

Synthesis of sulfur-containing organic compounds: sulfones, sulfonamides and benzoisothiazoles

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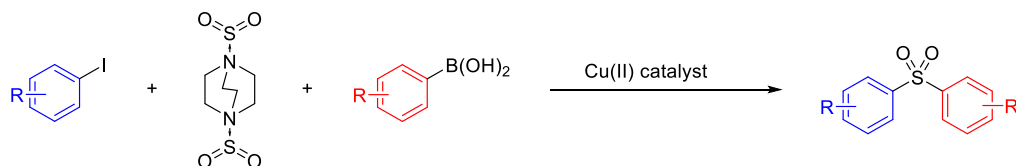
A thesis submitted in partial fulfilment of the requirements
for the degree of Doctor of Philosophy in Organic
Chemistry

Abstract

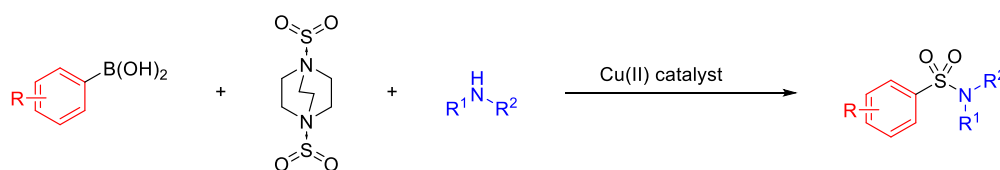
This thesis documents the development of novel methodologies for access to sulfur-containing compounds, including sulfones, sulfonamides and benzoisothiazoles.

Chapter 1 provides an overview of the applications and the synthesis of sulfonyl-containing compounds. A comprehensive introduction to the development of sulfur dioxide surrogates and their applications in transition metal-catalysed organic chemistry is given.

Chapter 2 describes the development of a one-step copper(I)-catalysed sulfonylative Suzuki-Miyaura cross coupling reaction.^[1] A wide range of aryl and alkenyl boronic acids are coupled with aryl and alkenyl iodides to give the corresponding sulfones. A two-step one-pot sulfination/derivatisation method was also developed, allowing access to compounds including β -hydroxy sulfones, sulfonamides and sulfonyl fluorides.

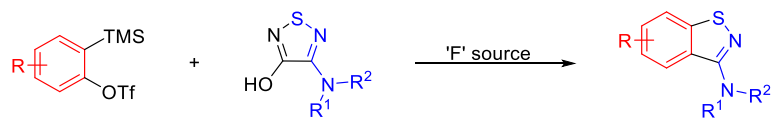


Chapter 3 illustrates a one-step copper(II)-catalysed sulfonamide synthesis using boronic acids, amines and SO₂. Various aryl and alkenyl boronic acids as well as amines and anilines are compatible, including active pharmaceutical ingredients such as amoxapine and desloratadine.



Chapter 4 details an aryne-based selective formation of substituted benzoisothiazoles.^[2]

Different substitution pattern of the aryne precursor and the thiadiazole are employed, with the target heterocycles being obtained in good to excellent yields.



Chapter 5 summarises the research and the future work.

Chapter 6 documents the experimental procedures and data.

Declaration

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

Yiding Chen

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I would like to dedicate this thesis to my grandparents, love you.

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Abbreviations and acronyms

Å	Angström
Ac	acetyl
acac	acetylacetonate
app.	apparent
aq.	aqueous
Ar	aryl
br.	broad
Bu	butyl
boc	tert-butyloxycarbonyl
CAN	ceric ammonium nitrate
cat.	catalyst or catalytic
cbz	carboxybenzyl
COSY	correlation spectroscopy
CRL	Chemistry Research Laboratory
d	doublet or deuterated
DABCO	1,4-diazabicyclo[2.2.2]octane
DABSO	1,4-diazabicyclo[2.2.2]octane-bis(sulfur dioxide) adduct
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCM	dichloromethane
DCE	1,2-dichloroethane
Dioxane	1,4-dioxane

DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone
DMSO	dimethyl sulfoxide
DPhil.	Doctor of Philosophy
DIPEA	<i>N,N</i> -diisopropylethylamine
E	electrophile
EI	electron ionisation
eq.	equation or equivalents
equiv.	equivalents
ESI	electrospray ionisation
ESR	electron spin resonance
Et	ethyl
FI	field ionisation
FT	Fourier transform
g	gram
h	hour(s)
hDA	hetero-Diels Alder
hept.	heptet

HIV	human immunodeficiency virus
HMBC	heteronuclear multiple bond correlation
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	Hertz
i	<i>iso</i>
IPA	2-propanol
IR	infrared
J	coupling constant
l	liquid
L	ligand or litre
LRMS	low resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital
M	metal or molar
m	meter or milli (10^{-3}) or multiplet
m	<i>meta</i>
<i>m</i> CPBA	3-chloroperoxybenzoic acid
Me	methyl
min	minute(s)
mol	mole

m.p.	melting point
MS	mass spectrometry
m/z	mass to charge ratio
n	<i>normal</i>
NCS	<i>N</i> -chlorosuccinimide
NFSI	<i>N</i> -Fluorobenzenesulfonimide
NHC	<i>N</i> -heterocyclic carbene
NMP	<i>N</i> -Methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Nu	nucleophile
o	<i>ortho</i>
[O]	oxidant
p	<i>para</i>
Ph	phenyl
phen	phenanthroline
ppm	parts per million
Pr	propyl
py	pyridine
q	quartet
quin.	quintet
R	generic group/substituent
red	reductant

RM	organometallic
RT	room temperature
s	singlet or solid
sat.	saturated
sec	second(s)
sext.	sextet
S _N 2	nucleophilic substitution (bimolecular)
S _N Ar	nucleophilic aromatic substitution
T	temperature
t	triplet
t	tertiary
TBAB	tetrabutylammonium bromide
TBAC	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBAI	tetrabutylammonium iodide
TBAOH	tetrabutylammonium hydroxide
TBPB	<i>tert</i> -butyl peroxybenzoate
TBS	<i>tert</i> -butyldimethylsilyl
TBHP	<i>tert</i> -butyl hydroperoxide
^t BuXPhos	2-di- <i>tert</i> -butylphosphino-2',4',6'-triisopropylbiphenyl
TC	thiophene-2-carboxylate

TEEDA	<i>N,N,N',N'</i> -Tetraethylethylenediamine
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
Tf	triflyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
ToF	time-of-flight
Tol	tolyl
tosyl	toluenesulfonyl
UV	ultraviolet
wt	weight
X	(pseudo)halide or generic counterion
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
Z	heteroatom
δ	chemical shift
μ	micro (10^{-6})
ν	frequency
Δ	heat

Chapter 1: Introduction

1.1. Sulfur-containing compounds

1.1.1. Application of sulfur-containing compounds

Sulfur and its derivatives have been involved in human civilisation since pre-historical era. Elementary sulfur was used in ancient traditional Chinese medicine and was believed to be the one of the key ingredient for the Elixir of Immortality.^[3] Sulfur dioxide was used in winemaking by the Romans and is still an important component in wine industry as a preservative.^[4] In modern science, sulfur-containing compounds are playing an essential role in our lives. The evidences are ubiquitous. For instance, sodium dodecyl sulfate (SDS) is one of the most common and effective surfactants in commercial detergents. Hexavalent sulfur dioxide derivatives like sulfones or sulfonamides are also of great importance due to their frequent appearance in biologically active molecules, medicines, agrochemicals, as well as polymeric materials (**Figure 1.1**).^[5]

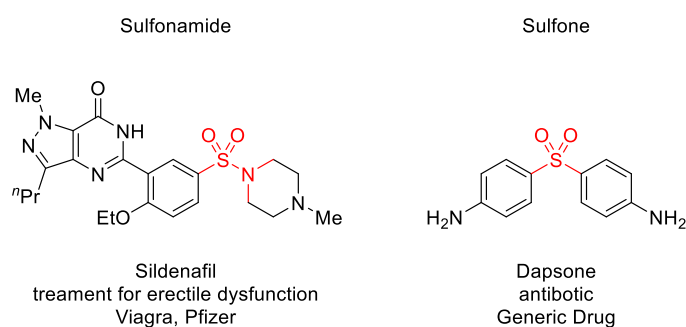


Figure 1.1 Application examples of sulfonyl-containing compounds, sulfonamide and sulfone

The discovery of antibiotics is arguably the most important advance in 20th century medical science, and sulfonyl-containing compounds together with β -lactams were involved at the very start. Not knowing the mechanism at the time, sulfonamide based Prontosil was

discovered to be active against bacterial infection in mice in 1932 by Gerhard Domagk and soon became the first systematically applied antibacterial drug in human history.^[6] In 1935, analysis determined its active form being sulfanilamide,^[7] which led to numerous sulfonamide derivatives being synthesised and tested as antibiotics in the next decade. These sulfonamide-based drugs were given a common name: sulfa drugs, and they extended the word sulfonamide from a chemical moiety to a class of medicine. Later studies revealed that the mechanism of their anti-bacterial activity is to act as analogues of *para*-aminobenzoic acid (*p*ABA), which is one of the substrates for *de novo* folic acid biosynthesis.^[8] The sulfonamides bind the active site of this enzyme, dihydropteroate synthase (DHPS), inhibiting the folic acid synthesis, therefore halting the growth and multiplication of bacteria.^[9]

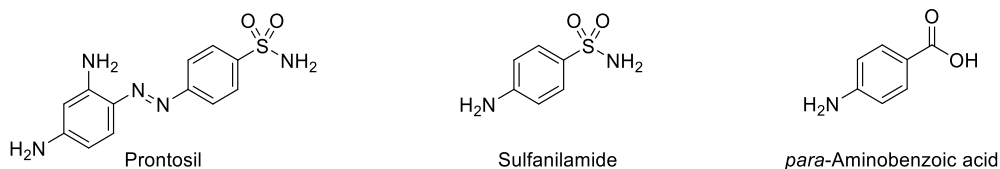
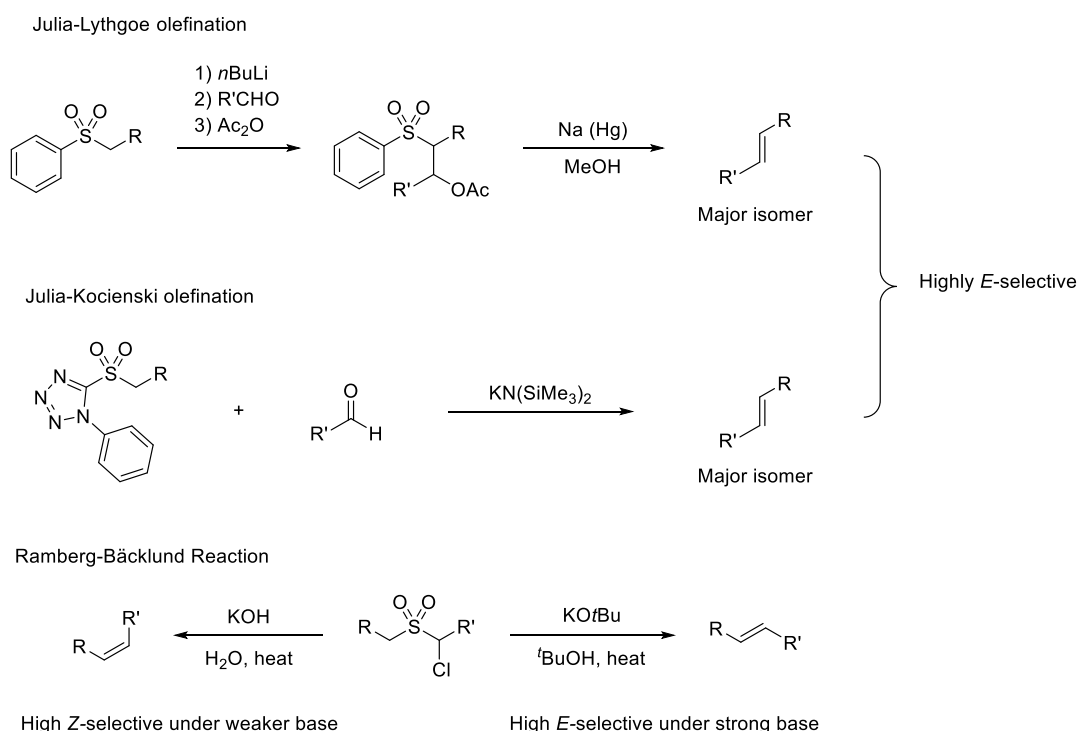


Figure 1.2 Prontosil, Sulfanilamide and *para*-aminobenzoic acid

The bacteriostatic property is merely one of the many biological properties sulfone and sulfonamide-containing compounds possess. Both sulfones and sulfonamides are potent HIV protease inhibitors and have been studied as potential anti-HIV drugs.^[10] In addition, sulfonamides have also shown ability to inhibit carbonic anhydrase and thus are used for glaucoma treatment^[11] and are being developed as anti-tumour agents for several different types of cancer.^[12] Other medicinal applications of sulfones and sulfonamides include diuretics,^[13] treatment of epileptic seizures,^[14] and as antivirals for hepatitis C.^[15]

Along with distinctive biological activities, compounds with the sulfonyl moiety are known as useful precursors and intermediates in organic synthesis. The primary application of sulfonyl-containing compounds is as protecting groups for amines or alcohols in the form of sulfonamides or sulfonates.^[16] In addition, the RSO_2 - or the $-\text{SO}_2$ - unit can serve as a leaving group, known as desulfonylation (**Scheme 1.1**). Famous examples are the Julia olefination^[17] and Ramberg-Bäcklund^[18] reaction, where sulfonyl moieties are cleaved to trigger the highly selective formation of alkenes. Both these methods and their modified versions^[19] are powerful and versatile synthetic transformations widely utilised in the construction of complex natural products with excellent control of geometrical isomerism.^[20]



Scheme 1.1 Julia olefination and Ramberg-Bäcklund reaction

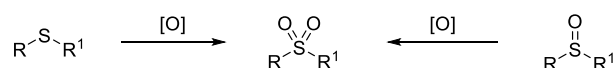
More details on the applications of sulfones and sulfonamides will be discussed later in

Chapter 2 and Chapter 3, respectively.

1.1.2. Synthesis of sulfonyl-containing compounds

Although the information above is obviously far from sufficient to cover every detail of the applications for sulfones and sulfonamides, it is intended to address the primacy of sulfonyl-containing compounds. Knowing that, it is understandable that countless methods have been developed to access these molecules in organic chemistry. This introduction will focus on the two broad approaches to prepare these molecules.

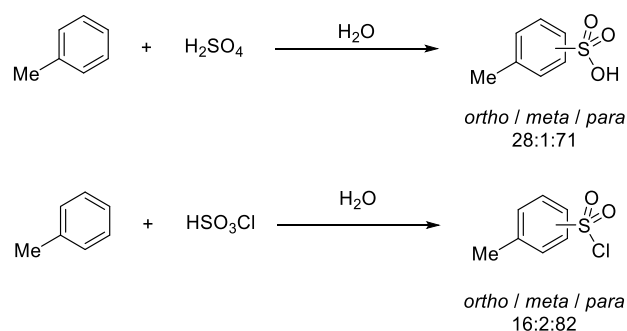
The first type, and arguably the most straightforward one, is through oxidation of the corresponding sulfides, sulfinamides^[21] or sulfoxides (**Scheme 1.2**). Choice of oxidant include *m*CPBA,^[22] H₂O₂,^[23] *tert*-butyl hydroperoxide and oxone.^[24] Convenient as they seem to be, these methods are constrained by the limited accessibility of the sulfides or sulfoxides. Additional steps, and the use of malodorous thiols, to access these compounds are often required. In addition, the use of these oxidative conditions can have a strong negative impact on the functional group compatibility of these reactions.



Scheme 1.2 Generic examples of sulfone synthesis from oxidation

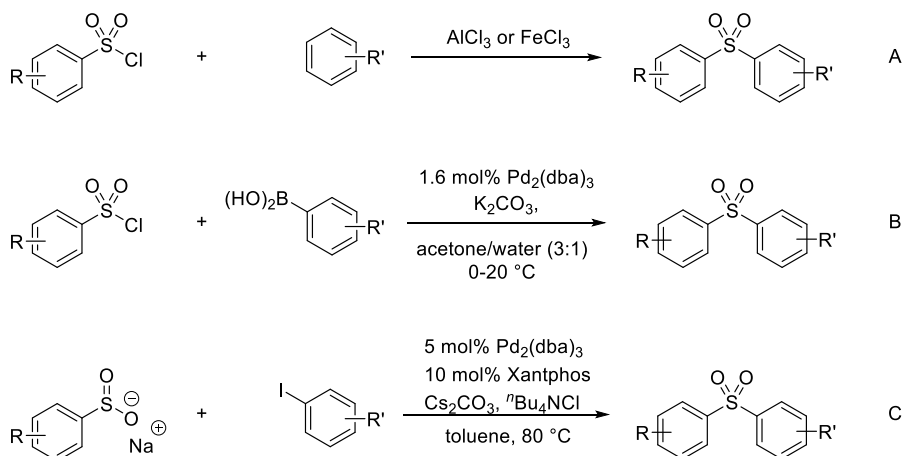
The second approach is to install the sulfonyl moiety directly onto the molecule. Treating hydrocarbons with sulfuric acid to obtain organic sulfonic acids was documented before 1870s.^[25] Beckurts and Otto also published their discovery of reactions between chlorosulfonic acid and toluene to give tolyl sulfonyl chloride in 1878.^[26] These processes display low functional group tolerance and poor regioselectivity due to their strongly acidic

and oxidative nature, and therefore are not applicable to the emerging concept of late stage functionalisation. Sulfur dioxide has been used directly in sulfonylation or hydrosulfinations as well. A more detailed description of these applications can be found in the following Section (1.2.1).



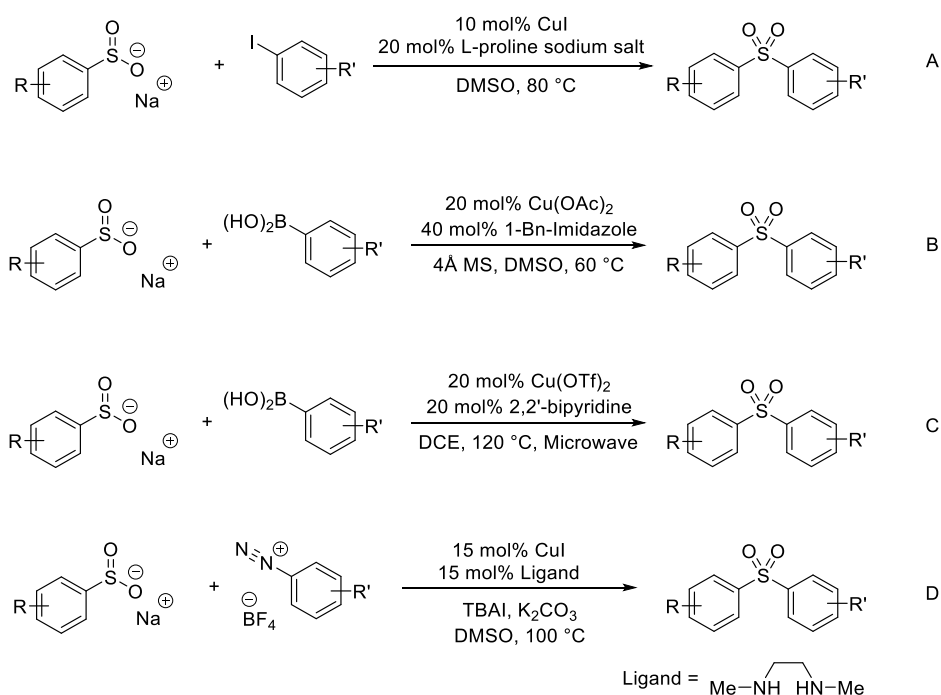
Scheme 1.3 Sulfonylation of toluene with sulfuric acid and chlorosulfonic acid

Broadly speaking, conversions between sulfonyl containing compounds, such as chlorination of sulfonic acid to give sulfonyl chlorides,^[27] are also under the same category above. Nucleophilic substitution of sulfonyl halides^[28] or *in situ* generated sulfonyl halides^[29] allows access to a wide range of sulfonyl-containing compounds such as sulfonamides, as does the electrophilic substitution of sulfinate salts for the synthesis of sulfones.^[30] Metal catalysts are used for the transformation of sulfonyl chlorides and sulfones as well (**Scheme 3.1**). With the help of the Lewis acids $AlCl_3$ or $FeCl_3$, Friedel-Crafts sulfonylation can be achieved between sulfonyl chlorides and arenes (**Equation A**).^[31] Reactions combining aryl sulfonyl chlorides and aryl boronic acids using palladium catalysis were also reported by Phopase group and Lei group respectively (**Equation B**).^[32] Similar palladium-catalysed diaryl sulfone syntheses was published by Cacchi *et al.* using sodium aryl sulfinate salts and aryl iodides (**Equation C**).^[33]



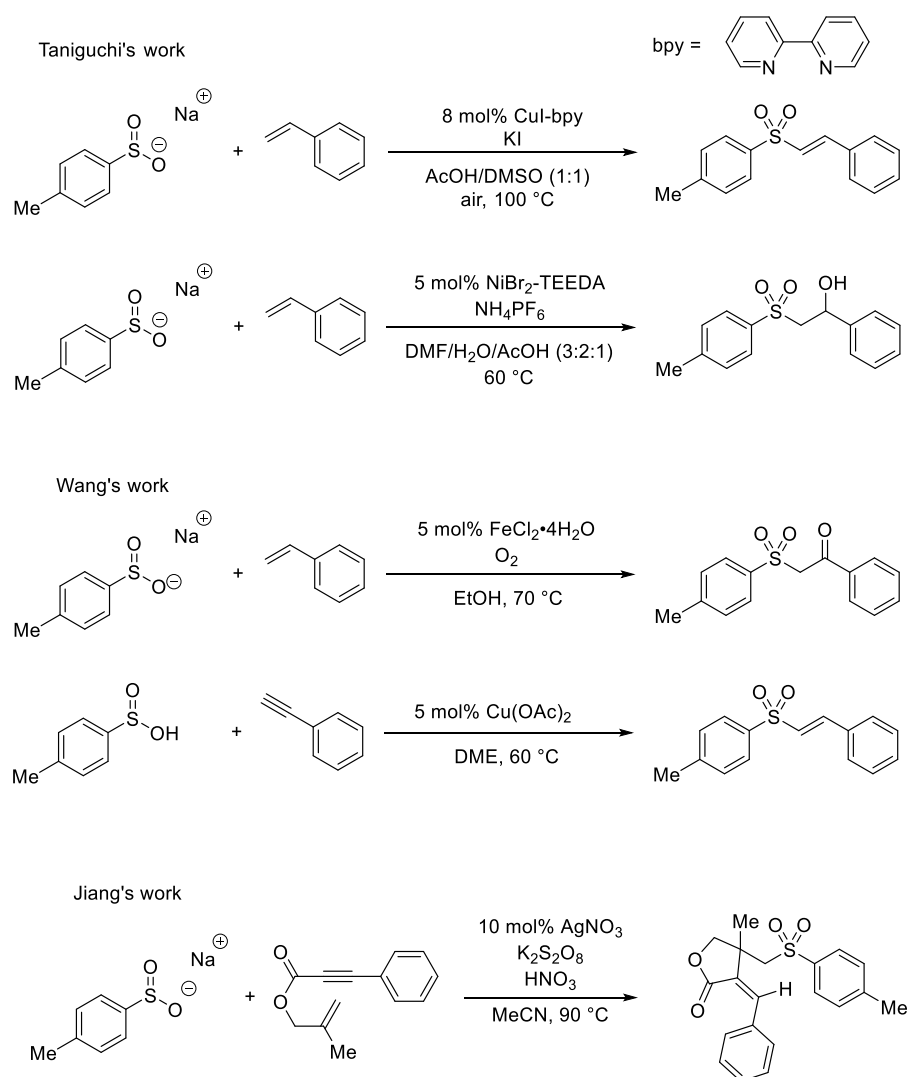
Scheme 1.4 Examples of diaryl synthesis from sulfonyl chloride and sodium sulfinate

Copper-catalysed sulfone synthesis from metal sulfinate and aryl halides was first reported by Suzuki *et al.* applying stoichiometric copper iodide.^[34] Follow-up improvements include lowering the catalyst loading to 10 mol% (**Equation A**)^[35] and utilising recoverable or magnetic separable catalysts.^[36] In addition, boronic acids^[37] and arenediazonium salts^[38] could also be combined with sulfonates under copper catalysis (**Equation B, C and D**).



Scheme 1.5 Examples of copper catalysed diaryl sulfone synthesis from metal sulfonates

Radical sulfonyl species could also be formed with the help of metal catalysts (**Scheme 1.6**). For example, Taniguchi published two articles presenting the radical-based alkene sulfonylation^[39] and hydroxysulfonylation^[40] with copper and nickel catalyst respectively. Wei *et al.* later published work on iron or copper catalysed sulfonylation of alkenes^[41] or alkynes.^[42] In 2017, Jiang and coworkers reported the silver catalysed cascade sulfonylation/cyclisation of 1,6-enynes with sodium sulfinates for the synthesis of sulfonylated lactones.^[43]



Scheme 1.6 Examples of radical based alkene/ alkyne sulfonylation

Apart from the strategies mentioned above, Buchwald and his team inventively used phenyl chlorosulfate to perform a palladium-catalysed chlorosulfonylation with aryl boronic acids, or directly with organozinc reagents to give aryl sulfonyl chlorides, which could either be isolated or trapped *in situ* with nucleophiles.^[44] A new method for sulfone and sulfonamide synthesis from thiosulfonate was discovered by Jang and his group this year.^[45] Jiang *et al.* and very recently Katrun *et al.* described decarboxylative^[46] and deacylative sulfonylation^[47] from sodium sulfinates. Many more pathways towards sulfonyl-containing products have been developed and it is not possible to cover everything in this short introduction. More details regarding the synthesis of sulfones and sulfonamides can be found in Chapter 2, and Chapter 3.

1.2. Sulfur dioxide, its surrogates and their application in organic chemistry

The concept of utilising gaseous carbon monoxide or CO surrogates in organic synthesis has attracted significant attention.^[48] A close comparison between carbon monoxide and sulfur dioxide has shown similarities in chemical properties;^[49] for example both CO and SO₂ can coordinate with transition metals as σ -donor and π -acceptor.^[50] Despite this, sulfur dioxide is relatively unexplored in synthetic chemistry, especially in transition metal-catalysed reactions.

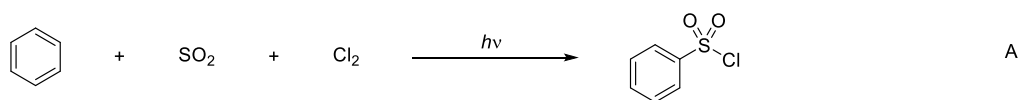
1.2.1. Sulfur dioxide in organic chemistry

Sulfur dioxide is the primary reactant for industrial production of sulfuric acid^[51] and is used as a preservative in multiple products like cured meat, wine and dried fruit.^[52] On the other hand, sulfur dioxide is also an air pollutant and is one of the sources of acid rain,^[53]

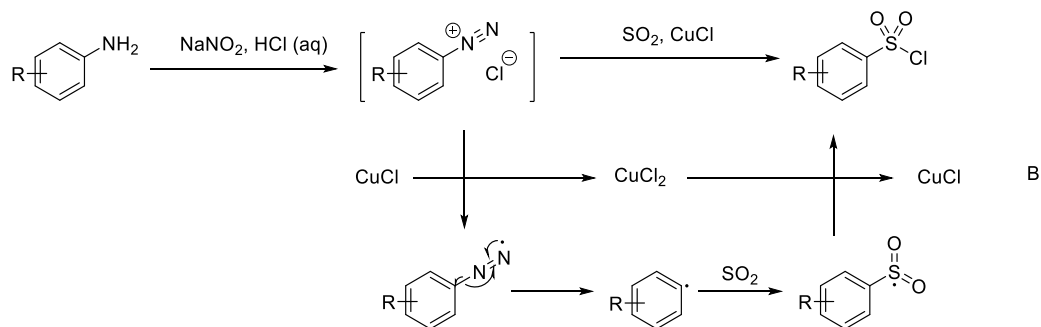
and was behind the tragedy of the Great Smog in 1950s.^[54] Another application of sulfur dioxide is the co-polymerisation with alkenes to give polysulfone which has excellent stability and is widely used in thermoplastic polymers.^[55] In small organic molecule synthesis, sulfur dioxide also appears in various organic reactions in different roles such as an electrophile or a component in cycloadditions.^[56]

In 1936, Reed and coworkers discovered that unactivated arenes could be transformed to sulfonyl chlorides using sulfur dioxide and chlorine gas under UV irradiation, presumably *via* a radical process (**Scheme 1.7, Equation A**).^[57] Radical-based sulfinic acid synthesis from organodiazonium compounds and sulfur dioxide was also described as early as 1890s.^[58] Later, Meerwein *et al.* published a radical-based Sandmeyer sulfonyl chloride synthesis using *in situ* formed diazonium species and a copper catalyst.^[59] The diazonium salts generated from anilines and nitrous acid extrude nitrogen with the help of a copper(I) catalyst, providing an aryl radical. Under sulfur dioxide atmosphere the aryl radical is trapped with molecular SO₂ and finally quenched by chlorination to deliver the sulfonyl chloride product (**Equation B**). Building on this concept, Pelzer *et al.* reported a palladium-on-charcoal catalysed synthesis of sulfinic acids from aryldiazonium tetrafluoroborates, sulfur dioxide and hydrogen gas (**Equation C**).^[60]

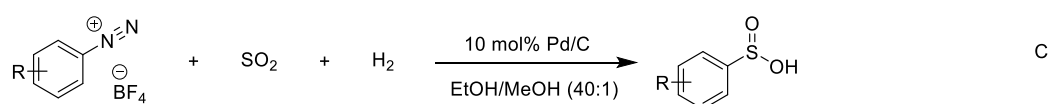
Reed Process



Meerwein's work

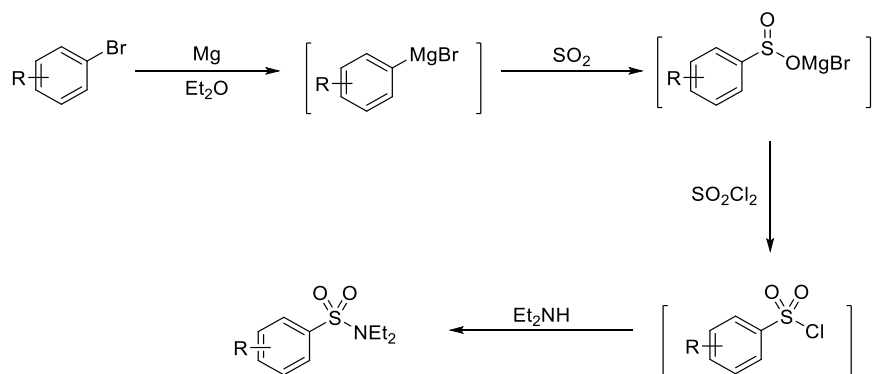


Pelzer's work



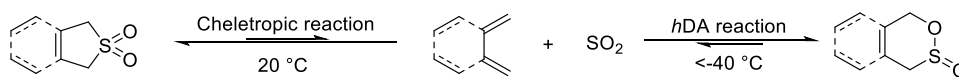
Scheme 1.7 Examples of radical-based sulfur dioxide sulfonylation reactions

Treatment of sulfur dioxide with activated organometallic compounds like organo lithium reagents or Grignard reagents produces the corresponding sulfinates, which could subsequently be trapped *via* halogenation to give useful sulfonyl halides or continue to react with amines to give sulfonamides (**Scheme 1.8**).^[61]



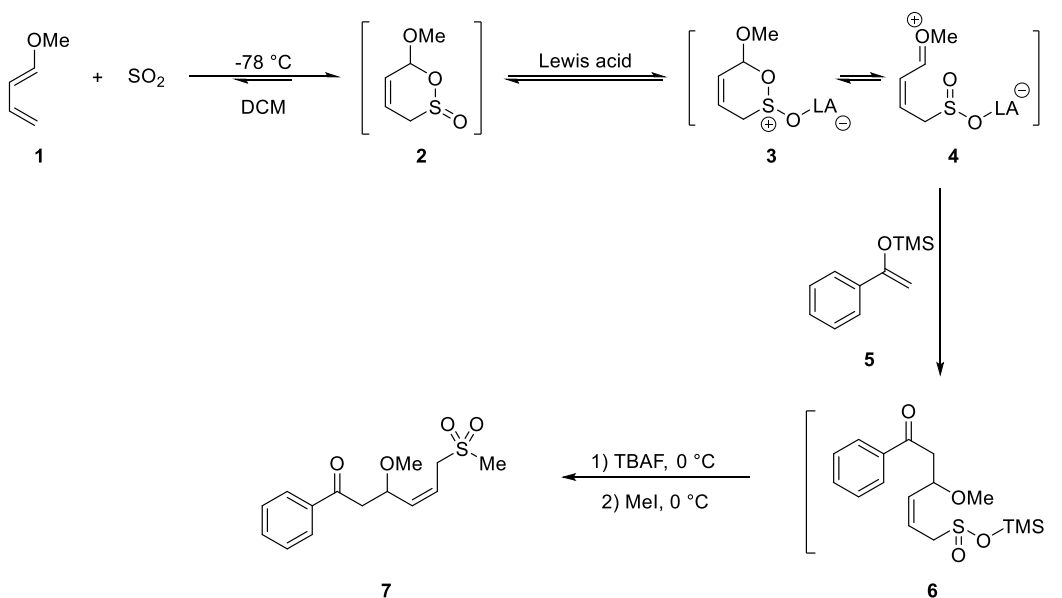
Scheme 1.8 Example of sulfonamide/sulfonyl chloride synthesis from sulfur dioxide and organometallic reagent

Alkenes are another important reaction partner for sulfur dioxide. It is well-known that dienes undergo [4+2] hetero-Diels-Alder (*hDA*) reaction with sulfur dioxide and form kinetic product sulfinate esters at lower temperature,^[62] whereas [4+1] cheletropic addition takes place to give thermodynamically favoured sulfolene derivatives at higher temperature (**Scheme 1.9**).^[63] At even higher temperatures, for example sulfolene at 120 °C, the cheletropic addition product decomposes to give back the diene and extrude sulfur dioxide gas. This property has been used as a method to protect corresponding dienes, which could be deprotected on heating then available for further reaction.^[64]



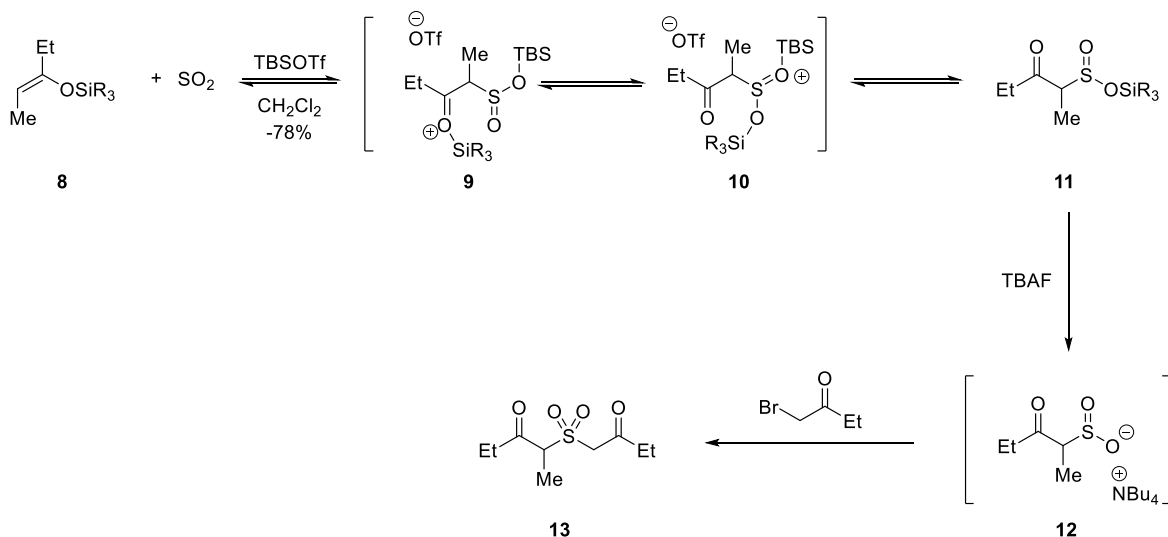
Scheme 1.9 Example of sulfur dioxide diene reaction

One recent advance in sulfur dioxide diene reaction was made by Vogel *et al.* with the development of a series of efficient transformations.^[56a] Specifically, they exploit Lewis acids to promote the sulfur dioxide *hDA* reaction that incorporates SO₂ insertion as well as new C-C bond formation. The procedures typically start with the hetero-Diels-Alder sulfur dioxide addition to a diene **1**, followed by the incorporation of a Lewis acid like TBSOTf. The resulting adduct **3** equilibrates with the zwitterionic intermediate **4**, which reacts with a silyl enol ether **5** thus realising a new C-C bond-forming reaction, giving a silyl sulfinate product **6**.^[65] Further desilylation and electrophilic substitution afford the sulfonyl-containing compound such as sulfones **7**^[66] (**Scheme 1.10**) or sulfonamides.^[67]



Scheme 1.10 Example of Lewis acid promoted sulfur dioxide insertion

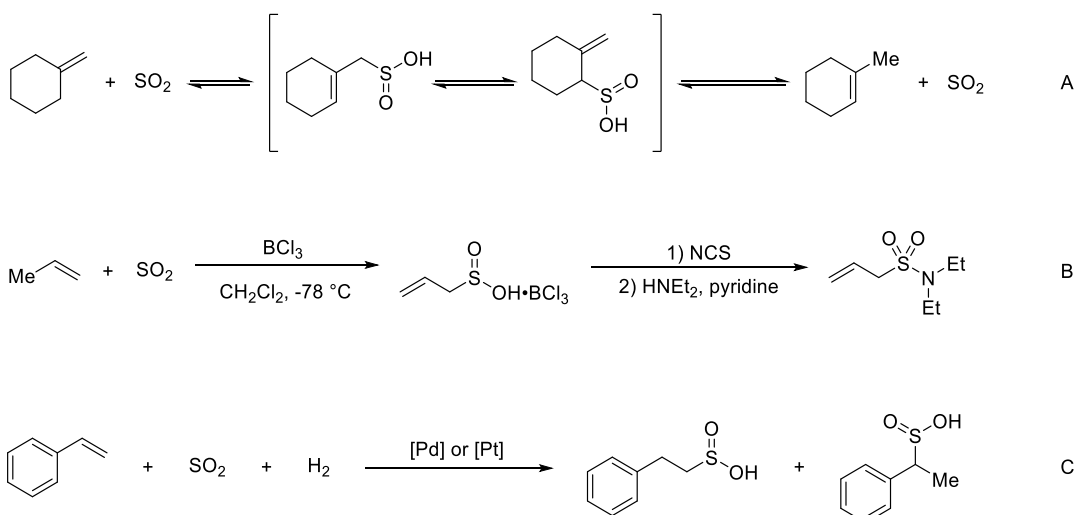
Another reaction Vogel and co-workers developed is the ene reaction between silyl enol ethers **8** and sulfur dioxide, also with a Lewis acid promoter (**Scheme 1.11**). Subsequent fluoride-induced desilylation of **11** and electrophile trapping results in formation of the corresponding sulfones **13**^[68] and sulfonamides with efficiency.^[69]



Scheme 1.11 Example of sulfur dioxide insertion with silyl enol ether

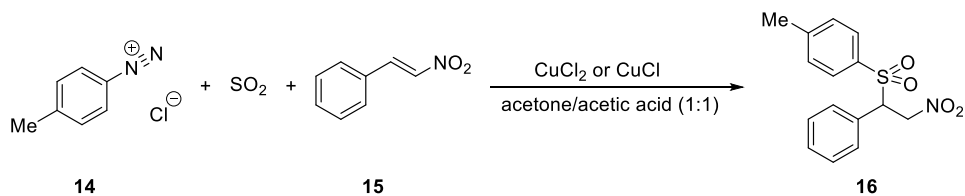
A similar sulfur dioxide Alder-ene reaction was previously reported, and presented as a sulfur dioxide mediated olefin isomerisation (**Scheme 1.12, equation A**).^[70] The reaction mechanism of the isomerisation is generally rationalised as an insertion of sulfur dioxide in alkenes followed by [1,3]-sigmatropic rearrangement then a retro-ene reaction to extrude sulfur dioxide. Although Vogel *et al.* have published evidence for possible involvement of a radical process *via* polysulfones. They reported that for some alkyl substituted alkenes like methylenecyclopentane, the isomerisations are inhibited by radical traps such as TEMPO and Bu₃SnH.^[56a] The polysulfones generated by 1:1 copolymerisation of SO₂ and alkenes are able to catalyse the isomerisation in the absence of sulfur dioxide and they showed typical signals for sulfonyl radicals in EPR spectroscopy.^[71]

Most recently, Vogel also published a novel sulfur dioxide-ene reaction promoted by BCl₃.^[72] The generally unstable β,γ -unsaturated sulfinic acids^[73] generated from simple alkenes and sulfur dioxide form a relatively stable complex with BCl₃ instead of proceeding to a retro-ene reaction. The sulfinic acid BCl₃ complex could be isolated and reacted with electrophiles to give sulfonyl-containing products such as sulfones or sulfonyl chlorides, which then give access to sulfonamides (**Equation B**). Transition metal catalysis, though not frequently used with sulfur dioxide in organic synthesis, has been described in an alkene hydrosulfination reaction.^[56b] Analogous to hydroformylation, alkenes are combined with sulfur dioxide gas and hydrogen gas under palladium or platinum catalysts to generate sulfinic acids as both regioisomers (**Equation C**).



Scheme 1.12 Examples of sulfur dioxide-ene reaction and metal-catalysed hydrosulfonylation reaction

Additionally, copper catalysts are used in sulfur dioxide reactions. A radical-based reaction of arenediazonium salts **14** and sulfur dioxide with α -nitroolefins **15** giving β -nitrosulfones **16** has been reported by Bilaya *et al.* (Scheme 1.13).^[74]



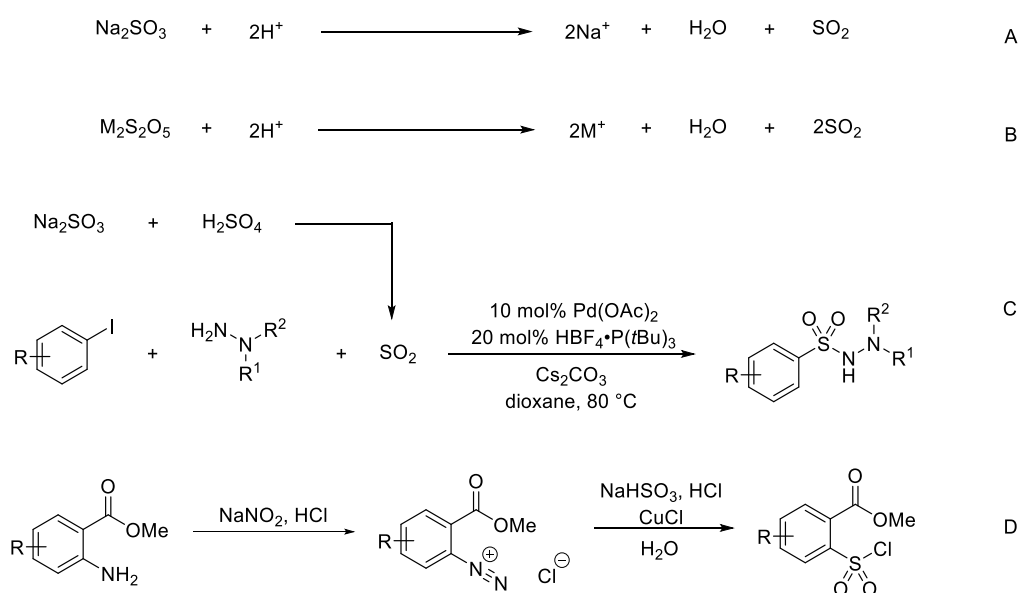
Scheme 1.13 Example of copper-catalysed reaction with sulfur dioxide, nitroolefin and diazonium salts

1.2.2. Sulfur dioxide surrogates

Despite the applications stated above, sulfur dioxide is otherwise rarely accepted as a reliable synthetic reagent, especially in transition metal catalysis. This is partially ascribed to the toxic and gaseous nature of sulfur dioxide which requires the use of pressurised gas cylinders and specialist glassware. To precisely measure or to control the quantity of sulfur dioxide in the reaction is also difficult. Therefore, it is usually used in large excess, which is not only environmentally hazardous, but more importantly, can also cause catalyst

sequestration in a transition metal catalysed reaction. Hence, the concept of a practical and easy-to-handle reagent that could deliver sulfur dioxide as a synthetic equivalent is highly attractive.

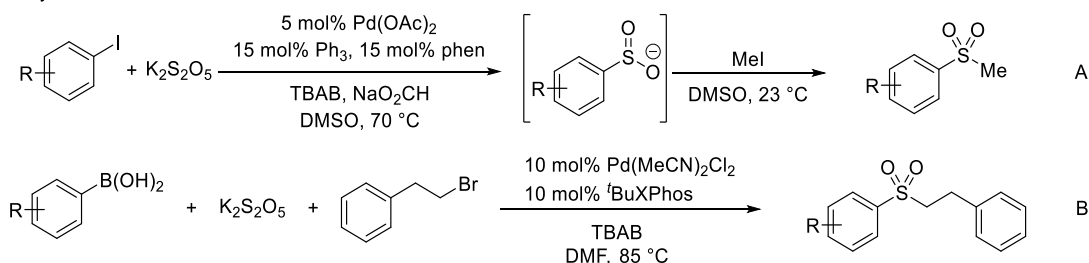
Sulfur dioxide surrogates are compounds or complexes that contain the SO₂ unit and are able to release sulfur dioxide gas or deliver the SO₂ moiety onto target molecules under appropriate conditions (**Scheme 1.12, equation A, B**). Examples of such surrogates are metal sulfites or metabisulfites which release sulfur dioxide under acidic conditions. Wu and co-workers demonstrated such an application, where sulfur dioxide was generated *ex situ* from sodium sulfite (Na₂SO₃) and concentrated sulfuric acid (H₂SO₄) in a separate chamber and then conducted into the other tube to complete the palladium-catalysed aminosulfonylation of aryl iodides (**Equation C**).^[75] Sodium bisulfite (NaHSO₃) is also used as a sulfur dioxide generator in flow chemistry for the synthesis of sulfonyl chlorides from diazonium salts (**Equation D**, also see **Scheme 1.7**).^[76] These synthetic strategies, although creative, still require a large excess of sulfur dioxide.



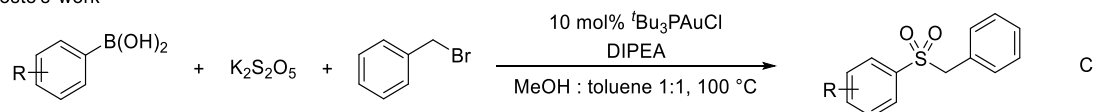
Scheme 1.14 Sulfur dioxide generation from metal sulfites and metabisulfites, and selected applications

Potassium metabisulfite ($\text{K}_2\text{S}_2\text{O}_5$) has also been used as a sulfur dioxide surrogate in transition metal catalysis (**Scheme 1.15**). Shavnya *et al.* have published two articles regarding a one-pot two-step sulfinate generation/derivatisation process^[77] and a one-step aryl alkyl sulfone synthesis,^[78] respectively (**Equation A, B**). Both reactions apply $\text{K}_2\text{S}_2\text{O}_5$ as sulfur dioxide surrogate in a palladium-catalysed reaction. Gold catalysts have been investigated by the Toste group, forming sulfones and sulfonamides from arylboronic acids and alkyl halides (**Equation C**).^[79] Wu at Fudan University has also reported a palladium-catalysed *N*-aminosulfonamide synthesis using $\text{K}_2\text{S}_2\text{O}_5$ to deliver the sulfonyl moiety (**Equation D**).^[80] Interestingly, none of these conditions are acidic, yet they are able to generate sulfur dioxide spontaneously.

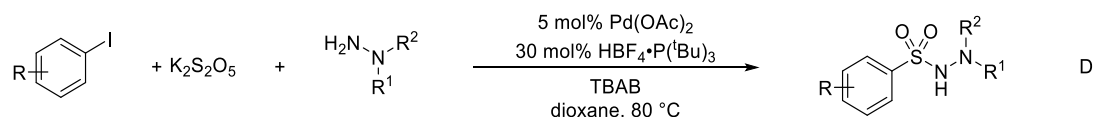
Shavnya's work



Toste's work

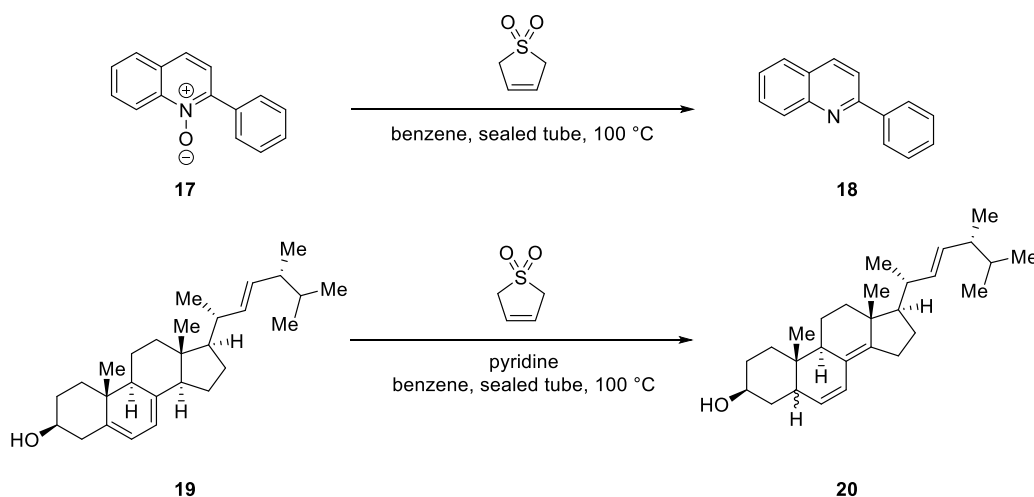


Wu's work



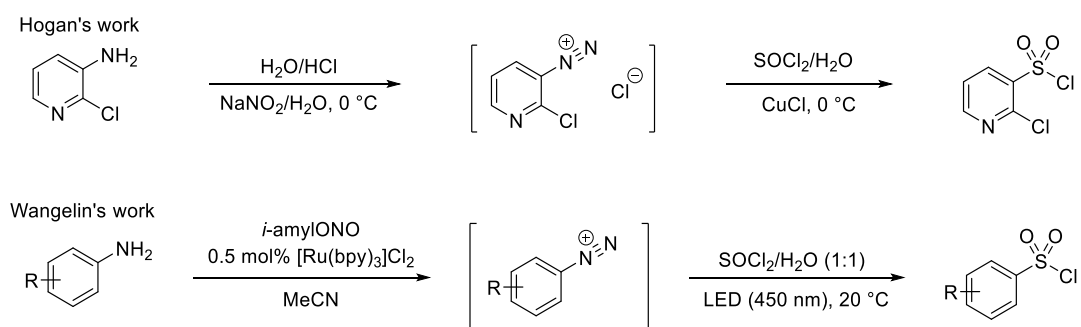
Scheme 1.15 Examples of $\text{K}_2\text{S}_2\text{O}_5$ as sulfur dioxide surrogate

The reversible sulfur dioxide-diene reaction described earlier (**Scheme 1.9**) has also been exploited as a means to release sulfur dioxide by Yamamoto and his team.^[81] They demonstrated that the sulfur dioxide released *in situ* upon heating could mediate the deoxygenation of aromatic *N*-oxides **17** as well as the isomerisation of double-bonds in steroids **19** (**Scheme 1.16**).



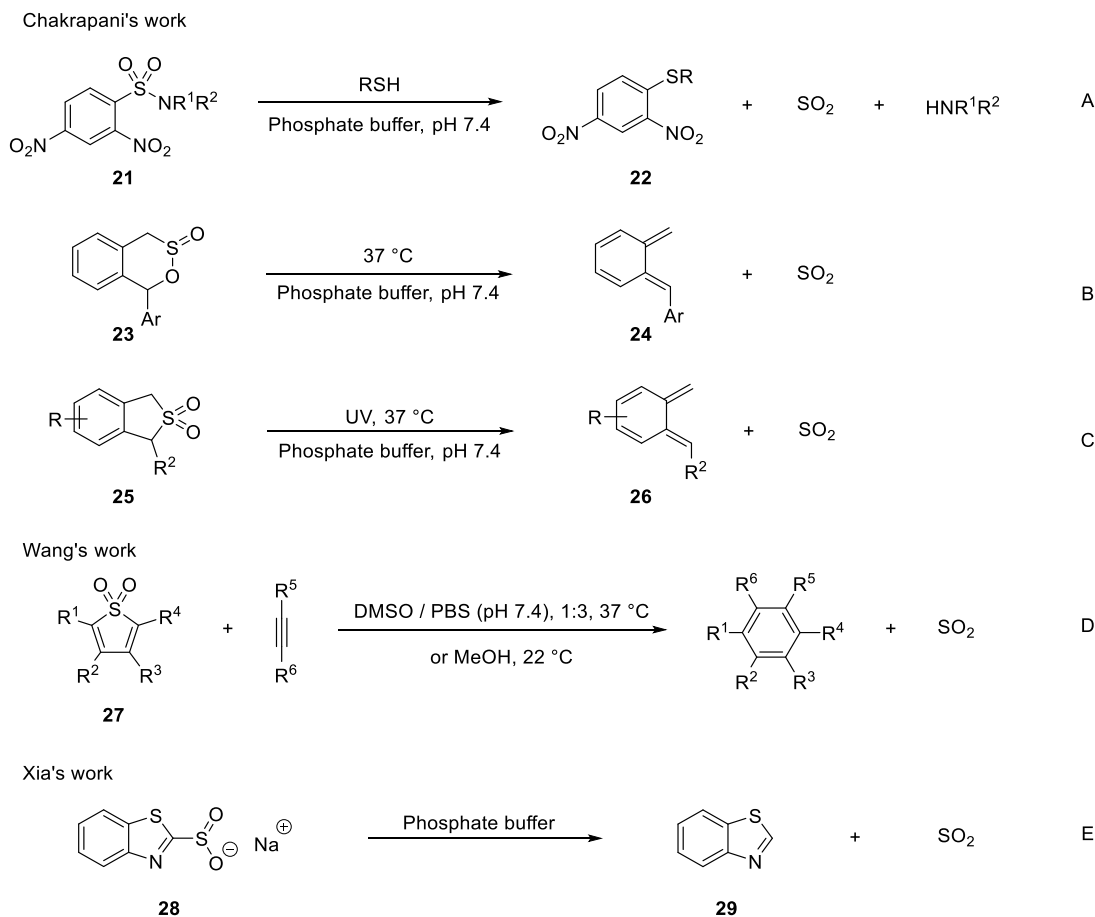
Scheme 1.16 Example of sulfolene as sulfur dioxide surrogate

Primarily used as a potent chlorination reagent,^[82] thionyl chloride reacts violently with water to give sulfur dioxide and HCl. Appearing in the works of both Hogan *et al.*^[83] and Majek *et al.*,^[84] this property has been employed to generate sulfur dioxide *in situ* as an improvement of the original diazonium salt Sandmeyer sulfonyl chloride synthesis (**Scheme 1.17**, also see **Scheme 1.7**).



Scheme 1.17 Examples of thionyl chloride as sulfur dioxide surrogate

Differing from other sulfur dioxide surrogates whose intentions are dominantly to deliver SO₂ into molecules in organic synthesis, a class of surrogates have also been developed as prodrugs to release sulfur dioxide in a controlled manner for antibacterial purpose (**Scheme 1.18**).^[85] Chakrapani and co-workers examined a series of 2,4-dinitrobenzenesulfonamides **21** which release sulfur dioxide upon activation *via* S_NAr reactions with thiols such as cysteine in pH 7.4 phosphate buffer. The processes are shown to be effective inhibiting *Mycobacterium tuberculosis* (Mtb)^[86] and methicillin-resistant *Staphylococcus aureus* (MRSA) (**Equation A**).^[87] Additionally, 1-phenyl-benzosultines **23**^[88] and benzosulfones **25**^[89] were also tested as sulfur dioxide donors (**Equation B, C**). Under mild heating or UV irradiation, these compounds undergo retro-hetero-Diels-Alder or retro-cheletropic reaction respectively to achieve slow extrusion of sulfur dioxide (also see **Scheme 1.9**). More types of SO₂ prodrugs have been reported recently; thiophene dioxide derivatives **27** reported by Wang *et al.* have also shown to extrude sulfur dioxide *via* click chemistry (**Equation D**)^[90] and sodium benzothiazole sulfinates **28** have been shown to slowly decompose in buffers of different pH according to Xian and his group (**Equation E**).^[91] A detailed discussion on the biological aspects of sulfur dioxide is not within the scope of this thesis but is available in recent reviews^[92] and the original articles referenced above.



Scheme 1.18 Examples of biological sulfur dioxide surrogates

Organic solvents sometimes serve as surrogates by pre-saturating the reaction solvents with sulfur dioxide.^[93] These type of surrogates behave similarly to directly introducing sulfur dioxide in the reaction thus is not discussed in this thesis.

Amines have been known to form 1:1 adduct with sulfur dioxide since the early twentieth century.^[94] Examples have explored a wide range of both aliphatic and aromatic amines including ammonia, primary, secondary and tertiary amines (**Figure 1.3**).^[95] For a long time, the major research focus of these sulfur dioxide-amine complexes was on the binding properties of the adducts, including the influence of solvents^[96] as well as spectroscopic analysis such as UV, IR, Raman, NMR spectroscopy and microwave analysis.^[97] These

studies have shown that the adducts are charge-transfer complexes formed between the lone-pair electron on the amine nitrogen atom and the empty LUMO orbital of sulfur in SO₂. The strength of this dative covalent bond and hence the stability of the complexes depends on the donor strength of the amine nitrogen, i.e. its Lewis basicity. For example, the trend of the thermodynamic stability of methylamines are: trimethylamine•SO₂ > dimethylamine•SO₂ > methylamine•SO₂ > ammonia•SO₂.

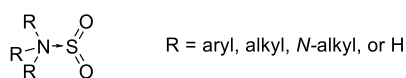
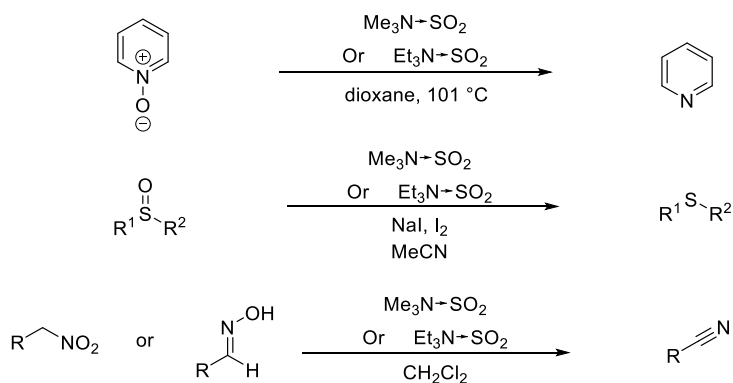


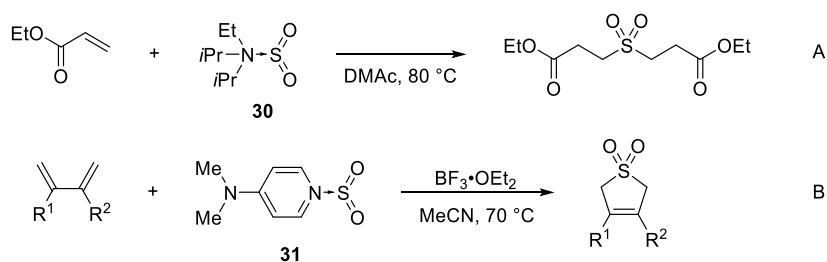
Figure 1.3 Sulfur dioxide-amine adduct

Despite many studies on their physical properties, sulfur dioxide-amine complexes have seldom been used in organic synthesis until recently. Some applications were reported in the 1970s, where Olah *et al.* showed that sulfur dioxide-trimethylamine or triethylamine adduct could perform a series of reductive reactions^[98] such as the deoxygenation of pyridine *N*-oxides^[99] and sulfoxides^[100] as well as the preparation of nitriles, from reduction of nitro compounds^[101] or the dehydration of aldoximes (**Scheme 1.19**).^[102] More recently they also published a report on the use of sulfur dioxide-poly(4-vinylpyridine) (PVP) complex as a solid phase mild acidic catalyst for a Strecker type α -aminonitrile synthesis.^[103] Several of these transformations are known to proceed with sulfur dioxide itself (**Scheme 1.16**), however the sulfur dioxide moiety is not incorporated into the products.



Scheme 1.19 Examples of the use of sulfur dioxide-amine adduct in synthesis

Early examples where SO_2 was incorporated into the target product using sulfur dioxide-amine surrogates were published by Eugene *et al.* They demonstrated that sulfur dioxide-diisopropylethylamine complex **30** reacts with Michael acceptors to perform hydrosulfonylation (**Scheme 1.20, equation A**).^[104] Recently, DMAP• SO_2 **31** was used to release sulfur dioxide *in situ* for the synthesis of protected dienes (**Equation B**).^[105] These applications are again known to proceed with sulfur dioxide gas (see **Scheme 1.12** and **Scheme 1.9**).



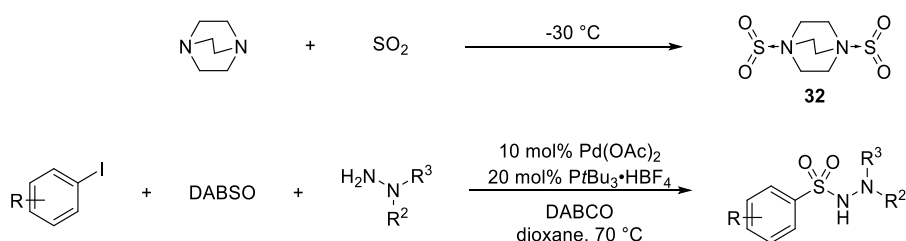
Scheme 1.20 Examples of sulfur dioxide-amine complexes in organic chemistry

1.2.3. 1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide), DABSO, and its application in transition metal catalysis

1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide), DABSO **32**, was prepared and documented by Santos and Mello in 1988.^[106] However, only its Raman spectroscopic

property was investigated before the Willis group first applied DABSO in organic synthesis as a sulfur dioxide surrogate in 2010 (**Scheme 1.21**).^[107] The bis(sulfur dioxide) adduct can be easily prepared without purification by refluxing sulfur dioxide with neat DABCO followed by evaporating the excess sulfur dioxide. It is also prepared from Karl-Fischer reagent in dry THF and purified *via* diethyl ether trituration.^[108] Very recently, a controlled method to generate sulfur dioxide from Na₂SO₃ and H₂SO₄ was also used to synthesis DABSO in a two-chamber system.^[109]

DABSO is an easy-to-handle white solid with much higher stability compared to that of trimethylamine SO₂ complex. It can be safely weighed in the open-air and has a decomposition temperature as high as 200 °C. More importantly, DABSO adduct has over 50 wt% of SO₂ and contains two sulfur dioxide unit per DABSO complex, hence is able to deliver more sulfur dioxide with minimum amine waste.



Scheme 1.21 DABSO and its first application in organic synthesis

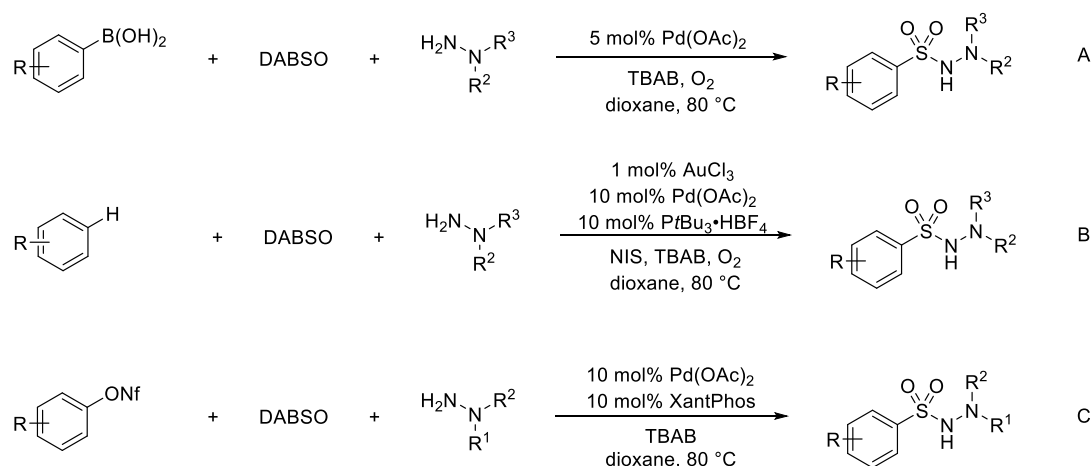
The innovative applications of DABSO in organometallic reagents have been emphasised by several articles published by the Willis group^[110] and others (**Scheme 1.22**). Organometallic reagents like organolithium reagents,^[111] Grignard reagents^[112] and zinc reagents^[113] react with DABSO to form the corresponding metal sulfinates. These versatile intermediates can be transformed *in situ* to various compounds such as sulfoxides, sulfones

or sulfonamides. In some cases, the second step sulfinate derivatisation involves palladium catalysis^[114] or the use of reagents like bleach or trimethylsilyl chloride.^[115]



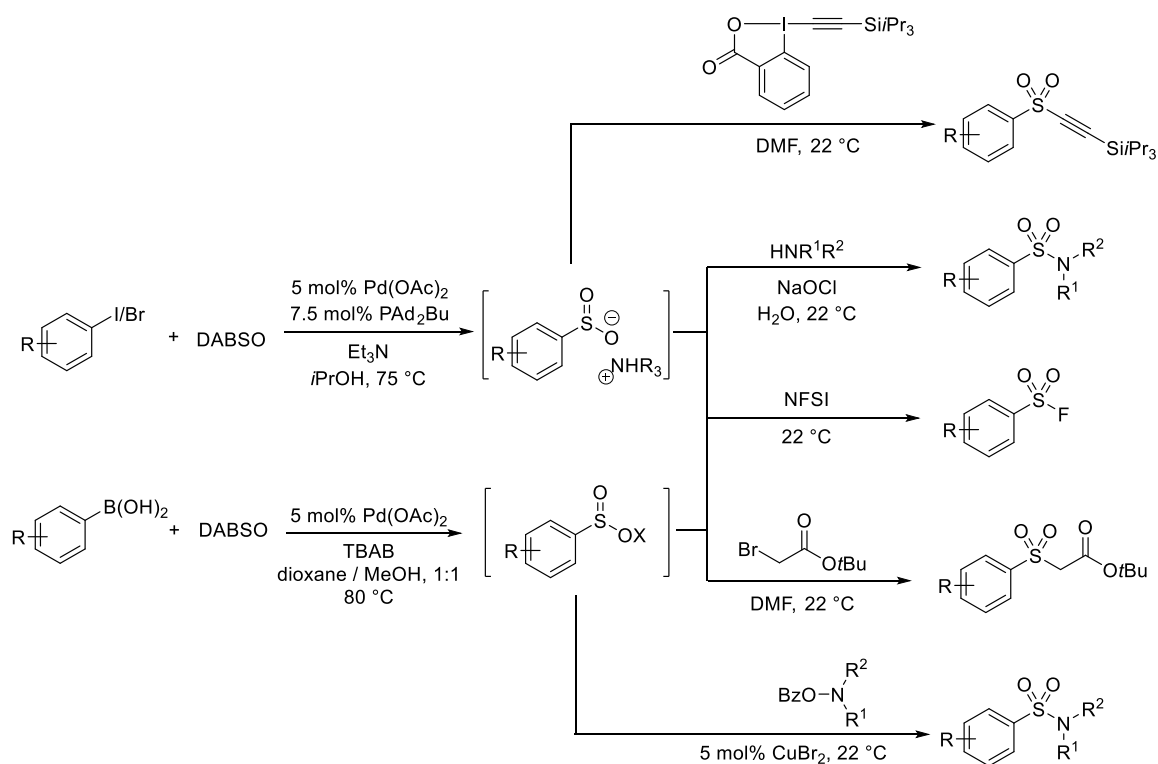
Scheme 1.22 General example of DABSO reaction with organometallic reagents

The incorporation of DABSO enables the addition of measurable equivalents of sulfur dioxide to the reaction mixture, which minimises the potential catalyst poisoning therefore improving the compatibility of sulfur dioxide with transition metal catalysis. Based on its first application in the palladium-catalysed one-step aminosulfonylation of aryl halides shown above, more pathways involving DABSO and palladium catalysts have been developed by us and others (**Scheme 1.23**).^[116] Ye *et al.* from Fudan demonstrated that, under oxidative conditions, aryl boronic acids could be applied as reaction partner in place of aryl halides in the palladium-catalysed aminosulfonylation reaction (**Equation A**).^[117] They also described that the aryl halides could be generated *in situ* using a gold-catalysed iodination with NIS (**Equation B**).^[118] More recently, aryl nonaflates have been reported by Wu to be compatible with the palladium-catalysed one-step aminosulfonylation (**Equation C**).^[119] Moreover, these reaction have shown to be tolerant of alkenyl halides and heteroaromatic halides. However, the other coupling partner is restricted to hydrazines, as other nucleophiles like amines are not reactive under these systems.



Scheme 1.23 Examples of DABSO-based one-step aminosulfonylation

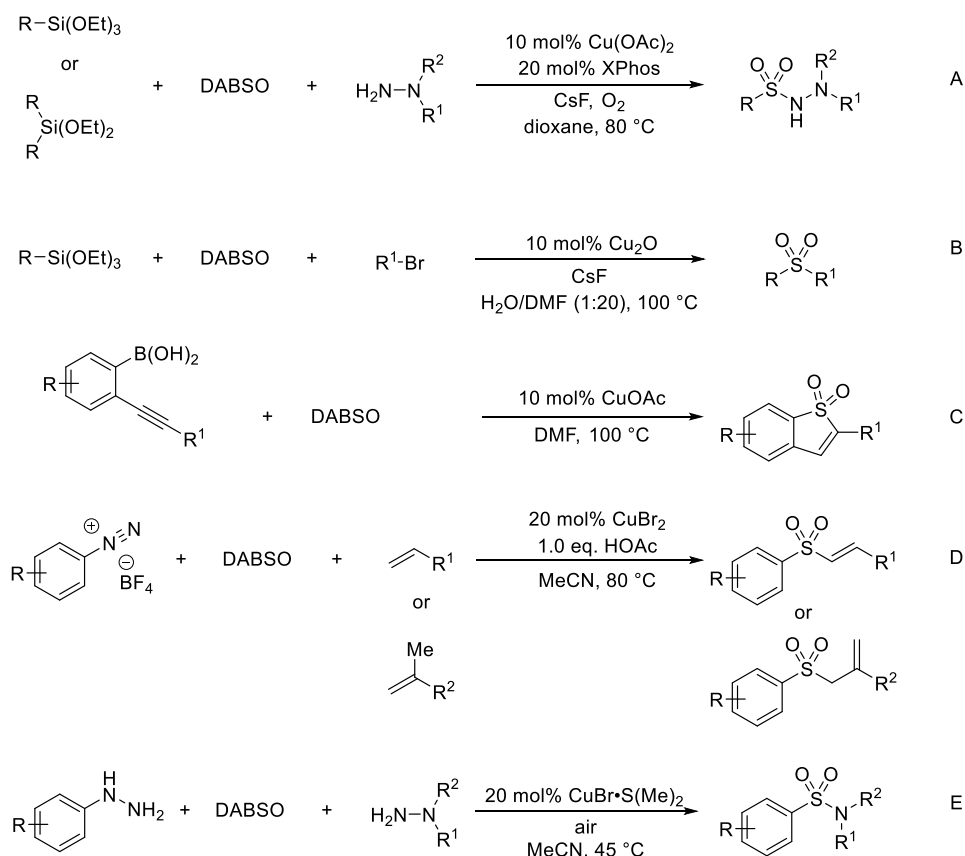
To deal with this shortcoming, one-pot two-step ammonium sulfinate generation and derivatisation procedure of aryl halides has been established by the Willis group.^[120] It requires lower catalyst/ligand loading with CataCXiumA as the ligand and introduces isopropanol as both solvent and reductant. The *in situ* generated sulfinates can be combined with electrophiles like epoxides, activated alkyl bromides, alkynyl iodonium salts^[121] and NFSI^[122] to give sulfonyl-containing derivatives. Synthesis of sulfonamides has been achieved with the addition of the oxidant, bleach (NaOCl), in conjunction with the reactant amines.^[123] Two-step sulfination and derivatisation of aryl boronic acids are exploited as starting material variant first by our group with a different catalytic system,^[124] which is redox neutral and ligand-free. Extension of this reaction has been described recently by Zhu *et al.* who applied a copper-catalysed amination reaction between *O*-benzoyl hydroxylamines and the *in situ* generated sulfinates.^[125]



Scheme 1.24 Palladium catalysed sulfonation and derivatisation using DABSO as SO₂ surrogate

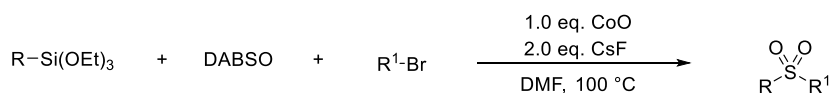
As an attractive alternative to palladium, copper catalysts generally have much lower cost. During the course of this DPhil., copper catalysis has been investigated in DABSO chemistry (**Scheme 1.25**). Both copper(I) and copper(II) catalysts have been reported catalysing reactions of aryl triethoxysilanes and DABSO with hydrazines^[126] and alkyl bromides,^[127] respectively to give the corresponding sulfones and aminosulfonamides (**Equation A, B**). A copper(I)-catalysed sulfonation and then intramolecular cyclisation of (2-alkynylaryl) boronic acids to generate benzo[*b*]thiophene 1,1-dioxides (**Equation C**) has been published by Wu and coworkers.^[128] The same group later reported a three-component reaction of aryldiazonium salts, DABSO and alkenes which produces arylvinylsulfones *via* radical-based copper(II) catalysis (**Equation D**).^[129] Most recently, hydrazines have also been used in a copper(I)-catalysed aerobic oxidative three-component

coupling reaction with DABSO and amines to form sulfonamides, potentially *via* a similar radical mechanism (**Equation E**).^[130] Although diverse and creative, these reactions require starting materials that are only commercially available with limited variations. A copper-catalysed system with readily available and versatile reagents is highly sought.



Scheme 1.25 Examples of copper-catalysed DABSO-based synthesis of sulfonyl-containing compounds

Cobalt oxide, although used in stoichiometric amount, is another transition metal catalyst which has been used to promote sulfur dioxide insertion, demonstrated by delivering alkylsulfones from triethoxysilanes, DABSO and alkylbromides with CsF as fluoride source (**Scheme 1.26**).^[131]



Scheme 1.26 Cobalt oxide promoted sulfur dioxide insertion of triethoxysilanes

Mostly recently, a novel application of DABSO was discovered by Yuan *et al.*, who used DABSO as an activator in palladium-catalysed carbon annulation of *ortho*-vinylanilines with DMSO to access 4-aryl quinolines (**Scheme 1.27**).^[132]



Scheme 1.27 DABSO used as a reaction activator

For a more detailed introduction to DABSO-based sulfone synthesis as well as some more recent works on metal-free DABSO reactions, see chapter 2. For sulfonamide synthesis, see chapter 3.

1.3. Project aims

Decorated by numerous awards, transition metal-catalysed cross-coupling reactions are some of the most important chemical reactions in modern day organic chemistry, and Suzuki-Miyaura and Chan-Lam coupling in particular have been well-investigated in the past few decades.^[133] Cross-coupling reaction using organoborane, carbon monoxide and aryl iodide was reported in 1986 by Kojima and his team.^[134] Later, carbonylative Suzuki-Miyaura coupling from boronic acids was reported by Suzuki and co-workers preliminarily in 1993^[135] and extended in 1998.^[136] Over the years, transition metal catalysis, including copper-catalysed carbonylative Suzuki reactions involving carbon monoxide have been developed into a powerful tool for synthesising ketones.^[137] Motivated by the recent success of DABSO-based transition-metal catalysed reactions, we set out to research the possibilities of a transition metal-catalysed sulfonylative Suzuki coupling reaction with

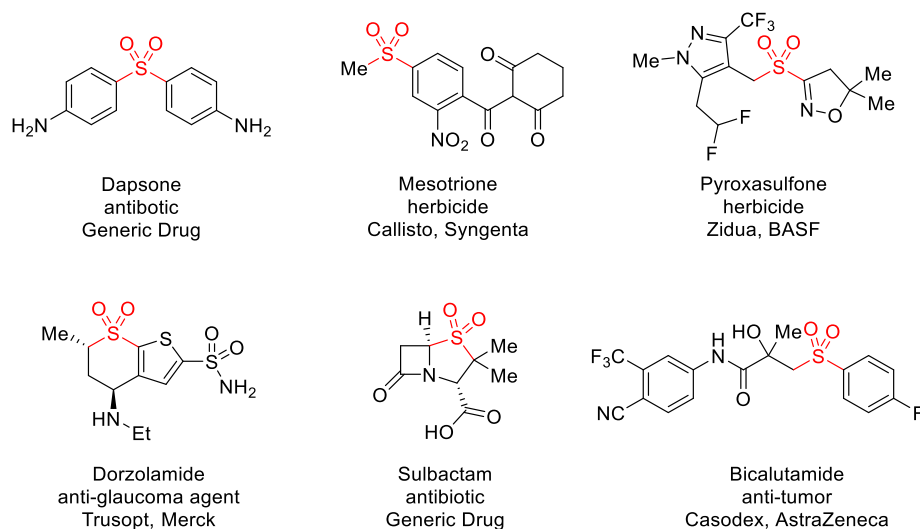
DABSO and the potential of a Chan-Lam type synthesis of sulfonyl-containing compounds.

In addition, high value synthetic targets such as sulfones and sulfonamides are no doubt within our research vision.

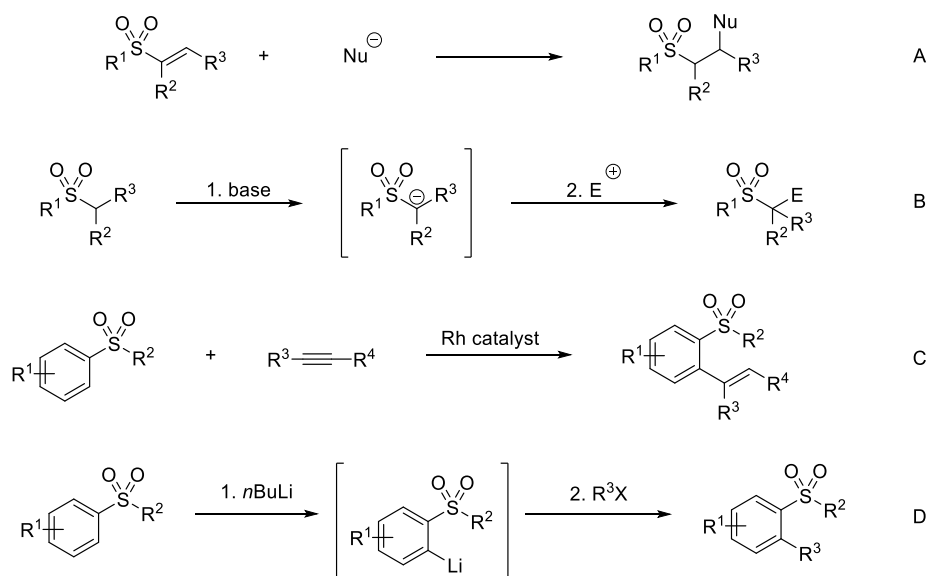
Chapter 2: Copper(I)-catalysed sulfonylative Suzuki-Miyaura reaction

2.1. Sulfones and their applications

Sulfones are a family of chemical compound containing a sulfonyl group linked to two carbons, both with σ bonds. Being one of the most common sulfonyl-containing compounds, sulfones have applications widely spread in every field of chemistry, biology, pharmacy and beyond,^[17, 138] from sulfolane in oil refining^[139] to aromatic poly(arylene ether sulfone) in polymer engineering.^[5] As with sulfonamides, one of the most prominent properties of sulfones is their biological activity. During more than a century of research and development on their antibacterial,^[140] antifungal^[141] and antitumor^[142] activities, various sulfones are already registered as herbicides,^[143] antibiotics,^[144] anti-glaucoma agents,^[145] and antiandrogen medicines (**Figure 2.1**)^[146] for the treatment of conditions such as leprosy, *Pneumocystis carinii* pneumonia and prostate cancer. In addition, diaryl sulfones were examined as a potential anti-HIV treatment, due to their good inhibitory potencies against HIV-1 integrase.^[147] More recently, medicinal studies revealed that diaryl sulfones could also act as a non-acetylenic metabotropic glutamate receptor 5 (mGluR5) negative allosteric modulator (NAM) for psychiatric indications.^[148]



Apart from their significance in medicinal chemistry, sulfones have also proven their worth in synthetic chemistry (**Scheme 2.1**).^[149] The high electron-withdrawing ability of the sulfonyl moiety makes vinyl sulfones excellent Michael acceptors (**Equation A**).^[150] Similarly, work from the Trost group has shown that sulfones can also acidify the α -protons (**Equation B**).^[151] Very recently, work by Nobushige *et al.* in 2015 showed the first example of the sulfonyl group acting as a directing group in rhodium-catalysed direct *ortho*-alkenylation (**Equation C**).^[152] Prior to that, the sulfonyl moiety was also employed as a directing group through a completely different approach, namely *via ortho*-lithiation and subsequent substitution with electrophiles such as methyl iodide (**Equation D**).^[153]



Scheme 2.1 Generic examples of chemical applications of sulfones

As demonstrated above, sulfones have important applications across the chemical sciences.

Efficient and versatile synthetic strategies to prepare sulfones are therefore highly desirable.

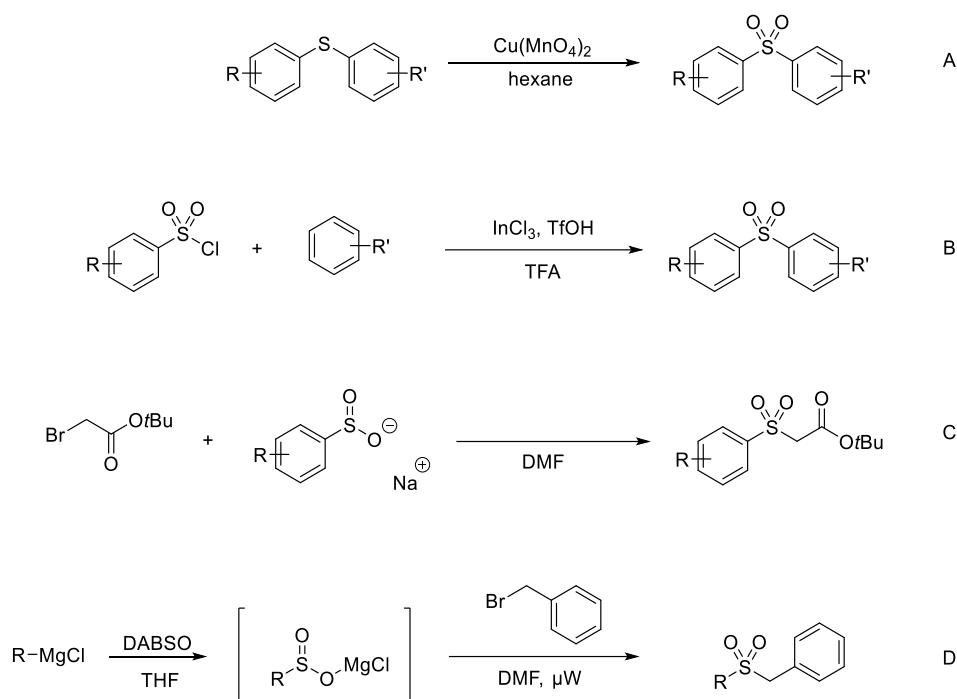
2.2. Preparation of sulfones

Means to access sulfones have long been investigated (**Scheme 2.2**). One common strategy is oxidation from the corresponding sulfides.^[154] Low commercial availability of sulfides requires one or more synthetic steps beforehand, which often involve the use of malodorous thiols. These multistep sequences lower the efficiency of this strategy and the oxidative conditions required (for example H_2O_2 , *m*CPBA or $t\text{BuCOOH}$), diminish the functional group tolerance (**Equation A**).

As described in the last chapter in **Section 1.1.2**, sulfinic acid derivatives can also act as sulfone precursors. Sulfonyl halides^[32a, 155] and sodium sulfinates^[37b, 156] are two commonly employed reagents in metal catalysed or non-catalytic sulfone synthesis (**Equation B, C**).

These methods largely avoid strong oxidative conditions, but few of these precursors are readily available and the halogenation conditions to prepare sulfonyl halides are highly oxidative, therefore restricting their scope. Other derivatives such as sulfonic esters^[157] or sulfonylmethyl isocyanides^[158] may also be used, but again they suffer from poor availability of starting materials.

Over the past decade, the Willis group and others have made great advances in synthesising sulfonyl containing compounds. The development and application of sulfur dioxide surrogates such as DABSO and $K_2S_2O_5$ has enabled the transformation of easily accessible reagents like organozinc reagents,^[113] organolithium reagents^[114] or Grignard reagents^[110b] to metal or ammonium sulfinates. The incorporation of palladium or copper catalysts also allowed the use of more versatile, bench-stable and widely available boronic acids^[79, 124] and aryl halides as substrates.^[77] These sulfinate salts could be transformed into sulfones with electrophilic trapping reagents, such as hypervalent iodonium salts and alkyl halides in a one-pot two-step process, allowing access to an expanded range of sulfones (**Equation D**).



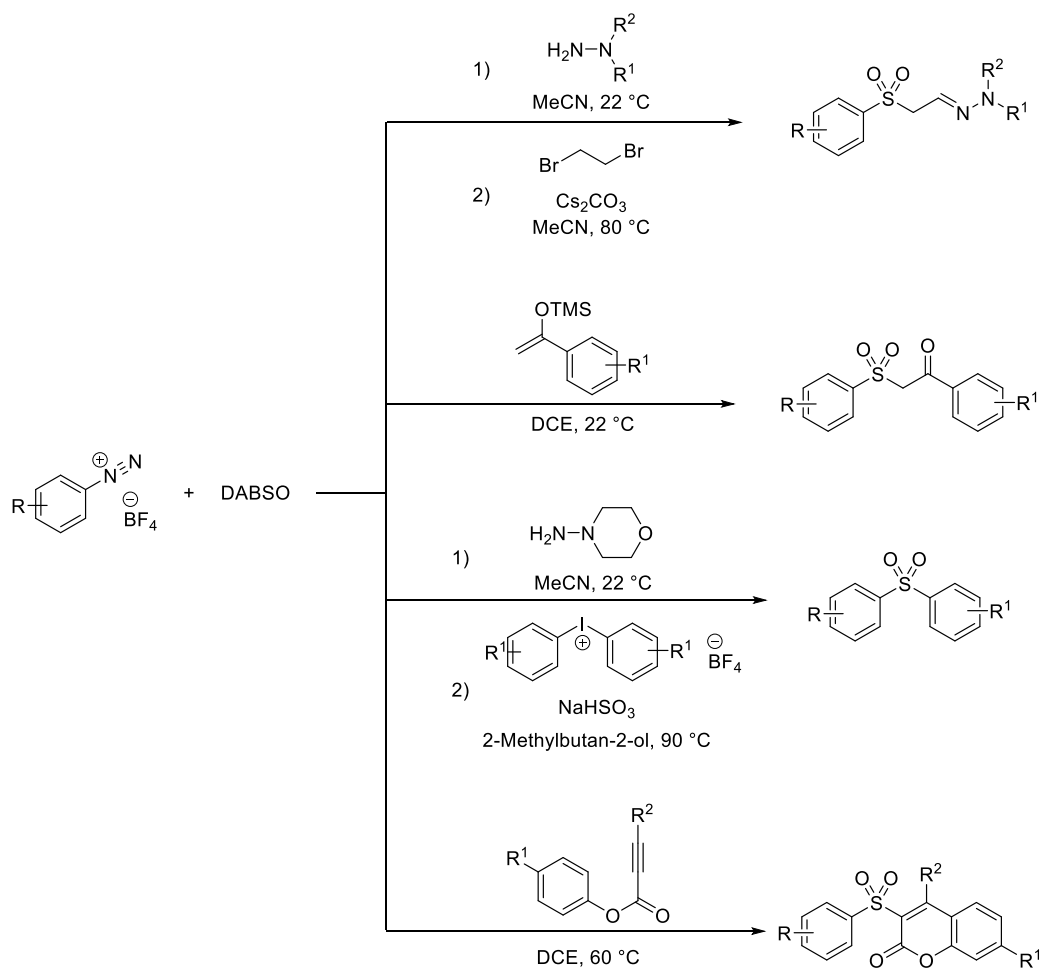
Scheme 2.2 Examples of recent methods for sulfone synthesis

Despite these breakthroughs, sulfonates remain a key intermediate, which has to be produced and stabilised in an independent step in most cases. Prior to this project, to the best of our knowledge, the only three examples of the one-step synthesis of aryl alkyl sulfones from these versatile materials, such as aryl halides and aryl boronic acids, were published by the Toste group in 2014,^[79] Pfizer in 2015^[78] and our group in 2016^[124] where alkyl bromides were used alongside aryl boronic acids as reaction partner with palladium or gold catalysts (see **Scheme 1.15**). Therefore, a more efficient one-step approach towards other sulfones such as diaryl sulfones was desired.

2.3. Recent advances using ‘SO₂’ surrogate in sulfone synthesis

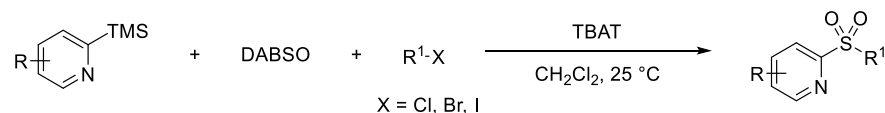
After the initiation of our copper(I)-catalysed sulfonylative Suzuki coupling project, several other reports of one-step sulfone syntheses were published by Wu’s group from

Fudan University (see **Scheme 1.25**).^[127-128, 131] Radical-based metal-free synthesis of 2-arylsulfonyl hydrazones,^[159] β -keto sulfones,^[160] diaryl sulfones^[161] and 3-sulfonated coumarins^[162] were published, although all start from sulfinations of aryldiazonium tetrafluoroborate salts, which have very limited commercial availability (**Scheme 2.3**).



Scheme 2.3 Examples of recent DABSO-based metal-free sulfone synthesis

By the time this thesis was written, Cantat and co-workers also reported a metal free aryl alkyl sulfone synthesis from arylsilanes, DABSO and alkyl halides.^[163] However, the arylsilane scope presented was limited to 2-(trimethylsilyl)pyridine derivatives (**Scheme 2.4**).

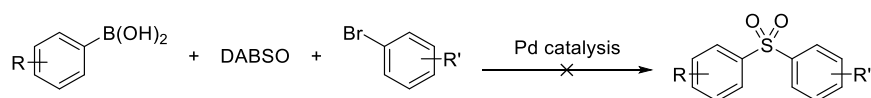


Scheme 2.4 Example of sulfone synthesis from organosilanes, DABSO and aryl/alkyl halides

Despite these discoveries, accessibility of diaryl sulfones remained poor. A straightforward sulfonylative aryl-aryl cross-coupling would be much desired.

2.4. Project aim and initial investigation

Although carbonylative Suzuki couplings are well-precedented, the analogous sulfonylative variant has not been reported. Nevertheless, the one-step reaction of SO₂, boronic acid and aryl halides would represent a significant advance in the preparation of sulfones. We were eager to achieve the sulfonylative version where aryl halides instead of more reactive electrophiles were coupled with boronic acids and involved in the catalytic process. Motivated by the success of synthesising sulfinates from boronic acids and palladium(II) catalysts, attempts within the group were made to combine aryl boronic acids and aryl bromides under similar conditions. Unfortunately, no desired product was obtained (**Scheme 2.5**). Large amounts of biaryl side products were formed, probably from direct Suzuki coupling. Alternative approaches were therefore required.



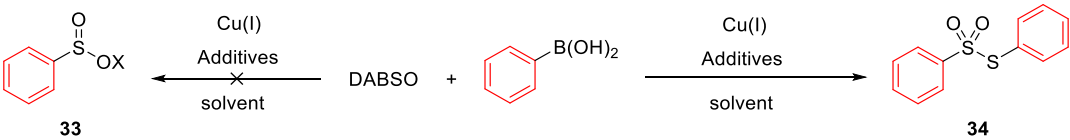
Scheme 2.5 Attempts on sulfonylative Suzuki coupling using palladium catalyst

The replacement of palladium catalysts with copper was desirable due to their lower costs.

Furthermore, copper catalysis has frequently been reported in cross-coupling^[164] and carbonylation reactions.^[165] It is also known that copper, as with palladium, is able to catalyse coupling reaction between sulfinates and aryl halides.^[126, 156a, 166] Hence, copper salts were selected as our catalyst of choice.

2.5. Reaction optimisation

Firstly, to ensure the validity of copper as a sulfination catalyst with aryl boronic acids, several experiments were conducted using phenylboronic acid and DABSO (**Table 2.1**), with a small library of copper catalysts (**entries 2, 7 – 11**) and solvents (**entries 2 – 5**). High catalyst loadings were applied at this stage. The initial target was to look for existence of the sulfination product of phenylboronic acid, phenylsulfinate **33**, in the reaction mixture. Although the starting boronic acid was fully consumed at higher temperatures in DMF (**entry 8**), only traces of the sulfinate was observed by mass spectroscopy, while no obvious signal was detected by HPLC. Isolation and characterisation, however, confirmed the resulting product being *S*-phenyl benzenesulfonothioate **34**, a signature product from disproportionation^[167] of phenylsulfinate. Moreover, both copper(I) and copper(II) catalysts proved competent for the reaction and pleasingly, an inert atmosphere was not essential.

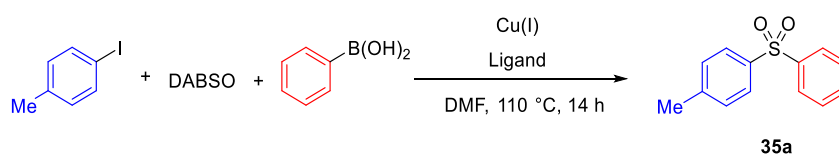
				
Entry ^a	Cu catalyst (50 mol%)	Solvent	Temperature (°C)	Conversion of boronic acid ^b (%)
1	CuOAc	DMF	60	11
2	CuOAc	DMF	100	76
3	CuOAc	dioxane	100	0
4	CuOAc	toluene	110	4
5	CuOAc	CH ₂ Cl ₂	40	0
6	-	DMF	110	4
7	Cu(TC) ^c	DMF	110	18
8	CuBr	DMF	110	94
9	Cu ₂ O	DMF	110	96
10 ^d	Cu ₂ O	DMF	110	94
11	Cu(OAc) ₂	DMF	110	59
12	Cu(OAc) ₂	DMF	130	96

^a Reaction conditions: DABSO (0.3 mmol, 1.5 equiv.), phenylboronic acid (0.2 mmol, 1.0 equiv.), solvent (1 mL).
^b Boronic acid conversion deduced from HPLC with acetophenone as an internal standard. ^c Copper(I) thiophene-2-carboxylate. ^d Reaction conducted under air atmosphere.

Table 2.1 Initial attempts for the copper-catalysed boronic acid sulfonation reaction.

Encouraged by this initial success, we then went on to pursue the one-pot synthesis of sulfones **35** with aryl iodides. Unlike the sulfonation reactions above however, different copper catalysts now exhibited different behaviour towards the reaction (**Table 2.2**). Many copper catalysts, especially copper(II) catalysts, led to only traces of sulfone product with the addition of iodobenzene (**entries 1 – 13**), while the sulfinates still underwent disproportionation. Air was no longer compatible with the reaction; thus, a nitrogen atmosphere was needed. A NHC-copper(I) complex, Cu(IPr),^[168] was inactive in this reaction (**entries 12 and 13**). The use of Cu(TC), (CuOTf)₂•PhH and Cu(MeCN)₄BF₄ gave yields of 20% (**entries 14, 17 and 20**). Further improvement came when 1,10-phenanthroline was used as a ligand, either combined with copper as a pre-formed catalyst

(entry 19) or added separately (entries 18 and 21). This kind of ligand effect was also observed with several different copper catalysts, among which Cu(MeCN)₄BF₄ was considered the best catalyst choice for further optimisation due to its lower cost and higher stability.



Entry ^a	Cu catalyst (mol%)	Ligand (mol%)	HPLC Yield of 35a (%) ^b
1	CuBr (40%)	-	11
2	Cu(OAc) ₂ (40%)	-	13
3	CuI (40%)	-	4
4	CuI (40%)	1,10-phenanthroline (40%)	6
5	CuOAc (40%)	-	13
6	Cu ₂ O (40%)	-	25
7	Cu ₂ O (10%)	1,10-phenanthroline (20%)	27
8	CuSCN (20%)	-	5
9	CuSCN (20%)	1,10-phenanthroline (20%)	3
10	CuFe ₂ O ₄ (10%)	-	7
11	CuFe ₂ O ₄ (10%)	1,10-phenanthroline (10%)	7
12	Cu(IPr) ^c (10%)	-	Trace
13	Cu(IPr) ^c (10%)	1,10-phenanthroline (20%)	Trace
14	Cu(TC) ^d (10%)	-	19
15	Cu(TC) ^d (10%)	1,10-phenanthroline (20%)	13
16	CuMeSal ^e (10%)	1,10-phenanthroline (20%)	9
17	(CuOTf) ₂ •PhH (10%)	-	26
18	(CuOTf) ₂ •PhH (10%)	1,10-phenanthroline (20%)	42
19	CuCF ₃ Phen (10%)	-	37
20	Cu(MeCN)₄BF₄ (10%)	-	23
21	Cu(MeCN)₄BF₄ (10%)	1,10-phenanthroline (10%)	32

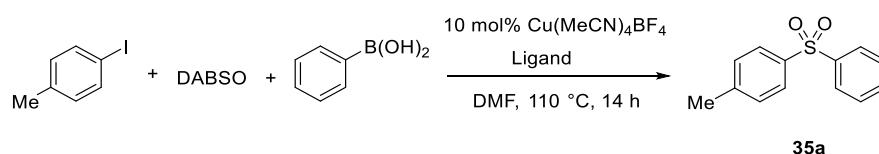
^a Reaction conditions: iodobenzene (0.2 mmol, 1.0 equiv.), DABSO (0.3 mmol, 1.5 equiv.), phenylboronic acid (0.6 mmol, 3.0 equiv.), DMF (1 mL), 110 °C, N₂, 14 h. ^b HPLC yield deduced using acetophenone as an internal standard.

^c Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]copper(I). ^d Copper(I) thiophene-2-carboxylate. ^e Copper(I) 3-methylsalicylate

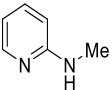
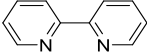
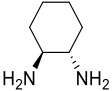
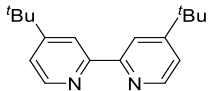
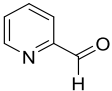
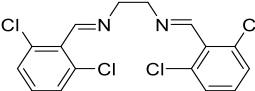
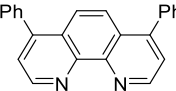
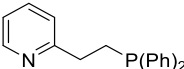
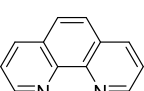
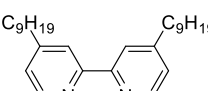
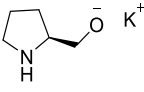
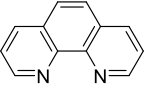
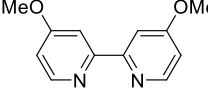
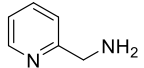
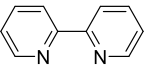
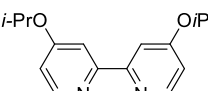
Table 2.2 Catalyst screening for the copper-catalysed sulfonylative Suzuki-Miyaura reaction.

Following the discovery on this ligand effect, the screening of different ligands was

conducted (**Table 2.3**). Disappointingly, neither the monodentate (**entries 1 – 3**) nor tridentate (**entries 4 – 6**) ligands gave any improvement compared to the original 1,10-phenanthroline. Oxygen- or phosphorus-based bidentate ligands were incompatible (**entries 7 – 13**), and primary or secondary amines also proved ineffective (**entries 14 – 17**). Instead, electron-donating group modified phenanthroline, and the structurally similar bipyridine ligands raised the yield to above 40%, among which 4,4'-dimethoxy-2,2'-bipyridine gave the best yield of 49% (**entries 23 – 27**). A similar observation was reported by Buchwald and his group in 2007 where electron-enriched nitrogen-based ligands improved the efficiency of the copper(I)-catalysed N-arylation of imidazoles and benzimidazoles.^[169] It is also interesting to note that a 1:1 molar ratio of ligand to catalyst gave a better yield than a 2:1 ligand to catalyst ratio (**entries 19 and 20, 21 and 22**).



Entry	Ligand	Entry	Ligand	Entry	Ligand
1		4		7	
	22% (20 mol%)		4% (20 mol%)		28% (20 mol%)
2		5		8	
	22% (20 mol%)		No Reaction (20 mol%)		20% (20 mol%)
3		6		9	
	24% (20 mol%)		22% (20 mol%)		16% (20 mol%)

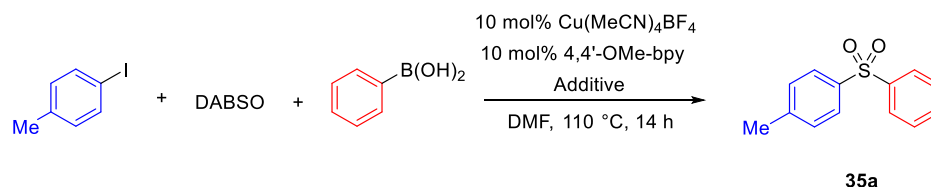
10		16		22	
	15% (20 mol%)		18% (10 mol%)		38% (10 mol%)
11		17		23	
	18% (10 mol%)		13% (20 mol%)		44% (10 mol%)
12		18		24	
	37% (10 mol%)		0% (10 mol%)		44% (10 mol%)
13		19		25	
	5% (20 mol%)		32% (20 mol%)		40% (10 mol%)
14		20		26	
	13% (20 mol%)		38% (10 mol%)		49% (10 mol%)
15		21		27	
	3% (10 mol%)		33% (20 mol%)		48% (10 mol%)

Reaction conditions: iodobenzene (0.2 mmol, 1.0 equiv.), DABSO (0.3 mmol, 1.5 equiv.), phenylboronic acid (0.6 mmol, 3.0 equiv.), Cu(MeCN)₄BF₄ (0.02 mmol, 10 mol%), DMF (1 mL), 110 °C, N₂, 14 h. HPLC yield deduced using acetophenone as an internal standard.

Table 2.3 Ligand screening for the copper-catalysed sulfonylative Suzuki-Miyaura reaction.

Other additives were also explored (**Table 2.4**). Addition of the phase transfer catalyst TBAB or the oxidant, Ag₂CO₃, lowered the yield to 18% and 27%, respectively (**entries 2 and 3**). No improvement in yields was observed with a series of base additives. Neither weak bases such as CsF or KOAc, nor strong bases like KOH, had any positive impact on

the reaction outcome (**entries 4 – 8**). The use of alcohol additives had no influence on yields (**entries 9 and 10**), despite the literature precedence that this could suppress the disproportionation of sulfinic acids.^[56b]

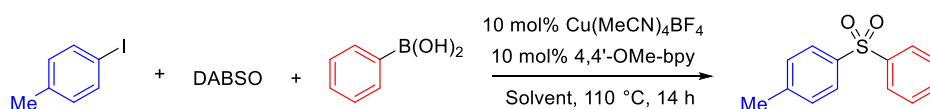


Entry ^a	Additives (equiv.)	HPLC Yield of 35a (%)
1	-	49%
2	TBAB (1.0)	18%
3	Ag ₂ CO ₃ (0.1)	27%
4	CsF (1.0)	13%
5	KOAc (1.0)	35%
6	K ₂ CO ₃ (1.0)	33%
7	K ₃ PO ₄ (2.0)	33%
8	KOH (1.0)	16%
9	MeOH (5.0)	44%
10	^t BuOH (5.0)	48%

Reaction conditions: iodobenzene (0.2 mmol, 1.0 equiv.), DABSO (0.3 mmol, 1.5 equiv.), phenylboronic acid (0.6 mmol, 3.0 equiv.), Cu(MeCN)₄BF₄ (0.02 mmol, 10 mol%), 4,4'-dimethoxy-2,2'-bipyridine (0.02 mmol, 10 mol%), DMF (1 mL), 110 °C, N₂, 14 h. HPLC yield deduced using acetophenone as an internal standard.

Table 2.4 Influence of additives on the copper-catalysed sulfonylative Suzuki-Miyaura reaction.

Our focus was then turned to reaction solvents. Several solvents were examined (**Table 2.5**) according to principle component analysis (PCA) derived solvent classification method.^[170] Not surprisingly, apolar or low boiling point solvents such as toluene or dichloromethane still gave little product (**entries 2 – 4**). Among other solvents, dioxane and nitrobenzene resulted in only trace product (**entries 5 and 6**), while benzonitrile and nitromethane led to a much lower yield compared to DMF (**entries 7 and 8**). Although both sulfolane (**entry 9**) and DMPU (**entry 14**) performed better than DMF with a 60% HPLC yield, only with DMPU was the sulfone product able to be extracted from the solvent and isolated.

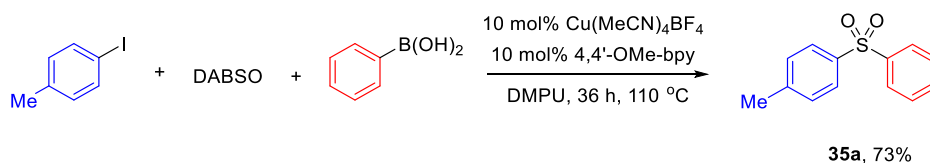


35a		
Entry ^a	Solvent	HPLC Yield of 3a (%) ^b
1	DMF	49
2	Dichloromethane	0
3	Toluene	0
4	<i>tert</i> -Butanol	37
5	Dioxane	0
6	Nitrobenzene	Trace
7	Benzonitrile	16
8	Nitromethane	18
9	Sulfolane	60 ^c
10	NMP	55
11	DMSO	35
12	DMA	33
13	DMI	53
14	DMPU	60

^a Reaction conditions: iodobenzene (0.2 mmol, 1.0 equiv.), DABSO (0.3 mmol, 1.5 equiv.), phenylboronic acid (0.6 mmol, 3.0 equiv.), Cu(MeCN)₄BF₄ (0.02 mmol, 10 mol%), 4,4'-dimethoxy-2,2'-bipyridine (0.02 mol, 10 mol%), solvent (1 mL), 110 °C, N₂, 14 h. ^b HPLC yield deduced using acetophenone as an internal standard. ^c Product inseparable from solvent.

Table 2.5 Solvent screening for the copper-catalysed sulfonylative Suzuki-Miyaura reaction.

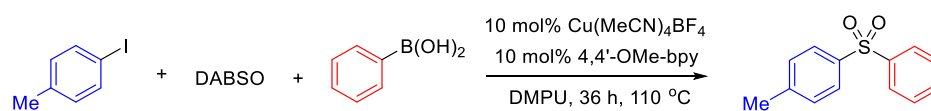
Different temperature and time combinations were also evaluated. Higher temperature accelerated the reaction, but the amount of side product increased, leaving 110 °C as the optimal temperature. Finally, an elongated 36-hour reaction time pushed the yield to 73% (Scheme 2.6).



Scheme 2.6 Optimised condition for copper-catalysed sulfonylative Suzuki-Miyaura reaction

Alternative boron reagents and other sulfur dioxide surrogates were also tested (Table 2.6).

Triphenyl boroxine gave a similar yield to the boronic acid, but changing to either the boronic ester or potassium phenyltrifluoroborate salt, shut down the reaction entirely (**entries 1 – 3**). Another sulfur dioxide surrogate, K₂S₂O₅, was completely inactive under the optimised conditions (**entry 4**).



35a			
Entry ^a	Boron reagent (3.0 equiv.)	SO ₂ surrogate (equiv.)	HPLC Yield (%)
1	Triphenyl boroxine	DABSO (1.5)	69%
2	Phenylboronic acid pinacol ester	DABSO (1.5)	Trace
3	PhBF ₃ K	DABSO (1.5)	Trace
4	Phenylboronic acid	K ₂ S ₂ O ₅ (5.0)	Trace

^a Reaction conditions: iodobenzene (0.2 mmol, 1.0 equiv.), boron reagent (0.6 mmol, 3.0 equiv.), Cu(MeCN)₄BF₄ (0.02 mmol, 10 mol%), 4,4'-dimethoxy-2,2'-bipyridine (0.02 mol, 10 mol%), DMPU (1 mL), 110 °C, N₂, 36 h. ^b HPLC yield deduced using acetophenone as an internal standard. ^c Product inseparable with the solvent.

Table 2.6 Alternative reagents for copper-catalysed sulfonyleative Suzuki-Miyaura reaction

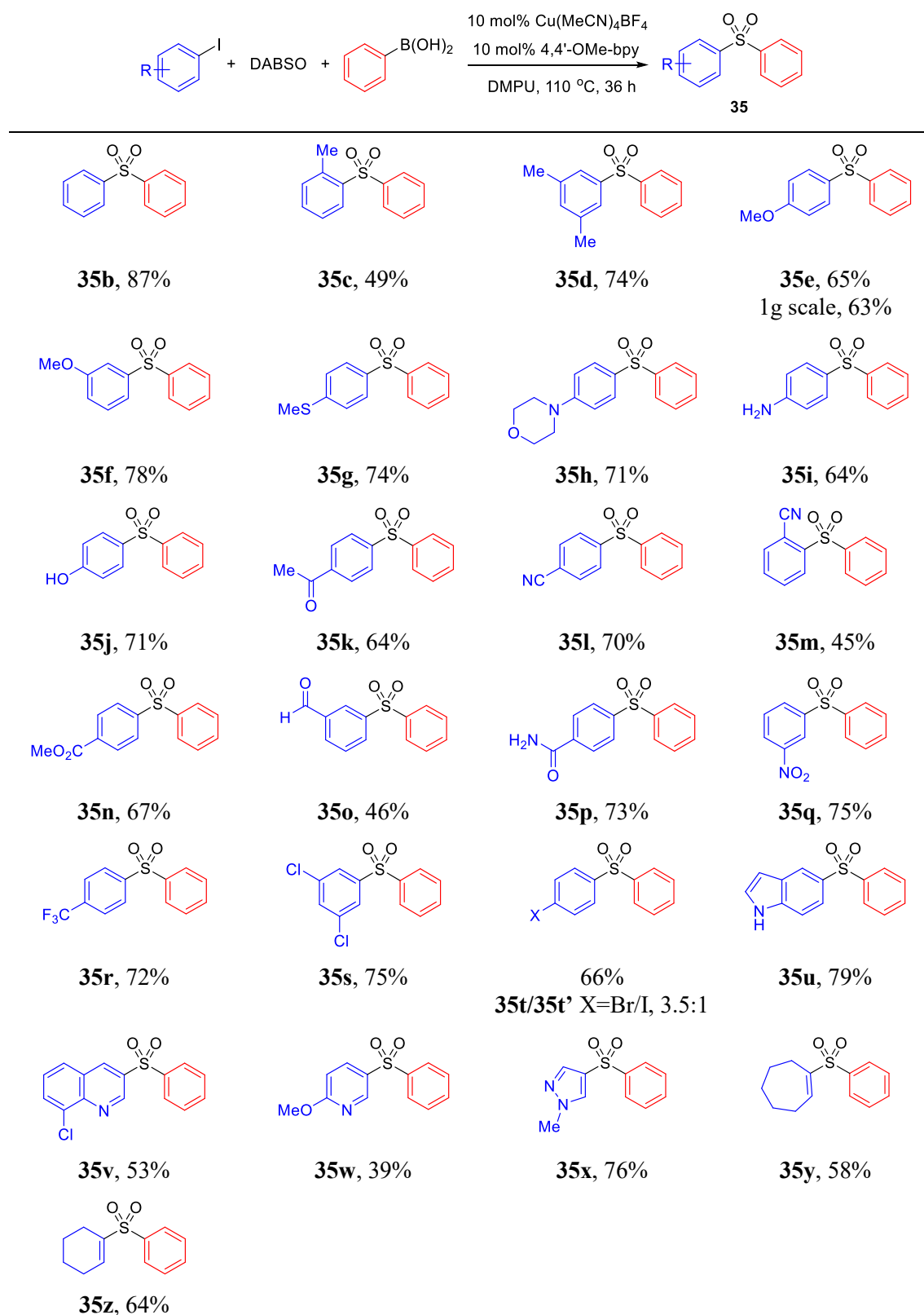
2.6. Initial reaction scope

2.6.1. Aryl/alkenyl iodide scope

With the optimised reaction conditions in hand, the focus moved on to explore the scope of this one-pot one-step reaction with various aryl iodides (**Table 2.7**). In general, the process was tolerant of a broad range of both electron-donating and electron-withdrawing functional groups located at all positions on the aromatic ring. Strong electron-donating groups such as methoxy (**35e** and **35f**), and electron-withdrawing groups such as nitro (**35q**) and trifluoromethyl (**35r**) were employed smoothly, giving good yields.

It is also worth noting that product **35g** possesses sulfur atoms at two different oxidation states, which would be a challenging arrangement to prepare *via* traditional sulfone methodology, yet underwent the reaction conditions without incident.

Free primary amine and alcohol groups were also well tolerated, resulting in sulfones **35i** and **35j**, with 64% and 71% yield, respectively. Other products containing reactive functional groups including tertiary amine (**35h**), ketone (**35k**), nitriles (**35l** and **35m**), ester (**35n**) and amide (**35p**) were obtained with good yields. Heterocycle-derived iodides could likewise be transformed into the corresponding sulfones, with indole (**35u**), quinoline (**35v**), pyridine (**35w**) and pyrazole (**35x**) derived products being obtained in moderate to good yields. Products **35y** and **35z** demonstrated that alkenyl iodide substrates can also be employed, although these alkenyl iodides were not stable at the reaction temperature of 110 °C. Reasonable yields (58% and 64%) were nevertheless obtained. Not surprisingly, *ortho*-substituted aryl iodides (**35c** and **35m**) showed lower reactivity compared to their *meta*- and *para*-isomers (**35a**, **35d**, **35l**), presumably due to steric hindrance.

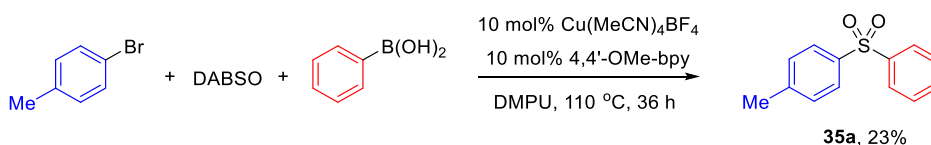


Reaction conditions: aryl iodide (0.2 mmol, 1.0 equiv.), DABSO (0.3 mmol, 1.5 equiv.), phenylboronic acid (0.6 mmol, 3.0 equiv.), Cu(MeCN)₄BF₄ (10 mol%), 4,4'-dimethoxy-2,2'-bipyridine (10 mol%), DMPU (1 mL), 110 °C, 36 h. Isolated yields.

Table 2.7 Variation of the aryl iodide coupling partner in the copper-catalysed sulfonylative Suzuki-Miyaura reaction.

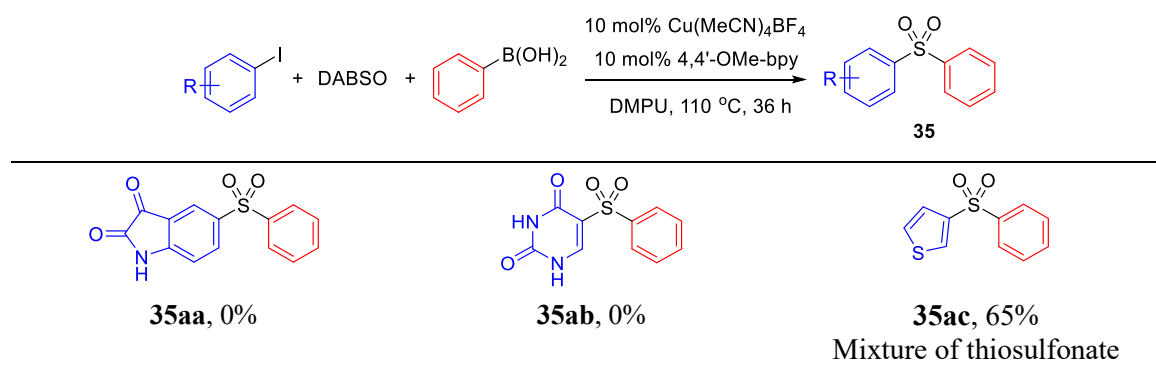
The experiments in **Table 2.7** were routinely performed on a 0.2 mmol scale, however, larger scale preparative reactions were also feasible. For example, sulfone **35e** was prepared on a 1-gram scale (5 mmol), in 63% yield.

Among different halogen-substituted aryl iodides, 3,5-dichloriodobenzene gave the targeted product (**35s**) in 75% yield without any side-reaction of chloride substituent, while 1-bromo-4-iodobenzene gave an inseparable mixture of both bromo and iodo-substituted sulfones (**35t**, **35t'**) in a ratio of 3.5:1; indicating some degree of reactivity for aryl bromide under these reaction conditions. To follow up this new discovery, an attempt was made to use bromotoluene instead of iodotoluene (**Scheme 2.7**). Unfortunately, under the same optimised conditions it only provided 23% of the desired product, with 70% of starting material remaining unreacted.



Scheme 2.7 Attempt on aryl bromide

During the scope of various aryl iodides, very few iodide derivatives failed to provide any product (**Table 2.8**). 5-Iodoisatin showed low solubility in DMPU solution as well as DMI therefore delivered no desired product (**35aa**), and 5-iodouracil resulted in only a trace of product (**35ab**) while giving high yield of the disproportionation side product, *S*-phenyl benzenesulfonylthioate **34**. 3-(Phenylsulfonyl)thiophene (**35ac**) was obtained as an inseparable mixture with the disproportionation side product **34**.

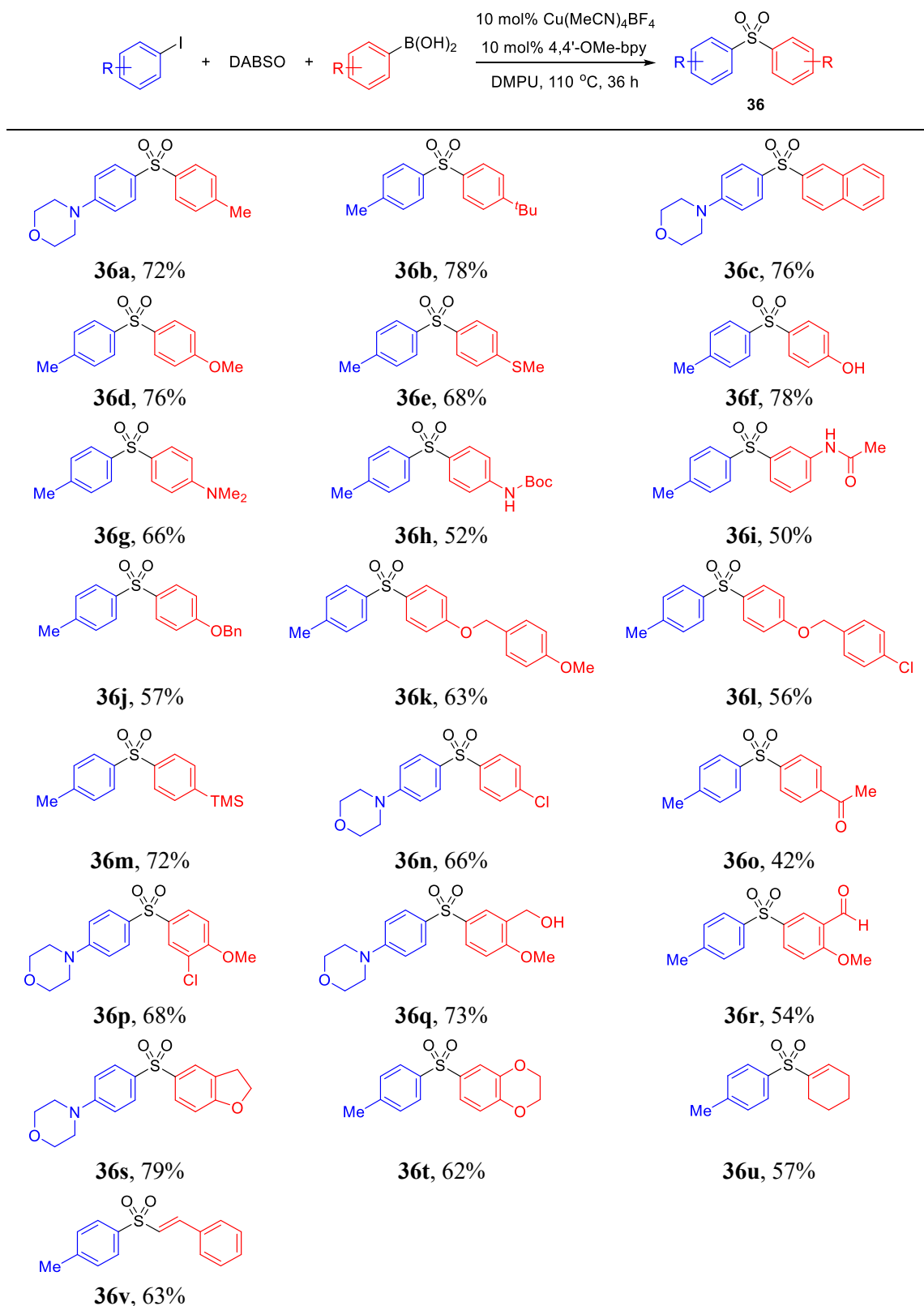


Reaction conditions: same as **Table 2.7**

Table 2.8 Unsuccessful attempts of the aryl iodide coupling partner in the copper-catalysed sulfonylative Suzuki-Miyaura reaction

2.6.2. Boronic acid scope

Following the wide scope of aryl iodides, significant variations of the boronic acid coupling partner were also viable (**Table 2.9**). Similar to iodides, several useful functional groups were incorporated with good yields, including methoxy (**36d**), thiomethyl (**36e**), amino (**36g**) and chloro (**36n**, **36p**) groups. Aromatic (**36f**) and aliphatic alcohols (**36q**) were also well tolerated with 78% and 73% yield respectively. Some other functional groups such as carbamate (**36h**), amide (**36i**), benzyloxide (**36j**, **36k**, **36l**), silane (**36m**) and aldehyde (**36o**) were obtained in slightly lower yields due to side reactions such as protodeboration, while electron-withdrawing groups such as a ketone (**36r**) resulted in lower reactivity of the boronic acids towards DABSO, leading to their decomposition under the reaction conditions. Heterocyclic variants (**36s**, **36t**) reacted smoothly to provide the corresponding products in 79% and 62% yield. Further extension of the scope to alkenyl boronic acids also proved to be effective. Cyclohexenylboronic acid (**36u**) and *trans*-phenylvinylboronic acid (**36v**) both successfully delivered the unsaturated sulfone products in reasonable yields.



Reaction conditions: aryl iodide (0.2 mmol, 1.0 equiv.), DABSO (0.3 mmol, 1.5 equiv.), boronic acid (0.6 mmol, 3.0 equiv.), Cu(MeCN)₄BF₄ (10 mol%), 4,4'-dimethoxy-2,2'-bipyridine (10 mol%), DMPU (1 mL), 100 °C, 36 h. Isolated yields.

Table 2.9 Variation of the aryl boronic acid coupling partner in the copper-catalysed sulfonylative Suzuki-Miyaura reaction

Although the scope of various boronic acids were pleasingly successful, there was one limitation of the developed reaction (**Table 2.10**). As mentioned earlier, unlike aryl iodides, boronic acids substituted with electron-withdrawing groups showed low reactivity under the reaction conditions. Electron-withdrawing groups such as 4-methyl ester (**36aa**) showed significantly lower yields comparing to that of the corresponding aryl iodides. Unfortunately, weakly electron-donating groups such as (4-acetamidophenyl)boronic acid (**36ab**) gave only 38% of desired product and alkenyl-substituted boronic acid (**36ac**) was completely incompatible with these reaction conditions, with no starting material conversion and no sign of sulfonation reaction being observed after 40 hours.

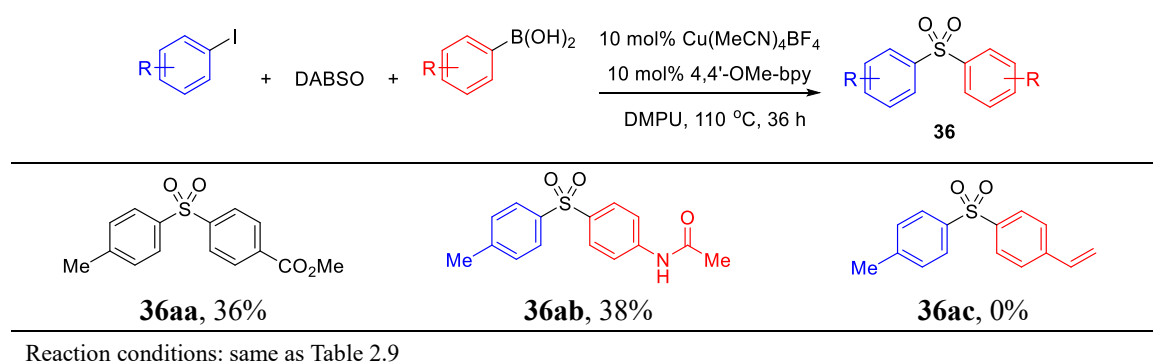
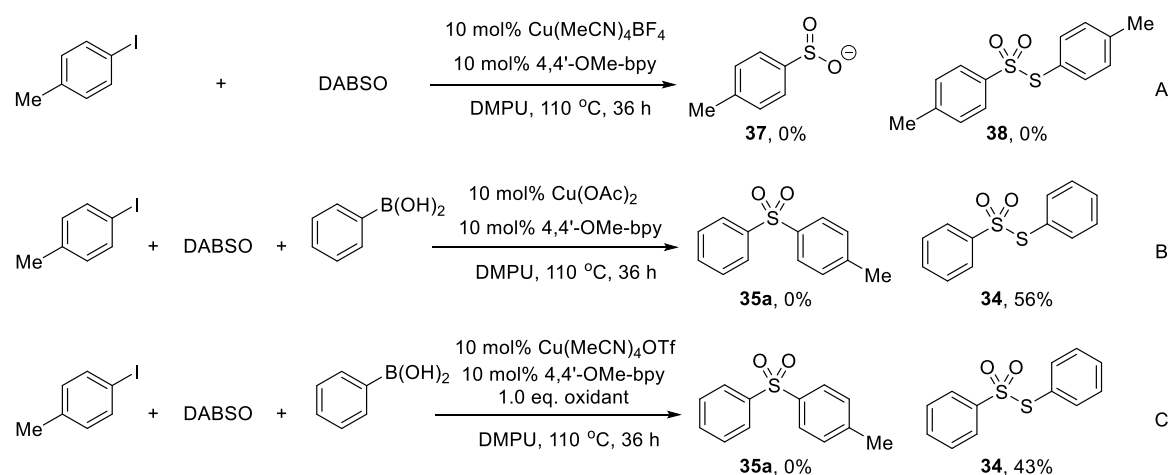


Table 2.10 Unsuccessful attempts of the aryl boronic acid coupling partner in the copper-catalysed sulfonyle Suzuki-Miyaura reaction

2.7. Proposed reaction mechanism

After demonstrating the utility of the reaction, a series of control experiments were performed to shed light on the mechanism. Omission of boronic acid from the reaction resulted in less than 1% of sulfinate **37** and thiosulfonate **38**, suggesting that the sulfinate intermediate is formed from the boronic acid (**Scheme 2.8, equation A**). Switching from a Cu(I) to Cu(II) catalyst shut down the Suzuki reaction completely, with only the sulfinate

disproportionation product thiosulfonate **34** being detected (**Equation B**). The addition of oxidants, for instance AgNO₃, benzoquinone or oxygen, also resulted in only thiosulfonate **34** formation (**Equation C**). This rules out the possibility of the active catalyst being a Cu(II) species. Other factors such as light did not affect the outcome of the reaction.



Scheme 2.8 Control experiment for mechanistic study

Based on our observations during the optimisation process and the control experiments shown above, together with relevant literature reports,^[34, 37b, 156a, 171] a plausible mechanism for the sulfonylative Suzuki-Miyaura coupling is illustrated below (**Figure 2.2**). The copper(I) catalyst first undergoes transmetalation with the boronic acid to generate intermediate **A**, which then undergoes sulfination to the copper arylsulfinate species **B**. Oxidative addition of **B** to the aryl iodide gives Cu(III) intermediate **C** and finally reductive elimination forms the desired sulfone and regenerates the Cu(I) catalyst to complete the catalytic cycle.

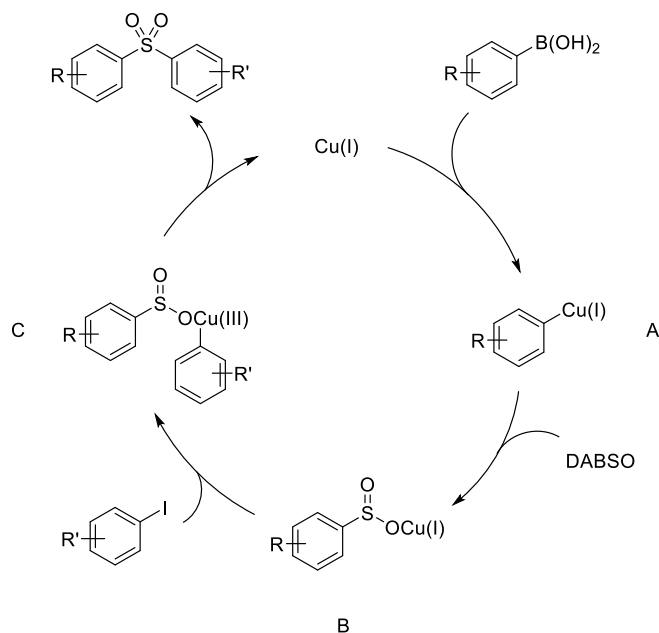
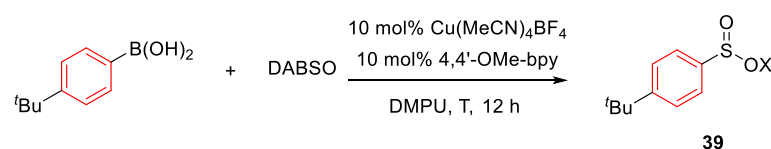


Figure 2.2 Proposed mechanism for copper(I)-catalysed sulfonylative Suzuki-coupling

2.8. One-pot, two-step sulfinate derivatisation reactions

After a fruitful scope of the direct copper-catalysed sulfonylative Suzuki-Miyaura reaction, we were intrigued to explore the possibility of preparing discrete sulfinate intermediates **B**, as can be seen in the first half of the proposed catalytic cycle (**Figure 2.2**). Employing the optimised reaction conditions without the aryl iodide coupling partner gave only arylsulfinate disproportionation product (**Table 2.11, entry 1**), *S*-[4-(*tert*-butyl)phenyl] 4-(*tert*-butyl)benzenesulfonothioate, which indicates the full decomposition of the sulfinate **39** after its formation. Even though lowering the reaction temperature to 100 °C or 80 °C (**entries 3 and 4**) slowed the disproportionation process significantly, and raised the yield of sulfinate to 16%, the reaction rate was considerably slower judged from the conversion of the starting material. This hinted that while copper catalysed sulfinate formation still occurred at 80 °C, a relatively stable copper sulfinate complex was formed and thus reduced

the catalyst turnover. Further lowering of the temperature contributed only 10% of sulfinate with 10 mol% catalyst loading; 20% yield was obtained with 20 mol% catalyst loading (**entries 6 and 7**), suggesting the catalyst did not turnover. The presence of a ligand proved no longer effective in this process since the reaction outcome remained the same with or without added ligand both at 120 °C and 80 °C.



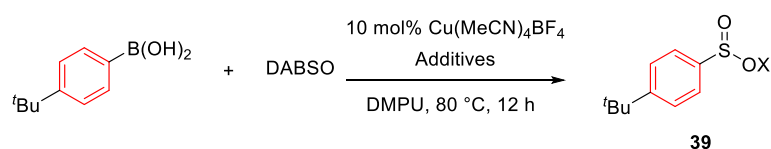
Entry ^a	Ligand	Temperature (°C)	Yield ^b (%)
1	10%	120	0%
2	-	120	0%
3	10%	100	8%
4	10%	80	16%
5	-	80	17%
6	-	60	10%
7	-	60	20% ^c

^a Reaction conditions: DABSO (0.1 mmol, 0.5 equiv.), boronic acid **2** (0.2 mmol, 1.0 equiv.), DMPU (1 mL), Cu(MeCN)₄BF₄ (10 mol%), 12 h. ^b Yield deduced from HPLC with acetophenone as an internal standard.

^c 20 mol% Cu(MeCN)₄BF₄

Table 2.11 Initial attempts of sulfinate formation

One of the plausible assumption was that after the copper sulfinate complex was formed, the reaction conditions above were not sufficient to release the copper and complete the catalytic process. Therefore, acids and bases were added in the hope of improving catalyst turnover (**Table 2.12**). Sadly, the presence of water (**entry 2**) or acids shut down the reaction completely, giving 0% conversion in either TFA (**entry 3**) or acetic acid (**entry 4**). On the other hand, both bases (**entries 5 and 6**) reduced the yield to 11% and 8% respectively, suggesting they were potentially stabilising the complex rather than releasing the copper catalyst.



Entry ^a	Additive (equiv.)	Yield ^b (%)
1	-	17%
2	H ₂ O (1.0)	No reaction
3	TFA (1.0)	No reaction
4	Acetic acid (1.0)	No reaction
5	Et ₃ N (1.0)	11%
6	NaOH (1.0)	8%

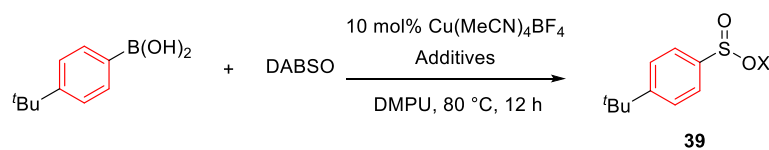
^a Reaction conditions: DABSO (0.1 mmol, 0.5 equiv.), boronic acid (0.2 mmol, 1.0 equiv.), DMPU (1 mL), Cu(MeCN)₄BF₄ (10 mol%), 80 °C, 12 h. ^b Yield deduced from HPLC with acetophenone as an internal standard

Table 2.12 Screening of acid/base additives for sulfinate intermediate stabilisation.

The next focus of our investigation was the addition of salts, in the hope of forming a stable sulfinate salt *via* cation exchange, allowing the release of copper back into the catalytic cycle (**Table 2.13**). To our surprise, salts such as NaCl (**entry 2**), NaI (**entry 3**) and ZnCl₂ (**entry 4**) proved to be detrimental to the reaction, almost completely suppressing the reaction. Phase transfer reagent TBAB (**entry 5**) also had a negative impact on the reaction outcome. KPF₆ (**entry 6**) was introduced in the hope that the PF₆⁻ anion would be able to free the sulfinate from copper thus reforming the catalyst, although the result proved it failed to improve the yield of sulfinate. Although the boronic acid conversion was high with the addition of a silver salt (**entry 7** and **8**), the majority of the product was disproportionation.

A significant breakthrough came from the addition of BF₄⁻ salts. NH₄BF₄ raised the yield to 23% (**entry 9**) and, pleasingly, 1.0 equivalent of NaBF₄ further increased it to 31% (**entry 10**). Encouraged by this result, larger amounts of NaBF₄ were added, and it was found that 5.0 equivalents achieved an 89% HPLC yield of sulfinate (**entry 12**) with just 5% of

disproportionation side products. Further increase of the NaBF₄ loading did not result in an improved yield (**entry 13**).



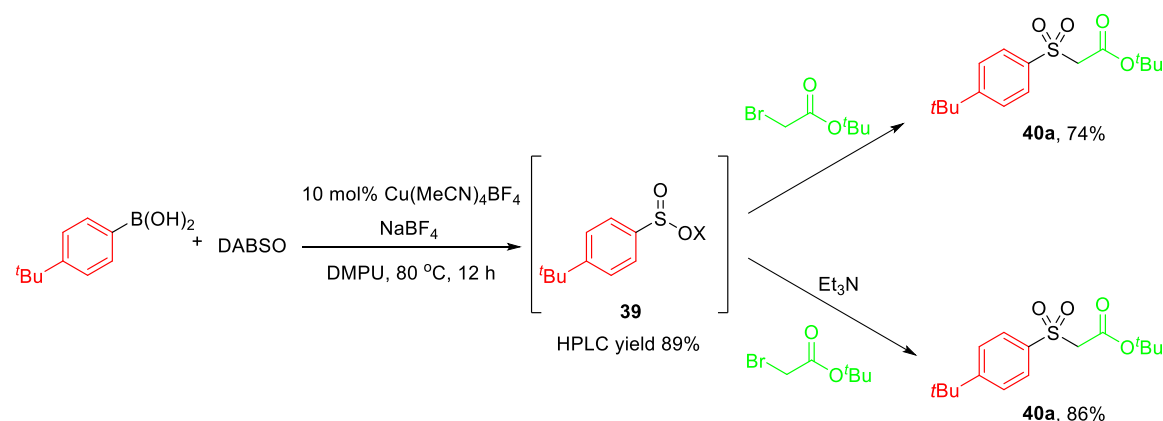
Entry ^a	Additive (equiv.)	Yield ^b (%)
1	-	17%
2	NaCl (1.0)	No reaction
3	NaI (1.0)	3%
4	ZnCl ₂ (1.0)	4%
5	TBAB (1.0)	5%
6	KPF ₆ (1.0)	13%
7	AgOTf (1.0)	0%
8	AgBF ₄ (1.0)	6%
9	NH ₄ BF ₄ (1.0)	24%
10	NaBF ₄ (1.0)	31%
11	NaBF ₄ (3.0)	66%
12	NaBF₄ (5.0)	89%
13	NaBF ₄ (10.0)	88%

^a Reaction conditions: DABSO (0.1 mmol, 0.5 equiv.), boronic acid **2** (0.2 mmol, 1.0 equiv.), DMPU (1 mL), Cu(MeCN)₄BF₄ (10 mol%), 80 °C, 12 h. ^b Yield deduced from HPLC with acetophenone as an internal standard.

Table 2.13 Screening of neutral salt additives for sulfinate intermediate stabilisation

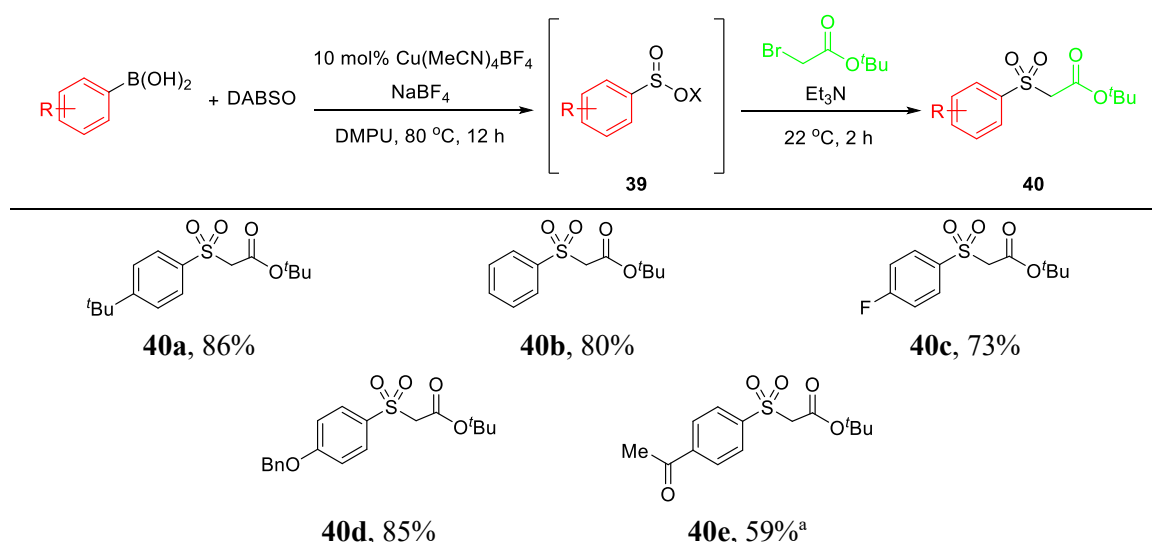
To examine the utility of the *in-situ* generated sulfinates, several electrophiles were used to trap the putative intermediate. Deeming^[124] in the group developed several methods for sulfination and derivatisation reaction from boronic acid with palladium catalysis, where he used electrophiles such as *tert*-butyl bromoacetate and epoxides in the derivatisation step after sulfinate transformation. Thus, *tert*-butyl bromoacetate^[121] was also chosen in this copper catalysed sulfination reaction (**Scheme 2.9**). Direct addition of bromoacetate upon sulfination resulted in 74% yield of **40a**, which is 15% lower compared to the 89% HPLC yield of the intermediate sulfinate. An extra 1.5 equivalents of Et₃N reduced this loss

and raised the yield up to 86%.



Scheme 2.9 One-pot two-step sulfonation derivatisation reaction with and without base

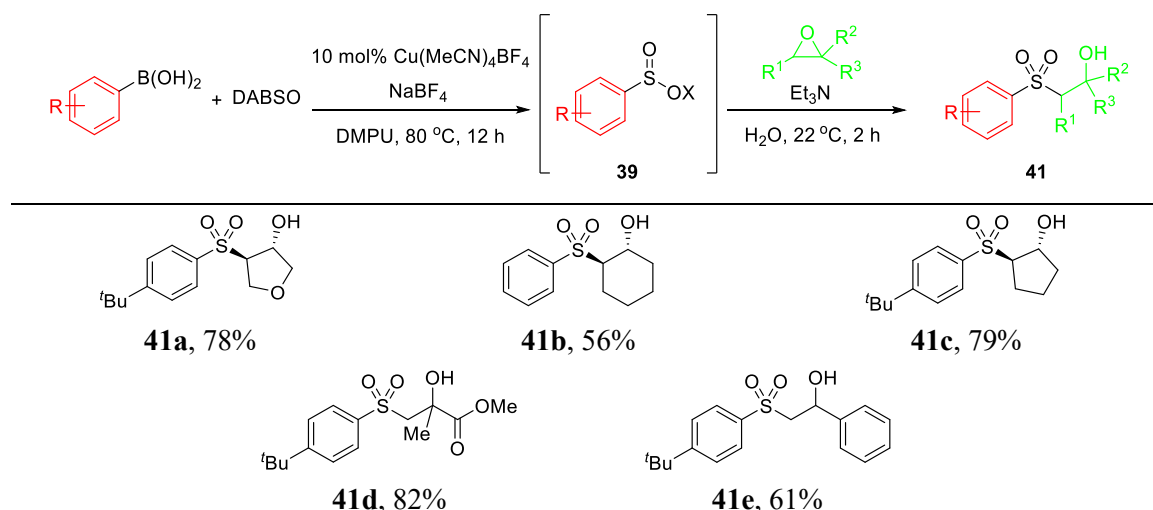
Other sulfinates were synthesised under the optimised reaction conditions (**Table 2.14**) and were subsequently transformed into the corresponding aryl alkyl sulfones. Good yields were maintained with simple phenylboronic acid as well as fluoro and benzyloxy-substituted boronic acids (**40c**, **40d**). Electron-withdrawing groups behaved similarly as discovered in the one-pot one-step reaction above (**Section 2.6**). The reaction rate of sulfinate formation from (4-acetylphenyl)boronic acid (**40e**) was significantly slower compared to that of phenyl or *tert*-butylphenylboronic acid. After 36 hours, conversion of the (4-acetylphenyl)boronic acid to sulfinate was only 65%, and subsequent reaction with *tert*-butyl bromoacetate resulted in 59% yield, considerably lower than those of other boronic acids presented.



Reaction conditions for sulfinate formation: DABSO (0.1 mmol, 0.5 equiv.), boronic acid (0.2 mmol, 1.0 equiv.), NaBF₄ (1.0 mmol, 5.0 equiv.), DMPU (1 mL), 80 °C, 12 h; then Et₃N (0.3 mmol, 1.5 equiv.), *tert*-butyl bromoacetate (0.4 mmol, 2.0 equiv.), 22 °C, 2 h. Isolated yields. ^a 36 h, then 2 h.

Table 2.14 Copper-catalysed sulfinate formation and conversion to alkyl aryl sulfones

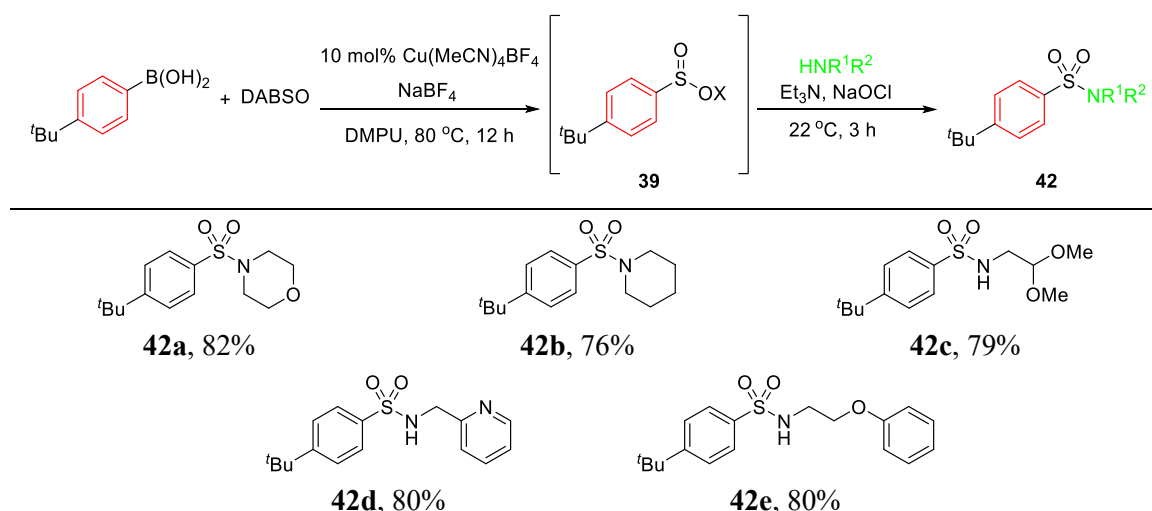
Several epoxides were also employed for the synthesis of β -hydroxy sulfones (Table 2.15), which are of medicinal and synthetic interests and could serve as precursors to vinyl sulfones.^[172] Without removing solvent, the crude sulfinate mixture was treated directly with water and an epoxide, giving the targeted β -hydroxy sulfones **41** in good yields.



Reaction conditions for sulfinate formation: DABSO (0.1 mmol, 0.5 equiv.), boronic acid (0.2 mmol, 1.0 equiv.), $NaBF_4$ (1.0 mmol, 5.0 equiv.), DMPU (1 mL), $80^\circ C$, 12 h; then Et_3N (0.3 mmol, 1.5 equiv.), epoxide (0.4 mmol, 2.0 equiv.), H_2O (2 mL), $22^\circ C$, 2 h. Isolated yields.

Table 2.15 Copper-catalysed sulfinate formation and conversion to β -hydroxy sulfones

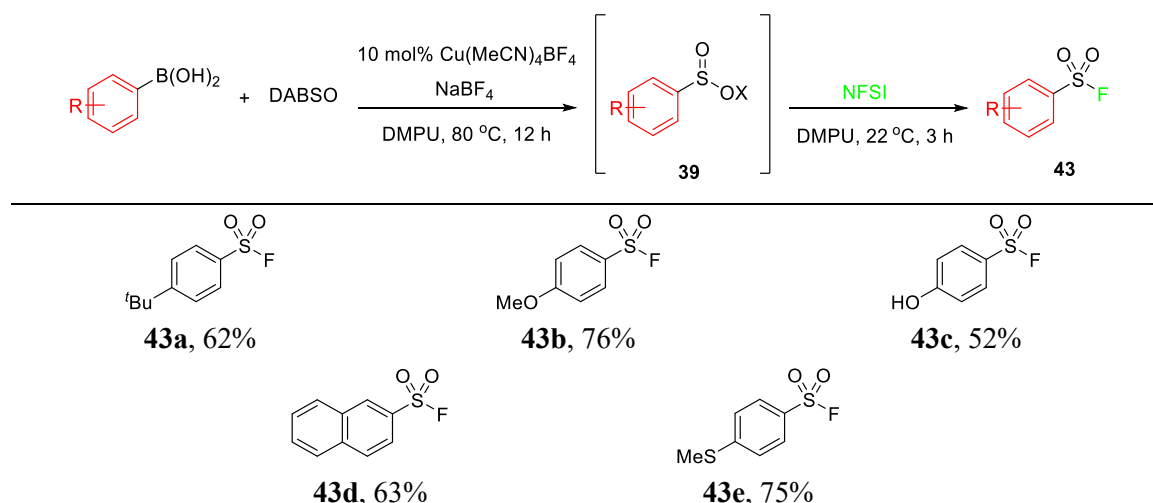
While carbon-based electrophiles were successfully coupled with sulfonates to make various sulfones, we sought another pathway to gain access to sulfonamides. A similar procedure to prepare sulfonamides from boronic acids was published by our group in early 2016^[124] using palladium catalysis. Applying a similar concept, a dilute $NaOCl$ solution was added after confirmation of sulfinate generation, followed by the addition of an amine,^[123] successfully forming the sulfonamide in good yields (Table 2.16). Both primary (**42c**, **42d** and **42e**) and secondary amines (**42a** and **42b**) proved competent.



Reaction conditions for sulfinate formation: DABSO (0.1 mmol, 0.5 equiv.), boronic acid (0.2 mmol, 1.0 equiv.), NaBF_4 (1.0 mmol, 5.0 equiv.), DMPU (1 mL), 80 °C, 12 h; then Et_3N (0.3 mmol, 1.5 equiv.), amine (0.4 mmol, 2.0 equiv.), NaOCl (0.4 mmol, 2% aq. solution, 2.0 equiv.), 22 °C, 3 h. Isolated yields.

Table 2.16 Copper-catalysed sulfinate formation and conversion to sulfonamides

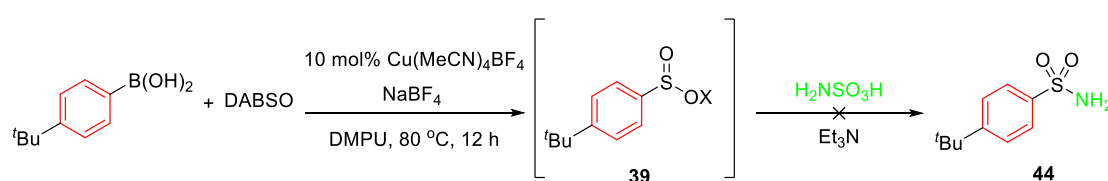
Sulfonyl fluorides are also valuable targets, as they are useful synthetic precursors and also synthetic probes for a number of biologically and pharmaceutically important molecules.^[122, 173] The electrophilic fluorination reagent *N*-fluorobenzenesulfonimide, NFSI, was added to the corresponding sulfinate intermediates at room temperature to generate the desired sulfonyl fluoride (**Table 2.17**). Functional groups like hydroxyl group (**43c**) and thiomethyl group (**43e**) were well tolerated. The addition of base was not necessary in this case as it did not enhance the overall yield.



Reaction conditions for sulfinate formation: DABSO (0.1 mmol, 0.5 equiv.), boronic acid (0.2 mmol, 1.0 equiv.), NaBF₄ (1.0 mmol, 5.0 equiv.), DMPU (1 mL), 80 °C, 12 h; then NFSI (0.3 mmol, 1.5 equiv.), DMPU (0.2 mL), 22 °C, 3 h. Isolated yields.

Table 2.17 Copper-catalysed sulfinate formation and conversion to sulfonyl fluorides.

In spite of the successful sulfinate derivatisation conducted above, efforts to combine sulfinic acid adduct with sulfamic acid failed to give any designed sulfonamide product **44**.^[124] After the sulfinate formation, no sign of further reaction was detected when sulfamic acid pre-dissolved in water was added at 22 °C or 80 °C. The sulfinate salt did not react even after 12-hours stirring.



Scheme 2.10 Failed attempts for sulfonamide

2.9. Project summary

In summary, a novel copper(I)-catalysed sulfonylative Suzuki-Miyaura cross-coupling reaction of boronic acids, DABSO and aryl iodides was achieved, which is the first true sulfonylative-variant of a classic cross-coupling process. This one-pot one-step reaction

bypasses the synthesis of sulfinates and directly delivers valuable sulfone products with high efficiency, using readily available substrates and sustainable catalysts. A good variation of aryl, heteroaryl and alkenyl substrates from both reaction partners were applied to give corresponding sulfones in high yields.

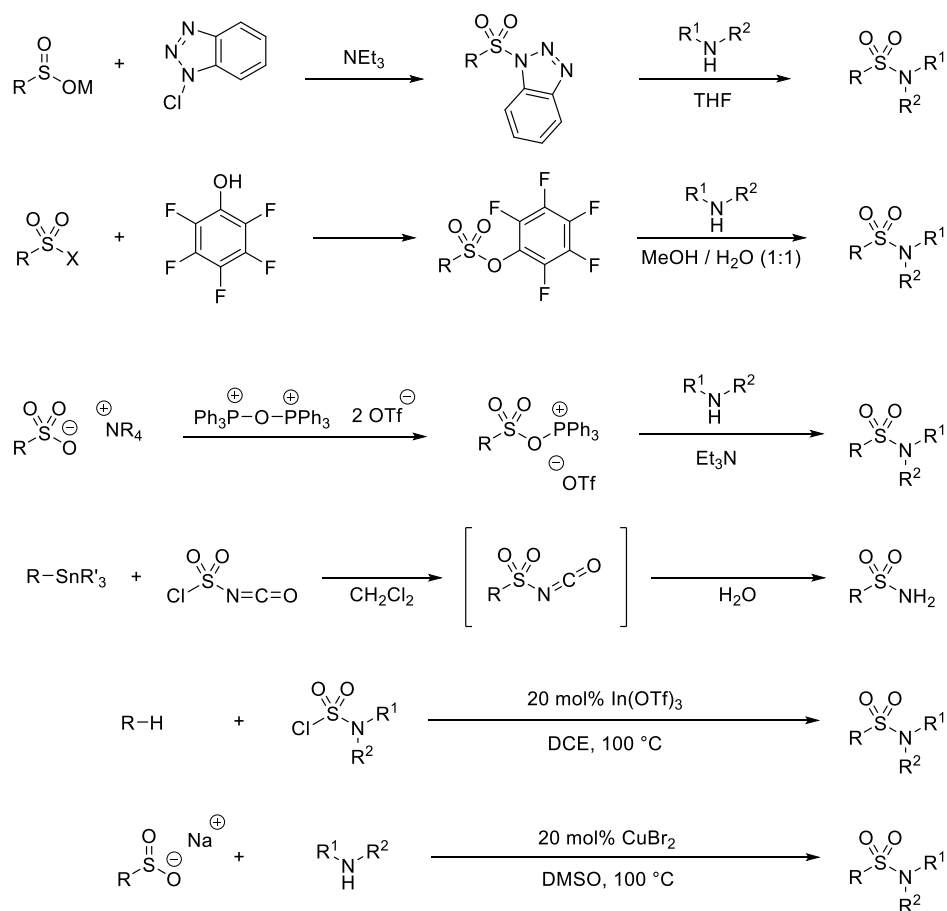
Additionally, a one-pot two-step process was also established based on a similar copper(I)-catalysed system. NaBF₄ stabilises the *in-situ* generated sulfinates, which otherwise disproportionate to thiosulfonate, allowing them be exploited for the synthesis of sulfonyl derivatives other than diaryl sulfones. Four types of additional reactions are demonstrated, each representing the utilisation of four different class of electrophiles, i.e. alkyl bromides, epoxides, primary and secondary amines, and an electrophilic fluorination reagent. Good yields and high substrate diversity are both realised in all four reactions, and a wide range of medicinally and synthetically interesting molecules such as β -hydroxysulfones, sulfonamides and sulfonyl fluorides are obtained.

3.2. Synthesis of sulfonamides

With the prevalence of sulfonamides in medicinal chemistry, efficient and versatile synthetic strategies for sulfonamide derivatives are of significant importance in organic chemistry. The classical method is to couple sulfonyl chlorides with the corresponding amines. This type of reaction was reported in 1880 by Gabriel and Dambergis, and has been used for sulfonamide synthesis for over 130 years.^[178] Though a robust and efficient reaction, it is limited by the accessibility of sulfonyl chlorides (see **Section 1.1.2**). Many routes have been developed to synthesise sulfonyl chlorides from various starting materials over the years, but most involve the use of hazardous reagents such as chlorine gas, sulfur dioxide gas, sulfuryl chloride or chlorosulfonic acid, which not only makes the reaction practically difficult to handle but significantly reduces the functional group compatibility. In addition, the moisture sensitivity of sulfonyl chlorides means in many cases that they must be prepared immediately before use, bringing in another layer of inconvenience.

In an attempt to avoid these problems, many analogues of sulfonyl chlorides have also been studied for the synthesis of sulfonamide (**Scheme 3.1**). *N*-Sulfonylbenzotriazoles,^[179] and pentafluorophenol- or triphenylphosphine- activated sulfonates^[180] avoid the instability of sulfonyl chlorides, but they still suffer from the limited availability of sulfonic acid derivatives. Alternative routes include the alkylation/ arylation of unstable sulfamoyl chloride derivatives, with either trialkylarylstannanes^[181] or arenes.^[182] Reports of copper catalysed sulfinate amination were also published recently by Tang *et al.*^[183] Iron- catalysed *N*-arylsulfonamide formation through nitroarenes and sodium sulfinate has also been

reported by Luo.^[184]



Scheme 3.1 Examples of sulfonyl chloride-free sulfonamide synthesis

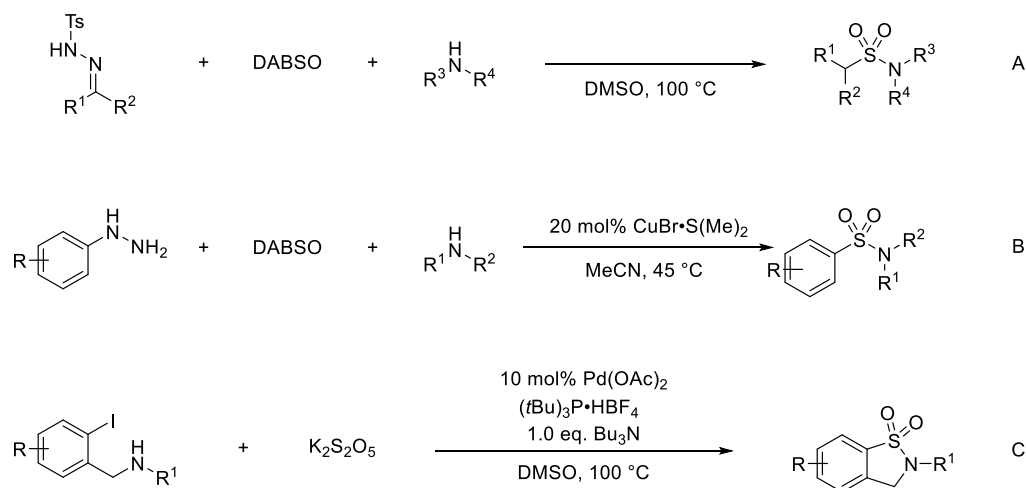
The development of sulfur dioxide surrogates (see **Section 1.2.3**) has enabled a range of versatile methods to form metal or amino sulfinate salts. Previous work from the Willis group has shown how DABSO can be used to generate these sulfinate salts, and how a further oxidation and sulfonamidation allows access to sulfonamides.^[185] Sulfonamides can therefore be synthesised in one-pot from readily available reagents like aryl halides,^[111, 123] boronic acids,^[124] lithium reagents^[110a] and Grignard reagents^[112] under relatively mild conditions. Rongalite, sodium hydroxymethylsulfinate, can also be used in place of DABSO as the sulfur dioxide surrogate to obtain alkyl sulfonamides in a similar manner.^[186]

Very recently, a palladium and copper catalysed one-pot two-step sulfonamide synthesis from boronic acid, DABSO and *O*-benzoyl hydroxylamines has been reported.^[125]

Despite these advances, the necessity of a sulfinate intermediate restrict these methods to at least two steps. Some progress has been made towards a one-step synthesis, including some metal-free radical reactions, however, the nucleophile tends to be restricted to hydrazine derivatives.^[107, 187] A one-step sulfonamide synthesis from readily available substrate feedstocks is therefore highly desirable and has yet been achieved.

3.3. Recent advances in one-step sulfonamide synthesis

In late 2016, after this project was initiated, Pfizer published a one-step sulfonamide synthesis from *N*-tosylhydrazones,^[188] DABSO and the corresponding amines (**Scheme 3.2, equation A**). Subsequently, aryl hydrazines have been reported by Du *et al.* to deliver sulfonamides under copper catalysis (**Equation B**).^[130] Konishi *et al.* have also reported a palladium-catalysed intermolecular synthesis of cyclic sulfonamides with K₂S₂O₅ as the sulfur dioxide surrogate (**Equation C**).^[189] These advances, while one-step reactions, have done so whilst sacrificing the versatility of the starting material, using materials with narrow commercial availability.



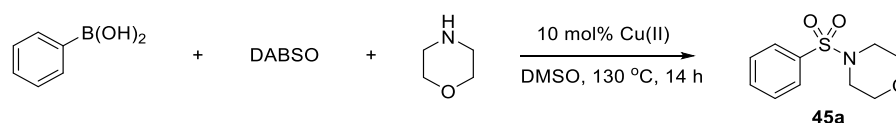
Scheme 3.2 Recent advances in one-step sulfonamide synthesis

3.4. Project aim

Circumventing any intermediates and directly obtaining targeted products gives unparalleled advantages to one-step reactions. In view of the prevalence of sulfonamides in medical and agriculture science, improved one-step sulfonamide synthetic pathways are always coveted. The lack of versatilities in current one-step strategies served as our initial motivation. It would be desirable if widely available reagents like boronic acids were compatible substrates, and high functional group tolerance was achieved. In addition, robust and easy to set-up conditions would be helpful. All factors combined, to develop a novel DABSO-based one-step sulfonamide synthesis was set as our project aim. Excited by the recent successful on copper(I) catalysed sulfonylative Suzuki-Miyaura coupling and inspired by the abundant literature precedence of Chan-Lam coupling, the idea of a copper catalysed sulfonylative amination reaction came to our vision. In addition, while screening copper(I) catalysts for the last chapter, it was found that copper(II) catalysts also promote sulfination/disproportionation processes similarly to Cu(I) reactions.

3.5. Reaction optimisation

Initial investigations were carried out under rudimentary conditions of 10 mol% of the copper(II) catalyst was applied with phenylboronic acid, morpholine and DABSO in DMSO as the solvent at 130 °C (**Table 3.1**). Surprisingly, all copper(II) catalysts tried delivered some degree of product. Cu(OAc)₂ and Cu(OTf)₂ offered the highest yield of 17% and 19%, respectively (**entries 1 and 2**). Similarly, 17% of **45a** was obtained using Cu₂(OH)₂CO₃ (**entry 3**), however, 20 mol% of copper was employed. Other catalysts were not as efficient for the transformation (**entries 4 – 8**). Accordingly, Cu(OTf)₂ was chosen as the catalyst for the next stage of optimisation.

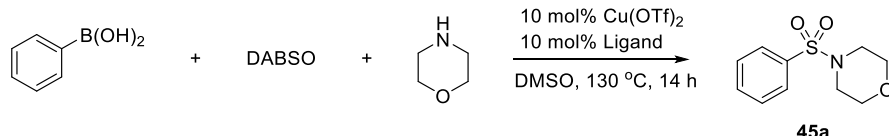
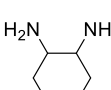
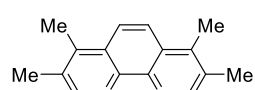
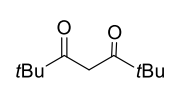
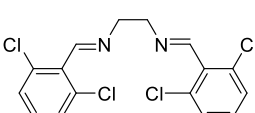
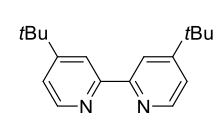
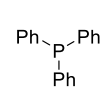
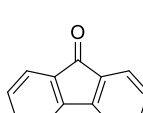
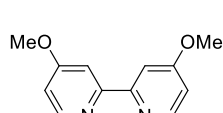
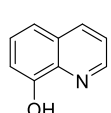
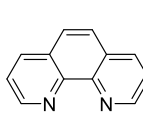
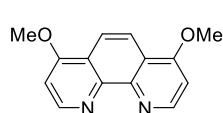
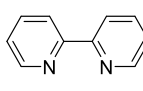
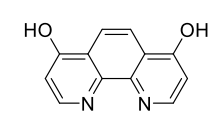
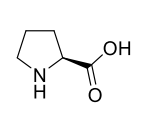
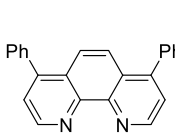
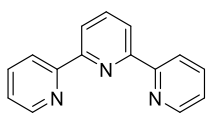
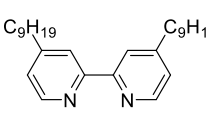


Entry ^a	Cu (II) catalyst (10 mol%)	Yield (%)
1	Cu(OAc) ₂	17
2	Cu(OTf)₂	19
3	Cu ₂ (OH) ₂ CO ₃	17
4	CuSO ₄	10
5	CuF ₂	11
6	Cu(NO ₂) ₂ ·2.5H ₂ O	8
7	CuBr ₂	6
8	Cu(OH) ₂	12

^a Reaction conditions: phenylboronic acid (0.2 mmol, 1.0 equiv.), DABSO (0.15 mmol, 0.75 equiv.), morpholine (0.3 mmol, 1.5 equiv.), DMSO (1 mL), 130 °C, N₂, 14 h

Table 3.1 Catalyst screening for the sulfonamide synthesis

Based on our experience from the copper(I)-catalysed sulfonylative Suzuki coupling, a significant ligand effect was expected. Therefore, a series of ligands were tested in the reaction to identify the best match (**Table 3.2**). Oxygen-based ligands like 1,2-cyclohexanedione or dipivalomethane (**entries 1 and 2**) did not enhance the catalyst performance and neither did triphenylphosphine (**entry 3**). Similar results were obtained from ligands such as 8-hydroxyquinoline, pyridine and L-proline (**entries 4 – 6**). The tridentate ligand terpyridine (**entry 7**), the primary amine 1,2-diaminocyclohexane (**entry 8**) and a bulky imine ligand (**entry 9**) shut down the reaction, and failed to give any product. Finally, some improvement was discovered when bipyridine and phenanthroline ligands were introduced. 1,10-Phenanthroline ligand (**entry 11**) raised the yield to 47%. Further exploration of ligand structure provided an increase in yield with the electron-rich 4,4'-dimethoxy-2,2'-bipyridine (**entry 17**), producing the product in 57% isolated yield.

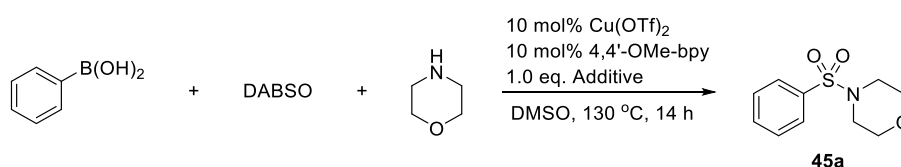
					
Entry ^a	Ligand	Entry	Ligand	Entry	Ligand
1	 16%	8	 Trace	15	 51%
2	 19%	9	 Trace	16	 53%
3	 21%	10	 28%	17	 57%
4	 23%	11	 47%	18	 53%
5	 21% (20 mol%)	12	 45%	19	 49%
6	 25%	13	 49%		
7	 Trace	14	 56%		

^a Reaction conditions: phenylboronic acid (0.4 mmol, 2.0 equiv.), DABSO (0.4 mmol, 1.5 equiv.), morpholine (0.2 mmol, 1.0 equiv.), Cu(OTf)₂ (10 mol%), DMSO (0.25 mL), 130 °C, N₂, 14 h

Table 3.2 Ligand Screening for the copper(II)-catalysed sulfonamide synthesis.

Subsequently, the use of a variety of additives was explored (Table 3.3). Although addition

of organic bases like pyridine and DBU did not offer any improvement (**entries 1 and 2**), each inorganic base examined enhanced the yield to some degree (**entries 3 – 7**). Among them, Cs₂CO₃ gave the best result with 74% yield (**entry 7**). On the other hand, additional oxidants diminished the yield (**entries 9 – 13**), and organic oxidants such as benzoquinone or TBPB even suppressed the reaction completely. Finally, the presence of acetic acid did not improve the yield but surprisingly did not impose a negative impact either (**entry 14**).



Entry ^a	Additive (1.0 equiv.)	Yield (%)
1	Pyridine	44
2	DBU	29
3	K ₂ CO ₃	61
4	K ₃ PO ₄	60
5	CsF	67
6	BaOH	56
7	Cs₂CO₃	74
8	K ₂ S ₂ O ₈	43
9	Benzoquinone	Trace
10	CAN ^b	Trace
11	TBPB ^c	Trace
12	O ₂	Trace
13	Ag ₂ CO ₃ + benzoquinone	23
14	HOAc	49

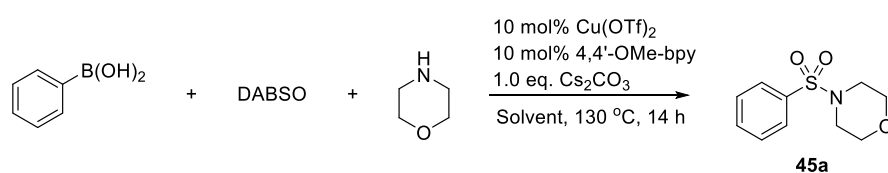
^a Reaction conditions: phenylboronic acid (0.4 mmol, 2.0 equiv.), DABSO (0.3 mmol, 2.0 equiv.), morpholine (0.2 mmol, 1.0 equiv.), Cu(OTf)₂ (10 mol%), 4,4'-dimethoxy-2,2'-bipyridine (10 mol%), DMSO (0.25 mL), 130 °C, air, 14 h. ^b Ceric ammonium nitrate. ^c *tert*-Butyl peroxybenzoate.

Table 3.3 Additive screening for the copper(II)-catalysed sulfonamide synthesis.

Having dealt with the optimisation of reagents, the solvent was our next target (**Table 3.4**).

When using a mixture of solvents, the scale of reaction was doubled for practical convenience. Unexpectedly, DMSO was the essential solvent which proved compatible

with the reaction. All other aprotic polar or apolar solvents assessed, including DMSO analogues like tetrahydrothiophene 1-oxide, resulted in no product formation. A clear trend could be seen when a co-solvent was added in DMSO. For example, the yield dropped from 74% to 41% when DMSO was diluted by half with DMF (**entry 12**), and it fell to zero when the DMSO:DMF ratio was 1:10 (**entry 13**). This high solvent dependency suggested the involvement of DMSO in the catalytic system.



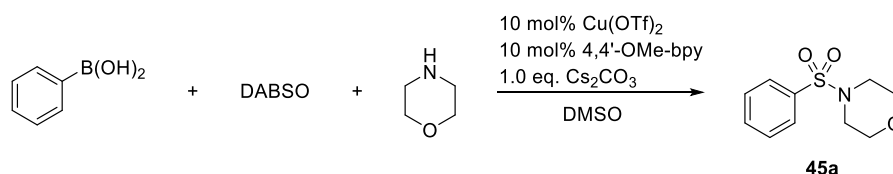
Entry ^a	Solvent (0.5 mL)	Yield (%)
1	DMSO	74
2	DMF	0
3	DMI	0
4	pentanol	0
5	DMPU	0
6	NMP	0
7	toluene	0
8	tetrahydrothiophene 1-oxide	0
9	sulfolane	20
10	pentanol : DMSO / 1:1	46
11	pentanol : DMSO / 10:1	Trace
12	DMF : DMSO / 1:1	41
13	DMF : DMSO / 10:1	Trace

^a Reaction conditions: phenylboronic acid (0.8 mmol, 2.0 equiv.), DABSO (0.8 mmol, 2.0 equiv.), morpholine (0.4 mmol, 1.0 equiv.), Cu(OTf)₂ (10 mol%), 4,4'-dimethoxybipyridine (10 mol%), Cs₂CO₃ (0.4 mmol, 1.0 equiv.), solvent (0.5 mL), 130 °C, air, 14 h

Table 3.4 Solvent screening for copper(II)-catalysed sulfonamide synthesis

At the final stage of optimisation, other variables such as temperature, time and atmosphere were studied (**Table 3.5**). Higher temperature provided a similar yield (**entry 2**) while a noticeable decrease of yield was observed with a drop in reaction temperature (**entry 2**

and **3**). Shorter reaction times left unreacted starting materials and provided a lower yield (**entry 5**), while elongated reaction time did not further improve it (**entry 6**). Conducting the reaction under an inert atmosphere did not affect the yield, meaning oxygen in the air was not a necessity of the reaction (**entry 7**). Minor water content in solvent did not affect the reaction. Both freshly distilled and dried DMSO and regularly stored DMSO presented similar results, which also marked the high robustness of this procedure. In addition, no difference was observed when the vial was covered with tin foil (**entry 8**), ruling out the possibility of a light induced mechanism.



Entry ^a	Temperature (°C)	Time (h)	Air/ N ₂	Yield (%)
1	130	14	Air	74
2	140	14	Air	72
3	125	14	Air	51
4	100	14	Air	43
5	130	6	Air	56
6	130	40	Air	73
7	130	14	N ₂	74
8 ^b	130	14	Air	74

^a Reaction conditions: phenylboronic acid (0.8 mmol, 2.0 equiv.), DABSO (0.8 mmol, 2.0 equiv.), morpholine (0.4 mmol, 1.0 equiv.), Cu(OTf)₂ (10 mol%), 4,4'-dimethoxybipyridine (10 mol%), Cs₂CO₃ (0.4 mmol, 1.0 equiv.), DMSO (0.5 mL). ^b Reaction vial was wrapped with tin foil.

Table 3.5 Optimisation of time, temperature and air content for copper(II)-catalysed sulfonamide synthesis

As a result, the optimised conditions for copper(II)-catalysed sulfonamide synthesis were identified as 1.0 equivalent of amine, 2.0 equivalents of DABSO, 2.0 equivalents of boronic acid, 1.0 equivalent of Cs₂CO₃, 10 mol% of Cu(OTf)₂ and 10 mol% of 4,4'-dimethoxybipyridine in a 0.8 M solution in DMSO, stirring under air at 130 °C for 14 hours.

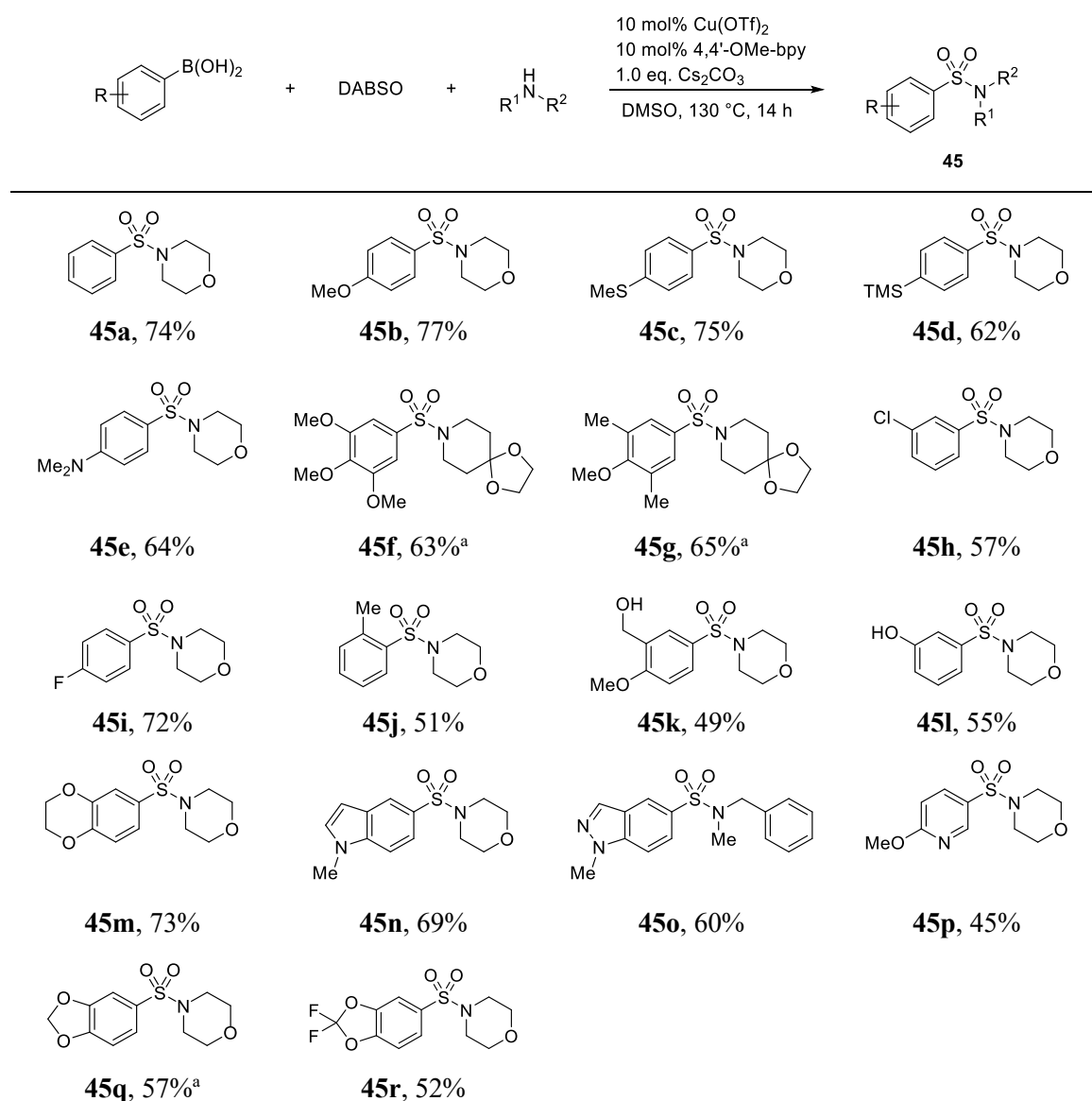
Alternative boron species and sulfur dioxide surrogates were examined under the optimised conditions. However, neither phenylboronic pinacol ester, phenyltrifluoroborate salt nor $K_2S_2O_5$ gave a comparable amount of product. Potassium phenyltrifluoroborate produced 11% of product whereas phenylboronic pinacol ester provided only 3%. The use of $K_2S_2O_5$ did not give any detectable sulfonamide product.

3.6. Reaction scope

3.6.1. Scope of boronic acids

With the optimal reaction system established, the substrate scope was examined with both reaction partners. A wide range of aryl boronic acids were initially tested using morpholine as the amine component. Towards the end of this project, part of the scope was carried out in collaboration with Dr A. Davies and Dr P. Murray. The reactions not conducted by the author are noted. Electron-rich substrates such as 4-methoxy, 4-thiomethyl, 4-trimethylsilyl and 4-dimethylaminophenylboronic acid all provided good yields (**45b** – **45e**). Changing amine partner to 1,4-dioxo-8-azaspiro[4.5]decane with the more electron-rich 3,4,5-trimethoxyphenyl and 3,5-dimethyl-4-methoxyphenylboronic acid gave similar yield of 63% and 65% respectively (**45f** and **45g**). Monochloro- and fluoro substituents provided comparable yields (**45h** and **45i**) despite their electron-withdrawing nature. Not surprisingly, the more sterically-hindered *o*-methylphenylboronic acid provided a lower 51% yield (**45j**). Reactive functional groups like benzylalcohol and phenol were well-tolerated under the reaction conditions and produced 49% and 53% of corresponding sulfonamides (**45k** and **45l**). Heterocyclic substrates were examined as well, with benzodioxane (**45m**), *N*-

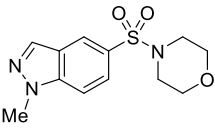
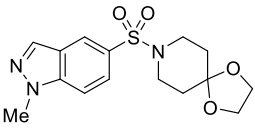
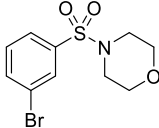
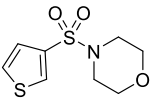
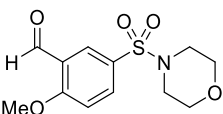
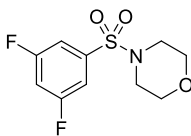
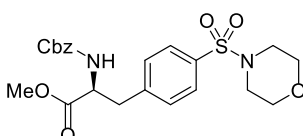
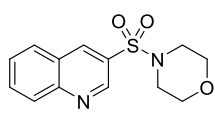
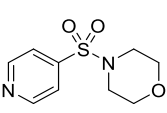
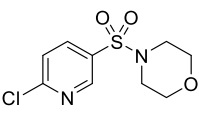
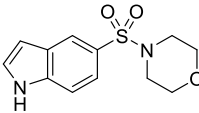
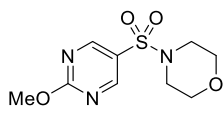
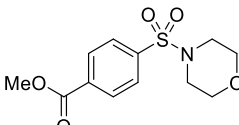
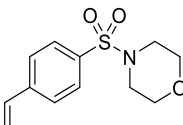
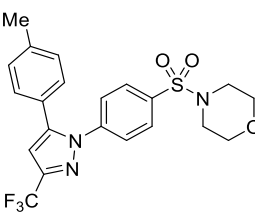
methylindole (**45n**) and *N*-methylindazole (**45o**) boronic acids providing good yields, and 2-methoxypyridyl (**45p**), benzodioxolyl (**45q**) and difluorobenzodioxolyl (**45r**) boronic acids being slightly less efficient. As for *N*-methylindazole boronic acid, methylbenzyl amine was used as the reaction partner instead of morpholine for purification reasons, but the product was still isolated in good yield.



Reaction conditions: phenylboronic acid (0.8 mmol, 2.0 equiv.), DABSO (0.8 mmol, 2.0 equiv.), morpholine (0.4 mmol, 1.0 equiv.), Cu(OTf)₂ (10 mol%), 4,4'-dimethoxybipyridine (10 mol%), Cs₂CO₃ (0.4 mmol, 1.0 equiv.), DMSO (0.5 mL), 130 °C, 14 h. ^a Product synthesised by Dr P. Murray

Table 3.6 Reaction scope of aryl boronic acids for the copper(II)-catalysed sulfonamide synthesis.

More challenging aryl boronic acids proved less successful (**Table 3.7**). As stated above, *N*-methylindazole gave mixtures of product and side product diaryl sulfide when reacting with morpholine or 1,4-dioxo-8-azaspiro[4.5]decane (**45aa** and **45ab**), albeit a high NMR yield of the designed product. 3-Bromophenylboronic acid gave a complex mixture while the NMR yield was only 20% (**45ac**). Use of a thiophene boronic acid provided just 39% yield (**45ad**). Aldehyde and difluoro substrates (**45ae** and **45af**) yielded 40% and 37%, respectively, possibly due to the high reactivity and strong electron-withdrawing nature of these functional groups. Amino ester substrate (**45ag**) was obtained with 30% yield. Quinolono boronic acid gave a clean 36% yield, however, 4-pyridyl and 2-chloro-5-pyridyl boronic acids proved incompatible (**45ah**, **45ai** and **45aj**). Employment of N-H indole (**45ak**) as well as imidazole (**45al**), 4-methyl benzoate (**45am**), 4-vinylphenyl (**45an**) and celecoxib (**45ao**) boronic acids fell into the same category and did not give any desired product. Protodeboration products as well as the diaryl sulfide were identified as major side products in these reactions.

$ \text{R-} \langle \text{C}_6\text{H}_4 \rangle \text{B(OH)}_2 + \text{DABSO} + \text{R}^1\text{NHR}^2 \xrightarrow[\text{DMSO, 130 }^\circ\text{C, 14 h}]{\begin{matrix} 10 \text{ mol\% Cu(OTf)}_2 \\ 10 \text{ mol\% 4,4'-OMe-bpy} \\ 1.0 \text{ eq. Cs}_2\text{CO}_3 \end{matrix}} \text{R-} \langle \text{C}_6\text{H}_4 \rangle \text{SO}_2\text{N(R}^1\text{)(R}^2\text{)} $		
		45
 45aa , 73% ^a + 15% diaryl sulfide	 45ab , 68% ^a + 9% diaryl sulfide	 45ac , 20% ^a + 12% diaryl sulfide
 45ad , 39%	 45ae , 40%	 45af , 37%
 45ag , 30% ^b	 45ah , 36%	 45ai , trace
 45aj , trace	 45ak , trace	 45al , trace High protodeboration
 45am , trace High protodeboration	 45an , trace High protodeboration	 45ao , trace High protodeboration

Reaction conditions: arylboronic acid (0.8 mmol, 2.0 equiv.), DABSO (0.8 mmol, 2.0 equiv.), amine (0.4 mmol, 1.0 equiv.), Cu(OTf)₂ (10 mol%), 4,4'-dimethoxybipyridine (10 mol%), Cs₂CO₃ (0.4 mmol, 1.0 equiv.), DMSO (0.5 mL), 130 °C, 14 h. ^a Inseparable mixture. ^b Product synthesised by Dr P. Murray

Table 3.7 Less successful examples of aryl boronic acids for the copper(II)-catalysed sulfonamide synthesis.

Alkenyl boronic acids were also examined (**Table 3.8**). An electron-rich styrene gave 52% yield of the desired product (**46a**), while styrene boronic acid gave a lower 43% yield (**46b**). A yield of 71% was obtained from cyclohexenyl boronic acid (**46c**), however, the related Cbz-protected amine produced only 38% of the desired product (**46d**). The less hindered *n*-hexenylboronic acid provided 37% yield (**46e**) while the acyclic methylbutenyl boronic acid failed to give any isolable product (**46h**).

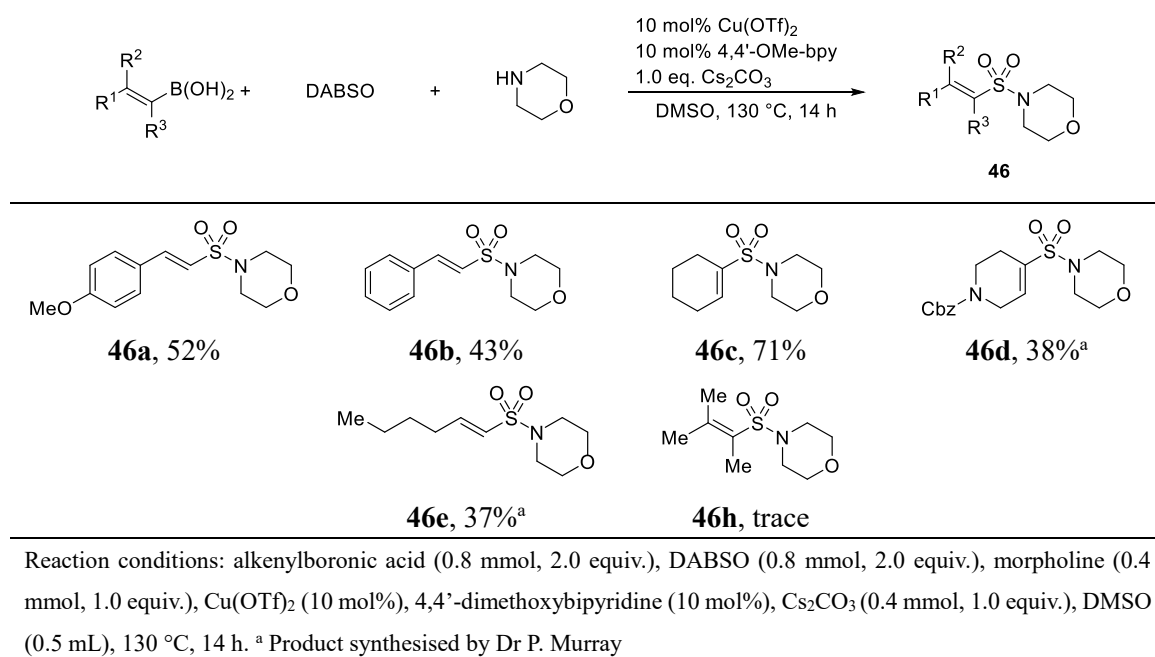


Table 3.8 Reaction scope of alkenyl boronic acids for the copper(II)-catalysed sulfonamide synthesis.

Alkyl boronic acids were also tested under the reaction conditions. No more than 6% of product could be identified from crude NMR sample with acetophenone as an internal standard, even using the higher temperature of 150 °C. As a result, further isolation and characterisation was not attempted.

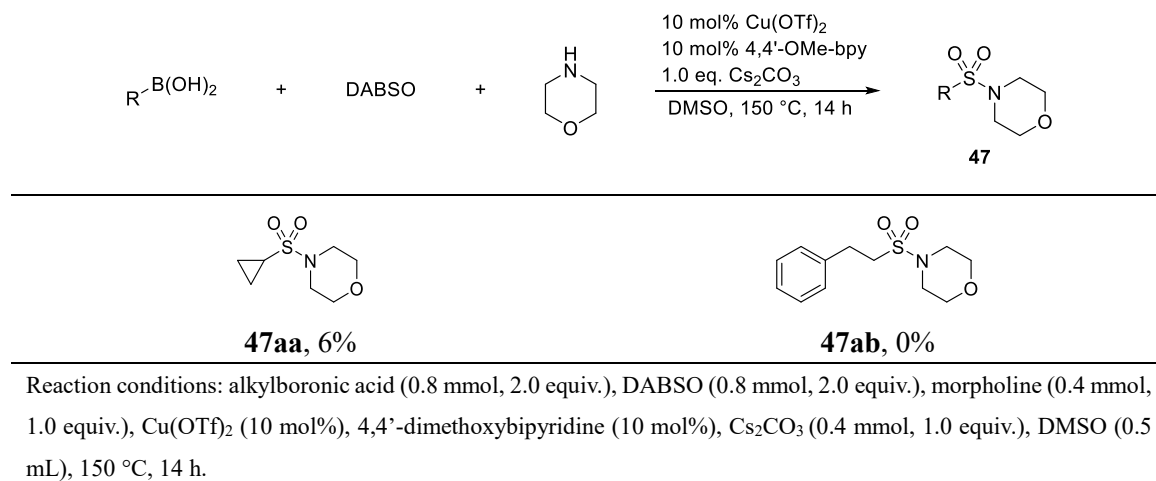
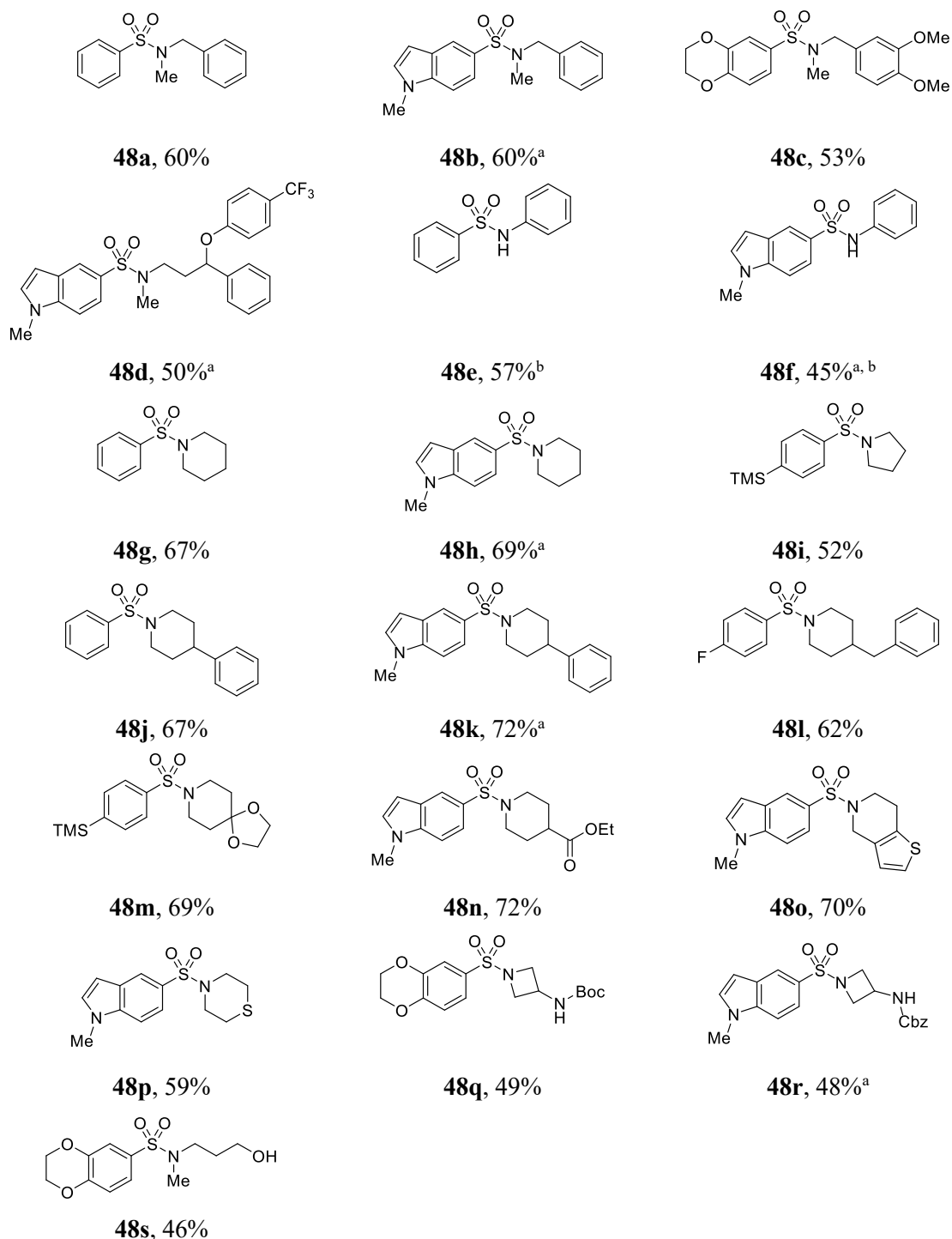
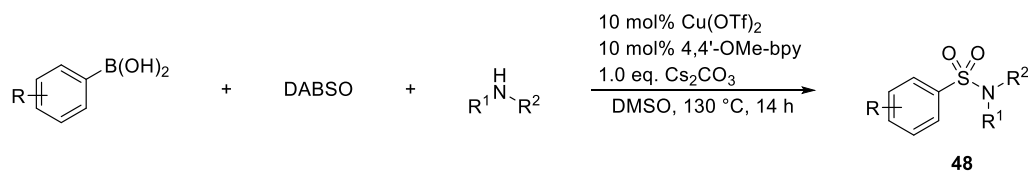


Table 3.9 Use of alkyl boronic acids in the copper(II)-catalysed sulfonamide synthesis.

3.6.2. Scope of amines

The success of the boronic acid scope allowed us to examine the amine scope in detail. Acyclic *N*-methylbenzyl amine derivatives provided good yields between 60% and 53% (**48a** – **48c**). The active pharmaceutical ingredient fluoxetine showed good compatibility with methyindole boronic acid, providing 50% of the desired sulfonamide product (**48d**). The introduction of a less nucleophilic aniline resulted in 57% of *N*-phenylbenzenesulfonamide (**48e**), albeit with an elongated 40-hour reaction time. Switching to indole boronic acid with aniline lowered the yield to 45% (**48f**). For amines with boiling points lower than the reaction temperature, such as piperidine and pyrrolidine, a sealed-tube reaction provided 67%, 69% and 52% of products, respectively (**48g**, **48h** and **48i**). A range of substituted piperidines, such as phenyl, benzyl, dioxolane, carboxyethyl and thiophenyl, were all compatible with the conditions regardless of the boronic acid reaction partner employed (**48j** – **48o**). Thiomorpholine only provided 59% product (**48p**) whilst more challenging amines like azetidines and alkanolamines resulted in slightly lower yields of 49%, 48% and 46% (**48q**, **48r** and **48s**).



Reaction conditions: boronic acid (0.8 mmol, 2.0 equiv.), DABSO (0.8 mmol, 2.0 equiv.), amine (0.4 mmol, 1.0 equiv.), Cu(OTf)₂ (10 mol%), 4,4'-dimethoxybipyridine (10 mol%), Cs₂CO₃ (0.4 mmol, 1.0 equiv.), DMSO (0.5 mL), 130 °C, 14 h. ^a Product synthesised by Dr P. Murray. ^b 40 h reaction time applied.

Table 3.10 Reaction scope of amines in the copper(II)-catalysed sulfonamide synthesis.

Piperazine derivatives showed great compatibility as well, reaction of 2-piperazinyl quinoline gave 66% yield (**48u**), and the derivatives of the active pharmaceutical ingredients amoxapine **48v** and desloratadine **48w** both provided excellent results of 71% and 74%, respectively.

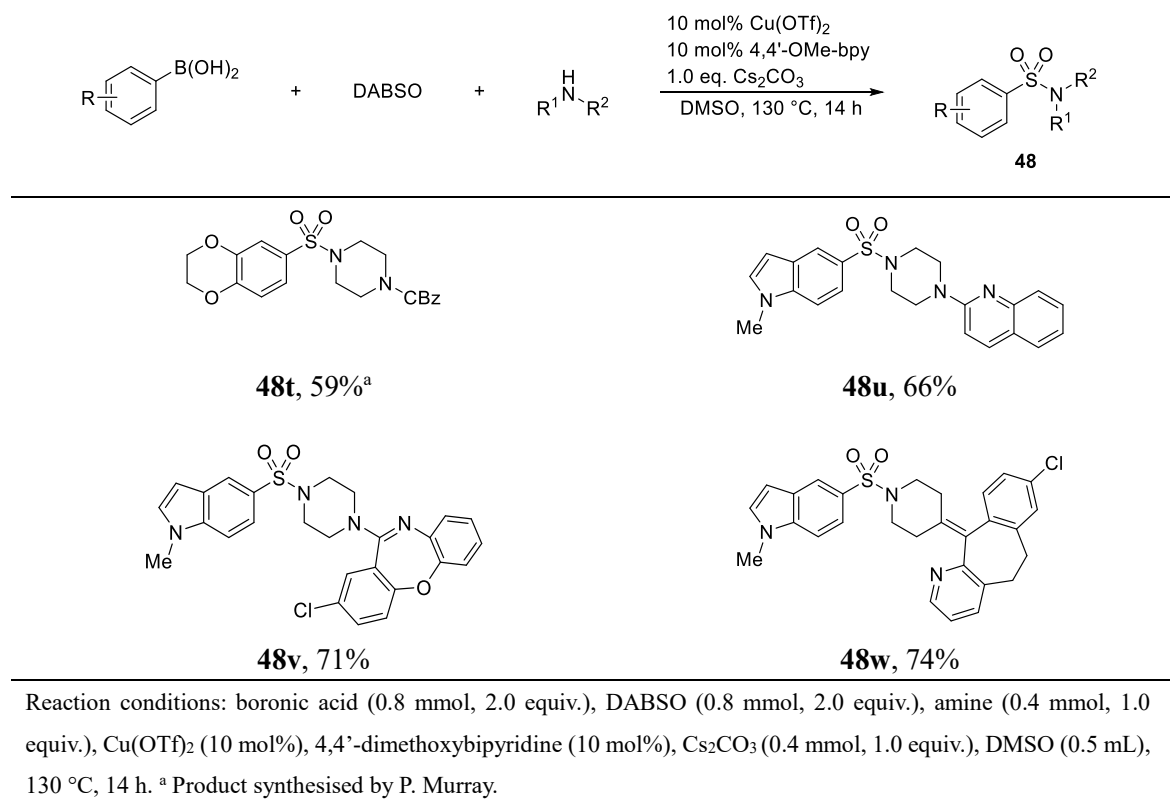
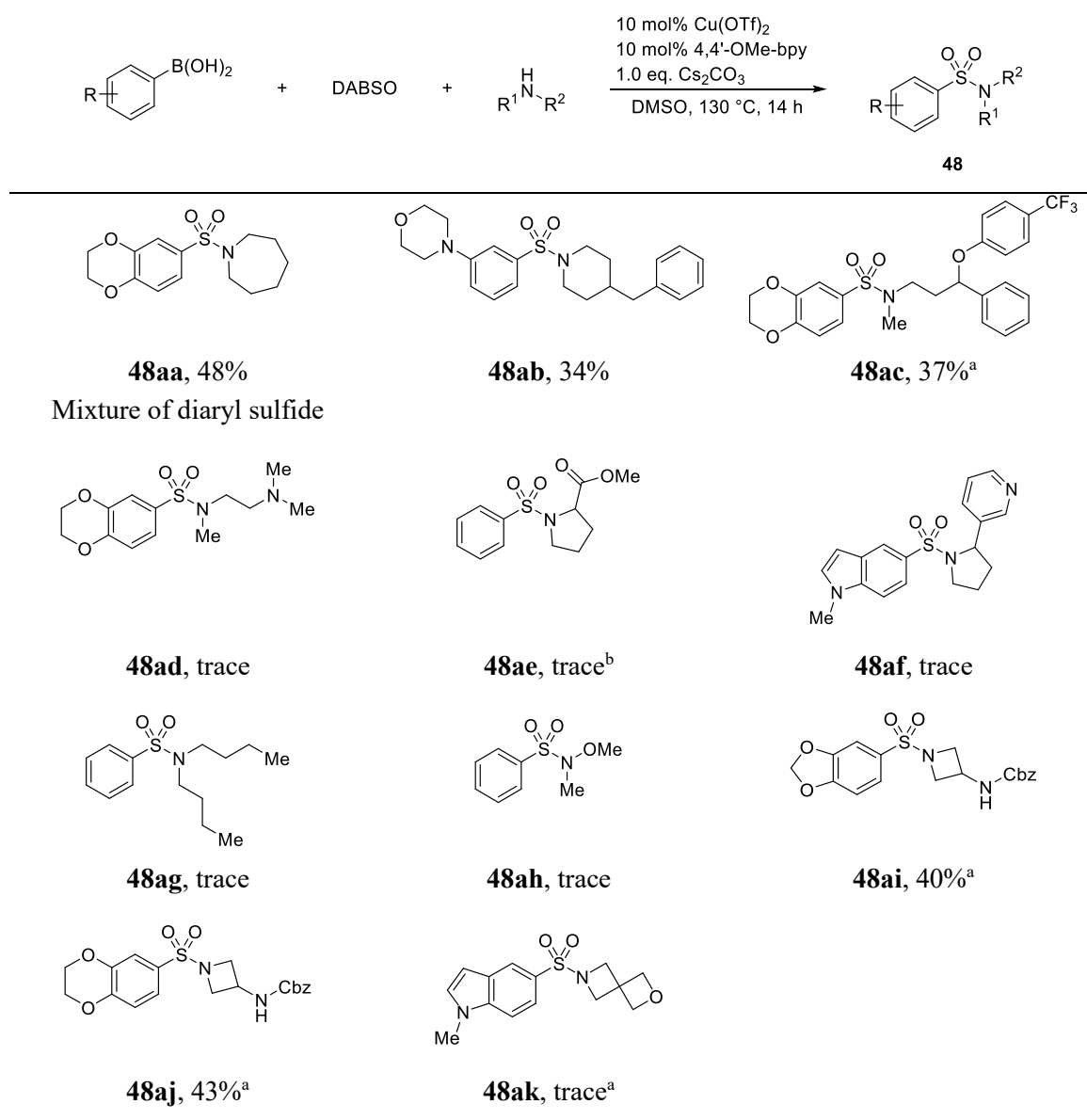


Table 3.11 Reaction scope of piperazine derivatives and active pharmaceutical ingredients.

For some amines, the results were not as satisfying (**Table 3.12**). Reaction with azepane unfortunately gave an inseparable mixture of product and the product of side-reaction, and the yield was only 48% (**48aa**). Fluoxetine with 1,4-benzodioxane-6-boronic acid produced only 37% of product (**48ac**), less efficient compared to the *N*-methylindole boronic acid (**48d**) above. *N,N',N'*-Trimethylethane-1,2-diamine and L-proline provided no trace of product (**48ad** and **48ae**), possibly due to the bidentate coordination ability of the amines.

More sterically hindered 3-(pyrrolidin-2-yl)pyridine and di-*n*-butyl amine did not produce any product either (**48af** and **48ag**). Benzodioxole and benzodioxane boronic acids provided less product compared to the *N*-methylindole variant when coupled with the Cbz-protected aminoazetidine, giving 40% and 43% yield respectively (**48ai** and **48aj**). The more challenging 2-oxa-6-azaspiro[3.3]heptane sublimed out of the reaction mixture under the reaction conditions (**48ak**).



Reaction conditions: boronic acid (0.8 mmol, 2.0 equiv.), DABSO (0.8 mmol, 2.0 equiv.), amine (0.4 mmol, 1.0 equiv.), Cu(OTf)₂ (10 mol%), 4,4'-dimethoxybipyridine (10 mol%), Cs₂CO₃ (0.4 mmol, 1.0 equiv.), DMSO (0.5 mL), 130 °C, 14 h. ^a Experiments conducted by P. Murray. ^b The same result was obtained when employing the corresponding HCl salt.

Table 3.12 Less successful examples of amines in the copper(II)-catalysed sulfonamide synthesis.

The alkyl primary amines employed were both unsuccessful (**Table 3.13**). Alternative ligands with higher steric hindrance such as 6,6'-dimethyl-2,2'-bipyridine and terpyridine were tested in combination with various equivalents of bases in order to try and reduce the likelihood of the primary amines coordinating to the copper. However, no product was detected.

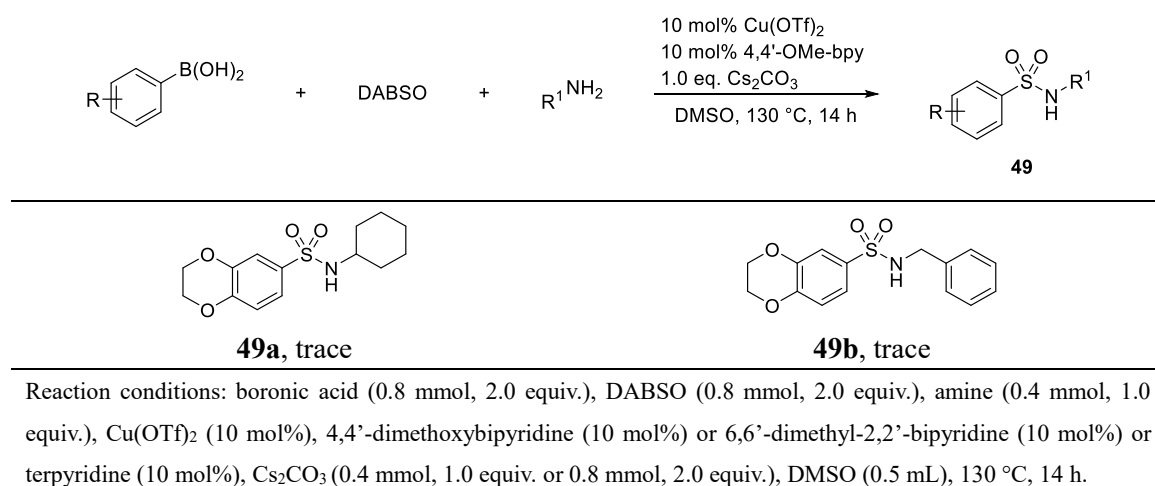


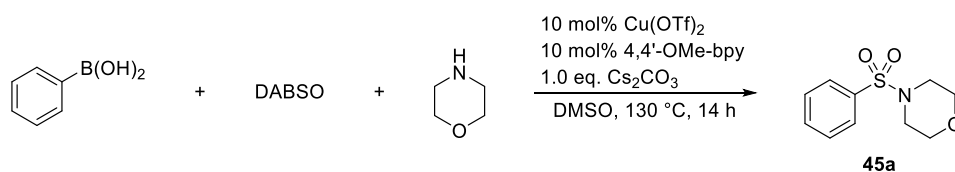
Table 3.13 Scope of alkyl primary amines in the copper(II)-catalysed sulfonamide synthesis.

3.7. Controlled experiments

Although at the first stage of optimisation we discovered that copper(II) catalysts gave results similar to copper(I) in the sulfonation reaction (**Table 2.1**), during the optimisation and the scope of this project, it was observed that there was a distinct difference between the copper(II)-catalysed sulfonamide synthesis and the previous copper(I)-catalysed sulfonylative Suzuki reaction. For example, thiosulfonates were never detected in the

sulfonamide reaction despite being a frequent side-product in the Suzuki process. Addition of inorganic bases was not effective in the sulfone chemistry, though a noticeable performance enhancement was observed here *via* the addition of cesium carbonate. Also, the high solvent dependency observed in this reaction was quite distinctive as the use of DMSO was essential. All of these suggested that two different mechanisms were taking place in these two reactions. Therefore, control experiments were executed to gain further understanding about the reaction mechanism of the copper(II)-catalysed sulfonamide reaction.

Initially we examined the reaction by removing the copper catalyst. Surprisingly the reaction still produced 12% product without base and 16% with Cs₂CO₃ (**Table 3.14**, **entries 1 and 2**), indicating a background reaction was occurring in the absence of metal catalyst, and base was only a promoter in both sets of conditions, with or without metal. Replacing copper with Lewis acids such as Sc(OTf)₂ and FeCl₃ did not promote the yield like the original Cu(OTf)₂ (**entries 3 and 4**), suggesting that the copper catalyst is not acting as a Lewis acid in the process.

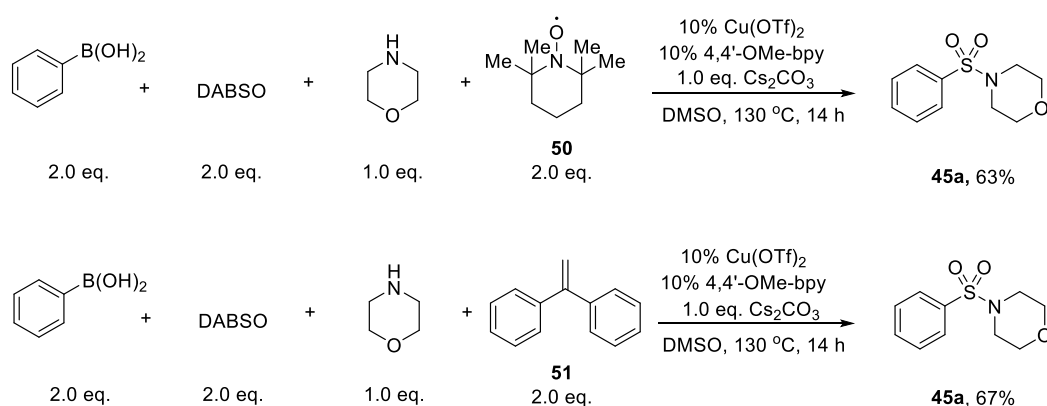


Entry ^a	Variation from optimised conditions	Yield (%)
1	No Cu(OTf) ₂ , 4,4'-OMe-bpy, or base	12
2	No Cu(OTf) ₂ or 4,4'-OMe-bpy	16
3	10 mol% Sc(OTf) ₂ instead of Cu(OTf) ₂ and 4,4'-OMe-bpy	18
4	1.0 eq. of FeCl ₃ instead of Cu(OTf) ₂ and 4,4'-OMe-bpy	16

^a Reaction conditions: phenylboronic acid (0.8 mmol, 2.0 equiv.), DABSO (0.8 mmol, 2.0 equiv.), morpholine (0.4 mmol, 1.0 equiv.), Cu(OTf)₂ (10 mol%), 4,4'-dimethoxybipyridine (10 mol%), Cs₂CO₃ (0.4 mmol, 1.0 equiv.), DMSO (0.5 mL), 130 °C, 14 h.

Table 3.14 Control experiments based on variation of the optimised conditions.

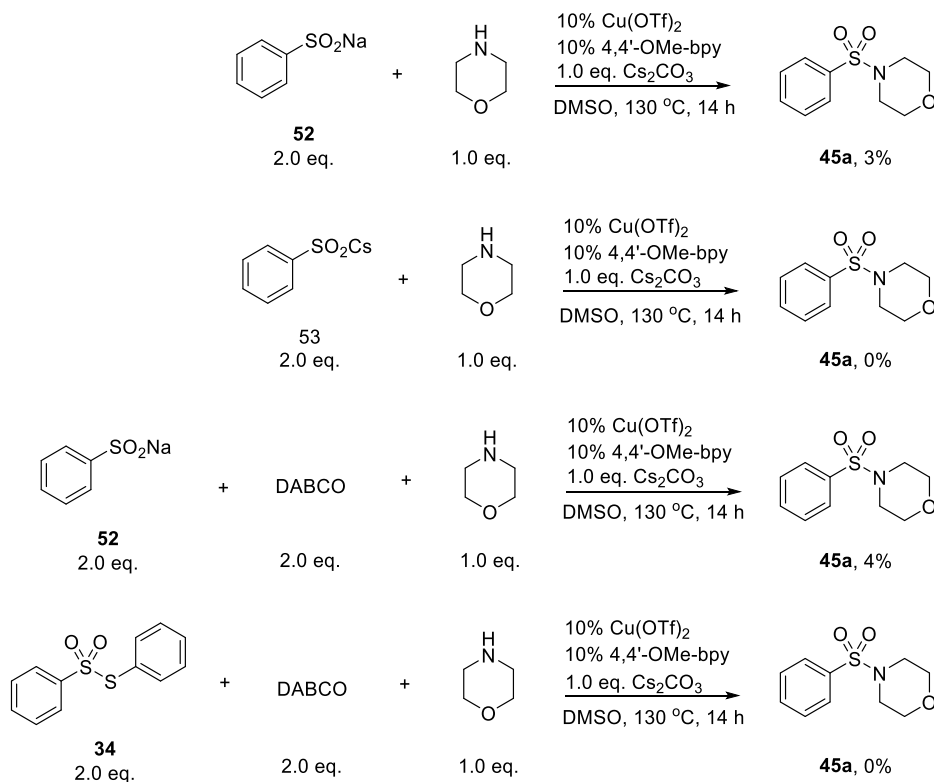
Copper catalysts are known promoters of radical sulfonylation reactions,^[190] which has also been reported using DABSO.^[129] However, when we applied two equivalents of TEMPO **50**, the reaction was not inhibited like other radical reactions, and 63% of sulfonamide product was isolated (**Scheme 3.3**). Addition of another radical trap, 1,1-diphenylethylene **51**, resulted in 67% of product **45a** and 83% of the radical trap being recovered. Therefore, we concluded that the copper(II)-catalysed sulfonamide synthesis of boronic acids does not proceed through a radical process.



Scheme 3.3 Test reactions with radical traps.

Some potential intermediates were also prepared and subjected to the reaction conditions to gain more insight about the reaction mechanism (**Scheme 3.4**). Sodium benzenesulfinate **52** and morpholine only produced trace sulfonamide product and additional DABCO in the system did not change the outcome. The more organo-soluble caesium benzenesulfinate **53** provided no product either, which is again surprising considering sodium sulfonates and amines have been reported producing sulfonamides under similar conditions, when CuBr2 and DMSO at 100 °C are used (see **Scheme 3.1**).^[183a] Another potential intermediate, the thiosulfonate **34**, also failed to give any sulfonamide, while NMR analysis after work-up

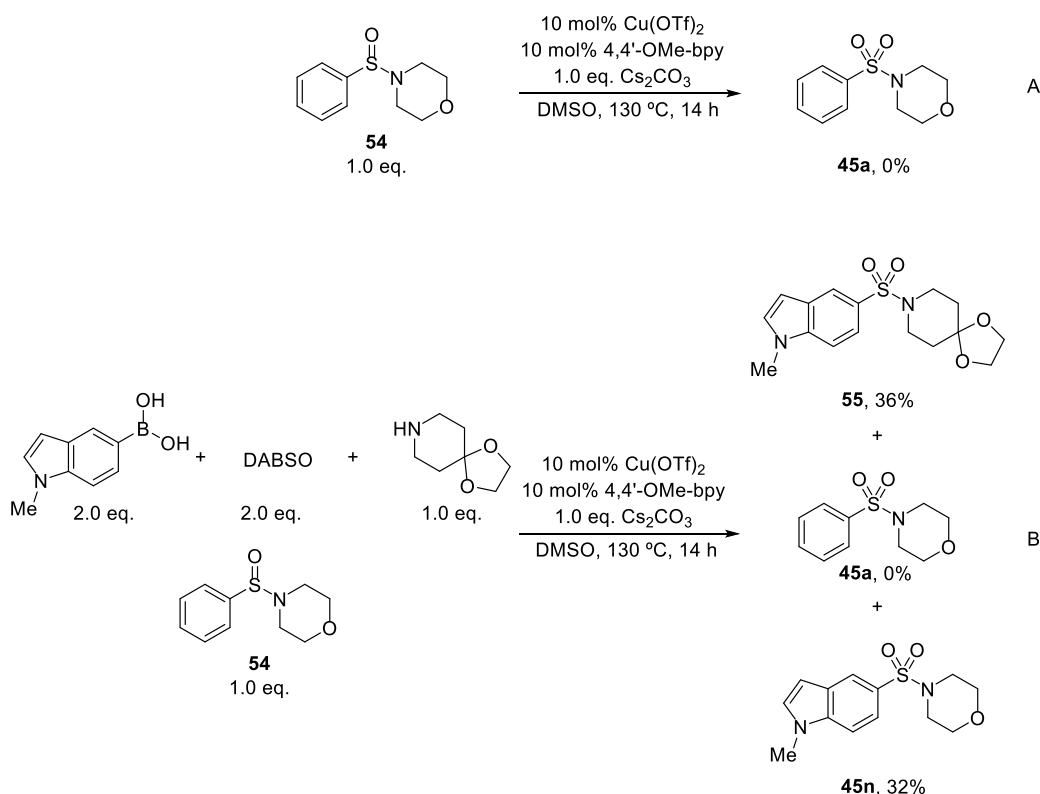
showed no sign of thiosulfonate left in the residue. This suggests that thiosulfonate is unlikely to be a key intermediate in the mechanism, but the possibility of disproportionation happening during the reaction process could not be ruled out completely.



Scheme 3.4 Test reactions with potential intermediates.

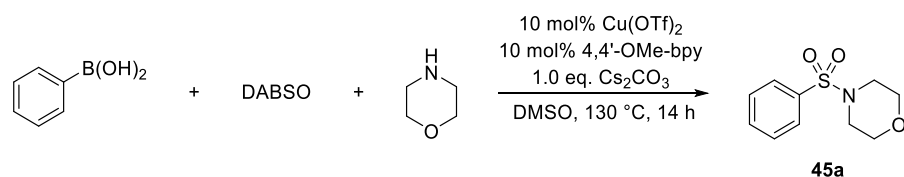
An aryl sulfinamide **54** was synthesised and subjected to the optimised conditions, to probe if the reaction proceeded *via* the oxidation of a sulfinamide (**Scheme 3.5**). No sulfonamide was detected when the phenyl morpholino sulfinamide was treated alone with the optimised system (**Equation A**). From a mixture of phenyl morpholino sulfinamide **54** with *N*-methylindole boronic acid, DABSO and 1,4-dioxo-8-azaspiro[4.5]decane, 36% of the indole piperidiny l sulfonamide **55** was obtained while no sign of the oxidised phenyl morpholino sulfonamide **45a** was detected (**Equation B**). The 32% of the cross product, indole morpholinyl sulfonamide **45n**, was most likely due to the generation of free

morpholine from the decomposition of sulfinamide **54** under the reaction conditions.^[191]



Scheme 3.5 Test reactions with sulfinamide, conducted by Dr A. Davies and Dr P. Murray.

During the optimisation and scoping of the reaction, we found that reactions involving amine hydrochloride salts all failed to proceed. To examine this problem, morpholine hydrochloride salt was prepared and subjected to the reaction (**Table 3.15, entries 1 and 2**). The reaction was almost completely shut down with only trace amount of product. Moreover, one equivalent of sodium chloride added to the optimised reaction conditions was also enough to stop the generation of the desired sulfonamide **45a** (**entry 3**), although the exact mechanism of chloride inhibition is unknown.



Entry ^a	Variation from optimised conditions	Yield (%)
1	Morpholine hydrochloride salt instead of morpholine	0
2	Morpholine hydrochloride salt instead of morpholine, 2.0 eq. Cs ₂ CO ₃	0
3	Additional 1.0 eq. NaCl	0

^a Reaction conditions: phenylboronic acid (0.8 mmol, 2.0 equiv.), DABSO (0.8 mmol, 2.0 equiv.), morpholine (0.4 mmol, 1.0 equiv.), Cu(OTf)₂ (10 mol%), 4,4'-dimethoxybipyridine (10 mol%), Cs₂CO₃ (0.4 mmol, 1.0 equiv.), DMSO (0.5 mL), 130 °C, 14 h.

Table 3.15 Test reactions with amine hydrochloride salts.

Based on our observations and the control experiments discussed above, and recent mechanistic studies of Chan-Lam amination,^[192] we hypothesise the mechanism of the reaction as follows (**Figure 3.2**). Firstly, sulfur dioxide is transferred from DABSO onto the amine with the help of base (**A**). The amine-sulfur dioxide intermediate then undergoes a ligand exchange with the copper(II) catalyst to form the copper (II) sulfamidite complex (**B**). Transmetallation with the boronic acid produces complex **C** and disproportionation of **C** gives a more reactive Cu(III) species (**D**). A reductive elimination finally provides the targeted product sulfonamide and the resulting Cu(I) catalyst (**E**) is oxidised back to copper(II) in the presence of DMSO. It should be noted that the distinctive smell of dimethylsulfide is present at the end of these reactions.

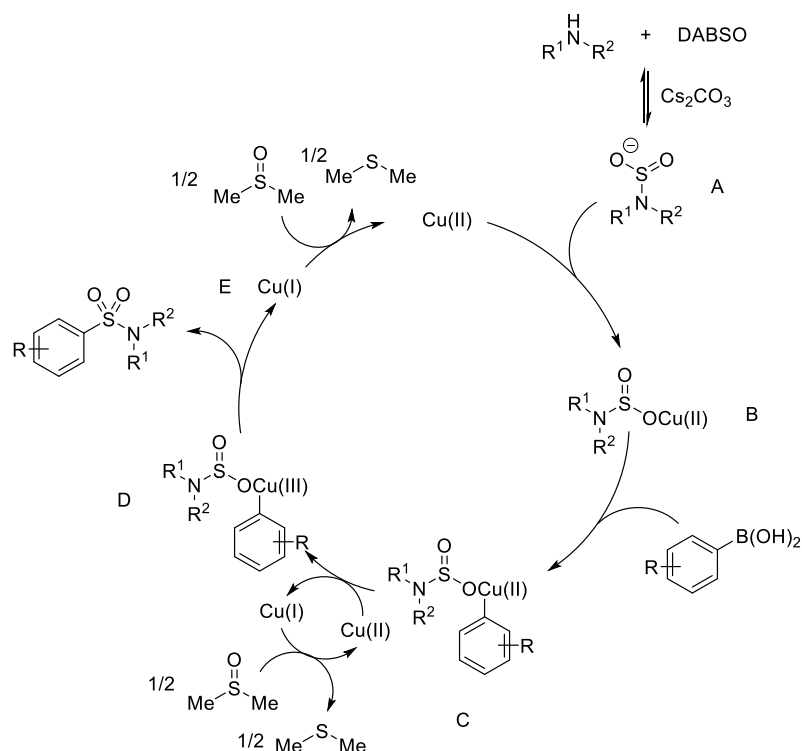
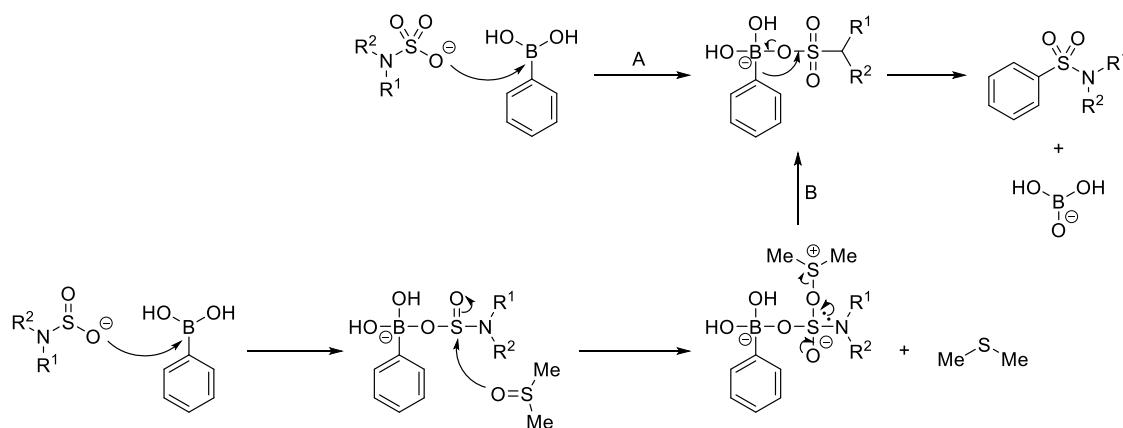


Figure 3.2 Proposed mechanism for copper(II)-catalysed sulfonamide synthesis.

For the background reaction that occurred without copper, we suggest an alternative mechanism shown below (**Scheme 3.6**). Sulfur trioxide amine complex is generated in the presence of DMSO under basic conditions. The sulfamidate then attacks the boron atom to give a boron anion and is followed by aryl migration and borate cleavage to produce the sulfonamide (**Route A**). On the other hand, the sulfamidite could attack the boron atom directly and the boron anion is oxidised by DMSO then the aryl group migrates to give the sulfonamide product (**Route B**).



Scheme 3.6 Proposed mechanism for the background reaction.

3.8. Project summary

In this project, a versatile one-step DABSO-based copper(II)-catalysed reaction was developed for the synthesis of sulfonamides from readily-available boronic acids and amines. This method avoids the use of either hazardous additives or difficult to synthesise starting materials. Good varieties of aromatic and heteroaromatic boronic acids as well as alkenyl boronic acids were tolerated. A wide range of amines and anilines are tolerated with excellent yields. Active pharmaceutical ingredients such as amoxapine, desloratadine and fluoxetine could also be employed to give the corresponding sulfonamides.

In addition, a series of control experiments were executed to elucidate the possible reaction mechanism. The involvement of radicals was ruled out along with the possibility of Lewis acid catalysis. Some potential intermediates such as sulfinate salts, thiosulfonates and sulfonamides were also tested and shown to be unlikely intermediates in the reaction. Further investigation is underway, whilst currently we propose our mechanism to be a copper(II)-catalysed Chan-Lam type sulfonamide synthesis.

Chapter 4: Synthesis of benzoisothiazoles *via* an aryne intermediate

4.1. Benzoisothiazoles and their preparation

Substituted benzoisothiazoles have been found in a number of molecules of medicinal importance.^[193] In particular, the 3-amino substituted benzoisothiazole is present in a series of atypical antipsychotics (AAPs), for example lurasidone, tiospirone, ziprasidone and perospirone (**Figure 4.1**).^[194]

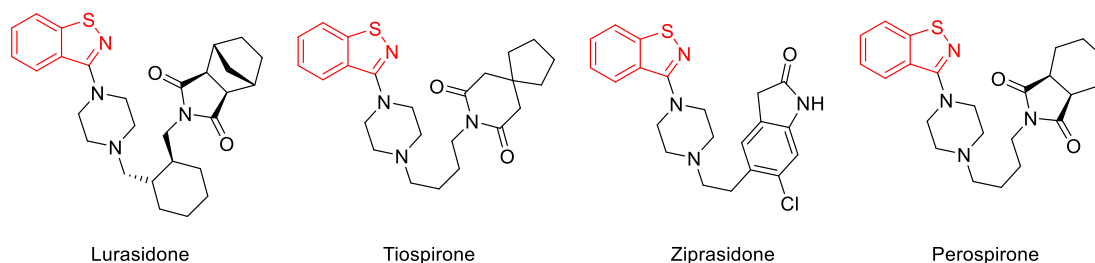
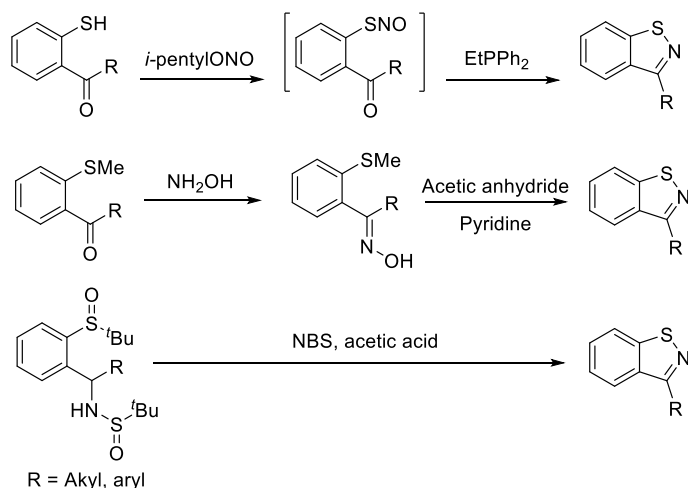


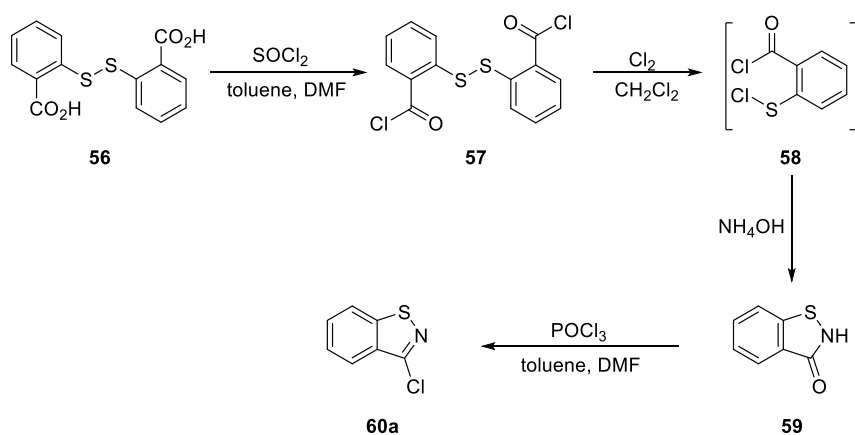
Figure 4.1 Benzoisothiazole containing drug molecules

Owing to their importance in medicinal chemistry, benzoisothiazoles have been synthesised *via* several routes (**Scheme 4.1**).^[195] However, many of these are applicable only to aryl or alkyl substrates, and have limitations when synthesising 3-hetero-substituted benzoisothiazoles.



Scheme 4.1 Examples of 3-substituted benzoisothiazole synthesis

Conventional syntheses of 3-amino substituted benzoisothiazoles usually consist of substitution reactions of 3-chlorobenzoisothiazole **60** (Scheme 4.2).^[196] This compound is in turn obtained from a series of transformation from 2,2'-dithiodibenzoic acid **56**, finishing with chlorination of benzoisothiazolinone **59**.^[197] This whole process requires the use of hazardous reagents such as thionyl chloride, chlorine gas, and phosphorus oxychloride. These strong chlorinating reagents not only raise safety concerns but also constrain the diversity of this procedure with poor functional group tolerance due to their high reactivity.



Scheme 4.2 Precedented synthesis of 3-chlorobenzoisothiazole

Hence, an improved route with which to access 3-heterosubstituted benzoisothiazoles is highly sought after, especially one that is more user- and environmental-friendly. In addition, it would also be helpful if functional groups could be readily tolerated in the benzoisothiazole products.

4.2. Benzyne and its precursors

Benzyne, especially *ortho*-benzyne, has been studied extensively for more than a century.^[198] Bearing a triple bond in a 6-membered ring aromatic system, benzyne is extremely reactive and typically appears as an intermediate. A range of precursors and associated experimental conditions have been developed. The first evidence for the existence of *ortho*-benzyne was published by Wittig *et al.* in 1940, where fluorobenzene was used as a benzyne precursor and phenyl lithium was used as a base to generate benzyne.^[199] In the following years, especially around the 1960s, more combinations of halobenzenes, *ortho*-substituted dihalobenzenes or their analogues, in combination with different strong bases, were developed as a means to generate benzyne in a similar manner.^[200] Additionally, different types of precursors and reaction conditions have also been discovered, such as the thermolysis of benzenediazonium-2-carboxylate,^[201] benzo-thiadiazole dioxide,^[202] diphenyliodonium-2-carboxylate,^[203] or the oxidative cleavage of aminobenzotriazole (**Figure 4.2**).^[204] These developments mark the advances from generations of chemists trying to understand benzyne chemistry and applying benzyne in organic synthesis.

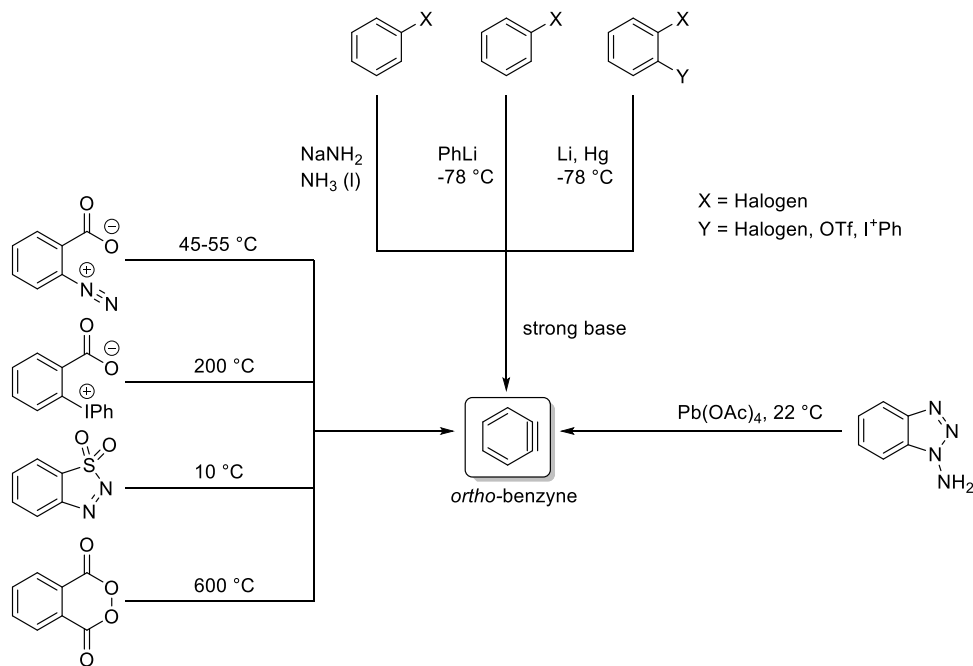
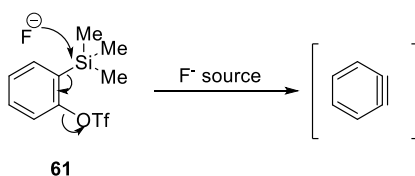


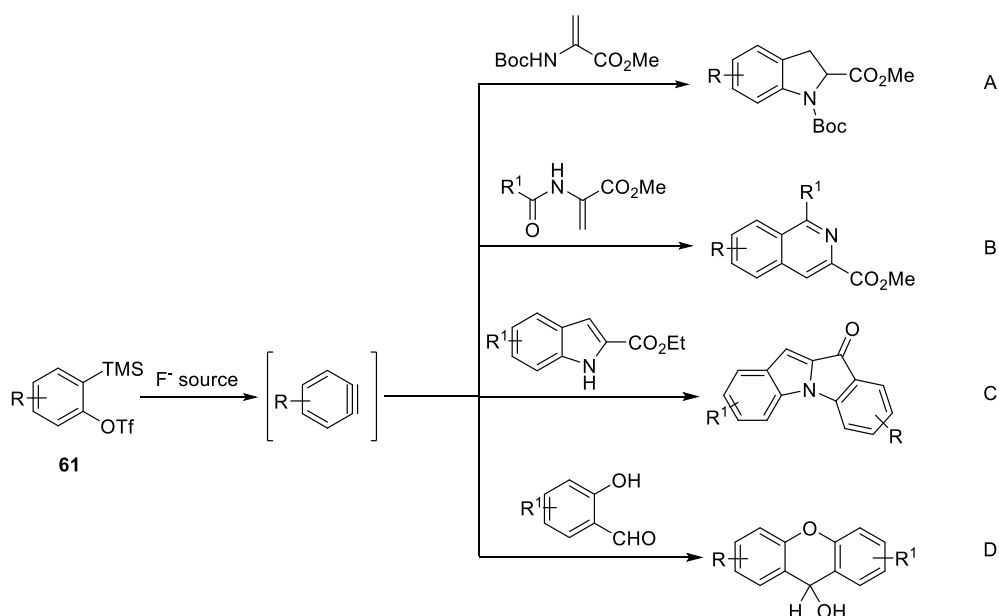
Figure 4.2 Examples of benzyne generation methods

In 1983, Kobayashi and his team reported a new approach to benzyne from a 2-(trimethylsilyl)phenyl triflate precursor **61**.^[205] When treated with a fluoride source, this precursor is attacked by the fluoride ion at the silicon atom. Subsequent extrusion of gaseous trimethylsilyl fluoride and elimination of the triflate anion complete the benzyne generation process (**Scheme 4.3**). This approach avoids the use of pyrophoric and highly reactive bases, heat- and shock-sensitive precursors, or toxic oxidants, providing more possibilities for the synthetic application of benzyne chemistry.



Scheme 4.3 Illustration of benzyne generation method from the Kobayashi precursor

Although the original research did not garner much attention at first, the fluoride-induced Kobayashi aryne protocol has since become one of the most popular methods for aryne generation. A number of exciting chemical transformations have been developed based on this precursor, including ones targeting benzene-fused heterocycles (**Scheme 4.4**).^[206] Notable examples are the indoline and isoquinoline syntheses by Stoltz and coworkers (**Equation A and B**),^[207] polycyclic indolone synthesis by Giacometti *et al.* (**Equation C**),^[208] and xanthene synthesis by Okuma *et al.* (**Equation D**).^[209]

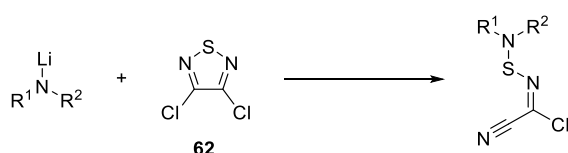


Scheme 4.4 Examples of benzyne based heterocycle synthesis

These examples encouraged us to seek potential routes from benzyne to benzoisothiazoles, which would require the formation of both C-S and C-C bonds in a one-pot process. To achieve this, the other reaction partner needed to be designed with care. One limitation of benzyne chemistry is the difficulty of controlling the regioselectivity of the product. However, it would still be intriguing to develop synthetic routes to benzoisothiazole using aryne chemistry.

4.3. Thiadiazoles as reactant

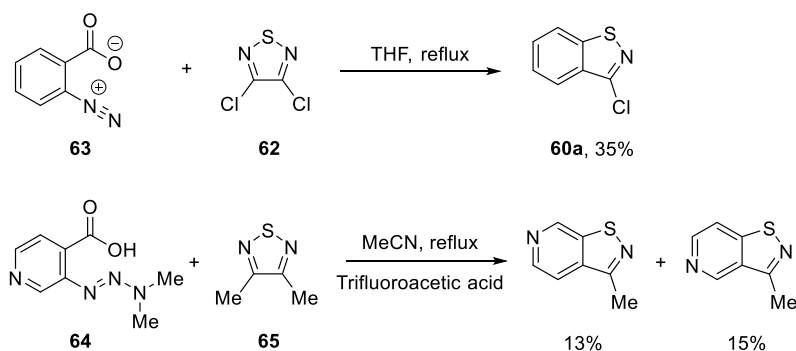
One of the ideas to realise this goal was to combine benzyne with a nucleophile that has a S-N=C motif in place, and here in this project, 1,2,5-thiadiazoles were chosen as our primary subject. 1,2,5-Thiadiazoles and their derivatives are of medicinal interest themselves. With properties such as antitumor effects or acting as a biological inhibitor to treat inflammation and metabolic disorders, they have been studied widely in medicinal chemistry and biology.^[210] Unlike their biological applications, their chemical reactivity is somewhat less developed.^[211] To the best of our knowledge, although there have been various reactions with thiadiazole derivatives reported, many of them involve substitution reaction on the 3- or 4- position.^[212] Very few example of reactions on the thiadiazole ring are reported; one example is the ring-opening reaction with lithium amides (**Scheme 4.5**).^[213]



Scheme 4.5 Example of reaction using 1,2,5-thiadiazole core

To our delight, among the very few reports, Bryce *et al.* and Chimichi *et al.* have independently shown that 1,2,5-thiadiazole is known to deliver the S-C=N fragment to arynes to form the targeted benzoisothiazole (**Scheme 4.6**).^[214] However, the use of benzenediazonium-2-carboxylate **63** or 3-(3,3-dimethyltriazene-1-yl)pyridine-4-carboxylic acid **64** as the aryne precursor only provided the products in low to modest yield with 7

examples being reported in total.



Scheme 4.6 Previous examples of benzyne/pyridyne and thiadiazole reaction

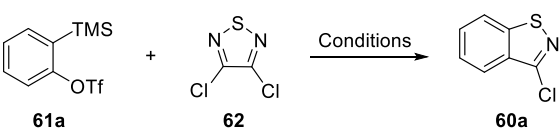
4.4. Project aim

To avoid the use of highly hazardous and difficult-to-handle reagents has been a goal of synthetic chemists for many years. With the value of 3-hetero substituted benzoisothiazoles and the limited substrate tolerance of conventional synthetic procedures, improved methods for the synthesis of these substrates are highly sought. Low yields and limited scope of current methods for benzoisothiazole synthesis from benzyne served as additional motivation for us to seek improvements, and to produce novel multi-substituted benzoisothiazole derivatives. In this project, we speculated that the use of the Kobayashi-type benzyne precursor **61**, and the associated mild reaction conditions, should enable us to solve this threefold challenge.

4.5. Reaction conditions and optimisation

The initial reaction was carried out under conditions frequently applied in benzyne chemistry using the Kobayashi benzyne precursor (**Table 4.1**).^[215] Using excess benzyne precursor **61a**, dichlorothiadiazoole **62** and CsF as fluoride source with acetonitrile as

solvent at 60 °C for 20 hours, the reaction resulted in 45% of 3-chlorobenzoisothiazole **60a** (**entry 1**). Changing the solvent to another commonly used solvent for benzyne chemistry, THF,^[216] provided a significant boost in the yield (**entry 2**). Unfortunately, further variation of the reaction conditions, such as longer reaction times (**entry 3**), lower temperature (**entry 4**) or variation of the stoichiometry between the two coupling partners (**entries 5-8**) failed to offer any improvement in yield. Higher temperature and switching the solvent back to acetonitrile, however, did not convert to a higher yield (**entry 9**). TBAF could also be employed as the fluoride source, with the use of a lower reaction temperature, allowing a 75% yield of the targeted benzoisothiazole to be achieved (**entry 10**). However, other fluoride sources, for example TBAT and KF, only served to diminish the yields (**entries 11 and 12**). Hence, the optimised condition was concluded as 1.4 equivalents of benzyne precursor, 1.0 equivalent of thiadiazole, 2.8 equivalents of CsF, in THF at 66 °C for 20 hours (**entry 2**).

						
Entry ^a	Equiv. 61a	Fluoride source (equiv.)	Solvent	Time (h)	Temperature (°C)	Yield (%) ^b
1	1.4	CsF (2.8)	MeCN	20	60	45
2	1.4	CsF (2.8)	THF	20	60	76
3	2.0	CsF (4.0)	THF	36	60	45
4	1.4	CsF (2.8)	THF	48	22	43
5 ^c	1.0	CsF (2.0)	THF	20	66	33
6 ^d	1.0	CsF (2.0)	THF	20	66	32
7	1.0	CsF (3.0)	THF	20	66	55
8	1.0	CsF (2.0)	THF	20	66	40
9	1.0	CsF (4.0)	MeCN	20	82	65
10 ^e	1.4	TBAF (2.8)	THF	8	22	75
11	1.4	TBAT (2.8)	THF	20	66	56
12	1.4	KF (2.8) + 18-crown-6 (2.8)	THF	20	66	26

^a Reaction conditions: **62** (1.0 equiv.), 0.33 M. ^b Isolated yields. ^c **62** (2.0 equiv.). ^d **62** (3.0 equiv.). ^e Reaction temperature -55 °C to 22 °C over 12 h.

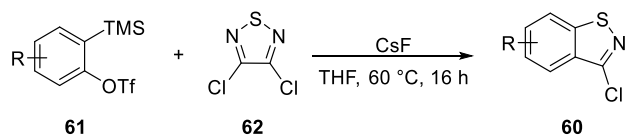
Table 4.1 Optimisation of reaction conditions for the formation of benzoisothiazole **60a** from **61a** and **62**.

4.6. Reaction Scope

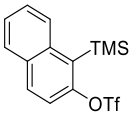
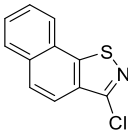
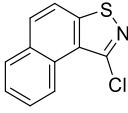
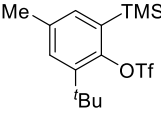
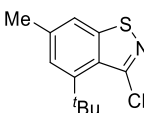
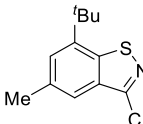
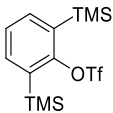
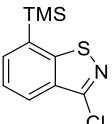
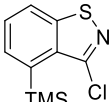
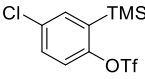
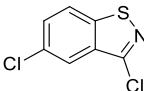
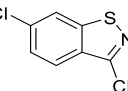
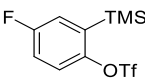
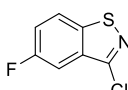
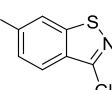
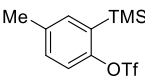
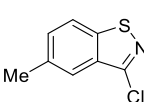
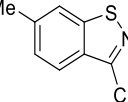
4.6.1. Scope of various benzyne precursors

Building on the initial optimised reaction, a range of benzyne precursors **61** were synthesised^[217] and submitted to the reaction conditions (**Table 4.2**). A series of symmetrical precursors combined effectively with thiadiazole to give the 3-chloro-substituted benzoisothiazoles **60b** – **60f** (**entries 1 – 5**), although the electron-poor difluoro-derivative was less efficient **60f** (**entry 5**) and the 3,6-dimethyl-substituted benzyne precursor **61e** gave a lower yield, likely due to the steric hindrance of the methyl groups

(**entry 4**). Among the remaining benzyne precursors, the 6-methoxy (**entry 6**) and 3-bromo (**entry 7**) variants **61g** and **61h** delivered only a single regioisomer, and the 4-bromo-6-methoxy disubstituted substrate **61i** provided the 6-bromo-4-methoxy-substituted adduct **60i** as a major product in a ratio of 8:1 (**entry 8**). The rest of the unsymmetrical benzyne precursors **61j** – **61q** synthesised in this project all delivered a mixture of both isomers with poor selectivity (**entries 9 – 15**). Substrates with substituents more remote from the reaction centre understandably demonstrated weaker control on the selectivity (**entries 13 – 15**). Interestingly, even with the high steric demand from 4-methyl-6-*t*-butyl (**entry 11**) and 6-trimethylsilyl substrates (**entry 12**), the reaction still generated benzoisothiazoles with poor regioselectivity.



Entry ^a	Precursor (1)	Product(s)	Yield (ratio)
1	61b	60b	96%
2	61c	60c	96%
3	61d	60d	93%
4	61e	60e	67%
5	61f	60f	52%
6	61g	60g	70%
7	61h	60h	40%
8	61i	60i 60i'	78% (8:1)
9	61j	60j 60j'	83% (1:1) ^b

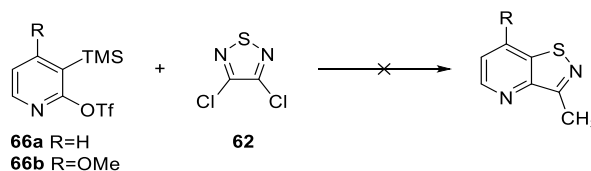
10	 61k	 60k	 60k'	97% (2.5:1)
11	 61l	 60l	 60l'	82% (2:1) ^b
12	 61m	 60m	 60m'	64% (2:1)
13	 61n	 60n	 60n'	76% (1.9:1) ^b
14	 61o	 60o	 60o'	68% (2:1) ^b
15	 61p	 60p	 60p'	64% (1:1) ^b

^a Reaction conditions: aryne precursor **61** (1.4 equiv.), dichlorothiadiazoole **62** (1.0 equiv.), CsF (2.8 equiv.), 0.33 M, 60 °C, 16 h. Isolated yields. ^b Regioisomers inseparable.

Table 4.2 The synthesis of 3-chlorobenzoisothiazoles **60** using thiadiazoole **62**.

Control of regioselectivity has been a long discussed topic in benzyne chemistry. Many of the literature precedents in benzyne chemistry employ mostly symmetrical benzyne for their scope, possibly due to the poor selectivity of unsymmetrical benzyne in the reaction. Multiple works presented by Neil Garg and his group provide an excellent study on selectivity, many of which, especially the aryne distortion model, have shown great consistency with our observations.^[32a, 218] For example, in this project we discovered that

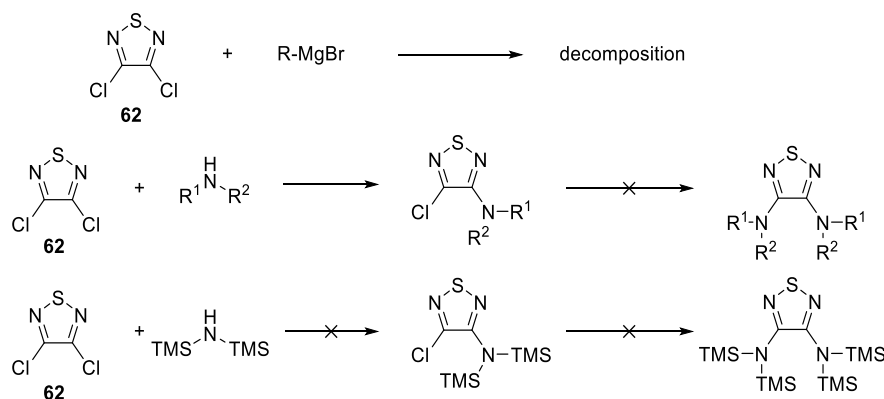
although the regioselectivity was affected by the aryne bond distortion, both steric and electronic effects, which were introduced *via* substituents on the benzene ring, the electronic effect showed a larger influence. The results from the reactions show single isomers could be obtained when a substituent with strong inductive electron-withdrawing effect was placed next to the benzyne^[219] (**entry 6**), while a significantly bulky group in the same position only resulted in poor selectivity (**entry 10**). Moreover, substituents with weak electronic effects, such as a methyl group, in the same position delivered no selectivity (**entry 8**). It was also worth noting that by switching the precursor substitution pattern from the 4-methyl-6-*t*-butyl benzyne precursor **61l** to a 6-trimethylsilyl substrate **61m** reversed the selectivity ratio from 2:1 to 1:2. Despite the small change in molar ratio, this suggested the electronic difference, the larger inductive electron-donating effect of the silyl group, outweighs the steric difference *i.e.* the larger size of the trimethylsilyl group. Although the scope of various benzyne precursors proceeded smoothly in the reaction, heteroarynes^[220] did not (**Scheme 4.7**). Neither the pyridyne precursor **66a** nor the more stable 4-methoxy pyridyl precursor **66b** gave the desired product under the reaction conditions. Complex mixtures were recovered as a result.



Scheme 4.7 Failed reaction with pyridyne precursors and dichlorothiadiazoles

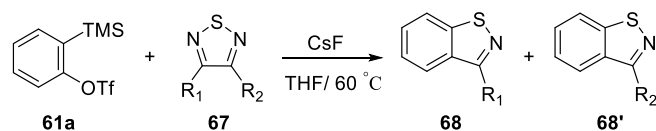
4.6.2. Scope of various thiadiazoles

Attention was then turned to identifying and synthesising a type of asymmetrically substituted thiadiazole to enable us to access a series of 3-substituted benzoisothiazoles with the generation of minimum side products. This would increase the atom efficiency for transferring the substituent onto the target product and would leave a small and easily separable side product. Another reason to explore unsymmetric thiadiazoles was that the symmetric thiadiazole starting materials have limited accessibility (**Scheme 4.8**). Only limited types of nucleophiles employed, such as sodium methoxide and sodium isopropoxide, were able to obtain symmetrical thiadiazoles. Strong nucleophiles such as metal amides, Grignard reagents or alkyl lithium reagents (see also **Scheme 4.5**) lead to decomposition of the starting material,^[213b] whereas weak nucleophiles such as HMDS or sterically hindered nucleophiles such as sodium *tert*-butoxide did not exhibit any reactivity. This left metal oxides and amines as suitable nucleophiles to perform substitution reactions on the dichlorothiadiazole **62**. In addition, the first substitution reaction on the chloride reduced the rate of the second, resulting in symmetrical thiadiazoles being much harder to obtain.

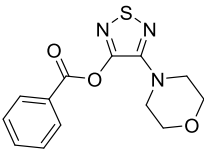
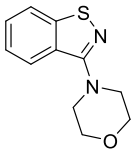
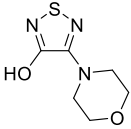
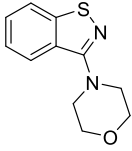
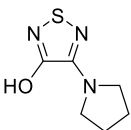
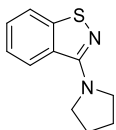
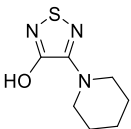
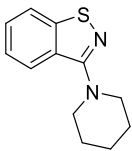
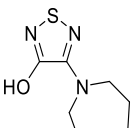
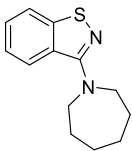
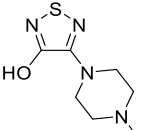
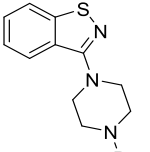
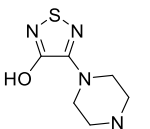
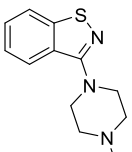


Scheme 4.8 Failed attempts towards the synthesis of symmetrical thiadiazoles

On the other hand, asymmetrically substituted thiadiazoles were much easier to obtain, using reagents with different nucleophilicity. Therefore, a series of unsymmetric thiadiazoles and some accessible symmetrical thiadiazoles were synthesised^[221] and applied to the reaction with the unsubstituted benzyne precursor (**Table 4.3**). With the symmetrical substrates, the methoxy **67a** and isopropoxy substituents **67b** (**entries 1 and 2**) showed similar reactivity compared to that of chloride. Thus, the fact that unsymmetrical 3-chloro-4-methoxy-1,2,5-thiadiazole **67c**^[222] provided a poor 1:3 mixture in favour of the 4-chloro-benzisothiazole **60a** (**entry 3**) was perhaps unsurprising. Similarly, the reaction showed zero selectivity between methoxy and thiomethyl groups (**entry 4**). In contrast, the 3-methylsulfonyl-4-methoxy-1,2,5-thiadiazole **67e** selectively transferred the sulfonyl group to the benzisothiazole product **68e**, albeit in poor 24% yield (**entry 5**), with 63% of unreacted thiadiazole starting material recovered. Changing the substituent to secondary amines (**entries 6 and 7**) did not improve the selectivity towards either regioisomer, although the trend of the selectivity ratio in **entries 3 – 7** suggested a possible bias for the substituent that is less electron-donating. Further attempts to control the selectivity made by increasing steric hindrance or employing a less electron-donating groups^[223] led to single isomers, however, with only moderate yields (**entries 8 and 9**).



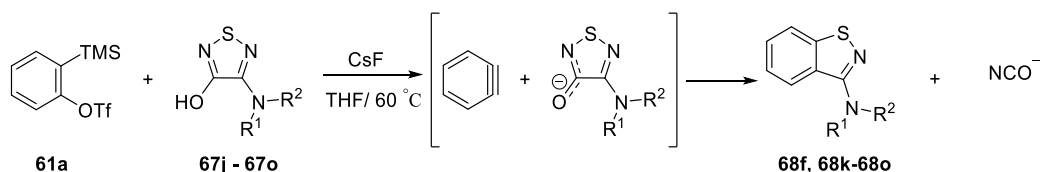
Entry ^a	Thiadiazole (2)	Product(s)	Yield (Ratio) ^b
1	67a	68a	81%
2	67b	68b	86%
3	67c	68a 60a	75% (1:3)
4	67d	68a 68d	61% ^c (1:1)
5	67e	68e	24% (1:>20)
6	67f	60a 68f	83% (3:1)
7	67g	68a 68f	86% (2:3)
8	67h	68f	36%

9	 67i	 68f	33%
10	 67j	 68f	96% (1:>20)
11	 67k	 68k	83% (1:>20)
12	 67l	 68l	78% (1:>20)
13	 67m	 68m	93% (1:>20)
14	 67n	 68n	85%
15	 67o	 68o	73%

^a Reaction conditions: **61a** (1.4 equiv.), **67** (1.0 equiv.), CsF (2.8 equiv.), 0.33 M, 60 °C, 16 h. ^b Isolated yields. ^c Products inseparable

Table 4.3 Evaluation of asymmetrically substituted thiadiazole derivatives in combination with aryl precursor.

A breakthrough came when a hydroxyl group was introduced in partnership with a secondary amine. 3-Hydroxy-4-morpholino-1,2,5-thiadiazole **67j** delivered the benzoisothiazole product 3-morpholino isomer **68f** exclusively with a yield of 96% (**entry 10**). Based on limited observation from this above result, we suggest that under basic conditions (with CsF) the hydroxyl group is deprotonated to form an anion where the negative charge is delocalised across the N-C-O bonds. This anionic intermediate creates high electron density around the 3-positioned carbon, which inhibits its reaction with benzyne and therefore transferred the amino substituent to the product selectively (**Scheme 4.9**).



Scheme 4.9 Possible reaction scheme for benzyne precursor and 3-hydroxy-4-amino-thiadiazole

Encouraged by this result, further 3-hydroxy-4-amino-1,2,5-thiadiazoles were synthesised^[223] and evaluated. Cyclic amines with various ring sizes all gave good yields (**entries 11 – 15**), notably boc- and tosyl-protected piperazinyl-benzoisothiazoles (**68n** and **68o**), whose structures appear frequently in medicinal chemistry, had promising yields (both above 80%).

4.6.3. Scope of the combination of benzyne precursors and asymmetrically substituted thiadiazoles

We next explored combinations of 3-hydroxy-4-(4'-tosylpiperazinyl)-1,2,5-thiadiazole **67o** and various benzyne precursors. As expected, the use of symmetrical benzyne precursors delivered the targeted 3-aminobenzoisothiazoles with excellent yields. All electron-donating (**69b**), -withdrawing (**69d**) and -neutral (**69a**) examples demonstrated high reactivity under the reaction conditions. The only substrate which showed lower efficiency was with the 3,6-dimethyl-substituted benzyne precursor **69e**, which was most likely due to steric hindrance. Unsymmetric precursors provided 3-amino-4-methoxybenzoisothiazole (**69f**) as a single isomer in 87% yield. Similarly, 3-amino-4-methoxy-6-bromobenzoisothiazole (**69g**) was obtained in 79% yield as an 8:1 mixture, together with 9% of the minor product **69g'**. In contrast to the use of dichlorothiadiazoled **62**, the combination of 3-hydroxy-4-piperazinyl-1,2,5-thiadiazole **67o** and 3-trimethylsilyl benzyne precursor **61m** gave an improved 5:1 ratio in favour of the 3-amino-7-trimethylsilylbenzoisothiazole **69h**. More surprisingly, 3-*tert*-butyl-5-methyl benzyne precursor **61l** provided 53% of 3-amino-5-methyl-7-*tert*-butylbenzoisothiazole (**69i**) as the major product, while 3-amino-4-*tert*-butyl-6-methylbenzoisothiazole **69i'** was isolated as a minor isomer in 35% yield. These differences in regioisomeric ratio can be attributed to the increased steric clash between substituents on the precursor and the piperazinyl group on the thiadiazole.

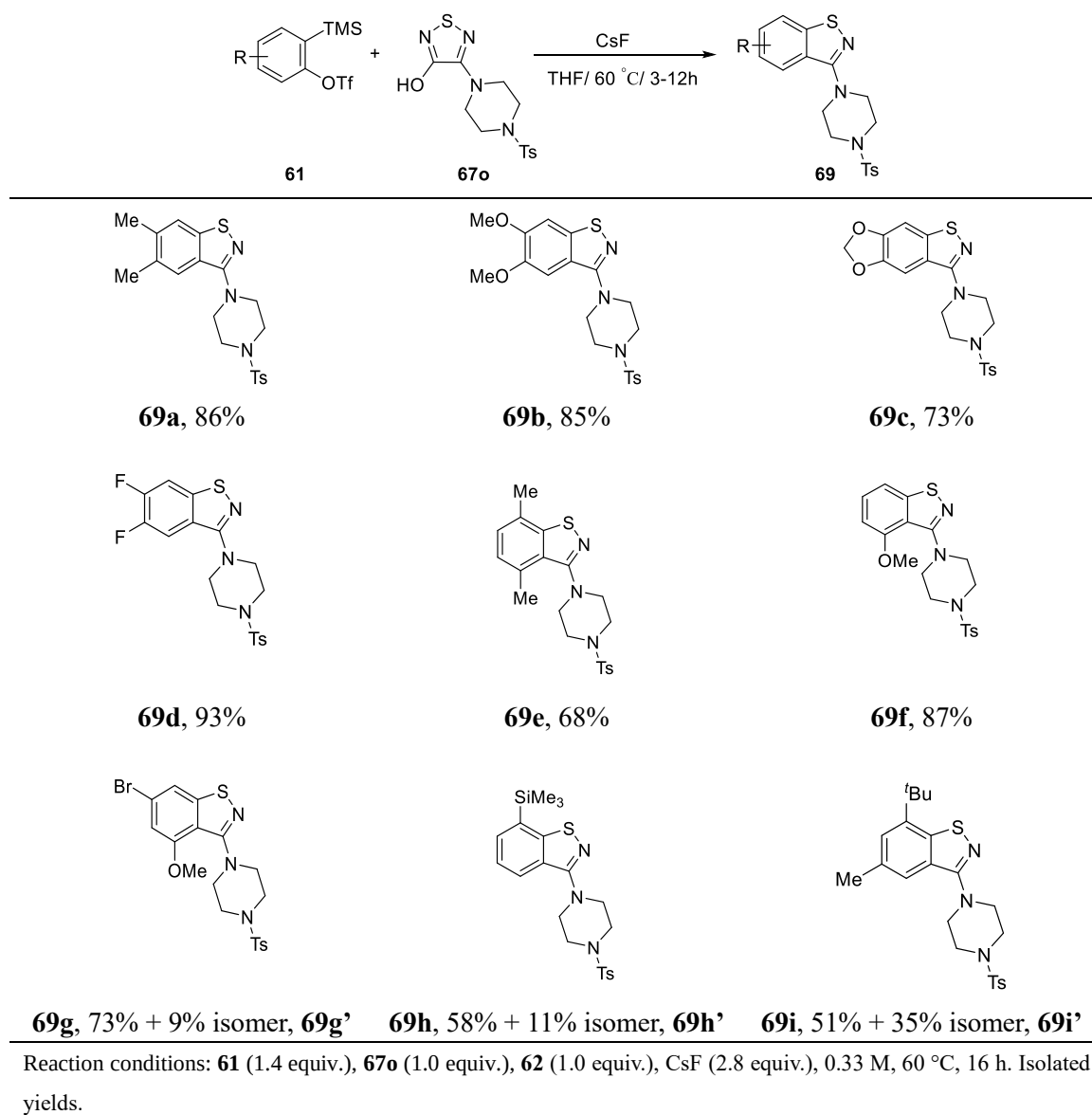
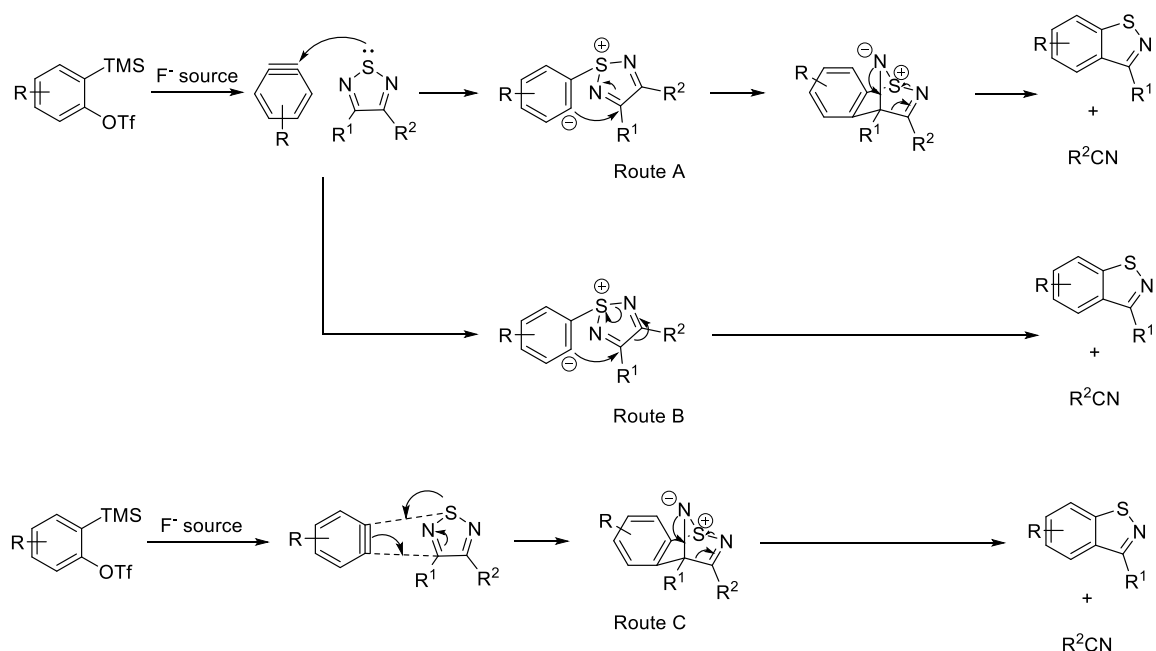


Table 4.4 The preparation of substituted 3-aminobenzoisothazoles using thiadiazole **67o**.

4.7. Proposed mechanism and project extension

Summarising the above observations, especially for regioselectivity, we propose the following reaction mechanism (**Scheme 4.10**). Upon the generation of benzyne from the precursor, the lone pair of electrons on sulfur attack one of the electron-poor or less sterically hindered sites of the benzyne triple bond, creating an anion on the benzene ring. The carbanion then cyclises with either of the carbons on the thiadiazole, likely the more

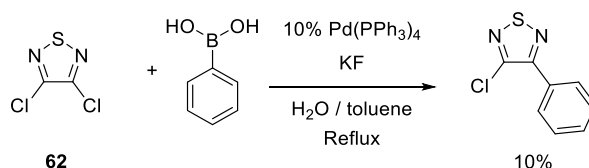
electron-poor carbon. The resulting second intermediate then subsequently re-aromatises to form the product benzoisothiazole and eliminates the nitrile side product (**Route A**). An alternative to this 5-endo-trig mechanism which is forbidden by Baldwin rules, involves a 5-exo-trig mechanism, which is not forbidden^[224] (**Route B**). This proceeds through a one-step cyclisation and nitrile elimination mechanism after the sulfur lone pair attack, achieving the same product. Also, we could not rule out the possibility of a direct [4+2] cycloaddition between benzyne and thiadiazole (**Route C**). Unfortunately, we were not able to isolate or characterise either of these two intermediates.



Scheme 4.10 Proposed mechanism for the reaction of benzyne precursor and thiadiazole

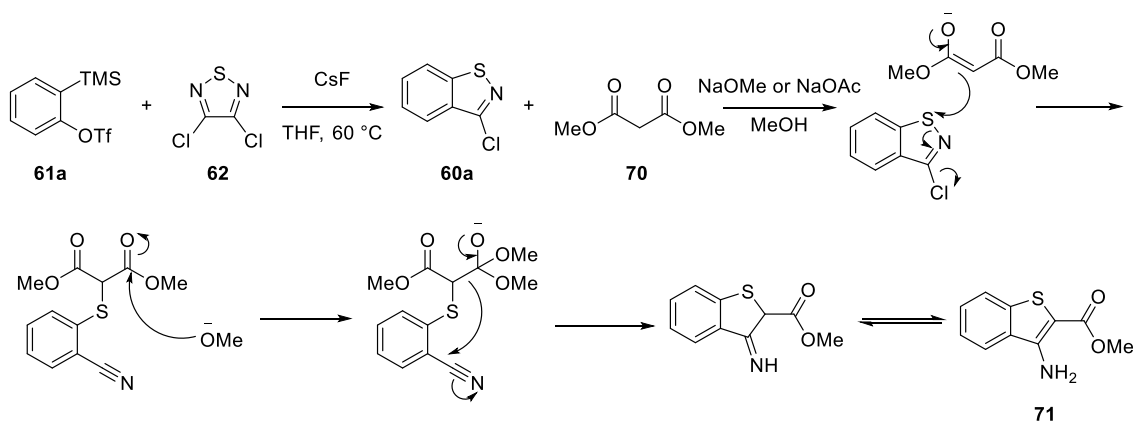
As noted before, the synthesis of 3-C substituted thiadiazoles was difficult, direct substitution with reactive organometallic compounds (alkyllithium and Grignard reagents) did not yield the desired product (**Scheme 4.8**). A precedented literature procedure^[225] *via* a palladium-catalysed Suzuki coupling did not provide a satisfying yield (**Scheme 4.11**).

This limited our access to 3-C substituted benzoisothiazoles, which was one of the variants we hoped to investigate.



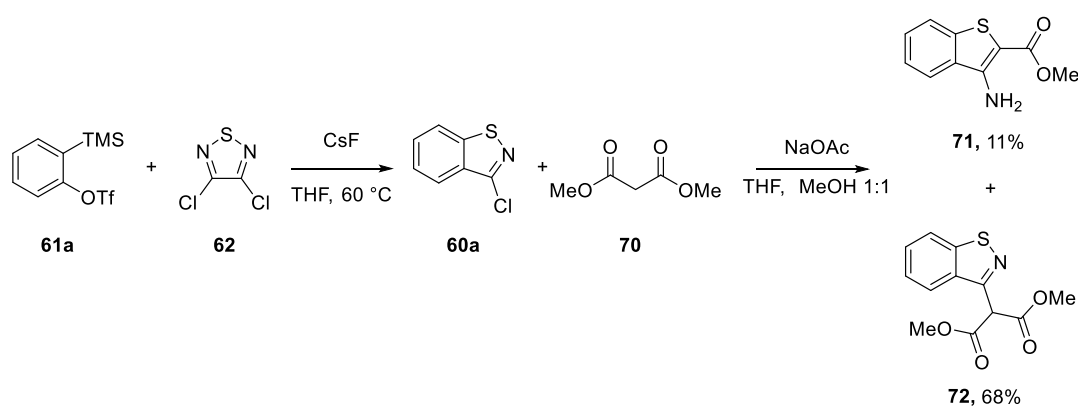
Scheme 4.11 Example for synthesis of 3-C substituted thiadiazoles

To resolve this shortcoming, a cascade sequence was developed where the initial 3-chlorobenzoisothiazole was generated, followed by nucleophilic substitution of the chloride group. As an example, 3-chlorobenzoisothiazole **60a** was chosen as the intermediate and dimethylmalonate **70** as the nucleophile, to generate the 3-dimethylmalonate substituted benzoisothiazole in a one-pot two-step process. Moreover, contrary to our expectation, treatment of 3-chlorobenzoisothiazole with dimethylmalonate with sodium methoxide in methanol lead to the formation of 3-aminobenzothiophene **71** rather than simple substitution product, possibly through a de-cyclisation/re-cyclisation mechanism (Scheme 4.12).^[226] Application of a weaker base, sodium acetate, made no difference to the result.



Scheme 4.12 Cascade Process for the Synthesis of 3-aminobenzothiophene

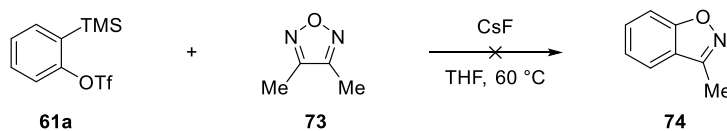
Further examination of the reaction showed that by switching the reaction solvent to a 1:1 mixture of THF and methanol, and using sodium acetate as base, the targeted substitution product dimethyl 2-(benzothiazol-3-yl)malonate **72** could be obtained in 68% yield with the aminobenzothiophene product **71** be suppressed to only 11%.



Scheme 4.13 Cascade process for the formation of C-substituted benzothiazole

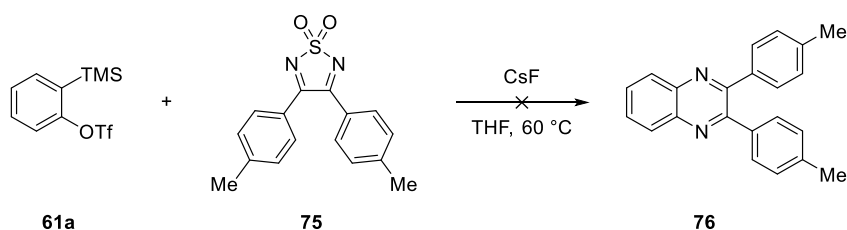
Given the success of the reaction between the benzyne precursor and thiadiazole, and its convenience in preparing substituted benzothiazoles, analogues of thiadiazole were also explored.

3,4-Dimethyl-1,2,5-oxadiazole **73**^[227] was treated under the optimised reaction conditions, however, the expected benzisoxazole **74** was not isolated. This could be attributed to the lack of nucleophilicity of the lone pair electron on the oxadiazole oxygen.



Scheme 4.14 Failed attempt for the synthesis of benzisoxazole

Another analogue examined was the oxidised thiadiazole, 3,4-ditolyl-1,2,5-thiadiazole-1,1'-dioxide **75**. The desired product was 2,3-di-*p*-tolylquinoxaline **76**; it was expected that the high electrophilicity of benzyne and the extrusion of sulfur dioxide gas would trigger an inverse electron demand hetero-Diels-Alder (ihDA).^[228] Unfortunately, likely due to the lack of nucleophilicity of both nitrogen atoms and the strong electron-withdrawing effect of the sulfonyl group, no product was observed after 24 hours of reaction.



Scheme 4.15 Failed attempt for the synthesis of 2,3-di-*p*-tolylquinoxaline

4.8. Project summary

In conclusion, a novel route for the synthesis of multi-substituted benzoisothiazoles from a range of benzyne precursors and thiadiazoles has been developed. In particular, high regioselectivity was achieved *via* the use of 3-amino-4-hydroxythiadiazoles, delivering the corresponding 3-aminobenzoisothiazoles. Good variation of benzyne precursors was established, providing access to a series of multi-substituted benzoisothiazoles. One-pot reactions towards further functionalisation of chlorobenzoisothiazoles was also possible, expanding the products beyond 3-aminobenzoisothiazole.

Chapter 5: Conclusion and future work

5.1. Synthesis of sulfonyl-containing compounds

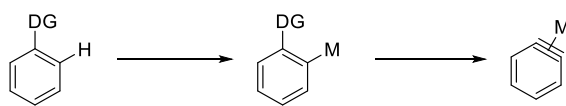
Since the development of DABSO as an easy-to-handle sulfur dioxide surrogate in the palladium-catalysed aminosulfonamide synthesis, various reaction pathways have been established for the synthesis of a variety of sulfonyl-containing compounds from versatile reagents. The Willis group is the pioneer in this field and has made significant contribution to these advances, especially in utilising organometallic reagents and transition metal catalysis.

In chapter 2 and 3 of this thesis, the work was focused on the development of synthetic pathways for diaryl sulfones and sulfonamides that allowed the use of less costly copper catalysts and readily available boronic acids and aryl halides. One-step direct syntheses were achieved as well as a two-step one-pot sulfonation/derivatisation process. Future work in this area includes a better understanding of the reaction mechanisms, which would likely lead to other novel synthetic strategies. For example, a clear knowledge of the background reaction in the copper(II)-catalysed sulfonamide synthesis could be a gateway to a viable metal-free reaction from boronic acids.

More generally, to combine DABSO with currently popular directing group assisted C-H activation for the sulfonylation on unactivated carbons is also of great interest. Studies into palladium or copper catalysed C-H activation/sulfonylation are underway within the group. In addition, other transition metals like cobalt and nickel are worth to be investigated as catalysts in DABSO chemistry.

5.2. Aryne-based heterocyclic chemistry

Chapter 4 presented an effective method to generate benzoisothiazoles from fluoride induced aryne precursors and thiadiazoles. The strategy is intriguing; however, it is restricted by the availability of the aryne precursor 2-(trimethylsilyl)phenyl triflate. A more versatile and easily-accessible aryne precursor using a mild generation method is therefore highly sought. Preliminary attempts inspired by palladium-catalysed C-H activation was not successful, but further experimentations are being designed.



Scheme 5.1 C-H activation inspired benzyne generation method

Chapter 6: Experimental procedures and compound data

6.1. General information

All procedures below were conducted under inert nitrogen atmosphere unless stated otherwise. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros and Fluorochem and were used as supplied unless stated otherwise. 1,2-Dichloroethane and 1,4-dioxane were distilled from CaH_2 . All dry solvents i.e. THF, MeOH, MeCN and toluene were dried over 4 Å molecular sieves and through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. Other solvents, i.e. sulfolane, DMF, DMA, DMSO, DMI (1,3-dimethyl-2-imidazolidinone), DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) and work-up solvents, were employed directly from commercial sources, i.e. Sigma-Aldrich unless stated otherwise. Petroleum ether refers to the fractions of petrol collected between 40-60 °C b.p.

Reactions were monitored *via* thin layer chromatography (TLC) on pre-coated aluminium plates (Merck Kieselgel 60 F₂₅₄). Products were visualized by UV light (254 nm) and/or with KMnO_4 stain. Flash column chromatography was conducted using silica gel 60 (Geduran Si 60, 40-63 µm) with head pressure from nitrogen tap.

^1H NMR, ^{13}C NMR and ^{19}F NMR data were obtained from a Bruker Avance AV 500 or a Bruker Avance AV 400 NMR spectrometer. Chemical shifts (δ) are referenced to the residual solvent as CDCl_3 or $\text{DMSO-}d_6$ in the unit of parts per million (ppm). Coupling constants J are quoted in the unit of hertz (Hz). Proton and carbon multiplicity is recorded as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). All compounds examined were dried *in vacuo* to remove residual solvents. Determination of

inseparable compounds were carried out on 500 MHz ^1H NMR, 125 MHz ^{13}C NMR spectra.

Low resolution mass spectra (LRMS) were recorded on a Fisons Platform II spectrometer.

High resolution mass spectrometry (HRMS) was performed on a Bruker MicroTof spectrometer using electrospray ionization method (ESI) or on a Micromass LCT spectrometer using field ionization method (FI) or electron ionization (CI).

Infra-red spectra were recorded neat on a Bruker Tensor 27 FT-IR spectrometer using a PIKE Miracle ATR module.

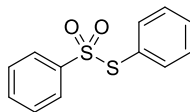
All compounds listed in the paper are >98% purity. Some sulfone products appear to be very hydroscopic therefore contain 0.2 – 0.5 mol equivalents of water (2 – 5 wt%) present in the ^1H NMR spectra as shown below.

The following starting materials were synthesised according to precedent literatures: substituted trimethylsilylphenyl trifluoromethanesulfonate benzyne precursors **61b** – **61h**, **61i** – **61k**, **61n** – **61p**,^[217] 3-(trimethylsilyl)pyridin-2-yl trifluoromethanesulfonate **66a** and 4-methoxy-3-(trimethylsilyl)pyridin-2-yl trifluoromethanesulfonate **66b**,^[220] 3-chloro-4-methoxy-1,2,5-thiadiazole **67c**,^[222] 3-methoxy-4-thiomethyl-1,2,5-thiadiazole **67d**,^[222] 3-chloro-4-methylsulfonyl-1,2,5-thiadiazole **67e**,^[222] 3-chloro-4-morpholino-1,2,5-thiadiazole **67f**,^[222] 2-(4-morpholino-1,2,5-thiadiazol-3-yl)-1-phenylethan-1-one **67h**, 4-morpholino-1,2,5-thiadiazol-3-yl benzoate **67i**,^[223] 3-amino-4-hydroxy-1,2,5-thiadiazoles **67j** – **67m**,^[221] 3,4-dimethyl-1,2,5-oxadiazole **73**.^[227]

Starting material (1-methyl-1*H*-indol-5-yl)boronic acid was synthesised by A. Davies in the group.

6.2. Chapter 2 data

S-Phenyl benzenesulfonothioate 34



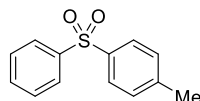
Phenylboronic acid (24 mg, 0.2 mmol, 1.0 eq.), Cu₂O (14.3 mg, 0.1 mmol, 50 mol%) and DABSO (72 mg, 0.3 mmol, 1.5 eq.) were mixed and dissolved in DMF (1 mL) under nitrogen. The reaction mixture was placed in a pre-heated oil bath at 110 °C and stirred for 14 hours prior to cooling to room temperature. TLC showed phenylboronic acid was fully consumed. Water (10 mL) was then added and the resulting mixture extracted with Et₂O (3 × 10 mL). The combined organic phases were washed with brine (3 × 10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (20% Et₂O in petroleum ether) to give the title compound as a white solid (21 mg, 84%).

¹H NMR (400 MHz, CDCl₃) δ 7.60 – 7.51 (m, 3H, *H*_{Ar}), 7.50 – 7.44 (m, 1H, *H*_{Ar}), 7.43 – 7.37 (m, 2H, *H*_{Ar}), 7.36 – 7.29 (m, 4H, *H*_{Ar}); ¹³C NMR (100 MHz, CDCl₃) δ 142.9, 136.6, 133.8, 131.5, 129.5, 128.9, 127.8, 127.6. LRMS (ESI, *m/z*) 273.0 ([M+Na]⁺, 100%). HRMS (ESI) calcd for C₁₂H₁₀O₂S₂Na [M+Na]⁺ 273.0021, found 273.0016. **M.p.:** 41 – 43 °C (lit. 42 – 44 °C). The data recorded are consistent with the literature.^[229]

6.2.1. Synthesis of diaryl sulfones

GENERAL PROCEDURE A for the synthesis of diaryl sulfones:

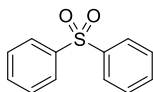
Phenyl *p*-tolyl sulfone **35a**



Phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene (44 mg, 0.2 mmol, 1.0 eq.) were mixed and dissolved in DMPU (1 mL) under nitrogen. Aryl iodide was added *via* syringe if liquid at room temperature. The reaction mixture was placed in a pre-heated oil bath at 110 °C and stirred for 36 hours prior to cooling to room temperature. Water (10 mL) was then added and the resultant mixture was extracted with Et₂O (3 × 10 mL). Combined organic phases were washed with brine (3 × 10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (25% Et₂O in petroleum ether) to give the title compound as a white solid (34 mg, 73%).

¹H NMR (400 MHz, CDCl₃) δ 7.93 (d, *J* = 7.2 Hz, 2H, *H*_{Ar}), 7.83 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 7.58 – 7.52 (m, 1H, *H*_{Ar}), 7.52 – 7.45 (m, 2H, *H*_{Ar}), 7.29 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 2.39 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 144.3, 142.1, 138.7, 133.1, 130.0, 129.3, 127.8, 127.6, 21.7. LRMS (ESI, *m/z*) 233.0 ([M+H]⁺, 100%). HRMS (ESI) calcd for C₁₃H₁₃O₂S [M+H]⁺ 233.0631, found 233.0634. **M.p.**: 123 – 125 °C (lit. 124 – 125 °C). The data recorded are consistent with the literature.^[114]

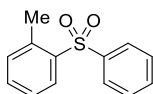
Diphenyl sulfone 35b



General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodobenzene (23 μ L, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (20% Et₂O in petroleum ether) to give the titled product as a white solid (37 mg, 87%).

¹H NMR (400 MHz, CDCl₃) δ 7.99 – 7.90 (m, 4H, *H*_{Ar}), 7.59 – 7.54 (m, 2H, *H*_{Ar}), 7.51 – 7.46 (m, 4H, *H*_{Ar}); ¹³C NMR (100 MHz, CDCl₃) δ 141.7, 133.3, 129.4, 127.8. LRMS (ESI, *m/z*) 217.1 ([M-H]⁻, 100%); HRMS (ESI) calcd for C₁₂H₁₀O₂SNa [M+Na]⁺ 241.0294, found 241.0294. **M.p.**: 123 – 124 °C (lit. 122 – 124 °C). The data recorded are consistent with the literature.^[154b]

Phenyl *o*-tolyl sulfone 35c

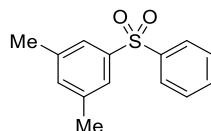


General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.01 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.01 mmol, 10 mol%) and 2-iodotoluene (25 μ L, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (15% Et₂O in petroleum ether) to give the titled product as a white solid (23 mg, 49%).

¹H NMR (400 MHz, CDCl₃) δ 8.22 (dd, *J* = 7.9, 1.4 Hz, 1H, *H*_{Ar}), 7.89 – 7.83 (m, 2H, *H*_{Ar}),

7.62 – 7.55 (m, 1H, H_{Ar}), 7.53 – 7.45 (m, 3H, H_{Ar}), 7.44 – 7.37 (m, 1H, H_{Ar}), 7.23 (d, J = 7.5 Hz, 1H, H_{Ar}), 2.44 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 138.9, 138.1, 133.8, 133.2, 132.8, 129.6, 129.2, 127.8, 126.6, 20.3. **LRMS** (ESI, m/z) 233.0 ($[M+H]^+$, 100%); **HRMS** (ESI) calcd for $C_{13}H_{13}O_2SNa$ $[M+H]^+$ 233.0631, found 233.0633. **M.p.**: 74 – 75 °C (lit. 73 – 75 °C). The data recorded are consistent with the literature.^[230]

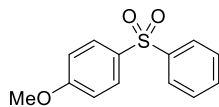
3,5-Dimethyl-1-(phenylsulfonyl)benzene 35d



General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), $Cu(MeCN)_4BF_4$ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 1-iodo-3,5-dimethylbenzene (28 μ L, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (20% Et_2O in petroleum ether) to give the titled product as a white solid (36 mg, 74%).

1H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.93 (m, 2H, H_{Ar}), 7.57 – 7.53 (m, 3H, H_{Ar}), 7.52 – 7.47 (m, 2H, H_{Ar}), 7.17 (s, 1H, H_{Ar}), 2.35 (s, 6H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 141.3, 139.5, 135.1, 133.1, 129.3, 127.7, 125.3, 21.4. **LRMS** (ESI, m/z) 247.1 ($[M+H]^+$, 100%); **HRMS** (ESI) calcd for $C_{14}H_{15}O_2S$ $[M+H]^+$ 247.0787, found 247.0790. **M.p.**: 89 – 90 °C (lit. 88 – 90 °C). The data recorded are consistent with the literature.^[120]

4-Methoxyphenyl phenyl sulfone 35e



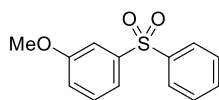
General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodoanisole (47 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (20% Et_2O in petroleum ether) to give the titled product as a white solid (32 mg, 65%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.94 – 7.89 (m, 2H, H_{Ar}), 7.89 – 7.83 (m, 2H, H_{Ar}), 7.57 – 7.51 (m, 1H, H_{Ar}), 7.51 – 7.45 (m, 2H, H_{Ar}), 7.00 – 6.91 (m, 2H, H_{Ar}), 3.84 (s, 3H, OCH_3);

$^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 163.5, 142.5, 133.2, 133.0, 130.0, 129.3, 127.4, 114.6, 55.8.

LRMS (ESI, m/z) 247.0 ($[\text{M}-\text{H}]^-$, 100%); **HRMS** (ESI) calcd for $\text{C}_{13}\text{H}_{12}\text{O}_3\text{SNa}$ $[\text{M}+\text{Na}]^+$ 271.0399, found 271.0340. **M.p.:** 89 – 90 °C (lit. 89 – 90 °C). The data recorded are consistent with the literature.^[30]

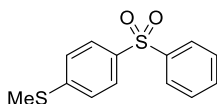
3-Methoxyphenyl phenyl sulfone 35f



General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 3-iodoanisole (47 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (30% Et_2O in petroleum ether) to give the titled product as a white solid (39 mg, 78%).

¹H NMR (400 MHz, CDCl₃) δ 7.96 – 7.93 (m, 2H, *H*_{Ar}), 7.58 – 7.54 (m, 1H, *H*_{Ar}), 7.52 – 7.48 (m, 3H, *H*_{Ar}), 7.47 – 7.43 (m, 1H, *H*_{Ar}), 7.43 – 7.36 (m, 1H, *H*_{Ar}), 7.11 – 7.03 (m, 1H, *H*_{Ar}), 3.83 (s, 3H, OCH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 160.1, 142.8, 141.6, 133.3, 130.5, 129.4, 127.8, 120.0, 119.7, 112.4, 55.8. **LRMS** (ESI, *m/z*) 249.0 ([M+H]⁺, 100%); **HRMS** (EI) calcd for C₁₃H₁₃O₃S [M]⁺ 249.0580, found 249.0582. **M.p.**: 82 °C (lit. 82 °C). The data recorded are consistent with the literature.^[230]

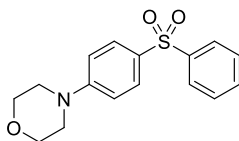
4-(Benzenesulfonyl)phenyl methyl sulphide 35g



General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodothioanisole (50 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (30% Et₂O in petroleum ether) to give the titled product as a white solid (39 mg, 74%).

¹H NMR (400 MHz, CDCl₃) δ 7.96 – 7.88 (m, 2H, *H*_{Ar}), 7.85 – 7.76 (m, 2H, *H*_{Ar}), 7.58 – 7.52 (m, 1H, *H*_{Ar}), 7.51 – 7.46 (m, 2H, *H*_{Ar}), 7.31 – 7.25 (m, 2H, *H*_{Ar}), 2.48 (s, 3H, CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 146.8, 142.0, 137.3, 133.2, 129.4, 128.1, 127.6, 125.6, 14.8. **LRMS** (ESI, *m/z*) 265.0 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₃H₁₃O₂S₂ [M+H]⁺ 265.0352, found 265.0354. **M.p.**: 110 – 112 °C (lit. 110 – 111 °C). The data recorded are consistent with the literature.^[231]

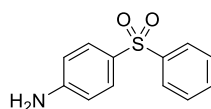
4-[4-(Phenylsulfonyl)phenyl]morpholine 35h



General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-(4-iodophenyl)morpholine (58 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (60% Et_2O in petroleum ether) to give the titled product as a white solid (43 mg, 71%).

^1H NMR (400 MHz, CDCl_3) δ 7.94 – 7.87 (m, 2H, H_{Ar}), 7.84 – 7.75 (m, 2H, H_{Ar}), 7.54 – 7.49 (m, 1H, H_{Ar}), 7.49 – 7.42 (m, 2H, H_{Ar}), 6.93 – 6.85 (m, 2H, H_{Ar}), 3.85 – 3.49 (m, 4H, OCH_2), 3.29 – 3.24 (m, 4H, NCH_2); **^{13}C NMR** (100 MHz, CDCl_3) δ 154.2, 142.9, 132.7, 130.1, 129.6, 129.2, 127.3, 113.9, 66.6, 47.5. **LRMS** (ESI, m/z) 304.1 ($[\text{M}+\text{H}]^+$, 100%); **HRMS** (ESI) calcd for $\text{C}_{16}\text{H}_{18}\text{O}_3\text{NS}$ $[\text{M}+\text{H}]^+$ 304.1002, found 304.1004. **IR** ν_{max} (film): 3062, 2850, 1591, 1507, 1449, 1297 (SO_2), 1245, 1150 (SO_2), 1105, 927, 762, 651 cm^{-1} . **M.p.:** 157 – 160 $^\circ\text{C}$.

4-Aminophenyl phenyl sulfone 35i



General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodoaniline (44 mg, 0.2

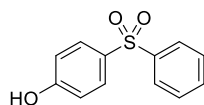
mmol, 1.0 eq.). The product was purified *via* flash column chromatography (70% Et₂O in petroleum ether) to give the titled product as a white solid (30 mg, 64%).

¹H NMR (400 MHz, CDCl₃) δ 7.94 – 7.85 (m, 2H, *H*_{Ar}), 7.74 – 7.65 (m, 2H, *H*_{Ar}), 7.54 – 7.49 (m, 1H, *H*_{Ar}), 7.48 – 7.41 (m, 2H, *H*_{Ar}), 6.70 – 6.59 (m, 2H, *H*_{Ar}), 4.18 (br, s, 2H, *NH*₂);

¹³C NMR (100 MHz, CDCl₃) δ 151.2, 143.1, 132.6, 130.0, 129.5, 129.2, 127.2, 114.3.

LRMS (ESI, *m/z*) 256.0 ([*M*+*Na*]⁺, 100%); **HRMS** (ESI) calcd for C₁₂H₁₁O₂NSNa [*M*+*Na*]⁺ 256.0403, found 256.0402. **M.p.**: 168 – 170 °C (lit. 169-172 °C). The data recorded are consistent with the literature.^[232]

4-Hydroxyphenyl phenyl sulfone 35j

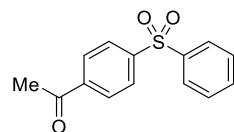


General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodophenol (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (50% Et₂O in petroleum ether) to give the titled product as a white solid (36 mg, 71%).

¹H NMR (400 MHz, CDCl₃) δ 7.93 – 7.86 (m, 2H, *H*_{Ar}), 7.80 (d, *J* = 8.8 Hz, 2H, *H*_{Ar}), 7.58 – 7.52 (m, 1H, *H*_{Ar}), 7.52 – 7.44 (m, 2H, *H*_{Ar}), 6.92 (d, *J* = 8.8 Hz, 2H, *H*_{Ar}), 6.29 (br s, 1H, *OH*); **¹³C NMR** (100 MHz, CDCl₃) δ 160.4, 142.1, 133.2, 132.8, 130.2, 129.4, 127.4, 116.3.

LRMS (ESI, *m/z*) 257.0 ([*M*+*Na*]⁺, 100%); **HRMS** (ESI) calcd for C₁₂H₁₀O₃SNa [*M*+*Na*]⁺ 257.0243, found 257.0243. **M.p.**: 136 – 138 °C (lit. 136 – 137 °C). The data recorded are consistent with the literature.^[35]

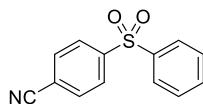
4'-(Phenylsulfonyl)acetophenone 35k



General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4'-iodoacetophenone (49 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (30% Et_2O in petroleum ether) to give the titled product as a white solid (33 mg, 64%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.10 – 8.01 (m, 4H, H_{Ar}), 7.98 – 7.93 (m, 2H, H_{Ar}), 7.63 – 7.57 (m, 1H, H_{Ar}), 7.56 – 7.49 (m, 2H, H_{Ar}), 2.62 (s, 3H, COCH_3); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 196.8, 145.5, 140.9, 140.4, 133.8, 129.6, 129.2, 128.1, 128.0, 27.0. **LRMS** (ESI, m/z) 283.0 ($[\text{M}+\text{Na}]^+$, 100%); **HRMS** (ESI) calcd for $\text{C}_{14}\text{H}_{12}\text{O}_3\text{SNa}$ $[\text{M}+\text{Na}]^+$ 283.0399, found 283.0401. **M.p.**: 133 – 135 °C (lit. 133 – 135 °C). The data recorded are consistent with the literature.^[36a]

4-(Phenylsulfonyl)benzonitrile 35l

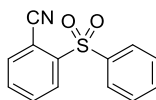


General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodobenzonitrile (46 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (40% Et_2O

in petroleum ether) to give the titled product as a white solid (34 mg, 70%).

¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, *J* = 8.7 Hz, 2H, *H*_{Ar}), 7.95 (d, *J* = 7.1 Hz, 2H, *H*_{Ar}), 7.80 (d, *J* = 8.7 Hz, 2H, *H*_{Ar}), 7.66 – 7.61 (m, 1H, *H*_{Ar}), 7.55 (t, *J* = 7.5 Hz, 2H, *H*_{Ar}); **¹³C NMR** (100 MHz, CDCl₃) δ 146.0, 140.2, 134.2, 133.2, 129.8, 128.4, 128.1, 117.3, 117.1. **LRMS** (ESI, *m/z*) 266.0 ([M+Na]⁺, 100%); **HRMS** (ESI) calcd for C₁₃H₉O₂NSNa [M+Na]⁺ 266.0246, found 266.0248. **M.p.:** 127 – 129 °C (lit. 125 – 127 °C). The data recorded are consistent with the literature.^[233]

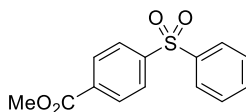
2-(Phenylsulfonyl)benzonitrile 35m



General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 2-iodobenzonitrile (46 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (40% Et₂O in petroleum ether) to give the titled product as a white solid (22 mg, 45%).

¹H NMR (400 MHz, CDCl₃) δ 8.35 (dd, *J* = 8.3, 1.1 Hz, 1H, *H*_{Ar}), 8.15 – 8.04 (m, 2H, *H*_{Ar}), 7.83 – 7.78 (m, 2H, *H*_{Ar}), 7.72 – 7.62 (m, 2H, *H*_{Ar}), 7.59 – 7.53 (m, 2H, *H*_{Ar}); **¹³C NMR** (100 MHz, CDCl₃) δ 143.8, 139.6, 135.8, 134.3, 133.5, 133.4, 129.9, 129.6, 128.8, 115.7, 111.6. **LRMS** (ESI, *m/z*) 266.0 ([M+Na]⁺, 100%); **HRMS** (ESI) calcd for C₁₃H₉O₂NSNa [M+Na]⁺ 266.0246, found 266.0245. **M.p.:** 101 – 104 °C (lit. 99 – 102 °C). The data recorded are consistent with the literature.^[234]

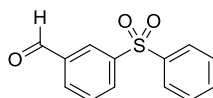
Methyl 4-(phenylsulfonyl)benzoate **35n**



General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and methyl 4-iodobenzoate (52 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (30% Et₂O in petroleum ether) to give the titled product as a white solid (37 mg, 67%).

¹H NMR (400 MHz, CDCl₃) δ 8.15 (d, *J* = 8.7 Hz, 2H, *H*_{Ar}), 8.01 (d, *J* = 8.7 Hz, 2H, *H*_{Ar}), 7.98 – 7.92 (m, 2H, *H*_{Ar}), 7.63 – 7.57 (m, 1H, *H*_{Ar}), 7.56 – 7.49 (m, 2H, *H*_{Ar}), 3.93 (s, 3H, CO₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 165.6, 145.6, 140.9, 134.4, 133.8, 130.6, 129.6, 128.0, 127.8, 52.8. LRMS (ESI, *m/z*) 299.0 ([M+Na]⁺, 100%); HRMS (ESI) calcd for C₁₄H₁₂O₄SNa [M+Na]⁺ 299.0349, found 299.0348. **M.p.**: 145 – 147 °C (lit. 147 °C). The data recorded are consistent with the literature.^[235]

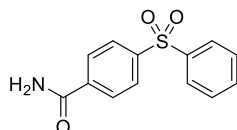
3-(Phenylsulfonyl)benzaldehyde **35o**



General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 3-iodobenzaldehyde (46 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (50% Et₂O in petroleum ether) to give the titled product as a white solid (22 mg, 46%).

¹H NMR (400 MHz, CDCl₃) δ 10.05 (s, 1H, CHO), 8.45 – 8.37 (m, 1H, H_{Ar}), 8.20 (ddd, *J* = 7.8, 1.9, 1.2 Hz, 1H, H_{Ar}), 8.08 (d, *J* = 7.7 Hz, 1H, H_{Ar}), 7.99 – 7.96 (m, 2H, H_{Ar}), 7.70 (t, *J* = 7.8 Hz, 1H, H_{Ar}), 7.63 – 7.59 (m, 1H, H_{Ar}), 7.57 – 7.52 (m, 2H, H_{Ar}); **¹³C NMR** (100 MHz, CDCl₃) δ 190.4, 143.3, 140.8, 137.2, 133.8, 133.6, 133.0, 130.4, 129.7, 129.0, 128.0. **LRMS** (ESI, *m/z*) 247.0 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₃H₁₁O₃S [M+H]⁺ 247.0423, found 247.0424. **IR** ν_{max} (film): 3065, 2849, 1702 (CO), 1595, 1582, 1447, 1323, 1306 (SO₂), 1204, 1151 (SO₂), 1095, 900, 730, 687 cm⁻¹. **M.p.**: 86 – 89 °C.

4-(Phenylsulfonyl)benzamide **35p**

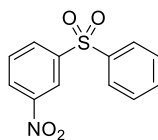


General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodobenzamide (49 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (10% EtOAc increased to 70% EtOAc in petroleum ether) to give the titled product as a white solid (38 mg, 73%).

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.19 (br s, 1H, NH), 8.04 (s, 4H, H_{Ar}), 8.00 – 7.95 (m, 2H, H_{Ar}), 7.73 – 7.67 (m, 1H, H_{Ar}), 7.67 – 7.59 (m, 3H, NH and H_{Ar}); **¹³C NMR** (100 MHz, DMSO-*d*₆) δ 166.5, 143.2, 140.7, 138.9, 134.0, 129.9, 128.8, 127.5, 127.5. **LRMS** (ESI, *m/z*) 284.0 ([M+Na]⁺, 100%); **HRMS** (ESI) calcd for C₁₃H₁₁O₃NSNa [M+Na]⁺ 284.0352, found 284.0352. **IR** ν_{max} (film): 3418 (NH₂), 2922, 1684 (CO), 1467, 1296 (SO₂), 1205,

1162 (SO₂), 1103, 1040, 996, 863, 723, 665 cm⁻¹. **M.p.**: 173 – 175 °C.

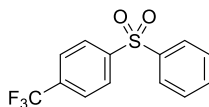
3-Nitrodiphenyl sulfone 35q



General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 3-iodonitrobenzene (50 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (40% Et₂O in petroleum ether) to give the titled product as a white solid (39 mg, 75%).

¹H NMR (400 MHz, CDCl₃) δ 8.77 (app. t, *J* = 2.0 Hz, 1H, *H*_{Ar}), 8.41 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1H, *H*_{Ar}), 8.28 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1H, *H*_{Ar}), 8.02 – 7.96 (m, 2H, *H*_{Ar}), 7.74 (app. t, *J* = 8.0 Hz, 1H, *H*_{Ar}), 7.67 – 7.61 (m, 1H, *H*_{Ar}), 7.60 – 7.52 (m, 2H, *H*_{Ar}); **¹³C NMR** (100 MHz, CDCl₃) δ 148.6, 144.1, 140.2, 134.2, 133.3, 130.9, 129.9, 128.1, 127.8, 123.1. **LRMS** (ESI, *m/z*) 286.0 ([M+Na]⁺, 100%); **HRMS** (ESI) calcd for C₁₂H₉O₄NSNa [M+Na]⁺ 286.0145, found 286.0146. **M.p.**: 78 – 80 °C (lit. 79 – 81 °C). The data recorded are consistent with the literature.^[36b]

1-(Phenylsulfonyl)-4-(trifluoromethyl)benzene 35r

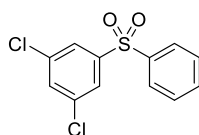


General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-

dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodobenzotrifluoride (29 μ L, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (20% Et₂O in petroleum ether) to give the titled product as a white solid (41 mg, 72%).

¹H NMR (500 MHz, CDCl₃) δ 8.07 (d, J = 8.2 Hz, 2H, H_{Ar}), 8.00 – 7.91 (m, 2H, H_{Ar}), 7.77 (d, J = 8.2 Hz, 2H, H_{Ar}), 7.66 – 7.58 (m, 1H, H_{Ar}), 7.53 – 7.49 (m, 2H, H_{Ar}); **¹³C NMR** (125 MHz, CDCl₃) δ 145.4, 140.7, 135.0 (q, $^2J_{C-F}$ = 33 Hz, C_{Ar}), 133.9, 129.7, 128.3, 128.0, 126.6 (q, $^3J_{C-F}$ = 4 Hz, C_{Ar}), 123.2 (q, $^1J_{C-F}$ = 273 Hz, CF₃); **¹⁹F NMR** (376 MHz, CDCl₃) δ 63.2. **LRMS** (ESI, m/z) 287.0 ([M+H]⁺, 100%). **HRMS** (EI) calcd for C₁₃H₁₀F₃O₂S [M]⁺ 287.0348, found 287.0448. **M.p.**: 93 – 95 °C (lit. 91 – 92 °C). The data recorded are consistent with the literature.^[30]

3,5-Dichloro-1-(phenylsulfonyl)benzene 35s

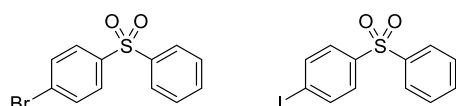


General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 1-iodo-3,5-dichlorobenzene (55 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (20% Et₂O in petroleum ether) to give the titled product as a white solid (43 mg, 75%).

¹H NMR (400 MHz, CDCl₃) δ 7.96 – 7.93 (m, 2H, H_{Ar}), 7.81 (d, J = 1.9 Hz, 2H, H_{Ar}), 7.67 – 7.61 (m, 1H, H_{Ar}), 7.59 – 7.51 (m, 3H, H_{Ar}); **¹³C NMR** (100 MHz, CDCl₃) δ 144.7, 140.4, 136.4, 134.1, 133.4, 129.8, 128.1, 126.2. **LRMS** (ESI, m/z) 308.2 ([³⁵M+Na]⁺, 100%);

HRMS (ESI) calcd for $C_{12}H_8O_2^{35}Cl_2SNa$ $[^{35}M+Na]^+$ 308.9514, found 308.9515. **IR** ν_{max} (film): 3071, 1566, 1477, 1449, 1329 (SO_2), 1179, 1163 (SO_2), 1140, 866, 802, 718, 686 cm^{-1} . **M.p.**: 125 – 128 °C.

4-Phenylsulfonylbromobenzene and 4-phenylsulfonyliodobenzene 35t/35t'



General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), $Cu(MeCN)_4BF_4$ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 1-bromo-4-iodobenzene (57 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (50% Et_2O in petroleum ether) to give the titled inseparable products as a white solid (39 mg), in a ratio of 3:1.

4-Phenylsulfonylbromobenzene 35t

1H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.90 (m, 2H, H_{Ar}), 7.82 – 7.78 (m, 2H, H_{Ar}), 7.67 – 7.62 (m, 2H, H_{Ar}), 7.61 – 7.56 (m, 1H, H_{Ar}), 7.55 – 7.46 (m, 2H, H_{Ar}); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 140.8, 133.6, 132.7, 129.6, 129.3, 128.6, 127.8. **LRMS** (ESI, m/z) 296.9 ($[M+H]^+$, 100%); **HRMS** (ESI) calcd for $C_{12}H_9O_2^{79}BrSNa$ $[^{79}M+Na]^+$ 318.9399 and $C_{12}H_9O_2^{81}BrSNa$ $[^{81}M+Na]^+$ 320.9378, found 318.9400 and 320.9379. The data recorded are consistent with the literature.^[236]

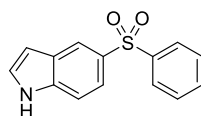
4-Phenylsulfonyliodobenzene 35t'

1H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.90 (m, 2H, H_{Ar}), 7.86 (d, J = 8.5 Hz, 2H, H_{Ar}), 7.67 – 7.62 (m, 2H, H_{Ar}), 7.61 – 7.56 (m, 1H, H_{Ar}), 7.55 – 7.46 (m, 2H, H_{Ar}); ^{13}C NMR (125

MHz, CDCl₃) δ 141.5, 141.3, 138.7, 133.6, 129.6, 129.2, 127.8, 101.2. **LRMS** (ESI, *m/z*) 366.9 ([*M*+*H*]⁺, 100%); **HRMS** (ESI) calcd for C₁₂H₉O₂ISNa [*M*+Na]⁺ 366.9260, found 366.9261. The data recorded are consistent with the literature.^[31b]

IR ν_{max} (film): 3087, 2917, 2849, 1572, 1446, 1387, 1320 (SO₂), 1155 (SO₂), 1104, 1068, 1008, 822, 741, 689, 686 cm⁻¹.

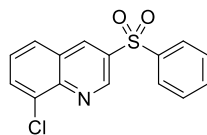
5-(Phenylsulfonyl)indole 35u



General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 5-iodoindole (49 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (20% EtOAc in petroleum ether) to give the titled product as a white solid (40 mg, 79%).

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.70 (br s, 1H, *NH*), 8.27 (d, *J* = 1.3 Hz, 1H, *H*_{Ar}), 7.94 (dd, *J* = 8.2, 1.3 Hz, 2H, *H*_{Ar}), 7.68 – 7.53 (m, 6H, *H*_{Ar}), 6.67 (d, *J* = 3.0 Hz, 1H, *H*_{Ar}); **¹³C NMR** (100 MHz, DMSO-*d*₆) δ 142.8, 138.0, 132.9, 131.2, 129.5, 128.5, 127.3, 126.9, 121.0, 119.7, 112.5, 102.9. **LRMS** (ESI, *m/z*) 280.0 ([*M*+Na]⁺, 100%); **HRMS** (ESI) calcd for C₁₄H₁₁O₂NNaS [*M*+Na]⁺ 280.0403, found 280.0403. **IR** ν_{max} (film): 3427 (*NH*), 2923, 1660, 1431, 1302 (SO₂), 1208, 1150 (SO₂), 1107, 1042, 996, 767, 731 cm⁻¹. **M.p.**: 133 – 135 °C.

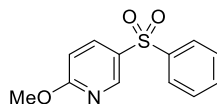
8-Chloro-3-(phenylsulfonyl)quinoline 35v



General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 8-chloro-3-iodoquinoline (58 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (60% Et₂O in petroleum ether) to give the titled product as a white solid (32 mg, 53%).

¹H NMR (400 MHz, CDCl₃) δ 9.36 (d, *J* = 2.3 Hz, 1H, *H*_{Ar}), 8.85 (d, *J* = 2.3 Hz, 1H, *H*_{Ar}), 8.07 – 8.02 (m, 2H, *H*_{Ar}), 7.99 (dd, *J* = 7.5, 1.3 Hz, 1H, *H*_{Ar}), 7.91 (dd, *J* = 8.3, 1.3 Hz, 1H, *H*_{Ar}), 7.65 – 7.59 (m, 2H, *H*_{Ar}), 7.58 – 7.52 (m, 2H, *H*_{Ar}); ¹³C NMR (100 MHz, CDCl₃) δ 147.9, 145.6, 140.7, 137.4, 135.9, 134.2, 134.1, 132.9, 129.8, 128.6, 128.4, 128.0, 128.0. LRMS (ESI, *m/z*) 304.0 ([³⁵M+H]⁺, 100%), 306.0 ([³⁷M+H]⁺, 25%); HRMS (ESI) calcd for C₁₅H₁₁O₂N³⁵ClS [³⁵M+H]⁺ 304.1094, found 304.1094. **M.p.**: 227 – 229 °C (lit. 226 – 227 °C). The data recorded are consistent with the literature.^[237]

2-Methoxy-5-(phenylsulfonyl)pyridine 35w

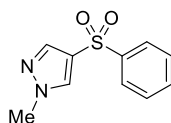


General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 5-iodo-2-methoxypyridine (47 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography

(10% EtOAc in petroleum ether) to give the titled product as a white solid (19 mg, 39%).

¹H NMR (400 MHz, CDCl₃) δ 8.74 (dd, *J* = 2.5, 0.5 Hz, 1H, *H*_{Ar}), 7.98 (dd, *J* = 8.8, 2.5 Hz, 1H, *H*_{Ar}), 7.93 – 7.89 (m, 2H, *H*_{Ar}), 7.59 – 7.55 (m, 1H, *H*_{Ar}), 7.53 – 7.49 (m, 2H, *H*_{Ar}), 6.78 (dd, *J* = 8.8, 0.5 Hz, 1H, *H*_{Ar}), 3.96 (s, 3H, OCH₃); **¹³C NMR** (125 MHz, CDCl₃) δ 166.9, 148.3, 141.8, 137.7, 133.5, 131.1, 129.6, 127.5, 111.8, 54.5. **LRMS** (ESI, *m/z*) 250.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₂H₁₂O₃NS [M+H]⁺ 250.0532, found 250.0534. **IR** ν_{max} (film): 3062, 2949, 1589, 1483, 1447, 1374, 1323 (SO₂), 1307, 1286, 1160 (SO₂), 1112, 1014, 833, 756, 727, 689 cm⁻¹. **M.p.**: 88 – 91 °C.

1-Methyl-4-(phenylsulfonyl)pyrazole 35x

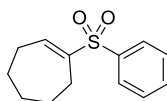


General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodo-1-methyl-1H-pyrazole (42 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (20% EtOAc in petroleum ether) to give the titled product as a white solid (33 mg, 76%).

¹H NMR (400 MHz, CDCl₃) δ 7.96 – 7.90 (m, 2H, *H*_{Ar}), 7.84 (s, 1H, *H*_{Ar}), 7.79 (s, 1H, *H*_{Ar}), 7.61 – 7.54 (m, 1H, *H*_{Ar}), 7.53 – 7.48 (m, 2H, *H*_{Ar}), 3.91 (s, 3H, CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 142.9, 139.3, 133.2, 132.4, 129.4, 127.0, 124.6, 39.8. **LRMS** (ESI, *m/z*) 223.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₀H₁₁O₂N₂S [M+H]⁺ 223.0536, found 223.0538. **M.p.**: 109 – 110 °C (lit. 107 – 108 °C). The data recorded are consistent with the

literature.^[238]

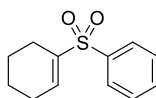
1-Cyclohepten-1-yl-phenylsulfone 35y



General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 1-iodocycloheptene (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (30% Et₂O in petroleum ether) to give the titled product as a colourless oil which solidified when left standing (27 mg, 58%).

¹H NMR (400 MHz, CDCl₃) δ 7.87 – 7.80 (m, 2H, *H*_{Ar}), 7.62 – 7.55 (m, 1H, *H*_{Ar}), 7.55 – 7.46 (m, 2H, *H*_{Ar}), 7.30 (t, *J* = 6.5 Hz, 1H, *CH*), 2.40 – 2.31 (m, 4H, *CH*₂), 1.77 – 1.63 (m, 2H, *CH*₂), 1.58 – 1.48 (m, 2H, *CH*₂), 1.42 – 1.33 (m, 2H, *CH*₂); ¹³C NMR (100 MHz, CDCl₃) δ 144.4, 143.2, 139.7, 133.1, 129.2, 128.1, 31.4, 28.7, 27.7, 26.2, 25.6. LRMS (ESI, *m/z*) 237.1 ([*M*+*H*]⁺, 100%); HRMS (ESI) calcd for C₁₃H₁₇O₂S [*M*+*H*]⁺ 237.0944, found 237.0946. **M.p.**: 33 – 35 °C (lit. 32 – 35 °C). The data recorded are consistent with the literature.^[239]

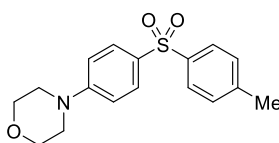
1-Cyclohexen-1-yl-phenylsulfone 35z



General procedure A was followed with phenylboronic acid (73 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 1-iodocyclohexene (42 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (30% Et₂O in petroleum ether) to give the titled product as a colourless oil which solidified when left standing (28 mg, 64%).

¹H NMR (400 MHz, CDCl₃) δ 7.89 – 7.84 (m, 2H, *H*_{Ar}), 7.63 – 7.58 (m, 1H, *H*_{Ar}), 7.56 – 7.50 (m, 2H, *H*_{Ar}), 7.07 (dt, *J* = 3.9, 2.2 Hz, 1H, *CH*), 2.32 – 2.22 (m, 2H, SO₂CCH₂), 2.19 – 2.13 (m, 1H, SO₂CCHCH₂), 1.69 – 1.61 (m, 2H, SO₂CCHCH₂), 1.61 – 1.53 (m, 2H, SO₂CCH₂CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 139.9, 139.6, 138.7, 133.2, 129.2, 128.2, 25.6, 23.0, 21.9, 20.9. LRMS (ESI, *m/z*) 223.1 ([*M*+*H*]⁺, 100%); HRMS (ESI) calcd for C₁₂H₁₅O₂S [*M*+*H*]⁺ 223.0787, found 223.0790. **M.p.**: 42 – 44 °C (lit. 43 °C). The data recorded are consistent with the literature.^[240]

4-(4-Tosylphenyl)morpholine 36a



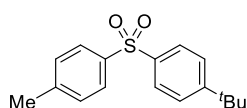
General procedure A was followed with 4-tolylboronic acid (82 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-(4-

136

iodophenyl)morpholine (58 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (20% EtOAc in petroleum ether) to give the titled product as a white solid (46 mg, 72%).

¹H NMR (400 MHz, CDCl₃) δ 7.83 – 7.72 (m, 4H, *H*_{Ar}), 7.26 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 6.87 (d, *J* = 9.1 Hz, 2H, *H*_{Ar}), 3.85 – 3.79 (m, 4H, OCH₂), 3.29 – 3.21 (m, 4H, NCH₂), 2.37 (s, 3H, CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 154.1, 143.6, 140.0, 130.7, 129.9, 129.5, 127.4, 114.0, 66.6, 47.6, 21.7. **LRMS** (ESI, *m/z*) 318.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₇H₂₀O₃NS [M+H]⁺ 318.1158, found 318.1151. **IR** *v*_{max} (film): 3062, 2580, 1591, 1507, 1449, 1297 (SO₂), 1245, 1150 (SO₂), 1121, 1105, 927, 821, 651 cm⁻¹. **M.p.**: 150 – 153 °C.

(4-*tert*-Butylphenyl)-*p*-tolyl sulfone **36b**

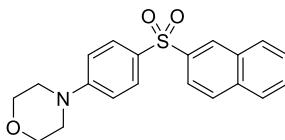


General procedure A was followed with 4-*tert*-butylphenylboronic acid (107 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (20% Et₂O in petroleum ether) to give the titled product as a white solid (45 mg, 78%).

¹H NMR (400 MHz, CDCl₃) δ 7.86 – 7.80 (m, 4H, *H*_{Ar}), 7.49 (d, *J* = 8.7 Hz, 2H, *H*_{Ar}), 7.29 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 2.39 (s, 3H, CH₃), 1.30 (s, 9H, C(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ 157.0, 144.1, 139.1, 139.1, 130.0, 127.8, 127.5, 126.4, 35.3, 31.2, 21.7. **LRMS** (ESI, *m/z*) 289.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₇H₂₁O₂S [M+H]⁺ 289.1257, found 289.1258. **M.p.**: 86 – 87 °C (lit. 80 – 81 °C). The data recorded are consistent with

the literature.^[241]

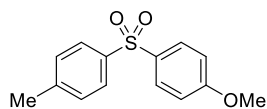
4-[4-(Naphthalen-2-ylsulfonyl)phenyl]morpholine 36c



General procedure A was followed with 2-naphthylboronic acid (103 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-(4-iodophenyl)morpholine (57.8 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (20% EtOAc in petroleum ether) to give the titled product as a white solid (54 mg, 76%).

¹H NMR (400 MHz, CDCl₃) δ 8.55 – 8.48 (m, 1H, *H*_{Ar}), 7.96 (dd, *J* = 7.3, 1.6 Hz, 1H, *H*_{Ar}), 7.92 – 7.79 (m, 5H, *H*_{Ar}), 7.64 – 7.55 (m, 2H, *H*_{Ar}), 6.88 (d, *J* = 9.1 Hz, 2H, *H*_{Ar}), 3.85 – 3.78 (m, 4H, OCH₂), 3.28 – 3.21 (m, 4H, NCH₂); ¹³C NMR (100 MHz, CDCl₃) δ 154.2, 139.7, 134.9, 132.4, 130.2, 129.7, 129.6, 129.5, 129.0, 128.4, 128.0, 127.6, 122.7, 114.0, 66.6, 47.5. LRMS (ESI, *m/z*) 376.1 ([M+Na]⁺, 100%); HRMS (ESI) calcd for C₂₀H₁₉O₃NaNS [M+Na]⁺ 376.0978, found 376.0974. IR *v*_{max} (film): 3649, 2980, 2856, 1591, 1505, 1449, 1299 (SO₂), 1245, 1149 (SO₂), 1131, 1095, 927, 819, 763, 649 cm⁻¹.
M.p.: 196 – 199 °C.

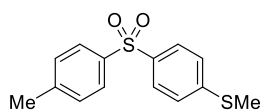
4-Tolyl 4-methoxyphenyl sulfone 36d



General procedure A was followed with 4-methoxyboronic acid (91 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (30% Et₂O in petroleum ether) to give the titled product as a white solid (40 mg, 76%).

¹H NMR (400 MHz, CDCl₃) δ 7.88 – 7.82 (m, 2H, *H*_{Ar}), 7.82 – 7.76 (m, 2H, *H*_{Ar}), 7.28 – 7.24 (m, 2H, *H*_{Ar}), 6.96 – 6.91 (m, 2H, *H*_{Ar}), 3.83 (s, 3H, OCH₃), 2.38 (s, 3H, CCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 163.3, 143.8, 139.5, 135.7, 129.9, 129.8, 127.5, 114.5, 55.7, 21.7. LRMS (ESI, m/z) 263.1 ([M+H]⁺, 100%); HRMS (ESI) calcd for C₁₄H₁₅O₃S [M+H]⁺ 263.0736, found 263.0738. **M.p.**: 103 – 104 °C (lit. 103 – 104 °C). The data recorded are consistent with the literature.^[241]

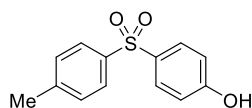
4-Tolyl 4-methylthiophenyl sulfone 36e



General procedure A was followed with 4-methylthiophenylboronic acid (101 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (30% Et₂O in petroleum ether) to give the titled product as a white solid (38 mg, 68%).

¹H NMR (400 MHz, CDCl₃) δ 7.85 – 7.76 (m, 4H, *H*_{Ar}), 7.31 – 7.25 (m, 4H, *H*_{Ar}), 2.48 (s, 3H, SCH₃), 2.39 (s, 3H, CCH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 146.5, 144.2, 139.1, 137.8, 130.1, 128.0, 127.7, 125.6, 21.7, 14.9. **LRMS** (ESI, m/z) 279.0 ([M+H]⁺, 100%), 301.0 ([M+Na]⁺, 30%); **HRMS** (ESI) calcd for C₁₄H₁₅O₂S₂ [M+H]⁺ 279.0508, found 279.0510. **IR** ν_{max} (film): 3046, 2922, 1580, 1493, 1397, 1314 (SO₂), 1154 (SO₂), 1112, 1085, 817, 757, 661 cm⁻¹. **M.p.**: 136 – 139 °C.

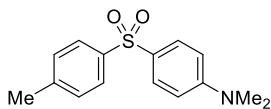
4-Tosylphenol 36f



General procedure A was followed with 4-hydroxyphenylboronic acid (132 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (40% EtOAc in petroleum ether) to give the titled product as a white solid (38 mg, 78%) with less than 2% of inseparable impurity.

¹H NMR (400 MHz, CDCl₃) δ 7.79 – 7.74 (m, 4H, *H*_{Ar}), 7.29 – 7.25 (m, 2H, *H*_{Ar}), 6.90 (d, *J* = 8.9 Hz, 2H, *H*_{Ar}), 6.39 (br, 1H, OH), 2.38 (s, 3H, CCH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 160.3, 144.1, 139.2, 133.2, 130.1, 130.1, 127.4, 116.3, 21.7. **LRMS** (ESI, m/z) 249.1 ([M+H]⁺, 100%), 271.0 ([M+Na]⁺, 40%); **HRMS** (ESI) calcd for C₁₃H₁₃O₃S [M+H]⁺ 249.0580, found 249.0583. **M.p.**: 137 – 139 °C (lit. 138 °C). The data recorded are consistent with the literature.^[36a]

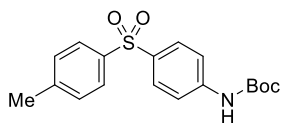
***N,N*-Dimethyl-4-tosylaniline 36g**



General procedure A was followed with 4-(dimethylamino)phenylboronic acid (99 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (30% EtOAc in petroleum ether) to give the titled product as a white solid (36 mg, 66%).

¹H NMR (500 MHz, CDCl₃) δ 7.77 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 7.74 (d, *J* = 9.1 Hz, 2H, *H*_{Ar}), 7.24 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 6.64 (d, *J* = 9.1 Hz, 2H, *H*_{Ar}), 3.01 (s, 6H, N(CH₃)₂), 2.36 (s, 3H, CCH₃); ¹³C NMR (125 MHz, CDCl₃) δ 153.2, 143.1, 140.7, 129.8, 129.5, 127.2, 127.1, 111.2, 40.2, 21.6. LRMS (ESI, *m/z*) 276.1 ([M+H]⁺, 100%), 298.0 ([M+Na]⁺, 30%); HRMS (ESI) calcd for C₁₅H₁₈O₂NS [M+H]⁺ 276.1053, found 276.1054. **M.p.**: 212 – 214 °C (lit. 212 – 213 °C). The data recorded are consistent with the literature.^[242]

***tert*-Butyl (4-tosylphenyl)carbamate 36h**

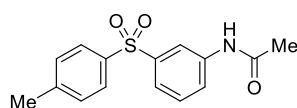


General procedure A was followed with 4-(*N*-Boc-amino)phenylboronic acid (142 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (30% EtOAc in petroleum ether) to give the titled product as a white solid (36 mg, 52%),

with less than 2% inseparable impurity.

¹H NMR (500 MHz, CDCl₃) δ 7.84 (d, *J* = 8.8 Hz, 2H, *H*_{Ar}), 7.78 (d, *J* = 8.3 Hz, 2H, *H*_{Ar}), 7.47 (d, *J* = 8.8 Hz, 2H, *H*_{Ar}), 7.28 (d, *J* = 8.3 Hz, 2H, *H*_{Ar}), 6.67 (br s, 1H, *NH*), 2.38 (s, 3H, CCH₃), 1.50 (s, 9H, C(CH₃)₃); **¹³C NMR** (125 MHz, CDCl₃) δ 152.1, 144.0, 143.0, 139.3, 135.5, 130.0, 129.1, 127.6, 118.2, 81.8, 28.4, 21.7. **LRMS** (ESI, *m/z*) 370.1 ([*M*+Na]⁺, 100%); **HRMS** (ESI) calcd for C₁₈H₂₁O₄NaS [*M*+Na]⁺ 370.1084, found 370.1083. **IR** *v*_{max} (film): 3341 (NH), 2926, 1730 (CO), 1592, 1522, 1403, 1368, 1321 (SO₂), 1232, 1147 (SO₂), 1107, 835, 708, 688, 646 cm⁻¹. **M.p.**: 186 – 188 °C.

N-(3-Tosylphenyl)acetamide **36i**

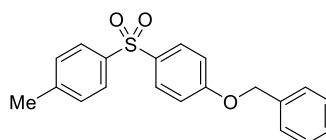


General procedure A was followed with 3-acetamidophenylboronic acid (107 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (10% EtOAc in petroleum ether) to give the titled product as a white solid (29 mg, 50%).

¹H NMR (400 MHz, CDCl₃) δ 8.04 (d, *J* = 8.1 Hz, 1H, *H*_{Ar}), 7.96 (br. s, 2H, *H*_{Ar}, OH), 7.81 (d, *J* = 8.2 Hz, 2H, *H*_{Ar}), 7.61 (d, *J* = 7.8 Hz, 1H, *H*_{Ar}), 7.44 (app. t, *J* = 8.1 Hz, 1H, *H*_{Ar}), 7.29 (d, *J* = 8.2 Hz, 2H, *H*_{Ar}), 2.40 (s, 3H, CH₃), 2.14 (s, 3H, COCH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 169.0, 144.7, 142.3, 139.3, 138.3, 130.3, 130.2, 127.8, 124.4, 122.7, 118.2, 24.6, 21.8. **LRMS** (ESI, *m/z*) 312.1 ([*M*+Na]⁺, 100%); **HRMS** (ESI) calcd for C₁₅H₁₅O₃NNaS [*M*+Na]⁺ 312.0665, found 312.0662. **IR** *v*_{max} (film): 3317 (NH), 2980,

1673 (CO), 1593, 1540, 1478, 1421, 1373 (SO₂), 1301, 1148 (SO₂), 1099, 814, 794, 703, 685 cm⁻¹. **M.p.**: 137 – 140 °C.

1-(Benzyloxy)-4-tosylbenzene **36j**

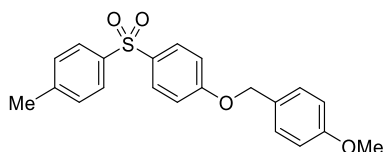


General procedure A was followed with 4-benzyloxyphenylboronic acid (137 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (10% EtOAc in petroleum ether) to give the titled product as a white solid (38 mg, 57%).

¹H NMR (400 MHz, CDCl₃) δ 7.86 (d, *J* = 9.0 Hz, 2H, *H*_{Ar}), 7.80 (d, *J* = 8.3 Hz, 2H, *H*_{Ar}), 7.42 – 7.37 (m, 4H, *H*_{Ar}), 7.37 – 7.32 (m, 1H, *H*_{Ar}), 7.28 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 7.02 (d, *J* = 9.0 Hz, 2H, *H*_{Ar}), 5.09 (s, 2H, CH₂), 2.39 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 162.5, 143.9, 139.4, 135.9, 133.9, 130.0, 129.8, 128.9, 128.5, 127.6, 127.5, 115.4, 70.5, 21.7. **LRMS** (ESI, *m/z*) 339.1 ([M+H]⁺, 100%), 361.0 ([M+Na]⁺, 30%); **HRMS** (ESI) calcd for C₂₀H₁₉O₃S [M+H]⁺ 339.1049, found 339.1052. **M.p.**: 165 – 167 °C (lit. 201 °C).

The data recorded are consistent with the literature.^[32a]

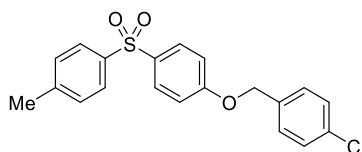
1-Methoxy-4-[(4-tosylphenoxy)methyl]benzene 36k



General procedure A was followed with 4-(4-methoxybenzloxy)phenylboronic acid (155 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (10% EtOAc in petroleum ether) to give the titled product as a light yellow solid (46 mg, 63%).

¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, *J* = 9.0 Hz, 2H, *H*_{Ar}), 7.79 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 7.32 (d, *J* = 8.8 Hz, 2H, *H*_{Ar}), 7.27 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 7.01 (d, *J* = 9.0 Hz, 2H, *H*_{Ar}), 6.91 (d, *J* = 8.8 Hz, 2H, *H*_{Ar}), 5.01 (s, 2H, OCH₂), 3.81 (s, 3H, OCH₃), 2.38 (s, 3H, CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 162.5, 159.8, 143.9, 139.5, 133.7, 130.0, 129.8, 129.4, 127.9, 127.5, 115.4, 114.3, 70.3, 55.5, 21.7. **LRMS** (ESI, *m/z*) 391.1 ([M+Na]⁺, 100%); **HRMS** (ESI) calcd for C₂₁H₂₀O₄NaS [M+Na]⁺ 391.0986, found 391.0968. **IR** ν_{max} (film): 3066, 2999, 1593, 1493, 1318 (SO₂), 1297, 1247, 1178, 1149 (SO₂), 1105, 850, 707, 689, 647 cm⁻¹. **M.p.**: 156 – 159 °C.

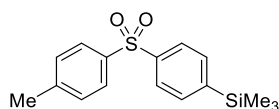
1-Chloro-4-[(4-tosylphenoxy)methyl]benzene 36l



General procedure A was followed with 4-(4-chlorobenzloxy)phenylboronic acid (158 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (10% EtOAc in petroleum ether) to give the titled product as a white solid (42 mg, 56%).

¹H NMR (500 MHz, CDCl₃) δ 7.86 (d, *J* = 8.9 Hz, 2H, *H*_{Ar}), 7.79 (d, *J* = 8.3 Hz, 2H, *H*_{Ar}), 7.39 – 7.03 (m, 4H, *H*_{Ar}), 7.28 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 7.00 (d, *J* = 8.9 Hz, 2H, *H*_{Ar}), 5.05 (s, 2H, OCH₂), 2.39 (s, 3H, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 162.2, 144.0, 139.4, 134.4, 134.4, 134.2, 130.0, 129.9, 129.1, 128.9, 127.6, 115.4, 69.7, 21.7. LRMS (ESI, *m/z*) 395.0 ([³⁵M+Na]⁺, 100%); HRMS (ESI) calcd for C₂₀H₁₇O₃³⁵ClNaS [³⁵M+Na]⁺ 395.0479, found 395.0480. IR ν_{max} (film): 3440, 2979, 1593, 1494, 1318 (SO₂), 1299, 1255, 1152 (SO₂), 1106, 1015, 811, 721, 669 cm⁻¹. M.p.: 137 – 140 °C.

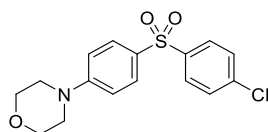
Trimethyl(4-tosylphenyl)silane 36m



General procedure A was followed with 4-(trimethylsilyl)phenylboronic acid (116 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene

(44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (10% EtOAc in petroleum ether) to give the titled product as a white solid (44 mg, 72%). **¹H NMR** (400 MHz, CDCl₃) δ 7.87 (d, *J* = 8.2 Hz, 2H, *H*_{Ar}), 7.83 (d, *J* = 8.3 Hz, 2H, *H*_{Ar}), 7.62 (d, *J* = 8.3 Hz, 2H, *H*_{Ar}), 7.29 (d, *J* = 8.2 Hz, 2H, *H*_{Ar}), 2.39 (s, 3H, CH₃), 0.26 (s, 9H, Si(CH₃)); **¹³C NMR** (100 MHz, CDCl₃) δ 147.6, 144.2, 142.2, 138.8, 134.2, 130.0, 127.9, 126.4, 21.7, -1.3. **LRMS** (ESI, *m/z*) 305.1 ([M+H]⁺, 30%); 327.0 ([M+Na]⁺, 100%); **HRMS** (ESI) calcd for C₁₆H₂₁O₂SSi [M+H]⁺ 305.106, found 305.1029. **M.p.**: 101 – 102 °C (lit. 99 °C). The data recorded are consistent with the literature.^[243]

4-{4-[(4-Chlorophenyl)sulfonyl]phenyl}morpholine 36n

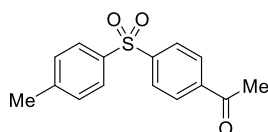


General procedure A was followed with 4-chlorophenylboronic acid (94 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-(4-iodophenyl)morpholine (58 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (50% EtOAc in petroleum ether) to give the titled product as a white solid (44 mg, 66%).

¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, *J* = 8.8 Hz, 2H, *H*_{Ar}), 7.77 (d, *J* = 9.1 Hz, 2H, *H*_{Ar}), 7.43 (d, *J* = 8.8 Hz, 2H, *H*_{Ar}), 6.88 (d, *J* = 9.1 Hz, 2H, *H*_{Ar}), 3.88 – 3.78 (m, 4H, OCH₂), 3.35 – 3.24 (m, 4H, NCH₂); **¹³C NMR** (100 MHz, CDCl₃) δ 154.4, 141.5, 139.3, 129.6, 129.6, 128.8, 114.0, 66.6, 47.4, one quaternary carbon is not seen on the spectrum. **LRMS**

(ESI, m/z) 360.0 ($[M+Na]^+$, 100%); **HRMS** (ESI) calcd for $C_{16}H_{16}O_3N^{35}ClNaS$ $[^{35}M+Na]^+$ 360.0432, found 360.0432. **IR** ν_{max} (film): 3086, 2850, 1589, 1506, 1383, 1306 (SO_2), 1245, 1149 (SO_2), 1103, 1012, 926, 823, 767, 615 cm^{-1} . **M.p.:** 140 – 143 °C.

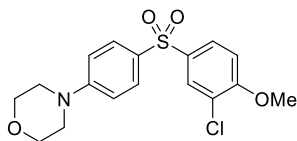
1-(4-Tosylphenyl)ethan-1-one 36o



General procedure A was followed with (4-acetylphenyl)boronic acid (98 mg, 0.6 mmol, 3.0 eq.), $Cu(MeCN)_4BF_4$ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (40% Et_2O in petroleum ether) to give the titled product as a white solid (23 mg, 42%).

1H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.99 (m, 4H, H_{Ar}), 7.84 (d, J = 8.3 Hz, 2H, H_{Ar}), 7.32 (d, J = 8.1 Hz, 2H, H_{Ar}), 2.61 (s, 3H, $COCH_3$), 2.41 (s, 3H, $ArCH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.8, 146.0, 144.9, 140.3, 138.0, 130.3, 129.2, 128.1, 128.0, 27.0, 21.8. **LRMS** (ESI, m/z) 275.1 ($[M+H]^+$, 100%); **HRMS** (ESI) calcd for $C_{15}H_{15}O_3S$ $[M+H]^+$ 275.0742, found 275.0750. **M.p.:** 145 – 149 °C (lit. 116 – 118 °C). The data recorded are consistent with the literature.^[36a]

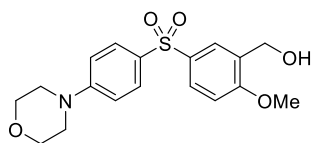
4-{4-[(3-Chloro-4-methoxyphenyl)sulfonyl]phenyl}morpholine 36p



General procedure A was followed with 3-chloro-4-methoxyphenylboronic acid (112 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-(4-iodophenyl)morpholine (58 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (50% EtOAc in petroleum ether) to give the titled product as a white solid (50 mg, 68%).

¹H NMR (500 MHz, CDCl₃) δ 7.87 (d, *J* = 2.3 Hz, 1H, *H*_{Ar}), 7.80 (dd, *J* = 8.7, 2.3 Hz, 1H, *H*_{Ar}), 7.76 (d, *J* = 9.1 Hz, 2H, *H*_{Ar}), 6.96 (d, *J* = 8.7 Hz, 1H, *H*_{Ar}), 6.87 (d, *J* = 9.1 Hz, 2H, *H*_{Ar}), 3.92 (s, 3H, OCH₃), 3.87 – 3.80 (m, 4H, OCH₂), 3.32 – 3.24 (m, 4H, NCH₂); **¹³C NMR** (125 MHz, CDCl₃) δ 158.4, 154.2, 135.4, 130.2, 129.4, 127.6, 123.5, 114.0, 111.8, 66.6, 56.6, 47.5, one quaternary carbon not observed. **LRMS** (ESI, *m/z*) 390.1 ([³⁵M+Na]⁺, 100%); **HRMS** (ESI) calcd for C₁₇H₁₈O₄N³⁵ClNaS [³⁵M+Na]⁺ 390.0537, found 390.0539. **IR** *v*_{max} (film): 3073, 2921, 2850, 1590, 1490, 1300 (SO₂), 1275, 1246, 1150 (SO₂), 1107, 1062, 927, 821, 762, 609 cm⁻¹. **M.p.**: 157 – 159 °C.

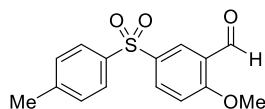
{2-Methoxy-5-[(4-morpholinophenyl)sulfonyl]phenyl}methanol 36q



General procedure A was followed with 3-hydroxymethyl-4-methoxyphenylboronic acid (109 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-(4-iodophenyl)morpholine (58 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (50% EtOAc in petroleum ether) to give the titled product as a white solid (53 mg, 73%).

¹H NMR (400 MHz, CDCl₃) δ 7.86 (dd, *J* = 8.6, 2.3 Hz, 1H, *H*_{Ar}), 7.83 (d, *J* = 2.3 Hz, 1H, *H*_{Ar}), 7.77 (d, *J* = 9.1 Hz, 2H, *H*_{Ar}), 6.91 (d, *J* = 8.6 Hz, 1H, *H*_{Ar}), 6.86 (d, *J* = 9.1 Hz, 2H, *H*_{Ar}), 4.66 (d, *J* = 6.6 Hz, 2H, HOCH₂), 3.88 (s, 3H, OCH₃), 3.84 – 3.79 (m, 4H, OCH₂), 3.28 – 3.19 (m, 4H, NCH₂), 2.24 (t, *J* = 6.6 Hz, 1H, OH); **¹³C NMR** (100 MHz, CDCl₃) δ 160.5, 154.0, 134.6, 130.9, 130.5, 129.3, 128.8, 127.5, 114.0, 110.3, 66.6, 61.2, 56.0, 47.6. **LRMS** (ESI, *m/z*) 364.1 ([M+H]⁺, 100%), 386.0 ([M+Na]⁺, 40%); **HRMS** (ESI) calcd for C₁₈H₂₂O₅NS [M+H]⁺ 364.1213, found 364.1214. **IR** ν_{max} (film): 3457 (OH), 2922, 2852, 1591, 1491, 1450, 1296 (SO₂), 1246, 1190, 1133 (SO₂), 1096, 1048, 821, 762, 684, 608 cm⁻¹. **M.p.**: 194 – 196 °C.

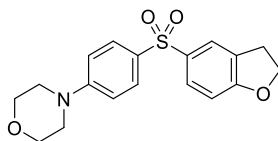
2-Methoxy-5-tosylbenzaldehyde 36r



General procedure A was followed with 3-formyl-4-methoxyphenylboronic acid (108 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (50% EtOAc in petroleum ether) to give the titled product as a white solid (31 mg, 54%).

¹H NMR (500 MHz, CDCl₃) δ 10.41 (s, 1H, CHO), 8.34 (d, *J* = 2.5 Hz, 1H, *H*_{Ar}), 8.13 (dd, *J* = 8.9, 2.5 Hz, 1H, *H*_{Ar}), 7.81 (d, *J* = 8.2 Hz, 2H, *H*_{Ar}), 7.30 (d, *J* = 8.2 Hz, 2H, *H*_{Ar}), 7.09 (d, *J* = 8.9 Hz, 1H, *H*_{Ar}), 3.99 (s, 3H, OCH₃), 2.39 (s, 3H, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 188.1, 164.6, 144.4, 138.7, 134.9, 134.8, 130.2, 128.9, 127.7, 125.1, 112.5, 56.5, 21.7. LRMS (ESI, *m/z*) 291.0 ([M+H]⁺, 30%), 313.0 ([M+Na]⁺, 100%); HRMS (ESI) calcd for C₁₅H₁₄O₄NaS [M+Na]⁺ 313.0505, found 313.0507. IR *v*_{max} (film): 2917, 2850, 1684 (CO), 1595, 1485, 1395, 1321 (SO₂), 1278, 1252, 1184, 1153 (SO₂), 1089, 1017, 911, 817, 681 cm⁻¹. M.p.: 120 – 123 °C.

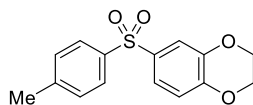
4-{4-[(2,3-Dihydrobenzofuran-5-yl)sulfonyl]phenyl}morpholine 36s



General procedure A was followed with 2,3-dihydrobenzofuran-5-boronic acid (98 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-(4-iodophenyl)morpholine (57.8 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (50% EtOAc in petroleum ether) to give the titled product as a white solid (54 mg, 79%).

¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, *J* = 9.1 Hz, 2H, *H*_{Ar}), 7.71 – 7.66 (m, 2H, *H*_{Ar}), 6.86 (d, *J* = 9.1 Hz, 2H, *H*_{Ar}), 6.78 (d, *J* = 9.0 Hz, 1H, *H*_{Ar}), 4.61 (t, *J* = 8.8 Hz, 2H, ArOCH₂CH₂), 3.83 – 3.76 (m, 4H, CH₂OCH₂), 3.28 – 3.13 (m, 6H, NCH₂ and ArOCH₂CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 164.0, 154.0, 134.5, 131.4, 129.2, 129.0, 128.6, 124.6, 114.0, 109.7, 72.4, 66.6, 47.6, 29.2. LRMS (ESI, *m/z*) 368.1 ([M+Na]⁺, 100%); HRMS (ESI) calcd for C₁₈H₁₉O₄NaNS [M+Na]⁺ 368.0927, found 368.0923. IR *v*_{max} (film): 2927, 2835, 1590, 1482, 1381, 1328, 1296 (SO₂), 1239, 1173, 1135 (SO₂), 1124, 1088, 923, 890, 819, 694, 607 cm⁻¹. M.p.: 188 – 191 °C.

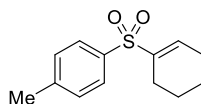
6-Tosyl-2,3-dihydrobenzo-1,4-dioxine 36t



General procedure A was followed with 1,4-benzodioxane-6-boronic acid (108 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (40% Et₂O in petroleum ether) to give the titled product as a white solid (36 mg, 62%).

¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, *J* = 8.3 Hz, 2H, *H*_{Ar}), 7.47 – 7.39 (m, 2H, *H*_{Ar}), 7.28 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 6.92 (d, *J* = 8.3 Hz, 1H, *H*_{Ar}), 4.32 – 4.22 (m, 4H, OCH₂), 2.39 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 147.9, 144.0, 143.8, 139.3, 134.5, 130.0, 127.6, 121.4, 118.1, 117.3, 64.7, 64.3, 21.7. LRMS (ESI, *m/z*) 313.1 ([M+Na]⁺, 100%); HRMS (ESI) calcd for C₁₅H₁₄O₄NaS [M+Na]⁺ 313.0505, found 313.0508. IR *v*_{max} (film): 3065, 2923, 1496, 1286 (SO₂), 1254, 1150 (SO₂), 1095, 1063, 878, 815, 710, 664 cm⁻¹. M.p.: 148 – 151 °C.

1-(Cyclohex-1-en-1-ylsulfonyl)-4-methylbenzene 36u

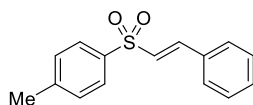


General procedure A was followed with 1-cyclohexen-1-yl-boronic acid (76 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (20%

Et₂O in petroleum ether) to give the titled product as a white solid (27 mg, 57%).

¹H NMR (400 MHz, CDCl₃) δ 7.73 (d, *J* = 7.9 Hz, 2H, *H*_{Ar}), 7.31 (d, *J* = 7.9 Hz, 2H, *H*_{Ar}), 7.03 (tt, *J* = 3.8, 1.7 Hz, 1H, *CH*), 2.43 (s, 3H, *CH*₃), 2.29 – 2.23 (m, 2H, SO₂CCH₂), 2.19 – 2.13 (m, 2H, SO₂CCHCH₂), 1.69 – 1.61 (m, 2H, SO₂CCHCH₂CH₂), 1.59 – 1.53 (m, 2H, SO₂CCH₂CH₂); **¹³C NMR** (100 MHz, CDCl₃) δ 144.1, 140.1, 138.0, 136.5, 129.8, 128.2, 25.6, 22.9, 22.0, 21.8, 21.0. **LRMS** (ESI, *m/z*) 237.1 ([*M*+*H*]⁺, 100%); **HRMS** (ESI) calcd for C₁₃H₁₇O₂S [*M*+*H*]⁺ 237.0944, found 237.0947. **M.p.**: 66 – 67 °C (lit. 64 – 65 °C). The data recorded are consistent with the literature.^[244]

***trans*-1-Methyl-4-(styrylsulfonyl)benzene 36v**

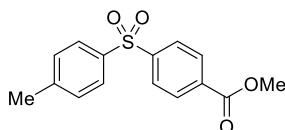


General procedure A was followed with *trans*-2-phenylvinylboronic acid (89 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (20% Et₂O in petroleum ether) to give the titled product as a white solid (32 mg, 63%).

¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, *J* = 8.3 Hz, 2H, *H*_{Ar}), 7.66 (d, *J* = 15.4 Hz, 1H, SO₂CH), 7.51 – 7.46 (m, 2H, *H*_{Ar}), 7.44 – 7.37 (m, 3H, *H*_{Ar}), 7.35 (d, *J* = 9.3 Hz, 2H, *H*_{Ar}), 6.85 (d, *J* = 15.4 Hz, 1H, ArCH), 2.44 (s, 3H, *CH*₃); **¹³C NMR** (100 MHz, CDCl₃) δ 144.5, 142.1, 137.8, 132.6, 131.2, 130.1, 129.2, 128.7, 127.9, 127.7, 21.8. **LRMS** (ESI, *m/z*) 259.0 ([*M*+*H*]⁺, 100%); **HRMS** (ESI) calcd for C₁₅H₁₅O₂S [*M*+*H*]⁺ 259.0787, found 259.0790.

M.p.: 110 – 111 °C (lit. 110 – 112 °C). The data recorded are consistent with the literature.^[245]

Methyl 4-tosylbenzoate 36aa

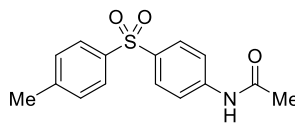


General procedure A was followed with [4-(methoxycarbonyl)phenyl]boronic acid (108 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (30% Et₂O in petroleum ether) to give the titled product as a white solid (21 mg, 36%).

¹H NMR (400 MHz, CDCl₃) δ 8.14 (d, *J* = 8.6 Hz, 2H, *H*_{Ar}), 7.99 (d, *J* = 8.6 Hz, 2H, *H*_{Ar}), 7.83 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 7.31 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 3.93 (s, 3H, OCH₃), 2.41 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 165.7, 146.0, 144.9, 138.0, 134.2, 130.6, 130.3, 128.1, 127.7, 52.8, 21.8.

LRMS (ESI, *m/z*) 291.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₅H₁₅O₄S [M+H]⁺ 291.0691, found 291.0684. **M.p.:** 122 – 126 °C (lit. 124 – 125 °C). The data recorded are consistent with the literature.^[32b]

***N*-(4-Tosylphenyl)acetamide 36ab**



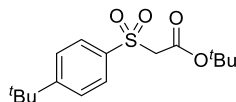
General procedure A was followed with (4-acetamidophenyl)boronic acid (107 mg, 0.6 mmol, 3.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (72 mg, 0.3 mmol, 1.5 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 10 mol%) and 4-iodotoluene (44 mg, 0.2 mmol, 1.0 eq.). The product was purified *via* flash column chromatography (40% Et₂O in petroleum ether) to give the titled product as a white solid (22 mg, 38%).

¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, *J* = 8.8 Hz, 2H, *H*_{Ar}), 7.79 (d, *J* = 8.2 Hz, 2H, *H*_{Ar}), 7.63 (d, *J* = 8.8 Hz, 2H, *H*_{Ar}), 7.51 (br s, 1H, NH), 7.28 (d, *J* = 8.2 Hz, 2H, *H*_{Ar}), 2.39 (s, 3H, ArCH₃), 2.19 (s, 3H, COCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 168.7, 144.2, 142.3, 139.0, 136.7, 130.1, 129.0, 127.7, 119.6, 24.9, 21.7. LRMS (ESI, *m/z*) 290.0 ([M+H]⁺, 100%); HRMS (ESI) calcd for C₁₅H₁₆NO₃S [M+H]⁺ 290.0851, found 290.0847. **M.p.:** 197 – 199 °C (lit. 196 – 199 °C). The data recorded are consistent with the literature.^[246]

6.2.2. Synthesis of *tert*-butyl 2-(arylsulfonyl)acetate

GENERAL PROCEDURE B for the synthesis of *tert*-butyl 2-(arylsulfonyl)acetate

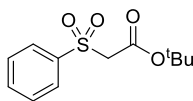
4-*tert*-Butyl 2-[[4-(*tert*-butyl)phenyl]sulfonyl]acetate **40a**



4-*tert*-Butylphenylboronic acid (36 mg, 0.2 mmol, 1.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.) were mixed and dissolved in DMPU (1 mL) under nitrogen. The reaction mixture was placed in a pre-heated oil bath at 90 °C and stirred for 12 hours prior to cooling to room temperature. Et₃N (42 μL, 0.3 mmol, 1.5 eq.) was then added, and *tert*-butylbromoacetate (59 μL, 0.4 mmol, 2.0 eq.) was immediately injected dropwise. The resulting mixture was stirred at room temperature for 2 hours before being quenched with water (10 mL) and extracted with Et₂O (3 × 10 mL). Combined organic phases were washed with brine (3 × 10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (40% Et₂O in petroleum ether) to give the title compound as a white solid (54 mg, 86%).

¹H NMR (400 MHz, CDCl₃) δ 7.86 (d, *J* = 8.8 Hz, 2H, *H*_{Ar}), 7.58 (d, *J* = 8.8 Hz, 2H, *H*_{Ar}), 4.02 (s, 2H, CH₂), 1.35 (s, 18H, C(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ 161.5, 158.3, 136.0, 128.5, 126.3, 83.6, 62.4, 35.5, 31.2, 27.8. **LRMS** (ESI, *m/z*) 335.0 ([M+Na]⁺, 100%). **HRMS** (ESI) calcd for C₁₆H₂₄O₄NaS [M+Na]⁺ 335.1288, found 335.1284. **M.p.**: 82 – 84 °C (lit. 107 – 108 °C). The data recorded are consistent with the literature.^[124]

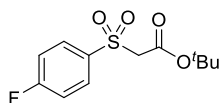
***tert*-Butyl 2-(phenylsulfonyl)acetate 40b**



General procedure B was followed with phenylboronic acid (24 mg, 0.2 mmol, 1.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.), Et₃N (42 μL, 0.3 mmol, 1.5 eq.) and *tert*-butylbromoacetate (59 μL, 0.4 mmol, 2.0 eq.). The crude product was purified *via* flash column chromatography (40% Et₂O in petroleum ether) to give the title compound as a colourless oil (41 mg, 80%).

¹H NMR (400 MHz, CDCl₃) δ 7.95 (dd, *J* = 8.4, 1.3 Hz, 2H, *H*_{Ar}), 7.72 – 7.65 (m, 1H, *H*_{Ar}), 7.62 – 7.56 (m, 2H, *H*_{Ar}), 4.04 (s, 2H, CH₂), 1.36 (s, 9H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 161.4, 139.0, 134.3, 129.3, 128.7, 83.8, 62.2, 27.8. LRMS (ESI, *m/z*) 279.1 ([M+Na]⁺, 100%); HRMS (ESI) calcd for C₁₂H₁₆O₄NaS [M+Na]⁺ 279.0662, found 279.0662. The data recorded are consistent with the literature.^[113]

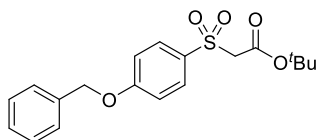
***tert*-Butyl 2-[(4-fluorophenyl)sulfonyl]acetate 40c**



General procedure B was followed with 4-fluorophenylboronic acid (28 mg, 0.2 mmol, 1.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.), Et₃N (42 μL, 0.3 mmol, 1.5 eq.) and *tert*-butylbromoacetate (59 μL, 0.4 mmol, 2.0 eq.). The crude product was purified *via* flash column chromatography (30% Et₂O in petroleum ether) to give the title compound as a colourless oil (40 mg, 73%).

¹H NMR (400 MHz, CDCl₃) δ 8.01 – 7.93 (m, 2H, *H*_{Ar}), 7.30 – 7.24 (m, 2H, *H*_{Ar}), 4.03 (s, 2H, CH₂), 1.38 (s, 9H, C(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ 166.2 (d, ¹*J*_{C-F} = 257 Hz, C_{Ar}), 161.4, 135.0 (d, ⁴*J*_{C-F} = 3.3 Hz, C_{Ar}), 131.7 (d, ³*J*_{C-F} = 9.7 Hz, C_{Ar}), 116.6 (d, ²*J*_{C-F} = 22.8 Hz, C_{Ar}), 84.0, 62.2, 27.8; **¹⁹F NMR** (376 MHz, CDCl₃) δ 102.6. **LRMS** (ESI, *m/z*) 297 ([M+H]⁺, 100%). **HRMS** (ESI) calcd for C₁₂H₁₅O₄NaFS [M+Na]⁺ 297.0567, found 297.0569. The data recorded are consistent with the literature.^[124]

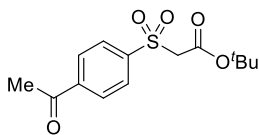
***tert*-Butyl 2-{{4-(benzyloxy)phenyl}sulfonyl}acetate 40d**



General procedure B was followed with 4-(benzyloxy)phenylboronic acid (46 mg, 0.2 mmol, 1.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.), Et₃N (42 μL, 0.3 mmol, 1.5 eq.) and *tert*-butylbromoacetate (59 μL, 0.4 mmol, 2.0 eq.). The crude product was purified *via* flash column chromatography (50% Et₂O in petroleum ether) to give the title compound as a white solid (62 mg, 85%).

¹H NMR (400 MHz, CDCl₃) δ 7.86 (d, *J* = 9.0 Hz, 2H, *H*_{Ar}), 7.44 – 7.32 (m, 5H, *H*_{Ar}), 7.09 (d, *J* = 9.0 Hz, 2H, *H*_{Ar}), 5.15 (s, 2H, OCH₂), 4.00 (s, 2H, SO₂CH₂), 1.37 (s, 9H, C(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ 163.3, 161.7, 135.8, 131.0, 130.8, 128.9, 128.6, 127.6, 115.2, 83.6, 70.5, 62.5, 27.8. **LRMS** (ESI, *m/z*) 361.1 ([M-H]⁻, 100%); **HRMS** (ESI) calcd for C₁₉H₂₁O₅S [M-H]⁻ 361.1115, found 361.1115. **IR** ν_{max} (film): 3658, 2980, 1731 (CO), 1593, 1497, 1393, 1326 (SO₂), 1258, 1144 (SO₂), 1086, 954, 834, 723, 699 cm⁻¹. **M.p.**: 81 – 83 °C.

***tert*-Butyl 2-[(4-acetylphenyl)sulfonyl]acetate 40e**



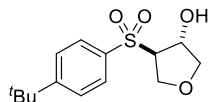
General procedure B was followed with 4-acetylphenylboronic acid (33 mg, 0.2 mmol, 1.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.), Et₃N (42 μL, 0.3 mmol, 1.5 eq.) and *tert*-butylbromoacetate (59 μL, 0.4 mmol, 2.0 eq.). The crude product was purified *via* flash column chromatography (40% Et₂O in petroleum ether) to give the title compound as a white solid (35 mg, 59%).

¹H NMR (400 MHz, CDCl₃) δ 8.13 (d, *J* = 8.7 Hz, 2H, *H*_{Ar}), 8.05 (d, *J* = 8.7 Hz, 2H, *H*_{Ar}), 4.07 (s, 2H, CH₂), 2.67 (s, 3H, CH₃), 1.38 (s, 9H, C(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ 196.8, 161.2, 142.7, 141.2, 129.2, 129.0, 84.2, 62.0, 27.9, 27.1. **LRMS** (ESI, *m/z*) 321.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₄H₁₈O₅NaS [M+H]⁺ 321.0767, found 321.0768. **M.p.:** 83 – 85 °C (lit. 85 °C). The data recorded are consistent with the literature.^[120]

6.2.3. Synthesis of β -hydroxysulfone

GENERAL PROCEDURE C for the synthesis of β -hydroxysulfone

4-{{4-(*tert*-Butyl)phenyl}sulfonyl}tetrahydrofuran-3-ol **41a**

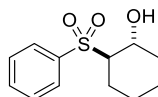


4-*tert*-Butylphenylboronic acid (36 mg, 0.2 mmol, 1.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.) were mixed and dissolved in DMPU (1 mL) under nitrogen. The reaction mixture was placed in a pre-heated oil bath at 90 °C and stirred for 12 hours prior to cooling to room temperature. Et₃N (42 μ L, 0.3 mmol, 1.5 eq.) was then added, and the mixture was diluted with water (1 mL). 3,4-Epoxytetrahydrofuran (35 mg, 0.4 mmol, 2.0 eq.) was injected in a suspension of water (1 mL). The resultant mixture was stirred at room temperature for 2 hours before being quenched with water (10 mL) and extracted with Et₂O (3 $\times$ 10 mL). Combined organic phases were washed with brine (3 $\times$ 10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (50% Et₂O in petroleum ether) to give the title compound as a white solid (44 mg, 78%).

¹H NMR (400 MHz, CDCl₃) δ 7.83 (d, *J* = 8.7 Hz, 2H, *H*_{Ar}), 7.60 (d, *J* = 8.7 Hz, 2H, *H*_{Ar}), 4.93 – 4.86 (m, 1H, (OH)CH), 4.19 – 4.05 (m, 2H, SO₂CHCH₂), 4.03 – 3.94 (m, 1H, CH(OH)CH_aH_b), 3.78 – 3.67 (m, 2H, CH(OH)CH_aH_b and SO₂CH), 2.52 (d, *J* = 5.2 Hz, 1H, OH), 1.35 (s, 9H, C(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ 158.6, 135.2, 128.3, 126.8, 74.9, 72.7, 72.0, 67.3, 35.5, 31.2. **LRMS** (ESI, *m/z*) 307.1 ([M+Na]⁺, 100%); **HRMS** (ESI) calcd for C₁₄H₂₀O₄NaS [M+Na]⁺ 307.0975, found 307.0973. **IR** ν_{max} (film): 3425 (OH),

2980, 2971, 1594, 1463, 1398, 1307 (SO₂), 1291, 1150 (SO₂), 1108, 1082, 967, 840, 757, 631 cm⁻¹. **M.p.**: 109 – 112 °C.

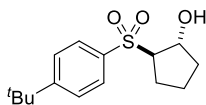
2-(Phenylsulfonyl)cyclohexan-1-ol **41b**



General procedure C was followed with phenylboronic acid (24 mg, 0.2 mmol, 1.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.), Et₃N (42 µL, 0.3 mmol, 1.5 eq.) and cyclohexene oxide (40 µL, 0.4 mmol, 2.0 eq.). The crude product was purified *via* flash column chromatography (50% Et₂O in petroleum ether) to give the title compound as a white solid (27 mg, 56%).

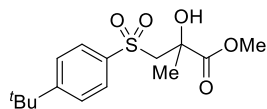
¹H NMR (400 MHz, CDCl₃) δ 7.95 – 7.89 (m, 2H, *H*_{Ar}), 7.73 – 7.66 (m, 1H, *H*_{Ar}), 7.63 – 7.56 (m, 2H, *H*_{Ar}), 4.30 (d, *J* = 1.1 Hz, 1H, OH), 3.96 – 3.88 (m, 1H, (OH)CH), 2.98 (ddd, *J* = 12.4, 9.7, 3.9 Hz, 1H, SO₂CH), 2.18 – 2.08 (m, 1H, CH(OH)CH_aH_b), 1.94 – 1.87 (m, 1H, SO₂CHCH_aH_b), 1.77 – 1.66 (m, 2H, CH₂), 1.37 – 1.03 (m, 4H, CH(OH)CH_aH_b, SO₂CHCH_aH_b and CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 136.9, 134.3, 129.4, 129.2, 69.1, 68.4, 34.3, 25.9, 24.7, 23.7. **LRMS** (ESI, *m/z*) 263.0 ([M+Na]⁺, 100%); **HRMS** (ESI) calcd for C₁₂H₁₆O₃NaS [M+Na]⁺ 263.0712, found 263.0712. **M.p.**: 103 – 105 °C (lit. 106 – 107 °C). The data recorded are consistent with the literature.^[247]

2-{{4-(*tert*-Butyl)phenyl}sulfonyl}cyclopentan-1-ol 41c



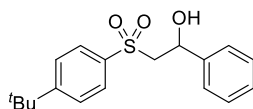
General procedure C was followed with 4-*tert*-butylphenylboronic acid (36 mg, 0.2 mmol, 1.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.), Et₃N (42 μL, 0.3 mmol, 1.5 eq.) and cyclopentene oxide (35 μL, 0.4 mmol, 2.0 eq.). The crude product was purified *via* flash column chromatography (30% Et₂O in petroleum ether) to give the title compound as a colourless oil which solidified when left standing (45 mg, 79%).

¹H NMR (400 MHz, CDCl₃) δ 7.81 (d, *J* = 8.7 Hz, 2H, *H*_{Ar}), 7.57 (d, *J* = 8.7 Hz, 2H, *H*_{Ar}), 4.68 (app. qd, *J* = 6.5, 2.8 Hz, 1H, OHCH), 3.35 (td, *J* = 8.7, 6.3 Hz, 1H, SO₂CH), 2.59 (d, *J* = 2.8 Hz, 1H, OH), 2.15 – 2.03 (m, 1H, CH(OH)CH_aH_b), 1.99 – 1.91 (m, 2H, SO₂CHCH₂), 1.80 – 1.64 (m, 3H, CH(OH)CH_aH_b, CH(OH)CH₂CH₂), 1.35 (s, 9H, C(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ 158.0, 135.6, 128.4, 126.5, 73.2, 71.5, 35.4, 34.3, 31.2, 26.2, 21.9. **LRMS** (ESI, *m/z*) 305.1 ([M+Na]⁺, 100%); **HRMS** (ESI) calcd for C₁₅H₂₂O₃NaS [M+Na]⁺ 305.1182, found 305.1184. **IR** ν_{max} (film): 3486 (OH), 2963, 1594, 1399, 1303 (SO₂), 1288, 1146 (SO₂), 1107, 1084, 985, 840, 755, 631 cm⁻¹. **M.p.**: 61 – 64 °C.

Methyl 3-{{[4-(*tert*-butyl)phenyl]sulfonyl}-2-hydroxy-2-methylpropanoate 41d

General procedure C was followed with 4-*tert*-butylphenylboronic acid (36 mg, 0.2 mmol, 1.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.), Et₃N (42 μL, 0.3 mmol, 1.5 eq.) and methyl 2-methylglycidate (42 μL, 0.4 mmol, 2.0 eq.). The crude product was purified *via* flash column chromatography (60% Et₂O in petroleum ether) to give the title compound as a white solid (51 mg, 82%).

¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, *J* = 8.7 Hz, 2H, *H*_{Ar}), 7.55 (d, *J* = 8.7 Hz, 2H, *H*_{Ar}), 3.82 (s, 1H, OH), 3.77 (s, 3H, CO₂CH₃), 3.73 (d, *J* = 14.6 Hz, 1H, SO₂CH_aH_b), 3.53 (d, *J* = 14.6 Hz, 1H, SO₂CH_aH_b), 1.46 (s, 3H, CCH₃), 1.34 (s, 9H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 174.5, 158.0, 137.6, 128.1, 126.3, 72.5, 64.0, 53.5, 35.4, 31.2, 27.3. LRMS (ESI, *m/z*) 337.1 ([M+Na]⁺, 100%). HRMS (ESI) calcd for C₁₅H₂₂O₅NaS [M+Na]⁺ 337.1080, found 337.1078. IR ν_{max} (film): 3497 (OH), 2871, 1743 (CO), 1594, 1494, 1453, 1317 (SO₂), 1291, 1206, 1150 (SO₂), 1108, 1083, 982, 840, 820, 761 cm⁻¹. M.p.: 122 – 125 °C.

2-{{[4-(*tert*-Butyl)phenyl]sulfonyl}-1-phenylethan-1-ol 41e

General procedure C was followed with 4-*tert*-butylphenylboronic acid (36 mg, 0.2 mmol, 1.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.), Et₃N (42 μL, 0.3 mmol, 1.5 eq.) and styrene oxide (46 μL, 0.4 mmol, 2.0 eq.). The

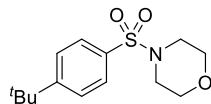
crude product was purified *via* flash column chromatography (30% Et₂O in petroleum ether) to give the title compound as a colourless oil which solidified when left standing (39 mg, 61%).

¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, *J* = 8.6 Hz, 2H, *H*_{Ar}), 7.59 (d, *J* = 8.6 Hz, 2H, *H*_{Ar}), 7.37 – 7.27 (m, 5H, *H*_{Ar}), 5.29 (d, *J* = 10.1 Hz, 1H, *OH*), 3.76 (d, *J* = 2.0 Hz, 1H, SO₂CH_aH_b), 3.49 (dd, *J* = 14.3, 10.1 Hz, 1H, (OH)CH), 3.34 (dd, *J* = 14.3, 1.8 Hz, 1H, SO₂CH_aH_b), 1.36 (s, 9H, C(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ 158.4, 140.8, 136.2, 128.9, 128.5, 128.0, 126.7, 125.8, 68.6, 64.1, 35.5, 31.2. **LRMS** (ESI, *m/z*) 341.1 ([M+Na]⁺, 100%); **HRMS** (ESI) calcd for C₁₈H₂₂O₃NaS [M+Na]⁺ 341.1182, found 341.1170. **IR** ν_{max} (film): 3497 (OH), 3064, 2961, 1595, 1496, 1455, 1399, 1306 (SO₂), 1289, 1200, 1149 (SO₂), 1108, 1086, 841, 781, 700, 649 cm⁻¹. **M.p.**: 56 – 58 °C.

6.2.4. Synthesis of sulfonamides

GENERAL PROCEDURE D for the synthesis of sulfonamides

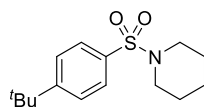
4-{[4-(*tert*-Butyl)phenyl]sulfonyl}morpholine **42a**



4-*tert*-Butylphenylboronic acid (36 mg, 0.2 mmol, 1.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.) were mixed and dissolved in DMPU (1 mL) under nitrogen. The reaction mixture was put into a pre-heated oil bath at 90 °C and stirred for 12 hours prior to cooling to room temperature. Et₃N (42 µL, 0.3 mmol, 1.5 eq.) was added, followed by morpholine (35 µL, 0.4 mmol, 2.0 eq.). NaOCl (1.20 mL, 2% aqueous solution w/w, 0.4 mmol, 2.0 eq.) was then added dropwise. The resulting mixture was stirred at room temperature for 3 hours before being quenched with water (10 mL) and extracted with Et₂O (3 × 10 mL). Combined organic phases were washed with brine (3 × 10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (10% EtOAc in petroleum ether) to give the title compound as a white solid (46 mg, 82%).

¹H NMR (400 MHz, CDCl₃) δ 7.67 (d, *J* = 8.6 Hz, 2H, *H*_{Ar}), 7.55 (d, *J* = 8.6 Hz, 2H, *H*_{Ar}), 3.78 – 7.67 (m, 4H, OCH₂), 3.05 – 2.94 (m, 4H, NCH₂), 1.35 (s, 9H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 157.0, 132.1, 127.9, 126.2, 66.3, 46.1, 35.3, 31.2. LRMS (ESI, *m/z*) 284.1 ([M+H]⁺, 100%); HRMS (ESI) calcd for C₁₄H₂₂O₃NS [M+H]⁺ 284.1315, found 284.1316. **M.p.**: 150 – 152 °C. The data recorded are consistent with the literature.^[248]

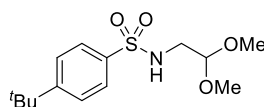
1-[[4-(*tert*-Butyl)phenyl]sulfonyl]piperidine 42b



General procedure D was followed with 4-*tert*-butylphenylboronic acid (36 mg, 0.2 mmol, 1.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.), Et₃N (42 μL, 0.3 mmol, 1.5 eq.), piperidine (39 μL, 0.4 mmol, 2.0 eq.) and NaOCl (1.2 mL, 2% aqueous solution w/w, 0.4 mmol, 2.0 eq.). The crude product was purified *via* flash column chromatography (10% EtOAc in petroleum ether) to give the title compound as a white solid (43 mg, 76%).

¹H NMR (400 MHz, CDCl₃) δ 7.66 (d, *J* = 8.7 Hz, 2H, *H*_{Ar}), 7.51 (d, *J* = 8.7 Hz, 2H, *H*_{Ar}), 3.01 – 2.94 (m, 4H, NCH₂), 1.63 (app. quin, *J* = 5.9 Hz, 4H, NCH₂CH₂), 1.45 – 1.37 (m, 2H, NCH₂CH₂CH₂), 1.33 (s, 9H, C(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ 156.3, 133.3, 127.7, 126.0, 47.0, 35.2, 31.2, 25.3, 23.6. **LRMS** (ESI, *m/z*) 304.1 ([M+Na]⁺, 100%); **HRMS** (ESI) calcd for C₁₅H₂₃O₂NNaS [M+Na]⁺ 304.1346, found 304.1341. **M.p.:** 127 – 130 °C (lit. 114 – 115 °C). The data recorded are consistent with the literature.^[249]

4-(*tert*-Butyl)-N-(2,2-dimethoxyethyl)benzenesulfonamide 42c

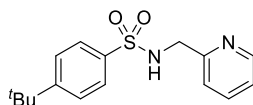


General procedure D was followed with 4-*tert*-butylphenylboronic acid (36 mg, 0.2 mmol, 1.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.), Et₃N (42 μL, 0.3 mmol, 1.5 eq.), 2,2-dimethoxyethylamine (43 μL, 0.4 mmol, 2.0 eq.) and NaOCl (1.2 mL, 2% aqueous solution w/w, 0.4 mmol, 2.0 eq.). The crude product was

purified *via* flash column chromatography (10% EtOAc in petroleum ether) to give the title compound as a colourless oil which solidified when left standing (47 mg, 79%).

¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, *J* = 8.5 Hz, 2H, *H*_{Ar}), 7.52 (d, *J* = 8.5 Hz, 2H, *H*_{Ar}), 4.62 (t, *J* = 6.2 Hz, 1H, *NH*), 4.33 (t, *J* = 5.6 Hz, 1H, *NCH₂CH*), 3.33 (s, 6H, *OCH₃*), 3.04 (t, *J* = 6.0 Hz, 2H, *NCH₂*), 1.34 (s, 9H, *C(CH₃)₃*); **¹³C NMR** (100 MHz, CDCl₃) δ 156.6, 136.6, 126.9, 126.2, 102.7, 54.8, 44.6, 35.2, 31.1. **LRMS** (ESI, *m/z*) 324 ([*M*+*Na*]⁺, 100%); **HRMS** (ESI) calcd for C₁₄H₂₃O₄NNaS [*M*+*Na*]⁺ 324.1240, found 324.1239. **IR** *v*_{max} (film): 3278 (*NH*), 2963, 1596, 1463, 1330 (SO₂), 1197, 1164 (SO₂), 1134, 1112, 1087, 977, 885, 838, 753, 628 cm⁻¹. **M.p.**: 45 – 49 °C.

4-(*tert*-Butyl)-*N*-(pyridin-2-ylmethyl)benzenesulfonamide 42d

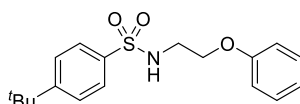


General procedure D was followed with 4-*tert*-butylphenylboronic acid (36 mg, 0.2 mmol, 1.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.), Et₃N (42 μL, 0.3 mmol, 1.5 eq.), 2-picolylamine (41 μL, 0.4 mmol, 2.0 eq.) and NaOCl (1.2 mL, 2% aqueous solution w/w, 0.4 mmol, 2.0 eq.). The crude product was purified *via* flash column chromatography (10% EtOAc in petroleum ether) to give the title compound as a colourless oil (48 mg, 80%).

¹H NMR (400 MHz, CDCl₃) δ 8.43 (d, *J* = 4.4 Hz, 1H, *H*_{Ar}), 7.75 (d, *J* = 8.7 Hz, 2H, *H*_{Ar}), 7.57 (dd, *J* = 7.8, 1.8 Hz, 1H, *H*_{Ar}), 7.43 (d, *J* = 8.7 Hz, 2H, *H*_{Ar}), 7.15 (d, *J* = 7.8 Hz, 1H, *H*_{Ar}), 7.14 – 7.10 (m, 1H, *H*_{Ar}), 6.01 (t, *J* = 5.3 Hz, 1H, *NH*), 4.25 (d, *J* = 5.6 Hz, 2H, *NCH₂*), 1.30 (s, 9H, *C(CH₃)₃*); **¹³C NMR** (100 MHz, CDCl₃) δ 156.4, 155.1, 149.1, 136.9, 136.6,

127.1, 126.1, 122.7, 122.1, 47.7, 35.2, 31.2. **LRMS** (ESI, m/z) 305.1 ($[M+H]^+$, 100%); **HRMS** (ESI) calcd for $C_{16}H_{21}O_2N_2S$ $[M+H]^+$ 305.1318, found 305.1316. The data recorded are consistent with the literature.^[250]

4-(*tert*-Butyl)-*N*-(2-phenoxyethyl)benzenesulfonamide **42e**



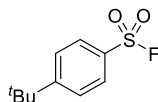
General procedure D was followed with 4-*tert*-butylphenylboronic acid (36 mg, 0.2 mmol, 1.0 eq.), $Cu(MeCN)_4BF_4$ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.), Et_3N (42 μ L, 0.3 mmol, 1.5 eq.), 2-phenoxyethylamine (52 μ L, 0.4 mmol, 2.0 eq.) and NaOCl (1.2 mL, 2% aqueous solution w/w, 0.4 mmol, 2.0 eq.). The crude product was purified *via* flash column chromatography (10% EtOAc in petroleum ether) to give the title compound as a colourless oil which solidified when left standing (53 mg, 80%).

1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.8 Hz, 2H, H_{Ar}), 7.50 (d, J = 8.8 Hz, 2H, H_{Ar}), 7.31 – 7.20 (m, 2H, H_{Ar}), 6.98 – 6.92 (m, 1H, H_{Ar}), 6.81 – 6.75 (m, 2H, H_{Ar}), 5.01 (t, J = 6.2 Hz, 1H, NH), 3.99 – 3.90 (m, 2H, OCH_2), 3.42 – 3.32 (m, 2H, NCH_2), 1.33 (s, 9H, $C(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.2, 156.7, 137.0, 129.7, 127.0, 126.3, 121.5, 114.5, 66.3, 42.8, 35.3, 31.2. **LRMS** (ESI, m/z) 356.1 ($[M+Na]^+$, 100%); **HRMS** (ESI) calcd for $C_{18}H_{23}O_3NNaS$ $[M+Na]^+$ 356.1291, found 356.1290. **IR** ν_{max} (film): 3283 (NH), 2962, 1598, 1496, 1398, 1325 (SO_2), 1244, 1161 (SO_2), 1112, 1087, 961, 835, 691, 628 cm^{-1} . **M.p.**: 38 – 41 $^{\circ}C$.

6.2.5. Synthesis of sulfonyl fluorides

GENERAL PROCEDURE E for the synthesis of sulfonyl fluorides

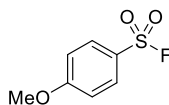
4-(*tert*-Butyl)benzenesulfonyl fluoride **43a**



4-*tert*-Butylphenylboronic acid (36 mg, 0.2 mmol, 1.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.) were mixed and dissolved in DMPU (1 mL) under nitrogen. The reaction mixture was put into a pre-heated oil bath at 90 °C and stirred for 12 hours prior to cooling to 0 °C. NFSI (95 mg, 0.3 mmol, 1.5 eq.) was pre-dissolved in DMPU (0.2 mL) and added dropwise. The resulting mixture was warmed to room temperature and stirred for 3 hours before being quenched with water (10 mL) and extracted with Et₂O (3 × 10 mL). Combined organic phases were washed with brine (3 × 10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (10% EtOAc in petroleum ether) to give the title compound as a white solid (27 mg, 62%).

¹H NMR (500 MHz, CDCl₃) δ 7.94 (d, *J* = 8.4 Hz, 2H, *H*_{Ar}), 7.63 (d, *J* = 8.4 Hz, 2H, *H*_{Ar}), 1.37 (s, 9H, C(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃) δ 160.1, 130.1 (d, ²*J*_{C-F} = 24.2 Hz, *C*_{Ar}), 128.5, 126.8, 35.7, 31.1; ¹⁹F NMR (376 MHz, CDCl₃) δ 66.2. HRMS (CI) calcd for C₁₀H₁₇FNO₂S [M+NH₄]⁺ 234.0964, found 234.0960. **M.p.**: 53 – 55 °C. The data recorded are consistent with the literature.^[251]

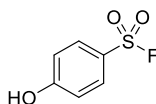
4-Methoxybenzenesulfonyl fluoride 43b



General procedure E was followed with 4-methoxyphenylboronic acid (30 mg, 0.2 mmol, 1.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.) and NFSI (95 mg, 0.3 mmol, 1.5 eq.). The crude product was purified *via* flash column chromatography (10% EtOAc in petroleum ether) to give the title compound as colourless oil (29 mg, 76%).

¹H NMR (500 MHz, CDCl₃) δ 7.95 (d, *J* = 8.9 Hz, 2H, *H*_{Ar}), 7.06 (d, *J* = 8.9 Hz, 2H, *H*_{Ar}), 3.92 (s, 3H, OCH₃); ¹³C NMR (125 MHz, CDCl₃) δ 165.3, 131.0, 124.3 (d, ²*J*_{C-F} = 24.7 Hz, *C*_{Ar}), 115.0, 56.1; ¹⁹F NMR (376 MHz, CDCl₃) δ 67.3. The data recorded are consistent with the literature.^[251]

4-Hydroxybenzenesulfonyl fluoride 43c

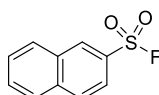


General procedure E was followed with 4-hydroxyphenylboronic acid (28 mg, 0.2 mmol, 1.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.) and NFSI (95 mg, 0.3 mmol, 1.5 eq.). The crude product was purified *via* flash column chromatography (10% EtOAc in petroleum ether) to give the title compound as a white solid (18 mg, 52%).

¹H NMR (500 MHz, CDCl₃) δ 7.91 (d, *J* = 8.8 Hz, 2H, *H*_{Ar}), 7.01 (d, *J* = 8.8 Hz, 2H, *H*_{Ar}), 6.09 (br, 1H, OH); ¹³C NMR (125 MHz, CDCl₃) δ 162.0, 131.4, 124.6 (d, ²*J*_{C-F} = 25.0 Hz,

C_{Ar}), 116.6; ^{19}F NMR (376 MHz, CDCl_3) δ 67.1. **LRMS** (ESI, m/z) 175.0 ($[\text{M-H}]^-$, 100%); **HRMS** (ESI) calcd for $\text{C}_6\text{H}_4\text{O}_3\text{FS}$ $[\text{M-H}]^-$ 174.9871, found 174.9869. **M.p.:** 74 – 75 °C (lit. 74 – 76 °C). The data recorded are consistent with the literature.^[252]

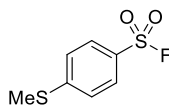
Naphthalene-2-sulfonyl fluoride 43d



General procedure E was followed with 2-naphthylboronic acid (34 mg, 0.2 mmol, 1.0 eq.), $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.) and NFSI (95 mg, 0.3 mmol, 1.5 eq.). The crude product was purified *via* flash column chromatography (10% EtOAc in petroleum ether) to give the title compound as a white solid (22 mg, 53%).

^1H NMR (400 MHz, CDCl_3) δ 8.63 – 8.60 (m, 1H, H_{Ar}), 8.10 – 8.02 (m, 2H, H_{Ar}), 8.00 – 7.92 (m, 2H, H_{Ar}), 7.78 – 7.67 (m, 2H, H_{Ar}); ^{13}C NMR (125 MHz, CDCl_3) δ 136.2, 132.0, 131.1, 130.5, 130.3, 129.9 (d, $^2J_{C-F} = 24.9$ Hz, C_{Ar}), 129.8, 128.5, 128.3, 122.3; ^{19}F NMR (376 MHz, CDCl_3) δ 66.3. **IR** ν_{max} (film): 2981, 2889, 1589, 1401 (SO_2), 1217, 1151 (SO_2), 1079, 954, 861, 756, 667 cm^{-1} . **M.p.:** 85 – 87 °C (lit. 85 – 87 °C). The data recorded are consistent with the literature.^[251]

4-Methylthiobenzenesulfonyl fluoride 43e



General procedure E was followed with 4-(methylthio)phenylboronic acid (34 mg, 0.2 mmol, 1.0 eq.), Cu(MeCN)₄BF₄ (6.4 mg, 0.02 mmol, 10 mol%), DABSO (24 mg, 0.1 mmol, 0.5 eq.) and NFSI (95 mg, 0.3 mmol, 1.5 eq.). The crude product was purified *via* flash column chromatography (10% EtOAc in petroleum ether) to give the title compound as a colourless oil (31 mg, 75%).

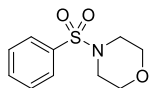
¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, *J* = 8.6 Hz, 2H, *H*_{Ar}), 7.38 (d, *J* = 8.6 Hz, 2H, *H*_{Ar}), 2.55 (s, 3H, SCH₃); ¹³C NMR (125 MHz, CDCl₃) δ 150.4, 128.8, 128.2 (d, ²*J*_{C-F} = 24.8 Hz, *C*_{Ar}), 125.5, 14.8; ¹⁹F NMR (376 MHz, CDCl₃) δ 66.8. HRMS (CI) calcd for C₇H₁₁FNO₂S₂ [M+NH₄]⁺ 224.215, found 224.212. IR ν_{max} (film): 1576, 1448, 1395 (SO₂), 1210, 1193, 1108 (SO₂), 1081, 818, 769, 738, 626 cm⁻¹.

6.3. Chapter 3 data

6.3.1. Synthesis of sulfonamides

GENERAL PROCEDURE F for the synthesis of sulfonamides

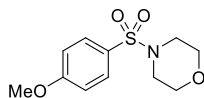
4-(Phenylsulfonyl)morpholine 45a



Phenylboronic acid (97.6 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.) and 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.) were added to a reaction tube. Morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL) were then added to create a suspension and the reaction mixture was heated to 130 °C with stirring for 16 h. After cooling, water (15 mL) was added to quench the reaction and the resulting mixture was washed with EtOAc (3 $\times$ 15 mL). The combined organic phases were further washed with LiCl (5% aqueous solution, 2 $\times$ 15 mL), dried with MgSO₄ and concentrated. The resulting residue was purified *via* silica column chromatography (10% Et₂O in petroleum ether) to give the title compound as an off-white solid (66 mg, 73%).

¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, J = 7.3 Hz, 2H, H_{Ar}), 7.66 – 7.59 (m, 1H, H_{Ar}), 7.58 – 7.51 (m, 2H, H_{Ar}), 3.77 – 3.67 (m, 4H, OCH₂), 3.03 – 2.94 (m, 4H, NCH₂); **¹³C NMR** (100 MHz, CDCl₃) δ 135.1, 133.2, 129.3, 127.9, 127.9, 66.2, 46.1. **LRMS** (ESI, m/z) 228.0 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₀H₁₄O₃NS [M+H]⁺ 228.0689, found 228.0692. **M.p.:** 114 – 115 °C (lit. 117 – 119 °C). The data recorded are consistent with the literature.^[253]

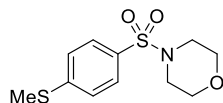
4-[(4-Methoxyphenyl)sulfonyl]morpholine **45b**



General procedure F was followed with 4-methoxyphenylboronic acid (122 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (40% Et₂O in petroleum ether) to give the title compound as an off-white solid (79 mg, 77%).

¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, J = 8.9 Hz, 2H, H_{Ar}), 7.00 (d, J = 8.9 Hz, 2H, H_{Ar}), 3.87 (s, 3H, OCH₃), 3.74 – 3.70 (m, 4H, OCH₂), 2.98 – 2.92 (m, 4H, NCH₂); **¹³C NMR** (100 MHz, CDCl₃) δ 163.3, 130.1, 126.6, 114.4, 66.2, 55.8, 46.1. **LRMS** (ESI, m/z) 258.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₁H₁₆O₄NS [M+H]⁺ 258.0795, found 258.0795. **M.p.:** 107 – 108 °C (lit. 109 – 111 °C). The data recorded are consistent with the literature.^[254]

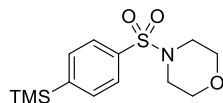
4-[[4-(Methylthio)phenyl]sulfonyl]morpholine **45c**



General procedure F was followed with 4-(methylthio)phenylboronic acid (134 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (30% Et₂O in petroleum ether) to give the title compound as an off-white solid (82 mg, 75%).

¹H NMR (400 MHz, CDCl₃) δ 7.63 (d, J = 8.6 Hz, 2H, H_{Ar}), 7.32 (d, J = 8.6 Hz, 2H, H_{Ar}), 3.79 – 3.66 (m, 4H, OCH₂), 3.02 – 2.88 (m, 4H, NCH₂), 2.53 (s, 3H, SCH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 146.4, 130.7, 128.2, 125.3, 66.2, 46.1, 14.9. **LRMS** (ESI, m/z) 274.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₁H₁₆O₃NS₂ [M+H]⁺ 274.0566, found 274.0567. **M.p.:** 77 – 78 °C (lit.^[255] 142 – 145 °C). The data recorded are consistent with the literature.^[255]

4-{{4-(Trimethylsilyl)phenyl}sulfonyl}morpholine 45d

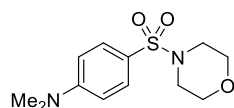


General procedure F was followed with 4-(trimethylsilyl)phenylboronic acid (155 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (10% Et₂O in petroleum ether) to give the title compound as an off-white solid (74 mg, 62%).

¹H NMR (400 MHz, CDCl₃) δ 7.72 – 7.65 (m, 4H, *H*_{Ar}), 3.76 – 3.70 (m, 4H, OCH₂), 3.03 – 2.96 (m, 4H, NCH₂), 0.30 (s, 9H, SiCH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 147.6, 135.2, 134.0, 126.8, 66.2, 46.1, -1.3. **LRMS** (ESI, *m/z*) 322.1 ([M+Na]⁺, 100%); **HRMS** (ESI) calcd for C₁₃H₂₁O₃NNaSSi [M+Na]⁺ 322.0904, found 322.0904. **M.p.**: 144 °C (lit. 144 °C).

The data recorded are consistent with the literature.^[254]

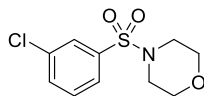
***N,N*-Dimethyl-4-(morpholinosulfonyl)aniline 45e**



General procedure F was followed with 4-(dimethylamino)phenylboronic acid (132 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (10% EtOAc in petroleum ether) to give the title compound as an off-white solid (69 mg, 64%).

¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, J = 9.0 Hz, 2H, H_{Ar}), 6.68 (d, J = 9.0 Hz, 2H, H_{Ar}), 3.74 – 3.70 (m, 4H, OCH₂), 3.05 (s, 6H, CH₃), 2.97 – 2.92 (m, 4H, NCH₂); **¹³C NMR** (100 MHz, CDCl₃) δ 153.1, 129.8, 120.1, 110.9, 66.3, 46.2, 40.2. **LRMS** (ESI, m/z) 271.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₂H₁₉O₃N₂S [M+H]⁺ 271.1111, found 271.1111. **IR** ν_{max} (neat)/cm⁻¹ 2918, 2852, 1598, 1321 (SO₂N), 1148 (SO₂N), 1111, 1097, 1069. **M.p.:** 157 °C.

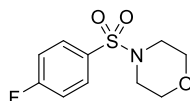
4-[(3-Chlorophenyl)sulfonyl]morpholine **45h**



General procedure F was followed with 3-chlorophenylboronic acid (125 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (20% Et₂O in petroleum ether) to give the title compound as an off-white solid (59 mg, 57%).

¹H NMR (400 MHz, CDCl₃) δ 7.74 (app. t, J = 1.9 Hz, 1H, H_{Ar}), 7.64 (dt, J = 7.7, 1.5 Hz, 1H, H_{Ar}), 7.60 (ddd, J = 8.1, 2.1, 1.1 Hz, 1H, H_{Ar}), 7.50 (t, J = 7.9 Hz, 1H, H_{Ar}), 3.77 – 3.71 (m, 4H, OCH₂), 3.04 – 2.97 (m, 4H, NCH₂); **¹³C NMR** (100 MHz, CDCl₃) δ 137.1, 135.6, 133.3, 130.6, 127.9, 126.0, 66.2, 46.1. **LRMS** (ESI, m/z) 262.0 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₀H₁₃O₃N³⁵ClS [³⁵M+H]⁺ 262.0299, found 262.0299. **IR** ν_{max} (neat)/cm⁻¹ 2922, 2861, 1447, 1348 (SO₂N), 1297, 1261, 1171 (SO₂N), 1115, 1073. **M.p.**: 140 – 141 °C.

4-[(4-Fluorophenyl)sulfonyl]morpholine **45i**

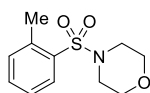


General procedure F was followed with 4-fluorophenylboronic acid (112 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.),

Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (20% Et₂O in petroleum ether) to give the title compound as an off-white solid (71 mg, 72%).

¹H NMR (400 MHz, CDCl₃) δ 7.81 – 7.70 (m, 2H, *H*_{Ar}), 7.27 – 7.17 (m, 2H, *H*_{Ar}), 3.79 – 3.68 (m, 4H, OCH₂), 3.03 – 2.93 (m, 4H, NCH₂); **¹³C NMR** (100 MHz, CDCl₃) δ 165.5 (d, ¹*J*_{C-F} = 255.2 Hz), 131.3 (d, ⁴*J*_{C-F} = 3.3 Hz), 130.6 (d, ³*J*_{C-F} = 9.5 Hz), 116.6 (d, ²*J*_{C-F} = 22.4 Hz), 66.2, 46.1; **¹⁹F NMR** (376 MHz, CDCl₃) δ -104.5. **LRMS** (ESI, *m/z*) 245.0 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₀H₁₂O₃NFNaS [M+Na]⁺ 268.0414, found 268.0415. **M.p.**: 99 – 100 °C (lit. 104 – 105 °C). The data recorded are consistent with the literature.^[256]

4-(*o*-Tolylsulfonyl)morpholine 45j

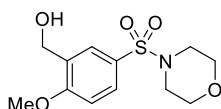


General procedure F was followed with *o*-tolylboronic acid (109 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (20% Et₂O in petroleum ether) to give the title compound as an off-white solid (49 mg, 51%).

¹H NMR (400 MHz, CDCl₃) δ 7.88 (dd, *J* = 8.2, 1.4 Hz, 1H, *H*_{Ar}), 7.47 (app. td, *J* = 7.5, 1.5 Hz, 1H, *H*_{Ar}), 7.37 – 7.28 (m, 2H, *H*_{Ar}), 3.74 – 3.67 (m, 4H, OCH₂), 3.16 – 3.10 (m, 4H, NCH₂), 2.64 (s, 3H, CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 138.3, 135.0, 133.2, 133.0, 130.6,

126.3, 66.4, 45.4, 21.0. **LRMS** (ESI, m/z) 242.0 ($[M+H]^+$, 100%); **HRMS** (ESI) calcd for $C_{11}H_{15}O_3NNaS$ $[M+Na]^+$ 264.0665, found 264.0664. **M.p.**: 87 °C (lit. 89 – 91 °C). The data recorded are consistent with the literature.^[256]

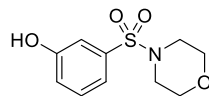
[2-Methoxy-5-(morpholinosulfonyl)phenyl]methanol **45k**



General procedure F was proceeded with 3-(hydroxymethyl)-4-methoxyphenylboronic acid (146 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), CS_2CO_3 (130 mg, 0.4 mmol, 1.0 eq.), $Cu(OTf)_2$ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.4 mg, 0.04 mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography with 50% EtOAc in petroleum ether to give the titled product as an off-white solid (56 mg, 49%).

1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 2.4 Hz, 1H, H_{Ar}), 7.67 (dd, J = 8.6, 2.4 Hz, 1H, H_{Ar}), 6.97 (d, J = 8.6 Hz, 1H, H_{Ar}), 4.71 (d, J = 6.0 Hz, 2H, CH_2OH), 3.93 (s, 3H, OCH_3), 3.75 – 3.68 (m, 4H, OCH_2), 2.99 – 2.94 (m, 4H, NCH_2), 2.38 (t, J = 6.4 Hz, 1H, OH), ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 130.5, 129.5, 127.7, 126.6, 110.2, 66.2, 60.9, 56.0, 46.1. **LRMS** (ESI, m/z) 288.0 ($[M+H]^+$, 100%); **HRMS** (ESI) calcd for $C_{12}H_{18}O_5NS$ $[M+H]^+$ 288.0900, found 288.0900; **IR** ν_{max} (neat)/ cm^{-1} 3057, 2967, 2888, 1642, 1512, 1329 (SO_2N), 1244, 1140 (SO_2N), 1114, 1073. **M.p.**: 165 – 166 °C.

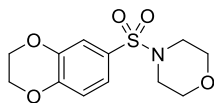
3-(Morpholinosulfonyl)phenol 45l



General procedure F was followed with 3-hydroxyphenylboronic acid (110 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (20% EtOAc in petroleum ether) to give the title compound as an off-white solid (54 mg, 55%).

¹H NMR (400 MHz, CDCl₃) δ 7.40 (app.t, J = 7.9 Hz, 1H, H_{Ar}), 7.31 – 7.27 (m, 1H, H_{Ar}), 7.27 – 7.21 (m, 1H, H_{Ar}), 7.09 (ddd, J = 8.2, 2.5, 1.0 Hz, 1H, H_{Ar}), 6.55 (br s, 1H, OH), 3.78 – 3.68 (m, 4H, OCH₂), 3.04 – 2.94 (m, 4H, NCH₂); **¹³C NMR** (100 MHz, CDCl₃) δ 156.8, 135.9, 130.7, 120.8, 119.8, 114.6, 66.2, 46.1. **LRMS** (ESI, m/z) 244.0 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₀H₁₄O₄NS [M+H]⁺ 244.0638, found 244.0640. **IR** ν_{max} (neat)/cm⁻¹ 3242 (OH), 2856, 1446, 1350 (SO₂N), 1260, 1167, 1158 (SO₂N), 1102, 1024. **M.p.:** 107 – 108 °C.

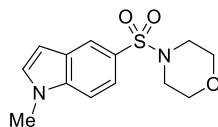
4-[(2,3-Dihydrobenzo-[1,4]dioxin-6-yl)sulfonyl]morpholine 45m



General procedure F was followed with 1,4-benzodioxane-6-boronic acid (144 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (40% Et₂O in petroleum ether) to give the title compound as an off-white solid (83 mg, 73%).

¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, J = 2.2 Hz, 1H, H_{Ar}), 7.21 (dd, J = 8.4, 2.2 Hz, 1H, H_{Ar}), 6.96 (d, J = 8.4 Hz, 1H, H_{Ar}), 4.33 – 4.26 (m, 4H, ArOCH₂), 3.74 – 3.69 (m, 4H, OCH₂), 2.99 – 2.93 (m, 4H, NCH₂); **¹³C NMR** (100 MHz, CDCl₃) δ 147.8, 143.7, 127.4, 121.7, 117.9, 117.5, 66.2, 64.7, 64.3, 46.1. **LRMS** (ESI, m/z) 286.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₂H₁₆O₅NS [M+H]⁺ 286.0744, found 286.0744. **IR** ν_{max} (neat)/cm⁻¹ 2969, 2860, 1498, 1346 (SO₂N), 1288, 1257, 1159 (SO₂N), 1115, 1082, 1057. **M.p.:** 134 °C.

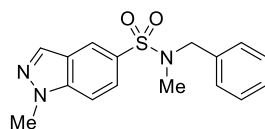
4-[(1-Methyl-1*H*-indol-5-yl)sulfonyl]morpholine **45n**



General procedure F was followed with (1-methyl-1*H*-indol-5-yl)boronic acid (140 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography with 20% EtOAc in petroleum ether to give the title compound as an off-white solid (77 mg, 69%).

¹H NMR (400 MHz, CDCl₃) δ 8.08 (dd, J = 1.8, 1.0 Hz, 1H, H_{Ar}), 7.57 (dd, J = 8.7, 1.8 Hz, 1H, H_{Ar}), 7.41 (d, J = 8.7 Hz, 1H, H_{Ar}), 7.20 (d, J = 3.2 Hz, 1H, H_{Ar}), 6.61 (dd, J = 3.2, 1.0 Hz, 1H, H_{Ar}), 3.84 (s, 3H, NCH₃), 3.74 – 3.69 (m, 4H, OCH₂), 3.01 – 2.95 (m, 4H, NCH₂); **¹³C NMR** (100 MHz, CDCl₃) δ 138.6, 131.4, 128.0, 125.4, 122.2, 120.8, 109.7, 102.7, 66.2, 46.2, 33.3. **LRMS** (ESI, m/z) 280.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₃H₁₆O₃N₂NaS [M+Na]⁺ 303.0774, found 303.0775. **IR** ν_{max} (neat)/cm⁻¹ 2861, 1339 (SO₂N), 1326, 1147 (SO₂N), 1111, 1070. **M.p.**: 122 – 123 °C.

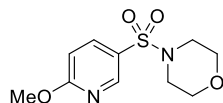
***N*-Benzyl-*N*,1-dimethyl-1*H*-indazole-5-sulfonamide 45o**



General procedure F was followed with 1-methyl-1*H*-indazole-5-boronic acid (71 mg, 0.4 mmol, 2.0 eq.), DABSO (96 mg, 0.4 mmol, 2.0 eq.), Cs₂CO₃ (65 mg, 0.2 mmol, 1.0 eq.), Cu(OTf)₂ (7.3 mg, 0.02 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.3 mg, 0.02 mmol, 0.1 eq.), *N*-benzylmethylamine (26 μ L, 0.2 mmol, 1.0 eq.) and DMSO (0.25 mL). The resulting residue was purified *via* silica column chromatography (30% EtOAc in petroleum ether) to give the title compound as an off-white solid (38 mg, 60%).

¹H NMR (400 MHz, CDCl₃) δ 8.32 (dd, J = 1.7, 0.9 Hz, 1H, H_{Ar}), 8.15 (d, J = 0.9 Hz, 1H, H_{Ar}), 7.83 (dd, J = 8.8, 1.7 Hz, 1H, H_{Ar}), 7.54 (d, J = 8.8 Hz, 1H, H_{Ar}), 7.36 – 7.25 (m, 5H, H_{Ar}), 4.17 – 4.13 (m, 5H, ArCH₂ + NNCH₃), 2.60 (s, 3H, NCH₃), **¹³C NMR** (100 MHz, CDCl₃) δ 141.0, 135.7, 134.5, 129.7, 128.8, 128.8, 128.5, 128.5, 128.1, 124.7, 123.5, 122.8, 109.8, 54.3, 36.1, 34.5. **LRMS** (ESI, m/z) 316.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₆H₁₈O₂N₃S [M+H]⁺ 316.1114, found 316.1115. **IR** ν_{max} (neat)/cm⁻¹ 3062, 2091, 1455, 1365, 1327 (SO₂N), 1148 (SO₂N), 1109, 1061. **M.p.**: 123 – 124 °C.

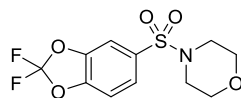
4-[(6-Methoxypyridin-3-yl)sulfonyl]morpholine 45p



General procedure F was followed with 3-quinolineboronic acid (120 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography with 20% EtOAc in petroleum ether to give the title compound as an off-white solid (46 mg, 45%).

¹H NMR (400 MHz, CDCl₃) δ 8.56 (dd, J = 2.5, 0.7 Hz, 1H, H_{Ar}), 7.86 (dd, J = 8.8, 2.5 Hz, 1H, H_{Ar}), 6.85 (dd, J = 8.8, 0.7 Hz, 1H, H_{Ar}), 4.01 (s, 3H, OCH₃), 3.78 – 3.72 (m, 4H, OCH₂), 3.04 – 2.97 (m, 4H, NCH₂); **¹³C NMR** (100 MHz, CDCl₃) δ 166.9, 148.1, 137.9, 124.6, 111.6, 66.2, 54.5, 46.0;. **LRMS** (ESI, m/z) 259.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₀H₁₅O₄N₂S [M+H]⁺ 259.0747, found 259.0748. **IR** ν_{max} (neat)/cm⁻¹ 2972, 2918, 2855, 1586, 1484, 1377, 1343 (SO₂N), 1290, 1259, 1169 (SO₂N), 1109, 1069, 1020. **M.p.:** 153 °C.

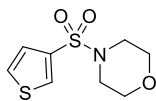
4-[(2,2-Difluorobenzo[d][1,3]dioxol-5-yl)sulfonyl]morpholine **45r**



General procedure F was followed with 2,2-difluorobenzodioxol-5-boronic acid (162 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (10% EtOAc in petroleum ether) to give the titled product as an off-white solid (64 mg, 52%).

¹H NMR (400 MHz, CDCl₃) δ 7.56 (dd, J = 8.3, 1.8 Hz, 1H, H_{Ar}), 7.47 (d, J = 1.8 Hz, 1H, H_{Ar}), 7.24 (d, J = 8.3 Hz, 1H, H_{Ar}), 3.79 – 3.69 (m, 4H, OCH₂), 3.05 – 2.97 (m, 4H, NCH₂); **¹³C NMR** (100 MHz, CDCl₃) δ 147.0, 144.0, 131.8 (t, $^1J_{C-F}$ = 259.1 Hz), 131.4, 124.9, 110.0, 109.5, 66.1, 46.1; **¹⁹F NMR** (376 MHz, CDCl₃) δ -49.2. **LRMS** (ESI, m/z) 308.0 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₁H₁₂O₅NF₂S [M+H]⁺ 308.0399, found 308.0400. **IR** ν_{max} (neat)/cm⁻¹ 3062, 2859, 1489, 1363, 1346 (SO₂N), 1248, 1218, 1154 (SO₂N), 1112, 1078. **M.p.**: 89 °C.

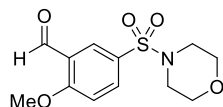
4-(Thiophen-3-ylsulfonyl)morpholine 45ad



General procedure F was proceeded with 3-thienylboronic acid (102 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.4 mg, 0.04 mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography with 30% Et₂O in petroleum ether to give the titled product as an off-white solid (36 mg, 39%).

¹H NMR (400 MHz, CDCl₃) δ 7.92 (dd, J = 3.1, 1.3 Hz, 1H, H_{Ar}), 7.47 (dd, J = 5.1, 3.1 Hz, 1H, H_{Ar}), 7.29 (dd, J = 5.1, 1.3 Hz, 1H, H_{Ar}), 3.82 – 3.71 (m, 4H, OCH₂), 3.08 – 2.99 (m, 4H, NCH₂), ¹³C NMR (100 MHz, CDCl₃) δ 135.4, 131.3, 128.1, 126.1, 66.2, 46.0. **LRMS** (ESI, m/z) 234.0 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₈H₁₂O₃NS₂ [M+H]⁺ 234.0253, found 234.0255. **M.p.**: 122 – 126 °C (lit. 123 – 125 °C). The data recorded are consistent with the literature.^[123]

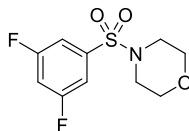
2-Methoxy-5-(morpholinosulfonyl)benzaldehyde 45ae



General procedure F was proceeded with 3-formyl-4-methoxyphenylboronic acid (144 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.4 mg, 0.04 mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography with 50% EtOAc in petroleum ether to give the titled product as an off-white solid (46 mg, 40%).

¹H NMR (400 MHz, CDCl₃) δ 10.48 (s, 1H, CHO), 8.19 (d, J = 2.4 Hz, 1H, H_{Ar}), 7.94 (dd, J = 8.8, 2.4 Hz, 1H, H_{Ar}), 7.15 (d, J = 8.8 Hz, 1H, H_{Ar}), 4.04 (s, 3H, CH₃), 3.77 – 3.68 (m, 4H, OCH₂), 3.03 – 2.95 (m, 4H, NCH₂), ¹³C NMR (100 MHz, CDCl₃) δ 188.2, 164.6, 135.2, 128.8, 127.8, 124.9, 112.5, 66.2, 56.5, 46.1. **LRMS** (ESI, m/z) 286.0 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₂H₁₆O₅NS [M+H]⁺ 286.0744, found 286.0743. **IR** ν_{max} (neat)/cm⁻¹ 3056, 2959, 2915, 2869, 1606, 1500, 1326 (SO₂N), 1266, 1141 (SO₂N), 1106, 1036. **M.p.:** 132 – 135 °C.

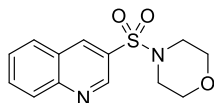
4-[(3,5-Difluorophenyl)sulfonyl]morpholine **45af**



General procedure F was proceeded with 3,5-difluorophenylboronic acid (126 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.4 mg, 0.04 mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography with 40% Et₂O in petroleum ether to give the titled product as an off-white solid (39 mg, 37%).

¹H NMR (400 MHz, CDCl₃) δ 7.33 – 7.27 (m, 2H, *H*_{Ar}), 7.09 (tt, *J* = 8.4, 2.3 Hz, 1H, *H*_{Ar}), 3.80 – 3.74 (m, 4H, OCH₂), 3.08 – 3.03 (m, 4H, NCH₂). ¹³C NMR (100 MHz, CDCl₃) δ 163.0 (dd, ¹*J*_{C-F} = 255.3, 11.6 Hz, *C*_{Ar}), 138.8 (t, ³*J*_{C-F} = 8.0 Hz, *C*_{Ar}), 111.4 (d, ²*J*_{C-F} = 28.3 Hz, *C*_{Ar}), 108.8 (t, ³*J*_{C-F} = 25.0 Hz, *C*_{Ar}), 66.2, 46.1, ¹⁹F NMR (376 MHz, CDCl₃) δ -105.1. **LRMS** (ESI, *m/z*) 264.1 ([*M*+*H*]⁺, 100%); **HRMS** (ESI) calcd for C₁₀H₁₂O₃NF₂S [*M*+*H*]⁺ 264.0501, found 264.0501. **IR** ν_{max} (neat)/cm⁻¹ 3060, 2089, 1444, 1372, 1320 (SO₂N), 1146 (SO₂N), 1107, 1053. **M.p.**: 109 – 111 °C.

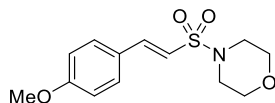
4-(Quinolin-3-ylsulfonyl)morpholine 45ah



General procedure F was proceeded with 3-quinolineboronic acid (138 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.4 mg, 0.04 mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography with 30% EtOAc in petroleum ether to give the titled product as an off-white solid (40 mg, 36%).

¹H NMR (400 MHz, CDCl₃) δ 9.17 (d, J = 2.2 Hz, 1H, H_{Ar}), 8.61 (dd, J = 2.2, 0.9 Hz, 1H, H_{Ar}), 8.22 (dd, J = 8.6, 0.9 Hz, 1H, H_{Ar}), 7.98 (d, J = 8.3 Hz, 1H, H_{Ar}), 7.92 (ddd, J = 8.6, 6.9, 1.4 Hz, 1H, H_{Ar}), 7.72 (ddd, J = 8.3, 6.9, 1.4 Hz, 1H, H_{Ar}), 3.79 – 3.72 (m, 4H, OCH₂), 3.14 – 3.06 (m, 4H, NCH₂), ¹³C NMR (100 MHz, CDCl₃) δ 149.6, 147.1, 137.3, 132.8, 129.8, 129.1, 128.9, 128.6, 126.5, 66.2, 46.0. **LRMS** (ESI, m/z) 279.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₃H₁₅O₃N₂S [M+H]⁺ 279.0798, found 279.0798. **IR** ν_{max} (neat)/cm⁻¹ 3058, 2091, 1443, 1374, 1323 (SO₂N), 1145 (SO₂N), 1111, 1056. **M.p.:** 110 – 113 °C.

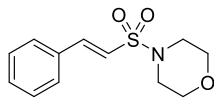
***trans*-4-[(4-Methoxystyryl)sulfonyl]morpholine 46a**



General procedure F was followed with *trans*-2-(4-methoxyphenyl)vinylboronic acid (144 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), morpholine (39 µL, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (20% EtOAc in petroleum ether) to give the title compound as an off-white solid (59 mg, 52%).

¹H NMR (400 MHz, CDCl₃) δ 7.48 – 7.39 (m, 3H, *CH* + *H*_{Ar}), 6.93 (d, *J* = 8.8 Hz, 2H, *H*_{Ar}), 6.52 (d, *J* = 15.4 Hz, 1H, *CH*), 3.85 (s, 3H, OCH₃), 3.80 – 3.74 (m, 4H, OCH₂), 3.22 – 3.13 (m, 4H, NCH₂); **¹³C NMR** (100 MHz, CDCl₃) δ 162.1, 144.2, 130.2, 125.1, 117.5, 114.7, 66.4, 55.6, 45.9. **LRMS** (ESI, *m/z*) 284.1 ([*M*+*H*]⁺, 100%); **HRMS** (ESI) calcd for C₁₃H₁₈O₄NS [*M*+*H*]⁺ 284.0951, found 284.0951. **IR** ν_{max} (neat)/cm⁻¹ 3060, 2971, 2921, 2868, 1601, 1510, 1324 (SO₂N), 1259, 1240, 1143 (SO₂N), 1109, 1071, 1025. **M.p.**: 150 – 151 °C.

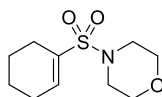
***trans*-4-(Styrylsulfonyl)morpholine 46b**



General procedure F was proceeded with *trans*-2-phenylvinylboronic acid (118 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.4 mg, 0.04 mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography with 40% Et₂O in petroleum ether to give the titled product as an off-white solid (44 mg, 43%).

¹H NMR (400 MHz, CDCl₃) δ 7.54 – 7.39 (m, 6H, CH + *H_{Ar}*), 6.68 (d, *J* = 15.5 Hz, 1H, CH), 3.81 – 3.74 (m, 4H, OCH₂), 3.22 – 3.16 (m, 4H, NCH₂), ¹³C NMR (100 MHz, CDCl₃) δ 144.4, 132.5, 131.3, 129.3, 128.5, 120.5, 66.4, 45.8. **LRMS** (ESI, *m/z*) 254.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₂H₁₆O₃NS [M+H]⁺ 254.0845, found 254.0847; **M.p.**: 114 – 117 °C (lit. 113 – 115 °C). The data recorded are consistent with the literature.^[257]

4-(Cyclohex-1-en-1-ylsulfonyl)morpholine 46c

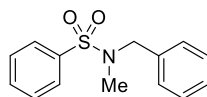


General procedure F was followed with 1-cyclohexen-1-yl-boronic acid (101 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04

mmol, 0.1 eq.), morpholine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (20% Et₂O in petroleum ether) to give the title compound as an off-white solid (65 mg, 71%).

¹H NMR (400 MHz, CDCl₃) δ 6.77 (app. quin, J = 2.0 Hz, 1H, CH), 3.75 – 3.71 (m, 4H, SO₂CCH₂ + SO₂CCHCH₂), 3.18 – 3.14 (m, 4H, OCH₂), 2.33 – 2.22 (m, 4H, NCH₂), 1.76 – 1.69 (m, 2H, SO₂CCH₂CH₂), 1.67 – 1.60 (m, 2H, SO₂CCHCH₂CH₂); **¹³C NMR** (100 MHz, CDCl₃) δ 139.3, 136.3, 66.7, 45.8, 25.5, 24.6, 22.1, 21.1. **LRMS** (ESI, m/z) 231.0 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₀H₁₇O₃NNaS [M+Na]⁺ 254.0821, found 254.0822. **M.p.**: 103-104 °C (lit. 108 – 109 °C). The data recorded are consistent with the literature.^[258]

***N*-Benzyl-*N*-methylbenzenesulfonamide 48a**

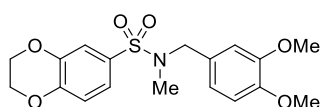


General procedure F was proceeded with phenylboronic acid (97.6 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.4 mg, 0.04 mmol, 0.1 eq.), *N*-benzylmethylamine (52 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography with 20% Et₂O in petroleum ether to give the titled product as an off-white solid (62 mg, 60%).

¹H NMR (400 MHz, CDCl₃) δ 7.88 – 7.83 (m, 2H, H_{Ar}), 7.67 – 7.60 (m, 1H, H_{Ar}), 7.61 – 7.52 (m, 2H, H_{Ar}), 7.38 – 7.26 (m, 5H, H_{Ar}), 4.15 (s, 2H, PhCH₂), 2.60 (s, 3H, NCH₃), **¹³C NMR** (100 MHz, CDCl₃) δ 137.4, 135.7, 132.8, 129.3, 128.8, 128.5, 128.1, 127.6, 54.3,

34.5. **LRMS** (ESI, m/z) 261.1 ($[M+H]^+$, 100%); **HRMS** (ESI) calcd for $C_{14}H_{16}O_2NS$ $[M+H]^+$ 262.0902, found 262.0905. **M.p.**: 87 – 91 °C (lit. 86 – 89 °C). The data recorded are consistent with the literature.^[259]

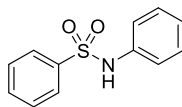
***N*-(3,4-Dimethoxybenzyl)-*N*-methyl-2,3-dihydrobenzo[*b*][1,4]dioxine-6-sulfonamide**
48c



General procedure A was followed with 1,4-benzodioxane-6-boronic acid (144 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), CS_2CO_3 (130 mg, 0.4 mmol, 1.0 eq.), $Cu(OTf)_2$ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), 3,4-dimethoxy-*N*-methylbenzylamine (77 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (20% EtOAc in petroleum ether) to give the title compound as an off-white solid (81 mg, 53%).

1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 2.2 Hz, 1H, H_{Ar}), 7.28 (dd, J = 8.4, 2.2 Hz, 1H, H_{Ar}), 6.97 (d, J = 8.4 Hz, 1H, H_{Ar}), 6.84 (d, J = 1.6 Hz, 1H, H_{Ar}), 6.78 – 6.71 (m, 2H, H_{Ar}), 4.34 – 4.26 (m, 4H, OCH_2), 4.02 (s, 2H, $ArCH_2$), 3.83 (d, J = 1.9 Hz, 6H, OCH_3), 2.53 (s, 3H, NCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.3, 148.8, 147.5, 143.7, 129.7, 128.2, 121.3, 120.9, 117.9, 117.2, 111.3, 110.9, 64.7, 64.3, 56.0, 56.0, 54.2, 34.3; **LRMS** (ESI, m/z) 402.1 ($[M+Na]^+$, 100%); **HRMS** (ESI) calcd for $C_{18}H_{21}O_6NNaS$ $[M+Na]^+$ 402.0982, found 402.0976; **IR** ν_{max} (neat)/ cm^{-1} 3004, 2983, 2938, 1517, 1495, 1334 (SO_2N), 1284, 1236, 1154 (SO_2N), 1142, 1131, 1064; **M.p.**: 102 – 104 °C.

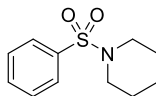
***N*-Phenylbenzenesulfonamide 48e**



General procedure F was proceeded with phenylboronic acid (97.6 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.4 mg, 0.04 mmol, 0.1 eq.), aniline (37 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography with 20% EtOAc in petroleum ether to give the titled product as an off-white solid (53 mg, 57%).

¹H NMR (400 MHz, CDCl₃) δ 7.84 – 7.75 (m, 2H, *H*_{Ar}), 7.57 – 7.48 (m, 1H, *H*_{Ar}), 7.45 – 7.39 (m, 2H, *H*_{Ar}), 7.27 – 7.20 (m, 2H, *H*_{Ar}), 7.19 (br s, 1H, NH), 7.14 – 7.07 (m, 3H, *H*_{Ar}), ¹³C NMR (100 MHz, CDCl₃) δ 139.0, 136.5, 133.2, 129.4, 129.2, 127.3, 125.6, 125.5, 121.8, 121.8. **LRMS** (ESI, *m/z*) 232.0 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₂H₁₀O₂NS [M+H]⁺ 232.0438, found 232.0437. **M.p.**: 108 – 111 °C (lit. 109 – 110 °C). The data recorded are consistent with the literature.^[184]

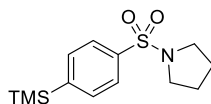
1-(Phenylsulfonyl)piperidine 48g



General procedure F was proceeded with phenylboronic acid (97.6 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.4 mg, 0.04 mmol, 0.1 eq.), piperidine (39 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography with 20% Et₂O in petroleum ether to give the titled product as an off-white solid (61 mg, 67%).

¹H NMR (400 MHz, CDCl₃) δ 7.77 – 7.71 (m, 2H, *H*_{Ar}), 7.62 – 7.55 (m, 1H, *H*_{Ar}), 7.54 – 7.46 (m, 2H, *H*_{Ar}), 3.00 – 2.94 (m, 4H, NCH₂), 1.67 – 1.56 (m, 4H, NCH₂CH₂), 1.45 – 1.36 (m, 2H, NCH₂CH₂CH₂), ¹³C NMR (100 MHz, CDCl₃) δ 136.3, 132.7, 129.0, 127.7, 47.1, 25.3, 23.6. **LRMS** (ESI, *m/z*) 226.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₁H₁₆O₂NS [M+H]⁺ 226.0896, found 226.0898. **M.p.**: 90 – 93 °C (lit. 91 – 93 °C). The data recorded are consistent with the literature.^[249]

1-{[4-(Trimethylsilyl)phenyl]sulfonyl}pyrrolidine 48i

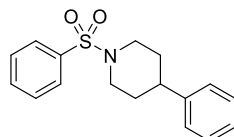


General procedure F was followed with 4-(trimethylsilyl)phenylboronic acid (155 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.),

Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), pyrrolidine (33 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (20% Et₂O in petroleum ether) to give the title compound as an off-white solid (59 mg, 52%).

¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, J = 8.2 Hz, 2H, H_{Ar}), 7.65 (d, J = 8.2 Hz, 2H, H_{Ar}), 3.28 – 3.20 (m, 4H, NCH₂), 1.80 – 1.71 (m, 4H, NCH₂CH₂), 0.29 (s, 9H, Si(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ 146.8, 137.1, 133.9, 126.5, 48.0, 25.3, 1.22. **LRMS** (ESI, m/z) 284.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₃H₂₂O₂NSSi [M+H]⁺ 284.1135, found 284.1136. **IR** ν_{max} (neat)/cm⁻¹ 2973, 1334 (SO₂N), 1250, 1157 (SO₂N), 1110 (SO₂N). **M.p.:** 99 °C.

4-Phenyl-1-(phenylsulfonyl)piperidine 48j

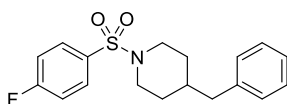


General procedure F was proceeded with phenylboronic acid (97.6 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.4 mg, 0.04 mmol, 0.1 eq.), 4-phenylpiperidine (65 mg, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography with 20% Et₂O in petroleum ether to give the titled product as an off-white solid (81 mg, 67%).

¹H NMR (400 MHz, CDCl₃) δ 7.83 – 7.78 (m, 2H, H_{Ar}), 7.64 – 7.60 (m, 1H, H_{Ar}), 7.60 –

7.54 (m, 2H, H_{Ar}), 7.34 – 7.26 (m, 2H, H_{Ar}), 7.24 – 7.18 (m, 1H, H_{Ar}), 7.16 – 7.12 (m, 2H, H_{Ar}), 3.99 – 3.93 (m, 2H, $\text{NCH}_2(\text{axial})$), 2.50 – 2.30 (m, 3H, $\text{ArCH} + \text{NCH}_2(\text{equatorial})$), 1.94 – 1.78 (m, 4H, NCH_2CH_2), ^{13}C NMR (100 MHz, CDCl_3) δ 145.0, 136.3, 132.8, 129.1, 128.7, 127.8, 126.8, 126.7, 47.0, 41.9, 32.6. **LRMS** (ESI, m/z) 302.1 ($[\text{M}+\text{H}]^+$, 100%); **HRMS** (ESI) calcd for $\text{C}_{17}\text{H}_{20}\text{O}_2\text{NS}$ $[\text{M}+\text{H}]^+$ 302.1209, found 302.1210. **IR** ν_{max} (neat)/ cm^{-1} 2940, 2912, 2836, 1599, 1442, 1338 (SO_2N), 1306, 1262, 1144 (SO_2N), 1155, 1095; **M.p.**: 107 – 109 °C (lit. 108 – 109 °C). The data recorded are consistent with the literature.^[260]

4-Benzyl-1-[(4-fluorophenyl)sulfonyl]piperidine **48l**

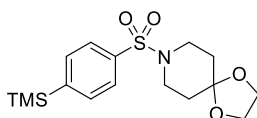


General procedure F was proceeded with 4-fluorophenylboronic acid (112 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs_2CO_3 (130 mg, 0.4 mmol, 1.0 eq.), $\text{Cu}(\text{OTf})_2$ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), 4-benzylpiperidine (70 μL , 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (10% EtOAc in petroleum ether) to give the title compound as an off-white solid (82 mg, 62%).

^1H NMR (400 MHz, CDCl_3) δ 7.74 (dd, $J = 8.8, 5.1$ Hz, 2H, H_{Ar}), 7.24 (app. t, $J = 7.3$ Hz, 2H, H_{Ar}), 7.20 – 7.12 (m, 3H, H_{Ar}), 7.07 (app. d, $J = 6.8$ Hz, 2H, H_{Ar}), 3.75 (d, $J = 11.8$ Hz, 2H, $\text{NCH}_2(\text{axial})$), 2.50 (d, $J = 6.8$ Hz, 2H, PhCH_2), 2.18 (td, $J = 11.8, 2.5$ Hz, 2H, $\text{NCH}_2(\text{equatorial})$), 1.68 (dd, $J = 12.6, 2.5$ Hz, 2H, $\text{NCH}_2\text{CH}_2(\text{axial})$), 1.49 – 1.38 (m, 1H, PhCH_2CH), 1.35 (app. qd, $J = 12.6, 4.1$ Hz, 2H, $\text{NCH}_2\text{CH}_2(\text{equatorial})$); **^{13}C NMR** (100 MHz,

CDCl₃) δ 165.2 (d, $^1J_{C-F}$ = 254.9 Hz), 139.8, 132.4 (d, $^4J_{C-F}$ = 3.2 Hz), 130.4 (d, $^3J_{C-F}$ = 9.4 Hz), 129.1, 128.4, 126.2, 116.2 (d, $^2J_{C-F}$ = 22.7 Hz), 46.5, 42.7, 37.4, 31.2; **¹⁹F NMR** (376 MHz, CDCl₃) δ -105.4. **LRMS** (ESI, m/z) 334.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₈H₂₁O₂NFS [M+H]⁺ 334.1272, found 334.1273. **IR** $\nu_{\max}$ (neat)/cm⁻¹ 2935, 2917, 2848, 1591, 1492, 1336 (SO₂N), 1307, 1226, 1165 (SO₂N), 1155, 1095. **M.p.**: 111 °C.

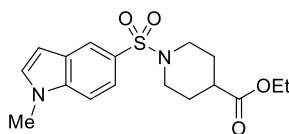
8-{[4-(Trimethylsilyl)phenyl]sulfonyl}-1,4-dioxo-8-azaspiro[4.5]decane 48m



General procedure F was followed with 4-(trimethylsilyl)phenylboronic acid (155 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), 1,4-dioxo-8-azaspiro[4.5]decane (58 mg, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (10% EtOAc in petroleum ether) to give the titled product as an off-white solid (98 mg, 69%).

¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, J = 8.3 Hz, 2H, H_{Ar}), 7.64 (d, J = 8.3 Hz, 2H, H_{Ar}), 3.89 (s, 4H, OCH₂), 3.21 – 3.09 (m, 4H, NCH₂), 1.83 – 1.73 (m, 4H, NCH₂CH₂), 0.29 (s, 9H, Si(CH₃)₃); **¹³C NMR** (100 MHz, CDCl₃) δ 147.1, 136.6, 134.0, 126.5, 106.2, 64.5, 44.6, 34.6, 1.2. **LRMS** (ESI, m/z) 356.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₆H₂₆O₄NSSi [M+H]⁺ 356.1346, found 356.1344. **IR** $\nu_{\max}$ (neat)/cm⁻¹ 2961, 2864, 1354, 1332 (SO₂N), 1165 (SO₂N), 1107, 1048. **M.p.**: 151 °C.

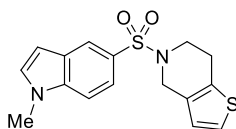
Ethyl 1-[(1-methyl-1*H*-indol-5-yl)sulfonyl]piperidine-4-carboxylate **48n**



General procedure F was followed with (1-methyl-1*H*-indol-5-yl)boronic acid (140 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), ethyl isonipecotatate (62 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (20% EtOAc in petroleum ether) to give the title compound as an off-white solid (101 mg, 72%).

¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, J = 1.7 Hz, 1H, H_{Ar}), 7.56 (dd, J = 8.7, 1.7 Hz, 1H, H_{Ar}), 7.39 (d, J = 8.7 Hz, 1H, H_{Ar}), 7.19 (d, J = 3.2 Hz, 1H, H_{Ar}), 6.60 (dd, J = 3.2, 0.8 Hz, 1H, H_{Ar}), 4.07 (q, J = 7.1 Hz, 2H, CH₂CH₃), 3.83 (s, 3H, NCH₃), 3.67 (dt, J = 11.5, 3.9 Hz, 2H, NCH_{2(axial)}), 2.39 (td, J = 11.5, 2.9 Hz, 2H, NCH_{2(equatorial)}), 2.21 – 2.10 (m, 1H, COCH), 1.94 (dd, J = 13.6, 3.8 Hz, 2H, NCH₂CH_{2(axial)}), 1.87 – 1.74 (m, 2H, NCH₂CH_{2(equatorial)}), 1.18 (t, J = 7.1 Hz, 3H, CH₂CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 174.1, 138.5, 131.3, 127.9, 126.3, 122.0, 120.6, 109.6, 102.7, 60.7, 45.7, 40.2, 33.9, 27.6, 14.2; **LRMS** (ESI, m/z) 351.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₇H₂₃O₄N₂S [M+H]⁺ 351.1373, found 351.1370; **IR** ν_{max} (neat)/cm⁻¹ 2974, 2934, 2848, 1731 (CO), 1324 (SO₂N), 1300, 1283, 1184, 1151 (SO₂N), 1119, 1067, 1039; **M.p.**: 117 – 118 °C.

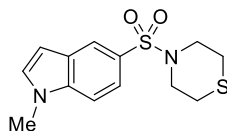
5-[(1-Methyl-1*H*-indol-5-yl)sulfonyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine 48o



General procedure A was followed with (1-methyl-1*H*-indol-5-yl)boronic acid (140 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (56 mg, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (10% EtOAc in petroleum ether) to give the title compound as an off-white solid (93 mg, 70%).

¹H NMR (400 MHz, CDCl₃) δ 8.17 (dd, *J* = 1.8, 0.6 Hz, 1H, *H*_{Ar}), 7.65 (dd, *J* = 8.7, 1.8 Hz, 1H, *H*_{Ar}), 7.40 (d, *J* = 8.7 Hz, 1H, *H*_{Ar}), 7.19 (d, *J* = 3.2 Hz, 1H, *H*_{Ar}), 7.07 (d, *J* = 5.3 Hz, 1H, *H*_{Ar}), 6.70 (d, *J* = 5.3 Hz, 1H, *H*_{Ar}), 6.62 (dd, *J* = 3.2, 0.9 Hz, 1H, *H*_{Ar}), 4.20 (t, *J* = 1.7 Hz, 2H, NCH₂Ar), 3.84 (s, 3H, CH₃), 3.42 (t, *J* = 5.7 Hz, 2H, NCH₂CH₂), 2.94 – 2.88 (m, 2H, NCH₂NCH₂); **¹³C NMR** (100 MHz, CDCl₃) δ 138.5, 132.7, 131.3, 131.0, 128.0, 126.9, 124.9, 123.6, 122.1, 120.6, 109.7, 102.8, 46.1, 44.2, 33.3, 25.4. **LRMS** (ESI, *m/z*) 333.0 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₆H₁₇O₂N₂S₂ [M+H]⁺ 333.0726, found 333.0725. **IR** ν_{max} (neat)/cm⁻¹ 2849, 1332 (SO₂N), 1316, 1278, 1206, 1147, 1109, 1075, 1058. **M.p.**: 153 – 154 °C.

4-[(1-Methyl-1*H*-indol-5-yl)sulfonyl]thiomorpholine 48p

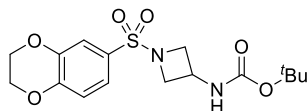


General procedure A was followed with (1-methyl-1*H*-indol-5-yl)boronic acid (140 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), thiomorpholine (40 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (10% EtOAc in petroleum ether) to give the title compound as an off-white solid (68 mg, 56%).

¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, J = 1.7 Hz, 1H, H_{Ar}), 7.55 (dd, J = 8.7, 1.7 Hz, 1H, H_{Ar}), 7.40 (d, J = 8.7 Hz, 1H, H_{Ar}), 7.19 (d, J = 3.2 Hz, 1H, H_{Ar}), 6.60 (dd, J = 3.2, 0.9 Hz, 1H, H_{Ar}), 3.84 (s, 3H, NCH₃), 3.31 (m, 3.29 – 3.21, 4H, NCH₂), 2.72 – 2.65 (m, 4H, SCH₂); **¹³C NMR** (100 MHz, CDCl₃) δ 138.5, 131.4, 128.0, 127.0, 121.8, 120.4, 109.8, 102.8, 48.1, 33.3, 27.4. **LRMS** (ESI, m/z) 297.0 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₃H₁₇O₂N₂S₂ [M+H]⁺ 297.0726, found 297.0725. **IR** ν_{max} (neat)/cm⁻¹ 3103, 2912, 2846, 1346 (SO₂N), 1328, 1151 (SO₂N), 1064. **M.p.**: 134-135 °C.

***tert*-Butyl {1-[(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfonyl]azetidin-3-yl}carbamate**

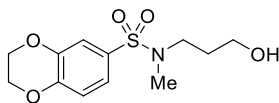
48q



General procedure F was proceeded with 1,4-benzodioxane-6-boronic acid (144 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.4 mg, 0.04 mmol, 0.1 eq.), 3-*N*-Boc-amino-azetidine (69 μ L, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography with 30% EtOAc in petroleum ether to give the titled product as an off-white solid (73 mg, 49%).

¹H NMR (400 MHz, CDCl₃) δ 7.35 (d, J = 2.1 Hz, 1H, H_{Ar}), 7.31 (dd, J = 8.3, 2.1 Hz, 1H, H_{Ar}), 7.01 (d, J = 8.3 Hz, 1H, H_{Ar}), 4.81 (br s, 1H, NH), 4.37 – 4.27 (m, 5H, OCH₂ + NHCH), 4.00 (t, J = 8.0 Hz, 2H, NCH_{2(axial)}), 3.55 (br t, J = 7.4 Hz, 2H, NCH_{2(equatorial)}), 1.40 (s, 9H, C(CH₃)₃), ¹³C NMR (100 MHz, CDCl₃) δ 154.7, 148.2, 143.9, 126.8, 122.2, 118.0, 118.0, 80.5, 64.7, 64.3, 58.3, 39.9, 28.4. **LRMS** (ESI, m/z) 393.0 ([M+Na]⁺, 100%); **HRMS** (ESI) calcd for C₁₆H₂₃O₆N₂S [M+H]⁺ 371.1271, found 371.1266. **IR** ν_{max} (neat)/cm⁻¹ 3027, 2991, 2893, 1610, 1456, 1324 (SO₂N), 1288, 1256, 1141 (SO₂N), 1120, 1078, 1024. **M.p.**: 102 – 104 °C.

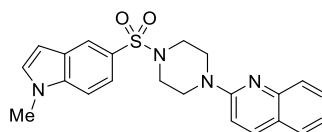
***N*-(3-Hydroxypropyl)-*N*-methyl-2,3-dihydrobenzo[*b*][1,4]dioxine-6-sulfonamide 48s**



General procedure F was proceeded with 1,4-benzodioxane-6-boronic acid (144 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.4 mg, 0.04 mmol, 0.1 eq.), 3-methylamino-1-propanol (36 mg, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography with 70% EtOAc in petroleum ether to give the titled product as an off-white solid (53 mg, 46%).

¹H NMR (400 MHz, CDCl₃) δ 7.29 (d, *J* = 2.2 Hz, 1H, *H*_{Ar}), 7.26 (dd, *J* = 8.5, 2.2 Hz, 1H, *H*_{Ar}), 6.95 (d, *J* = 8.4 Hz, 1H, *H*_{Ar}), 4.30 (t, *J* = 5.2 Hz, 2H, O₂SCCHCOCH₂CH₂O), 4.29 (t, *J* = 5.2 Hz, 2H, O₂SCCHCOCH₂CH₂O), 3.74 (app. q, *J* = 5.7 Hz, 3H, CH₂OH), 3.09 (t, *J* = 6.4 Hz, 2H, NCH₂), 2.72 (s, 3H, NCH₃), 2.41 (app. t, *J* = 6.0 Hz, 1H, OH), 1.72 (app. quin, *J* = 6.1 Hz, 2H, NCH₂CH₂), ¹³C NMR (100 MHz, CDCl₃) δ 147.5, 143.7, 129.8, 121.0, 117.9, 116.9, 64.6, 64.3, 58.9, 46.7, 35.1, 30.0. **LRMS** (ESI, *m/z*) 288.1 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₁₂H₁₈O₅NS [M+H]⁺ 288.0900, found 28.0899. **IR** ν_{max} (neat)/cm⁻¹ 2998, 2980, 2937, 1515, 1483, 1328 (SO₂N), 1281, 1232, 1151 (SO₂N), 1147, 1036. **M.p.:** 122 – 124 °C.

2-{4-[(1-Methyl-1*H*-indol-5-yl)sulfonyl]piperazin-1-yl}quinoline 48u



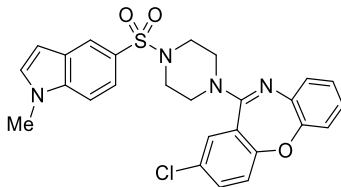
General procedure A was followed with (1-methyl-1*H*-indol-5-yl)boronic acid (140 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), 2-(1-piperazinyl)quinoline (85 mg, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (30% EtOAc in petroleum ether) to give the title compound as an off-white solid (105 mg, 66%).

¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, *J* = 1.6 Hz, 1H, *H*_{Ar}), 7.78 (d, *J* = 9.1 Hz, 1H, *H*_{Ar}), 7.62 (d, *J* = 8.4 Hz, 1H, *H*_{Ar}), 7.55 (dd, *J* = 8.7, 1.8 Hz, 1H, *H*_{Ar}), 7.51 (d, *J* = 8.0 Hz, 1H, *H*_{Ar}), 7.47 (t, *J* = 7.5 Hz, 1H, *H*_{Ar}), 7.32 (d, *J* = 8.7 Hz, 1H, *H*_{Ar}), 7.17 (t, *J* = 7.5 Hz, 1H, *H*_{Ar}), 7.11 (d, *J* = 3.2 Hz, 1H, *H*_{Ar}), 6.80 (d, *J* = 9.1 Hz, 1H, *H*_{Ar}), 6.56 (d, *J* = 3.2 Hz, 1H, *H*_{Ar}), 3.81 – 3.74 (m, 4H, ArNCH₂), 3.73 (s, 3H, CH₃), 3.09 – 3.07 (m, 4H, SO₂NCH₂);

¹³C NMR (100 MHz, CDCl₃) δ 156.5, 147.5, 138.4, 137.6, 131.3, 131.3, 129.6, 127.8, 127.2, 126.5, 125.4, 123.1, 122.7, 122.0, 120.5, 109.6, 109.3, 102.6, 46.1, 44.5, 33.1;

LRMS (ESI, *m/z*) 407.2 ([M+H]⁺, 100%); **HRMS** (ESI) calcd for C₂₂H₂₃O₂N₄S [M+H]⁺ 407.1536, found 407.1528; **IR** ν_{max} (neat)/cm⁻¹ 2854, 1618, 1604, 1507, 1433, 1338 (SO₂N), 1324, 1231, 1153 (SO₂N), 1065; **M.p.**: 196 – 197 °C.

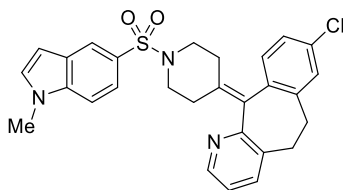
2-Chloro-11-{4-[(1-methyl-1*H*-indol-5-yl)sulfonyl]piperazin-1-yl}dibenzo[b,f][1,4]oxazepane 48v



General procedure A was followed with (1-methyl-1*H*-indol-5-yl)boronic acid (140 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), amoxapine (126 mg, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (15% EtOAc in petroleum ether) to give the title compound as an off-white solid (144 mg, 71%).

¹H NMR (400 MHz, CDCl₃) δ 8.12 (d, *J* = 1.8 Hz, 1H, *H*_{Ar}), 7.61 (dd, *J* = 8.7, 1.8 Hz, 1H, *H*_{Ar}), 7.43 (d, *J* = 8.7 Hz, 1H, *H*_{Ar}), 7.35 (dd, *J* = 8.7, 2.6 Hz, 1H, *H*_{Ar}), 7.20 (d, *J* = 3.1 Hz, 1H, *H*_{Ar}), 7.14 (dd, *J* = 5.6, 3.1 Hz, 2H, *H*_{Ar}), 7.11 – 7.02 (m, 3H, *H*_{Ar}), 7.00 – 6.94 (m, 1H, *H*_{Ar}), 3.84 (s, 3H, CH₃), 3.61 (br, s, 4H, SO₂NCH₂CH₂), 3.14 (br, s, 4H, SO₂NCH₂); **¹³C NMR** (100 MHz, CDCl₃) δ 159.3, 158.3, 151.7, 139.7, 138.6, 132.8, 131.4, 130.4, 128.7, 128.0, 127.1, 125.9, 125.8, 125.0, 124.6, 122.9, 122.1, 120.6, 120.1, 109.9, 102.8, 46.8, 46.0, 33.2; **LRMS** (ESI, *m/z*) 507.1 ([*M*+*H*]⁺, 100%); **HRMS** (ESI) calcd for C₂₆H₂₄O₃N₄³⁵ClS [³⁵*M*+*H*]⁺ 507.1252, found 507.1247; **IR** ν_{max} (neat)/cm⁻¹ 2845, 1604, 1470, 1450, 1396, 1340 (SO₂N), 1325, 1281, 1158 (SO₂N), 1102; **M.p.**: >220 °C.

8-Chloro-11-{1-[(1-methyl-1*H*-indol-5-yl)sulfonyl]piperidin-4-ylidene}-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine 48w



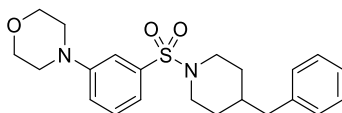
General procedure A was followed with (1-methyl-1*H*-indol-5-yl)boronic acid (140 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs₂CO₃ (130 mg, 0.4 mmol, 1.0 eq.), Cu(OTf)₂ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (8.6 mg, 0.04 mmol, 0.1 eq.), desloratadine (125 mg, 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography (40% EtOAc in petroleum ether) to give the title compound as an off-white solid (149 mg, 74%).

¹H NMR (400 MHz, CDCl₃) δ 8.33 (dd, *J* = 4.9, 1.7 Hz, 1H, *H*_{Ar}), 8.06 (d, *J* = 1.7 Hz, 1H, *H*_{Ar}), 7.57 (dd, *J* = 8.7, 1.8 Hz, 1H, *H*_{Ar}), 7.41 – 7.32 (m, 2H, *H*_{Ar}), 7.19 (d, *J* = 3.2 Hz, 1H, *H*_{Ar}), 7.11 – 7.05 (m, 2H, *H*_{Ar}), 7.05 – 7.01 (m, 1H, *H*_{Ar}), 6.98 (d, *J* = 8.0 Hz, 1H, *H*_{Ar}), 6.58 (dd, *J* = 3.2, 0.8 Hz, 1H, *H*_{Ar}), 3.83 (s, 3H, CH₃), 3.36 – 3.26 (m, 2H, NCH₂(axial)), 3.26 – 3.11 (m, 2H, NCH₂(equatorial)), 2.84 (app. dq, *J* = 11.3, 4.3 Hz, 2H, NCH₂CH₂(axial)), 2.79 – 2.63 (m, 2H, NCH₂CH₂(equatorial)), 2.58 (ddd, *J* = 13.3, 8.6, 4.2 Hz, 1H, PyCH₂(axial)CH₂Ar), 2.47 (ddd, *J* = 13.3, 8.6, 4.2 Hz, 1H, PyCH₂(equatorial)CH₂Ar), 2.34 (dtd, *J* = 14.1, 6.7, 3.7 Hz, 2H, PyCH₂CH₂Ar); **¹³C NMR** (100 MHz, CDCl₃) δ 156.8, 146.7, 139.6, 138.5, 137.6, 137.5, 136.2, 134.6, 133.4, 133.1, 131.3, 130.6, 129.1, 128.0, 126.7, 126.2, 122.4, 122.0, 120.7, 109.7, 102.7, 47.6, 33.3, 31.7, 31.5, 30.3, 30.1. **LRMS** (ESI, *m/z*) 504.1 ([*M*+*H*]⁺, 100%); **HRMS** (ESI) calcd for C₂₈H₂₇O₂N₃³⁵ClS [³⁵*M*+*H*]⁺ 504.1507, found 504.1499. **IR**

$\nu_{\max}$ (neat)/ cm^{-1} 2911, 2839, 2186, 1480, 1439, 1330 (SO_2N), 1282, 1151 (SO_2N), 1112.

M.p.: 133-135 °C (dec.).

4-{3-[(4-Benzylpiperidin-1-yl)sulfonyl]phenyl}morpholine 48ab



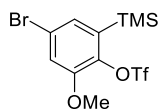
General procedure F was proceeded with 3-morpholinophenylboronic acid (166 mg, 0.8 mmol, 2.0 eq.), DABSO (192 mg, 0.8 mmol, 2.0 eq.), Cs_2CO_3 (130 mg, 0.4 mmol, 1.0 eq.), $\text{Cu}(\text{OTf})_2$ (14.5 mg, 0.04 mmol, 0.1 eq.), 4,4'-dimethoxy-2,2'-bipyridine (4.4 mg, 0.04 mmol, 0.1 eq.), 4-benzylpiperidine (70 μL , 0.4 mmol, 1.0 eq.) and DMSO (0.5 mL). The resulting residue was purified *via* silica column chromatography with 5% EtOAc in petroleum ether to give the titled product as an off-white solid (54 mg, 34%).

^1H NMR (400 MHz, CDCl_3) δ 7.54 – 7.43 (m, 1H, H_{Ar}), 7.40 – 7.31 (m, 2H, H_{Ar}), 7.31 – 7.24 (m, 3H, H_{Ar}), 7.20 – 7.11 (m, 3H, H_{Ar}), 4.06 – 3.92 (m, 4H, $\text{OCH}_2\text{CH}_2\text{N}$), 3.86 (d, J = 11.8 Hz, 2H, $\text{SO}_2\text{NCH}_2(\text{axial})\text{CH}_2$), 3.35 – 3.26 (m, 4H, $\text{OCH}_2\text{CH}_2\text{N}$), 2.61 (d, J = 6.6 Hz, 2H, PhCH_2), 2.30 (td, J = 11.8, 2.8 Hz, 2H, $\text{SO}_2\text{NCH}_2(\text{equatorial})\text{CH}_2$), 1.78 (dd, J = 12.8, 2.8 Hz, 2H, $\text{SO}_2\text{NCH}_2\text{CH}_2(\text{axial})$), 1.63 – 1.39 (m, 3H, PhCH_2CH + $\text{SO}_2\text{NCH}_2\text{CH}_2(\text{equatorial})$), ^{13}C NMR (100 MHz, CDCl_3) δ 151.6, 139.9, 136.9, 129.8, 129.1, 128.4, 126.2, 119.1, 118.5, 114.0, 66.7, 48.7, 46.6, 42.8, 37.5, 31.4. **LRMS** (ESI, m/z) 401.1 ($[\text{M}+\text{H}]^+$, 100%); **HRMS** (ESI) calcd for $\text{C}_{22}\text{H}_{29}\text{O}_3\text{N}_2\text{S}$ $[\text{M}+\text{H}]^+$ 401.1893, found 401.1897. **IR** $\nu_{\max}$ (neat)/ cm^{-1} 3000, 2973, 2936, 1512, 1330 (SO_2N), 1276, 1234, 1147 (SO_2N), 1130, 1061. **M.p.:** 106 – 109 °C.

6.4. Chapter 4 data

6.4.1. Synthesis of benzyne precursors

2-Methoxy-4-bromo-6-(trimethylsilyl)phenyl trifluoromethanesulfonate 61i



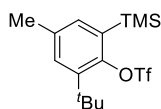
2,4-Dibromo-6-methoxyphenol^[261] (2.16 g, 10.0 mmol) was added to a solution of HMDS (4.3 mL, 20.0 mmol, 2.0 eq.) in dry THF (10 mL) under nitrogen. The mixture was heated to 85 °C and stirred for 5 h prior to cooling to room temperature. Unreacted HMDS and byproduct NH_3 were removed *in vacuo*. The crude (2,4-dibromo-6-methoxyphenoxy)trimethylsilane was used directly in the next step.

n-BuLi (12.5 mL, 1.6M in toluene, 20.0 mmol, 2.0 eq.) was added dropwise to a solution of the crude (2,4-dibromo-6-methoxyphenoxy)trimethylsilane in THF (10 mL) at -90 °C over a period of 10 min. The mixture was stirred for 1 h before triflate anhydride (3.31 mL, 20.0 mmol, 2.0 eq.) was added dropwise over a period of 15 min. The reaction mixture was stirred at -90°C for 1 h. Water (10 mL) was then added, and the crude product was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over MgSO_4 , filtered and concentrated. Flash column chromatography (100% petroleum ether) afforded the desired product as a colourless oil (2.52 g, 74%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.15 (d, $J = 2.4$ Hz, 1H, H_{Ar}), 7.14 (d, $J = 2.4$ Hz, 1H, H_{Ar}), 3.86 (s, 3H, OCH_3), 0.38 (s, 9H, $\text{Si}(\text{CH}_3)_3$); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 151.0, 142.2, 137.7, 129.4, 122.3, 122.2 (q, $J_{\text{C-F}} = 321$ Hz, CF_3), 117.4, 56.1, 0.5; $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -70.6. **HRMS** (FI) calcd for $\text{C}_{11}\text{H}_{14}\text{BrF}_3\text{O}_4\text{SSi}$ $[\text{M}]^+$ 405.9518 and 407.9497, found 405.9514 and 407.9508. **IR** ν_{max} (film): 2956, 1592, 1554, 1413, 1398, 1286, 1270,

1254, 1203, 1129, 1089, 1048, 881, 838 cm⁻¹.

2-*tert*-Butyl-4-methyl-6-(trimethylsilyl)phenyl trifluoromethanesulfonate 611



The procedure was based on the modification of S. Bronner *et al.*^[262] 2-Bromo-4-methyl-6-*tert*-butylphenol^[263] (1.21 g, 5.0 mmol) was mixed with HMDS (1.5 mL, 7.0 mmol, 1.2 eq.) and TMSCl (1.09 g, 10.0 mmol, 2.0 eq.) under nitrogen. The mixture was heated to 85 °C for 2 weeks before cooling to room temperature. Unreacted HMDS, TMSCl and byproduct NH₃ were removed *in vacuo*. The crude 1-bromo-2-trimethylsilyloxy-3-methyl-5-*tert*-butyl-benzene was confirmed by ¹H NMR spectroscopy and used directly in the next step.

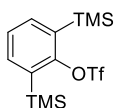
n-BuLi (5.0 mL, 1.6M in THF, 8.0 mmol, 2.0 eq.) was added dropwise over a period of 10 min to a solution of the crude 1-bromo-2-trimethylsilyloxy-3-*tert*-butyl-5-methyl-benzene (1.26 mg, 4.0 mmol) in THF (10 mL) at -100 °C. The mixture was stirred for 3 h at that temperature and then allowed to warm up to room temperature over 12 h. Aqueous NH₄Cl (10 mL) was added. The crude product was extracted with Et₂O (3 × 10 mL). Organic layer was combined, washed with brine (2 × 10 mL), dried over MgSO₄, filtered and concentrated. Flash column chromatography (100% petroleum ether) afforded 2-trimethylsilyl-4-methyl-6-*tert*-butylphenol as a colourless oil (760 mg, 79%). The product was used directly in the next step.

n-BuLi (2.5 mL, 1.6M in THF, 4.0 mmol, 2.0 eq.) was added dropwise to 2-trimethylsilyl-4-methyl-6-*tert*-butylphenol (484 mg, 2.0 mmol) in THF (10 mL) at -100 °C. The mixture

was stirred for 3 h at that temperature and then allowed to warm up to room temperature over 12 h. Then the reaction mixture was cooled to -100 °C and triflate anhydride (0.6 mL, 4.0 mmol, 2.0 eq.) was added dropwise. Then the reaction mixture was stirred at -90 °C, then warmed up to room temperature. After 12 h, saturated NaHCO₃ (10 mL) solution was added. The crude product was extracted with Et₂O (3 × 10 mL) and the organic layer was combined, washed with brine (2 × 10 mL), dried over MgSO₄, filtered and concentrated. Flash column chromatography (100% petroleum ether) afforded the desired product as a colourless oil (590 mg, 79%).

¹H NMR (400 MHz, CDCl₃) δ 7.31 (d, *J* = 2.1 Hz, 1H, *H*_{Ar}), 7.16 (d, *J* = 2.1 Hz, 1H, *H*_{Ar}), 2.34 (s, 3H, CH₃), 1.42 (s, 9H, C(CH₃)₃), 0.35 (s, 9H, Si(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 145.8, 143.2, 137.1, 136.3, 135.7, 132.6, 118.6 (q, *J*_{C-F} = 320 Hz, CF₃), 36.2, 32.1, 21.1, 1.1; ¹⁹F NMR (376 MHz, CDCl₃) δ -72.5. HRMS (FI) calcd for C₁₅H₂₃O₃F₃SSi [M]⁺ 368.1089, found 368.1071. IR *v*_{max} (film): 2963, 2359, 1587, 1394, 1251, 1212, 1157, 1140, 1056, 925, 871, 846, 611 cm⁻¹.

2,6-Bis(trimethylsilyl)phenyl trifluoromethanesulfonate 61m



Synthesised following the modified procedure of T. Akawa *et al.*^[264] 2-Bromo-6-(trimethylsilyl)phenol^[265] (1.96 g, 8.0 mmol) was added dropwise to a solution of imidazole (0.82 g, 12.0 mmol, 1.5 eq.) in dry THF (30 mL) under nitrogen. Freshly distilled trimethylsilyl chloride (1.52 mL, 12.0 mmol, 1.5 eq.) was added dropwise into the mixture under vigorous stirring. White precipitant formed instantly, the reaction mixture was left at

room temperature for 12 h. Saturated NaHCO_3 (20 mL) was added and the aqueous phase was extracted with Et_2O (3×20 mL). The combined organic phase was dried over MgSO_4 , filtered and concentrated to give the crude {3-bromo-2-[(trimethylsilyl)oxy]phenyl}trimethylsilane as a colourless oil (1.51 g, 60%). The compound was highly unstable either on silica column or in pure state, so the crude product was directly used in the next step without further purification.

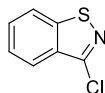
n-BuLi (6.25 mL, 1.6M in toluene, 10.0 mmol, 1.0 eq.) was added dropwise to a solution of {3-bromo-2-[(trimethylsilyl)oxy]phenyl}trimethylsilane (2.46 g, 10.0 mmol) in dry THF (40 mL) under nitrogen at 100°C with stirring. The reaction mixture was then stirred at -100°C for 3 h. Triflate anhydride (1.68 mL, 10.0 mmol, 1.0 eq.) was added slowly. After stirring for another 2 h, the reaction mixture was quenched with NaHCO_3 solution (50 mL) and then extracted with Et_2O (3×30 mL). The combined organic phase was dried over MgSO_4 , concentrated and purified by flash column chromatography (100% petroleum ether) to give the titled product as a colourless oil (2.37 g, 64 %).

^1H NMR (400 MHz, CDCl_3) δ 7.59 (d, $J = 7.3$ Hz, 2H, H_{Ar}), 7.37 (d, $J = 7.3$ Hz, 1H, H_{Ar}), 0.37 (s, 18H, $\text{Si}(\text{CH}_3)_3$); **^{13}C NMR** (100 MHz, CDCl_3) δ 155.0, 138.4, 135.1, 127.5, 118.6 (q, $^1J_{\text{C-F}} = 320$ Hz, CF_3), 0.5; **^{19}F NMR** (376 MHz, CDCl_3) δ -72.4. **HRMS** (FI) calcd for $\text{C}_{13}\text{H}_{21}\text{F}_3\text{O}_3\text{SSi}_2$ $[\text{M}]^+$ 370.0702, found 370.0694. **IR** ν_{max} (film): 2957, 1598, 1396, 1363, 1253, 1212, 1138, 1047, 875, 844, 781, 653 cm^{-1} .

6.4.2. Synthesis of 3-chloro-1,2-benzisothiazoles

GENERAL PROCEDURE G for the synthesis of benzoisothiazole derivatives using CsF

3-Chloro-1,2-benzisothiazole 60a



3,4-Dichloro-1,2,5-thiadiazole **62** (47 μ L, 0.5 mmol) was added dropwise to a suspension of freshly oven dried CsF (217 mg, 1.4 mmol, 2.8 eq.) in dry THF (1.5 mL) under nitrogen at room temperature. After 5 minutes, 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61a** (169 μ L, 0.7 mmol, 1.4 eq.) was then added dropwise. The mixture was stirred at 65 °C and monitored by TLC. Upon completion (normally after 17 h), water (10 mL) was added, and the mixture extracted with CH₂Cl₂ (3 $\times$ 10 mL). The combined organic phase was dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (10% Et₂O in petroleum ether), affording the titled compound as a colourless oil (64 mg, 76%).

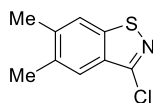
¹H NMR (400 MHz, CDCl₃) δ 8.01 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.90 (d, J = 8.2 Hz, 1H, H_{Ar}), 7.59 (app. t, J = 8.2 Hz, 1H, H_{Ar}), 7.50 (app. t, J = 8.1 Hz, 1H, H_{Ar}); ¹³C NMR (100 MHz, CDCl₃) δ 152.1, 146.2, 132.2, 129.0, 125.8, 123.9, 120.2. HRMS (FI) calcd for C₇H₄NS³⁵Cl [³⁵M]⁺ 168.9753, found 168.9756. IR ν_{max} (film): 2919, 2849, 2360, 1261, 1023, 617 cm⁻¹. M.p.: 39 °C. The data recorded are consistent with the literature.^[214a]

GENERAL PROCEDURE H for the synthesis of benzoisothiazole derivative using TBAF

3-Chloro-1,2-benzoisothiazole **60a**

2-(Trimethylsilyl)phenyl trifluoromethanesulfonate **61a** (169 μL , 0.7 mmol, 1.4 eq.) was added dropwise to a solution of 3,4-dichloro-1,2,5-thiadiazole **62** (47 μL , 0.5 mmol) in dry THF (1.5 mL), and the mixture was cooled to $-60\text{ }^{\circ}\text{C}$ under nitrogen. Then a solution of tetrabutylammonium fluoride (TBAF) (1.0 mL, 1 M in toluene, 1.0 mmol, 2.0 eq.) was added dropwise over 10 min. The reaction was then stirred for 20 min at that temperature prior to warming to room temperature. After 12 h, water (10 mL) was then added, and the resultant mixture extracted with CH_2Cl_2 ($3 \times 10\text{ mL}$). Combined organic phases were dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (10% Et_2O in petroleum ether) to give the titled compound as a colourless oil (63 mg, 75%). Data were consistent with the result from general procedure G.

3-Chloro-5,6-dimethyl-1,2-benzoisothiazole **60b**



General procedure G was followed using 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61b**^[266] (228 mg, 0.7 mmol), 3,4-dichloro-1,2,5-thiadiazole **62** (47 μL , 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (10% Et_2O in petroleum ether) to give 3-chloro-5,6-dimethyl-1,2-benzoisothiazole **60b** as a white solid (93 mg, 96%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.75 (s, 1H, H_{Ar}), 7.66 (s, 1H, H_{Ar}), 2.44 (s, 6H, CH_3); ^{13}C

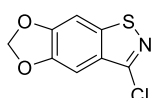
NMR (100 MHz, CDCl₃) δ 150.2, 139.7, 135.7, 132.0, 129.3, 123.5, 120.1, 20.8, 20.3.

LRMS (ESI, m/z) 198.0 ([M+H]⁺, 100%). **HRMS** (ESI) calcd for C₉H₉N³⁵ClS [35M+H]⁺

198.0139, found 198.0138. **IR** $\nu_{\max}$ (film): 2980, 2922, 1725, 1591, 1554, 1469, 1385, 1326,

1303, 1274, 1210, 1165, 1091, 1052, 1018, 954, 853 cm⁻¹. **M.p.**: 112-113 °C.

3-Chloro-5,6-dioxolo-1,2-benzisothiazole **60c**



General procedure G was followed using 6-(trimethylsilyl)benzo[1,3]dioxol-5-yl trifluoromethanesulfonate **61c**^[267] (240 mg, 0.7 mmol), 3,4-dichloro-1,2,5-thiadiazole **62** (47 μ L, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (10% Et₂O in petroleum ether) to give 3-chloro-5,6-dioxolo-1,2-benzisothiazole **60c** as a colourless oil (104 mg, 96%).

¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, J = 0.4 Hz, 1H, H_{Ar}), 7.18 (d, J = 0.4 Hz, 1H, H_{Ar}),

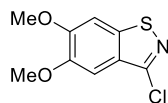
6.14 (s, 2H, CH₂); **¹³C NMR** (100 MHz, CDCl₃) δ 151.1, 148.6, 148.3, 144.8, 127.5, 102.8,

101.2, 98.7. **LRMS** (ESI, m/z) 214.0 ([M+H]⁺, 100%). **HRMS** (ESI) calcd for

C₈H₅O₂N³⁵ClS [35M+H]⁺ 213.9724, found 213.9722. **IR** $\nu_{\max}$ (film): 2917, 1859, 1617,

1595, 1500, 1476, 1460, 1410, 1397, 1210, 1139, 1126, 1071, 1028, 944, 917, 831 cm⁻¹.

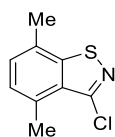
3-Chloro-5,6-dimethoxy-1,2-benzisothiazole **60d**



General procedure G was followed using 4,5-dimethoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61d**^[268] (107 mg, 0.3 mmol), 3,4-dichloro-1,2,5-thiadiazole **62** (47 μ L, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (10% Et₂O in petroleum ether) to give 3-chloro-5,6-dimethoxy-1,2-benzisothiazole **60d** as a white solid (63 mg, 93%).

¹H NMR (400 MHz, CDCl₃) δ 7.26 (s, 1H, *H*_{Ar}), 7.23 (s, 1H, *H*_{Ar}), 4.00 (s, 3H, OCH₃), 3.99 (s, 3H, OCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 152.3, 149.5, 146.7, 144.9, 126.0, 103.0, 100.5, 56.5, 56.4. LRMS (ESI, *m/z*) 230.1 ([M+H]⁺, 100%). HRMS (ESI) calcd for C₉H₈N³⁵ClSO₂ [³⁵M]⁺ 228.9964, found 228.9967. IR ν_{max} (film): 2947, 1661, 1585, 1533, 1435, 1324, 1182, 1085, 891, 791 cm⁻¹. M.p.: 235 – 237 °C.

3-Chloro-4,7-dimethyl-1,2-benzisothiazole **60e**

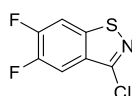


General procedure G was followed using 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61e**^[269] (65 mg, 0.2 mmol), 3,4-dichloro-1,2,5-thiadiazole **62** (23 μ L, 0.3 mmol) and CsF (62 mg, 0.4 mmol). The product was purified by flash column chromatography (10% Et₂O in petroleum ether) to give 3-chloro-4,7-dimethyl-1,2-benzisothiazole **60e** as a white solid (27 mg, 67%).

¹H NMR (400 MHz, CDCl₃) δ 7.18 (d, *J* = 7.2 Hz, 1H, *H*_{Ar}), 7.13 (d, *J* = 7.2 Hz, 1H, *H*_{Ar}),

2.87 (s, 3H, CH_3), 2.49 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 147.0, 133.2, 130.1, 128.9, 128.7, 128.1, 20.2, 19.1. **LRMS** (ESI, m/z) 198.1 ($[M+H]^+$, 100%). **HRMS** (ESI) calcd for $C_9H_9N^{35}ClS$ [^{35}M] $^+$ 198.0139, found 198.0135. **IR** ν_{max} (film): 2964, 2928, 2856, 1714, 1578, 1490, 1455, 1381, 1278, 1083, 917, 817 cm^{-1} . **M.p.**: 68 – 70 $^{\circ}C$.

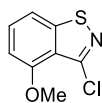
3-Chloro-5,6-difluoro-1,2-benzisothiazole **60f**



General procedure G was followed using 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61f**^[268] (107 mg, 0.3 mmol), 3,4-dichloro-1,2,5-thiadiazole **62** (47 μ L, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (10% Et_2O in petroleum ether) to give 3-chloro-5,6-difluoro-1,2-benzisothiazole **60f** as a white solid (63 mg, 52%).

1H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, J = 8.9, 6.8 Hz, 1H, H_{Ar}), 7.70 (dd, J = 8.9, 6.8 Hz, 1H, H_{Ar}); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4 (dd, $^1J_{C-F}$ = 258, $^2J_{C-F}$ = 16 Hz, C_{Ar}), 149.0 (dd, $^1J_{C-F}$ = 252, $^2J_{C-F}$ = 16 Hz, C_{Ar}), 146.9 (dd, $^3J_{C-F}$ = 8, $^4J_{C-F}$ = 1 Hz, C_{Ar}), 144.4 (d, $^4J_{C-F}$ = 5 Hz, C_{Ar}), 127.3 (dd, $^3J_{C-F}$ = 8, $^4J_{C-F}$ = 1 Hz, C_{Ar}), 109.9 (d, $^2J_{C-F}$ = 20 Hz, C_{Ar}), 107.0 (d, $^2J_{C-F}$ = 22 Hz, C_{Ar}). ^{19}F NMR (376 MHz, $CDCl_3$) δ -130.8 (ddd, J = 19.7, 8.9, 6.8 Hz, 1F, F_{Ar}), -135.9 (ddd, J = 19.7, 8.9, 6.8 Hz, 1F, F_{Ar}); **HRMS** (EI) calcd for $C_7H_2NF_2^{35}ClS$ [^{35}M] $^+$ 204.9565, found 204.9563. **IR** ν_{max} (film): 3109, 3051, 2919, 2851, 1571, 1482, 1419, 1299, 1207, 1165, 1040, 819, 799 cm^{-1} . **M.p.**: 107 – 109 $^{\circ}C$.

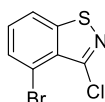
3-Chloro-4-methoxy-1,2-benzisothiazole **60g**



General procedure G was followed using 2-methoxy-6-(trimethylsilyl)phenyl trifluoromethanesulfonate **61g**^[270] (200 mg, 0.6 mmol), 3,4-dichloro-1,2,5-thiadiazole **62** (47 μ L, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (10% Et₂O in petroleum ether), resulted in the titled compound as a white solid (120 mg, 70%).

¹H NMR (400 MHz, CDCl₃) δ 7.51 – 7.46 (m, 1H, *H*_{Ar}), 7.41 (dd, *J* = 8.2, 0.7 Hz, 1H, *H*_{Ar}), 6.79 (d, *J* = 7.7 Hz, 1H, *H*_{Ar}), 4.00 (s, 3H, OCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 157.0, 155.5, 144.8, 130.6, 122.4, 112.2, 105.7, 55.9. LRMS (ESI, *m/z*) 200.0 ([M+H]⁺, 100%), 202.0 (36%). HRMS (ESI) calcd for C₈H₆ONS³⁵Cl [³⁵M+H]⁺ 199.9931, found 199.9931. IR ν_{max} (film): 2970, 1573, 1449, 1323, 1284, 1106, 1068, 1048, 937 cm⁻¹. M.p.: 112 – 114 °C.

3-Chloro-4-bromo-1,2-benzisothiazole **60h**



General procedure G was followed using 2-bromo-6-(trimethylsilyl)phenyl trifluoromethanesulfonate **61h**^[271] (180 mg, 0.5 mmol), 3,4-dichloro-1,2,5-thiadiazole **62** (102 μ L, 1.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (5% Et₂O in petroleum ether) to give 3-chloro-4-bromo-1,2-benzisothiazole **60h** as a white solid (49 mg, 40%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.86 (dd, $J = 8.2, 0.8$ Hz, 1H, H_{Ar}), 7.72 (dd, $J = 7.5, 0.8$ Hz, 1H, H_{Ar}), 7.38 (dd, $J = 8.1, 7.6$ Hz, 1H, H_{Ar}); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 155.1, 146.0, 131.6, 129.5, 129.0, 119.7, 118.4. **HRMS** (FI) calcd for $\text{C}_7\text{H}_3\text{N}^{79}\text{Br}^{35}\text{ClS}$ $[\text{M}]^+$ 246.8858 and $\text{C}_7\text{H}_3\text{N}^{81}\text{Br}^{35}\text{ClS}$ $[\text{M}]^+$ 248.8835, found 246.8865 and 248.8857. **IR** ν_{max} (film): 3076, 3056, 2925, 2852, 1580, 1538, 1459, 1263, 1197, 1168, 1091, 977, 788 cm^{-1} . **M.p.**: 125 – 127 $^{\circ}\text{C}$.

3-Chloro-4-methoxy-6-bromo-1,2-benzisothiazole 60i and 3-chloro-5-bromo-7-methoxy-1,2-benzisothiazole 60i'



General procedure G was followed using 4-bromo-2-methoxy-6-(trimethylsilyl)phenyl trifluoromethanesulfonate **61i** (121 mg, 0.3 mmol), 3,4-dichloro-1,2,5-thiadiazole **62** (19 μL , 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (10% Et_2O in petroleum ether) to give 3-chloro-4-methoxy-6-bromo-1,2-benzisothiazole **60i** (38 mg, 69%) as a white solid and 3-chloro-5-methoxy-7-bromo-1,2-benzisothiazole **60i'** (5 mg, 9%) as a white solid, in a ratio of 8:1.

3-Chloro-4-methoxy-6-bromo-1,2-benzisothiazole 60i

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.57 (d, $J = 1.3$ Hz, 1H, H_{Ar}), 6.89 (d, $J = 1.3$ Hz, 1H, H_{Ar}), 3.99 (s, 3H, OCH_3); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 156.6, 156.5, 144.8, 125.3, 121.5, 114.9, 110.0, 56.3. **HRMS** (EI) calcd for $\text{C}_8\text{H}_5\text{N}^{79}\text{Br}^{35}\text{ClOS}$ $[\text{M}+\text{H}]^+$ 276.8964 and $\text{C}_8\text{H}_5\text{N}^{81}\text{Br}^{35}\text{ClOS}$ $[\text{M}+\text{H}]^+$ 278.8941, found 276.8961 and 278.8938. **IR** ν_{max} (film): 3076,

2824, 2852, 1576, 1556, 1452, 1428, 1274, 1260, 1088, 1039, 687, 834, 816, 794 cm⁻¹.

M.p.: 173 – 175 °C.

3-Chloro-5-bromo-7-methoxy-1,2-benzisothiazole 60i'

¹H NMR (500 MHz, CDCl₃) δ 7.76 (d, *J* = 1.3 Hz, 1H, *H*_{Ar}), 7.03 (d, *J* = 1.3 Hz, 1H, *H*_{Ar}), 4.01 (s, 3H, OCH₃). ¹³C NMR (125 MHz, CDCl₃) δ 153.1, 145.2, 141.8, 134.8, 120.7, 118.5, 111.8, 56.5. **HRMS** (EI) calcd for C₈H₅NBrClOS [M]⁺ 276.8964 and 278.8941, found 276.8962 and 278.8938. **IR** *v*_{max} (film): 3076, 2927, 2870, 1567, 1483, 1346, 1292, 1106, 1005, 837, 806, 784 cm⁻¹. **M.p.:** 170 – 172 °C.

3-Chloro-5,7-dimethyl-1,2-benzisothiazole 60j and 3-chloro-4,6-dimethyl-1,2-benzisothiazole 60j'

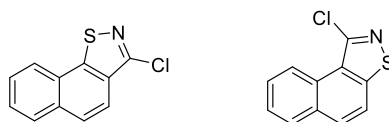


General procedure G was followed using 2,4-dimethyl-6-(trimethylsilyl)phenyl trifluoromethanesulfonate **61j**^[272] (228 mg, 0.7 mmol), 3,4-dichloro-1,2,5-thiadiazole **62** (47 μL, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (10% Et₂O in petroleum ether) to give 3-chloro-5,7-dimethyl-1,2-benzisothiazole **60j** and 3-chloro-4,6-dimethyl-1,2-benzisothiazole **60j'** as an inseparable colourless oil (82 mg, 83%), in a ratio of 1.3:1.

General procedure H was followed using the same amount of starting materials and TBAF (1.4 mL, 1M in toluene, 1.4 mmol). A colourless inseparable oil (79 mg, 80%) was isolated in a ratio of 1:1.

^1H NMR (400 MHz, CDCl_3) δ 7.61 (s, 1H, H_{Ar}), 7.47 (s, 1H, H_{Ar}), 7.19 (s, 1H, H_{Ar}), 7.01 (s, 1H, H_{Ar}), 2.84 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.45 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 154.2, 150.2, 146.3, 145.8, 139.7, 136.8, 135.2, 132.4, 131.1, 130.1, 130.0, 128.5, 120.8, 117.8, 21.5, 21.3, 20.4, 19.4. LRMS (ESI, m/z) 198.1 ($[\text{M}+\text{H}]^+$, 100%). HRMS (ESI) calcd for $\text{C}_9\text{H}_9\text{N}^{35}\text{ClS}$ [$^{35}\text{M}+\text{H}]^+$ 198.0139, found 198.0138. IR ν_{max} (film, mixture): 2980, 2919, 1597, 1481, 1459, 1410, 1381, 1341, 1304, 1274, 1215, 1174, 1112, 980, 855 cm^{-1} .

1-Chloronaphtho-1,2-isothiazole 60k and 3-chloronaphtho-2,1-isothiazole 60k'



General procedure G was followed using 1-(trimethylsilyl)naphthalen-2-yl trifluoromethanesulfonate **61k**^[273] (243 mg, 0.7 mmol), 3,4-dichloro-1,2,5-thiadiazole **62** (47 μL , 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (8% Et_2O in petroleum ether) yielded 1-chloronaphtho-1,2-isothiazole **60k** as a white solid (63 mg, 58%) and 3-chloronaphtho-2,1-isothiazole **60k'** as a white solid (43 mg, 39%), in a ratio of 1.5:1.

1-Chloronaphtho-1,2-isothiazole 60k

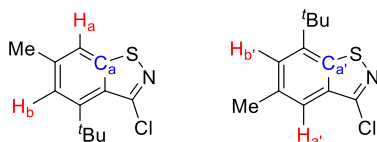
^1H NMR (400 MHz, CDCl_3) δ 8.14 – 8.07 (m, 1H, H_{Ar}), 8.06 – 8.00 (m, 1H, H_{Ar}), 7.93 – 7.83 (m, 2H, H_{Ar}), 7.75 – 7.63 (m, 2H, H_{Ar}); ^{13}C NMR (100 MHz, CDCl_3) δ 153.8, 147.1, 132.5, 130.1, 129.3, 128.9, 127.9, 127.7, 126.2, 124.7, 120.0. LRMS (ESI, m/z) 220.0 ($[\text{M}+\text{H}]^+$, 100%), 222.0 (40%). IR ν_{max} (film): 2989, 2870, 2361, 1589, 1558, 1442, 1413,

1301, 1258, 1210, 1141, 1080, 809, 746 cm^{-1} . **HRMS** (ESI) calcd for $\text{C}_{11}\text{H}_6\text{NS}^{35}\text{Cl}$ $[\text{}^{35}\text{M}+\text{H}]^+$ 219.9982, found 219.9983. **M.p.**: 110 – 112 $^{\circ}\text{C}$.

3-Chloronaphtho-2,1-isothiazole 60k'

^1H NMR (400 MHz, CDCl_3) δ 9.37 (d, $J = 8.5$ Hz, 1H, H_{Ar}), 8.04 – 7.97 (m, 1H, H_{Ar}), 7.92 (d, $J = 8.8$ Hz, 1H, H_{Ar}), 7.84 – 7.80 (m, 1H, H_{Ar}), 7.79 – 7.72 (m, 1H, H_{Ar}), 7.70 – 7.61 (m, 1H, H_{Ar}); **^{13}C NMR** (100 MHz, CDCl_3) δ 154.8, 146.1, 132.0, 131.0, 129.2, 128.6, 128.2, 126.9, 126.2, 122.8, 117.4. **LRMS** (ESI, m/z) 220.0 ($[\text{M}+\text{H}]^+$, 100%), 222 (40%). **IR** ν_{max} (film): 2993, 2362, 1558, 1438, 1283, 1222, 806, 743 cm^{-1} . **HRMS** (ESI) calcd for $\text{C}_{11}\text{H}_6\text{NS}^{35}\text{Cl}$ $[\text{}^{35}\text{M}+\text{H}]^+$ 219.9982, found 219.9979. **M.p.**: 72 – 75 $^{\circ}\text{C}$.

3-Chloro-4-*tert*-butyl-6-methyl-1,2-benzisothiazole 60l and 3-chloro-5-methyl-7-*tert*-butyl-1,2-benzisothiazole 60l'



General procedure G was followed using 2-bromo-6-(*tert*-butyl)-4-methylphenyl trifluoromethanesulfonate **61l** (110 mg, 0.3 mmol), 3,4-dichloro-1,2,5-thiadiazole **62** (19 μL , 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (1% Et_2O in petroleum ether) to give 3-Chloro-4-*tert*-butyl-6-methyl-1,2-benzisothiazole **60l** and 3-chloro-5-methyl-7-*tert*-butyl-1,2-benzisothiazole **60l'** as an inseparable white crystal (39 mg, 82%), in a ratio of 2.2:1.

3-Chloro-4-*tert*-butyl-6-methyl-1,2-benzisothiazole 60l

^1H NMR (500 MHz, CDCl_3) δ 7.54 (d, $J = 0.9$ Hz, 1H, H_{a}), 7.30 (d, $J = 0.9$ Hz, 1H, H_{b}),

2.49 (s, 3H, CH_3), 1.66 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.8, 148.4, 144.7, 138.6, 128.1, 126.0, 118.2, 36.1, 32.9, 21.7. **HRMS** (EI) calcd for $C_{12}H_{14}N^{35}ClS$ [^{35}M] $^+$ 239.0535, found 239.0532.

3-Chloro-5-methyl-7-*tert*-butyl-1,2-benzisothiazole 60I'

1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, $J = 0.8$ Hz, 1H, $H_{a'}$), 7.34 (d, $J = 0.8$ Hz, 1H, $H_{b'}$), 2.53 (s, 3H, CH_3), 1.49 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.4, 146.3, 144.0, 136.5, 133.3, 127.8, 121.4, 36.0, 30.0, 21.6. **HRMS** (EI) calcd for $C_{12}H_{14}N^{35}ClS$ [^{35}M] $^+$ 239.0535, found 239.0532.

IR ν_{max} (film, mixture): 2964, 2922, 2871, 1601, 1542, 1478, 1459, 1397, 1366, 1334, 1296, 1259, 1203, 1188, 1134, 1080, 974, 856, 821 cm^{-1} .

Regioisomers were interpreted by HMBC spectrum. C_a (δ 156.8) in 3-chloro-4-*tert*-butyl-6-methyl-1,2-benzisothiazole **60I** has shown interaction with H_a [δ 7.54 (d, $J = 0.9$ Hz, 1H, H_a)] but showed no interaction with H_b [δ 7.30 (d, $J = 0.9$ Hz, 1H, H_b)]. $C_{a'}$ (δ 147.4) in 3-chloro-5-methyl-7-*tert*-butyl-1,2-benzisothiazole **60I'** has shown remote interaction with $H_{a'}$ [δ 7.67 (d, $J = 0.8$ Hz, 1H, $H_{a'}$)] and also $H_{b'}$ [δ 7.34 (d, $J = 0.8$ Hz, 1H, $H_{b'}$)].

Another side proof was from comparing to NOE confirmed regioisomers 3-(4-tosylpiperazinyl)-4-*tert*-butyl-6-methyl-1,2-benzisothiazole **69i'** and 3-(4-tosylpiperazinyl)-5-methyl-7-*tert*-butyl-1,2-benzisothiazole **69i**. The chemical shift difference of the *tert*-butyl group between 3-chloro-4-*tert*-butyl-6-methyl-1,2-benzisothiazole **60I** [δ 1.66 (s, 9H, $C(CH_3)_3$)] and 3-(4-tosylpiperazinyl)-4-*tert*-butyl-6-methyl-1,2-benzisothiazole **69i'** [δ 1.45 (s, 9H, $C(CH_3)_3$)] was larger due to the substituent

change in 3 position, where the difference between 3-chloro-5-methyl-7-*tert*-butyl-1,2-benzisothiazole **60l'** [δ 1.49 (s, 9H, C(CH₃)₃)] and 3-(4-tosylpiperazinyl)-5-methyl-7-*tert*-butyl-1,2-benzisothiazole **69i** [δ 1.44 (s, 9H, C(CH₃)₃)] was much smaller as the butyl group was further away from the substituted carbon center.

3-Chloro-6-trimethylsilyl-1,2-benzisothiazole **60m** and 3-chloro-4-trimethylsilyl-1,2-benzisothiazole **60m'**



General procedure G was followed using 2,6-bis(trimethylsilyl)phenyl trifluoromethanesulfonate **61m** (74 mg, 0.2 mmol), 3,4-dichloro-1,2,5-thiadiazole (19 μ L, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (100% petroleum ether) to give 3-chloro-6-trimethylsilyl-1,2-benzisothiazole **60m** (21 mg, 43%) as a colourless oil and 3-chloro-4-trimethylsilyl-1,2-benzisothiazole **60m'** (10 mg, 21%) as a colourless oil, in a ratio of 2:1.

3-Chloro-6-trimethylsilyl-1,2-benzisothiazole **60m**

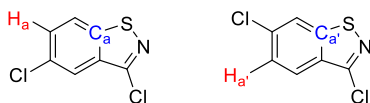
¹H NMR (400 MHz, CDCl₃) δ 8.02 (dd, J = 8.1, 1.1 Hz, 1H, H_{Ar}), 7.70 (dd, J = 6.9, 1.1 Hz, 1H, H_{Ar}), 7.50 (dd, J = 8.1, 6.9 Hz, 1H, H_{Ar}), 0.43 (s, 9H, Si(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 157.5, 146.7, 134.7, 133.1, 131.2, 125.4, 124.6, -1.2. LRMS (ESI, m/z) 242.0 ([M+H]⁺, 100%). HRMS (ESI) calcd for C₁₀H₁₃N³⁵ClSSi [³⁵M+H]⁺ 242.0221, found 242.0224. IR ν_{max} (film): 2956, 1574, 1552, 1463, 1439, 1362, 1306, 1294, 1252, 1147, 1091, 1027, 855, 840, 791, 754 cm⁻¹.

3-Chloro-4-trimethylsilyl-1,2-benzisothiazole 60m'

¹H NMR (500 MHz, CDCl₃) δ 7.93 (dd, *J* = 8.2, 0.9 Hz, 1H, *H*_{Ar}), 7.73 (dd, *J* = 7.0, 0.9 Hz, 1H, *H*_{Ar}), 7.52 (dd, *J* = 8.2, 7.0 Hz, 1H, *H*_{Ar}), 0.53 (s, 9H, Si(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃) δ 153.4, 147.0, 137.8, 135.7, 133.8, 127.6, 121.3, -1.9. LRMS (ESI, *m/z*) 241.9 ([M+H]⁺, 100%). HRMS (ESI) calcd for C₁₀H₁₃N³⁵ClSSi [³⁵M+H]⁺ 242.0221, found 242.0224. IR *v*_{max} (film): 2960, 2360, 1567, 1464, 1413, 1307, 1263, 1210, 1163, 1105, 1060, 1027, 982, 859, 841, 765, 748 cm⁻¹.

The regioisomers were interpreted compared to NOE confirmed regioisomers 3-(4-tosylpiperazinyl)-7-trimethylsilyl-1,2-benzisothiazole **69h** and 3-(4-tosylpiperazinyl)-4-trimethylsilyl-1,2-benzisothiazole **69h'**. The chemical shift difference of trimethylsilyl group between 3-chloro-6-trimethylsilyl-1,2-benzisothiazole **60m** [δ 0.43 (s, 9H, Si(CH₃)₃)] and 3-(4-tosylpiperazinyl)-7-trimethylsilyl-1,2-benzisothiazole **69h** [δ 0.39 (s, 9H, Si(CH₃)₃)] was smaller, where between 3-chloro-4-trimethylsilyl-1,2-benzisothiazole **60m'** [δ 0.53 (s, 9H, Si(CH₃)₃)] and 3-(4-tosylpiperazinyl)-4-trimethylsilyl-1,2-benzisothiazole **69h'** [δ 0.31 (s, 9H, Si(CH₃)₃)] the difference was much bigger due to the substituent change in 3 position.

3,5-Dichloro-1,2-benzisothiazole 60n and 3,6-dichloro-1,2-benzisothiazole 60n'



General procedure G was followed using 4-chloro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61n**^[273] (231 mg, 0.7 mmol), 3,4-dichloro-1,2,5-thiadiazole (47

225

μL , 0.5 mmol) **62** and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (10% Et₂O in petroleum ether) to yield the titled regioisomers as an inseparable colourless oil which solidified on sitting (77 mg, combined yield: 76%, ratio: **60n:60n'** = 1.9:1).

3,5-Dichloro-1,2-benzisothiazole **60n**

¹H NMR (400 MHz, CDCl₃) δ 8.00 (d, J = 1.9 Hz, 1H, H_{Ar}), 7.84 (d, J = 8.7 Hz, 1H, H_{Ar}), 7.57 (dd, J = 8.7, 1.9 Hz, 1H, H_{Ar}); ¹³C NMR (100 MHz, CDCl₃) δ 150.5, 145.4, 133.4, 132.5, 129.8, 123.4, 121.4. HRMS (FI) calcd for C₇H₃NS³⁵Cl₂ [³⁵M]⁺ 202.9363, found 202.9362.

3,6-Dichloro-1,2-benzisothiazole **60n'**

¹H NMR (400 MHz, CDCl₃) δ 7.93 (d, J = 8.6 Hz, 1H, H_{Ar}), 7.90 (d, J = 1.7 Hz, 1H, H_{Ar}), 7.48 (dd, J = 8.6, 1.7 Hz, 1H, H_{Ar}); ¹³C NMR (100 MHz, CDCl₃) δ 153.3, 146.1, 136.5, 130.9, 127.1, 124.8, 119.9. HRMS (FI) calcd for C₈H₆NS³⁵Cl₂ [³⁵M]⁺ 202.9363, found 202.9362. The data recorded are consistent with the literature.^[274]

IR ν_{max} (neat): 3096, 3077, 1590, 1549, 1455, 1422, 1323, 1298, 1255, 1134, 1106, 1076, 1048, 809, 782 cm⁻¹. Combined m.p.: 62 – 64 °C.

Regioisomers were interpreted by HMBC spectrum. H_a in 3,5-dichloro-1,2-benzisothiazole **60n** [δ 7.57 (dd, J = 8.7, 1.9 Hz, 1H, H_{Ar})] has shown remote interaction with C_a (δ 150.5) while H_{a'} in 3,6-dichloro-1,2-benzisothiazole **60n'** [δ 7.48 (dd, J = 8.6, 1.7 Hz, 1H, H_{Ar})] has not shown any interaction with C_{a'} (δ 153.3).

3-Chloro-5-fluoro-1,2-benzisothiazole 60o and 3-chloro-6-fluoro-1,2-benzisothiazole 60o'



General procedure G was followed using 4-fluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61o**^[273] (221 mg, 0.7 mmol), 3,4-dichloro-1,2,5-thiadiazole (47 μ L, 0.5 mmol) **62** and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (1% Et₂O in petroleum ether) to give 3-chloro-5-fluoro-1,2-benzisothiazole **60o** and 3-chloro-6-fluoro-1,2-benzisothiazole **60o'** as an inseparable white solid (63 mg, 68%), in a ratio of **60o:60o'** = 2:1.

General procedure H was followed using the same amount of starting materials and TBAF (1.4 mL, 1 M in toluene, 1.4 mmol). No product was detected.

3-Chloro-5-fluoro-1,2-benzisothiazole 60o

¹H NMR (500 MHz, CDCl₃) δ 7.87 (ddd, J = 9.0, 4.2, 0.5 Hz, 1H, H_{Ar}), 7.67 (ddd, J = 8.4, 2.2, 0.5 Hz, 1H, H_{Ar}), 7.43 – 7.36 (m, 1H, H_{Ar}); ¹³C NMR (125 MHz, CDCl₃) δ 161.3 (d, ¹ J_{C-F} = 246.9 Hz, C_{Ar}), 148.1 (d, ⁴ J_{C-F} = 1.0 Hz, C_{Ar}), 145.6 (d, ⁴ J_{C-F} = 5.3 Hz, C_{Ar}), 133.5 (d, ³ J_{C-F} = 9.6 Hz, C_{Ar}), 121.8 (d, ³ J_{C-F} = 9.2 Hz, C_{Ar}), 118.9 (d, ² J_{C-F} = 26.1 Hz, C_{Ar}), 109.1 (d, ² J_{C-F} = 24.2 Hz, C_{F2} , C_{Ar}). LRMS (ESI, m/z) 186.0 ([M+H]⁺, 100%). HRMS (ESI) calcd for C₇H₂N³⁵ClFS [M+H]⁺ 185.9586, found 185.9582.

3-Chloro-6-fluoro-1,2-benzisothiazole 60o'

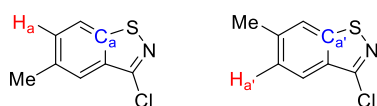
¹H NMR (500 MHz, CDCl₃) δ 7.99 (dd, J = 8.9, 4.8 Hz, 1H, H_{Ar}), 7.58 (dd, J = 8.0, 2.2 Hz, 1H, H_{Ar}), 7.27 (app. td, J = 8.7, 2.2 Hz, 1H, H_{Ar}); ¹³C NMR (125 MHz, CDCl₃) δ 163.4 (d, ¹ J_{C-F} = 253.7 Hz, C_{Ar}), 153.8 (d, ³ J_{C-F} = 10.7 Hz, C_{Ar}), 146.0 (s, C_{F5}), 129.1 (d, ⁴ J_{C-F} = 227

1.0 Hz, C_{Ar}), 125.7 (d, $^3J_{C-F} = 10.4$ Hz, C_{Ar}), 115.7 (d, $^2J_{C-F} = 25.8$ Hz, C_{Ar}), 106.4 (d, $^2J_{C-F} = 26.0$ Hz, C_{Ar}). **LRMS** (ESI, m/z) 186.0 ($[M+H]^+$, 100%). **HRMS** (ESI) calcd for $C_7H_2N^{35}ClFS$ $[^{35}M+H]^+$ 185.9586, found 185.9582.

IR ν_{max} (film, mixture): 3070, 2981, 1887, 1733, 1606, 1564, 1476, 1427, 1406, 1331, 1300, 1272, 1242, 1203, 1173, 1138, 1071, 1044, 993, 889, 808 cm^{-1} .

Regioisomers were distinguished by ^{13}C NMR spectrum. 3-Chloro-5-fluoro-1,2-benzisothiazole **60o** only has two carbons [δ 148.1 (d, $J = 1.0$ Hz, C_{F4}), and [δ 145.6 (d, $J = 5.3$ Hz, C_{F4})] which are four bonds away from the fluorine atom. 3-Chloro-6-fluoro-1,2-benzisothiazole **60o'** has one carbon [δ 129.1 (d, $^4J_{C-F} = 1.0$ Hz, C_{F4})] four bonds away and one carbon [δ 146.0 (s, C_{F5})] five bonds away from the fluorine atom.

3-Chloro-5-methyl-1,2-benzisothiazole **60p** and 3-chloro-6-methyl-1,2-benzisothiazole **60p'**



General procedure G was followed using 4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61p**^[273] (220 mg, 0.7 mmol), 3,4-dichloro-1,2,5-thiadiazole (47 μ L, 0.5 mmol) **62** and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (10% Et₂O in petroleum ether) yielded the titled regioisomers as an inseparable colourless oil (58 mg, 64%), in a ratio of 1:1.

General procedure H was followed using same amount of starting materials and TBAF (1.4 mL, 1 M in toluene, 1.4 mmol) instead of CsF. The same inseparable product mixture was

obtained in 43 mg, 47% combined yield.

3-Chloro-5-methyl-1,2-benzisothiazole 60p

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.79 (d, $J = 1.0$ Hz, 1H, H_{Ar}), 7.77 (d, $J = 8.3$ Hz, 1H, H_{Ar}), 7.43 (dd, $J = 8.3, 1.0$ Hz, 1H, H_{Ar}), 2.54 (s, 3H, CH_3); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 149.7, 145.7, 136.1, 132.6, 127.9, 123.4, 119.9, 21.5. **HRMS** (FI) calcd for $\text{C}_8\text{H}_6\text{NS}^{35}\text{Cl}$ [^{35}M] $^+$ 182.9910, found 182.9906.

3-Chloro-6-methyl-1,2-benzisothiazole 60p'

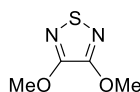
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.88 (d, $J = 8.3$ Hz, 1H, H_{Ar}), 7.67 (s, 1H, H_{Ar}), 7.32 (dd, $J = 8.3, 0.6$ Hz, 1H, H_{Ar}), 2.54 (s, 3H, CH_3); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 152.7, 146.0, 140.0, 131.1, 130.4, 123.3, 119.8, 21.9. **HRMS** (FI) calcd for $\text{C}_8\text{H}_6\text{NS}^{35}\text{Cl}$ [^{35}M] $^+$ 182.9910, found 182.9906.

IR ν_{max} (film): 2962, 2936, 1602, 1482, 1468, 1302, 1285, 1250, 1175, 1139, 1020, 986, 808 cm^{-1}

Regioisomers were distinguished by HMBC and HSQC spectrum. H_a in 3-chloro-5-methyl-1,2-benzisothiazole **60p** [δ 7.43 (dd, $J = 8.3, 1.2$ Hz, 1H, H_{Ar})] has shown remote interaction with C_a (δ 149.7) while $H_{a'}$ of 3-chloro-6-methyl-1,2-benzisothiazole **60p'** [δ 7.32 (dd, $J = 8.3, 0.6$ Hz, 1H, H_{Ar})] has not shown any interaction with $C_{a'}$ (δ 152.7). Other peaks in $^1\text{HNMR}$ and $^{13}\text{CNMR}$ spectra were assigned according to HMBC and HSQC spectra.

6.4.3. Synthesis of 1,2,5-thiadiazoles

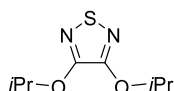
3,4-Dimethoxy-1,2,5-thiadiazole **67a**



3,4-Dichloro-1,2,5-thiadiazole **62** (0.94 mL, 10 mmol) was diluted by dry MeOH (5 mL) and cooled down to 0 °C. Sodium methoxide solution (5.77 mL, 25 wt% in MeOH, 25 mmol) was added dropwise. The reaction mixture was stirred for 20 min and then heated to reflux. Upon completion, the crude product was quenched with brine (25 mL) and extracted by dichloromethane (25 mL). The aqueous phase was washed twice by additional CH₂Cl₂ (2 × 15 mL) and the combined organic phase was dried over Mg₂SO₄, filtrated and concentrated. Flash column chromatography (100% petroleum ether degraded to 10% Et₂O in petroleum ether) resulted in the titled product as colourless crystal (490 mg, 34%).

¹H NMR (400 MHz, CDCl₃) δ 4.10 (s, 6H, OMe); ¹³C NMR (100 MHz, CDCl₃) δ 152.3, 57.7. HRMS (FI) calcd for C₄H₆O₂N₂S [M]⁺ 146.0150, found 146.0153. IR ν_{max} (film): 2932, 2084, 1711, 1553, 1524, 1415, 1246, 1082, 990 cm⁻¹. M.p.: 33 – 34 °C. The data recorded are consistent with the literature.^[275]

3,4-Diisopropyl-1,2,5-thiadiazole **67b**

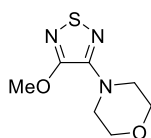


3,4-Dichloro-1,2,5-thiadiazole **62** (0.94 mL, 10 mmol) was diluted by dry MeOH (5 mL) and cooled down to 0 °C. Sodium hydride (600 mg, 25 mmol) was added slowly to a 25

mL round-bottom flask filled with isopropanol (5 mL) under ice bath with stirring. The mixture was kept cold and stirred for 1 hour before added dropwise into the thiadiazole solution. The reaction mixture was stirred for 20 min and then heated to reflux. Upon completion, the crude product was quenched with brine (25 mL) and extracted by CH₂Cl₂ (25 mL). The aqueous phase was washed twice by additional CH₂Cl₂ (2 × 15 mL) and the combined organic phase was dried over MgSO₄, filtrated and concentrated. Flash column chromatography (100% petroleum ether degraded to 10% Et₂O in petroleum ether) resulted in the titled product as colourless crystal (606 mg, 30%).

¹H NMR (400 MHz, CDCl₃) δ 5.11 (p, J = 6.2 Hz, 2H, (CH₃)₃CH), 1.43 (d, J = 6.2 Hz, 12H, CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 151.9, 74.3, 22.0. **HRMS** (FI) calcd for C₈H₁₄O₂N₂S [M]⁺ 202.0776, found 202.0772. **IR** ν_{max} (film): 2930, 2120, 1659, 1574, 1530, 1426, 1282, 1090, 903 cm⁻¹. **M.p.**: 56 – 59 °C.

3-Methoxy-4-morpholinyl-1,2,5-thiadiazole **67g**

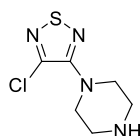


Sodium methoxide solution (0.68 mL, 25 wt% in MeOH, 3.0 mmol) was added dropwise to a solution of 3-chloro-4-morpholinyl-1,2,5-thiadiazole **67c**^[223] (510 mg, 2.5 mmol) in dry MeOH (5 mL) under nitrogen. After stirring at reflux for 12 h, the mixture was cooled to room temperature and water (20 mL) was then added. The mixture was extracted in Et₂O (3 × 10 mL). The combined organic layer was washed with water (2 × 10 mL), dried over MgSO₄, and concentrated *in vacuo*. The product was purified by flash column

chromatography (30% EtOAc in petroleum ether) to yield the titled compound as a white solid (479 mg, 95%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 4.07 (s, 3H, OCH_3), 3.83 – 3.75 (m, 4H, CH_2), 3.52 – 3.45 (m, 4H, CH_2); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 154.7, 149.9, 66.6, 57.6, 48.0. **HRMS** (FI) calcd for $\text{C}_7\text{H}_{11}\text{O}_2\text{N}_3\text{S}$ $[\text{M}]^+$ 201.0572, found 201.0576. **IR** ν_{max} (neat): 2854, 1623, 1538, 1446, 1404, 1263, 1112, 1070, 942, 924 cm^{-1} . **M.p.**: 75 – 77 $^\circ\text{C}$.

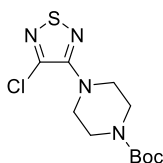
3-Chloro-4-piperazinyl-1,2,5-thiadiazole SI-67n-1



3,4-Dichloro-1,2,5-thiadiazole **62** (1.0 mL, 10.0 mmol) was added dropwise to a solution of piperazine (3.50 g, 20.0 mmol) in dry DMF (5 mL) at 0 $^\circ\text{C}$ under nitrogen. The reactant was heated to 70 $^\circ\text{C}$ and kept stirring for 4 h. After cooled to room temperature NaOH solution (10 mL, 1 M) was poured in slowly to basify the mixture. CH_2Cl_2 (3 $\times$ 15 mL) was used for extraction. The combined organic phase was washed with brine (2 $\times$ 10 mL), dried over MgSO_4 and concentrated *in vacuo*. Flash column chromatography (5% triethylamine in CH_2Cl_2) yielded the titled compound as a colourless oil (1.18 g, 59%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 3.40 (app. t, J = 5.0 Hz, 4H, NCH_2), 2.98 (app. t, J = 5.0 Hz, 4H, NHCH_2), 1.77 (b, s, 1H, NH); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 159.5, 135.4, 50.1, 45.7. **LRMS** (ESI, m/z) 205.1 ($[\text{M}+\text{H}]^+$, 100%), 207.0 (40%). **HRMS** (ESI) calcd for $\text{C}_6\text{H}_9\text{N}_4\text{S}^{35}\text{Cl}$ $[\text{M}+\text{H}]^+$ 205.0309, found 205.0306. **IR** ν_{max} (film): 2845, 1504, 1451, 1412, 1268, 1135, 1033, 810, 733 cm^{-1}

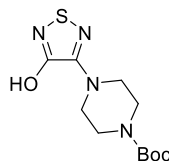
3-Chloro-4-(4-boc-piperazinyl)-1,2,5-thiadiazole SI-67n-2



Freshly distilled triethylamine (0.76 mL, 5.5 mmol) was added dropwise to 3-chloro-4-piperazinyl-1,2,5-thiadiazole **SI-67n-1** (0.50 g, 2.5 mmol) in dry MeCN (5 mL). Cold (0 °C) di-*tert*-butyl dicarbonate (1.10 g, 5.5 mmol) was added and the mixture was heated to reflux. Aqueous hydrochloric acid (1 M solution, 5 mL) was added to the reaction mixture and the aqueous phase was extracted with Et₂O (3 × 10 mL). Combined organic phase was washed with water (10 mL) and dried over MgSO₄. The solvent was removed and the crude product was purified by flash column chromatography (15% Et₂O in petroleum ether) to obtain the titled compound as a white solid (0.61 g, 80%).

¹H NMR (400 MHz, CDCl₃) δ 3.56 (t, *J* = 4.9 Hz, 4H, CONCH₂), 3.40 (t, *J* = 4.9 Hz, 4H, NCNCH₂), 1.46 (s, 9H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 159.1, 154.7, 135.6, 80.3, 48.8, 43.4 (br), 28.5. LRMS (ESI, *m/z*) 327.1 ([M+Na]⁺, 100%), 329.0 (30%). HRMS (ESI) calcd for C₁₁H₁₇O₂N₄³⁵ClS [M+Na]⁺ 327.0653, found 327.0649. IR ν_{max} (film): 2976, 1698, 1505, 1414, 1366, 1280, 1246, 1170, 1027, 811 cm⁻¹. M.p.: 94 – 96 °C.

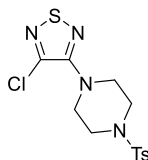
3-Hydroxy-4-(4-boc-piperazinyl)-1,2,5-thiadiazole **67n**



3-Chloro-4-(4-boc-piperazinyl)-1,2,5-thiadiazole **SI-67n-2** (0.916 g, 3.0 mmol) was added dropwise to a solution of potassium hydroxide (1.200 g, 20.0 mmol) in water (10 mL) and DMSO (3 mL). The system was heated to reflux and stirred with vigorously for 4 h. Additional water (10 mL) was added and the mixture was cooled in ice bath. Concentrated HCl was added dropwise to acidify the mixture to pH = 2 during which white precipitant crushed out. The solid was filtered, washed with water and dried, to give the titled compound (0.050 g, 6%).

^1H NMR (400 MHz, DMSO-*d*₆) δ 3.36 (s, 8H, CH_2), 1.36 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, DMSO-*d*₆) δ 154.1, 153.9, 150.2, 79.3, 46.9, 42.8, 28.2. **LRMS** (ESI, *m/z*) 309.1 ($[\text{M}+\text{Na}]^+$, 100%). **HRMS** (ESI) calcd for $\text{C}_{11}\text{H}_{17}\text{O}_3\text{N}_4\text{S}$ $[\text{M}-\text{H}]^+ 285.1027$, found 285.1028. **IR** ν_{max} (neat): 2977, 2846, 1686, 1518, 1416, 1364, 1248, 1221, 1162, 1123, 945, 763 cm^{-1} . **M.p.**: 197 – 200 °C.

3-Chloro-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **SI-67o**

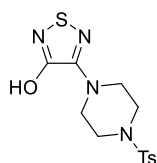


To a solution of 3-chloro-4-piperazinyl-1,2,5-thiadiazole **SI-67n-1** (102 mg, 0.5 mmol) in dry CH_2Cl_2 (2 mL), tosylchloride (191 mg, 1.0 mmol) was added after which triethylamine (133 μL , 1.0 mmol) was added dropwise. The reaction mixture was gradually heated to 45 °C

and was allowed to stir further for 12 h. Upon completion the mixture was cooled to room temperature and was quenched by water (10 mL). CH₂Cl₂ (3 × 10 mL) was used to extract the organic component and the combined organic phase was dried over MgSO₄. Solvent was removed to yield the titled product as a white solid (166 mg, 98%).

¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, *J* = 8.2 Hz, 2H, *H*_{Ar}), 7.30 (d, *J* = 8.2 Hz, 2H, *H*_{Ar}), 3.53 – 3.44 (m, 4H, NCNCH₂), 3.14 – 3.06 (m, 4H, ArNCH₂), 2.38 (s, 3H, Ts-CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 158.3, 143.9, 135.1, 132.2, 129.8, 127.7, 48.1, 45.4, 21.5. LRMS (ESI, *m/z*) 359.0 ([M+H]⁺, 100%), 381.0 ([M+Na]⁺, 80%). HRMS (ESI) calcd for C₁₃H₁₆O₂N₄S₂³⁵Cl [³⁵M+H]⁺ 359.0398, found 359.0391.

3-Hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **67o**



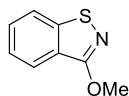
3-Chloro-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **SI-67o** (140 mg, 0.4 mmol) was added dropwise to a solution of potassium hydroxide (112 mg, 2.0 mmol) in water (2 mL) and DMSO (1 mL). The system was heated to reflux and vigorously stirred for 4 h. Additional water (10 mL) was added and the mixture was cooled in ice bath. Concentrated HCl was added dropwise to acidify the mixture to pH = 2 during which white precipitant appeared. The solid was filtered, washed with water and dried, to give the titled compound (93 mg, 68%).

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.87 (br, s, 1H, OH), 7.63 (d, *J* = 7.4 Hz, 2H, *H*_{Ar}), 7.46 (d, *J* = 7.4 Hz, 2H, *H*_{Ar}), 3.58 – 3.49 (m, 4H, NCNCH₂), 3.08 – 2.89 (m, 4H, ArNCH₂),

2.40 (s, 3H, Ts-CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 153.7, 149.6, 143.9, 131.7, 129.9, 127.7, 46.2, 45.4, 21.0. **LRMS** (ESI, *m/z*) 339.0 ([M-H]⁺, 100%). **HRMS** (ESI) calcd for C₁₃H₁₅O₃N₄S₂ [M-H]⁺ 339.0591, found 339.0588. **IR** ν_{max} (neat): 3029, 2919, 2858, 2637, 1631, 1595, 1549, 1511, 1441, 1390, 1345, 1301, 1263, 1223, 1164, 951, 725 cm⁻¹. **M.p.**: 198 – 201 °C.

6.4.4. Synthesis of 3-substituted-1,2-benzisothiazoles

3-Methoxy-1,2-benzisothiazole 68a



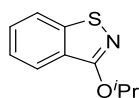
General procedure G was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61a** (170 μ L, 0.7 mmol), 3,4-dimethoxy-1,2,5-thiadiazole **67a**^[275] (73 mg, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (15% Et₂O in petroleum ether) to provide the titled compound as a colourless oil (67 mg, 81%).

¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.77 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.51 (app. t, J = 8.1 Hz, 1H, H_{Ar}), 7.38 (app. t, J = 8.0 Hz, 1H, H_{Ar}), 4.20 (s, 3H, OCH₃);

¹³C NMR (100 MHz, CDCl₃) δ 163.8, 151.9, 128.7, 125.4, 124.5, 123.1, 120.3, 56.0.

LRMS (ESI, m/z) 166.1 ([M+H]⁺, 100%). HRMS (ESI) calcd for C₈H₇ONS [M+H]⁺ 166.0321, found 166.0322. IR ν_{max} (film): 2923, 1596, 1571, 1513, 1469, 1439, 1366, 1260, 1147, 1116, 734 cm⁻¹.

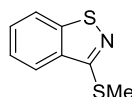
3-Isopropoxy-1,2-benzisothiazole 68b



General procedure G was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61a** (170 μ L, 0.7 mmol), 3,4-diisopropoxy-1,2,5-thiadiazole **67b** (101 mg, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (15% Et₂O in petroleum ether) to provide the titled compound as a colourless oil (83 mg, 86%).

¹H NMR (400 MHz, CDCl₃) δ 7.95 – 7.86 (m, 1H, *H*_{Ar}), 7.76 (dt, *J* = 8.2, 0.9 Hz, 1H, *H*_{Ar}), 7.50 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, *H*_{Ar}), 7.36 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, *H*_{Ar}), 5.40 (hept, *J* = 6.2 Hz, 1H, CH(CH₃)₂), 1.48 (d, *J* = 6.2 Hz, 6H, CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 162.7, 151.5, 128.6, 126.1, 124.3, 123.3, 120.2, 22.3. **LRMS** (ESI, *m/z*) 194.0 ([M+H]⁺, 100%). **HRMS** (ESI) calcd for C₁₀H₁₂ONS [M+H]⁺ 194.0640, found 194.0646. **IR** ν_{max} (film): 2920, 1573, 1588, 1504, 1455, 1432, 1375, 1258, 1137, 1100, 745 cm⁻¹.

3-Thiomethyl-1,2-benzisothiazole 68d



General procedure G was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61a** (170 μL, 0.7 mmol), 3-methoxy-4-thiomethyl-1,2,5-thiadiazole **67d**^[222] (81 mg, 0.5 mmol) and CsF (155 mg, 1.0 mmol). The product was purified by flash column chromatography (5% Et₂O in petroleum ether) to provide an inseparable 1:1 mixture of the titled compound and 3-methoxy-1,2-benzisothiazole **68a** as a colourless oil (49 mg, combined yield: 61%). 3-thiomethyl-1,2-benzisothiazole **68d** was then isolated through HPLC to confirm the structure.

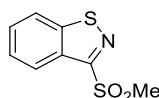
The spectra data of 3-methoxy-1,2-benzisothiazole **68a** is consistent with the data above.

3-Thiomethyl-1,2-benzisothiazole 68d:

¹H NMR (400 MHz, CDCl₃) δ 7.93 (d, *J* = 7.9 Hz, 1H, *H*_{Ar}), 7.88 (d, *J* = 7.9 Hz, 1H, *H*_{Ar}), 7.54 (app. t, *J* = 7.9 Hz, 1H, *H*_{Ar}), 7.42 (app. t, *J* = 7.9 Hz, 1H, *H*_{Ar}), 2.81 (s, 3H, SCH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 159.7, 151.9, 133.8, 128.3, 124.7, 123.0, 120.1, 13.5. **LRMS** (ESI, *m/z*) 182.0 ([M+H]⁺, 100%). **HRMS** (ESI) calcd for C₈H₇NS₂ [M+H]⁺

182.0093, found 182.0092. Combined **IR** ν_{max} (film): 2833, 1594, 1572, 1514, 1461, 1439, 1368, 1324, 1290, 1252, 1197, 1147, 1116, 761, 732 cm^{-1}

3-Methylsulfonyl-1,2-benzisothiazole 68e



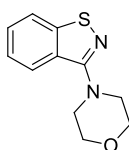
General procedure G was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61a** (170 μL , 0.7 mmol), 3-methoxy-4-methylsulfonyl-1,2,5-thiadiazole **67e**^[22] (97 mg, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (20% EtOAc in petroleum ether) 63% of starting material thiadiazole **67e** was recovered, and the titled product was isolated as a colourless oil (29 mg, 24%).

^1H NMR (400 MHz, CDCl_3) δ 8.61 (d, $J = 8.2$ Hz, 1H, H_{Ar}), 8.01 (d, $J = 8.1$ Hz, 1H, H_{Ar}), 7.65 (app. t, $J = 8.1$ Hz, 1H, H_{Ar}), 7.58 (app. t, $J = 8.2$ Hz, 1H, H_{Ar}), 3.43 (s, 3H, SO_2CH_3);

^{13}C NMR (100 MHz, CDCl_3) δ 160.3, 154.1, 131.1, 129.1, 126.7, 124.9, 119.9, 42.1.

LRMS (ESI, m/z) 236.0 ($[\text{M}+\text{Na}]^+$, 100%). **HRMS** (ESI) calcd for $\text{C}_8\text{H}_7\text{O}_2\text{NS}_2$ $[\text{M}+\text{Na}]^+$ 235.9180, found 235.9809. **IR** ν_{max} (film): 2865, 1314, 1144, 769 cm^{-1} .

3-Morpholino-1,2-benzisothiazole 68f



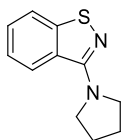
General procedure G was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61a** (170 μL , 0.7 mmol), 3-hydroxy-4-morpholino-1,2,5-

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thiadiazole **67j**^[223] (94 mg, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (25% EtOAc in petroleum ether) to yield the titled product as a colourless oil which solidified on sitting (106 mg, 96%).

¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, *J* = 8.1 Hz, 1H, *H*_{Ar}), 7.81 (d, *J* = 8.1 Hz, 1H, *H*_{Ar}), 7.47 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H, *H*_{Ar}), 7.35 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H, *H*_{Ar}), 3.93 (app. t, *J* = 4.7 Hz, 4H, OCH₂), 3.53 (app. t, *J* = 4.7 Hz, 4H, NCH₂); ¹³C NMR (100 MHz, CDCl₃) δ 163.8, 153.0, 127.9, 127.9, 124.2, 123.9, 120.8, 66.9, 50.8. LRMS (ESI, *m/z*) 221.1 ([M+H]⁺, 100%). HRMS (ESI) calcd for C₁₁H₁₂ON₂S [M+H]⁺ 221.0743, found 221.07408. IR *v*_{max} (film): 2998, 2918, 1736, 1493, 1369, 1262, 1152, 1117, 909, 734 cm⁻¹. M.p.: 52 – 55 °C. The data recorded are consistent with the literature.^[276]

3-Pyrrolidinyl-1,2-benzisothiazole **68k**

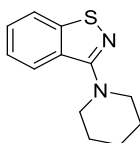


General procedure G was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61a** (170 μL, 0.7 mmol), 3-hydroxy-4-pyrrolidinyl-1,2,5-thiadiazole **67k**^[223] (93 mg, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (5% EtOAc in petroleum ether) to yield the titled product as a colourless oil which solidified on sitting (85 mg, 83%).

¹H NMR (400 MHz, CDCl₃) δ 8.12 (d, *J* = 8.2 Hz, 1H, *H*_{Ar}), 7.75 (d, *J* = 8.1 Hz, 1H, *H*_{Ar}), 7.42 (app. t, *J* = 8.1 Hz, 1H, *H*_{Ar}), 7.29 (app. t, *J* = 8.2 Hz, 1H, *H*_{Ar}), 3.86 (app. t, *J* = 6.7 Hz, 4H, NCH₂), 2.04 (app. t, *J* = 6.7 Hz, 4H, NCH₂CH₂); ¹³C NMR (100 MHz, CDCl₃) δ

160.5, 153.4, 127.6, 127.4, 124.8, 123.5, 120.5, 49.7, 25.8. **LRMS** (ESI, m/z) 205.1 ($[M+H]^+$, 100%). **HRMS** (ESI) calcd for $C_{11}H_{12}N_2S$ $[M+H]^+$ 205.0794, found 205.0791. **IR** $\nu_{\max}$ (film): 2764, 1563, 1485, 1433, 733 cm^{-1} . **M.p.**: 49 – 51 °C. The data recorded are consistent with the literature.^[277]

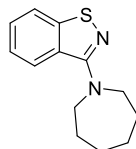
3-Piperidinyl-1,2-benzisothiazole **68l**



General procedure G was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61a** (170 μ L, 0.7 mmol), 3-hydroxy-4-piperidinyl-1,2,5-thiadiazole **67l**^[223] (93 mg, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (5% EtOAc in petroleum ether) to yield the titled product as a colourless oil (85 mg, 78%).

1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.79 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.45 (app. t, J = 8.1 Hz, 1H, H_{Ar}), 7.34 (app. t, J = 8.1 Hz, 1H, H_{Ar}), 3.55 – 3.41 (m, 4H, NCH_2), 1.84 – 1.74 (m, 4H, NCH_2CH_2), 1.75 – 1.60 (m, 2H, $NCH_2CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.1, 152.6, 128.5, 127.5, 124.2, 123.9, 120.6, 51.6, 26.1, 24.8. **LRMS** (ESI, m/z) 219.0 ($[M+H]^+$, 100%). **HRMS** (ESI) calcd for $C_{12}H_{14}N_2S$ $[M+H]^+$ 219.0951, found 219.0946. **IR** $\nu_{\max}$ (film): 2852, 1561, 1492, 1467, 1425, 1282, 1257, 1117, 1065, 736 cm^{-1} . The data recorded are consistent with the literature.^[278]

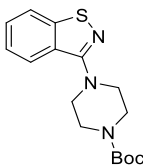
3-Azapanyl-1,2-benzisothiazole 68m



General procedure G was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61a** (170 μ L, 170 mmol), 3-azapanyl-4-hydroxy-1,2,5-thiadiazole **67m**^[223] (100 mg, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (5% Et₂O in petroleum ether) to yield the titled product as a colourless oil (107 mg, 93%).

¹H NMR (400 MHz, CDCl₃) δ 8.01 (d, J = 8.2 Hz, 1H, H_{Ar}), 7.76 (d, J = 8.2 Hz, 1H, H_{Ar}), 7.41 (app. t, J = 8.2 Hz, 1H, H_{Ar}), 7.30 (app. t, J = 8.2 Hz, 1H, H_{Ar}), 3.91 – 3.75 (m, 4H, NCH₂), 2.02 – 1.89 (m, 4H, NCH₂CH₂), 1.73 – 1.60 (m, 4H, NCH₂CH₂CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 162.7, 153.4, 127.4, 127.2, 124.8, 123.6, 120.6, 50.7, 29.5, 27.7. LRMS (ESI, m/z) 233.1 ([M+H]⁺, 100%). IR ν_{max} (film): 2926, 2852, 1591, 1561, 1506, 1469, 1429, 1369, 1261, 1168, 734 cm⁻¹.

3-(4-Boc-piperaziny)-1,2-benzisothiazole 68n

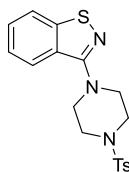


General procedure G was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61a** (80 μ L, 0.3 mmol), 3-hydroxy-4-(4-boc-piperaziny)-1,2,5-thiadiazole **67n** (57 mg, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (15% Et₂O in petroleum ether) to give 3-(4-boc-

piperazinyl)-1,2-benzisothiazole **68n** as a white solid (47 mg, 73%).

¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, *J* = 8.1 Hz, 1H, *H*_{Ar}), 7.82 (d, *J* = 8.1 Hz, 1H, *H*_{Ar}), 7.48 (app. t, *J* = 8.1 Hz, 1H, *H*_{Ar}), 7.37 (app. t, *J* = 8.1 Hz, 1H, *H*_{Ar}), 3.72 – 3.60 (m, 4H, NCNCH₂), 3.53 – 3.43 (m, 4H, ArNCH₂), 1.49 (s, 9H, CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 163.9, 155.0, 152.9, 128.1, 127.8, 124.2, 123.8, 120.8, 80.2, 50.1 (br), 43.9 (br), 28.6. **LRMS** (ESI, *m/z*) 320.1 ([M+H]⁺, 100%). **HRMS** (ESI) calcd for C₁₆H₂₁O₂N₃S [M+H]⁺ 320.1427, found 320.1421. **IR** ν_{max} (film): 1739, 1695, 1417, 1365, 1246, 1168, 1000, 864 cm⁻¹. **M.p.**: 105 – 108 °C.

3-(4-Tosylpiperazinyl)-1,2-benzisothiazole **68o**



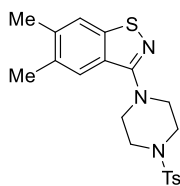
General procedure G was followed using 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61a** (170 μL, 0.7 mmol), 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **67o** (170 mg, 0.5 mmol) and CsF (217 mg, 1.4 mmol). The product was purified by flash column chromatography (40% Et₂O in petroleum ether) to give 3-(4-tosylpiperazinyl)-1,2-benzisothiazole **68o** as a white solid (158 mg, 85%).

¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, *J* = 8.2 Hz, 1H, *H*_{Ar}), 7.77 (d, *J* = 8.2 Hz, 1H, *H*_{Ar}), 7.69 (d, *J* = 8.2 Hz, 2H, *H*_{Ts-Ar}), 7.46 (app. t, *J* = 8.0 Hz, 1H, *H*_{Ar}), 7.35 (d, *J* = 8.2 Hz, 2H, *H*_{Ts-Ar}), 7.31 (app. t, *J* = 8.0 Hz, 1H, *H*_{Ar}), 3.63 – 3.58 (m, 4H, NCNCH₂), 3.27 – 3.22 (m, 4H, ArNCH₂), 2.45 (s, 3H, Ts-CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 163.1, 153.0, 144.0, 132.7, 130.0, 128.0, 127.9, 127.8, 124.2, 123.6, 120.8, 49.5, 45.9, 21.7. **LRMS** (ESI, *m/z*)

374.0 ($[M+H]^+$, 100%), 396.0 ($[M+Na]^+$, 80%). **HRMS** (ESI) calcd for $C_{18}H_{20}O_2N_3S_2$
 $[M+H]^+$ 374.0991, found 374.0985. **IR** $\nu_{\max}$ (film): 2852, 1596, 1493, 1452, 1423, 1384,
1347, 1326, 1264, 1166, 943, 728, 652 cm^{-1} . **M.p.:** 125 – 127 °C.

6.4.5. Synthesis of 3-piperazinyl-1,2-benzisothiazoles

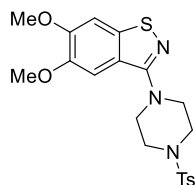
3-(4-Tosylpiperazinyl)-5,6-dimethyl-1,2-benzisothiazole **69a**



General procedure G was followed using 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61b**^[266] (98 mg, 0.3 mmol), 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **67o** (68 mg, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (40% Et₂O in petroleum ether) to give 3-(4-tosylpiperazinyl)-5,6-dimethyl-1,2-benzisothiazole **69a** as a white solid (69 mg, 86%).

¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 7.54 (s, 1H, *H*_{Ar}), 7.49 (s, 1H, *H*_{Ar}), 7.36 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 3.61 – 3.57 (m, 4H, NCNCH₂), 3.26 – 3.22 (m, 4H, ArNCH₂), 2.44 (s, 3H, Ts-CH₃), 2.37 (s, 3H, CH₃), 2.35 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 162.7, 151.1, 144.0, 138.1, 133.7, 132.7, 129.9, 128.0, 126.4, 123.3, 120.7, 49.5, 45.9, 21.7, 20.5, 20.4. LRMS (ESI, *m/z*) 402.1 ([M+H]⁺, 100%). HRMS (ESI) calcd for C₂₀H₂₄O₂N₃S₂ [M+H]⁺ 402.1304, found 402.1296. IR ν_{max} (film): 2920, 2854, 1597, 1549, 1492, 1452, 1419, 1370, 1348, 1308, 1266, 1167, 1135, 1117, 1093, 941, 728, 649 cm⁻¹. M.p.: 126 – 128 °C.

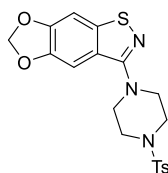
3-(4-Tosylpiperazinyl)-5,6-dimethoxy-1,2-benzisothiazole **69b**



General procedure G was followed using 4,5-dimethoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61d**^[268] (107 mg, 0.3 mmol), 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **67o** (68 mg, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (40% EtOAc in petroleum ether) to give 3-(4-tosylpiperazinyl)-5,6-dimethoxy-1,2-benzisothiazole **69b** as a white solid (73 mg, 85%).

¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 7.36 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 7.16 (s, 1H, *H*_{Ar}), 7.03 (s, 1H, *H*_{Ar}), 3.95 (s, 3H, OCH₃), 3.91 (s, 3H, OCH₃), 3.62 – 3.50 (m, 4H, NCNCH₂), 3.31 – 3.19 (m, 4H, ArNCH₂), 2.45 (s, 3H, Ts-CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 162.7, 151.2, 148.0, 147.3, 144.0, 132.8, 129.9, 128.0, 121.2, 103.6, 101.2, 56.4, 56.3, 49.5, 45.8, 21.7. LRMS (ESI, *m/z*) 434.1 ([M+H]⁺, 100%). HRMS (ESI) calcd for C₂₀H₂₄O₄N₃S₂ [M+H]⁺ 434.1203, found 434.1204. IR *v*_{max} (film): 2851, 1605, 1502, 1468, 1453, 1421, 1346, 1327, 1228, 1258, 1212, 1166, 1137, 1092, 1055, 1027, 812, 729 cm⁻¹. M.p.: 248 – 250 °C.

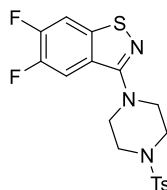
3-(4-Tosylpiperazinyl)-5,6-dioxolo-1,2-benzisothiazole **69c**



General procedure G was followed using 6-(trimethylsilyl)benzo[1,3]dioxol-5-yl trifluoromethanesulfonate **61c**^[267] (103 mg, 0.3 mmol), 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **67o** (68 mg, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (60% Et₂O in petroleum ether) to give 3-(4-tosylpiperazinyl)-5,6-dioxolo-1,2-benzisothiazole **69c** as a white solid (61 mg, 73%).

¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 7.36 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 7.10 (s, 1H, *H*_{Ar}), 7.01 (s, 1H, *H*_{Ar}), 6.07 (s, 2H, CH₂), 3.54 – 3.47 (m, 4H, NCNCH₂), 3.26 – 3.15 (m, 4H, ArNCH₂), 2.45 (s, 3H, Ts-CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 162.7, 149.9, 148.8, 147.1, 144.0, 132.7, 130.0, 128.0, 122.5, 102.3, 101.2, 99.3, 49.6, 46.0, 21.7. LRMS (ESI, *m/z*) 418.1 ([M+H]⁺, 100%). HRMS (ESI) calcd for C₁₉H₂₀O₄N₃S₂ [M+H]⁺ 418.0890, found 418.0887. IR ν_{max} (film): 2897, 2854, 1598, 1484, 1441, 1371, 1347, 1326, 1275, 1247, 1166, 1115, 1093, 1038, 979, 852, 728 cm⁻¹. M.p.: 111 – 114 °C.

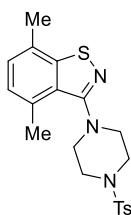
3-(4-Tosylpiperazinyl)-4,5-difluoro-1,2-benzisothiazole **69d**



General procedure G was followed using 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61f**^[268] (100 mg, 0.3 mmol), 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **67o** (68 μ L, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (40% Et₂O in petroleum ether) to give 3-(4-tosylpiperazinyl)-4,5-difluoro-1,2-benzisothiazole **69d** as a white solid (76 mg, 93%).

¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.55 (dd, J = 9.0, 6.8 Hz, 1H, H_{Ar}), 7.50 (dd, J = 10.0, 7.0 Hz, 1H, H_{Ar}), 7.36 (d, J = 8.1 Hz, 2H, H_{Ar}), 3.52 – 3.47 (m, 4H, NCNCH₂), 3.26 – 3.19 (m, 4H, ArNCH₂), 2.45 (s, 3H, Ts-CH₃); **¹³C NMR** (100 MHz, CDCl₃) δ 162.5 (d, $^4J_{C-F}$ = 4 Hz, C_{Ar}), 151.3 (dd, $^1J_{C-F}$ = 252, $^2J_{C-F}$ = 13 Hz, C_{Ar}), 148.7 (dd, $^1J_{C-F}$ = 245, $^2J_{C-F}$ = 12 Hz, C_{Ar}), 148.6 (d, $^3J_{C-F}$ = 8 Hz, C_{Ar}), 144.1, 132.6, 130.0, 128.0, 123.7 (d, $^3J_{C-F}$ = 6 Hz, C_{Ar}), 110.6 (d, $^2J_{C-F}$ = 19.1 Hz, C_{Ar}), 108.3 (d, $^2J_{C-F}$ = 21 Hz, C_{Ar}), 49.5, 45.8, 21.7; **¹⁹F NMR** (376 MHz, CDCl₃) δ 133.3 (ddd, J = 20.1, 9.8, 6.8 Hz, 1F, F_{Ar}), 138.4 (ddd, J = 20.1, 9.8, 6.8 Hz, 1F, F_{Ar}). **LRMS** (ESI, m/z) 410.0 ([M+H]⁺, 100%). **HRMS** (ESI) calcd for C₁₈H₁₇N₃O₂F₂S₂Na [M+Na]⁺ 432.0623, found 432.0621. **IR** ν_{max} (film): 2855, 1711, 1598, 1508, 1455, 1438, 1349, 1328, 1290, 1222, 1166, 1136, 947, 728 cm⁻¹. **M.p.**: 153 – 155 °C.

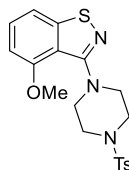
3-(4-Tosylpiperazinyl)-4,7-dimethyl-1,2-benzisothiazole **69e**



General procedure G was followed using 3,6-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **61e**^[269] (98 mg, 0.3 mmol), 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **67o** (68 mg, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (20% Et₂O in petroleum ether) to give 3-(4-tosylpiperazinyl)-4,7-dimethyl-1,2-benzisothiazole **69e** as a white solid (55 mg, 68%).

¹H NMR (500 MHz, CDCl₃) δ 7.70 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 7.37 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 7.10 (d, *J* = 7.2 Hz, 1H, *H*_{Ar}), 7.06 (d, *J* = 7.2 Hz, 1H, *H*_{Ar}), 3.41 – 3.31 (m, 4H, NCNCH₂), 3.28 – 3.06 (br, s, 4H, ArNCH₂), 2.64 (s, 3H, Ts-CH₃), 2.46 (s, 3H, CH₃), 2.44 (s, 3H, CH₃); **¹³C NMR** (125 MHz, CDCl₃) δ 166.7, 154.1, 143.9, 133.2, 132.3, 130.0, 127.9, 127.9, 127.8, 127.8 (overlap), 127.5, 51.4, 45.8, 21.7, 19.3, 18.9. **LRMS** (ESI, *m/z*) 402.1 ([M+H]⁺, 100%). **HRMS** (ESI) calcd for C₂₀H₂₄O₂N₃S₂ [M+H]⁺ 402.1294, found 402.1304. **IR** ν_{max} (film): 2918, 2849, 1738, 1451, 1373, 1343, 1326, 1263, 1240, 1166, 1093, 1046, 946, 821, 731 cm⁻¹. **M.p.**: 193 – 195 °C.

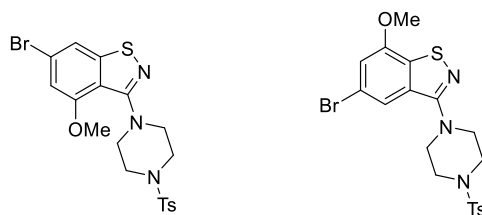
3-(4-Tosylpiperazinyl)-4-methoxy-1,2-benzisothiazole **69f**



General procedure G was followed using 2-methoxy-6-(trimethylsilyl)phenyl trifluoromethanesulfonate **61g**^[270] (98 mg, 0.3 mmol), 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **67o** (68 mg, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (40% Et₂O in petroleum ether) to give 3-(4-tosylpiperazinyl)-4-methoxy-1,2-benzisothiazole **69f** as a white solid (70 mg, 87%).

¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, *J* = 8.3 Hz, 2H, *H*_{Ar}), 7.44 – 7.37 (m, 1H, *H*_{Ar}), 7.36 – 7.35 (m, 2H, *H*_{Ar}), 7.35 – 7.34 (m, 1H, *H*_{Ar}), 6.70 (dd, *J* = 7.5, 0.8 Hz, 1H, *H*_{Ar}), 3.90 (s, 3H, OCH₃), 3.53 – 3.46 (m, 4H, CH₂), 3.27 – 3.18 (m, 4H, CH₂), 2.45 (s, 3H, Ts-CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 163.7, 156.0, 155.8, 143.9, 133.0, 129.9, 129.5, 128.0, 118.9, 112.9, 105.1, 55.8, 50.6, 45.9, 21.7. LRMS (ESI, *m/z*) 404.0 ([M+H]⁺, 100%). HRMS (ESI) calcd for C₁₉H₂₂O₃N₃S₂ [M+H]⁺ 404.1097, found 404.1084. IR *v*_{max} (film): 2980, 2852, 1712, 1589, 1570, 1484, 1451, 1383, 1348, 1275, 1216, 1166, 1042, 945, 728 cm⁻¹. M.p.: 153 – 155 °C.

3-(4-Tosylpiperazinyl)-4-methoxy-6-bromo-1,2-benzisothiazole 69g and 3-(4-tosylpiperazinyl)-5-bromo-7-methoxy-1,2-benzisothiazole 69g'



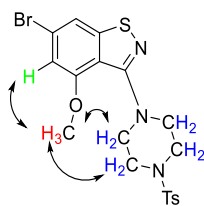
General procedure G was followed using 4-bromo-2-methoxy-6-(trimethylsilyl)phenyl trifluoromethanesulfonate **61i** (121 mg, 0.3 mmol), 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **67o** (68 mg, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (40% Et₂O in petroleum ether) to give 3-(4-tosylpiperazinyl)-4-methoxy-6-bromo-1,2-benzisothiazole (70 mg, 73%) **69g** as a white solid and 3-(4-tosylpiperazinyl)-5-bromo-7-methoxy-1,2-benzisothiazole **69g'** (9 mg, 9%) as a white solid, in a ratio of 8:1.

3-(4-Tosylpiperazinyl)-4-methoxy-6-bromo-1,2-benzisothiazole 69g

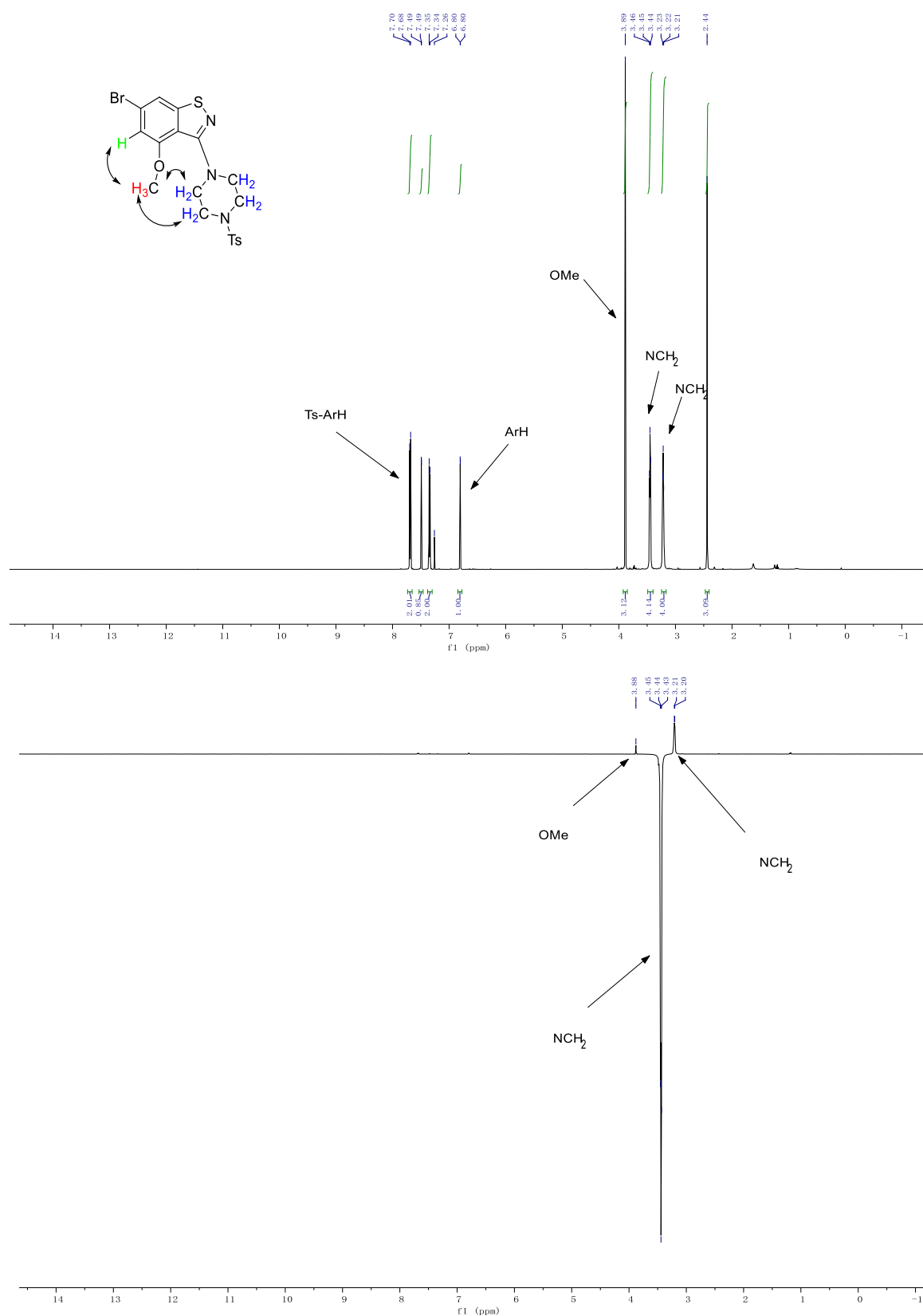
¹H NMR (500 MHz, CDCl₃) δ 7.68 (d, *J* = 8.2 Hz, 2H, *H*_{Ar}), 7.48 (d, *J* = 1.3 Hz, 1H, *H*_{Ar}), 7.34 (d, *J* = 8.2 Hz, 2H, *H*_{Ar}), 6.80 (d, *J* = 1.3 Hz, 1H, *H*_{Ar}), 3.88 (s, 3H, OCH₃), 3.46 – 3.43 (m, 4H, CH₂), 3.23 – 3.18 (m, 4H, CH₂), 2.44 (s, 3H, Ts-CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 163.4, 157.1, 155.6, 143.9, 132.9, 129.8, 128.0, 123.9, 118.0, 115.5, 109.2, 56.2, 50.5, 45.8, 21.7. LRMS (ESI, *m/z*) 482 and 484 ([M+H]⁺, 100%). HRMS (ESI) calcd for C₁₉H₂₁N₃O₃S₂Br [M+H]⁺ 482.0202 and 484.0180, found 482.0202 and 484.0182. IR *v*_{max} (film, mixture): 2852, 1574, 1561, 1452, 1379, 1347, 1327, 1268, 1166, 1043, 943, 728 cm⁻¹. M.p.: 193 – 196 °C.

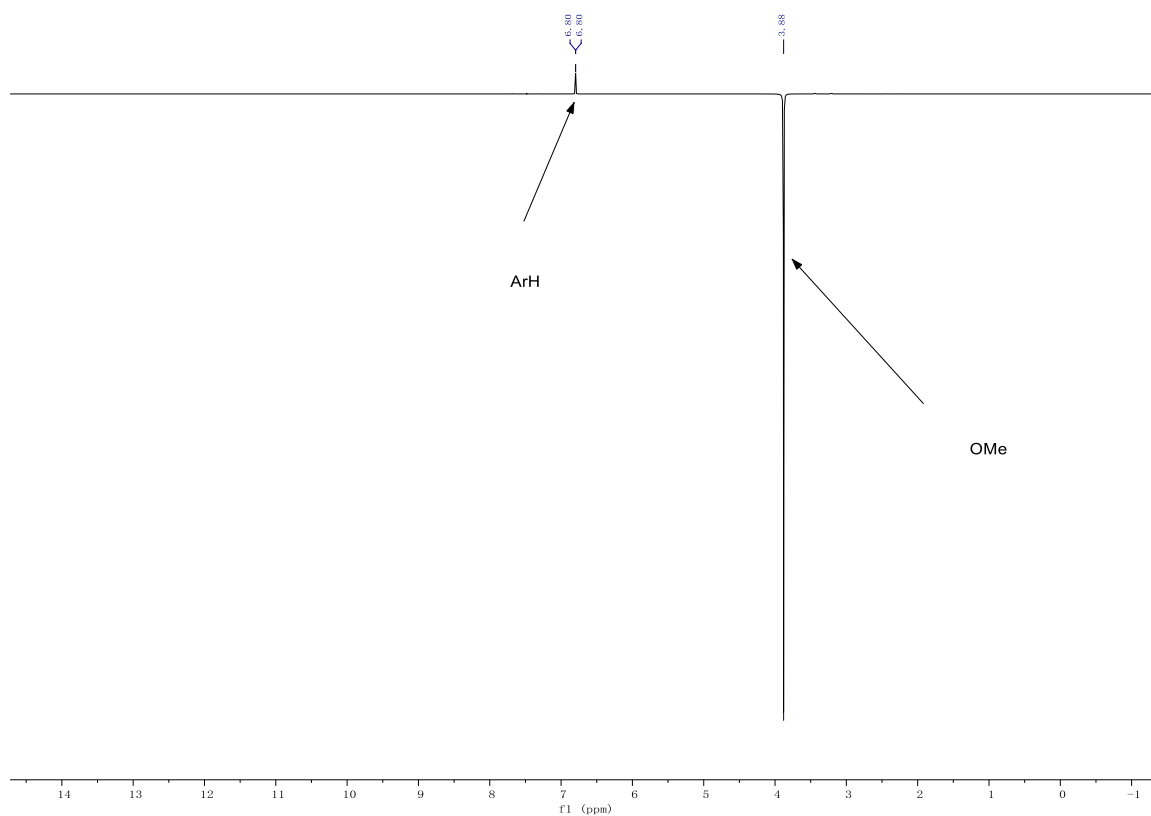
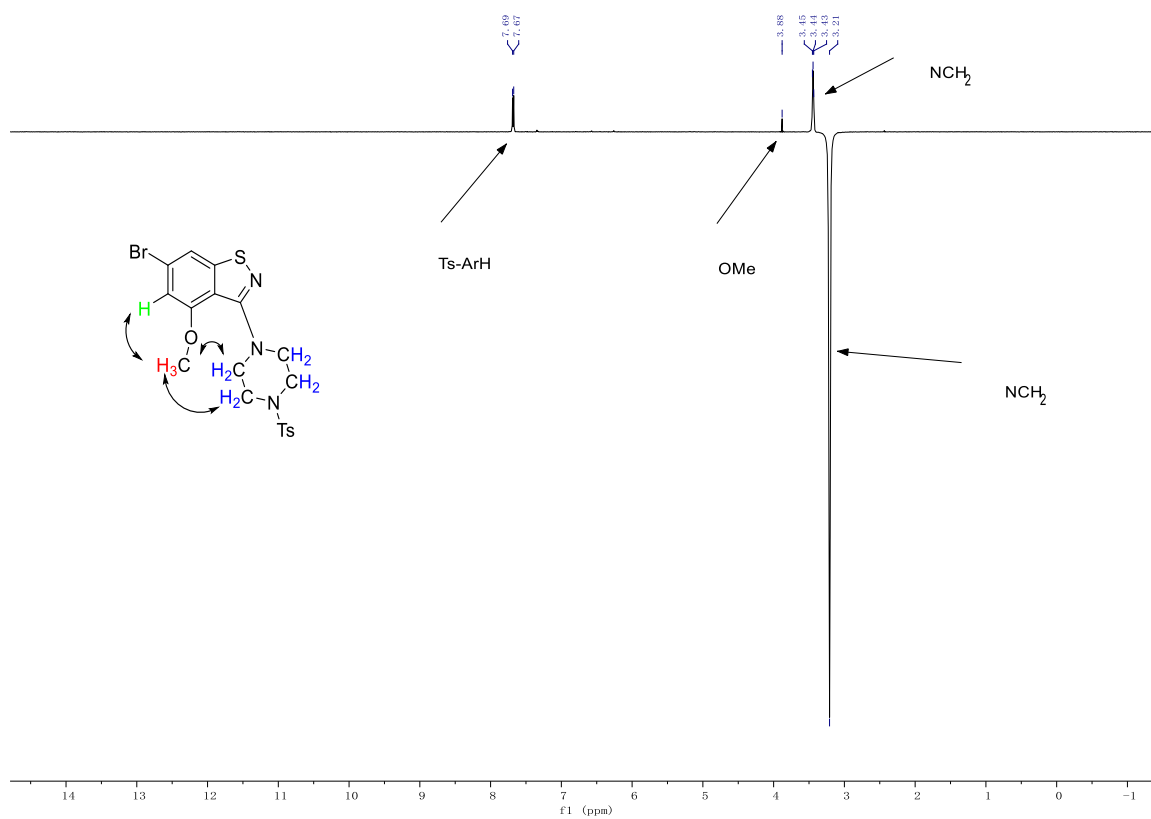
3-(4-Tosylpiperazinyl)-5-bromo-7-methoxy-1,2-benzisothiazole 69g'

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.69 (d, $J = 8.1$ Hz, 2H, H_{Ar}), 7.46 (d, $J = 1.3$ Hz, 1H, H_{Ar}), 7.37 (d, $J = 8.1$ Hz, 2H, H_{Ar}), 6.91 (d, $J = 1.3$ Hz, 1H, H_{Ar}), 3.96 (s, 3H, OCH_3), 3.59 – 3.53 (m, 4H, NCNCH_2), 3.25 – 3.20 (m, 4H, ArNCH_2), 2.45 (s, 3H, Ts-CH_3); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 162.5, 158.4, 144.1, 132.6, 130.9, 130.0, 128.0, 119.0, 118.9, 110.7, 56.2, 49.5, 45.9, 21.7. **LRMS** (ESI, m/z) 482.0 and 484.0 ($[\text{M}+\text{H}]^+$, 100%). **HRMS** (ESI) calcd for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_3\text{S}_2\text{Br}$ $[\text{M}+\text{H}]^+$ 482.0203 and 484.0180, found 482.0202 and 484.0183. **IR** ν_{max} (film, mixture): 2852, 1598, 1566, 1493, 1449, 1377, 1350, 1328, 1267, 1166, 1057, 952, 728 cm^{-1} . **M.p.:** 128 – 130 $^\circ\text{C}$.



Regioisomers were distinguished by NOE spectrum as presented below. Protons on methoxy group of 3-(4-tosylpiperazinyl)-4-methoxy-6-bromo-1,2-benzisothiazole **69g** [δ 3.88 (s, 3H, OCH_3)] have shown remote interaction with protons on both CH_2 of the piperazine group [δ 3.46 – 3.43 (m, 4H, NCNCH_2) and 3.23 – 3.18 (m, 4H, ArNCH_2)]. Remote interaction was also observed between protons on OMe group and proton on the aromatic ring [δ 6.83 (d, $J = 1.3$ Hz, 1H, H_{Ar})] next to it.

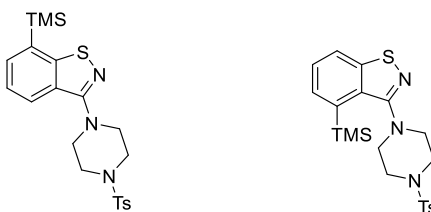




¹H and NOE spectra of 3-(4-tosylpiperazinyl)-4-methoxy-6-bromo-1,2-

benzothiazole 69g

3-(4-Tosylpiperazinyl)-7-trimethylsilyl-1,2-benzisothiazole 69h and 3-(4-tosylpiperazinyl)-4-trimethylsilyl-1,2-benzisothiazole 69h'



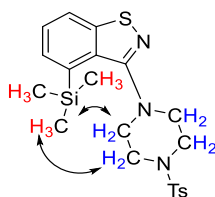
General procedure G was followed using 2,6-bis(trimethylsilyl)phenyl trifluoromethanesulfonate **61m** (74 mg, 0.2 mmol), 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **67o** (68 mg, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (20% Et₂O in petroleum ether) to give 3-(4-tosylpiperazinyl)-7-trimethylsilyl-1,2-benzisothiazole **69h** (52 mg, 58%) as a white crystal and 3-(4-tosylpiperazinyl)-4-trimethylsilyl-1,2-benzisothiazole **69h'** (10 mg, 11%) as a white crystal, in a ratio of 5:1.

3-(4-Tosylpiperazinyl)-7-trimethylsilyl-1,2-benzisothiazole 69h

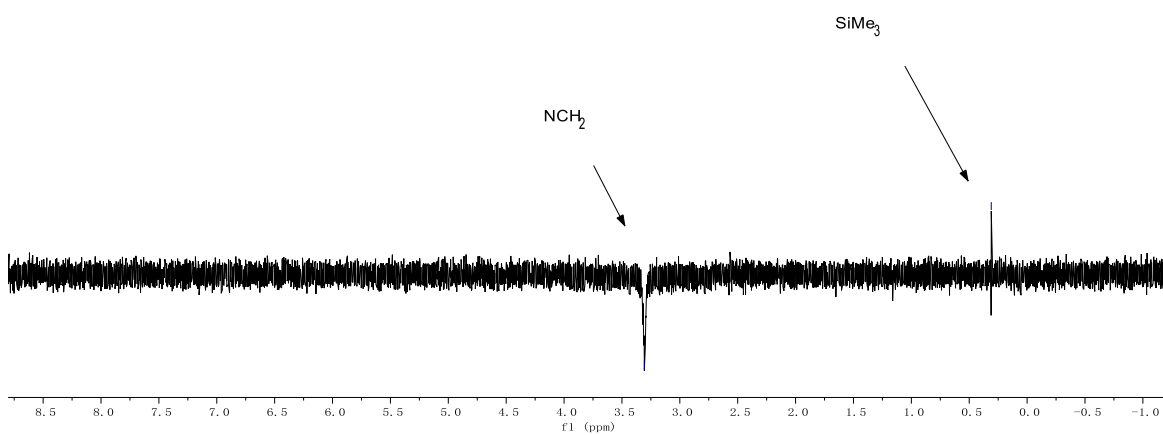
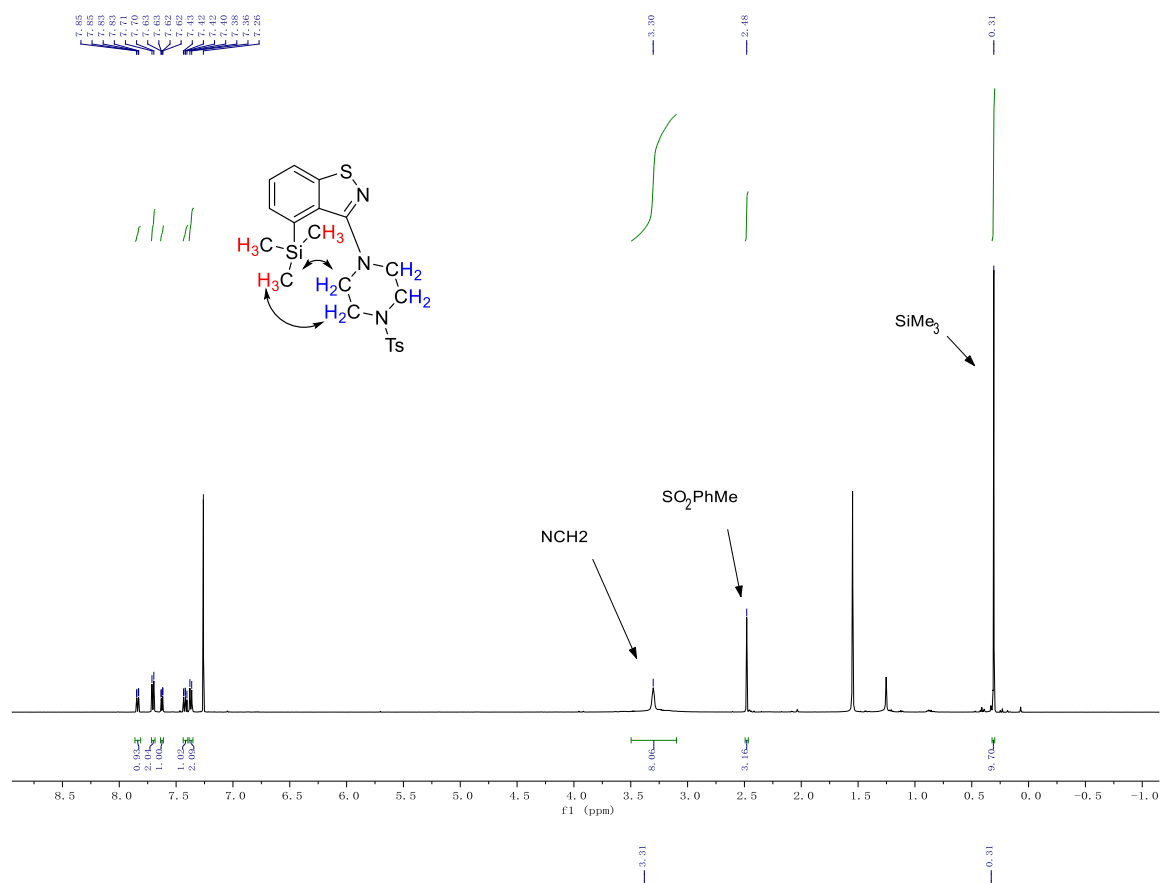
¹H NMR (400 MHz, CDCl₃) δ 7.75 (dd, *J* = 8.2, 1.1 Hz, 1H, *H*_{Ar}), 7.69 (d, *J* = 8.3 Hz, 2H, *H*_{Ar}), 7.57 (dd, *J* = 6.9, 1.1 Hz, 1H, *H*_{Ar}), 7.36 (d, *J* = 8.3 Hz, 2H, *H*_{Ar}), 7.31 (dd, *J* = 8.2, 6.9 Hz, 1H, *H*_{Ar}), 3.68 – 3.49 (m, 4H, NCNCH₂), 3.29 – 3.19 (m, 4H, ArNCH₂), 2.45 (s, 3H, Ts-CH₃), 0.39 (s, 9H, Si(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 163.4, 158.4, 144.0, 133.6, 133.3, 132.8, 130.0, 128.0, 126.6, 124.2, 123.8, 49.7, 46.0, 21.7, 1.3. LRMS (ESI, *m/z*) 446.1 ([M+H]⁺, 100%). HRMS (ESI) calcd for C₂₁H₂₈N₃O₂S₂Si [M+H]⁺ 446.1387, found 446.1386. IR *v*_{max} (film): 2955, 2924, 2853, 1598, 1557, 1484, 1452, 1391, 1350, 1265, 1251, 1168, 947, 915, 728 cm⁻¹. M.p.: 164 – 166 °C.

3-(4-Tosylpiperazinyl)-4-trimehysilyl-1,2-benzisothiazole **69h'**

¹H NMR (500 MHz, CDCl₃) δ 7.84 (dd, *J* = 8.1, 0.9 Hz, 1H, *H*_{Ar}), 7.70 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 7.62 (dd, *J* = 7.0, 0.9 Hz, 1H, *H*_{Ar}), 7.42 (dd, *J* = 8.1, 7.0 Hz, 1H, *H*_{Ar}), 7.37 (d, *J* = 8.1 Hz, 2H, *H*_{Ar}), 3.39 – 3.24 (br, s, 8H, NCH₂), 2.48 (s, 3H, Ts-CH₃), 0.31 (s, 9H, Si(CH₃)₃); **¹³C NMR** (125 MHz, CDCl₃) δ 168.2, 153.5, 143.9, 137.2, 133.5, 133.3, 133.1, 129.8, 128.0, 126.7, 121.2, 52.2, 45.0, 21.8, 1.6. **LRMS** (ESI, *m/z*) 446.1 ([M+H]⁺, 100%). **HRMS** (ESI) calcd for C₂₁H₂₈N₃O₂S₂Si [M+H]⁺ 446.1387, found 446.1386. **IR** ν_{max} (film): 2919, 2851, 2359, 1457, 1350, 1264, 1168, 1101, 945, 859, 731 cm⁻¹. **M.p.**: 189 – 192 °C.



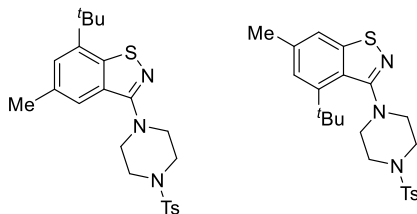
Regioisomers were distinguished by NOE spectrum as presented below. Protons on TMS group [δ 0.31 (s, 9H, Si(CH₃)₃)] of 3-(4-tosylpiperazinyl)-4-trimehysilyl-1,2-benzisothiazole **69h'** have shown remote interaction with protons on piperazine group [δ 3.39 – 3.24 (br, s, 8H, CH₂)].



¹H and NOE spectrum of 3-(4-tosylpiperazinyl)-4-trimethylsilyl-1,2-benzisothiazole

69h'

3-(4-Tosylpiperazinyl)-5-methyl-7-*tert*-butyl-1,2-benzisothiazole 69i and 3-(4-tosylpiperazinyl)-4-*tert*-butyl-6-methyl-1,2-benzisothiazole 69i'



General procedure G was followed using 2-*tert*-butyl-substituted benzyne precursor (110 mg, 0.3 mmol) **61l**, 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole **67o** (68 mg, 0.2 mmol) and CsF (93 mg, 0.6 mmol). The product was purified by flash column chromatography (40% Et₂O in petroleum ether) to give 3-(4-tosylpiperazinyl)-5-methyl-7-*tert*-butyl-1,2-benzisothiazole **69i** (49 mg, 55%) and 3-(4-tosylpiperazinyl)-4-*tert*-butyl-6-methyl-1,2-benzisothiazole **69i'** (32 mg, 36%) as white crystal, in a ratio of 3:2.

3-(4-Tosylpiperazinyl)-5-methyl-7-*tert*-butyl-1,2-benzisothiazole 69i

¹H NMR (400 MHz, CDCl₃) δ 7.70 (d, *J* = 8.3 Hz, 2H, *H*_{Ar}), 7.37 (s, 1H, *H*_{Ar}), 7.36 (d, *J* = 7.7 Hz, 2H, *H*_{Ar}), 7.21 (s, 1H, *H*_{Ar}), 3.59 – 3.51 (m, 4H, NCNCH₂), 3.30 – 3.20 (m, 4H, AeNCH₂), 2.46 (s, 3H, CH₃), 2.45 (s, 3H, CH₃), 1.45 (s, 9H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 163.4, 148.1, 144.2, 144.0, 134.7, 132.9, 130.0, 129.2, 128.0, 126.6, 121.0, 49.8, 46.0, 35.9, 29.9, 21.7, 21.7. LRMS (ESI, *m/z*) 444.1 ([M+H]⁺, 100%). HRMS (ESI) calcd for C₂₃H₃₀N₃O₂S₂ [M+H]⁺ 444.1774, found 444.1774. IR ν_{max} (film): 2956, 2923, 2854, 1598, 1490, 1455, 1351, 1327, 1259, 1233, 1167, 1116, 1093, 1019, 955, 729 cm⁻¹. M.p.: 204 – 206 °C.

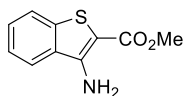
3-(4-Tosylpiperazinyl)-4-*tert*-butyl-6-methyl-1,2-benzisothiazole 69i'

¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, *J* = 8.3 Hz, 2H, *H*_{Ar}), 7.48 (s, 1H, *H*_{Ar}), 7.38 (d, *J* = 8.0 Hz, 2H, *H*_{Ar}), 7.19 (d, *J* = 1.1 Hz, 1H, *H*_{Ar}), 3.76 (d, *J* = 11.9 Hz, 2H, NCNCH_{2(axial)}), 3.37 (td, *J* = 12.0, 2.5 Hz, 2H, NCNCH_{2(equatorial)}), 3.07 (d, *J* = 12.6 Hz, 2H, ArNCH_{2(axial)}), 2.69 (td, *J* = 11.6 2.4 Hz, 2H, ArNCH_{2(equatorial)}), 2.49 (s, 3H, CH₃), 2.44 (s, 3H, CH₃), 1.44 (s, 9H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 167.3, 156.9, 148.7, 143.8, 137.6, 133.5, 129.8, 128.0, 126.3, 125.4, 118.0, 53.1, 45.9, 36.7, 31.6, 21.8, 21.7. LRMS (ESI, *m/z*) 444.1 ([M+H]⁺, 100%). HRMS (ESI) calcd for C₂₃H₃₀N₃O₂S₂ [M+H]⁺ 444.1774, found 444.1774. IR ν_{max} (film): 2956, 2923, 2853, 1713, 1598, 1454, 1347, 1325, 1264, 1224, 1165, 1119, 1095, 1061, 1018, 946, 722 cm⁻¹. M.p.: 212 – 214 °C.

Regioisomers was distinguished from comparasion with 3-(4-tosylpiperazinyl)-7-trimethylsilyl-1,2-benzisothiazole **69h** and 3-(4-tosylpiperazinyl)-4-trimethylsilyl-1,2-benzisothiazole **69h'**. Both ¹H NMR signals of the piperazinyl protons from 3-(4-tosylpiperazinyl)-4-*tert*-butyl-6-methyl-1,2-benzisothiazole **69i'** [δ 3.76 (d, *J* = 11.9 Hz, 2H, CH₂), 3.37 (td, *J* = 12.0, 2.5 Hz, 2H, CH₂), 3.07 (d, *J* = 12.6 Hz, 2H, CH₂), 2.69 (td, *J* = 11.6 2.4 Hz, 2H, CH₂)] and 3-(4-tosylpiperazinyl)-4-trimethylsilyl-1,2-benzisothiazole **69h'** [δ 3.39 – 3.24 (br, s, 8H, CH₂)] have shown distinctive broaden of signals. Both 3-(4-tosylpiperazinyl)-5-methyl-7-*tert*-butyl-1,2-benzisothiazole **69i** and 3-(4-Tosylpiperazinyl)-7-trimethylsilyl-1,2-benzisothiazole **69h** presented piperazinyl peaks similar to the rest of examples, i.e. two broad approximate triplets.

6.4.6. Cascade process for the formation of C-substituted benzoisothiazole

Methyl 3-aminobenzothiophene-2-carboxylate **71**



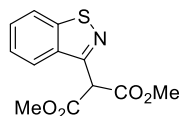
Sodium methoxide solution (33 μ L, 25 wt% in MeOH, 0.4 mmol) was added to a solution of dimethyl malonate (53 mg, 0.4 mmol) in dry MeOH (2 mL). After stirring under nitrogen for 5 min, the sodium enolate was added dropwise to 3-chlorobenzoisothiazole (34 mg, 0.2 mmol) and the resulting mixture was stirred at room temperature for 30 min, until the starting material was fully consumed. The product was purified by flash column chromatography (40% Et₂O in petroleum ether), resulting in the titled compound as a white solid (36 mg, 88%).

Same product was obtained using sodium acetate (2 eq.) and dimethyl malonate (2 eq.) in MeOH. Reflux for 12 hours afforded 40% yield of the product while 43% of starting material benzoisothiazole was recovered.

¹H NMR (400 MHz, CDCl₃) δ 7.73 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.64 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.47 (ddd, J = 8.1, 7.2, 1.2 Hz, 1H, H_{Ar}), 7.37 (ddd, J = 8.1, 7.2, 1.0 Hz, 1H, H_{Ar}), 5.92 (br, s, 2H, NH_2), 3.89 (s, 3H, OCH_3); **¹³C NMR** (100 MHz, DMSO-*d*₆) δ 164.9, 149.9, 138.9, 131.5, 128.6, 123.9, 123.2, 123.2, 94.4, 51.2. **LRMS** (ESI, m/z) 208.0 ([$M+H$]⁺, 100%). **HRMS** (ESI) calcd for C₁₀H₁₀O₂NS [$M+H$]⁺ 208.0427, found 208.0429. **M.p.**: 111 – 113 °C.

The data recorded are consistent with the literature.^[279]

Dimethyl 2,1-benzisothiazole-3-malonate **72**



Sodium acetate (33 mg, 0.4 mmol) was added to a solution of dimethyl malonate (53 mg, 0.4 mmol) in dry THF : EtOH (1:1, 2 mL). After stirring under nitrogen for 5 min, 3-chloro-1,2-benzisothiazole (33 mg, 0.2 mmol) was added into the suspension and the resulting mixture was stirred at room temperature for 30 min prior to refluxing for 24 h. Water (10 mL) was added and the mixture was extracted with CH₂Cl₂ (3 × 10 mL). Combined organic phase was dried over MgSO₄, filtered and concentrated. The product was purified by flash column chromatography (30% Et₂O in petroleum ether), 12 mg (36%) of starting material benzisothiazole was recovered and the titled compound was isolated as a colourless oil which solidified on sitting (30 mg, 57%).

Same product was obtained with the one-pot method below:

3,4-Dichloro-1,2,5 –thiadiazole (94 µL, 1.0 mmol) was added dropwise into a freshly oven dried suspension of CsF (320 mg, 2.8 mmol, 2.8 eq.) in dry THF (1.5 mL) under nitrogen at room temperature. 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (417 mg, 1.4 mmol, 1.4 eq.) was then added dropwise. The mixture was stirred at 65 °C and monitored by TLC. After consumption of starting material 3,4-dichloro-1,2,5 –thiadiazole, dimethyl malonate (254 mg, 1.5 mmol) was added dropwise together with sodium methoxide (320 µL, 25 wt% in MeOH, 1.4 mmol). The reaction mixture was then stirred at room temperature for 12 h before quenching with water (10 mL) and extracting with CH₂Cl₂ (3 × 10 mL). The combined organic phase was dried over MgSO₄, filtered and concentrated. The crude product was purified *via* flash column chromatography (30% Et₂O in petroleum

ether), resulting in the titled product as a colourless oil which solidified on sitting (180 mg, 68%). Methyl 3-aminobenzothiophene-2-carboxylate **71** was also obtained (22 mg, 11%).

^1H and ^{13}C NMR spectrum match the result above.

^1H NMR (400 MHz, CDCl_3) δ 8.00 (app. dt, $J = 8.2, 0.9$ Hz, 1H, H_{Ar}), 7.94 (app. dt, $J = 8.2, 0.9$ Hz, 1H, H_{Ar}), 7.54 (ddd, $J = 8.2, 5.1, 1.1$ Hz, 1H, H_{Ar}), 7.45 (ddd, $J = 8.2, 5.2, 1.1$ Hz, 1H, H_{Ar}), 5.40 (s, 1H, CH), 3.81 (s, 6H, COOCH_3); **^{13}C NMR** (100 MHz, CDCl_3) δ 166.8, 156.4, 153.1, 134.0, 128.0, 125.3, 123.9, 120.1, 55.6, 53.4. **LRMS** (ESI, m/z) 266.0 ($[\text{M}+\text{H}]^+$, 100%). **HRMS** (ESI) calcd for $\text{C}_{12}\text{H}_{12}\text{O}_4\text{NS}$ $[\text{M}+\text{H}]^+$ 266.0482, found 266.0482. **IR** ν_{max} (film): 2954, 1736, 1595, 1480, 1435, 1311, 1259, 1198, 1154, 1090, 1024, 933, 770 cm^{-1} . **M.p.**: 77 – 79 $^{\circ}\text{C}$.

References

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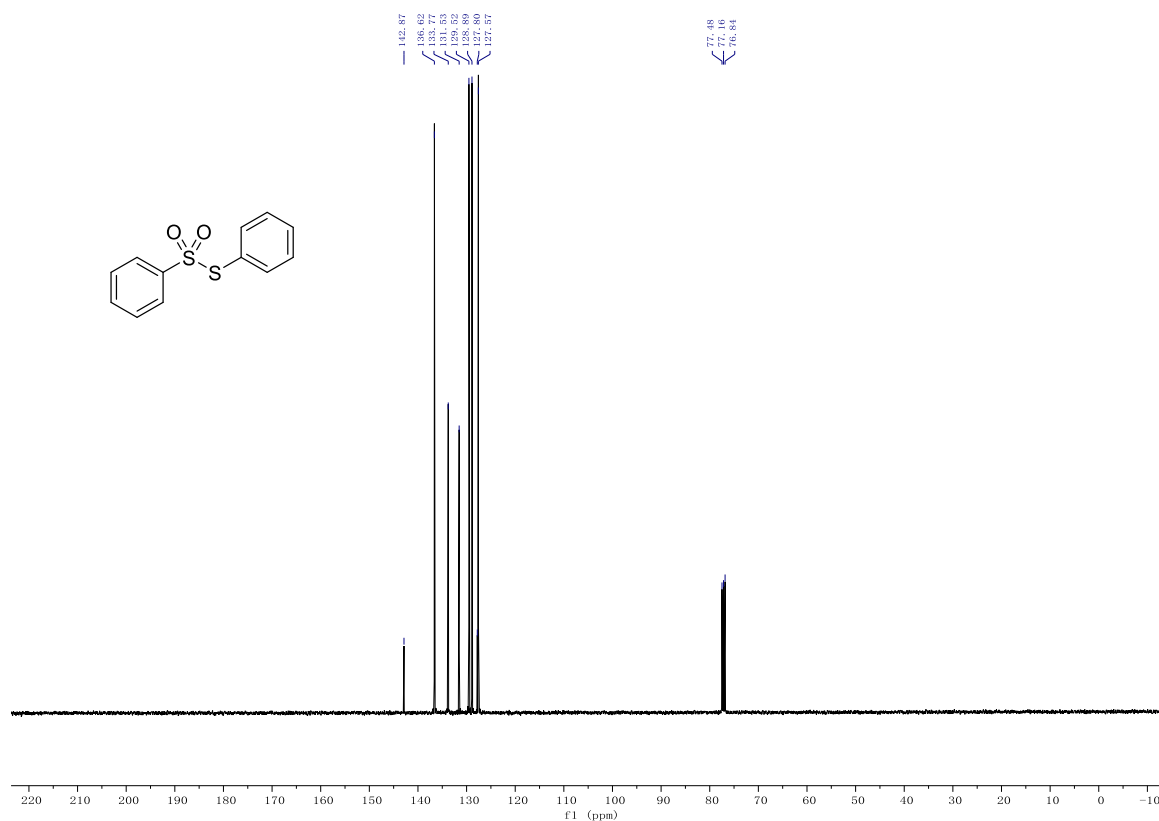
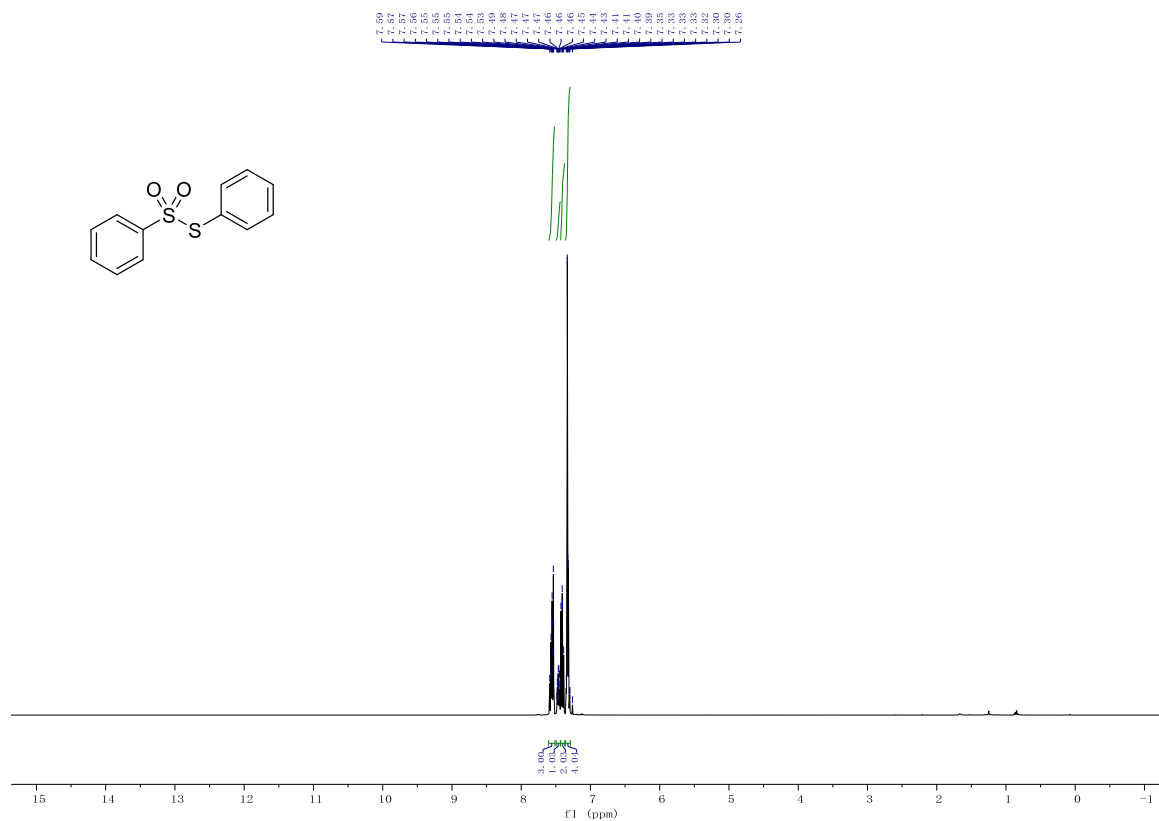
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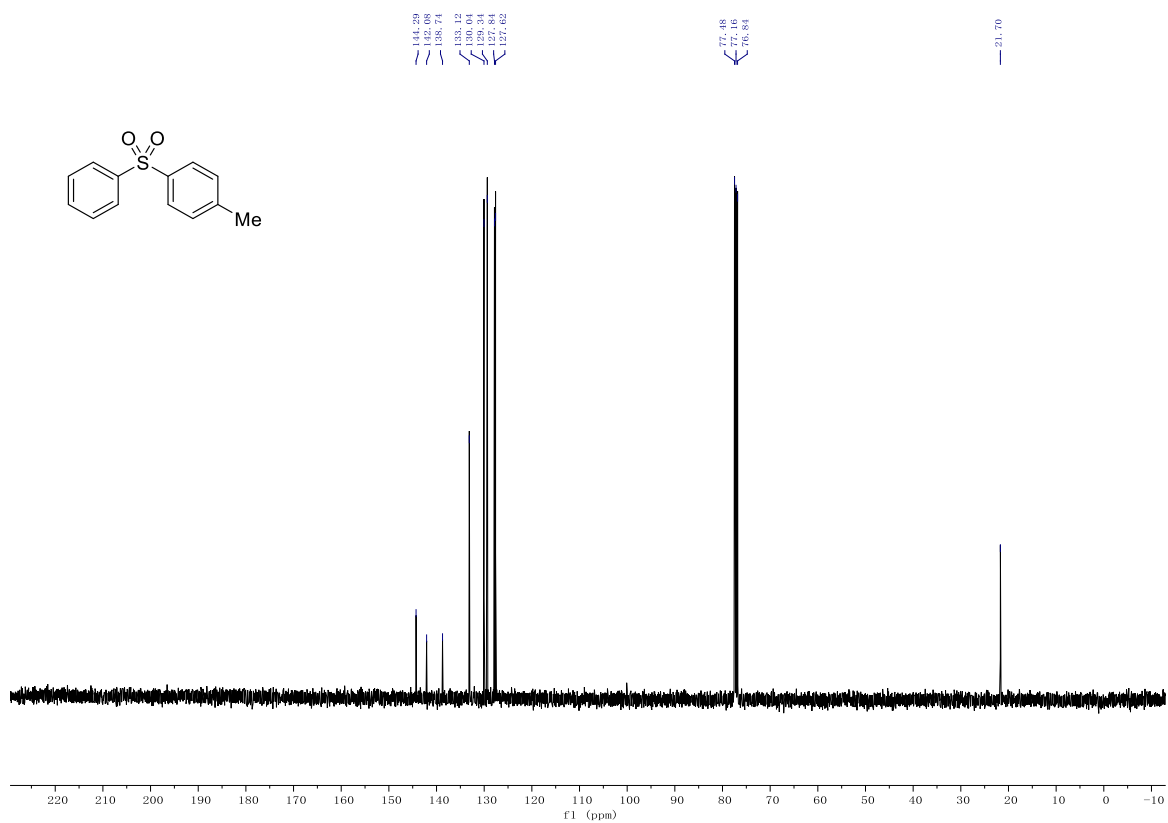
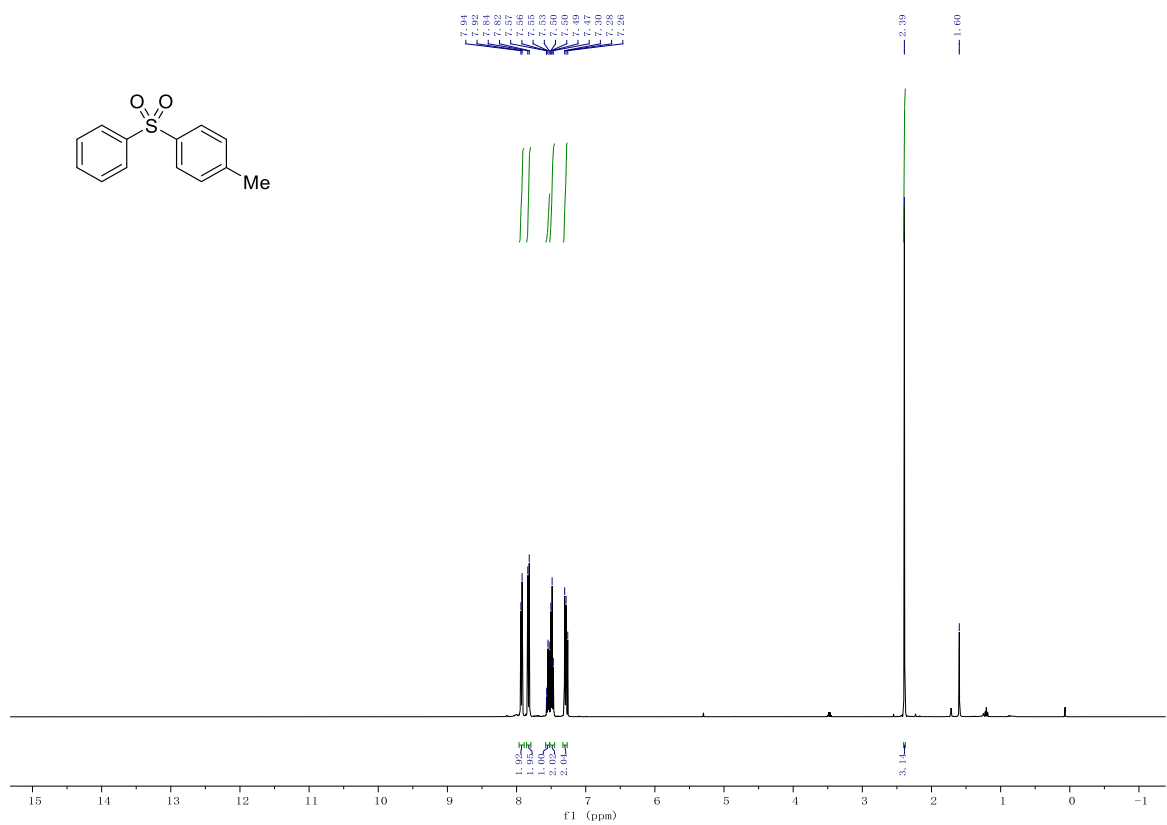
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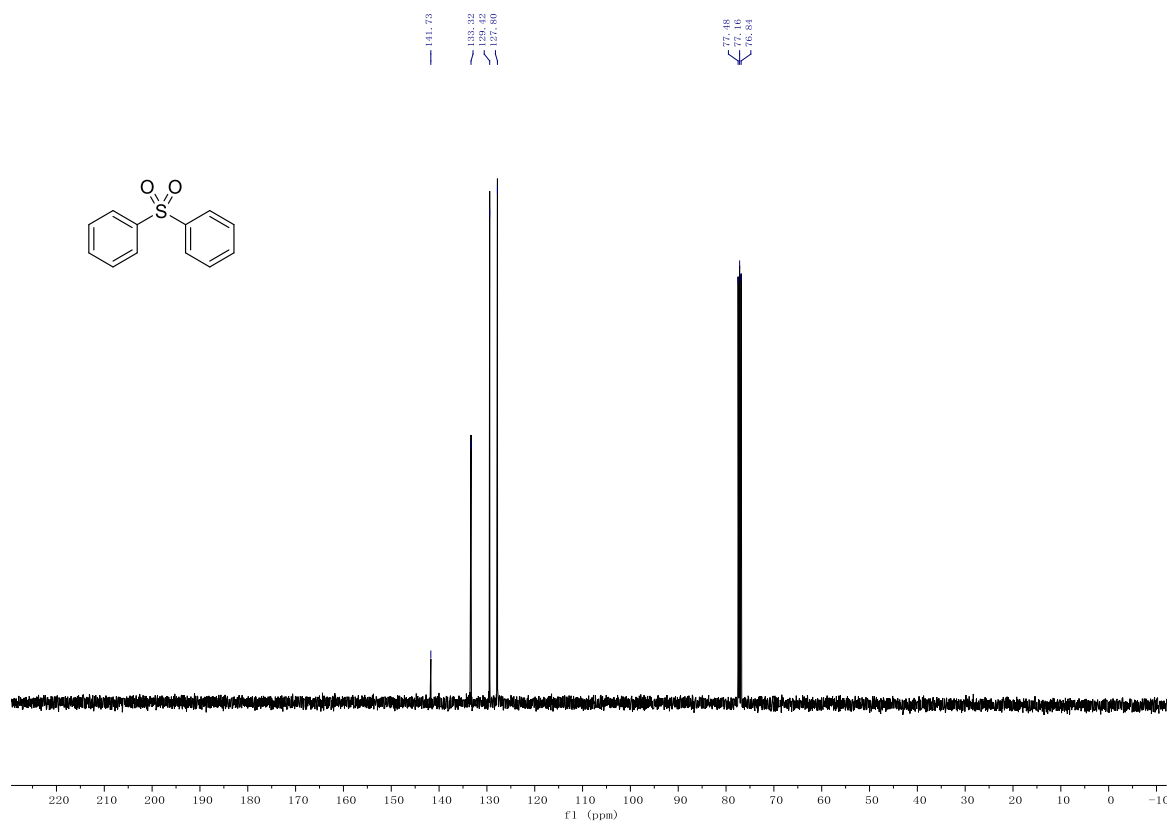
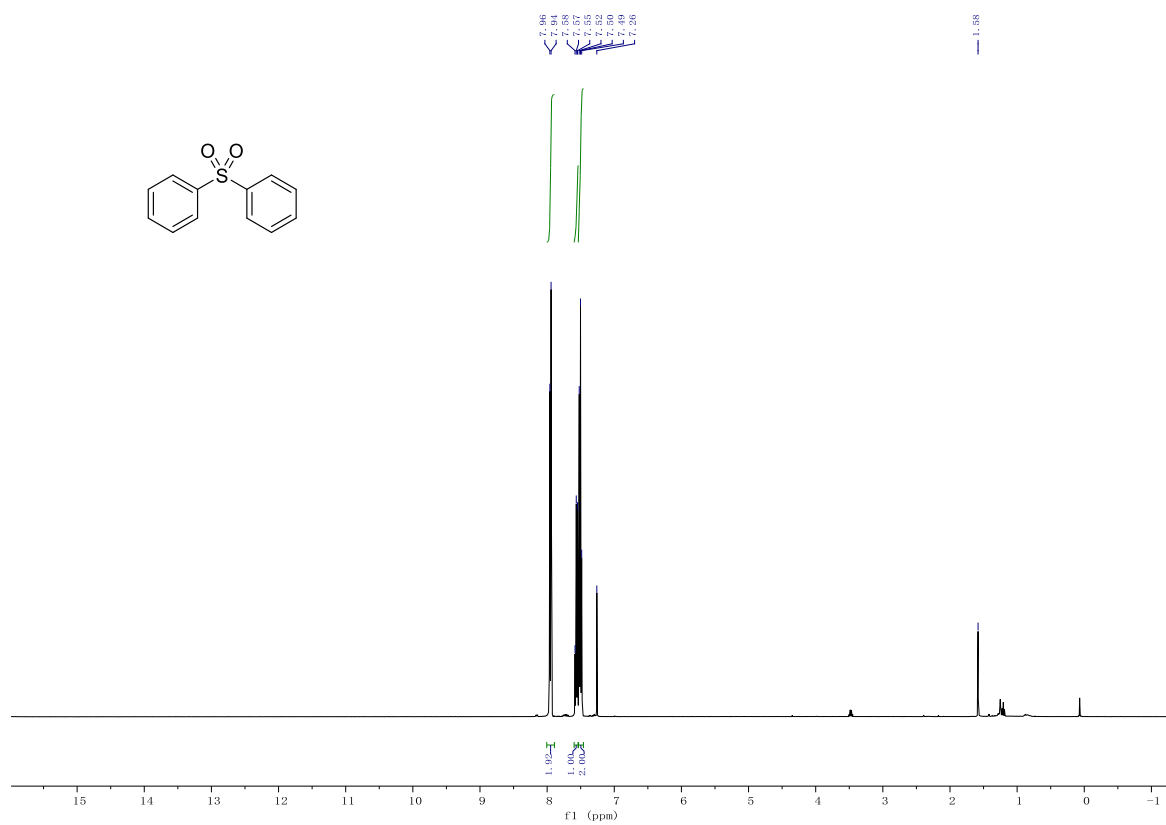
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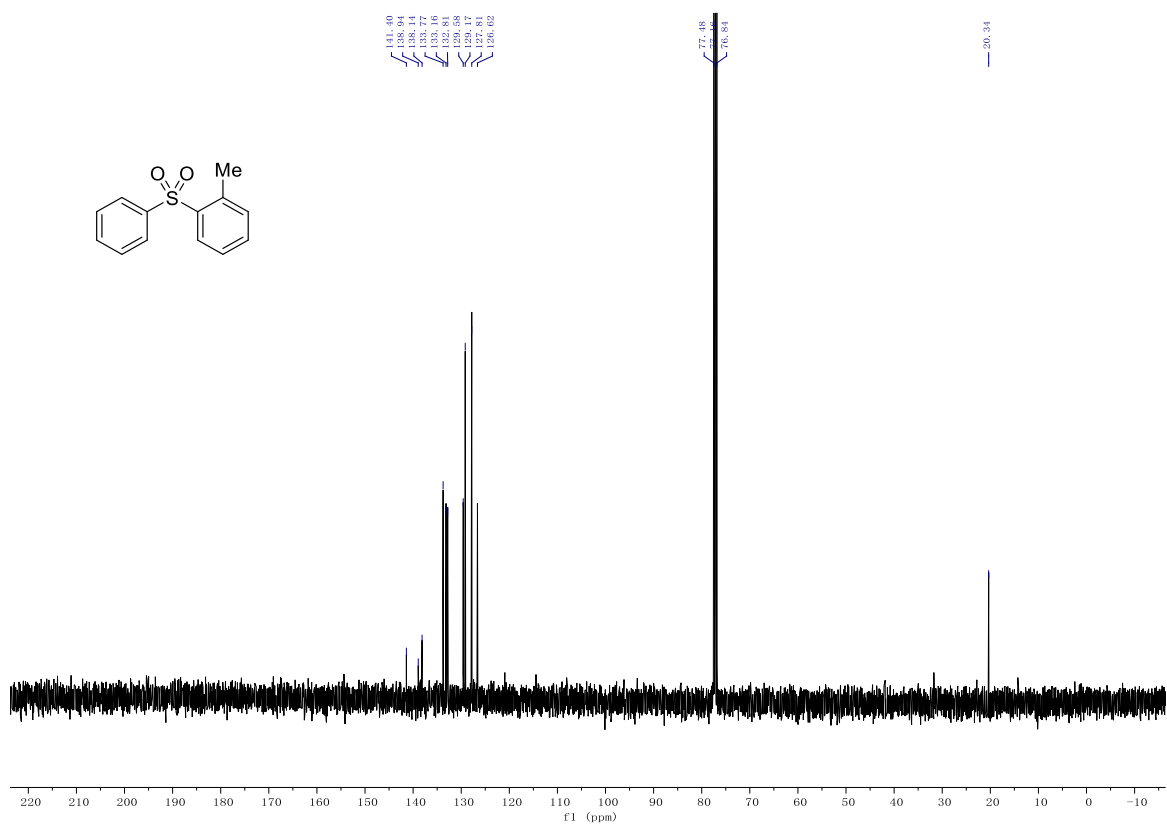
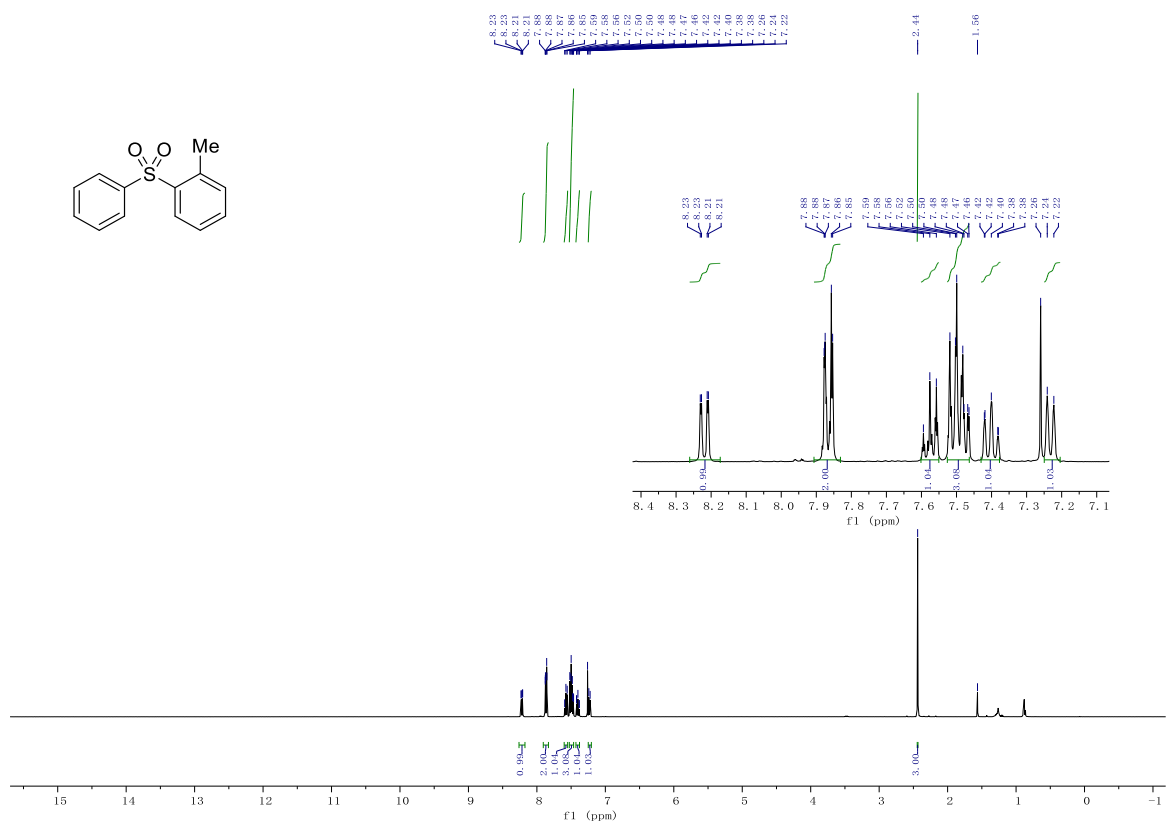
¹H NMR and ¹³C NMR spectra of *S*-phenyl benzenesulfonylthioate 34



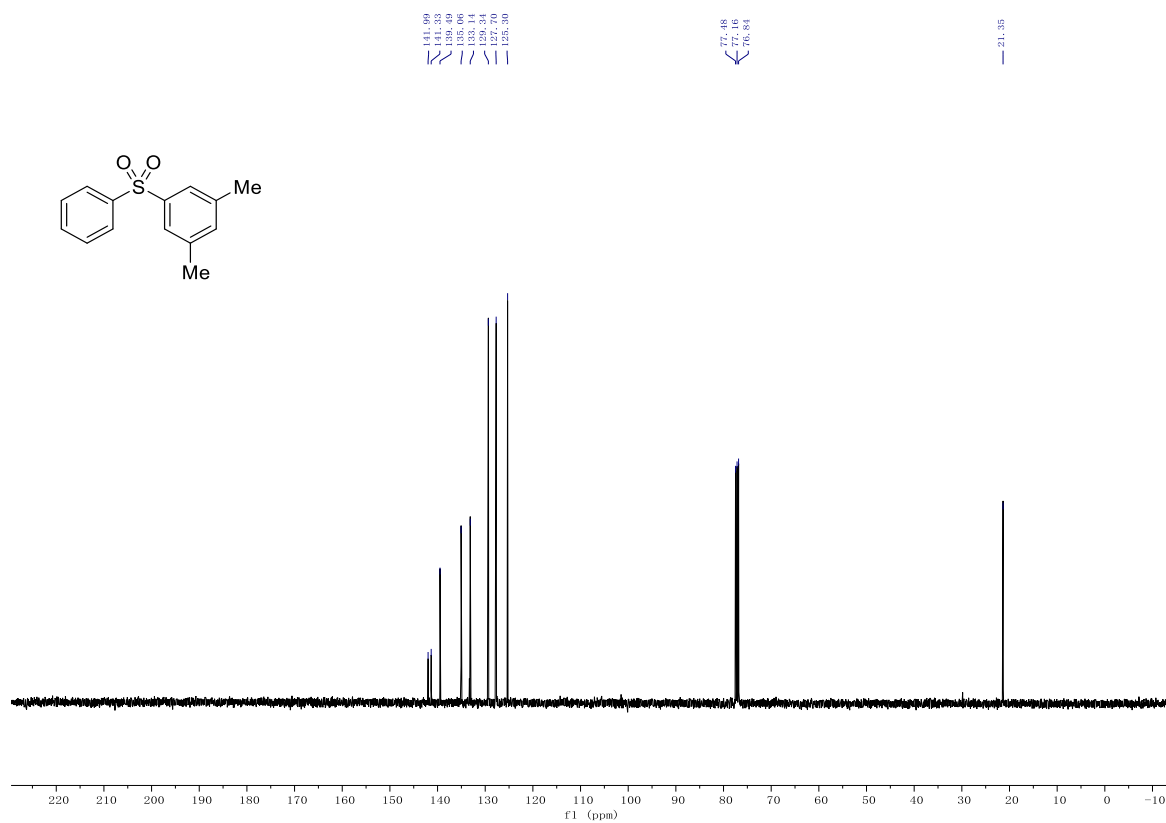
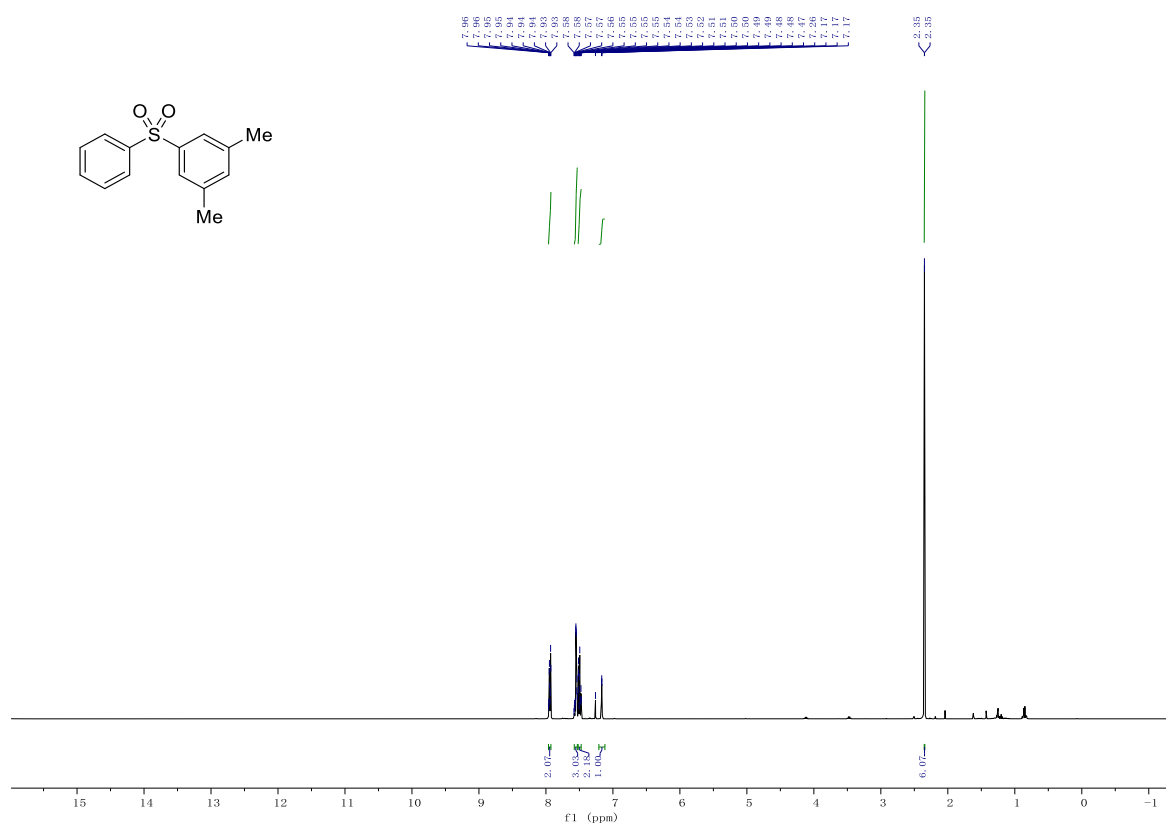
¹H NMR and ¹³C NMR spectra of phenyl *p*-tolyl sulfone 35a



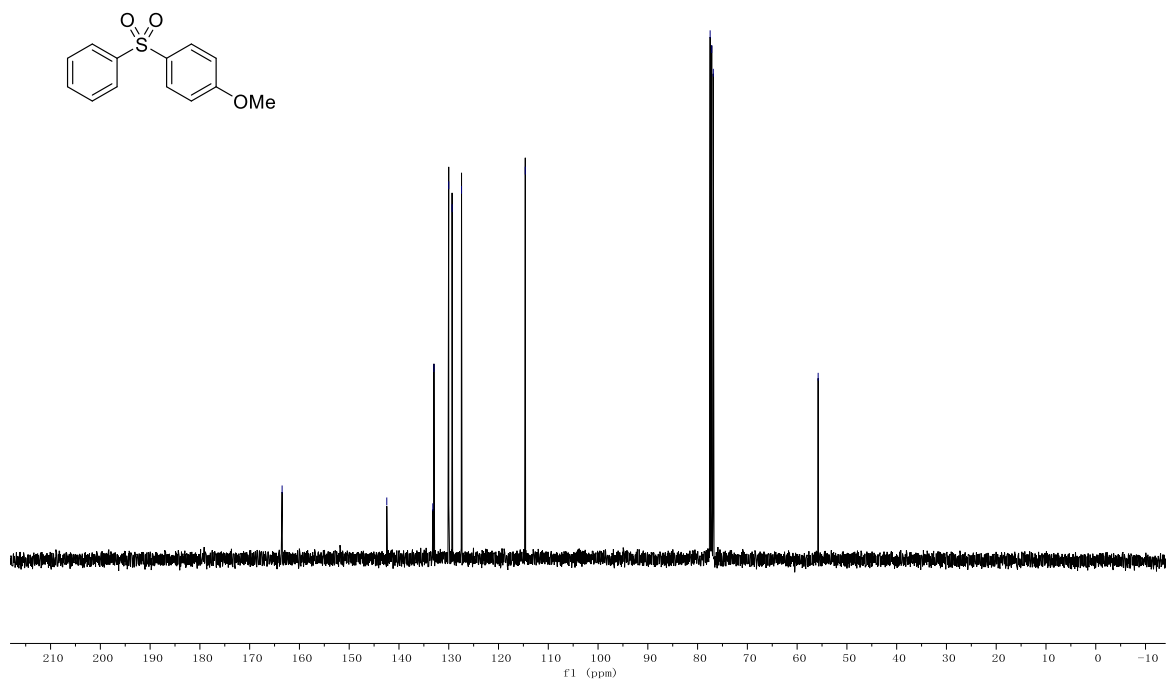
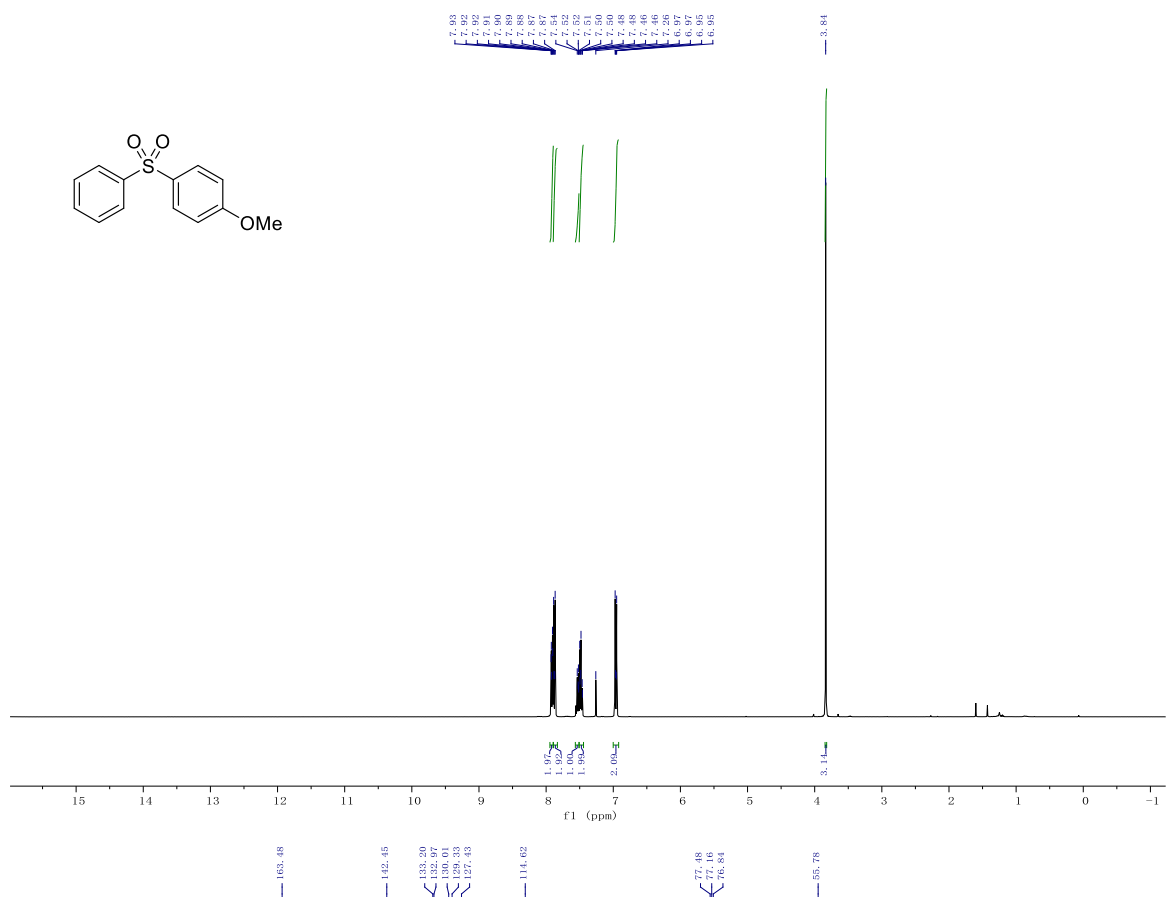
¹H NMR and ¹³C NMR spectra of diphenyl sulfone 35b



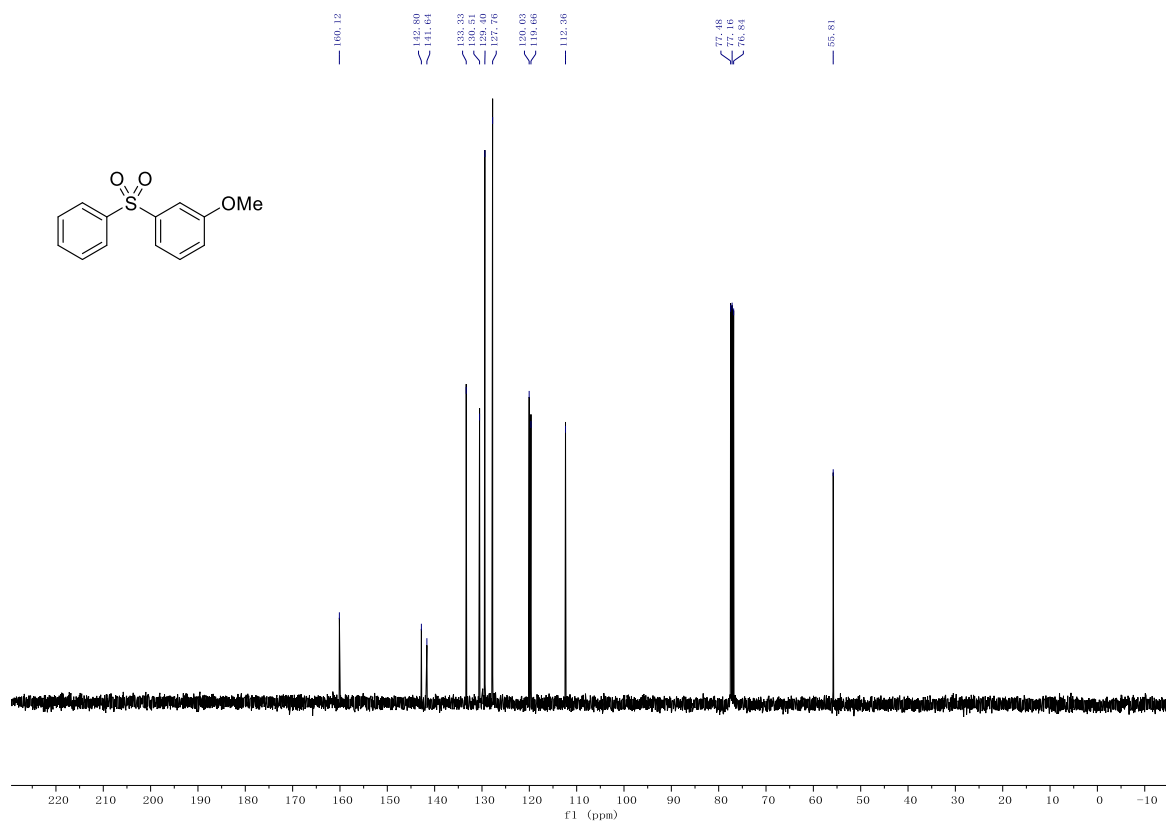
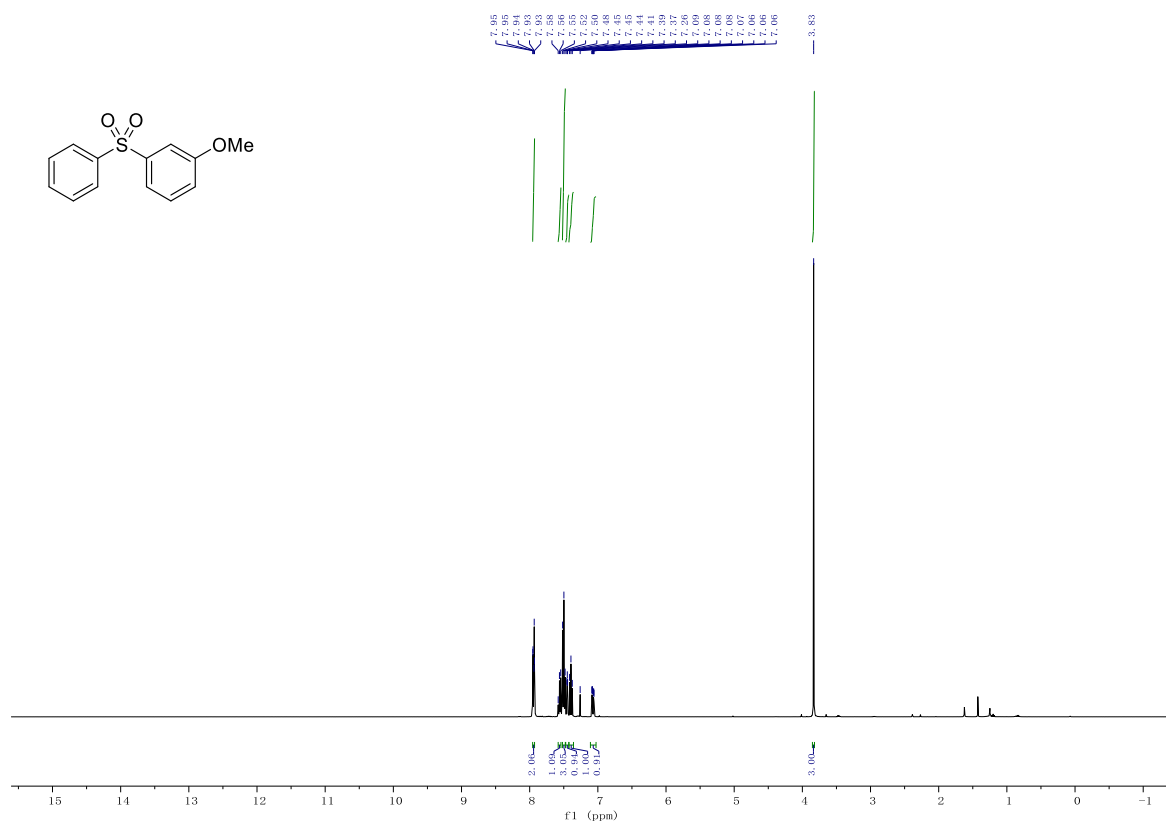
¹H NMR and ¹³C NMR spectra of **phenyl *o*-tolyl sulfone 35c**



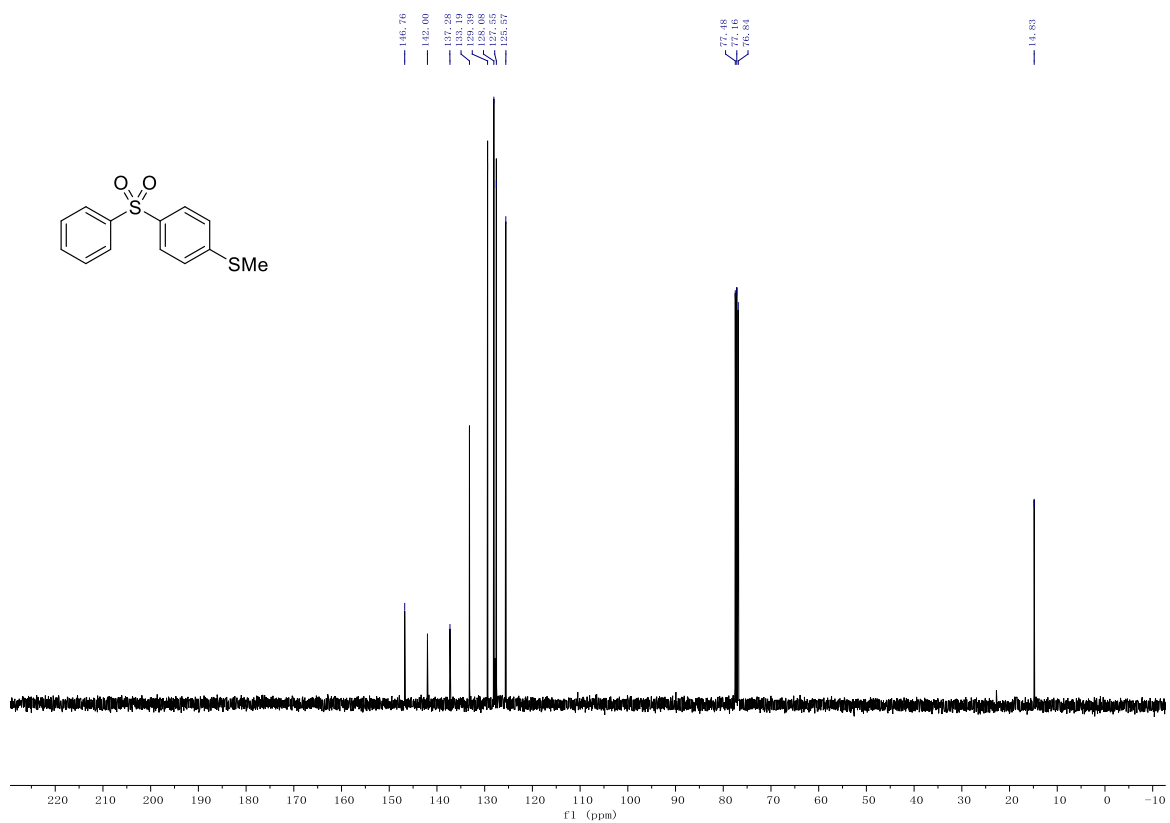
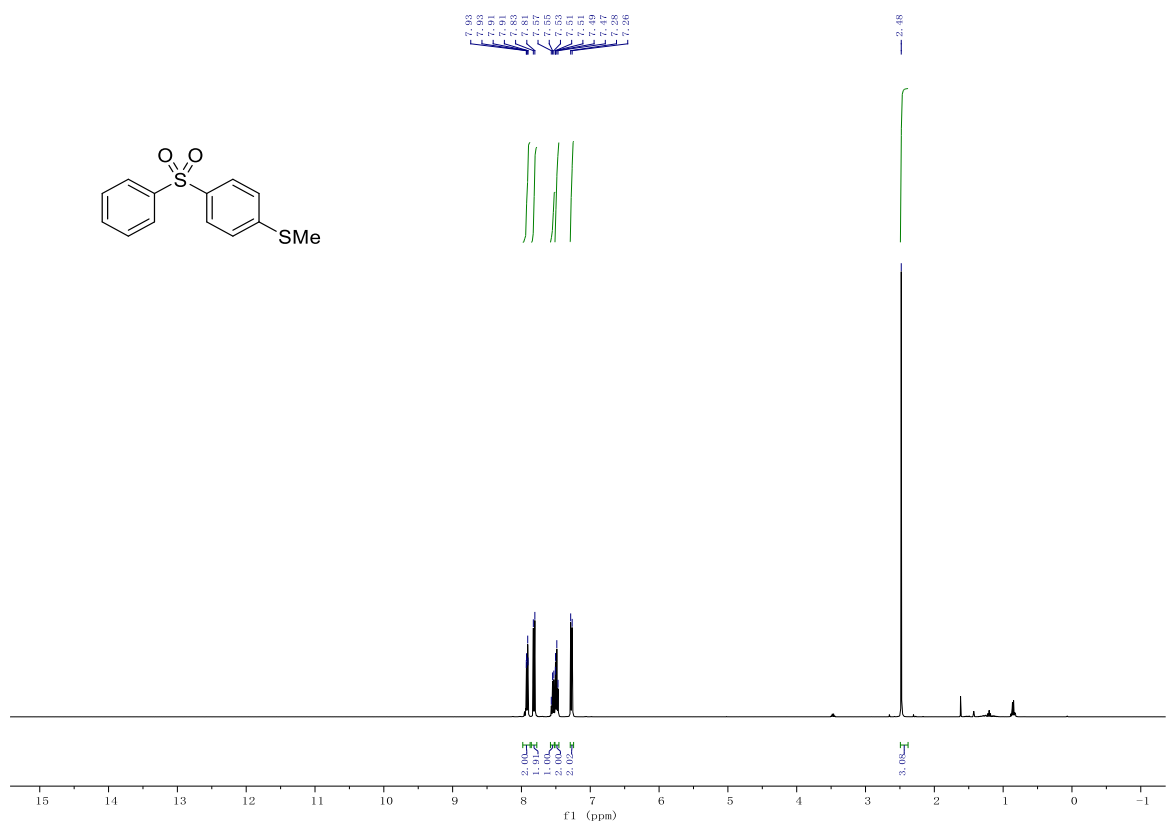
¹H NMR and ¹³C NMR spectra of **3,5-dimethyl-1-(phenylsulfonyl)benzene 35d**



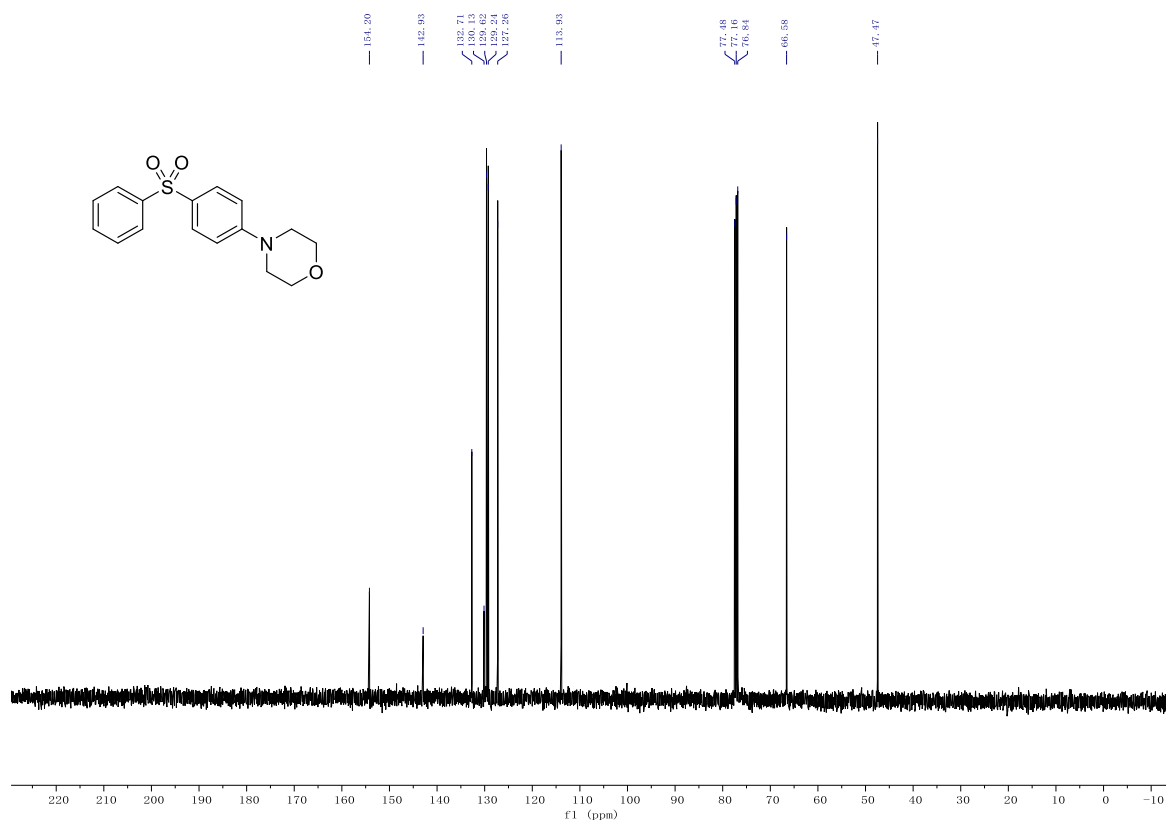
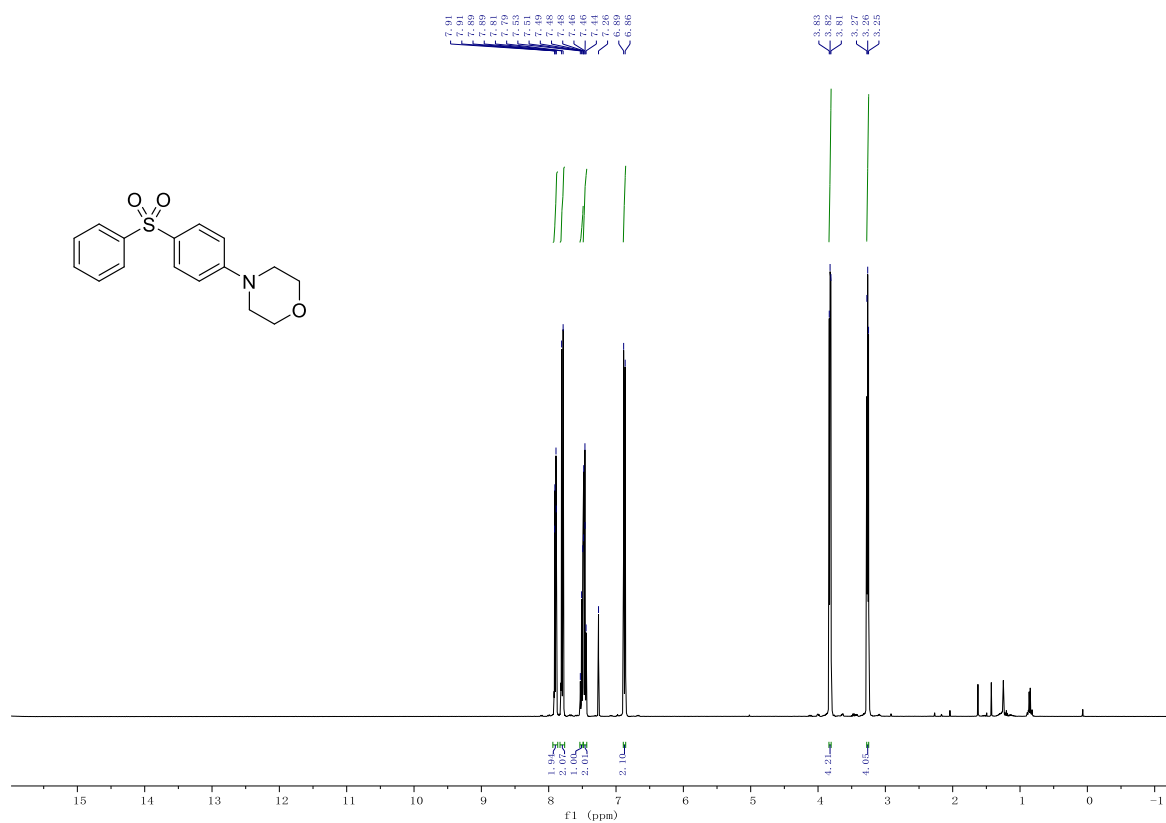
¹H NMR and ¹³C NMR spectra of 4-methoxyphenyl phenyl sulfone 35e



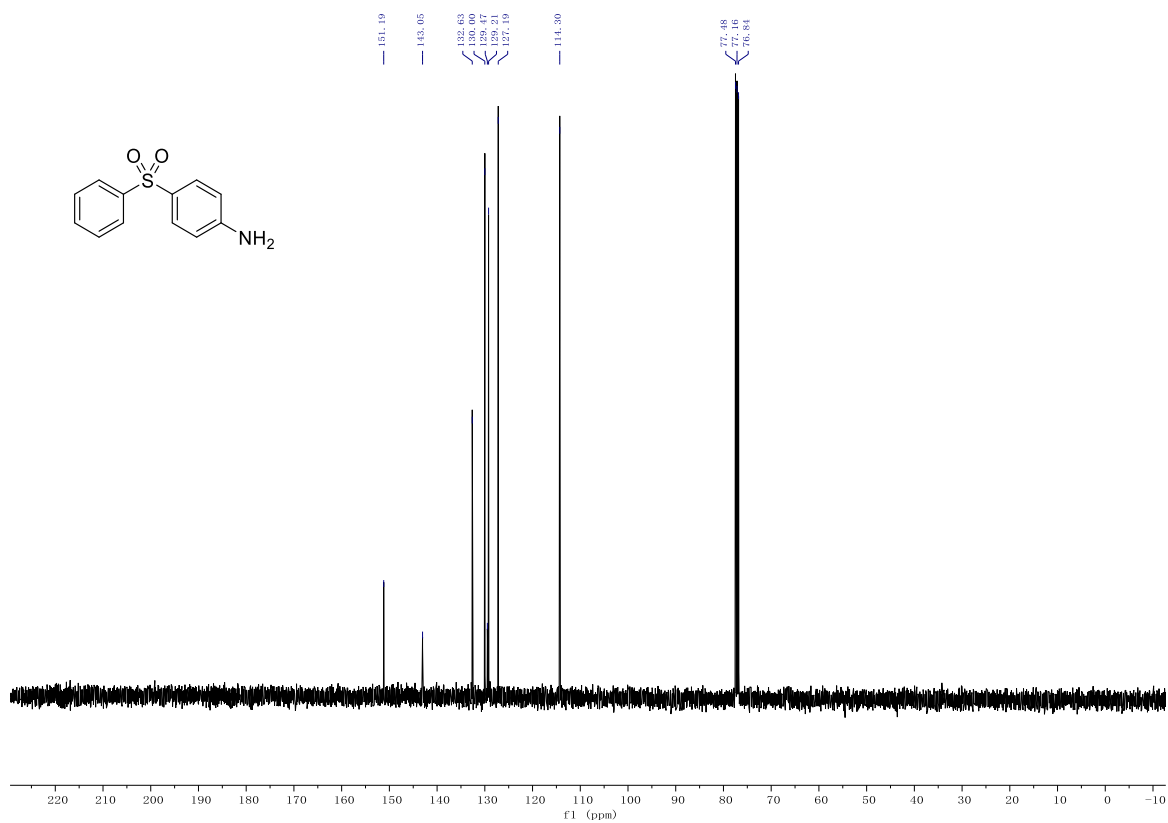
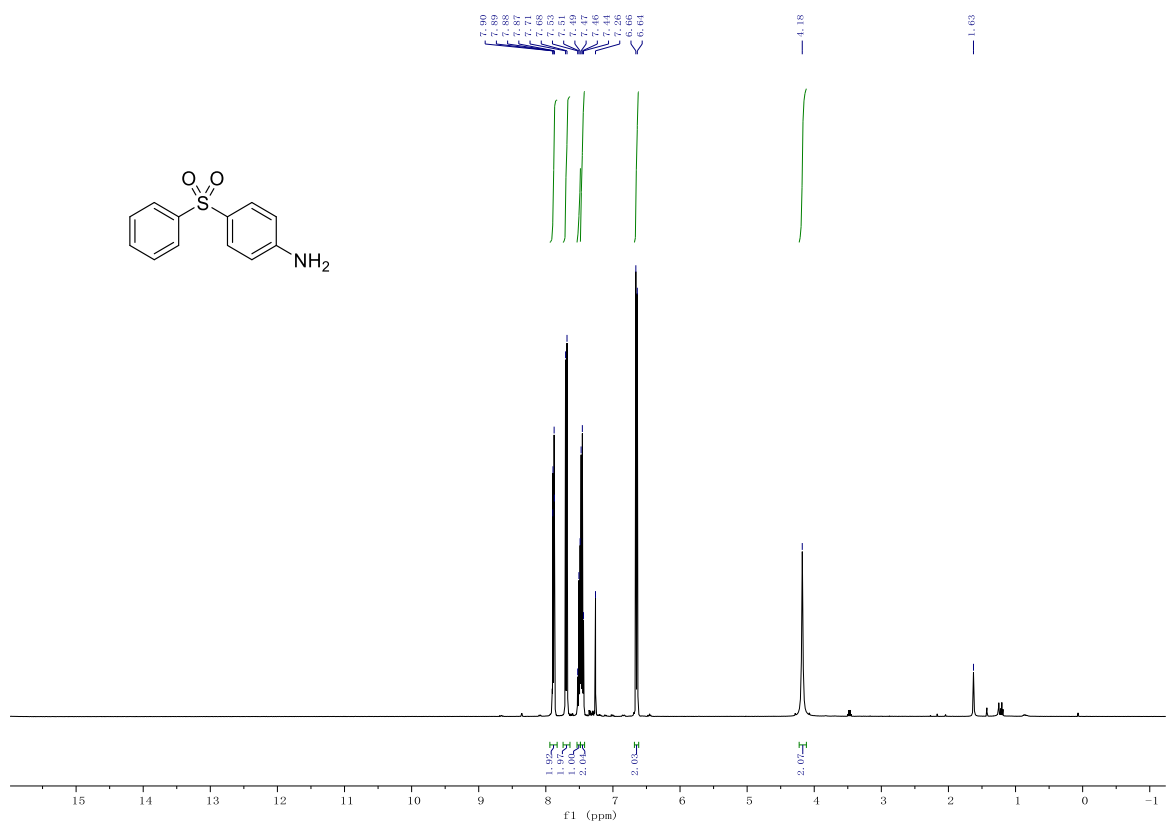
¹H NMR and ¹³C NMR spectra of **3-methoxyphenyl phenyl sulfone 35f**



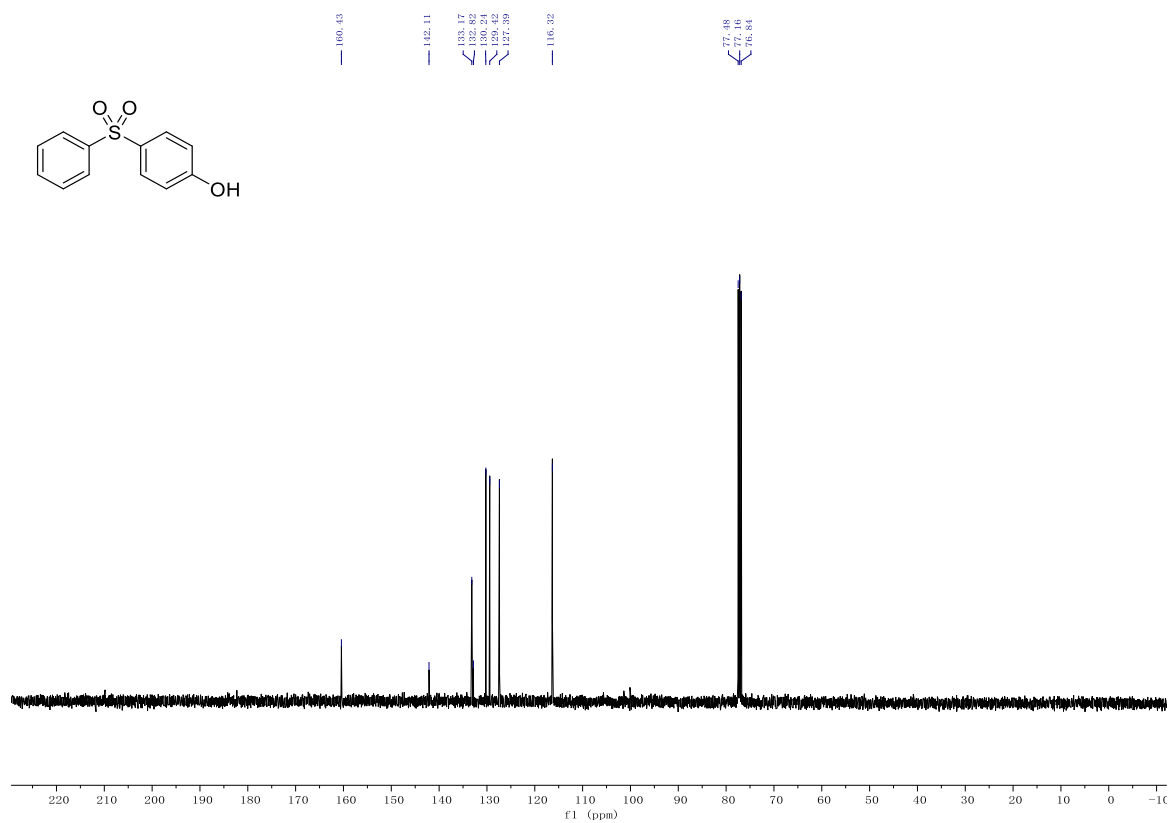
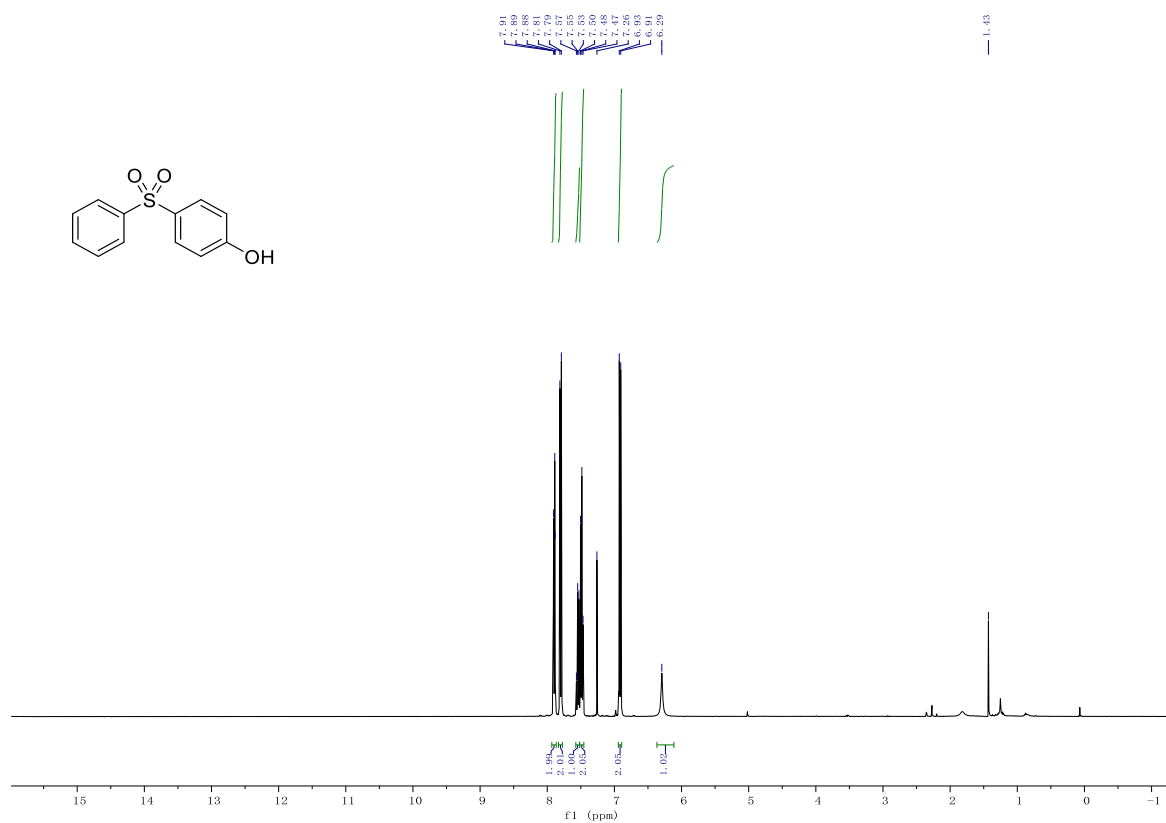
¹H NMR and ¹³C NMR spectra of 4-(benzenesulfonyl)phenyl methyl sulphide 35g



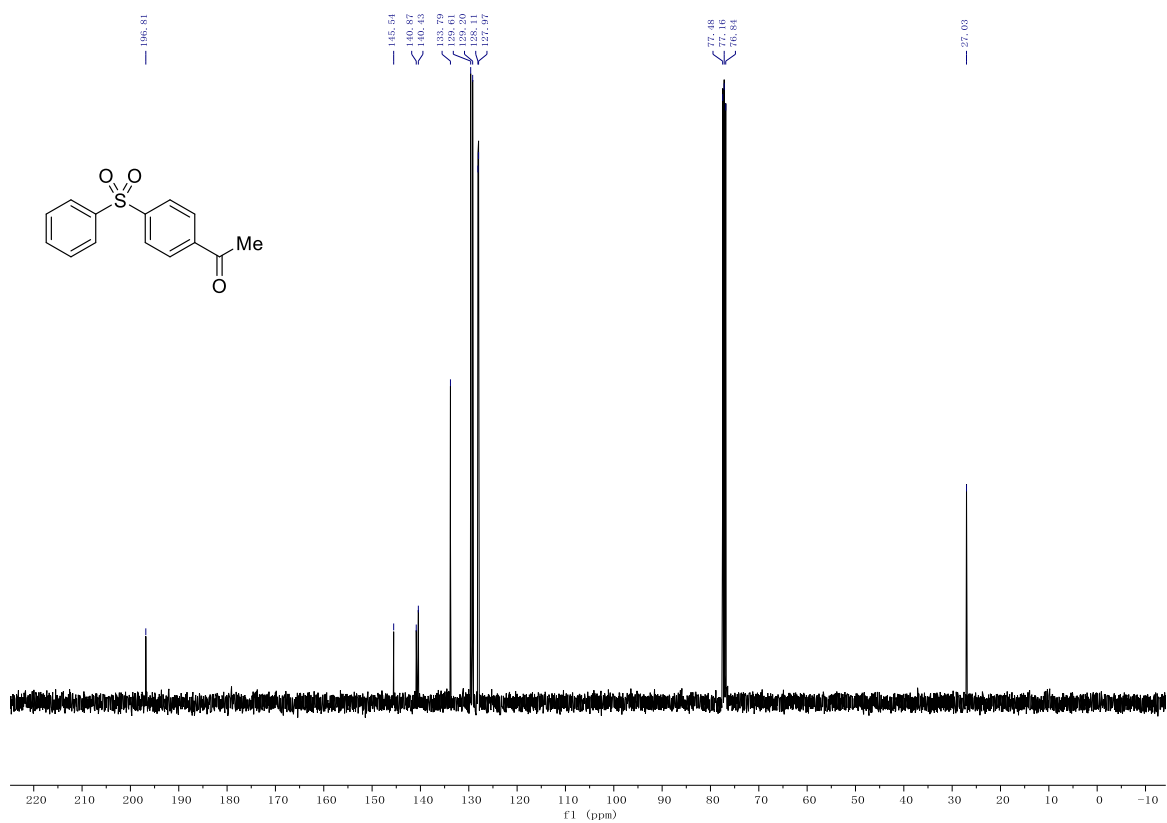
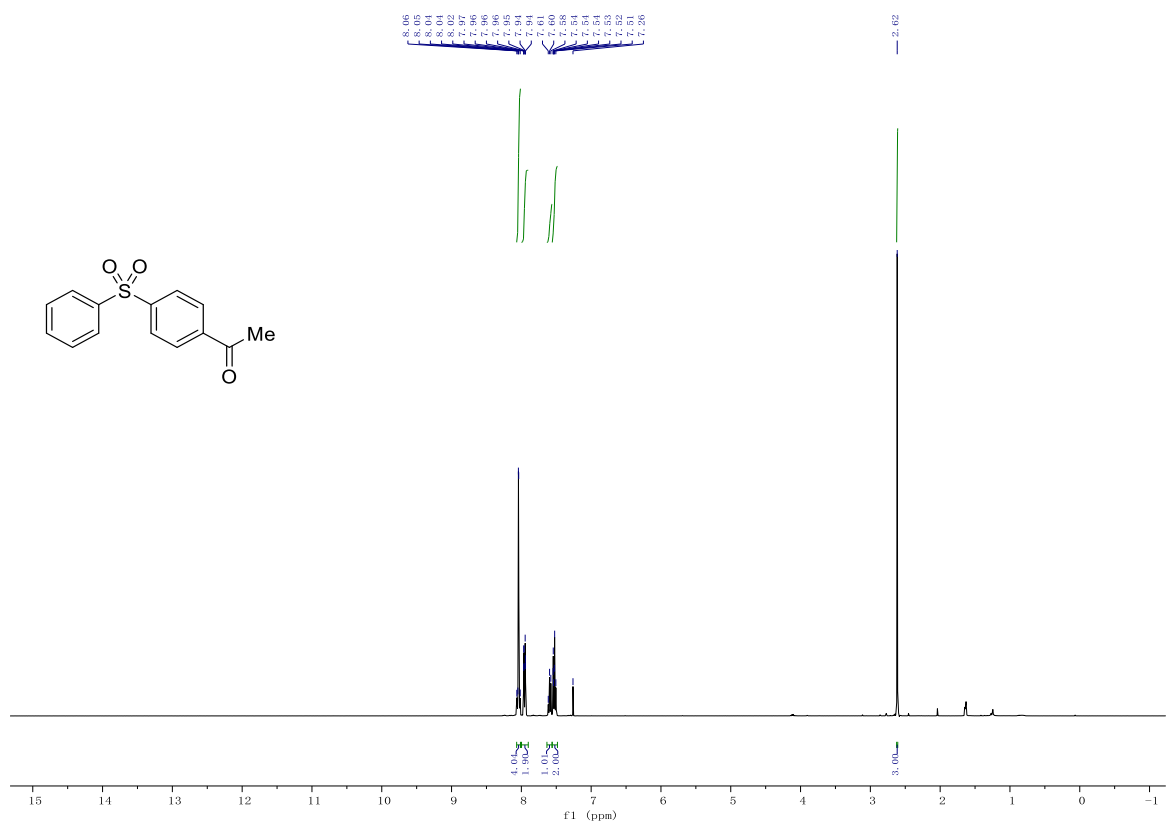
¹H NMR and ¹³C NMR spectra of 4-[4-(phenylsulfonyl)phenyl]morpholine 35h



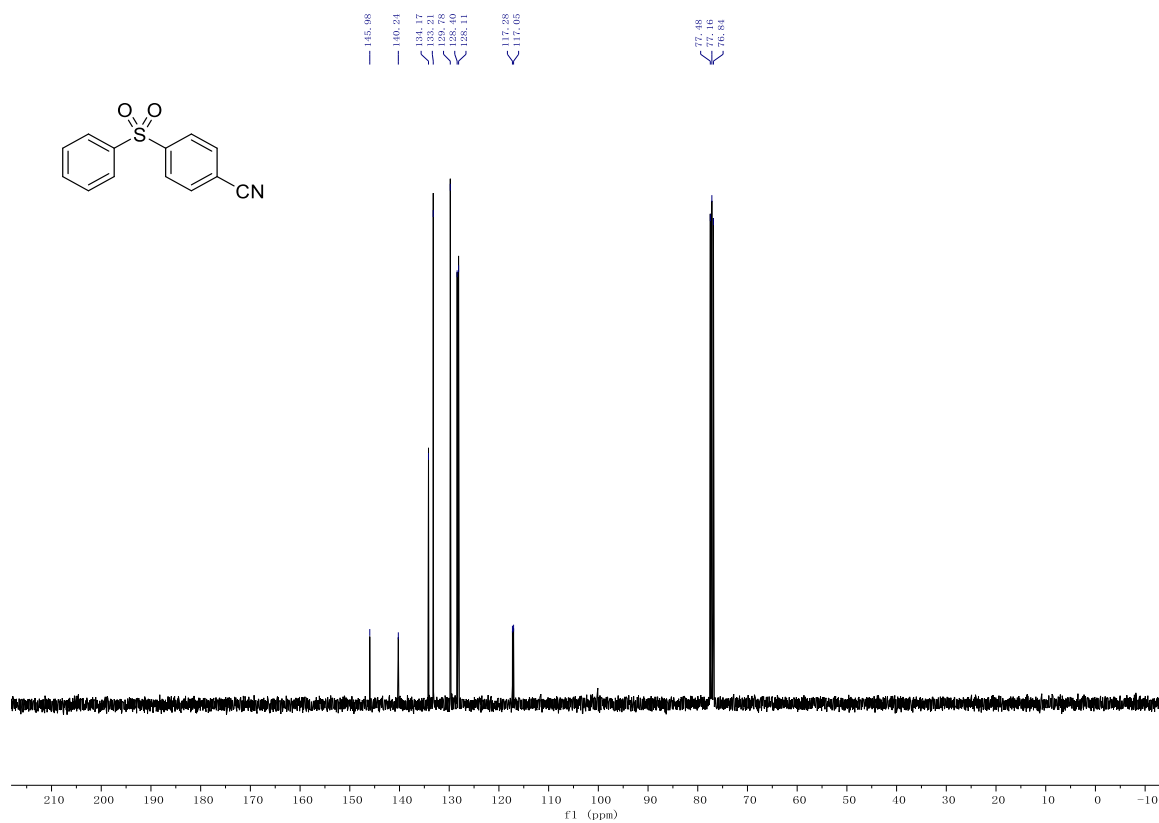
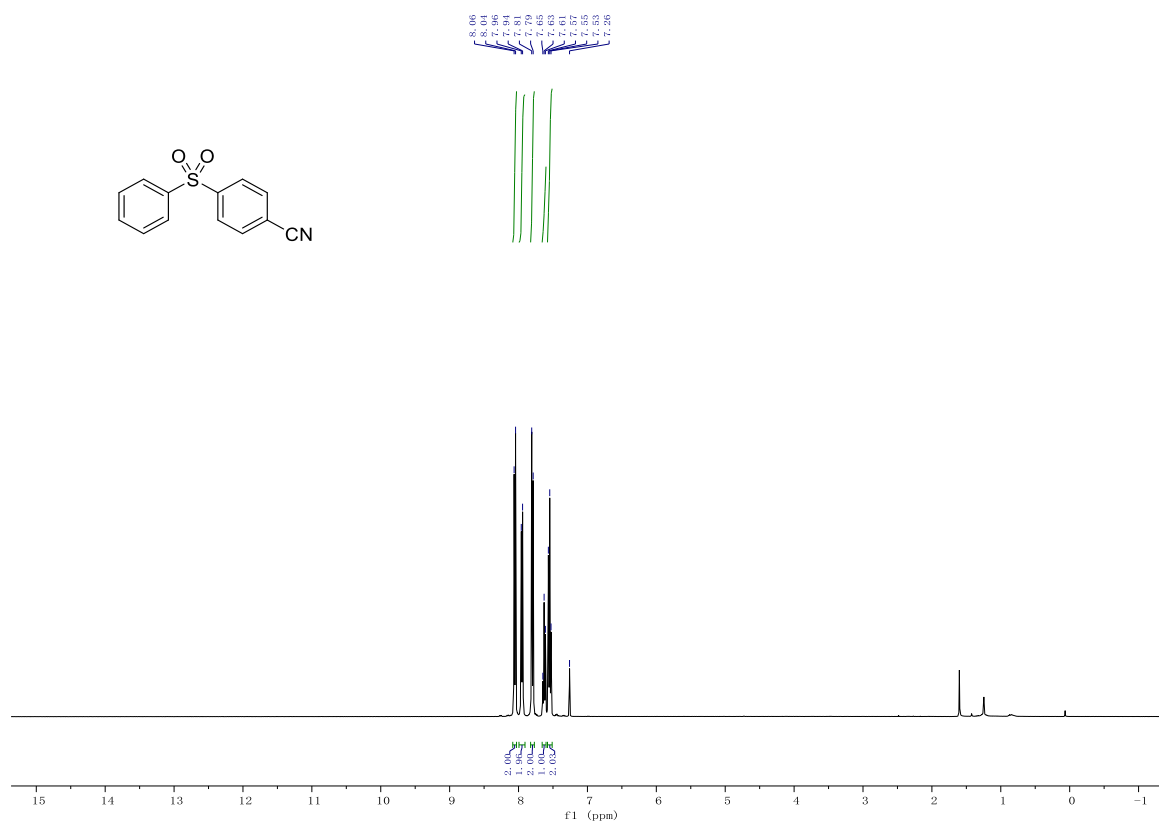
¹H NMR and ¹³C NMR spectra of 4-aminophenyl phenyl sulfone 35i



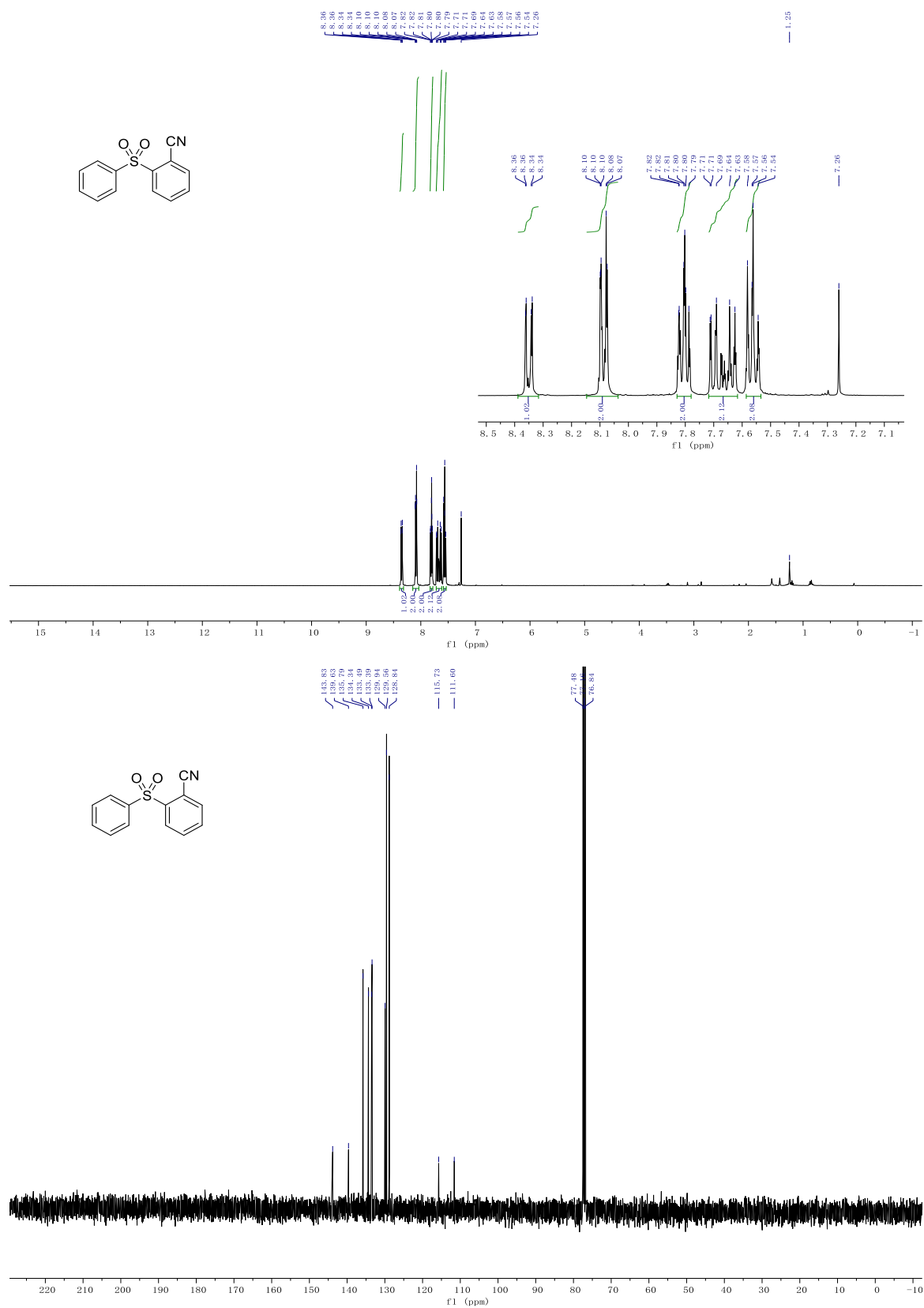
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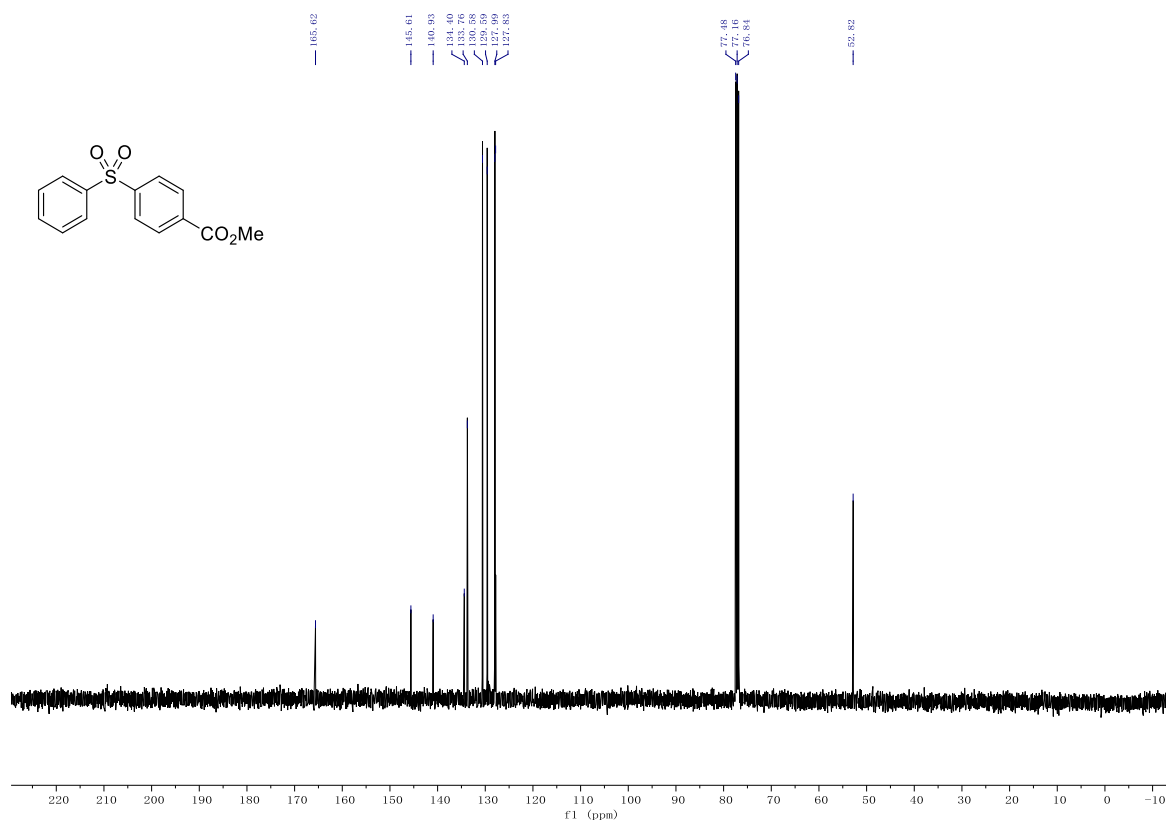
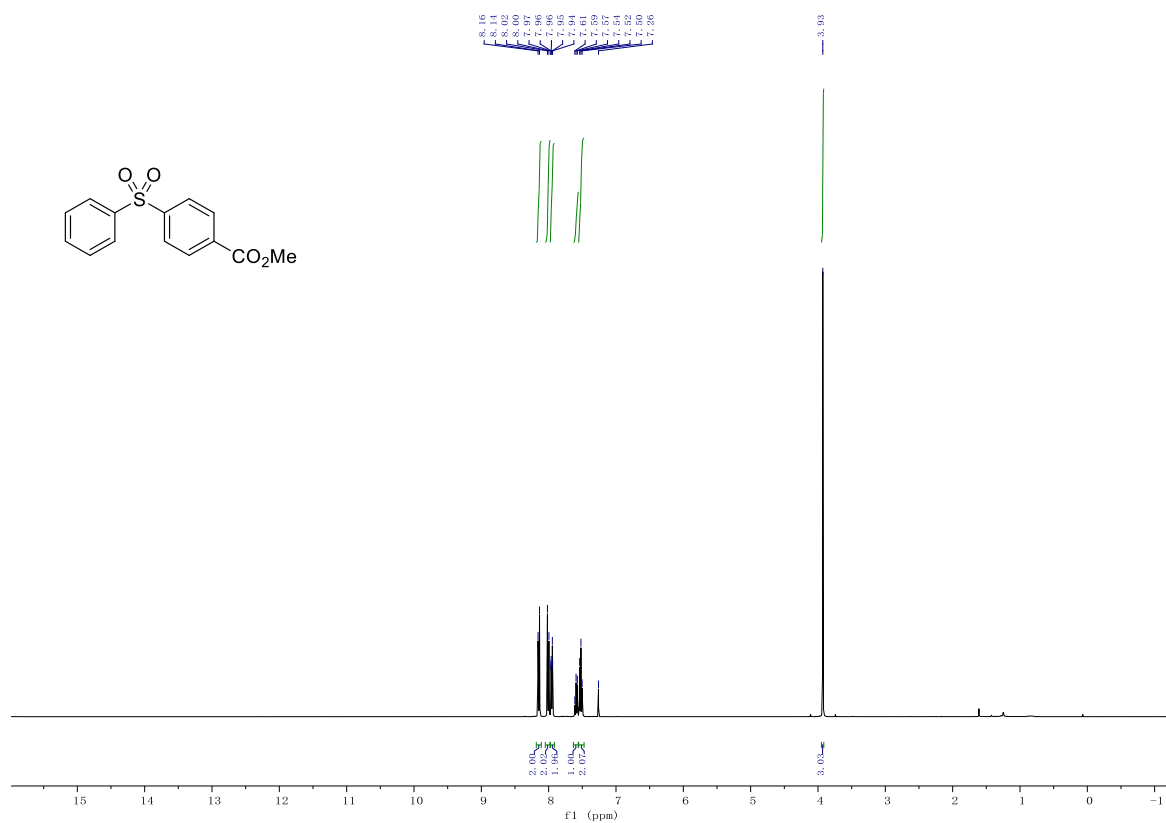
¹H NMR and ¹³C NMR spectra of 4'-(phenylsulfonyl)acetophenone 35k



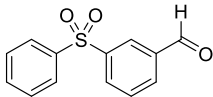
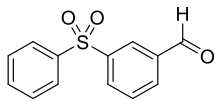
¹H NMR and ¹³C NMR spectra of 4-(phenylsulfonyl)benzonitrile 351

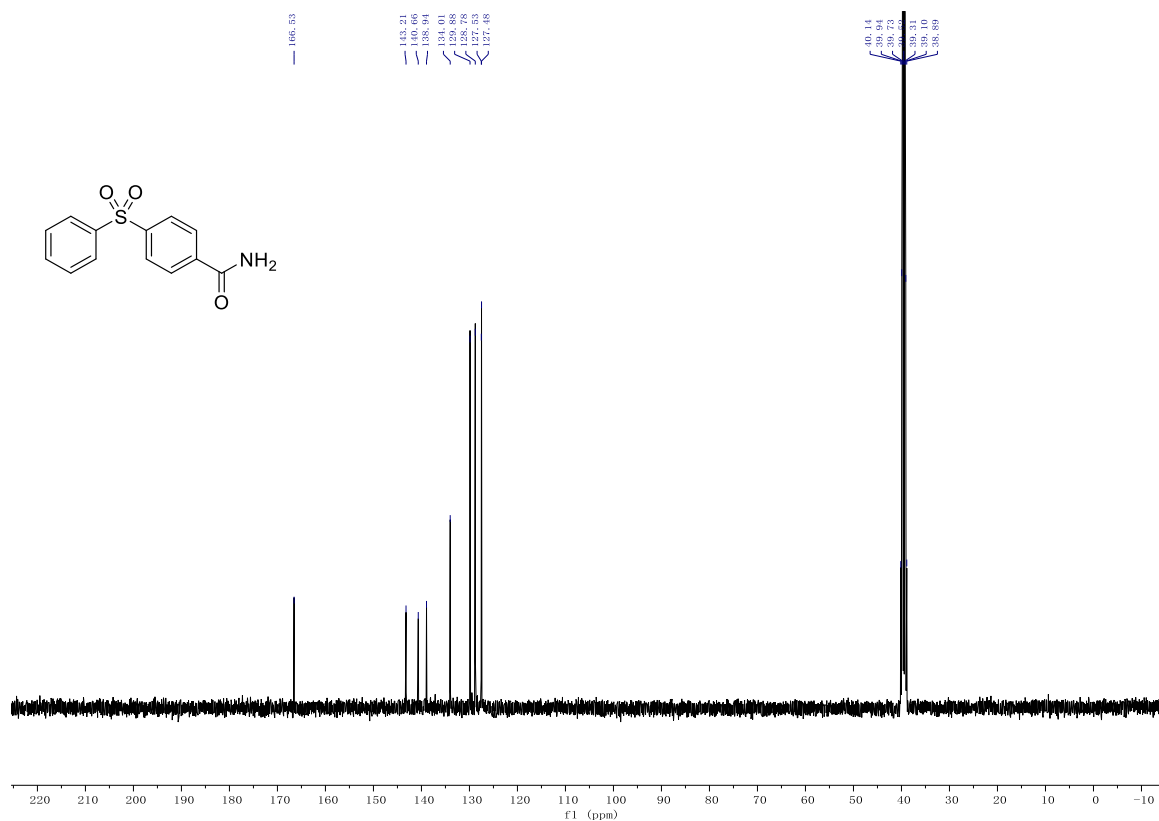
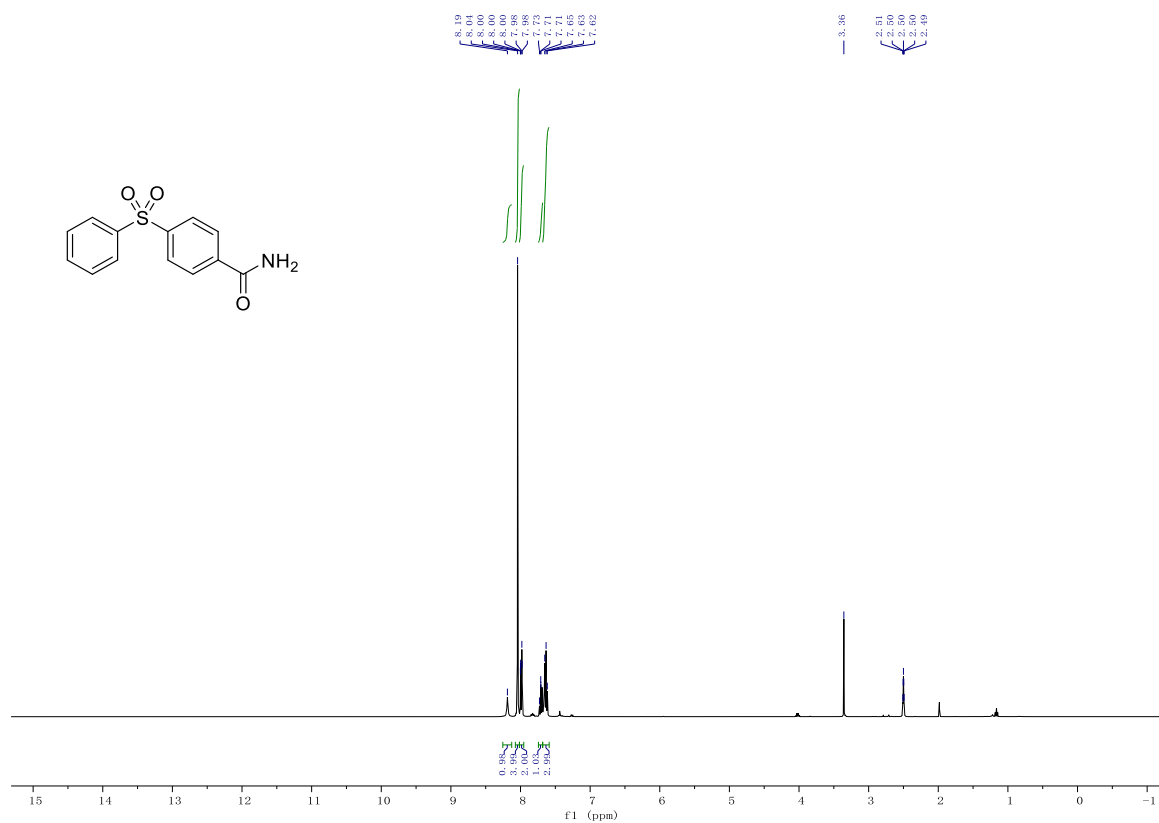


¹H NMR and ¹³C NMR spectra of **2-(phenylsulfonyl)benzonitrile 35m**

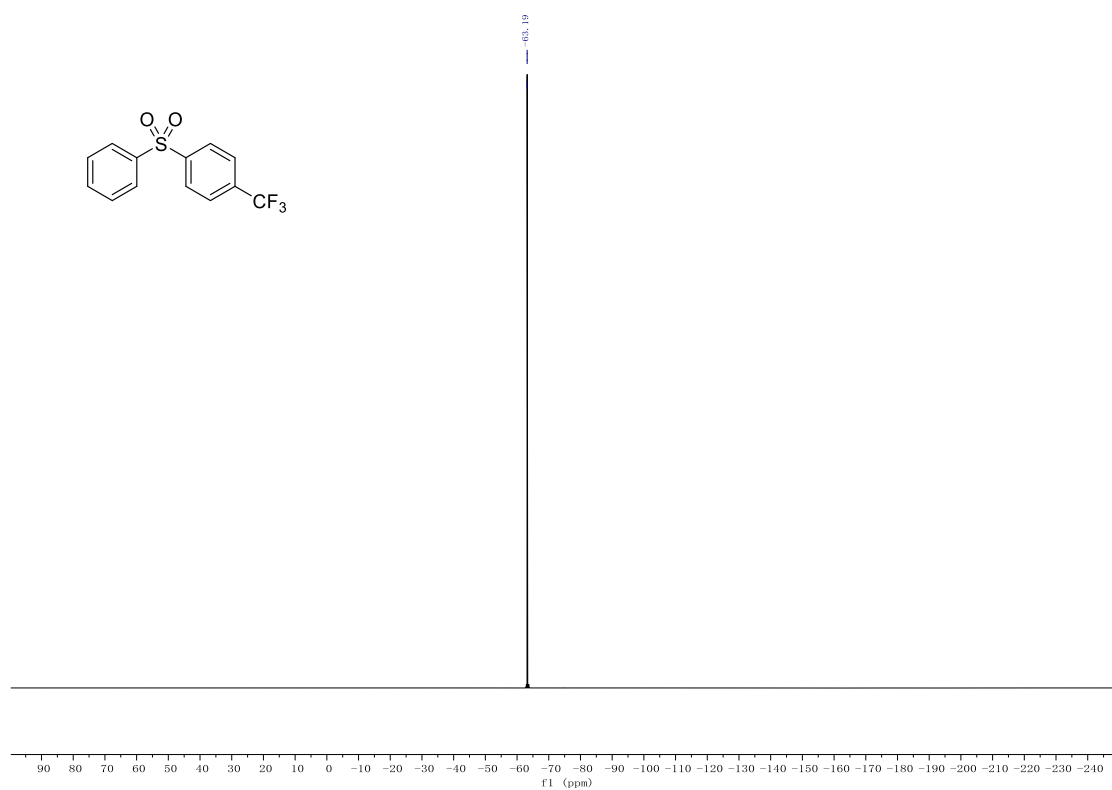


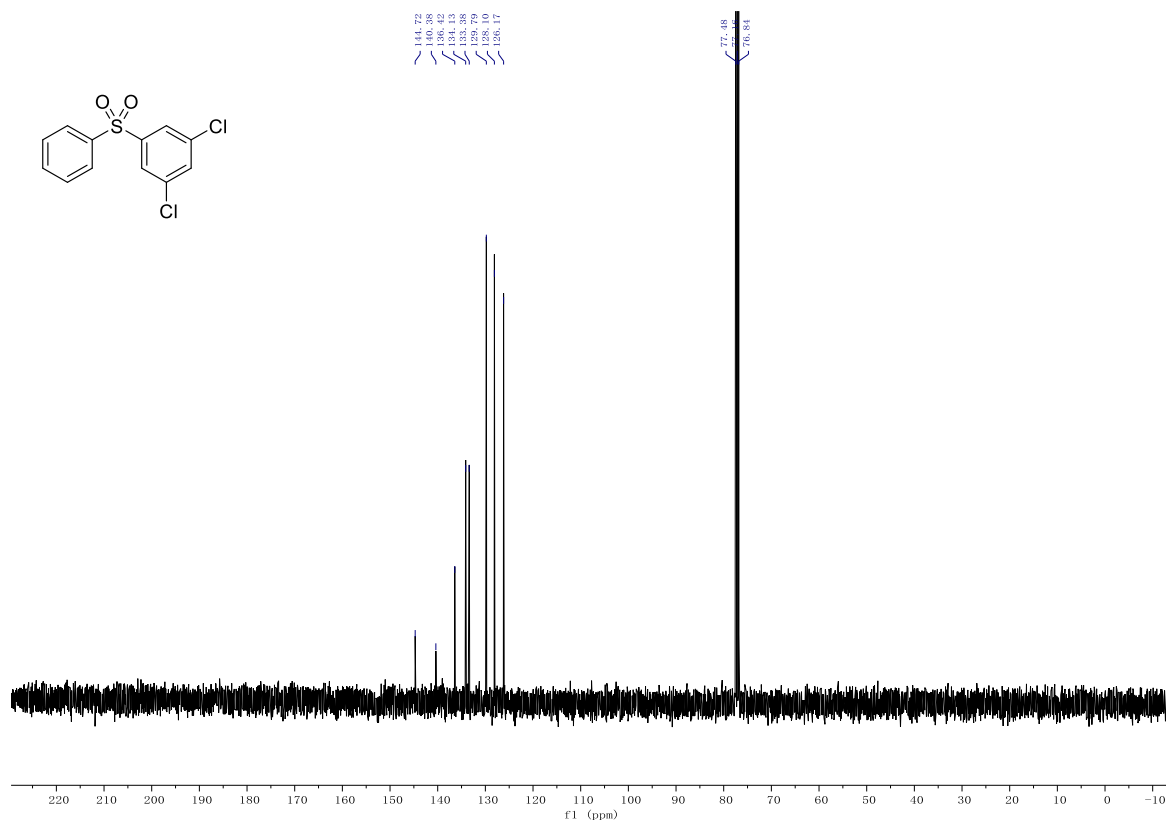
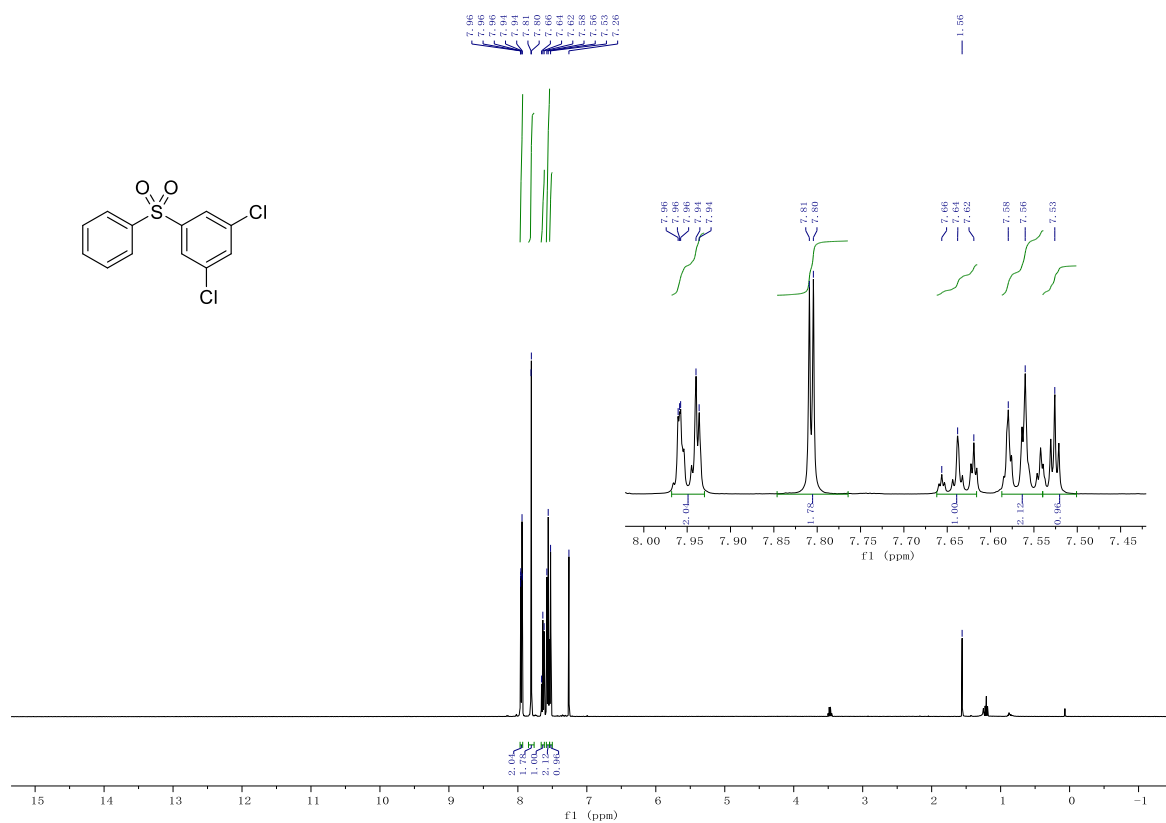
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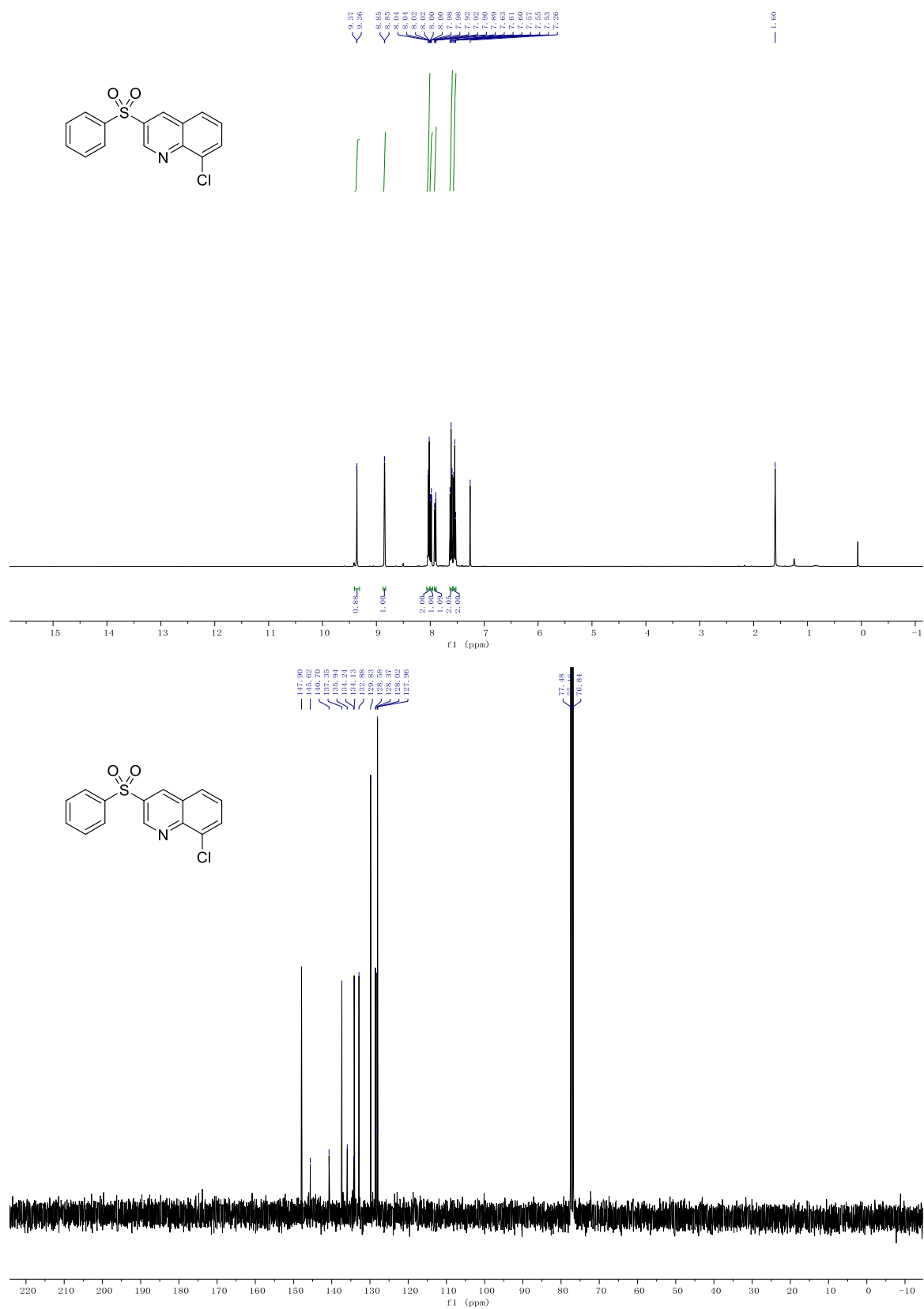


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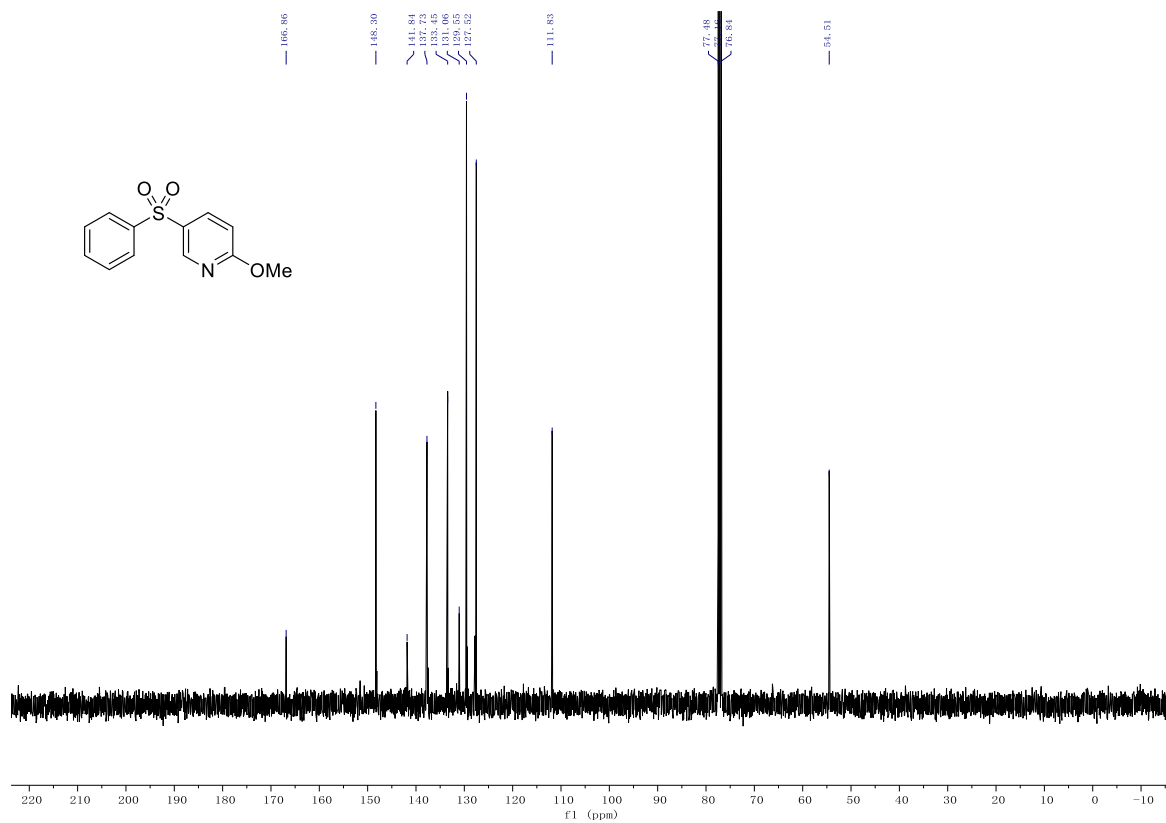
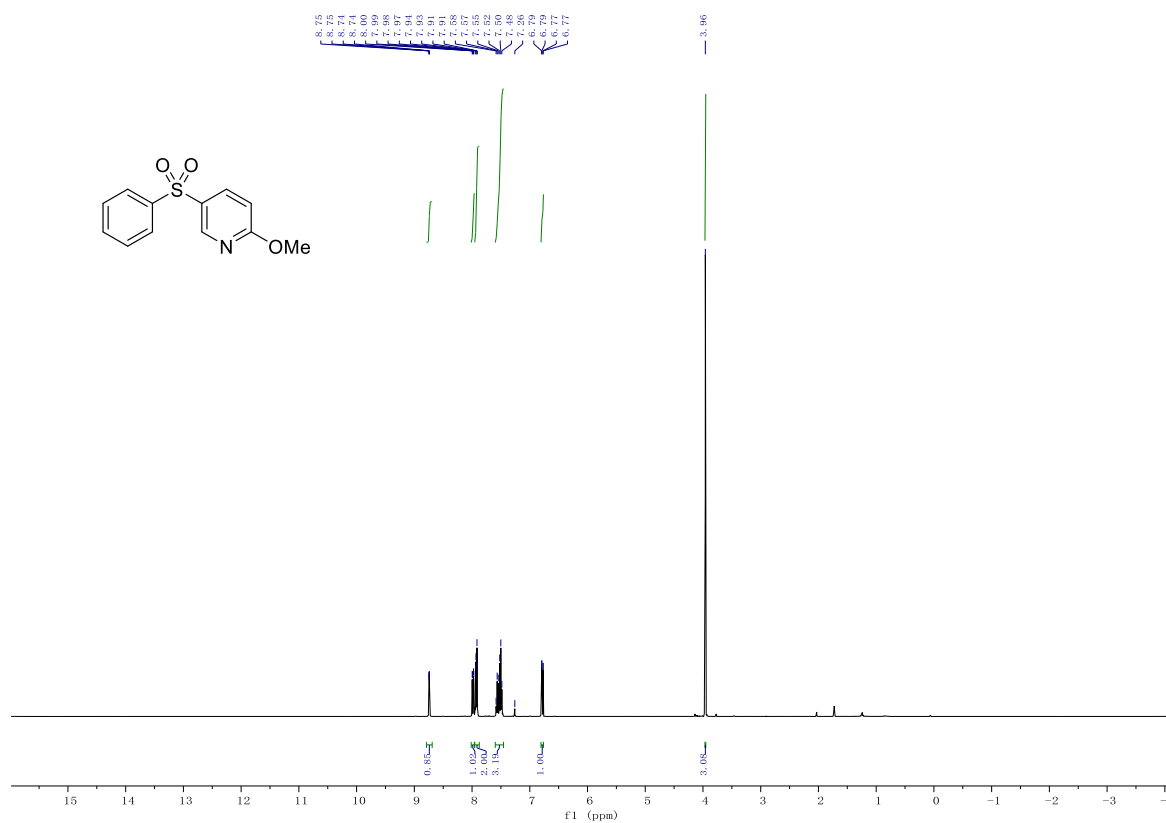


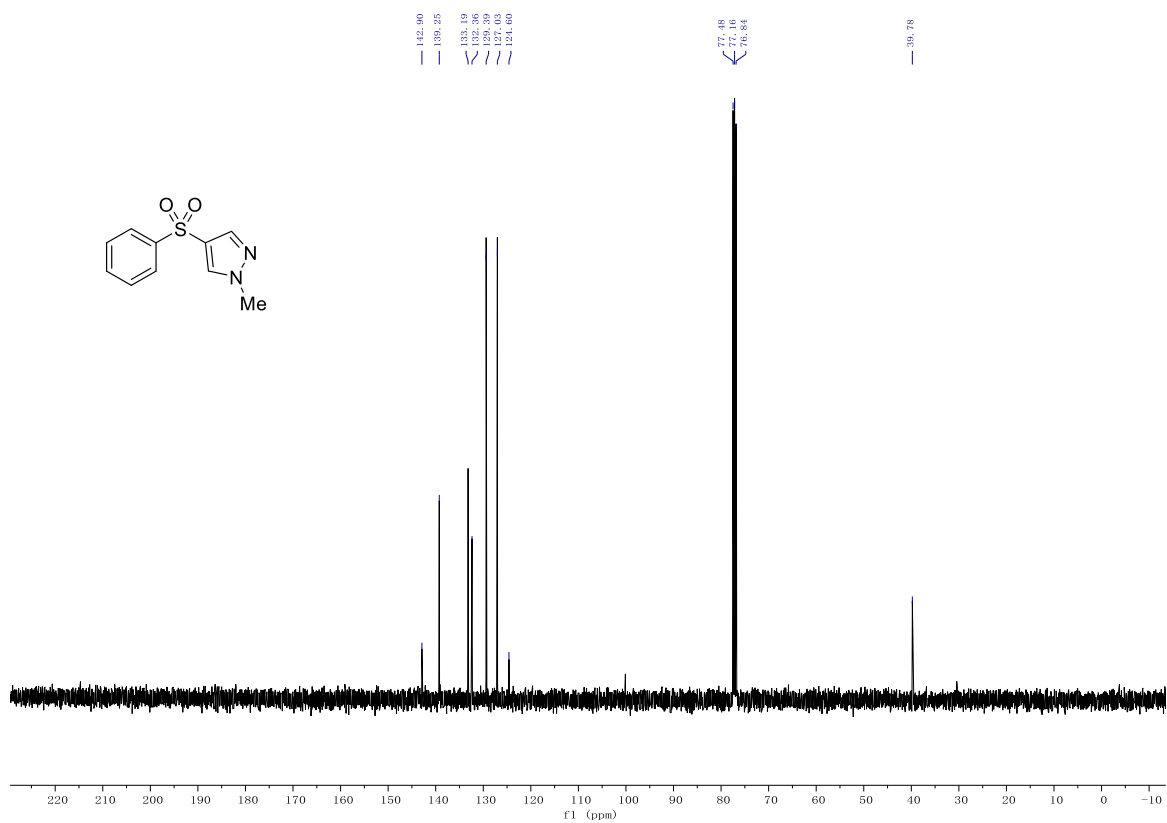
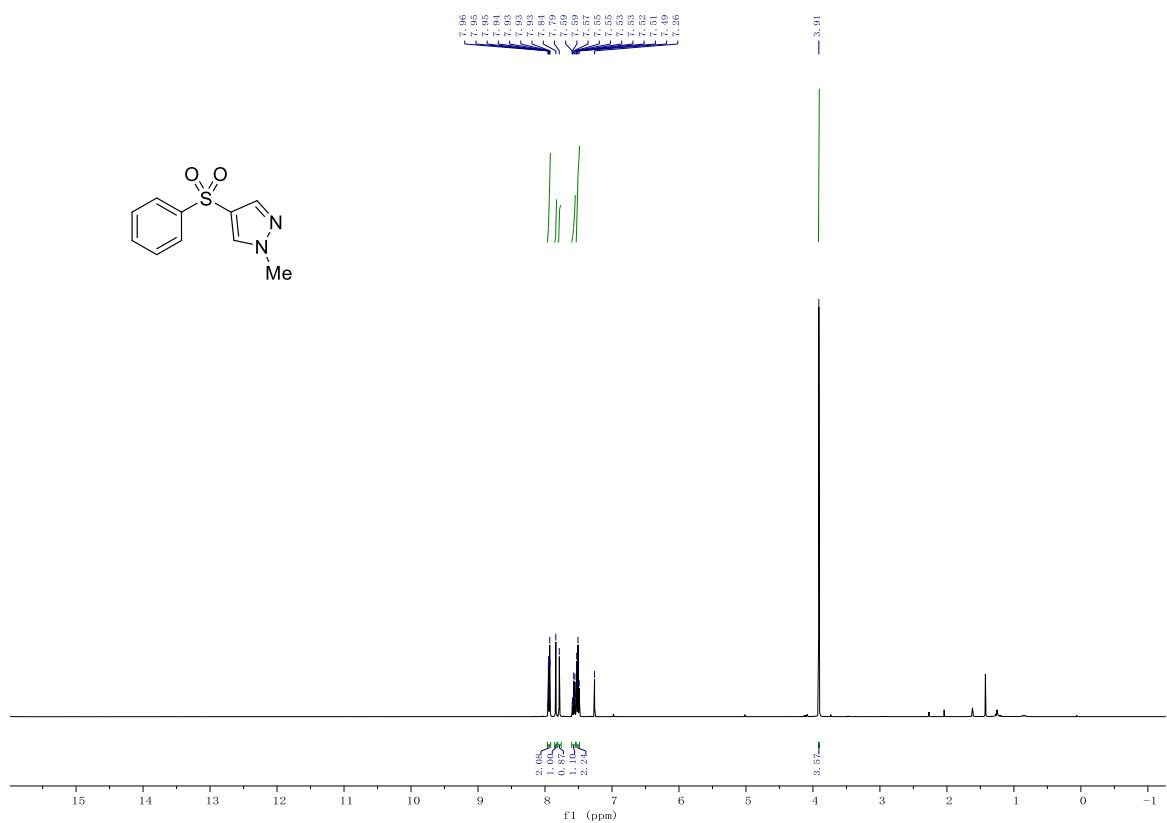


¹H NMR and ¹³C NMR spectra of 3,5-dichloro-1-(phenylsulfonyl)benzene 35s

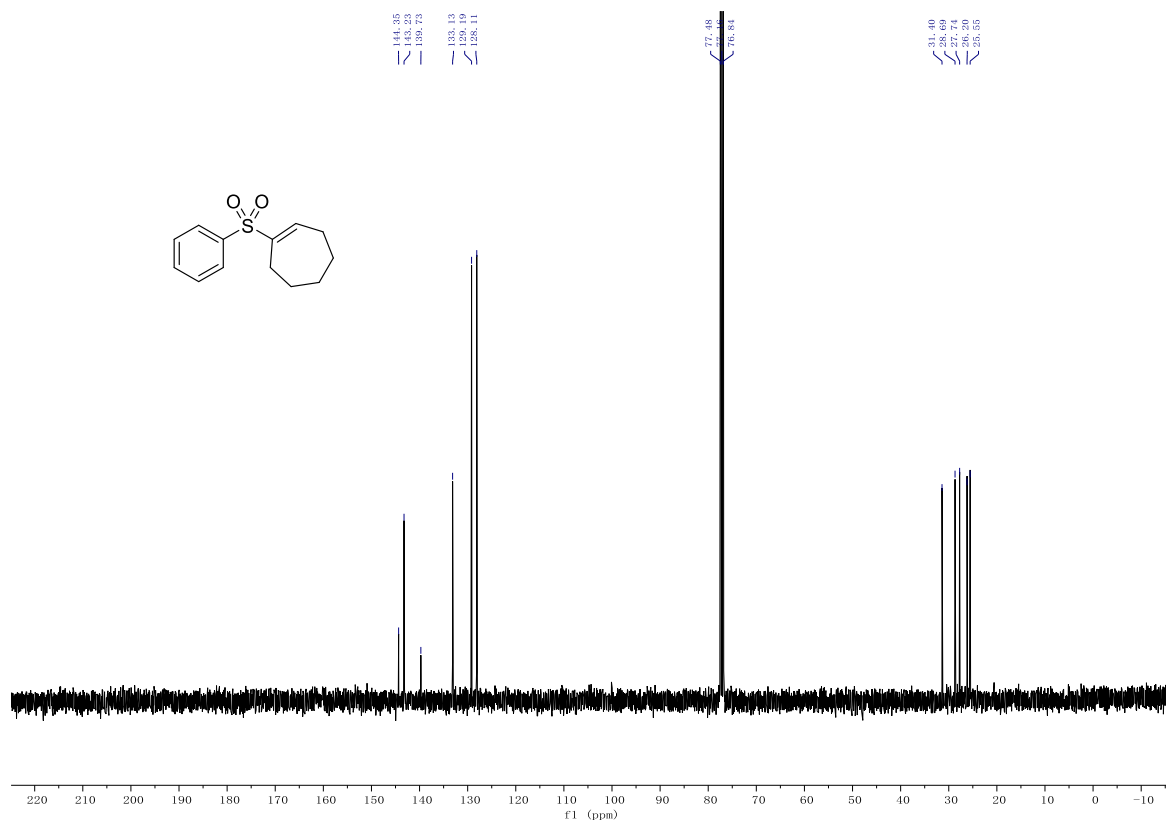
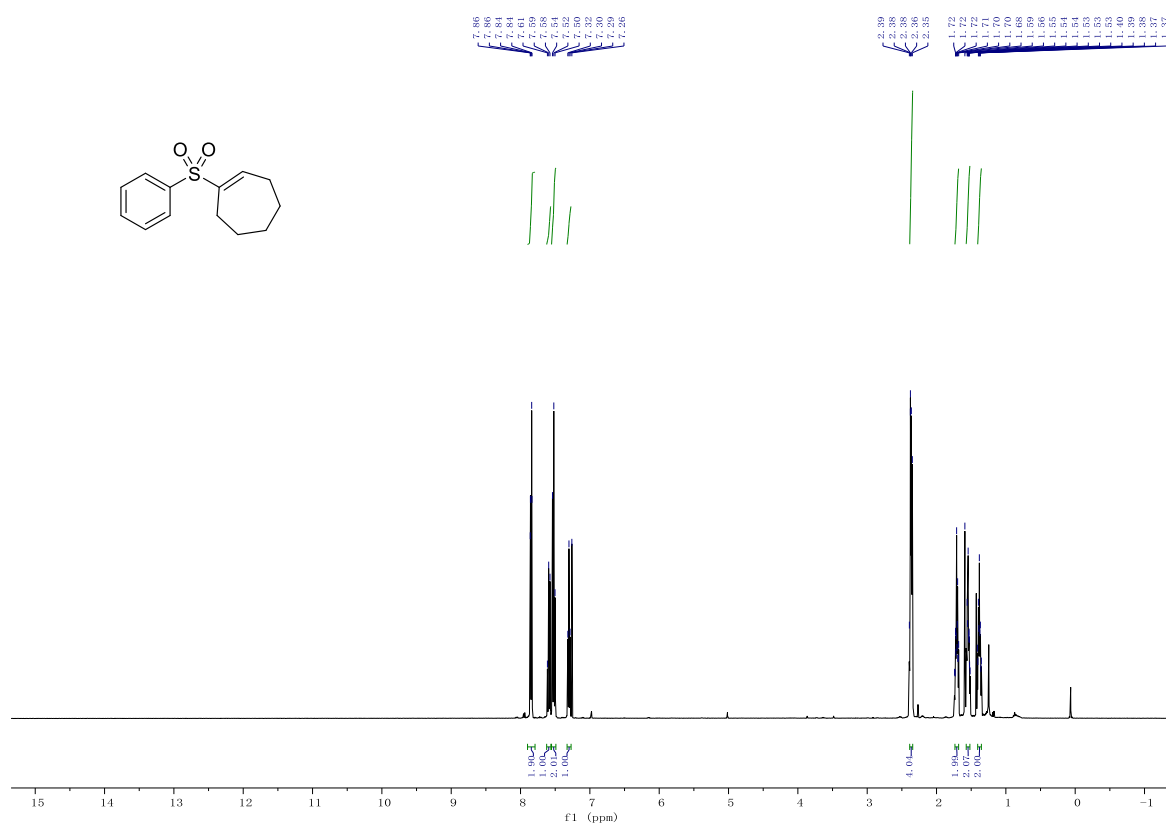


¹H NMR and ¹³C NMR spectra of 8-chloro-3-(phenylsulfonyl)quinoline 35v

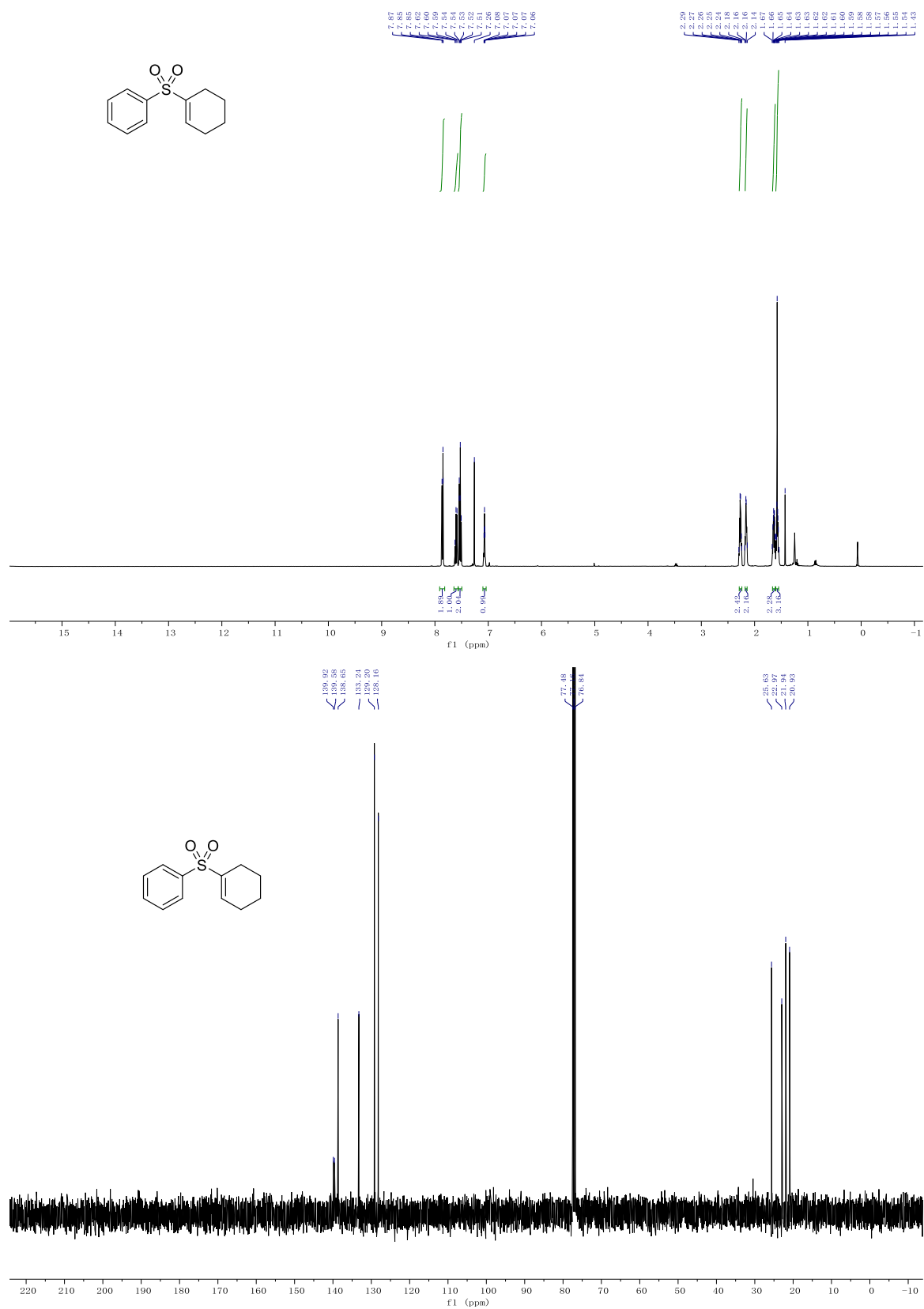
¹H NMR and ¹³C NMR spectra of **2-methoxy-5-(phenylsulfonyl)pyridine 35w**



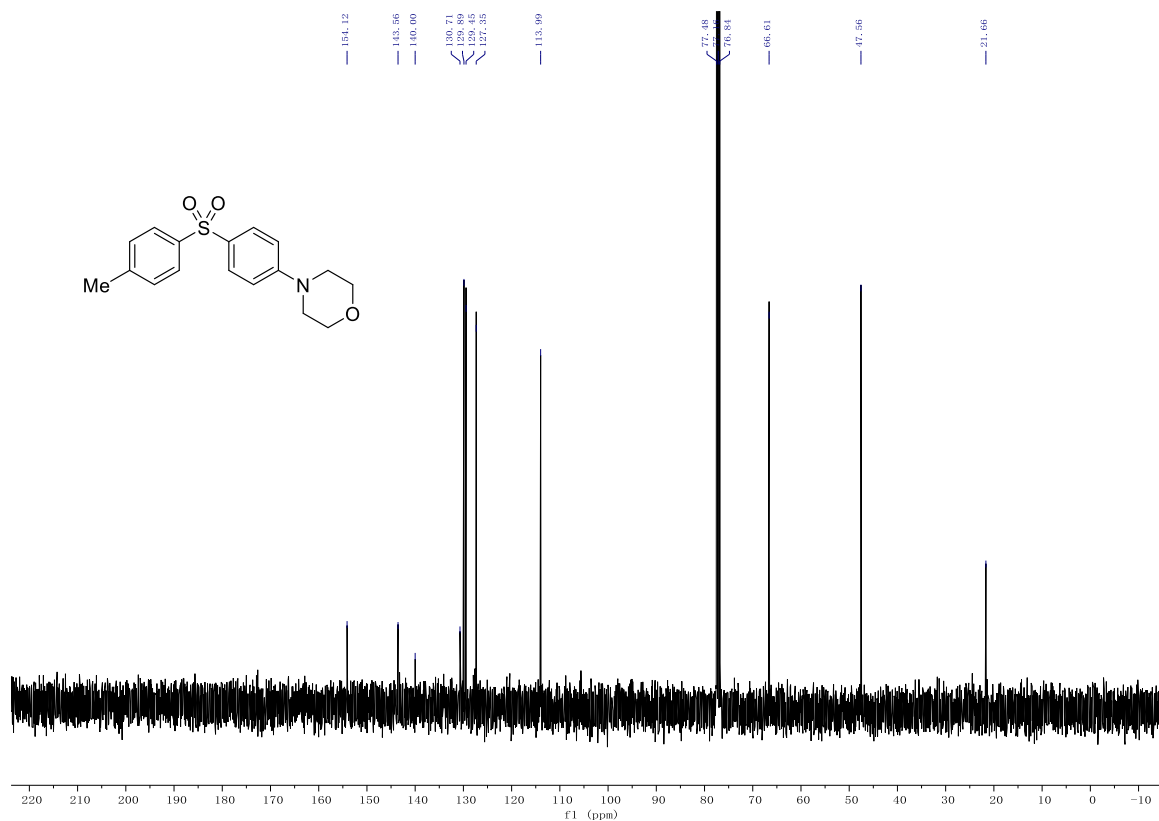
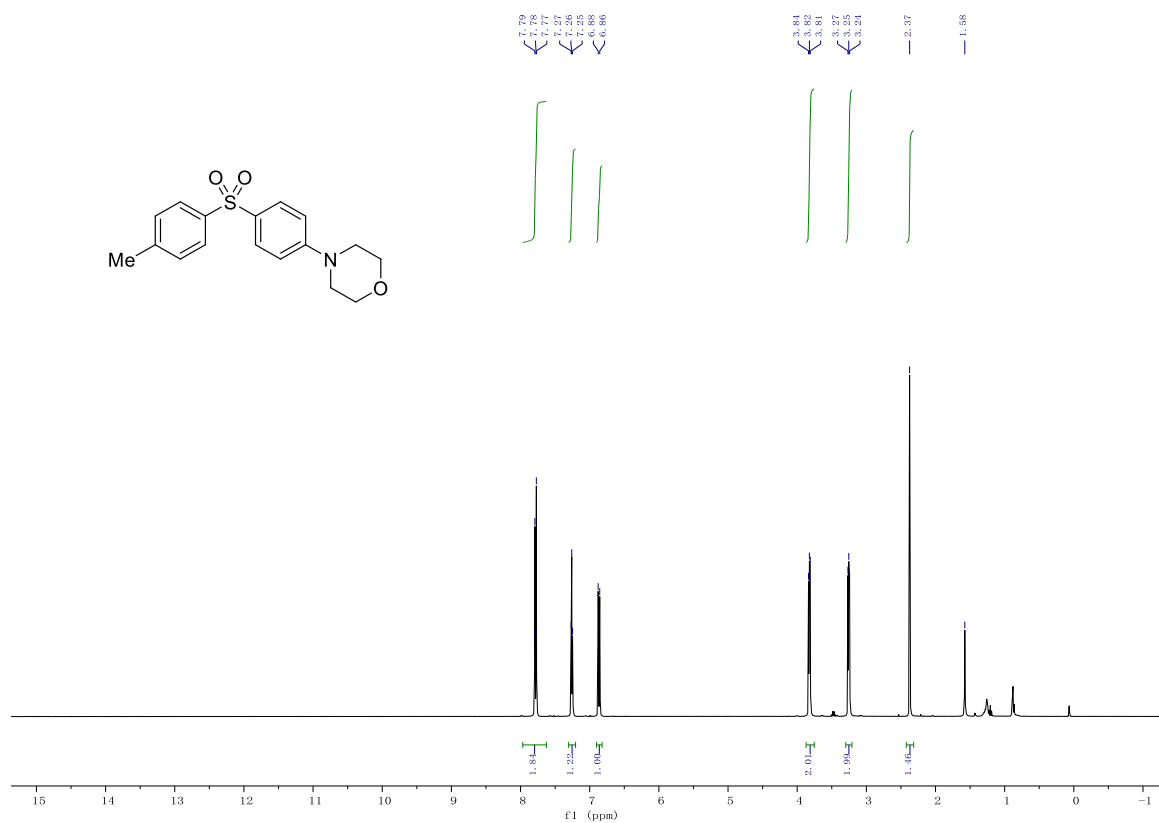
¹H NMR and ¹³C NMR spectra of 1-methyl-4-(phenylsulfonyl)pyrazole 35x



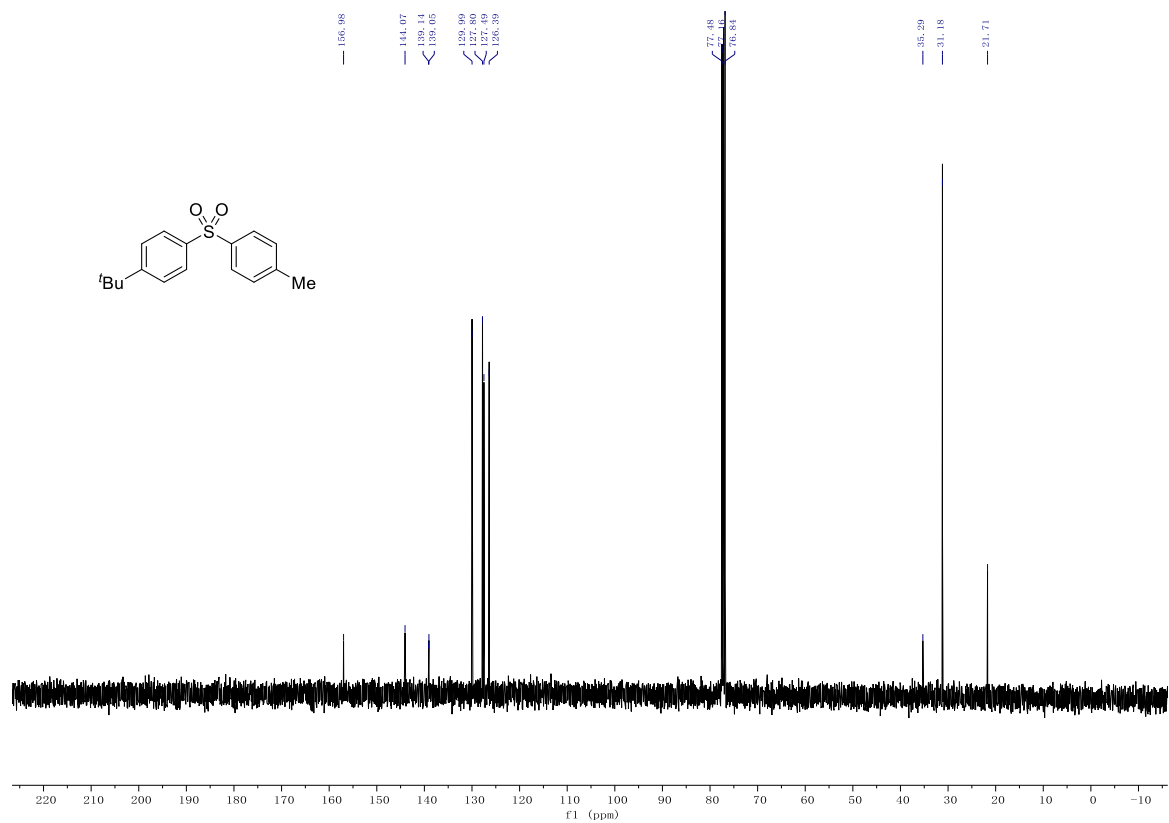
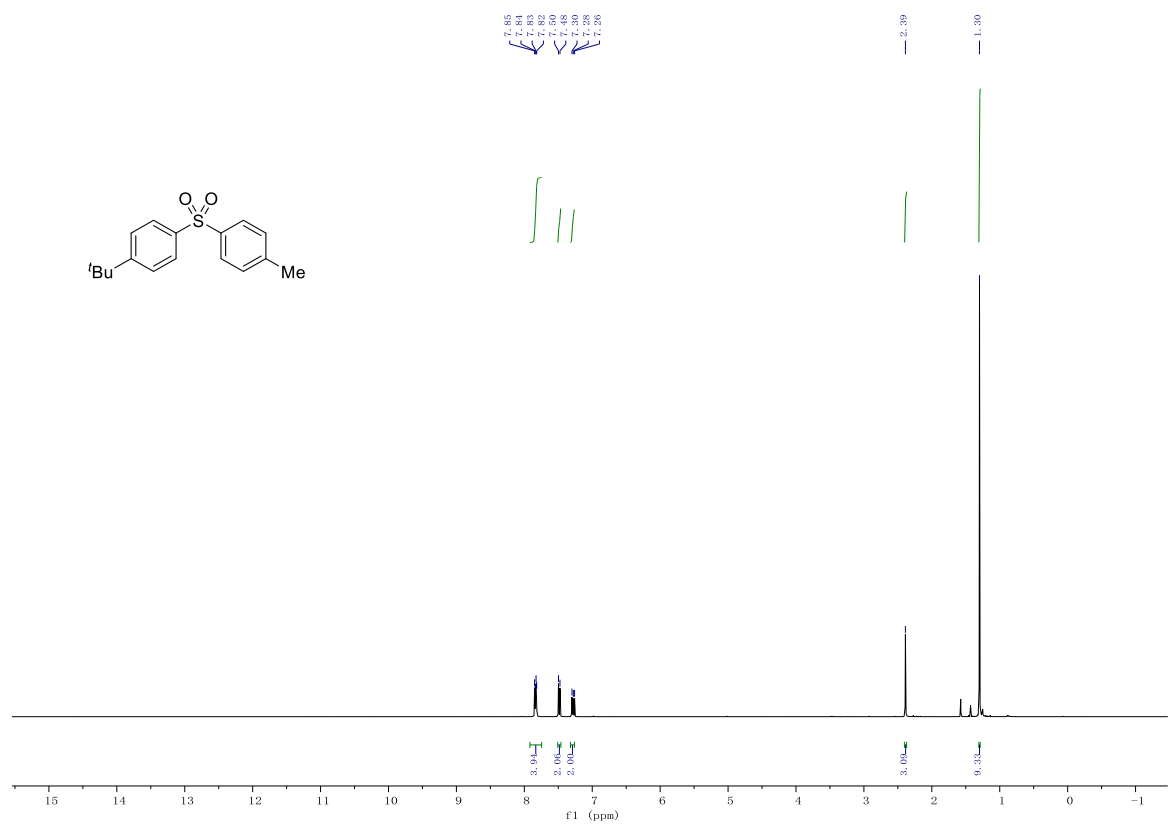
¹H NMR and ¹³C NMR spectra of 1-cyclohepten-1-yl-phenylsulfone 35y



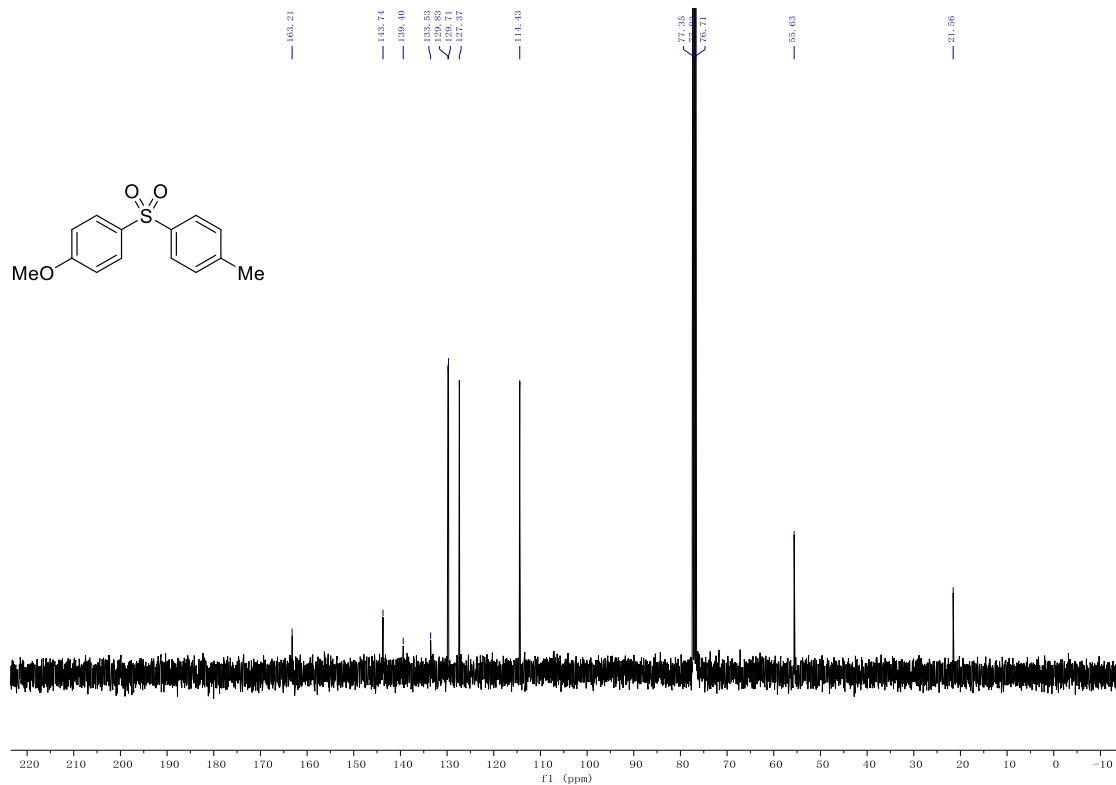
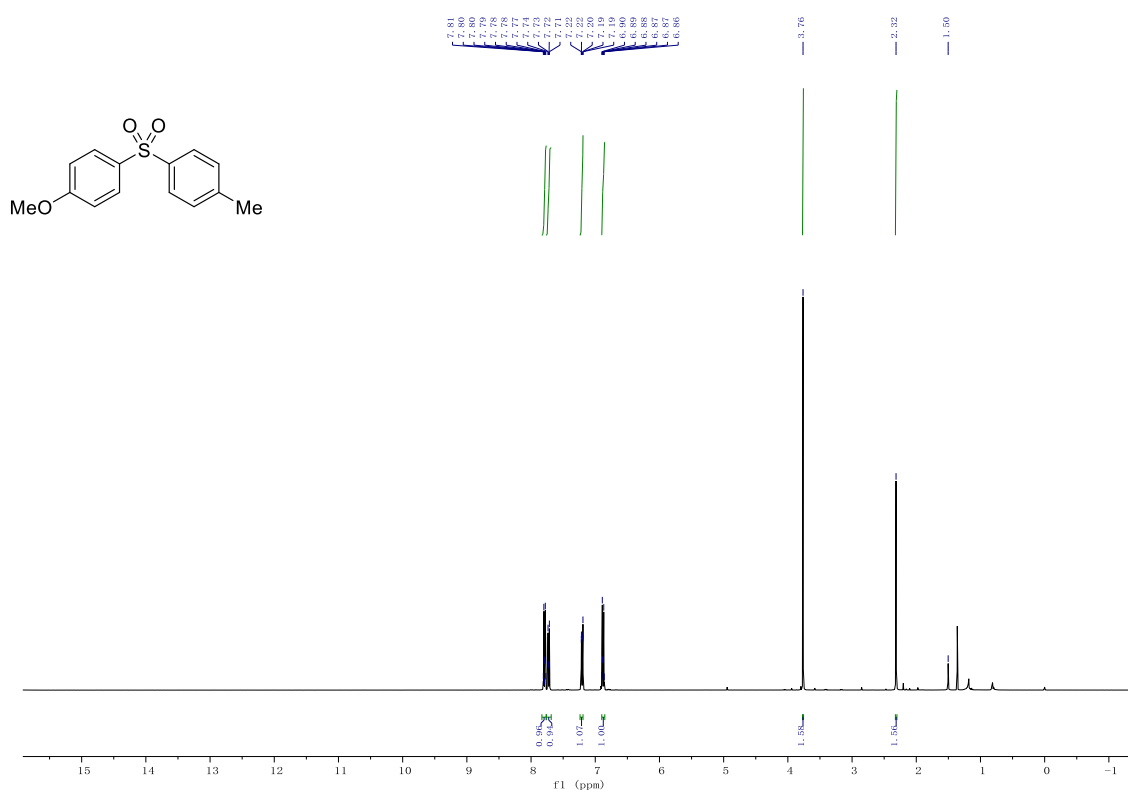
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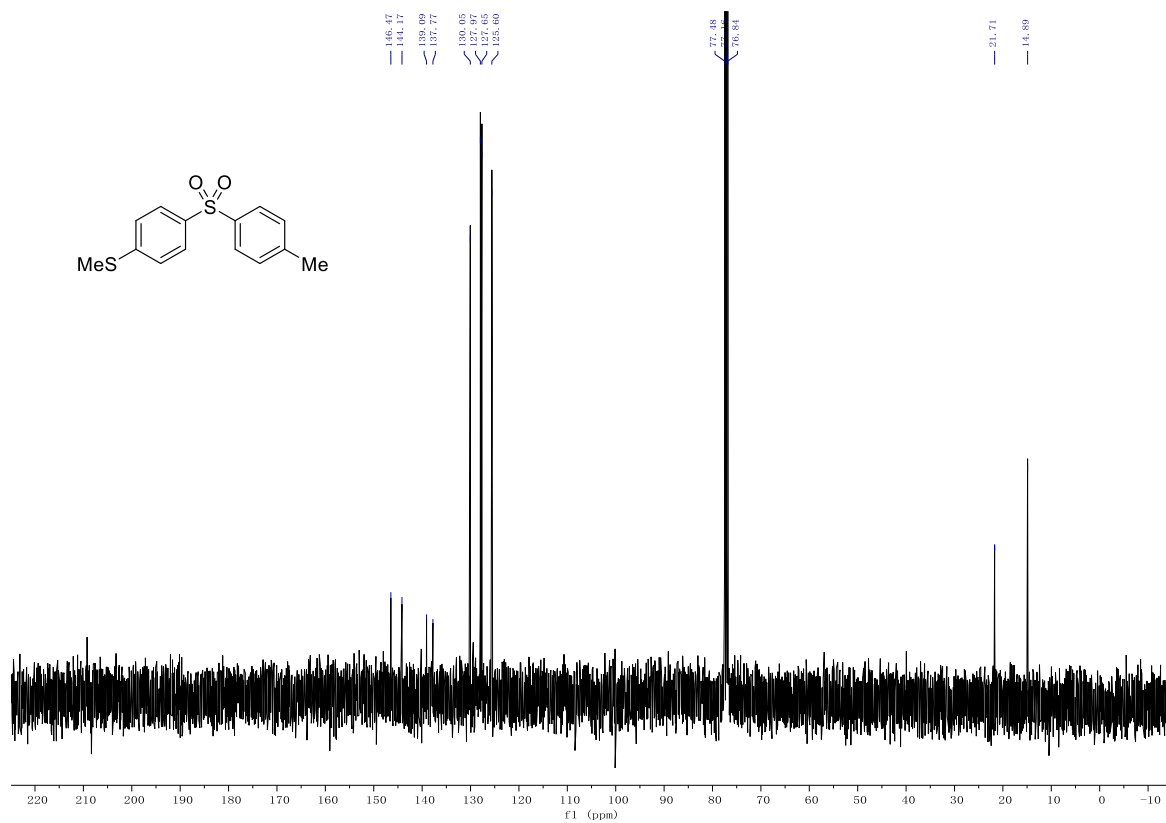
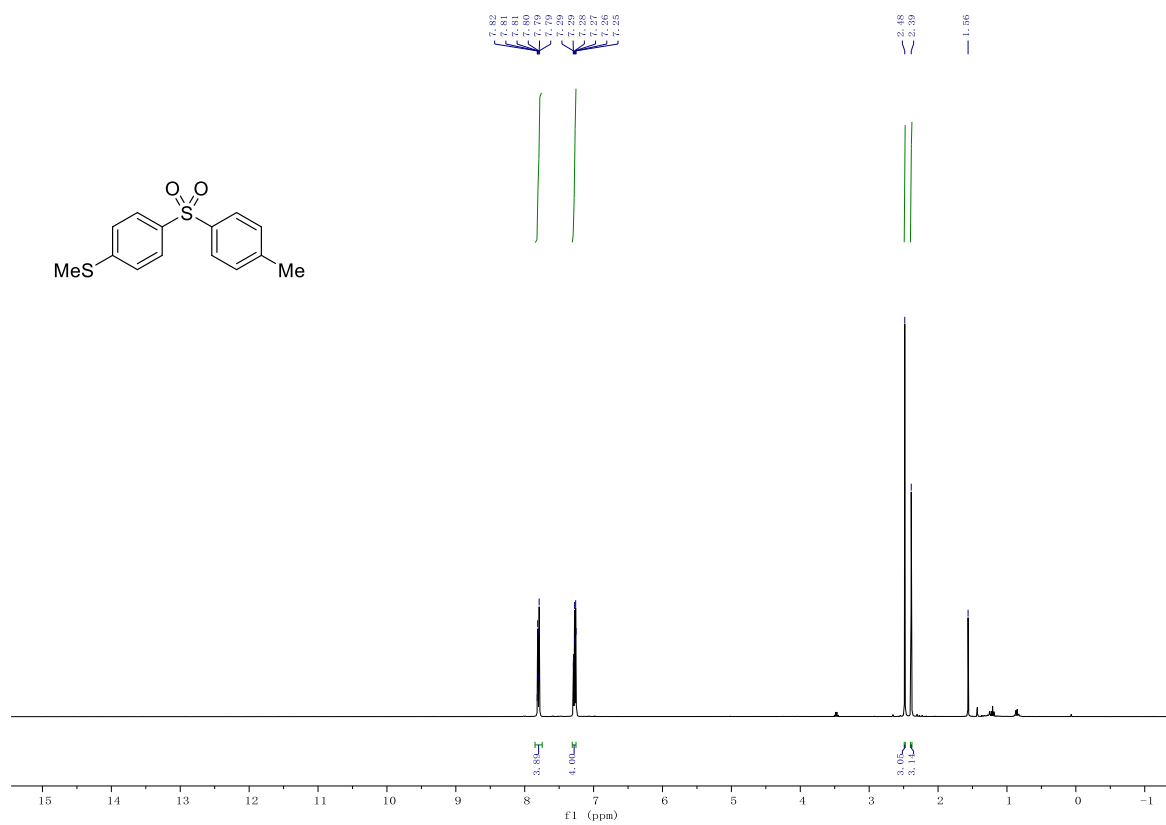
¹H NMR and ¹³C NMR spectra of 4-(4-tosylphenyl)morpholine 36a



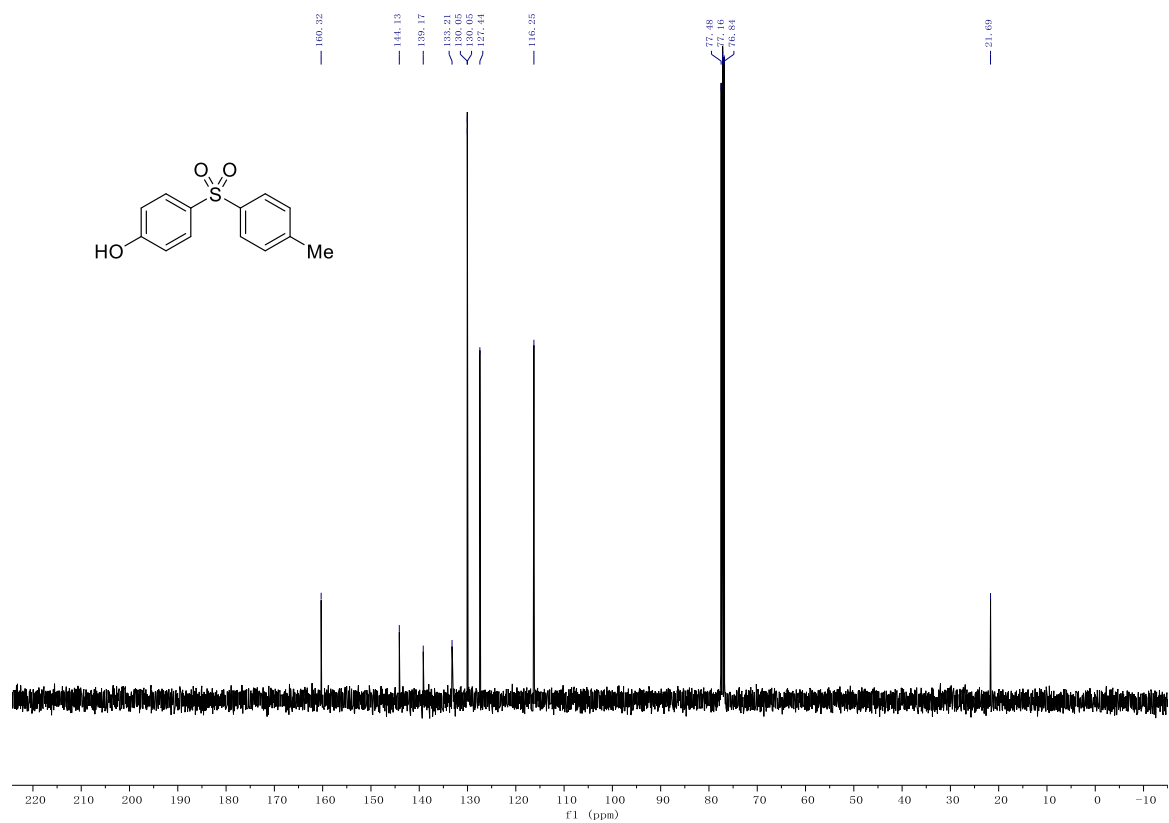
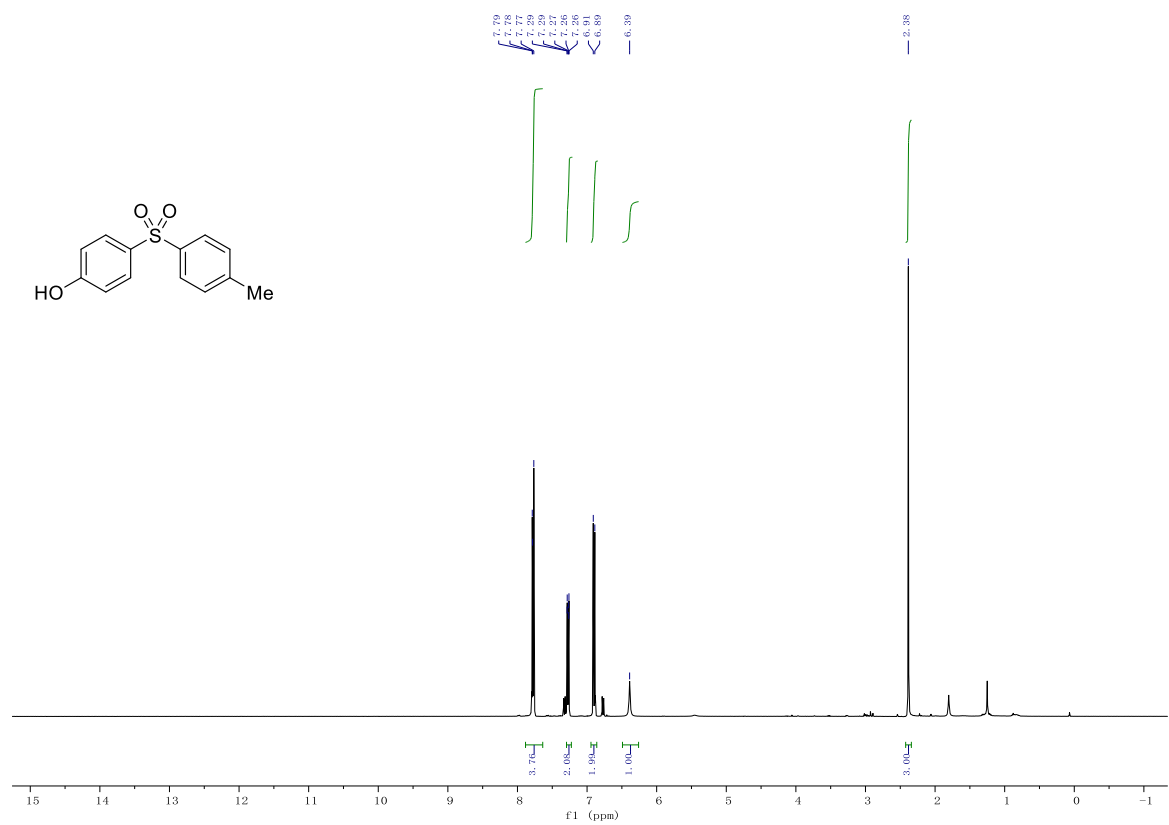
¹H NMR and ¹³C NMR spectra of (4-*tert*-butylphenyl)-*p*-tolyl sulfone 36b



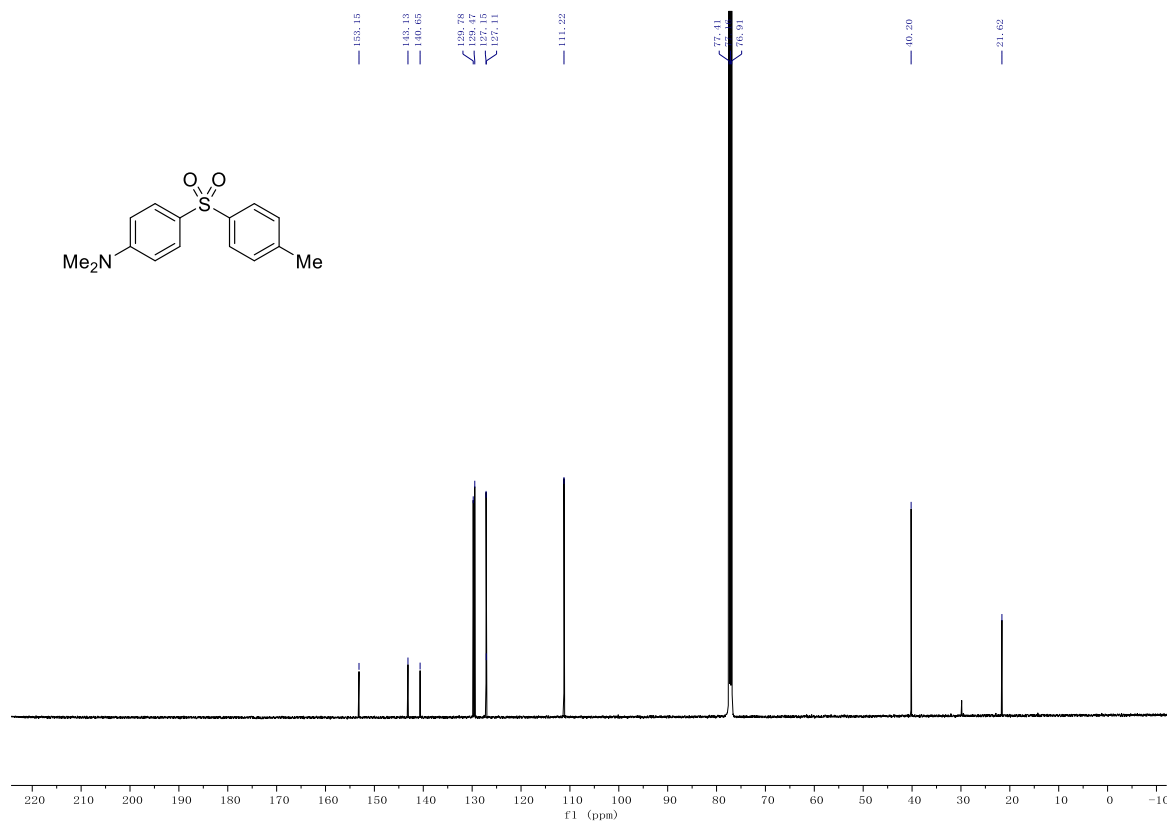
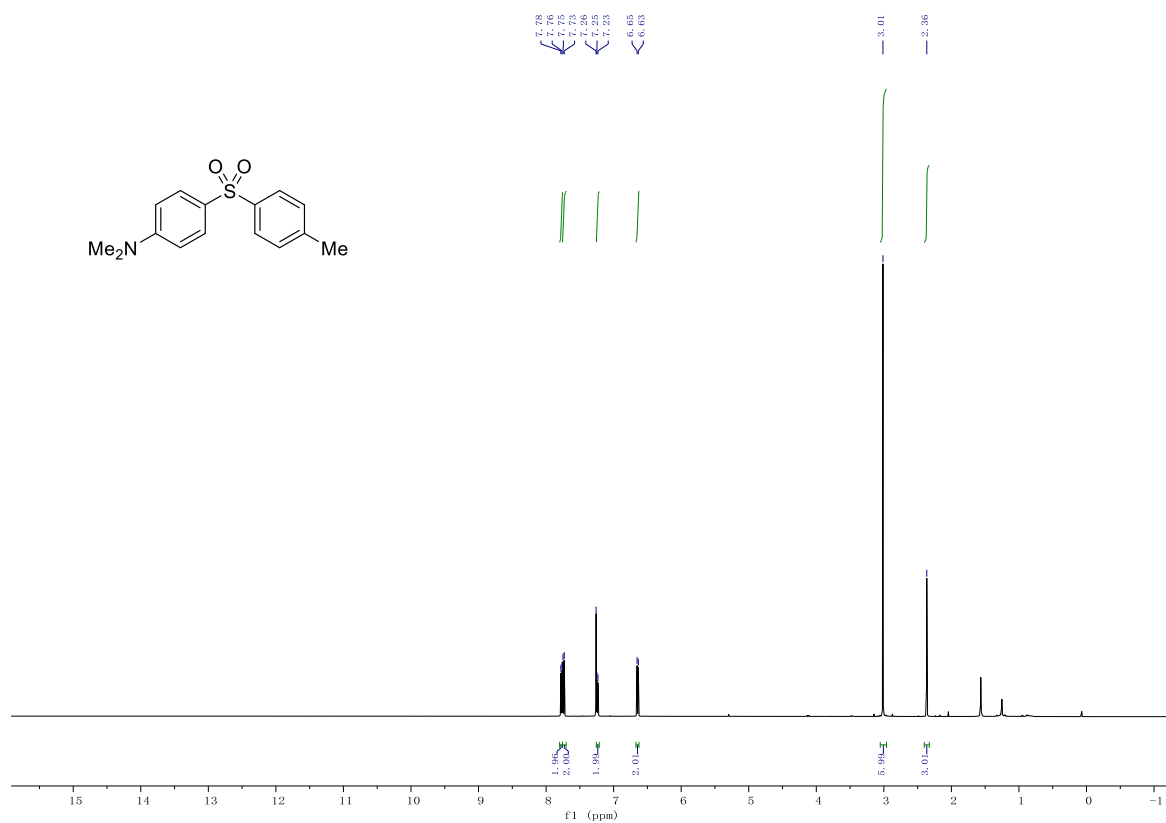
¹H NMR and ¹³C NMR spectra of 4-tolyl 4-methoxyphenyl sulfone 36d



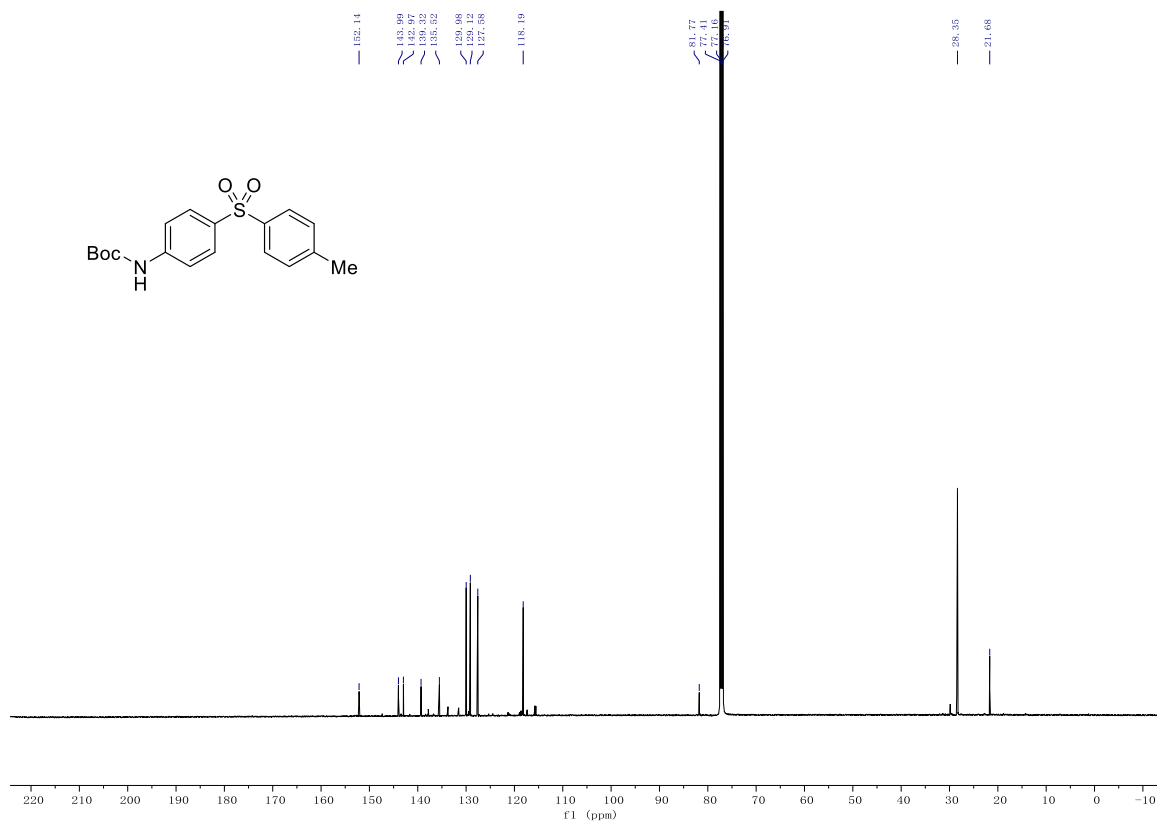
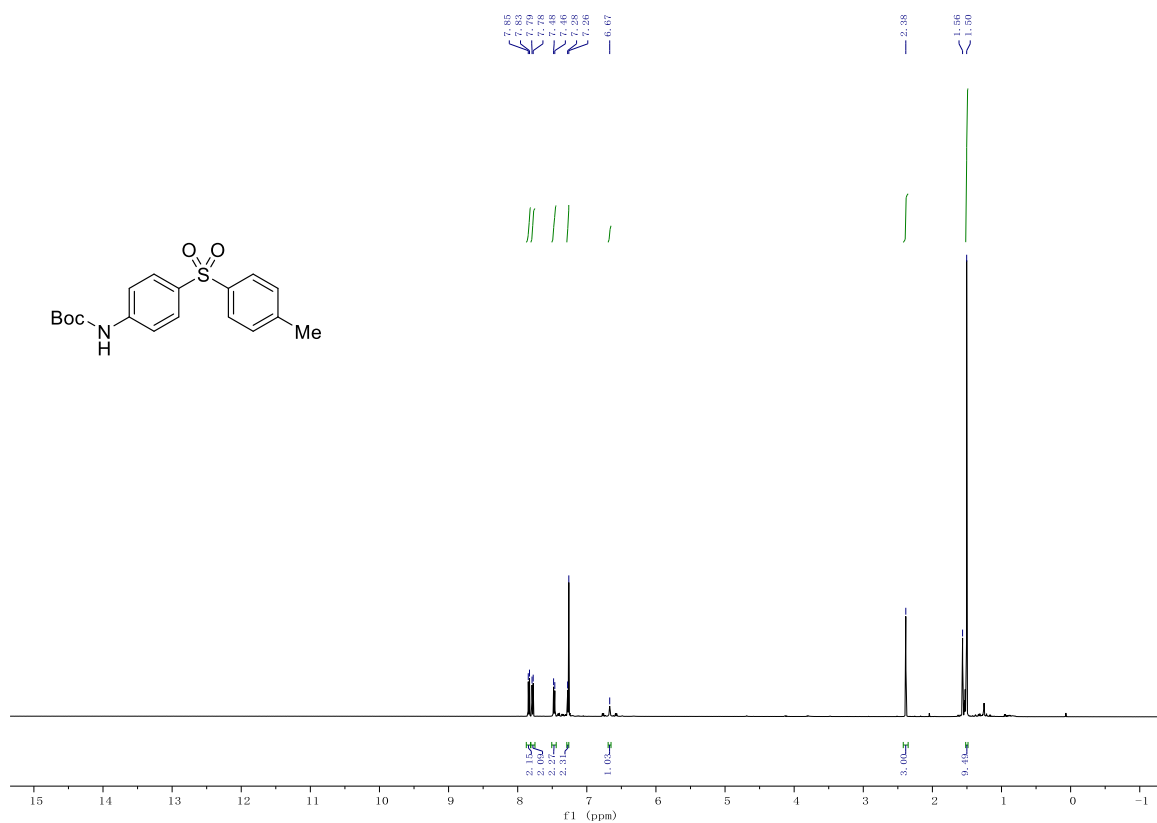
¹H NMR and ¹³C NMR spectra of 4-tolyl 4-methylthiophenyl sulfone 36e



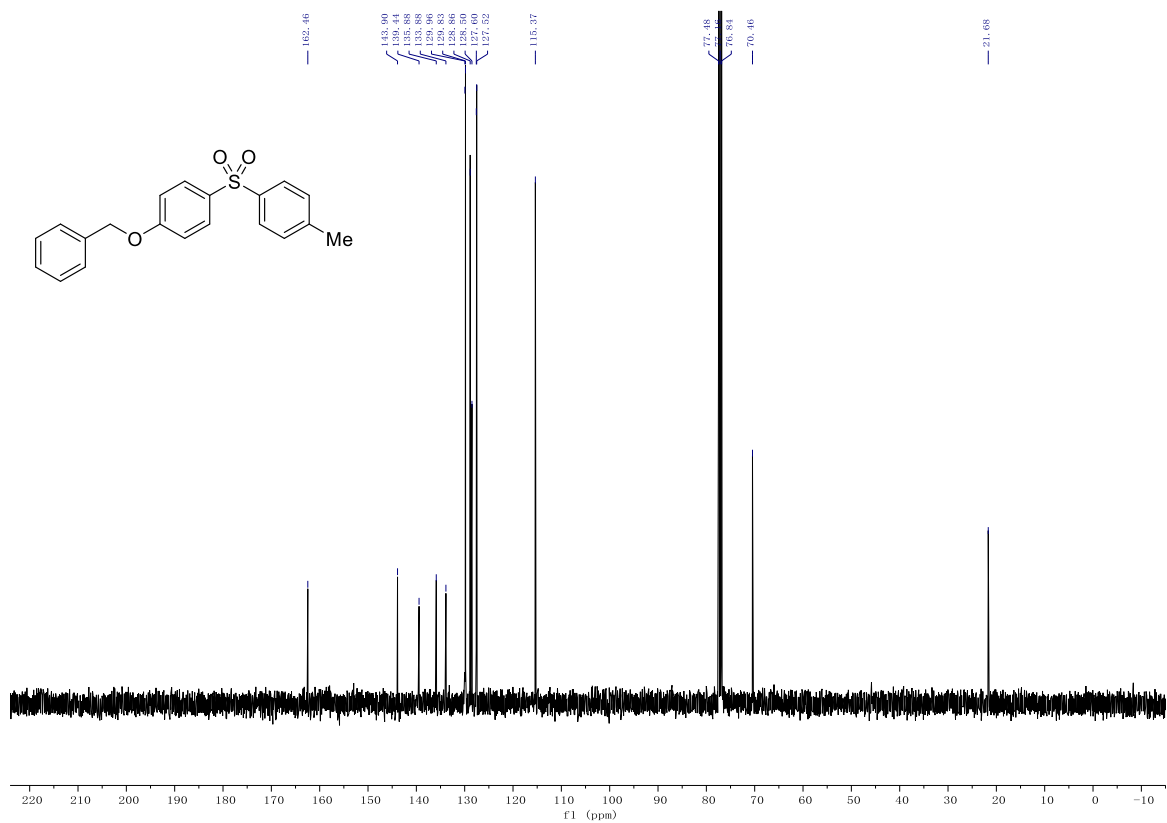
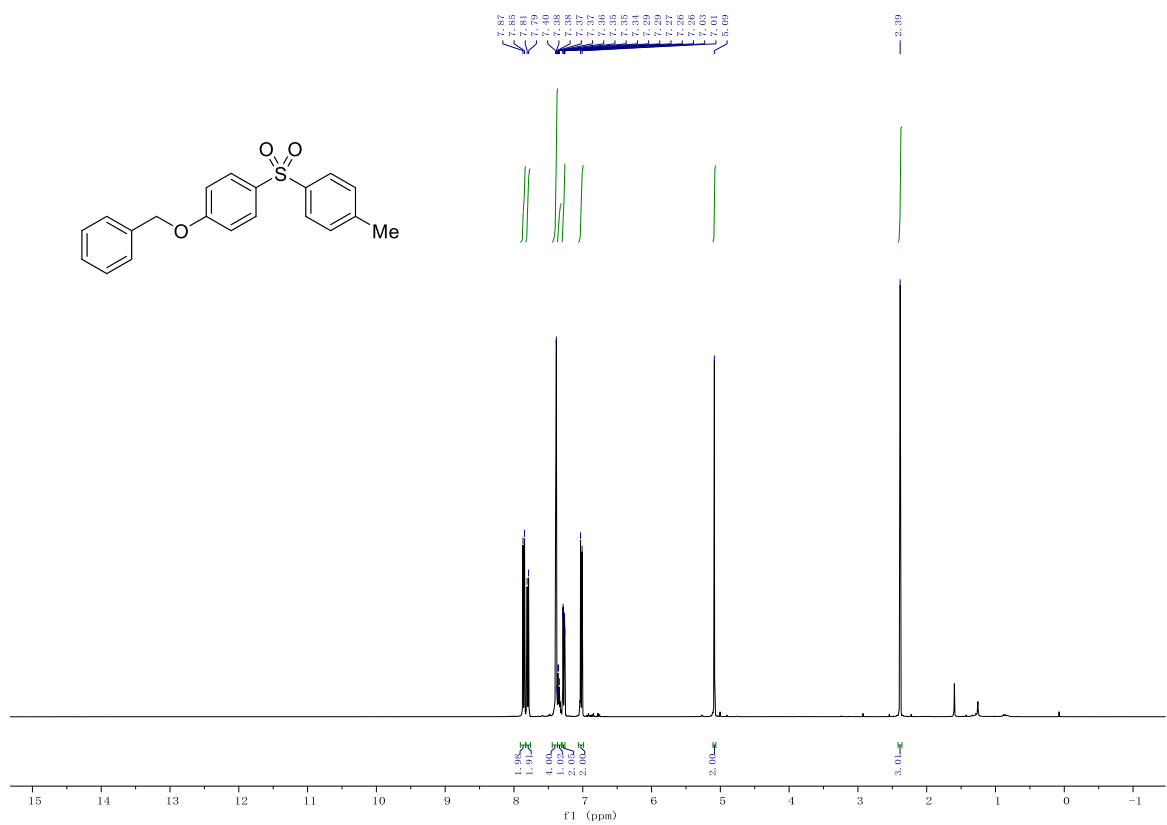
¹H NMR and ¹³C NMR spectra of 4-tosylphenol 36f



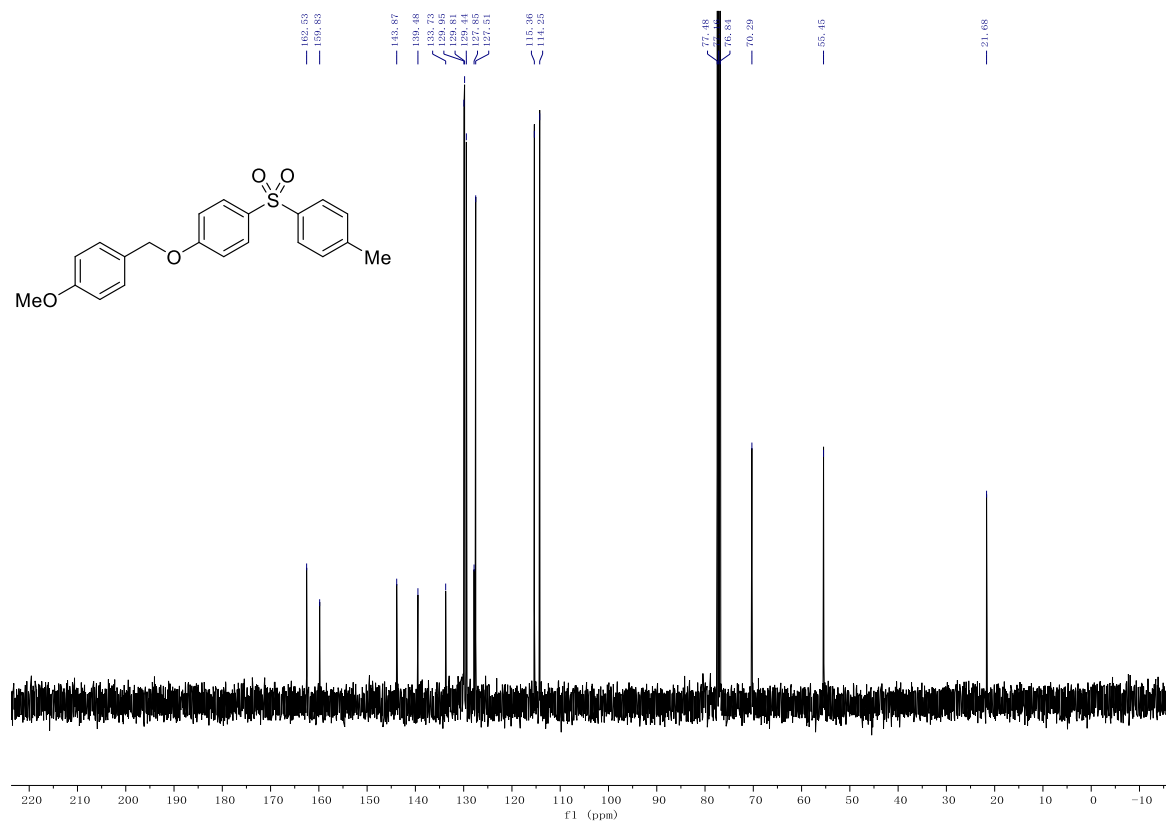
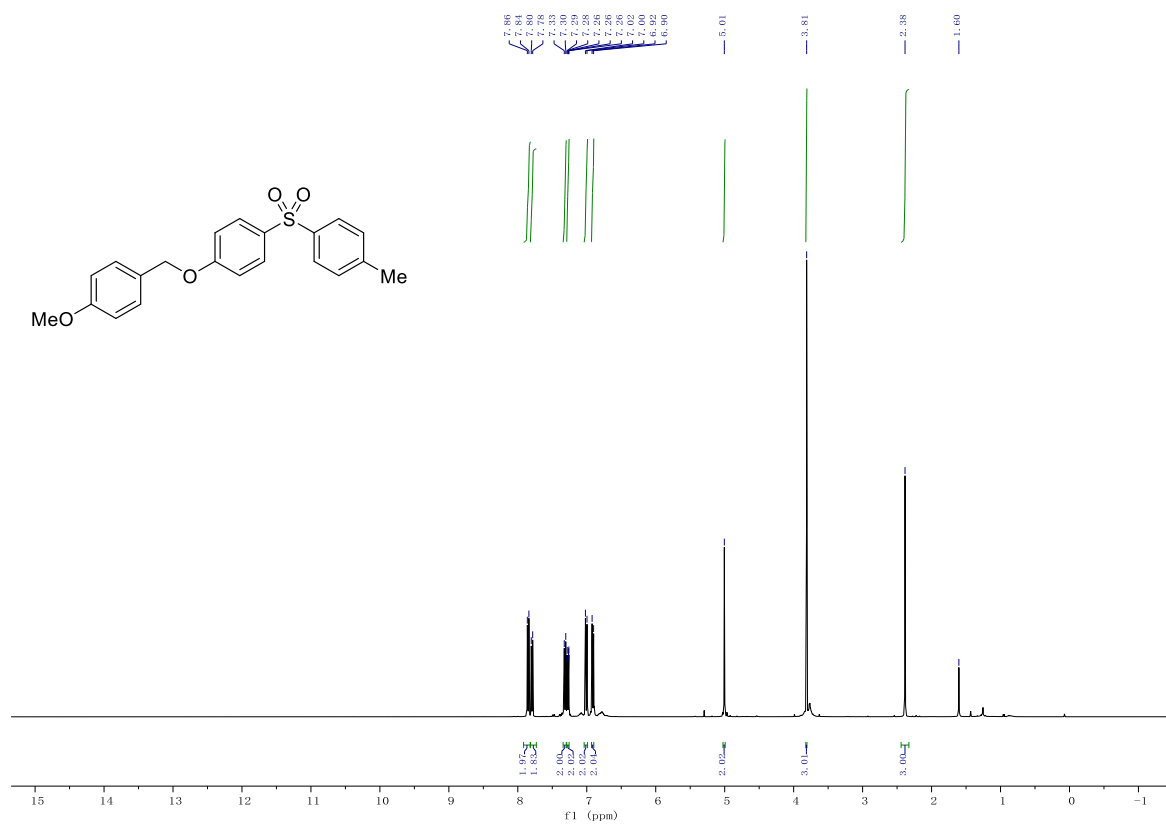
¹H NMR and ¹³C NMR spectra of *N,N*-dimethyl-4-tosylaniline 36g



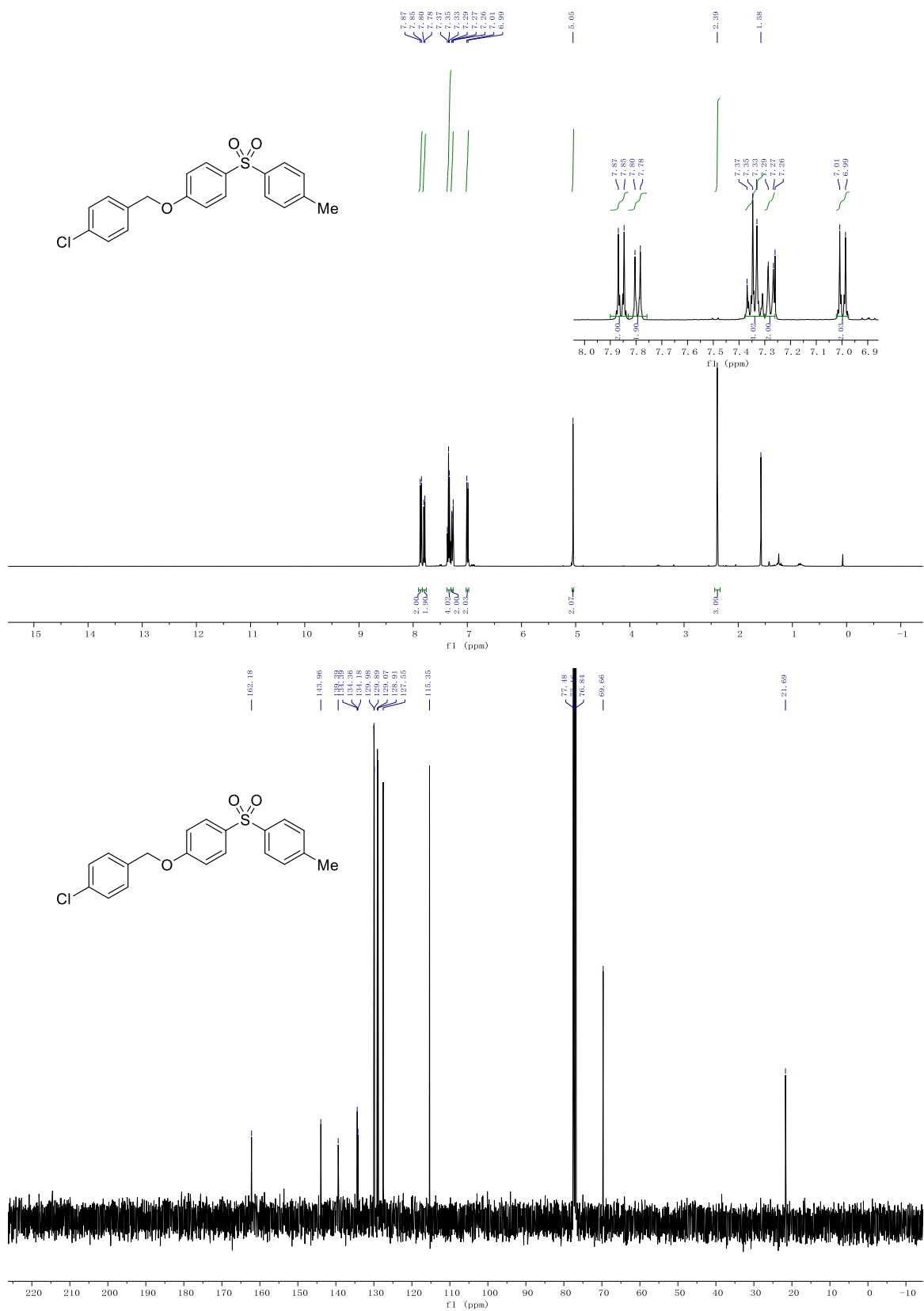
¹H NMR and ¹³C NMR spectra of *tert*-butyl (4-tosylphenyl)carbamate 36h



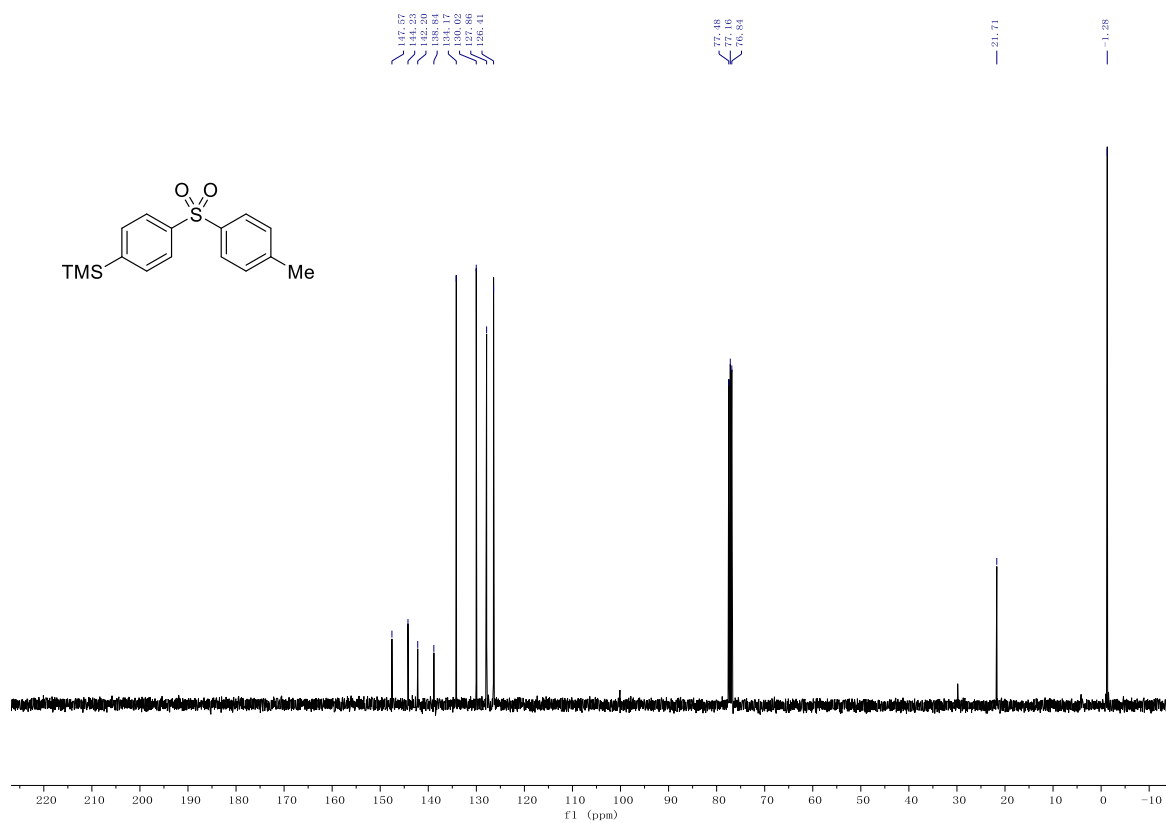
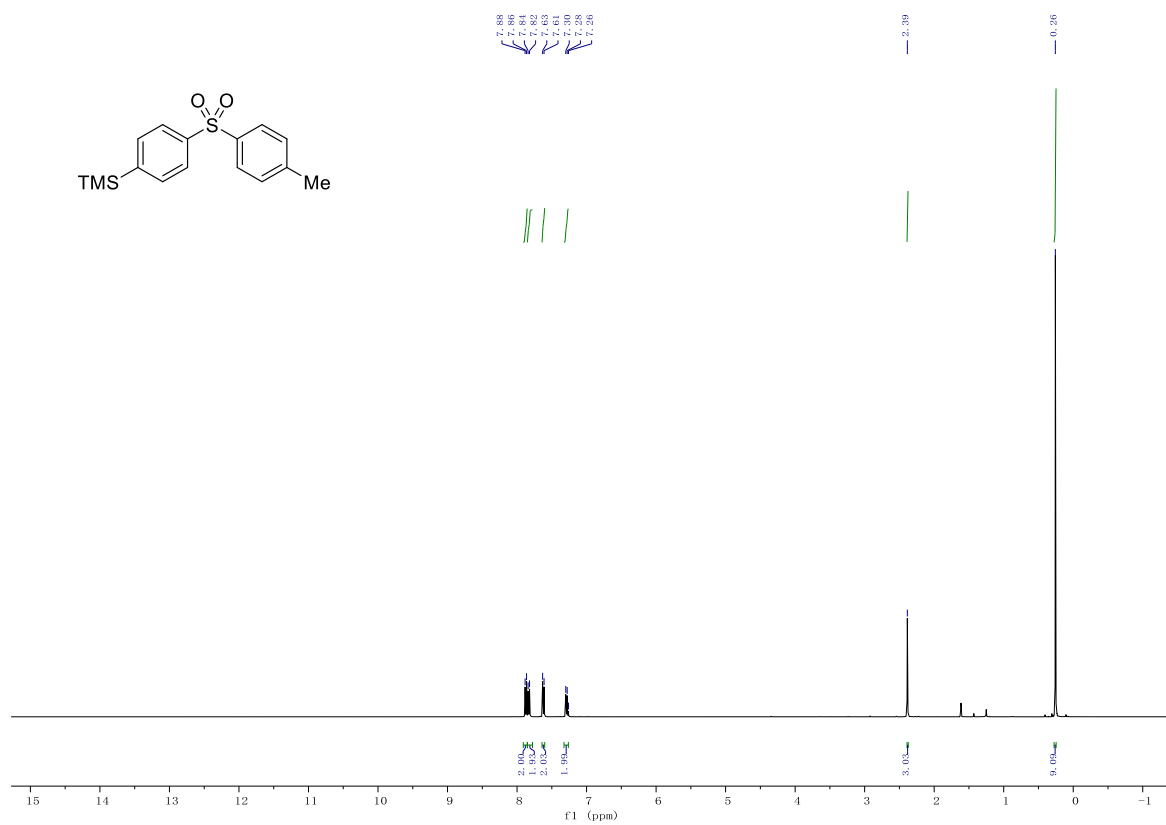
¹H NMR and ¹³C NMR spectra of 1-(benzyloxy)-4-tosylbenzene 36j



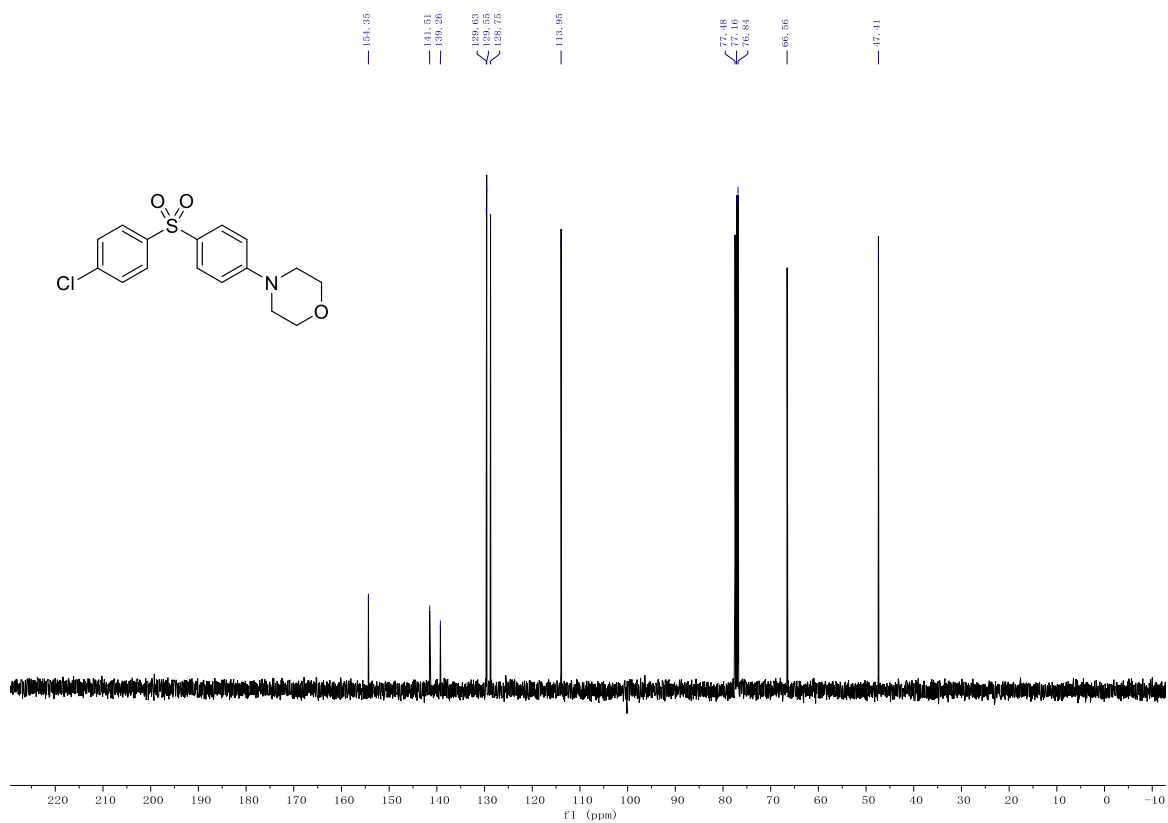
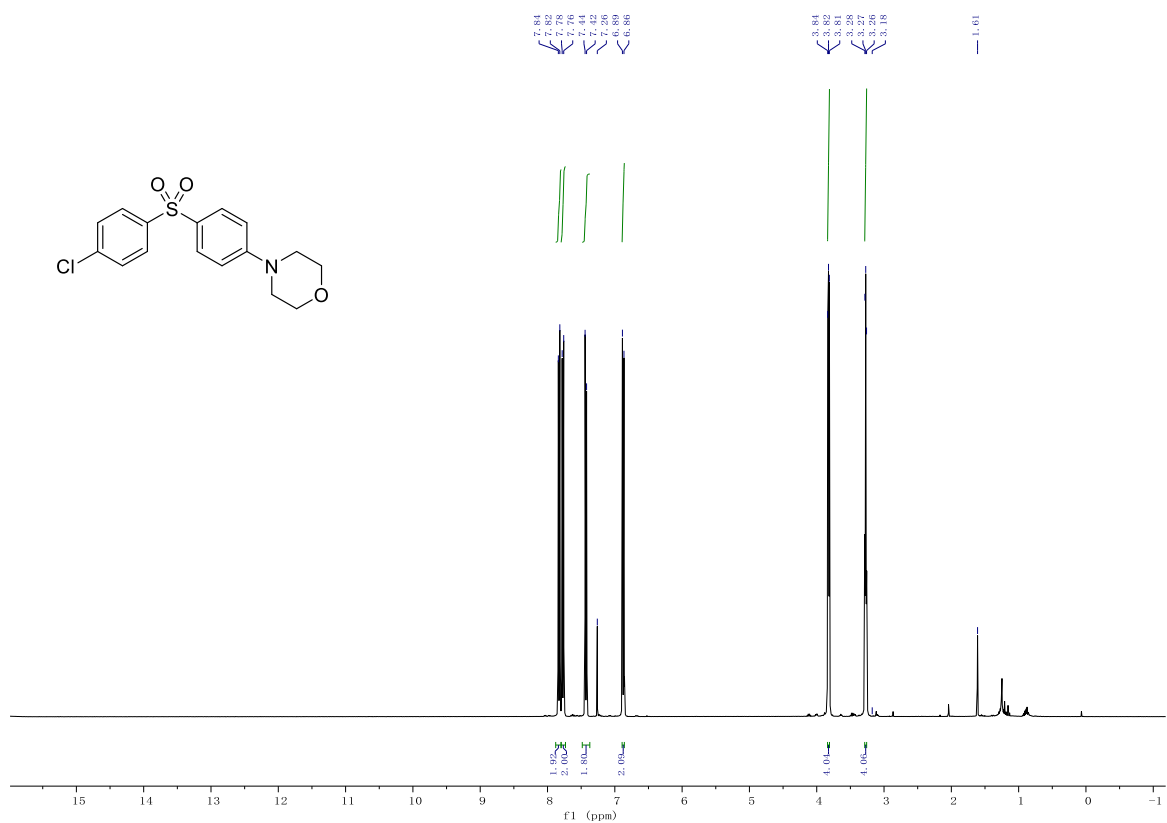
¹H NMR and ¹³C NMR spectra of 1-methoxy-4-[(4-tosylphenoxy)methyl]benzene 36k



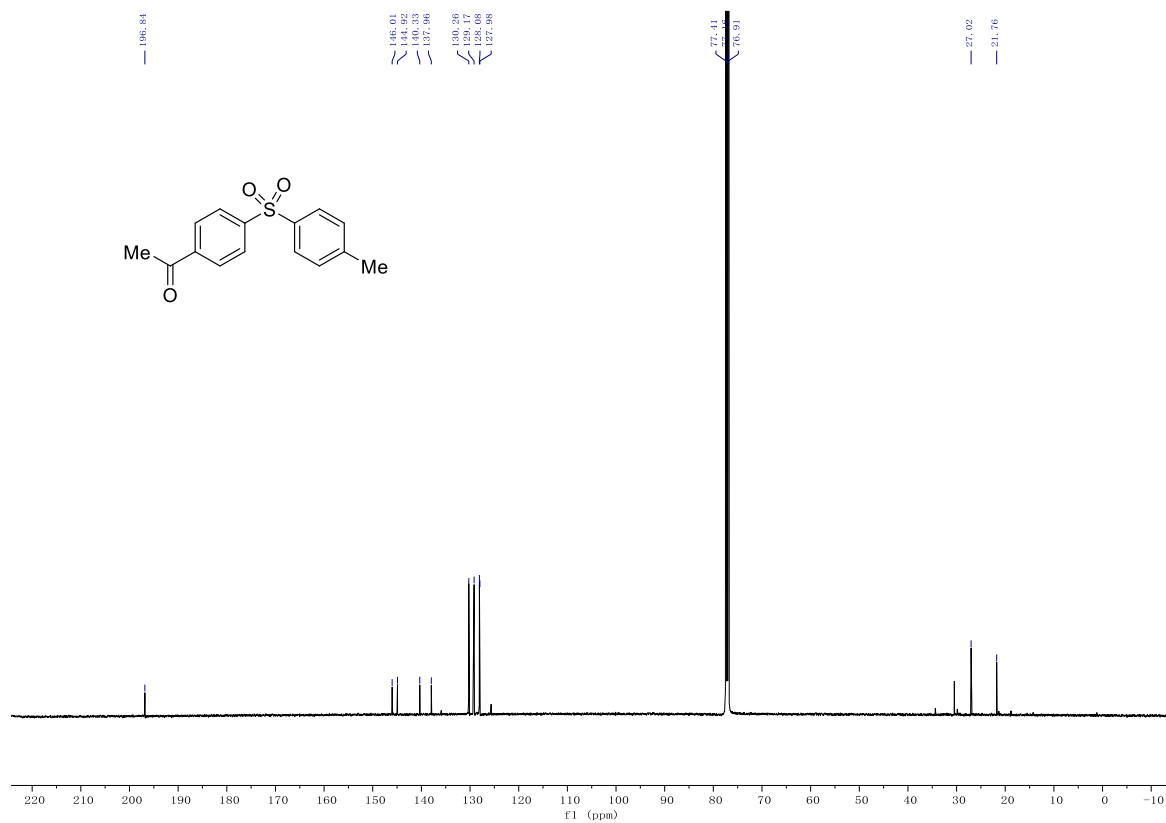
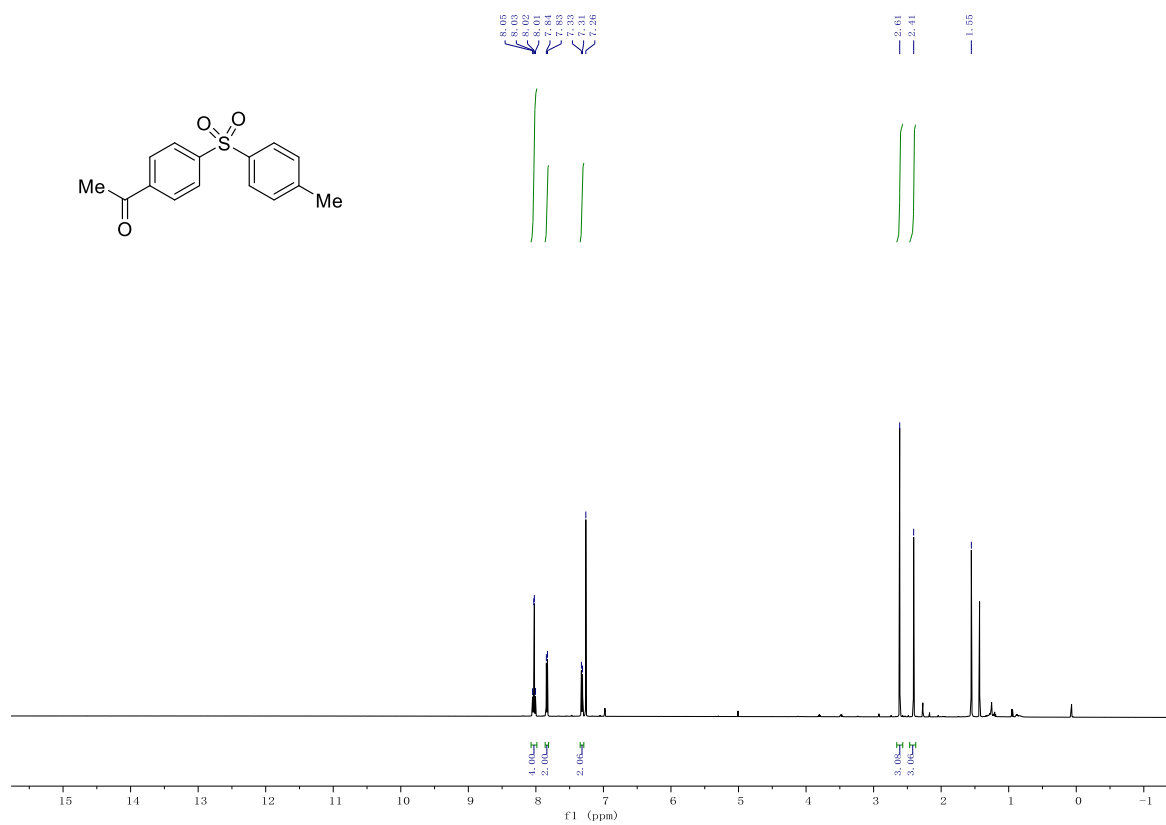
¹H NMR and ¹³C NMR spectra of 1-chloro-4-[(4-tosylphenoxy)methyl]benzene **361**



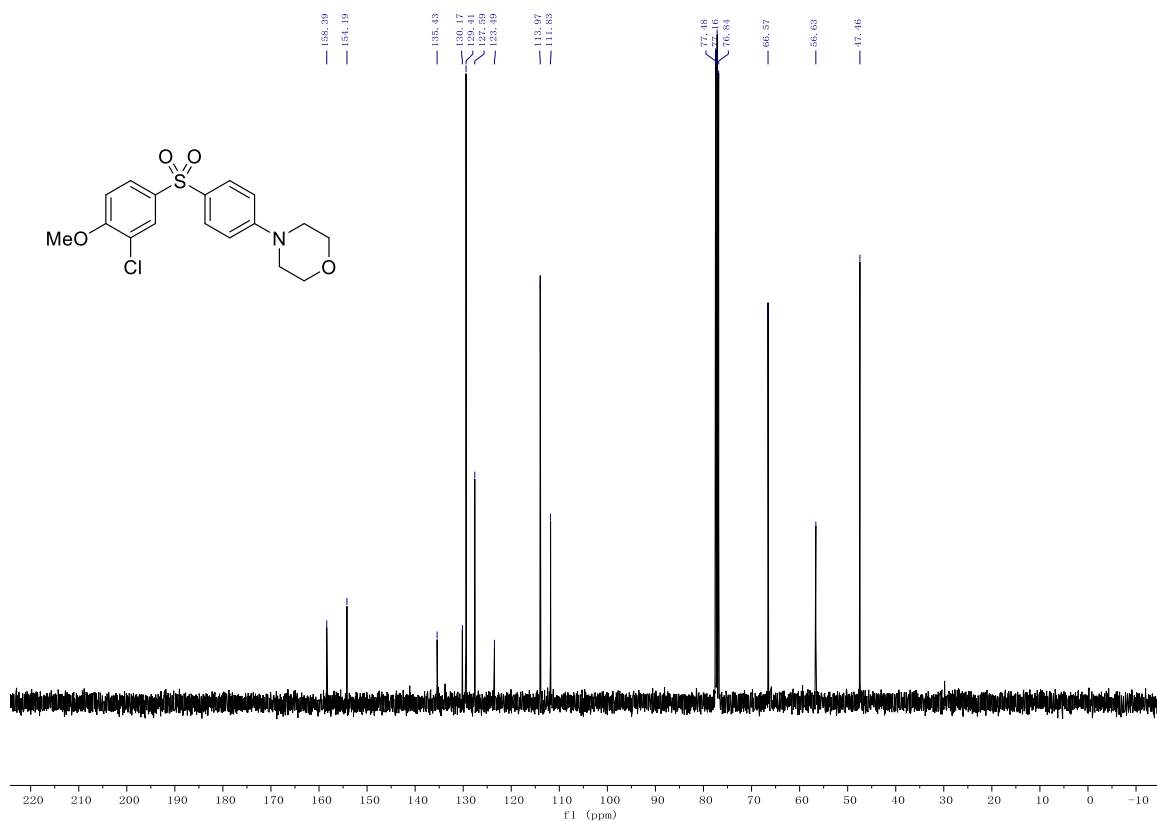
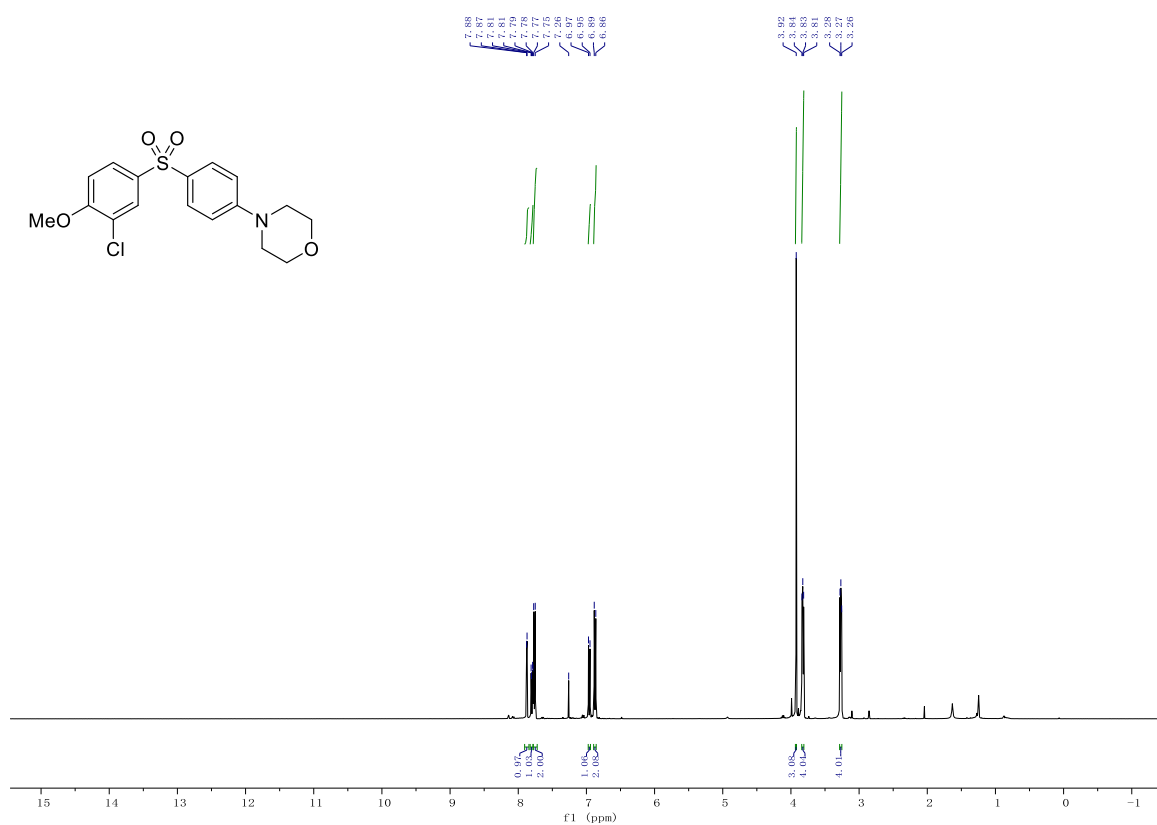
¹H NMR and ¹³C NMR spectra of trimethyl(4-tosylphenyl)silane 36m



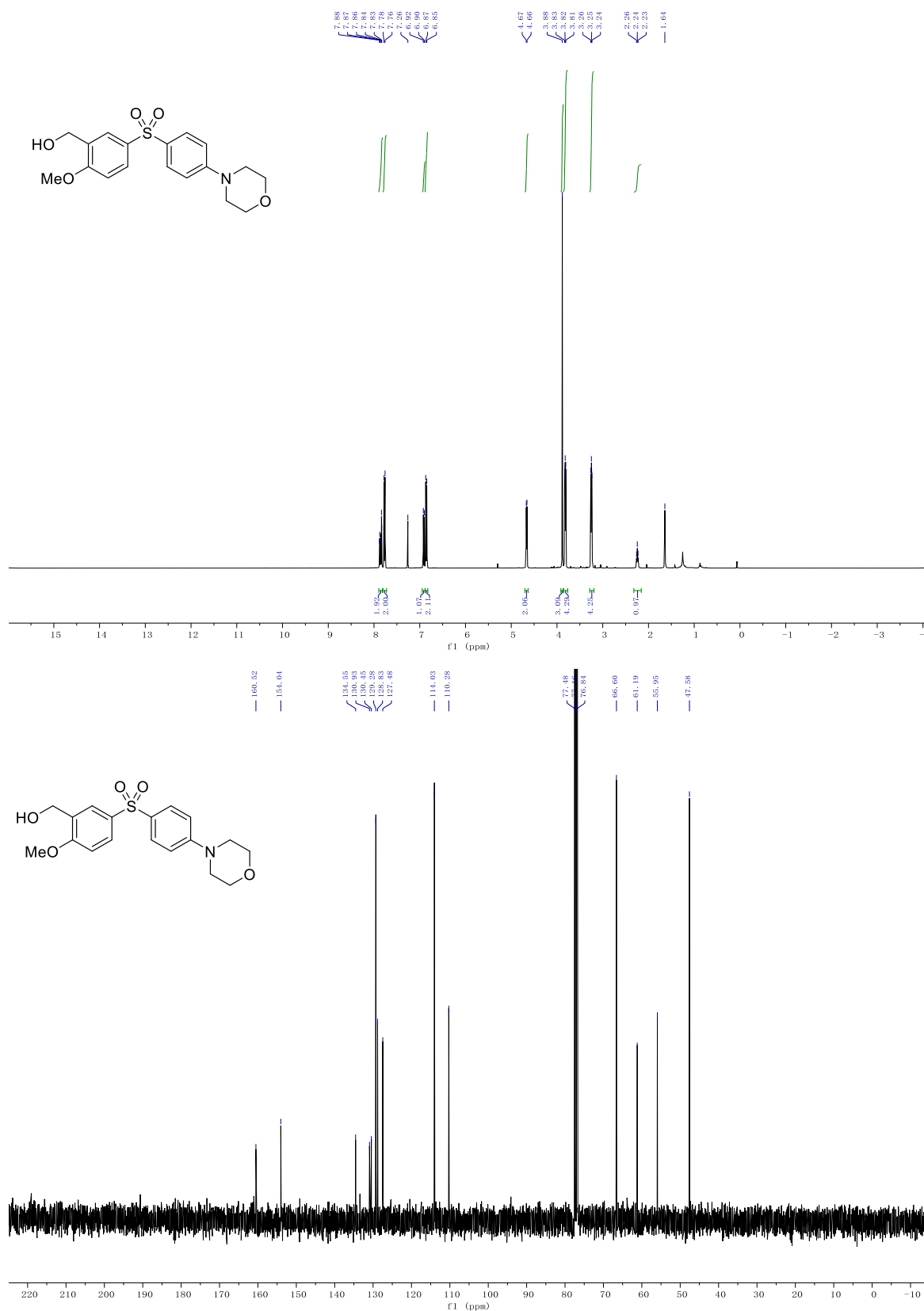
¹H NMR and ¹³C NMR spectra of 4-{4-[(4-chlorophenyl)sulfonyl]phenyl}morpholine 36n



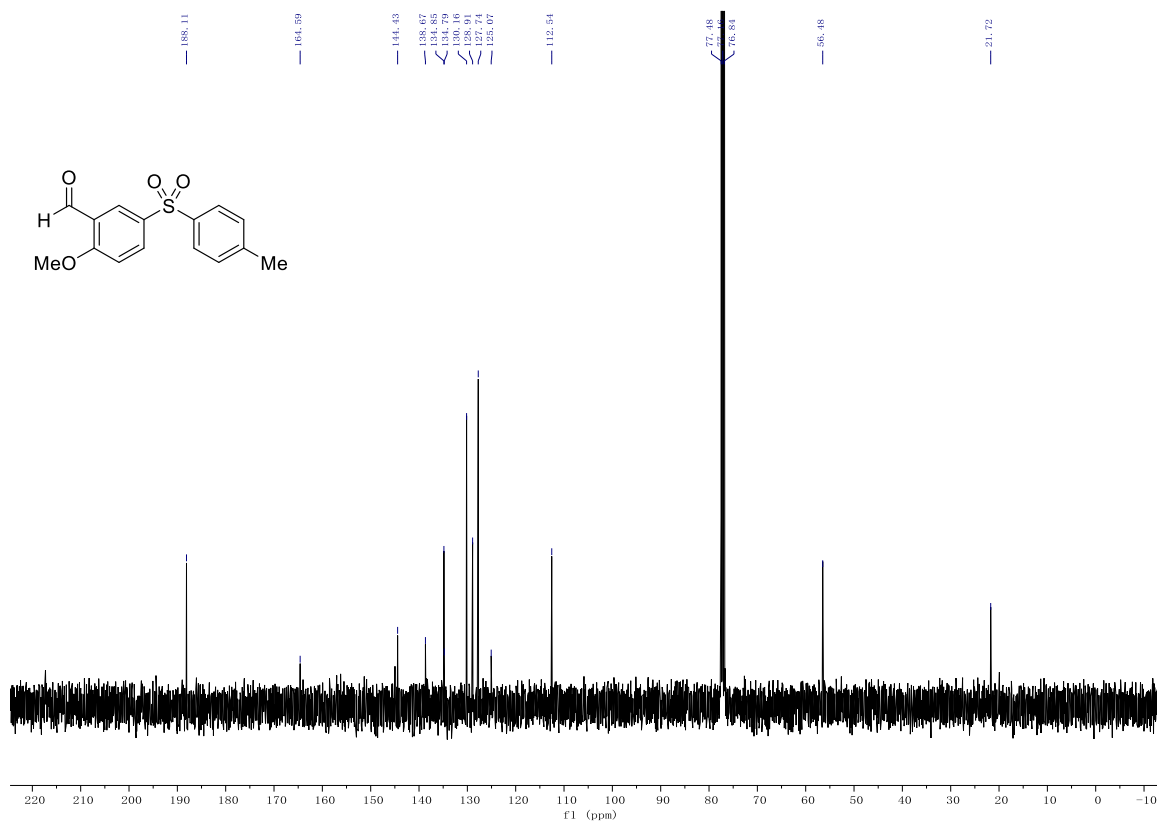
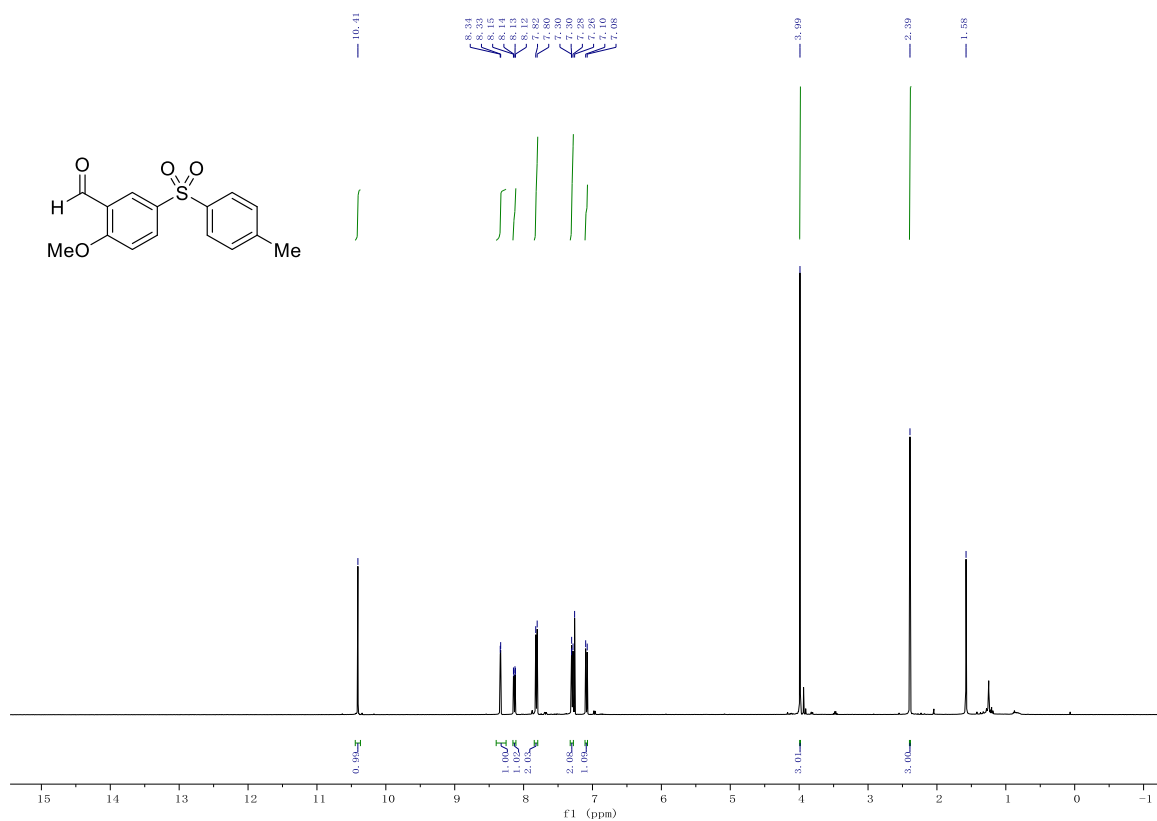
¹H NMR and ¹³C NMR spectra of **1-(4-tosylphenyl)ethan-1-one 360**



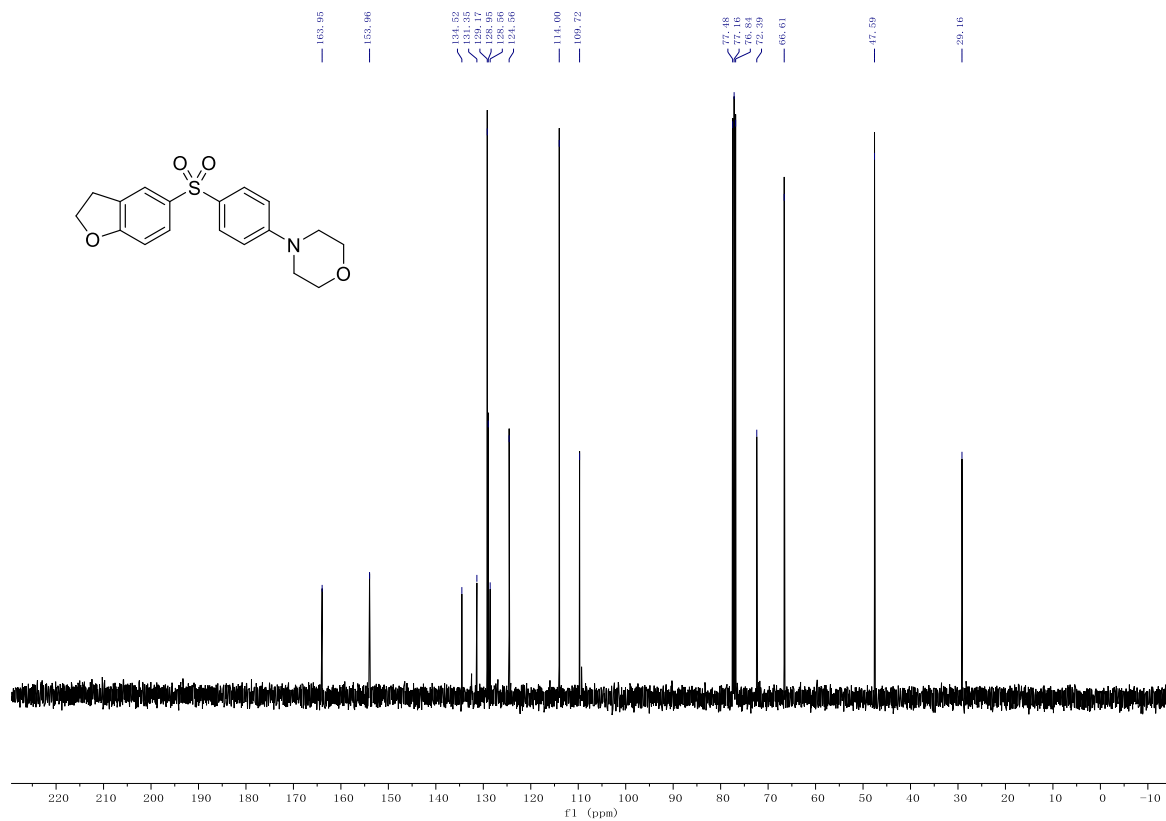
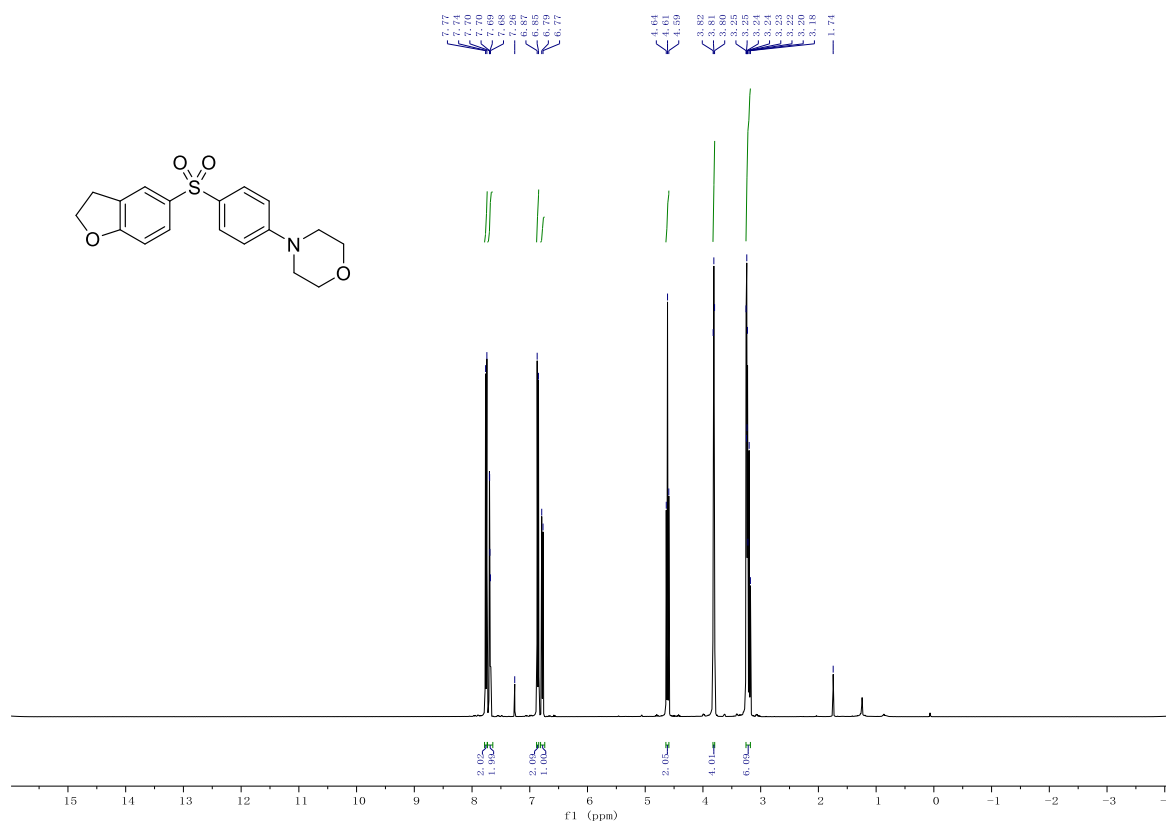
¹H NMR and ¹³C NMR spectra of 4-{4-[(3-chloro-4-methoxyphenyl)sulfonyl]phenyl}morpholine 36p



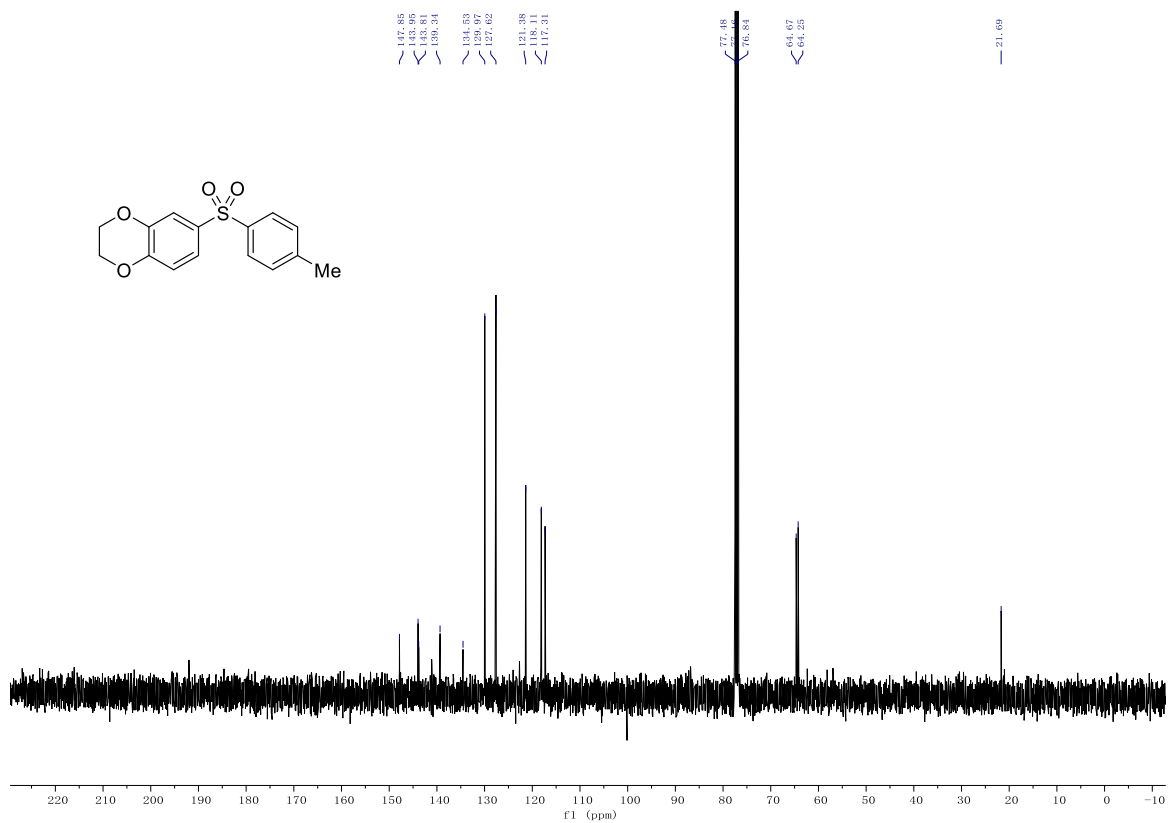
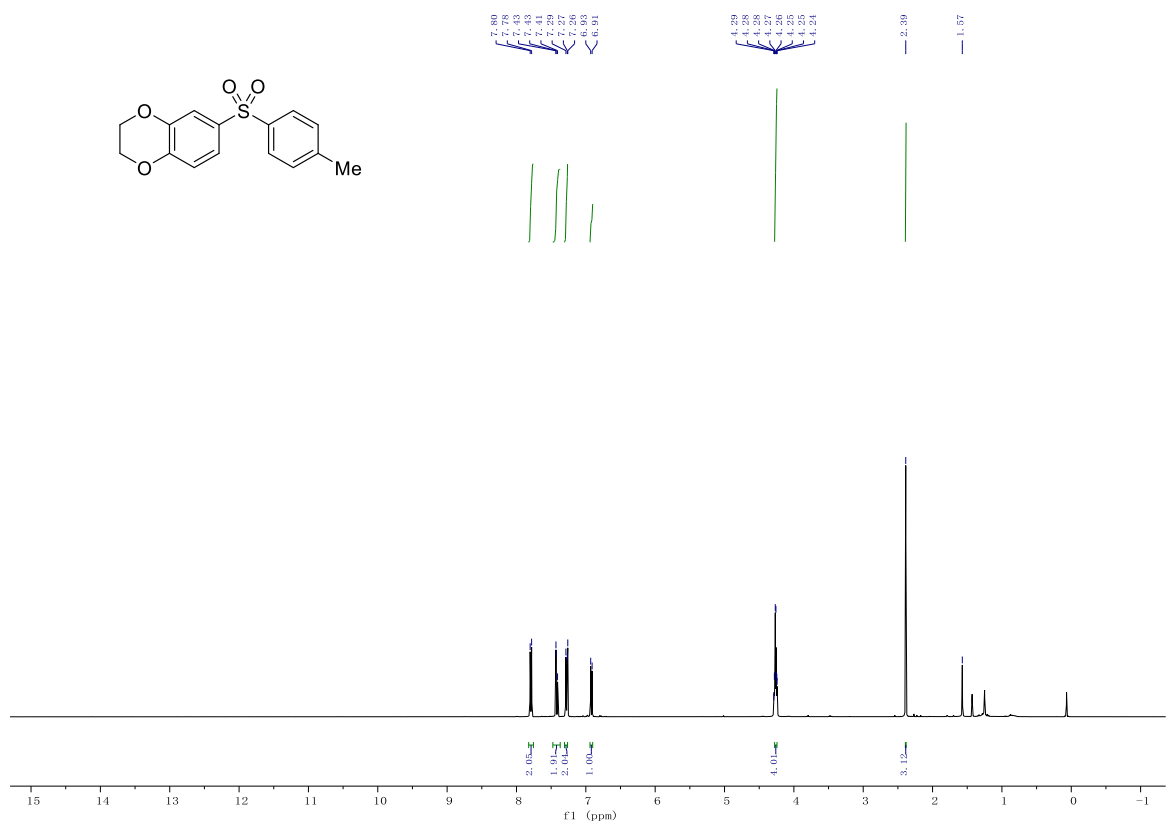
¹H NMR and ¹³C NMR spectra of {2-methoxy-5-[(4-morpholinophenyl)sulfonyl]phenyl}methanol 36q



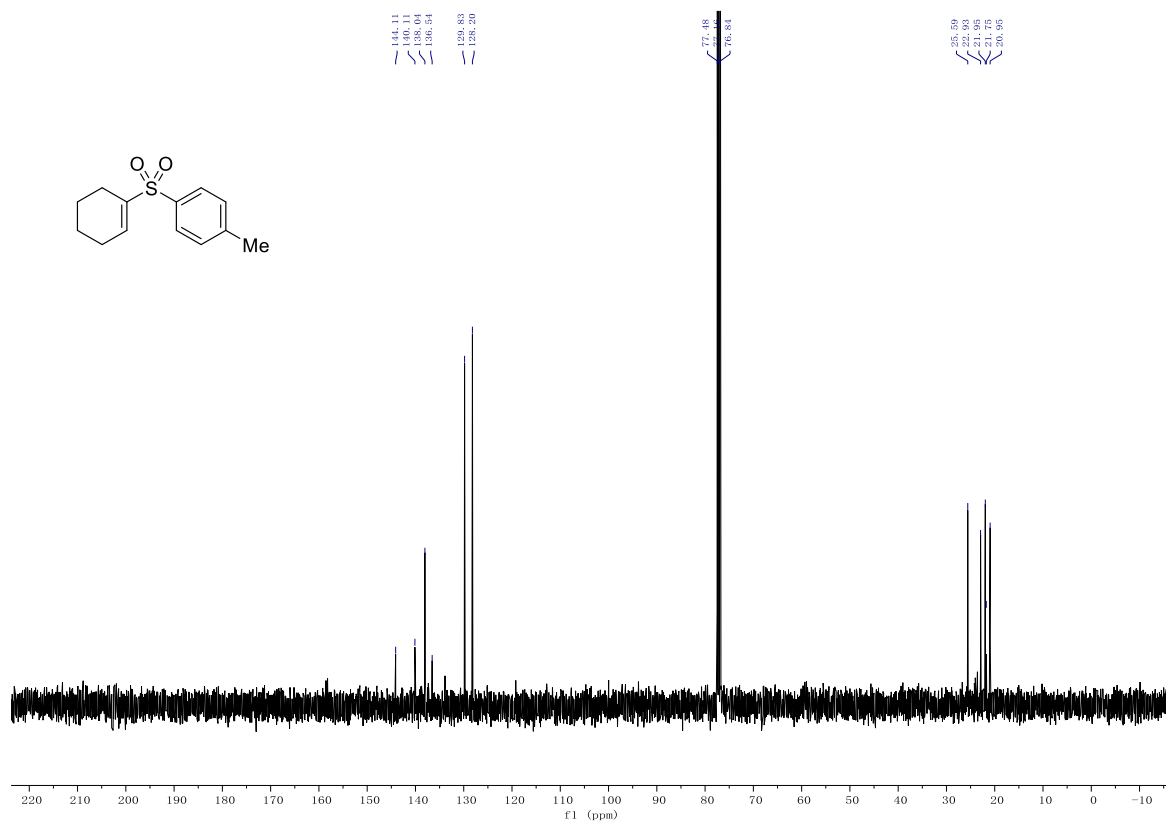
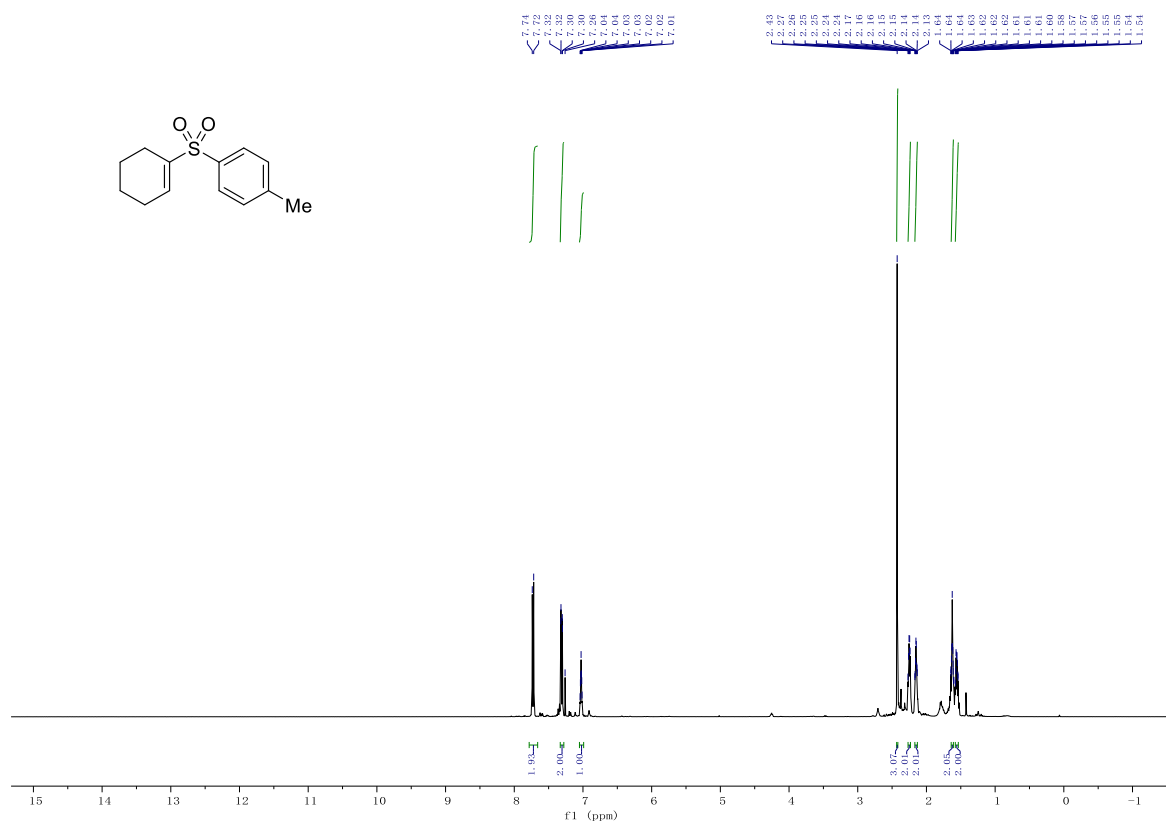
¹H NMR and ¹³C NMR spectra of 2-methoxy-5-tosylbenzaldehyde 36r



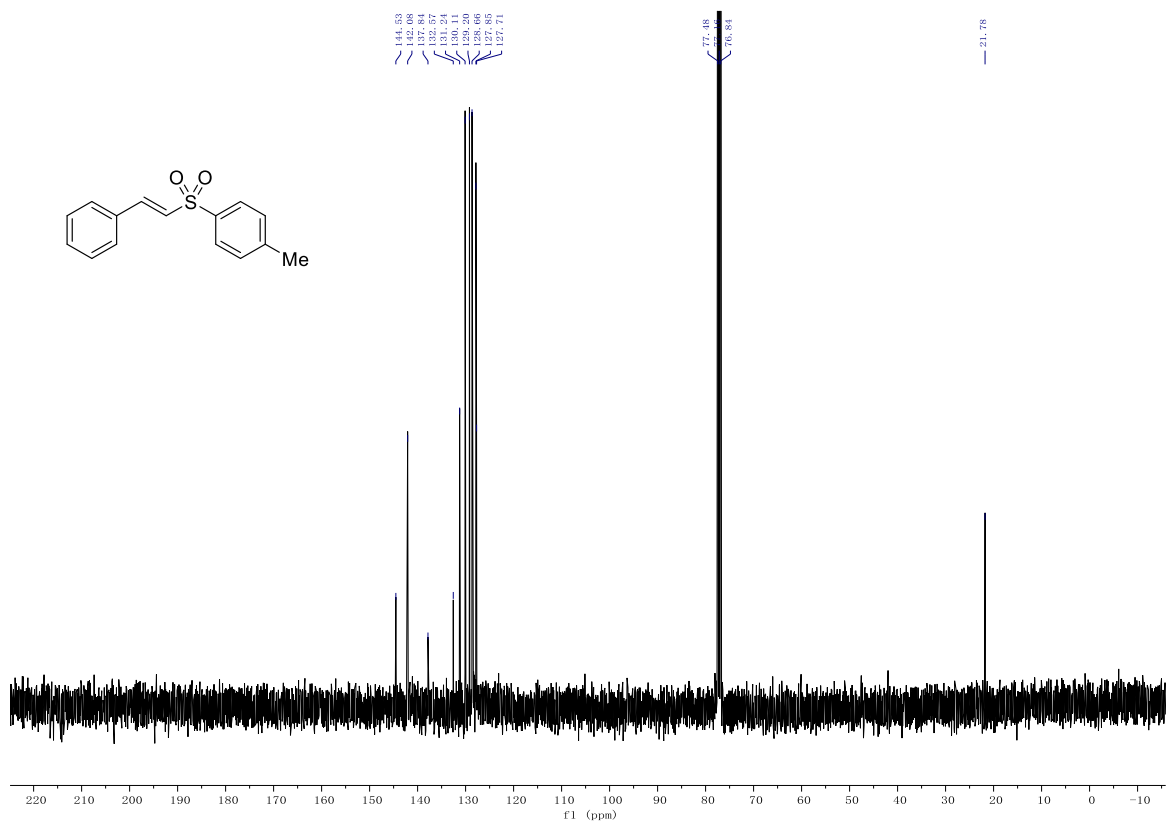
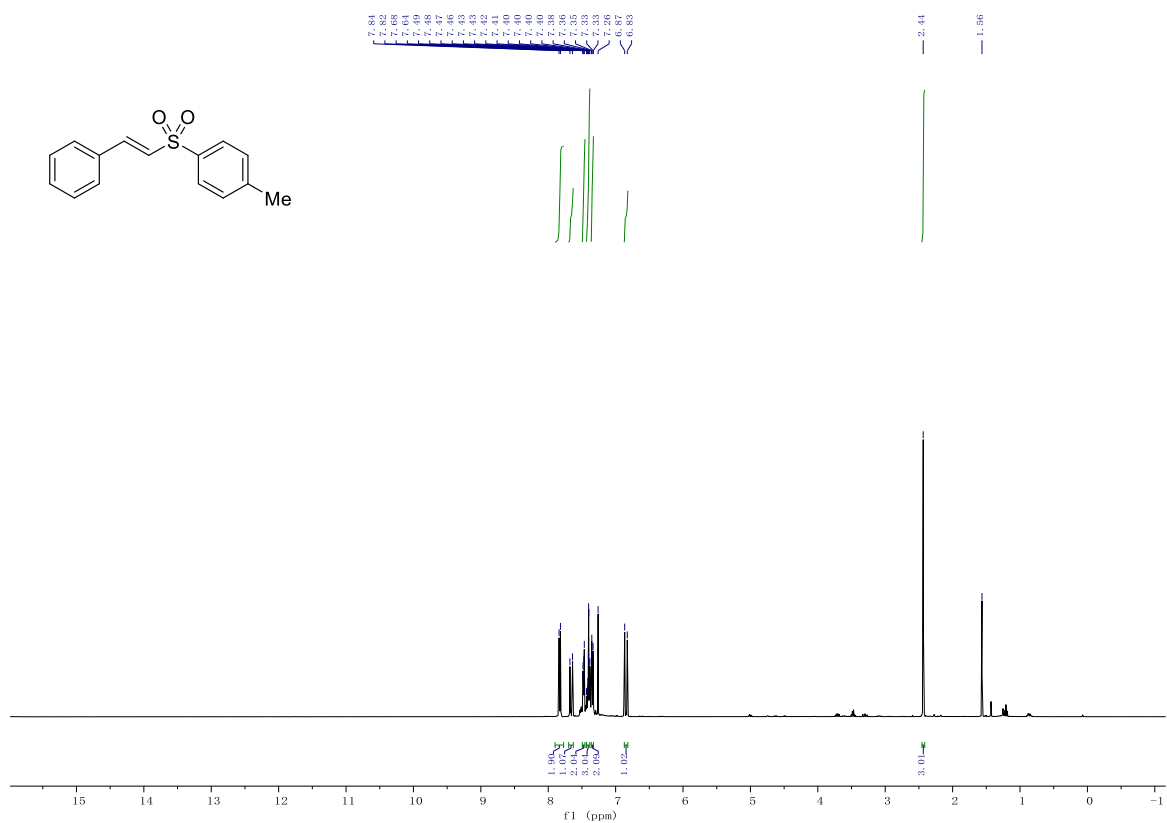
¹H NMR and ¹³C NMR spectra of 4-{4-[(2,3-Dihydrobenzofuran-5-yl)sulfonyl]phenyl}morpholine 36s



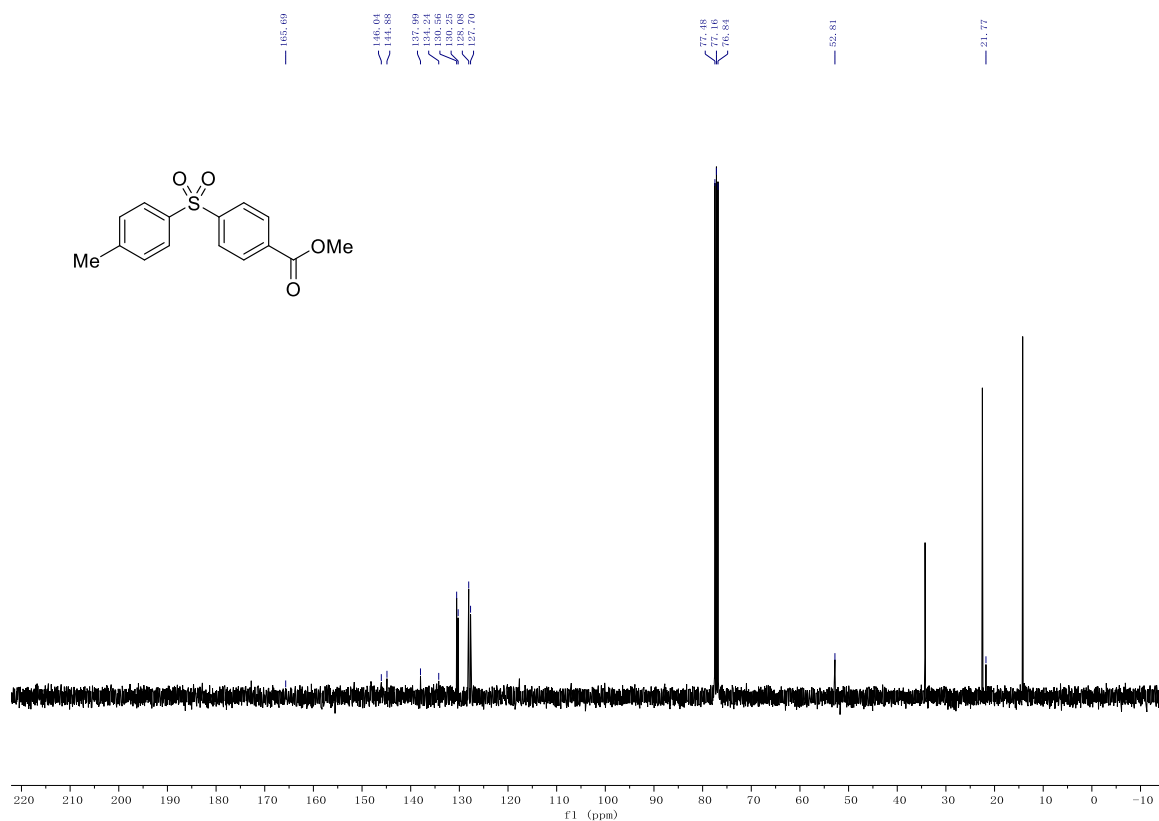
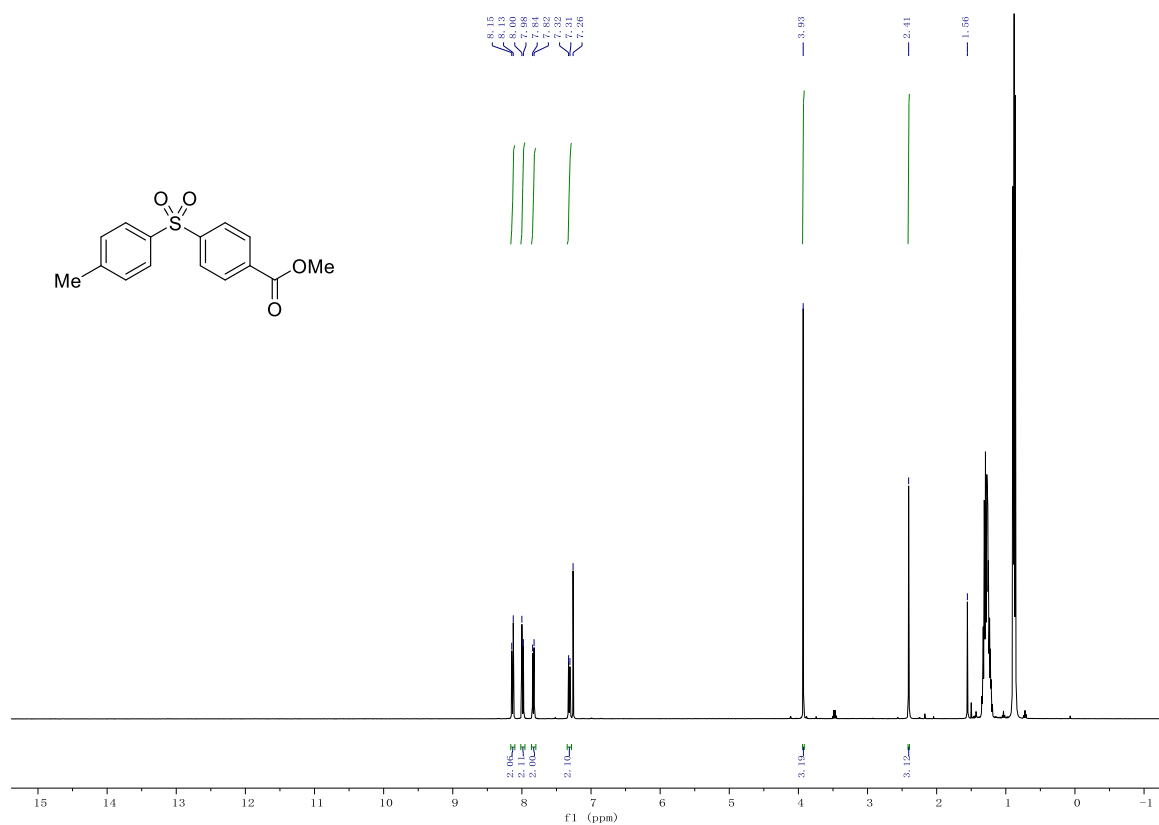
¹H NMR and ¹³C NMR spectra of 6-tosyl-2,3-dihydrobenzo-1,4-dioxine 36t



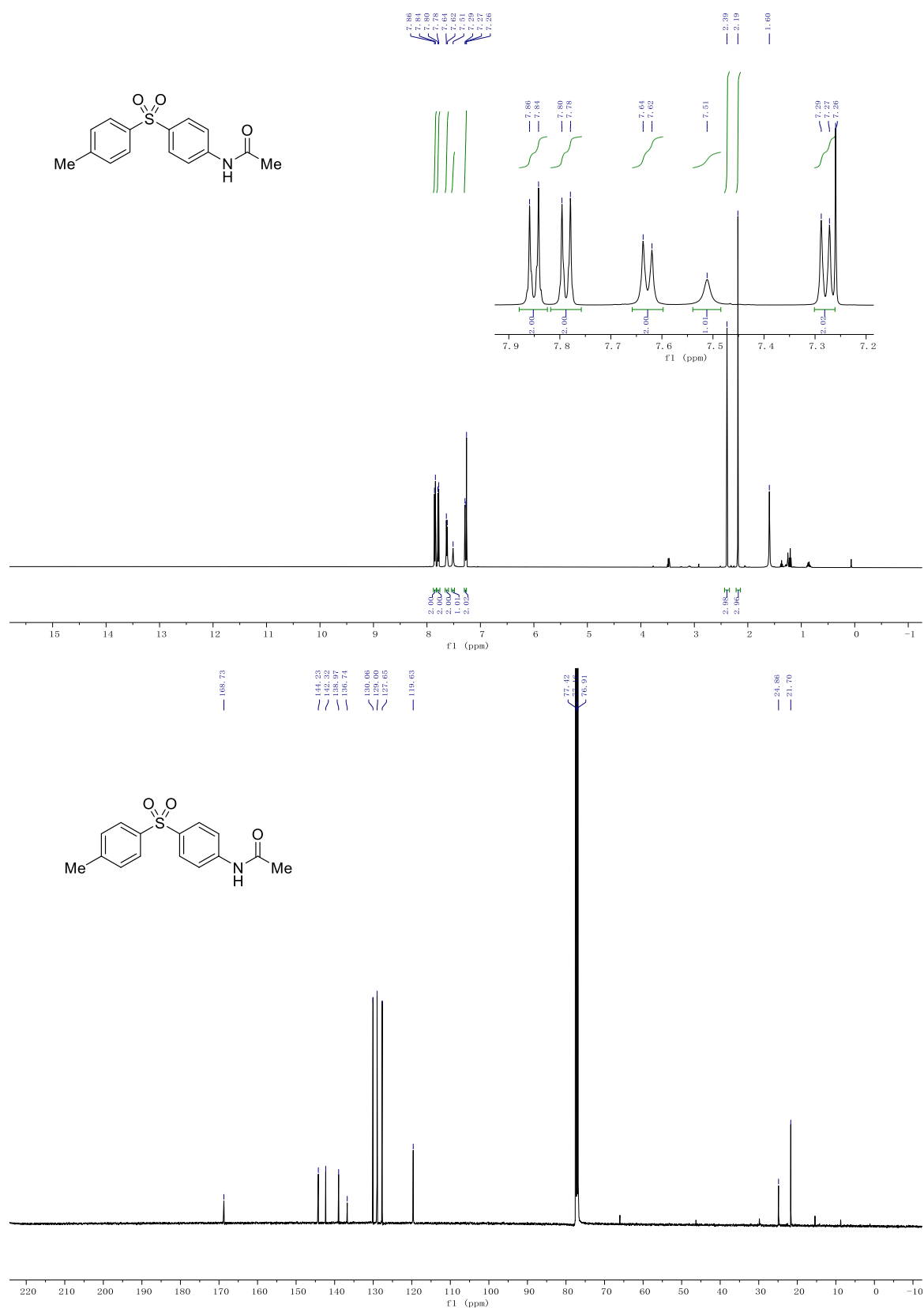
¹H NMR and ¹³C NMR spectra of 1-(cyclohex-1-en-1-ylsulfonyl)-4-methylbenzene 36u



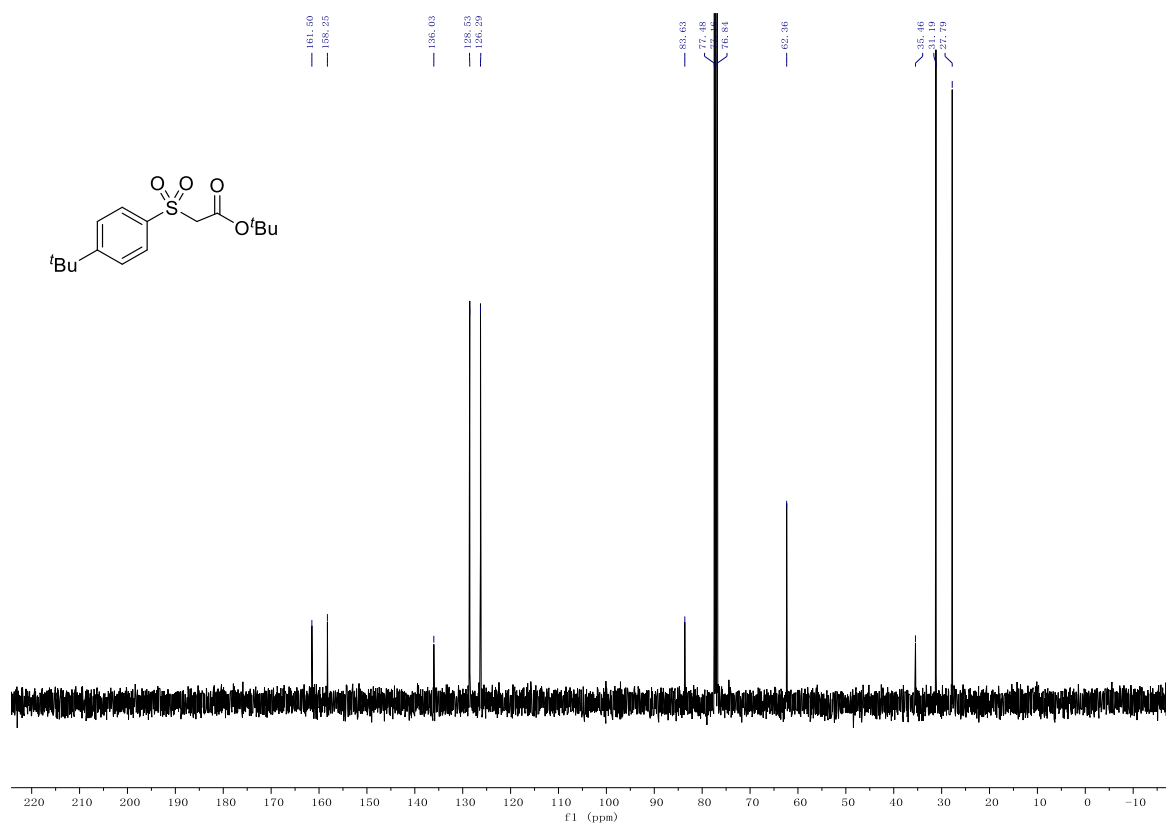
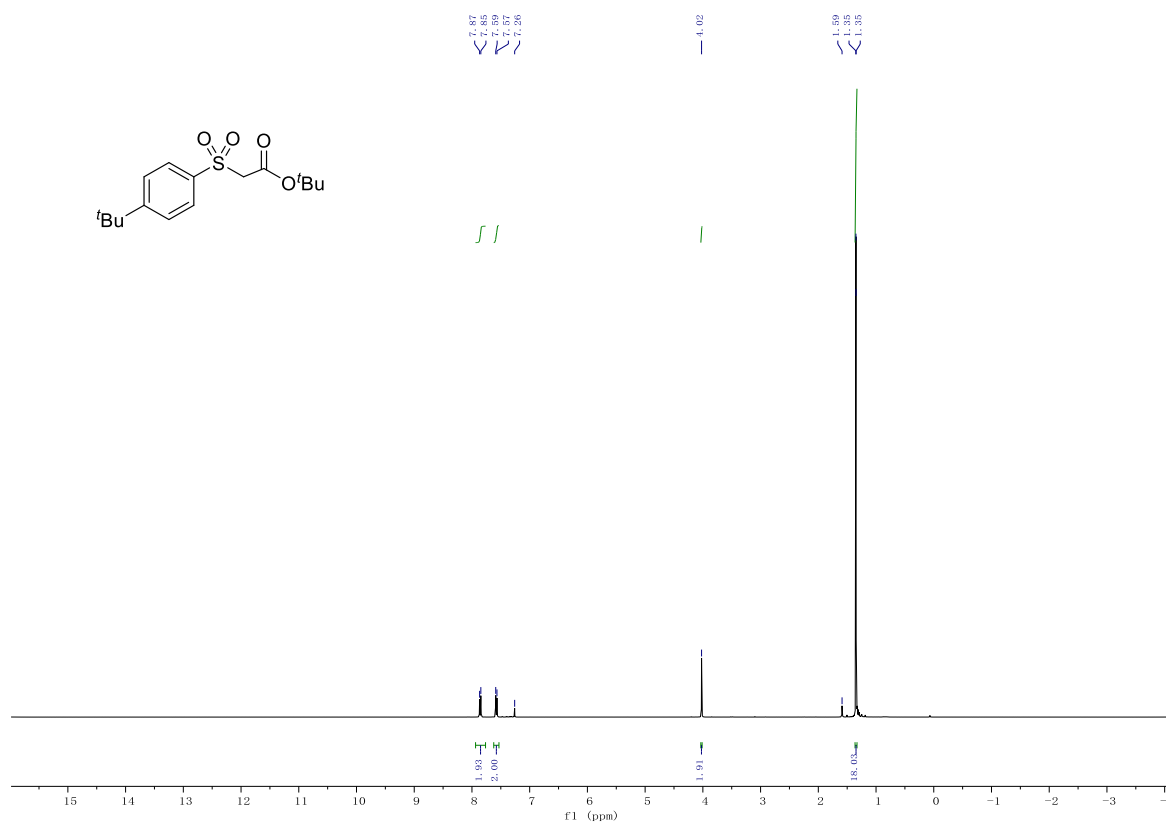
¹H NMR and ¹³C NMR spectra of *trans*-1-methyl-4-(styrylsulfonyl)benzene 36v



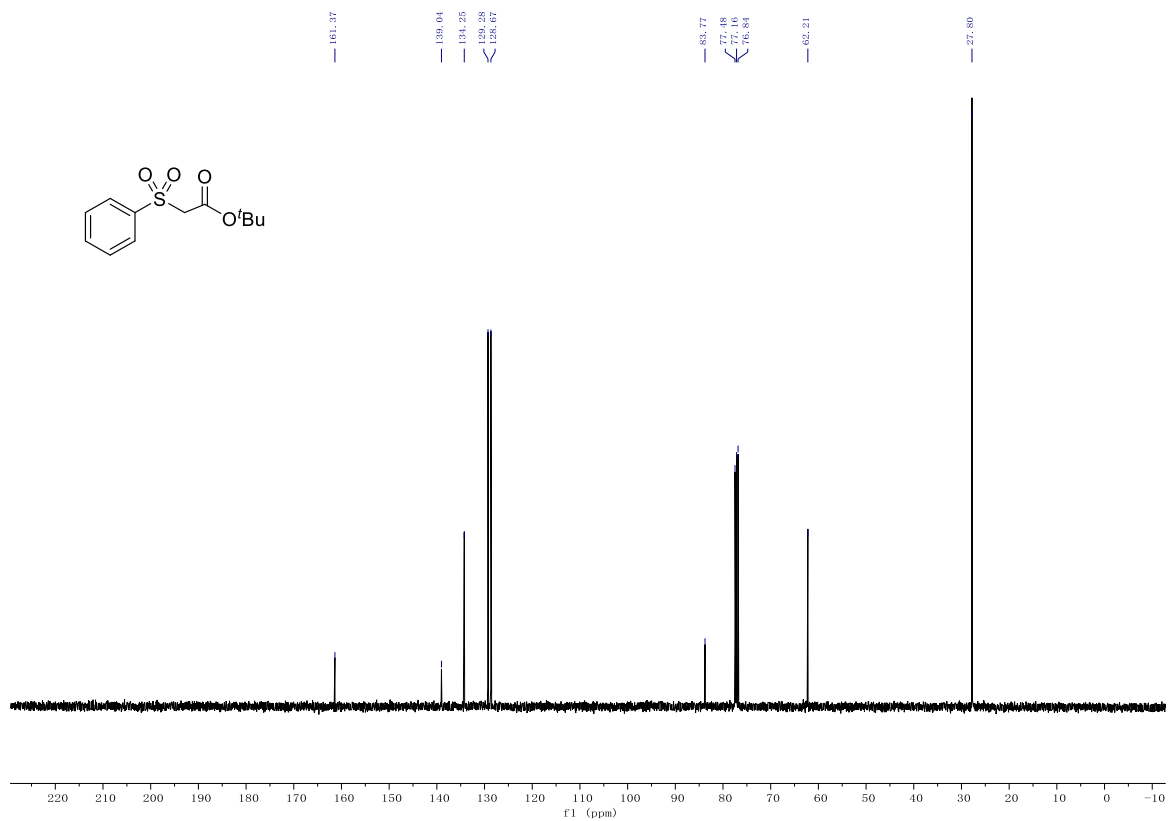
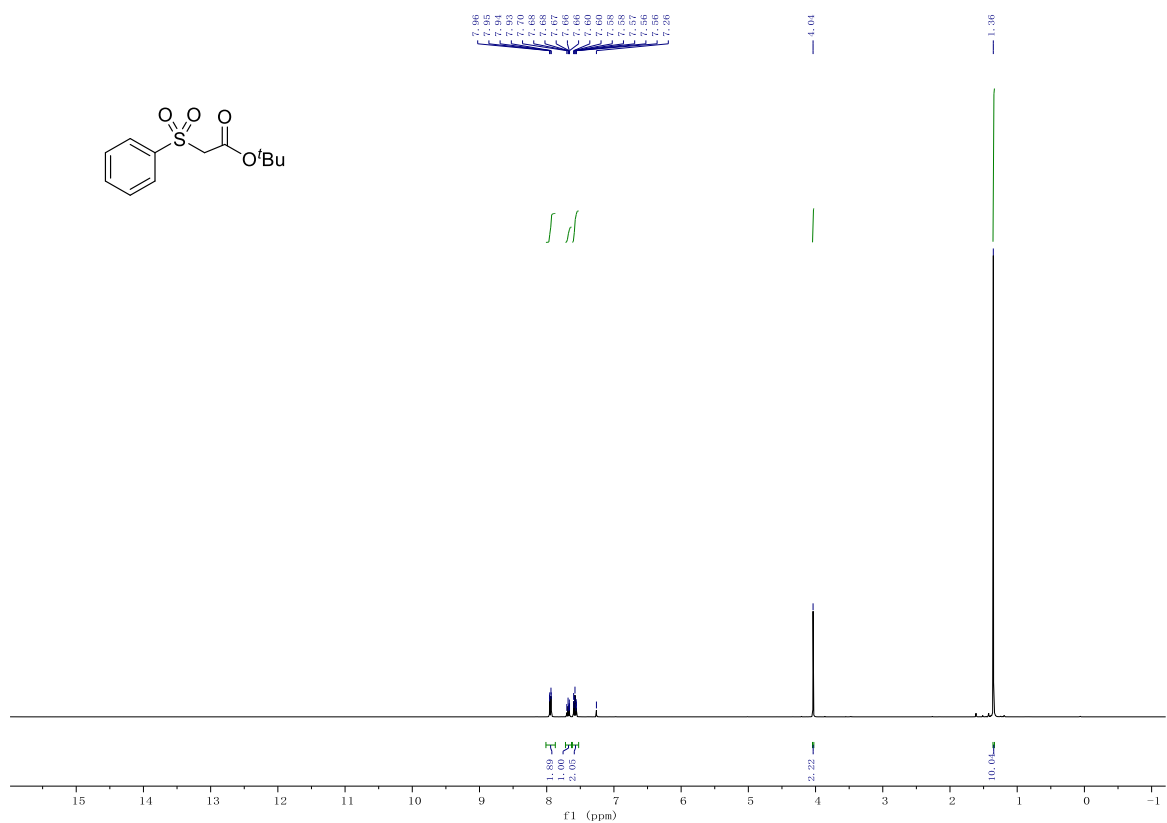
¹H NMR and ¹³C NMR spectra of methyl 4-tosylbenzoate 36aa



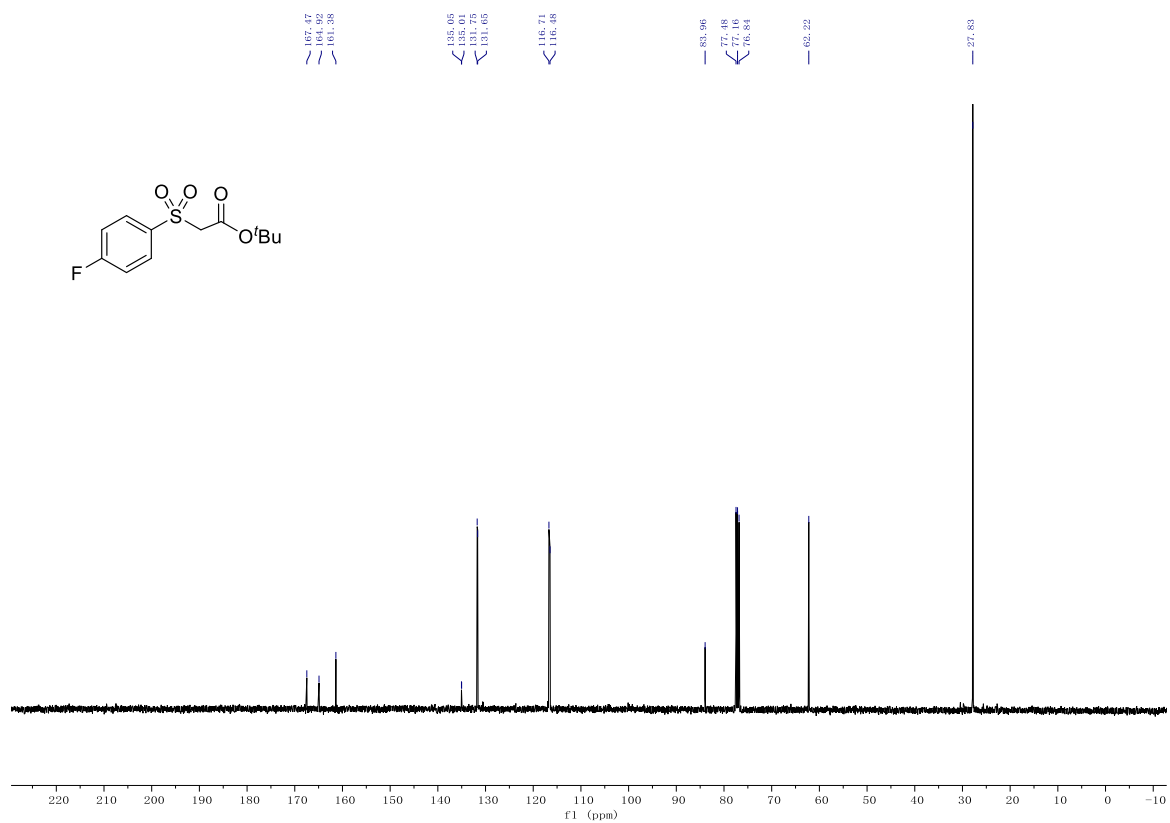
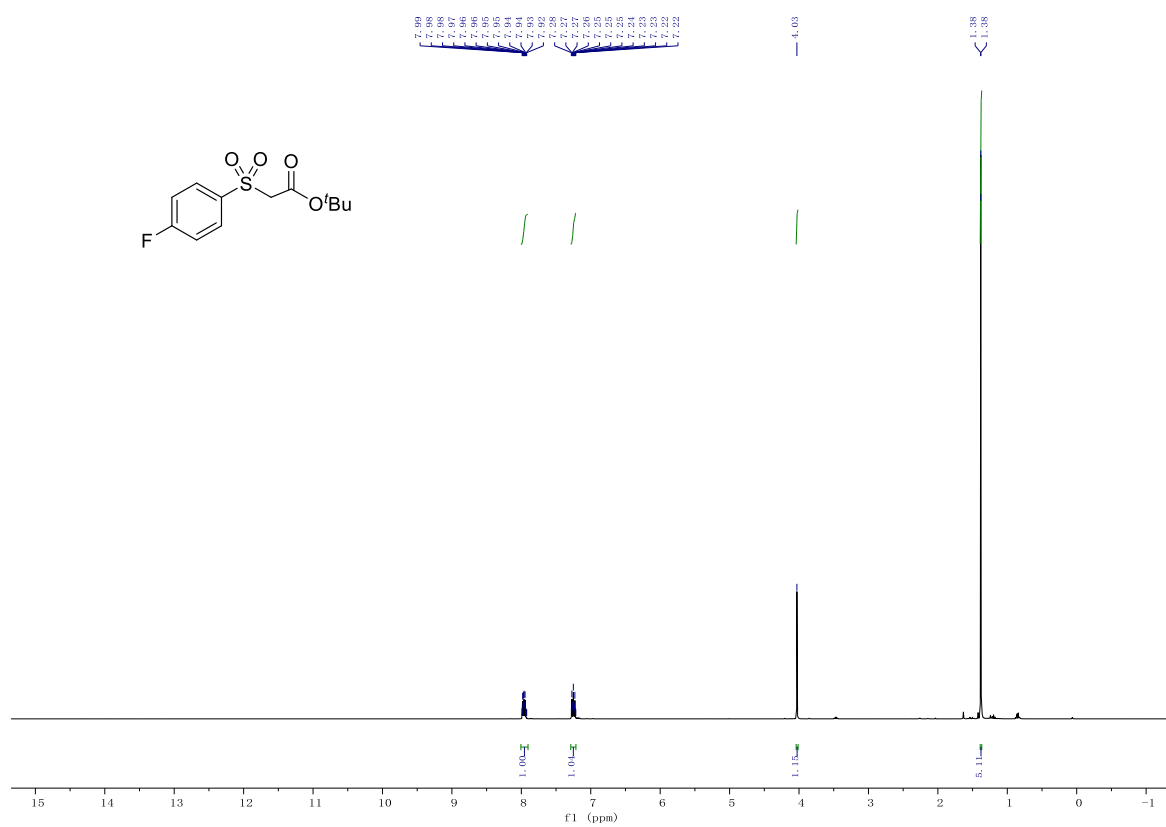
¹H NMR and ¹³C NMR spectra of *N*-(4-tosylphenyl)acetamide 36ab



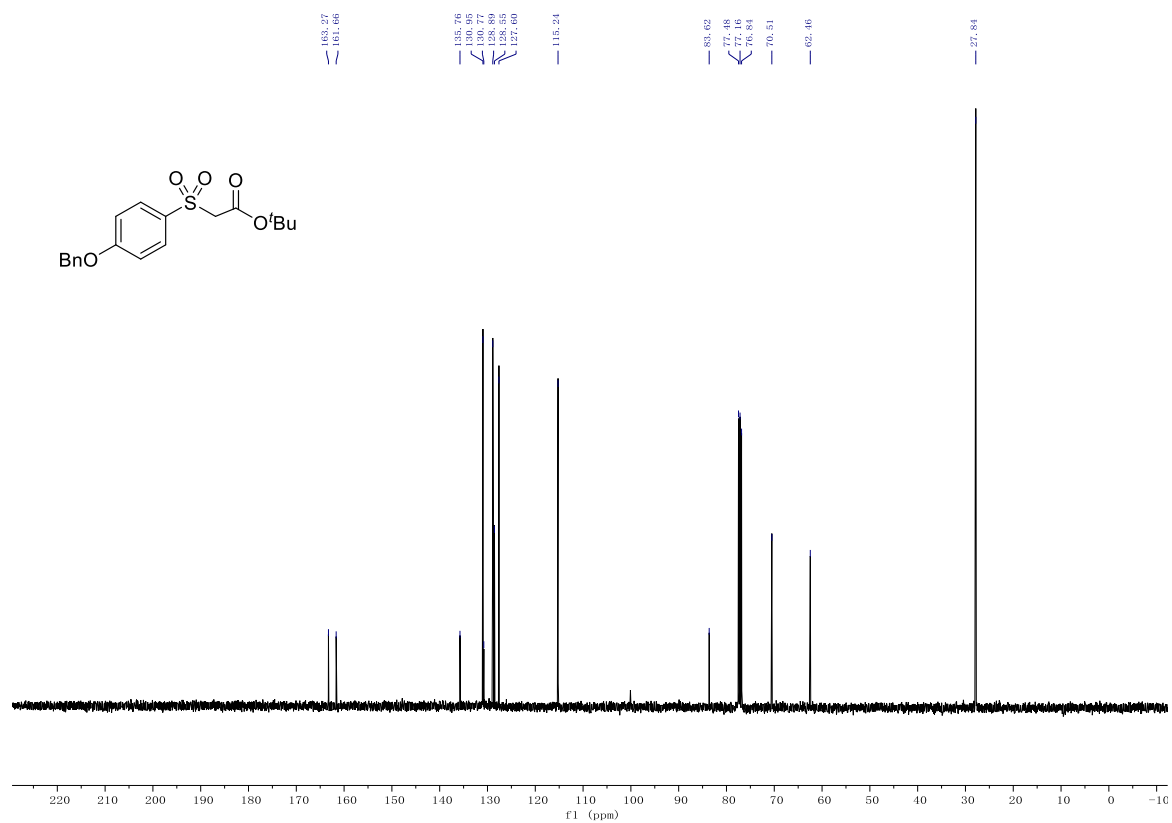
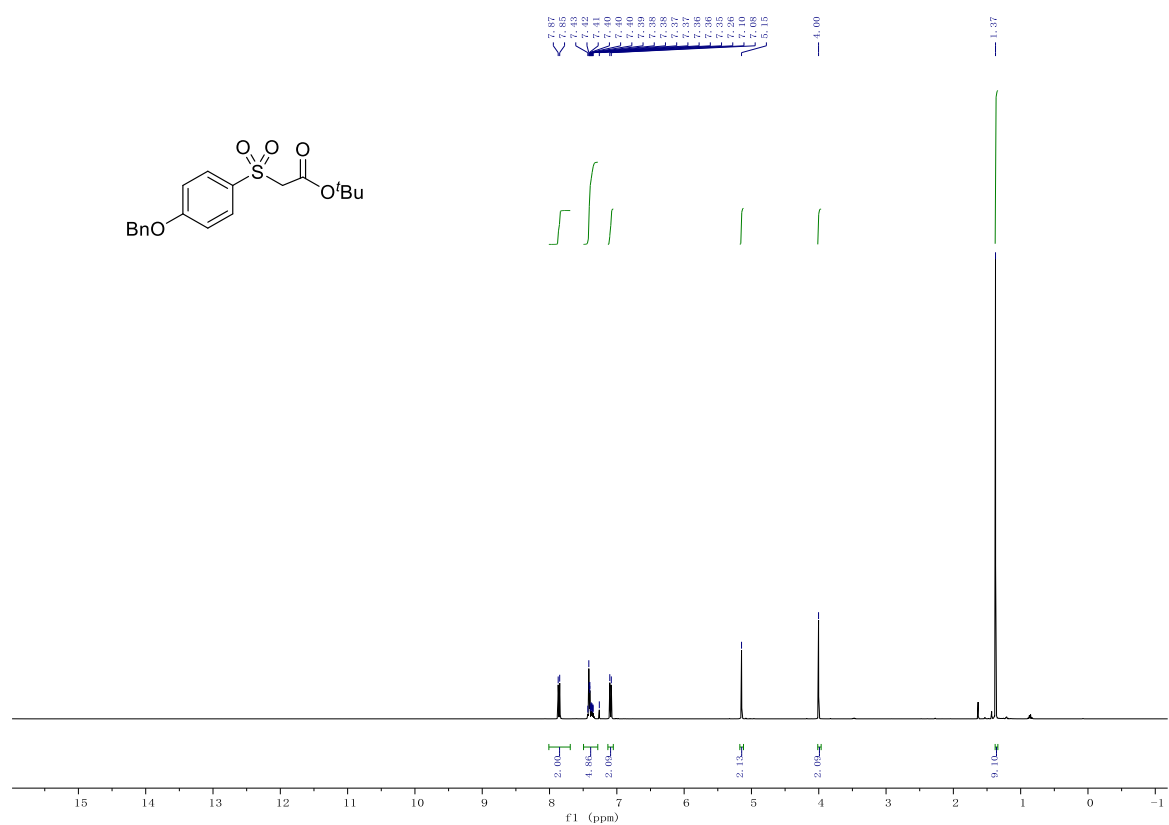
¹H NMR and ¹³C NMR spectra of 4-*tert*-butyl 2-([4-(*tert*-butyl)phenyl]sulfonyl)acetate 40a



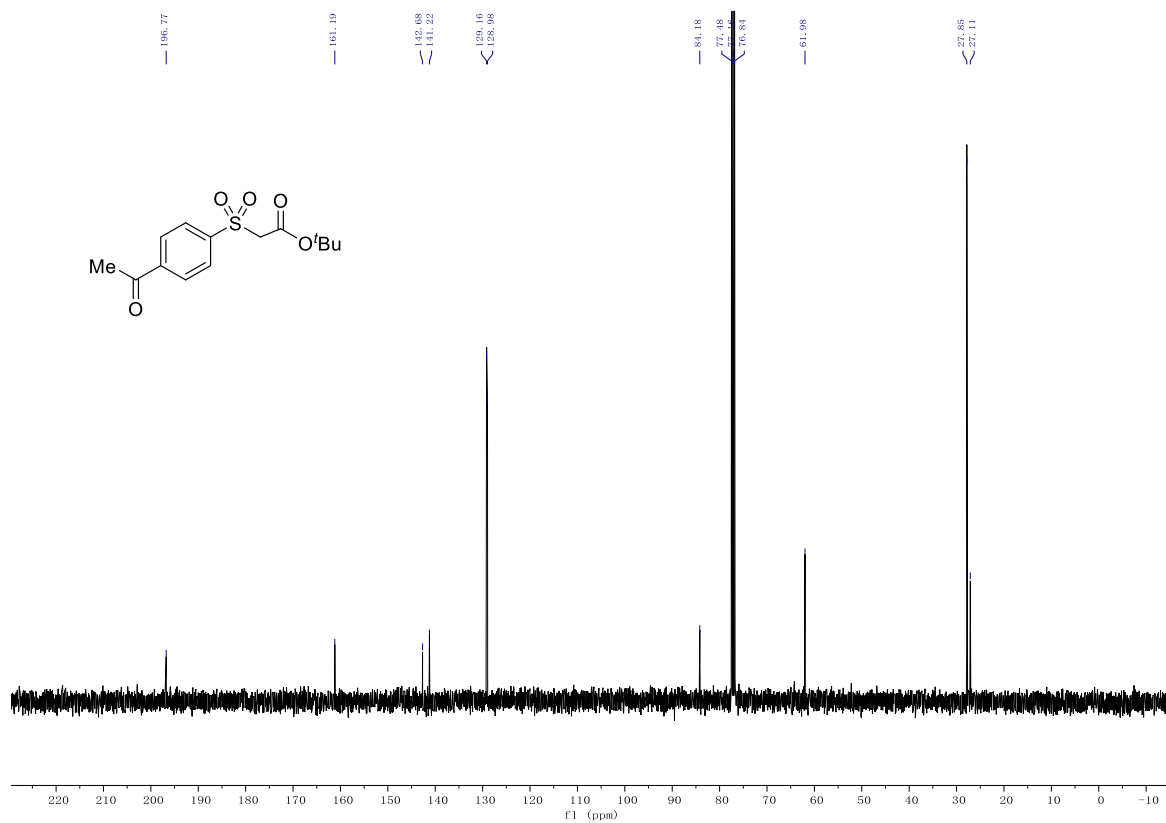
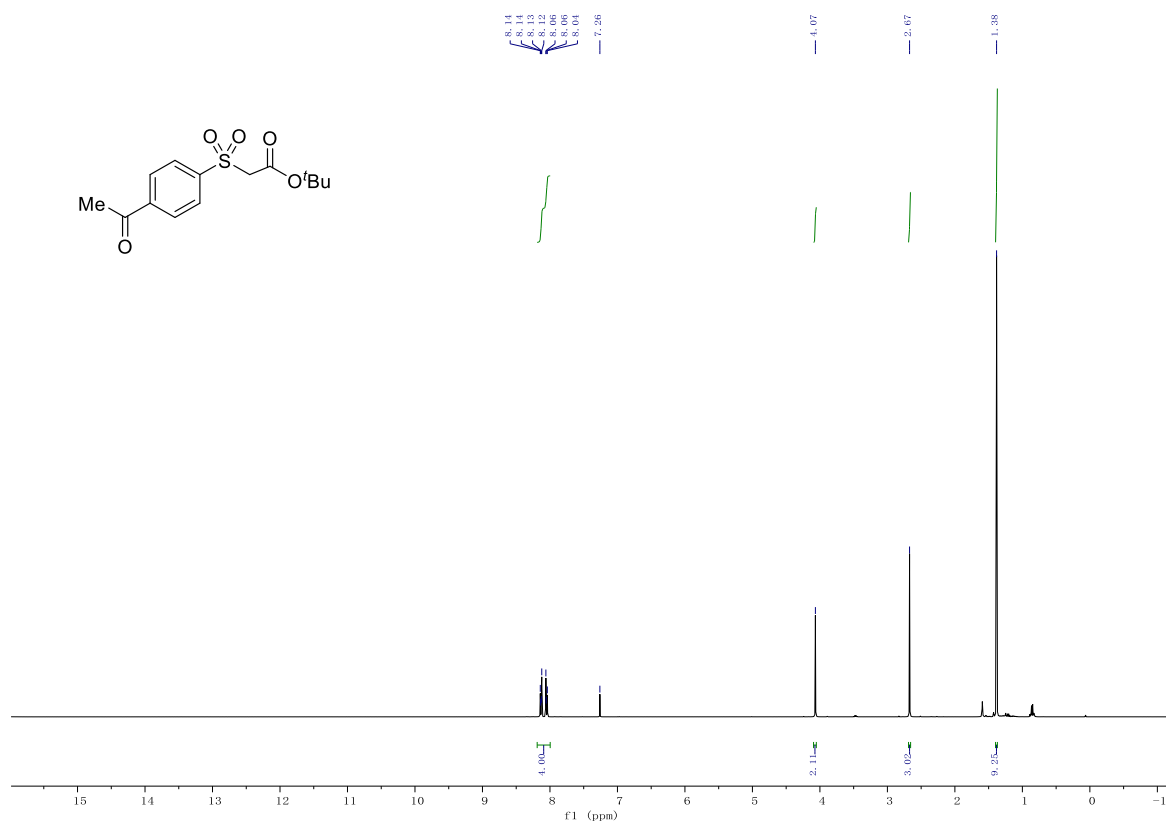
¹H NMR and ¹³C NMR spectra of *tert*-butyl 2-(phenylsulfonyl)acetate 40b



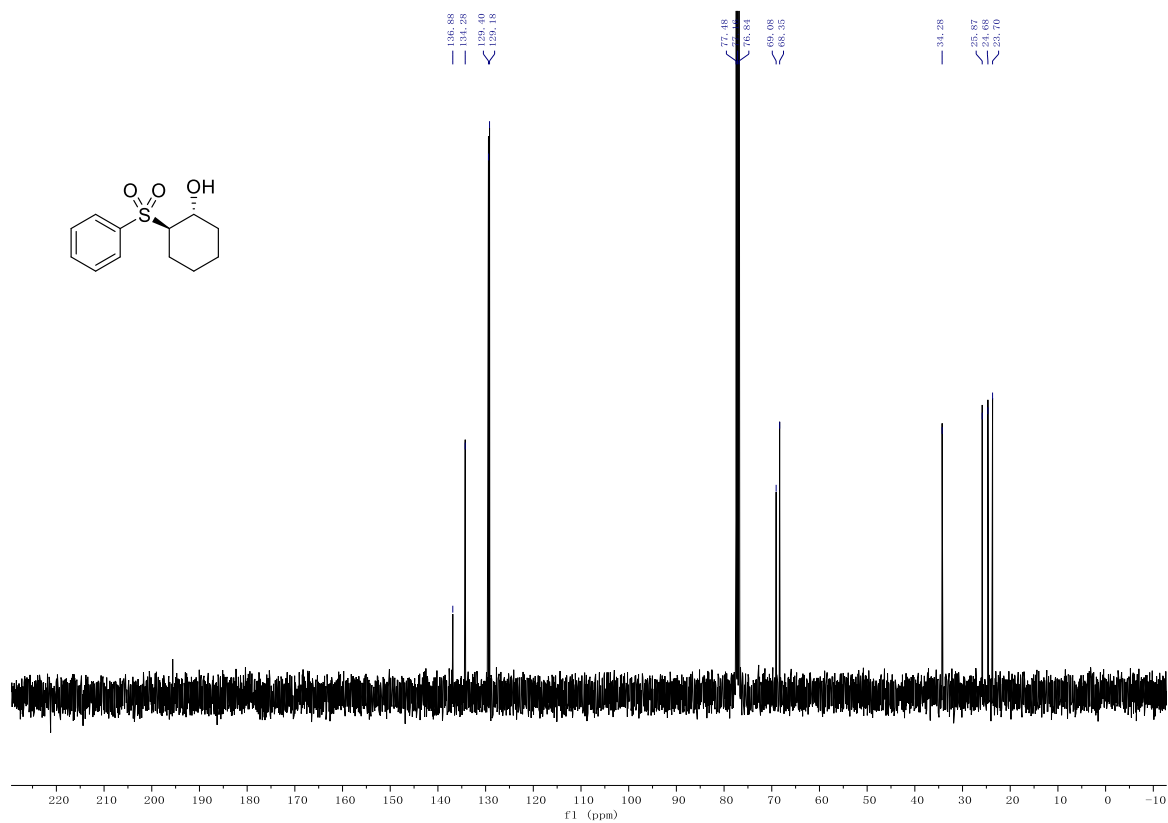
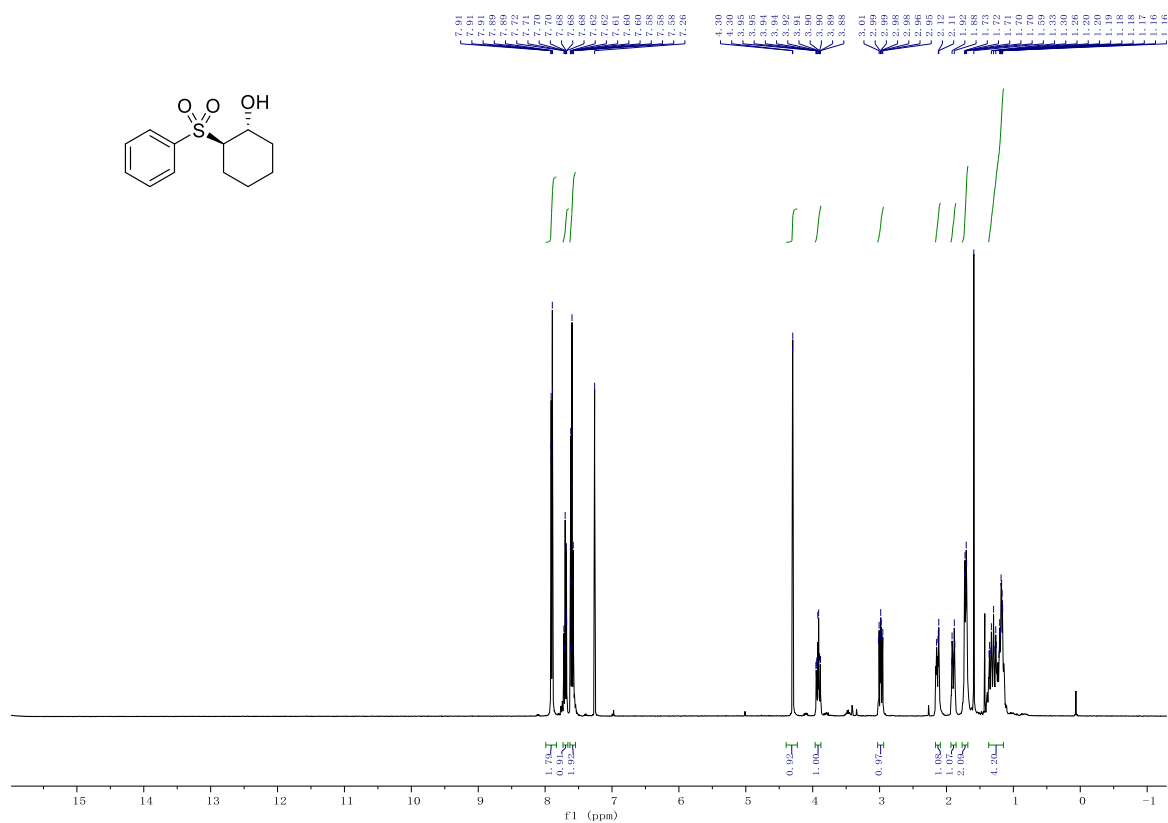
¹H NMR and ¹³C NMR spectra of *tert*-butyl 2-[(4-fluorophenyl)sulfonyl]acetate **40c**



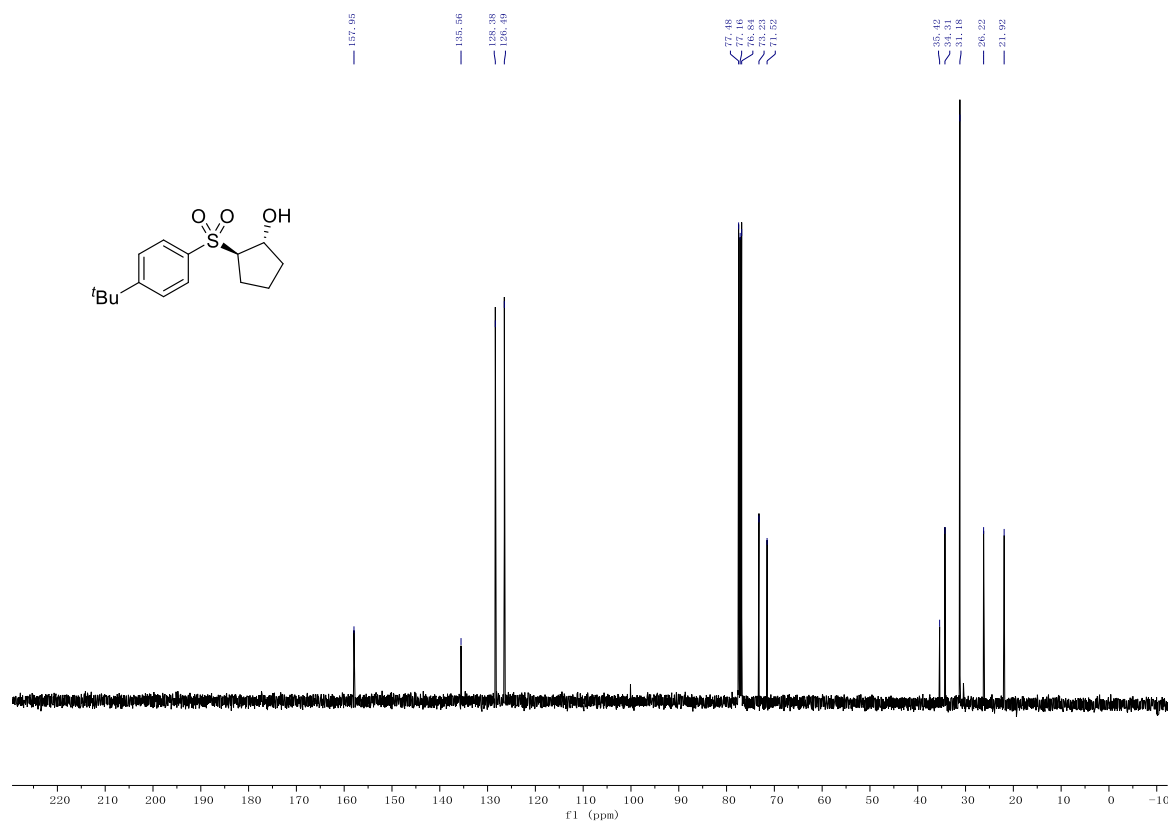
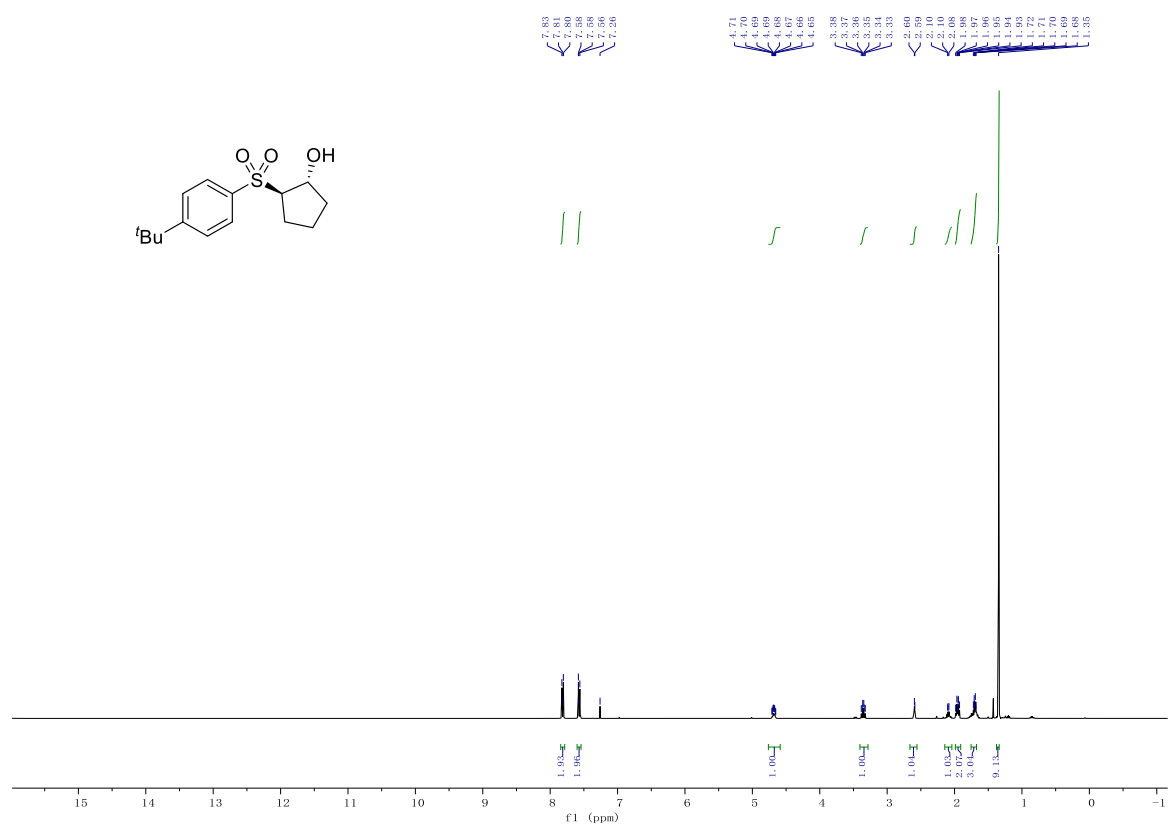
¹H NMR and ¹³C NMR spectra of *tert*-butyl 2-([4-(benzyloxy)phenyl]sulfonyl)acetate 40d



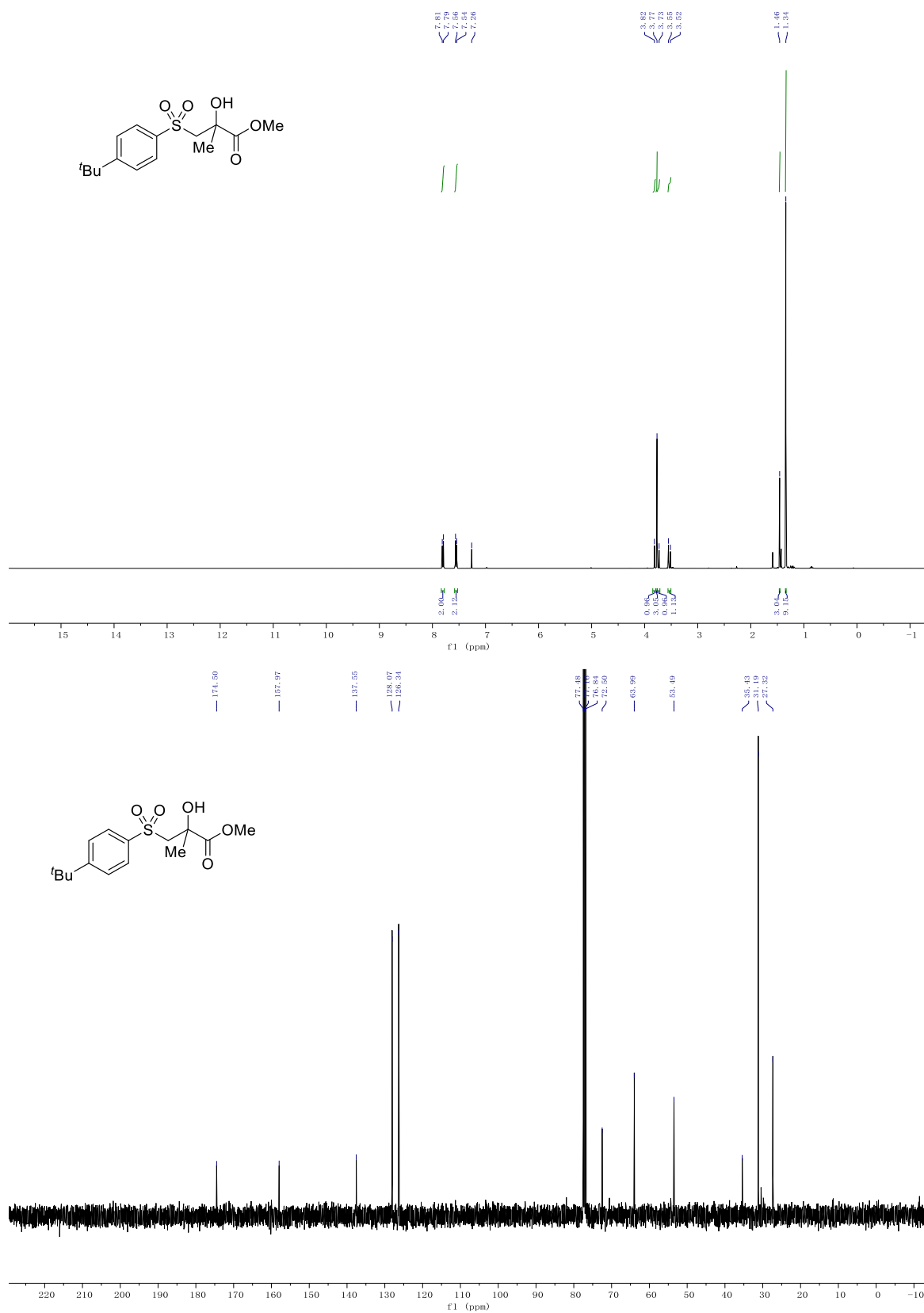
¹H NMR and ¹³C NMR spectra of *tert*-butyl 2-[(4-acetylphenyl)sulfonyl]acetate 40c



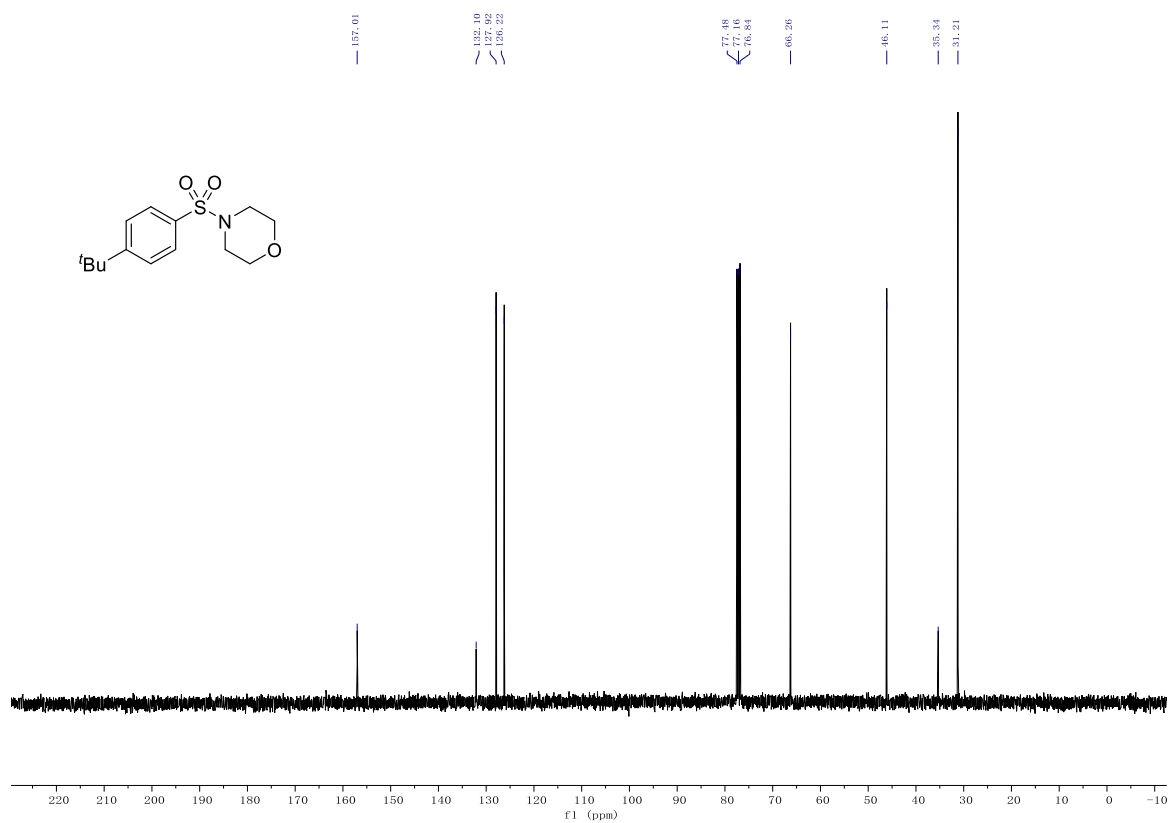
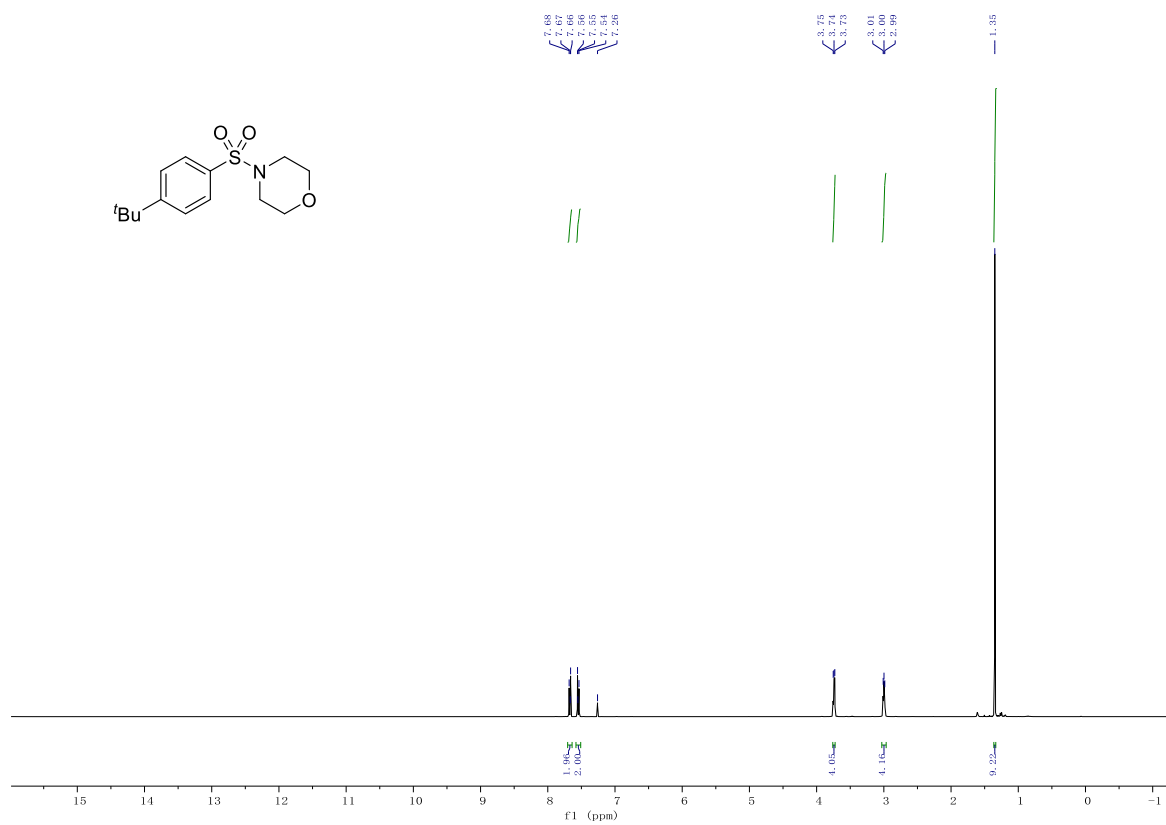
¹H NMR and ¹³C NMR spectra of **2-(phenylsulfonyl)cyclohexan-1-ol 41b**



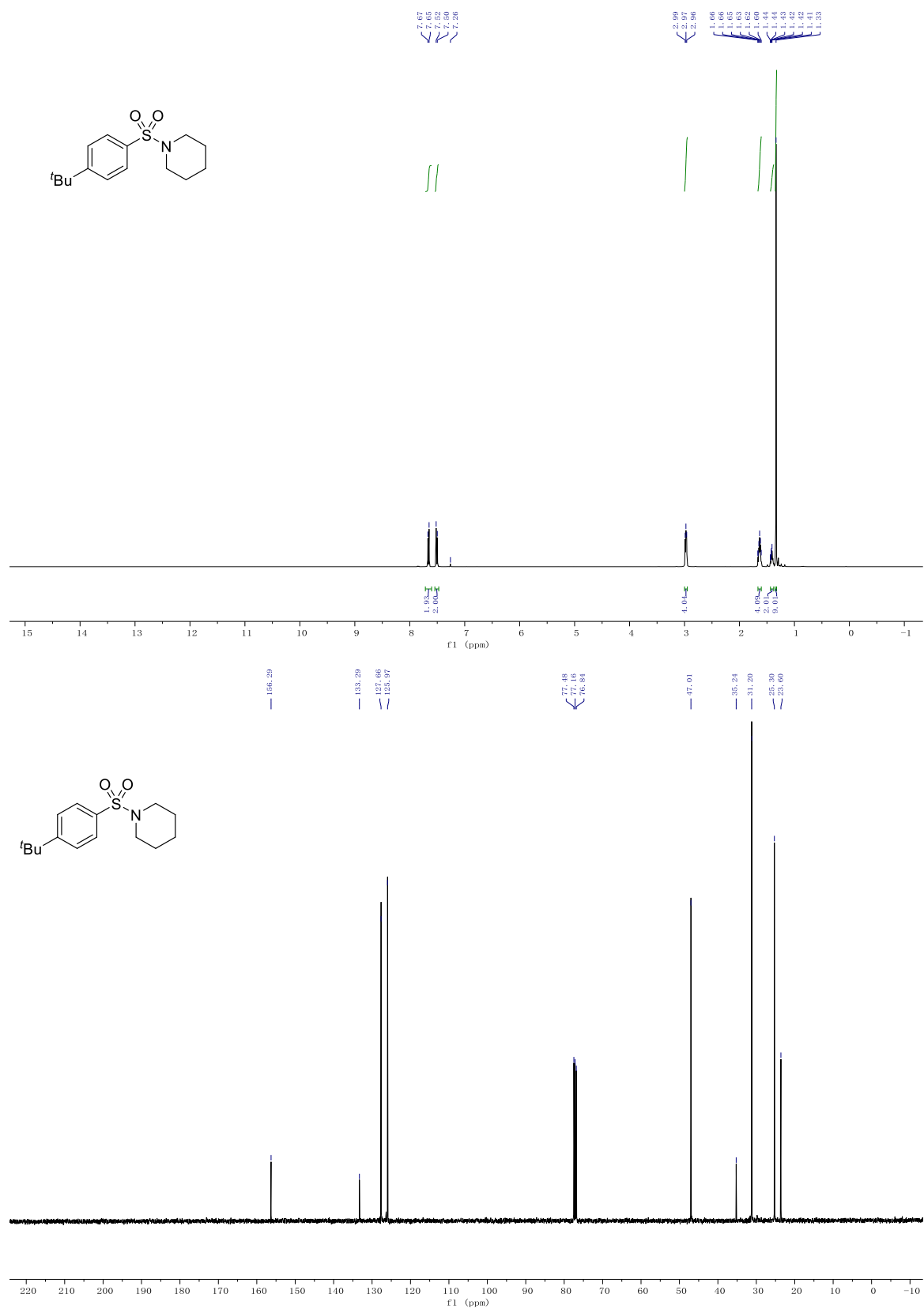
¹H NMR and ¹³C NMR spectra of 2-[[4-(*tert*-butyl)phenyl]sulfonyl]cyclopentan-1-ol 41c



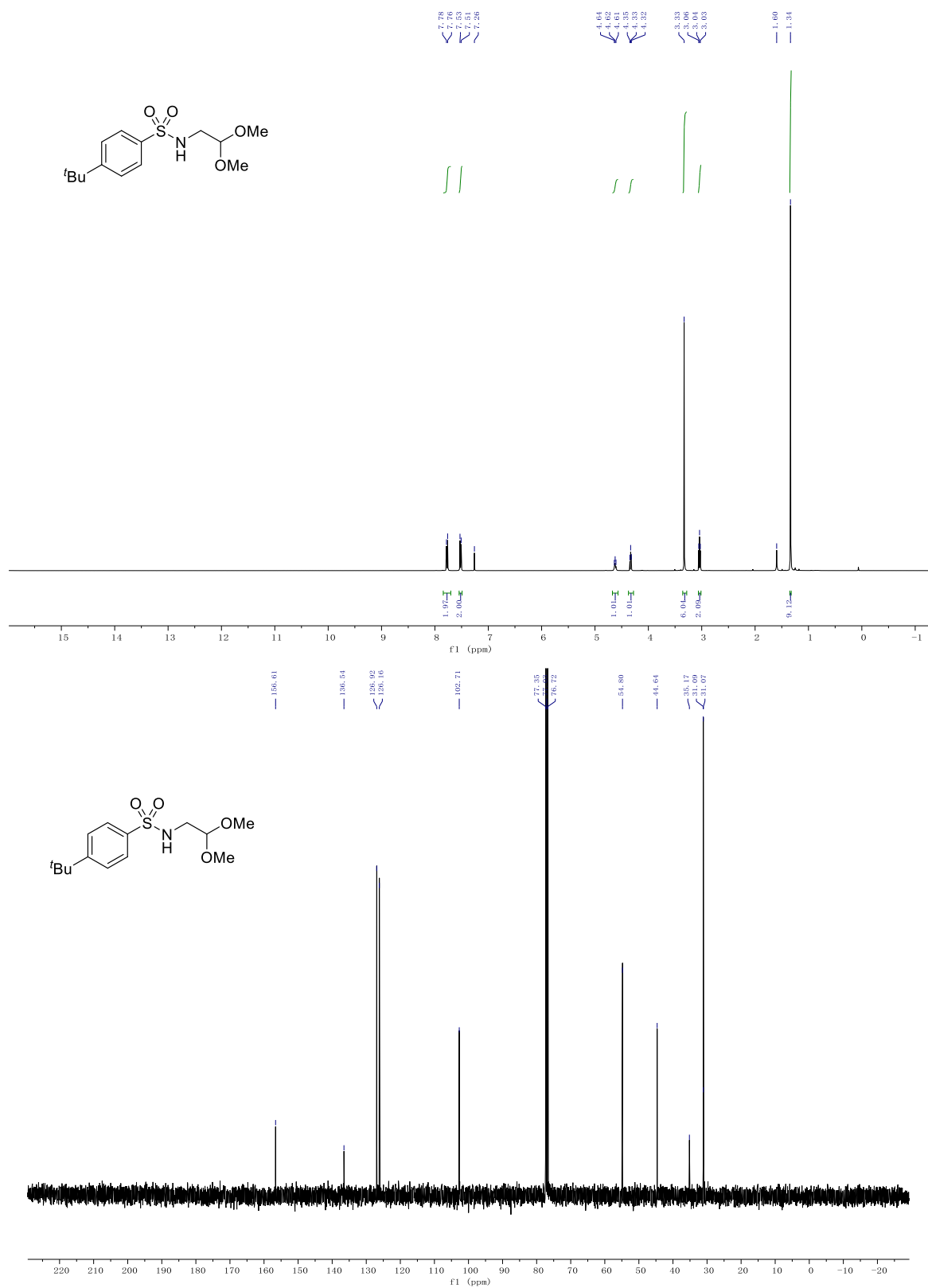
¹H NMR and ¹³C NMR spectra of 2-methyl 3-([4-(*tert*-butyl)phenyl]sulfonyl)-2-hydroxy-2-methylpropanoate 41d



¹H NMR and ¹³C NMR spectra of 4-([4-(*tert*-butyl)phenyl]sulfonyl)morpholine 42a

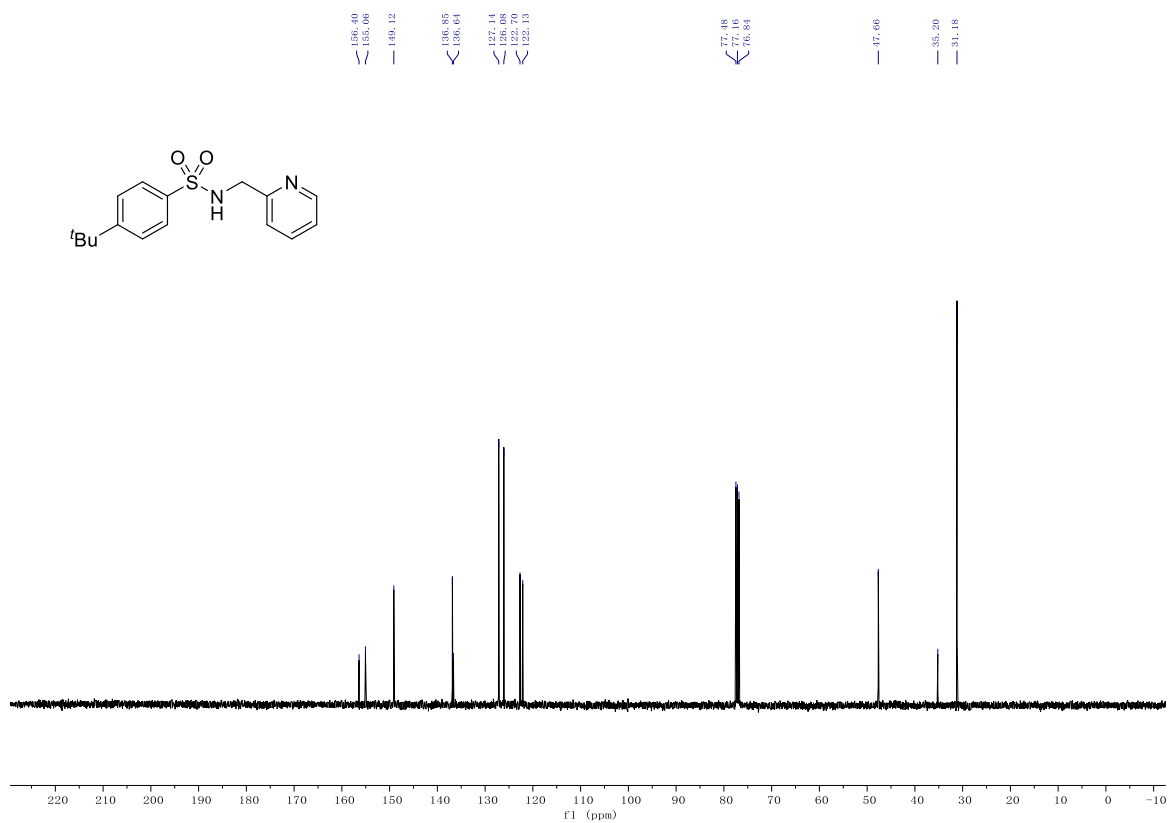
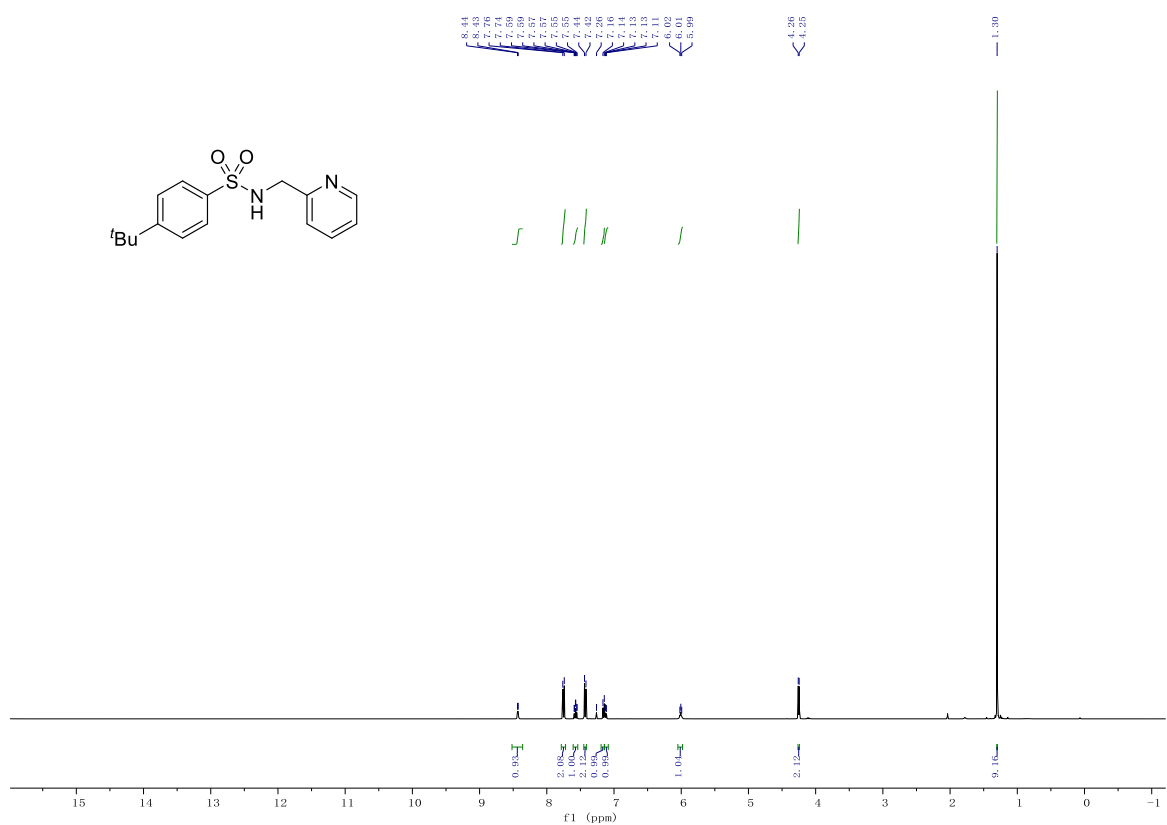


¹H NMR and ¹³C NMR spectra of 1-([4-(*tert*-butyl)phenyl]sulfonyl)piperidine 42b

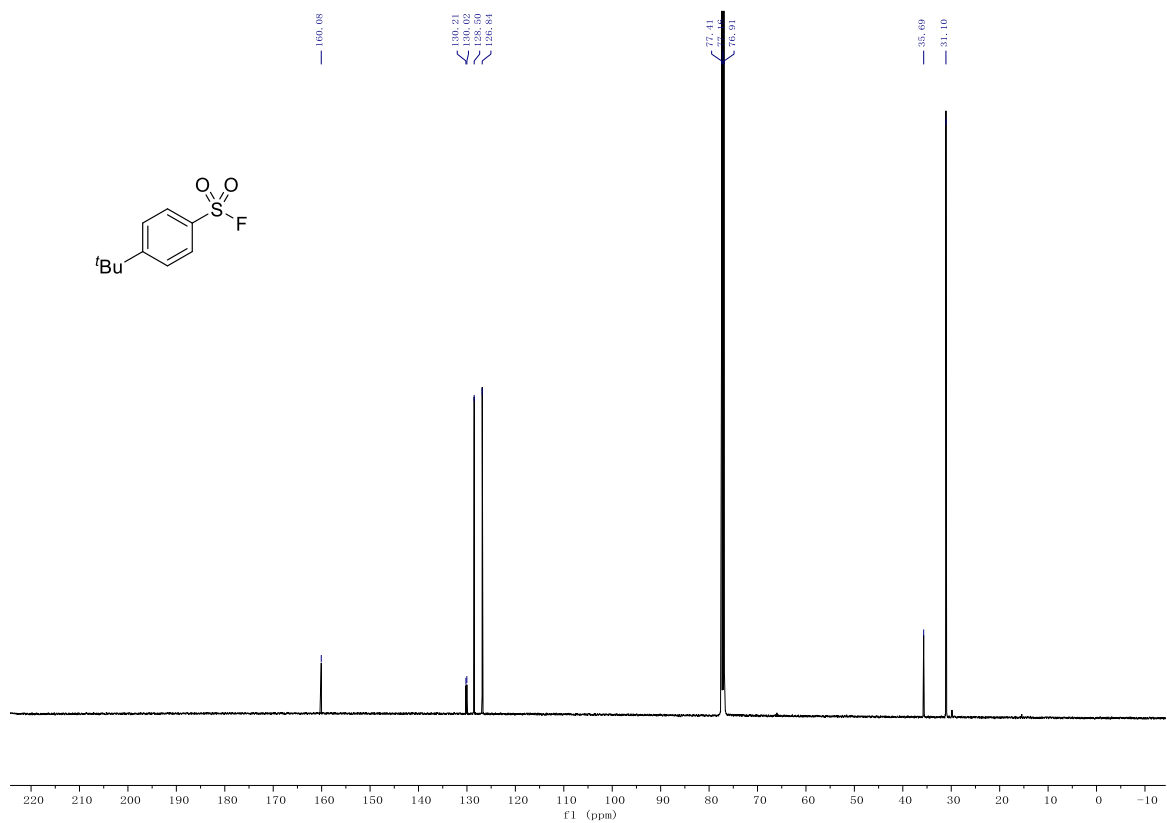
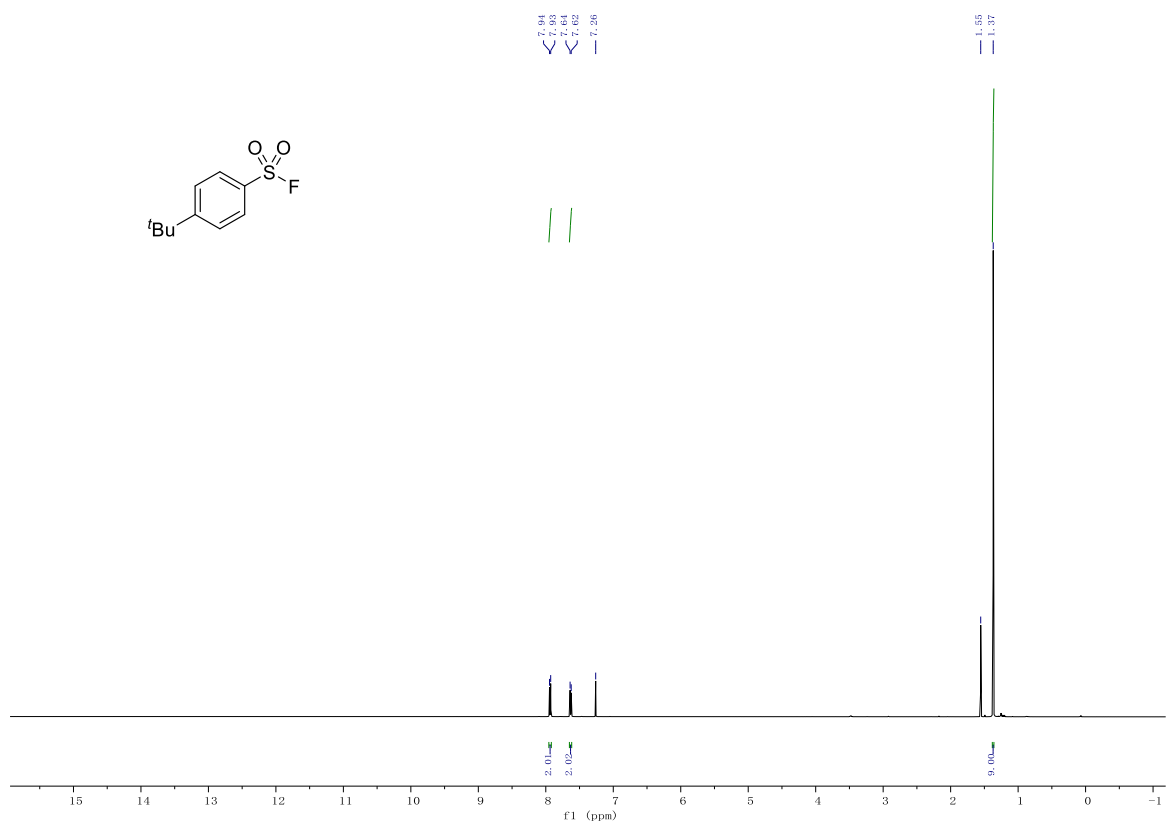


¹H NMR and ¹³C NMR spectra of 4-(*tert*-butyl)-*N*-(2,2-dimethoxyethyl)benzenesulfonamide

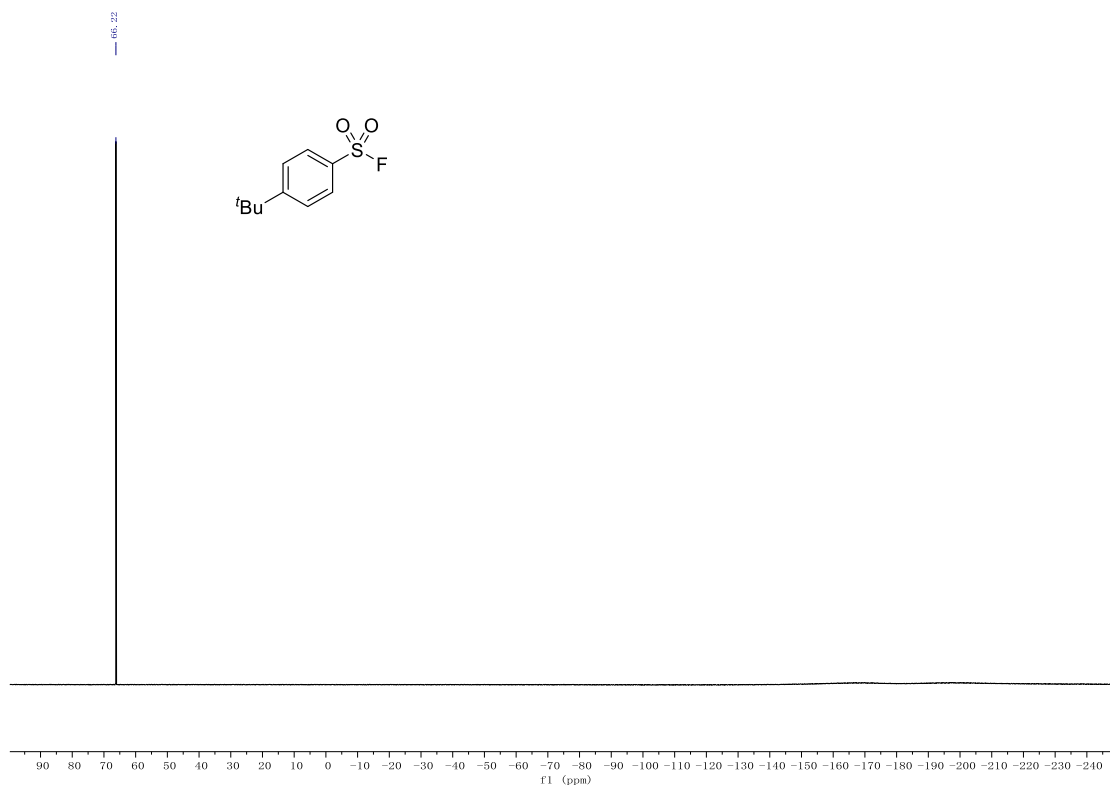
42c



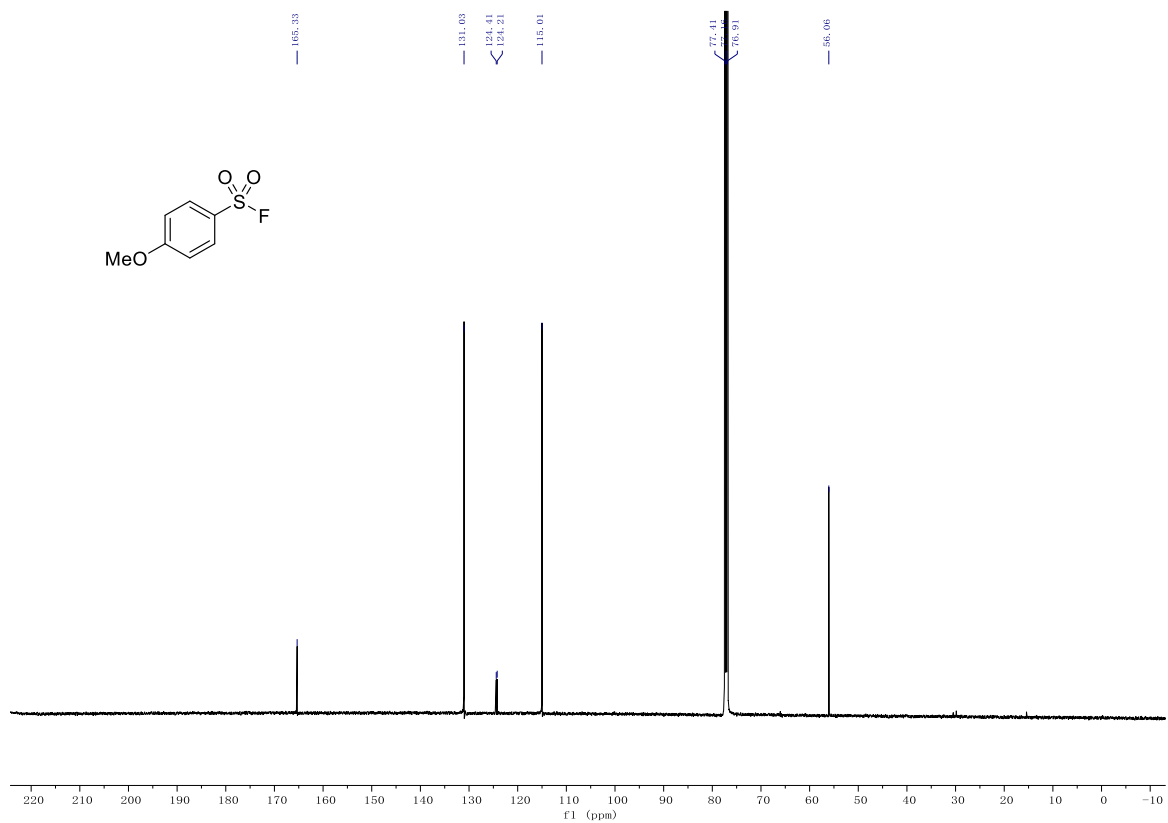
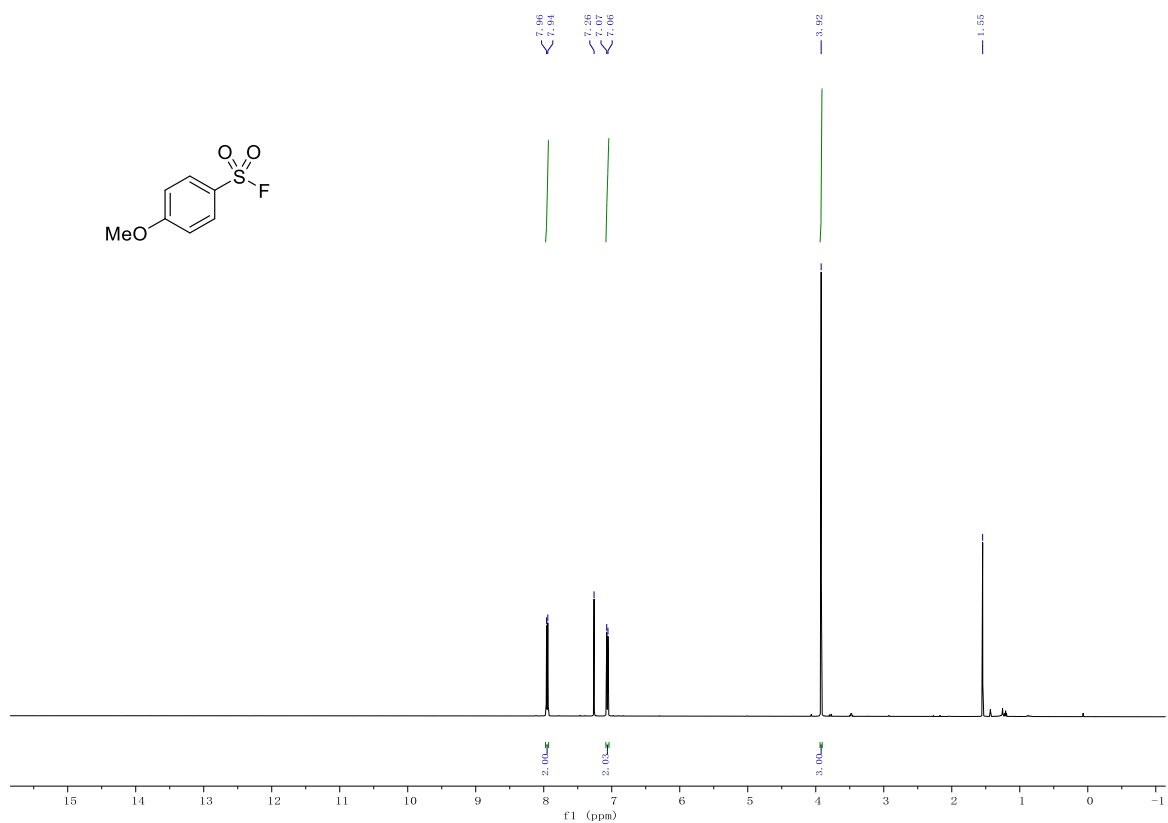
¹H NMR and ¹³C NMR spectra of 4-(*tert*-butyl)-*N*-(pyridin-2-ylmethyl)benzenesulfonamide 42d



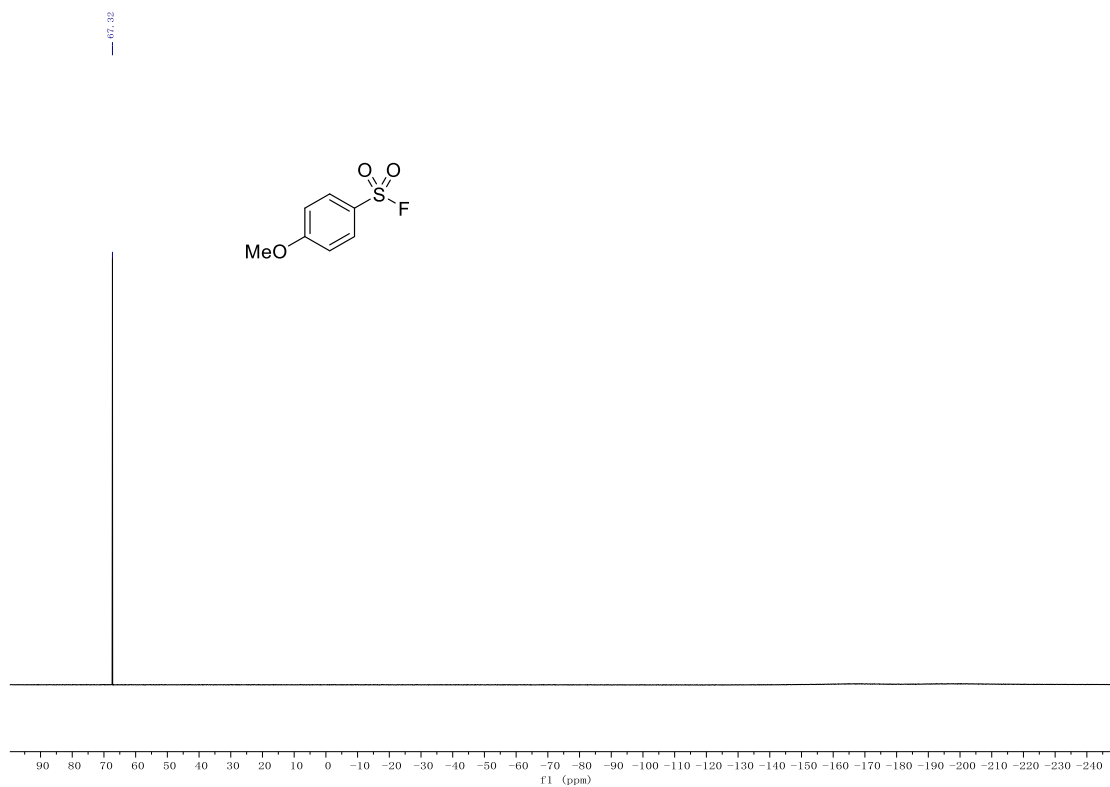
¹H NMR and ¹³C NMR spectra of 4-(*tert*-butyl)benzenesulfonyl fluoride 43a



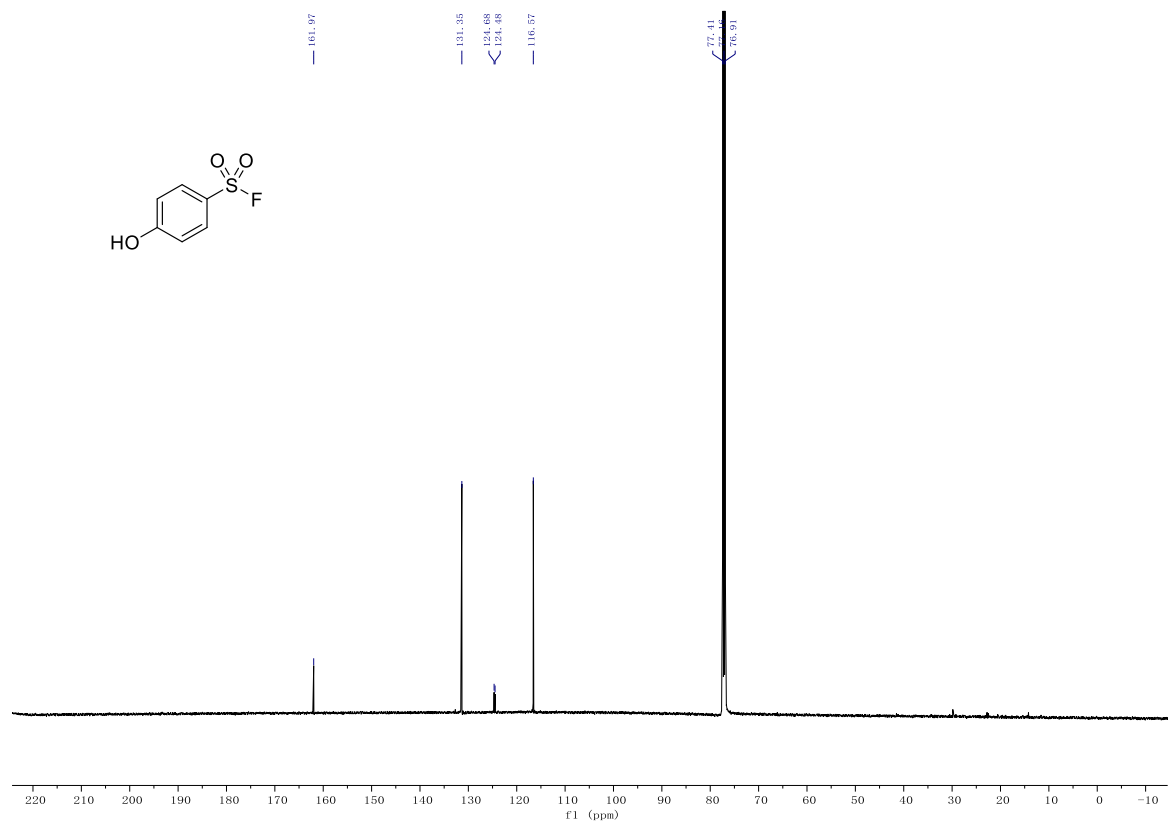
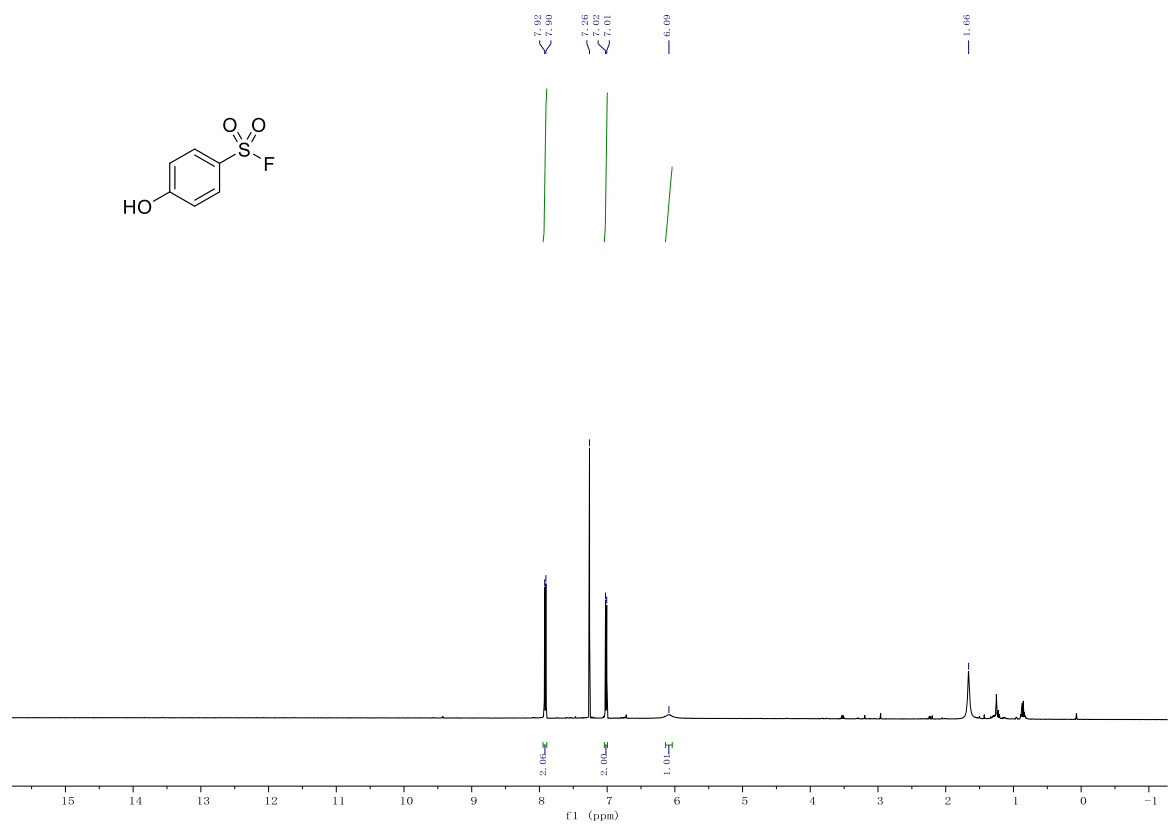
¹⁹F NMR spectrum of **4-(*tert*-butyl)benzenesulfonyl fluoride 43a**



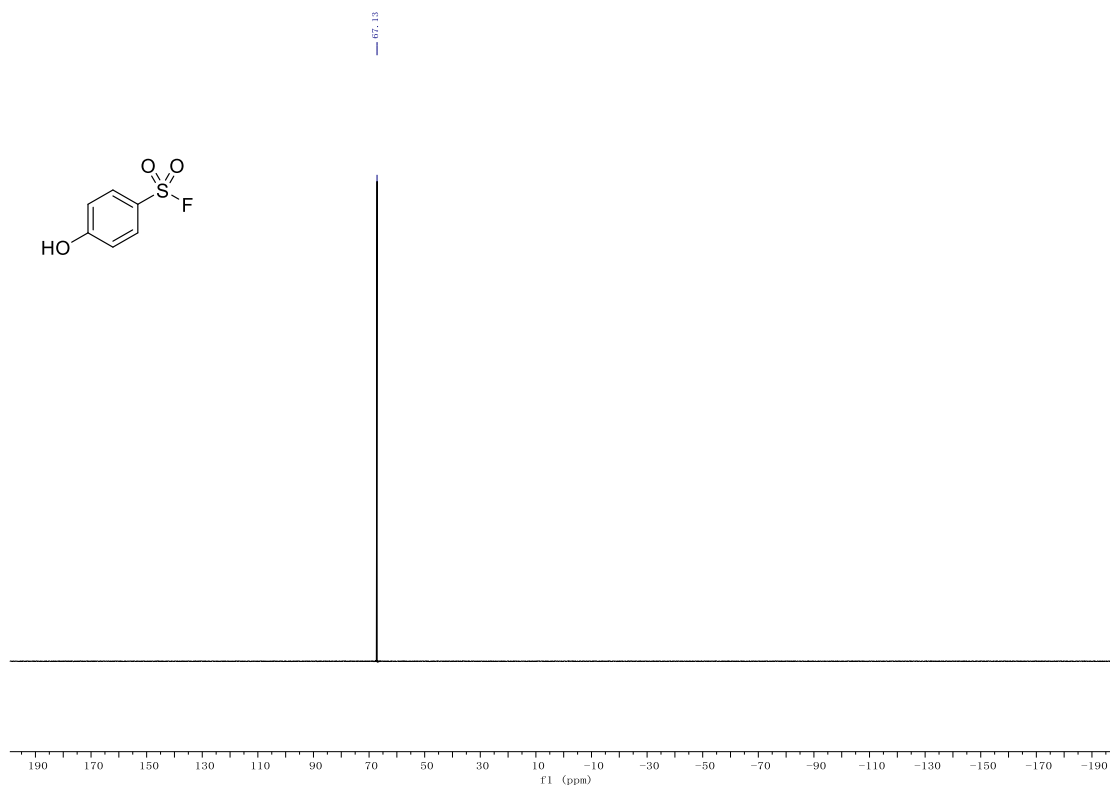
^1H NMR and ^{13}C NMR spectra of 4-methoxybenzenesulfonyl fluoride 43b



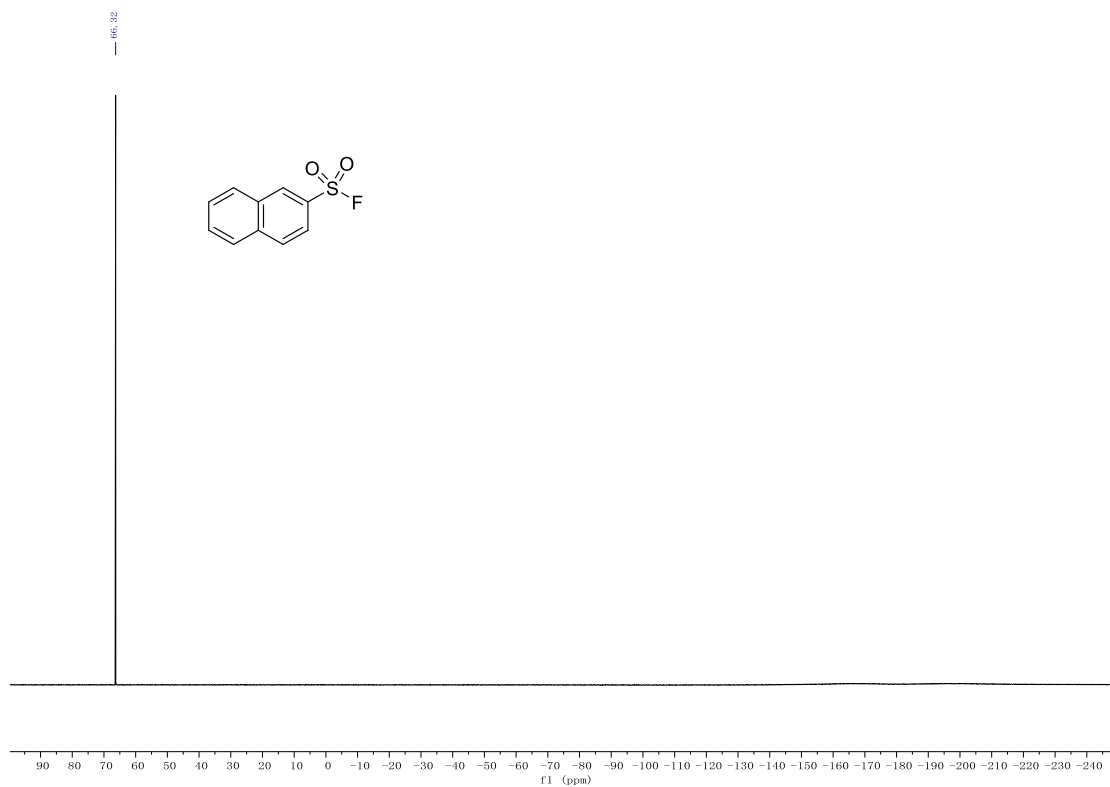
^{19}F NMR spectrum of **4-methoxybenzenesulfonyl fluoride 43b**



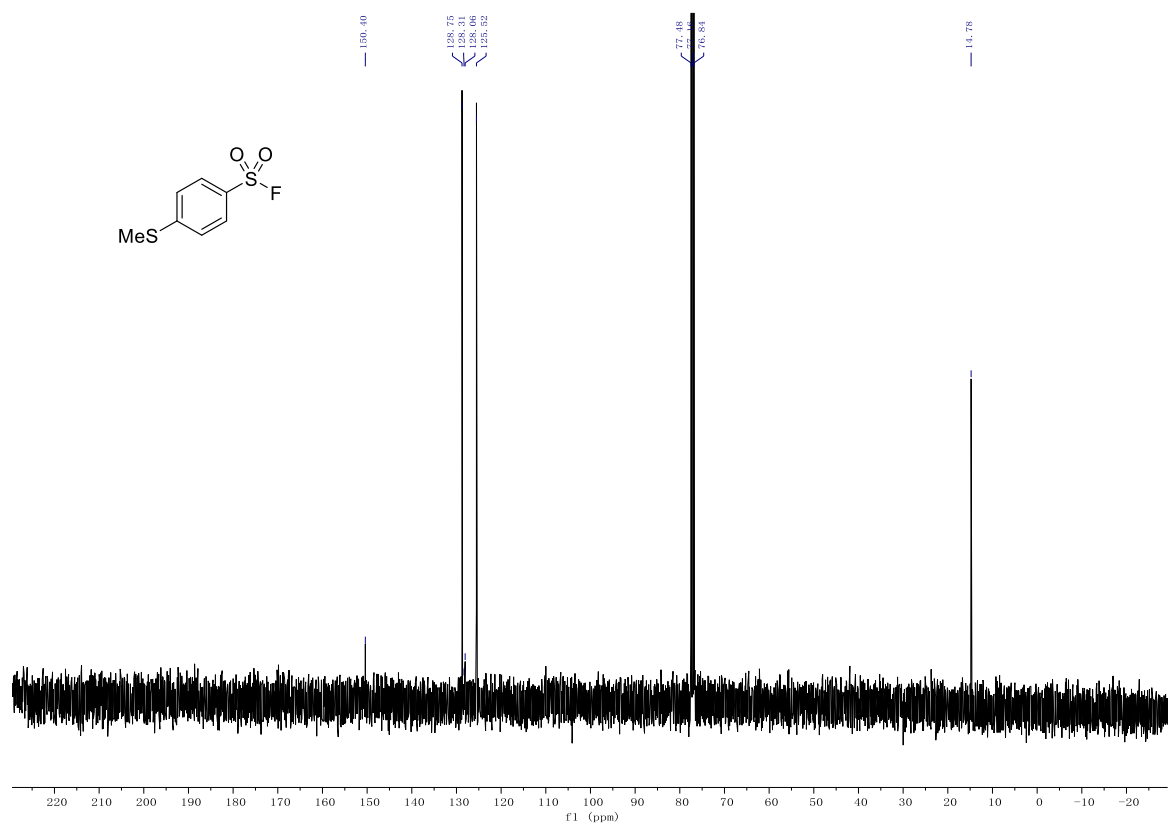
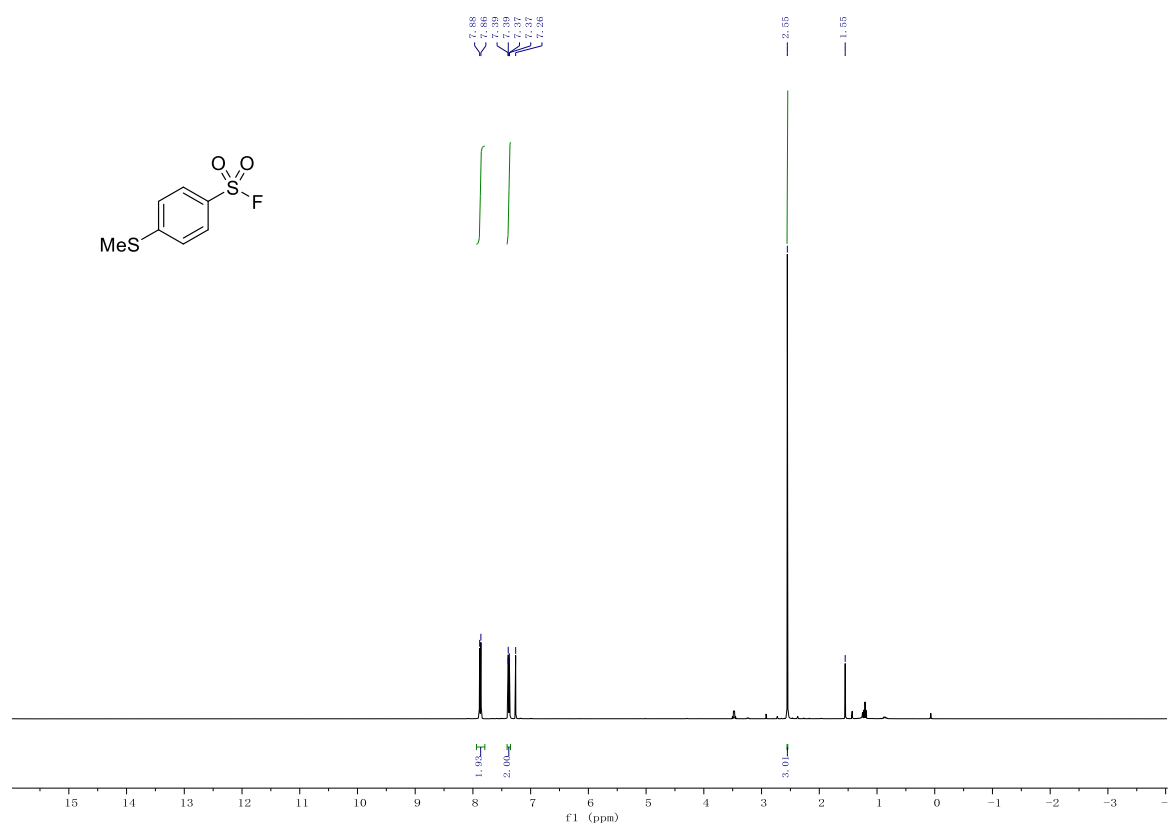
¹H NMR and ¹³C NMR spectra of **4-hydroxybenzenesulfonyl fluoride 43c**



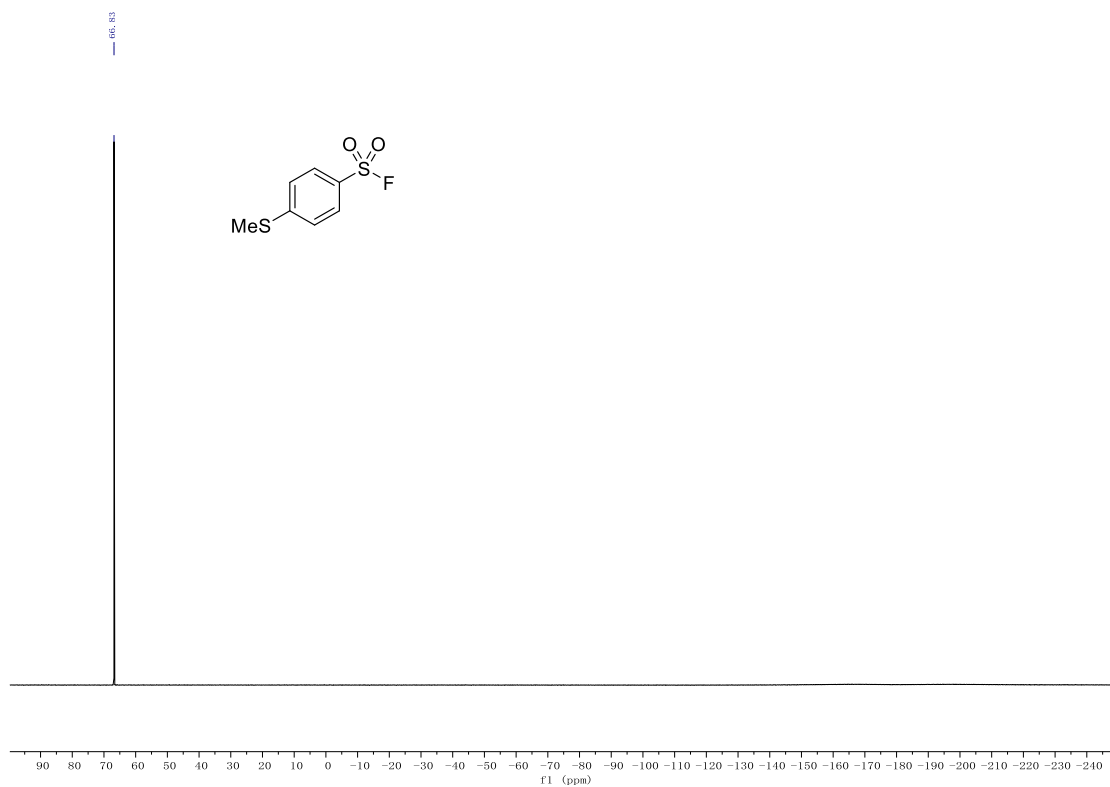
^{19}F NMR spectrum of **4-hydroxybenzenesulfonyl fluoride 43c**



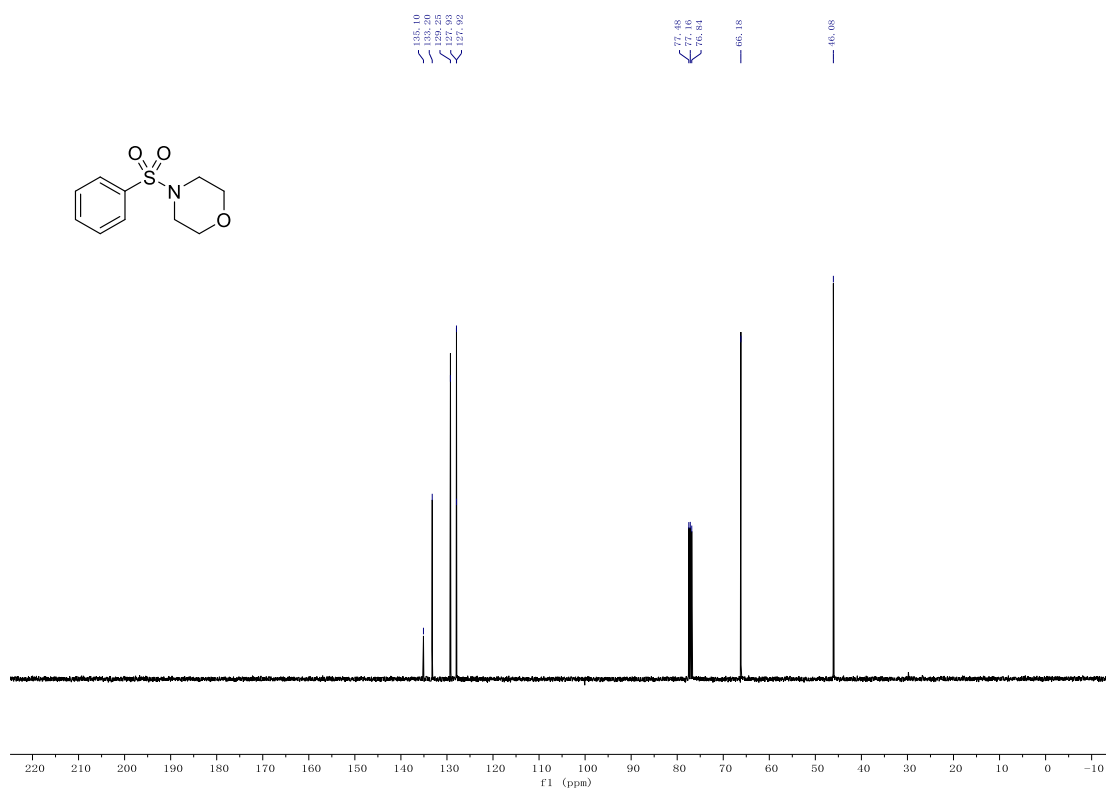
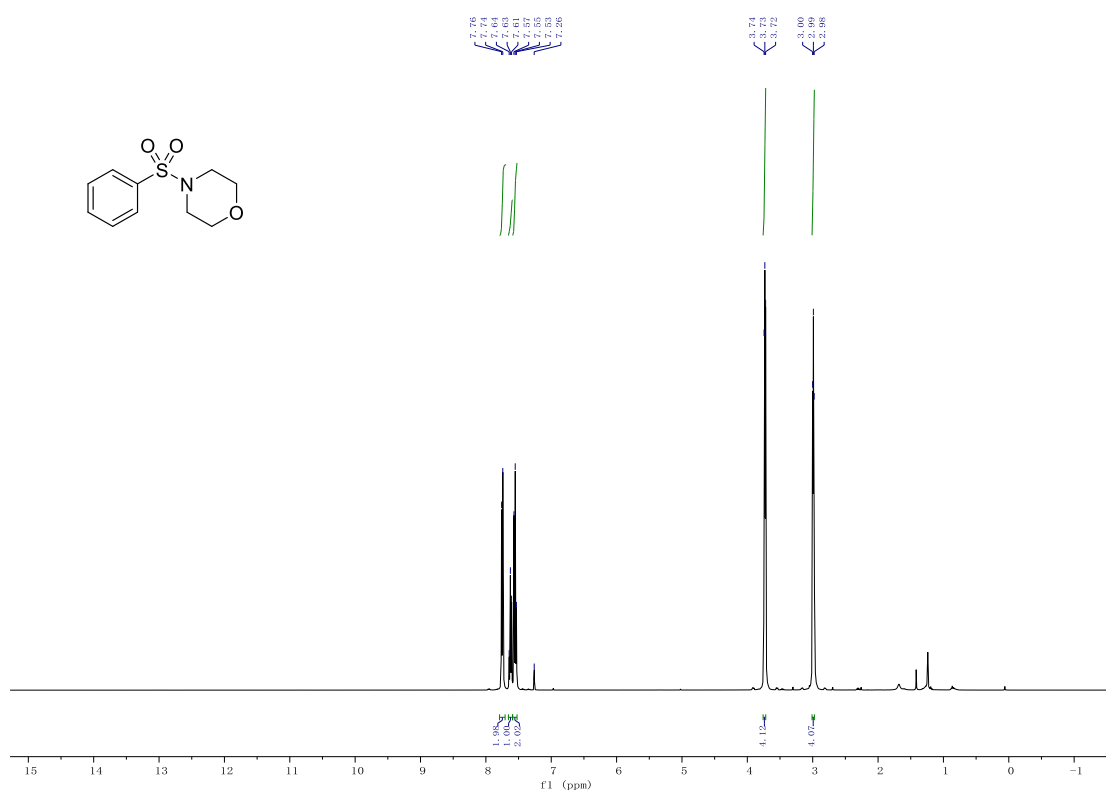
¹⁹F NMR spectrum of **naphthalene-2-sulfonyl fluoride 43d**



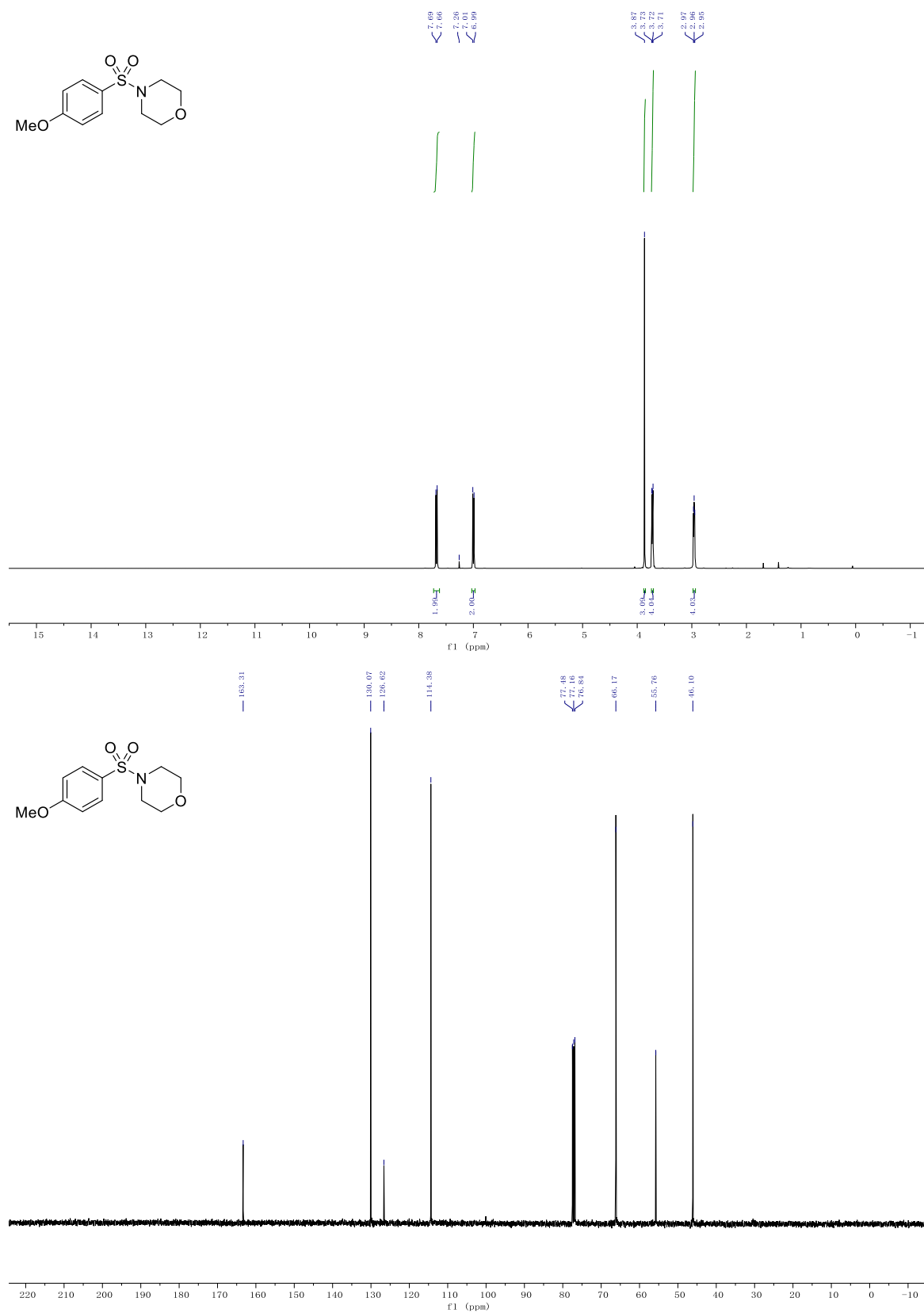
¹H NMR and ¹³C NMR spectra of 4-methylthiobenzenesulfonyl fluoride 43e



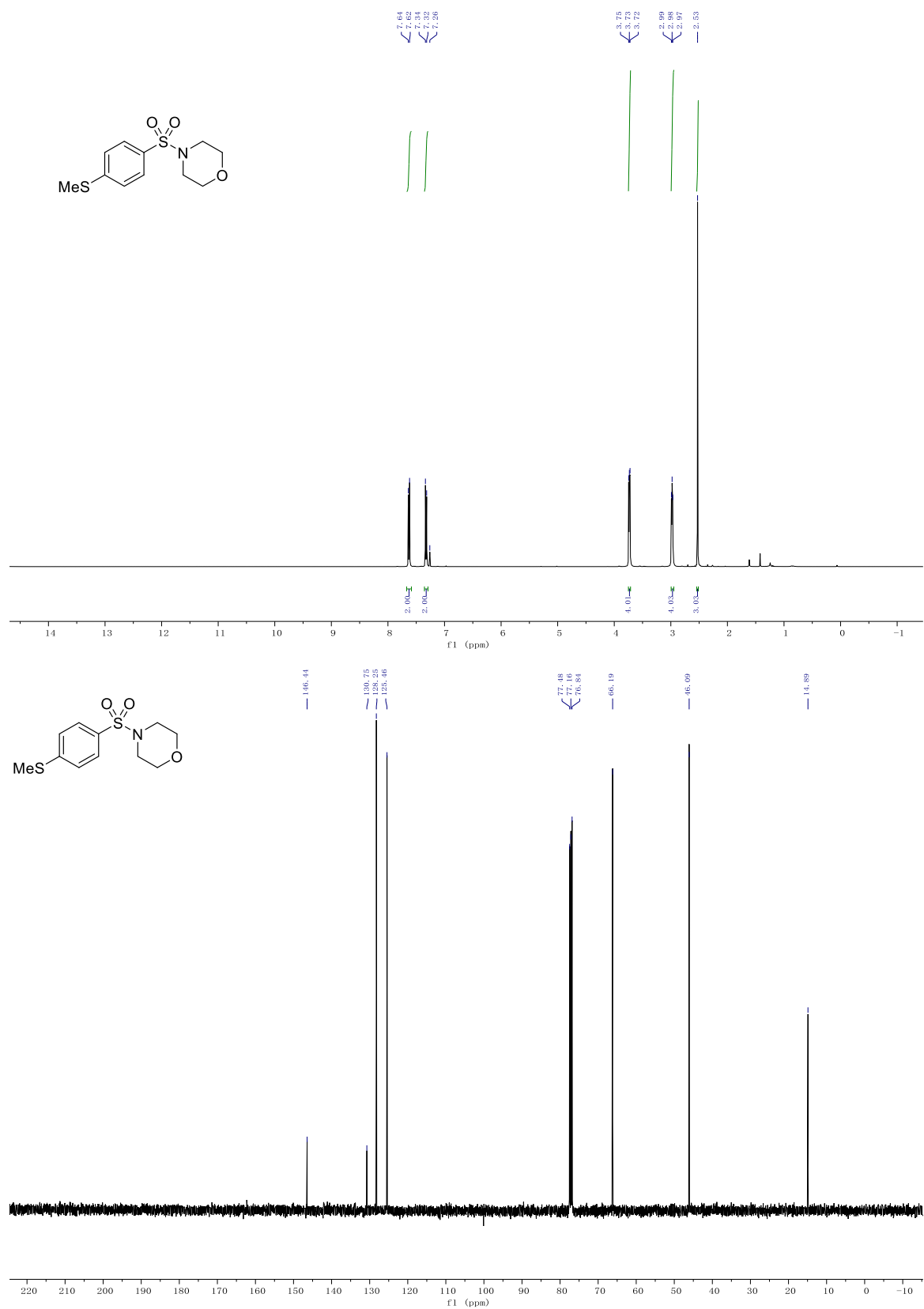
¹⁹F NMR spectrum of **4-methylthiobenzenesulfonyl fluoride 43e**



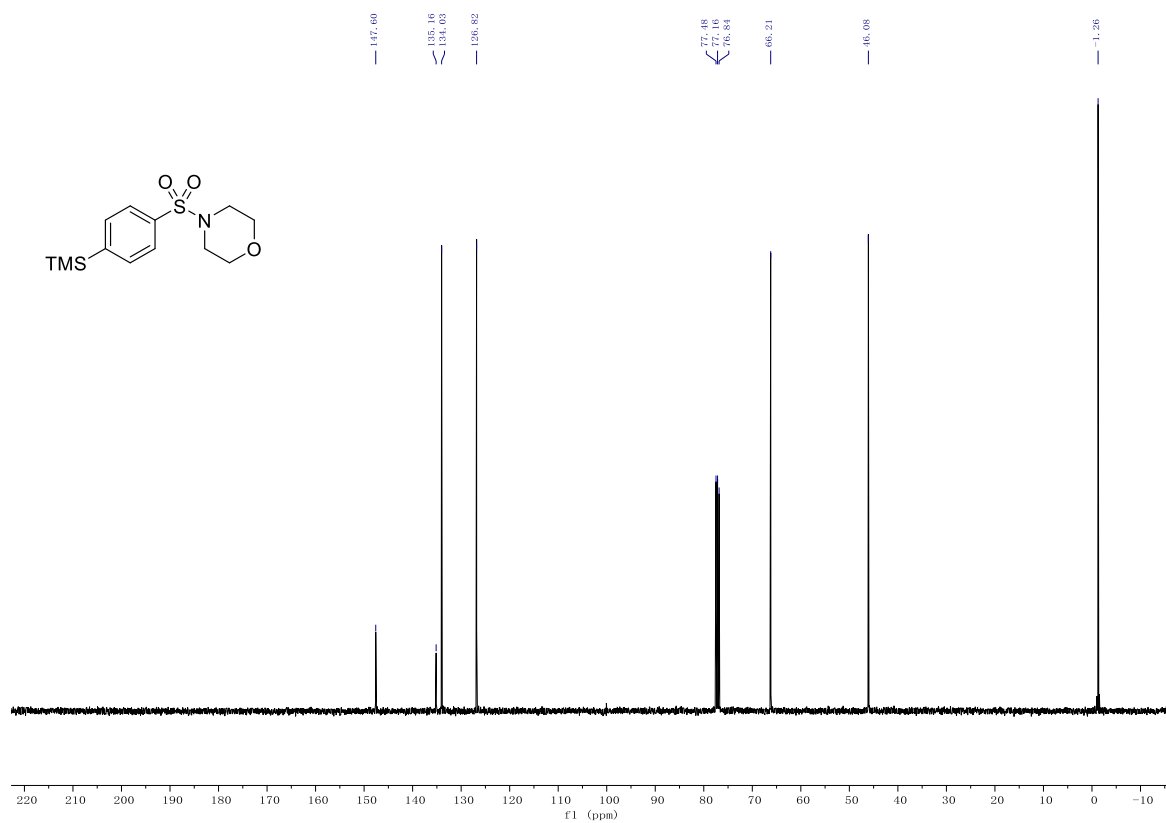
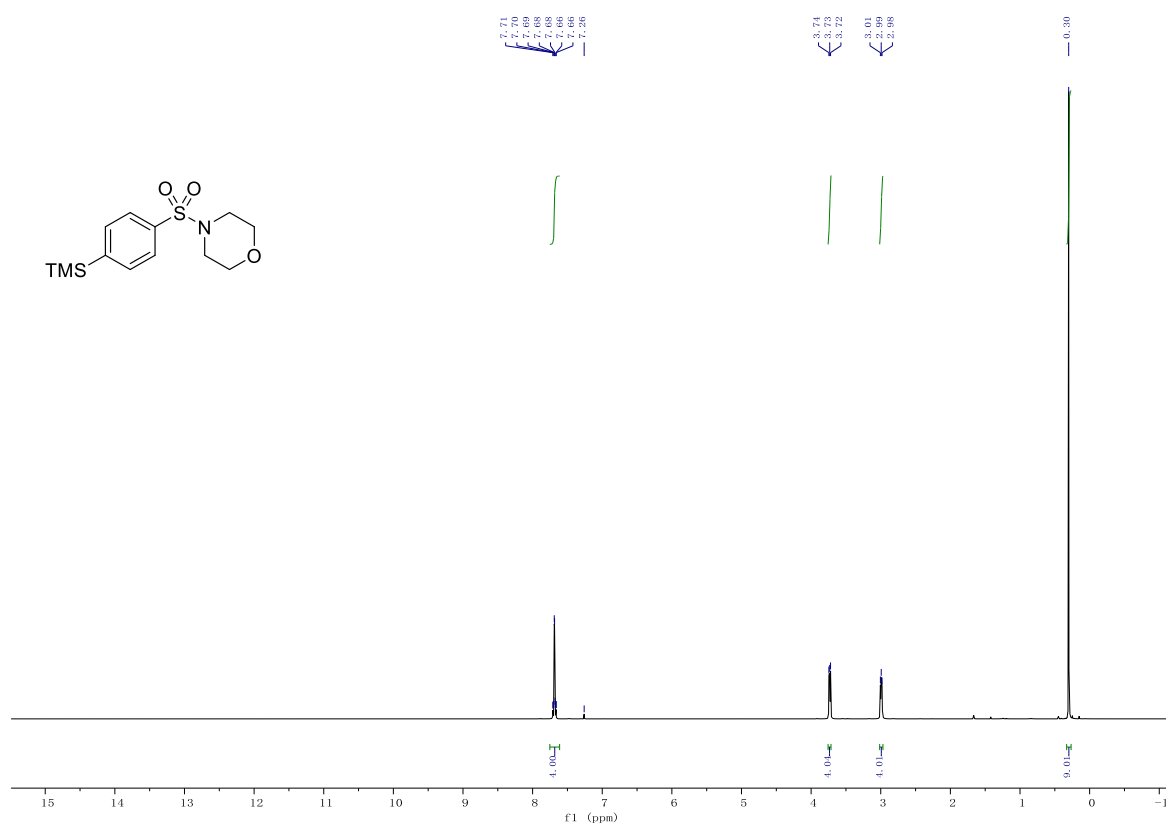
¹H NMR and ¹³C NMR spectra of 4-(phenylsulfonyl)morpholine 45a



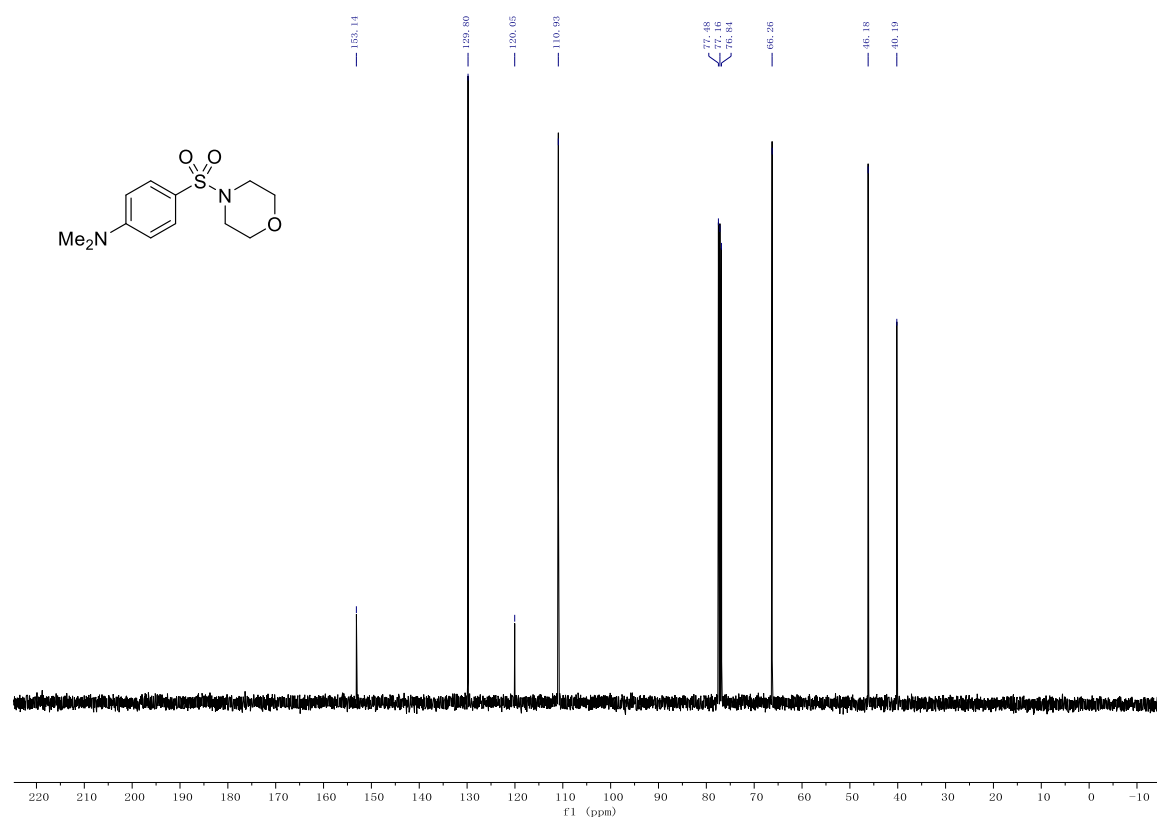
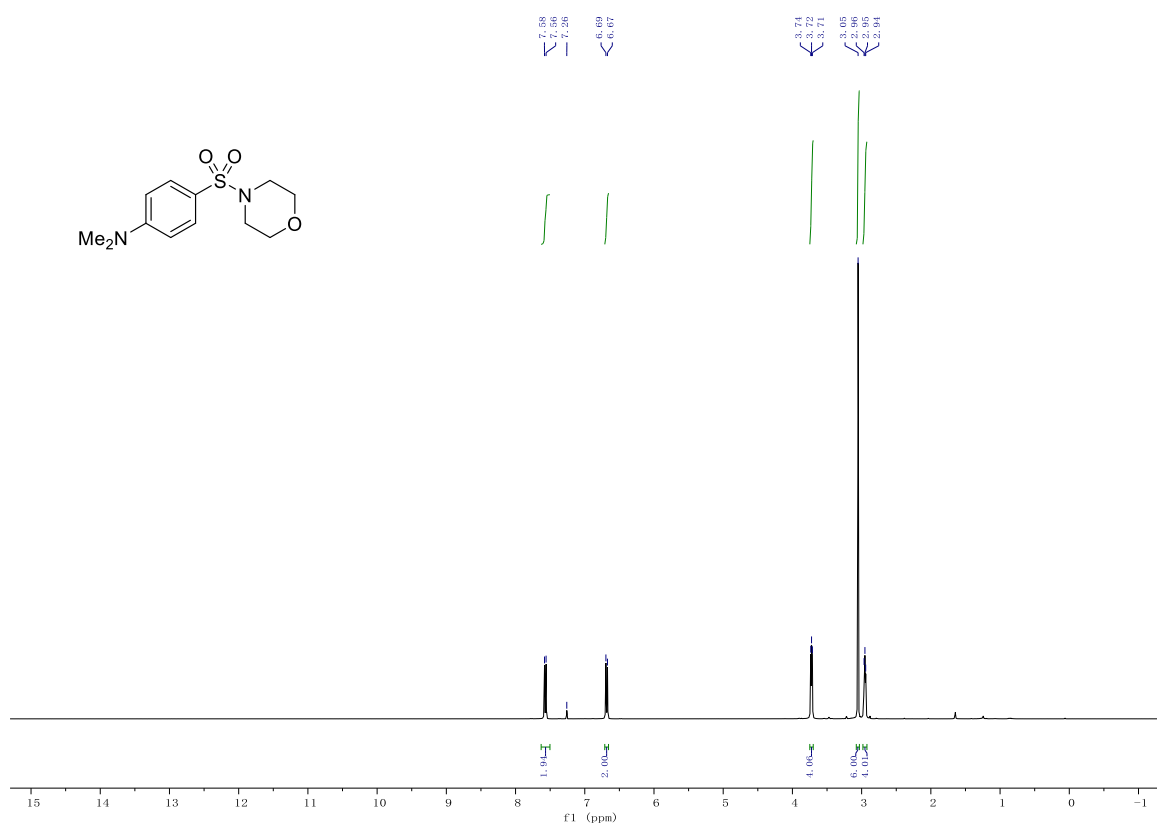
¹H NMR and ¹³C NMR spectra of 4-[4-methoxyphenyl]sulfonylmorpholine 45b



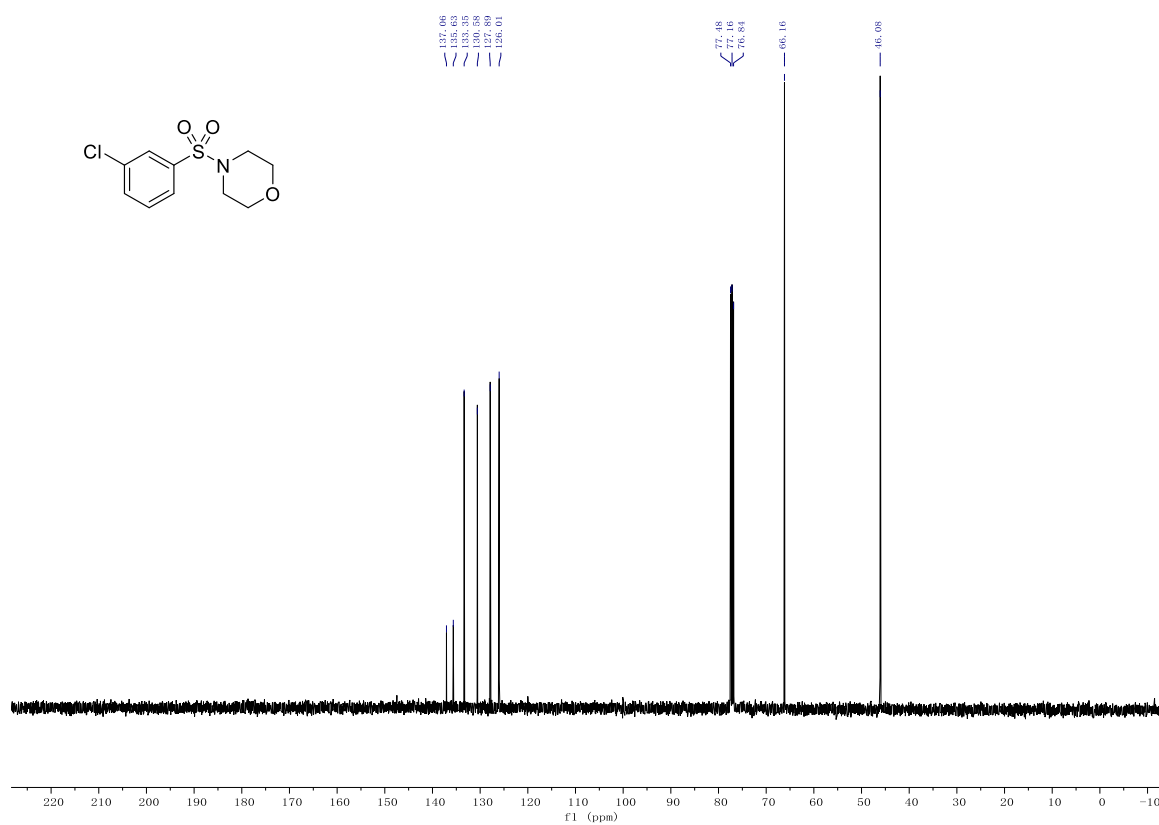
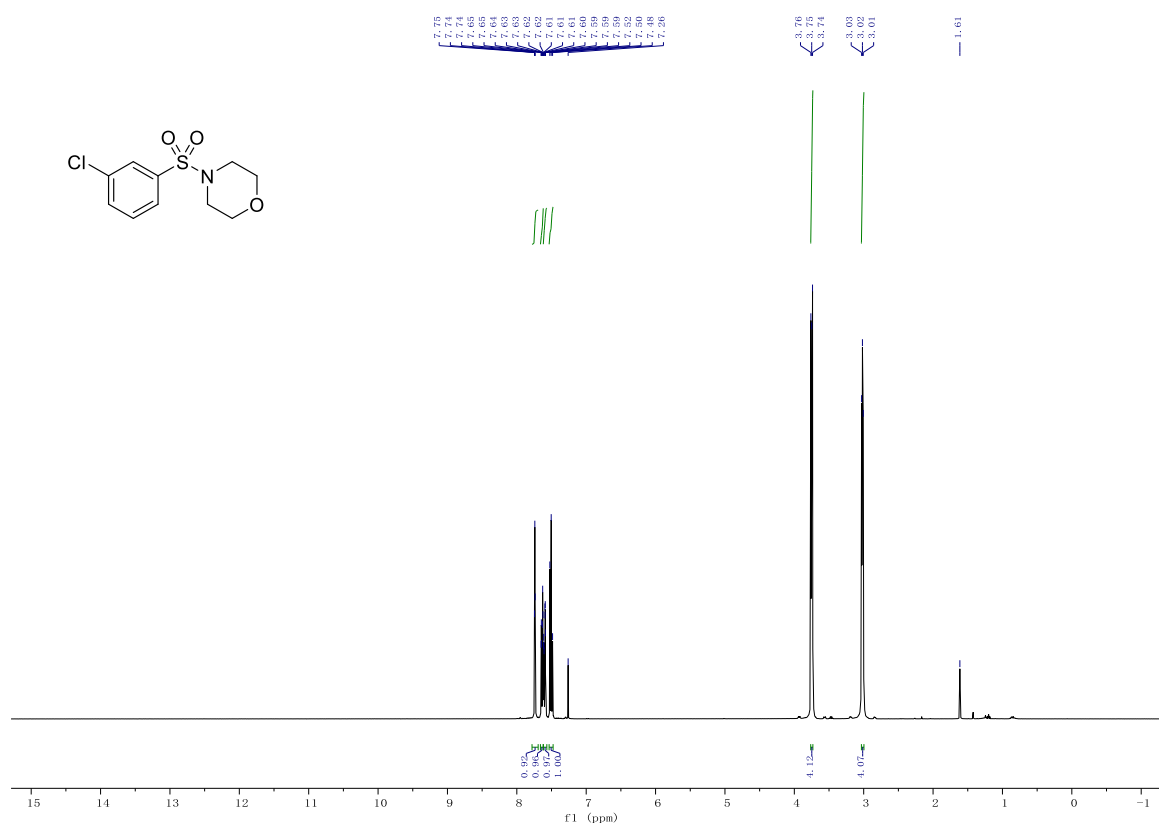
¹H NMR and ¹³C NMR spectra of 4-[[4-(methylthio)phenyl]sulfonyl]morpholine 45c

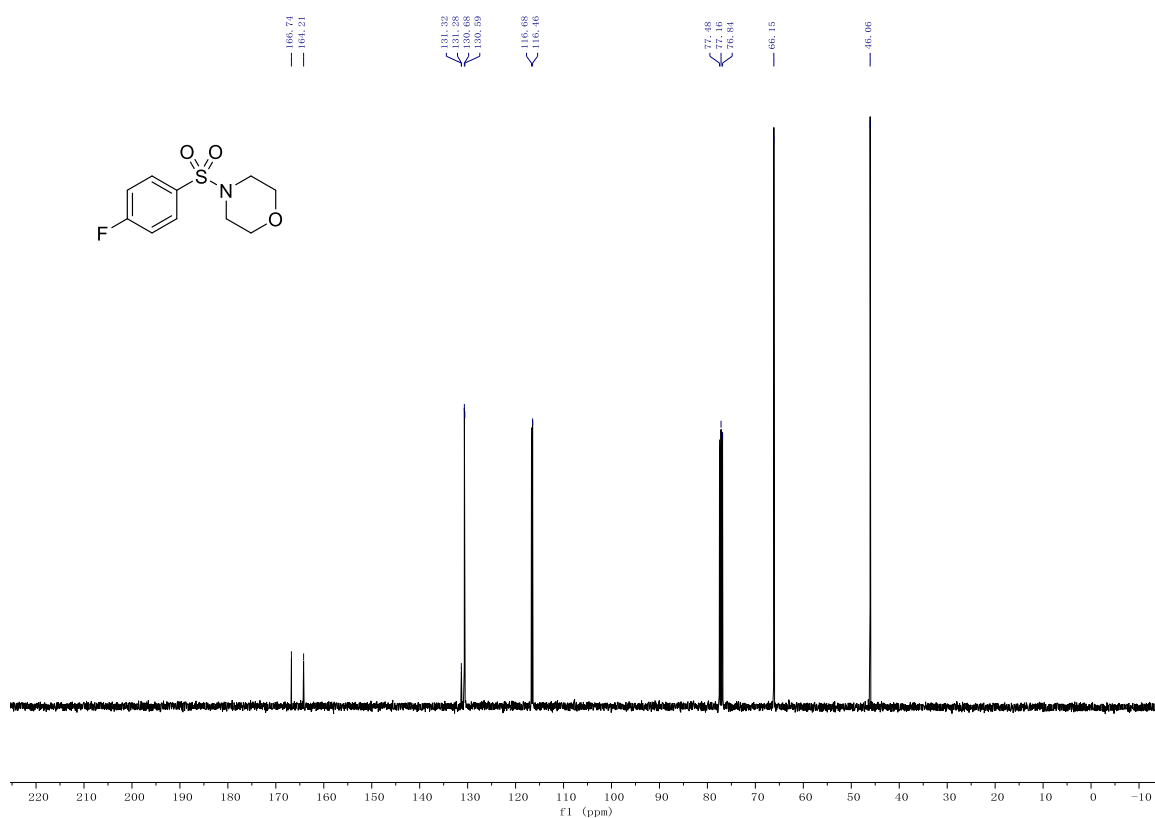
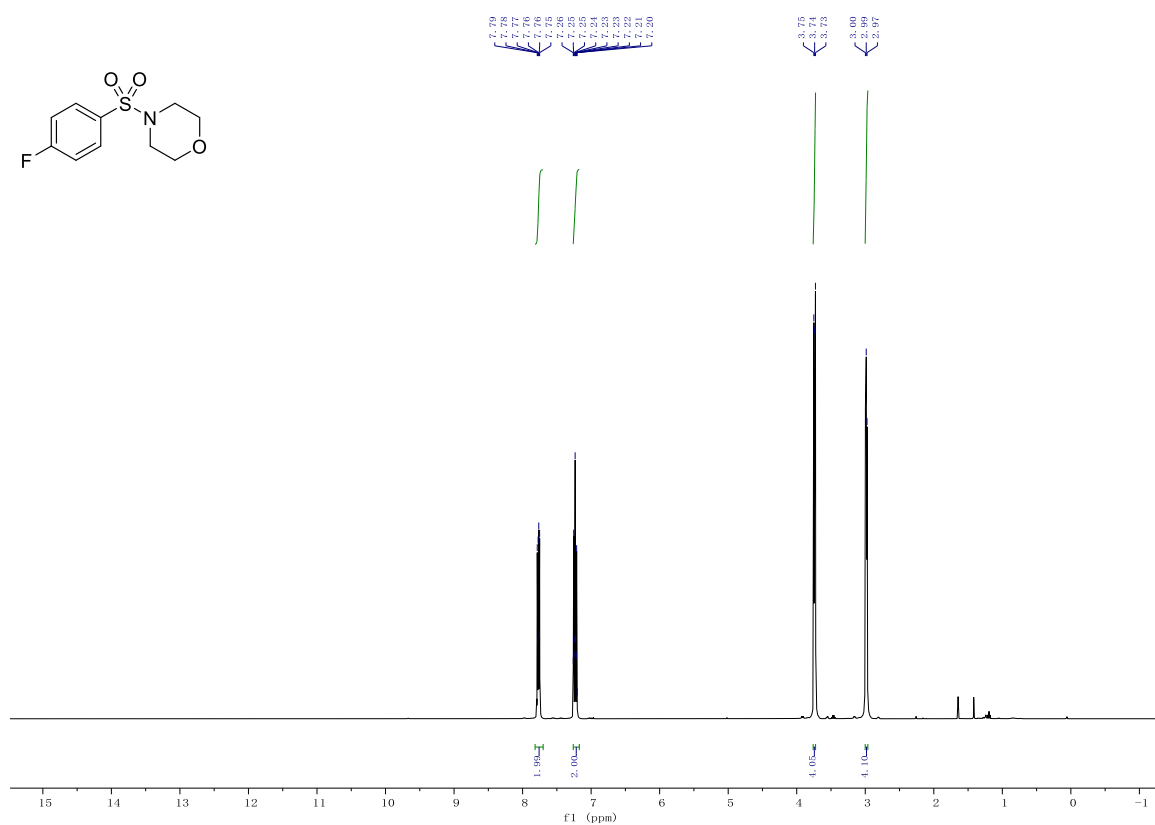


¹H NMR and ¹³C NMR spectra of 4-[(4-(trimethylsilyl)phenyl)sulfonyl]morpholine 45d

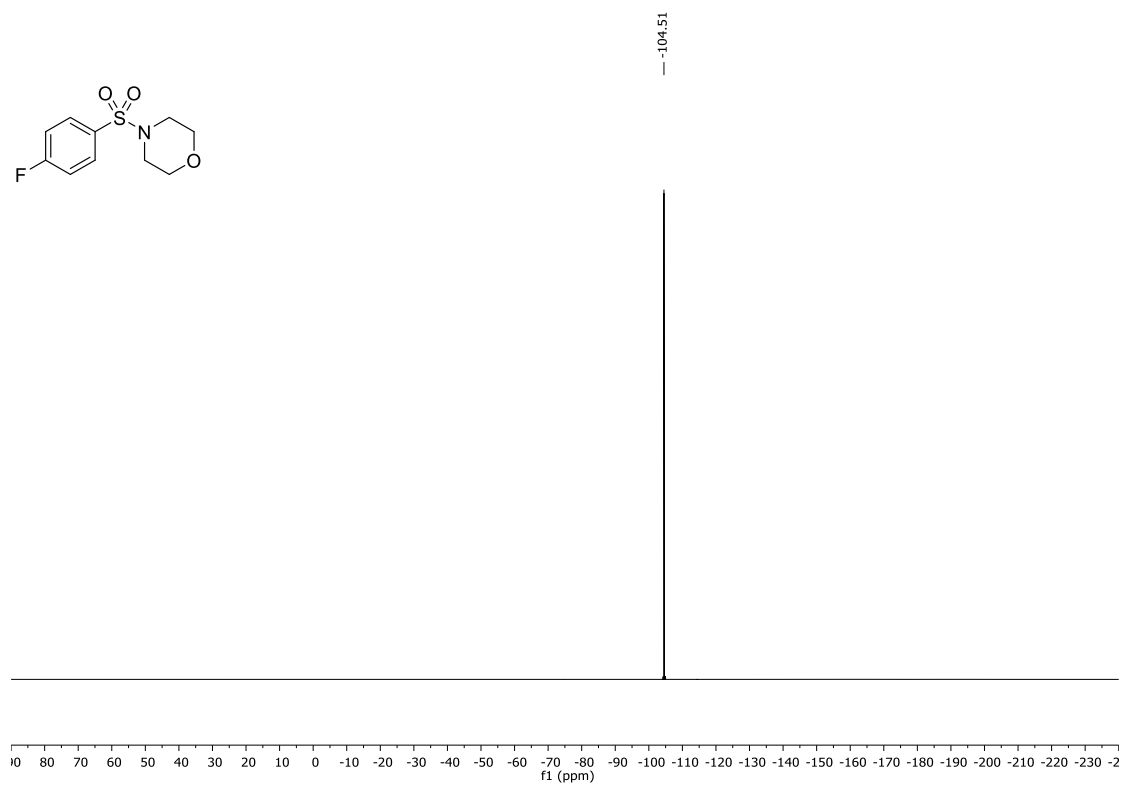


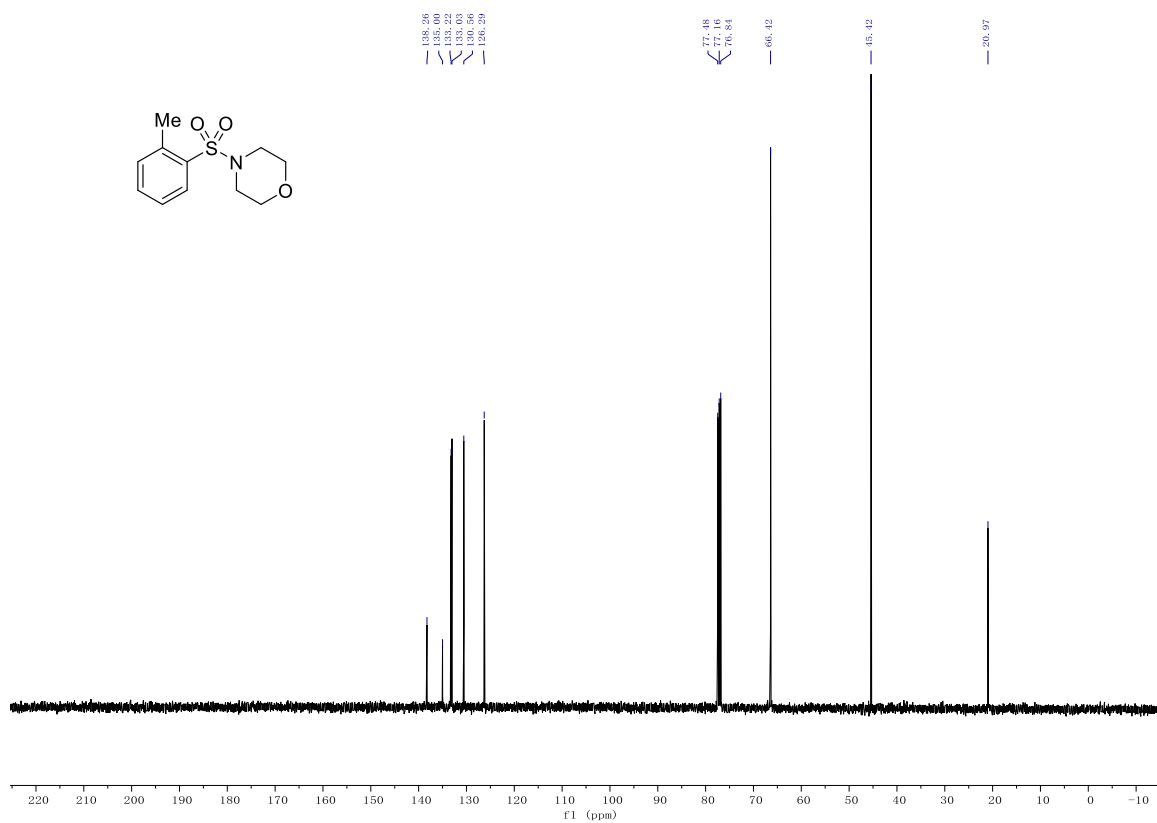
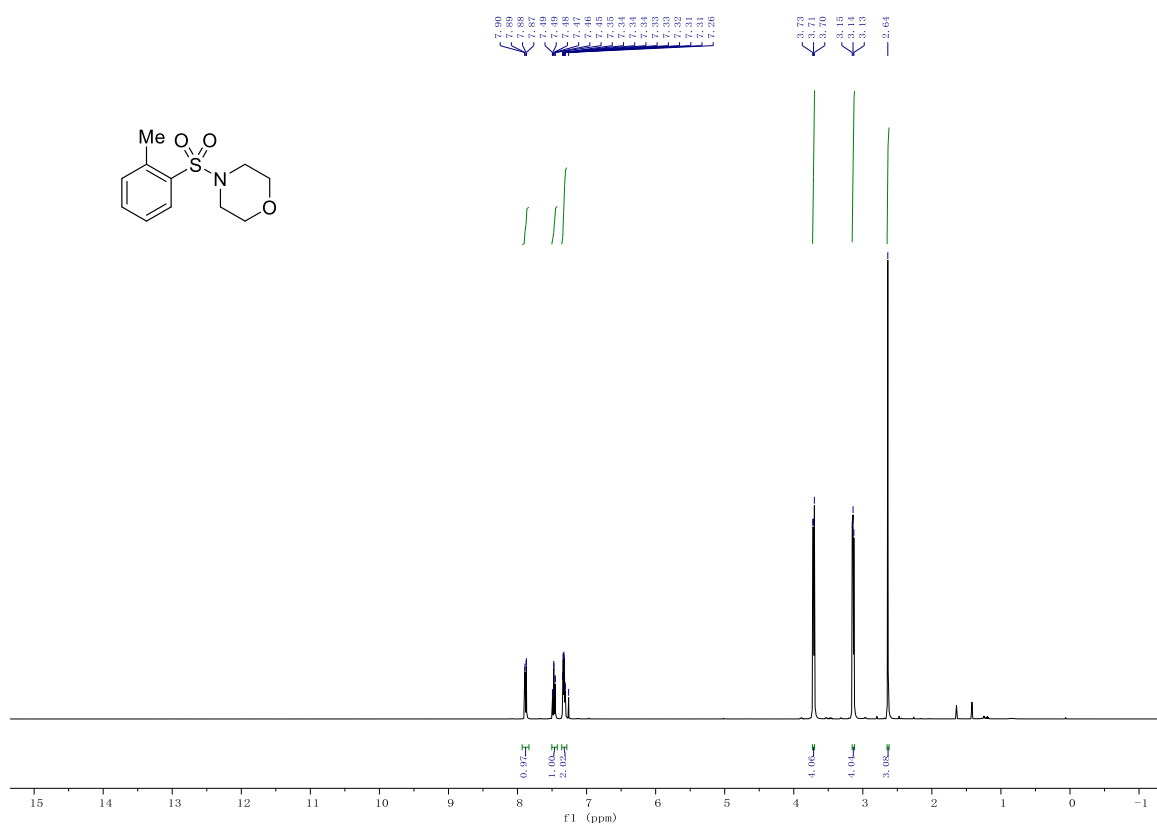
¹H NMR and ¹³C NMR spectra of *N,N*-dimethyl-4-(morpholinyl)sulfonyl aniline 45e

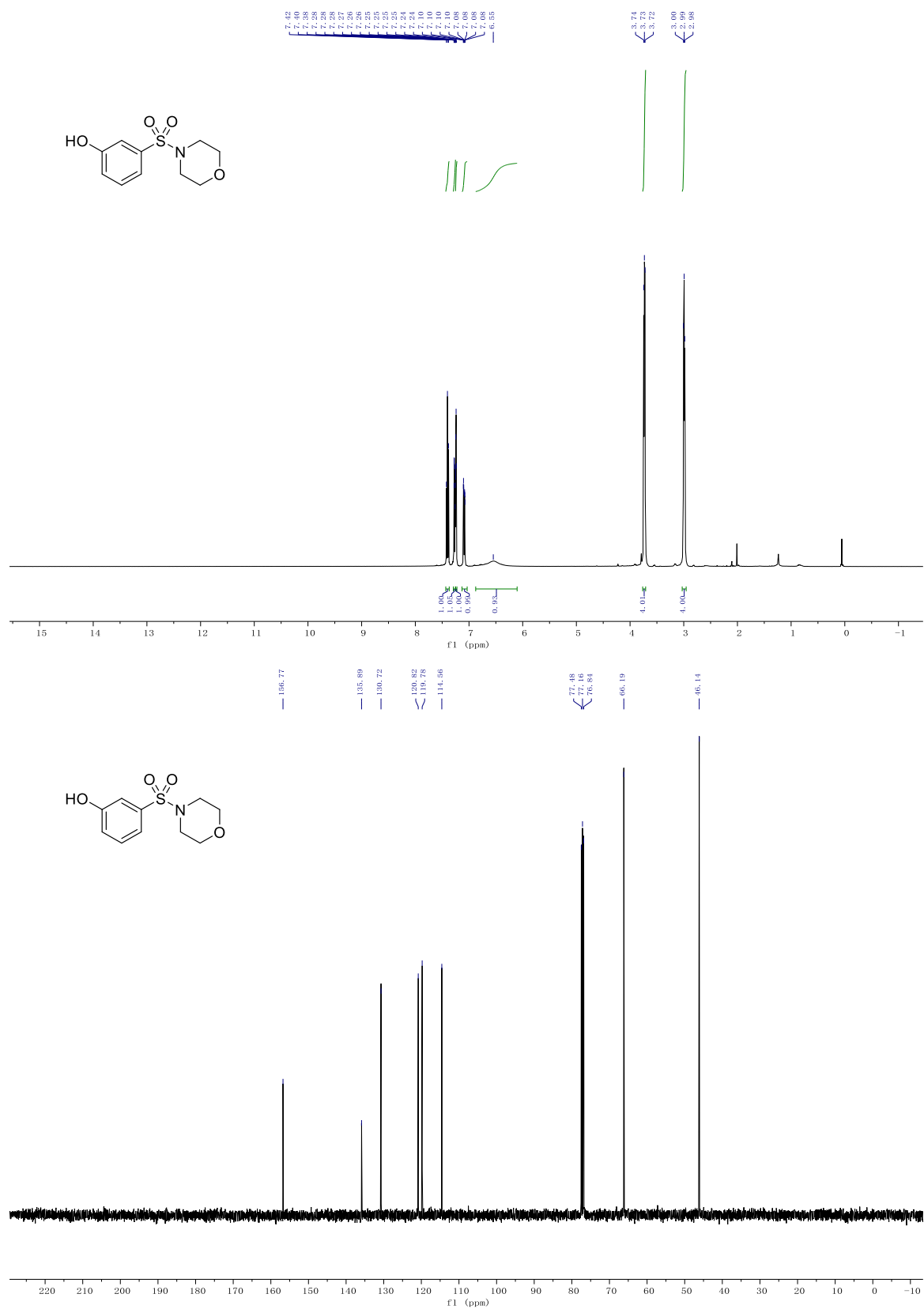
¹H NMR and ¹³C NMR spectra of 4-[(3-chlorophenyl)sulfonyl]morpholine 45h



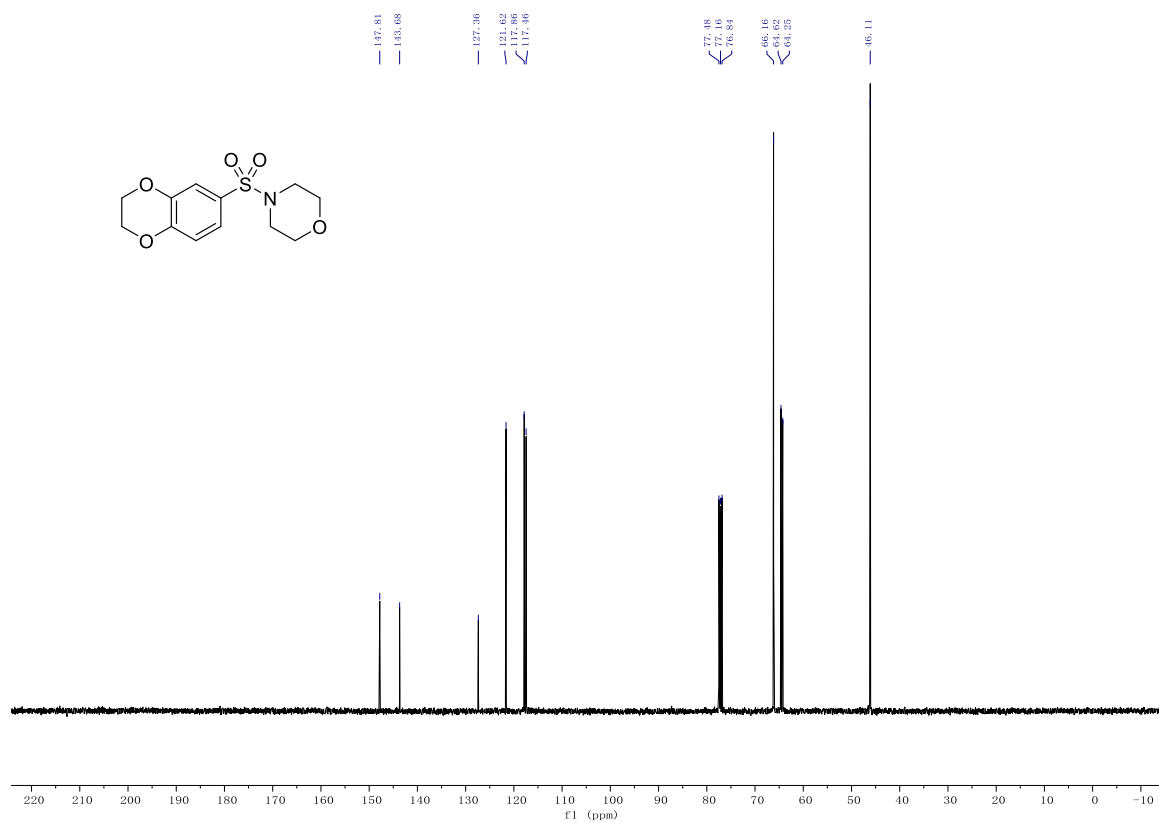
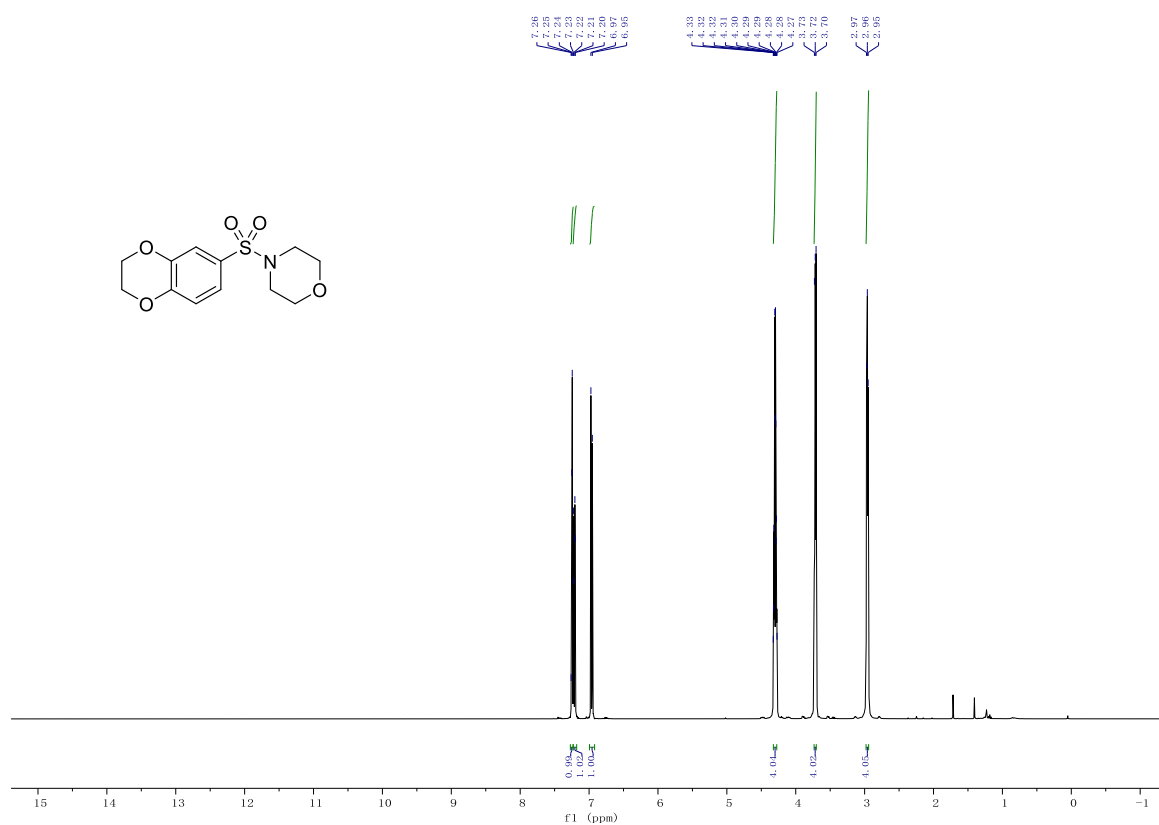
¹H NMR and ¹³C NMR spectra of 4-[(4-fluorophenyl)sulfonyl]morpholine 45i



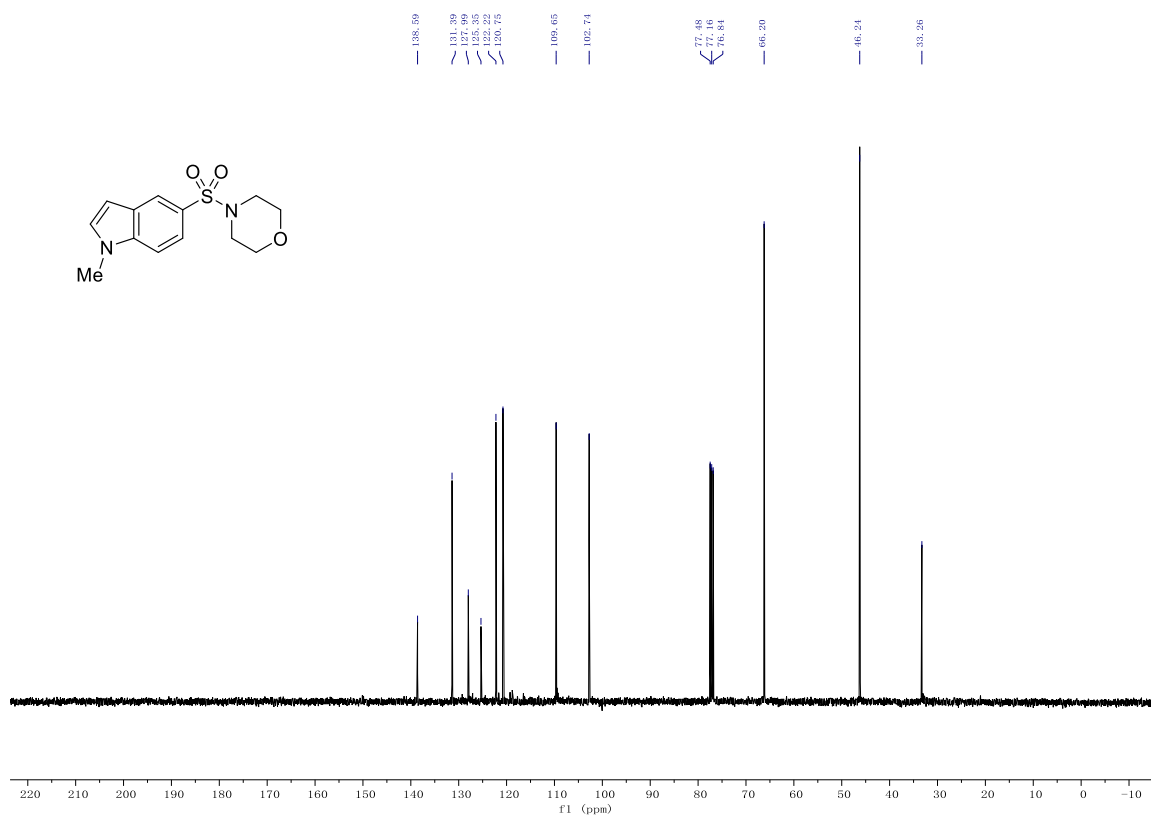
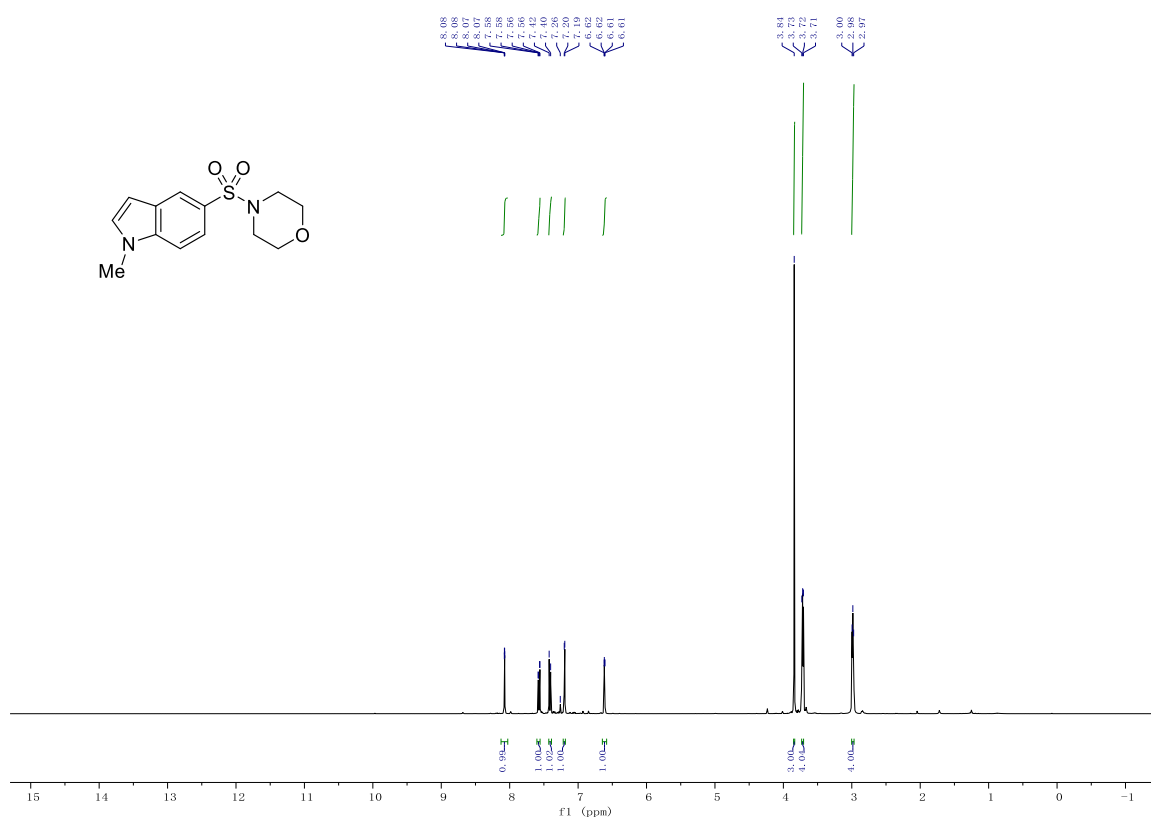
¹H NMR and ¹³C NMR spectra of **4-(*o*-tolylsulfonyl)morpholine 45j**



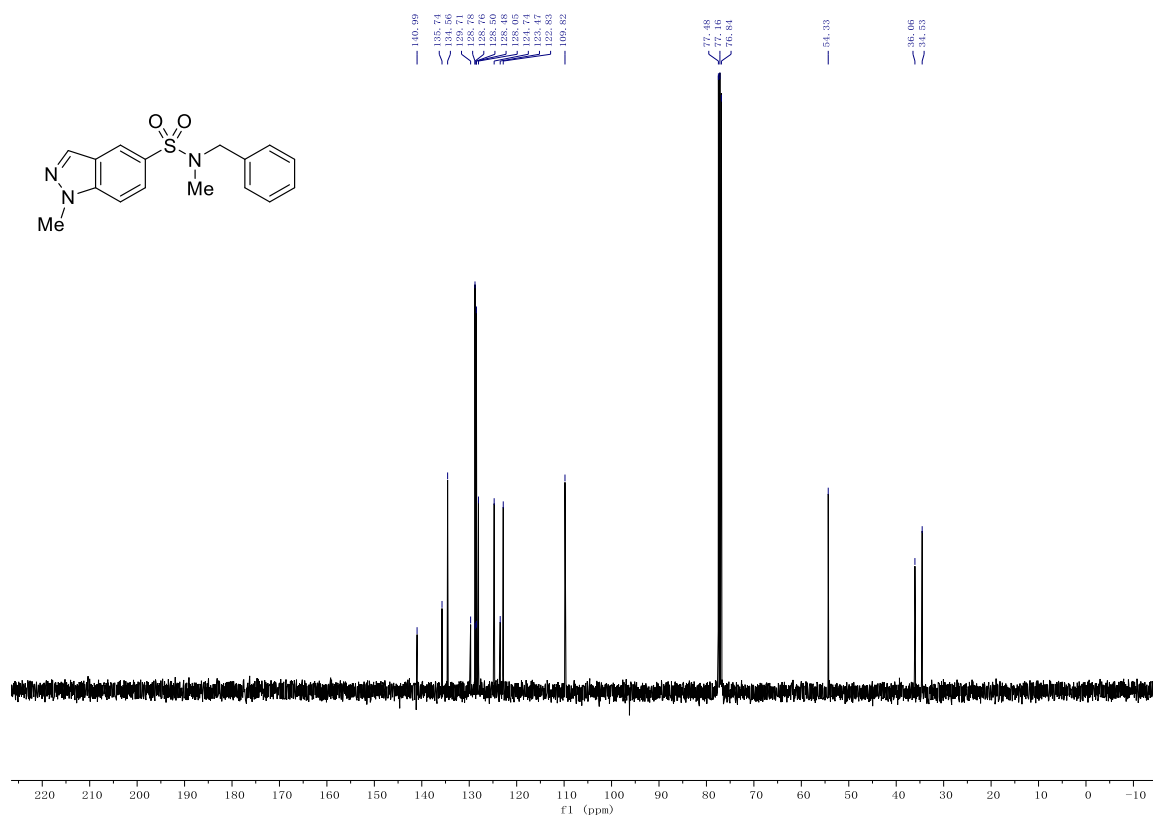
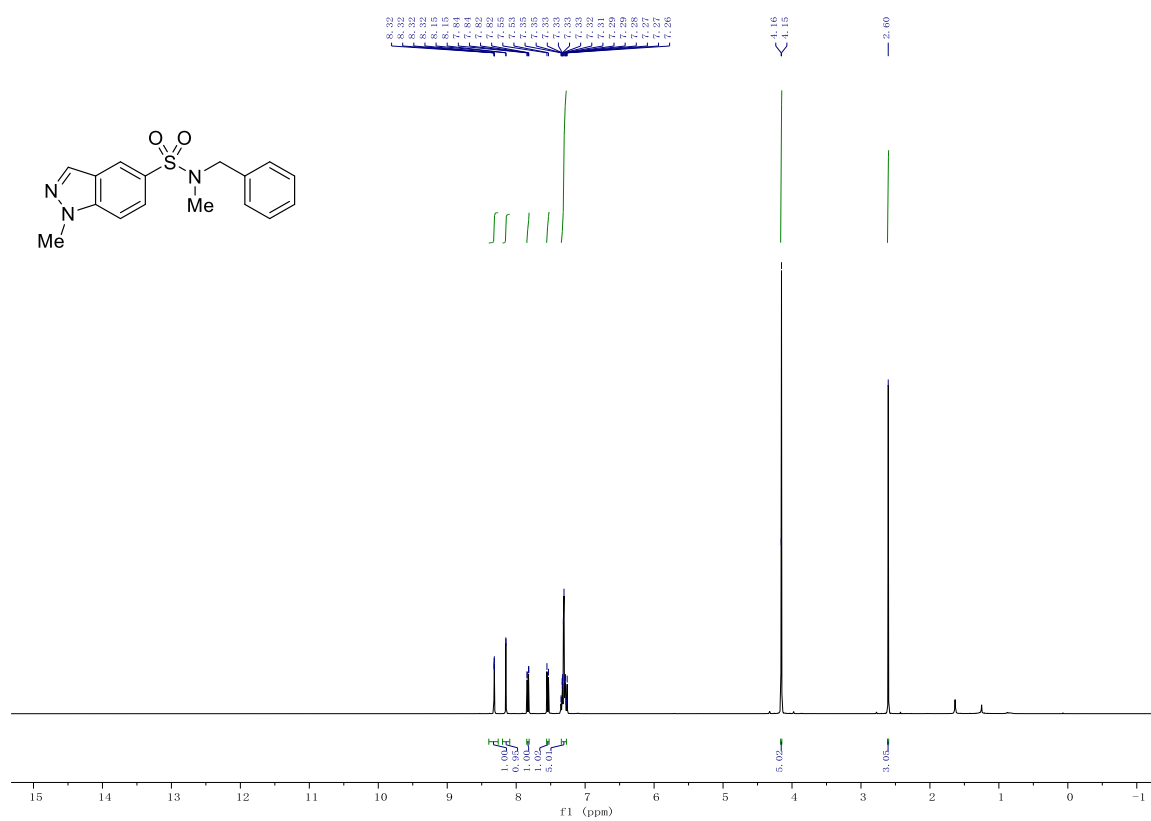
¹H NMR and ¹³C NMR spectra of 3-(morpholinosulfonyl)phenol 451

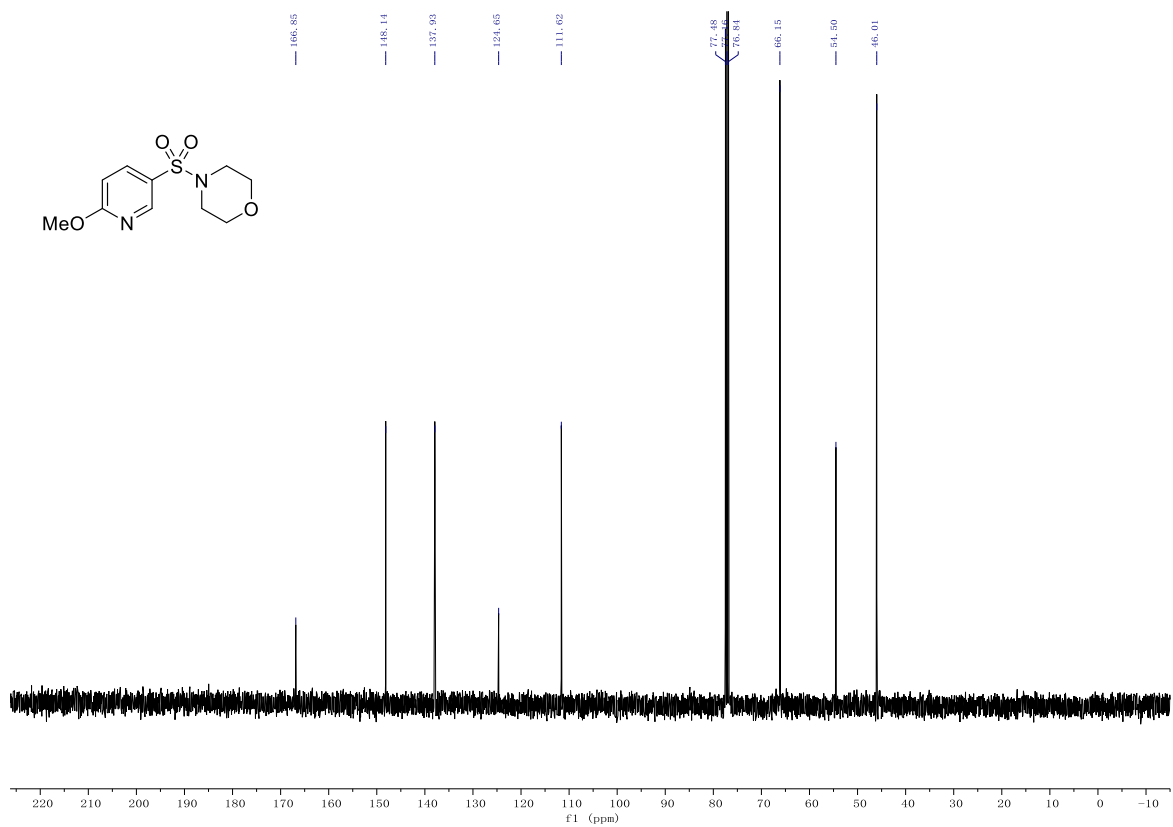
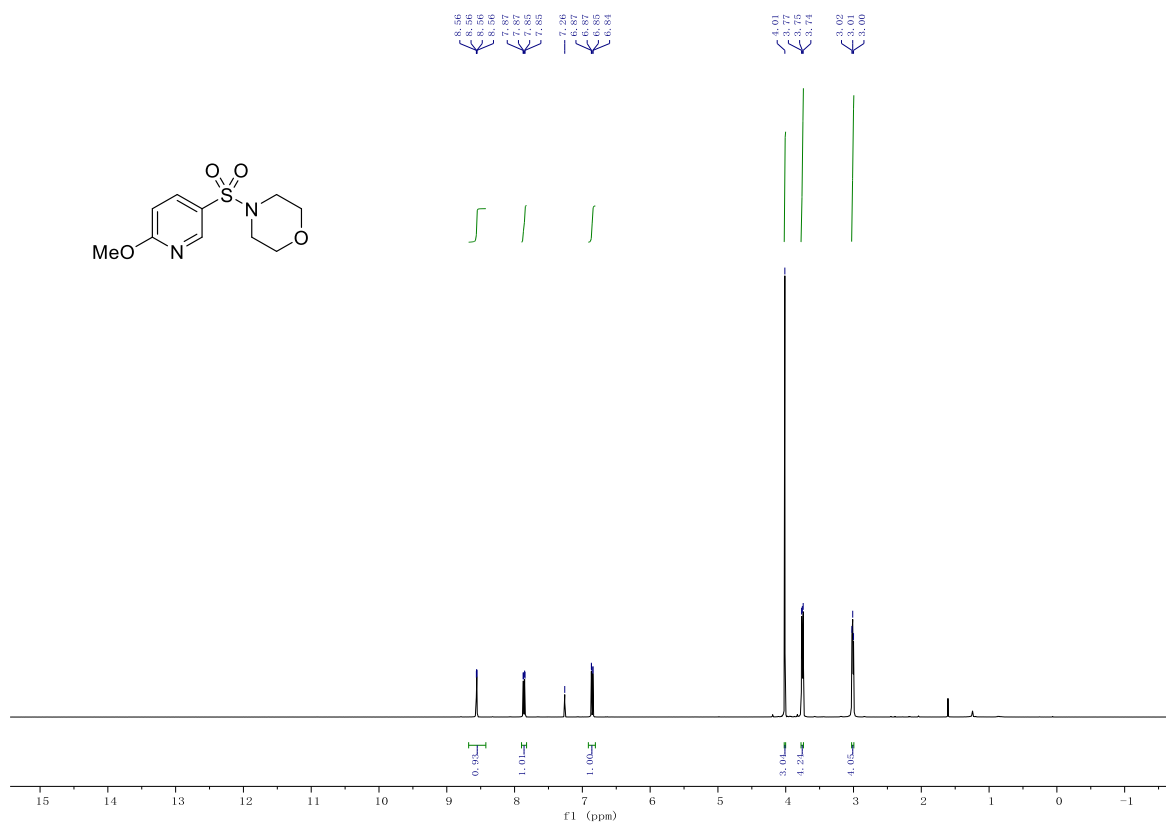


¹H NMR and ¹³C NMR spectra of 4-[(2,3-dihydrobenzo-[1,4]dioxin-6-yl)sulfonyl]morpholine
45m

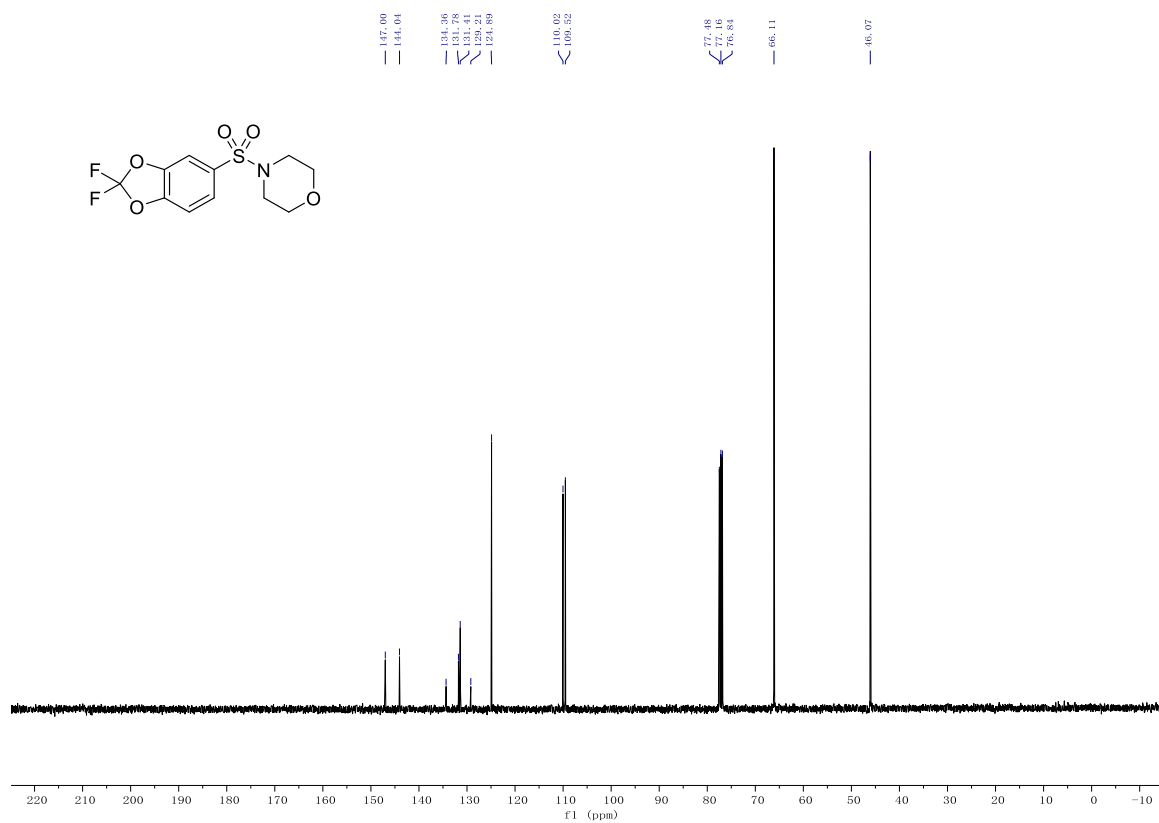
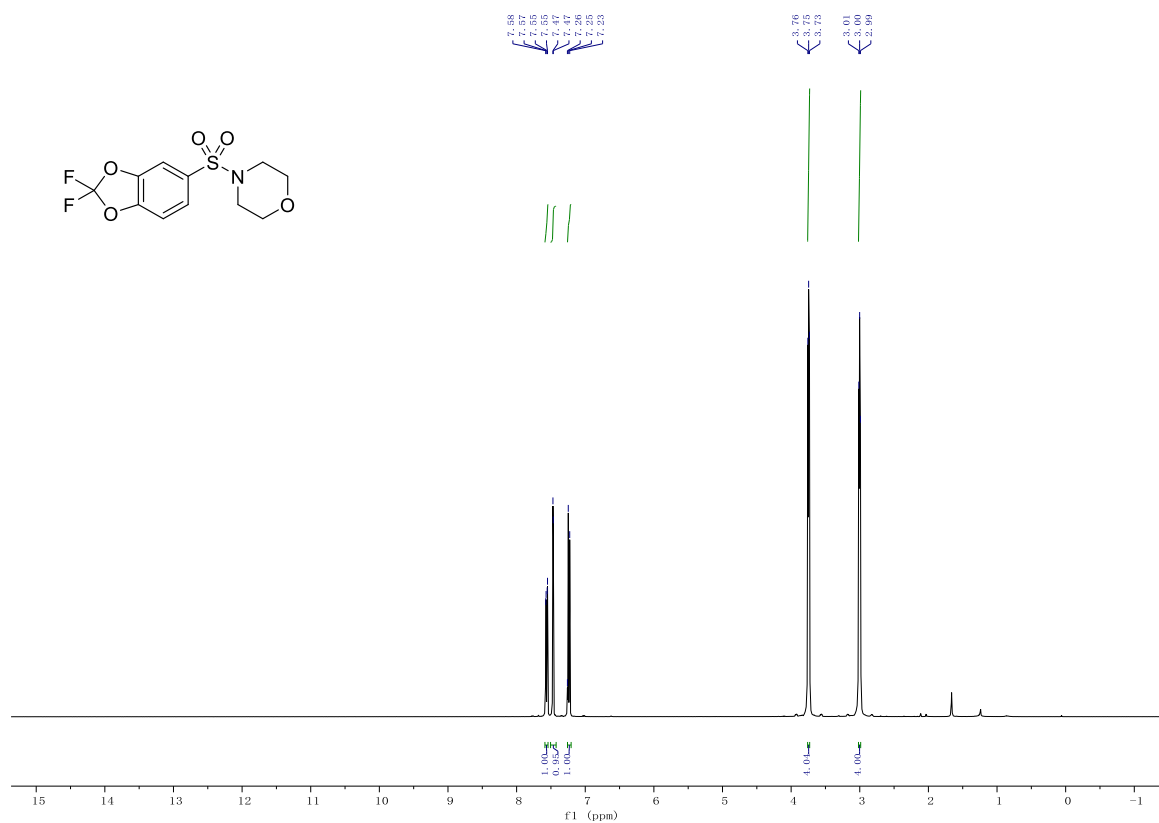


¹H NMR and ¹³C NMR spectra of 4-[(1-methyl-1*H*-indol-5-yl)sulfonyl]morpholine 45n

¹H NMR and ¹³C NMR spectra of *N*-benzyl-*N*,1-dimethyl-1*H*-indazole-5-sulfonamide 45o



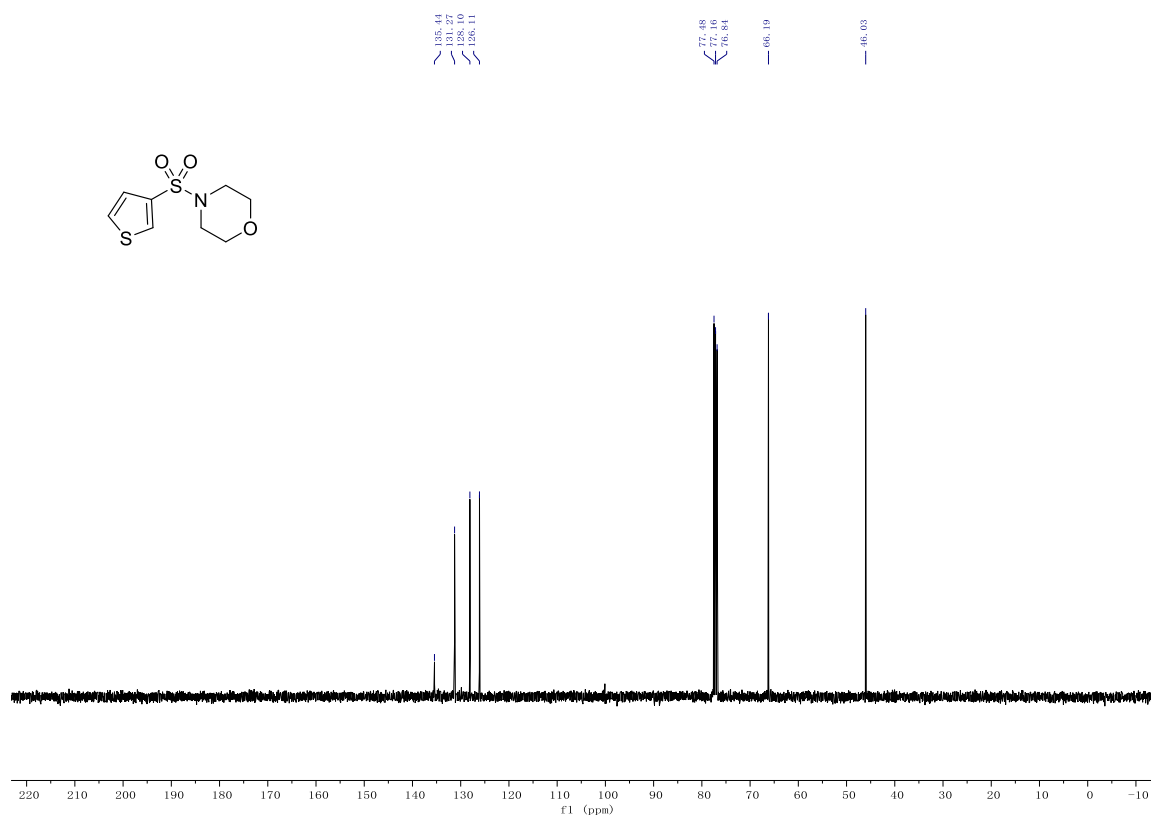
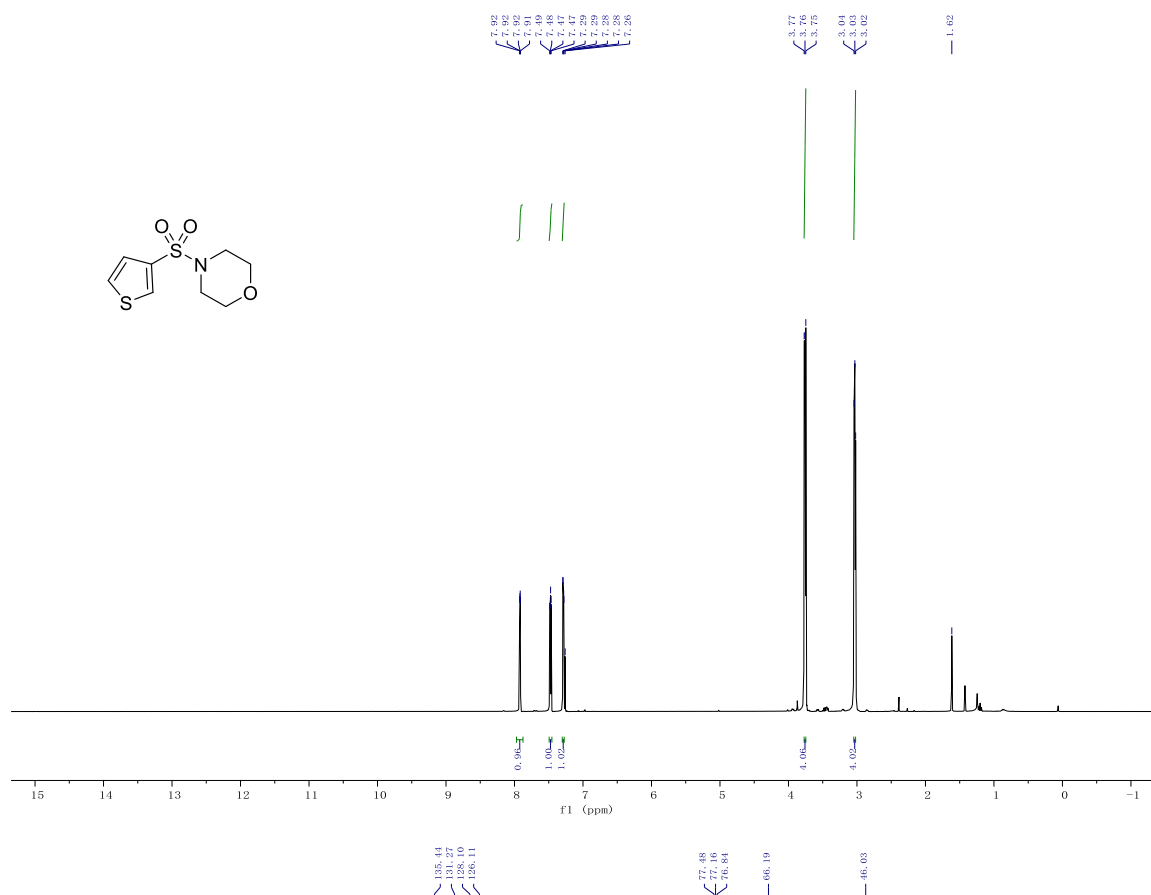
¹H NMR and ¹³C NMR spectra of 4-[(6-methoxypyridin-3-yl)sulfonyl]morpholine 45p



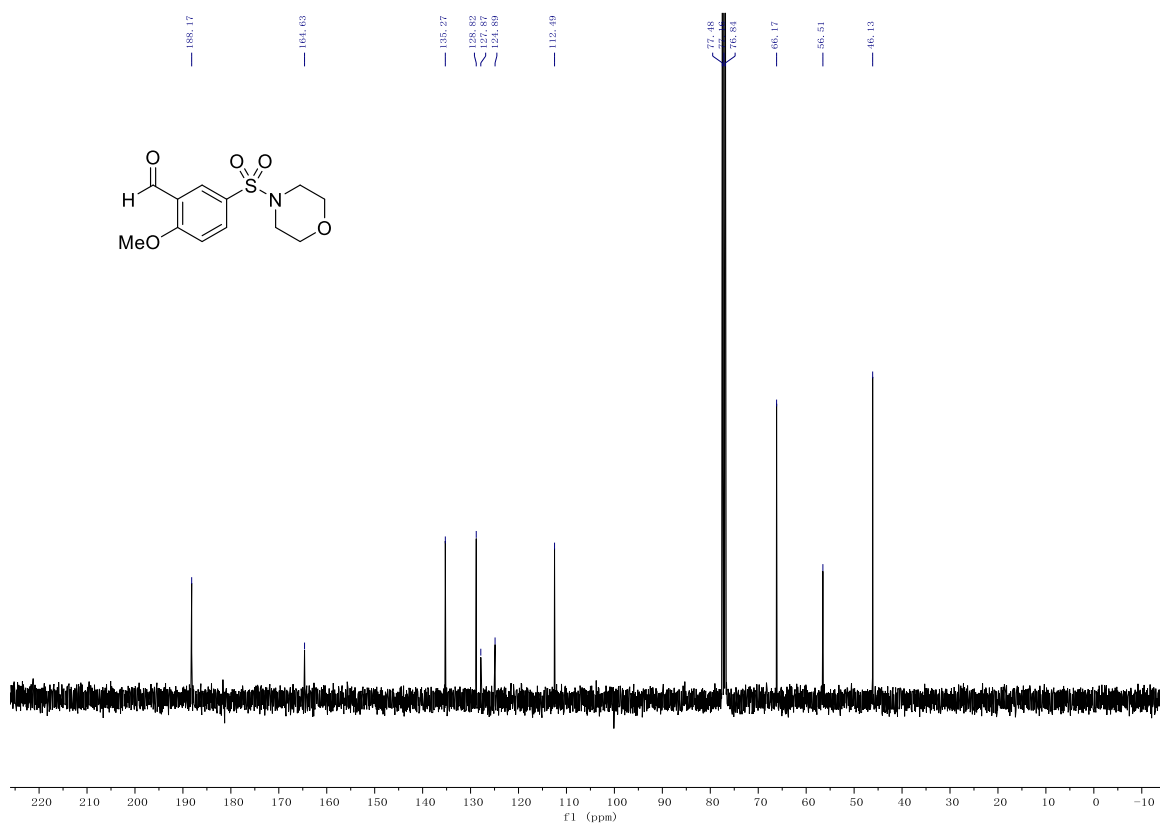
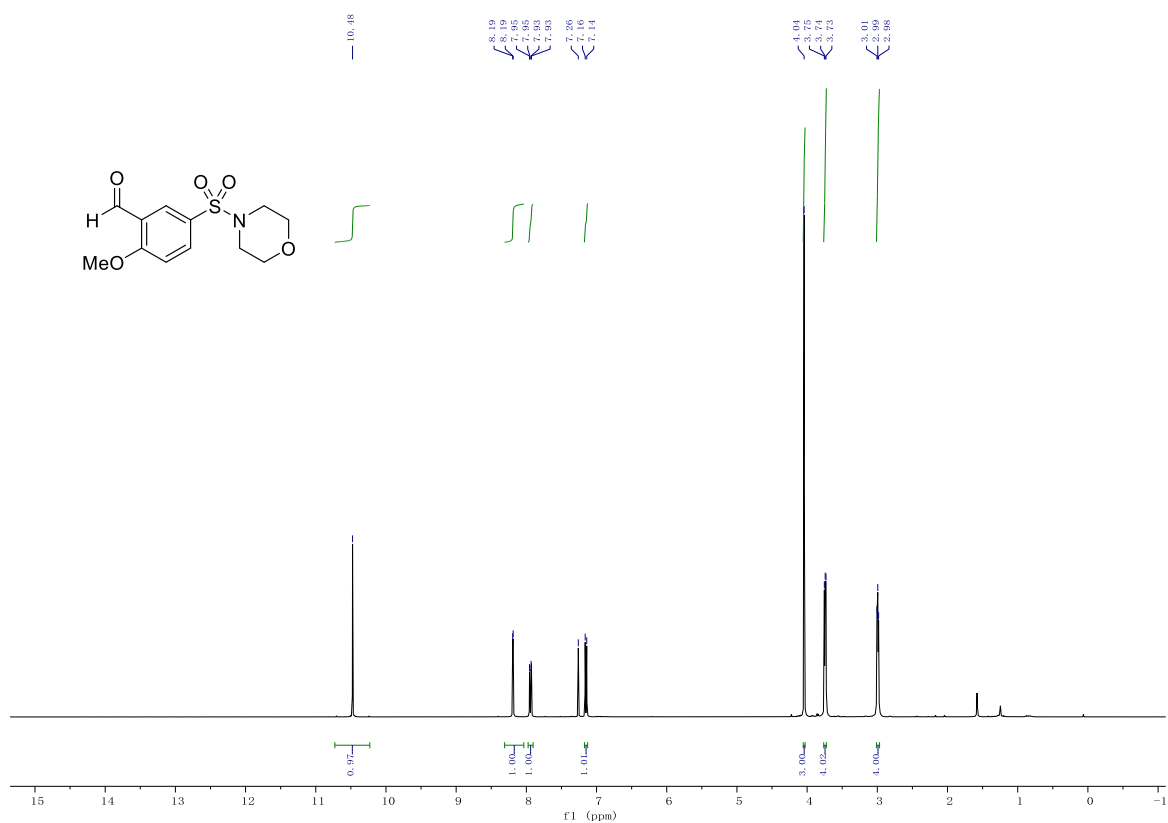
¹H NMR and ¹³C NMR spectra of 4-[(2,2-difluorobenzo[d][1,3]dioxol-5-yl)sulfonyl]morpholine 45r



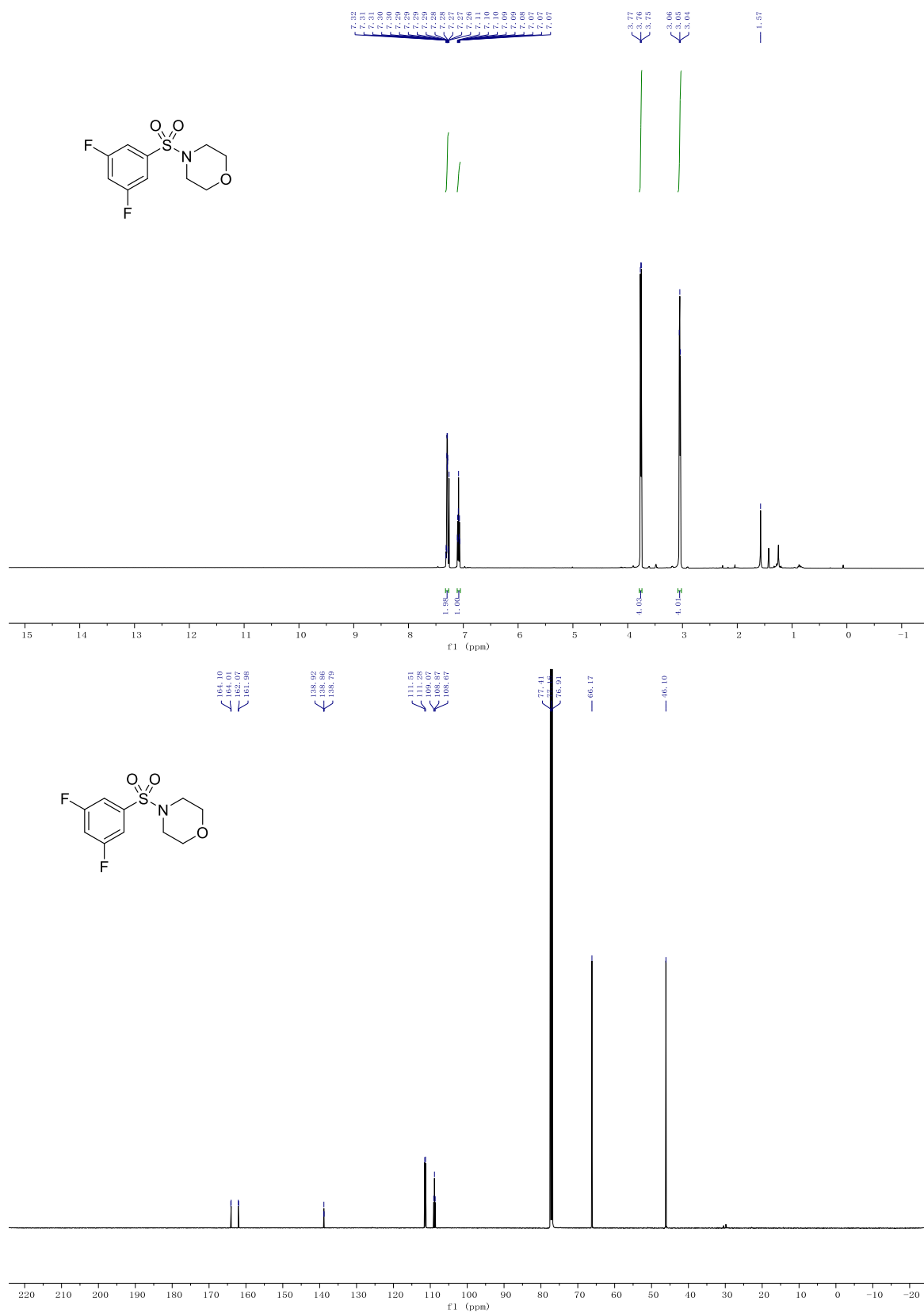
^{19}F NMR spectrum of 4-[(2,2-difluorobenzo[d][1,3]dioxol-5-yl)sulfonyl]morpholine 45r



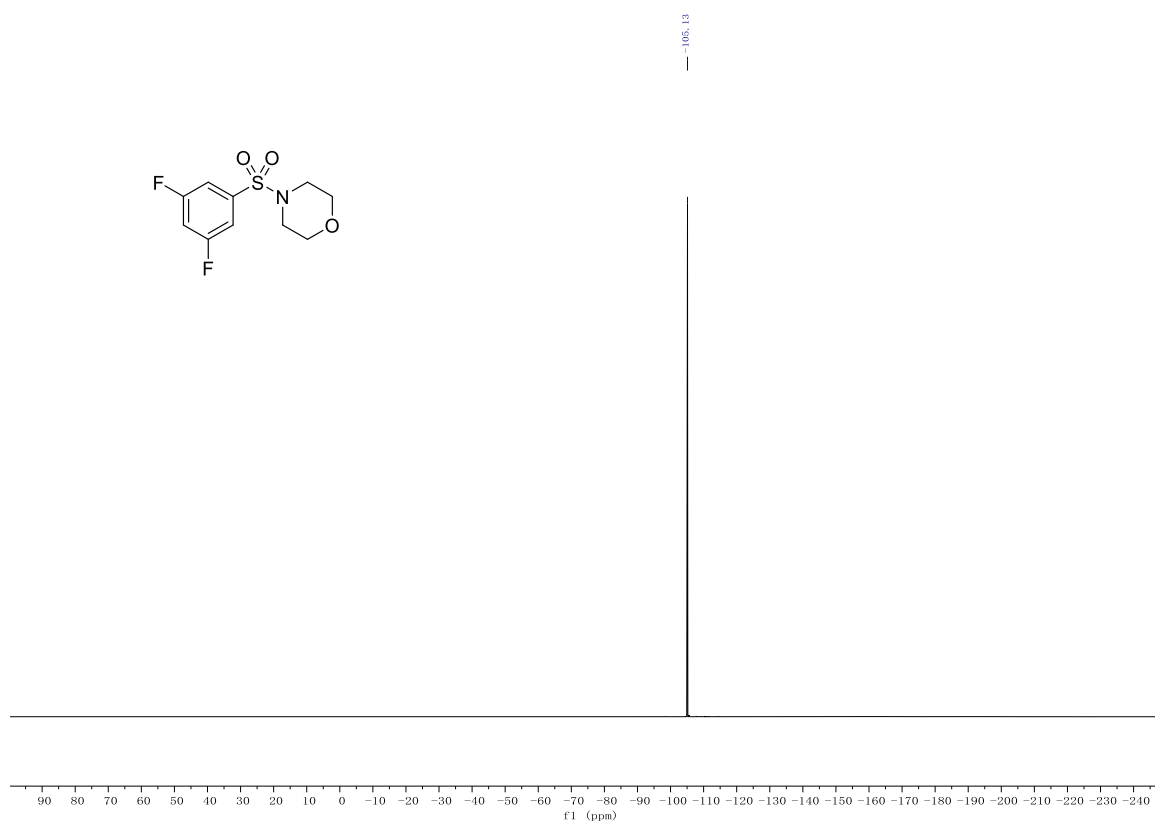
¹H NMR and ¹³C NMR spectra of 4-(thiophen-3-ylsulfonyl)morpholine 45ad



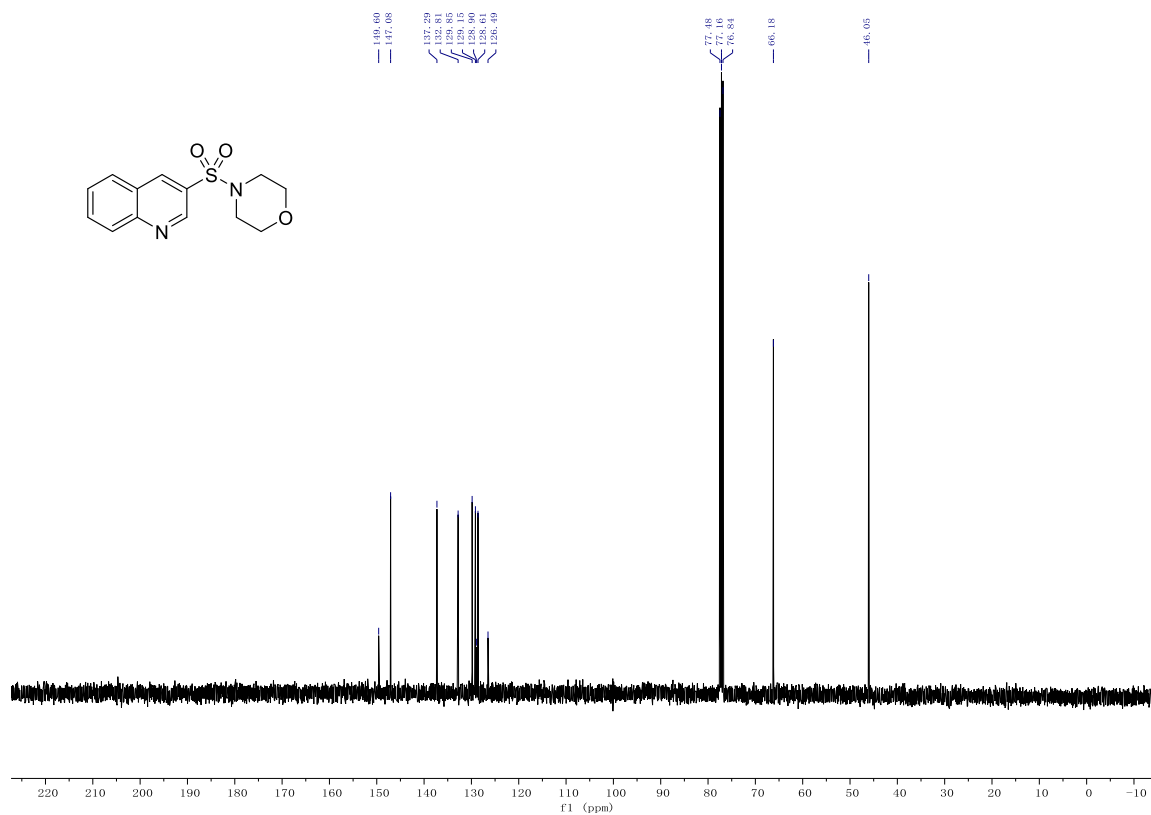
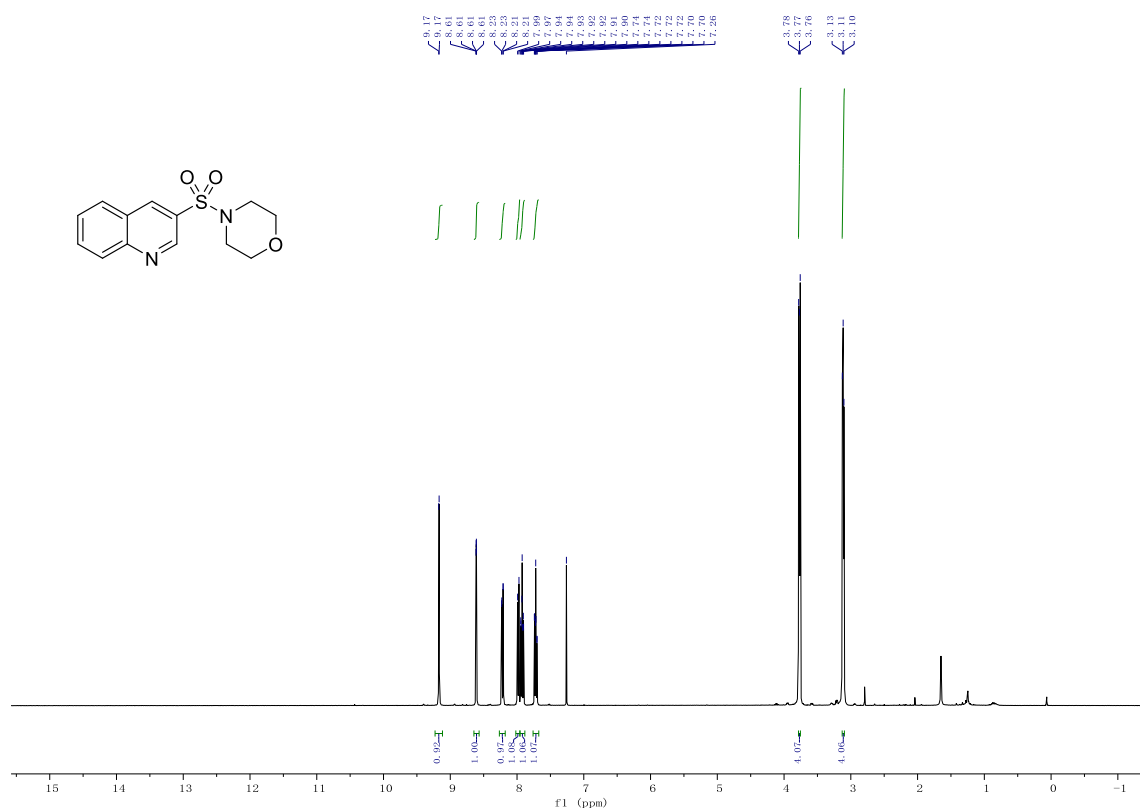
¹H NMR and ¹³C NMR spectra of 2-methoxy-5-(morpholinosulfonyl)benzaldehyde 45ae



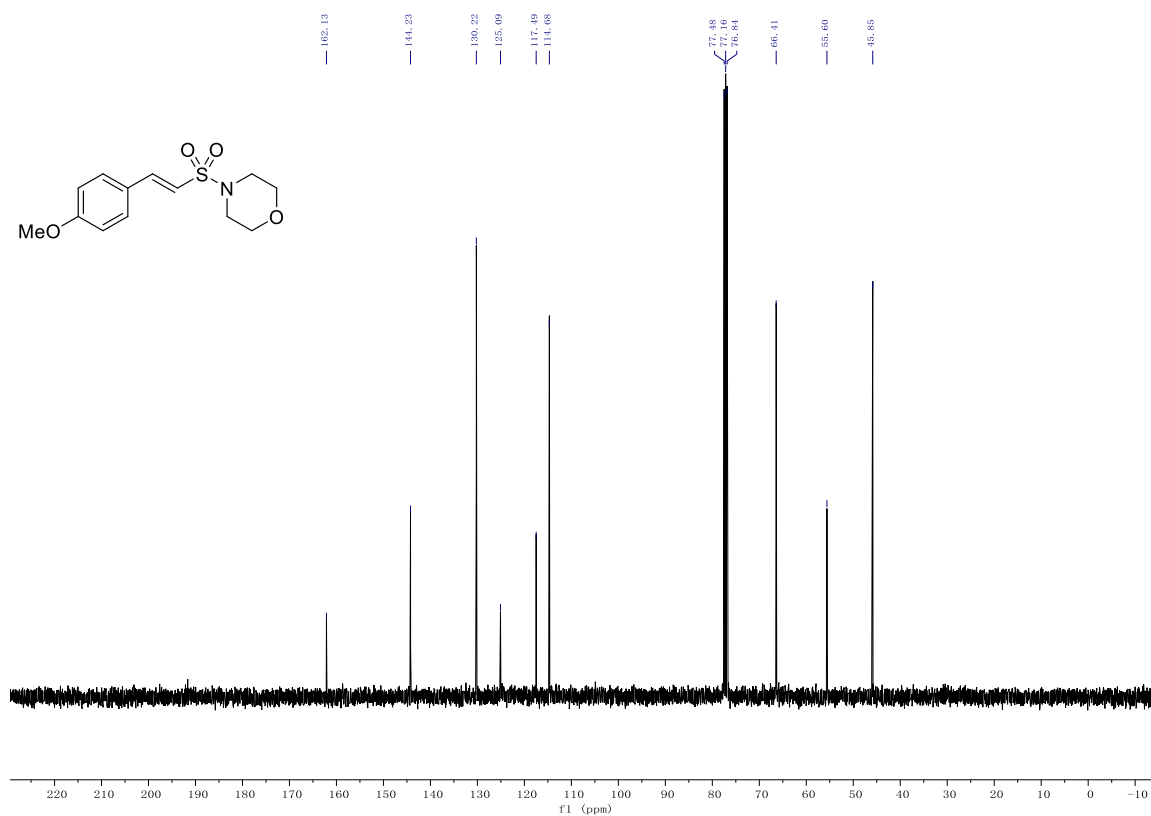
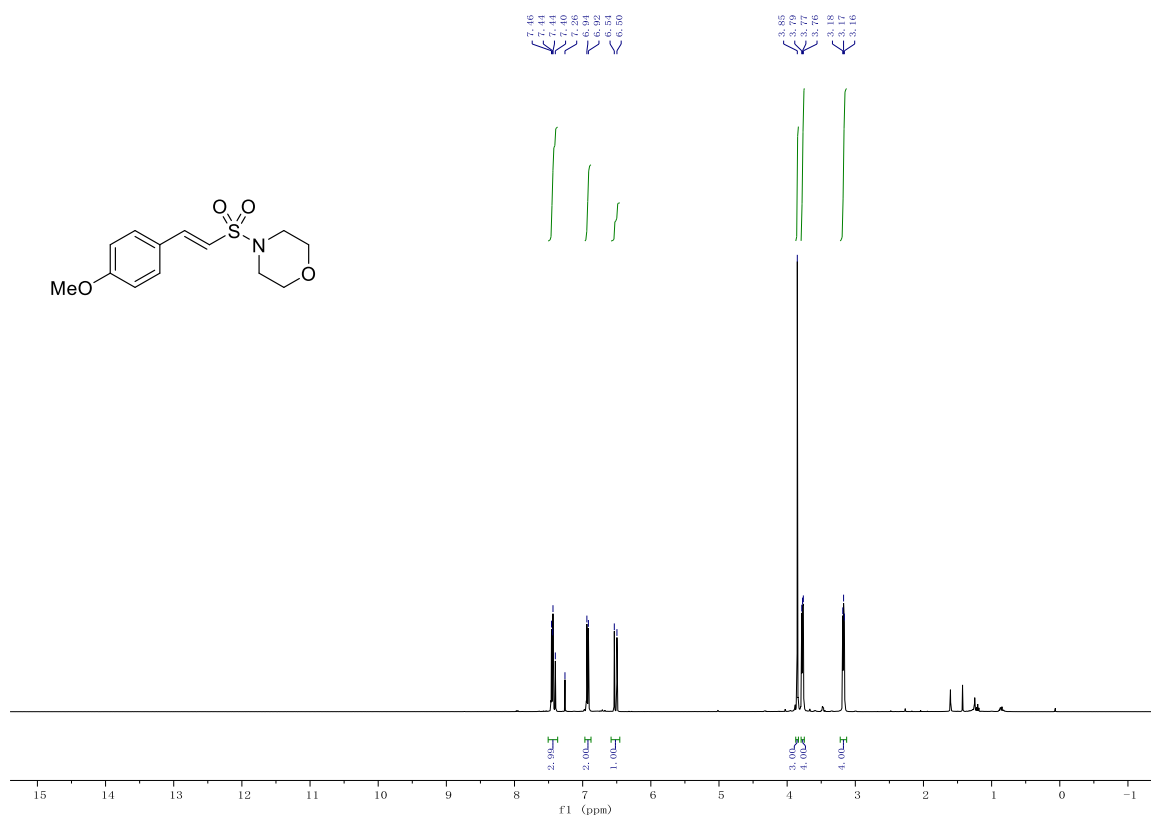
¹H NMR and ¹³C NMR spectra of 4-[(3,5-difluorophenyl)sulfonyl]morpholine 45af



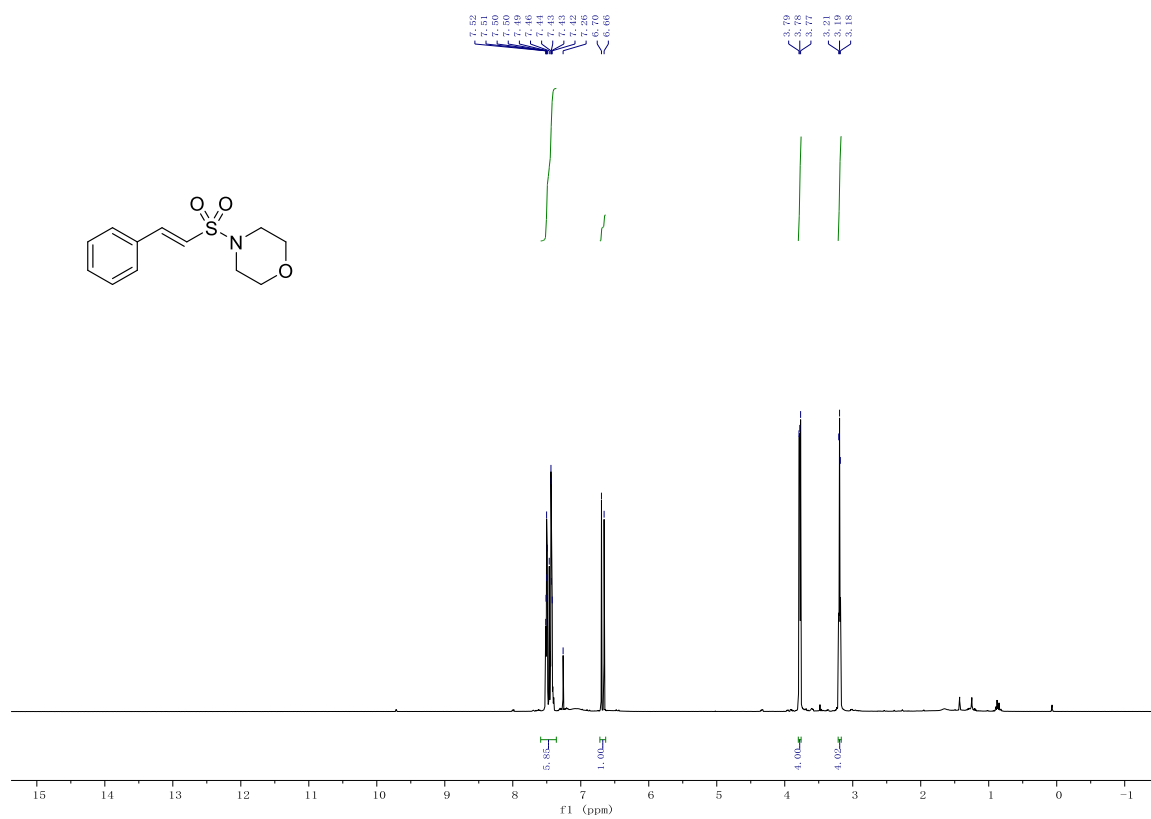
^{19}F NMR spectrum of 4-[(3,5-difluorophenyl)sulfonyl]morpholine 45af

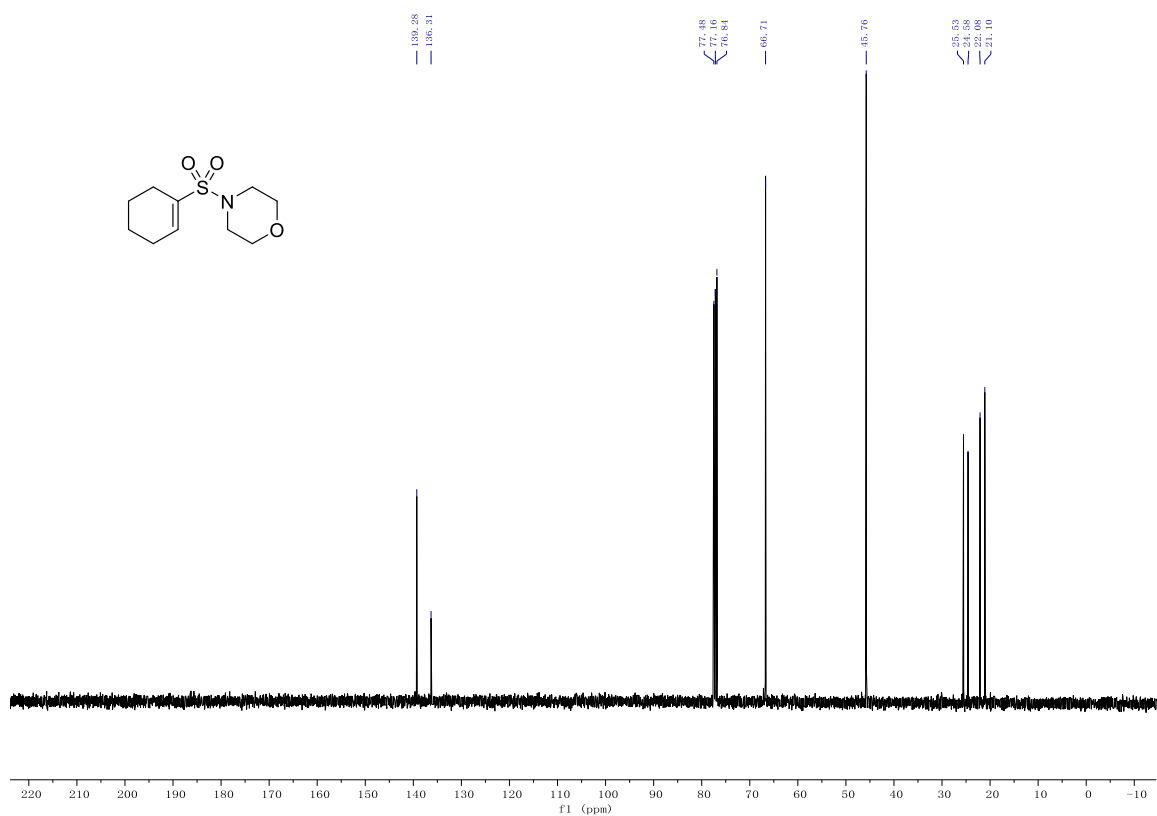
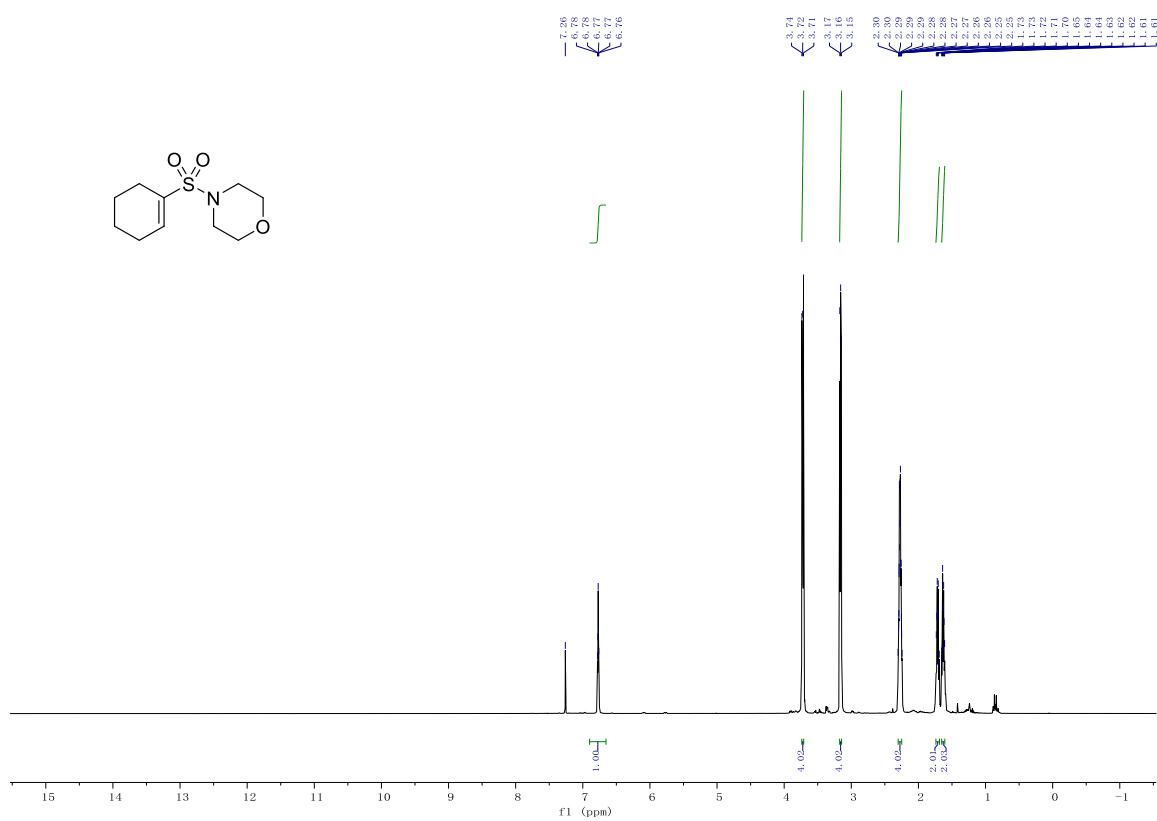


¹H NMR and ¹³C NMR spectra of 4-(quinolin-3-ylsulfonyl)morpholine 45ah

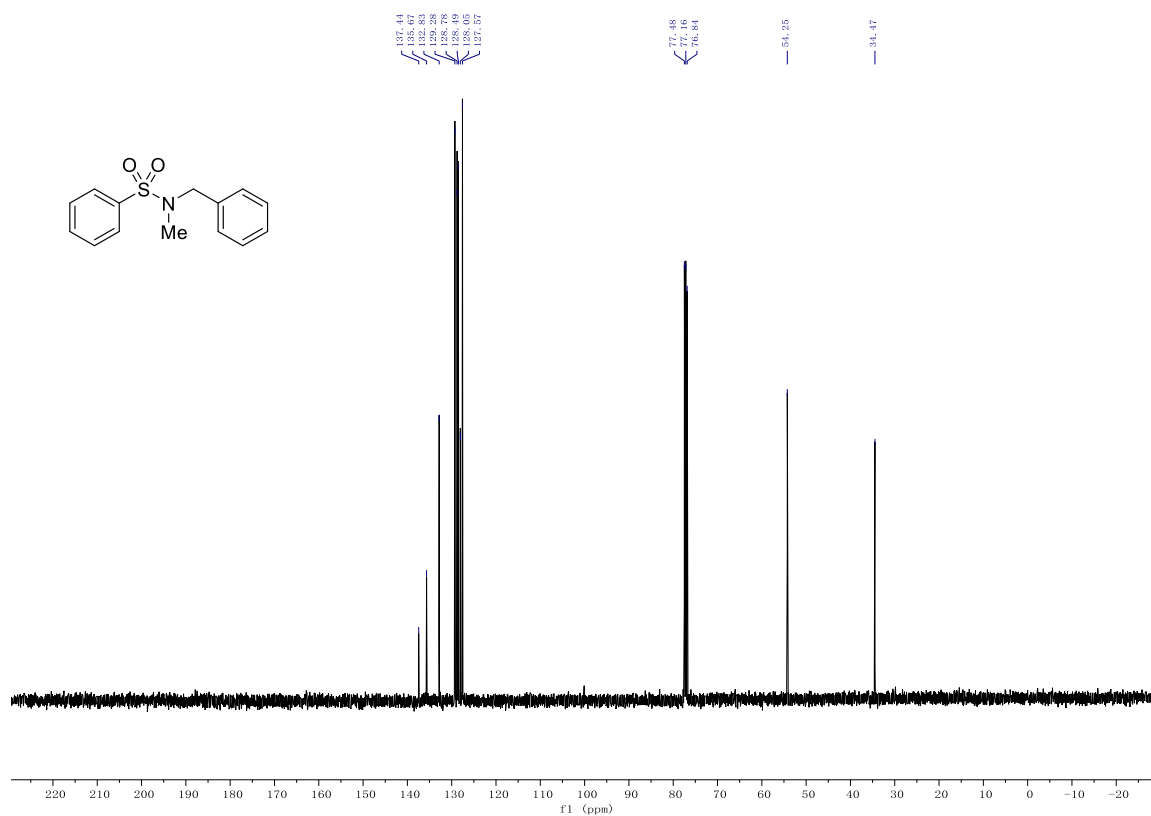
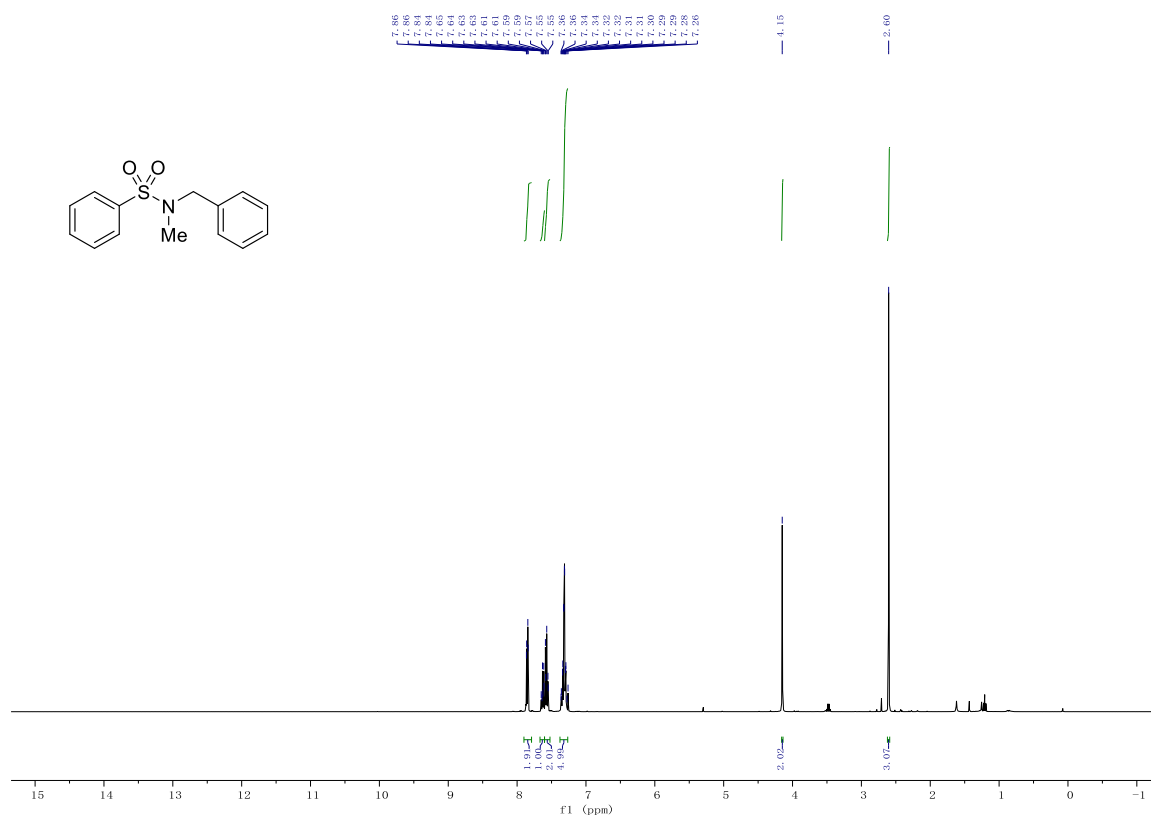


¹H NMR and ¹³C NMR spectra of *trans*-4-[(4-methoxystyryl)sulfonyl]morpholine 46a

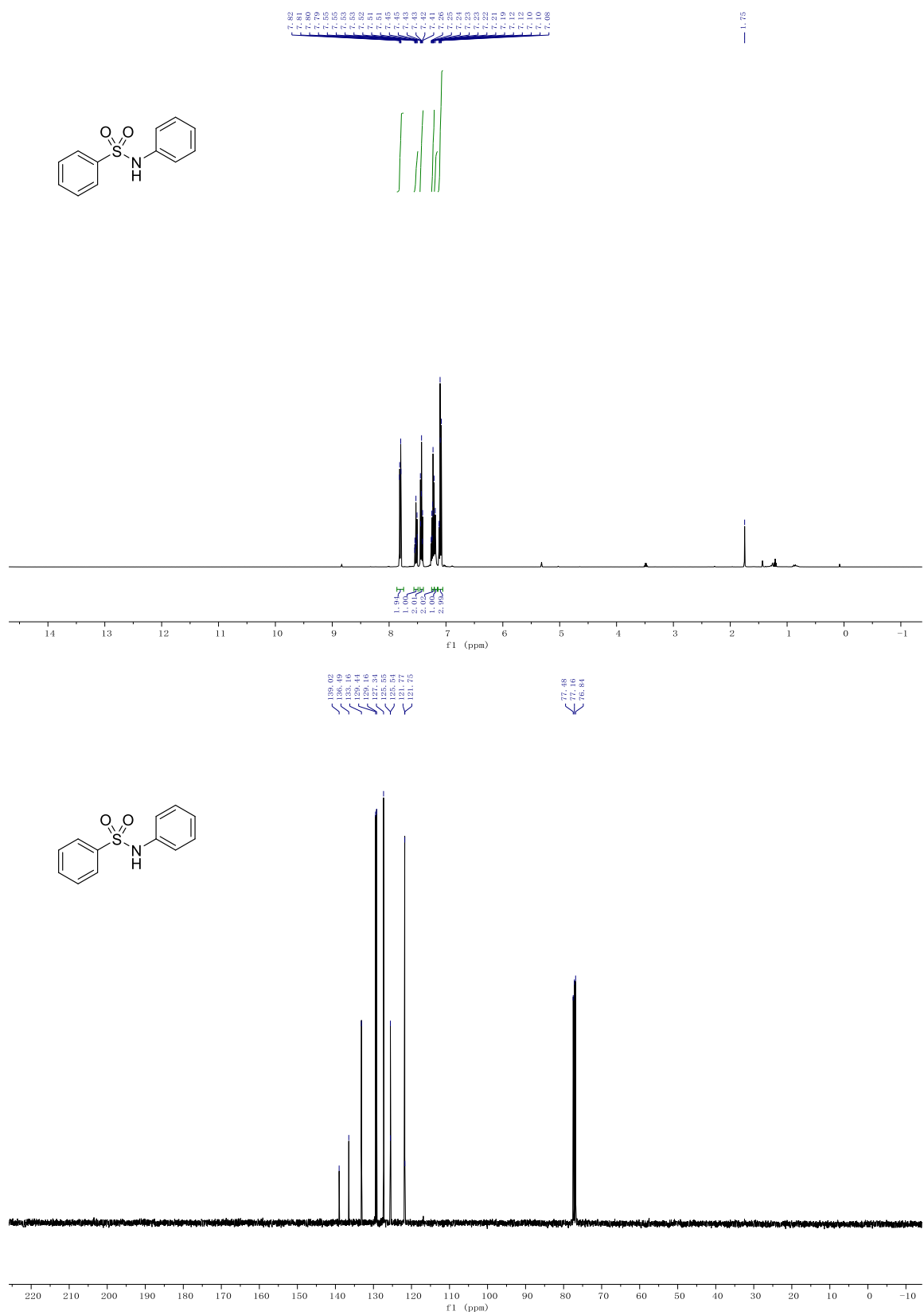




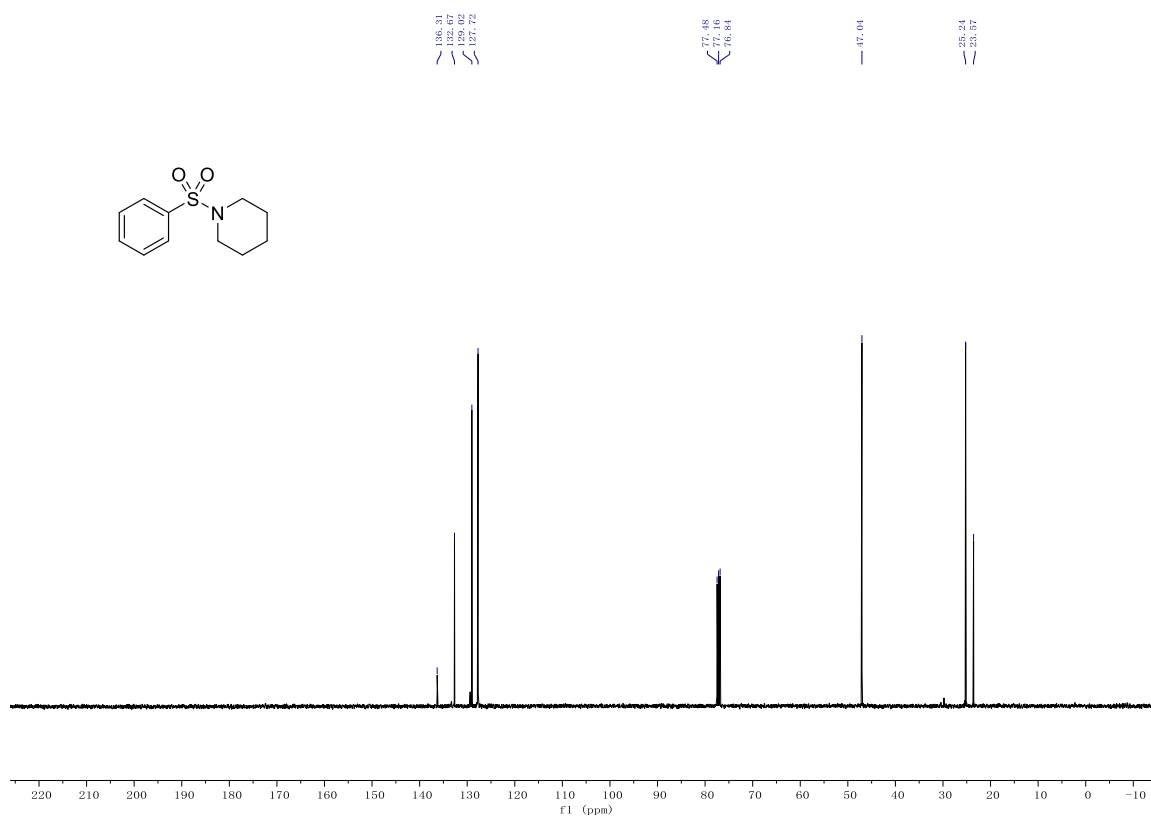
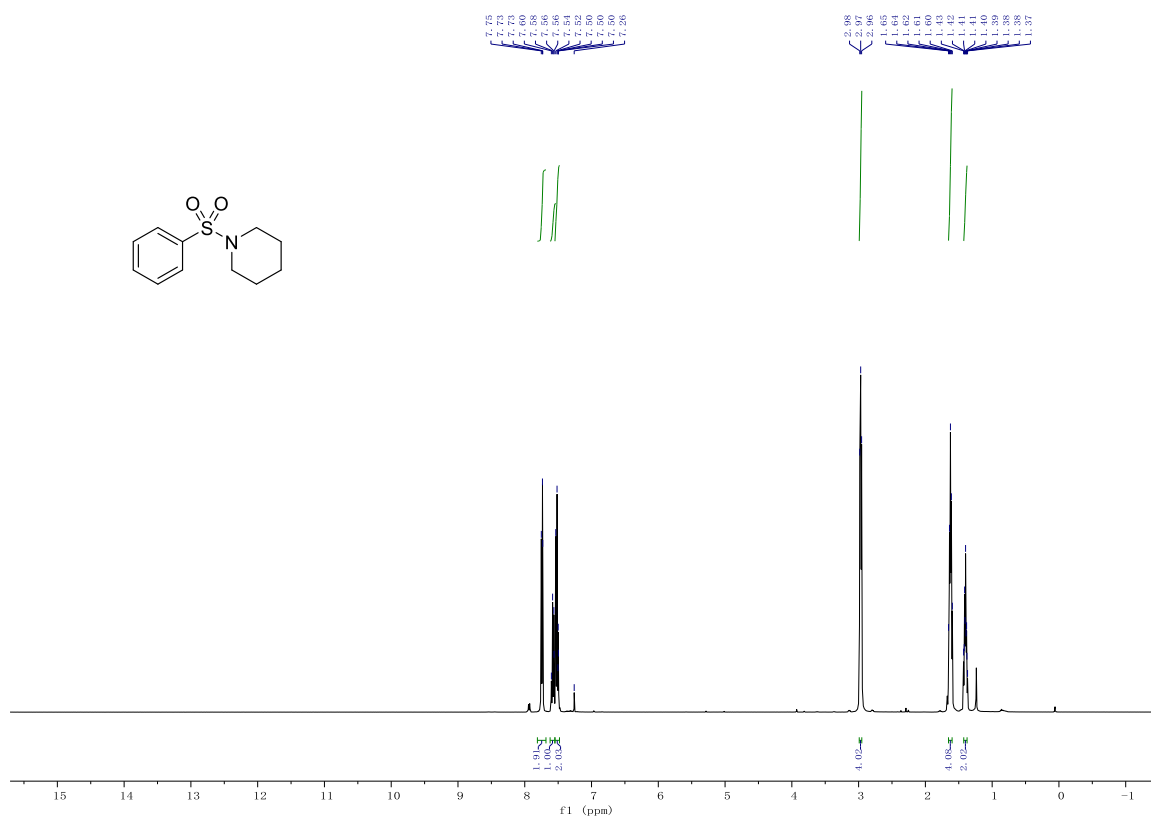
¹H NMR and ¹³C NMR spectra of 4-(cyclohex-1-en-1-ylsulfonyl)morpholine 46c



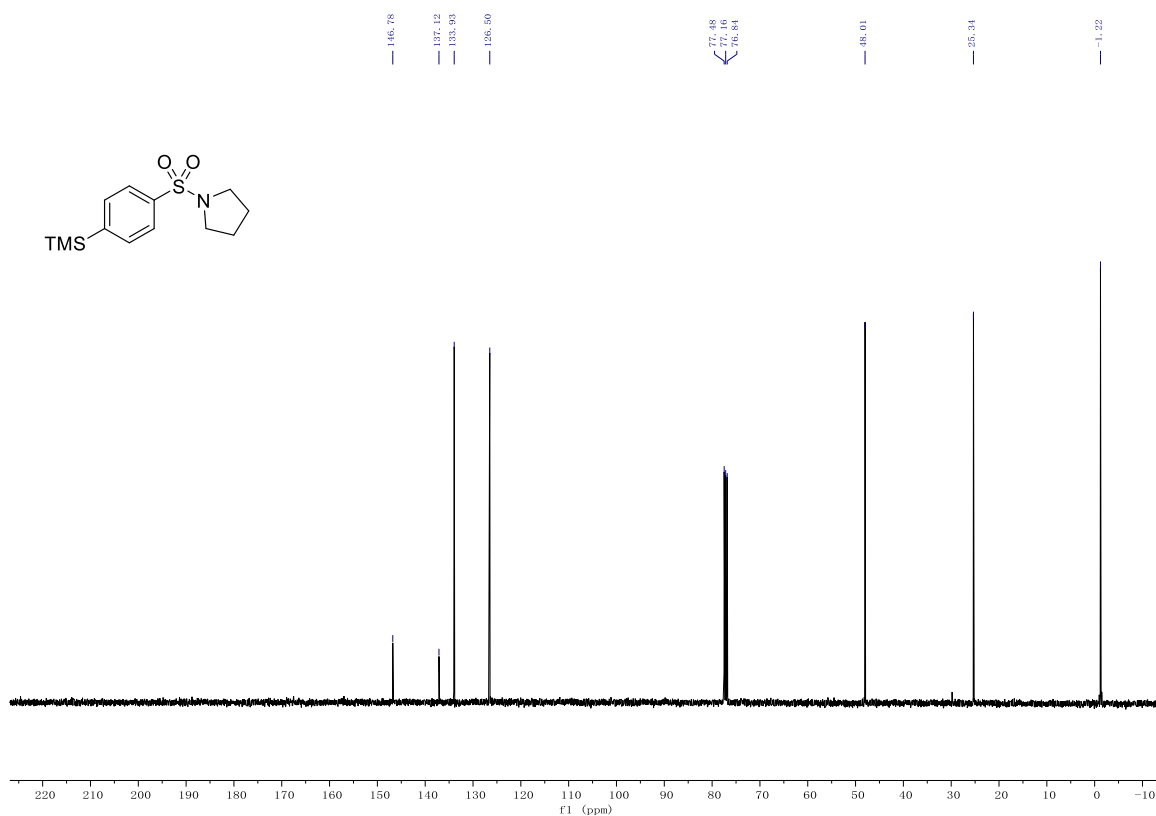
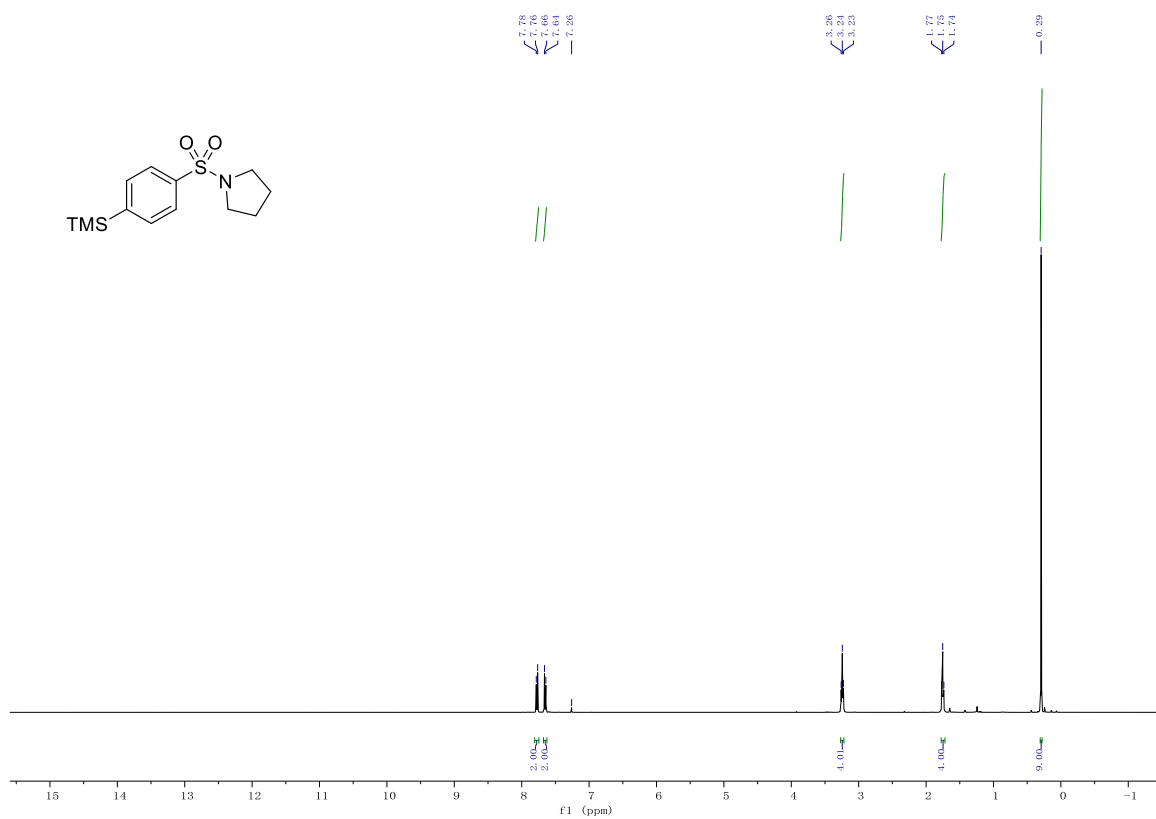
¹H NMR and ¹³C NMR spectra of *N*-benzyl-*N*-methylbenzenesulfonamide 48a



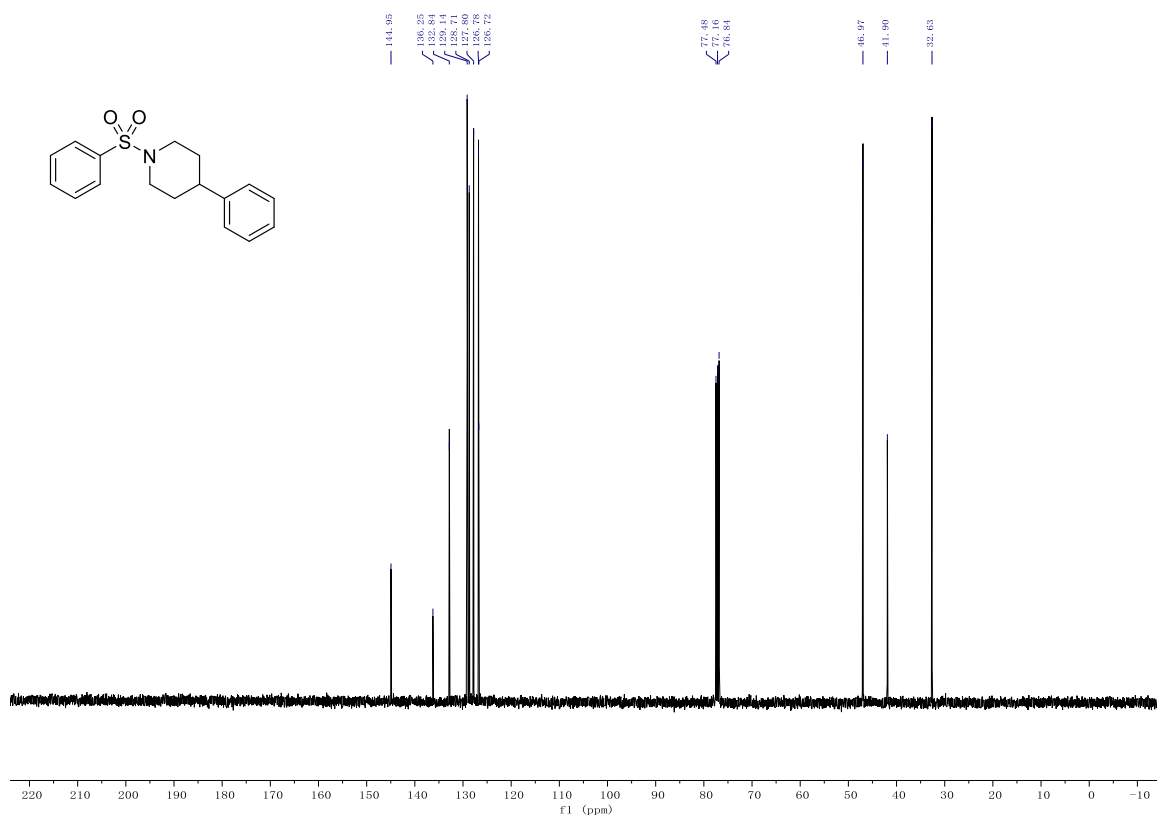
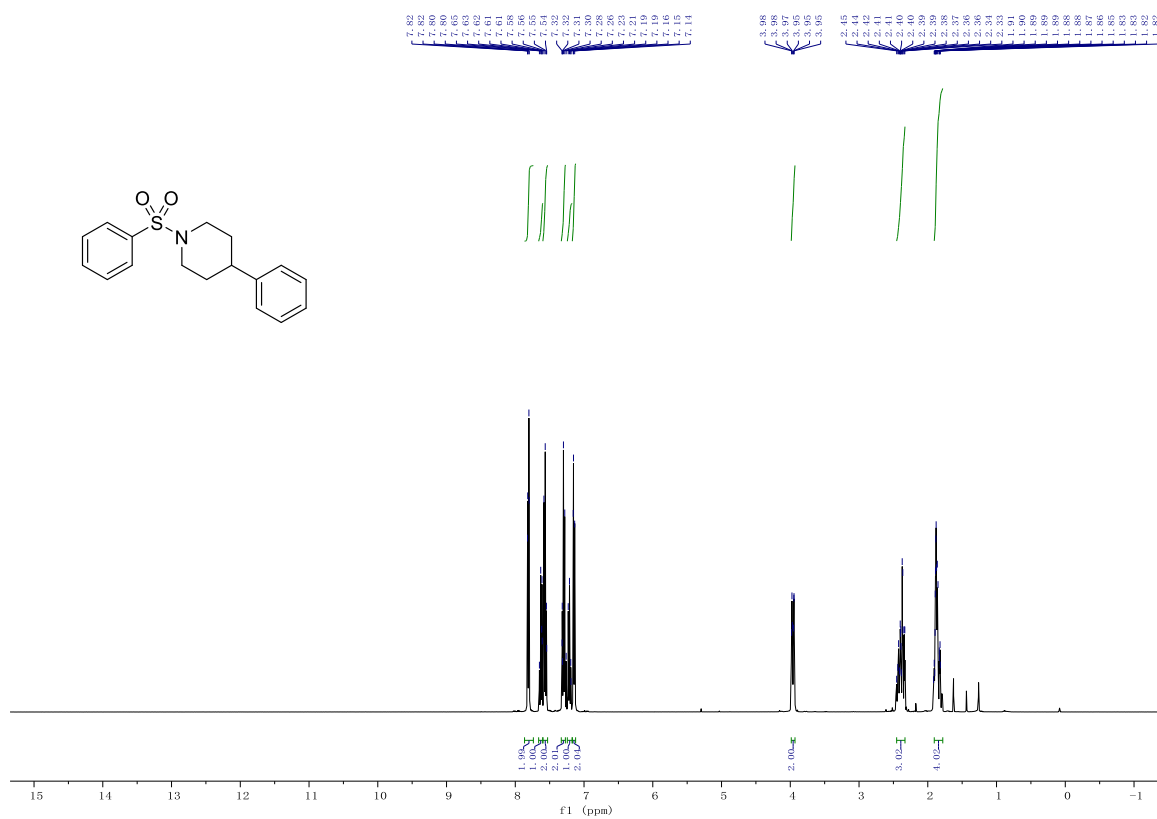
¹H NMR and ¹³C NMR spectra of *N*-phenylbenzenesulfonamide 48e

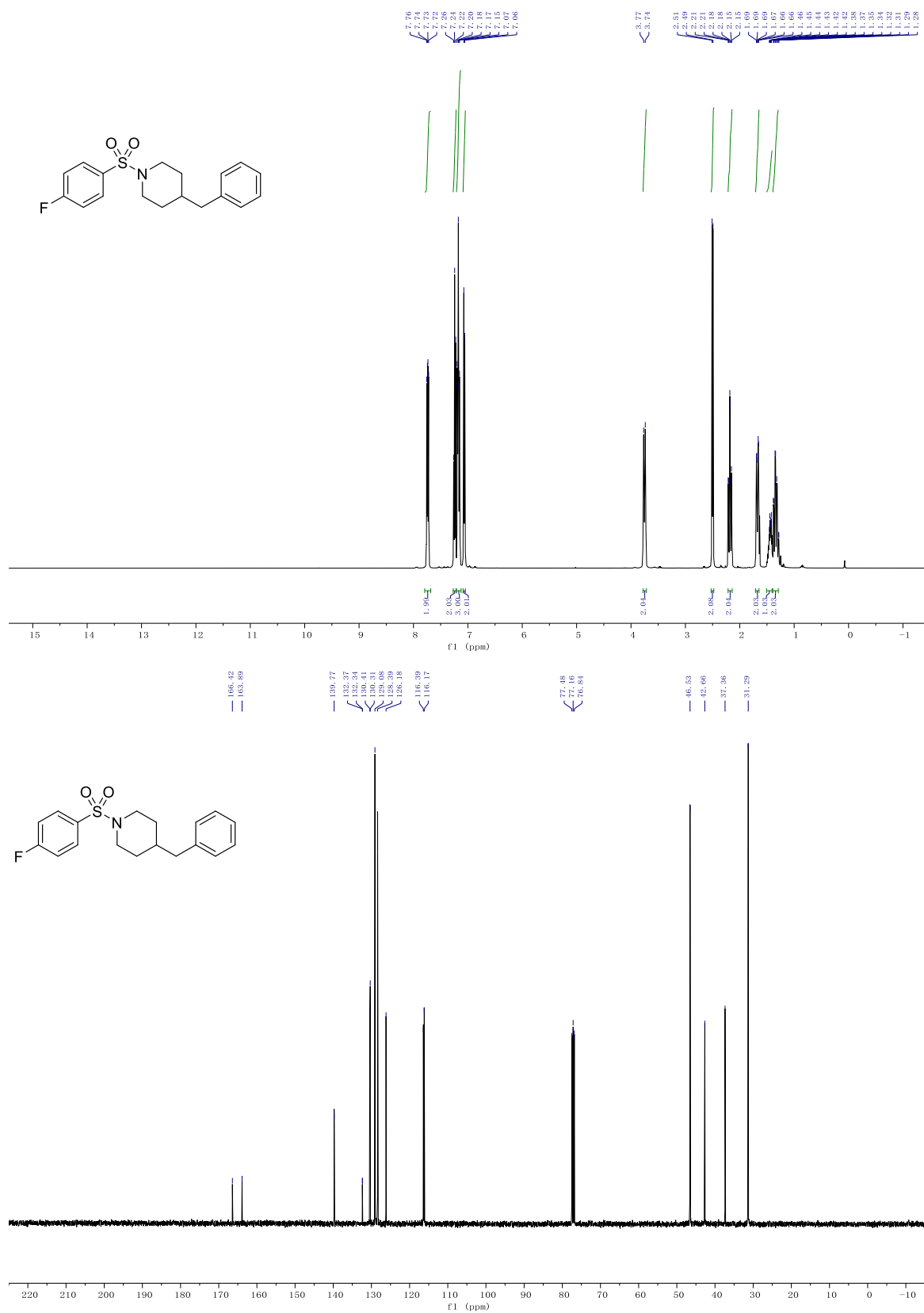


¹H NMR and ¹³C NMR spectra of 1-(phenylsulfonyl)piperidine 48g

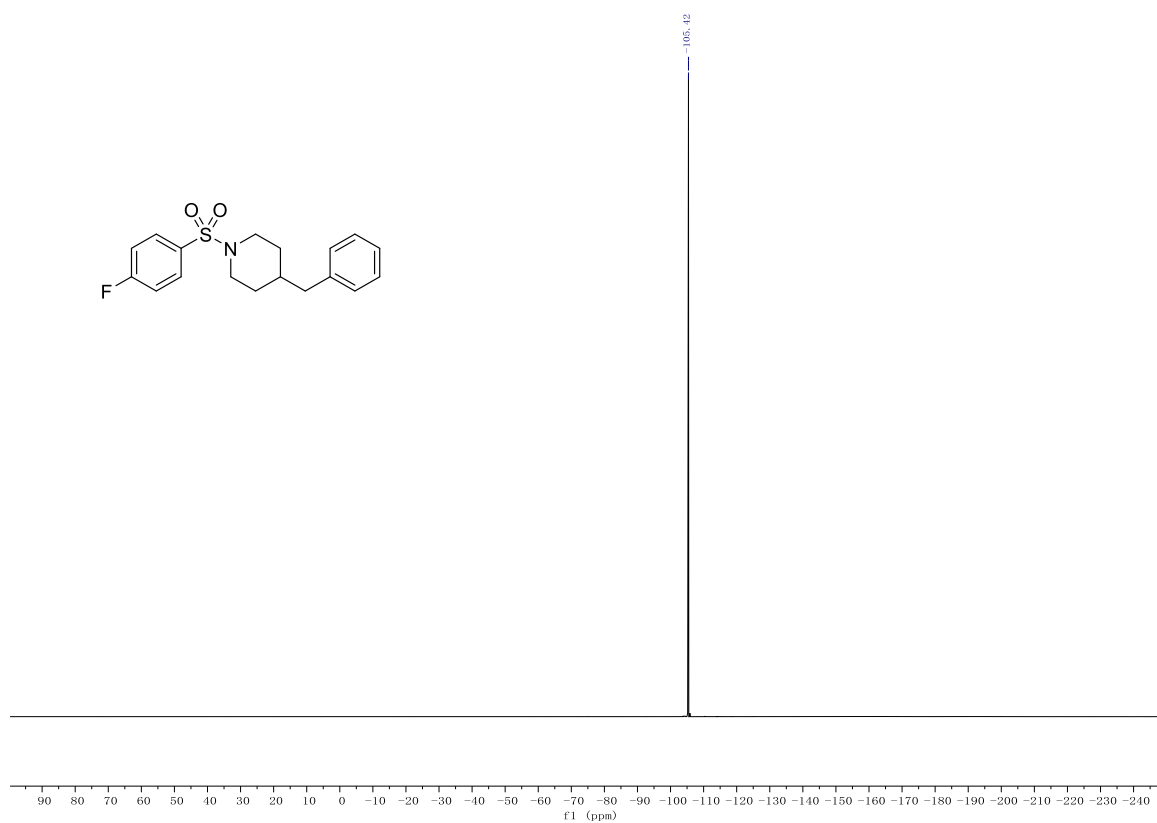


¹H NMR and ¹³C NMR spectra of 1-([4-(trimethylsilyl)phenyl]sulfonyl)pyrrolidine 48i

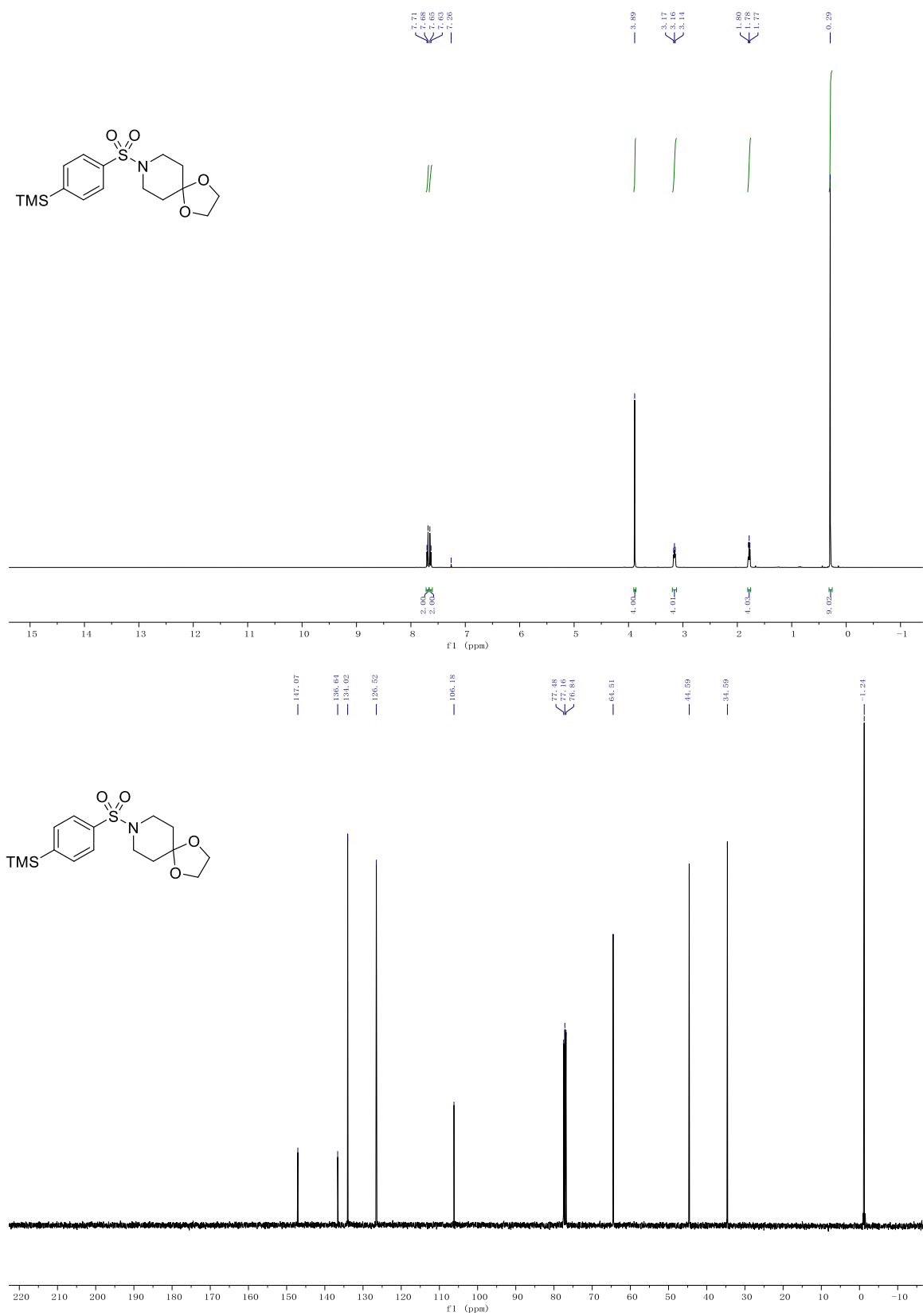
¹H NMR and ¹³C NMR spectra of **4-phenyl-1-(phenylsulfonyl)piperidine 48j**



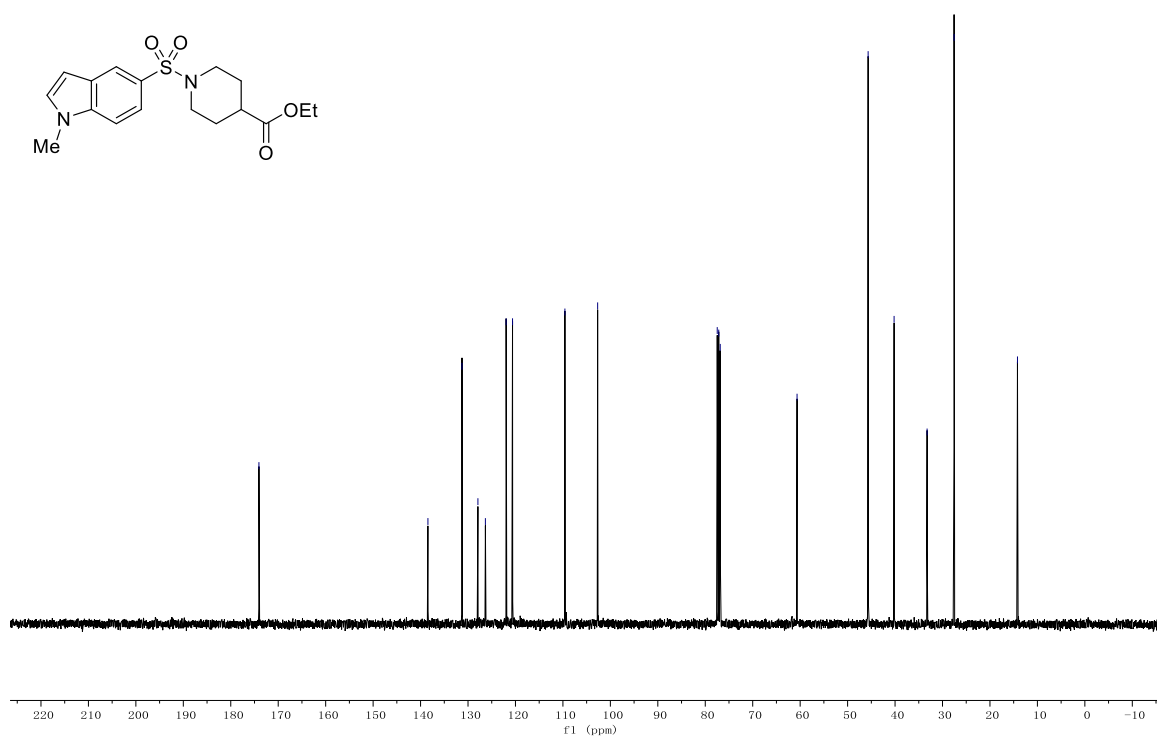
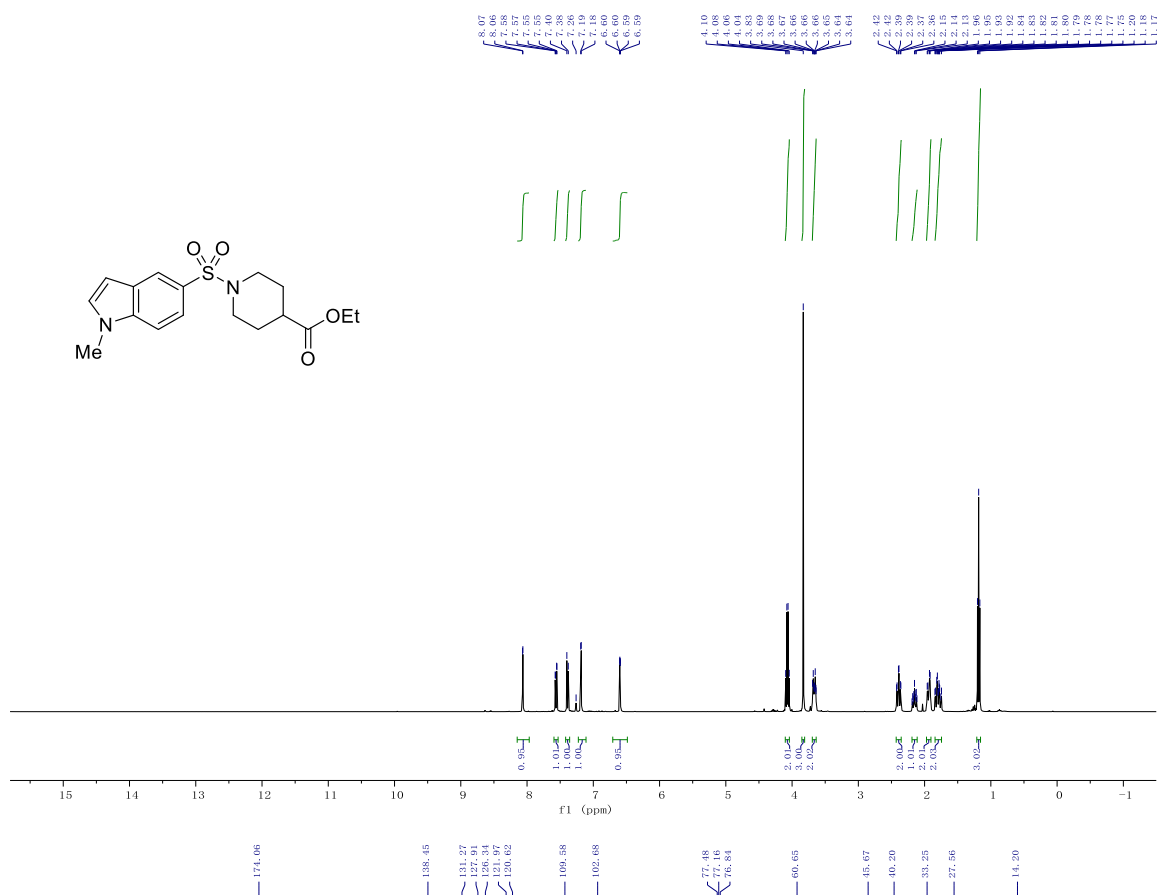
¹H NMR and ¹³C NMR spectra of **4-benzyl-1-[(4-fluorophenyl)sulfonyl]piperidine 481**



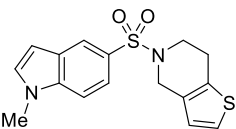
^{19}F NMR spectrum of **4-benzyl-1-[(4-fluorophenyl)sulfonyl]piperidine 48l**



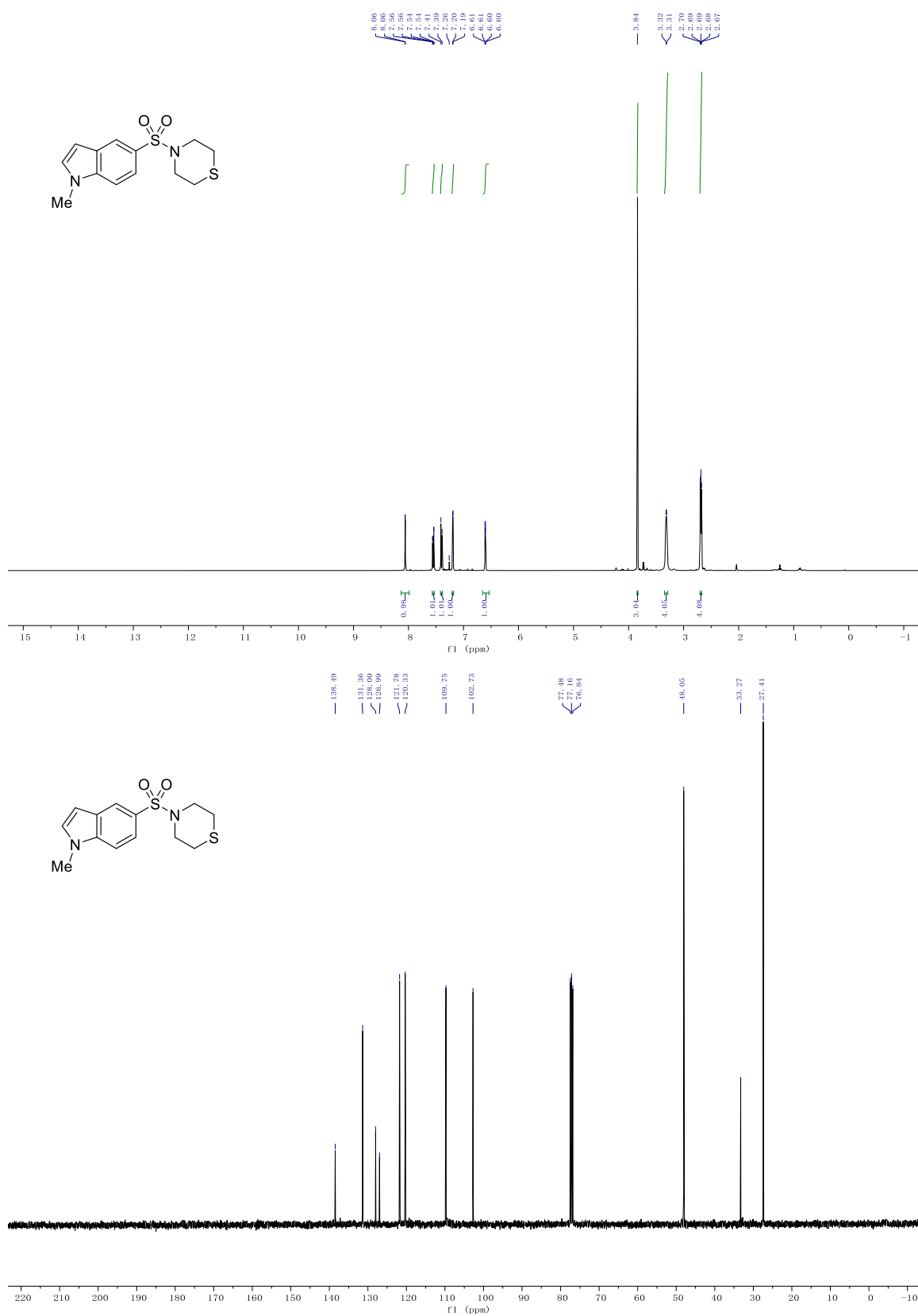
¹H NMR and ¹³C NMR spectra of 8-[[4-(trimethylsilyl)phenyl]sulfonyl]-1,4-dioxa-8-azaspiro[4.5]decane 48m



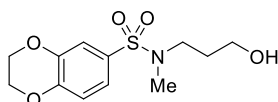
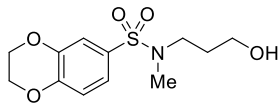
¹H NMR and ¹³C NMR spectra of ethyl 1-[(1-methyl-1H-indol-5-yl)sulfonyl]piperidine-4-carboxylate 48n

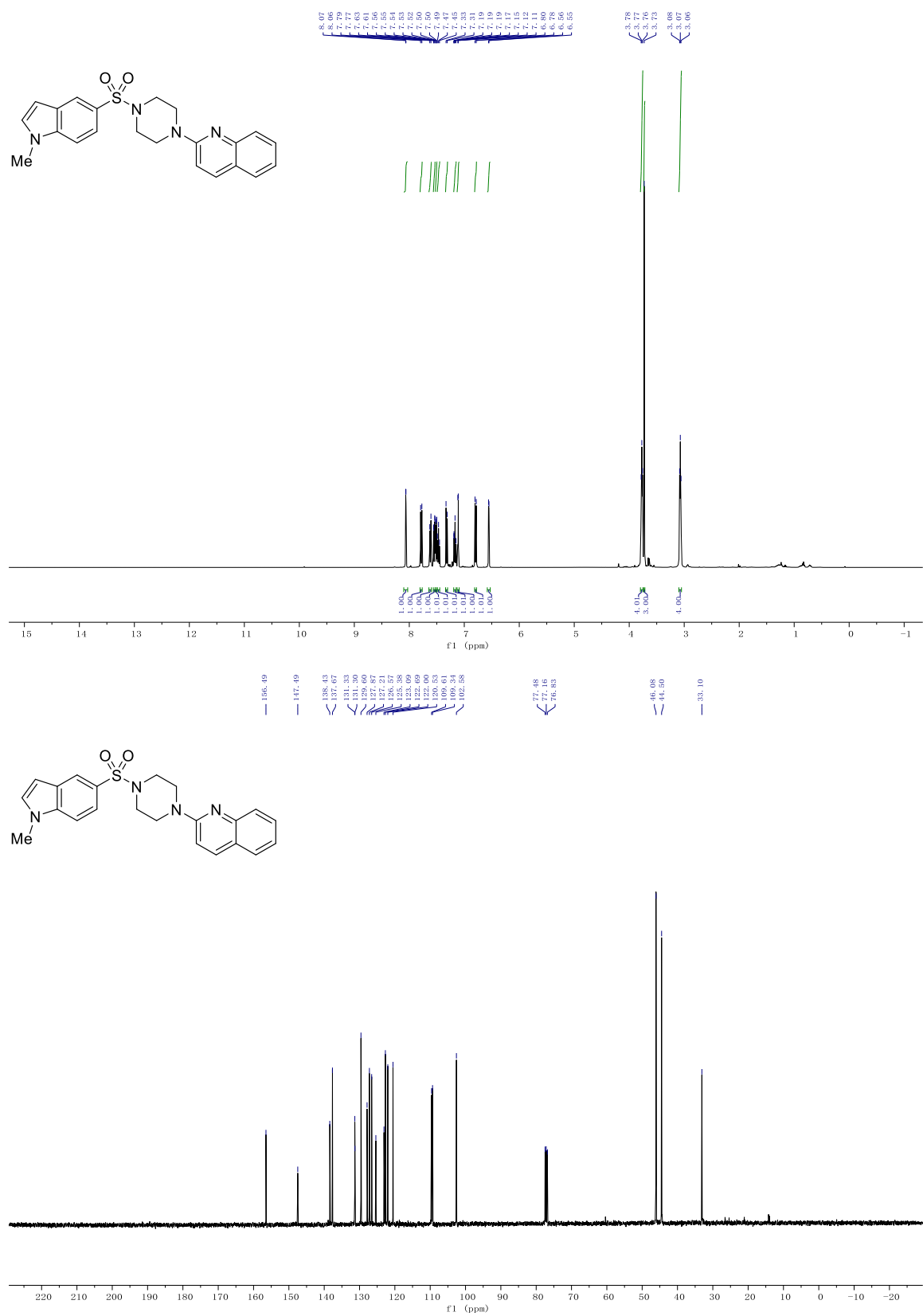


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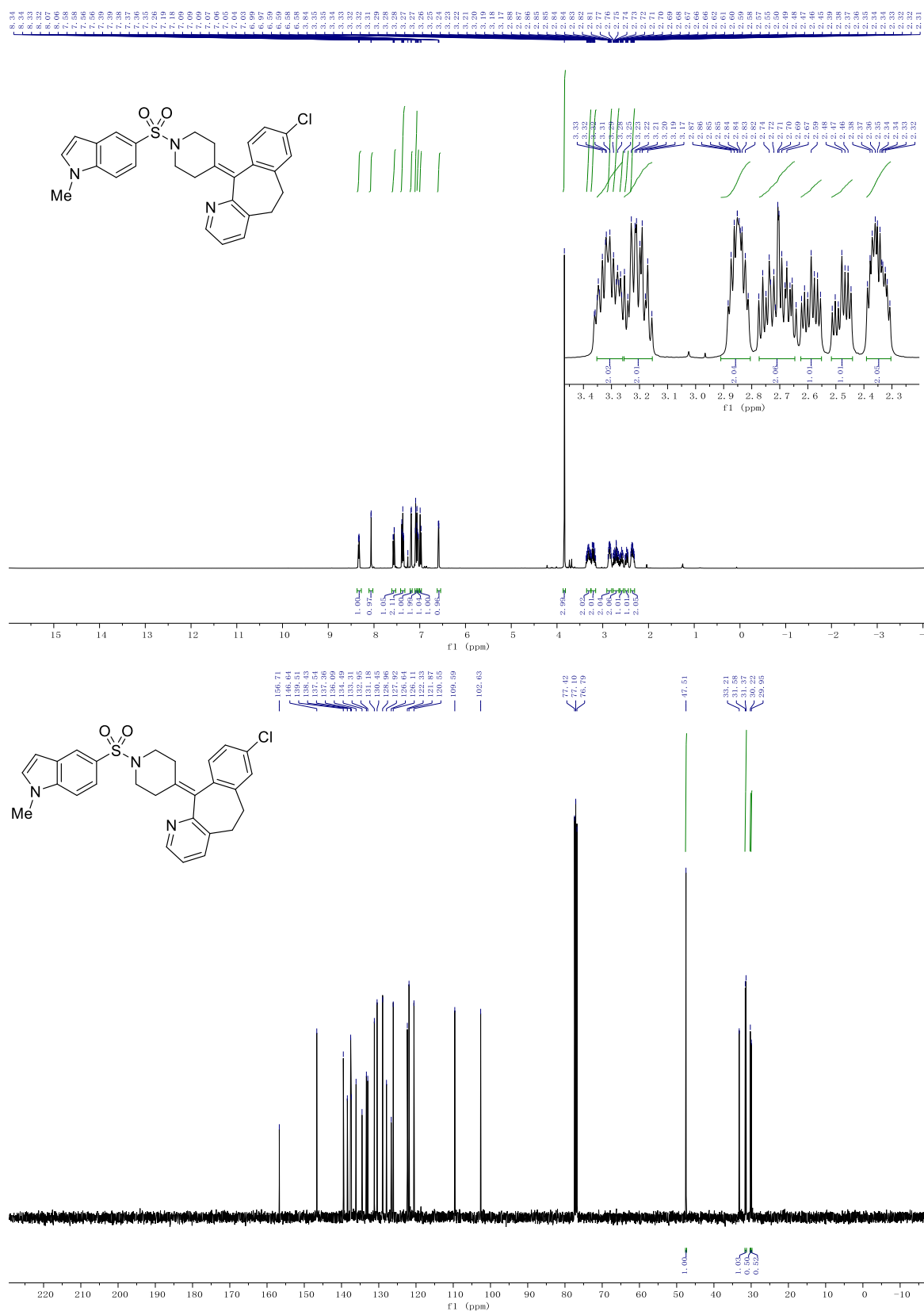


¹H NMR and ¹³C NMR spectra of 4-[(1-methyl-1H-indol-5-yl)sulfonyl]thiomorpholine 48p

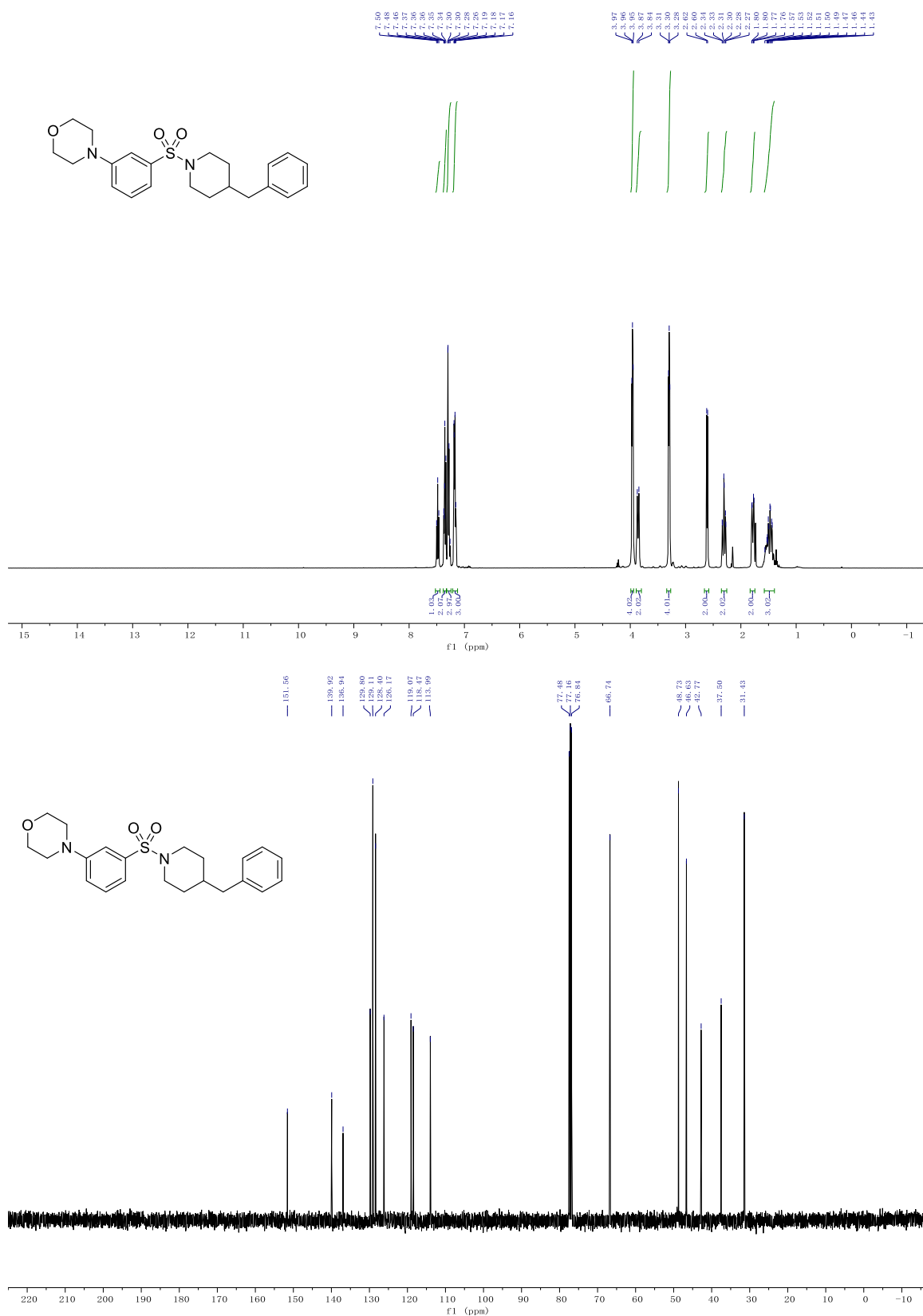




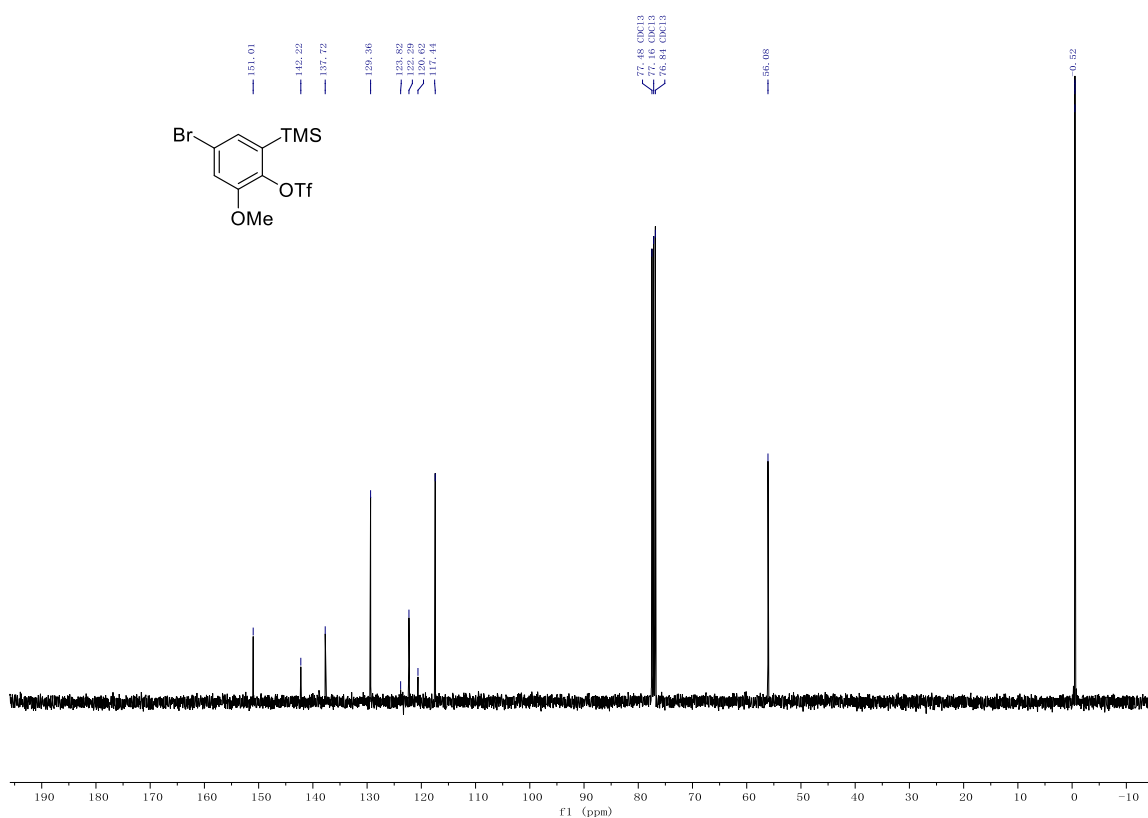
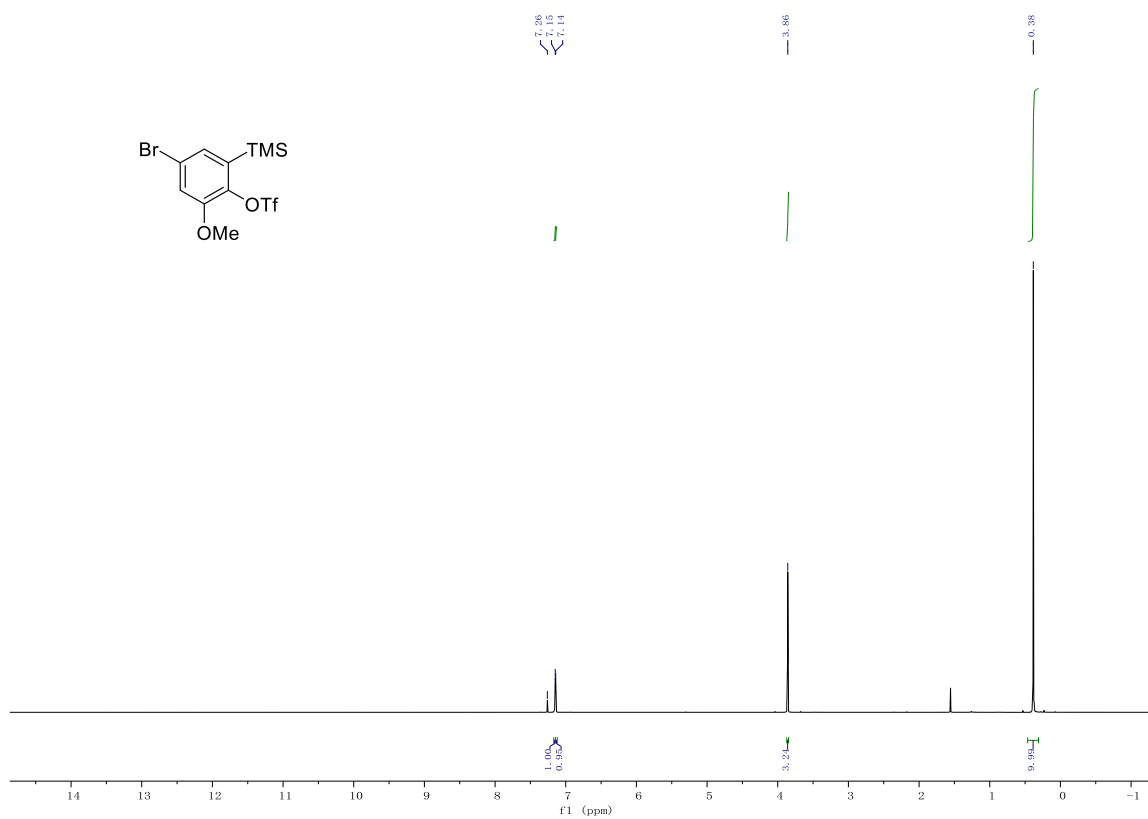
¹H NMR and ¹³C NMR spectra of 2-{4-[(1-methyl-1*H*-indol-5-yl)sulfonyl]piperazin-1-yl}quinoline 48u



¹H NMR and ¹³C NMR spectra of 8-chloro-11-{1-[(1-methyl-1H-indol-5-yl)sulfonyl]piperidin-4-ylidene}-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine 48w

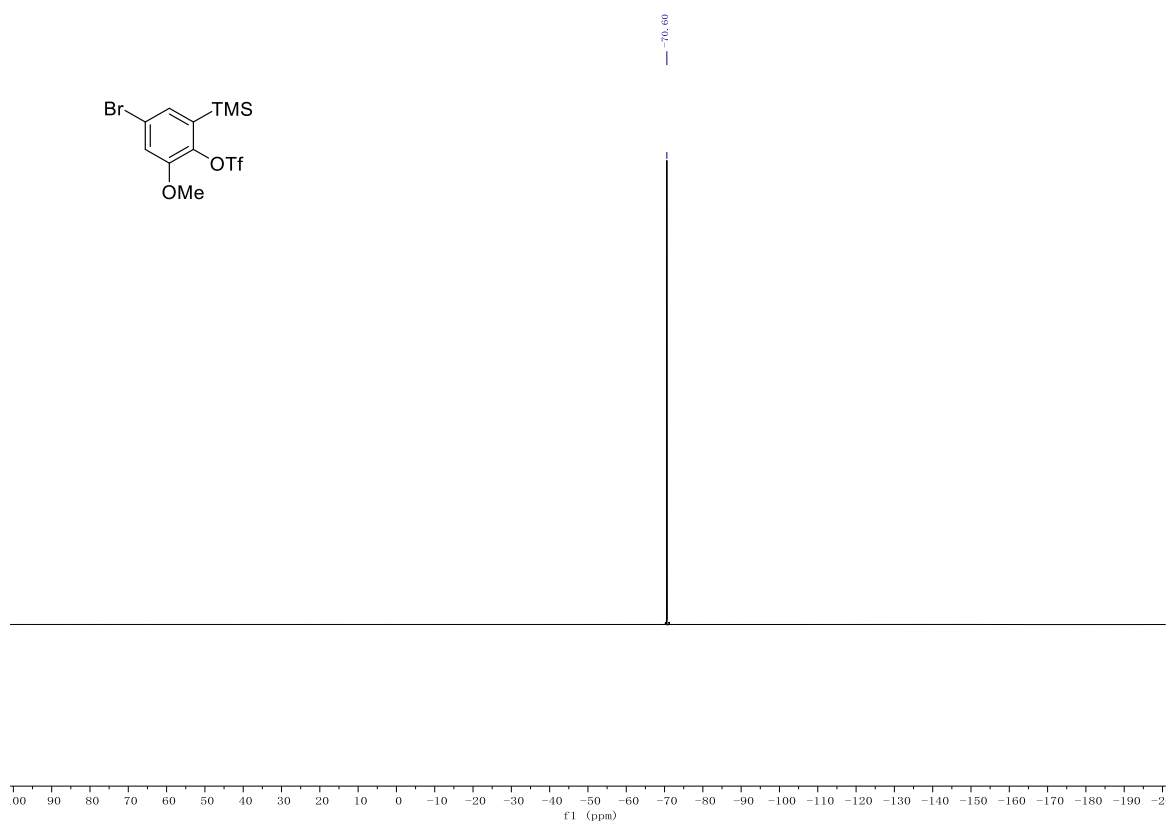


¹H NMR and ¹³C NMR spectra of 4-{3-[(4-benzylpiperidin-1-yl)sulfonyl]phenyl}morpholine
48ab



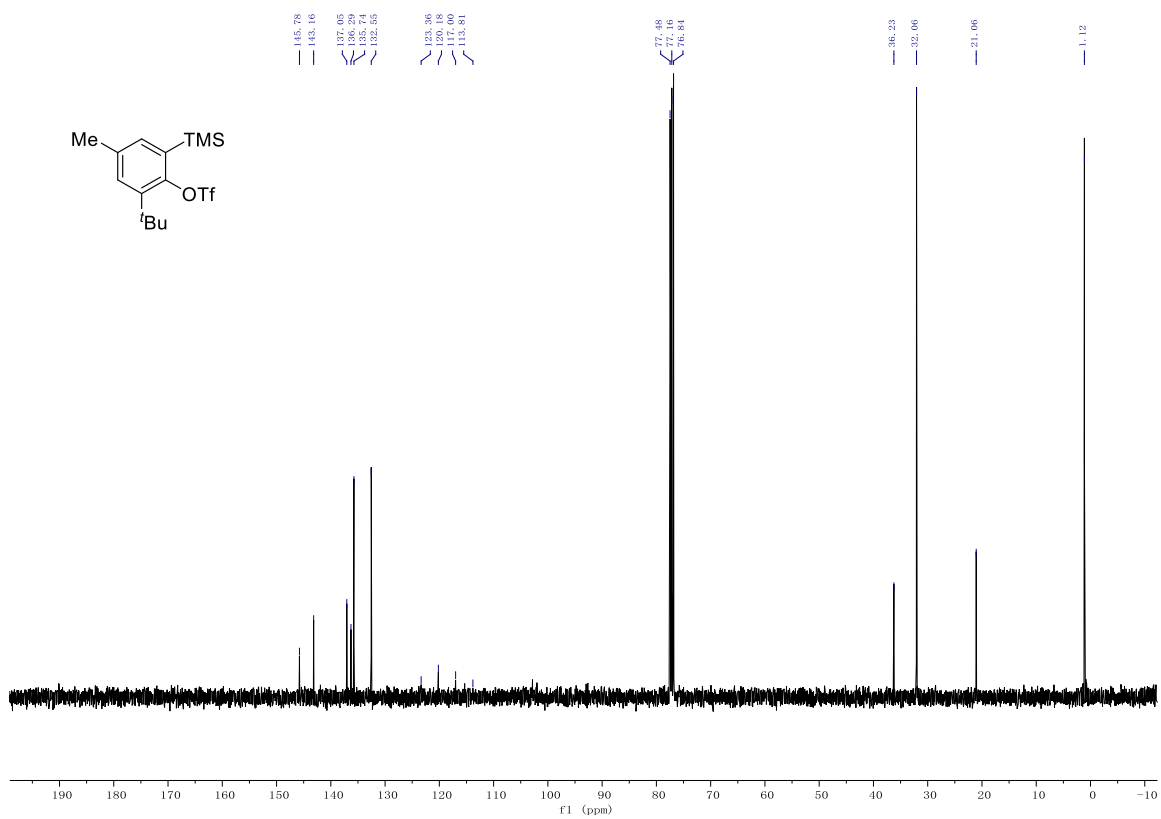
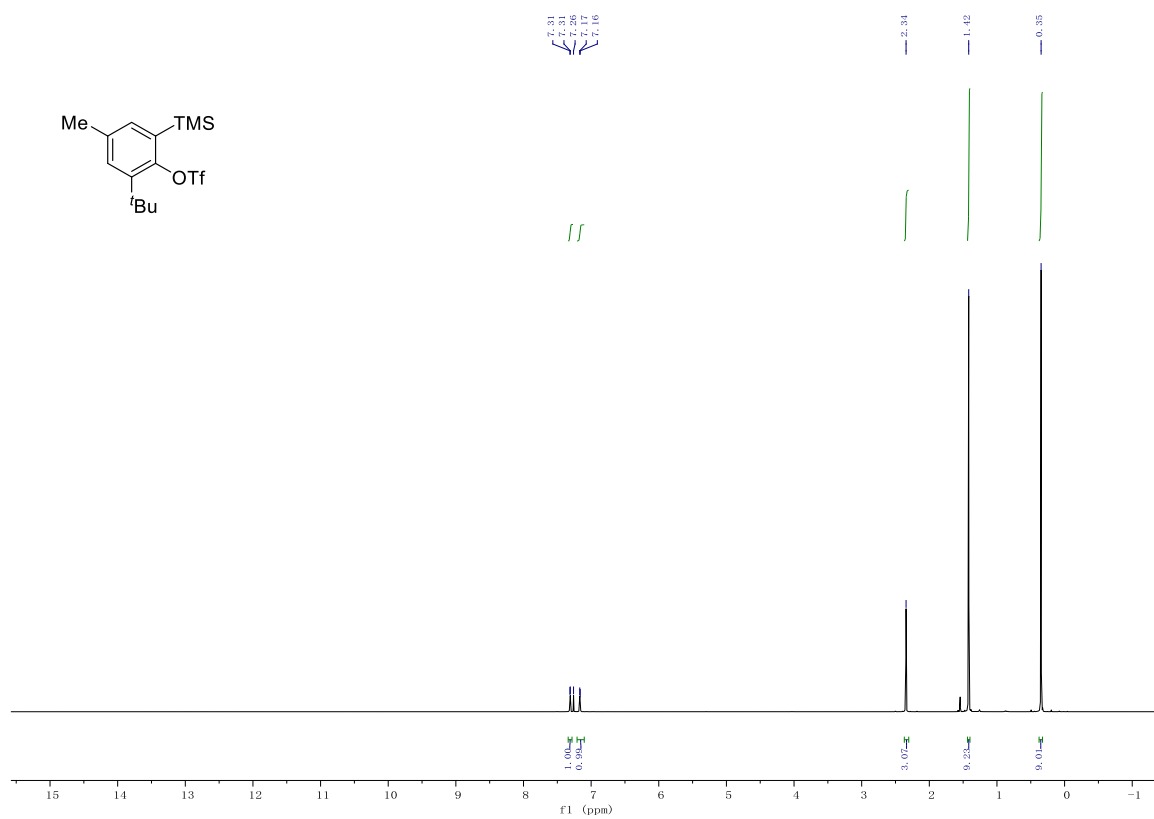
¹H NMR and ¹³C NMR spectra of 2-methoxy-4-bromo-6-(trimethylsilyl)phenyl

trifluoromethanesulfonate 61i



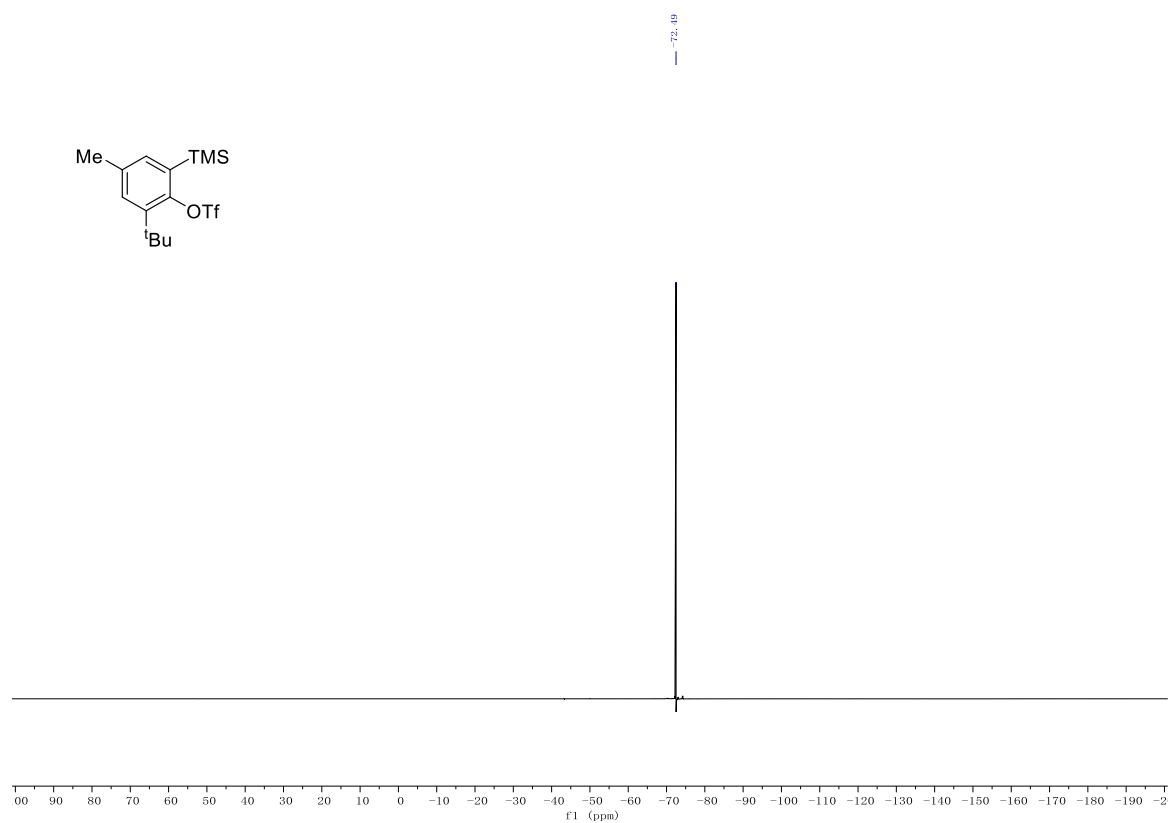
¹⁹F NMR spectrum of 2-methoxy-4-bromo-6-(trimethylsilyl)phenyl trifluoromethanesulfonate

61i



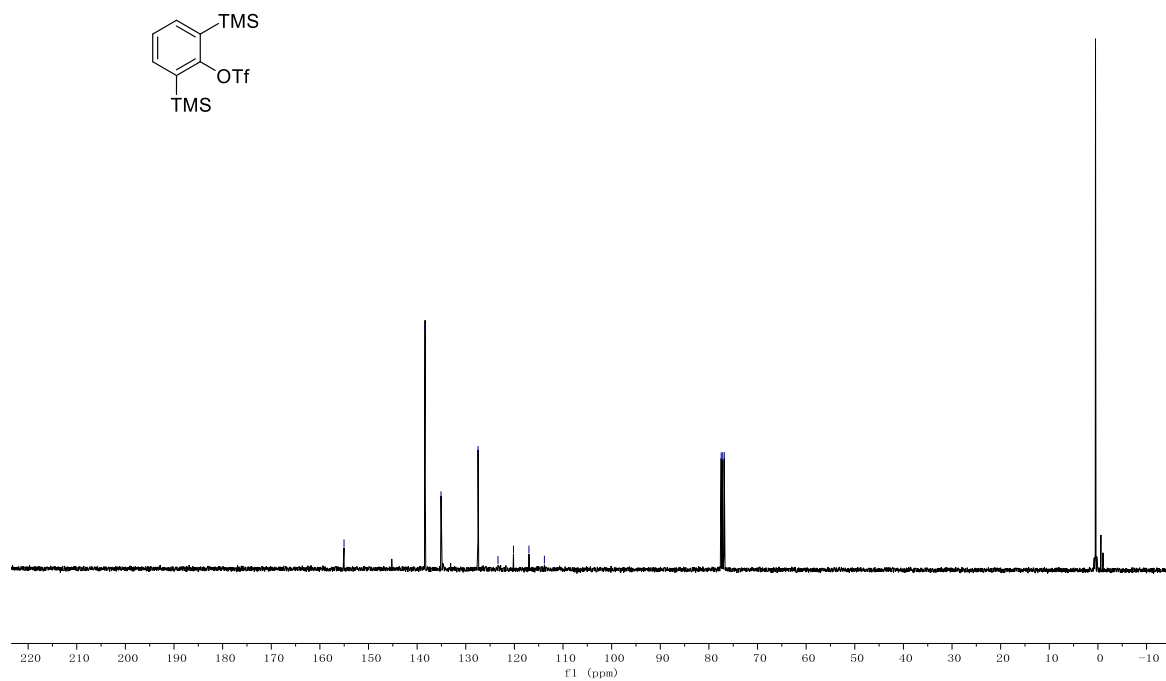
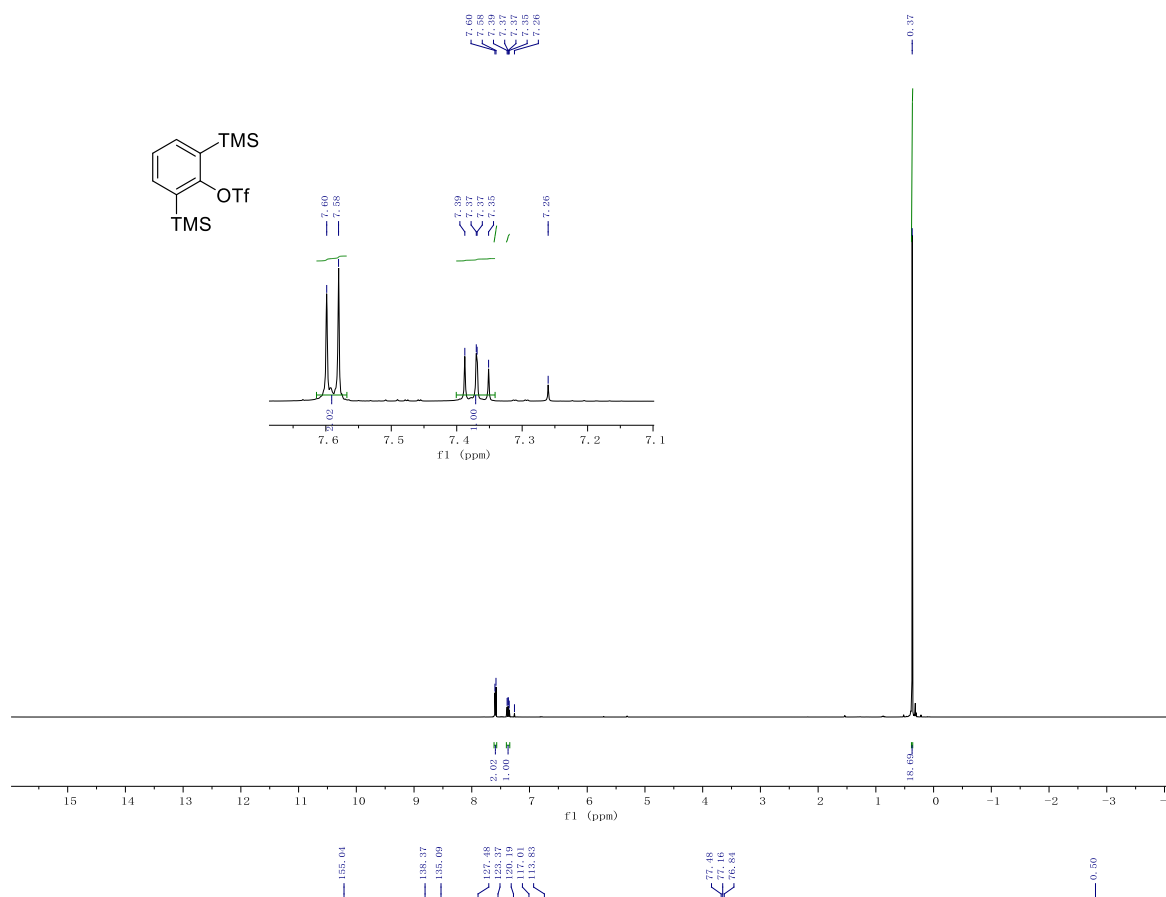
¹H NMR and ¹³C NMR spectra of 2-*tert*-butyl-4-methyl-6-(trimethylsilyl)phenyl

trifluoromethanesulfonate 611

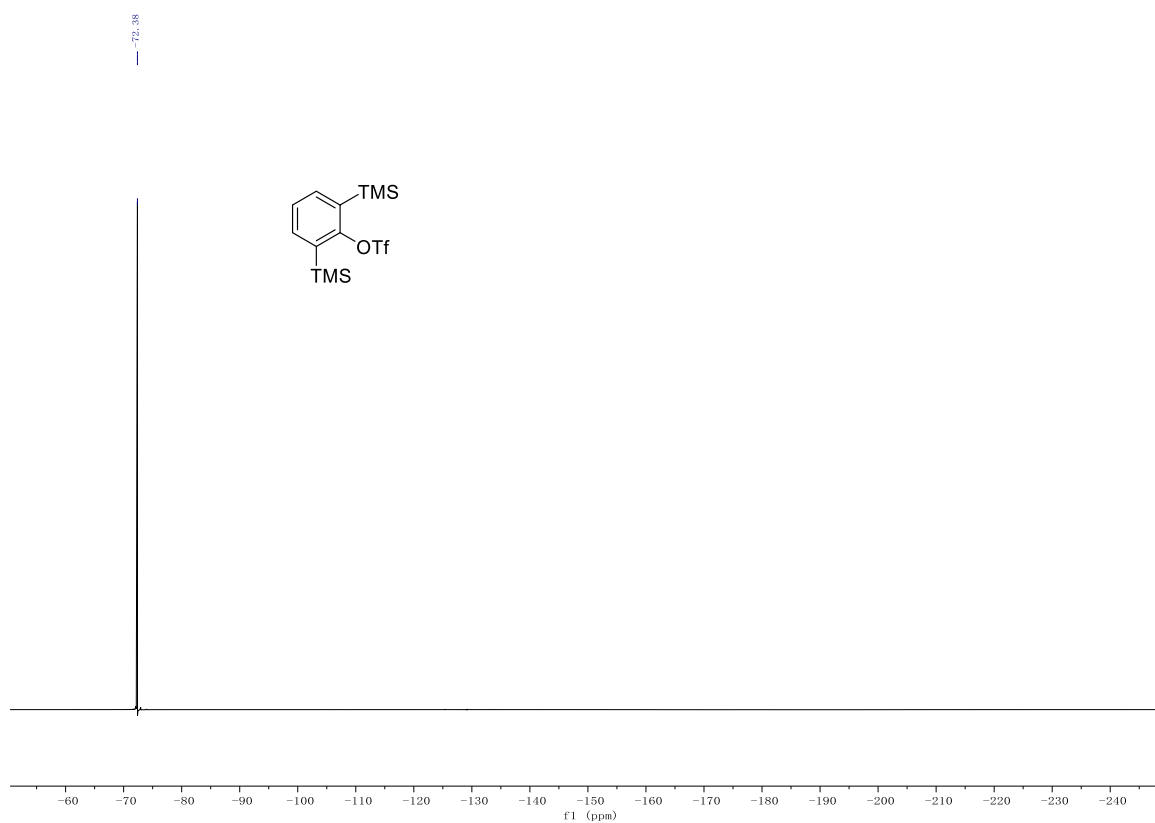


^{19}F NMR spectrum of **2-*tert*-butyl-4-methyl-6-(trimethylsilyl)phenyl**

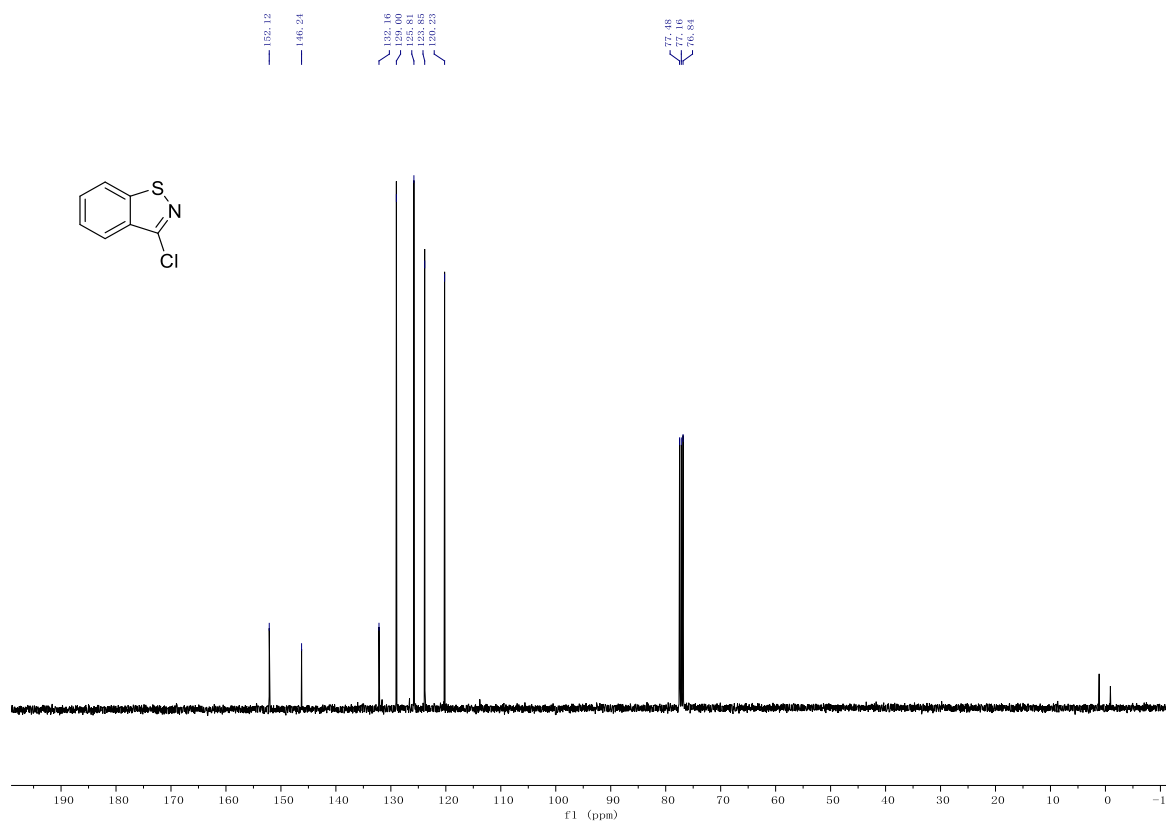
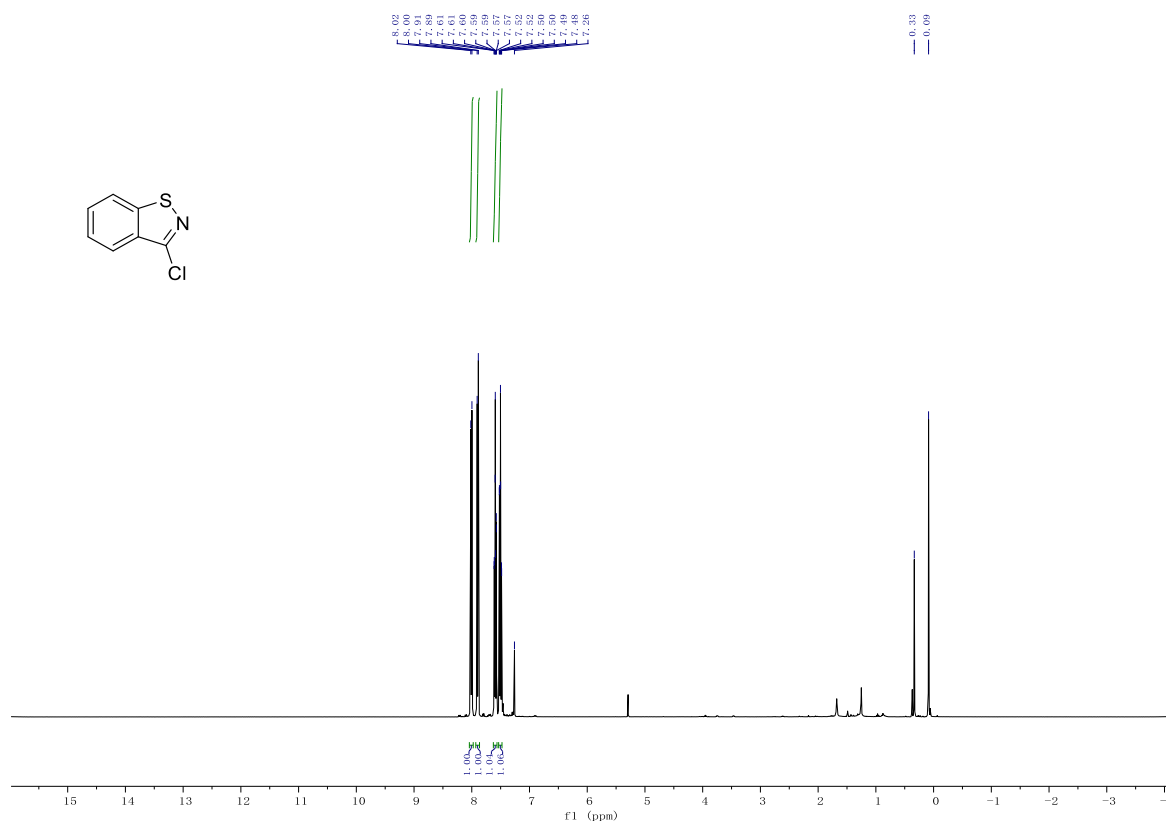
trifluoromethanesulfonate 611



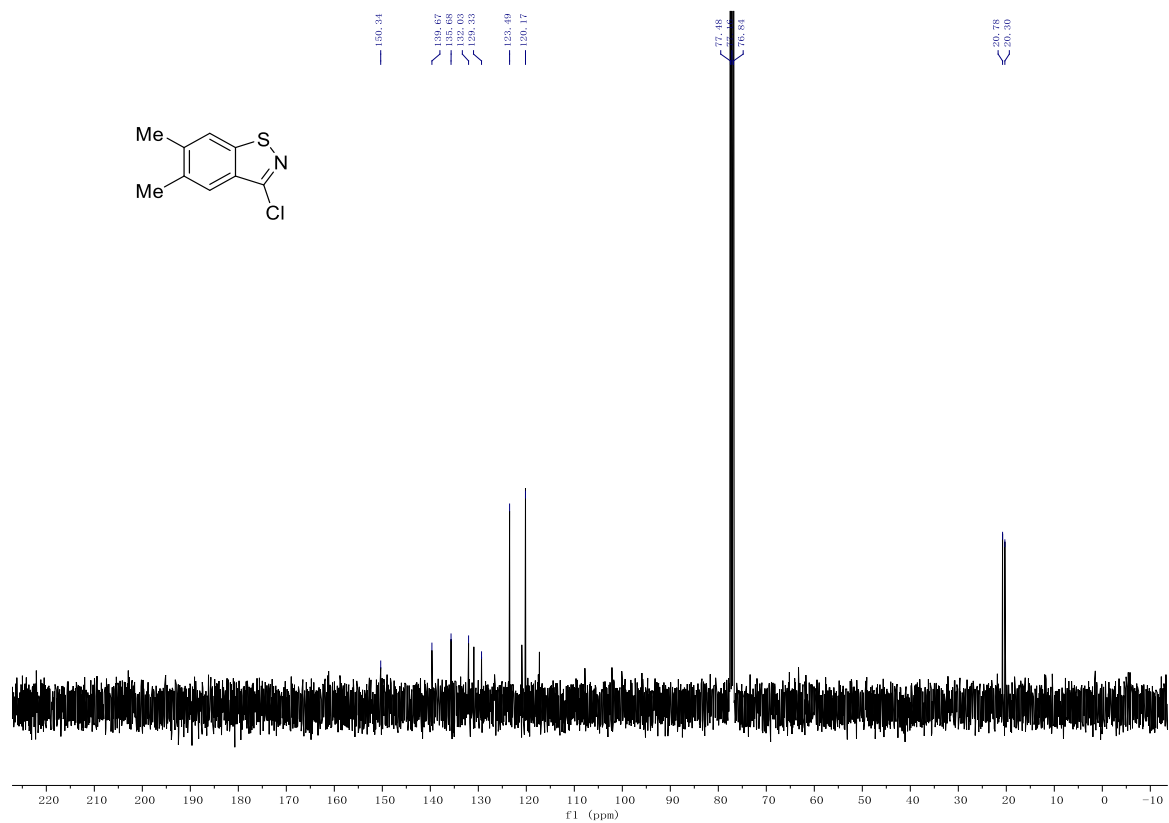
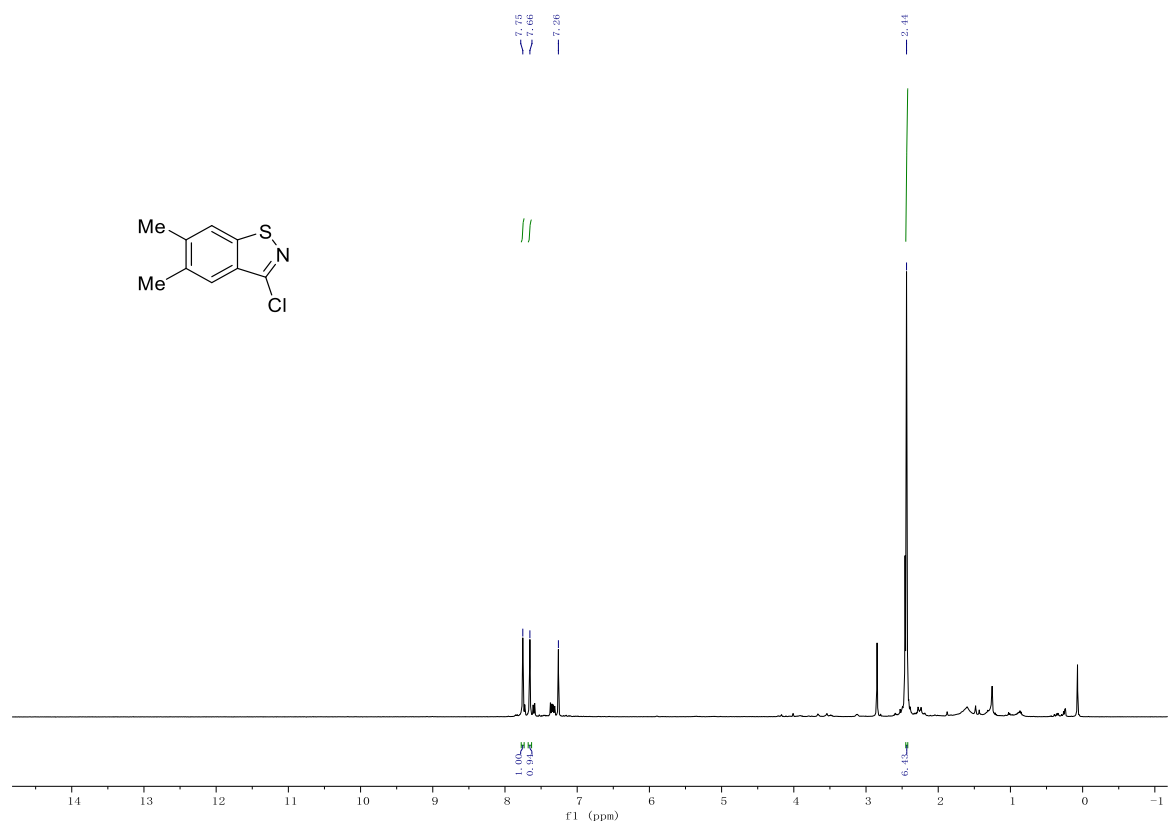
¹H NMR and ¹³C NMR spectra of 2,6-bis(trimethylsilyl)phenyl trifluoromethanesulfonate 61m



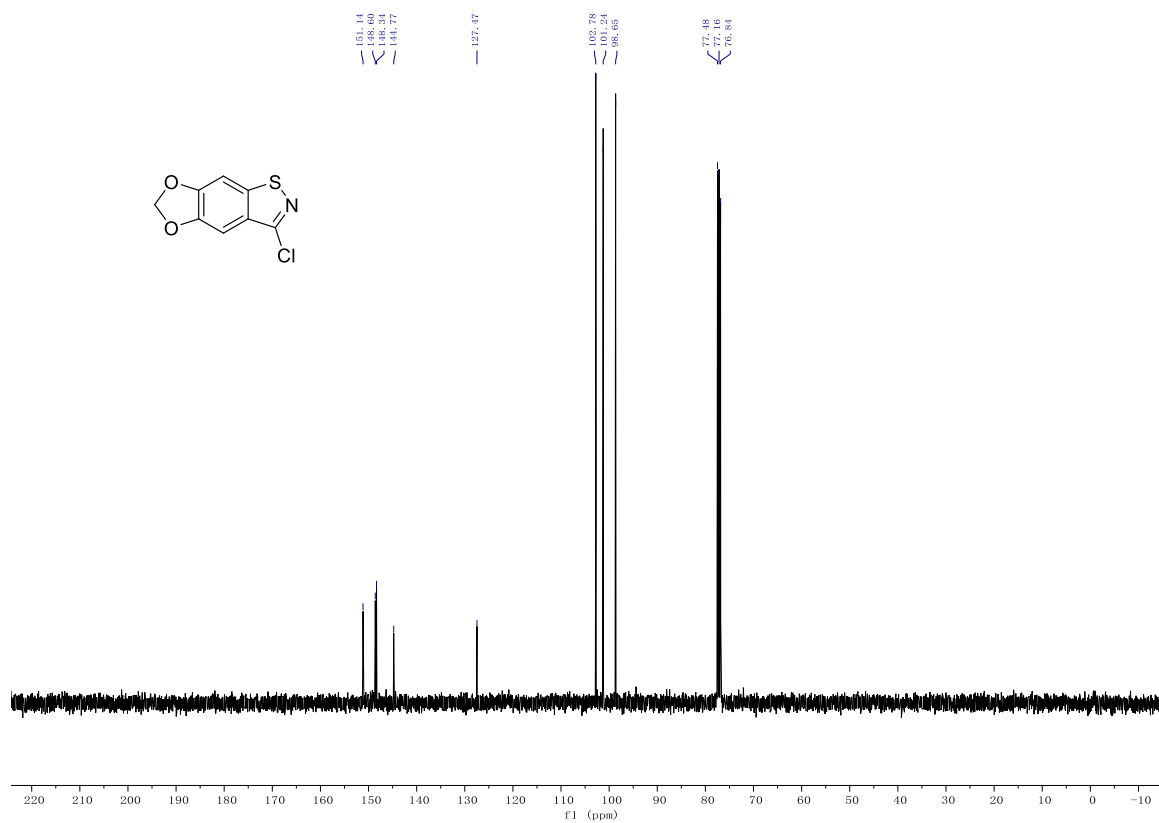
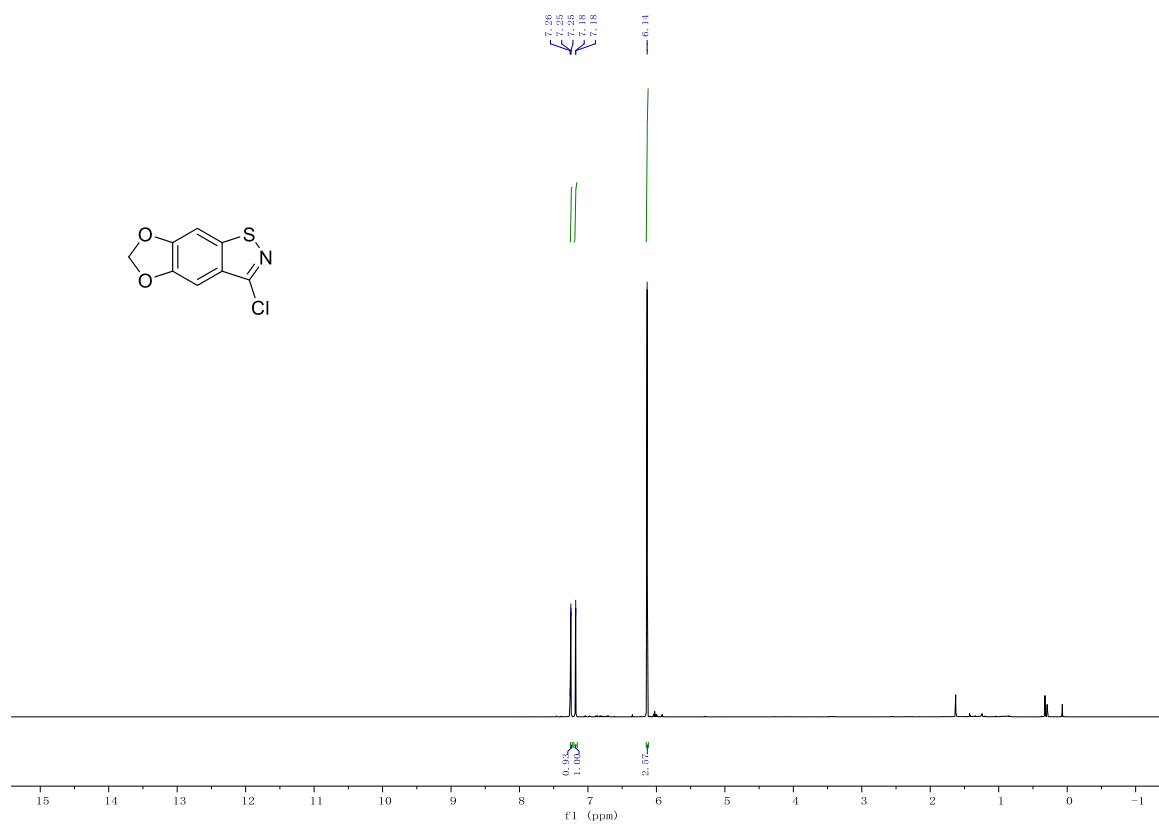
^{19}F NMR spectrum of **2,6-bis(trimethylsilyl)phenyl trifluoromethanesulfonate 61m**



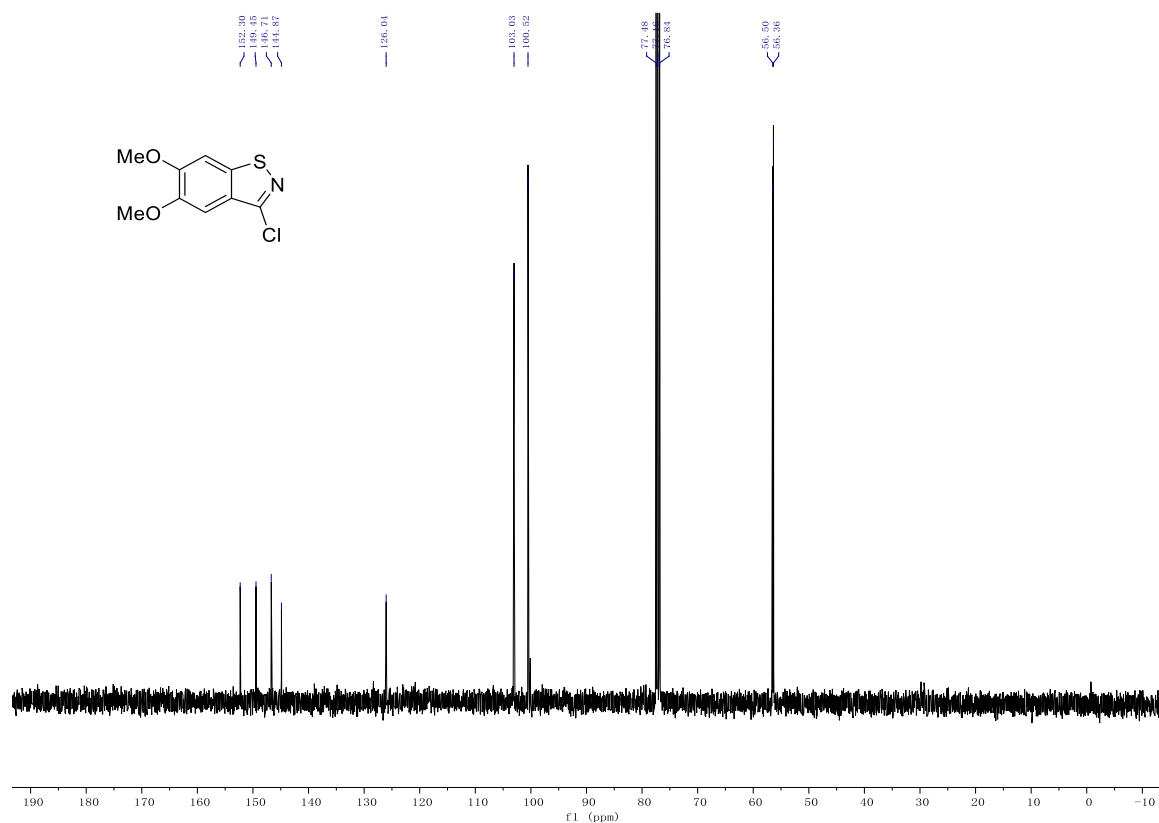
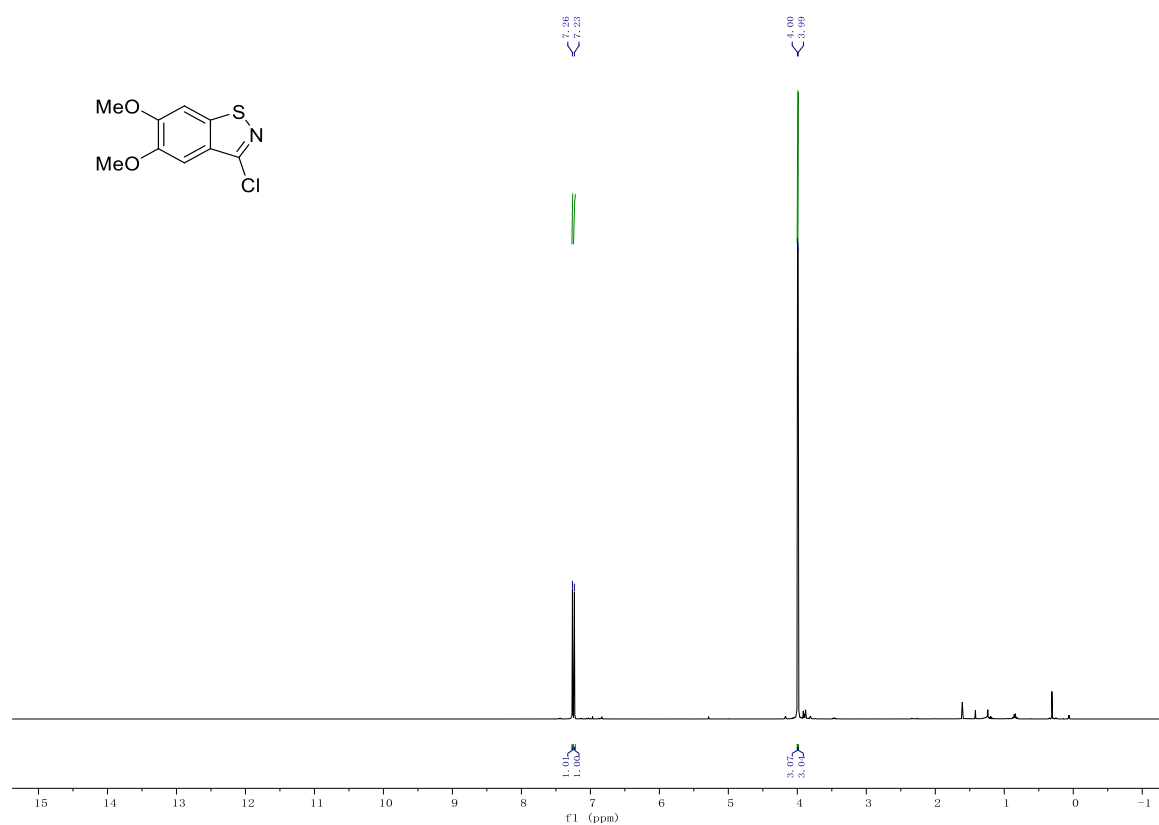
¹H NMR and ¹³C NMR spectra of 3-chloro-1,2-benzisothiazole (3a)



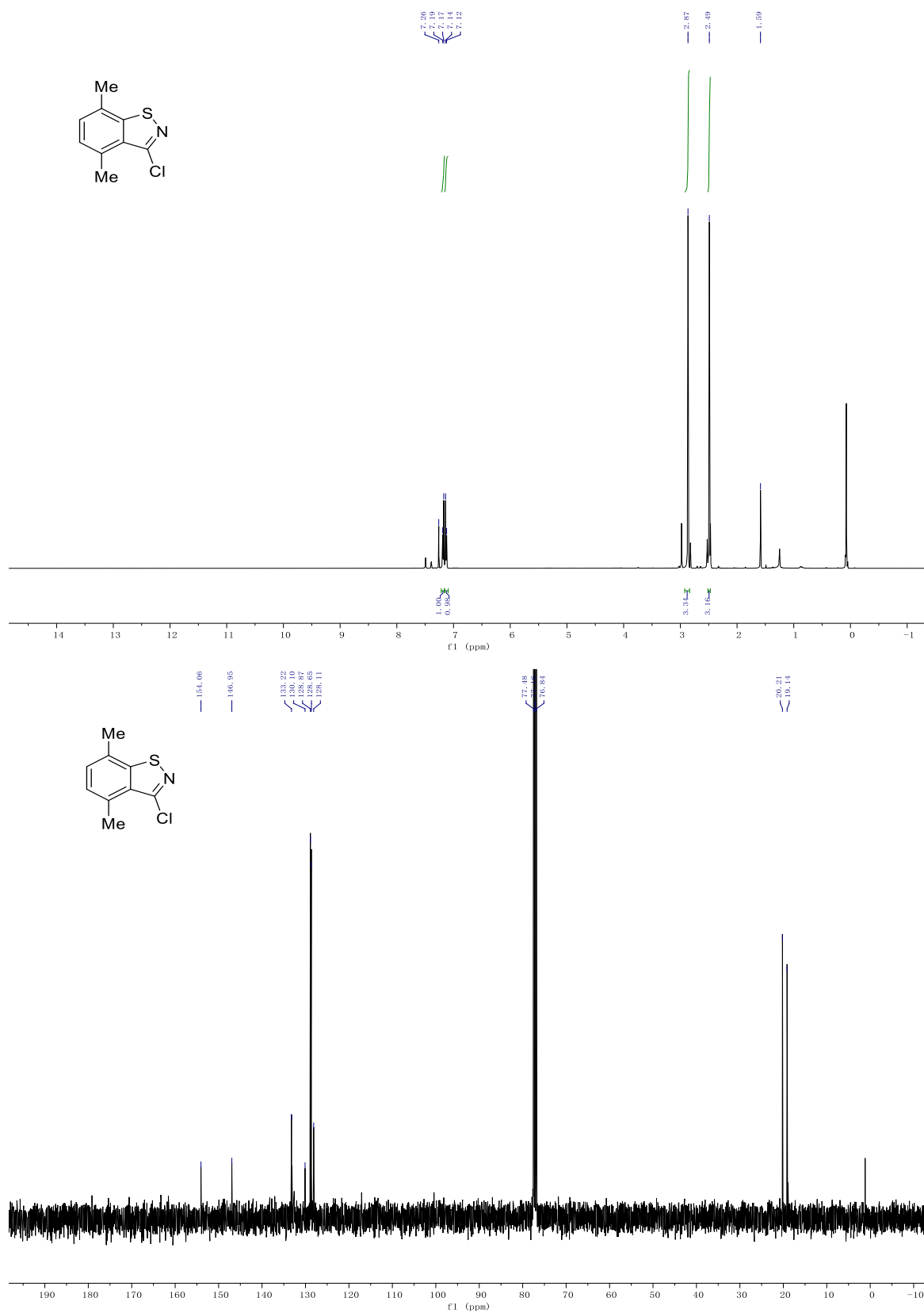
¹H NMR and ¹³C NMR spectra of 3-chloro-5,6-dimethyl-1,2-benzisothiazole 60b



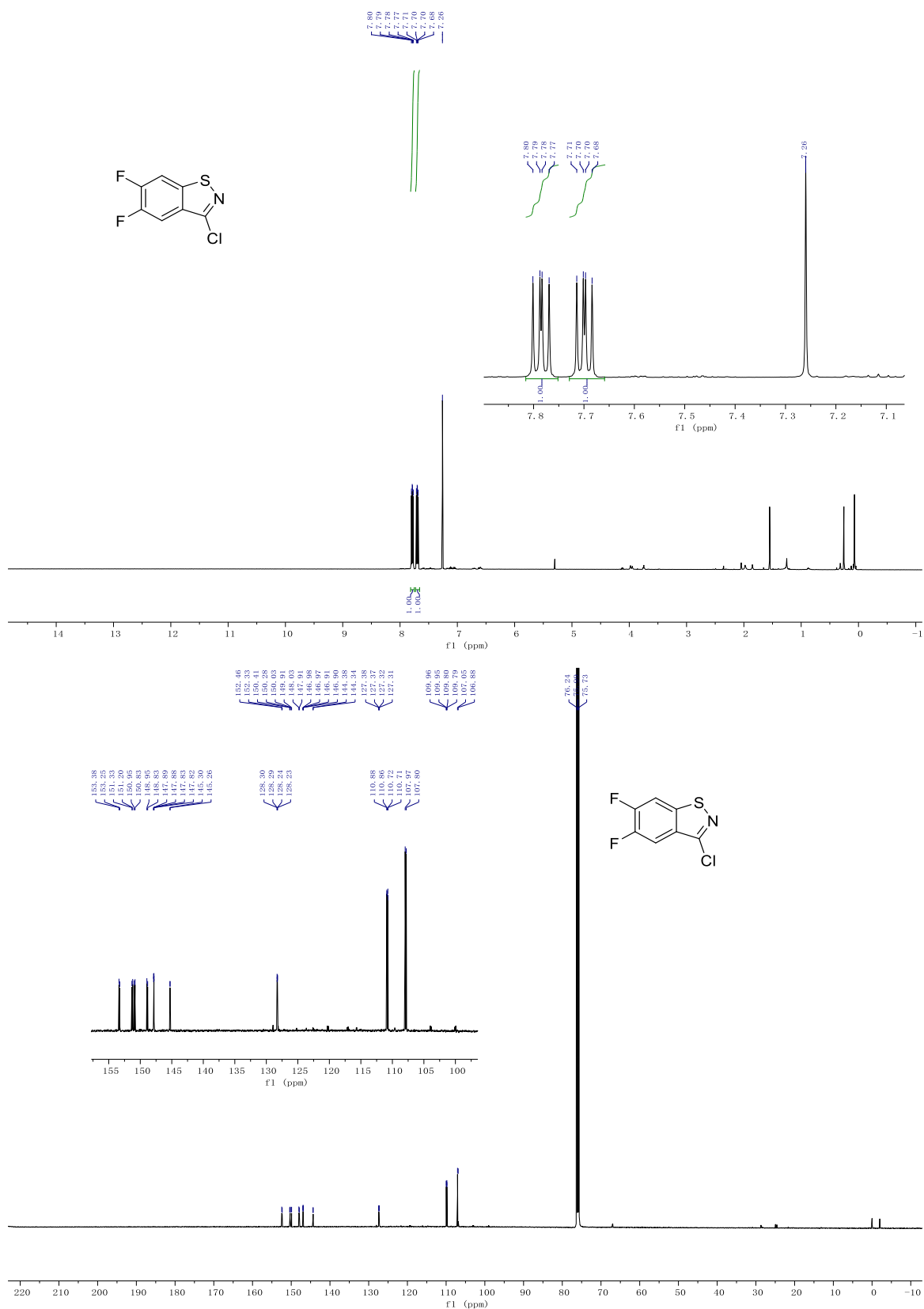
^1H NMR and ^{13}C NMR spectra of **3-chloro-5,6-dioxolo-1,2-benzisothiazole 60c**



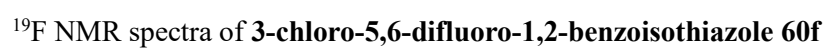
¹H NMR and ¹³C NMR spectra of **3-chloro-5,6-dimethoxy-1,2-benzisothiazole 60d**

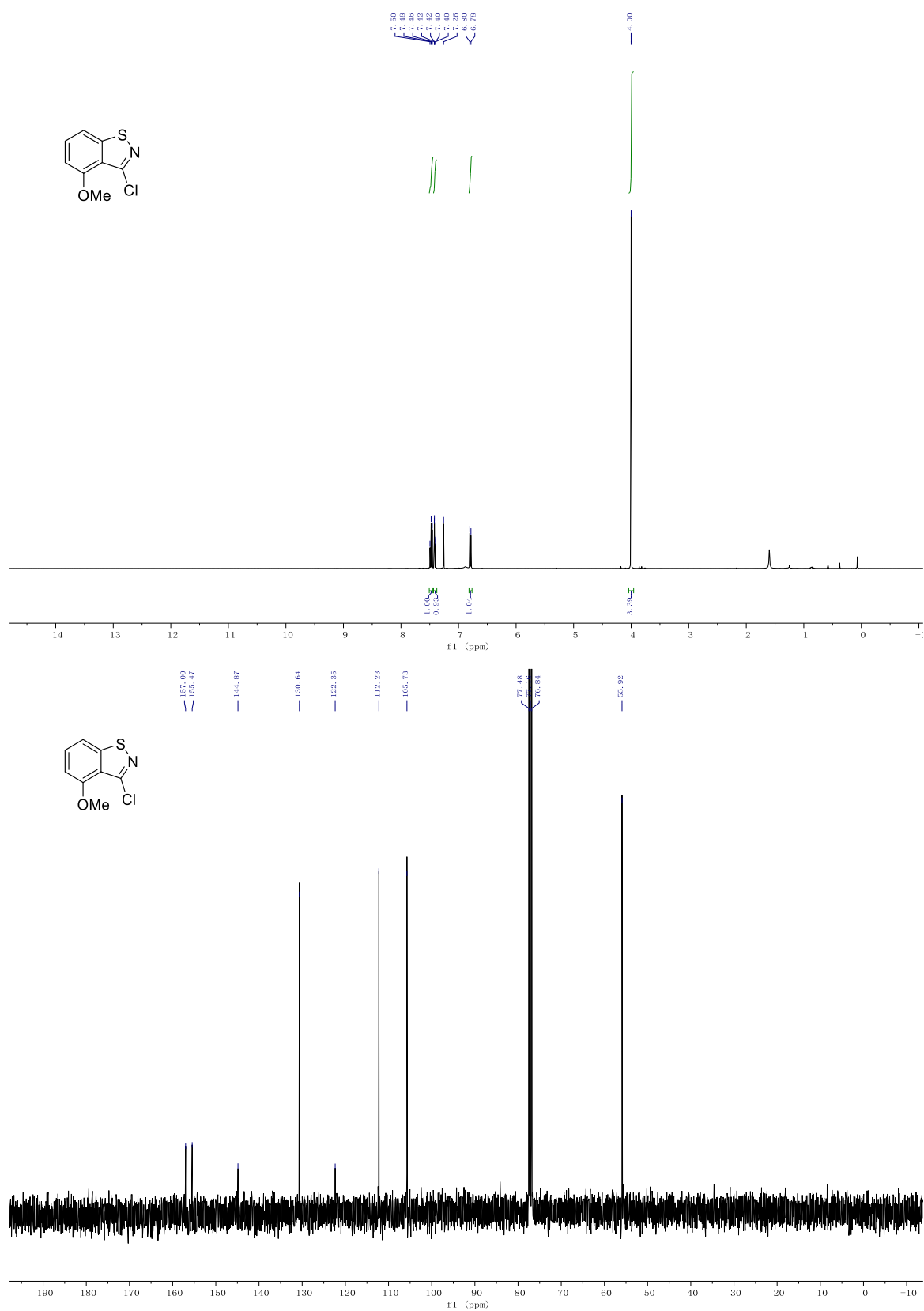


¹H NMR and ¹³C NMR spectra of 3-chloro-4,7-dimethyl-1,2-benzisothiazole 60e

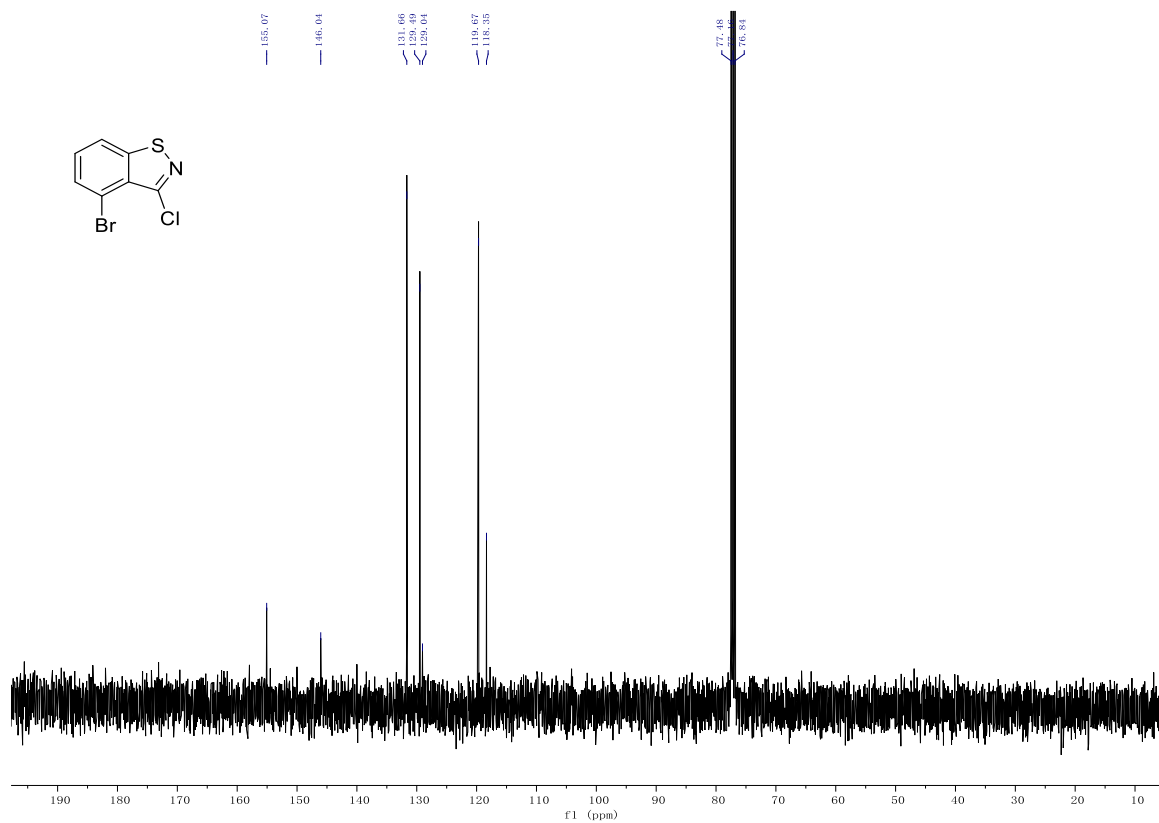
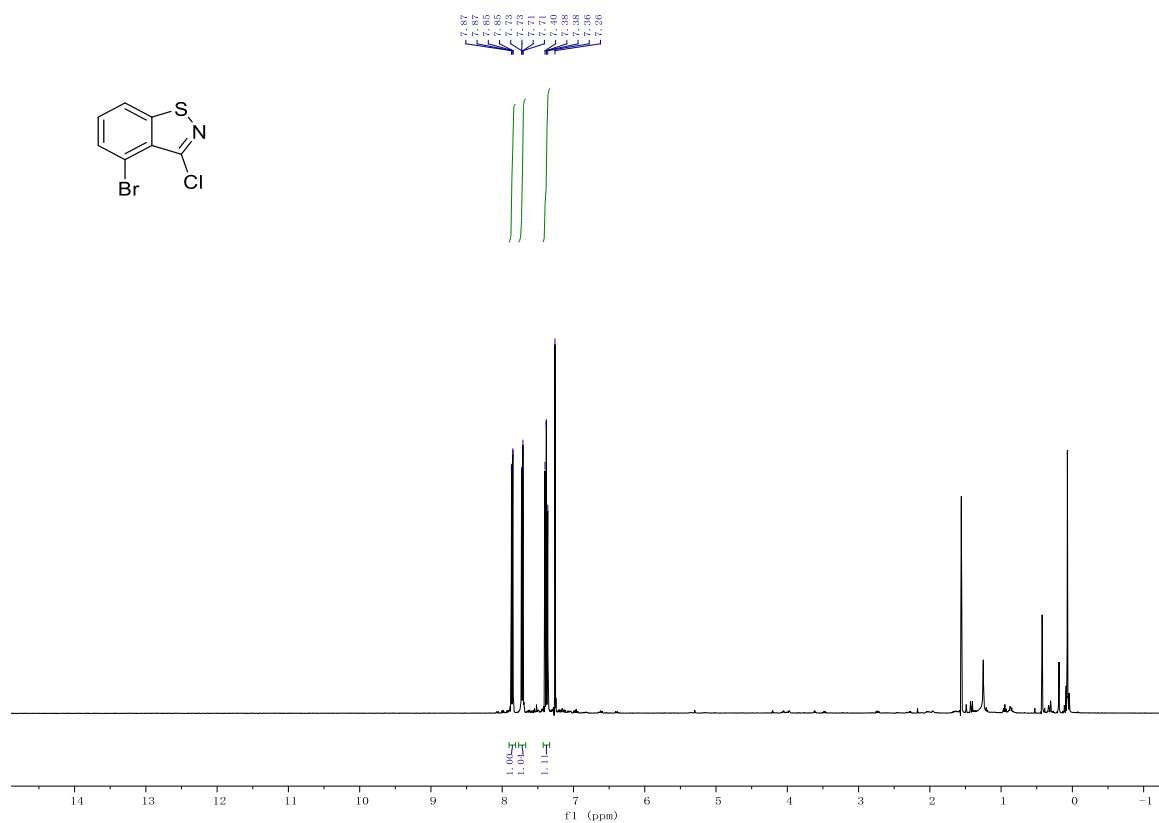


¹H NMR and ¹³C NMR spectra of 3-chloro-5,6-difluoro-1,2-benzisothiazole 60f

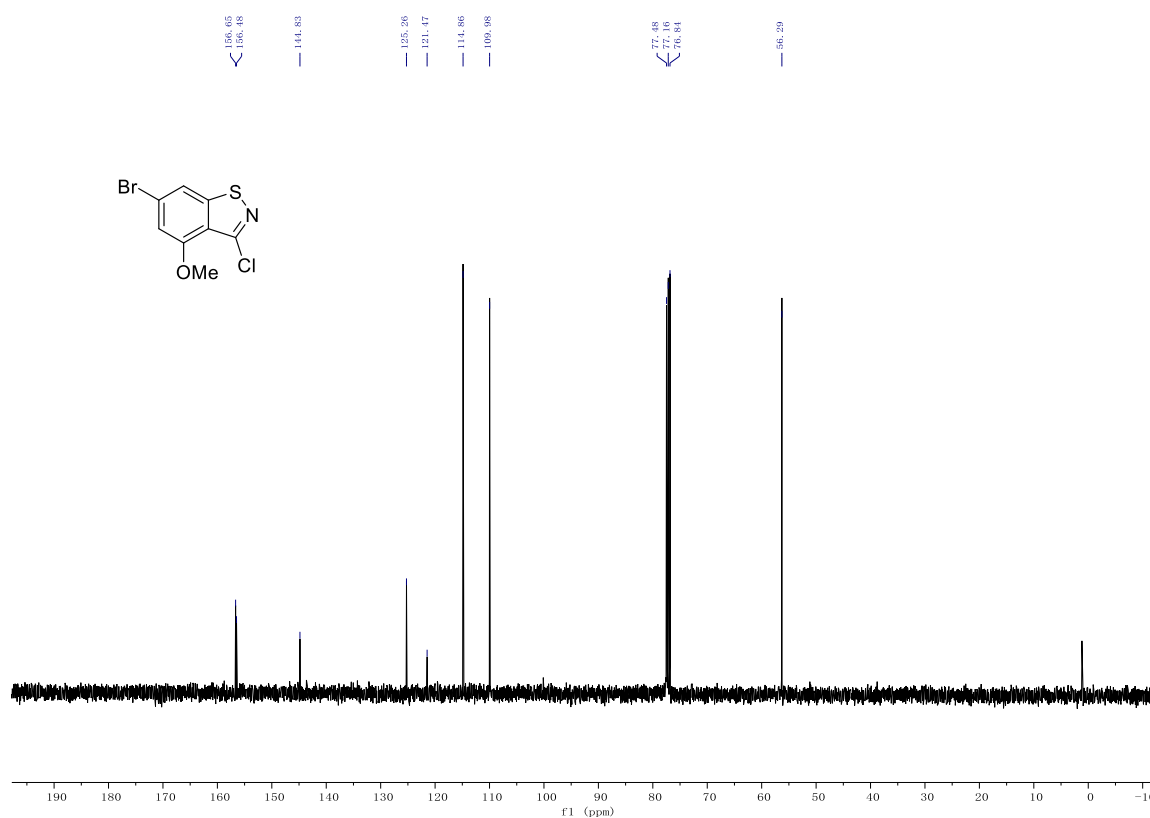
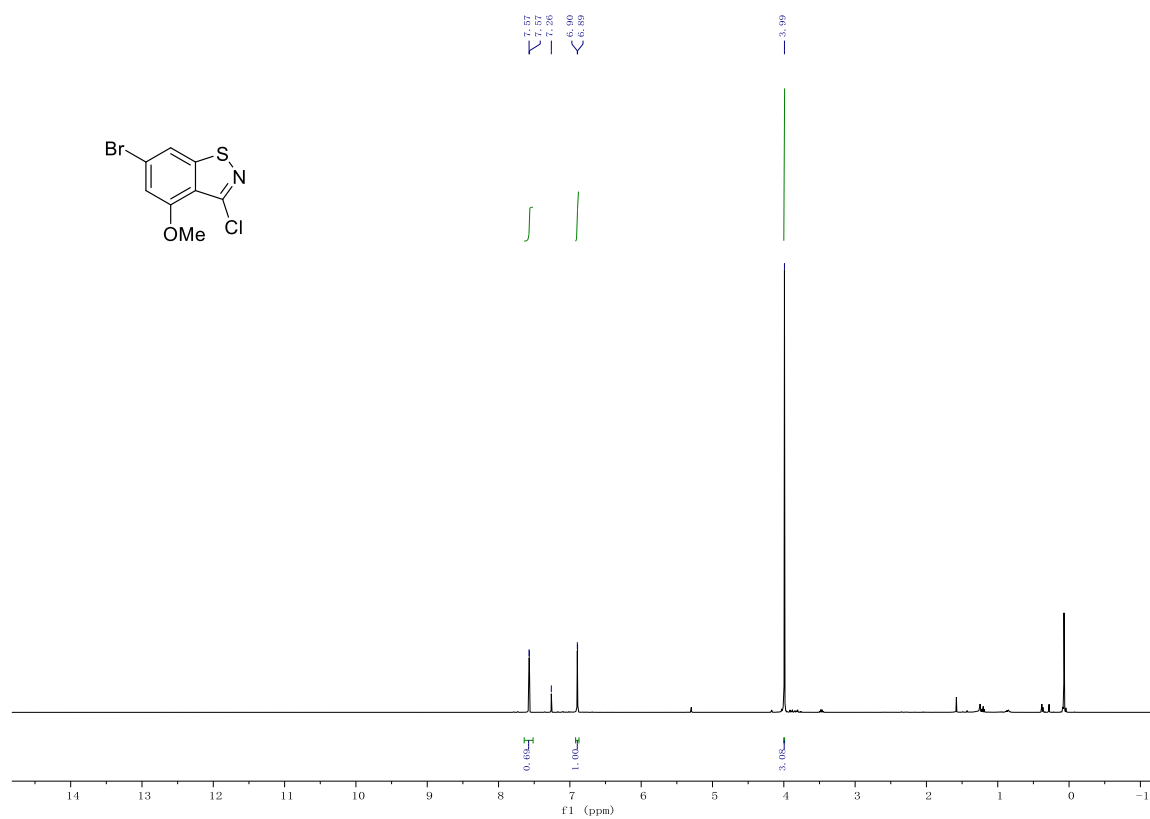




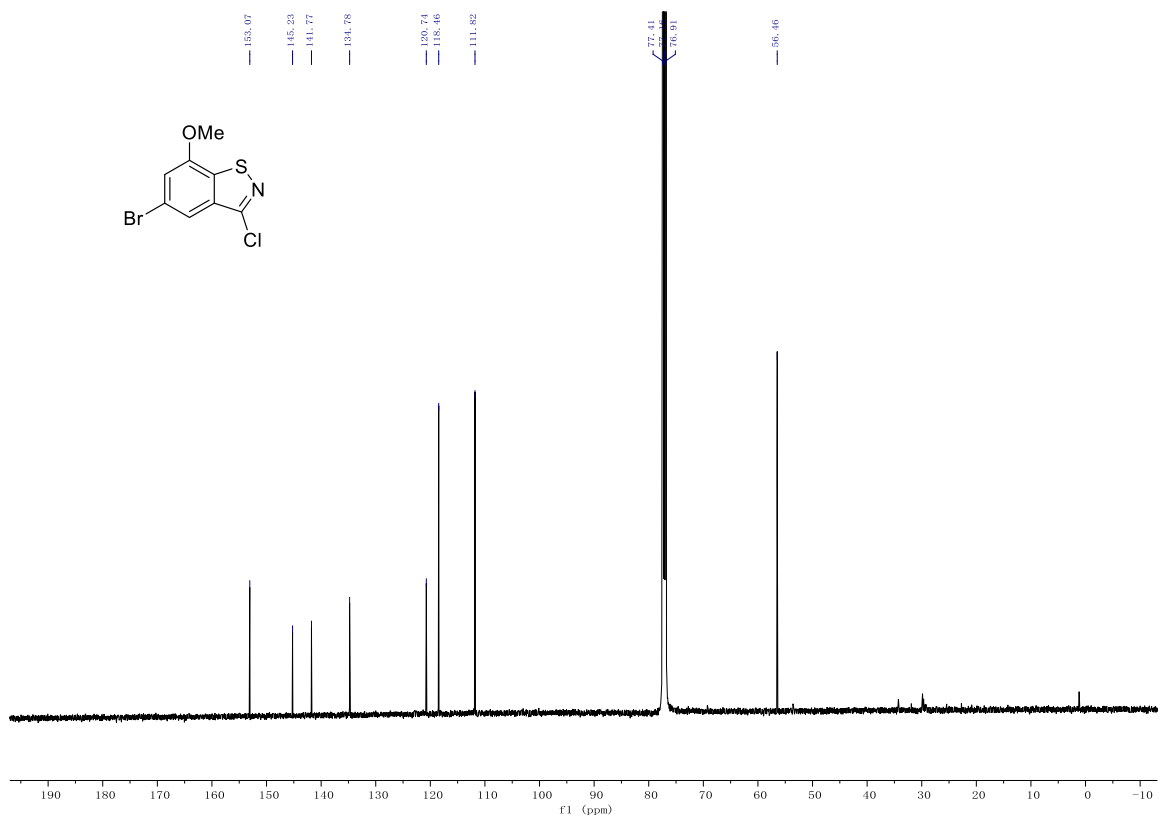
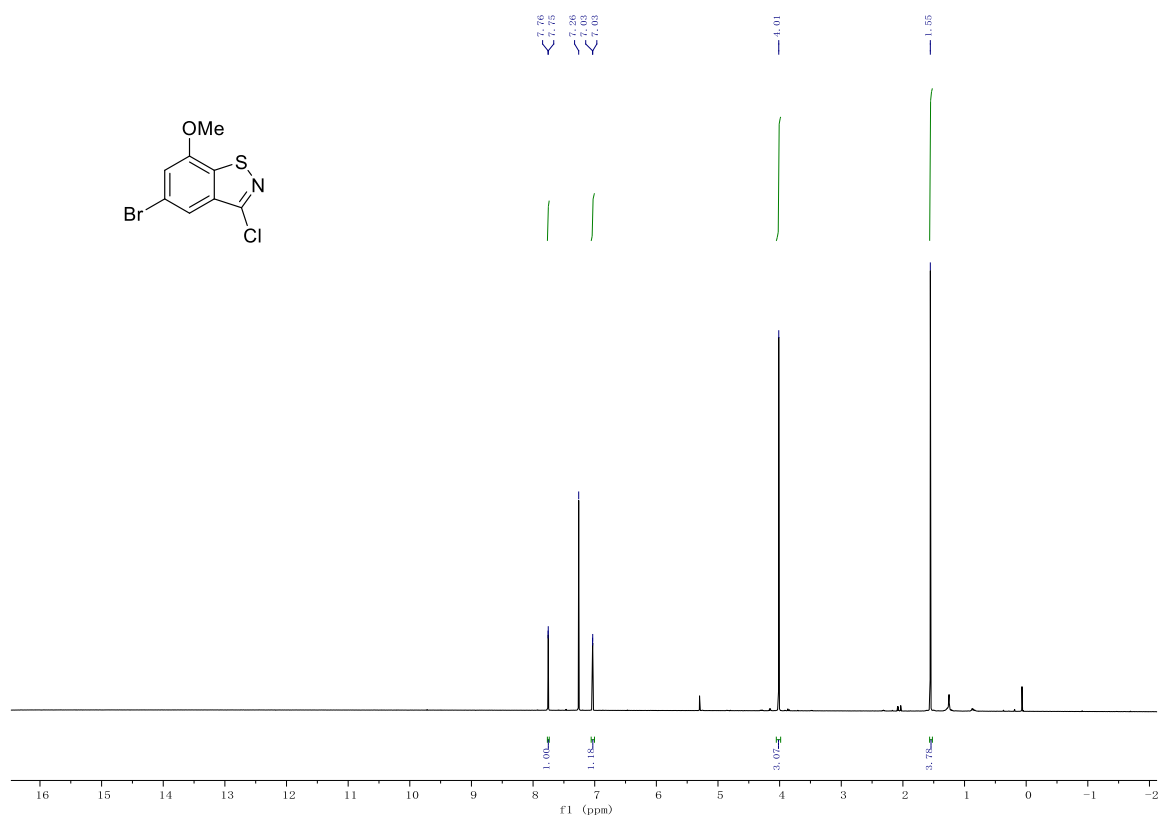
¹H NMR and ¹³C NMR spectra of **3-chloro-4-methoxy-1,2-benzisothiazole 60g**



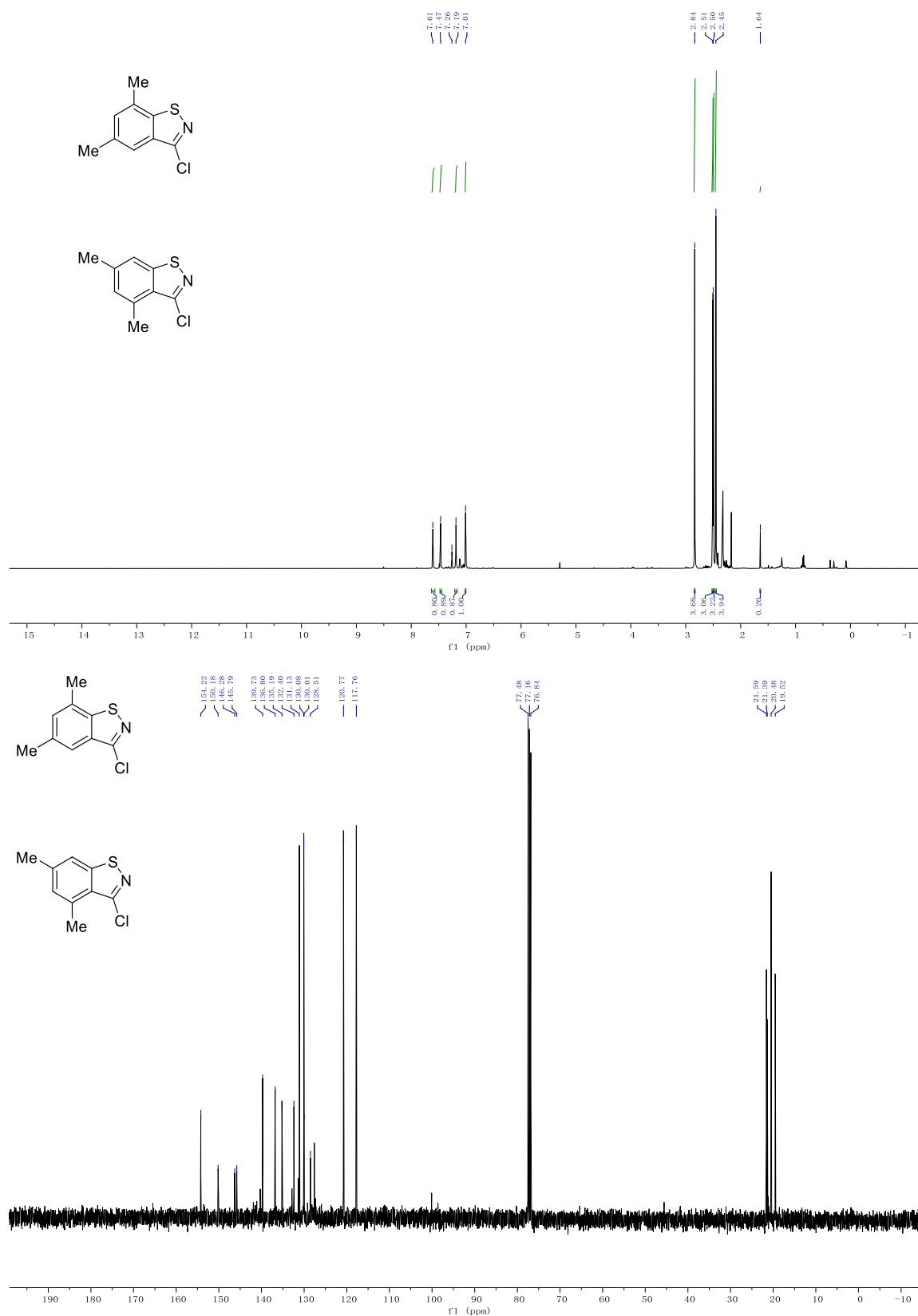
¹H NMR and ¹³C NMR spectra of 3-chloro-4-bromo-1,2-benzisothiazole 60h



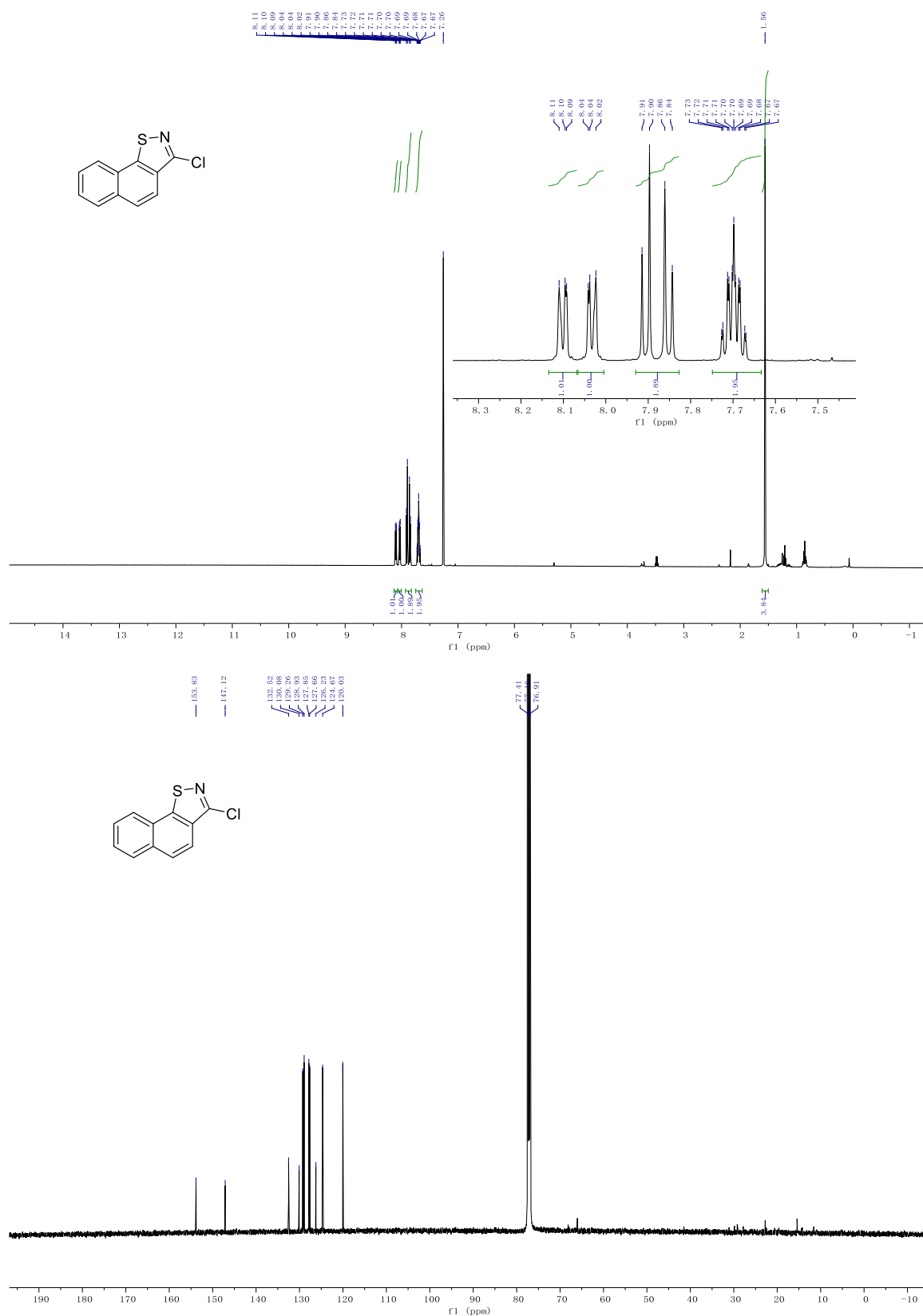
¹H NMR and ¹³C NMR spectra of 3-chloro-4-methoxy-6-bromo-1,2-benzisothiazole 60i



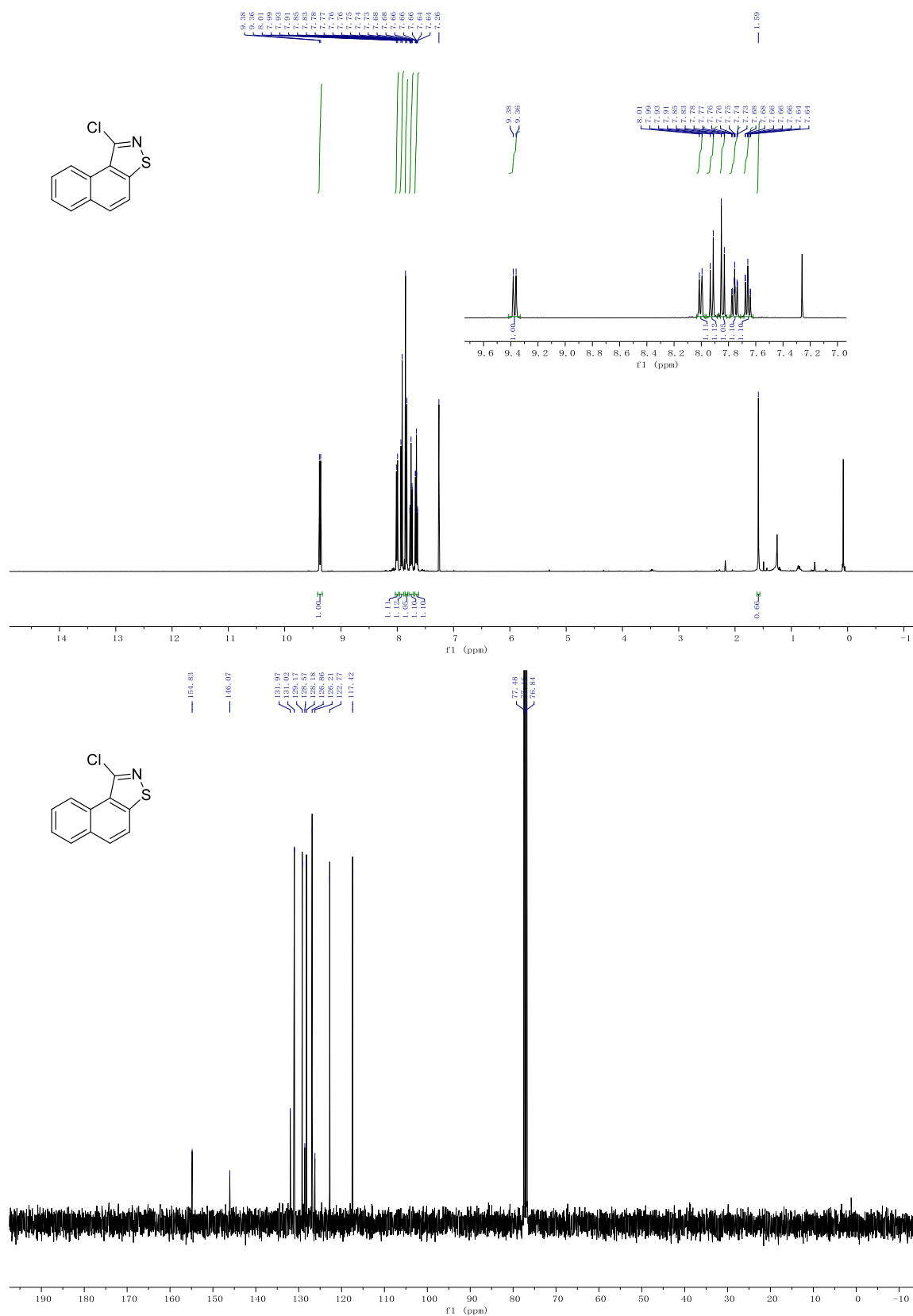
^1H NMR and ^{13}C NMR spectra of 3-chloro-5-bromo-7-methoxy-1,2-benzisothiazole 60i'



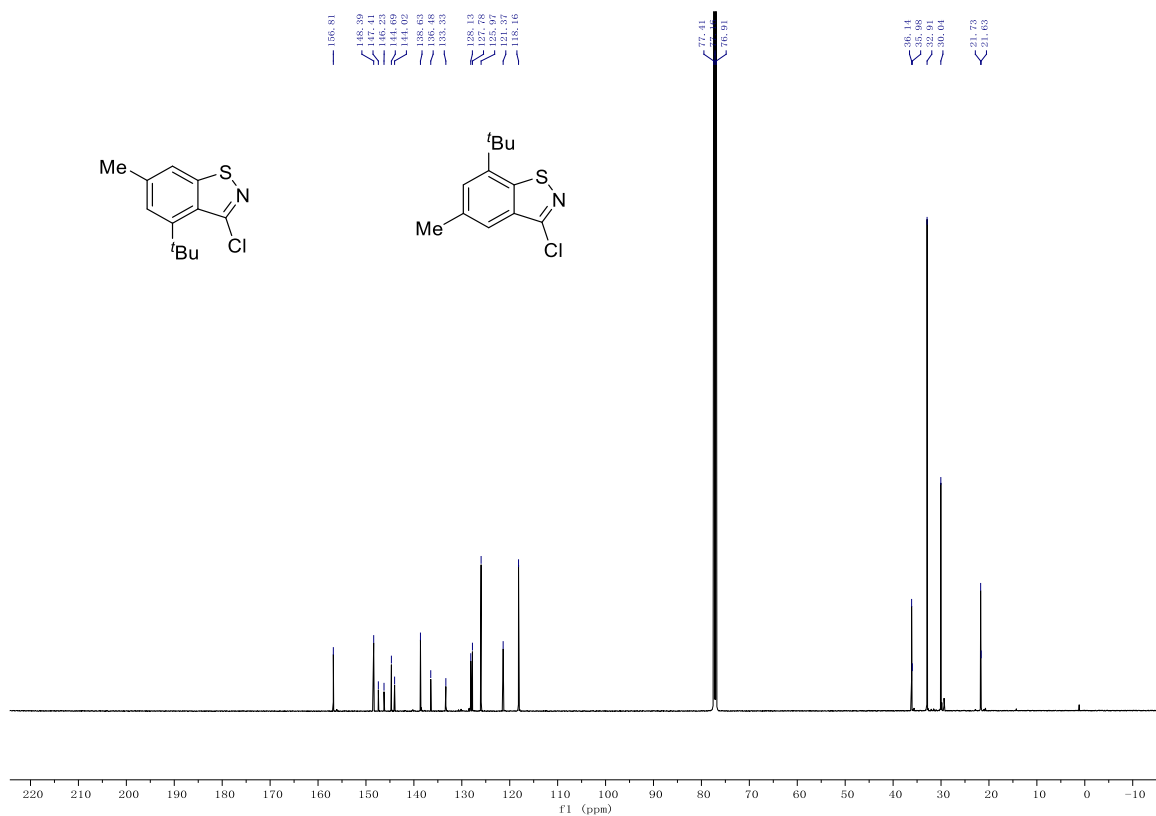
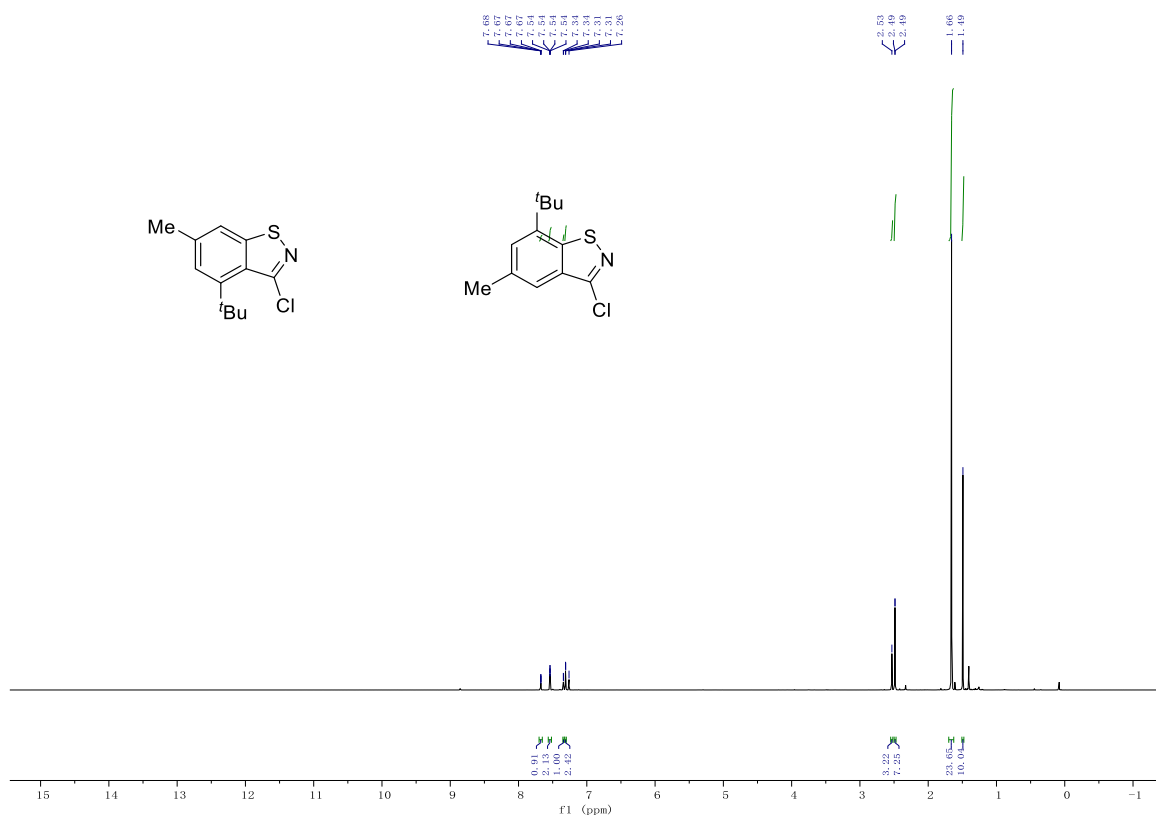
^1H NMR and ^{13}C NMR spectra of **3-chloro-5,7-dimethyl-1,2-benzisothiazole** & **3-chloro-4,6-dimethyl-1,2-benzisothiazole 61j & 60j'**



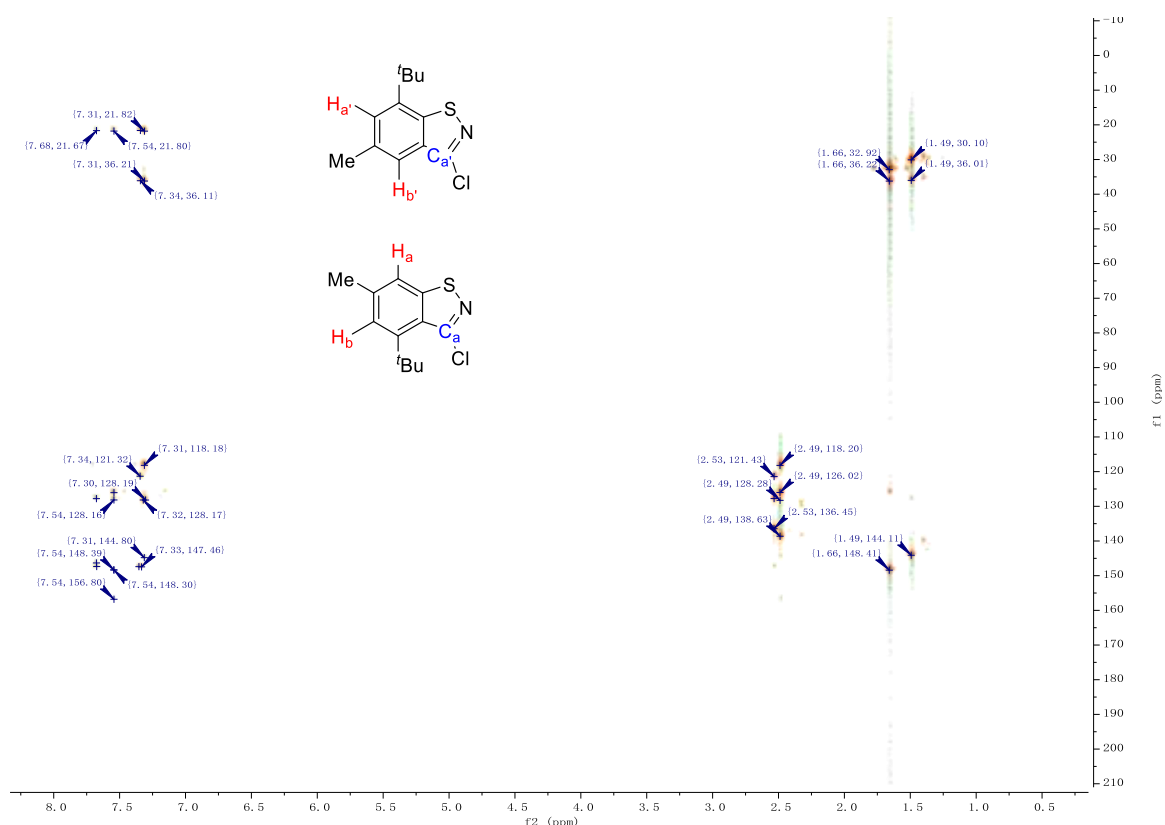
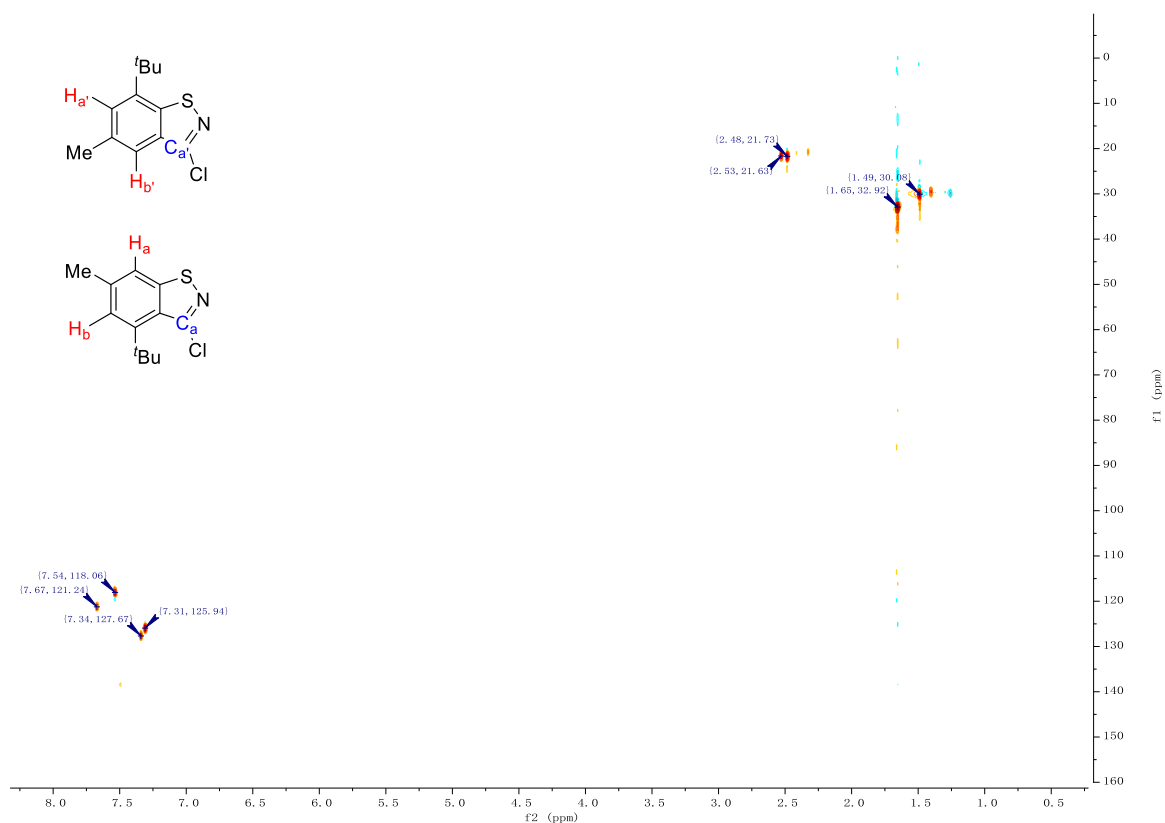
¹H NMR and ¹³C NMR spectra of 1-chloronaphtho-1,2-isothiazole 60k



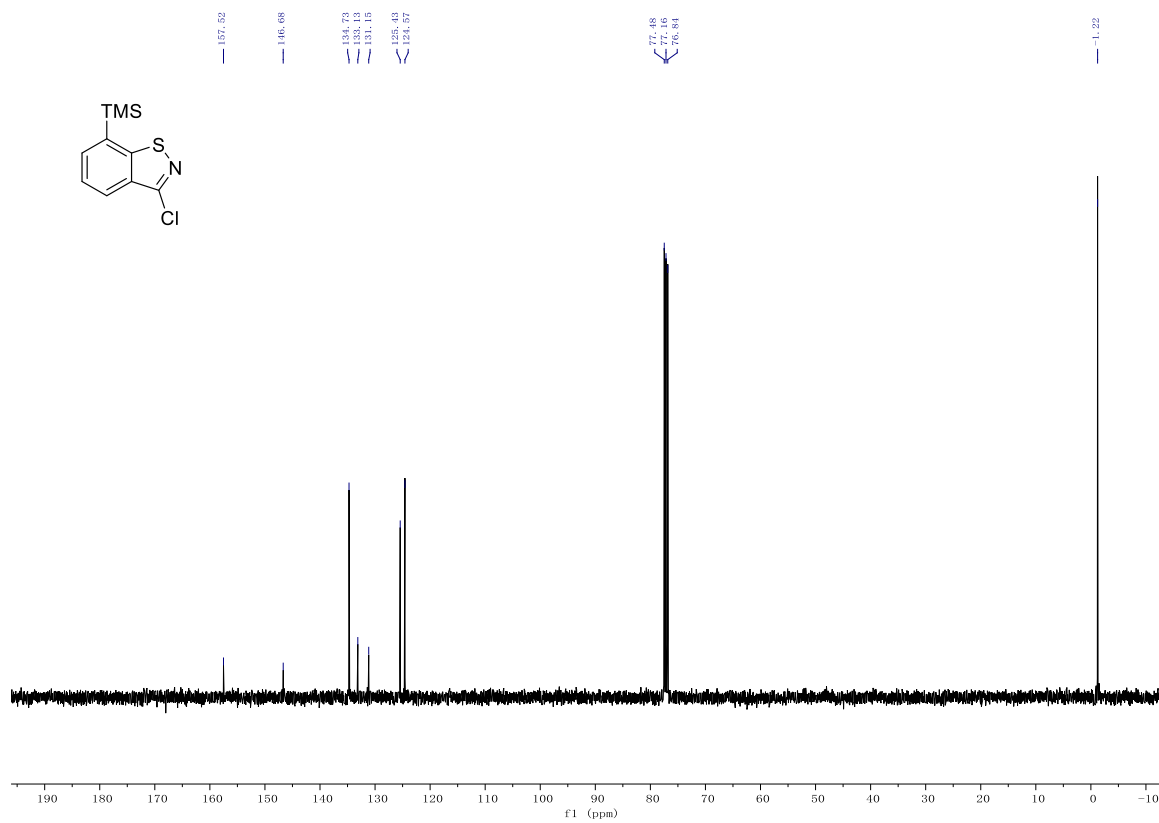
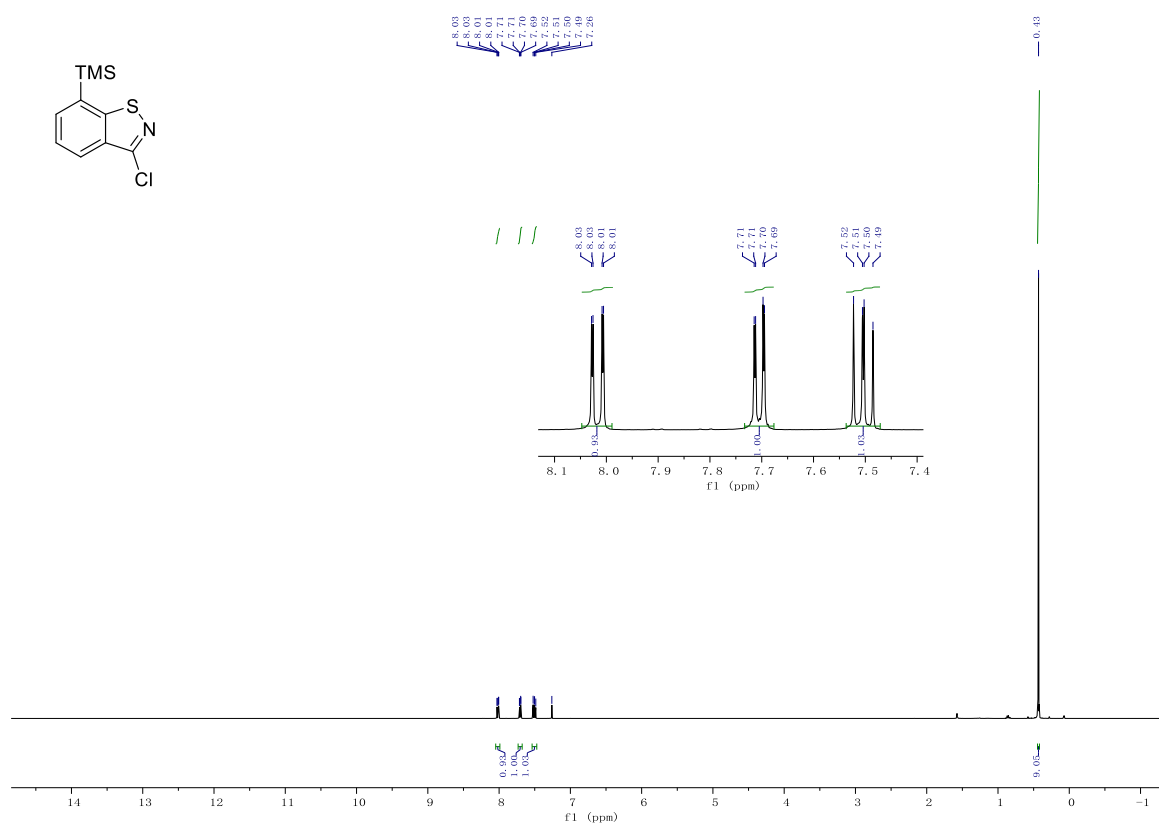
^1H NMR and ^{13}C NMR spectra of 3-chloronaphtho-2,1-isothiazole 60k'



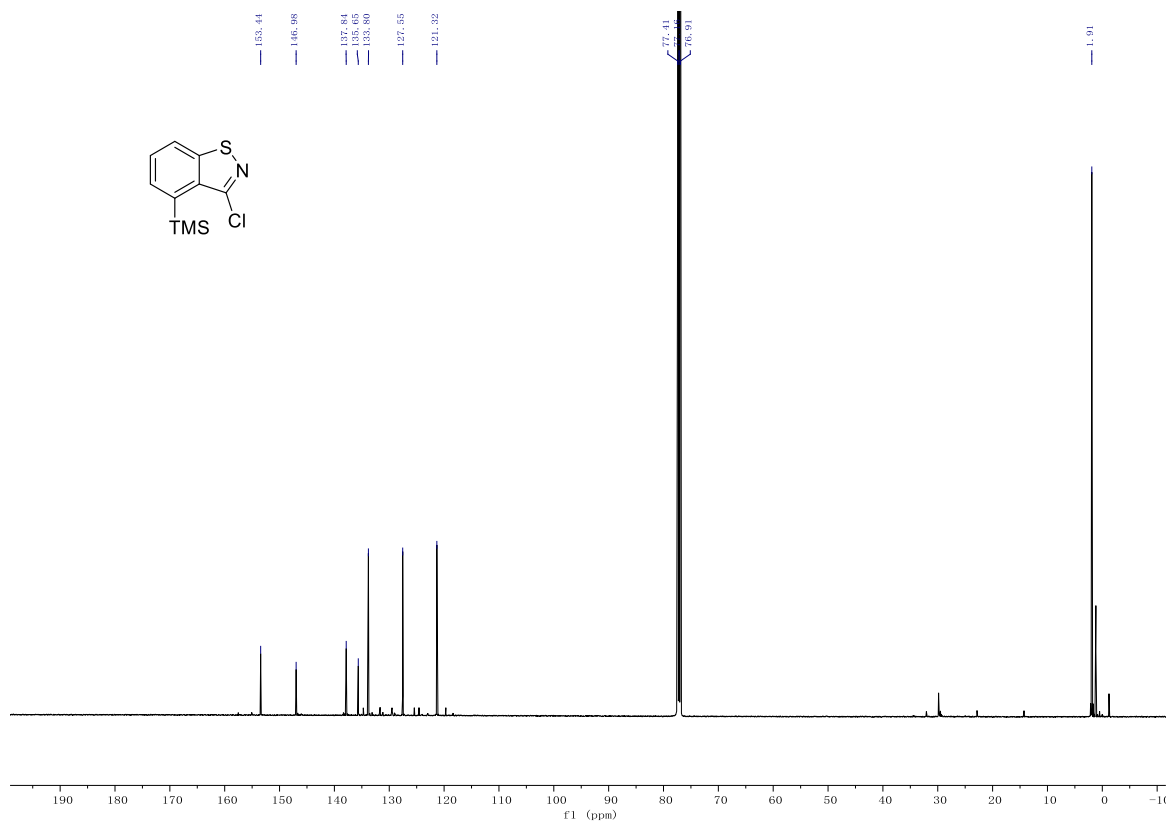
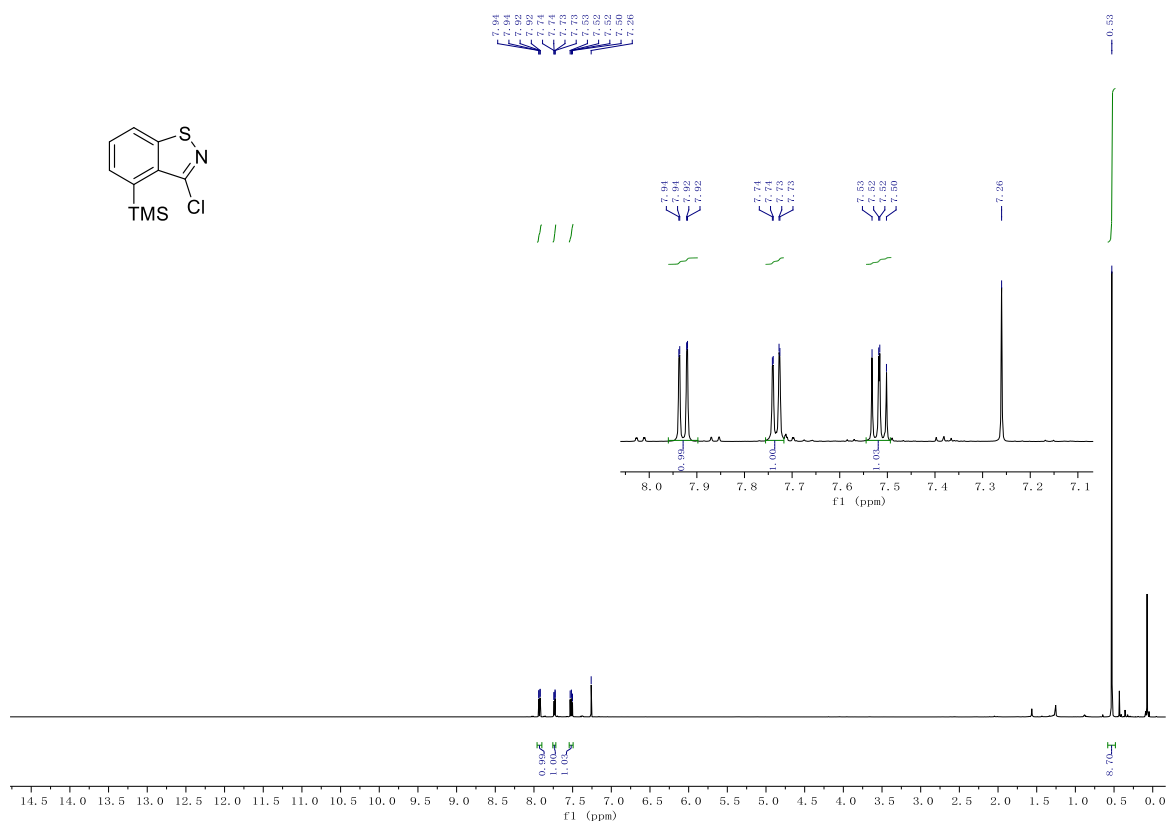
¹H NMR and ¹³C NMR spectra of 3-Chloro-4-*tert*-butyl-6-methyl-1,2-benzisothiazole & 3-chloro-5-methyl-7-*tert*-butyl-1,2-benzisothiazole mixture 60I & 60I'



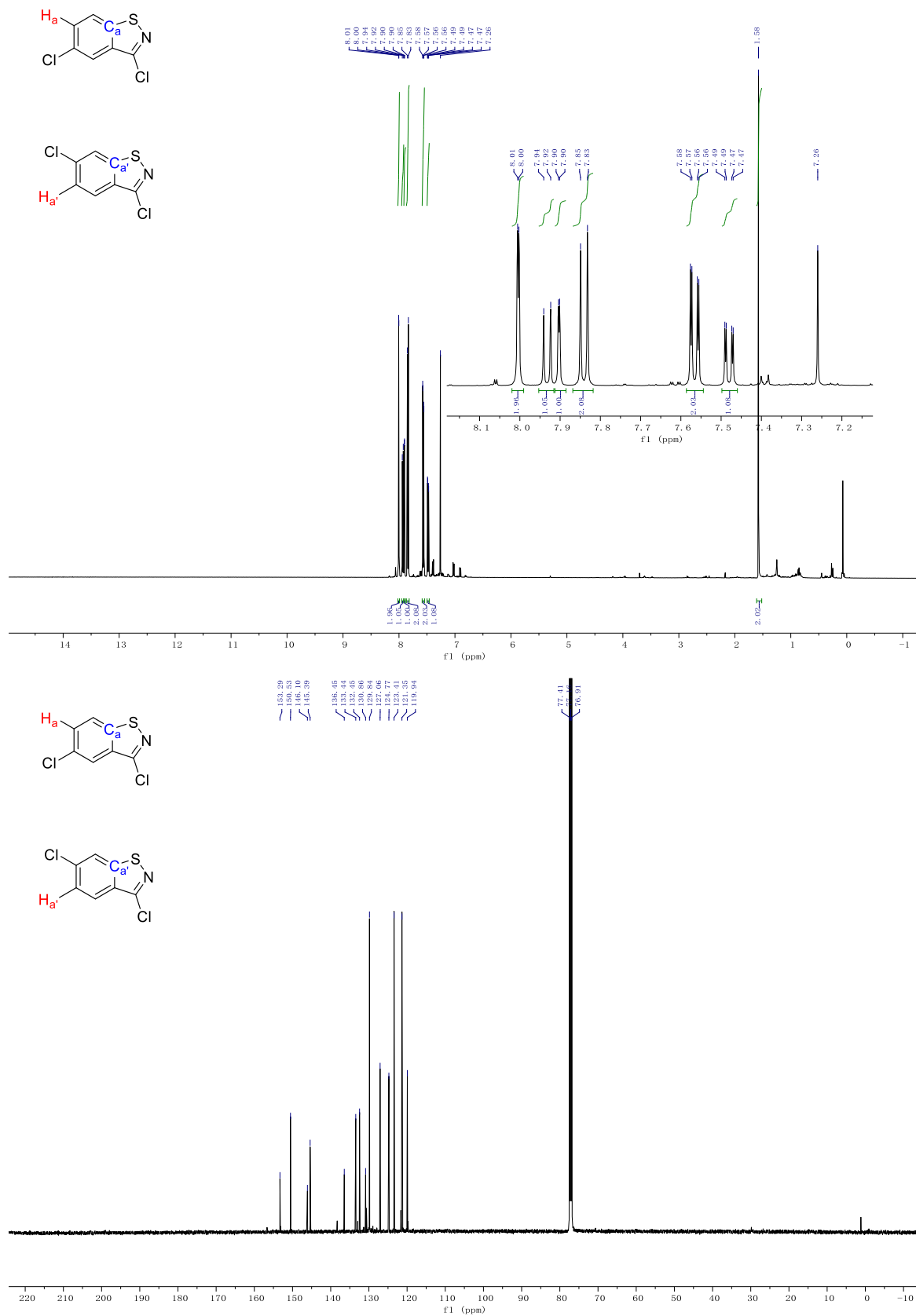
HSQC and HMBC spectrum of 3-chloro-4-*tert*-butyl-6-methyl-1,2-benzisothiazole & 3-chloro-5-methyl-7-*tert*-butyl-1,2-benzisothiazole mixture 60l & 60l'



¹H NMR and ¹³C NMR spectra of 3-chloro-6-trimethylsilyl-1,2-benzisothiazole 60m

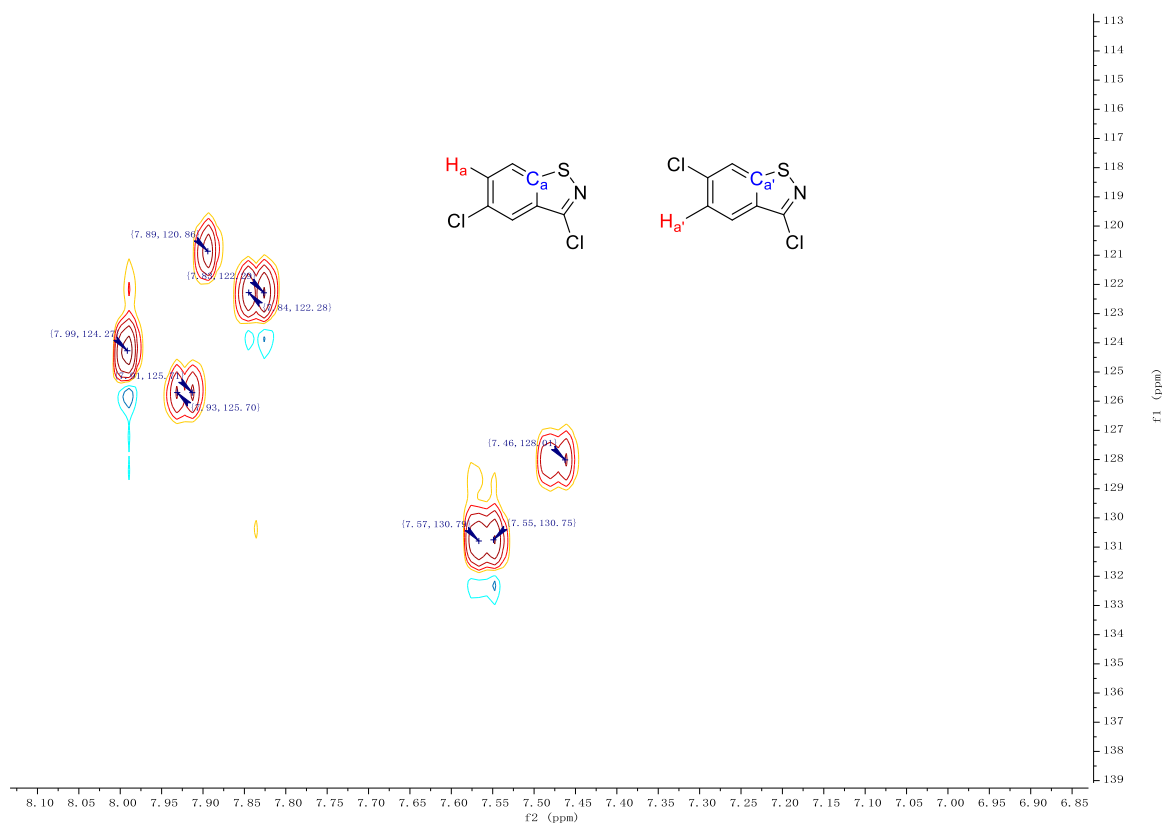


¹H NMR and ¹³C NMR spectra of 3-chloro-4-(trimethylsilyl)-1,2-benzisothiazole 60m'



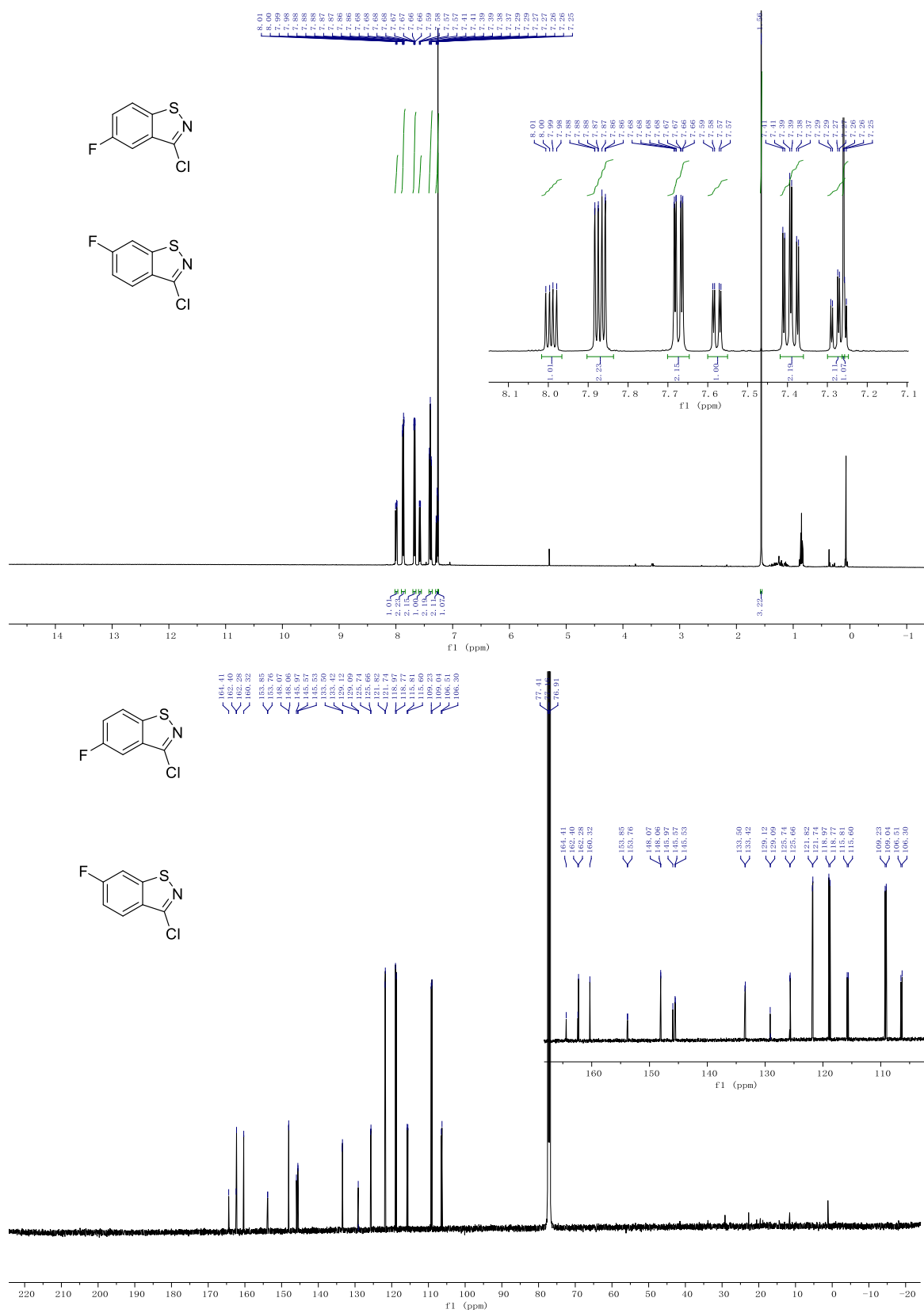
¹H NMR and ¹³C NMR spectra of 3,5-dichloro-1,2-benzisothiazole and 3,6-dichloro-1,2-

benzisothiazole 60n & 60n'

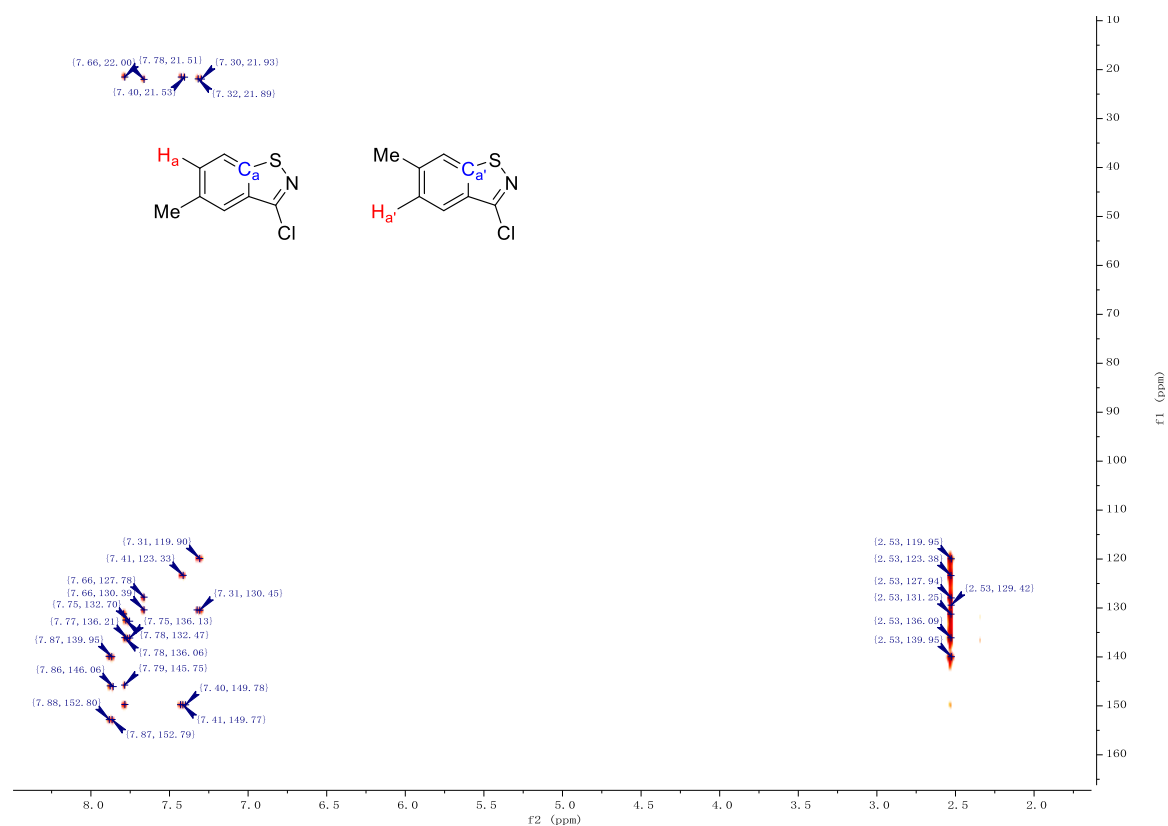
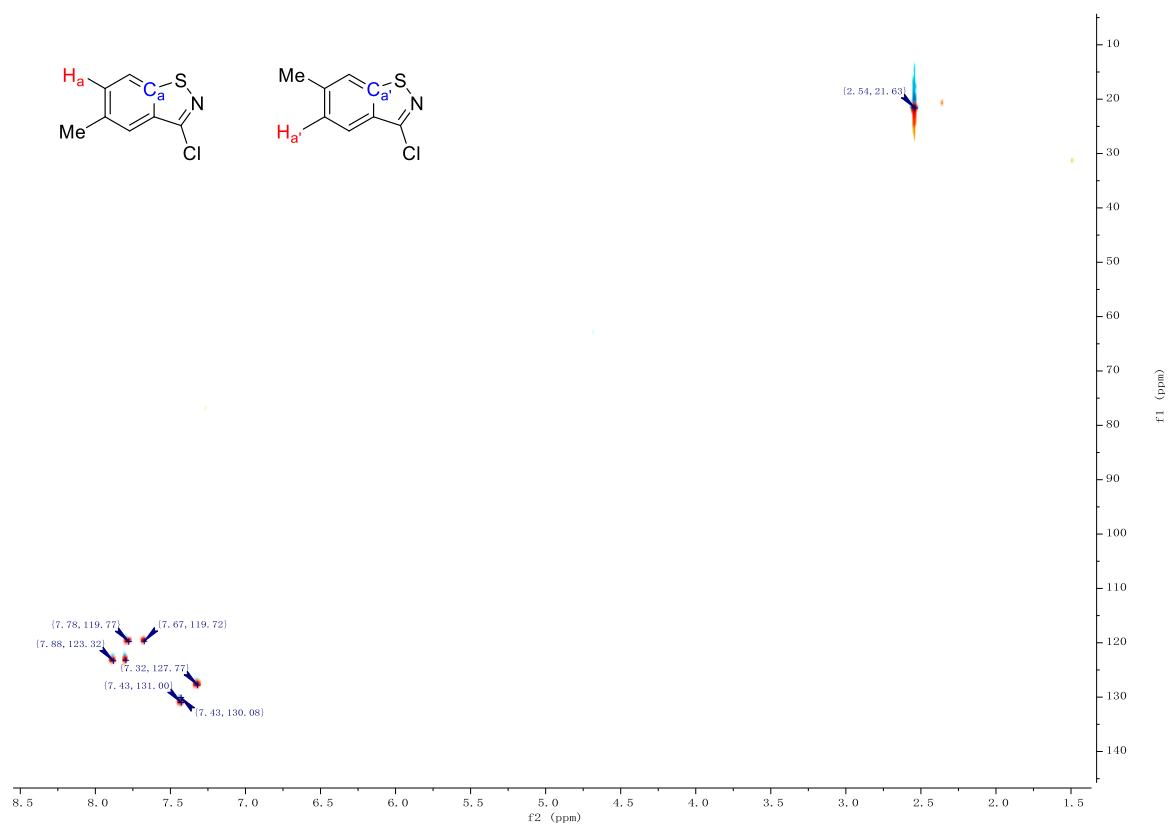


HSQC and HMBC spectrum of 3,5-dichloro-1,2-benzisothiazole and 3,6-dichloro-1,2-

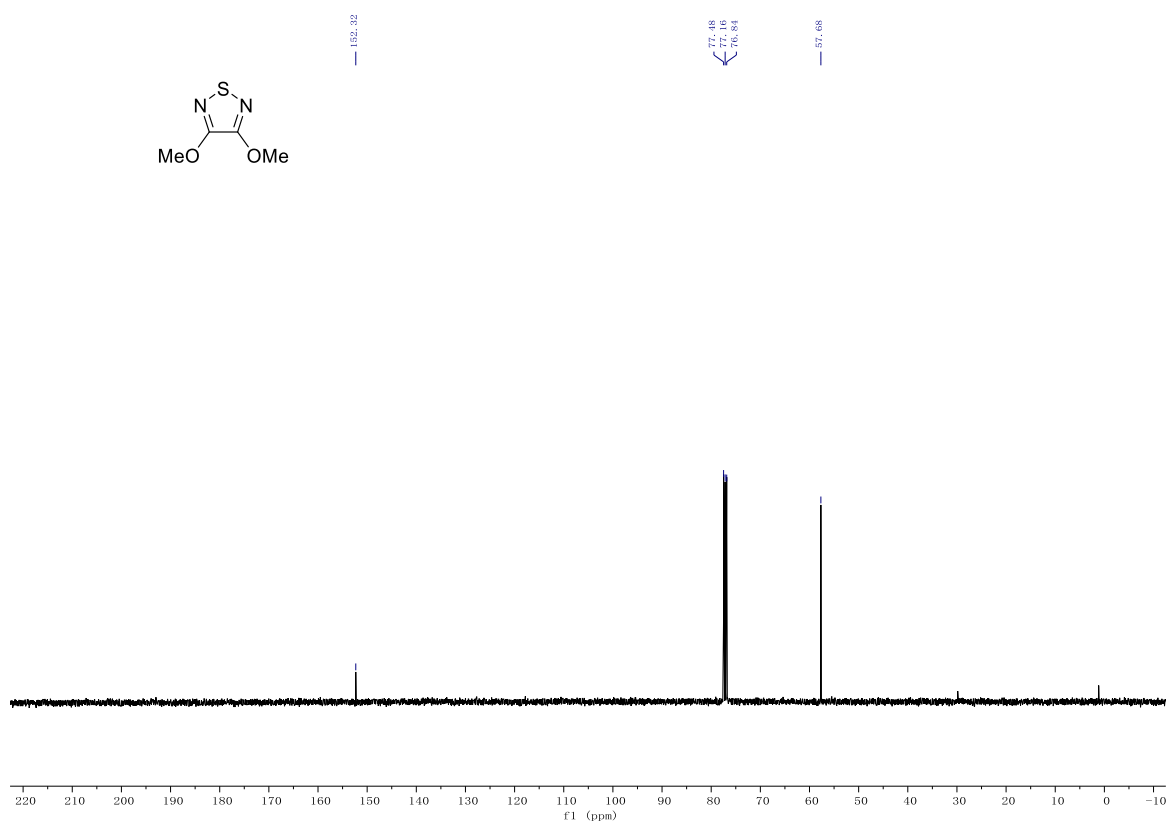
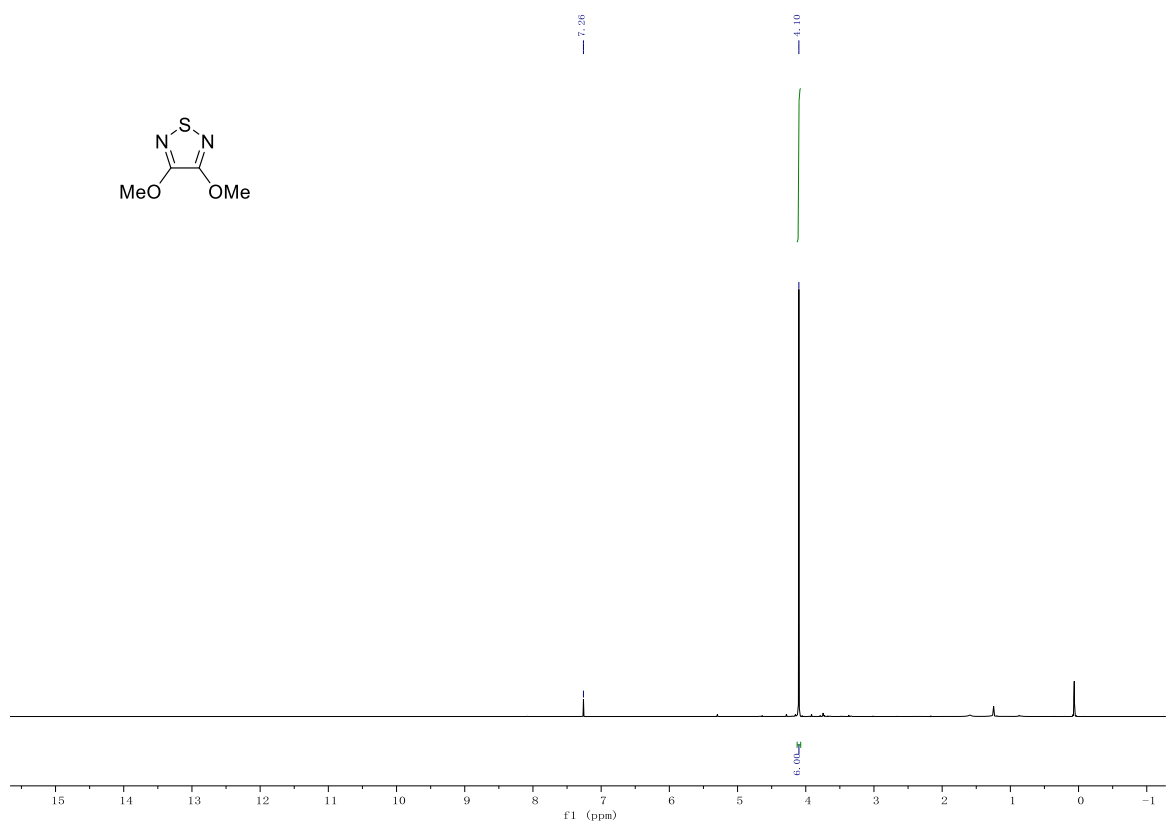
benzisothiazole 60n & 60n'



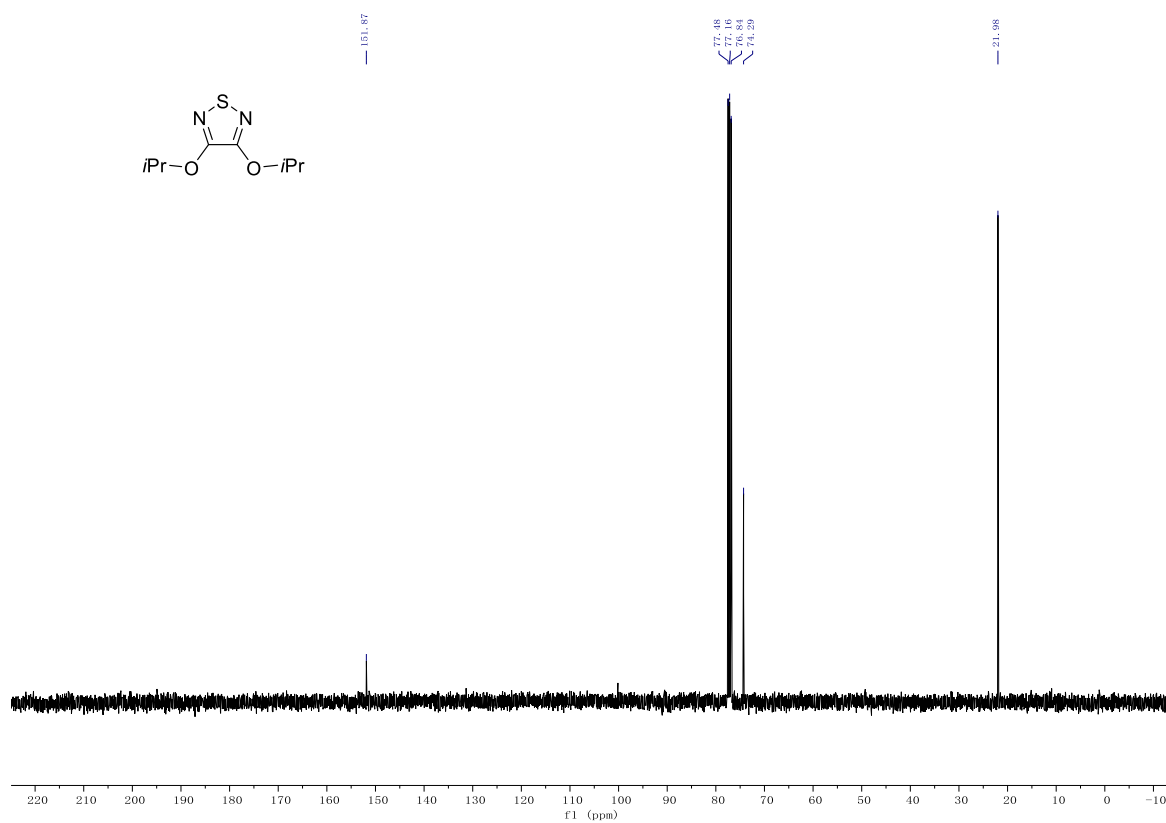
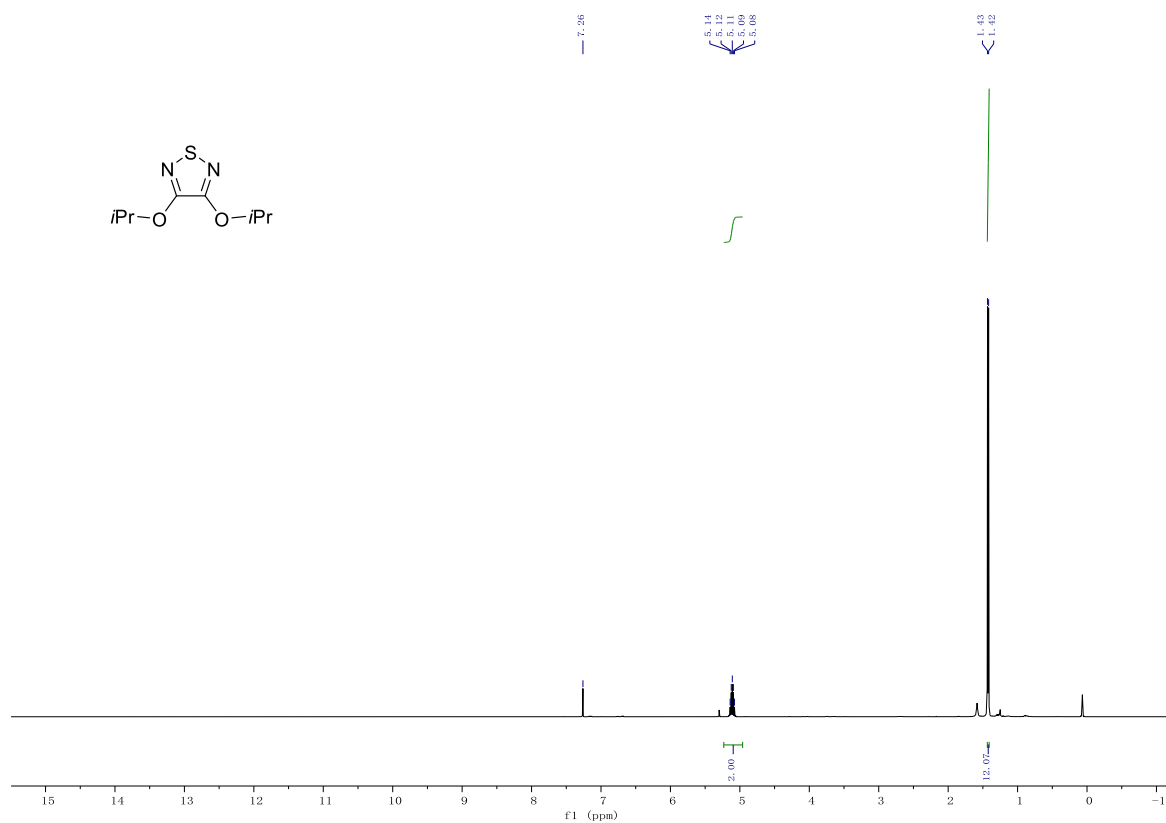
¹H NMR and ¹³C NMR spectra of 3-chloro-5-fluoro-1,2-benzisothiazole & 3-chloro-6-fluoro-1,2-benzisothiazole mixture 60o & 60o'



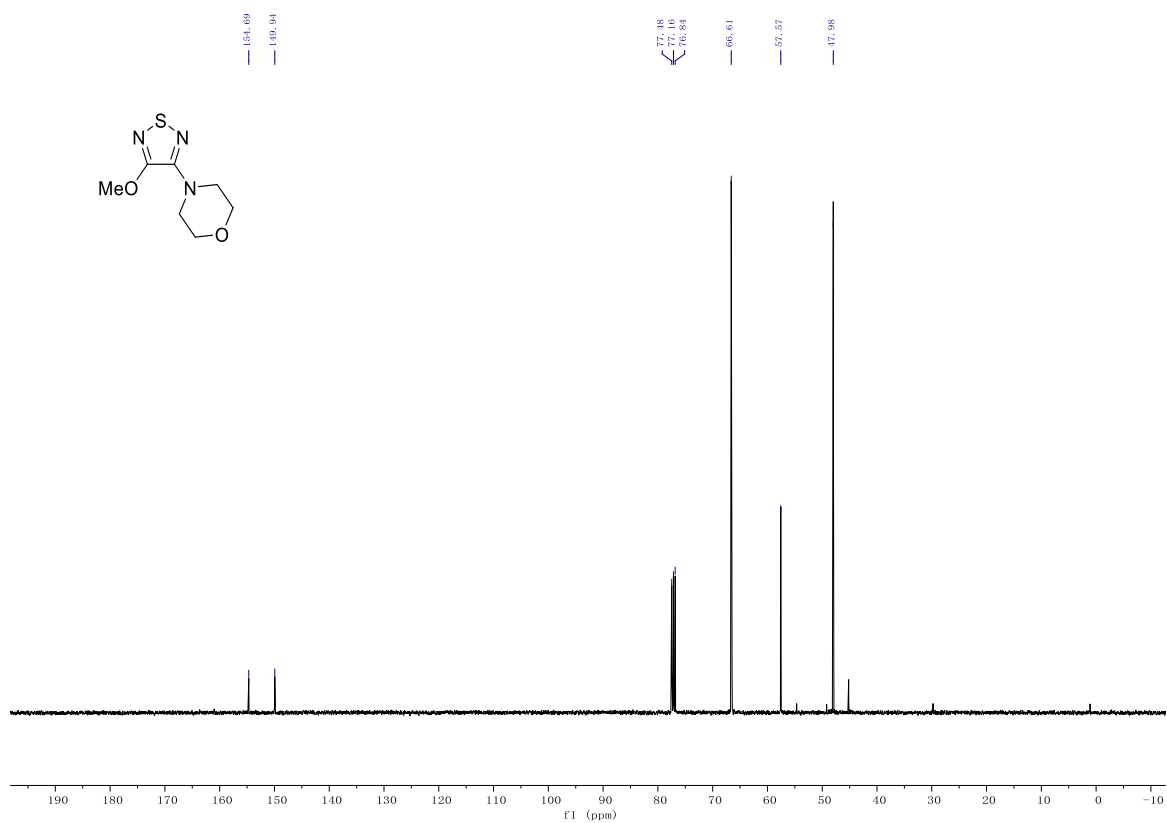
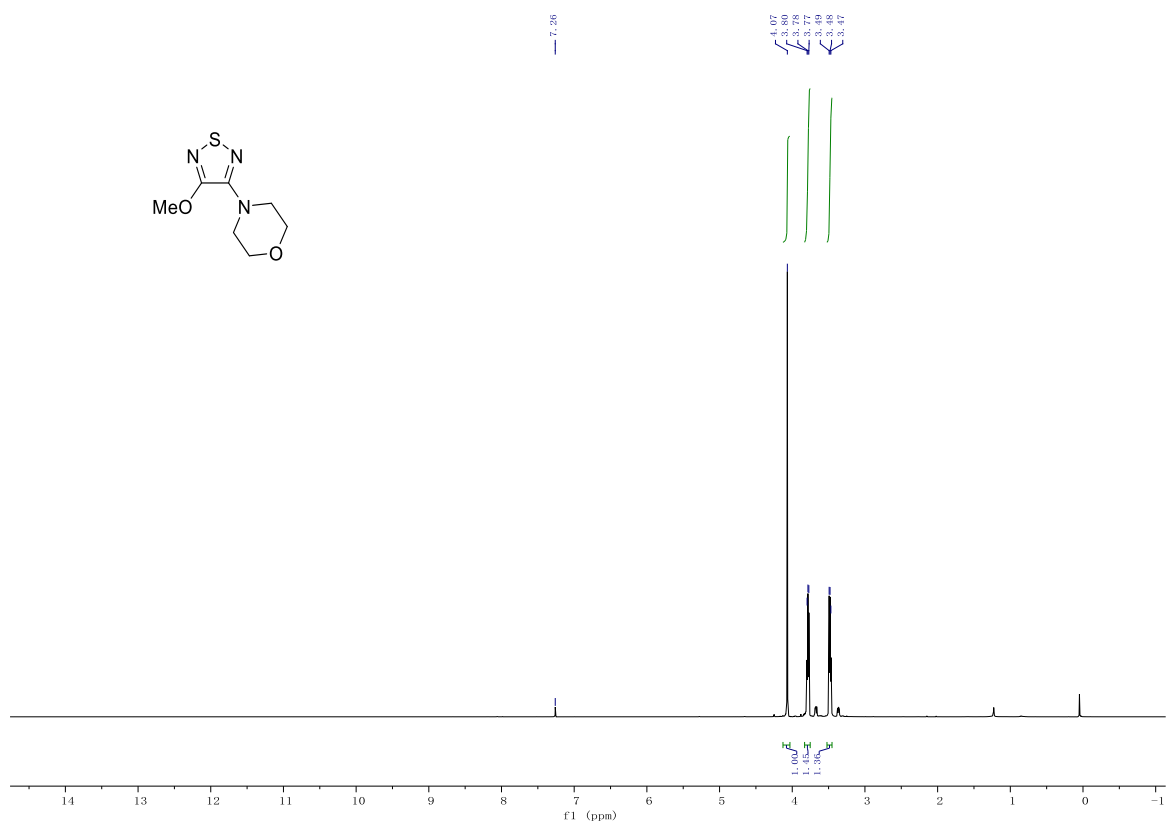
HSQC and HMBC spectrum of 3-chloro-5-methyl-1,2-benzisothiazole and 3-chloro-6-methyl-1,2-benzisothiazole 60p & 60p'



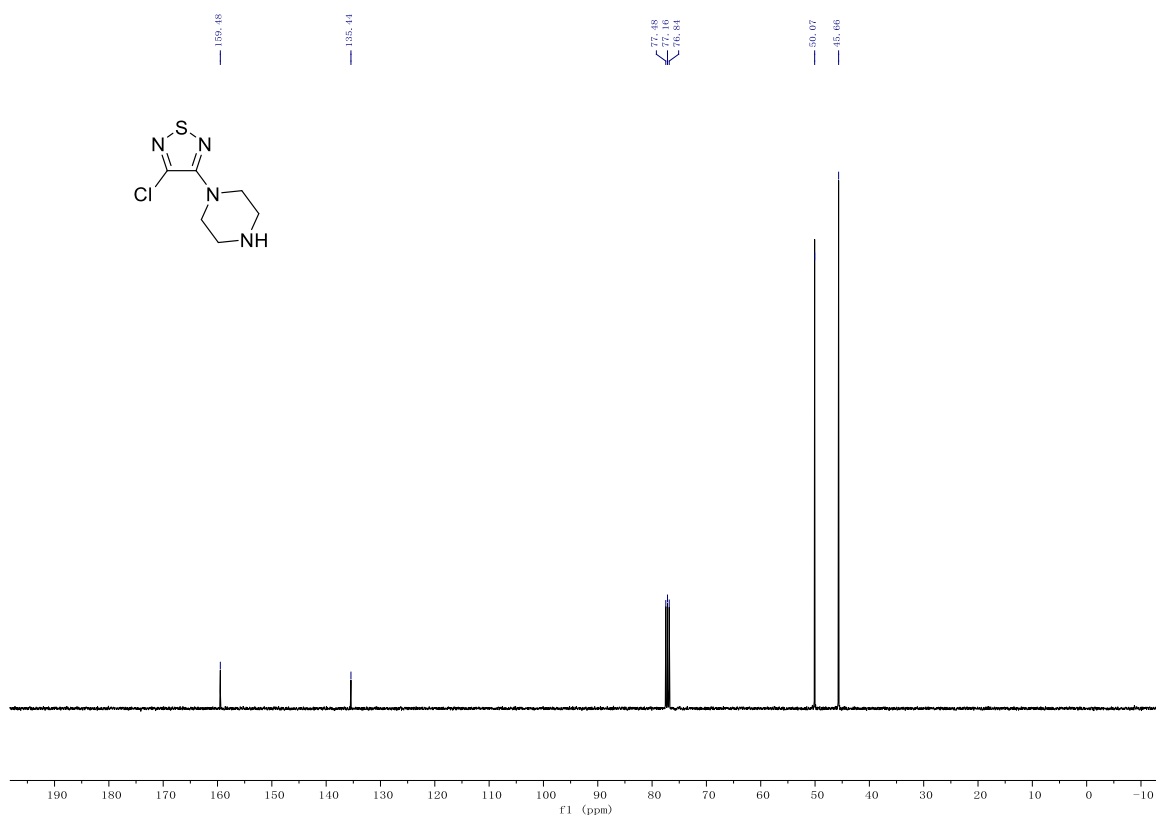
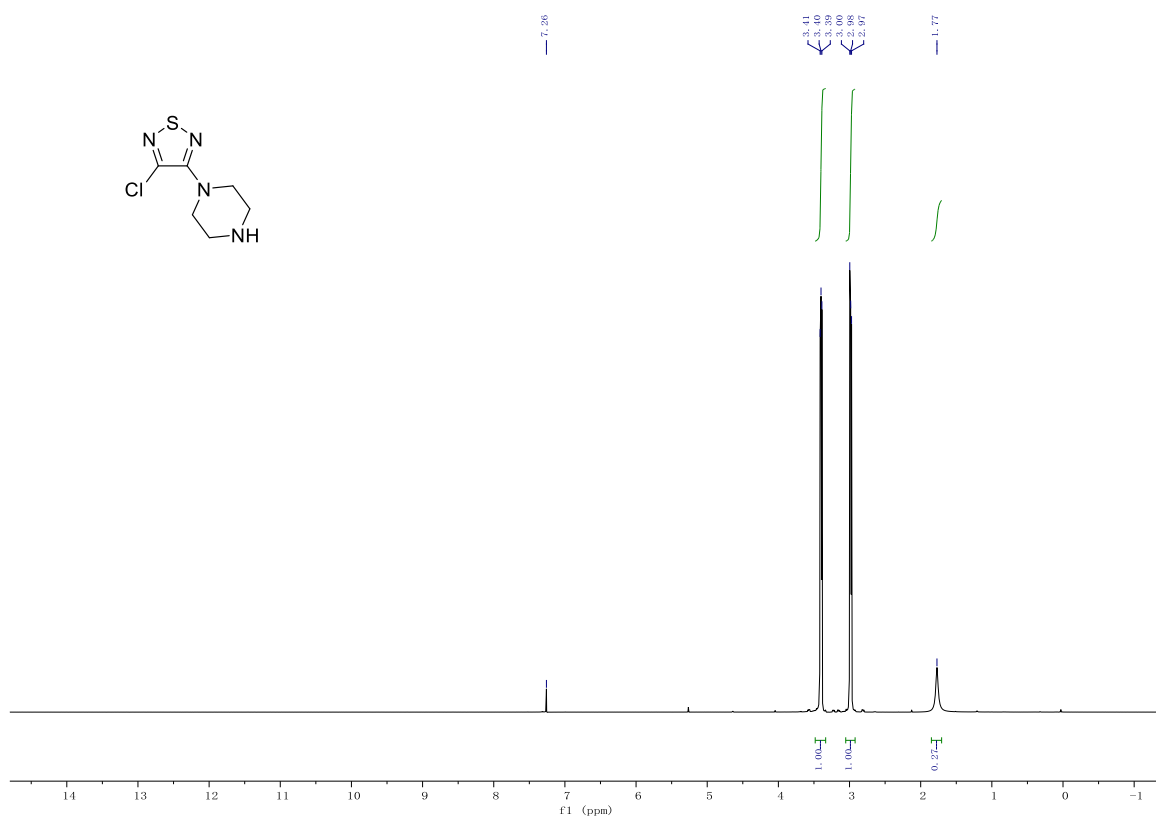
^1H NMR and ^{13}C NMR spectra of **3,4-dimethoxy-1,2,5-thiadiazole 67a**



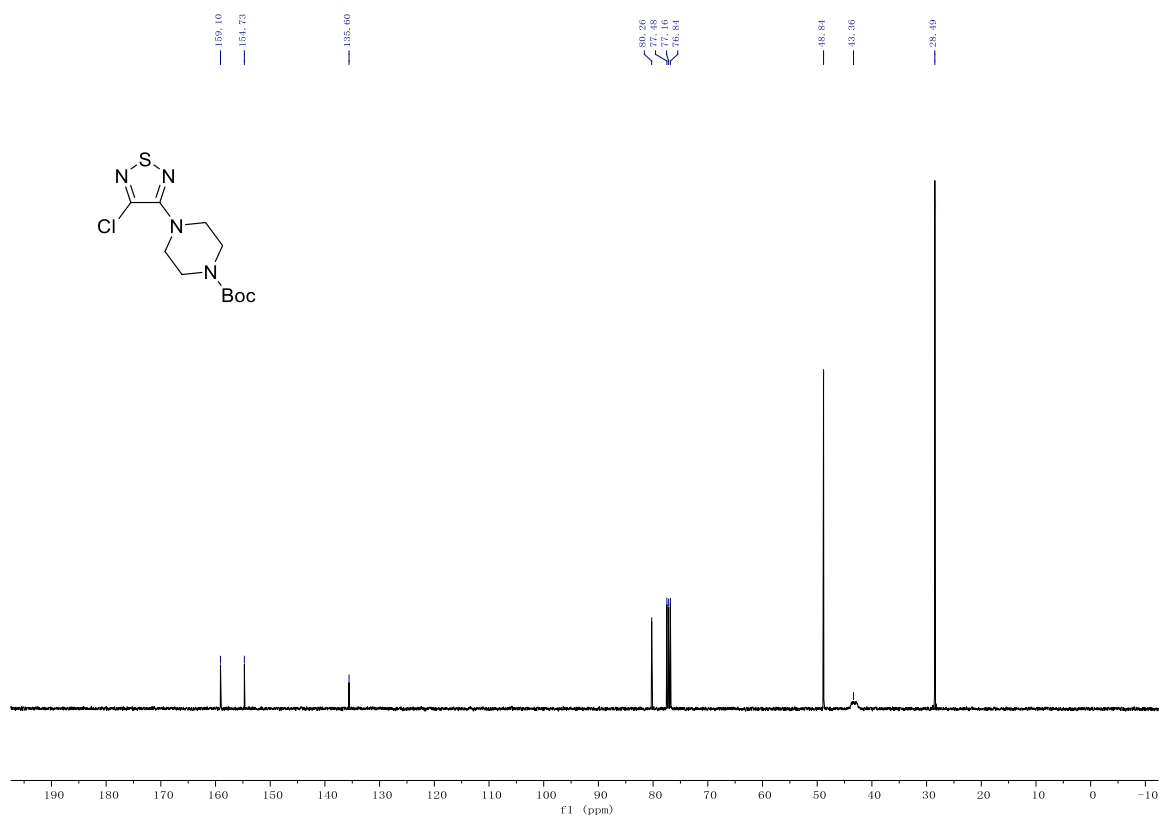
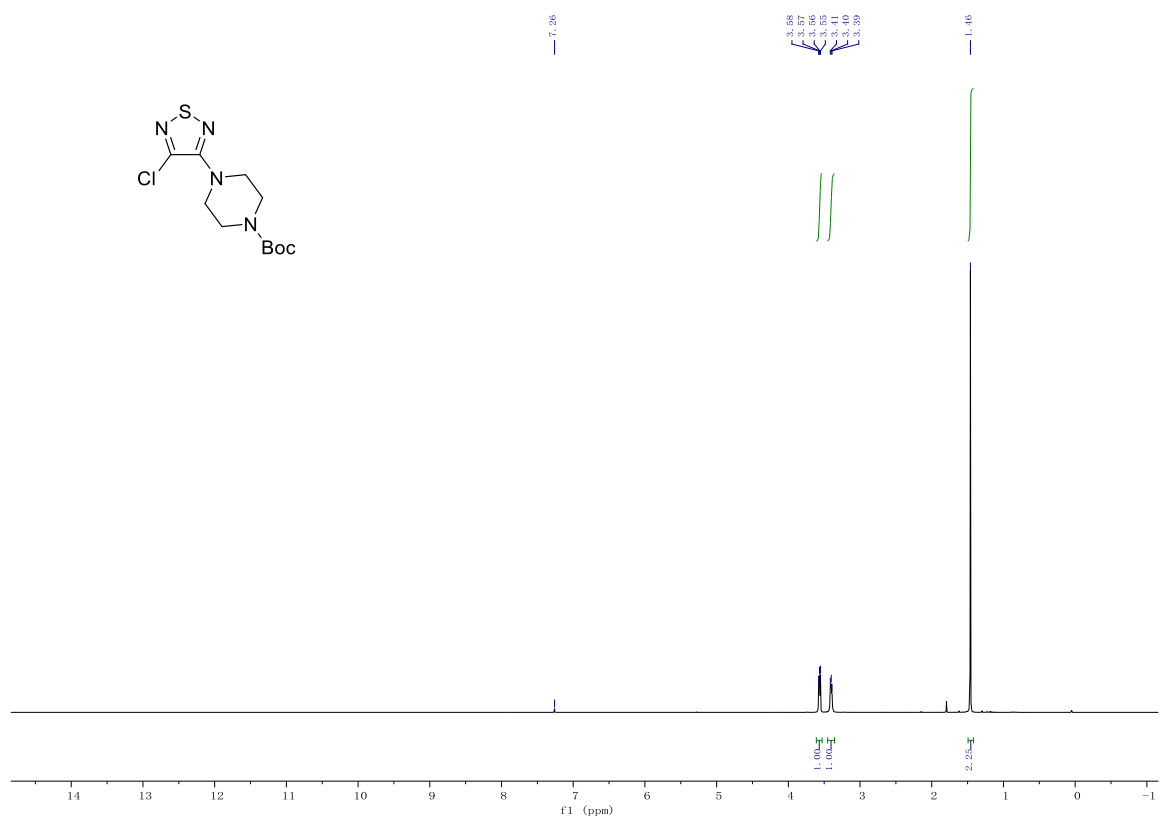
¹H NMR and ¹³C NMR spectra of 3,4-diisopropyl-1,2,5-thiadiazole 67b



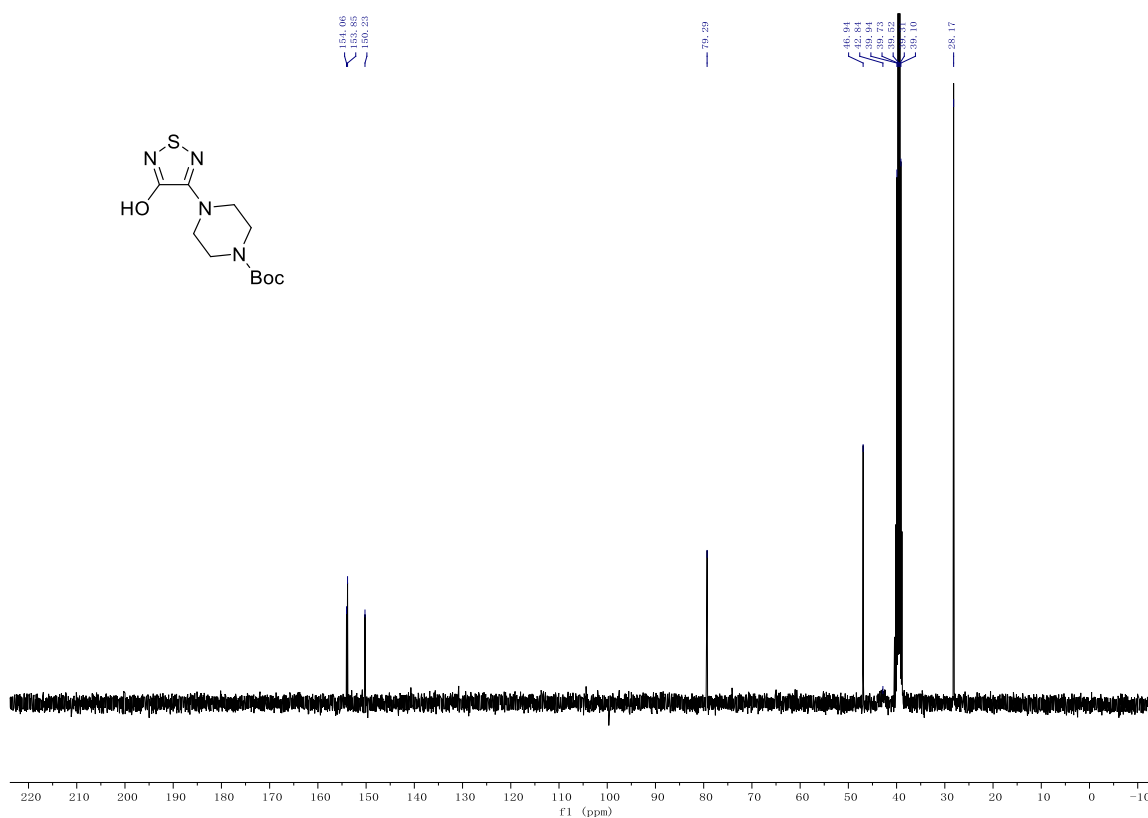
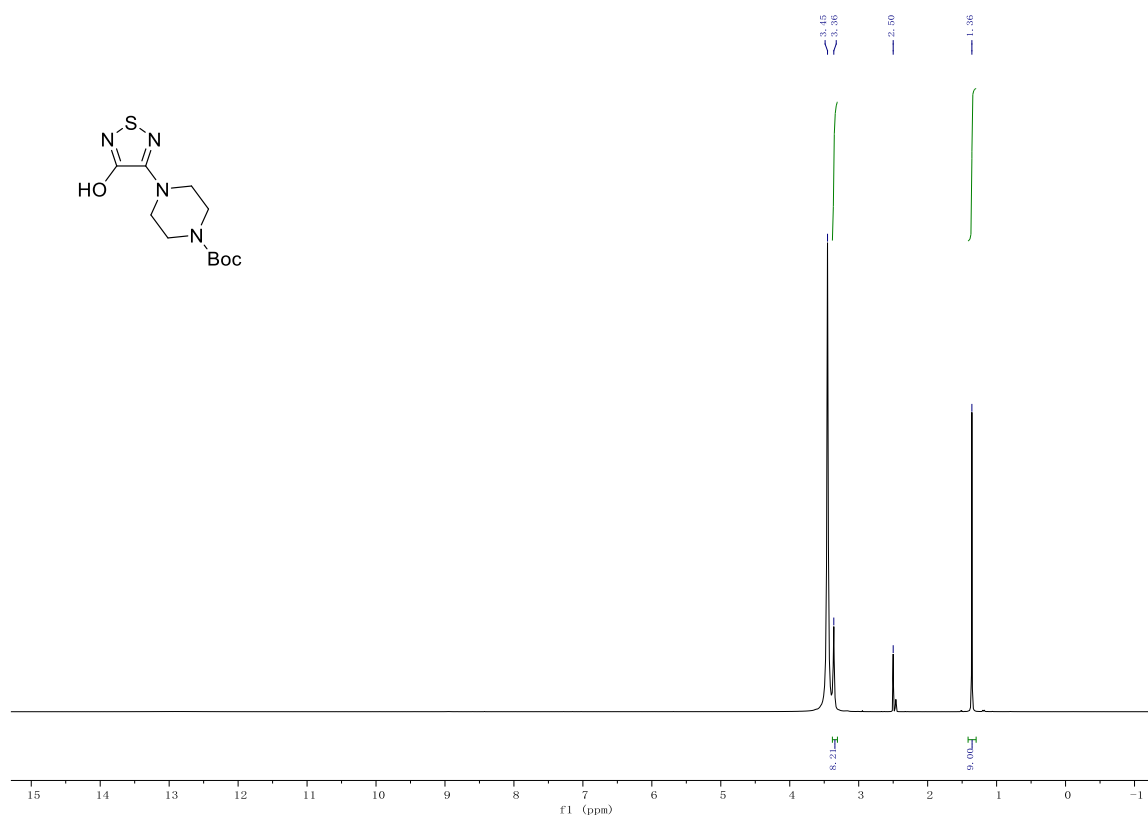
¹H NMR and ¹³C NMR spectra of **3-methoxy-4-morpholinyl-1,2,5-thiadiazole 67g**



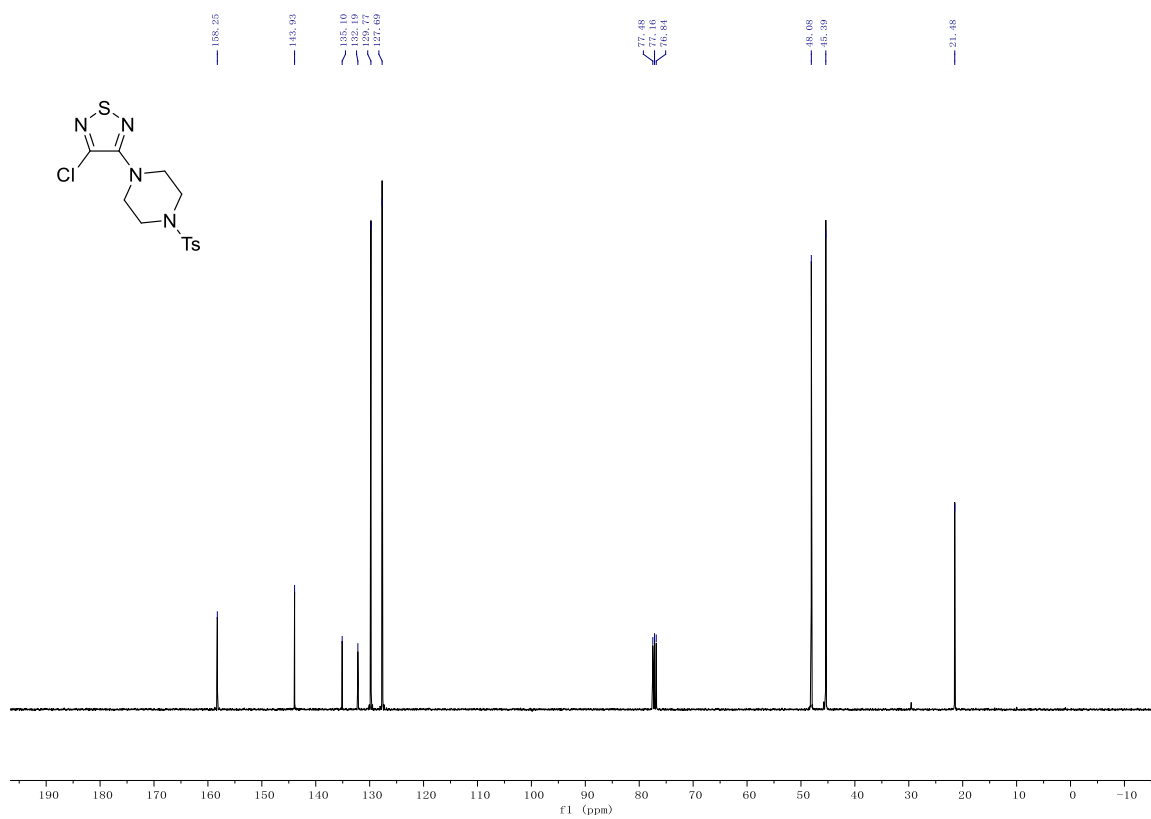
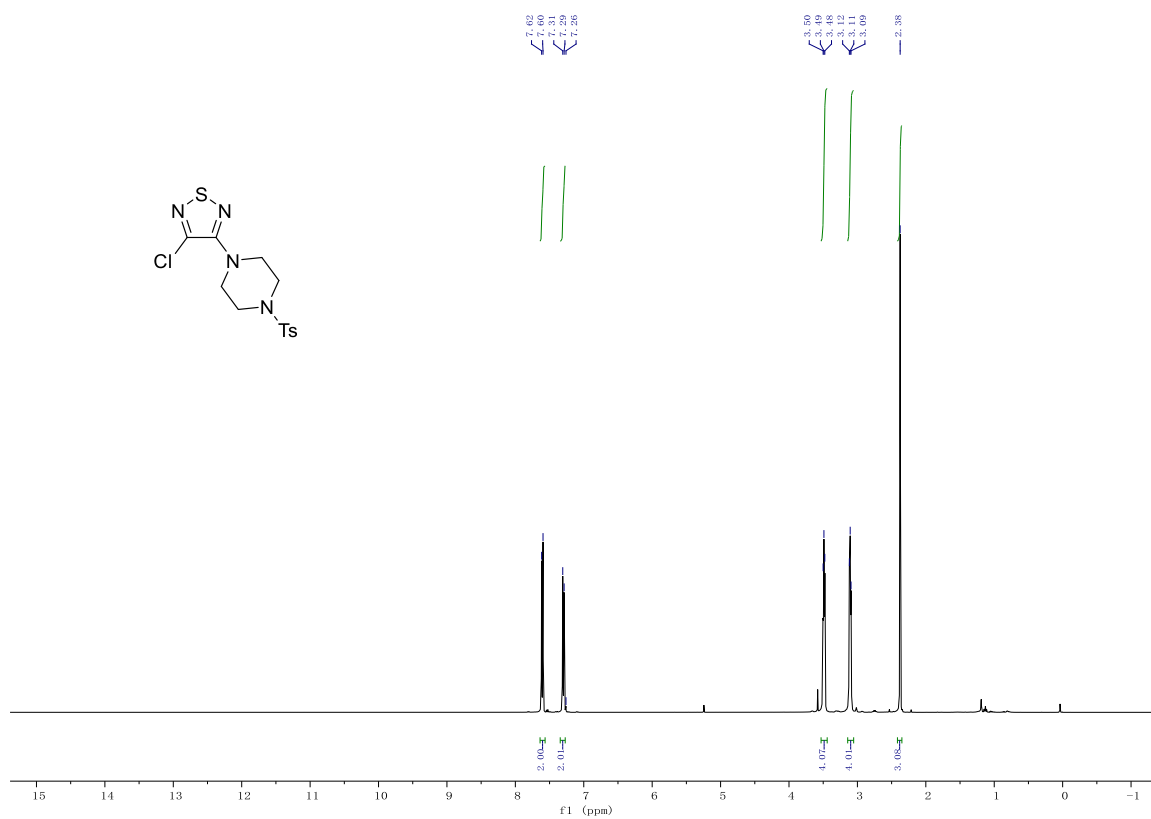
¹H NMR and ¹³C NMR spectra of 3-chloro-4-piperazinyl-1,2,5-thiadiazole SI-67n-1



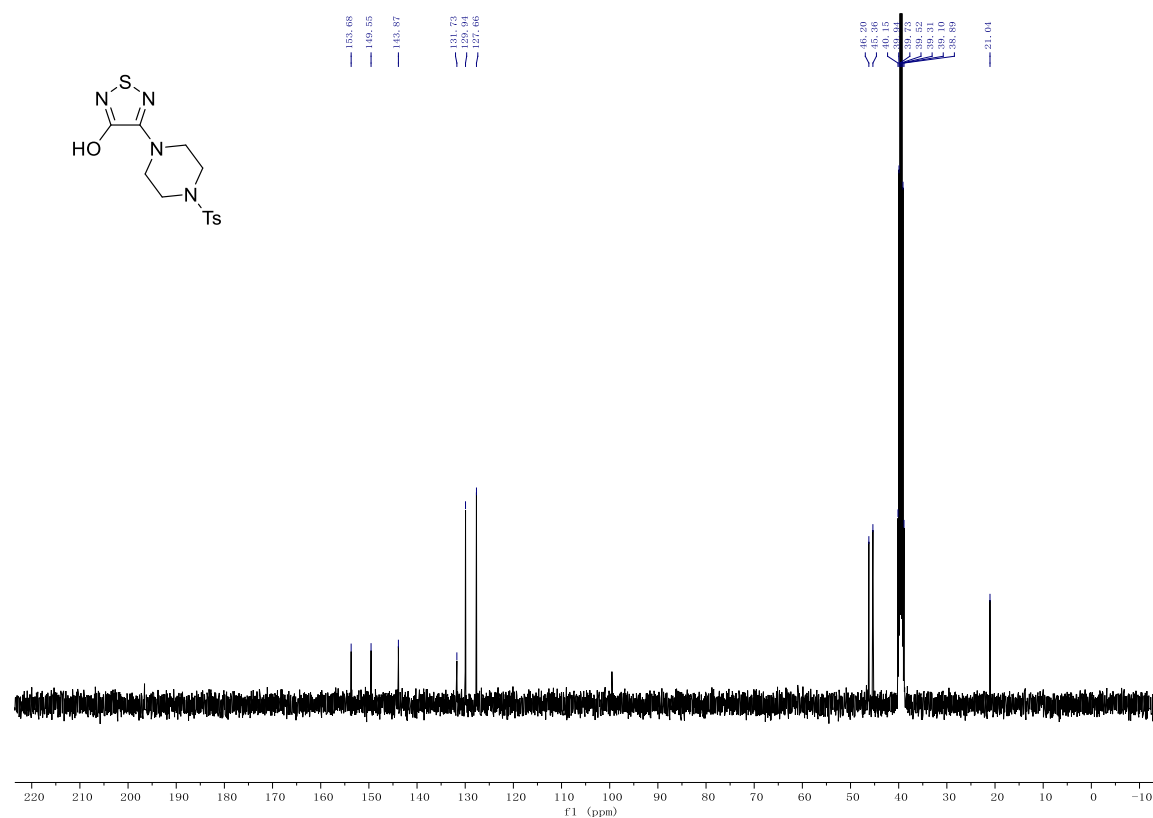
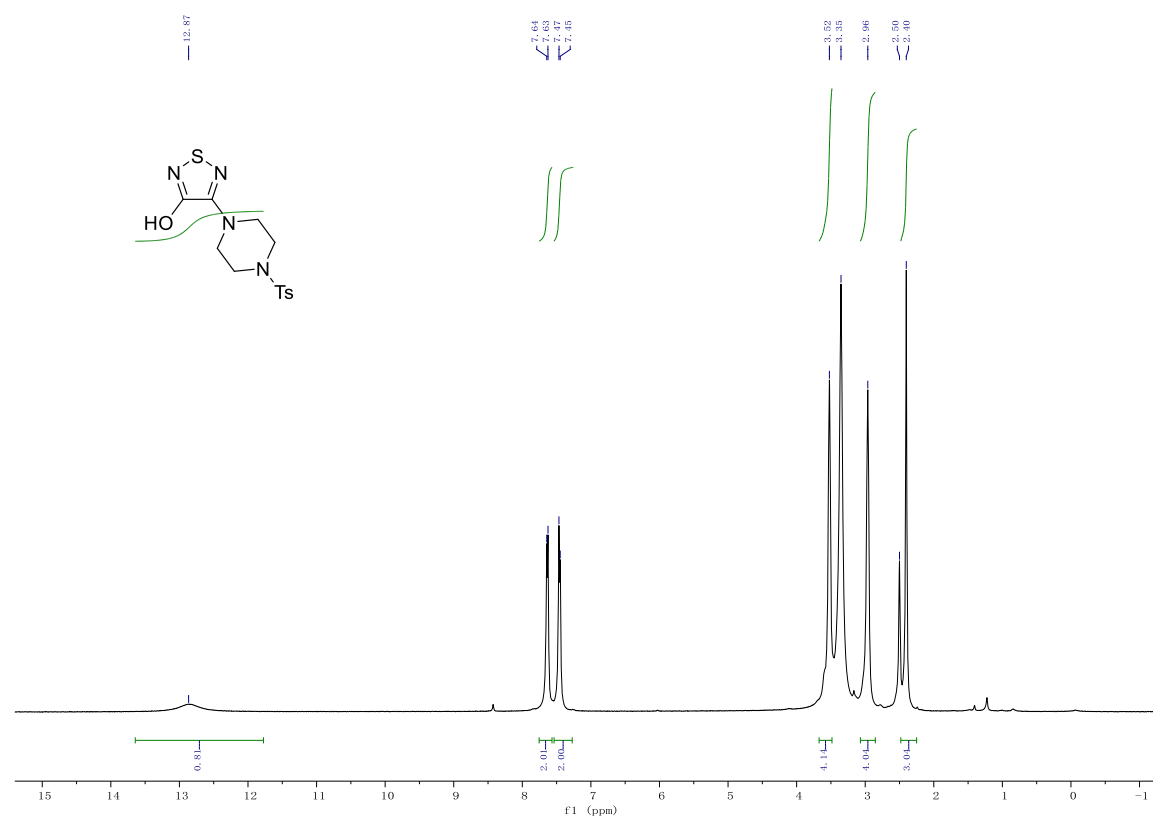
¹H NMR and ¹³C NMR spectra of 3-chloro-4-(4-boc-piperazinyl)-1,2,5-thiadiazole SI-67n-2



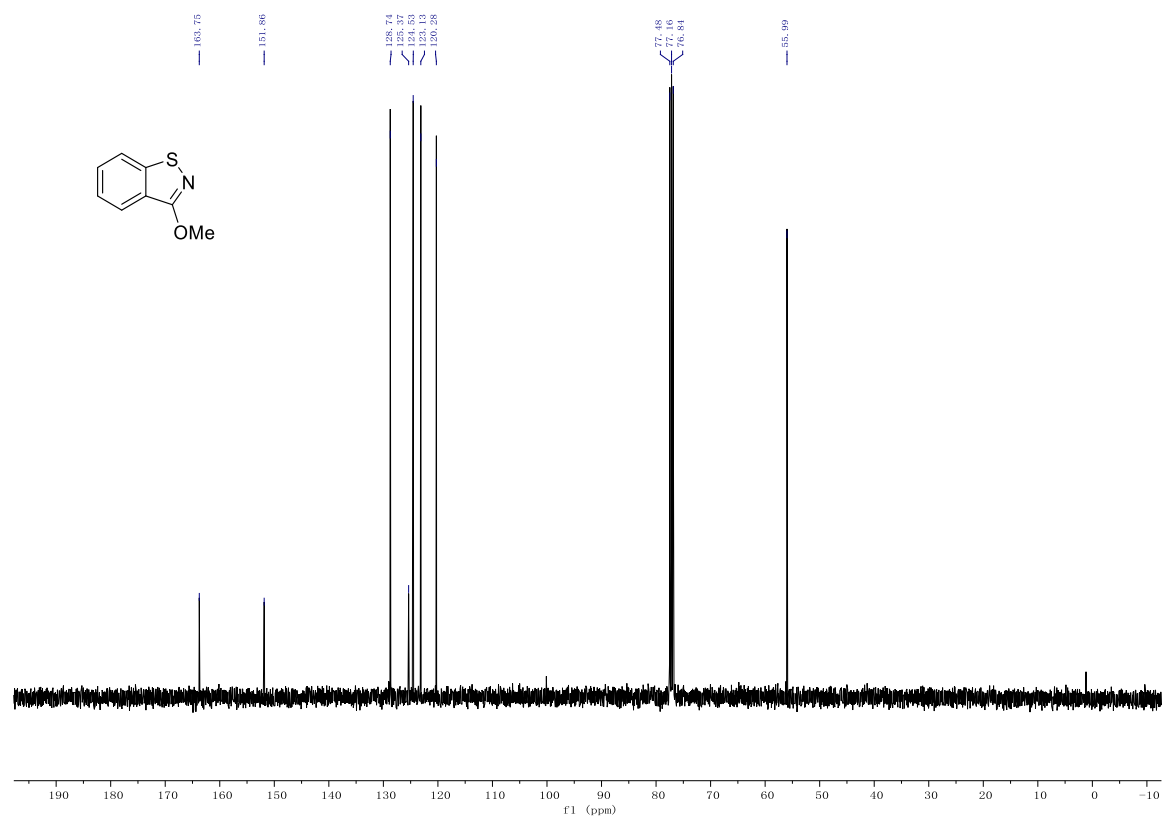
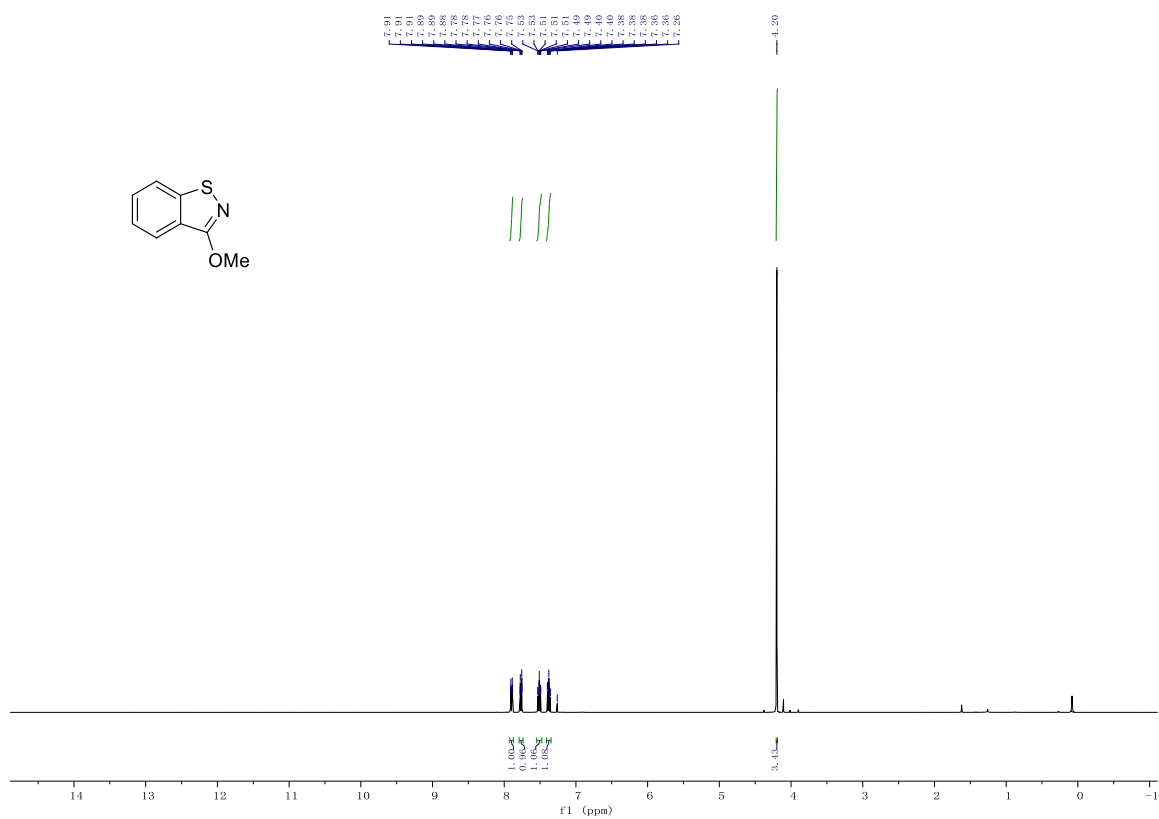
¹H NMR and ¹³C NMR spectra of 3-hydroxy-4-(4-boc-piperazinyl)-1,2,5-thiadiazole 67n



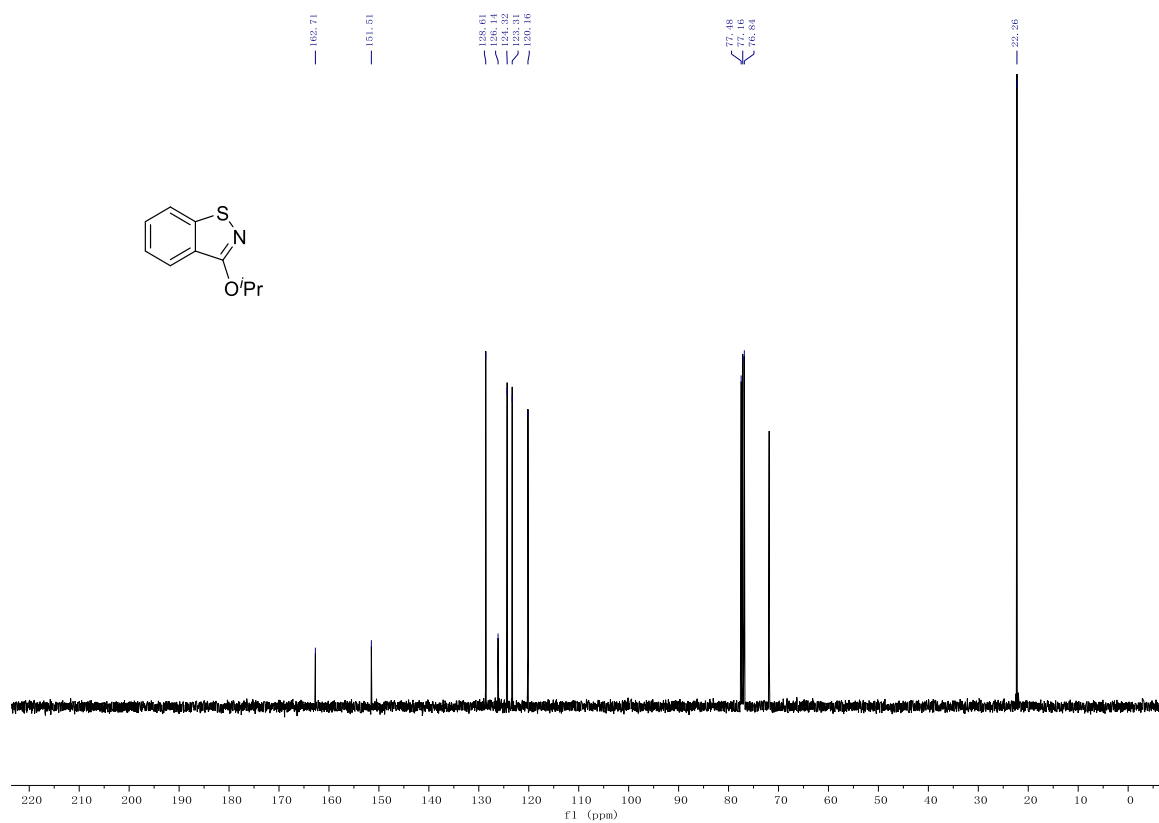
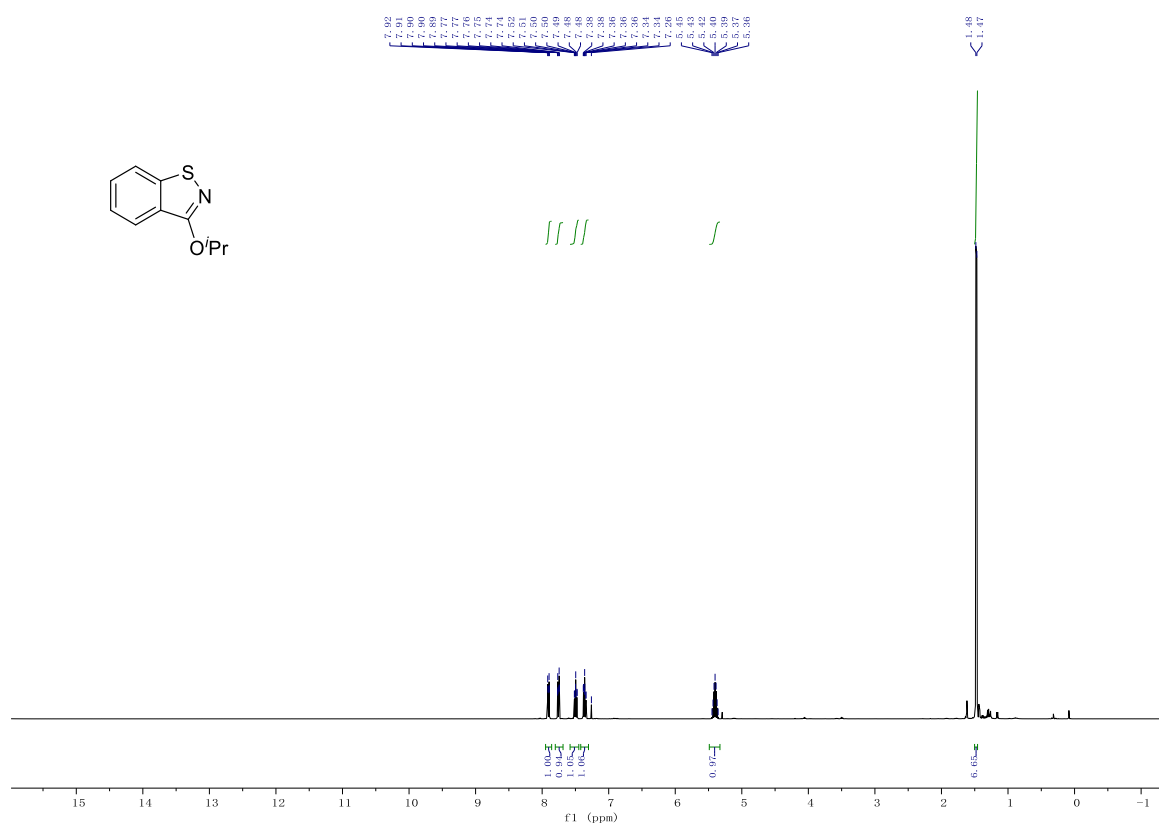
¹H NMR and ¹³C NMR spectra of 3-chloro-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole SI-67o



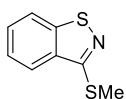
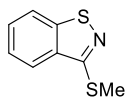
¹H NMR and ¹³C NMR spectra of 3-hydroxy-4-(4-tosylpiperazinyl)-1,2,5-thiadiazole 67o

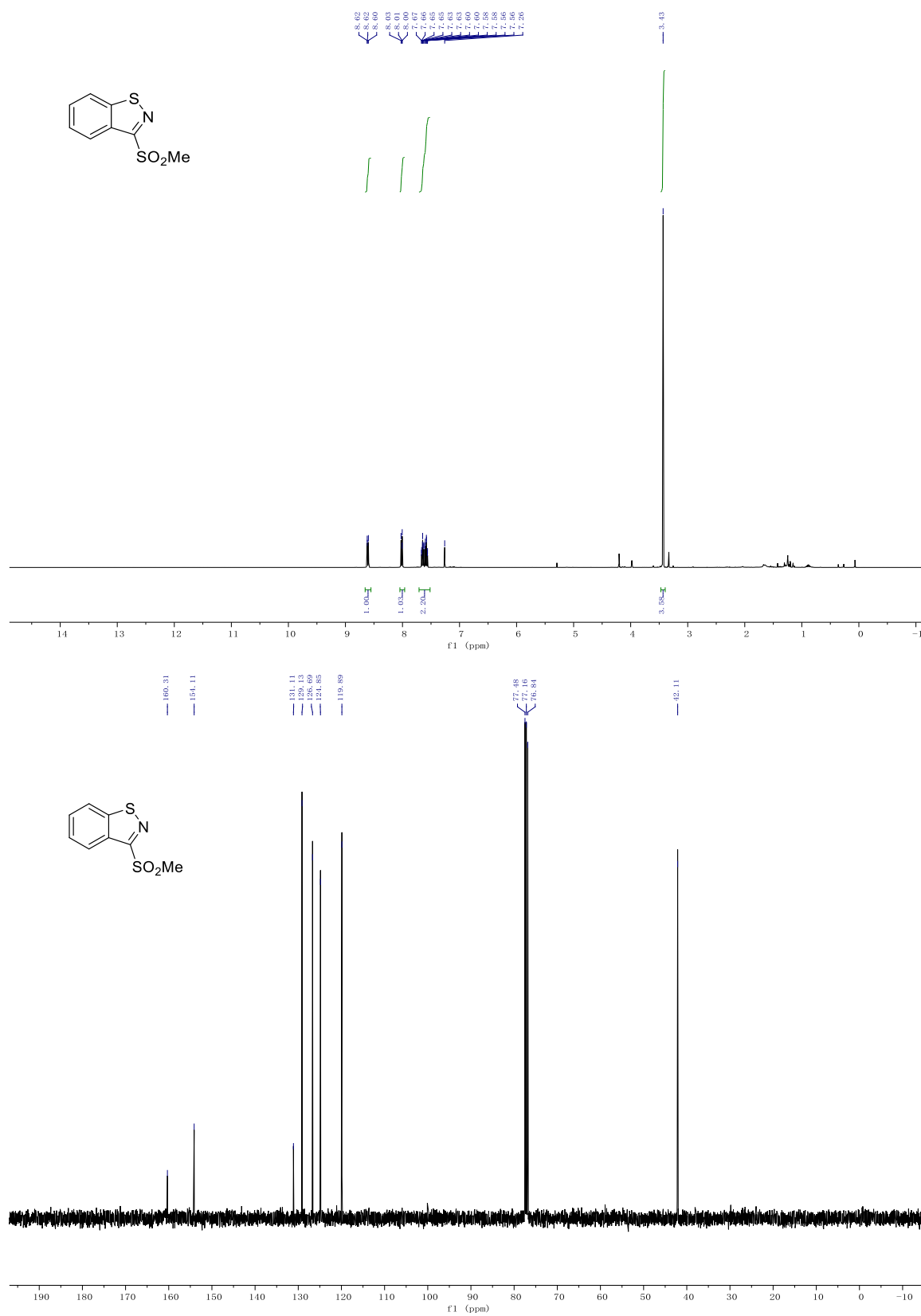


¹H NMR and ¹³C NMR spectra of 3-methoxy-1,2-benzisothiazole 68a

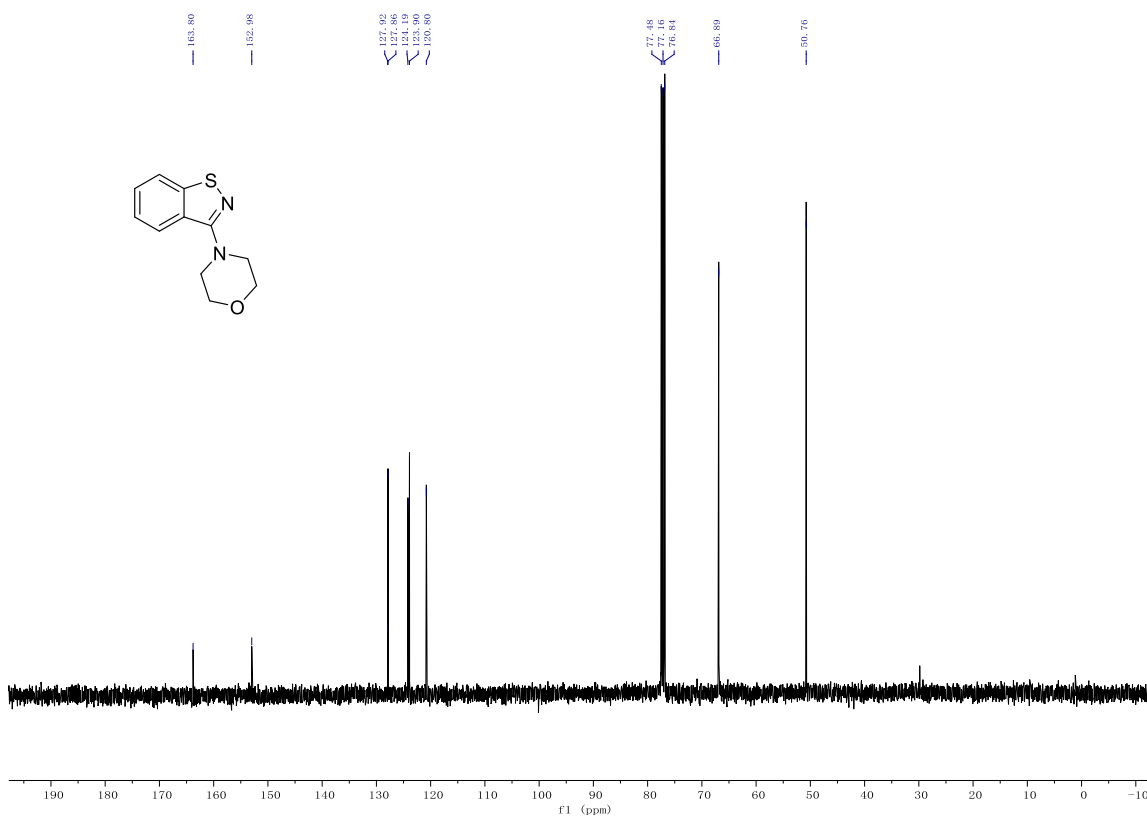
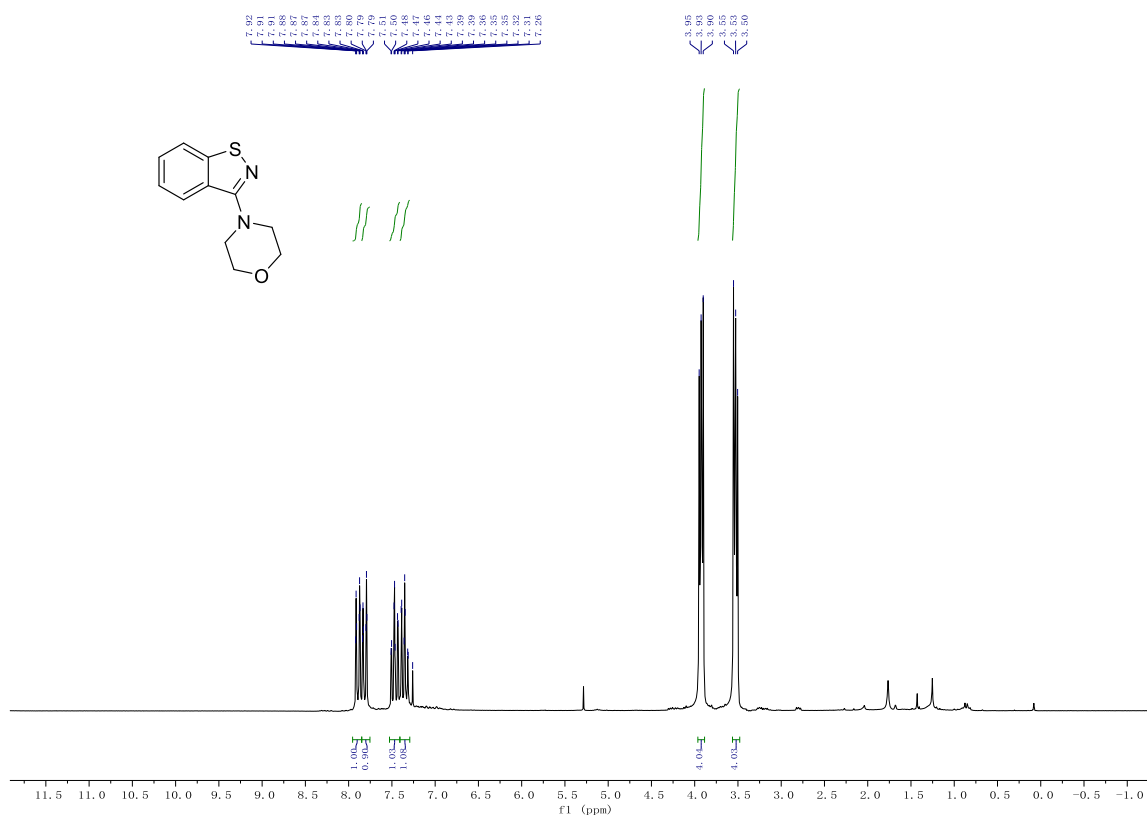


¹H NMR and ¹³C NMR spectra of **3-isopropoxy-1,2-benzisothiazole 68b**

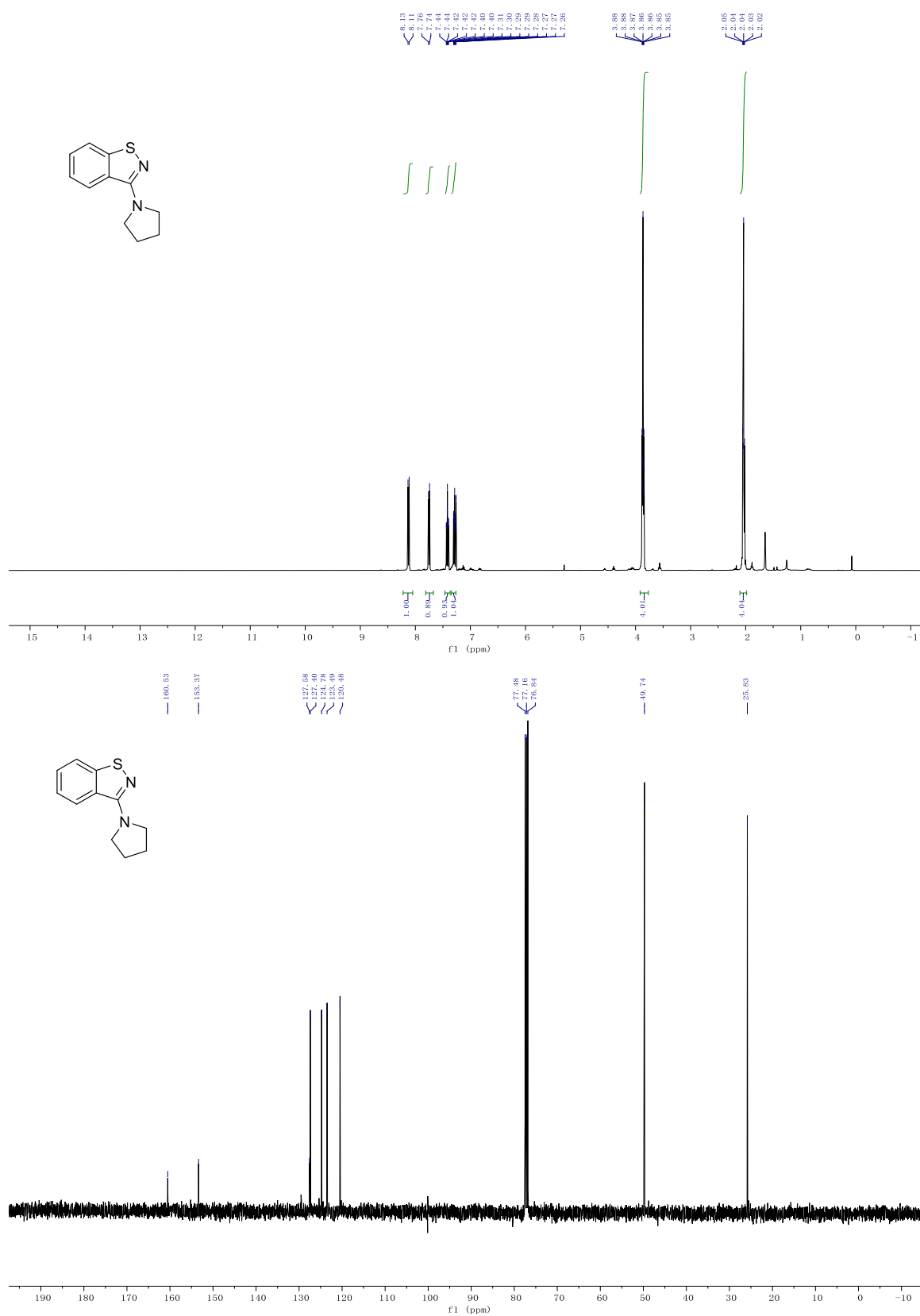




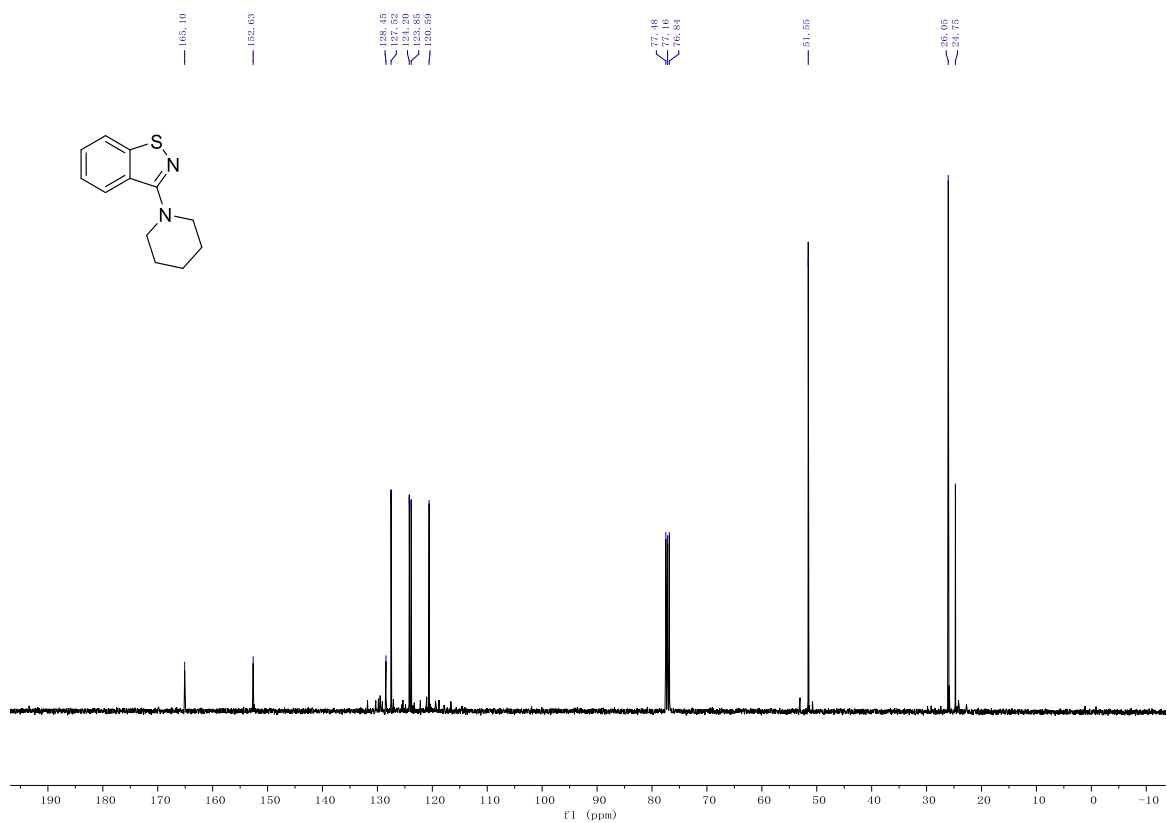
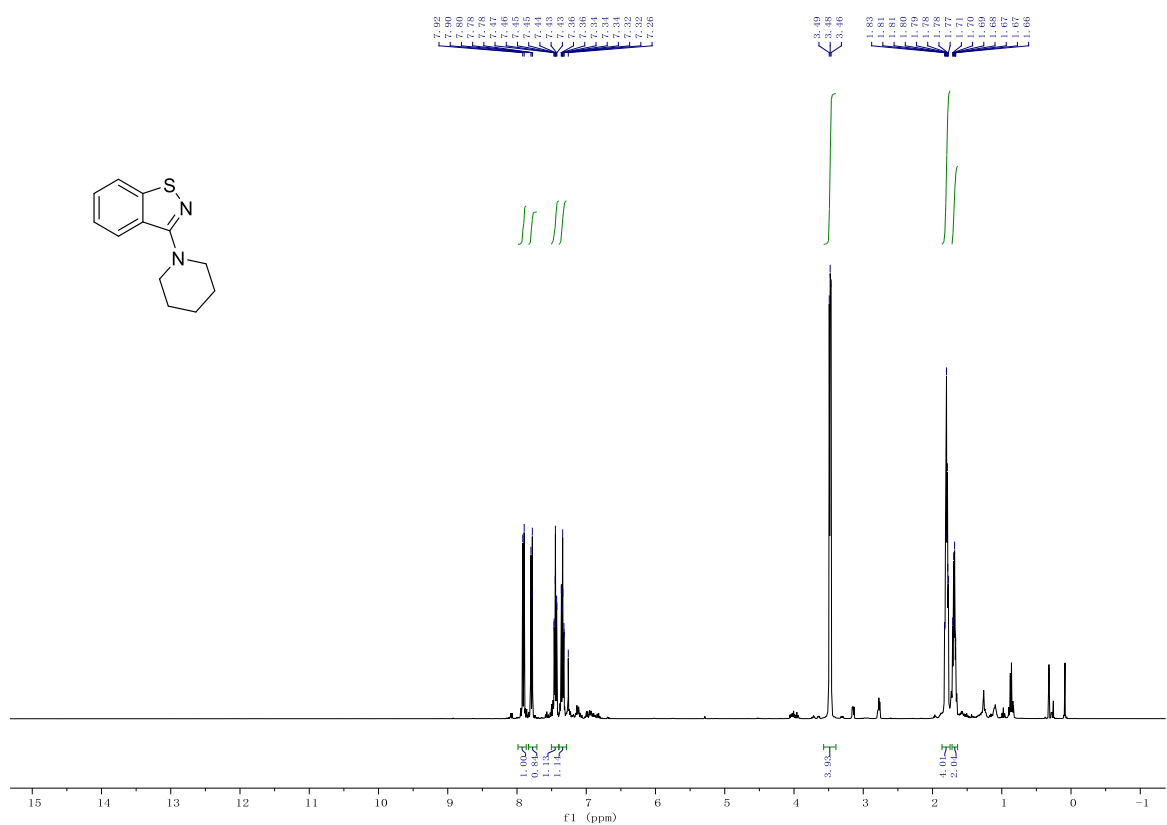
¹H NMR and ¹³C NMR spectra of 3-methylsulfonyl-1,2-benzisothiazole 68e



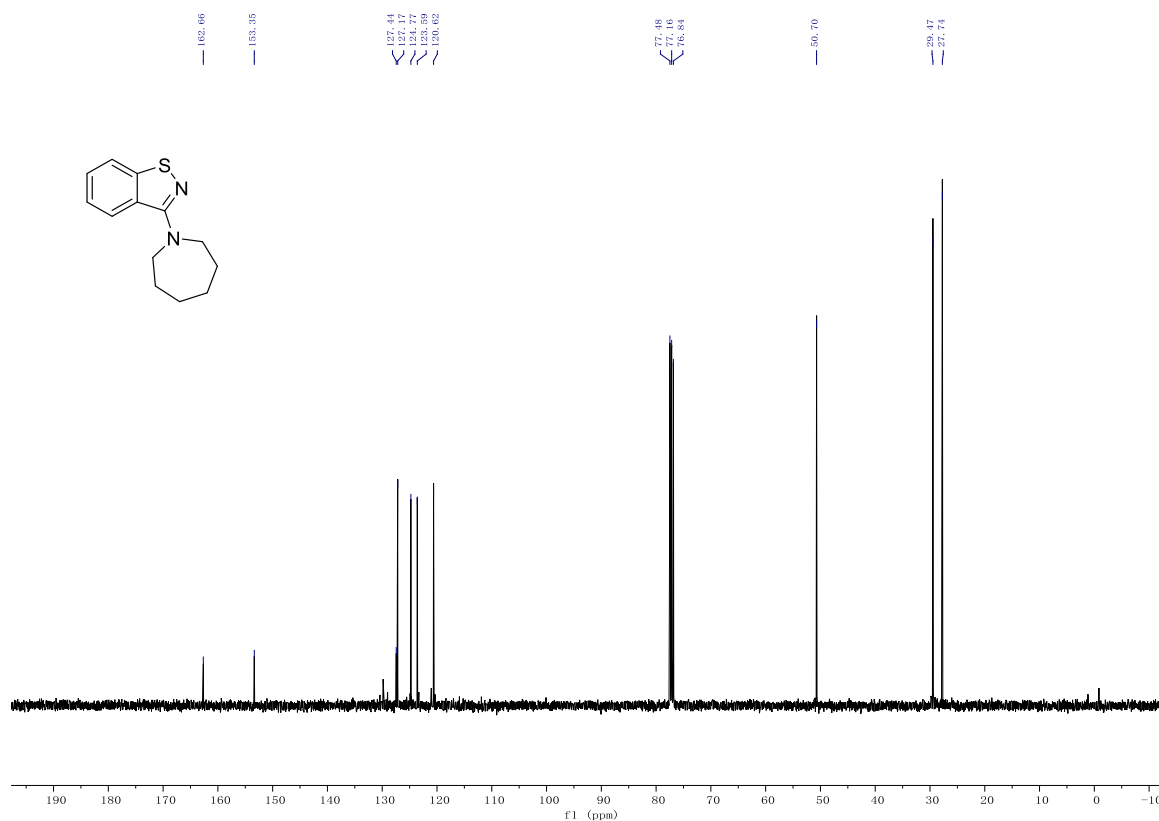
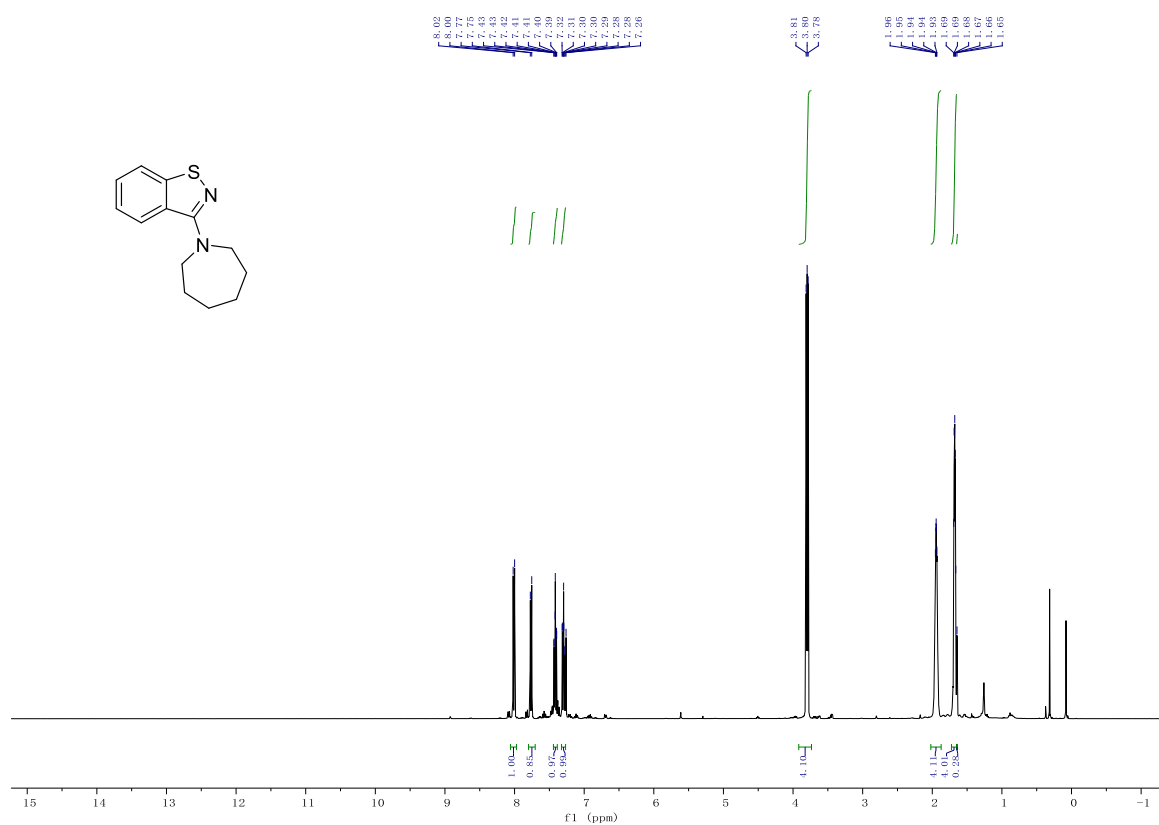
¹H NMR and ¹³C NMR spectra of 3-morpholino-1,2-benzisothiazole 68f



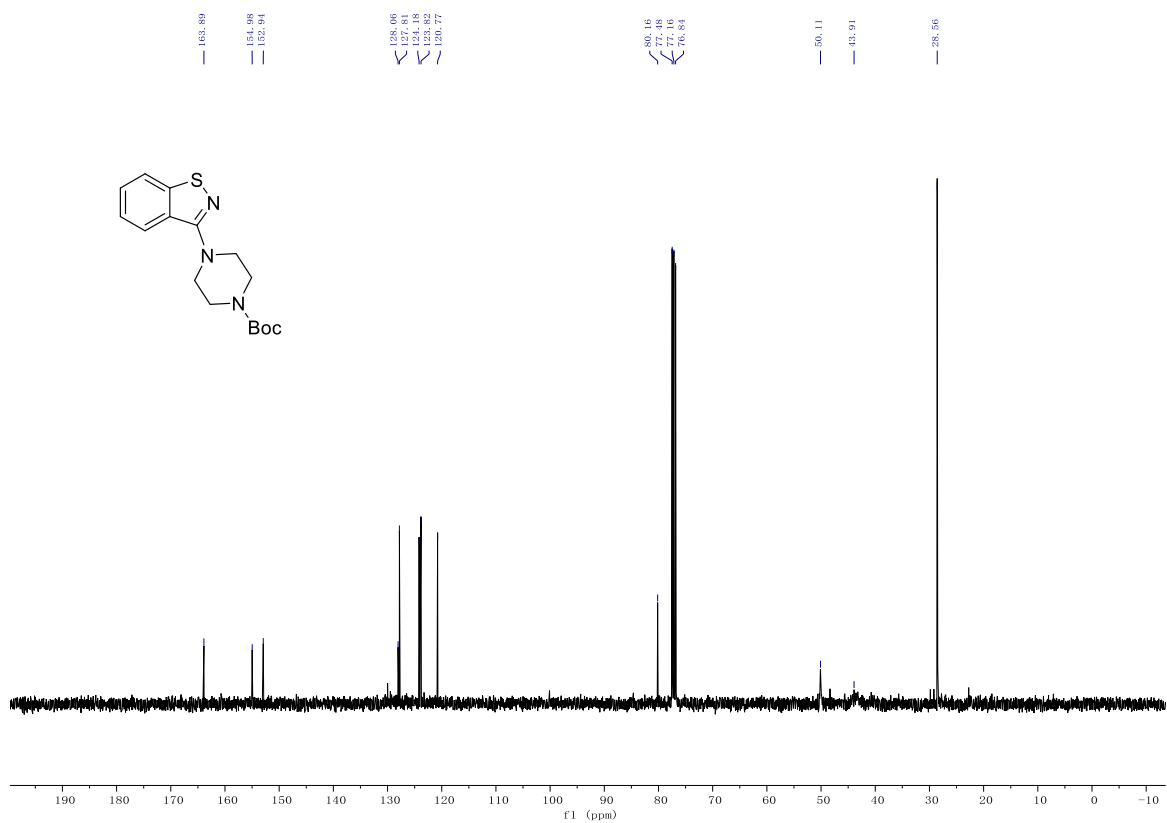
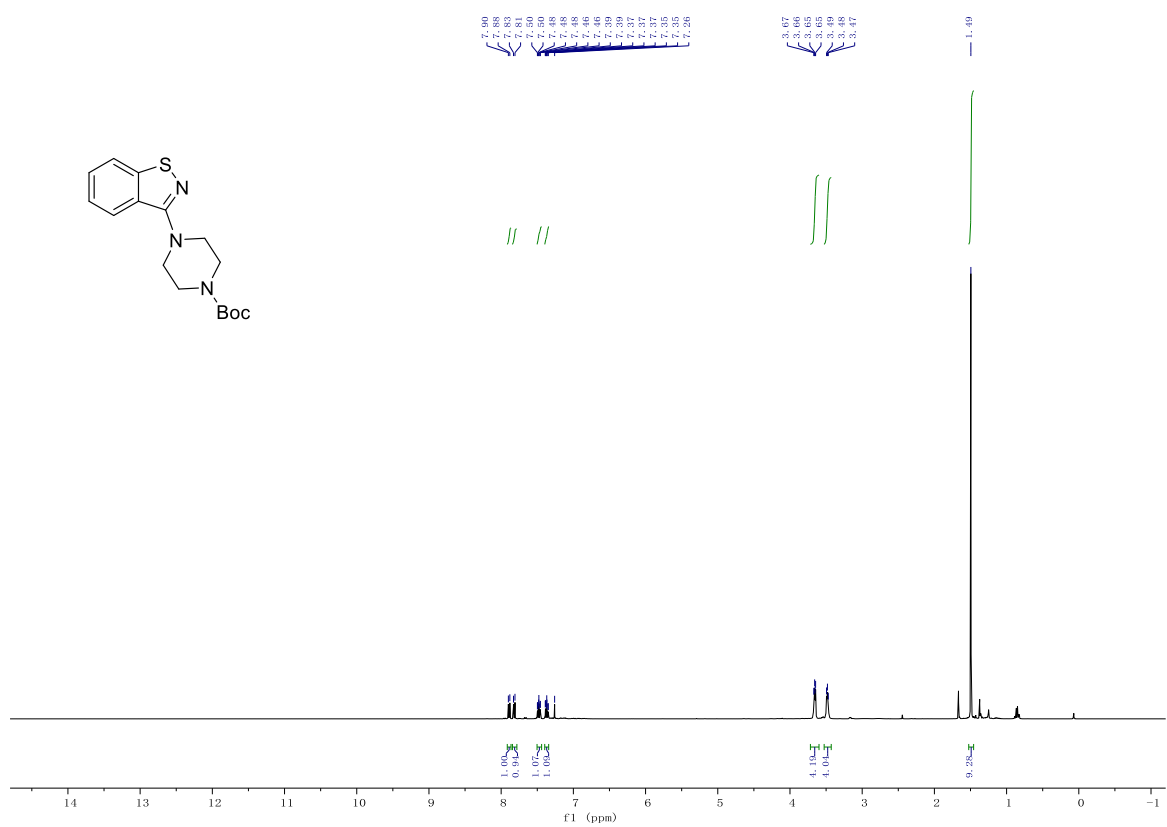
¹H NMR and ¹³C NMR spectra of 3-pyrrolidinyl-1,2-benzisothiazole 68k



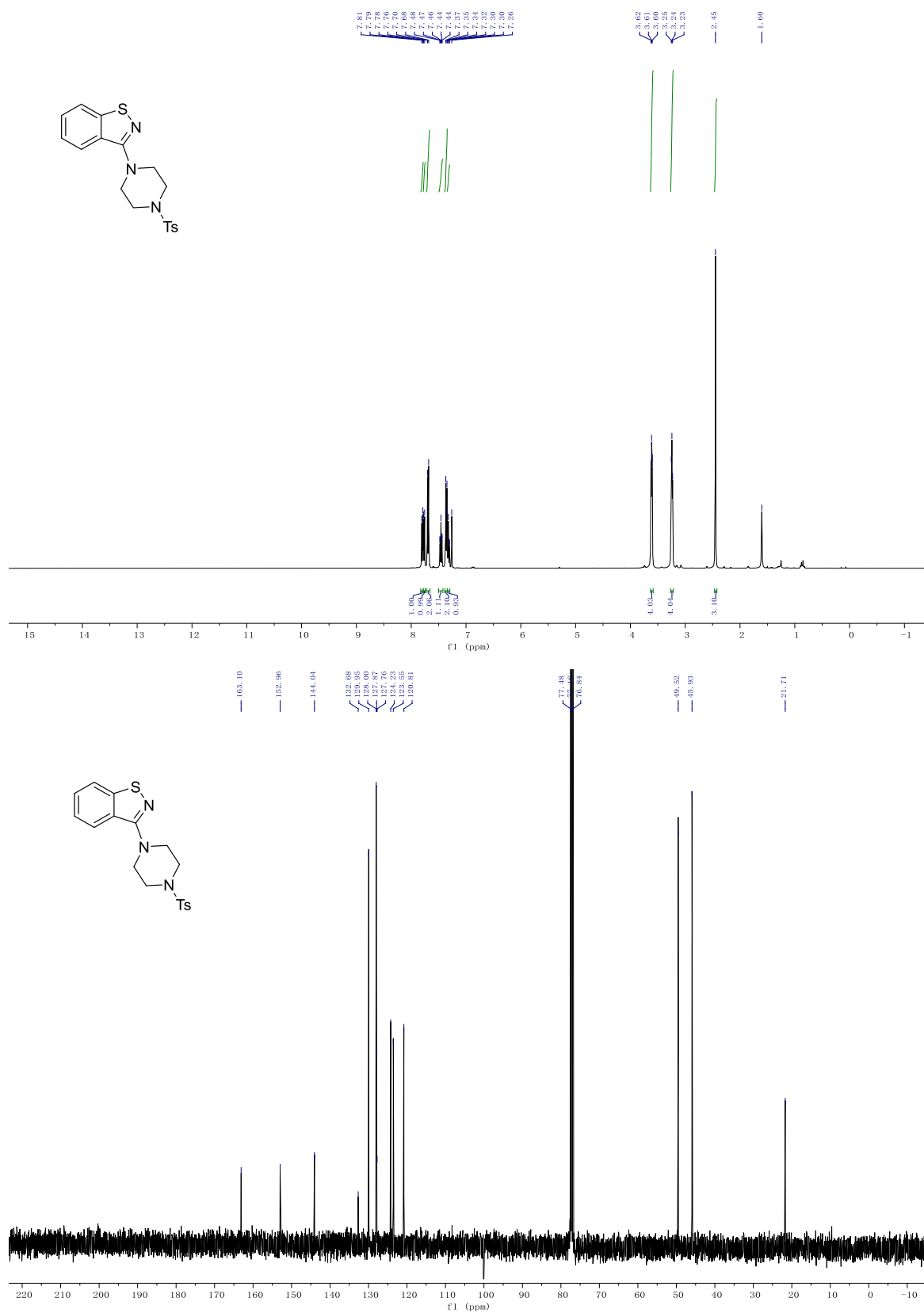
¹H NMR and ¹³C NMR spectra of **3-piperidinyl-1,2-benzisothiazole 68l**



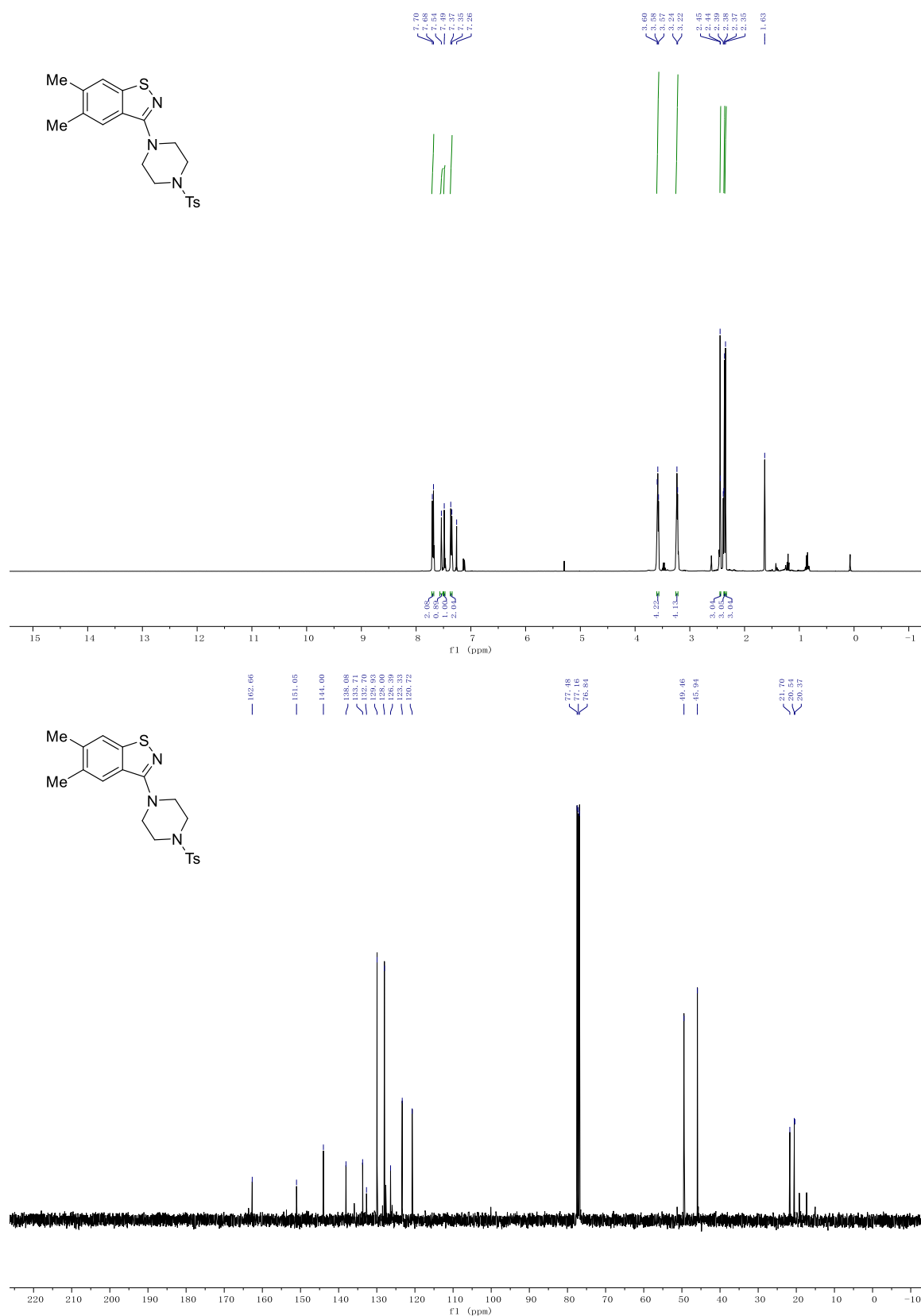
¹H NMR and ¹³C NMR spectra of 3-azapanyl-1,2-benzisothiazole 68m



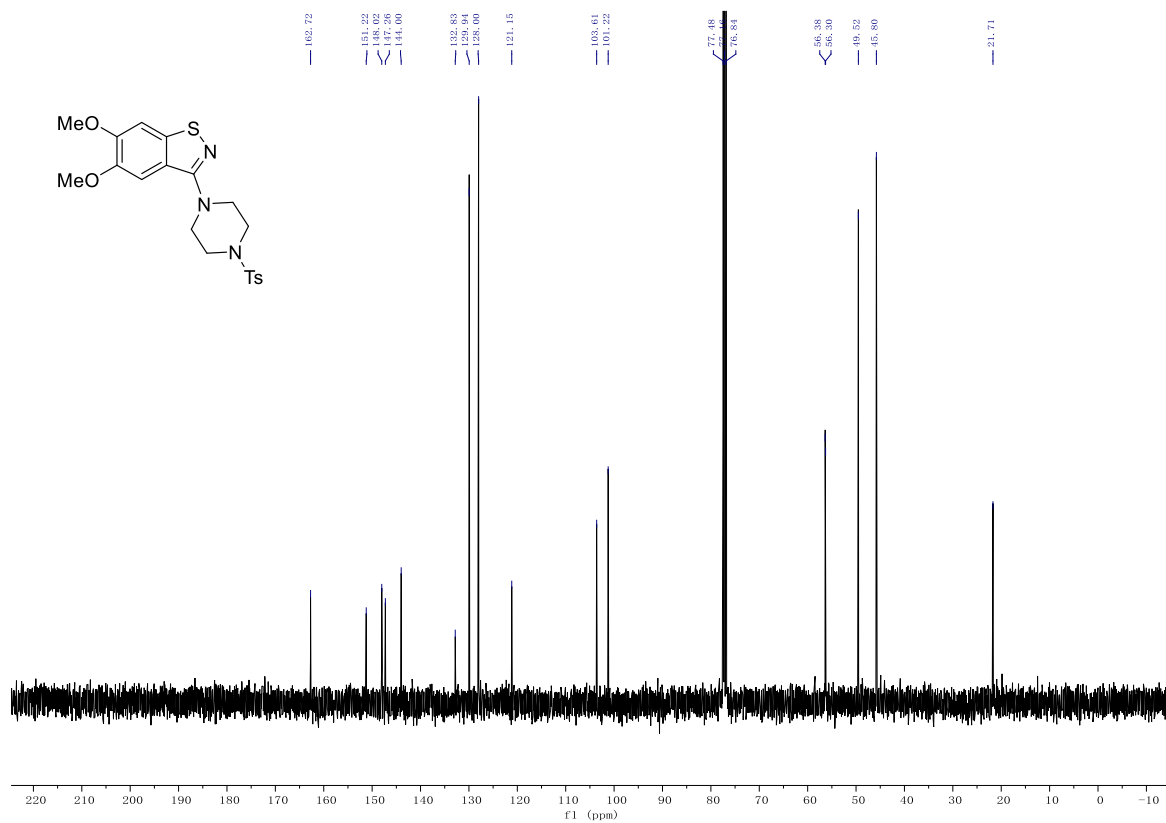
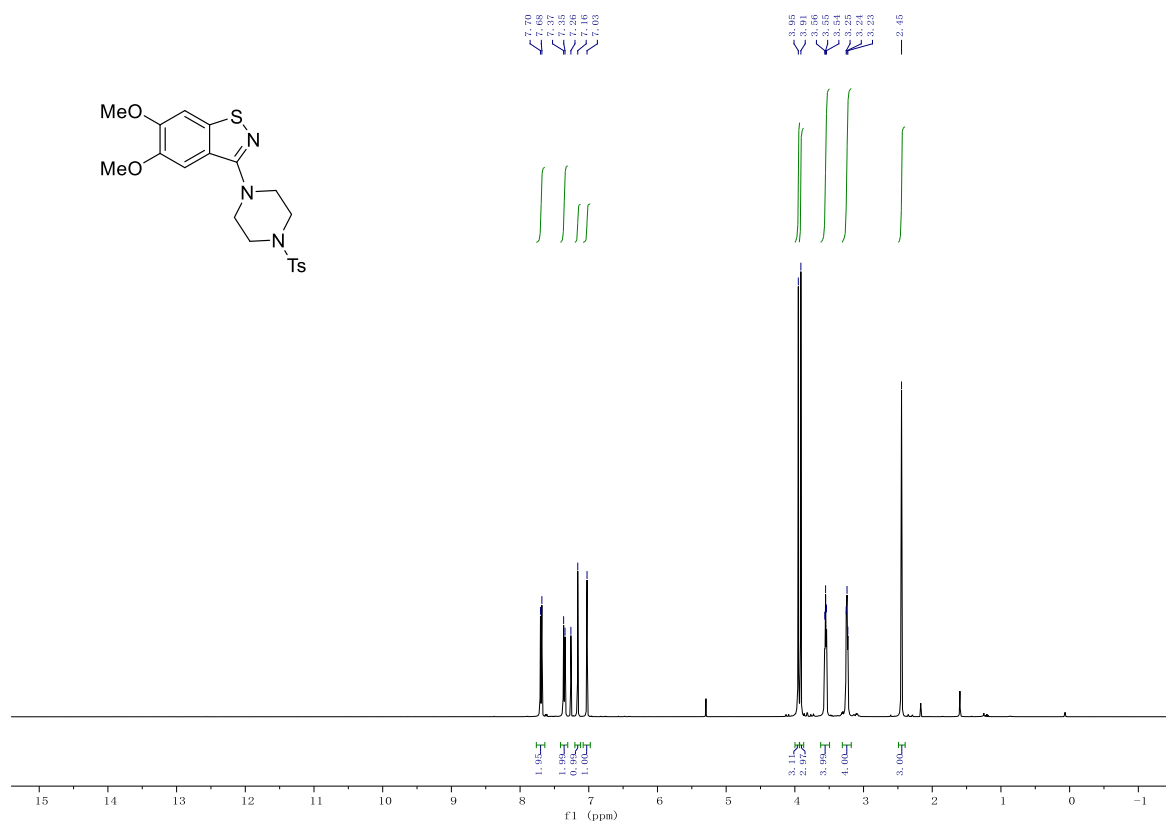
¹H NMR and ¹³C NMR spectra of 3-(4-boc-piperazinyl)-1,2-benzisothiazole 68n



¹H NMR and ¹³C NMR spectra of 3-(4-tosylpiperazinyl)-1,2-benzisothiazole **68o**



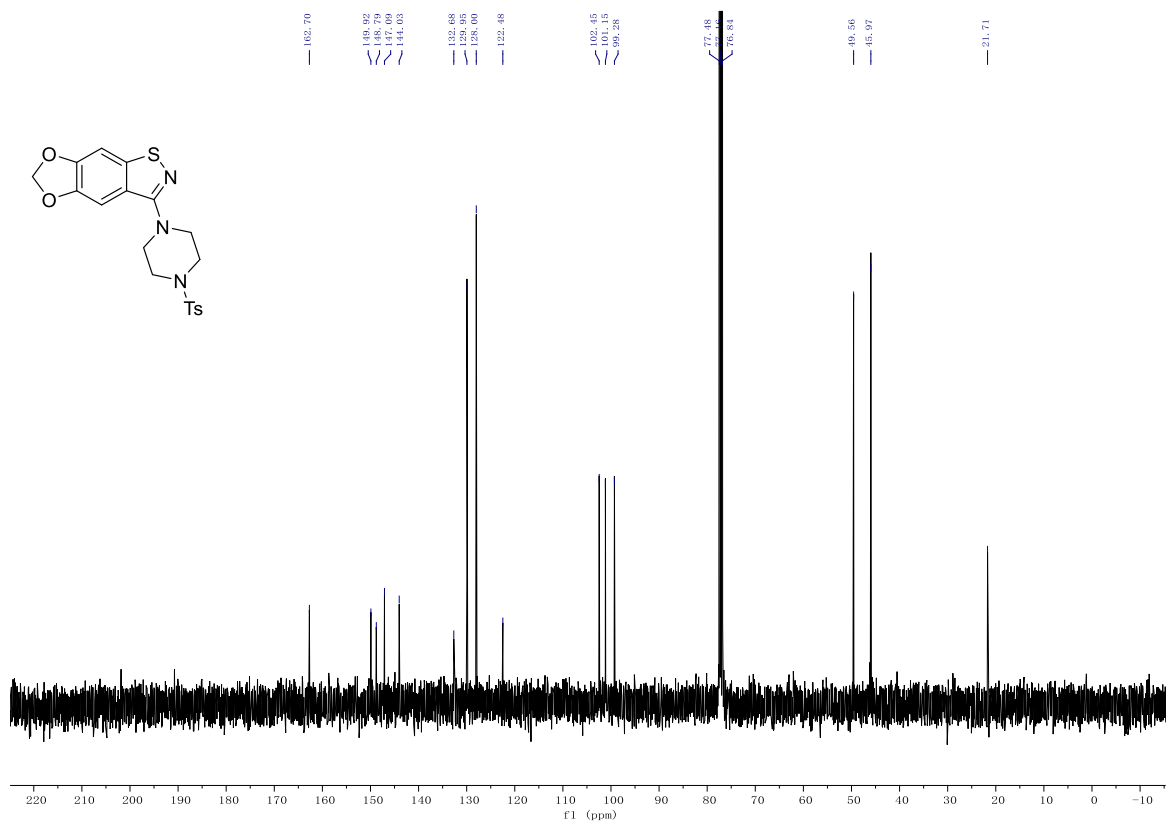
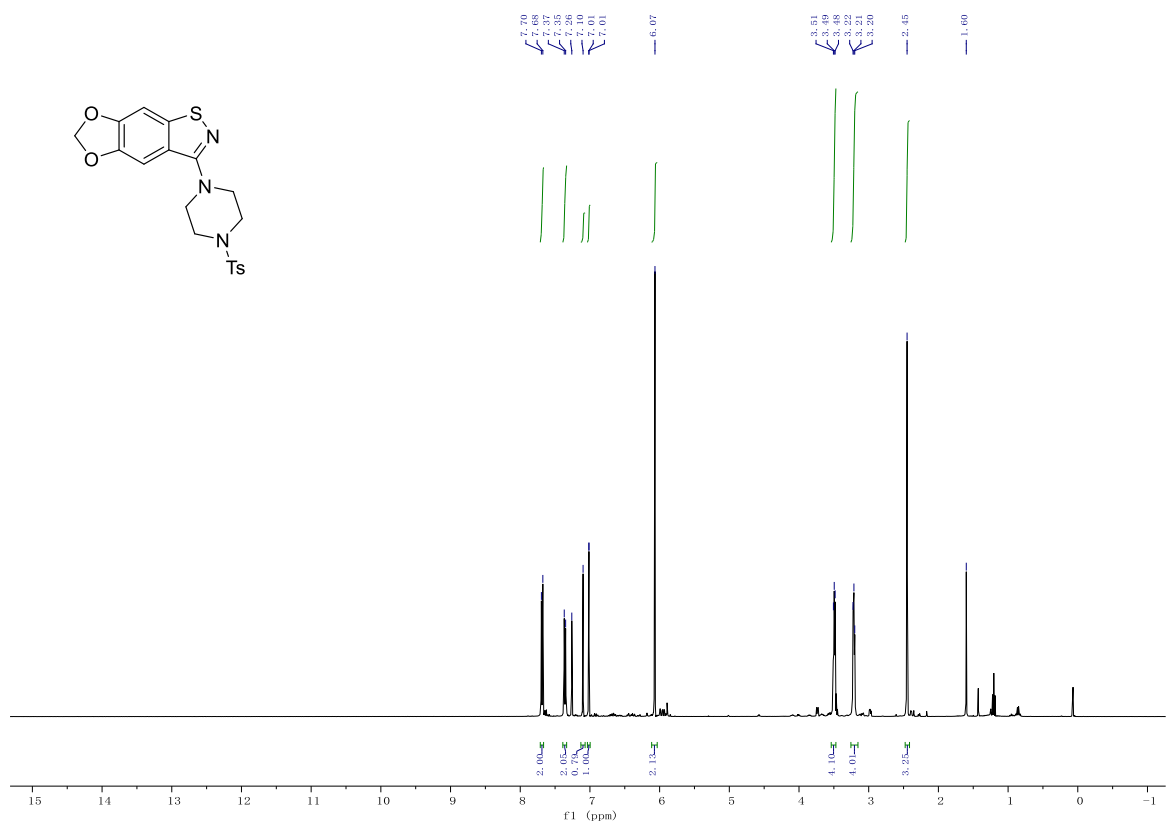
¹H NMR and ¹³C NMR spectra of 3-(4-tosylpiperazinyl)-5,6-dimethyl-1,2-benzisothiazole 69a



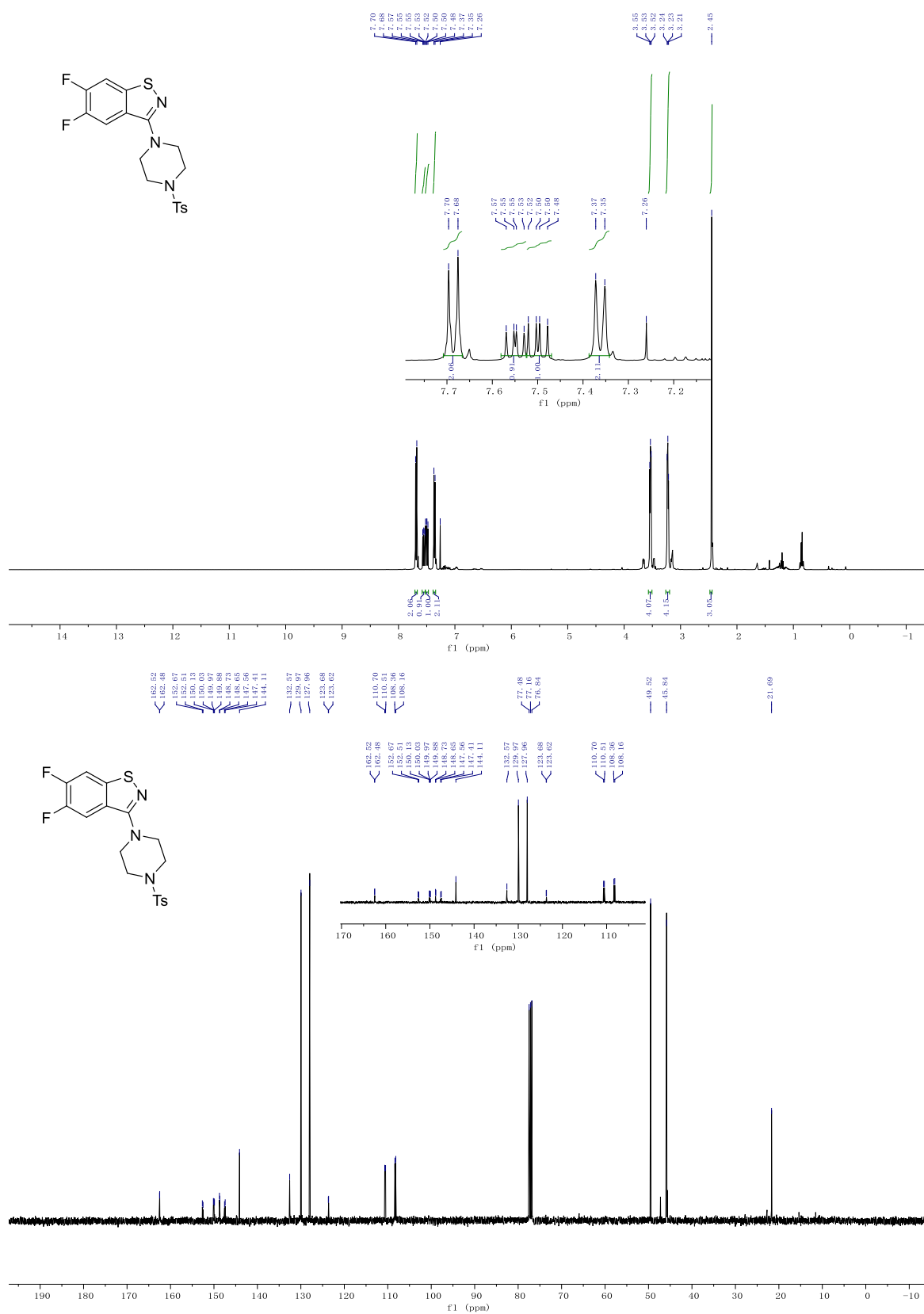
¹H NMR and ¹³C NMR spectra of 3-(4-tosylpiperazinyl)-5,6-dimethoxy-1,2-benzisothiazole

69b

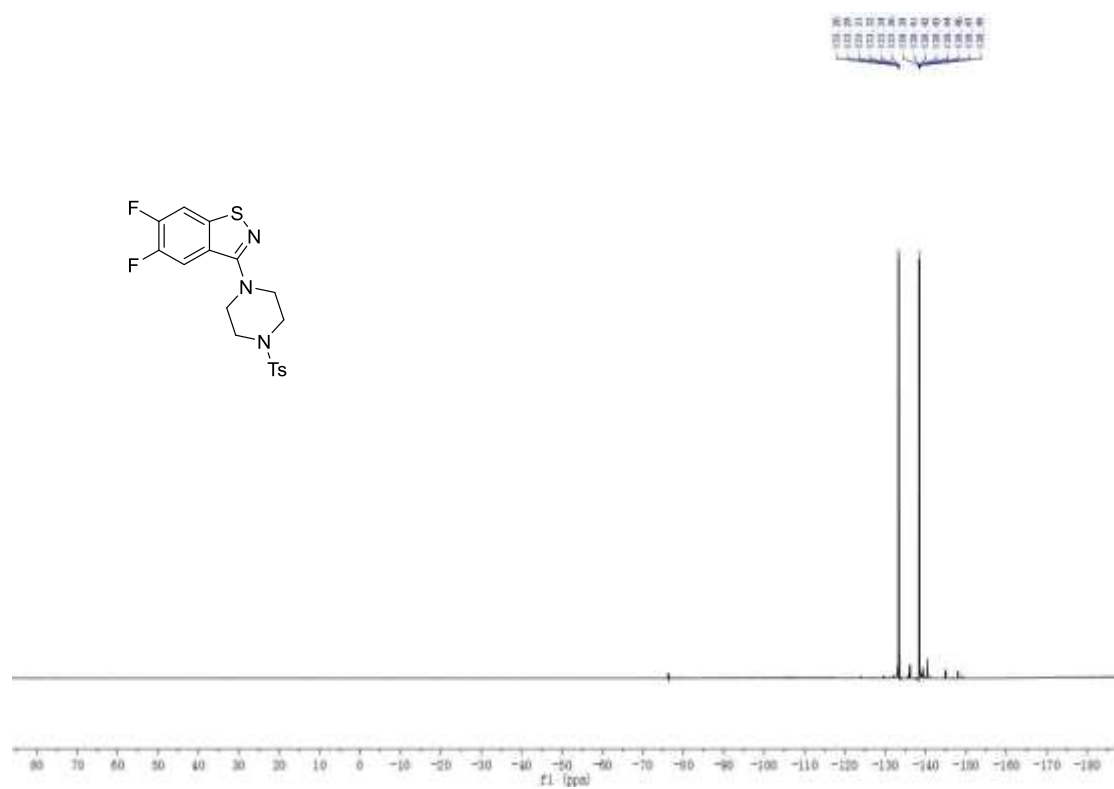
443



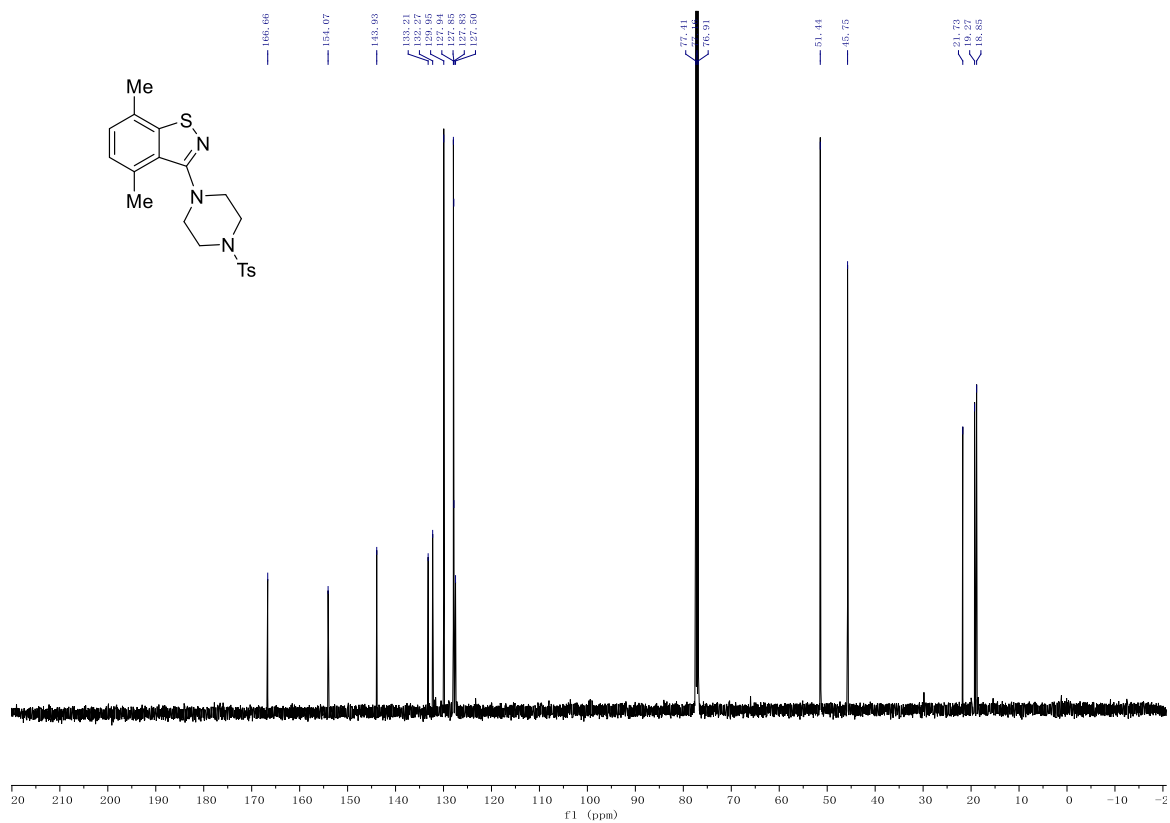
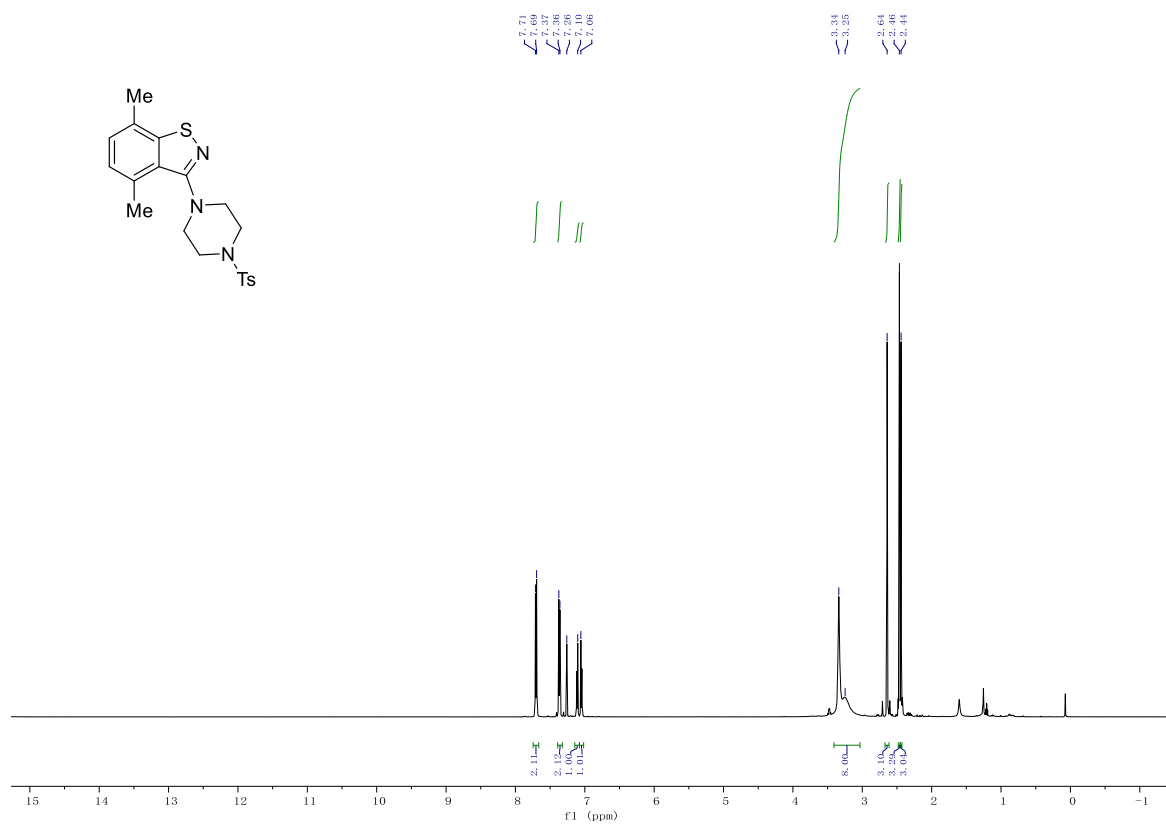
¹H NMR and ¹³C NMR spectra of 3-(4-tosylpiperazinyl)-5,6-dioxolo-1,2-benzisothiazole 69c



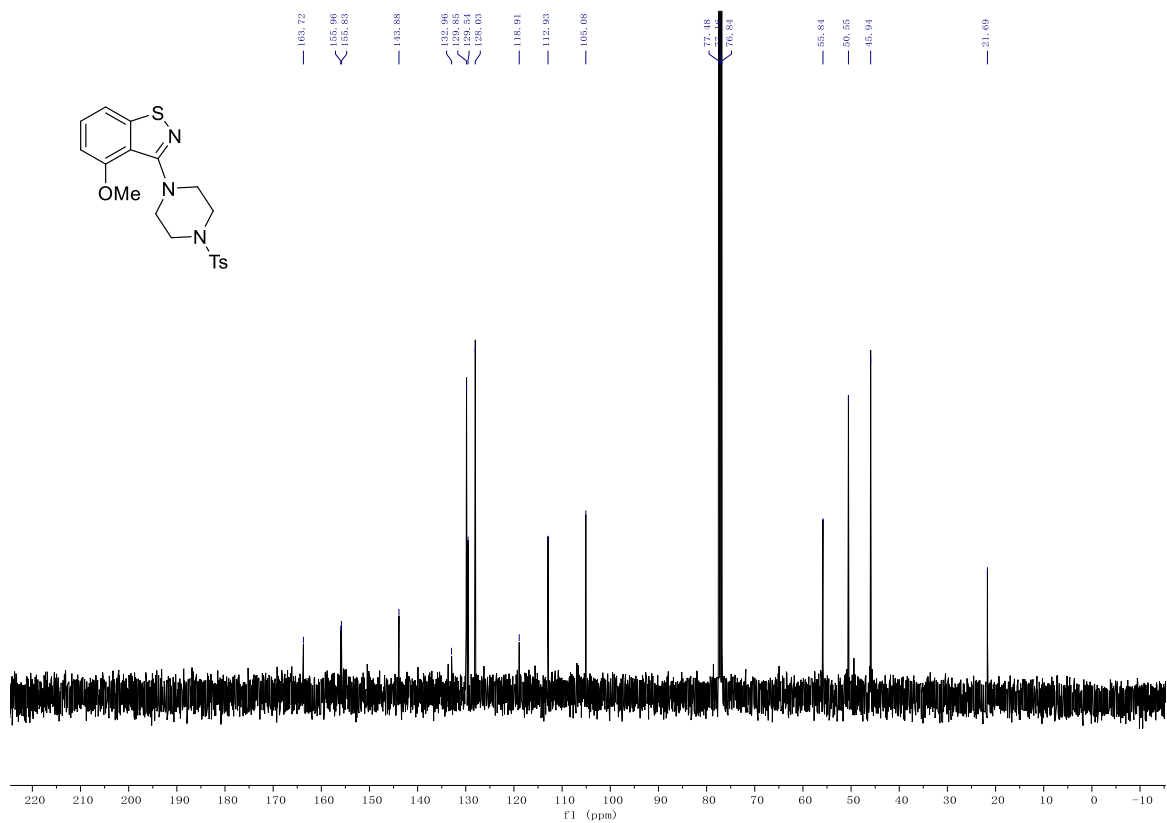
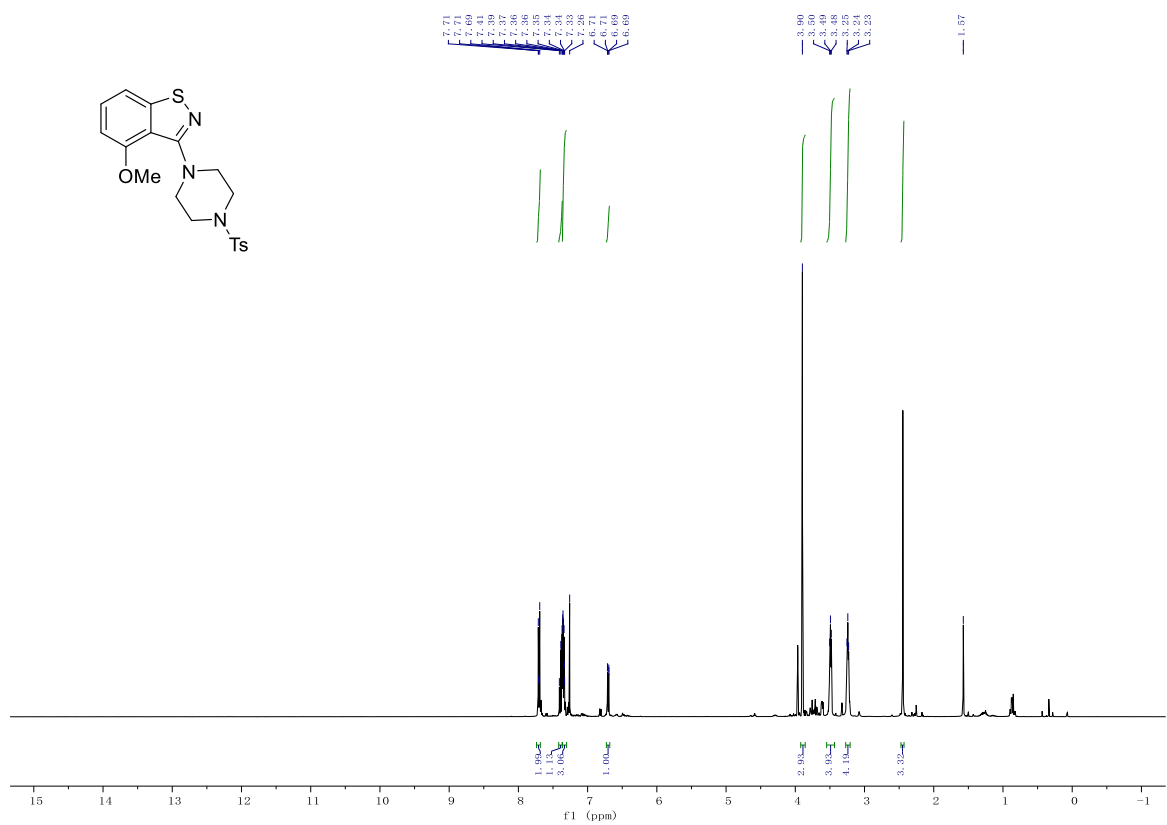
¹H NMR and ¹³C NMR spectra of 3-(4-tosylpiperazinyl)-4,5-difluoro-1,2-benzisothiazole 69d



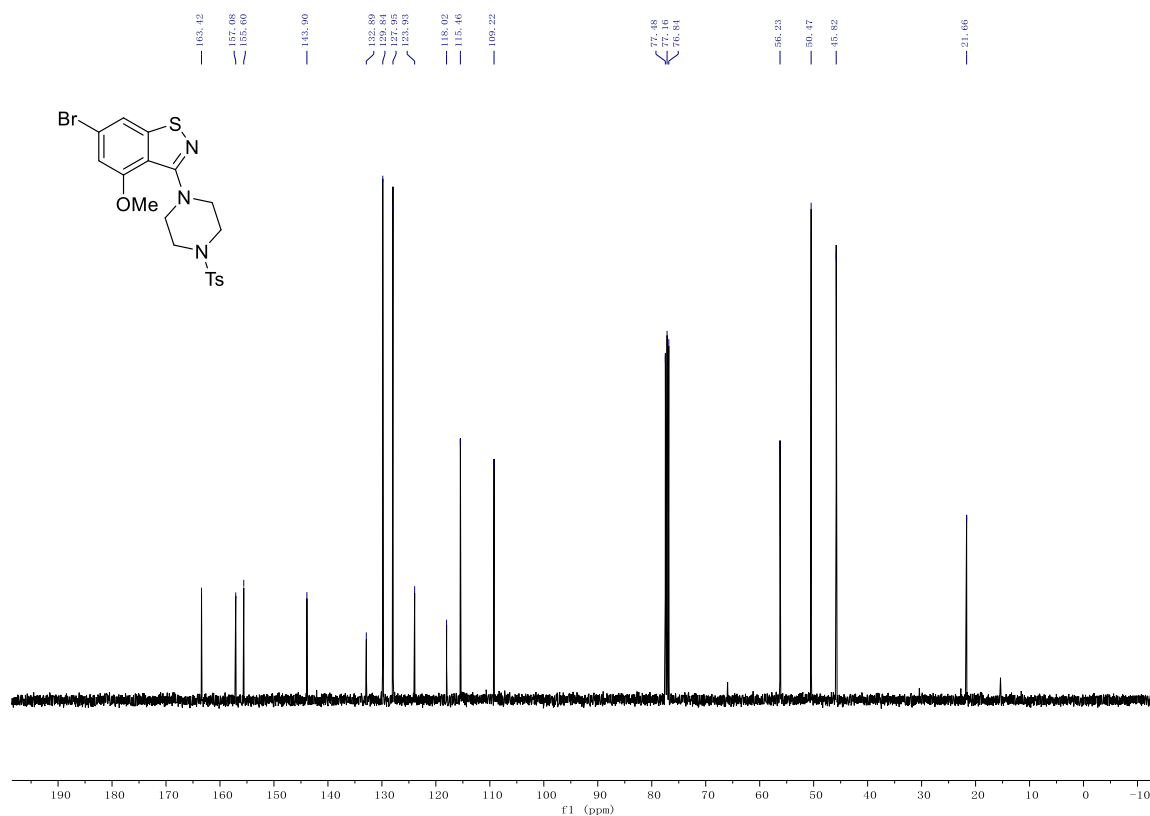
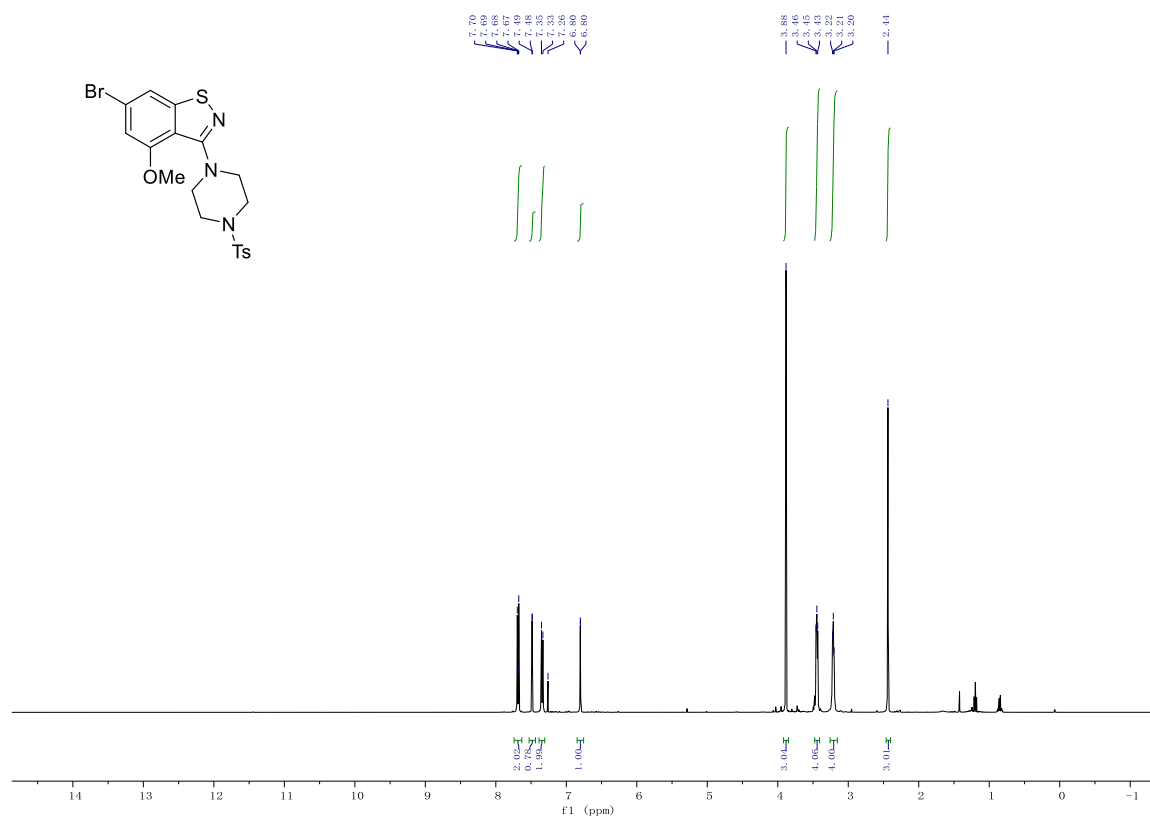
¹⁹F NMR spectra of **3-(4-tosylpiperazinyl)-4,5-difluoro-1,2-benzisothiazole 69d**



¹H NMR and ¹³C NMR spectra of 3-(4-tosylpiperazinyl)-4,7-dimethyl-1,2-benzisothiazole 69e

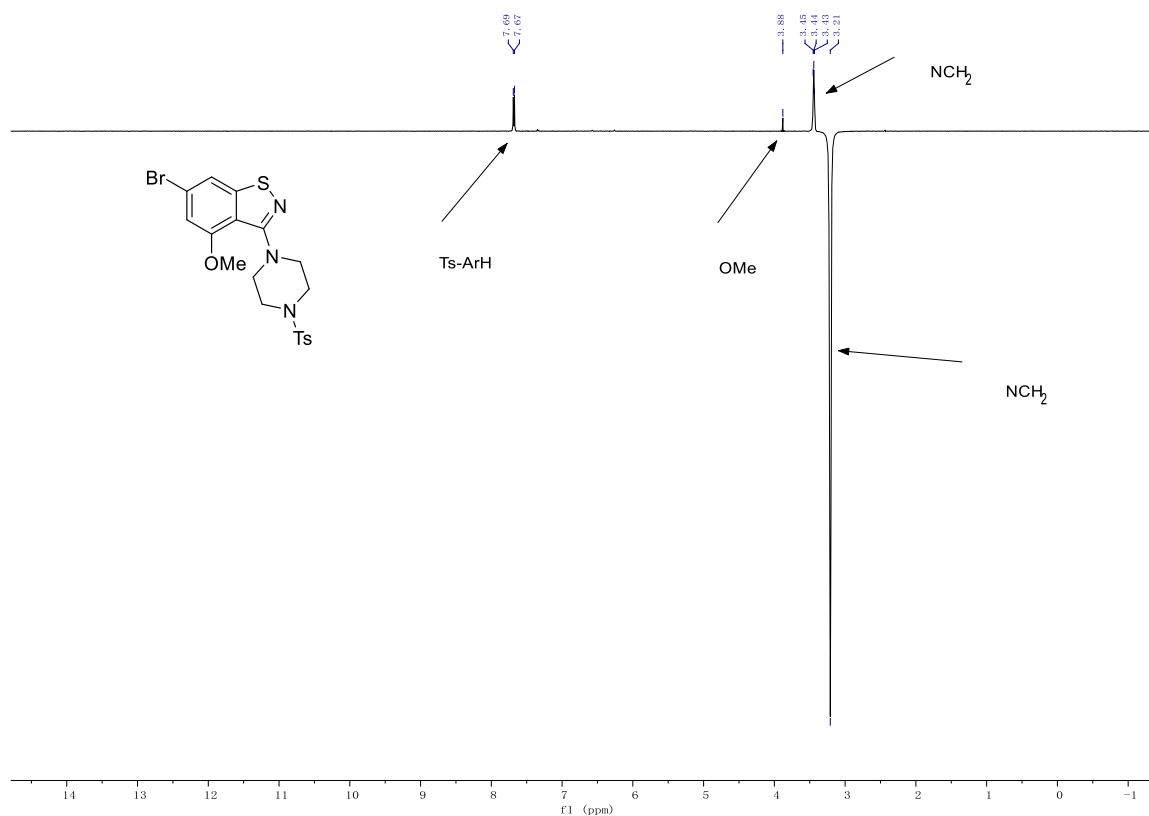
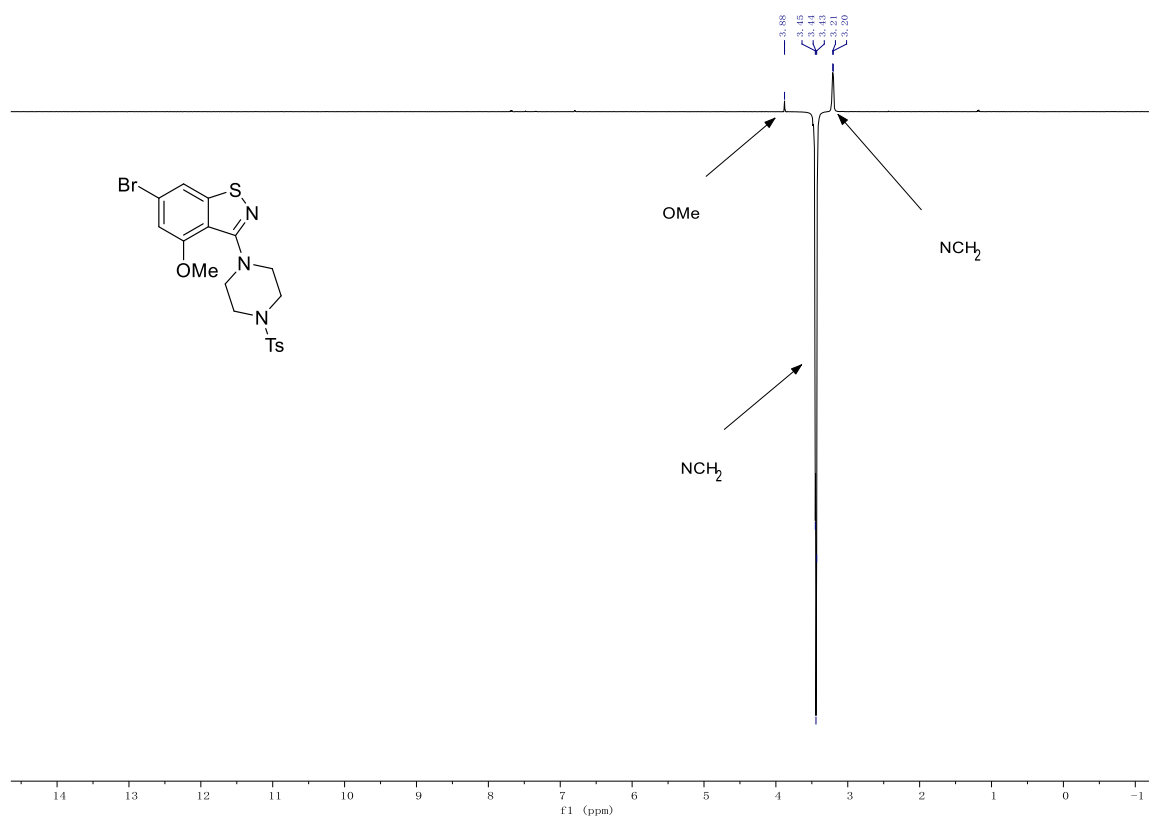


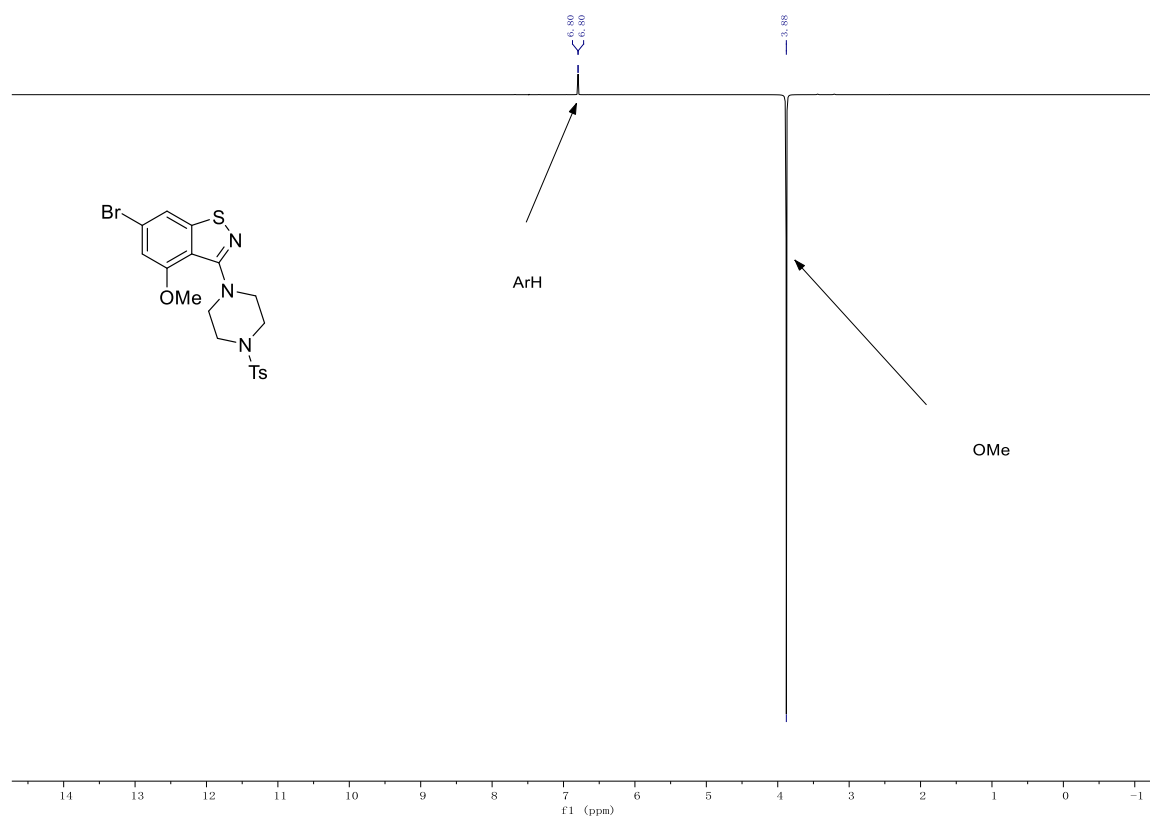
¹H NMR and ¹³C NMR spectra of 3-(4-tosylpiperazinyl)-4-methoxy-1,2-benzisothiazole 69f



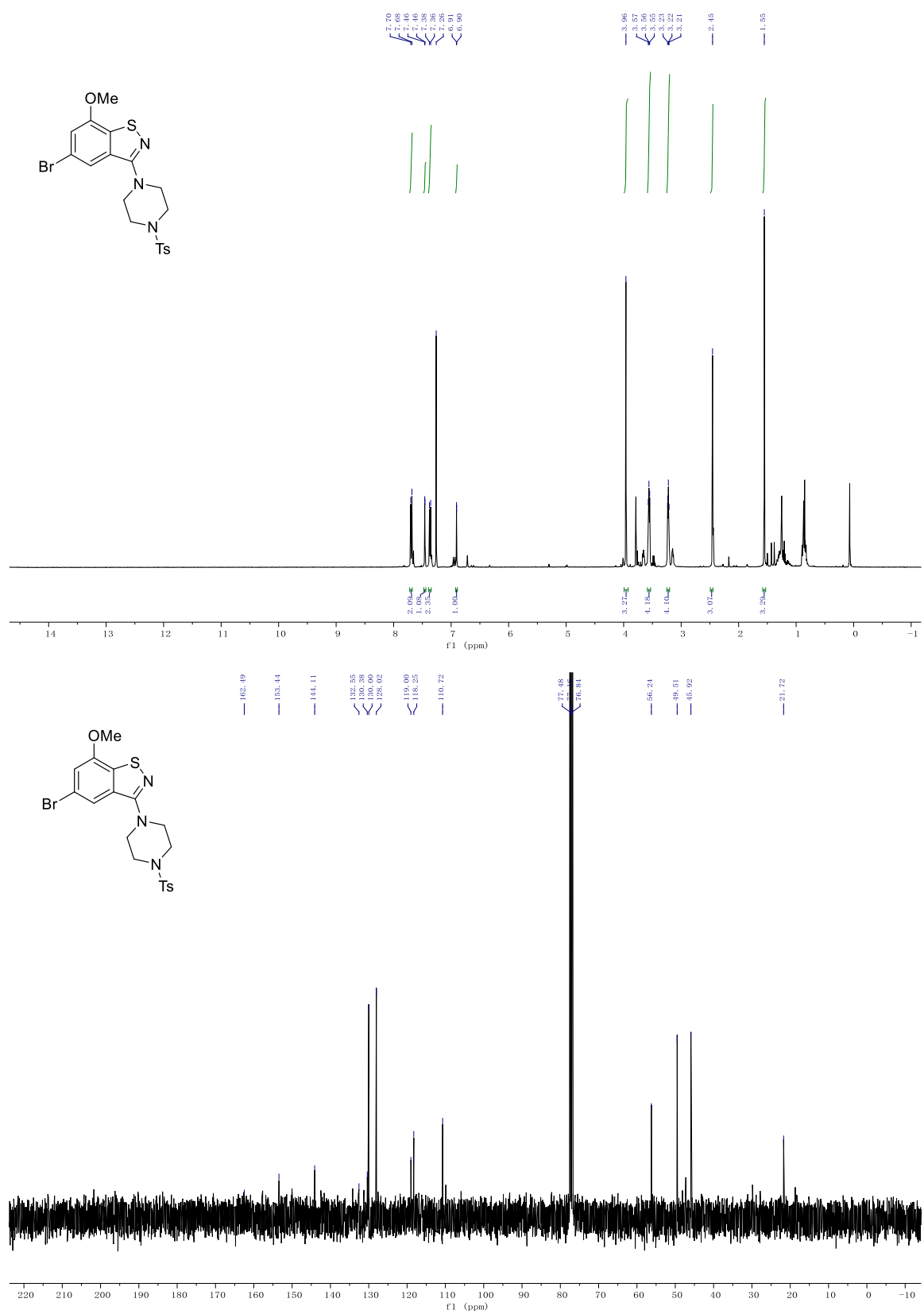
¹H NMR and ¹³C NMR spectra of 3-(4-tosylpiperazinyl)-4-methoxy-6-bromo-1,2-

benzothiazole 69g



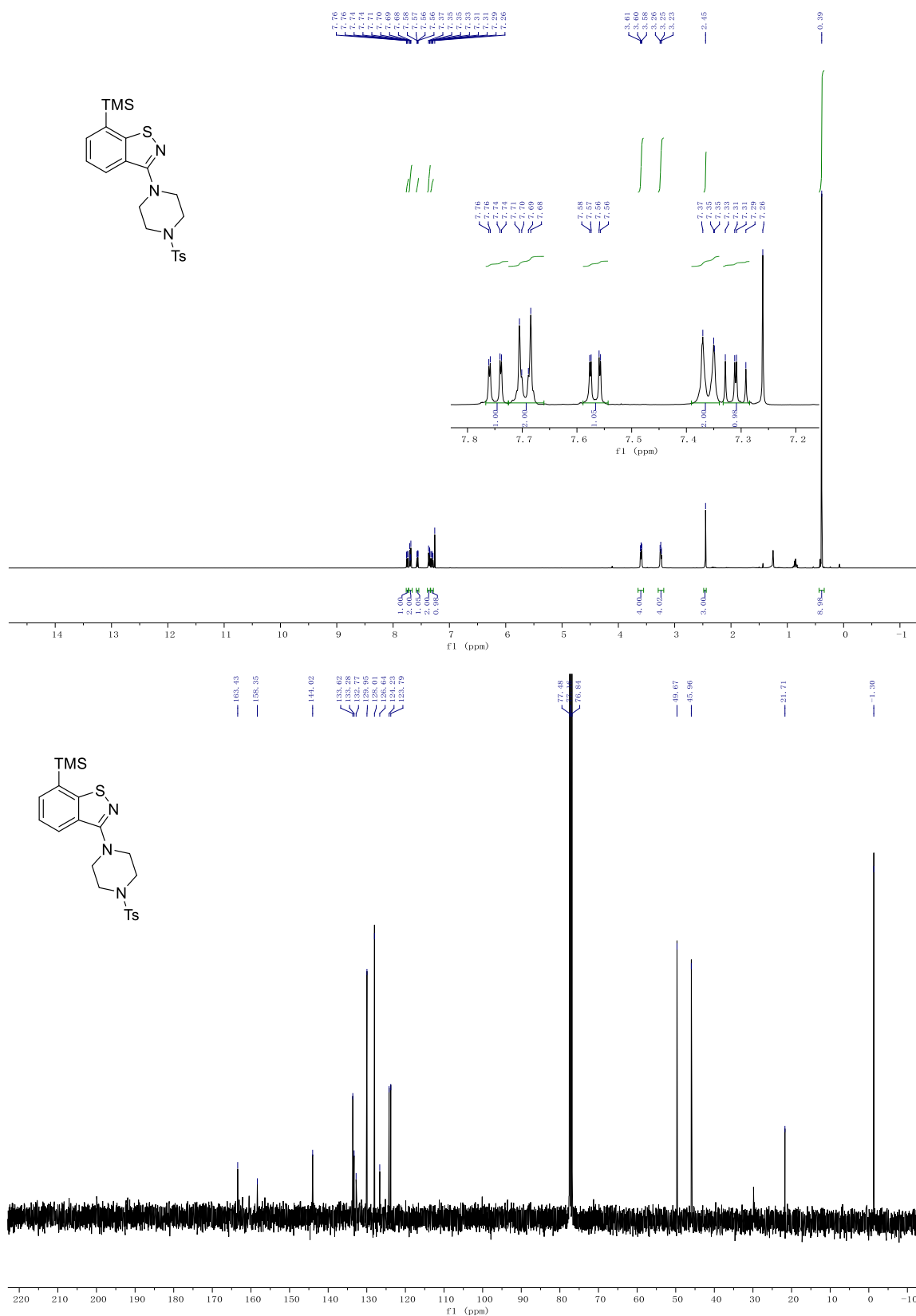


NOE spectra of 3-(4-tosylpiperazinyl)-4-methoxy-6-bromo-1,2-benzisothiazole 69g



¹H NMR and ¹³C NMR spectra of 3-(4-tosylpiperazinyl)-5-bromo-7-methoxy-1,2-

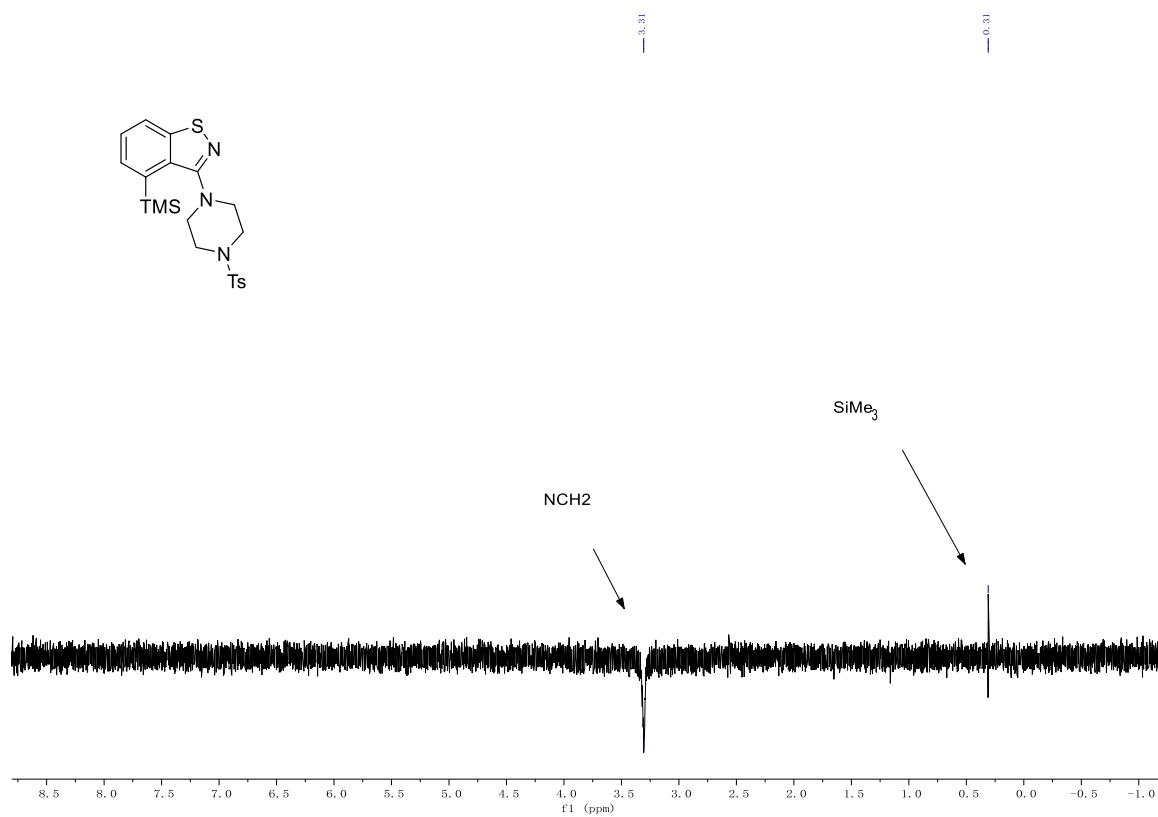
benzothiazole 69g'



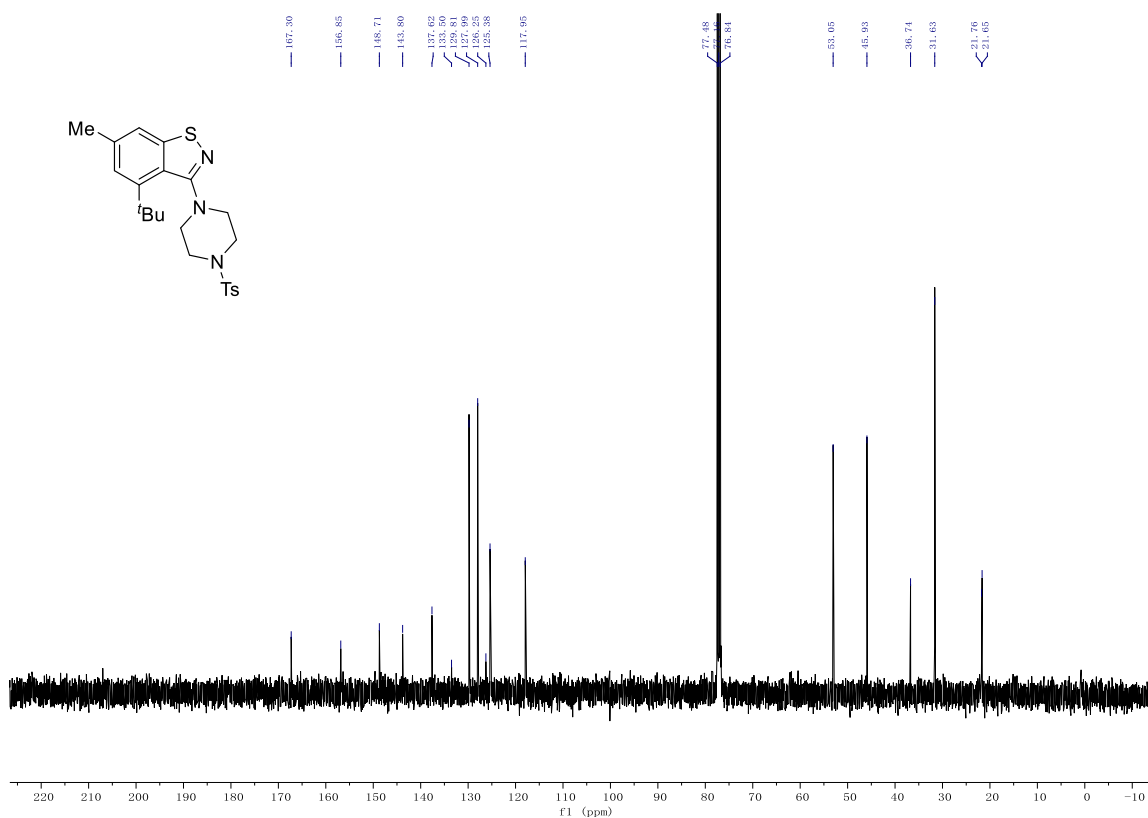
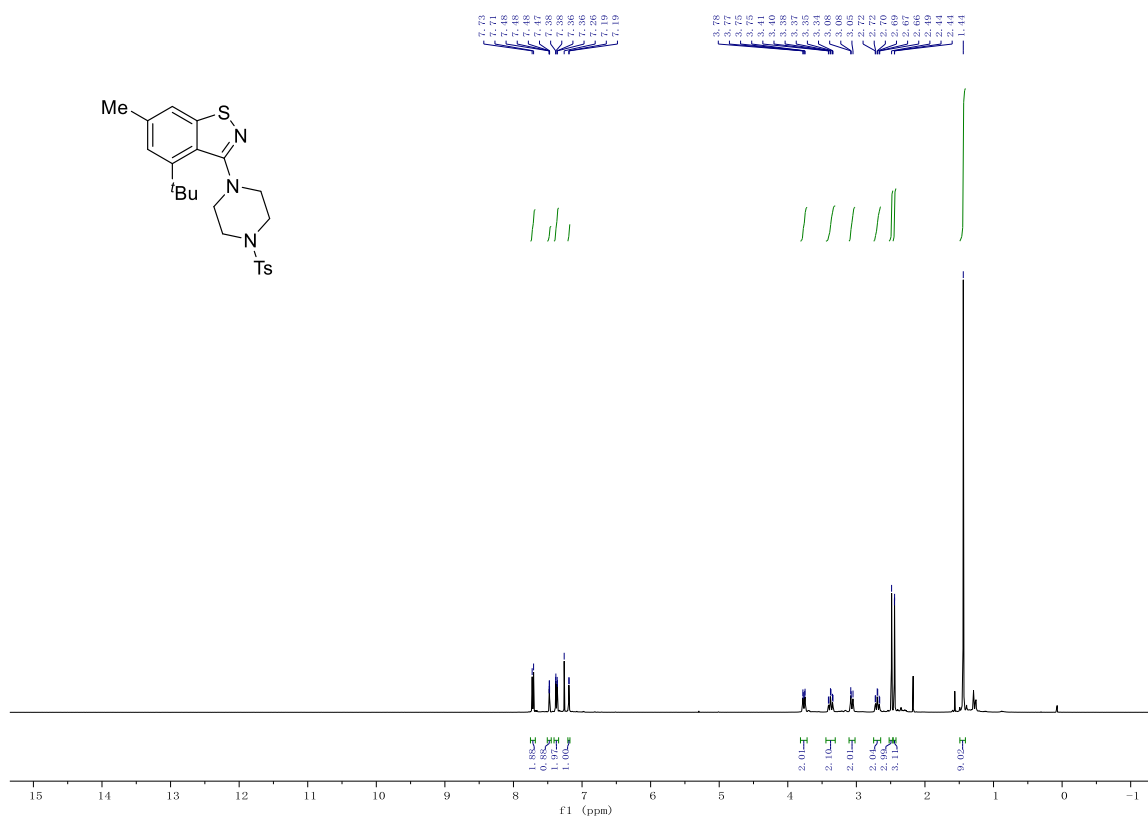
¹H NMR and ¹³C NMR spectra of 3-(4-Tosylpiperazinyl)-7-trimethylsilyl-1,2-benzisothiazole

69h

453

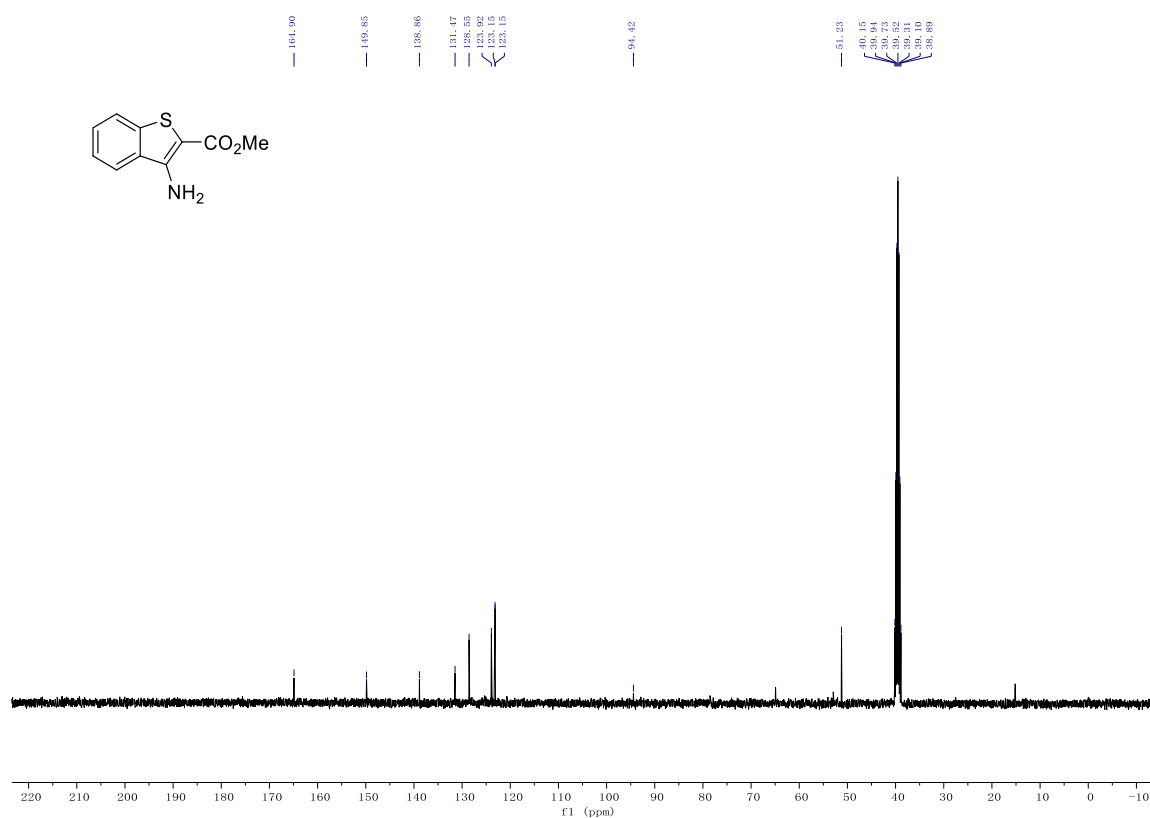
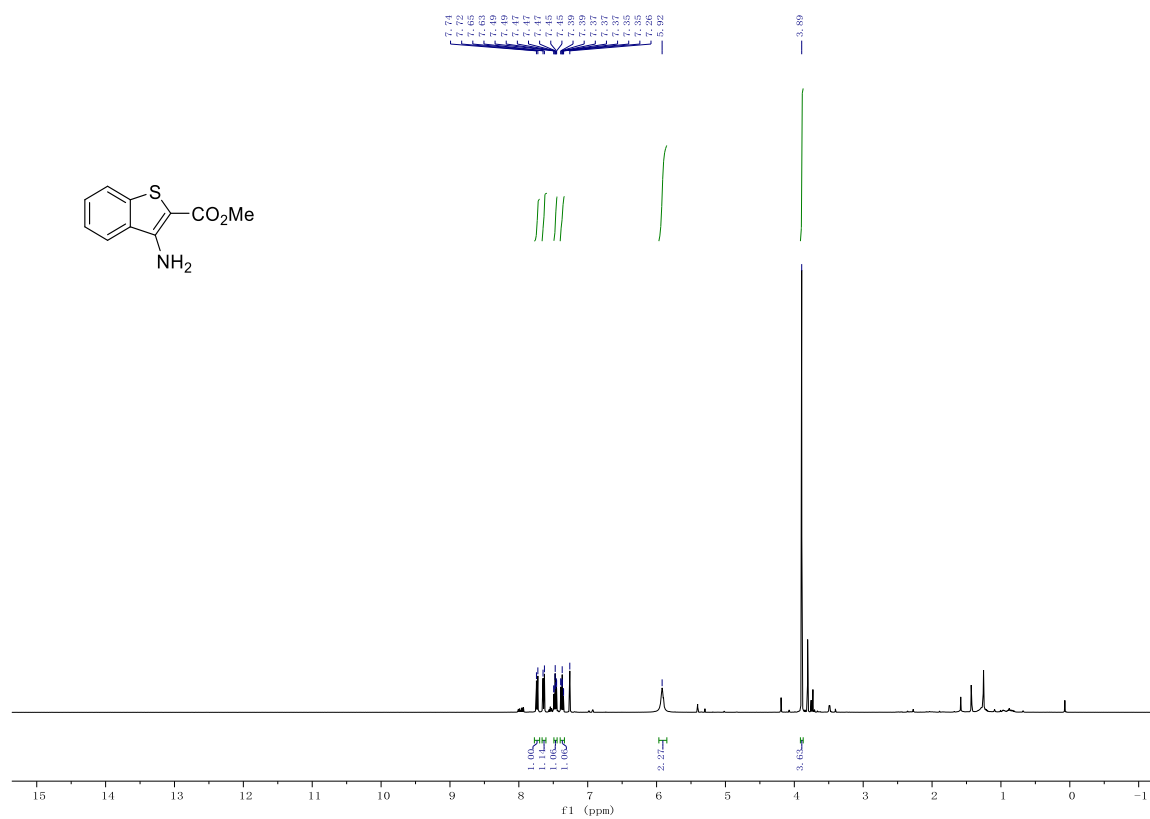


NOE spectrum of **3-(4-Tosylpiperazinyl)-4-trimethylsilyl-1,2-benzisothiazole 69h'**



^1H NMR and ^{13}C NMR spectra of 3-(4-tosylpiperazinyl)-4-*tert*-butyl-6-methyl-1,2-

benzothiazole 69i'



¹H NMR and ¹³C NMR spectra of methyl 3-aminobenzothiophene-2-carboxylate 71

