Applications of DABSO in metal catalysis

Charlotte S. Richards-Taylor

A thesis submitted for the degree of Doctor of Philosophy in Organic Chemistry

Hilary term 2014
Lincoln College
University of Oxford

Abstract

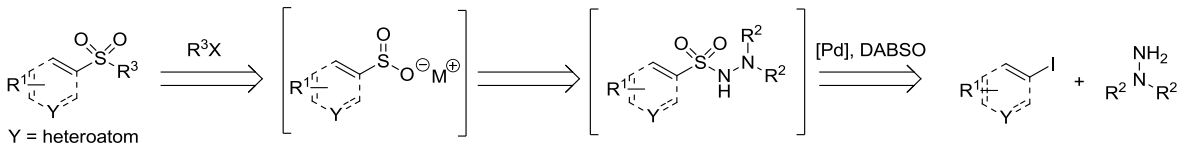
Applications of DABSO in metal catalysis

Charlotte Richards-Taylor, Lincoln College, Hilary term 2014

A thesis submitted for the degree of Doctor of Philosopy in Organic Chemistry

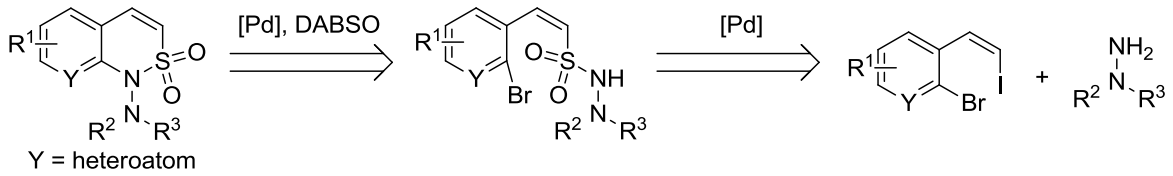
Chapter 1 discusses the importance of the sulfonyl moiety in biological compounds and the developments in the use of sulfur dioxide and sulfur dioxide donors in metal catalysis and organic synthesis.

Chapter 2 focuses on the serendipitous discovery, optimisation and exploration of a route towards the synthesis of sulfones *via* an *N*-aminosulfonamide intermediate exploiting both palladium-catalysed aminosulfonylation and the predisposition of *N*-aminosulfonamides to decompose to the sulfinate salt (Scheme 1).



Scheme 1

Chapter 3 investigates the synthesis of benzosultams with an aryl-N-SO_2 linkage. A range of benzosultams and its derivatives were prepared after optimisation of a synthetic sequence involving palladium-catalysed aminosulfonylation and a subsequent Buchwald–Hartwig coupling (Scheme 2).



Scheme 2

Chapter 4 describes efforts towards the synthesis of a benzosultam with an aryl-SO_2-N linkage through various precursors and metal-catalysed routes using DABSO as the sulfur dioxide source (Figure 1).

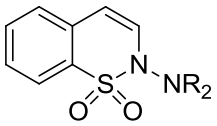
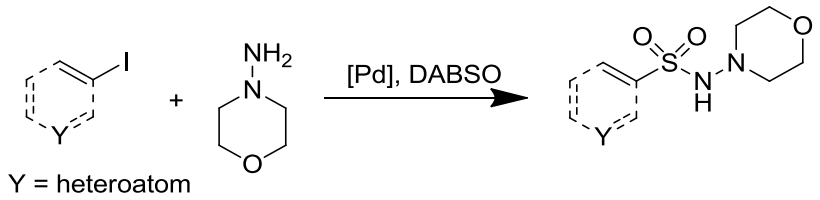


Figure 1

Chapter 5 provides a summary of this thesis and outlines possibilities for future work.

Chapter 6 provides experimental details and data for compounds discussed in this thesis.

Appendix A details a brief investigation into the synthesis of *N*-aminosulfonamides from heteroaryl iodides as an extension of the Willis group palladium-catalysed aminosulfonylation reaction (Scheme 3).



Scheme 3

Appendix B presents ^{1}H and ^{13}C NMR spectra as well as X-ray crystallographic data of key compounds.

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.

Charlotte Richards-Taylor

Hilary term 2014

Acknowledgments

My first and foremost thanks are to my supervisor Prof. Michael Willis for the opportunity to work in his group and the support and guidance he has given me over the course of my doctorate. I would also like to thank Dr. David Blakemore and Danny Ho from Pfizer Neusentis for their advice and encouragement. I am grateful to EPSRC, Pfizer and Lincoln College for financial support.

I thank all members of the Willis group, past and present, for a productive and friendly environment to work in. I am particularly grateful to Mat, Manu, Alex, Peng, Nate, Tom, James, Manjeet and Anais for taking the time to proof-read my thesis. I would also like to thank my lovely friend Sze-Kie for the proof-reading. I am very grateful to the NMR, mass spectrometry and CRL staff for their invaluable assistance. I am very grateful to Dr. Johannes Möller and Dr. Roger Johnson from the Department of Physics for the X-ray crystallographic analysis.

To my parents Andy and Suzannah and my brothers Alex and Seb, thank you for all the love and support. To Johannes, thank you for always being there for me.

Table of contents

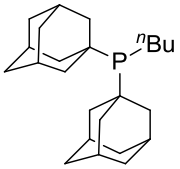
Abbreviations

Å	Angstroms
app	Apparent
aq	Aqueous
Ar	Aryl
B	Base
Bn	Benzyl
Boc	*tert*-Butylcarbonate
br	Broad
Bu	Butyl
°C	Degrees Celsius
Cata*CX*ium® A	Di(1-adamantyl)-*n*-butylphosphine
Cata*CX*ium® ABn	Di(1-adamantyl)benzylphosphine
Cata*CX*ium® PIn^{t}B	*N*-Phenyl-2-(di-*t*-butylphosphino)indol
cm^{-1}	Wavenumber
conc	Concentrated
COSY	COrrelation SpectroscopY
Cy	Cyclohexyl
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DABSO	1,4-Diazabicyclo[2.2.2]octane *bis*(sulfur dioxide)
DavePhos	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
dba	Dibenzylideneacetone
dd	Double doublet
dec	decomposition
DMAc	*N*,*N*-Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DMEDA	*N*,*N*′-Dimethylethylenediamine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DPEPhos	*Bis*(2-diphenylphosphino)phenyl ether
dppb	1,4-*Bis*(diphenylphosphino)butane
dppe	1,2-*Bis*(diphenylphosphino)ethane
dppp	1,3-*Bis*(diphenylphosphino)propane
δ_H	Proton (^{1}H) NMR chemical shift
δ_C	Carbon (^{13}C) NMR chemical shift
E	Electrophile
E	Entgegen
equiv.	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
FI	Field ionisation
g	Gram(s)
h	Hour(s)
Het	Heterocycle
Hex	Hexyl
HMQC	Heteronuclear Multiple Quantum Coherence

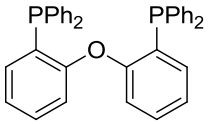
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
i	Iso
J	Coupling constant
L	Litre
L_n	Ligand(s)
lit.	Literature
m	Meta
m	Multiplet, milli (10^{-3}), metre
M	Molar/molarity
m/z	Mass to charge ratio
mCPBA	*meta*-Chloroperbenzoic acid
$[M]^+$	Molecular ion
$[M + H]^+$	Protonated molecular ion
$[M – H]^-$	Deprotonated molecular ion
Me	Methyl
mg	Milligram(s)
min	Minutes
mol	Moles
mp	Melting point
m/z	Mass to charge ratio
NIS	*N*-Iodosuccinimide
NMR	Nuclear magnetic resonance
o	*Ortho*
p	*Para*
Ph	Phenyl
ppm	Parts per million
Pr	Propyl
q	Quartet
QPhos	1,2,3,4,5-Pentaphenyl-1′-(di-tert-butylphosphino)ferrocene
quant	Quantitative
R	Generic group
RT	Room temperature
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
s	Singlet
sat.	Saturated
S_N	Nucleophilic substitution
t or *tert*	Tertiary
t	Triplet
TBAAc	Tetrabutylammonium acetate
TBAB	Tetrabutylammonium bromide
TBAC	Tetrabutylammonium chloride
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TFA	Trifluoroacetic acid
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography

Ts	Tosyl
tt	Triple triplet
µw	Microwave
Δ	Heat
ν_{max}	Frequency
Xantphos	9,9-Dimethyl-4,6-bis-(diphenylohpshino)-xanthane
^{t}Bu-Xantphos	9,9-Dimethyl-4,5-bis(di-*t*-butylphosphino)xanthene
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
Z	Zusammen

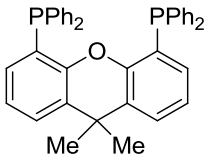
Ligands



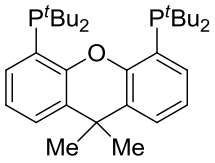
CataCXium® A



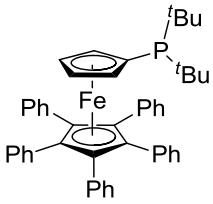
DPEPhos



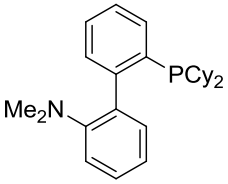
Xantphos



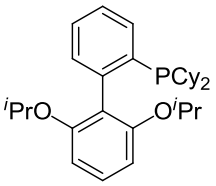
tBu-Xantphos



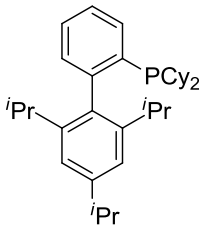
QPhos



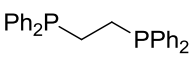
DavePhos



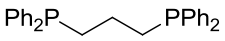
RuPhos



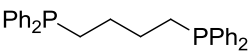
XPhos



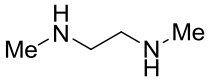
dppe



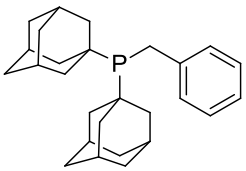
dppp



dppb



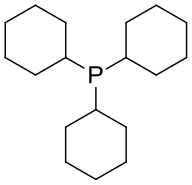
DMEDA



CataCXium® ABn

$^{t}Bu_3P.HBF_4$

Fu salt



PCy_3

Chapter 1

Introduction

The sulfonyl (–SO_2–) unit is abundant amongst many biologically active molecules where it is primarily found as either the sulfonamide or sulfone functionality.[1] As such, investigation into efficient and versatile routes towards the synthesis of sulfonyl containing compounds is an important area of research. The synthesis and applications of sulfones (Chapter 2) and sulfonamides (Chapters 3, 4 and Appendix A) are discussed in later chapters in this thesis. In this chapter, the various ways to introduce a sulfonyl moiety into organic molecules are discussed.

1.1 Sources of sulfur dioxide

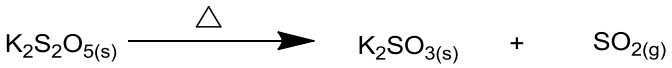
Sulfur dioxide is a colourless, toxic gas[2] that condenses at –10 °C to give a colourless liquid and forms white crystals at –75.5 °C. It is a covalent, planar molecule with a bent

structure (bond angle of 119° in the gas phase).[3] Sulfur dioxide is commonly produced by the combustion of sulfur or by the roasting of metal sulfide ores, such as pyrite and sphalerite, in fluidised bed furnaces at 650-1100 °C.[4] The most important commercial use of sulfur dioxide is the double-contact process, in which sulfur dioxide is converted to sulfur trioxide and then sulfuric acid. Sulfur dioxide can also be used as a reducing, bleaching, refrigerating agent, beverage and food preservative (E220), antioxidant or non-aqueous solvent.[5] A significant proportion of atmospheric sulfur dioxide, a primary cause of acid rain, is produced from the combustion of coal and oil.[6]

To insert a sulfonyl moiety into organic molecules, sulfur dioxide itself is most often used (see Sections 1.2 and 1.3). However, sulfur dioxide donors that avoid the need to directly use the toxic gas are becoming more commonly employed. The rest of this section will discuss sulfur dioxide donors, focusing on those that are utilised in organic transformations.

1.1.1 Inorganic sulfur dioxide donors

There are many sulfites in nature that are formed by the absorption of sulfur dioxide from the air. Consequently, the use of sulfites as a sulfur dioxide surrogate in organic transformations provides an environmentally benign process. Under various reaction conditions such as high temperatures, potassium metabisulfite ($K_2S_2O_5$) decomposes to sulfur dioxide gas (Scheme 1.1). It has recently been used as an effective sulfur dioxide donor in metal catalysis (see Section 1.2 for further details).[7,8,9] In 2014, the Beller and Wu group reported the use of Na_2SO_3 and H_2SO_4 as a source of SO_2 for a palladium-catalysed aminosulfonylation reaction.[10]



Scheme 1.1: Decomposition of potassium metabisulfite under high temperatures.

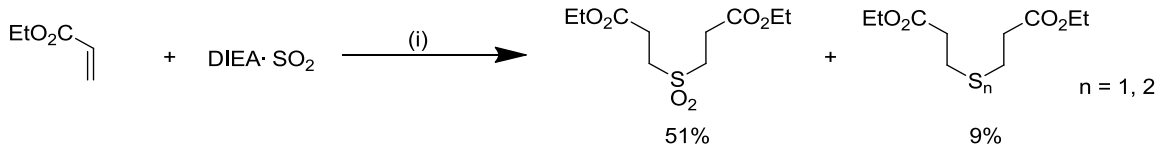
Similarly, other inorganic sulfites like sodium metabisulfite, sodium sulfite and sodium bisulfite, also release sulfur dioxide gas under certain reaction conditions, for example in the presence of a Brønsted acid. These sulfites are commonly used as sulfur dioxide donors in biological systems (see Section 1.1.3).

1.1.2 Organic sulfur dioxide donors

Sulfur dioxide is primed for forming charge-transfer complexes with a variety of electron donors, particularly with amines and aromatic hydrocarbons, due to its coordination properties.[11] Generally, the charge transfer weakens the bonds within the acceptor molecule, therefore becoming activated.[12] Experimental studies have shown that complexes of sulfur dioxide with NH_3, H_2O or H_2S involve an interaction between a lone pair orbital centred mainly on the N, O or S of the electron donor and the π^* orbital of sulfur dioxide located mainly on the S atom. The order of the strength of interaction is $H_2S < H_2O < NH_3$. In contrast, complexes of sulfur dioxide with HF or HCl have a hydrogen-bonding type interaction between a proton and one of the O atoms of the sulfur dioxide.[13]

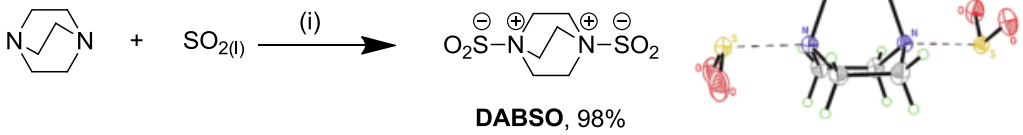
Amine-SO_2 complexes have been developed largely in order to investigate their structure and bonding properties.[14] They also have some applications as organic reagents and catalysts in organic synthesis. Olah and co-workers have used tertiary amine-SO_2 complexes extensively as organic reagents, for example in the dehalogenation of α-haloketones,[15] deoxygenation of sulfoxides[16] and pyridine *N*-oxides,[17] and as dehydrating

agents.[18] They have also designed a PVP(poly-4-vinylpyridine)·SO_2 complex as a mild acid catalyst for the Strecker synthesis of α-aminonitriles.[19] Eugène *et al*. discovered that the charge-transfer complex of DIEA and sulfur dioxide, DIEA·SO_2 forms a symmetrical sulfone and (di)sulfide upon reaction with a Michael acceptor (Scheme 1.2) and it can be used to reduce olefins.[20]



Scheme 1.2: Sulfonylation of a Michael acceptor by a DIEA and sulfur dioxide solution. *Reaction conditions*: (i) Michael acceptor (1 equiv.), DIEA·SO_2 (1.1 equiv.), DMAc, 80 °C, 2 h.

In the past, 1,4-diazabicyclo[2.2.2]octane *bis*(sulfur dioxide) (DABCO·SO_2 or DABSO – as referred to by the Willis group), prepared simply by condensing sulfur dioxide over sublimed DABCO, was primarily used for Raman spectroscopic investigations (Scheme 1.3).[21] It is an air-stable, white solid that has recently become commercially available.[22] The Willis group was the first to demonstrate its applications in organic transformations as an effective replacement for sulfur dioxide gas in both established and novel processes (see Sections 1.2 and 1.3).[23,24]



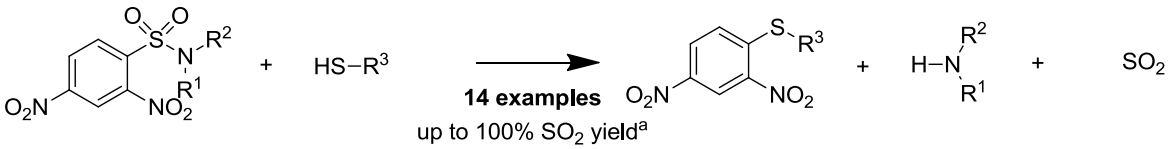
Scheme 1.3: Synthesis of DABSO. *Reaction conditions*: (i) –20 °C to –10 °C. X-Ray crystal structure of DABSO obtained by Dr. Isabel Marco and Dr. Amber L. Thompson (University of Oxford), with thermal ellipsoids shown at 50% probability; N...S distances are 2.0958(14) and 2.1732(15) A°.[24]

Other amine-sulfur dioxide charge-transfer complexes, for instance the known adducts $SO_2 \cdot NMe_3$ and $SO_2 \cdot$pyridine[14] as well as the novel adduct $SO_2 \cdot$4-aminomorpholine have also been investigated in the Willis group for their applications in catalysis.[25,26]

1.1.3 Sulfur dioxide donors in biology

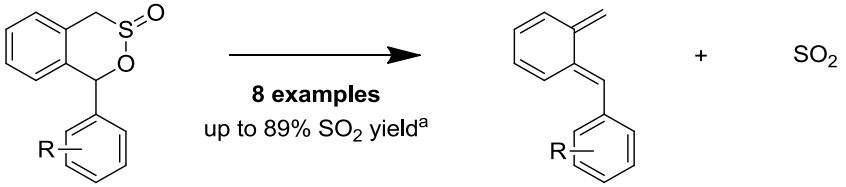
Sulfur dioxide is commonly used for its antimicrobial properties, hence its use as a preservative. In biological systems, sulfur dioxide gas cannot be used directly due to the lack of control in the rate it is released. As a result, alternative ways of releasing sulfur dioxide in a controlled manner have been investigated. Some of the most recent developments are described below.[27]

Inorganic sulfites such as sodium bisulfite or sodium bisulfite/sodium hydrogensulfite mixtures can be used as effective sulfur dioxide donors in biological systems.[28] Organic sulfur dioxide donors have also been developed. The Chakrapani group have designed pro-drug sulfonamides that allow for the controlled release of sulfur dioxide under physiological conditions (Scheme 1.4).[29] They found that reaction of 2,4-dinitrobenzenesulfonamides with a thiol produced sulfur dioxide. The bacteria *Mycobacterium tuberculosis* (*Mtb*) has a high concentration of a cysteine-derived thiol (mycothiol) that they were able to react with 2,4-dinitrobenzenesulfonamides, releasing sulfur dioxide intracellularly, consequently inhibiting *Mtb* growth.



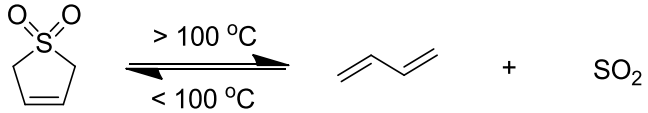
Scheme 1.4: Cysteine-mediated sulfur dioxide generation. [a] Yield of sulfur dioxide determined as a sulfite using an ion chromatograph attached with a conductivity detector, 30 minutes after treatment of the sulfonamide with 10 equivalents of cysteine in a pH 7.4 phosphate buffer.

The same authors have developed 1-aryl-benzosultine derivatives, which undergo cycloreversion upon dissolution at 37 °C in a phosphate buffer to deliver sulfur dioxide inside the cell, with the aim of investigating the role of sulfur dioxide as a gasotransmitter in human cells (Scheme 1.5).[30]



Scheme 1.5: Cycloreversion of 1-aryl-benzosultine derivatives to 1,3-dienes and sulfur dioxide. *Reaction conditions*: (i) Phosphate buffer, pH 7.4, 37 °C. [a] Yield of sulfur dioxide determined as a sulfite using an ion chromatograph attached with a conductivity detector.

Above 100 °C sulfolene decomposes to the gases 1,3-butadiene and sulfur dioxide through a *retro*-cheletropic process (Scheme 1.6).[31] This has been used in the production of biofuels and chemicals because sulfur dioxide in the presence of water can form sulfurous acid – a catalyst in the decomposition of lignocellulose in the plant cell wall of the perennial grass *Miscanthus* × *giganteus*.[32]



Scheme 1.6: Formation of sulfur dioxide from the decomposition of sulfolene which then forms sulfurous acid *in situ* that can deconstruct lignocellulosic biomass.

1.2 Applications of sulfur dioxide in metal catalysis

1.2.1 Sulfur dioxide in transition metal complexes

There are four main types of reaction between sulfur dioxide and metal centres: (1) sulfur dioxide binding to a metal centre, (2) sulfur dioxide binding to a ligand in a metal complex, (3) substitution of a ligand by sulfur dioxide, (4) insertion of sulfur dioxide into a M—H or M—C bond.

(1) *Sulfur dioxide binding to a metal centre.* There is a diverse range of coordination modes between sulfur dioxide and metal centres: coplanar MSO_2, pyramidal MSO_2, bridging MSO_2M or O,S-bonded SO_2 interactions.[33]

(2) *Sulfur dioxide binding to a ligand in a metal complex*. The binding of sulfur dioxide to a ligand in a metal complex is generally weak and usually reversible.[34] One of the first known examples of this interaction is the platinum complex $Pt(PPh_3)_2(CH_3)I{\cdot}SO_2$ where the sulfur dioxide is bound to the iodo-ligand.[35]

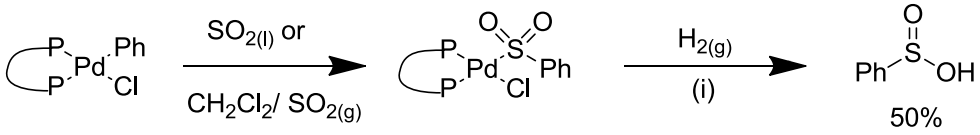
(3) *Substitution of a ligand by sulfur dioxide.* For example, the UV irradiation of *trans*-$(PEt_3)_2Fe(CO)_3$ in liquid sulfur dioxide gives *trans*-$(PEt_3)_2Fe(CO)_2(SO_2)$.[36]

(4) (a) *Insertion of sulfur dioxide into a M—H bond*. The first example of insertion of sulfur dioxide into a metal-hydride bond was by Kubas *et al.* who reported the synthesis of complexes such as $CpM(CO)_3(SO_2H)$ from $CpM(CO)_3H$, where M = Mo, W.[37]

(b) *Insertion of sulfur dioxide into a M—C bond.* The insertion reactions of CO with $MnMe(CO)_5$[38] and $Ru(Cl)(o\text{-Tol})(CO)(PPh_3)_2$[39] result in an acyl complex. Likewise, the insertion reactions of sulfur dioxide with the same complexes result in *S*-sulfinato complexes.[40] Intramolecular insertion of sulfur dioxide into the M—C σ bond can

occur following coordination of sulfur dioxide to an organometallic complex. Intermolecular insertion can also occur (without formation of an isolable complex).[41,42]

Pelzer *et al*. discovered the first example of a synthetic organic conversion of a transition metal sulfinato complex. They were able to synthesise a sulfinic acid by reaction of the sulfinato palladium complex [Pd(SO_2Ph)Cl(dppp)] with hydrogen (Scheme 1.7).[43] They developed catalytic versions, which are discussed in Sections 1.2.2 and 1.2.3.



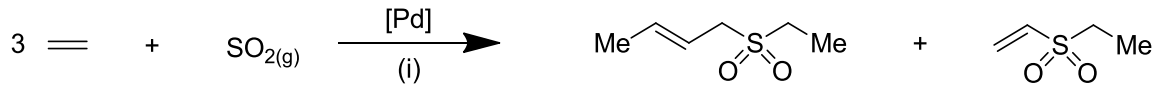
Scheme 1.7: Synthesis of a sulfinic acid from the palladium sulfinato complex. *Reaction conditions*: (i) RT, 4 h.

There is an extensive range of metal catalysis utilising carbon monoxide, particularly palladium catalysis.[44] As carbon monoxide and sulfur dioxide have related binding modes (both CO and SO_2 have been shown to be good π-bonding ligands towards low-valent transition metals),[45] which is indicative of comparable reaction behaviour, it is surprising that sulfur dioxide is not as well explored in metal catalysis. Interest in this area has recently grown, namely due to the use of sulfur dioxide donors. The rest of Section 1.2 will discuss the application of sulfur dioxide in metal catalysis.

1.2.2 Copolymerisation of alkenes and alkynes with sulfur dioxide

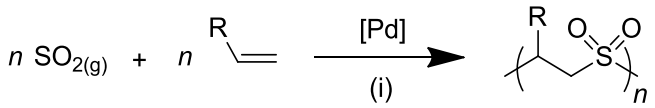
The first account of sulfur dioxide in transition-metal catalysis was in 1968 with the $PdCl_2$-catalysed reaction of ethylene with sulfur dioxide to afford *trans*-but-2-enyl sulfone and

ethyl vinyl sulfone (Scheme 1.8).[46] Klein suggested a possible mechanism involving a palladium hydride species generated from the small amount of water present in the reaction.



Scheme 1.8: Reaction of ethylene with sulfur dioxide. *Reaction conditions*: (i) $PdCl_2$, C_6H_6, 70 °C.

Copolymerisation of olefins with carbon monoxide catalysed by cationic palladium(II)-alkyl complexes is well known in the literature.[47,48] The same cationic palladium(II)-alkyl complexes also catalyse the alternating copolymerisation of ethene, propene and cyclopentene with sulfur dioxide, although carbon monoxide is an order of magnitude more reactive in these reactions (Scheme 1.9).[49,50]



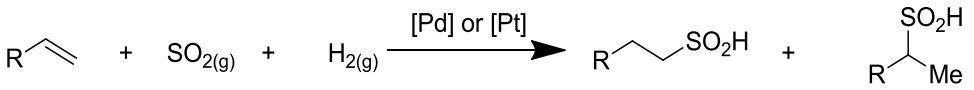
Scheme 1.9: Synthesis of an alkene-sulfur dioxide copolymer. *Reaction conditions*: (i) $[L_2Pd(Me)(MeCN)]BF_4$ (6 mol%), L = dppp, Me-Duphos, $CHCl_3$, 50 °C, 24 h.

Copolymerisation of an alkene or alkyne with sulfur dioxide can be carried out under a radical-initiated pathway,[51] although perfectly alternating copolymers are attained only when a palladium catalyst is employed.

1.2.3 Transition metal-catalysed hydrosulfination

Hydroformylation is a well-known reaction, whereas the comparable reaction with sulfur dioxide, hydrosulfination, has only been investigated over the last 20 years. The main reason for this being the rapid, radical-initiated polymerisation of alkenes with sulfur

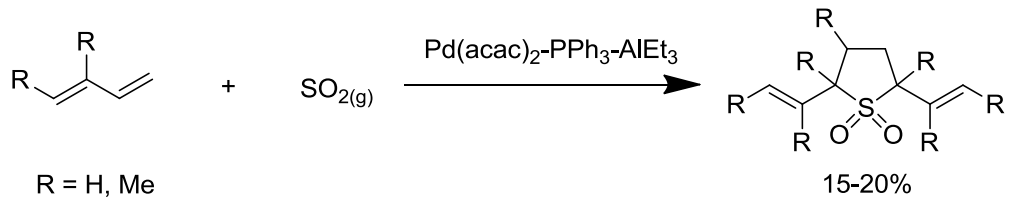
dioxide below the ceiling temperature T_c of the resulting copolymer (discussed in Section 1.2.2). Above the ceiling temperature T_c of the olefin/sulfur dioxide copolymer, the reaction of alkenes with sulfur dioxide and hydrogen provides the monomeric sulfinic acid (Scheme 1.10).[43,52] Palladium(II)- or platinium(II)-complexes with chelating diphosphines are used, with the palladium catalyst being more active than the corresponding platinum catalyst, although the platinum catalyst provides a higher *n*:*iso*-selectivity. The sulfinic acids are, however, unstable under standard reaction conditions and disproportionate to *S*-alkyl alkanethiosulfonates, alkane sulfonic acids and water.[53] This disproportionation can be suppressed by the addition of a small amount of a polar solvent, for example water or methanol.[52]



Scheme 1.10: Hydrosulfination to give the Markovnikov and anti-Markovnikov products. *Example reaction conditions*: (i) $[Pd(dppp)(MeCN)_2][BF_4]_2$, alkene (8 bar), SO_2/H_2 (25 bar), CH_2Cl_2/MeCN, 80 °C.

1.2.4 Sulfolane formation

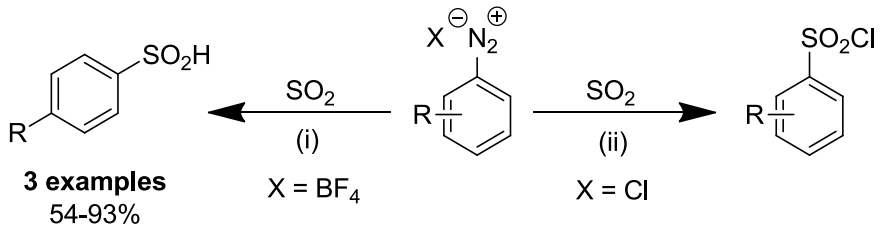
The $Pd(acac)_2$—PPh_3—$AlEt_3$ catalysed reaction of sulfur dioxide with conjugated dienes gives the 2,5-dialkenylsulfolanes in low yields of 15-20% (Scheme 1.11).[54,55] The low yield is possibly due to deactivation of the catalyst because of saturation of the palladium with sulfur dioxide. It was discovered that an excess of PPh_3 was necessary to give increased catalytic activity due to reaction of PPh_3 with sulfur dioxide to give a mixture of $Ph_3P{=}O$ and $Ph_3P{=}S$.



Scheme 1.11: Sulfolane formation.

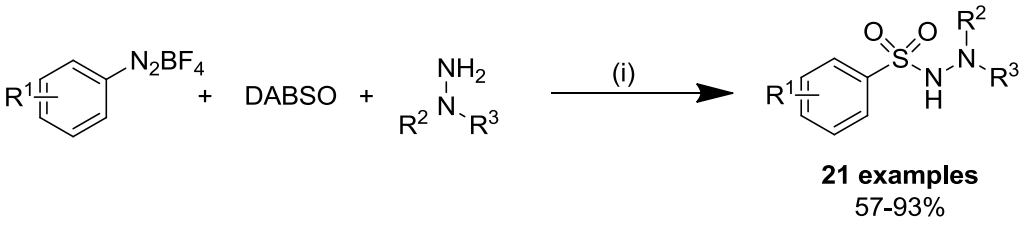
1.2.5 Reaction of diazonium salts with sulfur dioxide

In the late 1890s, Gatterman described the first synthesis of sulfinic acids from anilines that were diazotised in aqueous sulfuric acid and then converted to the final product with sulfur dioxide gas and overstoichiometric amounts of copper powder.[56] An improved method was reported by Pelzer and Keim for the synthesis of sulfinic acids from an aryldiazonium salt with sulfur dioxide and hydrogen gas under high pressure using a palladium catalyst (Scheme 1.12, (i)).[57] Sulfur dioxide gas can also be reacted with an aryl diazonium salt and catalytic copper chloride to give aromatic sulfonyl chlorides (Scheme 1.12, (ii)).[58]



Scheme 1.12: *Reaction conditions*: (i) 10% Pd/C, $SO_{2(g)}$ (2 bar), H_2 (30 bar), Et_2O/MeOH [0.06 M], RT; (ii) $CuCl_2$ (0.2-0.4 mol%), AcOH.

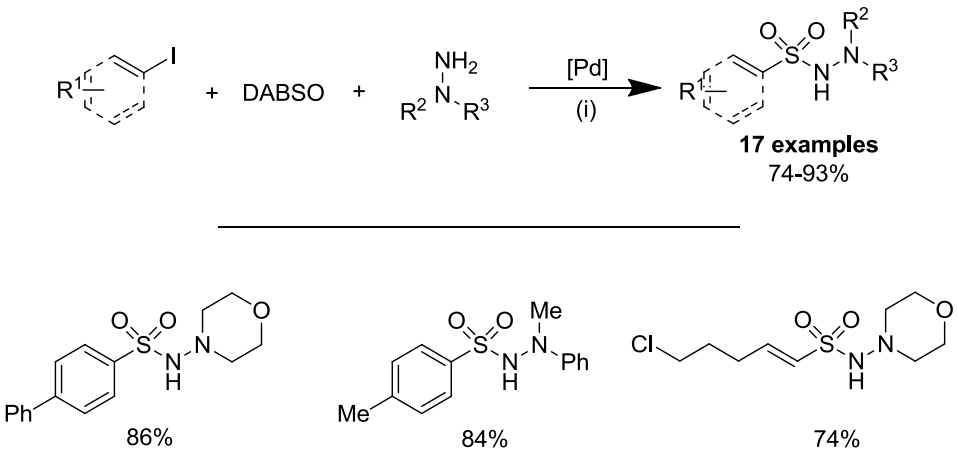
A recent breakthrough in this area was achieved by the Wu group who successfully synthesised aryl *N*-aminosulfonamides by the coupling of an aryldiazonium tetrafluoroborate, DABSO and hydrazine under metal-free conditions through a proposed radical process (Scheme 1.13).[59]



Scheme 1.13: Recent advancement in sulfur dioxide chemistry with diazonium salts. *Reaction conditions*: (i) Diazonium salt (1 equiv.), hydrazine (1.2 equiv.), DABSO (0.6 equiv.), MeCN [0.3 M], RT, 10 min.

1.2.6 Application of sulfur dioxide donors in metal catalysis

Guided by the analogy with palladium catalysed carbonylation chemistry, the Willis group pioneered the first palladium catalysed coupling of aryl iodides, hydrazines, and DABSO, to synthesise a range of *N*-aminosulfonamides (Scheme 1.14).[23] The equivalent reaction with sulfur dioxide gas was significantly less successful.

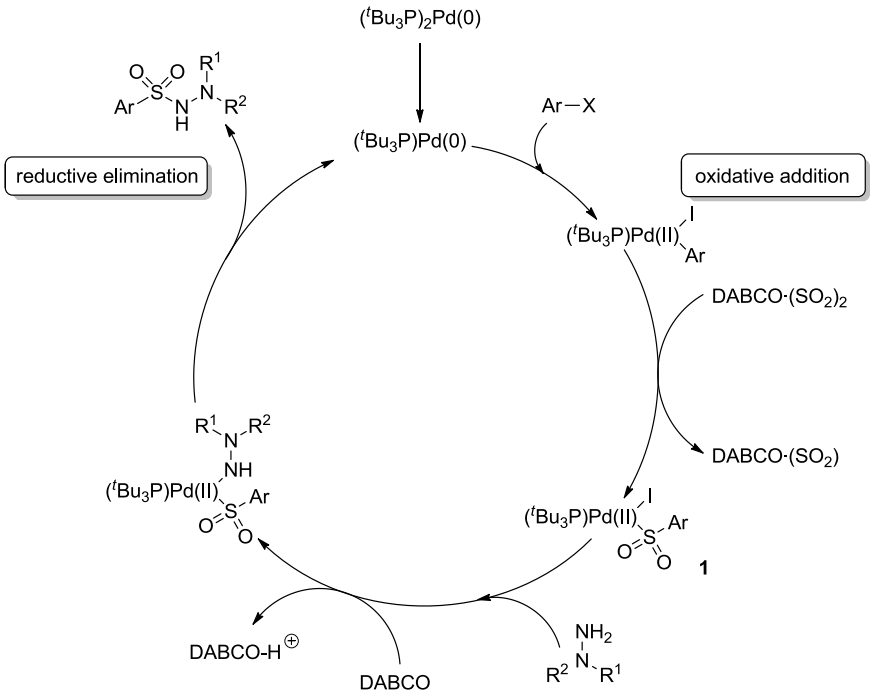


Scheme 1.14: *Reaction conditions*: (i) Iodosubstrate (1 equiv.), hydrazine (1.5 equiv.), $Pd(OAc)_2$ (10 mol%), $^tBu_3P.HBF_4$ (20 mol%), DABSO (0.6 equiv.) and DABCO (0.5 equiv.) or DABSO (1.1 equiv.) without DABCO, 1,4-dioxane [0.15 M], 70 °C, 16 h.

For electron-rich iodides, 0.6 equiv. of DABSO and 0.5 equiv. of DABCO were used; however, for slower-reacting substrates, such as those with electron-withdrawing groups,

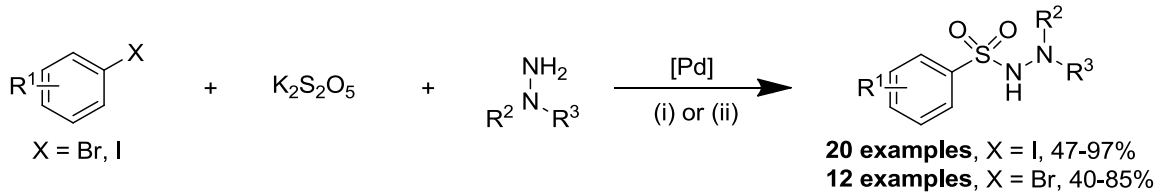
1.1 equiv. of DABSO without the addition of extra DABCO was found to be more fruitful. It was also possible to achieve the palladium catalysed aminosulfonylation by generating the amine·SO_2 complex *in situ*, although sulfur dioxide gas is then required. Several hydrazine coupling partners were successfully coupled; unfortunately, simple amines were unreactive under these reaction conditions. Aryl bromides gave reduced yields and increased temperatures were required.

By using palladium catalysed aminocarbonylation as a reference, a possible mechanism for the palladium catalysed aminosulfonylation reaction may be as shown in Scheme 1.15.[44(b)] Firstly oxidative addition occurs across the aryl-iodide bond and then sulfur dioxide insertion gives the sulfinato palladium complex **1**. Nucleophilic attack by the hydrazine and then reductive elimination provides the product *N*-aminosulfonamide and regenerates the Pd(0) catalyst. Alternatively, as also seen in some examples of carbonylation, direct attack of the hydrazine at the sulfur of the sulfinato palladium complex may also occur.



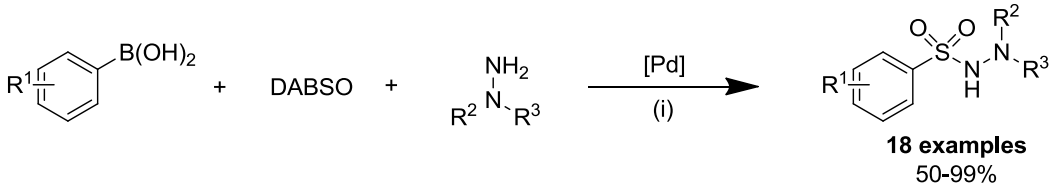
Scheme 1.15: Proposed mechanism for the palladium catalysed aminosulfonylation reaction employing DABSO as the sulfur dioxide source.

Following the publication of this work, the Wu group published two papers on the synthesis of *N*-aminosulfonamides.[7] They successfully achieved the palladium catalysed synthesis of *N*-aminosulfonamides from a combination of aryl iodides, hydrazine, and potassium metabisulfite in place of DABSO as the sulfur dioxide source (Scheme 1.16). With harsher reaction conditions, aryl bromides could also be used as the arylated partner. However, they provide no examples with alkenyl or heteroaryl halides.



Scheme 1.16: *Reaction conditions*: When X = I: (i) Aryl iodide (1 equiv.), $K_2S_2O_5$ (1 equiv.), hydrazine (1.2 equiv.), $Pd(OAc)_2$ (5 mol%), $^tBu_3P.HBF_4$ (10 mol%), HBF_4 (20 mol%), TBAB (1.5 equiv.), 1,4-dioxane [0.25 M], 80 °C, 12 h; when X = Br: (ii) Aryl bromide (1 equiv.), $K_2S_2O_5$ (2 equiv.), hydrazine (1.5 equiv.), $Pd(OAc)_2$ (10 mol%), $^tBu_3P.HBF_4$ (30 mol%), TBAB (1.5 equiv.), 1,4-dioxane [0.25 M], 100 °C, 12 h.

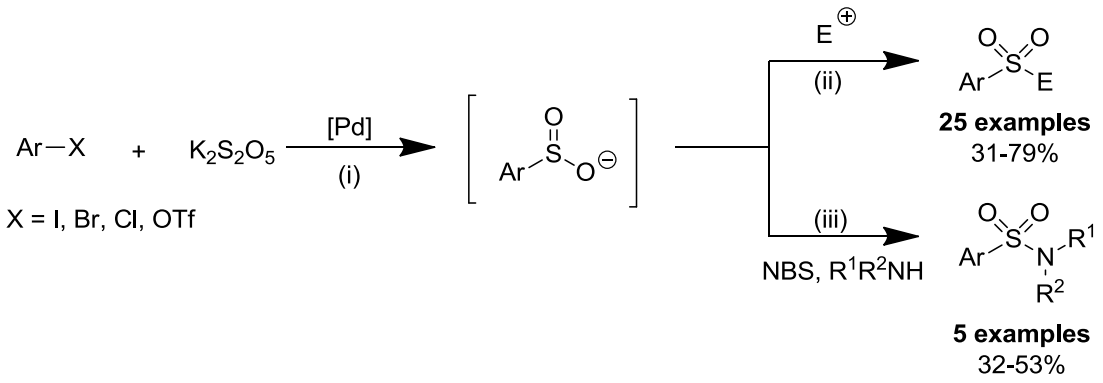
Additionally, they have also demonstrated that arylboronic acids can be used in the palladium catalysed aminosulfonylation reaction under oxidative conditions with the use of DABSO as the sulfur dioxide source (Scheme 1.17).[60]



Scheme 1.17: *Reaction conditions*: (i) Boronic acid (2 equiv.), DABSO (2 equiv.), hydrazine (1 equiv.), $Pd(OAc)_2$ (5 mol%), TBAB (1.5 equiv.), 1,4-dioxane [0.25 M], O_2, 80 °C.

Very recently, a group from Pfizer has reported the first palladium catalysed synthesis of a sulfinate salt from an aryl halide/triflate in the presence of potassium metabisulfite and sodium formate – as the sulfur dioxide and hydrogen donors respectively (Scheme 1.18).[8]

The sulfinate salt can be used directly to synthesise a wide range of sulfones and a small selection of sulfonamides.



Scheme 1.18: *Reaction conditions*: (i) Aryl halide/triflate (1 equiv.), $K_2S_2O_5$ (2 equiv.), TBAB (1.1 equiv.), NaO_2CH (2.2 equiv.), $Pd(OAc)_2$ (5 mol%), PPh_3 (15 mol%), phen (15 mol%), DMSO or MeCN [0.3 M], 70 °C, 3 h; (ii) Electrophile (1.5 equiv.), 23 °C, 18 h; (iii) NBS (2 equiv.), R^1R^2NH (2 equiv.), DMSO [0.6 M], 0 to 23 °C.

1.3 The organic chemistry of sulfur dioxide

The following section entails a brief summary of the applications of sulfur dioxide in non-transition metal catalysed organic synthesis.

1.3.1 Sulfination of organometallic reagents

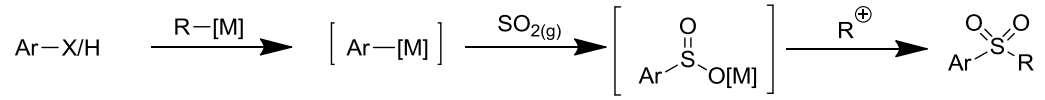
Metal sulfinates can be formed by the reaction of an organometallic compound with sulfur dioxide gas.[61,62] This has been widely utilised in the synthesis of sulfonyl chlorides by reaction of the metal sulfinate with an electrophilic chloride source[63] or in the synthesis of sulfones by reaction of the metal sulfinate with a range of electrophiles. Organozinc and

organolead compounds can also be used, but Grignard and organolithium compounds are preferably employed.[61(a)]

Direct transformation of an arene or aryl halide to a sulfone in one pot has been achieved by several groups utilising either direct lithiation of an arene or magnesium/lithium-halogen exchange of an aryl halide, with subsequent reaction with sulfur dioxide gas to obtain the desired metal sulfinate (Scheme 1.19, (A)).[64,65] As a more attractive alternative, the combination of an organometallic reagent with DABSO has been successfully achieved both in the Willis group and by a group from Pfizer to give an *in situ* metal sulfinate that can be reacted with a range of electrophiles, for example epoxides and iodonium salts, to give the corresponding sulfone (Scheme 1.19, (B)).[66,67]

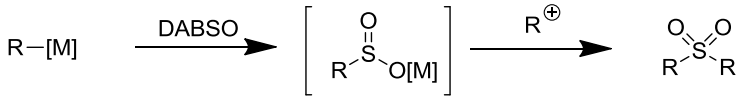
The Barrett group developed a one-pot synthesis of sulfonamides, by combination of aryl Grignard reagents and sulfur dioxide gas, with subsequent reaction with sulfuryl chloride and an amine (Scheme 1.19, (C)).[68] DABSO has also been successfully used as a replacement for sulfur dioxide gas in this reaction and the work was extended to include alkyl and alkenyl Grignard reagents as well as primary amines using either sulfuryl chloride or NCS as the electrophilic chloride source.[24,69] The yields were comparable to those from the original paper using sulfur dioxide gas.

(A) Preparation of metal sulfinates using sulfur dioxide gas



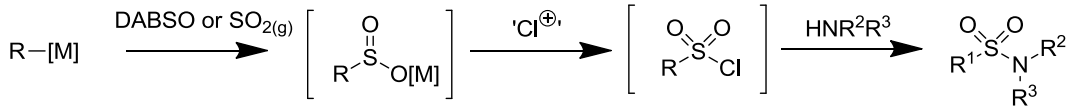
[M] = Li, MgX

(B) Combination of an organometallic reagent, DABSO and an electrophile



[M] = Li, MgX, ZnX

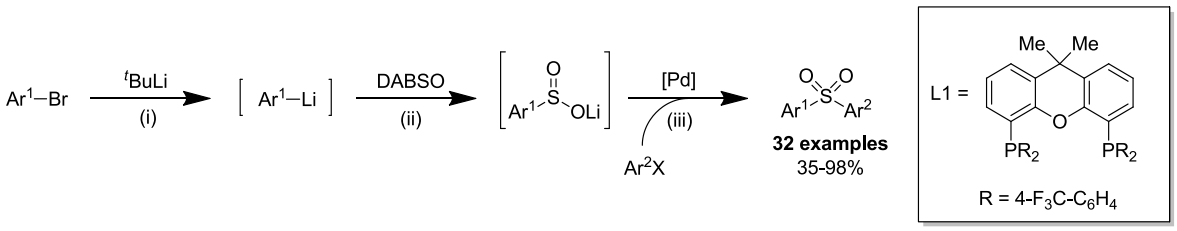
(C) Preparation of sulfonamides from an organometallic reagent, DABSO and an amine



[M] = Li, MgX

Scheme 1.19: Recent examples of the use of organometallics towards the synthesis of sulfonyl chlorides, sulfones and sulfonamides using either DABSO or sulfur dioxide gas.

The Willis group have also developed a palladium catalysed coupling of aryl (pseudo)halides and lithium aryl sulfinates to provide access to a range of diarylsulfones (Scheme 1.20).[70] This methodology employs DABSO as the sulfur dioxide source to generate the lithium sulfinate *in situ* from an aryl halide.



Scheme 1.20: *Reaction conditions*: (i) Aryl bromide (1 equiv.), ^{t}BuLi (2 equiv.), $^{n}Bu_2O$ [2.3 M], –10 °C to RT; (ii) DABSO (0.53 equiv.), 1,4-dioxane [0.25 M], RT, 2 h; (iii) $Pd(OAc)_2$ (7 mol%), L1 (7 mol%), Cs_2CO_3 (1.1 equiv.), Ar^2Br (0.7 equiv.), 110 °C, 16 h.

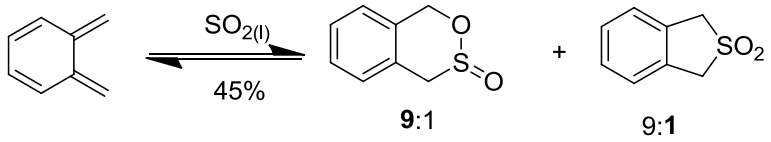
1.3.2 Friedel–Crafts sulfinylation

Friedel-Crafts sulfinylation of aromatic compounds to give aryl sulfinic acids can be achieved by passing sulfur dioxide gas through a mixture of the aromatic hydrocarbon, aluminium chloride and hydrogen chloride.[71]

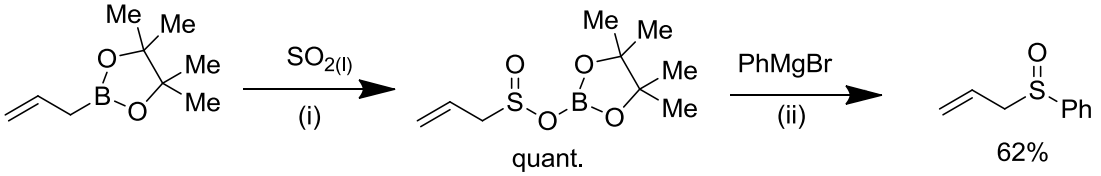
1.3.3 Pericyclic reactions with sulfur dioxide

Sulfur dioxide is used in several pericyclic reactions: the *hetero*-Diels-Alder reaction to give sultines (Scheme 1.21, (A)),[72] cheletropic reactions with dienes to give sulfolenes,[73] and also ene and metallo-ene reactions[41,74] (Scheme 1.21, (B)).[75] These reactions often require a large excess of sulfur dioxide. However, the Willis group was able to efficiently use DABSO in the cheletropic addition to 2,3-dimethylbutadiene to afford the sulfolene product (Scheme 1.21, (C)).[24]

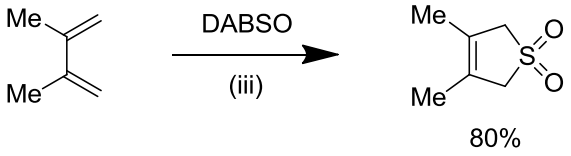
(A) An example *hetero*-Diels-Alder addition with sulfur dioxide



(B) An example metallo-ene reaction (bora-ene) with sulfur dioxide

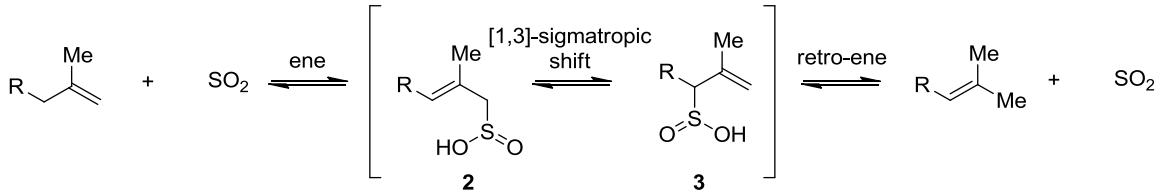


(C) An example cheletropic reaction using DABSO as the sulfur dioxide source



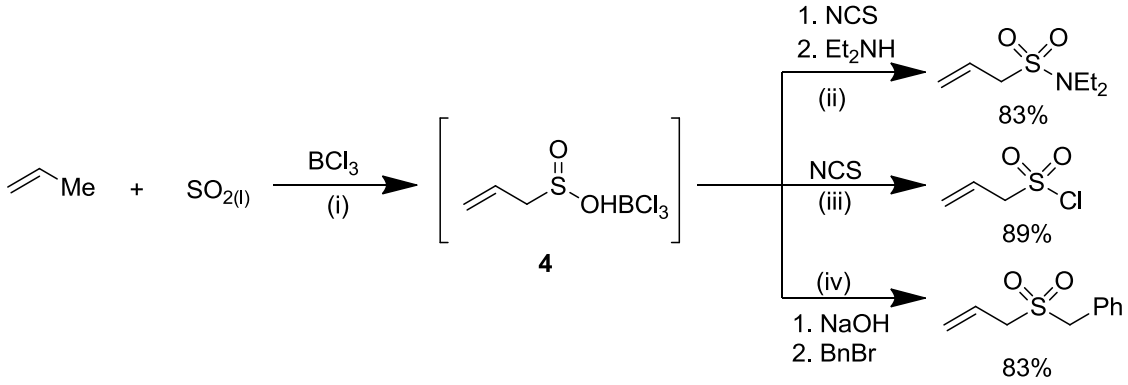
Scheme 1.21: Example pericyclic reactions of sulfur dioxide. *Reaction conditions*: (i) Allylboronic pinacolic ester (1 equiv.), CH_2Cl_2, –196 °C to –20 °C, 3 h; (ii) PhMgBr (1.1 equiv.), THF, –78 °C to 50 °C, 3.5 h;[74(b)] (iii) Diene (6 equiv.), DABSO (1 equiv.), 120 °C, 48 h.

Sulfur dioxide can induce double bond migration (Scheme 1.22). The mechanism for this reaction can be explained by an initial ene reaction, followed by a 1,3-sigmatropic shift (**2** to **3**) and then a *retro*-ene reaction.[76] The Vogel group suggest a radical process as a possible alternative mechanism. A polysulfone can be used to catalyse this reaction through a radical mechanism.[77] The isomerisation can also be induced by heating or UV irradiation in the presence of a catalytic amount of diphenylsulfone.[78]



Scheme 1.22: Proposed ene-mechanism for the alkene isomerisation with sulfur dioxide.[75]

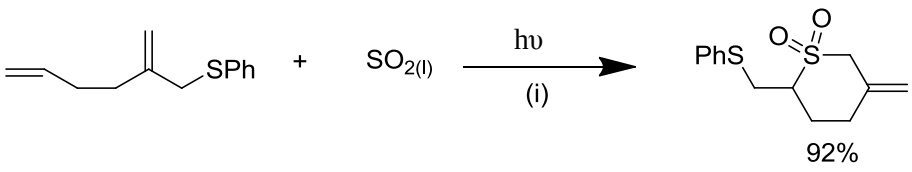
Marković *et al.* designed a one-pot, three-component synthesis of sulfonyl-containing compounds using a BCl_3-mediated ene reaction to prepare the intermediate sulfinate **4** (Scheme 1.23).[79]



Scheme 1.23: *Reaction conditions*: (i) CH_2Cl_2, –20 °C; (ii) NCS (1.1 equiv.), CH_2Cl_2, –20 °C to 20 °C, 2 h, then Et_2NH (1.2 equiv.), pyridine, –20 °C, 4 h; (iii) NCS (1.1 equiv.); (iv) NaOH (0.38 equiv.), H_2O/CH_2Cl_2, Bu_4NCl (10%), BnBr (1.2 equiv.), 12 h.

1.3.4 Radical reactions

Sulfur dioxide has also been used in radical reactions as it is a one-atom radical acceptor/donor, similar to carbon monoxide. Radical polymerisations, as described in Section 1.2.2, have been known since the 1940s.[51] Barton *et al.* used a thiohydroxamic ester to trap sulfur dioxide in a radical chain sequence.[80] Sulfur dioxide can act as a two-fold geminal radical acceptor in the *bis*-addition of perfluorinated nitroxides.[81] A recent example in this area is radical [*n* + 1] annulations to prepare cyclic sulfones, in which the *exo*- versus *endo*-selectivity is determined by either a linear or branched allylic sulfide terminating group (Scheme 1.24).[82]

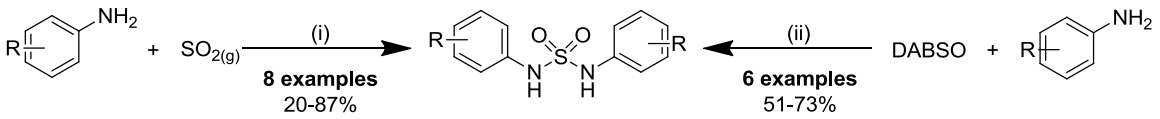


Scheme 1.24: An example radical [*n* + 1] annulation. *Reaction conditions*: (i) Alkene (1 equiv.), SO_2 (excess), hυ, PhSSPh (5 mol%), CH_2Cl_2, –78 °C to RT.

Terpolymers of sulfur dioxide, carbon monoxide and olefins can also be formed in the presence of free radical generating catalysts such as azo compounds.[83]

1.3.5 Miscellaneous reactions

Leontiev *et al*. were successful in the synthesis of *N*,*N*'-diarylsulfamides by combination of aniline, sulfur dioxide gas, iodine and pyridine (Scheme 1.25, (i)).[84] Through similar methodology they were also able to prepare shape-persistent sulfamide polymers from phenylenediamine. A significant drawback of this methodology is the need to employ approximately 100 equivalents of sulfur dioxide gas. The Willis group was able to replace the sulfur dioxide gas in this reaction with the easy-to-handle reagent DABSO, employing only two equivalents of DABSO (Scheme 1.25, (ii)).[24]



Scheme 1.25: *Reaction conditions*: (i) Aniline (1 equiv.), $SO_{2(g)}$ (~100 equiv.), Et_3N or pyridine (3 equiv.), I_2 (1 equiv.), MeCN, 2 h, RT; (ii) aniline (1 equiv.), DABSO (2 equiv.), I_2 (1.5 equiv.), MeCN, 0 °C to RT, 15 h.

Another small area of research using sulfur dioxide is the ring opening of epoxides and oxetanes by sulfur dioxide to give polysulfites by using a variety of Lewis bases as a catalyst.[85]

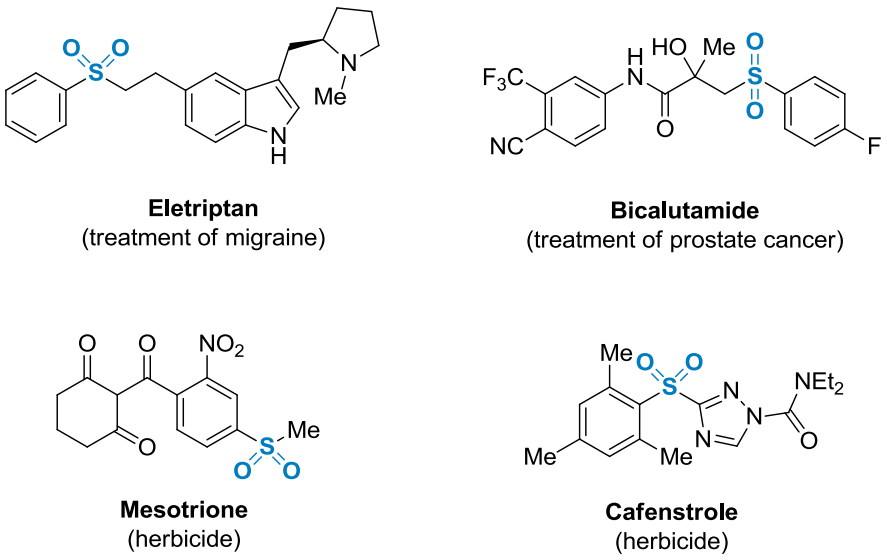
1.4 Conclusion

Sulfur dioxide has many applications in metal catalysis and organic synthesis although the majority of the research suffers from the toxicity and impracticality of the gas, as well as the large excess of sulfur dioxide often required. To expand this area of research a versatile sulfur dioxide analogue would be advantageous. Inorganic and organic sulfur dioxide donors overcome these problems as they supply an exact amount of sulfur dioxide and are operationally simple to use. The efficient synthesis of a large range of sulfonyl-containing compounds using these sulfur dioxide donors has become an expanding area of interest over the last four years. The rest of this thesis will describe the exploration of the sulfur dioxide donor, DABSO, in organic synthesis and catalysis to provide easy access to sulfonyl-containing compounds.

Chapter 2

Synthesis of sulfones

Sulfones, particularly aryl sulfones, are found in many biologically active molecules such as pharmaceuticals, including Eletriptan and Bicalutamide, as well as agrochemicals, for example the herbicides Mesotrione and Cafenstrole (Scheme 2.1).[86] They have been shown to inhibit various enzymatic processes, for example vinyl sulfones are known to inhibit cysteine protease[87] and diarylsulfones have been shown to inhibit HIV-1 reverse transcriptase.[88] Sulfones also have many industrial applications as they exhibit many interesting properties, for example polymers with sulfone functionalities often show good durability and structural properties.[89]



Scheme 2.1: Example biologically active sulfonyl-containing compounds.

Sulfones are also widely used in organic synthesis due to their versatility and easy removal. For example, in the Knoevenagel condensation,[90] Ramberg-Bäcklund reaction,[91] Sulfo-Cope rearrangement,[92] and as a lever to form C—C bonds in the Julia olefination reaction.[93] Additionally, β-hydroxy sulfones are utilised extensively for the preparation of lactones and 2,5-disubstituted tetrahydrofurans.[94] Futhermore, α,β-unsaturated sulfones are useful as Michael acceptors for a range of nucleophiles.[95]

2.1 Methodologies towards the synthesis of sulfones

As the sulfone functionality has a wide range of applications, the development of a convenient route to synthesise sulfones has been extensively investigated. In this section, both traditional routes and more recent developments towards the synthesis of sulfones are discussed.

2.1.1 Oxidation

Sulfones can be prepared by oxidation of the sulfoxide or sulfide.[96] Conventional oxidants include, among many others, H_2O_2,[97] MnO_2,[98] $KMnO_4$,[99] and $NaIO_4$.[100] This method has significant drawbacks. The oxidative conditions required limit the substrate scope as compounds containing oxidation-sensitive groups such as olefin, sulfide or amine functionalities are often incompatible under these conditions, despite the development of procedures to address some of these chemoselectivity issues.[101] This route can also suffer from under-oxidation giving mixtures of sulfoxides and sulfones.[102] In addition, the common starting material for a sulfoxide or sulfide is a thiol,[103] many of which are foul-smelling and there is limited commercial availability for alkenyl- or heteroaryl variants. Less commonly used starting materials, such as xanthates[104] and thiosilanes,[105] avoid the need for a thiol substrate.

2.1.2 Sulfonylation of arenes

Sulfonylation of arenes using an aryl sulfonyl halide[106] or an aryl sulfonic acid[107] often features harsh reaction conditions causing incompatibility with numerous functional groups. Various activators can be used, albeit often stoichiometrically, such as aluminium(III) chloride[106(a)] and zinc dust.[106(b)] Catalytic protocols have also been developed using iron(III) exchanged montmorillonite clay[108] and zeolites.[109] For unactivated aromatic rings, catalysts such as bismuth(III) triflate[110] and indium(III) triflate[106(c)] are found to be the most effective. Despite advances in this area, this methodology is inefficient for aromatic rings bearing strongly electron-withdrawing groups. In addition, the position the sulfonyl moiety is introduced depends on the

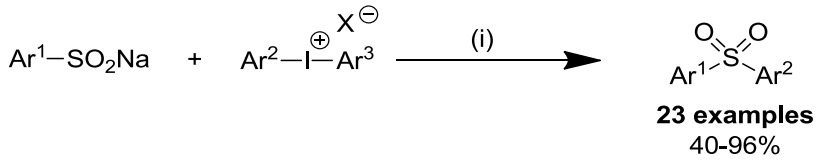
electronics and sterics of the aromatic ring, often resulting in mixtures of isomeric products.

2.1.3 Transition metal-free reaction with sulfinate salts

Alkyl-alkyl/aryl sulfones can be prepared by a nucleophilic displacement reaction between sulfinate anions and haloalkanes.[111,112] Sulfinate salts have extremely limited commercial availability, but can be prepared either by organometallic addition to sulfur dioxide gas with subsequent cation exchange[61(b)] or by reduction of the corresponding sulfonyl chloride.[113] These methods have significant disadvantages in that sulfur dioxide gas is toxic and sulfonyl chlorides can require multi-step procedures to synthesise, which often feature harsh reaction conditions.[114] Also, reduction of aliphatic sulfonyl chlorides is low yielding and suffers from contamination with other sulfur compounds.[62] The conjugate acids of sulfinate salts also tend to disproportionate (see Section 1.2.3).[115] As a result, the scope of sulfones prepared using sulfinate salt methodology is limited, typically employing only phenyl or *p*-tolyl sulfinate salts. Sodium sulfinate salts are most commonly used, although ammonium,[116] zinc,[67] and lithium[65] sulfinate salts also give high yields of sulfone products.

As described in Chapter 1, a group from Pfizer has very recently developed a synthesis of sulfones directly from the aryl halide or triflate using palladium-catalysis and potassium metabisulfite to synthesise the sulfinate salt *in situ* (Scheme 1.18).[8] However, this methodology generates the sulfones in only moderate yields.

Diarylsulfones can be prepared by coupling of a sulfinate salt with a highly activated haloarene.[117,118] A recent alternative uses a transition metal-free coupling of sodium sulfinates with diaryliodonium salts to afford the corresponding diarylsulfones (Scheme 2.2).[119,120]



Scheme 2.2: *Reaction conditions*: (i) Sodium sulfinate salt (1 equiv.), iodonium salt (1.1 equiv.), DMF, 90 °C, 24 h.[119]

Solvents such as DMSO,[121] polyethylene glycol[122] and water[112,123] are often used to address the solubility issues of sulfinate salts to give increased yields of the sulfone. It is thought these solvents improve both the solubility and nucleophilicity of the sulfinate salt.[121] Similarly, reactions can be performed more efficiently by using phase transfer catalysis.[111]

2.1.4 Organometallic sulfone synthesis

In 1925, Gilman reported the first reaction between aryl sulfonates and organomagnesium halides.[124] Subsequently, several groups exploited the use of organometallics in the synthesis of sulfones. In 1976, Baarschers discovered a novel sulfone synthesis by the coupling of sulfonate esters with organolithiums generating a range of sulfones.[125]

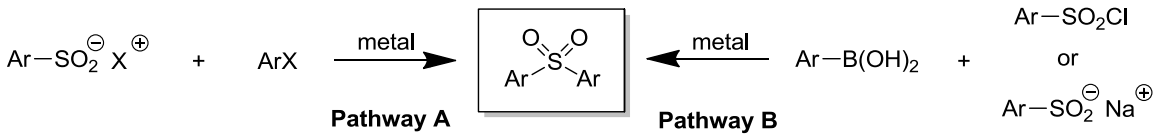
As mentioned in further detail in Section 1.3.1, metal sulfinates can be formed by reaction of an organometallic with sulfur dioxide gas or DABSO, which can then go on to react

with an electrophile to form a range of sulfones. Direct transformation of an arene or aryl halide to a sulfone in one-pot has been achieved by several groups.[64,65]

2.1.5 Metal-mediated sulfone synthesis

Palladium and copper catalysis has been extensively exploited in the synthesis of sulfones by the coupling of a sulfinate salt and an aryl (pseudo)halide (Scheme 2.3, pathway A). An early study by Suzuki showed a copper-assisted (1.5 equiv. of CuI) displacement of non-activated aryl iodides with arenesulfinates for the synthesis of diaryl sulfones.[126] A catalytic version was developed by Baskin *et al*. who used copper-catalysis to couple aryl iodides and sulfinic acid salts to synthesise diaryl and methyl sulfones.[127] Following on from this result, Zhu and Ma reported the coupling of aryl bromides with sulfinic acid salts.[128] Prompted by these results, Cacchi *et al*. developed a palladium catalysed coupling of aryl and alkenyl halides or triflates with sulfinic acid salts to synthesise diaryl and aryl vinyl sulfones.[129] A later report showed that tosylates could similarly be employed.[130] Building on from this, the Willis group have developed a palladium catalysed coupling of aryl halides and metal sulfinates which are generated by *in situ* combination of organolithiums and DABSO to provide access to a range of diaryl sulfones (Scheme 1.20).[70] The synthesis of diaryl sulfones by the palladium catalysed coupling of diaryliodonium salts and arenesulfinate salts was described by Zhou and Chen, although the sulfones were only obtained in moderate yields.[131]

Several groups have designed a palladium- or copper-catalysed sulfonylation of arylboronic acids with sulfonyl chlorides[132] or sulfinate acid salts[133] to prepare diaryl and alkyl-aryl sulfones (Scheme 2.3, pathway B).

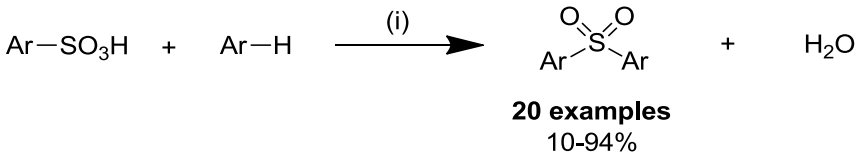


Scheme 2.3: Summary of metal-mediated sulfone synthesis.

The zinc-, telluride- or nickel-mediated coupling of sulfonyl chlorides with alkyl halides has been established, but requires activated halides and affords only moderate yields of sulfones.[134] Neumann and Wicenec have reported a route to diaryl sulfones by coupling sulfonyl chlorides with arylstannanes, although high reaction temperatures are required.[135]

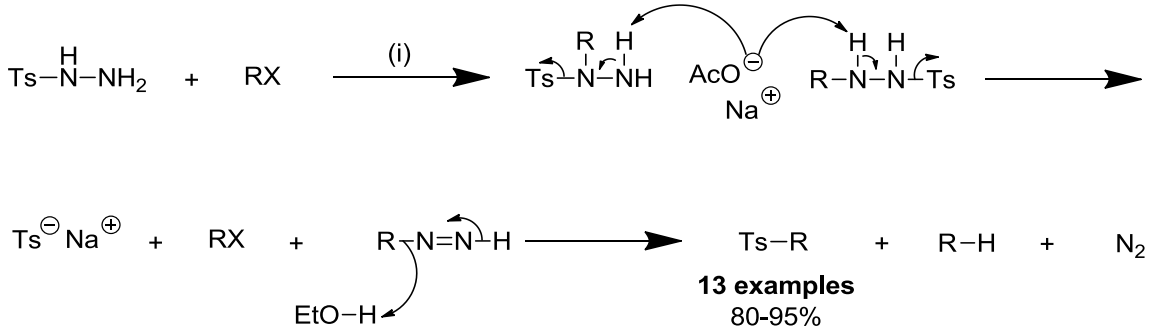
2.1.6 Sulfone synthesis through decomposition pathways

Dehydration of an aryl sulfonic acid and an aromatic hydrocarbon at elevated temperatures, or by a dehydrating agent such as phosphorus pentoxide, affords a range of diarylsulfones (Scheme 2.4).[107(a),136]



Scheme 2.4: *Reaction conditions*: (i) Sulfonic acid (1 equiv.), aromatic hydrocarbon (1 equiv.), polyphosphoric acid, 80 °C, 8 h.

Ballini *et al.* have reported a successful synthesis of sulfones by generation of a sulfinate anion *in situ* by decomposition of a tosyl hydrazide (Scheme 2.5).[137] However, only tosyl hydrazide was used as an example in the report.



Scheme 2.5: Proposed mechanism for sulfone formation from tosyl hydrazide. *Reaction conditions:* (i) Tosyl hydrazide (1 equiv.), RX (2 equiv.), NaOAc (6 equiv.), ethanol, 90 °C, 1-24 h.

2.1.7 Conclusion

Many of the methods to synthesise sulfones presented above are attractive because of their simplicity. Nevertheless, the lack of commercial availability of several of the starting materials and the harsh reaction conditions required reduces their scope of application. More recent advances, using metal-mediated synthesis are milder alternatives, although there is an opportunity for further development towards increased substrate scope and yields. Improved methods for the preparation of sulfones are therefore highly desirable that would enable easy variation of both groups attached to the sulfur dioxide linker.

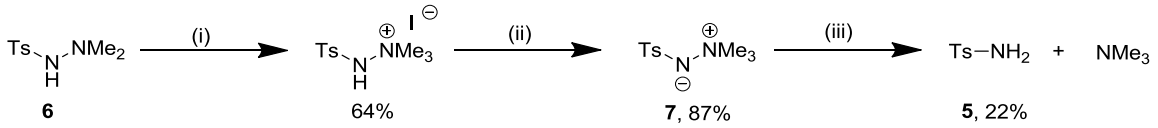
A sulfone synthesis based on the coupling of a sulfinate anion with an electrophile is a potentially useful pathway due to the wide range of electrophiles that can be successfully employed. The main challenge is to develop a route that avoids both the necessity of a sulfonyl chloride intermediate and the use of harsh reaction conditions.

2.2 Sulfone synthesis *via* an *N*-aminosulfonamide intermediate

2.2.1 *N*-Aminosulfonamide N—N bond cleavage

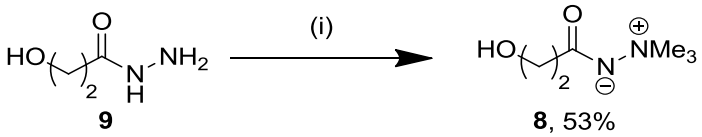
The Willis group palladium catalysed aminosulfonylation reaction with amines results in the recovery of starting material (see Chapter 1).[23] To address this limitation and to demonstrate the applicability of the reaction towards the synthesis of primary sulfonamides, investigation was undertaken into the cleavage of the N—N bond of the product *N*-aminosulfonamides.

Wawzonek *et al*. were able to form the primary sulfonamide **5** from the *N*-aminosulfonamide **6** through methylation and then deprotonation to give aminimide **7** and then subsequent reduction (Scheme 2.6).[138]



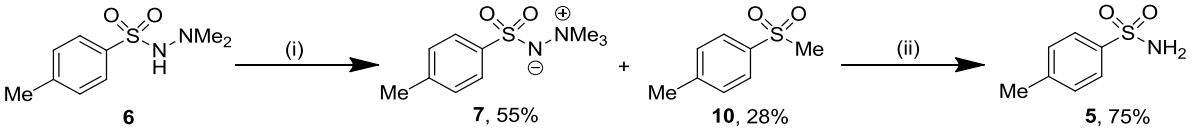
Scheme 2.6: Literature precedent for *N*-aminosulfonamide N—N bond cleavage. *Reaction conditions*: (i) MeI (15 equiv.), reflux, 22 h; (ii) 10% NaOH; (iii) Zn, AcOH, H_2O, reflux, 3 h.

In a related report, Musuyama *et al*. were able to form the aminimide **8** from the amide **9** in a one-pot methylation and deprotonation sequence (Scheme 2.7).[139]



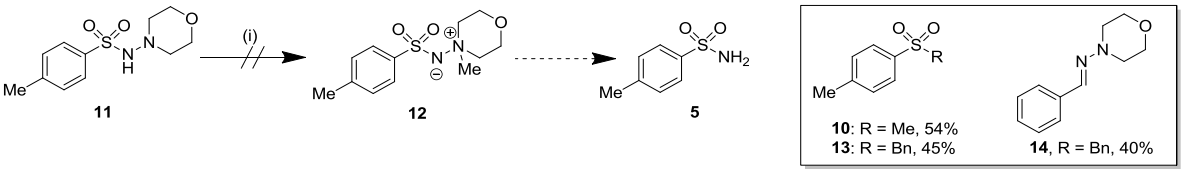
Scheme 2.7: Literature precedent for aminimide formation from an amide. *Reaction conditions*: (i) MeI (6 equiv.), K_2CO_3 (2 equiv.), MeOH, reflux, 8 h.

Following these reaction conditions, the *N*-aminosulfonamide **6** successfully gave the aminimide **7** in a 55% yield in a one-pot methylation and deprotonation reaction. The N—N bond was then cleaved with zinc and acetic acid to give the corresponding primary sulfonamide **5** (Scheme 2.8). Interestingly, an unexpected side-product from the first step was the sulfone **10**. The yield of the sulfone side-product **10** increased with higher temperatures. To minimise production of the side-product, the reaction was undertaken at room temperature. Reactions conducted below room temperature only resulted in decreased yields of both products.



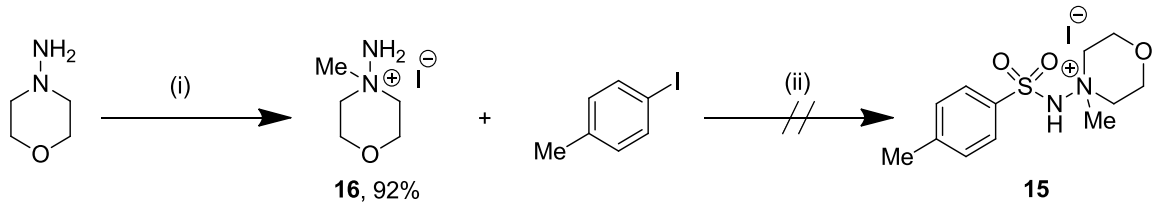
Scheme 2.8: *Reaction conditions*: (i) MeI (6 equiv.), K_2CO_3 (2 equiv.), MeOH [0.17 M], RT; (ii) Zn, AcOH [0.09 M], RT, 2 h.

The N—N bond cleavage reaction conditions were then applied to the *N*-aminosulfonamide **11** (Scheme 2.9). Instead of the desired aminimide product **12**, only sulfone **10** was formed. At lower temperatures, the aminimide was still not observed. This result was investigated further by reaction of the *N*-aminosulfonamide **11** with benzyl bromide to give the corresponding benzyl sulfone **13**, as well as the hydrazone **14**. An analogous hydrazone by-product was not detected in the previous reaction with methyl iodide.



Scheme 2.9: *Reaction conditions*: (i) MeI (6 equiv.) or BnBr (6 equiv.), K_2CO_3 (2 equiv.), MeOH [0.17 M], reflux, 24 h.

Attempts to prepare the *N*-aminosulfonamide salt **15** by the palladium catalysed coupling of 4-iodotoluene, DABSO and the *N*-amino-*N*-methylmorpholinium salt **16** were met with no success (Scheme 2.10).



Scheme 2.10: *Reaction conditions*: (i) MeI (1 equiv.), THF [1.7 M], 0 °C, 30 min; (ii) 4-Iodotoluene (1 equiv.), *N*-amino-*N*-methylmorpholinium salt **16** (1.5 equiv.), $Pd(OAc)_2$ (10 mol%), $^tBu_3P.HBF_4$ (20 mol%), DABSO (0.6 equiv.), DABCO (0.5 equiv.), 1,4-dioxane [0.15 M], 70 °C, 16 h.

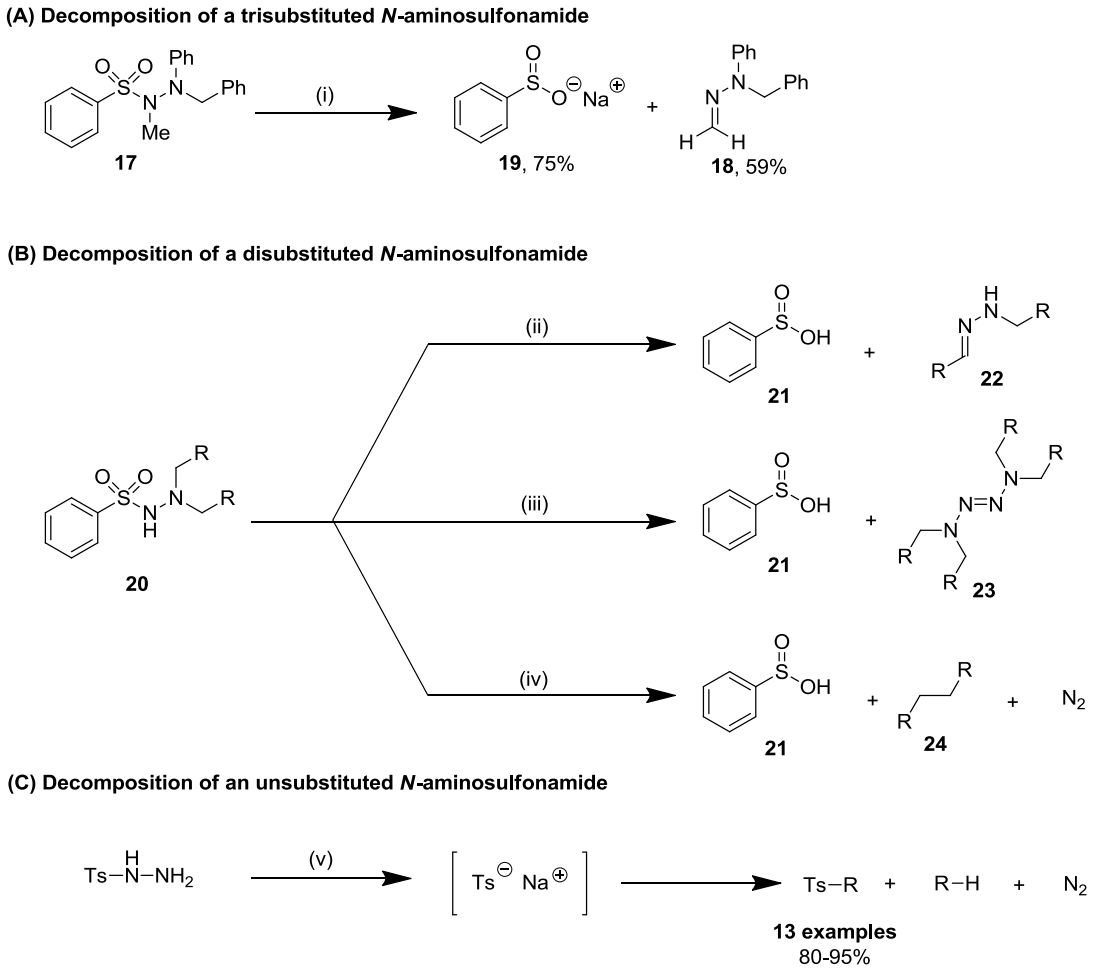
2.2.2 Literature precedent for aminosulfonamide decomposition to a sulfinate salt

The generation of the sulfone side-product from the reaction of *N*-aminosulfonamide under basic reaction conditions suggests that a sulfinate salt is formed *in situ* and then goes on to react with the electrophile present. *N*-Aminosulfonamide decomposition to a sulfinate salt is known in the literature. Dornow and Bartsch have demonstrated that the trisubstituted *N*-aminosulfonamide **17** can undergo base-induced elimination to give the hydrazone **18** and sodium sulfinate salt **19** (Scheme 2.11, (A)).[140] The fact that the hydrazone side-product **14** was observed in the reaction of *N*-aminosulfonamide **11** with benzyl bromide, suggests that a trialkylated aminosulfonamide intermediate is formed which then fragments to a sulfinate salt and a hydrazone.

Disubstituted *N*-aminosulfonamides **20** are also known to decompose in the presence of base to form a sulfinic acid leaving group **21** and either a hydrazone **22**, tetrazene **23**, or

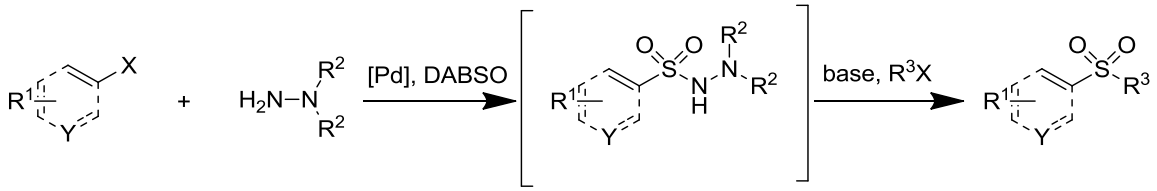
hydrocarbon **24** with evolution of nitrogen gas, depending on the *N*-substituent and the reaction conditions (Scheme 2.11, (B)).[141]

Additionally, unsubstituted *N*-aminosulfonamides have also been exploited to generate a sulfinate anion which is then reacted with an electrophile to give the corresponding sulfone (mechanism described in Scheme 2.5, Scheme 2.11 (C)).[137]



Scheme 2.11: Precedent for aminosulfonamide decomposition to a sulfinate salt. *Reaction conditions*: *N*-Aminosulfonamide (1 equiv.); (i) NaO^{i}Pr, ^{i}PrOH, RT; (ii) NaOH, diethylene glycol, 25 °C; (iii) NaOH, tetraglyme, 110-120 °C; (iv) $NaOH_{(aq)}$, 70-90 °C; (v) RX (2 equiv.), NaOAc (6 equiv.), ethanol, 90 °C, 1-24 h.

The proposed generation of the sulfinate salt from an *N*-aminosulfonamide could provide advantages over traditional methodology towards the synthesis of sulfones as it avoids both the necessity of a sulfinate salt or thiol starting material and also the use of harsh reaction conditions. The sulfinate salt formed could potentially be reacted with a wide range of electrophiles.[142] It was envisaged that this could potentially be an attractive methodology to synthesise a broad library of sulfones from commercially or readily available aryl, heteroaryl or alkenyl halides through an *N*-aminosulfonamide intermediate (Scheme 2.12).



Scheme 2.12: A potential one-pot synthesis of sulfones from the aryl-, heteroaryl- or alkenyl halide *via* an *N*-aminosulfonamide intermediate.

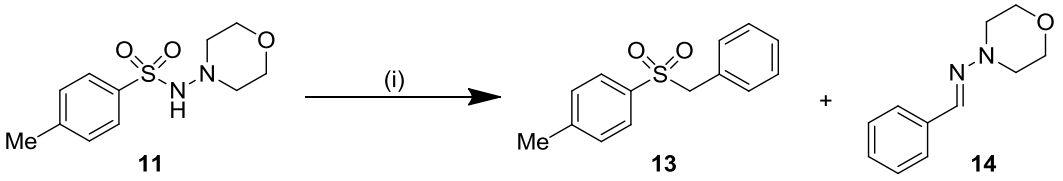
2.2.3 Optimisation of reaction conditions

To develop the planned route to sulfones, the reaction conditions necessary for sulfinate generation and subsequent electrophile-trapping using pre-formed *N*-aminosulfonamides was explored (Table 2.1). A variety of weak bases, solvents and temperatures was investigated, with benzyl bromide employed as the electrophile. The electrophile was present from the start of the reaction with the expectation that a trialkylated aminosulfonamide would be generated *in situ*.

Although ethanol gave complete conversion at 90 °C (entry 2), the palladium catalysed aminosulfonylation reaction gives the highest yield when 1,4-dioxane is used as the

solvent. As such, 1,4-dioxane was selected as the solvent for further investigations as it would provide potential for a one-pot synthesis of sulfones directly from the halide coupling partner. In 1,4-dioxane at 100 °C, near complete conversion was obtained after 30 minutes reaction time with two equivalents of both base and benzyl bromide (entry 5, *c.f.* entries 7 to 9). Cesium and potassium carbonate gave similar conversions to the sulfone (entries 4 and 5). Consequently, for later scoping reactions, potassium carbonate was chosen as the base as it is less expensive.

Table 2.1: Optimisation of the reaction conditions for the conversion of *N*-aminosulfonamide 11 to sulfone 13.

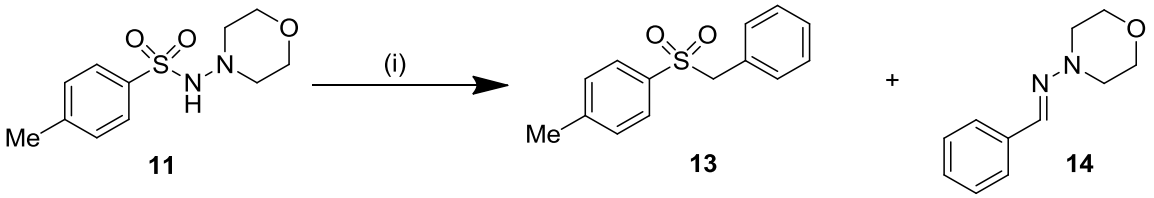


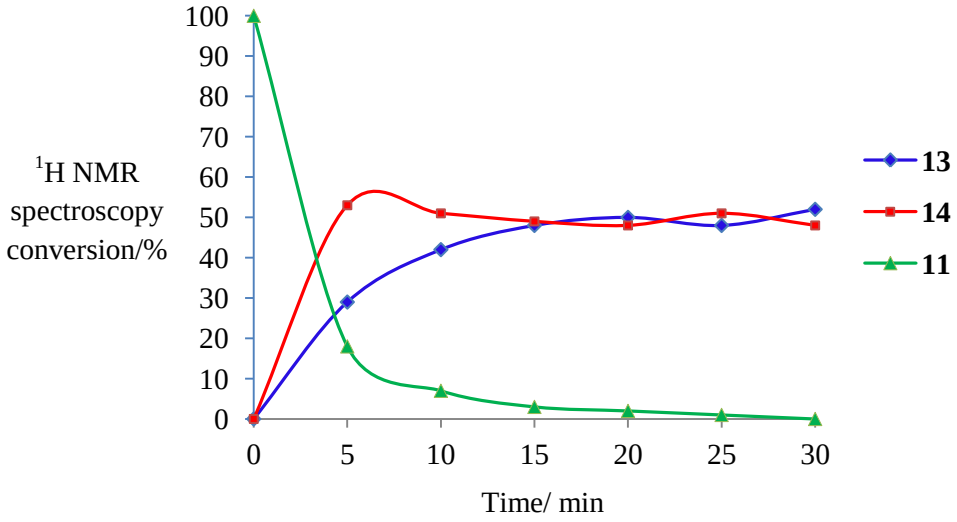
Entry	Solvent	Base (equiv.)	BnBr equiv.	Temp/ °C	Conversion/ % [a]	
					13	**14**
1	Ethanol	Cs_2CO_3 (2)	2	70	85	87
2	Ethanol	Cs_2CO_3 (2)	2	90	99	98
3	Toluene	Cs_2CO_3 (2)	2	110	95	96
4	1,4-Dioxane	Cs_2CO_3 (2)	2	100	98	94
5[c]	1,4-Dioxane	K_2CO_3 (2)	2	100	98	95
6	1,4-Dioxane	DABCO (2)	2	100	0	0
7	1,4-Dioxane	K_2CO_3 (1)	2	100	74	67
8	1,4-Dioxane	K_2CO_3 (2)	1	100	42	38
9	1,4-Dioxane	-	2	100	0	0

Reaction conditions: (i) *N*-Aminosulfonamide (1 equiv.), BnBr, base, 16 h, solvent [0.3 M]. [a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield. [c] Reaction time 30 min.

2.3.4 Mechanistic investigation

Mechanistic studies were conducted using cesium carbonate as the base, although it is assumed that similar observations would be made with potassium carbonate. The reaction composition was analysed every 5 minutes by ^{1}H NMR spectroscopy over a period of 30 minutes (Scheme 2.13).[i] The formation of the hydrazone **14** was observed first, followed by the formation of the sulfone **13**.





Time/ min		0	5	10	15	20	25	30
^{1}H NMR spectroscopy conversion/%	**13**	0	29	42	48	50	48	52
	14	0	53	51	49	48	51	48
	11	100	18	7	3	2	1	0

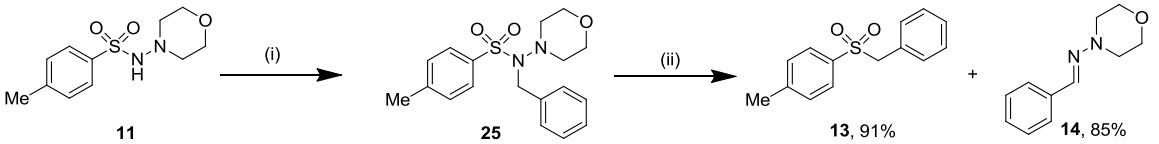
Scheme 2.13: *Reaction conditions*: (i) BnBr (2 equiv.), Cs_2CO_3 (2 equiv.), 1,4-dioxane [0.3 M], 100 °C.

In an attempt to isolate any intermediates, the temperature of the reaction was reduced to 40-50 °C. The trialkyl sulfonamide intermediate **25** was observed by ^{1}H NMR

[i] Samples were taken every 5 minutes, filtered through a short pad of Celite using diethyl ether, and reduce *in vacuo*.

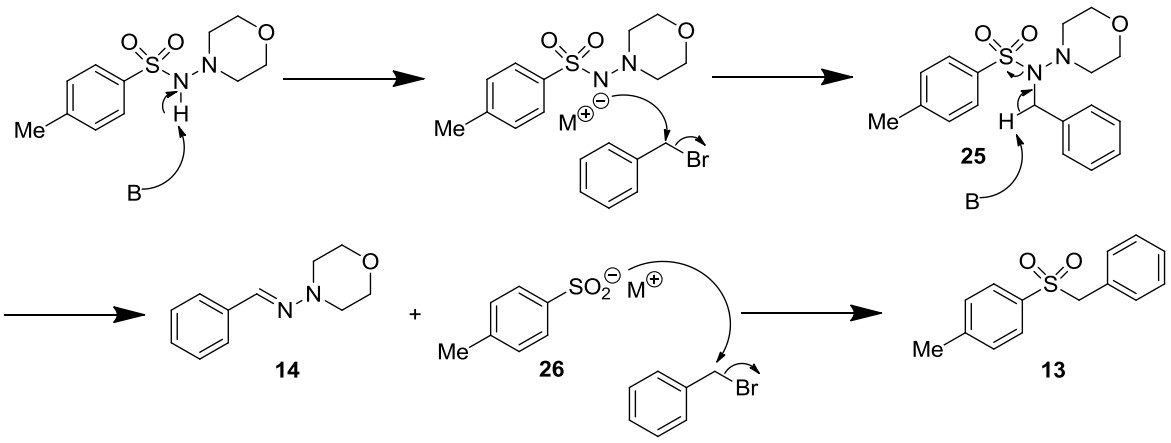
spectroscopy together with unreacted benzyl bromide (Scheme 2.14, see also Chapter 6 Experimental). Extended reaction times or higher temperatures resulted in mixtures of sulfone **13**, hydrazone **14**, intermediate **25**, as well as unreacted sulfinate salt **26**. Attempts to purify the intermediate **25** by column chromatography resulted only in decomposition.

The crude reaction mixture of intermediate **25** and unreacted benzyl bromide was subsequently reacted with base and benzyl bromide to give the sulfone **13,** as well as the hydrazone **14** (Scheme 2.14).



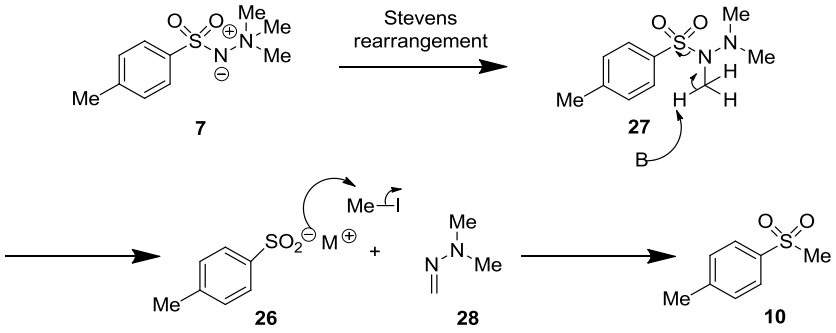
Scheme 2.14: *Reaction conditions*: (i) BnBr (2 equiv.), Cs_2CO_3 (2 equiv.), 1,4-dioxane [0.3 M], 40 °C, 20 min, then 50 °C, 20 min; (ii) BnBr (1 equiv.), Cs_2CO_3 (1 equiv.), 1,4-dioxane [0.3 M], 100 °C, 1 h.

Identification of the trialkyl intermediate **25** and hydrazone by-product **14**, together with the data for the reaction composition change with time (Scheme 2.13) and the observation that two equivalents of both base and alkylating agent were necessary for complete conversion (Table 2.1, entry 5), suggests a possible mechanism may be as shown in Scheme 2.15. It is postulated that the *N*-aminosulfonamide is deprotonated by the first equivalent of base, which then reacts with the electrophile benzyl bromide to give the trialkyl intermediate **25**. The second equivalent of base then gives the hydrazone by-product **14** and sulfinate salt **26**, which goes on to react with a further equivalent of benzyl bromide to give the sulfone product **13**.



Scheme 2.15: Proposed mechanism for sulfone synthesis from *N*-aminosulfonamide.

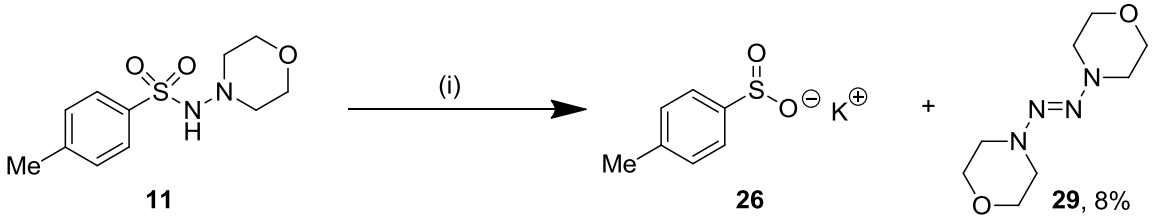
In the reaction of *N*-aminosulfonamide **6** with iodomethane, the aminimide **7** was isolated by column chromatography. In this case, another plausible mechanism may involve methylation on the terminal nitrogen and deprotonation to give the aminimide **7** (Scheme 2.16). A subsequent Stevens rearrangement would give intermediate **27**, which after deprotonation, would give the sulfinate salt **26**. The postulated by-product **28**, however, was not observed, perhaps due to its decomposition under the reaction conditions. This pathway could also occur for *N*-aminosulfonamide **11**, however no equivalent aminimide was observed in the reactions.



Scheme 2.16: Proposed mechanism for sulfone synthesis from *N*-aminosulfonamide **6**.

Investigation was undertaken into any possible dialkyl sulfonamide decomposition that may occur as described in Scheme 2.11, (B). The *N*-aminosulfonamide **11** was reacted

under basic conditions without the presence of an electrophile. After 1 h at 100 °C, with two equivalents of K_2CO_3, only unreacted *N*-aminosulfonamide was returned. A 40% conversion to the sulfinate salt was observed by ^{1}H NMR spectroscopy after 8 h, with complete decomposition of the starting material observed after 24 h. A by-product, tentatively assigned as the tetrazene **29**, was isolated in low yield (Scheme 2.17). In contrast, reaction with two equivalents of benzyl bromide and base allowed full conversion to the sulfone **13** to be achieved after only 30 minutes reaction (Table 2.1, entry 5). This suggests that in the presence of both a base and an electrophile, a faster decomposition pathway involving a trialkylated *N*-aminosulfonamide intermediate is occurring, in addition to the slower decomposition of the dialkylated *N*-aminosulfonamide.

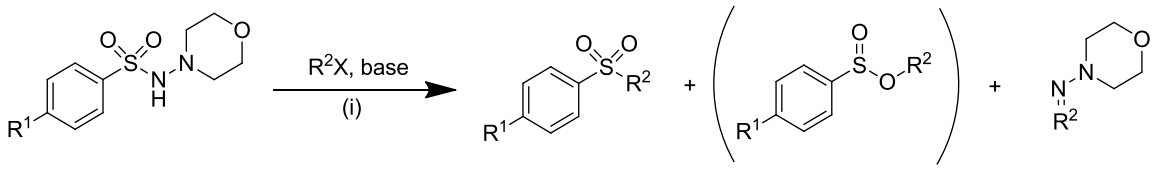


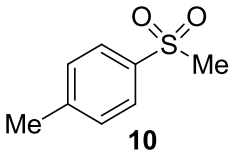
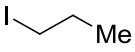
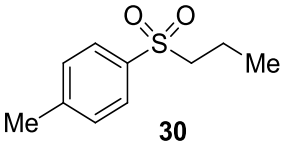
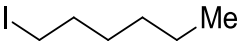
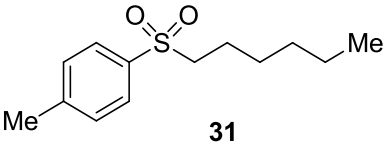
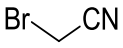
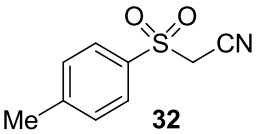
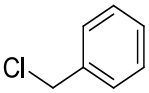
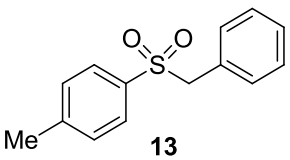
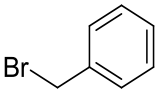
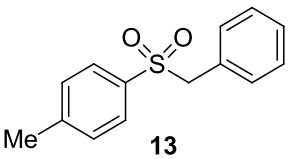
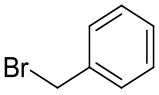
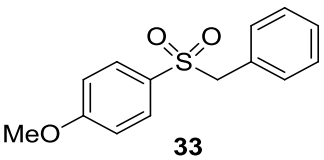
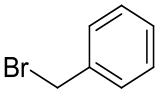
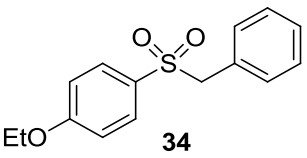
Scheme 2.17: *Reaction conditions*: (i) *N*-Aminosulfonamide (1 equiv.), K_2CO_3 (2 equiv.), 1,4-dioxane [0.3 M], 100 °C, 16 h.

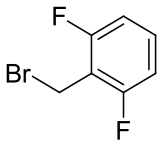
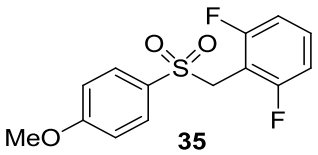
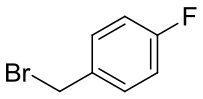
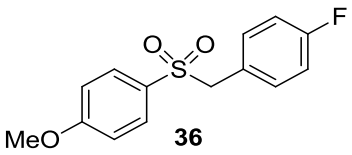
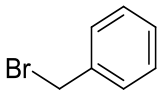
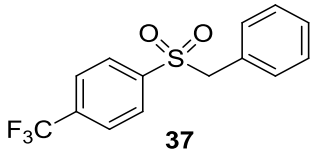
2.2.5 Sulfone synthesis from an *N*-aminosulfonamide

Using the optimised reaction conditions, a range of electrophiles was reacted with an *N*-aminosulfonamide to give the corresponding sulfones (Table 2.2).

Table 2.2: Scope of electrophiles employed in the synthesis of sulfones from an *N*-aminosulfonamide using Method I



Entry	R^1	R^2X	Sulfone product	Yield/ % [a] Sulfone	Hydrazone
1	Me	MeI	 **10**	77[b]	-
2	Me		 **30**	61 (5[c])	-
3	Me		 **31**	67 (8)	55
4	Me		 **32**	20	18
5	Me		 **13**	69	65
6	Me		 **13**	92 (2)	87
7	OMe		 **33**	89	-
8	OEt		 **34**	94	-

Entry	R^1	R^2X	Sulfone product	Yield/ % [a] Sulfone	Hydrazone
9	OMe		 **35**	85	72
10	OMe		 **36**	89	76
11	CF_3		 **37**	70	-

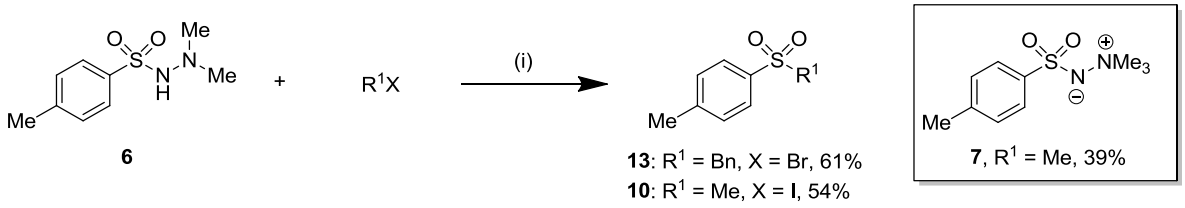
Reaction conditions: (i) *N*-aminosulfonamide (1 equiv.), R^2X (2 equiv.), K_2CO_3 (2 equiv.), 100 °C, 1,4-dioxane [0.3 M], 1-16 h. [a] Isolated yields. [b] 6 Equiv. of methyl iodide as the boiling point of methyl iodide is lower than the reaction temperature. [c] Determined by ^{1}H NMR spectroscopy. [e] Et_3N (1 equiv.) added. Number in parentheses corresponds to the sulfinate ester.

Despite the sulfinate anion being an ambident nucleophile, the sulfinate ester products, resulting from alkylation at the *O*-atom as opposed to the desired *S*-atom, were only observed in a greater than 5% conversion for the alkyl iodide examples (entries 2 and 3). This result is commonly seen in alkylation reactions of sulfinate ions.[143] Although the explanation for this reactivity is often through the HSAB model or Klopman-Salem concept,[144] Baidya *et al.* suggest the ambident reactivity of sulfinate ion is a result of both kinetic and thermodynamic effects, with stabilised carbocations giving the sulfone as the thermodynamic product, and under conditions of kinetic control a mixture of sulfone and sulfinate ester is obtained.[121] Baidya *et al*. also suggest that the solvent has an important effect on the nucleophilicity of a phenyl sulfinate ion. Rearrangement of sulfinate esters to the corresponding sulfone is possible by a probable ionisation-recombination mechanism, but it is highly dependent on the solvent and often low yielding.[145] In the hope of reducing the yield of the sulfinate ester products for the alkyl iodide examples, the reaction was

doped with either water or ethanol, however, no reduction in the sulfinate ester yield was observed.

N-Aminosulfonamides with electron-donating substituents gave high yields in reaction with benzyl bromide derivatives (entries 6 to 10), although reaction with benzyl chloride gave a reduced yield (entry 5). The *N*-aminosulfonamide with an electron-withdrawing group (entry 11) gave a lower yield possibly due to stabilisation of the sulfinate salt intermediate, consequently reducing its nucleophilicity.

The *N*-aminosulfonamide **6** was also investigated, but afforded the corresponding sulfone in lower yields compared to *N*-aminosulfonamide **11**. In the reaction with iodomethane, aminimide **7** was recovered in a 39% yield, despite the high reaction temperature (Scheme 2.18).



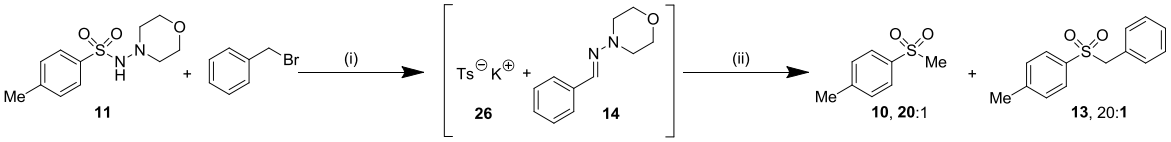
Scheme 2.18: *Reaction conditions*: (i) BnBr (2 equiv.) or MeI (6 equiv.), K_2CO_3 (2 equiv.), 1,4-dioxane [0.3 M], 100 °C, 16 h.

2.2.6 Synthesis of sulfones *via* a two-step procedure

This methodology is limited to electrophiles that can form the proposed trialkyl *N*-aminosulfonamide intermediate as described in Scheme 2.15. For example, generation of a diaryl sulfone either by an S_NAr reaction with an electron-poor arene or by reaction with an iodonium salt, would not be possible by the suggested mechanism and was

expected to be challenging. As the decomposition of the *N*-aminosulfonamide **11** to the sulfinate salt **26** with K_2CO_3 alone (with no electrophile) is slow, a procedure was sought that would provide faster generation of the sulfinate salt that could then react with the desired electrophile.

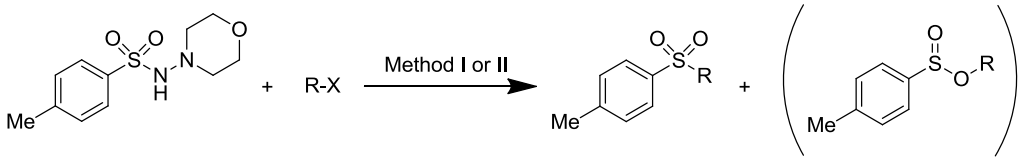
It was considered that benzyl bromide could be employed as a sacrificial electrophile to give controlled generation of the sulfinate salt and then a second, different electrophile could be added to the reaction mixture. After 1 h at 50 °C with 0.95 equivalents of benzyl bromide and two equivalents of base, analysis of the crude reaction mixture showed complete decomposition of the *N*-aminosulfonamide to the sulfinate salt **26** and hydrazone **14**. A second electrophile was then added and the temperature increased to 100 °C to give the sulfone corresponding to the second electrophile as the major product (Scheme 2.19).

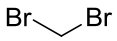
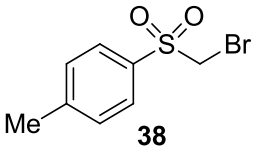
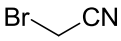
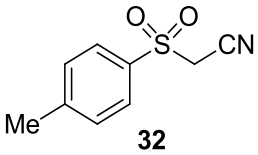
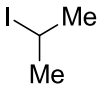
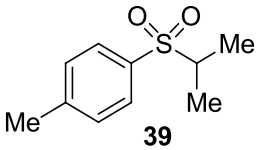
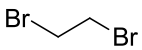
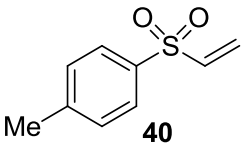
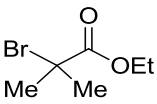
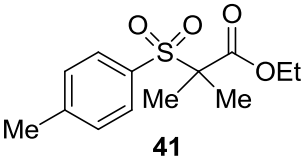
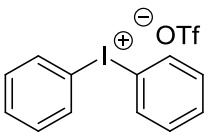
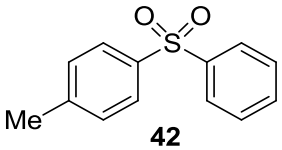
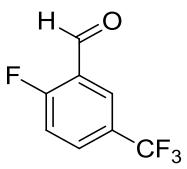
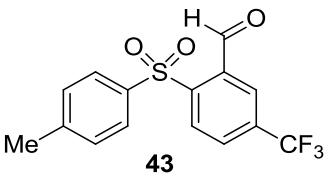
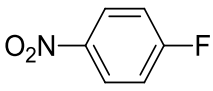
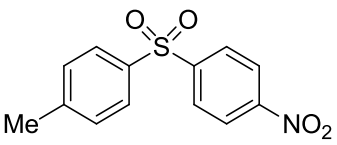


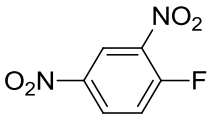
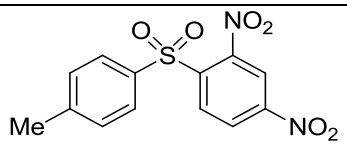
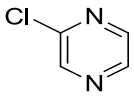
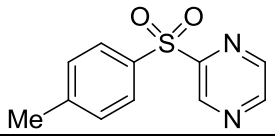
Scheme 2.19: *Reaction conditions*: (i) K_2CO_3 (2 equiv.), BnBr (0.95 equiv.), 50 °C, 1 h, 1,4-dioxane [0.3 M]; (ii) MeI (1.1 equiv.), 100 °C, 16 h

This method (Method II, Table 2.3) was explored with a small selection of electrophiles that had previously given lower yields using Method I (Table 2.3). Little or no improvement was observed for entries 1 to 3, suggesting it is the reaction of the potassium sulfinate salt with these particular electrophiles that is more challenging rather than formation of the sulfinate salt. On the other hand, Method II gave a much cleaner reaction and a significant improvement in yield for the synthesis of the α,β-unsaturated sulfone[142(a)] (entry 4).

Table 2.3: Scope of electrophiles employed in the sulfone synthesis from the *N*-aminosulfonamide 11 using either Method I or Method II.



Entry	RX	Sulfone product	Yield/ %[a] Method I	Yield/ %[a] Method II
1		 **38**	20	20
2		 **32**	20	22
3		 **39**	47(7)	44 (5)
4		 **40**	18[b]	53[b]
5		 **41**	51	58
6		 **42**	20	59
7		 **43**	n.d.	40
8			-	n.d.

Entry	RX	Sulfone product	Yield/ %[a] Method I	Yield/ %[a] Method II
9			-	n.d.
10			-	n.d.

Reaction conditions: Method I: RX (2 equiv.), K_2CO_3 (2 equiv.) 100 °C, 16 h, 1,4-dioxane [0.3 M]; Method II: (i) BnBr (0.95 equiv.), K_2CO_3 (2 equiv.), 1,4-dioxane [0.3 M], 50 °C, 1 h; (ii) RX (1.5 equiv.), 100 °C, 16 h. [a] Isolated yield. [b] Et_3N (1 equiv.) added. Number in parentheses corresponds to the sulfinate ester. n.d. = not detected.

Method I and Method II were then applied to electrophiles that would struggle to form the predicted trialkyl sulfonamide intermediate – a tertiary bromide (entry 5), an iodonium salt (entry 6)[65,119,146] and electron-poor arenes (entries 7 to 10).[118,147] The formation of the sulfone **41** (entry 5) and aryl sulfone **42** (entry 6) by Method I cannot be explained by the mechanism proposed in Scheme 2.15. Interestingly, in the reaction with an iodonium salt (entry 6), a trisubstituted intermediate **44** was also isolated in a 21% yield when using Method I reaction conditions (Figure 2.2).

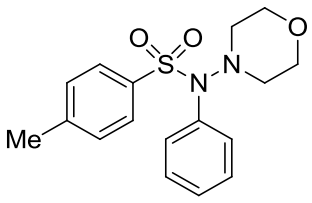


Figure 2.2: Trisubstituted intermediate **44**.

These results suggest that two decomposition pathways are operable: one where the *N*-aminosulfonamide undergoes *N*-alkylation to give a trialkyl intermediate, which after deprotonation gives a sulfinate salt, and the other is a slower decomposition of the

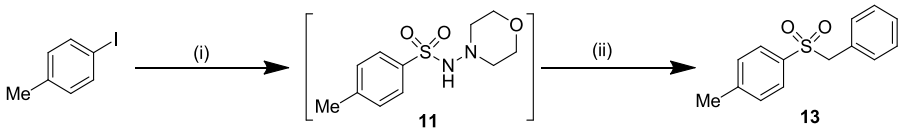
N-aminosulfonamide under basic conditions to give a sulfinate salt. This explains the formation of the sulfones **41** and **42** by Method I.

2.2.7 Optimisation of one-pot synthesis of sulfones directly from the aryl-, heteroaryl- or alkenyl iodide

Having established two complementary methods for the synthesis of sulfones from an *N*-aminosulfonamide, one-pot reaction conditions were then investigated to synthesise the sulfones directly from the aryl-, heteroaryl- or alkenyl iodides. For initial investigations into the one-pot procedure, 1.2 equivalents of 4-aminomorpholine were used as it was assumed that excess 4-aminomorpholine may react with the electrophile.[ii] 4-Iodotoluene was selected as the test substrate due to its good performance in previous reactions. The substrate was subjected to the palladium catalysed aminosulfonylation reaction conditions and after 16 h, K_2CO_3 and benzyl bromide were added. Using two equivalents of benzyl bromide and base resulted in no sulfone product (entries 1 to 3, Table 2.4). Only when a large excess (4 equivalents) was used was the sulfone observed in a 57% yield (entry 4).

[ii] The palladium catalysed reaction of 4-iodotoluene with 1.2 equivalents of 4-aminomorpholine gave a similar conversion to the *N*-aminosulfonamide by ^{1}H NMR spectroscopy as observed with 1.5 equivalents.

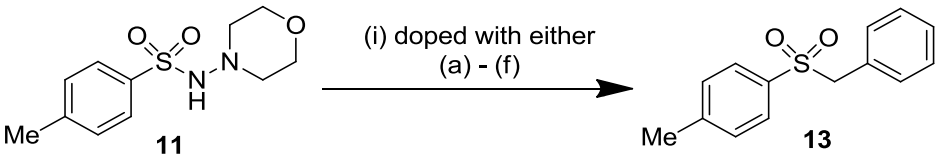
Table 2.4: Initial optimisation reactions for the one-pot synthesis of sulfone 13.



Entry	(i)		(ii)				Yield/ % [b]
	DABSO equiv.	DABCO equiv.	BnBr equiv.	K_2CO_3 equiv.	Co-Solvent [a]	Temp/ °C	
1	0.6	0.5	2	2	-	100	n.d.
2	0.6	0.5	2	2	Ethanol	90	n.d.
3	1.1	0	2	2	-	100	n.d.
4	0.6	0.5	4	4	-	100	57

Reaction conditions: (i) 4-Iodotoluene (1 equiv.), $Pd(OAc)_2$ (10 mol%), Fu salt (20 mol%), DABSO, DABCO, 4-aminomorpholine (1.2 equiv.), 1,4-dioxane [0.3 M], 70 °C, 16 h; (ii) K_2CO_3, BnBr, 16 h. [a] 0.5 mL of ethanol added. [b] Isolated yield. n.d. = not detected.

To examine which reagents from the palladium catalysed step were inhibiting the second step, a series of reactions was undertaken in which the second step alone was doped with each reagent from the palladium step (Scheme 2.20). It was observed that all reagents except $Pd(OAc)_2$ compromised the efficiency of the conversion of *N*-aminosulfonamide **11** to the sulfone **13**. This is presumably due to reaction of these reagents with the benzyl bromide.



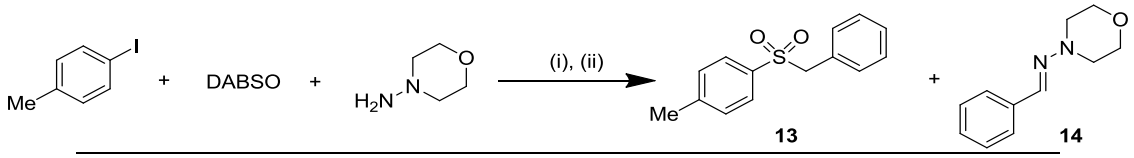
Scheme 2.20: *Reaction conditions*: (i) K_2CO_3 (2 equiv.), BnBr (2 equiv.), 1,4-dioxane [0.3 M], 100 °C; (a) $Pd(OAc)_2$ (10 mol%); (b) Fu salt (20 mol%); (c) $Pd(OAc)_2$ (10 mol%), Fu salt (20 mol%); (d) DABSO (0.6 equiv.); (e) DABCO (0.5 equiv.); (f) 4-Aminomorpholine (1.2 equiv.).

In light of this data, conditions for the first step were varied in order to reduce any excess reagents in the second step. When Cs_2CO_3 was used as the base in the aminosulfonylation reaction instead of DABCO, only a 56% conversion to the sulfonamide was observed. The most fruitful conditions were found to be with $Pd(OAc)_2$ (10 mol%), Fu salt (10 mol%), DABSO (0.5 equiv.), DABCO (0.5 equiv.) and 4-aminomorpholine (1.2 equiv.), which gave a 90% conversion to the *N*-aminosulfonamide **11** by ^{1}H NMR spectroscopy. These palladium conditions were implemented in the one-pot procedure with 4 equivalents of benzyl bromide and base to deliver no improvement in the yield of the sulfone **13**.

Literature precedent suggests that DMSO,[121] polyethylene glycol,[122] and DMF[148] are good solvents for sulfone formation from the sodium sulfinate salt as discussed in Section 2.1.3. Unfortunately, addition of these solvents in the second step resulted in a significant drop in conversion to the sulfone (Table 2.5). Pleasingly, the addition of water[112,123] allowed a dramatic increase in yield to 91% of the sulfone to be realised with only 2.5 equivalents each of K_2CO_3 and benzyl bromide and a total reaction time of 21 h (entry 8).[iii]

[iii] Lowering the reaction temperature to 90 °C was necessary to prevent hydrolysis of benzyl bromide which occurred at 100 °C.

Table 2.5: Optimisation of the one-pot conditions for conversion of 4-iodotoluene to sulfone 13.

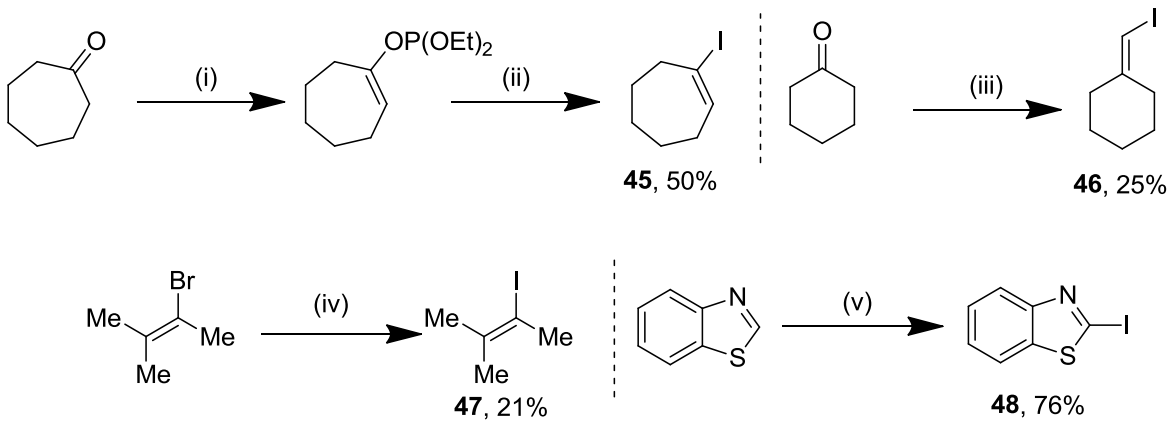


Entry	K_2CO_3 equiv.	BnBr equiv.	Co-solvent [a]	Sulfone yield/ % [b]
1	4	4	EtOH	10[c]
2	2.5	2.5	PEG-400	0[c]
3	2.5	2.5	Diglyme	0[c]
4	2.5	2.5	DMSO	15[c]
5	2.5	2.5	DMF	15[c]
6	4	4	H_2O	80
7[d]	2	2	H_2O	87
8[d,e]	2.5	2.5	H_2O	91

Reaction conditions: (i) 4-Iodotoluene (1 equiv.), $Pd(OAc)_2$ (10 mol%), $P^tBu_3.HBF_4$ (20 mol%), 4-aminomorpholine (1.5 equiv.), DABSO (0.6 equiv.), DABCO (0.5 equiv.), 70 °C, 16 h, 1,4-dioxane, [0.3 M]; (ii) BnBr, K_2CO_3, 20 h, 100 °C. [a] 0.5 mL of co-solvent. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy. [d] (i) 4-Iodotoluene (1 equiv.), $Pd(OAc)_2$ (10 mol%), $P^tBu_3.HBF_4$ (20 mol%), DABSO (0.6 equiv.), DABCO (0.5 equiv.), 4-aminomorpholine (1.2 equiv.), 70 °C, 16 h, 1,4-dioxane [0.30 M], (ii) BnBr, K_2CO_3, 90 °C, 20 h. [e] 5 h reaction time for step (ii).

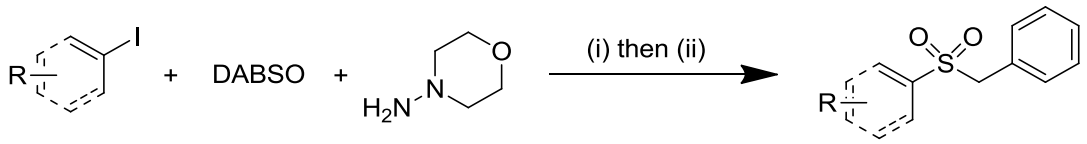
2.2.8 One-pot synthesis of sulfones directly from the aryl-, heteroaryl- or alkenyl iodide

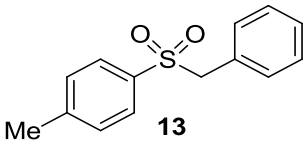
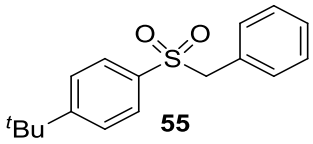
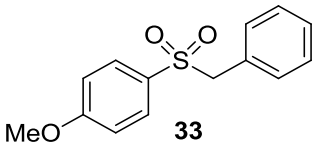
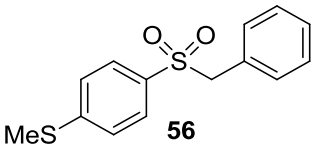
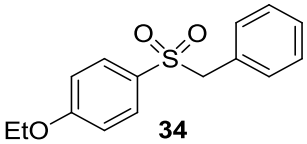
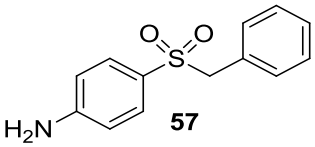
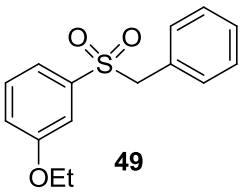
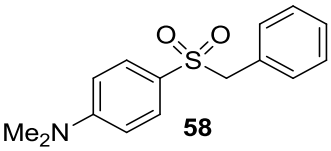
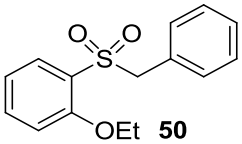
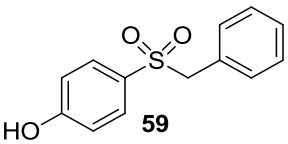
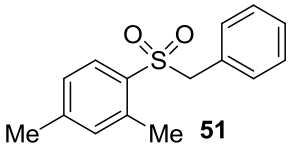
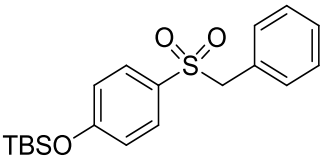
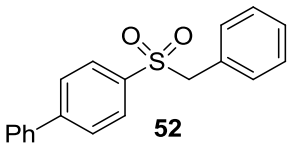
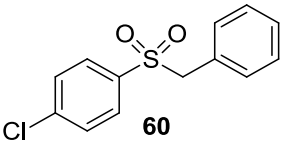
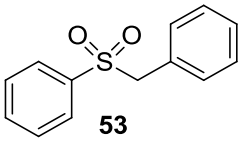
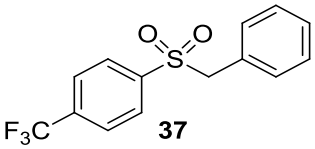
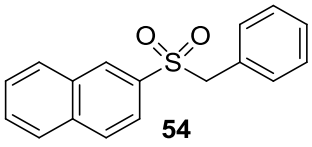
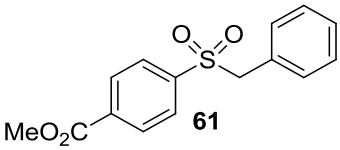
With the optimised conditions in hand, benzyl bromide was reacted with a range of halide coupling partners (Table 2.6). Previous results from the Willis group found slower reacting substrates, such as those with electron-withdrawing groups, gave improved yields when extra DABSO (1.1 equiv.) was employed without DABCO.[23,25] The preparation of heteroaryl- and alkenyl-iodides (**45**, **46**, **47** and **48**) that are not commercially available are shown in Scheme 2.21.

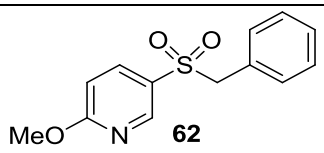
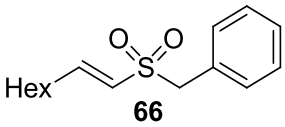
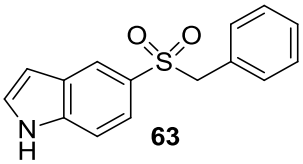
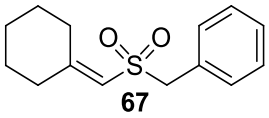
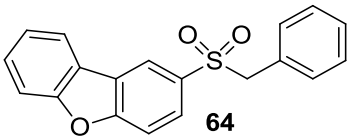
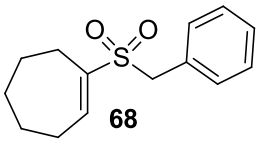
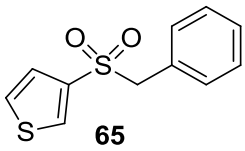
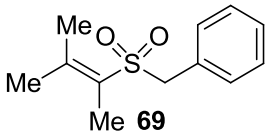
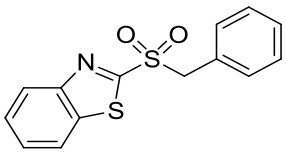


Scheme 2.21: *Reaction conditions*: (i) Cycloheptanone (1 equiv.), LDA (1.1 equiv.), THF, –78 °C, 45 min, $PO(OEt)_2Cl$ (1.1 equiv.), THF, 30 min, RT, 1 h; (ii) TMSCl (3 equiv.), NaI (3 equiv.), RT, 10 min; (iii) (Iodomethyl)triphenylphosphonium iodide (1.25 equiv), KO^{t}Bu (1.25 equiv), THF, –78 °C to –20 °C, 10 min, add cyclohexanone (1 equiv) at –78 °C to RT, 16 h; (iv) 2-Bromo-3-methyl-2-butene (1 equiv.), dimethylethylenediamine (0.1 equiv.), CuI (5 mol%), NaI (1.5 mmol), *n*-butanol, 120 °C, 24 h; (v) Benzothiazole (1 equiv.), MeLi (1.1 equiv.), I_2 (1.2 equiv.), Et_2O, –40 °C to RT, 15 min.

Table 2.6: Scope of aryl halides employed in the one-pot palladium catalysed conversion of aryl-, heteroaryl- or alkenyl halides to the corresponding sulfone.



Entry	Product	Yield / % [a]	Entry	Product	Yield / % [a]
1	 **13**	91 41[c] 55[d]	10	 **55**	87
2	 **33**	87 46[c]	11	 **56**	89
3	 **34**	90 75[e] 88[f]	12	 **57**	57
4	 **49**	87	13	 **58**	74
5	 **50**	75[b]	14	 **59**	8
6	 **51**	88	15	 **60**	n.d.
7	 **52**	78[b]	16	 **37**	67[b]
8	 **53**	65[b]	17	 **61**	42[b]
9	 **54**	72[b]	18		11[b]

Entry	Product	Yield / % [a]	Entry	Product	Yield / % [a]
19	 **62**	70[b]	24	 **66**	46[b]
20	 **63**	36[b]	25	 **67**	87[b]
21	 **64**	64[b]	26	 **68**	81[b]
22	 **65**	62[b]	27	 **69**	23[b]
23		0[b]			

Reaction conditions: (i) Aryl iodide (1 equiv.), $Pd(OAc)_2$ (10 mol%), $^tBu_3P.HBF_4$ (20 mol%), 4-aminomorpholine (1.2 equiv.), DABSO (0.6 equiv.), DABCO (0.5 equiv.), 70 °C, 16 h, 1,4-dioxane [0.3 M]; (ii) $K_2CO_{3(aq)}$ (2.5 equiv.), BnBr (2.5 equiv.), 90 °C, 5-20 h. [a] Isolated yield. [b] DABSO (1.1 equiv.), no added DABCO used. [c] ArBr (1 equiv.) used instead of the corresponding ArI. [d] Dimethylhydrazine (1.2 equiv.) used instead of 4-aminomorpholine. [e] BnCl (2.5 equiv.) used instead of BnBr. [f] 1-Aminopiperidine (1.2 equiv.) used instead of 4-aminomorpholine. n.d. = not detected.

Aryl iodides with neutral and electron-donating substituents gave excellent yields of the desired sulfone (entries 1 to 13). However, when an aryl bromide was used as the coupling partner, a reduced yield was obtained as expected due to its lower reactivity in the palladium catalysed step (entries 1 and 2).[23,25] Substrates with *ortho*-substituents did not pose a problem, giving the sulfones in high yields (entries 5 and 6). 1-Aminopiperidine was used as an alternative and viable hydrazine to 4-aminomorpholine (entry 3). Employing dimethylhydrazine as the hydrazine was less successful due to both its reduced

reactivity in the palladium catalysed step (65% yield)[25] and possibly due to the stability of the aminimide.

4-Iodophenol (entry 14) gave a low yield of the desired sulfone due to dibenzylation to give sulfone **70** which was isolated in 27% yield. TBS-protected 4-iodophenol was deprotected under the aqueous basic conditions to also give the dibenzylated product **70** under the reaction conditions (entry 15).

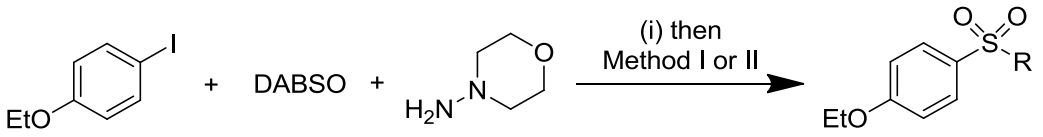
Aryl iodides with electron-withdrawing groups (entries 16 to 18) gave lower yields, which can be attributed to stabilisation of the sulfinate salt and the lower reactivity of substrates with electron-withdrawing groups in the palladium catalysed step as mentioned above. Entry 16 shows that an aryl chloride substituent remains intact during the transformation and so can potentially be used as a handle for subsequent functionalisation of the product.

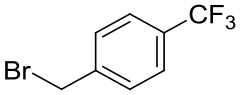
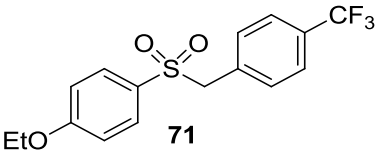
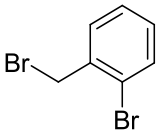
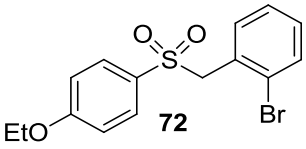
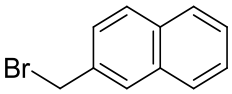
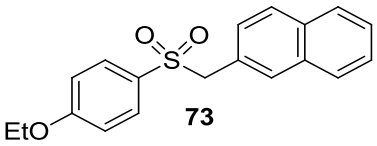
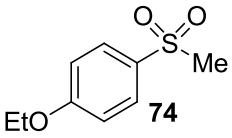
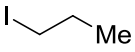
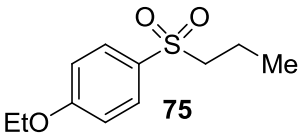
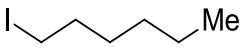
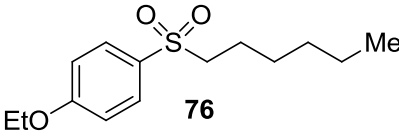
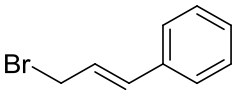
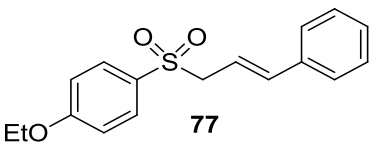
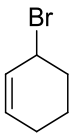
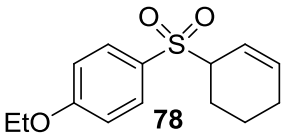
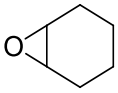
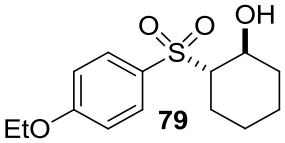
Heteroaryl iodides (entries 19 to 22) gave moderate yields, which is unsurprising considering the moderate yields obtained of the parent heteroaryl *N*-aminosulfonamide (see Appendix A). In the Julia-Kocienski olefination, a benzothiazol-2-yl sulfone can be used.[149] The synthesis of the thioazole sulfone (entry 23) was attempted, however the thioazole iodide **48** was unreactive under the palladium catalysed aminosulfonylation conditions. Similar 2-substituted heterocycles were also unreactive in the palladium catalysed aminosulfonylation reaction (see Appendix A). Pleasingly, alkenyl iodides gave the corresponding sulfone in moderate to high yields (entries 24 to 27).

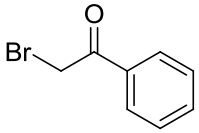
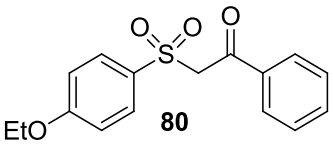
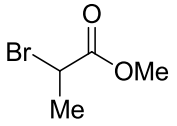
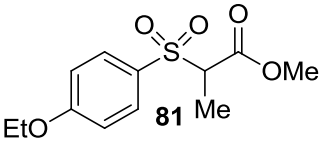
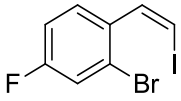
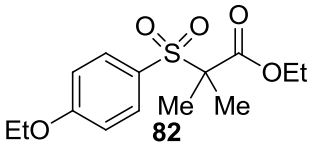
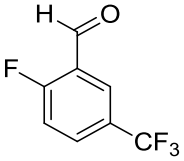
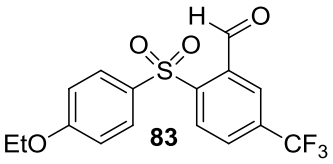
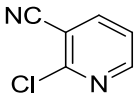
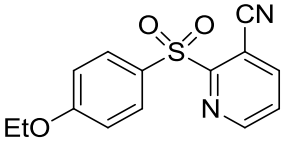
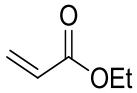
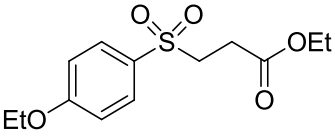
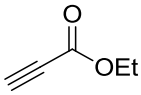
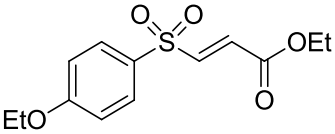
The sulfide (entry 11), amine (entries 12 and 13) and olefin (entries 24 to 27) functionalities were well tolerated under the mild reaction conditions, highlighting the applicability of the process to substrates with oxidation-sensitive functional groups.

The scope of the electrophilic component was then investigated. 1-Ethoxy-4-iodotoluene was used as the standard aryl halide, and Method I or II was employed as appropriate (Table 2.7). Method II had to be adapted for the one-pot procedure as a higher temperature was required for the formation of the sulfinate ion. It was found that 1 h at 90 °C with 0.95 equivalents of benzyl bromide was necessary to give the sulfinate ion, after which the second alkylating reagent was added.

Table 2.7: Scope of electrophiles employed in the one-pot palladium catalysed conversion of an aryl iodide to the corresponding sulfone.



Entry	RX	Sulfone	Yield/ % [a]	
			Method I	Method II
1		 **71**	91	-
2		 **72**	90	-
3		 **73**	93	-
4	MeI	 **74**	11	-
5		 **75**	55	-
6		 **76**	63	-
7		 **77**	51	83
8		 **78**	-	55
9		 **79**	35[b]	75[b]

Entry	RX	Sulfone	Yield/ % [a]	
			Method I	Method II
10		 **80**	n.d.	35
11		 **81**	26	47
12		 **82**	57	-
13		 **83**	-	35
14			-	n.d.
15			-	n.d.
16			-	n.d.

Reaction conditions: (i) 1-Ethoxy-4-iodobenzene (1 equiv.), $Pd(OAc)_2$ (10 mol%), $^tBu_3P.HBF_4$ (20 mol%), 4-aminomorpholine (1.2 equiv.), DABSO (0.6 equiv.), DABCO (0.5 equiv.), 70 °C, 16 h, 1,4-dioxane [0.3 M]; Method I: (ii) $K_2CO_{3(aq)}$ (2.5 equiv.), RX (2.5 equiv.), 90 °C, 16 h; Method II: (ii) $K_2CO_{3(aq)}$ (2.5 equiv.), BnBr (0.95 equiv.), 90 °C, 1 h; (iii) RX (2.5 equiv.), 90 °C, 16 h. [a] Isolated yield. [b] dr >20:1. n.d. = not detected.

A range of benzylic bromides were all incorporated in high yields (entries 1 to 3). Alkyl iodides (entries 4 to 6) gave reasonable yields, although methyl iodide gave a low yield possibly due to its low boiling point. Interestingly, the sulfinate ester products were not

observed as for similar alkyl iodides shown in Table 2.2. In the lower yielding reactions, both starting material and unreacted sulfinate salt were isolated.

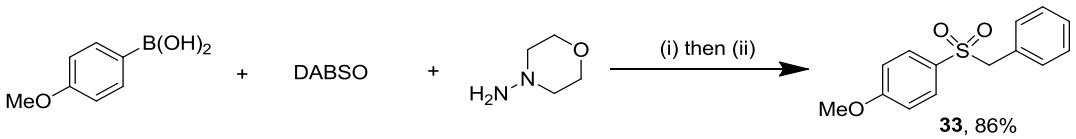
Allylic bromides delivered higher yields of the desired sulfones when Method II was utilised (entries 7 and 8). This was also seen in the case for cyclohexene oxide (entry 9). The yield of the sulfone[142(b)] increased as the electrophile was more substituted (entries 10 to 12). This suggests an S_N1 reaction of the sulfinate ion with the electrophile may be occurring. An S_NAr reaction was possible by implementing method II (entry 13) with an electron-poor aryl fluoride, albeit in low yield. Under the mild aqueous basic conditions, esters (entry 11 and 12), a β-hydroxy sulfone and epoxide starting material (entry 9) were well tolerated.

Ethyl acrylate (entry 15) and ethyl propiolate (entry 16) were ineffective electrophiles in the reaction. This is contrary to sodium sulfinates salts which are known to react well with enone electrophiles,[150] although less well with propiolates.[151]

2.2.9 Sulfone synthesis using palladium catalysed aminosulfonylation variants

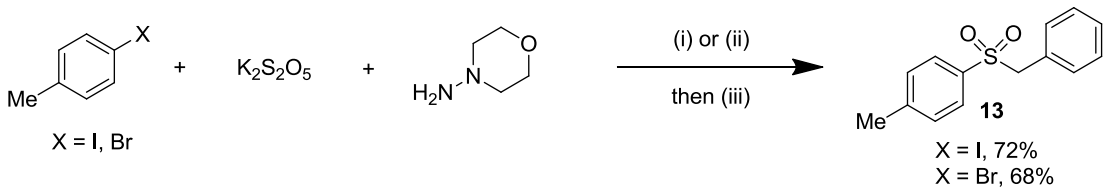
Recently, the Wu group successfully showed that boronic acids could be used instead of aryl halides in the palladium catalysed aminosulfonylation reaction using DABSO as the sulfur dioxide source.[60] In a related study, they have also demonstrated that a potassium metabisulfite/tetrabutylammonium bromide combination could replace DABSO in the palladium catalysed aminosulfonylation reaction with both aryl bromides and iodides in good to excellent yields (described further in Chapter 1).[7]

Investigation was undertaken to establish if these protocols would be amenable in the sulfone methodology. The sulfone **33** was synthesised directly from 4-methoxyphenylboronic acid, although additional benzyl bromide and base was required as consumption of the *N*-aminosulfonamide intermediate after 5 h was not observed (as is the case in the standard reaction with 4-iodoanisole), possibly due to the excess boronic acid starting material and DABSO (Scheme 2.22). The sulfone was formed in a comparable yield to the reaction with a 4-iodoanisole starting material (*c.f.* 87%, Table 2.6, entry 2).



Scheme 2.22: *Reaction conditions*: (i) 4-Methoxyphenylboronic acid (2 equiv.), $Pd(OAc)_2$ (5 mol%), DABSO (2 equiv.), TBAB (1.5 equiv.), 4-aminomorpholine (1 equiv.), O_2 balloon, 1,4-dioxane [0.25 M], 80 °C, 16 h; (iii) K_2CO_3 (2.5 equiv.), BnBr (2.5 equiv.), H_2O, 5 h, then K_2CO_3 (1 equiv.), BnBr (1 equiv.), 16 h, 90 °C.

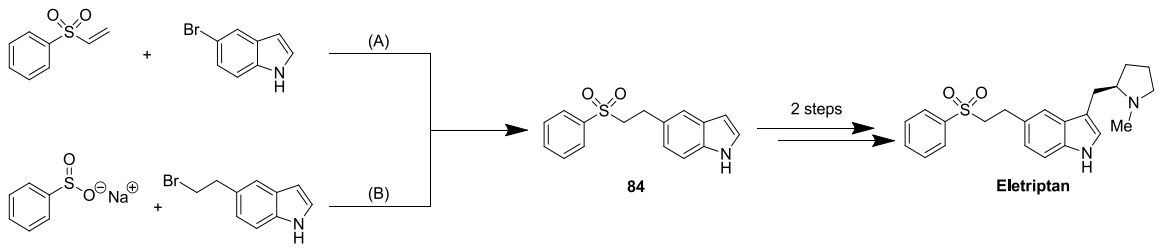
The potassium metabisulfite/tetrabutylammonium bromide procedure was then examined. Although the yield of sulfone **13** was significantly lower using the $K_2S_2O_5$/TBAB procedure with an aryl iodide (*c.f.* 91%, Table 2.6, entry 1), the aryl bromide gave much improved yields compared to the reaction of an aryl bromide with DABSO (*c.f.* 41%, Table 2.6, entry 1) (Scheme 2.23). The enhanced results for the aryl bromide case may be due to the harsher conditions used – a higher reaction temperature and increased equivalents of ligand and 4-aminomorpholine.



Scheme 2.23: *Reaction conditions*: (i) 4-Iodotoluene (1 equiv.), $Pd(OAc)_2$ (5 mol%), $P^tBu_3.HBF_4$ (10 mol%), $K_2S_2O_5$ (2 equiv.), TBAB (1.5 equiv.), HBF_4 (20 mol%), 4-aminomorpholine (1.2 equiv.), 1,4-dioxane [0.25 M], 80 °C, 21 h; (ii) 4-Bromotoluene (1 equiv.), $Pd(OAc)_2$ (10 mol%), $P^tBu_3.HBF_4$ (30 mol%), $K_2S_2O_5$ (2 equiv.), TBAB (1.5 equiv.), 4-aminomorpholine (2 equiv.), 1,4-dioxane [0.25 M], 100 °C, 21 h (iii) K_2CO_3 (2.5 equiv.), BnBr (2.5 equiv.), H_2O, 90 °C, 5 h.

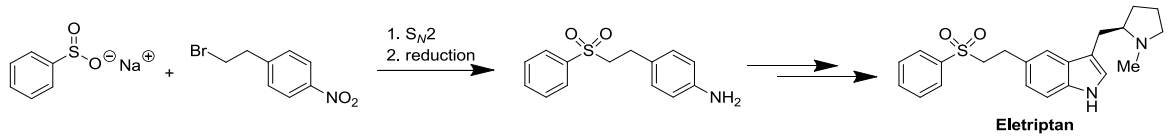
2.2.10 Synthesis of a pharmaceutical sulfone target

Eletriptan (trade name Relpax, marketed and manufactured by Pfizer) is an anti-migraine drug. There are many methods to synthesise Eletriptan,[152] many of which prepare Eletriptan from the sulfone intermediate **84** by two reported steps.[153] This intermediate can be synthesised by two common methods either by Heck reaction of a 5-bromoindole with phenyl vinyl sulfone[153] and then subsequent reduction (Scheme 2.24, (A)) or by reaction of a 5-substituted indole with the phenyl sulfinate ion[154] (Scheme 2.24, (B)). Phenyl vinyl sulfone is highly noxious, sensitising and hazardous to handle on a large scale.[153,155] Although both of these substrates are commercially available, functional variation of these substrates would require a multi-step synthesis.



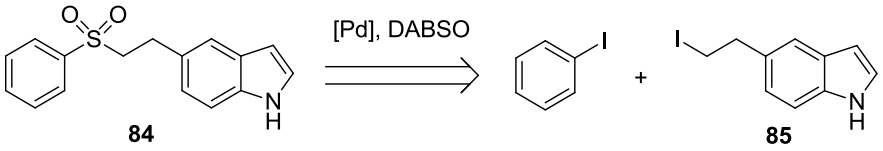
Scheme 2.24: The current routes towards the synthesis of Eletriptan *via* the sulfone intermediate **84**.

Another process involves a modified Fischer indole synthesis of Eletriptan (Scheme 2.25).[156] A drawback of this method is that the enantiomeric purity of the final product depends on the purity of an acetal intermediate. In the reported procedure, the enantiomeric excess was 94%.



Scheme 2.25: A Fischer indole approach towards the synthesis of Eletriptan.

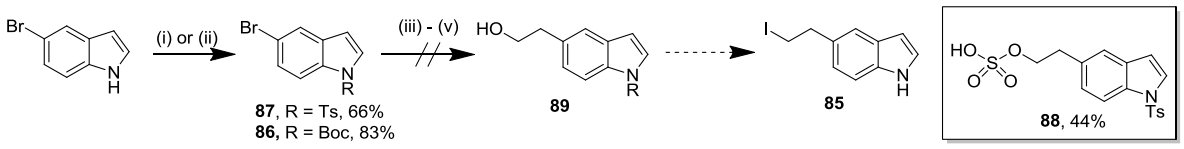
To demonstrate the utility of the sulfone methodology described above, an intermediate towards Eletriptan was synthesised. After comparison of the various synthetic routes, the synthesis of the intermediate **84** was focused on as from this only two reported steps are needed to obtain Eletriptan. The intermediate **84** could be obtained by the coupling of an appropriately 5-substituted indole, commercially available iodobenzene and DABSO (Scheme 2.26). This novel preparation of Eletriptan provides advantages over existing methods due to its synthetic flexibility.



Scheme 2.26: Retrosynthesis for the synthesis of the Eletriptan intermediate **84**.

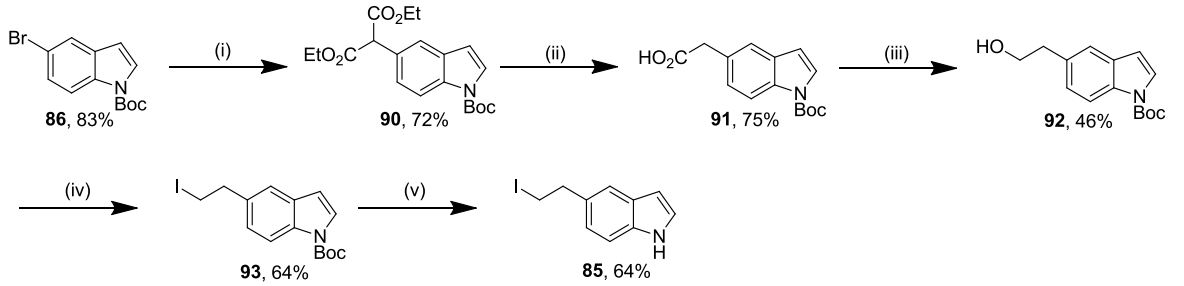
Investigation into the synthesis of 5-(2-iodoethyl)-1*H*-indole **85** was then undertaken. To introduce the hydroxylethyl chain, ethylene oxide was not used as it is toxic and has low emission limits.[157] In an attempt to synthesise the required electrophile, a literature procedure was followed in which a protected 5-bromoindole was reacted with butyl lithium and subsequently ethylene sulfate (Scheme 2.27).[154] Under these reaction conditions the *N*-Boc-protected indole **86** decomposed. Pleasingly, the tosyl-protected

indole **87** yielded the sulfate **88**, however under various acidic conditions, the alcohol **89** could not be obtained.



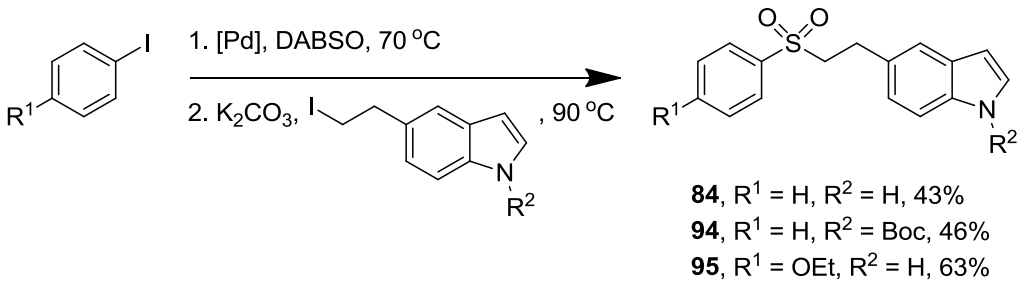
Scheme 2.27: *Reaction conditions*: (i) 5-Bromoindole (1 equiv.), TsCl (1.6 equiv.), KO^{t}Bu (1.6 equiv.), THF [0.22 M], RT; (ii) 5-Bromoindole (1 equiv.), Boc_2O (1.2 equiv.), DMAP (0.1 equiv.), THF [0.35 M], RT; (iii) **87** (1 equiv.), ^{n}BuLi (1 equiv.), THF [0.07 M], –78 °C, 2 h; (iv) Ethylene sulfate (1.2 equiv.), RT, 16 h; (v) H_2SO_4, H_2O, reflux or HCl, reflux.

An alternative synthetic route was therefore sought to synthesise the required indole (Scheme 2.28). The *N*-Boc-protected 5-bromoindole **86** underwent a palladium-catalysed coupling with diethyl malonate to give indole **90**. After hydrolysis and decarbonylation, indole **91** was obtained, which was then reduced with borane to give the indole **92**. After reaction with iodine and triphenylphosphine to generate iodide **93**, a final deprotection step gave the desired electrophile **85**.



Scheme 2.28: *Reaction conditions*: (i) Indole **86** (1 equiv.), $Pd(OAc)_2$ (5 mol%), XPhos (10 mol%), Cs_2CO_3 (3 equiv.), diethyl malonate (1 equiv.), toluene [0.1 M], 100 °C, 16 h; (ii) NaOH [2 M], EtOH, THF (1:10) [0.5 M], 60 °C, 16 h; (iii) BH_3.THF, THF [0.6 M], 0 °C, 90 min; (iv) I_2, PPh_3, 1*H*-imidazole, CH_2Cl_2 [0.3 M], RT, 16 h; (v) TFA, chloroform [0.8 M], RT, 30 min.

After obtaining both the protected and unprotected 5-substituted indoles **93** and **85**, they were used in the palladium catalysed one-pot synthesis of sulfones (Scheme 2.29). The Eletriptan intermediate **84** was obtained in a 43% yield in a one-pot procedure. The effect of a free NH group in the electrophile in the sulfone methodology was unknown, as such, the *N*-Boc-protected indole **93** was also coupled to give **94** and only a slight improvement in yield was observed. To demonstrate the ease with which variation of the sulfone can be undertaken, a functionalised aryl iodide was reacted to give a variant of the Eletriptan intermediate **95** in a 63% yield.



Scheme 2.29: One-pot synthesis of the protected and unprotected Eletriptan intermediates **94** and **84** respectively and functionalisation of the aryl ring.

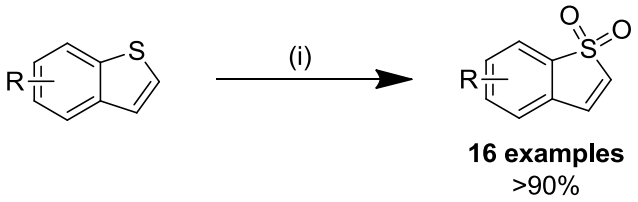
2.3 Benzo[*b*]thiophene 1,1-dioxide synthesis

The following section describes the investigation into using the sulfinate salt generated by decomposition of a *N*-aminosulfonamide to synthesise the cyclic sulfone benzothiophene 1,1-dioxide.

2.3.1 Common synthetic procedures towards the synthesis of benzothiophene 1,1-dioxide

Benzo[*b*]thiophene 1,1-dioxides are useful in many organic transformations,[158] for example in 1,3-dipolar and Diels-Alder cycloaddition reactions.[159] They are also of interest because they possess a variety of biological and physiological effects,[160] for example benzo[*b*]thiophene 1,1-dioxide derivatives have been used as a fungicide and bactericide.[161]

Current methodology to synthesise benzo[*b*]thiophene 1,1-dioxide is most commonly by oxidation of the corresponding benzo[*b*]thiophene or benzo[*b*]thiophene 1-oxide, thus limiting functionality to that not sensitive to oxidation.[162] A small number of oxidising reagents are available for those bearing electron-donating groups, however for those with electron-withdrawing groups (where the sulfur atom is more difficult to oxidise) there are far fewer (Scheme 2.30).[163] There are various methods to prepare benzo[*b*]thiophenes, often from phenylacetylene-based precursors; with recent developments providing the products in high yields.[164]

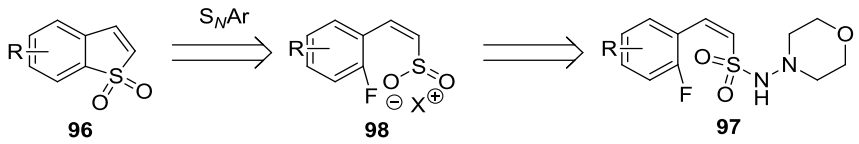


Scheme 2.30: An example synthesis of benzo[*b*]thiophene 1,1-dioxide by oxidation of the corresponding benzothiophene. *Reaction conditions*: (i) H_2O_2-$P_2O_{5(aq)}$ [0.88 M, 1.5 equiv.], CH_3CN, RT, 45 min.

Due to a lack of facile synthetic procedures to prepare benzo[*b*]thiophene 1,1-dioxide with a wide range of substituents, the potential of benzo[*b*]thiophene 1,1-dioxides is underexplored.

2.3.2 Attempted synthesis of benzo[*b*]thiophene 1,1-dioxide *via* decomposition of an alkenyl *N*-aminosulfonamide

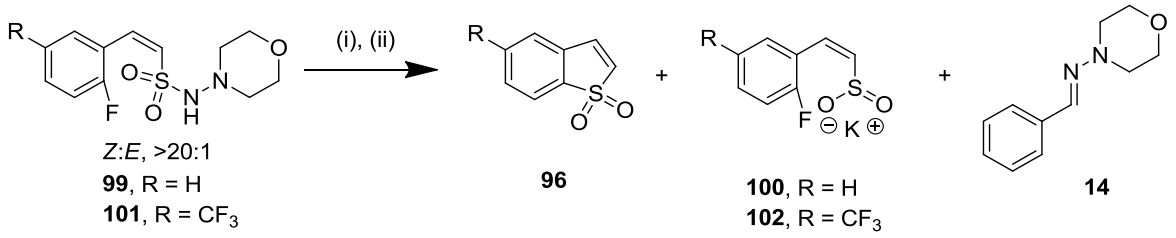
A retrosynthetic analysis for the synthesis of benzo[*b*]thiophene 1,1-dioxide **96** was conducted that interlinks the sulfone (Section 2.2) and benzosultam methodologies (Section 3.2) described in this thesis (Scheme 2.31). The alkenyl *N*-aminosulfonamide **97** can be prepared by the palladium catalysed coupling of DABSO, an alkenyl iodide and 4-aminomorpholine. It was hoped that this alkenyl *N*-aminosulfonamide may decompose to the alkenyl sulfinate ion **98** by application of the sulfone methodology described above. This may potentially cyclise by an S_NAr reaction to give the desired benzo[*b*]thiophene 1,1-dioxide (Scheme 2.31). Precedent for a sulfinate salt undergoing an S_NAr reaction is shown in Section 2.2 in Table 2.3 and Table 2.7 and also in literature reports.[118,147]



Scheme 2.31: Retrosynthetic analysis for benzo[*b*]thiophene 1,1-dioxide.

The alkenyl *N*-aminosulfonamide **99**, where R = H, was reacted under Method II reaction conditions (described in Section 2.2) to give a sulfinate salt *in situ* after which the temperature was increased to 100 °C in the anticipation of cyclisation. The hydrazone by-product **14** and sulfinate salt **100** were isolated, however no benzo[*b*]thiophene 1,1-dioxide **96** was detected (Scheme 2.32). To encourage an S_NAr reaction, an electron-withdrawing ($–CF_3$) group was added *para* to the fluoro group to give alkenyl *N*-aminosulfonamide **101**. Unfortunately, again no cyclisation was observed and only unreacted alkenyl sulfinate salt **102** and hydrazone **14** were isolated with complete

consumption of the starting material. The reaction was repeated with DMSO as the solvent and heated to 120 °C as well as 130 °C, both returning unreacted sulfinate salt.



Scheme 2.32: *Reaction conditions*: (i) BnBr (0.95 equiv.), K_2CO_3 (2 equiv.), 50 °C, 1 h, 1,4-dioxane [0.15 M]; (ii) 100 °C, 16 h.

By ^{1}H NMR spectroscopy, a doublet was observed at δ 6.24, *J* 11.5 and δ 6.26, *J* 11.0 for the sulfinate salts **100** and **102** respectively, indicative of a *Z* isomer, suggesting that it is not *Z* to *E* isomerisation that is preventing cyclisation.[iv]

There are several examples in the literature of alkenyl sulfinates reacting successfully with electrophiles such as benzyl bromide, so the lack of reactivity of the alkenyl sulfinate is not due to its inherent stability.[165] However, there are no examples of alkenyl sulfinates undergoing an S_NAr reaction with an electron-poor arene. Benzo[*b*]thiophene can be synthesised by cyclisation of *Z* styryl thiol,[166] although there are no reports of alkenyl sulfinates cyclising to form the corresponding benzo[*b*]thiophene 1,1-dioxide. This may be because the intramolecular ring-forming reaction of the alkenyl sulfinate salt is disfavoured possibly due the unfavourable bond angle and/or the electronics of the aryl ring.

[iv] In styryl sulfinates with *Z* geometry, the alkenyl hydrogens have a *J* coupling of ~10 Hz. Literature example: Chumachenko, N.; Sampson, P. *Tetrahedron* **2006**, *62*, 4540.

2.4 Conclusion

In summary, a one-pot palladium catalysed synthesis of sulfones from aryl-, heteroaryl- and alkenyl iodides *via* an *N*-aminosulfonamide intermediate has been developed, delivering access to a broad library of sulfones in good to excellent yields. This methodology uses commercially available or readily synthesised iodide coupling partners, thus avoiding the need for a thiol or sulfinate salt starting material. The mild reaction conditions provide compatibility with a large variety of functional groups, including oxidation-sensitive functionality. An intermediate in the synthesis towards the pharmaceutical Eletriptan was successfully synthesised in a one-pot procedure. Limitations of this methodology are the lack of reactivity towards certain electrophiles such as acrylates and some electron-poor arenes. Further studies into the use of electrophiles other than *C*-electrophiles are under investigation in the Willis group. The results of this investigation have been communicated.[167]

Unfortunately, the synthesis of benzo[*b*]thiophene 1,1-dioxide was unsuccessful as the alkenyl sulfinate salt proved to be too challenging a substrate to cyclise under the reaction conditions implemented.

Chapter 3

Synthesis of benzosultams: Aryl-N-SO_2 linkage

The sulfonamide functionality is often used as an amide replacement in biological systems due to its unique physical properties.[168] Benzosultams with an aryl-N-SO_2 linkage (1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide[v]) could represent an innovative bioisostere for 2-quinolones. Benzothiazine 2,2-dioxides are far less explored in their biological relevance compared to the regioisomer with an aryl-SO_2-N linkage (benzothiazine 1,1-dioxide – discussed in Chapter 4). However, there is growing interest in this structure with reports of its use as a reverse transcriptase (RT) inhibitor,[169] an interleukin-8 receptor antagonist,[170] and a factor Xa inhibitor (Figure 3.1).[171]

[v] Referred to as benzothiazine 2,2-dioxide for the rest of this thesis.

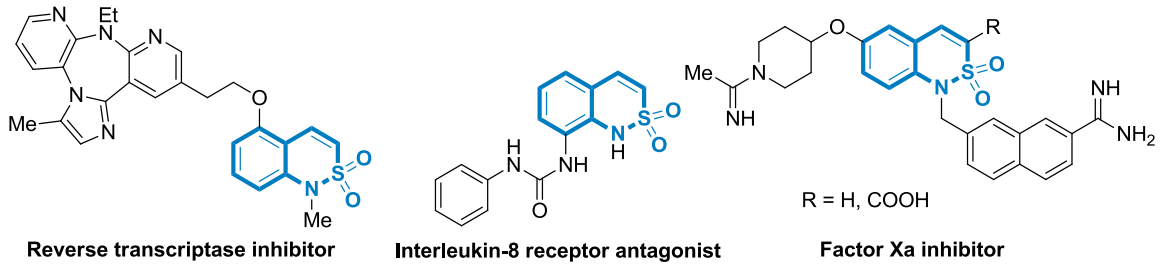


Figure 3.1: Example benzothiazine 2,2-dioxides demonstrating biological activity.

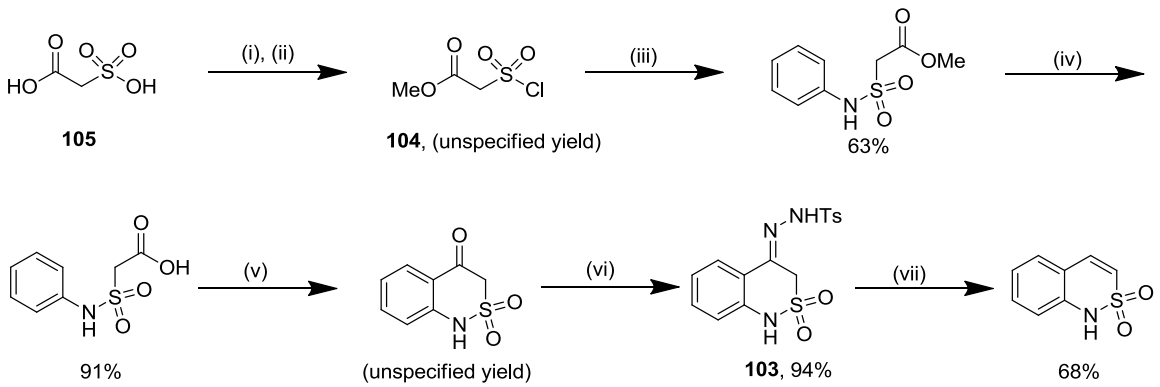
3.1 Methodologies towards the synthesis of benzothiazine 2,2-dioxide

There are only a handful of methods towards the synthesis of benzothiazine 2,2-dioxide, most of which use a sulfonyl chloride starting material. Sulfonyl chlorides themselves are frequently problematic to prepare. The most common method is oxidative chlorination of organosulfur compounds which requires hazardous reagents (e.g. aqueous chlorine[172]) or strong chlorinating agents (e.g. $SOCl_2$[173] and SO_2Cl_2[174]) that are often lachrymatory and water-sensitive. Furthermore, preparation of aromatic sulfonyl chlorides by electrophilic aromatic substitution (EAS) with chlorosulfonic acid[175] suffers from restricted substitution patterns due to the intrinsic sterics and electronics of the ring.

3.1.1 Current procedures to synthesise benzothiazine 2,2-dioxide

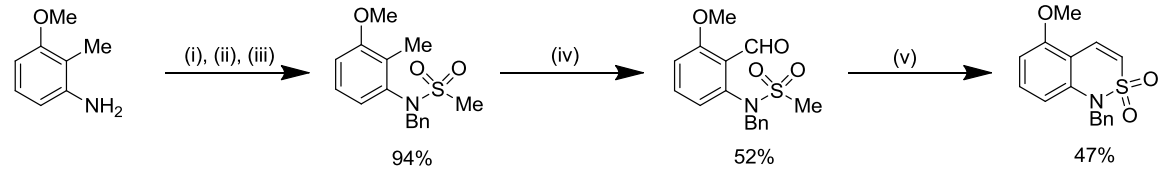
The first known synthesis of a benzothiazine 2,2-dioxide was reported in 1966 by two groups, Loev *et al.* and Rossi *et al.*, both describing a similar procedure.[176,177] Loev and co-workers prepared the benzothiazine 2,2-dioxide by performing a Bamford-Stevens reaction on the tosylhydrazone **103**, prepared by a 4-step procedure from the sulfonyl

chloride. The desired sulfonyl chloride **104** was synthesised from sulfoacetic acid **105**. This route was adapted in later years to synthesise benzosultam derivatives for investigation as interleukin-8 receptor anatagonists and for factor Xa inhibition (Scheme 3.1).[170,171]



Scheme 3.1: *Reaction conditions*: (i) HCl, MeOH; (ii) $SOCl_2$; (iii) Aniline; (iv) 10% NaOH; (v) Polyphosphoric acid; (vi) $TosNHNH_2$; (vii) NaOMe, EtOH.

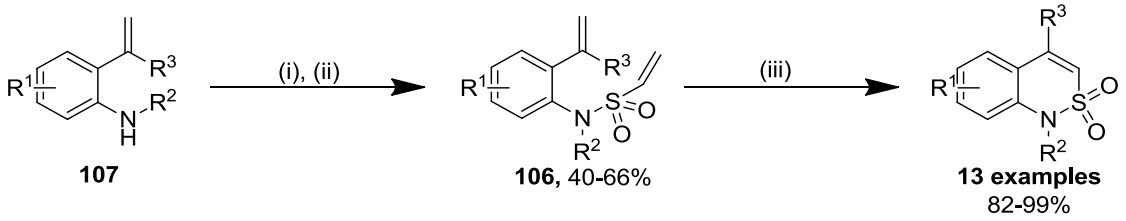
Blondet and Pascal have reported a five-step synthesis of benzothiazine 2,2-dioxide using strong basic conditions (Scheme 3.2).[178] This procedure has been implemented in several recent patents for the synthesis of reverse transcriptase inhibitors,[169] agents for the treatment or prophylaxis of HIV infection,[152] monoamine reuptake inhibitors,[179] and antiviral agents.[180]



Scheme 3.2: *Reaction conditions*: (i) $MeSO_2Cl$, pyridine, CH_2Cl_2, 5-25 °C; (ii) NaH, DMF, 5 °C; (iii) BnBr; (iv) $K_2S_2O_8$, $CuSO_4$, H_2O, MeCN, reflux; (v) NaH, DMF.

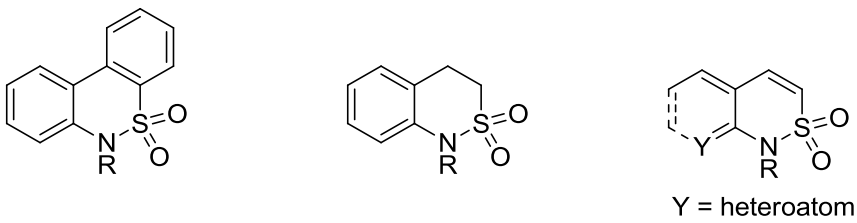
In 2008, a report by Minville and co-workers described the synthesis of benzothiazine 2,2-dioxides by implementing a ring-closing metathesis (Scheme 3.3).[181] The required

N-phenylethylenesulfonamides **106** were prepared by reaction of 2-chloroethanesulfonyl chloride with the corresponding *o*-vinylaniline **107**. The *o*-vinylanilines **107** themselves were prepared from the methyl anthranilates by reduction (Dibal-H), followed by oxidation (MnO_2), and finally olefination. They demonstrated that a variety of functional groups for R^1 and R^2 were possible, although alteration of R^3 from a hydrogen atom or methyl group resulted in inhibition of the ring-closing metathesis reaction.



Scheme 3.3: *Reaction conditions*: (i) 2-Chloroethanesulfonyl chloride, pyridine, CH_2Cl_2, –78 °C; (ii) Pyridine, 0 °C → RT; (iii) Grubbs II (10 mol%), CH_2Cl_2, 40 °C.

Literature examples for the synthesis of benzothiazine 2,2-dioxide derivatives such as dibenzosultam,[182] dihydrosulfostyril[176(a),183] and heteroarylsultams[180,184] also predominately involve either multi-step procedures from a sulfonyl chloride or are restricted in the functionality of the scaffold due to the synthetic procedure (Scheme 3.4).



Scheme 3.4: Example benozthiazine 2,2-derivatives.

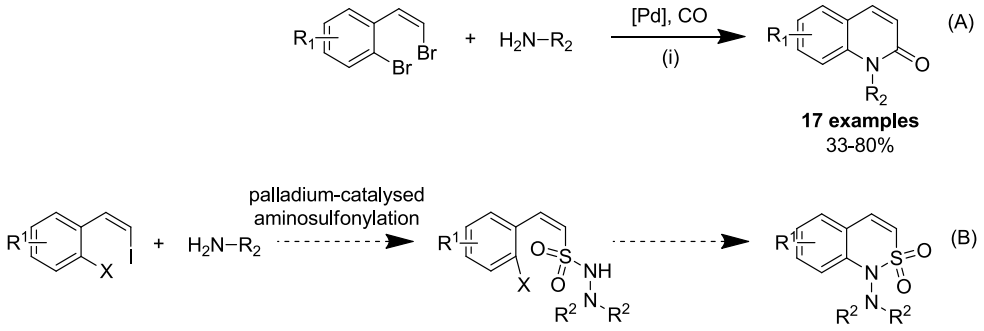
In summary, current methods for the preparation of benzothiazine 2,2-dioxide primarily feature multi-step sequences and lack functional group tolerance, consequently resulting in

limited substrate scope. The rest of this chapter will discuss the development of a more general route towards the synthesis of benzothiazine 2,2-dioxides.

3.2 Synthesis of benzothiazine 2,2-dioxide *via* an alkenyl iodide precursor

3.2.1 Introduction

Inspired by the Willis group tandem palladium catalysed carbonylation/amination sequence to obtain 2-quinolones, it was envisaged that a similar sulfonylation/amination sequence could give rise to benzothiazine 2,2-dioxides (Scheme 3.5).[185]

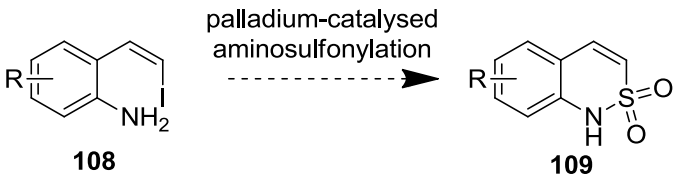


Scheme 3.5: (A) Willis group methodology for quinolone synthesis. *Reaction conditions*: (i) Dibromide (1 equiv., *Z*:*E*, 12:1), *N*-nucleophile (2 equiv.), $Pd_2(dba)_3$ (3 mol%), ligand (6 mol%), Cs_2CO_3 (3 equiv.), CO (balloon), toluene, 100 °C, 16 h; (B) Potential route towards the synthesis of benzothiazine 2,2-dioxide.

The palladium catalysed aminosulfonylation reaction using DABSO as the sulfur dioxide source would provide an efficient way to prepare the alkenyl sulfonamides whilst avoiding the need for a sulfonyl chloride starting material. This methodology would exploit the differing reactivity of the carbon-halide bonds as previous results in the Willis group have

shown that iodo-substrates are more reactive than their bromo counterparts under aminosulfonylation conditions.[25] As such, it was expected that the *N*-aminosulfonamide would form preferentially at the alkenyl iodide bond. Once the alkenyl *N*-aminosulfonamide has formed, subsequent ring closure at the remaining carbon-halide bond, either by a Buchwald–Hartwig coupling or by an S_NAr reaction, would give the desired benzothiazine 2,2-dioxide.

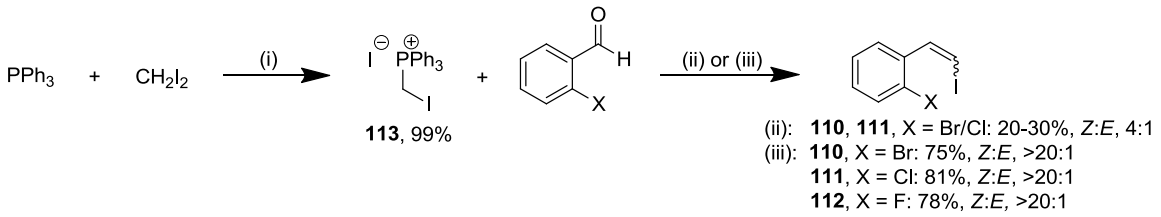
Alternatively, a palladium catalysed aminosulfonylation reaction with a 2-(2-iodoalkenyl)aniline **108** could provide an efficient route towards the synthesis of benzothiazine 2,2-dioxide **109** (Scheme 3.6).



Scheme 3.6: Potential synthesis of benzothiazine 2,2-dioxide from a 2-(2-iodoalkenyl)aniline.

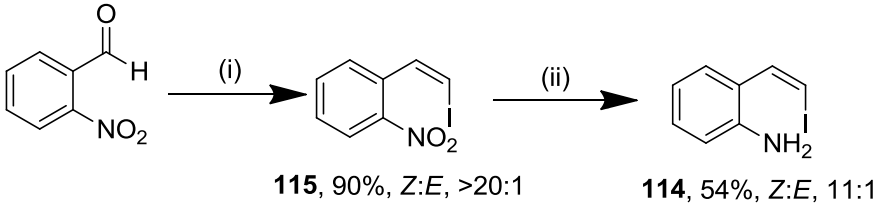
3.2.2 Synthesis of 2-(2-iodoalkenyl)aryl halide substrates

The 2-(2-iodoalkenyl)aryl halide substrates were prepared from the corresponding 2-halobenzaldehyde *via* a Wittig reaction. Initial Wittig reaction conditions gave poor yields (20-30%) and displayed low levels of *Z*-selectivity (*Z*:*E*, 4:1) where X = Br and Cl (**110** and **111** respectively) (Scheme 3.7, conditions (ii)). Improved yields and selectivity (*Z*:*E*, >20:1) were attained when the reaction was warmed to –20 °C during formation of the ylid (Scheme 3.7, conditions (iii)).



Scheme 3.7: *Reaction conditions*: (i) Triphenylphosphine (1 equiv.), diiodomethane (1.3 equiv.), PhMe, 50 °C, 48 h;[186] (ii) (Iodomethyl)triphenylphosphonium iodide **113** (1.2 equiv.), KO^{t}Bu (1.2 equiv.), THF, –78 °C, add 2-halobenzaldehyde (1 equiv.), RT, 16 h; (iii) (Iodomethyl)triphenylphosphonium iodide (1.2 equiv.), KO^{t}Bu (1.18 equiv.), THF, –78 °C to –20 °C, 10 min, add 2-halobenzaldehyde (1 equiv.) at –78 °C, warm to RT, 16 h.

The alkenyl iodide **114** was prepared from 2-nitrobenzaldehyde by the Wittig reaction and then subsequent reduction of the nitro group (Scheme 3.8).

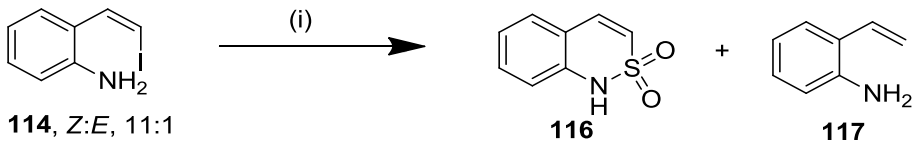


Scheme 3.8: *Reaction conditions*: (i) (Iodomethyl)triphenylphosphonium iodide (1.2 equiv.), KO^{t}Bu (1.18 equiv.), THF, –78 °C to –20 °C, 10 min, add 2-nitrobenzaldehyde (1 equiv.) at –78 °C, RT, 16 h; (ii) Alkenyl iodide **115** (1 equiv., *Z*:*E*, >20:1), $SnCl_2.2H_2O$ (4 equiv.), ethanol, reflux, 40 min.

3.2.3 Preliminary reactions

A brief investigation was undertaken into the reaction of alkenyl iodide **114** with DABSO under palladium catalysed conditions in an attempt to form benzothiazine 2,2-dioxide **116** directly (Table 3.1).

Table 3.1: Attempted formation of a benzothiazine 2,2-dioxide from alkenyl iodide 114.



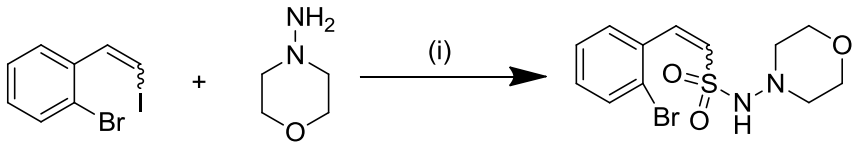
114, *Z*:*E*, 11:1 **116** **117**

Entry	Ligand (mol%)	Solvent	DABSO/ equiv.	Base	Temp/ °C	114 : 116 : 117[a]
1	$^{t}Bu_3P.HBF_4$ (20)	dioxane	1.1	-	70	0.2 : 0 : 0.8
2	Cata*CX*ium A (20)	dioxane	1.1	-	90	0 : 0 : 1[b]
3	Cata*CX*ium A (20)	dioxane	1.1	-	100	0 : 0 : 1
4	Xantphos (10)	toluene	1.1	-	100	0 : 0 : 1
5	Xantphos (10)	toluene	0.6	Cs_2CO_3	90	0 : 0 : 1
6	Xantphos (10)	toluene	0.6	Cs_2CO_3	100	0 : 0 : 1

Reaction conditions: (i) 2-(2-Iodovinyl)aniline **114** (1 equiv., *Z*:*E*, 11:1), $Pd(OAc)_2$ (10 mol%), ligand, DABSO, base (1.5 equiv.), solvent [0.15 M], 24 h. [a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield 87%.

However, all reaction conditions resulted in formation of the dehalogenated styrene product **117**. These results were in line with previous results that have shown that nucleophiles other than hydrazines, such as amines as well as *N*-substituted hydrazines, were unsuccessful in the palladium catalysed aminosulfonylation reaction. As a consequence, focus was turned to the cyclisation of alkenyl *N*-aminosulfonamides.

A preliminary reaction was performed using the alkenyl iodide **110** with a *Z*:*E* selectivity of 4:1 which gave the *N*-aminosulfonamide **118** in a total yield of 55% (Scheme 3.9). However, a large drop in the *Z*:*E* selectivity was observed (*Z*:*E*, 0.9:1). The rest of the material was observed to be an inseparable mixture of presumed homocoupling products (determined by ^{1}H NMR spectroscopy and mass spectrometry) and unreacted starting material. A similar yield and reduction in *Z*:*E* selectivity was observed for the alkenyl iodide **110** with *Z*:*E*, >20:1 (see Section 3.2.5 for discussion).



110, *Z*:*E*, 4:1
Z:*E*, >20:1

118, 55%, *Z*:*E*, 0.9:1
61%, *Z*:*E*, 4:1

Scheme 3.9: *Reaction conditions*: (i) 1-Bromo-2-(2-iodovinyl)benzene **110** (1 equiv.), 4-aminomorpholine (1.5 equiv.), $Pd(OAc)_2$ (10 mol%), $^tBu_3P.HBF_4$ (20 mol%), DABSO (1.1 equiv.), 1,4-dioxane [0.15 M], 70 °C, 16 h.

3.2.4 Optimisation of reaction conditions

A number of variables were investigated for the synthesis of alkenyl *N*-aminosulfonamides in an attempt to improve both the yield and the *Z*:*E* selectivity of the palladium catalysed aminosulfonylation reaction.[vi] By comparison to analogous 2-quinolone forming reactions that employ an alkenyl amide intermediate,[187] it was expected that a high *Z*:*E* selectivity was a prerequiste for the subsequent cyclisation step. The parameters selected for investigation were the ligand (Table 3.2), equivalents of DABSO (Table 3.3), concentration (Table 3.4), temperature (Table 3.5), base (Table 3.6), catalyst to ligand ratio (Table 3.7), solvent (Table 3.8) and reaction time (Table 3.9).

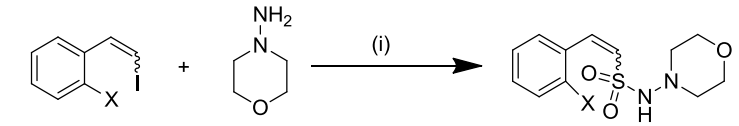
The chloro- and fluoro-substrates **111** and **112** were also examined because of their reduced steric influence compared with the bromo-substrate. However, little difference in the *Z*:*E* ratio or yield was observed (Table 3.2 and Table 3.7).

A range of *bis*- and *mono*-phosphines was investigated with varying bite angles, with the bulky ligand Cata*CX*ium A offering both the best yield and *Z*:*E* ratio (entry 2, Table 3.2).

[vi] Some of the optimisation reactions were performed using the alkenyl iodide **110** with *Z*:*E*, 4:1, as they were executed before the improved procedure to synthesise the alkenyl iodide (*Z*:*E*, >20:1) was developed.

On the other hand, an improved *Z*:*E* ratio was obtained with DPEPhos and dppb, although both gave reduced yields (entries 15 and 16).

Table 3.2: Optimisation of ligand.



110, X = Br, *Z*:*E*, 4:1
111, X = Cl, *Z*:*E*, 4:1

118, X = Br
119, X = Cl

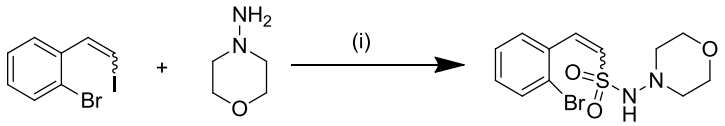
Entry	Ligand	Ligand/ mol%	X	*Z*:*E* product ratio[a]	Yield/ %[b]
1	^{t}Bu$_3$P.HBF$_4$	20	Br	0.9 : 1	55
2	Cata*CX*ium A	20	Br	1.2 : 1	55
3	^{t}Bu$_3$P.HBF$_4$	20	Cl	0.9 : 1	57
4	Cata*CX*ium A	20	Cl	1.2 : 1	58
5	^{t}Bu$_2$MeP.HBF$_4$	20	Br	1.4 : 1	9
6	PCy$_3$	20	Br	0.3 : 1	<5[a]
7	XPhos	20	Br	0.4 : 1	<5[a]
8	DavePhos	20	Br	1.1 : 1	23
9	RuPhos	20	Br	1.0 : 1	36
10	QPhos	20	Br	0.6 : 1	26
11	Cata*CX*ium ABn	20	Br	1 : 1	<5[a]
12	PPh$_3$	20	Br	1 : 1	38
13	dppe	10	Br	0.6 : 1	<5[a]
14	dppp	10	Br	1.0 : 1	<5[a]
15	dppb	10	Br	2.2 : 1	19
16	DPEPhos	10	Br	2.9 : 1	15
17	^{t}Bu-Xantphos	10	Br	0.7 : 1	<5[a]
18	Xantphos	10	Br	1.3 : 1	32

Reaction conditions: (i) 2-(2-Iodoalkenyl)aryl halide **110** or **111** (1 equiv., *Z*:*E*, 4:1), Pd(OAc)$_2$ (10 mol%), ligand, DABSO (1.1 equiv.), 4-aminomorpholine (1.5 equiv.), 1,4-dioxane [0.15 M], 70 °C, 16 h. [a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield.

The yield and isomerisation were relatively unaffected by an increase in the equivalents of DABSO (Table 3.3, entries 1 to 6). Surprisingly, when DABSO was replaced with potassium metabisulfite or morpholine·SO_2 as the sulfur dioxide source, only unreacted

starting material or a complex mixture of products, respectively, was returned (entries 7 and 8).

Table 3.3: Optimisation of sulfur dioxide source.



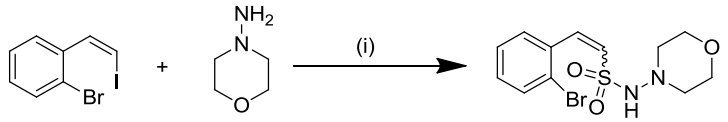
110, *Z*:*E*, 4:1 **118**

Entry	Ligand	SO_2 source (equiv.)	*Z*:*E* product ratio[a]	Yield/ %[b]
1	$^{t}Bu_3P.HBF_4$	DABSO (0.6)[c]	1.0 : 1	54
2	$^{t}Bu_3P.HBF_4$	DABSO (1.1)	0.9 : 1	55
3	$^{t}Bu_3P.HBF_4$	DABSO (1.6)	1.2 : 1	56
4	$^{t}Bu_3P.HBF_4$	DABSO (2.2)	1.2 : 1	55
5	Cata*CX*ium A	DABSO (1.1)	1.2 : 1	55
6	Cata*CX*ium A	DABSO (1.6)	1.3 : 1	50
7	Cata*CX*ium A	$K_2S_2O_5$	n.d.	n.d.
8	Cata*CX*ium A	morpholine·SO_2	n.d.	n.d.

Reaction conditions: (i) 1-Bromo-2-(2-iodovinyl)benzene **110** (1 equiv., *Z*:*E*, 4:1), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), DABSO, DABCO, 4-aminomorpholine (1.5 equiv.), 1,4-dioxane [0.15 M], 70 °C 16 h. [a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield. [c] 0.5 equiv. of DABCO added. n.d. = not detected.

Higher concentrations gave a lower *Z*:*E* ratio (Table 3.4) and a lower temperature gave a lower *Z*:*E* ratio and yield (entry 1, Table 3.5). Using Cs_2CO_3 as the base resulted in an increased yield but reduced *Z*:*E* selectivity, (entry 7, Table 3.6), whilst the other bases sampled gave poor results. When the catalyst to ligand ratio was 1:1 (entry 1, Table 3.7), rather than 1:2 or 1:3 (entries 2 and 3), there was a favourable increase in the *Z*:*E* ratio, but a decrease in yield. It was encouraging to see that despite a lower catalyst loading, the overall yield was only slightly reduced (entries 4 and 5). From the solvents surveyed, 1,4-dioxane gave the highest yield and *Z*:*E* ratio (Table 3.8).

Table 3.4: Optimisation of concentration.

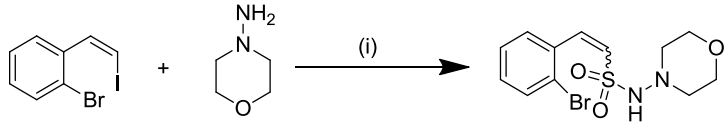


110, *Z*:*E*, >20:1 **118**

Entry	Concentration/ [M]	*Z*:*E* ratio[a]	Yield/ %[b]
1	0.48	1.8 : 1	37
2	0.24	4.0 : 1	63
3	0.12	3.5 : 1	55

Reaction conditions: (i) 1-Bromo-2-(2-iodovinyl)benzene **110** (1 equiv., *Z*:*E*, >20:1), $Pd(OAc)_2$ (10 mol%), Cata*CX*ium A (20 mol%), DABSO (1.1 equiv.), 4-aminomorpholine (1.5 equiv.), 1,4-dioxane, 70 °C, 16 h. [a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield.

Table 3.5: Optimisation of reaction temperature.

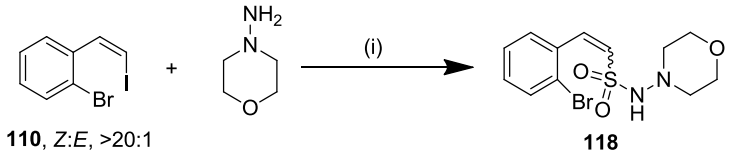


110, *Z*:*E*, >20:1 **118**

Entry	Temp/ °C	*Z*:*E* product ratio[a]	Yield / %[b]
1	50	1.0 : 1	16
2	70	4.0 : 1	63
3	80	4.5 : 1	64
4	90	4.3 : 1	63

Reaction conditions: (i) 1-Bromo-2-(2-iodovinyl)benzene **110** (1 equiv., *Z*:*E*, >20:1), $Pd(OAc)_2$ (10 mol%), Cata*CX*ium A (20 mol%), DABSO (1.1 equiv.), 4-aminomorpholine (1.5 equiv.), 1,4-dioxane [0.15 M], 16 h. [a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield.

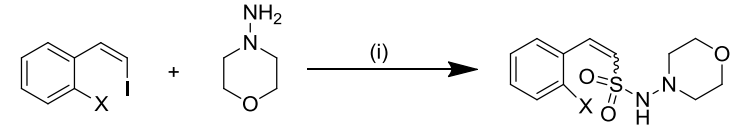
Table 3.6: Optimisation of base.



Entry	Base	*Z*:*E* product ratio[a]	Yield / %[b]
1	K_3PO_4	0.5 : 1	39
2	Na_3PO_4	0.4 : 1	39
3	Na_2HPO_4	1.3 : 1	22
4	NaH_2PO_4	5.3 : 1	30
5	K_2CO_3	2.2 : 1	36
6	Na_2CO_3	1.0 : 1	12
7	Cs_2CO_3	2.4 : 1	75

Reaction conditions: (i) 1-Bromo-2-(2-iodovinyl)benzene **110** (1 equiv., *Z*:*E*, >20:1), $Pd(OAc)_2$ (10 mol%), Cata*CX*ium A (20 mol%), DABSO (0.6 equiv.), 4-aminomorpholine (1.5 equiv.), base (1.5 equiv.), 1,4-dioxane [0.15 M], 70 °C, 16 h. [a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield.

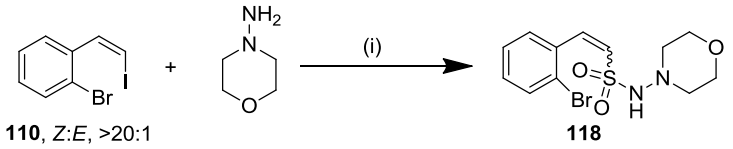
Table 3.7: Optimisation of catalyst to ligand ratio.



Entry	X	$Pd(OAc)_2$/ mol%	Cata*CX*ium A/ mol%	Ratio of catalyst: ligand	*Z*:*E* product ratio[a]	Yield/ %[b]
1	Br	10	10	1 : 1	8.0 : 1	38
2	Br	10	20	1 : 2	4.0 : 1	63
3	Br	10	30	1 : 3	3.4 : 1	61
4	Br	5	15	1 : 3	3.0 : 1	53
5	F	5	15	1 : 3	3.2 : 1	54
6	F	10	20	1 : 2	4.0 : 1	57

Reaction conditions: (i) 2-(2-Haloalkenyl)aryl halide **110** or **112** (1 equiv., *Z*:*E*, >20:1), $Pd(OAc)_2$, Cata*CX*ium A, DABSO (1.1 equiv.), 4-aminomorpholine (1.5 equiv.), 1,4-dioxane [0.15 M], 70 °C, 16 h. [a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield.

Table 3.8: Optimisation of solvent.



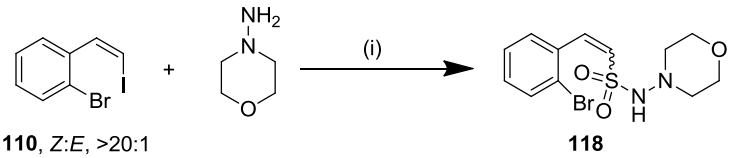
110, *Z*:*E*, >20:1 **118**

Entry	Solvent	*Z*:*E* product ratio[a]	Yield / %[b]
1	1,4-dioxane	4.0 : 1	63
2	toluene	1.2 : 1	40
3	*m*-xylene	-	n.d.
4	MeCN	1.0 : 1	15

Reaction conditions: (i) 1-Bromo-2-(2-iodovinyl)benzene **110** (1 equiv., *Z*:*E*, >20:1), $Pd(OAc)_2$ (10 mol%), Cata*CX*ium A (20 mol%), DABSO (1.1 equiv.), 4-aminomorpholine (1.5 equiv.), solvent [0.15 M], 70 °C, 16 h. [a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield. n.d. = not detected.

A reaction conducted over 96 h (Table 3.9A) showed that the *Z*:*E* ratio drastically decreased over time suggesting that the product was isomerising under the reaction conditions. Further investigation revealed that a reaction time between 6 to 8 hours gave the optimal *Z*:*E* ratio as well as a good conversion to the *Z* isomer (Table 3.9B).

Table 3.9: Optimisation of reaction time.



110, *Z*:*E*, >20:1 **118**

A

Time/ h	*Z*:*E* ratio[a]	Conversion to *Z* product / %[a]
6	8.5 : 1	58
24	5.0 : 1	58
30	4.3 : 1	55
60	3.0 : 1	53
96	2.1 : 1	47

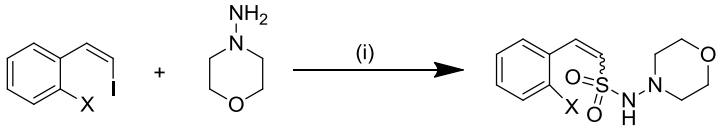
B

Time/ h	*Z*:*E* ratio[a]	Conversion to *Z* product / %[a]
3	>20 : 1	25
4	>20 : 1	36
5	9.0 : 1	48
6	8.0 : 1	58
8	6.8 : 1	64
10	6.0 : 1	59
24	4.5 : 1	57

Reaction conditions: (i) 1-Bromo-2-(2-iodovinyl)benzene **110** (1 equiv., *Z*:*E*, >20:1), $Pd(OAc)_2$ (10 mol%), Cata*CX*ium A (20 mol%), DABSO (1.1 equiv.), 4-aminomorpholine (1.5 equiv.), 1,4-dioxane [0.15 M], 70 °C. [a] Determined by ^{1}H NMR spectroscopy with respect to the starting material and *E* isomer product.

Cata*CX*ium A and a reduced reaction time were both employed in larger scale reactions in order to provide enough material to investigate the subsequent cyclisation step (*c.f.* normal scale 0.24 mmol, Table 3.10). Pleasingly, the *Z* products **99** and **118** were delivered in *Z*:*E* ratios and yields comparable to the smaller scale reactions.

Table 3.10: Larger scale reaction.



110, X= Br, *Z*:*E*, >20:1
112, X = F, *Z*:*E*, >20:1

118, X = Br
99, X = F

Entry	X	Substrate/ mmol	*Z*:*E* ratio[a]	*Z* product yield / %[b]
1	F	0.8	6.0 : 1	48
2	F	1.6	6.5 : 1	50
3	F	2.0	5.5 : 1	51
4	Br	0.7	7.0 : 1	53

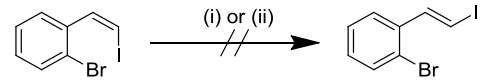
Reaction conditions: (i) 2-(2-Iodoalkenyl)aryl halide **110** or **112** (1 equiv., *Z*:*E*, >20:1), $Pd(OAc)_2$ (10 mol%), Cata*CX*ium A (20 mol%), DABSO (1.1 equiv.), 4-aminomorpholine (1.5 equiv.), 1,4-dioxane [0.15 M], 70 °C, 8 h. [a] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b] Isolated yield.

No reduction in the presumed homocoupling formation was observed during the optimisation reactions. Vinylic iodides are well-known to form homocoupling as well as decomposition products.[188] As an effort to suppress the formation of the homocoupling products, a literature procedure was used in which they reported reduced homocoupling formation with a similar alkenyl iodide substrate.[189] The alkenyl iodide was added in 4 portions over a 3 h period, (0.12 mmol at 0 h, 0.06 mmol at 0.5 h, 0.03 mmol at 1 h, then

0.03 mmol at 2 h) in the absence of light. However, this resulted in a worse *Z*:*E* ratio (3:1) and no reduction in the homocoupling product.

3.2.5 Investigation into the *Z* to *E* isomerisation of the alkenyl *N*-aminosulfonamide

It was first necessary to verify that the starting material did not isomerise under the reaction conditions. Thus, a reaction of only alkenyl iodide **110** and 4-aminomorpholine was conducted (Scheme 3.10, conditions (i)), followed by a separate reaction of **110** with all other reagents except 4-aminomorpholine (Scheme 3.10, conditions (ii)). Both these reactions returned alkenyl iodide **110** with *Z*:*E*, >20:1, suggesting it is the product alkenyl *N*-aminosulfonamide **118** that undergoes isomerisation.

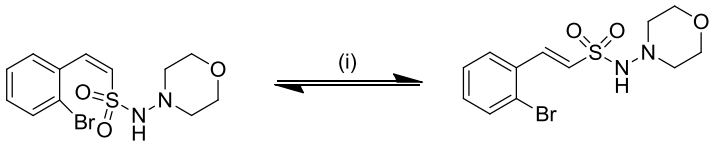


110, *Z*:*E*, >20:1 **110'**, *Z*:*E*, 1:>20

Scheme 3.10: *Reaction conditions*: 1-Bromo-2-(2-iodovinyl)benzene **110** (1 equiv., *Z*:*E*, >20:1), 1,4-dioxane [0.15 M], 70 °C, 16 h; (i) 4-Aminomorpholine (1.5 equiv.); (ii) $Pd(OAc)_2$, (10 mol%), Cata*CX*ium A (20 mol%), DABSO (1.1 equiv.).

Consequently, alkenyl *N*-aminosulfonamide **118** (*Z*:*E*, >20:1) was subjected to various reaction conditions in order to investigate the *Z* to *E* isomerisation (Table 3.11).

Table 3.11: Investigation into isomerisation of the *Z* isomer of alkenyl *N*-aminosulfonamide 118.



118, *Z*:*E*, >20:1 **118'**, *Z*:*E*, 1:>20

Entry	Reagents	*Z*:*E* ratio[a]
1	-	>20:1
2	DABCO (1.1 equiv.)	>20:1
3	DABSO (1.1 equiv.)	>20:1
4	4-Aminomorpholine (1.5 equiv.)	>20:1
5	Cata*CX*ium A (20 mol%)	>20:1
6	$Pd(OAc)_2$ (10 mol%)	3:1
7	$Pd(OAc)_2$ (10 mol%), Cata*CX*ium A (20 mol%)	1:>20
8	$Pd(OAc)_2$ (10 mol%), $^tBu_3P.HBF_4$ (20 mol%)	1:>20
9	$Pd(OAc)_2$ (10 mol%), dppb (10 mol%)	5:1
10	$Pd(OAc)_2$ (10 mol%), DPEPhos (10 mol%)	6:1
11	$(MeCN)_2PdCl_2$ (10 mol%)	10:1
12	$Pd(TFA)_2$ (10 mol%)	3:1
13	$(MeCN)_2Pd(OTs)_2$ **120** (10 mol%)	3:1
14	$Pd_2(dba)_3$ (10 mol%)	>20:1

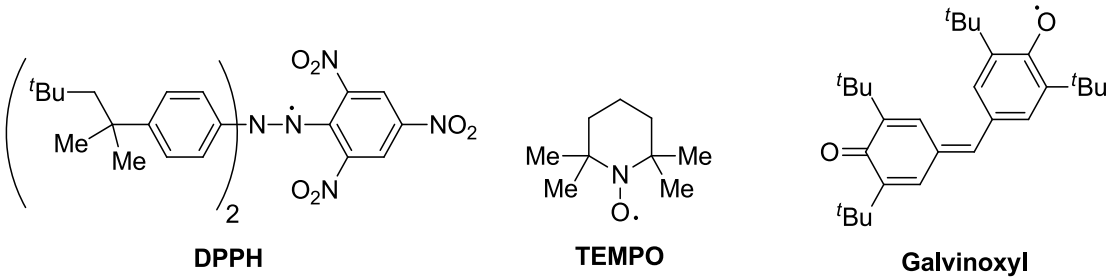
Reaction conditions: (i) Alkenyl *N*-aminosulfonamide **118** (1 equiv., *Z*:*E*, >20:1), 1,4-dioxane [0.15 M], 70 °C, 16 h. [a] Determined by ^1H NMR spectroscopy.

DABCO, DABSO, 4-aminomorpholine, and Cata*CX*ium A, in separate reactions, gave no isomerisation (entries 2 to 5). However, $Pd(OAc)_2$ (entry 6) decreased the *Z*:*E* ratio dramatically from >20:1 to 3:1 after 16 h. It has been reported that both Pd(0)[190] and Pd(II)[191] catalyse *cis* to *trans* alkene isomerisation and alkene migration. The mechanism for isomerisation using a Pd(II) catalyst is under debate and may involve either a [Pd-H] species,[192] β-carbocation,[193] π-allyl species[194] or a binuclear addition-elimination mechanism[195] as well as other theories.[196]

When the *Z* isomer **118** was exposed to both $Pd(OAc)_2$ and either Cata*CX*ium A or $^tBu_3P.HBF_4$ (entries 7 to 8), complete conversion to the *E* isomer **118'** was observed after

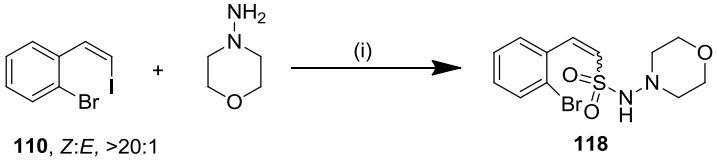
16 h. This may explain the improved *Z*:*E* ratio observed when the catalyst to ligand ratio was lowered to 1:1 (entry 1, Table 3.7). From the ligand investigation, dppb and DPEPhos had given the best *Z*:*E* selectivity (entries 15 and 16, Table 3.2). As such, the *N*-aminosulfonamide **118** was reacted with $Pd(OAc)_2$ and either dppb or DPEPhos as the ligand which resulted in reduced isomerisation (entries 9 and 10). However, reactions using these ligands were low yielding so were not investigated further. Palladium(II) sources with different counter-ions were explored in an effort to diminish the isomerisation as this has been reported to have an effect on the isomerisation.[192(c)] $(MeCN)_2PdCl_2$ gave reduced isomerisation (entry 11), but when $(MeCN)_2PdCl_2$ was used in the aminosulfonylation reaction (using Cata*CX*ium A as the ligand), the *Z*:*E* ratio (2:1) and *Z* isomer (36%) yield of *N*-aminosulfonamide **118** was low, suggesting that the ligand must accelerate the isomerisation. $Pd(TFA)_2$ and $(MeCN)_2Pd(OTs)_2$ gave no reduction in the isomerisation (entries 12 and 13). A palladium(0) source, $Pd_2(dba)_3$, was trialled and gave no isomerisation, however when it was used in the aminosulfonylation reaction (using Cata*CX*ium A as the ligand) it gave only returned starting material (entry 14).

Several reports have shown that the [Pd-H] traps, 2,2-di(4-*tert*-octylphenyl)-1-picrylhydrazyl (DPPH), 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), 2,6-di-*tert*-butyl-α-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)-*p*-tolyloxy (galvinoxyl) and *N*,*N*-diisopropylethylamine (DIPEA) can suppress the alkene migration or isomerisation significantly (Scheme 3.11).[195,197] These [Pd-H] traps were tested in the aminosulfonylation reaction.



Scheme 3.11: Example of [Pd-H] traps that have been shown to suppress palladium catalysed alkene migration and isomerisation.

Table 3.12 *Z* to *E* isomerisation in the presence of an additive.



Entry	Additive (equiv.)	Temp/ °C	Time/ h	*Z* : *E* ratio [a]	Yield/ % [b]
1	-	70	16	4 : 1	63
2	TEMPO (0.2)	70	6	2.5 : 1	54
3	DPPH (0.2)	70	6	1.0 : 0	19
4	Galvinoxyl (0.2)	70	16	3.5 : 1	71
5	DIPEA (0.2)	70	6	3.3 : 1	82
6	Galvinoxyl (0.2), DIPEA (0.2)	90	2.5	5.0 : 1	79
7	NEt_3 (0.2)	70	8	2.5 : 1	64
8	DBU (0.2)	70	8	-	n.d.
9	DABCO (0.2)	70	8	3.5 : 1	62
10	TBAB (1)	70	8	3.3 : 1	80
11	TBAB (0.5)	70	8	3.3 : 1	79
12	TBAB (1.5)	70	8	-	n.d.
13	TBAB (1)	70	3	10.0 : 1	76
14	TBAI (1)	70	3	12.0 : 1	75
15	TBAI (1)	60	3	10.0 : 1	58
16	TBAC (1)	70	8	-	n.d.
17	TBAAc (1)	70	3	5.0 : 1	54

Reaction conditions: (i) 1-Bromo-2-(2-iodovinyl)benzene **110** (1 equiv.), $Pd(OAc)_2$ (10 mol%), Cata*CX*ium A (20 mol%), DABSO (1.1 equiv.), 4-aminomorpholine (1.5 equiv.), 1,4-dioxane [0.15 M]. [a] Determined by ^{1}H NMR spectroscopy. [b] Isolated yield. n.d. = not detected.

The implementation of a dual additive system using Galvinoxyl and DIPEA proved effective providing the product in an increased yield and *Z*:*E* selectivity (entry 6). Alternative hindered bases to DIPEA were found to be not as productive (entries 7 to 9). On the other hand, the phase transfer catalyst tetrabutylammonium bromide (TBAB) had a dramatic effect on the rate of reaction (entry 13), with greatly improved *Z*:*E* selectivity of the product occurring after 3 h. When the TBAB:substrate ratio was greater than 1:1, a complex mixture of products was observed which is comparable to that reported in the literature (entry 12). Tetrabutylammonium salts are often used as an additive in Suzuki–Miyaura and Mizoroki–Heck cross-coupling reactions.[198] The stabilisation of palladium nanoparticles by $R_4N^+X^-$ is well documented and they are thought to slow down the aggregation process by forming a monolayer around the metal core.[199] These stimulating results led to investigation on the effect of the anion. TBAI proved to be the most effective promoter (entry 14) with TBAC and TBAAc giving returned starting material or a reduced yield respectively (entries 16 and 17).

3.2.6 Cyclisation of alkenyl *N*-aminosulfonamide

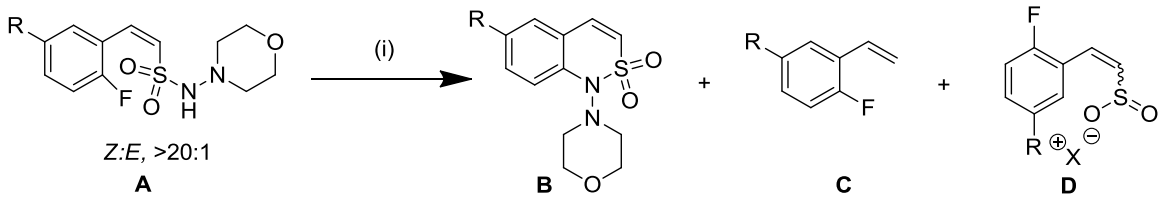
Investigation was then turned to the synthesis of the cyclised product. To cyclise the alkenyl *N*-aminosulfonamide, two possible intramolecular routes were investigated: (A) a S_NAr reaction with an aryl-F bond, and (B) a Buchwald–Hartwig reaction with an aryl-Br/Cl bond.

Firstly, the S_NAr process was investigated, focusing on variation of the base, solvent and temperature (Table 3.13). The reaction conditions employed were adapted from literature reports for related compounds. The cyclised product **122** was only observed in a maximum

27% yield under the reaction conditions examined when using the alkenyl *N*-aminosulfonamide **99** (entry 1). The rest of the material was observed to be the sulfinate salt **100** and the styrene product **123**. When alkenyl *N*-aminosulfonamide **99** was heated in the absence of base, starting material was recovered, suggesting that the *N*-aminosulfonamide decomposes in the presence of base and at high temperatures (as observed in Chapter 2) (entry 15). Attempts at disfavouring decomposition by lowering the reaction temperature resulted in an increase in returned starting material.

Inclusion of a strongly electron-withdrawing substituent on the aromatic ring proved to be an effective strategy. A $–CF_3$ group *para* to the aryl-fluoride afforded 88% of the desired cyclised product **124** (entry 16). When K_2CO_3 was used as the base, decomposition products became an issue (entry 17). Other bases such as triethylamine and DABCO gave no cyclised product (entries 19 to 20). Unfortunately, a *para* –F group gave no cyclised product and formed only the corresponding sulfinate salt (entry 21).

Table 3.13: Cyclisation using S_NAr.



99, R = H, **101**, R = CF_3, **121**, R = F

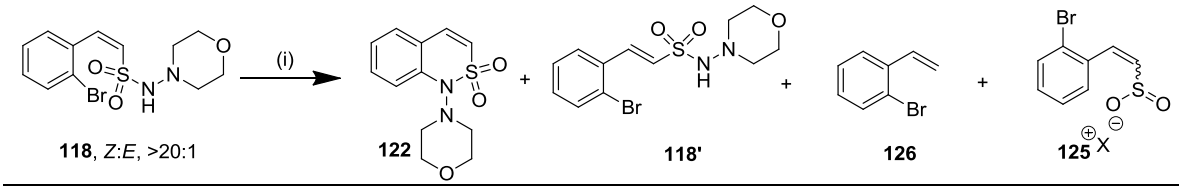
Entry	R	Base (equiv.)	Solvent	Temp/ °C	B yield/ %[a]	A : B : C : D [b]
1	H	Cs_2CO_3 (3)	1,4-dioxane	100	27	0 : 1 : 0 : 2.7
2	H	Cs_2CO_3 (3)	1,4-dioxane	90	18	0 : 1 : 0 : 4.5
3	H	Cs_2CO_3 (3)	1,4-dioxane	70	10	0 : 1 : 0 : 9
4	H	KO^{t}Bu (3)	1,4-dioxane	70	-	1 : 0 : 0 : 5
5	H	NaO^{t}Bu (3)	1,4-dioxane	70	-	1 : 0 : 0 : 5.5
6[200]	H	Cs_2CO_3 (3)	DMF	120	10	0 : 1 : 0.4 : 6.1
7	H	Cs_2CO_3 (3)	DMSO	150	-	0 : 0 : 1[c] : 0
8[201]	H	K_2CO_3 (3)	DMF	120	-	0 : 0 : 1 : 3
9[202]	H	K_2CO_3 (3)	DMF:THF(1:1)	60	-	1 : 0 : 0 : 0
10	H	K_2CO_3 (3)	DMF:THF(1:1)	90	10	0 : 1 : 1 : 8
11[203]	H	K_2CO_3 (3)	DMF	110[d]	-	0 : 0 : 1 : 1
12[204]	H	KO^{t}Bu (1)	DMF	100	-	1 : 0 : 5 : 3.5
13[205]	H	NaOH (1.5)	MeOH:DMF(1:1)	90	15	1 : 1 : 0.6 : 4
14[206]	H	NaH (1)	DMF	0 → 90	-	1 : 0 : 1.4 : 1
15	H	-	DMF	120	-	1 : 0 : 0 : 0
16[e]	CF_3	Cs_2CO_3 (3)	1,4-dioxane	100	88	0 : 1 : 0 : 0.1
17[e]	CF_3	K_2CO_3 (3)	1,4-dioxane	100	70	0 : 1 : 0.3 : 0.1
18[e]	CF_3	K_2CO_3 (3)	1,4-dioxane	70	68	0.3 : 1 : 0 : 0.2
19	CF_3	Et_3N (3)	1,4-dioxane	100	-	1 : 0 : 0 : 0
20	CF_3	DABCO (3)	1,4-dioxane	100	-	1 : 0 : 0 : 0
21	F	Cs_2CO_3 (3)	1,4-dioxane	100	-	0 : 0 : 0 : 1

Reaction conditions: (i) Alkenyl *N*-aminosulfonamide (1 equiv., *Z*:*E*, >20:1), base, solvent [0.15 M], 16 h h h. [a] Isolated yield. [b] Ratio of D determined by subtraction of other products after column chromatography from 100%. [c] 81% isolated yield. [d] μw, 45 min reaction time. [e] 1 h reaction time.

The Buchwald–Hartwig coupling was then explored as a potential route towards the synthesis of benzothiazine 2,2-dioxide. Palladium[207] or copper[208] catalysts were examined with focus on using comparable reaction conditions to the initial palladium catalysed aminosulfonylation step to allow for a potential one-pot reaction (Table 3.14). Initial results using $Pd(OAc)_2$ and Xantphos were encouraging giving the cyclised product **122** in a 55% yield (entry 1). The same reaction conditions were applied to the alkenyl

N-aminosulfonamide **119** with an aryl chloride group (entry 2). Disappointingly, this only resulted in isomerisation to the *E* isomer and decomposition to the sulfinate salt. Consequently, optimisation focused on using the alkenyl *N*-aminosulfonamide **118** with an aryl bromide group. At lower temperatures, *Z* to *E* isomerisation was dominant, but at higher temperatures, decomposition to the styrene **126** and sulfinate salt **125** was prevalent. An intricate balance between decomposition, isomerisation and product formation was obtained when the reaction mixture was heated at reflux in 1,4-dioxane using cesium carbonate as the base. These conditions afforded the desired cyclised product **122** in an 83% yield after 1 h reaction time.

Table 3.14: Cyclisation using Buchwald–Hartwig coupling.



Entry	Catalyst (mol%)	Ligand (mol%)	Solvent	Base	Temp / °C	122 yield/ %[a]	118:122:118' :126:125
1	$Pd(OAc)_2$ (10)	Xantphos (10)	toluene	Cs_2CO_3	100	55	0:1:0:0.1:0.7
2[c]	$Pd(OAc)_2$ (10)	Xantphos (10)	toluene	Cs_2CO_3	100	-	0:0:0.1:0:1
3	$Pd_2(dba)_3$ (5)	Xantphos (10)	dioxane	Cs_2CO_3	100	-	0:0:0:0:1
4	CuI (20)	DMEDA (10)	toluene	K_2CO_3	110	-	0:0:0:1[d]:0.2
5	$Pd(OAc)_2$ (10)	Cata*CX*ium A (20)	dioxane	NaO^{t}Bu	70	-	0:0:1:0:2
6	$Pd(OAc)_2$ (10)	Cata*CX*ium A (20)	dioxane	NaO^{t}Bu	100	34	0:1:0.4:0:1.5
7	$Pd(OAc)_2$ (10)	Cata*CX*ium A (20)	dioxane	Cs_2CO_3	100	63	0:1:0:0:0.6
8	$Pd(OAc)_2$ (10)	Cata*CX*ium A (20)	dioxane	Cs_2CO_3	70	5	0:1:10:3:6
9	$Pd(OAc)_2$ (10)	Cata*CX*ium A (20)	dioxane	Cs_2CO_3	90	60	0:1:0:0.1:0.5
10	$Pd(OAc)_2$ (10)	Cata*CX*ium A (20)	dioxane	Cs_2CO_3	reflux	75	0:1:0:0:0.3
11[e]	$Pd(OAc)_2$ (10)	Cata*CX*ium A (20)	dioxane	Cs_2CO_3	reflux	84	0:1:0:0:0.2
12[e,f]	$Pd(OAc)_2$ (10)	Cata*CX*ium A (20)	dioxane	Cs_2CO_3	reflux	83	0:1:0:0:0.2

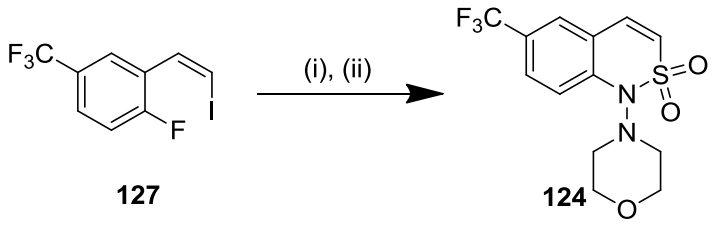
Reaction conditions: (i) Alkenyl *N*-aminosulfonamide **118** (1 equiv., *Z*:*E*, >20:1), catalyst, ligand, base (1.5 equiv.), solvent [0.15 M], 24 h. [a] Isolated yield. [b] Ratio of **125** determined by subtraction of other products after column chromatography from 100%. [c] Alkenyl *N*-aminosulfonamide **119** (1 equiv., *Z*:*E*, >20:1) used. [d] 83% isolated yield. [e] Catalyst, ligand, base (1.5 equiv.), solvent [0.15 M], stirred for 10 min, then alkenyl *N*-aminosulfonamide **118** (*Z*:*E*, 12:1) added. [f] Reaction time of 1 h.

3.2.7 A one-pot synthesis of benzothiazine 2,2-dioxide

Designing a one-pot procedure to synthesise the benzothiazine 2,2-dioxide directly from the alkenyl iodide *via* an alkenyl *N*-aminosulfonamide intermediate would potentially remove the complication of *Z* to *E* isomerisation by cyclising the *Z* product directly. Both S_NAr and Buchwald–Hartwig strategies were investigated.

The highest yielding aryl fluoride **127** was first subjected to the aminosulfonylation reaction conditions, after which base was added and the reaction temperature increased to 100 °C (entries 1 and 2). Significant *Z* to *E* isomerisation, along with decomposition to the sulfinate salt and styrene product, was thought to prevent the formation of the cyclised product **124**. Lowering the reaction temperature of the second step (entries 3 to 5) and addition of the base at the start of the reaction (entry 6) produced only trace product. Filtration through Celite after the first step and then reaction with base still resulted in minimal product formation, albeit no *Z* to *E* isomerisation occurred (entry 7).

Table 3.15: One-pot cyclisation using a S_NAr strategy.



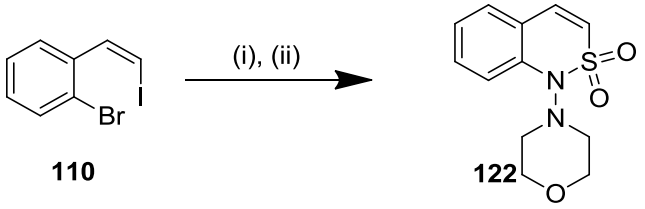
127 **124**

Entry	First step (i)			Second step (ii)		Product/ %[a]
	Temp/ °C	Time/ h	Cs_2CO_3 equiv.	Solvent added Temp/ °C	Cs_2CO_3 equiv.	
1	70	8	-	100	3	n.d.
2	70	16	-	100	3	n.d.
3	70	8	-	80	3	n.d.
4	70	8	-	70	3	4[b]
5	70	8	-	60	3	<5
6	70	16	3	-	-	n.d.
7[c]	70	8	-	100	3	<5

Reaction conditions: (i) 1-Fluoro-2-(2-iodovinyl)-4-(trifluoromethyl)benzene **127** (1 equiv., *Z*:*E*, >20:1), $Pd(OAc)_2$ (10 mol%), Cata*CX*ium A (20 mol%), DABSO (1.1 equiv.), 4-aminomorpholine (1.2 equiv.), 1,4-dioxane [0.15 M]; (ii) Cs_2CO_3, 24 h; [a] Determined by ^{1}H NMR spectrometry and mass spectroscopy. [b] Isolated yield. [c] Filtered through Celite after first step. n.d. = not detected.

One-pot reaction conditions were then examined using the Buchwald–Hartwig conditions (Table 3.16). As the cyclisation reaction conditions were deliberately sought to be as similar to the aminosulfonylation reaction conditions as possible, it was hoped that both steps would be compatible. Unfortunately, *Z* to *E* isomerisation and decomposition to the sulfinate salt was prevalent and no formation of the desired cyclised product was observed (entries 1 to 4). Filtration of the alkenyl *N*-aminosulfonamide intermediate through Celite gave only a low yield of the cyclised product (entry 5). It appeared that only purified alkenyl *N*-aminosulfonamide gave cyclised product in a good yield.

Table 3.16: One-pot cyclisation using Buchwald–Hartwig coupling.



110 **122**

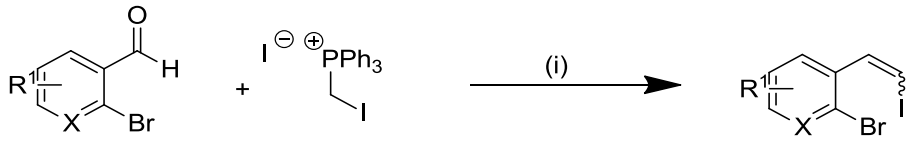
Entry	First step (i)			Second step (ii)		Product/ %[a]
	Temp/ °C	Time/ h	Cs_2CO_3 equiv.	Catalyst added (mol%)	Cs_2CO_3 equiv.	
1	70	8	-	-	1.5	n.d.
2	70	8	-	$Pd(OAc)_2$ (10) Cata*CX*ium A (20)	1.5	n.d.
3[b]	70	3	-	-	1.5	n.d.
4	70	8	1.5	-	-	n.d.
5[c]	70	8	-	$Pd(OAc)_2$ (10) Cata*CX*ium A (20)	1.5	13[d]

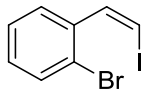
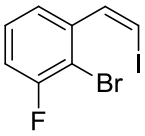
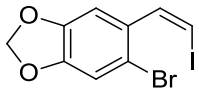
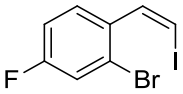
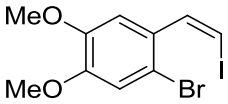
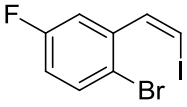
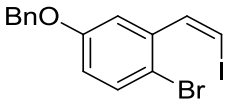
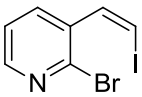
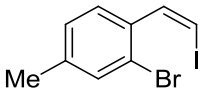
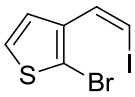
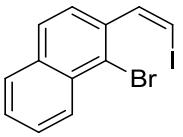
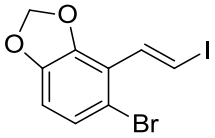
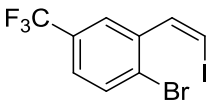
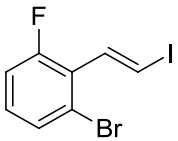
Reaction conditions: (i) 1-Bromo-2-(2-iodovinyl)benzene **110** (1 equiv., *Z*:*E*, >20:1), $Pd(OAc)_2$ (10 mol%), Cata*CX*ium A (20 mol%), DABSO (1.1 equiv.), 4-aminomorpholine (1.5 equiv.), 1,4-dioxane; (ii) reflux, 24 h. [a] Determined by ^{1}H NMR spectroscopy. [b] TBAI (1 equiv.) added in first step. [c] Filtered through Celite after first step. [d] Isolated yield. n.d. = not detected.

3.2.8 Synthesis of benzothiazine 2,2-dioxide and its derivatives

The improvements to the reaction conditions to suppress the decomposition and isomerisation of the alkenyl *N*-aminosulfonamide intermediate during both reaction steps were then implemented to synthesise a range of benzothiazine 2,2-dioxides and derivatives. Firstly, a selection of alkenyl iodides was prepared using the optimised Wittig reaction conditions (Table 3.17). After careful purification, a portion of the alkenyl iodides of entries 1 to 11 was obtained in a high *Z*:*E* selectivity ready to be used in the subsequent aminosulfonylation reaction. 2-Bromobenzaldehydes with substitution at position C-3 unfortunately gave predominantly the *E* isomer (entries 13 to 14).[209]

Table 3.17: Synthesis of alkenyl iodides.



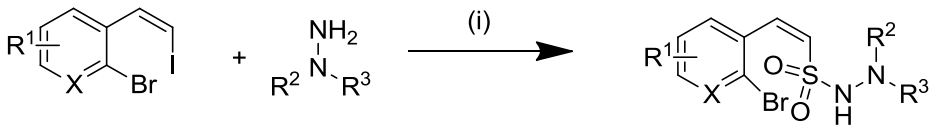
Entry	Product [a]	Yield/ %[b]	Entry	Product [a]	Yield/ %[b]
1	 **110**, *Z*:*E*, >20:1	75	8	 **135**, *Z*:*E*, >20:1	89
2	 **129**, *Z*:*E*, 15:1	79	9	 **136**, *Z*:*E*, 18:1	84
3	 **130**, *Z*:*E*, 15:1	67	10	 **137**, *Z*:*E*, 18:1	79
4	 **131**, *Z*:*E*, 15:1	72	11	 **138**, *Z*:*E*, >20:1	47
5	 **132**, *Z*:*E*, 15:1	70	12	 **139**, *Z*:*E*, 10:1	55
6	 **133,** *Z*:*E*, >20:1	72	13	 **140**, *Z*:*E*, 1:15	60
7	 **134**, *Z*:*E*, >20:1	88	14	 **141**, *Z*:*E*, 1:>20	65

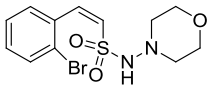
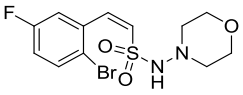
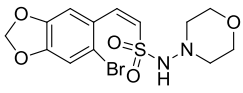
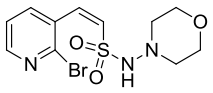
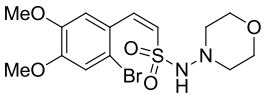
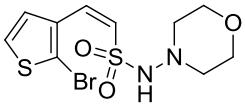
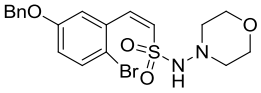
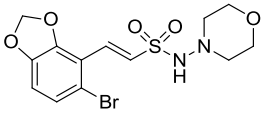
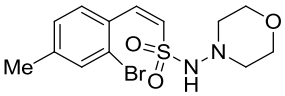
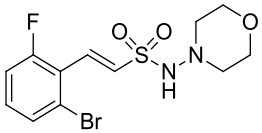
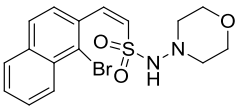
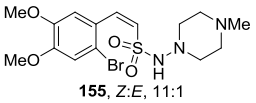
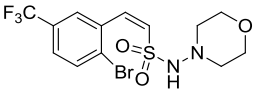
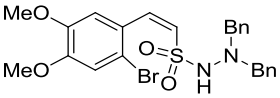
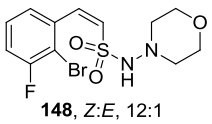
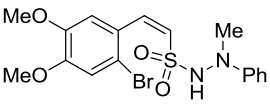
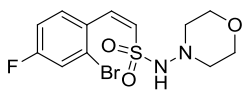
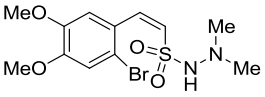
Reaction conditions: (i) (Iodomethyl)triphenylphosphonium iodide (1.2 equiv.), KO^{t}Bu (1.18 equiv.), THF, –78 °C to –20 °C, 10 min, add 2-halobenzaldehyde (1 equiv.) at –78 °C, warm to RT, 16 h. [a] The *Z*:*E* selectivities are determined by ^{1}H NMR spectroscopy of the crude reaction mixture. During purification, separation of the *Z* and *E* isomers was strived for to obtain a portion of the alkenyl iodide with the highest

possible *Z*:*E* selectivity to be used in following the aminosulfonylation reaction. [b] The yields reported in the table refer to the sum of the portions collected after column chromatography.

The alkenyl iodides were then reacted under the optimised palladium catalysed aminosulfonylation conditions (Table 3.18). As expected, a drop in *Z*:*E* selectivity was observed, but the alkenyl *N*-aminosulfonamides were obtained in moderate to high yields. Variation of both the aryl ring and hydrazine coupling partner was achieved successfully. The heteroaryl alkenyl iodides gave the corresponding products in good yields (entries 11 to 12). Unfortunately, the dimethylhydrazine gave no product. This hydrazine has previously been shown to give lower reactivity in the aminosulfonylation reaction (entry 18).[25]

Table 3.18: Synthesis of alkenyl *N*-aminosulfonamides.

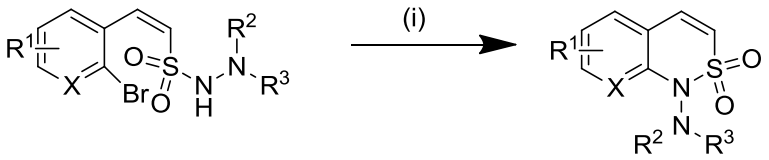


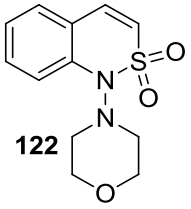
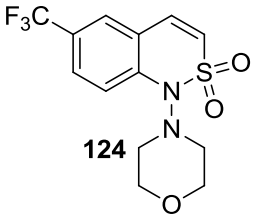
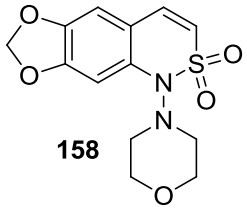
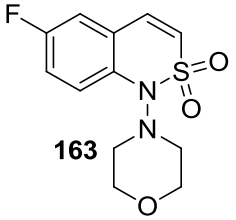
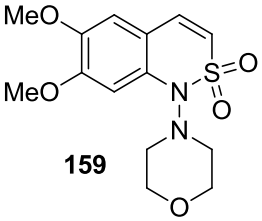
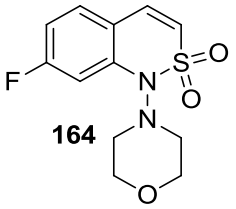
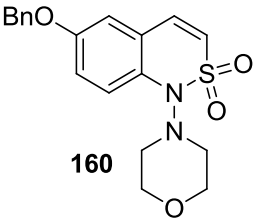
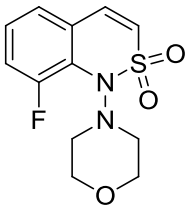
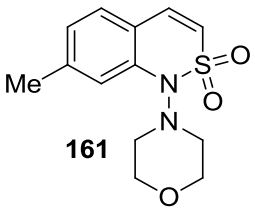
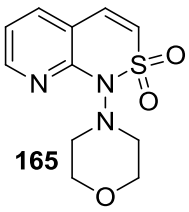
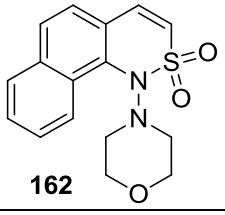
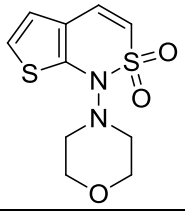
Entry	Product	Yield/ %[a]	Entry	Product	Yield/%[a]
1	 **118**, *Z*:*E*, 12:1	75	10	 **150**, *Z*:*E*, 15:1	65
2	 **142**, *Z*:*E*, 20:1	78	11	 **151**, *Z*:*E*, >20:1	83
3	 **143**, *Z*:*E*, 15:1	84	12	 **152**, *Z*:*E*, 10:1	59
4	 **144**, *Z*:*E*, 8:1	79	13	 **153**, *Z*:*E*, 1:15	72
5	 **145**, *Z*:*E*, 15:1	78	14	 **154**, *Z*:*E*, 1:>20	81
6	 **146**, *Z*:*E*, 15:1	75	15	 **155**, *Z*:*E*, 11:1	74
7	 **147**, *Z*:*E*, 15:1	79	16	 **156**, *Z*:*E*, 20:1	59
8	 **148**, *Z*:*E*, 12:1	72	17	 **157**, *Z*:*E*, 10:1	76
9	 **149**, *Z*:*E*, 20:1	70	18		0

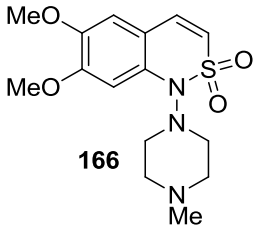
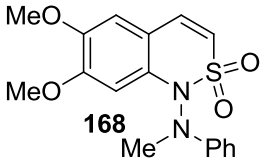
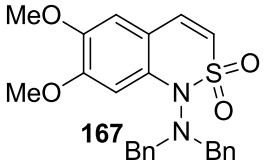
Reaction conditions: (i) 2-(2-Iodoalkenyl)aryl bromide (1 equiv.), $Pd(OAc)_2$ (10 mol%), Cata*CX*ium A (20 mol%), DABSO (1.1 equiv.), TBAI (1 equiv.), 4-aminomorpholine (1.5 equiv.), 1,4-dioxane [0.15 M], 70 °C, 3-4 h. [a] Isolated yield.

After purification of the alkenyl *N*-aminosulfonamides by column chromatography, they were subjected to the cyclisation reaction conditions (Table 3.19). The cyclised products were formed in moderate to high yields although some decomposition to the sulfinate salt was also observed. A significant drop in yield was observed for the cyclic product **168**, presumably due to steric hindrance of the hydrazine (entry 15). Unfortunately, no cyclised product was observed for the alkenyl *N*-aminosulfonamide with a C-6 fluoride (entry 10) and for the thiophene example (entry 12).

Table 3.19: Cyclisation of the alkenyl *N*-aminosulfonamide.



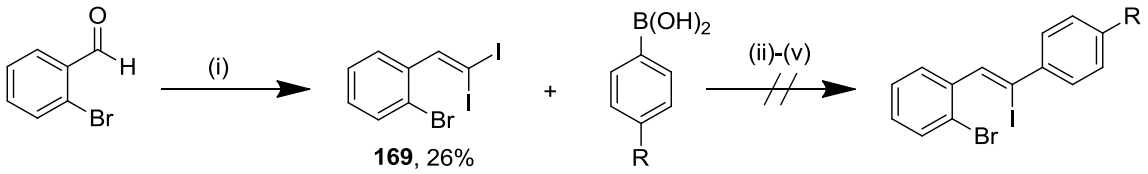
Entry	Product	Yield/ % [a]	Entry	Product	Yield/ % [a]
1	 **122**	83	7	 **124**	75
2	 **158**	80	8	 **163**	78
3	 **159**	85	9	 **164**	69
4	 **160**	79	10		0
5	 **161**	71	11	 **165**	77
6	 **162**	68	12		0

Entry	Product	Yield/ % [a]	Entry	Product	Yield/ % [a]
13	 **166**	82	15	 **168**	42
14	 **167**	75			

Reaction conditions: (i) Alkenyl *N*-aminosulfonamide (1 equiv.), $Pd(OAc)_2$ (10 mol%), Cata*CX*ium A (20 mol%), Cs_2CO_3, reflux, 1 h. [a] Isolated yield.

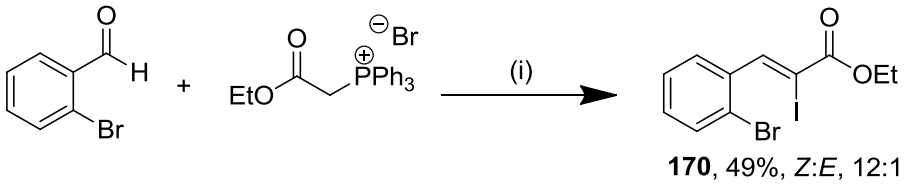
3.2.9 Functionalisation of the alkenyl moiety

The 2,2-dibromovinyl aryl precursor can be readily functionalised at the C-2 position of the alkenyl bond by performing a Suzuki reaction.[185] Using the same reaction conditions on the 2,2-diiodovinyl aryl precursor **169** gave no desired product (Scheme 3.12). Various catalytic routes that were successful for similar dihalovinyl aryl substrates were explored to no avail.[210]



Scheme 3.12: *Reaction conditions:* (i) 2-Bromobenzaldehyde (1 equiv.), tri*iso*propyl phosphite (2.2 equiv.), CI_4 (1.5 equiv.), CH_2Cl_2 [0.2 M], 0 °C to RT, 2 h; (ii) **169** (1 equiv.), *p*-tolyl boronic acid (1.3 equiv.), CuI (10 mol%), DABCO (20 mol%), Cs_2CO_3 (2 equiv.), TBAB (1 equiv.), DMF [0.1 M], 130 °C, 20 h; (iii) **169** (1 equiv.), *p*-tolyl boronic acid (1.3 equiv.), $Pd(PPh_3)_4$ (5 mol%), Na_2CO_3 (0.9 equiv.), toluene, ethanol, water (0.7:0.1:0.2) [0.06 M], reflux, 16 h; (iv) **169 (**1 equiv.), benzene boronic acid (1 equiv.), $Pd(OAc)_2$ (5 mol%), tri(*o*-tolylphosphine) (10 mol%), K_2CO_3 (2 equiv.), toluene, ethanol, water (0.6:0.3:0.1) [0.14 M]; (v) **169** (1 equiv.), 4-methoxybenzyl boronic acid (1.1 equiv.), P(2-fur)$_3$ (15 mol%), Na_2CO_3 (2 equiv.), $Pd_2(dba)_3$ (2.5 mol%), 1,4-dioxane [0.2 M], 70 °C, 24 h.

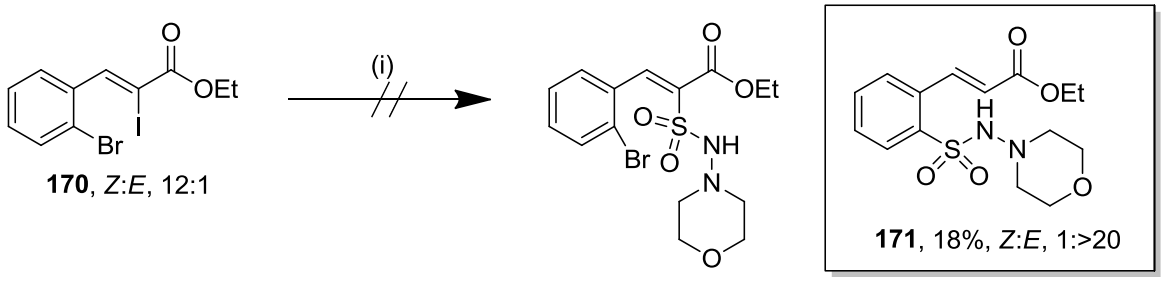
The alkenyl substituted iodide **170** was prepared *via* a literature procedure in a 49% yield (Scheme 3.13).[211]



170, 49%, *Z*:*E*, 12:1

Scheme 3.13 : *Reaction conditions:* (i) 2-Bromobenzaldehyde (1 equiv.), (ethoxycarbonylmethyl)triphenylphosphonium bromide salt (1.1 equiv.), iodine (2.3 equiv.), K_2CO_3 (0.9 equiv.), TBAB (0.05 equiv.), methanol [0.05 M], –5 to 40 °C, 16 h.

Under the palladium catalysed aminosulfonylation conditions alkenyl iodide **170** underwent reductive dehalogenation as well as aminosulfonylation at the aryl bromide position to generate *N*-aminosulfonamide **171** (Scheme 3.14). Similar dehalogenation of related alkenyl halides with an α-ester group has been observed in the literature as a side- or main-reaction pathway.[212] As aminosulfonylation reactions with aryl bromides and *ortho*-substituents typically result in reduced yield, the unexpected product **171** was only formed in an 18% yield.



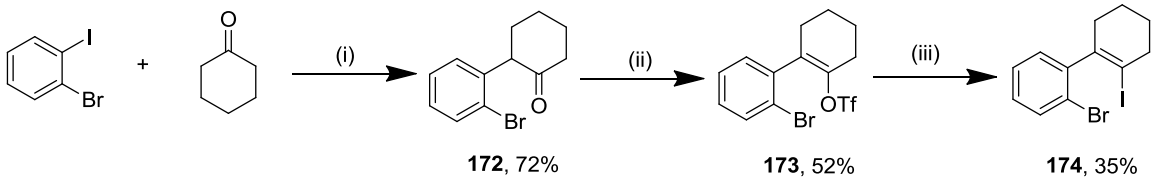
170, *Z*:*E*, 12:1

171, 18%, *Z*:*E*, 1:>20

Scheme 3.14: *Reaction conditions:* (i) Alkenyl iodide **170** (1 equiv.), $Pd(OAc)_2$ (10 mol%), Cata*CX*ium A (20 mol%), DABSO (1.1 equiv.), 4-aminomorpholine (1.5 equiv.), 1,4-dioxane [0.15 M], 70 °C, 16 h.

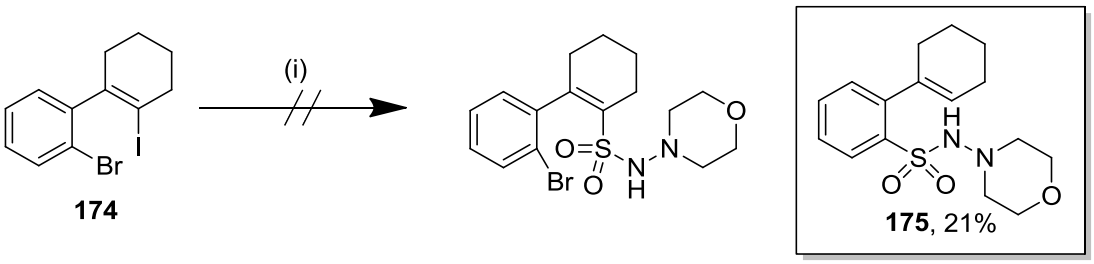
Another method of functionalising the alkenyl bond was through a ring structure. This moiety would also be beneficial as no *Z* to *E* isomerisation would be able to occur. The ketone **172** was synthesised by a palladium-catalysed coupling of 1-bromo-2-iodobenzene

and cyclohexanone (Scheme 3.15).[213] Formation of alkenyl triflate **173** from the ketone was achieved in a 52% yield[214] and after reaction with magnesium iodide the alkenyl iodide **174** was obtained.[215]



Scheme 3.15: *Reaction conditions:* (i) 1-Bromo-2-iodobenzene (1 equiv.), cyclohexanone (2 equiv.), $Pd_2(dba)_3$ (0.5 mol%), XantPhos (0.5 mol%), Cs_2CO_3 (0.9 equiv.), 1,4-dioxane [1.0 M], 80 °C, 24 h; (ii) **172** (1 equiv.), NaH (1.9 equiv.), *N*-Phenyl *bis*(trifluoromethanesulfonimide) (1.15 equiv.), DMF [0.03 M], RT, 16 h; (iii) **173** (1 equiv.), MgI_2 (3 equiv.), Et_3N (1.18 equiv.), cyclohexane [0.08], reflux, 20 h.

When this substrate was subjected to the palladium catalysed aminosulfonylation conditions the product **175** was formed in a 21% yield (Scheme 3.16). It appeared that dehalogenation of the alkenyl iodide and aminosulfonylation at the aryl bromide position had occurred as for alkenyl iodide **170** shown above. Similar iodocyclohexenes have been reported to undergo deiodonation.[216]

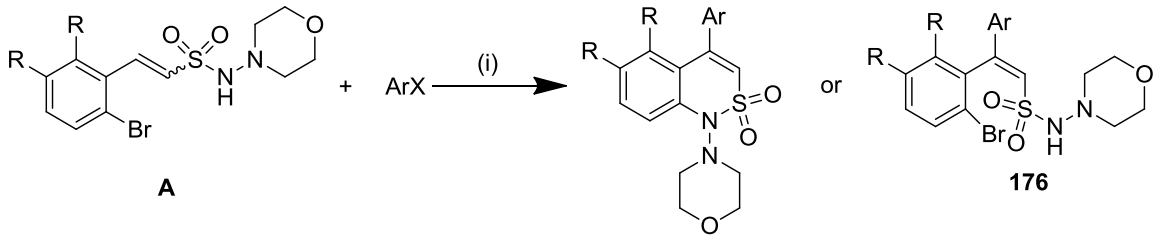


Scheme 3.16: *Reaction conditions:* (i) Alkenyl iodide **174** (1 equiv.), $Pd(OAc)_2$ (10 mol%), Cata*CX*ium A (20 mol%), DABSO (1.1 equiv.), 4-aminomorpholine (1.5 equiv.), 1,4-dioxane [0.15 M], 70 °C, 16 h.

Battistuzzi *et al.* have reported the synthesis of quinolones from an *E* α,β-unsaturated carbonyl compound through a pseudo-domino Mizoroki–Heck/Buchwald–Hartwig reaction using a molten TBAB and TBAAc system.[187(a)] This system was implemented on

alkenyl *N*-aminosulfonamide **118** (*Z*:*E*, >20:1); however, only decomposition to the sulfinate salt was observed (entry 1, Table 3.20). This potentially useful procedure was investigated further using the *E* isomer alkenyl *N*-aminosulfonamide **153** (*Z*:*E*, 1:15) as the palladium catalysed vinylic substitution was postulated to form alkenyl *N*-aminosulfonamide **176** in a configuration primed for cyclisation. However, again no product was detected and instead a mixture of predominantly returned starting material and sulfinate salt was observed (entries 2 to 5). This may be due to steric hindrance of the alkenyl bond.

Table 3.20: Pseudo-domino Mizoroki–Heck/Buchwald–Hartwig reaction.

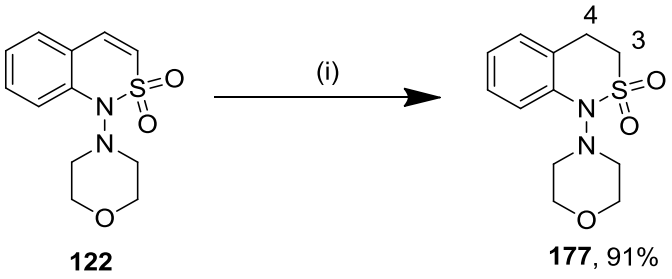


Entry	ArX	A	Catalyst	Solvent	Additive/ base (equiv.)	Temp/ °C	Product
1[187(a)]	TolI	**118**	$Pd(OAc)_2$ (10)	-	TBAB (3 equiv.), TBAAc (3 equiv.) (molten)	120	n.d.
2[217]	TolI	**153**	$Pd(OAc)_2$ (10)	DMF	TBAC (1), $NaHCO_3$ (4)	80	n.d
3	TolI	**153**	$Pd(OAc)_2$ (10)	-	Et_3N (20)	80	n.d.
4[218]	Ph_2I^+ Cl^-	**153**	$Pd(OAc)_2$ (10)	DMF	TEAB (1), Na_2CO_3 (2.5)	80	n.d.
5[219]	TolBr	**153**	$Pd_2(dba)_3$ (10), $^tBu_3P.HBF_4$ (10)	dioxane	Cy_2NMe (1.1)	70	n.d.

Reaction conditions: (i) Alkenyl *N*-aminosulfonamide (1 equiv.), ArX (1.5 equiv.), 16 h. n.d. = not detected.

Reduction of the double bond was achieved to give the 3,4-dihydrosulfostyril **177** in excellent yield. Further elaboration of the 3,4-dihydrosulfostyril scaffold has been

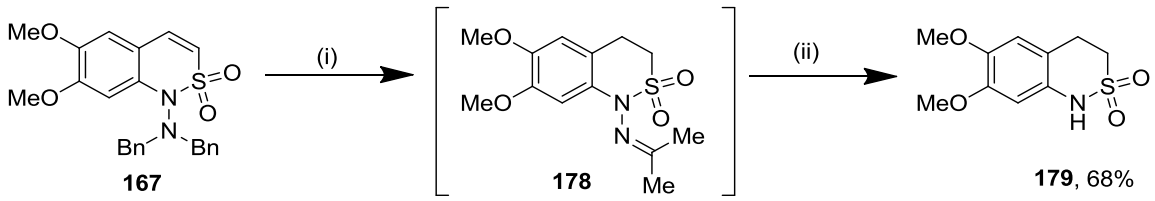
demonstrated by Fensome *et al*. at the C-3 position.[179,183(a)] Literature precedent to convert the dihydro species into the unsaturated benzothiazine 2,2-dioxide failed, suggesting it is not a simple procedure.[176(b)]



Scheme 3.17: *Reaction conditions*: (i) Benzothiazine 2,2-dioxide **122** (1 equiv.), 10% Pd/C, H_2 balloon, ethanol [0.04 M], RT, 3 h.

3.2.10 Cleavage of the N—N bond

A procedure to obtain the benozthiazine 2,2-dioxide with a free NH was sought as several groups have been able to successfully functionalise the free NH of related dihydrosultams.[220] As the dimethylhydrazine gave no product in the aminosulfonylation reaction (Table 3.18, entry 18), cleavage of the N—N bond could not be achieved by the method demonstrated in Section 2.2.1. Instead an alternative procedure that had been previously employed in the Willis group was implemented that involved the formation of a hydrazone intermediate **178** (Scheme 3.18).[25,221] Although the palladium catalysed reduction step also reduced the alkenyl bond of the benzosultam **179**, these 3,4-dihydrosulfostyrils are also useful structural motifs.



Scheme 3.18: *Reaction conditions*: (i) 10% $Pd(OH)_2/C$, H_2 balloon, acetone [0.03 M], RT, 16 h; (ii) Zn, AcOH [0.09 M], RT, 2 h.

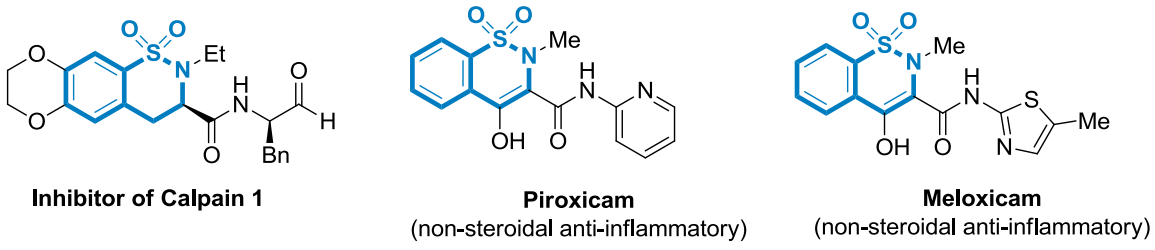
3.3 Conclusion

The isomerisation of the alkenyl bond of the *N*-aminosulfonamide and decomposition to the sulfinate salt and styrene were major barriers towards the synthesis of benzothiazine 2,2-dioxide and also ruled out a one-pot reaction as a viable option. Optimisation of reaction conditions reduced the competing isomerisation and decomposition to give a range of alkenyl *N*-aminosulfonamides that could be subsequently cyclised to give the corresponding benzothiazine 2,2-dioxide with variation on both the aryl and hydrazine moieties. The difficulty in preparing certain alkenyl iodide substrates unfortunately prevented substitution of the alkenyl moiety, although reduction of the alkenyl bond was successfully achieved. The N—N bond was cleaved to generate the free NH that could be used for further functionalisation.

Chapter 4

Synthesis of benzosultam: Aryl-SO_2-N linkage

The benzosultam scaffold, also known as 2*H*-benzo[*e*][1,2]thiazine 1,1-dioxide,[vii] is abundant amongst many pharmacologically important molecules. Examples include an inhibitor of Calpain 1[222] and the class of non-steroidal anti-inflammatory agents referred to as oxicams (Figure 4.1).[223]



Inhibitor of Calpain 1

Piroxicam
(non-steroidal anti-inflammatory)

Meloxicam
(non-steroidal anti-inflammatory)

Figure 4.1: Examples of the benzothiazine 1,1-dioxide motif in pharmaceuticals.

[vii] Referred to as benzothiazine 1,1-dioxide for the rest of the thesis.

The range in biological activity of benzothiazine 1,1-dioxides has prompted further exploration of these structures; one such example being the replacement of the benzo portion of benzothiazine 1,1-dioxide with a heteroaryl ring.[224] This suggests that continuing research into variants of this class of compounds may be fruitful.

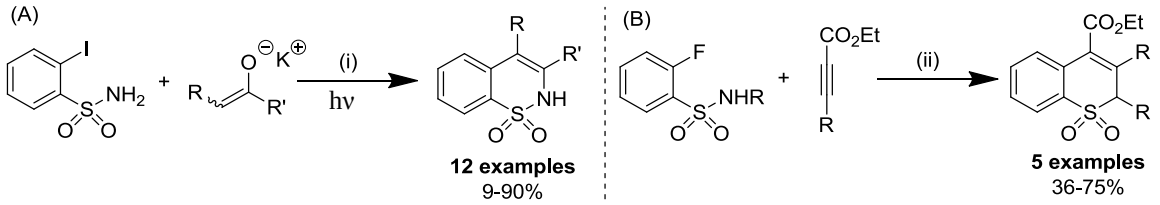
4.1 Current methodologies for the synthesis of benzothiazine 1,1-dioxides

Numerous methods for the preparation of benzothiazine 1,1-dioxide have been reported in the literature, however, in all cases it is first necessary to prepare the corresponding sulfonamide, most often by amination of a sulfonyl chloride. The various limitations of using a sulfonyl chloride precursor are described in Section 3.1. An overview of the common precursors to benzothiazine 1,1-dioxide is described in the rest of this section.

4.1.1 Benzothiazine 1,1-dioxide synthesis *via* an *ortho*-(halo)benzenesulfonamide precursor

Layman and co-workers demonstrated that benzothiazine 1,1-dioxides can be prepared by a radical chain nucleophilic aromatic substitution ($S_{RN}1$) reaction of 2-iodobenzenesulfonamide and potassium enolates in liquid ammonia (Scheme 4.1, (A)).[225] This method is highly dependent on the nature of the enolate, with reductive dehalogenation becoming a competing side reaction as the size of the R group, i.e. number of β-hydrogens, increases. Another example using an *ortho*-(halo)benzenesulfonamide precursor is demonstrated by the Juhl group who exploited 2-fluorobenzenesulfonamide

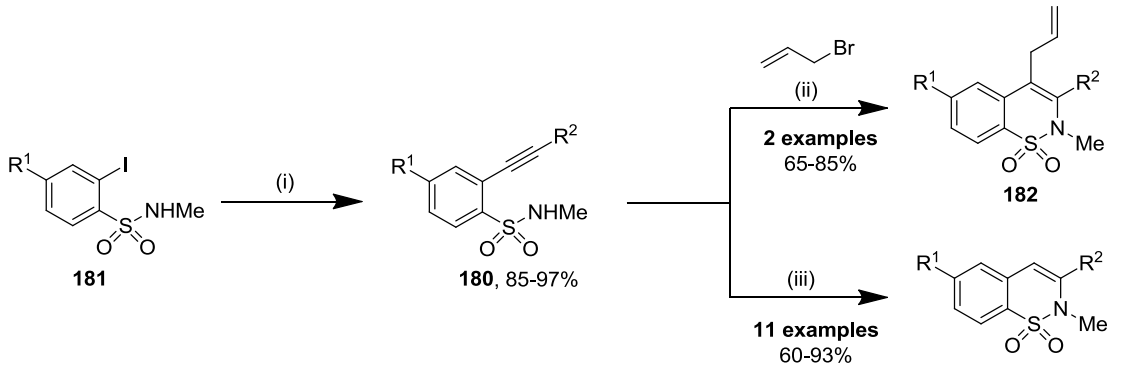
precursors which can undergo a conjugate addition-S_NAr domino reaction *via* an enolate intermediate.[226]



Scheme 4.1: *Reaction conditions*: (i) Sulfonamide (1 equiv.), ketone (4 equiv.), $Fe(NO_3)_3$ (cat.), K metal (5.3 equiv.), NH_3 (lq), hν; (ii) NaHMDS (1.2 equiv.), sulfonamide (1 equiv.), DMF, alkyne (2 equiv.), μw, 150-200 °C, 1-16 h.

4.1.2 Benzothiazine 1,1-dioxide synthesis *via* an *ortho*-(alkynyl)benzenesulfonamide precursor

Barange and co-workers reported that iodocyclisation of *ortho*-(alkynyl)benzenesulfonamides was possible, delivering the corresponding benzothiazine 1,1-dioxide with a C-4 iodo-group that could be further functionalised.[227] A more favourable strategy by the same group involved a Ag- or Cu-mediated cyclisation of *ortho*-(alkynyl)benzenesulfonamides, avoiding the requisite C-4 iodo-group as seen in their previous methodology (Scheme 4.2).[228] The best results were obtained when using silver salts to activate the triple bond, together with a base to enhance the nucleophilicity of the sulfonamide nitrogen. There is a high selectivity for the 6-membered ring *via* a 6-*endo*-dig ring closure, which they suggest is due to the longer S—N bond.[229] The required sulfonamide **180** was prepared in excellent yields by a Sonagashira coupling of the *ortho*-iodobenzenesulfonamide **181** (which they prepared by amination of the corresponding sulfonyl chloride) with a terminal alkyne. They were able to obtain the 3,4-disubstituted derivative **182** by a sequential copper-catalysed C—N and C—C bond forming reaction.

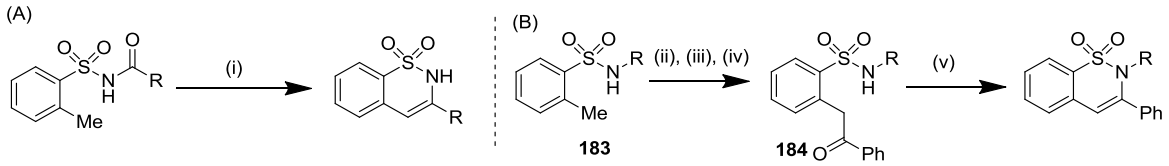


Scheme 4.2: *Reaction conditions*: (i) 10% Pd/C, PPh_3 (0.1 equiv.), CuI (5 mol%), Et_3N (3 equiv.), alkyne (3 equiv.), MeCN, 25 °C, 30 min, 80 °C, 10 h, N_2; (ii) Allyl bromide (10 equiv.), CuI (20 mol%), DMF, 130-140 °C, 8 h; (iii) Et_3N (3 equiv.), $AgSbF_6$ (15 mol%), EtOH, 80 °C, 5 min.

This cyclisation methodology has inspired several groups to design Sonogashira coupling/ cyclisation domino reactions from the common precursor *ortho*-(alkynyl)benzenesulfonamide.[230]

4.1.3 Benzothiazine 1,1-dioxide synthesis *via* an *ortho*-(methyl)benzenesulfonamide precursor using *ortho*-lithiation metholodogy

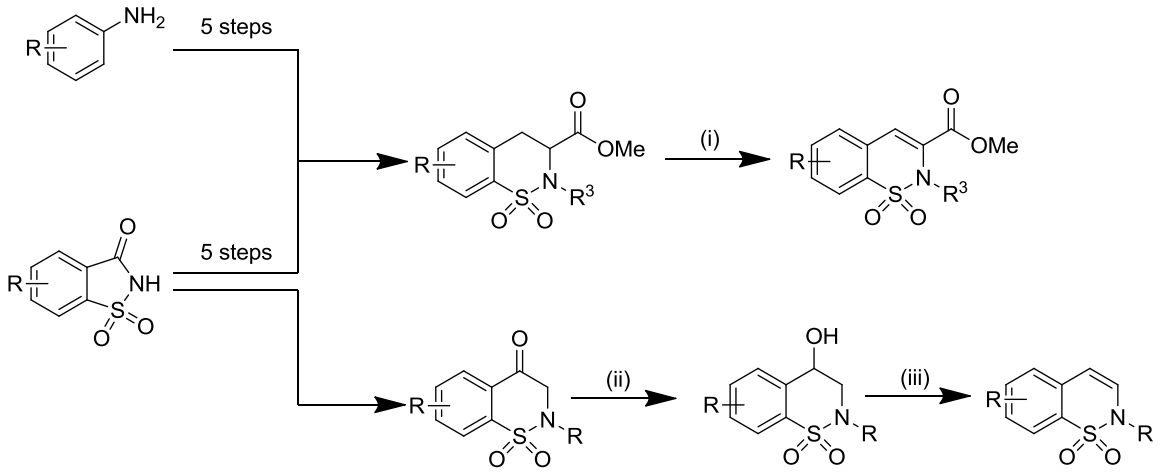
Several groups have achieved heteroannulation by an *ortho*-methyl lithiation/cyclisation sequence. Two related procedures are possible: (A) treatment of *N*-acetyl-*o*-toluenesulfonamides with *n*-butyl lithium[231] or (B) condensation of a dilithiosulfonamide (prepared from **183**) with benzonitrile and subsequent hydrolysis gives the sulfonamide **184**, after which thermal cyclodehydration ultimately gives the benzothiazine 1,1-dioxide (Scheme 4.3).[232] However, these methodologies only allow for a limited variation of substituents in position C-3.



Scheme 4.3: *Reaction conditions*: (i) ^{n}BuLi (2 equiv.); (ii) ^{n}BuLi (2.3 equiv.), 30 min, 0 °C; (iii) PhCN (1.3 equiv.), RT, 1 h; (iv) HCl; (v) conc. H_2SO_4 or 220-230 °C.

4.1.4 Benzothiazine 1,1-dioxide synthesis through multi-step procedures

Due to the numerous multi-step procedures available to synthesise benzothiazine 1,1-dioxide only recent methods with a large substrate scope are described. Three groups have reported multi-step procedures to synthesise benzothiazine 1,1-dioxides for potential Calpain inhibitors, antiosteoarthritis agents and investigation into serotonin-2 blocking action, either from a functionalised aniline or saccharin starting material (Scheme 4.4).[222,233]

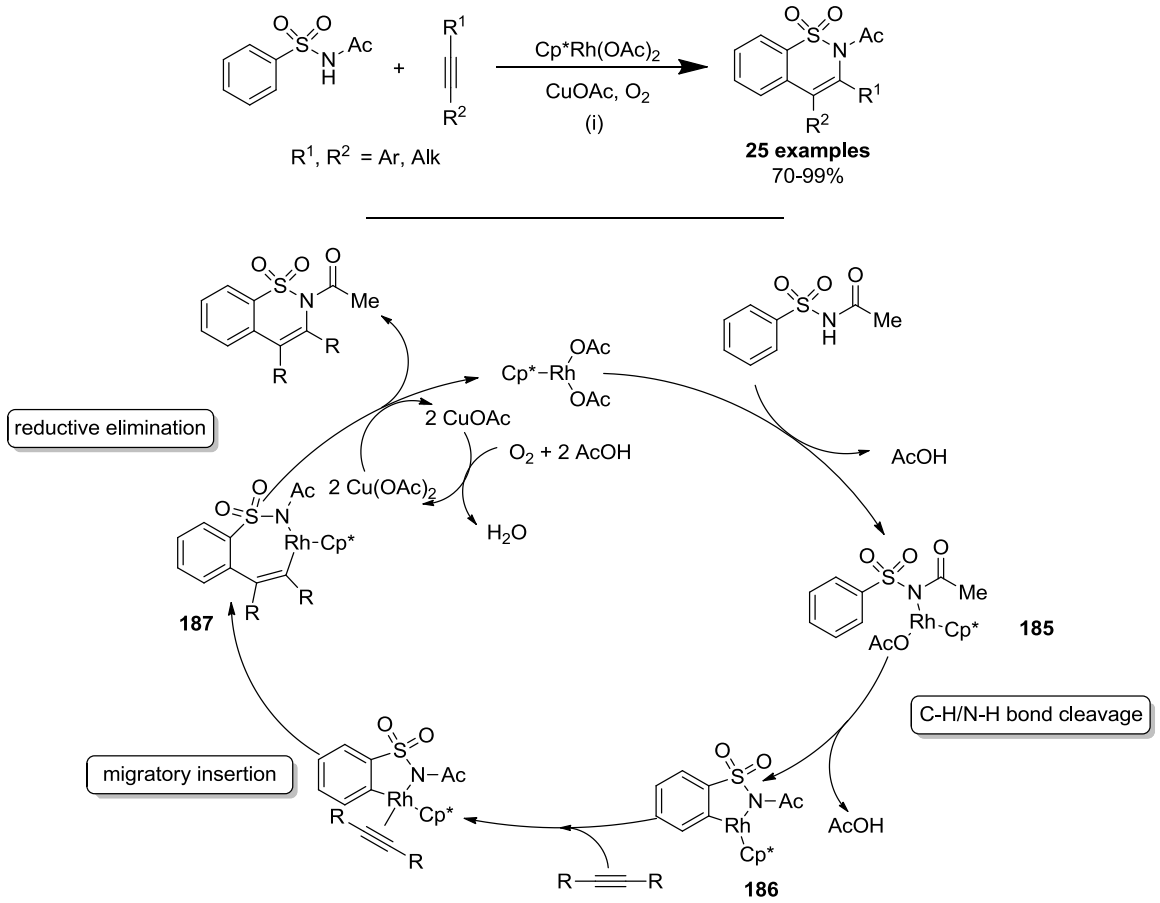


Scheme 4.4: *Reaction conditions:* (i) NBS (1.1 equiv.), $(BzO)_2$ (0.2 equiv.), CH_2Cl_2-CCl_4 (1:5), reflux, 3 h; (ii) $NaBH_4$; (iii) MsCl, Et_3N, CH_2Cl_2.

4.1.5 Benzothiazine 1,1-dioxide synthesis *via* C—H/N—H activation

In 2012, during the preparation of this thesis, the Cramer group achieved the rhodium(III)-catalysed synthesis of benzothiazine 1,1-dioxide using an acylated sulfonamide (prepared from a primary sulfonamide by various procedures) as the directing group (Scheme 4.5).[234] Primary, *N*-alkylated and *N*-pivaloyl sulfonamides were unreactive under their reaction conditions. They used $Cp^*Rh(OAc)_2$ rather than the more common $[RhCp^*Cl_2]_2$ precatalyst as it performed better under their reaction conditions. A competition reaction was performed between a sulfonamide and an amide by using tosyl benzamide. They found exclusive functionalisation of the benzamide portion, suggesting that the sulfonamide has a reduced directing group ability compared to an amide. They propose that this is due the difference in hybridisation (sp^3-hybridised sulfur versus sp^2-hybridised carbon) and a less favourable alignment for cyclometallation of the sulfonamide.

They postulate that the annulation proceeds by an analogous mechanism to amide directing groups. Initial carbometallation promoted by acetate-assisted N—H bond cleavage leads to the intermediate **185** with the rhodium bound directly to the directing group and pre-positions the metal centre for the C—H activation step (Scheme 4.5). Cyclometallation by an acetate-assisted concerted metallation-deprotonation (CMD) pathway[235] and acetic acid elimination forms the rhodacycle **186**. Migratory insertion of the alkyne provides the 7-membered rhodacycle **187**, after which reductive elimination reveals the product. Oxidisation of the Rh(I) species by copper(II) acetate completes the catalytic cycle.



Scheme 4.5: Synthesis of benzothiazine 1,1-dioxides by rhodium catalysis and proposed mechanism by the Cramer group. *Reaction conditions*: (i) $Cp^*Rh(OAc)_2$ (5 mol%), CuOAc (20 mol%), O_2 (50 mbar), toluene [0.2 M], 90 °C, 18 h.

4.1.6 Conclusion

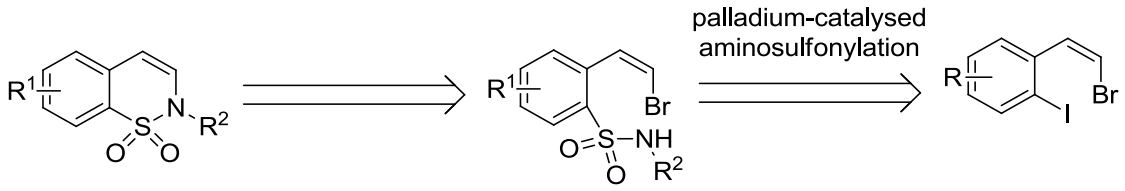
The majority of procedures to synthesise benzothiazine 1,1-dioxide require multi-step sequences and often the key starting material is a sulfonyl chloride. In addition, there are often restrictions on the functionalisation that can be incorporated on the benzothiazine 1,1-dioxide. The remainder of this chapter will describe the pursuit of a methodology to allow access to a wide range of benzothiazine 1,1-dioxides using readily available starting materials. Investigation focused on using either *ortho*-substituted benzenesulfonamide or

benzenesulfonamide precursors that could be generated efficiently by the palladium catalysed aminosulfonylation reaction.

4.2 Potential route towards the synthesis of benzothiazine 1,1-dioxide using an *ortho*-substituted precursor

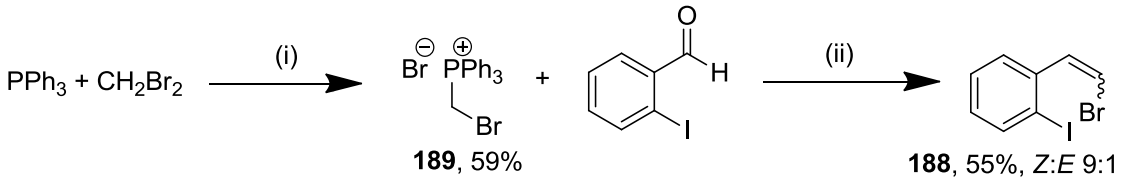
4.2.1 Synthesis of benzothiazine 1,1-dioxide *via* an *ortho*-(bromovinyl)iodobenzene precursor

A retrosynthetic analysis of benzothiazine 1,1-dioxide revealed an *ortho*-(bromovinyl)iodobenzene as a suitable precursor (Scheme 4.6). This methodology would exploit the differing reactivity of C—X bonds in the palladium catalysed aminosulfonylation reaction as it was presumed that the aryl iodide would be more reactive than the alkenyl bromide.



Scheme 4.6: Retrosynthetic analysis of benzothiazine 1,1-dioxide.

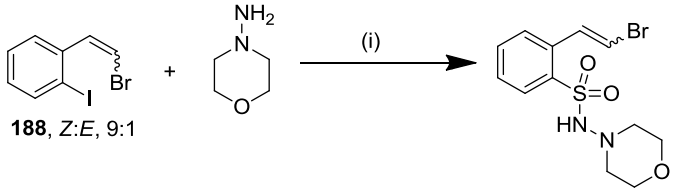
The alkenyl bromide **188** was synthesised from 2-iodobenzaldehyde *via* a Wittig reaction in modest yield and *Z*:*E* selectivity (Scheme 4.7).



Scheme 4.7: *Reaction conditions*: (i) Triphenylphosphine (1 equiv.), dibromomethane (2.3 equiv.), toluene, reflux, 24 h;[236] (ii) 2-Iodobenzaldehyde (1 equiv.), (bromomethyl)triphenylphosphonium bromide **189** (1.2 equiv.), KO^{t}Bu (1.2 equiv.), THF, –78 °C to RT, 16 h.

The alkenyl bromide **188** was treated under standard palladium catalysed aminosulfonylation conditions, but disappointingly gave unreacted starting material (Table 4.1, entries 1 and 2). It was hypothesised that the bulky ^{t}Bu$_3$P.HBF$_4$ ligand could be disfavouring the reaction. As such, a range of less bulky ligands was explored and the reaction temperature was raised to 90 °C (entries 4 to 10), however only starting material was observed. When RuPhos was employed as the ligand (entry 11), a trace amount of the indole was observed by ^{1}H NMR spectroscopy and mass spectrometry. These results were rationalised by the steric hindrance of the alkenyl bromide adjacent to the aryl iodide, as substrates with *ortho*-substituents had previously been found to be lower yielding.[23]

Table 4.1: Attempted palladium catalysed aminosulfonylation of *ortho*-(bromovinyl)iodobenzene 188.



188, *Z*:*E*, 9:1

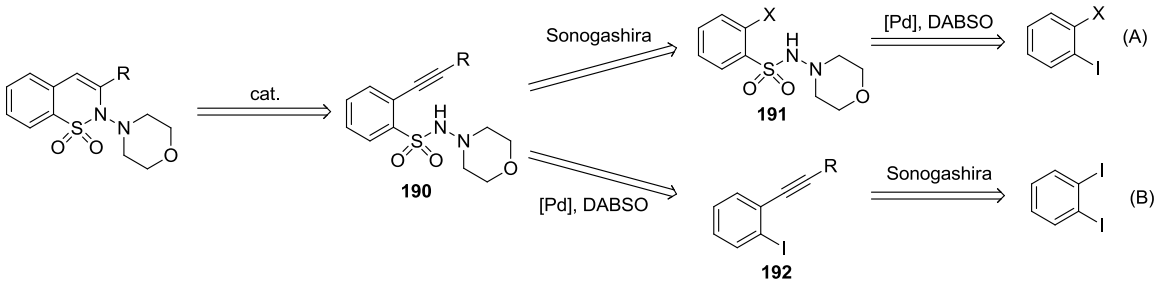
Entry	DABSO/ equiv	DABCO/ equiv	Ligand	Ligand/ mol%	Temp/ °C	Product[b]
1	1.1	-	$^{t}Bu_3P.HBF_4$	20	70	n.d.
2	0.6	0.5	$^{t}Bu_3P.HBF_4$	20	70	n.d.
3	1.1	1.1	$^{t}Bu_3P.HBF_4$	20	70	n.d.
4	2.2	-	$^{t}Bu_3P.HBF_4$	20	90	n.d.
5	1.1	-	dppb	10	90	n.d.
6	1.1	-	Xantphos	10	90	n.d.
7	1.1	-	PCy_3	20	90	n.d.
8	1.1	-	$^{t}Bu_2MeP.HBF_4$	20	90	n.d.
9	1.1	-	XPhos	20	90	n.d.
10	1.1	-	DavePhos	20	90	n.d.
11	1.1	-	RuPhos	20	90	n.d.

Reaction conditions: (i) 1-(2-Bromovinyl)-2-iodobenzene **188** (1 equiv, *Z*:*E*, 9:1), $Pd(OAc)_2$ (10 mol%), ligand, DABSO, DABCO, 4-aminomorpholine (1.5 equiv.), 1,4-dioxane [0.15 M], 24 h. [b] Determined by ^{1}H NMR spectroscopy. n.d. = not detected.

4.2.2 Synthesis of benzothiazine 1,1-dioxide *via* an *ortho*-(alkynyl)sulfonamide precursor

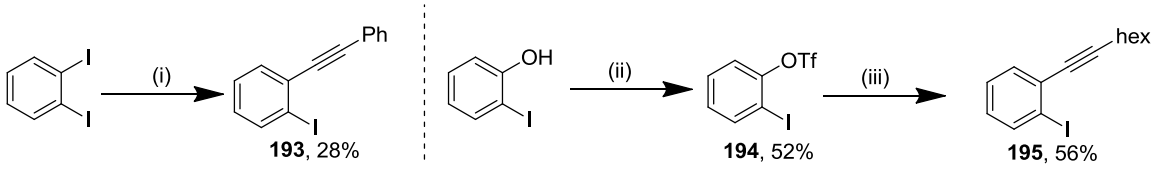
The *ortho*-(alkynyl)sulfonamide **190** was considered as an alternative precursor as it has been successfully implemented in the synthesis of benzothiazine 1,1-dioxide by Barange and co-workers as described in section 4.1.2.[228] We considered that the sulfonamide **190** could be potentially prepared by two different methods that would avoid the need for a sulfonyl chloride starting material by either (A) initial palladium catalysed aminosulfonylation of an *ortho*-(halo)substituted aryl iodide to give sulfonamide **191** and then subsequent Sonogashira coupling with an alkyne or (B) initial Sonogashira coupling

to give the *ortho*-(alkynyl)aryl iodide **192** and then a subsequent aminosulfonylation reaction (Scheme 4.8).



Scheme 4.8: Retrosynthetic analysis of benzothiazine 1,1-dioxide using **190** as a common precursor.

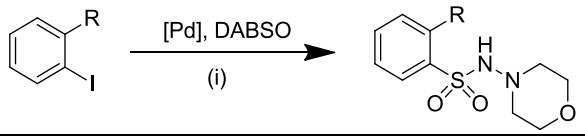
The *ortho*-substituted iodobenzene compounds **193**, **194** and **195** were prepared by known procedures as shown in Scheme 4.9.



Scheme 4.9: *Reaction conditions*: (i) 1,2-Diiodobenzene (1 equiv.), phenylacetylene (0.8 equiv.), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (5 mol%), NEt_3 [0.8 M], 70 °C, 16 h; (ii) Triflic anhydride (1.1 equiv.), 2-iodophenol (1 equiv.), NEt_3 (2 equiv.), CH_2Cl_2 [0.4 M], –78 °C to RT, 16 h; (iii) 1-Octyne (1.5 equiv.), triflate **194** (1 equiv.), ^{n}BuLi (1.3 equiv.), THF [0.04 M], –78 °C to 0 °C, 5 h.

ortho-Halo and -triflate aryl iodides were subjected to the palladium catalysed aminosulfonylation reaction conditions (Table 4.2, entries 1 to 5). Disappointingly, the expected *ortho*-substituted sulfonamide was only formed under harsh reaction conditions and in low yield (entries 3 and 4). Implementation of the *ortho*-(alkenyl)iodobenzenes **193** and **195** (entries 6 to 10) also afforded none of the expected sulfonamide and instead only returned starting material and a complex mixture of products was generated in which no morpholine peaks were observed in the ^{1}H NMR spectrum.

Table 4.2: Effect of an *ortho*-substituent in palladium catalysed aminosulfonylation.



Entry	Temp/ °C	R	Conversion to sulfonamide/ %[a]
1	70	I	n.d.
2	70	Br	n.d.
3	90[b]	Br	20 (14)
4	70	Cl	<5
5	70	OTf **194**	n.d.
6	70	≡—hex **195**	n.d.
7	90	≡—hex **195**	n.d.
8	70	≡—Ph **193**	n.d.
9	80	≡—Ph **193**	n.d.
10	90	≡—Ph **193**	n.d.

Reaction conditions: (i) *ortho*-Substituted iodobenzene (1 equiv.), $Pd(OAc)_2$ (10 mol%), $^tBu_3P.HBF_4$ (20 mol%), DABSO (1.1 equiv.), 4-aminomorpholine (1.5 equiv.), 1,4-dioxane [0.15 M], 16 h. [a] Determined by ^1H NMR spectroscopy. [b] *ortho*-Substituted iodobenzene (1 equiv.), $Pd(OAc)_2$ (20 mol%), $^tBu_3P.HBF_4$ (40 mol%), DABSO (2.2 equiv.), 4-aminomorpholine (1.5 equiv.), 1,4-dioxane [0.15 M], 16 h. Number in parentheses corresponds to isolated yield. n.d. = not detected.

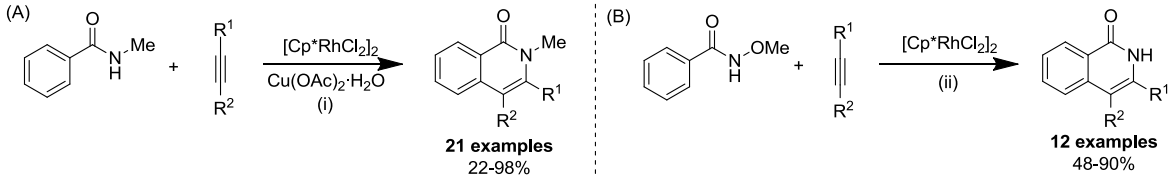
4.2.3 Conclusion

The lack of reactivity of the iodobenzenes with the selected *ortho*-substituents investigated in the palladium catalysed aminosulfonylation reaction cannot be explained merely by steric hindrance, as *ortho*-substituted sulfonamides can be readily prepared from *ortho*-substituted aryl iodides such as 2-iodoanisole and 1-ethoxy-2-iodobenzene **210** as demonstrated in Chapter 2. The nature of the *ortho*-substituent appears to be crucial for success in the aminosulfonylation reaction.

4.3 Potential route towards the synthesis of benzothiazine 1,1-dioxide from an *N*-aminosulfonamide precursor *via* C—H/N—H activation

A rapidly expanding area of research over the last couple of years is the synthesis of isoquinolones through C—H/N—H activation *via* palladium, rhodium or ruthenium catalysis. This avoids the need for prefunctionalised starting materials and also provides good atom- and step-economy.

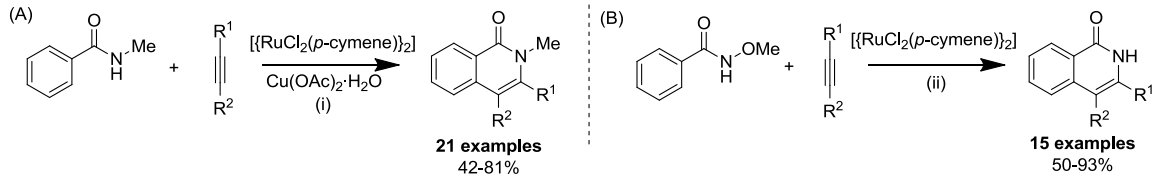
The most commonly used rhodium catalyst in these reactions is the dimer $[Cp^*RhCl_2]_2$ (Cp^* = pentamethylcyclopentadienyl) which can be employed with an external oxidant to give the corresponding isoquinolones in high regioselectivies with aryl/alkyl alkynes (Scheme 4.10, (A)).[237] Substrates with a reactive N—O bond provide an 'internal oxidant'[viii] that can be used to obtain the isoquinolone with a free NH (Scheme 4.10, (B)).[238]



Scheme 4.10: Synthesis of isoquinolones by rhodium catalysis. (A) An example external oxidant strategy.[237(a)] (B) An example internal oxidant strategy.[238(b)] *Reaction conditions*: (i) $[Cp^*RhCl_2]_2$ (2.5 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv.), ^{t}AmOH, 110 °C, 16 h; (ii) $[Cp^*RhCl_2]_2$ (0.5 mol%), alkyne (1.1 equiv.), CsOAc (30 mol%), MeOH [0.2 M], 60 °C, 16 h.

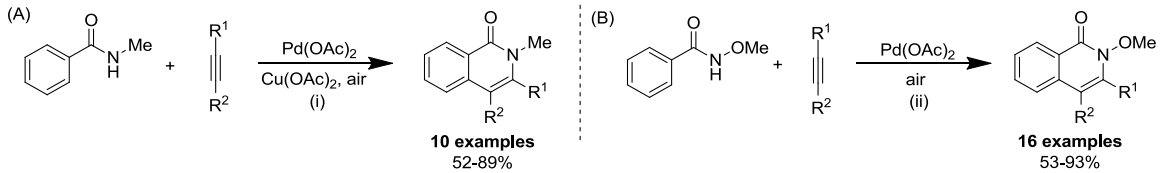
[viii] The 'internal oxidant' strategy refers to a covalent bond within the directing group which oxidises the metal catalyst to regenerate the active catalyst. Patureau, F. W.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1977.

The most widely applicable ruthenium catalyst for the synthesis of isoquinolones by C—H/N—H activation, is the dimer $[RuCl_2(p\text{-cymene})]_2$. The annulation process occurs with excellent regioselectivity with both unsymmetical aryl/alkyl and alkenyl/alkyl alkynes (Scheme 4.11, (A)).[239] As in rhodium catalysis, substrates with a reactive N—O bond obviate the need for an external oxidant and form the isoquinolone with a free NH (Scheme 4.11, (B)).[240]



Scheme 4.11: Synthesis of isoquinolones by ruthenium catalysis. (A) An example external oxidant strategy.[239(a)] (B) An example internal oxidant strategy.[240(a)] *Reaction conditions*: (i) Benzamide (1 equiv.), alkyne (1 equiv.), $[\{RuCl_2(p\text{-cymene})\}_2]$ (5 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2 equiv.), ^{t}AmOH [0.25 M], 100 °C, 22 h; (ii) Hydroxamic acid ester (1 equiv.), alkyne (2 equiv.), $[\{RuCl_2(p\text{-cymene})\}_2]$ (2.5 mol%), KO_2CMes (30 mol%), H_2O [0.25 M], 60 °C, 16 h.

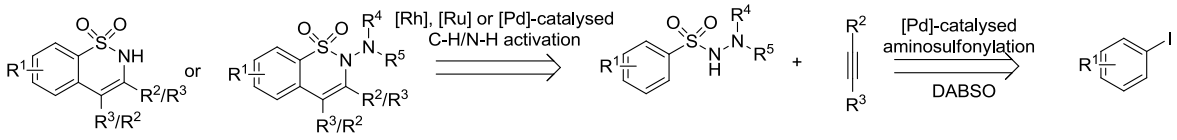
A far less well developed area is the formation of isoquinolones *via* palladium catalysed C—H/N—H activation. It was discovered by the Huang group in 2012 who used palladium acetate as the catalyst (Scheme 4.12).[241] Unlike the rhodium- and ruthenium-catalysed synthesis of isoquinolones, when an alkoxyl benzamide is reacted with an alkyne, no N—O bond cleavage occurs; the reason for this has not been fully elaborated.



Scheme 4.12: Synthesis of isoquinolones by palladium catalysis. *Reaction conditions*: (i) Benzamide (1 equiv.), alkyne (3 equiv.), $Pd(OAc)_2$ (10 mol%), $NaI{\cdot}2H_2O$ (2 equiv.), $Cu(OAc)_2$ (0.4 equiv.), air, K_2CO_3 (1 equiv.), 120 °C, DMF [0.2 M], 36 h;[241(c)] (ii) Benzamide (1 equiv.), alkyne (3 equiv.), $Pd(OAc)_2$ (10 mol%), $NaI{\cdot}2H_2O$ (1 equiv.), air, 120 °C, DMF [0.2 M], 4-12 h.[241(a)]

There are a few methods for C—H activation of benzene derivatives without a directing group, although they are very challenging.[242] Directing groups other than amides have also been utilised; for example hydroxyl,[243] pyridyl,[244] carbamate,[245] imine,[246] carboxyl,[247] and *N*-aryl acetamides,[248] to provide an array of regioselectively decorated heterocycles. Significantly, sulfonamides have also recently been employed as directing groups, primarily using palladium or rhodium catalysis.[249] One example employing the sulfonamide directing group is the recent synthesis of benzothiazine 1,1-dioxides (as described in Section 4.1.5).[234] The substituents on the nitrogen are crucial for reactivity, with a more acidic nitrogen being beneficial. Fagnou and co-workers investigated the N—N moiety as a built-in oxidant for isoquinolone synthesis, however they were unsuccessful, possibly due to the strength of the N—N bond.[250] Encouragingly, a recent report has been able to use hydrazone as an oxidising directing group which involves breaking the N—N bond.[251]

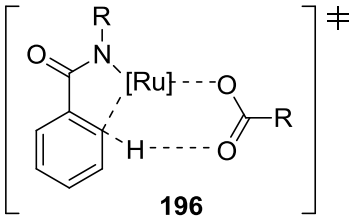
In light of these examples, the decision was made to further investigate the directing-group ability of a sulfonamide. To potentially allow for a large scope of benzothiazine 1,1-dioxide products, the palladium catalysed aminosulfonylation reaction would be employed to generate the sulfonamide, avoiding any need for a sulfonyl chloride starting material (Scheme 4.13). Investigation into the use of the N—N bond as an internal oxidant would also be conducted.



Scheme 4.13: Retrosynthetic analysis of benzothiazine 1,1-dioxide *via* a palladium catalysed aminosulfonylation and subsequent C—H/N—H activation sequence.

4.3.1 A brief overview of palladium, rhodium, and ruthenium catalysis in the synthesis of isoquinolones and benzothiazine 1,1-dioxides *via* C—H/N—H activation

External oxidants: Metal complexes derived from the bifunctional acetate ligand have proven to be instrumental for C—H activation.[252] $Cu(OAc)_2 \cdot H_2O$ tends to be the terminal oxidant of choice, serving not only as an oxidant but also as a source of acetate for the proposed carboxylate-assisted metal manifold **196** (Scheme 4.14).[253]



Scheme 4.14: Proposed carboxylate-assisted manifold for ruthenium C—H/N—H activation.

Internal oxidants: The use of internal oxidants can lead to improved reactivity and selectivity compared to using an external oxidant due to the milder reaction conditions employed.[238(a)] Terminal alkynes tend not to be applicable in reactions using $Cu(OAc)_2 \cdot H_2O$ as a co-catalyst due to alkyne dimerisation (Glaser coupling). However, with internal oxidants, Cu(II) can be avoided, thus allowing terminal alkynes to be used in the reaction.[250] Additives such as CsOPiv and CsOAc can also be used.[238(b)]

4.3.2 Palladium, rhodium or ruthenium catalysed cycloaddition of an *N*-aminosulfonamide to an alkyne *via* C—H/N—H activation

Initial investigation was focused on the ruthenium complex $[RuCl_2(p\text{-cymene})]_2$ as it is significantly less expensive than rhodium complexes,[254] as well as being better explored in isoquinolone synthesis than palladium complexes. It also has improved selectivities when

using unsymmetrical alkynes as shown in a diverse range of literature examples.[255] Diphenylacetylene was the alkyne of choice as the majority of literature reports obtain the highest yields with this particular substrate.

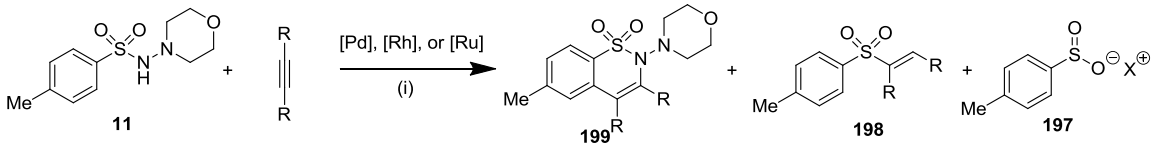
The *N*-aminosulfonamide **11** was reacted under various literature reaction conditions and a carboxylate was added as a co-catalyst in most cases (Table 4.3). Unfortunately, complete decomposition of *N*-aminosulfonamide **11** was observed to give the sulfinate salt **197** (see Chapter 2) which consequently reacted with the diphenylacetylene to give the alkenyl sulfone **198a** (entries 1 and 2). This decomposition was only observed when both the ruthenium catalyst and copper co-catalyst were present (entries 3 and 4). This suggests that perhaps the acetate-assisted metallation occurs (Scheme 4.5) but rather than C—H activation occurring, the *N*-aminosulfonamide decomposes to the sulfinate salt. Lowering the reaction temperature and changing the solvent resulted only in a lower yield of the alkenyl sulfone without the desired benzothazine 1,1-dioxide product **199** (entries 5 and 6). The reaction with 4-octyne resulted in decomposition of the sulfonamide to a sulfinate ion, although no comparable alkenyl sulfone was detected (entry 7). Alternative oxidants, such as silver carbonate, potassium metabisulfite and benzoquinone, were examined leading to only returned starting material (entries 9 and 10) or, in the case of silver carbonate, the alkenyl sulfone (entry 8).

Next the C—H/N—H activation of *N*-aminosulfonamide **11** with the rhodium catalysts $[Cp^*RhCl_2]_2$ and $Cp^*Rh(OAc)_2$, prepared by known procedures from $RhCl_3.3H_2O$,[256] were investigated. Reaction conditions that were successful for the Cramer group (for the synthesis of benzothiazine 1,1-dioxide) and the Rovis group (for the synthesis of

isoquinolones) were employed. Unfortunately, only starting material or decomposition to the sulfinate salt was observed (entries 11 to 15).

Attention was then turned to palladium catalysed C—H/N—H activation using reaction conditions exploited by the Huang group. In all cases only complete decomposition of the sulfonamide starting material was observed alongside other decomposition products (entries 16 to 18).

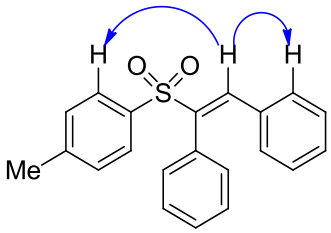
Table 4.3: Attempted oxidative cycloaddition of *N*-aminosulfonamide 11 to an alkyne *via* C—H/N—H activation.



Entry	R	[Cat]/ mol%	Solvent	Temp / °C	Oxidant/ additive (equiv.)	11 : 199 : 198 : 197 [a]	198 yield/ % [a]
1	Ph	[Ru] (5)	^{t}AmOH	100	$Cu(OAc)_2·H_2O$ (2)	0 : 0 : 1 : 4	22
2	Ph	[Ru] (5)	^{t}AmOH	120	$Cu(OAc)_2·H_2O$ (2)	0 : 0 : 1 : 2	32
3	Ph	-	^{t}AmOH	100	$Cu(OAc)_2·H_2O$ (2)	1 : 0 : 0 : 0	-
4	Ph	[Ru] (5)	^{t}AmOH	100	-	1 : 0 : 0 : 0	-
5	Ph	[Ru] (5)	^{t}AmOH	70	$Cu(OAc)_2·H_2O$ (2)	0 : 0 : 1 : 9	10
6	Ph	[Ru] (5)	dioxane	100	$Cu(OAc)_2·H_2O$ (2)	0.5 : 0 : 1 : 5	15
7	*n*-Pr	[Ru] (10)	^{t}AmOH	110	$Cu(OAc)_2·H_2O$	0 : 0 : 0 : 1	-
8	Ph	[Ru] (10)	MeCN	115	Ag_2CO_3 (1.3)	0 : 0 : 1 : 19	5
9	Ph	[Ru] (10)	^{t}AmOH	100	$K_2S_2O_8$ (2)	1 : 0 : 0 : 0	-
10	Ph	[Ru] (10)	^{t}AmOH	100	BQ (2)	1 : 0 : 0 : 0	-
11	Ph	$[Cp^*RhCl_2]_2$ (5)	^{t}AmOH	110	$Cu(OAc)_2$ (2)	0 : 0 : 1 : 9	10
12	Ph	$[Cp^*RhCl_2]_2$ (5)	DMF	80	$Cu(OAc)_2·H_2O$ (2)	0 : 0 : 1 : 9	10
13	Ph	$[Cp^*RhCl_2]_2$ (5)	MeOH	60	Ag_2O (0.2), AcOH(1)	0 : 0 : 1 : 19	5
14	Ph	$Cp^*Rh(OAc)_2$ (5)	toluene	90	CuOAc (0.2), O_2 balloon	1 : 0 : 0 : 0	-
15	Ph	$Cp^*Rh(OAc)_2$ (5)	toluene	90	$Cu(OAc)_2·H_2O$ (2.5)	1 : 0 : 0 : 0	-
16	Ph	$Pd(OAc)_2$ (10)	DMF	120	air, $NaI·2H_2O$ (1)	0 : 0 : 0 : 1	-
17	Ph	$Pd(OAc)_2$ (10)	DMF	120	$Cu(OAc)_2$ (0.4), air, $NaI·2H_2O$ (2), K_2CO_3 (1)	0 : 0 : 0 : 1	-
18	Ph	$Pd(OAc)_2$ (10)	DMF	120	$CuCl_2·2H_2O$ (0.4), air, NaBr (2), KOH (1)	0 : 0 : 0 : 1	-

Reaction conditions: (i) *N*-Aminosulfonamide **11** (1 equiv.), alkyne (2 equiv.), oxidant, solvent, heat, 16 h. [Ru] = $[RuCl_2(p\text{-cymene})]_2$. [a] Ratio of **197** determined by subtraction of other products after column chromatography from 100%. [b] Isolated yield.

The sulfone product **198a** was confirmed as the *E* isomer by NOE NMR spectroscopy (Scheme 4.15).



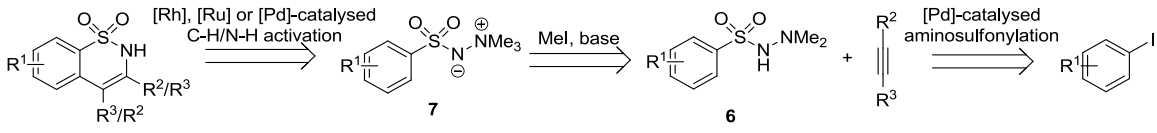
198a

Scheme 4.15: NOE analysis.

The propensity of the *N*-aminosulfonamide **11** to decompose to the sulfinate salt is a major obstacle to its use as a directing group in C—H/N—H activation. An alternative sulfonamide directing group was then sought.

4.3.3 Palladium, rhodium or ruthenium catalysed cycloaddition of an aminimide to an alkyne *via* C—H activation

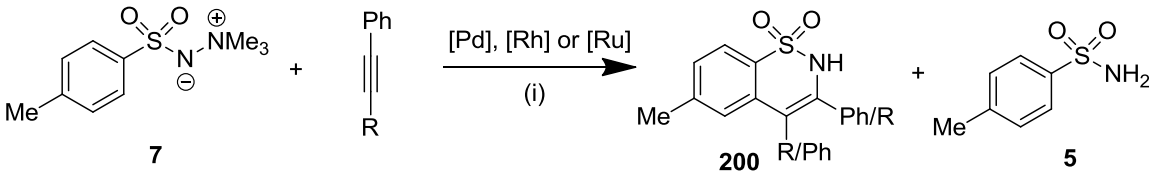
Azomethine ylids have been used as oxidising directing groups.[257] As such, the aminimide **7** was considered as a possible oxidising directing group due to its reactive N—N bond.



Scheme 4.16: Retrosynthetic analysis of benzothiazine 1,1-dioxide *via* a palladium catalysed aminosulfonylation, ylid formation, and C—H/N—N bond cleavage.

Palladium, rhodium and ruthenium catalysts were investigated with a range of additives or oxidants that are commonly seen in literature reports that employ an internal oxidant strategy. Both phenyl and diphenylacetylene were investigated as the alkyne coupling partner. Unfortunately, under the given reaction conditions, the desired benzothiazine 1,1-dioxide **200** was not detected and only starting material or the primary sulfonamide **5** was observed (Table 4.4, entries 1 and 2). Cleavage of the N—N bond in the absence of the ruthenium catalyst was not observed (*c.f.* entry 3 to entry 7). In an attempt to diminish the ease of cleavage of the N—N bond, the temperature was lowered, but no desired product was observed. Rhodium and palladium catalysts also returned unreacted starting material or the primary sulfonamide **5** as the sole product.

Table 4.4: Attempted palladium-, rhodium- or ruthenium-catalysed cycloaddition of aminimide 7 and an alkyne *via* C—H activation.



Entry	R	Catalyst	Solvent	Temp/ °C	Additive/ oxidant (equiv.)	Observed[a]
1	Ph	[Ru]	^{t}AmOH	110	$Cu(OAc)_2 \cdot H_2O$ (2)	**5**
2	Ph	[Ru]	^{t}AmOH	110	CuOAc (1)	**5**
3	Ph	-	^{t}AmOH	110	-	**7**
4	Ph	[Ru]	^{t}AmOH	60	$Cu(OAc)_2 \cdot H_2O$ (2)	**5**
5	Ph	[Ru]	H_2O	60	CsOAc (2)	**7**
6	Ph	[Ru]	MeOH	60	-	**7**
7	H	[Ru]	^{t}AmOH	60	-	**5**
8	Ph	$[Cp^*RhCl_2]_2$[b]	MeOH	60	CsOAc (2)	**7**
9	Ph	$[Cp^*RhCl_2]_2$[b]	MeOH	60	Ag_2O (0.2), AcOH (1equiv)	**7**
10	Ph	$Cp^*Rh(OAc)_2$[b]	toluene	90	CuOAc (0.2), O_2 balloon	**7**
11	Ph	$Cp^*Rh(OAc)_2$[b]	toluene	90	$Cu(OAc)_2 \cdot H_2O$	**7**
12	Ph	$Pd(OAc)_2$	DMF	120	air, $NaI \cdot 2H_2O$ (1)	**5**
13	Ph	$Pd(OAc)_2$	DMF	120	$Cu(OAc)_2$ (0.4), air, $NaI \cdot 2H_2O$ (2), K_2CO_3 (1)	**5**
14	Ph	$Pd(OAc)_2$	DMF	120	$CuCl_2 \cdot 2H_2O$ (0.4), air, NaBr (2), KOH (1)	**5**

Reaction conditions: (i) Aminimide **7** (1 equiv.), alkyne (2-3 equiv.), catalyst (10 mol%), solvent [0.05-0.2 M], 16 h; [a] Determined by ^{1}H NMR spectroscopy. [b] Catalyst (5 mol%). [Ru] = $[RuCl_2(p\text{-cymene})]_2$.

4.4 Conclusion

Various routes towards the synthesis of benzothiazine 1,1-dioxide have been explored using palladium, rhodium and ruthenium catalysis. Three palladium catalysed routes were investigated using the general precursors *ortho*-(alkynyl)iodobenzene,

ortho-(halo)iodobenzene and *ortho*-(bromovinyl)iodobenzene. The aminosulfonylation of these precursors proved challenging. An alternative strategy employing C—H activation of an *N*-aminosulfonamide and an aminimide using palladium, rhodium or ruthenium catalysis, led only to decomposition of the starting material.

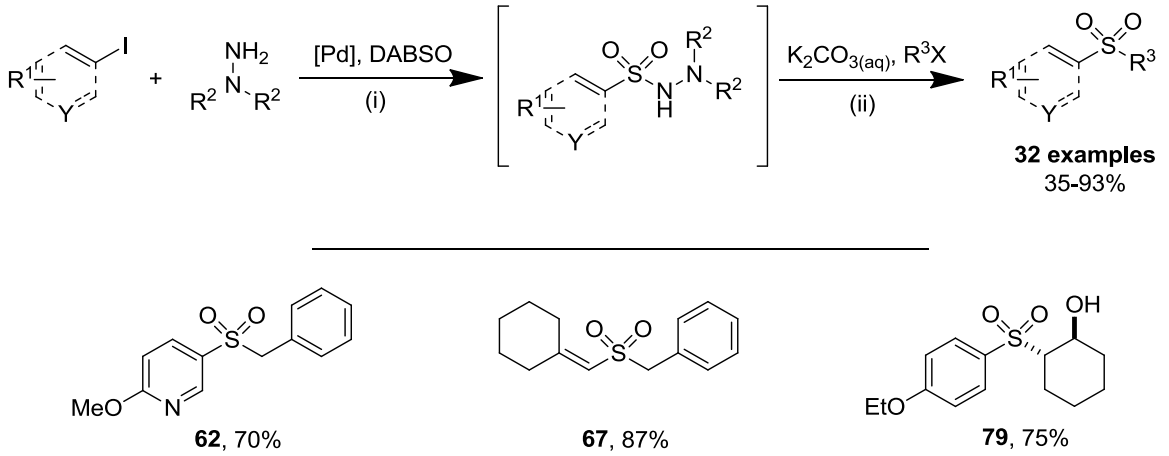
Chapter 5

Summary and future work

The desire to find milder and more selective transformations for the synthesis of sulfonyl-containing compounds is a consequence of the many important biological and synthetic uses of these compounds.[258] To this end, this thesis has focused on the development of novel applications of the sulfur dioxide donor, DABSO (1,4-diazabicyclo[2.2.2]octane *bis*(sulfur dioxide), an air-stable, commercially available solid), to provide efficient and highly functional group tolerant routes towards the synthesis of sulfones and sulfonamides.

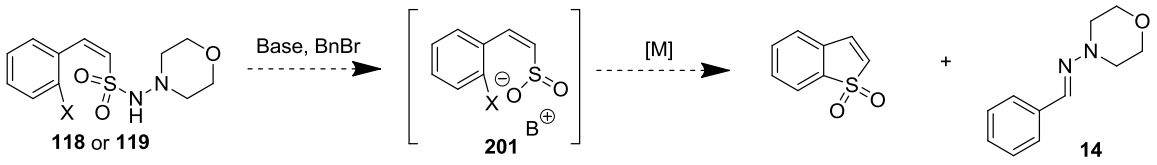
A novel one-pot palladium catalysed synthesis of sulfones *via* an *in situ* *N*-aminosulfonamide intermediate was developed (Scheme 5.1).[167] This methodology uses commercially available or readily synthesised aryl-, heteroaryl- and alkenyl iodide coupling partners, thus removing the need for oxidation and thiol starting materials as required in many current procedures to prepare sulfones. The mild reaction conditions

enable compatibility with a large variety of functional groups thus allowing a diverse substrate scope to be obtained.



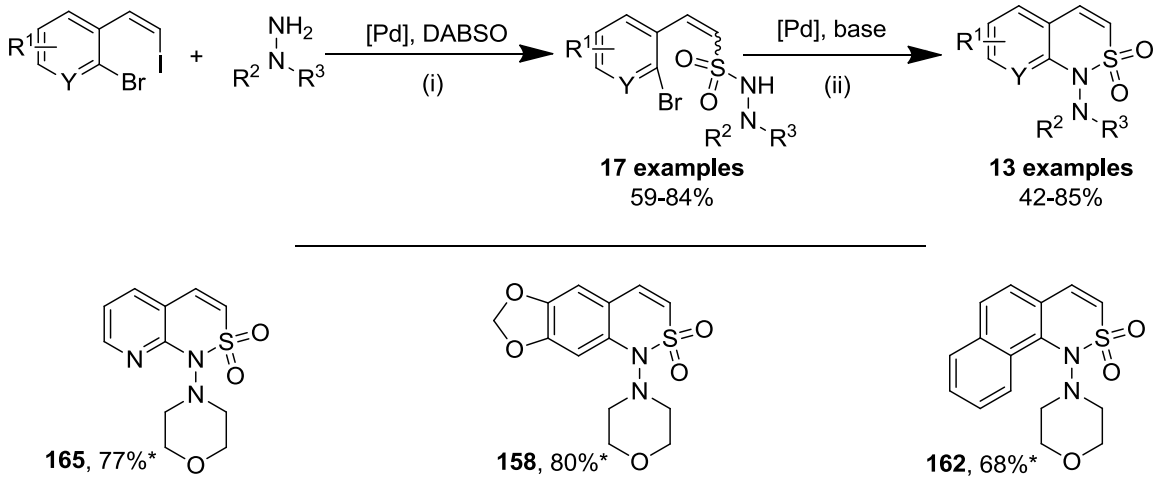
Scheme 5.1: Synthesis of sulfones *via* an *N*-aminosulfonamide intermediate. *Reaction conditions*: (i) Aryl-, heteroaryl- or alkenyl iodide (1 equiv.), $Pd(OAc)_2$ (10 mol%), $^tBu_3P.HBF_4$ (20 mol%), DABSO (1.1 equiv.) or DABSO (0.6 equiv.) and DABSO (0.5 equiv.), hydrazine (1.2 equiv.), 1,4-dioxane [0.3 M], 70 °C, 16 h; (ii) $K_2CO_{3(aq)}$ (2.5 equiv.), R^3X (2.5 equiv.), 90 °C, 5 to 16 h.

Inspired by this sulfone methodology, an investigation was conducted into the synthesis of benzo[*b*]thiophene 1,1-dioxide by a potential S_NAr reaction of the alkenyl sulfinate salt **99**. Unfortunately, only unreacted sulfinate salt was returned. Metal-mediated sulfone synthesis using either copper or palladium catalysis to couple a sulfinate salt and an aryl (pseudo)halide is well documented (see Section 2.1.5). A more profitable route to benzo[*b*]thiophene 1,1-dioxide may be provided by using metal-catalysis to potentially cyclise the alkenyl sulfinate salt (**201**, X = Br or Cl) (Scheme 5.2).



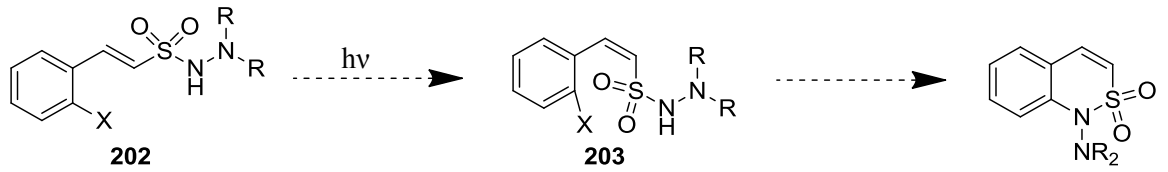
Scheme 5.2: An alternative route towards the synthesis of benzo[*b*]thiophene 1,1-dioxide *via* a metal-catalysed cyclisation step.

Benzothiazine 2,2-dioxide is a highly desirable structural motif due to its recently reported biological properties.[169,170,171] However, as of yet, no general and mild synthetic route has been realised. A novel route towards this class of compound was discovered by the cyclisation of an alkenyl *N*-aminosulfonamide (Scheme 5.3). Various reaction conditions were applied in an attempt to reduce the *Z* to *E* isomerisation of the double bond, with the discovery that the addition of the phase transfer catalyst TBAI had a significant effect on both *Z*:*E* selectivity and reaction time. Unfortunately, due to the incompatibility of the two metal-catalysed steps, a one-pot procedure could not be developed. Variation of the aryl group and hydrazine coupling partner was possible to provide a range of benzosultams.



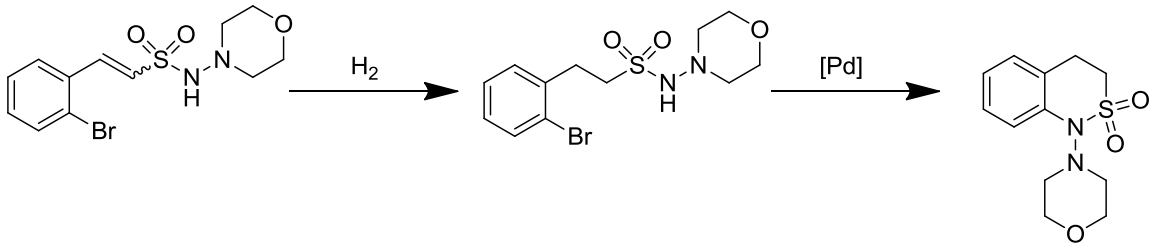
Scheme 5.3: Synthesis of benzothiazine 2,2-dioxide and its derivatives. *Reaction conditions*: (i) 2-(2-Iodoalkenyl)aryl bromide (1 equiv.), $Pd(OAc)_2$ (10 mol%), Cata*CX*ium A (20 mol%), DABSO (1.1 equiv.), TBAI (1 equiv.), 4-aminomorpholine (1.5 equiv.), 1,4-dioxane [0.15 M], 70 °C, 3-4 h; (ii) Alkenyl *N*-aminosulfonamide (1 equiv.), $Pd(OAc)_2$ (10 mol%), Cata*CX*ium A (20 mol%), Cs_2CO_3 (1.5 equiv.), 1,4-dioxane [0.15 M], reflux, 1 h. *Yields of examples are from the alkenyl *N*-aminosulfonamide.

Another possible way to tackle the competing *Z* to *E* isomerisation could be by a photocyclisation reaction in which the *E* isomer **202** is irradiated to give the *Z* isomer **203** followed by an intramolecular cyclisation (Scheme 5.4). Precedent for this has been reported in the synthesis of quinolines.[259]



Scheme 5.4: Potential photocyclisation to synthesise benzothiazine 2,2-dioxide from the *E* alkenyl *N*-aminosulfonamide.

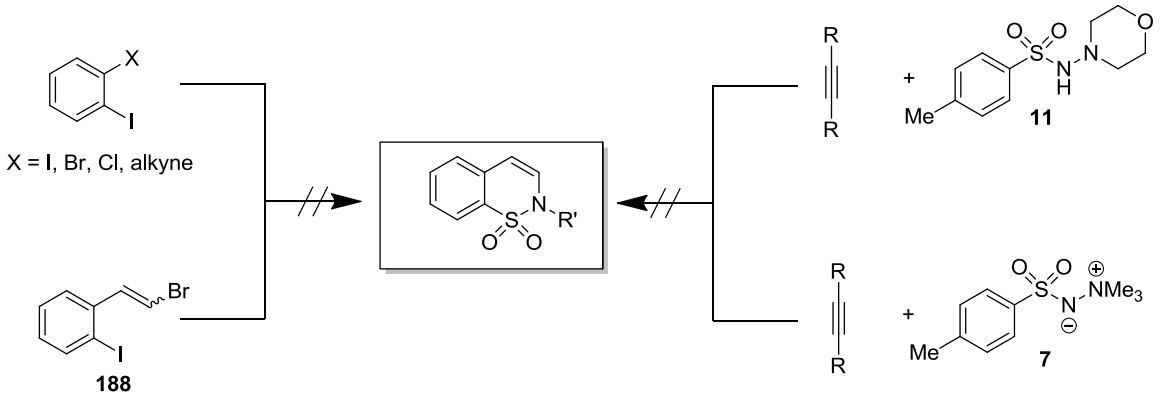
Another alternative would be to reduce the double bond of the alkenyl *N*-aminosulfonamide and then cyclise by a Buchwald–Hartwig coupling step. This procedure would be particularly relevant for the alkenyl *N*-aminosulfonamides predominately formed as the *E* isomer, i.e. those with a substituent in position C-3. Although the 3,4-dihydrosulfostyril is also a useful product, it would not allow access to the desired benzothiazine 2,2-dioxide as mentioned in Section 3.2.9.[176(b)]



Scheme 5.5: Potential synthesis of 3,4-dihydrosulfostyril from the alkenyl *N*-aminosulfonamide.

Investigation into the regioisomer, benzothiazine 1,1-dioxide, was also conducted. Palladium catalysed routes using the general precursors *ortho*-(alkynyl)iodobenzene, *ortho*-(halo)iodobenzene and *ortho*-(bromovinyl)iodobenzene, and also C—H activation of an *N*-aminosulfonamide and an aminimide using palladium, rhodium or ruthenium catalysis, were all unsuccessful in the preparation of the benzothiazine 1,1-dioxide (Scheme 5.6). This was due, in part, to the instability of the starting material under the reaction conditions employed and also the difficulty in preparing certain *ortho*-substituted *N*-aminosulfonamides. Further exploration of the C—H activation procedure could involve

variation of the hydrazine group as sulfonamides with a more acidic nitrogen have been found to give the most success as a directing group.[234,249(e)]



Scheme 5.6: Attempted routes towards the synthesis of benzothiazine 1,1-dioxide.

The main focus of this thesis was on the use of DABSO as the sulfur dioxide donor. However, alternative sulfur dioxide donors could be applied. Future work could involve investigation into frustrated Lewis pair sulfur dioxide adducts as potential sulfur dioxide donors in organic transformations.[260]

In summary, novel routes towards the synthesis of sulfones and benzothiazine 2,2-dioxide have been developed that employ DABSO as the sulfur dioxide source. These methods provide high functional group tolerance and mild reaction conditions to enable access to range of sulfonyl-containing compounds.

Chapter 6

Experimental

6.1 General experimental

All glassware was dried in an oven (>200 °C) and allowed to cool under a positive nitrogen pressure (passed through a Drierite® filled tube) prior to use. All reactions were conducted with continuous magnetic stirring under a nitrogen atmosphere with anhydrous solvents unless otherwise stated.

HPLC grade solvents were purchased from Sigma Aldrich, Fischer Scientific or Rathburn. Dichloromethane, tetrahydrofuran, toluene and methanol were obtained from an in-house solvent purification system having passed through anhydrous alumina columns. Water was purified by an Elix® UV-10 system. 1,4-Dioxane and *t*-amyl alcohol were distilled over calcium hydride and stored over 4 Å molecular sieves and degassed prior to use. Chemicals were purchased from Sigma Aldrich, Alfa Aesar, Acros or Fluorochem and used without prior purification, with the exception of 1,4-diazabicyclo[2.2.2]octane

(DABCO), which was purified by sublimation (50 °C, 1 mbar). Ether refers to diethyl ether and petrol to 40-60 °C petroleum ether.

Thin Layer Chromatography (TLC) was performed on Merck Kieselgel 60 F254 pre-coated aluminium plates which were visualised using UV light (254 nm), 1% $KMnO_{4(aq)}$ and vanillin. Column chromatography was performed on silica gel (Fluka Kieselgel 60, particle size 0.040-0.063 nm) with the indicated eluents.

^{1}H, ^{13}C and ^{19}F Nuclear Magnetic Resonance experiments were carried out using Brüker DPX-200 (200 MHz), AVN-400 (400 MHz) or AVC-500 (500 MHz) spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) and referenced relative to the residual solvent peak(s). Assignments were made on the basis of chemical shifts, coupling constants, COSY, HSQC, HMBC, NOE data and comparison with spectra of related compounds. The abbreviations s, d, dd, t, dt, td, tt, q, quin, br. s, m and app, denote singlet, doublet, doublet of doublets, triplet, doublet of triplets, triplet of doublets, triplet of triplets, quartet, quintet, broad singlet, multiplet and apparent. The coupling constants (*J*) are reported in Hertz (Hz) and rounded to the nearest 0.5 Hz.

Elemental microanalysis was performed by Stephen Boyer at the Microanalysis Service, London Metropolitan University using a Thermo Scientific (Carlo Erba) Flash 2000 Elemental Analyser, configured for %CHN. X-Ray crystallography was performed by Dr. Johannes Möller and Dr. Roger Johnson from the Department of Physics. The measurements were performed at room temperature using an *Oxford Diffraction Supernova* diffractometer employing a molybdenum X-Ray source.

Melting points were recorded on a Leica Gallen III hot-stage microscope and are uncorrected. Infra-red spectra were recorded neat on a Brüker Tensor 27 FT-IR spectrometer retrofitted with a diamond attenuated total reflectance (ATR) module, with an internal range of 600-4000 cm^{-1}. Low-resolution mass spectra (*m/z*) were recorded on a LCT Premier Open Access spectrometer (ESI). High resolution mass measurements were run on a Brüker MicroTOF or a Micromass GCT instrument by the mass spectrometry department of the Chemistry Research Laboratory, University of Oxford. Values are quoted as ratio of mass to charge in Daltons and relative intensities of assignable peaks observed are quoted as a percentage value. High resolution values are calculated to four decimal places from the molecular formula, all found within a tolerance of 5 ppm.

6.2 General procedures

General procedure A

An oven-dried tube was evacuated and backfilled with N_2. It was then charged with ligand (20 mol%), palladium(II) acetate (10 mol%) and the halogenated substrate (1 equiv.). Either 1,4-diazabicyclo[2.2.2]octane *bis*(sulfur dioxide) (DABSO) (1.1 equiv.) or (DABSO) (0.6 equiv.) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (0.5 equiv.) were added as specified. The solid reagents were weighed out in the air. The tube was then evacuated and backfilled with N_2. Hydrazine (1.5 equiv.) and 1,4-dioxane [0.15 M] were added *via* microsyringe through a suba-seal under N_2. The reaction mixture was stirred at 70 °C for the specified length of time. After cooling to RT, the suspension was filtered through a short pad of Celite and the residue washed sequentially with CH_2Cl_2 (20 mL

mmol^{-1}) and ether (20 mL mmol^{-1}) before being concentrated *in vacuo*. Purification *via* column chromatography yielded the corresponding *N*-aminosulfonamide.

General procedure B (Method I)

The electrophile (2 equiv.), *N*-aminosulfonamide (1 equiv.) and K_2CO_3 (2 equiv.) were added to a round-bottomed flask. 1,4-Dioxane [0.30 M] was added and the reaction mixture was stirred at 100 °C for the specified length of time. After cooling to RT, the reaction mixture was diluted with water (20 mL mmol^{-1}) and washed with CH_2Cl_2 (3 × 20 mL mmol^{-1}). The combined organic extracts were washed with brine (20 mL mmol^{-1}), dried over $MgSO_4$, filtered and then concentrated *in vacuo*. Purification *via* column chromatography yielded the corresponding sulfone.

General procedure C (Method II)

Benzyl bromide (0.95 equiv.), *N*-aminosulfonamide (1 equiv.) and K_2CO_3 (2 equiv.) were added to a round-bottomed flask. 1,4-Dioxane [0.30 M] was added and the reaction mixture was stirred at 50 °C for 1 h. The electrophile (1.5 equiv.) was then added and the reaction mixture was warmed to 100 °C and stirred at this temperature for a further 15 h. After cooling to RT, the reaction mixture was diluted with water (20 mL mmol^{-1}) and washed with CH_2Cl_2 (3 × 20 mL mmol^{-1}). The combined organic extracts were washed with brine (20 mL mmol^{-1}), dried over $MgSO_4$, filtered and then concentrated *in vacuo*. Purification *via* column chromatography yielded the corresponding sulfone.

General procedure D

An oven-dried tube was charged with $^{t}Bu_3P.HBF_4$ (20 mol%), palladium(II) acetate (10 mol%) and the halogenated substrate (1 equiv.). Either DABSO (1.1 equiv.) or

DABSO (0.6 equiv.) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (0.5 equiv.) were added as specified. The solid reagents were weighed out in air. The tube was then evacuated and backfilled with N_2. The hydrazine (1.2 equiv.) and 1,4-dioxane [0.30 M] were added *via* microsyringe. The reaction mixture was stirred at 70 °C for 16 h. Either Method I or Method II was then followed as stated.

Method I: $K_2CO_{3(aq)}$ [2.40 M, 2.5 equiv.] and the electrophile (2.5 equiv.) were added and the reaction mixture stirred at 90 °C for the specified length of time.

Method II: $K_2CO_{3(aq)}$ [2.40 M, 2.5 equiv.] and benzyl bromide (0.95 equiv.) were added and the reaction mixture was stirred at 90 °C for 1 h. The second electrophile (2 equiv.) was then added and the reaction mixture stirred at 90 °C for 19 h.

After cooling to RT, the suspension was filtered through a short pad of Celite and washed sequentially with CH_2Cl_2 (20 mL $mmol^{-1}$) and water (20 mL $mmol^{-1}$). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL $mmol^{-1}$). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and then concentrated *in vacuo*. Purification *via* column chromatography yielded the corresponding sulfone.

General procedure E

(Iodomethyl)triphenylphosphonium iodide (1.2 equiv.) was added portion-wise to a stirred solution of KO^{t}Bu (1.18 equiv.) in THF [0.08 M] at –78 °C. The mixture was warmed to –20 °C over 10 min and then cooled to –78 °C. A solution of aldehyde (1 equiv.) in THF [0.4 M] was added slowly to the suspension and was stirred for 16 h, in the absence of light, allowing to warm to RT. The reaction mixture was cast into petrol. The suspension was filtered through a Celite pad and then concentrated *in vacuo*. Purification *via* column chromatography yielded the corresponding alkenyl iodide.

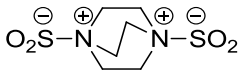
General procedure F

An oven-dried tube was evacuated and backfilled with N_2. It was then charged with alkenyl iodide (1 equiv.), Cata*CX*ium A (20 mol%), palladium(II) acetate (10 mol%), TBAI (1 equiv.) and DABSO (1.1 equiv.). The solid reagents were weighed out in the air. The tube was then evacuated and backfilled with N_2. Hydrazine (1.5 equiv.) and 1,4-dioxane [0.15 M] were added *via* microsyringe through a suba-seal under N_2. The reaction mixture was stirred at 70 °C for the specified length of time. After cooling to RT, the suspension was filtered through a short pad of Celite and the residue washed sequentially with CH_2Cl_2 (20 mL $mmol^{-1}$) and ether (20 mL $mmol^{-1}$) before being concentrated *in vacuo*. Purification *via* column chromatography yielded the corresponding alkenyl *N*-aminosulfonamide.

General procedure G

An oven-dried tube was evacuated and backfilled with N_2. It was then charged with Cata*CX*ium A (20 mol%), palladium(II) acetate (10 mol%), and Cs_2CO_3 (1.5 equiv.). The solid reagents were weighed out in the air. The tube was then evacuated and backfilled with N_2. 1,4-Dioxane [0.05 M] was added *via* syringe through a suba-seal under N_2. The reaction mixture was stirred for 10 minutes. A solution of the alkenyl *N*-aminosulfonamide (1 equiv.) in 1,4-dioxane [0.1 M] was added *via* microsyringe. The reaction mixture was stirred at reflux for 1 h. After cooling to RT, the suspension was filtered through a short pad of Celite and the residue washed sequentially with CH_2Cl_2 (20 mL $mmol^{-1}$) and ether (20 mL $mmol^{-1}$) before being concentrated *in vacuo*. Purification *via* column chromatography yielded the corresponding alkenyl *N*-aminosulfonamide.

1,4-Diazabicyclo[2.2.2]octane *bis*(sulfur dioxide) (DABSO)[6,4]

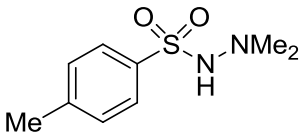


A round-bottom flask was fitted with a condenser and the outlet attached to a standard 2-bubbler system. The apparatus was flushed with argon gas for 10 minutes. 1,4-Diazabicyclo[2.2.2]octane (DABCO) (2.00 g, 16.4 mmol) was added to the flask and the system was flushed with argon for a further 5 mins. The argon line was removed and replaced with sulfur dioxide gas which was passed through the system at approx. 1 bubble/sec for 5 min. A cooling bath (–20 °C to –30 °C) was introduced and the condenser trap cooled to –78 °C. Sulfur dioxide was condensed dropwise onto DABCO and allowed to continue until the liquefied sulfur dioxide completely covered the DABCO (approx. 20 mL). The sulfur dioxide cylinder was closed off and the apparatus was allowed to warm up to –10 °C and left stirring at reflux for 30 min. The condenser was removed and the flask sealed with a suba-seal with a fine venting needle and the sulfur dioxide evaporated to dryness by warming to RT, yielding DABSO as a white powder (4.20 g, 98%). No further purification was performed; mp 200-201 °C (dec); ν_{max} (neat)/cm^{-1} 3015, 2800, 1413, 1178; δ_H (400 MHz, *d*$_4$-MeOH) 3.26 (12H, s); δ_C (126 MHz, *d*$_4$-MeOH) 44.4 (CH_2).

6.3 Synthesis of sulfones

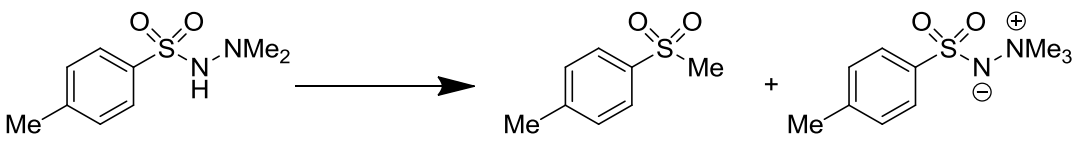
6.3.1 Preparation of substrates and sulfonamides

_N'_, _N'_, 4-Trimethylbenzenesulfonohydrazide 6



General procedure A was followed with the use of $^{t}Bu_3P.HBF_4$ (139 mg, 0.48 mmol), 4-iodotoluene (520 mg, 2.40 mmol), DABSO (350 mg, 1.44 mmol), DABCO (135 mg, 1.20 mmol) and *N*,*N*-dimethylhydrazine (0.28 mL, 3.60 mmol). The reaction mixture was stirred at 70 °C for 16 h. Column chromatography (eluent: 50-100% ether in petrol) yielded *N*-aminosulfonamide **6** as a white crystalline solid (320 mg, 63%); mp 74-76 °C (CH_2Cl_2) {lit.[23] 76-77 °C (CH_2Cl_2)}; δ_H (400 MHz, $CDCl_3$) 7.84 (2H, d, *J* 8.5, 2 × Ar*H*), 7.32 (2H, d, *J* 8.5, 2 × Ar*H*), 5.34 (1H, br. s, N*H*), 3.71 (6H, s, N*Me*$_2$), 2.40 (3H, s, Ar*Me*); δ_C (101 MHz, $CDCl_3$) 143.8 (C), 135.8 (C), 129.5 (2 × CH), 128.2 (2 × CH), 48.4 (2 × CH_3), 21.6 (CH_3); *m/z* (ESI^+) 451 ($[2M + Na]^+$, 100%), 237 ($[M + Na]^+$, 40%). Data in accordance with literature data.[25]

Methyl 4-methylphenyl sulfone 10 and 2,2,2-trimethyl-1-[(4-methylphenyl)sulfonyl]diazan-2-ium-1-ide 7

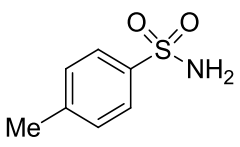


Iodomethane (0.17 mL, 2.80 mmol) was added dropwise to a solution of *N*',*N*'-4-trimethylbenzenesulfonohydrazide **6** (100 mg, 0.47 mmol) and K_2CO_3 (130 mg, 0.93 mmol) in methanol (2.7 mL). The reaction mixture was stirred at RT for 24 h and then concentrated *in vacuo*. Column chromatography (eluent: 7:3, petrol:ether to 10% MeOH in CH_2Cl_2) yielded, in order of elution, methyl 4-methylphenyl sulfone **10** as a white crystalline solid (22 mg, 28%) and aminimide **7** as a pale orange crystalline solid (59 mg, 55%).

Sulfone **10**: mp 87-88 °C (CH_2Cl_2) {lit.[261] 88 °C (ethanol)}; δ_H (400 MHz, $CDCl_3$) 7.86-7.79 (2H, m, 2 × Ar*H*), 7.39-7.35 (2H, m, 2 × Ar*H*), 3.03 (3H, s, SO_2*Me*), 2.45 (3H, s, Ar*Me*); δ_C (101 MHz, $CDCl_3$) 144.8 (C), 137.8 (C), 130.1 (2 × CH), 127.5 (2 × CH), 44.7 (CH_3), 21.7 (CH_3); HRMS (FI^+) $C_8H_{10}O_2S^+$ ($[M]^+$) requires 170.0401, found 170.0402; Anal. Calcd. (%) for $C_8H_{10}O_2S$: C 56.44, H 5.92; found C 56.39, H 5.81. Data in accordance with literature data.[262]

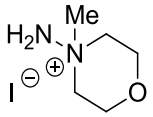
Aminimide **7**: mp 180-184 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3041, 2921, 1664, 1629, 1598, 1482, 1403, 1387, 1252, 1179, 1123, 1089, 1044, 1024; δ_H (400 MHz, $CDCl_3$) 7.81 (2H, d, *J* 8.5, 2 × Ar*H*), 7.21 (2H, d, *J* 8.5, 2 × Ar*H*), 3.29 (9H, s, NMe_3), 2.37 (3H, s, Ar*Me*); δ_C (101 MHz, $CDCl_3$) 144.2 (C), 141.2 (C), 129.4 (2 × CH), 126.7 (2 × CH), 58.8 (3 × CH_3), 21.4 (CH_3); *m/z* (ESI^+) 707 ($[3M + Na]^+$, 100%), 479 ($[2M + Na]^+$, 98%), 251 ($[M + Na]^+$, 73%); HRMS (ESI^+) $C_{10}H_{16}N_2NaO_2S^+$ ($[M + Na]^+$) requires 251.0826, found 251.0825.

4-Methylbenzenesulfonamide 5



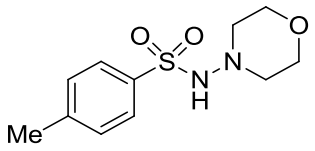
A solution of 2,2,2-trimethyl-1-[(4-methylphenyl)sulfonyl]diazan-2-ium-1-ide **7** (0.03 g, 0.13 mmol), zinc dust (221 mg, 3.38 mmol) and acetic acid (1.4 mL) was stirred at RT for 2 h. CH_2Cl_2 (5 mL) was added and the suspension filtered over Celite. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield sulfonamide **5** as a white crystalline solid (17 mg, 75%); mp 135-137 °C {lit.[263] 136-138 °C}; δ_H (400 MHz, $CDCl_3$) 7.82 (2H, d, *J* 8.5, 2 × Ar*H*), 7.32 (2H, d, *J* 8.5, 2 × Ar*H*), 4.90 (2H, br. s, NH_2), 2.44 (3H, s, Ar*Me*); δ_C (100 MHz, $CDCl_3$) 143.6 (C), 139.1 (C), 129.7 (2 × CH), 126.5 (2 × CH), 21.5 (CH_3); *m/z* (ESI^-) 170 ($[M - H]^-$, 100%). Data in accordance with literature.[263]

Morpholinium iodide 16[264]



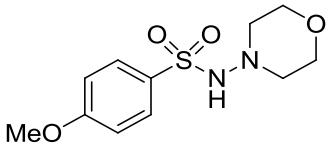
To a solution of 4-aminomorpholine (0.48 mL, 5.00 mol) in THF (3 mL) at 0 °C was added iodomethane (0.33 mL, 5.30 mol) dropwise over 5 min. The mixture was warmed to RT for 30 min and a white precipitate formed. Ether (5 mL) was added and the white solid was isolated by filtration and subsequently washed with ether (20 mL). The solid was recrystallised from EtOH:MeOH (3:1) to yield **16** as a white crystalline solid (1.13 g, 92%); mp 174-177 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3271, 3219, 2976, 2929, 1459, 1105, 1091, 1074, 1055; δ_H (400 MHz, $(CD_3)_2SO$) 5.96 (2H, s, NH_2), 4.03-3.93 (2H, m, CH_2), 3.91-3.82 (2H, m, CH_2), 3.63-3.54 (2H, m, CH_2), 3.39-2.47 (2H, m, CH_2), 3.36 (3H, s, *Me*); δ_C (101 MHz, $(CD_3)_2SO$) 63.5 (2 × CH_2), 61.2 (2 × CH_2), 56.4 (CH_3); *m/z* (ESI^+) 117 ($[M - I]^+$, 100%); HRMS (ESI^+) $C_5H_{13}N_2O^+$ ($[M - I]^+$) requires 117.1023, found 117.1022; Anal. Calcd. (%) for $C_5H_{13}N_2$: C 24.60, H 5.37, N 11.48; found C 24.52, H 5.48, N 11.43. Data in accordance with literature data.[264]

4-Methyl-*N*-(morpholin-4-yl)benzenesulfonamide 11



General procedure A was followed with the use of $^{t}Bu_3P.HBF_4$ (14 mg, 20 mol%), 4-iodotoluene (52 mg, 0.24 mmol), DABSO (35 mg, 0.14 mmol), DABCO (13 mg, 0.12 mmol) and 4-aminomorpholine (35 μL, 0.36 mmol). The reaction mixture was stirred at 70 °C for 16 h. Column chromatography (eluent: 50-100% ether in petrol) yielded the *N*-aminosulfonamide **11** as a white crystalline solid (57 mg, 92%); mp 154-156 °C (CH_2Cl_2) {lit.[23] 154-155 °C (CH_2Cl_2)}; δ_H (400 MHz, $(CD_3)_2SO$) 8.78 (1H, s, N*H*), 7.73 (2H, d, *J* 8.0, 2 × Ar*H*), 7.39 (2H, d, *J* 8.0, 2 × Ar*H*), 3.43 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.46 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.39 (3H, s, Ar*Me*); δ_C (101 MHz, $(CD_3)_2SO$) 143.9 (C), 137.6 (C), 130.3 (2 × CH), 128.4 (2 × CH), 66.8 (2 × CH_2), 56.7 (2 × CH_2), 21.9 (CH_3); *m/z* (ESI^+) 535 ($[2M + Na]^+$, 100%), 279 ($[M + Na]^+$, 25%). Data in accordance with literature data.[23]

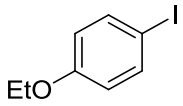
4-Methoxy-*N*-(morpholin-4-yl)benzenesulfonamide 204



General procedure A was followed with the use of $^{t}Bu_3P.HBF_4$ (14 mg, 20 mol%), 4-iodoanisole (56 mg, 0.24 mmol), DABSO (35 mg, 0.14 mmol), DABCO (13 mg, 0.12 mmol) and 4-aminomorpholine (35 μL, 0.36 mmol). The reaction mixture was stirred at 70 °C for 16 h. Column chromatography (eluent: 50-100% ether in petrol) yielded the *N*-aminosulfonamide **204** as a white crystalline solid (58 mg, 89%); mp 173-175 °C (CH_2Cl_2) {lit.[23] 174-175 °C (CH_2Cl_2)}; δ_H (400 MHz, $CDCl_3$) 7.93-7.87 (2H, m, 2 × Ar*H*),

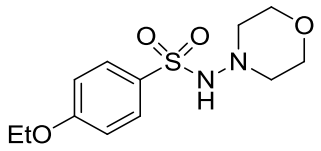
7.02-6.96 (2H, m, 2 × Ar*H*), 5.51 (1H, br. s, N*H*), 3.88 (3H, s, O*Me*), 3.61 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.63 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$); δ_C (101 MHz, $CDCl_3$) 163.3 (C), 130.3 (2 × CH), 130.1 (C), 114.0 (2 × CH), 66.7 (2 × CH_2), 56.7 (2 × CH_2), 55.6 (CH_3); *m/z* (ESI^+) 567 ($[2M + Na]^+$, 100%), 295 ($[M + Na]^+$, 35%); *m/z* (ESI^-) 271 ($[M – H]^-$, 100%). Data in accordance with literature data.[23]

1-Ethoxy-4-iodobenzene 205[265]



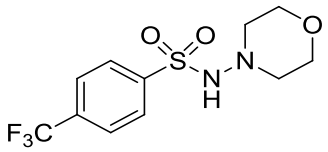
To a suspension of 4-iodophenol (10.0 g, 45.5 mmol) and potassium carbonate (8.70 g, 62.0 mmol) in ethanol (60 mL) was added ethyl iodide (3.3 mL, 41.3 mmol) at RT. The reaction mixture was stirred for 24 h at reflux. The mixture was filtered, and the filtrate concentrated *in vacuo*. The residue was diluted in ether and the organic layer was washed sequentially with 1 M $NaOH_{(aq)}$ (30 mL), 3 M $HCl_{(aq)}$ (30 mL), sat. $NaHCO_{3(aq)}$ (30 mL) and brine (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: 4:1, petrol: ether) yielded aryl iodide **205** as a colourless oil (8.31 g, 74%); ν_{max} (neat)/cm^{-1} 2979, 1585, 1570, 1484, 1473, 1390, 1282, 1239, 1173, 1113, 1045; δ_H (400 MHz, $CDCl_3$) 7.59-7.51 (2H, m, 2 × Ar*H*), 6.72-6.64 (2H, m, 2 × Ar*H*), 4.00 (2H, q, *J* 7.0, OCH_2CH_3), 1.41 (3H, t, *J* 7.0, OCH_2CH_3); δ_C (101 MHz, $CDCl_3$) 158.8 (C), 138.2 (2 × CH), 116.9 (2 × CH), 82.5 (C), 63.5 (CH_2), 14.7 (CH_3); HRMS (FI^+) $C_8H_9IO^+$ ($[M]^+$) requires 247.9698, found 247.9705. Data in accordance with literature data.[265]

4-Ethoxy-*N*-(morpholin-4-yl)benzenesulfonamide 206



General procedure A was followed with the use of $^{t}Bu_3P.HBF_4$ (14 mg, 20 mol%), 1-ethoxy-4-iodobenzene (60 mg, 0.24 mmol), DABSO (35 mg, 0.14 mmol), DABCO (13 mg, 0.12 mmol) and 4-aminomorpholine (35 μL, 0.36 mmol). The reaction mixture was stirred at 70 °C for 16 h. Column chromatography (eluent: 50-100%, ether in petrol) yielded the *N-aminosulfonamide* **206** as a white crystalline solid (69 mg, 92%); mp 144-145 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3209, 2987, 1595, 1577, 1496, 1463, 1327, 1303, 1264, 1183, 1160, 1111, 1041; δ_H (400 MHz, $CDCl_3$) 7.91-7.82 (2H, m, 2 × Ar*H*), 7.00-6.91 (2H, m, 2 × Ar*H*), 5.86 (1H, s, N*H*), 4.08 (2H, q, *J* 7.0, OCH_2CH_3), 3.58 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.61 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 1.43 (3H, t, *J* 7.0, OCH_2CH_3); δ_C (101 MHz, $CDCl_3$) 162.8 (C), 130.4 (2 × CH), 129.9 (C), 114.5 (2 × CH), 66.7 (2 × CH_2), 64.1 (CH_2), 56.7 (2 × CH_2), 14.7 (CH_3); *m/z* (ESI^+) 595 ($[2M + Na]^+$, 100%), 309 ($[M + Na]^+$, 63%), 287 ($[M + H]^+$, 93%); HRMS (ESI^+) $C_{12}H_{18}N_2NaO_4S^+$ ($[M + Na]^+$) requires 309.8079, found 309.8078.

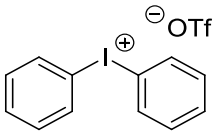
***N*-(Morpholin-4-yl)-4-(trifluoromethyl)benzenesulfonamide 207**



General procedure A was followed with the use of $^{t}Bu_3P.HBF_4$ (14 mg, 0.20 mmol), 4-iodobenzotrifluoride (65 mg, 0.24 mmol), DABSO (65 mg, 0.26 mmol) and 4-aminomorpholine (35 μL, 0.36 mmol). The reaction mixture was stirred at 70 °C for 16 h. Column chromatography (eluent: 50-100% ether in petrol) yielded the

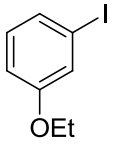
N-aminosulfonamide **207** as a white crystalline solid (58 mg, 78%); mp 167-169 °C (CH_2Cl_2) {lit.[23] 168-169 °C (CH_2Cl_2)}; δ_H (400 MHz, $CDCl_3$) 8.12 (2H, d, *J* 8.5, 2 × Ar*H*), 7.80 (2H, d, *J* 8.5, 2 × Ar*H*), 5.45 (1H, br. s, N*H*), 3.64 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.67 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$); δ_C (101 MHz, $CDCl_3$) 142.3 (C), 134.9 (C, q, J_{CF} 33.0), 128.7 (2 × CH), 126.0 (2 × CH, q, J_{CF} 4.0), 123.2 (C, q, J_{CF} 273.5), 66.6 (2 × CH_2), 56.9 (2 × CH_2); δ_F (377 MHz, $CDCl_3$) –63.1 (s, CF_3) {^{1}H}; *m/z* (ESI^+) 643 ($[2M + Na]^+$, 100%), 333 ($[M + Na]^+$, 97%); *m/z* (ESI⁻) 340 ($[M + Cl]^-$, 100%). Data in accordance with literature data.[23]

Diphenyliodonium triflate 208[266]



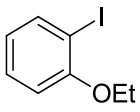
To a solution of *m*CPBA (154 mg, 0.69 mmol) and iodobenzene (77 μL, 0.69 mmol) in CH_2Cl_2 (3 mL) was added benzene (61 μL, 0.69 mmol). The reaction mixture was cooled to 0 °C. Triflic acid (0.18 mL, 2.07 mmol) was added dropwise and the reaction mixture stirred at RT for 30 min and then concentrated *in vacuo*. Ether (3 mL) was added and the reaction mixture was stirred for 10 min to precipitate out a white solid. The flask was stored in a freezer overnight and the solid filtered-off to yield diphenyliodonium triflate **208** as a white crystalline solid (230 mg, 78%); mp 174-176 °C (ether) {lit.[267] 177-178 °C}; δ_H (400 MHz, $CDCl_3$) 8.01 (4H, dd, *J* 8.5, 1.0, 4 × Ar*H*), 7.69-7.64 (2H, m, 2 × Ar*H*), 7.51 (4H, app t, *J* 8.0, 4 × Ar*H*); δ_C (101 MHz, $CDCl_3$) 135.1 (4 × CH), 132.7 (2 × CH), 132.4 (4 × CH), 121.4 (C, q, J_{CF} 314.0, O*Tf*), 113.3 (2 × C); δ_F (377 MHz, $CDCl_3$) –78.3 (s, O*Tf*) {^{1}H}; *m/z* (ESI^+) 281 ($[M – OTf]^+$, 100%). Data in accordance with literature data.[267]

1-Ethoxy-3-iodobenzene 209



To a suspension of 3-iodophenol (1.50 g, 6.80 mmol) and K_2CO_3 (1.32 g, 9.50 mmol) in ethanol (10 mL) was added ethyl iodide (0.5 mL, 6.10 mmol) at RT. The reaction mixture was stirred at reflux for 24 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was diluted in ether and the organic layer was washed sequentially with 1 M $NaOH_{(aq)}$ (30 mL), 3 M $HCl_{(aq)}$ (30 mL), sat. $NaHCO_{3(aq)}$ (30 mL) and brine (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: 4:1, petrol:ether) yielded aryl iodide **209** as a colourless oil (1.30 g, 77%); ν_{max} (neat)/cm^{-1} 3061, 2979, 2929, 2879, 1581, 1565, 1466, 1417, 1388, 1284, 1241, 1159, 1113, 1089, 1042; δ_H (500 MHz, $CDCl_3$) 7.31-7.27 (2H, m, 2 × Ar*H*), 7.01 (1H, app t, *J* 8.0, Ar*H*), 6.88 (1H, ddd, *J* 8.0, 2.5, 1.0, Ar*H*), 4.00 (2H, q, *J* 7.0, O*CH*$_2$CH$_3$), 1.43 (3H, t, *J* 7.0, OCH$_2$C*H*$_3$); δ_C (126 MHz, $CDCl_3$) 159.6 (C), 130.8 (CH), 129.7 (CH), 123.6 (CH), 114.2 (CH), 94.5 (C), 63.7 (CH_2), 14.9 (CH_3); HRMS (FI^+) $C_8H_9IO^+$ ($[M]^+$) requires 247.9698, found 247.9702. ^{1}H NMR spectroscopy data in accordance with literature data.[268]

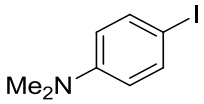
1-Ethoxy-2-iodobenzene 210



To a suspension of 2-iodophenol (0.77 mL, 6.80 mmol) and K_2CO_3 (1.32 g, 9.50 mmol) in ethanol (10 mL) was added ethyl iodide (0.5 mL, 6.10 mmol) at RT. The reaction mixture was stirred at reflux for 24 h. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was diluted in ether and the organic layer was washed sequentially with

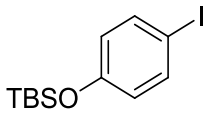
1 M $NaOH_{(aq)}$ (30 mL), 3 M $HCl_{(aq)}$ (30 mL), sat. $NaHCO_{3(aq)}$ (30 mL) and brine (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: 4:1, petrol:ether) yielded aryl iodide **210** as a colourless oil (1.21 g, 72%); ν_{max} (neat)/cm^{-1} 3060, 2980, 2930, 2882, 1581, 1568, 1465, 1438, 1389, 1275, 1243, 1161, 1108, 1088, 1049, 1016; δ_H (400 MHz, $CDCl_3$) 7.79 (1H, dd, *J* 7.5, 1.5, Ar*H*), 7.35-7.27 (1H, m, Ar*H*), 6.82 (1H, dd, *J* 8.5, 1.5, Ar*H*), 6.71 (1H, app td, *J* 7.5, 1.5, Ar*H*), 4.10 (2H, q, *J* 7.0, OCH_2CH_3), 1.50 (3H, t, *J* 7.0, OCH_2CH_3); δ_C (101 MHz, $CDCl_3$) 157.6 (C), 139.5 (CH), 129.5 (CH), 122.5 (CH), 112.3 (CH), 86.9 (C), 64.9 (CH_2), 14.9 (CH_3); HRMS (FI^+) $C_8H_9OI^+$ ($[M]^+$) requires 247.9698, found 247.9702. ^1H NMR spectroscopy data in accordance with literature data.[268]

4-Iodo-*N*,*N*-dimethylaniline 211[269]



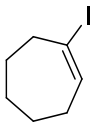
Iodomethane (1.87 g, 30.0 mmol) was added to a solution of 4-iodoaniline (2.19 g, 10.0 mmol) and K_2CO_3 (3.45 g, 25.0 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at reflux for 24 h. After cooling to RT, water (50 mL) was added and extracted with EtOAc (2 × 30 mL) then washed with brine. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: petrol:ether, 19:1) yielded aryl iodide **211** as pale yellow solid (223 mg, 9%); mp 74-79 °C (CH_2Cl_2) {lit.[270] 78-80 °C}; δ_H (400 MHz, $CDCl_3$) 7.52-7.45 (2H, m, 2 × Ar*H*), 6.54-6.47 (2H, m, 2 × Ar*H*), 2.93 (6H, s, N*Me*$_2$); δ_C (101 MHz, $CDCl_3$) 150.0 (C), 137.6 (2 × CH), 114.8 (2 × CH), 77.5 (C), 40.4 (2 × CH_3); HRMS (FI^+) $C_8H_{10}IN^+$ ($[M]^+$) requires 246.9858, found 246.9848. Data in accordance with literature data.[270]

tert-Butyl(4-iodophenoxy)dimethylsilane 212[271]



To a solution of 4-iodophenol (1.00 g, 4.54 mmol) in toluene (6.0 mL) was added Et_3N (0.76 mL, 5.44 mmol), DMAP (28 mg, 0.23 mmol) and *tert*-butyldimethylsilyl chloride (0.82 g, 5.44 mmol) at 0 °C. The reaction was warmed to RT and stirred for 16 h. The reaction mixture was quenched with 2 M $HCl_{(aq)}$ (3.5 mL), washed with water (5 mL) and extracted with ether (2 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: petrol) yielded aryl iodide **212** as a colourless oil (1.33 g, 88%); δ_H (500 MHz, $CDCl_3$) 7.53-7.49 (2H, m, 2 × Ar*H*), 6.64-6.60 (2H, m, 2 × Ar*H*), 0.98 (9H, s, OSi^t*Bu*), 0.19 (6H, s, OSi*Me*$_2$); δ_C (125 MHz, $CDCl_3$) 155.6 (C), 138.3 (2 × CH), 122.5 (2 × CH), 83.7 (C), 25.6 (3 × CH_3), 18.2 (C), –4.5 (2 × CH_3); *m/z* (ESI^+) 279 ([(M – ^{t}Bu) + H^+], 100%); HRMS (FI^+) $C_{12}H_{19}IOSi^+$ ($[M]^+$) requires 334.0250, found 334.0241. Data in accordance with literature data.[272]

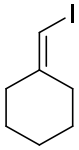
1-Iodocycloheptene 45[273, 274]



Cycloheptanone (1.2 mL, 10.0 mmol) was added dropwise to a stirred solution of lithium diisopropylamide [11.0 mmol, prepared from *in situ* diisopropylamine (1.5 mL, 11.0 mmol) and ^{n}BuLi (6.9 mL, 11.0 mmol, 1.6 M in hexanes)] in THF (20 mL) at –78 °C. After 45 min, a solution of diethylchlorophosphate (1.6 mL, 11.0 mmol) in THF (5.0 mL) was added dropwise and stirred for 30 min. The reaction mixture was warmed to RT and stirred for a further 1 h. The reaction mixture was quenched with sat. $NH_4Cl_{(aq)}$ (10 mL)

and extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. TMSCl (3.8 mL, 30.0 mmol) was added dropwise to a solution of the crude alkenyl phosphate and sodium iodide (4.50 g, 30.0 mmol) in CH_2Cl_2 (20 mL) at RT. After 10 min, the reaction mixture was quenched with sat. $NaHCO_{3(aq)}$ (10 mL) and sat. $Na_2SO_{3(aq)}$ (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification *via* column chromatography (eluent: *n*-pentane) and vacuum distillation (42 Torr, 115 °C)[275] yielded alkenyl iodide **45** as a pale yellow oil (1.11 g, 50%); ν_{max} (neat)/cm^{-1} 2920, 2849, 1627, 1443, 1335, 1272, 1204, 1032; δ_H (500 MHz, $CDCl_3$) 6.52 (1H, t, *J* 6.5, IC=C*H*), 2.78-2.75 (2H, m, CH_2), 2.08-2.04 (2H, m, CH_2), 1.76-1.70 (2H, m, CH_2), 1.58-1.53 (4H, m, 2 × CH_2); δ_C (126 MHz, $CDCl_3$) 142.8 (CH), 100.7 (C), 45.0 (CH_2), 31.4 (CH_2), 30.9 (CH_2), 26.6 (CH_2), 26.3 (CH_2); HRMS (FI^+) $C_7H_{11}I^+$ ($[M]^+$) requires 221.9906, found 221.9915. Data in accordance with literature data.[276]

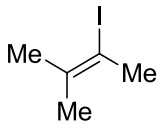
(Iodomethylidene)cyclohexane 46[277]



To a suspension of iodomethyltriphenylphosphonium iodide (3.85 g, 7.25 mmol) in THF (16.0 mL) at –20 °C, was slowly added a solution of potassium *tert*-butoxide (810 mg, 7.25 mmol) in THF (7.0 mL). The reaction mixture was stirred for 10 min. Cyclohexanone (0.6 mL, 5.80 mmol) was added dropwise over 5 min. The cold bath was removed, and stirring was continued for a further 30 min. Petrol (100 mL) was added and the suspension filtered through a plug of Celite. Column chromatography (eluent: hexane) yielded alkenyl iodide **46** as a pale yellow oil (320 mg, 25%); ν_{max} (neat)/cm^{-1} 2927, 2852, 1445, 1331,

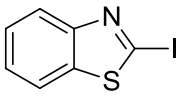
1316, 1274, 1254, 1226, 1159, 1123; δ_H (500 MHz, $CDCl_3$) 5.79-5.78 (1H, m, C=C*H*I), 2.32-2.27 (4H, m, 2 × CH_2), 1.60-1.49 (6H, m, 3 × CH_2); δ_C (126 MHz, $CDCl_3$) 151.3 (C), 71.0 (CH), 37.2 (CH_2), 35.9 (CH_2), 28.0 (CH_2), 27.0 (CH_2), 26.0 (CH_2); HRMS (FI^+) $C_7H_{11}I^+$ ($[M]^+$) requires 221.9906, found 221.9906. Data in accordance with literature data.[278]

2-Iodo-3-methylbut-2-ene 47[279]



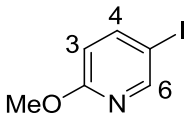
Copper iodide (288 mg, 1.51 mmol) and sodium iodide (6.78 g, 45.2 mmol) were added under argon to a 50 mL Schlenk tube. Dimethylethylenediamine (324 μL, 3.01 mmol), 2-bromo-3-methyl-2-butene (3.5 mL, 30 mmol) and *n*-butanol (15 mL) were then added. The reaction mixture was stirred at 120 °C for 24 h. The reaction mixture was cooled to RT, poured into pentane (150 mL) and washed with a solution of 30% $NH_{3(aq)}$ (7.5 mL) in water (150 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated (~10 mL volume). The residue was distilled (120-130 °C) to yield alkenyl iodide **47** as a colourless liquid (1.23 g, 21%); ν_{max} (neat)/cm^{-1} 2993, 2915, 2855, 1434, 1373, 1289, 1211, 1168, 1131, 1054; δ_H (400 MHz, $CDCl_3$) 2.50 (3H, br. s, C(1)H_3), 1.96-1.92 (3H, m, C(3)*Me*), 1.82 (3H, s, C(3)*Me*); δ_C (101 MHz, $CDCl_3$) 136.0 (C), 93.2 (C), 31.4 (CH_3), 30.3 (CH_3), 18.9 (CH_3); HRMS (FI^+) $C_5H_9I^+$ ($[M]^+$) requires 195.9762, found 195.9749. Data in accordance with literature data.[280,279]

2-Iodobenzothiazole 48[281]



To a 100 mL round-bottom flask was added ether (27 mL) and benzothiazole (1.5 mL, 14.0 mmol). The reaction mixture was cooled to –40 °C (dry ice/MeOH). Methyl lithium (9.8 mL, 15.7 mmol, 1.6 M in ether) was added over 15 min, followed by a solution of iodine (5.18 g, 17.0 mmol) in ether (30 mL), and the reaction mixture was warmed to RT. Ether (75 mL) was added and the organic layer was washed with water (25 mL) and then brine (15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: CH_2Cl_2) yielded 2-iodobenzothiazole **48** as a pale yellow solid (1.98 g, 76%); mp 77–78 °C (CH_2Cl_2) {lit.[282] 77–78 °C (ethanol)}; δ_H (400 MHz, $CDCl_3$) 8.03 (1H, dd, *J* 8.0, 0.5, Ar*H*), 7.85-7.80 (1H, m, Ar*H*), 7.47-7.32 (2H, m, 2 × Ar*H*); δ_C (101 MHz, $CDCl_3$) 154.2 (C), 139.1 (C), 126.4 (CH), 125.6 (CH), 122.6 (CH), 120.5 (CH), 105.8 (C); HRMS (FI^+) $C_7H_4NSI^+$ ($[M]^+$) requires 260.9109, found 260.9116. Data in accordance with literature data.[281]

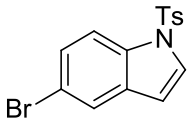
5-Iodo-2-methoxypyridine 213[283]



2-Hydroxy-5-iodopyridine (0.50 g, 2.26 mmol) was added to a solution of silver carbonate (3.43 g, 12.4 mmol), iodomethane (3.9 mL, 63.3 mmol) and chloroform (25 mL). This was stirred at RT for 24 h in the absence of light. The reaction mixture was then filtered and concentrated *in vacuo*. Column chromatography (eluent: 3:2, hexane: EtOAc) yielded iodopyridine **213** as a colourless oil (770 mg, 72%); ν_{max} (neat)/cm^{-1} 2981, 2939, 2839, 1579, 1557, 1471, 1426, 1402, 1359, 1301, 1278, 1241, 1176, 1152, 1125, 1077, 1018; δ_H (500 MHz, $CDCl_3$) 8.34-8.33 (1H, m, *J* 2.5, 0.5, C(6)*H*), 7.77 (1H, dd, *J* 8.5, 2.5, C(4)*H*), 6.58 (1H, dd, *J* 8.5, 0.5, C(3)*H*), 3.89 (3H, s, O*Me*); δ_C (126 MHz, $CDCl_3$) 163.4 (C),

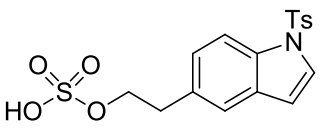
152.7 (CH), 146.2 (CH), 113.3 (CH), 82.1 (C), 53.5 (CH_3); *m/z* (ESI^+) 493 ($[2M + Na]^+$, 30%), 258 ($[M + Na]^+$, 100%). Data in accordance with literature data.[284]

5-Bromo-1-tosyl-1*H*-indole 87



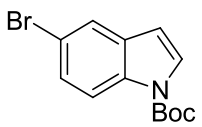
A solution of potassium *tert*-butoxide (1.83 g, 16.0 mmol) in THF (16 mL) was added to a solution of 5-bromoindole (2.00 g, 10.2 mmol) in THF (30 mL). The reaction mixture was stirred at RT for 30 min. *p*-Toluenesulfonyl chloride (3.11 g, 16.0 mmol) was added and stirred at RT overnight. The reaction mixture was diluted with water (100 mL), 1 M $NaOH_{(aq)}$ (35 mL), and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Column chromatography (eluent: 1:4, ether:petrol) yielded indole **87** as a white crystalline solid (2.36 g, 66%); mp 128-129 °C (CH_2Cl_2) {lit.[285] 135 °C}; δ_H (400 MHz, $CDCl_3$) 7.80-7.77 (1H, m, Ar*H*), 7.68-7.64 (2H, m, 2 × SO_2Ar*H*), 7.58 (1H, d, *J* 2.0, Ar*H*), 7.49 (1H, d, *J* 3.5, CH=C*H*N), 7.32 (1H, dd, *J* 8.5, 2.0, Ar*H*), 7.16 (2H, d, *J* 8.0, 2 × SO_2Ar*H*), 6.60 (1H, dd, *J* 3.5, 0.5, C*H*=CHN), 2.27 (3H, s, Ar*Me*); δ_C (101 MHz, $CDCl_3$) 145.3 (C), 135.0 (C), 133.5 (C), 132.5 (C), 130.0 (2 × CH), 127.6 (CH), 127.5 (CH), 126.8 (2 × CH), 124.1 (CH), 116.8 (C), 115.0 (CH), 108.3 (CH), 21.6 (CH_3); *m/z* (ESI^+) 374 ($[M + Na]^+$, 100%), 372 ($[M + Na]^+$, 60%. Data in accordance with literature data.[285]

3-{1-[(4-Methylphenyl)sulfonyl]-1*H*-indol-5-yl}propan-1-ol 88[286]



n-Butylithium (1.2 mL, 2.43 mmol, 2 M in cyclohexane) was added dropwise to a solution of 5-bromo-1-tosyl-1*H*-indole **87** (851 mg, 2.43 mmol) in THF (35 mL) at –78 °C over 30 min. The reaction mixture was stirred for 2 h at –78 °C. A solution of 1,3,2-dioxathiolane 2,2-dioxide (361 mg, 2.92 mmol) in THF (5 mL) was added dropwise. The reaction mixture was warmed to RT over 16 h. H_2SO_4 (1.8 mL) was added dropwise and then water (10 mL). The reaction mixture was heated at reflux for 48 h. The solution was made alkaline with 5 M $NaOH_{(aq)}$ (20 mL) and extracted with CH_2Cl_2 (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: 1:1, petrol:ether) yielded **88** as a white crystalline solid (429 mg, 44%); 126-127 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3371, 3295, 2979, 2948, 2886, 1590, 1444, 1330, 1190, 1174, 1160, 1132, 1092, 1068, 1049, 1019; δ_H (400 MHz, $CDCl_3$) 8.05 (1H, d, *J* 9.0, Ar*H*), 7.63-7.57 (2H, m, 2 × SO_2Ar*H*), 7.56 (1H, d, *J* 2.0, Ar*H*), 7.38 (1H, dd, *J* 9.0, 2.0, Ar*H*), 7.27-7.19 (3H, m, Ar*H*, 2 × SO_2Ar*H*), 6.45 (1H, app s, Ar*H*), 4.01 (2H, t, *J* 6.0, $ArCH_2CH_2SO_2OH$), 3.28 (2H, t, *J* 6.0, $ArCH_2CH_2SO_2OH$), 2.36 (3H, Ar*Me*), 1.58 (1H, br. s, $ArCH_2CH_2SO_2OH$); δ_C (126 MHz, $CDCl_3$) 145.3 (C), 139.8 (CH), 136.1 (C), 135.8 (C), 131.6 (C), 130.1 (2 × CH), 127.2 (CH), 126.4 (2 × CH), 123.1 (CH), 117.3 (C), 116.5 (CH), 109.8 (CH), 61.8 (CH_2), 32.6 (CH_2), 21.7 (CH_3); *m/z* (ESI^+) 418 ($[M + Na]^+$, 100%), 396 ($[M + H]^+$, 70%).

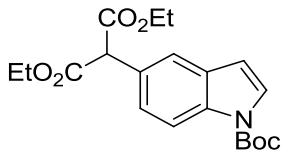
tert-Butyl 5-bromo-1*H*-indole-1-carboxylate 86[287]



Di-*tert*-butyl dicarbonate (7.3 mL, 31.8 mmol) was added dropwise to a stirred solution of 5-bromoindole (5.20 g, 26.5 mmol) and 4-dimethylaminopyridine (0.32 g, 2.65 mmol) in THF (75 mL) at RT. The reaction mixture was stirred for 16 h at RT and then quenched

with 1 N $HCl_{(aq)}$ (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: 30:1, petrol:ether) yielded indole **86** as a white crystalline solid (6.51 g, 83%); mp 59-60 °C (CH_2Cl_2) {lit.[288] 58-60 °C}; δ_H (400 MHz, $CDCl_3$) 8.05 (1H, d, *J* 8.0, Ar*H*), 7.72 (1H, d, *J* 2.0, Ar*H*), 7.61 (1H, d, *J* 3.5, CH=C*H*N), 7.42 (1H, dd, *J* 9.0, 2.0, Ar*H*), 6.53 (1H, d, *J* 3.5, C*H*=CHN), 1.69 (9H, s, O^t*Bu*); δ_C (126 MHz, $CDCl_3$) 149.4 (C), 133.9 (C), 132.2 (C), 127.0 (2 × CH), 123.5 (CH), 116.6 (CH), 116.0 (C), 106.5 (CH), 84.1 (C), 28.2 (3 × CH_3); HRMS (FI^+) $C_{13}H_{14}BrNO_2^+$ ($[M]^+$) requires 295.0208, found 295.0206. Data in accordance with literature data.[289]

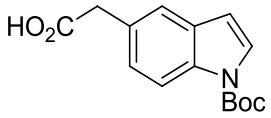
Diethyl [1-(*tert*-butoxycarbonyl)-1*H*-indol-5-yl]propanedioate 90



A mixture of *tert*-butyl 5-bromo-1*H*-indole-1-carboxylate **86** (5.32 g, 18.0 mmol), $Pd(OAc)_2$ (202 mg, 0.90 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos) (0.86 g, 1.80 mmol), Cs_2CO_3 (17.6 g, 53.9 mmol) and diethyl malonate (2.7 mL, 18.0 mmol) in toluene (200 mL) was stirred for 16 h at 100 °C. The reaction mixture was cooled to RT and concentrated *in vacuo*, then partitioned between EtOAc (150 mL) and water (100 mL). The mixture was filtered through Celite and the aqueous layer was extracted with EtOAc (2 × 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: 15% ether in petrol) yielded *indole* **90** as a white crystalline solid (4.86 g, 72%); mp 80-81 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2985, 2160, 2026, 2009, 1977, 1748, 1721, 1467, 1443, 1385, 1367, 1335, 1314, 1299, 1283, 1256, 1223, 1172, 1143, 1129, 1115, 1079, 1030; δ_H (400 MHz, $CDCl_3$) 8.12 (1H, d, *J* 8.5, Ar*H*), 7.67-7.63 (2H, m, Ar*H*, CH=C*H*N), 7.35 (1H, dd, *J* 8.5, 2.0,

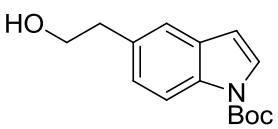
Ar*H*), 6.56 (1H, d, *J* 4.0, C*H*=CHN), 4.70 (1H, s, C*H*($COOCH_2CH_3$)$_2$), 4.27-4.17 (4H, m, CH($COOCH_2CH_3$)$_2$), 1.66 (9H, s, O^t*Bu*), 1.26 (6H, t, *J* 7.0, CH($COOCH_2CH_3$)$_2$); δ_C (101 MHz, $CDCl_3$) 168.6 (2 × C), 149.8 (C), 135.0 (C), 130.9 (C), 127.3 (C), 126.6 (CH), 125.4 (CH), 121.9 (CH), 115.4 (CH), 107.5 (CH), 83.9 (C), 61.9 (2 × CH_2), 57.9 (CH), 28.3 (3 × CH_3), 14.2 (2 × CH_3); *m/z* (ESI^+) 774 ($[2M + Na]^+$, 25%), 398 ($[M + Na]^+$, 10%), 376 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{25}NNaO_6^+$ ($[M + Na]^+$) requires 398.1574, found 398.1565.

[1-(*tert*-Butoxycarbonyl)-1*H*-indol-5-yl]acetic acid 91



A solution of indole **90** (4.84 g, 12.9 mmol) in THF (25 mL) and EtOH (2.5 mL) was treated with 2 M $NaOH_{(aq)}$ (5.6 mL). The solution was stirred at 60 °C for 16 h. The reaction mixture was concentrated *in vacuo* and the aqueous residue was acidified to pH 1 with 2 M $HCl_{(aq)}$. The aqueous solution was washed with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield *indole* **91** as a brown solid (2.66 g, 75%) that was used in the subsequent step without further purification.

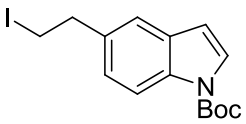
***tert*-Butyl 5-(2-hydroxyethyl)-1*H*-indole-1-carboxylate 92**



To a solution of indole **91** (1.56 g, 5.44 mmol) in THF (9.0 mL) was added BH_3.THF (18.8 mL, 1 M solution in THF) dropwise over 10 minutes at 0 °C. The reaction mixture was stirred for a further 90 min at 0 °C and then quenched by slow addition of MeOH. The

reaction mixture was concentrated *in vacuo*. Column chromatography (eluent: 3:7 to 1:1, ether:petrol) yielded *indole* **92** as a colourless oil (0.68 g, 46%); ν_{max} (neat)/cm^{-1} 3359, 2979, 2935, 1729, 1470, 1442, 1371, 1347, 1327, 1254, 1217, 1192, 1161, 1129, 1082, 1040, 1022; δ_H (400 MHz, $CDCl_3$) 8.08 (1H, d, *J* 8.0, Ar*H*), 7.58 (1H, d, *J* 3.5, CH=C*H*N), 7.40 (1H, d, *J* 1.0, Ar*H*), 7.17 (1H, dd, *J* 8.5, 1.5, Ar*H*), 6.52 (1H, d, *J* 3.5, C*H*=CHN), 3.85 (2H, t, *J* 6.5, $ArCH_2CH_2OH$), 2.93 (2H, t, *J* 6.5, $ArCH_2CH_2OH$), 2.20 (1H, s, $ArCH_2CH_2OH$), 1.67 (9H, s, O^t*Bu*); δ_C (101 MHz, $CDCl_3$) 149.8 (C), 134.0 (C), 132.8 (CH), 130.9 (C), 126.2 (CH), 125.4 (CH), 121.1 (CH), 115.2 (CH), 107.1 (CH), 83.7 (C), 64.0 (CH_2), 39.1 (CH_2), 28.2 (3 × CH_3); *m/z* (ESI$^+$) 545 ([2M + Na]$^+$, 100%), 284 ([M + Na]$^+$, 20%); HRMS (ESI$^+$) $C_{15}H_{19}NNaO_3^+$ ([M + Na]$^+$) requires 284.1257, found 284.1254.

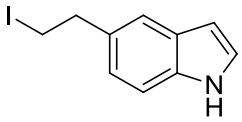
tert-Butyl 5-(2-iodoethyl)-1*H*-indole-1-carboxylate 93



To a solution of PPh_3 (0.84 g, 3.22 mmol) and 1*H*-imidazole (0.23 g, 3.35 mmol) in CH_2Cl_2 (6.0 mL) was added iodine (0.82 g, 3.22 mmol) at 0 °C. A solution of indole **92** (0.68 g, 2.48 mmol) in CH_2Cl_2 (3.0 mL) was added dropwise. The reaction mixture was stirred at RT for 16 h and then washed with H_2O (10 mL), sat. $NaHSO_{3(aq)}$ (10 mL), and brine (10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Heptane (50 mL) was added and the mixture filtered through Celite and the filtrate was concentrated *in vacuo*. Column chromatography (eluent: 0-10%, ether in petrol) yielded *indole* **93** as a colourless oil (0.59 g, 64%); ν_{max} (neat)/cm^{-1} 2978, 2932, 1730, 1469, 1443, 1370, 1348, 1326, 1294, 1255, 1217, 1192, 1161, 1129, 1107, 1081, 1040, 1022; δ_H (400 MHz, $CDCl_3$) 8.07 (1H, d, *J* 8.0, Ar*H*), 7.59 (1H, d, *J* 4.0, CH=C*H*N),

7.38 (1H, d, *J* 1.5, Ar*H*), 7.14 (1H, dd, *J* 8.5, 1.5, Ar*H*), 6.54 (1H, d, *J* 4.0, C*H*=CHN), 3.42-3.36 (2H, m, $ArCH_2CH_2I$), 3.29-3.23 (2H, m, $ArCH_2CH_2I$), 1.67 (9H, s, O*t*Bu); δ_C (101 MHz, $CDCl_3$) 149.9 (C), 135.2 (C), 134.3 (C), 131.0 (C), 126.5 (CH), 124.8 (CH), 120.6 (CH), 115.4 (CH), 107.2 (CH), 83.8 (C), 40.5 (CH_2), 28.3 ($3 \times CH_3$), 6.6 (CH_2); *m/z* (ESI^+) 394 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{15}H_{18}INNaO_2^+$ ($[M + Na]^+$) requires 394.0274, found 394.0263.

5-(2-Iodoethyl)-1*H*-indole 85



Trifluoroacetic acid (9.9 mL) was added dropwise to a solution of indole **93** (0.59 g, 1.59 mmol) in chloroform (2.0 mL). The reaction mixture was stirred for 30 min at RT and then concentrated *in vacuo*. EtOAc (20 mL) was added and washed with sat. $NaHCO_{3(aq)}$ (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: 3:7, ether:petrol) yielded *indole* **85** as a pale yellow crystalline solid (276 mg, 64%); mp 91-92 °C ($CHCl_3$); ν_{max} (neat)/cm^{-1} 3412, 2958, 2922, 2852, 1474, 1454, 1416, 1342, 1280, 1260, 1235, 1222, 1166, 1137, 1089, 1064, 1019; δ_H (400 MHz, $CDCl_3$) 8.10 (1H, br. s, N*H*), 7.48 (1H, app s, Ar*H*), 7.34 (1H, d, *J* 8.5, Ar*H*), 7.21 (1H, app t, *J* 3.0, CH=C*H*N), 7.04 (1H, dd, *J* 8.5, 1.5, Ar*H*), 6.55-6.52 (1H, m, C*H*=CHN), 3.44-3.37 (2H, m, $ArCH_2CH_2I$), 3.31-3.25 (2H, m, $ArCH_2CH_2I$); δ_C (101 MHz, $CDCl_3$) 134.9 (C), 132.5 (C), 128.2 (C), 124.8 (CH), 122.7 (CH), 120.3 (CH), 111.2 (CH), 102.6 (CH), 40.9 (CH_2), 7.2 (CH_2); *m/z* (ESI^+) 272 ($[M + H]^+$, 100%); HRMS (ESI^-) $C_{10}H_9IN^-$ ($[M - H]^-$) requires 269.9785, found 269.9779.

6.3.2 Synthesis of sulfones

Methyl 4-methylphenyl sulfone 10

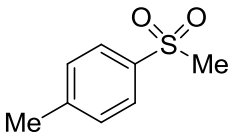


Table 2.2, entry 1: General procedure B (Method I) was followed using 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and iodomethane (179 μL, 2.88 mmol). The reaction mixture was stirred at 100 °C for 1 h. Column chromatography (eluent: 7:3, petrol:ether) yielded sulfone **10** as a white crystalline solid (63 mg, 77%).

Scheme 2.18: General procedure B (Method I) was followed using *N*', *N*', 4-trimethylbenzenesulfonohydrazide **6** (103 mg, 0.48 mmol) and iodomethane (0.18 mL, 2.88 mmol). The reaction mixture was stirred at 100 °C for 16 h. Column chromatography (eluent: 7:3, petrol:ether) yielded sulfone **10** as a white crystalline solid (44 mg, 54%) and 2,2,2-trimethyl-1-[(4-methylphenyl)sulfonyl]diazan-2-ium-1-ide **7** as a white crystalline solid (43 mg, 39%).

4-Methylphenyl propyl sulfone 30

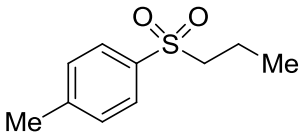


Table 2.2, entry 2: General procedure B (Method I) was followed using 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and 1-iodopropane (94 μL, 0.96 mmol). The reaction mixture was stirred at 100 °C for 16 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **30** as a white crystalline solid (58 mg, 61%); mp 50-52 °C {lit.[290] 53-55 °C}; ν_{max} (neat)/cm^{-1} 2971, 2937, 2880, 1595, 1494, 1466, 1407, 1383, 1347, 1300, 1285, 1252, 1221, 1184, 1140, 1086, 1067, 1020; δ_H (400 MHz, $CDCl_3$)

7.73-7.69 (2H, m, 2 × Ar*H*), 7.31-7.26 (2H, m, 2 × Ar*H*), 3.00-2.95 (2H, m, SC*H*$_2$CH$_2$CH$_3$), 2.38 (3H, s, Ar*Me*), 1.71-1.60 (2H, m, SCH$_2$C*H*$_2$CH$_3$), 0.91 (3H, t, *J* 7.5, SCH$_2$CH$_2$C*H*$_3$); δ_C (101 MHz, $CDCl_3$) 144.6 (C), 136.2 (C), 129.9 (2 × CH), 128.1 (2 × CH), 58.1 (CH_2), 21.6 (CH_2), 16.6 (CH_3), 13.0 (CH_3); *m/z* (ESI$^+$) 419 ([2M + Na]$^+$, 100%), 221 ([M + Na]$^+$, 67%); HRMS (ESI$^+$) $C_{10}H_{14}NaO_2S^+$ ([M + Na]$^+$) requires 221.0607, found 221.0606. ^{1}H NMR spectroscopy data in accordance with literature data.[291]

Hexyl 4-methylbenzenesulfinate 31', hexyl 4-methylphenyl sulfone 31, and *N*-[(1*E*)-hexylidene]morpholin-4-amine 31''

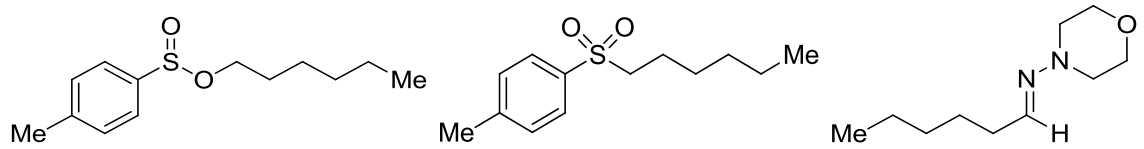


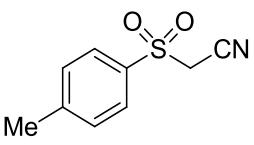
Table 2.2, entry 3: General procedure B (Method I) was followed using 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and 1-iodohexane (142 μL, 0.96 mmol). The reaction mixture was stirred at 100 °C for 16 h. Column chromatography (eluent: 7:3, petrol:ether) yielded, in order of elution, *sulfinate ester* **31'** as a pale yellow oil (9 mg, 8%), *sulfone* **31** as a colourless oil (77 mg, 67%), and *hydrazone* **31''** (49 mg, 55%) as a colourless oil.

Sulfinate ester **31'**: ν_{max} (neat)/cm^{-1} 2955, 2939, 2859, 1597, 1492, 1465, 1379, 1302, 1260, 1178, 1133, 1080, 1038, 1017; δ_H (400 MHz, $CDCl_3$) 7.64-7.57 (2H, m, 2 × Ar*H*), 7.36-7.31 (2H, m, 2 × Ar*H*), 4.02 (1H, dt, *J* 10.0, 6.5, OCH$_a$*H*$_b$), 3.61 (1H, dt, *J* 10.0, 6.5, OC*H*$_a$H$_b$), 2.43 (3H, s, Ar*Me*), 1.66-1.58 (2H, m, OCH$_2$C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.38-1.20 (6H, m, OCH$_2$CH$_2$(C*H*$_2$)$_3$CH$_3$), 0.87 (3H, t, *J* 7.0, O(CH$_2$)$_5$C*H*$_3$); δ_C (101 MHz, $CDCl_3$) 142.7 (C), 142.0 (C), 129.8 (2 × CH), 125.4 (2 × CH), 64.7 (CH_2), 31.4 (CH_2), 29.8 (CH_2), 25.5 (CH_2), 22.6 (CH_2), 21.6 (CH_3), 14.1 (CH_3); HRMS (FI$^+$) $C_{13}H_{20}O_2S^+$ ([M]$^+$) requires 240.1184, found 240.1184.

Sulfone **31**: ν_{max} (neat)/cm^{-1} 2957, 2928, 2855, 1597, 1457, 1285, 1141, 1087; δ_H (400 MHz, $CDCl_3$) 7.79-7.75 (2H, m, 2 × Ar*H*), 7.37-7.32 (2H, m, 2 × Ar*H*), 3.08-3.01 (2H, m, SC*H*$_2$(CH$_2$)$_4$CH$_3$), 2.44 (3H, s, Ar*Me*), 1.76-1.61 (2H, m, SCH$_2$C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.37-1.29 (2H, m, S(CH$_2$)$_2$C*H*$_2$(CH$_2$)$_2$CH$_3$), 1.28-1.19 (4H, m, S(CH$_2$)$_3$(C*H*$_2$)$_2$CH$_3$), 0.84 (3H, t, *J* 7.0, S(CH$_2$)$_5$C*H*$_3$); δ_C (101 MHz, $CDCl_3$) 144.6 (C), 136.3 (C), 129.9 (2 × CH), 128.1 (2 × CH), 56.5 (CH_2), 31.2 (CH_2), 28.0 (CH_2), 22.8 (CH_2), 22.3 (CH_2), 21.7 (CH_3), 14.0 (CH_3); HRMS (FI$^+$) $C_{13}H_{20}O_2S^+$ ([M]$^+$) requires 240.1184, found 240.1181.

Hydrazone **31''**: ν_{max} (neat)/cm^{-1} 2957, 2924, 2855, 1681, 1453, 1377, 1304, 1271, 1117, 1091, 1072; δ_H (400 MHz, $CDCl_3$) 6.97 (1H, app t, *J* 5.5, C*H*=N), 3.82 (4H, t, *J* 5.0, N(CH$_2$C*H*$_2$)$_2$O), 2.94 (4H, t, *J* 5.0, N(C*H*$_2$CH$_2$)$_2$O), 2.24 (2H, td, *J* 7.5, 5.5, C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.54-1.43 (2H, m, C*H*$_2$), 1.36-1.28 (4H, m, 2 × C*H*$_2$), 0.93-0.85 (3H, m, (CH$_2$)$_4$C*H*$_3$); δ_C (101 MHz, $CDCl_3$) 142.6 (CH), 66.6 (2 × CH_2), 52.6 (2 × CH_2), 33.2 (CH_2), 31.5 (CH_2), 27.6 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (FI$^+$) $C_{10}H_{20}N_2O^+$ ([M]$^+$) requires 184.1576, found 183.9764.

[(4-Methylphenyl)sulfonyl]acetonitrile 32 and (2*E*)-(morpholin-4-ylimino)acetonitrile 32'



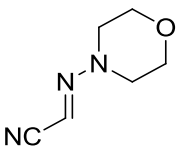


Table 2.2, entry 4: General procedure B (Method I) was followed using 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and bromoacetonitrile (67 μL, 0.96 mmol) and stirred for 16 h at 100 °C. Column chromatography (eluent: 7:3, petrol:ether) yielded, in order of elution, *sulfone* **32** (19 mg, 20%) and *hydrazone* **32'** (12 mg, 18%), both as a white crystalline solids.

Table 2.3, entry 2: General procedure C (Method II) was followed using 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and bromoacetonitrile (50 μL, 0.72 mmol). Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **32** as a white crystalline solid (25 mg, 22%).

Sulfone **32**: mp 153-155 °C (CH_2Cl_2) {lit.[292] 153-154 °C (ethanol)}; δ_H (400 MHz, $CDCl_3$) 7.93-7.89 (2H, m, 2 × Ar*H*), 7.47-7.43 (2H, m, 2 × Ar*H*), 4.04 (2H, s, SCH_2), 2.50 (3H, s, Ar*Me*); δ_C (101 MHz, $CDCl_3$) 147.0 (C), 133.8 (C), 130.6 (2 × CH), 129.0 (2 × CH), 110.6 (C), 46.0 (CH_2), 22.0 (CH_3); *m/z* (ESI^+) 218 ($[M + Na]^+$, 100%). Data in accordance with literature data.[293]

Hydrazone **32'**: mp 69-71 °C {lit.[294] 71-72 °C}; ν_{max} (neat)/cm^{-1} 2985, 2932, 2258, 1595, 1576, 1496, 1475, 1463, 1433, 1417, 1396, 1360, 1327, 1303, 1263, 1209, 1183, 1159, 1111, 1096, 1086, 1071, 1040, 1010; δ_H (400 MHz, $CDCl_3$) 6.22 (1H, s, C*H*=N), 3.86 (4H, t, *J* 5.0, N(CH_2CH_2)$_2$O), 3.30 (4H, t, *J* 5.0, N(CH_2CH_2)$_2$O); δ_C (101 MHz, $CDCl_3$) 134.0 (C), 102.3 (CH), 65.7 (2 × CH_2), 50.1 (2 × CH_2); *m/z* (ESI^+) 162 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_6H_9N_3NaO^+$ ($[M + Na]^+$) requires 162.0638, found 162.0636.

_N_-[(_E_)-Phenylmethylidene]morpholin-4-amine 14, benzyl 4-methylbenzenesulfonate, 13' and benzyl 4-methylphenyl sulfone 13

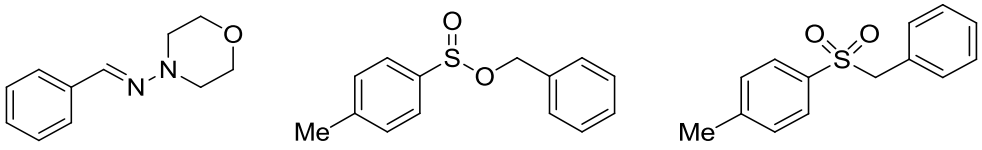


Table 2.2, entry 5: General procedure B (Method I) was followed using 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and benzyl chloride (110 μL, 0.96 mmol). The reaction mixture was stirred at 100 °C for 1 h. Column chromatography (eluent: 7:3, petrol:ether) yielded, in order of elution, hydrazone **14** (59 mg, 65%) and sulfone **13** (82 mg, 69%), both as white crystalline solids.

Table 2.2, entry 6: General procedure B (Method I) was followed using 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and benzyl bromide (114 μL, 0.96 mmol). The reaction mixture was stirred at 100 °C for 1 h. Column chromatography (eluent: 7:3, petrol:ether) yielded, in order of elution, hydrazone **14** (79 mg, 87%), *sulfinate ester* **13'** (2 mg, 2%), and sulfone **13** (109 mg, 92%), all as white crystalline solids.

Scheme 2.18: General procedure B (Method I) was followed using *N*', *N*', 4-trimethylbenzenesulfonohydrazide **6** (103 mg, 0.48 mmol) and benzyl bromide (114 μL, 0.96 mmol). The reaction mixture was stirred at 100 °C for 16 h. Column chromatography (eluent: 7:3, petrol:ether) yielded sulfone **13** as a white crystalline solid (72 mg, 61%).

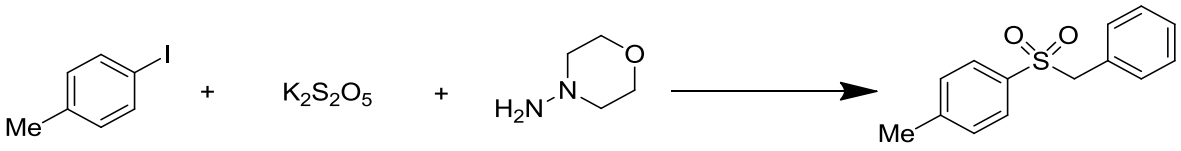
Table 2.6, entry 1: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and 4-iodotoluene (105 mg, 0.48 mmol). The reaction mixture was stirred at 90 °C for 5 h. Column chromatography (eluent: 7:3, petrol:ether) yielded sulfone **13** as a white crystalline solid (108 mg, 91%). The use of 4-bromotoluene (82 mg, 0.48 mmol) yielded sulfone **13** (48 mg, 41%). The use of dimethylhydrazine (44 μL, 0.58 mmol) yielded sulfone **13** (65 mg, 55%).

Hydrazone **14**: mp 85-87 °C (CH_2Cl_2) {lit.[295] 89 °C (ethanol)}; δ_H (400 MHz, $CDCl_3$) 7.66-7.59 (3H, m, ArC*H*=N, 2 × Ar*H*), 7.40-7.34 (2H, m, 2 × Ar*H*), 7.32-7.26 (1H, m, Ar*H*), 3.90 (4H, t, *J* 5.0, $N(CH_2CH_2)_2O$), 3.19 (4H, t, *J* 5.0, $N(CH_2CH_2)_2O$); δ_C (101 MHz, $CDCl_3$) 136.3 (CH), 136.0 (C), 128.6 (2 × CH), 128.4 (CH), 126.3 (2 × CH), 66.5 (2 × CH_2), 51.9 (2 × CH_2); HRMS (FI^+) $C_{11}H_{14}N_2O^+$ ($[M]^+$) requires 190.1106, found 190.1110; Anal. Calcd. (%) for $C_{11}H_{14}N_2O_2$: C 69.45, H 7.42, N 14.73; found C 69.33, H 7.54, N 14.64. Data in accordance with literature data.[296]

Sulfinate ester **13'**: 49-51 °C (CH_2Cl_2) {lit.[145(d)] 51-52 °C}; ν_{max} (neat)/cm^{-1} 3033, 2922, 1596, 1496, 1454, 1397, 1368, 1303, 1261, 1211, 1178, 1130, 1080, 1030, 1018; δ_H (400 MHz, $CDCl_3$) 7.70-7.59 (2H, m, 2 × Ar(Me)*H*), 7.40-7.26 (7H, m, 2 × Ar(Me)*H*, 5 × ArH), 5.04 (1H, d, *J* 11.5, OC$H_a$$H_b$Ar), 4.56 (1H, d, *J* 11.5, OC$H_a$$H_b$Ar), 2.45 (3H, s, Ar*Me*); ^{13}C NMR not obtained due to insufficient material; *m/z* (ESI^+) 515 ([2M + Na]$^+$, 100%), 269 ([M + Na]$^+$, 97%); HRMS (ESI^+) $C_{14}H_{14}NaO_2S^+$ ([M + Na]$^+$) requires 269.0607, found 269.0603. Data in accordance with literature data.[297]

Sulfone **13**: mp 139-141 °C (CH_2Cl_2) {lit.[4] 141-142 °C}; δ_H (400 MHz, $CDCl_3$) 7.54-7.48 (2H, m, 2 × Ar(Me)*H*), 7.37-7.21 (5H, m, 5 × Ar*H*), 7.14-7.06 (2H, m, 2 × Ar(Me)*H*), 4.29 (2H, s, SCH_2), 2.42 (3H, s, Ar*Me*); δ_C (101 MHz, $CDCl_3$) 144.8 (C), 135.1 (C), 131.0 (2 × CH), 129.6 (2 × CH), 128.8 (CH), 128.7(7) (2 × CH), 128.6(7) (2 × CH), 128.4 (C), 63.0 (CH_2), 21.8 (CH_3); *m/z* (ESI^+) 515 ([2M + Na]$^+$, 100%), 269 ([M + Na]$^+$, 95%); Anal. Calcd. (%) for $C_{14}H_{14}O_2S$: C 68.26, H 5.73; found C 68.10, H 5.84. Data in accordance with literature data.[298]

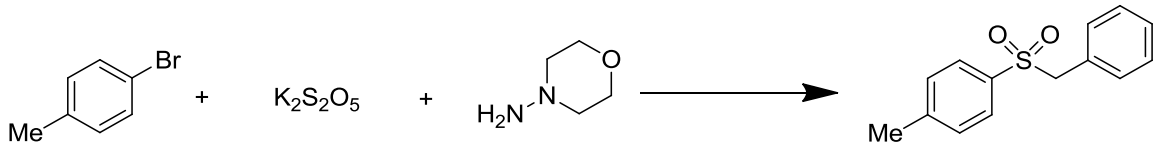
Synthesis of benzyl 4-methylphenyl sulfone 13 using potassium metabisulfite and 4-iodotoluene.



An oven-dried tube was charged with ^{t}Bu$_3$P.HBF$_4$ (15 mg, 10 mol%), Pd(OAc)$_2$ (5 mg, 5 mol%), 4-iodotoluene (109 mg, 0.50 mmol), potassium metabisulfite (111 mg, 0.50 mmol), HBF_4 (14 μL, 0.10 mmol, HBF_4 54 wt.% in ether), and tetrabutylammonium bromide (242 mg, 0.75 mmol). 4-Aminomorpholine (58 μL, 0.60 mmol) and 1,4-dioxane (2.0 mL) were added. The reaction mixture was stirred at 80 °C for 21 h.[7] $K_2CO_{3(aq)}$

(0.52 mL, 2.40 M) and benzyl bromide (149 μL, 1.25 mmol) were added and the reaction mixture stirred at 90 °C for 5 h. After cooling to RT, the suspension was filtered through a short pad of Celite and washed sequentially with CH_2Cl_2 (5 mL) and water (5 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and then concentrated *in vacuo*. Column chromatography (eluent: 7:3, petrol:ether) yielded sulfone **13** as a white crystalline solid (89 mg, 72%).

Synthesis of benzyl 4-methylphenyl sulfone 13 using potassium metabisulfite and 4-bromotoluene.



An oven-dried tube was charged with $^tBu_3P.HBF_4$ (44 mg, 30 mol%), $Pd(OAc)_2$ (11 mg, 10 mol%), 4-bromotoluene (62 μL, 0.50 mmol), potassium metabisulfite (222 mg, 1.00 mmol), and tetrabutylammonium bromide (242 mg, 0.75 mmol). 4-Aminomorpholine (72 μL, 1.00 mmol) and 1,4-dioxane (2.0 mL) were added. The reaction mixture was stirred at 100 °C for 21 h.[31] $K_2CO_{3(aq)}$ (0.52 mL, 2.40 M) and benzyl bromide (149 μL, 1.24 mmol) were added and the reaction mixture stirred at 90 °C for 5 h. After cooling to RT, the suspension was filtered through a short pad of Celite and washed sequentially with CH_2Cl_2 (5 mL) and water (5 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and then concentrated *in vacuo*. Column chromatography (eluent: 7:3, petrol:ether) yielded sulfone **13** as a white crystalline solid (83 mg, 68%).

Benzyl 4-methoxyphenyl sulfone 33

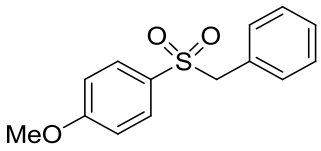
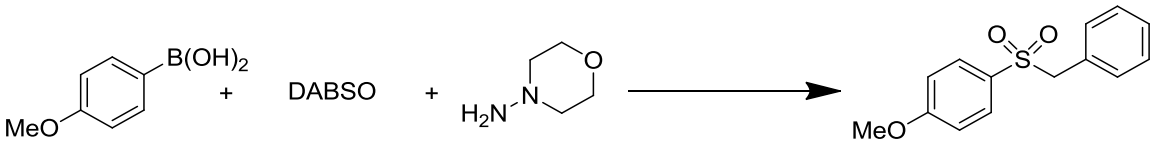


Table 2.2, entry 7: General procedure B (Method I) was followed using 4-methoxy-*N*-(morpholin-4-yl)benzenesulfonamide **204** (131 mg, 0.48 mmol) and benzyl bromide (114 μL, 0.96 mmol). The reaction mixture was stirred at 100 °C for 1 h. Column chromatography (eluent: 7:3, petrol:ether) yielded sulfone **33** as a white crystalline solid (112 mg, 89%).

Table 2.6, entry 2: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and 4-iodoanisole (112 mg, 0.48 mmol). The reaction mixture was stirred at 90 °C for 5 h. Column chromatography (eluent: 7:3, petrol:ether) yielded sulfone **33** as a white crystalline solid (110 mg, 87%). The use of 4-bromoanisole (60 μL, 0.48 mmol) yielded sulfone **33** (58 mg, 46%).

Sulfone **33**: mp 82-83 °C (CH_2Cl_2) {lit.[299] 83 °C}; δ_H (400 MHz, $CDCl_3$) 7.53 (2H, d, *J* 8.0, 2 × Ar(OMe)*H*), 7.36-7.24 (3H, m, 3 × Ar*H*), 7.09 (2H, d, *J* 7.5, 2 × Ar(OMe)*H*), 6.90 (2H, d, *J* 8.0, 2 × Ar*H*), 4.29 (2H, s, SCH_2), 3.86 (3H, s, O*Me*); δ_C (101 MHz, $CDCl_3$) 163.8 (C), 130.9 (4 × CH), 129.6 (C), 128.8 (CH), 128.7 (2 × CH), 128.6 (C), 114.2 (2 × CH), 63.2 (CH_2), 55.8 (CH_3); *m/z* (ESI^+) 285 ($[M + Na]^+$, 100%). Data in accordance with literature data.[300]

Synthesis of benzyl 4-methoxyphenyl sulfone 33 using DABSO and 4-methoxyphenylboronic acid.



An oven-dried tube was charged with 4-methoxyphenylboronic acid (152 mg, 1.00 mmol), $Pd(OAc)_2$ (5 mg, 5 mol%), DABSO (240 mg, 1.00 mmol), and tetrabutylammonium bromide (242 mg, 0.75 mmol). 4-Aminomorpholine (48 μL, 0.50 mmol) and 1,4-dioxane (2.0 mL) were added. The reaction mixture was stirred at 80 °C for 16 h under a balloon of O_2.[60] $K_2CO_{3(aq)}$ (0.52 mL, 2.40 M) and benzyl bromide (149 μL, 1.25 mmol) were added and the reaction mixture stirred at 90 °C for 5 h. After this time, K_2CO_3 (69 mg, 0.50 mmol) and benzyl bromide (59 μL, 0.50 mmol) were added and the reaction mixture stirred at 90 °C for a further 16 h. After cooling to RT, the suspension was filtered through a short pad of Celite and washed sequentially with CH_2Cl_2 (5 mL) and water (5 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and then concentrated *in vacuo*. Column chromatography (eluent: 7:3, petrol:ether) yielded sulfone **33** as a white crystalline solid (113 mg, 86%).

Benzyl 4-ethoxyphenyl sulfone 34

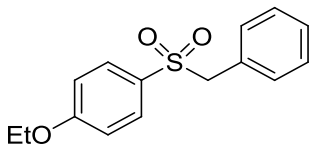


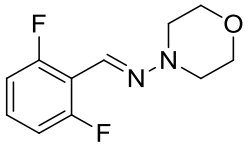
Table 2.2, entry 8: General procedure B (Method I) was followed using 4-ethoxy-*N*-(morpholin-4-yl)benzenesulfonamide **206** (137 mg, 0.48 mmol) and benzyl bromide (114 μL, 0.96 mmol). The reaction mixture was stirred at 100 °C for 1 h. Column

chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **34** as a white crystalline solid (124 mg, 94%).

Table 2.6, entry 3: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and 1-ethoxy-4-iodobenzene **205** (119 mg, 0.48 mmol). The reaction mixture was stirred at 90 °C for 5 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **34** as a white crystalline solid (119 mg, 90%). The use of benzyl chloride (138 μL, 1.20 mmol) yielded *sulfone* **34** (99 mg, 75%). The use of 1-aminopiperidine (62 μL, 0.58 mmol) yielded *sulfone* **34** (117 mg, 88%).

Sulfone **34**: mp 93-96 °C ($(CD_3)_2CO$); ν_{max} (neat)/cm^{-1} 2972, 2930, 2893, 1594, 1577, 1493, 1482, 1454, 1428, 1415, 1389, 1317, 1298, 1270, 1176, 1145, 1132, 1114, 1084, 1033, 1007; δ_H (400 MHz, $(CD_3)_2CO$) 7.62-7.54 (2H, m, 2 × Ar(OEt)*H*), 7.36-7.25 (3H, m, 3 × Ar*H*), 7.21-7.15 (2H, m, 2 × Ar*H*), 7.06-6.99 (2H, m, 2 × Ar(OEt)*H*), 4.45 (2H, s, SCH_2), 4.15 (2H, q, *J* 7.0, OCH_2CH$_3$), 1.40 (3H, t, *J* 7.0, OCH$_2$CH_3); δ_C (101 MHz, $(CD_3)_2CO$) 163.9 (C), 131.8 (2 × CH), 131.5 (2 × CH), 131.1 (C), 130.3 (C), 129.1 (CH), 129.0 (2 × CH), 115.3 (2 × CH), 64.7 (CH_2), 62.8 (CH_2), 14.8 (CH_3); *m/z* (ESI^+) 575 ([2M + Na]$^+$, 100%), 299 ([M + Na]$^+$, 88%); *m/z* (ESI^-) 311 ([M + Cl]$^-$, 100%); HRMS (ESI^+) $C_{15}H_{16}NaO_3S^+$ ([M + Na]$^+$) requires 299.0712, found 299.0707.

(*E*)-1-(2,6-Difluorophenyl)-*N*-(morpholin-4-yl)methanimine 35' and 2,6-difluorobenzyl 4-methoxyphenyl sulfone 35



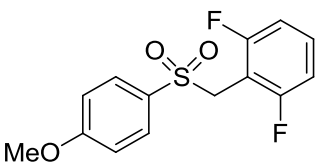
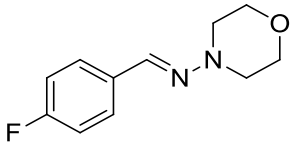


Table 2.2, entry 9: General procedure B (Method I) was followed using 4-methoxy-*N*-(morpholin-4-yl)benzenesulfonamide **204** (131 mg, 0.48 mmol) and 2,6-difluorobenzyl

bromide (199 mg, 0.96 mmol). The reaction mixture was stirred at 100 °C for 1 h. Column chromatography (eluent: 7:3, petrol:ether) yielded, in order of elution, *hydrazone* **35'** (78 mg, 72%) and *sulfone* **35** (122 mg, 85%), both as white crystalline solids. *Hydrazone* **35'**: mp 83-86 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2963, 2919, 2854, 2361, 2341, 1685, 1622, 1594, 1463, 1359, 1262, 1235, 1118, 1099, 1064, 1018; δ_H (400 MHz, $CDCl_3$) 7.62 (1H, s, C*H*=N), 7.19 (1H, app quin, *J* 7.0, Ar*H*), 6.91 (2H, app t, *J* 8.5, 2 × Ar*H*), 3.91 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 3.24 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O); δ_C (101 MHz, $CDCl_3$) 160.8 (2 × C, dd, J_{CF} 253.5, 6.5), 128.9 (2 × CH, t, J_{CF} 10.5), 125.7 (CH), 113.7 (C, t, J_{CF} 13.5), 112.0-111.7 (CH, m), 66.5 (2 × CH_2), 51.4 (2 × CH_2); δ_F (377 MHz, $CDCl_3$) –114.2 (s, Ar*F*) {^{1}H} HRMS (FI^+) $C_{11}H_{12}F_2N_2O^+$ ($[M]^+$) requires 226.0918, found 226.0921. *Sulfone* **35**: mp 88-90 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2920, 2849, 1625, 1591, 1579, 1499, 1471, 1440, 1414, 1318, 1297, 1258, 1239, 1186, 1165, 1139, 1112, 1087, 1020; δ_H (500 MHz, $CDCl_3$) 7.68-7.63 (2H, m, 2 × Ar(OMe)*H*), 7.34-7.27 (1H, m, Ar*H*), 6.96-6.92 (2H, m, 2 × Ar(OMe)*H*), 6.86 (2H, dd, *J* 8.0, 7.5, 2 × Ar*H*), 4.46 (2H, s, CH_2), 3.88 (3H, s, O*Me*); δ_C (126 MHz, $CDCl_3$) 164.1 (C), 161.7 (2 × C, dd, J_{CF} 252.5, 7.5), 131.1 (CH, t, J_{CF} 10.5), 130.9 (2 × CH), 129.9 (C), 114.3 (2 × CH), 111.6 (2 × CH, dd, J_{CF} 20.0, 5.0), 106.1 (C, t, J_{CF} 19.0), 55.8 (CH_3), 51.0 (CH_2, app d, J_{CF} 2.0); δ_F (377 MHz, $CDCl_3$) –112.6 (s, Ar*F*) {^{1}H}; *m/z* (ESI^+) 619 ($[2M + Na]^+$, 100%), 321 ($[M + Na]^+$, 90%); HRMS (ESI^+) $C_{14}H_{12}F_2NaO_3S^+$ ($[M + Na]^+$) requires 321.0367, found 321.0370.

(*E*)-1-(4-Fluorophenyl)-*N*-(morpholin-4-yl)methanimine 36' and 4-fluorobenzyl 4-methoxyphenyl sulfone 36



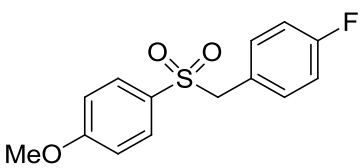


Table 2.2, entry 10: General procedure B (Method I) was followed using 4-methoxy-*N*-(morpholin-4-yl)benzenesulfonamide **204** (131 mg, 0.48 mmol) and 4-fluorobenzyl bromide (120 μL, 0.96 mmol). The reaction mixture was stirred at 100 °C for 1 h. Column chromatography (eluent: 7:3, petrol:ether) yielded, in order of elution, *hydrazone* **36'** (76 mg, 76%) and *sulfone* **36** (120 mg, 89%) both as white crystalline solids. *Hydrazone* **36'**: mp 72-74 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2975, 2954, 2916, 2851, 1601, 1575, 1503, 1451, 1435, 1356, 1269, 1227, 1212, 1151, 1131, 1116, 1101, 1088, 1023; δ_H (400 MHz, $CDCl_3$) 7.62-7.55 (3H, m, C*H*=N, 2 × Ar*H*), 7.09-7.01 (2H, m, 2 × Ar*H*), 3.90 (4H, t, *J* 5.0, $N(CH_2CH_2)_2O$), 3.16 (4H, t, *J* 5.0, $N(CH_2CH_2)_2O$); δ_C (101 MHz, $CDCl_3$) 163.0 (C, d, J_{CF} 247.5), 135.2 (CH), 132.3 (C, d, J_{CF} 3.0), 127.9 (2 × CH, d, J_{CF} 8.0), 115.7 (2 × CH, d, J_{CF} 22.0), 66.6 (2 × CH_2), 52.0 (2 × CH_2); δ_F (337 MHz, $CDCl_3$) -113.1 (s, Ar*F*) {^{1}H}; HRMS (FI^+) $C_{11}H_{13}FN_2O^+$ ($[M]^+$) requires 208.1012, found 208.1007. *Sulfone* **36**: mp 125-128 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2975, 2931, 2893, 1596, 1577, 1494, 1438, 1414, 1312, 1282, 1260, 1222, 1177, 1145, 1087, 1027; δ_H (500 MHz, $CDCl_3$) 7.56-7.51 (2H, m, 2 × Ar(OMe)*H*), 7.10-7.04 (2H, m, 2 × Ar(F)*H*), 7.00-6.94 (2H, m, 2 × Ar(F)*H*), 6.94-6.88 (2H, m, 2 × Ar(OMe)*H*), 4.25 (2H, s, CH_2), 3.87 (3H, s, O*Me*); δ_C (126 MHz, $CDCl_3$) 164.0 (C), 163.1 (C, d, J_{CF} 249.0), 132.7 (2 × CH, d, J_{CF} 8.5), 130.9 (2 × CH), 129.4 (C), 124.6 (C, d, J_{CF} 3.0), 115.8 (2 × CH, d, J_{CF} 22.0), 114.3 (2 × CH), 62.4 (CH_2), 55.8 (CH_3); δ_F (377 MHz, $CDCl_3$) –112.6 (s, Ar*F*) {^{1}H}; *m/z* (ESI^+) 583 ($[2M + Na]^+$, 100%), 303 ($[M + Na]^+$, 83%); HRMS (ESI^+) $C_{14}H_{13}FNaO_3S^+$ ($[M + Na]^+$) requires 303.0462, found 303.0456.

Benzyl 4-(trifluoromethyl)phenyl sulfone 37

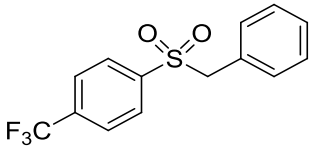


Table 2.2, entry 11: General procedure B (Method I) was followed using *N*-(morpholin-4-yl)-4-(trifluoromethyl)benzenesulfonamide **207** (149 mg, 0.48 mmol) and benzyl bromide (114 μL, 0.96 mmol). The reaction mixture was stirred at 100 °C for 16 h. Column chromatography (eluent: 7:3, petrol:ether) yielded sulfone **37** as a white crystalline solid (101 mg, 70%).

Table 2.6, entry 17: General procedure D (Method I) was followed using DABSO (127 mg, 0.53 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and 4-iodobenzotrifluoride (71 μL, 0.48 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded sulfone **37** as a white crystalline solid (61 mg, 42%); mp 162-164 °C (CH_2Cl_2) {lit.[23] 163-165 °C}; δ_H (500 MHz, $CDCl_3$) 7.77-7.68 (4H, m, 4 × Ar*H*), 7.38-7.33 (1H, m, Ar*H*), 7.31-7.27 (2H, m, 2 × Ar*H*), 7.13-7.06 (2H, m, 2 × Ar*H*), 4.35 (2H, s, SC*H*$_2$); δ_C (126 MHz, $CDCl_3$) 141.4 (C), 135.6 (C, q, J_{CF} 33.0), 130.9 (2 × CH), 129.5 (2 × CH), 129.3 (CH), 128.9 (2 × CH), 127.6 (C), 126.1 (2 × CH, q, J_{CF} 4.0), 123.2 (C, q, J_{CF} 273.0), 63.0 (CH_2); δ_F (377 MHz, $CDCl_3$) –63.2 (s, ArC*F*$_3$) {^{1}H}; *m/z* (ESI$^+$) 623 ([2M + Na]$^+$, 100%), 323 ([M + Na]$^+$, 99%). Data in accordance with literature data.[23]

Bromomethyl 4-methylphenyl sulfone 38

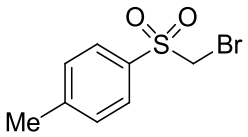
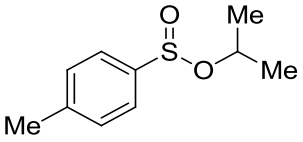


Table 2.3, entry 1: General procedure B (Method I) was followed using 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and dibromomethane (67 μL, 0.96 mmol) and heated for 16 h at 100 °C. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **38** as a white crystalline solid (48 mg, 20%).

Table 2.3, entry 1: General procedure C (Method II) was followed using 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and dibromomethane (50 μL, 0.72 mmol). Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **38** as a white crystalline solid (48 mg, 20%).

Sulfone **38**: mp 87-88 °C (CH_2Cl_2) {lit.[301] 89-91 °C (ethanol)}; ν_{max} (neat)/cm^{-1} 3016, 2947, 2915, 2850, 1595, 1312, 1295, 1261, 1213, 1179, 1145, 1115, 1104, 1085, 1016; δ_H (400 MHz, $CDCl_3$) 7.89-7.84 (2H, m, 2 × Ar*H*), 7.41 (2H, app d, *J* 8.5, 2 × Ar*H*), 4.43 (2H, s, SCH_2), 2.49 (3H, s, Ar*Me*); δ_C (101 MHz, $CDCl_3$) 146.1 (C), 132.9 (C), 130.1 (2 × CH), 129.5 (2 × CH), 44.8 (CH_2), 21.9 (CH_3); *m/z* (ESI^+) 521 ($[2M + Na]^+$, 62%), 519 ($[2M + Na]^+$, 35%), 273 ($[M + Na]^+$, 100%), 271 ($[M + Na]^+$, 95%). ^1H NMR spectroscopy data in accordance with literature data.[302]

Propan-2-yl 4-methylbenzenesulfinate 39' and 4-methylphenyl propan-2-yl sulfone 39



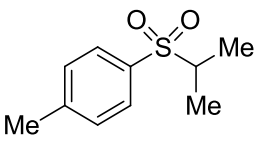


Table 2.3, entry 3: General procedure B (Method I) was followed using 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and 2-iodopropane (96 μL, 0.96 mmol). The reaction mixture was stirred at 100 °C for 16 h. Column chromatography (eluent: 7:3, petrol:ether) yielded, in order of elution, sulfinate ester **39'** as a colourless oil (6 mg, 7%) and sulfone **39** as a white crystalline solid (45 mg, 47%).

General procedure C (Method II) was followed using 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and 2-iodopropane (72 μL, 0.72 mmol). Column chromatography (eluent: 7:3, petrol:ether) yielded, in order of elution, sulfinate ester **39'** as a colourless oil (5 mg, 5%) and sulfone **39** as a white crystalline solid (42 mg, 44%).

Sulfinate ester **39'**: ν_{max} (neat)/cm^{-1} 2950, 2940, 2861, 1594, 1491, 1470, 1377, 1301, 1265, 1179, 1131, 1051; δ_H (400 MHz, $(CD_3)_2SO$) 7.48 (2H, d, *J* 7.0, 2 × Ar*H*), 7.12 (2H, d, *J* 7.0, 2 × Ar*H*), 3.77 (1H, sept, *J* 6.0, C*H*Me$_2$), 2.29 (3H, s, Ar*Me*), 1.03 (6H, d, *J* 6.0, CH*Me*$_2$); δ_C (101 MHz, $(CD_3)_2SO$) 138.6 (C), 131.0 (C), 129.0 (2 × CH), 126.3 (2 × CH), 62.9 (CH), 26.4 (2 × CH_3), 21.7 (CH_3); *m/z* (ESI$^+$) 419 ([2M + Na]$^+$. Data in accordance with literature data.[303]

Sulfone **39**: mp 81-83 °C (CH_2Cl_2) {lit.[304] 81-83 °C}; δ_H (400 MHz, $(CD_3)_2SO$) 7.72 (2H, d, *J* 8.0, 2 × Ar*H*), 7.47 (2H, d, *J* 8.0, 2 × Ar*H*), 3.77 (1H, sept, *J* 7.0, C*H*Me$_2$), 2.42 (3H, s, Ar*Me*), 1.13 (6H, d, *J* 7.0, CH*Me*$_2$); δ_C (101 MHz, $(CD_3)_2SO$) 144.4 (C), 133.9 (C), 129.8 (2 × CH), 128.6 (2 × CH), 54.1 (CH), 21.1 (CH_3), 15.2 (2 × CH_3); *m/z* (ESI$^+$) 419 ([2M + Na]$^+$, 100%), 221 ([M + Na]$^+$, 45%). Data in accordance with literature data.[305]

Ethenyl 4-methylphenyl sulfone 40

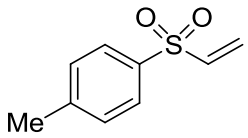


Table 2.3, entry 4: General procedure B (Method I) was followed using 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and 1,2-dibromoethane (83 μL, 0.96 mmol). The reaction mixture was stirred for 1 h at 100 °C, then triethylamine (67 μL, 0.48 mmol) was added and the reaction stirred for a further 15 h. Column chromatography (eluent: 7:3, petrol:ether) yielded sulfone **40** as a white crystalline solid (16 mg, 18%).

General procedure C (Method II) was followed using 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and 1,2-dibromoethane (62 μL, 0.72 mmol). The reaction mixture was stirred for 1 h at 100 °C, then triethylamine (67 μL,

0.48 mmol) was added and the reaction stirred for a further 15 h. Column chromatography (eluent: 7:3, petrol:ether) yielded sulfone **40** as a white crystalline solid (46 mg, 53%).

Sulfone **40**: mp 63-65 °C (CH_2Cl_2) {lit.[306] 65.0-66.0 °C (2-PrOH)}; δ_H (400 MHz, $CDCl_3$) 7.80-7.75 (2H, m, 2 × Ar*H*), 7.37-7.32 (2H, m, 2 × Ar*H*), 6.64 (1H, dd, *J* 16.5, 10.0, C*H*=CH_2), 6.42 (1H, d, *J* 16.5, CH=CH_{trans}H), 6.00 (1H, d, *J* 10.0, CH=CHH_{cis}), 2.44 (3H, s, Ar*Me*); δ_C (101 MHz, $CDCl_3$) 144.8 (C), 138.9 (CH), 136.7 (C), 130.1 (2 × CH), 128.0 (2 × CH), 127.3 (CH_2), 21.8 (CH_3); *m/z* (ESI^+) 205 ($[M + Na]^+$, 100%), 183 ($[M + H]^+$, 10%). Data in accordance with literature data.[307,306]

Ethyl 2-methyl-2-[(4-methylphenyl)sulfonyl]propanoate 41

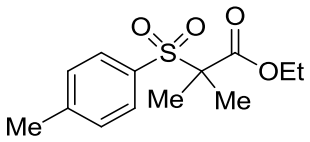


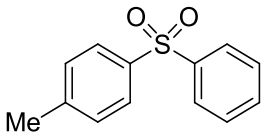
Table 2.3, entry 5: General procedure B (Method I) was followed using 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and methyl 2-bromo-2-methylpropionate (141 μL, 0.96 mmol). The reaction mixture was stirred at 100 °C for 16 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **41** as a white crystalline solid (66 mg, 51%).

General procedure C (Method II) was followed using 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and methyl 2-bromo-2-methylpropionate (106 μL, 0.72 mmol). Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **41** as a white crystalline solid (75 mg, 58%).

Sulfone **41**: mp 73-75 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2988, 2940, 1733, 1688, 1593, 1544, 1493, 1467, 1443, 1402, 1386, 1364, 1312, 1302, 1272, 1186, 1157, 1127, 1113, 1077, 1021; δ_H (400 MHz, $CDCl_3$) 7.73 (2H, d, *J* 8.0, 2 × Ar*H*), 7.34 (2H, d, *J* 8.0, 2 × Ar*H*), 4.14 (2H, q, *J* 7.0, OCH_2CH_3), 2.45 (3H, s, Ar*Me*), 1.61 (6H, s, 2 × SC*Me*), 1.22

(3H, t, *J* 7.0, OCH_2CH_3); δ_C (101 MHz, $CDCl_3$) 169.0 (C), 145.3 (C), 132.8 (C), 130.5 (2 × CH), 129.4 (2 × CH), 69.1 (C), 62.4 (CH_2), 21.8 (CH_3), 20.4 (2 × CH_3), 13.9 (CH_3); *m/z* (ESI^+) 564 ($[2M + Na]^+$, 100%), 293 ($[M + Na]^+$, 75%), 270 ($[M + H]^+$, 65%); HRMS (ESI^+) $C_{13}H_{18}NaO_4S^+$ ($[M + Na]^+$) requires 293.0818, found 293.0810.

1-Methyl-4-(phenylsulfonyl)benzene 42 and 4-methyl-*N*-(morpholin-4-yl)-*N*-phenylbenzenesulfonamide 44



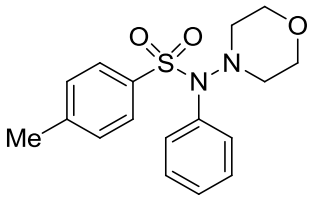


Table 2.3, entry 6: General procedure B (Method I) was followed using 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and diphenyliodonium triflate **208** (413 mg, 0.96 mmol). The reaction mixture was stirred at 100 °C for 16 h. Column chromatography (eluent: 7:3, petrol:ether) yielded, in order of elution, sulfone **42** (22 mg, 20%) and *sulfone* **44** (34 mg, 21%), both as a white crystalline solids.

General procedure C (Method II) was followed using 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and diphenyliodonium triflate **208** (320 mg, 0.72 mmol). Column chromatography (eluent: 7:3, petrol:ether) yielded sulfone **42** as a white crystalline solid (66 mg, 59%).

Sulfone **42**: mp 124-125 °C (CH_2Cl_2) {lit.[128] 125-127 °C}; δ_H (400 MHz, $CDCl_3$) 7.95-7.91 (2H, m, 2 × Ar*H*), 7.85-7.81 (2H, m, 2 × Ar*H*), 7.57-7.52 (1H, m, Ar*H*), 7.51-7.46 (2H, m, 2 × Ar*H*), 7.29 (2H, d, *J* 8.0, 2 × Ar*H*), 2.39 (3H, s, Ar*Me*); δ_C (126 MHz, $CDCl_3$) 144.1 (C), 142.0 (C), 138.6 (C), 133.0 (CH), 129.9 (2 × CH), 129.2 (2 × CH), 127.7 (2 × CH), 127.5 (2 × CH), 21.5 (CH_3); *m/z* (ESI^+) 255 ($[M + Na]^+$, 100%); HRMS

(FI$^+$) $C_{13}H_{12}O_2S^+$ ([M]$^+$) requires 232.0558, found 232.0555. Data in accordance with literature data.[17]

Sulfone **44**: mp 173-174 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2960, 2921, 2867, 2800, 1595, 1492, 1452, 1386, 1337, 1300, 1276, 1258, 1230, 1206, 1166, 1111, 1092; δ_H (500 MHz, $CDCl_3$) 8.03 (1H, br. s, NAr*H*), 7.70 (2H, d, *J* 8.0, 2 × Ar(Me)*H*), 7.59 (1H, dd, *J* 8.0, 1.5, NAr*H*), 7.21 (2H, d, *J* 8.0, 2 × Ar(Me)*H*), 7.17-7.03 (3H, m, 3 × NAr*H*), 3.77 (4H, br. t, *J* 4.5, N(CH_2CH_2)$_2$O), 2.56 (4H, br. s, N(CH_2CH_2)$_2$O), 2.36 (3H, s, Ar*Me*); δ_C (126 MHz, $CDCl_3$) 144.1 (C), 136.9 (C), 133.3 (C), 129.8 (2 × CH), 127.1 (2 × CH), 126.7 (CH), 124.8 (2 × CH), 122.1 (2 × CH), 67.4 (2 × CH_2), 53.1 (2 × CH_2), 21.7 (CH_3); *m/z* (ESI$^+$) 355 ([M + Na]$^+$, 30%), 333 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{20}N_2NaO_3S^+$ ([M + Na]$^+$) requires 355.1087, found 355.1093.

2-[(4-Methylphenyl)sulfonyl]-5-(trifluoromethyl)benzaldehyde 43

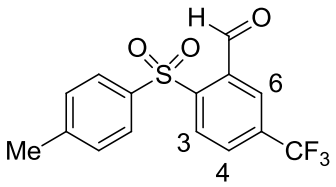


Table 2.3, entry 7: General procedure C (Method II) was followed using 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and 2-fluoro-5-(trifluoromethyl)benzaldehyde (101 μL, 0.72 mmol). Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **43** as a white crystalline solid (63 mg, 40%); mp 64-66 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2930, 1692, 1598, 1494, 1323, 1297, 1251, 1157, 1125, 1078, 1046, 1020; δ_H (500 MHz, $CDCl_3$) 10.90 (1H, s, C*H*O), 8.30-8.26 (2H, m, Ar(6)*H*, Ar(3)*H*), 7.99 (1H, dd, *J* 8.5, 2.0, Ar(4)*H*), 7.82-7.78 (2H, m, 2 × Ar(Me)*H*), 7.37 (2H, d, *J* 8.0, 2 × Ar(Me)*H*), 2.45 (3H, s, Ar*Me*); δ_C (126 MHz, $CDCl_3$) 188.1 (CH), 146.1 (C), 145.9 (C), 137.6 (C), 135.7 (C, q, J_{CF} 35.0), 134.6 (C), 130.7 (2 × CH), 130.4 (CH, q,

J_{CF} 3.5), 130.2 (CH), 127.9 (2 × CH), 126.8 (CH, q, J_{CF} 3.5), 122.8 (C, q, J_{CF} 273.5), 21.8 (CH_3); δ_F (377 MHz, $CDCl_3$) –63.4 (s, C*F*$_3$) {^{1}H}; HRMS (FI$^+$) $C_{15}H_{11}F_3O_3S^+$ ([M]$^+$) requires 328.0381, found 328.0388.

Benzyl 3-ethoxyphenyl sulfone 49

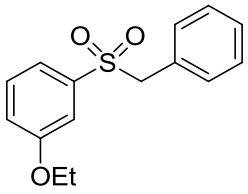


Table 2.6, entry 4: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and 1-ethoxy-3-iodobenzene **209** (119 mg, 0.48 mmol). The reaction mixture was stirred at 90 °C for 5 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **49** as a white crystalline solid (115 mg, 87%); mp 103-105 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2987, 2922, 2878, 1594, 1580, 1492, 1480, 1467, 1456, 1437, 1390, 1307, 1286, 1239, 1200, 1181, 1164, 1151, 1126, 1096, 1072, 1048; δ_H (500 MHz, $CDCl_3$) 7.37-7.30 (2H, m, 2 × Ar*H*), 7.30-7.22 (3H, m, 3 × Ar*H*), 7.13-7.09 (3H, m, 3 × Ar*H*), 7.05 (1H, app t, *J* 2.0, Ar*H*), 4.30 (2H, s, SC*H*$_2$), 3.92 (2H, q, *J* 7.0, OC*H*$_2$CH$_3$), 1.38 (3H, t, *J* 7.0, OCH$_2$C*H*$_3$); δ_C (126 MHz, $CDCl_3$) 159.2 (C), 139.0 (C), 131.0 (2 × CH), 130.1 (CH), 128.9 (CH), 128.7 (2 × CH), 128.4 (C), 121.2 (CH), 120.8 (CH), 113.4 (CH), 64.1 (CH_2), 63.0 (CH_2), 14.7 (CH_3); *m/z* (ESI$^+$) 299 ([M + Na]$^+$, 100%); *m/z* (ESI$^-$) 311 ([M + Cl]$^-$, 100%); HRMS (ESI$^+$) $C_{15}H_{16}NaO_3S^+$ ([M + Na]$^+$) requires 299.0712, found 299.0717.

Benzyl 2-ethoxyphenyl sulfone 50

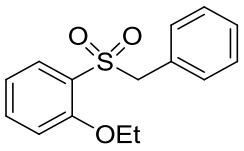


Table 2.6, entry 5: General procedure D (Method I) was followed using DABSO (127 mg, 0.53 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and 1-ethoxy-2-iodobenzene **210** (119 mg, 0.48 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **50** as a white crystalline solid (99 mg, 75%); mp 78-80 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3064, 3030, 2987, 2934, 2885, 1592, 1577, 1483, 1469, 1445, 1401, 1391, 1308, 1281, 1245, 1198, 1153, 1138, 1118, 1061, 1037; δ_H (400 MHz, $CDCl_3$) 7.68 (1H, dd, *J* 8.0, 1.5, Ar(OEt)*H*), 7.53 (1H, app t, *J* 8.0, Ar(OEt)*H*), 7.29-7.19 (5H, m, 5 × Ar*H*), 7.04 (1H, d, *J* 8.0, Ar(OEt)*H*), 6.95 (1H, app t, *J* 8.0, Ar(OEt)*H*), 4.63 (2H, s, SCH_2), 4.29 (2H, q, *J* 7.0, OCH_2CH_3), 1.61 (3H, t, *J* 7.0, OCH_2CH_3); δ_C (101 MHz, $CDCl_3$) 156.9 (C), 135.6 (CH), 131.1 (CH), 130.8 (2 × CH), 128.7 (CH), 128.6 (2 × CH), 128.4 (C), 126.4 (C), 120.7 (CH), 113.1 (CH), 65.3 (CH_2), 60.6 (CH_2), 14.9 (CH_3); *m/z* (ESI^+) 299 ([M + Na]$^+$, 100%); HRMS (ESI^+) $C_{15}H_{16}NaO_3S^+$ ([M + Na]$^+$) requires 299.0712, found 299.0709.

Benzyl 2,4-dimethylphenyl sulfone 51

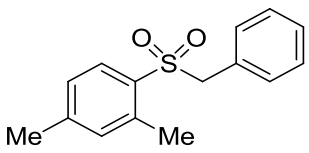


Table 2.6, entry 6: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and 4-iodo-*m*-xylene (68 μL, 0.48 mmol). The

reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **51** as a white crystalline solid (110 mg, 88%); mp 81-84 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2979, 2937, 2924, 2879, 1592, 1574, 1496, 1476, 1465, 1415, 1402, 1384, 1347, 1311, 1290, 1261, 1214, 1180, 1138, 1115, 1088, 1038; δ_H (400 MHz, $CDCl_3$) 7.60 (1H, d, *J* 8.0, Ar*H*), 7.41-7.24 (3H, m, 3 × Ar*H*), 7.13-7.08 (3H, m, 3 × Ar*H*), 7.05 (1H, d, *J* 8.0, ArH), 4.33 (2H, s, SCH_2), 2.48 (3H, s, Ar*Me*), 2.38 (3H, s, Ar*Me*); δ_C (101 MHz, $CDCl_3$) 144.6 (C), 138.6 (C), 133.2 (CH), 131.1 (CH), 130.9 (2 × CH), 128.8 (CH), 128.6 (2 × CH), 128.2 (C), 127.2 (CH), 127.1 (C), 62.4 (CH_2), 21.5 (CH_3), 20.3 (CH_3); *m/z* (ESI^+) 283 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{15}H_{16}NaO_2S^+$ ($[M + Na]^+$) requires 283.0763, found 283.0751.

4-(Benzylsulfonyl)biphenyl 52

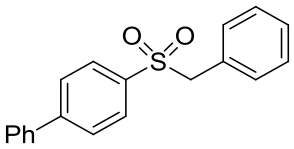


Table 2.6, entry 7: General procedure D (Method I) was followed using DABSO (127 mg, 0.53 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and 4-iodobiphenyl (134 mg, 0.48 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **52** as a white crystalline solid (115 mg, 78%); mp 204-207 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2947, 1562, 1491, 1479, 1454, 1403, 1325, 1305, 1284, 1201, 1183, 1147, 1119, 1090, 1038, 1025, 1005; δ_H (500 MHz, $CDCl_3$) 7.71-7.65 (4H, m, 4 × Ar*H*), 7.63-7.59 (2H, m, 2 × Ar*H*), 7.51-7.47 (2H, m, 2 × Ar*H*), 7.46-7.42 (1H, m, Ar*H*), 7.36-7.32 (2H, m, 2 × Ar*H*), 7.31-7.27 (1H, m, Ar*H*), 7.16-7.12 (2H, m, 2 × Ar*H*), 4.36 (2H, s, SCH_2); δ_C (126 MHz, $CDCl_3$) 146.7 (C), 139.2 (C), 136.6 (C), 131.0 (2 × CH), 129.3 (2 × CH), 129.2 (2 × CH), 128.9 (CH), 128.8 (CH), 128.7 (2 × CH), 128.3 (C), 127.6 (2 × CH), 127.5 (2 × CH), 63.1

(CH_2); *m/z* (ESI^+) 331 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{16}NaO_2S^+$ ($[M + Na]^+$) 331.0763, found 331.0761.

Benzyl phenyl sulfone 53

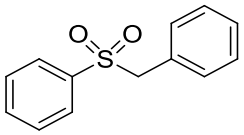


Table 2.6, entry 8: General procedure D (Method I) was followed using DABSO (127 mg, 0.53 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and iodobenzene (54 μL, 0.48 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded sulfone **53** as a white crystalline solid (72 mg, 65%); mp 147-148 °C (CH_2Cl_2) {lit.[308] 147-148 °C (ethanol)}; δ_H (400 MHz, $CDCl_3$) 7.68-7.56 (3H, m, 3 × Ar*H*), 7.50-7.42 (2H, m, 2 × Ar*H*), 7.36-7.23 (3H, m, 3 × Bn*H*), 7.08 (2H, d, *J* 7.5, 2 × Bn*H*), 4.32 (2H, s, SCH_2); δ_C (101 MHz, $CDCl_3$) 137.9 (C), 133.8 (CH), 130.9 (2 × CH), 129.0 (2 × CH), 128.8 (CH), 128.7(3) (2 × CH), 128.7 (2 × CH), 128.2 (C), 63.0 (CH_2); *m/z* (ESI^+) 255 ($[M + Na]^+$, 100%). Data in accordance with literature data.[309]

Benzyl 2-naphthyl sulfone 54

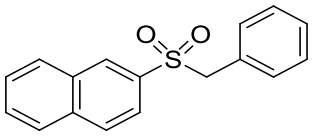


Table 2.6, entry 9: General procedure D (Method I) was followed using DABSO (127 mg, 0.53 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and 2-iodonaphthalene (70 μL, 0.48 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded sulfone **54** as a white crystalline solid (98 mg, 72%); mp 190-191 °C (CH_2Cl_2) {lit.[310] 192-193 °C}; ν_{max}

(neat)/cm^{-1} 3062, 2968, 2922, 1593, 1508, 1495, 1458, 1401, 1346, 1314, 1256, 1201, 1186, 1158, 1118, 1075, 1030; δ_H (500 MHz, $CDCl_3$) 8.78 (1H, d, *J* 8.5, Ar*H*), 8.09 (1H, d, *J* 8.5, Ar*H*), 8.00-7.95 (2H, m, 2 × Ar*H*), 7.70 (1H, ddd, *J* 8.5, 7.0, 1.5, Ar*H*), 7.64 (1H, ddd, *J* 8.0, 7.0, 1.0, Ar*H*), 7.44 (1H, app t, *J* 8.0, Ar*H*), 7.27-7.23 (1H, m, Ar*H*), 7.18-7.14 (2H, m, 2 × Ar*H*), 6.97-6.93 (2H, m, 2 × Ar*H*), 4.52 (2H, s, SCH_2); δ_C (126 MHz, $CDCl_3$) 135.3 (CH), 134.1 (C), 133.1 (C), 131.6 (CH), 130.8 (2 × CH), 129.4 (CH), 129.3 (C), 128.8(2) (CH), 128.7(9) (CH), 128.6 (2 × CH), 128.1 (C), 127.0 (CH), 124.3 (CH), 124.2 (CH), 62.5 (CH_2); *m/z* (ESI^+) 305 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{17}H_{14}NaO_2S^+$ ($[M + Na]^+$) requires 305.0607, found 305.0608. ^{1}H NMR spectroscopy data in accordance with literature data.[311]

Benzyl 4-*tert*-butylphenyl sulfone 55

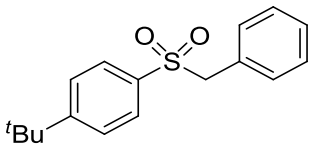


Table 2.6, entry 10: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and 4-*tert*-butyliodobenzene (85 μL, 0.48 mmol). The reaction mixture was stirred at 90 °C for 10 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **55** as a white crystalline solid (120 mg, 87%); mp 98-101 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3062, 3032, 2964, 2924, 2871, 1594, 1493, 1473, 1456, 1400, 1363, 1317, 1304, 1288, 1266, 1204, 1164, 1154, 1132, 1106, 1085, 1028, 1015; δ_H (400 MHz, $CDCl_3$) 7.60-7.54 (2H, m, 2 × Ar(^{t}Bu)*H*), 7.49-7.43 (2H, m, 2 × Ar(^{t}Bu)*H*), 7.36-7.23 (3H, m, 3 × Bn*H*), 7.11 (2H, d, *J* 8.0, 2 × Bn*H*), 4.30 (2H, s, SCH_2), 1.33 (9H, s, Ar^t*Bu*); δ_C (101 MHz, $CDCl_3$) 157.8 (C), 135.1 (C), 131.0 (2 × CH), 128.8 (CH), 128.6 (2 × CH), 128.6 (2 × CH), 128.3 (C), 126.0 (2 × CH), 63.0 (CH_2), 35.3 (C), 31.1 (3 × CH_3);

m/z (ESI$^+$) 311 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{20}NaO_2S^+$ ([M + Na]$^+$) requires 311.1076, found 311.1074.

Benzyl 4-(methylsulfanyl)phenyl sulfone 56

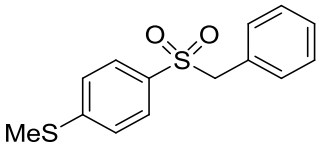


Table 2.6, entry 11: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and 4-iodothioanisole (120 mg, 0.48 mmol). The reaction mixture was stirred at 90 °C for 5 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **56** as a white crystalline solid (119 mg, 89%); mp 150-153 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3060, 3030, 2998, 2947, 2921, 1579, 1477, 1455, 1428, 1404, 1394, 1310, 1295, 1284, 1274, 1190, 1150, 1094, 1074, 1026, 1012; δ_H (500 MHz, $CDCl_3$) 7.50-7.46 (2H, m, 2 × Ar(SMe)*H*), 7.35-7.31 (1H, m, Bn*H*), 7.30-7.26 (2H, m, 2 × Bn*H*), 7.23-7.20 (2H, m, 2 × Ar(SMe)*H*), 7.12-7.09 (2H, m, 2 × Bn*H*), 4.30 (2H, s, SCH_2), 2.51 (3H, s, S*Me*); δ_C (126 MHz, $CDCl_3$) 147.4 (C), 133.6 (C), 131.0 (2 × CH), 129.0 (2 × CH), 128.9 (CH), 128.7 (2 × CH), 128.4 (C), 125.0 (2 × CH), 63.1 (CH_2), 14.8 (CH_3); HRMS (FI$^+$) $C_{14}H_{14}O_2S_2^+$ ([M]$^+$) requires 278.0435, found 278.0448.

4-(Benzylsulfonyl)aniline 57

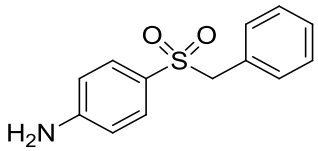


Table 2.6, entry 12: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol),

benzyl bromide (142 μL, 1.20 mmol) and 4-iodoaniline (105 mg, 0.48 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded sulfone **57** as a white crystalline solid (68 mg, 57%); mp 218-220 °C (CH_2Cl_2) {lit.[312] 218 °C (butan-2-one, ethanol, 1:1)}; ν_{max} (neat)/cm^{-1} 3471, 3377, 3033, 2971, 2918, 1638, 1591, 1504, 1456, 1436, 1401, 1327, 1303, 1280, 1253, 1200, 1184, 1163, 1144, 1121, 1081, 1031, 1002; δ_H (400 MHz, $(CD_3)_2SO$) 7.29-7.21 (5H, m, 2 × Ar(NH_2)*H*, 3 × Bn*H*), 7.12-7.08 (2H, m, 2 × Bn*H*), 6.55-6.52 (2H, m, 2 × Ar(NH_2)*H*), 6.08 (2H, s, NH_2), 4.41 (2H, s, SCH_2); δ_C (126 MHz, $(CD_3)_2SO$) 153.6 (C), 130.9 (2 × CH), 129.9 (2 × CH), 129.6 (C), 128.1 (2 × CH), 128.0 (CH), 123.0 (C), 112.4 (2 × CH), 61.5 (CH_2); *m/z* (ESI^+) 517 ($[2M + Na]^+$, 25%), 270 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{13}H_{13}NNaO_2S^+$ ($[M + Na]^+$) requires 270.0559, found 270.0568. ^{1}H NMR spectroscopy data in accordance with literature data.[24]

4-(Benzylsulfonyl)-*N*,*N*-dimethylaniline 58

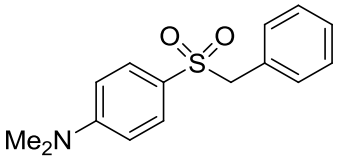
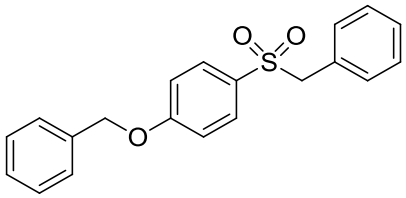


Table 2.6, entry 13: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and 4-iodo-*N*,*N*-dimethylaniline **211** (119 mg, 0.48 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **58** as a white crystalline solid (97 mg, 74%); mp 147-149 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2926, 1592, 1550, 1561, 1493, 1455, 1442, 1403, 1374, 1331, 1300, 1285, 1229, 1201, 1159, 1135, 1086, 1062, 1029; δ_H (500 MHz, $CDCl_3$) 7.43-7.38 (2H, m, 2 × Ar(NMe_2)), 7.33-7.25 (3H, m, 3 × Bn*H*), 7.13-7.10 (2H, m, 2 × Ar*H*), 6.60-6.56 (2H, m, 2 × Ar(NMe_2)), 4.26 (2H, s, SCH_2), 3.04 (6H, s, NMe_2); δ_C (126

MHz, $CDCl_3$) 153.5 (C), 131.0 (2 × CH), 130.4 (2 × CH), 129.2 (C), 128.5 (2 × CH, C), 123.2 (CH), 110.7 (2 × CH), 63.4 (CH_2), 40.2 (2 × CH_3); *m/z* (ESI^+) 298 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{15}H_{17}NNaO_2S^+$ ($[M + Na]^+$) requires 298.0872, found 298.0864.

Benzyl 4-(benzyloxy)phenyl sulfone 70 and 4-(benzylsulfonyl)phenol 59



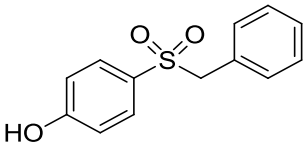


Table 2.6, entry 14: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), benzyl bromide (143 μL, 1.20 mmol) and 4-iodophenol (119 mg, 0.48 mmol). Column chromatography (eluent: 7:3, petrol:ether) yielded, in order of elution, *sulfone* **70** (46 mg, 27%) and *sulfone* **59** (9 mg, 8%), both as white crystalline solids.

Sulfone **70**: mp 134-137 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3063, 3032, 2949, 2908, 1594, 1578, 1491, 1467, 1455, 1407, 1380, 1326, 1310, 1294, 1284, 1247, 1179, 1146, 1109, 1089, 1025, 1000; δ_H (400 MHz, $CDCl_3$) 7.56-7.51 (2H, m, 2 × Ar*H*), 7.44-7.35 (5H, m, 5 × Ar*H*), 7.34-7.24 (3H, m, 3 × Ar*H*), 7.12-7.06 (2H, m, 2 × Ar*H*), 7.00-6.95 (2H, m, 2 × Ar*H*), 5.12 (2H, s, OCH_2), 4.29 (2H, s, SCH_2); δ_C (126 MHz, $CDCl_3$) 162.8 (C), 135.6 (C), 131.5 (C), 130.8 (3 × CH), 129.6 (C), 128.7 (2 × CH), 128.6 (CH), 128.5 (2 × CH), 128.4(3) (CH), 128.3(9) (CH), 127.5 (2 × CH), 114.9 (2 × CH), 70.3 (CH_2), 63.1 (CH_2); *m/z* (ESI^+) 699 ($[2M + Na]^+$, 100%), 361 ($[M + Na]$, 70%); HRMS (ESI^+) $C_{20}H_{18}NaO_3S^+$ ($[M + Na]^+$) requires 361.0869, found 361.0861.

Sulfone **59**: mp 204-207 °C (CH_2Cl_2) {lit.[313] 208 °C}; ν_{max} (neat)/cm^{-1} 3382, 2917, 2849, 1587, 1493, 1467, 1376, 1260, 1231, 1127, 1083; δ_H (200 MHz, $CDCl_3$) 7.50 (2H, d, *J* 9.0, 2 × Ar(OH)*H*), 7.35-7.25 (3H, m, 3 × Bn*H*), 7.14-7.04 (2H, m, 2 × Bn*H*), 6.85 (2H,

d, *J* 9.0, 2 × Ar(OH)*H*), 5.57 (1H, br. s, O*H*), 4.29 (2H, s, SCH_2); ^{13}C NMR not obtained due to insufficient material; *m/z* (ESI$^+$) 519 ([2M + Na]$^+$, 100%), 271 ([M + Na]$^+$, 93%); *m/z* (ESI$^-$) 495 ([2M – H]$^-$, 100%), 283 ([M + Cl]$^-$, 60%), 247 ([M – H]$^-$, 68%); HRMS (ESI$^+$) $C_{13}H_{12}NaO_3S^+$ ([M + Na]$^+$) requires 271.0399, found 271.0399.

Benzyl 4-chlorophenyl sulfone 60

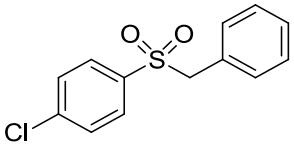


Table 2.6, entry 16: General procedure D (Method I) was followed using DABSO (127 mg, 0.53 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and 1-chloro-4-iodobenzene (114 mg, 0.48 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded sulfone **60** as a white crystalline solid (86 mg, 67%); mp 139-142 °C (CH_2Cl_2) {lit.[314] 142.5-143.0 °C (methanol)}; δ_H (400 MHz, $CDCl_3$) 7.54 (2H, d, *J* 8.5, 2 × Ar(Cl)*H*), 7.41 (2H, d, *J* 8.5, 2 × Ar(Cl)*H*), 7.37-7.25 (3H, m, 3 × Bn*H*), 7.09 (2H, d, *J* 7.5, 2 × Bn*H*), 4.32 (2H, s, SCH_2); δ_C (101 MHz, $CDCl_3$) 140.6 (C), 136.3 (C), 130.9 (2 × CH), 130.2 (2 × CH), 129.3 (2 × CH), 129.1 (CH), 128.8 (2 × CH), 128.0 (C), 63.0 (CH_2); *m/z* (ESI$^+$) 291 ([M + Na]$^+$, 40%), 289 ([M + Na]$^+$, 100%). Data in accordance with literature data.[315]

Methyl 4-(benzylsulfonyl)benzoate 61

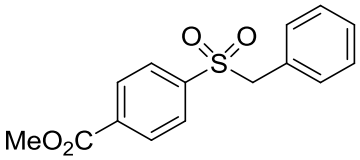


Table 2.6, entry 18: General procedure D (Method I) was followed using DABSO (127 mg, 0.53 mmol), benzyl bromide (143 μL, 1.20 mmol) and methyl 4-iodobenzoate

(131 mg, 0.48 mmol). Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **61** as a white crystalline solid (16 mg, 11%); mp 95-100 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2958, 1715, 1592, 1430, 1398, 1280, 1178, 1107, 1014; δ_H (500 MHz, $CDCl_3$) 8.10 (2H, d, *J* 8.5, 2 × Ar(CO_2Me)*H*), 7.69 (2H, d, *J* 8.5, 2 × Ar(CO_2Me)*H*), 7.37-7.31 (1H, m, Bn*H*), 7.30-7.24 (2H, m, 2 × Bn*H*), 7.08 (2H, d, *J* 7.5, 2 × Bn*H*), 4.35 (2H, s, SCH_2), 3.97 (3H, s, ArCO_2*Me*); δ_C (126 MHz, $CDCl_3$) 165.7 (C), 141.7 (C), 134.9 (C), 130.9 (2 × CH), 130.1 (2 × CH), 129.1 (CH), 128.9(4) (2 × CH), 128.8(8) (2 × CH), 127.8 (C), 63.0 (CH_2), 52.9 (CH_3); *m/z* (ESI^+) 313 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{15}H_{14}NaO_4S^+$ ($[M + Na]^+$) requires 313.0502, found 313.0505.

5-(Benzylsulfonyl)-2-methoxypyridine 62

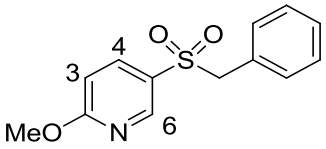


Table 2.6, entry 19: General procedure D (Method I) was followed using DABSO (127 mg, 0.53 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and 5-iodo-2-methoxypyridine **213** (113 mg, 0.48 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **62** as a white crystalline solid (88 mg, 70%); mp 114-116 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2977, 2950, 2930, 1589, 1559, 1484, 1454, 1431, 1408, 1375, 1310, 1286, 1272, 1257, 1200, 1163, 1126, 1098, 1071, 1029, 1006; δ_H (500 MHz, $CDCl_3$) 8.39 (1H, dd, *J* 2.5, 0.5, Ar(6)*H*), 7.60 (1H, dd, *J* 9.0, 2.5, Ar(4)*H*), 7.37-7.33 (1H, m, Bn*H*), 7.32-7.28 (2H, m, 2 × Bn*H*), 7.14-7.12 (2H, m, 2 × Bn*H*), 6.71 (1H, dd, *J* 9.0, 0.5, Ar(3)*H*), 4.33 (2H, s, SCH_2), 3.99 (3H, s, O*Me*); δ_C (126 MHz, $CDCl_3$) 167.2 (C), 149.3 (CH), 138.7 (CH), 131.0 (2 × CH), 129.1 (CH), 128.9 (2 × CH), 128.1 (C), 127.2 (C),

111.2 (CH), 63.5 (CH_2), 54.5 (CH_3); *m/z* (ESI^+) 286 ($[M + Na]^+$, 100%), 264 ($[M + H]^+$, 60%); HRMS (ESI^+) $C_{13}H_{13}NNaO_3S^+$ ($[M + Na]^+$) requires 286.0508, found 286.0509.

5-(Benzylsulfonyl)-1*H*-indole 63

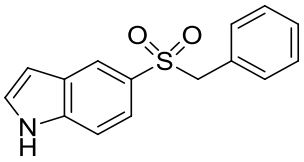


Table 2.6, entry 20: General procedure D (Method I) was followed using DABSO (127 mg, 0.53 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and 5-iodoindole (117 mg, 0.48 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **63** as a white crystalline solid (47 mg, 36%); mp 229-231 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3366, 3142, 3082, 3031, 2916, 1606, 1503, 1467, 1455, 1424, 1407, 1348, 1327, 1291, 1254, 1204, 1162, 1150, 1133, 1112, 1095, 1060, 1030; δ_H (500 MHz, $(CD_3)_2CO$) 10.80 (1H, br. s, N*H*), 8.00-7.99 (1H, m, Ar*H*), 7.59-7.55 (2H, m, 2 × Ar*H*), 7.44 (1H, dd, *J* 8.5, 2.0, Ar*H*), 7.33-7.23 (3H, m, 3 × Bn*H*), 7.18-7.15 (2H, m, 2 × Bn*H*), 6.66-6.64 (1H, m, Ar*H*), 4.47 (2H, s, SCH_2); δ_C (126 MHz, $(CD_3)_2CO$) 139.4 (C), 131.9 (2 × CH), 130.7 (C), 130.5 (C), 128.9 (2 × CH), 128.4 (CH), 128.3 (C), 123.2 (CH), 121.7 (CH), 112.4 (CH), 104.0 (CH), 79.2 (CH), 63.3 (CH_2); *m/z* (ESI^-) 270 ($[M – H]^-$, 100%); HRMS (ESI^+) $C_{15}H_{13}NNaO_2S^+$ ($[M + Na]^+$) requires 294.0559, found 294.0558.

2-(Benzylsulfonyl)dibenzo[*b*,*d*]furan 64

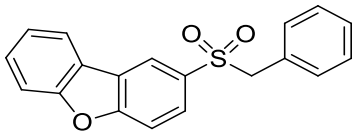


Table 2.6, entry 21: General procedure D (Method I) was followed using DABSO (127 mg, 0.53 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and 2-iododibenzo[*b*,*d*]furan (141 mg, 0.48 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **64** as white needles (99 mg, 64%); mp 205-208 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2960, 2927, 2852, 1584, 1442, 1422, 1406, 1346, 1327, 1307, 1295, 1260, 1244, 1199, 1184, 1164, 1154, 1118, 1104, 1071, 1021; δ_H (200 MHz, $CDCl_3$) 8.25 (1H, d, *J* 2.0, Ar*H*), 7.92 (1H, d, *J* 8.0, Ar*H*), 7.73-7.51 (5H, m, 5 × Ar*H*), 7.47-7.38 (1H, m, Ar*H*), 7.34-7.19 (2H, m, 2 × Ar*H*), 7.15-7.03 (2H, m, 2 × Ar*H*), 4.40 (2H, s, SCH_2); δ_C (126 MHz, $CDCl_3$) 158.9 (C), 157.1 (C), 132.4 (C), 131.0 (2 × CH), 129.0 (CH), 128.7(9) (CH), 128.7(7) (2 × CH), 128.5 (C), 127.8 (CH), 125.0 (C), 123.9 (CH), 123.1 (C), 122.5 (CH), 121.3 (CH), 112.3 (CH), 112.2 (CH), 63.5 (CH_2); *m/z* (ESI^+) 345 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{14}NaO_3S^+$ ($[M + Na]^+$) requires 345.0556, found 345.0552.

Benzyl thiophen-3-yl sulfone 65

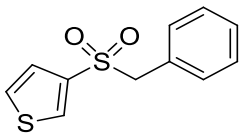


Table 2.6, entry 22: General procedure D (Method I) was followed using DABSO (127 mg, 0.53 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and 3-iodothiophene (49 μL, 0.48 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **65** as a white crystalline solid (71 mg, 62%); mp 123-125 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3117, 3093, 3032, 2973, 2920, 1603, 1496, 1457, 1405, 1363, 1295, 1259, 1207, 1186, 1165, 1150, 1120, 1094, 1073, 1030; δ_H (400 MHz, $CDCl_3$) 7.75 (1H, d, *J* 2.0, C=C*H*S), 7.40-7.25 (4H, m, 4 × Ar*H*), 7.18-7.06 (3H, m, 3 × Ar*H*), 4.34 (2H, s, SCH_2); δ_C (101

MHz, $CDCl_3$) 138.3 (C), 133.5 (CH), 130.9 (2 × CH), 129.0 (CH), 128.7 (2 × CH), 128.3 (C), 127.8 (CH), 126.6 (CH), 63.3 (CH_2); *m/z* (ESI^+) 261 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{11}H_{10}NaO_2S_2^+$ ($[M + Na]^+$) requires 261.0014, found 261.0012.

Benzyl (1*E*)-oct-1-en-1-yl sulfone 66

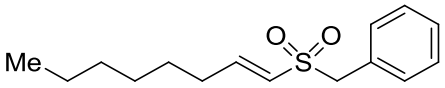


Table 2.6, entry 24: General procedure D (Method I) was followed using DABSO (127 mg, 0.53 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and *trans*-1-iodo-1-octene (114 mg, 0.48 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **66** as a white crystalline solid (59 mg, 46%); mp 28-29 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2928, 2870, 2858, 1496, 1456, 1376, 1303, 1285, 1256, 1221, 1202, 1161, 1151, 1113, 1072, 1030; δ_H (500 MHz, $CDCl_3$) 7.39-7.33 (5H, m, 5 × Ar*H*), 6.71 (1H, dt, *J* 15.0, 7.0, C*H*=CHS), 6.13 (1H, d, *J* 15.0, CH=C*H*S), 4.21 (2H, s, SCH_2), 2.21-2.15 (2H, m, $CH_2(CH_2)_4CH_3$), 1.37 (2H, app quin, *J* 6.5, CH_2), 1.28 (2H, app quin, *J* 6.5, CH_2) overlapping 1.26-1.15 (4H, m, 2 × CH_2), 0.95-0.81 (3H, m, $(CH_2)_5CH_3$); δ_C (126 MHz, $CDCl_3$) 150.9 (CH), 130.9 (2 × CH), 128.9(0) (CH), 128.8(6) (2 × CH), 128.4 (C), 126.8 (CH), 61.5 (CH_2), 31.7 (CH_2), 31.5 (CH_2), 28.7 (CH_2), 27.6 (CH_2), 22.6 (CH_2), 14.1 (CH_3); *m/z* (ESI^+) 289 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{15}H_{22}NaO_2S^+$ ($[M + Na]^+$) requires 289.1233, found 289.1223.

{[(Cyclohexylidenemethyl)sulfonyl]methyl}benzene benzyl cyclohexylidenemethyl sulfone 67

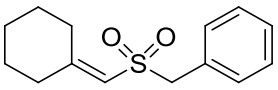


Table 2.6, entry 25: General procedure D (Method I) was followed using DABSO (127 mg, 0.53 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and (iodomethylidene)cyclohexane **46** (106 mg, 0.48 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **67** as a white crystalline solid (104 mg, 87%); mp 74-76 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2922, 2855, 1495, 1450, 1439, 1407, 1357, 1339, 1317, 1298, 1251, 1234, 1202, 1179, 1159, 1150, 1115, 1073, 1029; δ_H (400 MHz, $CDCl_3$) 7.39-7.33 (5H, m, 5 × Ar*H*), 5.85 (1H, s, C=C*H*S), 4.20 (2H, s, SCH_2), 2.37 (2H, t, *J* 6.0, CH_2C=CH), 2.15 (2H, t, *J* 6.0, CH_2C=CH), 1.66-1.59 (2H, m, CH_2), 1.54-1.47 (2H, m, CH_2), 1.43-1.35 (2H, m, CH_2); δ_C (101 MHz, $CDCl_3$) 164.7 (C), 131.2 (2 × CH), 128.8(3) (CH), 128.8(0) (2 × CH), 128.7(6) (C), 119.5 (CH), 62.6 (CH_2), 37.8 (CH_2), 29.1 (CH_2), 28.4 (CH_2), 27.4 (CH_2), 25.8 (CH_2); *m/z* (ESI^+) 523 ($[2M + Na]^+$, 100%), 273 ($[M + Na]^+$, 50%); HRMS (ESI^+) $C_{14}H_{18}NaO_2S^+$ ($[M + Na]^+$) requires 273.0920, found 273.0922.

Benzyl cyclohept-1-en-1-yl sulfone 68

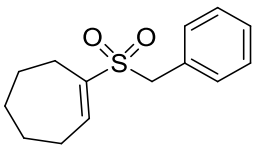


Table 2.6, entry 26: General procedure D (Method I) was followed using DABSO (127 mg, 0.53 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), benzyl bromide (142 μL, 1.20 mmol) and 1-iodocycloheptene **45** (107 mg, 0.48 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **68** as a white crystalline solid (97 mg, 81%); mp 57-58 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3063, 2922, 2849, 1602, 1494, 1445, 1415, 1360, 1297, 1284, 1224, 1147, 1128, 1114, 1077, 1044, 1031; δ_H (400 MHz, $CDCl_3$) 7.38-7.30 (5H, m, 5 × Ar*H*), 6.85 (1H, t, *J* 6.5, SC=C*H*), 4.16 (2H, s, SCH_2), 2.48-2.43 (2H, m, CH_2), 2.26-2.20 (2H, m,

C*H*$_2$), 1.78-1.71 (2H, m, C*H*$_2$), 1.61-1.54 (2H, m, C*H*$_2$), 1.54-1.47 (2H, m, C*H*$_2$); δ_C (101 MHz, $CDCl_3$) 146.4 (CH), 142.3 (C), 130.9 (2 × CH), 128.8(6) (CH), 128.8(0) (2 × CH), 128.6 (C), 59.6 (CH_2), 31.3 (CH_2), 28.8 (CH_2), 28.3 (CH_2), 26.2 (CH_2), 25.5 (CH_2); *m/z* (ESI$^+$) 523 ([2M + Na]$^+$, 50%), 273 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{18}O_2S^+$ ([M + Na]$^+$) requires 273.0920, found 273.0925.

Benzyl 3-methylbut-2-en-2-yl sulfone 69

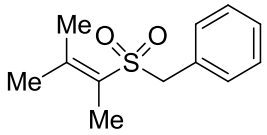


Table 2.6, entry 27: General procedure D (Method I) was followed using DABSO (127 mg, 0.53 mmol), benzyl bromide (143 μL, 1.20 mmol) and 2-iodo-3-methylbut-2-ene **47** (94 mg, 0.48 mmol). Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **69** as a pale yellow oil (25 mg, 23%); ν_{max} (neat)/cm^{-1} 3032, 2922, 1632, 1496, 1455, 1407, 1386, 1297, 1250, 1236, 1198, 1143, 1117, 1089, 1073, 1029; δ_H (400 MHz, $CDCl_3$) 7.39-7.33 (3H, m, 3 × Ar*H*), 7.33-7.28 (2H, m, 2 × Ar*H*), 4.19 (2H, s, SCH_2), 1.94 (3H, app d, *J* 1.5, C(1)*H*$_3$), 1.83 (6H, br. s, C(3)*Me*$_2$); δ_C (126 MHz, $CDCl_3$) 149.5 (C), 131.2 (C), 130.9 (2 × CH), 128.8 (CH), 128.7(2) (C), 128.7(0) (2 × CH), 60.8 (CH_2), 24.2 (CH_3), 22.2 (CH_3), 16.4 (CH_3); *m/z* (ESI$^+$) 471 ([2M + Na]$^+$, 10%), 247 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{16}NaO_2S^+$ ([M + Na]$^+$) requires 247.0763, found 247.0763.

4-Ethoxyphenyl 4-(trifluoromethyl)benzyl sulfone 71

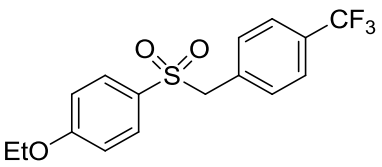


Table 2.7, entry 1: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), 1-ethoxy-4-iodobenzene **205** (119 mg, 0.48 mmol) and 4-(trifluoromethyl)benzyl bromide (186 μL, 1.20 mmol). The reaction mixture was stirred at 90 °C for 5 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **71** as a white crystalline solid (150 mg, 91%); mp 226-228 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2989, 2952, 2916, 1596, 1577, 1497, 1477, 1446, 1411, 1396, 1331, 1312, 1295, 1286, 1261, 1205, 1176, 1146, 1131, 1117, 1089, 1067, 1040, 1019; δ_H (500 MHz, $CDCl_3$) 7.56-7.52 (4H, m, 2 × Ar(OEt)*H*, 2 × Ar(CF_3)*H*), 7.26-7.22 (2H, m, 2 × Ar(CF_3)*H*), 6.95-6.84 (2H, m, 2 × Ar(OEt)*H*), 4.33 (2H, s, SCH_2), 4.09 (2H, q, *J* 7.0, O$CH_2$$CH_3$), 1.45 (3H, t, *J* 7.0, OCH_2CH_3); δ_C (126 MHz, $CDCl_3$) 163.5 (C), 132.7 (C), 131.3 (2 × CH), 131.0 (C, q, J_{CF} 32.0), 129.0 (2 × CH), 128.8 (C), 125.6 (2 × CH, q, J_{CF} 4.0), 124.0 (C, q, J_{CF} 272.5), 114.9 (2 × CH), 64.3 (CH_2), 62.8 (CH_2), 14.7 (CH_3); δ_F (470 MHz, $CDCl_3$) –62.9 (s, CF_3) {^{1}H}; *m/z* (ESI$^-$) 343 ([M – H]$^-$, 100%); HRMS (ESI$^+$) $C_{16}H_{15}F_3NaO_3S^+$ ([M + Na]$^+$) requires 367.0586, found 367.0588.

2-Bromobenzyl 4-ethoxyphenyl sulfone 72

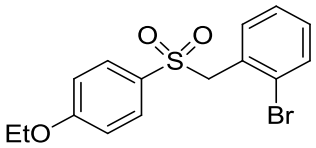


Table 2.7, entry 2: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), 1-ethoxy-4-iodobenzene **205** (119 mg, 0.48 mmol) and 2-bromobenzylbromide (300 mg, 1.20 mmol). The reaction mixture was stirred at 90 °C for 5 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **72** as a white crystalline solid (153 mg, 90%); mp 136-138 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2987, 2922, 1592, 1575, 1493, 1477, 1443, 1412, 1394, 1313, 1301, 1292, 1281, 1262, 1244, 1202, 1178, 1152, 1132, 1114, 1083,

1045, 1024; δ_H (500 MHz, $CDCl_3$) 7.55-7.51 (2H, m, Ar(OEt)*H*), 7.49 (1H, dd, *J* 8.0, 1.5, Ar(Br)*H*), 7.46 (1H, dd, *J* 8.0, 1.5, Ar(Br)*H*), 7.32 (1H, app td, *J* 7.5, 1.5, Ar(Br)*H*), 7.18 (1H, app td, *J* 7.5, 1.5, Ar(Br)*H*), 6.90-6.86 (2H, m, Ar(OEt)*H*), 4.57 (2H, s, SCH_2), 4.09 (2H, q, *J* 7.0, OCH_2CH$_3$), 1.44 (3H, t, *J* 7.0, OCH$_2$CH_3); δ_C (126 MHz, $CDCl_3$) 163.5 (C), 133.1(0) (CH), 133.0(7) (CH), 131.1 (2 × CH), 130.4 (CH), 129.5 (C), 128.8 (C), 127.8 (CH), 126.1 (C), 114.7 (2 × CH), 64.2 (CH_2), 62.0 (CH_2), 14.7 (CH_3); HRMS (FI^+) $C_{15}H_{15}BrO_3S^+$ ($[M]^+$) requires 355.9905 and 353.9925, found 355.9903 and 353.9921.

4-Ethoxyphenyl naphthalen-2-ylmethyl sulfone 73

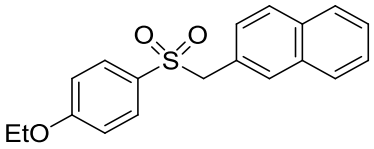


Table 2.7, entry 3: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), 1-ethoxy-4-iodobenzene **205** (119 mg, 0.48 mmol) and 2-(bromomethyl)naphthalene (265 mg, 1.20 mmol). The reaction mixture was stirred at 90 °C for 5 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **73** as a white crystalline solid (146 mg, 93%); mp 128-130 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3052, 2977, 2938, 1596, 1579, 1498, 1477, 1442, 1210, 1393, 1365, 1313, 1295, 1256, 1211, 1179, 1146, 1114, 1089, 1044; δ_H (500 MHz, $CDCl_3$) 7.84-7.81 (1H, m, Ar*H*), 7.75 (1H, d, *J* 8.0, Ar*H*) overlapping 7.75-7.73 (1H, m, Ar*H*), 7.56 (1H, app br. s, Ar*H*), 7.54-7.46 (4H, m, 2 × Ar(OEt)*H*, 2 × Ar*H*), 7.20 (1H, dd, *J* 8.5, 2.0, Ar*H*), 6.87-6.83 (2H, m, 2 × Ar(OEt)*H*), 4.45 (2H, s, SCH_2), 4.06 (2H, q, *J* 7.0, OCH_2CH$_3$), 1.43 (3H, t, *J* 7.0, OCH$_2$CH_3); δ_C (126 MHz, $CDCl_3$) 163.3 (C), 133.2 (2 × C), 131.0 (2 × CH), 130.6 (CH), 129.3 (C), 128.4 (CH), 128.1(3) (CH), 128.0(6) (CH), 127.8 (CH), 126.8 (CH), 126.5 (CH), 126.1 (C), 114.6 (2 ×

CH), 64.2 (CH_2), 63.5 (CH_2), 14.7 (CH_3); *m/z* (ESI^+) 349 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{18}NaO_3S^+$ ($[M + Na]^+$) requires 349.0869, found 349.0879.

4-Ethoxyphenyl methyl sulfone 74

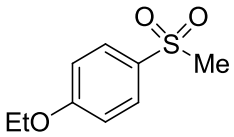


Table 2.7, entry 4: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), 1-ethoxy-4-iodobenzene **205** (119 mg, 0.48 mmol) and methyl iodide (0.18 mL, 2.88 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **74** as a white crystalline solid (11 mg, 11%); mp 85-87 °C (CH_2Cl_2) {lit.[316] 87-89 °C}; ν_{max} (neat)/cm^{-1} 3010, 2928, 1597, 1575, 1496, 1474, 1449, 1409, 1391, 1325, 1311, 1295, 1258, 1178, 1143, 1115, 1093, 1040, 1007; δ_H (500 MHz, $CDCl_3$) 7.89-7.84 (2H, m, 2 × Ar*H*), 7.04-6.99 (2H, m, 2 × Ar*H*), 4.12 (2H, q, *J* 7.0, OC*H*$_2$CH$_3$), 3.04 (3H, s, S*Me*), 1.46 (3H, t, *J* 7.0, OCH$_2$C*H*$_3$); δ_C (126 MHz, $CDCl_3$) 163.3 (C), 132.2 (C), 129.7 (2 × CH), 115.0 (2 × CH), 64.2 (CH_2), 45.0 (CH_3), 14.7 (CH_3); *m/z* (ESI^+) 223 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_9H_{12}NaO_3S^+$ ($[M + Na]^+$) requires 223.0399, found 223.0399. ^{1}H NMR spectroscopy data in accordance with literature data.[316]

4-Ethoxyphenyl propyl sulfone 75

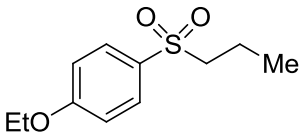


Table 2.7, entry 5: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), 1-ethoxy-4-iodobenzene **205** (119 mg, 0.48 mmol) and 1-iodopropane (117 μL, 1.20 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **75** as a white crystalline solid (60 mg, 55%); mp 39-40 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2979, 2937, 2879, 1593, 1574, 1496, 1476, 1465, 1402, 1384, 1348, 1311, 1290, 1261, 1214, 1180, 1138, 1115, 1089, 1038; δ_H (400 MHz, $CDCl_3$) 7.85-7.78 (2H, m, 2 × Ar*H*), 7.04-6.96 (2H, m, 2 × Ar*H*), 4.11 (2H, q, *J* 7.0, OC*H*$_2$CH$_3$), 3.07-3.02 (2H, m, SC*H*$_2$CH$_2$CH$_3$), 1.80-1.66 (2H, m, SCH$_2$C*H*$_2$CH$_3$), 1.46 (3H, t, *J* 7.0, OCH$_2$C*H*$_3$), 0.99 (3H, t, *J* 7.5, SCH$_2$CH$_2$C*H*$_3$); δ_C (101 MHz, $CDCl_3$) 163.2 (C), 130.6 (C), 130.3 (2 × CH), 114.9 (2 × CH), 64.2 (CH_2), 58.5 (CH_2), 16.8 (CH_2), 14.7 (CH_3), 13.1 (CH_3); *m/z* (ESI^+) 251 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{11}H_{16}NaO_3S^+$ ($[M + Na]^+$) requires 251.0712, found 251.0707.

4-Ethoxyphenyl hexyl sulfone 76

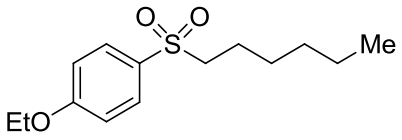


Table 2.7, entry 6: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), 1-ethoxy-4-iodobenzene **205** (119 mg, 0.48 mmol) and 1-iodohexane (177 μL, 1.20 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **76** as a colourless oil (82 mg, 63%); ν_{max} (neat)/cm^{-1} 2931, 2871, 1595, 1578, 1496, 1475, 1395, 1314, 1296, 1257, 1216, 1138, 1115, 1089, 1039; δ_H (400 MHz, $CDCl_3$) 7.84-7.70 (2H, m, 2 × Ar*H*), 7.03-6.95 (2H, m, 2 × Ar*H*), 4.10 (2H, q, *J* 7.0, OC*H*$_2$CH$_3$), 3.10-2.99 (2H, m, SC*H*$_2$(CH$_2$)$_4$CH$_3$), 1.75-1.61

(2H, m, $SCH_2CH_2(CH_2)_3CH_3$), 1.44 (3H, t, *J* 7.0, OCH_2CH_3), 1.33 (2H, app quin, *J* 7.0, $S(CH_2)_2CH_2(CH_2)_2CH_3$) overlapping 1.29-1.18 (4H, m, $S(CH_2)_3(CH_2)_2CH_3$), 0.84 (3H, t, *J* 7.0, $S(CH_2)_5CH_3$); δ_C (101 MHz, $CDCl_3$) 163.2 (C), 130.6 (C), 130.3 (2 × CH), 114.9 (2 × CH), 64.1 (CH_2), 56.7 (CH_2), 31.3 (CH_2), 28.0 (CH_2), 22.9 (CH_2), 22.4 (CH_2), 14.7 (CH_3), 14.0 (CH_3); *m/z* (ESI^+) 293 ($[M + Na]^+$, 100%), 271 ($[M + H]^+$, 70%); HRMS (ESI^+) $C_{14}H_{22}NaO_3S^+$ ($[M + Na]^+$) requires 293.1182, found 293.1178.

4-Ethoxyphenyl (2*E*)-3-phenylprop-2-en-1-yl sulfone 77

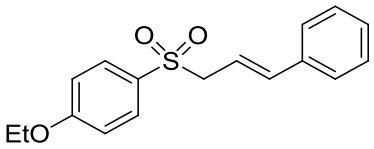


Table 2.7, entry 7: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), 1-ethoxy-4-iodobenzene **205** (119 mg, 0.48 mmol) and 3-bromo-1-phenyl-1-propene (178 μL, 1.20 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **77** as a white crystalline solid (75 mg, 51%).

General procedure D (Method II) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), 1-ethoxy-4-iodobenzene **205** (119 mg, 0.48 mmol) and 3-bromo-1-phenyl-1-propene (142 μL, 0.96 mmol). Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **77** as a white crystalline solid (120 mg, 83%).

Sulfone **77**: mp 102-104 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2938, 1595, 1574, 1494, 1471, 1453, 1414, 1390, 1315, 1296, 1262, 1178, 1141, 1117, 1087, 1039; δ_H (500 MHz, $CDCl_3$) 7.80-7.76 (2H, m, 2 × Ar(OEt)*H*), 7.32-7.28 (5H, m, 5 × Ar*H*), 6.98-6.94 (2H, m, 2 × Ar(OEt)*H*), 6.38 (1H, app d, *J* 16.0, $SCH_2CH{=}CH$), 6.11 (1H, dt, *J* 16.0, 7.5,

SCH_2CH=CH), 4.09 (2H, q, *J* 7.0, OCH_2CH_3), 3.92 (2H, dd, *J* 7.5, 1.0, SCH_2CH=CH), 1.44 (3H, t, *J* 7.0, OCH_2CH_3); δ_C (126 MHz, $CDCl_3$) 163.3 (C), 139.1 (CH), 136.0 (C), 130.8 (2 × CH), 129.9 (C), 128.8 (2 × CH), 128.6 (CH), 126.8 (2 × CH), 115.7 (CH), 114.8 (2 × CH), 64.2 (CH_2), 60.9 (CH_2), 14.7 (CH_3); *m/z* (ESI^+) 325 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{17}H_{18}NaO_3S^+$ ($[M + Na]^+$) requires 325.0869, found 325.0866.

Cyclohex-2-en-1-yl 4-ethoxyphenyl sulfone 78

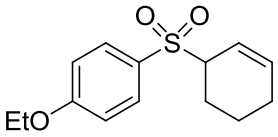


Table 2.7, entry 8: General procedure D (Method II) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), 1-ethoxy-4-iodobenzene **205** (119 mg, 0.48 mmol) and 3-bromocyclohexene (110 μL, 0.96 mmol). Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **78** as a white crystalline solid (70 mg, 55%); mp 128-130 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2962, 2933, 2863, 1591, 1575, 1491, 1471, 1456, 1428, 1410, 1392, 1312, 1285, 1261, 1238, 1216, 1188, 1173, 1137, 1124, 1113, 1105, 1083, 1040, 1018; δ_H (400 MHz, $CDCl_3$) 7.80-7.75 (2H, m, 2 × Ar*H*), 7.01-6.96 (2H, m, 2 × Ar*H*), 6.09-6.03 (1H, m, CH=C*H*), 5.78 (1H, app dq, *J* 10.0, 2.5, C*H*=CH), 4.10 (2H, q, *J* 7.0, OCH_2CH_3), 3.75-3.68 (1H, m, SC*H*), 2.03-1.93 (3H, m), 1.89-1.70 (2H, m), 1.54-1.46 (1H, m) overlapping 1.45 (3H, t, *J* 7.0, OCH_2CH_3); δ_C (101 MHz, $CDCl_3$) 163.3 (C), 135.1 (CH), 131.4 (2 × CH), 128.7 (C), 119.1 (CH), 114.7 (2 × CH), 64.2 (CH_2), 62.1 (CH), 24.5 (CH_2), 22.9 (CH_2), 19.7 (CH_2), 14.7 (CH_3); *m/z* (ESI^+) 289 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{14}H_{18}NaO_3S^+$ ($[M + Na]^+$) requires 289.0869, found 289.0874.

2-[(4-Ethoxyphenyl)sulfonyl]cyclohexanol 79

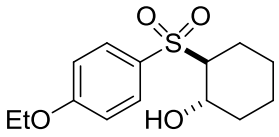


Table 2.7, entry 9: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), 1-ethoxy-4-iodobenzene **205** (119 mg, 0.48 mmol) and cyclohexene oxide (121 μL, 1.20 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3 to 1:1, petrol:ether) yielded *sulfone* **79** as a white crystalline solid (48 mg, 35%, >20:1 dr by ^{1}H NMR spectroscopy).

General procedure D (Method II) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), 1-ethoxy-4-iodobenzene (119 mg, 0.48 mmol) and cyclohexene oxide (97 μL, 0.96 mmol). Column chromatography (eluent: 7:3 to 1:1, petrol:ether) yielded *sulfone* **79** as a white crystalline solid (102 mg, 75%, >20:1 dr by ^{1}H NMR spectroscopy).

Sulfone **79**: mp 69-72 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3511, 2985, 2943, 2861, 1592, 1574, 1494, 1468, 1449, 1394, 1357, 1333, 1312, 1262, 1211, 1177, 1131, 1113, 1086, 1062, 1040; δ_H (400 MHz, $CDCl_3$) 7.83-7.77 (2H, m, 2 × Ar*H*), 7.08-6.99 (2H, m, 2 × Ar*H*), 4.40 (1H, br. s, O*H*), 4.12 (2H, q, *J* 7.0, OC*H*$_2$CH$_3$), 3.86 (1H, td, *J* 10.0, 5.0, C*H*OH), 2.98-2.90 (1H, m, SC*H*), 2.16-2.08 (1H, m), 1.96-1.89 (1H, m), 1.77-1.67 (2H, m), 1.46 (3H, t, *J* 7.0, OCH$_2$C*H*$_3$), 1.40-1.13 (4H, m); δ_C (101 MHz, $CDCl_3$) 163.7 (C), 131.3 (2 × CH), 127.7 (C), 114.9 (2 × CH), 69.1 (CH), 68.4 (CH), 64.3 (CH_2), 34.2 (CH_2), 25.9 (CH_2), 24.7 (CH_2), 23.7 (CH_2), 14.7 (CH_3); *m/z* (ESI$^+$) 307 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{20}NaO_4S^+$ ([M + Na]$^+$) requires 307.0975, found 307.0980; Anal. Calcd. (%) for $C_{14}H_{20}O_4S$: C 59.13, H 7.09; found C 59.24, H 7.27.

2-[(4-Ethoxyphenyl)sulfonyl]-1-phenylethanone 80

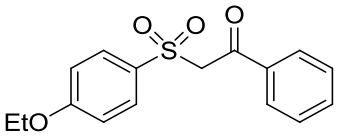


Table 2.7, entry 10: General procedure D (Method II) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (56 μL, 0.58 mmol), 1-ethoxy-4-iodobenzene **205** (119 mg, 0.48 mmol) and 2-bromoacetophenone (191 mg, 0.96 mmol). Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **80** as an off-white crystalline solid (51 mg, 35%); mp 125-128 °C (CH_2Cl_2) {lit.[317] 130 °C (ethanol)}; ν_{max} (neat)/cm^{-1} 3062, 2920, 2851, 1674, 1594, 1575, 1496, 1466, 1447, 1407, 1319, 1301, 1264, 1221, 1180, 1149, 1116, 1088, 1036; δ_H (500 MHz, $CDCl_3$) 7.98-7.94 (2H, m, 2 × Ar(CO)*H*), 7.82-7.78 (2H, m, 2 × Ar(OEt)*H*), 7.65-7.61 (1H, m, Ar(CO)*H*), 7.52-7.47 (2H, m, 2 × Ar(CO)*H*), 6.99-6.95 (2H, m, 2 × Ar(OEt)*H*), 4.72 (2H, s, SCH_2CO), 4.11 (2H, q, *J* 7.0, OCH_2CH_3), 1.45 (3H, t, *J* 7.0, OCH_2CH_3); δ_C (126 MHz, $CDCl_3$) 188.5 (C), 163.7 (C), 136.0 (C), 134.4 (CH), 131.0 (2 × CH), 130.0 (C), 129.5 (2 × CH), 129.0 (2 × CH), 114.9 (2 × CH), 64.3 (CH_2), 64.0 (CH_2), 14.7 (CH_3); *m/z* (ESI^+) 327 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{16}H_{16}NaO_4S^+$ ($[M + Na]^+$) requires 327.0662, found 327.0663.

Methyl 2-[(4-ethoxyphenyl)sulfonyl]propanoate 81

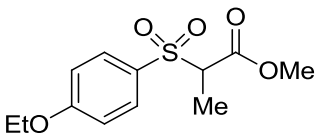


Table 2.7, entry 11: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 1-ethoxy-4-iodobenzene **205** (119 mg, 0.48 mmol) and methyl 2-bromopropionate (139 μL, 1.20 mmol). Column

chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **81** as a colourless oil (34 mg, 26%).

General procedure D (Method II) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (56 μL, 0.58 mmol), 1-ethoxy-4-iodobenzene **205** (119 mg, 0.48 mmol) and methyl 2-bromopropionate (107 μL, 0.96 mmol). Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **81** as a colourless oil (61 mg, 47%).

Sulfone **81**: ν_{max} (neat)/cm^{-1} 2983, 2952, 1739, 1593, 1577, 1497, 1475, 1452, 1415, 1395, 1320, 1300, 1259, 1201, 1169, 1140, 1115, 1086, 1038, 1008; δ_H (400 MHz, $CDCl_3$) 7.82-7.76 (2H, m, 2 × Ar*H*), 7.05-6.96 (2H, m, 2 × Ar*H*), 4.12 (2H, q, *J* 7.0, OC*H*$_2$CH$_3$), 4.04 (1H, q, *J* 7.0, SC*H*Me), 3.71 (3H, s, O*Me*), 1.55 (3H, d, *J* 7.0, SCH*Me*), 1.46 (3H, t, *J* 7.0, OCH$_2$C*H*$_3$); δ_C (101 MHz, $CDCl_3$) 167.2 (C), 163.8 (C), 131.7 (2 × CH), 127.9 (C), 114.7 (2 × CH), 65.6 (CH), 64.3 (CH_2), 53.1 (CH_3), 14.7 (CH_3), 12.3 (CH_3); *m/z* (ESI$^+$) 295 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{16}NaO_5S^+$ ([M + Na]$^+$) requires 295.0611, found 295.0607.

Ethyl 2-[(4-ethoxyphenyl)sulfonyl]-2-methylpropanoate 82

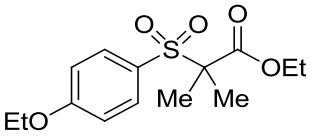


Table 2.7, entry 12: General procedure D (Method I) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), 1-ethoxy-4-iodobenzene **205** (119 mg, 0.48 mmol) and methyl 2-bromo-2-methylpropionate (176 μL, 1.20 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **82** as a white crystalline solid (82 mg, 57%); mp 86-89 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2983, 2941, 1731,

1594, 1577, 1497, 1473, 1415, 1394, 1367, 1316, 1298, 1259, 1153, 1128, 1079, 1038, 1023; δ_H (500 MHz, $CDCl_3$) 7.78-7.74 (2H, m, 2 × Ar*H*), 7.02-6.92 (2H, m, 2 × Ar*H*), 4.15 (2H, q, *J* 7.0, COOC*H*$_2$CH$_3$) overlapping 4.12 (2H, q, *J* 7.0, ArOC*H*$_2$CH$_3$), 1.61 (6H, s, 2 × SC*Me*), 1.46 (3H, t, *J* 7.0, ArOCH$_2$C*H*$_3$), 1.24 (3H, t, *J* 7.0, COOCH$_2$C*H*$_3$); δ_C (126 MHz, $CDCl_3$) 169.2 (C), 163.7 (C), 132.7 (2 × CH), 127.0 (C), 114.4 (2 × CH), 69.1 (C), 64.2 (CH_2), 62.4 (CH_2), 20.5 (2 × CH_3), 14.7 (CH_3), 14.0 (CH_3); *m/z* (ESI^+) 323 ([M + $Na]^+$, 100%); HRMS (ESI^+) $C_{14}H_{20}NaO_5S^+$ ([M + $Na]^+$) requires 323.0924, found 323.0913.

2-[(4-Ethoxyphenyl)sulfonyl]-5-(trifluoromethyl)benzaldehyde 83

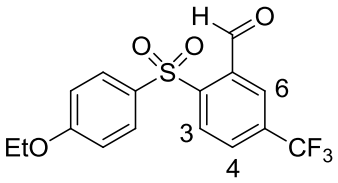
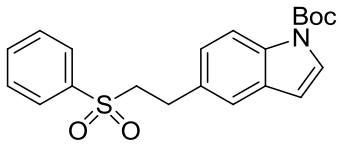


Table 2.7, entry 13: General procedure D (Method II) was followed using DABSO (69 mg, 0.29 mmol), DABCO (27 mg, 0.24 mmol), 4-aminomorpholine (55 μL, 0.58 mmol), 1-ethoxy-4-iodobenzene **205** (119 mg, 0.48 mmol) and 2-fluoro-5-(trifluoromethyl)benzaldehyde (136 μL, 0.96 mmol). Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **83** as a pale yellow crystalline solid (60 mg, 35%); mp 88-90 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2987, 2920, 1705, 1593, 1579, 1496, 1473, 1446, 1417, 1397, 1328, 1256, 1178, 1166, 1151, 1128, 1077, 1039; δ_H (500 MHz, $CDCl_3$) 10.92 (1H, s, ArC*H*O), 8.26 (1H, d, *J* 1.5, Ar(6)*H*), 8.24 (1H, d, *J* 8.0, Ar(3)*H*), 7.97 (1H, dd, *J* 8.0, 1.5, Ar(4)*H*), 7.85-7.81 (2H, m, 2 × Ar(OEt)*H*), 7.05-6.98 (2H, m, 2 × Ar(OEt)*H*), 4.10 (2H, q, *J* 7.0, OC*H*$_2$CH$_3$), 1.44 (3H, t, *J* 7.0, OCH$_2$C*H*$_3$); δ_C (126 MHz, $CDCl_3$) 188.3 (CH), 163.8 (C), 146.6 (C), 135.5 (C, q, J_{CF} 34.0), 134.4 (C), 131.4 (C), 130.3(1) (CH, q, J_{CF} 3.5) overlapping 130.2(7) (2 × CH), 130.0 (CH), 126.7 (CH, q, J_{CF} 3.5), 122.8 (C, q,

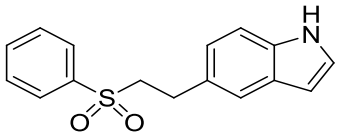
J_{CF} 273.0), 115.7 (2 × CH), 64.5 (CH_2), 14.6 (CH_3); δ_F (470 MHz, $CDCl_3$) -63.4 (s, CF_3) {^{1}H}; *m/z* (ESI^+) 413 ($[M + Na + MeOH]^+$, 100%); *m/z* (ESI^-) 425 ($[M + Cl + MeOH]^-$, 100%); HRMS (ESI^+) $C_{16}H_{13}F_3NaO_4S^+$ ($[M + Na]^+$) 381.0379, found 381.0367.

tert-Butyl 5-[2-(phenylsulfonyl)ethyl]-1*H*-indole-1-carboxylate 94



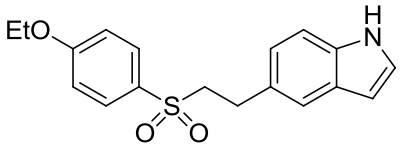
General procedure D (Method I) was followed using DABSO (53 mg, 0.22 mmol), 4-aminomorpholine (25 μL, 0.24 mmol), iodobenzene (22 μL, 0.20 mmol) and *tert*-butyl 5-(2-iodoethyl)-1*H*-indole-1-carboxylate **93** (186 mg, 0.50 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3, petrol:ether) yielded *sulfone* **94** as an off-white crystalline solid (35 mg, 46%) mp 82-84 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2978, 2928, 1731, 1471, 1446, 1373, 1353, 1325, 1308, 1258, 1218, 1150, 1132, 1084, 1024; δ_H (400 MHz, $CDCl_3$) 8.03 (1H, d, *J* 8.5, Ar*H*), 7.98-7.94 (2H, m, 2 × Ar*H*), 7.70-7.65 (1H, m, Ar*H*), 7.61-7.56 (3H, m, 3 × Ar*H*), 7.30 (1H, d, *J* 1.5, Ar*H*), 7.05 (1H, dd, *J* 8.5, 1.5, Ar*H*), 6.48 (1H, d, *J* 4.0 Ar*H*), 3.43-3.38 (2H, m, SCH_2CH_2Ar), 3.16-3.11 (2H, m, SCH_2CH_2Ar), 1.66 (9H, s, O^t*Bu*); δ_C (126 MHz, $CDCl_3$) 149.8 (C), 139.2 (C), 134.3 (C), 133.9 (CH), 131.8 (C), 131.1 (C), 129.5 (2 × CH), 128.3 (2 × CH), 126.6 (CH), 124.6 (CH), 120.6 (CH), 115.6 (CH), 107.0 (CH), 83.9 (C), 58.2 (CH_2), 28.9 (CH_2), 28.3 (3 × CH_3); *m/z* (ESI^+) 408 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{21}H_{23}NNaO_4S^+$ ($[M + Na]^+$) requires 408.1240, found 408.1228.

5-[2-(Phenylsulfonyl)ethyl]-1*H*-indole 84



General procedure D (Method I) was followed using DABSO (53 mg, 0.22 mmol), 4-aminomorpholine (25 μL, 0.24 mmol), iodobenzene (22 μL, 0.20 mmol) and 5-(2-iodoethyl)-1*H*-indole **85** (136 mg, 0.50 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column chromatography (eluent: 7:3 to 3:7, petrol:ether) yielded sulfone **84** as an off-white crystalline solid (25 mg, 43%); ν_{max} (neat)/cm^{-1} 3394, 2920, 2851, 1447, 1304, 1149, 1085; δ_H (200 MHz, $CDCl_3$) 8.14 (1H, br. s, N*H*), 8.01-7.92 (2H, m, 2 × Ar*H*), 7.69-7.53 (3H, m, 3 × Ar*H*), 7.40-7.36 (1H, m, Ar*H*), 7.31 (1H, d, *J* 8.5, Ar*H*), 7.23-7.19 (1H, m, Ar*H*), 6.94 (1H, dd, *J* 8.5, 1.5, Ar*H*), 6.47 (1H, ddd, *J* 3.0, 2.0, 1.0, Ar*H*), 3.48-3.37 (2H, m, SC*H*$_2$CH$_2$Ar), 3.19-3.08 (2H, m, SCH$_2$C*H*$_2$Ar); δ_C (126 MHz, $CDCl_3$) 139.3 (C), 134.9 (C), 133.8 (CH), 129.4 (2 × CH), 128.9 (C), 128.4 (CH), 128.3 (2 × CH), 124.9 (C), 122.6 (CH), 120.2 (CH), 111.5 (CH), 102.5 (CH), 58.5 (CH_2), 29.1 (CH_2); HRMS (ESI$^+$) $C_{16}H_{15}NNaO_2S^+$ ([M + Na]$^+$) requires 308.0716, found 308.0718. Data in accordance to literature data.[153]

5-{2-[(4-Ethoxyphenyl)sulfonyl]ethyl}-1*H*-indole 95

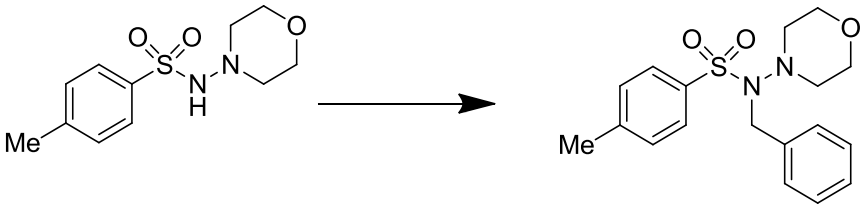


General procedure D (Method I) was followed using DABSO (29 mg, 0.12 mmol), DABCO (11 mg, 0.10 mmol), 4-aminomorpholine (25 μL, 0.24 mmol), 4-ethoxy-*N*-(morpholin-4-yl)benzenesulfonamide (56 mg, 0.20 mmol) and 5-(2-iodoethyl)-1*H*-indole **85** (136 mg, 0.50 mmol). The reaction mixture was stirred at 90 °C for 20 h. Column

chromatography (eluent: 7:3 to 3:7, petrol:ether) yielded *sulfone* **95** as an off-white crystalline solid (41 mg, 63%); mp 89-91 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3400, 2981, 2929, 1594, 1578, 1496, 1475, 1454, 1416, 1395, 1342, 1313, 1260, 1180, 1137, 1087, 1039; δ_H (400 MHz, $CDCl_3$) 8.13 (1H, br. s, N*H*), 7.88-7.83 (2H, m, 2 × Ar(OEt)*H*), 7.38-7.35 (1H, m, Ar*H*), 7.29 (1H, d, *J* 8.5, Ar*H*), 7.21-7.18 (1H, m, Ar*H*), 7.03-6.98 (2H, m, 2 × Ar(OEt)*H*), 6.94 (1H, dd, *J* 8.5, 1.5, Ar*H*), 6.46 (1H, ddd, *J* 3.0, 2.0, 1.0, Ar*H*), 4.11 (2H, q, *J* 7.0, ArOC$H_2$$CH_3$), 3.41-3.35 (2H, m, SC$H_2$$CH_2$Ar), 3.14-3.07 (2H, m, SCH_2CH_2Ar), 1.46 (3H, t, *J* 7.0, $ArOCH_2C$$H_3$); δ_C (126 MHz, $CDCl_3$) 163.3 (C), 134.9 (C), 130.6 (C), 130.4 (2 × CH), 129.1 (C), 128.4 (C), 124.9 (CH), 122.6 (CH), 120.2 (CH), 115.0 (2 × CH), 111.4 (CH), 102.5 (CH), 64.2 (CH_2), 58.8 (CH_2), 29.3 (CH_2), 14.8 (CH_3); *m/z* (ESI^+) 681 ($[2M + Na]^+$, 40%), 352 ($[M + Na]^+$, 100%); *m/z* (ESI^-) 278 ($[M – H]^-$, 100%); HRMS (ESI^+) $C_{18}H_{19}NNaO_3S^+$ ($[M + Na]^+$) requires 352.0978, found 352.0964.

6.3.3 Mechanistic investigation

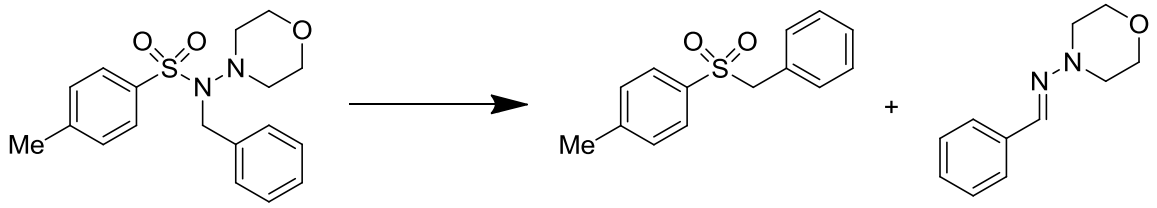
Reaction of *N*-aminosulfonamide 11 to give the presumed trialkylated intermediate *N*-benzyl-4-methyl-*N*-morpholinobenzenesulfonamide 25.



To a round-bottomed flask, benzyl bromide (114 μL, 0.96 mmol) was added to a solution of 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (123 mg, 0.48 mmol) and Cs_2CO_3 (313 mg, 0.96 mmol) in 1,4-dioxane (1.6 mL). The reaction mixture was stirred at 40 °C for 20 min and then stirred at 50 °C for 20 min. After cooling to RT, the suspension was filtered through filter paper and the residue washed with CH_2Cl_2 (5 mL). The filtrate was

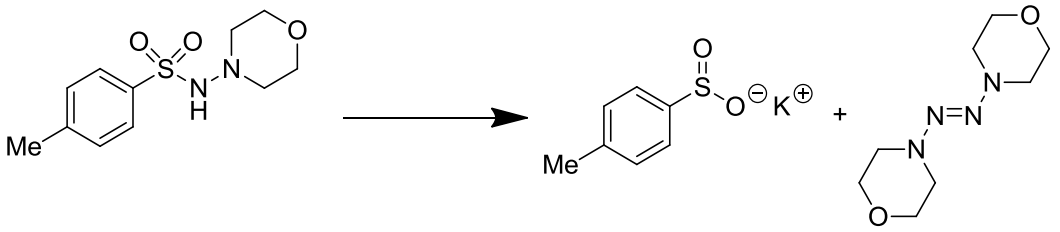
concentrated *in vacuo* to afford a thick pale yellow oil that was determined by ^{1}H NMR spectroscopy to be a mixture of unreacted benzyl bromide and the presumed trialkylated intermediate, *N-benzyl-4-methyl-N-morpholinobenzenesulfonamide* **25**: δ_H (400 MHz, $CDCl_3$) 7.89-7.85 (2H, m, 2 × Ar*H*), 7.48-7.43 (2H, m, 2 × Ar*H*), 7.48-7.43 (5H, m, 5 × Ar*H*), 4.62 (2H, s, NCH_2Ar), 3.48 (4H, br. s, N(CH_2CH_2)$_2$O), 2.54 (4H, br. s, N(CH_2CH_2)$_2$O), 2.45 (3H, s, Ar*Me*); δ_C (101 MHz, $CDCl_3$) 143.7 (C), 137.8 (C), 129.4 (2 × CH), 128.6(2) (2 × CH), 128.5(5) (2 × CH), 128.3 (2 × CH), 127.8 (CH), 67.2 (2 × CH_2), 52.3 (2 × CH_2), 46.2 (CH_2), 21.6 (CH_3) (one carbon unable to identify); *m/z* (ESI$^+$) 715 ([2M + Na]$^+$, 100%), 369 ([M + Na]$^+$, 90%), 347 ([M + H]$^+$, 93%); HRMS (ESI$^+$) $C_{18}H_{22}N_2O_3S^+$ ([M + Na]$^+$) requires 347.1424, found 347.1431.

Reaction of the presumed trialkyl intermediate *N*-benzyl-4-methyl-*N*-morpholinobenzenesulfonamide 25 to give the sulfone 13 and the hydrazone 14.



To the crude reaction mixture of the presumed *trialkyl intermediate* **25** was added benzyl bromide (57 μL, 0.48 mmol), Cs_2CO_3 (150 mg, 0.48 mmol) and 1,4-dioxane (1.6 mL). The reaction mixture was stirred at 100 °C for 1 h and then cooled to RT. The reaction mixture was diluted with water (5 mL) and washed with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered and then concentrated *in vacuo*. Column chromatography (eluent: 7:3, petrol:ether) yielded, in order of elution, hydrazone **14** (77 mg, 85%) and sulfone **13** (108 mg, 91%), both as a white crystalline solids.

Decomposition of 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide 11 to give potassium toluene-*p*-sulfinate 26 and the presumed tetrazene 4,4'-(*E*)-diazene-1,2-diyldimorpholine 29.

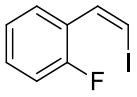


A mixture of 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (300 mg, 1.20 mmol) and potassium carbonate (165 mg, 2.40 mmol) in 1,4-dioxane (4 mL) was stirred at 100 °C for 16 h. After cooling to RT, the suspension was filtered through filter paper and the residue washed with CH_2Cl_2 (5 mL). The residue was identified to include the potassium toluene-*p*-sulfinate salt **26**; ν_{max} (neat)/cm^{-1} 3350, 2943, 1605, 1490, 1349, 1230, 1097, 1010; δ_H (400 MHz, $(CD_3)_2SO$) 7.35-7.31 (2H, m, 2 × Ar*H*), 7.10 (2H, app d, *J* 7.5, 2 × Ar*H*), 2.28 (3H, s, Ar*Me*); δ_C (101 MHz, $(CD_3)_2SO$) 158.4 (C), 136.7 (C), 128.5 (2 × CH), 124.8 (2 × CH), 21.3 (CH_3); *m/z* (ESI⁻) 155 ([M – K]⁻, 100%); HRMS (ESI⁺) $C_7H_7O_2S^-$ ([M – K]⁻) requires 155.0172, found 155.0171.

The filtrate was concentrated *in vacuo*. Column chromatography (eluent: 1:1, petrol:ether) yielded tetrazene **29** as a white crystalline solid (20 mg, 8%); mp 146-147 °C (dec) (CH_2Cl_2) {lit.[318] 153-154 °C (acetic acid) (dec)}; ν_{max} (neat)/cm^{-1} 2966, 2959, 2924, 2870, 2854, 2842, 1451, 1269, 1109, 1090, 1074; δ_H (400 MHz, $CDCl_3$) 3.78-3.74 (8H, m, $N(CH_2CH_2)_2O$), 3.15-3.12 (8H, m, $N(CH_2CH_2)_2O$); δ_C (101 MHz, $CDCl_3$) 66.3 (4 × CH_2), 50.3 (4 × CH_2); HRMS (FI⁺) $C_8H_{16}N_4O_2^+$ ([M]⁺) requires 200.1273, found 200.1281. Data in accordance with literature data.[318]

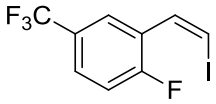
6.3.4 Benzo[*b*]thiophene 1,1-dioxide investigation

(*Z*)-1-Fluoro-2-(2-iodovinyl)benzene 112



General procedure E was followed using 2-fluorobenzaldehyde (0.50 mL, 4.71 mmol). Column chromatography (eluent: hexane) yielded *alkenyl iodide* **112** as a yellow oil (0.92 g, 78%, *Z*:*E*, >20:1); ν_{max} (neat)/cm^{-1} 3063, 2965, 1501, 1308, 1111; δ_H (400 MHz, $CDCl_3$) 7.86 (1H, app t, *J* 8.5, Ar*H*), 7.41 (1H, d, *J* 8.5, ArC*H*=CHI), 7.39-7.31 (1H, m, Ar*H*), 7.19 (1H, app t, *J* 8.5, Ar*H*), 7.09 (1H, app t, *J* 8.5, Ar*H*), 6.74 (1H, d, *J* 8.5, ArCH=C*H*I); δ_H (400 MHz, $CDCl_3$, *E* isomer observable peaks) 7.72 (1H, d, *J* 8.0, Ar*H*), 7.56 (1H, d, *J* 15.0, ArC*H*=CHI), 7.02 (1H, d, *J* 15.0, ArCH=C*H*I); δ_C (101 MHz, $CDCl_3$) 156.0 (C, d, J_{CF} 250.0), 132.4 (CH, d, J_{CF} 5.0), 130.2 (CH, d, J_{CF} 8.0), 129.2 (CH, d, J_{CF} 3.0), 125.0 (C, d, J_{CF} 13.5), 123.6 (CH, d, J_{CF} 3.0), 115.6 (CH, d, J_{CF} 22.5), 83.0 (CH, d, J_{CF} 1.5); δ_F (377 MHz, $CDCl_3$) –115.0 (s, Ar*F*) {^{1}H}; *m/z* (FI^+) $C_8H_6FI^+$ ($[M]^+$) requires 248.9532, found 248.9633.

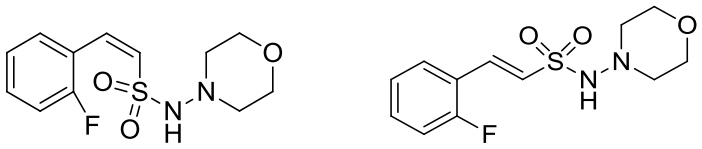
(*Z*)-1-Fluoro-2-(2-iodovinyl)-4-(trifluoromethyl)benzene 127



General procedure E was followed using 2-fluoro-5-(trifluoromethyl)benzaldehyde (0.74 mL, 5.20 mmol). Column chromatography (eluent: petrol) yielded *alkenyl iodide* **127** as a yellow oil (1.19 g, 73%, *Z*:*E*, >20:1); ν_{max} (neat)/cm^{-1} 2965, 1495, 1330, 1273, 1165, 1123, 1107, 1070; δ_H (400 MHz, $CDCl_3$) 8.16 (1H, d, *J* 5.0, Ar*H*), 7.66-7.59 (1H, m, Ar*H*), 7.39 (1H, d, *J* 9.0, ArC*H*=CHI), 7.20 (1H, app t, *J* 9.0, Ar*H*), 6.89 (1H, d, *J* 9.0,

ArCH=C*H*I); δ_C (126 MHz, $CDCl_3$) 161.5 (C, d, J_{CF} 255.5), 131.1 (CH, d, J_{CF} 4.0), 127.3 (CH, dq, J_{CF} 9.5, 4.0), 127.0 (CH, dq, J_{CF} 3.5, 3.5), 126.4 (C, qd, J_{CF} 32.5, 3.5), 126.0 (C, d, J_{CF} 15.0), 123.8 (C, q, J_{CF} 272.5), 116.4 (CH, d, J_{CF} 23.0), 85.3 (CH); δ_F (377 MHz, $CDCl_3$) –62.1 (s, ArC*F*$_3$), –109.6 (s, Ar*F*) {^{1}H}; HRMS (FI^+) $C_9H_5F_4I^+$ ($[M]^+$) requires 315.9372, found 315.9364.

(*Z*) and (*E*)-2-(2-Fluorophenyl)-*N*-(morpholin-4-yl)ethenesulfonamide 99 and 99'



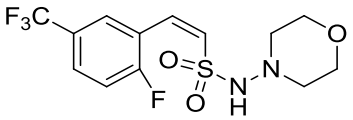
General procedure A was followed using DABSO (63 mg, 0.28 mmol), Cata*CX*ium A (17 mg, 0.05 mmol), (*Z*)-1-fluoro-2-(2-iodovinyl)benzene **112** (69 mg, 0.24 mmol, *Z*:*E*, >20:1), 4-aminomorpholine (35 µL, 0.36 mmol) and 1,4-dioxane (1.6 mL). The reaction mixture was stirred at 70 °C for 8 h. Column chromatography (eluent: 0—50%, ether in hexane) yielded, in order of elution, *alkenyl N-aminosulfonamide* **99** (31 mg, 45%) and *alkenyl N-aminosulfonamide* **99'** (8 mg, 11%), as off-white crystalline solids.

Z isomer **99**: mp 96-98 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3212, 2827, 2777, 1325, 1311, 1278, 1265, 1243, 1211, 1203, 1170, 1142, 1100, 1070, 1029, 1008; δ_H (400 MHz, $CDCl_3$) 7.95 (1H, app t, *J* 8.0, Ar*H*), 7.40 (1H, app q, *J* 8.0, Ar*H*), 7.26-7.16 (2H, m, Ar*H*, ArC*H*=CHS), 7.09 (1H, app t, *J* 8.0, Ar*H*), 6.58 (1H, d, *J* 12.0, ArCH=C*H*S), 5.43 (1H, s, N*H*), 3.72 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 2.83 (4H, br. t, *J* 4.5, N(CH_2CH_2)$_2$O); δ_C (101 MHz, $CDCl_3$) 160.5 (C, d, J_{CF} 249.5), 134.0 (CH, d, J_{CF} 5.0), 132.0 (CH, d, J_{CF} 2.0), 131.9 (CH, d, J_{CF} 8.5), 128.8 (CH), 123.9 (CH, d, J_{CF} 3.0), 120.8 (C, d, J_{CF} 13.0), 115.2 (CH, d, J_{CF} 21.0), 66.6 (2 × CH_2), 57.1 (2 × CH_2); δ_F (377 MHz, $CDCl_3$) –113.3 (s, Ar*F*) {^{1}H}; *m/z* (ESI^+) 595 ($[2M + Na]^+$, 100%), 309 ($[M + Na]^+$, 42%); *m/z* (ESI^-) 285 ($[M – H]^-$, 100%);

HRMS (ESI$^+$) $C_{12}H_{15}FN_2NaO_3S^+$ ([M + Na]$^+$) requires 309.0680, found 309.0675; Anal. Calcd. (%) for $C_{12}H_{15}FN_2O_3S$: C 50.34, H 5.28, N 9.78; found C 50.45, H 5.18, N 9.75.

E isomer **99'**: mp 137-140 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3280, 2917, 2850, 1368, 1333, 1318, 1293, 1264, 1238, 1221, 1138, 1106, 1032; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, d, *J* 15.5, ArC*H*=CHS), 7.49 (1H, app t, *J* 7.5, Ar*H*), 7.46-7.38 (1H, m, Ar*H*), 7.22 (1H, app t, *J* 7.5, Ar*H*), 7.19-7.11 (1H, m, Ar*H*), 6.99 (1H, d, *J* 15.5, ArCH=C*H*S), 5.45 (1H, s, N*H*), 3.74 (4H, t, *J* 4.5, N(C*H*$_2$CH$_2$)$_2$O), 2.89 (4H, br. t, *J* 4.5, N(CH$_2$C*H*$_2$)$_2$O); δ_C (101 MHz, $CDCl_3$) 161.7 (C, d, J_{CF} 261.5), 137.0 (CH), 132.7 (CH, d, J_{CF} 9.0), 130.5 (CH, d, J_{CF} 3.0), 126.8 (CH, d, J_{CF} 9.5), 124.9 (CH, d, J_{CF} 5.0), 120.9 (C, d, J_{CF} 11.0), 116.6 (CH, d, J_{CF} 21.5), 66.7 (2 × CH$_2$), 57.5 (2 × CH$_2$); *m/z* (ESI$^+$) 595 ([2M + Na]$^+$, 100%), 309 ([M + Na]$^+$, 42%); *m/z* (ESI$^-$) 285.1 ([M – H]$^-$, 100%); δ_F (377 MHz, $CDCl_3$) –112.6 (s, Ar*F*) {^{1}H}; HRMS (ESI$^+$) $C_{12}H_{15}FN_2NaO_3S^+$ ([M + Na]$^+$) requires 309.0680, found 309.0675.

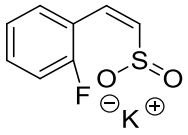
(*Z*)-2-[2-Fluoro-5-(trifluoromethyl)phenyl]-*N*-(morpholin-4-yl)ethenesulfonamide 101



General procedure A was followed using DABSO (126 mg, 0.53 mmol), Cata*CX*ium A (34 mg, 0.10 mmol), (*Z*)-1-fluoro-2-(2-iodovinyl)-4-(trifluoromethyl)benzene **127** (152 mg, 0.24 mmol, *Z*:*E*, >20:1) and 4-aminomorpholine (69 µL, 0.72 mmol). The reaction mixture was stirred at 70 °C for 6 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **101** as a pale yellow crystalline solid (38 mg, 45%, *Z*:*E*, >20:1); mp 87-89 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3200, 2963, 1635, 1499, 1459, 1329, 1287, 1259, 1208, 1105, 1073, 1015; δ_H (500 MHz, $CDCl_3$) 8.28 (1H, dd, *J* 7.0, 2.0 Ar*H*), 7.67-7.62 (1H, m, Ar*H*), 7.24-7.16 (2H, m, Ar*H*, ArC*H*=CHS), 6.58 (1H, d, *J* 12.0, ArCH=C*H*S), 5.70 (1H, s, N*H*), 3.73 (4H, t, *J* 4.5, N(CH$_2$C*H*$_2$)$_2$O), 2.88

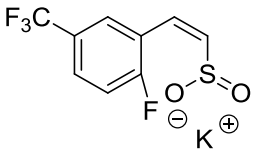
(4H, br. t, *J* 4.5, N(C*H*$_2$CH$_2$)$_2$O); δ_C (126 MHz, $CDCl_3$) 162.0 (C, d, J_{CF} 255.5), 132.8 (CH, d, J_{CF} 4.0), 130.1 (CH), 129.9 (CH, app quin, J_{CF} 4.0), 128.8 (CH, dq, J_{CF} 9.5, 4.0), 126.4 (CH, qd, J_{CF} 30.0, 4.0), 123.7 (C, q, J_{CF} 272.5), 121.3 (C, d, J_{CF} 14.5), 115.9 (CH, d, J_{CF} 23.0), 66.6 (2 × CH_2), 57.4 (2 × CH_2); δ_F (377 MHz, $CDCl_3$) –61.8 (s, ArC*F*$_3$), –107.9 (s, Ar*F*) {^{1}H}; *m/z* (ESI$^+$) 731 ([2M + Na], 98%), 377 ([M + Na]$^+$, 100%), 355 ([M + H]$^+$, 12%); *m/z* (ESI$^-$) 353 ([M – H]$^-$, 100%); HRMS (ESI$^+$) $C_{13}H_{14}F_4N_2NaO_3S^+$ ([M + Na]$^+$) requires 377.0553, found 377.0544.

Potassium (*Z*)-2-(2-fluorophenyl)ethenesulfinate 100



Benzyl bromide (11 μL, 0.09 mmol) was added to a stirred solution of (*Z*)-2-(2-fluorophenyl)-*N*-(morpholin-4-yl)ethenesulfonamide **99** (29 mg, 0.10 mmol, *Z*:*E*, >20:1) and K_2CO_3 (28 mg, 0.20 mmol) in 1,4-dioxane (0.7 mL). The reaction mixture was stirred at 50 °C for 1 h, then 100 °C for 16 h. The reaction mixture was cooled to RT and then filtered. The filtrate was concentrated *in vacuo* to yield hydrazone **14** (15 mg, 79%). The off-white solid residue contained the *sulfinate salt* **100**; ν_{max} (neat)/cm^{-1} 3347, 1636, 1483, 1352, 1233, 1097, 1010; δ_H (400 MHz, MeOD) 7.76 (1H, app td, *J* 8.0, 1.0, Ar*H*), 7.35-7.28 (1H, m, Ar*H*), 7.15 (1H, app td, *J* 8.0, 1.0, Ar*H*), 7.11-7.04 (1H, m, Ar*H*), 6.79 (1H, d, *J* 11.5, ArCH=C*H*S), 6.24 (1H, d, *J* 11.5, ArC*H*=CHS); ^{13}C NMR not obtained due to insufficient material; δ_F (377 MHz, $CDCl_3$) –117.7 (s, Ar*F*) {^{1}H}; *m/z* (ESI$^-$) 185 ([M – K]$^-$, 100%).

Potassium (*Z*)-2-[2-fluoro-5-(trifluoromethyl)phenyl]ethenesulfinate 102



Benzyl bromide (11 μL, 0.09 mmol) was added to a stirred solution of (*Z*)-2-[2-fluoro-5-(trifluoromethyl)phenyl]-*N*-(morpholin-4-yl)ethenesulfonamide **101** (35 mg, 0.10 mmol, *Z*:*E*, >20:1) and K_2CO_3 (28 mg, 0.20 mmol) in 1,4-dioxane (0.7 mL). The reaction mixture was stirred at 50 °C for 1 h, then 100 °C for 16 h. The reaction mixture was cooled to RT and then filtered. The filtrate was concentrated *in vacuo* to yield hydrazone **14** (16 mg, 85%). The off-white solid residue contained *sulfinate salt* **102**; ν_{max} (neat)/cm^{-1} 3333, 2953, 1635, 1604, 1487, 1350, 1111, 1010; δ_H (200 MHz, D_2O) 7.83-7.73 (1H, m, Ar*H*), 7.69-7.55 (1H, m, Ar*H*), 7.22 (1H, app t, *J* 9.0, Ar*H*), 6.84 (1H, d, *J* 11.0, ArC*H*=CHS), 6.26 (1H, d, *J* 11.0, ArCH=C*H*S); ^{13}C NMR not obtained due to insufficient material; δ_F (377 MHz, $CDCl_3$) –68.0 (s, ArCF_3), –111.8 (s, Ar*F*); *m/z* (ESI^-) 253 ($[M - K]^-$, 100%); HRMS (ESI^-) $C_9H_5F_4O_2S^-$ ($[M - K]^-$) requires 253.9952, found 253.9948.

6.4 Synthesis of benzosultam: Ar-N-SO_2 linkage

6.4.1 Decomposition products

1-Fluoro-2-vinylbenzene 123

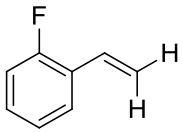


Table 3.13, entry 7: Cs_2CO_3 (68 mg, 0.21 mmol) was added to a solution of (*Z*)-2-(2-fluorophenyl)-*N*-(morpholin-4-yl)ethenesulfonamide **99** (20 mg, 0.07 mmol, *Z*:*E*, >20:1) in

DMSO (0.5 mL). The reaction mixture was stirred at 150 °C for 24 h. After cooling to RT, the reaction mixture was poured into $HCl_{(aq)}$ (5 mL, 1 M) and extracted with EtOAc (10 mL). The organic layer was washed with brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: 1:1, ether:petrol) yielded styrene **123** as a pale yellow oil (6 mg, 81%); ν_{max} (neat)/cm^{-1} 3010, 2925, 2853, 1604, 1455, 1235, 1097; δ_H (500 MHz, $CDCl_3$) 7.39 (1H, dd, *J* 8.0, 1.5, Ar*H*), 7.15 (1H, app td, *J* 8.0, 1.5, Ar*H*), 6.94 (2H, app s, 2 × Ar*H*), 6.82-6.79 (1H, m, ArC*H*=CH_2), 5.75 (1H, dd, *J* 17.5, 1.5, ArCH=C$H_{trans}H_{cis}$), 5.37 (1H, dd, *J* 11.0, 1.5, ArCH=$CH_{trans}H_{cis}$); δ_C (126 MHz, $CDCl_3$) 152.8 (C, d, J_{CF} 240.5), 131.5 (CH, d, J_{CF} 5.5), 128.9 (CH, d, J_{CF} 9.5), 127.4 (CH, d, J_{CF} 2.5), 124.8 (C, d, J_{CF} 3.0), 120.9 (CH), 115.9 (CH_2), 115.8 (CH, d, J_{CF} 20.5); δ_F (126 MHz, $CDCl_3$) –116.0 (s, Ar*F*) {^{1}H}; *m/z* (FI$^+$) $C_8H_7F^+$ ([M]$^+$) requires 122.0532, found 122.0535. Data in accordance with literature data.[319]

1-Bromo-2-vinylbenzene 126

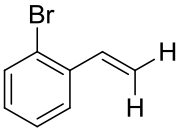


Table 3.14, entry 4: K_2CO_3 (32 mg, 0.23 mmol), copper iodide (4 mg, 0.02 mmol) and *N*,*N*-dimethylethylenediamine (14 µL, 0.01 mmol) were added to a solution of (*Z*)-2-(2-bromophenyl)-*N*-(morpholin-4-yl)ethenesulfonamide **118** (40 mg, 0.12 mmol, *Z*:*E*, >20:1) in toluene (0.8 mL). The reaction mixture was stirred at 110 °C for 24 h. After cooling to RT, the reaction mixture was filtered through a short pad of Celite and washed sequentially with CH_2Cl_2 (5 mL) and ether (5 mL) before being concentrated *in vacuo*. Column chromatography (eluent: 1:1, ether:petrol) yielded styrene **126** as a pale yellow oil (18 mg, 83%); ν_{max} (neat)/cm^{-1} 3055, 3030, 2920, 1458, 1256, 1013; δ_H (200 MHz, $CDCl_3$) 7.56 (2H, d, *J* 8.0, 2 × Ar*H*), 7.34-6.96 (3H, m, 2 × Ar*H*, ArC*H*=CH_2), 5.71 (1H, dd, *J* 17.5, 1.0,

ArCH=CH_{trans}H$_{cis}$), 5.37 (1H, dd, *J* 11.0, 1.0, ArCH=CH$_{trans}$$H_{cis}$); δ_C (101 MHz, $CDCl_3$) 138.2 (C), 136.6 (CH), 132.2 (CH), 129.0 (CH), 128.7 (CH), 127.2 (CH), 124.4 (C), 116.3 (CH_2); *m/z* (FI^+) $C_8H_7Br^+$ ($[M]^+$) requires 183.9711 and 181.9731, found 183.9711 and 181.9727. ^{1}H data in accordance with literature data.[320]

2-Vinylaniline 117

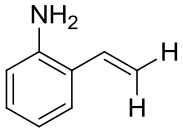
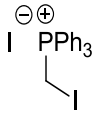


Table 3.1, entry 2: General procedure A was followed using Cata*CX*ium A (17 mg, 0.05 mmol), 2-iodovinylaniline **114** (59 mg, 0.24 mmol, *Z*:*E*, 11:1), DABSO (63 mg, 0.26 mmol) and 4-aminomorpholine (35 μL, 0.36 mmol). The reaction mixture was stirred at 90 °C for 24 h. Column chromatography (eluent: 1:1, ether:petrol) yielded styrene **117** as a pale yellow oil (25 mg, 87%); ν_{max} (neat)/cm^{-1} 3443, 3367, 3060, 3031, 1626, 1491, 1455, 1421, 1362, 1304, 1258, 1196, 1157, 1064, 1021; δ_H (400 MHz, $CDCl_3$) 7.32-7.29 (1H, m, Ar*H*), 7.11 (1H, app td, *J* 7.5, 1.5, Ar*H*), 6.87-6.65 (3H, m, 2 × Ar*H*, ArC*H*=CH_2), 5.65 (1H, dd, *J* 17.5, 1.5, ArCH=CH_{trans}H$_{cis}$), 5.33 (1H, dd, *J* 11.0, 1.5, ArCH=CH$_{trans}$$H_{cis}$), 3.76 (2H, br. s, N$H_2$); δ_C (101 MHz, $CDCl_3$) 143.6 (C), 132.7 (CH), 128.7 (CH), 127.3 (CH), 124.1 (C), 118.9 (CH), 116.1 (CH), 115.7 (CH_2); *m/z* (FI^+) $C_8H_9N^+$ ($[M]^+$) requires 119.0735, found 119.0732. Data in accordance with literature data.[321]

6.4.2 Preparation of substrates and catalysts

(Iodomethyl)triphenylphosphonium iodide 113[185]

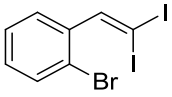


A solution of triphenylphosphine (10.0 g, 38.1 mmol) and diiodomethane (4.0 mL, 49.6 mmol) in toluene (10 mL) was stirred at 50 °C for 48 h. The reaction mixture was cooled to RT and filtered. The precipitate was washed with toluene (25 mL) and ether (25 mL) sequentially, then dried under vacuum to yield (iodomethyl)triphenylphosphonium iodide **113** as a white powder (20.2 g, 99%); mp 232-235 °C (IPA) {lit.[322] 231-233 °C}; δ_H (400 MHz, $(CD_3)_2SO$) 7.98-7.72 (15H, m, 15 × Ar*H*), 5.05 (2H, d, J_{HP} 9.0, C*H*$_2$I); δ_C (101 MHz, $(CD_3)_2SO$) 136.1 (3 × CH, d, J_{CP} 3.0), 134.7 (6 × CH, d, J_{CP} 11.0), 131.1 (6 × CH, d, J_{CP} 13.0), 119.2 (3 × C, d, J_{CP} 88.0), -14.1 (CH_2, d, J_{CP} 51.0); *m/z* (ESI^+) 403.0 ($[M - I]^+$, 100%). Data in accordance with literature data.[186]

bis(Acetonitrile) palladium(II) _p_-toluenesulfonate $(MeCN)_2Pd(OTs)_2$ 120[48]

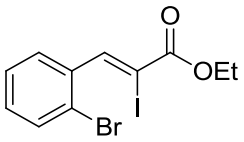
A solution of *p*-toluenesulfonic acid monohydrate (0.30 g, 1.58 mmol) in acetonitrile (3.8 mL) was heated over 3 Å molecular sieves for 10 min at 50 °C. This solution was added dropwise with stirring to a solution of $Pd(OAc)_2$ (66 mg, 0.30 mmol) in acetonitrile (5.7 mL). A colour change was observed from orange to pale yellow. Ether (7 mL) was added which resulted in precipitation of a yellow crystalline solid and the suspension was left for 1 h. The supernatant liquid was decanted and the crystals were washed with ether and dried under vacuum to give **120** as a yellow solid (140 mg, 90%); ν_{max} (neat)/cm^{-1} 3007, 2928, 2337, 1671, 1596, 1555, 1494, 1466, 1409, 1360, 1348, 1283, 1204, 1177, 1143, 1124, 1097, 1035; δ_H (400 MHz, $(CD_3)_2SO$) 7.57-7.45 (4H, m, 4 × Ar*H*), 7.23-7.05 (4H, m, 4 × Ar*H*), 2.31 (6H, s, 2 × Ar*Me*), 2.10 (6H, s, 2 × *Me*CN); δ_C (101 MHz, $(CD_3)_2SO$) 146.4 (2 × C), 138.7 (2 × C), 129.0 (4 × CH), 126.4 (4 × CH), 116.7 (2 × C), 21.7 (2 × CH_3), 2.00 (2 × CH_3); Anal. Calcd. (%) for $C_{18}H_{20}N_2O_6PdS_2$: C, 40.72; H, 3.80; N, 5.28; found: C, 39.48; H, 3.64; N, 5.10. Data in accordance with literature data.[48]

1-Bromo-2-(2,2-diiodovinyl)benzene 169[323]



A solution of tri*iso*propyl phosphite (6.8 mL, 27.5 mmol) in CH_2Cl_2 (10 mL) was added over 1 h to a solution of 2-bromobenzaldehyde (1.5 mL, 12.5 mmol) and carbon tetraiodide (9.74 g, 18.8 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was warmed to RT and stirred for 2 h before being cooled to 0 °C and slowly quenched with sat. $NaHCO_{3(aq)}$ (30 mL). The reaction mixture was diluted with water (30 mL) and the organic phase extracted. The organic phase was washed with $Na_2S_2O_{3(aq)}$ (50 mL) and then brine (50 mL) before being dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: petrol) yielded the *alkene* **169** as a yellow oil (1.39 g, 26%); ν_{max} (neat)/cm^{-1} 2921, 2360, 1560, 1460, 1435, 1252, 1044, 1026; δ_H (200 MHz, $CDCl_3$) 8.08 (1H, s, ArC*H*=CI_2), 7.59 (1H, dd, *J* 87.5, 1.5, Ar*H*), 7.51-7.42 (1H, m, Ar*H*), 7.35 (1H, app td, *J* 7.5, 1.5, Ar*H*), 7.25 (1H, app td, *J* 7.5, 1.5, Ar*H*); δ_C (101 MHz, $CDCl_3$) 151.0 (CH), 140.7 (C), 132.7 (CH), 130.2 (CH), 129.9 (CH), 127.3 (CH), 122.2 (C), 16.4 (C); HRMS (FI^+) $C_8H_5BrI_2^+$ ($[M]^+$) requires 433.7664, found 433.7670.

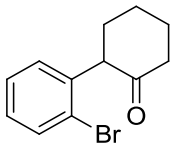
Ethyl 3-(2-bromophenyl)-2-iodoacrylate 170[211]



(Ethoxycarbonylmethyl)triphenylphosphonium bromide salt (2.58 g, 6.00 mmol) was dissolved in methanol (100 mL) and cooled to –5 °C. Iodine (3.00 g, 12.0 mmol) and K_2CO_3 (414 mg, 3.00 mmol) were added and stirred for 1.5 h at a temperature between –5 °C and 5 °C. 2-Bromobenzaldehyde (60 μL, 5.20 mmol), TBAB (84 mg, 0.26 mmol) and K_2CO_3 (116 mg, 0.84 mmol) were then added. The reaction mixture was stirred at 40 °C

and after 2 h K_2CO_3 (116 mg, 0.84 mmol) was added, this was repeated after another 2 h. The reaction mixture was stirred at 40 °C for a further 16 h. The reaction mixture was concentrated *in vacuo*. Column chromatography (eluent: 20:1, hexane:EtOAc) yielded *alkenyl iodide* **170** as a yellow oil (971 mg, 49%, *Z*:*E*, 12:1); ν_{max} (neat)/cm^{-1} 2981, 1713, 1609, 1462, 1462, 1433, 1366, 1230, 1200, 1094, 1028; δ_H (400 MHz, $CDCl_3$, *Z* isomer) 8.23 (1H, s, ArC*H*=CICO), 7.67-7.61 (2H, m, Ar*H*), 7.39 (1H, app t, *J* 7.5 Ar*H*), 7.27 (1H, app td, *J* 7.5, 1.5, Ar*H*), 4.37 (2H, q, *J* 7.0, OC$H_2$$CH_3$), 1.40 (3H, t, *J* 7.0, OCH_2CH_3); δ_H (400 MHz, $CDCl_3$, *E* isomer observable peaks) 8.29 (1H, s, ArC*H*=CICO), 7.46-7.42 (1H, m, Ar*H*); δ_C (101 MHz, $CDCl_3$) 163.2 (C), 148.1 (CH), 137.3 (C), 132.7 (CH), 130.7 (CH), 130.3 (CH), 127.0 (CH), 123.5 (C), 96.0 (C), 63.2 (CH_2), 14.3 (CH_3); HRMS (FI^+) $C_{11}H_{10}BrIO_2^+$ ([M^+]) requires 381.8889 and 379.8909, found 381.8839 and 379.8928.

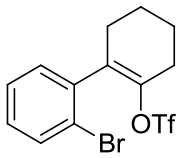
2-(2-Bromophenyl)cyclohexanone 172[213]



Cs_2CO_3 (9.10 g, 28.0 mmol), $Pd_2(dba)_3$ (58 mg, 0.06 mmol) and Xantphos (88 mg, 0.15 mmol) were added to a reaction flask. 1-Bromo-2-iodobenzene (1.6 mL, 12.7 mmol), cyclohexanone (2.7 mL, 25.5 mmol) and then 1,4-dioxane (13 mL) were added. The resulting suspension was stirred at 80 °C for 24 h. The reaction mixture was cooled to RT and then partitioned between ether (50 mL) and water (50 mL). The aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Column chromatography (eluent: 9:1, petrol:ether) yielded ketone **172** (2.31 g, 72%) as a white crystalline solid; mp 55-56 °C (CH_2Cl_2) {lit.[324] 57-58 °C}; δ_H (400 MHz, $CDCl_3$) 7.56 (1H, dd, *J* 8.0, 1.0, Ar*H*), 7.31 (1H, app dt, *J* 7.5, 1.5, Ar*H*), 7.21 (1H, dd, *J* 7.5, 1.5, Ar*H*), 7.15-7.10 (1H, m, Ar*H*),

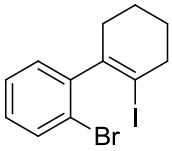
4.11 (1H, dd, *J* 12.5, 5.0, COC*H*Ar), 2.58-2.52 (2H, m, CH_2), 2.32-2.16 (2H, m, CH_2), 2.09-1.73 (4H, m, 2 × CH_2); δ_C (101 MHz, $CDCl_3$) 208.5 (C), 138.4 (C), 132.7 (CH), 129.5 (CH), 128.5 (CH), 127.4 (CH), 125.2 (C), 56.7 (CH), 42.5 (CH_2), 34.3 (CH_2), 27.2 (CH_2), 25.7 (CH_2); *m/z* (ESI^+) 529 ($[2M + Na]^+$, 100%), 527 ($[2M + Na]^+$, 50%). Data in accordance with the literature data.[213]

2'-Bromo-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate 173[214]



A solution of 2-(2-bromophenyl)cyclohexanone **172** (1.06 g, 4.20 mmol) in DMF (3.5 mL) was added slowly to a suspension of sodium hydride (0.32 g, 7.98 mmol, 60% in mineral oil) in DMF (10 mL) at RT. The reaction mixture was stirred for 2 h at RT under N_2. *N*-Phenyl *bis*(trifluoromethanesulfonimide) (1.70 g, 4.83 mmol) was added in one portion to the yellow solution. The reaction mixture was stirred at RT overnight and then diluted with ether, washed with sat. $NH_4Cl_{(aq)}$ (80 mL), H_2O (50 mL) and then brine (2 × 50 mL), and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: hexane: EtOAc, 20:1) yielded *triflate* **173** as a colourless oil (836 mg, 52%); ν_{max} (neat)/ cm^{-1} 3020, 2923, 1415, 1207; δ_H (400 MHz, $CDCl_3$) 7.61-7.57 (1H, m, Ar*H*), 7.34-7.30 (1H, m, Ar*H*), 7.19 (1H, d, *J* 7.5, Ar*H*), 7.20-7.15 (1H, m, Ar*H*), 2.62-2.52 (1H, m, C*H*), 2.51-2.45 (2H, m, CH_2), 2.32-2.22 (1H, m, C*H*), 1.95-1.87 (2H, m, CH_2), 1.83-1.76 (2H, m, CH_2); δ_C (101 MHz, $CDCl_3$) 144.5 (C), 137.8 (C), 132.8 (CH), 131.1 (C), 130.1 (CH), 129.5 (CH), 127.4 (CH), 122.4 (C), 30.6 (CH_2), 27.6 (CH_2), 22.9 (CH_2), 21.8 (CH_2), (OTf not observed); δ_F (377 MHz, $CDCl_3$) –75.3 (s, O*Tf*) {^{1}H}; HRMS (FI^+) $C_{13}H_{12}BrF_3O_3S^+$ ($[M]^+$) requires 385.9622 and 383.9643, found 385.9651 and 383.9647.

2'-Bromo-6-iodo-2,3,4,5-tetrahydro-1,1'-biphenyl 174[215]



Triethylamine (111 mL, 0.79 mmol) was added to a solution of 2'-bromo-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate **173** (260 mg, 0.67 mmol) and magnesium iodide (560 mg, 2.01 mmol) in cyclohexane (40 mL). The reaction mixture was stirred at reflux for 20 h and then cooled to RT. Ether (30 mL) was added and then washed with sat. $NaHSO_{3(aq)}$, H_2O and then dried over $MgSO_4$, filtered and concentrated in *vacuo*. Column chromatography (eluent: petrol) yielded *alkenyl iodide* **174** as a colourless oil (85 mg, 35%); ν_{max} (neat)/cm^{-1} 2930, 2857, 2830, 1467, 1432, 1325, 1256, 1172, 1136, 1110, 1074, 1049, 1025; δ_H (400 MHz, $CDCl_3$) 7.58 (1H, dd, *J* 7.5, 1.0, Ar*H*), 7.31 (1H, app td, *J* 7.5, 1.0, Ar*H*), 7.15 (1H, app td, *J* 7.5, 1.5, Ar*H*), 7.07 (1H, dd, *J* 7.5, 1.5, Ar*H*), 2.83-2.73 (2H, m, CH_2), 2.55-2.44 (1H, m, C*H*), 2.27-2.17 (1H, m, C*H*), 1.90-1.72 (4H, m, 2 × CH_2); δ_C (101 MHz, $CDCl_3$) 147.3 (C), 144.3 (C), 132.8 (CH), 129.8 (CH), 128.8 (CH), 127.7 (CH), 122.2 (C), 100.8 (C), 40.8 (CH_2), 32.7 (CH_2), 25.5 (CH_2), 22.7 (CH_2); HRMS (FI^+) $C_{12}H_{12}BrI^+$ ($[M]^+$) requires 363.9147 and 361.9167, found 363.9186 and 361.9167.

6.4.3 Alkenyl iodide synthesis

(*Z*)-1-Bromo-2-(2-iodovinyl)benzene 110

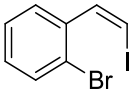
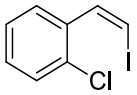


Table 3.17, entry 1: General procedure E was followed using 2-bromobenzaldehyde (0.55 mL, 4.71 mmol). Column chromatography (eluent: hexane) yielded *alkenyl iodide*

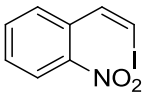
110 as a yellow oil (1.09 g, 75%, *Z*:*E*, >20:1); ν_{max} (neat)/cm^{-1} 3057, 2887, 1478, 1311, 1110; δ_H (400 MHz, $CDCl_3$, *Z* isomer) 7.65 (1H, d, *J* 8.0, Ar*H*) overlapping 7.61 (1H, d, *J* 8.0, Ar*H*), 7.39-7.33 (2H, m, Ar*H*, ArC*H*=CHI), 7.22 (1H, app t, *J* 8.0, Ar*H*), 6.75 (1H, d, *J* 8.0, ArCH=C*H*I); δ_H (400 MHz, $CDCl_3$, *E* isomer observable peaks) 7.77 (1H, d, *J* 15.0, ArC*H*=CHI), 6.87 (1H, d, *J* 15.0, ArCH=C*H*I); δ_C (101 MHz, $CDCl_3$) 139.2 (CH), 137.7 (C), 132.8 (CH), 130.3 (CH), 129.8 (CH), 127.0 (CH), 123.5 (C), 83.8 (CH); *m/z* (FI^+) $C_8H_6BrI^+$ ($[M]^+$) requires 309.8677 and 307.8698, found 309.8667 and 307.8697.

(*Z*)-1-Chloro-2-(2-iodovinyl)benzene 111



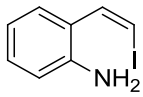
General procedure E was followed using 2-chlorobenzaldehyde (0.53 mL, 4.71 mmol). Column chromatography (eluent: hexane) yielded *alkenyl iodide* **111** as a yellow oil (1.00 g, 81%, *Z*:*E*, >20:1); ν_{max} (neat)/cm^{-1} 3059, 2967, 1464, 1439, 1430, 1302, 1274, 1156, 1126, 1093, 1047, 1033; δ_H (200 MHz, $CDCl_3$, *Z* isomer) 7.75-7.64 (1H, m, Ar*H*), 7.46-7.36 (2H, m, Ar*H*, ArC*H*=CHI), 7.34-7.27 (2H, m, 2 × Ar*H*), 6.76 (1H, d, *J* 8.5, ArCH=C*H*I); δ_H (200 MHz, $CDCl_3$, *E* isomer observable peaks) 7.83 (1H, d, *J* 15.0, ArC*H*=CHI), 7.56-7.50 (2H, m, 2 × Ar*H*), 6.92 (1H, d, *J* 15.0, ArCH=C*H*I); δ_C (101 MHz, $CDCl_3$) 136.8 (CH), 135.7 (C), 133.4 (C), 129.9 (CH), 129.5 (CH), 126.7 (CH), 126.3 (CH), 83.8 (CH); *m/z* (FI^+) $C_8H_6ClI^+$ ($[M]^+$) requires 265.9174 and 263.9203, found 265.9175 and 263.9210.

(*Z*)-1-(2-Iodovinyl)-2-nitrobenzene 115



General procedure E was followed using 2-nitrobenzaldehyde (0.71 g, 4.71 mmol). Column chromatography (eluent: 3:1, petrol:EtOAc) yielded alkenyl iodide **115** as a pale yellow solid (1.17 g, 90%, *Z*:*E*, >20:1); mp 50-51 °C (MeOH) {lit.[325] 52-54 °C (MeOH)}; δ_H (400 MHz, $CDCl_3$) 8.13 (1H, dd, *J* 8.0, 1.0, Ar*H*), 7.76-7.48 (4H, m, 3 × Ar*H*, ArC*H*=CHI), 6.77 (1H, d, *J* 8.5, ArCH=C*H*I); δ_C (101 MHz, $CDCl_3$) 147.1 (C), 137.2 (CH), 133.7 (C), 133.4 (CH), 131.6 (CH), 129.1 (CH), 124.7 (CH), 84.5 (CH); *m/z* (FI^+) $C_8H_6INO_2^+$ ($[M]^+$) requires 274.9443, found 274.9447. Data in accordance with literature data.[325]

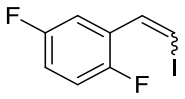
2-Iodovinylaniline 114[326]



$SnCl_2.2H_2O$ (1.64 g, 7.30 mmol) was added to a solution of 2-iodovinyl-2-nitrobenzene **115** (0.50 g, 1.81 mmol) in ethanol (50 mL). The suspension was stirred at reflux for 45 min and then cooled to RT. The reaction mixture was concentrated *in vacuo* and EtOAc (50 mL) and H_2O (50 mL) were added. Potassium carbonate was added carefully until the mixture was pH > 10. The organic layer was separated, and the aqueous phase was extracted with EtOAc (5 × 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (eluent: 9:1, hexane:EtOAc) yielded *alkenyl iodide* **114** as an orange oil (0.24 g, 54%, *Z*:*E*, 11:1); ν_{max} (neat)/cm^{-1} 3444, 3365, 3057, 2968, 1614, 1572, 1486, 1454, 1392, 1296, 1273, 1223, 1198, 1156, 1136, 1031; δ_H (400 MHz, $CDCl_3$, *Z* isomer) 7.31 (1H, d, *J* 7.5, Ar*H*), 7.22 (1H, d, *J* 8.0, ArC*H*=CHI), 7.17 (1H, app td, *J* 7.5, 1.5, Ar*H*), 6.82 (1H, app td, *J* 7.5, 1.5, Ar*H*), 6.73 (2H, app d, *J* 8.0, ArCH=C*H*I, Ar*H*), 3.66 (2H, br. s, N*H*); δ_H (400 MHz, $CDCl_3$, *E* isomer observable peaks) 7.50 (1H, d, *J* 15.0, ArC*H*=CHI); δ_C (101 MHz,

$CDCl_3$, *Z* isomer) 143.5 (C), 136.5 (CH), 129.4 (CH), 128.9 (CH), 123.6 (C), 118.2 (CH), 115.7 (CH), 84.9 (CH); *m/z* (FI^+) $C_8H_8NI^+$ ($[M]^+$) requires 244.9702, found 244.9702.

1,4-Difluoro-2-(2-iodovinyl)benzene 214



General procedure E was followed using 2,5-difluorobenzaldehyde (1.02 mL, 9.40 mmol). Column chromatography (eluent: petrol) yielded *alkenyl iodide* **214** as a pale yellow oil (1.85 g, 74%, *Z*:*E*, 4:1); ν_{max} (neat)/cm^{-1} 2965, 1480, 1428, 1282, 1245, 1191, 1128, 1086; δ_H (500 MHz, $CDCl_3$, *Z* isomer) 7.67-7.59 (1H, m, Ar*H*), 7.36 (1H, d, *J* 9.0, ArC*H*=CHI), 7.09-7.00 (2H, m, 2 × Ar*H*), 6.81 (1H, d, *J* 9.0, ArCH=C*H*I); δ_H (500 MHz, $CDCl_3$, *E* isomer observable peaks) 7.50 (1H, d, *J* 15.0, ArC*H*=CHI), 7.07-7.06 (1H, m, Ar*H*); δ_C (126 MHz, $CDCl_3$, *Z* isomer) 158.0 (C, dd, J_{CF} 253.5, 2.5), 156.0 (C, dd, J_{CF} 256.6, 2.5), 131.3 (CH, m), 126.3 (C, dd, J_{CF} 16.0, 8.5), 116.7 (CH, dd, J_{CF} 44.0, 9.0) overlapping 116.5 (CH, dd, J_{CF} 9.0, 5.0), 115.4 (CH, dd, J_{CF} 25.5, 3.0), 84.2 (CH, d, J_{CF} 2.0); δ_C (126 MHz, $CDCl_3$, *E* isomer) 158.7 (C, dd, J_{CF} 243.0, 2.5), 155.7 (C, dd, J_{CF} 246.5, 1.5), 137.0 (CH, app t, J_{CF} 2.5), 126.6 (C, dd, J_{CF} 15.0, 8.0), 117.2 (CH, dd, J_{CF} 25.0, 8.5), 116.2 (CH, dd, J_{CF} 24.0, 8.5), 113.6 (CH, dd, J_{CF} 24.5, 3.5), 81.7 (CH, d, J_{CF} 2.0); δ_F (377 MHz, $CDCl_3$, *Z* isomer) –118.4 (d, *J* 17.0, Ar*F*), –121.0 (d, *J* 17.0, Ar*F*) $\{^1H\}$; δ_F (377 MHz, $CDCl_3$, *E* isomer) –118.0 (d, *J* 17.0, Ar*F*), –120.1 (d, *J* 17.0, Ar*F*) $\{^1H\}$; HRMS (FI^+) $C_8H_5F_2I^+$ ($[M]^+$) requires 265.9404, found 265.9401.

5-Bromo-6-(2-iodovinyl)benzo[*d*][1,3]dioxole 129

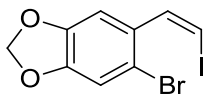


Table 3.17, entry 2: General procedure E was followed using 6-bromo-1,3-benzodioxole-5-carboxaldehyde (2.16 g, 9.42 mmol). Column chromatography (eluent: 2.5% ether in

petrol) yielded *alkenyl iodide* **129** as a white crystalline solid (2.62 g, 79%, *Z*:*E*, 15:1); mp 61-62 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2895, 1500, 1474, 1409, 1335, 1295, 1248, 1230, 1178, 1152, 1104, 1038; δ_H (400 MHz, $CDCl_3$) 7.26 (1H, d, *J* 8.5, ArC*H*=CHI), 7.20 (1H, s, Ar*H*), 7.06 (1H, s, Ar*H*), 6.64 (1H, d, *J* 8.5, ArCH=C*H*I), 6.03 (2H, s, OCH_2O); δ_C (101 MHz, $CDCl_3$) 148.3 (C), 146.8 (C), 138.7 (CH), 130.5 (C), 114.8 (C), 112.7 (CH), 109.6 (CH), 102.0 (CH_2), 82.7 (CH); HRMS (FI^+) $C_9H_6BrIO_2^+$ ($[M]^+$) requires 351.8596, found 351.8587.

1-Bromo-2-(2-iodovinyl)-4,5-dimethoxybenzene 130

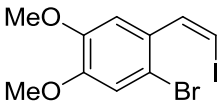


Table 3.17, entry 3: General procedure E was followed using 6-bromoveratraldehyde (1.00 g, 4.08 mmol). Column chromatography (eluent: 3:7, ether:petrol) yielded *alkenyl iodide* **130** as a white crystalline needles (1.01 g, 67%, *Z*:*E*, 15:1); mp 70-71 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3080, 2994, 2927, 2839, 1596, 1564, 1498, 1463, 1449, 1433, 1381, 1327, 1292, 1265, 1209, 1172, 1149, 1041, 1026; δ_H (400 MHz, $CDCl_3$) 7.33 (1H, s, Ar*H*), 7.31 (1H, d, *J* 8.5, ArC*H*=CHI), 7.05 (1H, s, Ar*H*), 6.61 (1H, d, *J* 8.5, ArCH=C*H*I), 3.91 (3H, s, O*Me*), 3.88 (3H, s, O*Me*); δ_C (101 MHz, $CDCl_3$) 149.6 (C), 147.7 (C), 138.4 (CH), 129.1 (C), 115.3 (CH), 114.5 (C), 112.4 (CH), 81.7 (CH), 56.3(0) (CH_3), 56.2(6) (CH_3); HRMS (FI^+) $C_{10}H_{10}BrIO_2^+$ requires 369.8889 and 367.8909, found 369.8904 and 367.8921.

4-(Benzyloxy)-1-bromo-2-(2-iodovinyl)benzene 131

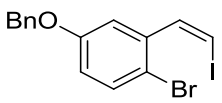


Table 3.17, entry 4: General procedure E was followed using 5-benzyloxy-2-bromobenzaldehyde (1.57 g, 5.40 mmol). Column chromatography (eluent: 2.5% ether in

petrol) yielded *alkenyl iodide* **131** as white crystalline solid (1.60 g, 72%, *Z*:*E*, 15:1); mp 42-45 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3062, 3030, 2987, 2932, 2879, 1613, 1585, 1495, 1472, 1461, 1391, 1307, 1281, 1234, 1182, 1141, 1079, 1035, 1010; δ_H (400 MHz, $CDCl_3$) 7.49-7.29 (8H, m, ArC*H*=CHI, 7 × Ar*H*), 6.87 (1H, dd, *J* 9.0, 3.0, Ar*H*), 6.73 (1H, d, *J* 8.5, ArCH=C*H*I), 5.11 (2H, s, ArCH_2O); δ_C (101 MHz, $CDCl_3$) 157.6 (C), 139.0 (CH), 138.2 (C), 136.6 (C), 133.5 (CH), 128.8 (2 × CH), 128.3 (CH), 127.6 (2 × CH), 117.2 (CH), 116.2 (CH), 114.3 (C), 83.6 (CH), 70.5 (CH_2); HRMS (FI^+) $C_{15}H_{12}BrIO^+$ ($[M]^+$) requires 415.9097 and 413.9116; found 415.9104 and 413.9114.

2-Bromo-1-(2-iodovinyl)-4-methylbenzene 132

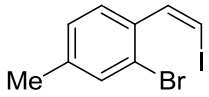


Table 3.17, entry 5: General procedure E was followed using 2-bromo-4-methylbenzaldehyde (1.88 g, 9.42 mmol). Column chromatography (eluent: petrol) yielded *alkenyl iodide* **132** as a pale yellow oil (2.13 g, 70%, *Z*:*E*, 15:1); ν_{max} (neat)/cm^{-1} 3058, 2917, 1598, 1555, 1479, 1444, 1388, 1300, 1270, 1217, 1180, 1144, 1109, 1038; δ_H (400 MHz, $CDCl_3$, *Z* isomer) 7.61 (1H, d, *J* 8.0, Ar*H*), 7.48 (1H, s, Ar*H*), 7.35 (1H, d, *J* 8.5, ArC*H*=CHI), 7.20 (1H, d, *J* 8.0, Ar*H*), 6.72 (1H, d, *J* 8.5, ArCH=C*H*I), 2.39 (3H, s, Ar*Me*); δ_H (400 MHz, $CDCl_3$, *E* isomer observable peaks) 7.76 (1H, d, *J* 15.0, ArC*H*=CHI), 6.83 (1H, d, *J* 15.0, ArCH=C*H*I); δ_C (101 MHz, $CDCl_3$, *Z* isomer) 140.2 (C), 139.0 (CH), 134.6 (C), 133.2 (CH), 129.9 (CH), 127.8 (CH), 123.4 (C), 83.1 (CH), 21.1 (CH_3); HRMS (FI^+) $C_9H_8BrI^+$ ($[M]^+$) requires 321.8854, found 321.8844.

(*Z*)-1-Bromo-2-(2-iodovinyl)naphthalene 133

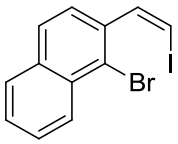


Table 3.17, entry 6: General procedure E was followed using 1-bromo-2-napthaldehyde (1.00 g, 4.30 mmol). Column chromatography (eluent: hexane) yielded *alkenyl iodide* **133** as a white crystalline solid (1.11 g, 72%, *Z*:*E*, >20:1); mp 59-61 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3150, 1550, 1496, 1348, 1327, 1296, 1256, 1230, 1151; δ_H (400 MHz, $CDCl_3$, *Z* isomer) 8.36 (1H, d, *J* 8.5, Ar*H*), 7.86-7.82 (2H, m, 2 × Ar*H*), 7.69 (1H, d, *J* 8.5, Ar*H*), 7.64-7.54 (2H, m, ArC*H*=CHI, Ar*H*) overlapping 7.61 (1H, d, *J* 8.5, Ar*H*), 6.83 (1H, d, *J* 8.5, ArCH=C*H*I); δ_H (400 MHz, $CDCl_3$, *E* isomer observable peaks) 8.11 (1H, d, *J* 15.0, ArC*H*=CHI), 7.46 (1H, d, *J* 8.5, Ar*H*), 7.00 (1H, d, *J* 15.0, ArCH=C*H*I); δ_C (101 MHz, $CDCl_3$, *Z* isomer) 140.4 (CH), 136.0 (C), 134.0 (C), 132.3 (C), 128.3 (CH), 127.6 (CH), 127.3 (2 × CH), 127.1 (2 × CH), 123.7 (C), 84.2 (CH); HRMS (FI^+) $C_{12}H_8BrI^+$ ($[M]^+$) requires 359.8835 and 357.8854, found 359.8827 and 357.8862.

(*Z*)-1-Bromo-2-(2-iodovinyl)-4-(trifluoromethyl)benzene 134

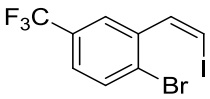


Table 3.17, entry 7: General procedure E was followed using 2-bromo-5-(trifluoromethyl)benzaldehyde (1.00 g, 3.95 mmol). Column chromatography (eluent: hexane) yielded *alkenyl iodide* **134** as a pale yellow oil (1.31 g, 88%, *Z*:*E*, >20:1); ν_{max} (neat)/cm^{-1} 3066, 1602, 1573, 1466, 1411, 1329, 1302, 1268, 1167, 1123, 1077, 1028; δ_H (400 MHz, $CDCl_3$) 7.92 (1H, d, *J* 1.5, Ar*H*), 7.74 (1H, d, *J* 8.5, Ar*H*), 7.47 (1H, dd, *J* 8.5, 1.5, Ar*H*), 7.35 (1H, d, *J* 8.5, ArC*H*=CHI), 6.88 (1H, d, *J* 8.5, ArCH=C*H*I); δ_C (126 MHz, $CDCl_3$) 149.6 (C), 138.6 (C), 138.0 (CH), 133.4 (CH), 129.7 (C, q, J_{CF} 33.0), 127.3 (CH,

q, J_{CF} 4.0), 126.2 (CH, q, J_{CF} 3.5), 123.8 (C, q, J_{CF} 271.0), 85.8 (CH); δ_F (377 MHz, $CDCl_3$) –62.7 (s, Ar*F*) {^{1}H}; HRMS (FI^+) $C_9H_5BrF_3I^+$ ($[M]^+$) 277.8551 and 375.8571, found 377.8509 and 375.8568.

(*Z*)-2-Bromo-1-fluoro-3-(2-iodovinyl)benzene 135

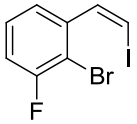


Table 3.17, entry 8: General procedure E was followed using 2-bromo-3-fluorobenzaldehyde (1.00 g, 4.92 mmol). Column chromatography (eluent: hexane) yielded *alkenyl iodide* **135** as a yellow oil (1.43 g, 89%, *Z*:*E*, >20:1); ν_{max} (neat)/cm^{-1} 3062, 1594, 1567, 1462, 1423, 1302, 1282, 1260, 1248, 1152, 1090, 1037; δ_H (400 MHz, $CDCl_3$) 7.44-7.40 (1H, m, Ar*H*), 7.35-7.29 (2H, m, Ar*H*, ArC*H*=CHI), 7.11 (1H, app td, *J* 8.5, 1.5, Ar*H*), 6.81 (1H, d, *J* 8.5, ArCH=C*H*I); δ_C (101 MHz, $CDCl_3$) 159.6 (C, d, J_{CF} 247.0), 140.0 (C), 138.3 (CH, d, J_{CF} 3.0), 128.1 (CH, d, J_{CF} 9.0), 125.6 (CH, d, J_{CF} 3.5), 116.0 (CH, d, J_{CF} 22.0), 110.4 (C, d, J_{CF} 21.0), 84.9 (CH); δ_F (377 MHz, $CDCl_3$) –104.8 (s, Ar*F*) {^{1}H}; HRMS (FI^+) $C_8H_5BrFI^+$ ($[M]^+$) requires 327.8583 and 325.8604, found 327.8585 and 325.8602.

2-Bromo-4-fluoro-1-(2-iodovinyl)benzene 136

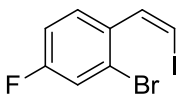


Table 3.17, entry 9: General procedure E was followed using 2-bromo-4-fluorobenzaldehyde (1.91 g, 9.43 mmol). Column chromatography (eluent: petrol) yielded *alkenyl iodide* **136** as a pale yellow oil (2.56 g, 84%, *Z*:*E*, 18:1); ν_{max} (neat)/cm^{-1} 3065, 1594, 1574, 1458, 1408, 1304, 1270, 1218, 1183, 1137, 1102, 1031; δ_H (400 MHz, $CDCl_3$)

7.63 (1H, dd, *J* 8.5, 6.0, Ar*H*), 7.35 (1H, dd, *J* 8.5, 2.5, Ar*H*), 7.27 (1H, d, *J* 8.5, ArC*H*=CHI), 7.08 (1H, app td, *J* 8.5, 3.0, Ar*H*), 6.74 (1H, d, *J* 8.5, ArCH=C*H*I); δ_C (126 MHz, $CDCl_3$) 162.0 (d, J_{CF} 252.0), 138.2, 133.9 (d, J_{CF} 3.5), 131.3 (d, J_{CF} 8.5), 132.8 (d, J_{CF} 9.5), 120.1 (d, J_{CF} 24.5), 114.4 (d, J_{CF} 21.0), 84.2; δ_F (377 MHz, $CDCl_3$) –110.9 (s, Ar*F*) {^{1}H}; HRMS (FI^+) $C_8H_5BrFI^+$ ($[M]^+$) requires 327.8583 and 325.8604, found 327.8571 and 325.8601.

(*Z*)-1-Bromo-4-fluoro-2-(2-iodovinyl)benzene 137

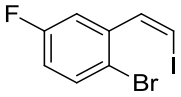


Table 3.17, entry 10: General procedure E was followed using 2-bromo-4-fluorobenzaldehyde (1.91 g, 9.43 mmol). Column chromatography (eluent: petrol) yielded *alkenyl iodide* **137** as a pale yellow oil (2.44 g, 79%, *Z*:*E*, 18:1); ν_{max} (neat)/cm^{-1} 2361, 1595, 1575, 1460, 1409, 1306, 1271, 1219, 1102, 1032; δ_H (400 MHz, $CDCl_3$) 7.56 (1H, dd, *J* 9.0, 5.5, Ar*H*), 7.41 (1H, dd, *J* 9.0, 2.5, Ar*H*), 7.30 (1H, d, *J* 9.0, ArC*H*=CHI), 6.98-6.92 (1H, m, Ar*H*), 6.82 (1H, d, *J* 9.0, ArCH=C*H*I); δ_C (101 MHz, $CDCl_3$) 161.5 (C, d, J_{CF} 246.0), 139.3 (C, d, J_{CF} 8.0), 138.3 (CH, d, J_{CF} 1.5), 134.0 (CH, d, J_{CF} 8.0), 117.7 (C, d, J_{CF} 3.0), 117.3 (CH, d, J_{CF} 23.4), 116.9 (CH, d, J_{CF} 22.5), 84.8 (C); δ_F (377 MHz, $CDCl_3$) –114.3 (s, Ar*F*) {^{1}H}; HRMS (FI^+) $C_8H_5BrFI^+$ ($[M]^+$) requires 327.8583 and 325.8604, found 327.8590 and 325.8597.

(*Z*)-2-Bromo-3-(2-iodovinyl)pyridine 138

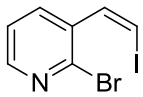


Table 3.17, entry 11: General procedure E was followed using 2-bromo-3-pyridine carboxaldehyde (1.00 g, 5.38 mmol). Column chromatography (eluent: hexane) yielded

alkenyl iodide **138** as a pale yellow crystalline solid (0.79 g, 47%, *Z*:*E*, >20:1); mp 53-56 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3064, 3001, 1566, 1556, 1547, 1447, 1383, 1310, 1247, 1183, 1157, 1115, 1049; δ_H (400 MHz, $CDCl_3$) 8.27 (1H, d, *J* 4.5, Ar*H*), 7.90 (1H, d, *J* 7.5, Ar*H*), 7.28-7.19 (2H, m, ArH, ArC*H*=CHI), 6.80 (1H, d, *J* 8.5, ArCH=C*H*I); δ_C (101 MHz, $CDCl_3$) 149.5 (CH), 142.9 (C), 138.4 (CH), 137.1 (CH), 135.0 (C), 122.4 (CH), 85.8 (CH); HRMS (FI^+) $C_7H_5BrIN^+$ ($[M]^+$) requires 310.8630 and 308.8650, found 310.8568 and 308.8651.

2-Bromo-3-(2-iodovinyl)thiophene 139

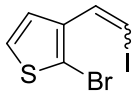


Table 3.17, entry 12: General procedure E was followed using 3-bromothiophene-2-carboxaldehyde (1.03 g, 5.40 mmol). Column chromatography (eluent: hexane) yielded *alkenyl iodide* **139** as a yellow oil (0.93 g, 55%, *Z*:*E*, 10:1); ν_{max} (neat)/cm^{-1} 3294, 3065, 2995, 1596, 1482, 1414, 1346, 1300, 1250, 1212, 1176, 1154, 1143, 1124, 1077; δ_H (400 MHz, $CDCl_3$, *Z* isomer) 7.76 (1H, dd, *J* 9.0, 0.5, ArC*H*=CHI), 7.38 (1H, d, *J* 5.5, CH=C*H*S), 7.07 (1H, d, *J* 5.5, C*H*=CHS), 6.63 (1H, d, *J* 9.0, ArCH=C*H*I); δ_H (400 MHz, $CDCl_3$, *E* isomer) 7.54 (1H, dd, *J* 15.0, 0.5, ArC*H*=CHI), 7.19 (1H, d, *J* 5.5, CH=C*H*S), 6.94 (1H, d, *J* 5.5, C*H*=CHS), 6.78 (1H, d, *J* 15.0, ArCH=C*H*I); δ_C (101 MHz, $CDCl_3$, *Z* isomer) 136.2 (C), 131.5 (CH), 130.0 (CH), 125.9 (CH), 115.2 (C), 78.8 (CH); δ_C (101 MHz, $CDCl_3$, *E* isomer observable peaks) 134.3 (CH), 130.7 (CH), 125.1 (CH); HRMS (FI^+) $C_6H_4BrIS^+$ ($[M]^+$) requires 315.8241 and 313.8262, found 315.8249 and 313.8265.

(*E*)-5-Bromo-4-(2-iodovinyl)benzo[*d*][1,3]dioxole 140

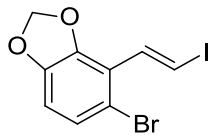


Table 3.17, entry 13: General procedure E was followed using 5-bromo-1,3-benzodioxole-4-carboxaldehyde (1.00 g, 4.37 mmol). Column chromatography (eluent: petrol) yielded *alkenyl iodide* **140** as a white crystalline solid (0.92 g, 60%, *Z*:*E*, 1:15); mp 23-25 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3088, 2894, 2779, 1574, 1496, 1446, 1428, 1399, 1339, 1309, 1239, 1214, 1189, 1156, 1123, 1101, 1053, 1021; δ_H (400 MHz, $CDCl_3$, *E* isomer) 7.64 (1H, d, *J* 15.0, ArC*H*=CHI), 7.34 (1H, d, *J* 15.0, ArCH=C*H*I), 7.03 (1H, d, *J* 8.5, Ar*H*), 6.62 (1H, d, *J* 8.5, Ar*H*), 6.03 (2H, s, OCH_2O); δ_H (400 MHz, $CDCl_3$, *Z* isomer) 7.26 (1H, d, *J* 8.5, ArC*H*=CHI), 7.07 (1H, d, *J* 8.5, ArCH=C*H*I), 6.93 (1H, d, *J* 8.5, Ar*H*), 6.70 (1H, d, *J* 8.5, Ar*H*), 6.04 (2H, s, OCH_2O); δ_C (101 MHz, $CDCl_3$, *E* isomer) 147.4 (C), 146.3 (C), 139.1 (CH), 125.7 (CH), 120.2 (C), 113.8 (C), 109.0 (CH), 102.0 (CH_2), 85.3 (CH); δ_C (101 MHz, $CDCl_3$, *Z* isomer observable peaks) 135.5 (CH), 125.1 (CH), 109.1 (CH), 101.7 (CH_2), 88.2 (CH); HRMS (FI^+) $C_9H_6BrIO_2^+$ ($[M]^+$) requires 353.8576 and 351.8596, found 353.8634 and 351.8608.

(*E*)-1-Bromo-3-fluoro-2-(2-iodovinyl)benzene 141

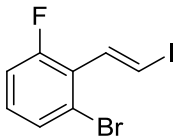
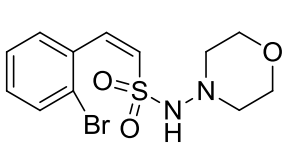
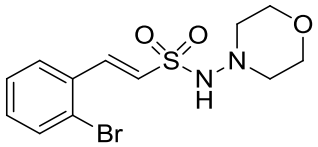


Table 3.17, entry 14: General procedure E was followed using 2-bromo-6-fluorobenzaldehyde (1.00 g, 4.92 mmol). Column chromatography (eluent: hexane) yielded *alkenyl iodide* **141** as a pale yellow oil (1.05 g, 65%, *Z*:*E*, 1:>20); ν_{max} (neat)/cm^{-1} 3094, 1597, 1582, 1561, 1453, 1431, 1318, 1271, 1246, 1206, 1188, 1165, 1133, 1067; δ_H (400 MHz, $CDCl_3$) 7.60 (1H, d, *J* 15.0, ArC*H*=CHI), 7.41 (1H, d, *J* 8.0, Ar*H*), 7.24 (1H, d,

J 15.0, ArCH=C*H*I), 7.17-7.03 (2H, m, 2 × Ar*H*); δ_C (101 MHz, $CDCl_3$) 160.9 (C, d, J_{CF} 254.5), 137.7 (CH, d, J_{CF} 2.0), 129.7 (CH, d, J_{CF} 10.0), 129.0 (CH, d, J_{CF} 3.5), 125.8 (C, d, J_{CF} 14.5), 123.6 (C, d, J_{CF} 7.0), 115.6 (CH, d, J_{CF} 24.0), 86.5 (CH, d, J_{CF} 14.0); δ_F (377 MHz, $CDCl_3$) –110.9 (s, Ar*F*) {^{1}H}; HRMS (FI^+) $C_8H_5BrFI^+$ ($[M]^+$) requires 327.8583 and 325.8604, found 327.8532 and 325.8610.

6.4.4 Alkenyl *N*-aminosulfonamide synthesis

(*Z*) and (*E*)-2-(2-Bromophenyl)-*N*-(morpholin-4-yl)ethenesulfonamide 118 and 118'

General procedure A was followed using DABSO (63 mg, 0.28 mmol), Cata*CX*ium A (17 mg, 0.05 mmol), (*Z*)-1-bromo-2-(2-iodovinyl)benzene **110** (74 mg, 0.24 mmol, *Z*:*E*, >20:1) and 4-aminomorpholine (35 µL, 0.36 mmol). The reaction mixture was stirred at 70 °C for 8 h. Column chromatography (eluent: 0—50%, ether in hexane) yielded, in order of elution, *Z isomer* **118** (42 mg, 50%) and *E isomer* **118'** (11 mg, 13%), both as off-white crystalline solids.

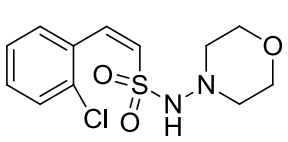
Table 3.18, entry 1: General procedure F was followed using (*Z*)-1-bromo-2-(2-iodovinyl)benzene **110** (74 mg, 0.24 mmol, *Z*:*E*, >20:1). The reaction mixture was stirred at 70 °C for 3.5 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **118** as an off-white crystalline solid (63 mg, 75%, *Z*:*E*, 12:1).

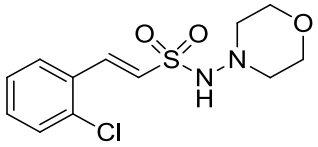
Z isomer **118**: mp 89-92 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3202, 3061, 2960, 2922, 2853, 1463, 1434, 1387, 1363, 1334, 1277, 1263, 1220, 1150, 1110, 1071, 1043, 1025; δ_H (400 MHz, $CDCl_3$) 7.89 (1H, dd, *J* 7.5, 1.5, Ar*H*), 7.61 (1H, dd, *J* 7.5, 1.5, Ar*H*), 7.41-7.31 (1H, app td, *J* 7.5, 1.5, Ar*H*), 7.31-7.21 (1H, m, Ar*H*), 7.23 (1H, d, *J* 12.0, ArC*H*=CHS),

6.57 (1H, d, *J* 12.0, ArCH=C*H*S), 5.33 (1H, s, N*H*), 3.73 (4H, t, *J* 4.5, N($CH_2C\mathit{H}_2$)$_2$O), 2.81 (4H, t, *J* 4.5, N($C\mathit{H}_2CH_2$)$_2$O); δ_C (101 MHz, $CDCl_3$) 140.3 (CH), 133.1 (C), 132.3 (CH), 132.0 (CH), 131.0 (CH), 128.4 (CH), 126.9 (CH), 123.4 (C), 66.6 (2 × CH_2), 57.2 (2 × CH_2); *m/z* (ESI^+) 719 ($[2M + Na]^+$, 60%), 717 ($[2M + Na]^+$, 100%), 715 ($[2M + Na]^+$, 50%); *m/z* (ESI^-) 383 ($[M + Cl]^-$, 100%), 381 ($[M + Cl]^-$, 77%); HRMS (ESI^+) $C_{12}H_{15}BrN_2NaO_3S^+$ ($[M + Na]^+$) requires 370.9859 and 368.9879, found 370.9855 and 368.9869.

E isomer **118'**: mp 137-140 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3196, 2963, 2922, 2856, 1359, 1327, 1307, 1278, 1260, 1200, 1156, 1132, 1110, 1085, 1022; δ_H (400 MHz, $CDCl_3$) 7.97 (1H, d, *J* 15.5, ArC*H*=CHS), 7.66 (1H, d, *J* 7.5, Ar*H*), 7.54 (1H, d, *J* 7.5, Ar*H*), 7.37 (1H, app t, *J* 7.5, Ar*H*), 7.30 (1H, app t, *J* 7.5 Ar*H*), 6.80 (1H, d, *J* 15.5, ArCH=C*H*S), 5.52 (1H, s, N*H*), 3.75 (4H, t, *J* 4.5, N($CH_2C\mathit{H}_2$)$_2$O), 2.90 (4H, t, *J* 4.5, N($C\mathit{H}_2CH_2$)$_2$O); δ_C (101 MHz, $CDCl_3$) 142.5 (CH), 133.8 (CH), 133.1 (C), 132.1 (CH), 128.4 (CH), 128.1 (CH), 126.7 (CH), 125.3 (C), 66.8 (2 × CH_2), 57.5 (2 × CH_2); *m/z* (ESI^+) 719 ($[2M + Na]^+$, 60%), 717 ($[2M + Na]^+$, 100%), 715 ($[2M + Na]^+$, 50%); *m/z* (ESI^-) 383 ($[M + Cl]^-$, 100%), 381 ($[M + Cl]^-$, 77%); HRMS (ESI^+) $C_{12}H_{15}BrN_2NaO_3S^+$ ($[M + Na]^+$) requires 370.9859 and 368.9879, found 370.9855 and 368.9869.

(*Z*) and (*E*)-2-(2-Chlorophenyl)-*N*-(morpholin-4-yl)ethenesulfonamide 119 and 119'





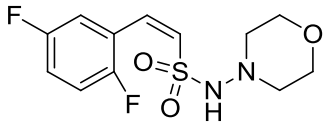
General procedure A was followed using DABSO (63 mg, 0.28 mmol), Cata*CX*ium A (17 mg, 0.05 mmol), (*Z*)-1-chloro-2-(2-iodovinyl)benzene **111** (63 mg, 0.24 mmol, *Z*:*E*, >20:1) and 4-aminomorpholine (35 µL, 0.36 mmol). The reaction mixture was stirred at

70 °C for 8 h. Column chromatography (eluent: 0—50%, ether in hexane) yielded, in order of elution, *Z isomer* **119** (33 mg, 46%) and *E isomer* **119'** (8 mg, 11%), both as white crystalline solids.

Z isomer **119**: mp 87-90 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3201, 2918, 2897, 2851, 1358, 1317, 1290, 1273, 1263, 1216, 1200, 1157, 1144, 1113, 1072, 1050, 1036, 1015; δ_H (400 MHz, $CDCl_3$) 7.95-7.87 (1H, m, Ar*H*), 7.44-7.39 (1H, m, Ar*H*), 7.38-7.28 (3H, m, 2 × Ar*H*, ArC*H*=CHS), 6.59 (1H, d, *J* 12.0, ArCH=C*H*S), 5.28 (1H, s, N*H*), 3.72 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.81 (4H, br. t, *J* 4.5, $N(CH_2CH_2)_2O$); δ_C (101 MHz, $CDCl_3$) 138.4 (CH), 133.5 (C), 132.1 (CH), 131.4 (C), 131.0 (CH), 129.2 (CH), 128.8 (CH), 126.5 (CH), 66.7 (2 × CH_2), 57.3 (2 × CH_2); *m/z* (ESI^+) 630 ($[2M + Na]^+$, 25%), 629 ($[2M + Na]^+$, 80%), 627 ($[2M + Na]^+$, 100%); *m/z* (ESI^-) 303 ($[M - H]^-$, 45%), 301 ($[M - H]^-$, 100%); HRMS (ESI^+) $C_{12}H_{15}ClN_2NaO_3S^+$ ($[M + Na]^+$) requires 327.0355 and 325.0384, found 327.0358 and 325.0380.

E isomer **119'**: mp 135-136 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3195, 2919, 2856, 1360, 1328, 1279, 1265, 1199, 1153, 1110, 1050, 1036; δ_H (400 MHz, $CDCl_3$) 8.00 (1H, d, *J* 15.5, ArC*H*=CHS), 7.55 (1H, dd, *J* 8.0, 1.5, Ar*H*), 7.4.7 (1H, dd, *J* 8.0, 1.5, Ar*H*), 7.38 (1H, app td, *J* 7.5, 1.5, Ar*H*), 7.33 (1H, app td, *J* 7.5, 1.5, Ar*H*), 6.86 (1H, d, *J* 15.5, ArCH=C*H*S), 5.37 (1H, s, N*H*), 3.73 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.89 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$); δ_C (101 MHz, $CDCl_3$) 140.0 (CH), 135.2 (C), 131.9 (CH), 131.2 (C), 130.6 (CH), 128.4 (CH), 127.5 (CH), 126.6 (CH), 66.8 (2 × CH_2), 57.6 (2 × CH_2); *m/z* (ESI^+) 630 ($[2M + Na]^+$, 25%), 629 ($[2M + Na]^+$, 80%), 627 ($[2M + Na]^+$, 100%); *m/z* (ESI^-) 303 ($[M - H]^-$, 45%), 301 ($[M - H]^-$, 100%); HRMS (ESI^+) $C_{12}H_{15}ClN_2NaO_3S^+$ ($[M + Na]^+$) requires 327.0355 and 325.0384, found 327.0358 and 325.0380.

(*Z*)-2-(2,5-Difluorophenyl)-*N*-(morpholin-4-yl)ethenesulfonamide 121



General procedure A was followed using DABSO (63 mg, 0.26 mmol), Cata*CX*ium A (17 mg, 0.05 mmol), (*Z*)-1,4-difluoro-2-(2-iodovinyl)benzene **214** (64 mg, 0.24 mmol, *Z*:*E*, >20:1) and 4-aminomorpholine (35 µL, 0.72 mmol). The reaction mixture was stirred at 70 °C for 5 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **121** as a pale yellow crystalline solid (38 mg, 52%, Z:*E* >20:1); mp 128-129 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3107, 1629, 1485, 1458, 1432, 1324, 1277, 1226, 1198, 1144, 1100, 1069; δ_H (400 MHz, $CDCl_3$) 7.91-7.80 (1H, m, Ar*H*), 7.16 (1H, d, *J* 12.0, ArC*H*=CHS), 7.11-6.97 (2H, m, 2 × Ar*H*), 6.55 (1H, d, *J* 12.5, ArCH=C*H*S), 5.43 (1H, s, N*H*), 3.74 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.87 (4H, br. t, *J* 4.5, $N(CH_2CH_2)_2O$); δ_C (126 MHz, $CDCl_3$) 158.0 (C, dd, J_{CF} 241.0, 2.5), 156.5 (C, dd, J_{CF} 244.0, 2.5), 135.5 (C, br. s), 133.1 (CH, d, J_{CF} 3.5), 129.5 (CH), 118.6 (CH, dd, J_{CF} 19.5, 2.0) overlapping 118.4 (CH, dd, J_{CF} 26.5, 9.0), 116.2 (CH, dd, J_{CF} 24.5, 8.5), 66.6 (2 × CH_2), 57.3 (2 × CH_2); δ_F (377 MHz, $CDCl_3$) –118.5 (d, J_{CF} 17.5, Ar*F*), –119.3 (d, J_{CF} 17.5, Ar*F*) {^{1}H}; *m/z* (ESI^+) 327 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{12}H_{14}F_2N_2NaO_3S^+$ ($[M + Na]^+$) requires 327.0585, found 327.0579.

(*Z*)-2-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)-*N*-morpholinoethenesulfonamide 142

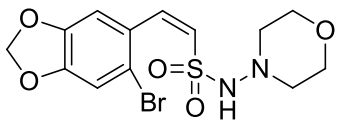


Table 3.18, entry 2: General procedure F was followed using (*Z*)-bromo-6-(2-iodovinyl)benzo[*d*][1,3]dioxole **129** (85 mg, 0.24 mmol, *Z*:*E*, >20:1). The reaction mixture was stirred at 70 °C for 3 h. Column chromatography (eluent: 7:3, ether:petrol) yielded

alkenyl N-aminosulfonamide **142** as a white crystalline solid (73 mg, 78%, *Z*:*E*, 20:1); mp 128-131 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3157, 3044, 2958, 2931, 2852, 1621, 1502, 1275, 1415, 1388, 1363, 1318, 1260, 1246, 1197, 1142, 1106, 1070, 1036; δ_H (400 MHz, $CDCl_3$) 7.67 (1H, s, Ar*H*), 7.15 (1H, d, *J* 12.0, ArC*H*=CHS), 7.04 (1H, s, Ar*H*), 6.40 (1H, d, *J* 12.0, ArCH=C*H*S), 6.03 (2H, s, OCH_2O), 5.58 (1H, s, N*H*), 3.74 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 2.86 (4H, br. t, *J* 4.5, N(CH_2CH_2)$_2$O); δ_C (101 MHz, $CDCl_3$) 149.8 (C), 147.0 (C), 140.5 (CH), 126.9 (CH), 125.9 (C), 116.1 (C), 112.4 (CH), 112.0 (CH), 102.3 (CH), 66.7 (2 × CH_2), 57.3 (2 × CH_2); *m/z* (ESI^-) 391 ([M – H]$^-$, 100%), 389 ([M – H]$^-$, 98%); HRMS (ESI^-) $C_{13}H_{14}BrN_2O_5S^-$ ([M – H]$^-$) requires 390.9792 and 388.9812, found 390.9793 and 388.9819.

2-(2-Bromo-4,5-dimethoxyphenyl)-*N*-morpholinoethenesulfonamide 143

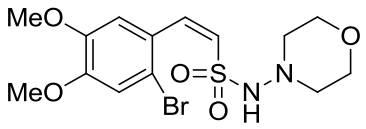


Table 3.18, entry 3: General procedure F was followed using 1-bromo-2-(2-iodovinyl)-4,5-dimethoxybenzene **130** (89 mg, 0.24 mmol, *Z*:*E*, >20:1). The reaction mixture was stirred at 70 °C for 3 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **143** as a white crystalline solid (82 mg, 84%, *Z*:*E*, 15:1); mp 181-185 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3217, 3006, 2973, 2932, 2858, 1596, 1500, 1463, 1442, 1392, 1325, 1308, 1267, 1232, 1203, 1186, 1157, 1132, 1114, 1021; δ_H (400 MHz, $CDCl_3$) 7.67 (1H, s, Ar*H*), 7.17 (1H, d, *J* 12.0, ArC*H*=CHS), 7.05 (1H, s, Ar*H*), 6.51 (1H, d, *J* 12.0, ArCH=C*H*S), 5.19 (1H, s, N*H*), 3.91 (3H, s, O*Me*) overlapping 3.90 (3H, s, O*Me*), 3.69 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 2.76 (4H, br. t, *J* 4.5, N(CH_2CH_2)$_2$O); δ_C (126 MHz, $CDCl_3$) 150.9 (C), 148.0 (C), 140.0 (CH), 127.7 (CH), 124.9 (C), 115.5 (C), 115.0 (2 × CH), 66.7 (2 × CH_2), 57.3 (2 × CH_2), 56.5 (CH_3), 56.4 (CH_3); *m/z* (ESI^+) 431

([M + Na]$^+$, 95%), 429 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{19}BrN_2NaO_5S^+$ ([M + Na]$^+$) requires 431.0070 and 429.0090, found 431.0083 and 429.0104.

2-(5-(Benzyloxy)-2-bromophenyl)-*N*-morpholinoethenesulfonamide 144

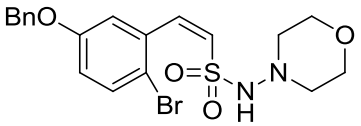


Table 3.18, entry 4: General procedure F was followed using 4-(benzyloxy)-1-bromo-2-(2-iodovinyl)benzene **131** (100 mg, 0.24 mmol, *Z*:*E*, 15:1). The reaction mixture was stirred at 70 °C for 4 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **144** as white needles (86 mg, 79%, 8:1); mp 178-180 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3207, 3059, 2952, 2855, 2820, 1616, 1589, 1460, 1446, 1404, 1363, 1333, 1262, 1249, 1231, 1179, 1156, 1112, 1046, 1016; δ_H (400 MHz, $CDCl_3$, *Z* isomer) 7.61 (1H, d, *J* 3.0, Ar*H*), 7.46 (1H, d, *J* 9.0, Ar*H*), 7.44-7.32 (5H, m, 5 × OBn*H*), 7.16 (1H, d, *J* 12.0, ArC*H*=CHS), 6.90 (1H, dd, *J* 9.0, 3.0, Ar*H*), 6.54 (1H, d, *J* 12.0, ArCH=C*H*S), 5.11 (2H, s, OCH_2Ph), 4.99 (1H, s, N*H*), 3.67 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 2.68 (4H, br. t, *J* 4.5, N(CH_2CH_2)$_2$O); δ_H (400 MHz, $CDCl_3$, *E* isomer observable peaks) 7.90 (1H, d, *J* 15.5, ArC*H*=CHS), 7.52 (1H, d, *J* 9.0, Ar*H*), 6.73 (1H, d, *J* 15.5, ArCH=C*H*S), 5.07 (1H, s, OCH_2Ph), 3.73 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 2.86 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O); δ_C (101 MHz, $CDCl_3$, *Z* isomer) 157.5 (C), 140.1 (CH), 136.6 (CH), 133.6(4) (CH), 133.1 (CH), 129.0 (C), 128.8 (2 × CH), 128.2 (C), 127.6(4) (2 × CH), 118.9 (CH), 118.1 (CH), 114.5 (C), 70.3 (CH_2), 66.6 (2 × CH_2), 57.2 (2 × CH_2); δ_C (101 MHz, $CDCl_3$, *E* isomer observable peaks) 158.3 (C), 142.5 (CH), 136.1 (CH), 134.4 (CH), 133.6(7) (CH), 129.0 (2 × CH), 128.9 (CH), 128.5 (C), 127.5(8) (2 × CH), 114.6 (C), 70.6 (CH_2), 66.8 (2 × CH_2), 57.5 (2 × CH_2); *m/z* (ESI$^+$) 477 ([M + Na]$^+$, 95%) 475 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{21}BrN_2NaO_4S^+$ ([M + Na]$^+$) requires 477.0278 and 475.0298, found 477.0287 and

475.0306; Anal. Calcd. (%) for $C_{19}H_{21}BrN_2O_4S$: C 50.34, H 4.67, N 6.18; found C 50.06, H 4.52, N 6.03.

2-(2-Bromo-4-methylphenyl)-*N*-morpholinoethenesulfonamide 145

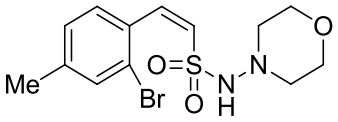


Table 3.18, entry 5: General procedure F was followed using 2-bromo-1-(2-iodovinyl)-4-methylbenzene **132** (78 mg, 0.24 mmol, *Z*:*E*, 18:1). The reaction mixture was stirred at 70 °C for 3.5 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **145** as a white crystalline solid (68 mg, 78%, *Z*:*E*, 15:1); mp 148-149 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3245, 2852, 1619, 1600, 1446, 1360, 1330, 1283, 1267, 1152, 1106, 1071, 1042; δ_H (500 MHz, $CDCl_3$) 7.81 (1H, d, *J* 8.0, Ar*H*), 7.43 (1H, d, *J* 1.0, Ar*H*), 7.20 (1H, d, *J* 12.0, ArC*H*=CHS), 7.16-7.13 (1H, m, Ar*H*), 6.51 (1H, d, *J* 12.0, ArCH=C*H*S), 5.31 (1H, s, N*H*), 3.71 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.80 (4H, br. t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.35 (3H, s, Ar*Me*); δ_C (126 MHz, $CDCl_3$) 141.9 (CH), 140.4 (CH), 132.9 (CH), 131.9 (CH), 130.1 (C), 128.0 (2 × CH), 123.6 (C), 66.7 (2 × CH_2), 57.3 (2 × CH_2), 21.2 (CH_3); *m/z* (ESI$^-$) 361 ($[M - H]^-$, 95%), 359 ($[M - H]^-$, 100%); HRMS (ESI^+) $C_{13}H_{17}BrN_2NaO_3S^+$ ($[M + Na]^+$) requires 385.0015 and 383.0035, found 385.0026 and 383.0048; Anal. Calcd. (%) for $C_{13}H_{17}BrN_2O_3S$: C 43.22, H 4.74, N 7.75; found C 43.01, H 4.81, N 7.66.

2-(1-Bromonaphthalen-2-yl)-*N*-morpholinoethenesulfonamide 146

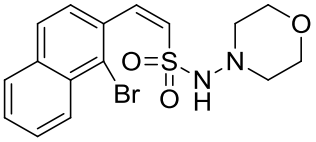


Table 3.18, entry 6: General procedure F was followed using (*Z*)-1-bromo-2-(2-iodovinyl)naphthalene **133** (86 mg, 0.24 mmol, *Z*:*E*, >20:1). The reaction mixture was stirred at 70 °C for 4 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **146** as a white crystalline solid (72 mg, 75%, *Z*:*E*, 15:1); mp 152-156 °C (CH_2Cl_2), ν_{max} (neat)/cm^{-1} 3191, 3041, 2959, 2926, 2857, 1632, 1553, 1498, 1457, 1417, 1386, 1364, 1320, 1270, 1238, 1142, 1105, 1072, 1016; δ_H (400 MHz, $(CD_3)_2SO$) 8.88 (1H, s, N*H*), 8.23 (1H, d, *J* 8.5, Ar*H*), 8.03-7.90 (3H, m, 3 × Ar*H*), 7.71 (1H, app t, *J* 7.0 Ar*H*) overlapping 7.65 (1H, app t, *J* 8.0, Ar*H*), 7.43 (1H, d, *J* 11.5, ArC*H*=CHS), 6.75 (1H, d, *J* 11.5, ArCH=C*H*S), 3.64 (4H, br. t, *J* 4.0, $N(CH_2CH_2)_2O$), 2.84-2.78 (4H, m, $N(CH_2CH_2)_2O$); δ_C (126 MHz, $CDCl_3$) 141.5 (CH), 134.6 (C), 131.8(9) (C), 131.7(7) (C), 128.4 (CH), 128.3(3) (CH), 128.2(6) (CH), 127.9 (CH), 127.7 (CH), 127.3 (CH), 127.1 (CH), 124.2 (C), 66.8 (2 × CH_2), 57.4 (2 × CH_2); *m/z* (ESI$^-$) 397 ([M – H]$^-$, 100%), 395 ([M – H]$^-$, 80%); HRMS (ESI$^+$) $C_{16}H_{17}BrN_2NaO_3S^+$ ([M + Na]$^+$) requires 421.0015 and 419.0035, found 421.0019 and 419.0042.

(*Z*)-2-(2-Bromo-5-(trifluoromethyl)phenyl)-*N*-morpholinoethenesulfonamide 147

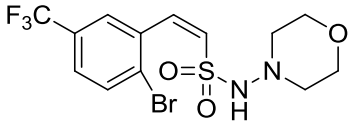


Table 3.18, entry 7: General procedure F was followed using (*Z*)-1-bromo-2-(2-iodovinyl)-4-(trifluoromethyl)benzene **134** (90 mg, 0.24 mmol, *Z*:*E*, >20:1). The reaction mixture was stirred at 70 °C for 4 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **147** as a white crystalline solid (79 mg, 79%, *Z*:*E*, 15:1); mp 212-215 °C (dec.); ν_{max} (neat)/cm^{-1} 3206, 2962, 2926, 2856, 1603, 1459, 1414, 1327, 1262, 1206, 1155, 1128, 1112, 1081, 1029; δ_H (400 MHz, $CDCl_3$) 8.15 (1H, d, *J* 1.5, Ar*H*), 7.72 (1H, d, *J* 8.5, Ar*H*), 7.49 (1H, dd, *J* 8.5, 1.5, Ar*H*), 7.21 (1H, d, *J* 12.0, ArC*H*=CHS), 6.54

(1H, d, *J* 12.0, ArCH=C*H*S), 5.34 (1H, br. s, N*H*), 3.75 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 2.87 (4H, br. t, *J* 4.5, N(CH_2CH_2)$_2$O); δ_C (126 MHz, $CDCl_3$) 139.5 (CH), 134.0 (C), 132.8 (CH), 129.4(3) (C, q, J_{CF} 32.5), 129.3(8) (CH), 129.2 (CH, q, J_{CF} 3.5), 127.3 (CH, q, J_{CF} 4.0), 127.0 (C, m), 123.8 (C, q, J_{CF} 272.5), 66.6 (2 × CH_2), 57.6 (2 × CH_2); δ_F (377 MHz, $CDCl_3$) –62.4 (s, ArC*F*$_3$) {^{1}H}; *m/z* (ESI$^+$) 439 ([M + Na]$^+$, 100%), 437 ([M + Na]$^+$, 95%); HRMS (ESI$^+$) $C_{13}H_{14}BrF_3N_2NaO_3S^+$ ([M + Na]$^+$) requires 438.9732 and 436.9753; found 438.9745 and 436.9761.

2-(2-Bromo-3-fluorophenyl)-*N*-morpholinoethenesulfonamide 148

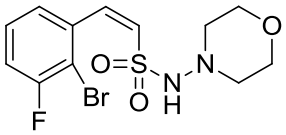


Table 3.18, entry 8: General procedure F was followed using (*Z*)-2-bromo-1-fluoro-3-(2-iodovinyl)benzene **135** (78 mg, 0.24 mmol, *Z*:*E*, >20:1). The reaction mixture was stirred at 70 °C for 4 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **148** as a white crystalline solid (63 mg, 72%, *Z*:*E*, 12:1); mp 125-127 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3189, 2961, 2923, 2856, 1598, 1570, 1510, 1465, 1430, 1388, 1360, 1325, 1263, 1217, 1154, 1111, 1072, 1035; δ_H (400 MHz, $CDCl_3$) 7.63 (1H, d, *J* 8.0, Ar*H*), 7.31 (1H, app td, *J* 8.0, 5.5, Ar*H*), 7.18 (1H, d, *J* 12.0, ArC*H*=CHS) overlapping 7.14 (1H, app td, *J* 8.0, 1.0, Ar*H*), 6.59 (1H, d, *J* 12.0, ArCH=C*H*S), 5.51 (1H, s, N*H*), 3.72 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 2.82 (4H, br. t, *J* 4.5, N(CH_2CH_2)$_2$O); δ_C (126 MHz, $CDCl_3$) 159.0 (C, d, J_{CF} 248.0), 139.2 (CH, d, J_{CF} 3.0), 135.4 (C), 129.4 (CH), 128.2 (CH, d, J_{CF} 8.5), 127.4 (CH, d, J_{CF} 3.0), 117.1 (CH, d, J_{CF} 22.5), 110.3 (C, d, J_{CF} 20.0), 66.7 (2 × CH_2), 57.4 (2 × CH_2); δ_F (377 MHz, $CDCl_3$) –105.7 (s, Ar*F*) {^{1}H}; *m/z* (ESI$^-$) 365 ([M – H]$^-$, 100%), 363 ([M – H]$^-$, 90%); HRMS (ESI$^+$) $C_{12}H_{14}BrFN_2NaO_3S^+$ ([M + Na]$^+$]) requires 388.9764 and 386.9785, found 388.9763 and 386.9787.

(*Z*)-2-(2-Bromo-4-fluorophenyl)-*N*-morpholinoethenesulfonamide 149

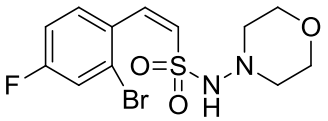


Table 3.18, entry 9: General procedure F was followed using 2-bromo-4-fluoro-1-(2-iodovinyl)benzene **136** (78 mg, 0.24 mmol, *Z*:*E*, 20:1). The reaction mixture was stirred at 70 °C for 3.5 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **149** as a white crystalline solid (61 mg, 70%, *Z*:*E*, 20:1); mp 116-118 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3191, 3048, 2978, 2923, 2855, 1622, 1591, 1477, 1457, 1390, 1357, 1315, 1265, 1239, 1189, 1158, 1140, 1114, 1073, 1033; δ_H (400 MHz, $CDCl_3$) 7.92 (1H, dd, *J* 9.0, 6.0, Ar*H*), 7.35 (1H, dd, *J* 8.0, 3.0, Ar*H*), 7.16 (1H, d, *J* 12.0, ArC*H*=CHS), 7.07 (1H, app td, *J* 8.5, 2.5, Ar*H*), 6.53 (1H, d, *J* 12.0, ArCH=C*H*S), 5.35 (1H, s, NH), 3.72 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.83 (4H, br t, *J* 4.5, $N(CH_2CH_2)_2O$); δ_C (126 MHz, $CDCl_3$) 163.0 (C, d, J_{CF} 255.0), 139.4 (CH), 133.6 (CH, d, J_{CF} 9.0), 129.3 (C, d, J_{CF} 4.0), 128.5 (CH), 124.0 (C, d, J_{CF} 10.0), 119.8 (CH, d, J_{CF} 24.5), 114.5 (CH, d, J_{CF} 21.5), 66.6 (2 × CH_2), 57.4 (2 × CH_2); δ_F (377 MHz, $CDCl_3$) –108.8 (s, Ar*F*) {^{1}H}; *m/z* (ESI$^-$) 365 ([M – H]$^-$, 90%), 363 ([M – H]$^-$, 100%); HRMS (ESI$^+$) $C_{12}H_{14}BrFN_2NaO_3S^+$ ([M + Na]$^+$) requires 388.9764 and 386.9785, found 388.9771 and 386.9792

(*Z*)-2-(2-Bromo-5-fluorophenyl)-*N*-morpholinoethenesulfonamide 150

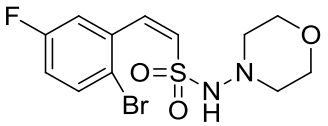


Table 3.18, entry 10: General procedure F was followed using (*Z*)-1-bromo-4-fluoro-2-(2-iodovinyl)benzene **137** (78 mg, 0.24 mmol, *Z*:*E*, 18:1). The reaction mixture was stirred at 70 °C for 3.5 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **150** as a white crystalline solid (57 mg, 65%, *Z*:*E*, 15:1); mp

125-127 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3135, 2867, 1575, 1460, 1340, 1267, 1200, 1156, 1104, 1069, 1033; δ_H (500 MHz, $CDCl_3$) 7.78 (1H, dd, *J* 9.0, 3.0, Ar*H*), 7.53 (1H, dd, *J* 9.0, 5.0, Ar*H*), 7.16 (1H, d, *J* 12.0, ArC*H*=CHS), 7.00-6.95 (1H, m, Ar*H*), 6.52 (1H, d, *J* 12.0, ArCH=C*H*S), 5.36 (1H, s, N*H*), 3.75 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.86 (4H, br. t, *J* 4.5, $N(CH_2CH_2)_2O$); δ_C (126 MHz, $CDCl_3$) 161.2 (C, d, J_{CF} 247.0), 139.6 (CH, d, J_{CF} 2.0), 134.7 (C, d, J_{CF} 9.0), 133.5 (CH, d, J_{CF} 7.5), 129.0 (CH), 119.5 (CH, d, J_{CF} 24.5), 118.3 (CH, d, J_{CF} 23.0), 117.7 (C, d, J_{CF} 3.5), 66.7 (2 × CH_2), 57.5 (2 × CH_2); δ_F (377 MHz, $CDCl_3$) –114.5 (s, Ar*F*) {^{1}H}; *m/z* (ESI^-) 365 ($[M - H]^-$, 95%), 363 ($[M - H]^-$, 100%); HRMS (ESI^-) $C_{12}H_{13}BrFN_2O_3S^-$ ($[M - H]^-$) requires 364.9801 and 362.9825, found 364.9799 and 362.9820.

(*Z*)-2-(2-Bromopyridin-3-yl)-*N*-morpholinoethenesulfonamide 151

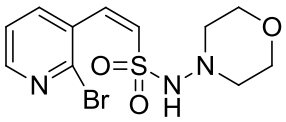


Table 3.18, entry 11: General procedure F was followed using (*Z*)-2-bromo-3-(2-iodovinyl)pyridine **138** (74 mg, 0.24 mmol, *Z*:*E*, >20:1). The reaction mixture was stirred at 70 °C for 3 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **151** as a pale yellow crystalline solid (69 mg, 83%, *Z*:*E*, >20:1), mp 118-121 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3140, 3031, 2978, 2887, 1618, 1572, 1555, 1460, 1396, 1370, 1337, 1279, 1265, 1206, 1150, 1123, 1103, 1070, 1061, 1051, 1012; δ_H (400 MHz, $CDCl_3$) 8.37 (1H, dd, *J* 5.0, 1.5, Ar*H*), 8.21-8.13 (1H, m, Ar*H*), 7.32 (1H, dd, *J* 7.5, 5.0, Ar*H*), 7.16 (1H, d, *J* 11.5, ArC*H*=CHS), 6.61 (1H, d, *J* 11.5, ArCH=C*H*S), 5.36 (1H, s, N*H*), 3.72 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.85 (4H, br. t, *J* 4.5, $N(CH_2CH_2)_2O$); δ_C (101 MHz, $CDCl_3$) 138.3 (C), 138.1 (CH), 135.1 (CH), 134.3 (CH), 133.5 (CH), 127.9 (CH), 120.2 (C), 66.6 (2 × CH_2), 56.7 (2 × CH_2); *m/z* (ESI^+) 372 ($[M + Na]^+$, 100%), 370 ([M +

$Na]^+$, 95%); HRMS (ESI^+) $C_{11}H_{14}BrN_3NaO_3S^+$ ($[M + Na]^+$) requires 371.9811 and 369.9831, found 371.9826 and 369.9849.

(*Z*)-2-(2-Bromothiophen-3-yl)-*N*-morpholinoethenesulfonamide 152

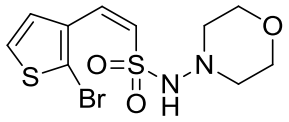


Table 3.18, entry 12: General procedure F was followed using 2-bromo-3-(2-iodovinyl)thiophene **139** (76 mg, 0.24 mmol, *Z*:*E*, 10:1). The reaction mixture was stirred at 70 °C for 3 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **152** as a white crystalline solid (50 mg, 59%, *Z*:*E*, 10:1); mp 185-186 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3207, 3108, 2962, 2920, 2855, 1605, 1456, 1412, 1362, 1337, 1264, 1149, 1109; δ_H (400 MHz, $CDCl_3$, *Z* isomer) 7.60 (1H, d, *J* 5.5, CH=C*H*S), 7.31 (1H, dd, *J* 12.0, 1.0, ArC*H*=CHS), 7.09 (1H, d, *J* 5.5, C*H*=CHS), 6.32 (1H, d, *J* 12.0, ArCH=C*H*S), 5.53 (1H, s, N*H*), 3.65 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.83 (4H, br. t, *J* 4.5, $N(CH_2CH_2)_2O$); δ_H (400 MHz, $CDCl_3$, *E* isomer observable peaks) 7.74 (1H, dd, *J* 15.5, 1.0, ArC*H*=CHS), 6.72 (1H, d, *J* 15.5, ArCH=C*H*S); δ_C (126 MHz, $CDCl_3$, *Z* isomer) 132.7 (CH), 132.0 (CH), 130.0 (CH), 128.9 (C), 123.2 (CH), 120.0 (C), 66.7 (2 × CH_2), 57.2 (2 × CH_2); *m/z* (ESI^+) 377 ($[M + Na]^+$, 90%), 375 ($[M + Na]^+$, 100%); HRMS (ESI^+) $C_{10}H_{13}BrN_2NaO_3S_2^+$ ($[M + Na]^+$) requires 376.9422 and 374.9443, found 376.9432 and 374.9455.

(*E*)-2-(5-bromobenzo[*d*][1,3]dioxol-4-yl)-*N*-morpholinoethenesulfonamide 153

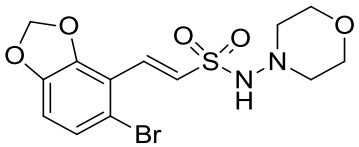


Table 3.18, entry 13: General procedure F was followed using (*E*)-5-bromo-4-(2-iodovinyl)benzo[*d*][1,3]dioxole **140** (85 mg, 0.24 mmol, *Z*:*E*, 1:15). The reaction mixture was stirred at 70 °C for 4 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **153** as a white crystalline solid (68 mg, 72%, *Z*:*E*, 1:15); mp 182-186 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3220, 2977, 2918, 2852, 1427, 1406, 1391, 1359, 1329, 1305, 1276, 1265, 1242, 1201, 1143, 1113, 1056, 1021; δ_H (400 MHz, $CDCl_3$) 7.82 (1H, d, *J* 15.5, ArC*H*=CHS), 7.22 (1H, d, *J* 15.5, ArCH=C*H*S), 7.14 (1H, d, *J* 8.5, Ar*H*), 6.74 (1H, d, *J* 8.5, Ar*H*), 6.11 (2H, s, OCH_2O), 5.34 (1H, s, N*H*), 3.74 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 2.88 (4H, br. t, *J* 4.5, N(CH_2CH_2)$_2$O); δ_C (101 MHz, $CDCl_3$) 147.8 (C), 147.6 (C), 137.4 (CH), 129.2 (CH), 126.3 (CH), 116.4 (C), 115.8 (C), 111.2 (CH), 102.6 (CH_2), 66.8 (2 × CH_2), 57.4 (2 × CH_2); Anal. Calcd. (%) for $C_{13}H_{15}BrN_2O_5S$: C 39.91, H 3.86, N 7.16; found C 40.03, H 3.94, N 7.02.

(*E*)-2-(2-Bromo-6-fluorophenyl)-*N*-morpholinoethenesulfonamide 154

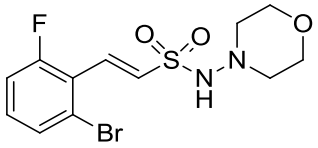


Table 3.18, entry 14: General procedure F was followed using (*E*)-1-Bromo-3-fluoro-2-(2-iodovinyl)benzene **141** (78 mg, 0.24 mmol, *Z*:*E*, 1:>20). The reaction mixture was stirred at 70 °C for 4 h. Column chromatography (eluent: 7:3, ether:petrol) yielded *alkenyl N-aminosulfonamide* **154** as a white crystalline solid (71 mg, 81%, *Z*:*E*, 1:>20); mp 162-164 °C; ν_{max} (neat)/cm^{-1} 3210, 2963, 2859, 1598, 1563, 1456, 1389, 1362, 1336, 1336, 1265, 1248, 1196, 1150, 1111, 1073; δ_H (400 MHz, $CDCl_3$) 7.78 (1H, d, *J* 16.0, ArC*H*=CHS), 7.48 (1H, d, *J* 8.0, ArH), 7.27-7.21 (1H, m, Ar*H*), 7.17-7.09 (1H, m, Ar*H*), 7.08 (1H, d, *J* 16.0, ArCH=C*H*S), 5.45 (1H, br. s, N*H*), 3.75 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 2.90 (4H, br. t, *J* 4.5, N(CH_2CH_2)$_2$O); δ_C (126 MHz, $CDCl_3$) 161.7 (C, d, J_{CF} 257.0), 136.2

(CH, d, J_{CF} 1.5), 132.2 (CH, d, J_{CF} 10.5), 130.8 (CH, d, J_{CF} 14.5), 129.7 (CH, d, J_{CF} 3.0), 126.3 (C, d, J_{CF} 3.5), 121.7 (C, d, J_{CF} 13.5), 115.8 (CH, d, J_{CF} 23.0), 66.8 (2 × CH_2), 57.5 (2 × CH_2); δ_F (377 MHz, $CDCl_3$) –107.1 (s, Ar*F*) {^{1}H}; *m/z* (ESI$^+$) 389 ([M + Na]$^+$, 100%), 387 ([M + Na]$^+$, 95%), 367 ([M + H]$^+$, 65%), 365 ([M + H]$^+$, 70%); HRMS (ESI$^+$) $C_{12}H_{15}BrFN_2NaO_3S^+$ ([M + H]$^+$) requires 366.9950 and 364.9965, found 366.9938 and 364.9960.

2-(2-Bromo-4,5-dimethoxyphenyl)-*N*-(4-methylpiperazin-1-yl)ethenesulfonamide 155

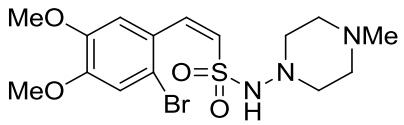


Table 3.18, entry 15: General procedure F was followed using (*Z*)-1-bromo-2-(2-iodovinyl)-4,5-dimethoxybenzene **130** (89 mg, 0.24 mmol, *Z*:*E*, >20:1). The reaction mixture was stirred at 70 °C for 3 h. Column chromatography (eluent: 4% MeOH in CH_2Cl_2) yielded *alkenyl N-aminosulfonamide* **155** as a white crystalline solid (75 mg, 74%, *Z*:*E*, 11:1); mp 160 °C (dec) (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3227, 2926, 2851, 1597, 1502, 1463, 1439, 1389, 1326, 1271, 1209, 1181, 1150, 1027; δ_H (400 MHz, $CDCl_3$, *Z* isomer) 7.63 (1H, s, Ar*H*), 7.16 (1H, d, *J* 12.0, ArC*H*=CHS), 7.04 (1H, s, Ar*H*), 6.46 (1H, d, *J* 12.0, ArCH=C*H*S), 6.15 (1H, br. s, N*H*), 3.91 (3H, s, O*Me*) overlapping 3.90 (3H, s, O*Me*), 3.12 (4H, br. s, N(CH_2CH$_2$)$_2$NMe) overlapping 3.03 (4H, br. s, N(CH$_2$CH_2)$_2$NMe), 2.64 (3H, s, N*Me*); δ_H (400 MHz, $CDCl_3$, *E* isomer observable peaks) 7.86 (1H, d, *J* 15.5, ArC*H*=CHS), 7.52 (1H, s, Ar*H*), 6.68 (1H, d, *J* 15.5, ArCH=C*H*S); δ_C (126 MHz, $CDCl_3$, *Z* isomer) 151.1 (C), 148.1 (C), 140.3 (CH), 127.6 (CH), 124.8 (C), 115.3 (C), 115.0(0) (CH), 114.9(7) (CH), 56.5 (CH_3), 56.4 (CH_3), 53.7 (2 × CH_2), 43.9 (2 × CH_2), 29.8 (CH_3); HRMS (FI$^+$) $C_{15}H_{22}BrN_3NaO_4S^+$ ([M]$^+$) requires 422.0523 and 421.0495, found 422.0348 and 421.0372.

(*Z*)-*N*',*N*'-Dibenzyl-2-(2-bromo-4,5-dimethoxyphenyl)ethenesulfonohydrazide 156

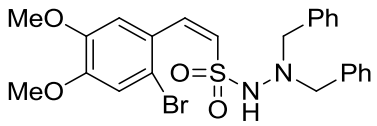


Table 3.18, entry 16: General procedure F was followed using (*Z*)-1-bromo-2-(2-iodovinyl)-4,5-dimethoxybenzene **130** (89 mg, 0.24 mmol, *Z*:*E*, >20:1). The reaction mixture was stirred at 70 °C for 3 h. Column chromatography (eluent: 70:29:1, ether:petrol:Et_3N to ether) yielded *alkenyl N-aminosulfonamide* **156** as an off-white crystalline solid (73 mg, 59%, *Z*:*E*, 20:1); mp >300 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3225, 2935, 2849, 1599, 1502, 1455, 1440, 1389, 1323, 1268, 1211, 1143, 1028; δ_H (400 MHz, $CDCl_3$) 7.53 (1H, s, Ar(OMe)*H*), 7.39-7.32 (6H, m, 6 × Ph*H*), 7.31-7.27 (4H, m, 4 × Ph*H*), 7.02 (1H, s, Ar(OMe)*H*), 6.86 (1H, d, *J* 12.0, ArC*H*=CHS), 5.80 (1H, d, *J* 12.0, ArCH=C*H*S), 5.34 (1H, s, N*H*), 3.89 (3H, s, O*Me*) overlapping 3.89 (3H, s, O*Me*), 3.87 (4H, s, 2 × CH_2Ph); δ_C (126 MHz, $CDCl_3$) 151.9 (C), 148.8 (C), 138.1 (CH), 137.9 (CH), 130.9 (4 × CH), 129.1 (4 × CH), 129.0 (2 × C), 128.5 (2 × CH), 126.0 (C), 116.7 (CH), 115.8 (CH), 115.5 (C), 61.6 (2 × CH_2), 56.4(4) (CH_3), 56.4(2) (CH_3); *m/z* (ESI^+) 541 ([M + Na]$^+$), 95%), 539 ([M + Na]$^+$, 100%); HRMS (ESI^+) $C_{24}H_{26}O_4N_2BrS^+$ ([M + H]$^+$) requires 519.0782 and 517.0802, found 519.0769 and 517.0788.

2-(2-Bromo-4,5-dimethoxyphenyl)-*N*'-methyl-*N*'-phenylethenesulfonohydrazide 157

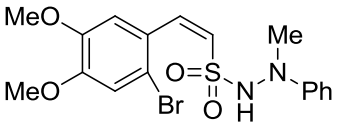
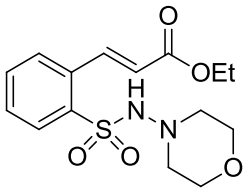


Table 3.18, entry 17: General procedure F was followed using 1-bromo-2-(2-iodovinyl)-4,5-dimethoxybenzene **130** (89 mg, 0.24 mmol, *Z*:*E*, >20:1). The reaction mixture was stirred at 70 °C for 3 h. Column chromatography (eluent: 70:29:1, ether:petrol:Et_3N to ether) yielded *alkenyl N-aminosulfonamide* **157** as an off-white solid (78 mg, 76%, *Z*:*E*,

10:1); mp 91-94 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3226, 2928, 2852, 1599, 1502, 1464, 1439, 1390, 1337, 1275, 1210, 1182, 1152, 1029; δ_H (400 MHz, $CDCl_3$) 7.61 (1H, s, Ar(OMe)*H*), 7.31-7.26 (2H, m, 2 × Ph*H*), 7.21 (1H, d, *J* 12.0, ArC*H*=CHS), 7.05-7.00 (3H, m, Ar(OMe)*H*, 2 × Ph*H*), 6.95 (1H, t, *J* 7.5, Ph*H*), 6.47 (1H, d, *J* 12.0, ArCH=C*H*S), 6.04 (1H, s, N*H*), 3.88 (3H, s, O*Me*), 3.76 (3H, s, O*Me*), 3.21 (3H, s, N*Me*); δ_C (126 MHz, $CDCl_3$) 151.0 (C), 149.8 (C), 147.9 (C), 140.5 (CH), 129.4 (2 × CH), 126.8 (CH), 124.6 (C), 121.5 (CH), 115.8 (C), 115.0 (CH), 114.7(3) (CH), 114.6(8) (2 × CH), 56.3 (CH_3), 56.2 (CH_3), 43.7 (CH_3); *m/z* (ESI^+) 451 ($[M + Na]^+$, 100%), 449 ($[M + Na]^+$, 95%); HRMS (ESI^+) $C_{17}H_{20}O_4N_2BrS^+$ ($[M + H]^+$) requires 429.0312 and 427.0333, found 429.0312 and 427.0332.

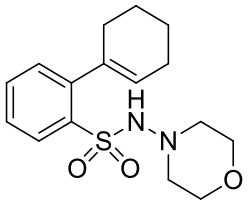
(*E*)-Ethyl 3-(2-(*N*-morpholinosulfamoyl)phenyl)acrylate 171



General procedure F was followed using ethyl 3-(2-bromophenyl)-2-iodoacrylate **170** (50 mg, 0.13 mmol, *Z*:*E*, 12:1). The reaction mixture was stirred at 70 °C for 16 h. Column chromatography (eluent: 3:7, petrol:ether) yielded *alkenyl N-aminosulfonamide* **171** as a white crystalline solid (8 mg, 18%, *Z*:*E*, 1:>20); mp 190 °C (dec) (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3225, 2923, 2854, 1712, 1634, 1457, 1366, 1319, 1265, 1159, 1042; δ_H (400 MHz, $CDCl_3$) 8.67 (1H, d, *J* 16.0, ArCH=C*H*CO), 8.13 (1H, dd, *J* 7.5, 1.0, Ar*H*), 7.70 (1H, dd, *J* 7.5, 1.0, Ar*H*), 7.62 (1H, app td, *J* 7.5, 1.0, Ar*H*), 7.51 (1H, app td, *J* 7.5, 1.0, Ar*H*), 6.38 (1H, d, *J* 16.0, ArC*H*=CHCO), 5.64 (1H, s, N*H*), 4.29 (2H, q, *J* 7.0, OCH_2CH_3), 3.59 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.66 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 1.35 (3H, t, *J* 7.0, OCH_2CH_3); ^{13}C NMR not obtained due to insufficient material; *m/z* (ESI^+)

363 ([M + Na]$^+$, 100%), 341 ([M + H]$^+$, 40%); HRMS (ESI$^+$) $C_{15}H_{21}O_5N_2S^+$ ([M + H]$^+$) requires 341.1166, found 341.1160.

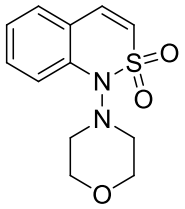
_N_-Morpholino-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2-sulfonamide 175



General procedure F was followed using 2'-bromo-6-iodo-2,3,4,5-tetrahydro-1,1'-biphenyl **174** (87 mg, 0.24 mmol). The reaction mixture was stirred at 70 °C for 16 h. Column chromatography (eluent: 3:7, petrol:ether) yielded *alkenyl N-aminosulfonamide* **175** as a pale yellow crystalline solid (16 mg, 21%); mp 91-93 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3220, 3019, 2930, 2859, 1457, 1387, 1361, 1327, 1265, 1216, 1163, 1111, 1073; δ_H (400 MHz, $CDCl_3$) 8.07 (1H, dd, *J* 7.5, 1.0, Ar*H*), 7.52 (1H, app td, *J* 7.5, 1.0, Ar*H*), 7.39 (1H, app td, *J* 7.5, 1.0, Ar*H*), 7.19 (1H, dd, *J* 7.5, 1.0, Ar*H*), 5.52 (1H, app sept, *J* 2.0, C=C*H*), 5.31 (1H, s, N*H*), 3.58 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 2.58 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 2.35-2.28 (2H, m, CH_2), 2.22-2.14 (2H, m, CH_2), 1.82-1.66 (4H, m, 2 × CH_2); δ_C (101 MHz, $CDCl_3$) 140.0 (C), 133.8 (C), 133.1 (CH), 131.2 (CH), 131.0 (CH), 126.9 (CH), 125.5 (CH), 92.8 (C), 66.7 (2 × CH_2), 56.9 (2 × CH_2), 31.7 (CH_2), 25.5 (CH_2), 22.9 (CH_2), 21.9 (CH_2); HRMS (FI$^+$) $C_{16}H_{22}N_2O_3S^+$ ([M$^+$]) requires 322.1351, found 322.1341.

6.4.5 Synthesis of benzothiazine 2,2-dioxide

1-(Morpholin-4-yl)-1*H*-2,1-benzothiazine 2,2-dioxide 122 and cesium (*Z*)-2-(2-bromophenyl)ethenesulfinate 125



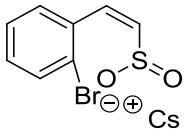


Table 3.19, entry 1: General procedure G was followed using 2-(2-bromophenyl)-*N*-(morpholin-4-yl)ethenesulfonamide **118** (50 mg, 0.14 mmol, *Z*:*E*, 12:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide* **122** as a white crystalline solid (32 mg, 83%); mp 150-153 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2955, 2915, 2863, 1612, 1559, 1453, 1360, 1320, 1270, 1213, 1159, 1145, 1111, 1070, 1037; δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.74 (1H, d, *J* 8.0, Ar*H*), 7.61-7.53 (2H, m, 2 × Ar*H*), 7.50 (1H, d, *J* 10.0, ArC*H*=CHS), 7.25-7.19 (1H, m, Ar*H*) overlapping 7.19 (1H, d, *J* 10.0, ArCH=C*H*S), 3.74 (4H, br. t, *J* 4.5, $N(CH_2CH_2)_2O$), 3.43 (4H, br. s, $N(CH_2CH_2)_2O$); δ_C (126 MHz, $CDCl_3$) 141.5 (C), 135.6 (CH), 131.5 (CH), 129.9 (CH), 125.8 (CH), 123.0 (CH), 120.5 (C), 116.9 (CH), 67.1 (2 × CH_2), 53.5 (2 × CH_2); *m/z* (ESI^+) 289 ($[M + Na]^+$, 100%), 267 ($[M + H]^+$, 45%); HRMS (ESI^+) $C_{12}H_{14}N_2NaO_3S^+$ ($[M + Na]^+$) requires 289.0617, found 289.0617. The residue after filtration through Celite contained *sulfinate salt* **125**; ν_{max} (neat)/cm^{-1} 3531, 3330, 2916, 1605, 1483, 1110; δ_H (400 MHz, MeOD) 7.74 (1H, dd, *J* 7.5, 1.0, Ar*H*), 7.58 (1H, dd, *J* 7.5, 1.0, Ar*H*), 7.36-7.31 (1H, m, Ar*H*), 7.23-7.15 (1H, m, Ar*H*), 6.83 (1H, d, *J* 11.0, ArC*H*=CHS), 6.24 (1H, d, *J* 11.0, ArCH=C*H*S); ^{13}C NMR not obtained due to insufficient material; *m/z* (ESI^-) 247 ($[M – Cs]^-$, 100%), 245 ($[M – Cs]^-$, 95%).

1-Morpholino-1*H*-[1,3]dioxolo[4',5':4,5]benzo[1,2-*c*][1,2]thiazine 2,2-dioxide 158

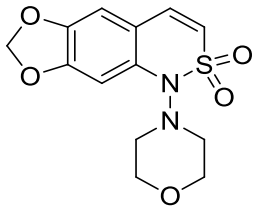


Table 3.19, entry 2: General procedure G was followed using (*Z*)-2-(6-bromobenzo[*d*][1,3]dioxol-5-yl)-*N*-morpholinoethenesulfonamide **142** (62 mg, 0.16 mmol, *Z*:*E*, 20:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide* **158** as a white crystalline solid (39 mg, 80%); mp 188-189 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2912, 2852, 1625, 1574, 1499, 1475, 1432, 1383, 1311, 1260, 1241, 1221, 1180, 1156, 1124, 1103, 1073, 1037; δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.36 (1H, d, *J* 10.0, ArC*H*=CHS), 7.28 (1H, s, Ar*H*), 7.10 (1H, s, Ar*H*), 7.00 (1H, d, *J* 10.0, ArCH=C*H*S), 6.10 (2H, s, OCH_2O), 3.72 (4H, br. t, *J* 4.5, N(CH_2CH_2)$_2$O), 3.39 (4H, br. s, N(CH_2CH_2)$_2$O); δ_C (126 MHz, $(CD_3)_2SO$) 150.2 (C), 143.7 (C), 138.1 (C), 135.3 (CH), 122.8 (CH), 114.6 (C), 107.6 (CH), 102.0 (CH_2), 99.0 (CH), 67.0 (2 × CH_2), 53.3 (2 × CH_2); HRMS (FI^+) $C_{13}H_{14}N_2O_5S^+$ ($[M]^+$) requires 310.0623, found 310.0625.

6,7-Dimethoxy-1-morpholino-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 159

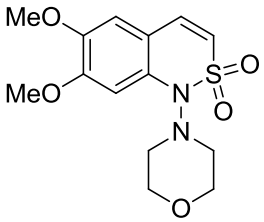


Table 3.19, entry 3: General procedure G was followed using 2-(2-bromo-4,5-dimethoxyphenyl)-*N*-morpholinoethenesulfonamide **143** (70 mg, 0.17 mmol, *Z*:*E*, 15:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide* **159** as a white crystalline solid (48 mg, 85%); mp 189-190 °C (CH_2Cl_2:petrol, 1:1); ν_{max}

(neat)/cm^{-1} 3046, 2851, 1613, 1557, 1501, 1459, 1363, 1302, 1276, 1239, 1203, 1181, 1152, 1133, 1112, 1039, 1004; δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.37 (1H, d, *J* 10.0, ArC*H*=CHS), 7.26 (1H, s, Ar*H*), 7.15 (1H, s, Ar*H*), 6.96 (1H, d, *J* 10.0, ArCH=C*H*S), 3.90 (3H, s, O*Me*), 3.80 (3H, s, O*Me*), 3.72 (4H, br. t, *J* 4.5, $N(CH_2CH_2)_2O$), 3.39 (4H, br. t, *J* 4.5, $N(CH_2CH_2)_2O$); δ_C (126 MHz, $CDCl_3$) 152.3 (C), 145.8 (C), 137.3 (C), 135.2 (CH), 122.3 (CH), 113.7 (C), 111.1 (CH), 101.2 (CH), 68.2 (2 × CH_2), 56.5 (CH_3), 56.2 (CH_3), 53.9 (2 × CH_2); HMRS (FI^+) $C_{14}H_{18}N_2O_5S^+$ ($[M]^+$) requires 326.0928, found 326.0937.

6-(Benzyloxy)-1-morpholino-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 160

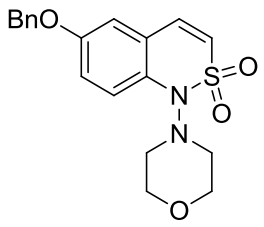


Table 3.19, entry 4: General procedure G was followed using 2-(5-(benzyloxy)-2-bromophenyl)-*N*-morpholinoethenesulfonamide **144** (75 mg, 0.17 mmol, *Z*:*E*, 8:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide* **160** as a white crystalline solid (49 mg, 79%); mp 195-198 °C (dec.); ν_{max} (neat)/cm^{-1} 2923, 2852, 1599, 1564, 1455, 1332, 1270, 1243, 1161, 1111, 1013; δ_H (500 MHz, $CDCl_3$) 7.61 (1H, d, *J* 9.0, Ar*H*), 7.44-7.34 (5H, m, 5 × OBn*H*), 7.14 (1H, d, *J* 10.0, ArC*H*=CHS) overlapping 7.16-7.12 (1H, m, Ar*H*), 6.94 (1H, d, *J* 2.5, Ar*H*), 6.78 (1H, d, *J* 10.0, ArCH=C*H*S), 5.08 (2H, s, OCH_2Ph), 3.80 (4H, br. s, $N(CH_2CH_2)_2O$), 3.51 (4H, br. s, $N(CH_2CH_2)_2O$); δ_C (126 MHz, $CDCl_3$) 154.8 (C), 136.5 (C), 135.9 (C), 135.2 (CH), 128.8 (2 × CH), 128.3 (CH), 127.5 (2 × CH), 126.0 (CH), 121.8 (C), 119.9 (CH), 119.6 (CH), 113.8 (CH), 70.7 (CH_2), 68.0 (2 × CH_2), 53.8 (2 × CH_2); HMRS (FI^+) $C_{19}H_{20}N_2O_4S^+$ ($[M]^+$) requires 372.1144, found 372.1140.

7-Methyl-1-morpholino-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 161

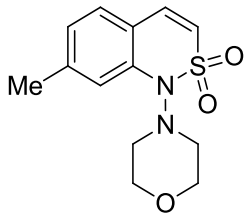


Table 3.19, entry 5: General procedure G was followed using 2-(2-bromo-4-methylphenyl)-*N*-morpholinoethenesulfonamide **145** (53 mg, 0.15 mmol, *Z*:*E*, 15:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide* **161** as a white crystalline solid (29 mg, 71%); mp 115-118 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2957, 2920, 2854, 1613, 1550, 1488, 1452, 1362, 1319, 1268, 1213, 1159, 1146, 1110, 1071, 1039; δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.53 (1H, s, Ar*H*), 7.49-7.42 (2H, m, Ar*H*, ArC*H*=CHS), 7.09 (1H, d, *J* 10.0, ArCH=C*H*S), 7.04 (1H, d, *J* 7.5, Ar*H*), 3.74 (4H, br. t, *J* 4.5, $N(CH_2CH_2)_2O$), 3.42 (4H, br. s, $N(CH_2CH_2)_2O$), 2.43 (3H, s, Ar*Me*); δ_C (126 MHz, $(CD_3)_2SO$) 141.9 (C), 141.5 (C), 135.5 (CH), 129.9 (CH), 124.7 (CH), 124.1 (CH), 118.1 (C), 117.0 (CH), 67.0 (2 × CH_2), 53.4 (2 × CH_2), 21.6 (CH_3); HRMS (FI^+) $C_{13}H_{16}N_2O_3S^+$ ($[M]^+$) requires 280.0882, found 280.0887.

1-Morpholino-1*H*-naphtho[1,2-*c*][1,2]thiazine 2,2-dioxide 162

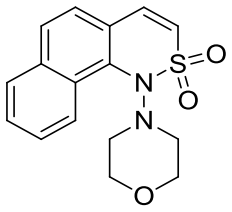


Table 3.19, entry 6: General procedure G was followed using 2-(1-bromonaphthalen-2-yl)-*N*-morpholinoethenesulfonamide **146** (60 mg, 0.15 mmol, *Z*:*E*, 15:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide* **162** as a white crystalline solid (32 mg, 68%); mp 204-207 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3058,

2916, 2851, 1593, 1504, 1459, 1371, 1335, 1305, 1261, 1205, 1162, 1130, 1102, 1019; δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 8.24 (1H, d, *J* 8.0, Ar*H*), 7.98 (1H, d, *J* 8.0, Ar*H*), 7.91 (1H, d, *J* 8.5, Ar*H*), 7.70-7.59 (4H, m, ArC*H*=CHS, 3 × Ar*H*) 7.25 (1H, d, *J* 10.0, ArCH=C*H*S), 3.45 (4H, br. t, *J* 4.5, $N(CH_2CH_2)_2O$), 3.36 (4H, br. t, *J* 4.5, $N(CH_2CH_2)_2O$); δ_C (126 MHz, $(CD_3)_2SO$) 137.0 (CH), 136.9 (C), 134.4 (C), 128.8 (C), 128.4 (CH), 128.2 (CH), 127.8 (CH), 127.4 (CH), 127.3 (CH), 125.3 (CH), 124.6 (CH), 122.8 (C), 67.0 (2 × CH_2), 52.2 (2 × CH_2); HRMS (FI^+) $C_{16}H_{16}N_2O_3S^+$ ($[M]^+$) requires 316.0882, found 316.0894.

1-(Morpholin-4-yl)-6-(trifluoromethyl)-1*H*-2,1-benzothiazine 2,2-dioxide 124

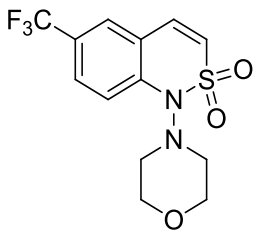


Table 3.13, entry 16: 2-[2-Fluoro-5-(trifluoromethyl)phenyl]-*N*-(morpholin-4-yl)ethenesulfonamide **101** (30 mg, 0.08 mmol, *Z*:*E*, >20:1) was added to a mixture of Cs_2CO_3 (83 mg, 0.24 mmol) and 1,4-dioxane (0.5 mL). The reaction mixture was stirred at 100 °C for 1 h. The reaction mixture was cooled to RT and filtered through a short pad of Celite with CH_2Cl_2 (5 mL) and ether (5 mL). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide* **124** as a white crystalline solid (24 mg, 88%).

Table 3.19, entry 7: General procedure G was followed using 2-(2-bromo-5-(trifluoromethyl)phenyl)-*N*-morpholinoethenesulfonamide **147** (68 mg, 0.16 mmol, *Z*:*E*, 15:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide* **124** as a white crystalline solid (41 mg, 75%); mp 120-122 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3082, 2869, 1620, 1359, 1320, 1299, 1277, 1202, 1162, 1133, 1104, 1075, 1029, 1012; δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 8.06 (1H, s, Ar*H*), 7.96 (1H, d, *J* 9.0, Ar*H*),

7.86 (1H, d, *J* 9.0, Ar*H*), 7.68 (1H, d, *J* 10.5, ArC*H*=CHS), 7.41 (1H, d, *J* 10.5, ArCH=C*H*S), 3.78 (4H, br. s, N(CH_2CH_2)$_2$O), 3.47 (4H, br. s, N(CH_2CH_2)$_2$O); δ_C (126 MHz, $CDCl_3$) 144.5 (C), 134.6 (CH), 128.1 (CH, q, J_{CF} 3.5), 127.1 (CH, q, J_{CF} 3.5), 126.0 (CH), 125.2 (C, q, J_{CF} 33.0), 123.6 (C, q, J_{CF} 272.0), 119.7 (C), 117.1 (CH), 67.8 (2 × CH_2), 53.9 (2 × CH_2); δ_F (377 MHz, $CDCl_3$) –62.1 (s, ArCF_3) {^{1}H}; *m/z* (ESI$^+$) 357 ([M + Na]$^+$, 100%); 334 ([M + H]$^+$, 30%); HRMS (ESI$^+$) $C_{13}H_{13}F_3N_2NaO_3S^+$ ([M + Na]$^+$) requires 357.0491, found 357.0477.

6-Fluoro-1-morpholino-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 163

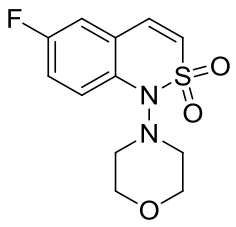


Table 3.19, entry 8: General procedure G was followed using 2-(2-bromo-5-fluorophenyl)-*N*-morpholinoethenesulfonamide **150** (42 mg, 0.11 mmol, *Z*:*E*, 15:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide* **163** as a white crystalline solid (25 mg, 78%); mp 145-148 °C; ν_{max} (neat)/cm^{-1} 3078, 2959, 2923, 2850, 1608, 1564, 1471, 1426, 1370, 1346, 1318, 1265, 1239, 1157, 1109, 1071, 1029, 1012; δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.76 (1H, dd, *J* 9.0, 5.0, Ar*H*), 7.50 (1H, d, *J* 10.0, ArC*H*=CHS) overlapping 7.48 (1H, dd, *J* 9.0, 3.0, Ar*H*), 7.43-7.37 (1H, m, Ar*H*), 7.30 (1H, d, *J* 10.0, ArCH=C*H*S), 3.73 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 3.42 (4H, br. t, *J* 4.5, N(CH_2CH_2)$_2$O); δ_C (126 MHz, $(CD_3)_2SO$) 157.6 (C, d, J_{CF} 241.5), 138.0 (C), 134.5 (CH, d, J_{CF} 2.0), 127.5 (CH), 121.9 (C, d, J_{CF} 9.0), 120.0 (CH, d, J_{CF} 8.0), 118.6 (CH, d, J_{CF} 23.0), 115.1 (CH, d, J_{CF} 23.7), 67.1 (2 × CH_2), 53.4 (2 × CH_2); δ_F (377 MHz, $(CD_3)_2SO$) –120.2 (s, Ar*F*) {^{1}H}; HRMS (FI$^+$) $C_{12}H_{13}FN_2O_3S^+$ ([M]$^+$ requires 284.0631 and 284.0630.

7-Fluoro-1-morpholino-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 164

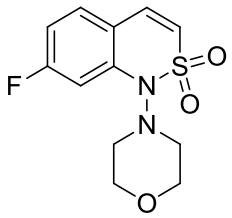


Table 3.19, entry 9: General procedure G was followed using 2-(2-bromo-4-fluorophenyl)-*N*-morpholinoethenesulfonamide **149** (50 mg, 0.14 mmol, *Z*:*E*, 20:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide* **164** as a white crystalline solid (27 mg, 69%); mp >250 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2918, 2853, 1617, 1567, 1493, 1457, 1315, 1268, 1214, 1164, 1107; δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 7.67 (1H, dd, *J* 8.5, 6.5, Ar*H*), 7.52 (1H, d, *J* 10.0, ArC*H*=CHS) overlapping 7.52-7.49 (1H, m, Ar*H*), 7.18 (1H, d, *J* 10.0, ArCH=C*H*S), 7.04 (1H, td, *J* 8.5, 3.0, Ar*H*), 3.76 (3H, br. t, *J* 4.5, $N(CH_2CH_2)_2O$), 3.45 (3H, br. s, $N(CH_2CH_2)_2O$); δ_C (126 MHz, $(CD_3)_2SO$) 163.4 (d, J_{CF} 248.0), 143.4 (d, J_{CF} 12.0), 134.4, 132.1 (d, J_{CF} 10.0), 123.9 (d, J_{CF} 3.0), 116.6 (d, J_{CF} 3.0), 110.0 (d, J_{CF} 23.0), 103.1 (d, J_{CF} 28.0), 66.6 (2C), 53.1 (2C); δ_F (377 MHz, $CDCl_3$) –105.8 (s, Ar*F*) {^{1}H}; HRMS (FI^+) $C_{12}H_{13}FN_2O_3S^+$ ($[M]^+$) requires 284.0631 and 284.0626.

1-Morpholino-1*H*-pyrido[2,3-*c*][1,2]thiazine 2,2-dioxide 165

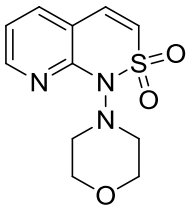


Table 3.19, entry 11: General procedure G was followed using 2-(2-bromopyridin-3-yl)-*N*-morpholinoethenesulfonamide **151** (54 mg, 0.16 mmol, *Z*:*E*, >20:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide* **165** as a

yellow crystalline solid (32 mg, 77%); mp 240-243 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3054, 2923, 2866, 1622, 1588, 1560, 1458, 1420, 1363, 1304, 1271, 1250, 1171, 1154, 1127, 1104, 1013; δ_H (500 MHz, $(CD_3)_2SO$, 363 K) 8.49 (1H, dd, *J* 5.0, 2.0, Ar*H*), 8.03 (1H, dd, *J* 7.5, 2.0, Ar*H*), 7.50 (1H, d, *J* 10.5, ArC*H*=CHS), 7.25 (1H, d, *J* 10.5, ArCH=C*H*S) overlapping 7.23 (1H, dd, *J* 7.5, 5.0, Ar*H*), 3.79-3.73 (4H, m, $N(CH_2CH_2)_2O$), 3.57 (4H, br. s, $N(CH_2CH_2)_2O$); δ_C (126 MHz, $(CD_3)_2SO$) 151.9 (C), 149.2 (CH), 139.4 (CH), 131.8 (CH), 122.5 (CH), 118.3 (CH), 113.9 (C), 66.8 (2 × CH_2), 52.8 (2 × CH_2); HRMS (FI^+) $C_{11}H_{13}N_3O_3S^+$ ($[M]^+$) requires 267.0677, found 267.0681.

6,7-Dimethoxy-1-(4-methylpiperazin-1-yl)-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 166

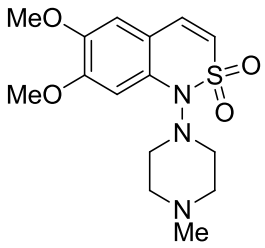


Table 3.19, entry 13: General procedure G was followed using 2-(2-bromo-4,5-dimethoxyphenyl)-*N*-(4-methylpiperazin-1-yl)ethenesulfonamide **155** (60 mg, 0.14 mmol, *Z*:*E*, 11:1). Column chromatography (eluent: 1% MeOH in CH_2Cl_2) yielded *benzothiazine 2,2-dioxide* **166** as a yellow solid (40 mg, 82%); mp 218-220 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2940, 2739, 2603, 2495, 1510, 1475, 1398, 1245, 1206, 1171, 1073, 1036; δ_H (200 MHz, CD_3CN) 7.26 (1H, s, Ar*H*) overlapping 7.25 (1H, d, *J* 10.0, ArC*H*=CHS), 7.00 (1H, s, Ar*H*), 6.71 (1H, d, *J* 10.0, ArCH=C*H*S), 3.90 (3H, s, O*Me*), 3.81 (3H, s, O*Me*), 3.42 (4H, br. s, $N(CH_2CH_2)_2NMe$), 2.52 (4H, br. s, $N(CH_2CH_2)_2NMe$), 2.25 (3H, s, N*Me*); δ_C (126 MHz, CD_3CN) 153.2 (C), 146.5 (C), 138.1 (C), 136.3 (CH), 123.2 (CH), 114.5 (C), 112.3 (CH), 102.3 (CH), 56.7 (CH_3), 53.6 (CH_3), 46.0 (CH_3), 37.3 (CH_2), 37.2 (CH_2), 28.8

(CH_2), 28.7 (CH_2); *m/z* (ESI^+) 340 ($[M + H]^+$, 100%); HMRS (ESI^+) $C_{15}H_{22}N_3O_4S^+$ ($[M + H]^+$) requires 340.1326, found 340.1321.

1-(Dibenzylamino)-6,7-dimethoxy-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 167

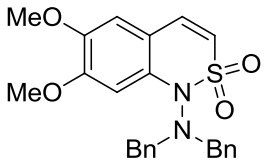


Table 3.19, entry 14: General procedure G was followed using *N*',*N*'-dibenzyl-2-(2-bromo-4,5-dimethoxyphenyl)ethenesulfonohydrazide **156** (55 mg, 0.11 mmol, *Z*:*E*, 20:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide* **167** as a pale yellow crystalline solid (35 mg, 75%); mp 190 °C (dec.) (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2923, 2853, 1603, 1508, 1463, 1321, 1242, 1208, 1152, 1118, 1029, 1012; δ_H (200 MHz, CD_3CN) 7.39-7.22 (10H, m, 10 × Bn*H*), 7.06 (1H, d, *J* 10.0, ArC*H*=CHS), 6.75 (1H, s, Ar*H*), 6.67 (1H, d, *J* 10.0, ArCH=C*H*S), 6.62 (1H, s, Ar*H*), 4.54 (2H, d, *J* 13.0, NCH_2Ph), 4.30 (2H, d, *J* 13.0, NCH_2Ph), 3.71 (3H, s, O*Me*), 3.64 (3H, s, O*Me*); δ_C (126 MHz, $CDCl_3$) 152.5 (C), 146.5 (C), 138.5 (C), 138.3 (C), 136.3 (CH), 130.8 (4 × CH), 129.2 (4 × CH), 128.7 (2 × CH), 126.4 (C), 122.9 (CH), 114.8 (C), 111.3 (CH), 104.0 (CH), 60.7 (2 × CH_2), 56.6 (CH_3), 56.5 (CH_3); *m/z* (ESI^+) 459 ($[M + Na]^+$, 100%); HMRS (ESI^+) $C_{24}H_{24}N_2NaO_4S^+$ ($[M + Na]^+$) requires 459.1349, found 459.1356.

6,7-Dimethoxy-1-(methyl(phenyl)amino)-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 168

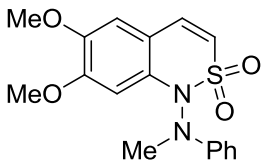
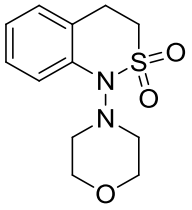


Table 3.19, entry 15: General procedure G was followed using 2-(2-bromo-4,5-dimethoxyphenyl)-*N*'-methyl-*N*'-phenylethenesulfonohydrazide **157** (65 mg, 0.15 mmol,

Z:*E*, 10:1). Column chromatography (eluent: 3:7, petrol:ether) yielded *benzothiazine 2,2-dioxide* **168** (22 mg, 42%) as an off-white crystalline solid; mp 205-208 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2934, 2867, 1605, 1510, 1474, 1245, 1208, 1152, 1110; δ_H (200 MHz, $(CD_3)_2CO$) 7.46 (1H, d, *J* 10.0, ArC*H*=CHS), 7.19-6.55 (8H, m, ArCH=C*H*S, 7 × Ar*H*), 3.83 (3H, s, O*Me*), 3.63 (3H, s, O*Me*), 2.83 (3H, s, N*Me*); δ_C (126 MHz, $(CD_3)_2CO$) 152.7 (C), 146.3 (C), 135.7 (CH), 131.5 (2 × CH), 129.6 (C), 126.0 (2 × CH), 121.4 (CH), 115.5 (C), 114.5 (C), 113.1 (CH), 112.6 (CH), 103.3 (CH), 56.5 (CH_3), 56.1 (CH_3), 35.0 (CH_3); *m/z* (ESI^+) 369 ($[M + Na]^+$, 50%), 347 ($[M + H]^+$, 100%); HMRS (ESI^+) $C_{17}H_{18}N_2NaO_4S^+$ ($[M + Na]^+$) requires 347.1060, found 347.1066.

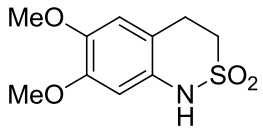
1-Morpholino-3,4-dihydro-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 177



To a solution of 1-(morpholin-4-yl)-1*H*-2,1-benzothiazine 2,2-dioxide **122** (53 mg, 0.20 mmol) in degassed ethanol (5 mL) was added Pd/C 10 wt.% (5 mg) and the flask flushed with H_2. The reaction mixture was stirred at RT under a H_2 balloon for 3 h. The flask was flushed with N_2 and the suspension filtered through Celite and washed with ethanol. The filtrate was concentrated *in vacuo* to yield *3,4-dihydrosulfostyril* **177** as a white crystalline solid (49 mg, 91%); mp 270 °C (dec) (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 2924, 2857, 1434, 1452, 1337, 1294, 1269, 1160, 1134, 1110; δ_H (500 MHz, $CDCl_3$) 7.52 (1H, dd, *J* 8.5, 1.0, Ar*H*), 7.29-7.24 (1H, m, Ar*H*), 7.13 (1H, d, *J* 7.5, Ar*H*), 7.04 (1H, app td, *J* 7.5, 1.0, Ar*H*), 3.79 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 3.47-3.41 (6H, m, $N(CH_2CH_2)_2O$, $ArCH_2CH_2S$), 3.37-3.33 (2H, m, $ArCH_2CH_2S$); δ_C (126 MHz, $CDCl_3$) 141.3 (C), 129.5 (CH), 128.0 (CH), 123.7 (CH), 122.1 (C), 118.4 (CH), 68.1 (2 × CH_2), 53.2 (2 × CH_2),

47.9 (CH_2), 28.3 (CH_2); *m/z* (ESI^+) 291 ($[M + Na]^+$, 100%), 269 ($[M + H]^+$, 20%); HMRS (ESI^+) $C_{12}H_{17}N_2O_3S^+$ ($[M + H]^+$) requires 269.0954, found 269.0959.

6,7-Dimethoxy-3,4-dihydro-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide 179[25,221]

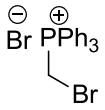


To a solution of 1-(dibenzylamino)-6,7-dimethoxy-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide **167** (45 mg, 0.10 mmol) in degassed acetone (0.3 mL) was added Pearlman's catalyst (9 mg, 20 wt.% 60% moisture, $Pd(OH_2)/C$) and the reaction flask was flushed with H_2. The reaction mixture was stirred at RT under a H_2 balloon for 16 h. The flask was then flushed with N_2 and the suspension filtered through Celite and washed with acetone. The filtrate was concentrated *in vacuo*. Acetic acid (1.1 mL) and zinc dust (17 mg, 2.60 mmol) was added and the reaction mixture stirred for 2 h at RT. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and the suspension filtered through Celite. Water was added and the organic layer extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: ether) yielded *3,4-dihydrosulfostyril* **179** as a white crystalline solid (16 mg, 68%); mp 145-148 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3225, 2925, 2850, 1605, 1503, 1463, 1325, 1270, 1152, 1121, 1111; δ_H (500 MHz, $CDCl_3$) 6.64 (1H, s, Ar*H*), 6.31 (1 H, s, Ar*H*), 6.01 (1H, s, N*H*), 3.85 (3H, s, O*Me*), 3.84 (3H, s, O*Me*), 3.43-3.37 (2H, m, CH_2), 3.31-3.26 (2H, m, CH_2); δ_C (126 MHz, $CDCl_3$) 149.9, 146.2, 129.9, 113.4, 112.2, 104.0, 56.4, 56.2, 45.9, 28.2; HMRS (ESI^-) $C_{10}H_{12}NO_4S^-$ ($[M - H]^-$) requires 242.0493, found 242.0495.

6.5 Synthesis of benzosultam: Ar-SO_2-N linkage

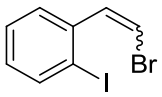
6.5.1 Preparation of substrates and catalysts

(Bromomethyl)triphenylphosphonium bromide 189[236]



A solution of triphenylphosphine (30.0 g, 114.0 mmol) and dibromomethane (17.5 mL, 257.0 mmol) in toluene (120 mL) was stirred at reflux for 24 h. After cooling to 0 °C, the precipitate was collected and washed with hot toluene (50 mL) and ether (50 mL) to give **189** as an off-white solid (29.4 g, 59%); mp 230-231 °C (IPA) {lit.[236] 232-235 °C}; δ_H (400 MHz, $CDCl_3$) 8.02-7.93 (6H, m, 6 × Ar*H*), 7.87-7.80 (3H, m, 3 × Ar*H*), 7.75-7.68 (6H, m, 6 × Ar*H*), 5.91 (2H, d, J_{HP} 6.0, CH_2); δ_C (101 MHz, $CDCl_3$) 135.5 (3 × C, d, J_{CP} 3.0), 134.3 (6 × CH, d, J_{CP} 9.5), 130.4 (6 × CH, d, J_{CP} 13.0), 116.9 (3 × C, d, J_{CP} 86.5), 18.4 (CH_2, d, J_{CP} 54.5); *m/z* (ESI^+) 794 ($[2M - Br]^+$, 40%), 793 ($[2M - Br]^+$, 100%), 792 ($[2M - Br]^+$, 43%), 791 ($[2M - Br]^+$, 97%). Data in accordance with literature data.[236]

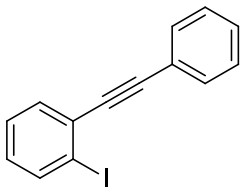
1-(2-Bromovinyl)-2-iodobenzene 188[185]



(Bromomethyl)triphenylphosphonium bromide **189** (0.56 g, 1.29 mmol) was added portion-wise to a stirred solution of KO^{t}Bu (0.14 g, 1.26 mmol) in anhydrous THF (10 mL) at –78 °C and stirred for 90 min. 2-Iodobenzaldehyde (0.25 g, 1.08 mmol) was added slowly to the resultant pale orange suspension at –78 °C, then warmed to RT and stirred for 16 h. The reaction mixture was diluted with petrol (150 mL). The white

suspension was filtered through a Celite pad and the filtrate was reduced *in vacuo*. Column chromatography (eluent: petrol) yielded *alkenyl bromide* **188** as a yellow oil (0.18 g, 55%, *Z*:*E*, 9:1); ν_{max} (neat)/cm^{-1} 3060, 2987, 1561, 1453, 1319, 1270, 1244, 1200, 1189, 1166, 1137, 1069; δ_H (200 MHz, $CDCl_3$, *Z* isomer) 7.90 (1H, dd, *J* 8.0, 1.5, Ar*H*), 7.69 (1H, dd, *J* 8.0, 1.5, Ar*H*), 7.44-7.34 (1H, m, Ar*H*), 7.12 (1H, d, *J* 8.0, ArC*H*=CHBr) overlapping 7.08-6.98 (1H, m, Ar*H*), 6.58 (1H, d, *J* 8.0, ArCH=C*H*Br); δ_H (200 MHz, $CDCl_3$, *E* isomer observable peaks) 6.71 (1H, d, *J* 14.0, ArC*H*=CHBr); δ_C (101 MHz, $CDCl_3$, *Z* isomer) 139.2 (CH), 138.9 (C) 136.8 (CH), 130.2 (CH), 129.8 (CH), 127.9 (CH), 109.5 (CH), 99.5 (C); *m/z* (FI^+) $C_8H_6BrI^+$ ($[M]^+$) requires 309.8677 and 307.8698, found 309.8681 and 307.8693.

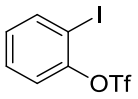
1-Iodo-2-(phenylethynyl)benzene 193



To a solution of 1,2-diiodobenzene (198 μL, 1.51 mmol) in ether (1.5 mL) was added $PdCl_2(PPh_3)_2$ (53 mg, 5 mol%), CuI (14 mg, 5 mol%), and NEt_3 (1.8 mL). The reaction mixture was stirred at RT for 30 min. Phenylacetylene (133 μL, 1.21 mmol) was added dropwise to the reaction mixture and then stirred at 70 °C for 16 h. The reaction mixture was cooled to RT and water (5 mL) was added. The organic layer was extracted with ether (3 × 10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Column chromatography (eluent: hexane) yielded alkyne **193** as a yellow oil (127 mg, 28%); ν_{max} (neat)/cm^{-1} 3100, 1490, 1460, 1429, 1015; δ_H (400 MHz, $CDCl_3$) 7.89 (1H, dd, *J* 8.0, 1.0, Ar*H*), 7.64-7.59 (2H, m, 2 × Ar*H*), 7.55 (1H, dd, *J* 8.0, 1.0, Ar*H*), 7.41-7.35 (3H, m, 3 × Ar*H*), 7.37-7.32 (1H, m, Ar*H*), 7.06-7.00 (1H, m, Ar*H*); δ_C (101 MHz, $CDCl_3$) 138.8

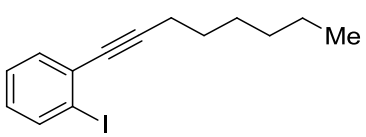
(CH), 132.4 (CH), 131.7 (2 × CH), 129.8 (C), 129.4 (CH), 128.7 (CH), 128.4 (2 × CH), 127.8 (CH), 122.9 (C), 101.2 (C), 93.1 (C), 91.6 (C); HRMS (FI^+) $C_{14}H_9I^+$ ($[M]^+$) requires 303.9749, found 303.9759. Data in accordance with literature data.[327]

2-Iodophenyl trifluoromethanesulfonate 194[328]



Trifluoromethanesulfonic anhydride (0.57 mL, 3.39 mmol) was added dropwise to a solution of 2-iodophenol (0.34 mL, 3.00 mmol) and triethylamine (0.84 mL, 6.00 mmol) in CH_2Cl_2 (7 mL) at –78 °C. The reaction mixture was stirred for 1.5 h at –78 °C and then stirred at RT overnight. The reaction mixture was diluted with ice-water (10 mL) and washed with CH_2Cl_2 (30 mL). The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: hexane) yielded triflate **194** as a colourless oil (553 mg, 52%); ν_{max} (neat)/cm^{-1} 2985, 1462, 1423, 1247, 1205, 1160, 1134, 1041, 1022; δ_H (400 MHz, $CDCl_3$) 7.92 (1H, dd, *J* 8.0, 1.5, Ar*H*), 7.47-7.41 (1H, m, Ar*H*), 7.36 (1H, dd, *J* 8.0, 1.5, Ar*H*), 7.12 (1H, app td, *J* 8.0, 1.5, Ar*H*); δ_C (101 MHz, $CDCl_3$) 150.3 (C), 140.8 (CH), 130.1 (CH), 129.6 (CH), 122.1 (CH), 118.7 (C, q, J_{CF} 318.0), 89.1 (C); δ_F (377 MHz, $CDCl_3$) –73.2 (s, O*Tf*) {^{1}H}; HRMS (FI^+) $C_7H_4F_3IO_3S^+$ ($[M]^+$) requires 351.8878, found 351.8870. Data in accordance with literature data.[328]

1-Iodo-2-(oct-1-yn-1-yl)benzene 195[329]



To a solution of 1-octyne (300 μL, 2.00 mmol) in THF (15 mL) was added ^{n}BuLi (1.1 mL, 1.76 mmol, 1.6 M in hexanes) at 0 °C. After 10 min, the reaction mixture was cooled to – 78 °C. Triflate **194** (477 mg, 1.35 mmol) in THF (15 mL) was added slowly. The reaction mixture was warmed to 0 °C and stirred for 5 h at this temperature. H_2O (15 mL) was added dropwise and the organic layer extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: 9:1, petrol:ether) yielded alkyne **195** as an orange oil (237 mg, 56%); ν_{max} (neat)/cm^{-1} 2928, 2857, 1463, 1428, 1016; δ_H (400 MHz, $CDCl_3$) 7.82 (1H, dd, *J* 7.5, 1.0, Ar*H*), 7.40 (1H, dd, *J* 7.5, 1.5, Ar*H*), 7.26 (1H, app td, *J* 7.5, 1.0, Ar*H*), 6.95 (1H, app td, *J* 7.5, 1.5, Ar*H*), 2.47 (2H, t, *J* 7.0, CC*H*$_2$), 1.70-1.61 (2H, m, CCH$_2$C*H*$_2$(CH$_2$)$_3$CH$_3$), 1.57-1.48 (2H, m, C(CH$_2$)$_2$C*H*$_2$(CH$_2$)$_2$CH$_3$), 1.37-1.31 (4H, m, C(CH$_2$)$_3$(C*H*$_2$)$_2$CH$_3$), 0.92 (3H, t, *J* 7.0, C(CH$_2$)$_5$C*H*$_3$); δ_C (101 MHz, $CDCl_3$) 138.6 (CH), 132.4 (CH), 130.6 (C), 128.4 (CH), 127.7 (CH), 101.1 (C), 94.9 (C), 82.9 (C), 31.4 (CH$_2$), 28.7 (CH$_2$), 28.5 (CH$_2$), 22.6 (CH$_2$), 19.6 (CH$_2$), 14.1 (CH$_3$); HRMS (FI$^+$) $C_{14}H_{17}I^+$ ([M]$^+$) requires 312.0375, found 312.0379. Data in accordance with literature data.[330]

2-Bromo-*N*-morpholinobenzenesulfonamide 215

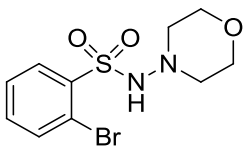


Table 4.2, entry 3: General procedure A was followed with the use of 2-bromoiodobenzene (31 μL, 0.24 mmol), $Pd(OAc)_2$ (10 mg, 0.05 mmol), $^{t}Bu_3P.HBF_4$ (28 mg, 0.10 mmol), DABSO (127 mg, 0.53 mmol) and 4-aminomorpholine (35 μL, 0.36 mmol). The reaction mixture was stirred at 90 °C for 16 h. Column chromatography (eluent: 3:7, petrol:ether to ether) yielded *sulfonamide* **215** as a white crystalline solid (11 mg, 14%); mp 136-140 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3164, 2966, 2925, 2850, 1573, 1455, 1444, 1431, 1386, 1364,

1339, 1282, 1263, 1171, 1127, 1099, 1070, 1022; δ_H (400 MHz, $CDCl_3$) 8.24 (1H, dd, *J* 7.5, 1.5, Ar*H*), 7.74 (1H, dd, *J* 7.5, 1.0, Ar*H*), 7.50 (1H, app td, *J* 7.5, 1.0, Ar*H*), 7.45 (1H, m, *J* 7.5, 1.5, Ar*H*), 6.09 (1H, s, N*H*), 3.56 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.70 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$); δ_C (126 MHz, $CDCl_3$) 138.1 (C), 135.1 (CH), 134.3 (CH), 133.5 (CH), 127.9 (CH), 120.2 (C), 66.6 (2 × CH_2), 56.7 (2 × CH_2); *m/z* (ESI^+) 345 ($[M + Na]^+$, 80%), 321 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{10}H_{13}BrN_2NaO_3S^+$ ($[M + Na]^+$) requires 344.9702 and 342.9722, found 344.9706 and 342.9725.

(*E*)-1,2-Diphenylethenyl 4-methylphenyl sulfone 198a

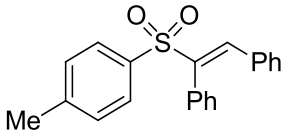


Table 4.3, entry 2: An oven-dried tube was evacuated and backfilled with N_2. It was then charged with 4-methyl-*N*-(morpholin-4-yl)benzenesulfonamide **11** (64 mg, 0.25 mmol), $[RuCl_2(p\text{-cymene})]_2$ (8 mg, 0.01 mmol), $Cu(OAc)_2.H_2O$ (100 mg, 0.50 mmol) and diphenylacetylene (90 μL, 0.50 mmol). The solid reagents were weighed out in the air. The tube was then evacuated and backfilled with N_2. ^{t}AmOH (1.0 mL) was added through a suba-seal under N_2. The reaction mixture was stirred at 120 °C for 20 h. After cooling to RT, the suspension was filtered through a short pad of Celite and the residue washed sequentially with CH_2Cl_2 (5 mL) and ether (5 mL) before being concentrated *in vacuo*. Column chromatography (eluent: 7:3, petrol:ether to ether) yielded the sulfone **198a** as a white crystalline solid (27 mg, 32%); mp 177-179 °C (CH_2Cl_2) {lit.[331] 179-180 °C (ethanol)}; δ_H (400 MHz, $CDCl_3$) 7.95 (1H, s, CPh=C*H*Ph), 7.53-7.49 (2H, m, 2 × Ar*H*), 7.40-7.35 (1H, m, Ar*H*), 7.32-7.23 (3H, m, 3 × Ar*H*), 7.21-7.15 (4H, m, 4 × Ar*H*), 7.09-7.02 (4H, m, 4 × Ar*H*), 2.40 (3H, s, Ar*Me*); δ_C (101 MHz, $CDCl_3$) 144.1 (C), 141.6 (C), 137.3 (CH), 135.8 (C), 132.9 (C), 131.4 (C), 130.8 (2 × CH), 130.5 (2 × CH), 130.0

(CH), 129.4 (2 × CH), 129.1 (CH), 128.8 (2 × CH), 128.7 (2 × CH), 128.5 (2 × CH), 21.6 (CH_3); *m/z* (ESI^+) 357 ($[M + Na]^+$, 100%), 335 ($[M + H]^+$, 70%); HRMS (ESI^+) $C_{21}H_{18}NaO_2S^+$ ($[M + Na]^+$) requires 357.0920, found 357.0931. Data in accordance with literature data.[332]

Di-*μ*-chloro-dichloro *bis*(η^5-pentamethylcyclopentadienyl)dirhodium(III)[333]

Rhodium trichloride trihydrate (0.50 g, 1.90 mmol), pentamethylcyclopentadiene (0.31 μL, 2.00 mmol) and methanol (13.5 mL) were placed in a round-bottomed flask fitted with a reflux condenser under N_2. The apparatus was purged with N_2 for 5 min and the reaction mixture refluxed gently for 48 h. The reaction mixture was cooled to RT and the dark red precipitate filtered off in air. The filtrate was reduced *in vacuo* to approximately 5 mL which was then also filtered and washed with diethyl ether (3 × 10 mL). Air drying and recrystallisation from chloroform and hexane yielded $[Cp^*RhCl_2]_2$ as a dark red solid (0.56 g, 47%); ν_{max} (neat)/cm^{-1} 2964, 2913, 1446, 1371, 1162, 1076, 1027; δ_H (400 MHz, $CDCl_3$) 1.65 (*Me*); δ_C (126 MHz, $CDCl_3$) 94.3 (10 × C, d, J_{RhC} 9.0), 9.53 (10 × CH_3); Anal. Calcd. (%) for $C_{20}H_{30}Cl_4Rh_2$: C 38.86, H 4.89; found C 37.75, H 4.75. Data in accordance with literature data.[334]

$Cp^*Rh(OAc)_2$[256]

$[Cp^*RhCl_2]_2$ (0.20 g, 0.32 mmol), silver acetate (25 mg, 0.15 mmol) and toluene (13 mL) were added to a round-bottomed flask. The apparatus was purged with N_2 for 5 min and the reaction mixture was stirred for 1 h at RT. Silver chloride was filtered off and washed with toluene. The filtrate was reduced *in vacuo* to yield $Cp^*Rh(OAc)_2$ as a red-orange solid (90 mg, 79%); δ_H (200 MHz, $CDCl_3$) 1.99 (6H, s, CO_2*Me*), 1.69 (15H, s, Cp**Me*); δ_C

(101 MHz, $CDCl_3$) 181.8 (2 × C), 90.6 (5 × C, d, J_{RhC} 9.0), 23.6 (2 × CH_3), 9.0 (5 × CH_3). Data in accordance with literature data.[256]

Appendix A

Synthesis of *N*-aminosulfonamides

This section describes brief investigation into the palladium catalysed aminosulfonylation reaction using heteroaryl iodides and DABSO as the sulfur dioxide donor.

A.1 Methods to synthesise sulfonamides

Nearly 10% of the top 200 pharmaceuticals in 2012 contained either a sulfonamide functionality or were co-administered with a sulfonamide-containing drug.[1(a),(b)] Sulfonamides with a heteroaryl moiety, in particular, are found in numerous pharmaceuticals, such as Methazolamide,[335] Torasemide[336] and Brinzolamide,[337] and also agrochemicals, such as Cyazofamid[338] and Sulfosulfuron (Figure A.1).[339]

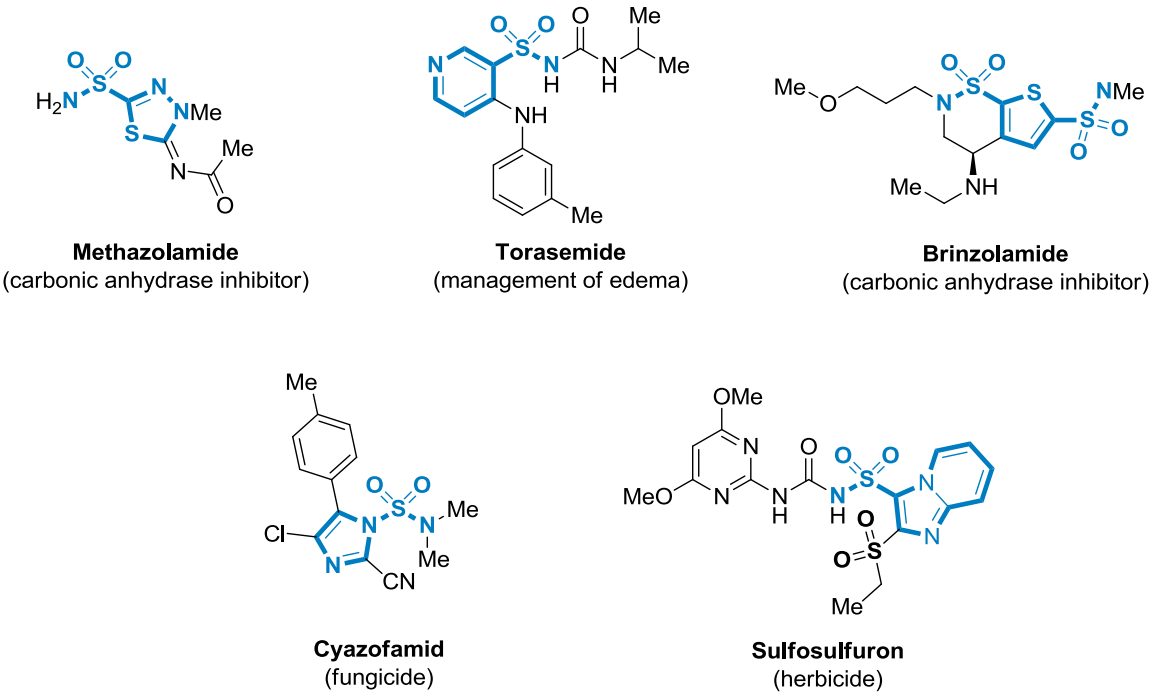
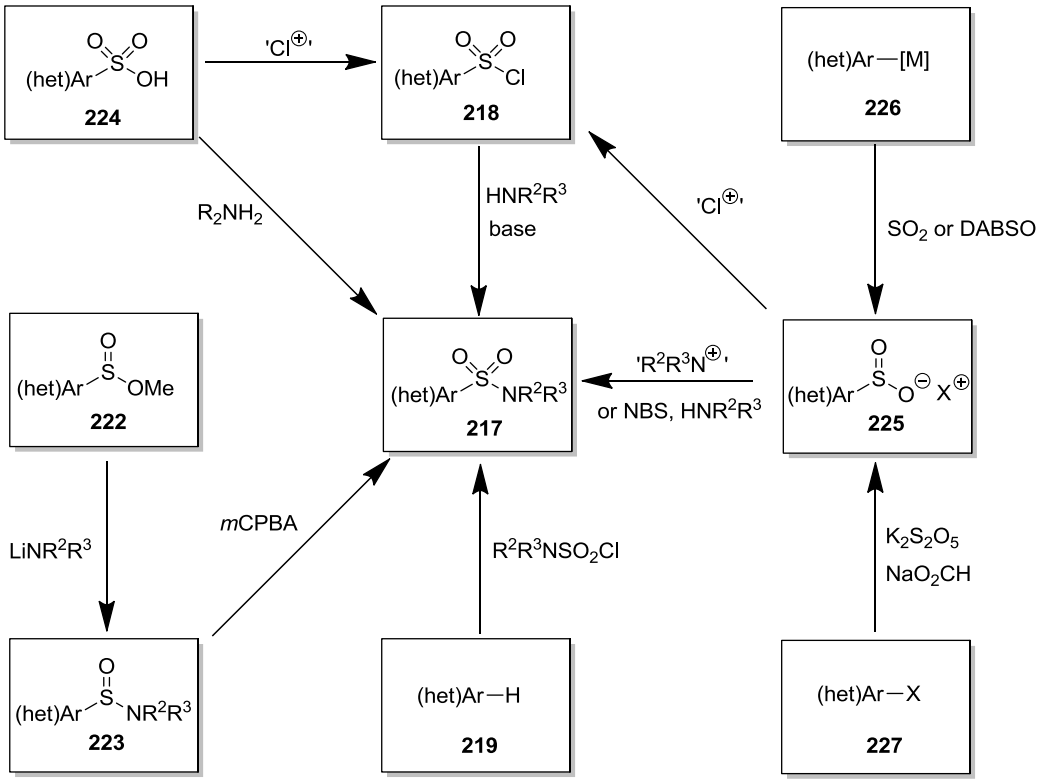


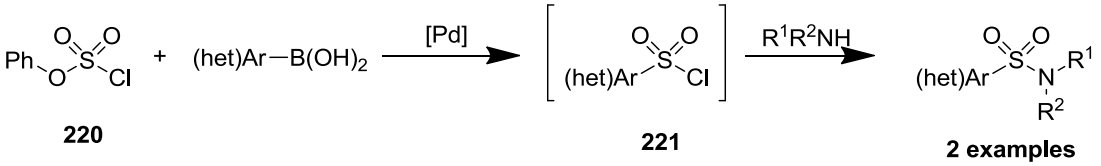
Figure A.1: Example of heteroaryl sulfonamide pharmaceuticals and agrochemicals.

An overview of the methods to synthesise heteroaryl sulfonamides **217** is depicted in Scheme A.1. The classical approach to sulfonamides is by amination of a sulfonyl chloride (**218** → **217**).[340] Sulfonyl chlorides themselves can require harsh conditions to prepare as discussed in further detail in Section 3.1. Introducing the sulfonamide moiety directly by electrophilic aromatic substitution is also possible, for example by sulfamoylation (**219** → **217**).[341]



Scheme A.1: Synthesis of heteroaryl sulfonamides.

Milder reaction conditions have recently been reported, for example using trichloroisocyanuric acid to prepare sulfonamides from a (hetero)aromatic thiol *via* a sulfonyl chloride intermediate.[342] In 2013, Buchwald *et al*. achieved palladium catalysed chlorosulfonylation, followed by amination to give the desired (hetero)aromatic sulfonamides (Scheme A.2).[343] The aryl chlorosulfate species **220** was specifically designed with two leaving groups of different reactivity to generate the arylsulfonyl chloride **221** by a palladium catalysed Suzuki-Miyaura coupling. The reaction thus avoids the direct use of strong chlorinating agents in the reaction.

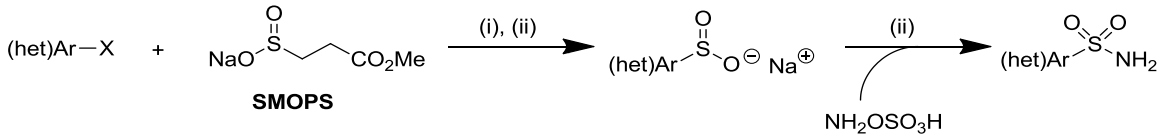


Scheme A.2: Preparation of sulfonamides *via* a sulfonyl chloride intermediate. *Reaction conditions:* (i) [Pd] (2 mol%), Na_2CO_3 (5 mol%), acetone [0.5 M], 50–70 °C, 12 h; (ii) R^1R^2NH, RT, 1.5 h.

Methodologies that use leaving groups other than chloride have also been developed. For example, methyl sulfinate **222** can be converted to a sulfinamide **223** and then oxidised to a sulfonamide, although the methyl sulfinates themselves are not commercially available (**222** → **223** → **217**).[344]

Sulfonamides can be prepared from sulfonic acids **224** by aminolysis of PFP (pentafluorophenol)- or TCP (trichlorophenol)-sulfonates (**224**→**217**).[345] Alternatively, an *in situ* sulfonyl chloride can be formed from the sulfonic acid, which is then reacted with a suitable amine (**224**→ **218** →**217**).[346]

Sulfinate salts **225** can also be used in heteroaryl sulfonamide synthesis by reaction with an electrophilic nitrogen source such as hydroxylamine-*O*-sulfonic acid[347] and *bis*(2,2,2-trichloroethyl)-azodicarboxylate (**225**→**217**).[221] For example, SMOPS (sodium 3-methoxy-3-oxopropane-1-sulfinate), through alkylation and then β-elimination, can be used as a SO_2^{2-} surrogate to give a sulfinate salt from aryl or alkyl halides. The sulfinate salt can then react with the electrophilic nitrogen source, hydroxylamine-*O*-sulfonic acid, to give a range of sulfonamides (Scheme A.3).[348]



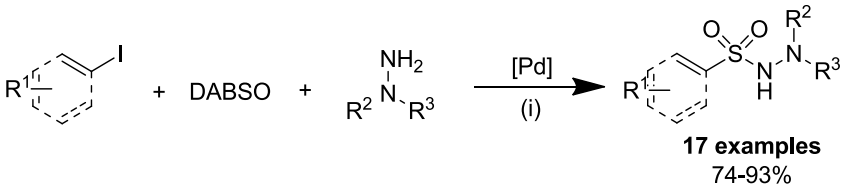
Scheme A.3: *Reaction conditions*: (i) SMOPS (3 equiv.), CuI (3 equiv.), DMSO, RT, 10 min to 24 h; (ii) Base (1 equiv.), DMSO, RT, 15 min; (iv) NH_2OSO_3H (5 equiv.), NaOAc (3.75 equiv.), H_2O, RT, 20 h.

Sulfinate salts, however, have limited commercial availability and their preparation often involves multi-step procedures or the use of organometallic reagents which are incompatible with many functional groups. Several groups have been able to prepare sulfonamides directly from organometallic reagents **226** *via* a sulfinate salt intermediate

225 or *via* a sulfonyl chloride **218** prepared using an electrophilic chloride source such as NCS, SO_2Cl_2, or *N*-chlorobenzotriazole (**226→225→218→217**).[24,68,69,349] Both sulfur dioxide gas and DABSO have been used successfully in these reactions. A recent paper from Pfizer reported the synthesis of a small range of sulfonamides directly from the aryl halide or triflate **227** using palladium-catalysis and potassium metabisulfite (as the sulfur dioxide donor) and sodium formate (as the hydrogen source) *via* a sulfinate salt intermediate (**227 → 225 → 217**) (described in further detail in Chapter 1).[8]

The major disadvantages of the methodologies described above are the lack of commercial availability or difficulty in preparation of the starting material, and the reduced functional group tolerance due to the harsh reaction conditions often required. There is also a lack of methodology that forms the C—S and S—N bonds in the same synthetic step.

The Willis group have recently investigated the synthesis of sulfonamides, focussing on using readily available starting materials and using milder reaction conditions to provide a more general route to sulfonamides. A palladium catalysed aminosulfonylation reaction was developed using aryl halides, hydrazines, and DABSO (as a sulfur dioxide donor) to synthesise a range of *N*-aminosulfonamides in excellent yields (discussed further in Section 1.2.6) (Scheme A.4). This methodology provides high functional group tolerance and uses easy-to-handle reagents. The rest of this chapter will examine the scope of this reaction with heteroaryl halides.



Scheme A.4: *Reaction conditions*: (i) Iodosubstrate (1 equiv.), hydrazine (1.5 equiv.), $Pd(OAc)_2$ (10 mol%), $^tBu_3P.HBF_4$ (20 mol%), DABSO (0.6 equiv.) and DABCO (0.5 equiv.) or DABSO (1.1 equiv.) without DABCO, 1,4-dioxane [0.15 M], 70 °C, 16 h.

A.2 Synthesis of *N*-aminosulfonamides *via* palladium catalysed aminosulfonylation of heteroaryl halides

Investigation was undertaken to examine the effect of heteroaryl halo-coupling partners in the palladium catalysed aminosulfonylation reaction as previous work in the Willis group[350] found that many heteroaryl iodides returned only unreacted starting material (Figure A.2).

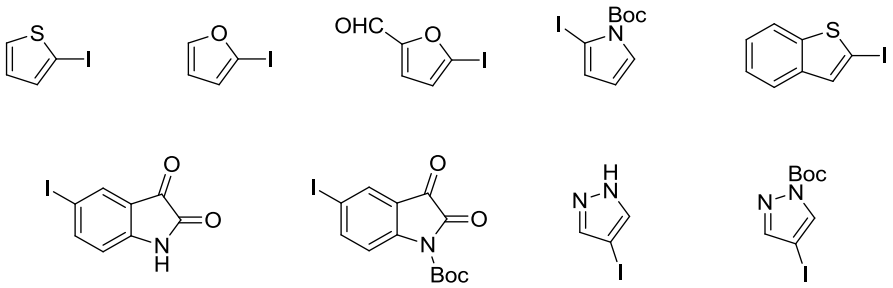
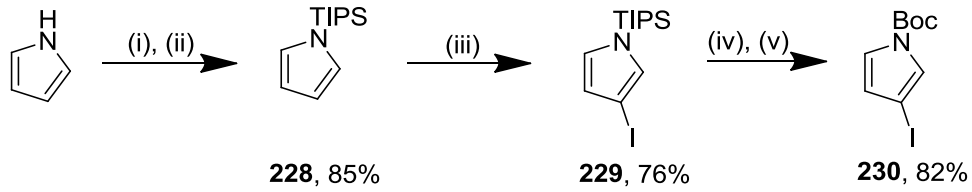


Figure A.2: Heteroaryl iodides previously employed in the Willis group[350] affording no heteroaryl *N*-aminosulfonamide product. *Reaction conditions*: Heteroaryl iodide (1 equiv.), 4-aminomorpholine (1.5 equiv.), $Pd(OAc)_2$ (10 mol%), $^tBu_3P.HBF_4$ (20 mol%), DABSO (1.1 equiv.), 1,4-dioxane [0.15 M], 70 °C, 16 h.

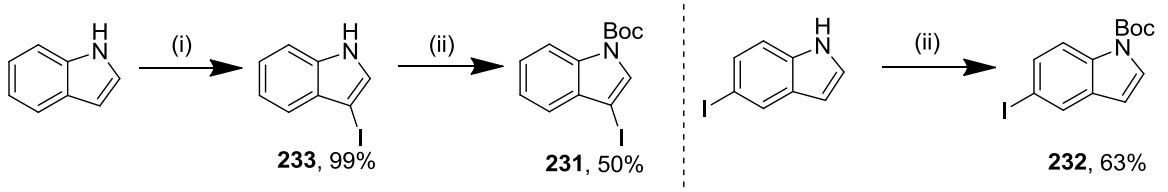
A.2.1 Synthesis of heteroaryl iodide substrates

Firstly, a range of iodo-substituted *N*-, *O*- and *S*-containing heterocycles were synthesised to test for their compatibility with the desired palladium catalysed reaction. A range of 3-iodosubstituted heterocycles were prepared, as previous work had found that 2-iodosubstituted heteroaryl substrates returned only starting materials. Literature precedent has shown that heterocycles containing a free NH group can be troublesome due to the competing Buchwald–Hartwig reaction, so a selection of both protected and unprotected *N*-heterocycles were also synthesised.[351] *N*-TIPS- and *N*-Boc-protected 3-iodopyrroles **229** and **230**,[352] and *N*-Boc-protected 3- and 5-iodoindoles **231** and **232**,[353] were synthesised according to routes shown in Scheme A.5 and Scheme A.6 respectively.



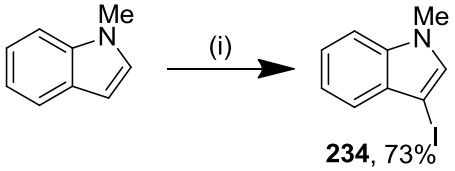
Scheme A.5: *Reaction conditions*: (i) Pyrrole (1 equiv.), NaH (1.1 equiv.), DMF [0.5 M], 0 °C, 1.5 h; (ii) TIPS-Cl (1.2 equiv.), 0 °C, 45 min; (iii) NIS (0.9 equiv.), acetone [0.13 M], –78 °C, 6 h, RT, 3 h; (iv) TBAF (1.1 equiv.), THF [0.3 M], 10 min, RT; (v) DMAP (0.11 equiv.), Boc_2O (1.2 equiv.), MeCN [0.3 M], RT, 1.5 h.

3-Iodoindole **233** readily decomposes therefore it was used immediately in the subsequent protection step without purification, which may account for the modest yield of 50% obtained for indole **231**.[354]



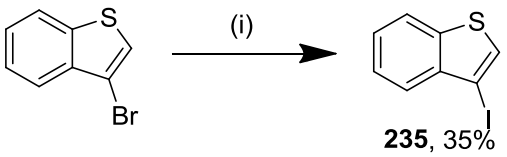
Scheme A.6: *Reaction conditions:* (i) Indole (1 equiv.), I_2 (1 equiv.), KOH (2.5 equiv.), DMF [0.4 M], RT, 2 h; (ii) Substituted indole (1 equiv.), Boc_2O (1.1 equiv.), NEt_3 (3 equiv.), DMAP (0.1 equiv.), CH_2Cl_2 [0.2 M], RT, 1 h.

To synthesise 3-iodo-1-methylindole **234** it was decided not to methylate the 3-iodoindole **233** due to its instability, but instead to iodinate 1-methylindole with NIS (Scheme A.7).



Scheme A.7: *Reaction conditions*: (i) 1-Methylindole (1 equiv.), NIS (1.1 equiv.), DMF [0.2 M], 0 °C, 30 min.

Iodobenzothiophene **235** was obtained by transhalogenation of 3-bromobenzothiophene by the aromatic Finkelstein reaction using copper iodide, sodium iodide and a diamine ligand (Scheme A.8).[279] Despite a 70% conversion to benzothiophene **235**, determined by ^1H NMR spectroscopy, only a 35% yield was isolated due to difficultly in separation from the starting material by column chromatography.

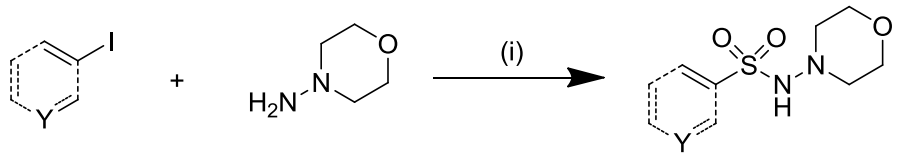


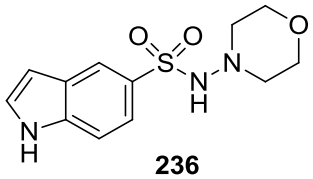
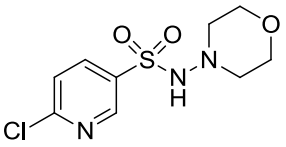
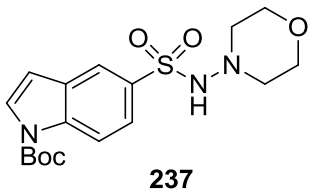
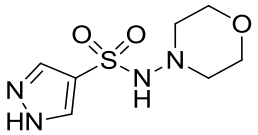
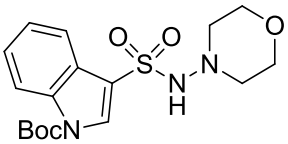
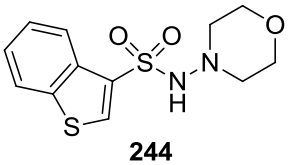
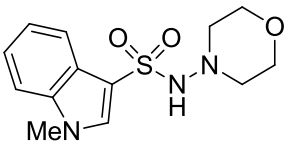
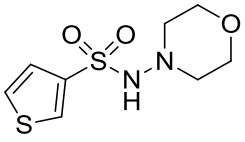
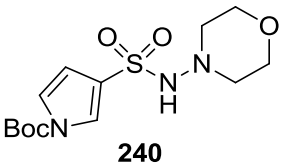
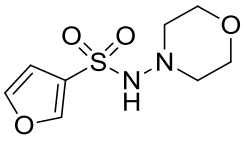
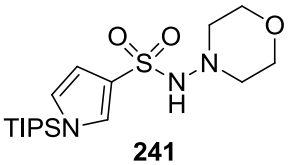
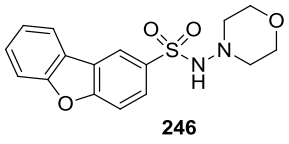
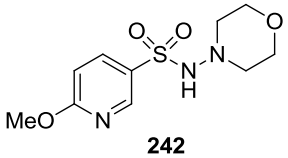
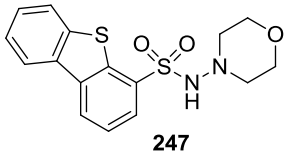
Scheme A.8: *Reaction conditions*: (i) 3-Bromobenzothiophene (1 equiv.), CuI (5 mol%), NaI (2 equiv.), racemic *trans-N,N'*-dimethyl-1,2-cyclohexanediamine (10 mol%), *m*-xylene, diglyme (4:1) [1 M], 130 °C, 22 h.

A.2.2 Synthesis of *N*-aminosulfonamides from heteroaryl halides

For the investigation of the palladium catalysed aminosulfonylation reactions with heteroaryl halides, 4-aminomorpholine was chosen as the hydrazine source as it had previously afforded the highest yields.[23] For slower-reacting substrates, such as those with electron-withdrawing groups, 1.1 equiv. of DABSO without the addition of extra DABCO was found to be the most effective and was applied in this investigation. The corresponding *N*-aminosulfonamides were synthesised in low to excellent yields (Table A.1). The remaining material was found to be either decomposed starting material as in the case for *N*-TIPS-protected 3-iodopyrrole **229** and 3-bromofuran or unreacted starting material.

Table A.1: Synthesis of heteroaryl *N*-aminosulfonamides *via* palladium catalysed aminosulfonylation of heteroaryl halides.



Entry	Product	Yield/ %[a]	Entry	Product	Yield/ %[a]
1	 **236**	74	8	 **243**	29
2	 **237**	81	9		0
3	 **238**	48	10	 **244**	73
4	 **239**	42	11	 **245**	24[b]
5	 **240**	20	12		0[b]
6	 **241**	24	13	 **246**	89
7	 **242**	76	14	 **247**	92

Reaction conditions: (i) Heteroaryl halide (1 equiv.), 4-aminomorpholine (1.5 equiv.), $Pd(OAc)_2$ (10 mol%), $^tBu_3P.HBF_4$ (20 mol%), DABSO (1.1 equiv.), 1,4-dioxane [0.15 M], 70 °C, 16 h. [a] Isolated yields. [b] ArBr used instead of ArI.

Unprotected 5-iodoindole (entry 1) and *N*-Boc-protected (entry 2) sulfonamides were formed in similar yields, demonstrating that the free NH group was well tolerated; possibly because the lack of a strong base resulted in no competing *N*-arylation.[355] In the case of the pyrrole/indole-ring structures (entries 1 to 6), higher yields were obtained when the iodide was on the benzene (entries 1 to 2) rather than the pyrrole moiety (entries 3 to 6), which was unsurprising considering that palladium catalysed reactions with heteroaryl substrates can be limited and lower yielding.[356]

2-Chloro-5-iodopyridine gave a much lower yield of the sulfonamide compared to the *O*-methylated pyridine **242** (entries 7 and 8). This result correlates to previous findings that showed electron-rich coupling partners performed better in the palladium catalysed aminosulfonylation reaction. In comparison, the weakly basic 4-iodopyrazole[357] returned only starting material (entry 9), possibly due to the strong binding of the pyrazole to palladium, deactivating the catalyst.[358]

3-Iodo-1-benzothiophene (entry 10) gave a comparable yield to 3-iodothiophene (76% – a previous result from the Willis group).[23] Heteroaryl bromides were also investigated, but with limited success: 3-bromothiophene gave a low yield of 24% (entry 11), whereas 3-bromofuran decomposed under the reaction conditions (entry 12). Excellent yields of *O*- and *S*-heteroaryl sulfonamides were obtained when the 2-iododibenzo[*b,d*]furan and 4-iododibenzo[*b,d*]thiophene were implemented (entries 13 and 14).

A.3 Conclusion

The palladium catalysed aminosulfonylation reaction employing DABSO as the sulfur dioxide source was successful with the majority of heteroaryl iodide substrates implemented. These results demonstrate that the palladium catalysed aminosulfonylation reaction is a viable system to synthesise a range of *N*-aminosulfonamides from aryl, heteroaryl and alkenyl iodides. As expected from the original palladium catalysed reaction results, bromides gave diminished yields.

After publication of results from this chapter,[25] the Wu group were able to successfully use potassium metabisulfite as the sulfur dioxide source under similar palladium catalysed conditions to synthesise *N*-aminosulfonamides. As a further extension, they were able to use boronic acids under oxidative palladium catalysed conditions to prepare *N*-aminosulfonamides, with DABSO as the sulfur dioxide source. However, in both cases, no heteroaryl examples were synthesised.

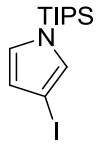
A.4 Experimental details

A.4.1 Preparation of substrates

1-(Triisopropylsilyl)-1*H*-pyrrole 228[352]

A solution of pyrrole (3.0 mL, 43.3 mmol) in DMF (10 mL) was added dropwise to a suspension of NaH (1.90 g, 47.5 mmol, 60% dispersion in mineral oil) in DMF (70 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h. Triisopropylsilyl chloride (10.0 g, 51.9 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 45 min. The reaction mixture was quenched with H_2O (100 mL) and the aqueous phase extracted with ether (2 × 200 mL). The organic layers were washed with H_2O (2 × 200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (eluent: petrol) yielded the pyrrole **228** as a colourless oil (8.22 g, 85%); ν_{max} (neat)/cm^{-1} 3048, 2989; δ_H (400 MHz, $CDCl_3$) 6.81 (2H, app t, *J* 2.0, 2 × CH=C*H*N), 6.33 (2H, app t, *J* 2.0, 2 × C*H*=CHN), 1.46 (3H, sept, *J* 7.5, Si(C*H*(Me)$_2$)$_3$), 1.11 (18H, d, *J* 7.5, Si(CH(*Me*)$_2$)$_3$); δ_C (101 MHz, $CDCl_3$) 124.0 (2 × CH), 110.0 (2 × CH), 17.8 (3 × CH), 11.7 (6 × CH_3); *m/z* (FI$^+$) $C_{13}H_{25}NSi^+$ ([M]$^+$) requires 223.1756, found 223.1750. Data in accordance with literature data.[359]

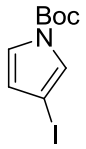
3-Iodo-1-(triisopropylsilyl)-pyrrole 229[352]



N-Iodosuccinimide (2.72 g, 12.1 mmol) was added in one portion to a solution of 1-(triisopropylsilyl)-1*H*-pyrrole **228** (3.00 g, 13.4 mmol) in acetone (100 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 6 h in the absence of light and then warmed to RT over 3 h. After evaporation of the solvents, hexane (50 mL) was added and the solution was filtered through a plug of alumina. The filtrate was concentrated *in vacuo*. Column chromatography (eluent: petrol) yielded pyrrole **229** as a pale yellow oil (3.56 g, 76%); ν_{max} (neat)/cm^{-1} 3038, 2995; δ_H (400 MHz, $CDCl_3$) 6.80 (1H, dd, *J* 2.5, 1.5, CI=C*H*N), 6.67 (1H, dd, *J* 2.5, 2.5, CH=C*H*N), 6.37 (1H, dd, *J* 2.5, 1.5, C*H*=CHN), 1.43

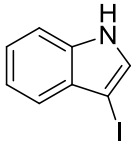
(3H, sept, *J* 7.5, Si(C*H*(Me)$_2$)$_3$), 1.08 (18H, d, *J* 7.5, Si(CH(*Me*)$_2$)$_3$); δ_C (101 MHz, $CDCl_3$) 128.7 (CH), 125.7 (CH), 117.5 (CH), 62.1 (C), 17.7 (3 × CH), 11.6 (6 × CH_3); *m/z* (FI^+) $C_{13}H_{24}INSi^+$ ($[M]^+$) requires 349.0723, found 349.0728. Data in accordance with literature data.[360]

***tert*-Butyl 3-iodo-pyrrole-1-carboxylate 230**[352]



Tetrabutylammonium fluoride (0.79 g, 3.00 mmol) was added to a solution of 3-iodo-1-(triisopropylsilyl)-pyrrole **229** (1.00 g, 2.86 mmol) in THF (10 mL) at RT for 10 min. Ether (45 mL) was added and the reaction mixture was washed with H_2O (30 mL) and brine (30 mL). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in MeCN (10 mL), then 4-dimethylaminopyridine (42 mg, 0.34 mmol) and di-*tert*-butyldicarbonate (0.75 g, 3.43 mmol) were added sequentially. The reaction mixture was stirred for 1.5 h at RT, then ether (50 mL) and 1 M $KHSO_{4(aq)}$ (20 mL) were added. The organic layer was washed with 1 M $KHSO_{4(aq)}$ (5 × 10 mL), H_2O (20 mL), 1 M $NaHCO_{3(aq)}$ (10 mL), and brine (2 × 20 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: petrol) yielded pyrrole **230** as an orange oil (0.67 g, 82%); ν_{max} (neat)/cm^{-1} 3050, 2989, 1728; δ_H (200 MHz, $CDCl_3$) 7.30 (1H, dd, *J* 2.0, 1.5, CI=C*H*N), 7.13 (1H, dd, *J* 3.5, 2.0, CH=C*H*N), 6.29 (1H, dd, *J* 3.5, 1.5, C*H*=CHN), 1.59 (9H, s, 3 × *Me*); δ_C (101 MHz, $CDCl_3$) 147.7 (C), 123.3 (CH), 121.5 (CH), 115.1 (CH), 84.3 (C), 65.3 (C), 28.1 (3 × CH_3); *m/z* (FI^+) $C_9H_{12}INO_2^+$ ($[M]^+$) requires 292.9913, found 292.9919. Data in accordance with literature data.[361]

3-Iodo-1*H*-indole 233[353]



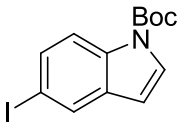
A solution of iodine (4.34 g, 17.1 mmol) in DMF (20 mL) was added dropwise to a solution of indole (2.00 g, 17.1 mmol) and KOH (2.40 g, 42.7 mmol) in DMF (20 mL) at RT. The reaction mixture was stirred for 2 h at RT and then poured onto a mixture of ice and water (200 mL) containing $Na_2S_2O_5$ (5% aqueous solution). The precipitate was filtered and washed with water to yield indole **233** as a light brown solid (4.16 g, 99%) which was used without further purification; mp 79-81 °C (dec) {lit.[354] mp 77–78 °C (dec)}; δ_H (200 MHz, $CDCl_3$) 8.19-8.09 (1H, m, Ar*H*), 7.74 (1H, s, CI=C*H*N), 7.46-7.30 (4H, m, 3 × Ar*H*, N*H*); δ_C (101 MHz, $CDCl_3$) 135.8 (C), 130.0 (C), 128.7 (CH), 123.4 (CH), 121.2 (CH), 121.1 (CH), 111.6 (CH), 57.7 (C); *m/z* (ESI^-) 242 ($[M - H]^-$, 100%). Data in accordance with literature data.[354]

***tert*-Butyl 3-iodo-1*H*-indole-1-carboxylate 231**[353]

Di-*tert*-butyldicarbonate (0.49 g, 2.26 mmol), NEt_3 (0.9 mL, 6.17 mmol) and 4-dimethylaminopyridine (25 mg, 0.21 mmol) were added to a solution of 3-iodo-1*H*-indole **233** (0.50 g, 2.06 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at RT for 1 h, and then washed twice with $Na_2S_2O_5$ (5% aqueous solution), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: 95:5, petrol:EtOAc) yielded indole **231** as a colourless oil (253 mg, 50%); ν_{max} (neat)/cm^{-1} 3100, 2985, 2929, 1727; δ_H (400 MHz, $CDCl_3$) 8.14 (1H, d, *J* 8.0, Ar*H*), 7.74 (1H, s, CI=C*H*N), 7.45-7.29

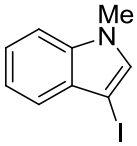
(3H, m, 3 × Ar*H*), 1.68 (9H, s, ^{t}*Bu*); δ_C (101 MHz, $CDCl_3$) 150.0 (C), 134.9 (C), 132.2 (C), 130.3 (CH), 125.4 (CH), 124.1 (CH), 121.6 (CH), 115.0 (CH), 84.4 (C), 65.6 (C), 28.1 (3 × CH_3); *m/z* (ESI^+) 366 ($[M + Na]^+$, 100%). Data in accordance with literature data.[353]

tert-Butyl 5-iodo-1*H*-indole-1-carboxylate 232[353]



Di-*tert*-butyldicarbonate (1.55 g, 7.11 mmol), NEt_3 (2.7 mL, 19.4 mmol) and 4-dimethylaminopyridine (79 mg, 0.65 mmol) were added to a solution of 5-iodoindole (1.57 g, 6.46 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was stirred at RT for 1 h and then washed twice with $Na_2S_2O_5$ (5% aqueous solution), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: 95:5, petrol:EtOAc) yielded *indole* **232** as a pale yellow solid (1.41 g, 63%); mp 45-46 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3115, 2979, 2933, 1731, 1597, 1572, 1530, 1454, 1244, 1158, 1082, 1023; δ_H (400 MHz, $CDCl_3$) 7.93 (1H, d, *J* 8.5, Ar*H*) overlapping 7.90 (1H, d, *J* 2.0, Ar*H*), 7.59 (1H, dd, *J* 8.5, 2.0, Ar*H*) overlapping 7.56 (1H, d, *J* 3.5, CH=C*H*N), 6.49 (1H, d, *J* 3.5, C*H*=CHN), 1.68 (9H, s, ^{t}*Bu*); δ_C (101 MHz, $CDCl_3$) 149.5 (C), 134.6 (C), 133.0 (C), 132.8 (CH), 129.8 (CH), 126.8 (CH), 117.1 (CH), 106.3 (CH), 86.8 (C), 84.2 (C), 28.3 (3 × CH_3); *m/z* (FI^+) $C_{13}H_{14}INO_2^+$ ($[M]^+$) requires 343.0096, found 343.0092.

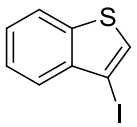
3-Iodo-1-methyl-1*H*-indole 234



1-Methylindole (1.00 g, 7.62 mmol) was dissolved in DMF (35 mL) and cooled to 0 °C. *N*-Iodosuccinimide (1.89 g, 8.38 mmol) was added in one portion and the reaction mixture

was stirred for 30 min. The reaction mixture was quenched with sat. $NaHCO_{3(aq)}$ (30 mL) and stirred for 10 min, then diluted with H_2O (30 mL) and extracted with ether (30 mL). The organic layer was subsequently washed with H_2O (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (eluent: 97:3, hexane:EtOAc) yielded *indole* **234** as a pale yellow crystalline solid (1.43 g, 73%); mp 55-56 °C (CH_2Cl_2) {lit.[362] 58-59 °C (hexane)}; ν_{max} (neat)/cm^{-1} 3125, 3047, 2908, 2874, 2816, 1503, 1455, 1331, 1237, 1176, 1040; δ_H (400 MHz, $(CD_3)_2SO$) 7.53 (1H, app s, Ar*H*), 7.45 (1H, d, *J* 8.0, Ar*H*), 7.31-7.27 (1H, m, Ar*H*), 7.25-7.20 (1H, m, Ar*H*), 7.18-7.11 (1H, m, CI=C*H*N), 3.80 (3H, s, N*Me*); δ_C (101 MHz, $(CD_3)_2SO$) 136.6 (C), 133.4 (CH), 129.8 (C), 122.2 (CH), 120.1 (CH), 120.0 (CH), 110.2 (CH), 54.5 (C), 32.7 (CH_3); *m/z* (FI^+) $C_9H_8IN^+$ ($[M]^+$) requires 256.9702, found 256.9700.

3-Iodo-1-benzothiophene 235[279]

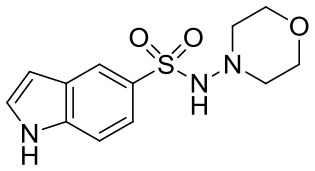


CuI (10 mg, 0.05 mmol) and NaI (300 mg, 2.00 mmol) were added to a 15 mL Schlenk tube, and then evacuated and backfilled with Ar. Racemic *trans-N,N'*-dimethyl-1,2-cyclohexanediamine (16 µL, 0.10 mmol), 3-bromothanaphthene (131 µL, 1.00 mmol), *m*-xylene (0.8 mL) and diglyme (0.2 mL) were added under Ar. The reaction mixture was stirred at 130 °C for 22 h. The reaction mixture was then cooled to RT, diluted with hexane (10 mL) and filtered through silica gel, eluting with hexane (50 mL), and the filtrate was concentrated *in vacuo*. Column chromatography (eluent: hexane) yielded benzothiophene **235** as a yellow oil (92 mg, 35%); ν_{max} (neat)/cm^{-1} 3068, 2979, 2956; δ_H (400 MHz, $CDCl_3$) 7.87 (1H, d, *J* 8.0, Ar*H*), 7.78 (1H, d, *J* 8.0, Ar*H*), 7.62 (1H, s, CI=C*H*S), 7.48 (1H, app t, *J* 8.0, Ar*H*), 7.41 (1H, app t, *J* 8.0, Ar*H*); δ_C (101 MHz, $CDCl_3$)

140.2 (C), 138.2 (CH), 129.1 (C), 125.3(3) (CH), 125.3(1) (CH), 125.2 (CH), 122.4 (CH), 78.2 (C); *m/z* (FI^+) $C_8H_5IS^+$ ($[M]^+$) requires 259.9157, found 259.9158. Data in accordance with literature data.[279]

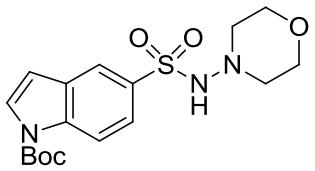
A.4.2 Synthesis of *N*-aminosulfonamides

1*H*-Indole-5-sulfonamide, *N*-4-morpholinyl- 236



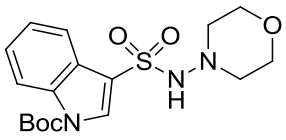
The general procedure A was followed with the use of 5-iodo-1*H*-indole (58 mg, 0.24 mmol), $^tBu_3P.HBF_4$ (14 mg, 0.05 mmol), DABSO (63 mg, 0.26 mmol) and 4-aminomorpholine (35 μL, 0.36 mmol). The reaction mixture was stirred at 70 °C for 16 h. Column chromatography (eluent: 25-100%, ether in petrol) yielded *N-aminosulfonamide* **236** as a white crystalline solid (50 mg, 74%); mp 143-145 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3356, 3224, 2858, 1326, 1206, 1151, 1109, 1064; δ_H (400 MHz, $CDCl_3$) 8.47 (1H, br. s, N(indole)*H*), 8.32 (1H, app br. d, *J* 1.0, Ar*H*), 7.78 (1H, dd, *J* 8.5, 1.0, Ar*H*), 7.49 (1H, d, *J* 8.5, Ar*H*), 7.36 (1H, app t, *J* 3.0, CH=C*H*N), 6.71-6.68 (1H, m, C*H*=CHN), 5.24 (1H, br. s, SO_2NH), 3.58 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.58 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$); δ_C (101 MHz, $CDCl_3$) 138.1 (C), 129.4 (C), 127.4 (C), 126.8 (CH), 122.6 (CH), 121.3 (CH), 111.6 (CH), 104.1 (CH), 66.8 (2 × CH_2), 56.8 (2 × CH_2); *m/z* (ESI^-) 280 ($[M - H]^-$, 100%); HRMS (ESI^+) $C_{12}H_{15}N_3NaO_3S^+$ ($[M + Na]^+$) requires 304.0726, found 304.0725.

tert-Butyl 5-(morpholin-4-ylsulfamoyl)-1*H*-indole-1-carboxylate 237



The general procedure A was followed with the use of *tert*-butyl 5-iodo-1*H*-indole-1-carboxylate **232** (82 mg, 0.24 mmol), $^{t}Bu_3P.HBF_4$ (14 mg, 0.05 mmol), DABSO (63 mg, 0.26 mmol) and 4-aminomorpholine (35 μL, 0.36 mmol). The reaction mixture was stirred at 70 °C for 16 h. Column chromatography (eluent: 25-100%, ether in petrol) yielded *N-aminosulfonamide* **237** as an off-white crystalline solid (75 mg, 81%); mp 167-170 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3211, 2977, 2858, 1740, 1533, 1457, 1335, 1156, 1112, 1087, 1070, 1024; δ_H (400 MHz, $CDCl_3$) 8.30 (1H, br. d, *J* 9.0, Ar*H*), 8.23 (1H, d, *J* 1.5, Ar*H*), 7.90 (1H, dd, *J* 9.0, 1.5, Ar*H*), 7.72 (1H, d, *J* 3.5, CH=C*H*N), 6.69 (1H, d, *J* 3.5, C*H*=CHN), 5.56 (1H, s, N*H*), 3.58 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 2.61 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 1.69 (9H, s, ^{t}Bu); δ_C (101 MHz, $CDCl_3$) 149.3 (C), 137.6 (C), 132.7 (C), 130.3 (C), 128.2 (CH), 123.8 (CH), 122.1 (CH), 115.5 (CH), 107.6 (CH), 85.0 (C), 66.8 (2 × CH_2), 56.9 (2 × CH_2), 28.3 (3 × CH_3); *m/z* (ESI$^-$) 380 ([M – H]$^-$, 100%); HRMS (ESI$^+$) $C_{17}H_{23}N_3NaO_5S^+$ ([M + Na]$^+$) requires 404.1251, found 404.1245.

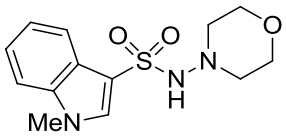
tert-Butyl 3-(morpholin-4-ylsulfamoyl)-1*H*-indole-1-carboxylate 238



The general procedure A was followed with the use of *tert*-butyl 3-iodo-1*H*-indole-1-carboxylate **231** (92 mg, 0.24 mmol), $^{t}Bu_3P.HBF_4$ (14 mg, 0.05 mmol), DABSO (63 mg, 0.26 mmol) and 4-aminomorpholine (35 μL, 0.36 mmol). The reaction mixture was stirred at 70 °C for 16 h. Column chromatography (eluent: 25-100%, ether in petrol) yielded

N-aminosulfonamide **238** as a white crystalline solid (44 mg, 48%); mp 149-153 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3161, 2976, 2857, 2360, 1748, 1537, 1452, 1361, 1341, 1255, 1234, 1146, 1113, 1067; δ_H (400 MHz, $CDCl_3$) 8.24 (1H, s, C=C*H*N) overlapping 8.23 (1H, d, *J* 9.5, Ar*H*), 8.02-7.95 (1H, m, Ar*H*), 7.44 (1H, app td, *J* 8.0, 1.0), 7.38 (1H, app td, *J* 8.0, 1.0), 5.52 (1H, s, N*H*), 3.60 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.69 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 1.70 (9H, s, ^tBu); δ_C (101 MHz, $CDCl_3$) 148.7 (C), 135.6 (C), 131.5 (CH), 126.1 (CH), 125.3 (C), 124.3 (CH), 120.8 (CH), 118.8 (C), 115.7 (CH), 86.0 (C), 66.7 (2 × CH_2), 57.2 (2 × CH_2), 28.2 (3 × CH_3); *m/z* (ESI^+) 785 ($[2M + Na]^+$, 100%), 404 ($[M + Na]^+$, 48%), 382 ($[M + H]^+$, 18%); HRMS (ESI^+) $C_{17}H_{23}N_3NaO_5S^+$ ($[M + Na]^+$) requires 404.1251, found 404.1244.

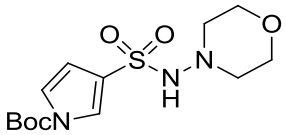
1-Methyl-*N*-(morpholin-4-yl)-1*H*-indole-3-sulfonamide 239



The general procedure A was followed with the use of 3-iodo-1-methyl-1*H*-indole **234** (62 mg, 0.24 mmol), $^tBu_3P.HBF_4$ (14 mg, 0.05 mmol), DABSO (63 mg, 0.26 mmol) and 4-aminomorpholine (35 μL, 0.36 mmol). The reaction mixture was stirred at 70 °C for 16 h. Column chromatography (eluent: 25-100%, ether in petrol) yielded *N-aminosulfonamide* **239** as a white crystalline solid (30 mg, 42%); mp 183-185 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3205, 2964, 2918, 2850, 1334, 1146; δ_H (400 MHz, $CDCl_3$) 8.00 (1H, d, *J* 7.5, Ar*H*), 7.74 (1H, s, C=C*H*N), 7.41-7.28 (3H, m, 3 × Ar*H*), 5.48 (1H, s, N*H*), 3.87 (3H, s, N*Me*), 3.57 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.65 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$); δ_C (101 MHz, $CDCl_3$) 137.2 (C), 134.5 (CH), 124.5 (C), 123.7 (CH), 122.3 (CH), 120.6 (CH), 112.0 (C), 110.3 (CH), 66.7 (2 × CH_2), 57.1 (2 × CH_2), 33.7

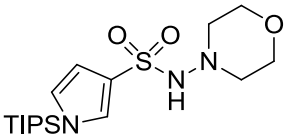
(CH_3); *m/z* (ESI$^+$) 908 ([3M + Na]$^+$, 100%), 613 ([2M + Na]$^+$, 75%), 318 ([M + Na]$^+$, 20%); HRMS (ESI$^+$) $C_{13}H_{17}N_3NaO_3S^+$ ([M + Na]$^+$) requires 318.0883, found 318.0881.

tert-Butyl 3-(morpholin-4-ylsulfamoyl)-1*H*-pyrrole-1-carboxylate 240



The general procedure A was followed with the use of *tert*-butyl 3-iodo-pyrrole-1-carboxylate **230** (70 mg, 0.24 mmol), ^{t}Bu$_3$P.HBF$_4$ (14 mg, 0.05 mmol), DABSO (63 mg, 0.26 mmol) and 4-aminomorpholine (35 μL, 0.36 mmol). The reaction mixture was stirred at 70 °C for 16 h. Column chromatography (eluent: 25-100%, ether in petrol) yielded *N-aminosulfonamide* **240** as a white crystalline solid (16 mg, 20%); mp 130-132 ºC (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3227, 2979, 2925, 2857, 1755, 1334, 1154; δ_H (400 MHz, $CDCl_3$) 7.84-7.81 (1H, m, C=C*H*N), 7.30-7.28 (1H, m, CH=C*H*N), 6.55 (1H, dd, *J* 3.5, 2.0, C*H*=CHN), 5.47 (1H, s, N*H*), 3.68 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 2.75 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 1.63 (9H, s, *Me*); δ_C (101 MHz, $CDCl_3$) 147.5 (C), 125.3 (C), 124.2 (CH), 121.5 (CH), 110.5 (CH), 86.0 (C), 66.6 (2 × CH_2), 57.0 (2 × CH_2), 27.9 (3 × CH_3); *m/z* (ESI$^+$) 686 ([2M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{21}N_3NaO_5S^+$ ([M + Na]$^+$) requires 354.1095, found 354.1094.

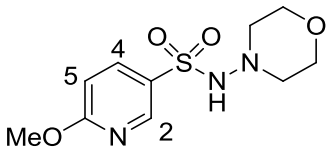
***N*-(Morpholin-4-yl)-1-(triisopropylsilyl)-1*H*-pyrrole-3-sulfonamide 241**



The general procedure A was followed with the use of *tert*-butyl 3-iodo-1*H*-indole-1-carboxylate **229** (92 mg, 0.24 mmol), ^{t}Bu$_3$P.HBF$_4$ (14 mg, 0.05 mmol), DABSO (63 mg, 0.26 mmol) and 4-aminomorpholine (35 μL, 0.36 mmol). The reaction mixture was stirred

at 70 °C for 16 h. Column chromatography (eluent: 25-100%, ether in petrol) yielded *N-aminosulfonamide* **241** as an off-white crystalline solid (22 mg, 24%); mp 197-198 °C (dec.) (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3131, 2953, 2867, 1470, 1387, 1360, 1336, 1263, 1214, 1147, 1091, 1069, 1016; δ_H (400 MHz, $CDCl_3$) 7.38 (1H, app t, *J* 2.5, C=C*H*N), 6.76 (1H, app t, *J* 2.5, CH=C*H*N), 6.63 (1H, dd, *J* 2.5, 1.5, C*H*=CHN), 5.46 (1H, s, N*H*), 3.61 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.67 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 1.47 (3H, sept, *J* 7.5, $Si(CH(Me)_2)_3$), 1.10 (18H, d, *J* 7.5, $Si(CH(Me)_2)_3$); δ_C (101 MHz, $CDCl_3$) 129.7 (CH), 125.9 (CH), 123.3 (C), 110.4 (CH), 66.8 (2 × CH_2), 56.9 (2 × CH_2), 17.7 (3 × CH) 11.6 (6 × CH_3); *m/z* (ESI^+) 797 ($[2M + Na]^+$, 100%), 410 ($[M + Na]^+$, 80%); HRMS (ESI^+) $C_{17}H_{34}N_3O_3SSi^+$ ($[M + H]^+$) requires 388.2085, found 388.2076.

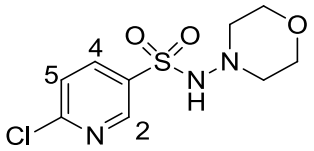
6-Methoxy-*N*-(morpholin-4-yl)pyridine-3-sulfonamide 242



General procedure A was followed using 5-iodo-2-methoxypyridine **213** (56 mg, 0.24 mmol), $^tBu_3P.HBF_4$ (14 mg, 0.05 mmol), DABSO (63 mg, 0.26 mmol) and 4-aminomorpholine (35 μL, 0.36 mmol). The reaction mixture was stirred at 70 °C for 16 h. Column chromatography (eluent: 25-100%, ether in petrol) yielded the *N-aminosulfonamide* **242** as white needles (50 mg, 76%); mp 159-160 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3196, 2947, 2896, 2864, 1587, 1480, 1394, 1367, 1336, 1306, 1168, 1123, 1111, 1086, 1068, 1015; δ_H (400 MHz, $CDCl_3$) 8.68 (1H, dd, *J* 2.5, 0.5, C(2)*H*), 7.99 (1H, dd, *J* 9.0, 2.5, C(4)*H*), 6.76 (1H, dd, *J* 9.0, 0.5, C(5)*H*), 5.50 (1H, s, N*H*), 3.95 (3H, s, O*Me*), 3.57 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.61 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$); δ_C (101 MHz, $CDCl_3$) 166.9 (C), 148.7 (CH), 138.3 (CH), 127.9 (C), 111.3 (CH), 66.8 (2 × CH_2), 56.9 (2

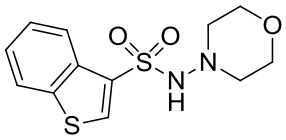
× CH_2), 54.5 (CH_3); *m/z* (ESI^+) 296 ($[M + Na]^+$, 100%), 274 ($[M + H]^+$, 20%); HRMS (ESI^+) $C_{10}H_{15}N_3O_4S^+$ ($[M + Na]^+$) requires 296.0675, found 296.0676.

6-Chloro-*N*-(morpholin-4-yl)pyridine-3-sulfonamide 243



General procedure A was followed using 2-chloro-5-iodopyridine (58 mg, 0.24 mmol), $^tBu_3P.HBF_4$ (14 mg, 0.05 mmol), DABSO (63 mg, 0.26 mmol) and 4-aminomorpholine (35 μL, 0.36 mmol). The reaction mixture was stirred at 70 °C for 16 h. Column chromatography (eluent: 25-100%, ether in petrol) yielded the *N-aminosulfonamide* **243** as a white crystalline solid (19 mg, 29%); mp 120-125 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3117, 3093, 3032, 2973, 2920, 1603, 1496, 1457, 1405, 1363, 1295, 1259, 1207, 1186, 1165, 1150, 1120, 1094, 1073, 1030; δ_H (400 MHz, $CDCl_3$) 8.96 (1H, d, *J* 2.5, C(2)*H*), 8.19 (1H, dd, *J* 8.5, 2.5, C(4)*H*), 7.51 (1H, d, *J* 8.5, C(5)*H*), 5.73 (1H, s, N*H*), 3.65 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.70 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$); δ_C (101 MHz, $CDCl_3$) 156.1 (C), 149.5 (CH), 138.3 (CH), 134.3 (C), 124.6 (CH), 66.7 (2 × CH_2), 57.0 (2 × CH_2); *m/z* (ESI^-) 278 ($[M – H]^-$, 50%), 276 ($[M – H]^-$, 100%); HRMS (ESI^-) $C_9H_{11}ClN_3O_3S^-$ ($[M – H]^-$) requires 278.0186 and 276.0215, found 278.0190 and 276.0223.

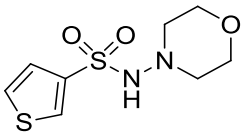
***N*-(Morpholin-4-yl)-1-benzothiophene-3-sulfonamide 244**



The general procedure A was followed with the use of 3-iodo-1-benzothiophene **235** (62 mg, 0.24 mmol), $^tBu_3P.HBF_4$ (14 mg, 0.05 mmol), DABSO (63 mg, 0.26 mmol) and

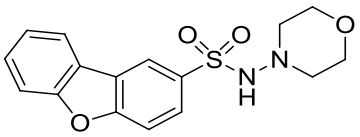
4-aminomorpholine (35 μL, 0.36 mmol). The reaction mixture was stirred at 70 °C for 16 h. Column chromatography (eluent: 25-100%, ether in petrol) yielded the *N-aminosulfonamide* **244** as a white crystalline solid (53 mg, 73%); mp 142-144 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3242, 2963, 2857, 2361, 1336, 1158, 1109; δ_H (400 MHz, $CDCl_3$) 8.37 (1H, s, C=C*H*S), 8.34 (1H, d, *J* 8.0, Ar*H*), 7.91 (1H, d, *J* 8.0, Ar*H*), 7.57-7.44 (2H, m, 2 × Ar*H*), 5.68 (1H, s, N*H*), 3.55 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 2.60 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O); δ_C (101 MHz, $CDCl_3$) 140.3 (C), 136.4 (CH), 134.0 (C), 132.4 (C), 125.9 (CH), 125.8 (CH), 123.9 (CH), 123.0 (CH), 66.7 (2 × CH_2), 57.1 (2 × CH_2); *m/z* (ESI^+) 619 ($[2M + Na]^+$, 100%), 321 ($[M + Na]^+$, 69%); HRMS (ESI^+) $C_{12}H_{14}N_2NaO_3S_2^+$ ($[M + Na]^+$) requires 321.0344, found 321.0335.

_N_-(Morpholin-4-yl)thiophene-3-sulfonamide 245



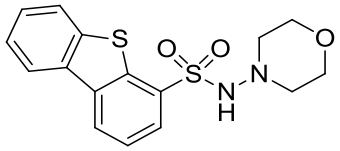
The general procedure A was followed with the use of 3-bromothiophene (23 μL, 0.24 mmol), $^tBu_3P.HBF_4$ (14 mg, 0.05 mmol), DABSO (63 mg, 0.26 mmol) and 4-aminomorpholine (35 μL, 0.36 mmol). The reaction mixture was stirred at 70 °C for 16 h. Column chromatography (eluent: 25-100%, ether in petrol) yielded *N-aminosulfonamide* **245** as a white crystalline solid (14 mg, 24%); mp 152-154 °C (CH_2Cl_2) {lit.[23] 157-158 °C (CH_2Cl_2}; δ_H (400 MHz, $CDCl_3$) 8.10 (1H, d, *J* 2.0, SC=C*H*S), 7.46–7.41 (2H, m, C*H*=CHS, CH=C*H*S), 5.67 (1H, s, N*H*), 3.65 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O), 2.66 (4H, t, *J* 4.5, N(CH_2CH_2)$_2$O); δ_C (101 MHz, $CDCl_3$) 138.5 (C), 132.0 (CH), 127.6 (CH), 126.2 (CH), 66.6 (2 × CH_2), 56.8 (2 × CH_2); *m/z* (ESI^-) 247 ($[M - H]^-$, 100%). Data in accordance with literature data.[23]

_N_-(Morpholin-4-yl)dibenzo[*b,d*]furan-2-sulfonamide 246



The general procedure A was followed with the use of 3-iododibenzofuran (71 mg, 0.24 mmol), $^{t}Bu_3P.HBF_4$ (14 mg, 0.05 mmol), DABSO (63 mg, 0.26 mmol) and 4-aminomorpholine (35 μL, 0.36 mmol). The reaction mixture was stirred at 70 °C for 16h. Column chromatography (eluent: 25-100%, ether in petrol) yielded *N-aminosulfonamide* **246** as a white crystalline solid (71 mg, 89%); mp 197-199 °C (dec.) (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3196, 2962, 2917, 2859, 1444, 1324, 1261, 1199, 1159, 1106; δ_H (400 MHz, $CDCl_3$) 8.63 (1H, d, *J* 2.0, Ar*H*), 8.10 (1H, dd, *J* 8.5, 2.0, Ar*H*), 8.05-8.00 (1H, m, Ar*H*), 7.69 (1H, d, *J* 8.5, Ar*H*), 7.67-7.62 (1H, m, Ar*H*), 7.57 (1H, app td, *J* 7.5, 1.5, Ar*H*), 7.47-7.42 (1H, m, Ar*H*), 5.50 (1H, s, N*H*), 3.60 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.65 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$); δ_C (101 MHz, $CDCl_3$) 158.6 (C), 157.1 (C), 133.2 (C), 128.8 (CH), 127.4 (CH), 124.9 (CH), 123.9 (C), 123.2 (C), 121.9 (CH), 121.3 (CH), 112.3 (CH), 112.2 (CH), 66.8 (2 × CH_2), 57.0 (2 × CH_2); *m/z* (ESI^+) 687 ($[2M + Na]^+$, 100%), 355 ($[M + Na]^+$, 77%); HRMS (ESI^+) $C_{16}H_{16}N_2NaO_4S^+$ ($[M + Na]^+$) requires 355.0723, found 355.0707.

_N_-(Morpholin-4-yl)dibenzo[*b,d*]thiophene-4-sulfonamide 247



The general procedure A was followed with the use of 4-iododibenzothiophene (74 mg, 0.24 mmol), $^{t}Bu_3P.HBF_4$ (14 mg, 0.05 mmol), DABSO (63 mg, 0.26 mmol) and 4-aminomorpholine (35 μL, 0.36 mmol). The reaction mixture was stirred at 70 °C for

16 h. Column chromatography (eluent: 25-100%, ether in petrol) yielded *N-aminosulfonamide* **247** as a white crystalline solid (77 mg, 92%); mp 169-172 °C (CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3218, 2964, 2922, 2858, 1453, 1441, 1390, 1361, 1335, 1312, 1265, 1249, 1197, 1166, 1142, 1109, 1079, 1036, 1018; δ_H (400 MHz, $CDCl_3$) 8.40 (1H, dd, *J* 8.0, 1.0, Ar*H*), 8.23-8.19 (1H, m, Ar*H*), 8.17 (1H, dd, *J* 7.5, 1.0, Ar*H*), 7.95-7.91 (1H, m, Ar*H*), 7.64 (1H, app t, *J* 7.5, Ar*H*), 7.60-7.51 (1H, m, Ar*H*), 7.27 (1H, app s, Ar*H*), 5.70 (1H, s, N*H*), 3.51 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$), 2.54 (4H, t, *J* 4.5, $N(CH_2CH_2)_2O$); δ_C (126 MHz, $CDCl_3$) 140.2 (C), 137.8(1) (C), 137.7(7) (C), 134.2 (C), 132.5 (C), 128.9 (CH), 128.0 (CH), 126.2 (CH), 125.1 (CH), 124.5 (CH), 122.8 (CH), 122.0 (CH), 66.7 (2 × CH_2), 56.8 (2 × CH_2); *m/z* (ESI^-) 347 ($[M - H]^-$, 100%); HRMS (ESI^+) $C_{16}H_{16}N_2NaO_3S_2^+$ ($[M + Na]^+$) requires 371.0495, found 371.0490.

Appendix B

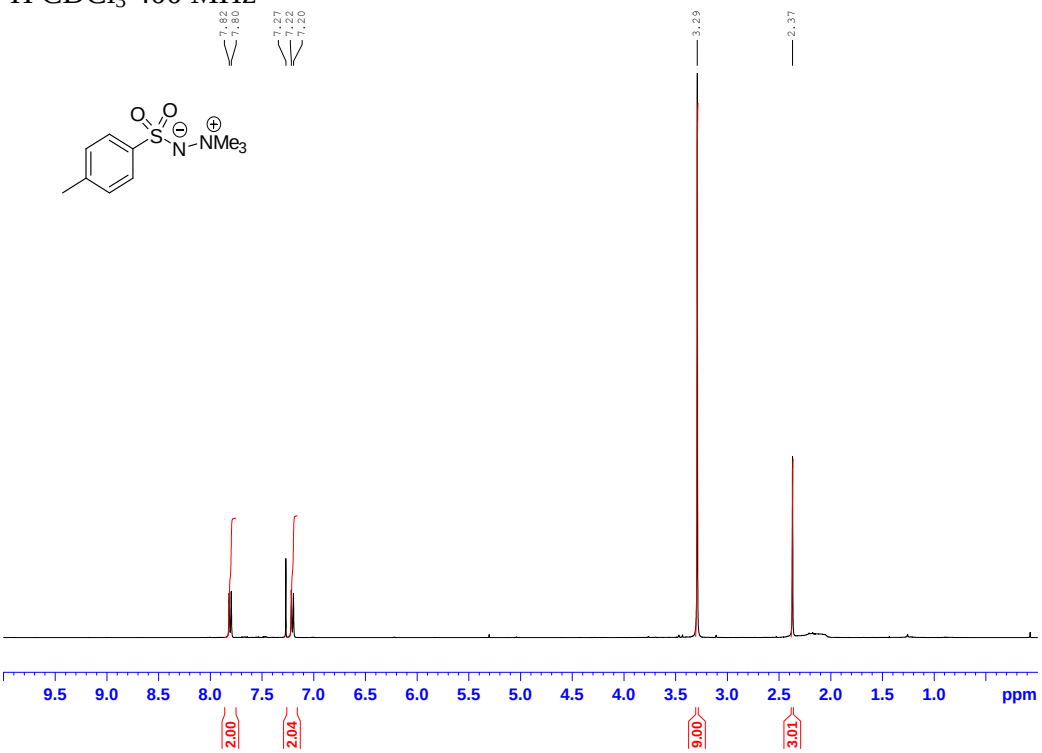
Crystallographic data and NMR spectra of key compounds

The images of ^{1}H and ^{13}C NMR spectra and X-ray crystallographic data of novel and key compounds synthesised in Chapters 2, 3, 4 and Appendix A are shown.

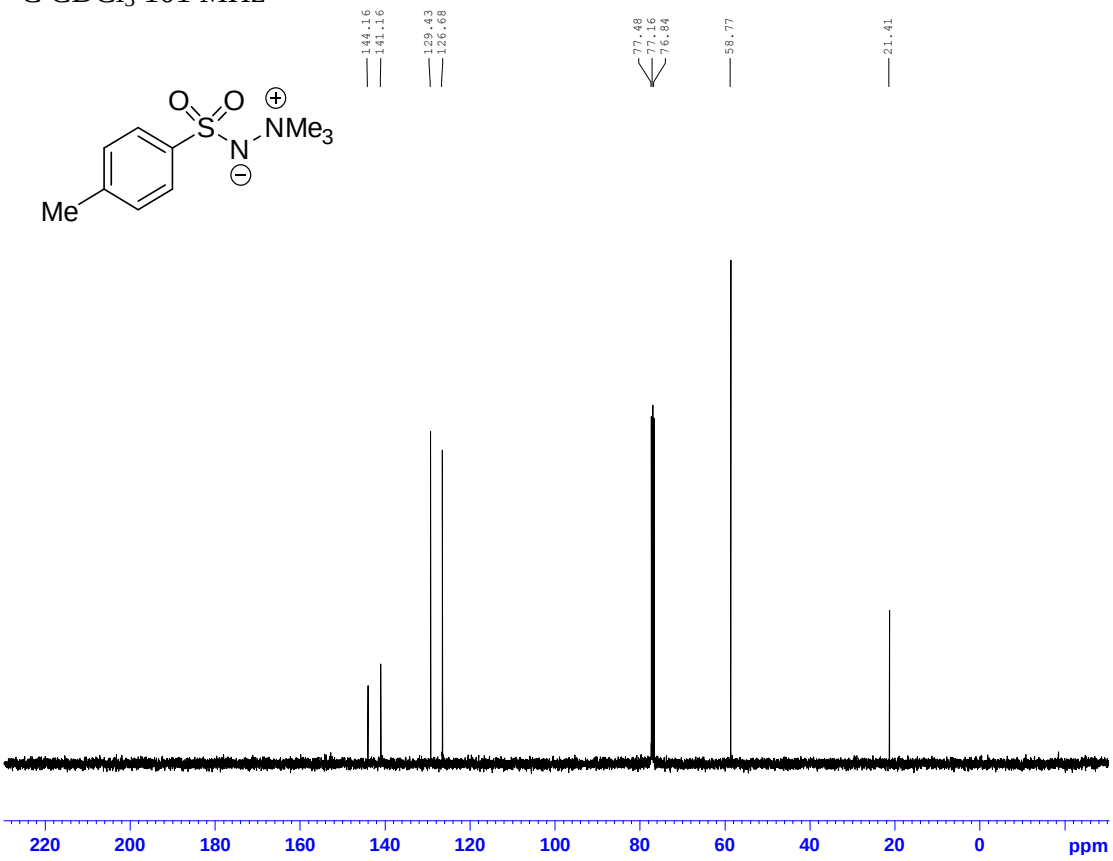
B.1 Synthesis of sulfones

2,2,2-Trimethyl-1-[(4-methylphenyl)sulfonyl]diazan-2-ium-1-ide

^{1}H $CDCl_3$ 400 MHz

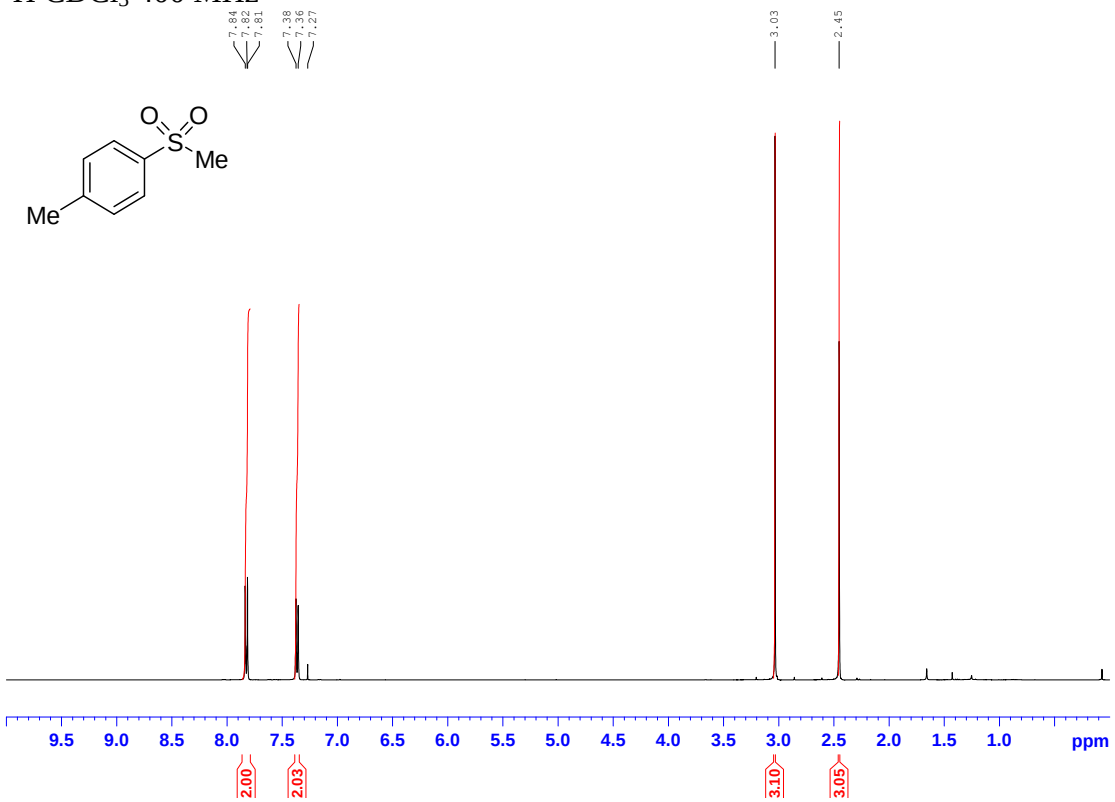


^{13}C $CDCl_3$ 101 MHz

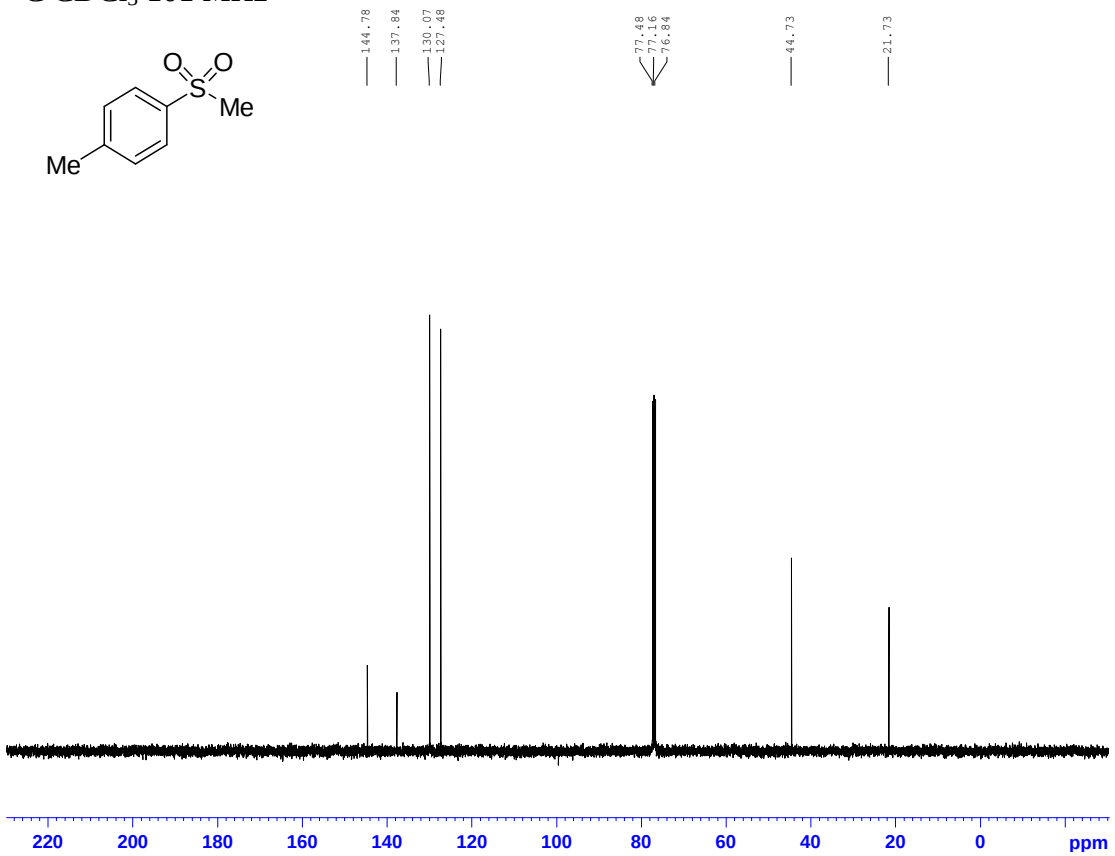


Methyl 4-methylphenyl sulfone

^{1}H $CDCl_3$ 400 MHz

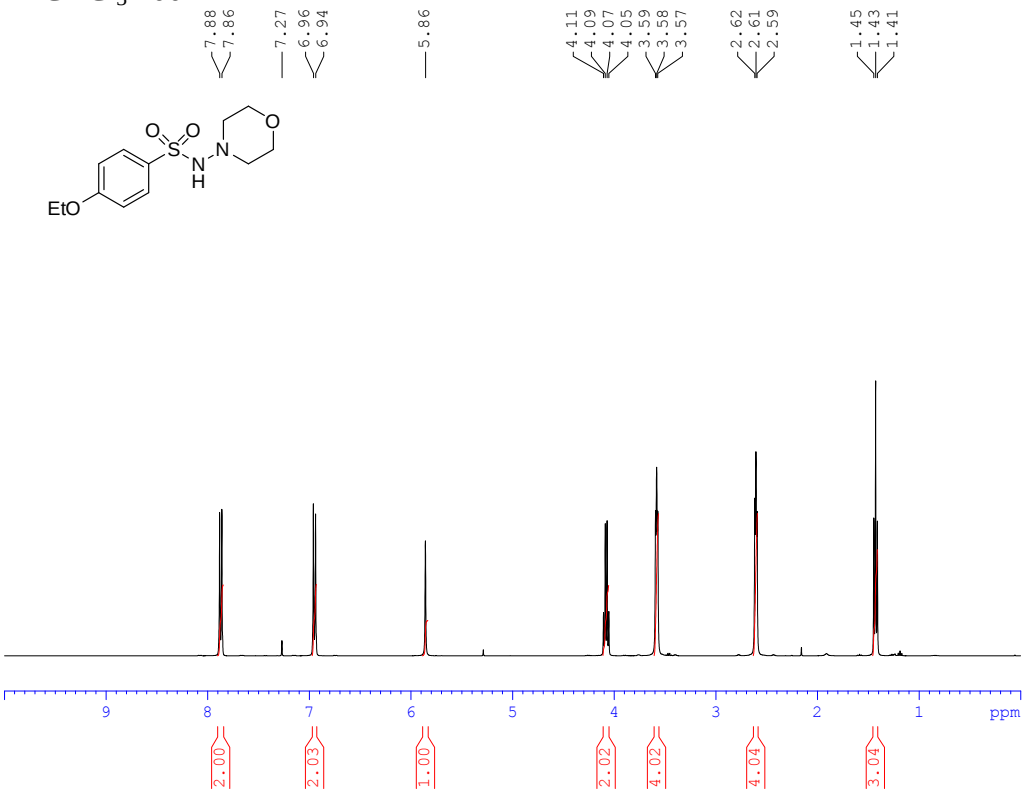


^{13}C $CDCl_3$ 101 MHz

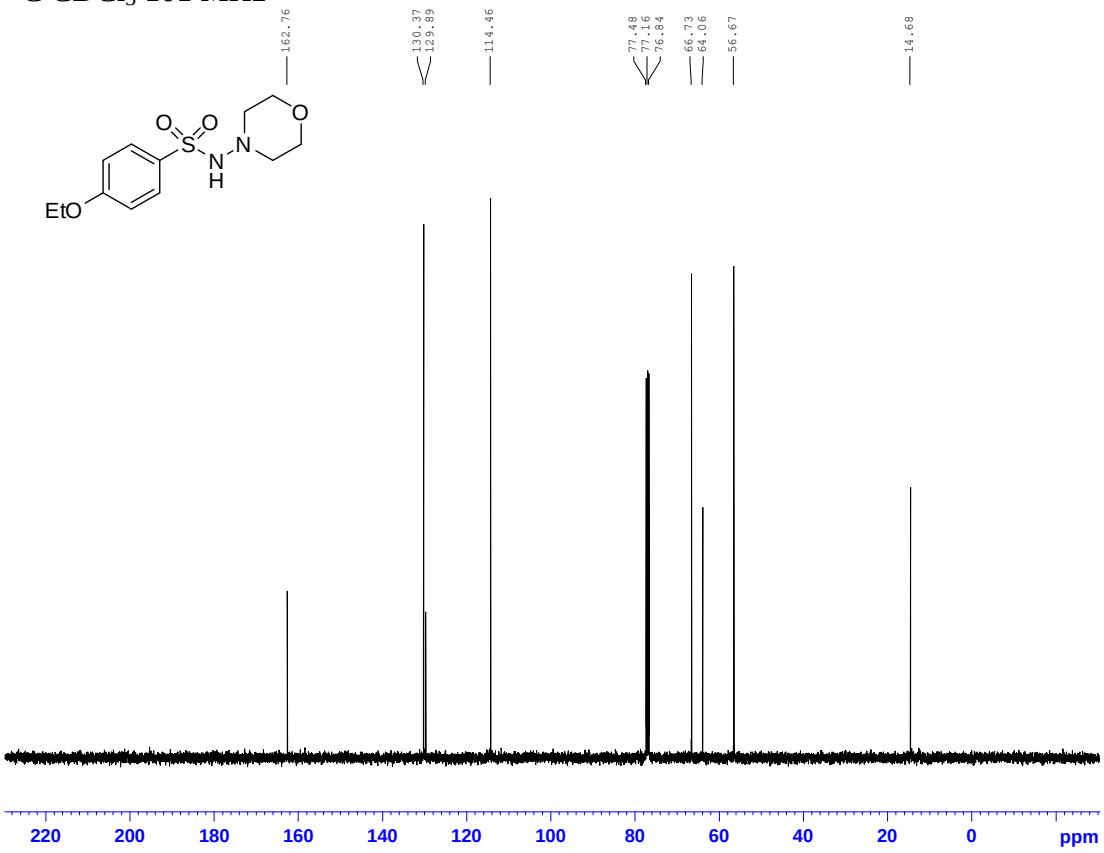


4-Ethoxy-*N*-(morpholin-4-yl)benzenesulfonamide

^{1}H $CDCl_3$ 400 MHz

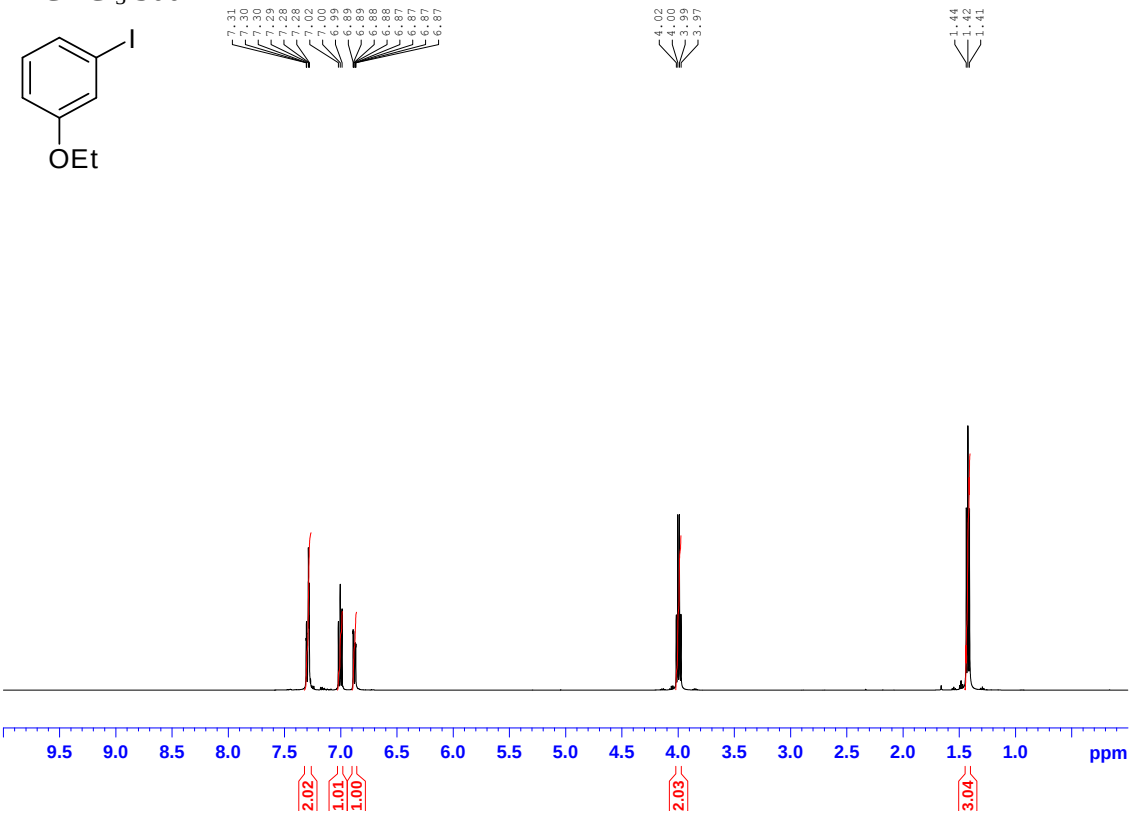


^{13}C $CDCl_3$ 101 MHz

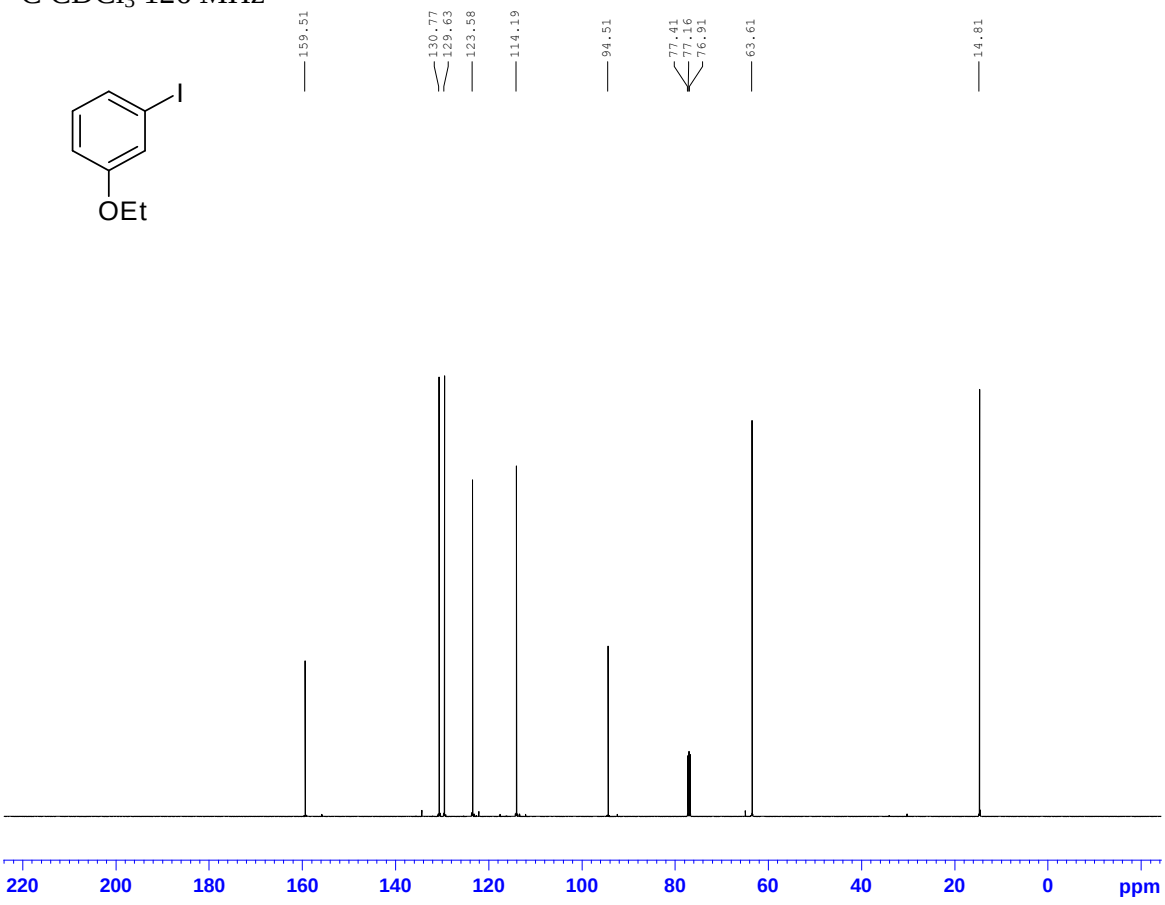


1-Ethoxy-3-iodobenzene

^{1}H $CDCl_3$ 500 MHz

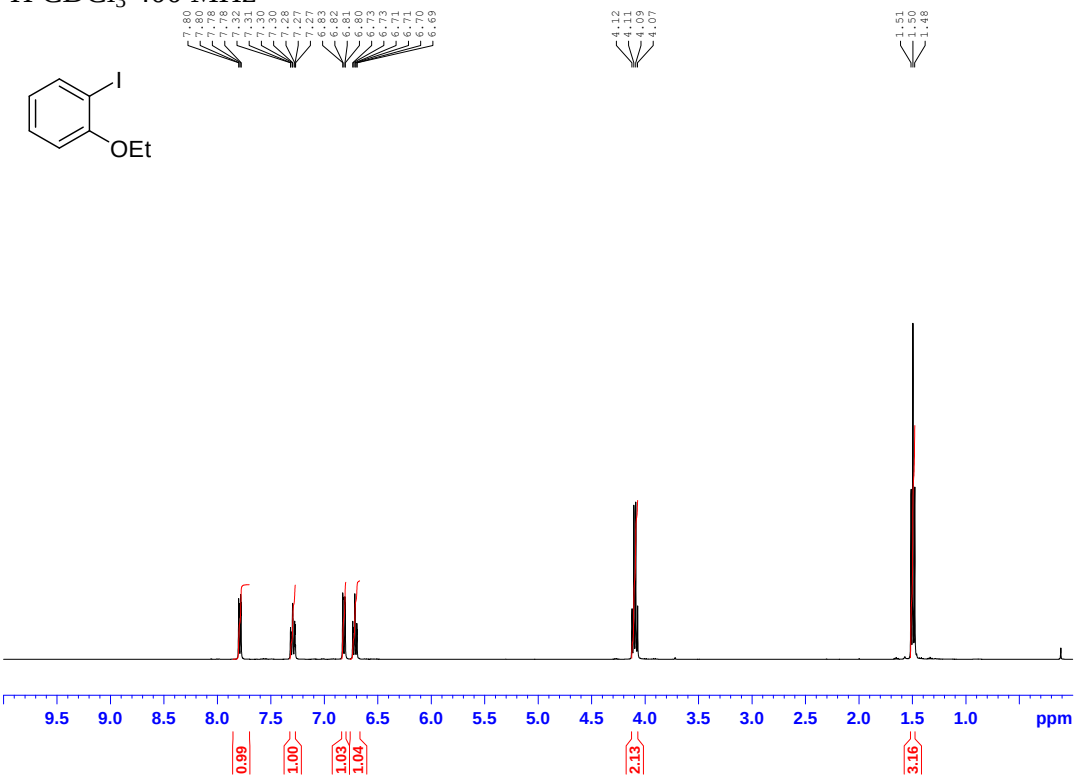


^{13}C $CDCl_3$ 126 MHz

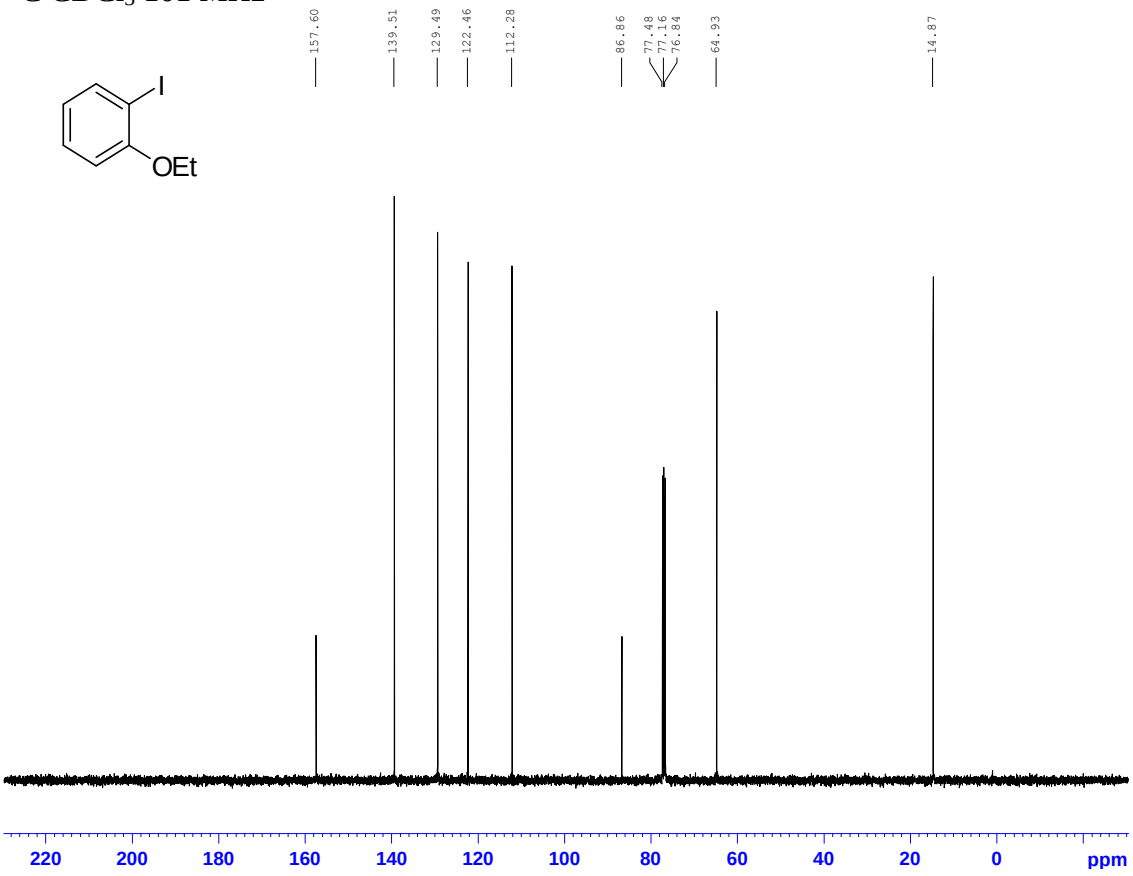


1-Ethoxy-2-iodobenzene

^{1}H $CDCl_3$ 400 MHz

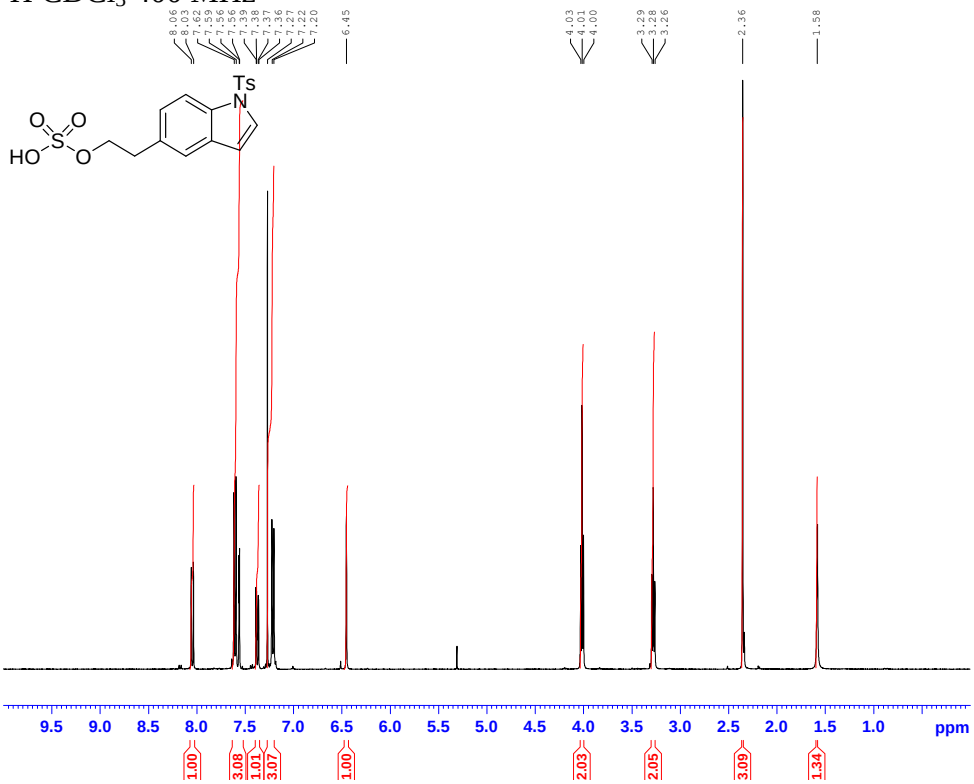


^{13}C $CDCl_3$ 101 MHz

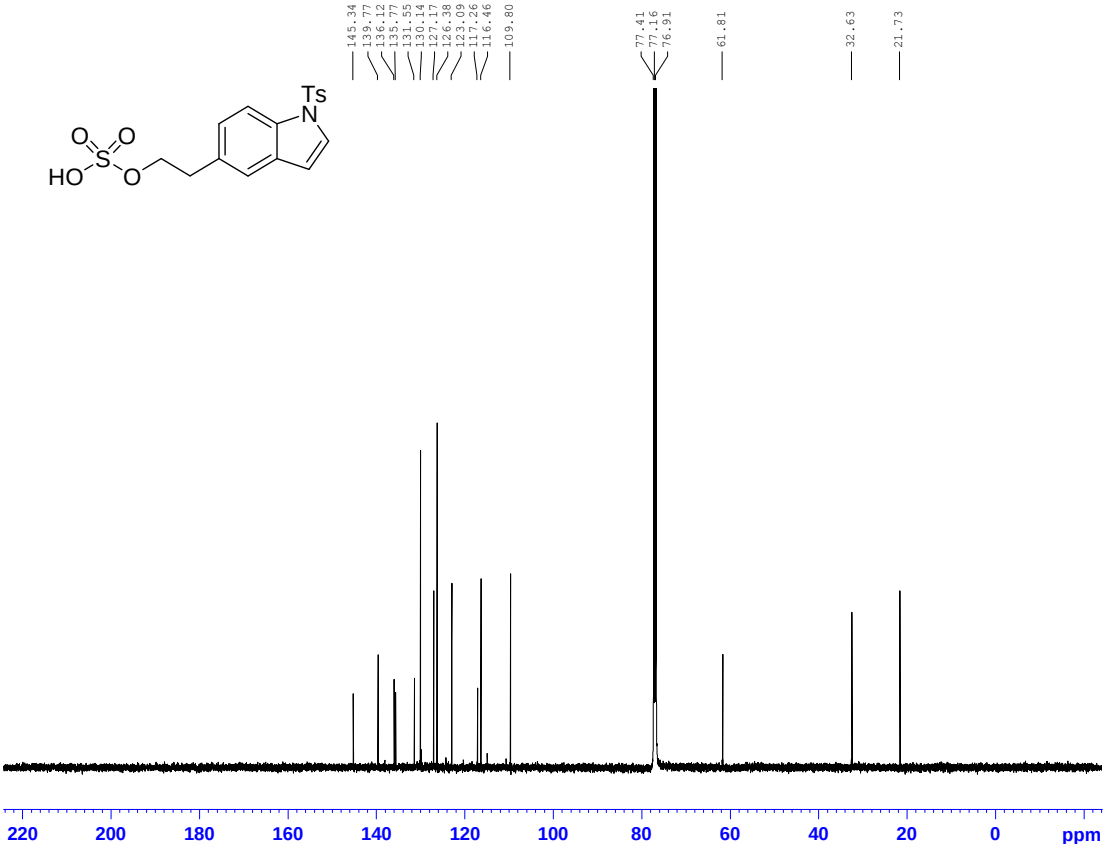


3-{1-[(4-Methylphenyl)sulfonyl]-1*H*-indol-5-yl}propan-1-ol

^{1}H $CDCl_3$ 400 MHz

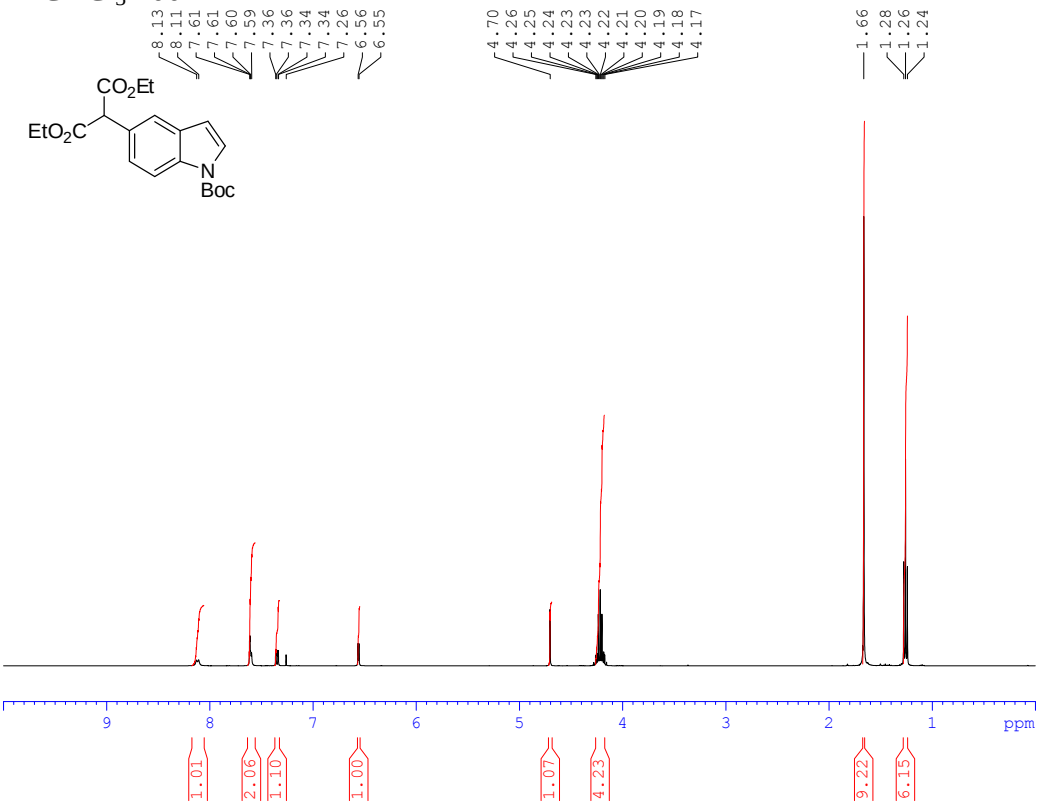


^{13}C $CDCl_3$ 126 MHz

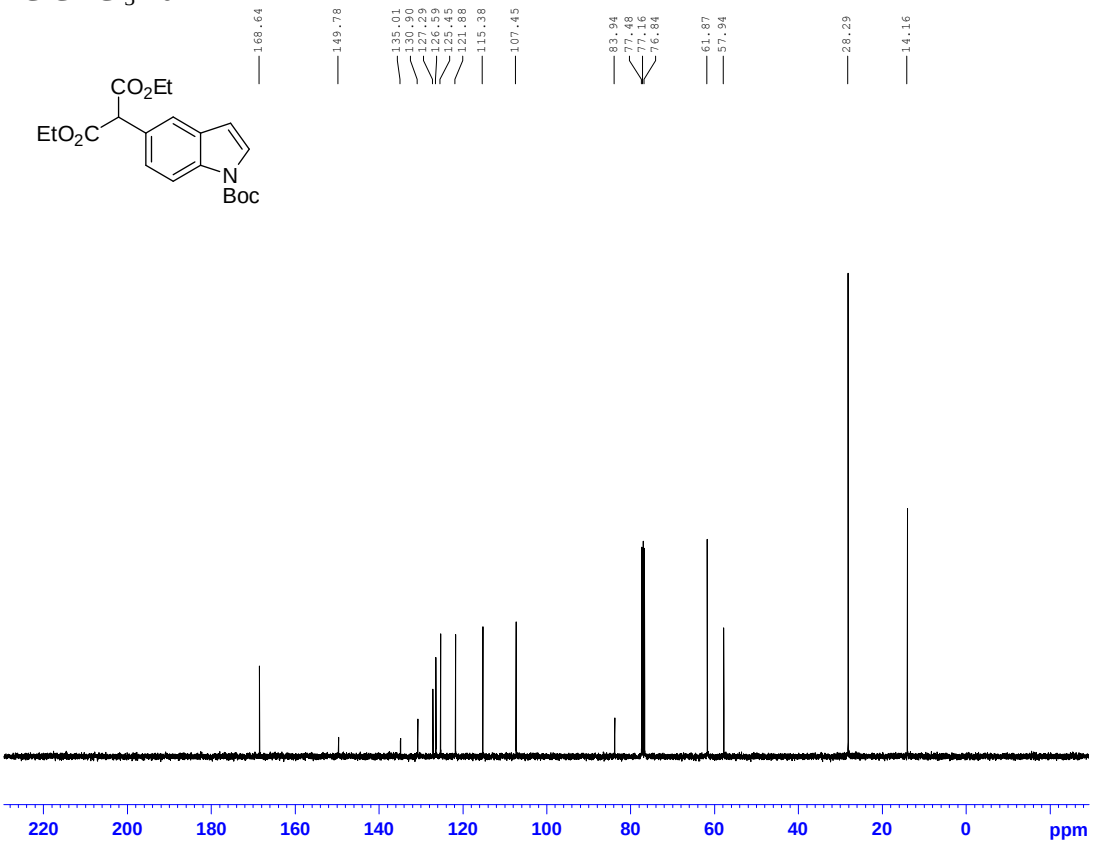


Diethyl [1-(*tert*-butoxycarbonyl)-1*H*-indol-5-yl]propanedioate

^{1}H $CDCl_3$ 400 MHz

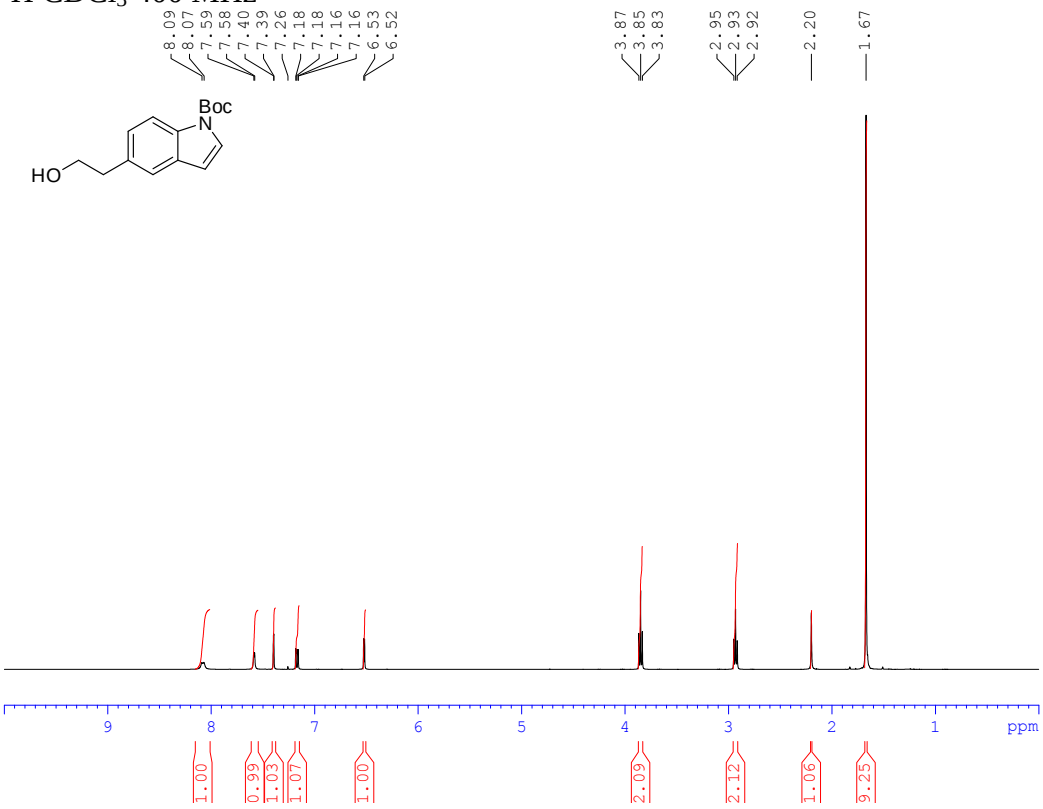


^{13}C $CDCl_3$ 101 MHz

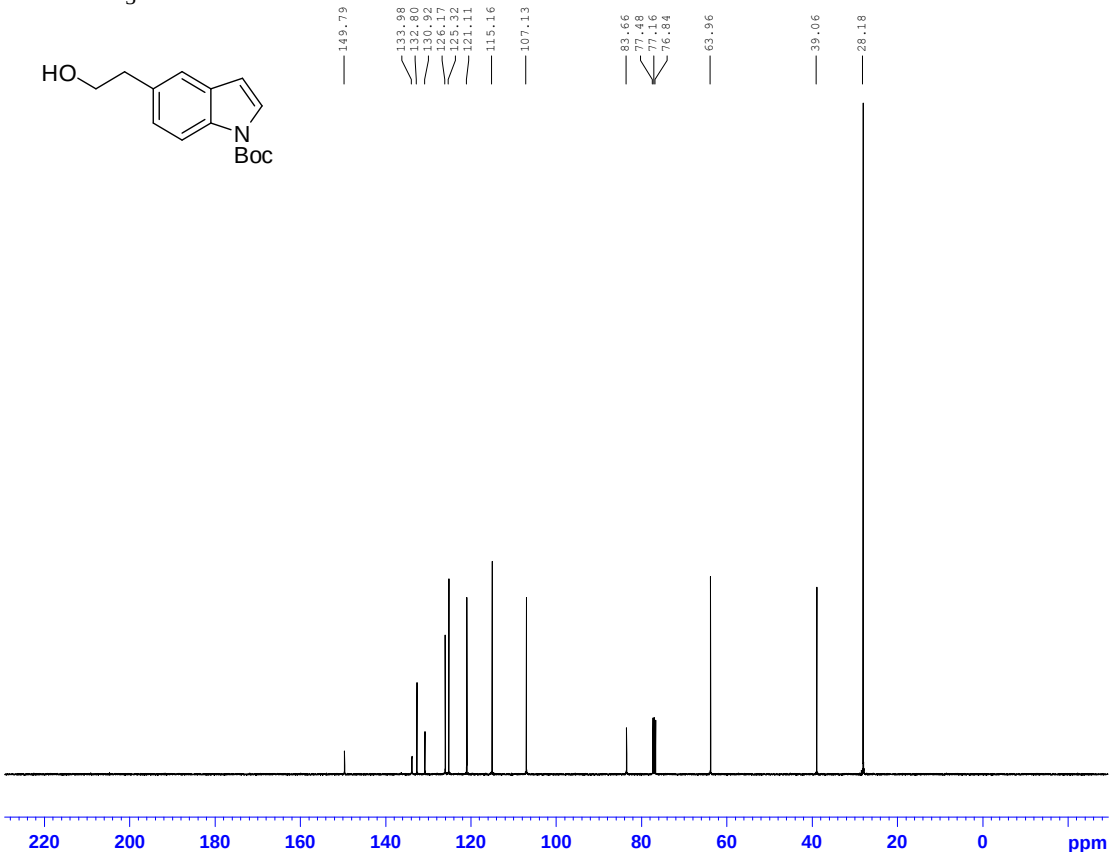


tert-Butyl 5-(2-hydroxyethyl)-1*H*-indole-1-carboxylate

^{1}H $CDCl_3$ 400 MHz

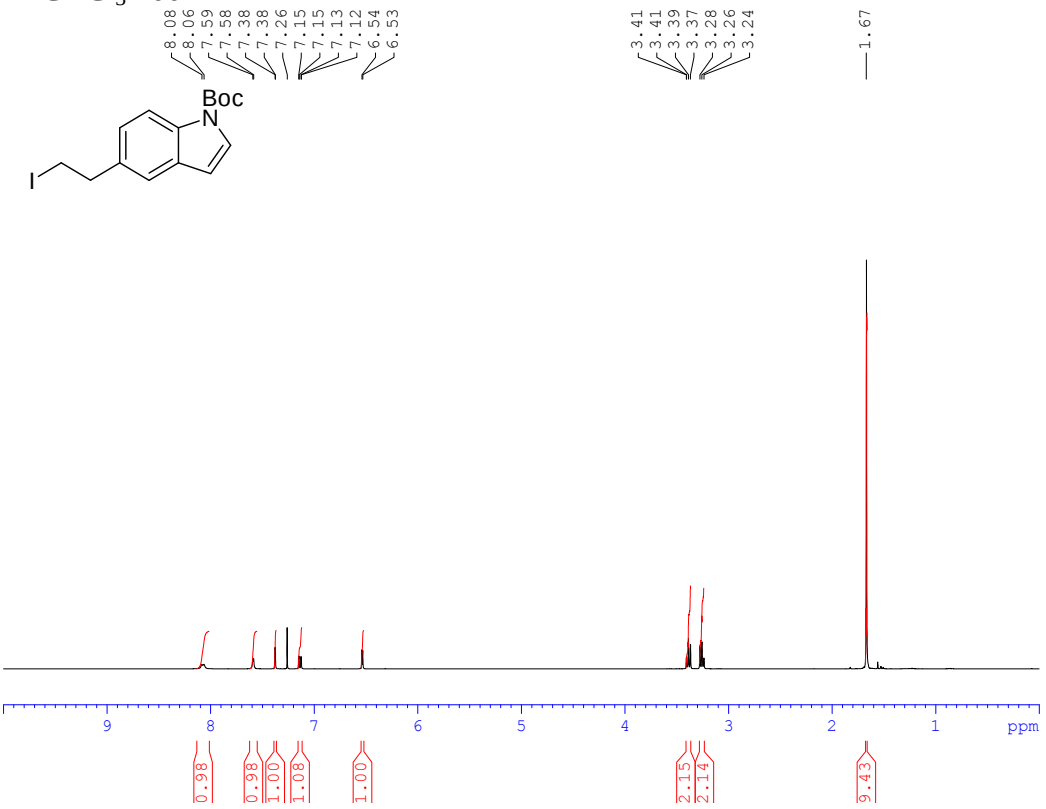


^{13}C $CDCl_3$ 101 MHz

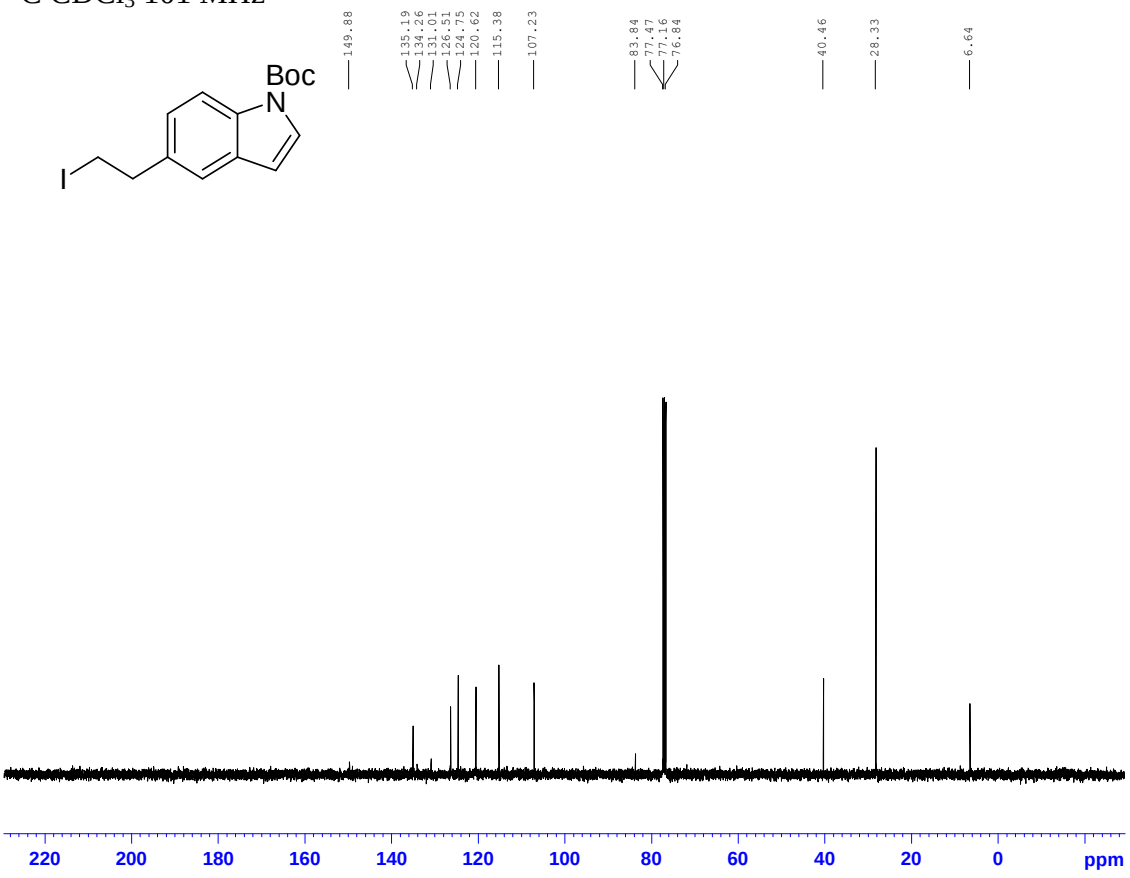


tert-Butyl 5-(2-iodoethyl)-1*H*-indole-1-carboxylate

^{1}H $CDCl_3$ 400 MHz

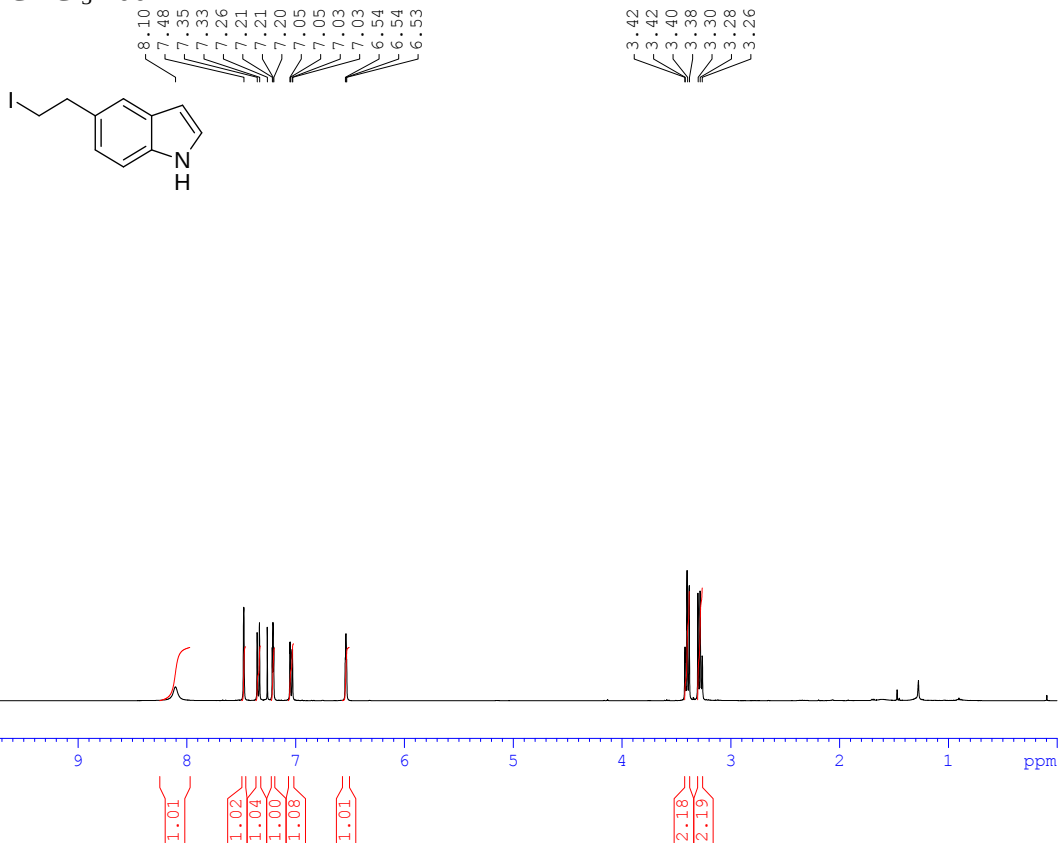


^{13}C $CDCl_3$ 101 MHz

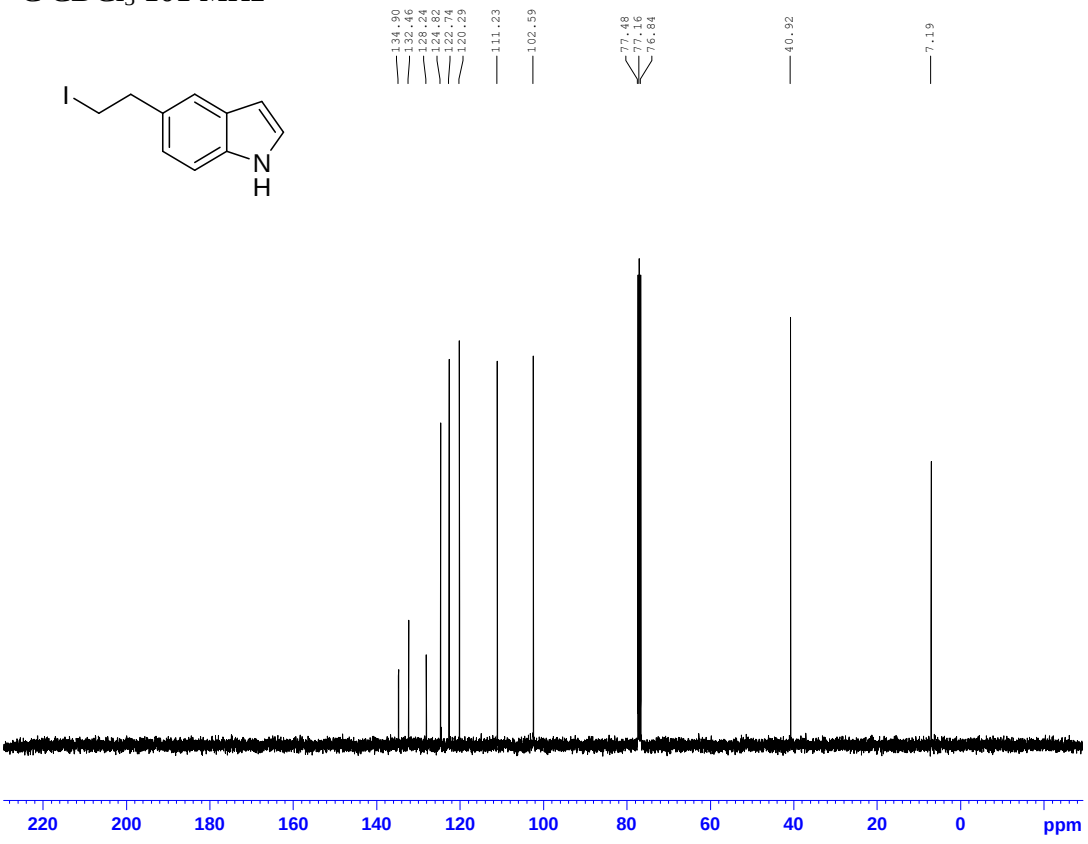


5-(2-Iodoethyl)-1*H*-indole

^{1}H $CDCl_3$ 400 MHz

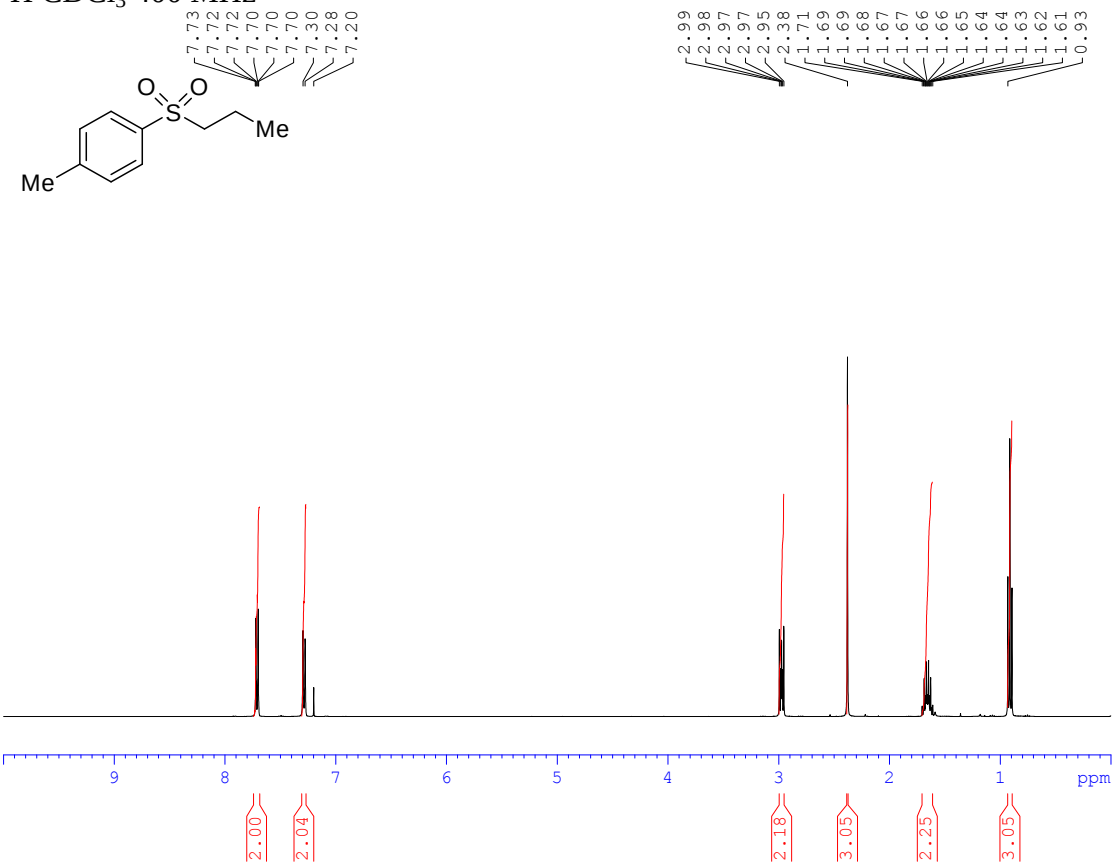


^{13}C $CDCl_3$ 101 MHz

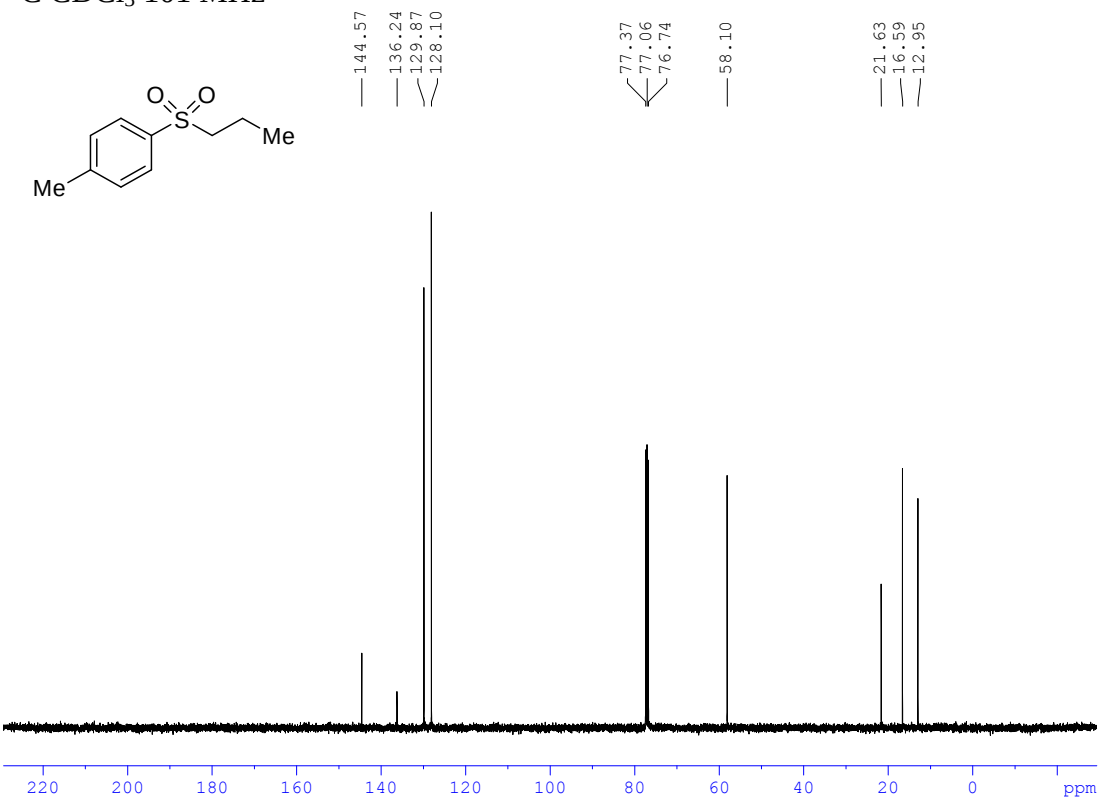


4-Methylphenyl propyl sulfone

^{1}H $CDCl_3$ 400 MHz

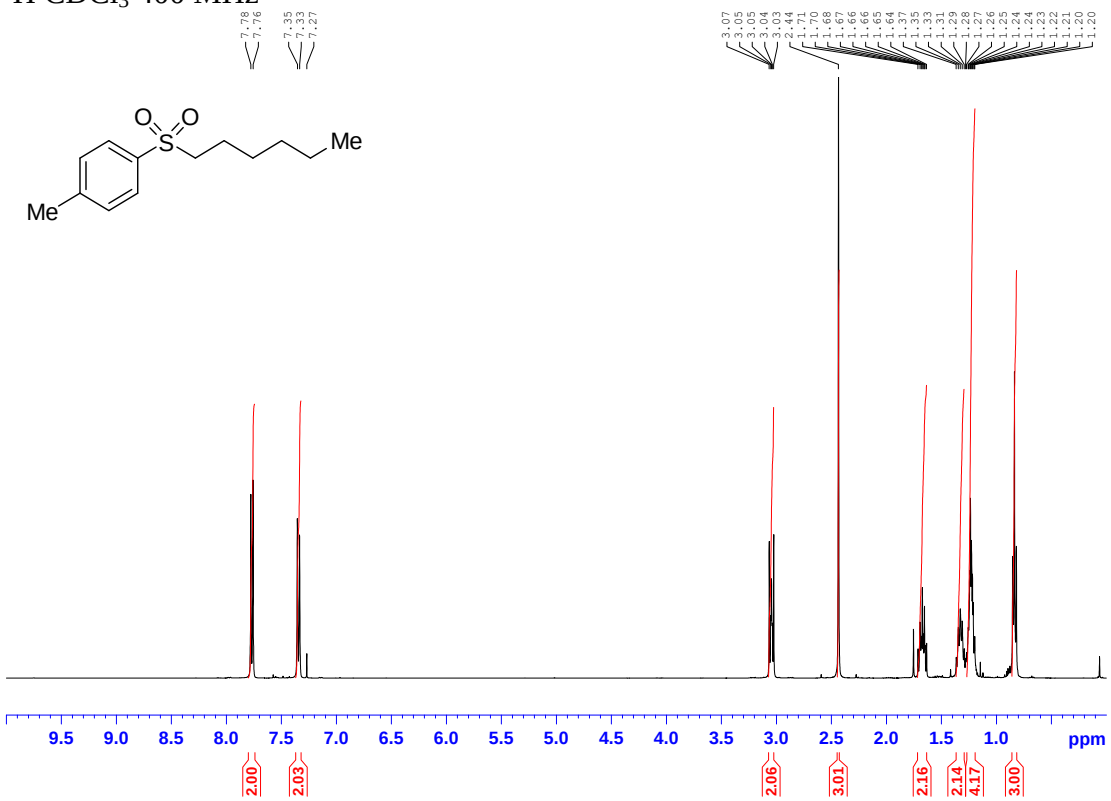


^{13}C $CDCl_3$ 101 MHz

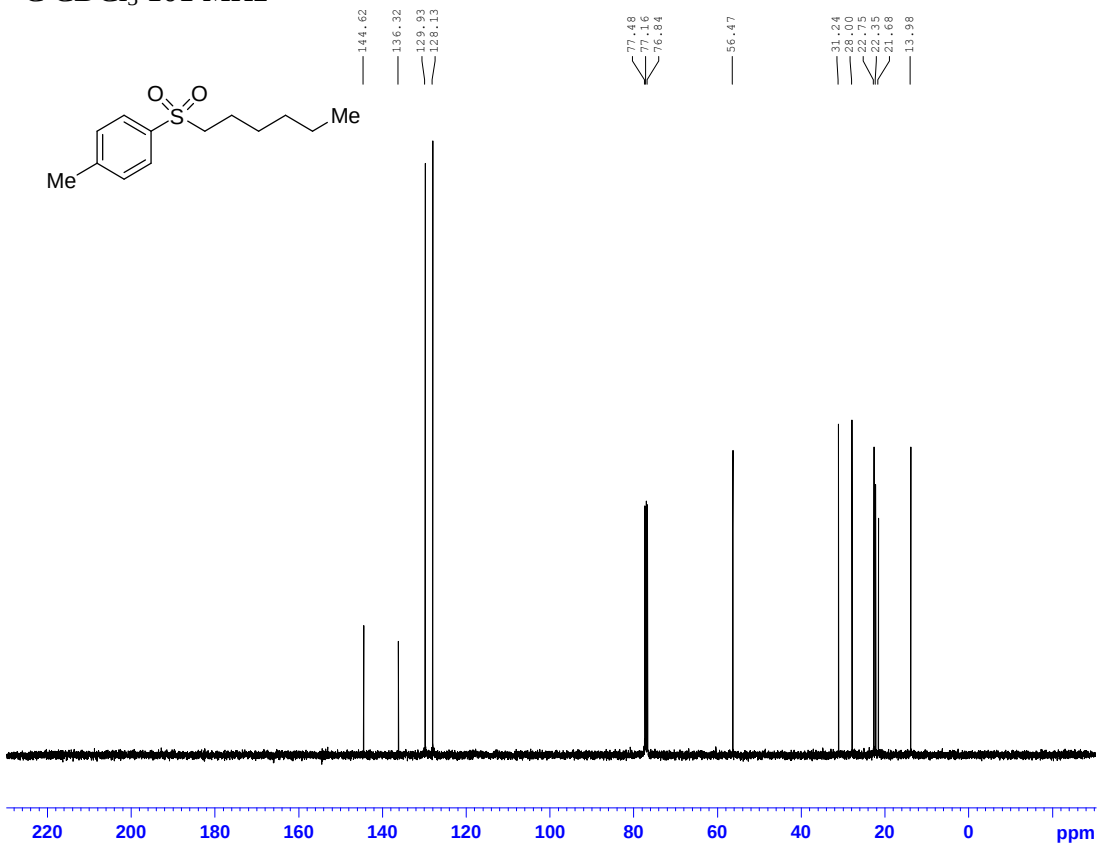


Hexyl 4-methylphenyl sulfone

^{1}H $CDCl_3$ 400 MHz

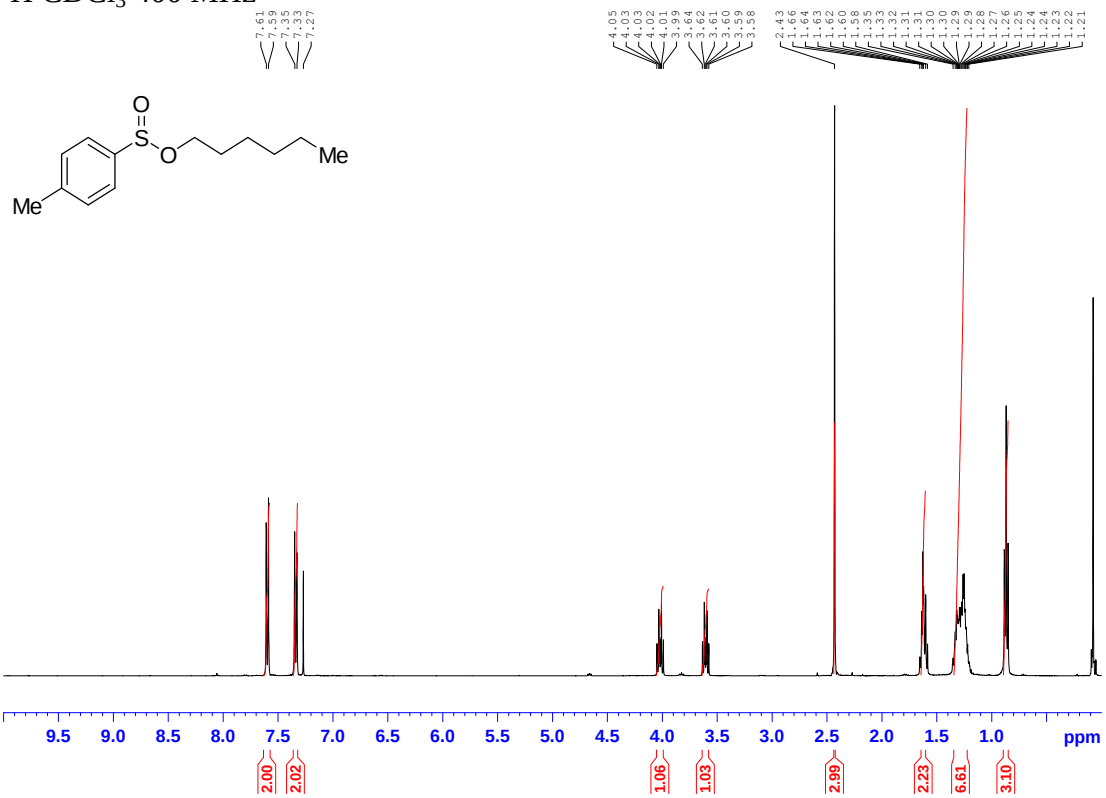


^{13}C $CDCl_3$ 101 MHz

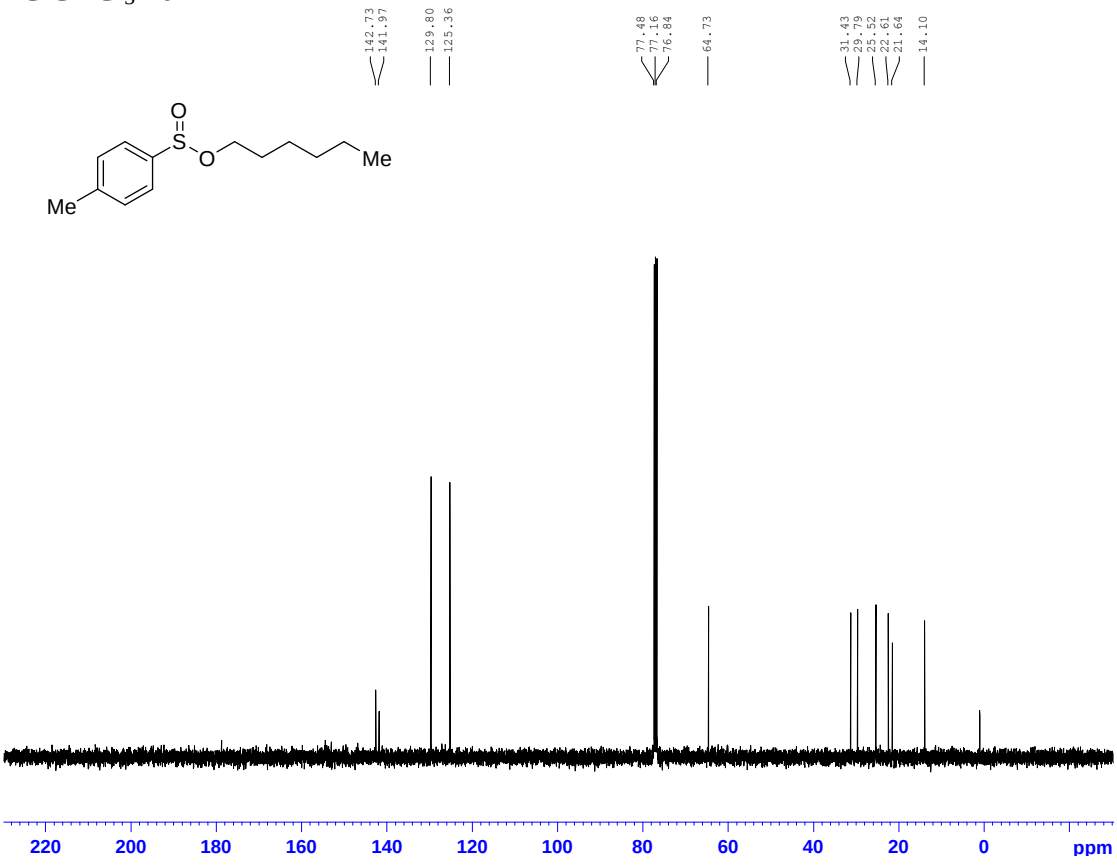


Hexyl 4-methylbenzenesulfinate

^{1}H $CDCl_3$ 400 MHz

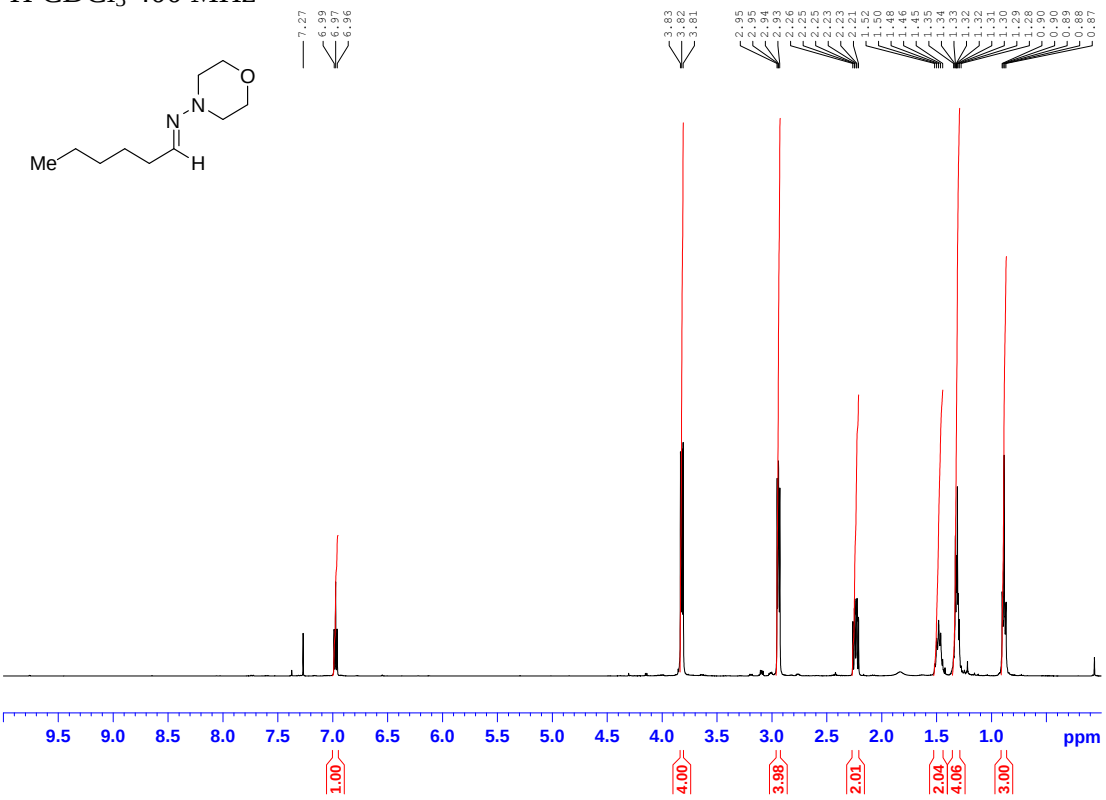


^{13}C $CDCl_3$ 101 MHz

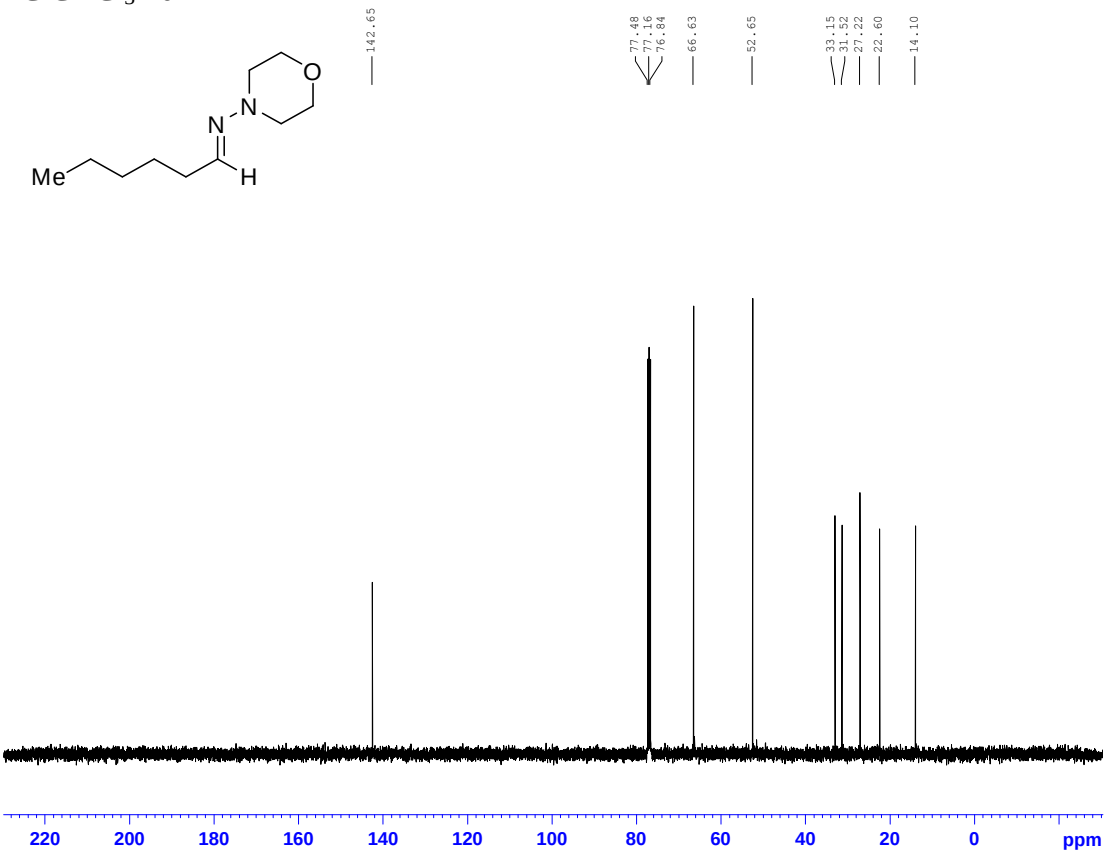


_N_-[(1_E_)-Hexylidene]morpholin-4-amine

^{1}H $CDCl_3$ 400 MHz

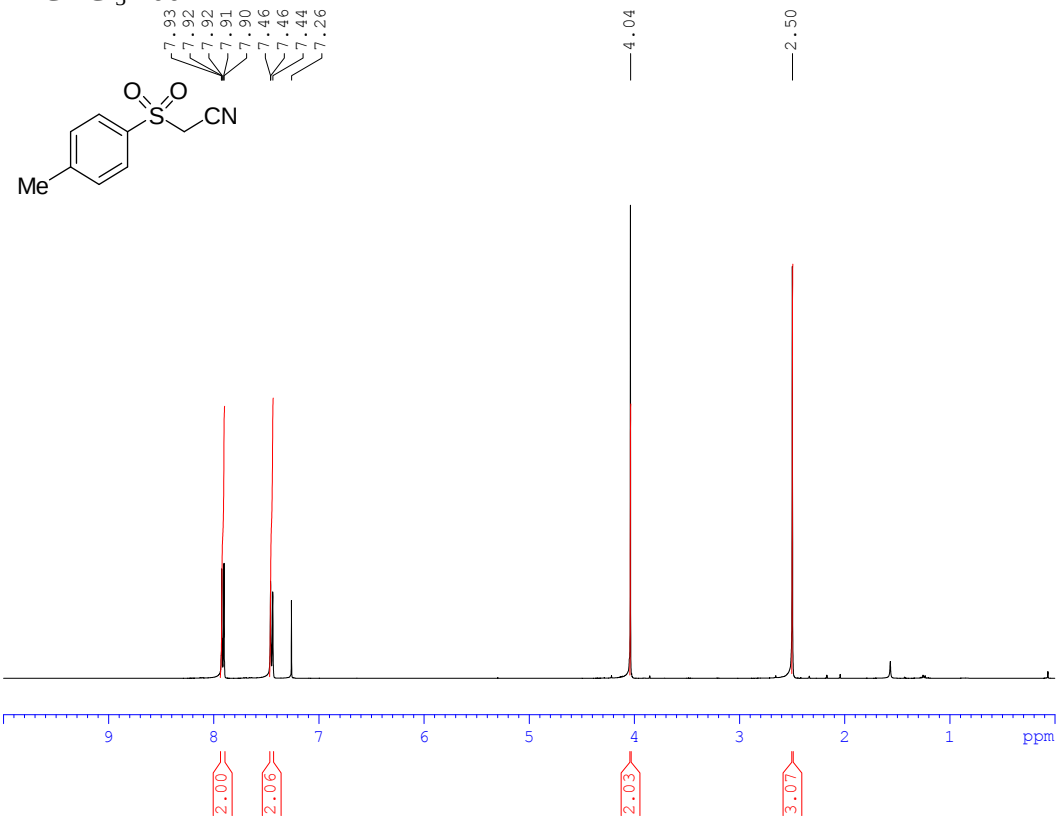


^{13}C $CDCl_3$ 101 MHz

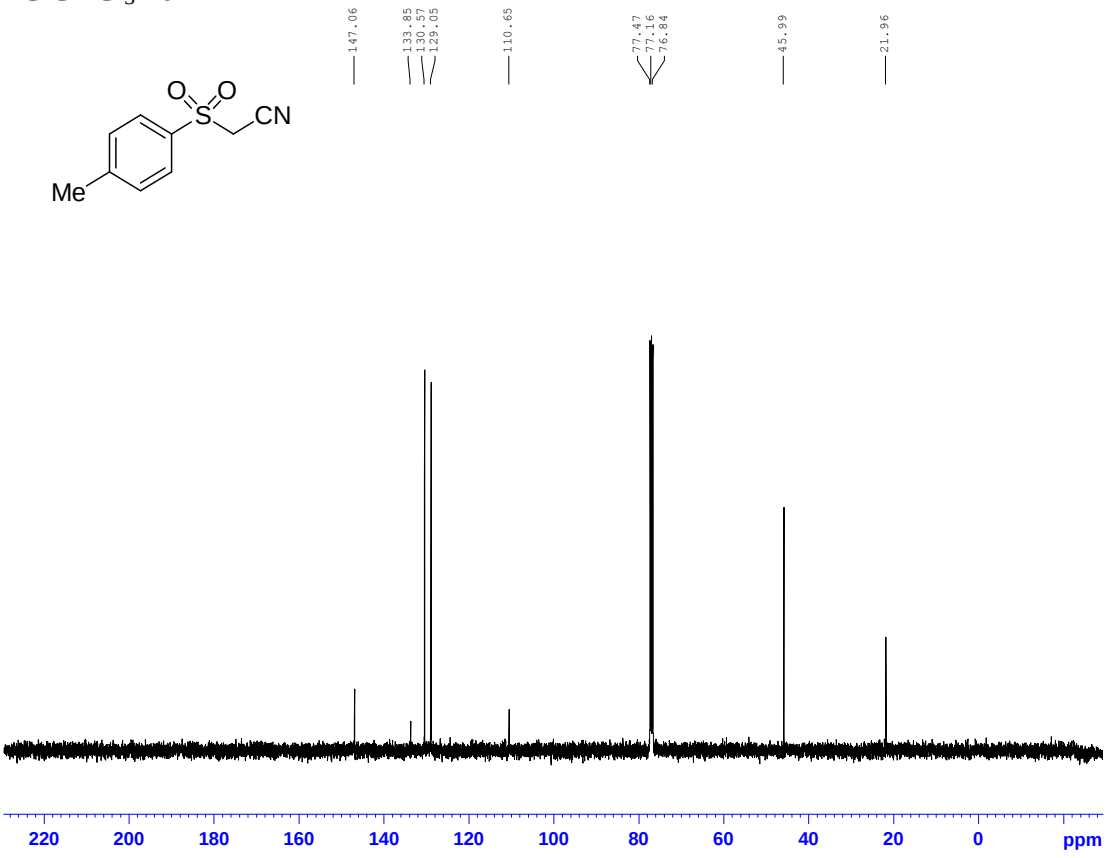


[(4-Methylphenyl)sulfonyl]acetonitrile

^{1}H $CDCl_3$ 400 MHz

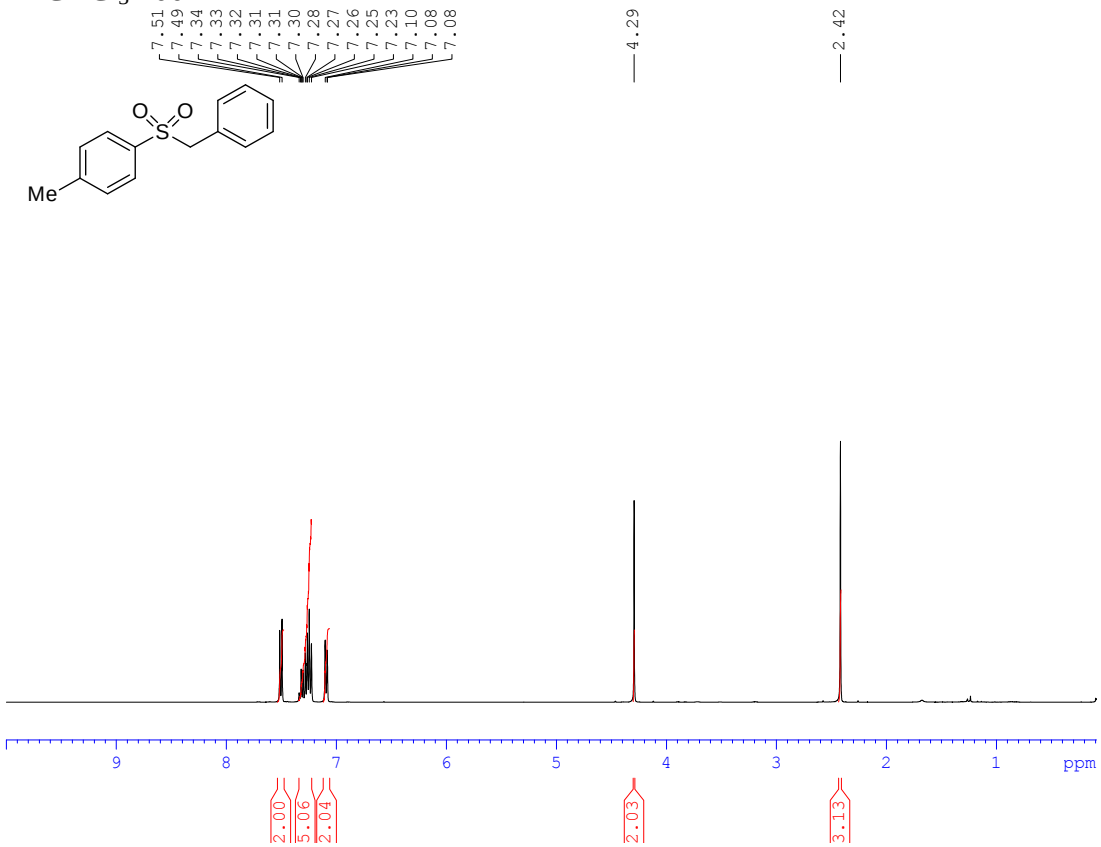


^{13}C $CDCl_3$ 101 MHz

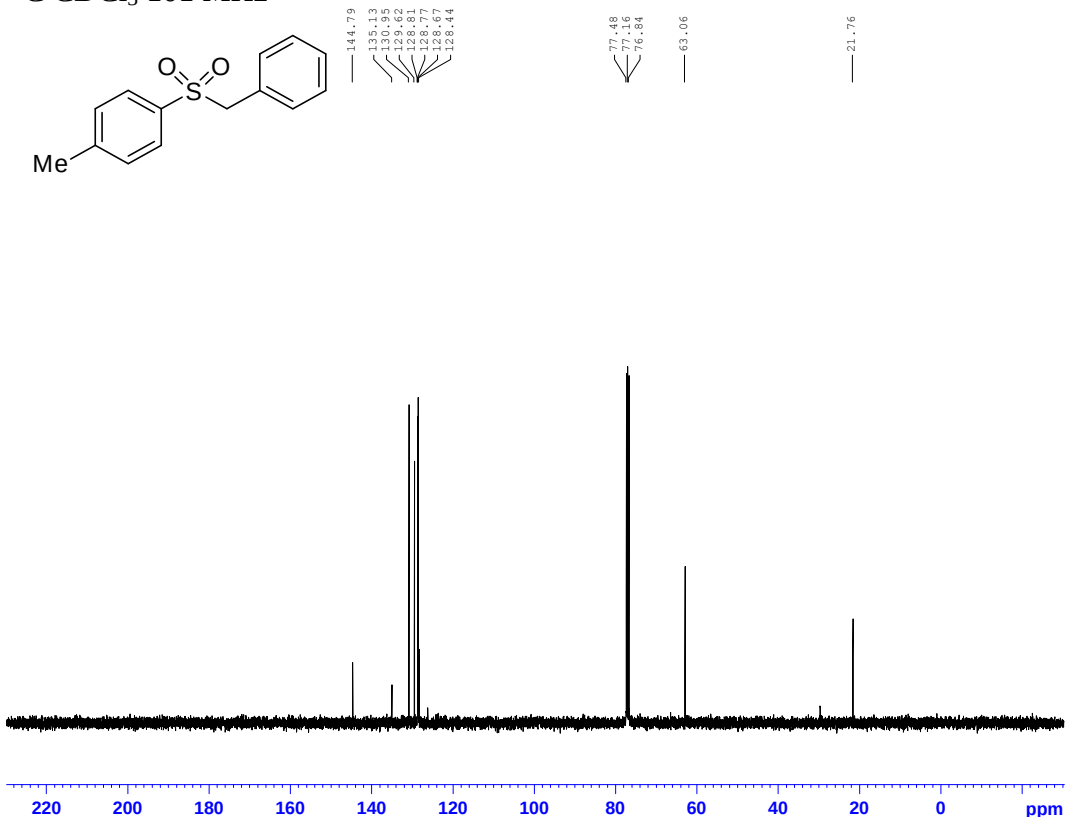


Benzyl 4-methylphenyl sulfone

^{1}H $CDCl_3$ 400 MHz

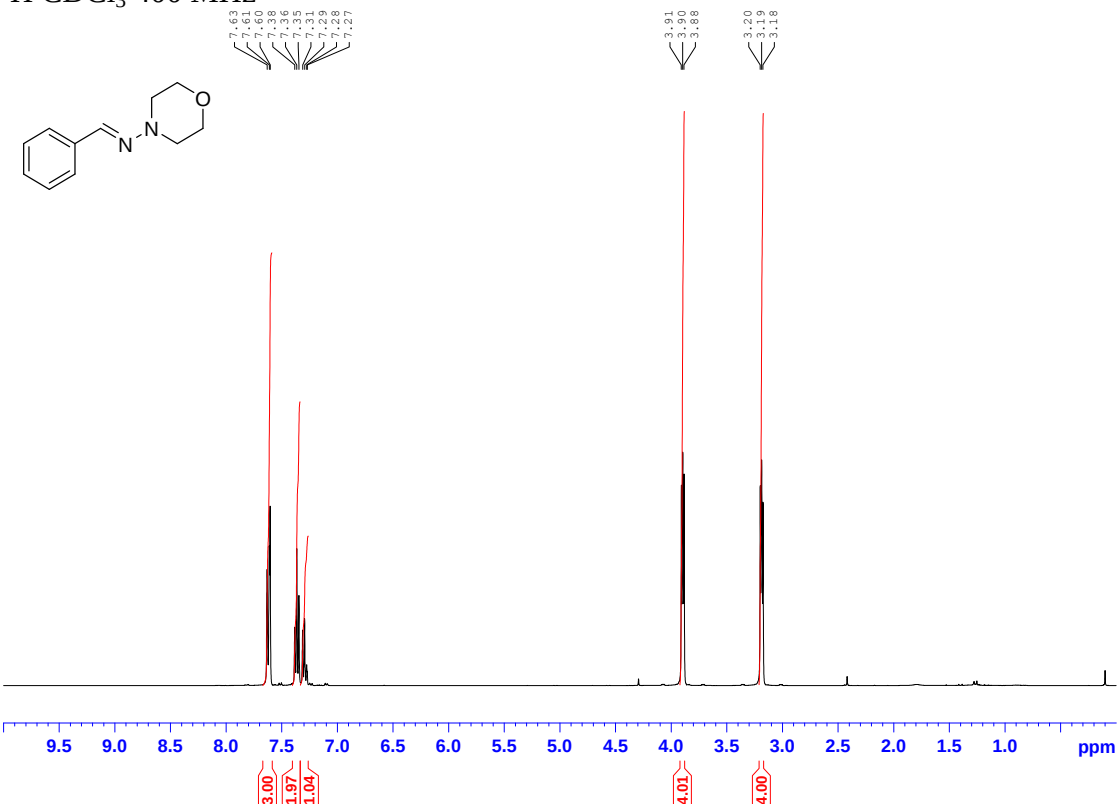


^{13}C $CDCl_3$ 101 MHz

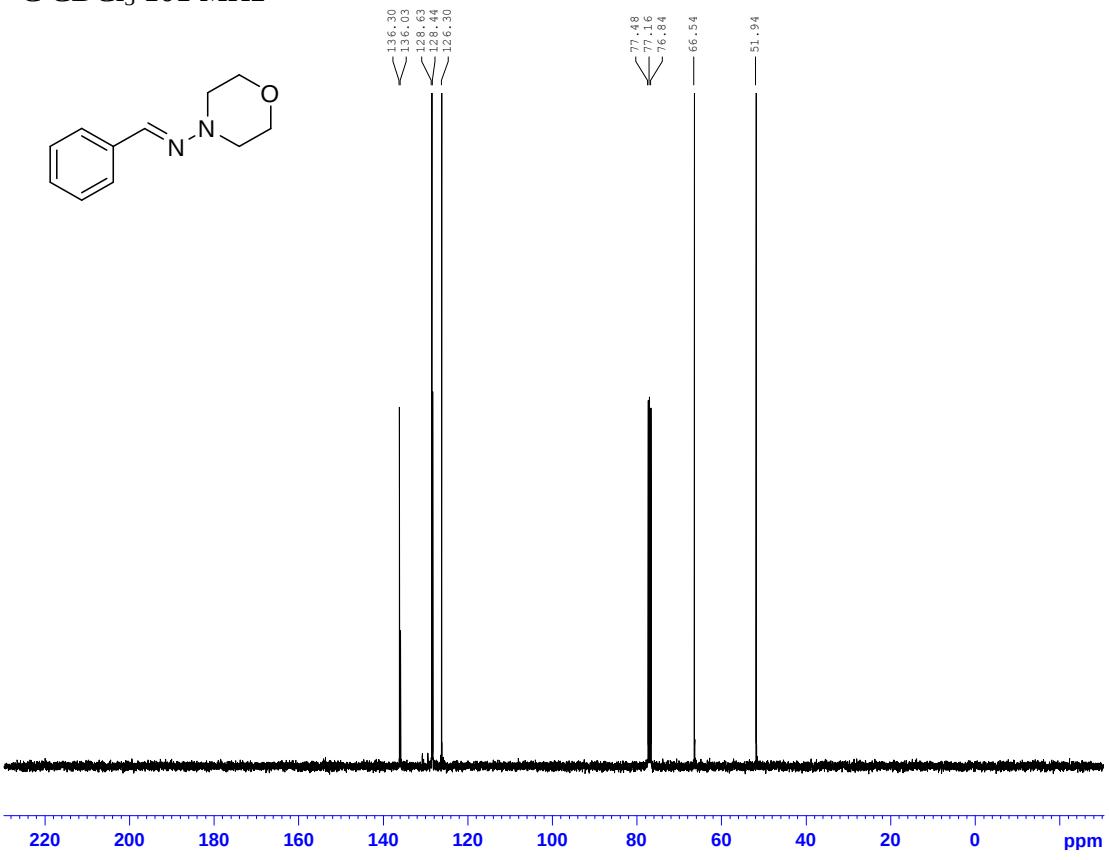


_N_-[(_E_)-Phenylmethylidene]morpholin-4-amine

^{1}H $CDCl_3$ 400 MHz

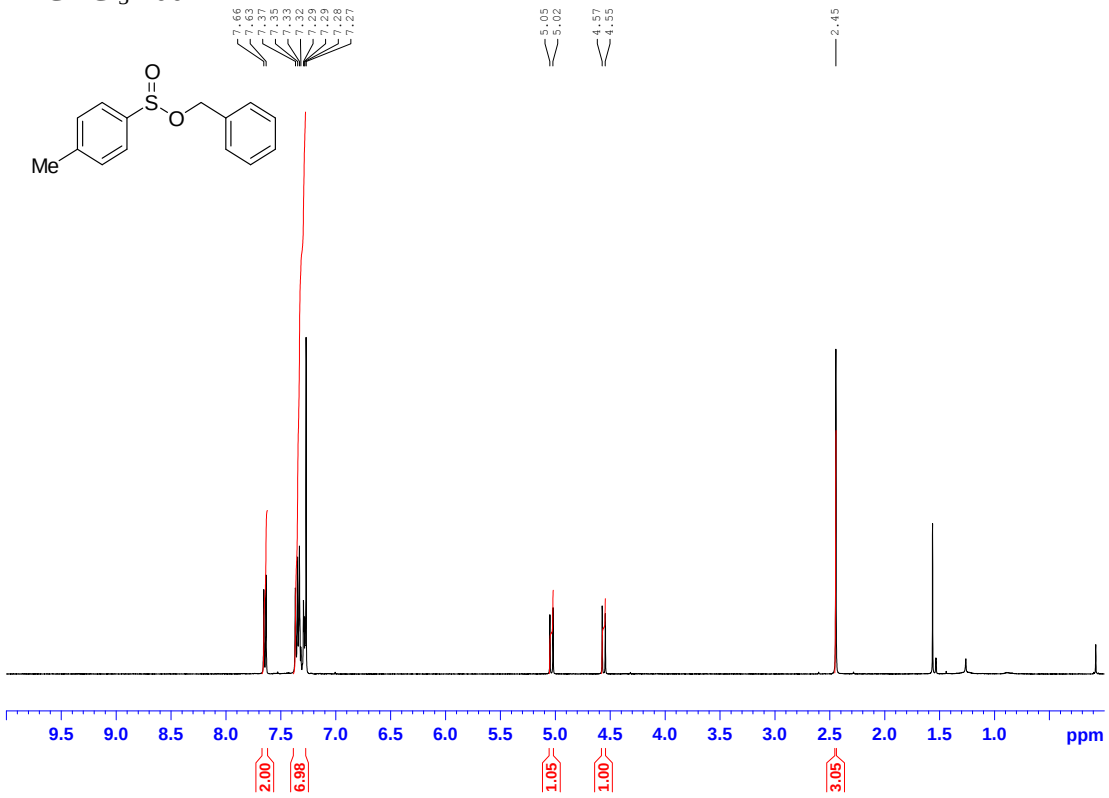


^{13}C $CDCl_3$ 101 MHz



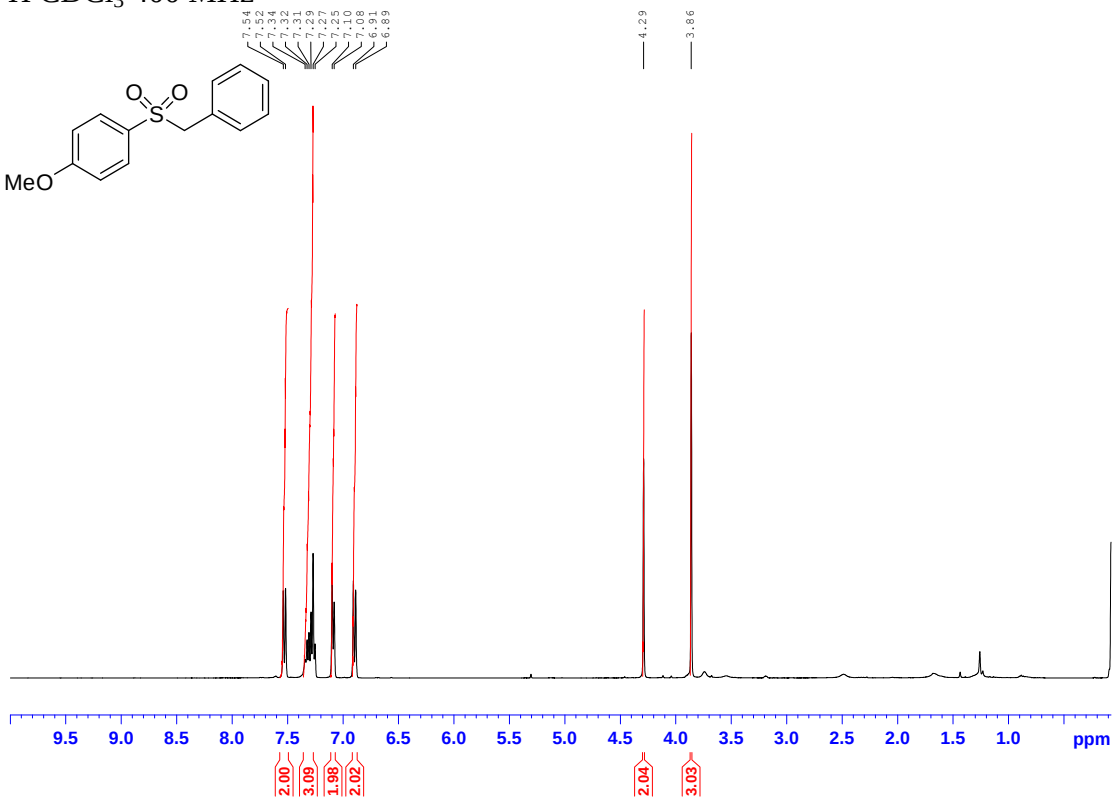
Benzyl 4-methylbenzenesulfonate

^{1}H $CDCl_3$ 400 MHz

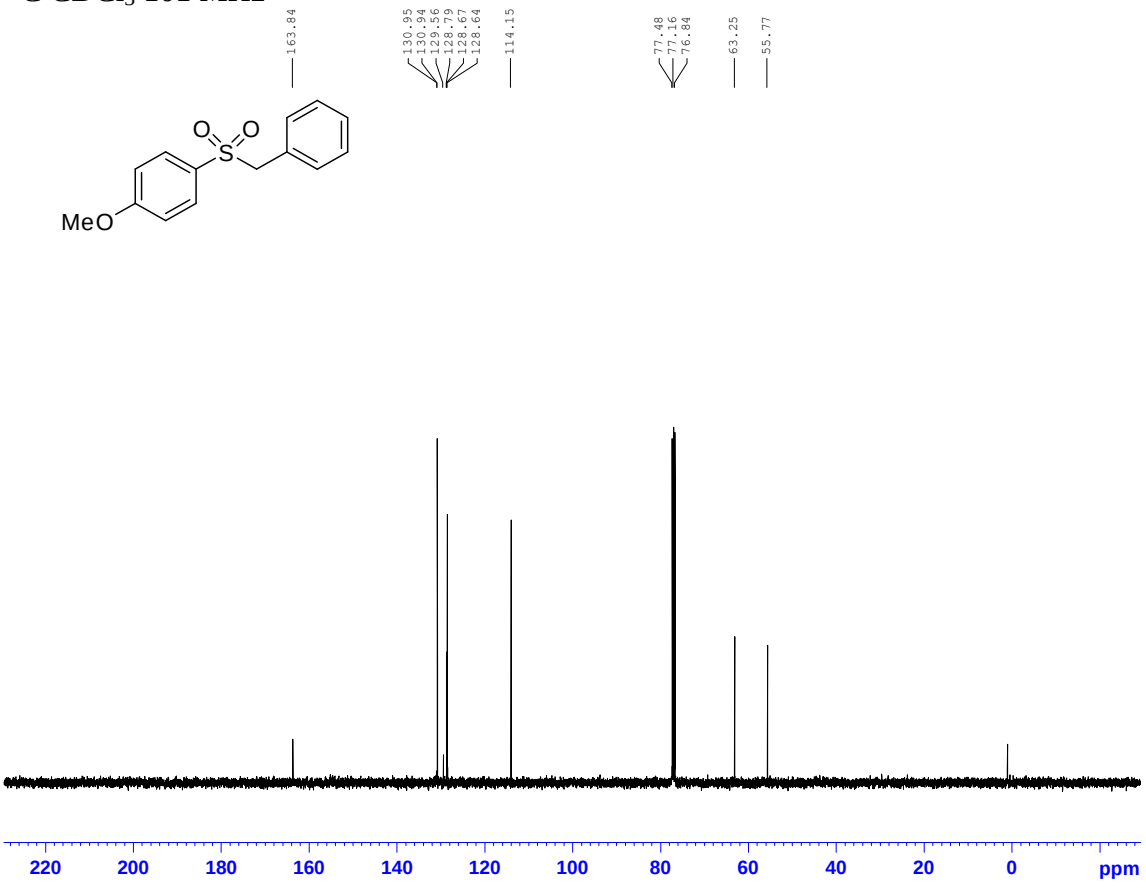


Benzyl 4-methoxyphenyl sulfone

^{1}H $CDCl_3$ 400 MHz

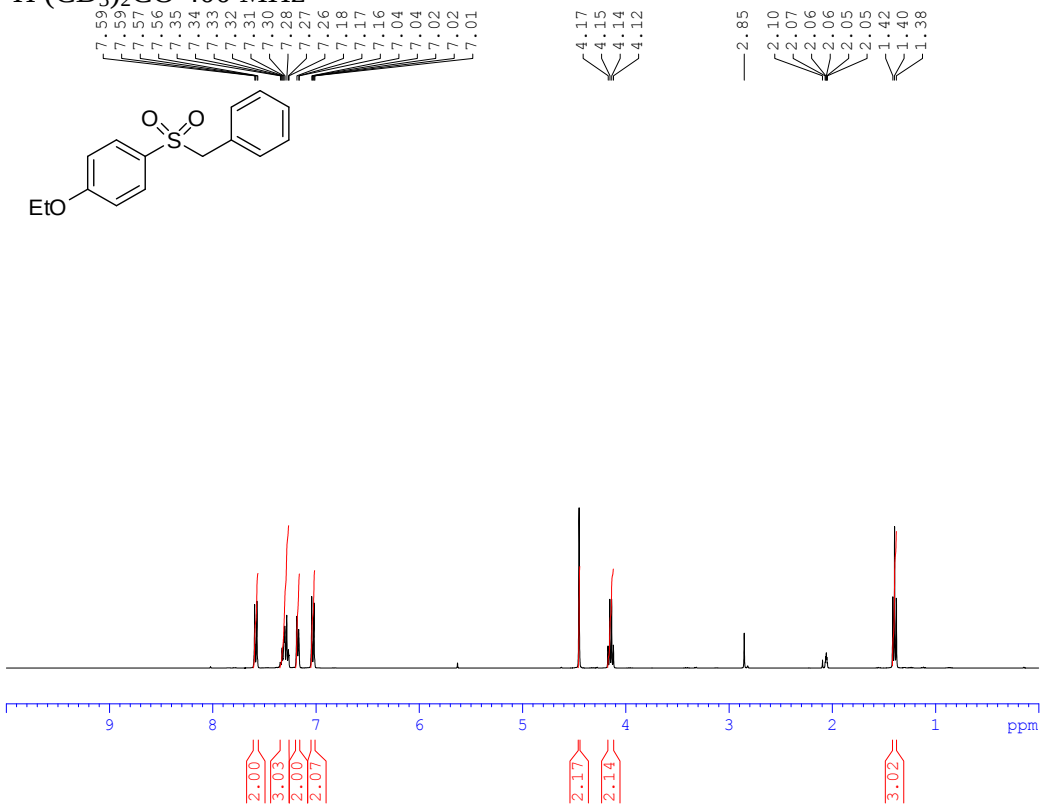


^{13}C $CDCl_3$ 101 MHz

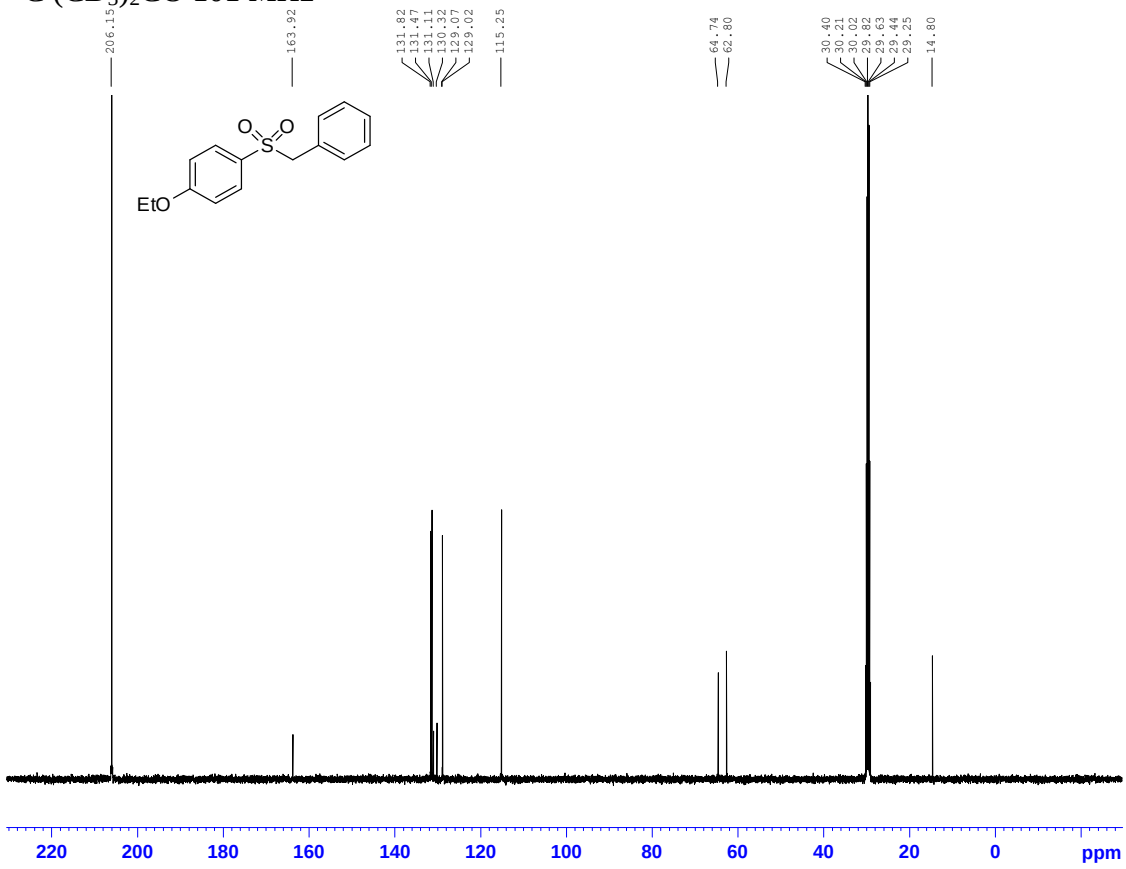


Benzyl 4-ethoxyphenyl sulfone

^{1}H $(CD_3)_2CO$ 400 MHz

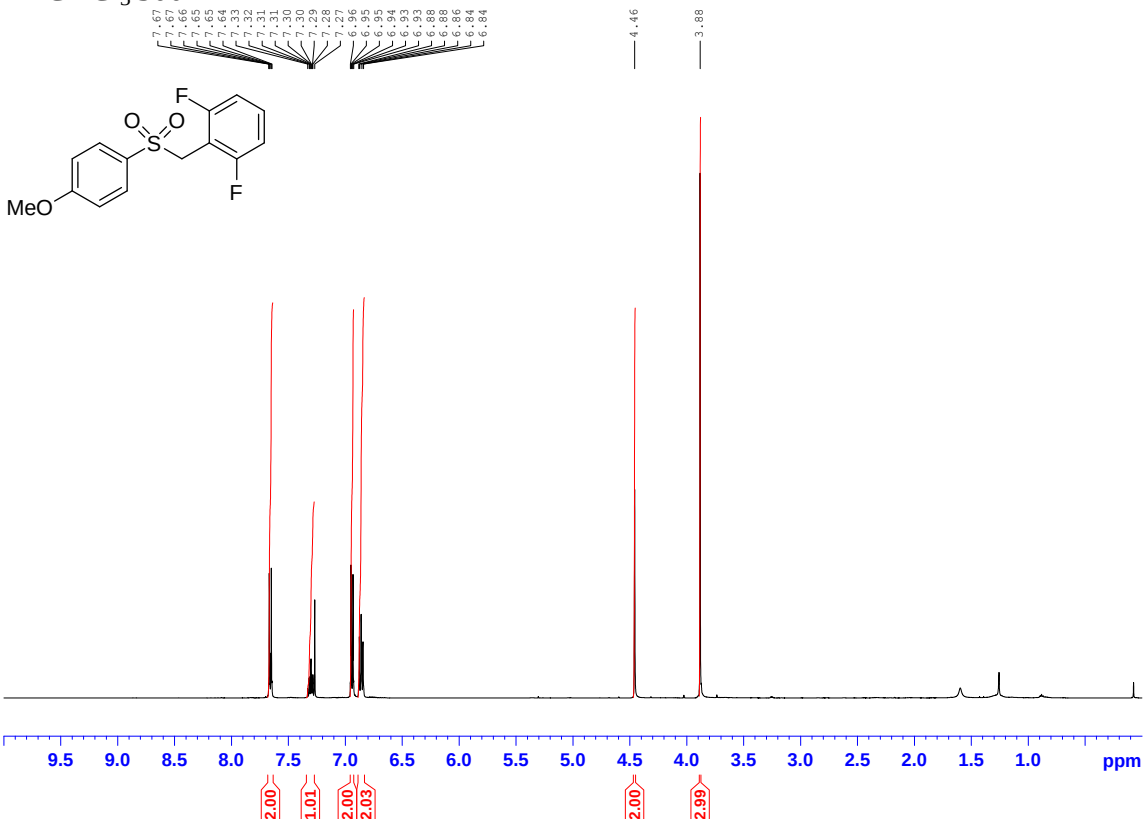


^{13}C $(CD_3)_2CO$ 101 MHz

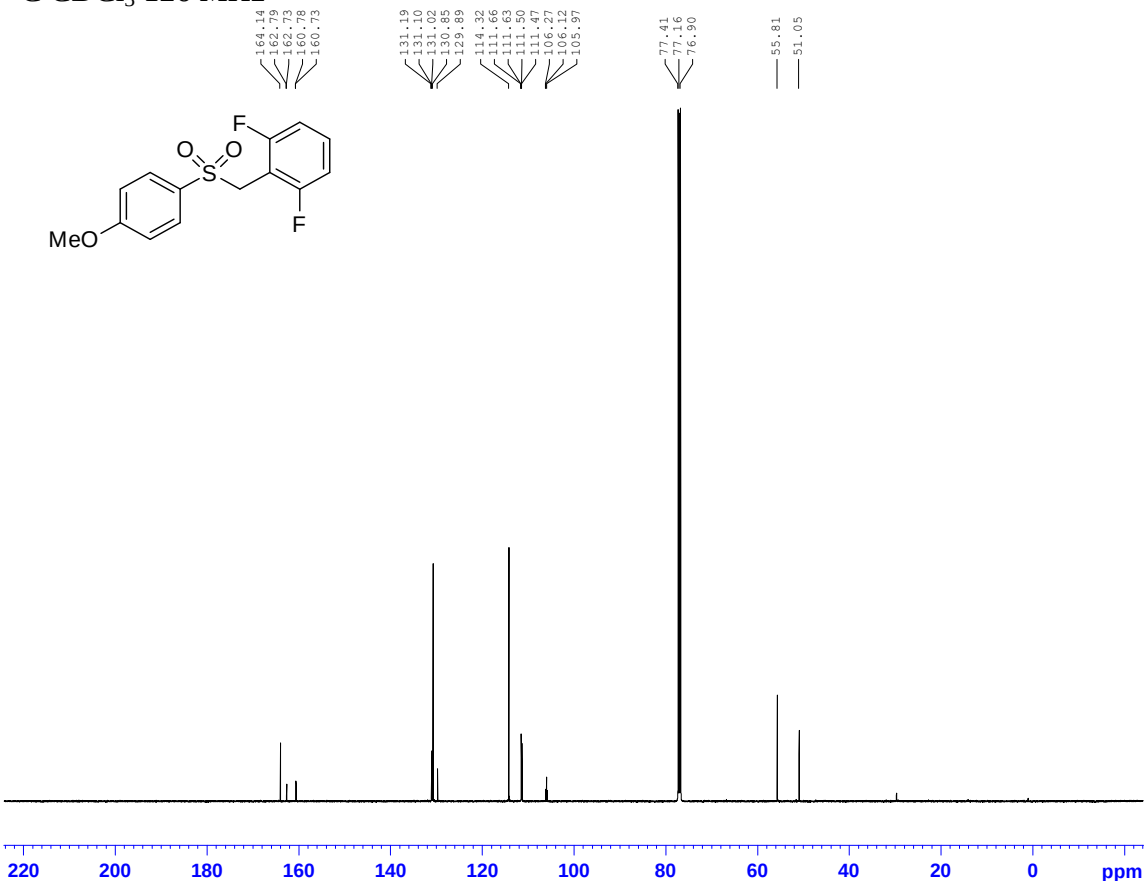


2,6-Difluorobenzyl 4-methoxyphenyl sulfone

1H $CDCl_3$ 500 MHz

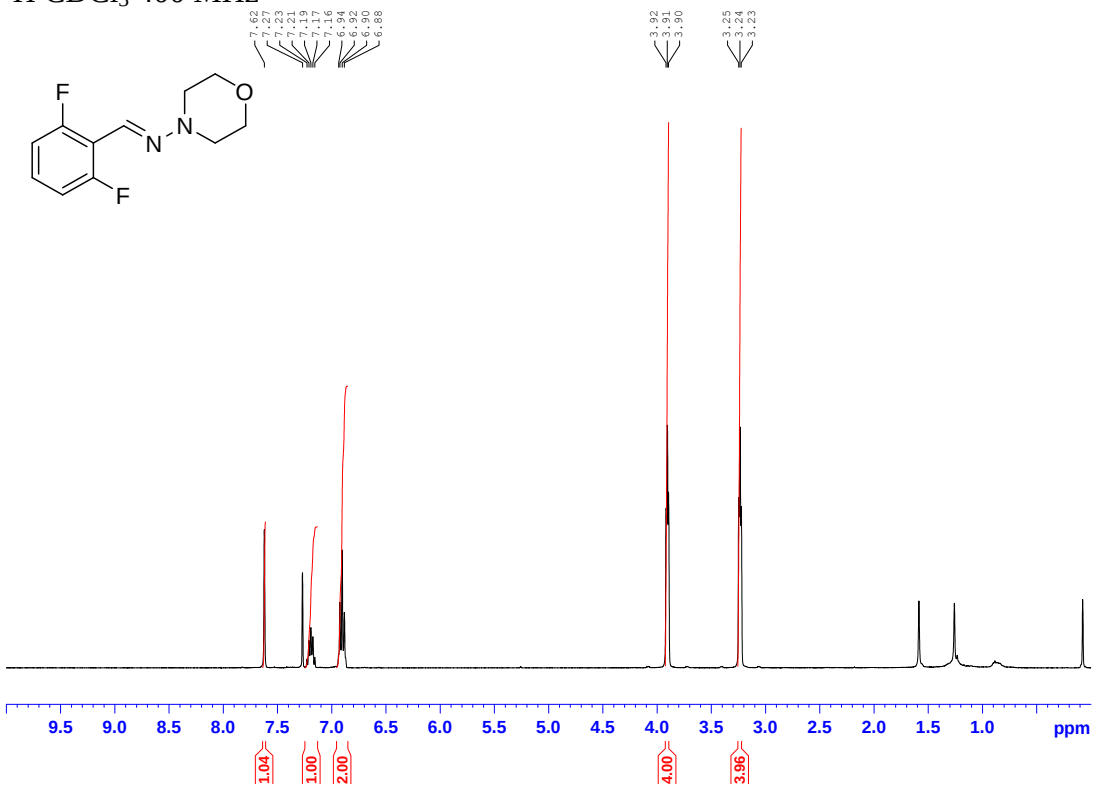


^{13}C $CDCl_3$ 126 MHz

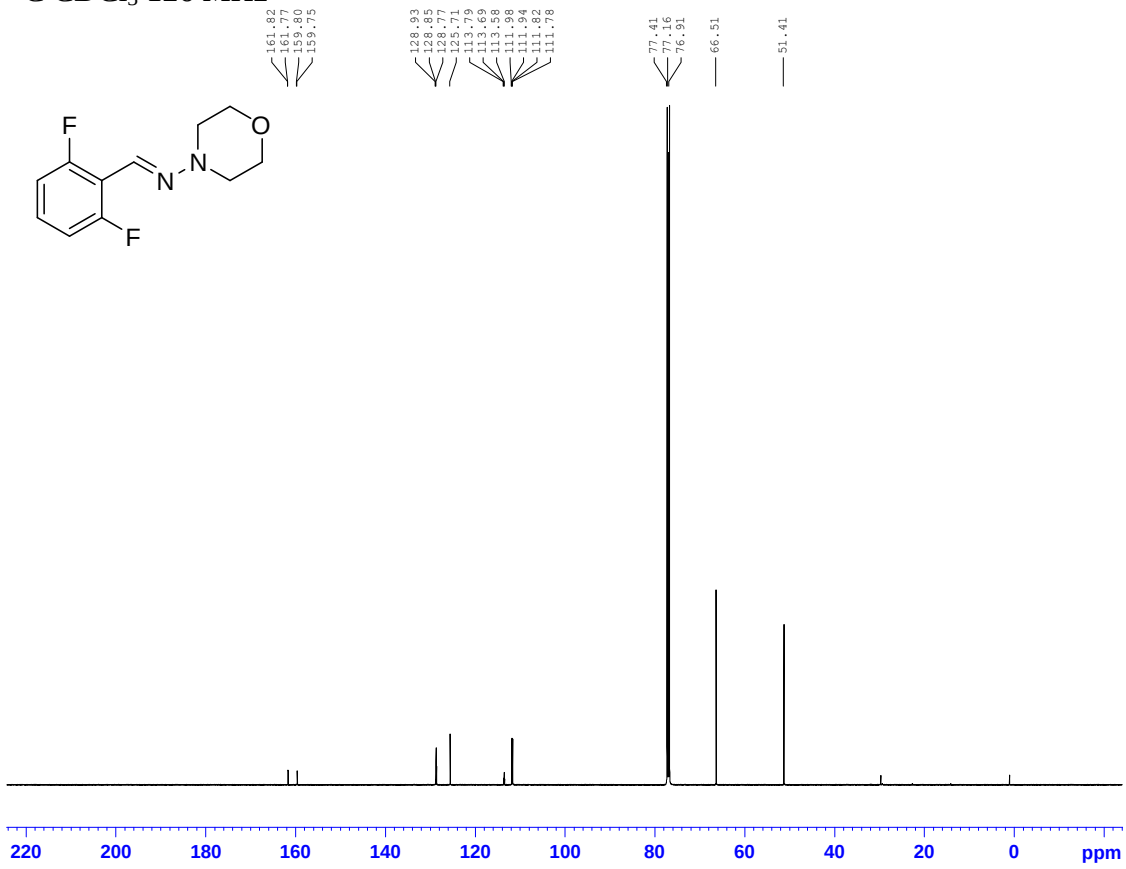


(*E*)-1-(2,6-Difluorophenyl)-*N*-(morpholin-4-yl)methanimine

^{1}H $CDCl_3$ 400 MHz

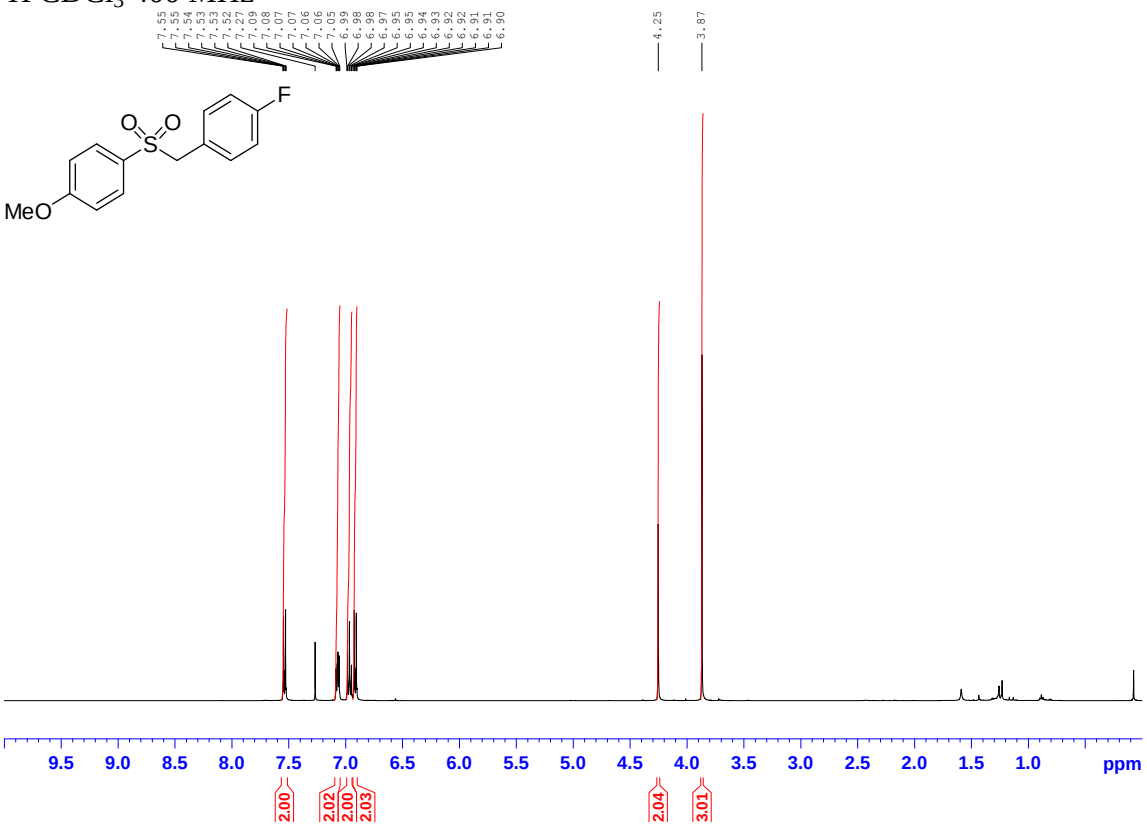


^{13}C $CDCl_3$ 126 MHz

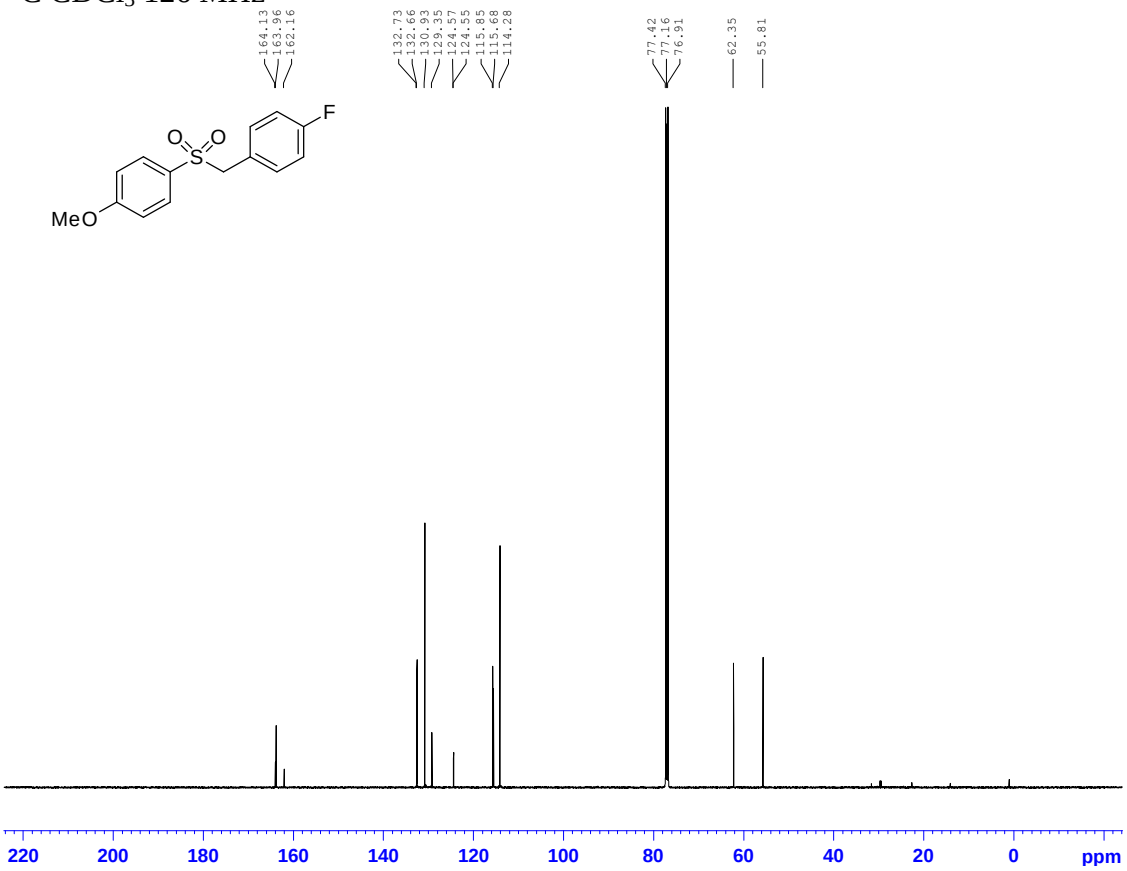


4-Fluorobenzyl 4-methoxyphenyl sulfone

^{1}H $CDCl_3$ 400 MHz

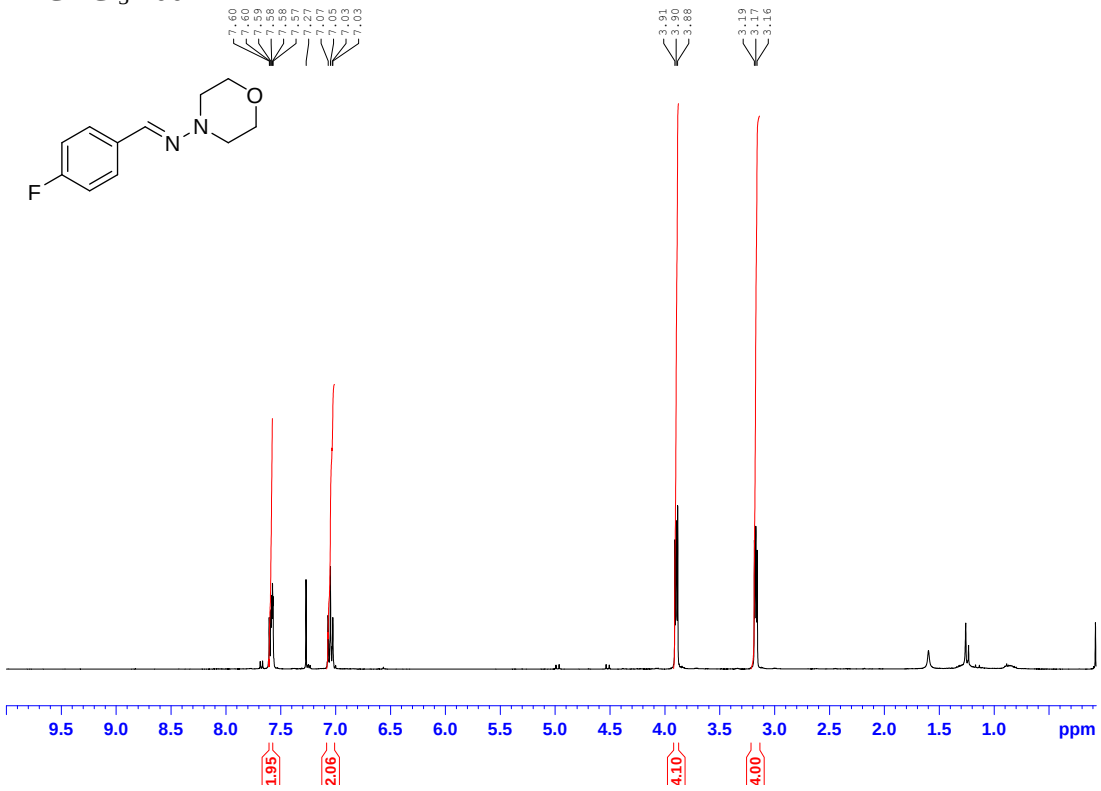


^{13}C $CDCl_3$ 126 MHz

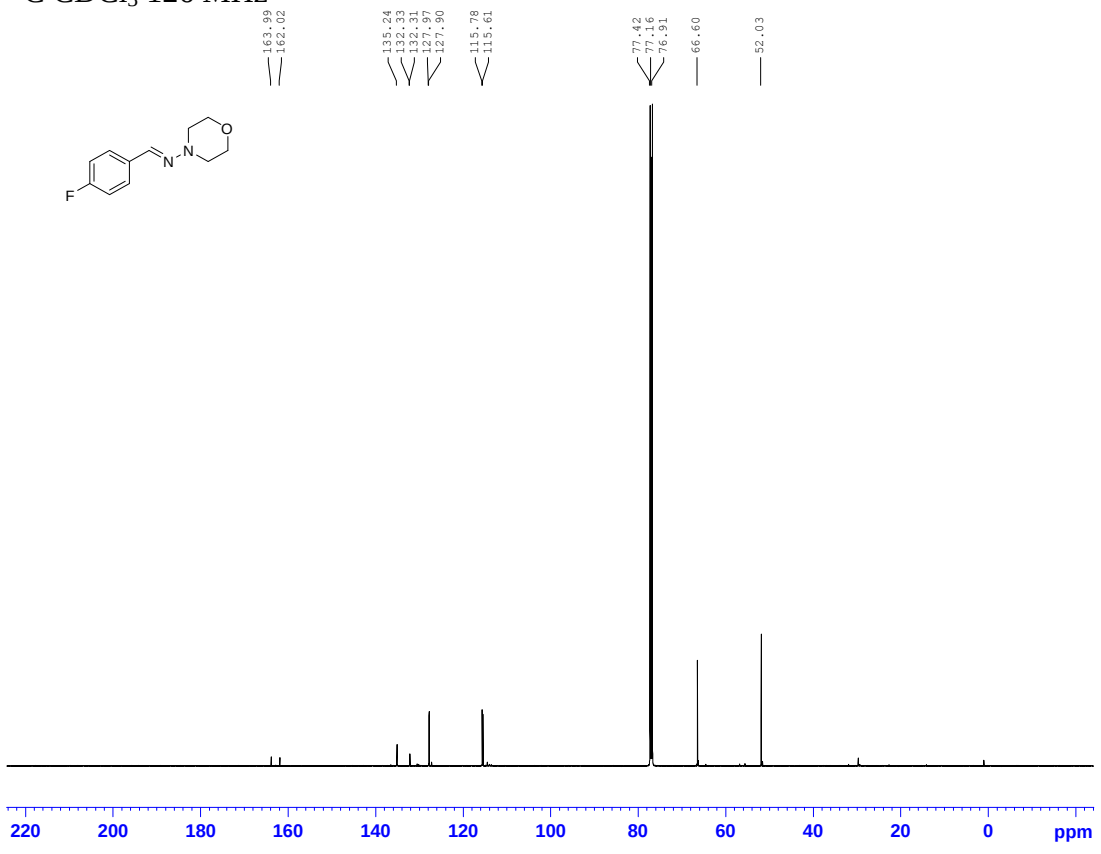


(*E*)-1-(4-Fluorophenyl)-*N*-(morpholin-4-yl)methanimine

^{1}H $CDCl_3$ 400 MHz

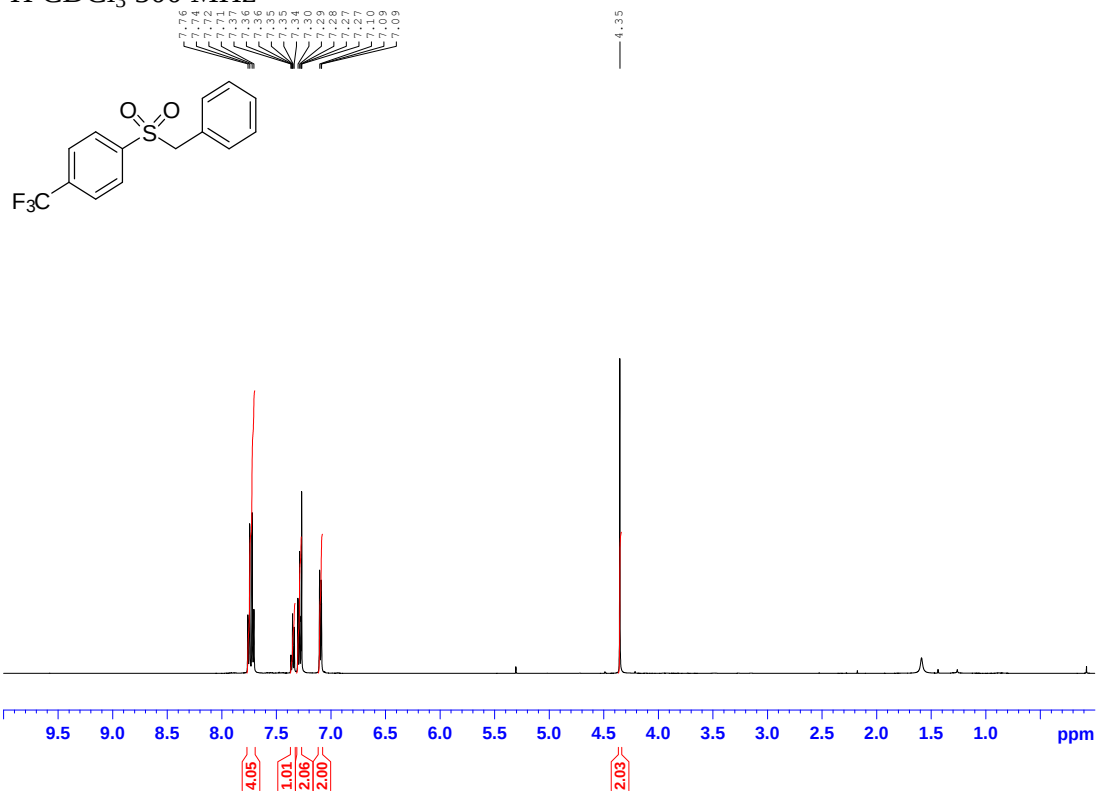


^{13}C $CDCl_3$ 126 MHz

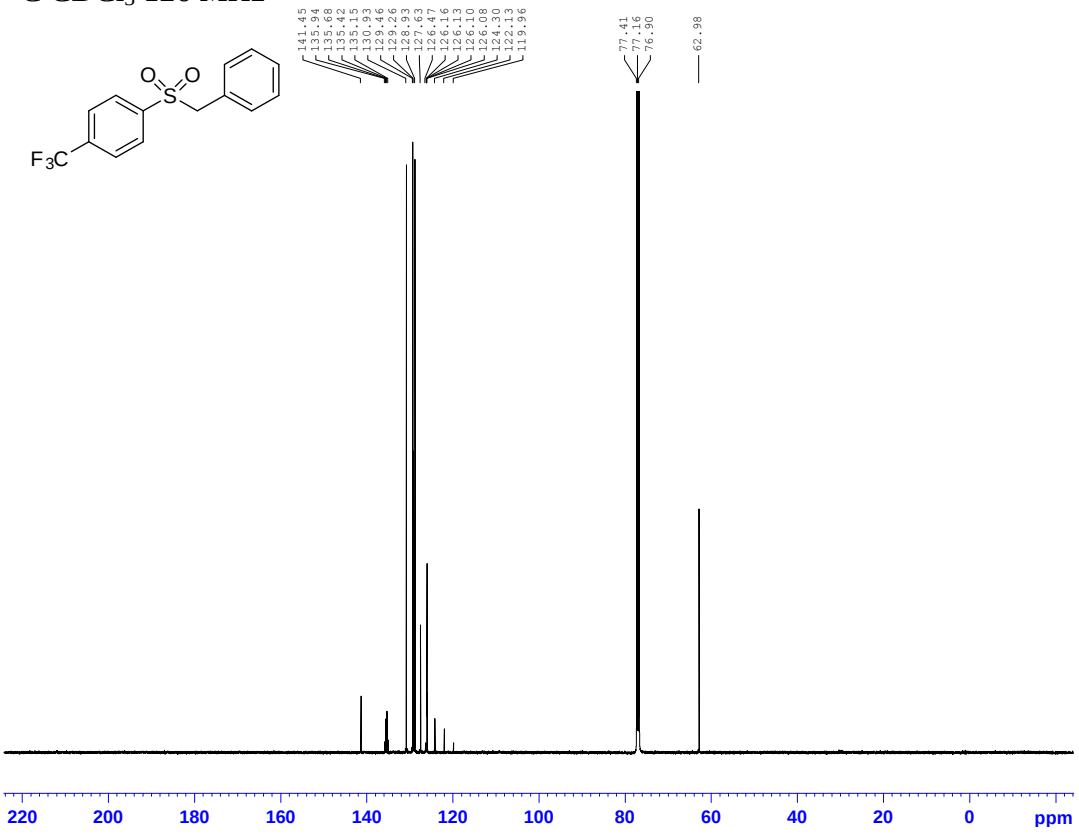


Benzyl 4-(trifluoromethyl)phenyl sulfone

^{1}H $CDCl_3$ 500 MHz

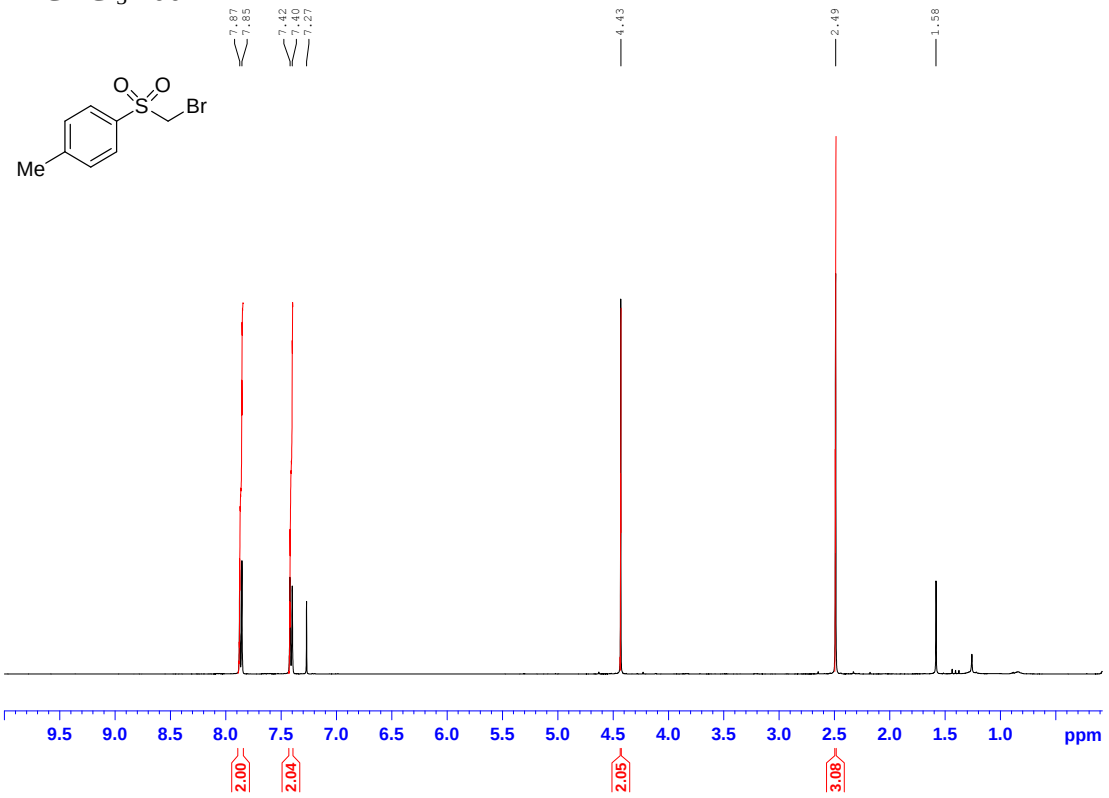


^{13}C $CDCl_3$ 126 MHz

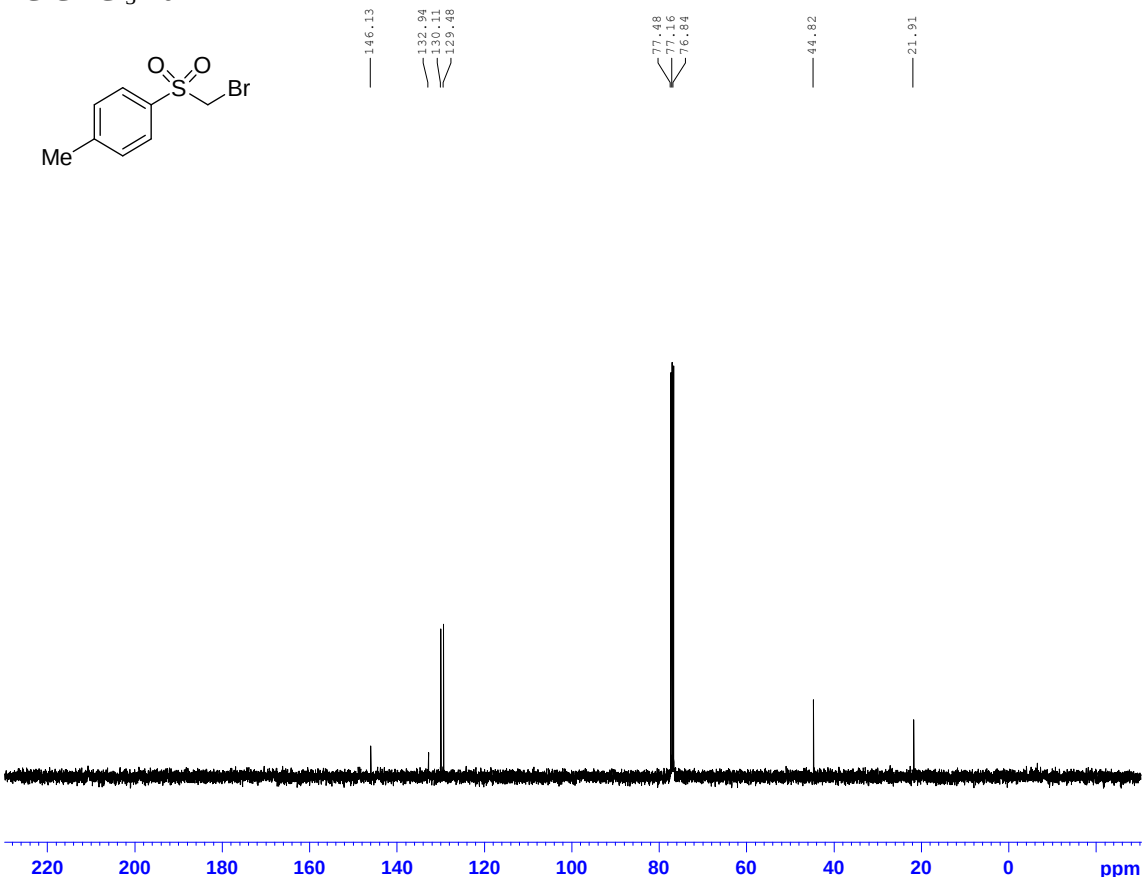


Bromomethyl 4-methylphenyl sulfone

^{1}H $CDCl_3$ 400 MHz

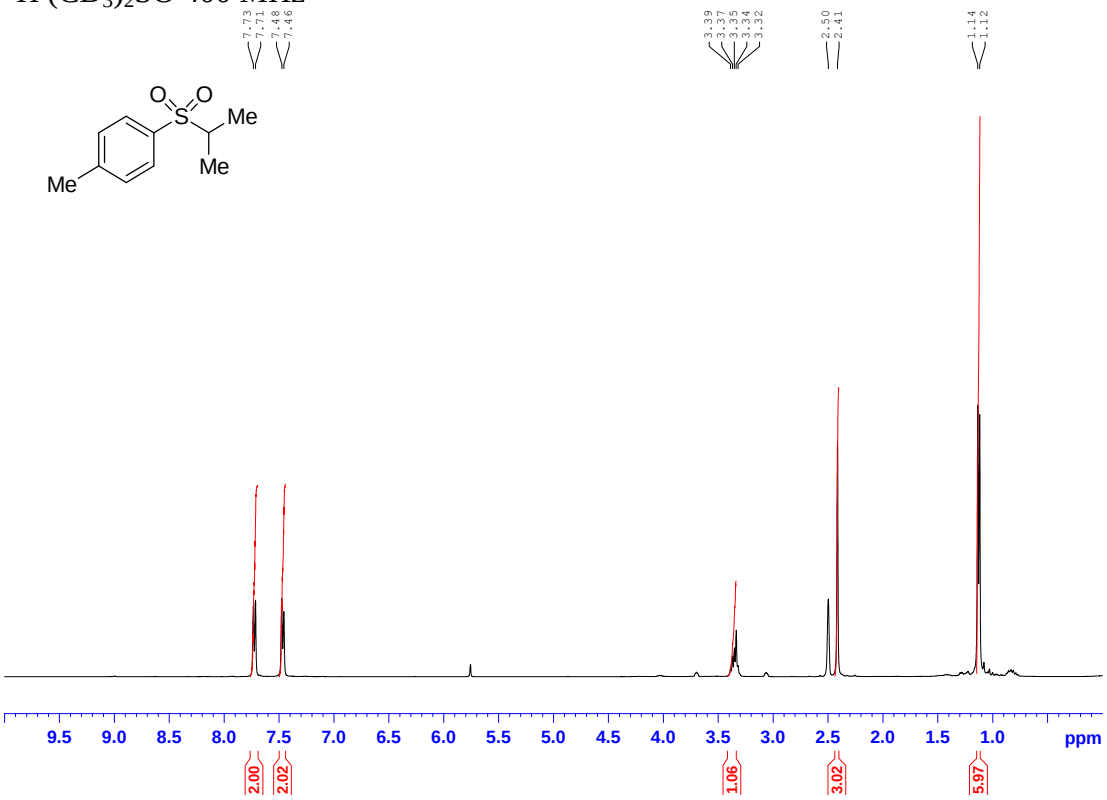


^{13}C $CDCl_3$ 101 MHz

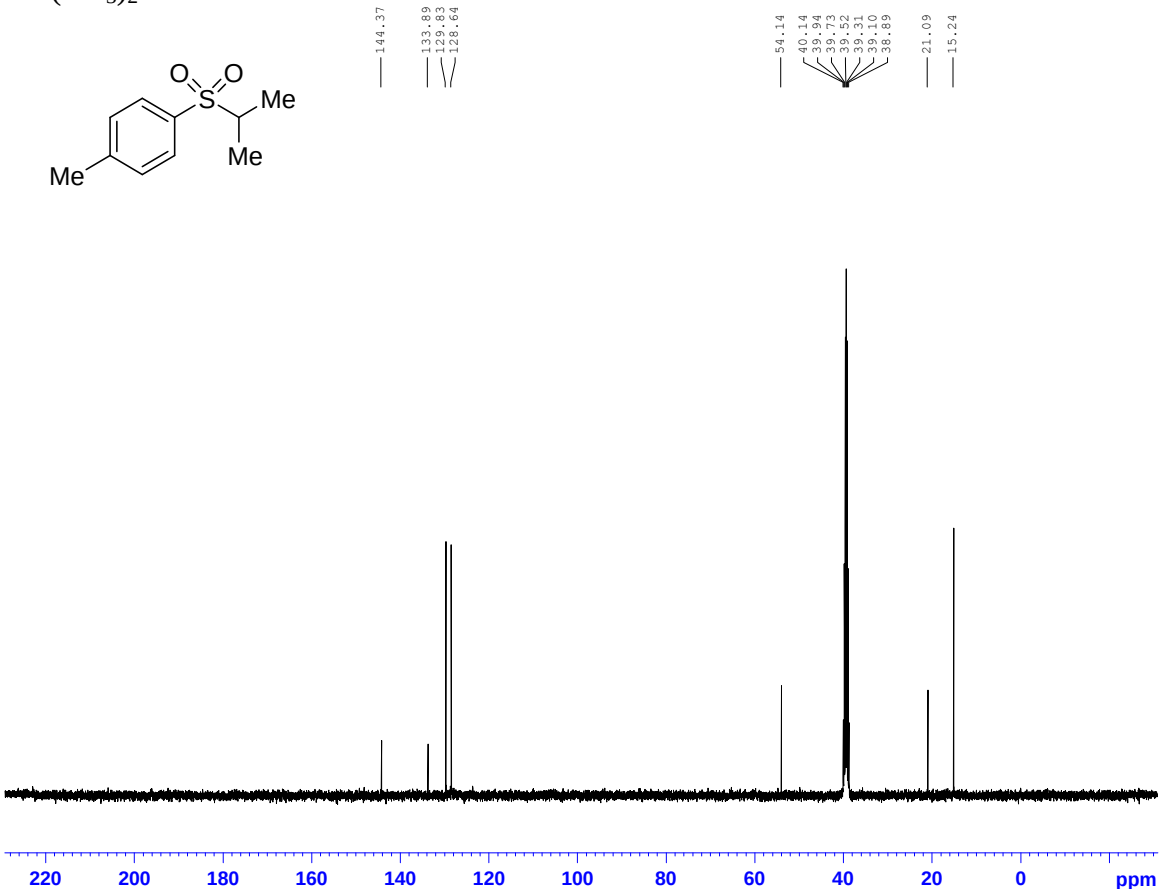


4-Methylphenyl propan-2-yl sulfone

^{1}H $(CD_3)_2SO$ 400 MHz

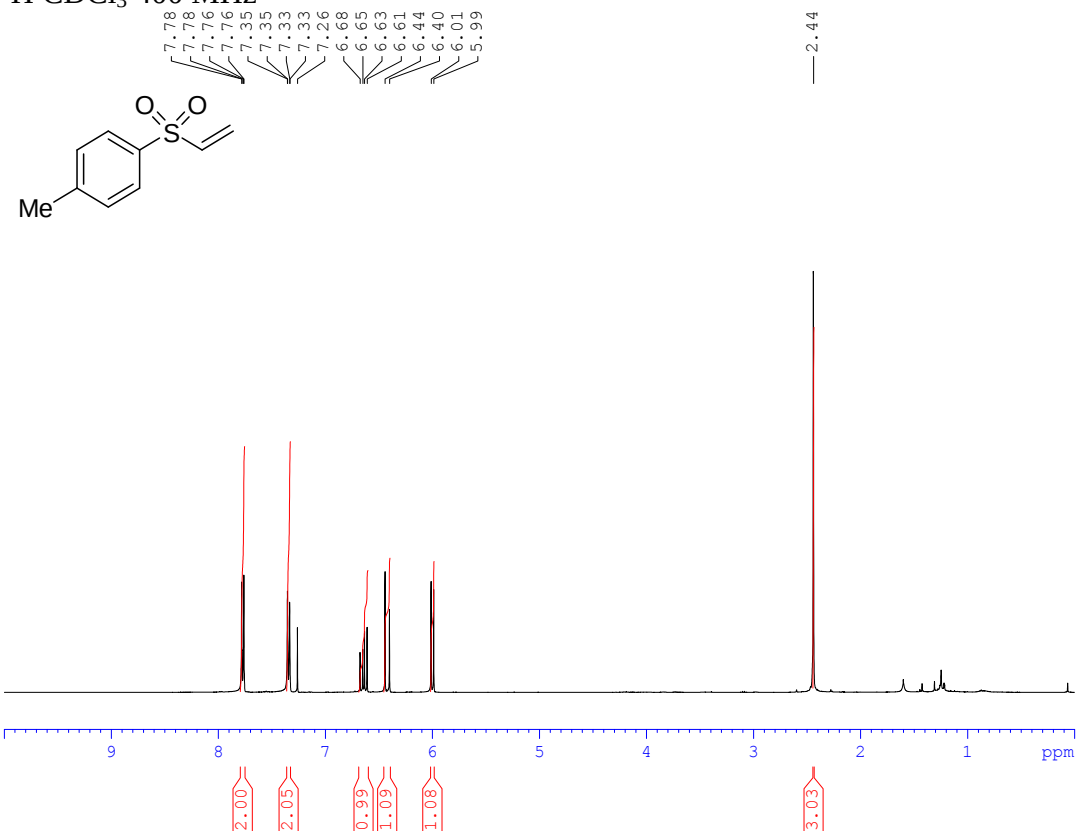


^{13}C $(CD_3)_2SO$ 101 MHz

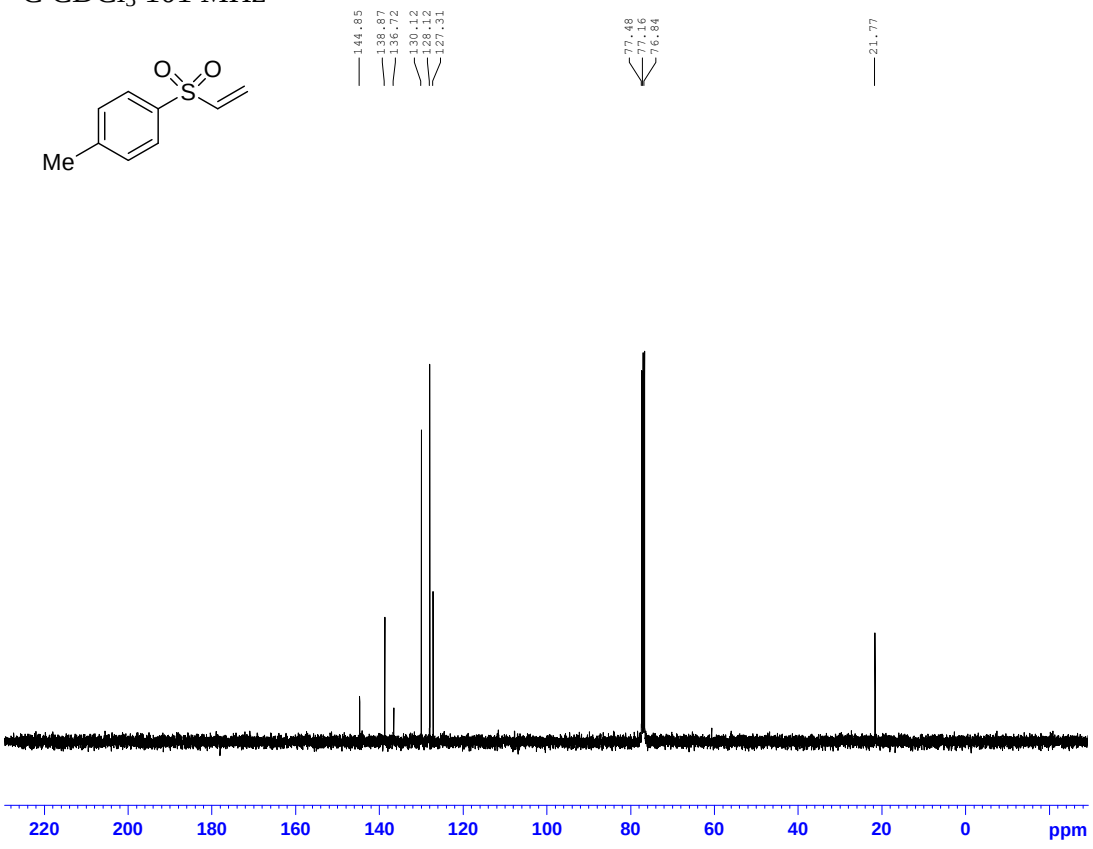


Ethenyl 4-methylphenyl sulfone

^{1}H $CDCl_3$ 400 MHz

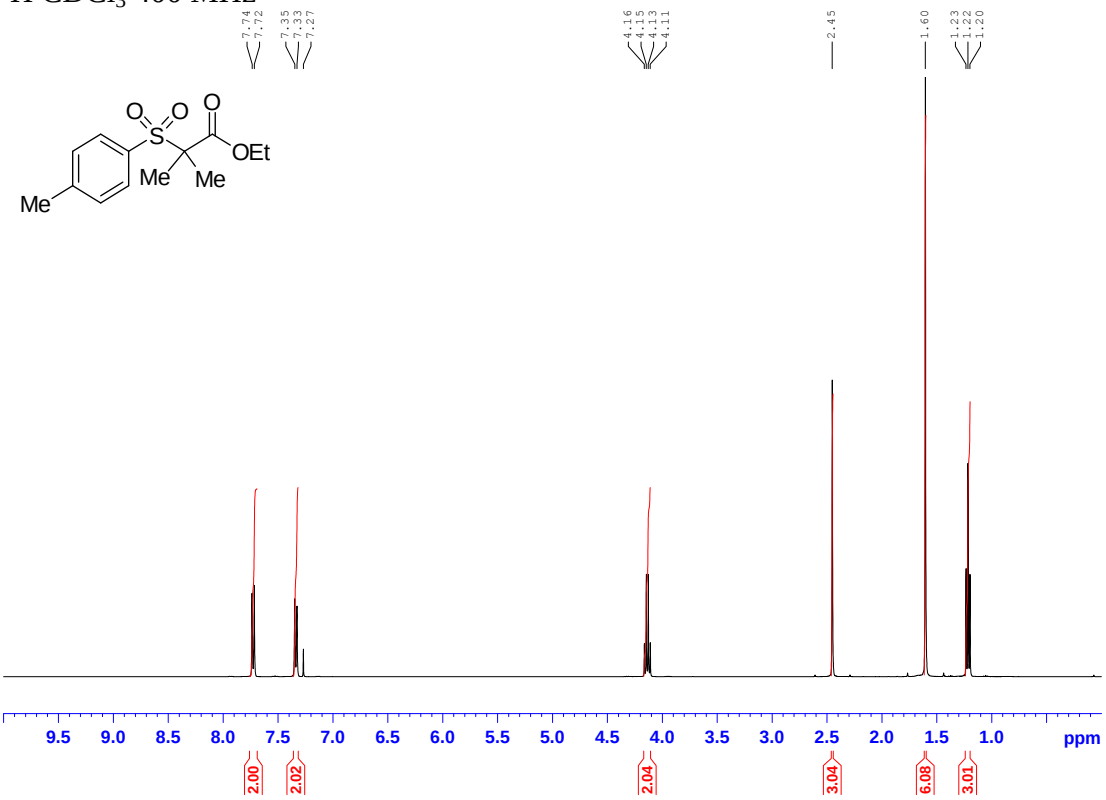


^{13}C $CDCl_3$ 101 MHz

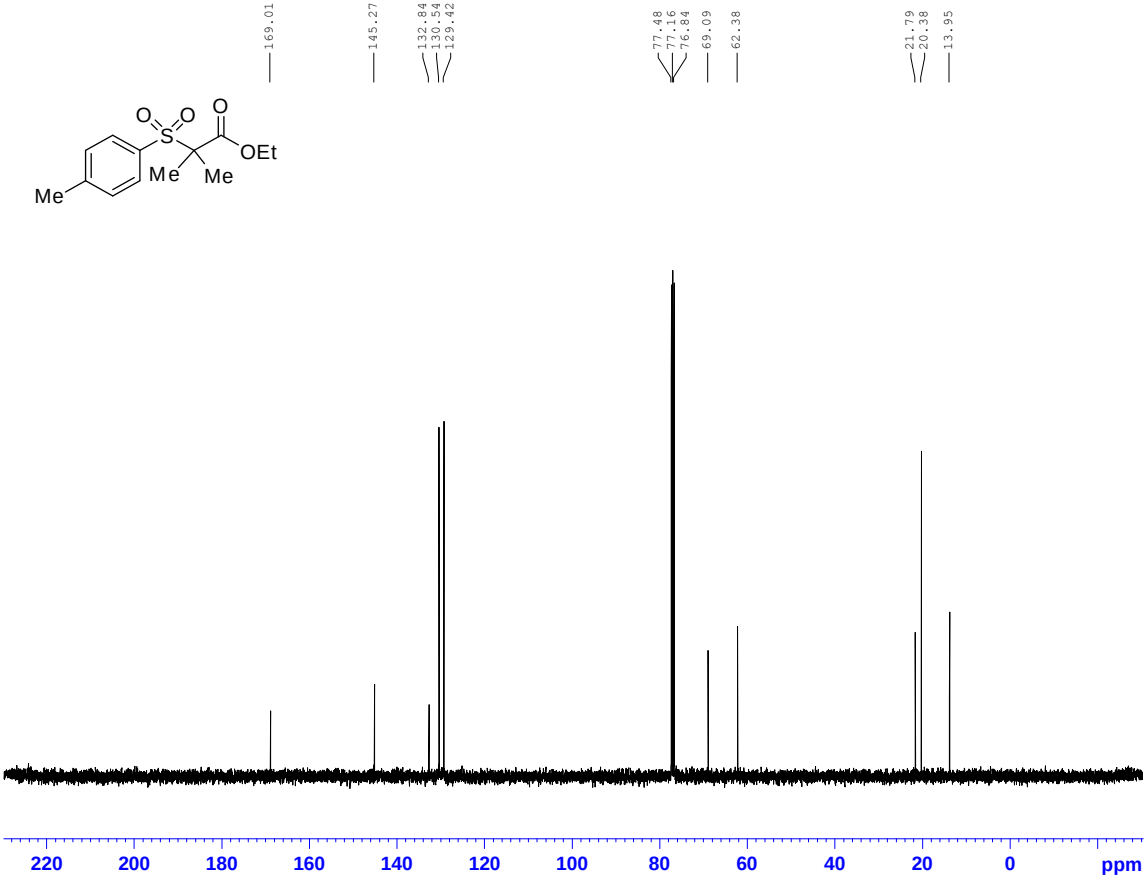


Ethyl 2-methyl-2-[(4-methylphenyl)sulfonyl]propanoate

^{1}H $CDCl_3$ 400 MHz

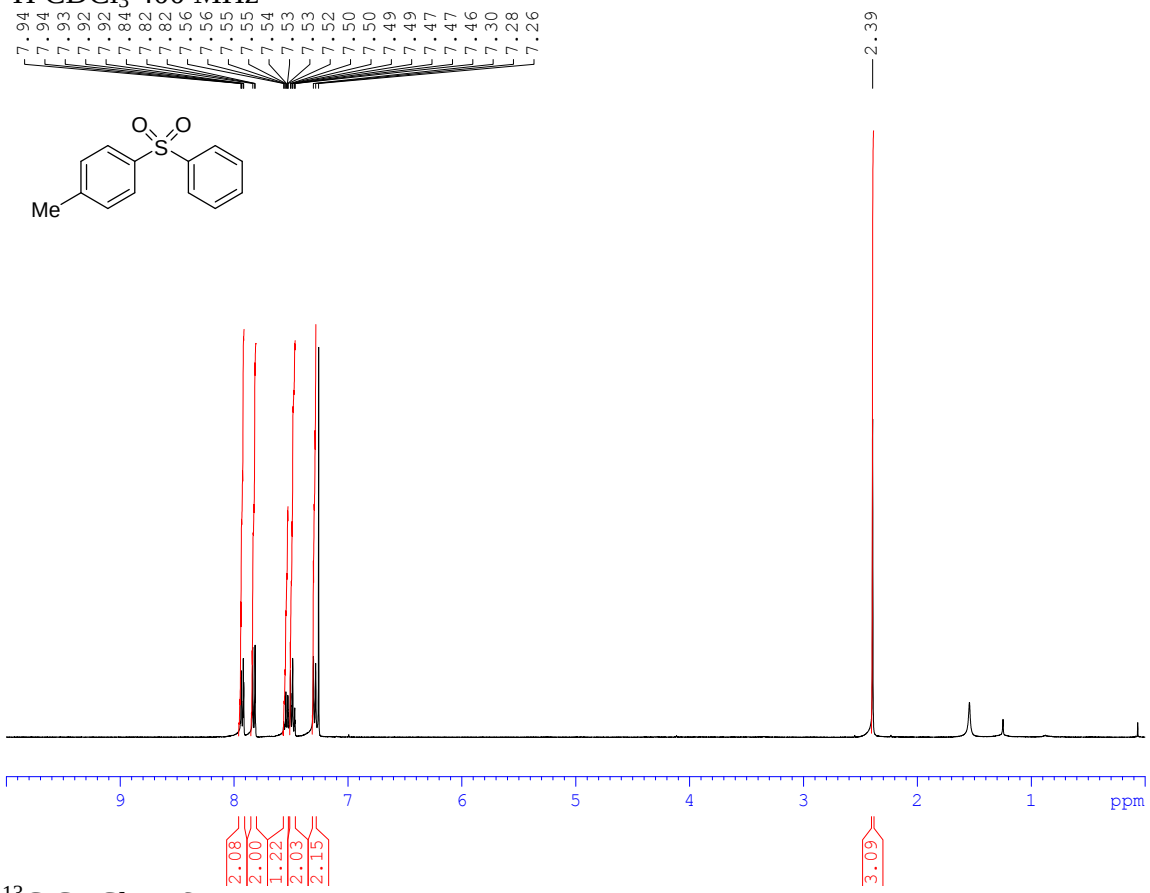


^{13}C $CDCl_3$ 101 MHz

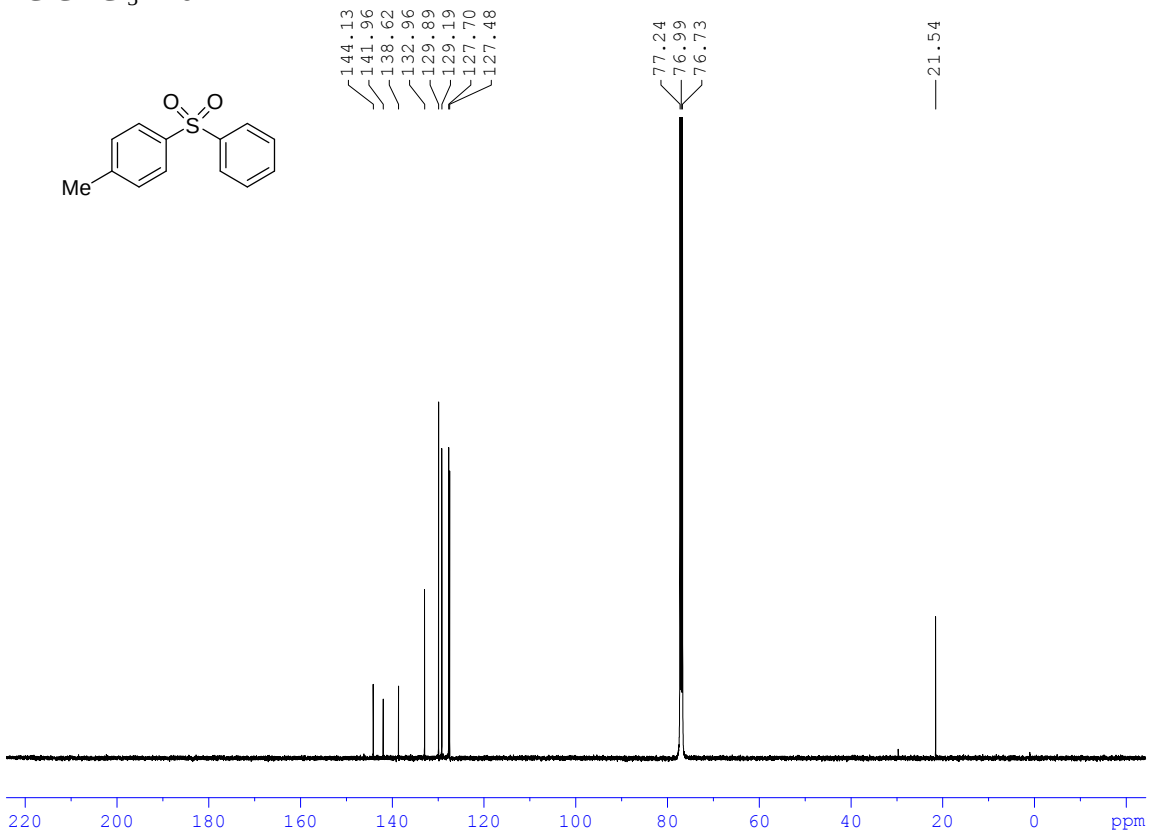


1-Methyl-4-(phenylsulfonyl)benzene

^{1}H $CDCl_3$ 400 MHz

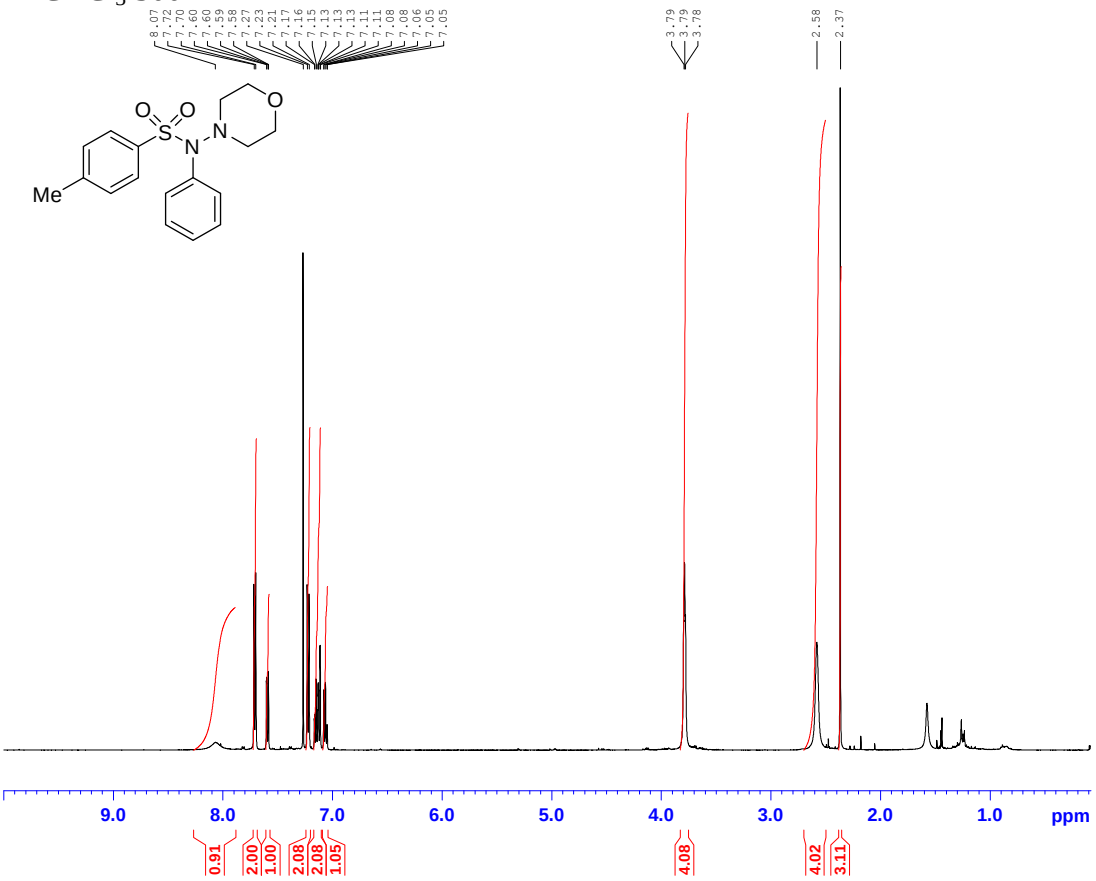


^{13}C $CDCl_3$ 126 MHz

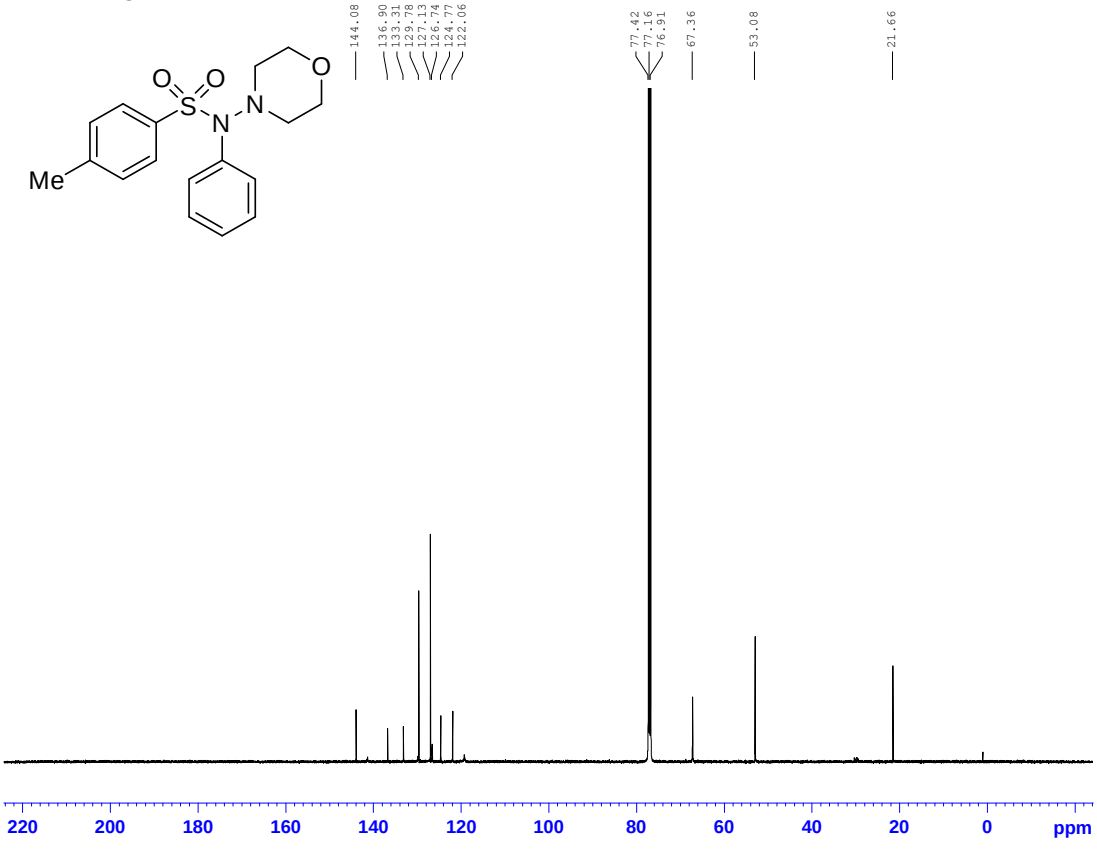


4-Methyl-*N*-(morpholin-4-yl)-*N*-phenylbenzenesulfonamide

^{1}H $CDCl_3$ 500 MHz

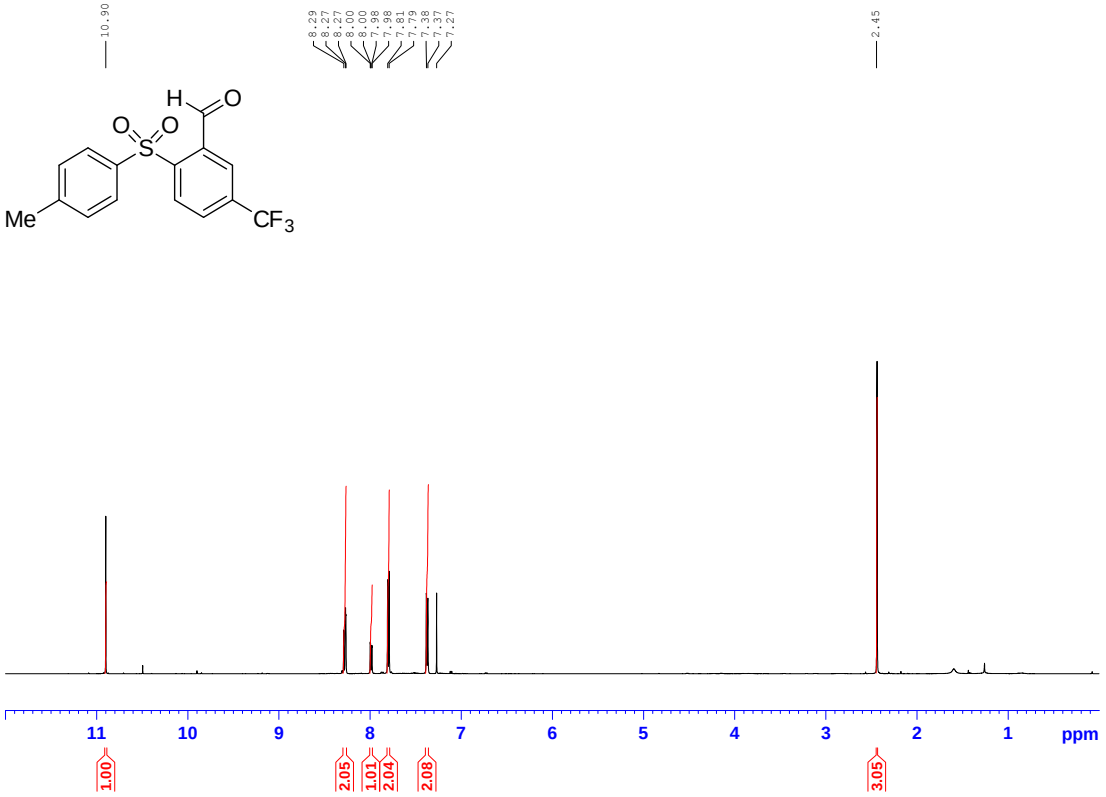


^{13}C $CDCl_3$ 126 MHz

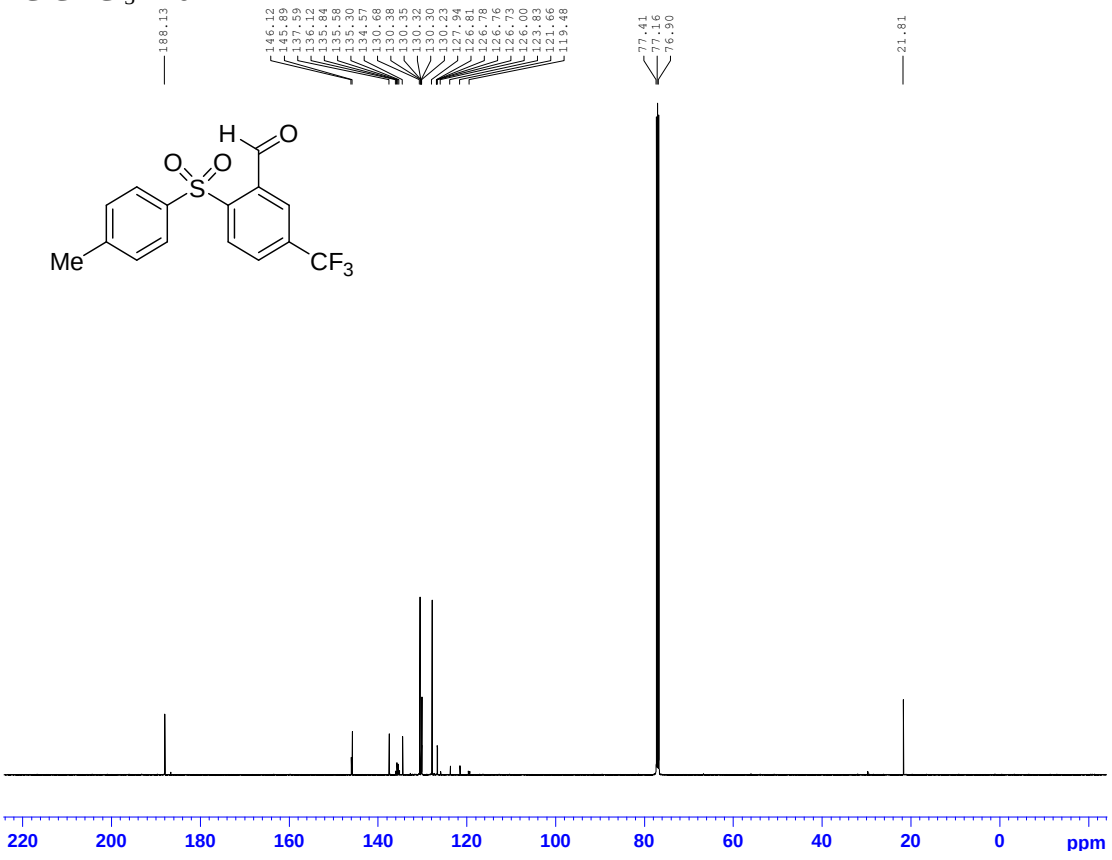


2-[(4-Methylphenyl)sulfonyl]-5-(trifluoromethyl)benzaldehyde

^{1}H $CDCl_3$ 500 MHz

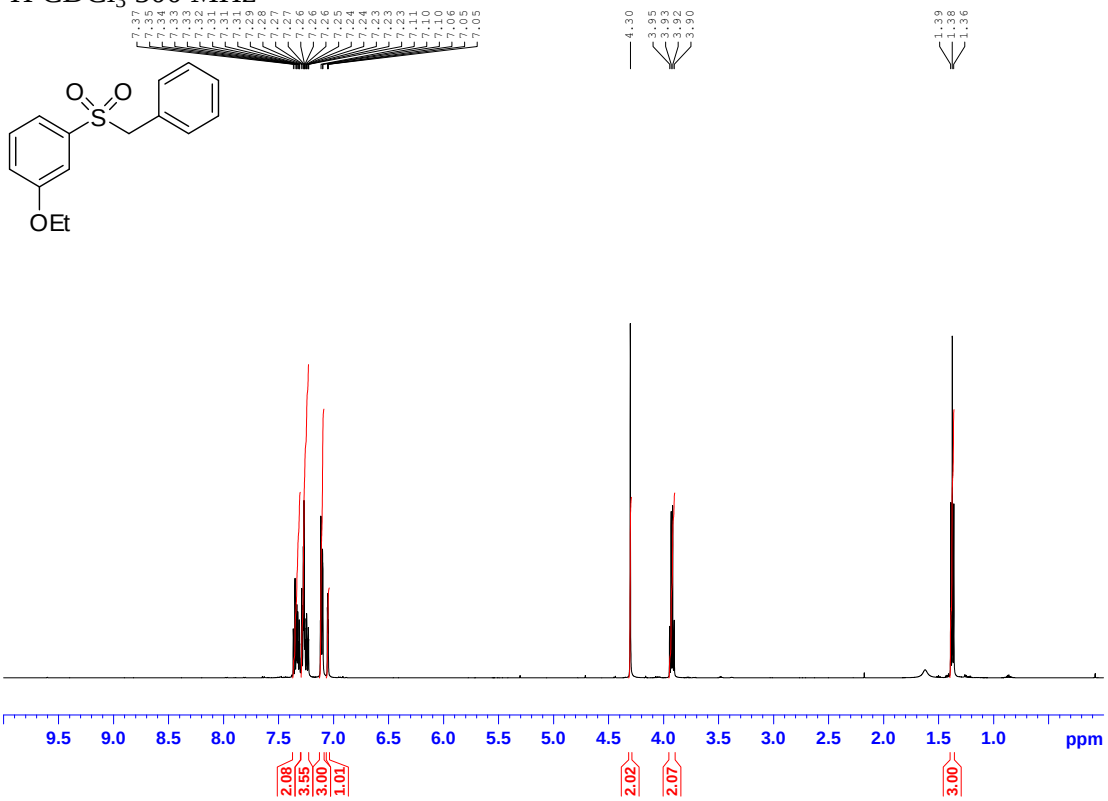


^{13}C $CDCl_3$ 126 MHz

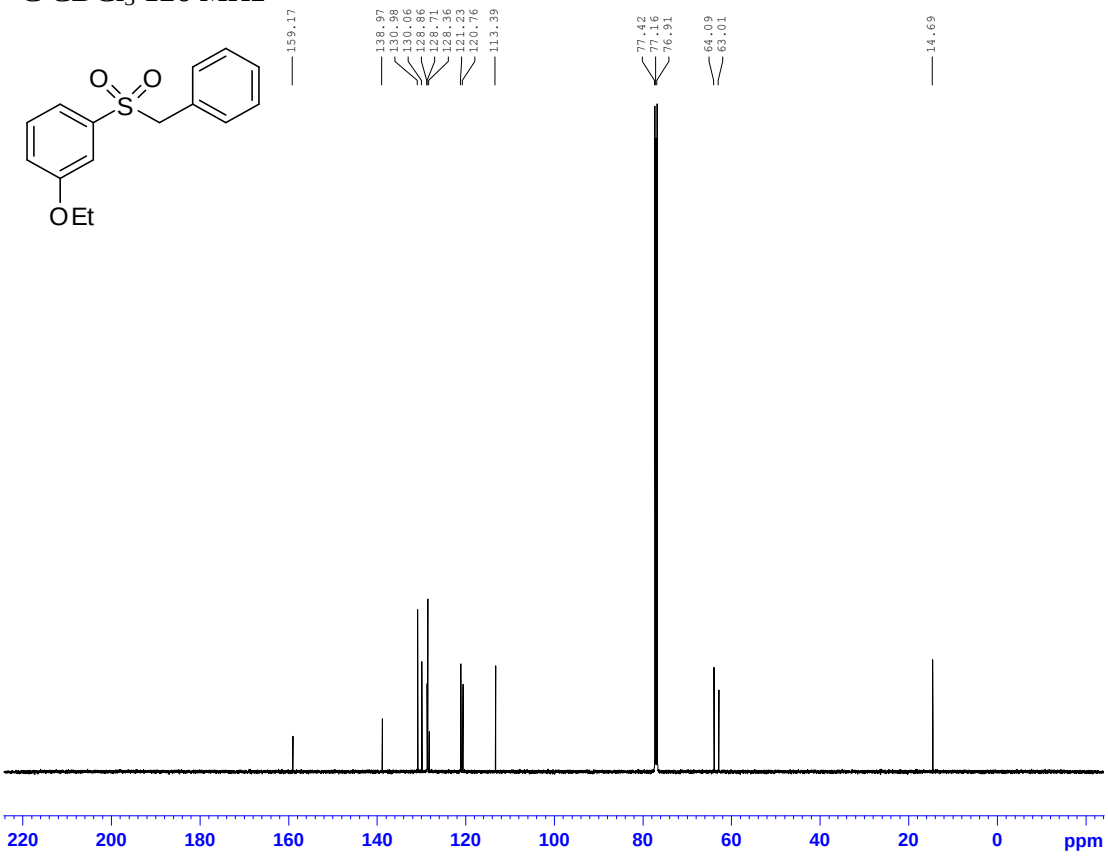


Benzyl 3-ethoxyphenyl sulfone

^{1}H $CDCl_3$ 500 MHz

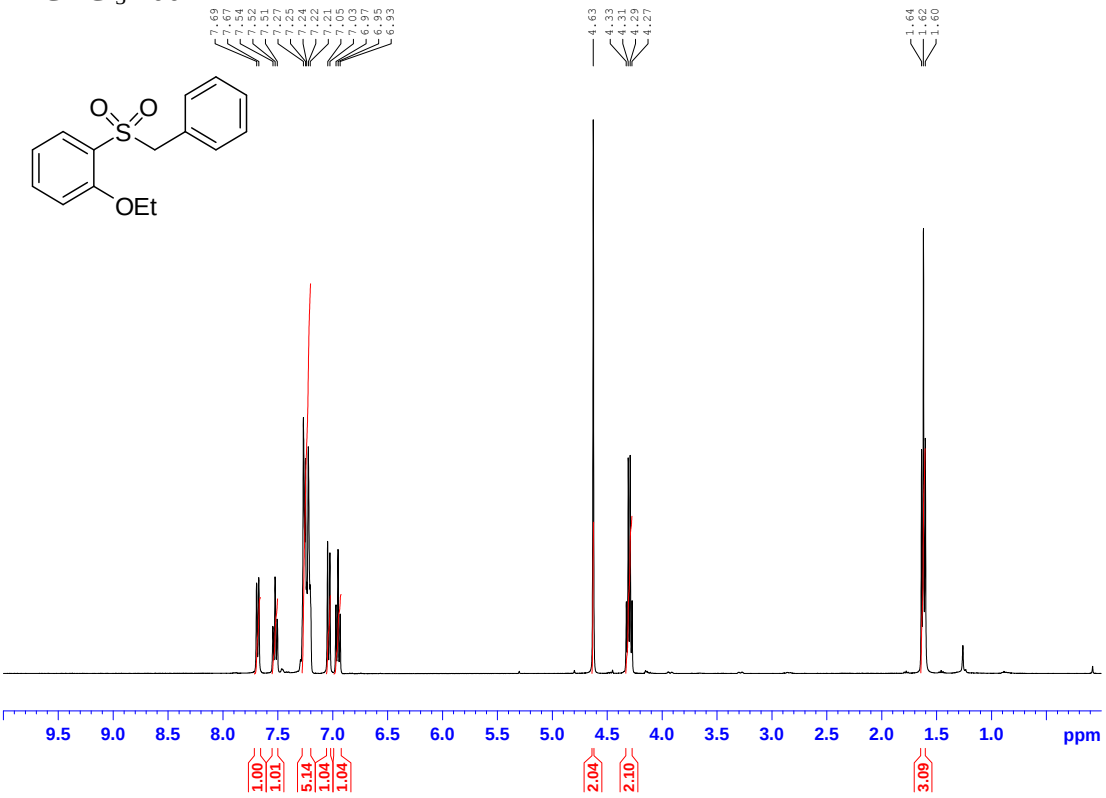


^{13}C $CDCl_3$ 126 MHz

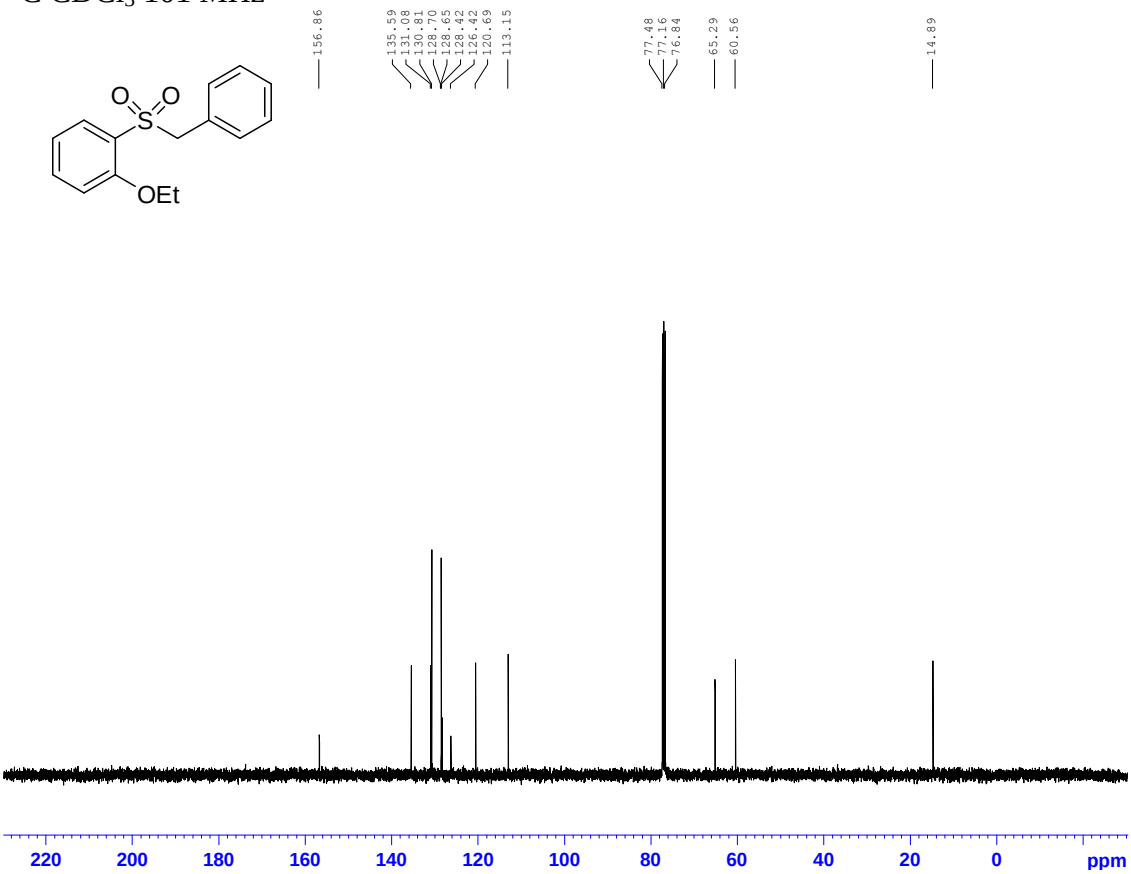


Benzyl 2-ethoxyphenyl sulfone

^{1}H $CDCl_3$ 400 MHz

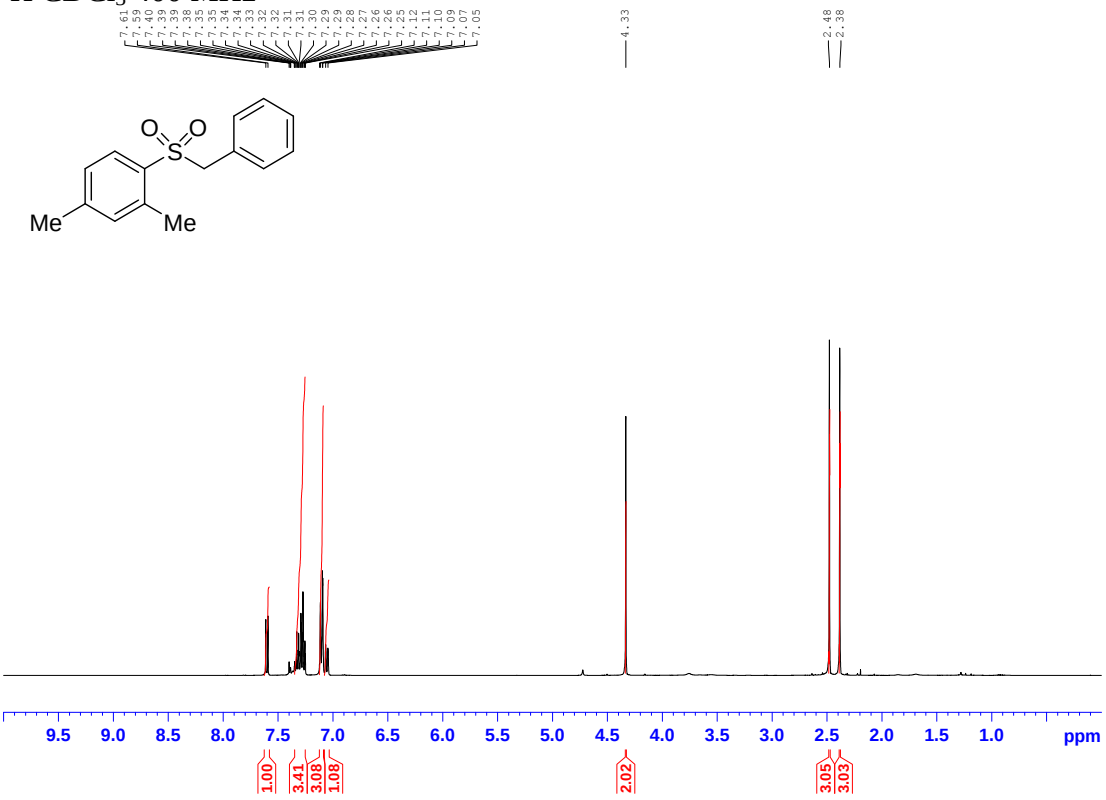


^{13}C $CDCl_3$ 101 MHz

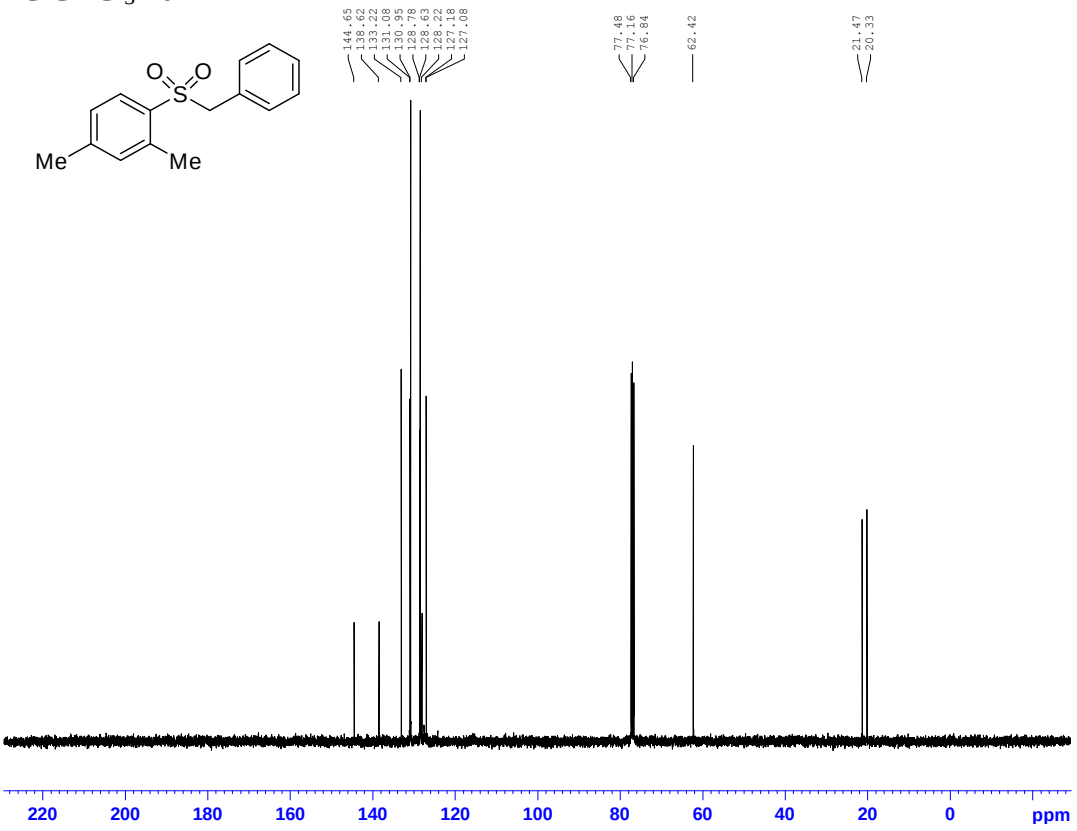


Benzyl 2,4-dimethylphenyl sulfone

^{1}H $CDCl_3$ 400 MHz

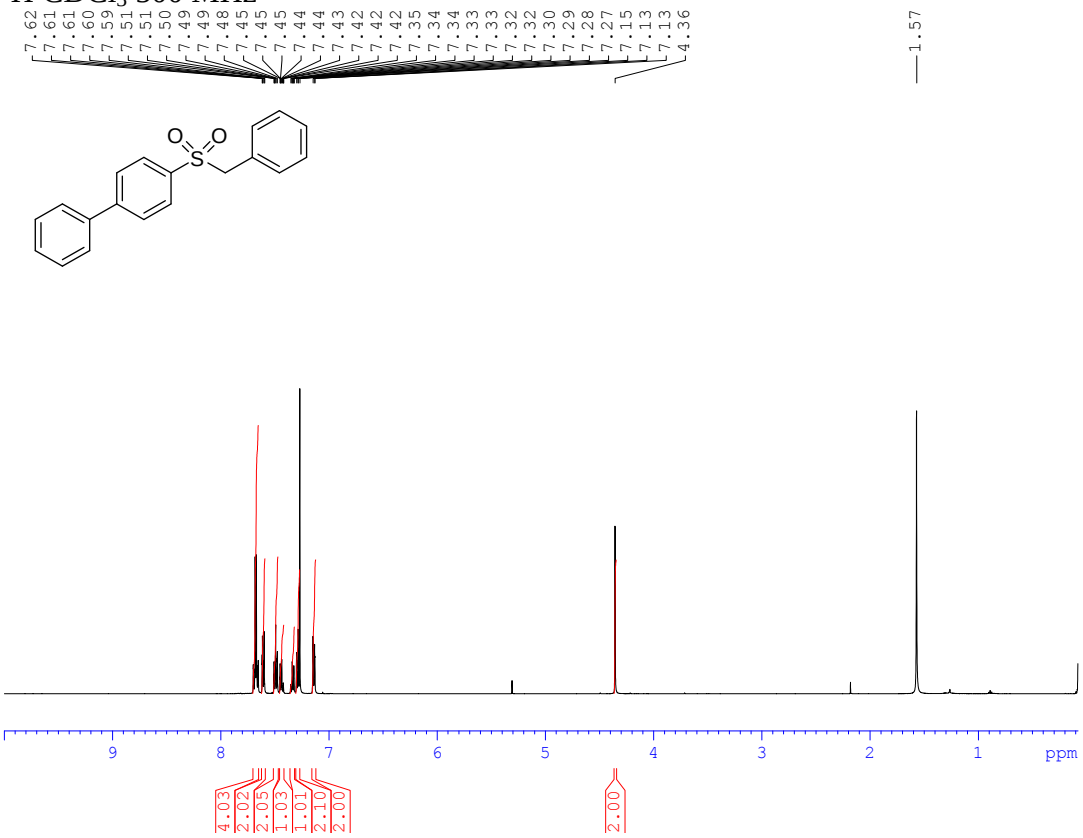


^{13}C $CDCl_3$ 101 MHz

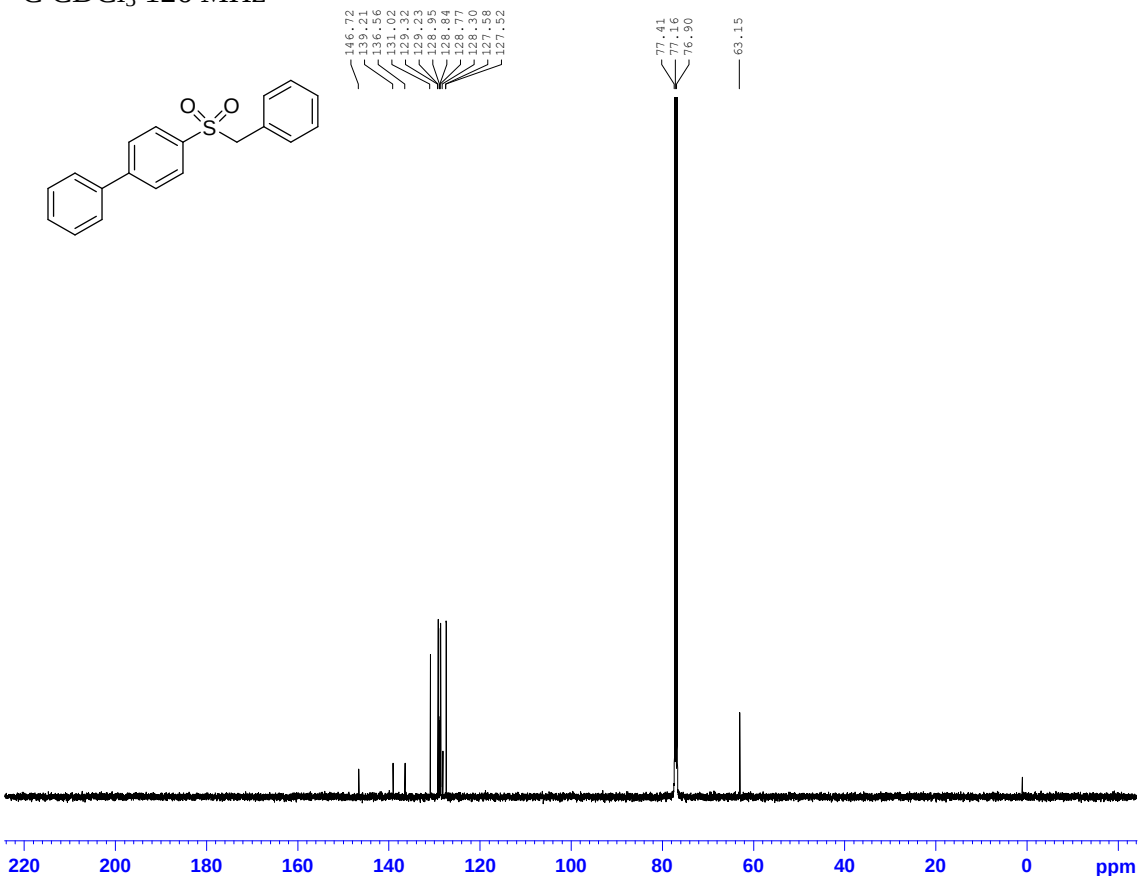


Benzyl biphenyl-4-yl sulfone

^{1}H $CDCl_3$ 500 MHz

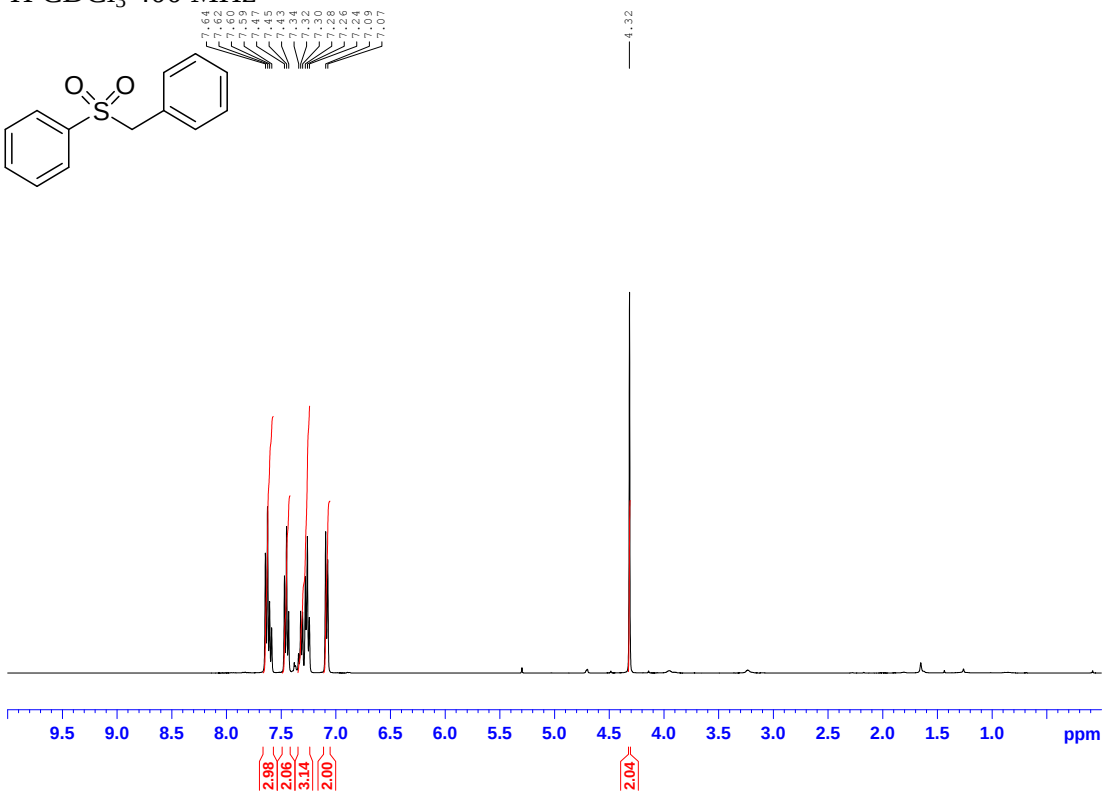


^{13}C $CDCl_3$ 126 MHz

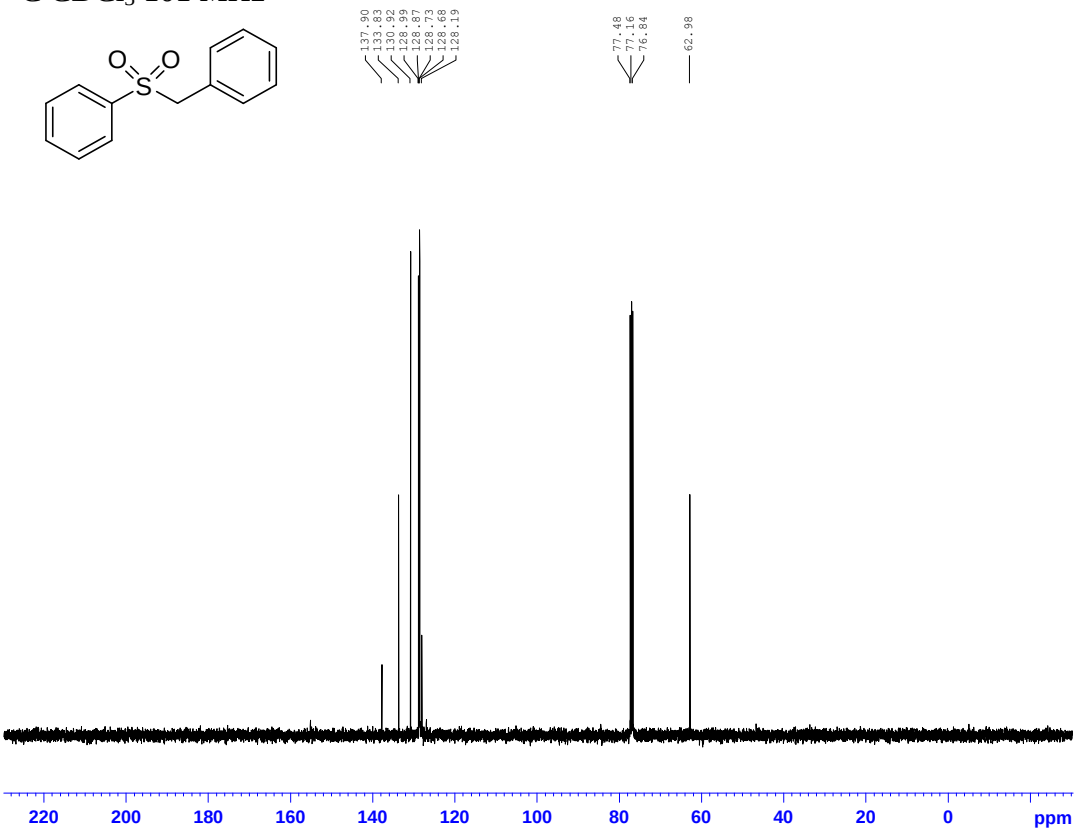


Benzyl phenyl sulfone

^{1}H $CDCl_3$ 400 MHz

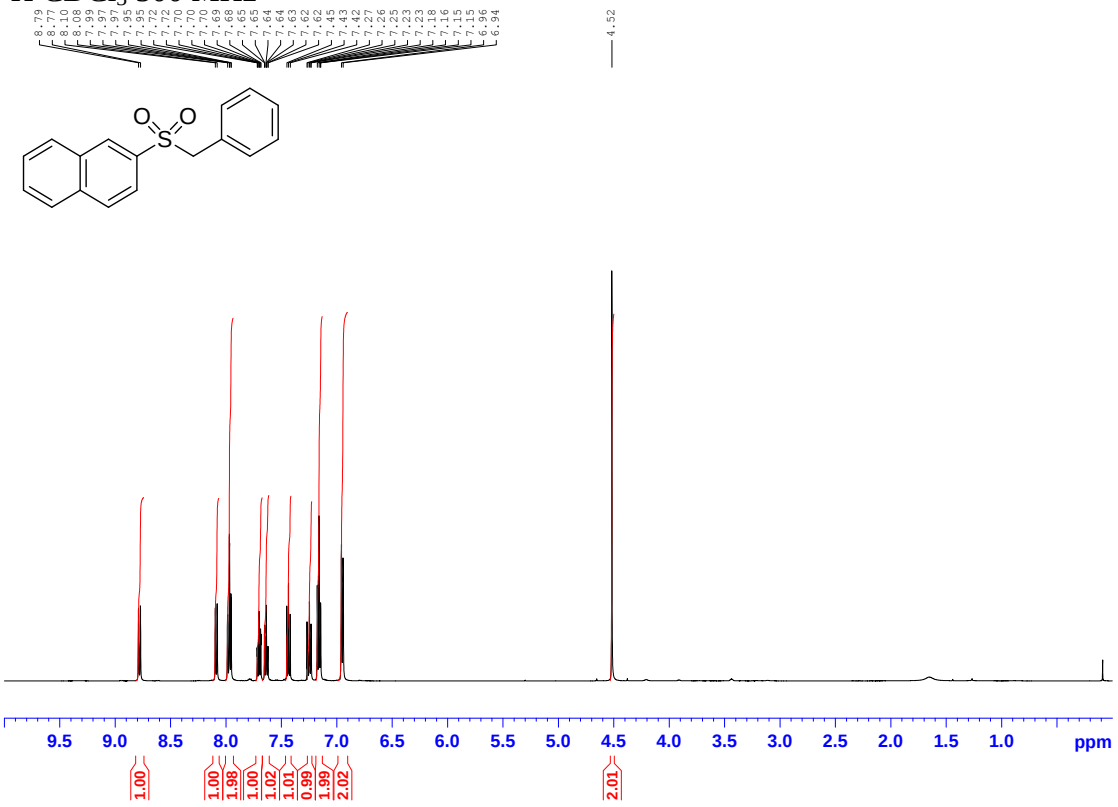


^{13}C $CDCl_3$ 101 MHz

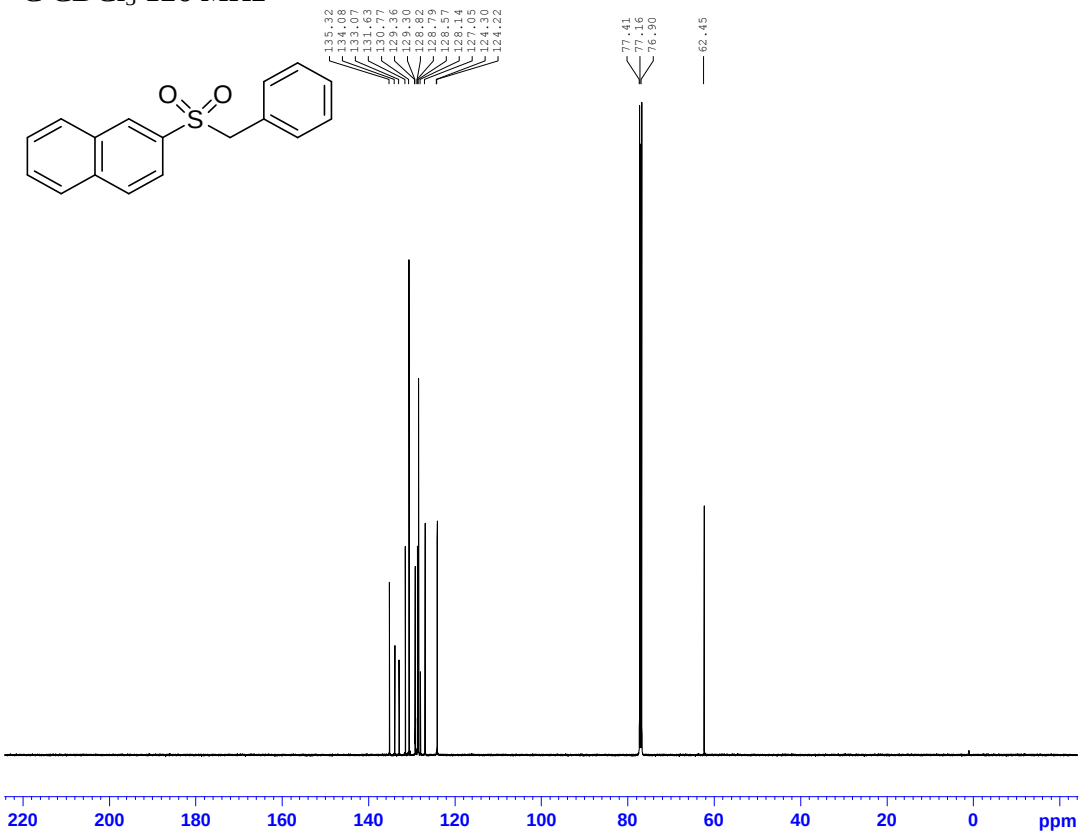


Benzyl 2-naphthyl sulfone

^{1}H $CDCl_3$ 500 MHz

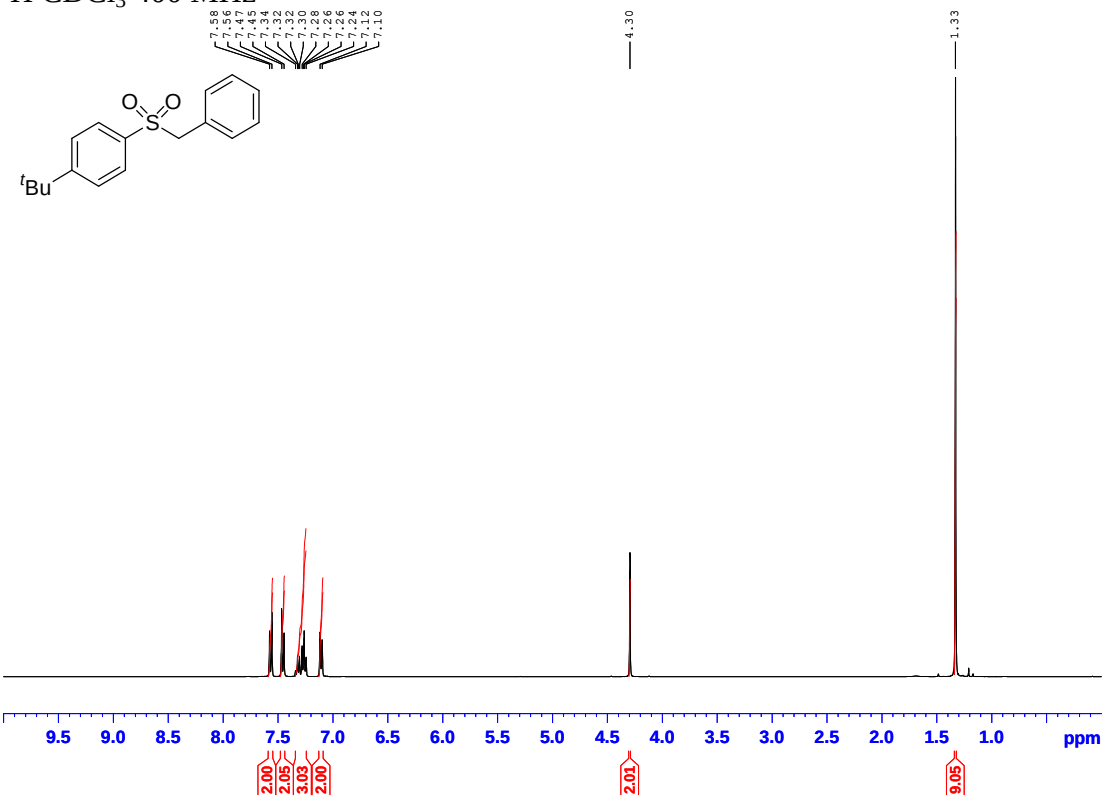


^{13}C $CDCl_3$ 126 MHz

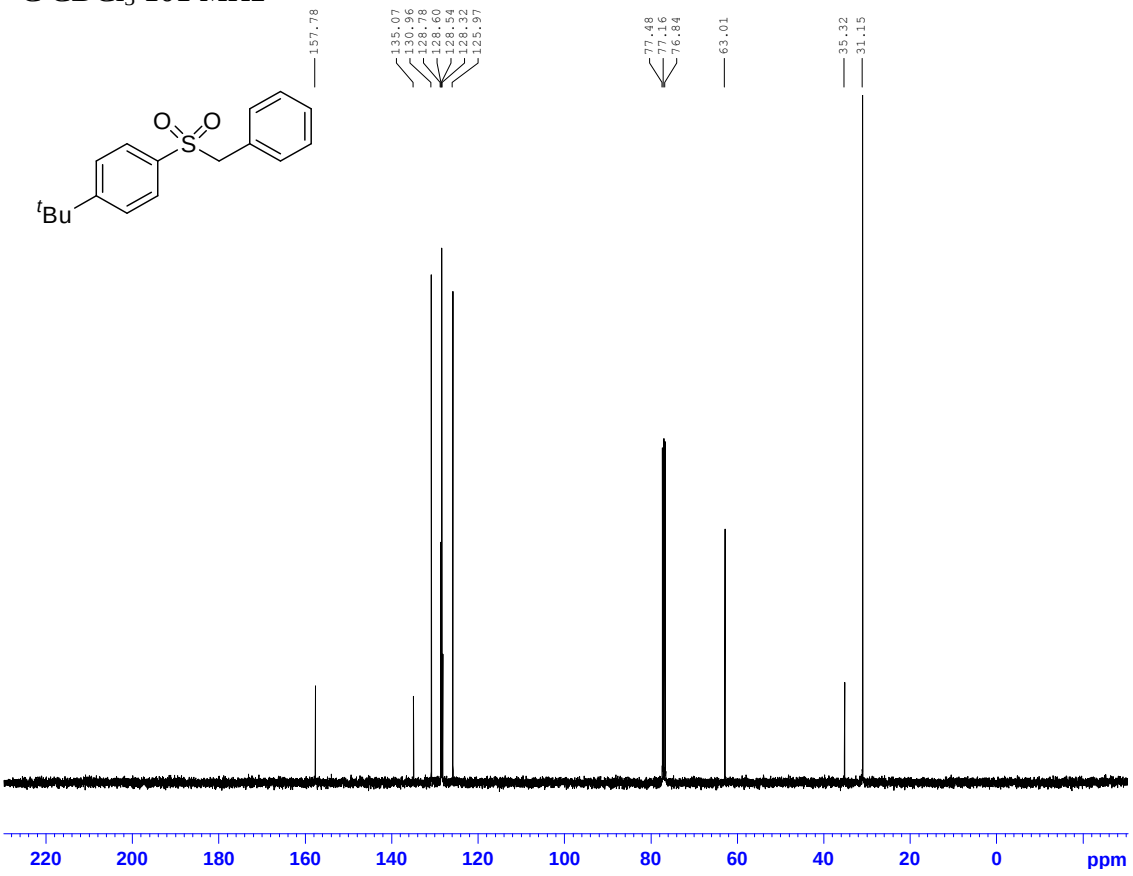


Benzyl 4-*tert*-butylphenyl sulfone

^{1}H $CDCl_3$ 400 MHz

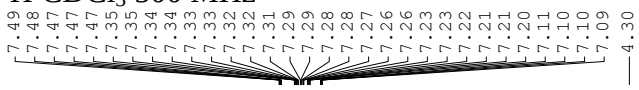


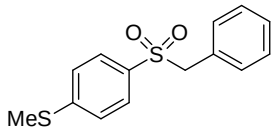
^{13}C $CDCl_3$ 101 MHz

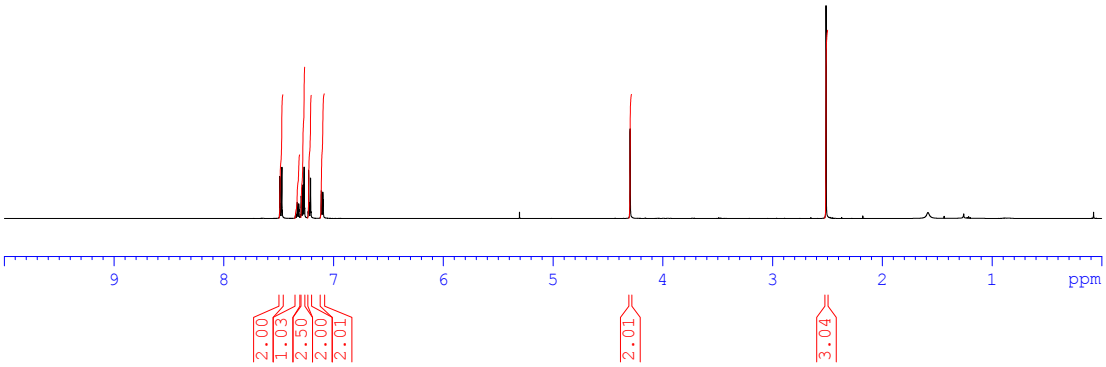


Benzyl 4-(methylsulfanyl)phenyl sulfone

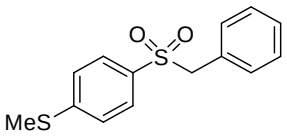
^{1}H $CDCl_3$ 500 MHz





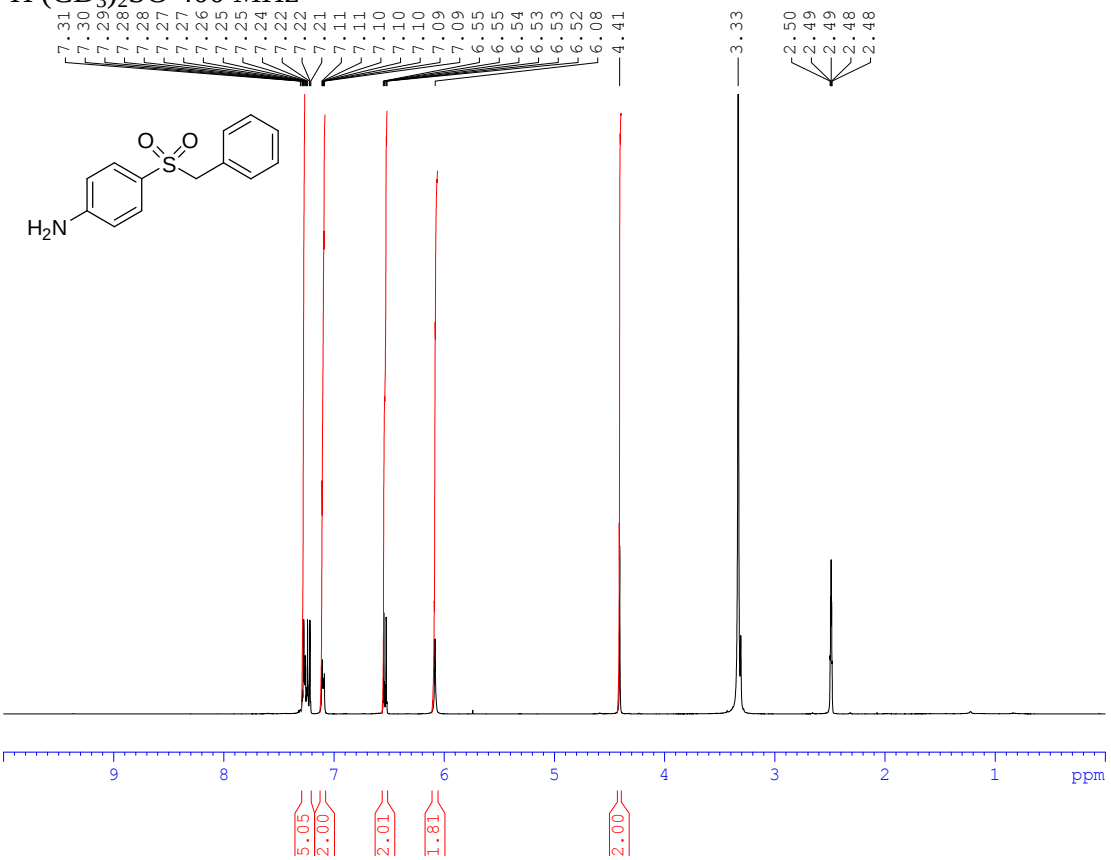


^{13}C $CDCl_3$ 126 MHz



4-(Benzylsulfonyl)aniline

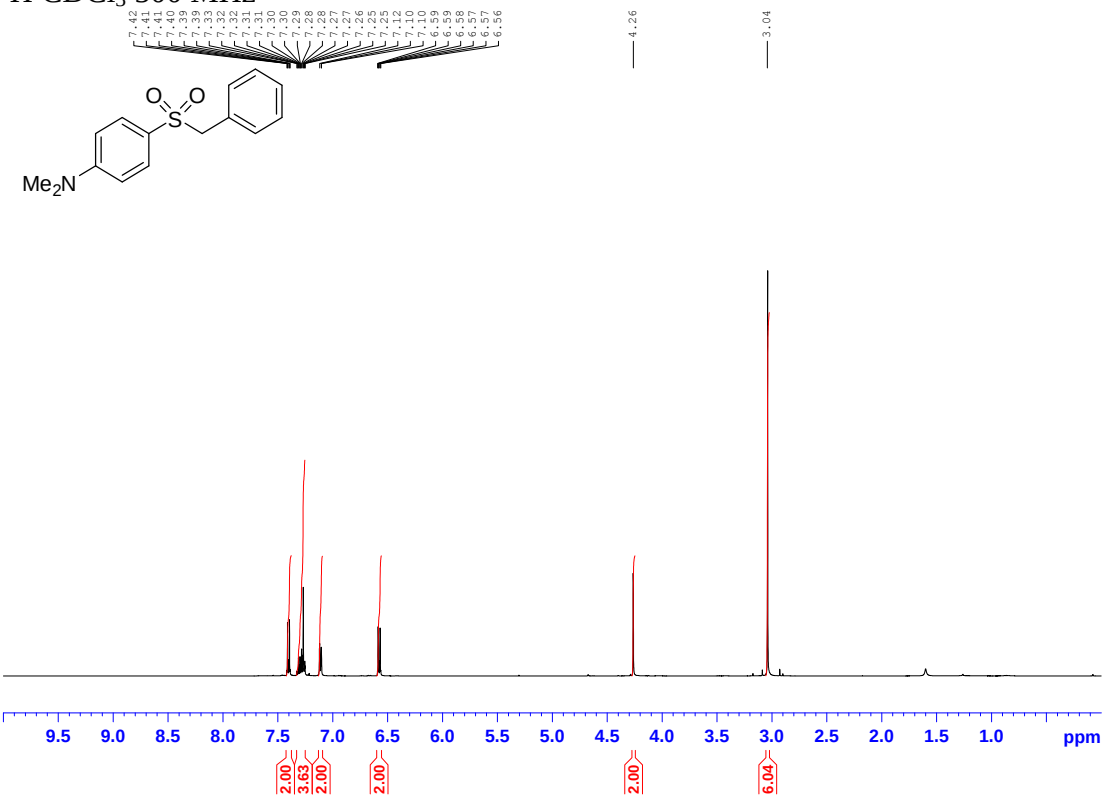
^{1}H $(CD_3)_2SO$ 400 MHz



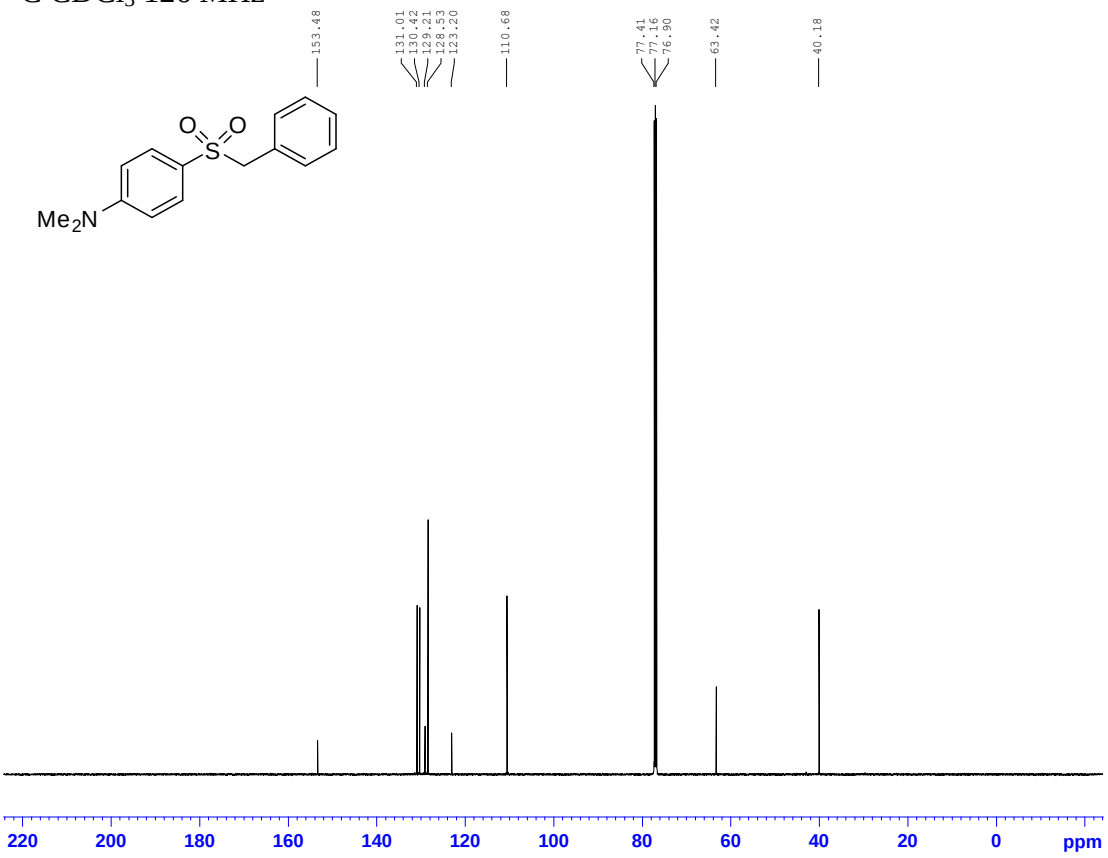
^{13}C $(CD_3)_2SO$ 101 MHz

4-(Benzylsulfonyl)-*N*,*N*-dimethylaniline

^{1}H $CDCl_3$ 500 MHz

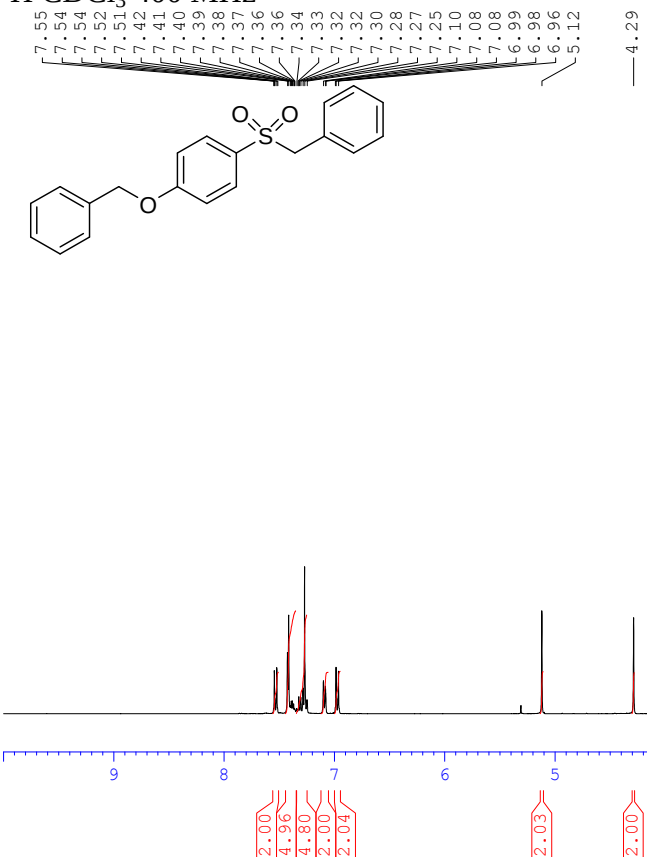


^{13}C $CDCl_3$ 126 MHz

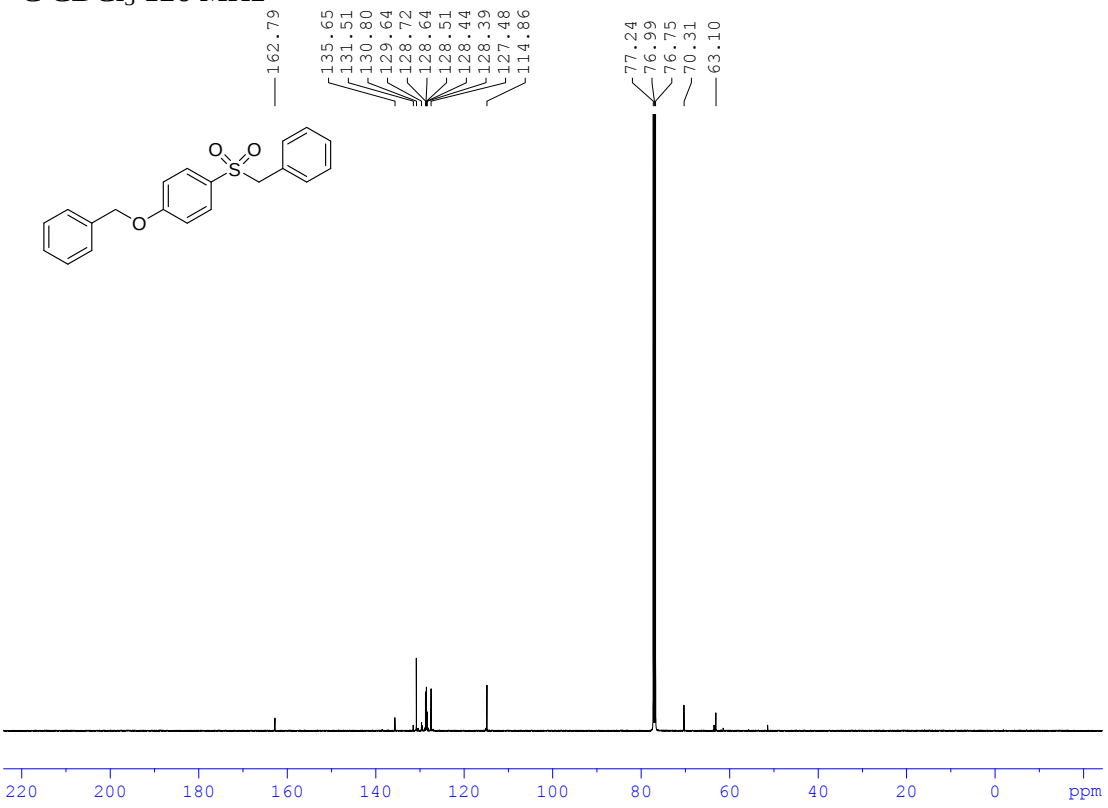


Benzyl 4-(benzyloxy)phenyl sulfone

^{1}H $CDCl_3$ 400 MHz

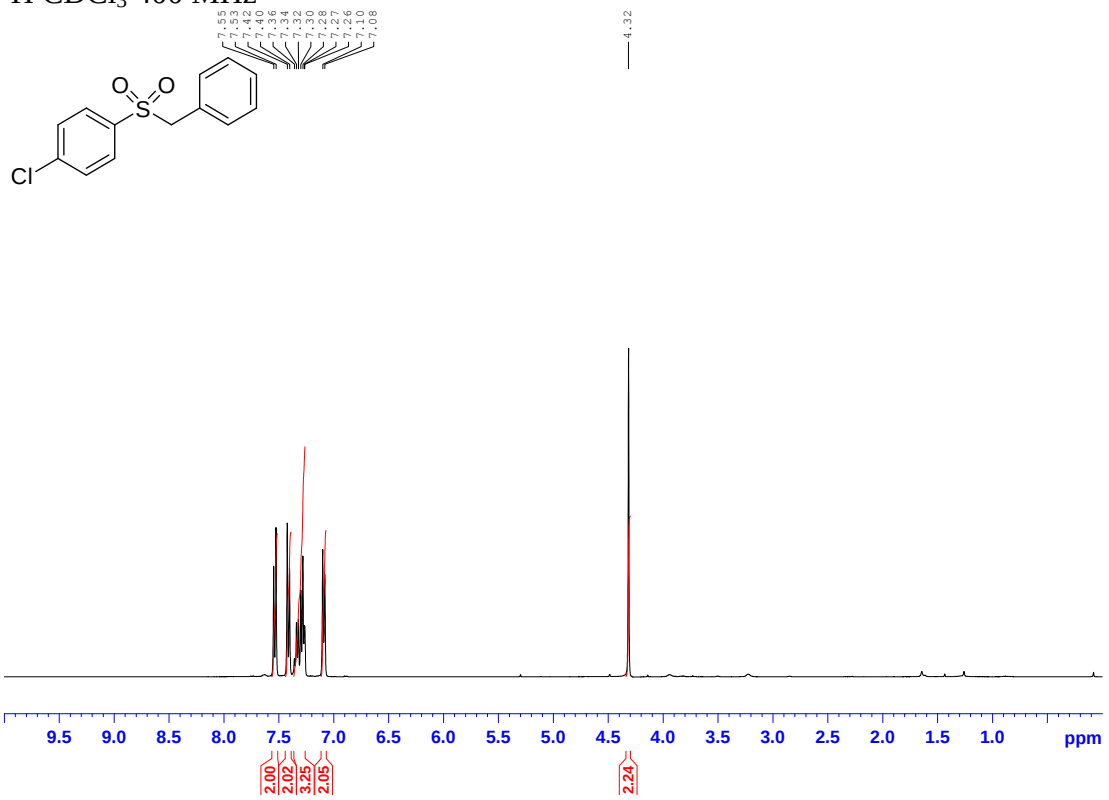


^{13}C $CDCl_3$ 126 MHz

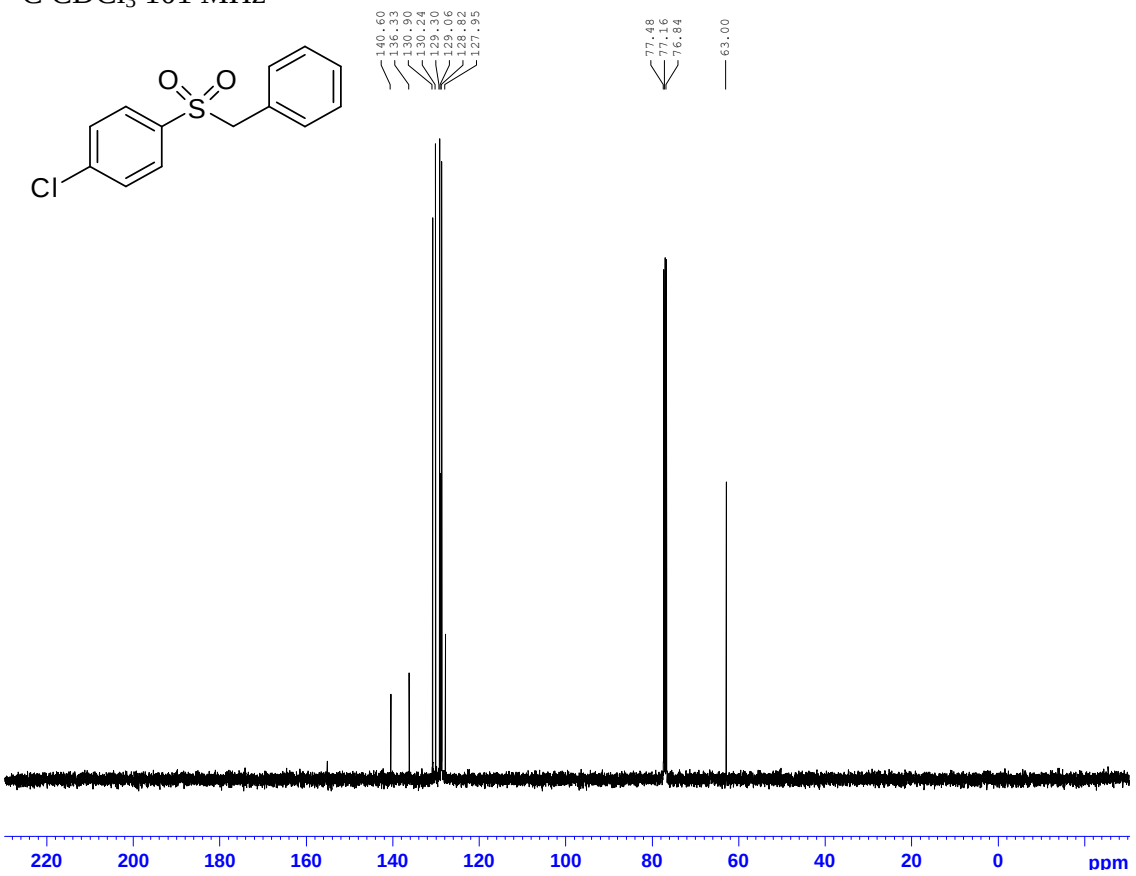


Benzyl 4-chlorophenyl sulfone

^{1}H $CDCl_3$ 400 MHz

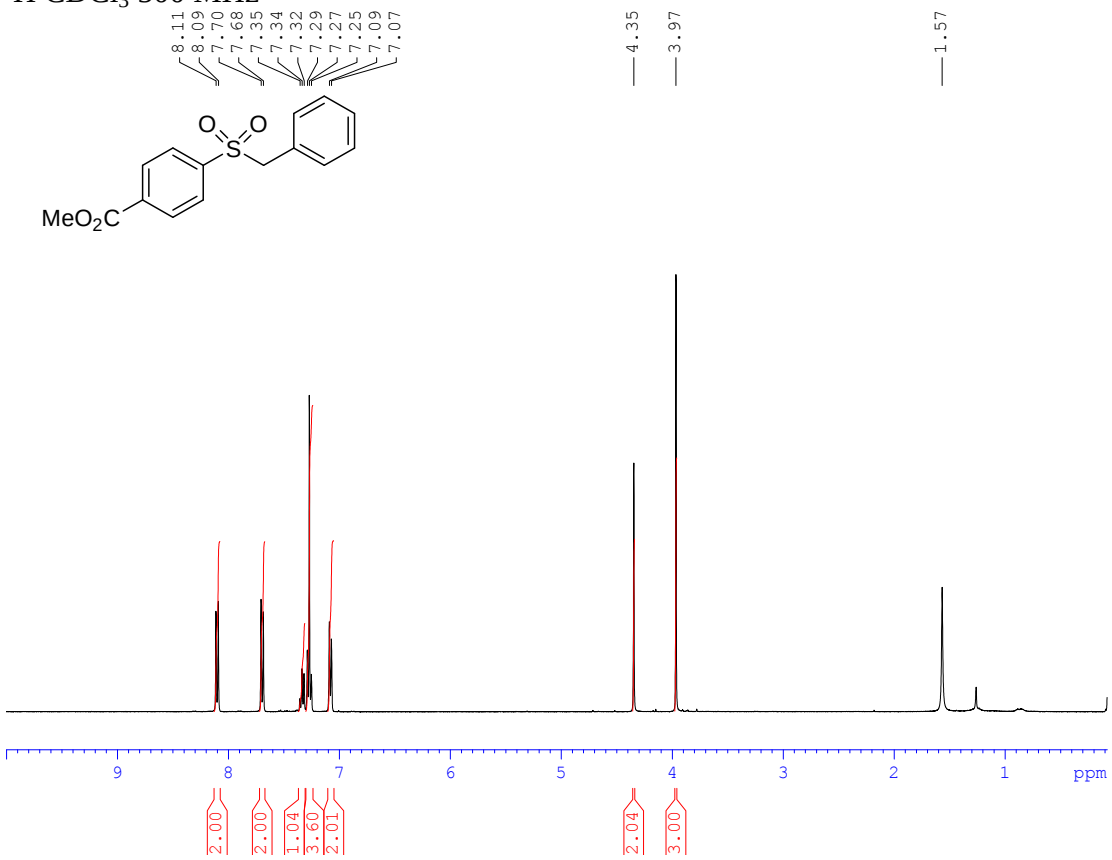


^{13}C $CDCl_3$ 101 MHz

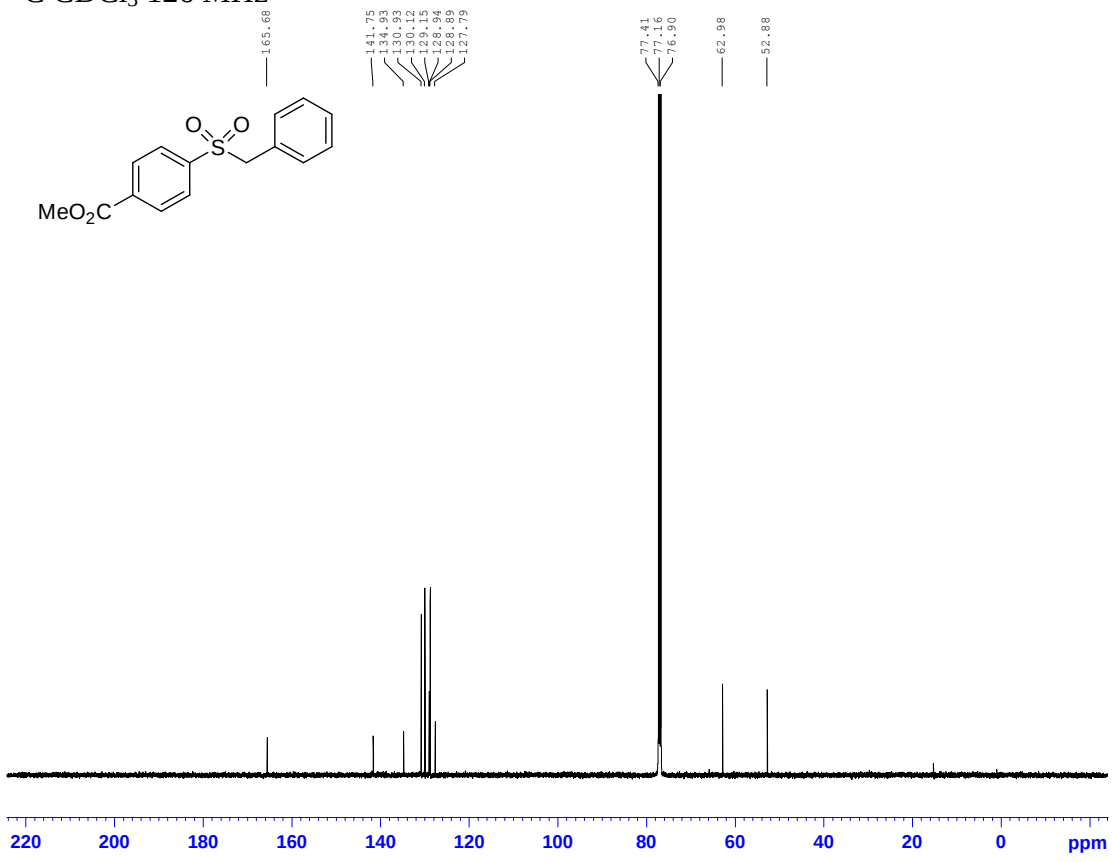


Methyl 4-(benzylsulfonyl)benzoate

^{1}H $CDCl_3$ 500 MHz

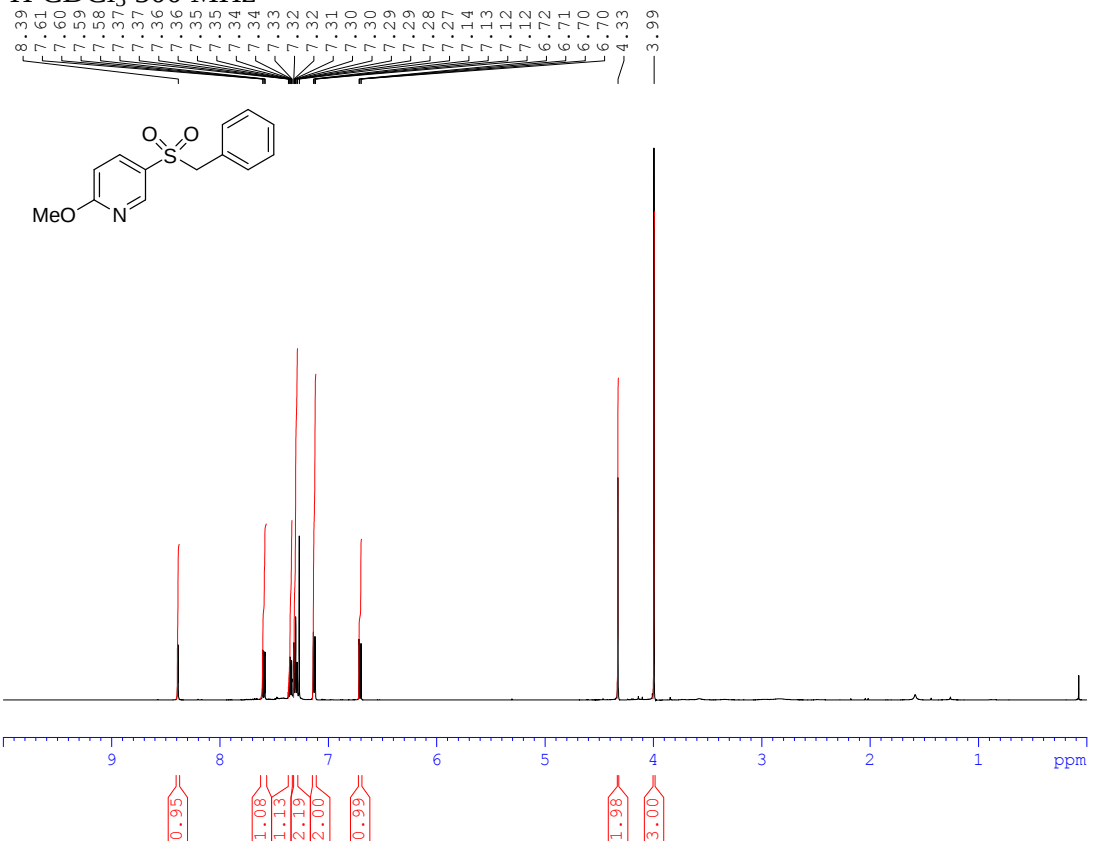


^{13}C $CDCl_3$ 126 MHz

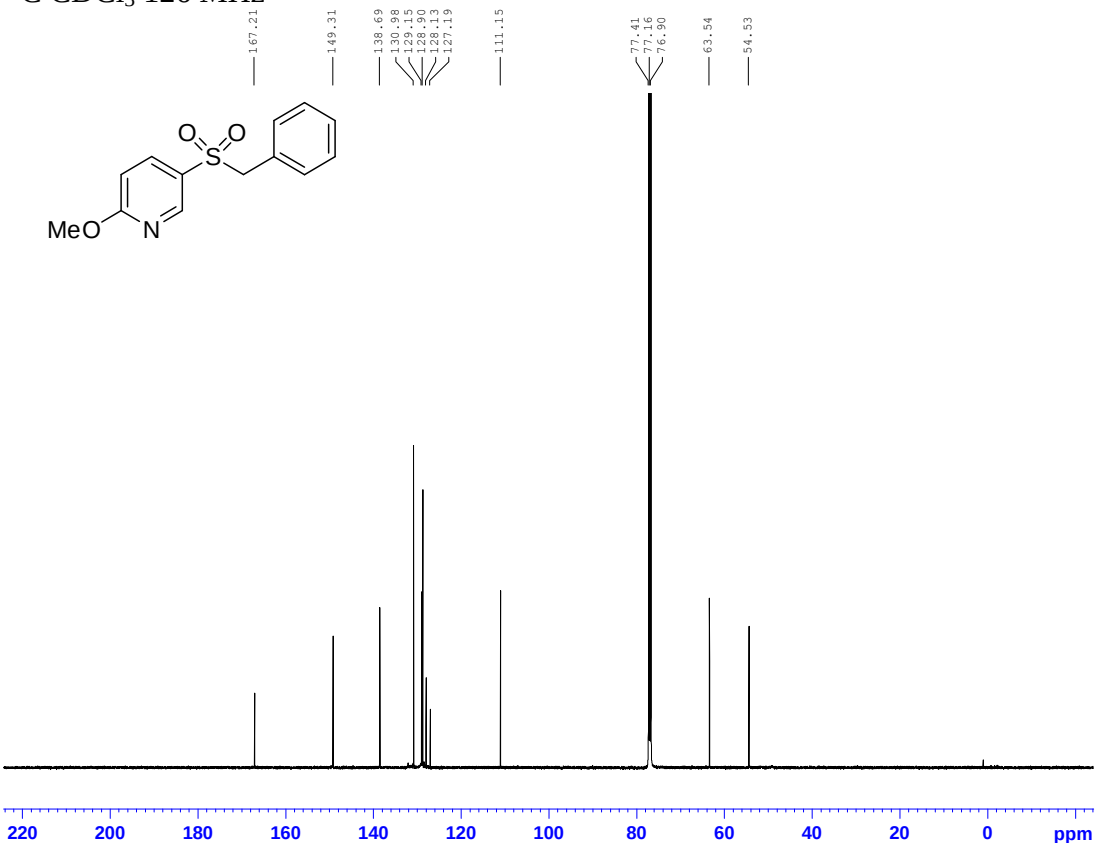


5-(Benzylsulfonyl)-2-methoxypyridine

^{1}H $CDCl_3$ 500 MHz

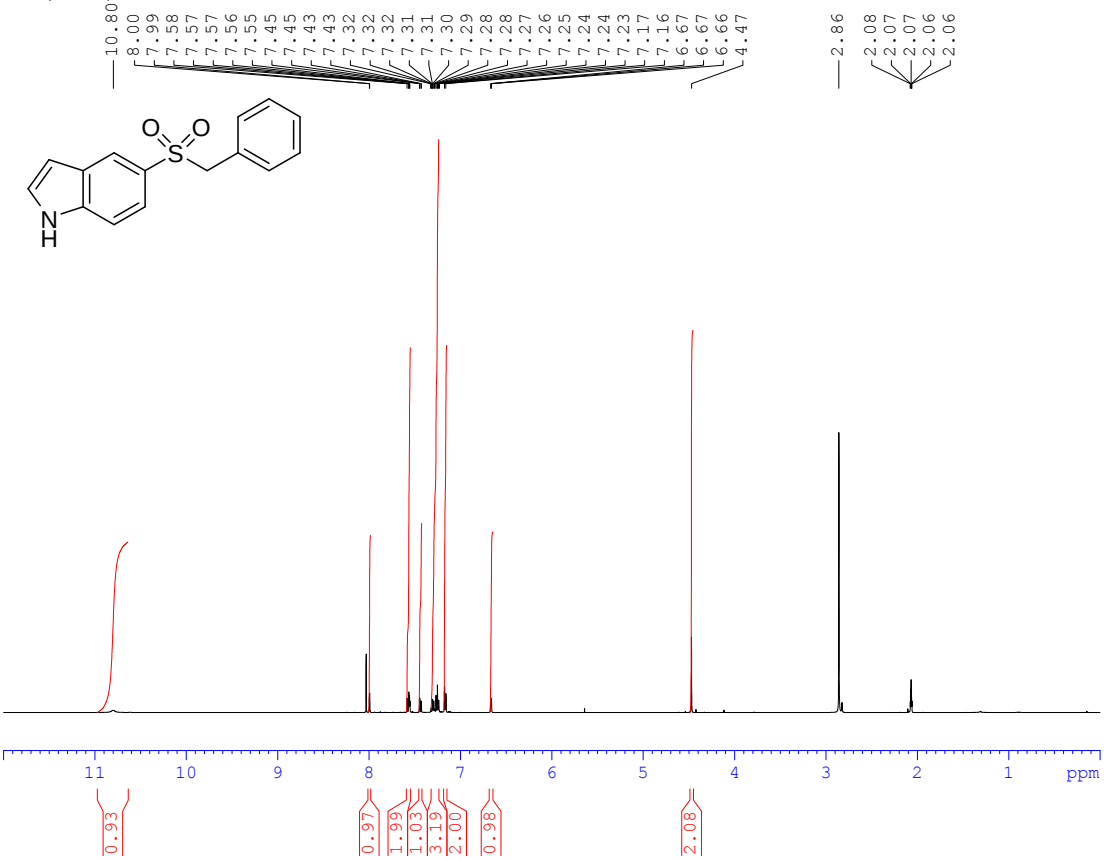


^{13}C $CDCl_3$ 126 MHz

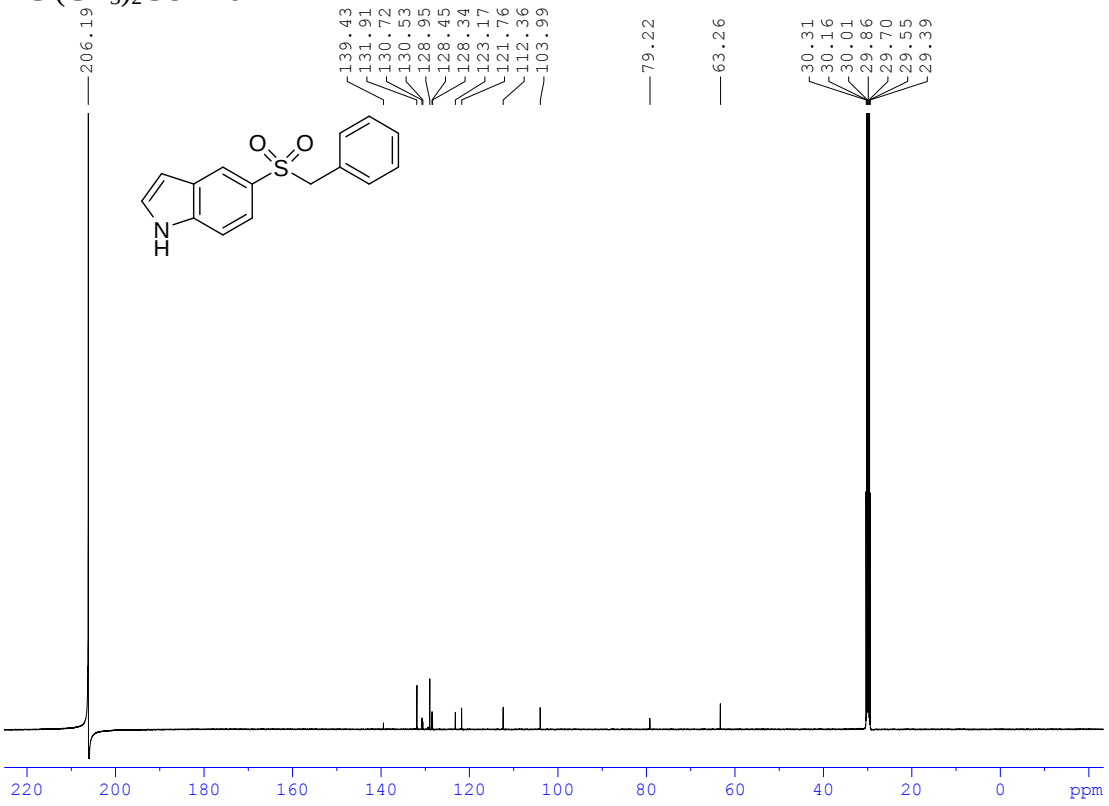


5-(Benzylsulfonyl)-1*H*-indole

^{1}H $(CD_3)_2CO$ 500 MHz

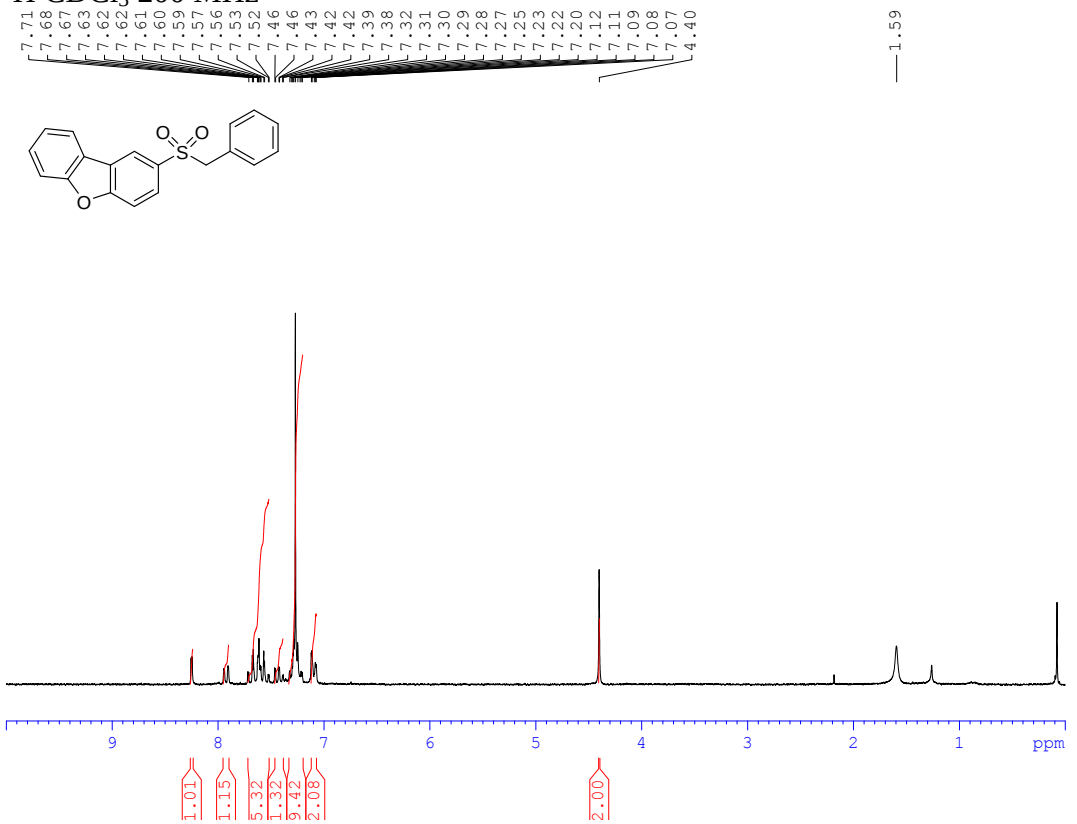


^{13}C $(CD_3)_2CO$ 126 MHz

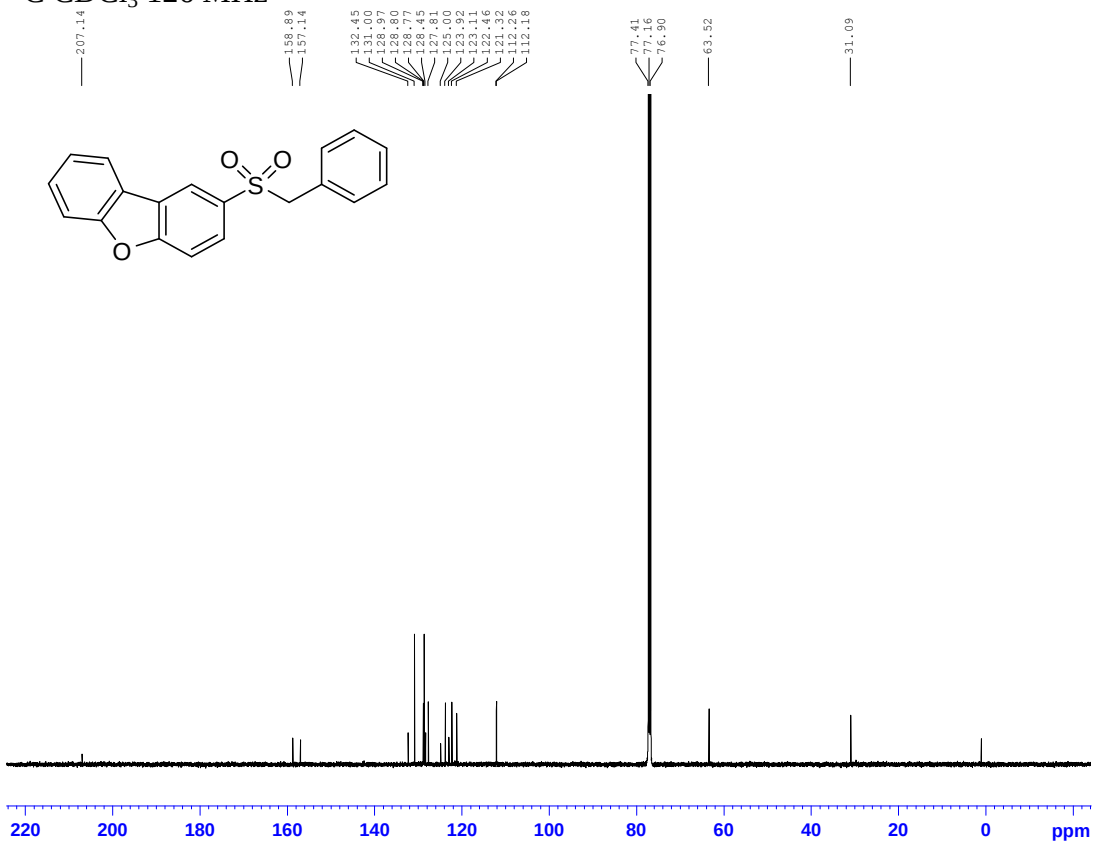


2-(Benzylsulfonyl)-4a,9b-dihydrodibenzo[*b*,*d*]furan

^{1}H $CDCl_3$ 200 MHz

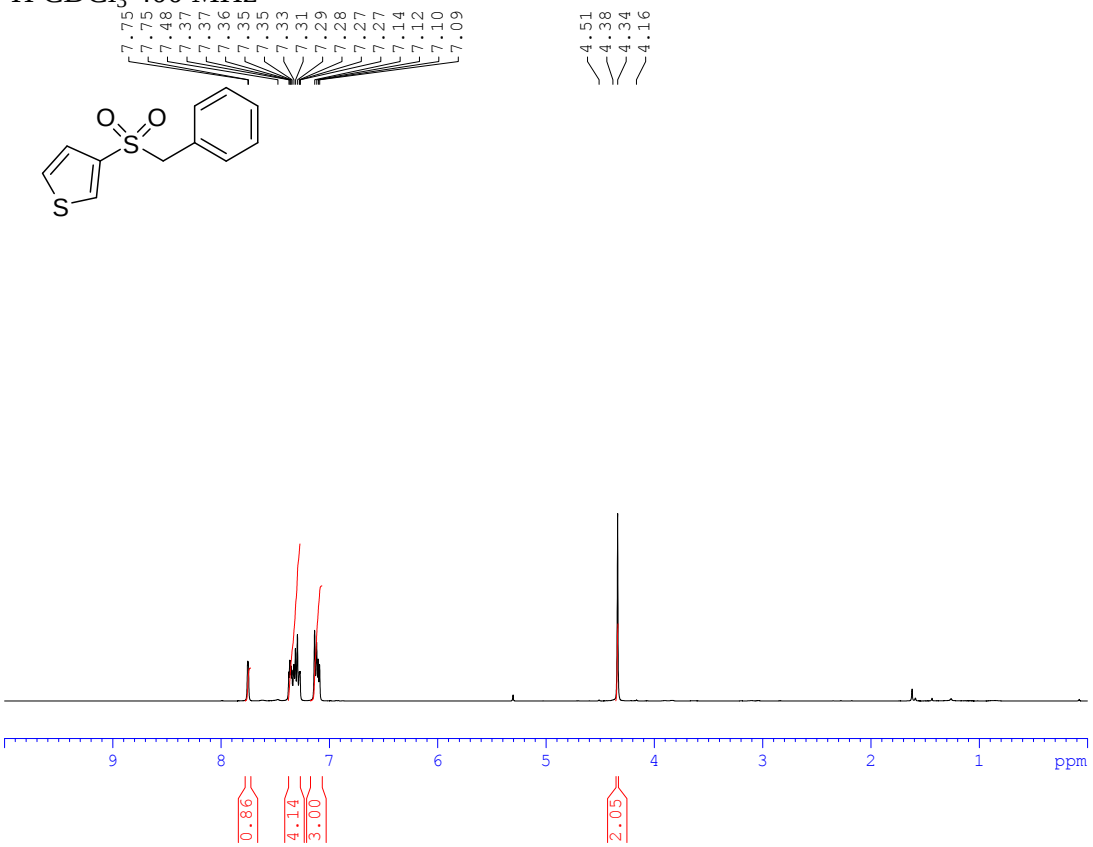


^{13}C $CDCl_3$ 126 MHz

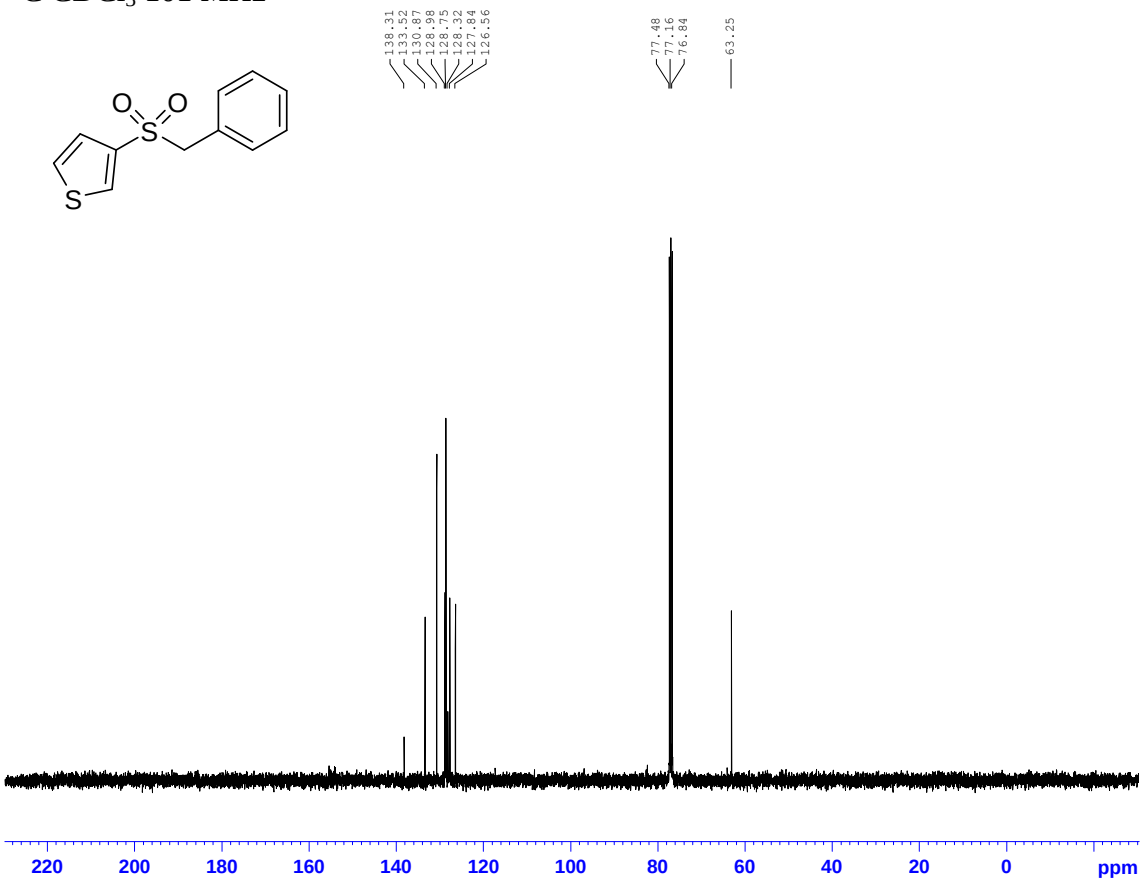


Benzyl thiophen-3-yl sulfone

^{1}H $CDCl_3$ 400 MHz

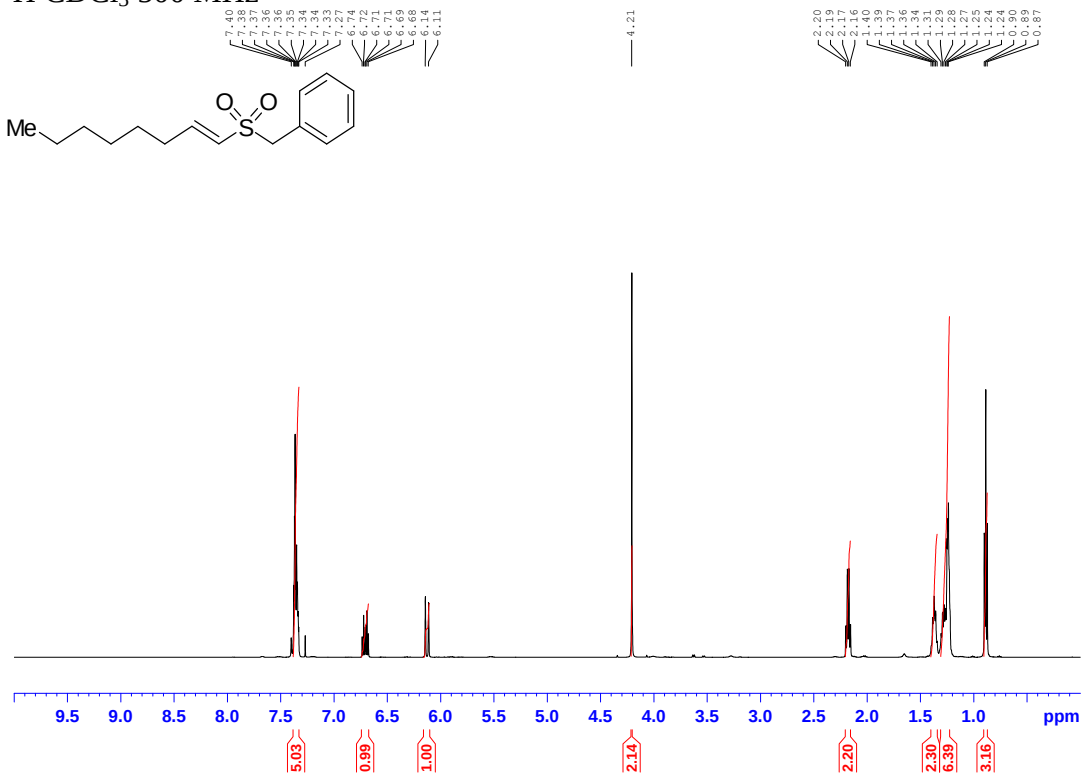


^{13}C $CDCl_3$ 101 MHz

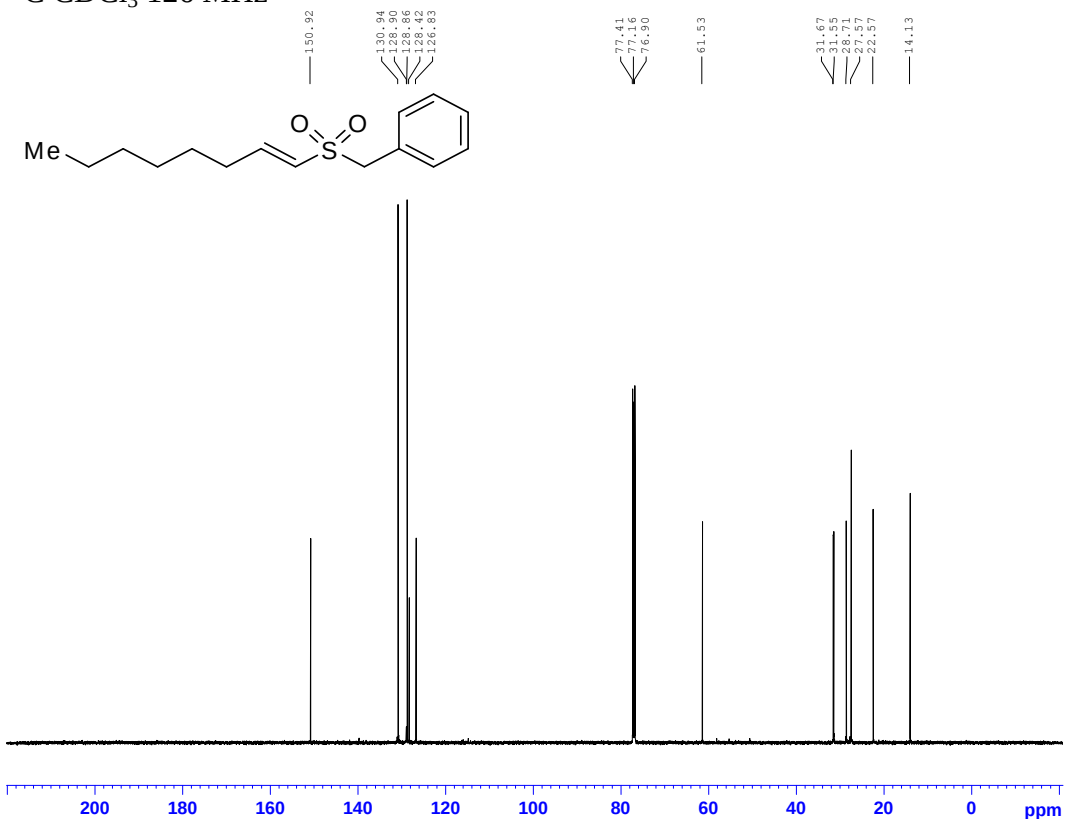


Benzyl (1*E*)-oct-1-en-1-yl sulfone

^{1}H $CDCl_3$ 500 MHz

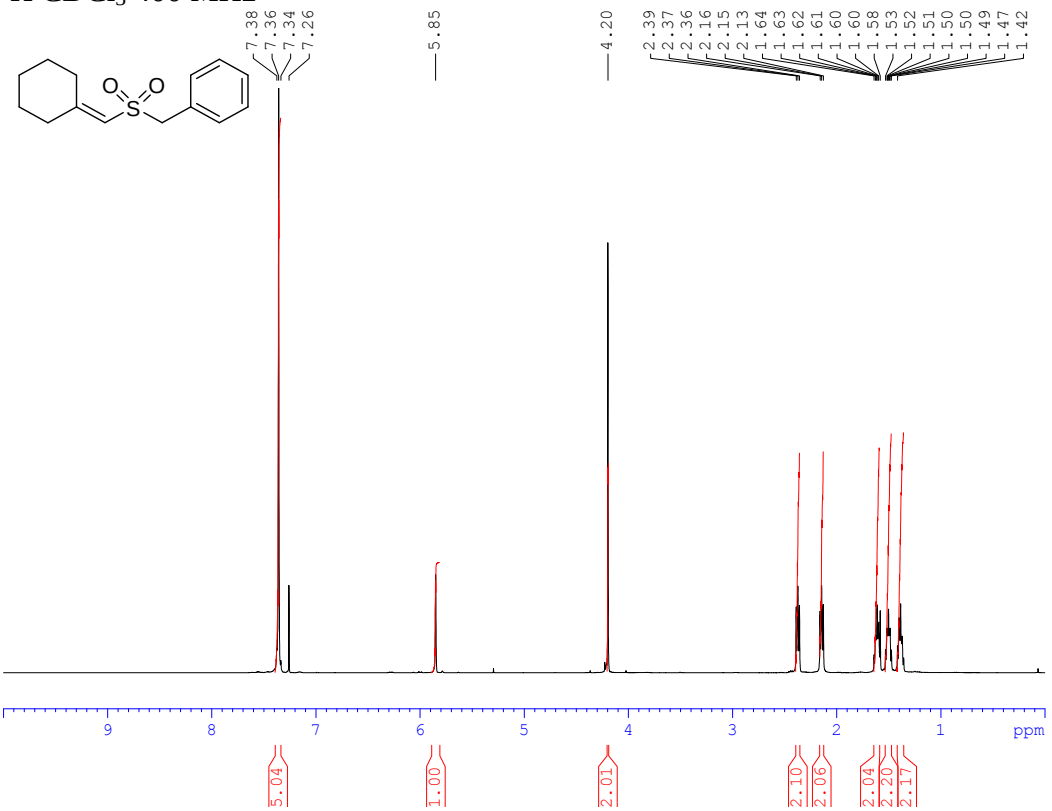


^{13}C $CDCl_3$ 126 MHz

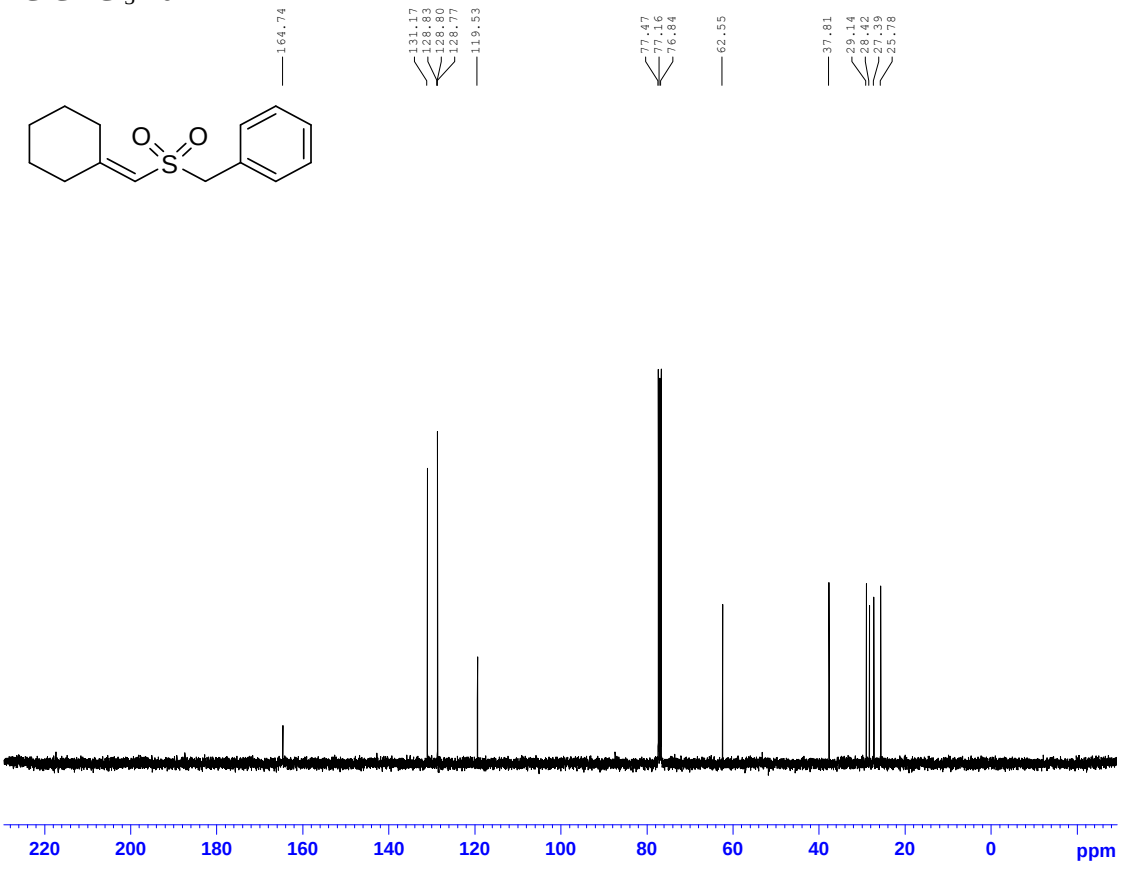


{[(Cyclohexylidenemethyl)sulfonyl]methyl}benzene benzyl cyclohexylidenemethyl sulfone

^{1}H $CDCl_3$ 400 MHz

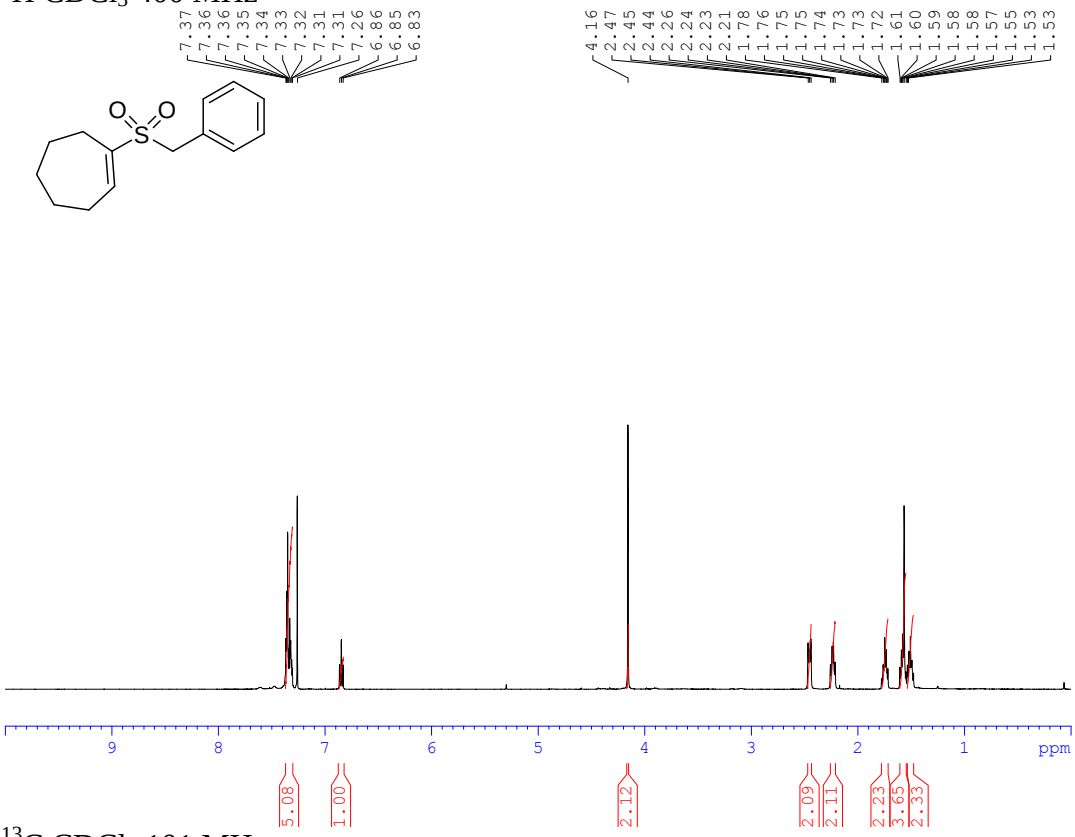


^{13}C $CDCl_3$ 101 MHz

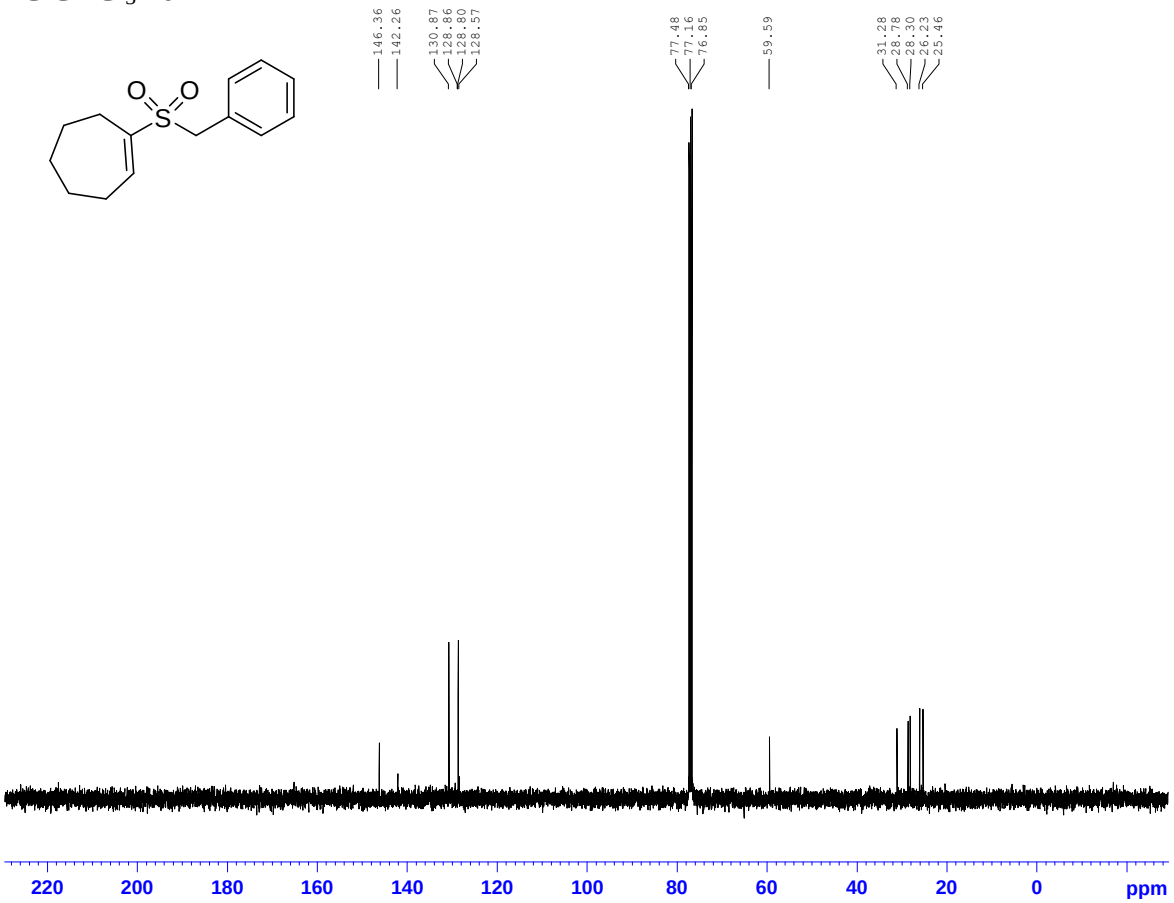


Benzyl cyclohept-1-en-1-yl sulfone

^{1}H $CDCl_3$ 400 MHz

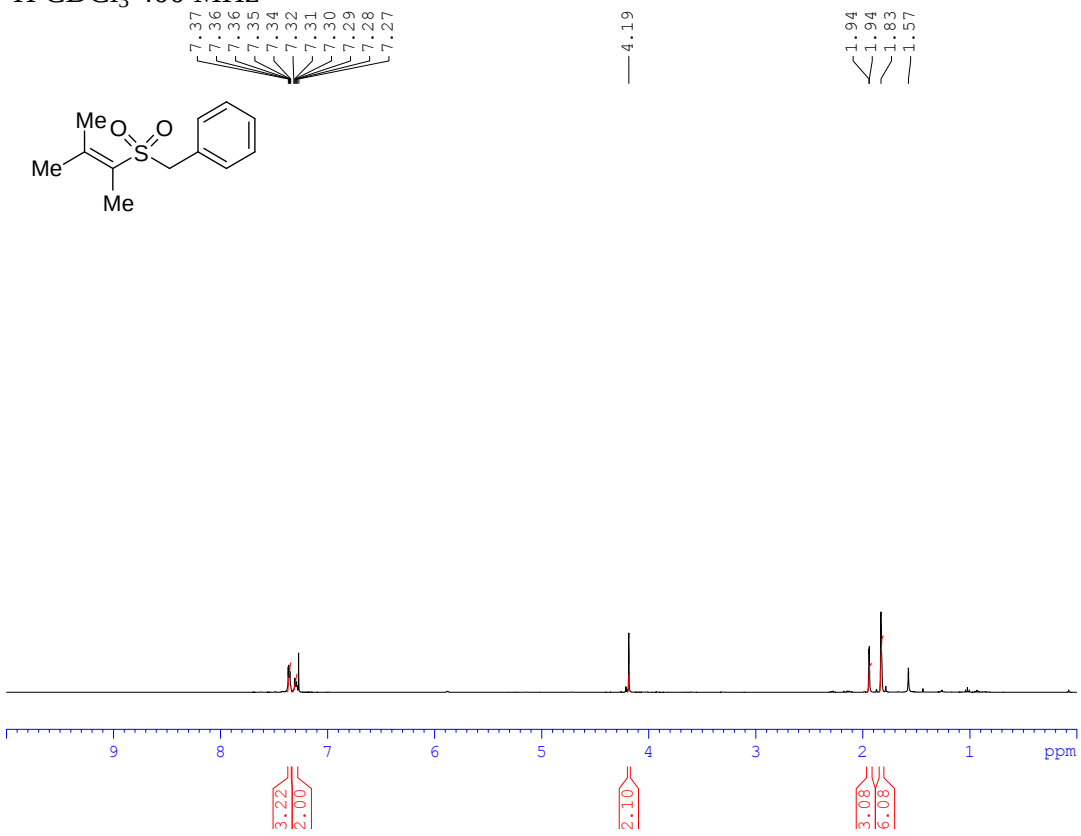


^{13}C $CDCl_3$ 101 MHz

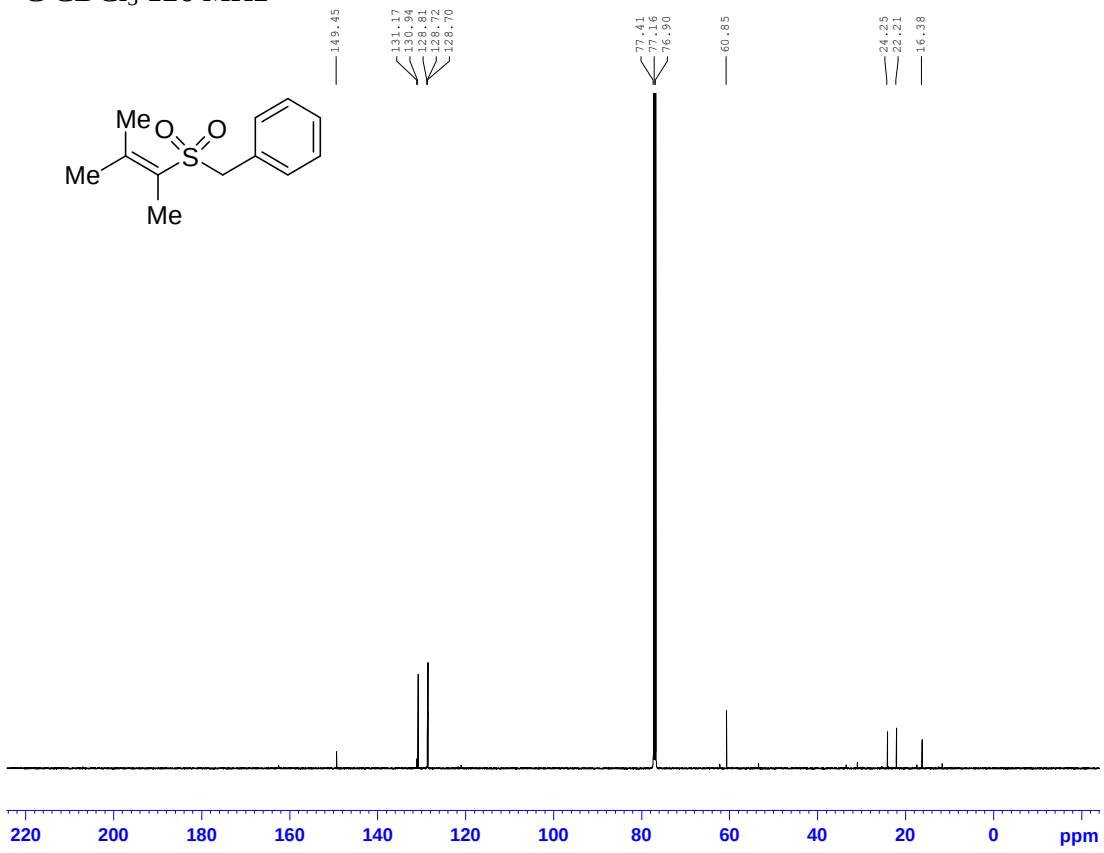


Benzyl 3-methylbut-2-en-2-yl sulfone

^{1}H $CDCl_3$ 400 MHz

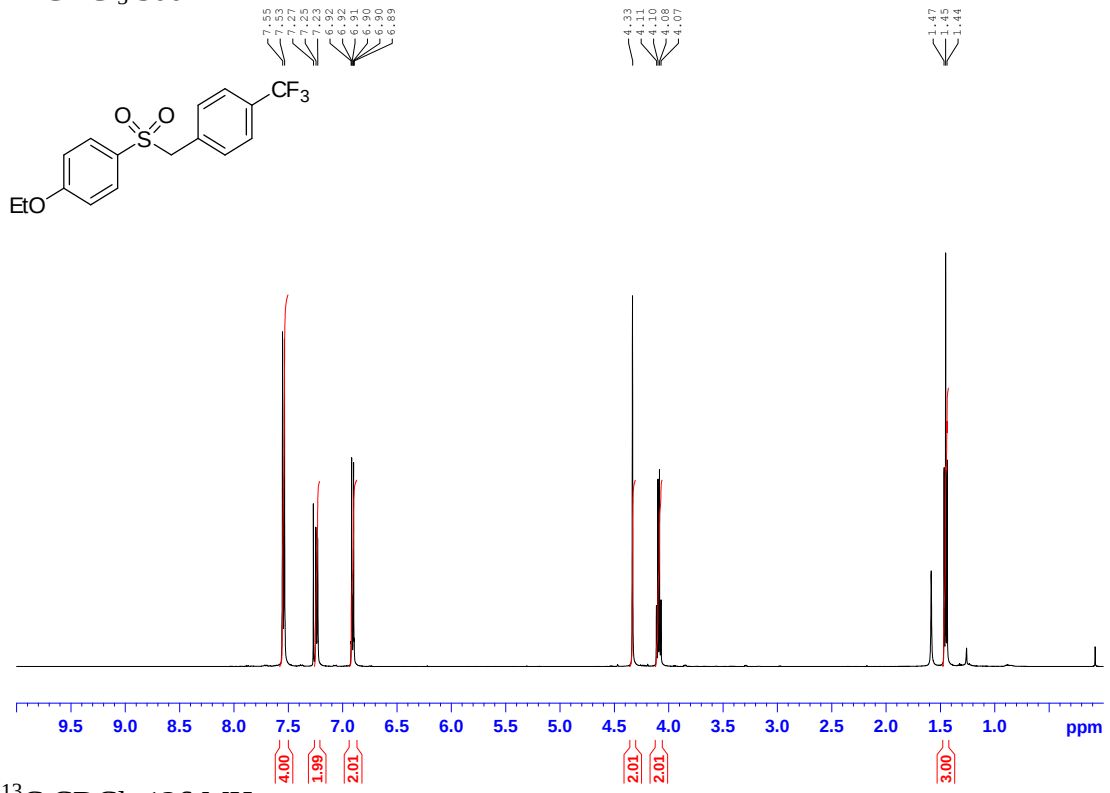


^{13}C $CDCl_3$ 126 MHz

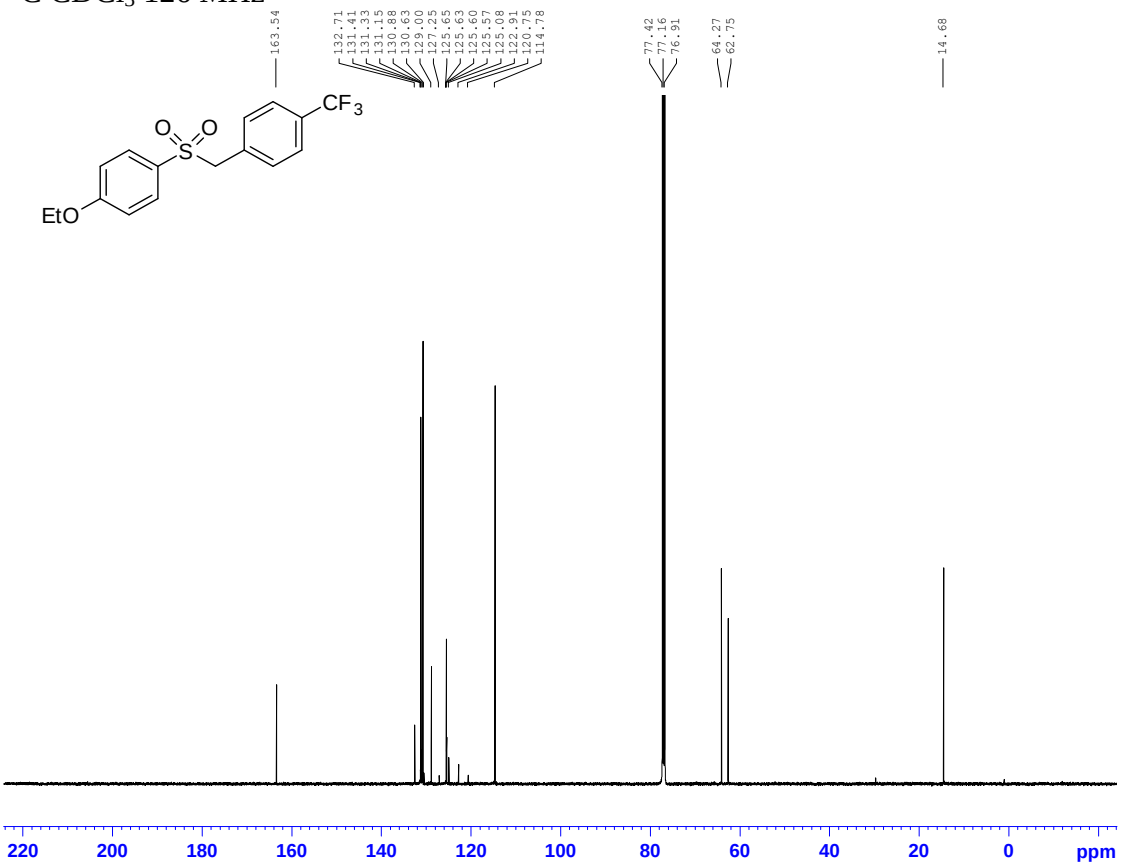


4-Ethoxyphenyl 4-(trifluoromethyl)benzyl sulfone

^{1}H $CDCl_3$ 500 MHz

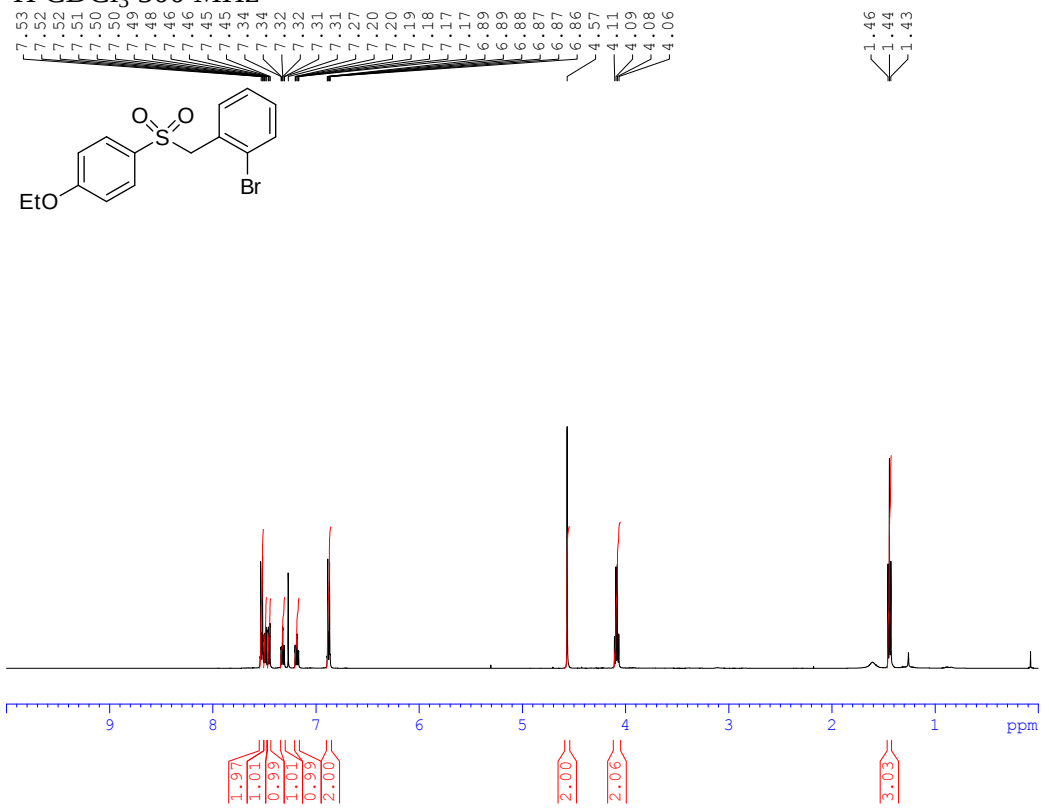


^{13}C $CDCl_3$ 126 MHz

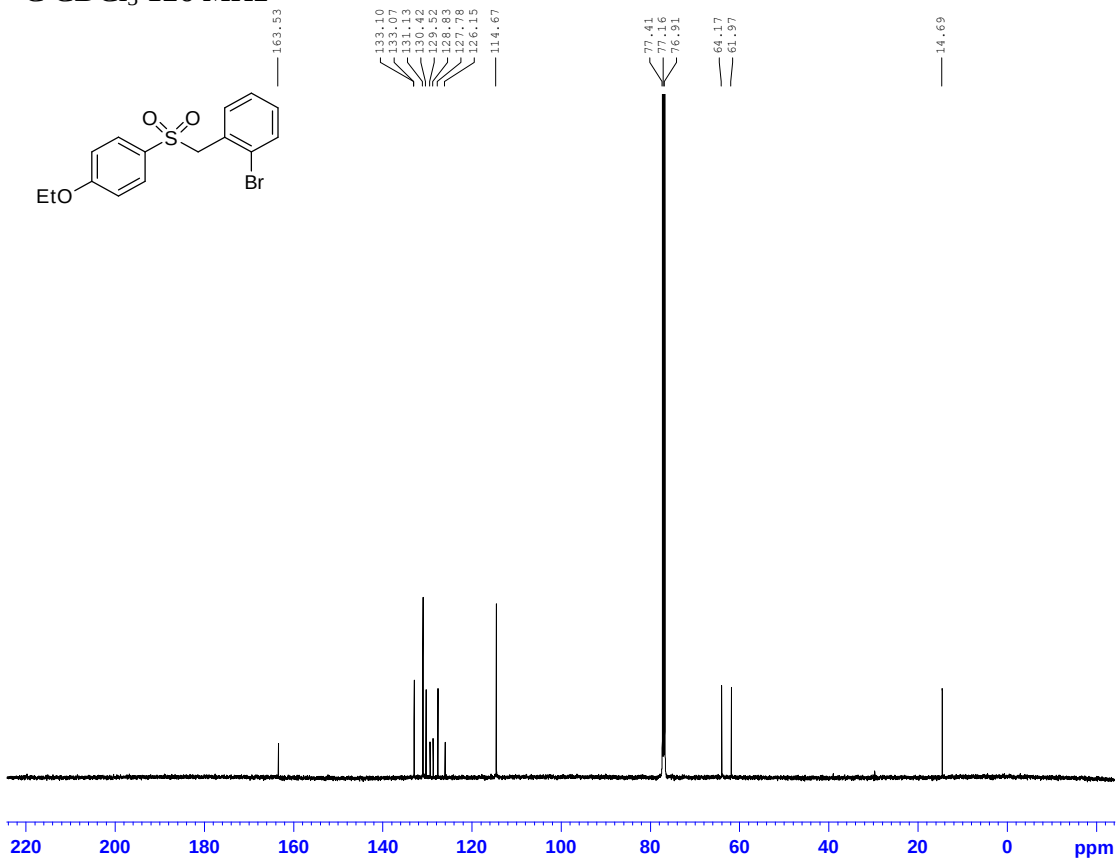


2-Bromobenzyl 4-ethoxyphenyl sulfone

^{1}H $CDCl_3$ 500 MHz

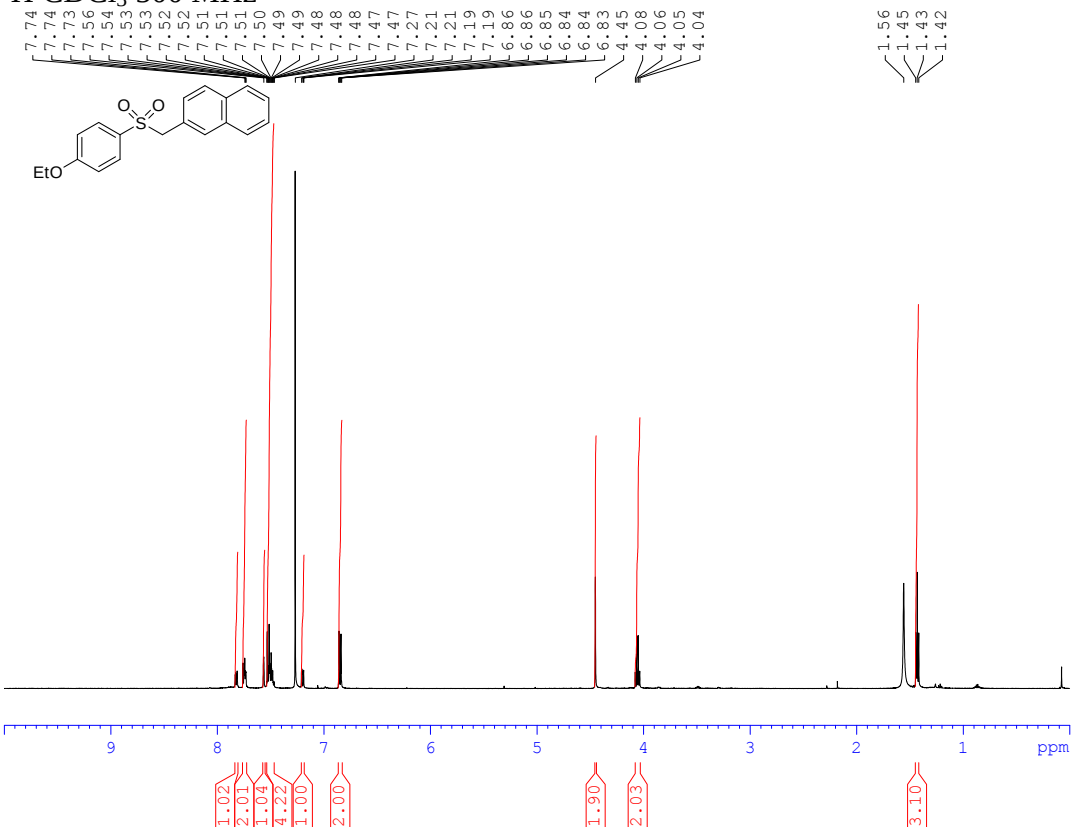


^{13}C $CDCl_3$ 126 MHz

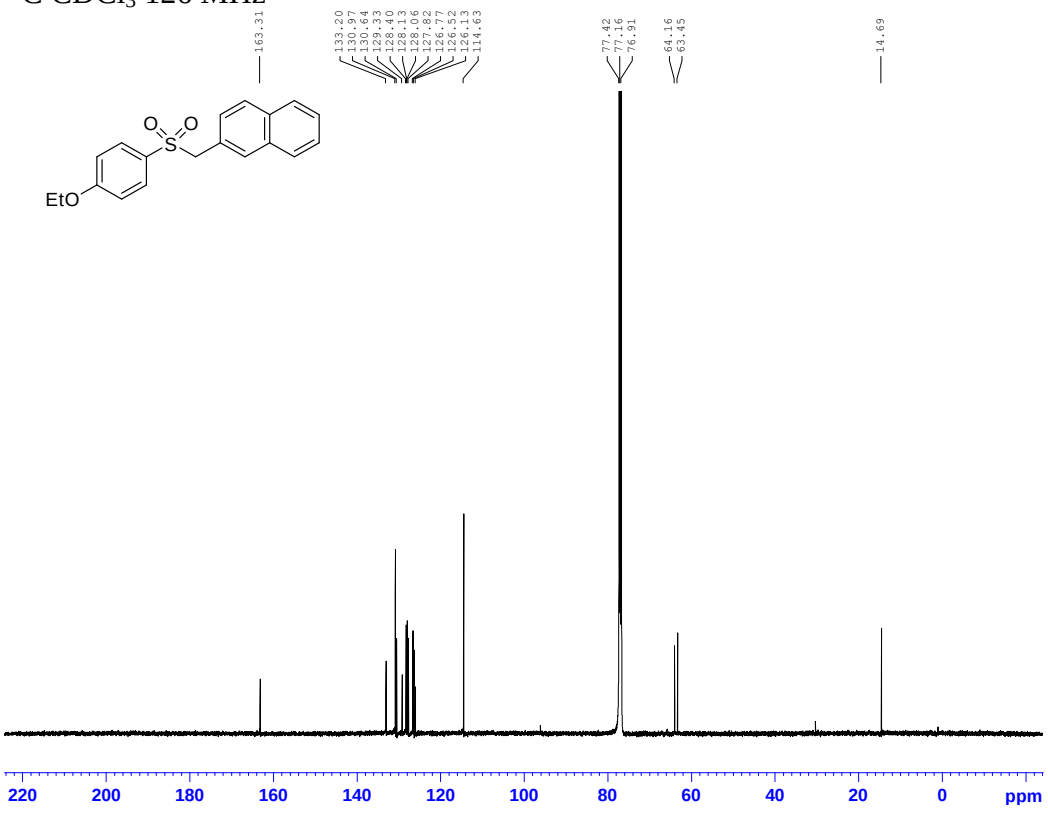


4-Ethoxyphenyl naphthalen-2-ylmethyl sulfone

^{1}H $CDCl_3$ 500 MHz

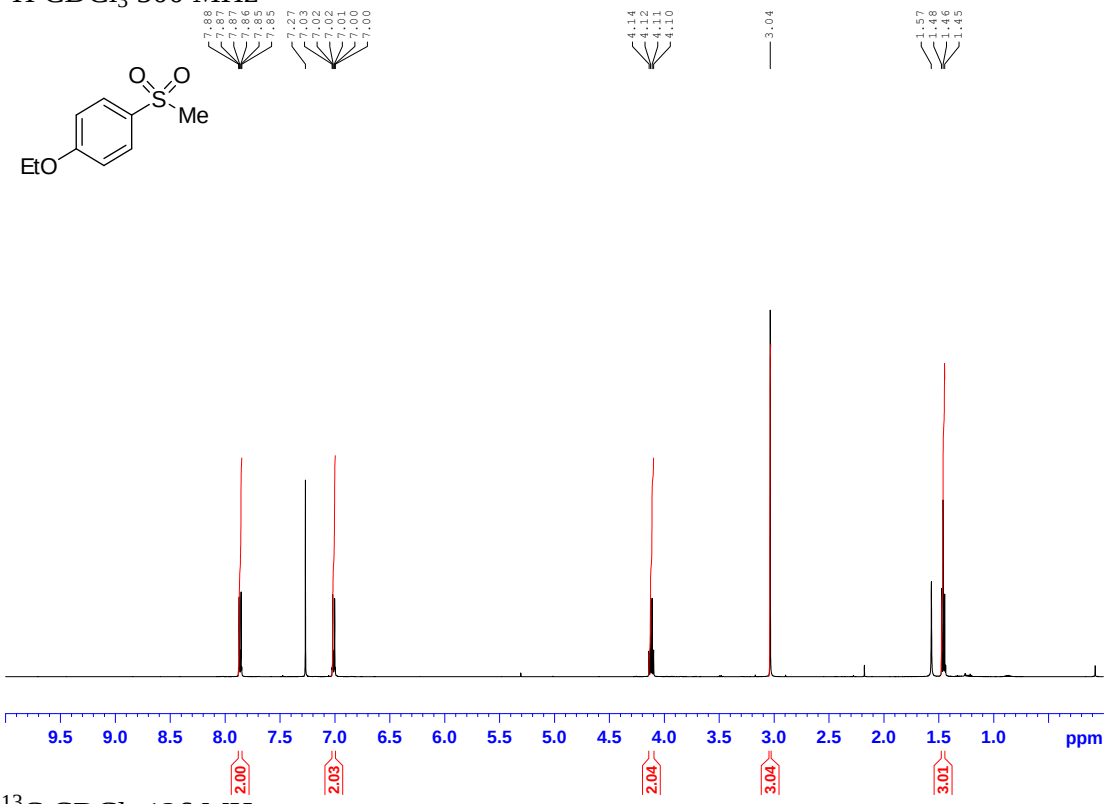


^{13}C $CDCl_3$ 126 MHz

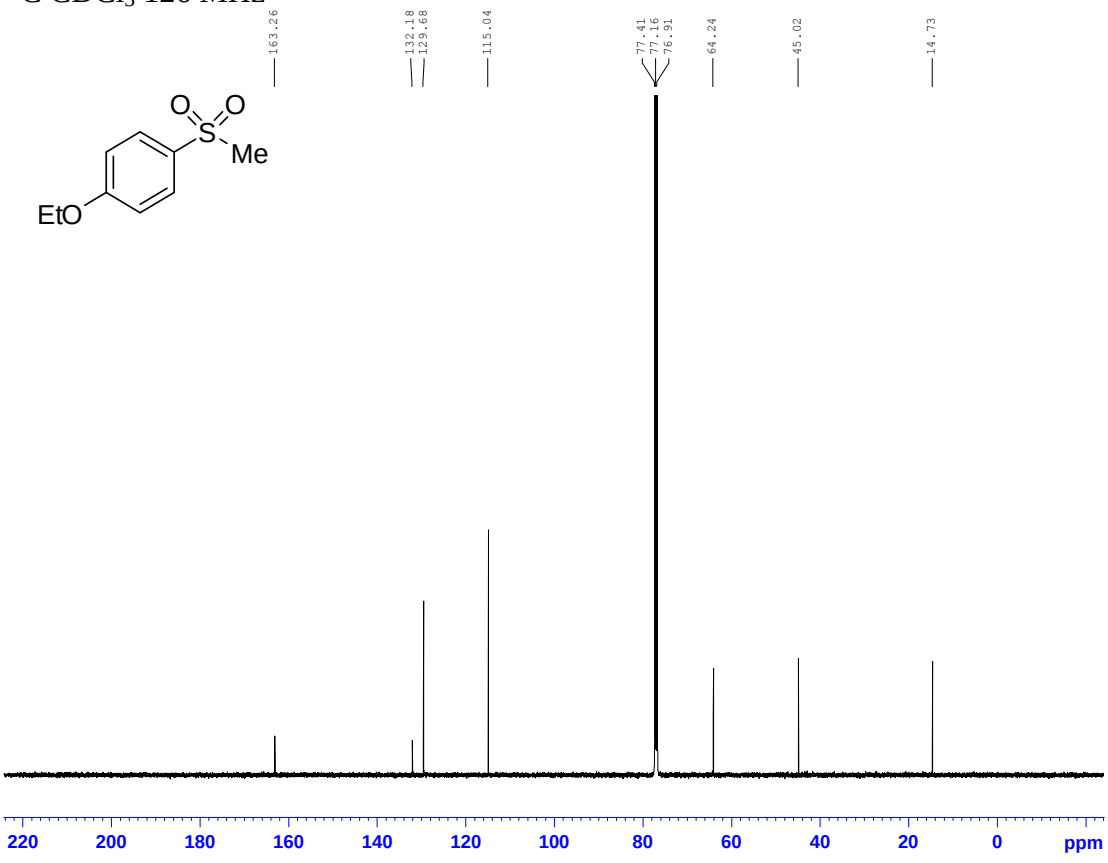


4-Ethoxyphenyl methyl sulfone

^{1}H $CDCl_3$ 500 MHz

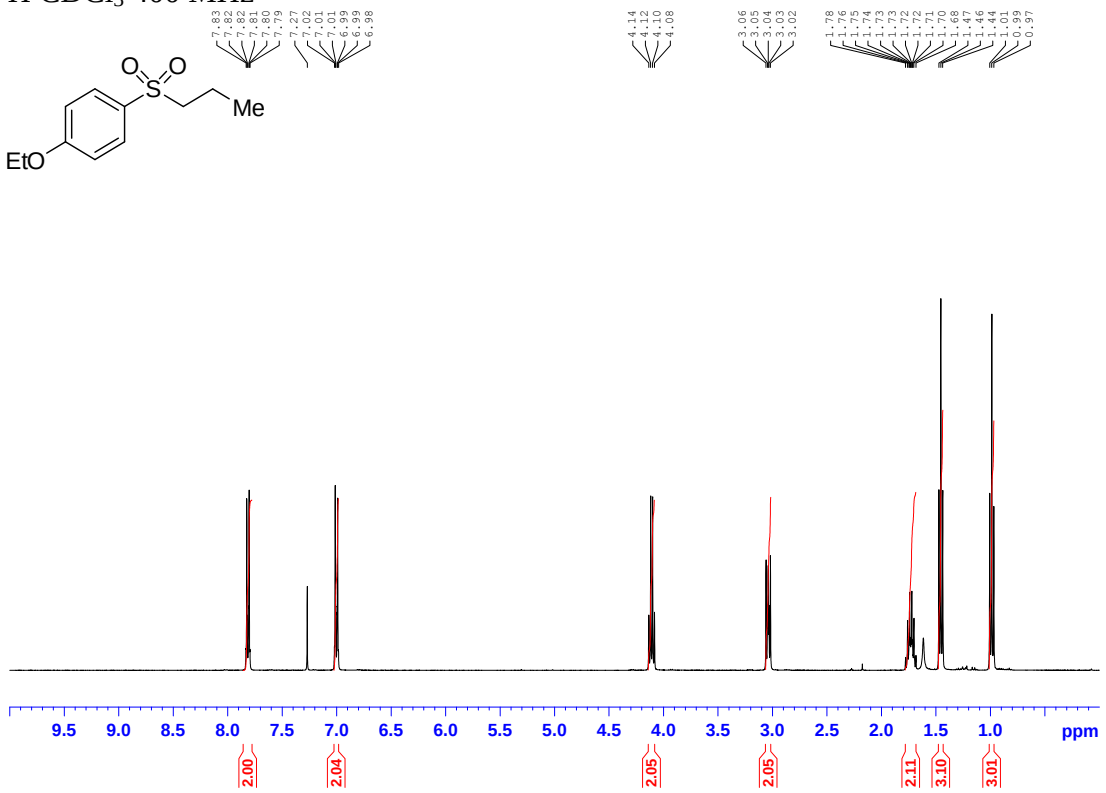


^{13}C $CDCl_3$ 126 MHz

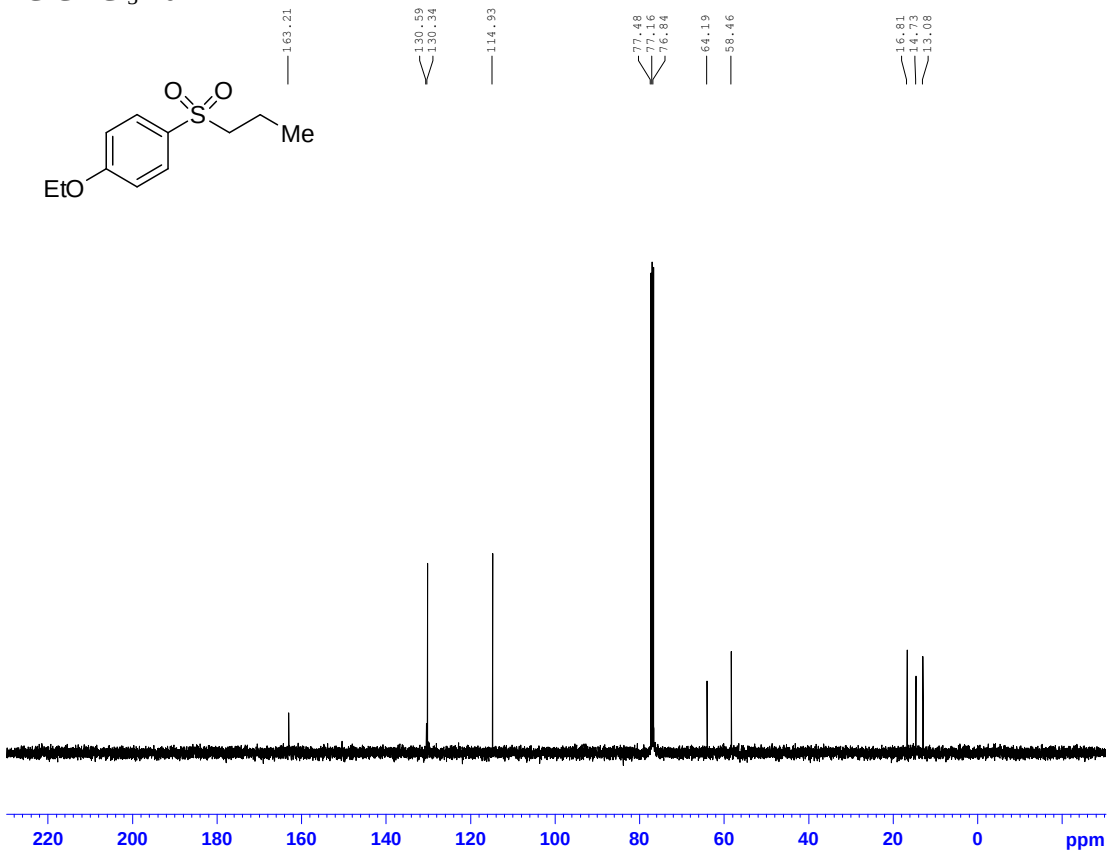


4-Ethoxyphenyl propyl sulfone

^{1}H $CDCl_3$ 400 MHz

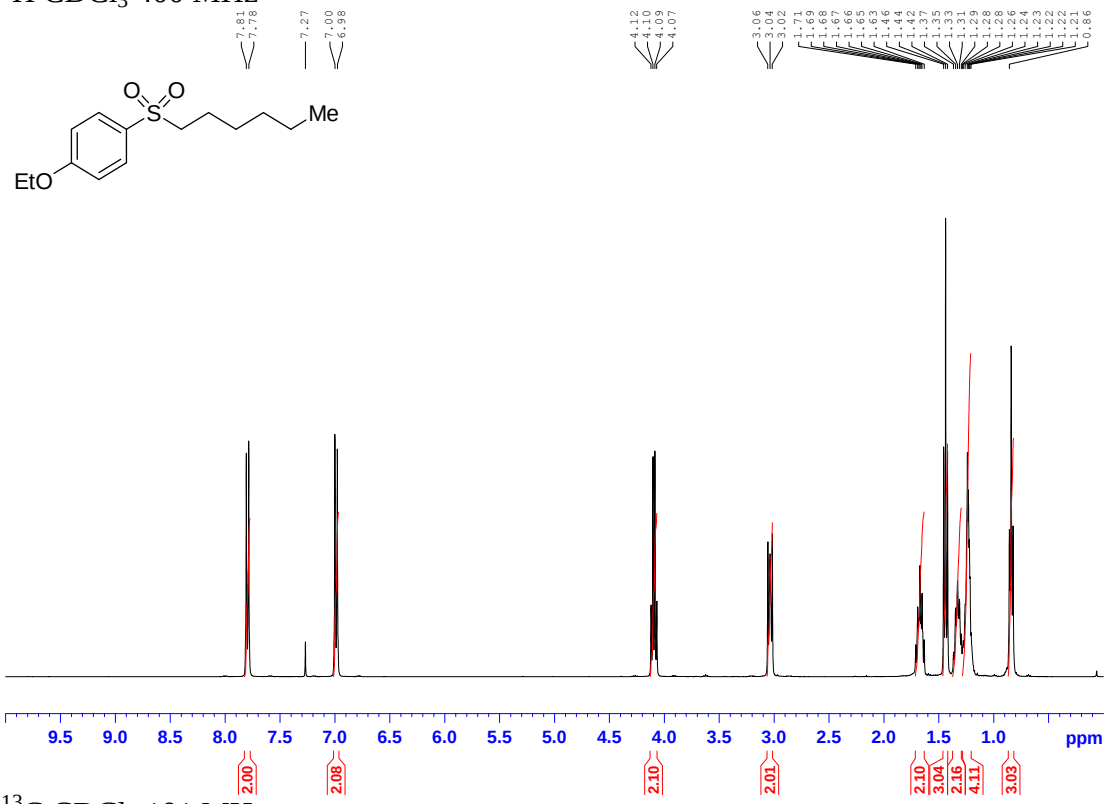


^{13}C $CDCl_3$ 101 MHz

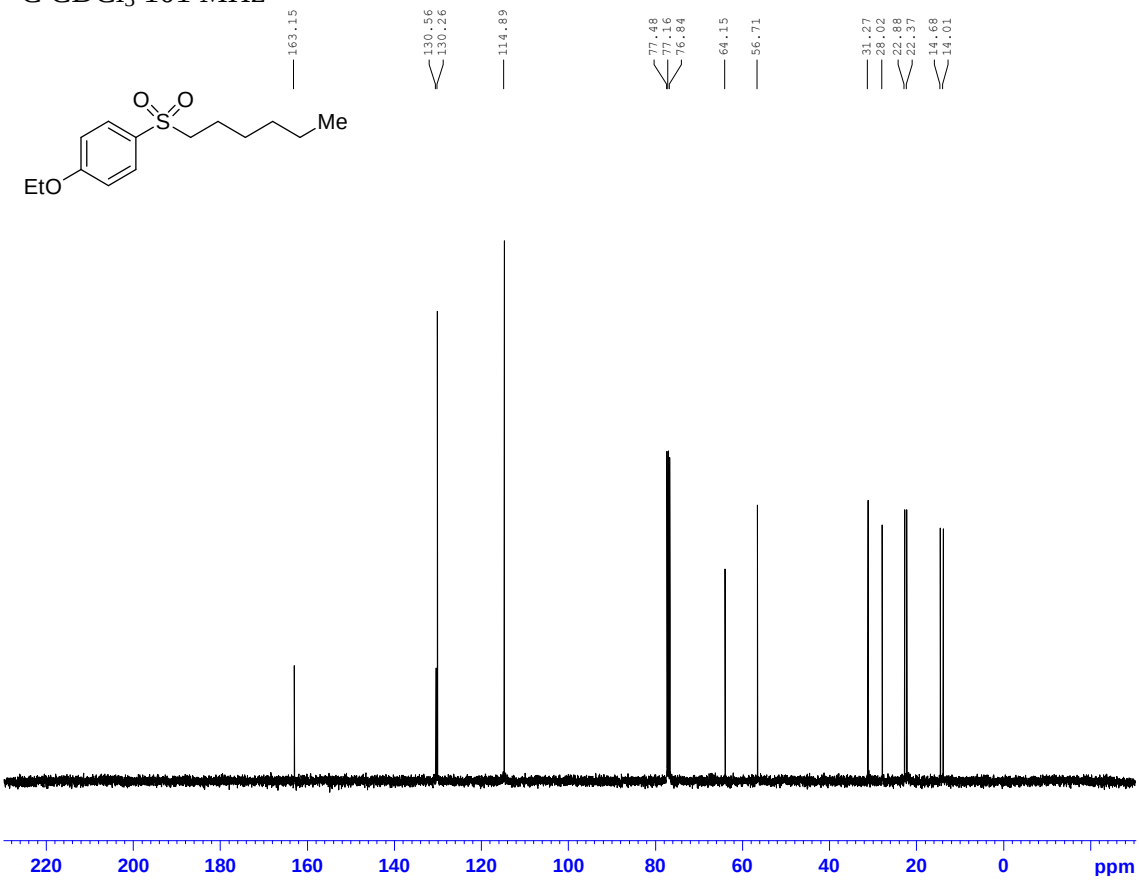


4-Ethoxyphenyl hexyl sulfone

^{1}H $CDCl_3$ 400 MHz

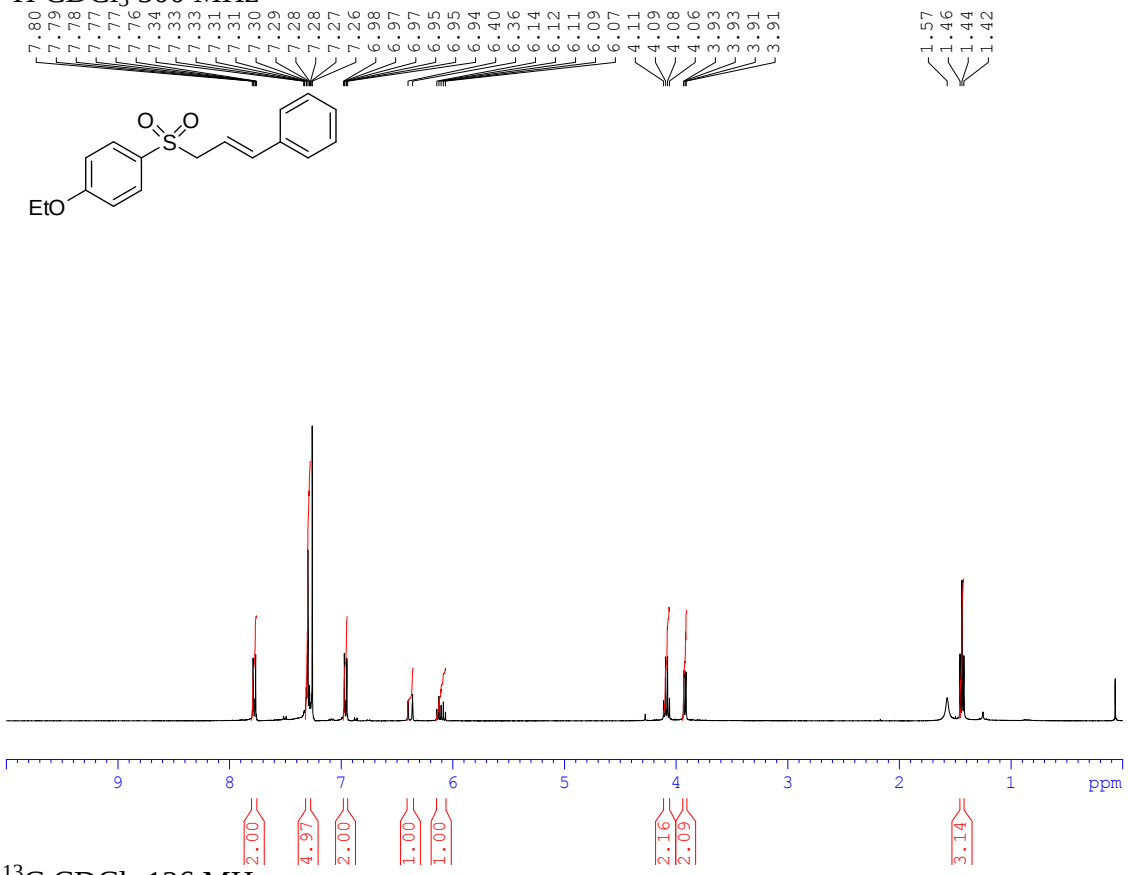


^{13}C $CDCl_3$ 101 MHz

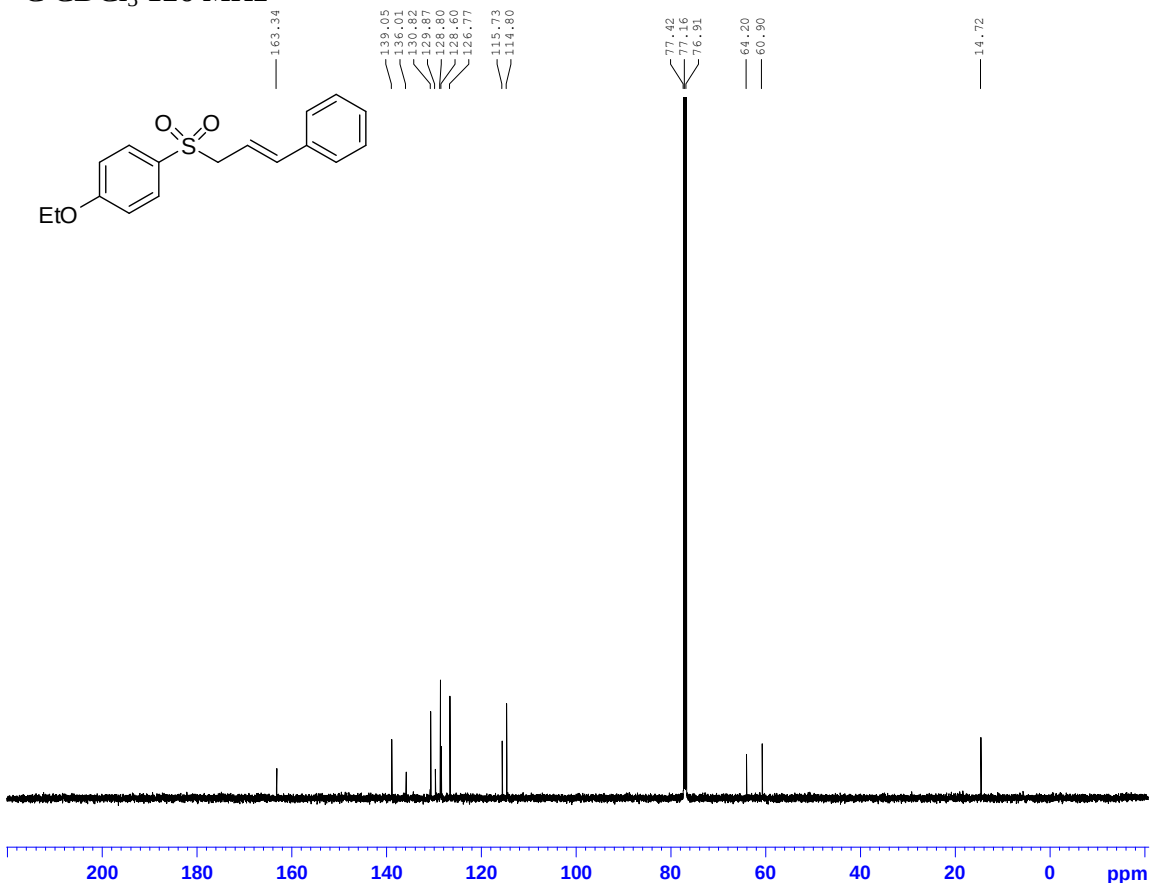


4-Ethoxyphenyl (2*E*)-3-phenylprop-2-en-1-yl sulfone

^{1}H $CDCl_3$ 500 MHz

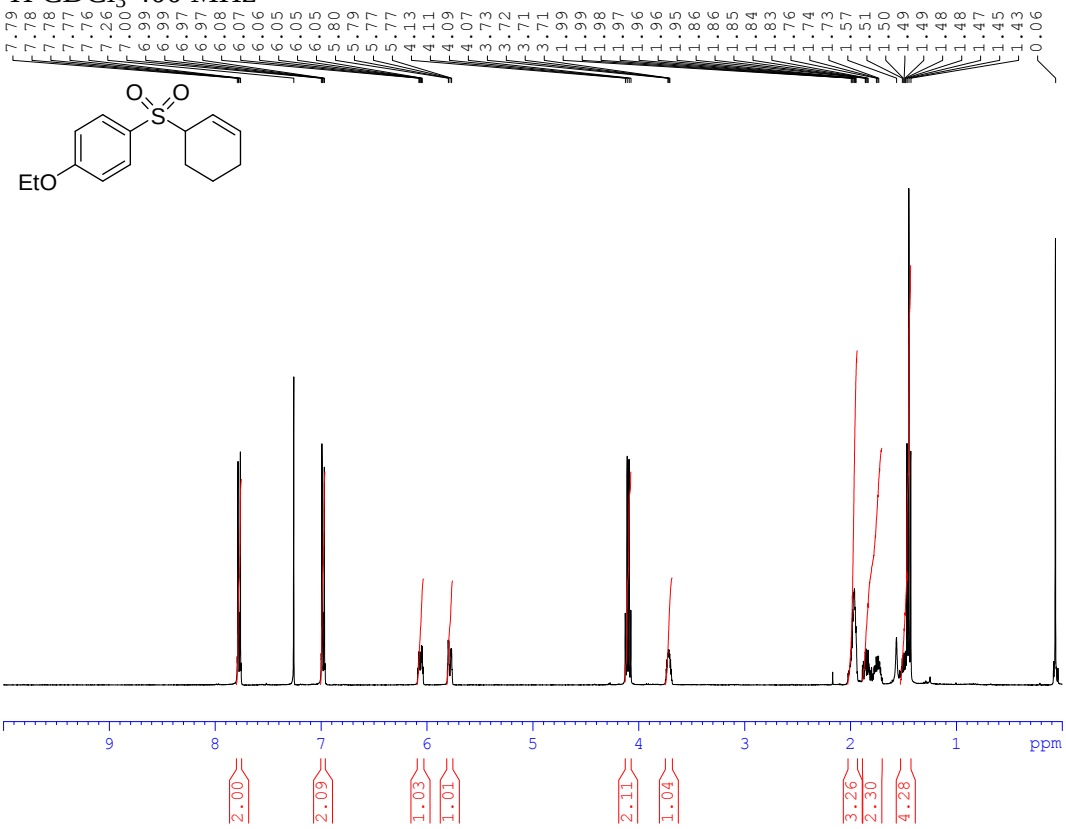


^{13}C $CDCl_3$ 126 MHz

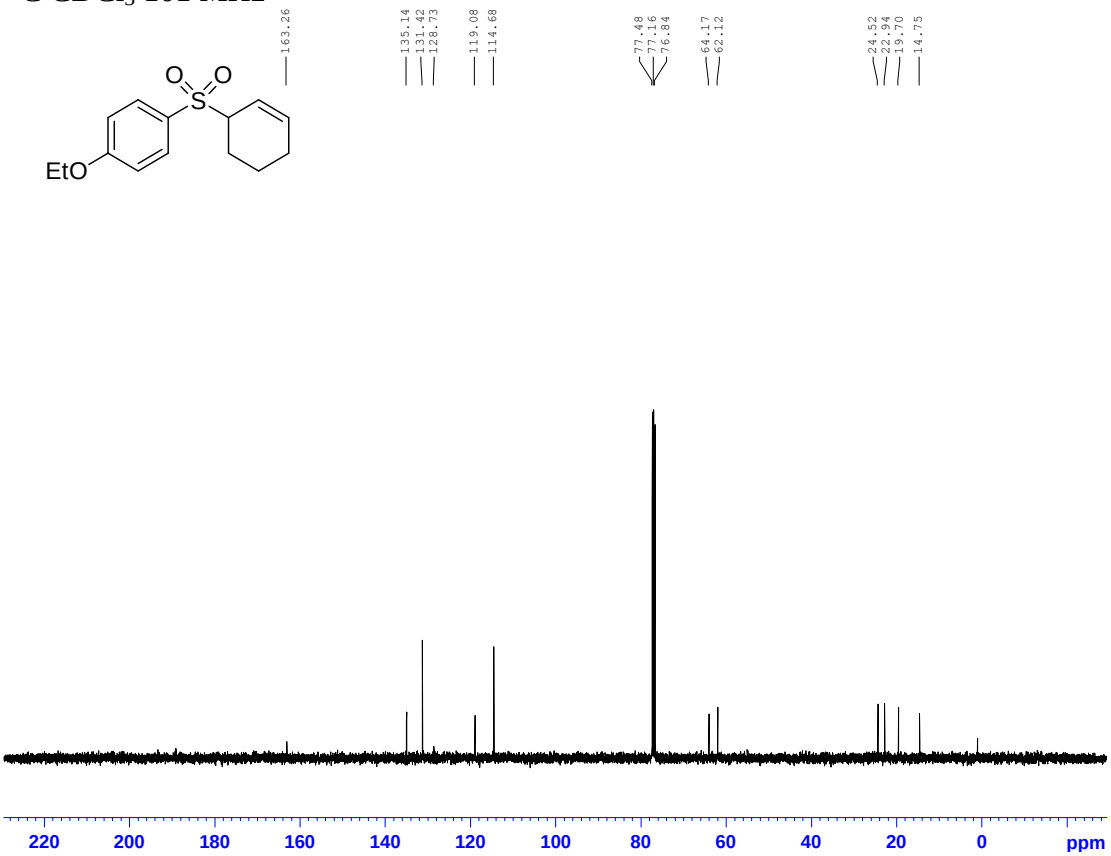


Cyclohex-2-en-1-yl 4-ethoxyphenyl sulfone

^{1}H $CDCl_3$ 400 MHz

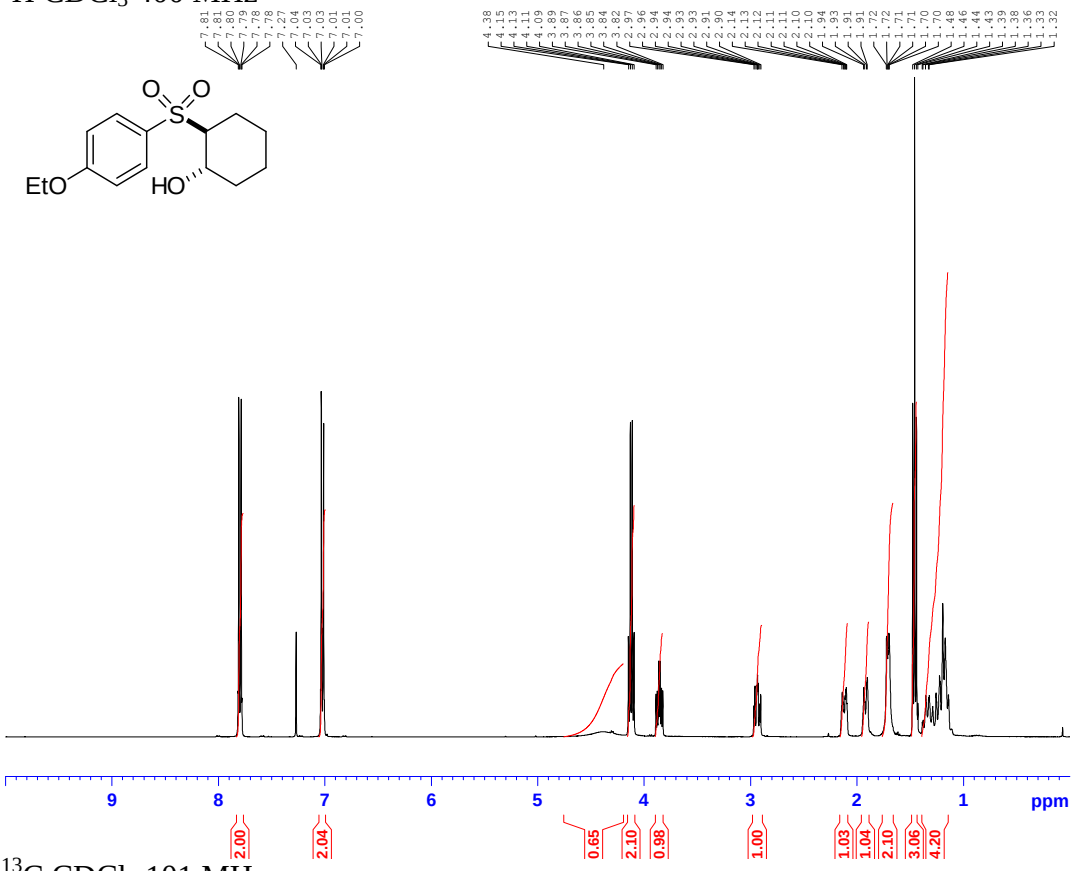


^{13}C $CDCl_3$ 101 MHz

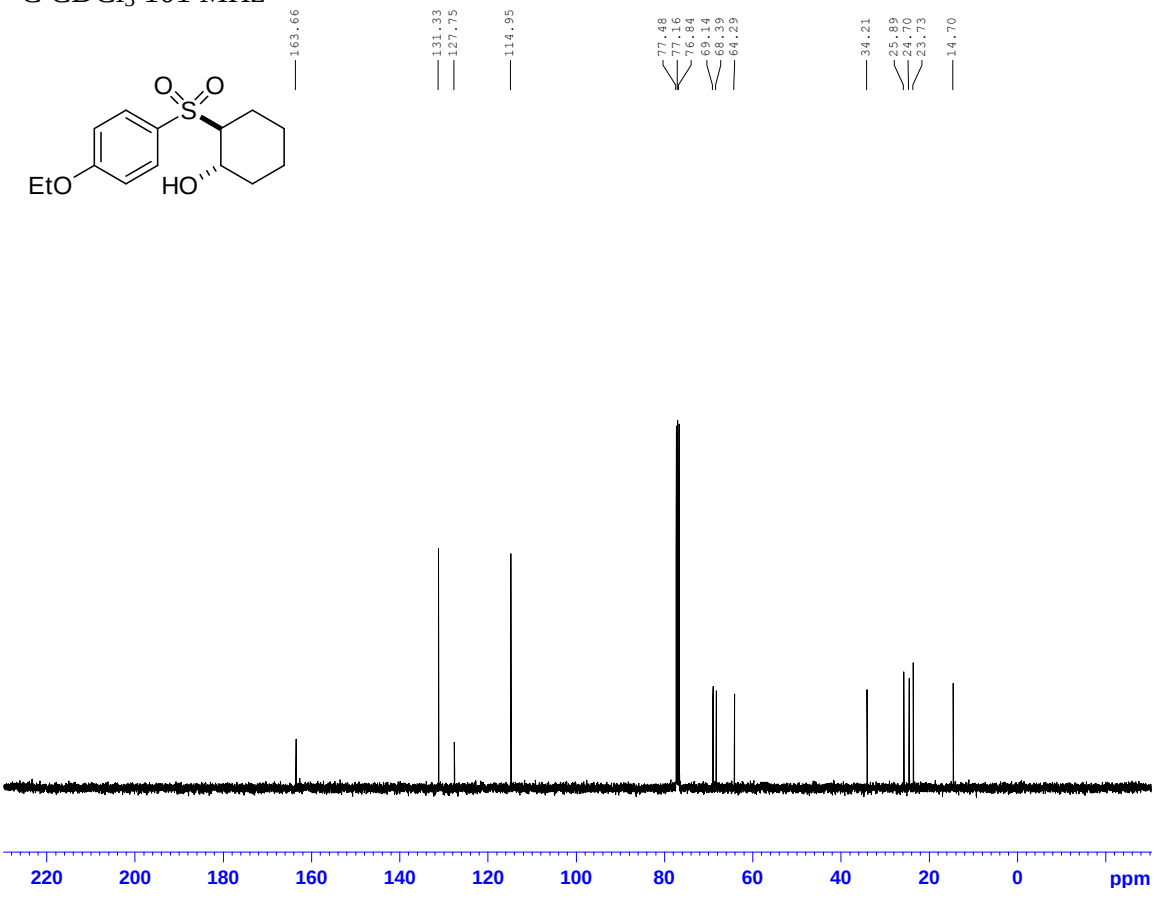


2-[(4-Ethoxyphenyl)sulfonyl]cyclohexanol

^{1}H $CDCl_3$ 400 MHz

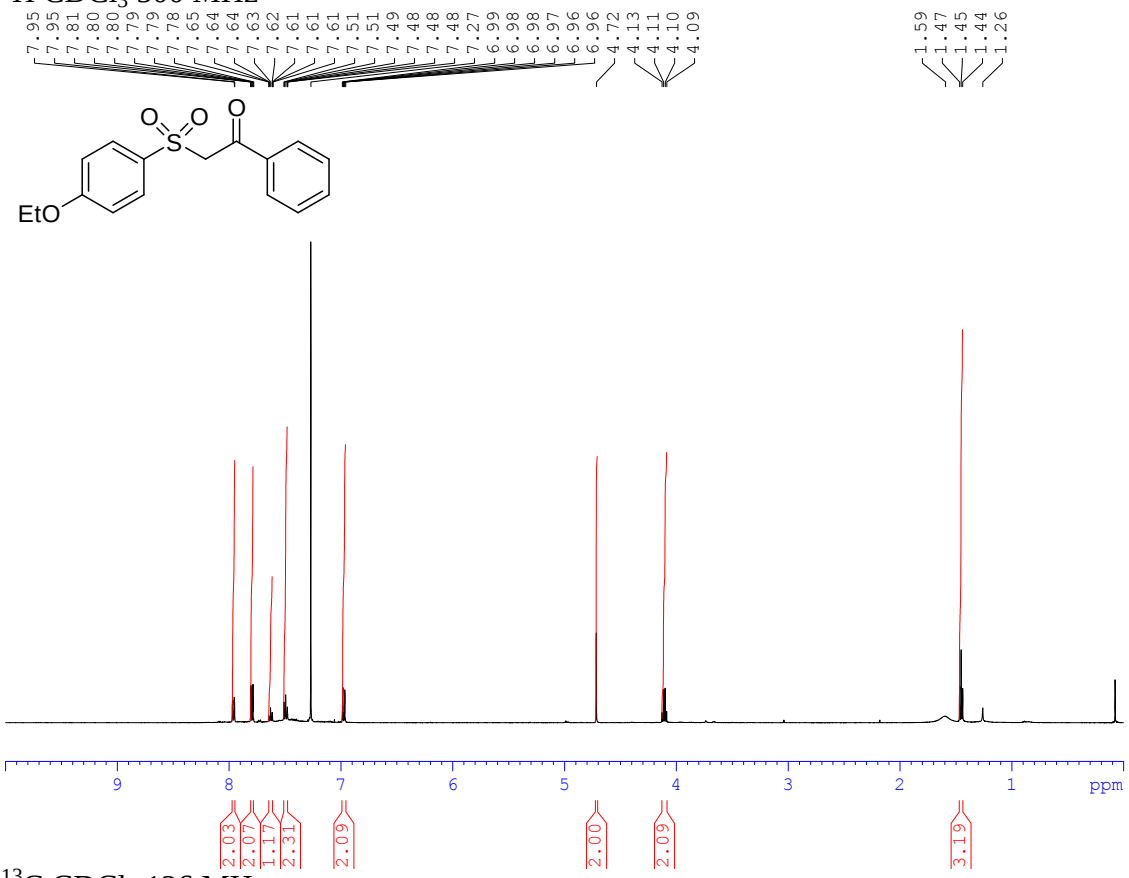


^{13}C $CDCl_3$ 101 MHz



2-[(4-Ethoxyphenyl)sulfonyl]-1-phenylethanone

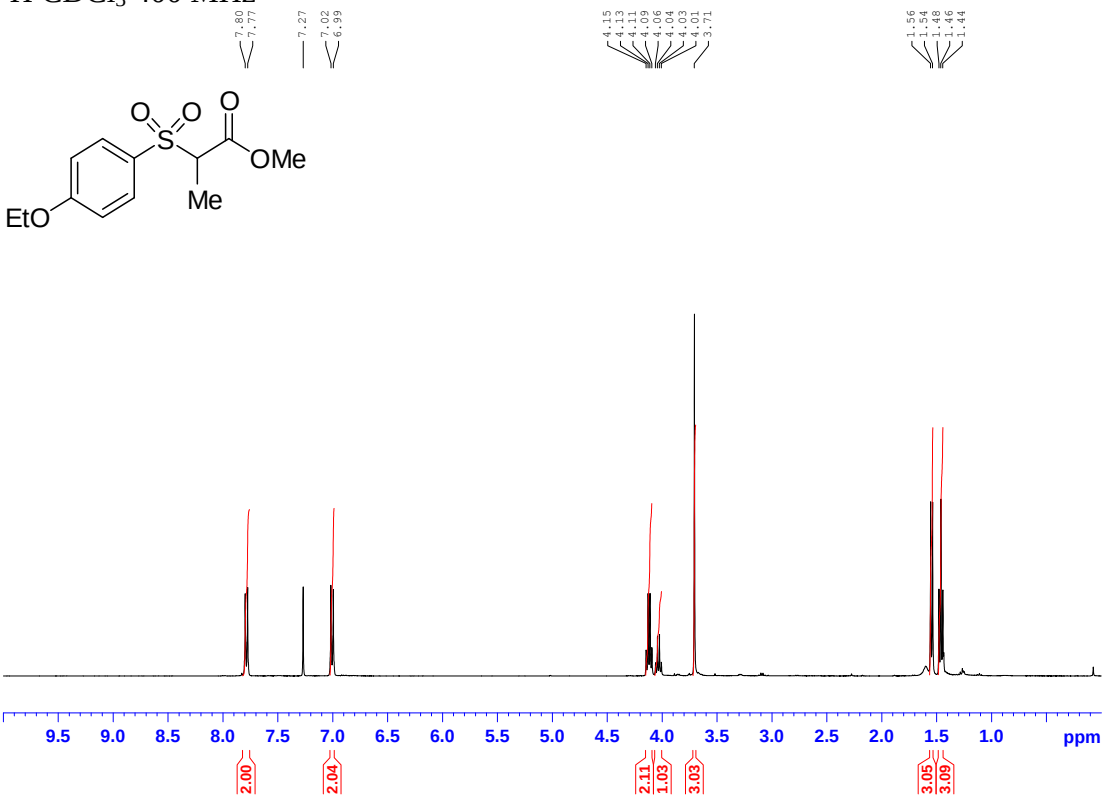
^{1}H $CDCl_3$ 500 MHz



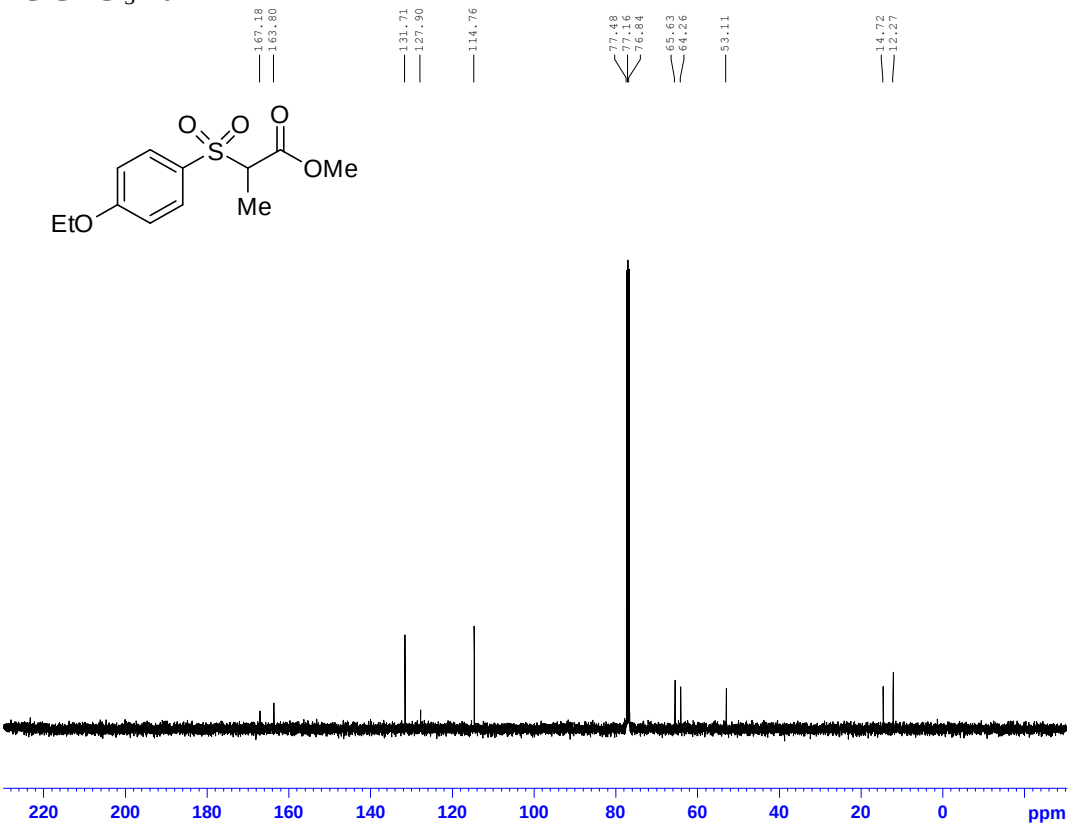
^{13}C $CDCl_3$ 126 MHz

Methyl 2-[(4-ethoxyphenyl)sulfonyl]propanoate

^{1}H $CDCl_3$ 400 MHz

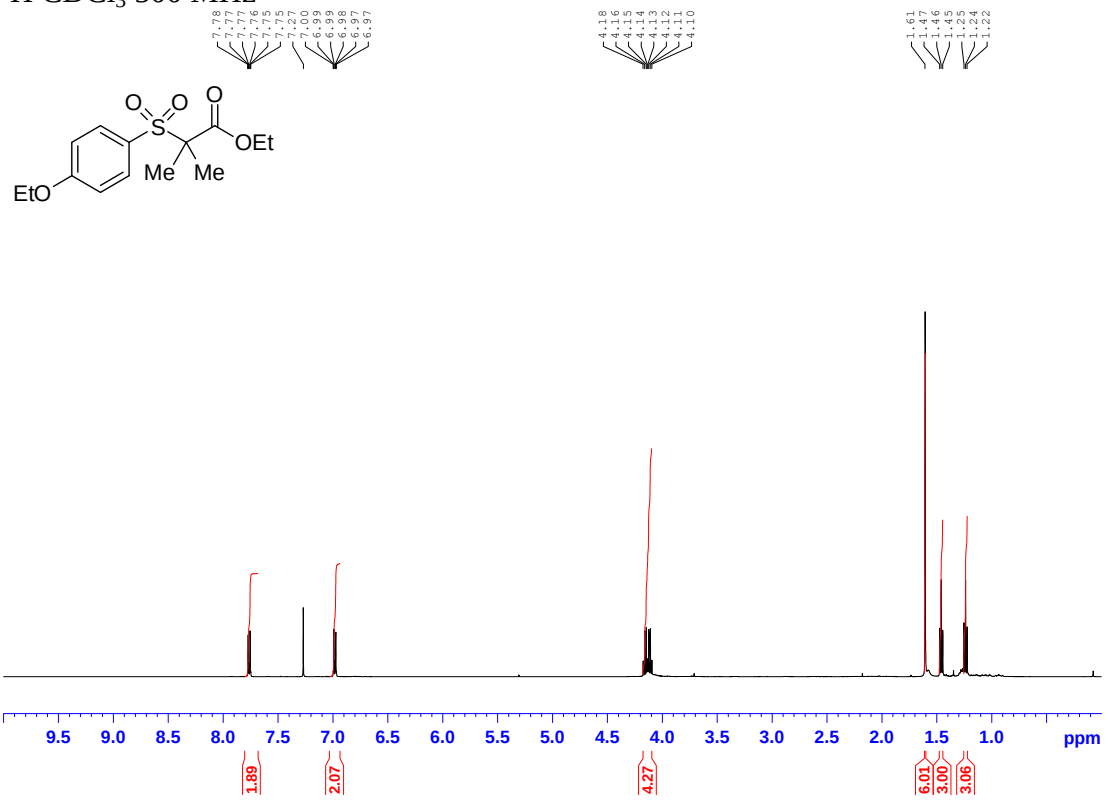


^{13}C $CDCl_3$ 101 MHz

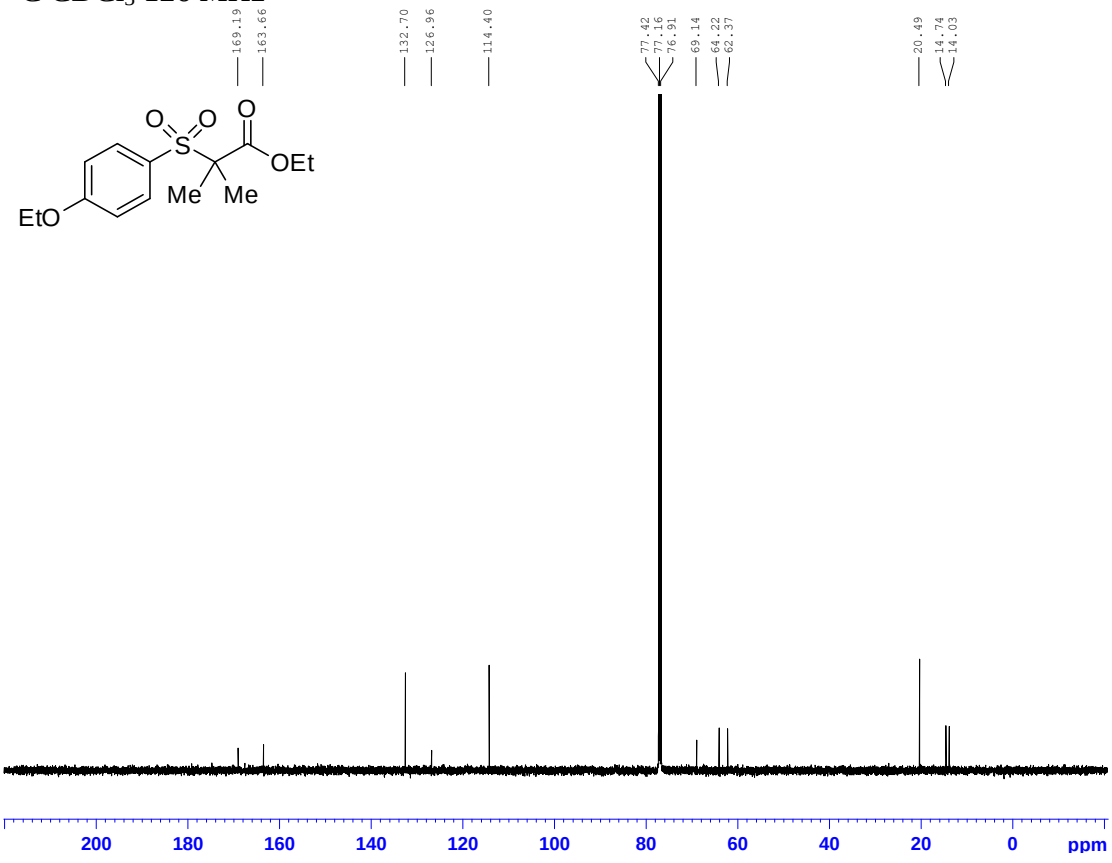


Ethyl 2-[(4-ethoxyphenyl)sulfonyl]-2-methylpropanoate

^{1}H $CDCl_3$ 500 MHz

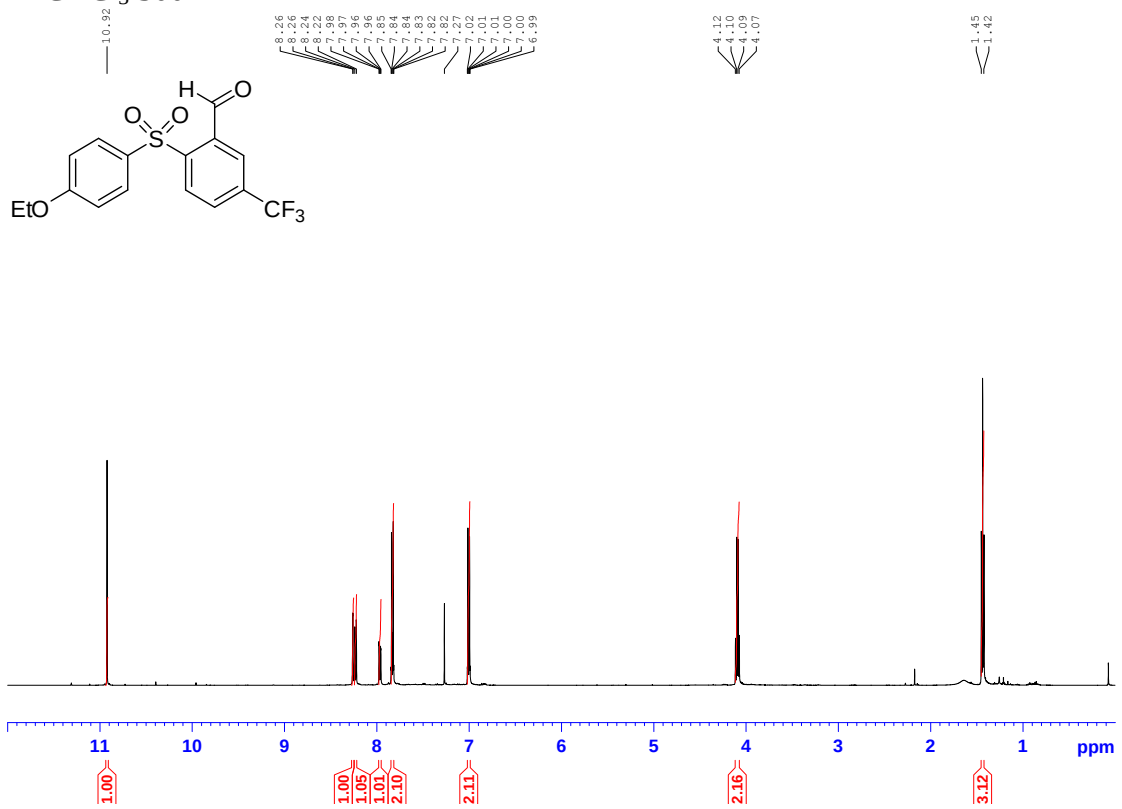


^{13}C $CDCl_3$ 126 MHz

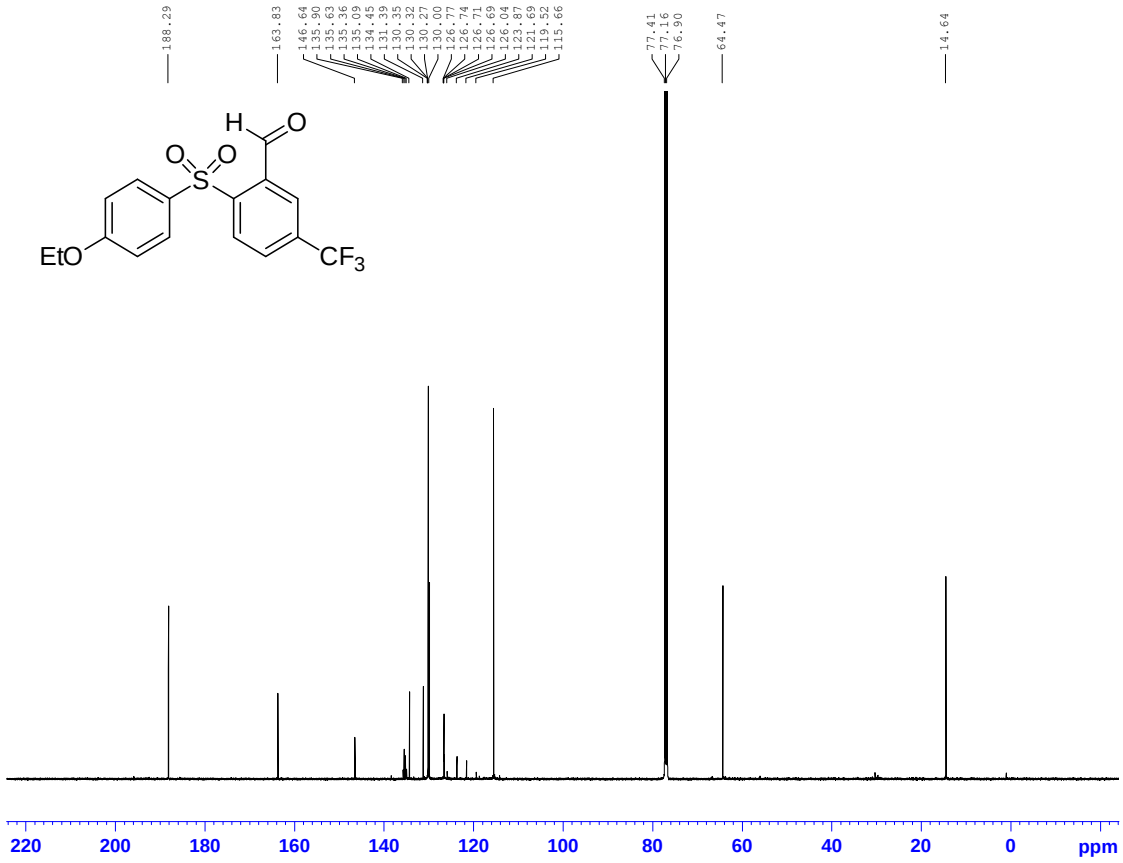


2-[(4-Ethoxyphenyl)sulfonyl]-5-(trifluoromethyl)benzaldehyde

^{1}H $CDCl_3$ 500 MHz

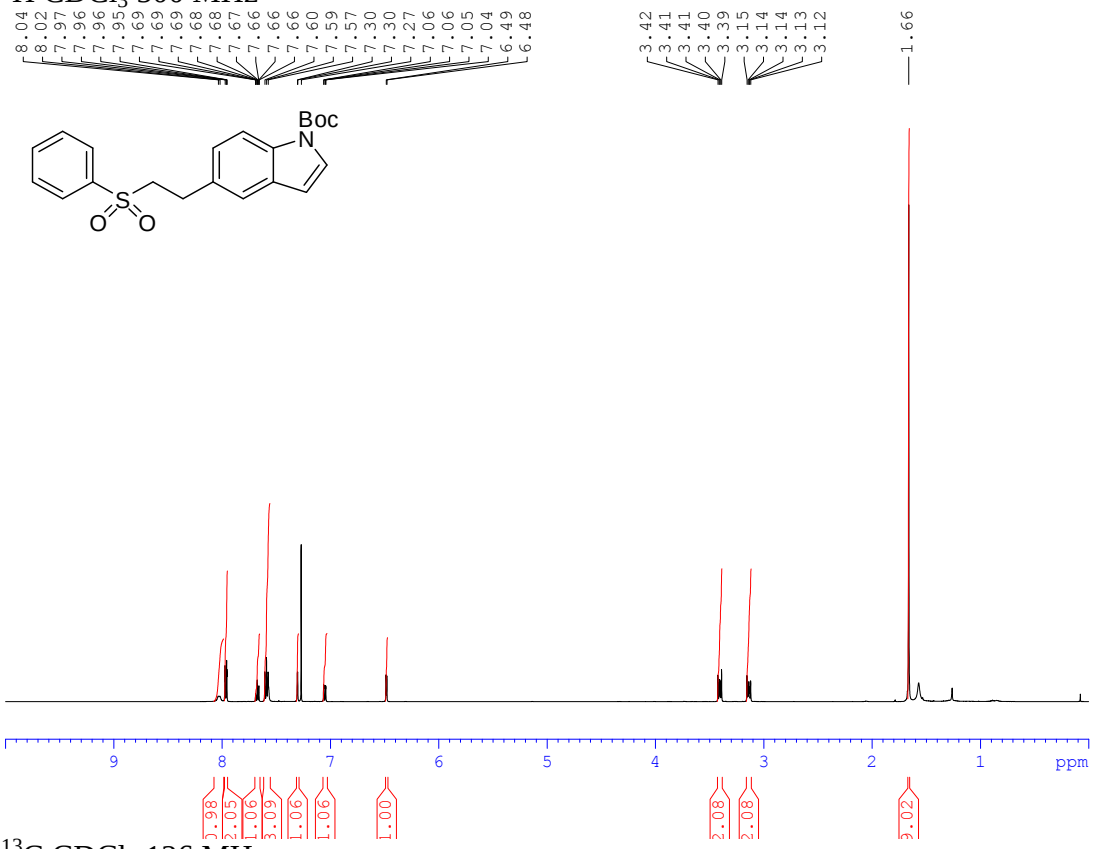


^{13}C $CDCl_3$ 126 MHz

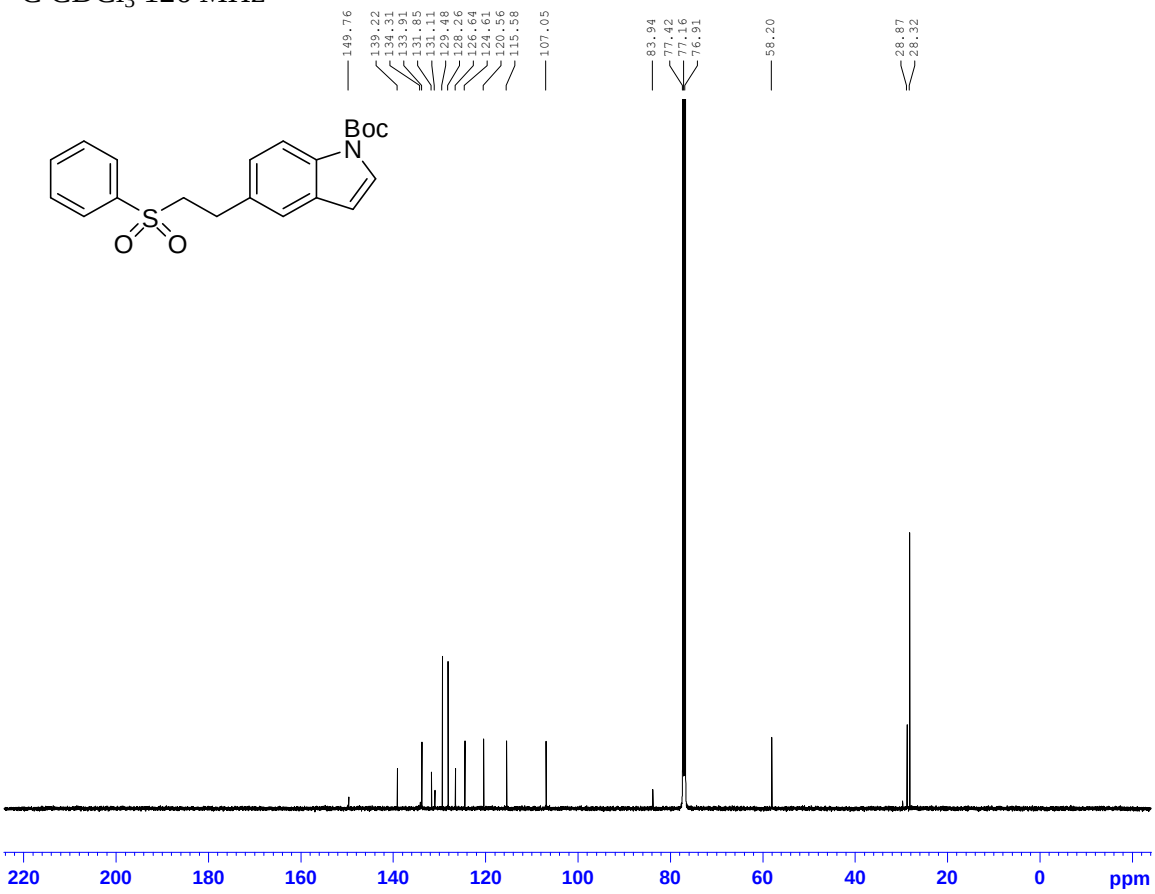


***tert*-Butyl 5-[2-(phenylsulfonyl)ethyl]-1*H*-indole-1-carboxylate,**

^{1}H $CDCl_3$ 500 MHz

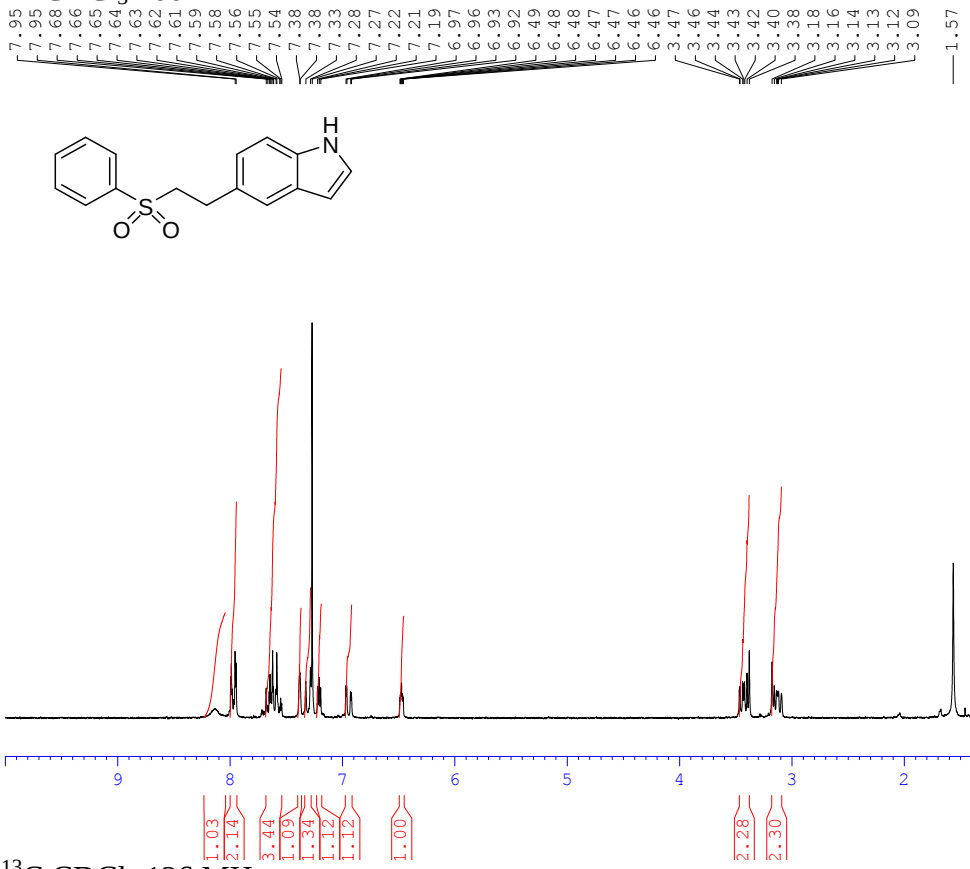


^{13}C $CDCl_3$ 126 MHz

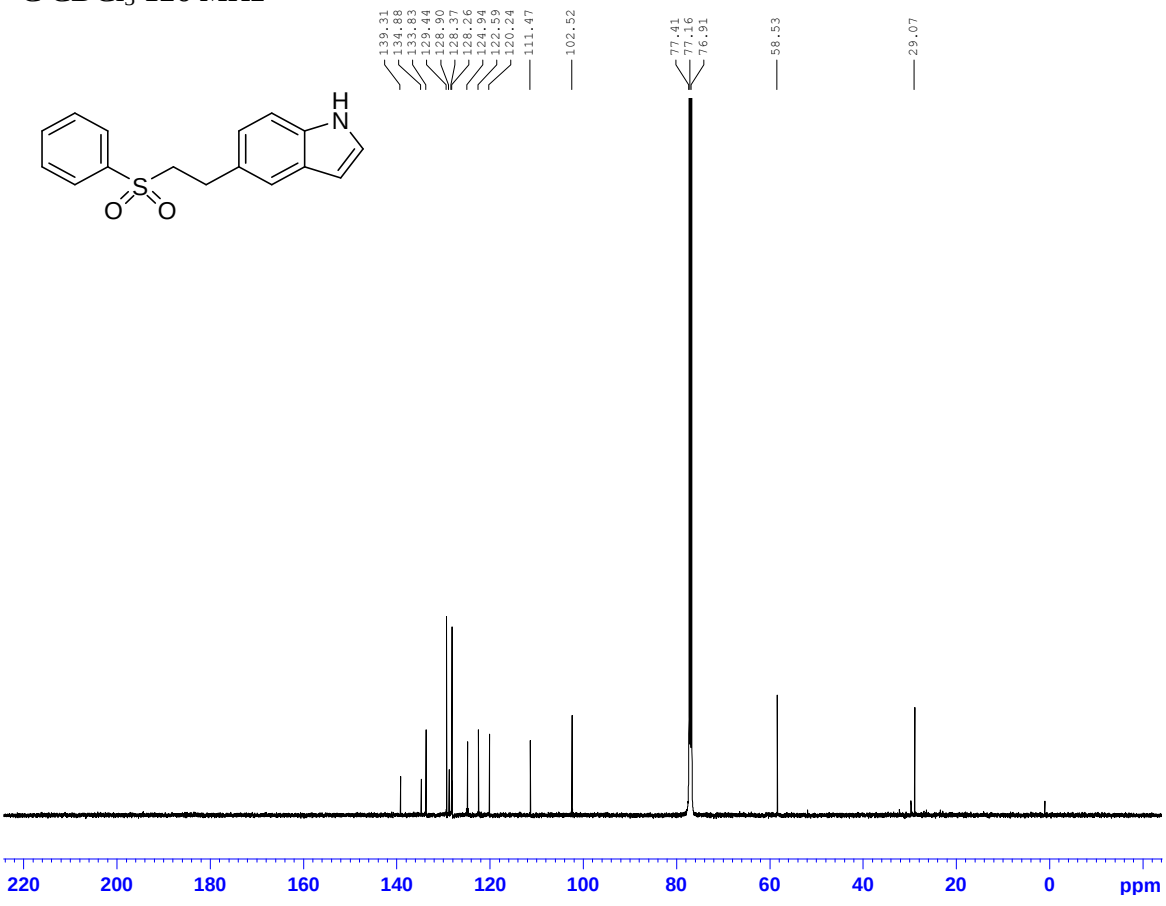


5-[2-(Phenylsulfonyl)ethyl]-1*H*-indole

^{1}H $CDCl_3$ 200 MHz

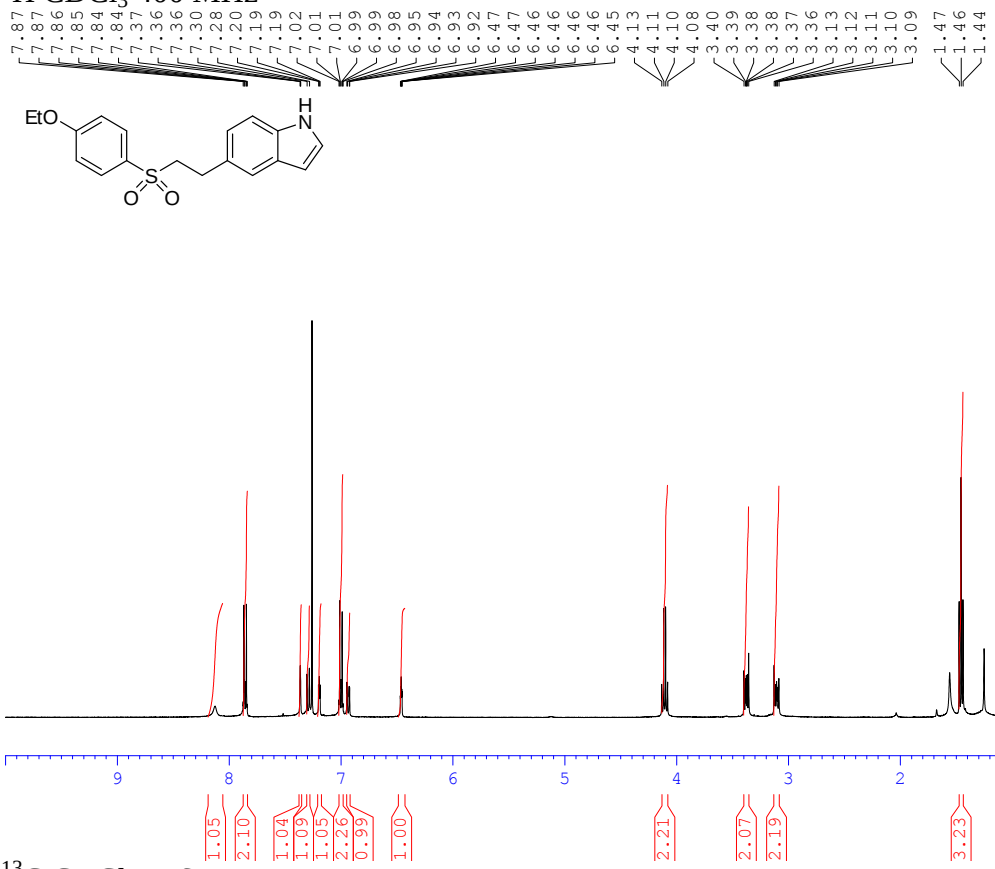


^{13}C $CDCl_3$ 126 MHz

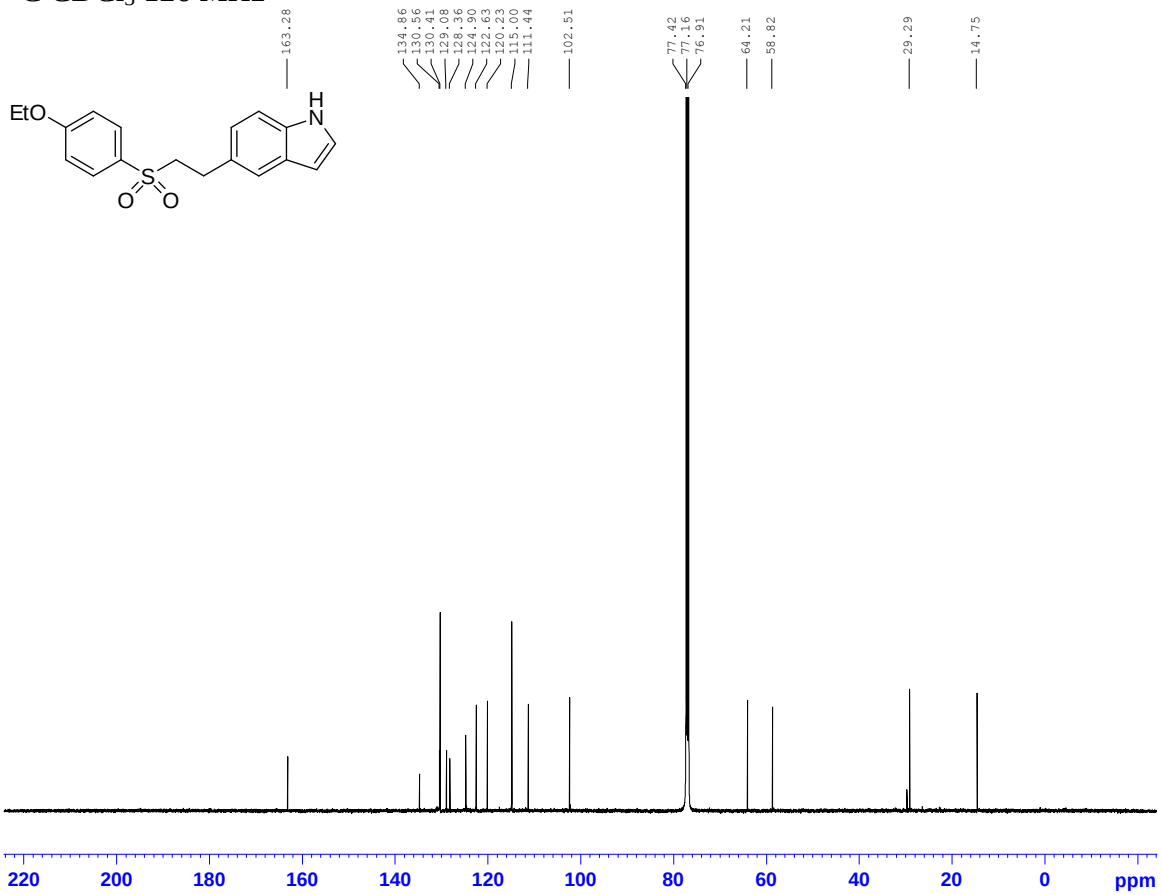


5-{2-[(4-Ethoxyphenyl)sulfonyl]ethyl}-1*H*-indole

^{1}H $CDCl_3$ 400 MHz

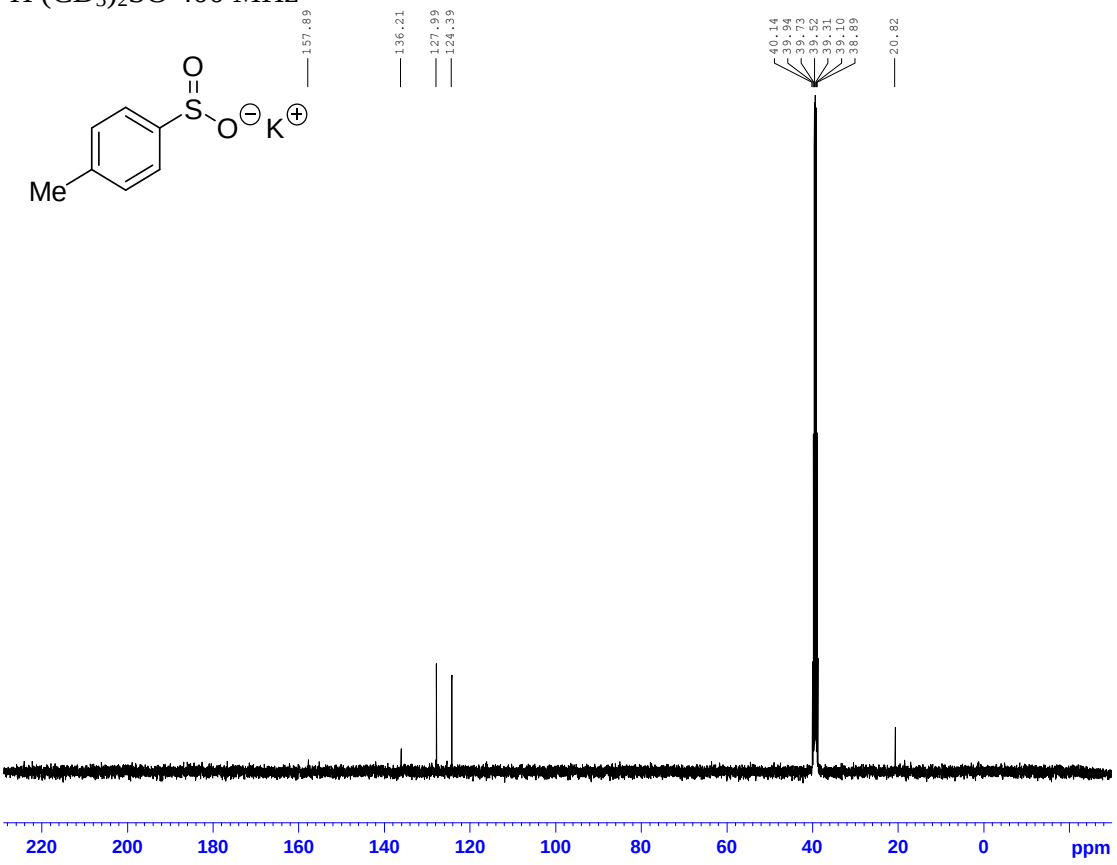


^{13}C $CDCl_3$ 126 MHz

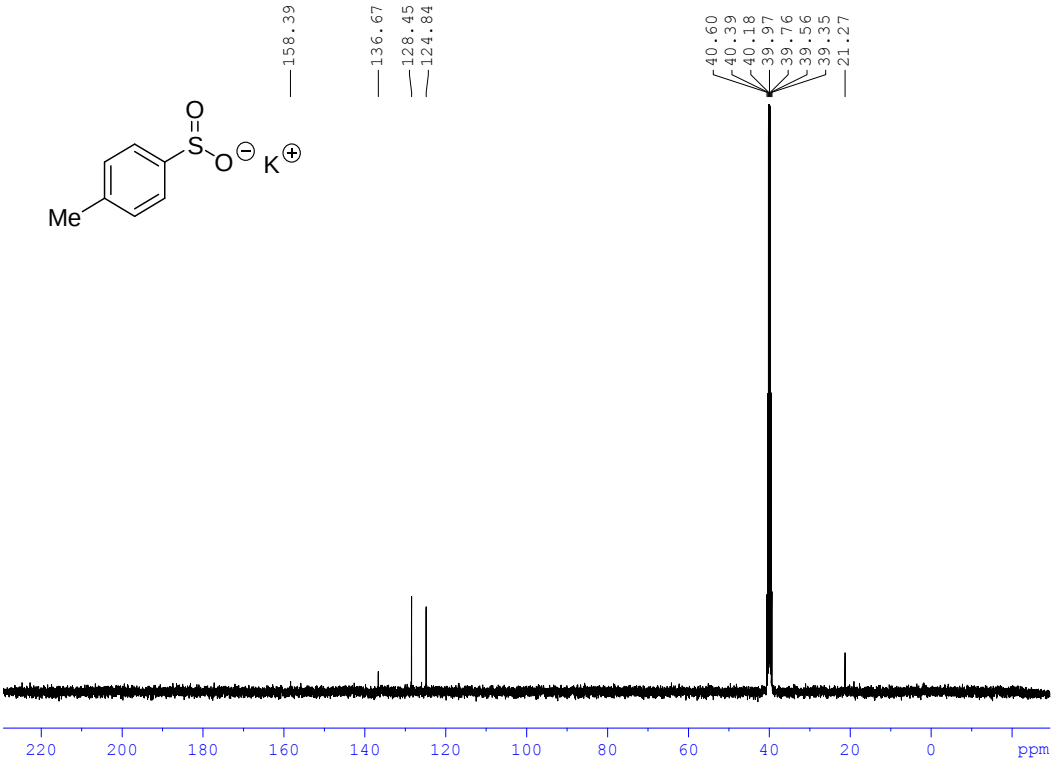


Potassium toluene-*p*-sulfinate

^{1}H $(CD_3)_2SO$ 400 MHz

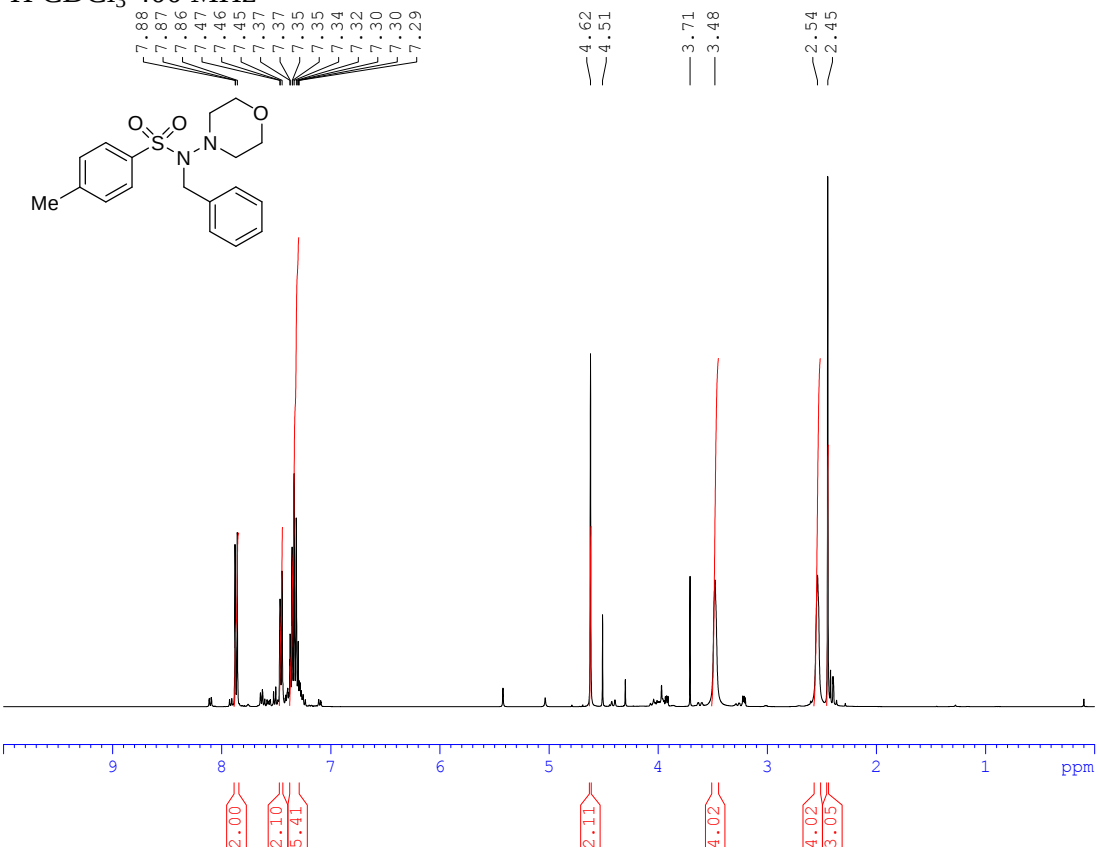


^{13}C $(CD_3)_2SO$ 126 MHz

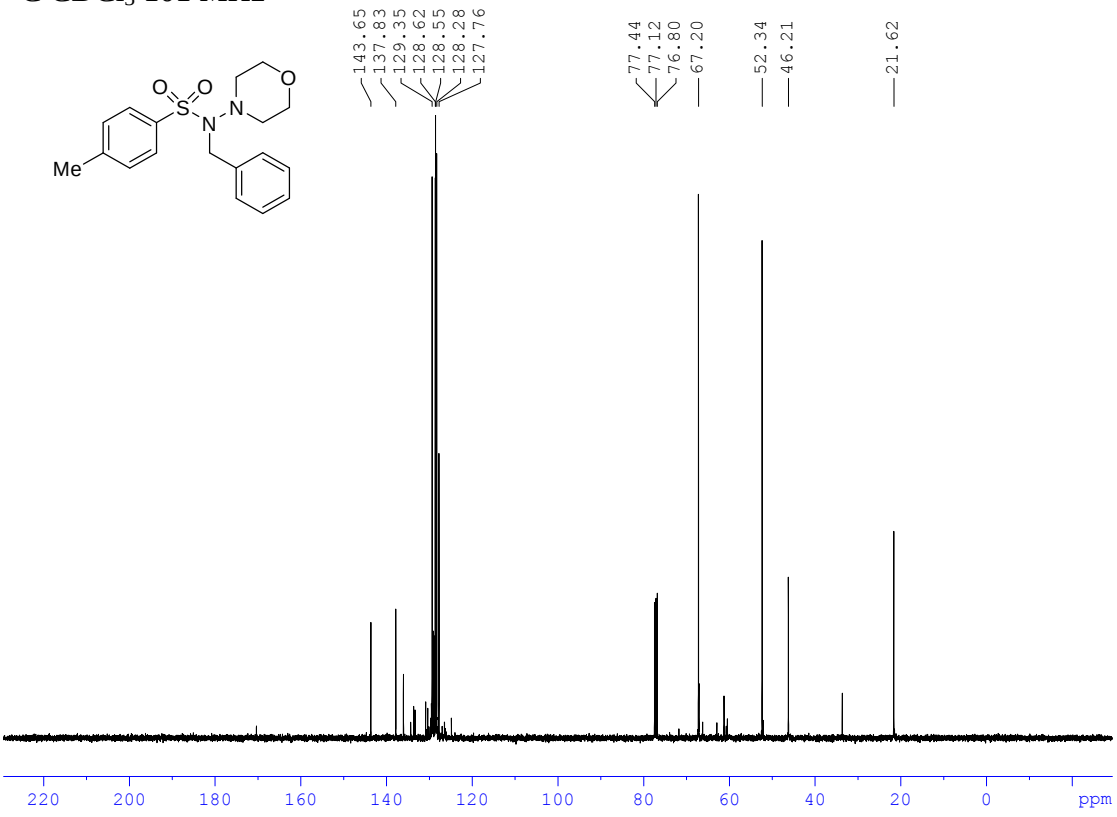


_N_-Benzyl-4-methyl-_N_-(morpholin-4-yl)benzenesulfonamide

^{1}H $CDCl_3$ 400 MHz

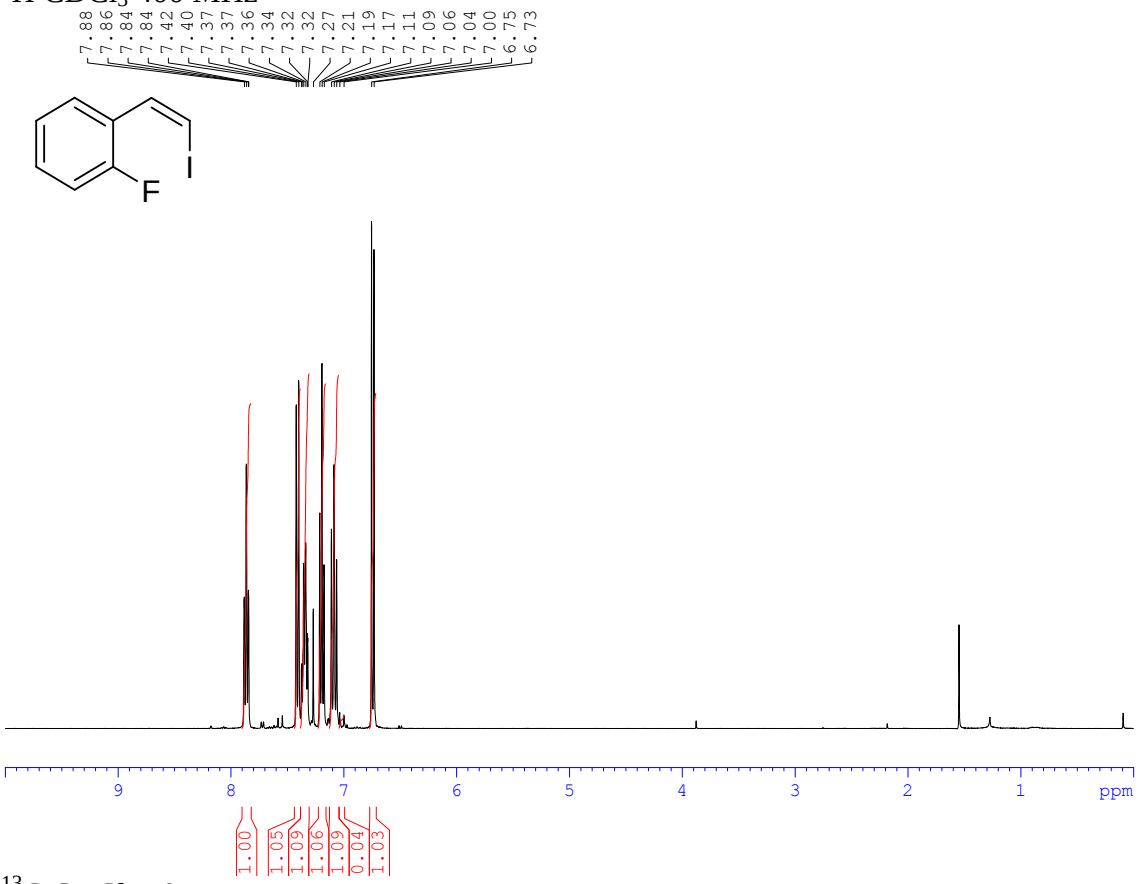


^{13}C $CDCl_3$ 101 MHz

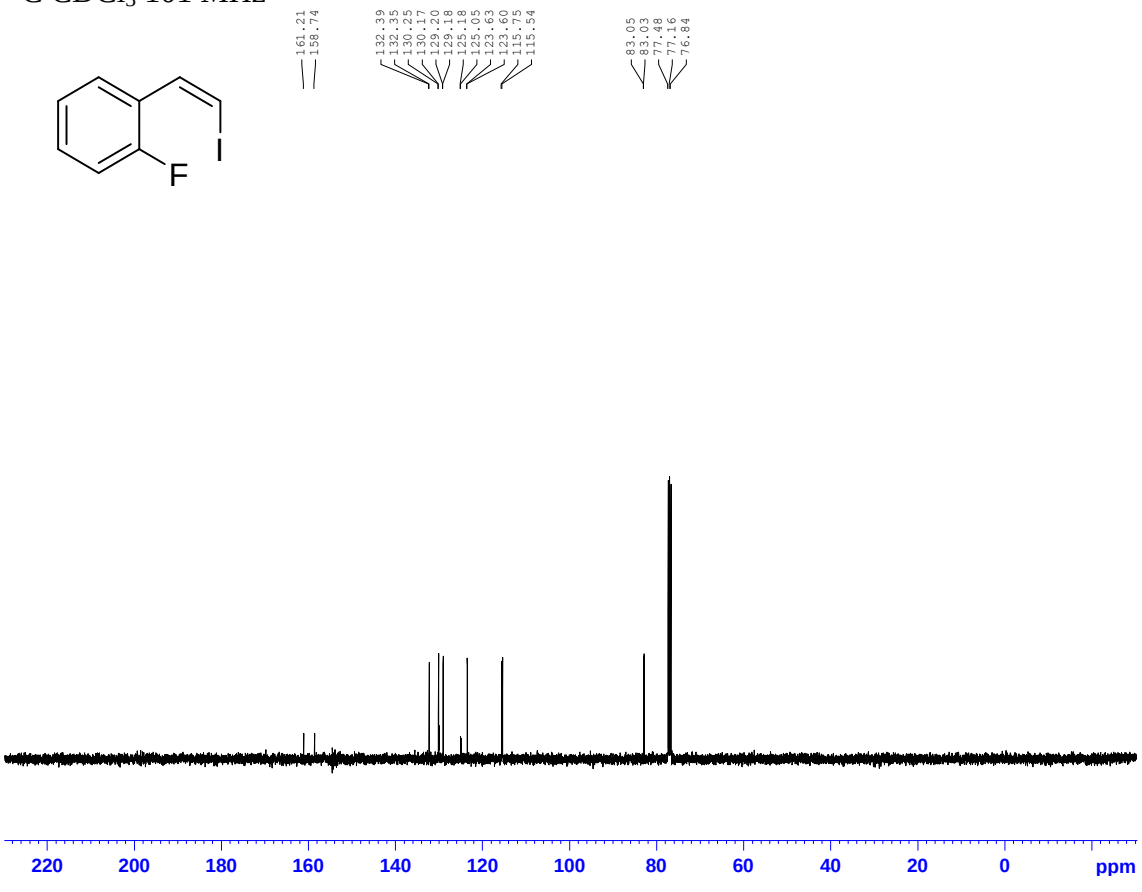


(*Z*)-1-Fluoro-2-(2-iodovinyl)benzene

^{1}H $CDCl_3$ 400 MHz

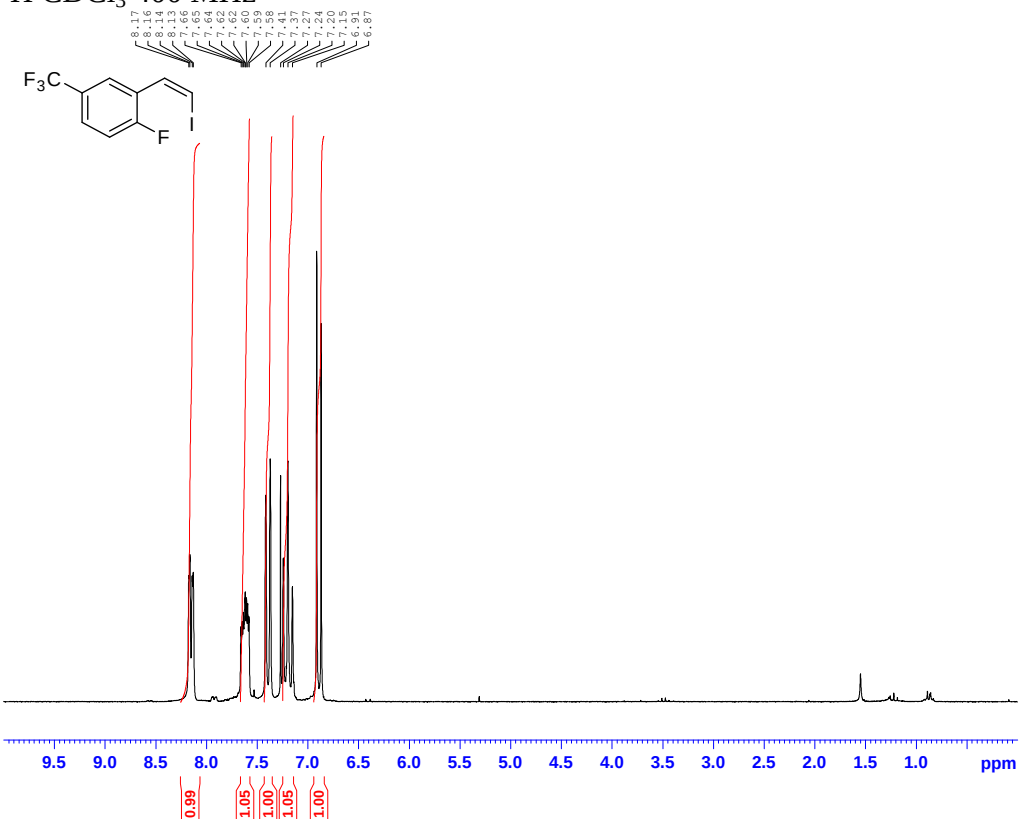


^{13}C $CDCl_3$ 101 MHz

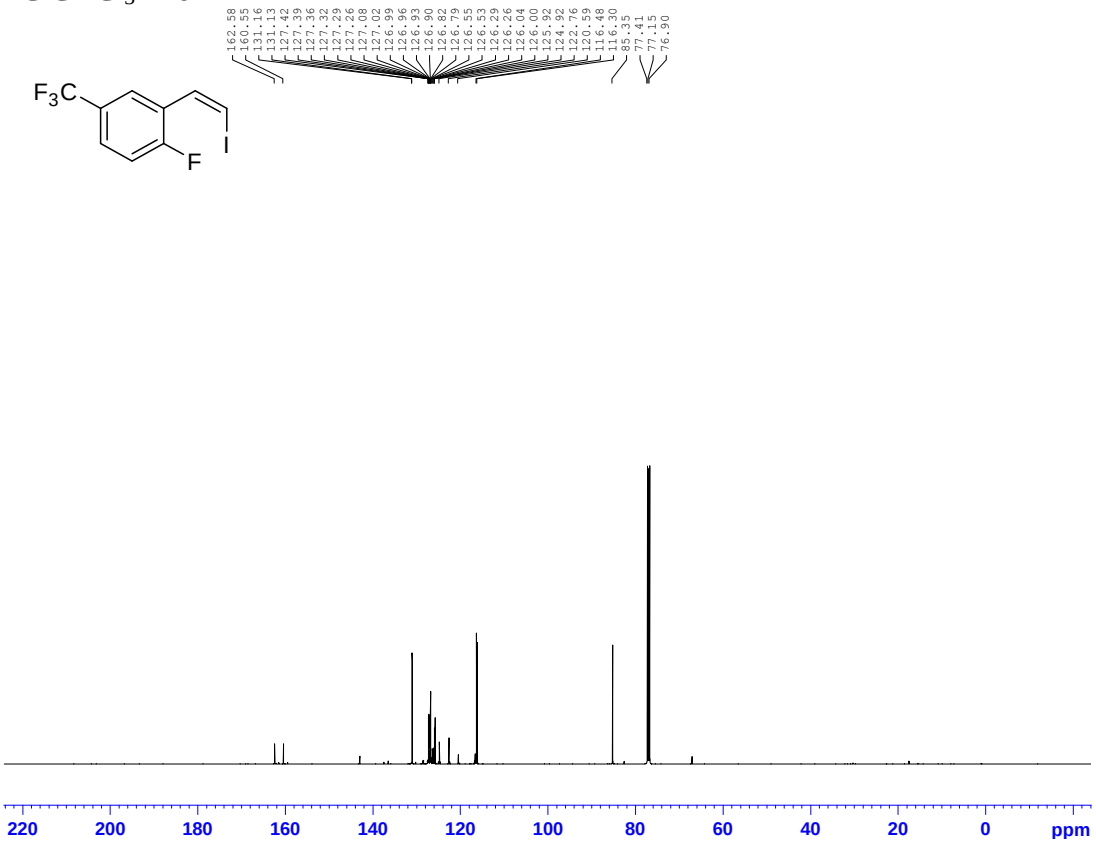


1-Fluoro-2-[(*Z*)-2-iodovinyl]-4-(trifluoromethyl)benzene

^{1}H $CDCl_3$ 400 MHz

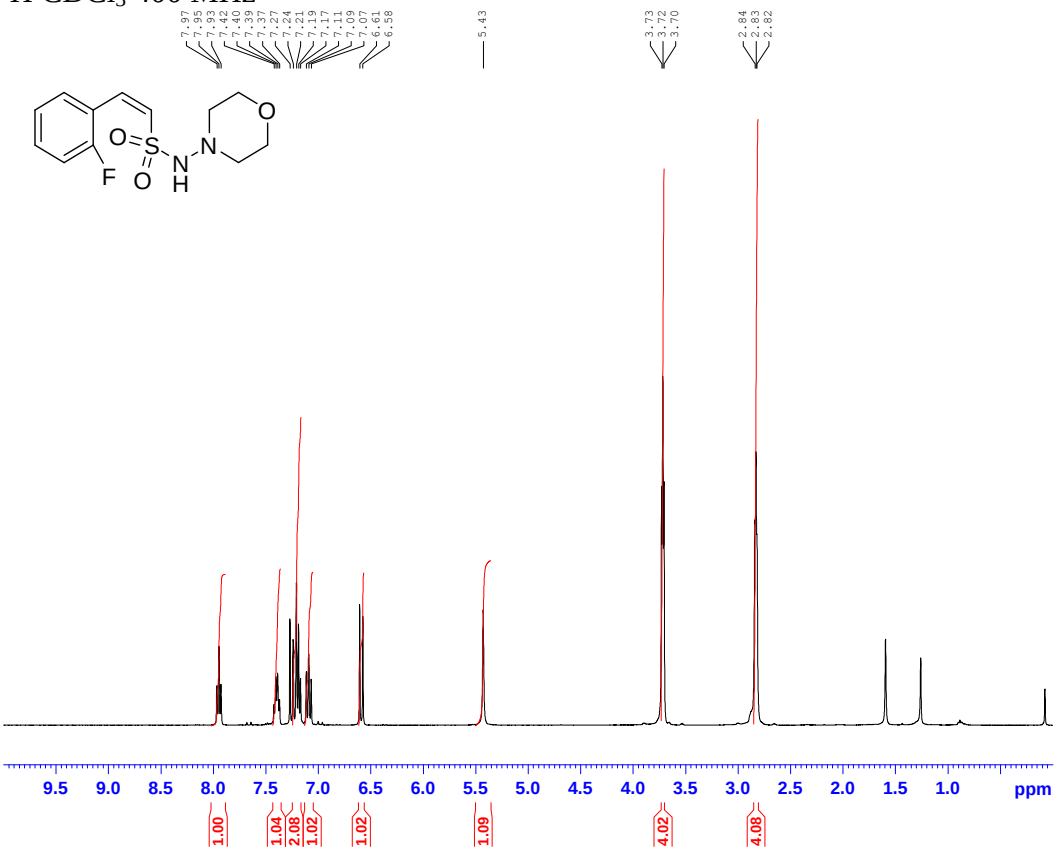


^{13}C $CDCl_3$ 126 MHz

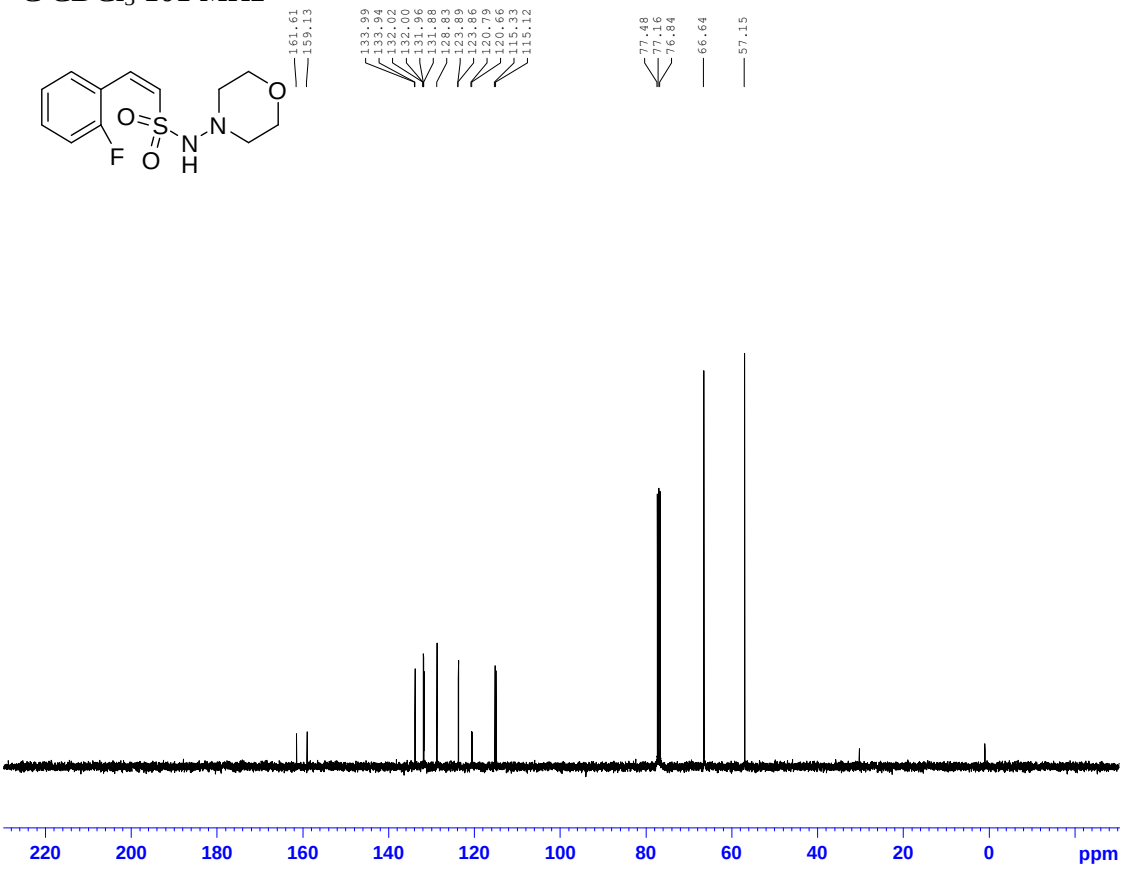


(*Z*)-2-(2-Fluorophenyl)-*N*-(morpholin-4-yl)ethenesulfonamide

^{1}H $CDCl_3$ 400 MHz

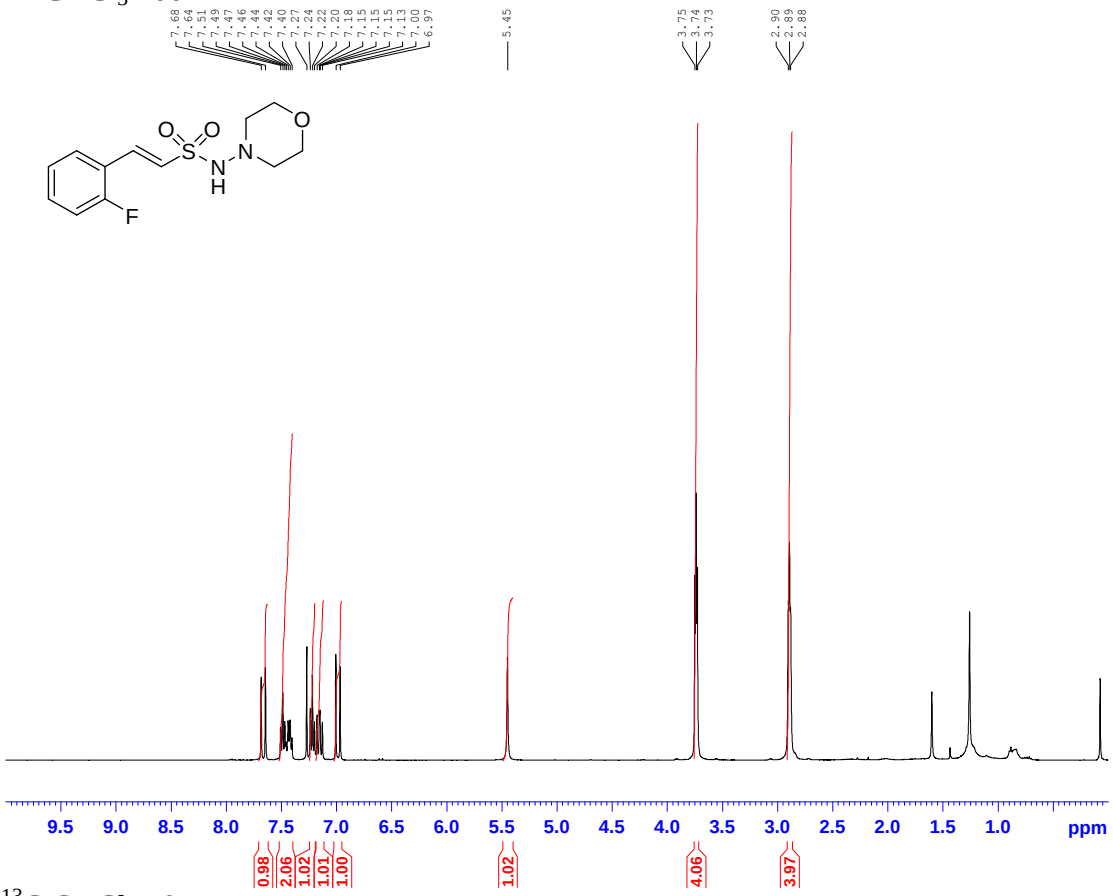


^{13}C $CDCl_3$ 101 MHz

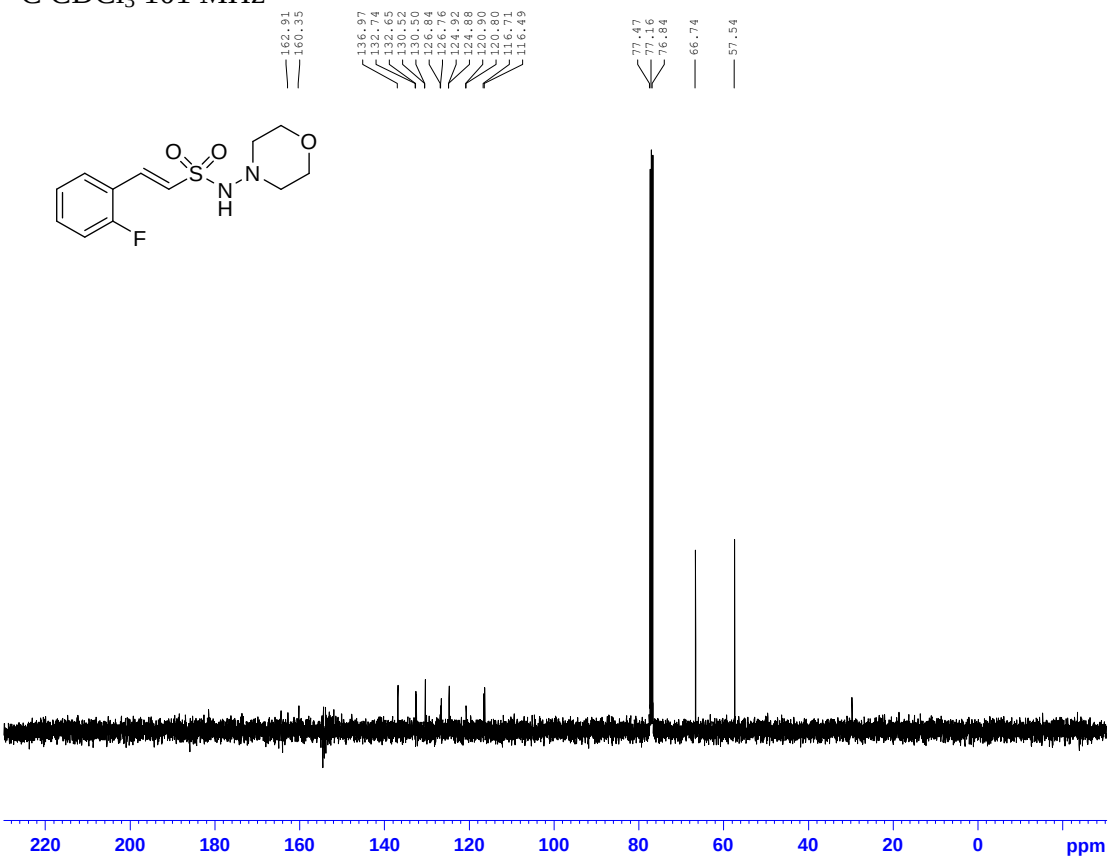


(*E*)-2-(2-Fluorophenyl)-*N*-(morpholin-4-yl)ethenesulfonamide

^{1}H $CDCl_3$ 400 MHz

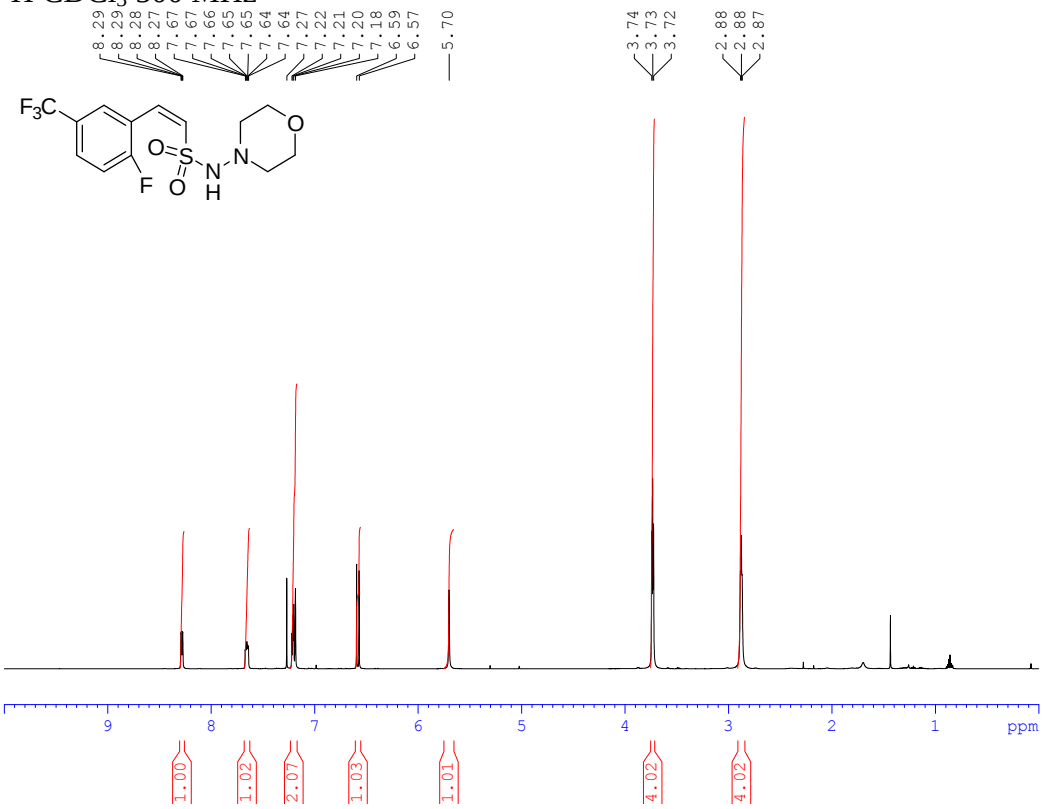


^{13}C $CDCl_3$ 101 MHz

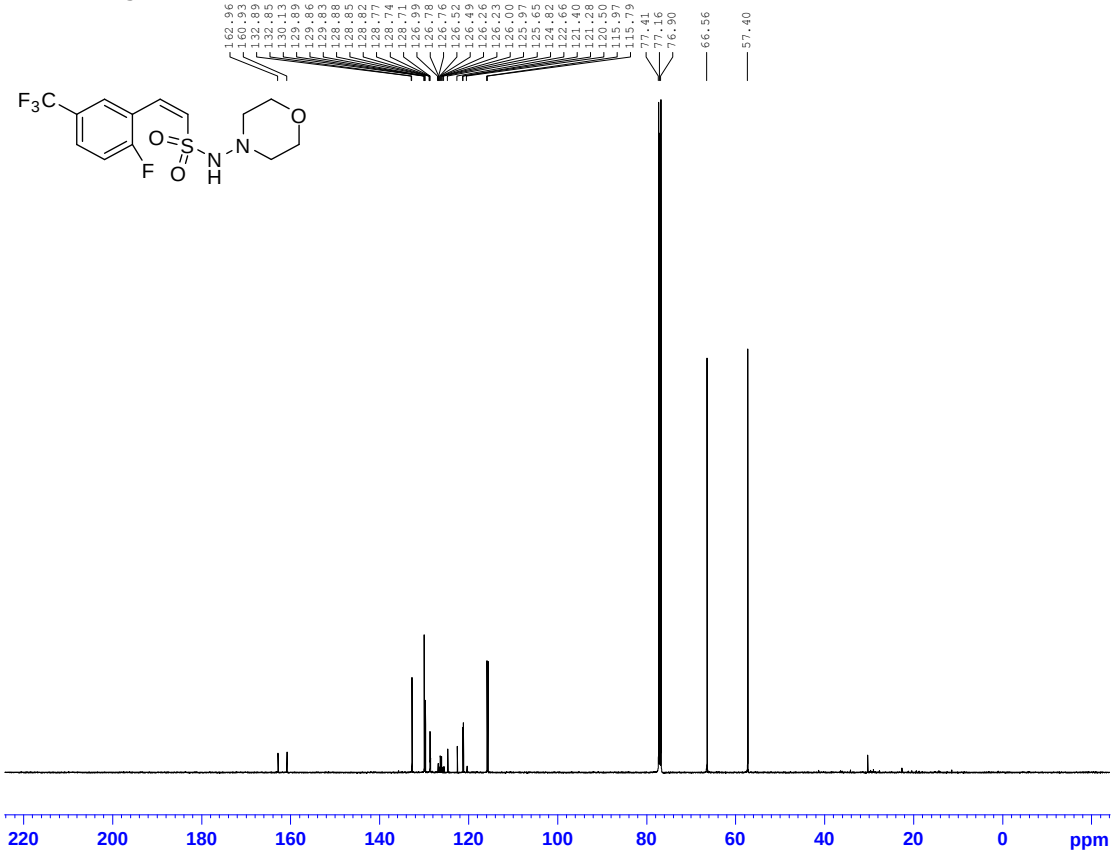


(*Z*)-2-[2-Fluoro-5-(trifluoromethyl)phenyl]-*N*-(morpholin-4-yl)ethenesulfonamide

^{1}H $CDCl_3$ 500 MHz



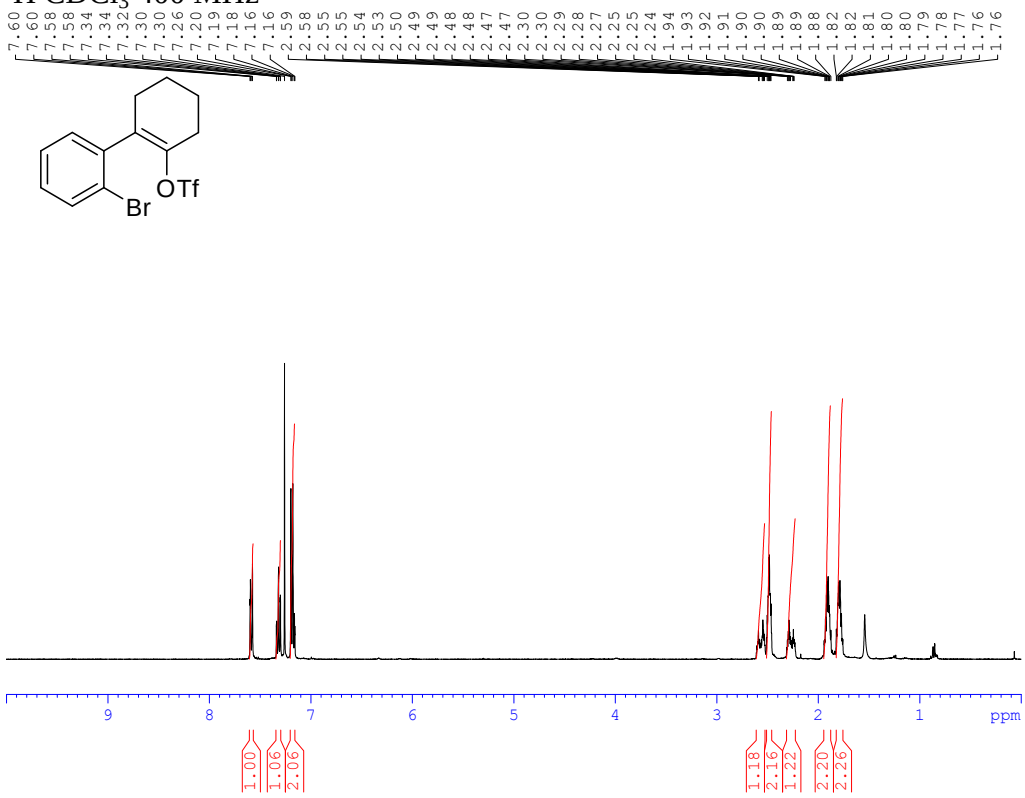
^{13}C $CDCl_3$ 126 MHz



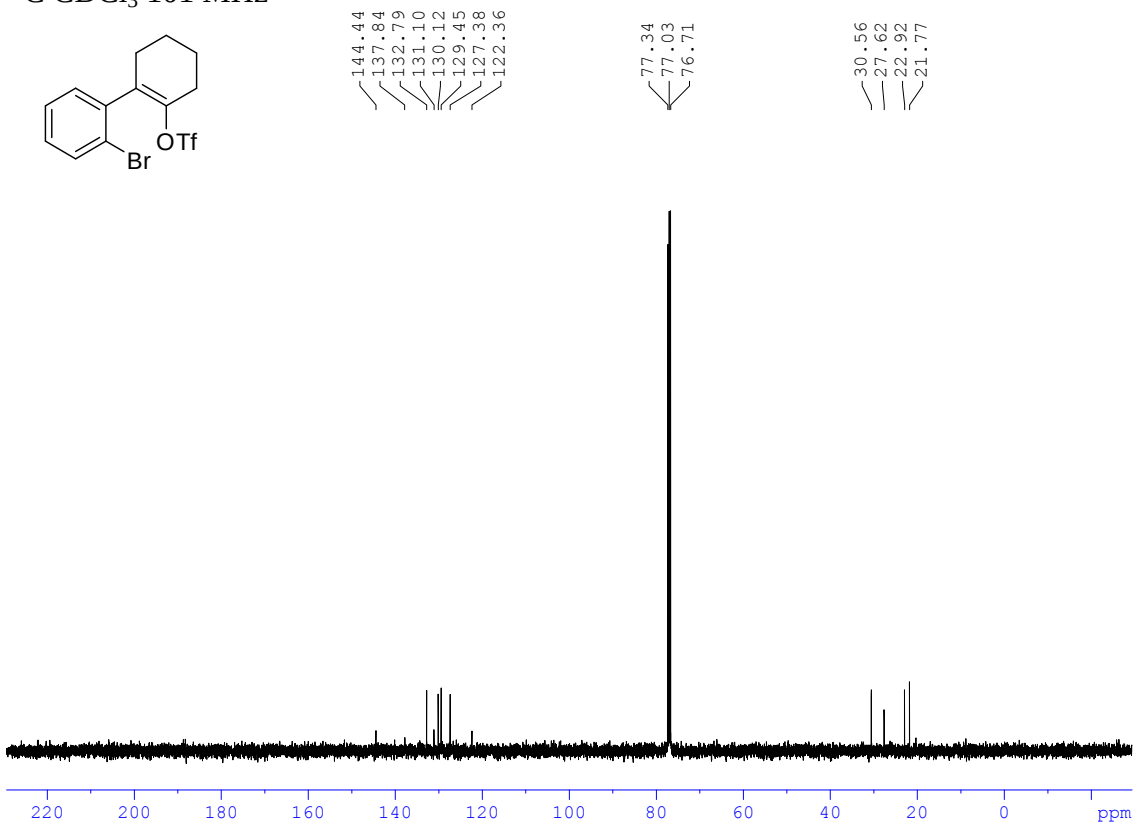
B.2 Synthesis of benzosultam: Aryl-N-SO_2 linkage

2'-Bromo-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate

^{1}H $CDCl_3$ 400 MHz

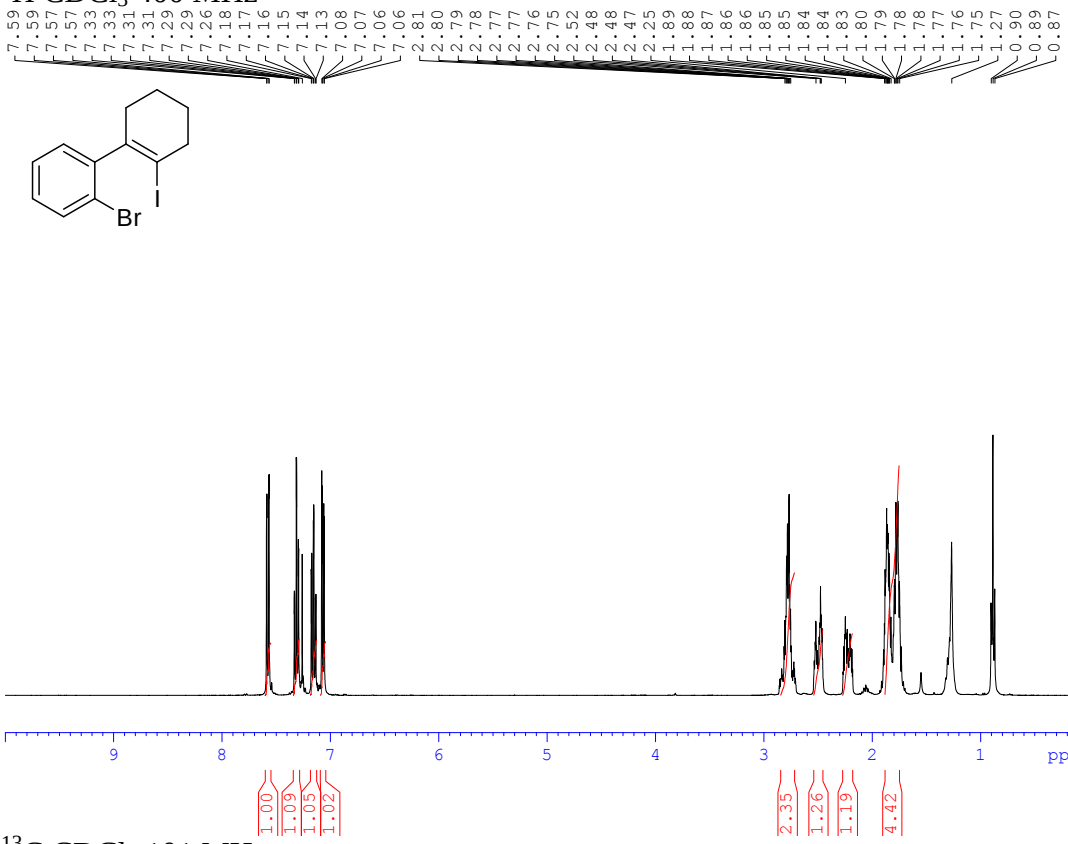


^{13}C $CDCl_3$ 101 MHz

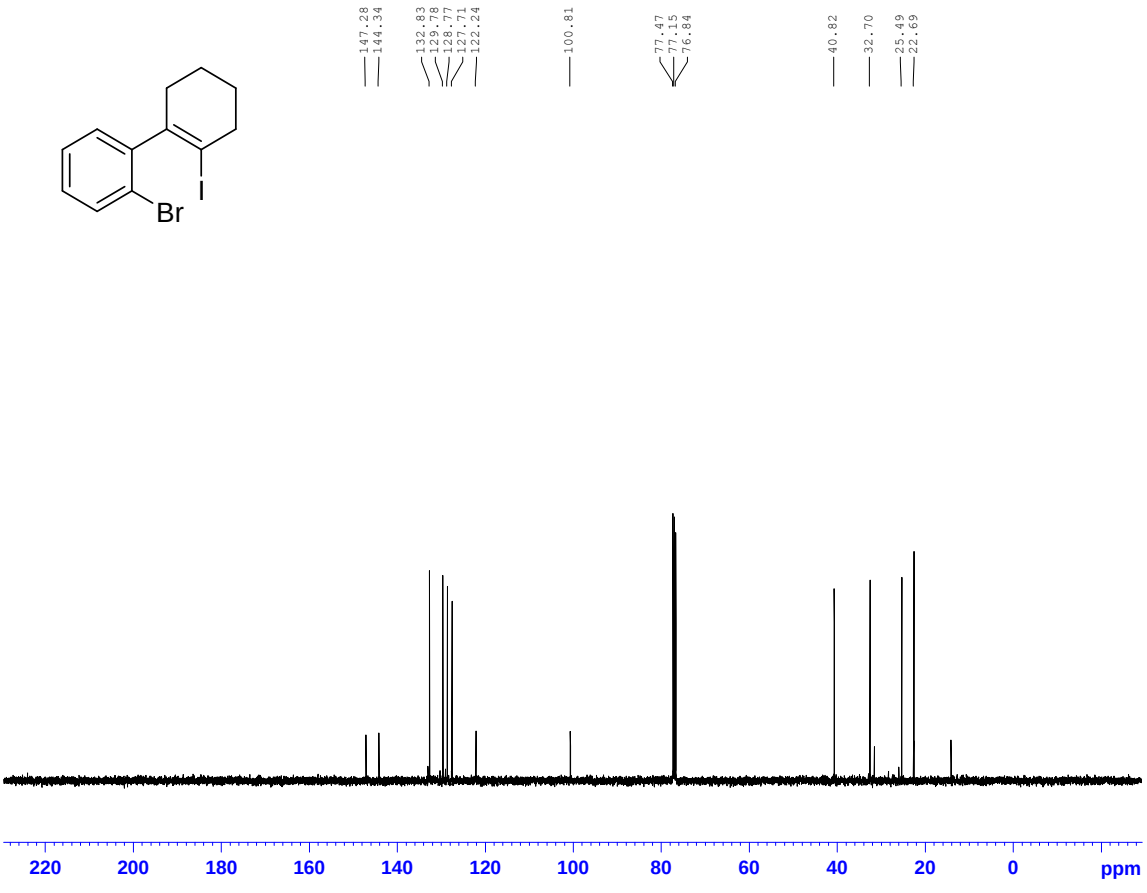


2'-Bromo-6-iodo-2,3,4,5-tetrahydro-1,1'-biphenyl

^{1}H $CDCl_3$ 400 MHz

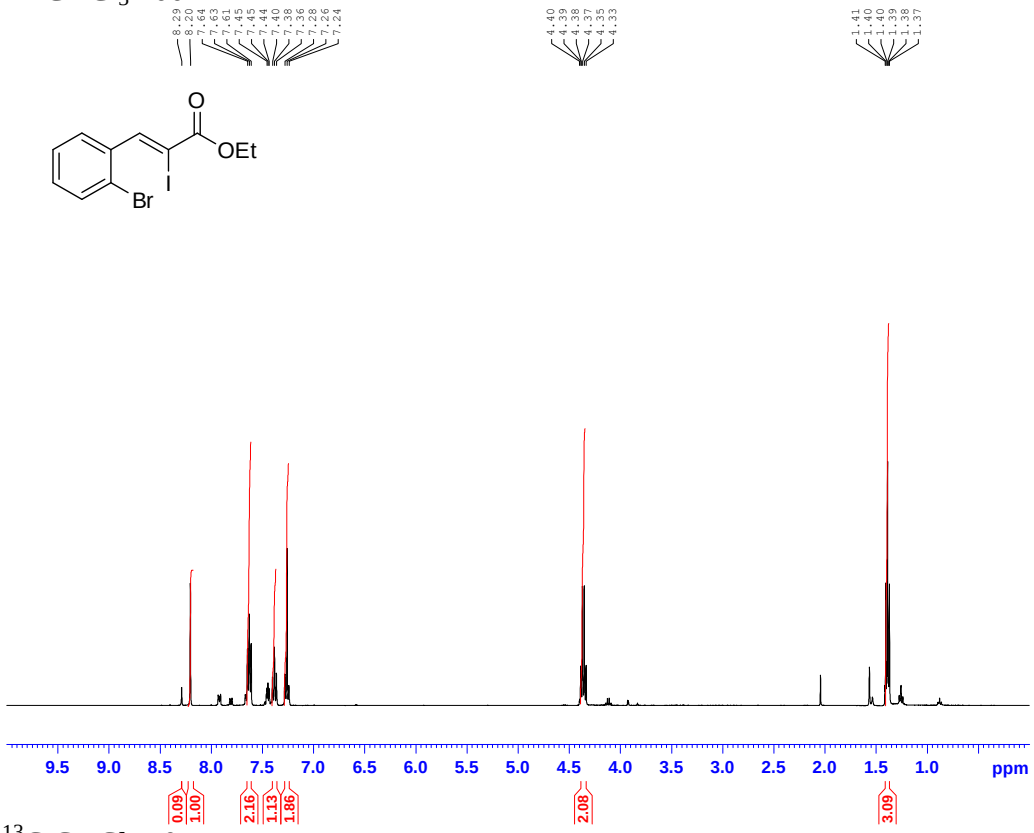


^{13}C $CDCl_3$ 101 MHz

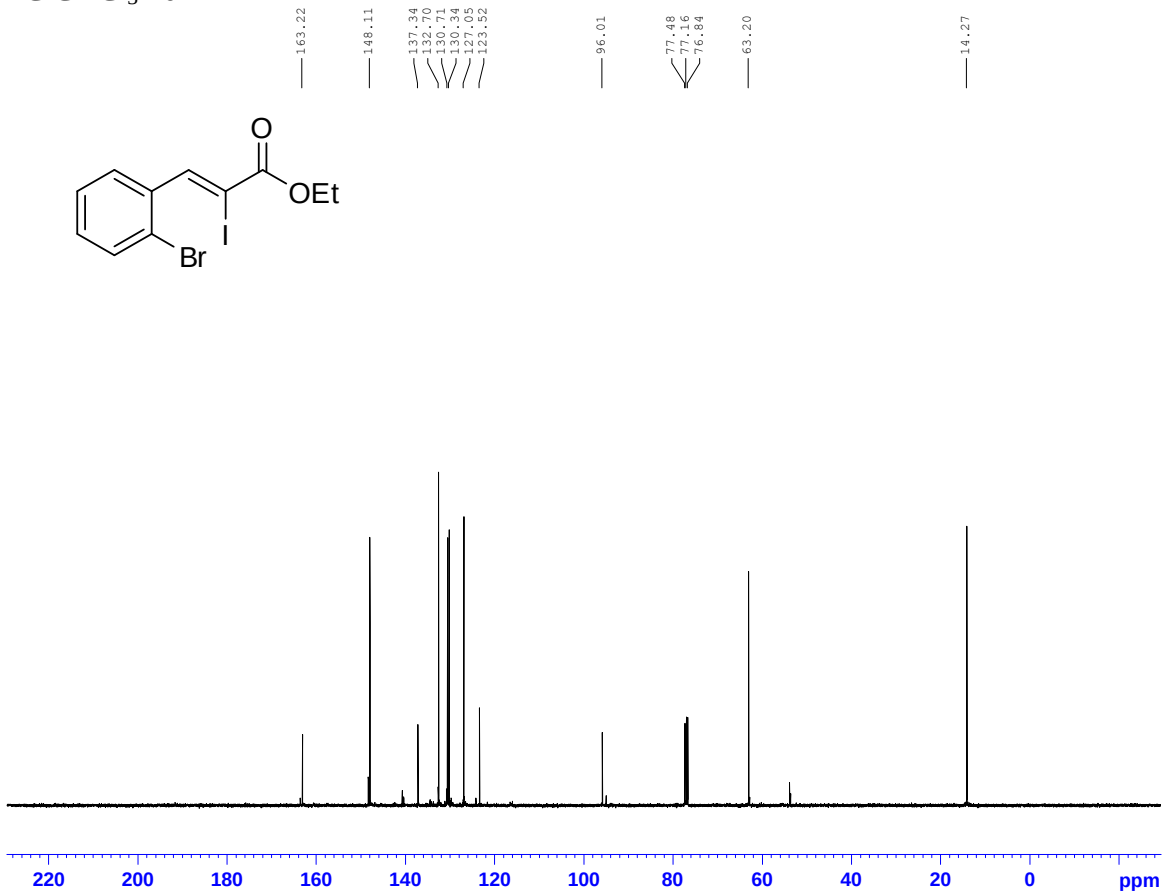


Ethyl 3-(2-bromophenyl)-2-iodoacrylate

^{1}H $CDCl_3$ 400 MHz

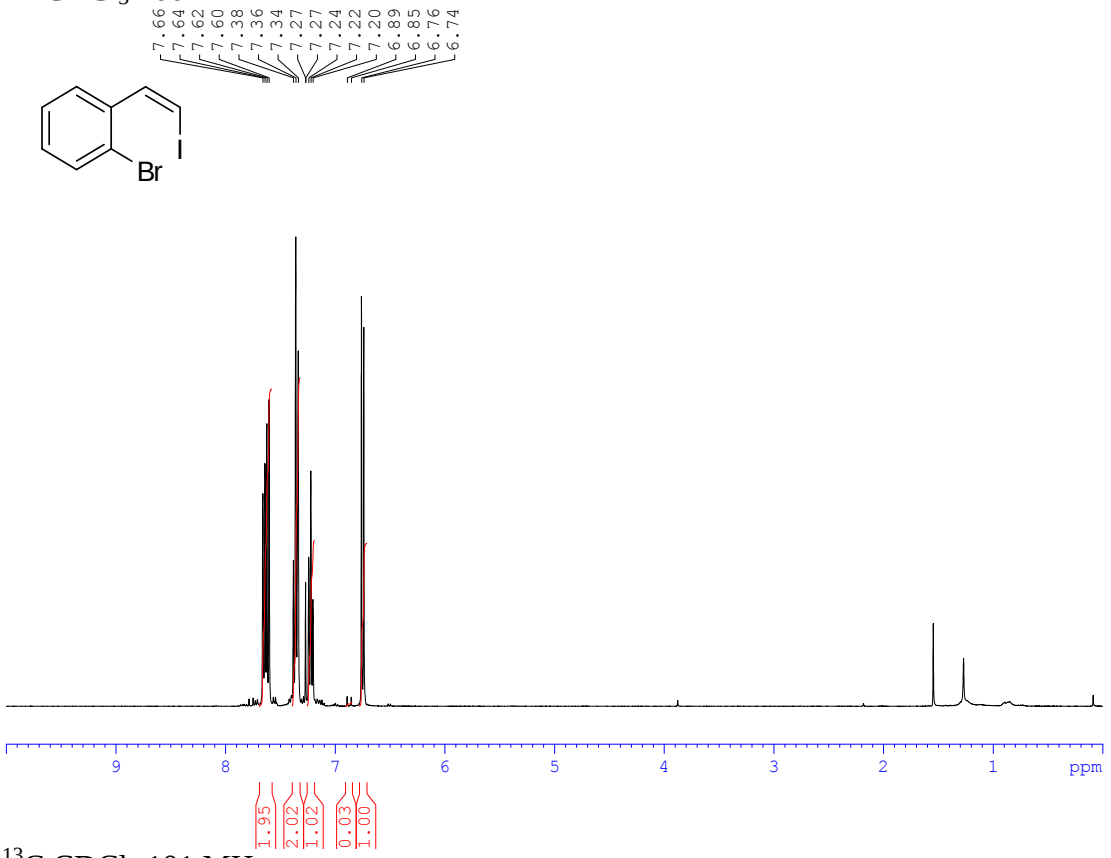


^{13}C $CDCl_3$ 101 MHz

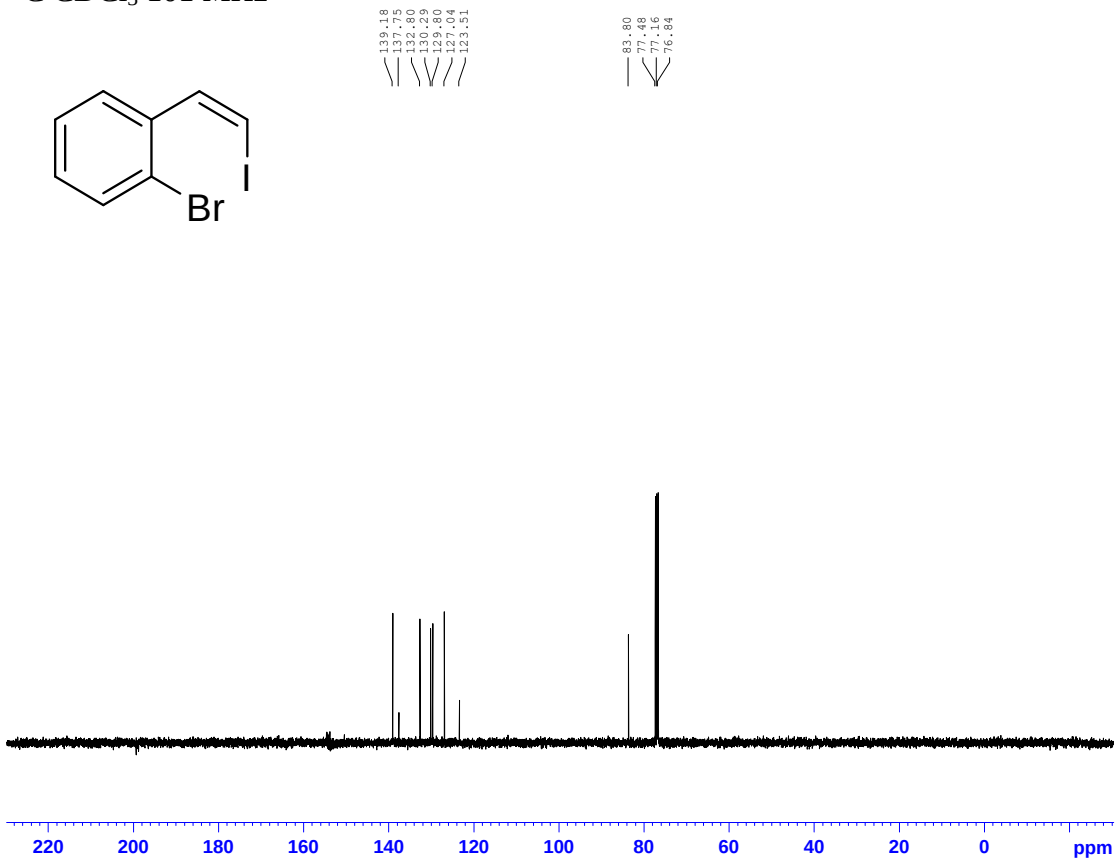


(*Z*)-1-Bromo-2-(2-iodovinyl)benzene

^{1}H $CDCl_3$ 400 MHz

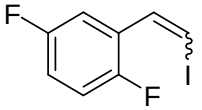


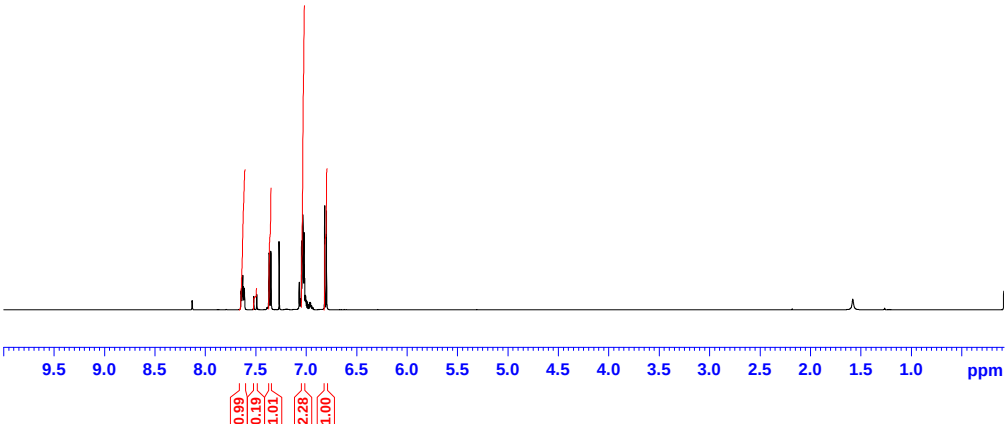
^{13}C $CDCl_3$ 101 MHz



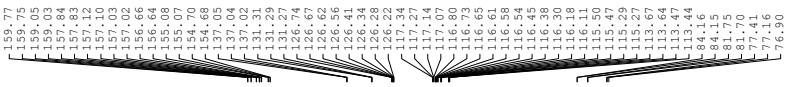
1,4-Difluoro-2-[(*Z*)-2-iodovinyl]benzene

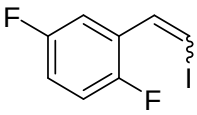
^{1}H $(CD_3)_2SO$ 500 MHz

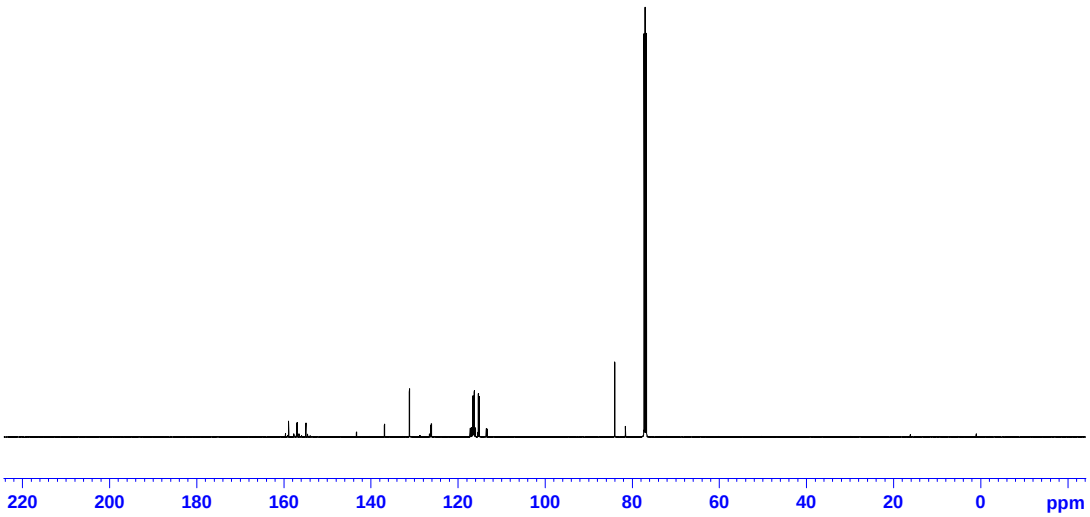




^{13}C $CDCl_3$ 126 MHz

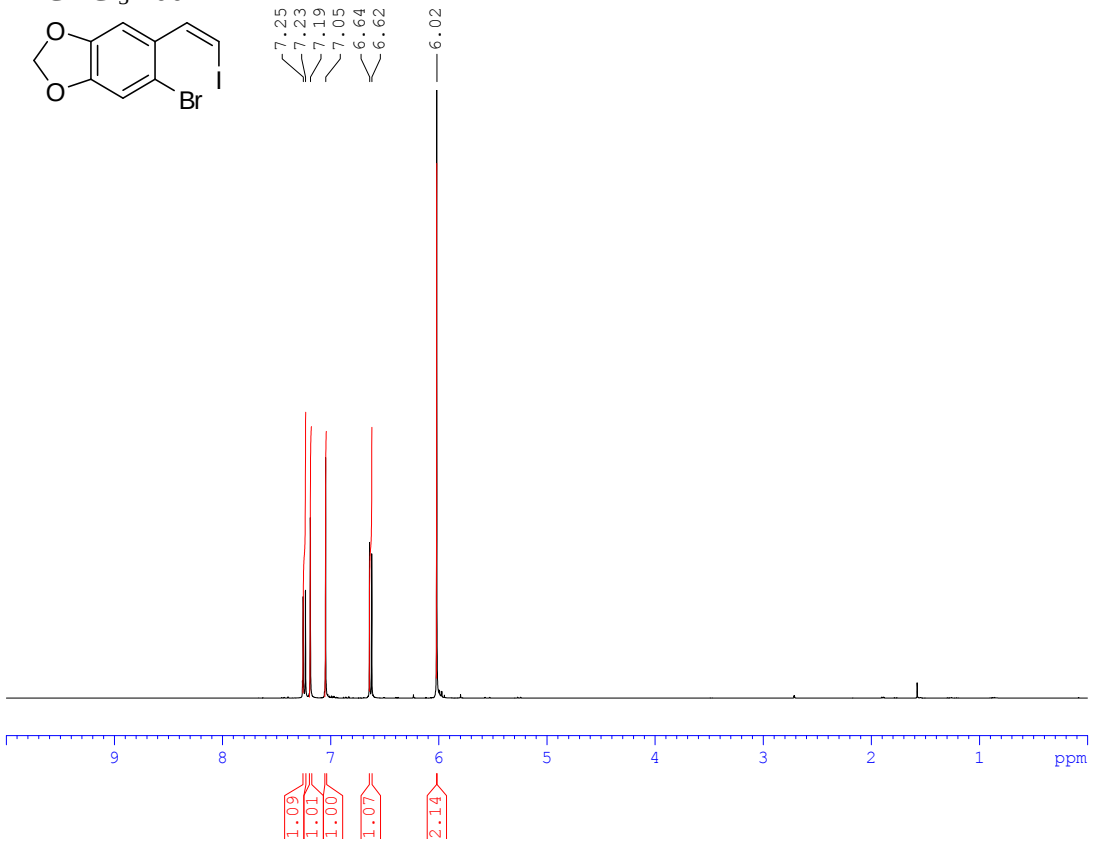




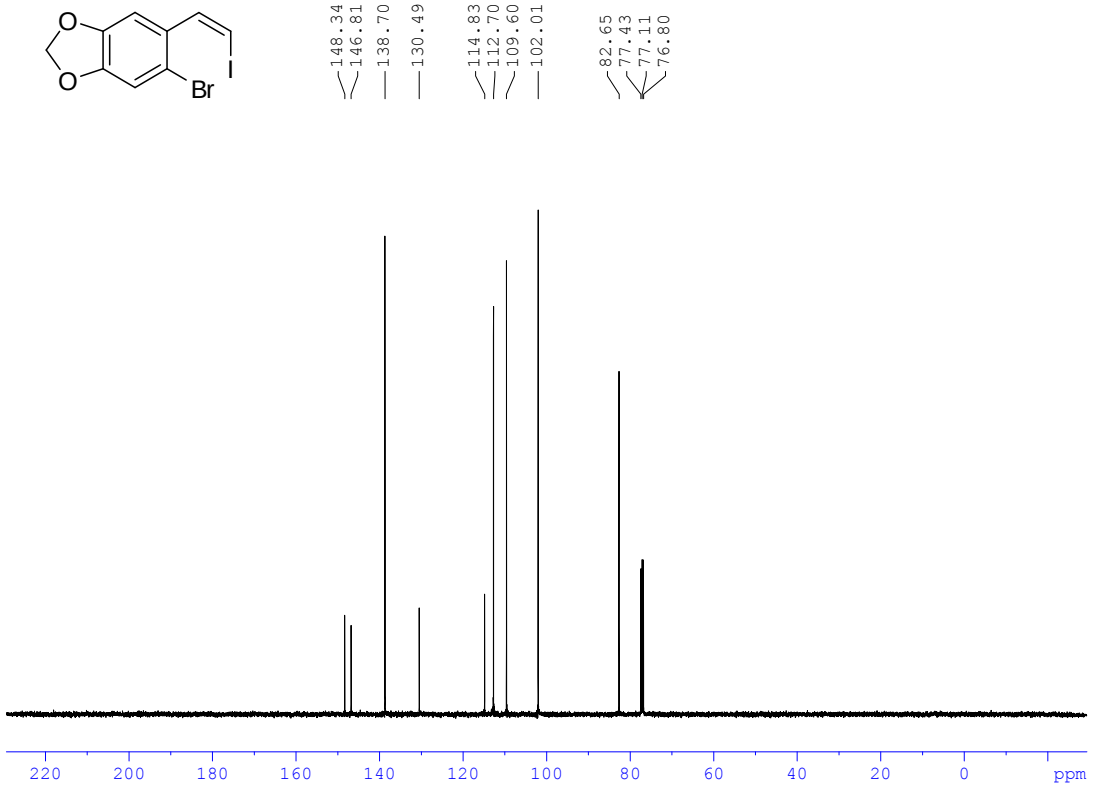


(Z)-5-Bromo-6-(2-iodovinyl)benzo[d][1,3]dioxole

^{1}H $CDCl_3$ 400 MHz

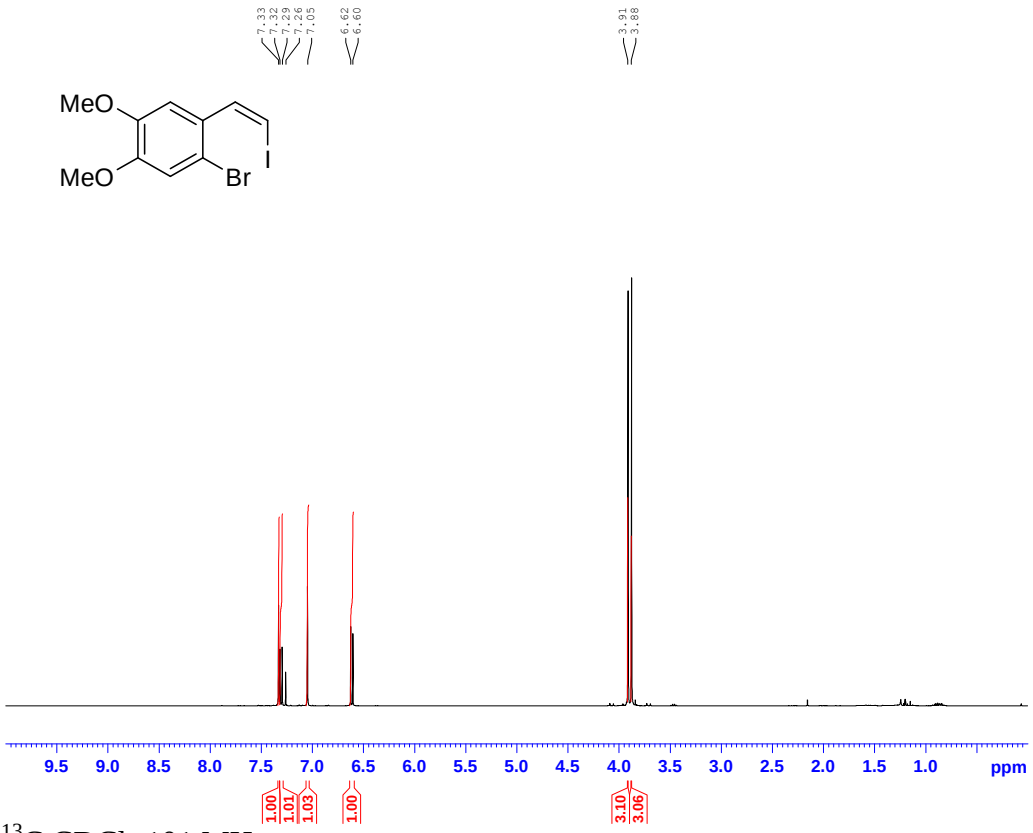


^{13}C $CDCl_3$ 101 MHz

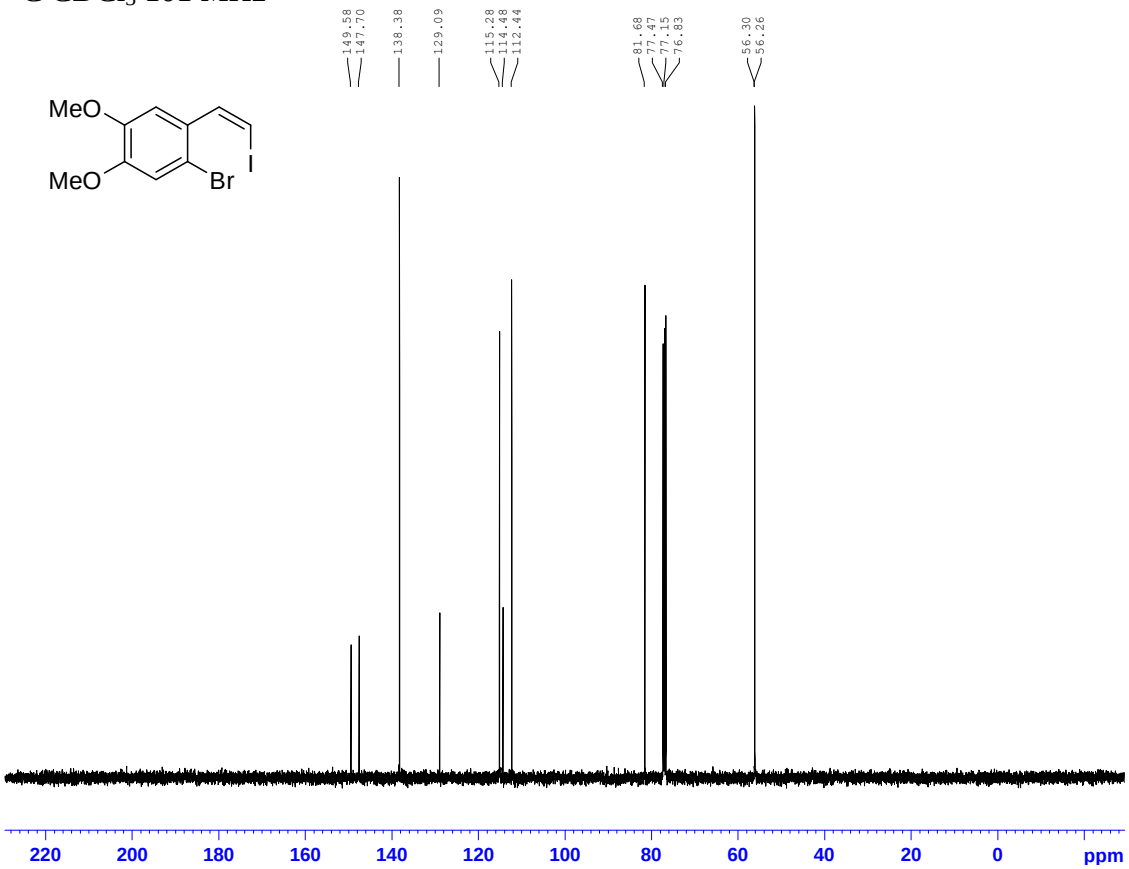


(*Z*)-1-Bromo-2-(2-iodovinyl)-4,5-dimethoxybenzene

^{1}H $CDCl_3$ 400 MHz

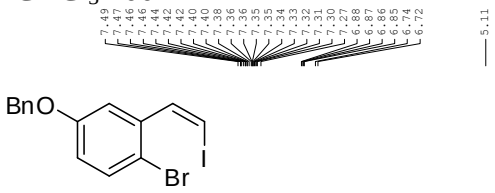


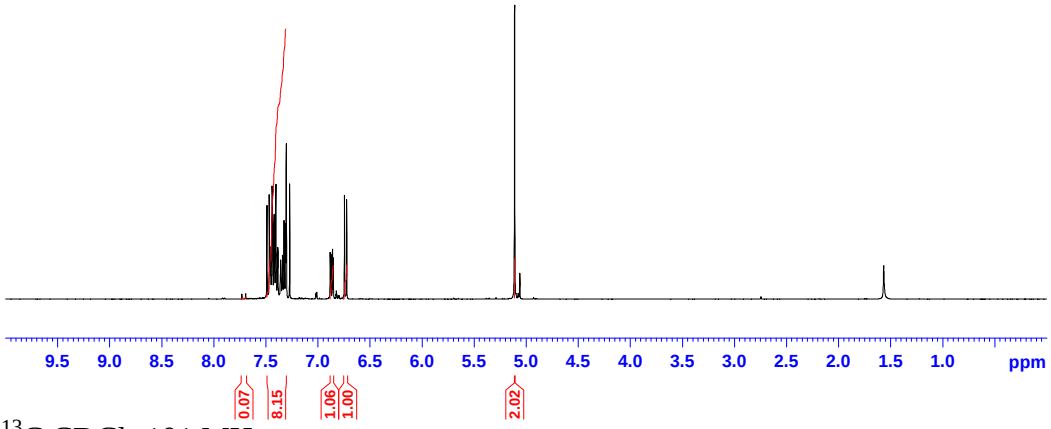
^{13}C $CDCl_3$ 101 MHz



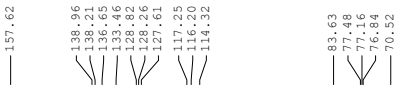
(Z)-4-(Benzyloxy)-1-bromo-2-(2-iodovinyl)benzene

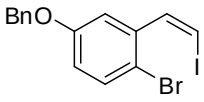
^{1}H $CDCl_3$ 400 MHz

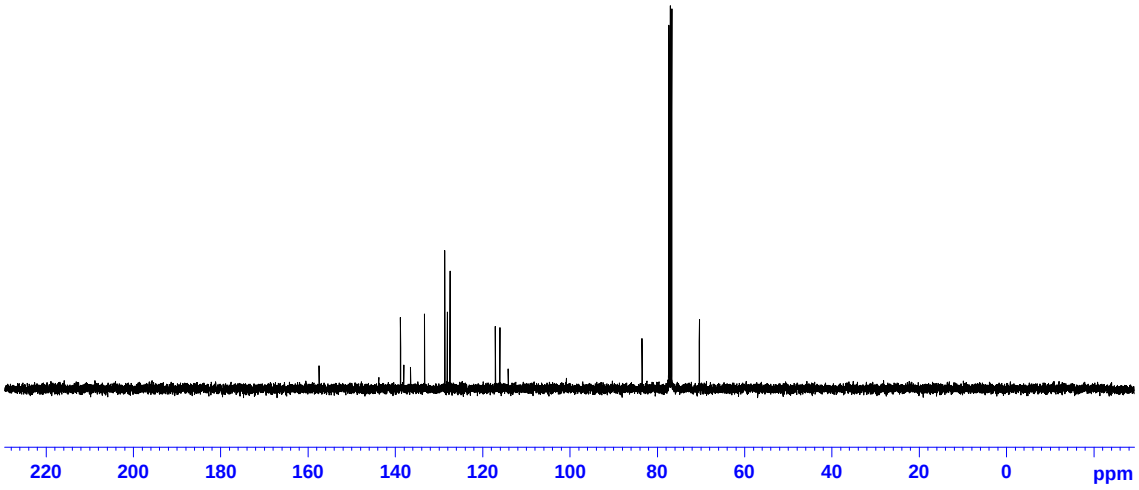




^{13}C $CDCl_3$ 101 MHz

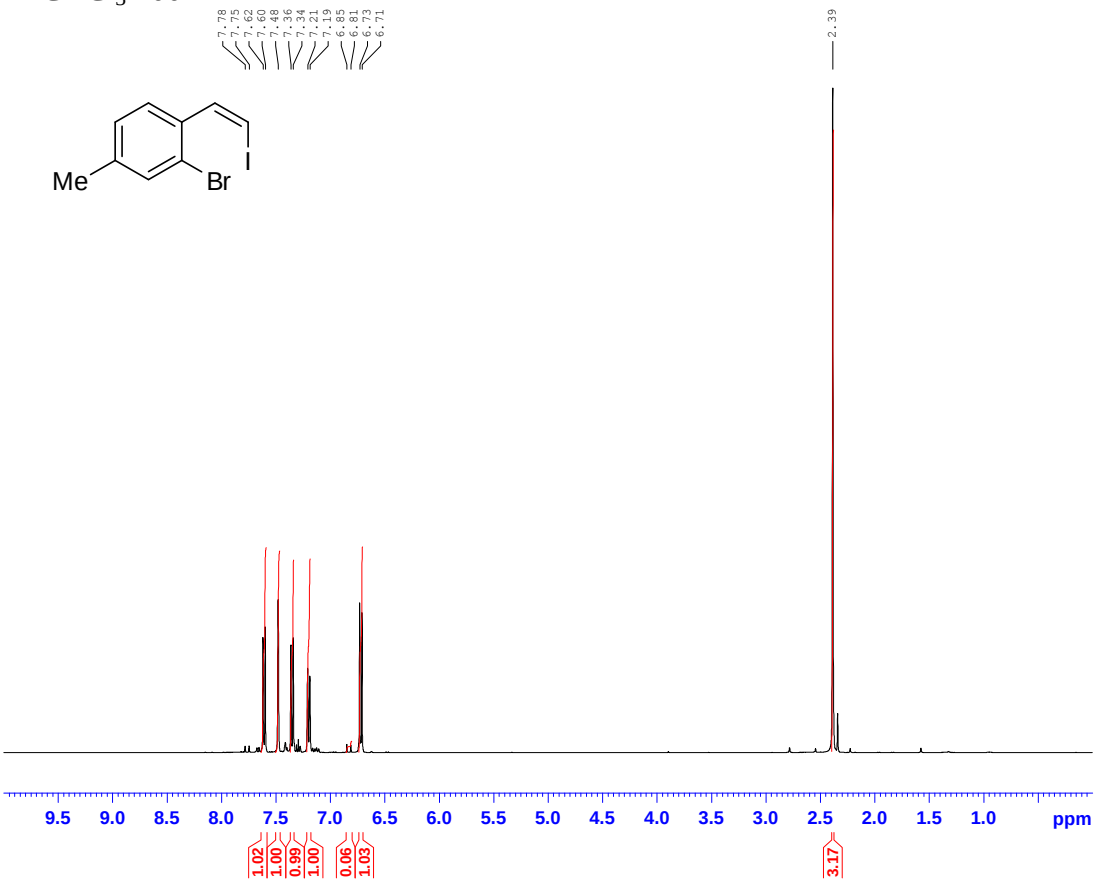




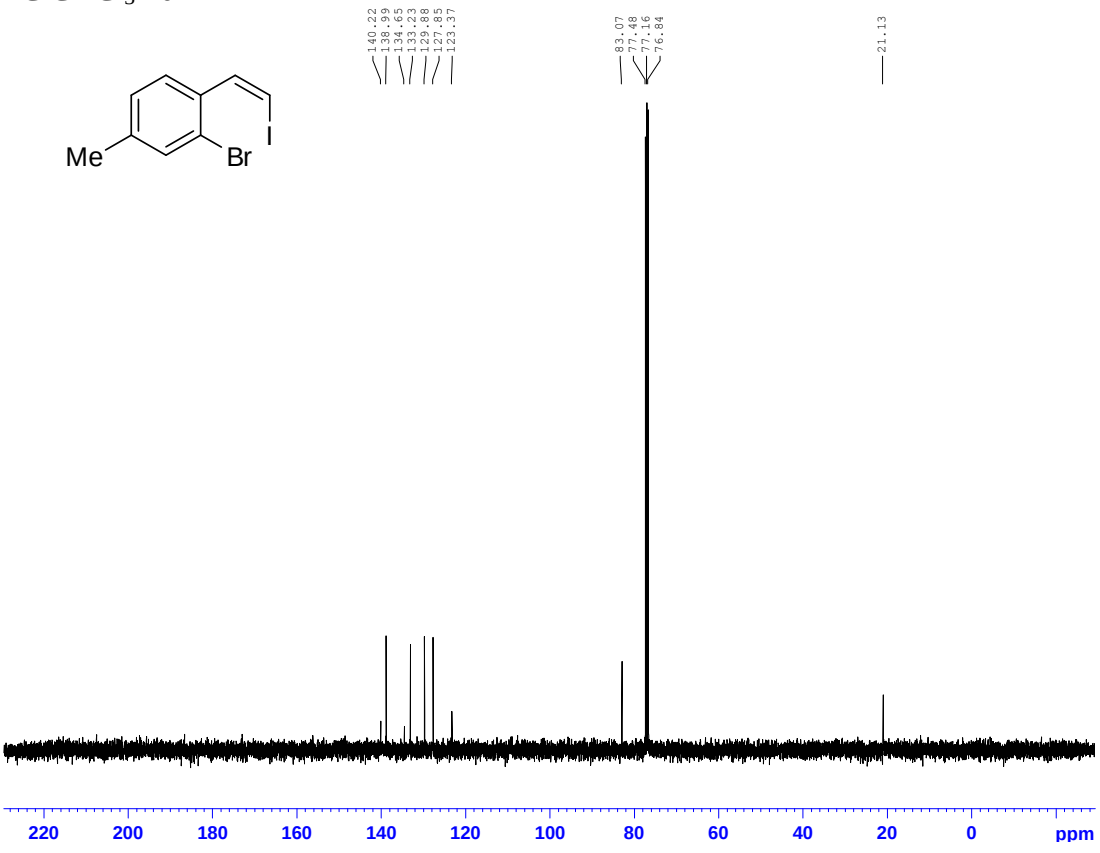


(*Z*)-2-Bromo-1-(2-iodovinyl)-4-methylbenzene

^{1}H $CDCl_3$ 400 MHz

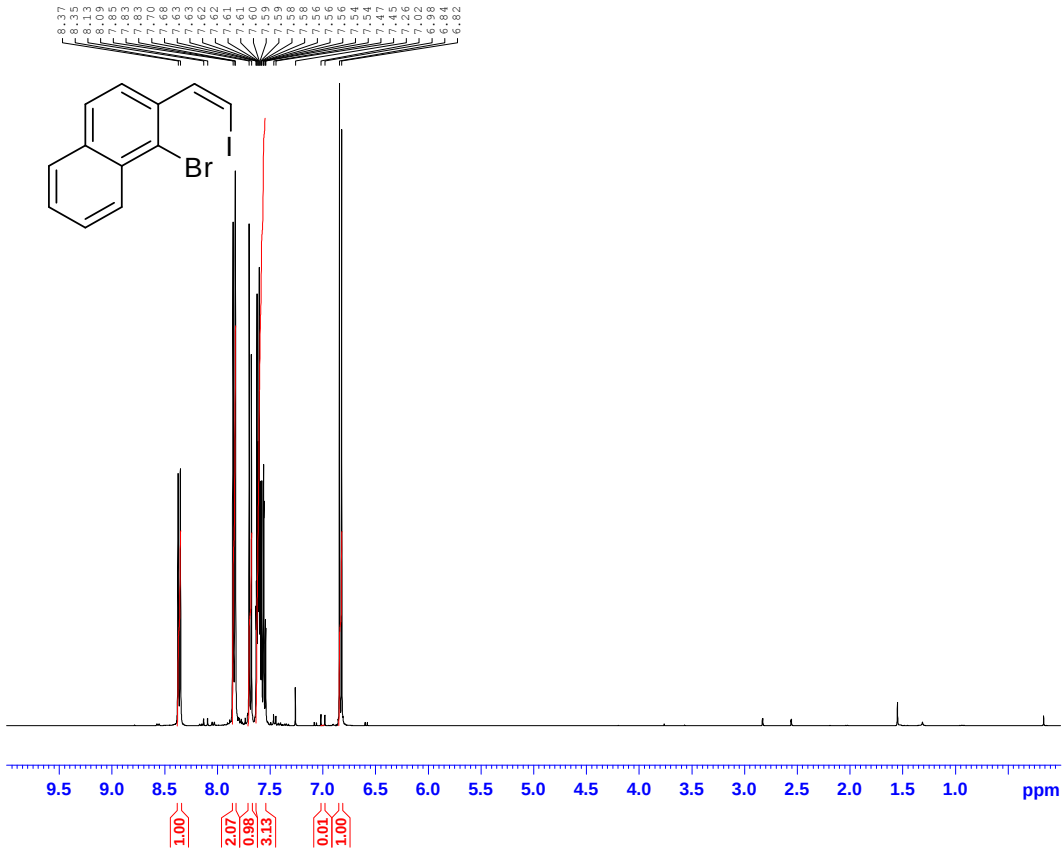


^{13}C $CDCl_3$ 101 MHz

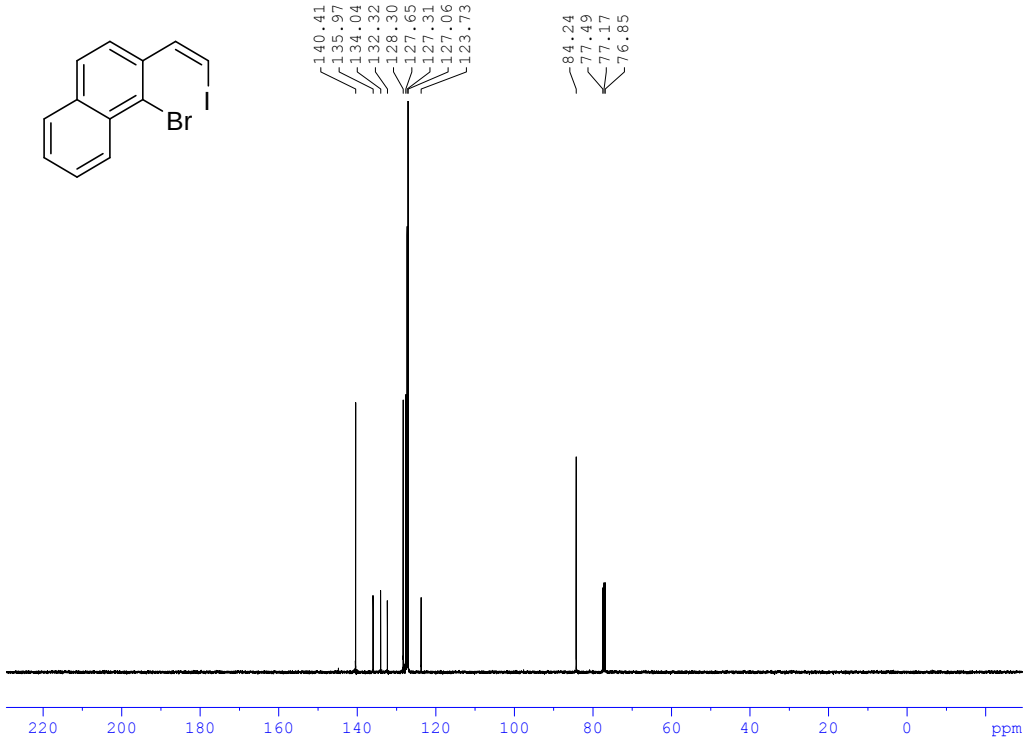


(*Z*)-1-Bromo-2-(2-iodovinyl)naphthalene

^{1}H $CDCl_3$ 400 MHz

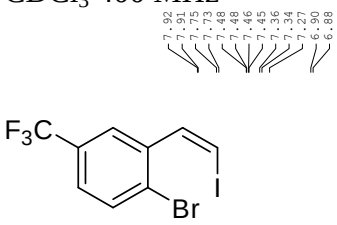


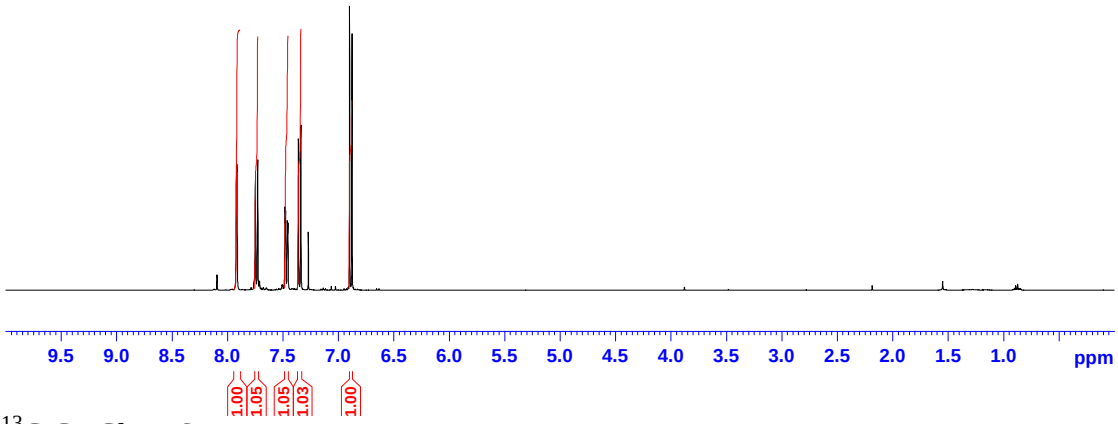
^{13}C $CDCl_3$ 101 MHz



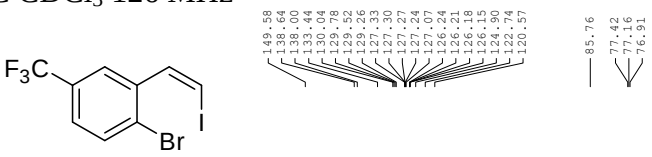
(*Z*)-1-Bromo-2-(2-iodovinyl)-4-(trifluoromethyl)benzene

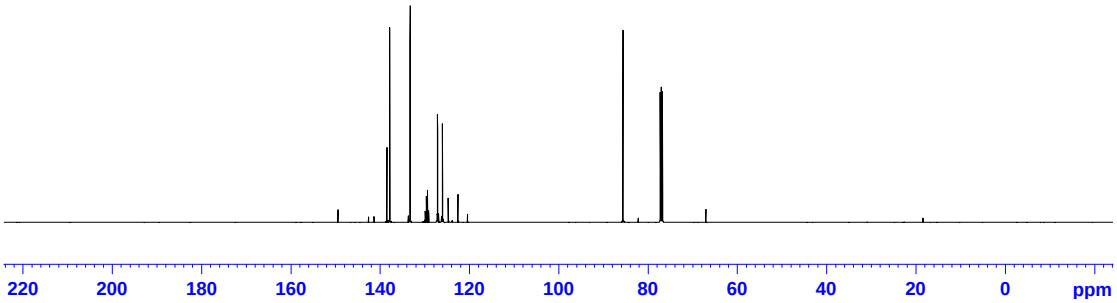
^{1}H $CDCl_3$ 400 MHz





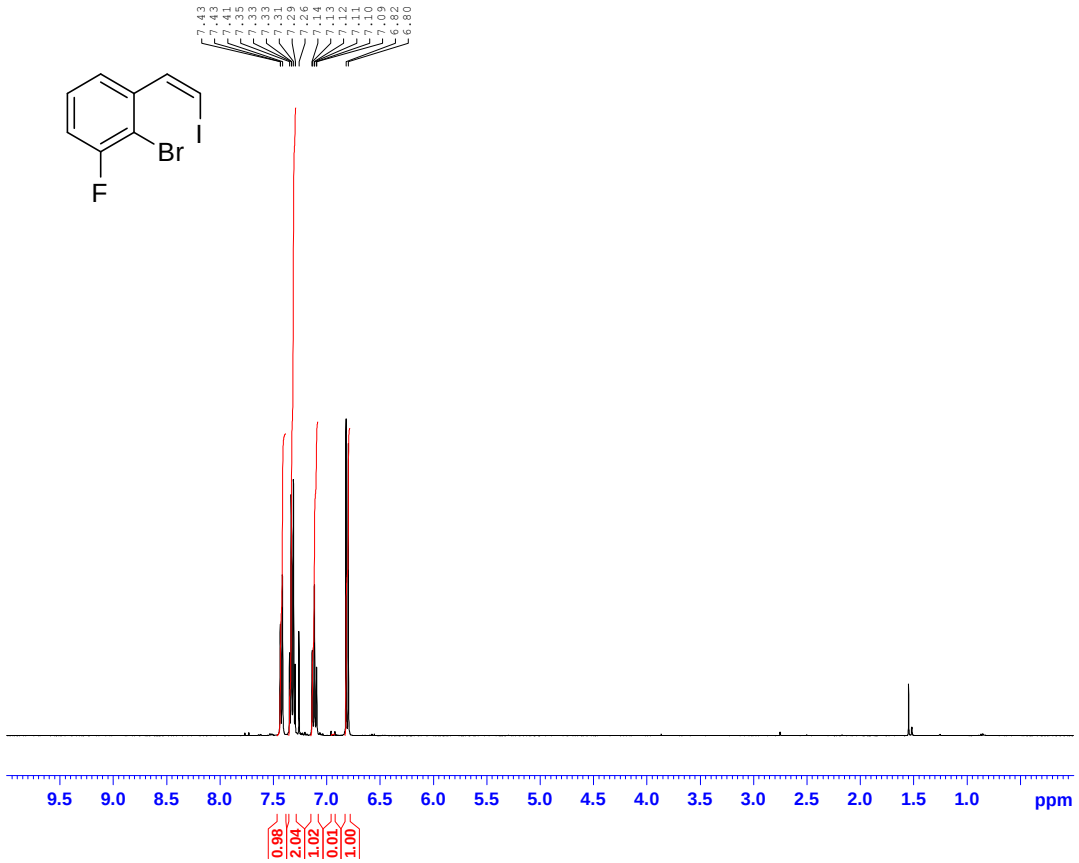
^{13}C $CDCl_3$ 126 MHz



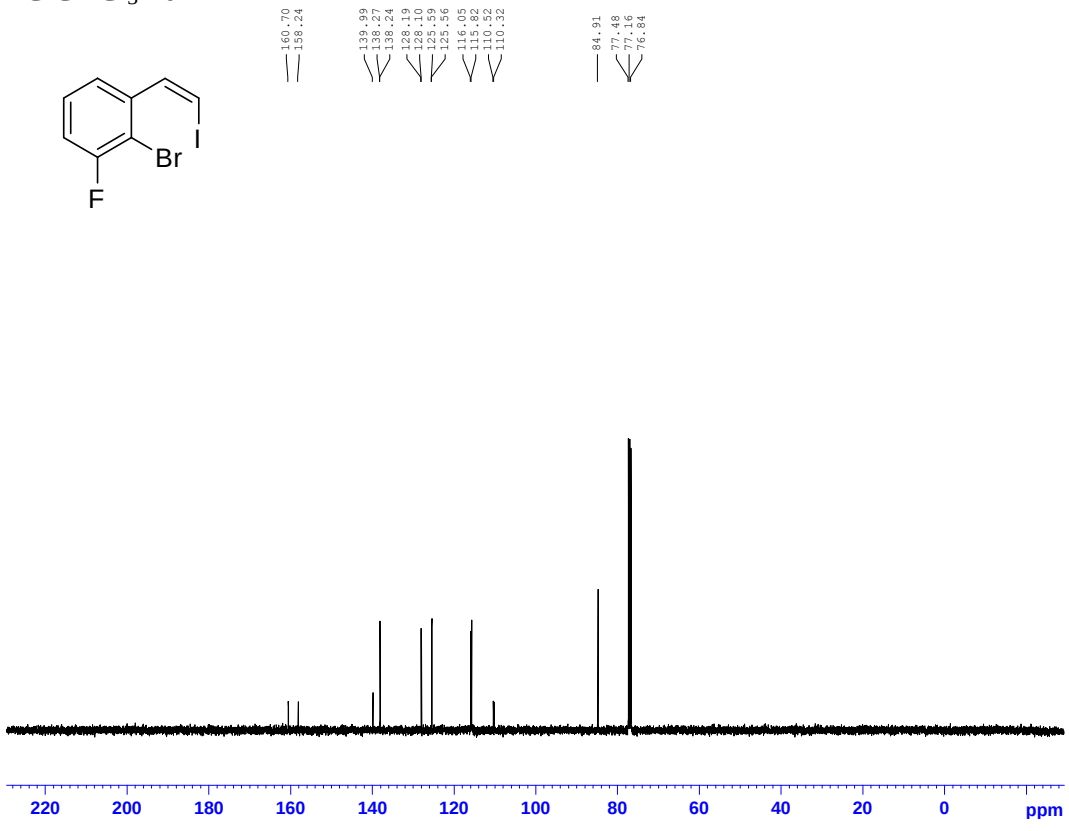


(*Z*)-2-Bromo-1-fluoro-3-(2-iodovinyl)benzene

^{1}H $CDCl_3$ 400 MHz

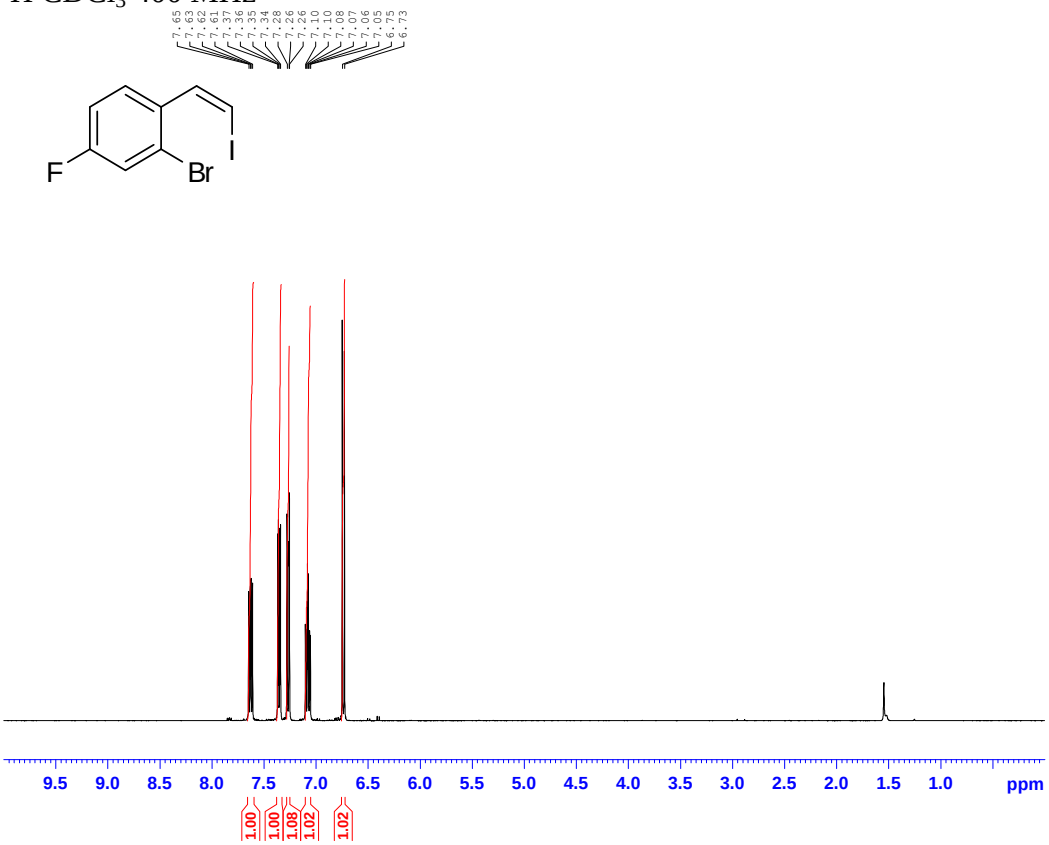


^{13}C $CDCl_3$ 101 MHz

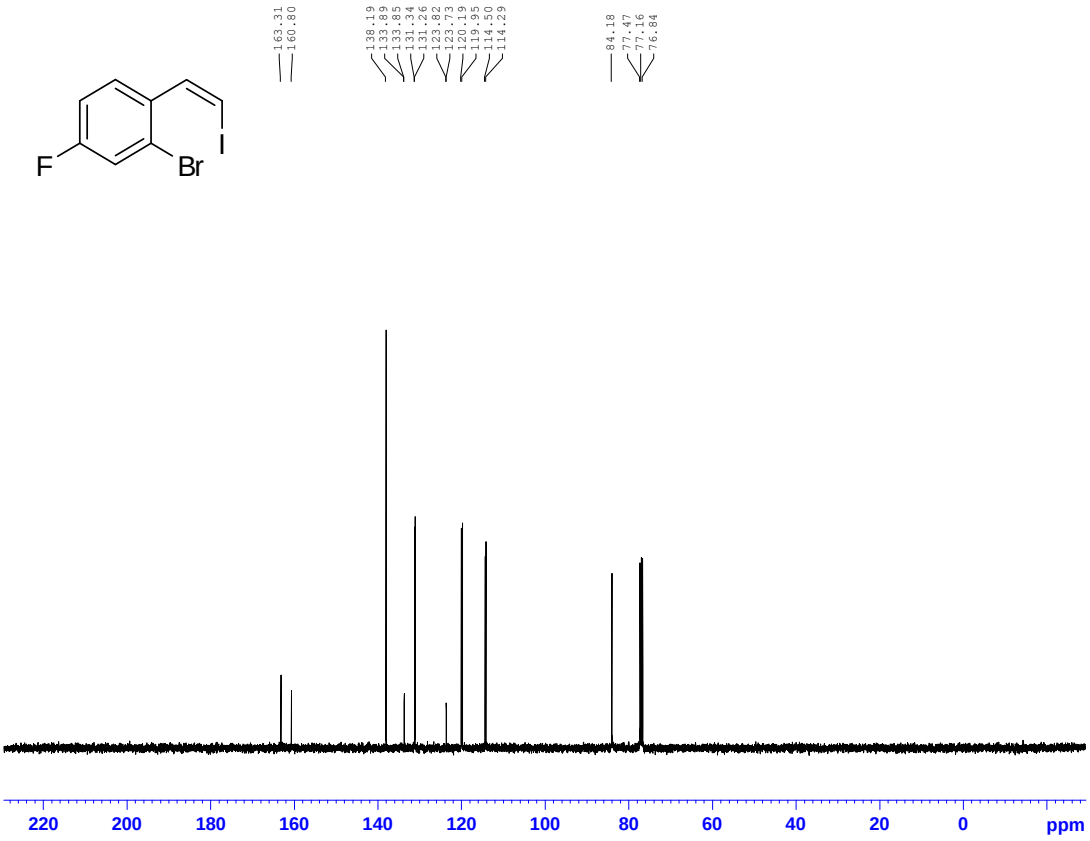


(*Z*)-2-Bromo-4-fluoro-1-(2-iodovinyl)benzene

^{1}H $CDCl_3$ 400 MHz

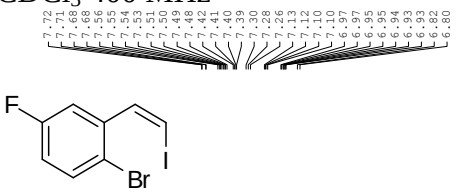


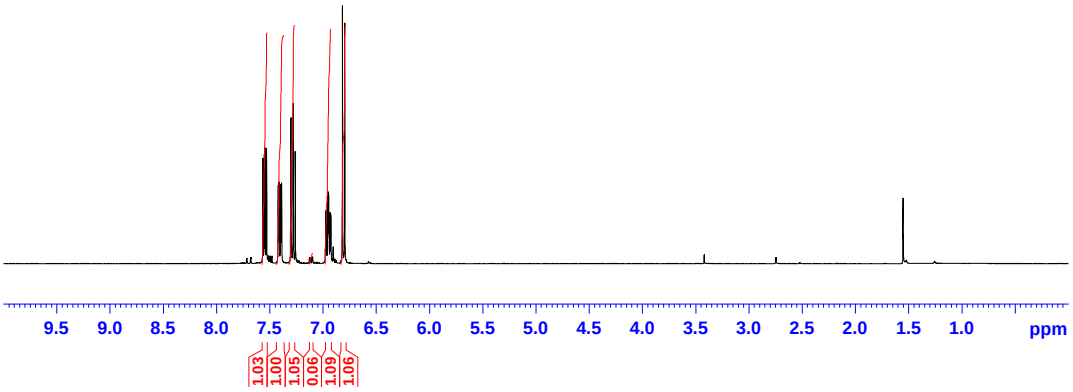
^{13}C $CDCl_3$ 101 MHz



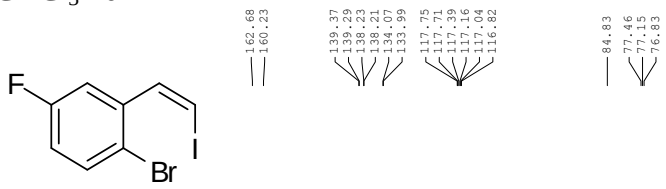
(*Z*)-1-Bromo-4-fluoro-2-(2-iodovinyl)benzene

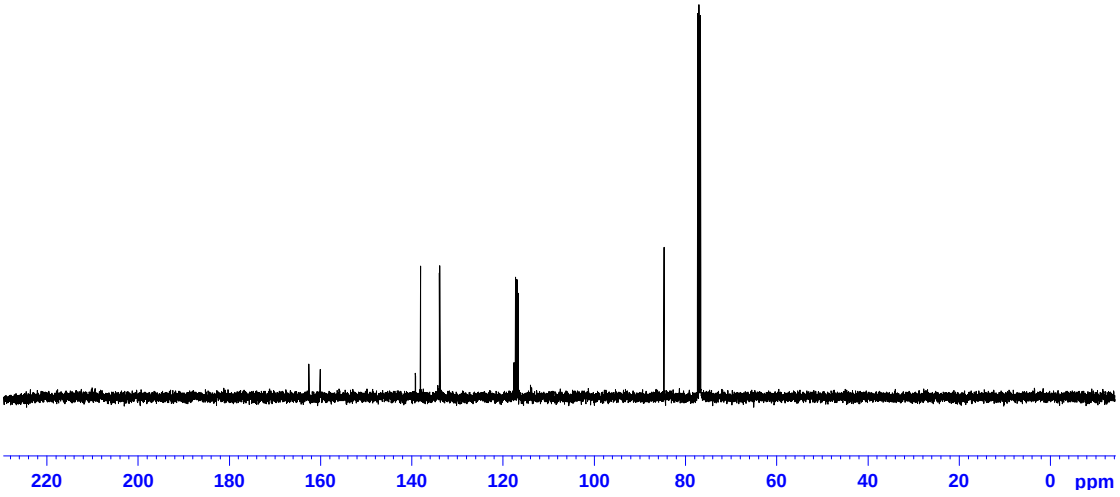
^{1}H $CDCl_3$ 400 MHz





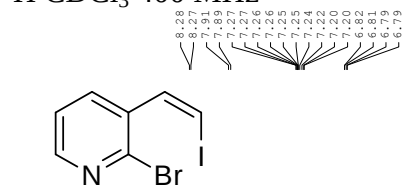
^{13}C $CDCl_3$ 101 MHz

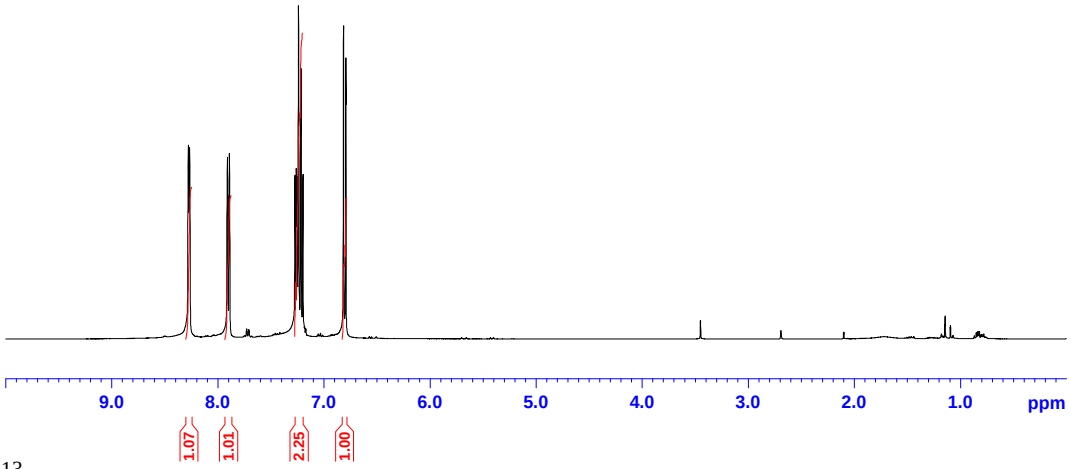




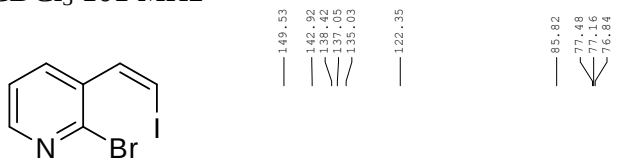
(*Z*)-2-Bromo-3-(2-iodovinyl)pyridine

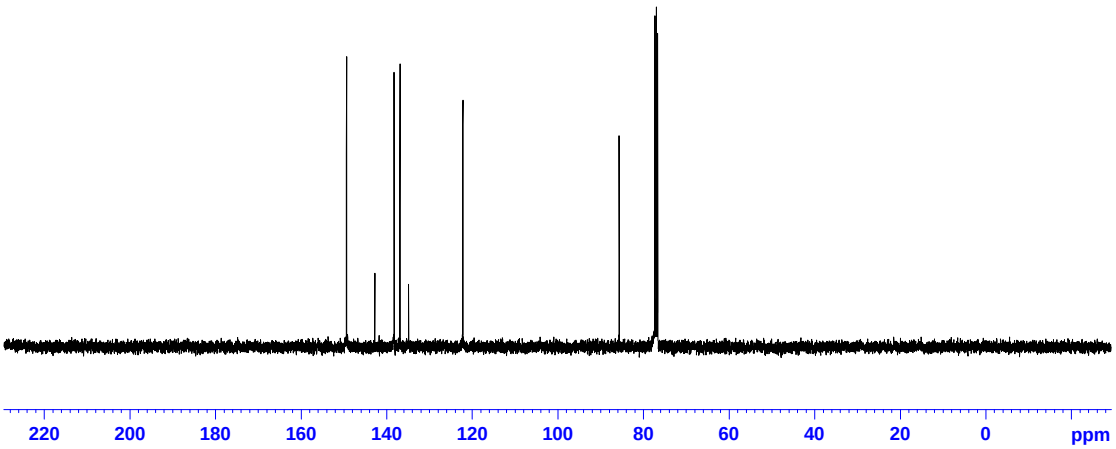
^{1}H $CDCl_3$ 400 MHz





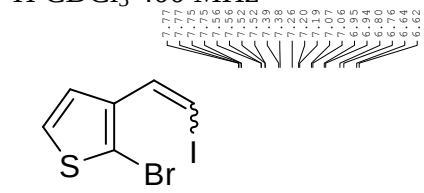
^{13}C $CDCl_3$ 101 MHz

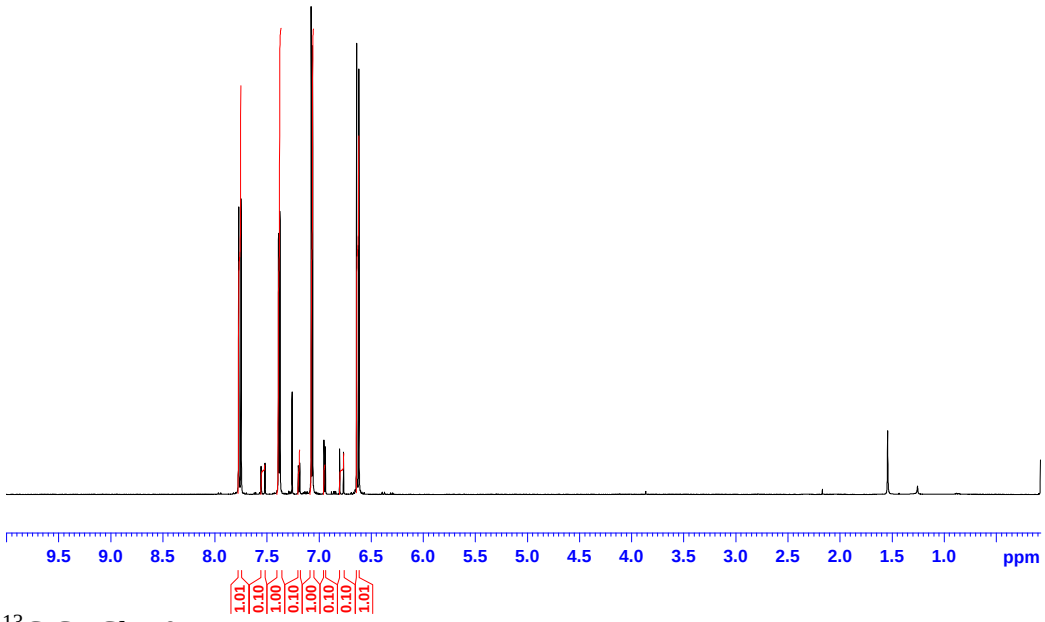




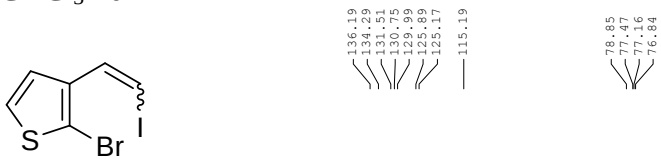
2-Bromo-3-(2-iodovinyl)thiophene

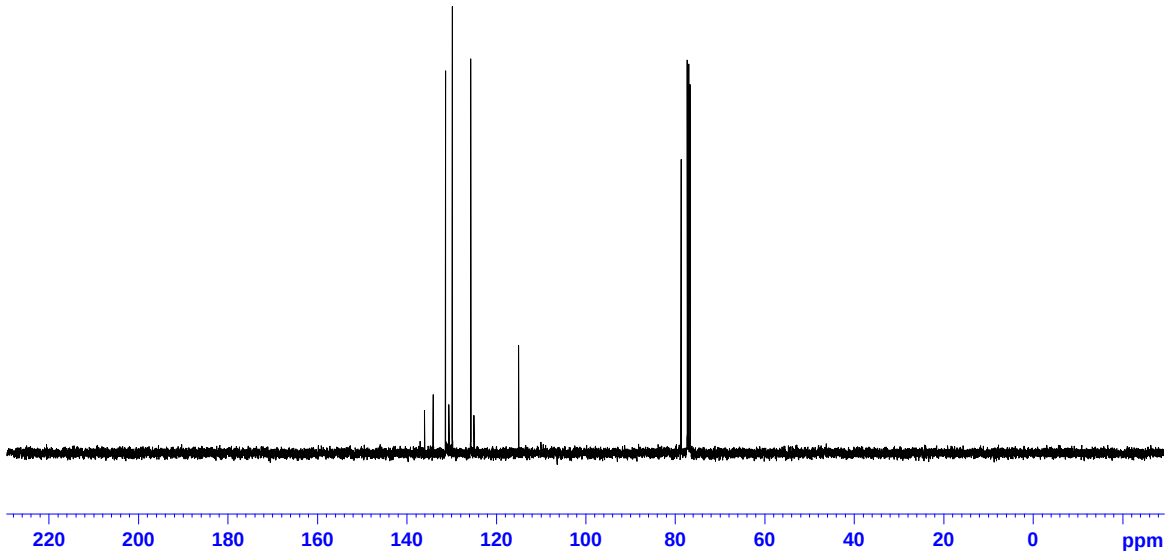
^{1}H $CDCl_3$ 400 MHz





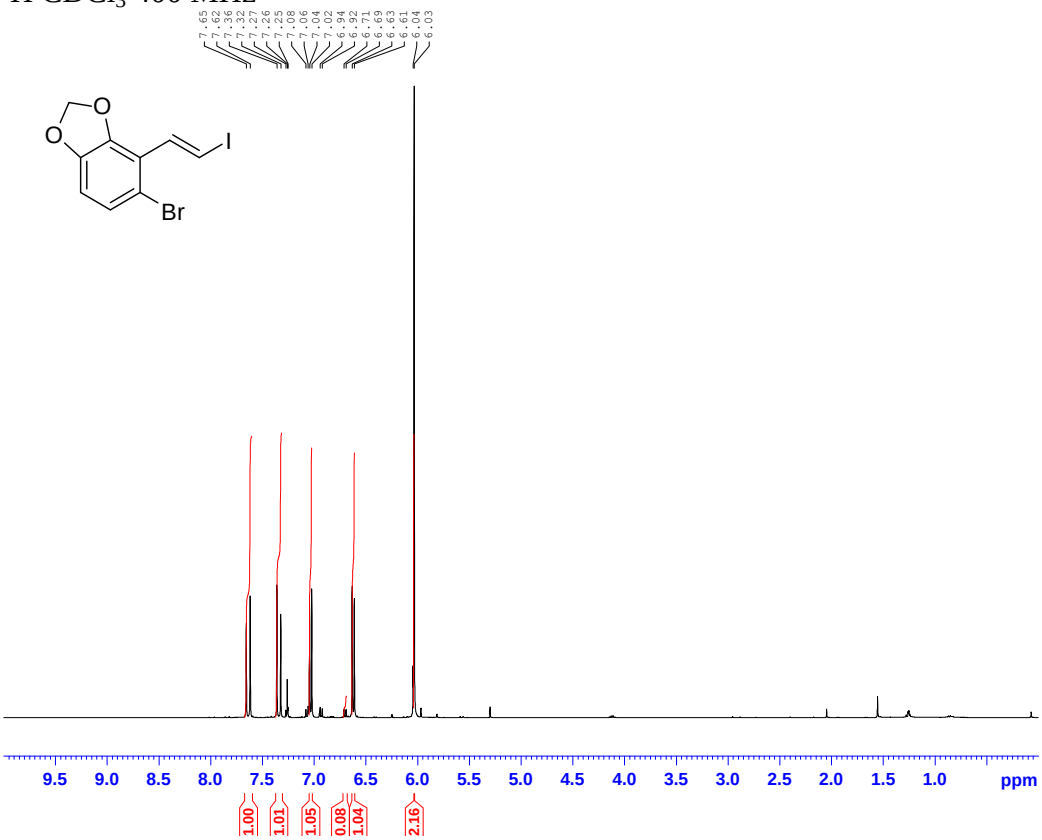
^{13}C $CDCl_3$ 101 MHz



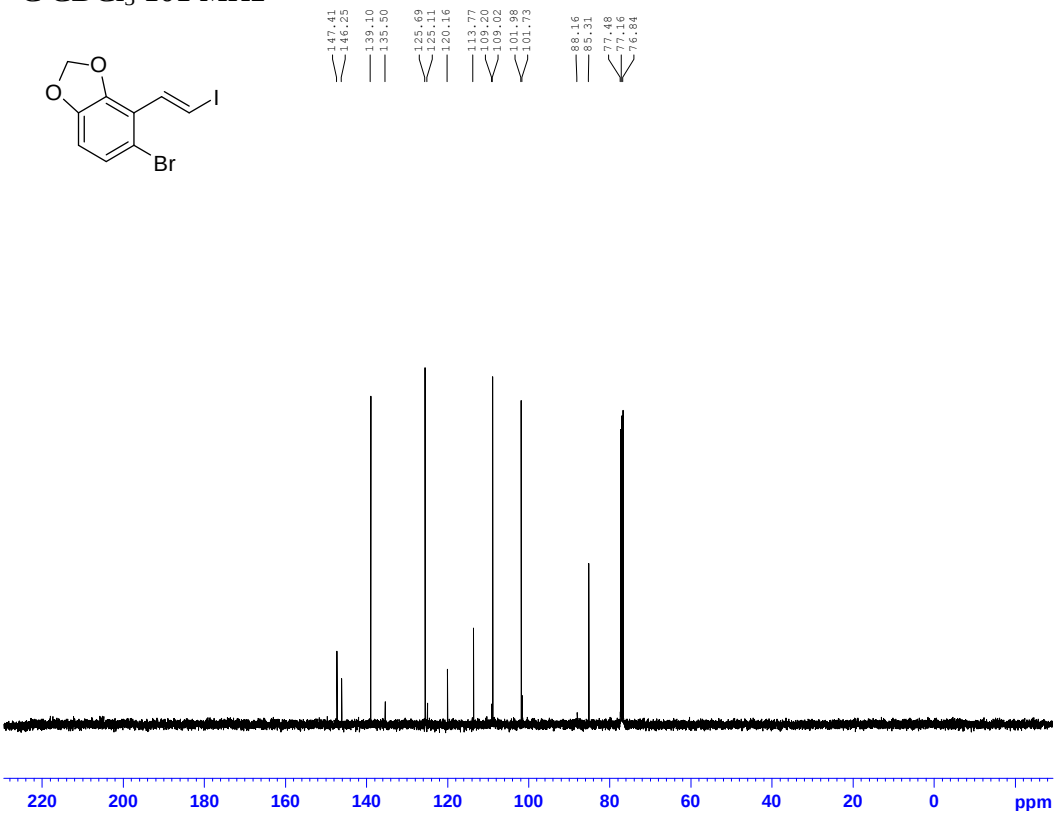


(*Z*)-5-Bromo-4-(2-iodovinyl)benzo[d][1,3]dioxole

^{1}H $CDCl_3$ 400 MHz

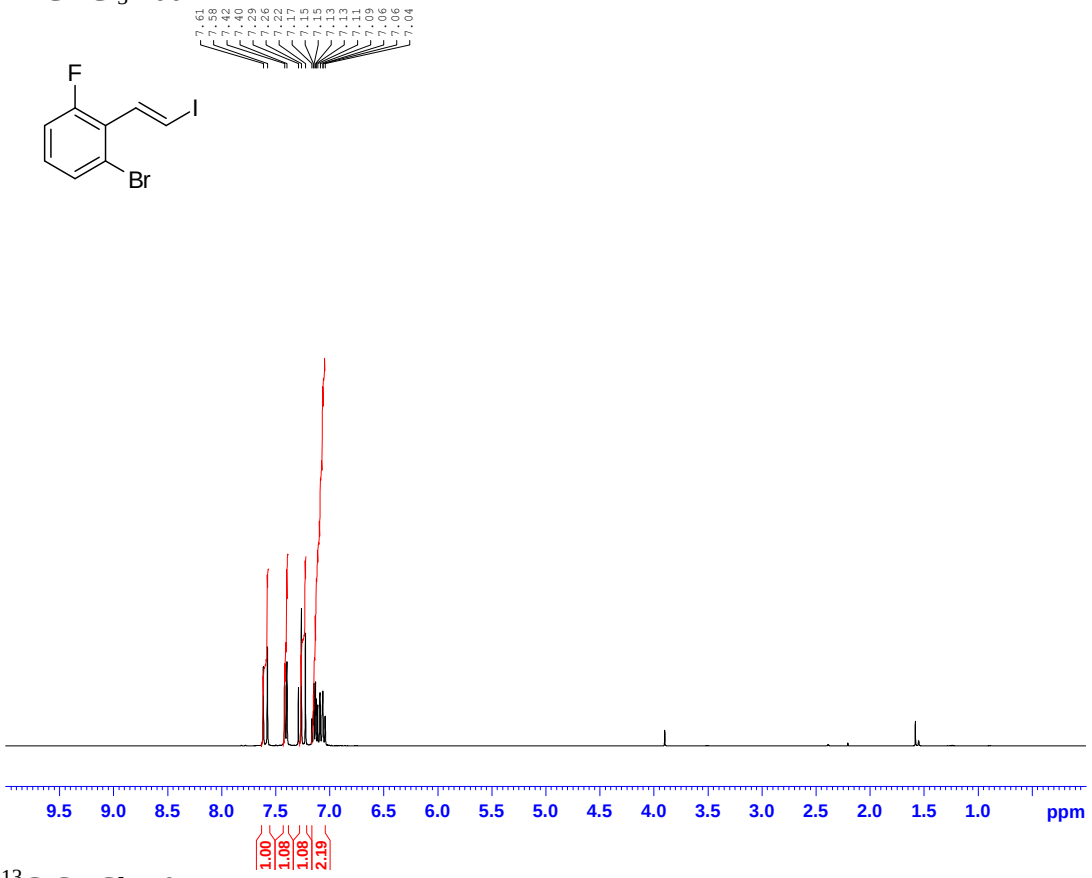


^{13}C $CDCl_3$ 101 MHz

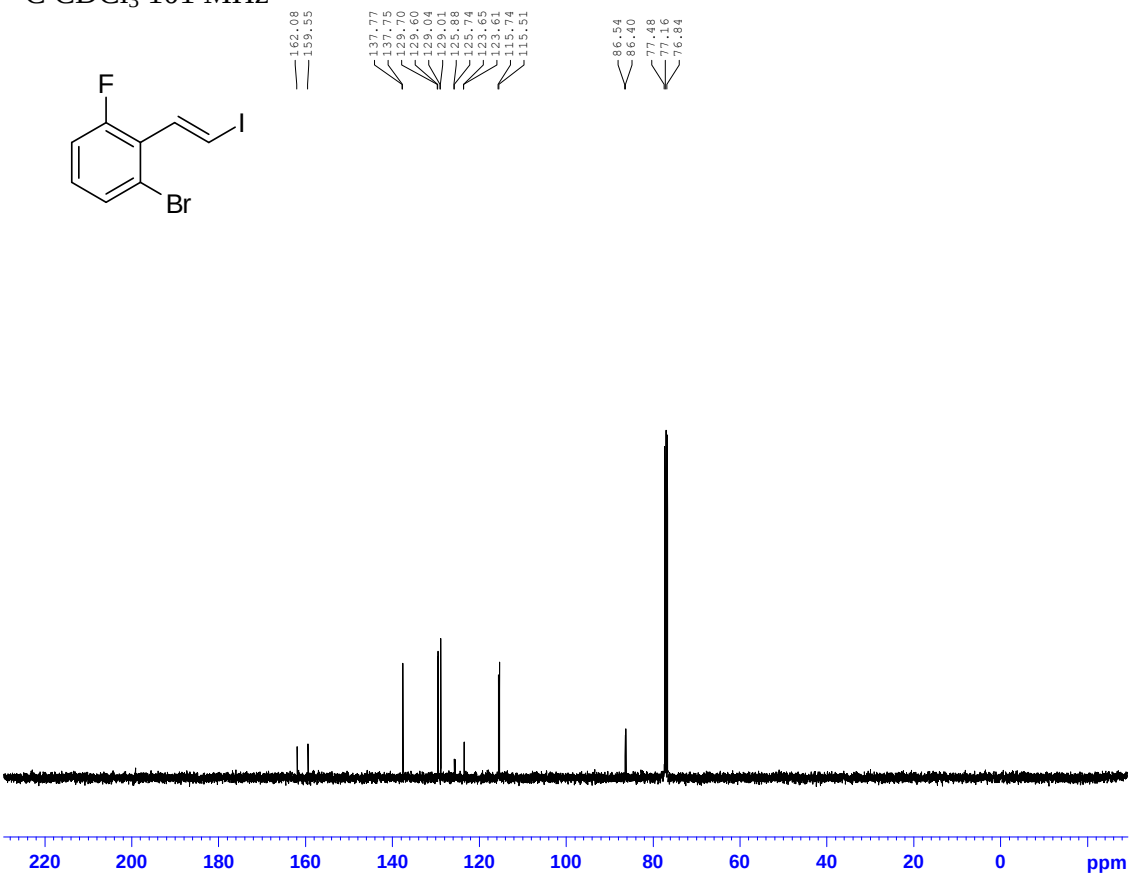


(*Z*)-1-Bromo-3-fluoro-2-(2-iodovinyl)benzene

^{1}H $CDCl_3$ 400 MHz

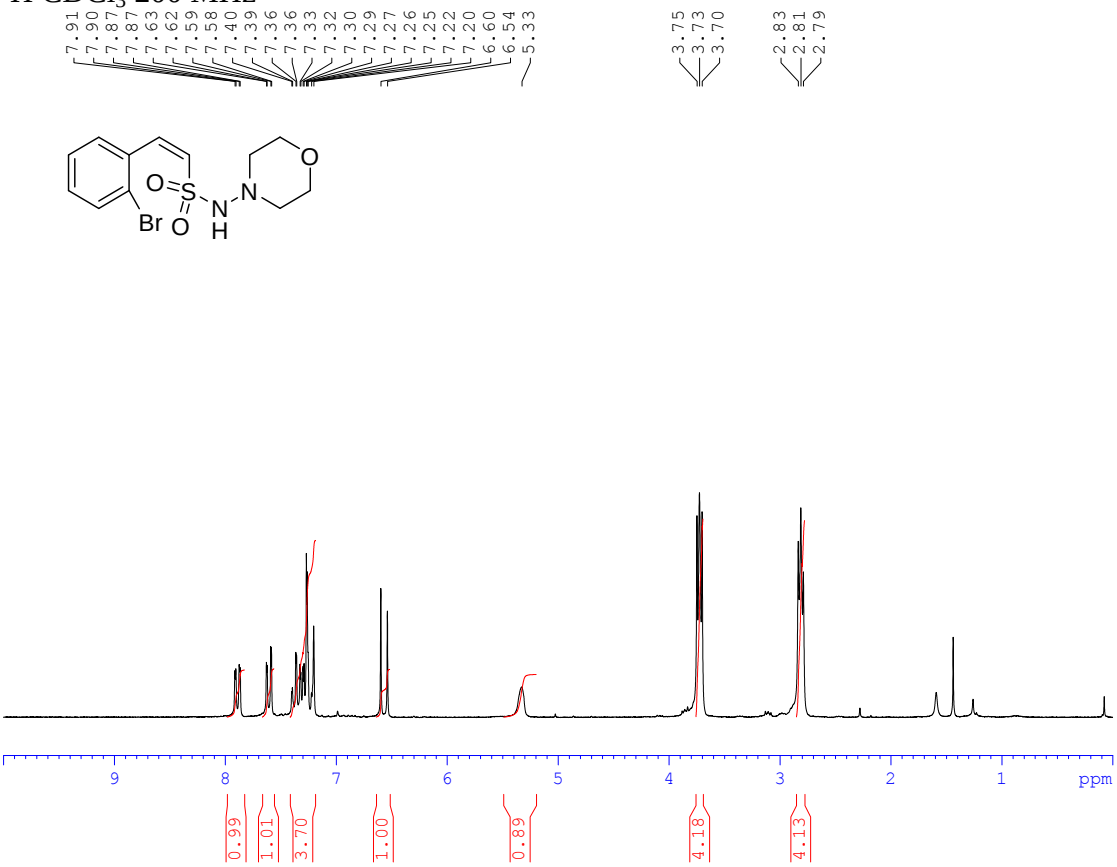


^{13}C $CDCl_3$ 101 MHz

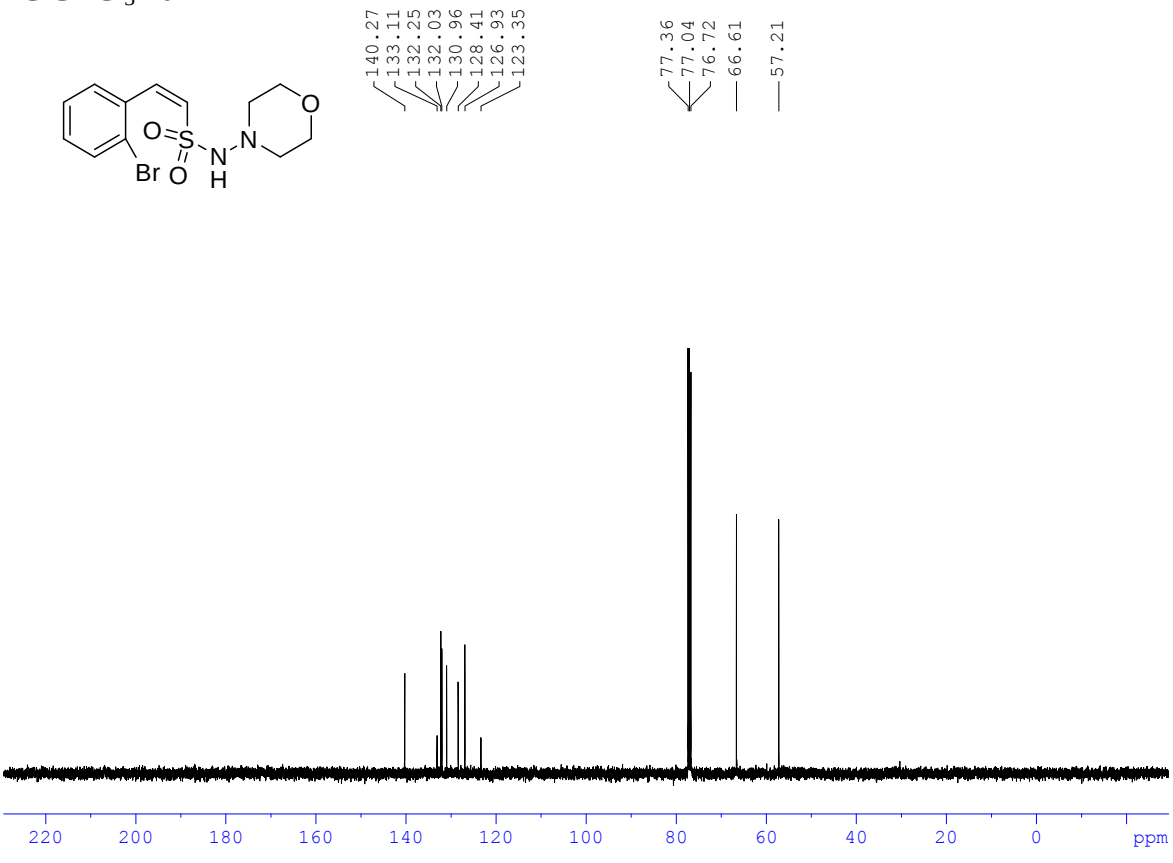


(*Z*)-2-(2-Bromophenyl)-*N*-(morpholin-4-yl)ethenesulfonamide

^{1}H $CDCl_3$ 200 MHz

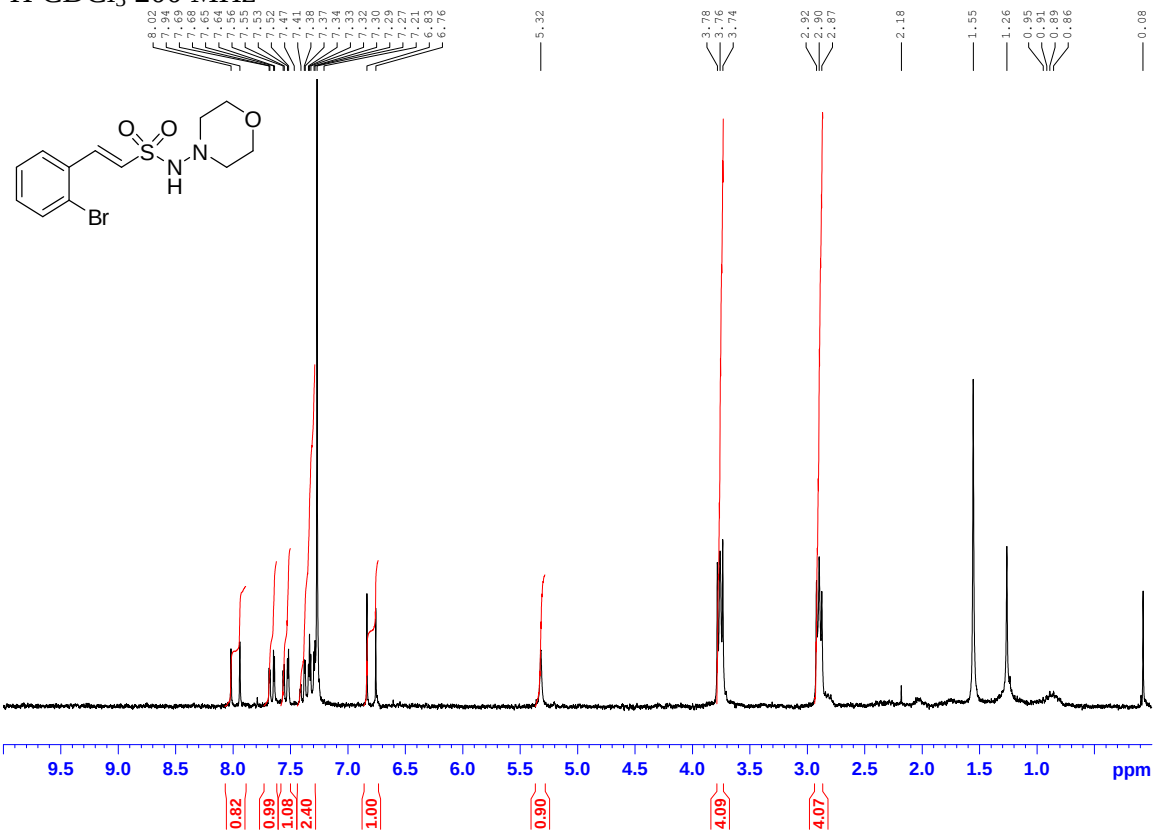


^{13}C $CDCl_3$ 101 MHz

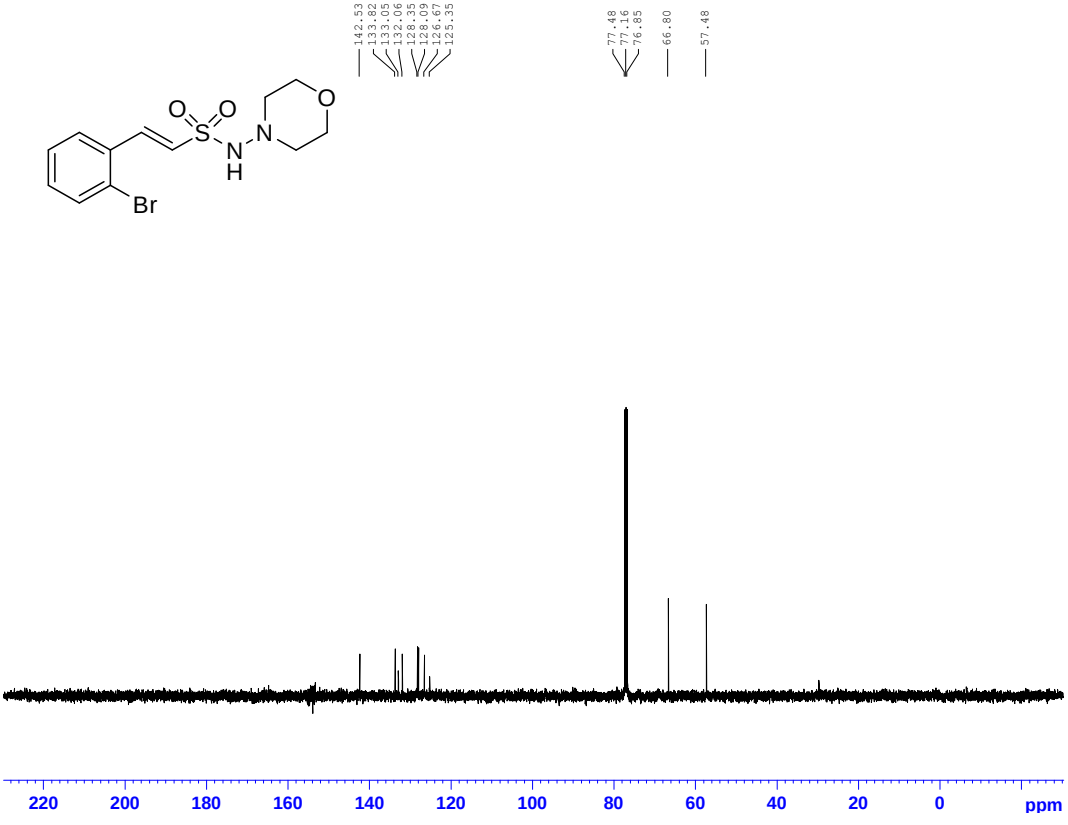


(*E*)-2-(2-Bromophenyl)-*N*-(morpholin-4-yl)ethenesulfonamide

^{1}H $CDCl_3$ 200 MHz

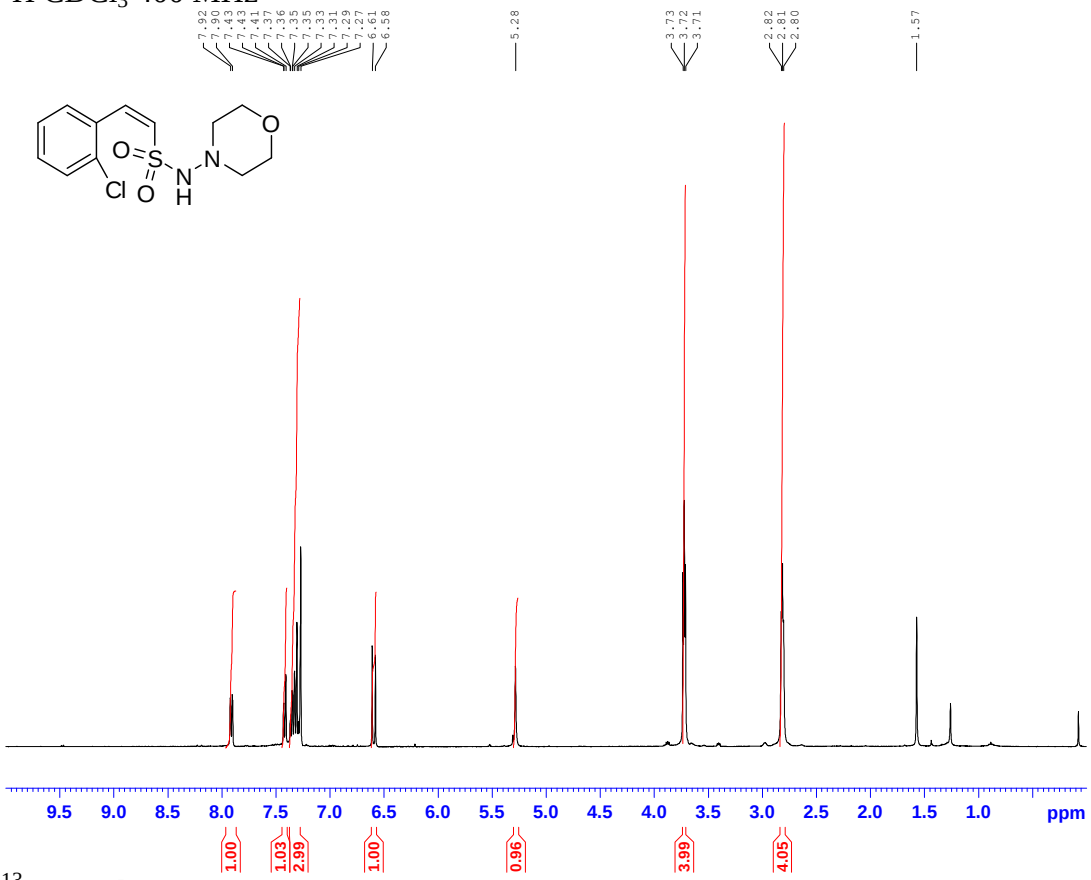


^{13}C $CDCl_3$ 101 MHz

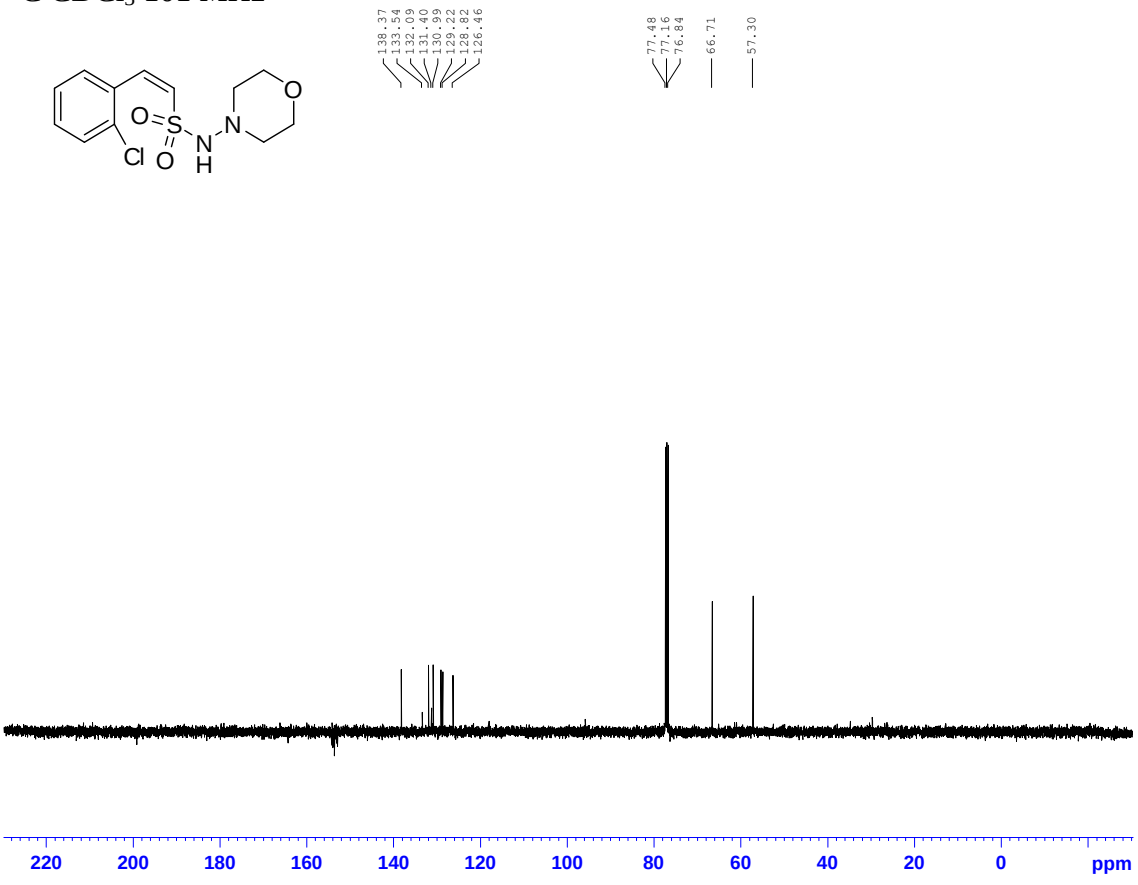


(*Z*)-2-(2-Chlorophenyl)-*N*-(morpholin-4-yl)ethenesulfonamide

^{1}H $CDCl_3$ 400 MHz

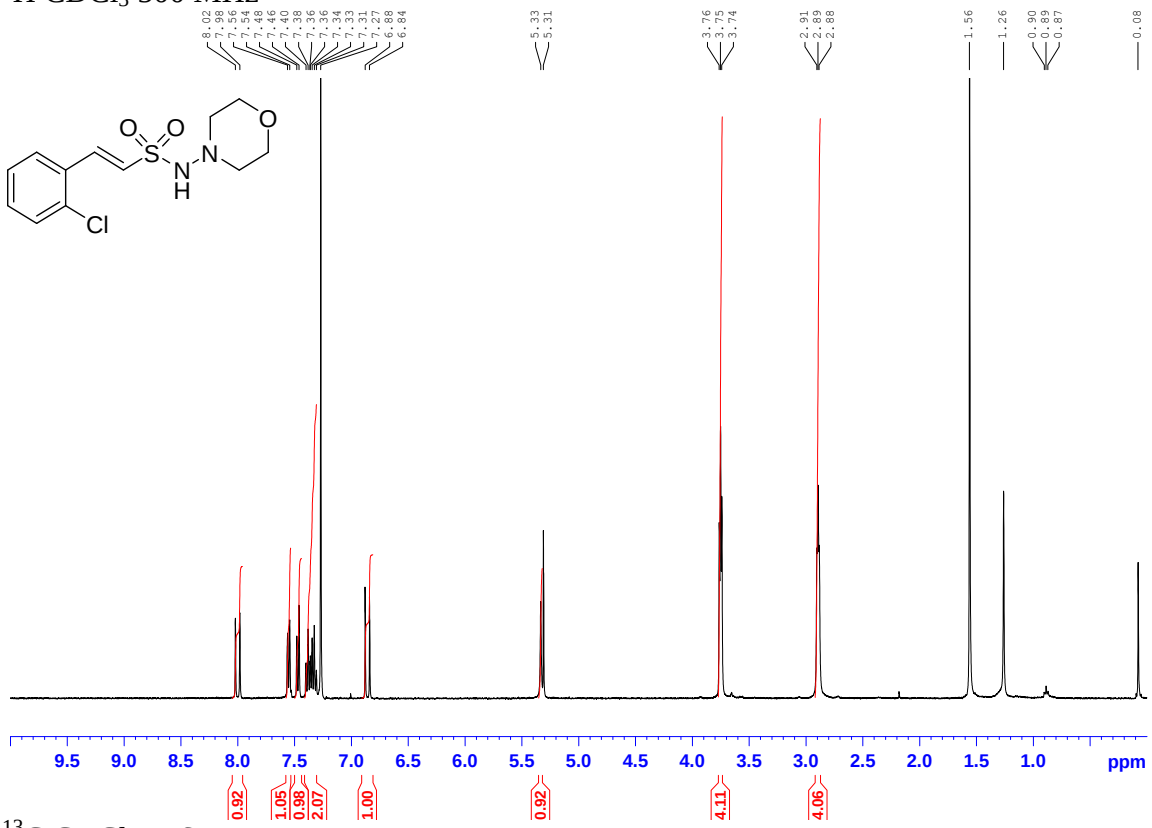


^{13}C $CDCl_3$ 101 MHz

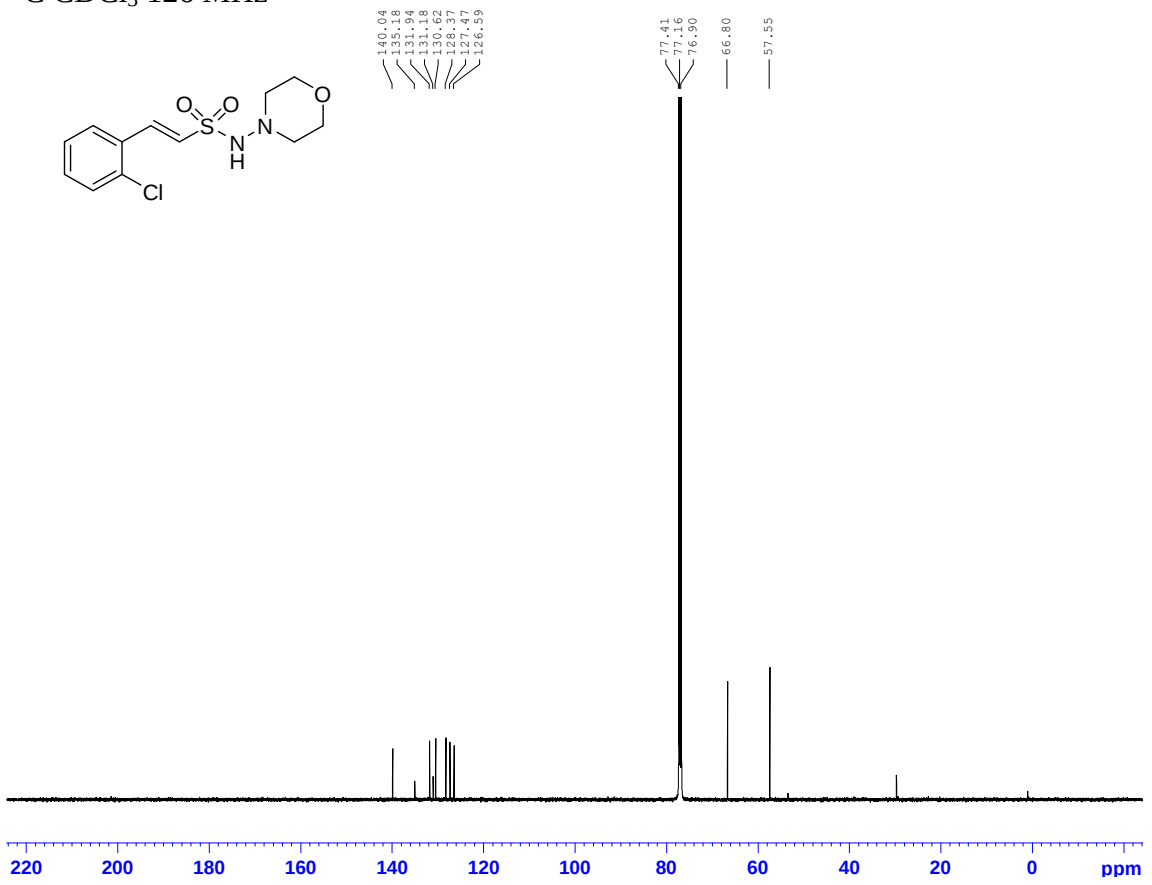


(*E*)-2-(2-Chlorophenyl)-*N*-(morpholin-4-yl)ethenesulfonamide

^{1}H $CDCl_3$ 500 MHz

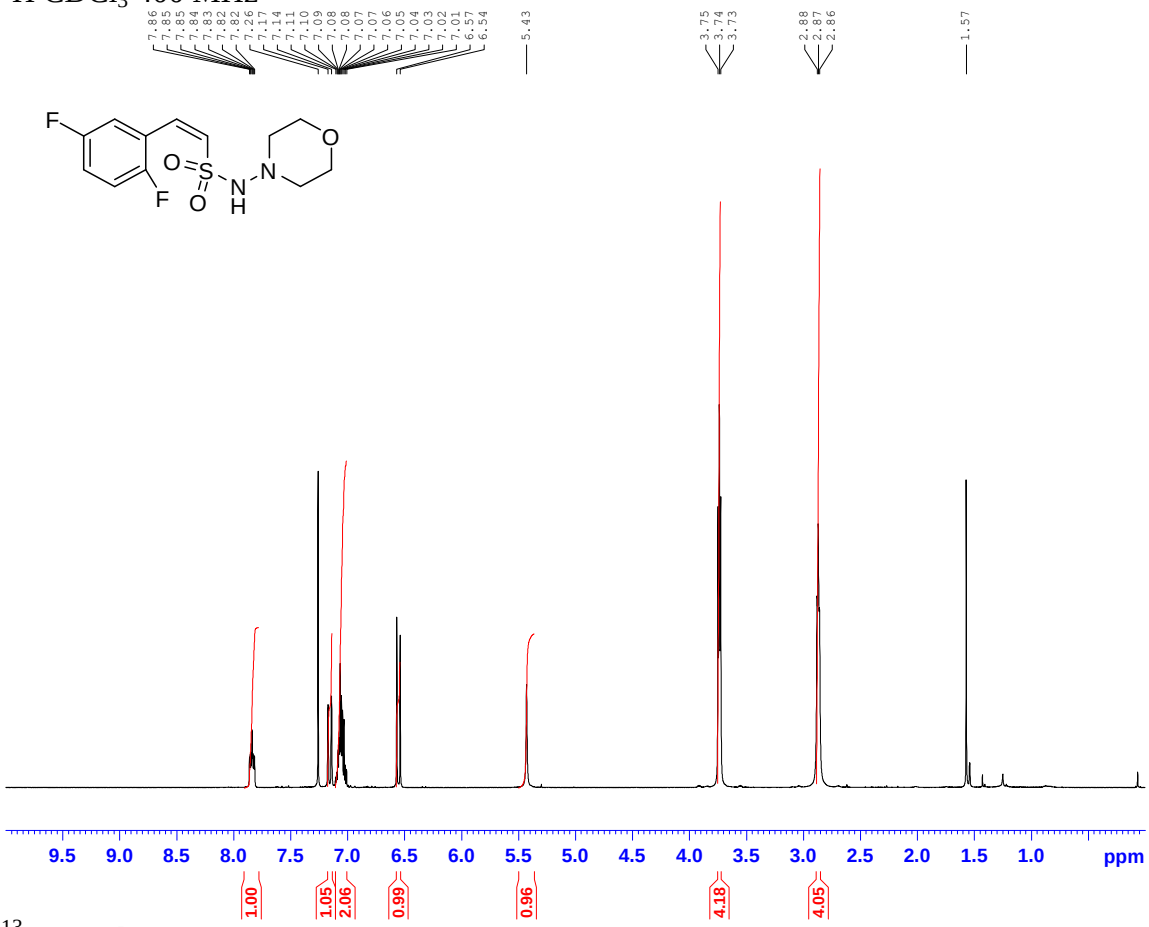


^{13}C $CDCl_3$ 126 MHz

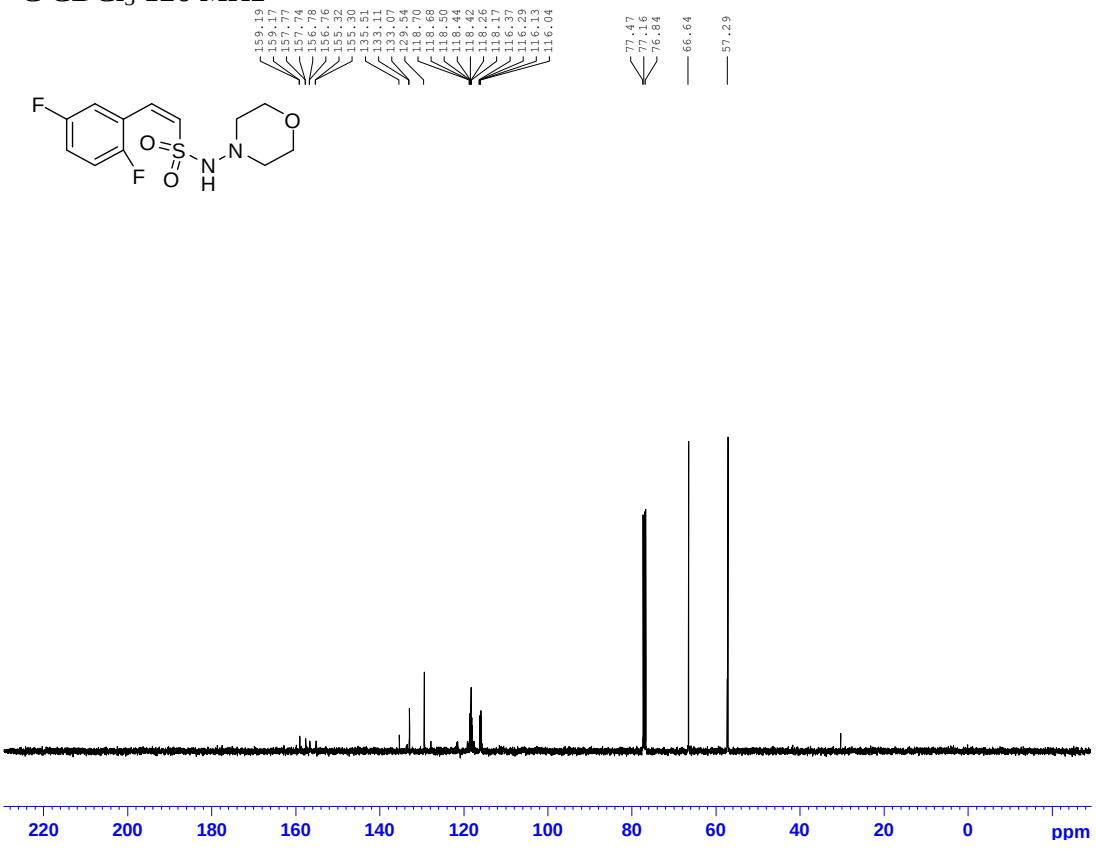


(*Z*)-2-(2,5-Difluorophenyl)-*N*-(morpholin-4-yl)ethenesulfonamide

^{1}H $CDCl_3$ 400 MHz

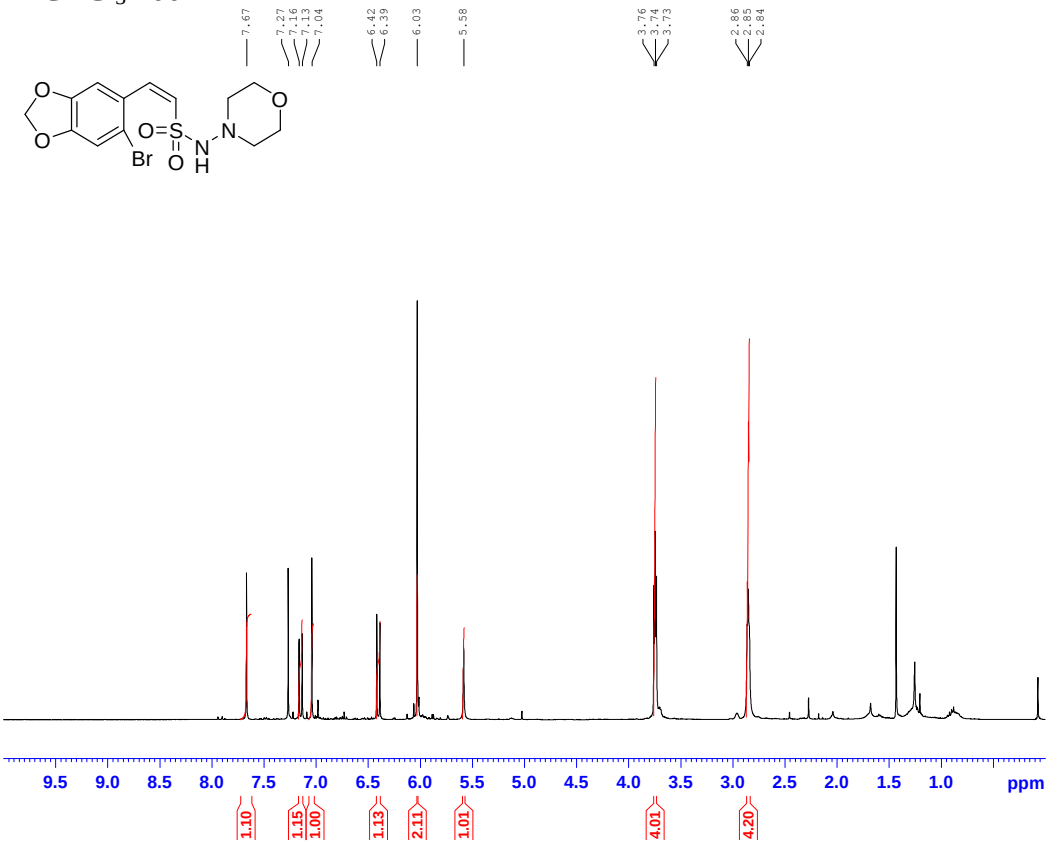


^{13}C $CDCl_3$ 126 MHz

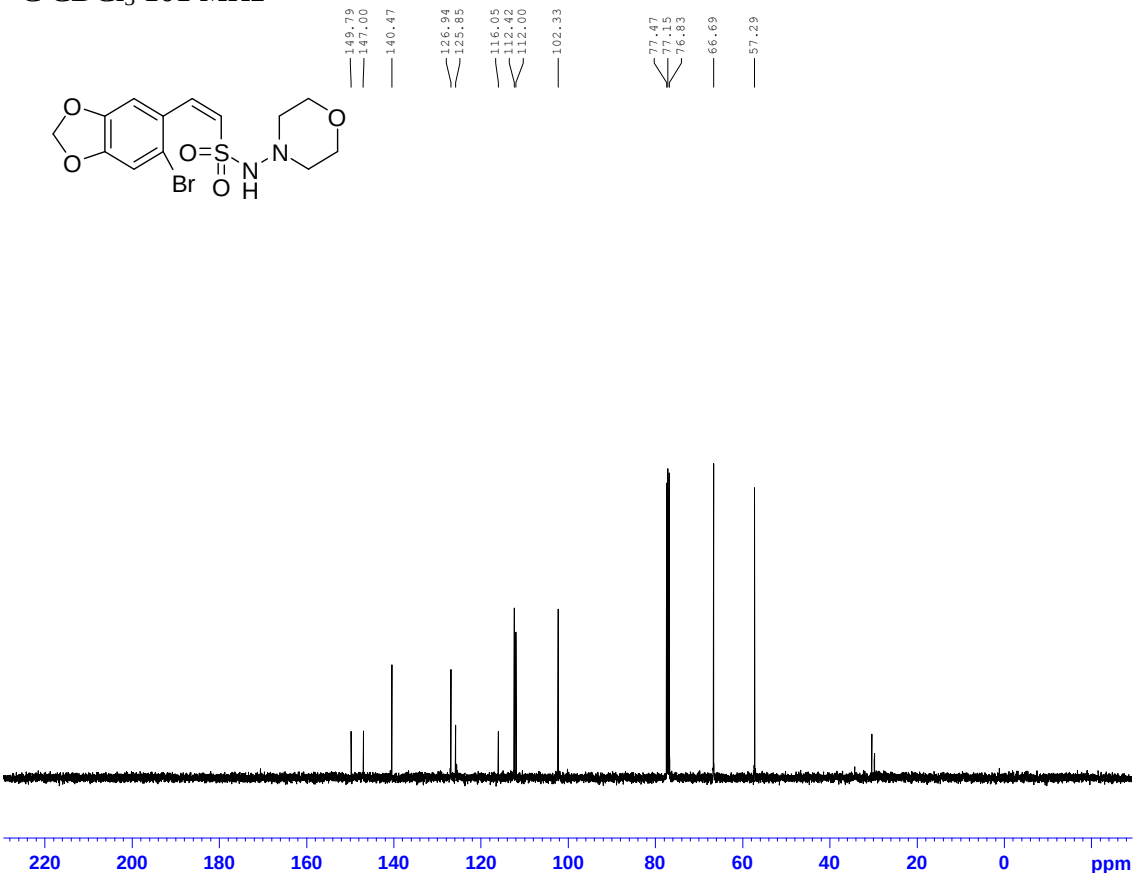


(*Z*)-2-(6-Bromobenzo[d][1,3]dioxol-5-yl)-*N*-morpholinoethenesulfonamide

^{1}H $CDCl_3$ 400 MHz

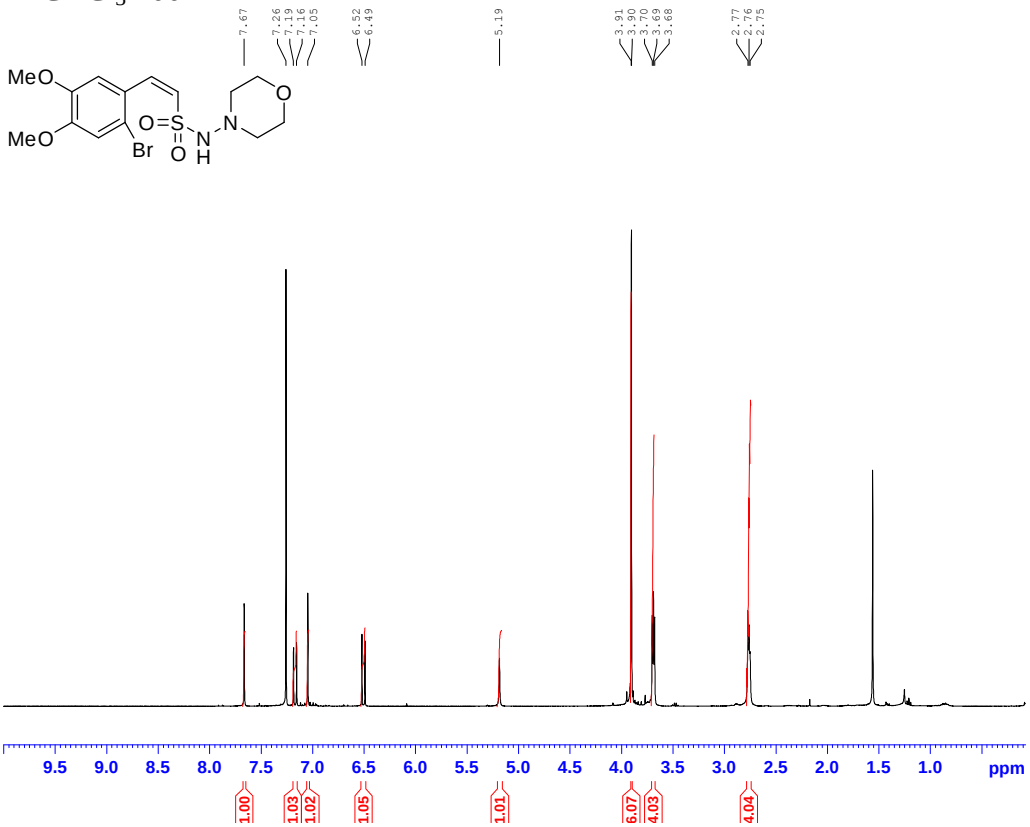


^{13}C $CDCl_3$ 101 MHz

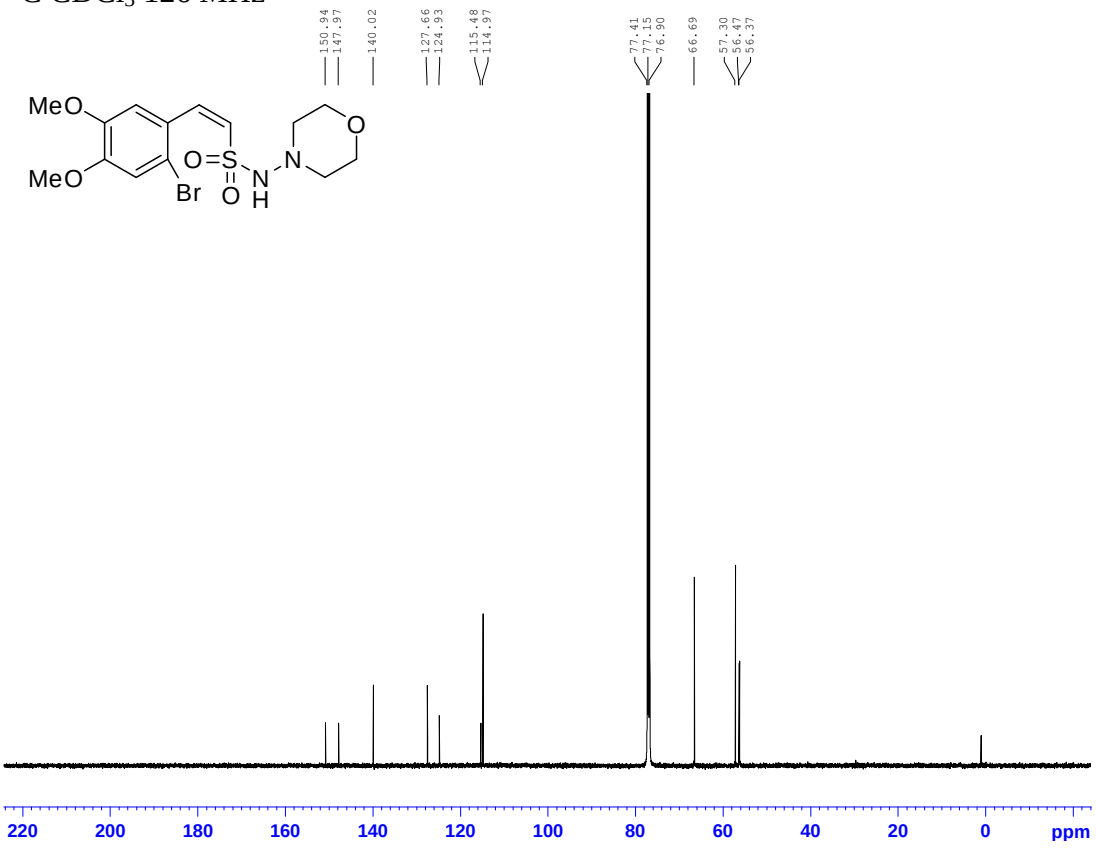


(*Z*)-2-(2-Bromo-4,5-dimethoxyphenyl)-*N*-morpholinoethenesulfonamide

^{1}H $CDCl_3$ 400 MHz

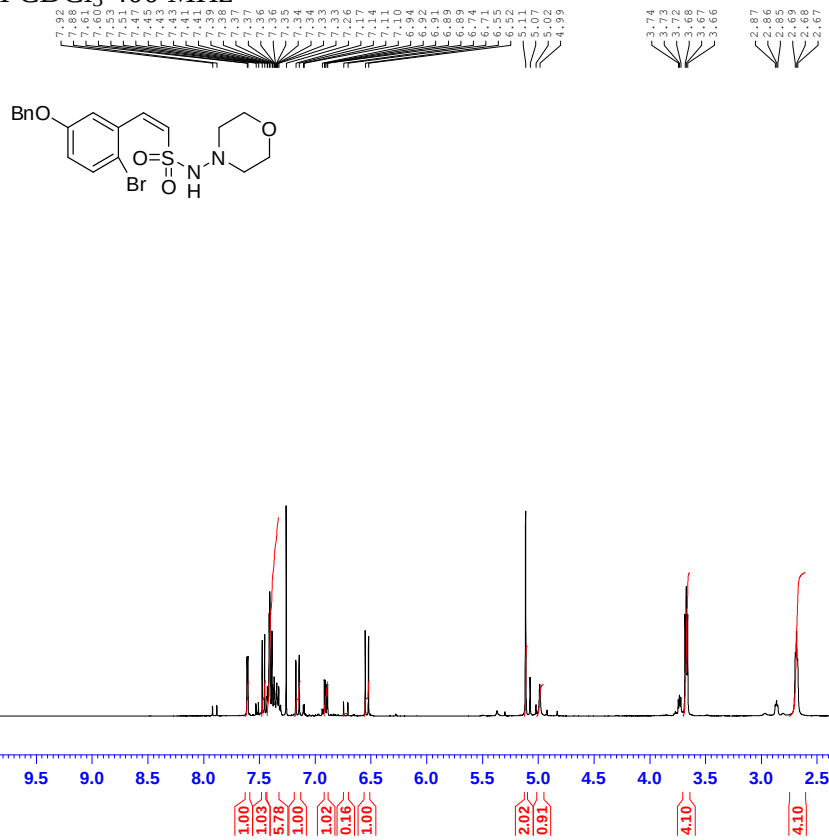


^{13}C $CDCl_3$ 126 MHz

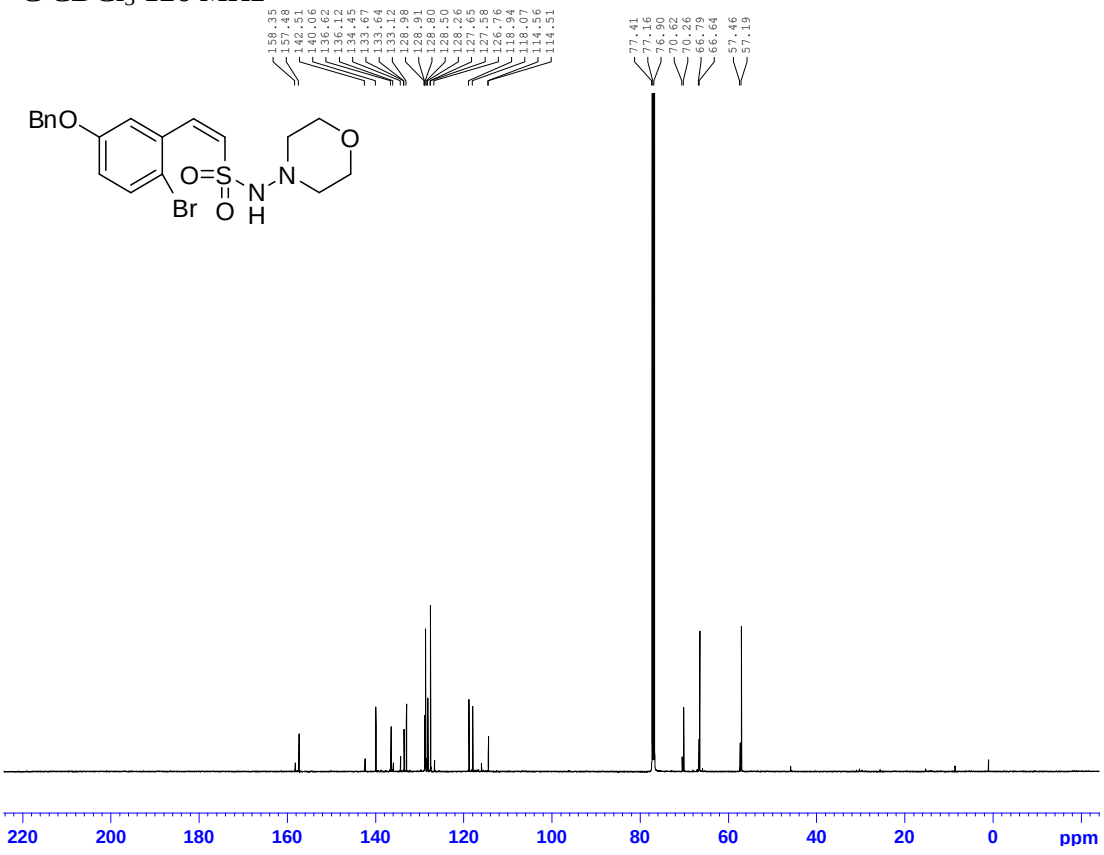


2-(5-(Benzyloxy)-2-bromophenyl)-*N*-morpholinoethenesulfonamide

^{1}H $CDCl_3$ 400 MHz

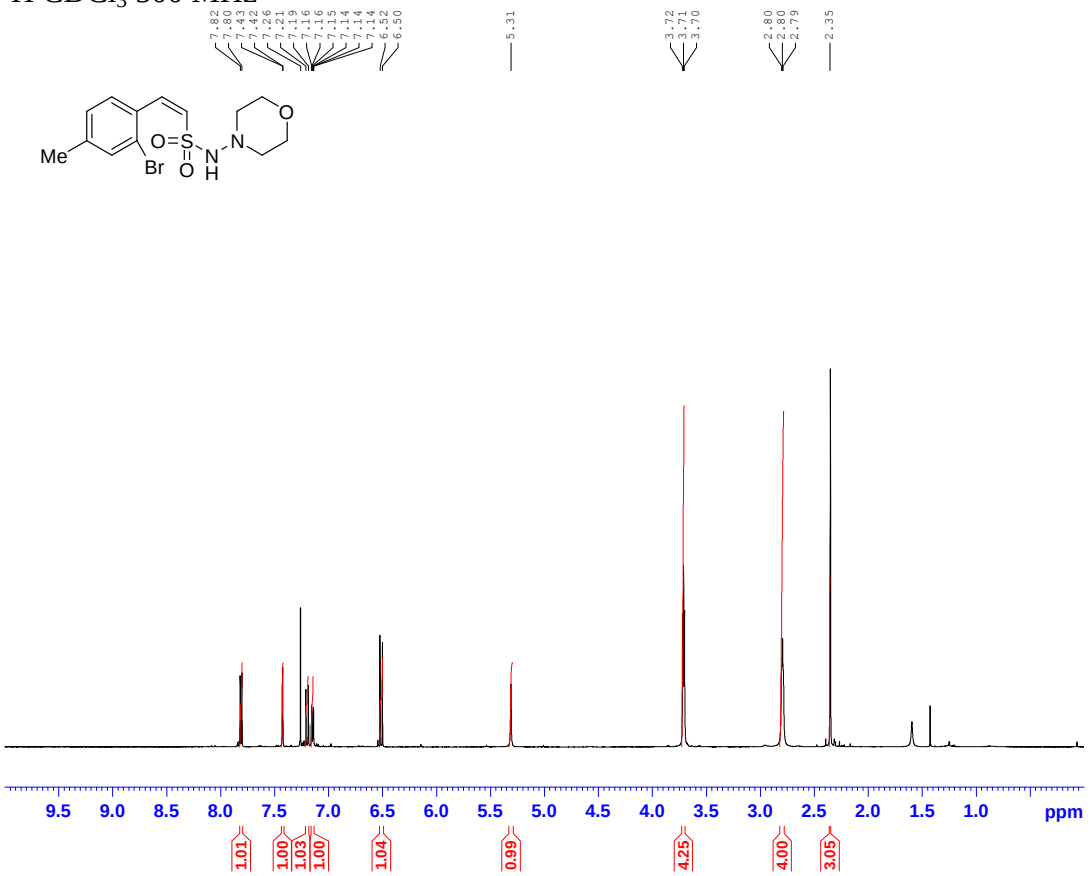


^{13}C $CDCl_3$ 126 MHz

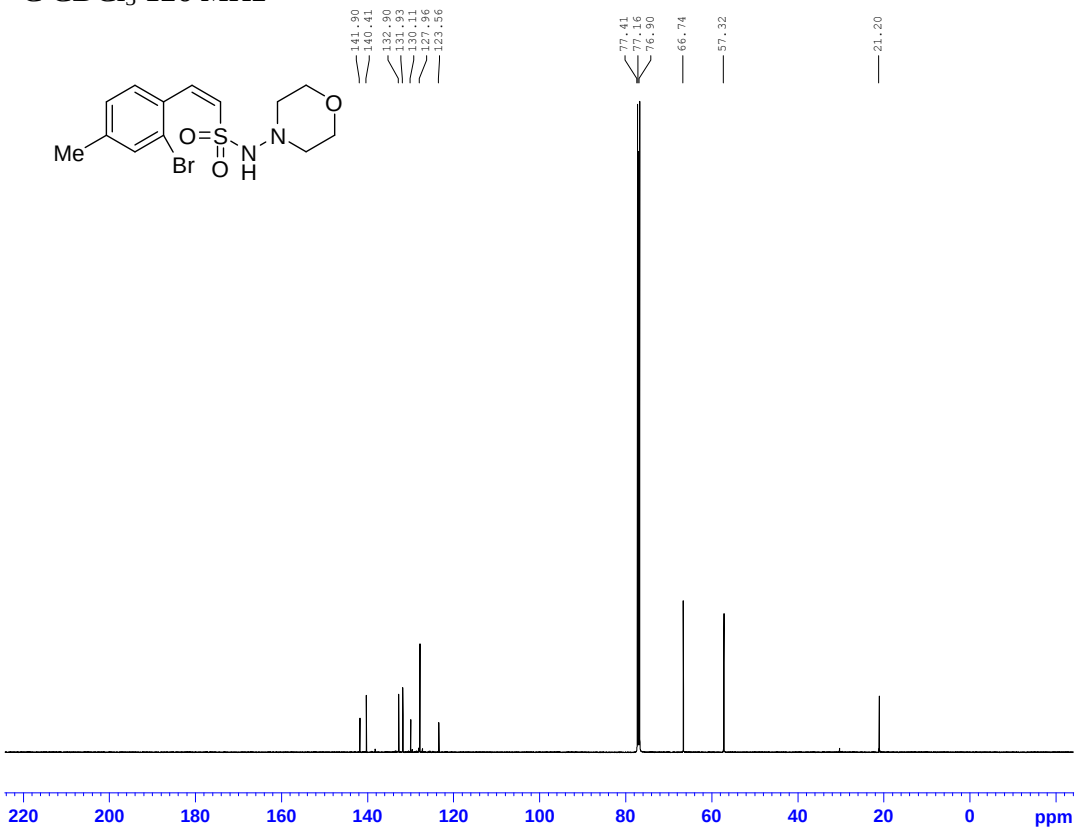


(Z)-2-(2-Bromo-4-methylphenyl)-N-morpholinoethenesulfonamide

^{1}H $CDCl_3$ 500 MHz

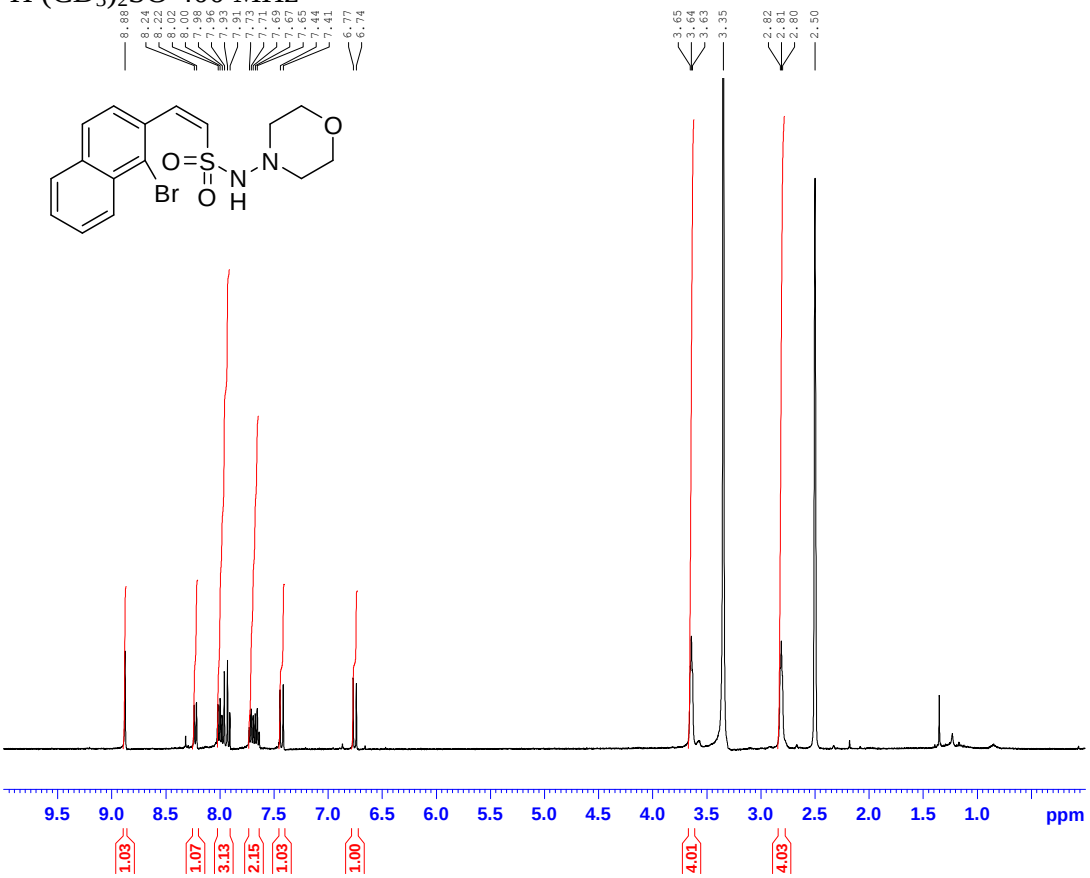


^{13}C $CDCl_3$ 126 MHz

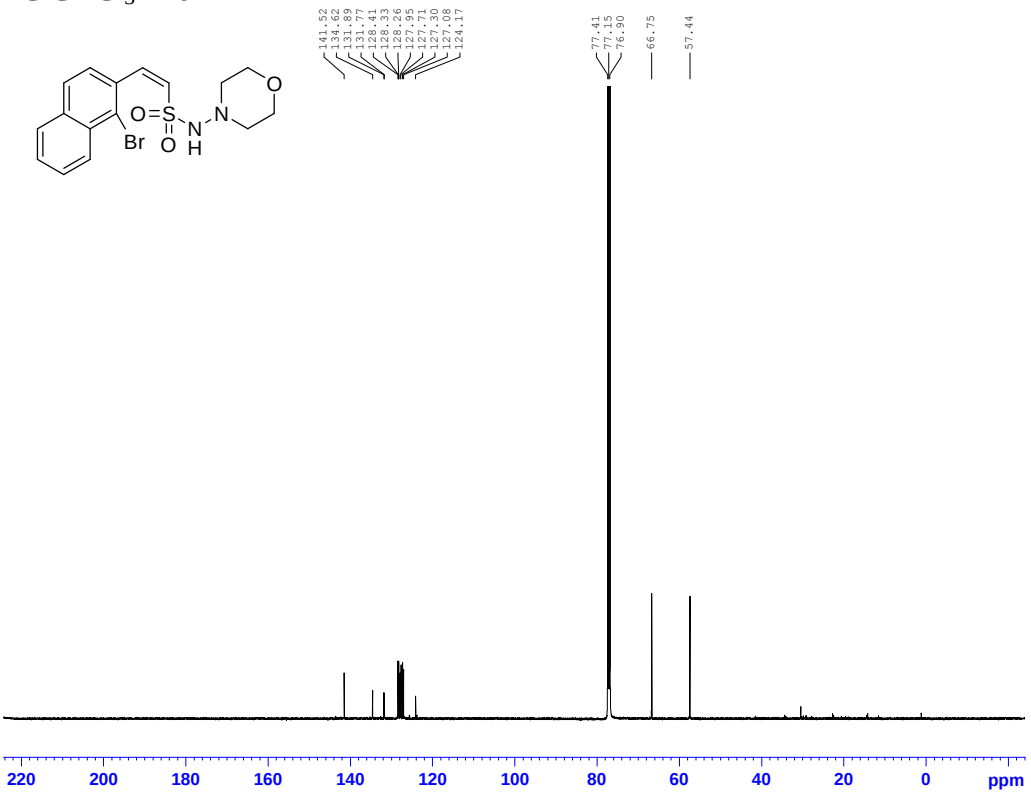


(*Z*)-2-(1-Bromonaphthalen-2-yl)-*N*-morpholinoethenesulfonamide

^{1}H $(CD_3)_2SO$ 400 MHz

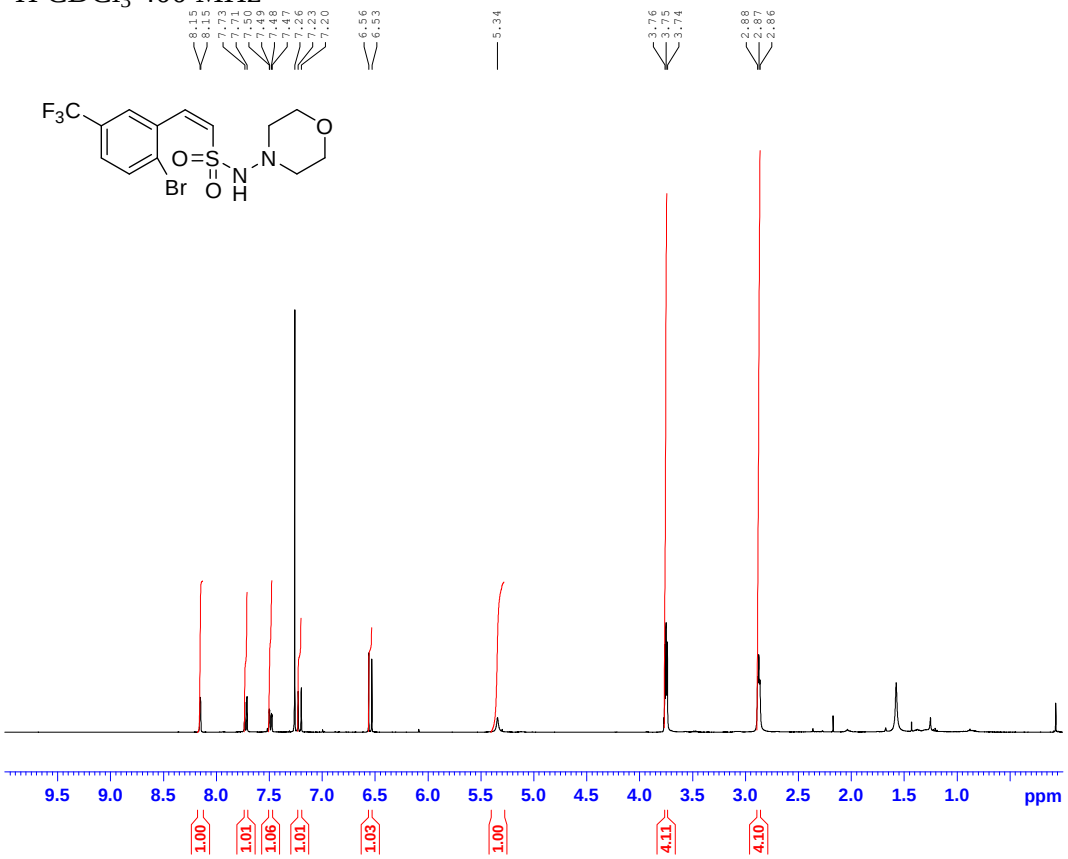


^{13}C $CDCl_3$ 126 MHz

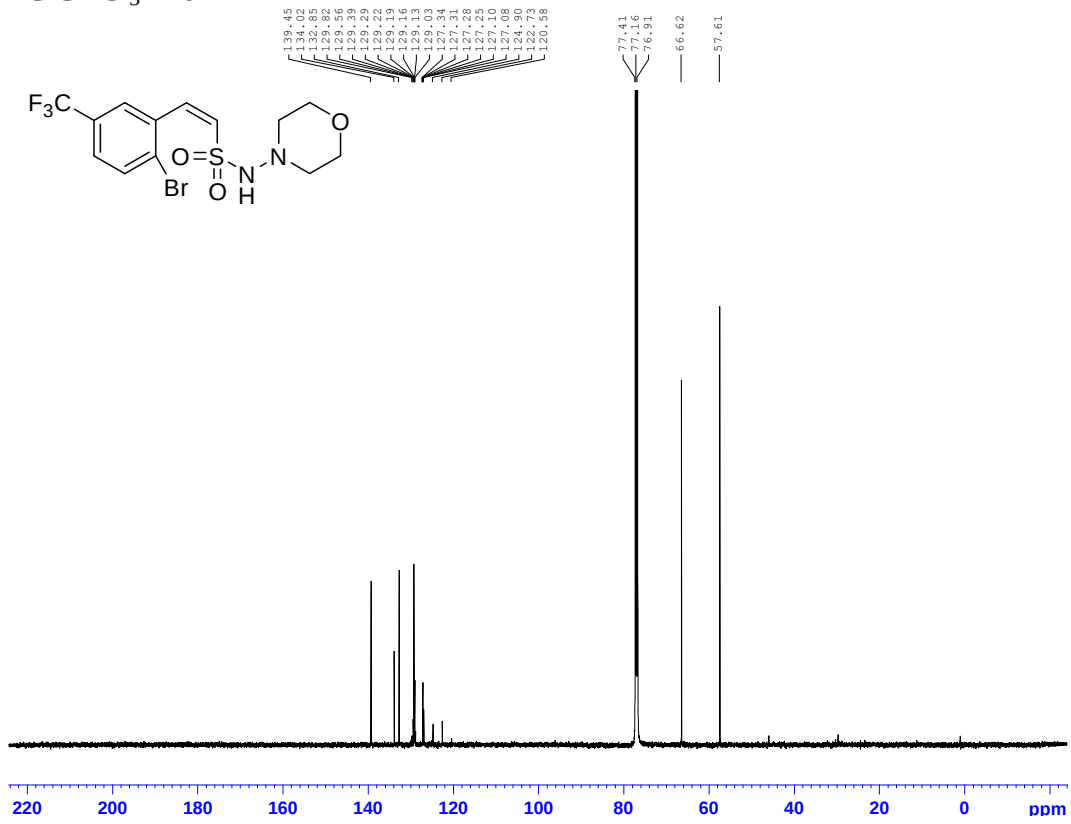


(*Z*)-2-(2-Bromo-5-(trifluoromethyl)phenyl)-*N*-morpholinoethenesulfonamide

^{1}H $CDCl_3$ 400 MHz

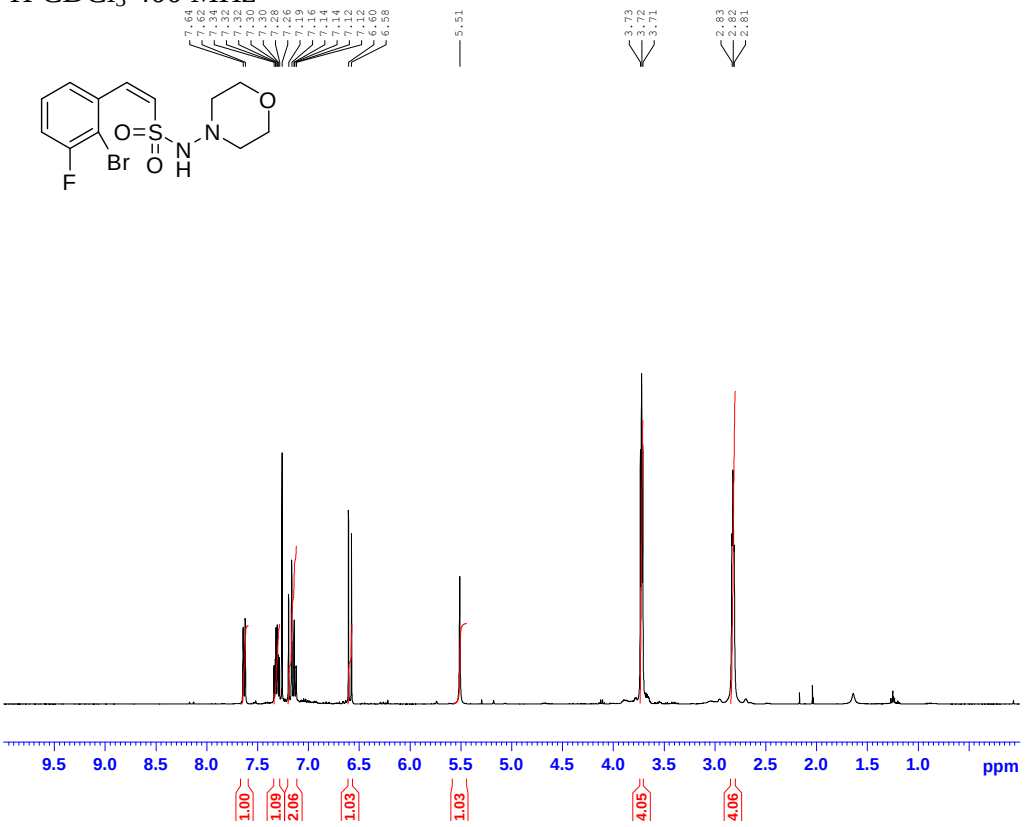


^{13}C $CDCl_3$ 126 MHz

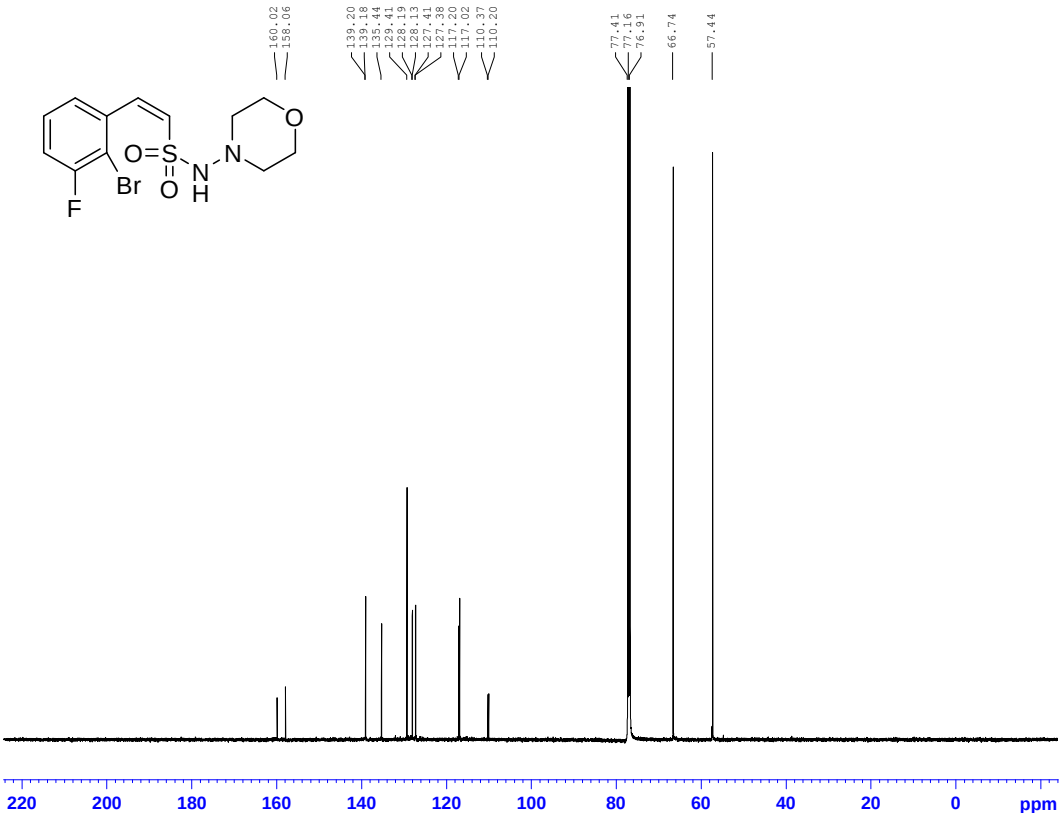


(*Z*)-2-(2-Bromo-3-fluorophenyl)-*N*-morpholinoethenesulfonamide

^{1}H $CDCl_3$ 400 MHz

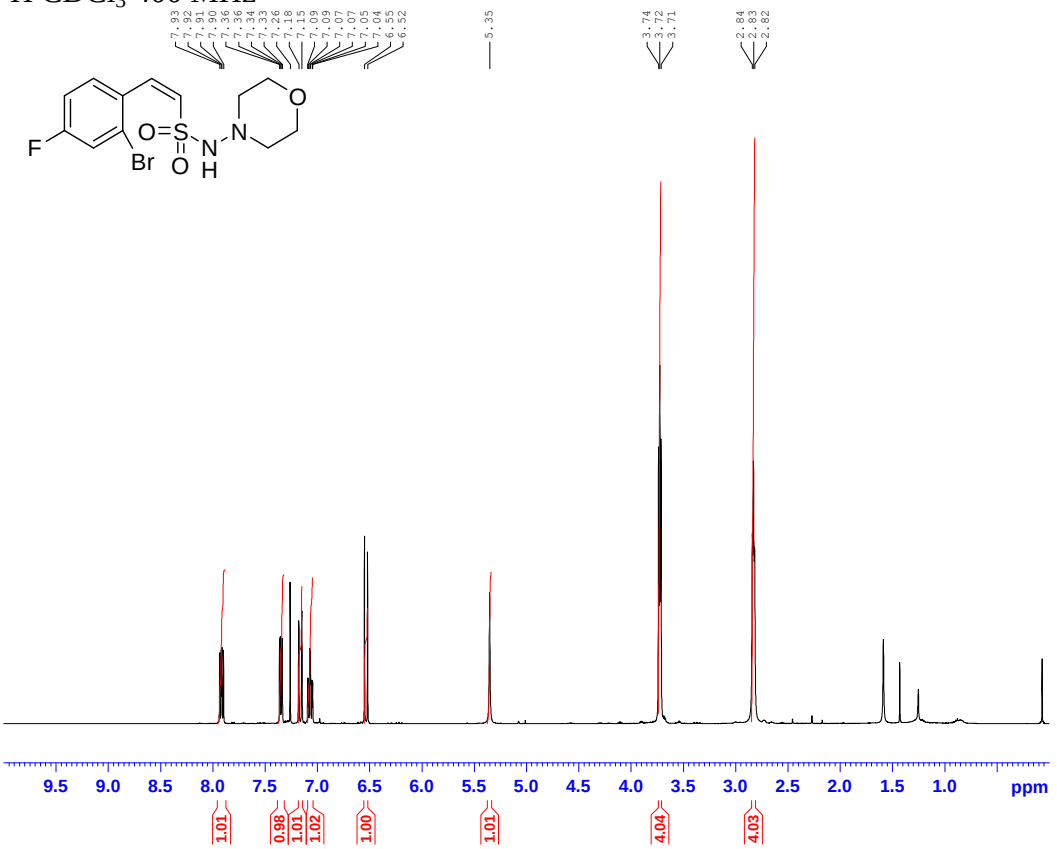


^{13}C $CDCl_3$ 126 MHz

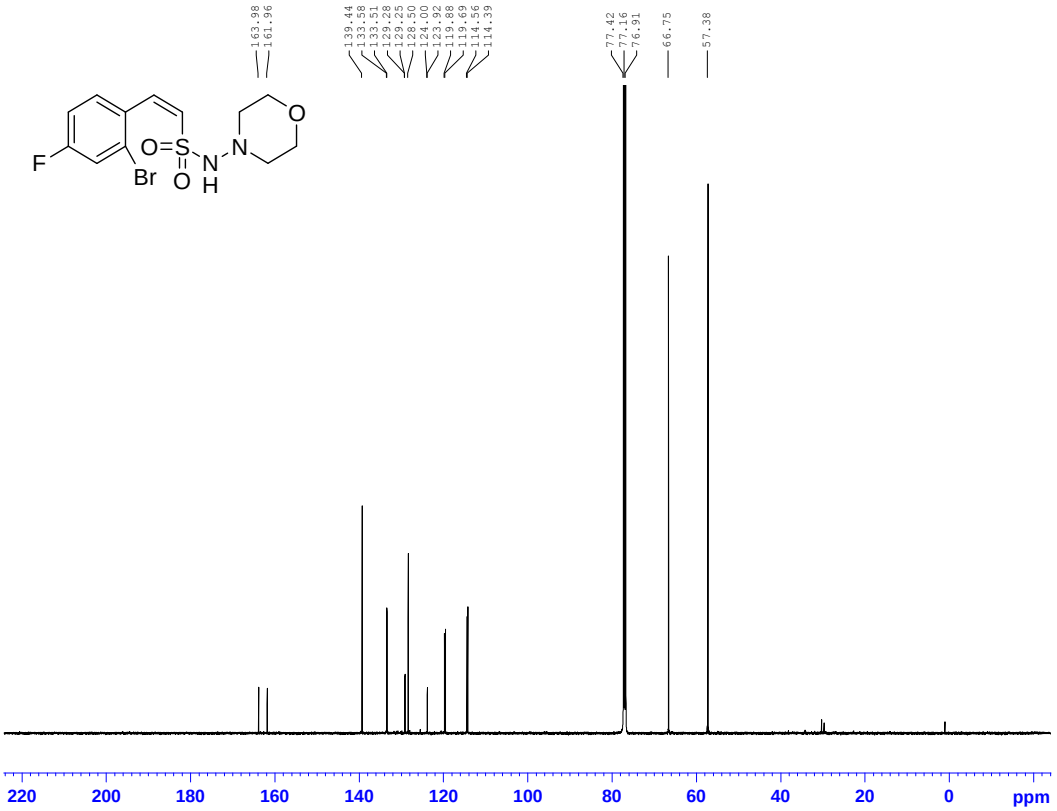


(*Z*)-2-(2-Bromo-4-fluorophenyl)-*N*-morpholinoethenesulfonamide

^{1}H $CDCl_3$ 400 MHz

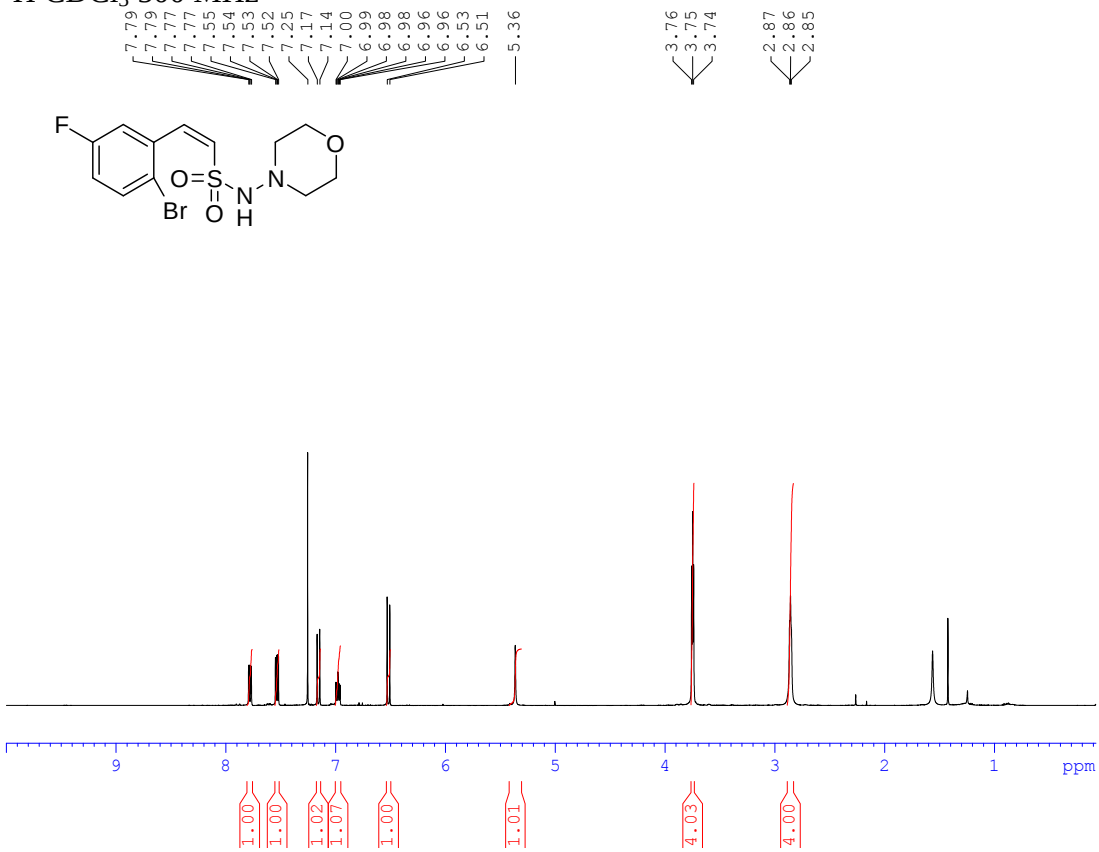


^{13}C $CDCl_3$ 126 MHz

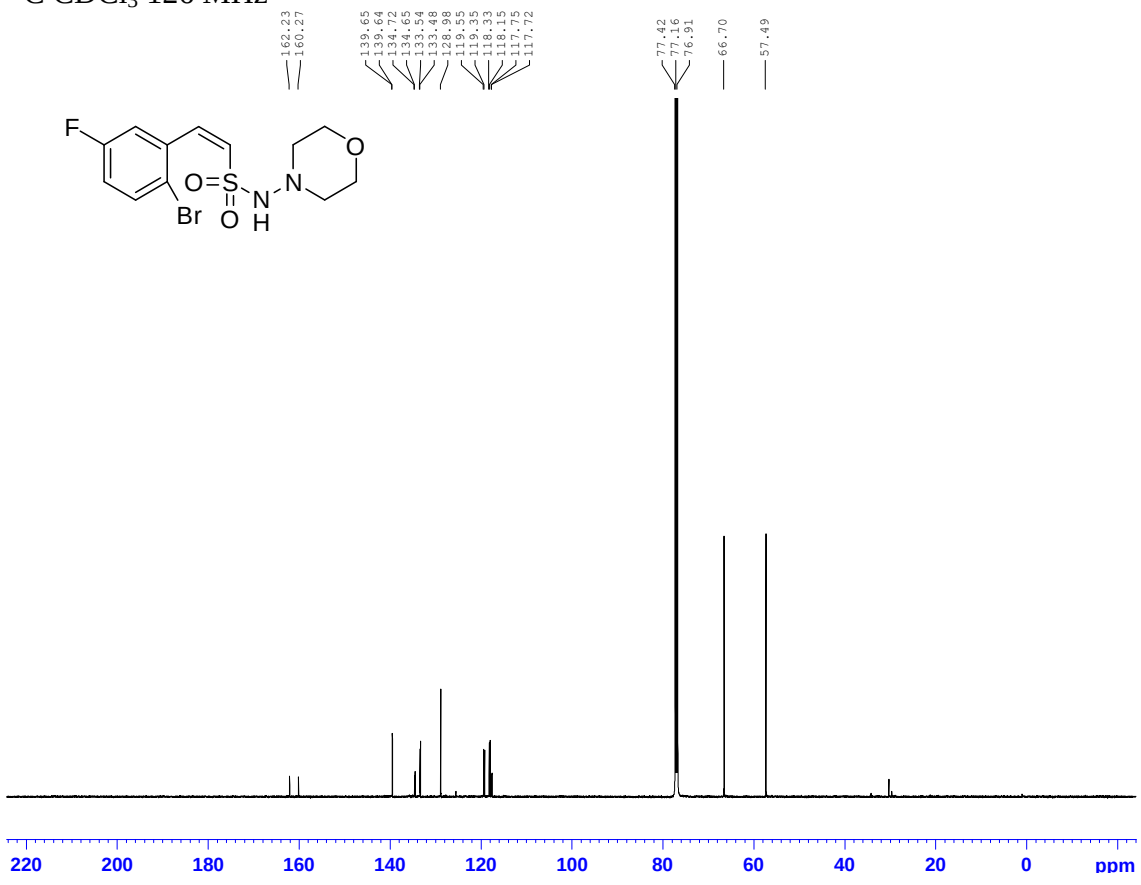


(Z)-2-(2-Bromo-5-fluorophenyl)-N-morpholinoethenesulfonamide

^{1}H $CDCl_3$ 500 MHz

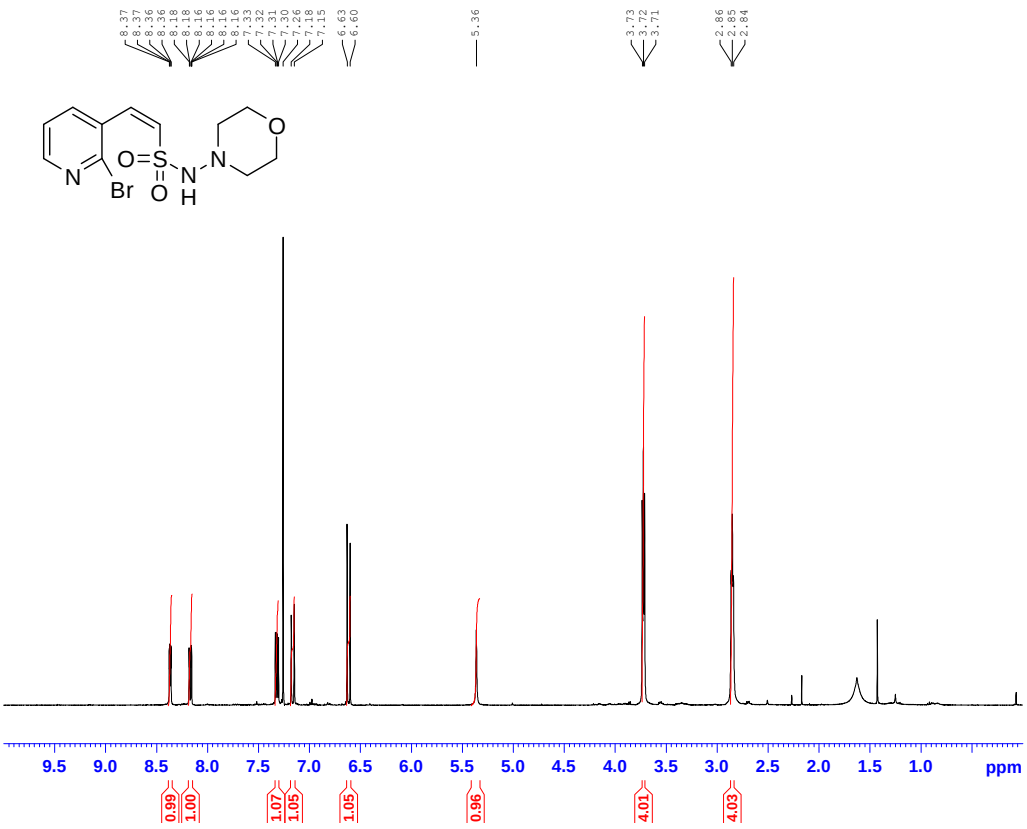


^{13}C $CDCl_3$ 126 MHz



(*Z*)-2-(2-Bromopyridin-3-yl)-*N*-morpholinoethenesulfonamide

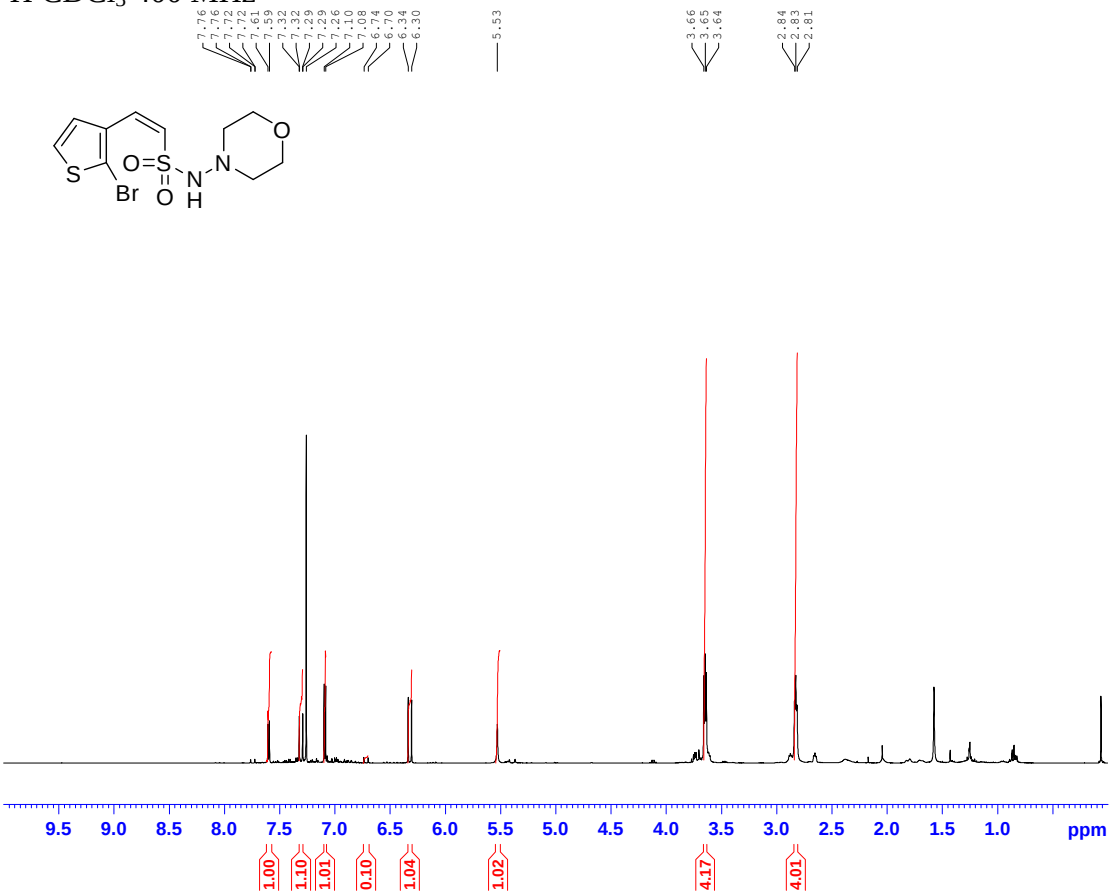
^{1}H $CDCl_3$ 400 MHz



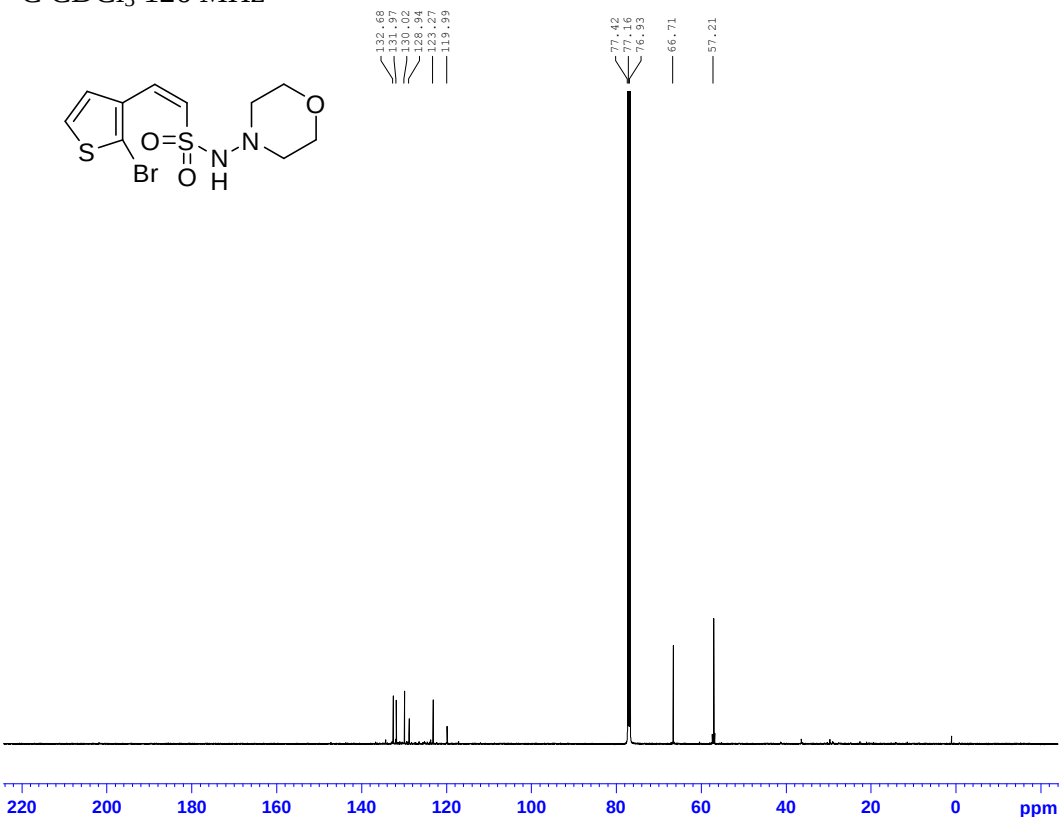
^{13}C $CDCl_3$ 126 MHz

2-(2-Bromothiophen-3-yl)-*N*-morpholinoethenesulfonamide

^{1}H $CDCl_3$ 400 MHz

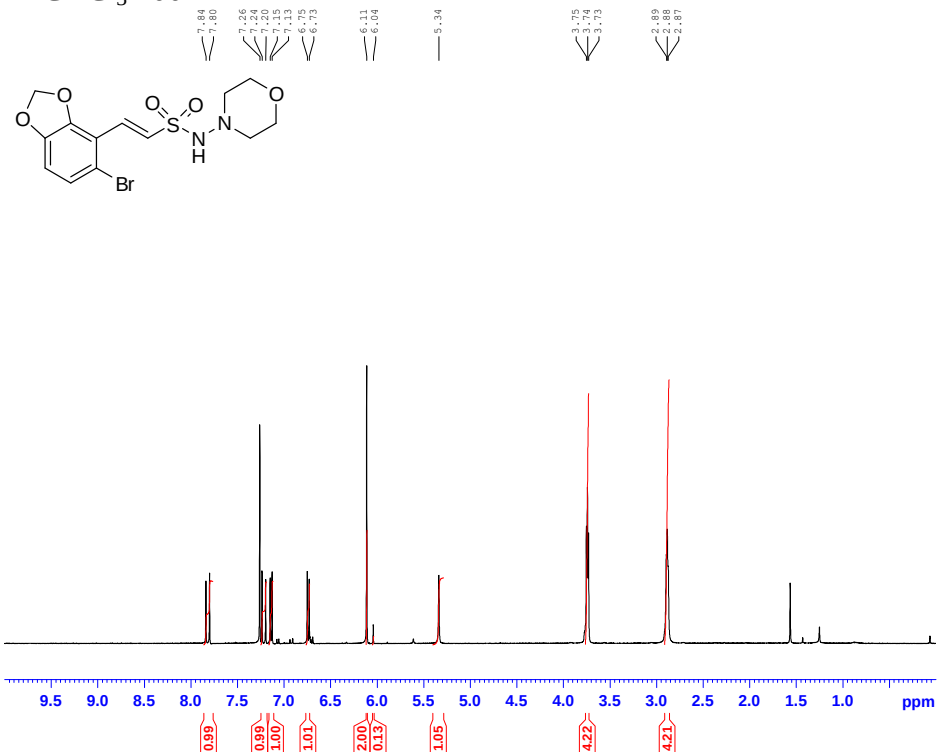


^{13}C $CDCl_3$ 126 MHz

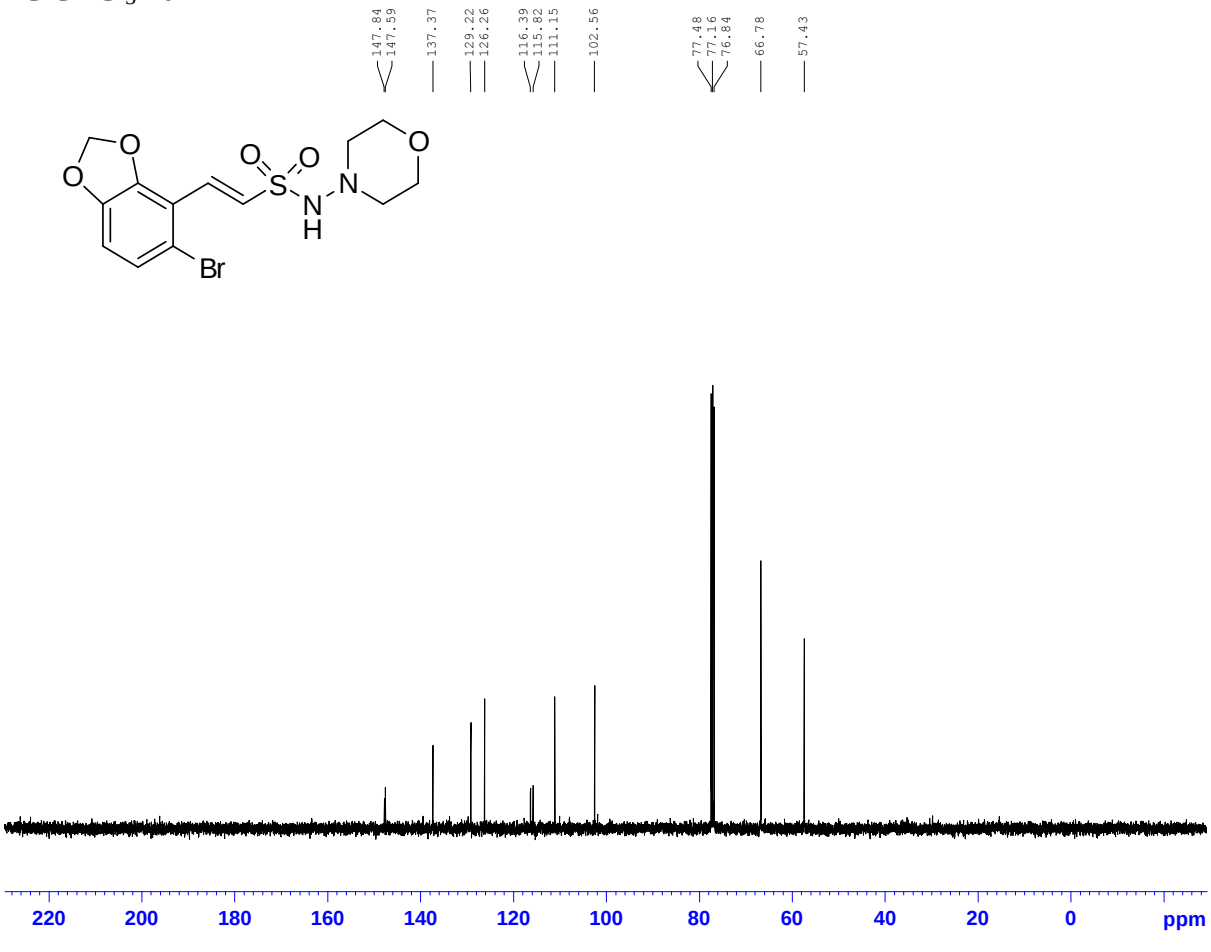


2-(5-Bromobenzo[*d*][1,3]dioxol-4-yl)-*N*-morpholinoethenesulfonamide

^{1}H $CDCl_3$ 400 MHz

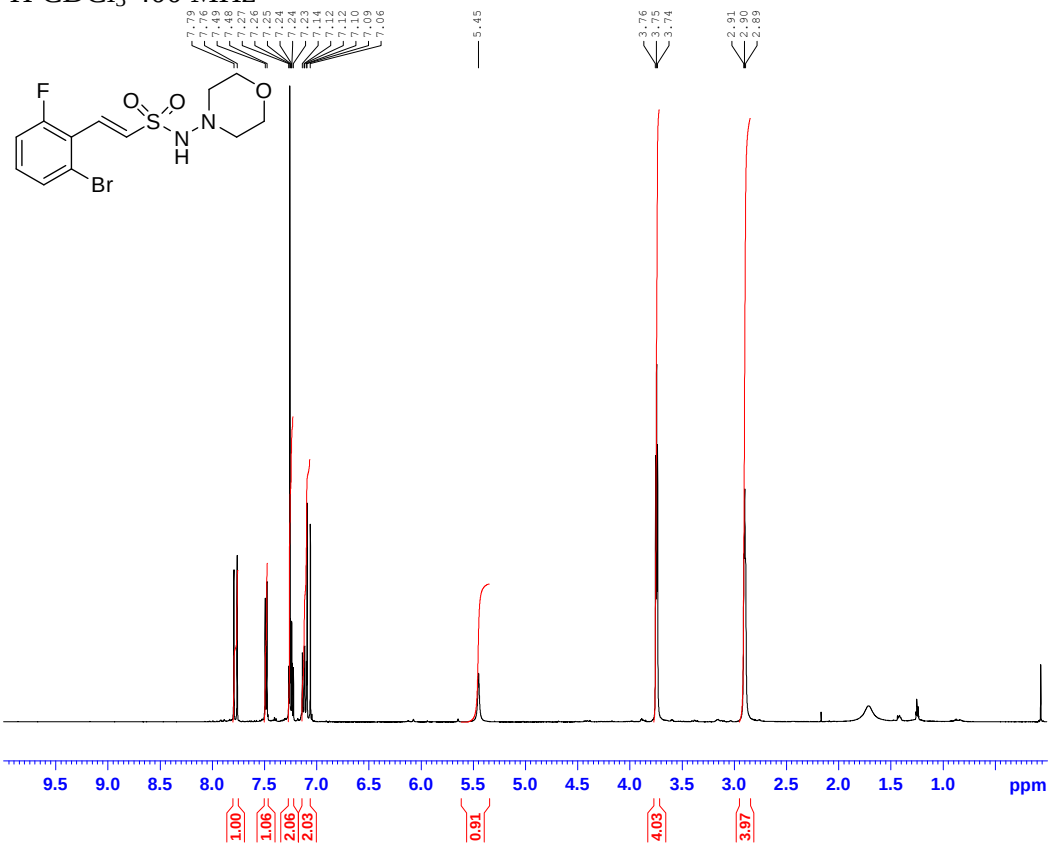


^{13}C $CDCl_3$ 101 MHz

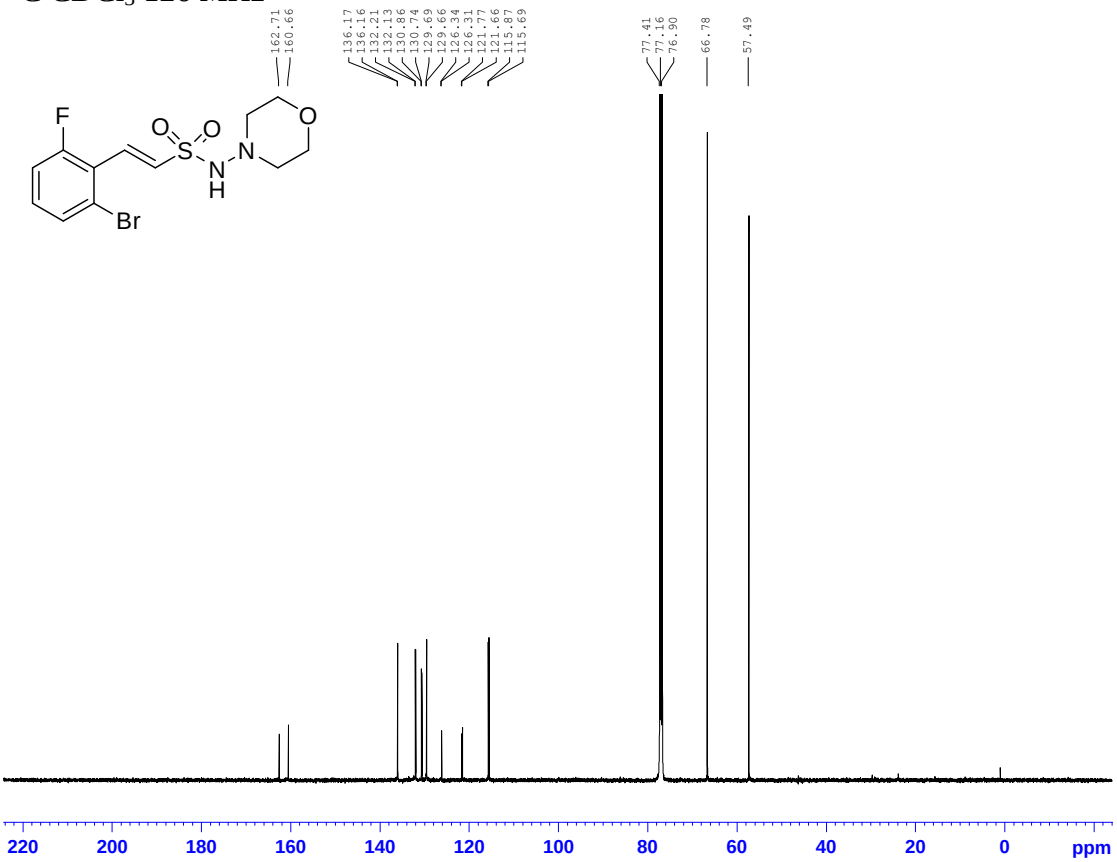


(*E*)-2-(2-Bromo-6-fluorophenyl)-*N*-morpholinoethenesulfonamide

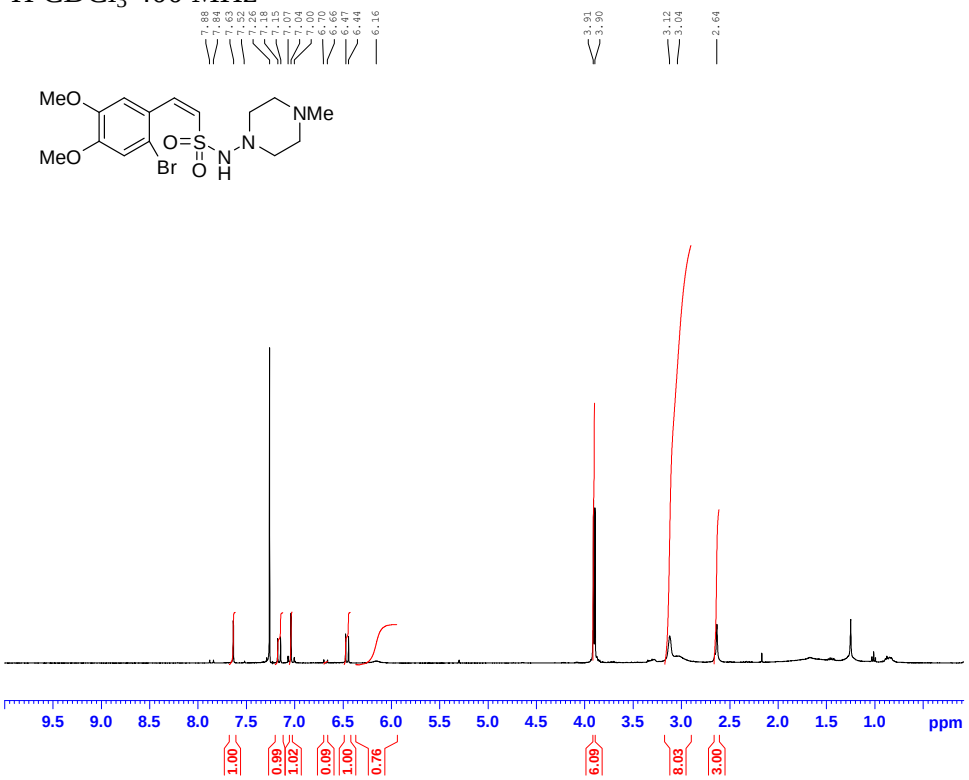
^{1}H $CDCl_3$ 400 MHz



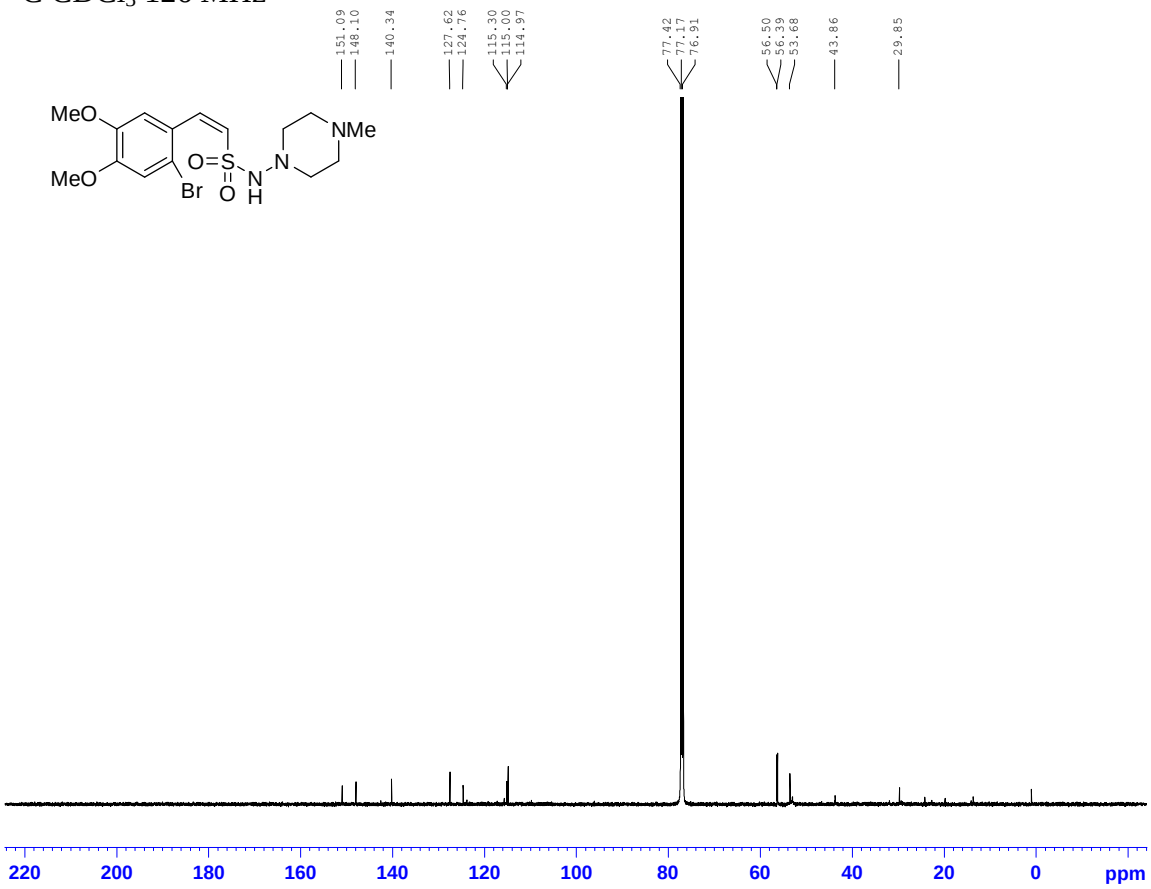
^{13}C $CDCl_3$ 126 MHz



(*Z*)-2-(2-Bromo-4,5-dimethoxyphenyl)-*N*-(4-methylpiperazin-1-yl)ethenesulfonamide,
^{1}H $CDCl_3$ 400 MHz

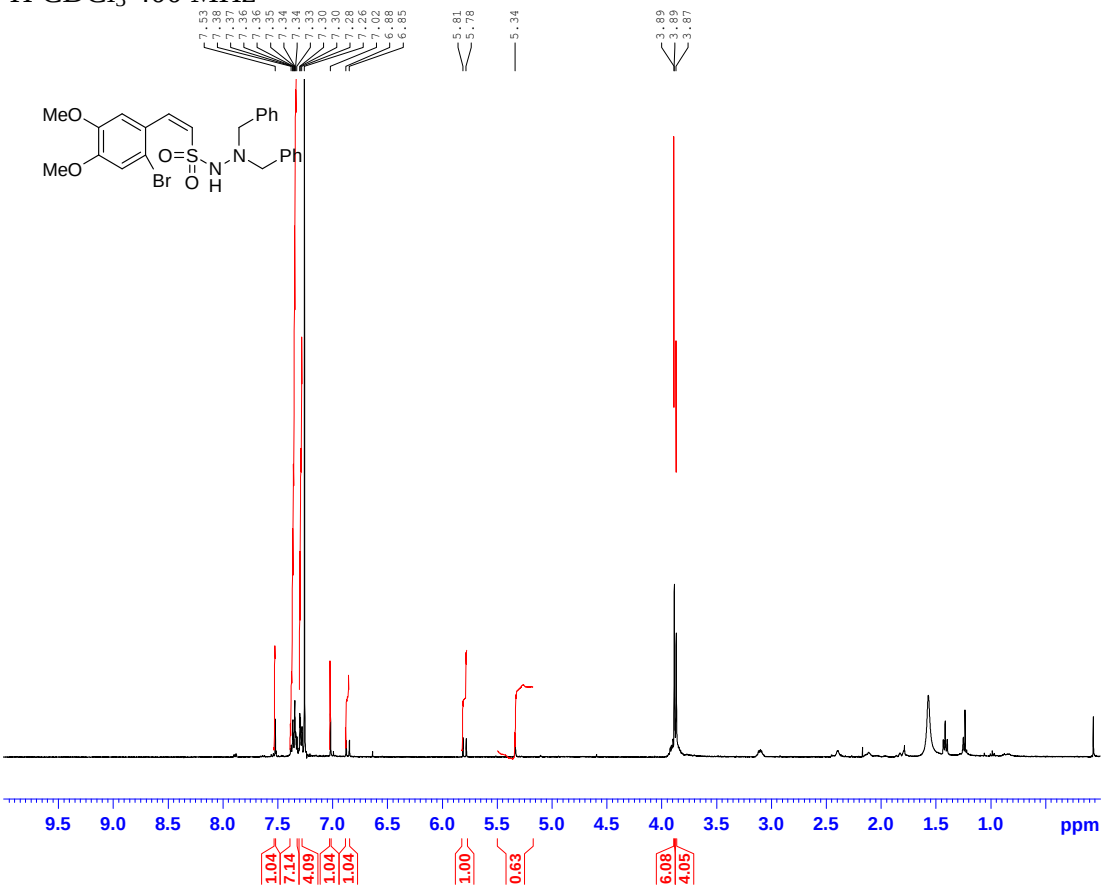


^{13}C $CDCl_3$ 126 MHz

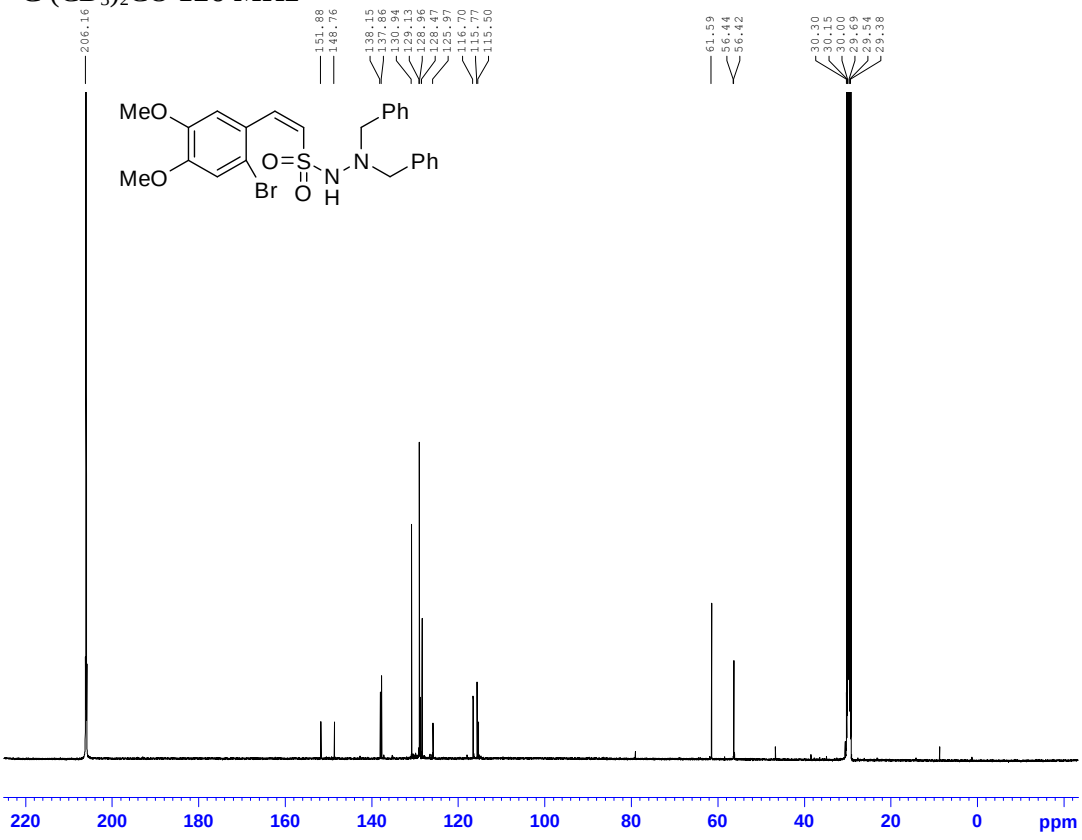


(*Z*)-*N*',*N*'-dibenzyl-2-(2-bromo-4,5-dimethoxyphenyl)ethenesulfonohydrazide,

^{1}H $CDCl_3$ 400 MHz

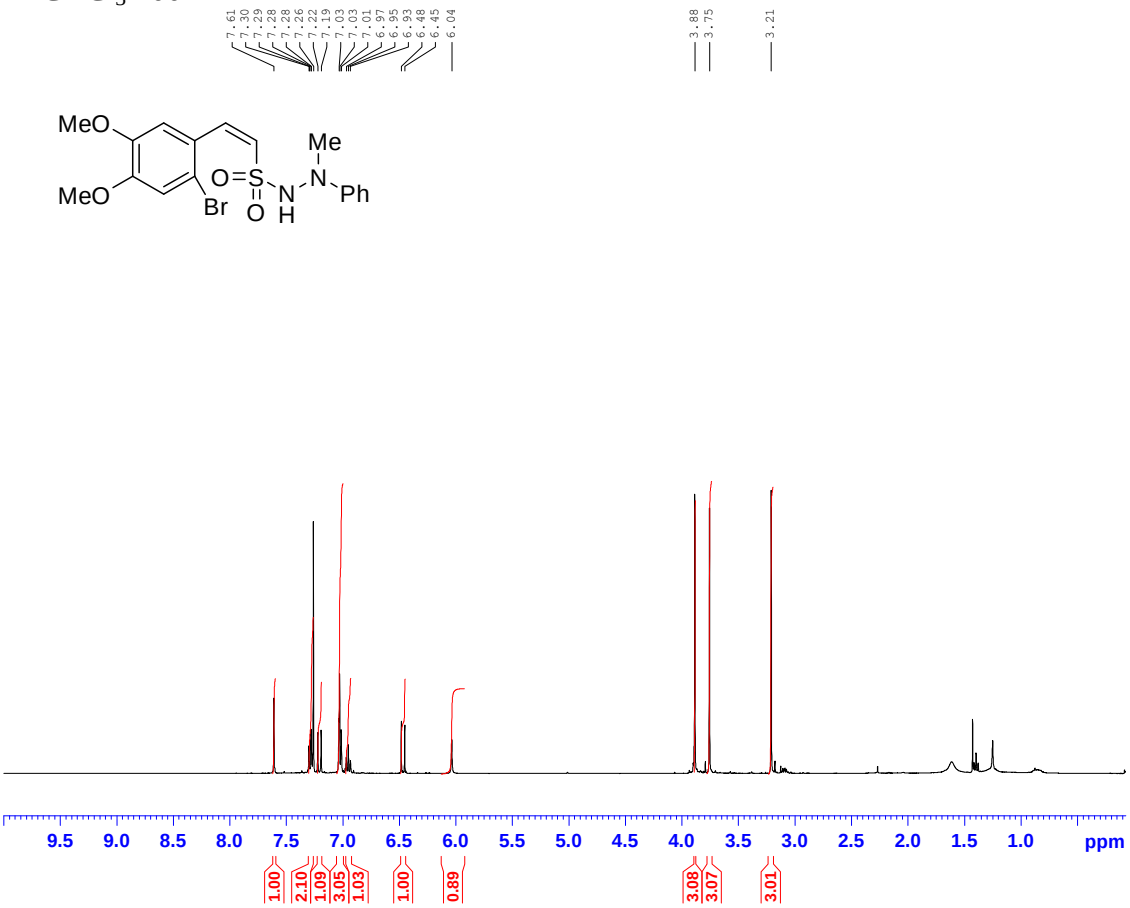


^{13}C $(CD_3)_2CO$ 126 MHz

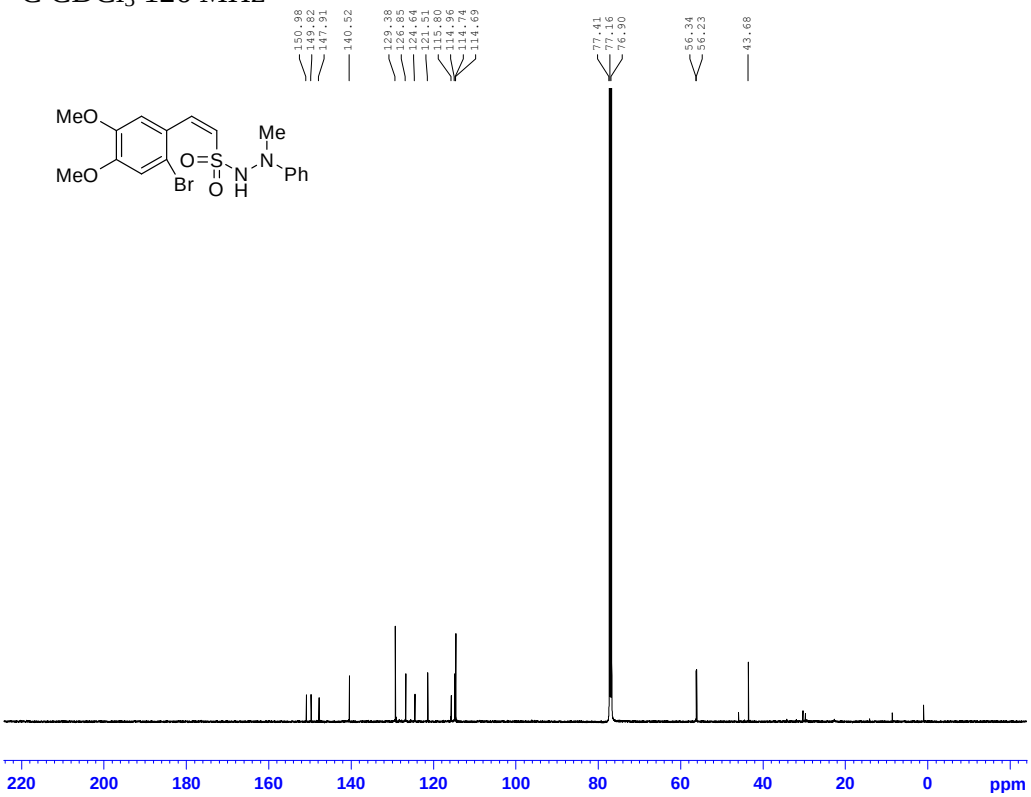


(*Z*)-2-(2-Bromo-4,5-dimethoxyphenyl)-*N*'-methyl-*N*'-phenylethenesulfonohydrazide

^{1}H $CDCl_3$ 400 MHz

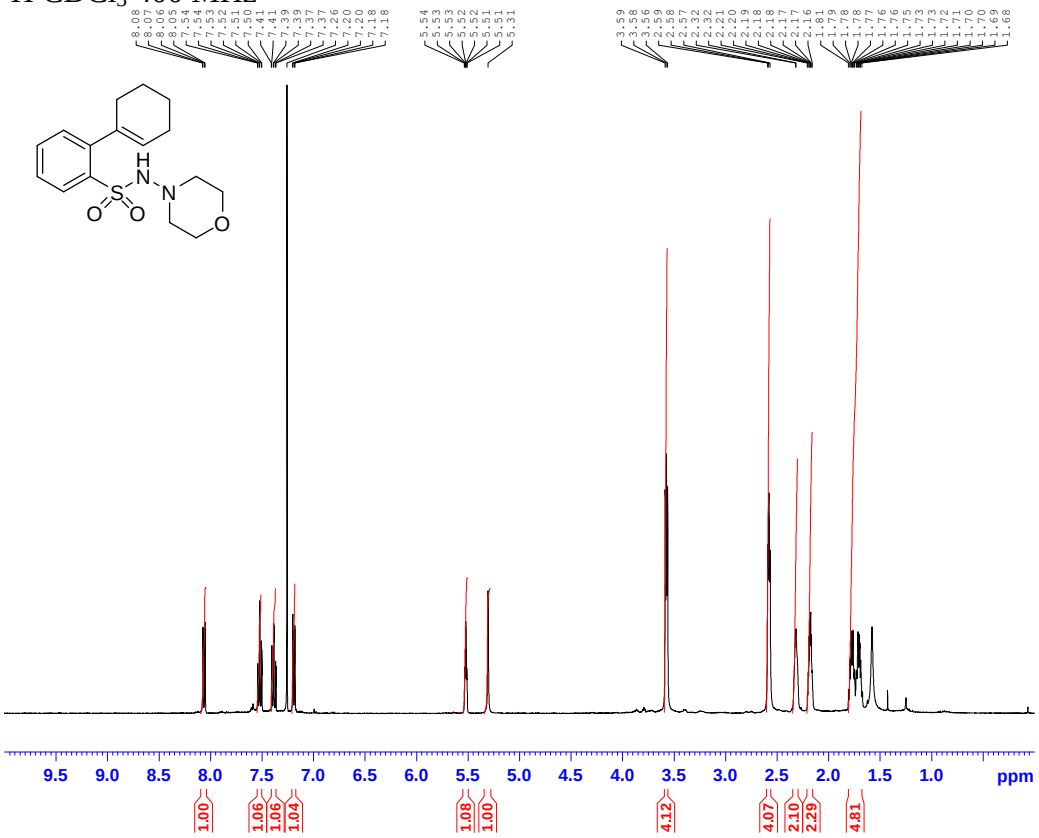


^{13}C $CDCl_3$ 126 MHz

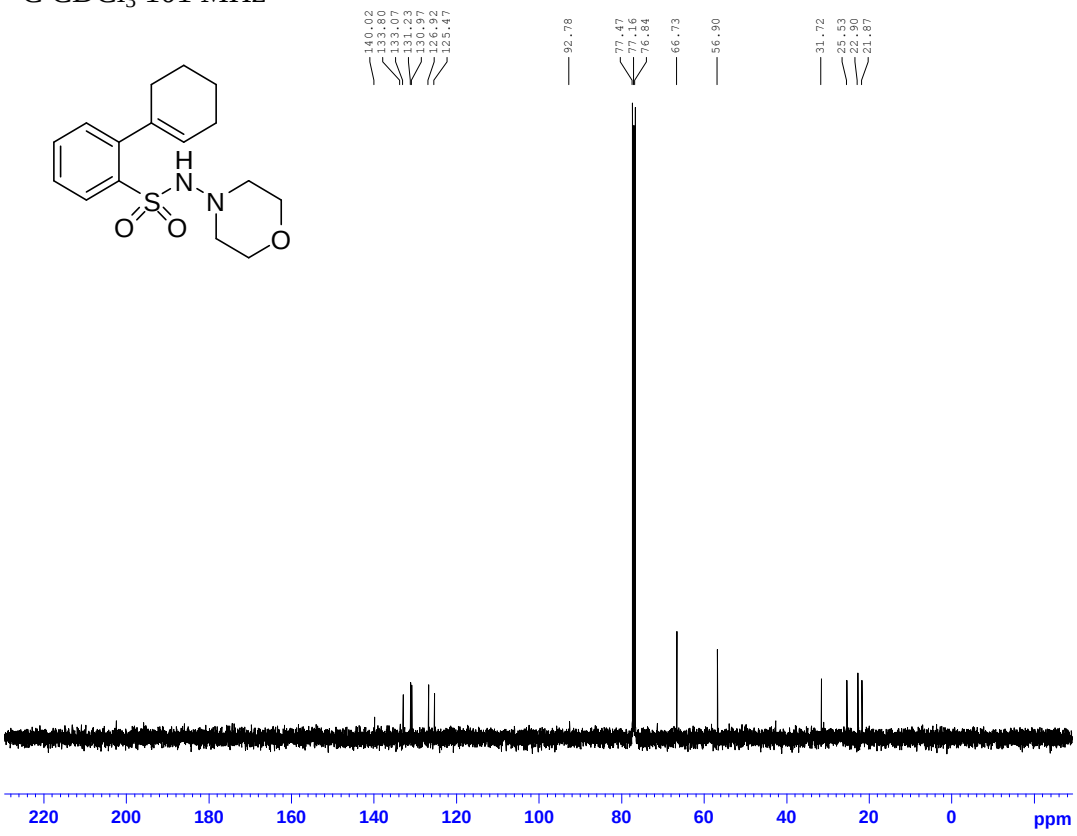


_N_-Morpholino-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2-sulfonamide

^{1}H $CDCl_3$ 400 MHz

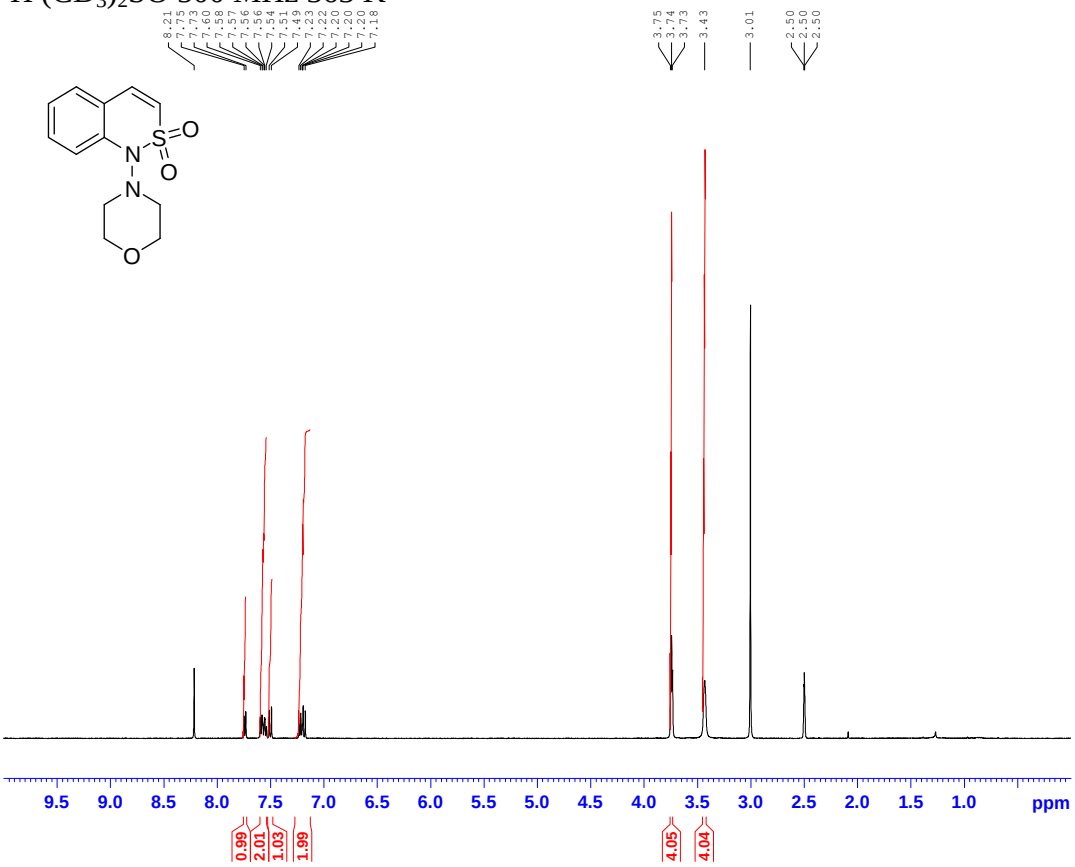


^{13}C $CDCl_3$ 101 MHz

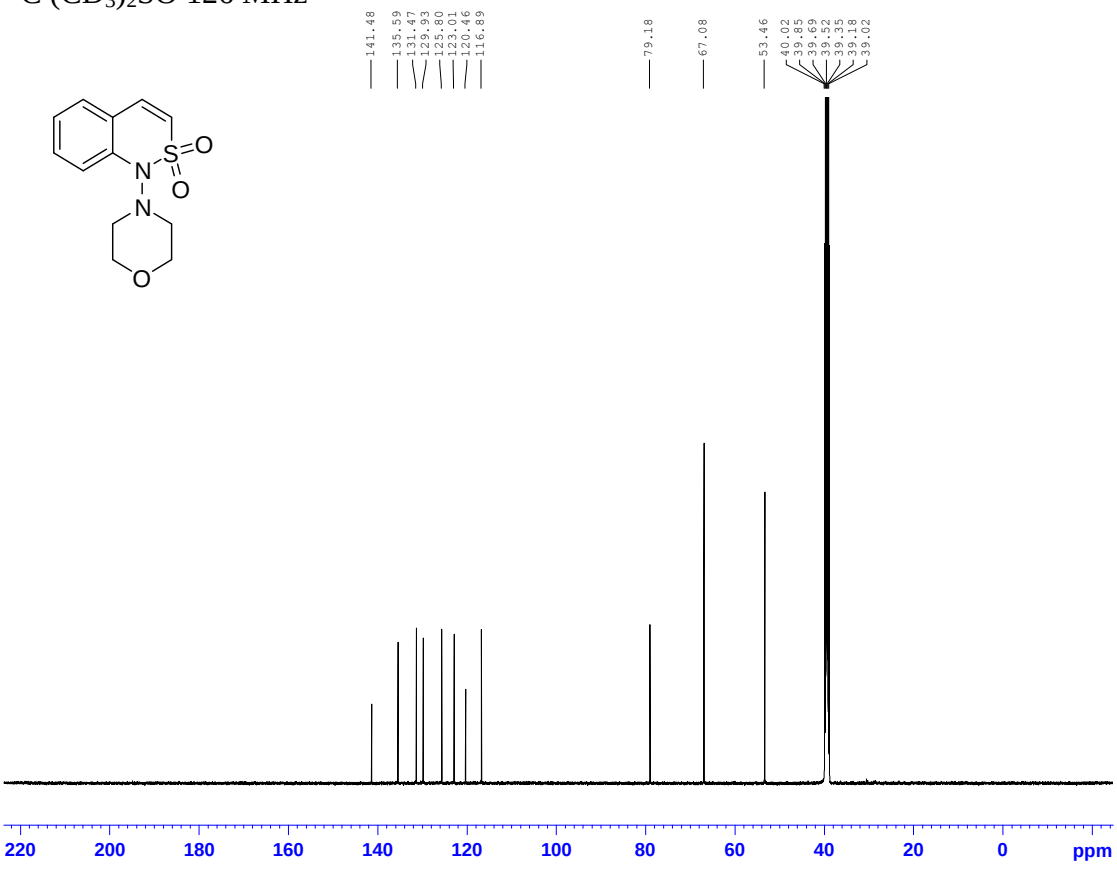


1-(Morpholin-4-yl)-1*H*-2,1-benzothiazine 2,2-dioxide,

^{1}H $(CD_3)_2SO$ 500 MHz 363 K

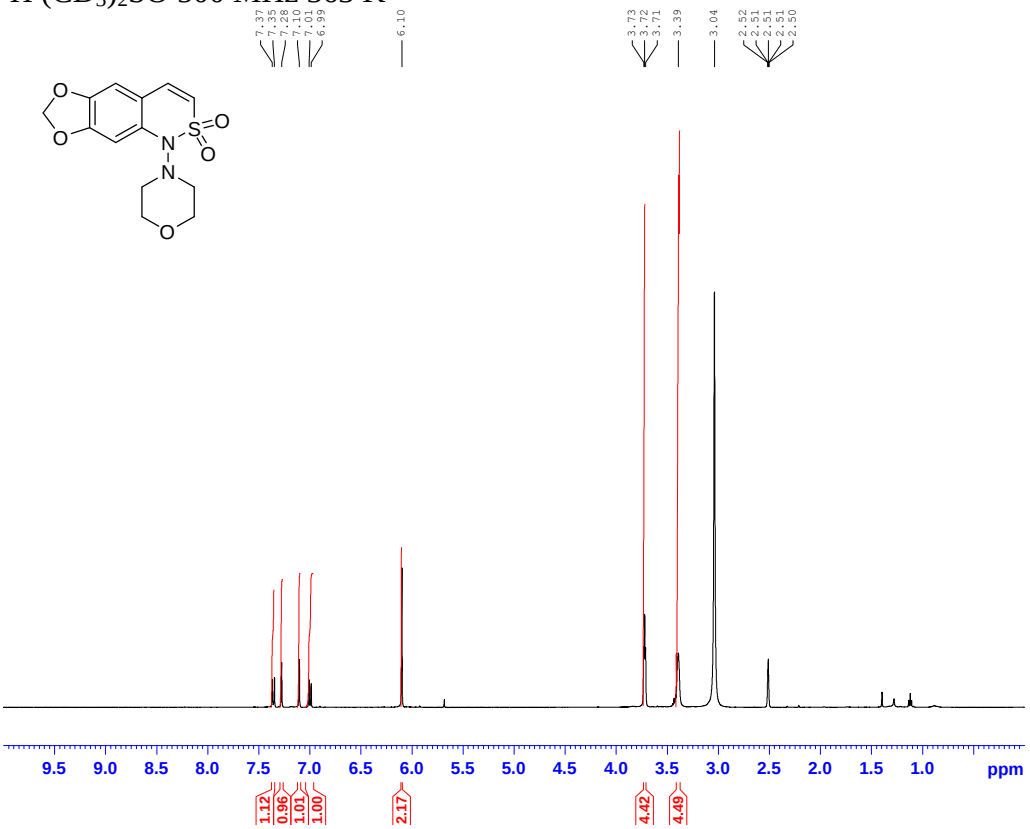


^{13}C $(CD_3)_2SO$ 126 MHz

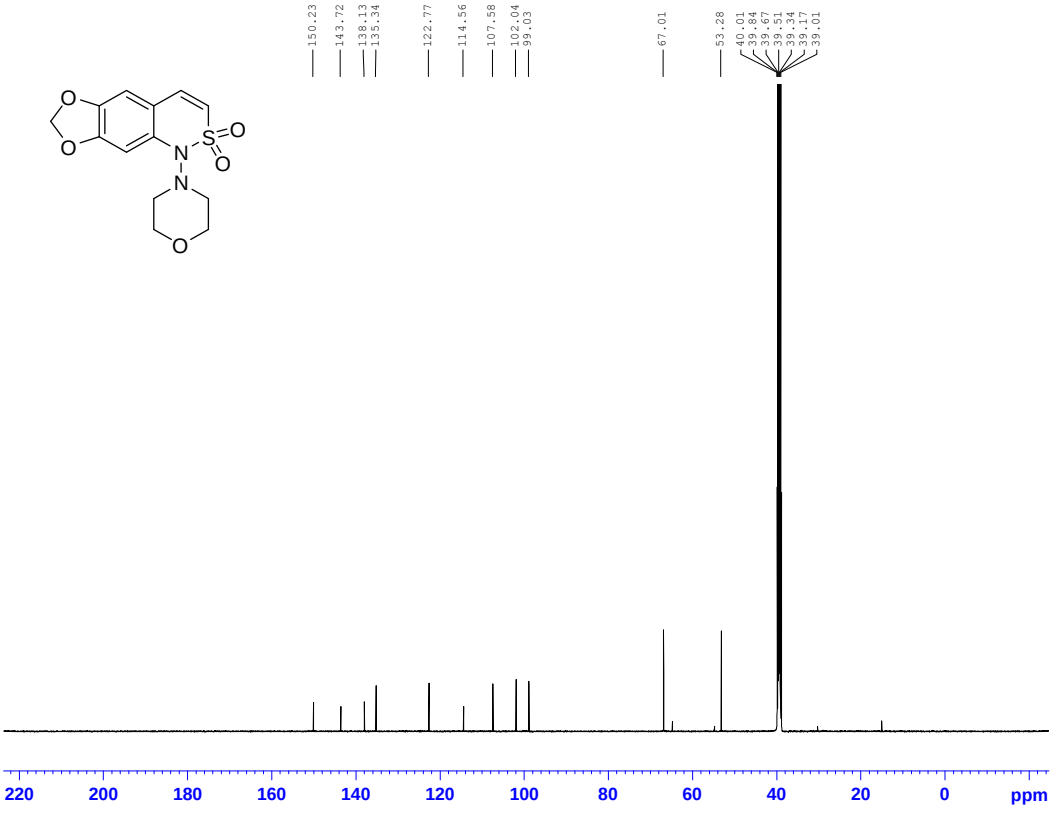


1-Morpholino-1H-[1,3]dioxolo[4',5':4,5]benzo[1,2-c][1,2]thiazine 2,2-dioxide

^{1}H $(CD_3)_2SO$ 500 MHz 363 K

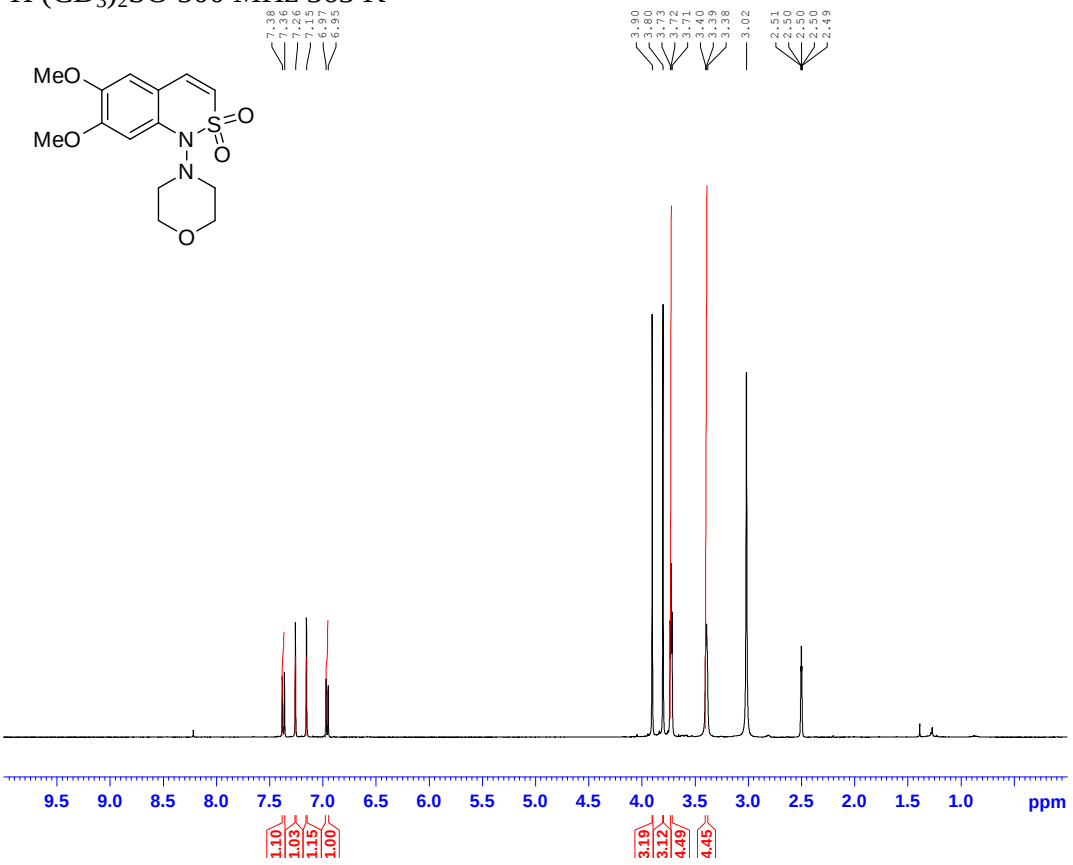


^{13}C $(CD_3)_2SO$ 101 MHz

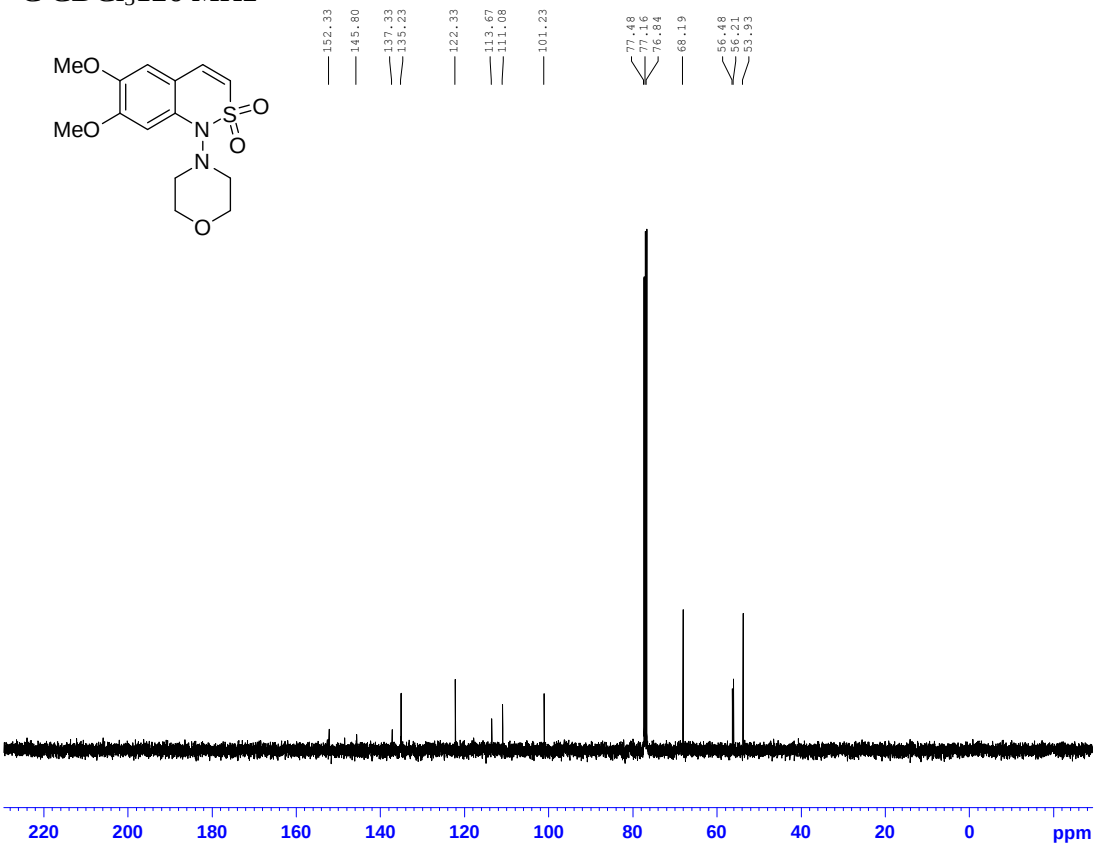


6,7-Dimethoxy-1-morpholino-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide

^{1}H $(CD_3)_2SO$ 500 MHz 363 K

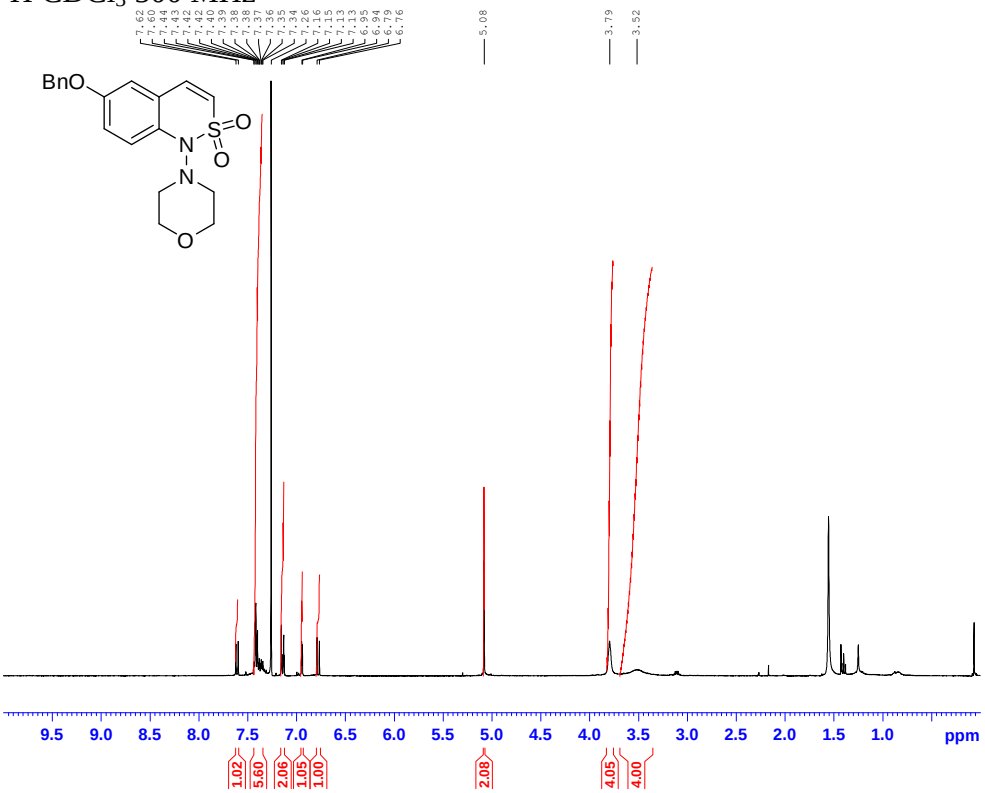


^{13}C $CDCl_3$126 MHz

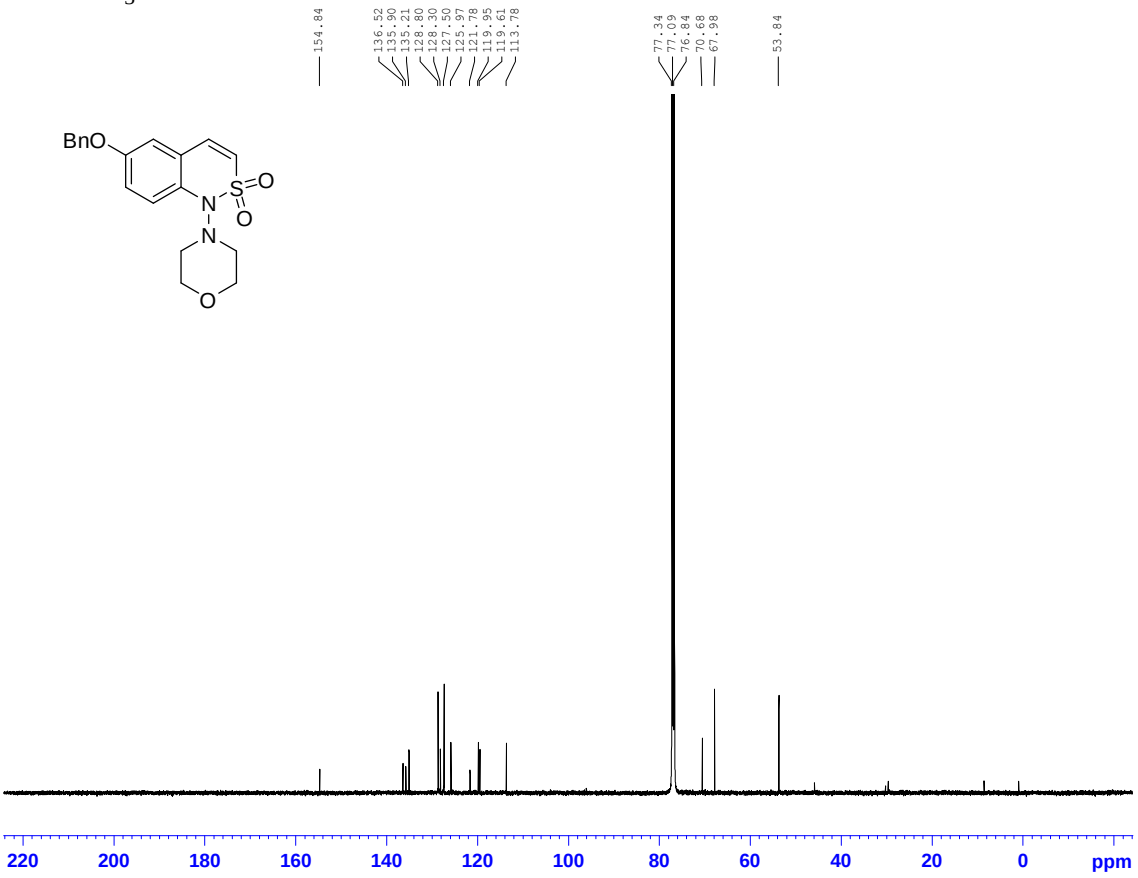


6-(Benzyloxy)-1-morpholino-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide

^{1}H $CDCl_3$ 500 MHz

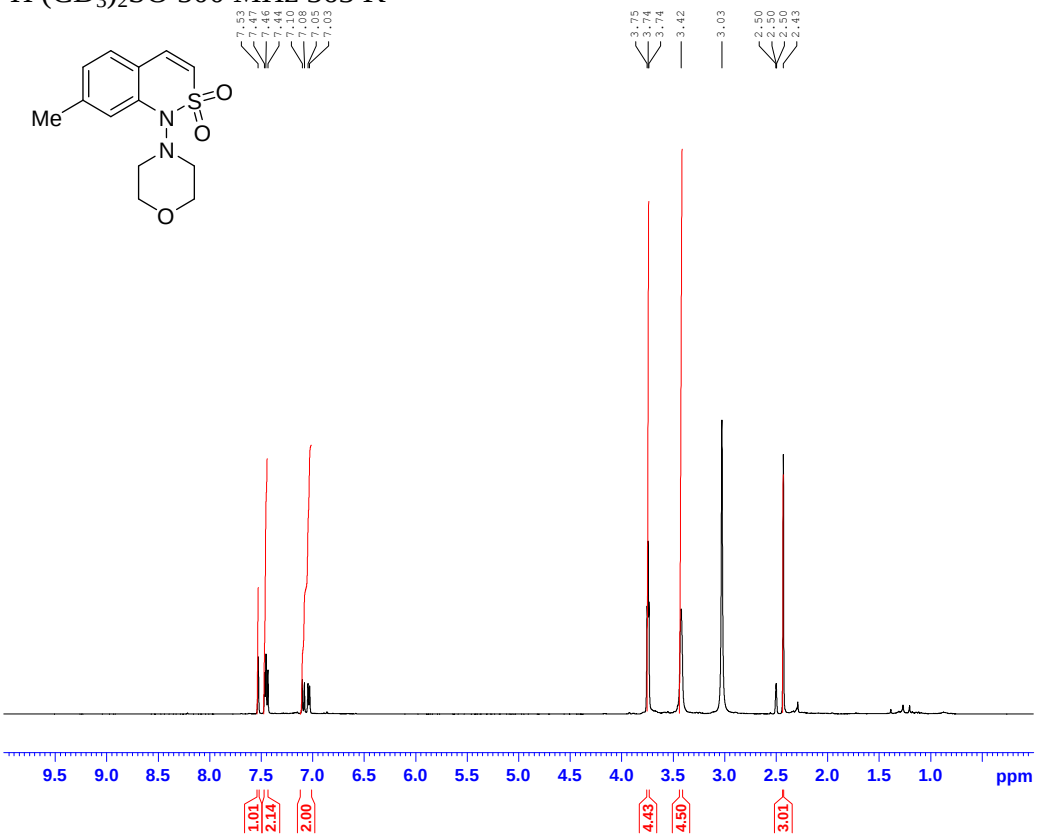


^{13}C $CDCl_3$ 126 MHz

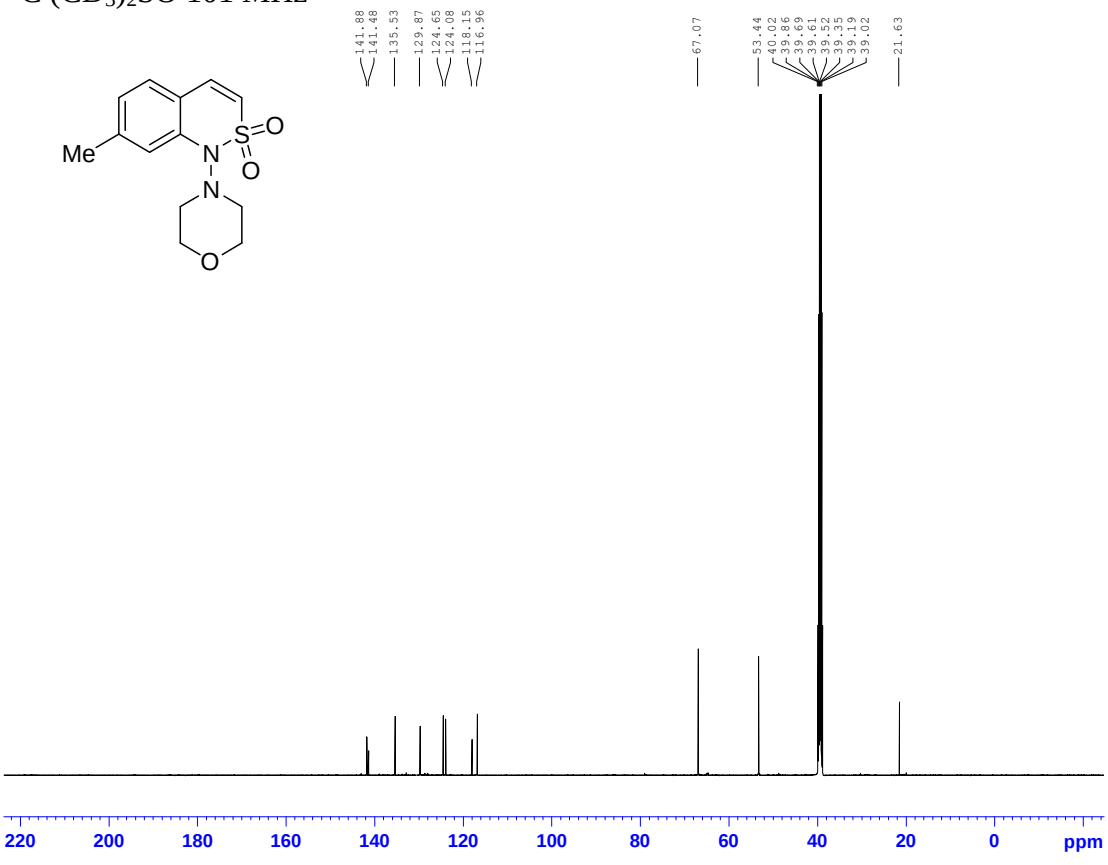


7-Methyl-1-morpholino-1H-benzo[c][1,2]thiazine 2,2-dioxide

^{1}H $(CD_3)_2SO$ 500 MHz 363 K

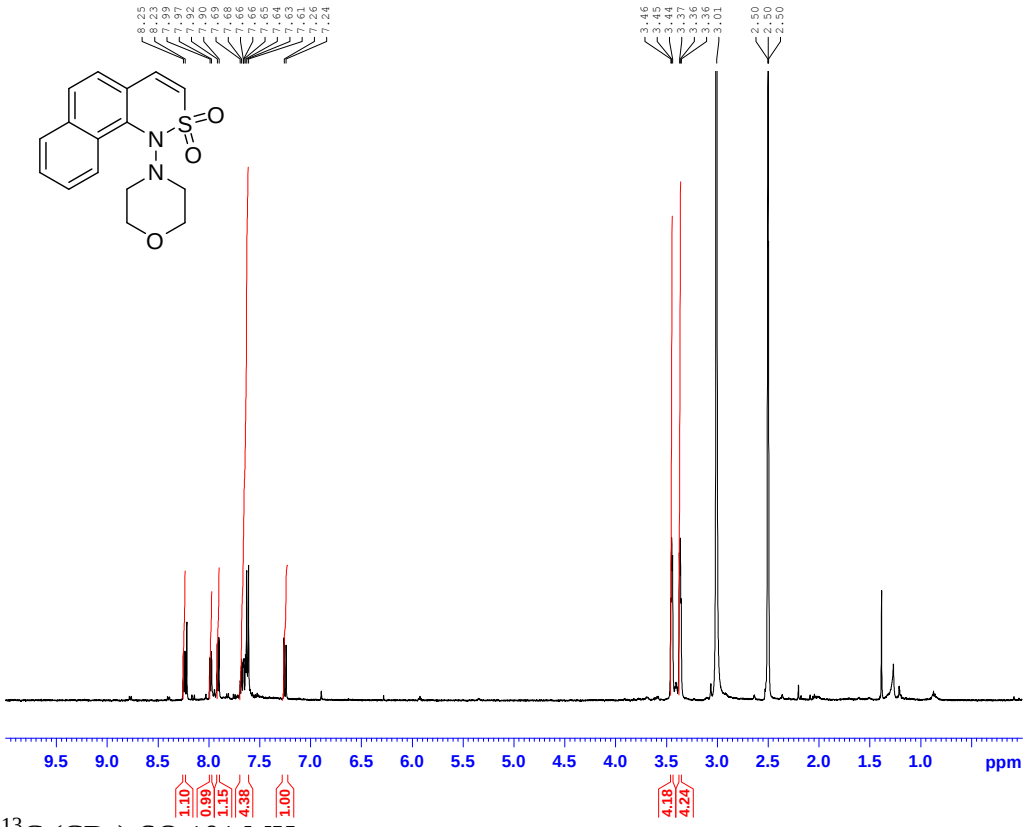


^{13}C $(CD_3)_2SO$ 101 MHz

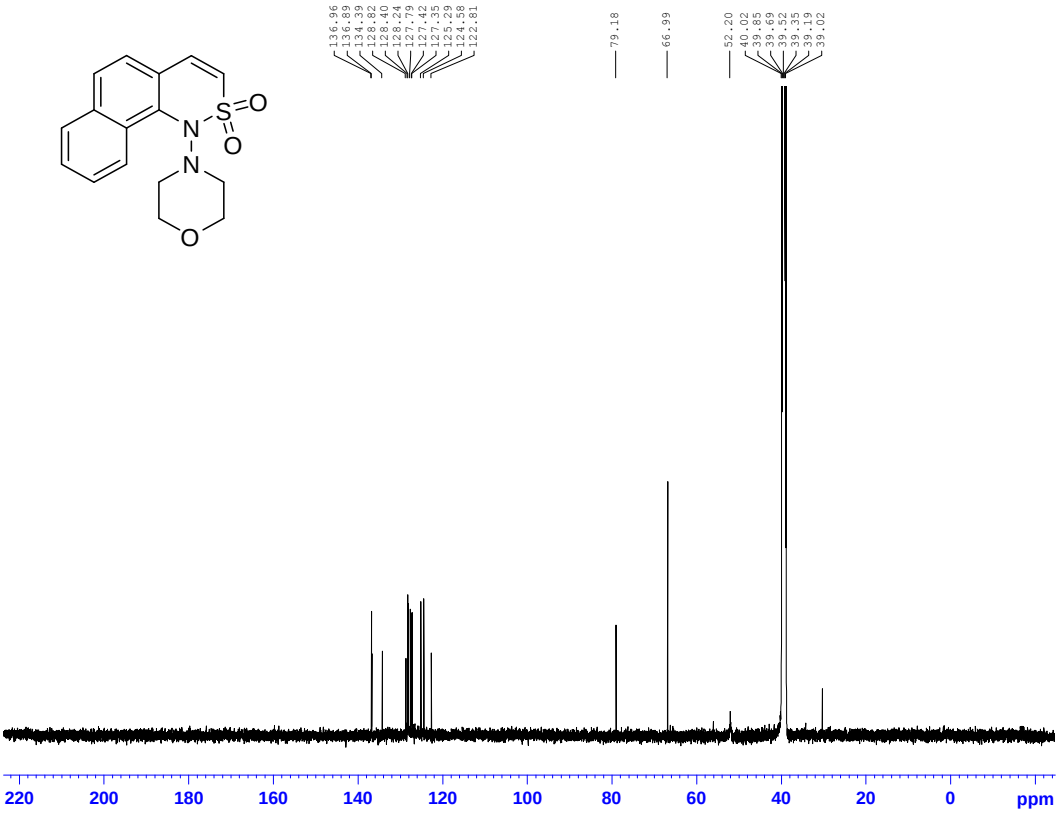


1-Morpholino-1*H*-naphtho[1,2-*c*][1,2]thiazine 2,2-dioxide

^{1}H $(CD_3)_2SO$ 500 MHz 363 K

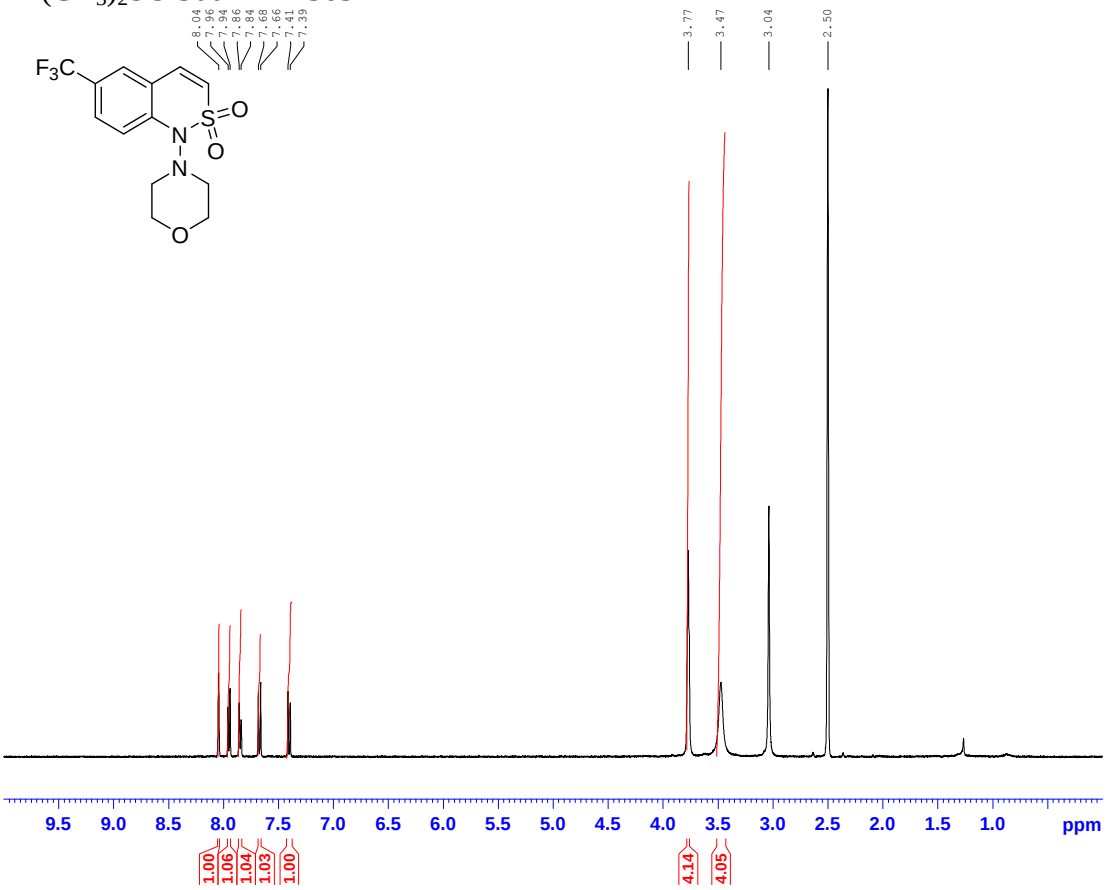


^{13}C $(CD_3)_2SO$ 101 MHz

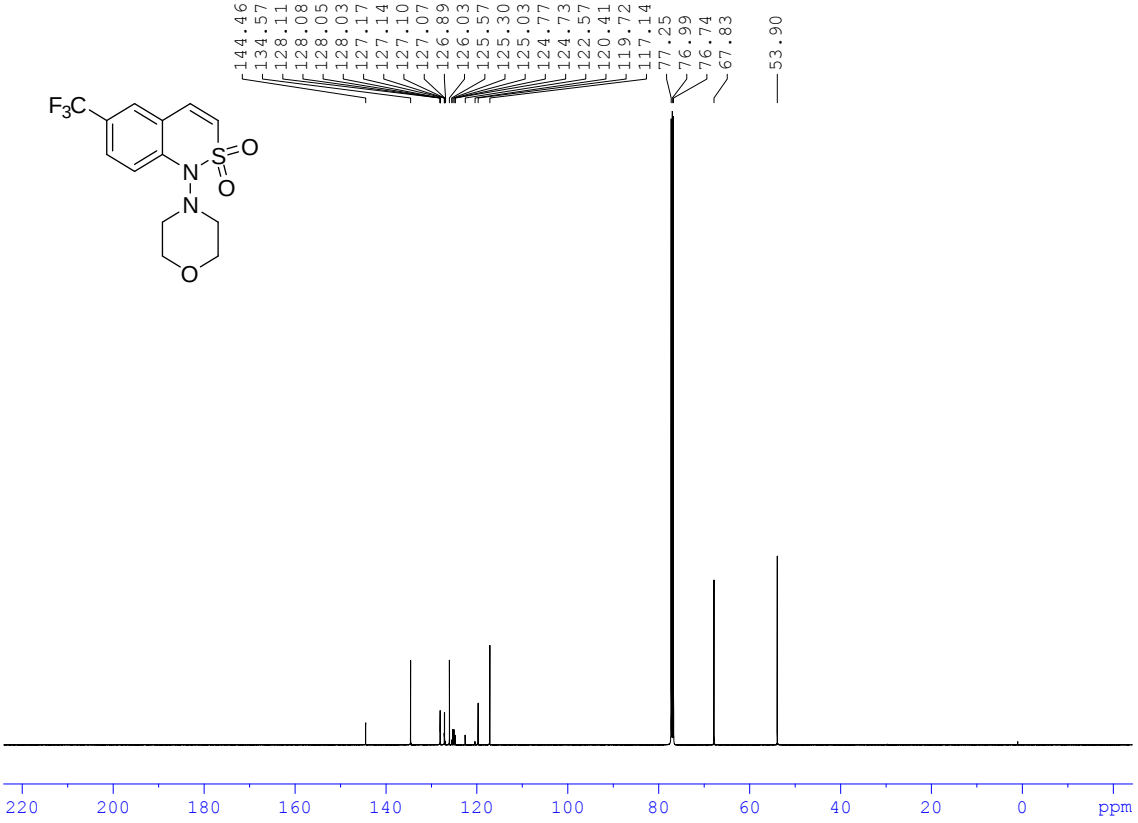


1-(Morpholin-4-yl)-6-(trifluoromethyl)-1*H*-2,1-benzothiazine 2,2-dioxide

^{1}H $(CD_3)_2SO$ 500 MHz 363 K

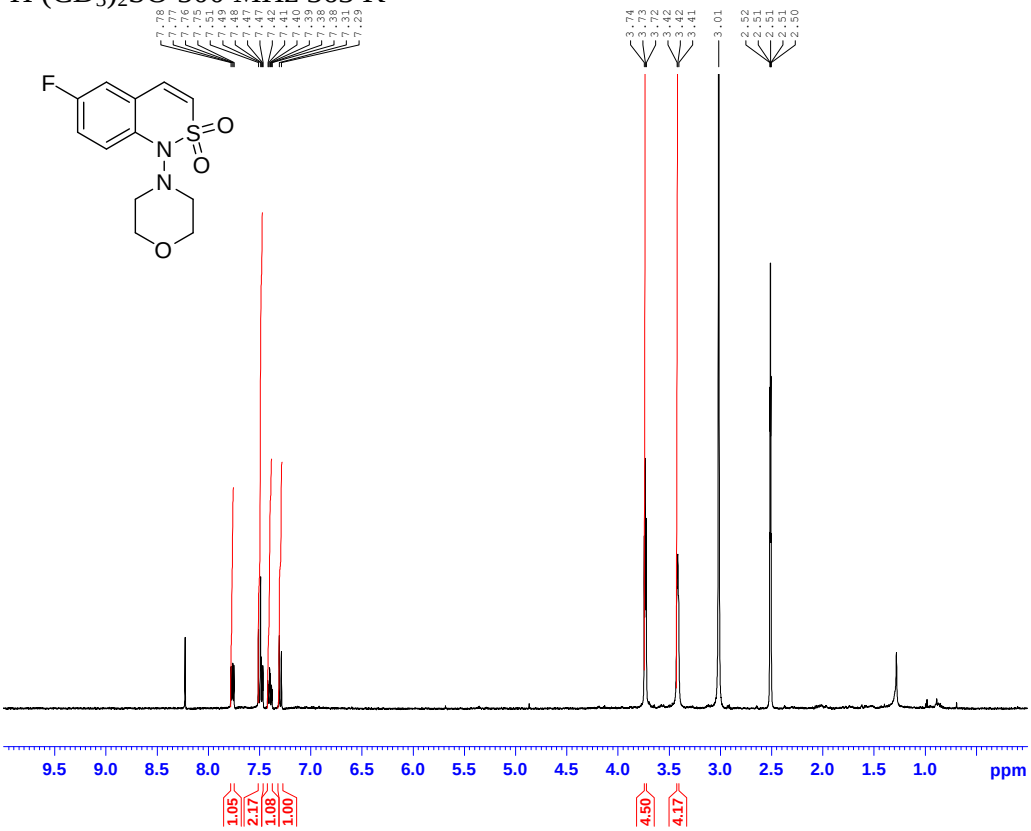


^{13}C $CDCl_3$ 126 MHz

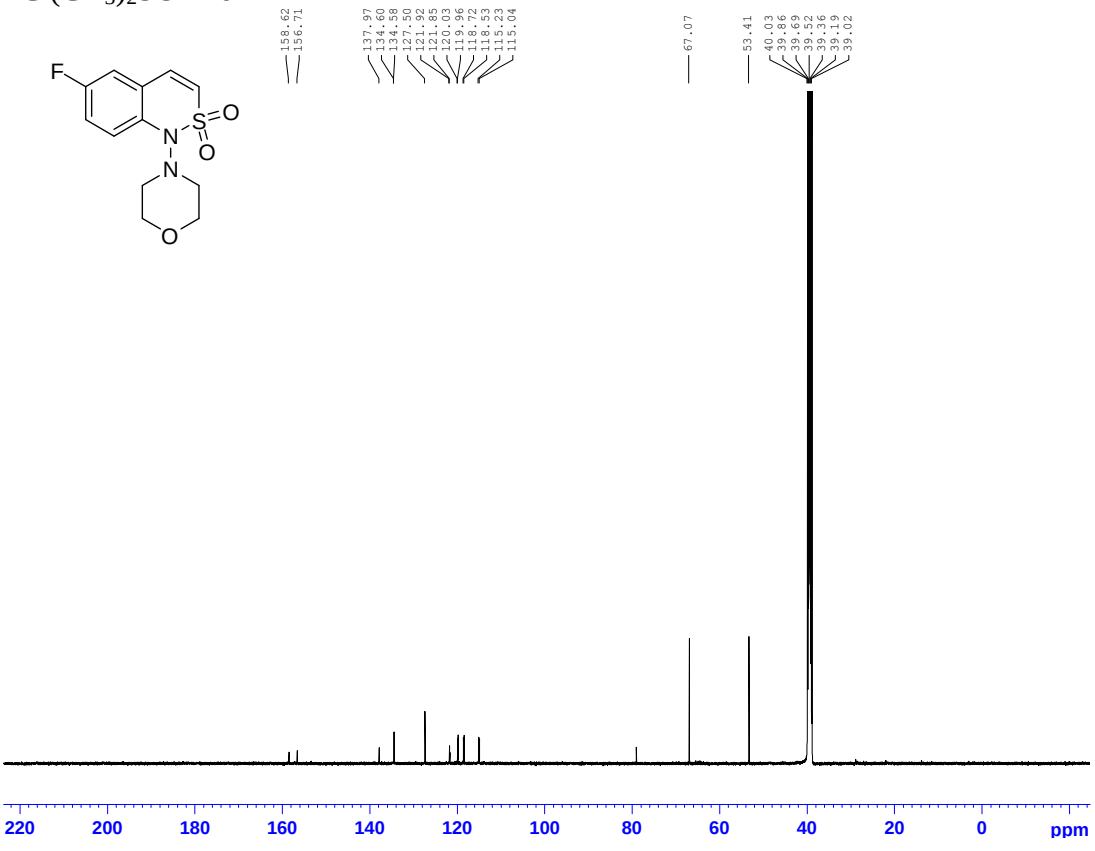


6-Fluoro-1-morpholino-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide

^{1}H $(CD_3)_2SO$ 500 MHz 363 K

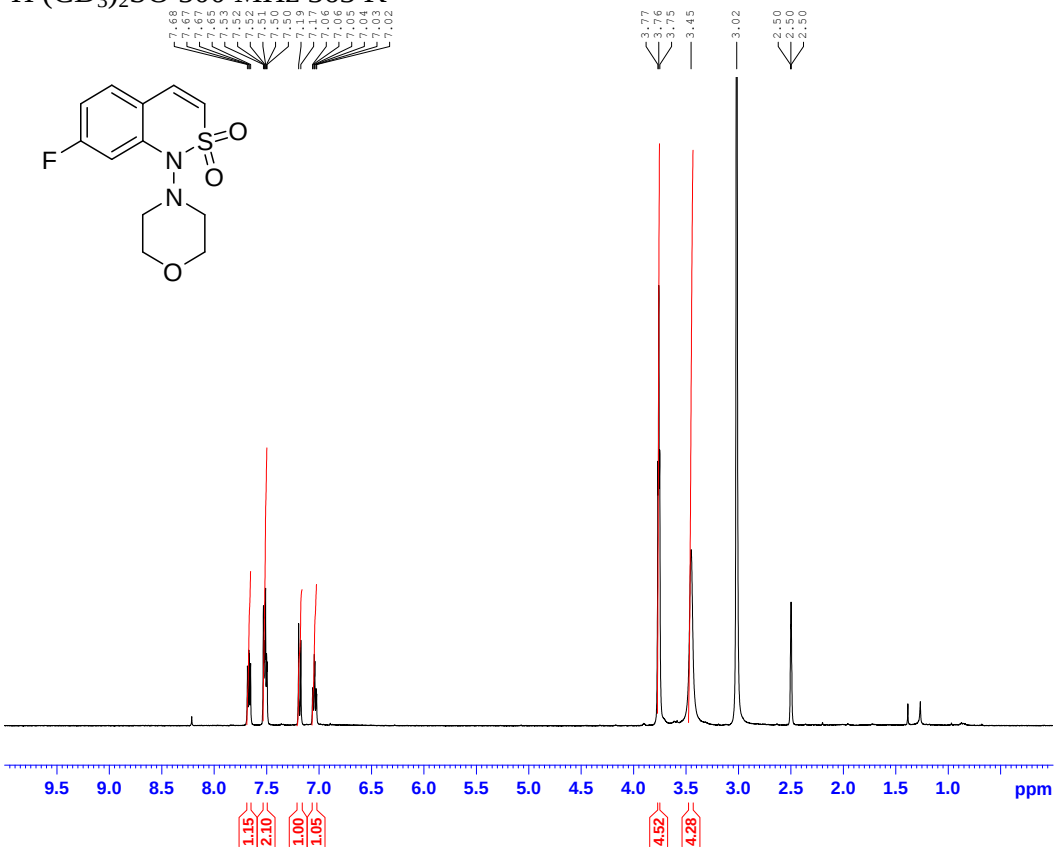


^{13}C $(CD_3)_2SO$ 126 MHz

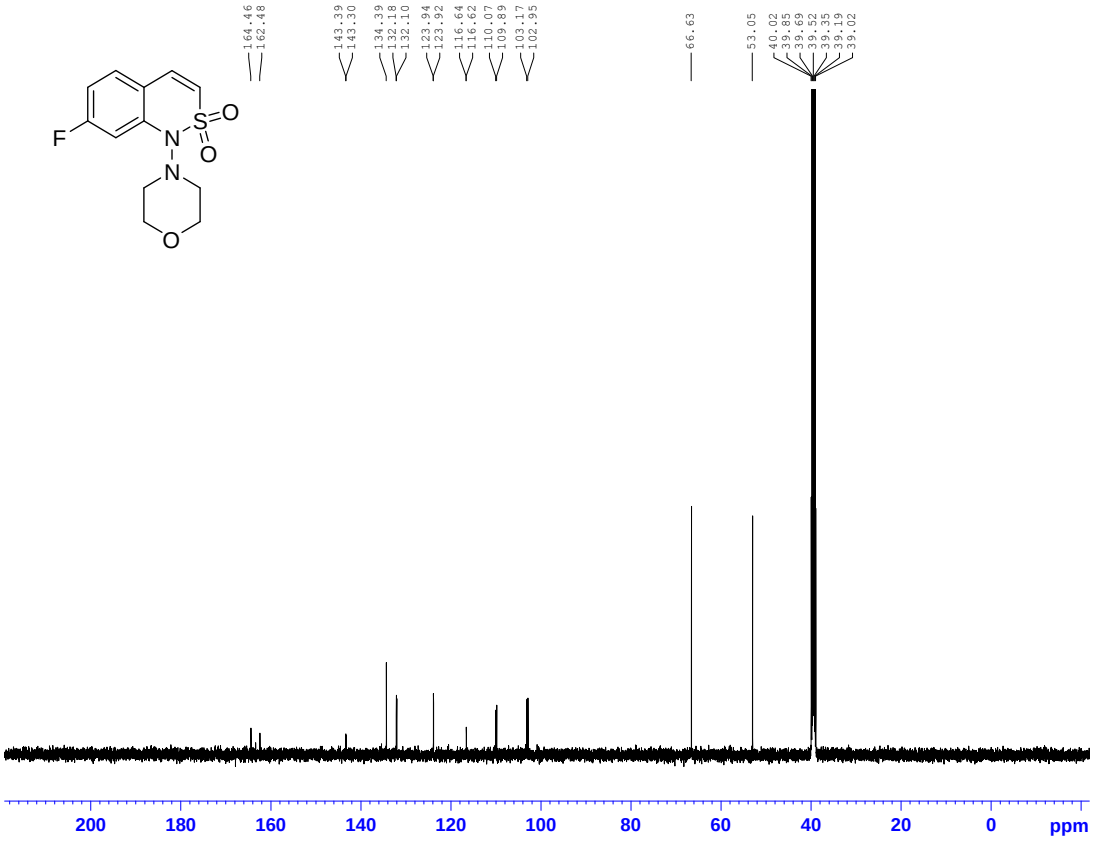


7-Fluoro-1-morpholino-1H-benzo[c][1,2]thiazine 2,2-dioxide

^{1}H $(CD_3)_2SO$ 500 MHz 363 K

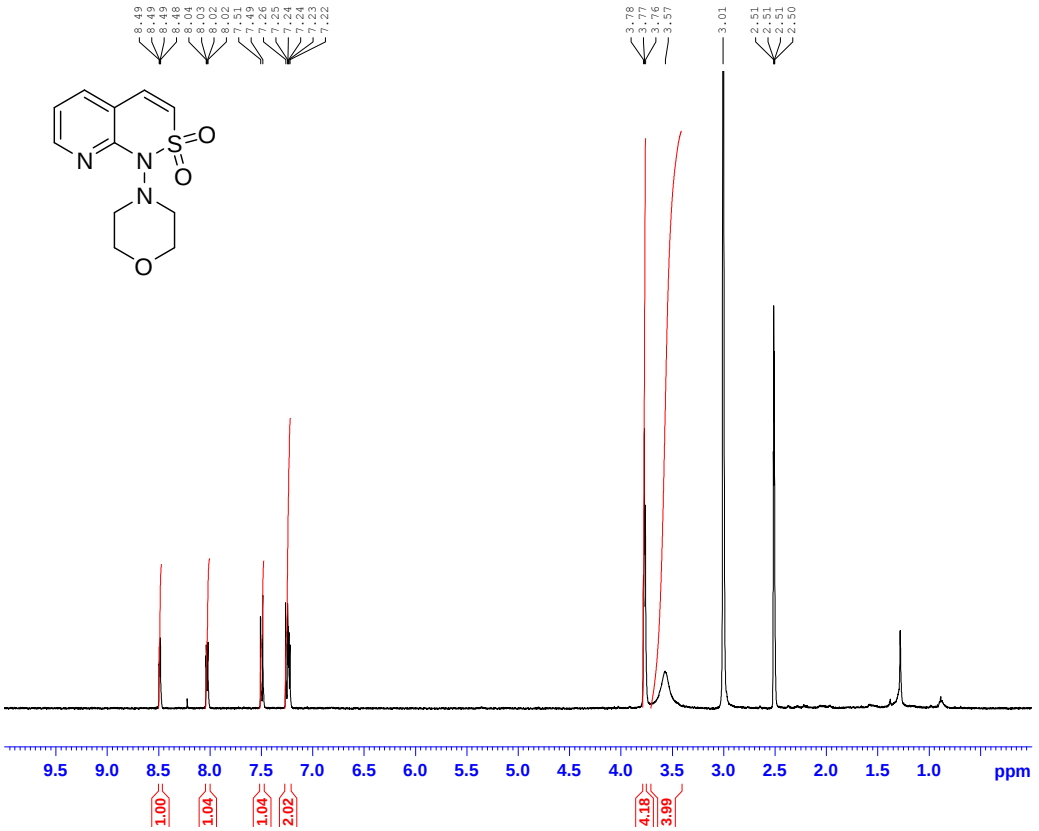


^{13}C $(CD_3)_2SO$ 101 MHz

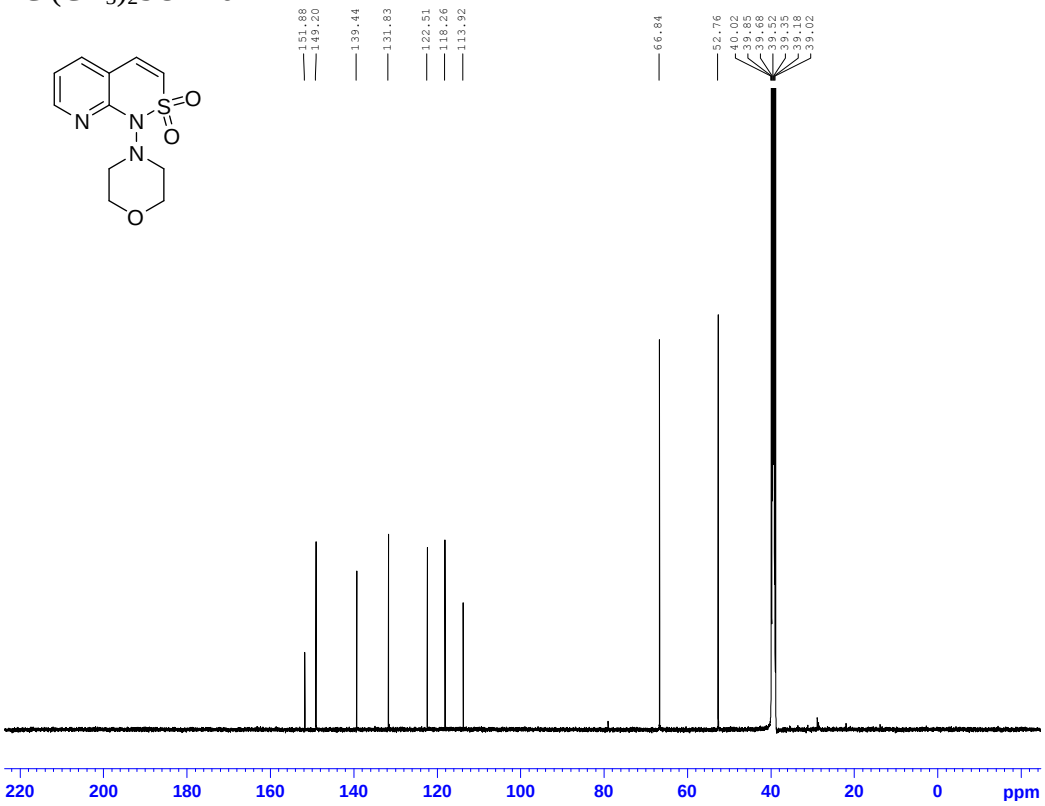


1-Morpholino-1*H*-pyrido[2,3-*c*][1,2]thiazine 2,2-dioxide

^{1}H $(CD_3)_2SO$ 500 MHz 363 K

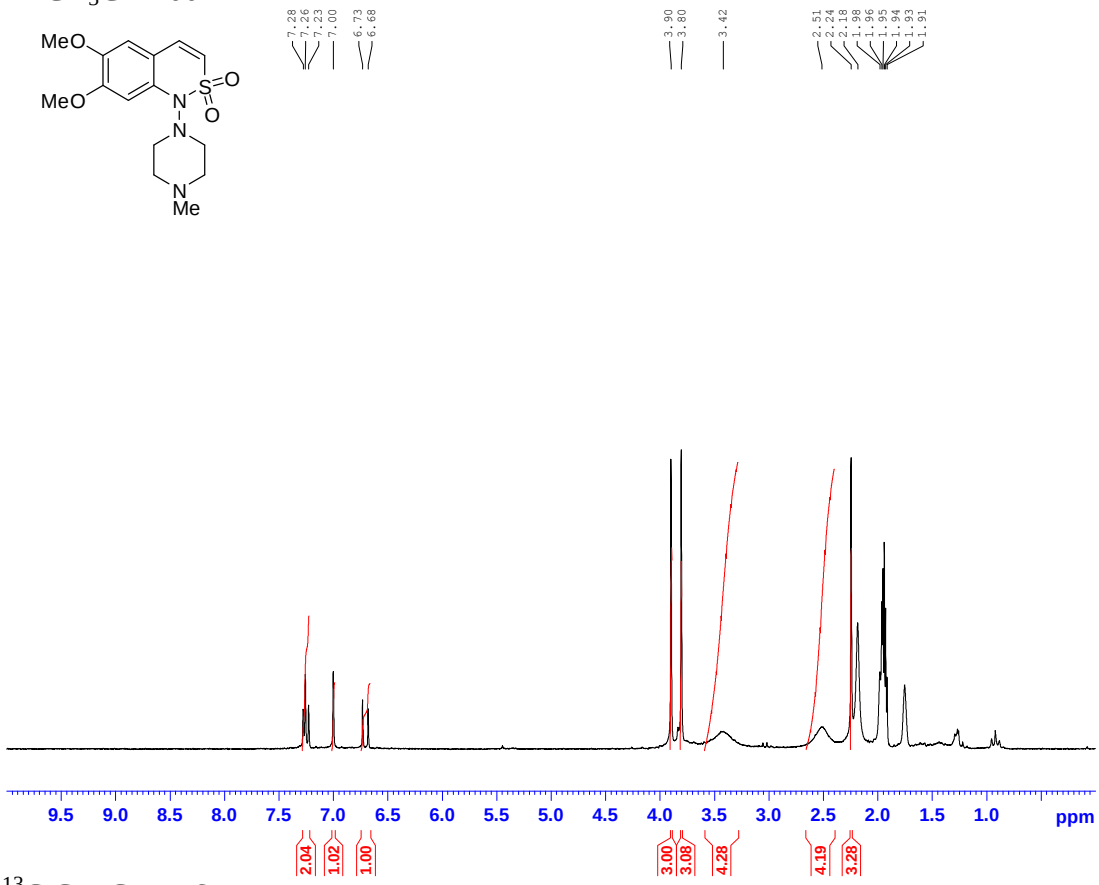


^{13}C $(CD_3)_2SO$ 126 MHz

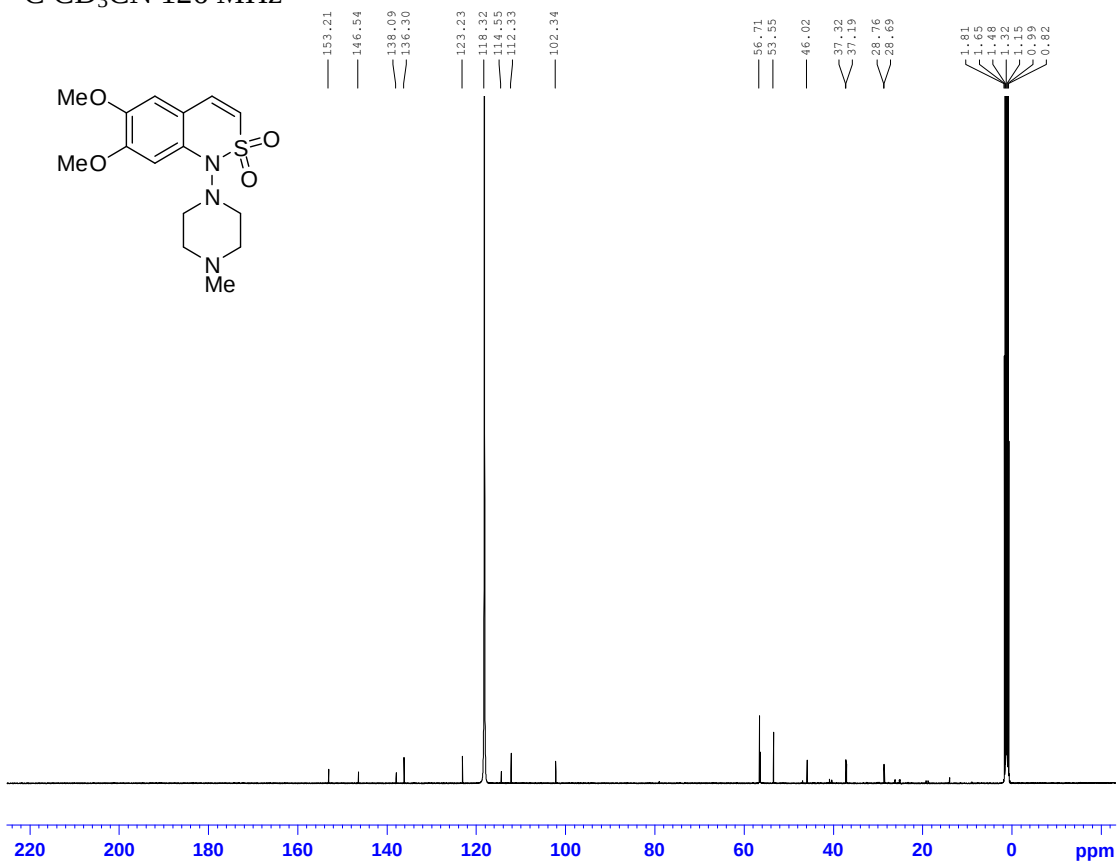


6,7-Dimethoxy-1-(4-methylpiperazin-1-yl)-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide

^{1}H CD_3CN 200 MHz

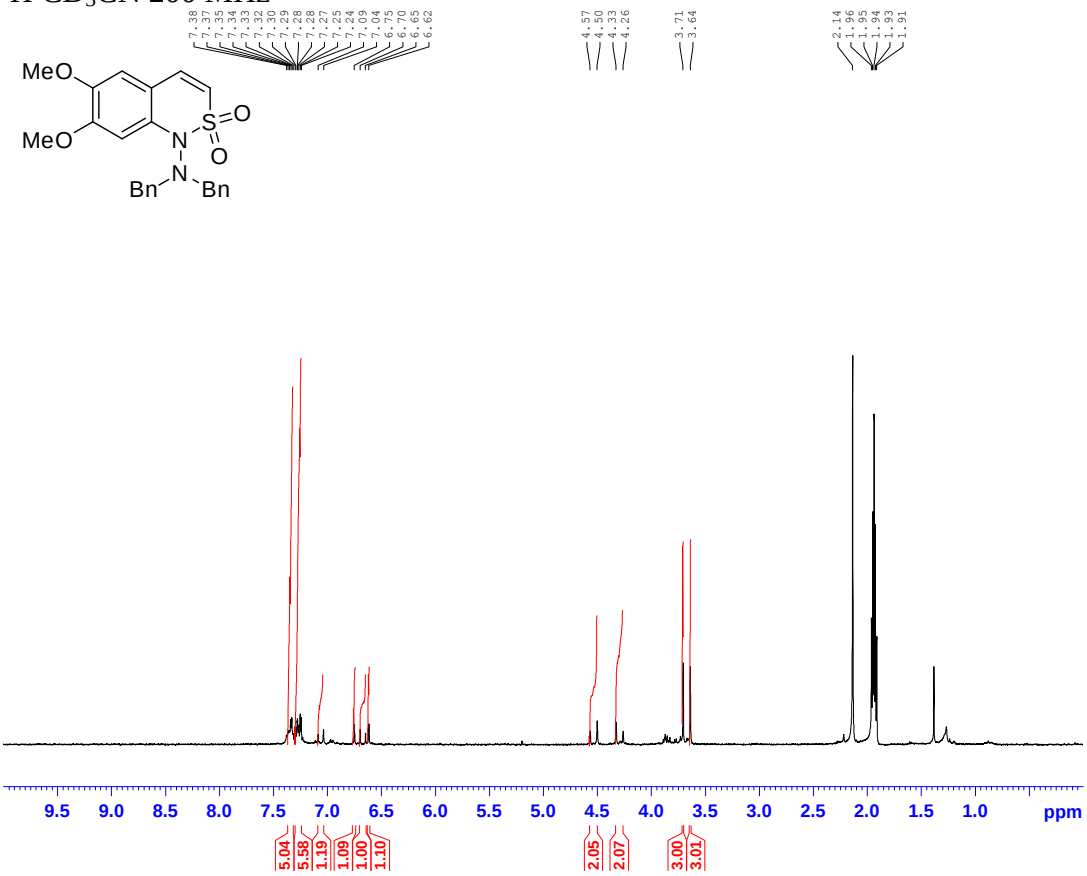


^{13}C CD_3CN 126 MHz

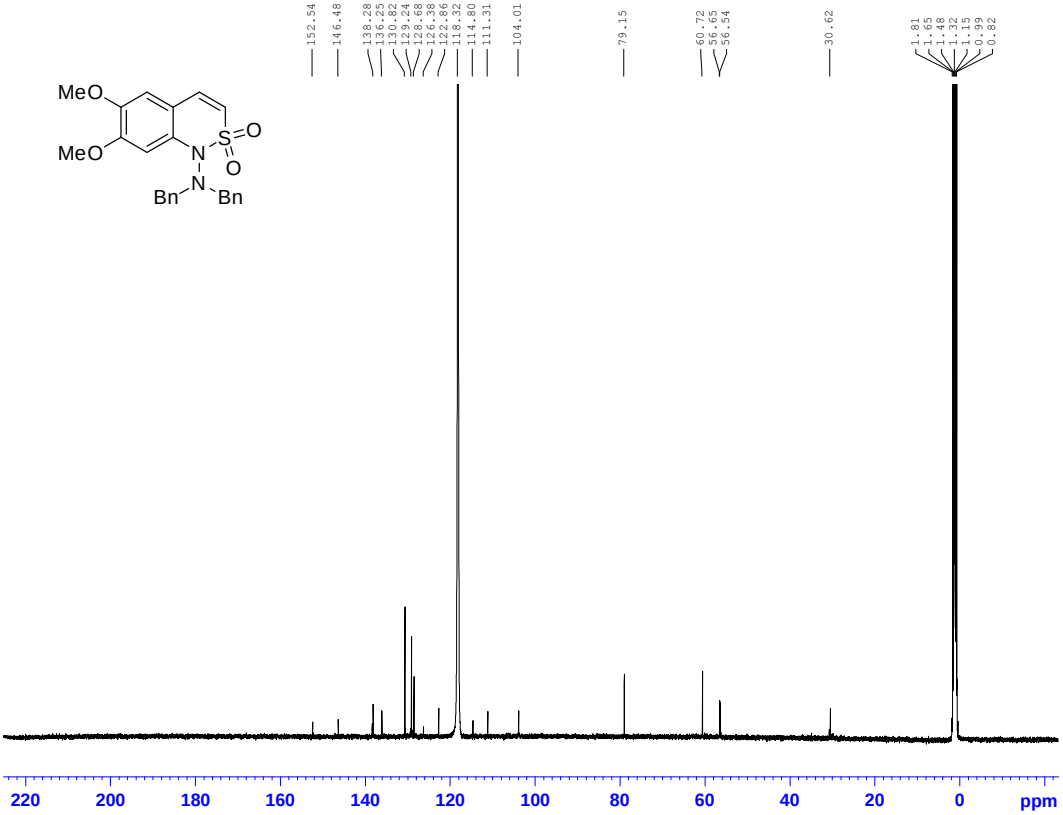


1-(Dibenzylamino)-6,7-dimethoxy-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide

^{1}H CD_3CN 200 MHz

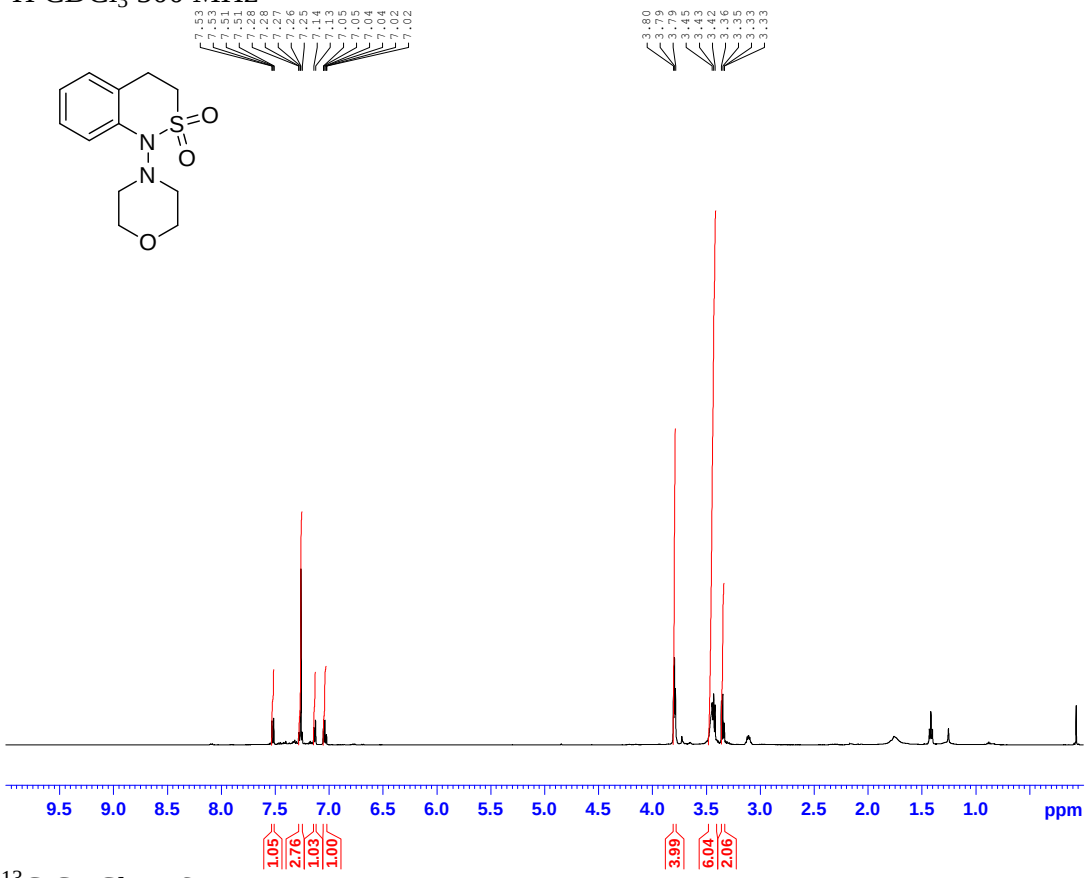


^{13}C CD_3CN 126 MHz

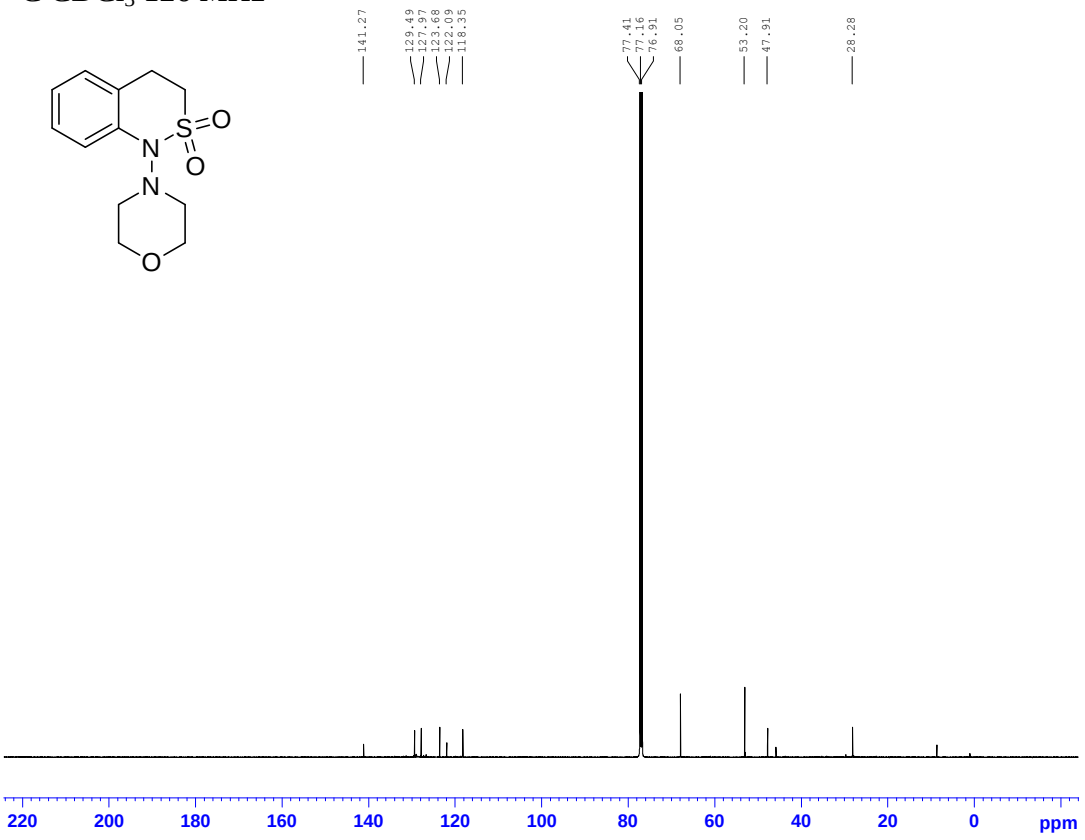


1-Morpholino-3,4-dihydro-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide

^{1}H $CDCl_3$ 500 MHz

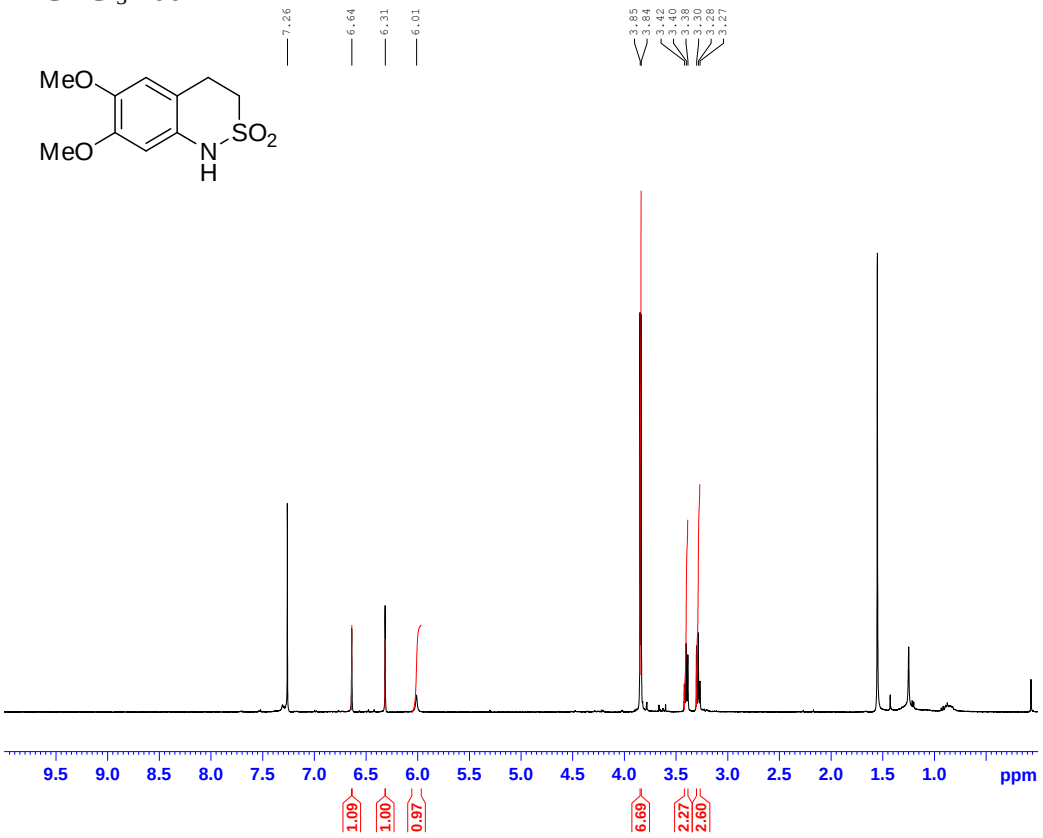


^{13}C $CDCl_3$ 126 MHz

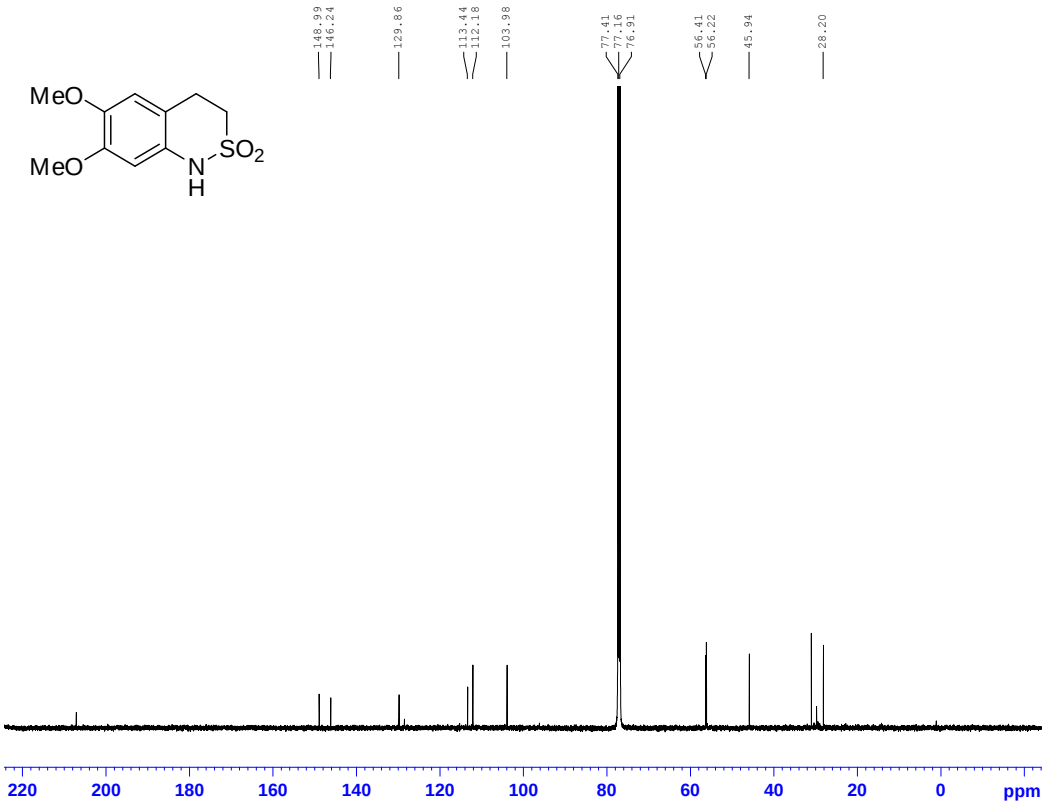


6,7-Dimethoxy-3,4-dihydro-1*H*-benzo[*c*][1,2]thiazine 2,2-dioxide

^{1}H $CDCl_3$ 400 MHz



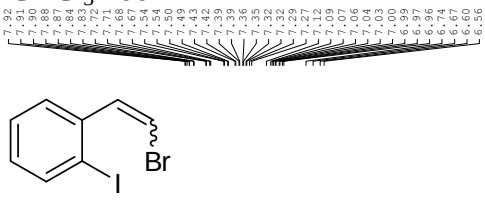
^{13}C $CDCl_3$ 126 MHz

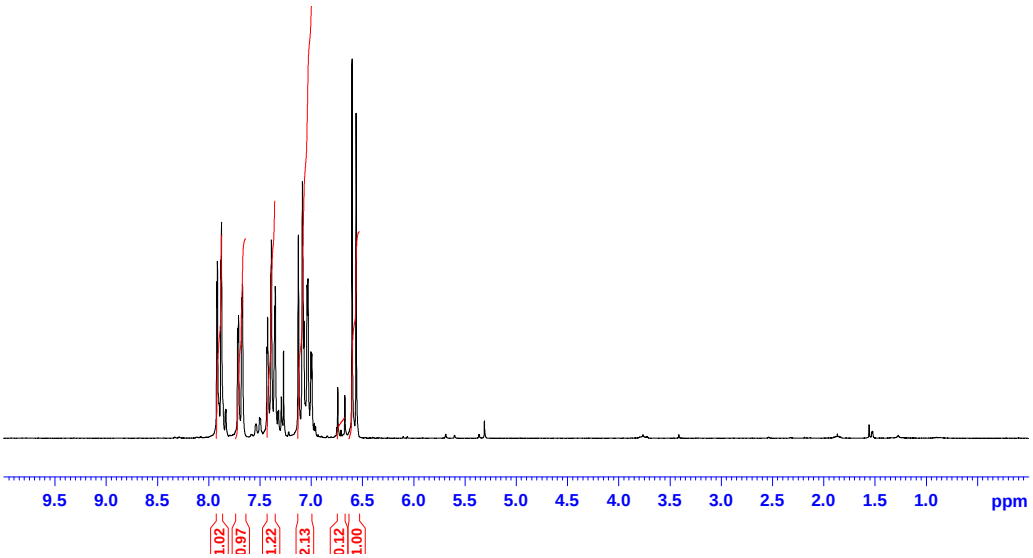


B.3 Synthesis of benzosultam: Aryl-SO_2-N linkage

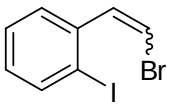
1-2-Bromovinyl]-2-iodobenzene

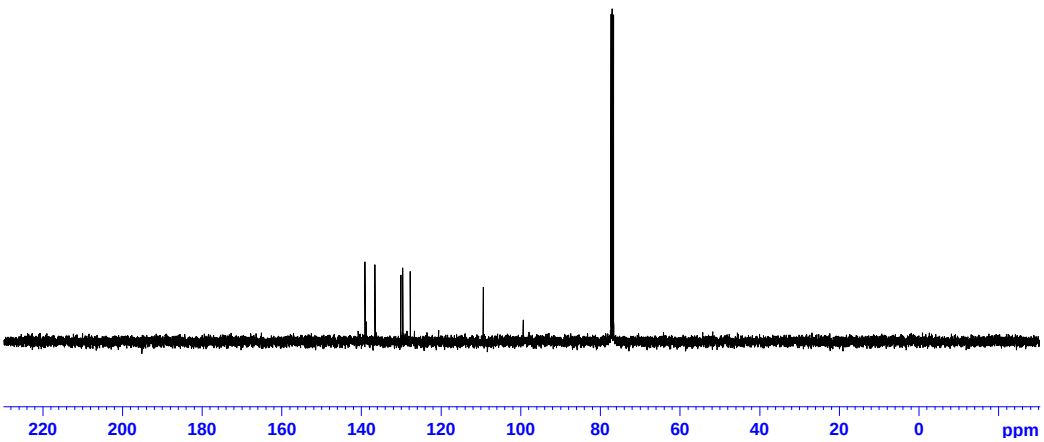
^{1}H $CDCl_3$ 200 MHz





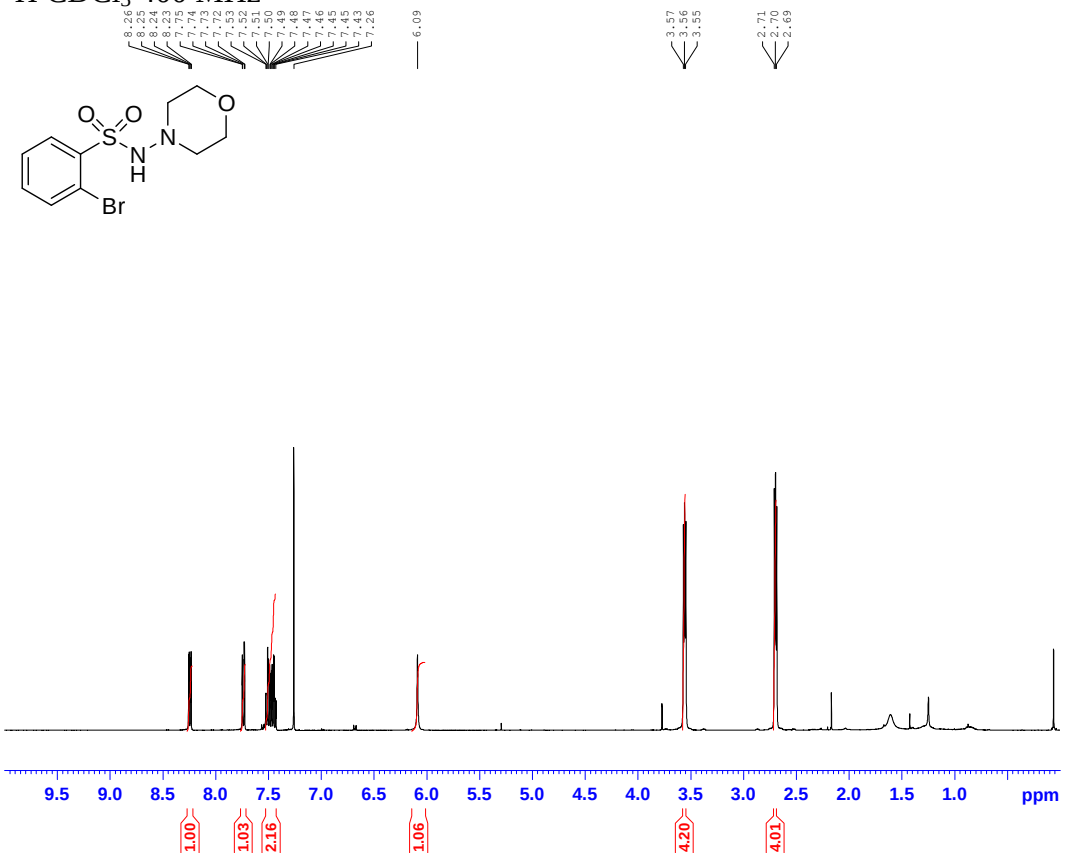
^{13}C $CDCl_3$ 101 MHz



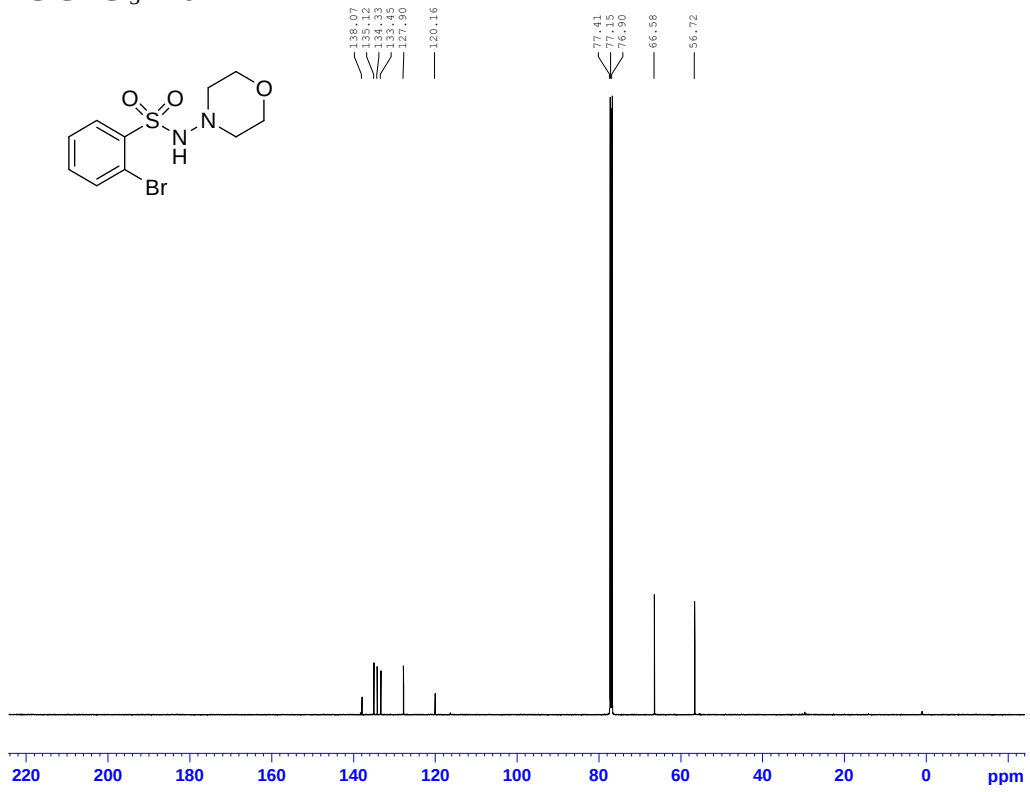


2-Bromo-*N*-morpholinobenzenesulfonamide

^{1}H $CDCl_3$ 400 MHz



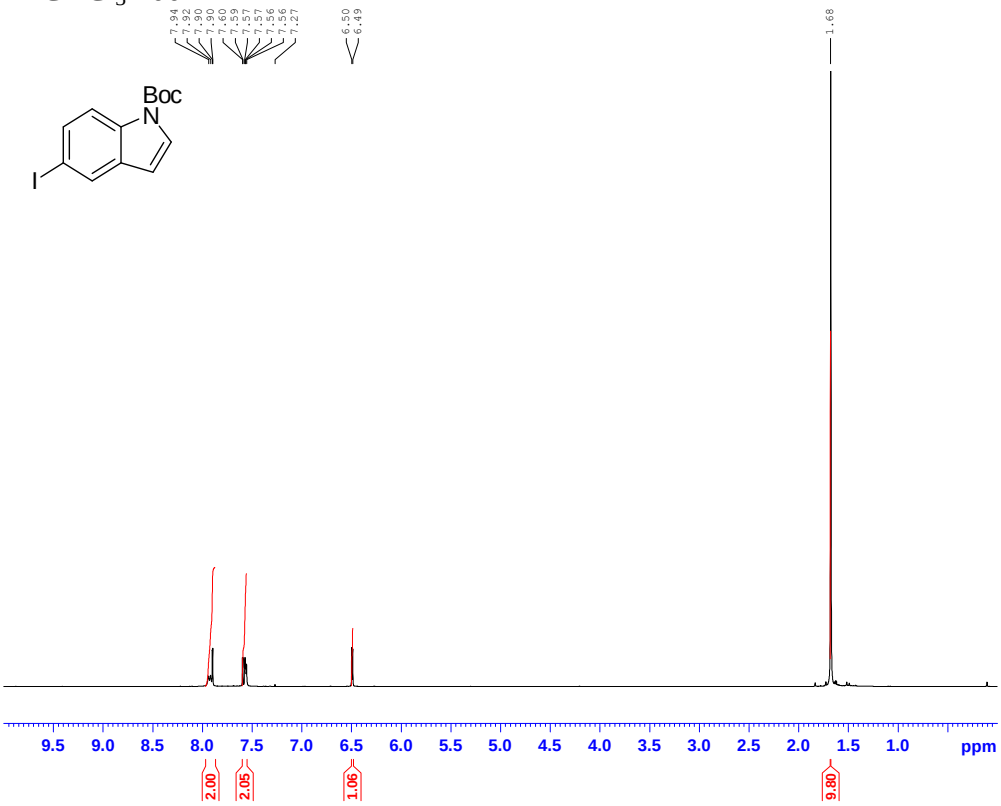
^{13}C $CDCl_3$ 126 MHz



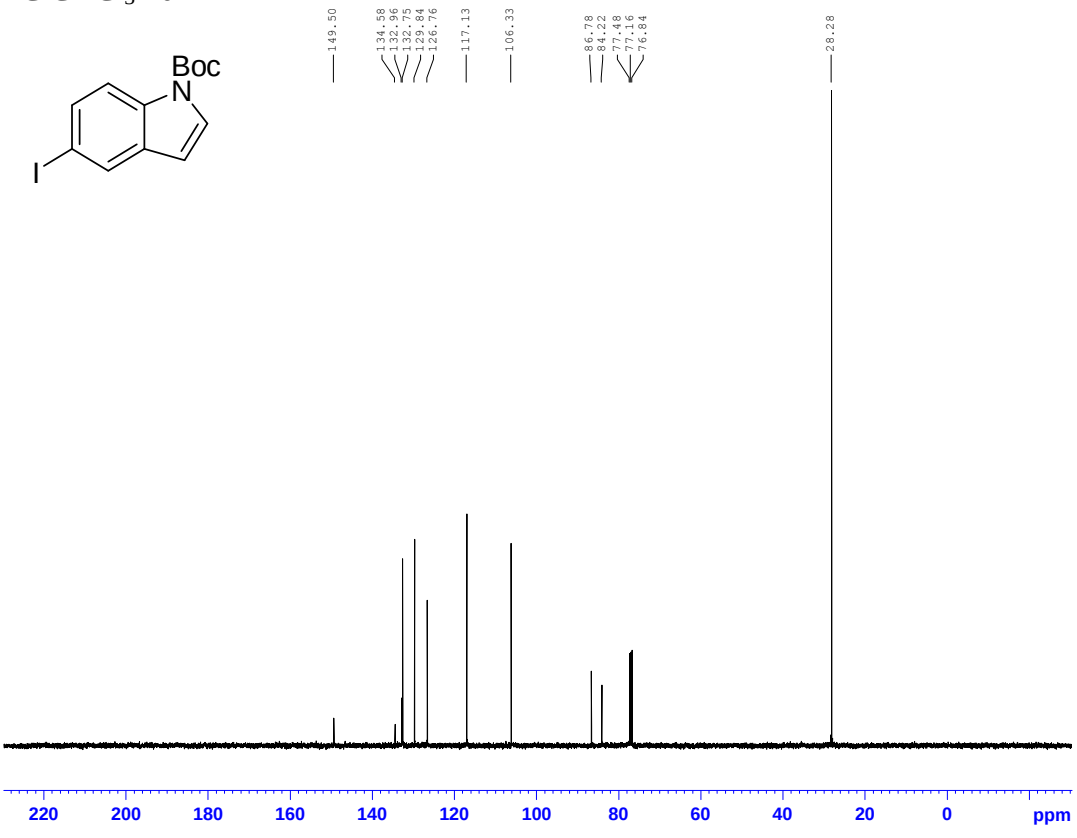
B.4 Synthesis of *N*-aminosulfonamides

***tert*-Butyl 5-iodo-1*H*-indole-1-carboxylate**

^{1}H $CDCl_3$ 400 MHz

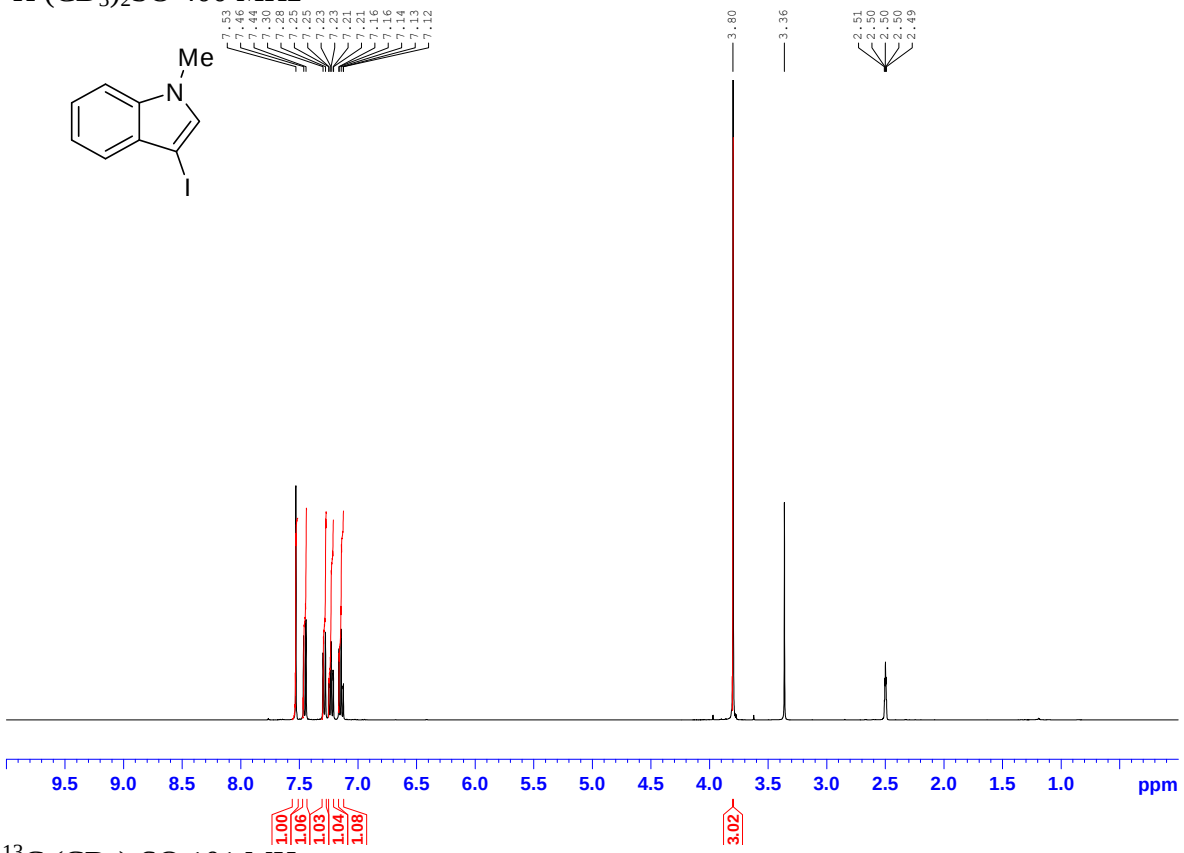


^{13}C $CDCl_3$ 101 MHz

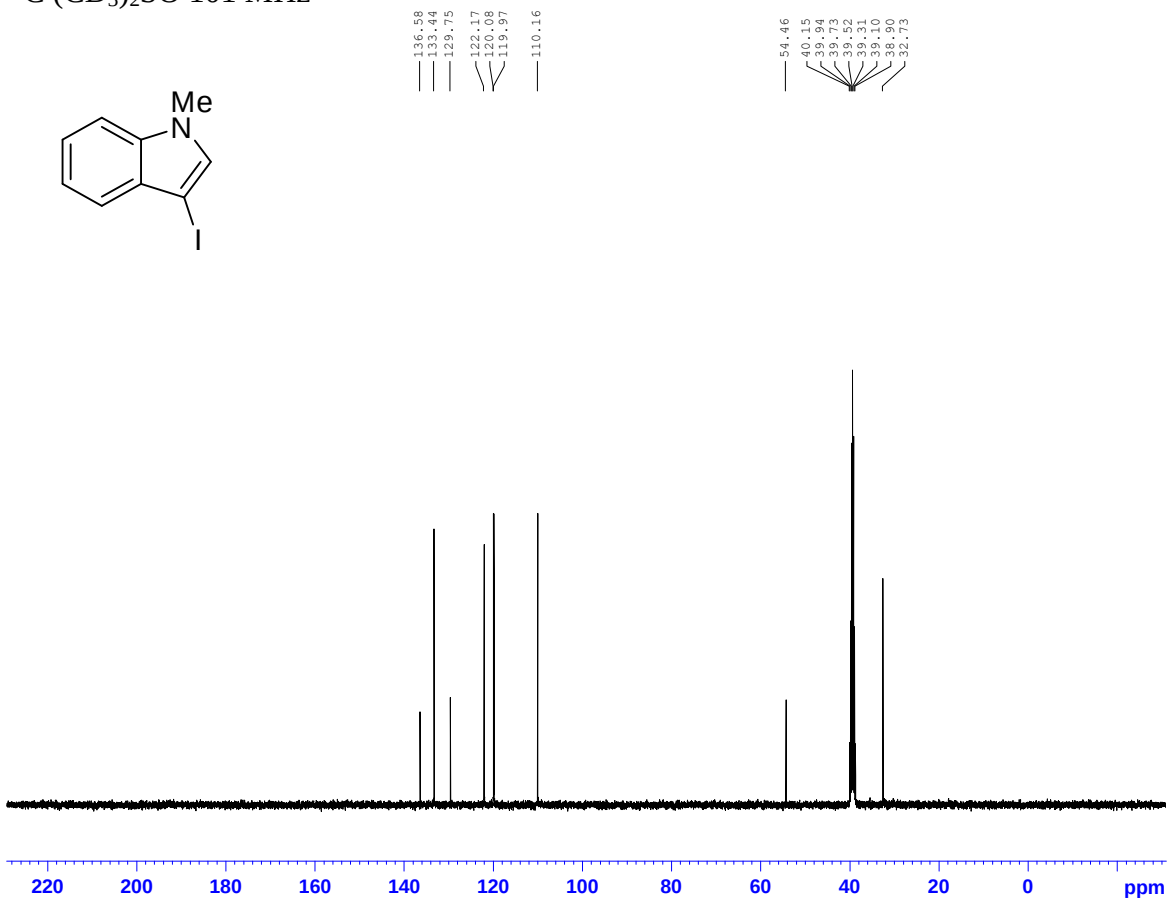


3-Iodo-1-methyl-1*H*-indole

^{1}H $(CD_3)_2SO$ 400 MHz

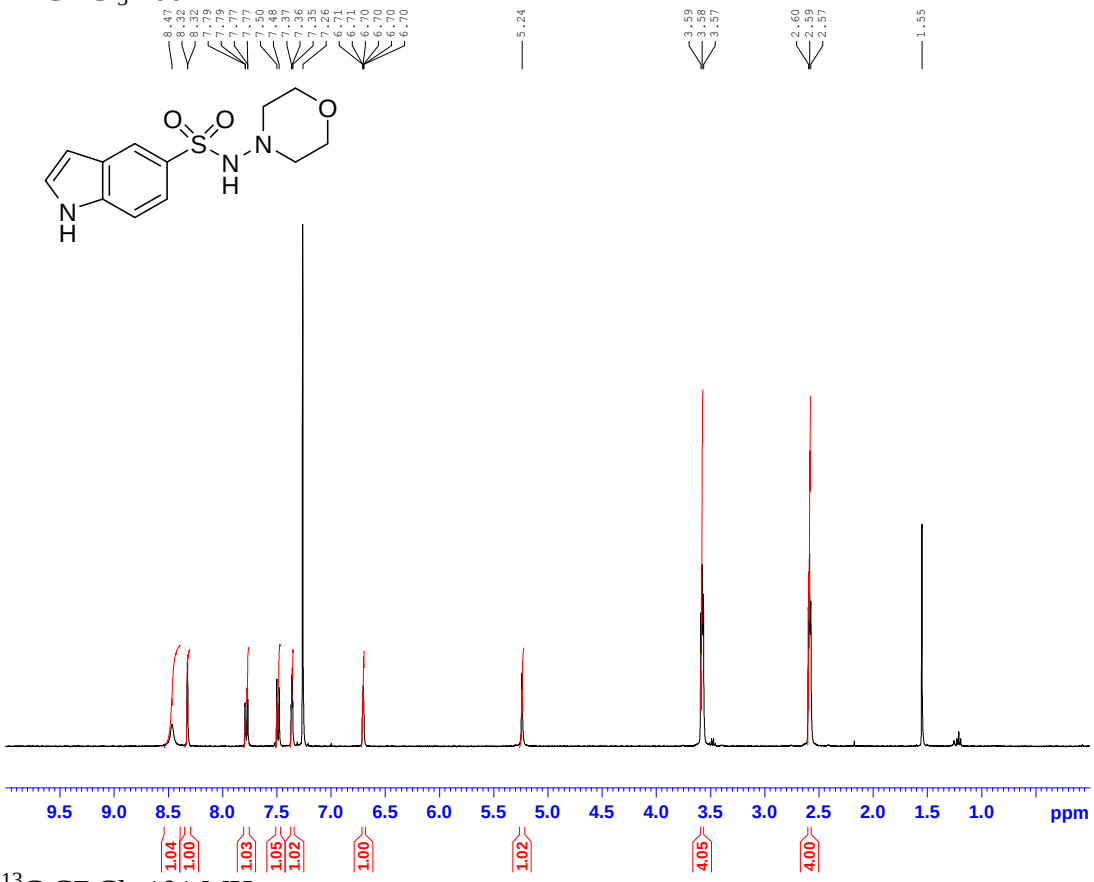


^{13}C $(CD_3)_2SO$ 101 MHz

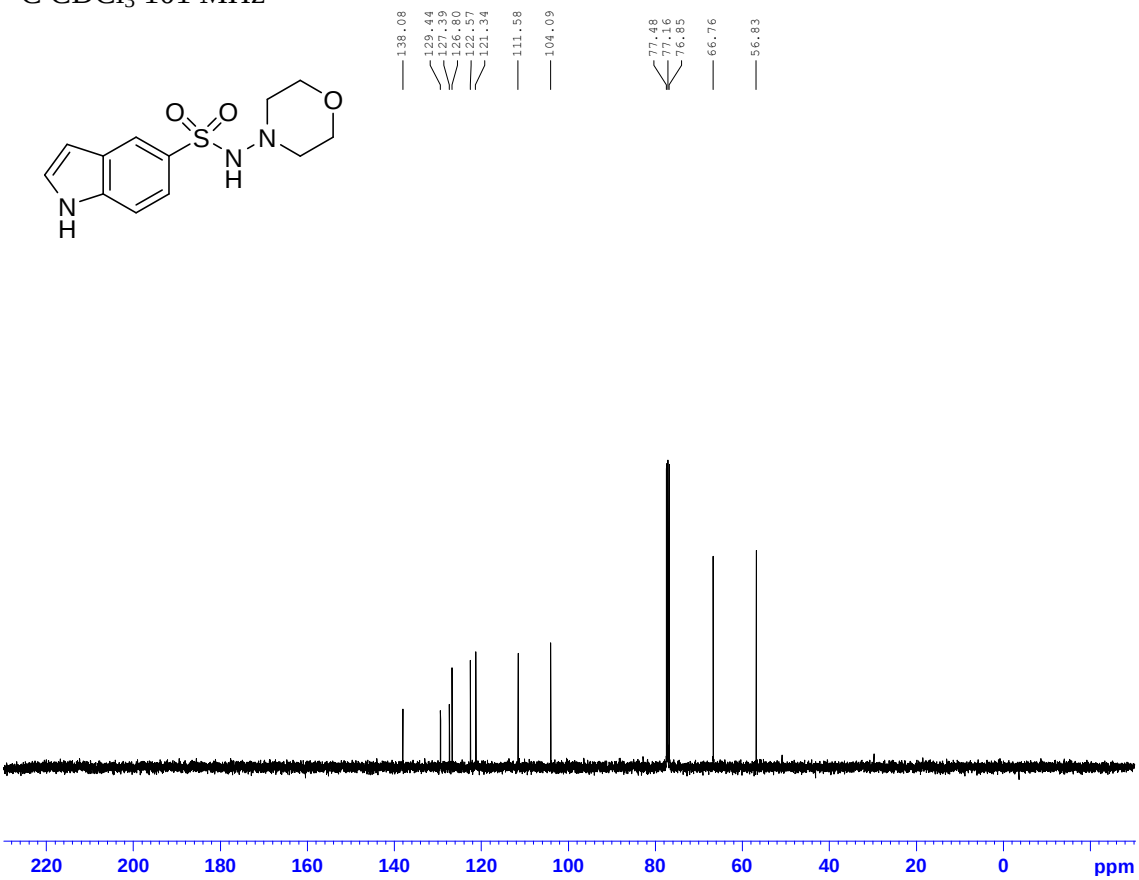


1*H*-Indole-5-sulfonamide, *N*-4-morpholinyl-

^{1}H $CDCl_3$ 400 MHz

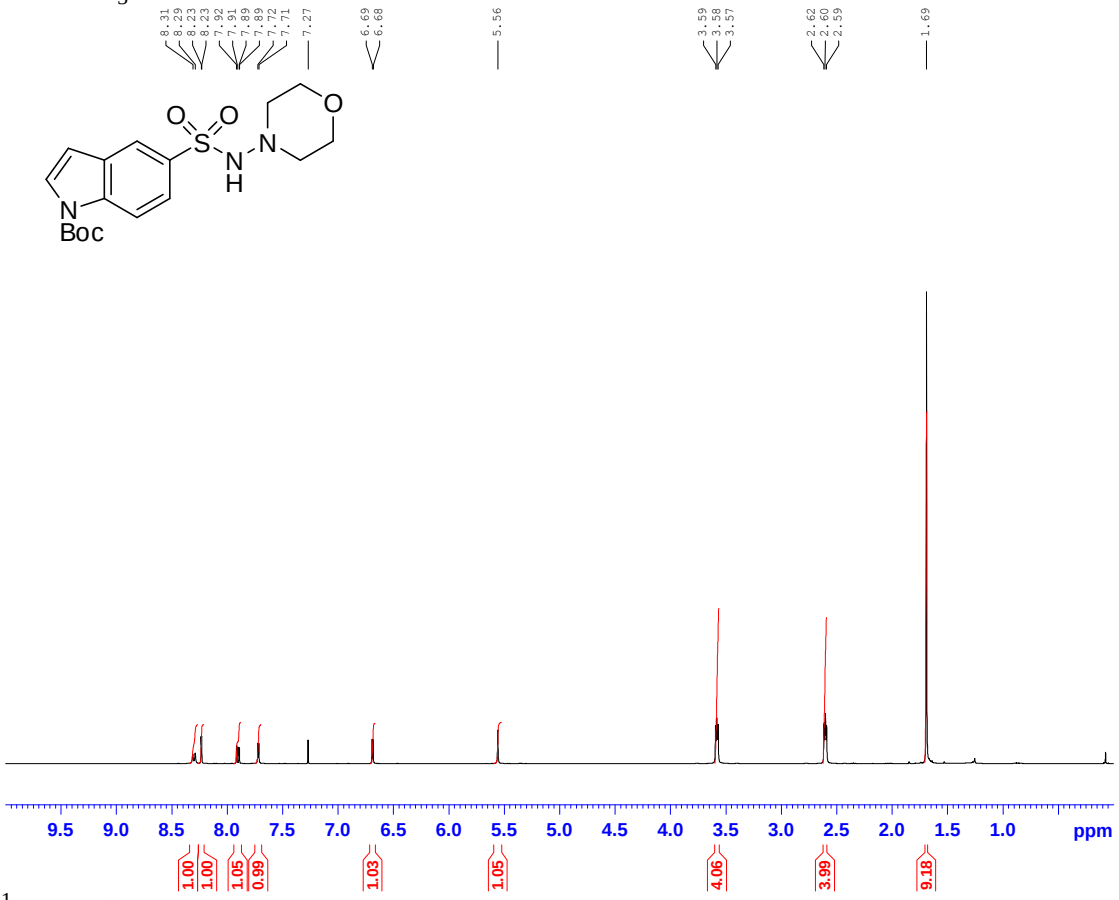


^{13}C $CDCl_3$ 101 MHz

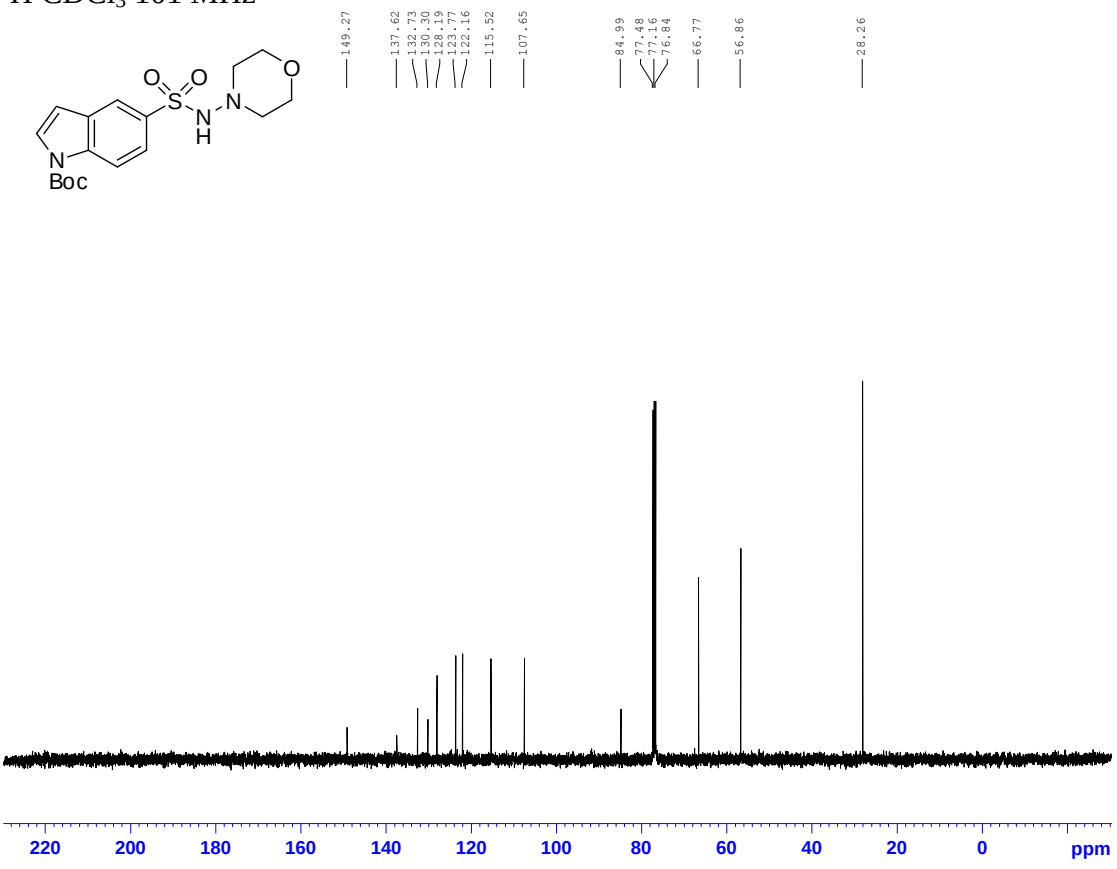


tert-Butyl 5-(morpholin-4-ylsulfamoyl)-1_H_-indole-1-carboxylate

^{1}H $CDCl_3$ 400 MHz

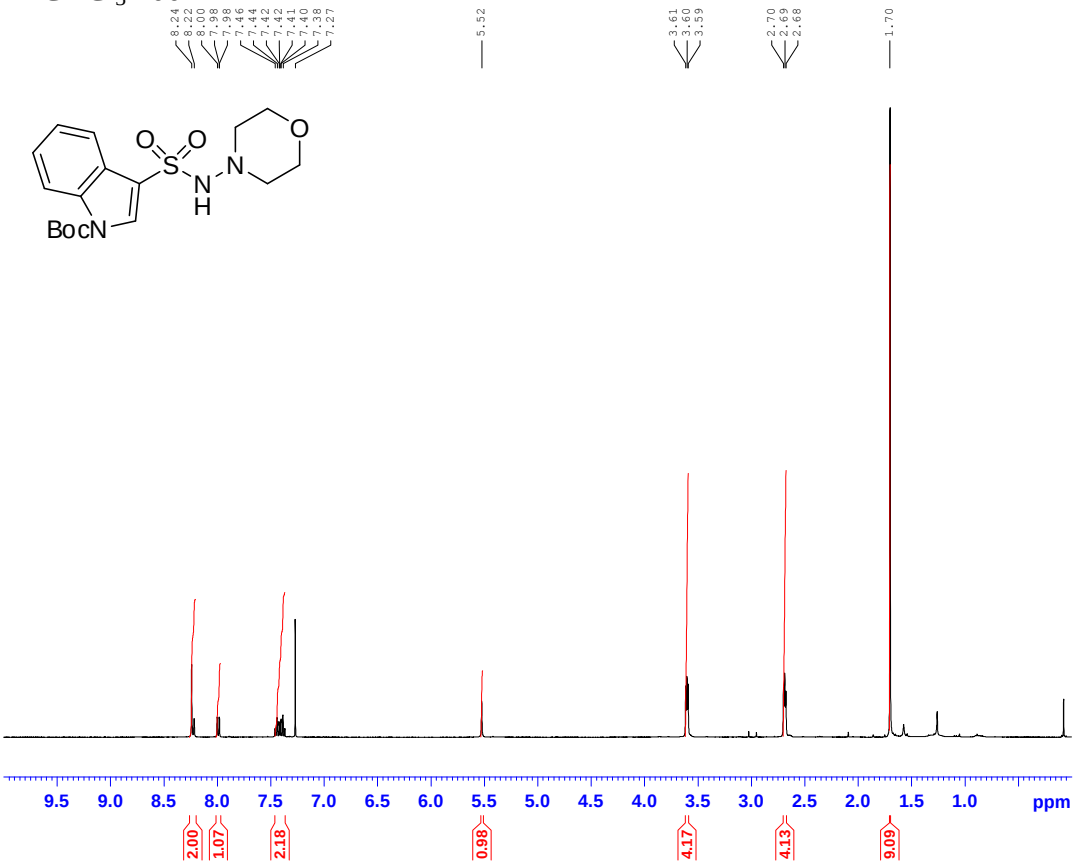


^{1}H $CDCl_3$ 101 MHz

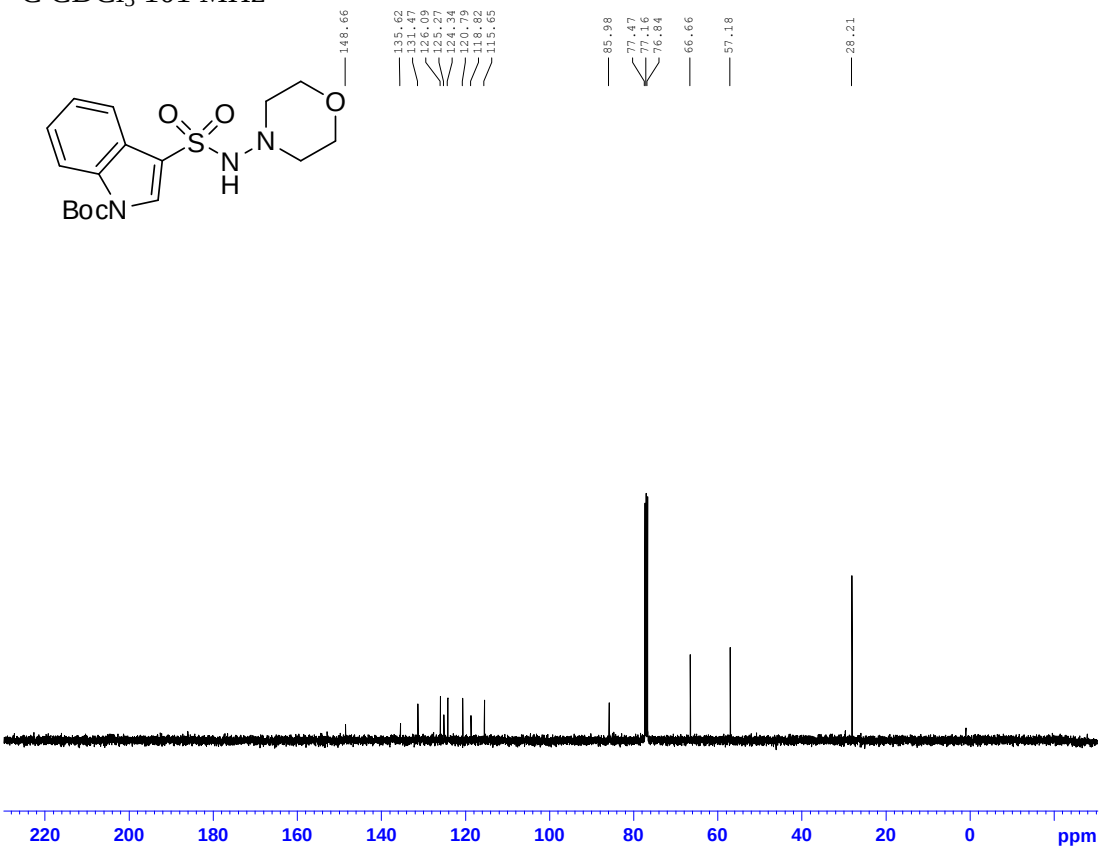


tert-Butyl 3-(morpholin-4-ylsulfamoyl)-1_H_-indole-1-carboxylate

^{1}H $CDCl_3$ 400 MHz

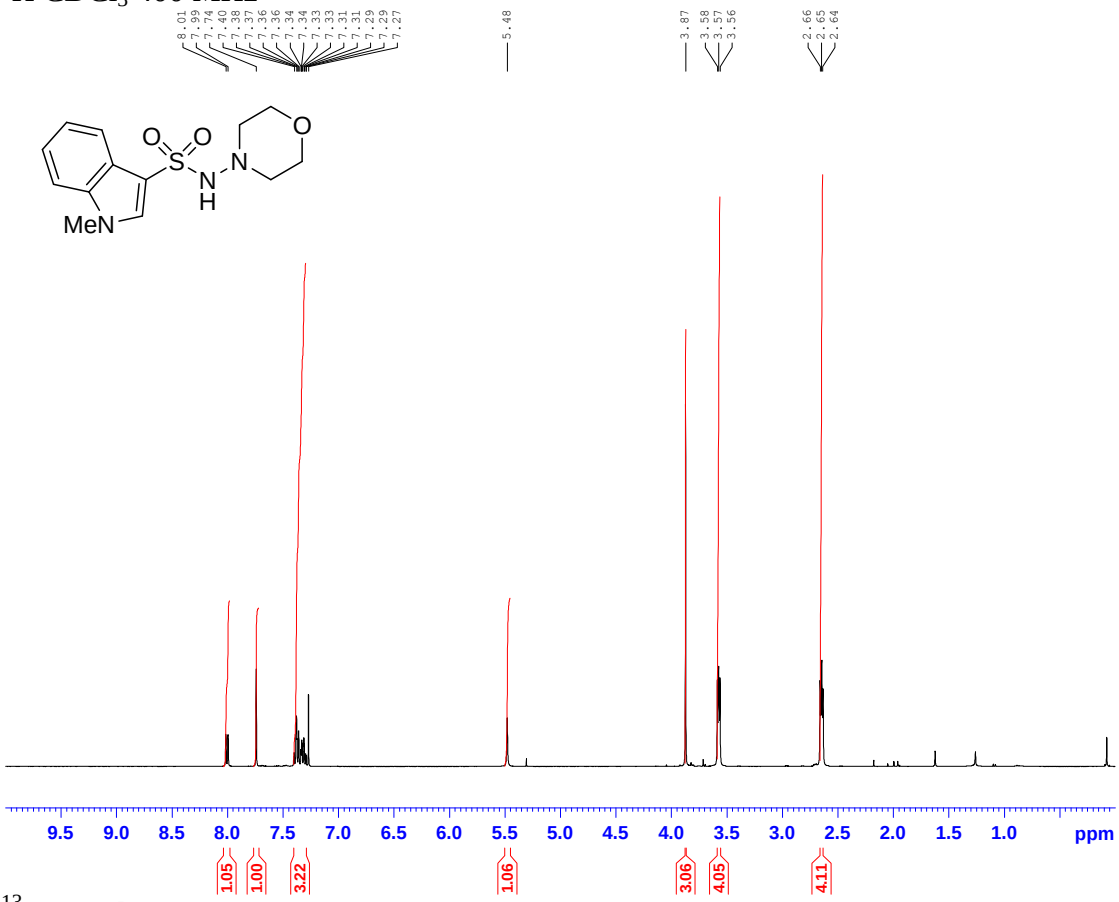


^{13}C $CDCl_3$ 101 MHz

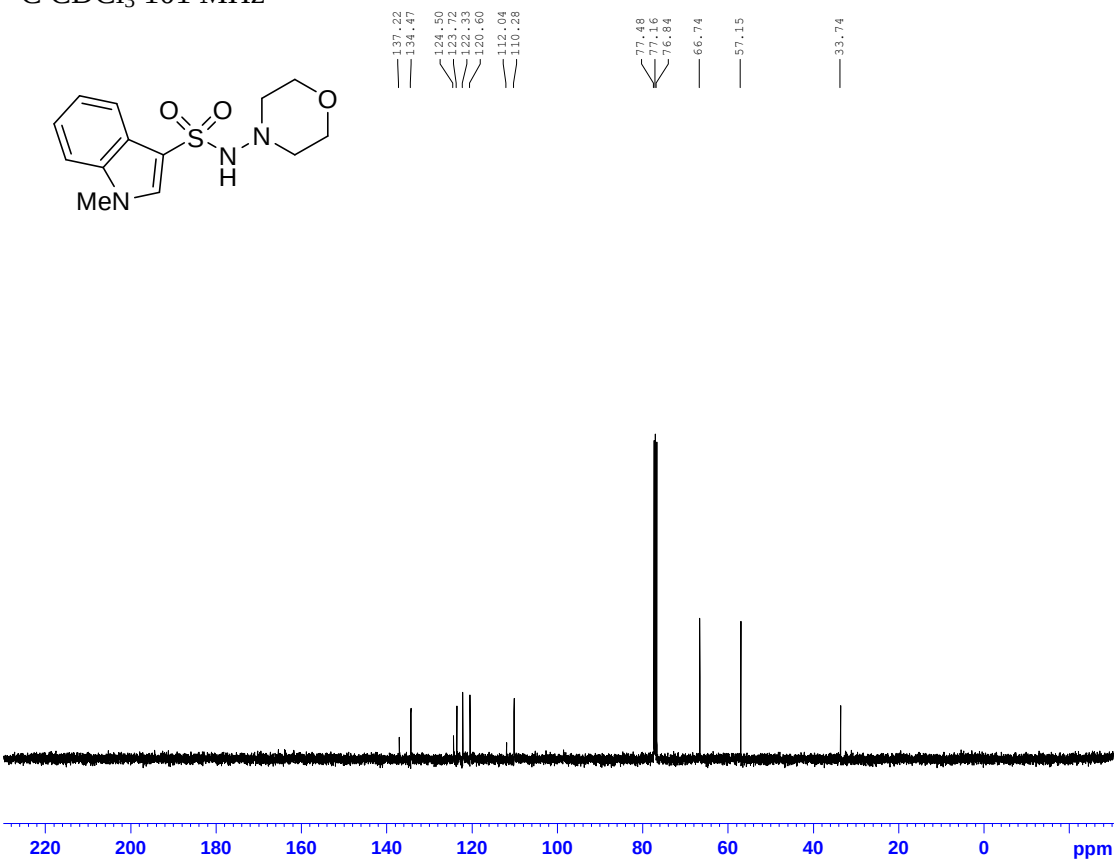


1-Methyl-*N*-(morpholin-4-yl)-1*H*-indole-3-sulfonamide

^{1}H $CDCl_3$ 400 MHz

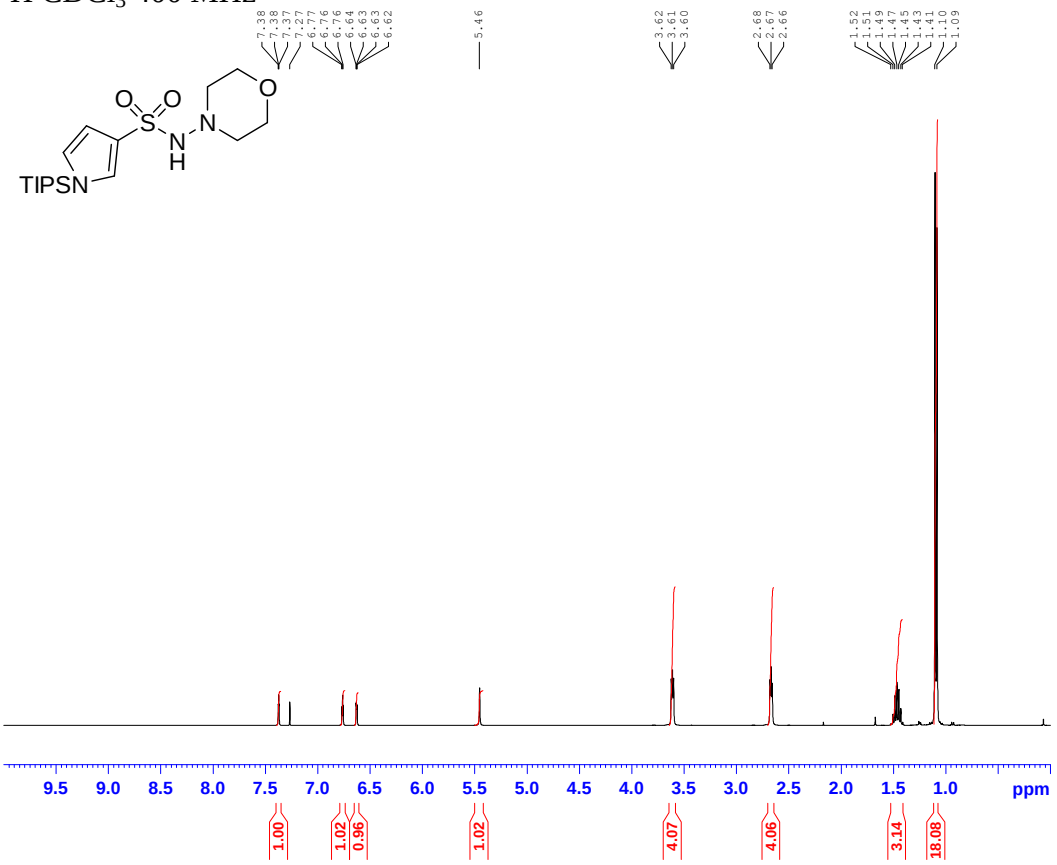


^{13}C $CDCl_3$ 101 MHz

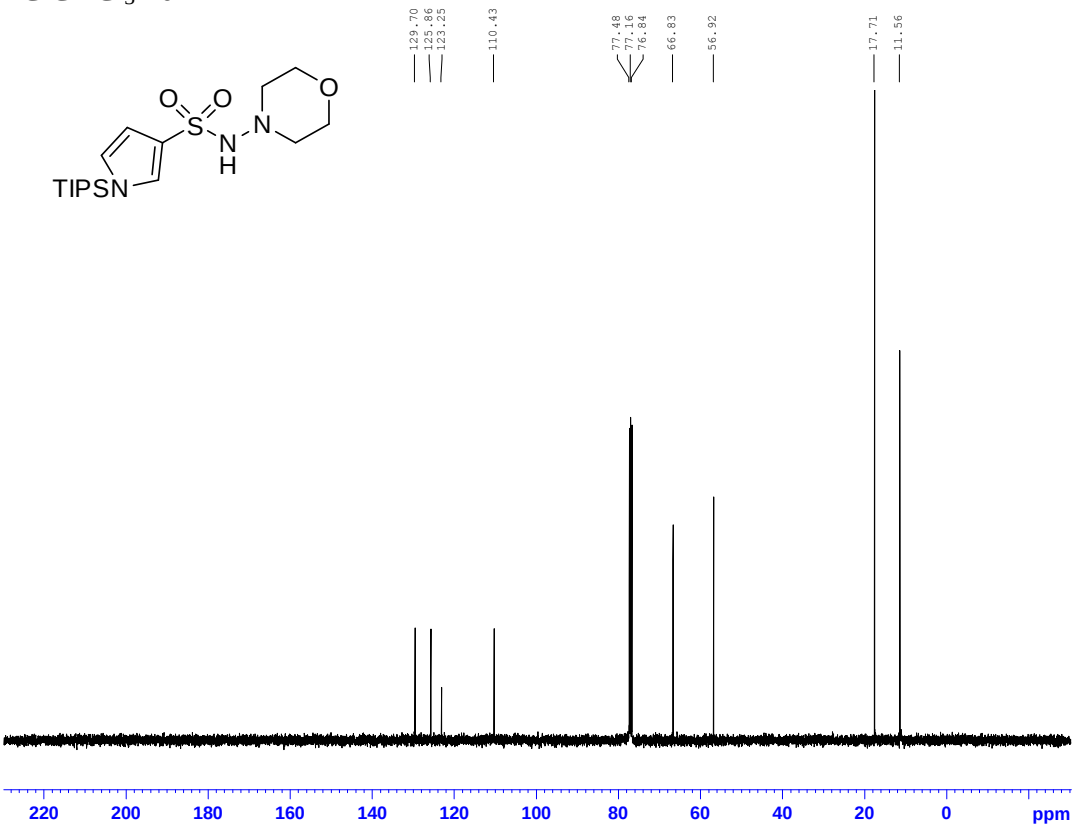


_N_-(morpholin-4-yl)-1-(triisopropylsilyl)-1_H_-pyrrole-3-sulfonamide

^{1}H $CDCl_3$ 400 MHz

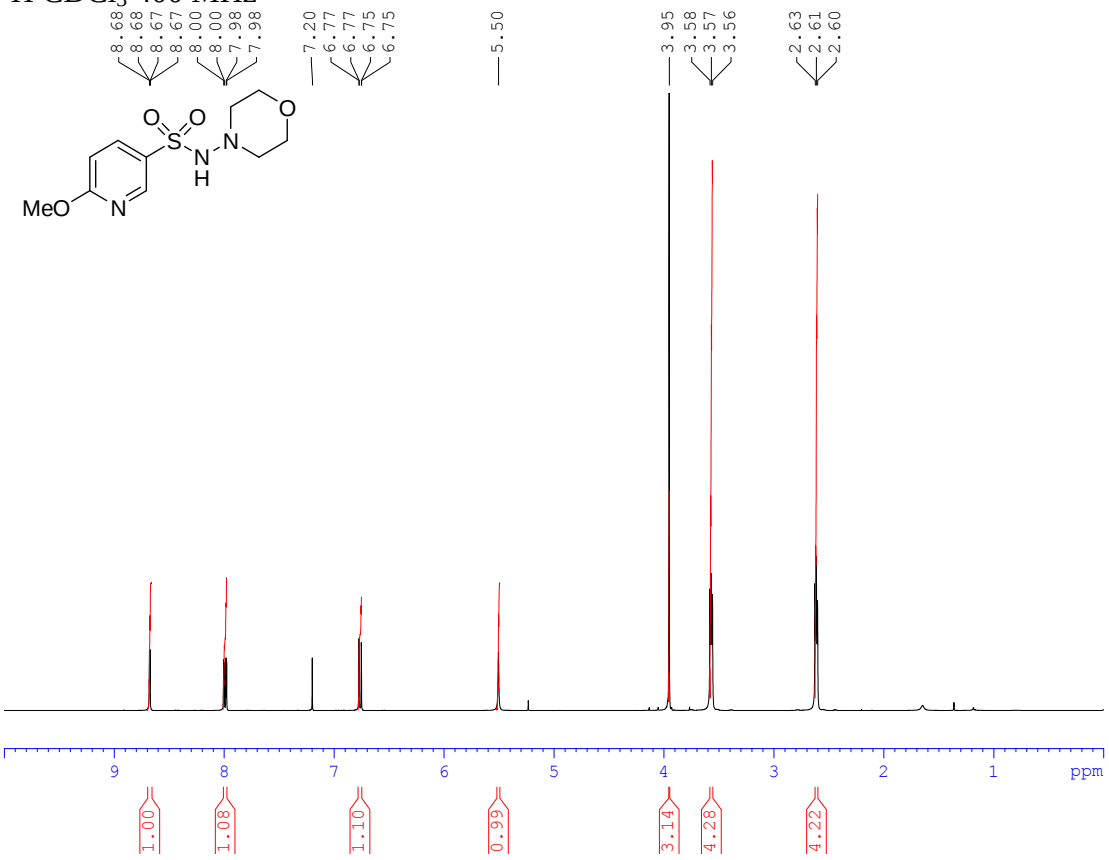


^{13}C $CDCl_3$ 101 MHz

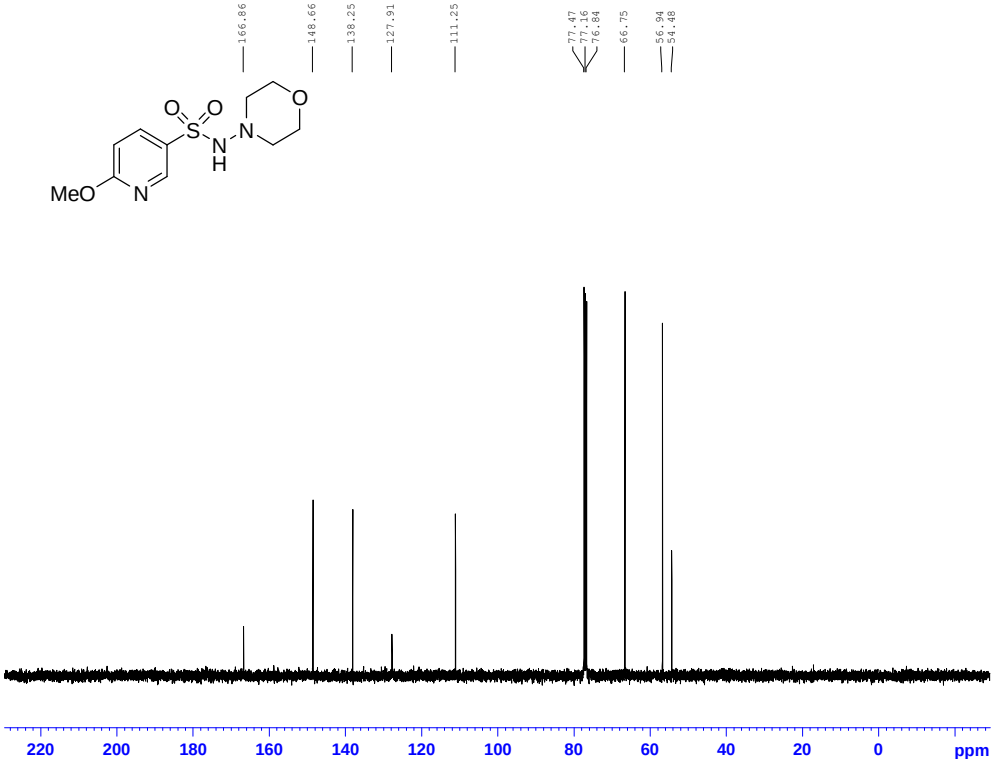


6-Methoxy-*N*-(morpholin-4-yl)pyridine-3-sulfonamide

^{1}H $CDCl_3$ 400 MHz

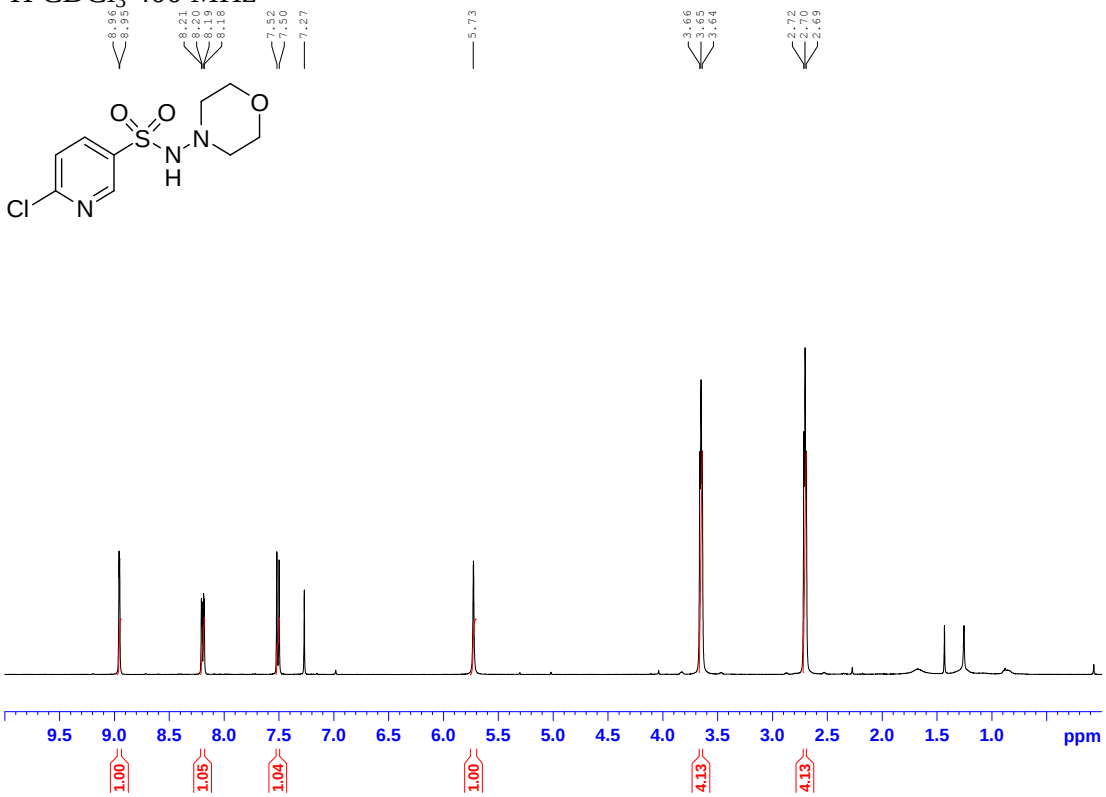


^{13}C $CDCl_3$ 101 MHz

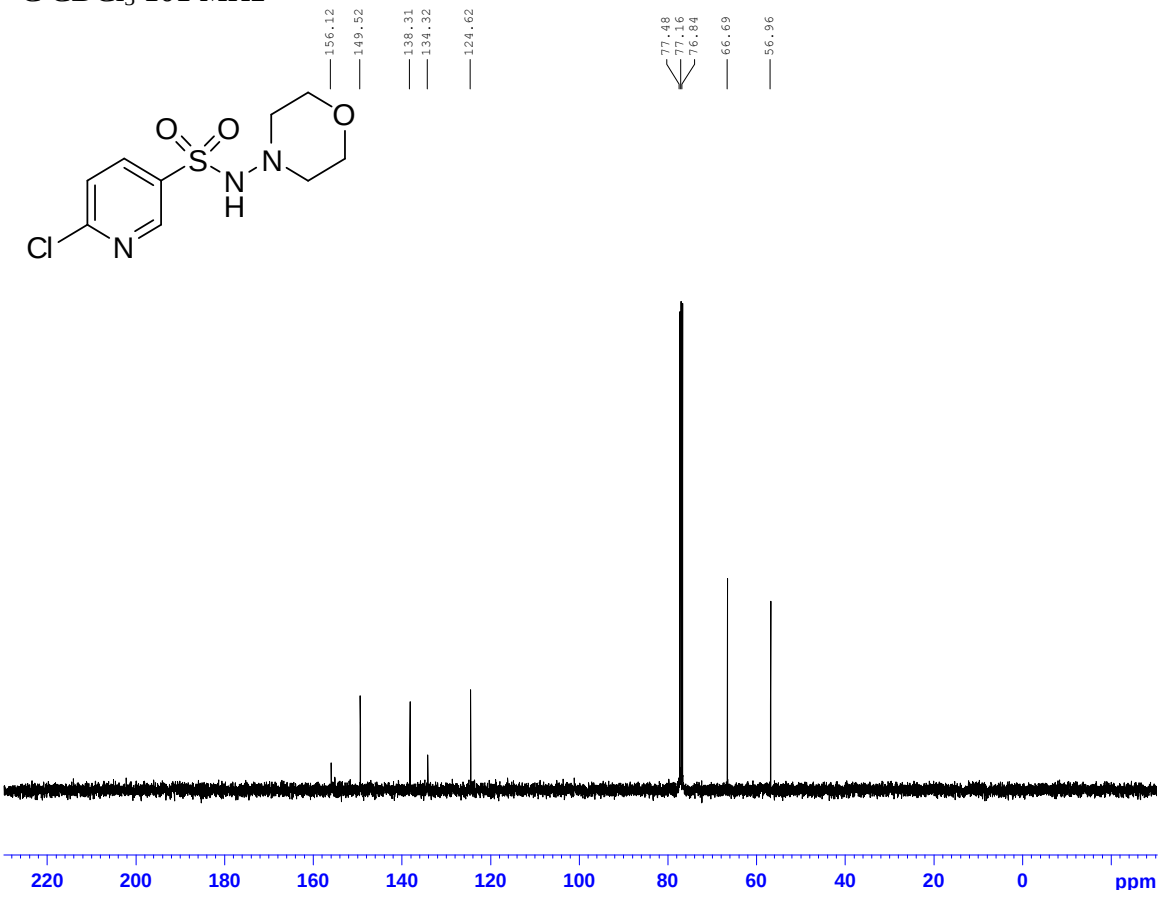


6-Chloro-*N*-(morpholin-4-yl)pyridine-3-sulfonamide

^{1}H $CDCl_3$ 400 MHz

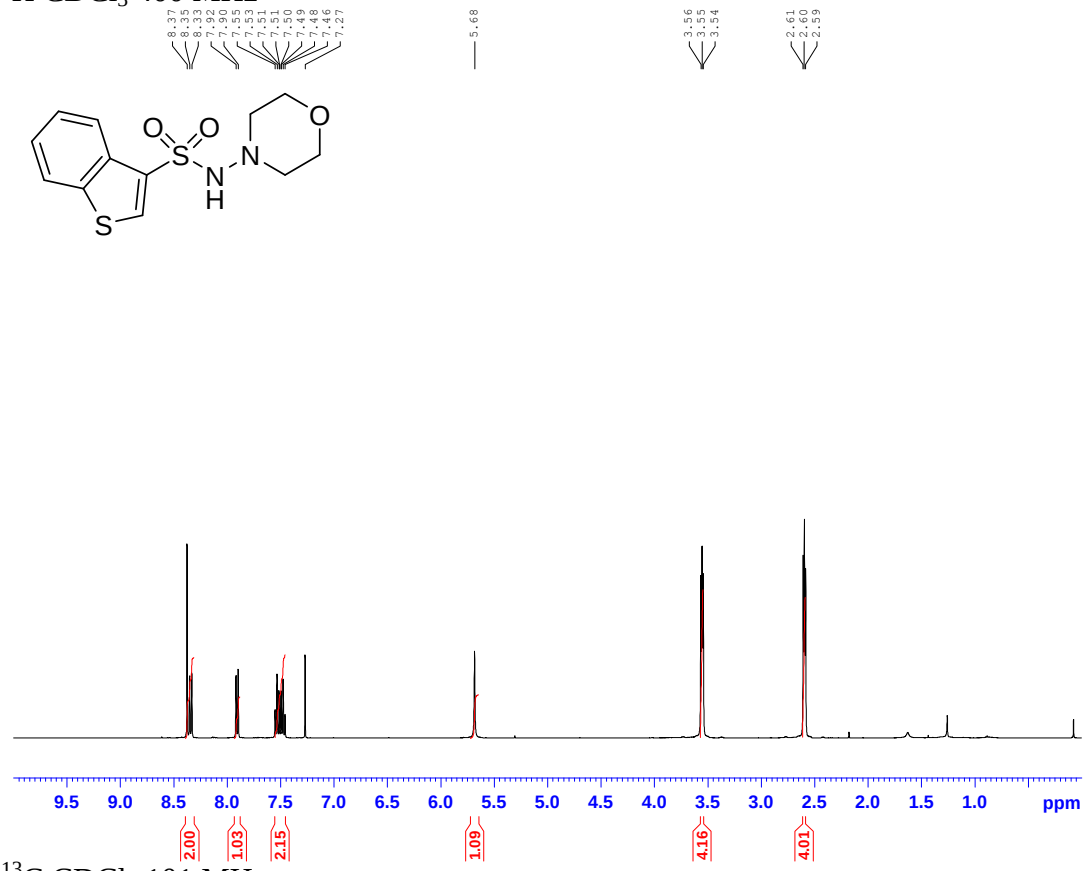


^{13}C $CDCl_3$ 101 MHz

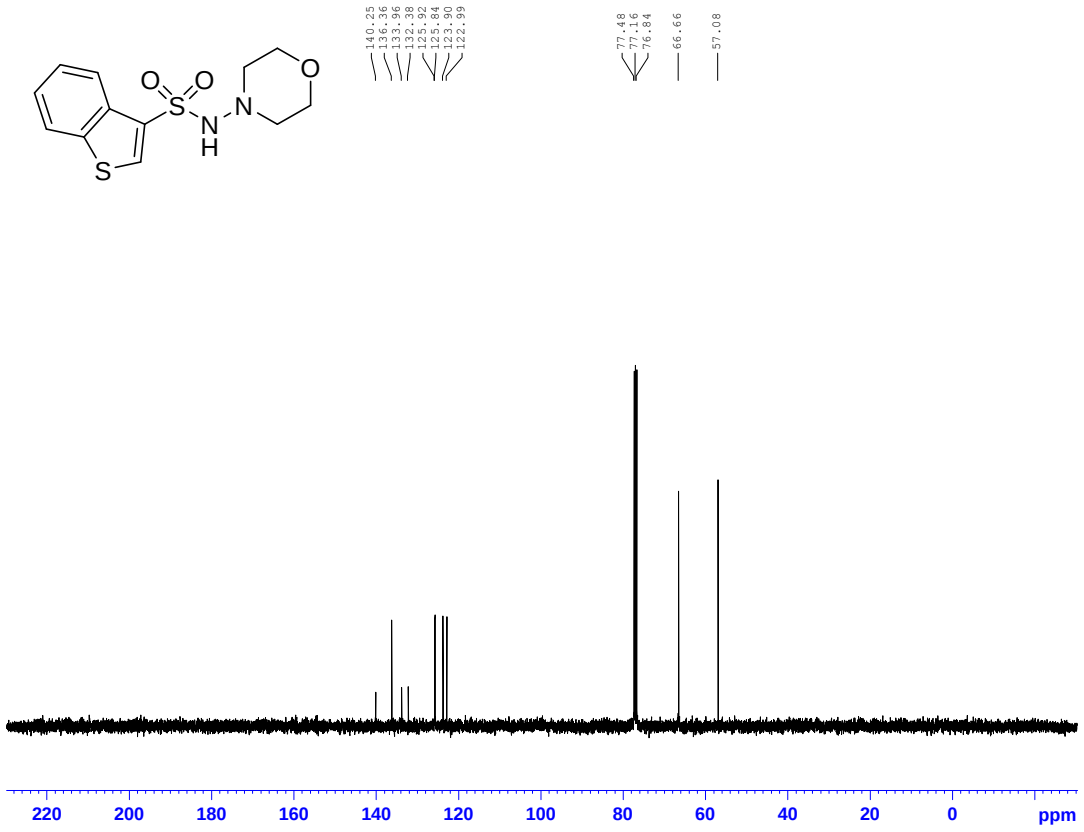


_N_-(morpholin-4-yl)-1-benzothiophene-3-sulfonamide

^{1}H $CDCl_3$ 400 MHz

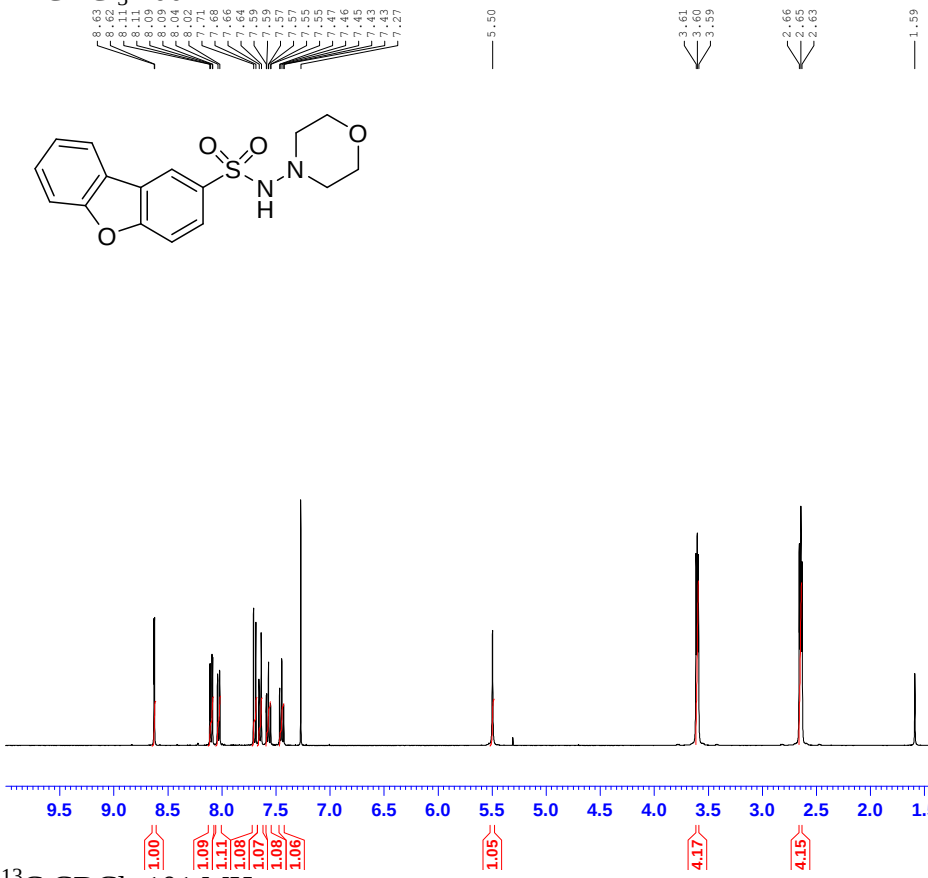


^{13}C $CDCl_3$ 101 MHz

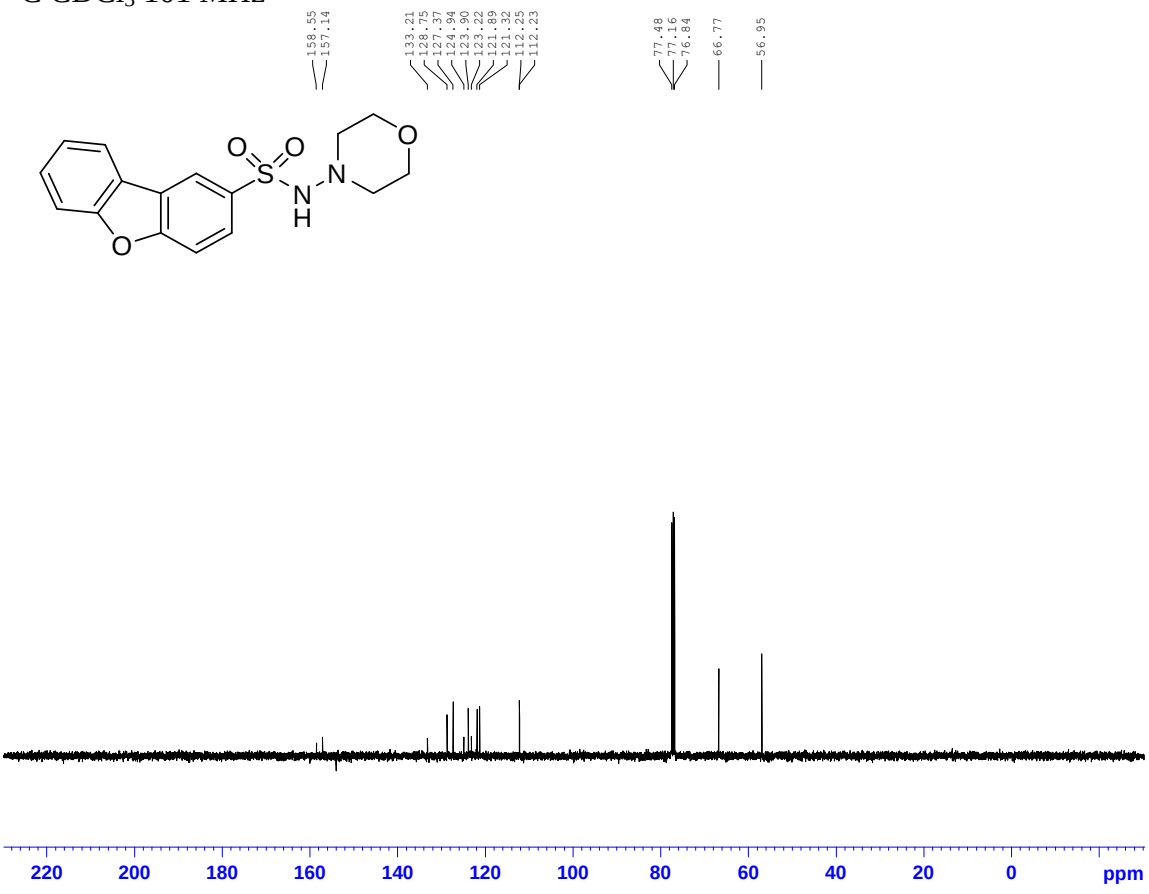


_N_-(Morpholin-4-yl)dibenzo[_b,d_]furan-2-sulfonamide

^{1}H $CDCl_3$ 400 MHz

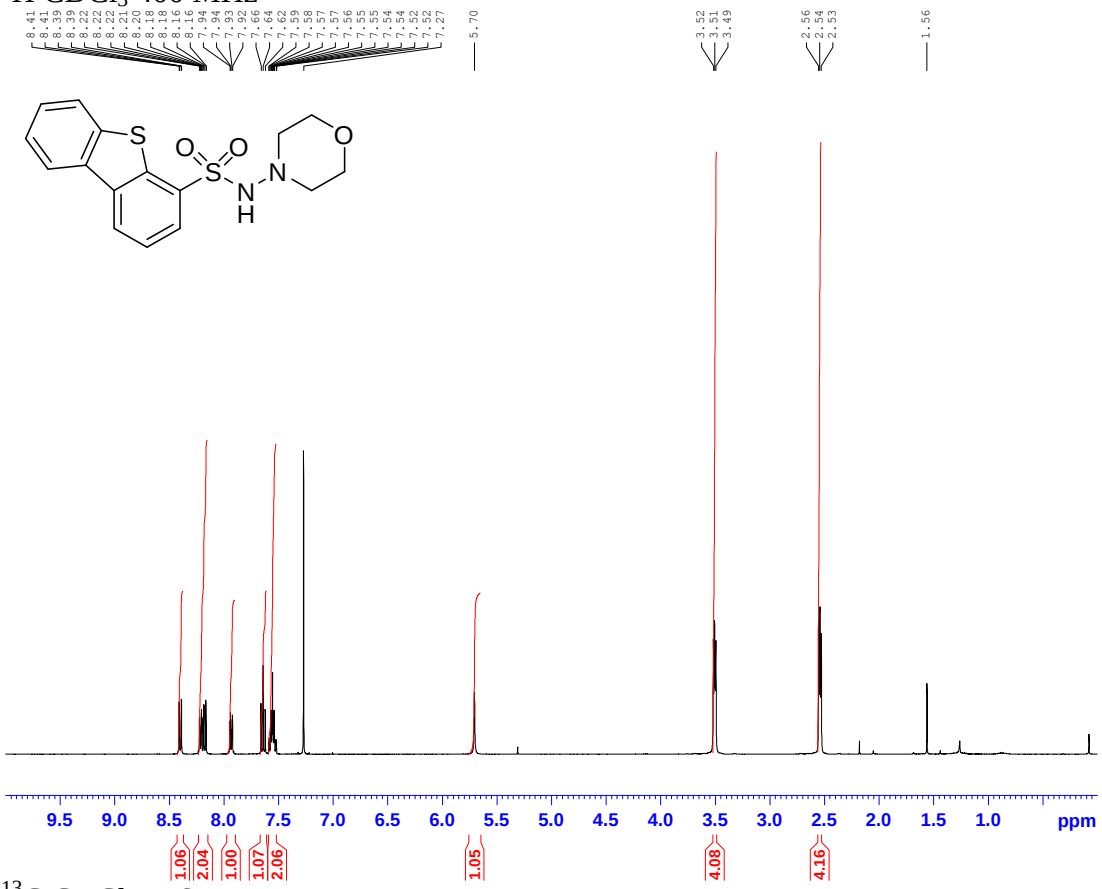


^{13}C $CDCl_3$ 101 MHz

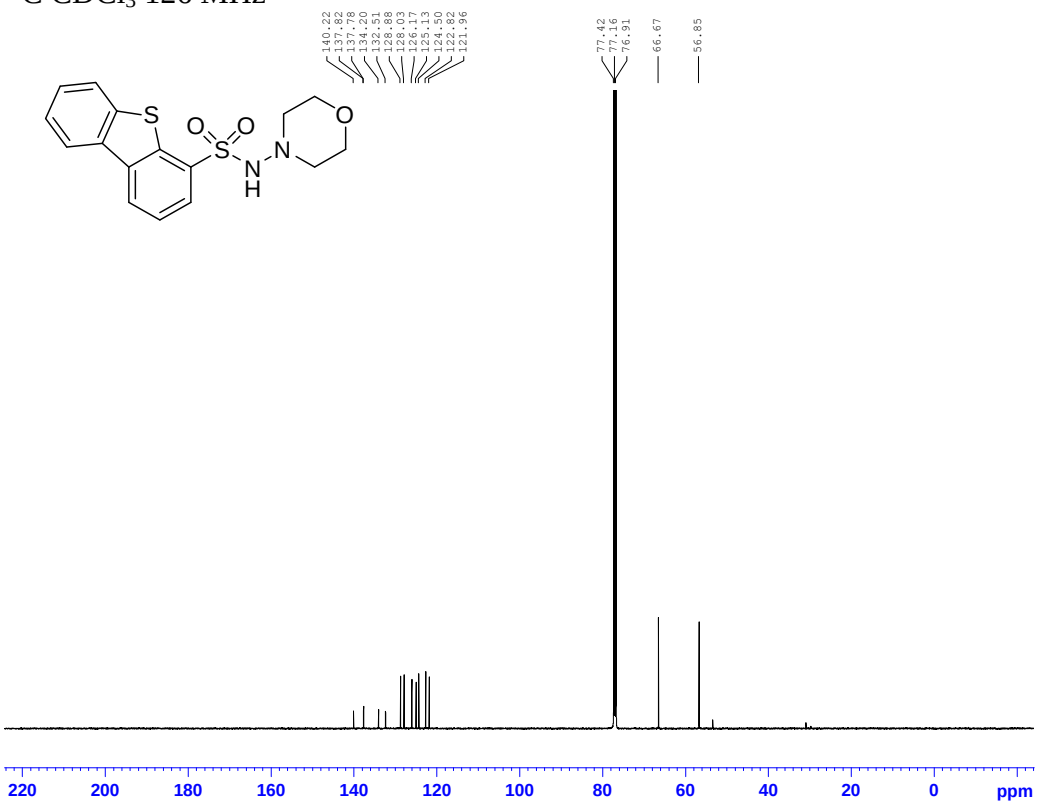


_N_-(Morpholin-4-yl)dibenzo[_b,d_]thiophene-4-sulfonamide

^{1}H $CDCl_3$ 400 MHz



^{13}C $CDCl_3$ 126 MHz



B.5 X-Ray crystallographic data

1-Morpholino-1*H*-pyrido[2,3-*c*][1,2]thiazine 2,2-dioxide 165

X-Ray crystallography was performed by and the data analysed by Dr. Johannes Möller and Dr. Roger Johnson from the Department of Physics.

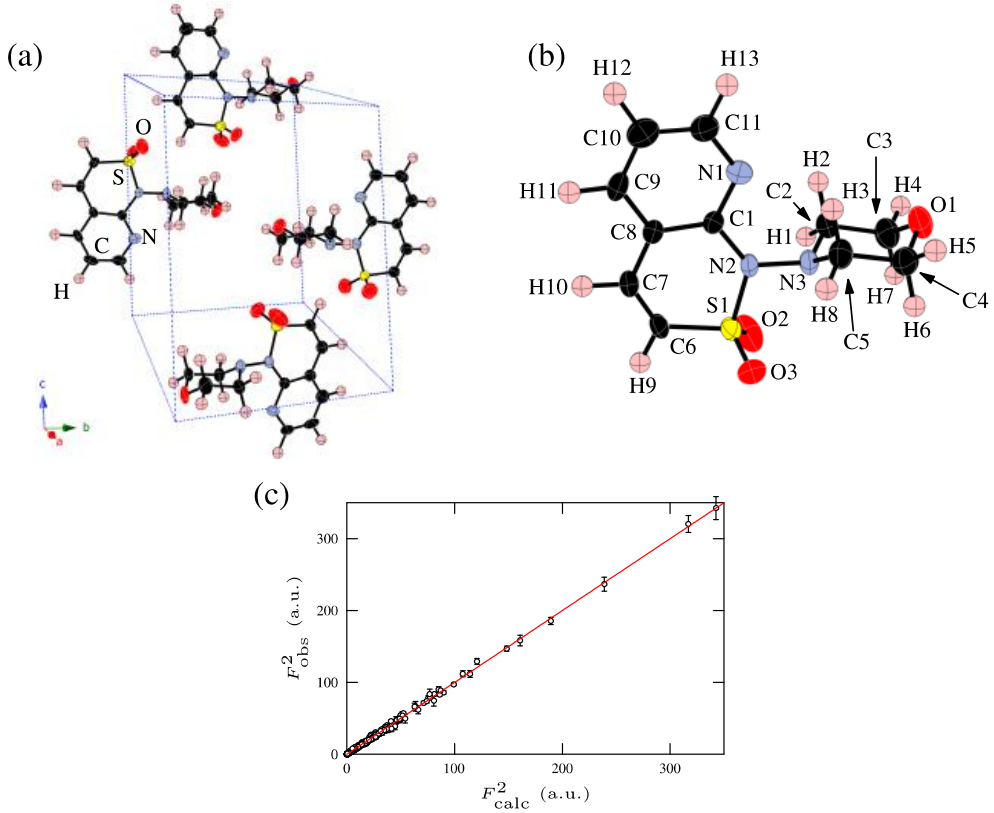


Figure B.1 (a) The crystal structure is shown for the 'molecular unit cell' where molecular fragments from molecules of neighbouring cells are omitted. Thermal ellipsoids represent refined values except for hydrogen, for which the coordinates were obtained through density-functional theory calculations. (b) View of single molecule. (c) Observed versus calculated diffraction peak intensities showing excellent agreement of the refined model with the observed peaks.

A single crystal sample of approximately 200 μm in diameter was selected under a microscope and mounted on a four-circle kappa goniometer. 29105 reflections were collected in total. The space group was determined to be monoclinic $P2_1/n$ (no. 14) with lattice parameters $a = 9.6496(3)$ Å, $b = 10.1391(3)$ Å, $c = 13.0616(4)$ Å, $\beta =$

110.607(3) using the Agilent *CrysAlis*^{Pro} program.[363] This implies 3166 inequivalent reflections. As is common for monoclinic materials, it was found that the crystal chosen for the measurement was comprised of two twins (related through a 180° rotation around the crystallographic *c*-axis) and only the data for the dominant twin was analysed further to determine the atomic coordinates. Overlapping peaks from the two twins were excluded leading to a 1588 reflections, of which 1058 peaks were significant and were used in the refinement, which was performed using *FullProf*.[364] An absorption correction was applied. The coordinates of all atoms except hydrogen, as well as the anisotropic thermal ellipsoids for each atom except hydrogen, an overall scale factor, and an isotropic extinction parameter (accounting for multiple scattering) – a total of 164 parameters – were refined.

Hydrogen does not scatter X-Rays sufficiently strongly to allow the sites of the hydrogen atoms to be determined by X-Ray diffraction in this instance. Therefore we have performed density-functional theory calculations using the Quantum Espresso package.[365] The calculations employed a plane-wave basis set and ultrasoft[366] PBE pseudopotentials.[367] The unit cell was fixed to the experimental parameters and the hydrogen atoms (placed initially in estimated locations) were allowed to relax until the forces on each hydrogen atom and the energy change in subsequent steps had fallen below a convergence threshold. The other atoms were fixed to their experimental positions during this procedure (when all atoms were allowed to relax in a different calculation, only minor changes in the positions were observed). The final

$$R_F^2 = 100 \left| \frac{\sum_{n=1}^{N} \left[G_{obs,n}^2 - \sum_k G_{calc,k}^2 \right]}{\sum_{n=1}^{N} G_{obs,n}^2} \right| = 5.88$$

(with hydrogen atoms fixed in their calculated positions) demonstrates excellent agreement of the model with the observed diffraction data. Here the outermost sum is over $N = 1058$

observed peaks, $G^2_{obs,n}$is the observed intensity of the k-integrated peak n, and $G^2_{calc,k}$ is the calculated intensity for the wavevectors k that contribute to n. For comparison, $R_F^2 = 12.99$ without the hydrogen atoms. The resulting structure is shown in Figure B.1 and is summarized in Table B.1.

Space group	Monoclinic $P2_1/n$ (no. 14)		
Lattice parameters	$a = 9.6496(3)$ Å	b = 10.1391(3) Å	c = 13.0616(4) Å
Angles	$\alpha = 90°$	$\beta = 110.607(3)°$	$\gamma = 90°$
Unit cell volume	$V = 1196.17$ Å^3		
Estimated density	$\rho = 1484.304$ kg/m^3		
Formula units	4 per unit cell		
Atom	**Fractional coordinates**		
	x	y	z
S1	0.27731(12)	-0.03325(9)	0.67988(7)
O1	0.2824(4)	0.4100(3)	0.4840(3)
O2	0.4144(4)	0.0103(3)	0.7568(2)
O3	0.1493(4)	0.0131(3)	0.6976(3)
N1	0.2370(3)	-0.0116(3)	0.3721(2)
N2	0.2700(3)	0.0108(3)	0.5559(2)
N3	0.2746(3)	0.1501(3)	0.5533(2)
C1	0.2439(4)	-0.0711(4)	0.4648(3)
C2	0.4092(4)	0.2023(4)	0.5419(3)
C3	0.4113(5)	0.3494(4)	0.5599(3)
C4	0.1515(5)	0.3584(4)	0.4979(3)
C5	0.1392(4)	0.2118(4)	0.4784(3)
C6	0.2751(4)	-0.2025(4)	0.6719(3)
C7	0.2504(4)	-0.2683(3)	0.5792(3)
C8	0.2304(4)	-0.2086(3)	0.4750(3)
C9	0.1986(4)	-0.2825(4)	0.3801(3)
C10	0.1867(4)	-0.2229(4)	0.2832(3)
C11	0.2083(5)	-0.0880(4)	0.2834(3)
H1	0.50473	0.15737	0.60503
H2	0.41453	0.17978	0.46081
H3	0.12285	0.1898	0.39246
H4	0.50696	0.39382	0.54617
H5	0.05742	0.40847	0.43751
H6	0.15384	0.38246	0.58088
H7	0.41827	0.37155	0.64421
H8	0.04483	0.17297	0.49692
H9	0.2915	0.74907	0.74991
H10	0.24846	0.62408	0.58184
H11	0.18683	0.61103	0.38522

H12	0.16456	0.72004	0.20865
H13	0.20394	0.962	0.20834

Atoms	**Selected bond distances and angles**		
	Bond length	**Angle**	**Bond length**
O2—S1—O3	1.421 Å	115.48°	1.415 Å
S1—N2—N3	1.657 Å	107.56°	1.414 Å
N1—C1—N2	1.333 Å	116.13°	1.399 Å
C3—O1—C4	1.428 Å	110.20°	1.437 Å

Table B.1: Summary of crystallographic refinement for benzosultam **165**. The hydrogen positions are the relaxed coordinates calculated using density-functional theory with the other atoms fixed in their refined positions.

References

[1] (a) Bartholow, M. Top 200 Drugs of 2012. Pharmacy Times. http://www.pharmacytimes.com/publications/issue/2013/July2013/Top-200-Drugs-of-2012; (b) For a list of top 200 pharmauceutical products by US retail sales in 2012 see: http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster; (c) Smith, D. A.; Jones, R. M. *Curr. Opin. Drug Disc. Dev*. **2008**, *11*, 72.

[2] Mahn, W. J. *In Academic Laboratory Chemical Hazards Guidebook*; Van Norstrand R.: New York, **1991**.

[3] Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements* **2005**, 2nd Ed., Elsevier Butterworth-Heinemann.

[4] Mitchel, S. *Biological Interactions of Sulfur Compounds*, Taylor & Francis Ltd. **1996**.

[5] (a) Waddington, T. C. *In Nonaqueous Solvent Systems* **1965**, Academic Press: New York, Chapt. 6, pp. 253-84; (b) Compton, B. W. *Sulfur dioxide: properties, applications and hazards* **2011**, New York: Nova Science Publisher's.

[6] Mahahan, S. E. *Environmental Science and Technology: A Sustainable Approach to Green Science and Technology* **2007**, 2nd ed., Taylor & Francis.

[7] Ye, S.; Wu, J. *Chem. Commun*. **2012**, *48*, 10037.

[8] Shavnya, A.; Coffey, S. B.; Smith, A. C.; Mascitti, V. *Org. Lett.* **2013**, *15*, 6226.

[9] Johnson, M. W.; Bagley, S. W.; Mankad, N. P.; Bergman, R. G.; Mascitti, V.; Toste, F. D. *Angew. Chem. Int. Ed.* **2014**, *53*, 4404

[10] Li, W.; Li, H.; Langer, P.; Beller, M.; Wu, X.-F. *Eur. J. Org. Chem.* **2014**, *2014*, 3101.

[11] (a) Andrews, L. J. *Chem. Rev*. **1954**, *54*, 749; (b) Ault, B. S. *J. Mol. Struct*. **1990**, *238*, 111; (c) Ford, T. A. *J. Mol. Struct*. **2009**, *924-926*, 466.

[12] Steudel, R.; Steudel, Y. *Eur. J. Inorg. Chem*. **2007**, *27*, 4385.

[13] (a) Pradeep, T.; Rao, C. N. R. *J. Mol. Struct*. **1989**, *200*, 339; (b) Pradeep, T.; Rao, C. N. R. *J. Mol. Struct*. **1990**, *224*, 21.

[14] (a) Divers, E.; Ogawa, M. *J. Chem. Soc., Trans*. **1900**, *77*, 327; (b) Moede, J. A.; Curran, C. *J. Am. Chem. Soc.* **1949**, *71*, 852; (c) Hata, T.; Kinumaki *Nature* **1964**, *203*, 1378; (d) van der Helm, D.; Childs, J. D.; Christian, S. D. *J. Chem. Soc., Chem. Commun*. **1969**, *15*, 887; (e) Douglas, J. E.; Kollman, P. A. *J. Am. Chem. Soc.* **1978**, *100*, 5226; (f) Wong, M. W.; Wiberg, K. B. *J. Am. Chem. Soc*. **1992**, *114*, 7527.

[15] Olah, G. A.; Vankar, Y. D.; Fung, A. P. *Synthesis* **1979**, 59.

[16] Olah, G. A.; Vankar, Y. D.; Arvanaghi, M. *Synthesis* **1979**, 984.

[17] Olah, G. A.; Arvanaghi, M.; Vankar, Y. D. *Synthesis* **1980**, 660.

[18] (a) Olah, G. A.; Vankar, Y. D. *Synthesis* **1978**, 702; (b) Olah, G. A.; Vankar, Y. D.; Gupta, B. G. B. *Synthesis* **1979**, 36.

[19] Olah, G. A.; Mathew, T.; Panja, C.; Smith, K.; Prakash, G. K. S. *Cat. Lett.* **2007**, *114*, 1.

[20] (a) Eugène, F.; Langlois, B.; Laurent, E. *J. Org. Chem.* **1994**, *59*, 2599; (b) Eugène, F.; Langlois, B.; Laurent, E. *Phosphorus, Sulfur and Silicon* **1993**, *74*, 377.

[21] Santos, P. S.; Mello, M. T. S. *J. Mol. Struct.* **1988**, 178, 121.

[22] Sigma Aldrich 742937 and Key Organics LH-0733

[23] Nguyen, B.; Emmett, E. J.; Willis, M. C. *J. Am. Chem. Soc*. **2010**, *132*, 16372.

[24] Woolven, H.; González-Rodríguez, C.; Marco, I.; Thompson, A. L.; Willis, M. C. *Org. Lett*. **2011**, *13*, 4876.

[25] Emmett, E. J.; Richards-Taylor, C. S.; Nguyen, B.; Garcia-Rubia, A.; Hayter, B. R.; Willis, M. C. *Biomol. Org. Chem.* **2012**, 10, 4007.

[26] Unpublished work by Nguyen, B.; Emmett, E. J.; Norris, R.; Willis, M. C. group, University of Oxford

[27] Bisseret, P.; Blanchard, N. *Org. Biomol. Chem.* **2013**, *11*, 5393.

[28] (a) Meng, Z.; Yang, Z.; Li, J.; Zhang, Q. *Chemosphere* **2012**, *89*, 579; (b) Huang, X.-L.; Liu, Y.; Zhou, J.-L.; Qin, Y.-C.; Ren, X.-B.; Zhou, X.-H.; Cao, H. *J. Biochem. Mol. Tox.* **2013**, *27*, 389.

[29] Malwal, S. R.; Sriram, D.; Yogeeswari, P.; Konkimalla, V. B.; Chakrapani, H. *J. Med. Chem.* **2012**, *55*, 553.

[30] Malwal, S. R.; Gudem, M.; Hazra, A.; Chakrapani, H. *Org. Lett*., **2013**, *15*, 1116.

[31] Drake, L. R.; Stowe, S. C.; Partansky, A. M. *J. Am. Chem. Soc*. **1946**, *68*, 2521.

[32] Atilio de Frias, J.; Feng, H. *Green Chem*. **2013**, *15*, 1067.

[33] (a) Mingos, D. M. P.; Wardle, R. W. M. *J. Chem. Soc., Dalton Trans.* **1986**, 73; (b) Schenk, W. A. *Angew. Chem., Int. Ed.* **1987**, *99*, 101; (c) Kubas, G. J. *Acc. Chem. Res.* **1994**, *27*, 183; (d) Kubas, G. J. *Inorg. Chem.* **1979**, *18*, 182; (e) Mingos, D. M. P. *Transition Met. Chem.* **1978**, *3*, 1.

[34] Darkwa, J.; Moutloali, R. M.; Nyokong, T. *J. Organomet. Chem.* **1998**, *564*, 37.
[35] Snow, M. R.; Ibers, J. A. *Inorg. Chem.* **1973**, *12*, 224.
[36] Burt, R.; M. Cooke, M.; Green, M. *J. Chem. Soc. A*, **1969**, 2645.
[37] (a) Kubas, G. J.; Wasserman, H. J.; Ryan, R. R. *Organometallics* **1985**, *4*, 2012; (b) Kubas, G. J.; Ryan, R. R. *Polyhedron* **1986**, *5*, 473.
[38] Coffield, T. H.; Kozikowski, J.; Closson, R. D. *J. Org. Chem.* **1957**, *22*, 598.
[39] Roper, W. R.; Wright, L. J. *J. Organomet. Chem.* **1977**, *142*, 1.
[40] (a) Hartman, F. A.; Wojcicki, A. *J. Am. Chem. Soc.* **1966**, *88*, 844; (b) Herberhold, M.; Hill, A. F. *J. Organomet. Chem.* **1988**, *353*, 243.
[41] Kitching, W.; Fong, C. W. *Organomet. Chem. Rev., A.* **1970**, *5*, 281.
[42] (a) Wojcicki, A. *Acc. Chem. Res.* **1971**, *4* 344; (b) Wojcicki, A. *Adv. Organomet. Chem.* **1974**, *12*, 31.
[43] Pelzer, G.; Herwig, J.; Keim, W.; Goddard, R. *Russ. Chem. Bull.* **1998**, *47*, 904.
[44] (a) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114; (b) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402.
[45] Strohmeier, W.; Guttenberger, J. F. *Chem. Ber*. **1964**, *97*, 1871.
[46] Klein, H. S. *J. Chem. Soc. Chem. Commun.* **1968**, 377.
[47] (a) Sen, A. *Acc. Chem. Res.* **1993**, *26*, 303; (b) Drent, E.; Budzelaar, P. H. M. *Chem. Rev.* **1996**, *96*, 663.
[48] Drent, E.; van Broekhoven, J. A. M.; Doyle, M. J. *J. Organomet. Chem.*, **1991**, *417*, 235.
[49] Wojcinski, L. M.; Boyer, M. T.; Sen, A. *Inorg. Chim. Acta* **1998**, *270*, 8.
[50] Drent, E. US 4808697 **1989**;. EP 220765 **1987**.
[51] (a) Snow, R. D.; Frey, F. E. *J. Am. Chem. Soc.* **1943**, *65*, 2417; (b) De Jong, R. B.; Robinson, I. M. US 2943077 **1960**; (c) Hammer, C. F.; Sashihara, T. F. US 3657202 A **1972**; (d) Marvel, C. S.; Audrieth, L. F.; Sharkey, W. H. *J. Am. Chem. Soc.* **1942**, *64*, 1229.
[52] Herwig, J.; Keim, W. *Inorg. Chim. Acta* **1994**, *222*, 381.
[53] (a) Keim, W.; Herwig, J. *J. Chem. Soc., Chem. Commun*. **1993**, 1592; (b) Herwig, J.; Keim, W. EP 641755 A1, **1995**.
[54] Dzhemilev, U. M.; Kunakova, R. V. *Organomet. Chem.* **1993**, *455*, 1.
[55] Dzhemilev, U. M.; Kunakova, R. V.; Struchkov, Y. T.; Tolstikov, G. A.; Sharipova, F. V.; Kuzmina, L. G.; Rafikov, S. R. *Dokl. Akad. Nauk SSSR* **1980**, *250*, 105.
[56] Gattermann, L. *Chem. Ber.* **1899**, *32*, 1136;
[57] Pelzer, G.; Keim, W. *J. Mol. Catal. A: Chem.* **1999**, *139*, 235.
[58] (a) Hoffmann, R. V. *Org. Synth.* **1981**, *60*, 121; (b) Meerwein, H.; Dittmar, G.; Gollner, R.; Hafner, K.; Mensch, F.; Steinfort, O. *Chem. Ber.* **1957**, *50*, 841; (c) Malet-Sanz, L.; Madrzak, J.; Ley, S. V.; Baxendale, I. R. *Org. Biomol. Chem.* **2010**, 8, 5324; (d) Chavan, K.; Medhi, S.; Sharma, R.; Deka, N. *Chem. Bio. Interface* **2011**, *1*, 360.
[59] Zheng, D.; An, Y.; Li, Z.; Wu, J. *Angew. Chem., Int. Ed*. **2014**, *53*, 2451.
[60] Ye, S.; Wu, J. *Chem. Commun*. **2012**, *48*, 7753.
[61] (a) Marvel, C. S.; Johnson, R. S. *J. Org. Chem.* **1948**, *13*, 822; (b) Schubart, R. *Sulfinic Acids and Derivatives* **2000**, Ullman's Encyclopedia of Industrial Chemistry, Wiley-VCH, Weinheim.
[62] Truce, W. E.; Murphy, A. M. *Chem. Rev*. **1951**, *48*, 69.
[63] Hamada, T.; Yonemitsu, O. *Synthesis*, **1986**, 852.
[64] Wu, J.-P.; Emeigh, J.; Su, X.-P. *Org. Lett*. **2005**, *7*, 1223.
[65] Umierski, N.; Manolikakes, G. *Org. Lett*. **2013**, *15*, 4972.
[66] Deeming, A. S., Russell, C. J., Hennessy, A. J., Willis, M. C. *Org. Lett*, **2014**, *16*, 150.
[67] Rocke, B. N.; Bahnck, K. B.; Herr, M.; Lavergne, S.; Mascitti, V.; Perreault, C.; Polivkova, J.; Shavnya, A. *Org. Lett.* **2014**, *16*, 154.
[68] Pandya, R.; Murashima, T.; Tedeschi, L.; Barrett, A. G. M. *J. Org. Chem.* **2003**, *68*, 8274.
[69] Waldmann, C.; Schober, O.; Haufe, G.; Kopka, K. *Org. Lett.* **2013**, *15*, 2954.
[70] Emmett, E. J., Hayter, B., Willis, M. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 12679.
[71] (a) Knoevenagel, E., Kenner, J. *Ber. Dtsch. Chem. Ges.* **1909**, *41*, 3315; (b) Fu, H. Liu, D.; Meng, L.; Luo, T.; Wei, F.; Wu, Y. *Faming Zhuanli Shenqing* 102731349, **2012**.
[72] (a) Durst, T.; Tetreault-Ryan, L. *Tetrahedron Lett.* **1978**, *19*, 2353; (b) Deguin, B.; Vogel, P. *J. Am. Chem. Soc*. **1992**, *114*, 9210; (c) Narkevitch, V.; Megevand, S.; Schenk, K.; Vogel, P. *J. Org. Chem.* **2001**, *66*, 5080.
[73] (a) Backer, H. J.; Strating, J. *Recl. Trav. Chim. Pays-Bas*, **1934**, *53*, 525; (b) Vogel, P; Sordo, J. Á. *Curr. Org. Chem*. **2006**, *10*, 2007.
[74] (a) Bouchez, L.; Vogel, P. *Synthesis* **2002**, 225; (b) Turks, M.; Lawrence, A. K.; Vogel, P. *Tetrahedron Lett*. **2006**, *47*, 2783; (c) Bouchez, L. C.; Dubbaka, S. R; Turks, M.; Vogel, P. *J. Org. Chem*. **2004**, *69*, 6413.

[75] Vogel, P.; Turks, M.; Bouchez, L.; Marković, D.; Varela-Álvarez, A.; Sordo, J. Á. *Acc. Chem. Res.* **2007**, *40*, 931.
[76] Rogic, M. M.; Masilamani, D. *J. Am. Chem. Soc*. **1977**, *99*, 5219.
[77] Marković, D.; Vogel, P. *Angew. Chem., Int. Ed*. **2004**, *43*, 2928.
[78] Thoi, H. H.; Ito, O.; Iino, M.; Matsuda, M. *J. Phys. Chem.* **1978**, *82*, 314.
[79] Marković, D.; Volla, C. M. R; Vogel, P.; Varela-Álvarez, A.; Sordo, J. Á. *Chem.–Eur. J.* **2010**, *16*, 5969.
[80] Barton, D. H. R.; Lacher, B.; Misterkiewicz, B.; Zard, S. Z. *Tetrahedron* **1988**, *44*, 1153.
[81] Arfaei, A.; Smith, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1791.
[82] Tsimelzon, A.; Braslau, R. *J. Org. Chem.* **2005**, 70, 10854.
[83] (a) Lipscomb, R. D. US 2634254 **1953**; (b) Johnson, R.; Steinberg, M. DE 3013187 A1 **1980**
[84] Leontiev, A. V.; Rasika Dias, H. V.; Rudkevich, D. M. *Chem. Commun*. **2006**, 2887.
[85] (a) Florjanczyk, Z.; Raducha, D. *Pol. J. Chem.* **1995**, *69*, 481; (b) Florjanczyk, Z.; Raducha, D. *Makromol. Chem.* **1993**, *194*, 2605; (c) Soga, K.; Kiyohara, K.; Hattori, I.; Ikeda, S. *Makromol. Chem.* **1980**, *181*, 2151; (d) Soga, K.; Hattori, I.; Kinoshita, J.; Ikeda, S. *J. Polym. Sci., Polym. Chem. Ed*. **1977**, *15*,745.
[86] (a) Tfelt-Hansen, P.; De Vries, P.; Saxena, P. R. *Drugs* **2000**, *60*, 1259; (b) Schnellhammer, P. F. *Expert Opin. Pharmaco.* **2002**, *3*, 1313; (c) Mitchell, G.; Bartlett, D. W.; Fraser, T. E. M.; Hawkes, T. R.; Holt, D. C.; Townson, J. K.; Wichert, R. A. *Pest Manag. Sci.* **2001**, *57*, 120; (d) Boger, P. *J. Pestic. Sci.* **2003**, *28*, 324.
[87] Meadows, D. C.; Gervay-Hague, J.; *Med. Res. Rev.*, **2006**, *26*, 793.
[88] Neamati, N.; Mazumder, A.; Zhao, H.; Sunder, S.; Burke, T. R., Jr.; Schultz, R. J.; Pommier, Y. *Antimicrob. Agents Chemother*. **1997**, *41*, 385.
[89] (a) Roy, K. M. In Ullmann's Encyclopedia of Industrial Chemistry; Gerhartz, W., Ed.; VCH: Weinheim, **1985**; Vol. A25, pp 487-501; (b) Hama, F.; Kondo, M. JP61271271 A, **1986**; (c) Sato, K.; Ogoshi, T.; Shimizu, A. JP04120050, **1992**; (d) Mitchell, M. A.; Tomida, M.; Padias, A. B.; Hall, H. K., Jr.; Lackritz, H. S.; Robello, D. R.; Willand, C. S.; Williams, D. J. *Chem. Mater.* **1993**, *5*, 1044; (e) Takahashi, T.; Yoshino, T. JP2001260544, **2001**.
[90] Trost, B. M.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 7260.
[91] Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019.
[92] King, J. F.; Harding, D. R. K. *J. Am. Chem. Soc.* **1976**, *98*, 3312.
[93] (a) Julia, M.; Arnould, D. *Bull. Soc. Chim. Fr.* **1973**, 743; (b) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 49, 4833; (c) Julia, M.; Launay, M.; Stacino, J.-P.; Verpeaux, J.-N. *Tetrahedron Lett.* **1982**, *23*, 2465; (d) Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. I* **1980**, 1045.
[94] (a) Tanaka, K.; Ootake, K.; Imai, K.; Tanaka, N.; Kaji, A. *Chem. Lett.* **1983**, 633; (b) Kozikowski, A. P.; Mugrage, B. B.; Li, C. S.; Felder, L. *Tetrahedron Lett.* **1986**, *27*, 4817; (c) Sato, T.; Okumura, Y.; Itai, J.; Fujisawa, T. *Chem. Lett.* **1988**, 1537; (d) Tanikaga, R.; Hosoya, K.; Kaji, A. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 1799.
[95] (a) McDowel, S. T.; Stirling, C. J. M. *J. Chem. Soc. (B)* **1967**, 351; (b) Horner, L.; Lindel, H. *Liebigs Ann. Chem.*, **1985**, 22.
[96] Simpkins, N. S. *Sulfones in Organic Synthesis*, Pergamon Press, Oxford, **1993**.
[97] Gazdar, M.; Smiles, S. *J. Chem. Soc*. **1908**, *93*, 1833.
[98] Edwards, D.; Stenlake, J. B. *J. Chem. Soc*. **1954**, 3272
[99] Gokel, G. W.; Gerdes, H. M.; Dishong, D. M. *J. Org. Chem*. **1980**, *45*, 3634.
[100] Varma, R. S.; Saini, R. K.; Meshram, H. M., *Tetrahedron Lett*. **1997**, *38*, 6525.
[101] (a) Trost, B. M.; Braslau, R. *J. Org. Chem*. **1988**, *53*, 532; (b) Yu, B.; Liu, A.-H.; He, L.-N.; Li, B.; Diao, Z.-F.; Li, Y.-N. *Green Chemistry*, **2012**, *14*, 957.
[102] Bharadwaj, S. K.; Sharma, S. N.; Hussain, S.; Chaudhuri, M. K. *Tetrahedron Lett*. **2009**, *50*, 3767.
[103] (a) Rayner, C. M. *Contemporary Organic Synthesis* **1995**, *2*, 409; (b) Murata, M.; Buchwald, S. L. *Tetrahedron* **2004**, *60*, 7397.
[104] Akkilagunta, V. K.; Kakulapati, R. R. *J. Org. Chem.* **2011**, *76*, 6819.
[105] Nishimoto, Y.; Okita, A.; Yasuda, M.; Baba, A. *Org. Lett.* **2012**, *14*, 1846.
[106] (a) Nara, S. J.; Harjani, J. R.; Salunkhe, M. M. *J. Org. Chem.* **2001**, *66*, 8616; (b) Bandgar, B. P.; Kasture, S. P. *Synth. Commun.* **2001**, *31*, 1065; (c) Frost, C. G.; Hartley, J. P.; Whittle, A. J. *Synlett* **2001**, 830;
[107] (a) Graybill, B. M. *J. Org. Chem.* **1967**, *32*, 2931; (b) Ueda, M.; Uchiyama, K.; Kano, T. *Synthesis* **1984**, 323.
[108] Choudary, B. M.; Chowdari, N. S.; Kantam, M. L.; Kannan, R. *Tetrahedron Lett*. **1999**, *40*, 2859.
[109] Smith, K.; Ewart, G. M.; Randles, K. R. *J. Chem. Soc., Perkin Trans. I* **1997**, 1085.
[110] Répichet, S.; Le Roux, C.; Hernandez, P.; Dubac, J. *J. Org. Chem*. **1999**, *64*, 6479.
[111] Crandall, J. K.; Pradat, C. *J. Org. Chem*. **1985**, *50*, 1327.

[112] Ju, Y.; Kumar, D.; Varma, R. S. *J. Org. Chem*., **2006**, *71*, 6697.
[113] Chumachenko, N.; Sampson, P. *Tetrahedron* **2006**, *62*, 4540.
[114] (a) Fujita, S. *Synthesis* **1982**, 423; (b) Barco, A.; Benetti, S.; Pollini, G. P.; Taddia, R. *Synthesis* **1974**, 877.
[115] Kice, J. L.; Bowers, K. W. *J. Am. Chem. Soc*. **1962** *84*, 605.
[116] Manescalchi, F.; Orena, M.; Savoia, D. *Synthesis* **1979**, 445.
[117] (a) Robello, D. R.; Ulman, A.; Urankar, E. J. *Macromolecules* **1993**, *26*, 6718; (b) Roblin, R. O., Jr.; Williams, J. H.; Anderson, G. W. *J. Am. Chem. Soc.* **1941**, *63*, 1930.
[118] Ulman, A.; Urankar, E. *J. Org. Chem.* **1989**, *54*, 4691.
[119] Umierski, N.; Manolikakes, G. *Org. Lett*. **2013**, *15*, 188.
[120] Kumar, D.; Arun, V.; Pilania, M.; Shekar, K. P. C. *Synlett* **2013**, *24*, 831.
[121] Baidya, M.; Kobayashi, S.; Mayr, H. *J. Am. Chem. Soc.* **2010**, 132, 4796.
[122] (a) Maiti, A. K.; Bhattacharyya, P. *Tetrahedron* **1994**, *50*, 10483; (b) Sukata, K. *Bull. Chem. Soc. Jpn* **1984**, *57*, 613.
[123] Caupène, C.; Martin, C.; Lemarié, M.; Perrio, S.; Metzner, P. *J. Sulfur Chem.* **2009**, *30*, 338.
[124] Gilman, H.; Beaber, N. J.; Myers, C. H. *J. Am. Chem. Soc*. **1925**, *47*, 2047.
[125] Baarschers, W. H. *Can. J. Chem.* **1976**, *54*, 3056.
[126] Suzuki, H.; Abe, H. *Tetrahedron Lett.* **1995**, *36*, 6239.
[127] (a) Baskin, J. M.; Wang, Z. *Org. Lett.* **2002**, *4*, 4423; (b) Bian, M.; Xu, F.; Ma, C. *Synthesis* **2007**, *19*, 2951.
[128] Zhu, W.; Ma, D. *J. Org. Chem.* **2005**, *70*, 2696.
[129] (a) Cacchi, S.; Fabrizi, G.; Goggoamani, A.; Parisi, L. M.; Bernini, R. *J. Org. Chem*. **2004**, *69*, 5608; (b) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M. *Synlett* **2003**, *3*, 361.
[130] Reeves, D. C.; Rodriguez, S.; Heewon, L.; Haddad, N.; Krishnamurthy, D.; Senanayake, C. H. *Tetrahedron Lett.* **2009**, *50*, 2870.
[131] Zhou, T.; Chen, Z.-C. *J. Chem. Res.* **2000**, 474.
[132] Bandgar, B. P.; Bettigeri, S. V.; Phopase, J. *Org. Lett.* **2004**, *6*, 2105.
[133] (a) Kar, A.; Sayyed, I. A.; Lo, W. F.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Org. Lett*. **2007**, *9*, 3405; (b) Beaulieu, C.; Guay, D.; Wang, Z.; Evans, D. A. *Tetrahedron Lett.* **2004**, *45*, 3233; (c) Huang, F.; Batey, R. A. *Tetrahedron* **2007**, 63, 7667.
[134] (a) Sun, X.; Wang, L. Zhang, Y. *Synth. Commun.* **1998**, *28*, 1785; (b) Li, H.; Wang, H.; Pan, Y.; Shi, Y. *Synth. Commun.* **1998**, *28*, 409; (c) Huang, X., Pi, J.-H. *Synth. Commun.* **1990**, *20*, 2291.
[135] Neumann, W. P.; Wicenec, C. *Chem. Ber.* **1993**, *126*, 763.
[136] (a) Michael, A.; Adair, A. *Deut. Chem. Ges. Ber*. **1877**, *10*, 583; (b) Meyer, H. *Liebigs Ann. Chem*. **1923**, *433*, 327.
[137] Ballini, R.; Marcantoni, E.; Petrini, M. *Tetrahedron*, **1989**, *45*, 6791.
[138] Wawzonek, S.; Meyer, D *J. Am. Chem. Soc.* **1954**, *76*, 2918.
[139] Musuyama, A.; Tsuchiya, K.; Okahara, M. *Bull. Chem. Soc. Jpn*. **1985**, *58*, 2855.
[140] Dornow, A.; Bartsch, W. *Liebigs Ann Chem.* **1957**, *602*, 23.
[141] (a) Powell, B. F.; Overberger, C. G.; Anselme, J. P. *J. Heterocyclic Chem.* **1983**, *20*, 121; (b) Carter, P.; Stevens, T. S. *J. Chem. Soc.* **1961**, 1743; (c) Lemal, D. M.; Rave, T. W.; McGregor, S. D. *J. Am. Chem. Soc*. **1963**, *85*, 1944; (d) Lemal, D. M.; Menger, F.; Coats, E. *J. Am. Chem. Soc*. **1964**, *86*, 2395; (e) Carpino, L. A. *Chem. Ind. (London)* **1957**, 172; *J . Am. Chem. Soc*. **1957**, *79*, 4427; (f) Baker, W.; McOmie, J. F. W.; Preston, D. R. *J . Chem.* Soc. **1961**, 2971.
[142] (a) Das, B.; Lingaiah, M.; Damodar, K.; Bhunia, N. *Synthesis* **2011**, 2941; (b) Suryakiran, N.; Reddy, T. S.; Ashalatha, K.; Lakshman, M.; Venkateswarlu, Y. *Tetrahedron Lett*. **2006**, *47*, 3853; (c) Murthy, S. N.; Madhav, B.; Reddy, P.; Rao, K. R.; Nageswar, Y. V. D. *Tetrahedron Lett*. **2009**, *50*, 5009.
[143] Meek, J. S.; Fowler, J. S. *J. Org. Chem*. **1968**, *33*, 3422.
[144] (a) Klopman, G. *J. Am. Chem. Soc*. **1968**, *90*, 223; (b) Salem, L. *J. Am. Chem. Soc.* **1968**, *90*, 543; (c) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley-Blackwell **1976**.
[145] (a) Darwish, D.; McLaren, R. *Tetrahedron Lett*. **1962**, *3*, 1231; (b) Darwish, D.; Preston, E. A. *Tetrahedron Lett.* **1964**, *5*, 113; (c) Arcus, C. L.; Balfe, M. P.; Kenyon, J. *J. Chem. Soc.* **1938**, 485; (d) Wragg, A. H.; McFadyen, J. S.; Stevens, T. S. *J. Chem. Soc.* **1958**, 3603; (e) Cope, A. C.; Morrison, D. E.; Field, L. *J. Am. Chem. Soc.* **1950**, *72*, 59; (f) Ciuffarin, E.; Isola, M.; Fava, A. *J. Am. Chem. Soc.* **1968**, *90*, 3594.
[146] Wang, F.-Y.; Chen, Z.-C.; Zheng, Q.-G. *J. Chem. Res.-S.* **2003**, *10*, 620.
[147] (a) Zou, J.; Li, F.; Tao, F. G. *Chinese Chem. Lett.* **2009**, *20*, 17; (b) Bruce, I.; Akhlaq, M.; Bloomfield, G. C.; Budd, E.; Cox, B.; Cuenoud, B.; Finan, P.; Gedeck, Pe.; Hatto, J.; Hayler, J. F.; Head, D.; Keller, T.;

Kirman, L.; Leblanc, C.; Le Grand, D.; McCarthy, C.; O'Connor, D.; Owen, C.; Oza, M. S.; Pilgrim, G.; Press, N. E.; Sviridenko, L.; Whitehead, L. *Bioorg. Med. Chem. Lett*. **2012**, *22*, 5445.
[148] Guan, Z.-H.; Zuo, W.; Zhao, L.-B.; Ren, Z.-H.; Liang, Y.-M. *Synthesis* **2007**, *10*, 1465.
[149] (a) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. I* **1978**, 829; (b) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.
[150] Pinnick, H. W.; Reynolds, M. A. *J. Org. Chem.* **1979**, *44*, 160.
[151] Kohler, E. P.; Barrett, G. R. *J. Am. Chem. Soc.* **1924**, *46*, 747.
[152] Ogilvie, W. W.; Déziel, R.; Naud, J.; O'Meara, J. WO 02/076982 A2 **2002**.
[153] Pullagurla, M. R.; Rangisetty, J. B.; Naidu, N.; Maddela, N.; Nagarapu, R.; Polagani, P. R. WO2010049952 A2, **2010**.
[154] Wang, X.; Li, J.; Li, L.; Xu, Y.; Le, Y.; Xia, Q.; Tian, H.; Wei, W.; Wang, L.; Yang, Z.; Shen, J.; Zhou, H. CN 102786514, **2012**.
[155] Reddy, R. B.; Kumar, U. S.; Sahu, N.; Mariappan, K.; Ibrahim, G. P. M. S.; Susi, S. WO 2011145019, **2011**.
[156] (a) Ashcroft, C. P.; Hellier, P.; Pettman, A.; Watkinson, S. *Org. Proc. Res. Dev*. **2011**, 15, 98; (b) Ashcroft, C. P. WO 2005/103035 A1 **2005**.
[157] Jiang, X.; Gong, B.; Prasad, K.; Repič, O. *Org. Proc. Res. Dev*. **2008**, *12*, 1164.
[158] (a) Zhang, F.; Mitchell, D.; Pollock, P.; Zhang, T. Y. *Tetrahedron Lett*. **2007**, *48*, 2349; (b) Carpino, L. A.; Philbin, M.; Ismail, M.; Truran, G. A.; Mansour, E. M. E.; Iguchi, S.; Ionescu, D.; El-Faham, A.; Riemer, C.; Warrass, R.; Weiss, M. S. *J. Am. Chem. Soc.* **1997**, *119*, 9915.
[159] (a) Malatesti, N.; Boa, A. N.; Clark, S.; Westwood, R. *Tetrahedron Lett*. **2006**, *47*, 5139; (b) Dmowski, W.; Manko, V. A.; Nowak, I. *J. Fluorine Chem.* **1998**, *88*, 143.
[160] (a) Kim, S. H.; Tran, M. T.; Ruebsam, F.; Xiang, A. X.; Ayida, B.; McGuire, H.; Ellis, D.; Blazel, J.; Tran, C. V.; Murphy, D. E.; Webber, S. E.; Zhou, Y.; Shah, A. M.; Tsan, M.; Showalter, R. E.; Patel, R.; Gobbi, A.; LeBrun, L. A.; Bartkowski, D. M.; Nolan, T. G.; Norris, D. A.; Sergeeva, M. V.; Kirkovsky, L.; Zhao, Q.; Han, Q.; Kissinger, C. R. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 4181; (b) Schust, J.; Sperl, B.; Hollis, A.; Mayer, T. U.; Berg, T. *Chem. Biol.* **2006**, *13*, 1235; (c) Iley, J.; Moreira, R.; Martins, L.; Guedes, R. C.; Soares, C. M. *Bioorg. Med. Chem. Lett*., **2006**, *16*, 2738; (d) Encío, I.; Morre, D. J.; Villar, R.; Gil, M. J.; Martinez-Merino, V. *Br. J. Cancer*, **2005**, *92*, 690.
[161] Von Schmeling, B.; Davis, R. A.; Relyea, D. I. DE 2002801 A 19701001, **1970**.
[162] Cravotto, G.; Garella, D.; Carnaroglio, D.; Gaudino, E. C.; Rosati, O. *Chem. Commun*. **2012**, *48*, 11632.
[163](a) Pouzet, P.; Erdelmeier, I.; Dansette, P. M.; Mansuy, D. *Tetrahedron* **1998**, *54*, 14811; (b) Antonow, D.; Marrafa, T.; Dawood, I.; Ahmed, T.; Haque, M. R.; Thurston, D. E.; Zinzalla, G., *Chem. Commun*. **2010**, *46*, 2289.
[164] (a) Kitamura, T.; Kobayashi, S.; Taniguchi, H. *Chem. Lett.* **1988**, 1637; (b) Kashiki, T.; Shinamura, S.; Kohara, M.; Miyazaki, E.; Takimiya, K.; Ikeda, M.; Kuwabara, H. *Org. Lett.*, **2009**, *11*, 2473; (c) Sashida, H.; Sadamori, K.; Tsuchiya, T. *Synth. Commun*. **1998**, *28*, 713; (d) Yue, D.; Larock, R. C. *J. Org. Chem*. **2002**, *67*, 1905.
[165] (a) Reddy, D. B.; Reddy, N. S.; Reddy, S.; Reddy, M. V. R.; Balasubramanyan, S. *Org. Prep. Pro. Int.* **1988**, *20*, 205; (b) Reddy, M. V. A.; Reddy, D. B.; Reddy, P. V. R.; Vijayalakshmi, S. *Org. Prep. Pro. Int.* **1991**, *23*, 633.
[166] Allen, D.; Callaghan, O.; Cordier, F. L.; Dobson, D. R.; Harris, J. R.; Hotten, T. M.; W. Martin Owton, W. M.; Rathmell, R. E.; Wood, V. A. *Tetrahedron Lett*. **2004**, 45, 9645
[167] Richards-Taylor, C. S.; Blakemore, D. C.; Willis, M. C. *Chem. Sci*. **2014**, *5*, 222.
[168] Srivastava, A.; Varghese, B.; Loganathan, D. *Chem. Eur. J.* **2013**, *19*, 17720.
[169] Yoakim, C.; O'Meara, J.; Simoneau, B.; Ogilvie, W. W.; Deziel, R. WO 2004026875, **2004**.
[170] Nie, H.; Widdowson, K. L. WO 9834929, **1998**.
[171] Li, W.; Marlowe, C. K.; Scarborough, R. M. WO 2001072725, **2001**.
[172] Watson, R. J.; Batty, D.; Baxter, A. D.; Hannah, D. R.; Owen, D. A.; Montana, J. G. *Tetrahedron Lett.* **2002**, *43*, 683.
[173] Bahrami, K.; Khodaei, M. M.; Soheilizad, M. *J. Org. Chem.* **2009**, *74*, 9287.
[174] Monovich, L. G.; Tommasi, R. A.; Fujimoto, R. A.; Blancuzzi, V.; Clark, K.; Cornell, W. D.; Doti, R.; Doughty, J.; Fang, J.; Farley, D.; Fitt, J.; Ganu, V.; Goldberg, R.; Goldstein, R.; Lavoie, S.; Kulathila, R.; Macchia, W.; Parker, D. T.; Melton, R.; O'Byrne, E.; Pastor, G.; Pellas, T.; Quadros, E.; Reel, N.; Roland, D. M.; Sakane, Y.; Singh, H.; Skiles, J.; Somers, J.; Toscano, K.; Wigg, A.; Zhou, S.; Zhu, L.; Shieh, W.; Xue, S.; McQuire, L. W. *J. Med. Chem.* **2009**, *52*, 3523.

[175] (a) Cremlyn, R. J. *Chlorosulfonic Acid: A Versatile Reagent*; Royal Society of Chemistry: Cambridge, **2002**; pp 7−21; (b) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*; 5th ed., **1989**.
[176] (a) Loev, B.; Kormendy, M. F. *J. Org. Chem.* **1965**, *30*, 3163; (b) Loev, B.; Kormendy, M. F.; Snader, K. M. *J. Org. Chem.* **1966**, *31*, 3531.
[177] Rossi, S.; Pagani, G. *Ann. Chim.-Rome* **1966**, *56*, 741.
[178] Blondet, D.; Pascal, J.-C. *Tetrahedron Lett.* **1994**, *35*, 2911.
[179] Fensome, A.; Goldberg, J. A.; McComas, C. C.; Mann, C. W.; Melenski, E. G.; Sabatucci, J. P.; Woodworth, R. P. Jr. WO2008073956, **2008**.
[180] Bundy, G. L.; Ciske, F. L.; Genin, M. J.; Heasley, S. E.; Larsen, S. D.; Lee, B. H.; May, P. D.; Palmer, J. R.; Schnute, M. E.; Vaillancourt, V. A.; Thorarensen, A.; Wolf, A. J.; Wicienski, N. A.; Wilhite, D. WO2002004444, **2002**.
[181] (a) Minville, J.; Poulin, J.; Dufresne, C.; Sturino, C. F. *Tetrahedron Lett*. **2008**, *49*, 3677; (b) Hanson, P. R.; Probst, D. A.; Robinson, R. E.; Yau, M. *Tetrahedron Lett.* **1999**, *40*, 4761.
[182] (a) Bheeter, C. B.; Bera, J. K.; Doucet, H. *Adv. Synth. Catal.* **2012**, *354*, 3533; (b) Abramovitch, R. A.; Miyashita, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 23, 2413; (c) Li, Y.; Ding, Q.; Qiu, G.; Wu, J. *Org. Biomol. Chem.* **2014**, *12*, 149.
[183] (a) Fensome, A., Goldberg, J., McComas, C. C.; Trybulski, E. J., Woodworth, R. P.; Deecher, D. C.; Garth T. Whiteside, G. T., Zhang, P. *Bioorg. Med. Chem.* **2010**, *20*, 1555; (b) Togo, H.; Nabana, T.; Yamaguchi, K. *J. Org. Chem.* **2000**, *65*, 8391.
[184] (a) Coppola, G. M. *J. Het. Chem.* **1981**, *18*, 845; (b) Coppola, G. M.; Hardtmann, G. E. *J. Het. Chem.* **1977**, *14*, 1117; (c) Coppola, G. M.; Hardtmann, G. E. *J. Het. Chem*. **1979**, *16*, 1361.
[185] Tadd, A. C., Matsuno, A.; Fielding, M. R.; Willis, M. C. *Org. Lett*. **2009**, *11*, 583
[186] Li, P.; Li, J.; Arikan, F.; Ahlbrecht, W.; Dieckmann, M.; Menche, D. *J. Am. Chem. Soc*. **2009**, *131*, 11678.
[187] (a) Battistuzzi, G.; Bernini, R.; Cacchi, S.; De Salve, I.; Fabrizi, G. *Adv. Synth. Catal.* **2007**, *349*, 297; (b) Bernini, R.; Cacchi, S.; De Salve, I.; Fabrizi, G. *Synlett* **2006**, 2947.
[188] Larock, R. C.; Gong, W. H. *J. Org. Chem.* **1989**, *54*, 2047.
[189] Tietze, L. F.; Brasche, G.; Grube, A.; Böhnke, N.; Stadler, C. *Chem. Eur. J.* **2007**, *13*, 8543.
[190] Canovese, L.; Santo, C.; Visentin, F. *Organometallics* **2008**, *27*, 3577.
[191](a) Yu, J.; Gaunt, M. J.; Spencer, J. B. *J. Org. Chem.* **2002**, *67*, 4627; (b) Sparke, M. B.; Turner, L.; Wenham, A. J. M. *J. Catal.* **1965**, *4*, 332.
[192] (a) Harrod, J. F.; Chalk, A. J. *J. Am. Chem. Soc*. **1964**, *86*, 1776; (b) Asinger, F.; Fell, B.; Krings, P. *Tetrahedron Lett*. **1966**, *6*, 633; (c) Sakaki, S.; Kanai, H.; Tarama, K. *Can. J. Chem.* **1974**, *52*, 2857; (d) Harrod, J. F.; Chalk, A. J. *Nature* **1965**, *205*, 280; (e) Cramer, R.; Lindsey, R. V. *J. Am. Chem. Soc.* **1966**, *88*, 3534.
[193] (a) Sen, A.; Lai, T.-W. *Inorg. Chem*. **1981**, *20*, 4036; (b) Sen, A.; Lai, T.-W. *Inorg. Chem*. **1984**, *23*, 3257; (c) Sen, A.; Lai, T.-W. *J. Am. Chem. Soc.* **1981**, *103*, 4627.
[194] (a) Bingham, D.; Hudson, B.; Webster, D. E.; Wells, P. B. *J. Chem. Soc., Dalton Tran.* **1974**, 1521; b) Bond, G. C.; Hellier, M. *J. Catal.* **1965**, *4*, 1; (c) Golborn, P. Scheinmann, F. *J. Chem. Soc. Perkin Trans. 1* **1973**, 2870.
[195] Tan, E. H. P.; Lloyd-Jones, G. C.; Harvey, J. N.; Lennox, A. J. J.; Mills, B. M.; *Angew. Chem. Int. Ed*. **2011**, *50*, 9602.
[196] (a) Davies, N. R. *Nature* **1964**, *201*, 490; (b) Hudson, B.; Webster, D. E.; Wells, P. B. *J. Chem. Soc. Dalton Trans.* **1972**, 1204; (c) Ponec, R.; Rericha, R. *J. Organomet. Chem.* **1988**, *341*, 549.
[197] Albéniz, A. C.; Espinet, P.; López-Fernández, R.; Sen, A. *J. Am. Chem. Soc.* **2002**, 124, 11278.
[198] (a) Cívicos, J. F.; Alonso, D. A.; Najera, C. *Adv. Synth. Cat.* **2011**, *353*, 1683; (b) Castanet, A.-S.; Colobert, F.; Desmurs, J.-R.; Schlama, T. *J. Mol. Catal. A: Chem.* **2002**, *182*, 481; (c) Xu, H.-J.; Zhao, Y.-Q.; Zhou, X.-F. *J. Org. Chem.* **2011**, *76*, 8036.
[199] (a) Reetz, M. T.; Helbig, W.; Quaiser, S. A.; Stimming, U.; Breuer, N.; Vogel, R. *Science* **1995**, *267*, 367; (b) Dhas, N. A.; Gedanken, A. *J. Mater. Chem.* **1998**, *8*, 445; (c) Reetz, M. T.; Westermann, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 165; (d) Calo, V.; Nacci, A.; Monopoli, A.; Laera, S.; Cioffi, N. *J. Org. Chem.* **2003**, *68*, 2929; (e) Bönnemann, H.; Braun, G.; Brijoux, W.; Brinkmann, R.; Schulze Tilling, A.; Seevogel, K.; Siepen, K. *J. Organomet. Chem.* **1996**, *520*, 143; (f) Amadio, E.; Scrivanti, A.; Bortoluzzi, M.; Bertoldini, M.; Beghetto, V.; Matteoli, U.; Chessa, G. *Inorg. Chim. Acta* **2013**, *405*, 188.
[200] Urmann, M.; Nazare, M.; Wehner, V.; Matter, H.; Bauer, A.; Wagner, M. EP 1571154 A1 20050907, **2005**.
[201] Kim, J. N.; Lee, H. J.; Lee, K. Y.; Kim, H. S. *Tetrahedron Lett.* **2001**, *42*, 3737.

[202] Naidu, B. N.; Banville, J.; Beaulieu, F.; Connolly, T. P.; Krystal, M. R.; Matiskella, J. D.; Ouellet, C.; Plamondon, S.; Remillard, R.; Sorenson, M. E.; Ueda, Y.; Walker, M. A. WO 2007064316 A1 20070607, **2007**.
[203] St. Jean, D. J., Jr.; Poon, S. F.; Schwarzbach, J. L. *Org. Lett*. **2007**, *9*, 4893.
[204] Norman, B. H., Lander, P. A.; Gruber, J. M.; Kroin, J. S.; Cohen, J. D.; Jungheim, L. N.; Starling, J. J.; Law, K. L.; Self, T. D.; Tabas, L. B.; Williams, D. C.; Paul, D. C.; Dantzig, A. H. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5526.
[205] Norman, B. H., Lander, P. A.; Gruber, J. M.; Kroin, J. S.; Cohen, J. D.; Jungheim, L. N.; Starling, J. J.; Law, K. L.; Self, T. D.; Tabas, L. B.; Williams, D. C.; Paul, D. C.; Dantzig, A. H. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5526.
[206] (a) Bunce, R. A.; Smith, C. L.; Knight, C. L. *Org. Prep. Proced. Int.* **2004**, *36*, 482; (b) Naidu, B. N.; Connolly, T. P.; Ueda, Y. US 7419969 B2 20080902, **2008**.
[207] Yang, B. H.; Buchwald, S. L. *Org Lett* **1999**, *1*, 35.
[208] Swapna, K.; Murthy, S. N.; Nageswar, Y. V. D. *Eur. J. Org. Chem.* **2010**, *34*, 6678.
[209] Dunne, E. C.; Coyne, E. J.; Crowley, P. B.; Gilheany, D. G. *Tetrahedron Lett.* **2002**, *43*, 2449.
[210] (a) Li, J.-H.; Li, J.-L.; Wang, D.-P.; Pi, S.-F.; Xie, Y.-X.; Zhang, M.-B.; Hu, X.-C. *J. Org. Chem.* **2007**, *72*, 2053; (b) Jasper, C.; Montenegro, E.; Pauluth, D.; Reiffenrath, V.; Manabe, A. DE 102010047702 A1, **2011**.
[211] Roy, S.; Basak, A. *Tetrahedron* **2013**, *69*, 2184.
[212] (a) Simard-Mercier, J.; Jiang, J. L.; Ho, M. L.; Flynn, A. B.; Ogilvie, W. W. *J. Org. Chem.* **2008**, *73*, 5899; (b) Rossi, R.; Bellina, F.; Carpita, A.; Mazzarella, F. *Tetrahedron* **1996**, *52*, 4095.
[213] Willis, M. C.; Taylor, D.; Gillmore, A. T. *Org. Lett.* **2004**, *6*, 4755.
[214] Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 403.
[215] (a) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, 63, 2002; (b) Garcia Martinez, A.; Martinez Alvarez, R.; Garcia Fraile, A.; Subramanian, L. R.; Hanack, M. *Synthesis* **1986**, 222.
[216] Kropp, P. J.; McNeely, S. A.; Davis, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 6907.
[217] Amorese, A.; Arcadi, A.; Bernocchi, E.; Cacchi, S.; Cerrini, S.; Fedeli, W.; Ortar, G. *Tetrahedron* **1989**, *45*, 813.
[218] Xia, M.; Chen, Z. *Synth. Commun*. **2000**, *30*, 1281.
[219] Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.
[220] (a) Hellwinkel, D.; Lenz, R.; Laemmerzahl, F. *Tetrahedron* **1983**, *39*, 2073; (b) Malleron, Jean L.; Comte, M. T.; Gueremy, C.; Peyronel, J. F.; Truchon, A.; Blanchard, J. C.; Doble, A.; Piot, O.; Zundel, J. L.; Huon, C; Martin, B.; Mouton, P.; Virouladt, A.; Allam, D.; Betschard, J. *J. Med. Chem.* **1993**, 36, 1194.
[221] Chan, W. Y.; Berthelette, C. *Tetrahedron Lett.* **2002**, *43*, 4537.
[222] Wells, G. J.; Tao, M.; Josef, K. A.; Bihovsky, R. *J. Med. Chem*. **2001**, *44*, 3488.
[223] (a) Lombardino, J. G.; Wiseman, E. H. *Med. Res. Rev*. **1982**, *2*, 127; (b) Lazer, E. S.; Miao, C. K.; Cywin, C. L.; Sorcek, R.; Wong, H.-C.; Meng, Z.; Potocki, I.; Hoermann, M.; Snow, R. J.; Tschantz, M. A.; Kelly, T. A.; McNeil, D. W.; Coutts, S. J.; Churchill, L.; Graham, A. G.; David, E.; Grob, P. M.; Engel, W.; Meier, H.; Trummlitz, G. *J. Med. Chem*. **1997**, *40*, 980; (c) Engelhardt, G.; Homma, D.; Schlegel, K.; Utzmann, R.; Schnitzler, C. *Inflamm. Res*. **1995**, *44*, 423.
[224] May, J. A.; Namil, A.; Chen, H.-H.; Dantanarayana, A. P.; Dupre, B.; Liao, J. C. *Bioorg. Med. Chem.* **2006** *14*, 2052.
[225] Layman, W. J., Jr.; Greenwood, T. D.; Downey, A. L.; Wolfe, J. F. *J. Org. Chem*. **2005**, *70*, 9147.
[226] Nørager, N. G.; Juhl, K. *Synthesis* **2010**, 4273.
[227] Barange, D. K.; Batchu, V. R.; Gorja, D.; Pattabiraman, V. R.; Tatini, L. K.; Babu, J. M.; Pal, M. *Tetrahedron* **2007**, *63*, 1775.
[228] Barange, D. K.; Nishad T. C.; Swamy N. K.; Bandameedi V.; Kumar D.; Sreekanth B. R.; Vyas K.; Manojit P. *J. Org. Chem.* **2007**, *72*, 8547.
[229] Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.
[230] (a) Rambabu, D.; Murthy, P. V. N. S.; Prasad, K. R. S.; Kandale, A.; Deora, G. S.; Rao, M. V. B.; Pal, M. *Tetrahedron Lett*. **2012**, *53*, 6577; (b) Varela-Fernández, A.; Varela, J.; Carlos, S. *Synthesis* **2012**, *44*, 3285; (c) Hellal, M.; Cuny, G. D. *Tetrahedron Lett.* **2011**, *52*, 5508.
[231] Takeuchi, Y.; Liu, Z.; Satoh, A.; Shiragami, T.; Shibata, N. *Chem. Pharma. Bull.* **1999**, *47*, 1730.
[232] (a) Watanabe, H.; Mao, C.-L.; Barnish, I. T.; Hauser, C. R. *J. Org. Chem*. **1969**, *34*, 919; (b) Watanabe, H.; Hauser, C. R. *J. Org. Chem.* **1968**, 4278; (c) Yu, C.-B.; Gao, K.; Wang, D.-S.; Shi, L.; Zhou, Y-G. *Chem. Commun*. **2011**, *47*, 5052.

[233] (a) Vidal, A.; Madelmont, J.-C.; Mounetou, E. *Synthesis* **2006**, 591; (b) Akira Mizuno, K.; Makoto Shibata, A.; Tomoe Iwamori, I.; Norio Inomata, M. US005874429A, **1999**.
[234] Pham, M. V.; Ye, B.; Cramer, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 10610.
[235] Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1119.
[236] Lawrence, N. J.; Liddle, J.; Jackson, D. *J. Chem. Soc., Perkin Trans. 1* **2002**, *20*, 2260.
[237] (a) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc*. **2010**, *132*, 10565; (b) Mochida, S.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2010**, *39*, 744; (c) Song, G.; Chen, D.; Pan, C.-L.; Crabtree, R. H.; Li, X. *J. Org. Chem.* **2010**, *75*, 7487.
[238] (a) Patureau, F. W.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1977; (b) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc*. **2010**, *132*, 6908.
[239] (a) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem. Int. Ed*. **2011**, *50*, 6379; (b) Deponti, M.; Kozhushkov, S. I.; Yufit, D. S.; Ackermann, L. *Org. Biomol. Chem.* **2013**, *11*, 142.
[240] (a) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548; (b) Li, B.; Feng, H.; Xu, S.; Wang, B *Chem. Eur. J.* **2011**, *17*, 12573.
[241] (a) Zhong, H.; Yang, D.; Wang, S.; Huang, J. *Chem. Comm.* **2012**, *48*, 3236; (b) Lu, S.; Lin, Y.; Zhong, H.; Zhao, K.; Huang, J. *Tetrahedron Lett.* **2013**, *54*, 2001; (c) Zhang, N.; Li, B.; Zhong, H.; Huang, J. *Org. Biomol. Chem.* **2012**, *10*, 9429.
[242] (a) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed*. **2012**, *51*, 10236; (b) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res*. **2012**, *45*, 936.
[243] Chidipudi, S. R.; Wieczysty, M. D.; Khan, I.; Lam, H. W. *Org. Lett.* **2013**, *15*, 570.
[244] Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019.
[245] Gong, T.-J.; Xiao, B.; Liu, Z.-J.; Wan, J.; Xu, J.; Luo, D.-F.; Fu, Y.; Liu, L. *Org. Lett.* **2011**, *13*, 3235.
[246] Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 66.
[247] Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem., Int. Ed*. **2011**, *50*, 1064.
[248] Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474.
[249] (a) Li, X.; Gong, X.; Zhao, M.; Song, G.; Deng, J.; Li, X. *Org. Lett.* **2011**, *13*, 5808; (b) Cochet, T.; Bellosta, V.; Roche, D.; Ortholand, J.-Y.; Greiner, A.; Cossy, J. *Chem. Commun*. **2012**, *48*, 10745; (c) Youn, S. W.; Bihn, J. H.; Kim, B. S. *Org. Lett*. **2011**, *13*, 3738; (d) Miura, M.; Tsuda, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem*. **1998**, *63*, 5211; (e) Dai, H.-X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc*. **2011**, *133*, 7222.
[250] Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc*. **2011**, *133*, 6449.
[251] Chuang, S.-C.; Gandeepan, P.; Cheng, C.-H. *Org. Lett.* **2013**, *15*, 5750.
[252] (a) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299; (b) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett*. **2010**, *12*, 5032; (c) Ackermann, L.; Pospech, J.; Potukuchi, H. K. *Org. Lett*. **2012**, *14*, 2146.
[253] Ackermann, L. *Chem Rev.* **2011**, *111*, 1315.
[254] 10th January 2014 http://www.platinum.matthey.com/ Prices of rhodium, palladium and ruthenium: $1,050, $746, $57 per troy ounce, respectively.
[255] (a) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Org. Lett*. **2011**, *13*, 3278; (b) Su, Y.; Zhao, M.; Han, K.; Song, G.; Li, X.-W. *Org. Lett*. **2010**, *12*, 5462; (c) Ackermann, L.; Wang, L.; Lygin, A. V. *Chem. Sci.* **2012**, *3*, 177.
[256] Boyer, P. M.; Roy, C. P.; Bielski, J. M.; Merola, J. S. *Inorg. Chim. Acta* **1996**, *245*, 7.
[257] Zhen, W.; Wang, F.; Zhao, M.; Du, Z.; Li, X. *Angew. Chem., Int. Ed*. **2012**, *51*, 11819;
[258] Chen, X.; Hussain, S.; Parveen, S.; Zhang, S.; Yang, Y.; Zhu, C. *Curr. Med. Chem.* **2012**, *19*, 3578.
[259] Horaguchi, T.; Hosokawa, N.; Tanemura, K.; Suzuki, T. *J. Heterocyclic Chem*. **2002**, *39*, 61.
[260] (a) Sajid, M.; Klose, A.; Birkmann, B.; Liang, L.; Schirmer, B.; Wiegand, T.; Eckert, H.; Lough, A. J.; Frohlich, R.; Daniliuc, C. G.; Grimme, S.; Stephan, D. W.; Kehr, G.; Erker, G. *Chem. Sci.* **2013**, *4*, 213; (b) For a review on frustrated Lewis pairs: Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 46.
[261] Rozen; S.; Bareket, Y. *J. Org. Chem.* **1997**, *62*, 1457.
[262] Findlay, N. J.; Park, S. R.; Schoenebeck, F.; Cahard, E.; Zhou, S.-Z.; Berlouis, L. E. A.; Spicer, M. D.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc*. **2010**, *132*, 15462.
[263] Boominathan, M.; Muthusaubramanian, S.; Nagaraj, M.; Perumal, D.; Bhuvanesh, N. *J. Org. Chem.* **2012**, *77*, 6319.
[264] Armstrong, A.; Carbery, D. R.; Lamont, S. G.; Pape, A. R.; Wincewicz, R. *Synlett* **2006**, *15*, 2504.
[265] Yoshida, M.; Doi, T.; Kang, S.; Watanabe, J.; Takahashi, T. *Chem. Commun.* **2009**, *19*, 2756.
[266] Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Syn. Cat.* **2007**, *349*, 2610.
[267] Hossain, M. D.; Kitamura, T. *Tetrahedron* **2006**, *62*, 6955.
[268] Deacon, G. B.; Tunaley, D.; Smith, R. N. M. *J. Organomet. Chem.* **1978**, *144*, 111.

[269] Kung, H. F.; Kung, M. P.; Zhuang, Z.-P. WO 2004032975 A2 **2004**.
[270] Knauber, T.; Arikan, F.; Roeschenthaler, G.-V.; Goossen, L. J. *Chem. Eur. J.* **2011**, *17*, 2689.
[271] Butcher, K. J. WO 2009098612 A2, **2009**.
[272] Rey, J.; O'Riordan, T. J. C.; Hu, H.; Snyder, J. P.; White, A. J. P.; Barrett, A. G. M. *Eur. J. Org. Chem.* **2012**, *20*, 3781.
[273] Calogeropoulou, T.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1987**, *52*, 4185.
[274] Lee, K.; Wiemer, D. F. *Tetrahedron Lett*. **1993**, *34*, 2433.
[275] Hooijdonk, M. C. J. M.; Peters, T. H. A.; Vasilevsky, S. F.; Brandsma, L. *Synth. Comm*. **1994**, *24*, 1261.
[276] Cheung, L. L. W.; Yudin, A. K. *Org. Lett*. **2009**, *11*, 1281.
[277] Stork, G.; Zhao, K. *Tetrahedron Lett*. **1989**, *30*, 2173.
[278] Lin, Y.-Y.; Wang, Y.-J.; Lin, C.-H.; Cheng, J.-H.; Lee, C.-F. *J. Org. Chem.* **2012**, *77*, 6100.
[279] Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 14844.
[280] Bergman, R. G.; Sherrod, S. A. *J. Am. Chem. Soc.* **1971**, *93*, 1925.
[281] Van den Hoven, B. G.; Alper, H. *J. Am. Chem. Soc.* **2001**, *123*, 1017.
[282] Hrobárik, P.; Hrobárikova, V.; Sigmundová, I.; Zahradnik, P.; Mihalis, F.; Polyzos, I.; Persephonis, P. *J. Org. Chem.* **2011**, 76, 8726.
[283] Kozikowski, A. P.; Xia, Y. US 4929731 A1, **1990**.
[284] Nara, S. J.; Jha, M.; Brinkhorst, J.; Zemanek, T. J.; Pratt, D. A. *J. Org. Chem.* **2008**, 73, 9326.
[285] Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890.
[286] Wang, X.; Li, J.; Li, L.; Xu, Y.; Le, Y.; Xia, Q.; Tian, H.; Wei, W.; Wang, L.; Yang, Z.; Shen, J.; Zhou, H. *Faming Zhuanli Shenqing*, CN 102786514, **2012**.
[287] Furuya, T., Strom, A. E.; Ritter, T. *J. Am. Chem. Soc*. **2009**, *131*, 1662.
[288] Chakrabarty, M.; Kundu, T.; Harigaya, Y. *Synth. Commun.* **2006**, *36*, 2069.
[289] Shen, X.; Hyde, A. M.; Buchwald, S. L. *J. Am. Chem. Soc*. **2010**, *132*, 14076.
[290] Oxley, P.; Partridge, M. W.; Robson, T. D.; Short, W. F. *J. Chem. Soc*. **1946**, 763.
[291] Stevenson, P. J. *Org. Biomol. Chem.* **2011**, *9*, 2078.
[292] Ono, N.; Tamura, R.; Tanikaga, R.; Kaji, A. *Synthesis*, **1977**, 690.
[293] Gao, Y.; Lam, Y. *Adv. Syn. Cat.* **2008**, *350*, 2937.
[294] Asahi, Y.; Shinozaki, K.; Nagaoka, M. *Chem. Pharmaceutical Bulletin* **1971**, *19*, 1079.
[295] Knorr, L.; Brownsdon, H. W. *Chem. Ber.* **1902**, *35*, 4474.
[296] (a) Perdicchia, D.; Licandro, E.; Maiorana, S.; Baldoli, C.; Giannini, C. *Tetrahedron*, **2003**, *59*, 7733; (b) Gruendemann, E.; Brehme, R.; Nikolajewski, H. E. *J. Prakt. Chem.* **1982**, *324*, 575.
[297] Hajipour, A. R.; Falahati, A. R.; Ruoho, A. E. *Tetrahedron Lett.* **2006**, *47*, 2717.
[298] Treece, J. L.; Goodell, J. R.; Vander Velde, D.; Porco, J. A., Jr.; Aubé, J. *J. Org. Chem.* **2010**, *75*, 2028.
[299] Dass Gupta, B.; Roy, M.; Roy, S.; Kumar, M.; Das, I. *J. Chem. Soc. Perk. T. II*, **1990**, *4*, 537.
[300] Niwa, T.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2009**, *65*, 1971.
[301] Vennstra, G. E.; Zwaneburg, B. *Synthesis* **1975**, *8*, 519.
[302] Suryakiran, N.; Srinivasulu, M.; Venkateswarlu, Y. *J. Sulfur Chem.* **2007**, *28*, 345.
[303] Hajipour, A. R.; Mallakpour, S. E.; Afrousheh, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2000**, *160*, 67.
[304] Tiecco, M.; Testaferri, L.; Tingoli, M.; Wenkert, E. *Tetrahedron* **1983**, *39*, 2289.
[305] Yang, D. Y.; Han, O.; Liu, H. W. *J. Org. Chem.* **1989**, *54*, 5402.
[306] Kohori, K.; Hashimoto, M.; Kinoshita, H.; Inomata, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3088.
[307] Alonso, D. A.; Arques, A.; Najera, C.; Sansano, J. M. *An. Quim.* **1995**, *91*, 449.
[308] Bordwell, F. G.; Jarvis, B. B. *J. Org. Chem.* **1968**, *33*, 1182.
[309] (a) Zhou, G.; Ting, P. C.; Aslanian, R. G. *Tetrahedron Lett.* **2010**, *51*, 939; (b) Kropp, P. J.; Breton, G. W.; Fields, J. D.; Tung, J. C.; Loomis, B. R. *J. Am. Chem. Soc.* **2000**, *122*, 4280.
[310] Lamm, B.; Anker, K. *Acta Chem. Scand., Ser. B.* **1978**, *32*, 264.
[311] Bryliakov, K. P.; Talsi, E. P. *Eur. J. Org. Chem.* **2011**, *24*, 4693.
[312] Courtin, A. *Helv. Chim. Acta* **1983**, *66*, 1046.
[313] Farbenind, I. G. FR 49285 **1939**.
[314] Schank, K.; Werner, F. *Liebigs Ann. Chem.* **1979**, 1977.
[315] Choudary, B. M.; Bharathi, B.; Reddy, Ch. V.; Kantam, M. L. *J. Chem. Soc., Perkin Trans. I*, **2002**, 2069.
[316] Chianelli, D.; Testaferri, L.; Tiecco, M.; Tingoli, M. *Synthesis* **1982**, 475.
[317] Troger, J.; Beck, O. *J. Prakt. Chem.* **1913**, *87*, 289.
[318] Hoesch, L. *Helv. Chim. Acta* **1981**, *64*, 890.
[319] Hollywood, F.; Suschitzky, H.; Hull, R. *Synthesis* **1982**, *8*, 662.
[320] Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961.
[321] Vo, G. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11049.

[322] Schlosser, M. *Chem. Ber*. **1964**, *97*, 3219.
[323] Gavina, F.; Luis, S. V.; Ferrer, P.; Costero, A. M.; Marco, J. A. *J. Chem. Res.* **1986**, 330.
[324] Bonnamour, J.; Piedrafita, M.; Bolm, C. *Adv. Syn. Cat.* **2010**, *352*, 1577.
[325] Beshai, M., Dhudshia B., Mills R.,Thadani A. N. *Tetrahedron Lett.* **2008**, *49*, 6794.
[326] Fang, Y.-Q.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 538.
[327] Prasad, D. J. C.; Sekar, G. S. *Org. Biomol. Chem*. **2013**, *11*, 1659.
[328] Qing, F.-L.; Fan, Junfa; Sun, Hong-Bin; Yue, Xiang-Jun *J. Chem. Soc., Perk.Trans. 1: Org. BioOrg. Chem*. **1997**, 3053.
[329] Hamura, T.; Chuda, Y.; Nakatsuji, Y.; Suzuki, K.; *Angew. Chem., Int. Ed.* **2012**, *51*, 3368.
[330] Bruns, D.; Miura, H.; Vollhardt, K. P. C.; Stanger, A. *Org. Lett.* **2003**, *5*, 549.
[331] Cristol, S. J.; Pappas, P. *J. Org. Chem.* **1963**, *28*, 2066.
[332] Taniguchi, N. *Synlett* **2012**, *23*, 1245.
[333] White, C.; Yates A.; Maitlis, P. M.; Heinekey, D. M. *Inorganic Syntheses* **1992**, *29*, 228.
[334] Geoffrey, F.; Cloke, N.; Day, J. P.; Greenway, A. M.; Seddon, K. R.; Shimran, A. A.; Swain, A. C. *J. Organomet. Chem*. **1989**, *372*, 231.
[335] Gray, W. D.; Maren, T. H.; Sisson, G. M.; Smith, F. H. J. *Pharmacol. Exp. Therapeutics* **1957**, *121*, 160.
[336] Knauf, H.; Mutschler, E. Clin. Pharmacokinet. **1998**, *34*, 1.
[337] Vullo, D.; Innocenti, A.; Nishimori, I.; Pastorek, J.; Scozzafava, A.; Pastorekova, S.; Supuran, C. T. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 963.
[338] Mitani, S.; Araki, S.; Takii, Y.; Ohshima, T.; Matsuo, N.; Miyoshi, H. *Pest. Biochem. Phys.* **2001**, *71*, 107.
[339] Baghestani, M. A.; Zand, E.; Soufizadeh, S.; Jamali, M.; Maighany, F. *Crop Protection* **2007**, *26*, 1385.
[340] Anderson, K. K. *In Sulfonic Acids and Their Derivatives in Comprehensive Organic Chemistry*; Barton, D. H. R.; Ollis, W. D.; Jones, D. N. Eds.; Pergamon Press: Oxford **1979**, *3*, pp 331−350.
[341] Budzinski, J. C.; Zimmerman, D. F.; Levitt, G. EP 39239 **1981**.
[342] Bonk, J. D.; Amos, D. T.; Olson, S. J. *Synth. Commun*. **2007**, *37*, 2039.
[343] DeBergh, J. R.; Niljianskul, N.; Buchwald, S. J. *J. Am. Chem. Soc*. **2013**, *135*, 10638.
[344] Ruano, J. L. G.; Parra, A.; Yuste, F.; Mastranzo, V. M. *Synthesis* **2008**, 311;
[345] (a) Caddick, S.; Wilden, J. D.; Judd, D. B. *J. Am. Chem. Soc*. **2004**, *126*, 1024; (b) Wilden, J. D.; Judd, D. B.; Caddick, S. *Tetrahedron Lett*. **2005**, *46*, 7637; (c) Chantarasriwong, O.; Jang, D. O.; Chavasiri, W. *Tetrahedron Lett*. **2006**, *47*, 7489; (d) Wilden, J. D.; Geldeard, L.; Lee, C. C.; Judd, D. B.; Caddick, S. *Chem. Commun*. **2007**, 1074.
[346] De Luca, L.; Giacomelli, G. *J. Org. Chem.* **2008**, *73*, 3967.
[347] Graham, S. L.; Scholz, T. H. *Synthesis* **1986**, 1031.
[348] Baskin, J. M.; Wang, Z. *Tetrahedron Lett*. **2002**, *43*, 8479.
[349] (a) Ho, D. K. H.; Chan, L.; Hooper, A.; Brennan, P. E. *Tetrahedron Lett.* **2011**, *52*, 820; (b) Katritzky, A. R.; Rodriguez-Garcia, V.; Nair, S. K. *J. Org. Chem.* **2004**, *69*, 1849.
[350] Garcia-Rubia, A. Summer project report, Prof. M. C. Willis group, University of Oxford, **2010**.
[351] (a) Dong, Z.; Manolikakes, G.; Li, J.; Knochel, P. *Synthesis* **2009**, 681; (b) Gundersen, L.-L. *Tetrahedron Lett.* **1994**, *35*, 3155; (c) Joucla, L.; Batail, N.; Djakovitch, L. *Adv. Synth. Cat.* **2010**, *352*, 2929.
[352] Conrad, J. C.; Kong, J.; Laforteza, B. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11640.
[353] Mothes, C.; Lavielle, S.; Karoyan, P. *J. Org. Chem.* **2008**, *73*, 6706.
[354] Oakdale, J. S.; Boger, D. L. *Org. Lett.* **2010**, *12*, 1132.
[355] Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem*. **2003**, *68*, 2861.
[356] (a) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2005**, *44*, 1371; (b) Shen, Q.; Tokutaro, O.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 8564; (c) Guram, A. S.; Wang, X.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J. *J. Org. Chem*. **2007**, *72*, 5105; (d) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 6523.
[357] Pyrrole: K_a =23.0 (DMSO); indole: K_a =20.95 (DMSO); pyrazole: K_a=19.8 (DMSO); see: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.
[358] (a) Li, K.; Darkwa, J.; Guzei, I. A.; Mapolie, S. F. *J. Organomet. Chem.* **2002**, *660*, 108; (b) Godoy Netto, A. V.; Mauro, A. E.; Frem, R. C. G.; Santana, A. M.; Santos, R. H. A.; Zoia, J. R. *J. Coord. Chem*. **2001**, *54*, 129; (c) Mostafa Hossain, A. G. M.; Nagaoka, T.; Ogura, K. *Electrochimica Acta* **1996**, *41*, 2773.
[359] John, E. A.; Pollet, P.; Gelbaum, L.; Kubanek, J. *J. Nat. Prod.* **2004**, *67*, 1929.
[360] Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317.
[361] Liu, J.-H., Chan, H.-W., Xue, F., Wang, Q.-G., Mak, T. C. W., Wong, H. N. C. *J. Org. Chem.* **1999**, *64*, 1630.

[362] Shvartsberg, M. S.; Vasilevskii, S. F.; Prikhod'ko, T. A. *Izv. Akad. Nauk SSSR, Ser. Khim*. **1982**, *11*, 2524.
[363] Agilent Technologies UK Limited, http://www.chem.agilent.com.
[364] The refinement was performed using *FullProf*, Rodriguez-Carvjal, J. *Physica B* **1993**, *192*, 55.
[365] Giannozzi, P.; Baroni, S.; Bonini, N.; Calandra, M.; Car, R.; Cavazzoni, C.; Ceresoli D.; Chiarotti, G. L; Cococcioni, M.; Dabo Ismaila; Dal Corso, A.; de Gironcoli, S.; Fabris, S.; Fratesi, G.; Gebauer, R.; Gertsmann, U.; Gougoussis, C.; Kokalj, A.; Lazzeri, M.; Martin-Samos, L.; Marsari, N.; Mauri, F.; Mazzarello, R.; Paolini, S.; Pasquarello, A.; Paulatto, L.; Sbraccia, C.; Scandolo, S.; Sclauzero, G.; Seitsonen, A. P.; Smogunov, A.; Umari, P.; Wentzcovtich, R. M. *J. Phys.: Condens. Matter* **2009**, *21*, 395502.
[366] Vanderbilt, D. *Phys. Rev. B* **1990**, *41*, 7892.
[367] Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1996**, *77*, 3865.