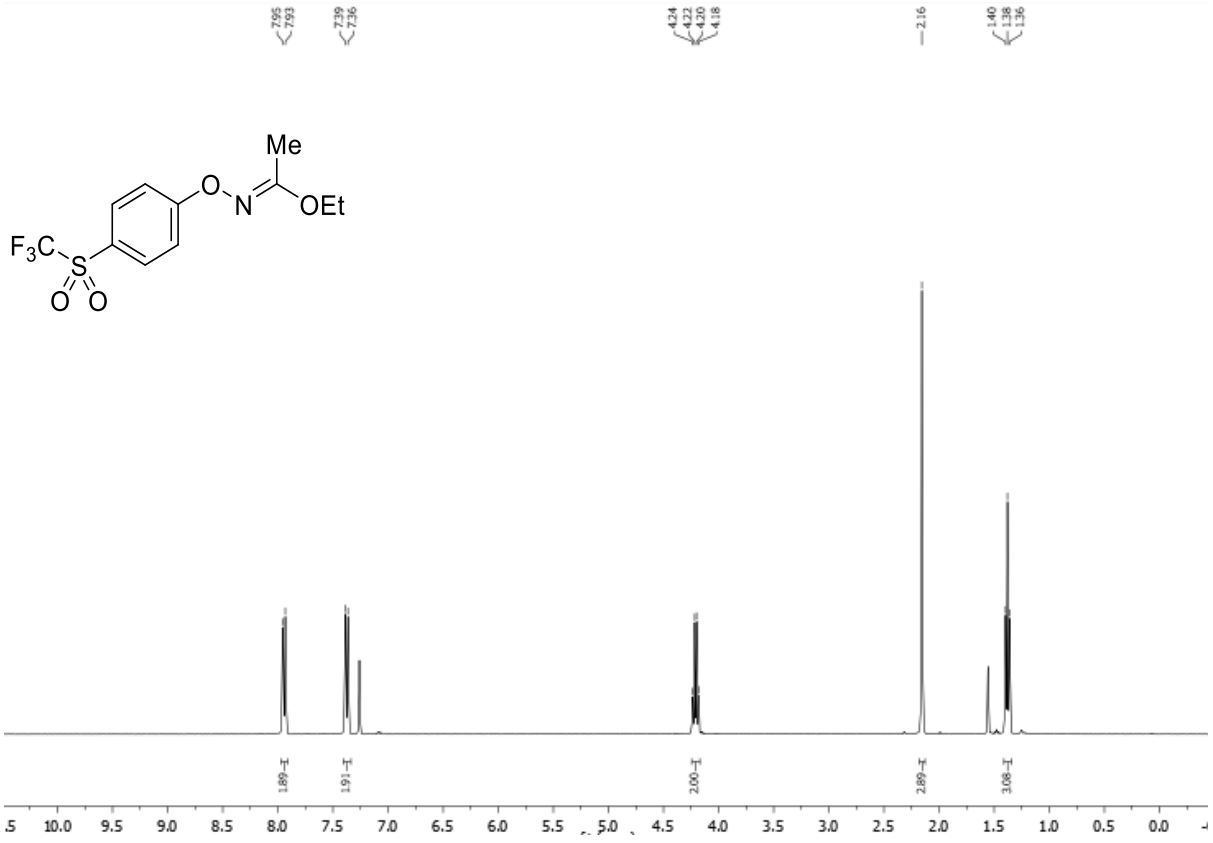
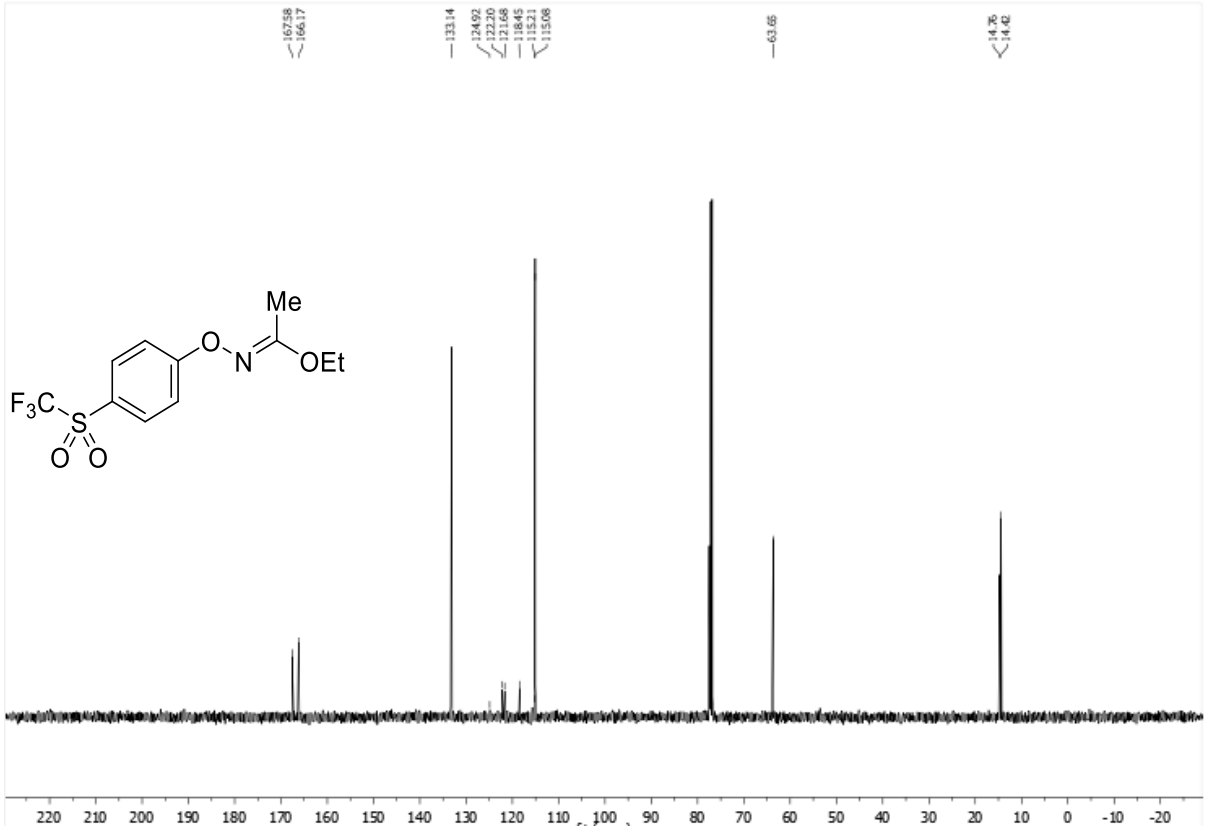
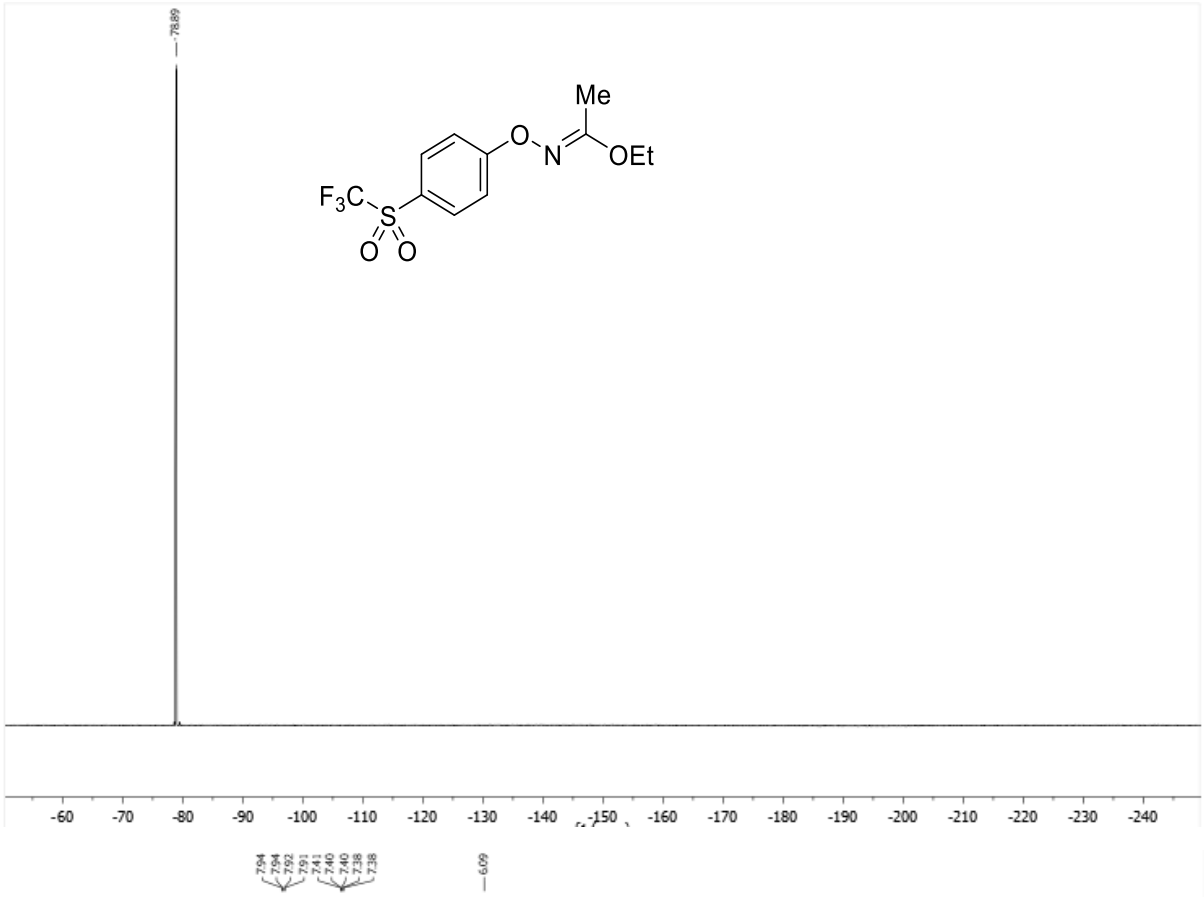
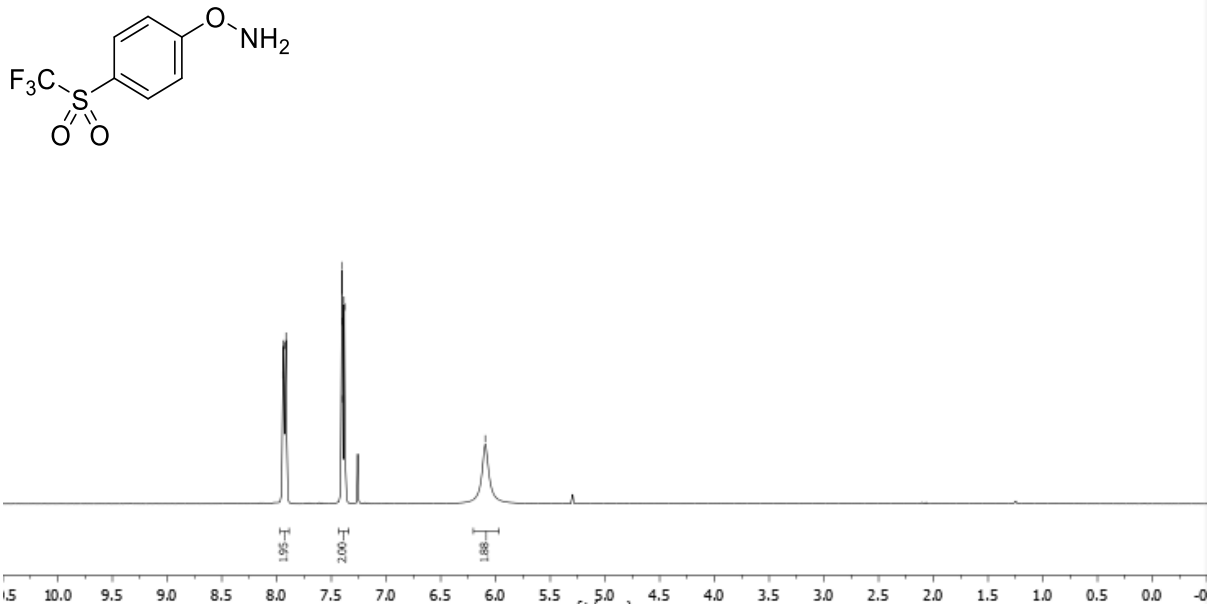
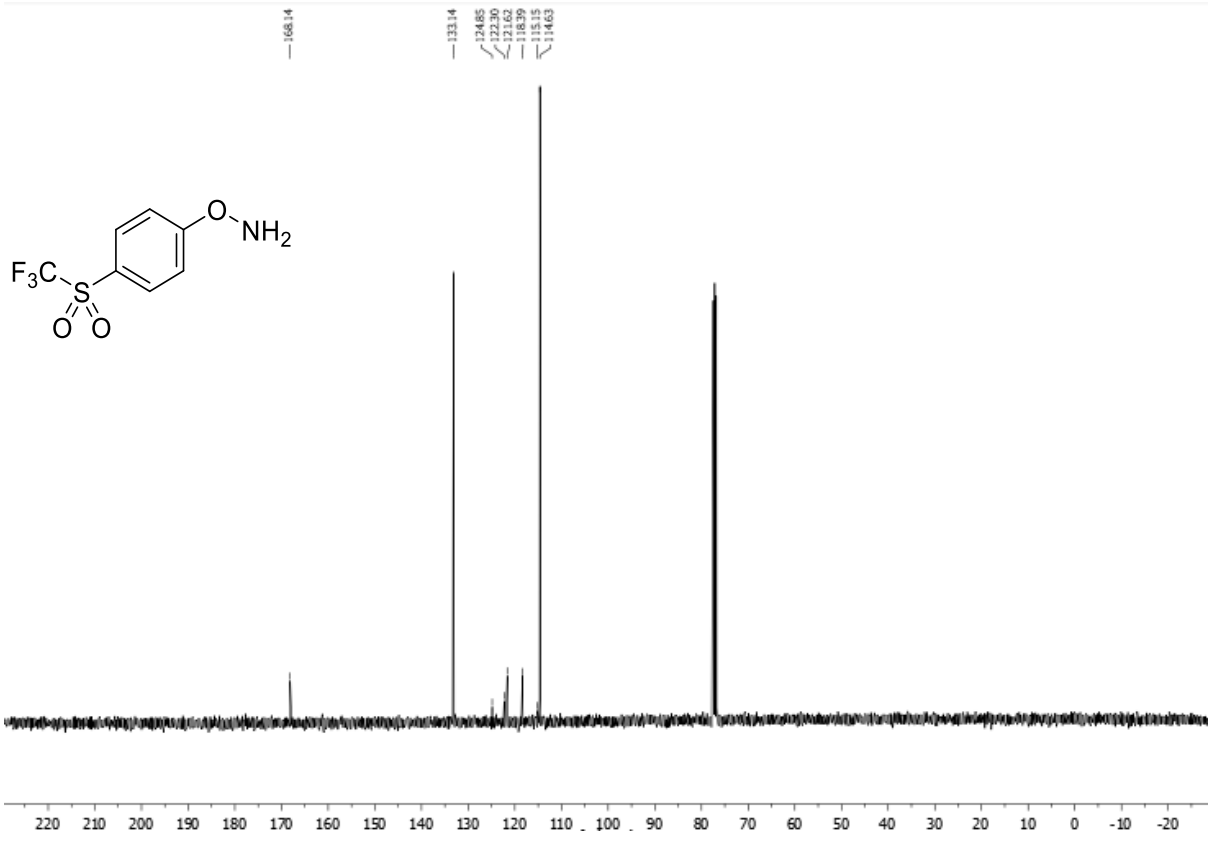

158.54
129.79
125.20
114.53
O
N
S
O
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20

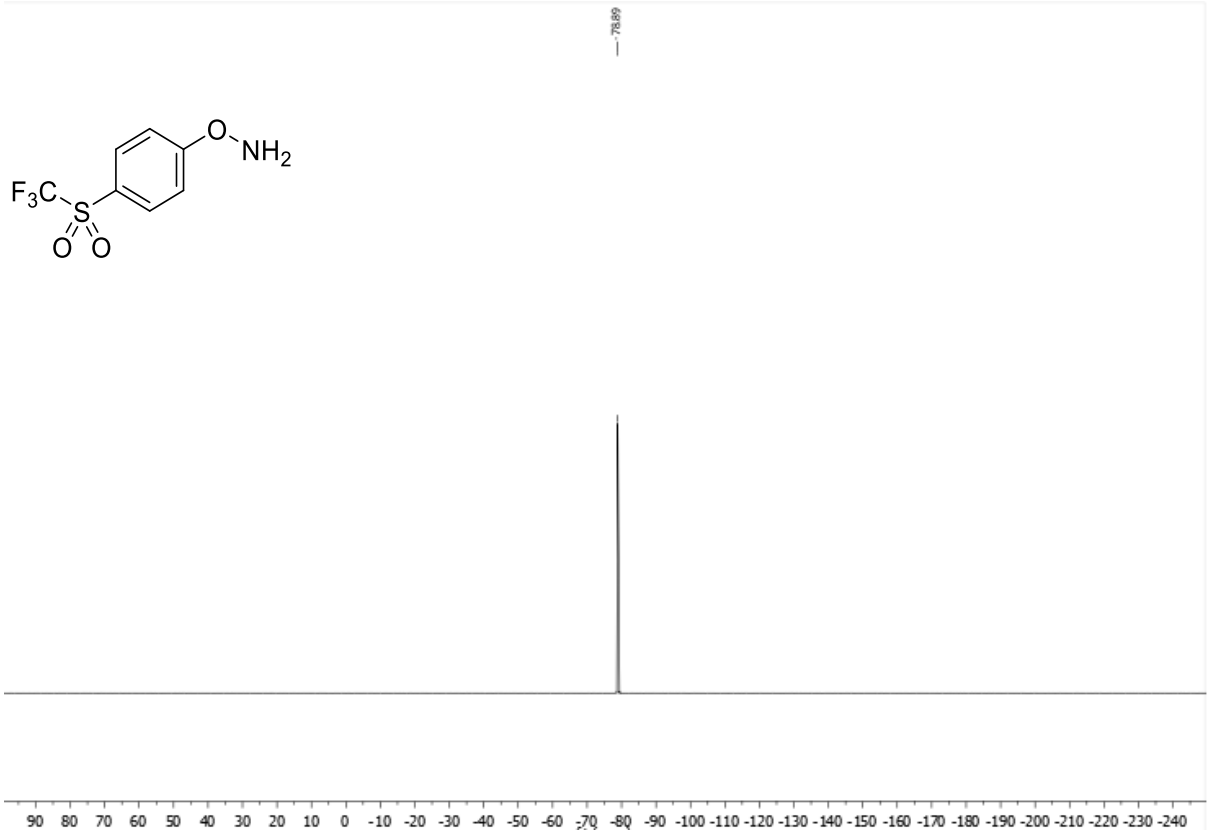

Me
O
N
OEt
F3C
S
O
O

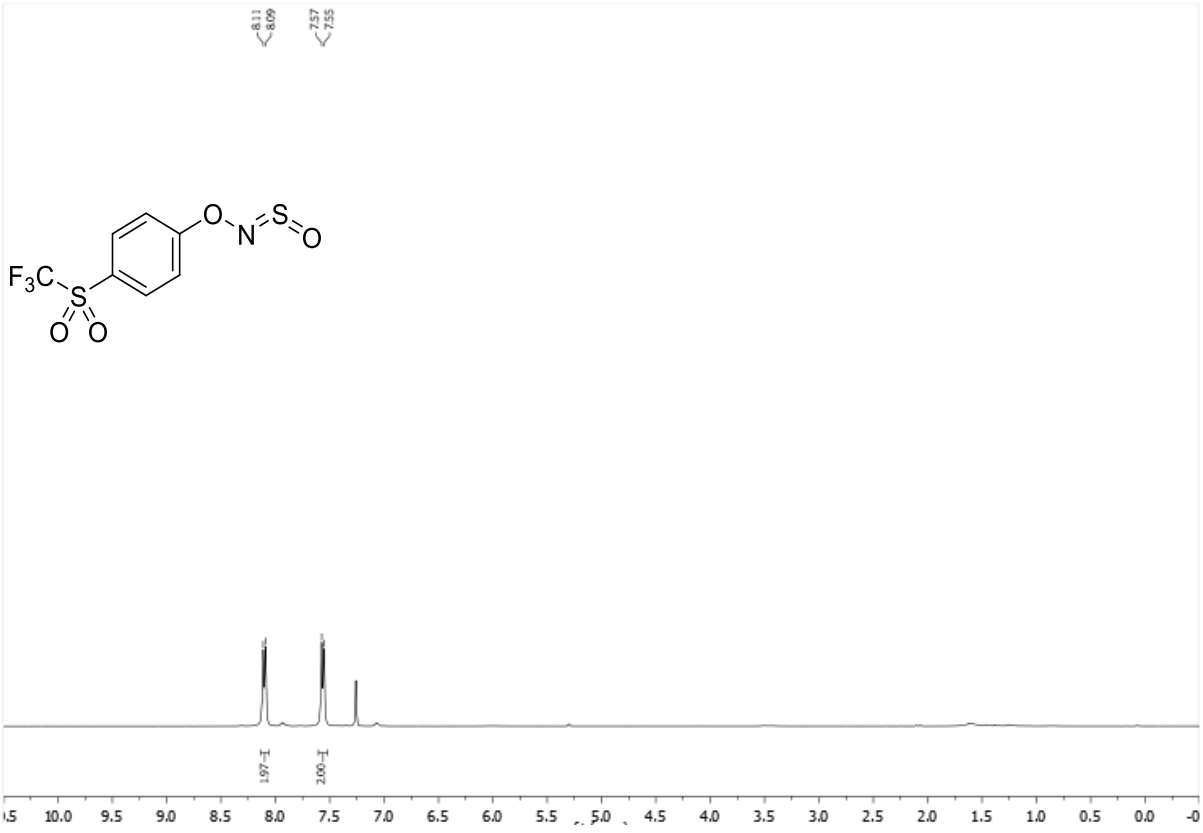

Me
O
N
OEt
F3C
S
O
O

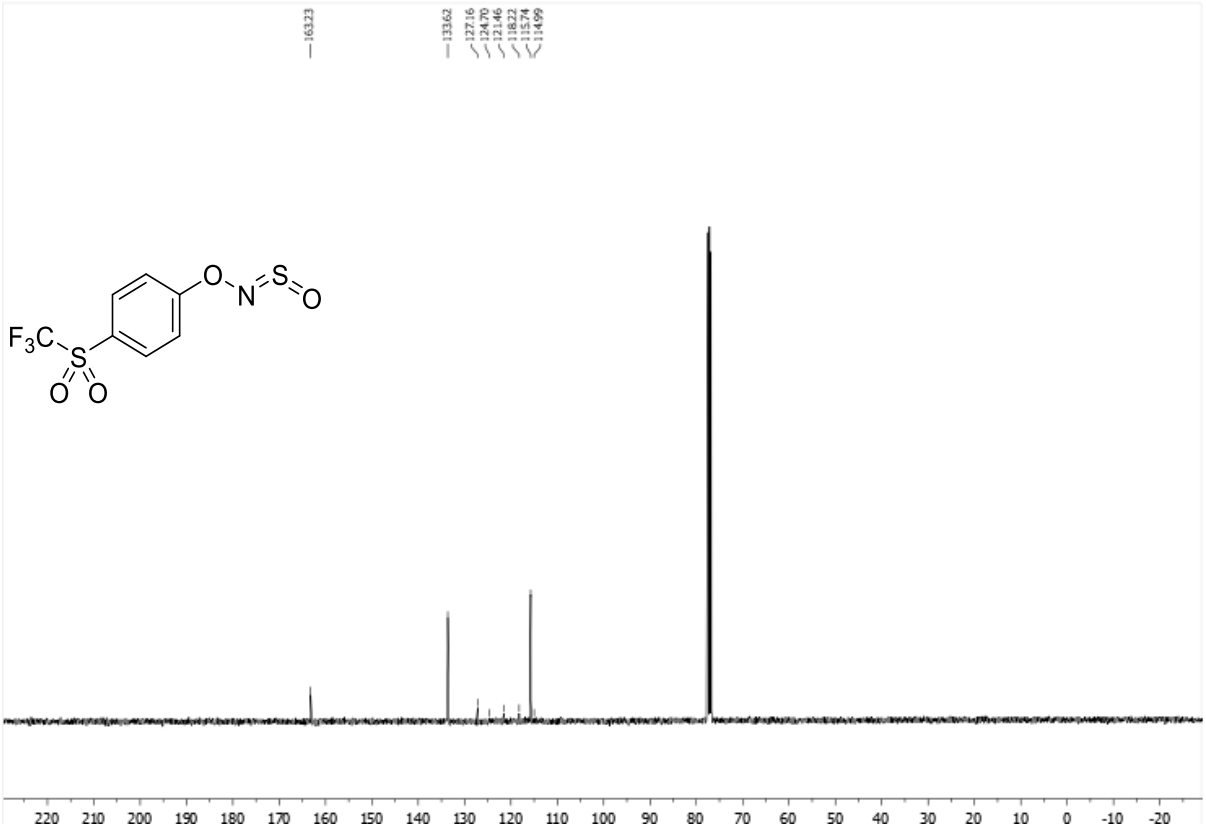

-78.69
Me
O
N
OEt
F3C
S
O
O
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
-230
-240
7.94
7.94
7.92
7.91
7.41
7.40
7.40
7.38
7.38
6.09


O
NH2
F3C
S
O
O
1.95
2.00
1.88
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


168.14
133.14
124.85
122.30
121.62
118.39
115.15
114.63
O
NH2
F3C
S
O
O
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


-78.89
O
NH2
F3C
S
O
O
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


8.11
8.09
7.57
7.55
O
N
S
O
F3C
S
O
O
1.97
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


163.23
133.62
127.16
124.70
121.46
118.22
115.74
114.99
O
N
S
O
F3C
S
O
O
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
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50
40
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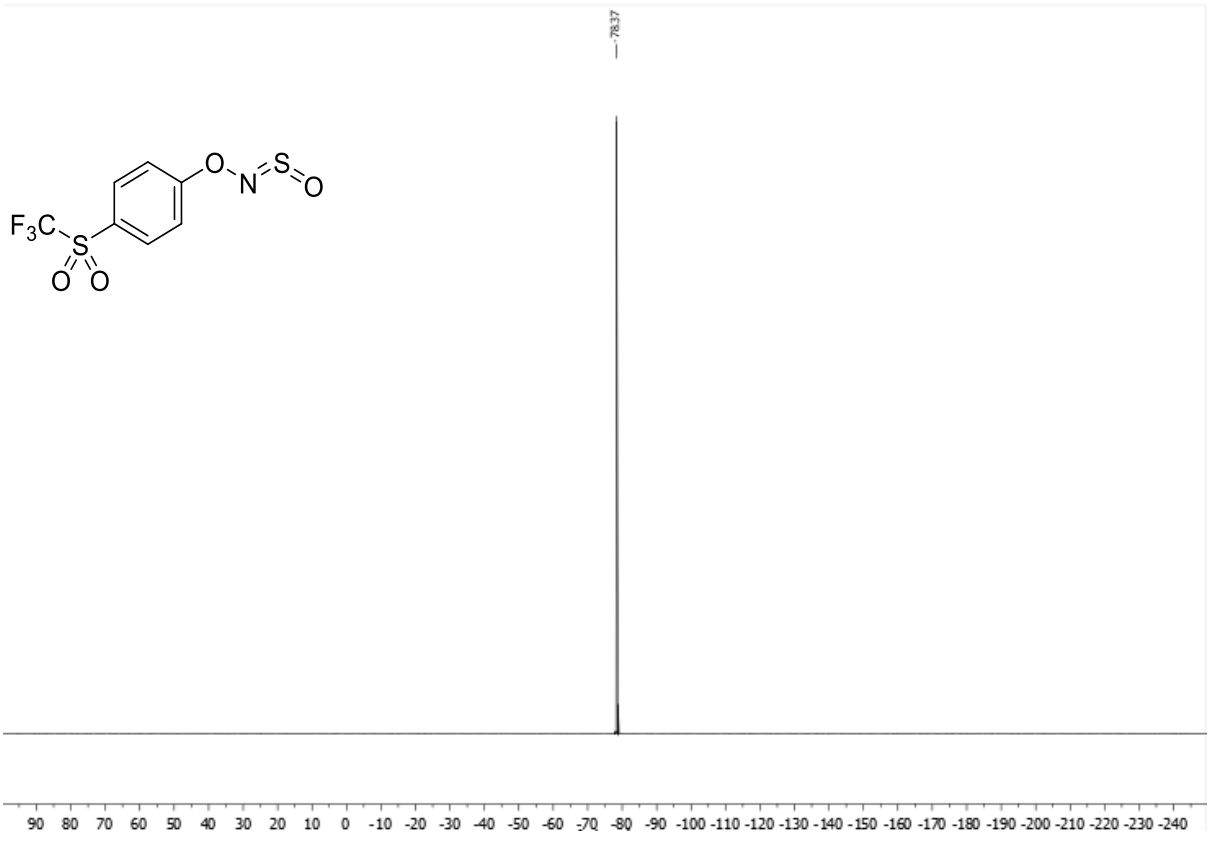
10
0
-10
-20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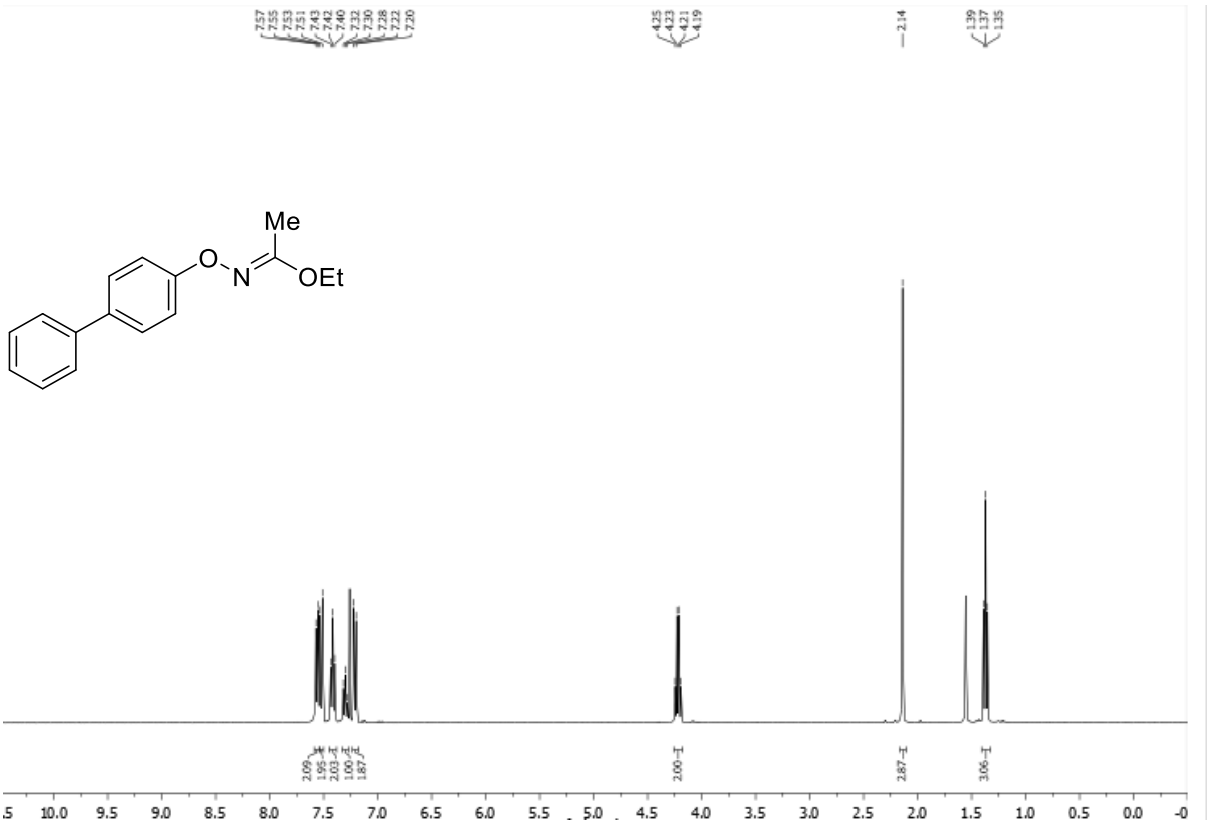
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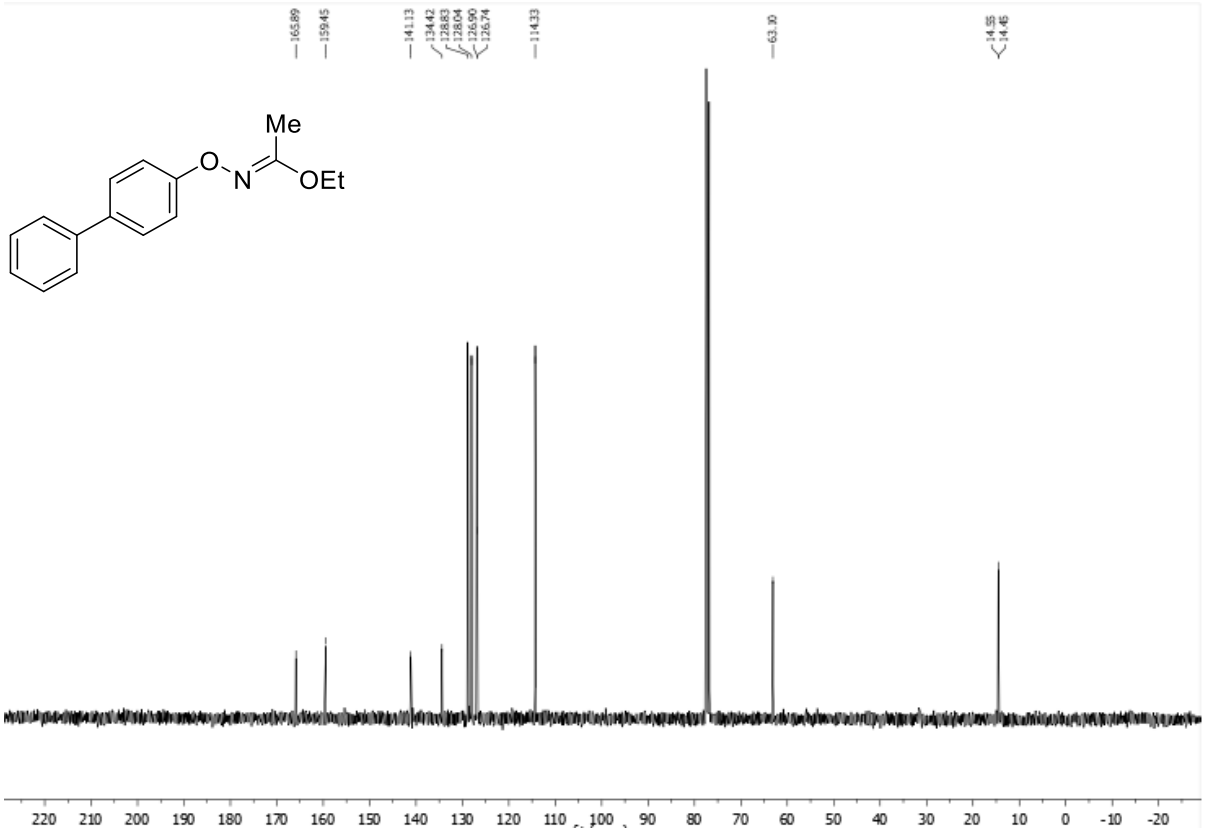
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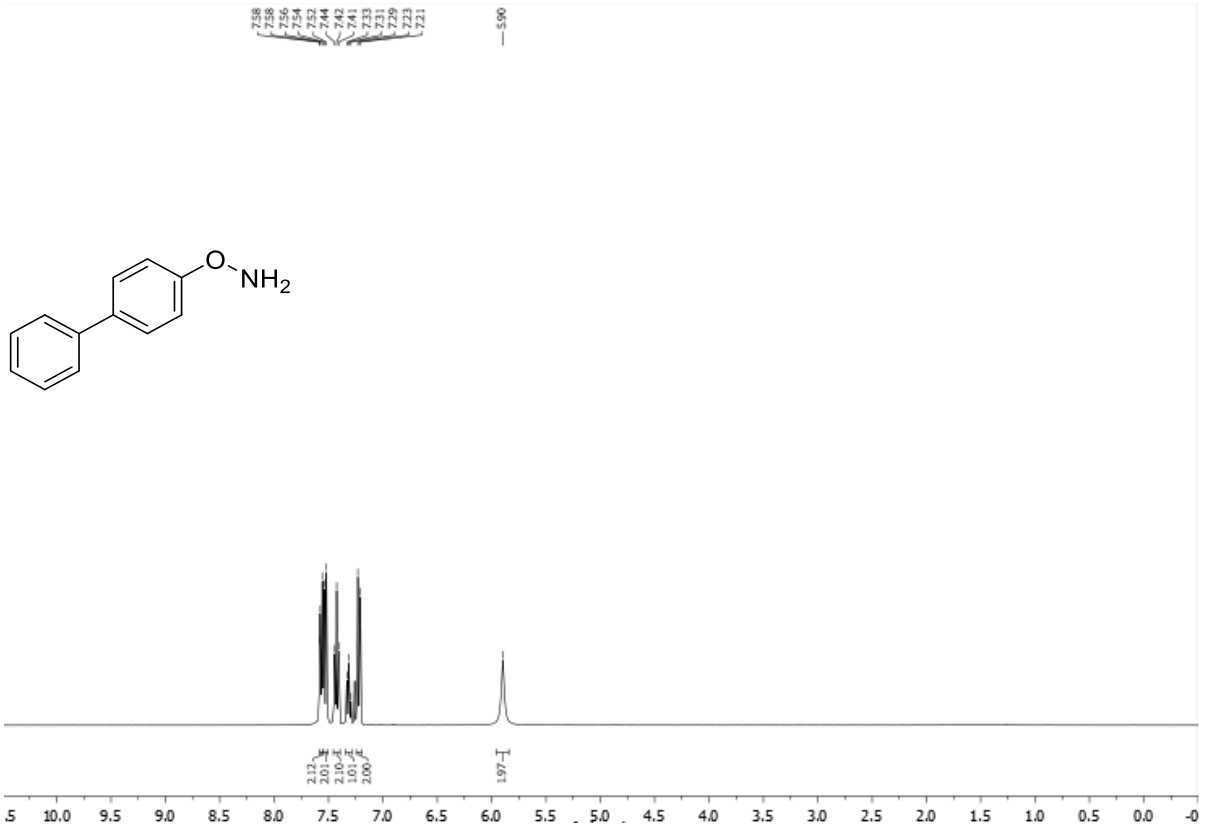
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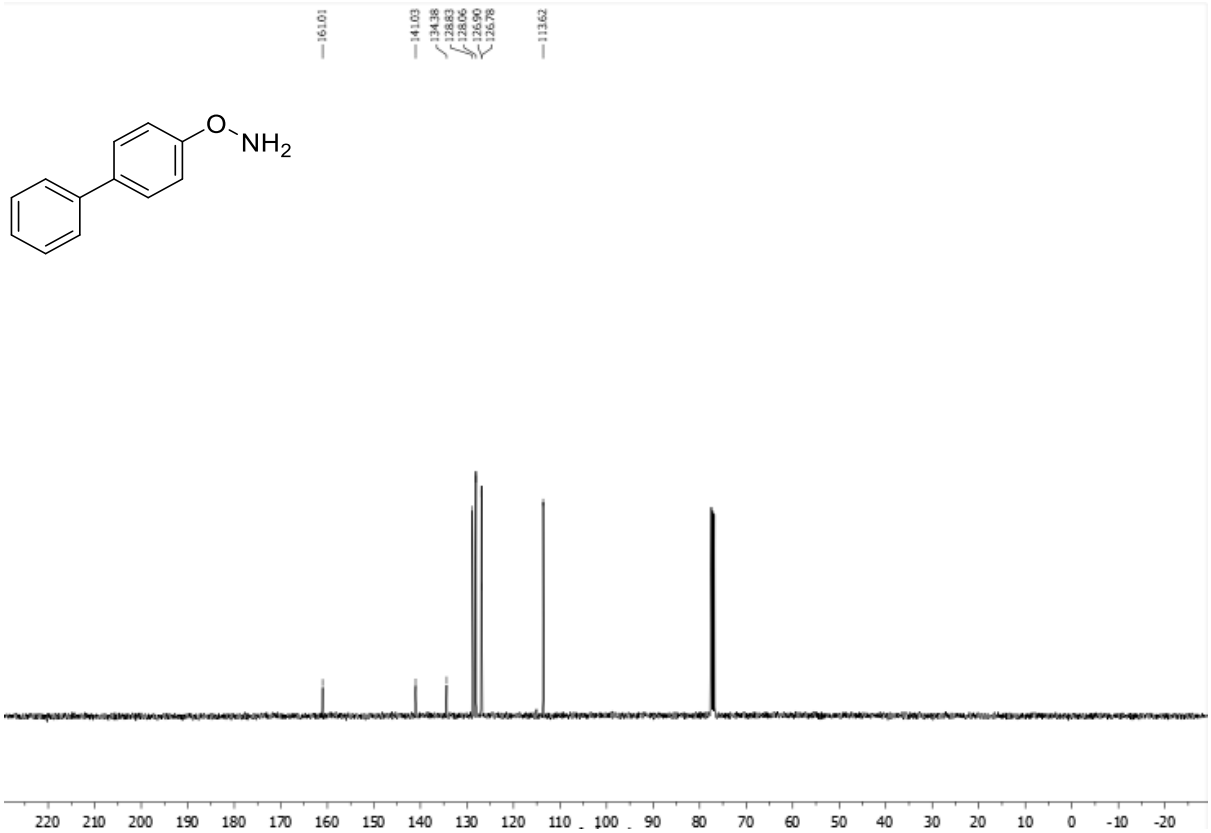
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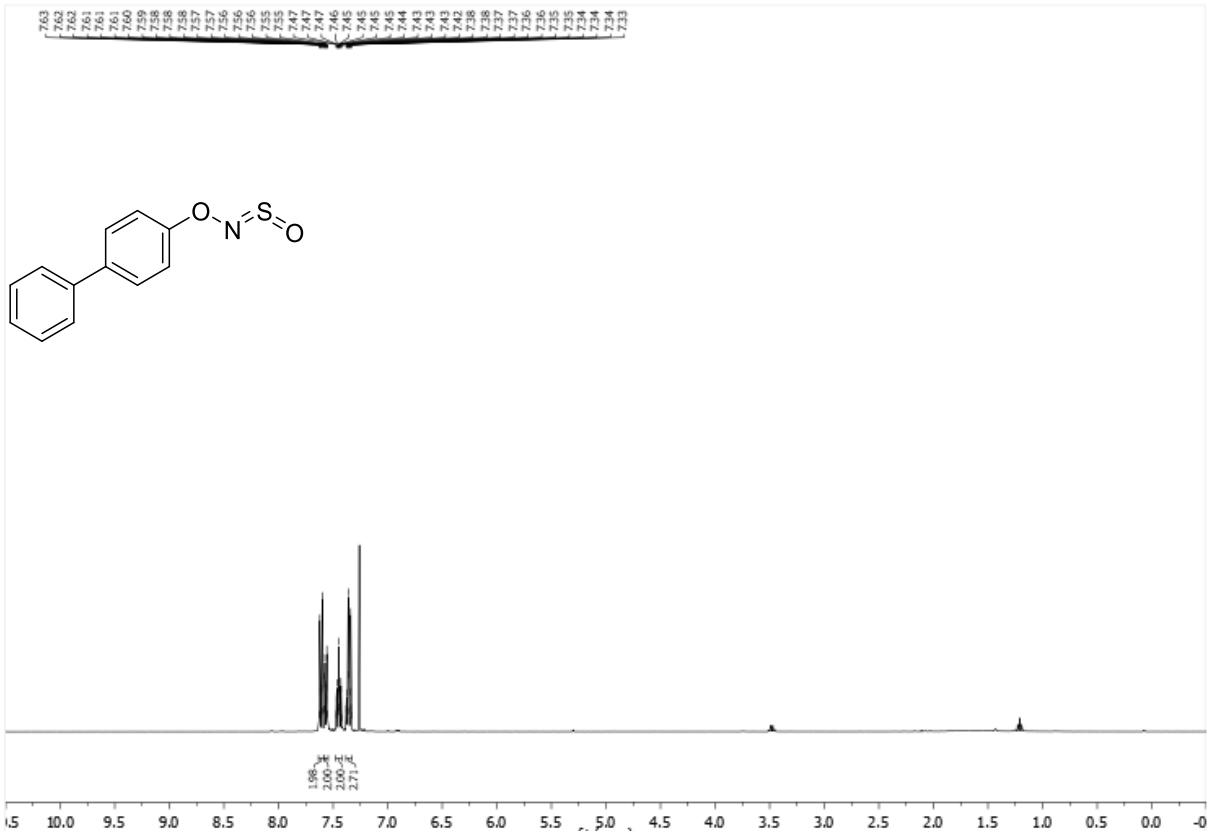
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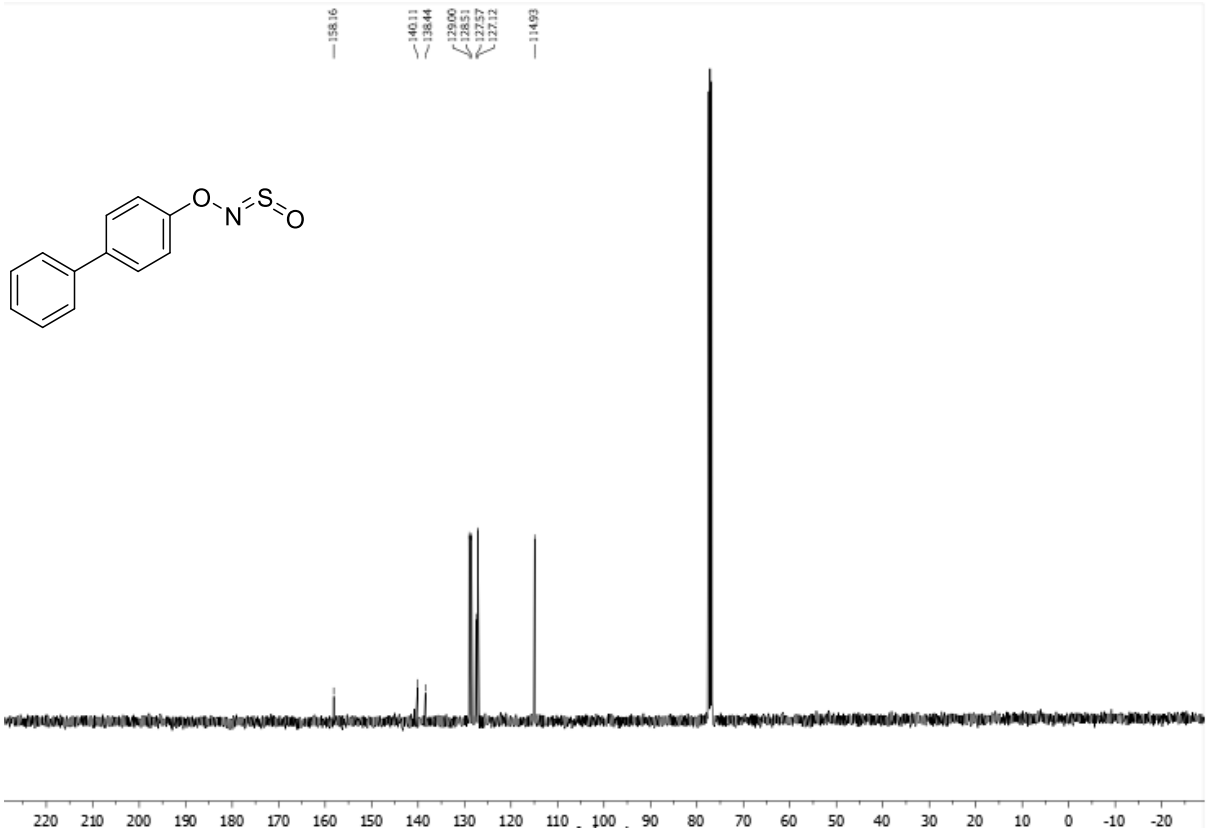
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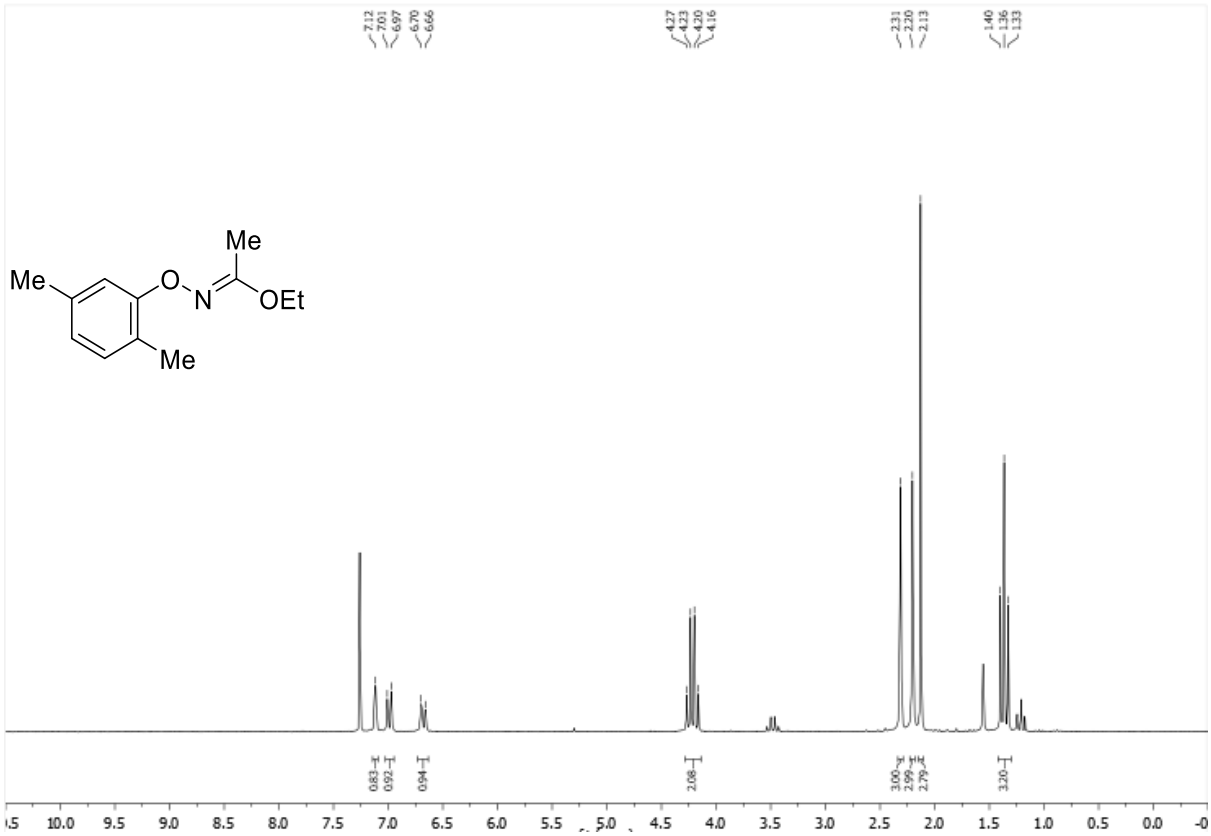
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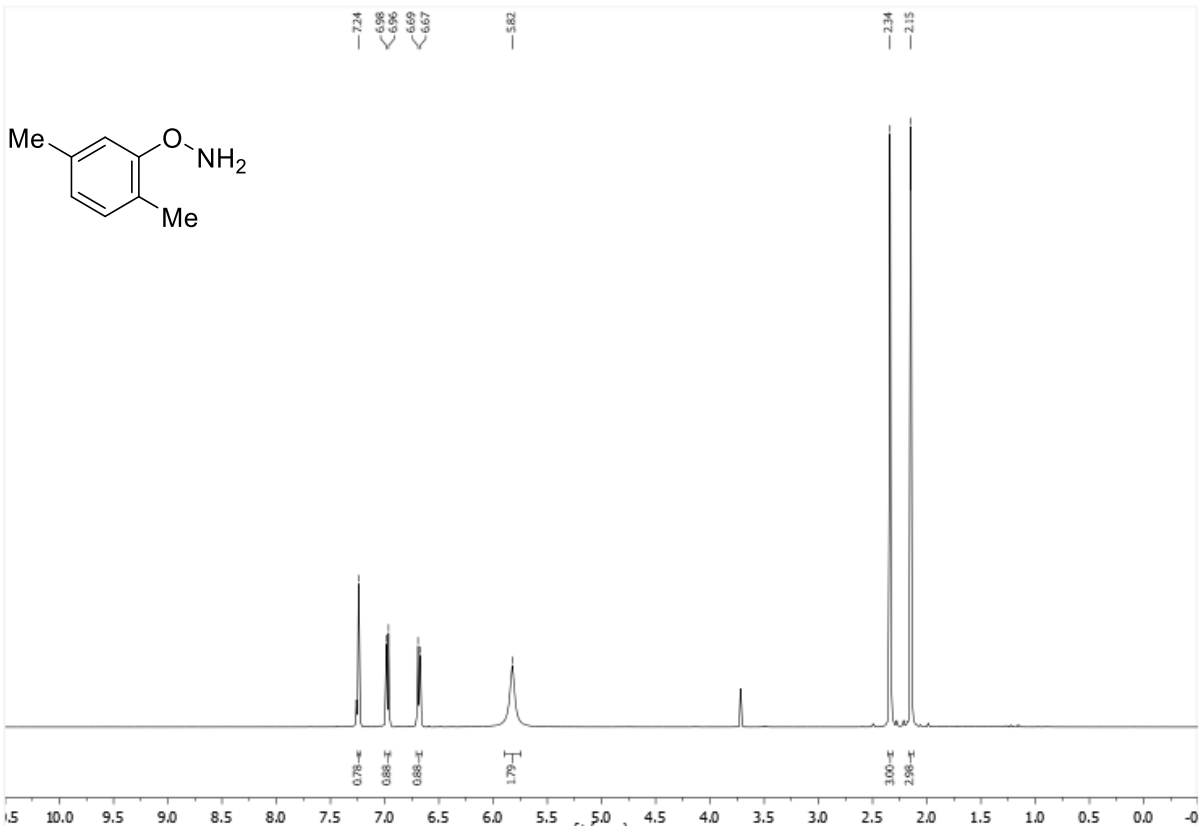
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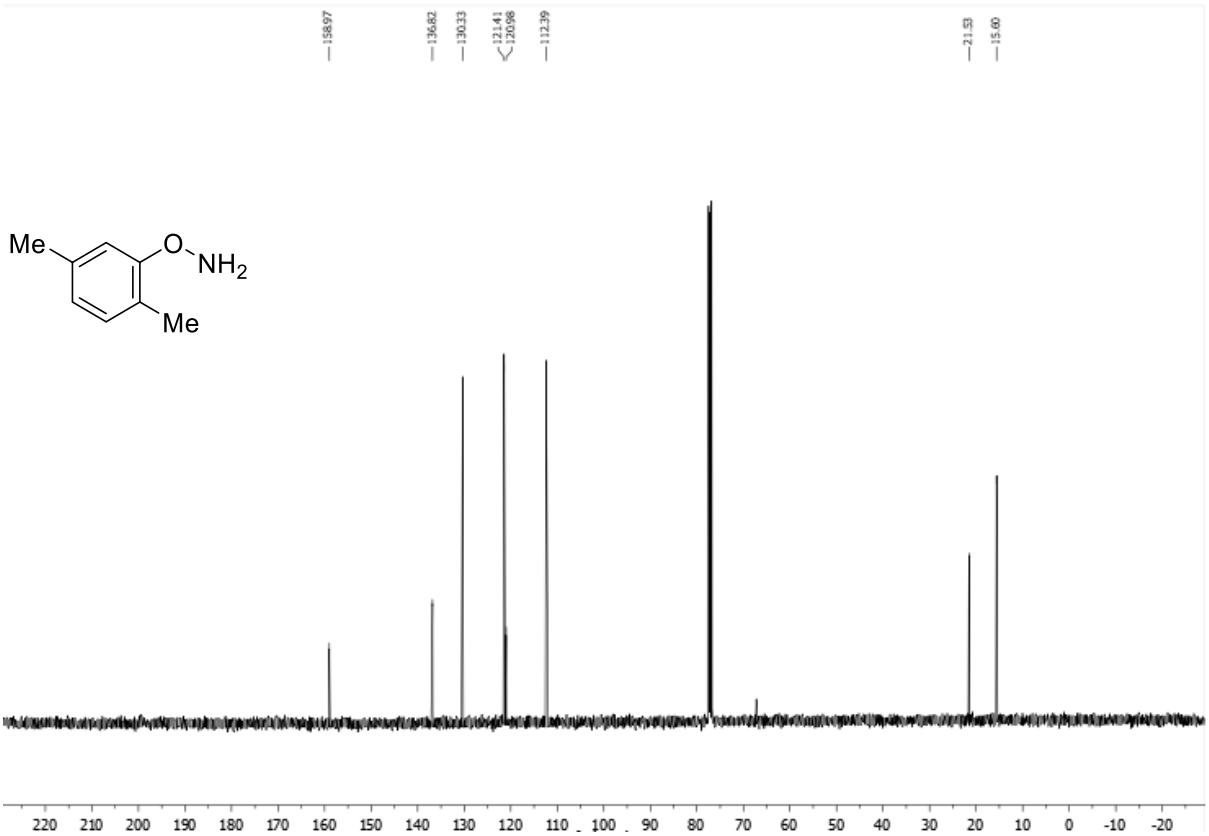
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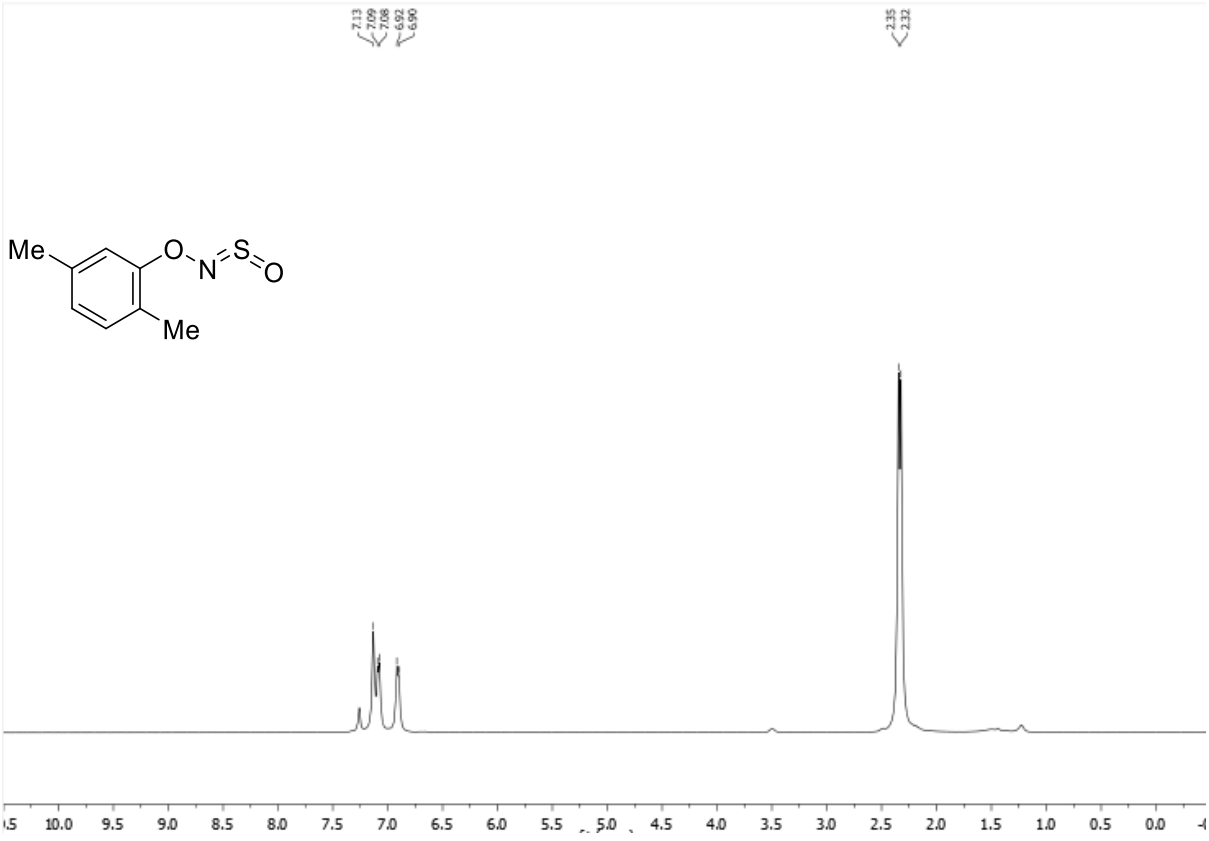
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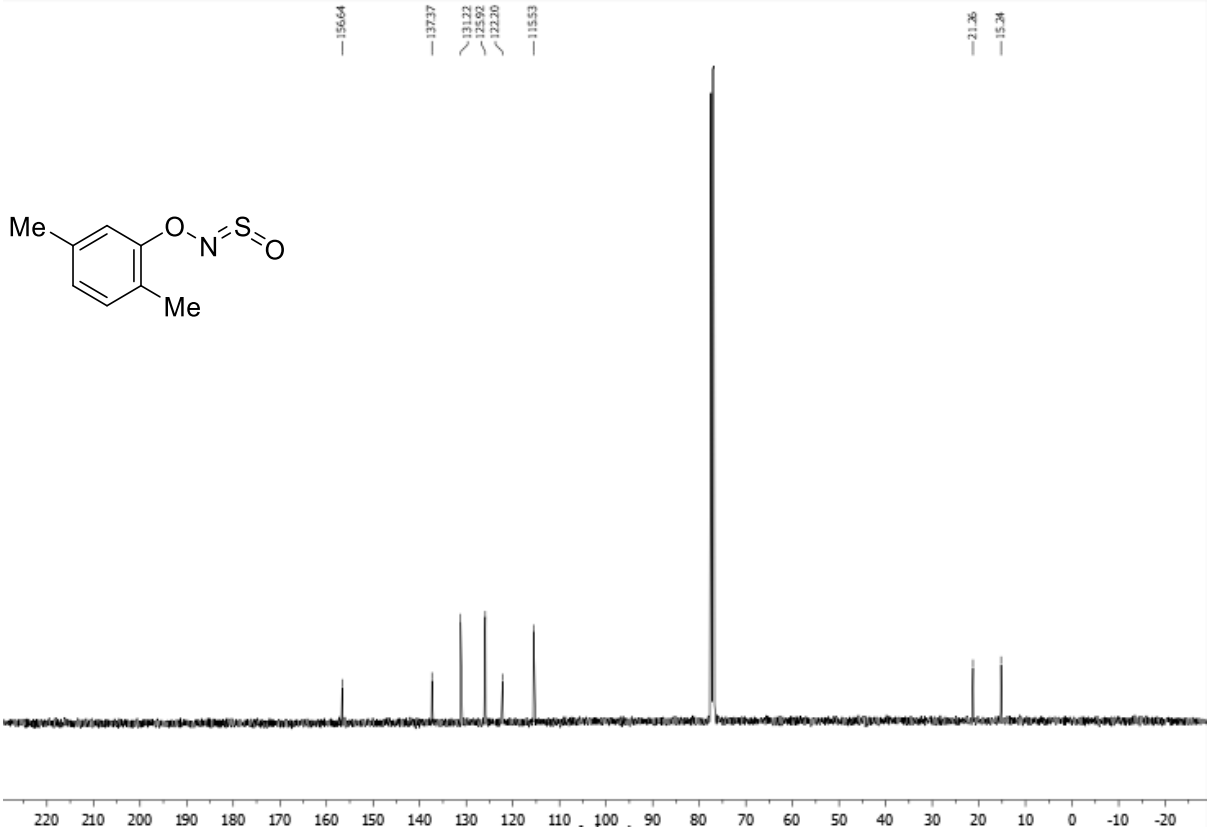
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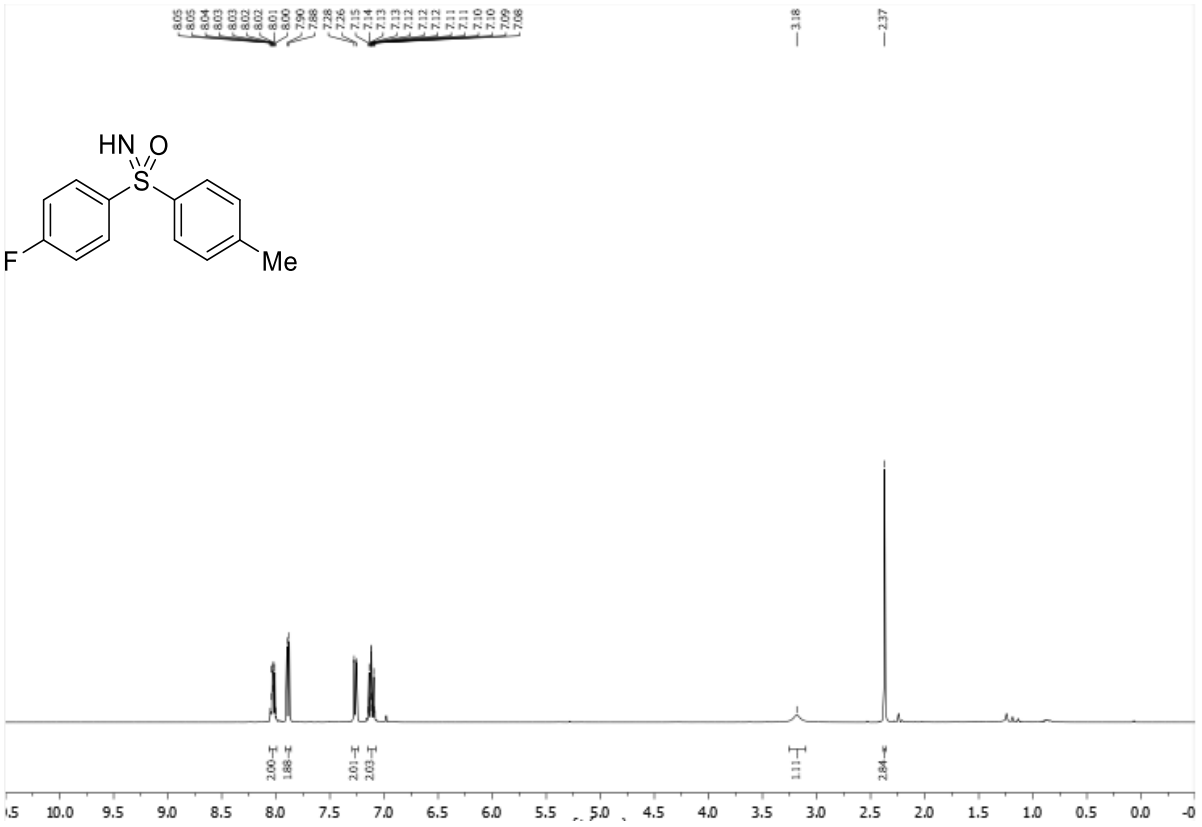
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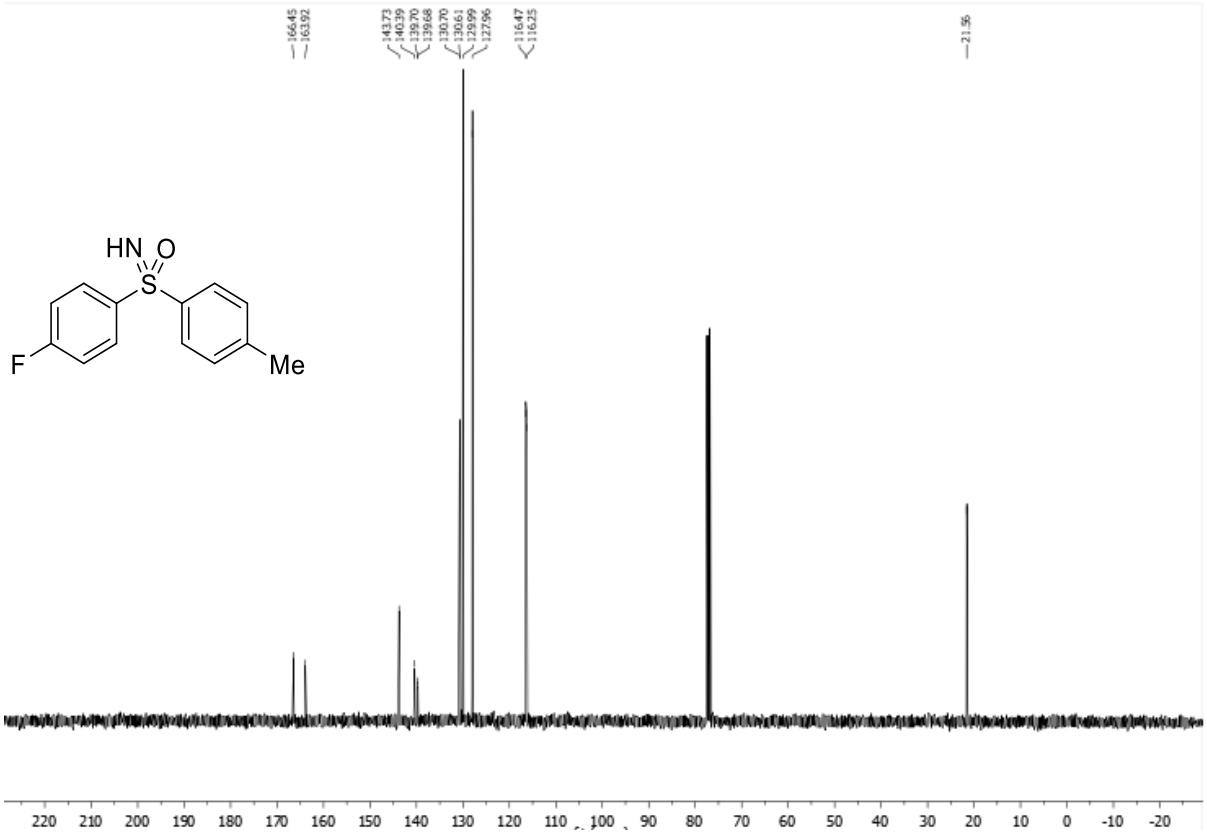
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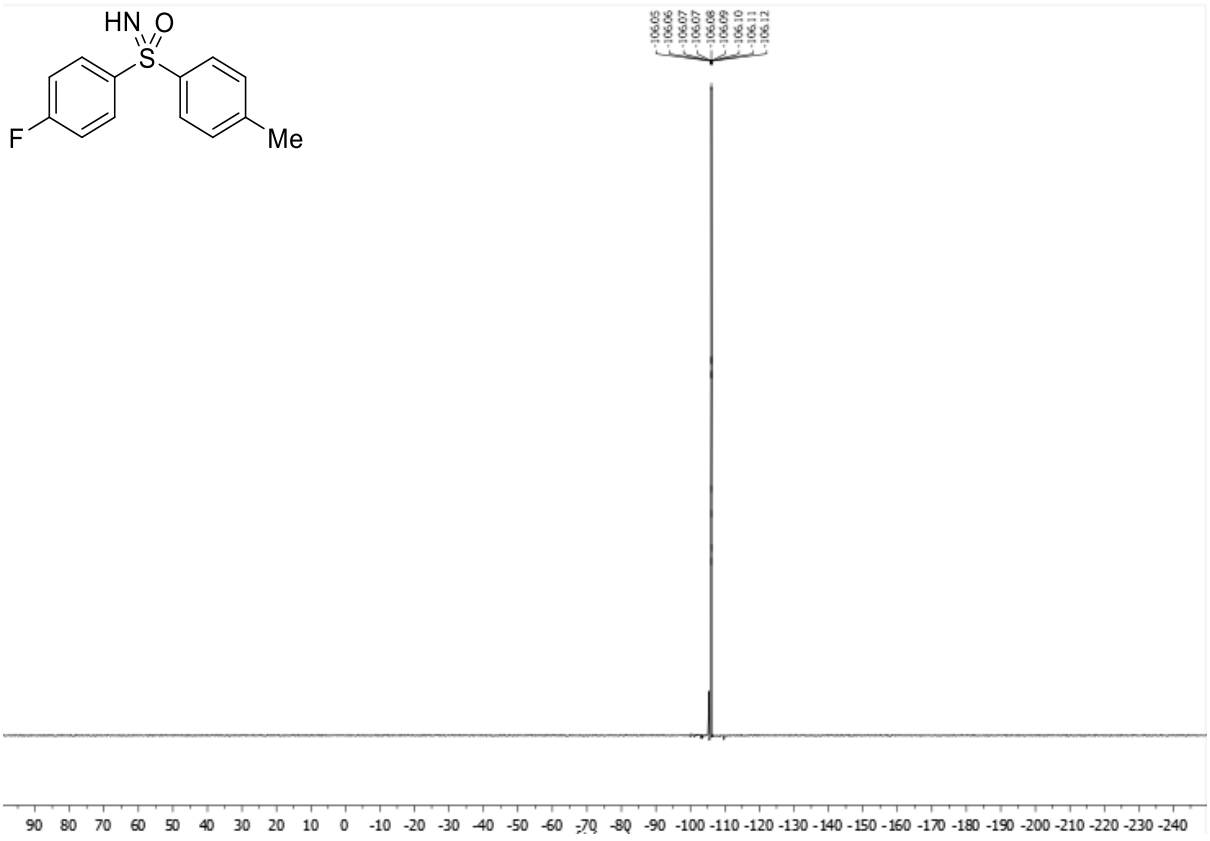
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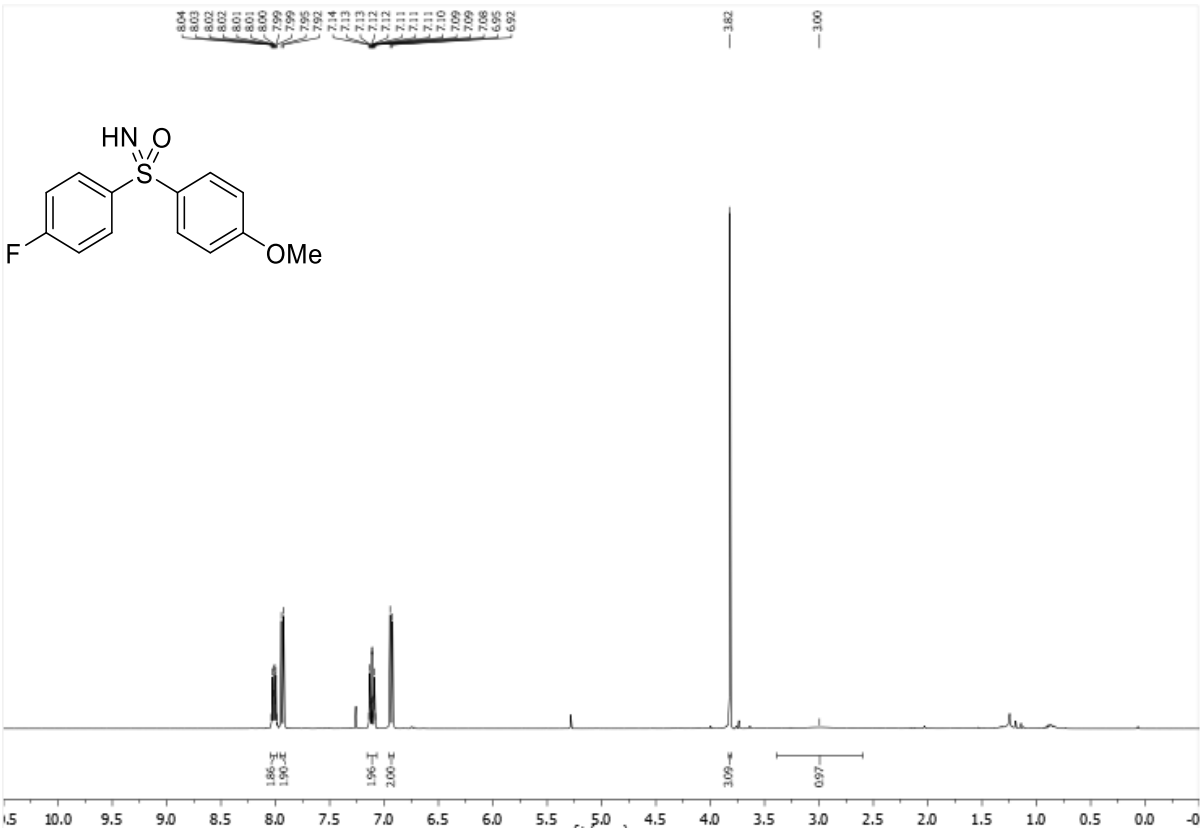
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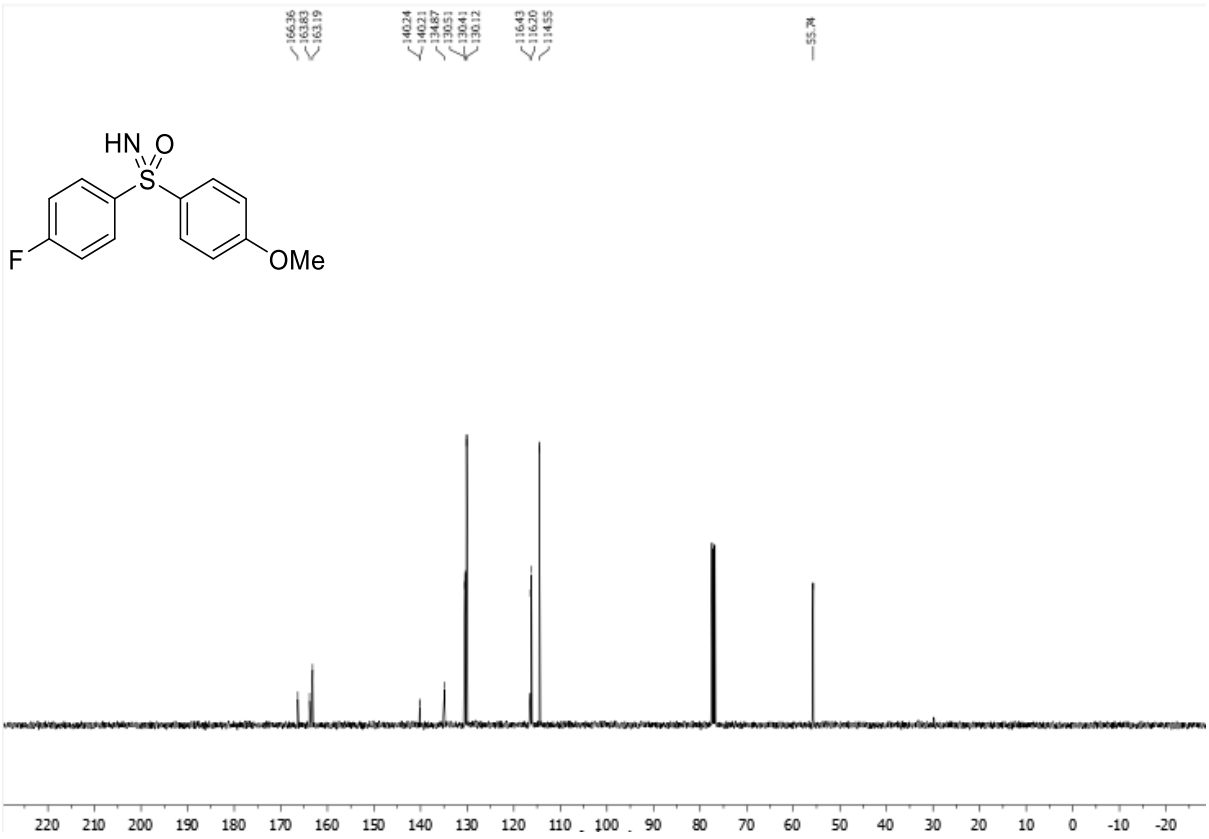
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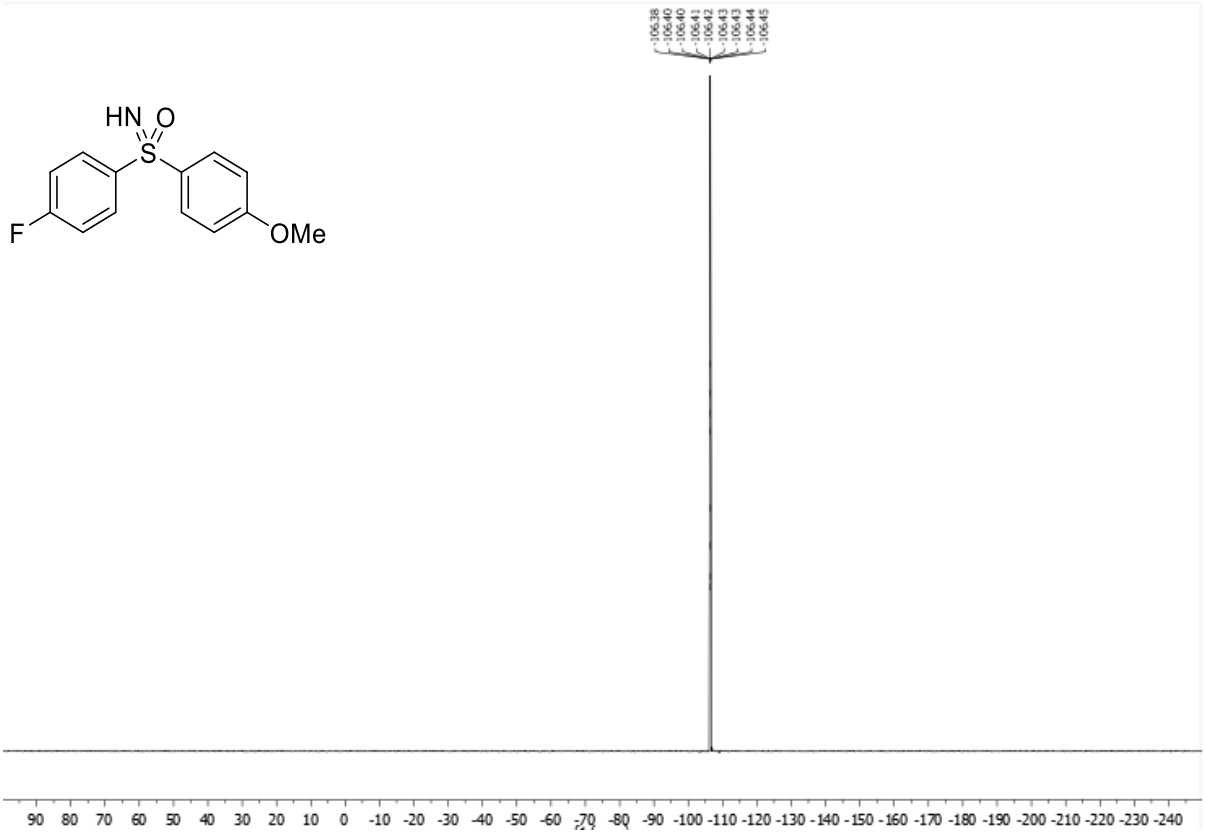
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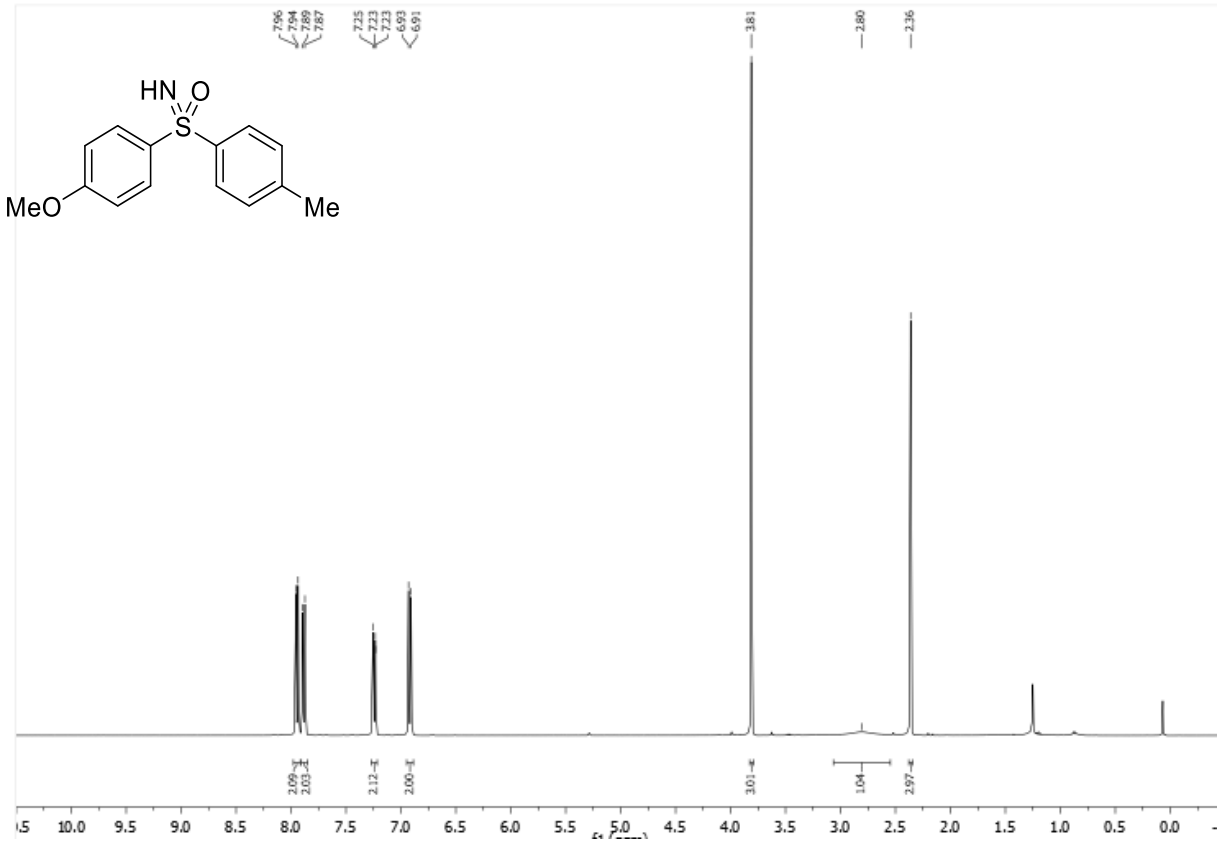
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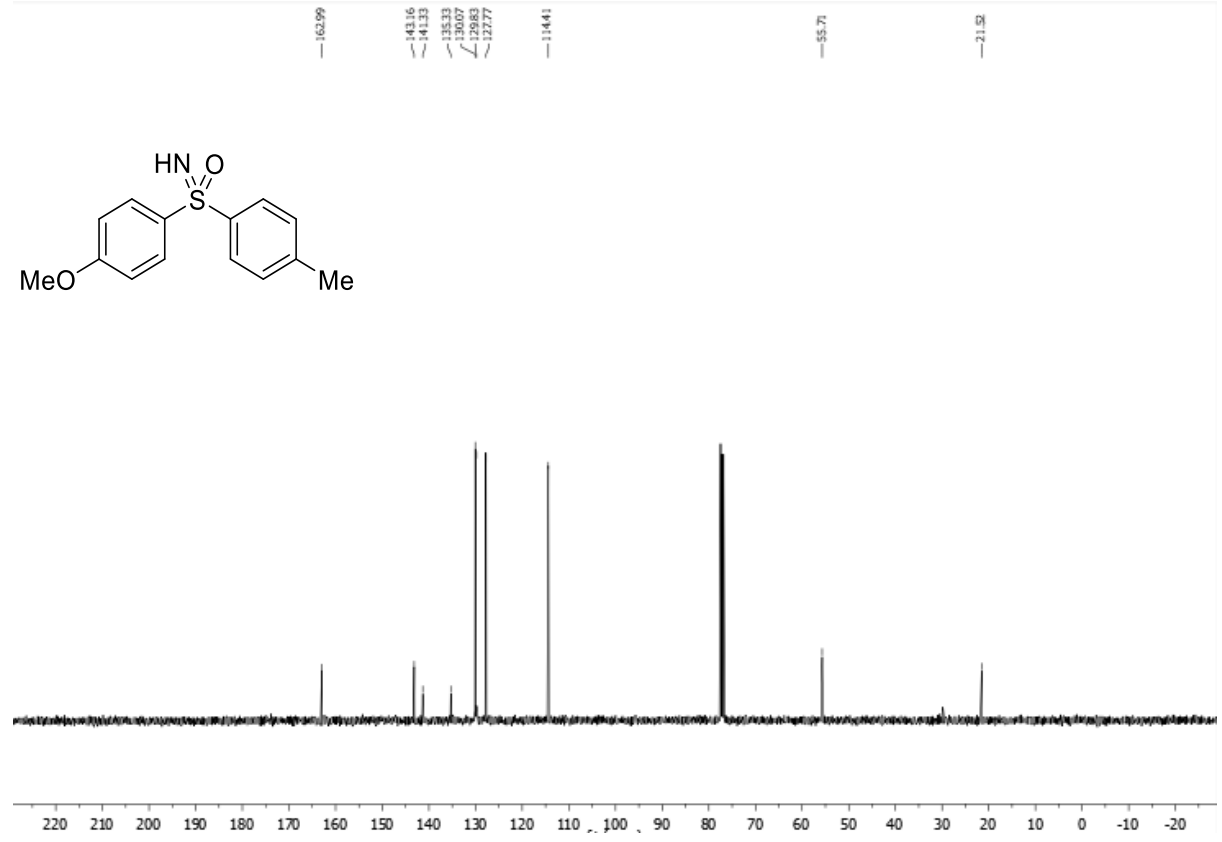
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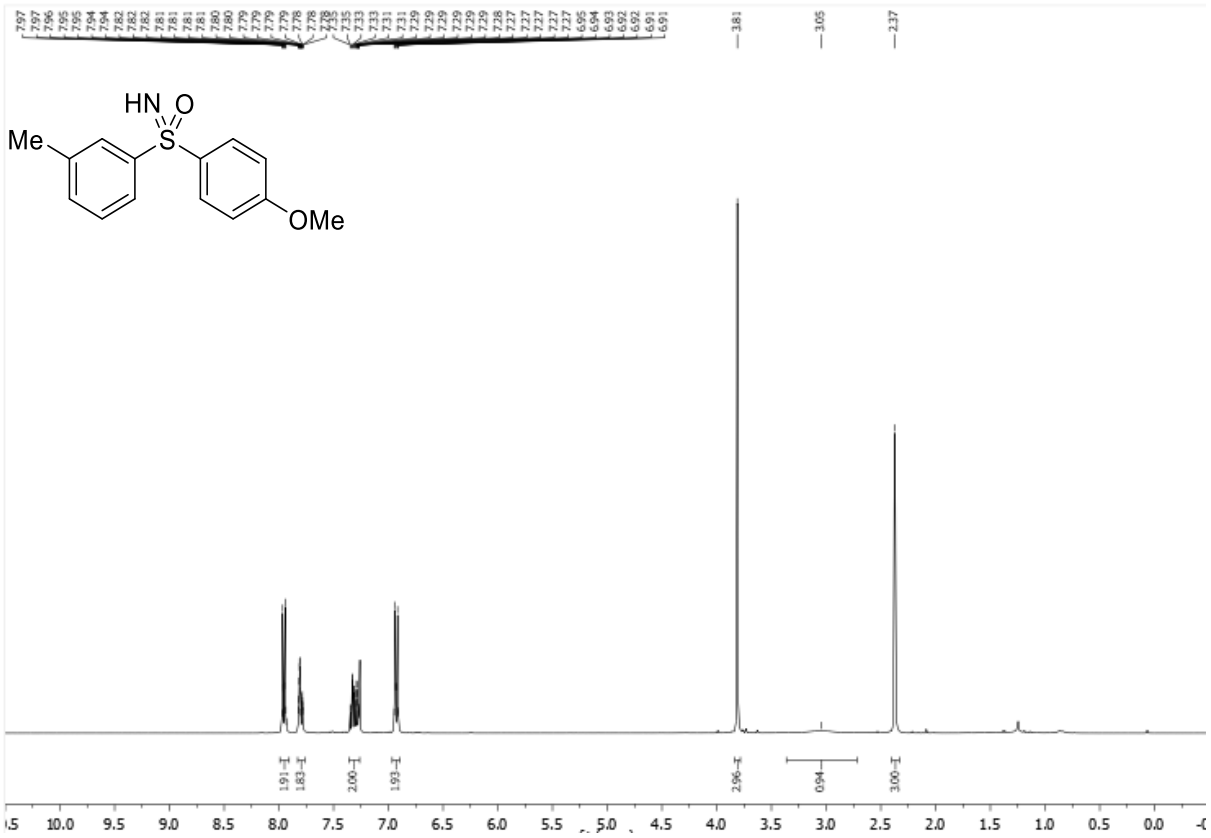
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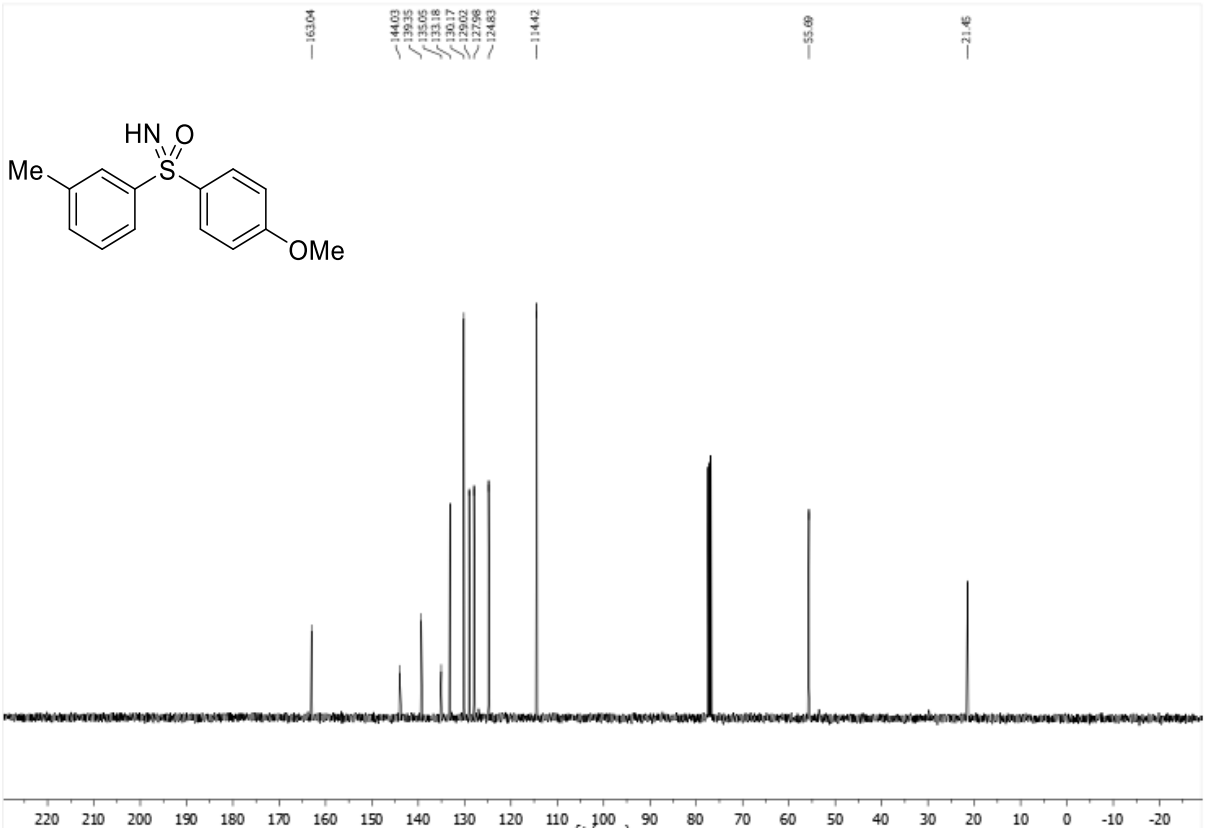
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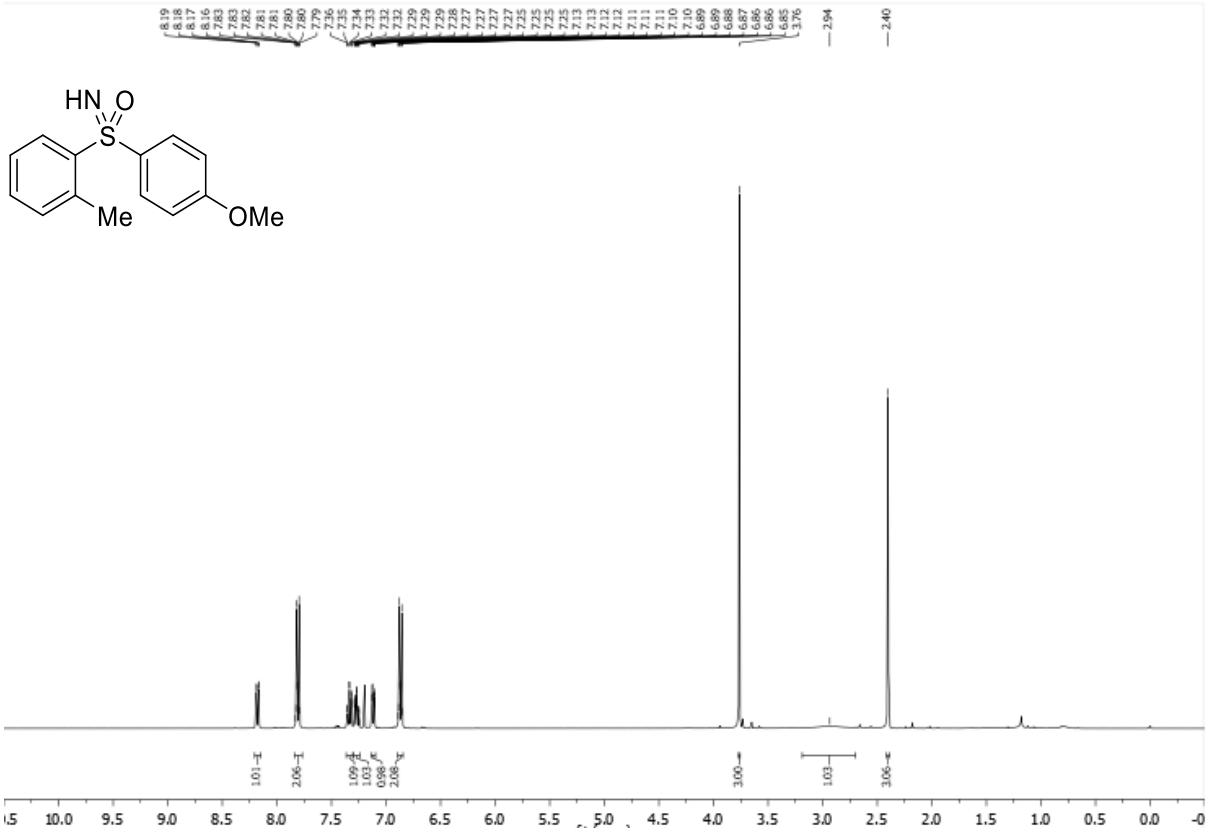
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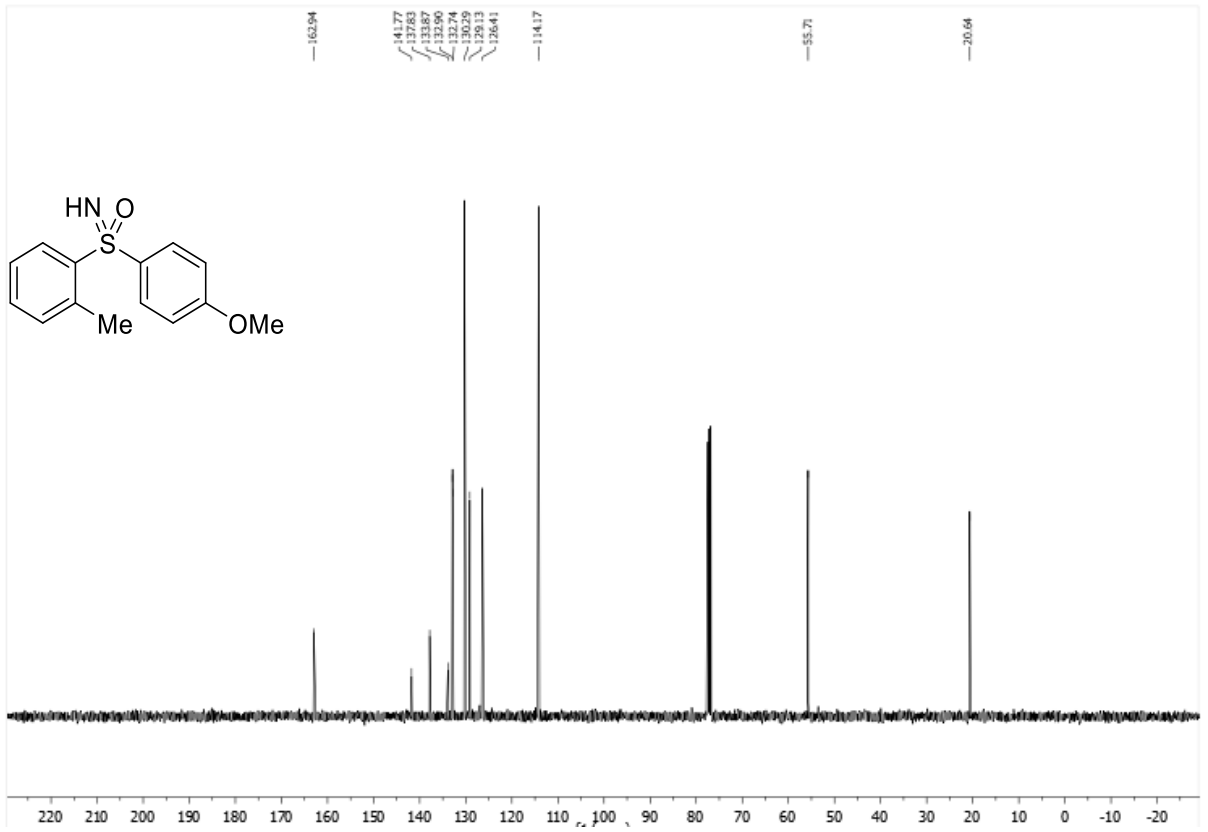
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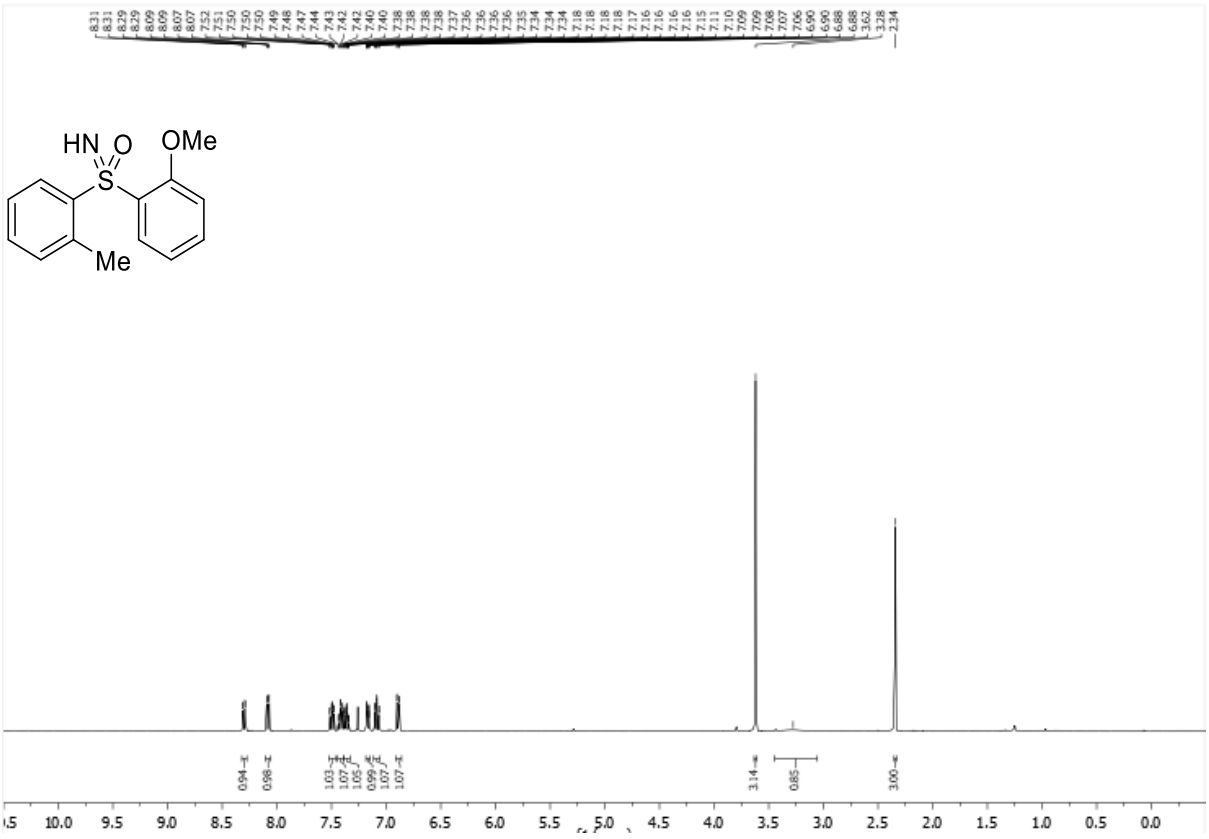
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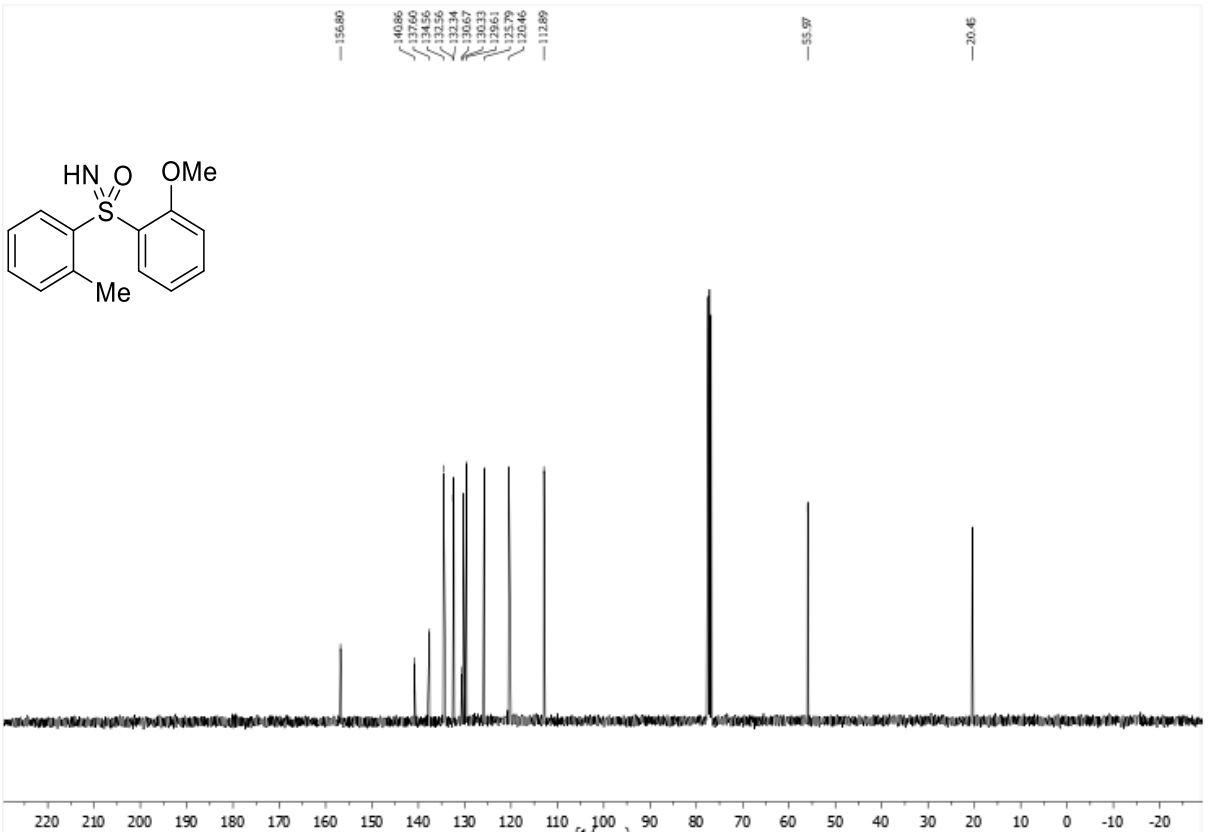
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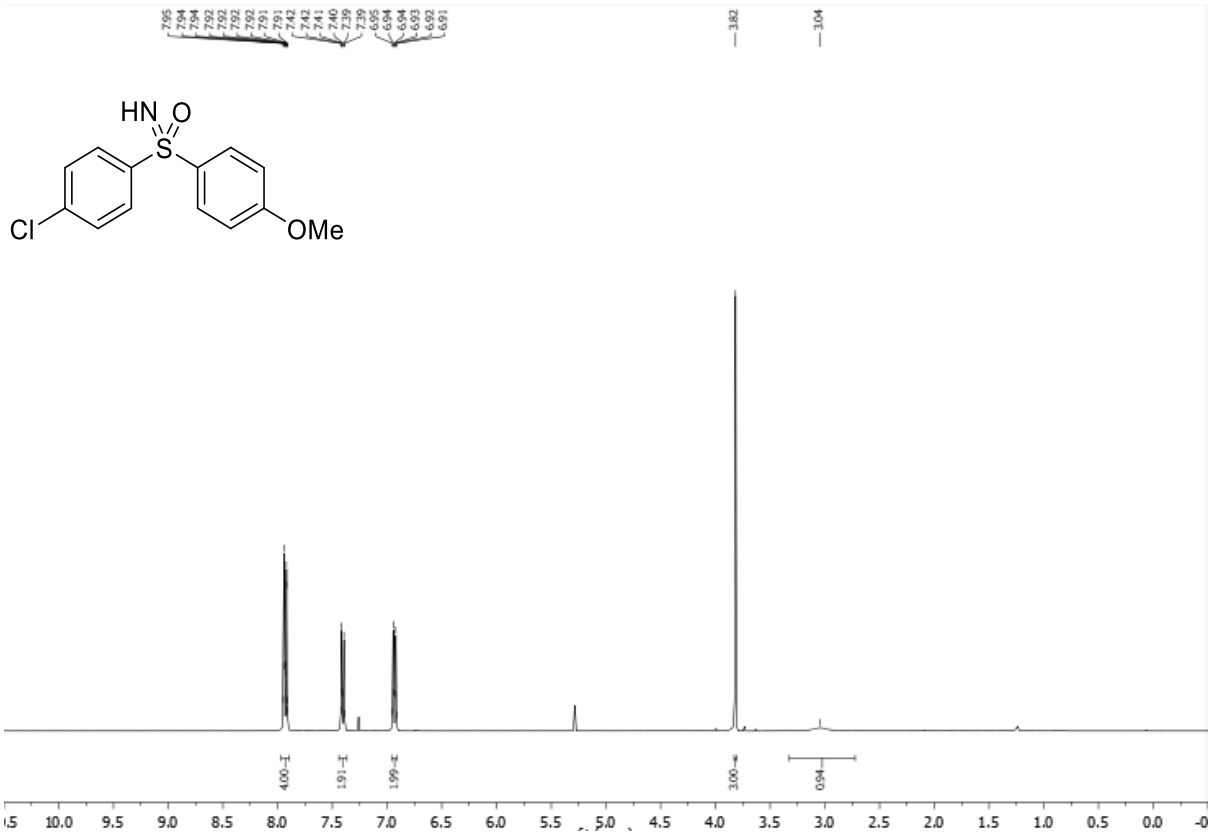
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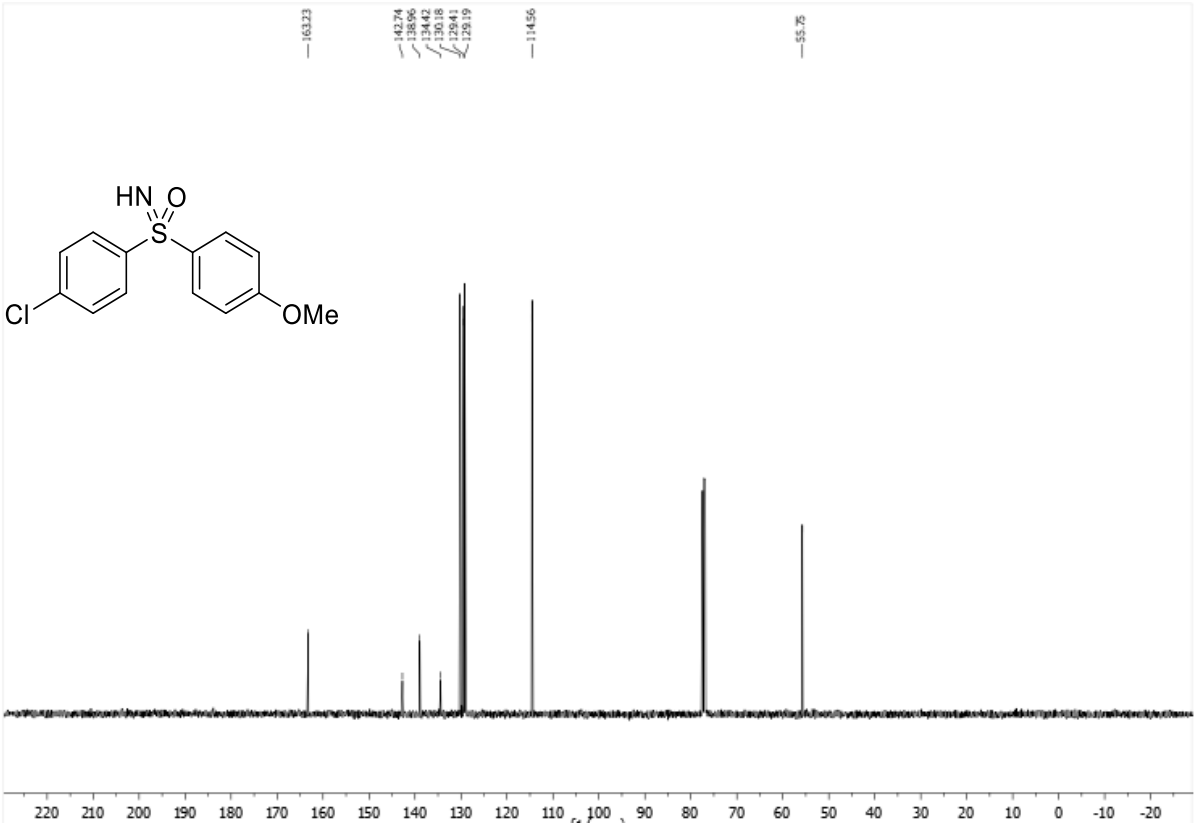
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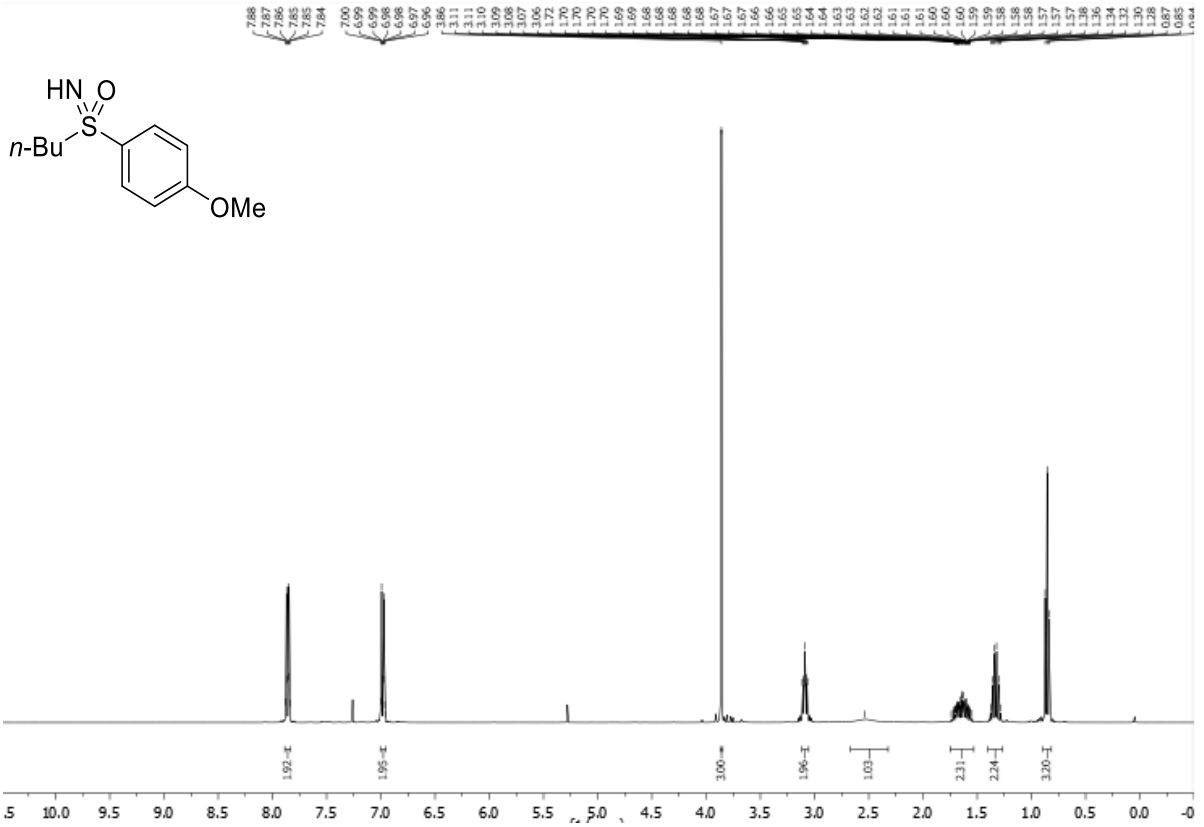
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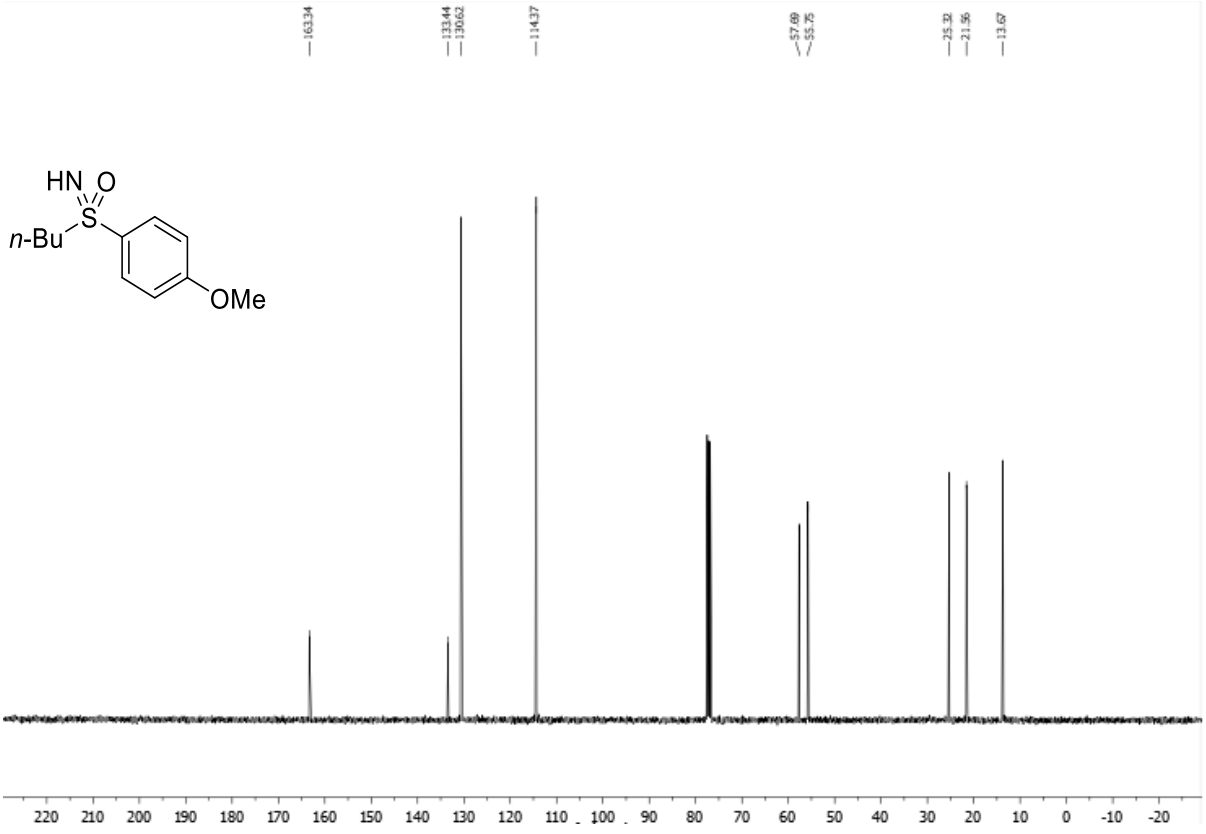
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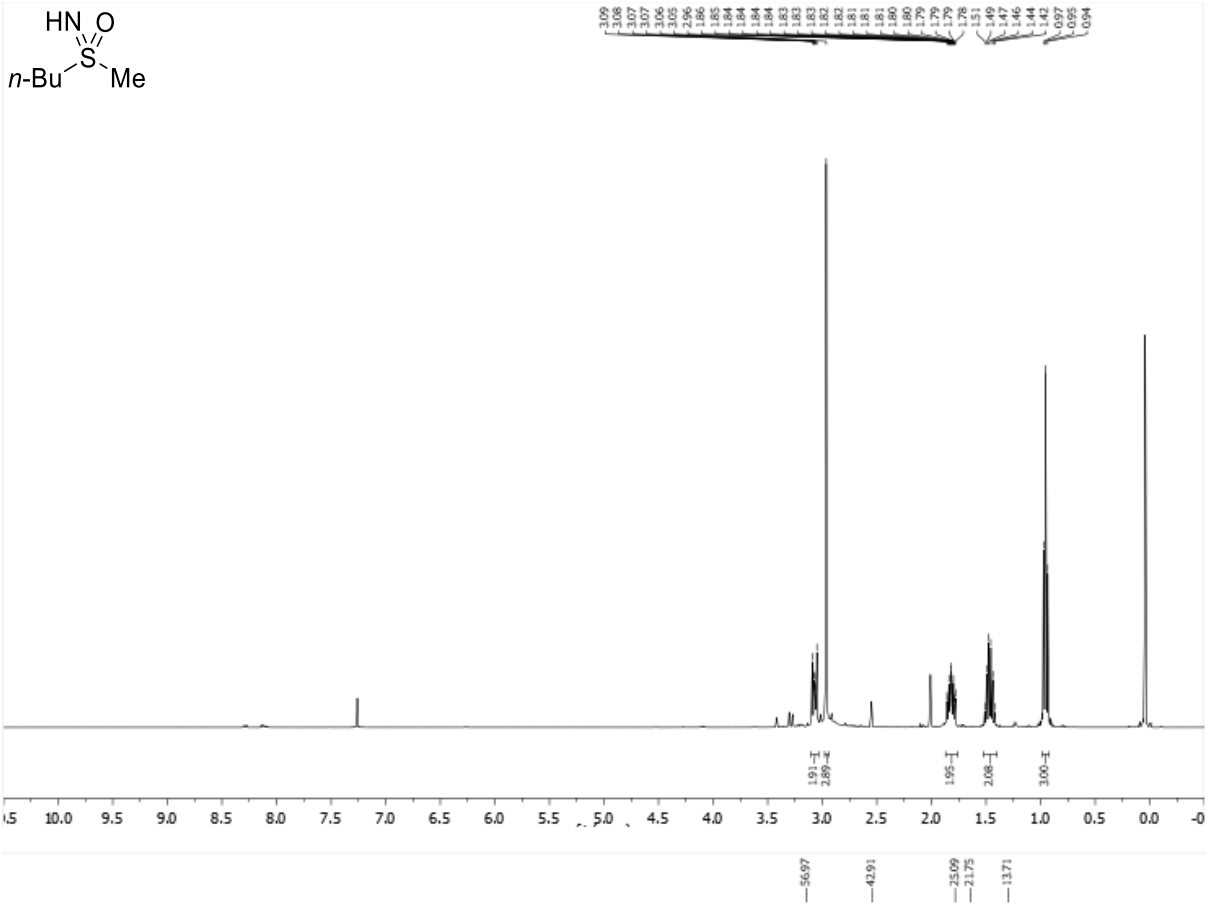
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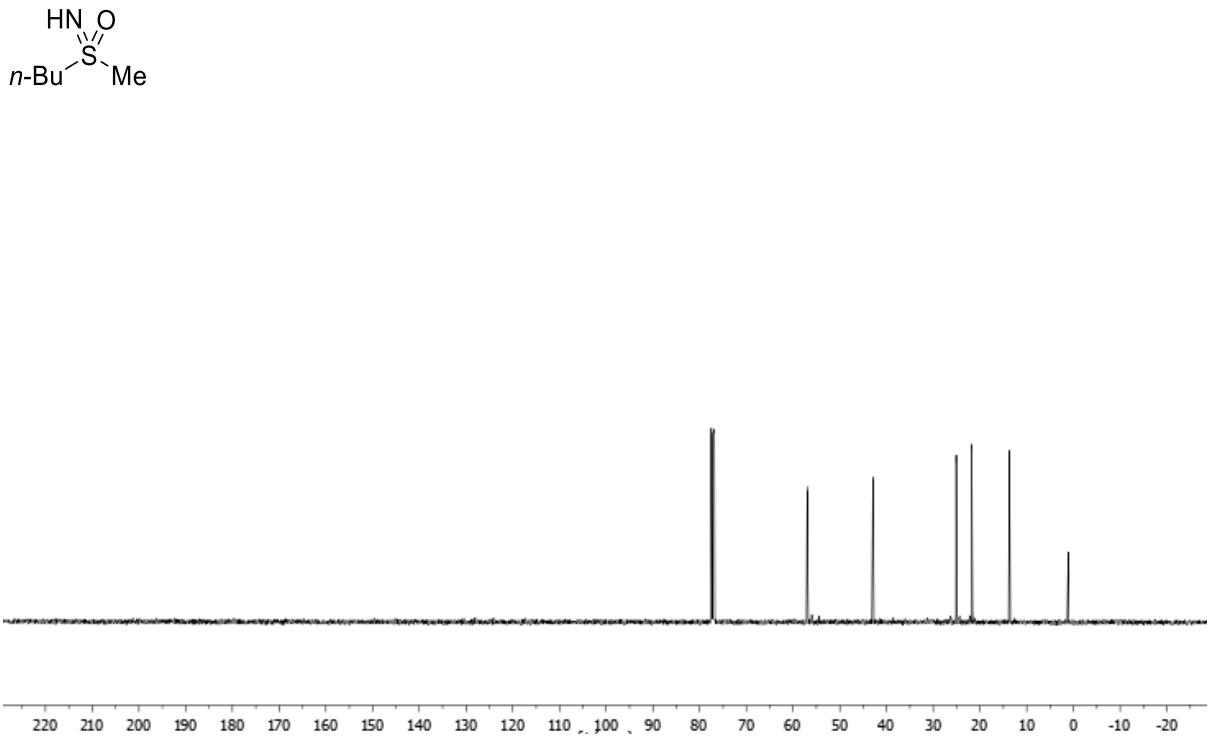
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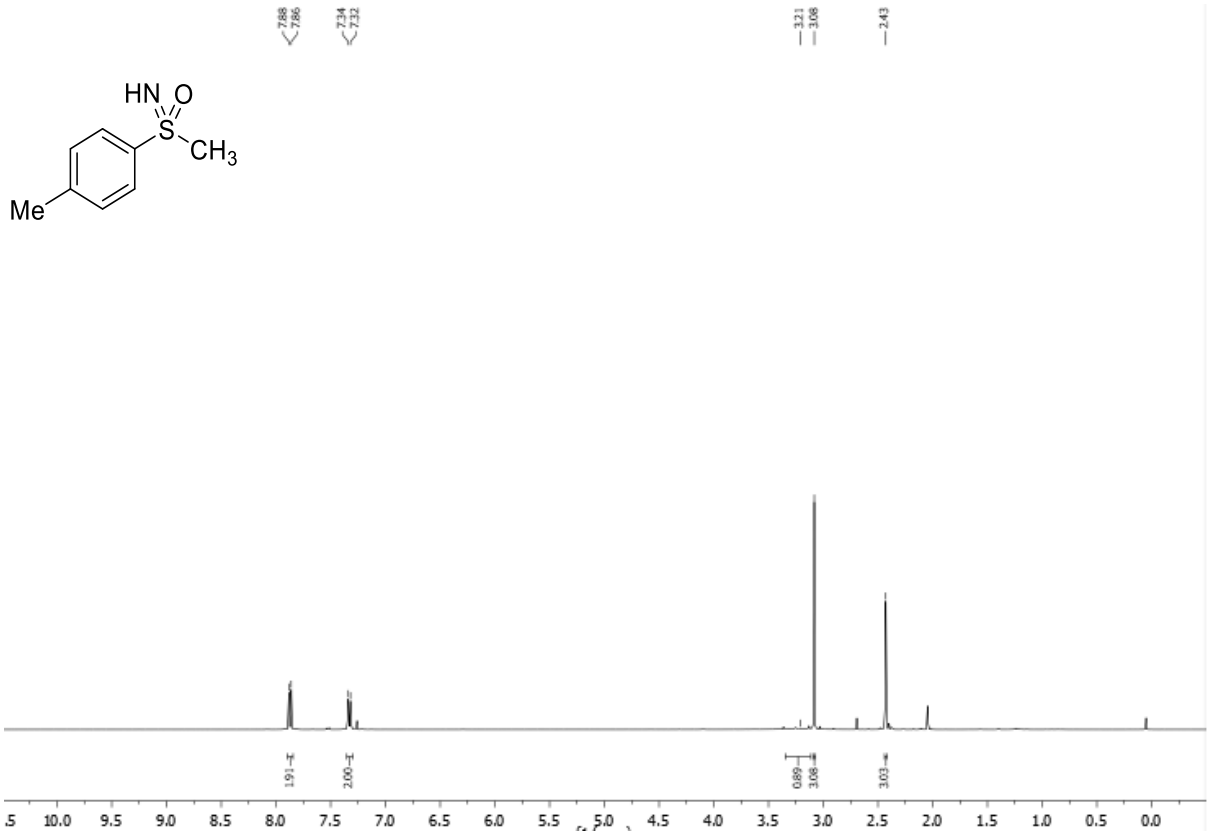
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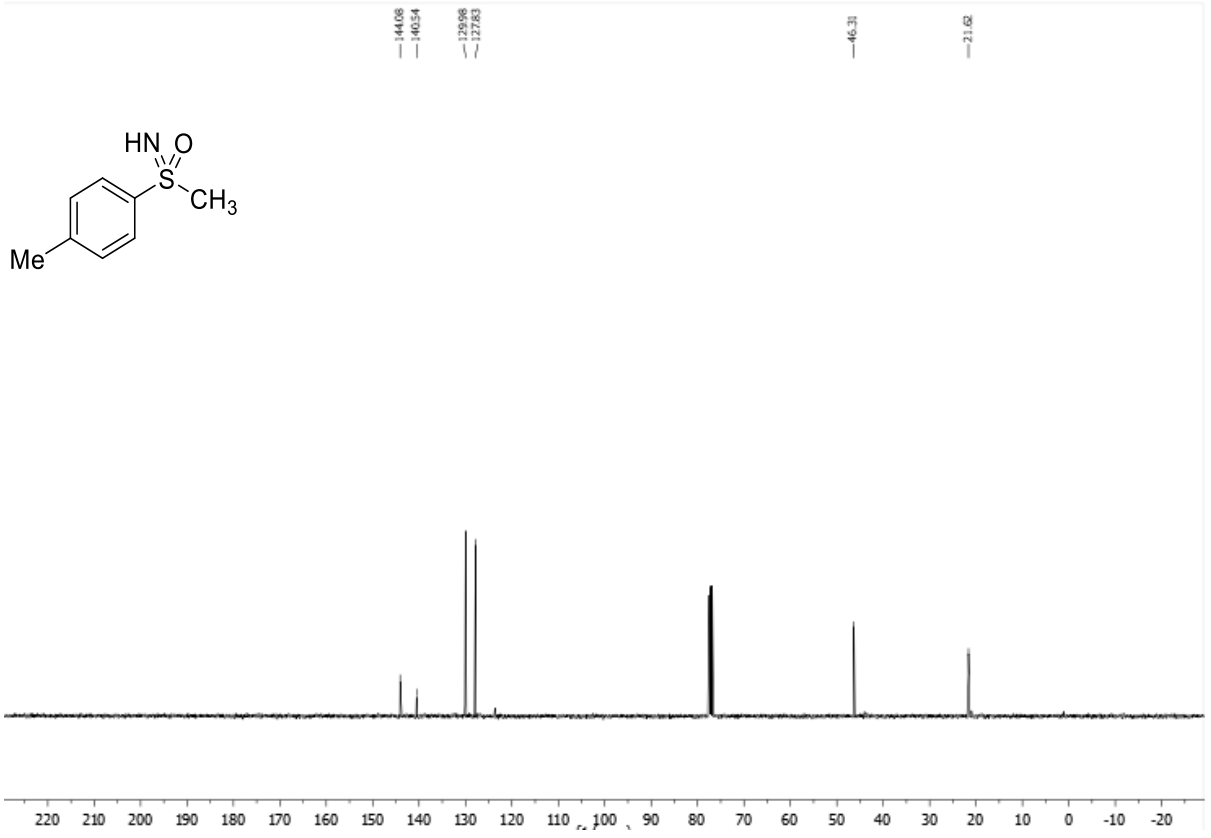
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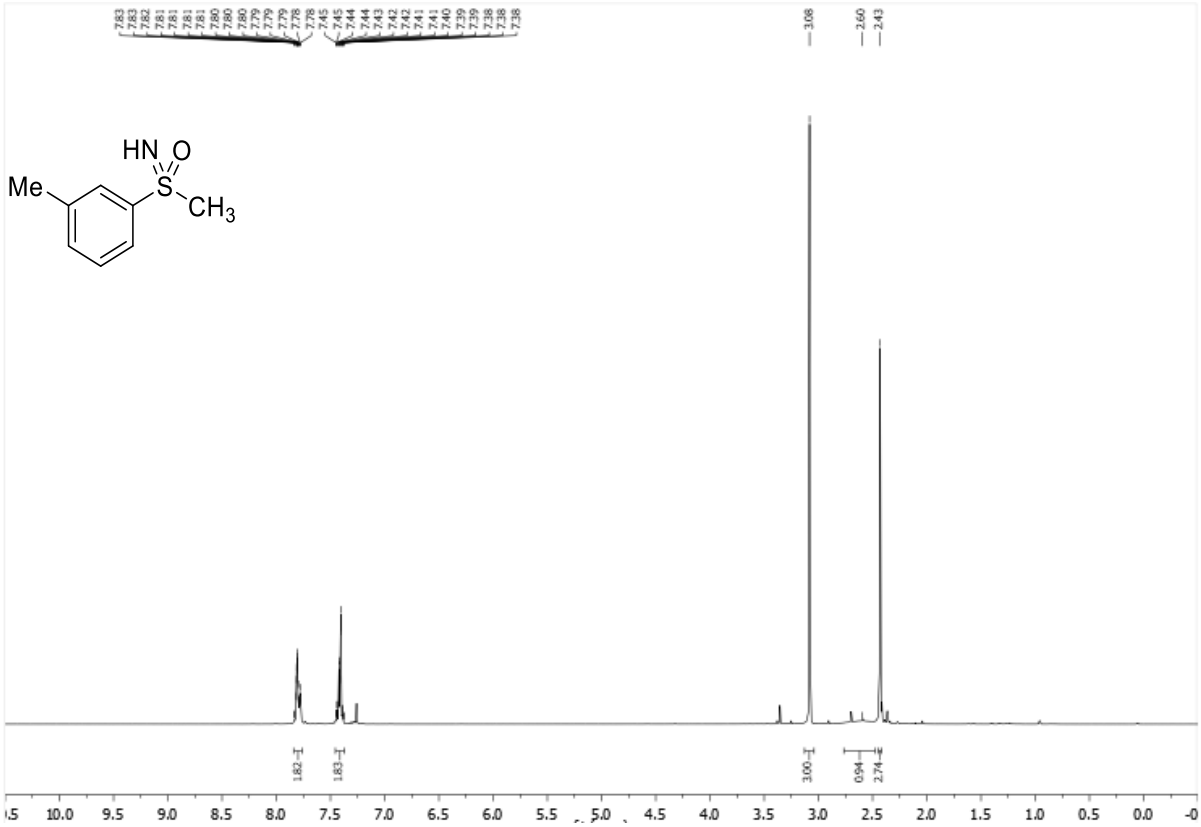
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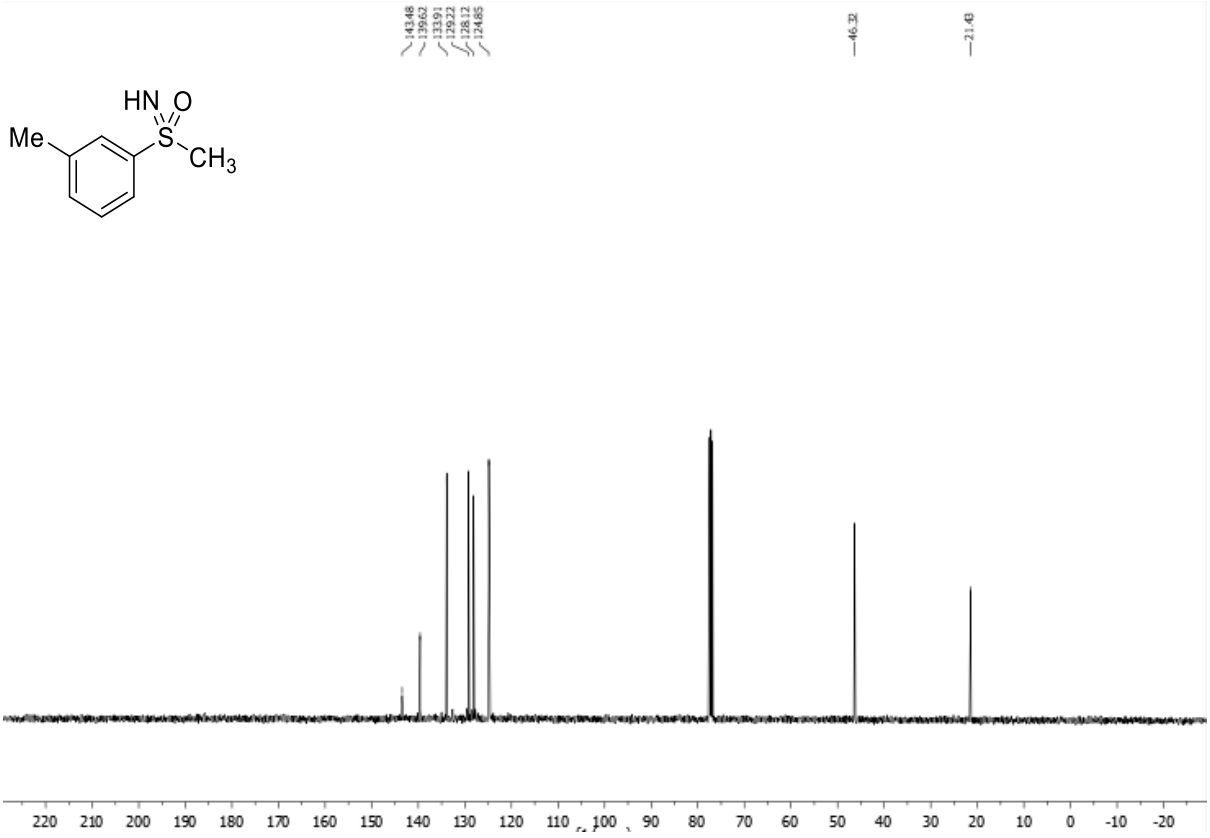
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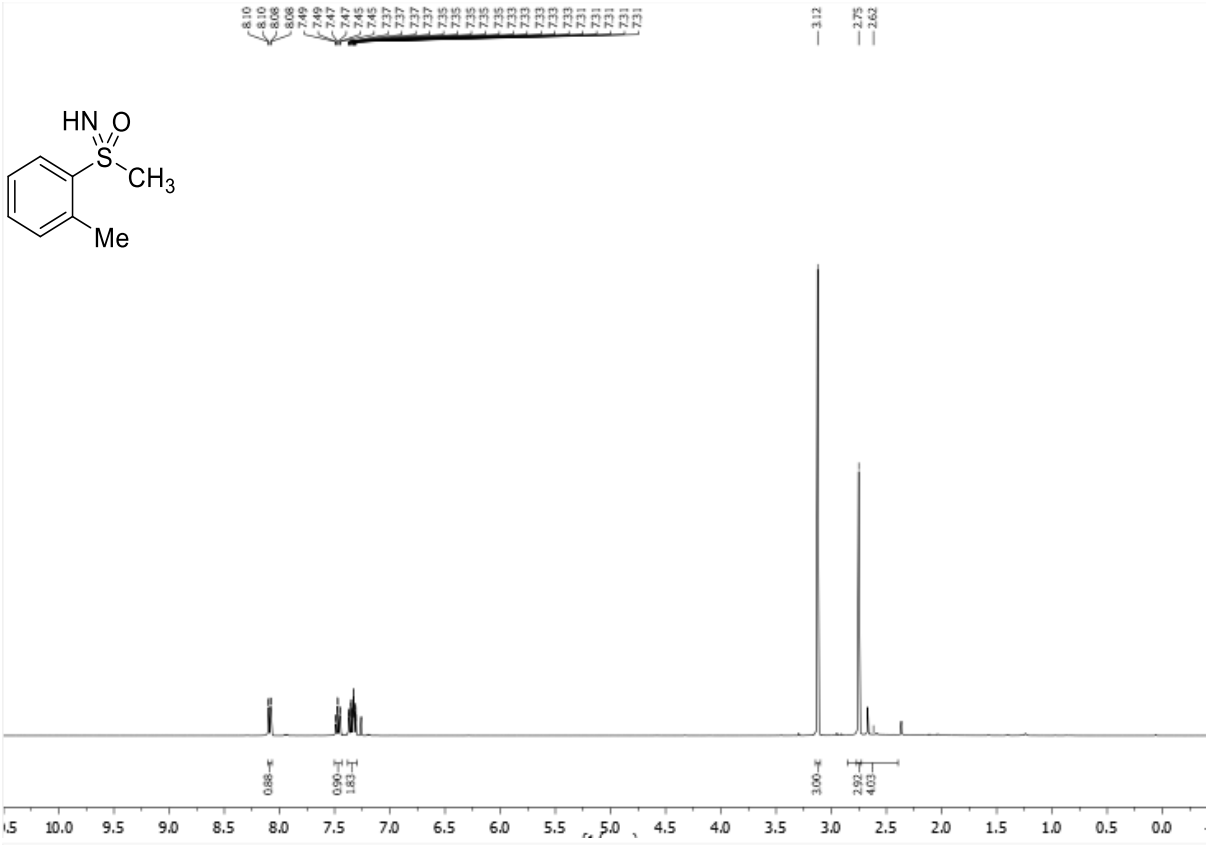
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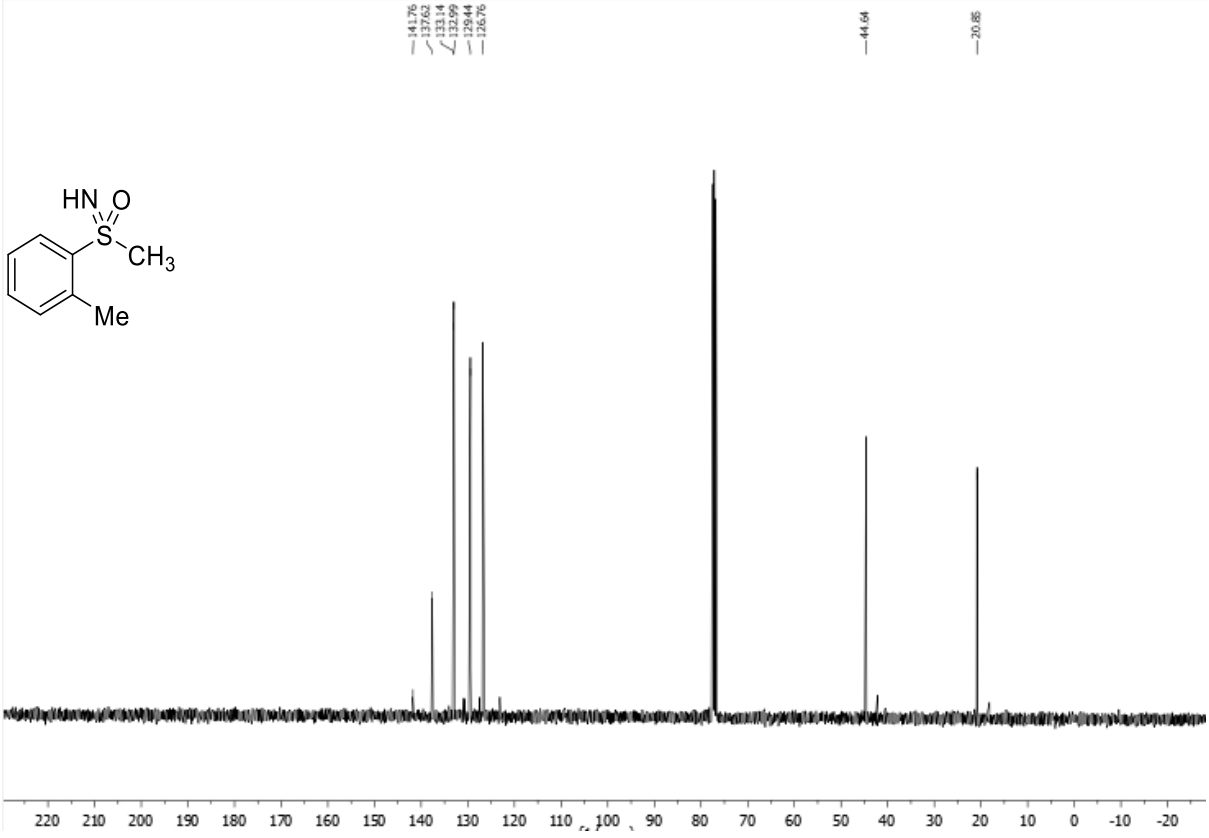
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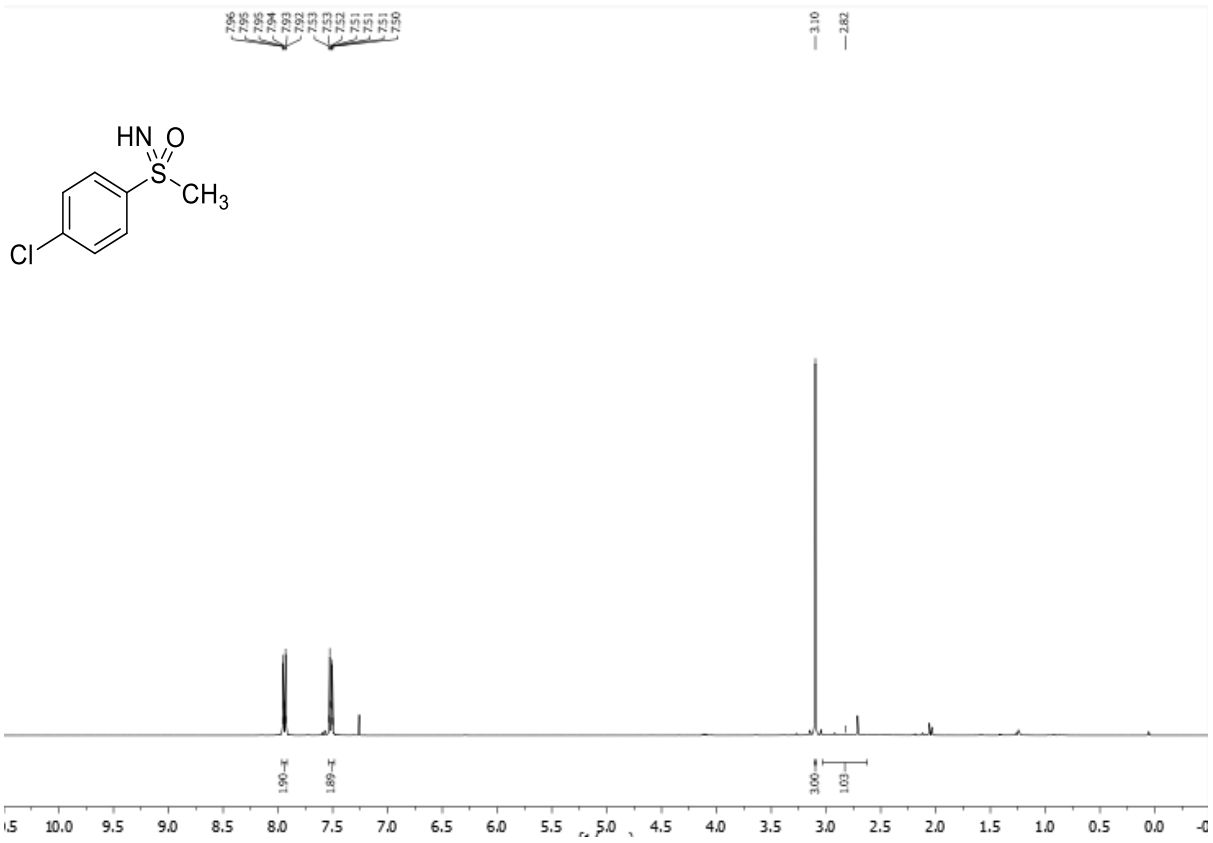
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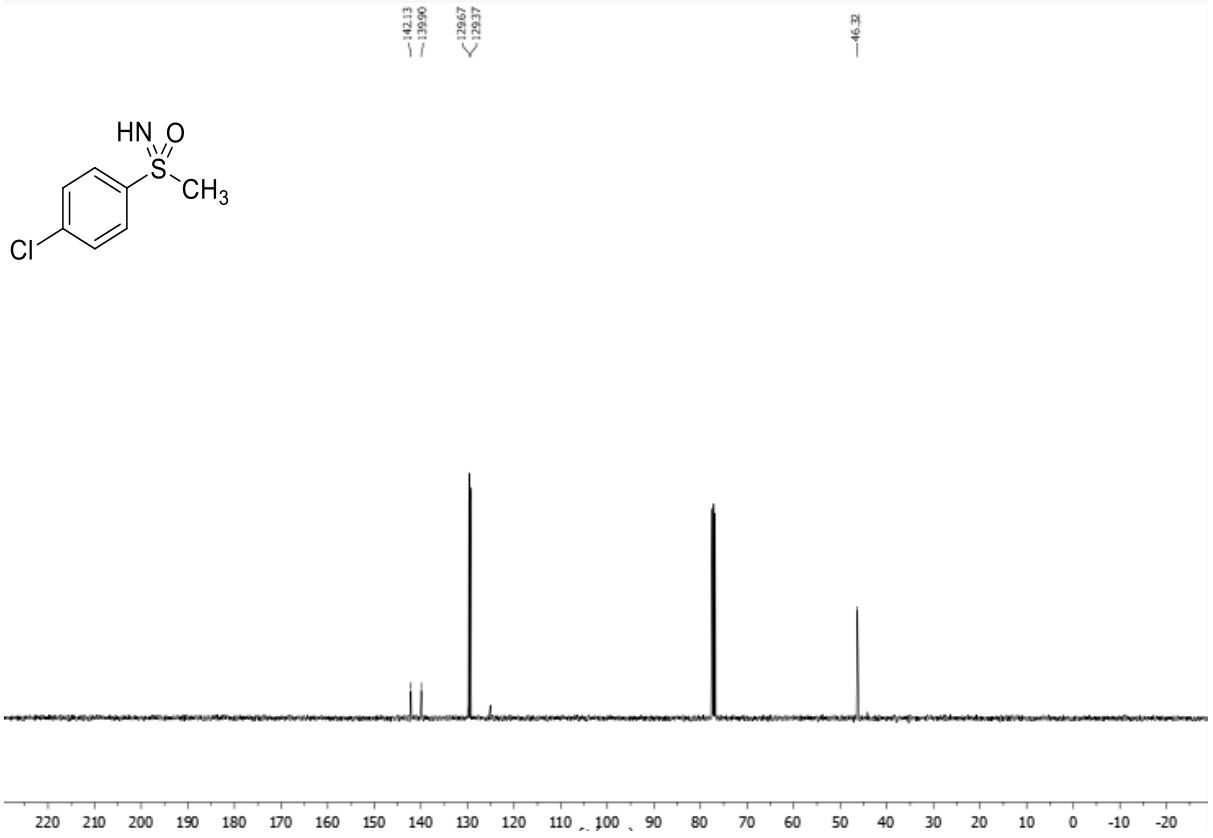
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-10
-20


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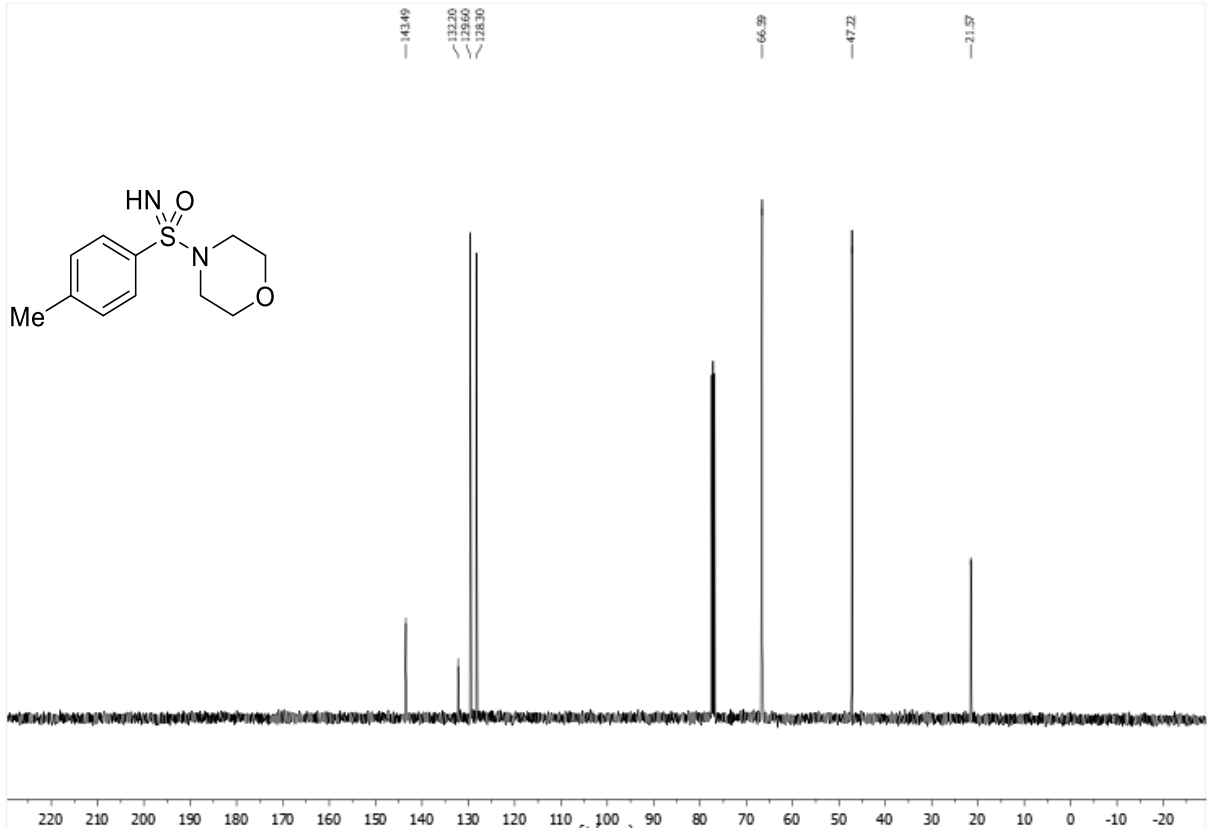
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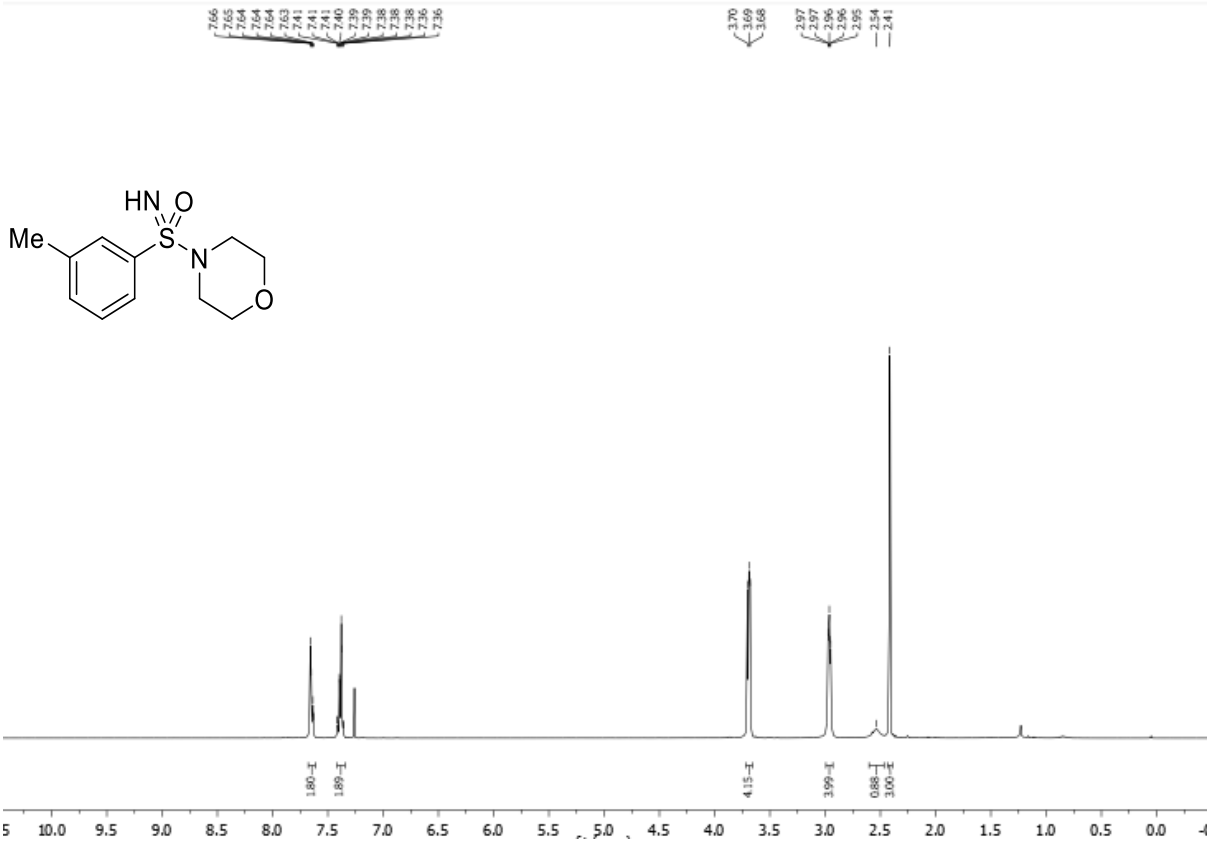
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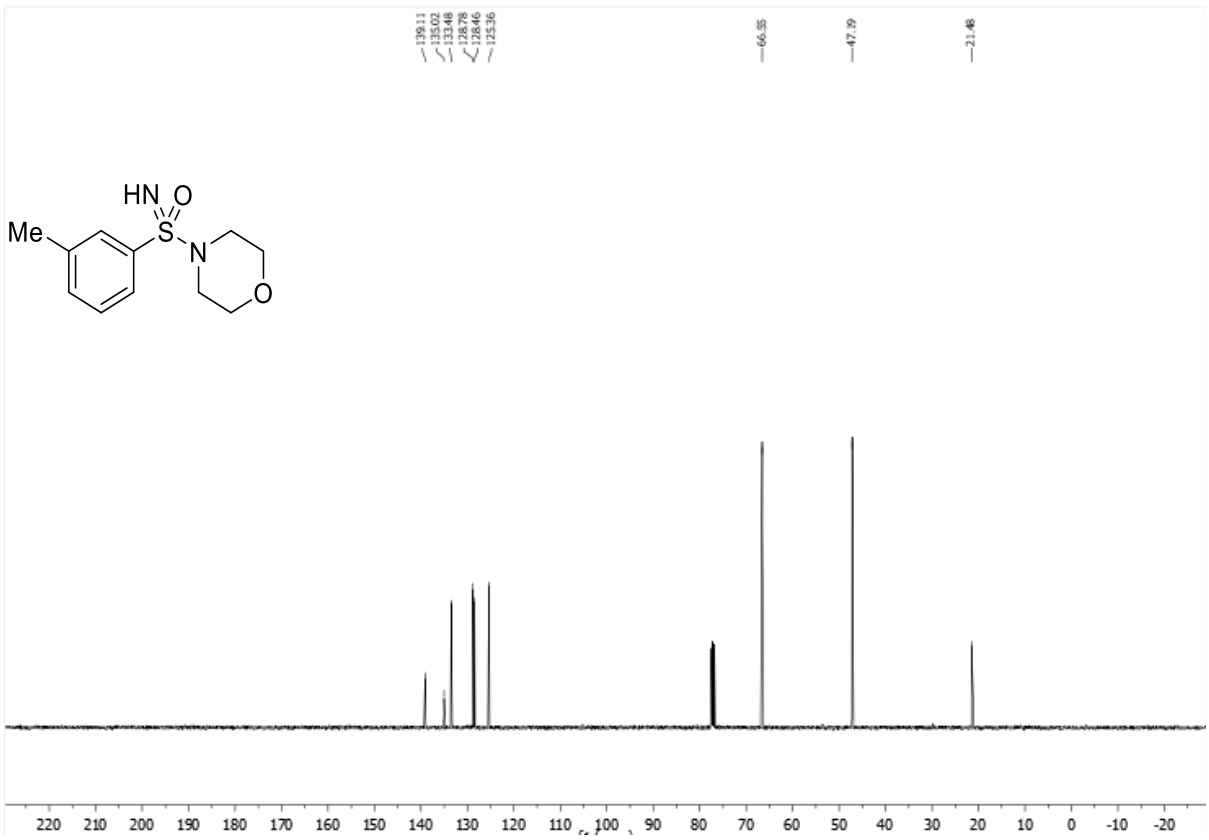
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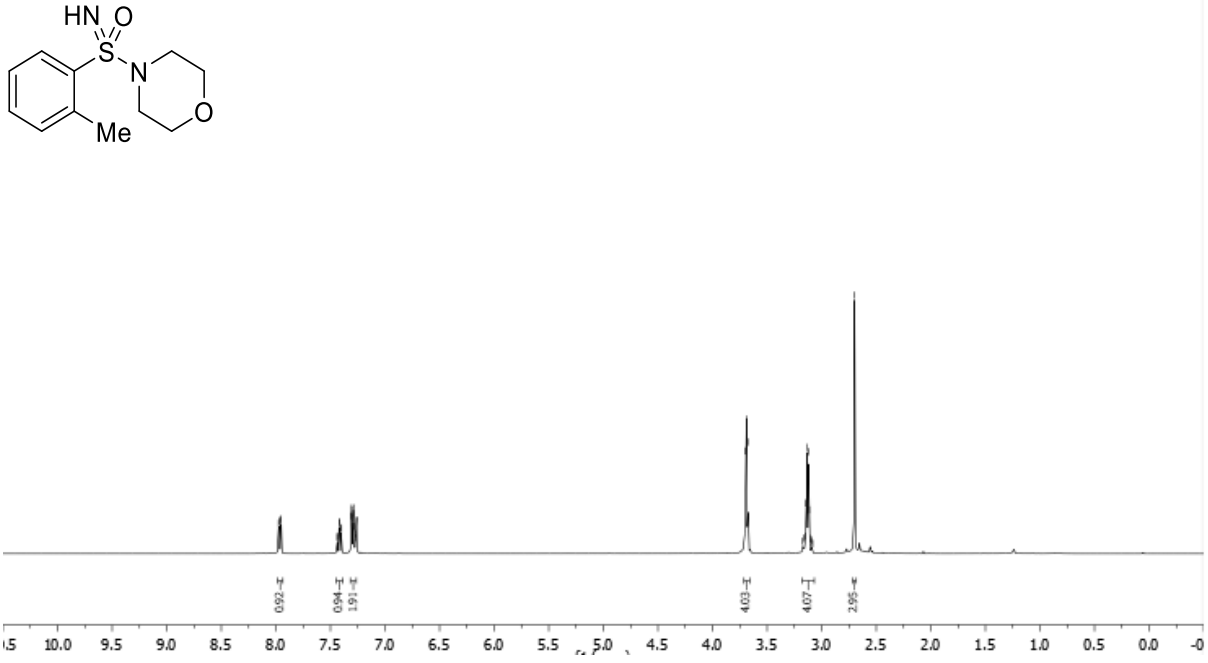
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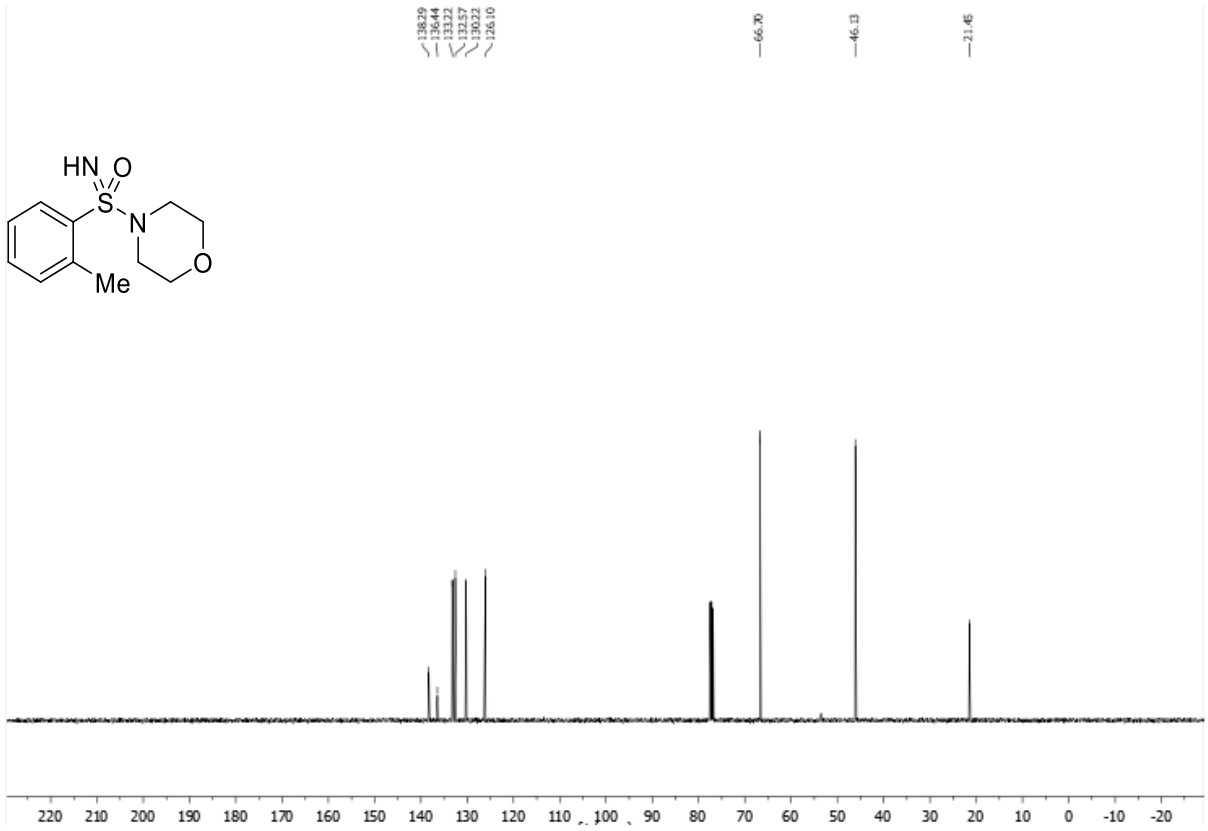
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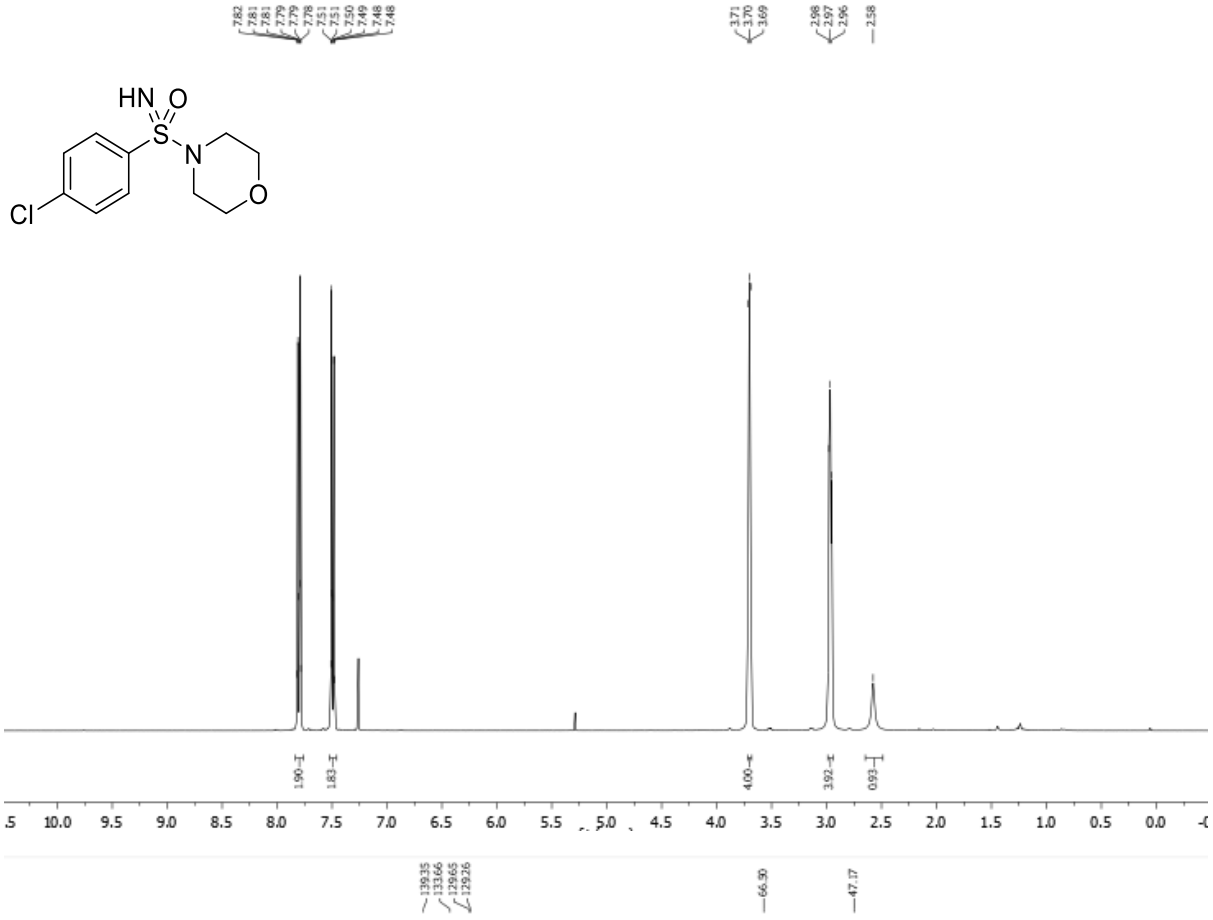
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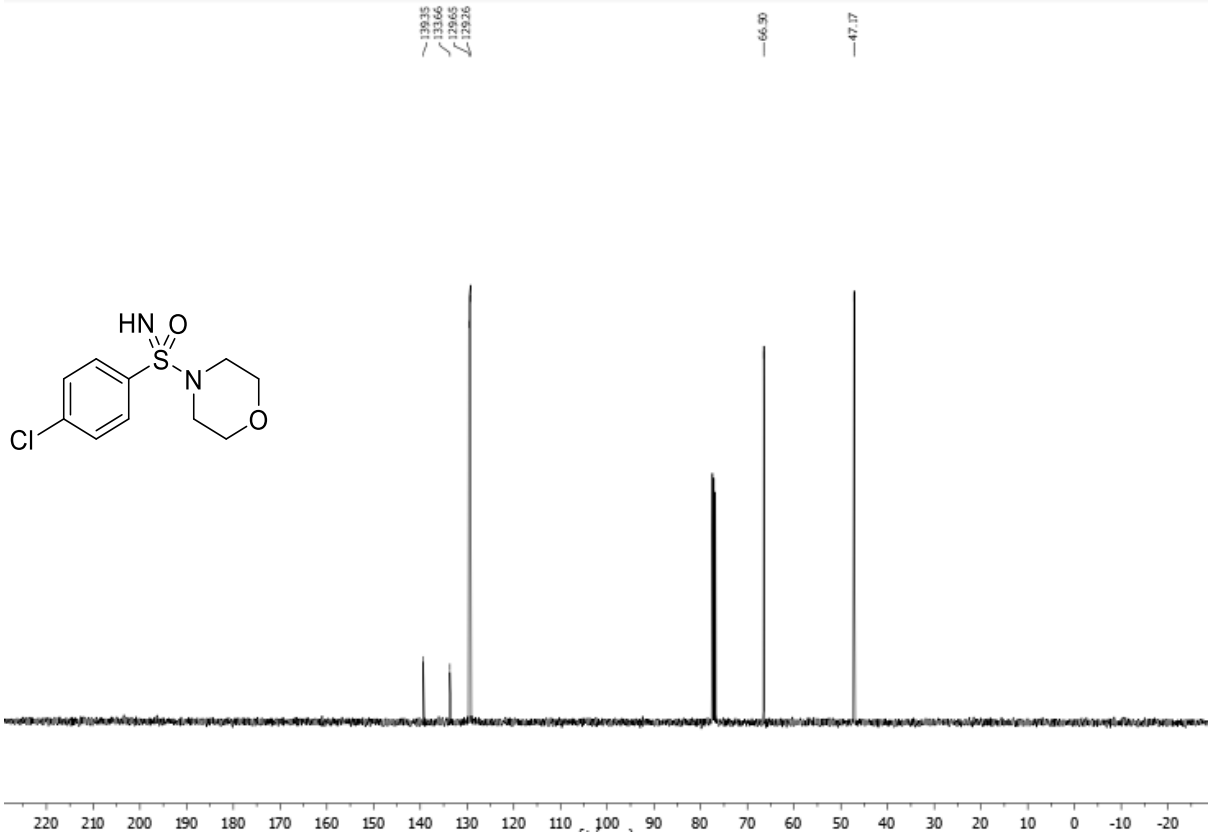
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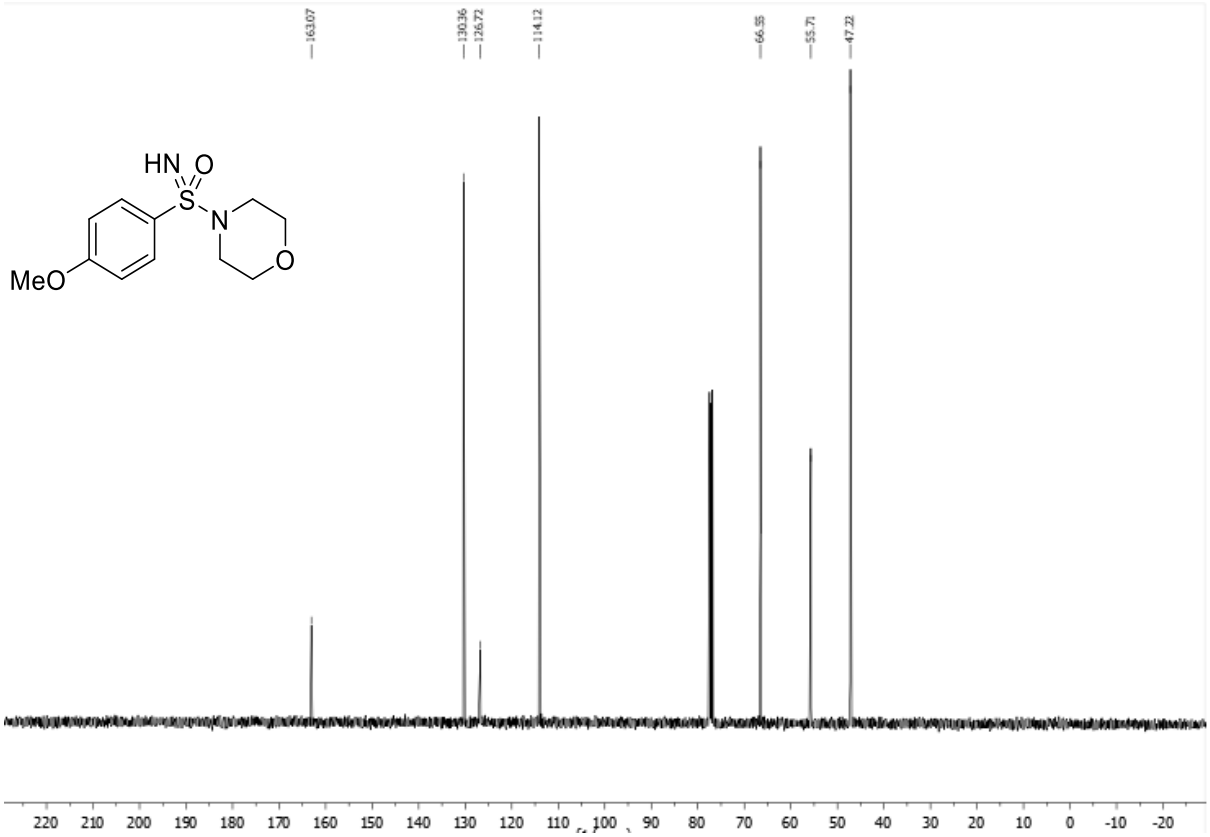
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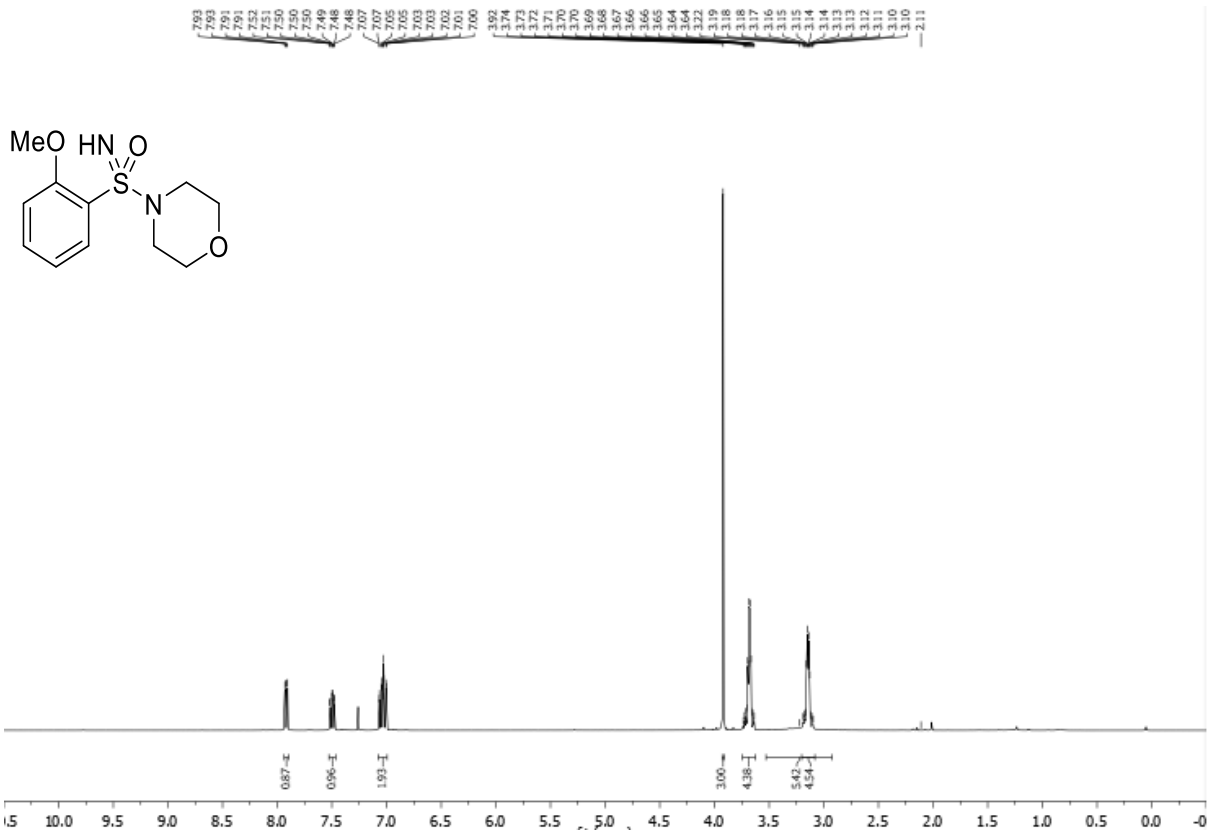
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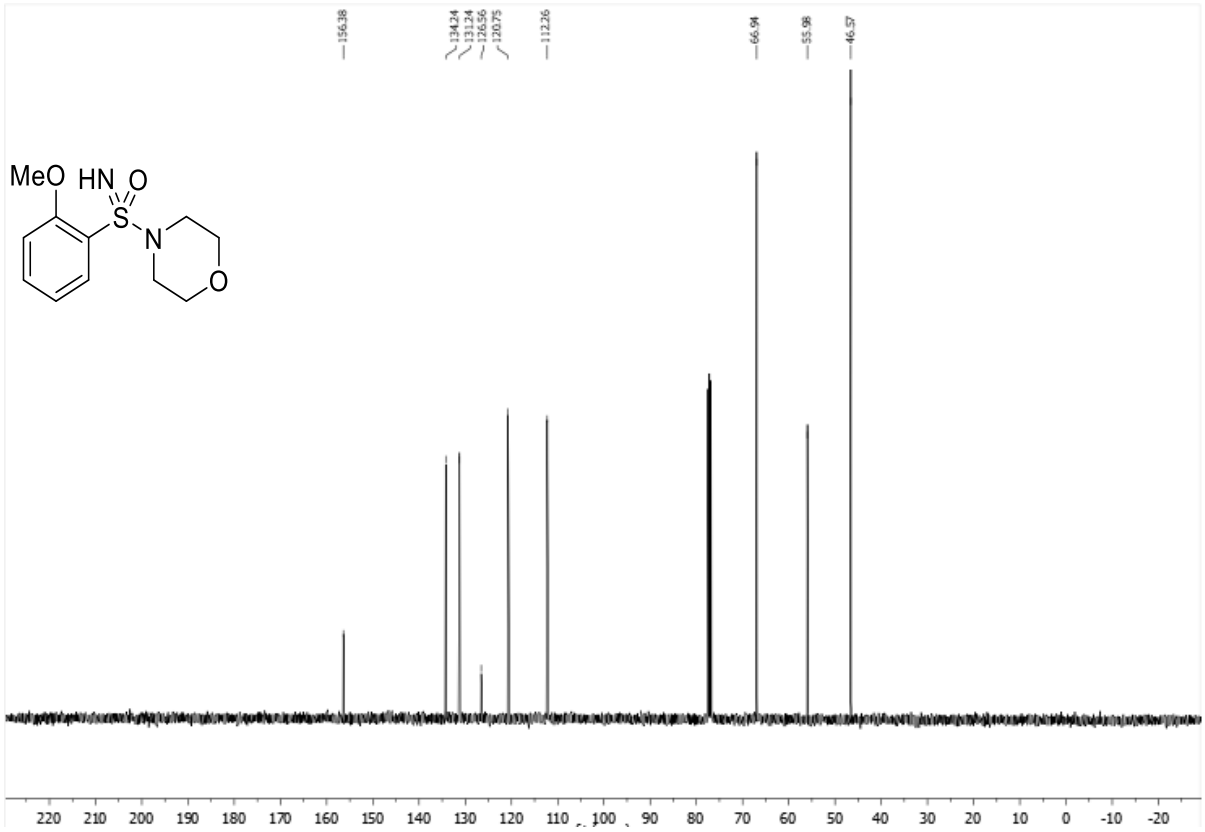
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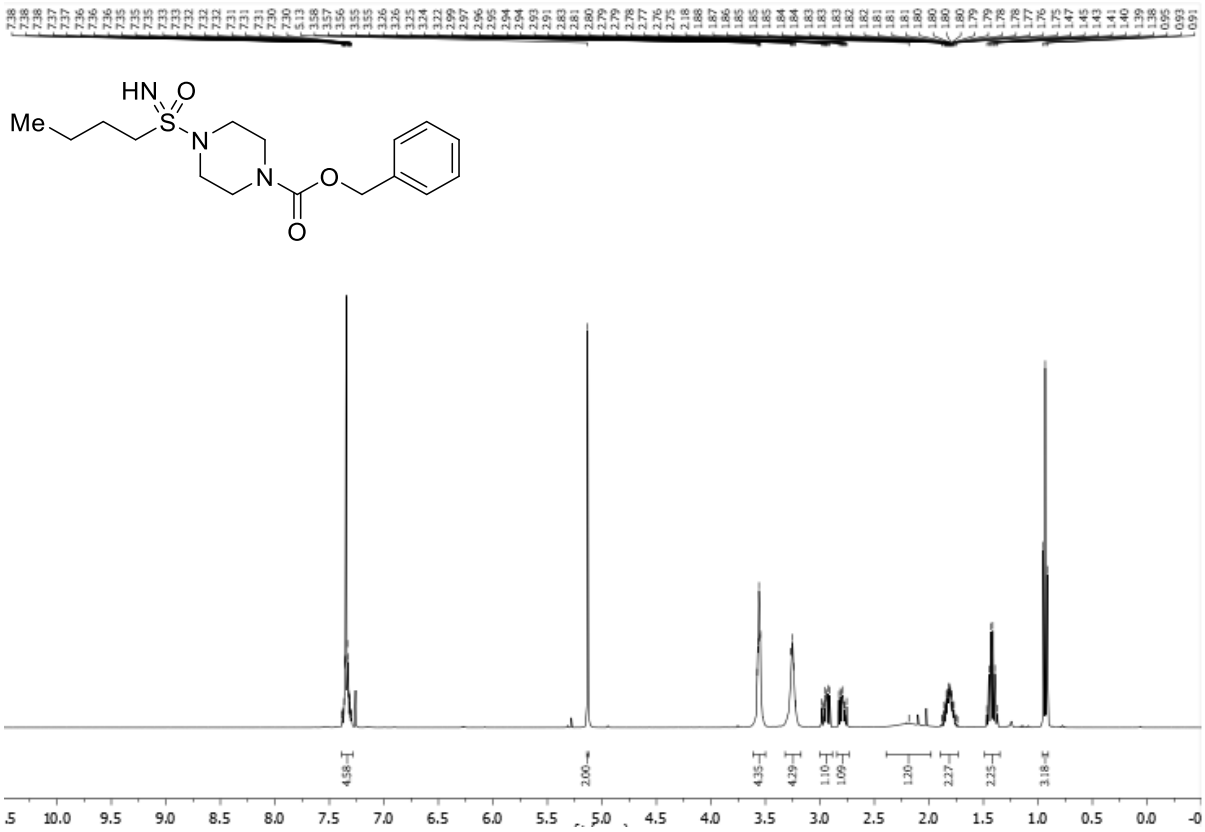
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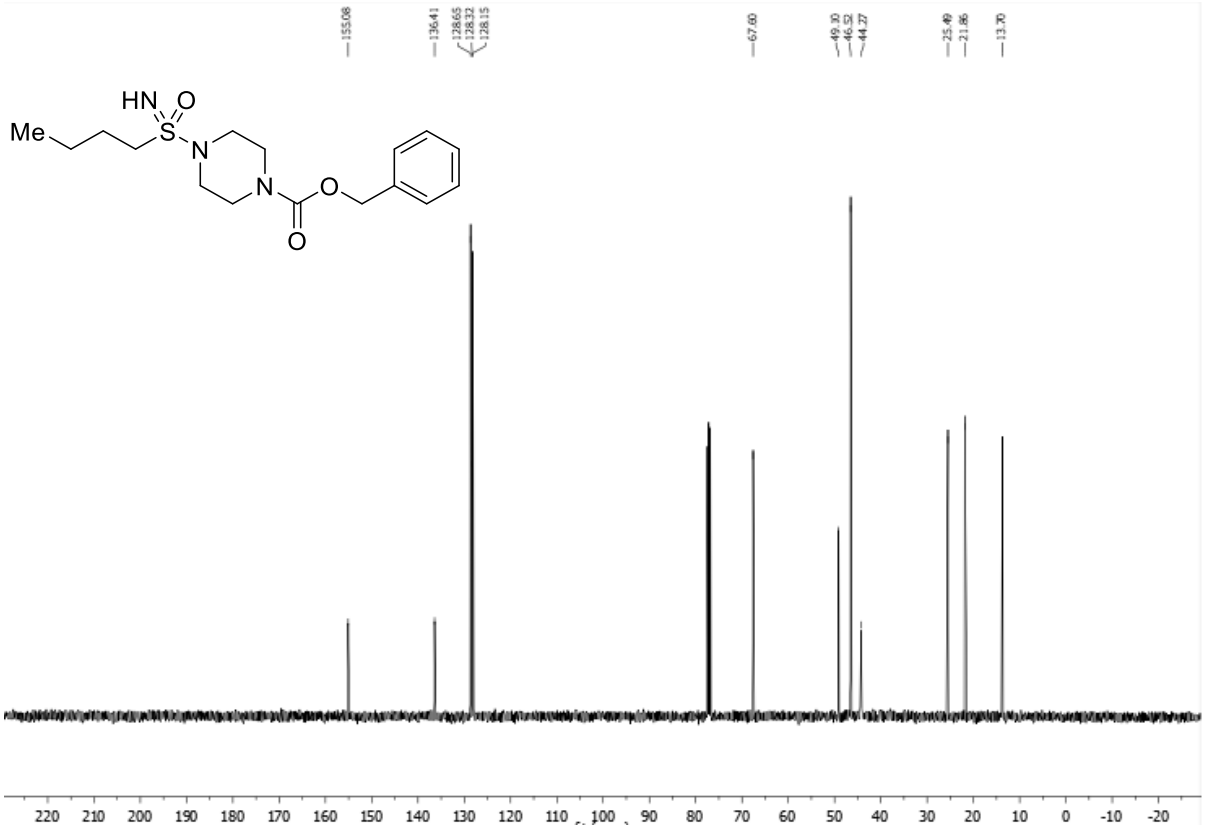
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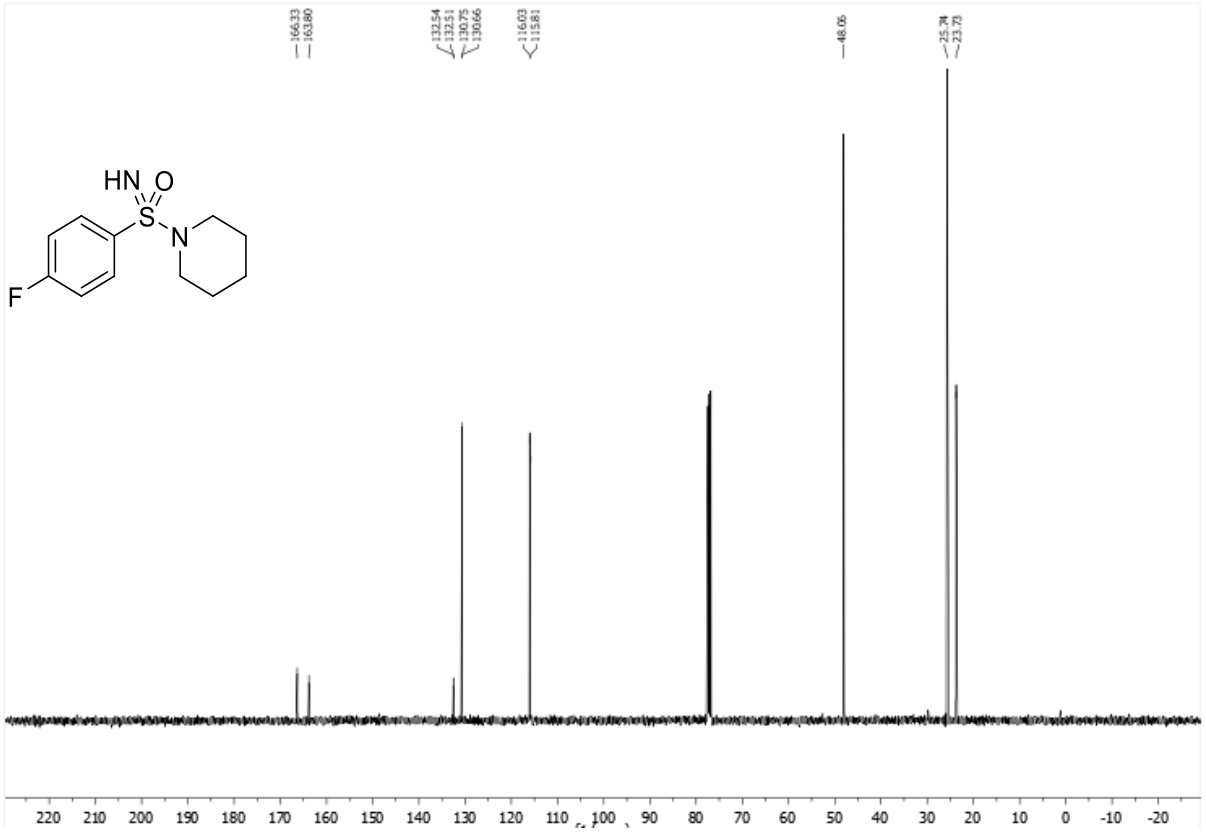
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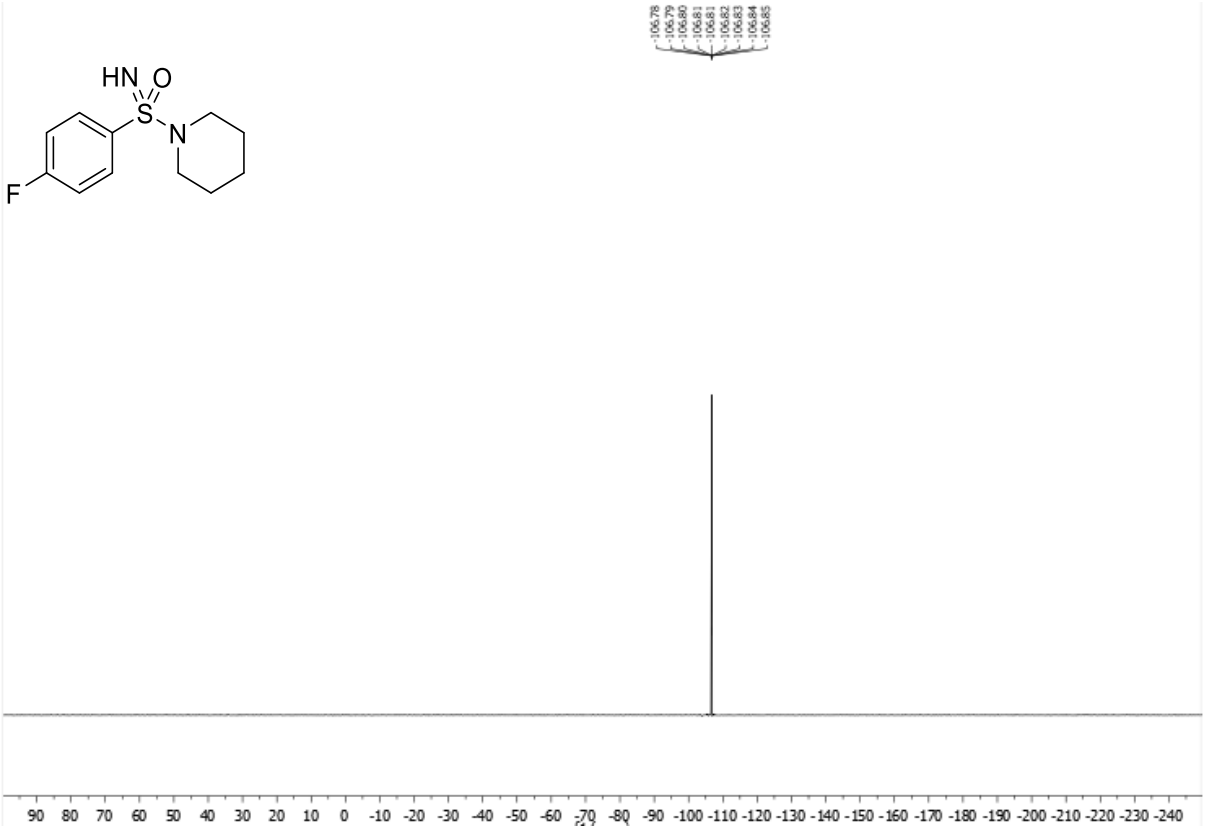
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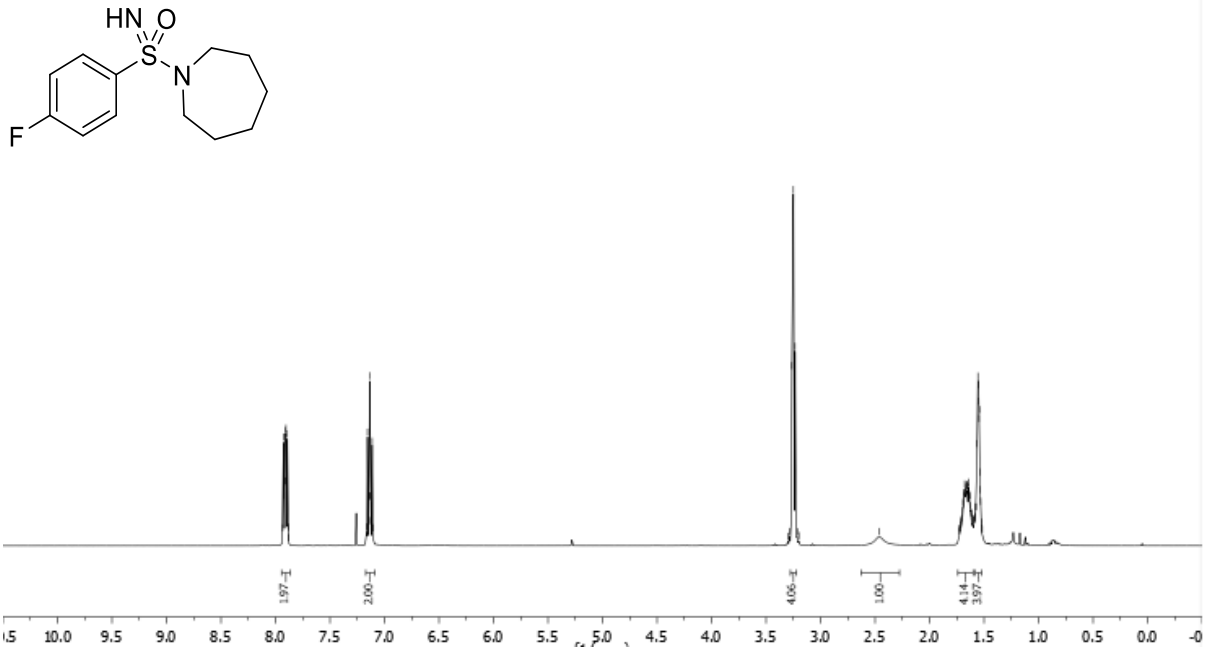
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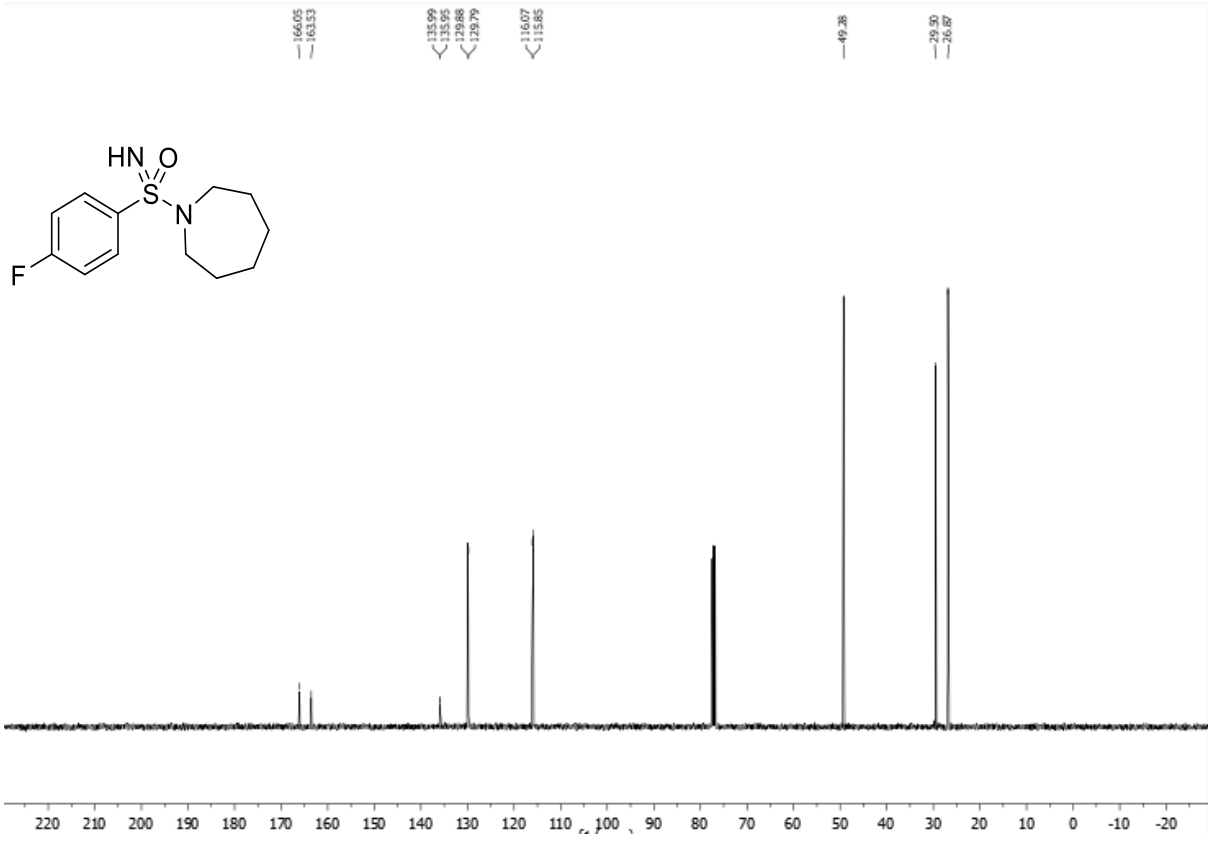
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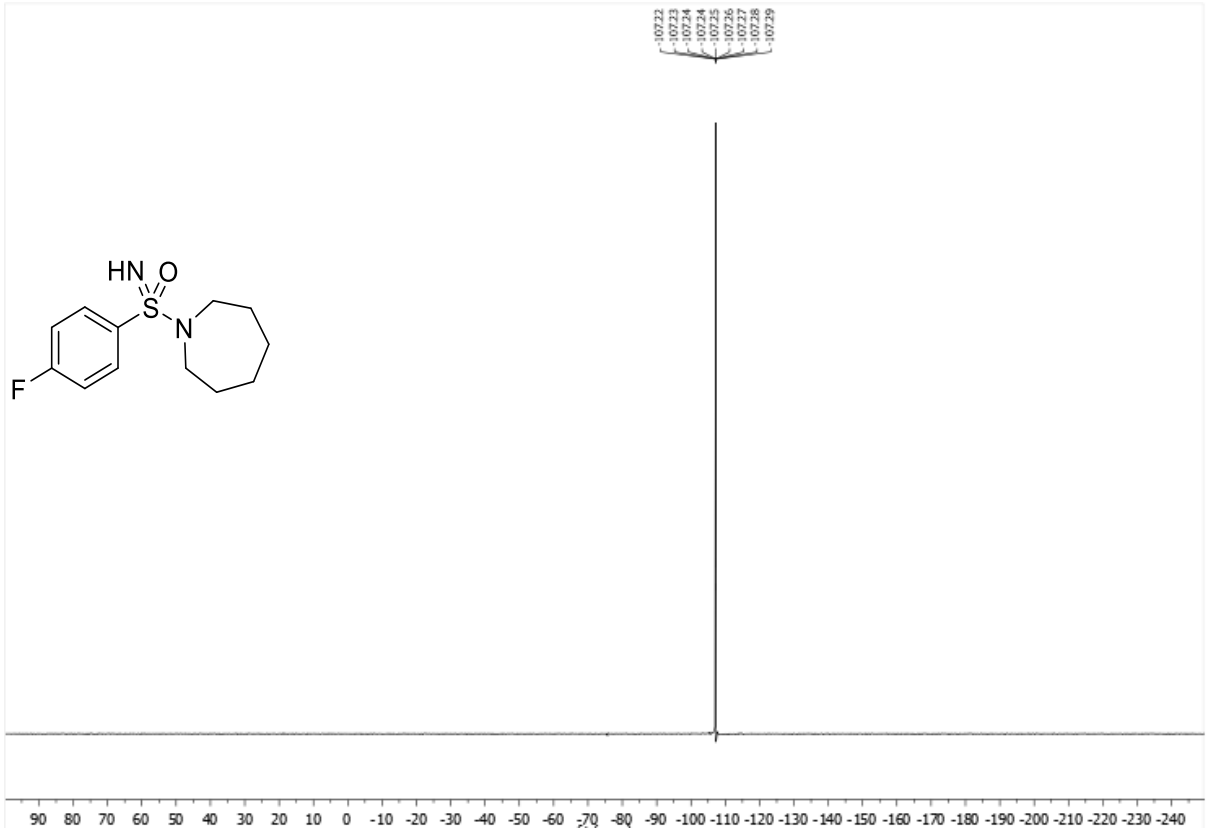
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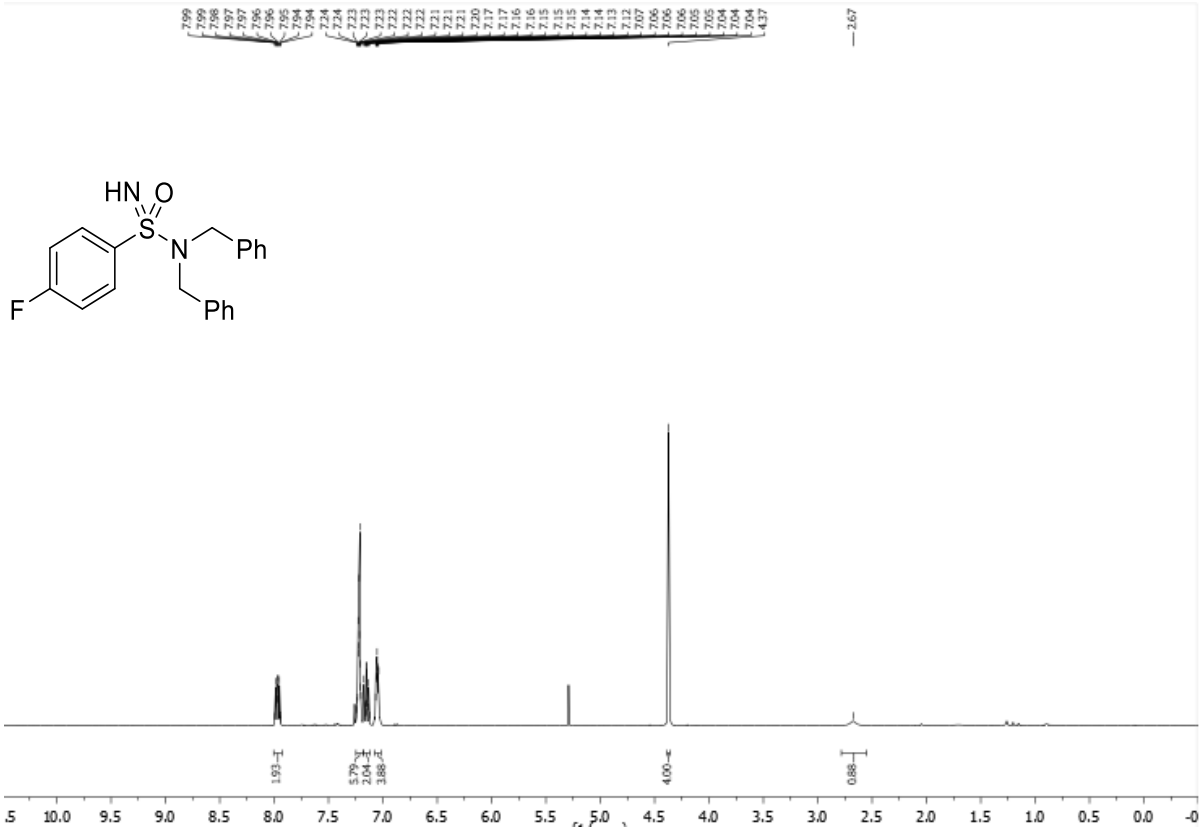
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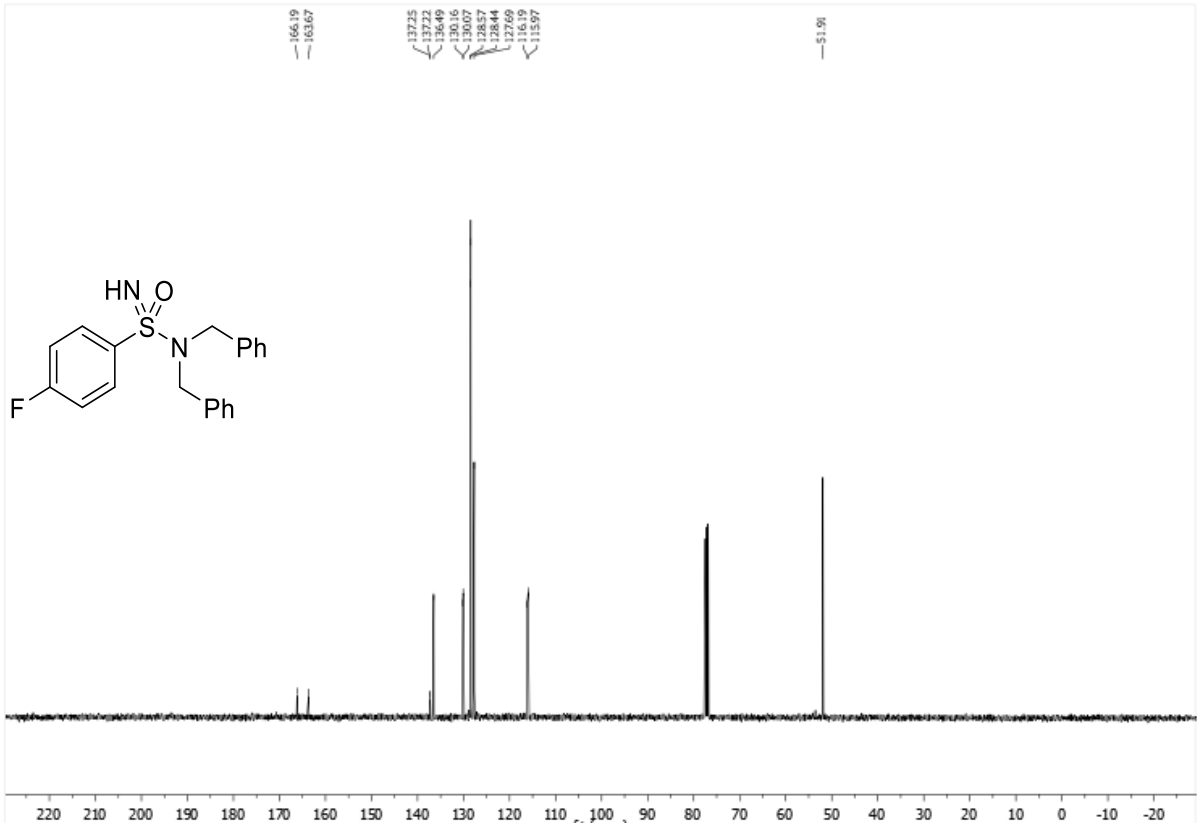
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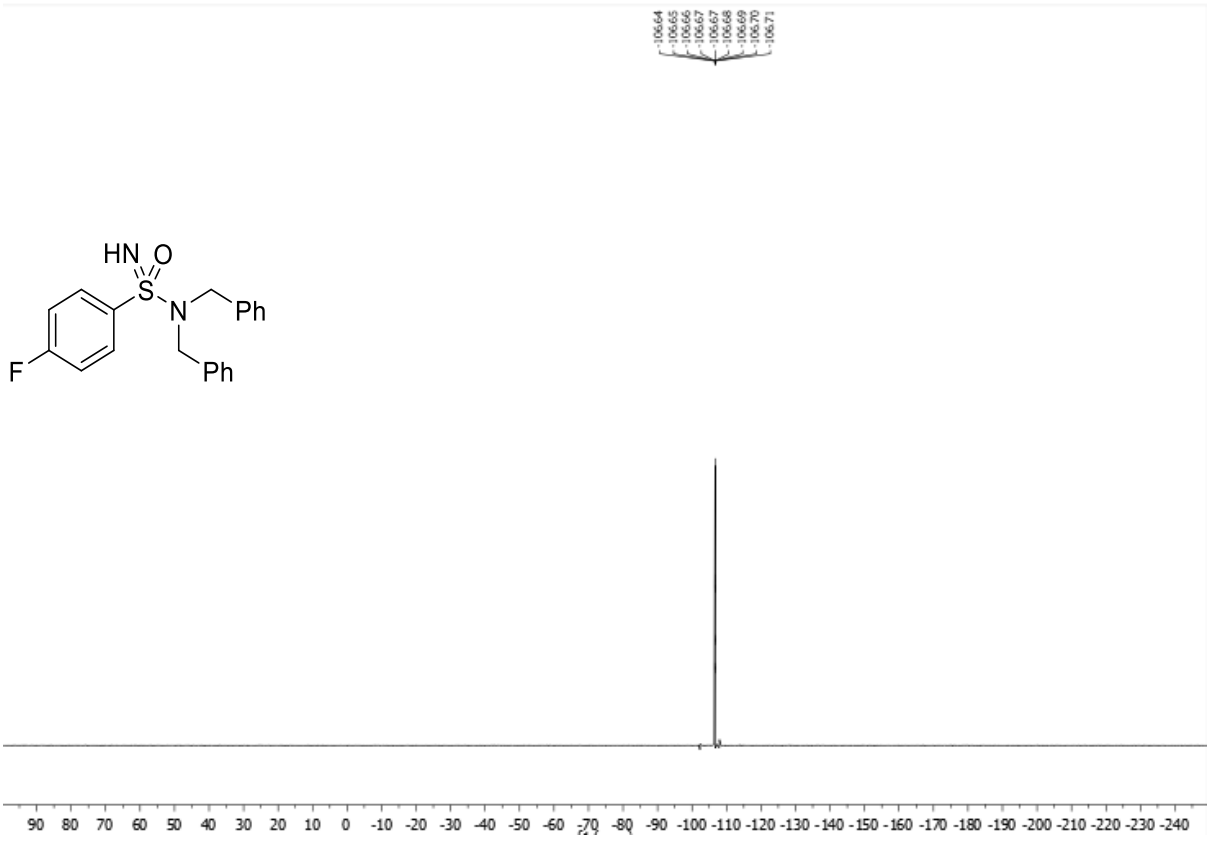
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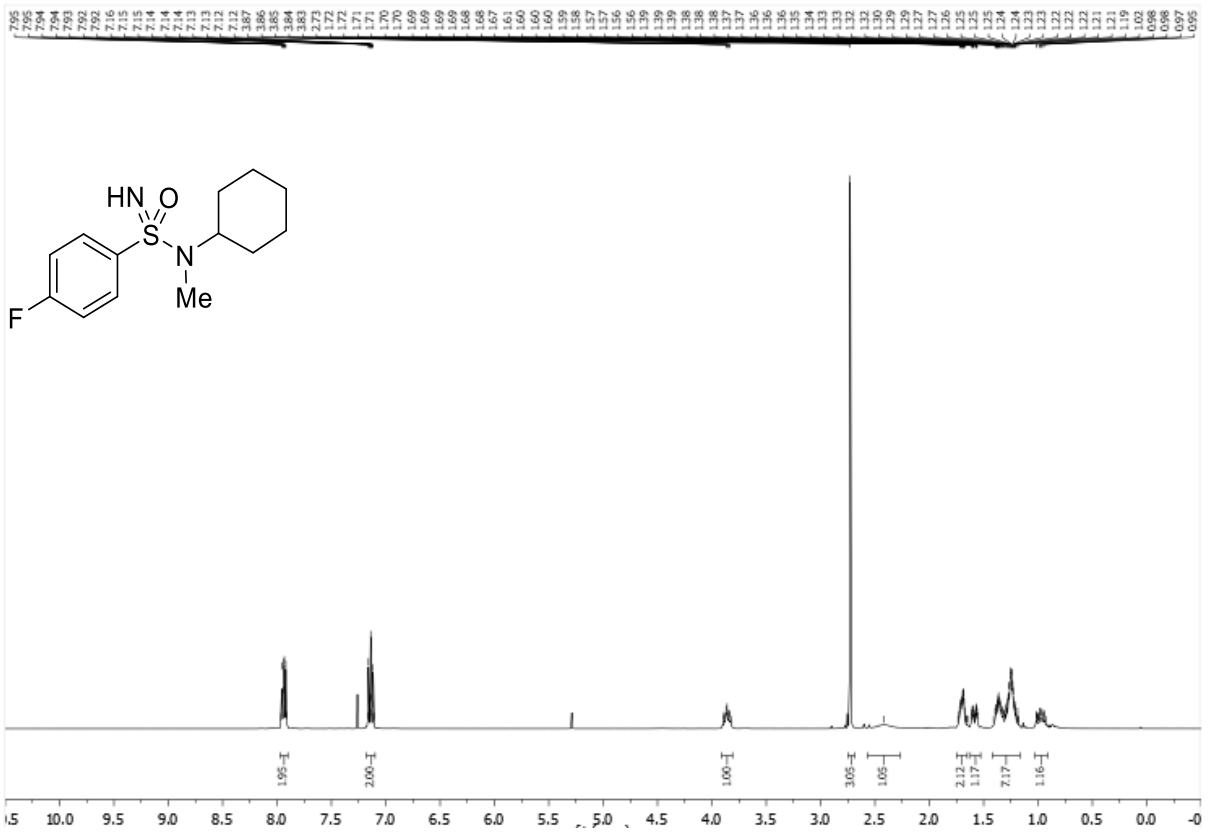
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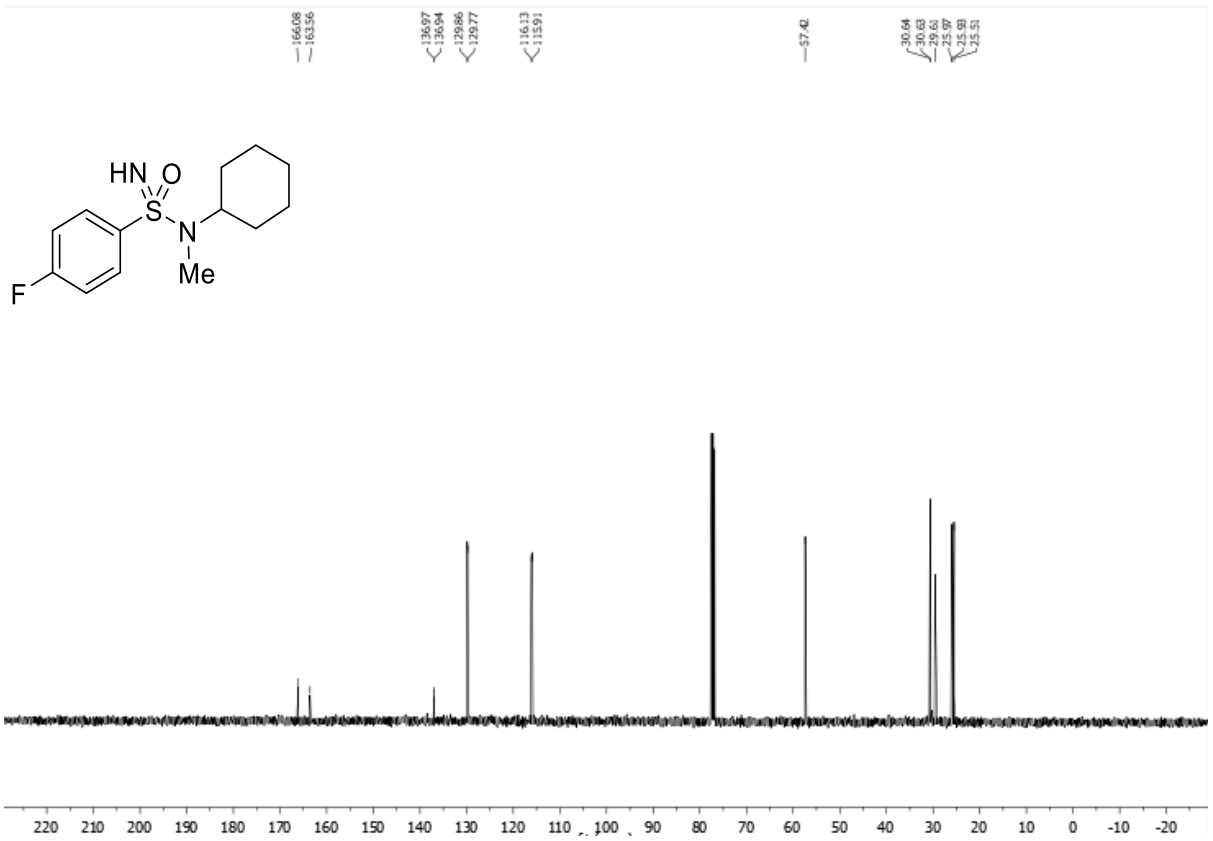
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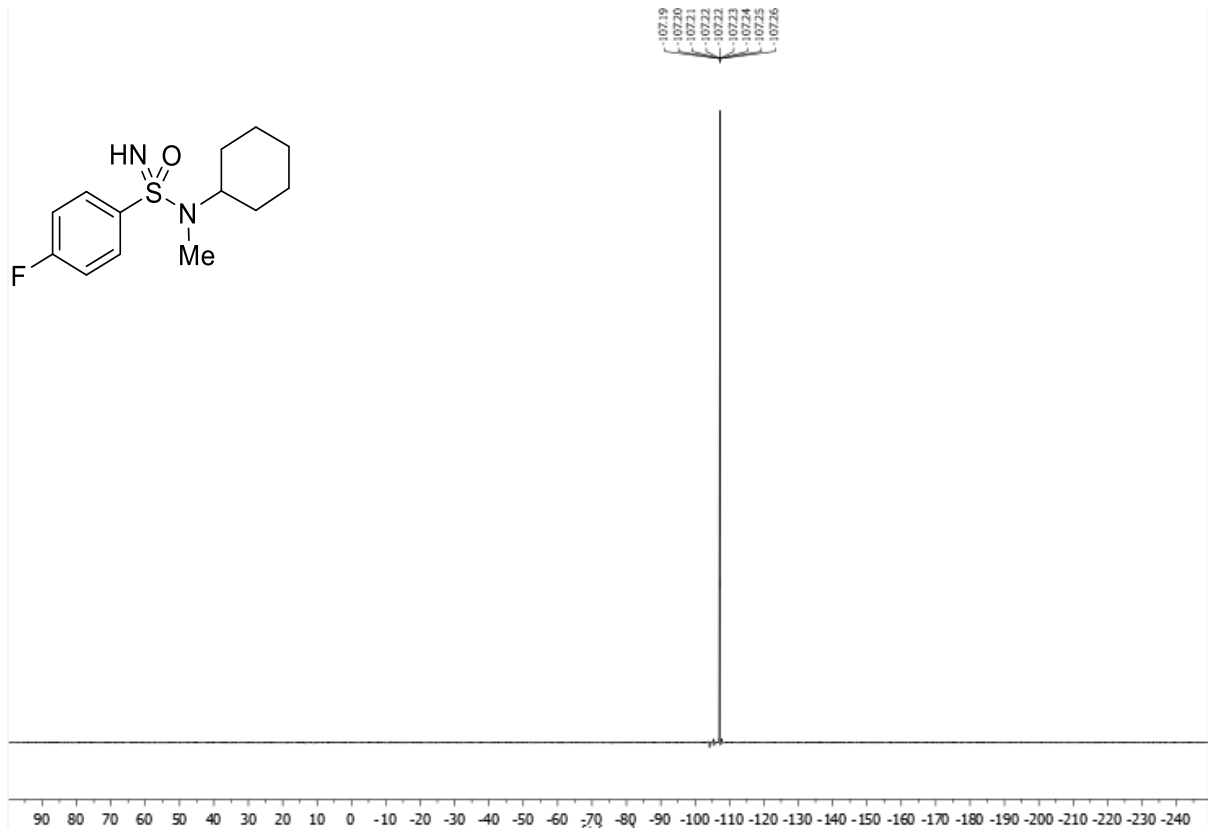
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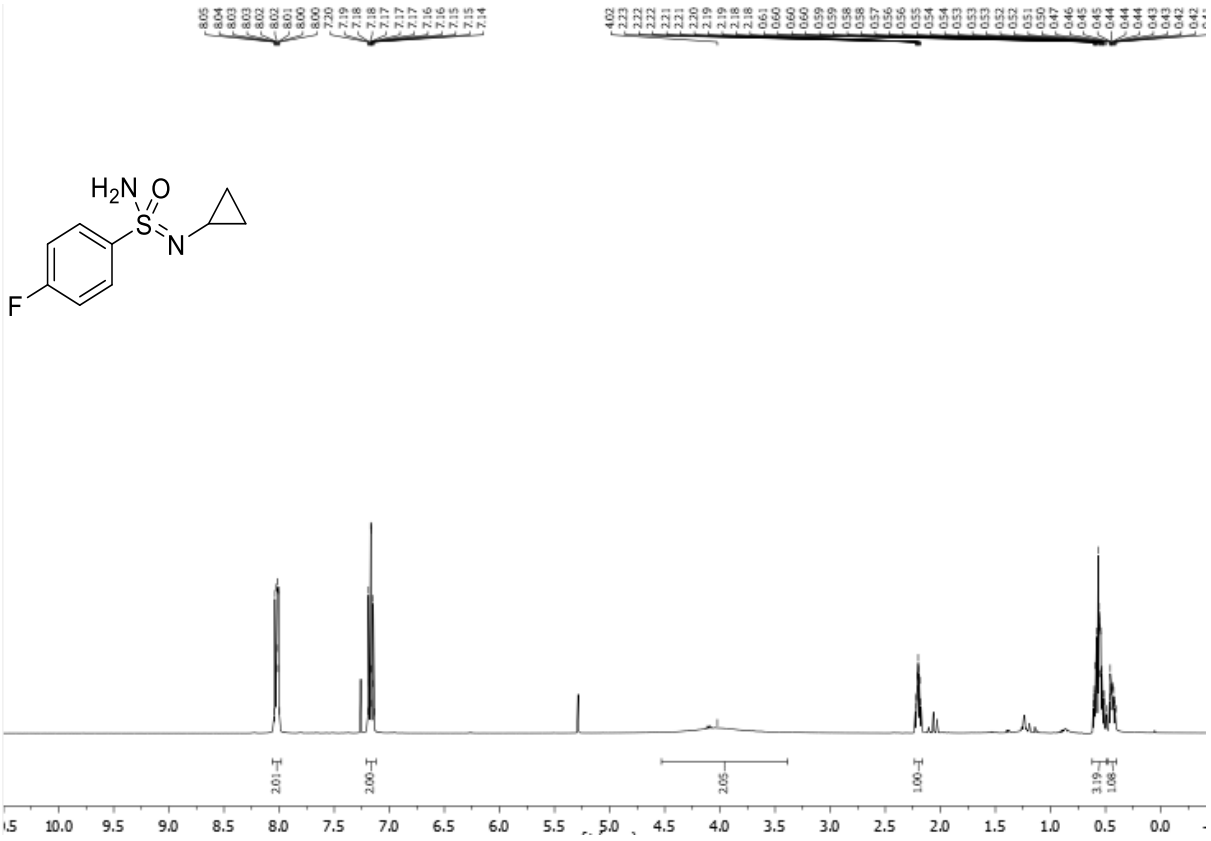
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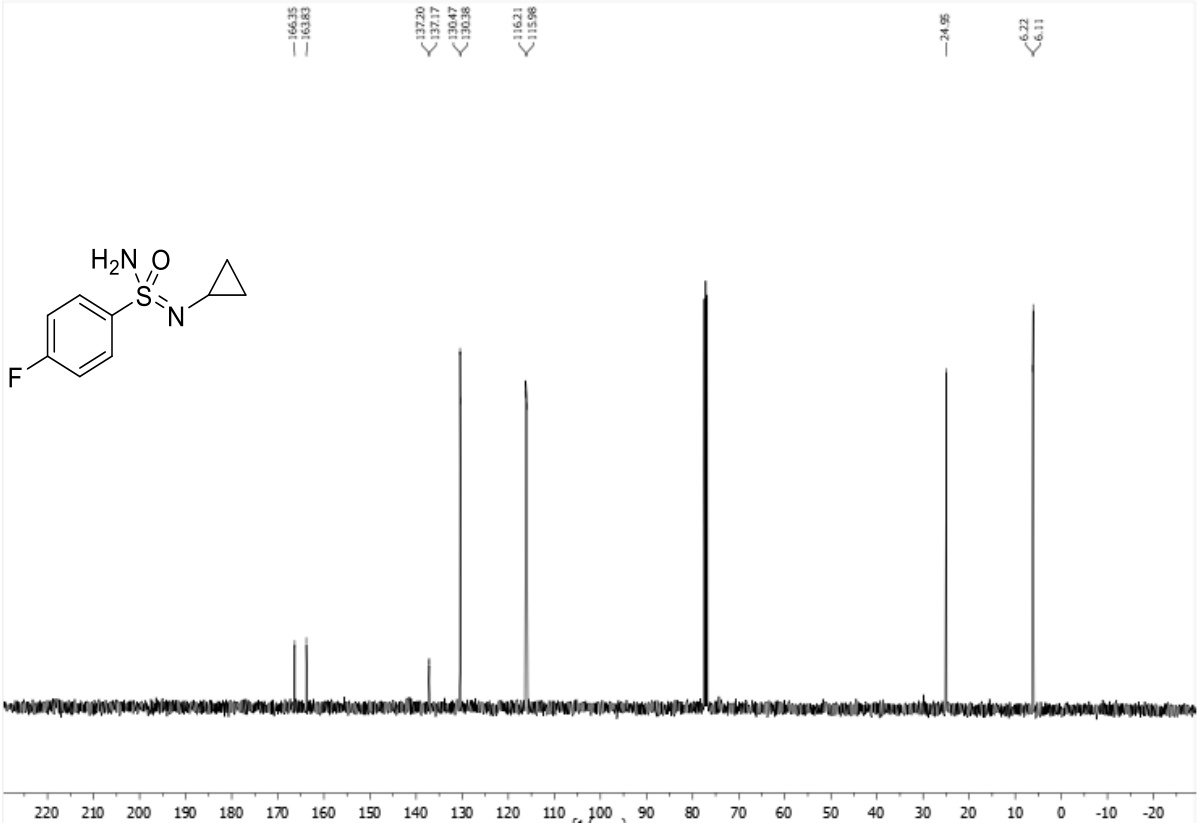
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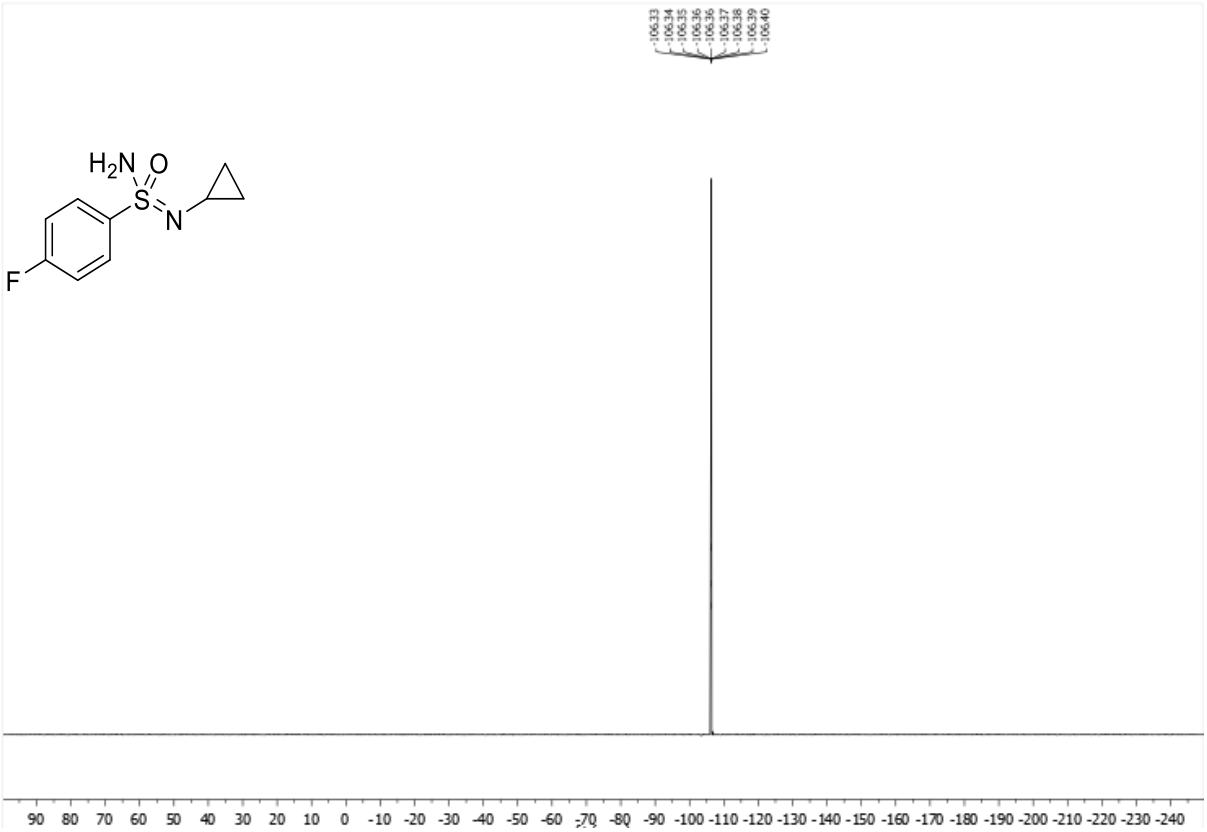
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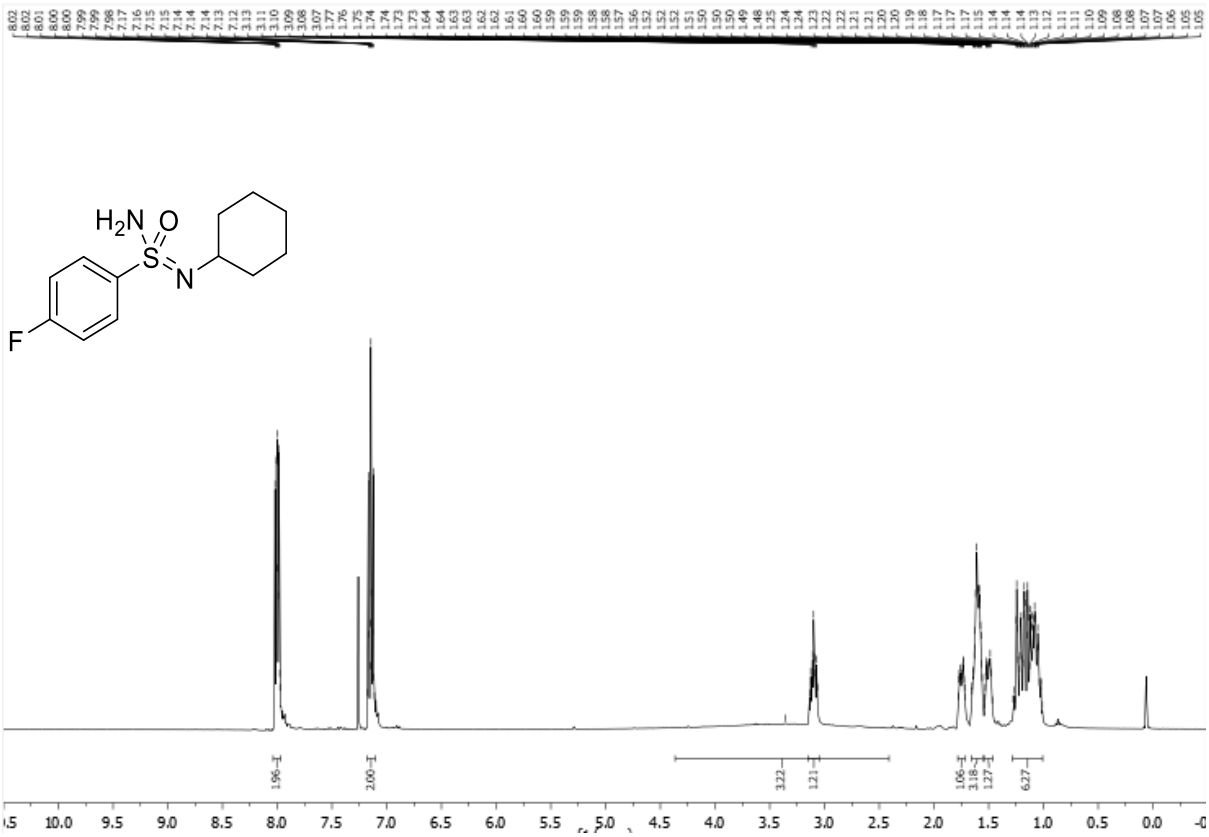
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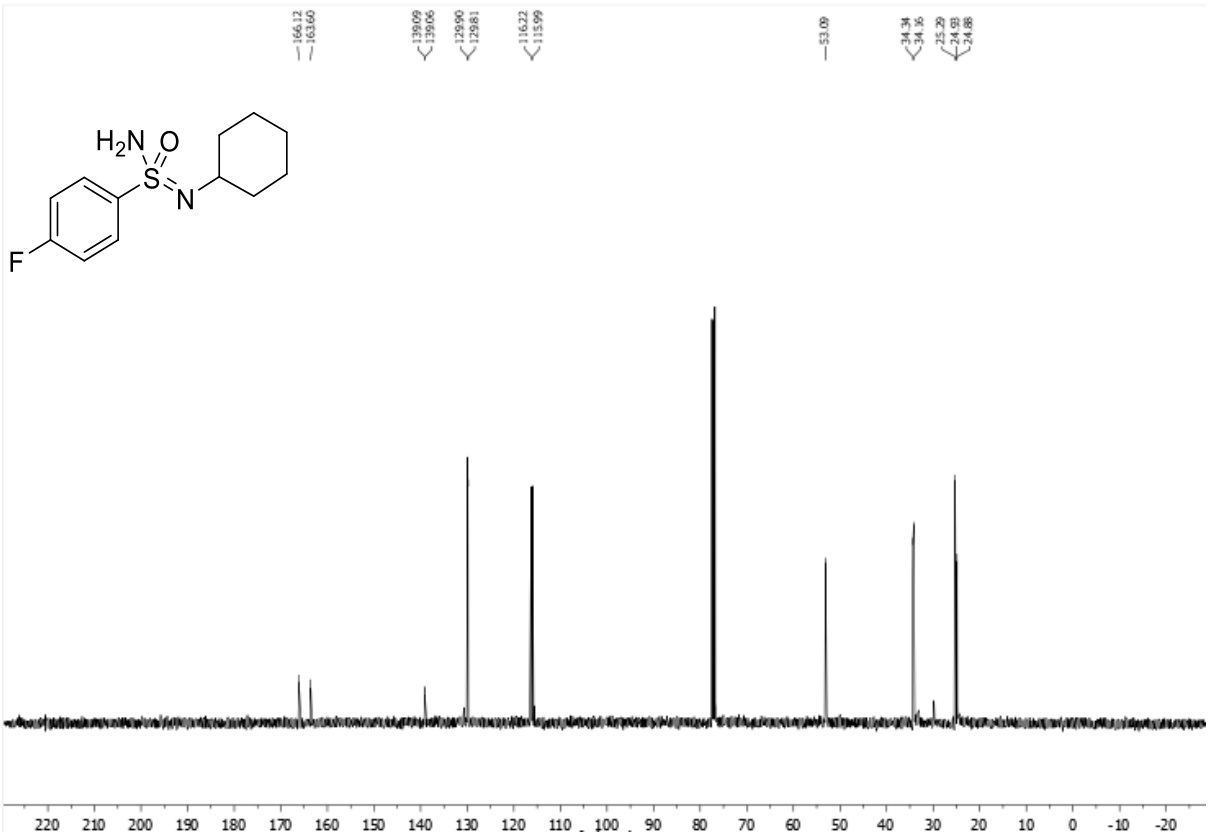
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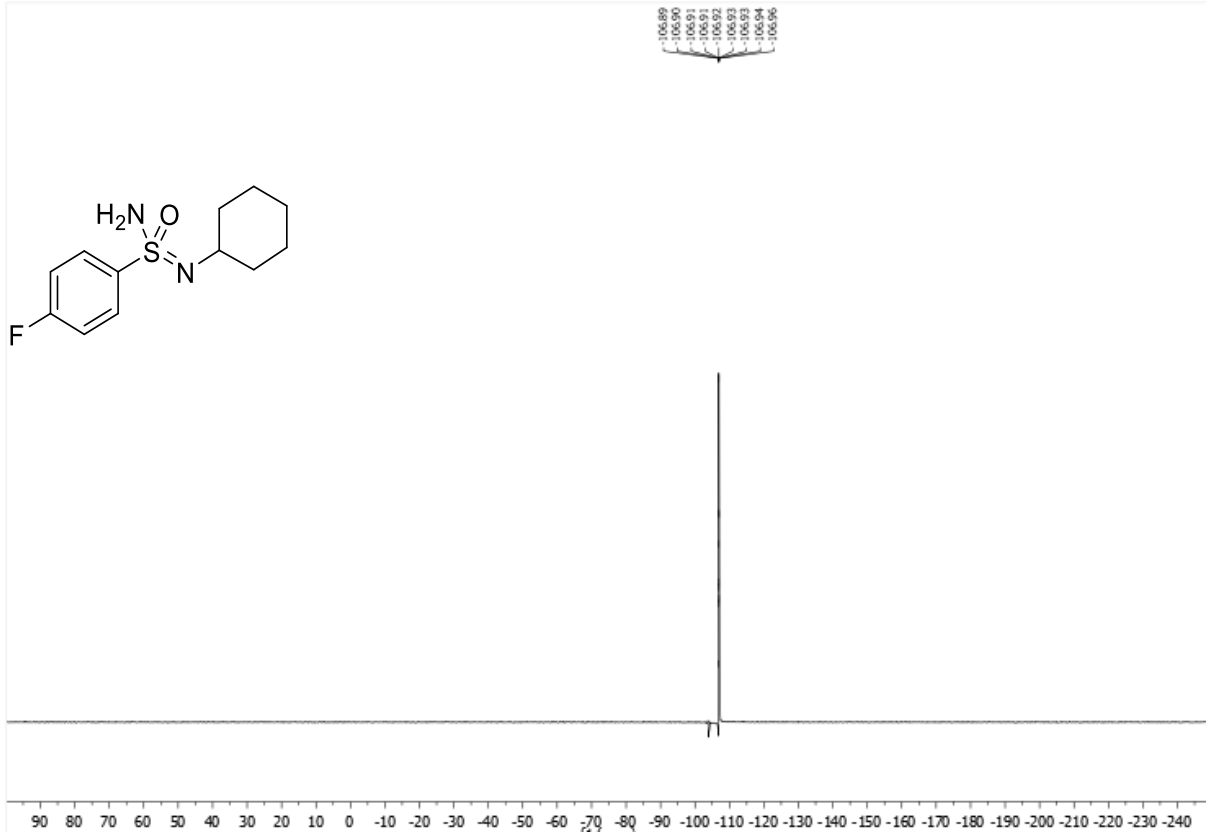
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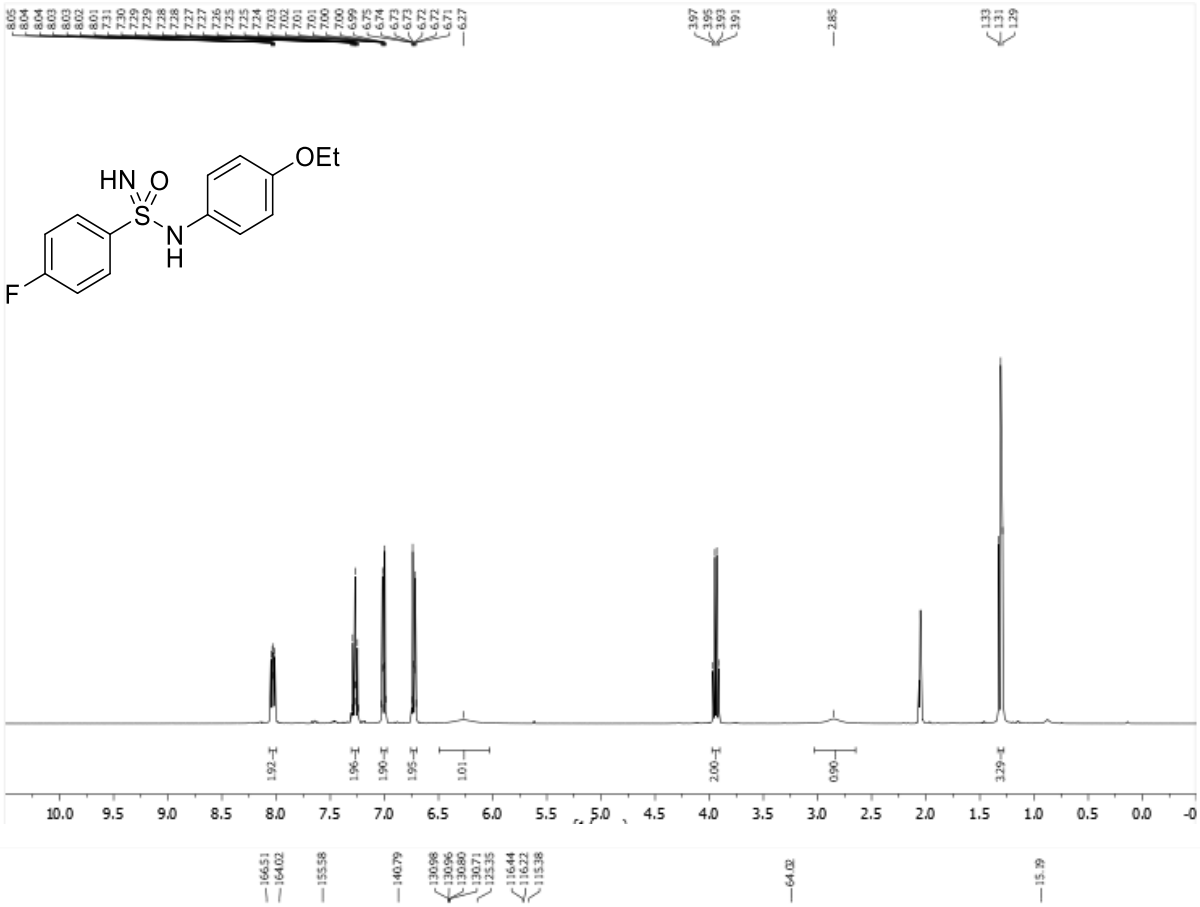
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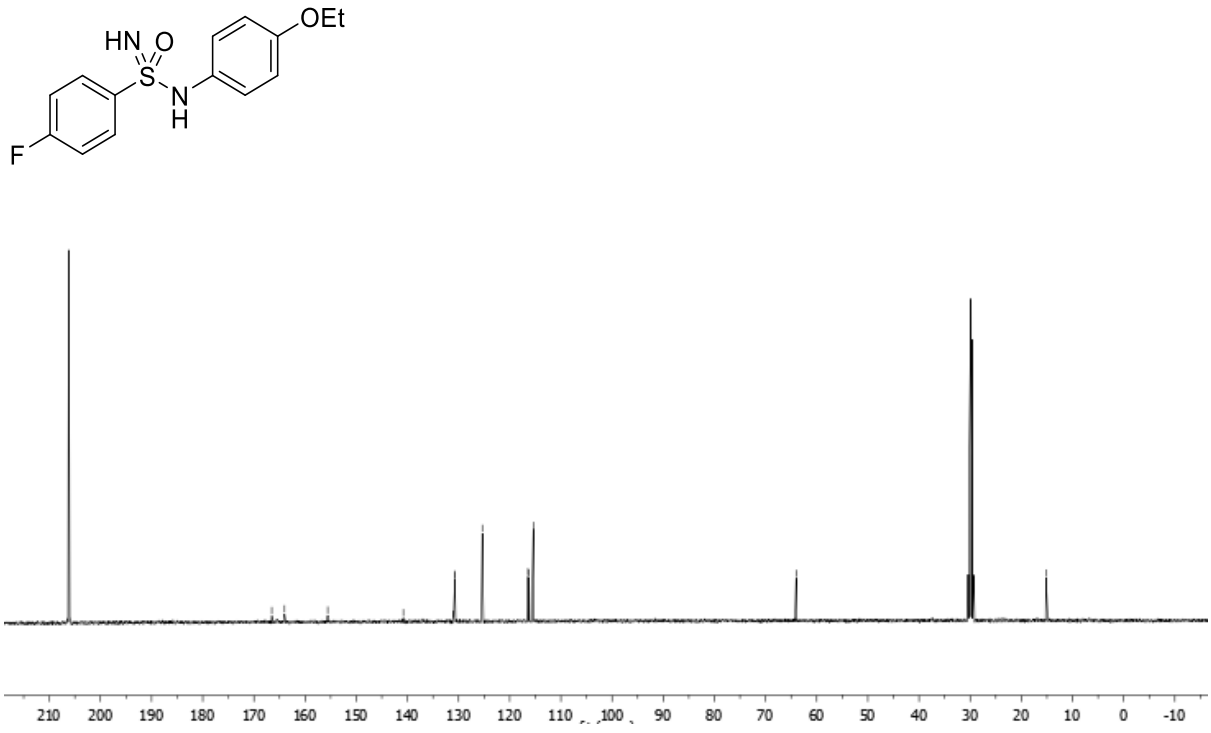
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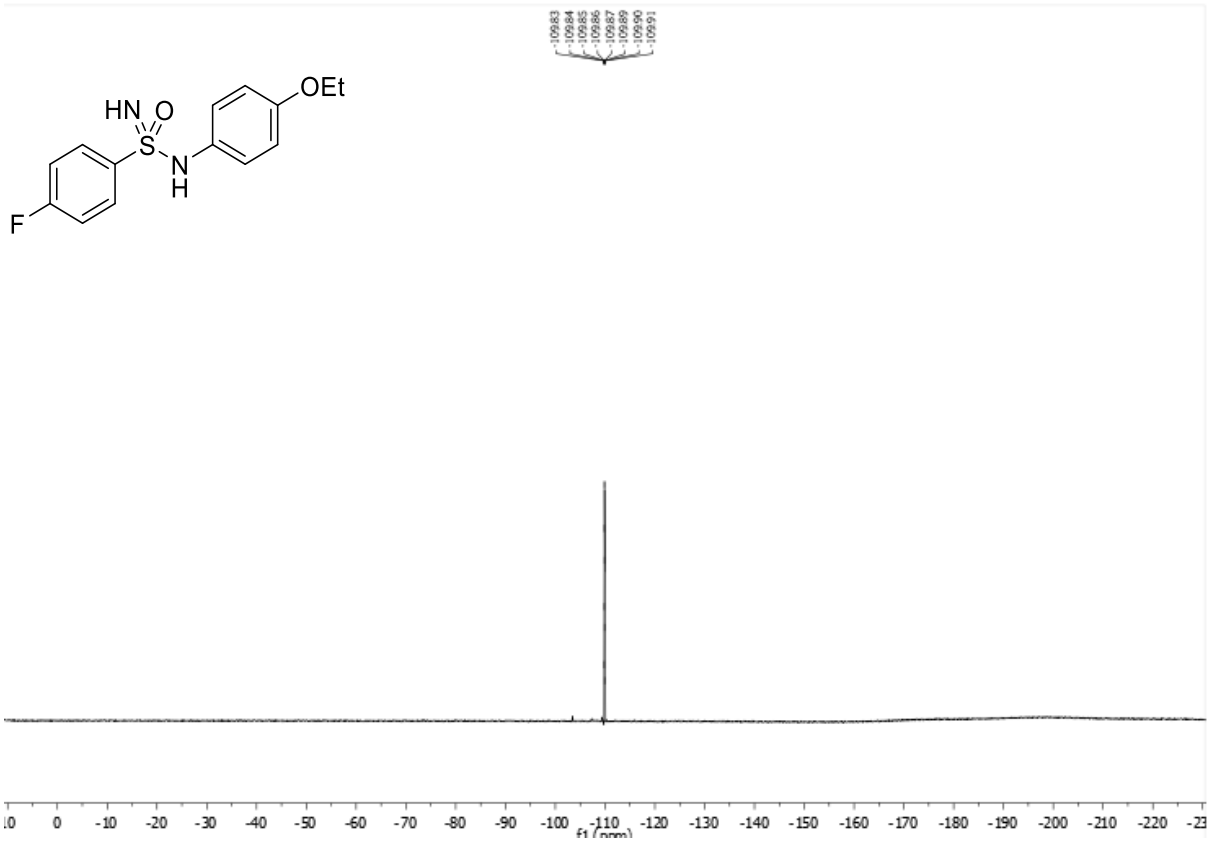
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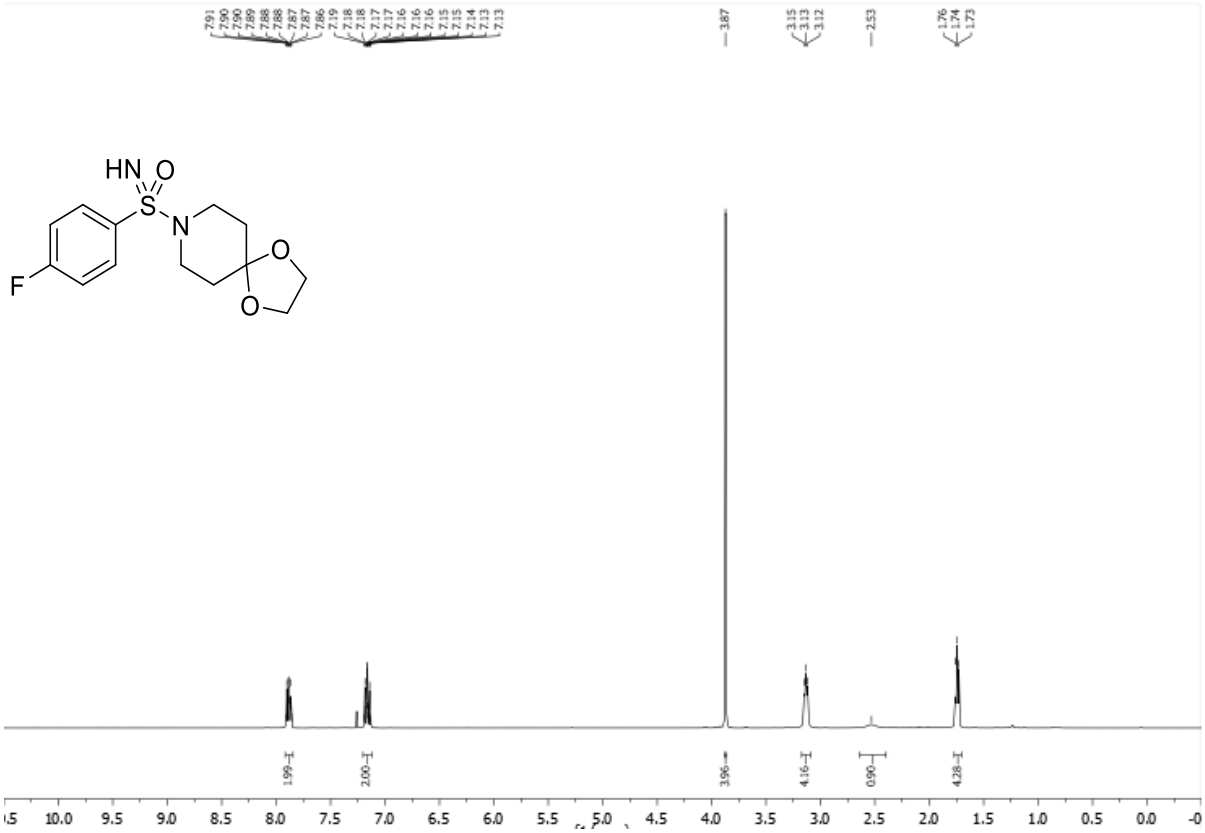
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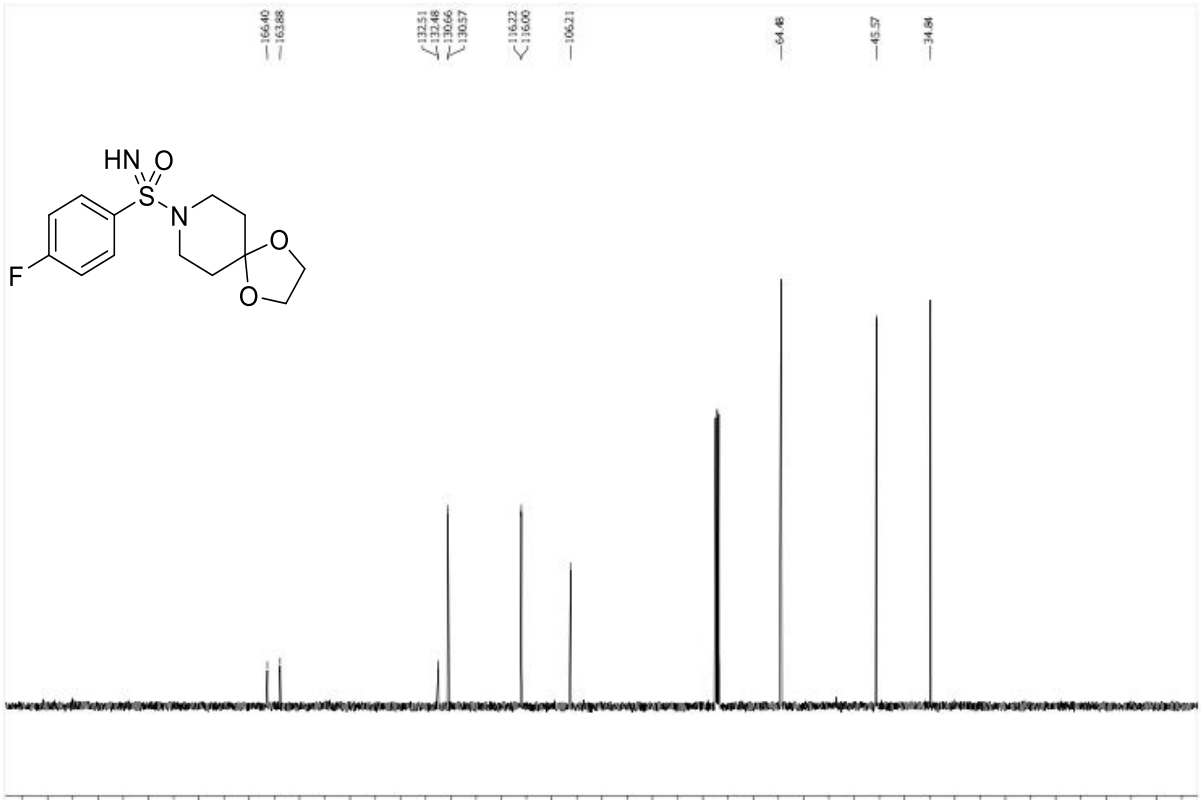
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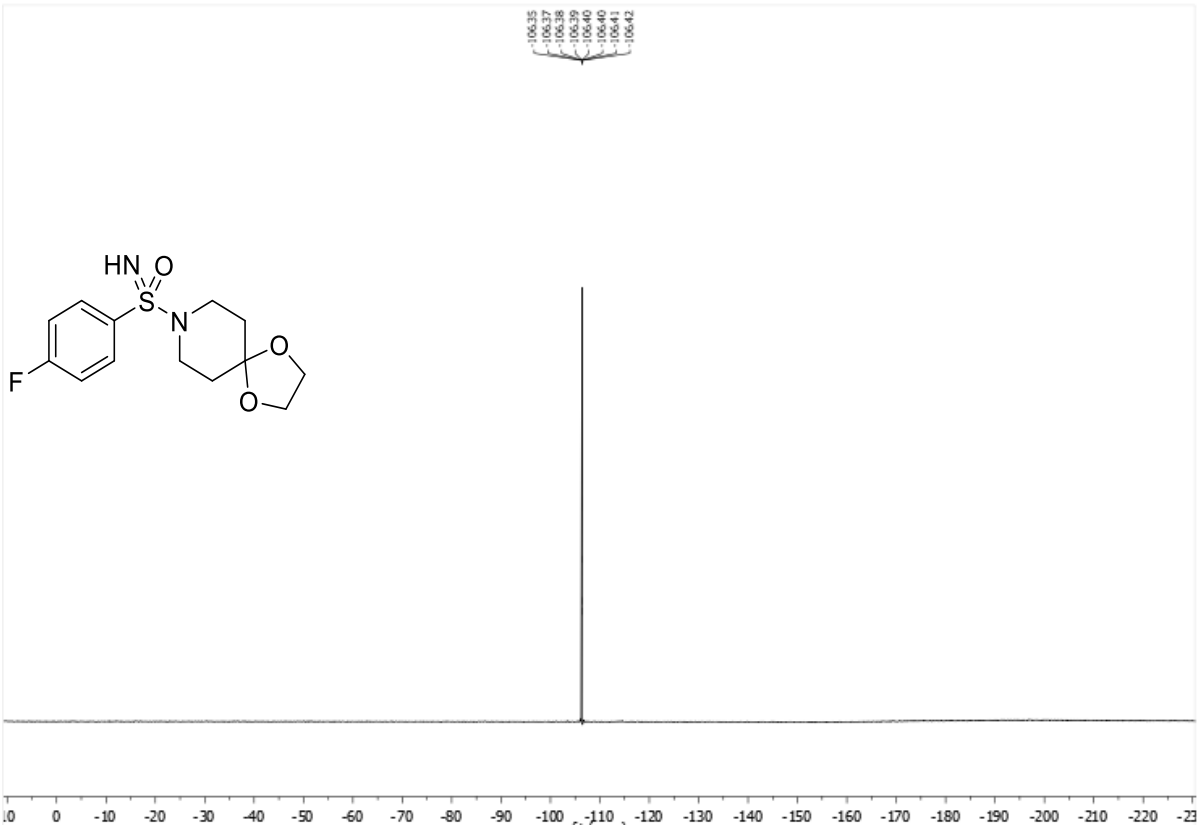
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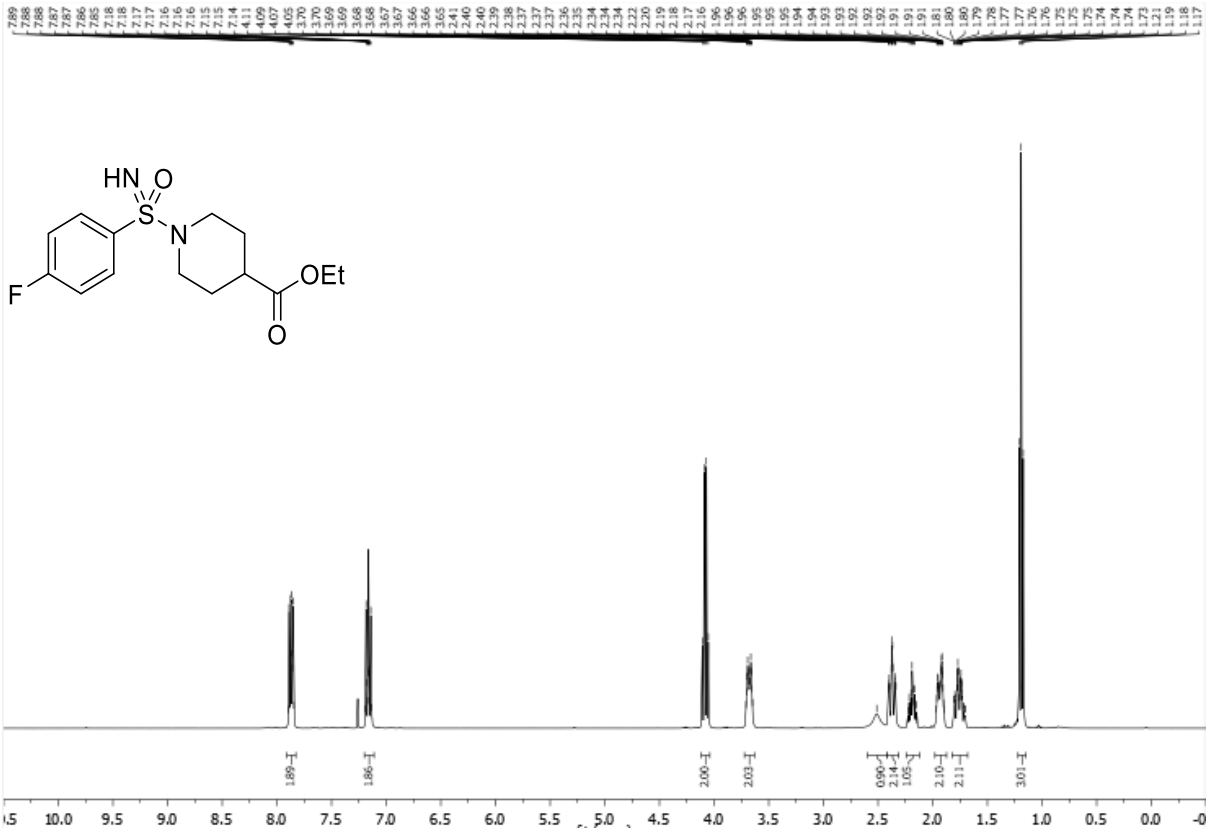
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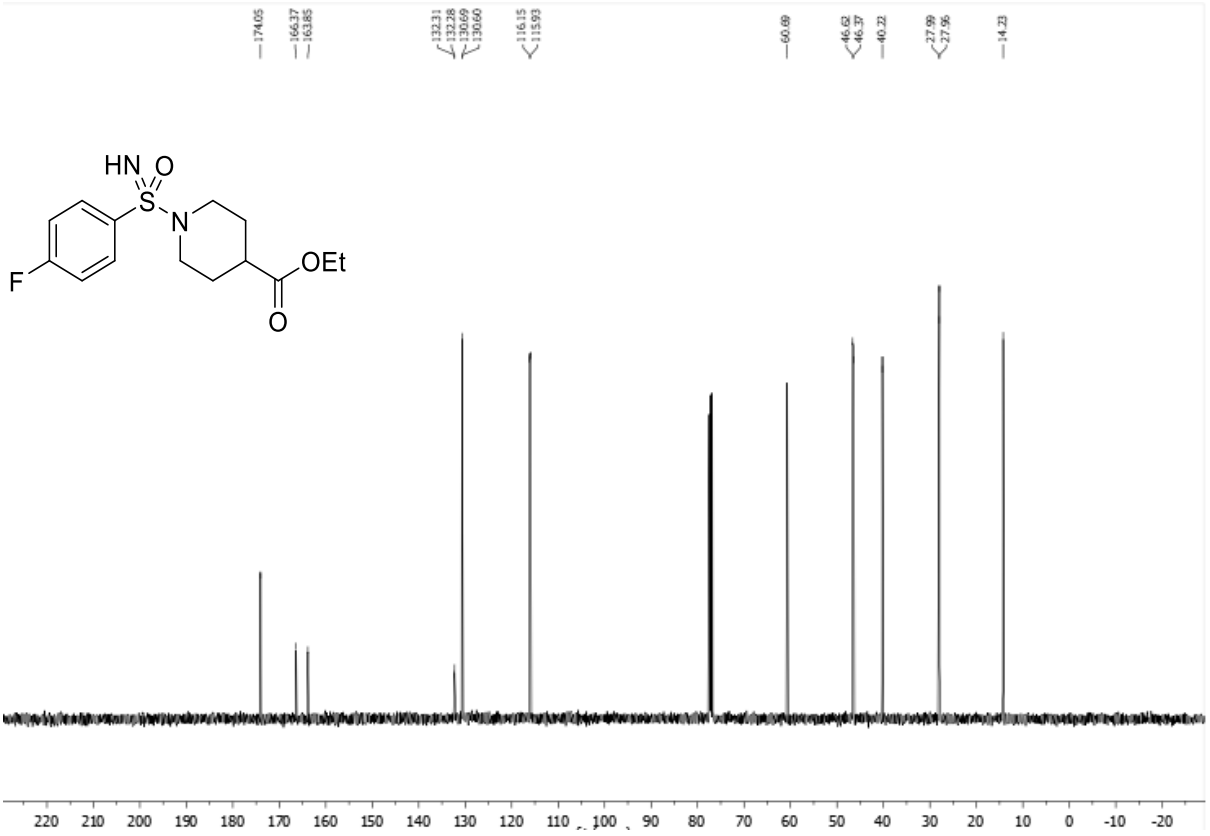
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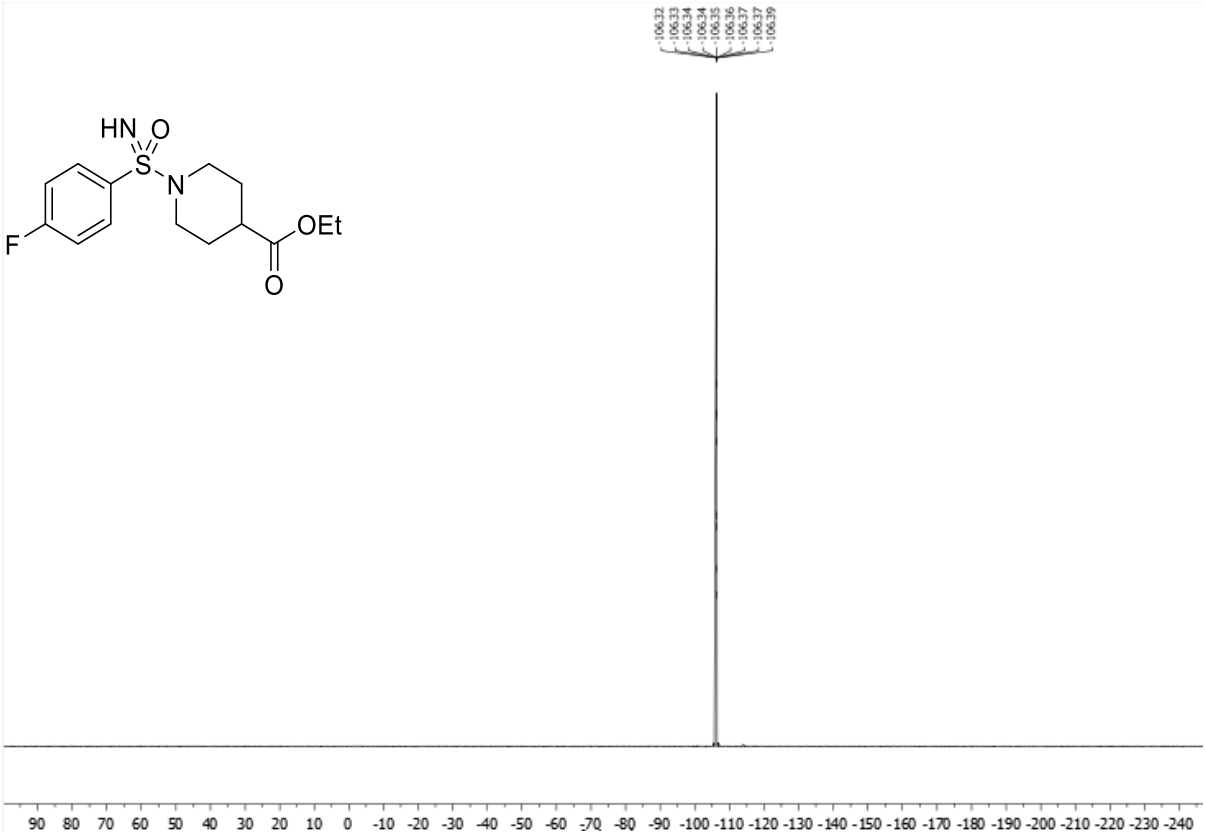
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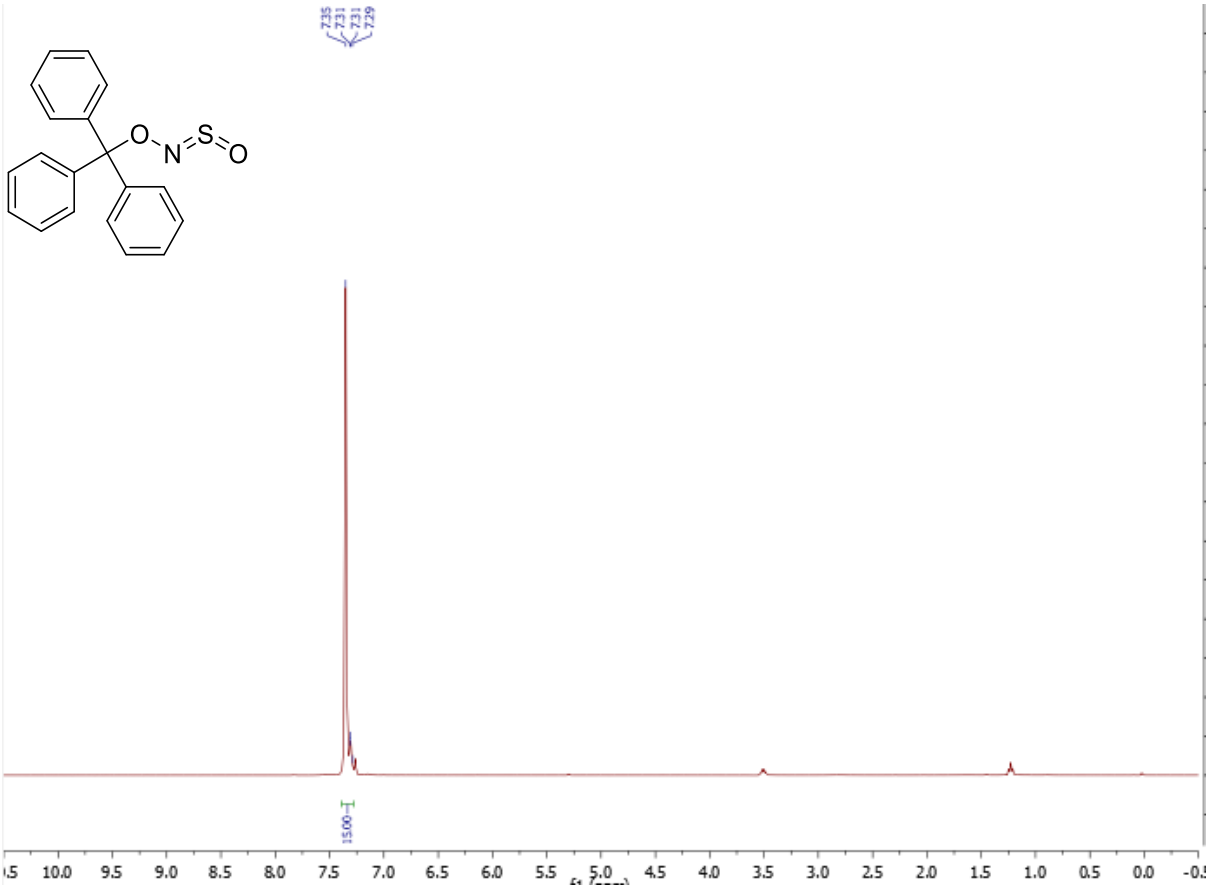
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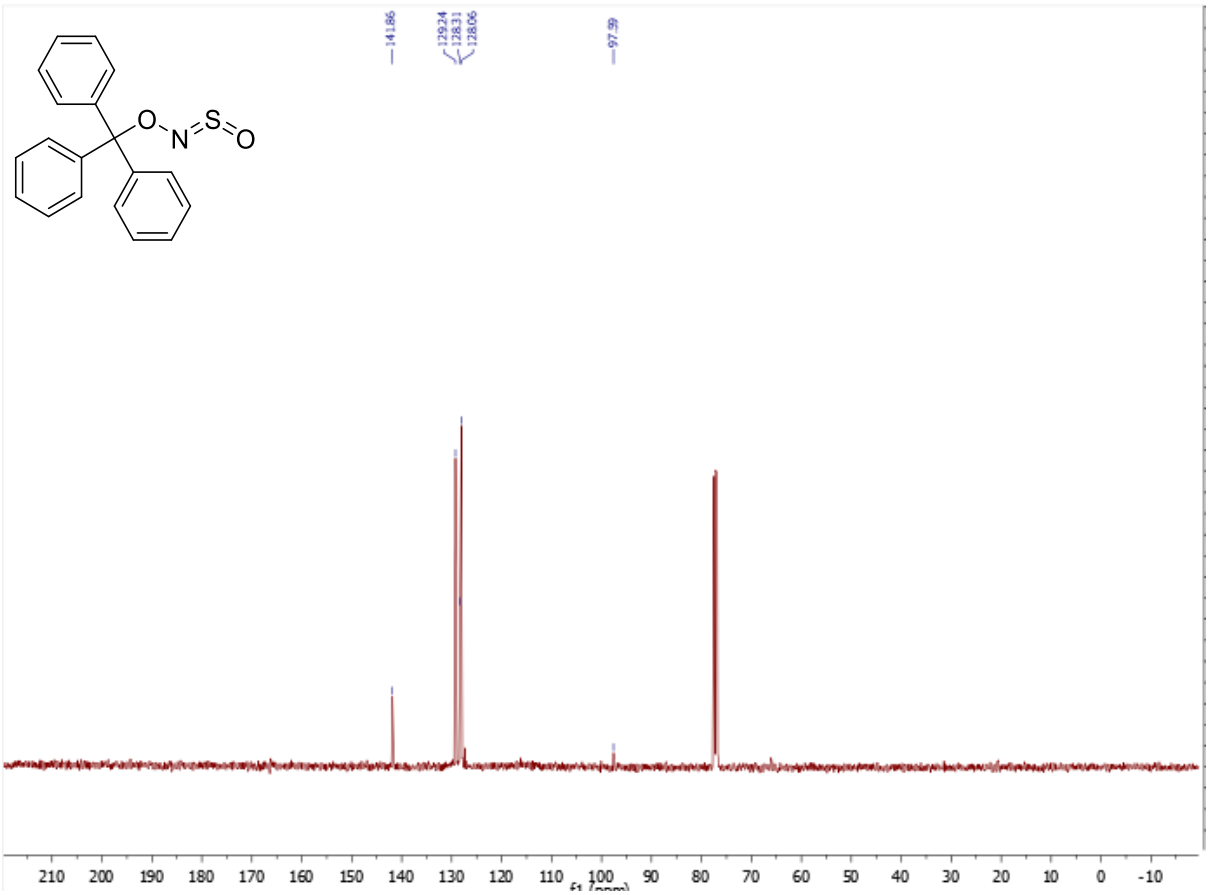
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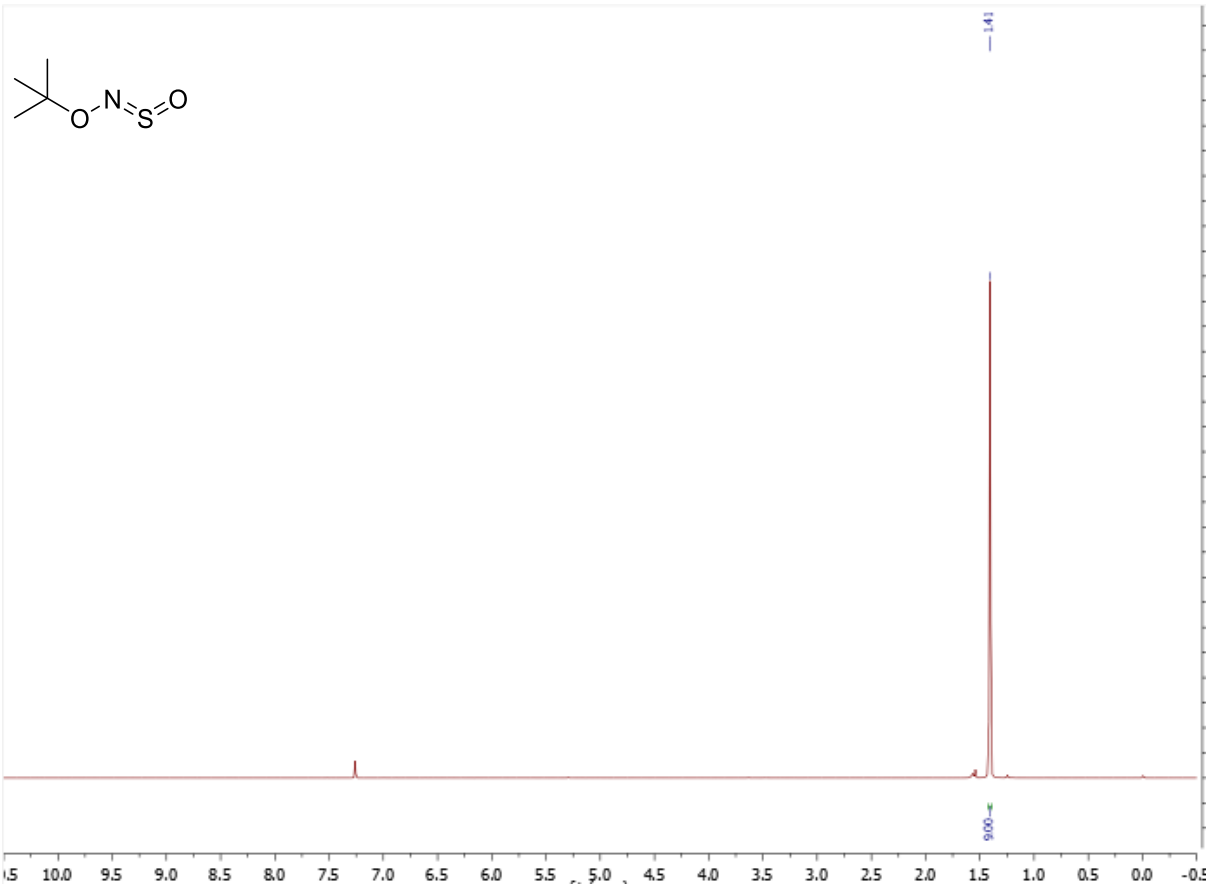
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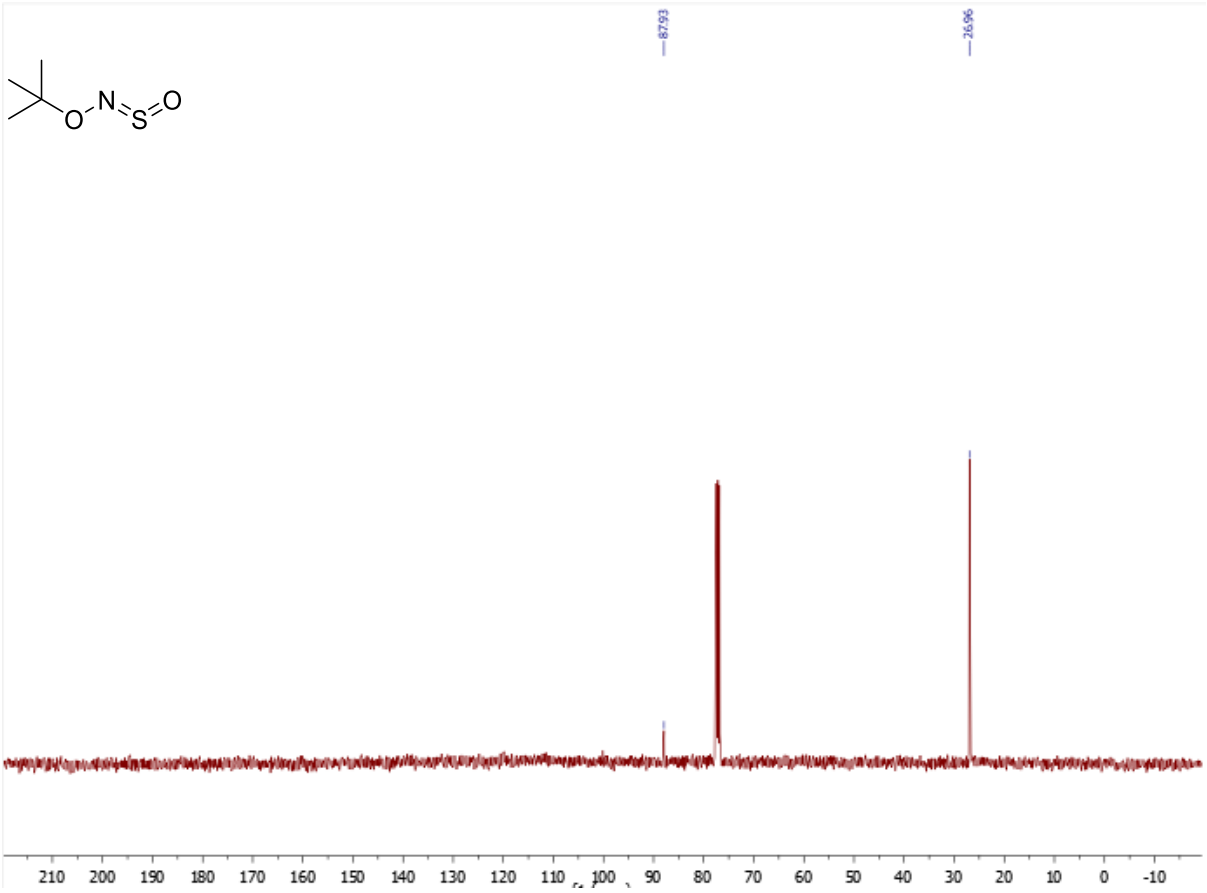
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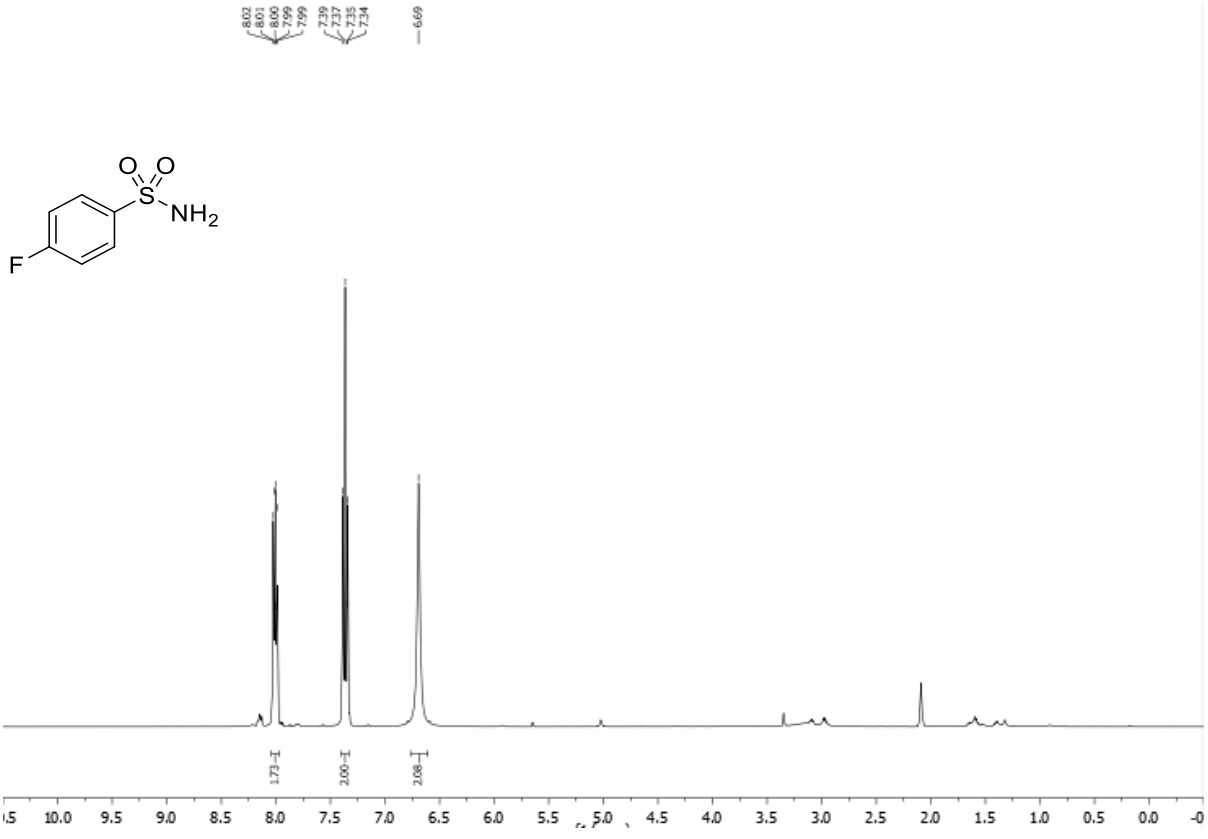
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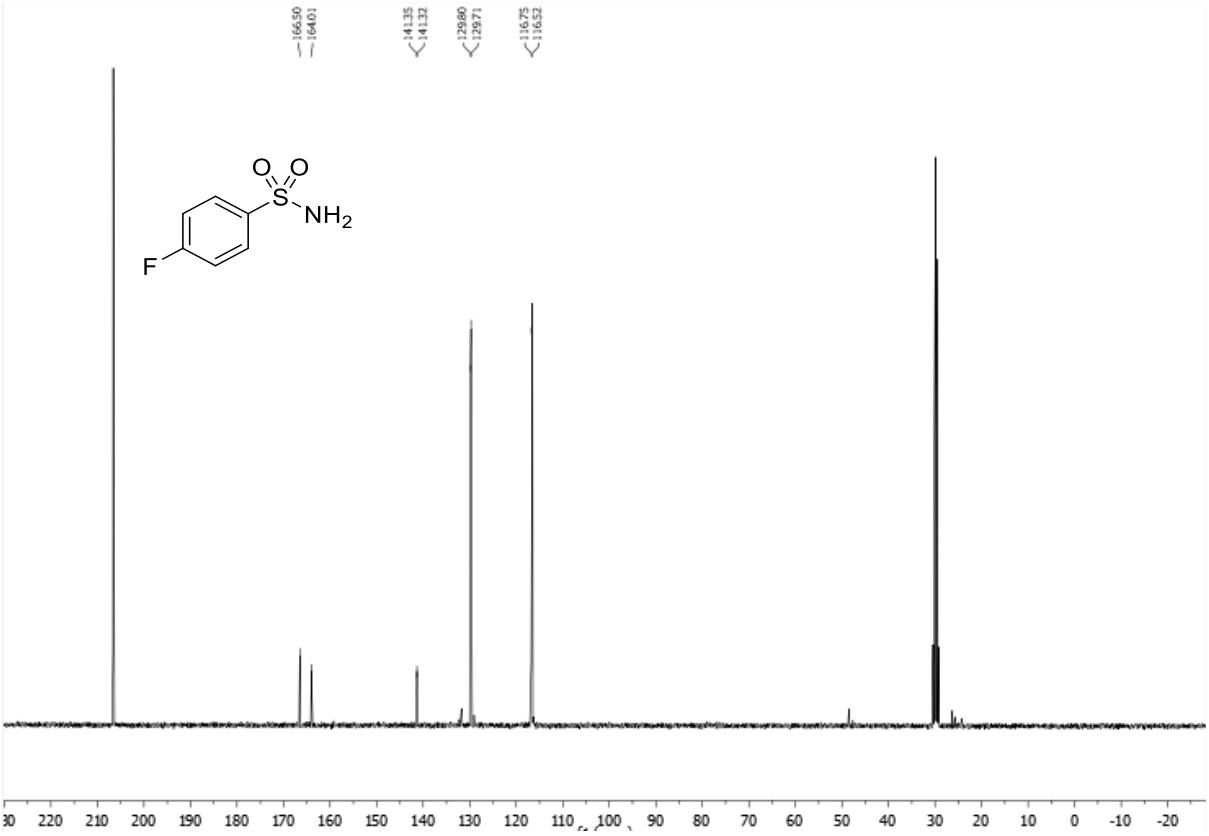
7.35
7.34
6.69
1.73
2.00
2.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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F
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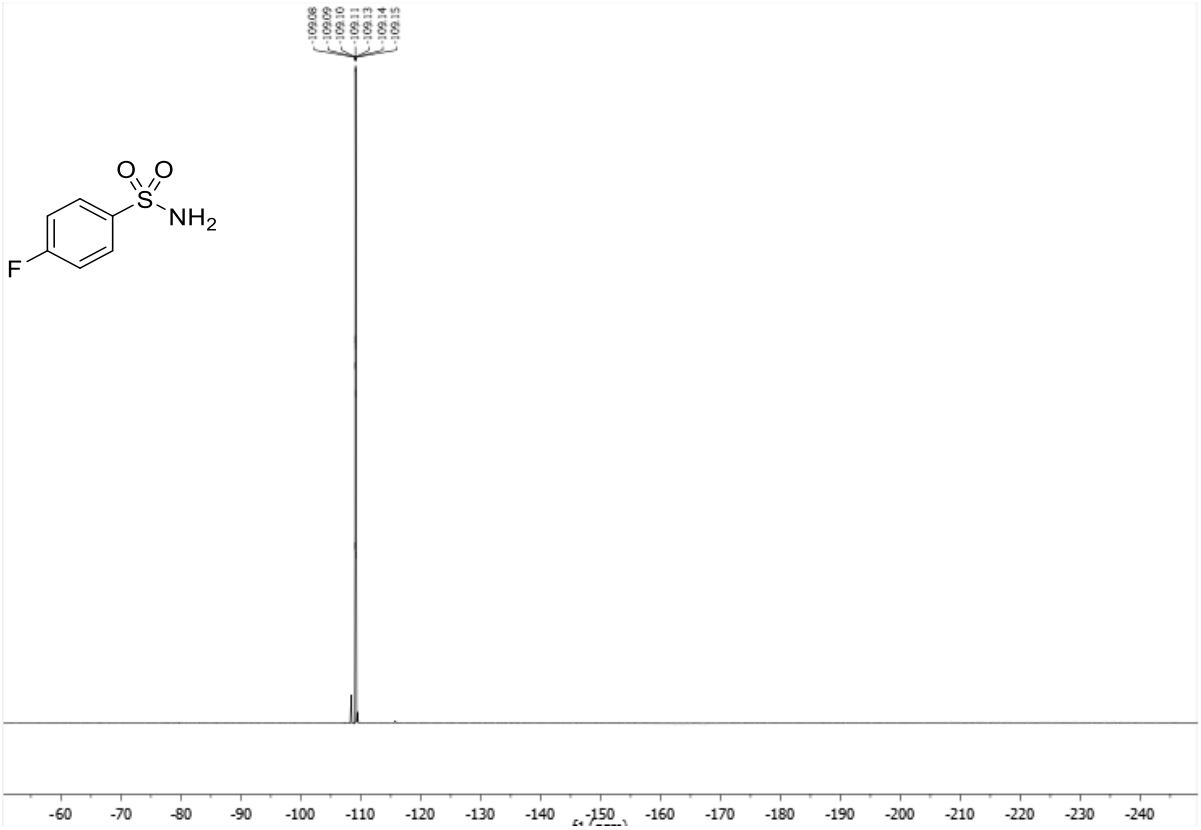
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F
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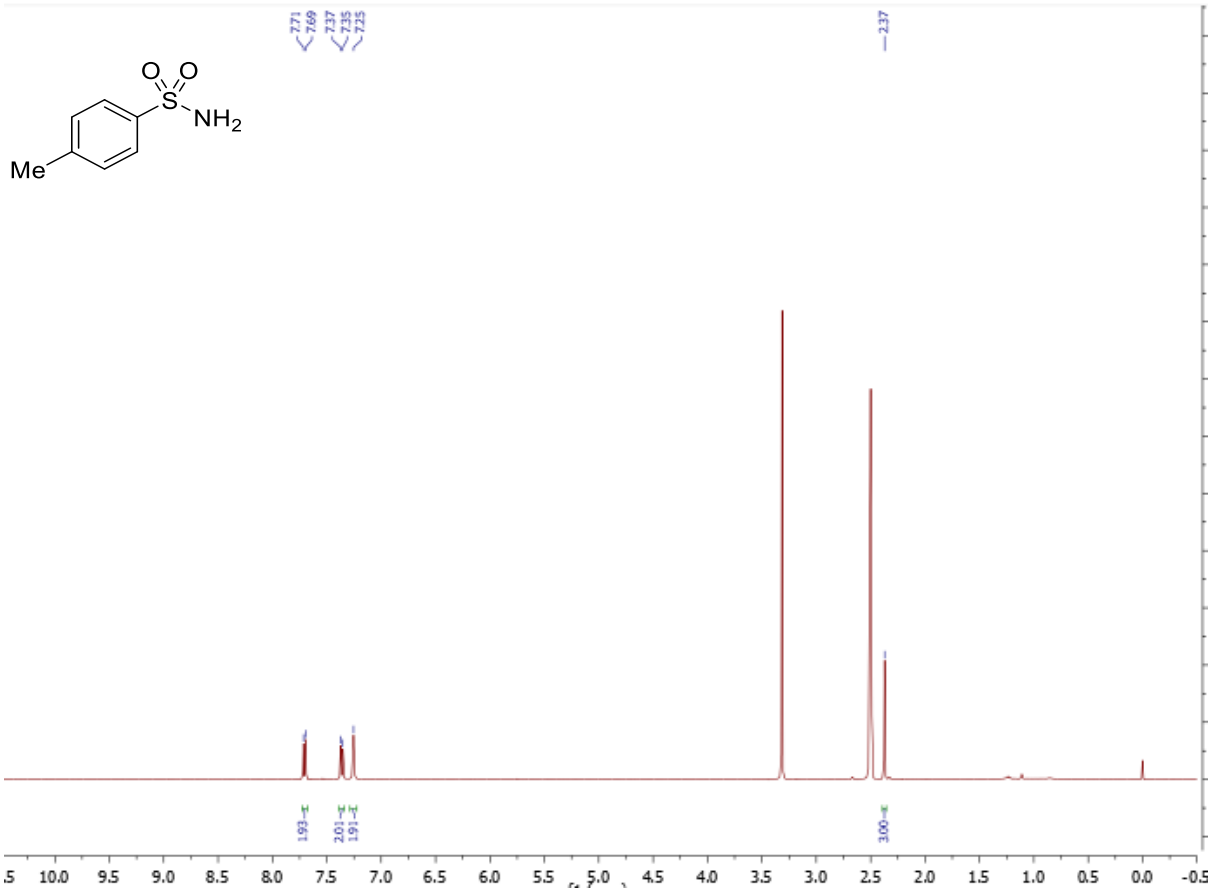
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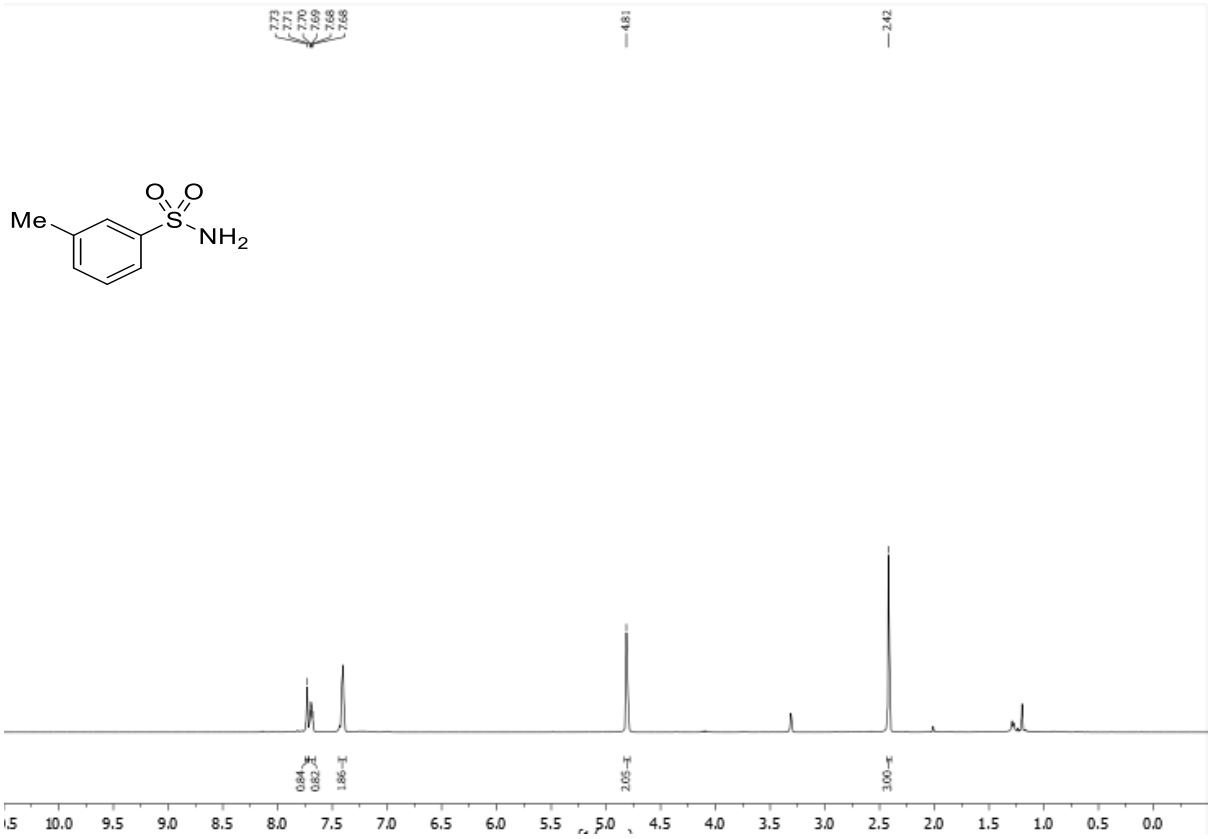
3.00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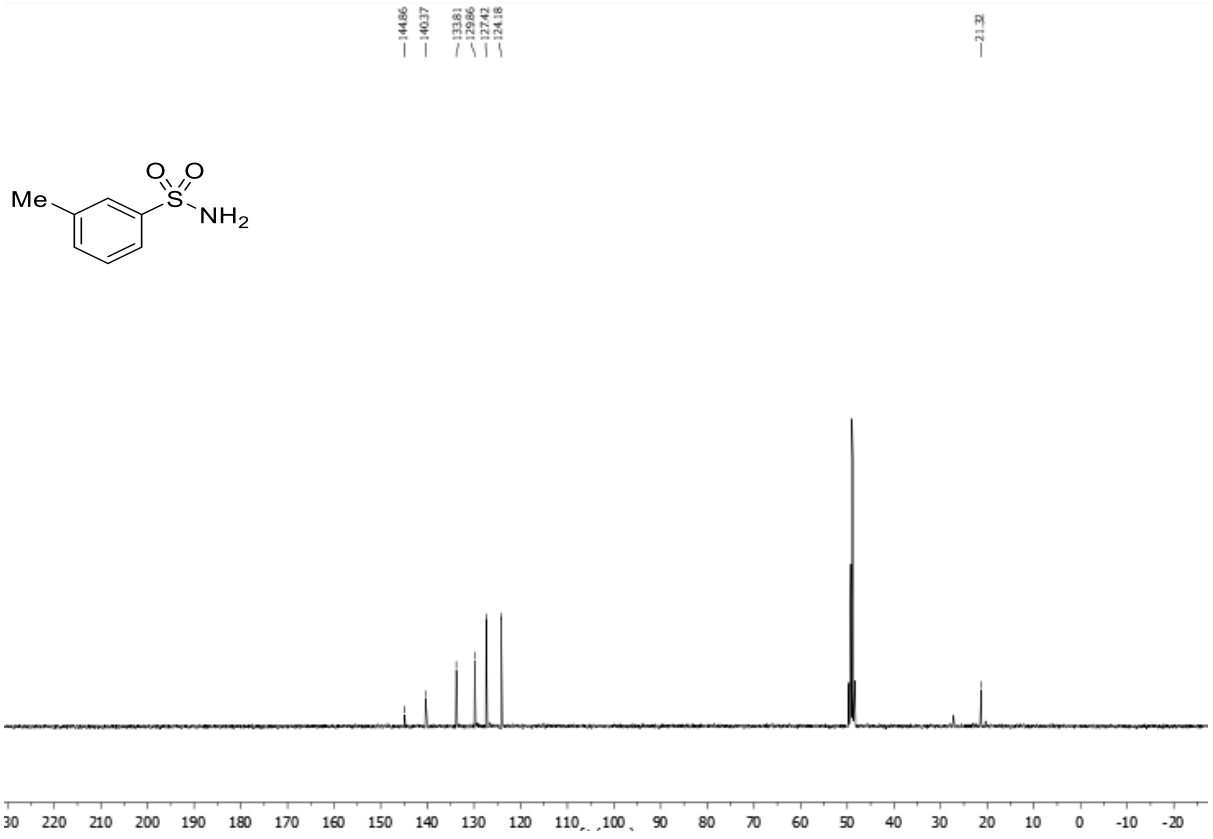
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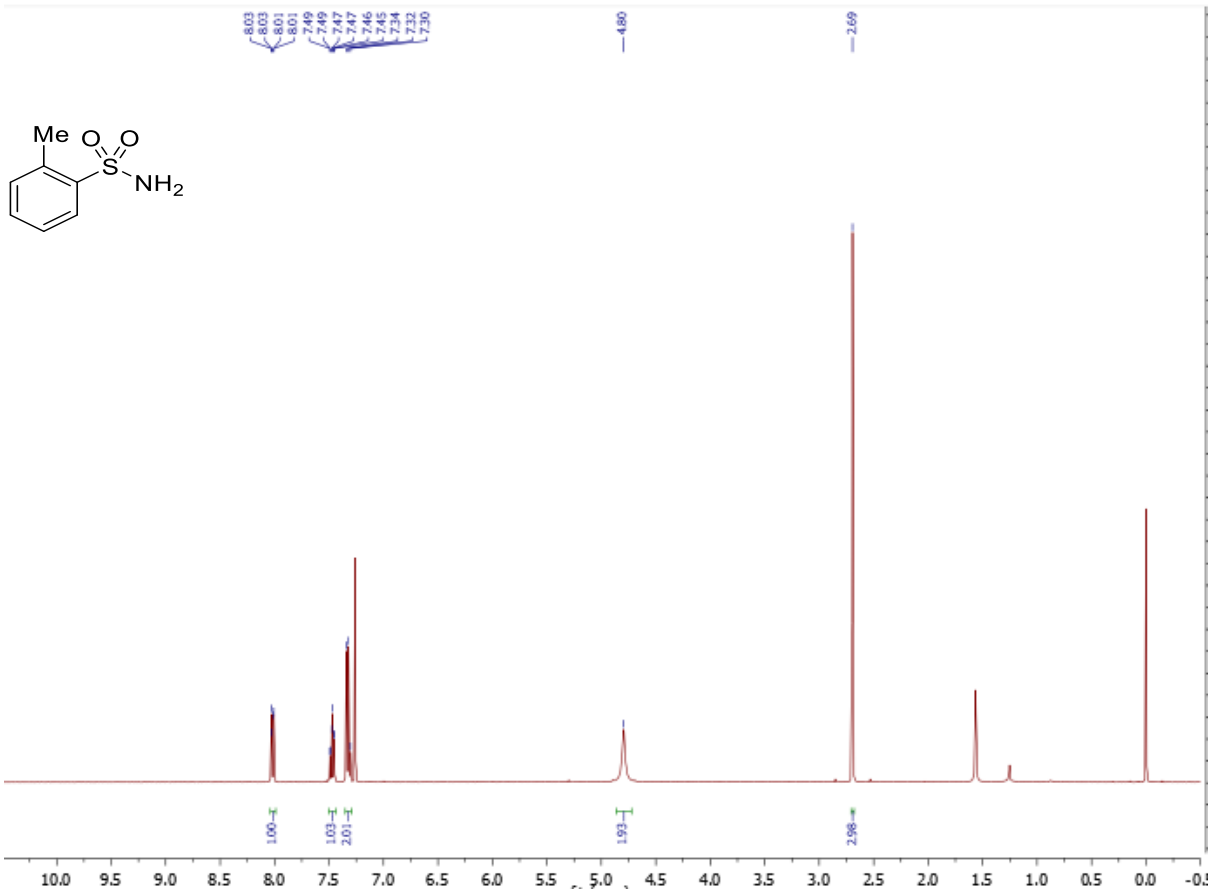
NH2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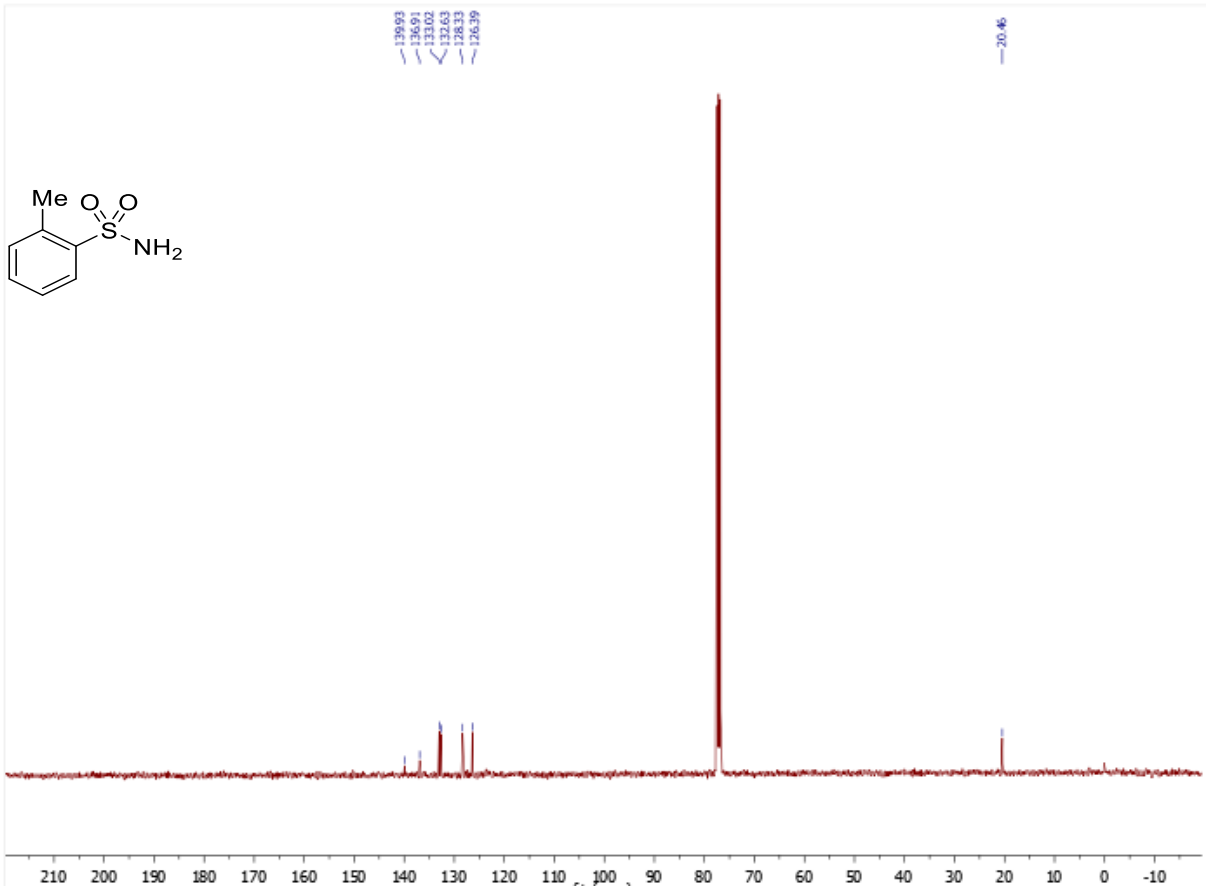
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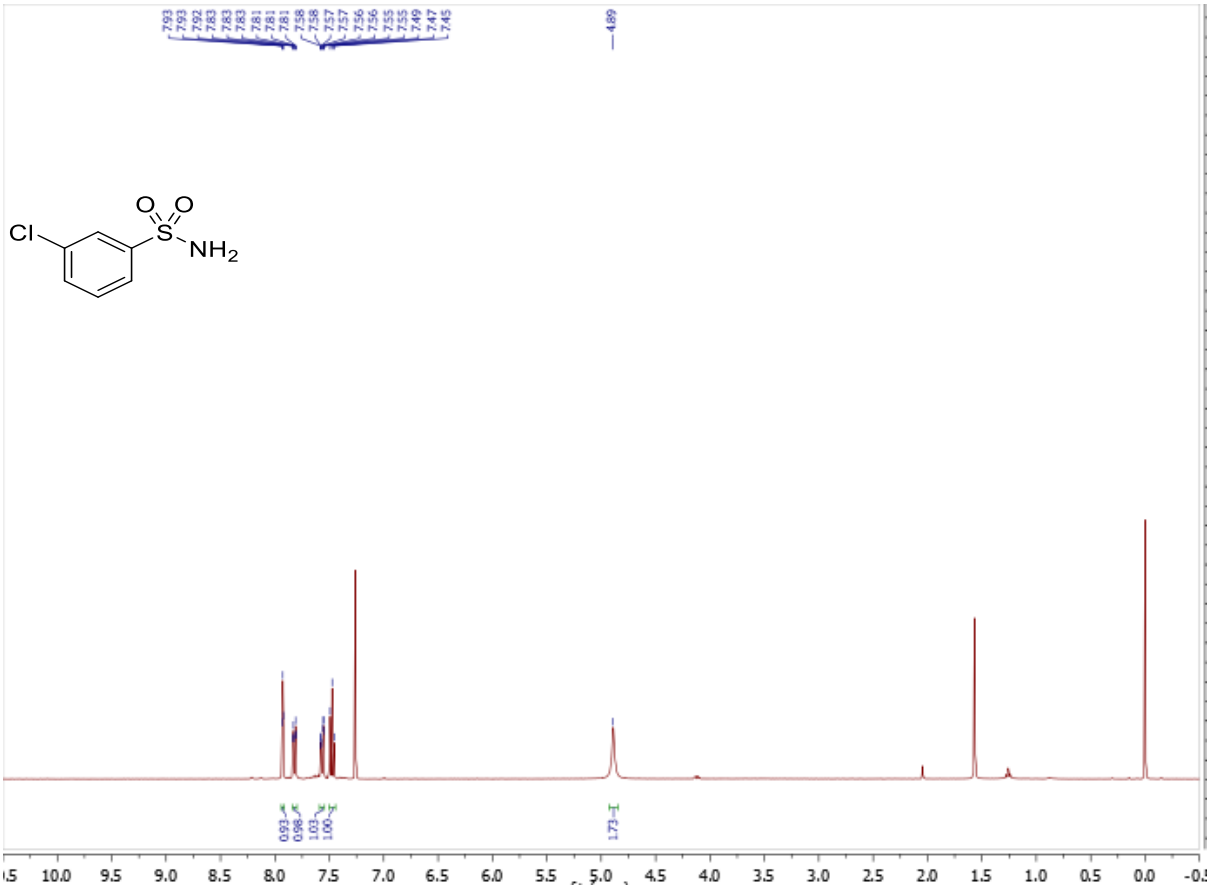
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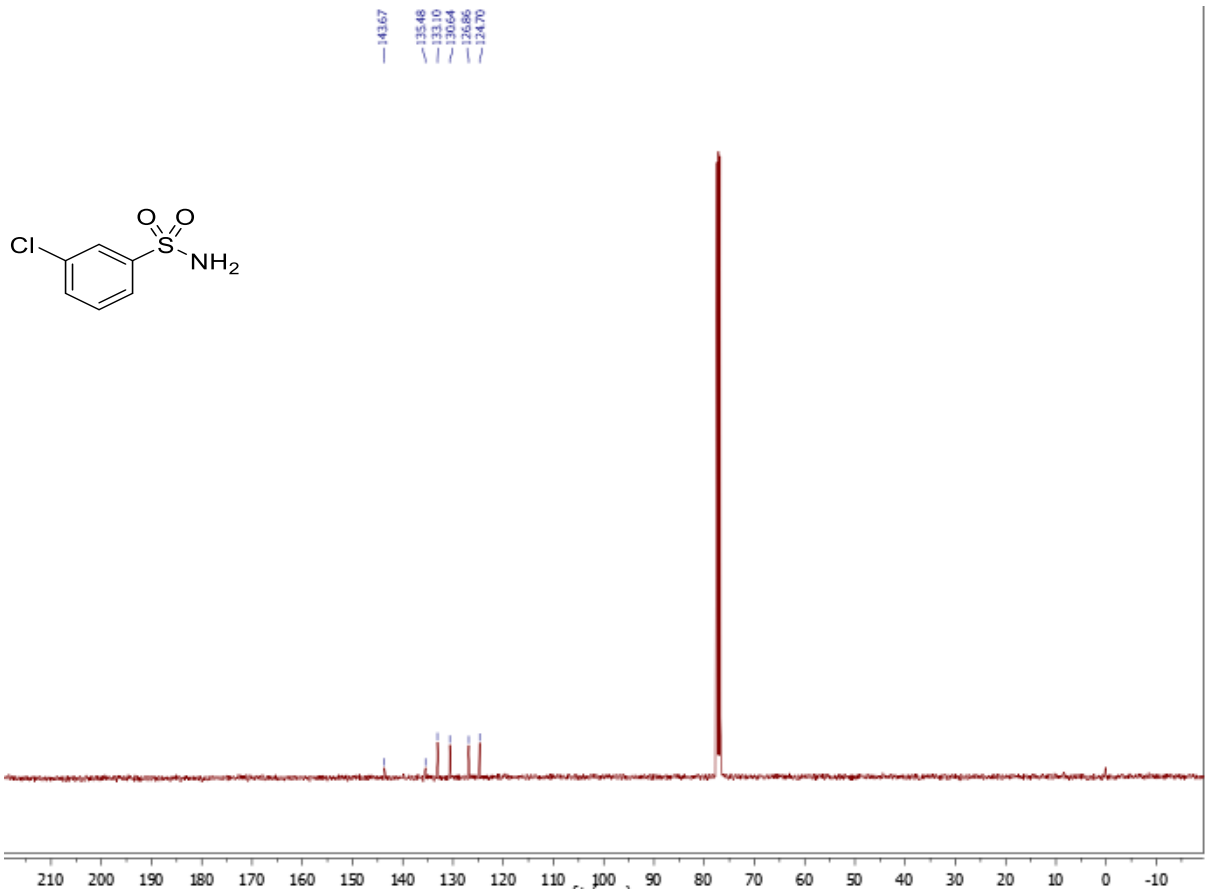
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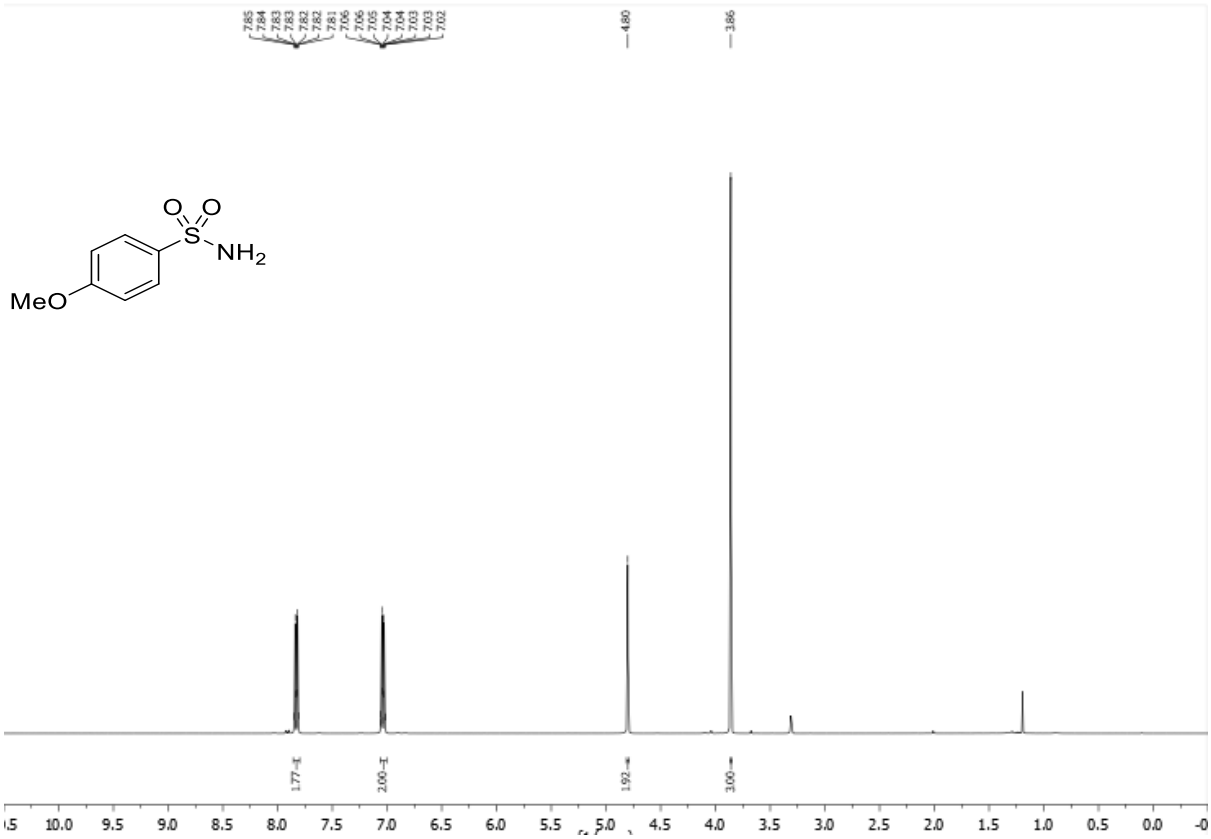
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O
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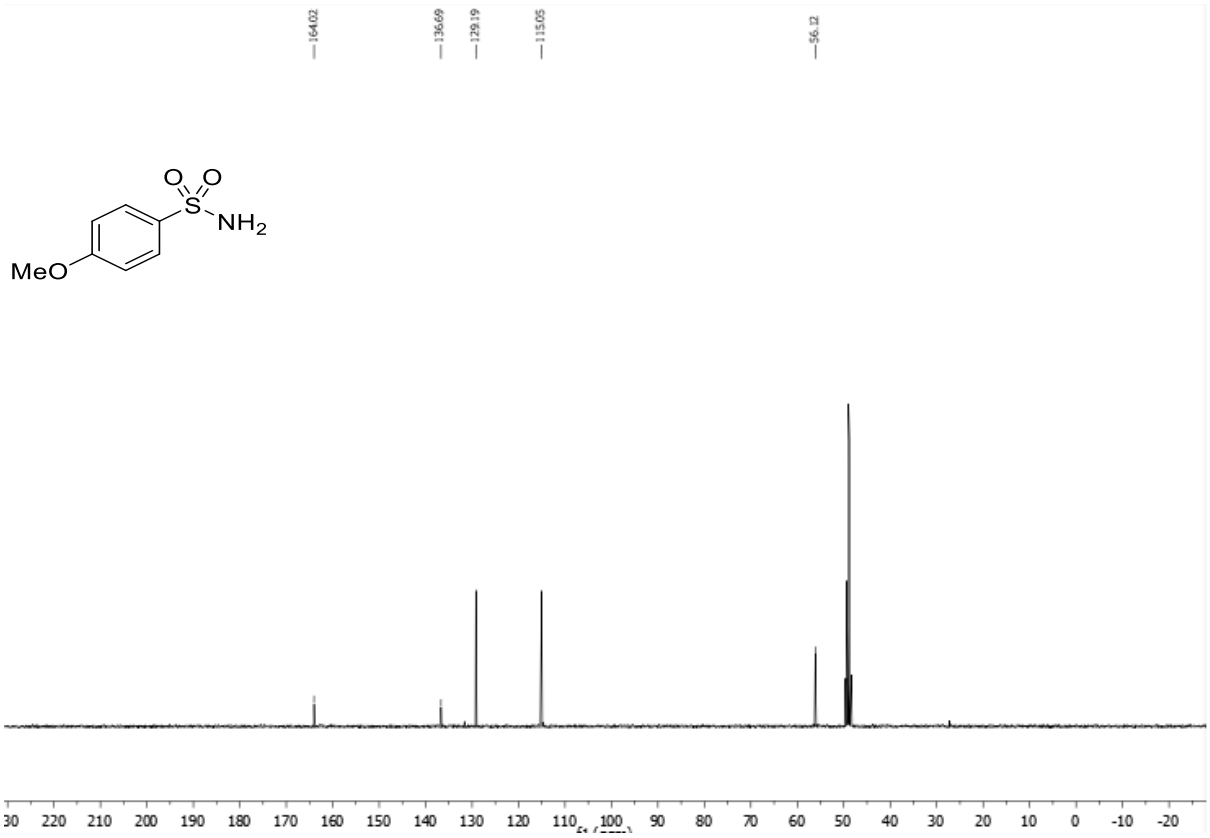
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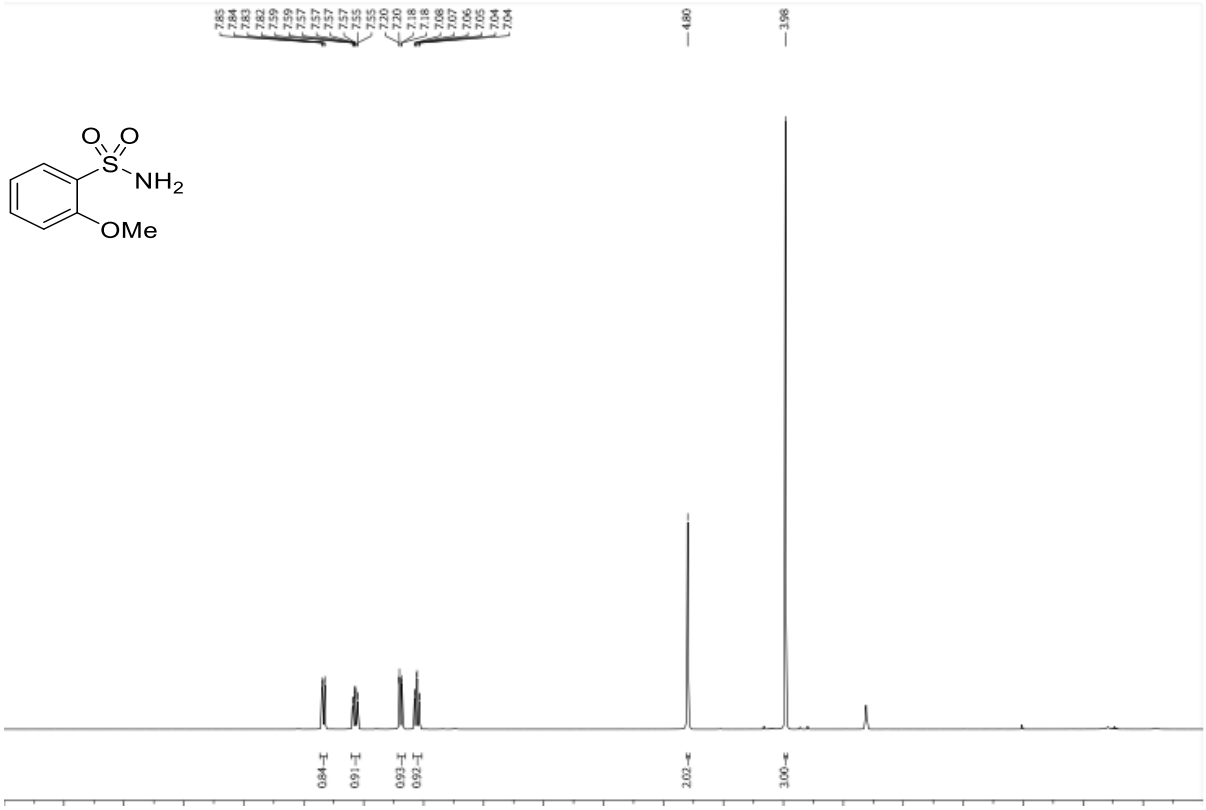
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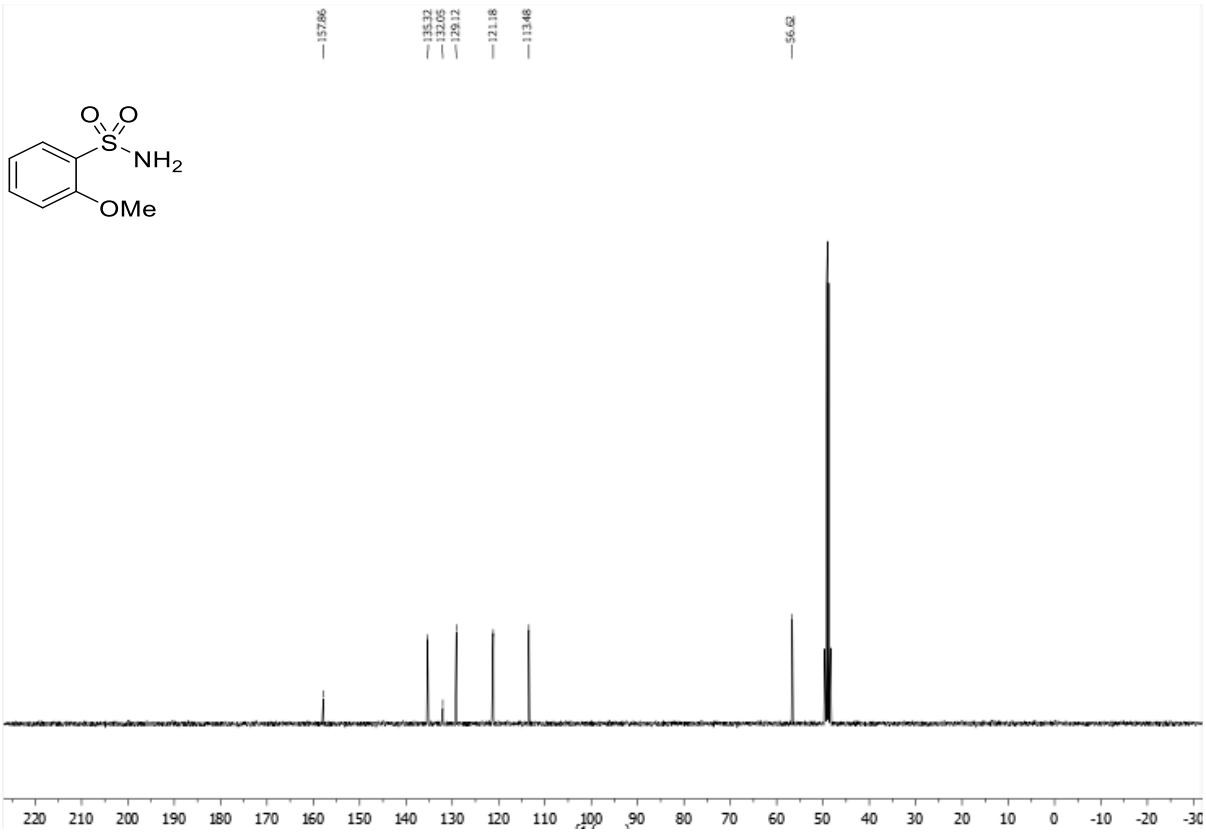
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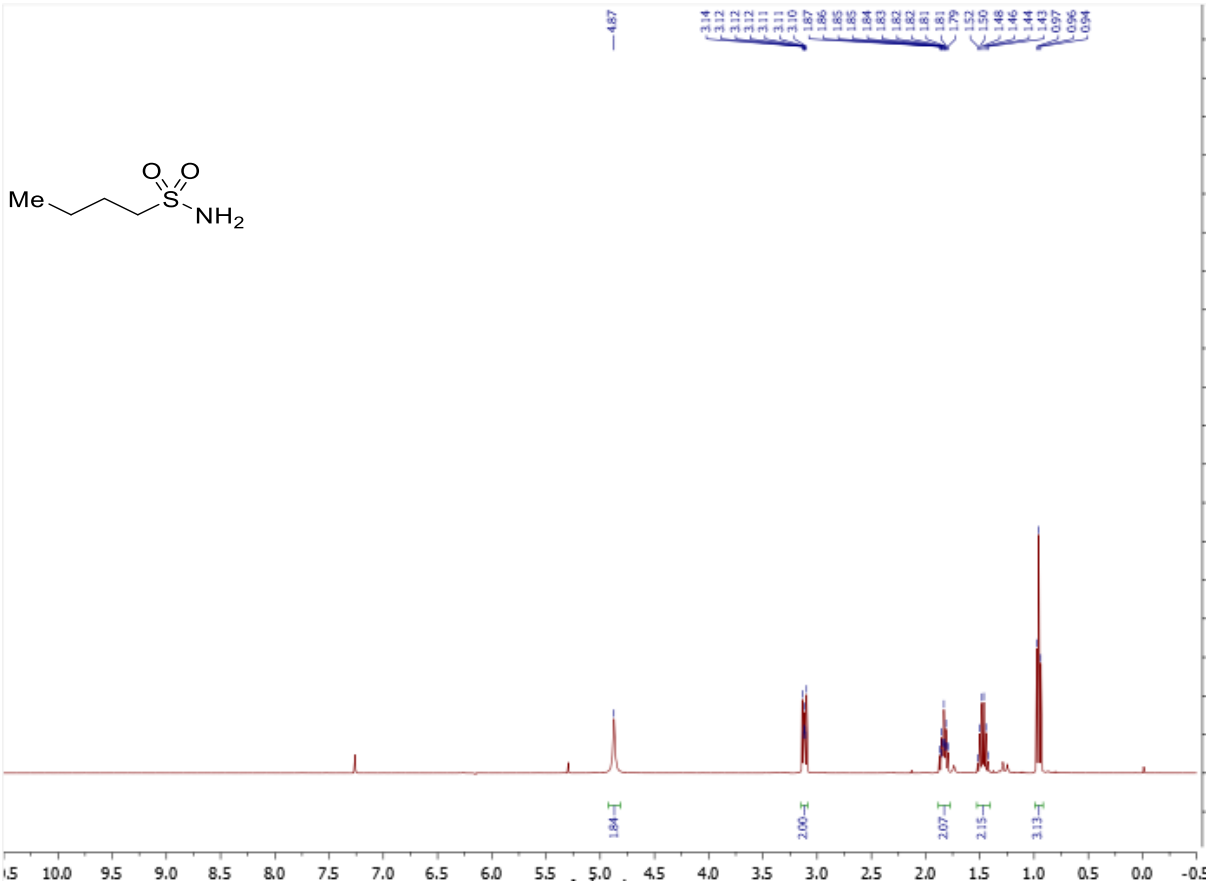
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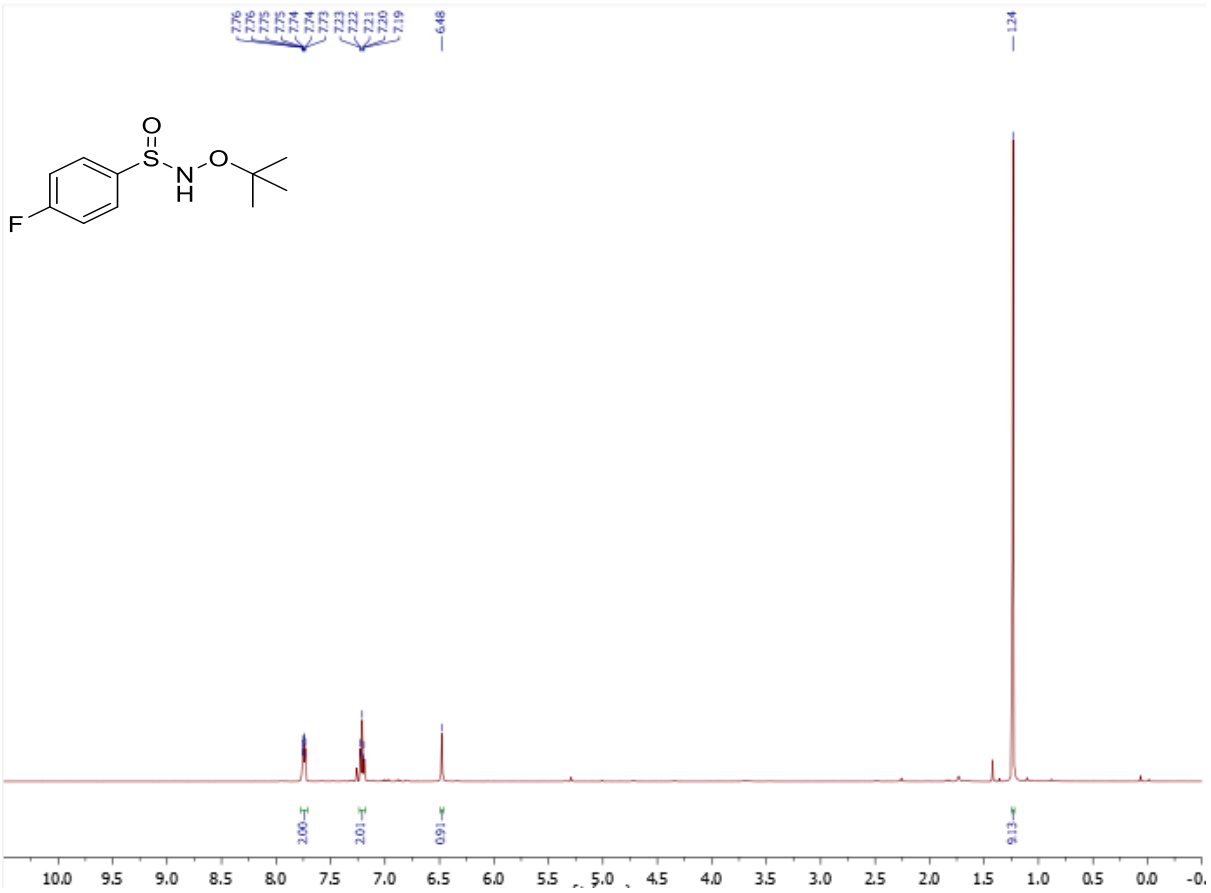
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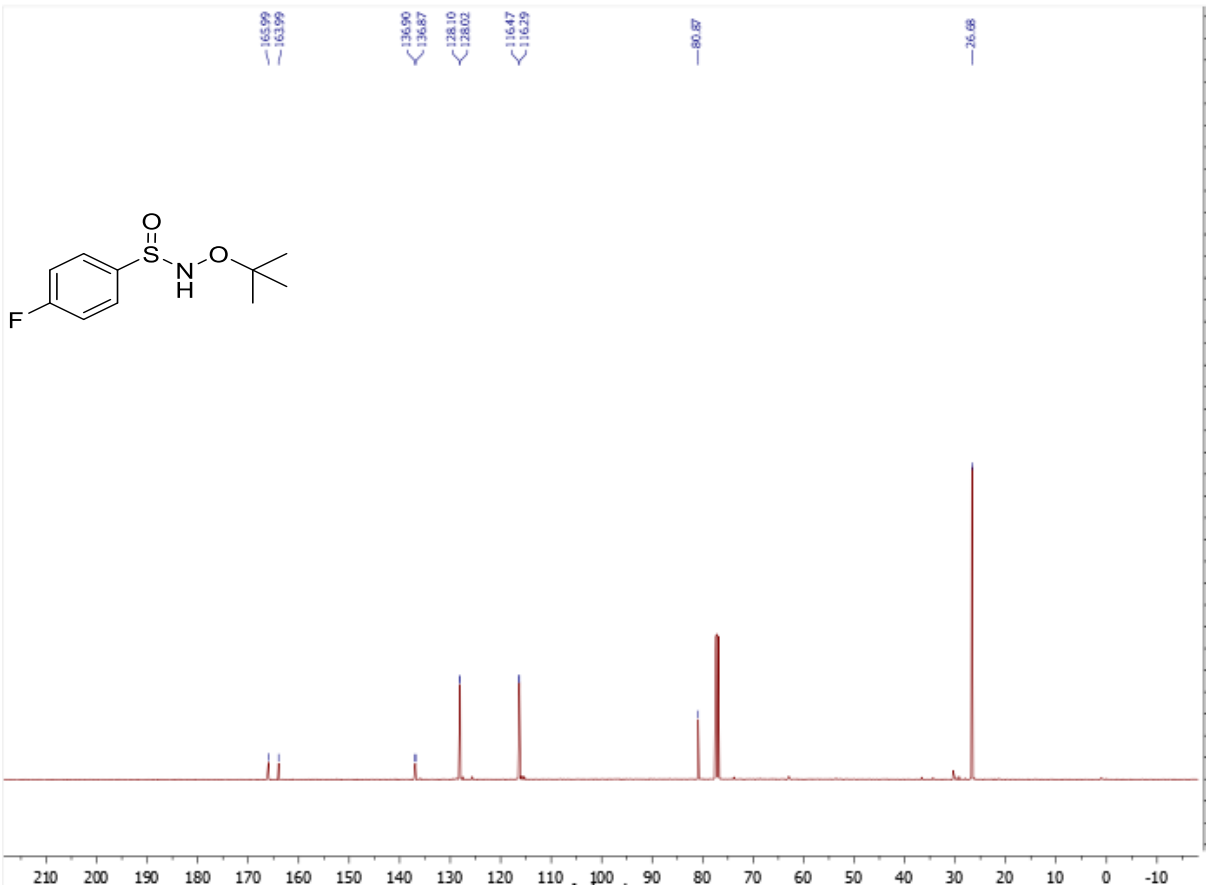
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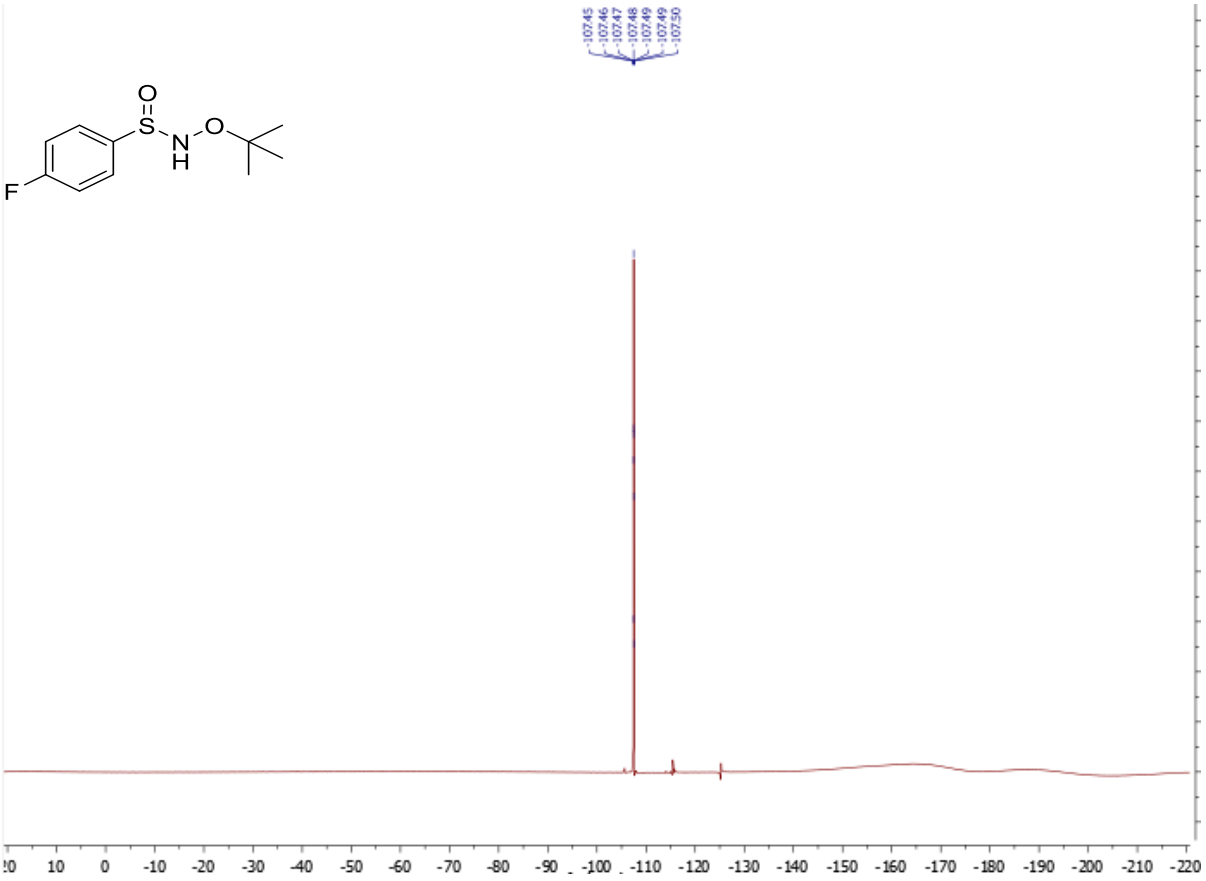
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