Lewis Acid Mediated N-aryl Nitrone Synthesis from Benzyl Alcohols

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Title: Lewis Acid Mediated N-aryl Nitrone Synthesis from Benzyl Alcohols

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Abstract.

A novel approach to access N-Aryl nitrones via copper catalyzed coupling of benzyl alcohols with nitrosobenzenes is described. The results of mechanistic studies are conflicting but suggest this reaction proceeds through either redox process or a nucleophilic nitroso hydrate intermediate formed in situ, which was previously unprecedented. The unique electronics of this process allow access to nitrones with excellent step and atom economy, which are otherwise difficult to make using conventional methods. In this work, a total of 22 nitrones have been made. 15 of which from pure starting materials with yields ranging from 26 - 89 % and another 7 from two step, one pot reactions where the nitrosobenzenes were made in situ from commercially available anilines and reacted in a subsequent step to produce the nitrone in 8 - 46 % yield. In addition to the nitrone forming reaction occurring in the second step of a two-step sequence, we have also shown that subsequent reactions can be done on newly formed nitrones in one pot. This was demonstrated with a newly synthesized nitrone and a donor-acceptor cyclopropane in a [3+3] annulation reaction forming the cycloadduct in 90% yield.

Acknowledgements.

I would like to thank my supervisor, Dr. Jakob Magolan, for all of his support and guidance over the past two years. His composure, determination and leadership qualities are inspiring and will certainly be a driving force to all future success of the research lab.

I would like to thank Dr. Jarrod Johnson for being a great mentor and friend. He is an incredible person who I have been lucky to work with and learn from. His ideas, humor and enthusiasm show in every project and make this group a special place to be.

I have to thank all of my lab comrades who I have worked alongside for the past two years that keep the room upbeat and exciting. Anyone who has laughed at my jokes has made my time at McMaster so much better.

Finally, I would like to thank my parents for all of their encouragement and support. They are the most important and influential people in my life. I look up to them in every aspect and appreciate everything they have worked for and taught me. They are perfect role models.

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List of Abbreviations

Ac	Acetyl
Ar	Aryl functional group
BHT	butylatedhydroxytoluene
BIGN	*N*-benzyl-2,3-O-isopropylidine-D-Glyceraldehyde nitrone
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
BTF	Triflurotoluene
t-Bu	*tert*-Butyl
CN	Nitrile
CNT	Carbon nanotube
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DMA	*N*,*N*-dimethylacetamide
DMAP	*N*,*N*-dimethylamino-4-pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethyl Sulfoxide
EDG	Electron donating group
Et	Ethyl
EWG	Electron withdrawing group
FICI	Fractional inhibitory concentration index
HFIP	Hexafluoroisopropanol
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectromwtry
Hz	Hertz

IBX	2-iodoxybenzoic acid
IM	Inner membrane
IR	Infrared
LA	Lewis Acid
LPS	Lipopolysaccharide
m	Multiplet
m	*meta* substitution
Me	Methyl
MIC	Minimum inhibitory concentration
Ms	Mesyl
MS	Molecular Sieves
MTO	Methyltrioxorhenium
MW	Monowave
NBS	*N*-bromosuccinimide
NMR	Nuclear magnetic resonance
Ns	Nosyl
Nu	Nucleophile
o	*ortho* substitution
p	*para* substitution
Ph	Phenyl
Py	Pyridine
q	Quartet
Rf	Retention factor
rt	Room temperature
s	Singlet
t	Triplet
TDAB	Tetradecylammonium bromide
Tf	Triflate
TFA	Trifluoroacetic acid

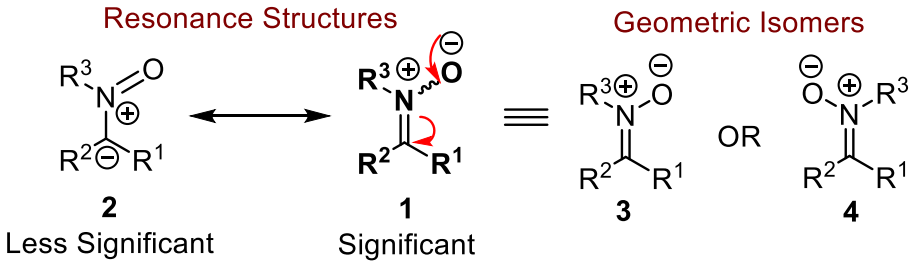
THF	Tetrahydrofuran
TLC	Thin-layer chromotography
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Ts	Toluenesulfonyl
UHP	Urea hydrogen peroxide
3CR	Three Component Reaction

Chapter 1: Lewis Acid Mediated *N*-aryl Nitrone Synthesis from Benzyl Alcohols

1.1. Introduction

1.1.1 Nomenclature and Connectivity of Nitrones

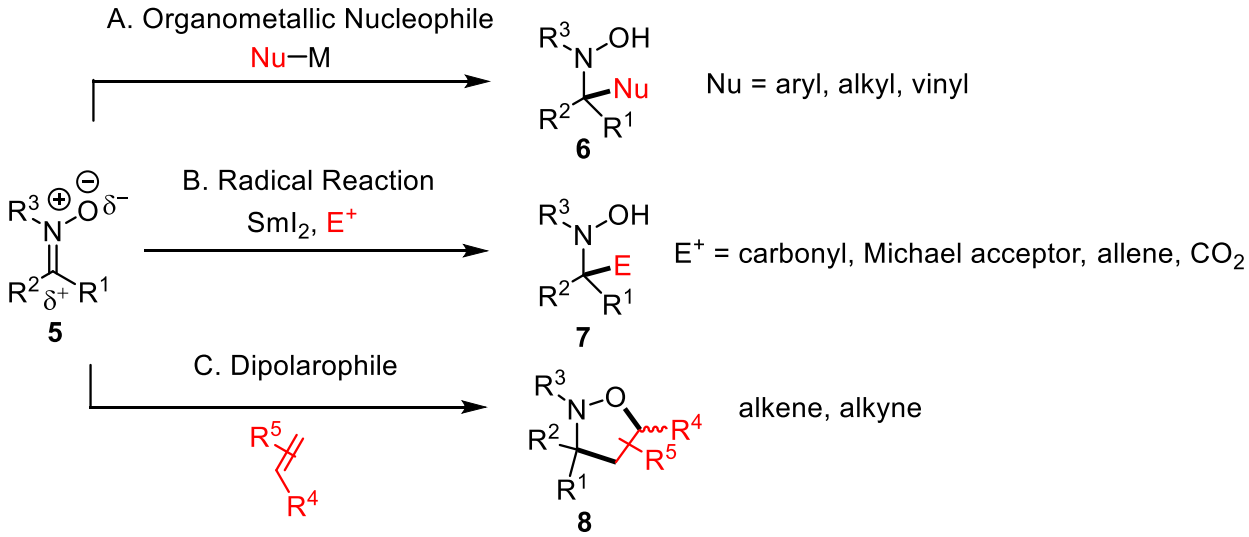
Nitrones are compounds containing an N-oxide of an imine shown in Scheme 1. General nomenclature used to describe these functionalities are aldonitrones and ketonitrones.[1] Aldonitrones have a proton on the unsaturated alpha carbon similar to that of an aldehyde (R^2 or R^1 = H, Scheme 1), while a ketonitrone contains a fully substituted alpha carbon with aryl or alkyl groups (R^2 and R^1 = alkyl or aryl, Scheme 1), analogous to a ketone. With respect to nitrogen substitution, alkyl, aryl, and allyl nitrones possess alkyl, aryl, and allylic connectivity to the nitrogen respectively.[2] Additionally, these structures display geometric isomerism if the alpha carbon substituents are different due to the restrictive rotation of the double bond (Scheme 1, **3** and **4**)[3]. Nitrones are commonly drawn as their most significant resonance structure (Scheme 1, compound **1**), as proven by dipole moment analysis[4].



Scheme 1. General structure of a nitrone with resonance structure and geometric isomers.

1.1.2. Reactivity of Nitrones

Nitrones are useful synthetic intermediates that have proven to be valuable functionalities since their unique electronics can be exploited to effect a variety of transformations[5]. Several comprehensive reviews have been published summarizing nitrone reactivity. The most common synthetic applications of nitrones are shown in Scheme 2. These compounds can be used as prochiral starting materials in reactions with organometallic nucleophiles (Scheme 2, A)[6], or to generate nucleophilic radical reagents that can react with electrophilic radical species (Scheme 2, B)[5]. Both of these processes can generate new carbon-carbon bonds. Most significantly, these compounds can be used as 1,3-dipolar reagents and react with various dipolarophiles (Scheme 2, C)[7]. This dipolar cycloaddition is a powerful synthetic tool, as it results in a new carbon-carbon bond as well as a carbon-oxygen bond in the product.

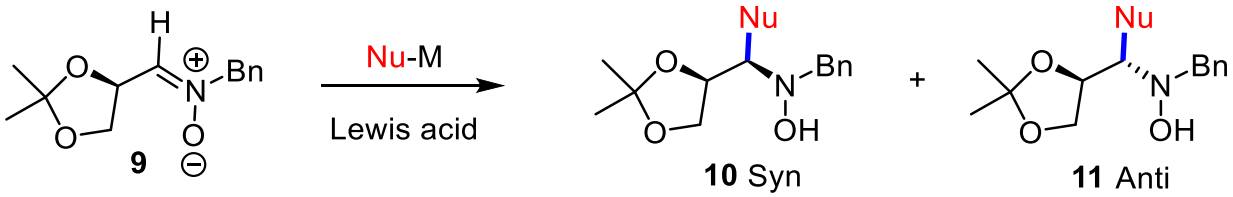


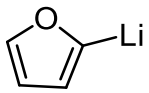
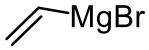
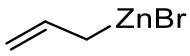
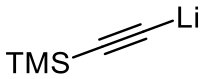
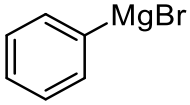
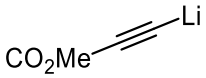
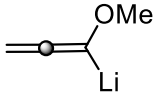
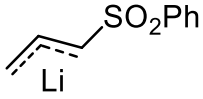
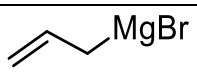
Scheme 2. Three most common uses of nitrones; A. electrophiles with organometallic nucleophiles, B. radical electrophiles, C. 1,3-dipolar reagents.

1.1.2.1.1. Reactions of Nitrones with Organometallic Nucleophiles

Organometallic nucleophiles are useful tools for making carbon-carbon bonds at the alpha position of nitrones. In specific, N-benzyl-2,3-O-isopropylidine-D-glyceraldehyde nitrone (BIGN) (compound **9**) has shown considerable utility as a synthon in organic chemistry. Diastereoselective reactions have been established using a variety of conditions to convert prochiral nitrones, such as BIGN, into a majority single isomer product (Table 1). As a result, chiral nitrones have been used in the synthesis of natural products as the diastereofacial addition of nucleophiles can be controlled affording asymmetric products. Syn addition is generally favoured in these reactions, however variation of solvent, Lewis acid and temperature each have a profound influence on the diastereoface differentiation of nitrones and anti-products are easily attainable.

Table 1. Conditions for syn or anti addition of various organometallic nucleophiles to BIGN, a chiral nitrone.



Entry	Nu-M	Lewis acid	Conditions	Syn/ Anti	Yield (%)	Year[ref]
1		-	THF•Et_2O, -80 ºC	**96**:4	92	1993[8]
		Et_2AlCl	THF•Et_2O, -80 ºC	5:**95**	89	
2		-	THF, 0 ºC	**76**:24	86	1996[9]
		Et_2AlCl	Et_2O, 0 ºC	8:**92**	86	
3		-	THF, 0 ºC	25:**75**	92	1997[10]
		Et_2AlCl	THF, -40 ºC	**63**:35	80	
4		-	THF, -80 ºC	>**95**:5	100	1997[11]
		Et_2AlCl	Et_2O, -80 ºC	29:**71**	96	
5		-	THF, -60 ºC	**80**:20	84	1998[12]
		$ZnBr_2$	Et_2O, -60 ºC	**90**:10	86	
		Et_2AlCl	Et_2O, -60 ºC	5:**95**	72	
6		-	THF, -80 ºC	>**95**:5	100	1998[13]
		Et_2AlCl	Et_2O, -80 ºC	30:**70**	92	
7		-	THF, -80 ºC	**98**:2	81	1999[14]
		Et_2AlCl	Et_2O, -80 ºC	3:**97**	61	
8		HMPA	THF, -80 ºC	**98**:2	-	2005[15]
9		$ZnBr_2$	Et_2O, -50 ºC	>**95**:5	100	2008[16]
		BF_3•Et_2O	THF, -50 ºC	5:**95**	90	

BIGN as a synthon can be mapped onto a variety of biologically active natural products and the syn/anti relationship has demonstrated to be crucial with respect to their activity (figure 1).

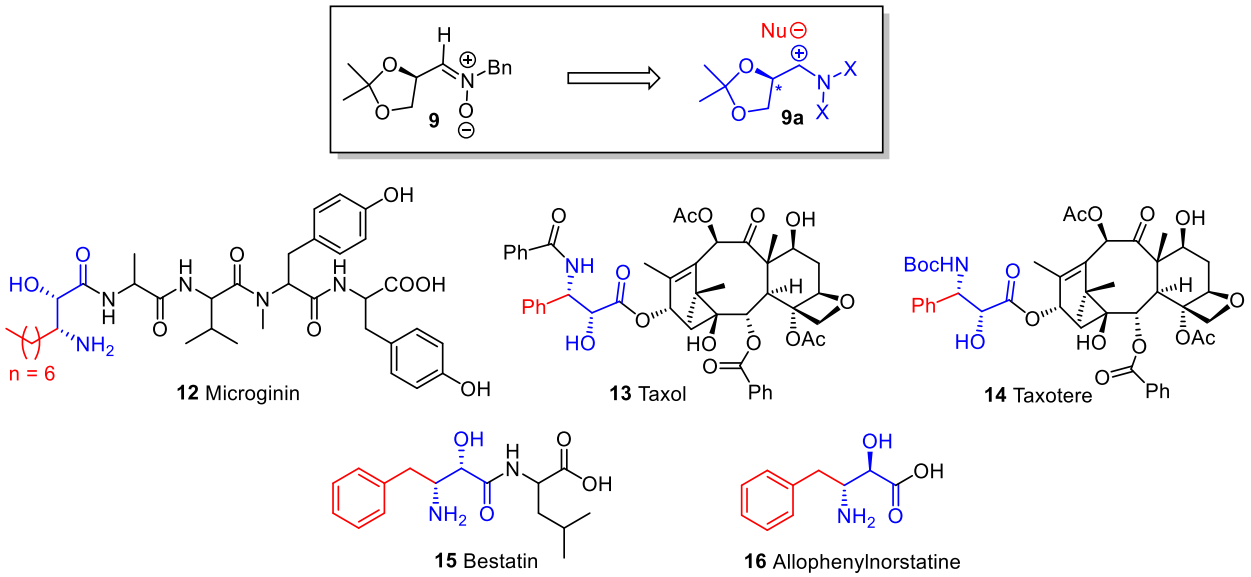
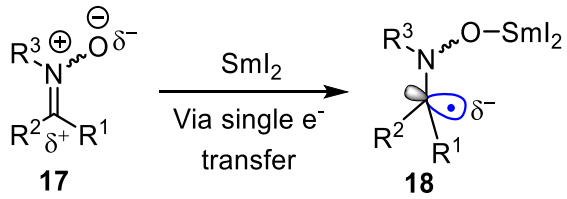


Figure 1. BIGN synthon mapped onto natural products; Microginin, Taxol, Taxotere, Bestatin, Allophenylnorstatine.

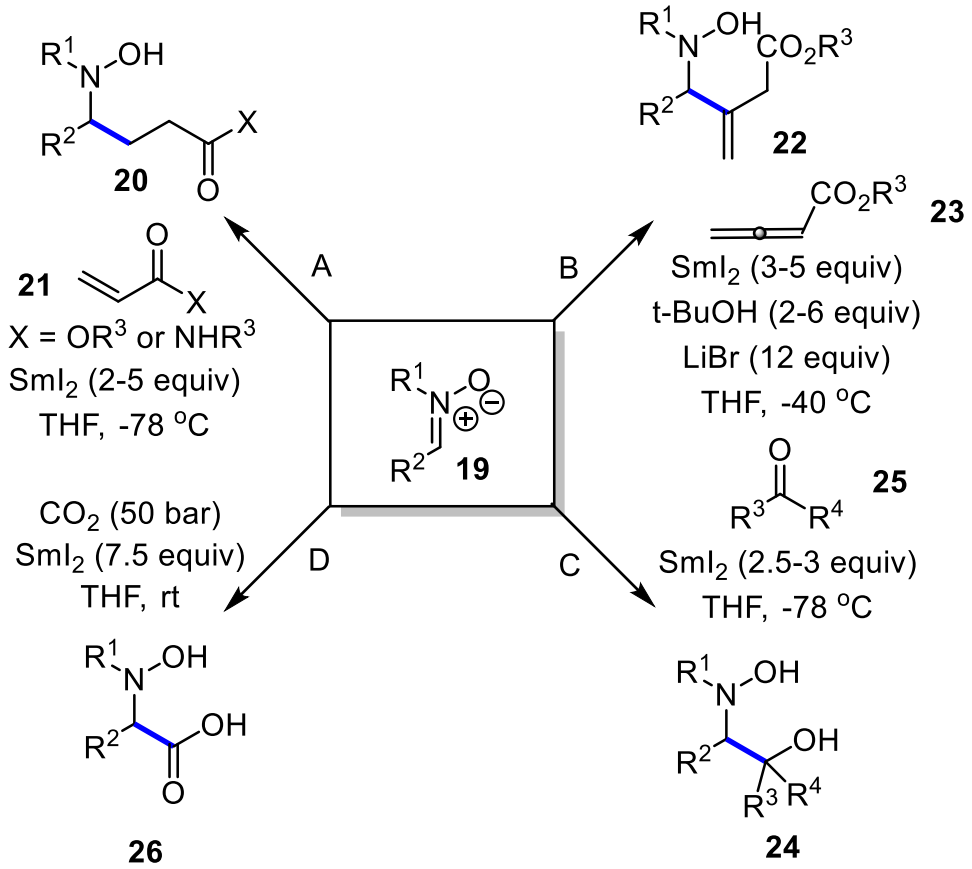
1.1.2.2. Formation of Carbon-Carbon Bonds with Nitrones by Radical Processes

Nitrones can participate in radical reactions to yield new carbon-carbon bonds at the alpha carbon with various electrophilic coupling partners. The alpha carbon is generally an electrophilic site as seen with reactions of organometallic nucleophiles above. However, this polarity can be reversed in the presence of samarium diiodide through a single electron transfer process converting the nitrone to a nitrogen equivalent of a ketyl radical anion (Scheme 3, compound **18**).[17]



Scheme 3. Radical activation of nitrones as ketyl radical anion equivalents.

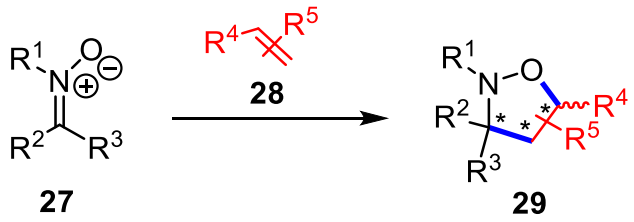
This radical process gives rise to a transient intermediate capable of reacting with a variety of electrophilic coupling partners. Various acrylates have been reacted in this way (Scheme 4, A)[18]. Similarly, allenes participate in this process by coupling at the sp carbon, leaving an alkene at the beta carbon of the product (Scheme 4, B)[19]. Ketones and aldehydes are useful coupling partners as they form ketyl radicals, and their reactions with nitrones can form new sigma bonds resulting in sterically hindered secondary or tertiary alcohols that are otherwise difficult to make (Scheme 4, C)[20]. Finally, carboxylic acid derivatives can be formed by using carbon dioxide under pressure as an electrophile (Scheme 4, D)[21].



Scheme 4. Common radical transformations of nitrones using samarium diiodide. A. acrylates as electrophilic radical coupling partners, B. allenes as coupling partners, C. ketones or aldehydes as coupling partners, D. carbon dioxide as a coupling partner.

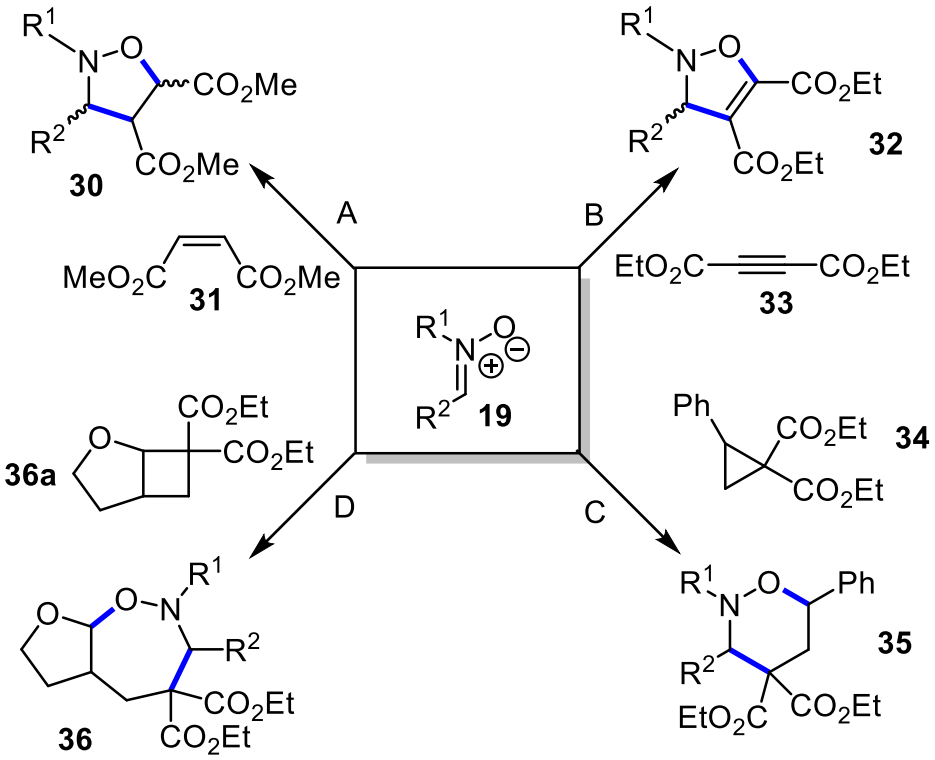
1.1.2.3. Nitrones as 1,3-Dipolar Reagents

Nitrones have been commonly used as 1,3 dipoles given their ready reactivity with various dipolarophiles (Scheme 5)[22]. These reactions are incredibly powerful synthetic tools as the products contain a new carbon-carbon, and carbon-oxygen bond, resulting in a cycloadduct with up to three new stereocenters. The newly formed heterocycles are common cores of various biologically active compounds, and can be used in subsequent reactions[23].



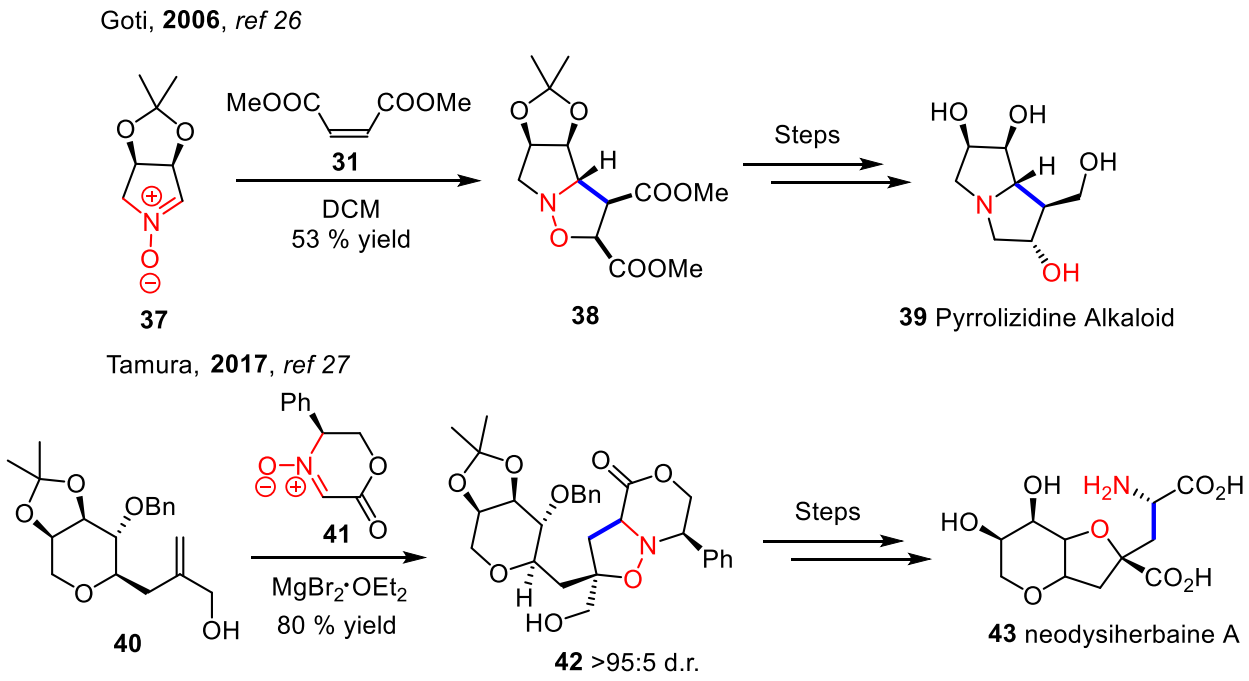
Scheme 5. General reaction between a nitrone and an alkene.

Several options for dipolarophiles (Scheme 6), and conditions to attain diastereoselective products are reported with these dipolar cycloadditions. Electron deficient alkenes and alkynes (Scheme 6, arrows A and B respectively) are used to make five membered heterocycles while donor- acceptor cyclopropanes and cyclobutanes can make six and seven membered rings (Scheme 6, arrows C and D respectively)[24],[25].



Scheme 6. Generic dipolarophiles commonly used in reactions with nitrones. A. alkenes, B. alkynes, C. cyclopropanes, D. cyclobutanes.

There are many instances of nitrones being employed as 1,3-dipolar reagents in the synthesis of complex natural products. In 2006, Goti used a cyclic nitrone to rapidly access the core scaffold of pyrrolizidine alkaloids through a dipolar cycloaddition with an electron poor alkene (Scheme 7, top)[26]. Similarly, in 2017, Tamura applied a similar strategy in the total synthesis of neodysiherbaine A (Scheme 7 bottom)[27]. In both of these sequences, the N-O bond is reductively cleaved in subsequent steps. The result of the nitrone cycloaddition is a carbon-carbon bond, and two heteroatoms in each of the final compounds.

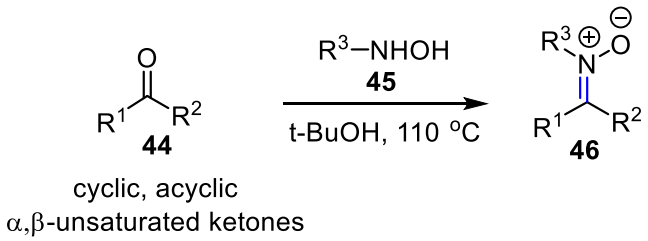


Scheme 7. 1,3-dipolar cycloadditions between nitrones and alkenes as key steps in the synthesis of core scaffolds to pyrrolizidine alkaloids (top) and neodysiherbaine A (bottom).

1.1.3. Synthesis of Nitrones

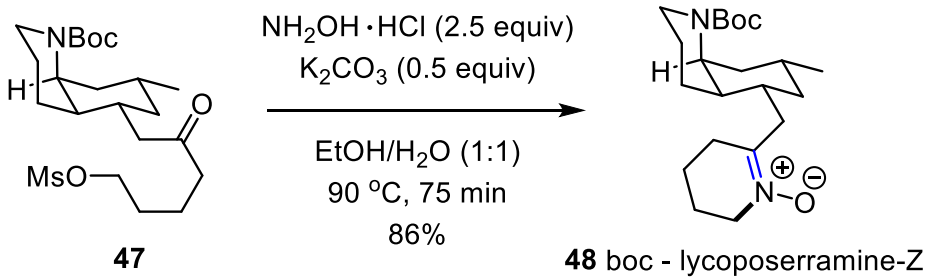
1.1.3.1. Nitrones from Condensation Reactions of Hydroxylamines and Carbonyls

The most straightforward synthesis of nitrones comes from a condensation reaction between a nucleophilic N-monosubstituted hydroxylamine with aldehydes and ketones. (Scheme 8)[28]



Scheme 8. General condensation reaction between hydroxylamine and carbonyl compounds yielding nitrones.

In the synthesis of lycoposerramine-Z, hydroxylamine hydrochloride displaces a mesylated alcohol via an S_n2 reaction to form an N-alkyl hydroxylamine, followed by condensation onto a ketone to yield the desired nitrone (Scheme 9)[29].

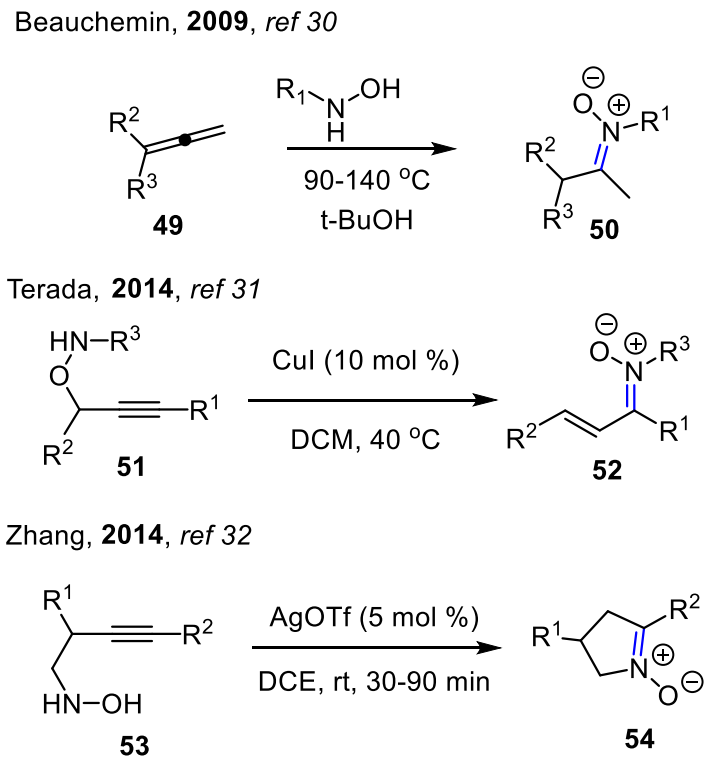


47 **48** boc - lycoposerramine-Z

Scheme 9. Nitrone formation by in situ generation of N-alkyl hydroxylamine followed by condensation.

1.1.3.2. Nitrones from Rearrangement/ Cyclization Reactions from Hydroxylamines with Allenes/ Alkynes

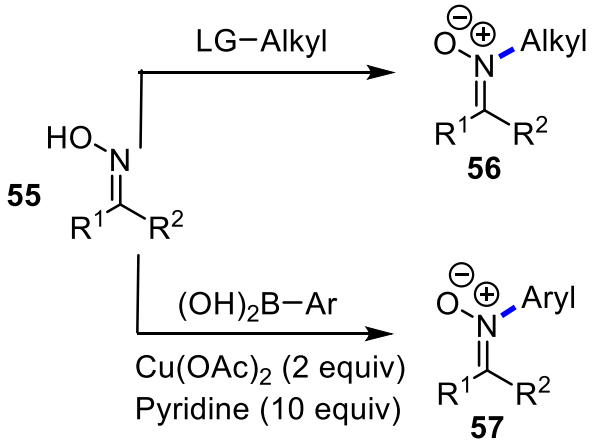
Other instances where N-monosubstituted hydroxylamine nucleophiles can be used in nitrone synthesis is through reactions with allenes and alkynes. These reactions can proceed by intermolecular or intramolecular processes with N, or O tethered hydroxylamines. Beauchemin reported a method to synthesize Ketonitrones from Monosubstituted allene electrophiles through a Cope-type hydroamination reaction (Scheme 10, top)[30]. In 2014, a report came from Terada describing an intramolecular rearrangement process to form α,β-unsaturated ketonitrones using Propargyloxyamines in the presence of copper iodide (Scheme 10, middle)[31]. Again in 2014, Zhang used an *N*-tethered hydroxylamines and cyclized with electrophilic alkynes activated by silver triflate as a lewis acid to make cyclic nitrones (Scheme 10, bottom)[32].



Scheme 10. Synthesis of ketonitrones (top), α,β-unsaturated ketonitrones (middle), and cyclic nitrones (bottom).

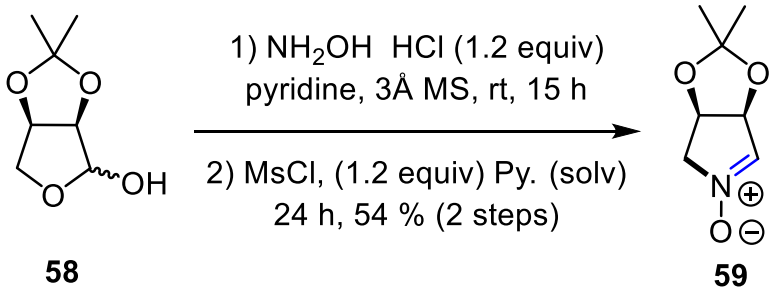
1.1.3.3. Nitrones from Oxime Nucleophiles

Oximes can also serve as nucleophilic nitrogen sources capable of forming nitrones. They are stable, isolable functionalities that can be made through condensation reactions of hydroxylamine with ketones and aldehydes. The nitrogen is capable of attacking various electrophiles in S_N2 or cross coupling processes (Scheme 11)[33].



Scheme 11. General reactions of oximes to nitrones by S_N2 and copper cross coupling.

Goti and coworkers were able to access the enantiomerically pure nitrone shown in scheme 7 through a one pot process using a lactol electrophile. In this sequence, hydroxylamine was condensed onto the lactol carbon to form an oxime followed by an intramolecular S_n2 displacement of a mesylated alcohol (Scheme 12)[34].



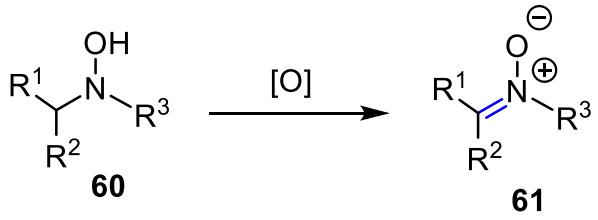
Scheme 12. Synthesis of enantiomerically pure nitrone by hydroxylamine S_N2 and subsequent condensation.

1.1.3.4. Nitrone Synthesis from Oxidation Reactions of Hydroxylamines, Secondary Amines and Imines

Nitrones can also be synthesized using various oxidizing conditions of *N*,*N*-disubstituted hydroxylamines, secondary amines and imines. These three starting materials must come from either an S_n2 process or condensation reaction from a ketone or aldehyde.

1.1.3.5. Nitrones from Oxidation of Hydroxylamines

Several oxidizing conditions have been reported for the oxidation of *N*,*N*-disubstituted hydroxylamines using both stoichiometric and catalytic amounts of oxidizing reagents (Scheme 13).

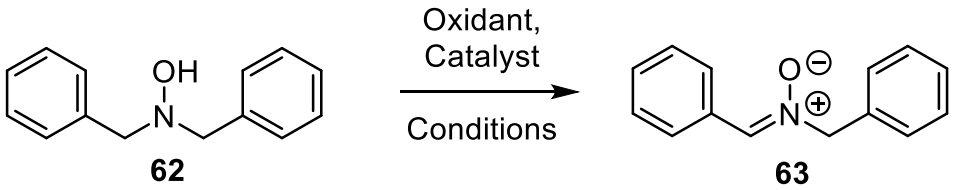


Scheme 13. General reaction of hydroxylamine to nitrone.

A comparison of oxidizing conditions for *N*,*N*-dialkylhydroxylamines is shown in Table 2 below. Catalytic oxidation of hydroxylamines to nitrones using platinum black was reported for the first time in 1983[35]. More recently, two other aerobic oxidations have been reported using gold nanoparticles fixed to silica[36], and rhodium catalyzed oxidations[37]. TPAP has also proven to be an effective catalyst for the conversion of hydroxylamines to nitrones using N-methylmorpholine N-oxide[38] or molecular oxygen as an oxidizing agent[26]. Rhenium and rhodium have been reported as capable transition metals to catalyze this conversion. Methyltrioxorhenium can be used with hydrogen peroxide[39], and rhodium nanoparticles supported by carbon nanotubes with aerobic oxidation are also effective[37]. Stoichiometric

oxidizing reagents have been demonstrated to carry out this transformation. NaOCl is a green oxidizing agent suitable for large scale reactions[40], MnO_2 is compatible with many other functionalities[41], as is IBX[42].

Table 2. Catalytic and stoichiometric oxidation of N,N-benzyl hydroxylamine.

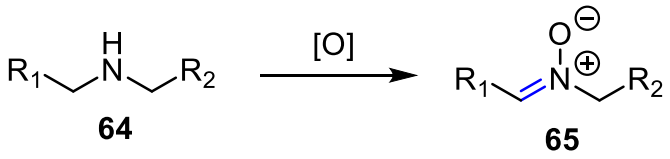


62 **63**

Entry	Oxidant (equiv)	Catalyst (loading)	Conditions	Yield %	Year (ref)
1	air	Pd black (4 mol %)	toluene, 110 °C, 12 h	87	1983[35]
2	NMO (1.5 equiv)	TPAP (5 mol %)	MeCN, rt, 0.5 h	92	1994[38]
3	NaOCl (1.3 equiv)	-	DCM, 0 °C, 0.5 h	85	1999[40]
4	MnO_2 (1.5 equiv)	-	DCM, 0 °C, 0.5 h	93	2001[41]
5	H_2O_2 (1.5 equiv)	MTO, py (2 mol %, 10 mol %)	EtOH, rt, 0.25 h	93	2004[39]
6	O_2	TPAP (5 mol %)	BTF, rt, 18 h	79	2006[26]
7	IBX (1.5 equiv)	-	DCM, rt, 2 h	95	2015[42]
8	air	Au/SiO_2 (5 mol %)	MeOH, rt, 48 h	98	2015[36]
9	air	RhCNT (1 mol %)	MeOH, rt, 8 h	99	2017[37]

1.1.3.6. Nitrones from Oxidation of Secondary Amines

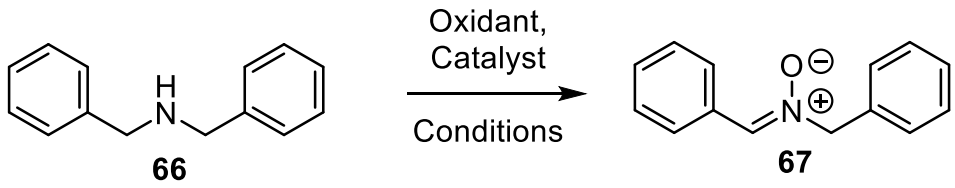
Secondary amines serve as useful starting materials for nitrone synthesis since they are common functionalities in organic chemistry. Similarly to the oxidations of *N*,*N*-dialkylhydroxylamines, several methods have been reported to effect these transformations (Table 3). Oxidation of secondary amines to nitrones can be carried out using stoichiometric or catalytic reagents with various oxidizing agents (Scheme 14).



Scheme 14. General reaction for the oxidation of secondary amines to nitrones.

Davis oxaziridines can achieve this transformation in poor yield[43], while Oxone is a much more effective oxidizing agent without the use of metal catalysts[44]. Aqueous 30% hydrogen peroxide in the presence of disodium tungstate, $Na_2WO_4 \bullet 2H_2O$, is a useful method that has been used on preparative scale synthesis[45]. If substrates are not able to tolerate aqueous conditions, UHP can be used as a hydrogen peroxide source with a tungstate catalyst rather than aqueous hydrogen peroxide. Molybdate catalysts are effective with UHP as the oxidizing agent[46]. Several other transition metal catalysts have been shown to be effective using varying concentrations of hydrogen peroxide such as rhenium (MTO)[47], titanium[48], and platinum[49].

Table 3. Catalytic and stoichiometric oxidation of N,N-dibenzylamine.

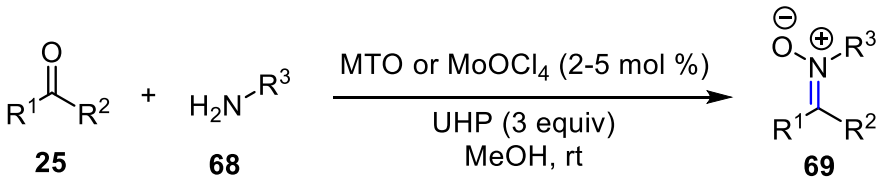


66 67

Entry	Oxidant (equiv)	Catalyst (loading)	Conditions	Yield %	Year (ref)
1	Davis Oxaziridine (1 equiv)	-	$CHCl_3$, rt, 1 h	10	1988[43]
2	30 % H_2O_2 (3 equiv)	Na_2WO_4 $2H_2O$ (4 mol %)	MeOH, 0 °C to rt, 3 h	85	1990[45]
3	UHP (4 equiv)	Na_2WO_4 (5 mol %)	MeOH, rt, 4 h	84	1995[46]
		Na_2MoO_4 (5 mol %)		90	
4	50 % H_2O_2 (10 equiv)	MTO (3 mol %)	EtOH, rt, 0.5 h	85	1996[47]
5	70 % H_2O_2	Ti (IV) (5 mol %)	CD_3OD, 60 °C, 2 h	92	2008[48]
6	35 % H_2O_2	Pt (II) (10 mol %)	DCM, 50 °C, 24 h	28	2008[49]
7	Oxone (1.05 equiv)	-	MeCN/THF 5 °C, 2 h	86	2009[44]

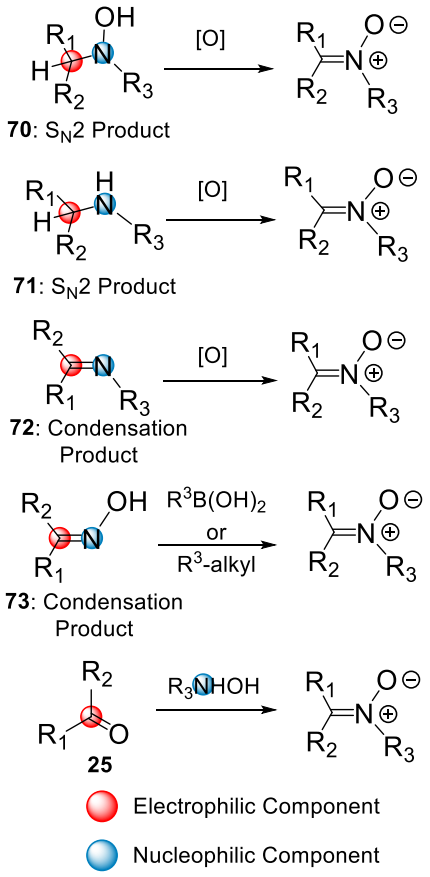
1.1.3.7. Nitrones from Oxidation of Imines

Imines have also been used as starting materials for nitrone synthesis through oxidation reactions similar to those of *N*,*N*-disubstituted hydroxylamines and secondary amines. One pot reactions where imines are made in situ and are subsequently oxidized have been reported using rhenium and molybdenum catalysts (Scheme 15)[50],[51].



Scheme 15. General reaction of imine formation and subsequent oxidation.

Although widely used, methods of nitrone synthesis that depend on nucleophilic nitrogen species and/ or strong oxidizing conditions have limitations. Despite a choice of nitrogen reagents and conditions available capable of affording nitrones, these processes offer little electronic flexibility as seen in Scheme 16.



Scheme 16. Electronic trends of nitrone forming reactions using nucleophilic nitrogen reagents.

Compounds with many electrophilic sites may have regioselectivity issues when a nucleophilic nitrogen is introduced. Several common functionalities in organic chemistry are also incompatible with oxidative conditions that are required in most cases[52]. Despite various options for nitrogen sources and oxidative conditions allowing for mild and selective oxidations, even in the absence of sensitive functionalities, certain nitrones cannot be accessed this way. These processes rely on the nitrogen sources being sufficiently nucleophilic to do condensation or S_n2 reactions and as a result nitrogen substitution restrict their reactivity (Figure 2). Formation of N-aryl nitrones from carbonyl starting materials have proven difficult since anilines and N-aryl hydroxylamines have diminished nucleophilic character. These functionalities may even be inert in the described processes rendering the above methods ineffective if other electron poor substituents are on the ring.

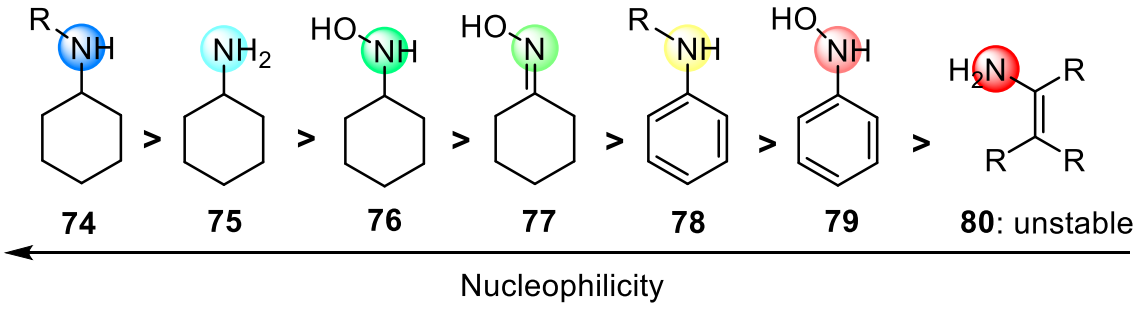
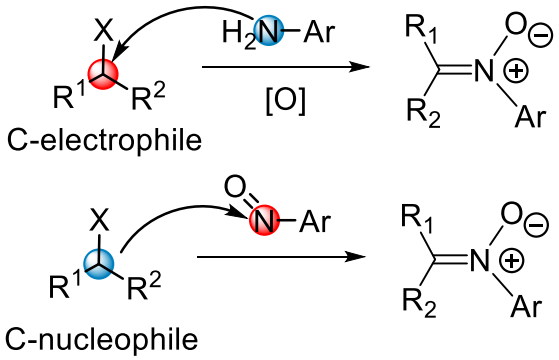


Figure 2. Nucleophilicity trends of nitrogen reagents common in nitrone synthesis.

1.1.3.8. Nitrone Synthesis via Nucleophilic Carbon Sources

Recent reports of nitrone formation have addressed the issue of insufficient nitrogen nucleophilicity inherent to certain N-aryl hydroxylamines and anilines, by switching the electronics of the coupling partners such that nucleophilic carbons attack an electrophilic nitrogen source. Common reagents used as electrophilic nitrogen sources are nitrosobenzenes, since the

electronics of the nitroso functional group favour the nitrogen as the electrophilic component as the oxygen can act as an electron sink (Scheme 17)[53].

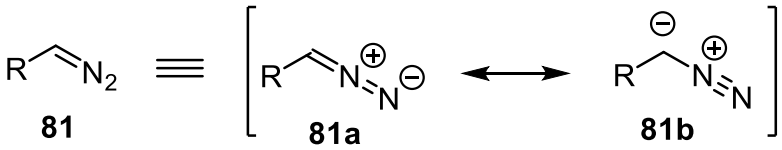


Scheme 17. Electronic switch in the synthesis of nitrones, carbon electrophiles (top) vs carbon nucleophiles (bottom).

Methods that circumvent the dependence on nitrogen nucleophiles through nitrosobenzenes are convenient, since nitrosobenzenes can be synthesized easily from commercially available anilines through various oxidation reactions.

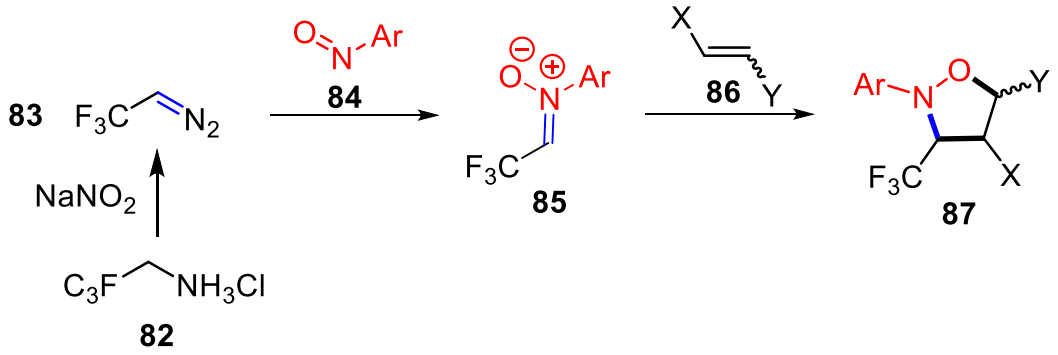
1.1.3.9. Nitrone Synthesis from Diazoalkanes

Diazo alkanes contain two nitrogen atoms bound to an alkyl carbon (Scheme 18). These compounds have a significant resonance structure where the carbon bonded to the diazo group bears a negative charge capable of attacking various electrophiles and liberating nitrogen gas[54].



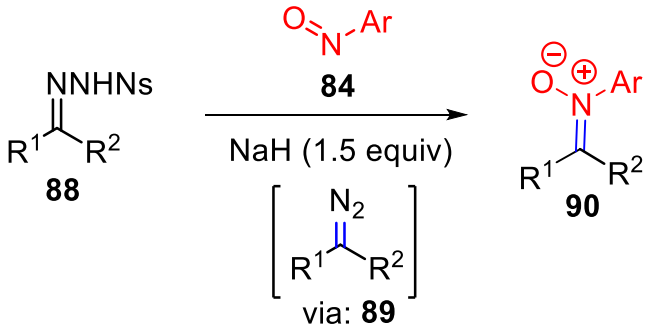
Scheme 18. Resonance structures of diazo compounds.

In 2013, Molander developed a nitrone forming reaction using trifluoromethyl diazomethane made in situ from primary amines, and nitrosobenzenes. These nitrones were subsequently reacted with electron deficient alkenes in one pot to make various isoxazolidines (Scheme19)[55].



Scheme 19. Nitrone synthesis from diazo compounds generated in situ from primary amines and subsequent reaction with dipolarophiles.

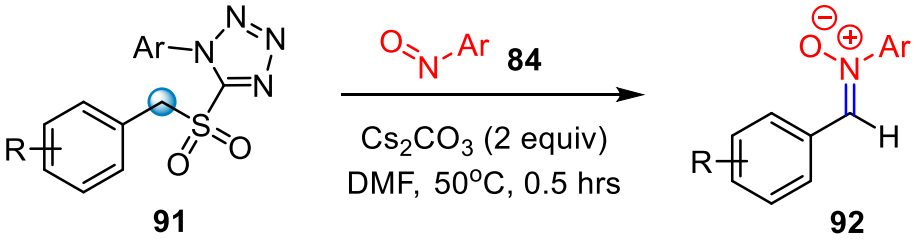
Another report generating diazo alkanes in situ came from Liu in 2018. In this work, diazo reagents were made via base mediated decomposition of *N*-Nosylhydrazones in the presence of nitrosobenzenes (Scheme 20)[55b].



Scheme 20. Nitrone synthesis from diazo compounds formed in situ by N-Nosylhydrazone decomposition.

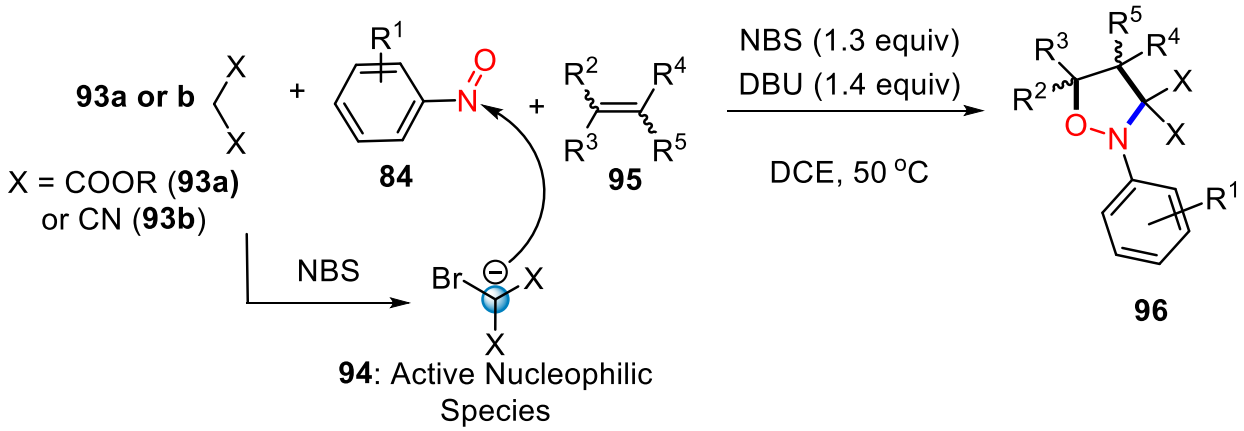
1.1.3.10. Nitrone Synthesis via Carbanions.

The chemistry of pKa's for alkyl protons with various neighbouring functional groups is well known, and conditions to generate carbon anions this way have been developed. These processes have also recently been applied to nitrone synthesis. In 2018, Cid demonstrated that heteroaryl benzyl sulfones can be converted to nitrones by exploiting the acidity of the benzylic protons to generate a carbanion capable of attacking nitroso compounds (Scheme 21)[56].



Scheme 21. Base mediated reaction of heteroaryl sulfones to nitrones by carbanion generation.

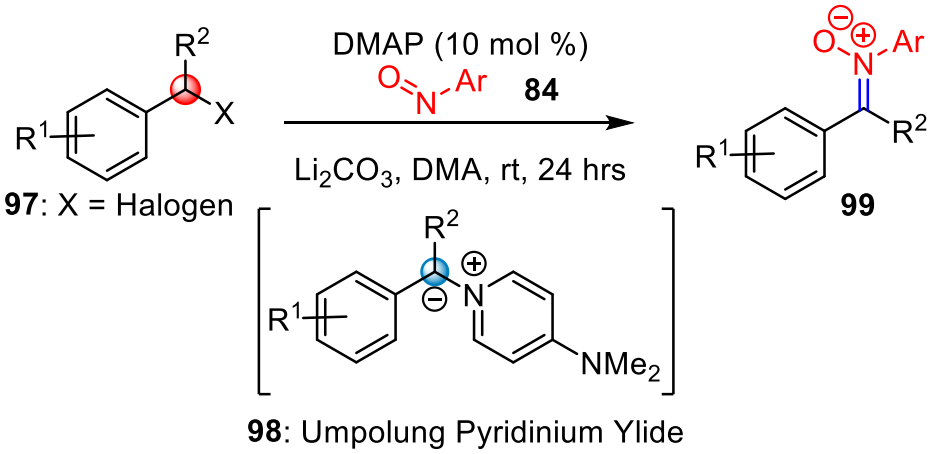
Furthermore, a report in 2020 by Li took an approach where the acidity of malonic acid derivatives were exploited to carry out a one-pot, three component reaction similar to that of Molander in scheme 20. In this work, isoxazolidine compounds were made following an NBS oxidation and nitrone formation in the presence of a dipolarophile (Scheme 22)[57].



Scheme 22. Nitrone synthesis from malonic acid derivative anions and subsequent dipolar cycloaddition with various alkenes.

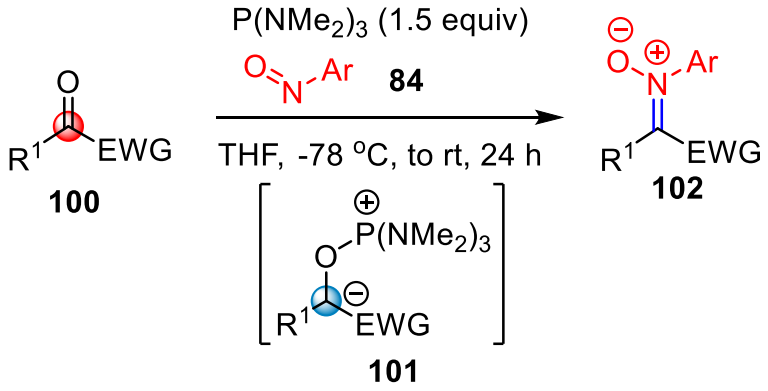
1.1.3.11. Umpolung approaches towards N-aryl nitrones.

Umpolung processes are powerful tools in organic synthesis as they expand the possibilities for retrosynthetic disconnections. Polarity reversal chemistry in nitrone synthesis literature has been gaining traction as alternative routes to access *N*-aryl nitrones are developed. A single step approach to make nitrones from benzyl halides and nitrosobenzenes was reported by Park in 2021. This reaction proceeds via the generation of pyridinium ylides in situ capable of attacking nitrosobenzene electrophiles (Scheme 23)[58].



Scheme 23. Generation of umpolung benzyl halide by pyridinium ylide *in situ* and subsequent attack of nitrosobenzene.

Another umpolung approach used to make nitrones was reported by Ashfeld in 2014, where phosphines are used to generate 1,2-dicarbonyl nucleophiles capable of attacking nitrosobenzenes. The in situ generation of α-alkoxy anion acts as a carbene equivalent to add the carbonyl carbon to nitrosoarenes (Scheme 24)[59].



Scheme 24. Generation of umpolung ketone and attack of nitrosobenzene.

1.1.4. This Work in the Context of Previous Methods.

Nitrones are useful synthetic intermediates capable of effecting a variety of transformations[5]. Their application as 1,3-dipolar reagents in total synthesis and occurrence in natural products have been extensively documented[60]. As a result, synthesis and reactivity of nitrones has garnered massive interest, and new methods to access these compounds continue to be developed. Synthesis of *N*-aryl nitrones in particular have been a major focus in recent times, as they are difficult to make using methods commonly relied on for their *N*-alkyl counterparts. Figure 3 depicts common approaches to access *N*-aryl nitrones. Conventional methods for nitrone synthesis employ nucleophilic nitrogen reagents and electrophilic carbon species in condensation[28], S_N2[34], cross coupling[33], (Figure 3, A) or by oxidation reactions (Figure 3, B, Tables 2 and 3). These processes are therefore limited by the nucleophilicity of the nitrogen reagent, as electron withdrawing substituents on anilines or N-aryl hydroxylamines will impair

reactivity. Carbon electrophilicity could be a problem since S_N2 reactions are difficult to achieve on sp^2 carbons, and substrates may also not be able to tolerate strong oxidizing conditions[52].

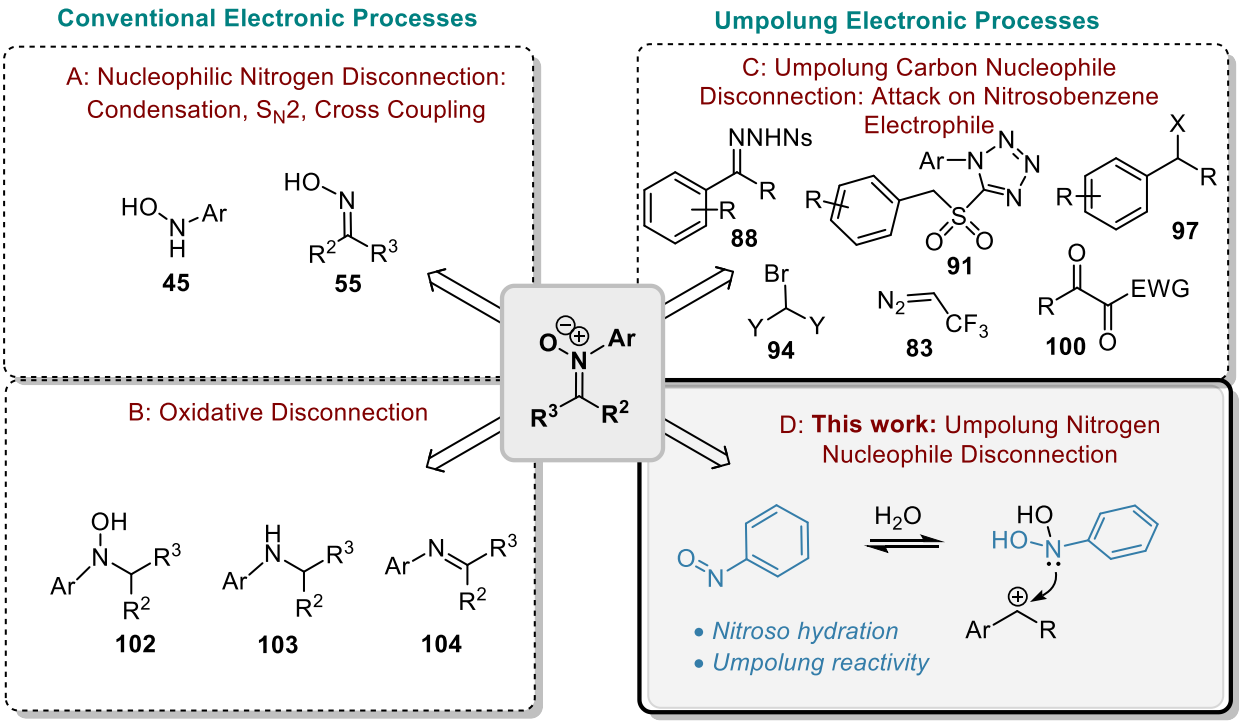


Figure 3. Common approaches to *N*-aryl nitrone synthesis.

An alternative approach to nitrone synthesis utilizes nitrosobenzenes as electrophilic nitrogen reagents reacting with carbon nucleophiles. Various starting materials such as 1,2-dicarbonyls[59], nosyl hydrazones[55b], heteroaryl sulfones[56], and benzyl halides[61] have been shown to form carbon nucleophiles in situ that react with nitrosobenzene electrophiles (Figure 3, C). These processes circumvent problems presented by boxes A and B at the expense of atom and step economy, as the starting materials are not common functionalities and large amounts of molecular weight gets discarded. In this work, *N*-aryl nitrones are synthesized through a novel bond forming process in which the reaction conditions result in umpolung electronics of the

nitrosobenzene (Figure 3, D) allowing it to attack carbon electrophiles. This process is step and atom economical, as various transformations have been done in one pot using catalytic reagents.

1.2. Results and Discussion.

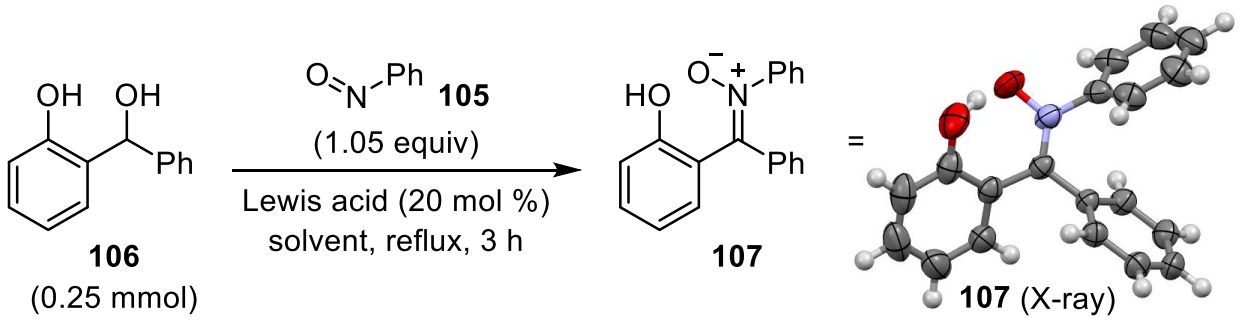
It has been established that the nitrogen atom of the nitroso functionality is electrophilic compared to the oxygen, as seen in nitrone forming reactions involving nitrosobenzenes[62]. However, an equilibrium between nitrosobenzene and its hydrate form exist in water through solvation, which may liberate the nitrogen lone pair[3]. This umpolung process would create a more nucleophilic nitrogen without changing its oxidation state in the nitroso functionality[63]. We postulated that if the transient hydrated species can exist for enough time to act as a nucleophile in the presence of a sufficiently electrophilic carbon source, this may be a viable new method to access *N*-aryl nitrones.

1.2.1 Optimization of Nitrone Forming Reaction.

We began our optimization with the conversion of benzyl alcohol **106** to nitrone **107**, as we believed this would be a sufficiently electrophilic carbon source in situ, in the presence of a Lewis acid. This process was optimized using 1.05 equivalents of commercially available nitrosobenzene **105**, so that reaction completion can be monitored by disappearance of the alcohol by TLC. We began this investigation by screening various Lewis acids using benchtop wet DCM as the solvent at reflux. This transformation turned out to be remarkably robust with various different Lewis acid catalysts at 20 mol %. Several Lewis acids gave moderate to good yields (Entries 1-4, Table 4) with $Yb(OTf)_2$, $Zn(OTf)_2$ and $CuBr_2$ (Entries 5-7, Table 4) resulting in comparable yields of **107** all over 80 %. Of these three Lewis acids, $CuBr_2$ gave the best yield

without the deliquescent nature of $Zn(OTf)_2$, while also being less expensive than $Yb(OTf)_2$. Interestingly, CuBr (Entry 8, Table 4) did not yield any desired product by TLC, and decreasing the catalyst loading to 10 mol % $CuBr_2$ (Entry 9, Table 4) was detrimental to yield. The requirement of a metal catalyst was tested in Entry 10 where the reaction was done in the absence of a metal additive and no reaction occurred. With $CuBr_2$ selected as the best Lewis acid, a solvent screen was carried out, however, no improvement was seen with a variety of solvents used (Entry 11-18) (see supporting information for full optimization). The structure of nitrone **107**, was confirmed by NMR and X-ray crystallography (Table 4).

Table 4. Optimization of nitrone formation.

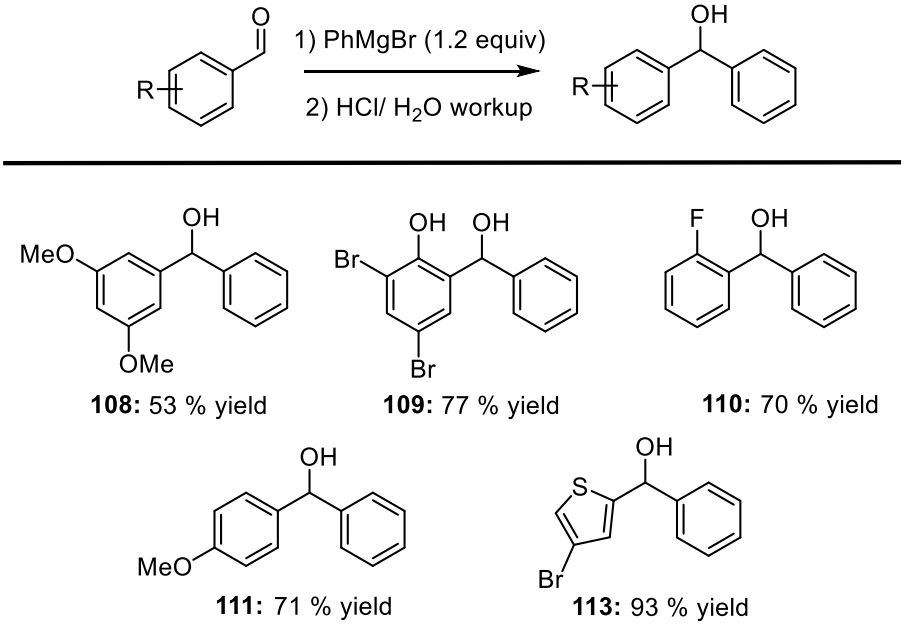


Entry	Solvent	Lewis Acid	Cat. Loading (mol %)	Yield (isolated)
1	DCM	$Sc(OTf)_3$	20	55
2	DCM	AgOTf	20	62
3	DCM	$Bi(OTf)_3$	20	63
4	DCM	$FeCl_3 \cdot 6H_2O$	20	74
5	DCM	$Yb(OTf)_2$	20	80
6	DCM	$Zn(OTf)_2$	20	81
7	**DCM**	**$CuBr_2$**	**20**	**82**
8	DCM	CuBr	20	NR
9	DCM	$CuBr_2$	10	51
10	DCM	Metal Free	-	NR
11	HFIP	$CuBr_2$	20	79
12	DCE	$CuBr_2$	20	77
13	MeCN	$CuBr_2$	20	74
14	THF	$CuBr_2$	20	69
15	$CHCl_3$	$CuBr_2$	20	66
16	MeOH	$CuBr_2$	20	16
17	Dioxane	$CuBr_2$	20	NR
18	Toluene	$CuBr_2$	20	Trace

1.2.2. Substrate Scope.

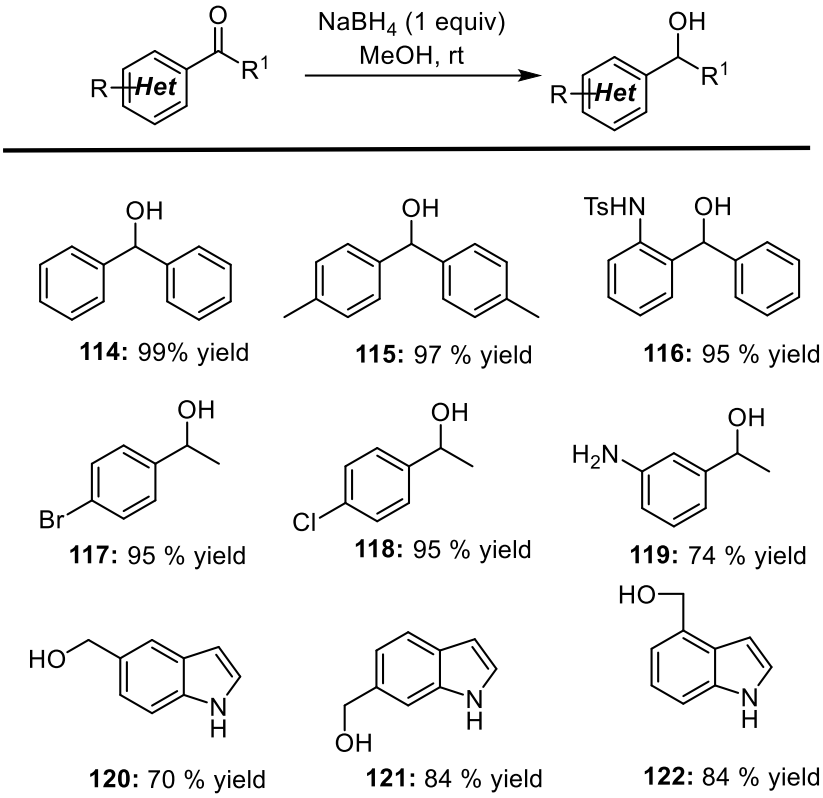
With optimized conditions from Table 4, we set out to study the scope of this reaction. Two common ways of making the benzylic alcohol starting materials required are by addition of organometallic nucleophiles to aldehydes, or by reduction of benzaldehydes and acetophenones to the corresponding alcohols. Our first plan was to react various benzaldehydes with phenyl magnesium bromide to acquire the corresponding biaryl benzyl alcohols (Table 5).

Table 5. Synthesis of unsymmetrical biaryl starting materials through Grignard reactions.



Additionally, we wanted to include various heterocycles, primary and secondary benzyl alcohols which could be made by treating the precursor aldehydes or ketones with sodium borohydride (Table 6). The starting materials for these compounds were commercially available benzaldehydes and acetophenones.

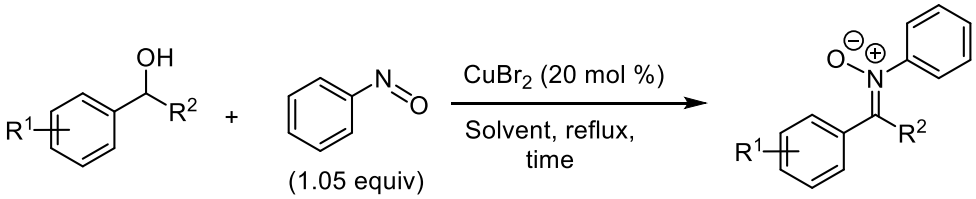
Table 6. Synthesis of benzyl alcohol starting materials by sodium borohydride reduction.

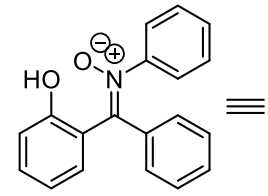


In early investigations of the substrate scope, the alcohol starting materials of substrates **124** and **125** (Table 7) would persist on TLC after long reaction times. To combat this, we changed solvents to the next best option, HFIP, and both reactions were complete in 4 and 14 hours respectively. As a result, HFIP became the favored solvent for all other examples. Substrate **107** was made as the cis isomer exclusively due to the 7 membered intramolecular hydrogen bond between the *o*-phenol and nitrone oxygen, as seen in the crystal structure. Compound **125** was also formed as the cis isomer exclusively due to this intramolecular hydrogen bond, while **129** was formed in >20:1 cis/trans isomers by NMR (Table 7). Interestingly, compound **130** was formed exclusively as a single isomer. Symmetrical systems such as **124** and **126** could only result in one isomer of nitrone as did the aldonitrones **127** and **134,** likely due to steric hindrance of the nitrosobenzene attack (Table 7). The yield of substrate **127** was substantially higher than **134** due to the electronics favoring carbocation stability from the *o*-methoxy compared to the 2-

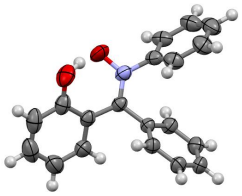
furanmethanol (Table 7). Unsymmetrical biaryl systems **128**, **131**, and **132** produced cis/trans isomers of nitrones in approximately 1:1 ratios (See supporting information).

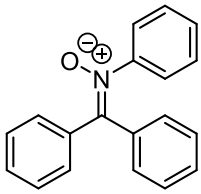
Table 7. Benzyl Alcohol Substrate Scope.



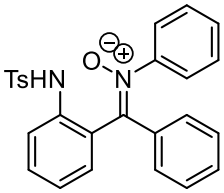


107: HFIP: 79%, 3 h
DCM: 82%, 3 h

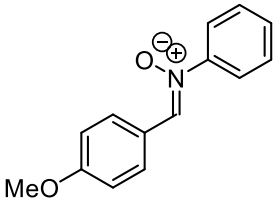




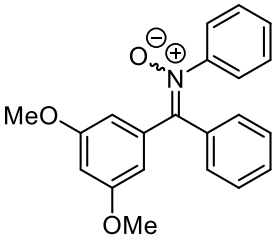
124: HFIP: 89%, 4 h
DCM: incomplete, 24 h



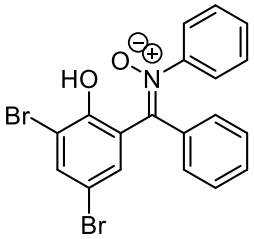
125: HFIP: 62%, 14 h
DCM: incomplete 24 h



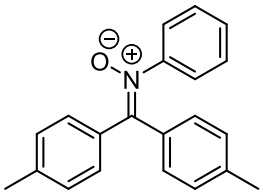
127: 78%, 4 h



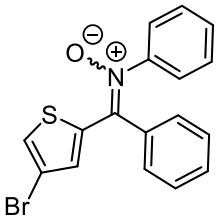
128: 65%, 1.5 h (1.5:1)



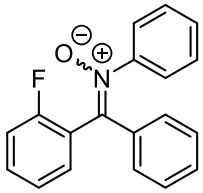
129: 72%, 14 h (>20:1)



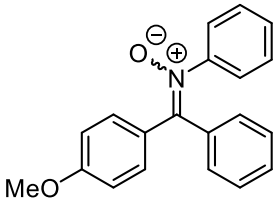
126: 75%, 1.5 h



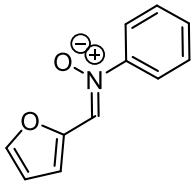
130: 75%, 3 h (1.5:1)



131: 73%, 2 h (1.5:1)



132: 82%, 1.5 h (1.5:1)

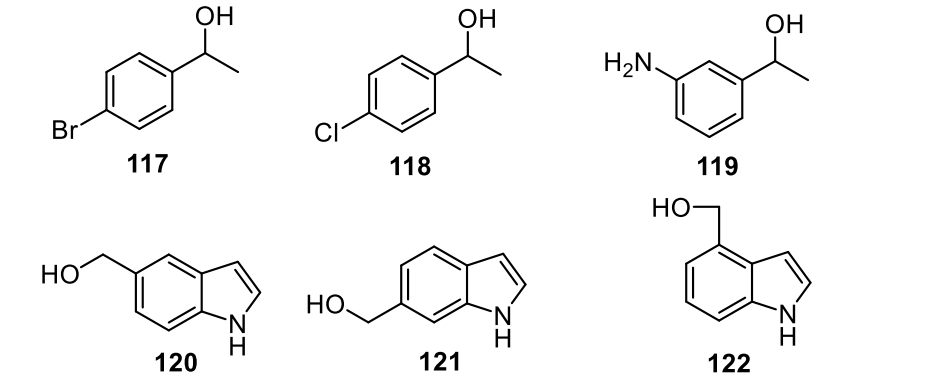


134: 8%, 5 h

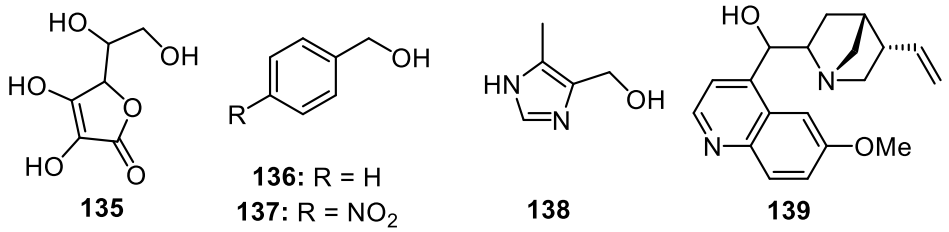
Without sufficiently electron rich substrates capable of stabilizing sufficient positive charge on the benzylic carbon, this reaction will not work. Thus, several alcohol starting materials that were made for this substrate scope (Table 8) turned out to be ineffective in this chemistry.

Table 8. Benzylic alcohols that were unable to afford desired nitrones.

Synthesized starting matrials that could not produce nitrones:

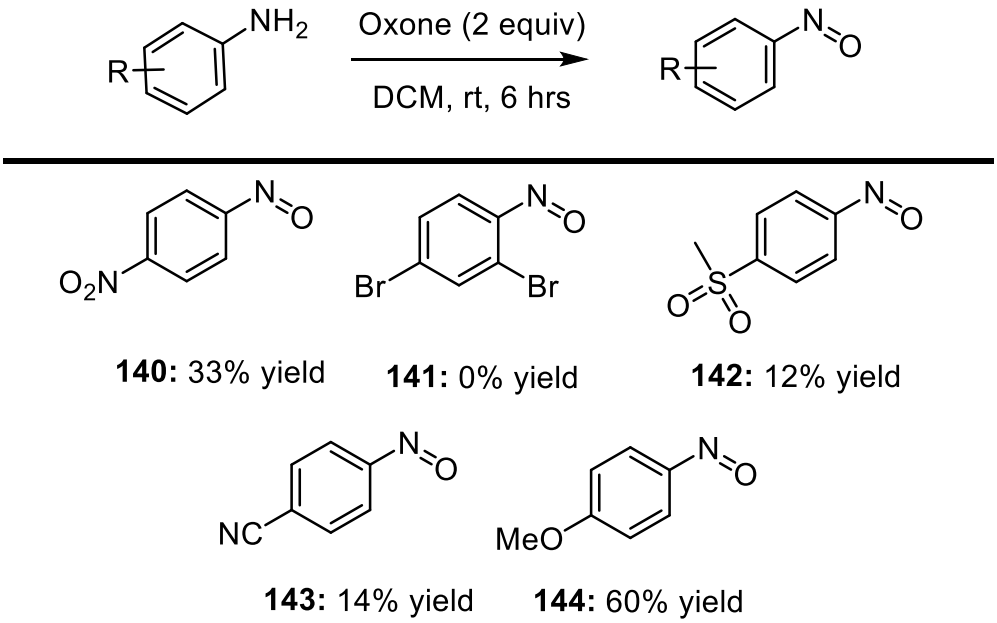


Commercially available starting matrials that could not produce nitrones:



We next set out to explore the functional group tolerance of nitrosobenzenes. A common procedure to make nitrosobenzenes is by oxidation of anilines using Oxone (Table 9)[64].

Table 9. Synthesis of nitrosobenzenes from anilines by Oxone oxidation.

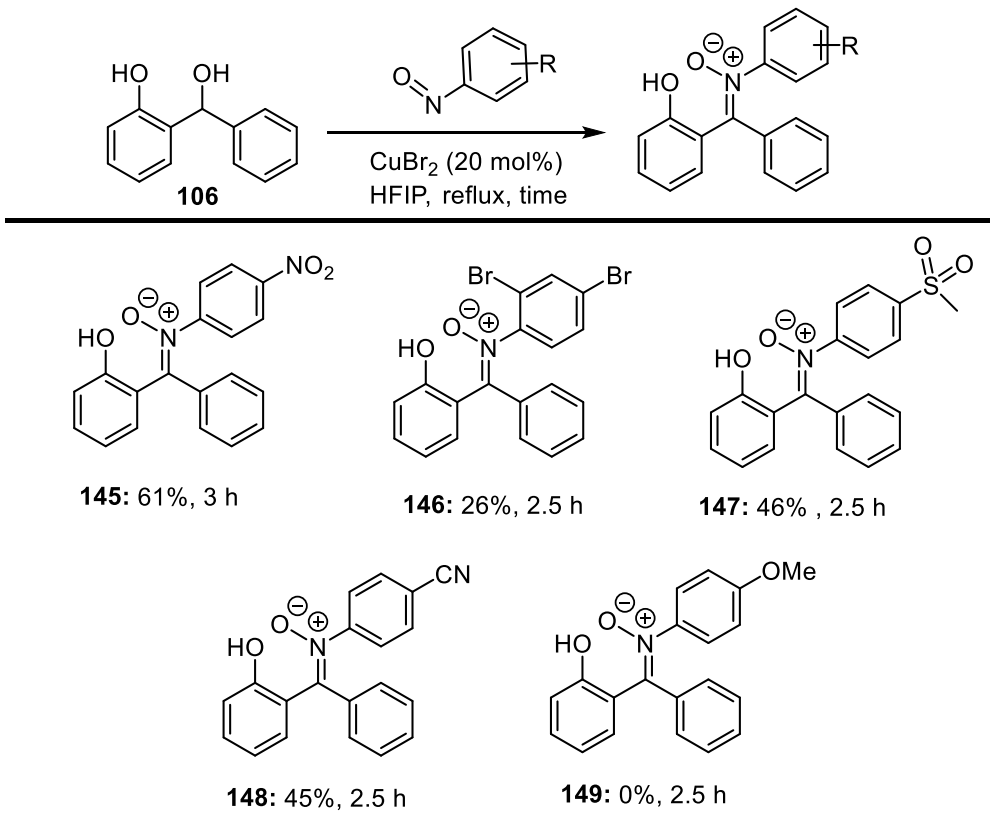


140: 33% yield **141:** 0% yield **142:** 12% yield

143: 14% yield **144:** 60% yield

Due to the hydrogen bonding observed with the *o*-phenol in substrate **107** above, we decided to continue with benzyl alcohol **106** in order to get cis isomers selectively from the reactions. We also continued with HFIP for these substrates to stay consistent with Table 8. Moderate yields were observed in these examples when *p*-electron withdrawing groups were present on the nitrosobenzenes as seen in examples **145**, **147** and **148** (Table 10). The yield decreased in substrate **146** with the *o*-bromine likely providing steric hindrance to the nitroso functionality, and no detectable conversion of **149** was seen on TLC (Table 10).

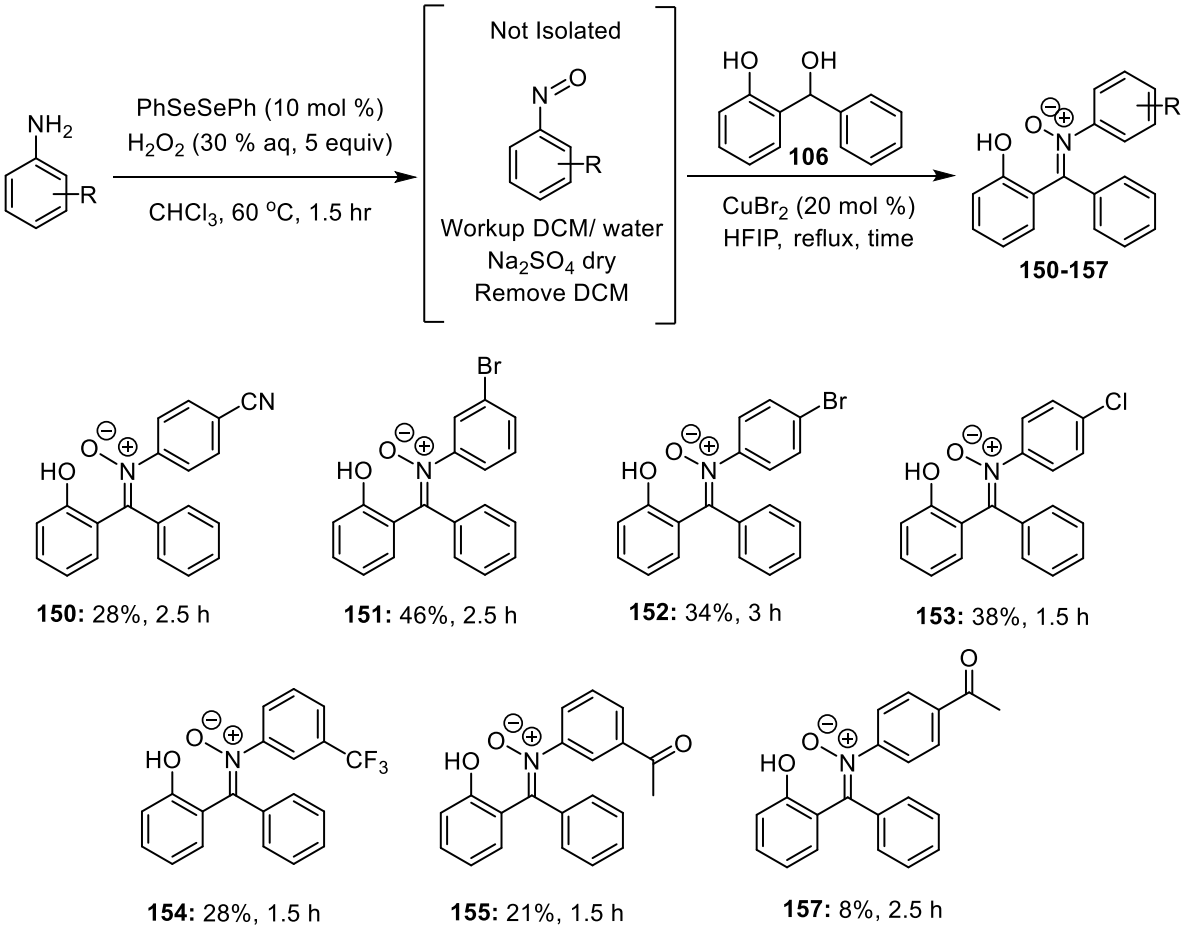
Table 10. Nitrosobenzene substrate scope with isolated nitrosobenzenes.



Nitrosobenzenes used in Table 10 came from commercially available aniline starting materials that had been oxidized with excess Oxone[64]. Due to the large molecular weight of Oxone, and its excess stoichiometric requirement, we sought after a way to make this process more step, and atom economical through one pot reactions where anilines could be oxidized selectively to nitrosobenzenes and subsequently reacted with benzyl alcohols. Using previously reported conditions[65], we were able to make nitrones using a one pot process with substituted nitrosobenzenes formed in a prior step by oxidation of anilines with catalytic diphenyl diselenide and hydrogen peroxide (Table 11, see supporting information). This strategy greatly increases the diversity of the N-aryl component since substituted anilines are readily commercially available as opposed to nitrosobenzenes. The yield of substrate **150** (Table 11) decreased from 45 to 28% using this one pot method compared to **148** (Table 11) when pure nitrosobenzene was used. Compound

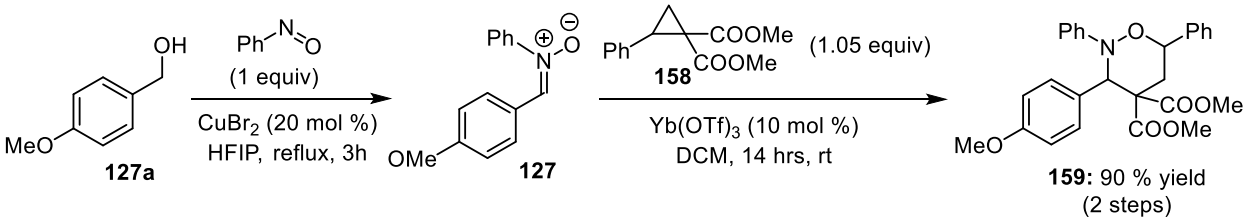
151 with a *m*-bromine (Table 11) was obtained in good yield compared to the examples with pure nitrosobenzenes in Table 11 while *p*-bromine and *p*-chlorine (**152** and **153** respectively, Table 11) were formed in moderate yield comparatively. The yields of *m*-substituted substrates (**154** and **155**, Table 11) were modest**.** Compound **157** with the *p*-acetyl was the only poorly yielding substrate with respect to the one pot process.

Table 11. One pot Nitrone reactions with nitrosobenzenes formed in situ from anilines.



In addition to two step, one pot processes where the nitrone was made in the second step, we also wanted to explore the possibilities of further modifications of the nitrone following its synthesis in one pot. We applied a procedure demonstrating a nitrone, cyclopropane [3+3]

annulation reaction[24] following our nitrone formation, and the [3+3] adduct was isolated in 90% yield over 2 steps (Scheme 25). This result suggests that the nitrones may be forming in higher yields than are being isolated, and potentially degrading on silica during purification, since nitrone **127** used in this sequence was isolated in 78% yield compared to the 90% isolated of **159**, a potentially more stable compound, over 2 steps.

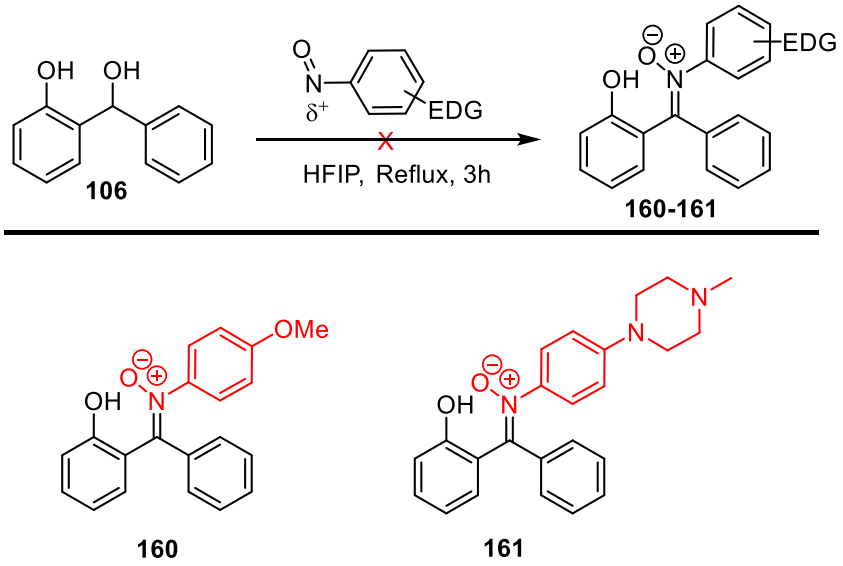


Scheme 25. One pot reaction with further modification to nitrone product.

1.2.3. Mechanistic Studies.

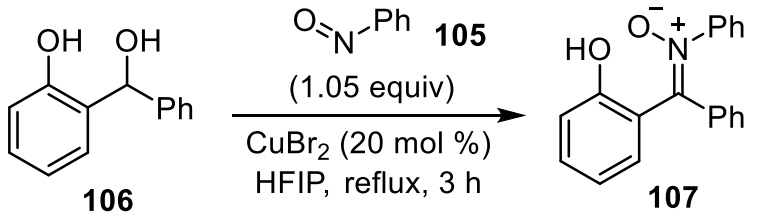
Further investigation was required to confirm that the nitroso functionality was being hydrated and acting as a nucleophile. An electronic trend observed in the nitrosobenzene scope was that electron rich nitrosobenzenes were unable to undergo these transformations, likely due to the fact that they are not as effectively hydrated as those that are electron poor (Table 12). Our working hypothesis for this observation is that electron density from ring substituents is diminishing the electrophilicity of the nitrogen inhibiting the formation of the reactive umpolung species.

Table 12. Electron rich nitrosobenzenes do not react to form nitrones under standard conditions.



To verify the requirement of water in this process, the reaction was done in dry dichloromethane with various amounts of water as an additive (Table 13). In the presence of 4 Å Molecular sieves, no product was observed by TLC (Entry 1, Table 13) while 10 % water also resulted in no reaction (Entry 2, Table 13). However, between 5% and 1% water added by volume slightly improved isolated yield with 84% and 83% respectively, and 0.5% improved yield to 89% (Entries 3-5, Table 13). We rationalize that, in excessive amounts, water is outcompeting the nitroso hydrate nucleophile resulting in a non-productive pathway. Nitroso compounds are known to do radical chemistry[62], however, Entry 6 in Table 13 demonstrates that the reaction is unaffected by the addition of 5 equivalents of BHT.

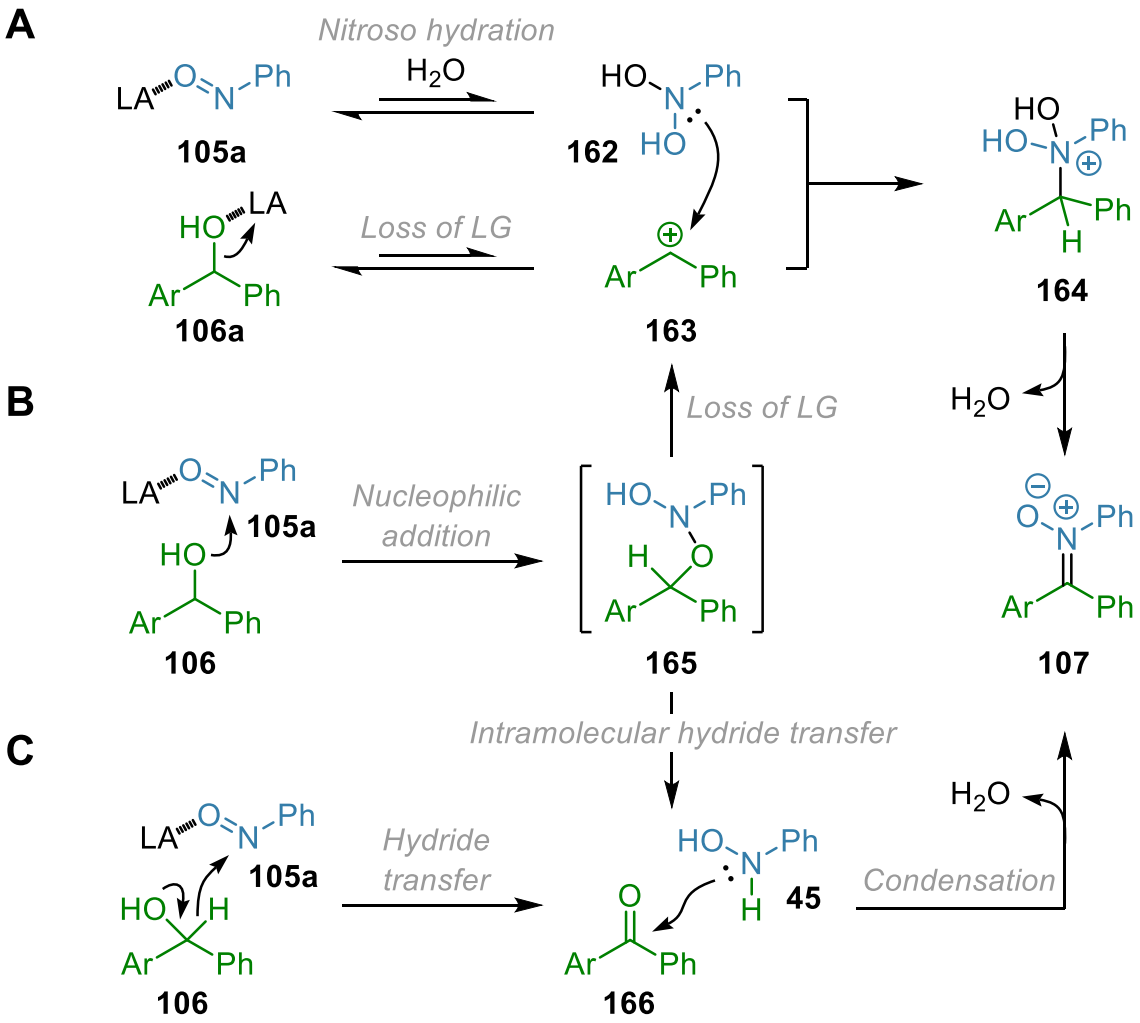
Table 13. Mechanistic studies to show the dependence of water and the dismissal of a potential radical intermediate.



Entry	Additive	yield
1	4 Å MS	NR
2	H_2O (10% vol)	NR
3	H_2O (5% vol)	84
4	H_2O (1% vol)	83
5	H_2O (0.5% vol)	89
6	BHT (5 equiv)	81

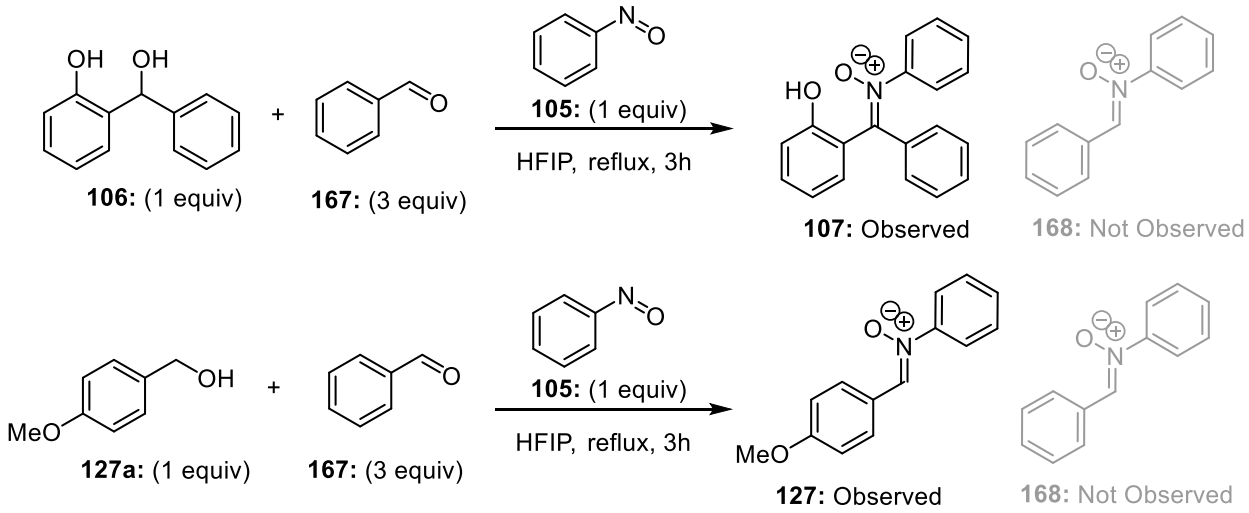
With confirmation of the requirement of water and electronic trends of both benzyl alcohols and nitrosobenzene we set out to study the mechanism of this reaction. Due to the wide range of Lewis acids that were effective in this transformation (Table 4) it is likely that the copper species is only acting as a Lewis acid, rather than participating in a more involved catalytic cycle. Three possible pathways that this reaction could go through are shown in scheme 26. In pathway A (Scheme 26), the nitrosobenzene and benzyl alcohol each interact with copper (ll) bromide as a Lewis acid in separate processes, whereby departure of the benzyl alcohol is assisted by the Lewis acid to form **163**, and nitrosobenzene hydrolysis is Lewis acid mediated to form **162**. Both of these transformations happen in equilibrium but the products are capable of reacting to form **184** in a productive step that can be subsequently oxidized to a stable nitrone. Pathway C (Scheme 26) involves a Lewis acid mediated hydride transfer where **105a** acts as an oxidizing agent that becomes reduced to hydroxylamine **45** as alcohol **106** is oxidized to ketone **166**. After this hydride

transfer, the working mechanism for this transformation would be a condensation reaction between the hydroxylamine and ketone. Another option would be pathway B (Scheme 26) where copper (II) bromide coordinates with the nitrosobenzene to make compound **105a** with a more electrophilic nitrogen that alcohol **106** is able to attack and form intermediate **165**. This intermediate could feed into either pathway A or C via a loss of leaving group or intramolecular hydride shift respectively.



Scheme 26. Potential mechanistic pathways.

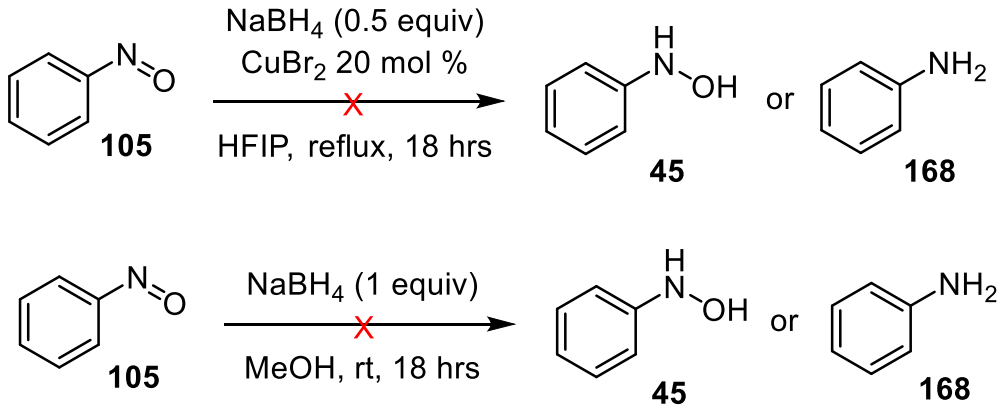
To rule out pathway C, competition experiments were done in the presence of three equivalents of benzaldehyde, as the more electrophilic aldehyde would be expected to react with the hydroxylamine faster than the resulting ketone or *p*-methoxy benzaldehyde product of the redox step (Scheme 27). Analysis of the crude reaction mixture by low resolution mass spectrometry indicated that the exact masses of the expected ketonitrone **107** and *p*-methoxy benzyl nitrone **127** were the only observed products in their respective reactions, and not the aldonitrone from condensation with benzaldehyde.



Scheme 27. Competition experiments addressing the possibility of a redox hydride transfer between the nitroso and benzyl alcohol reagents.

In addition to these competition experiments, control reactions were done in attempts to reduce nitrosobenzene using sodium borohydride as a more reactive hydride species. It was surprising to us that this was not a reported method of reducing nitroso functionalities to hydroxylamines or anilines, and reducing metals are commonly used instead of hydride reagents. In one control experiment, nitrosobenzene was treated with 0.5 equivalents of sodium borohydride as well as 0.2 equivalents of copper (II) bromide and refluxed for 18 hours in HFIP. The second control attempted to reduce nitrosobenzene using more standard reduction conditions

of 1 equivalent of sodium borohydride in methanol at ambient temperature for 18 hours (Scheme 28). Neither of these experiments appeared to result in any change by TLC, and the nitrosobenzene seemed to be inert in these conditions.

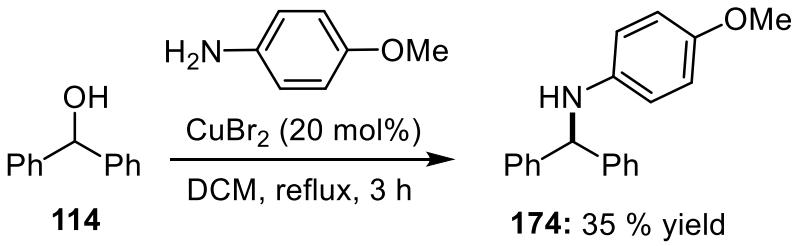


Scheme 28. Control experiments of nitrosobenzene reduction be sodium borohydride.

Mechanistic studies suggest that the working mechanism of this transformation must be pathway A, or pathway B through loss of hydroxyl leaving group rather than intramolecular hydride shift (Scheme 26) since the presence of hydroxylamine is unlikely as shown by competition experiments. We propose that $CuBr_2$ acts as a Lewis acid to assist departure of the benzyl alcohol **106** in either an S_N1 like process where carbocation **163** is stabilized, or by departure of nitroso hydrate as a leaving group whereby the nitroso hydrate intermediate **165** feeds into pathway A. From this stage, oxidation to nitrone **107** is the driving force as it is a stable functionality, and the only productive pathway.

To further support the possibility of a nitroso hydrate attacking a carbocation, we set out to trap the carbocation situ. To do this, 4-anisidine was used as the nucleophile in place of a nitrosobenzene with otherwise standard conditions. The result of this experiment was the isolation

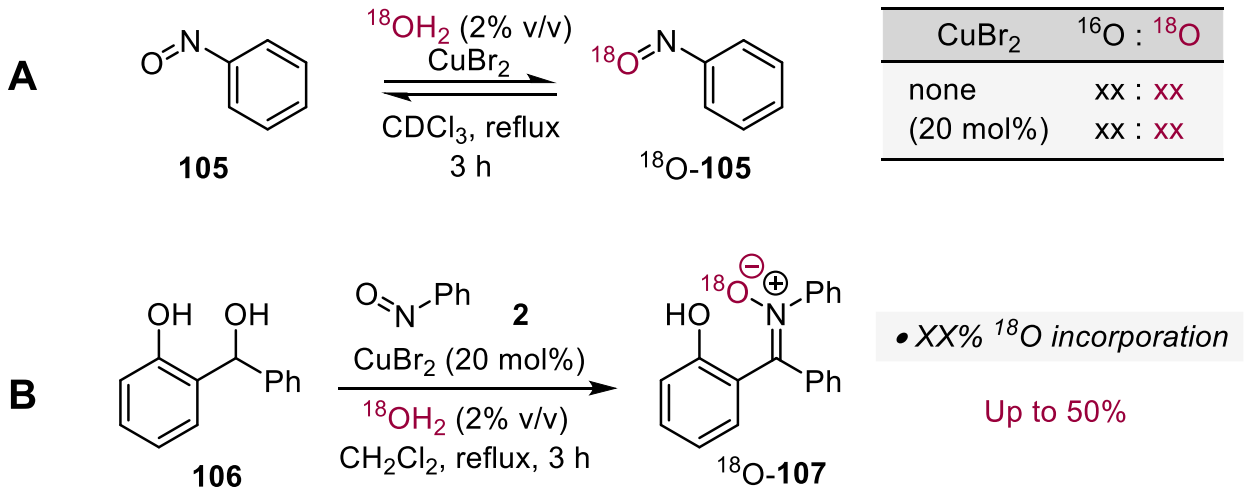
of compound 174 after column chromatography in a 35 % yield, comparable to other nitrosobenzene derivatives.



Scheme 29. Trapping of carbocation with 4-anisidine

1.2.3. Conclusions and Future Work

Although our experimental evidence supports our hypothesis of a nitroso hydrate nucleophile, further mechanistic studies must be done to unequivocally state this is the case. We are planning on conducting labelling experiments with $^{18}OH_2$ in attempts to incorporate oxygen 18 into the nitrosobenzene and, therefore prove that this exchange is taking place (Scheme 29). It is our expectation that both in nitrosobenzene equilibrium with heavy water (Scheme 29, A) and the reaction with heavy water as an additive in 2% by volume (Scheme 29, B), ^{18}O will be incorporated into the products, as supported by the water studies in Table 14. These studies should also indicate whether or not copper (II) bromide is required for the hydration of nitrosobenzene to occur. If copper (II) bromide does not have any effect on ^{18}O incorporation into nitrosobenzene, it likely only coordinates with the benzyl alcohol to assist its departure while the hydration happened independently resulting in the umpolung species.



Scheme 29. ^{18}O labelling experiments to demonstrate hydration equilibrium

In summary, we have developed a new preparation of *N*-Aryl Nitrones from benzyl alcohols through an unprecedented reaction pathway utilizing in situ generated nitroso hydrate nucleophiles. We demonstrated that the conditions of this reaction are compatible in one pot processes with either oxidative nitrosobenzene synthesis preceding the nitrone step, or subsequent reaction of the newly formed nitrone in a [3+3] annulation reaction. This process improves step and atom economy of known *N*-Aryl nitrone forming reactions and offers an alternative approach to nitrone synthesis.

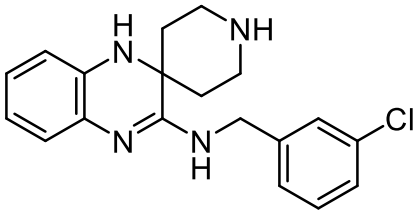
Chapter 2: Liproxstatin-1; A Chemical Probe of the Gram-negative Outer Membrane. Summary of Published Results.[66]

2.1. Background.

With over 250 000 cases of resistant bacterial infections reported, and more than 5 400 directly causing Canadian deaths in 2018, we are currently facing an antibiotic crisis[67]. A particularly worrying class of resistance involves Gram-negative bacteria, as their highly

impermeable outer membrane poses added complexity to their evolved resistance mechanisms[68]. The outer membrane restricts the chemical matter able to cross, making the bacteria intrinsically resistant to small molecule antibiotics and other compounds which may have intracellular targets[69],[70]. This barrier is therefore a major bottleneck for cellular mechanistic studies and compound mechanism of action, as these small molecules cannot gain entry to the cell. To circumvent this issue, outer membrane permeabilizing compounds must be discovered so that these systems can be more effectively studied. Commonly used membrane active compounds such as colistin and its derivatives, interact with both the outer and inner membranes of Gram-negative bacteria, and are toxic to cells[71]. Therefore, molecules that are outer membrane selective and nontoxic to Gram negative bacteria would be useful tools to expedite the study of biological systems.

In an effort to discover compounds capable of selectively perturbing the outer membrane of Gram-negative bacteria, the Brown lab developed a screening platform to enrich for non-lethal molecules capable of sensitizing these bacteria to otherwise impermeable compounds[72]. They leveraged this screening tool and preformed a library screen of approximately 140 000 diverse synthetic compounds in order to find probes for the outer membrane of Gram-negative bacteria[66]. Of the 39 active compounds, 17 were verified, and one of the best molecules found was an analog of commercially available liproxstatin-1 (Figure 4)[66].



2-1: Liproxstatin

Figure 4. Structure of spiroquinoxaline liproxstatin-1

Liproxstatin-1 was able to potentiate of a variety of large scaffold antibiotics in various Gram-negative bacteria that would otherwise not be susceptible to these compounds due to outer membrane permeability issues[66]. E.coli, a common model for Gram-negative bacteria became increasingly sensitized to linezolid, erythromycin, novobiocin and rifampicin in a dose dependant manner as a function of liproxstatin-1 concentration (Figure 5)[66].

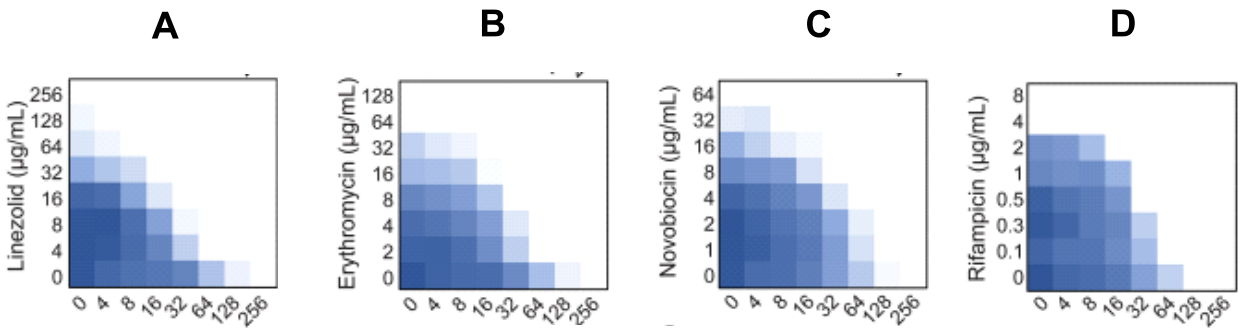


Figure 5: Potentiation effect of liproxstatin-1 on Linezolid (A), Erythromycin (B), Novobiocin (C), and Rifampicin (D) against E. coli. Blue indicates cell growth, white indicates absence of cell growth, liproxstatin-1 is on the X-axis and the antibiotic on the Y-axis.

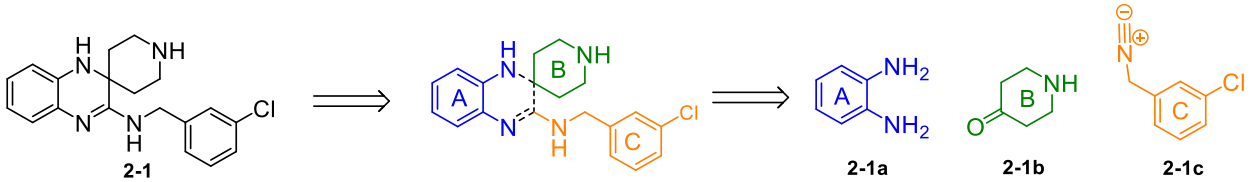
It was found that liproxstatin-1 affects this susceptibility by physically disrupting the outer membrane through interactions with a key building block, lipopolysaccharide, while exhibiting minimal interaction with the inner membrane[66].

2.2. Results and Discussion.

2.2.1. Synthesis of Liproxstatin-1 Analogs.

This observed affinity to the outer membrane by liproxstatin-1 encouraged us to benchmark it as a lead compound and initiate a medicinal chemistry effort to study the effects of scaffold changes on its potentiation. We found that spiroquinoxaline compounds and their derivatives are

readily accessible using a three component reaction (3CR) between an *o*-phenylenediamine, a benzyl isocyanide and a carbonyl derivative (Scheme 30)[73].

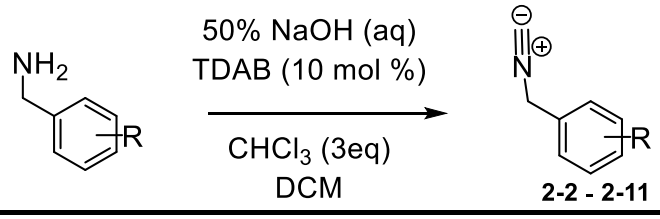


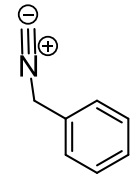
Scheme 30. Liproxstatin-1 retrosynthesis

When planning analog development, rings B and C were identified as the most convenient building blocks to modify, as non-symmetrical ring A substituents may result in mixtures of regioisomers that would be difficult to separate. Ring B components come from carbonyl derivatives such as commercial ketones or aldehydes while ring C isocyanides can be made in 1 step from commercial benzylamines.

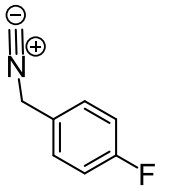
The procedure to make benzyl isocyanides was modified from a published method using a quaternary ammonium salt as an ionic liquid and large excess of base[74]. Instead of using Aliquot 336 as an ionic liquid, we used catalytic tetradecyl ammonium bromide instead to make a small library of isocyanides from benzylamines (Table 14).

Table 14. Synthesis of benzyl isocyanides from substituted benzylamines

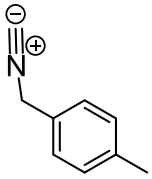




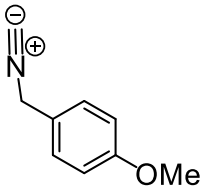
2-2: 12% Yield



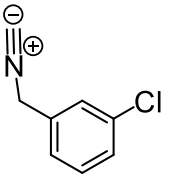
2-3: 19% Yield



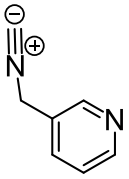
2-4: 41% Yield



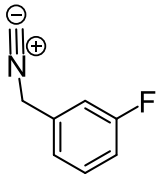
2-5: 61% Yield



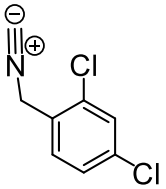
2-6: 20% Yield



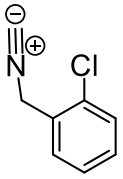
2-7: 10% Yield



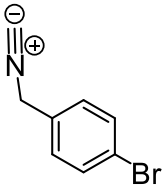
2-8: 29% Yield



2-9: 57% Yield



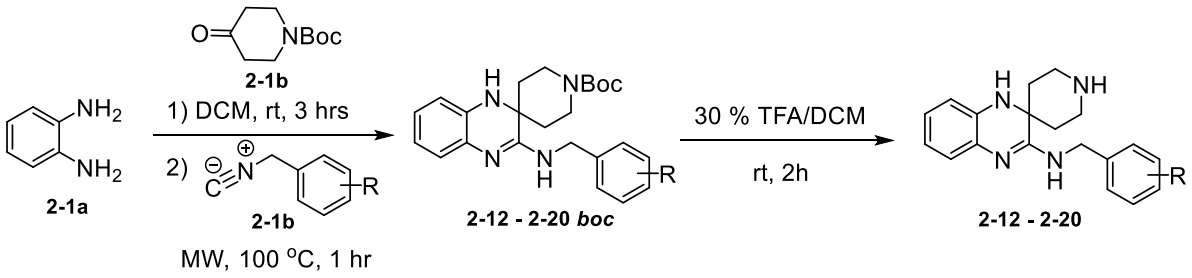
2-10: 51% yield

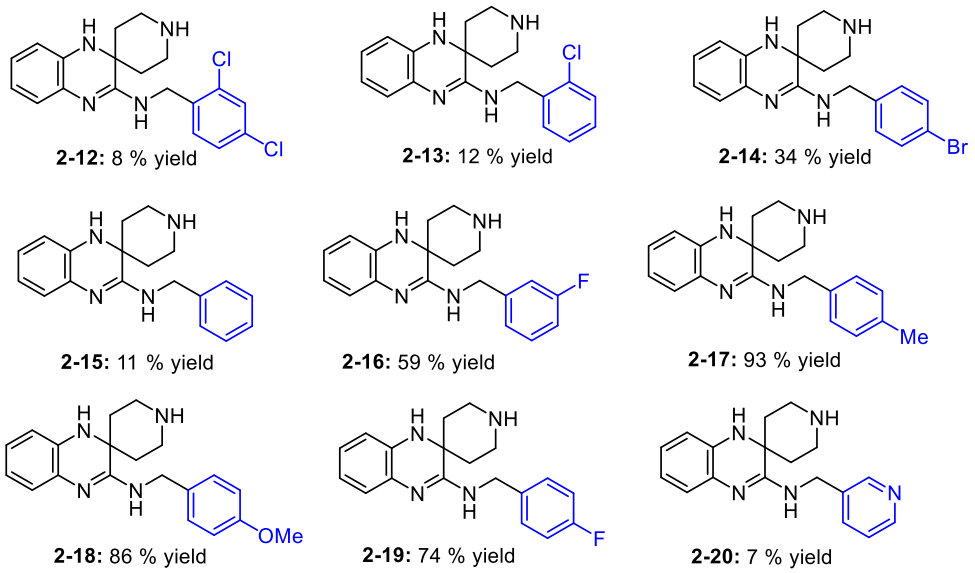


2-11: 32% Yield

With the desired Benzyl isocyanides in hand, we set out to make liproxstatin-1 analogs with variations on ring C. It was found that none of the reaction conditions described in literature were able to form any desired 3 component product, as the various acids used in these methods would remove the Boc from the B ring and result in complicated reaction mixtures [73],[75]. Instead, the imine had to first be formed in DCM from the o-phenylenediamine and ketone followed by addition of the isocyanide and reaction in the monowave at 100 ^{O}C for 1 hour. These reaction mixtures could then be subject to column chromatography. In most cases, the 3CR product would co-elute with the imine since this reaction seldom went to completion, however, the mixture could be subject to Boc deprotection conditions and pure amines could be isolated (Table 15, See supporting information).

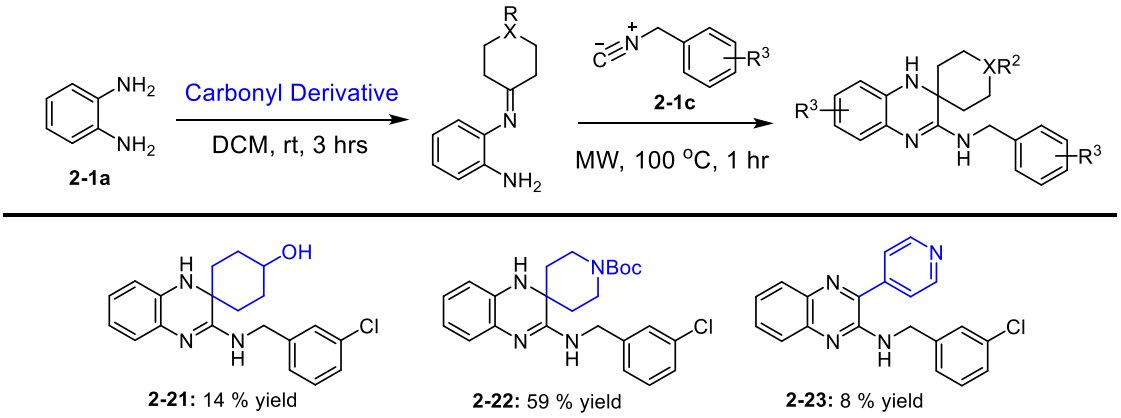
Table 15. Synthesis of liproxstatin-1 analogs with various C ring substituents





Ring B analogs were made with a similar sequence as shown in Table 16 but without the Boc removal step. For these compounds various carbonyl derivatives were employed to study the effects of the presence and position of the basic nitrogen (Table 16).

Table 16. Synthesis of liproxstatin-1 with various B ring substitutions



2.2.2. Biological Evaluation of Liproxstatin-1 Analogs.

Liproxstatin-1 was originally tested for synergy with rifampicin, a narrow spectrum antibiotic with sub lethal accumulation in Gram-negatives due to poor permeability[76]. Synergy was confirmed using E. coli as a Gram-negative model in checkerboard broth microdilution assays. Despite having a high MIC, lipiroxstatin-1 was able to potentiate the activity of several poorly permeable antibiotics to a variety of different Gram-negative bacteria (figure 5 and 6)[66].

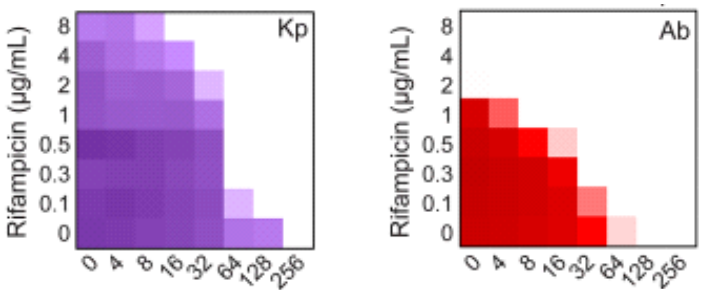


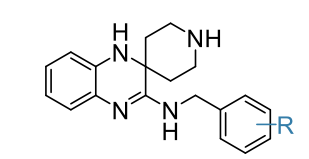
Figure 5. Liproxstatin potentiating the activity of rifampicin in Gram-negative bacteria K. pneumoniae (purple) and A. baumannii (red)

This observed potentiation of narrow spectrum Gram-positive targeting antibiotics is caused by outer membrane disruption of Gram negative cells. Selective targeting of the outer

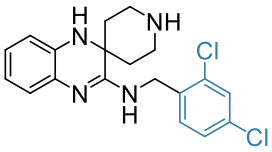
membrane is a result of high affinity of liproxstatin-1 with lipopolysaccharide (LPS), a major component of the outer membrane. The affinity of Liproxstatin-1 and its analogs to LPS was confirmed by the observation that the ability of these compounds to synergize these large scaffold antibiotics was suppressed by the addition of exogenous LPS. Synergistic effects of the potentiating compounds was measured by a fractional inhibitory concentration index (FICI), whereby the sum of FICs for the two compounds being tested, antibiotic and potentiator, is indicative of the degree of potentiation. FICI values ≤ 0.5 are considered synergistic.

Linezolid was chosen as the partner antibiotic for liproxstatin-1, rather than rifampicin, as it showed a stronger synergy in the checkerboard assay, with an FICI of 0.19 compared to 0.38 (Figure 6; A vs D). First, modification of ring C resulted in slight reduction in potentiation activity relative to liproxstatin-1 for seven analogues (**2-12** - **2-14**, **2-16** - **2-19**) and complete loss in potentiation activity for compound **2-15** (Table 17). The loss of synergy by compound **2-15** indicates that chlorine atoms of both liproxstatin-1 and **2-12** have a beneficial effect on this activity. Complete loss potentiation was observed for the pyridine-containing derivative (**2-20**) (Table 17). Similarly, three modifications to ring B of the spiroquinoxaline scaffold of liproxstatin-1 all resulted in complete loss of antibiotic potentiation (**2-21** - **2-23**). All of the compounds with FICI values ≤ 0.5 and potentiation concentrations lower than their respective MICs were tested for IM activity. Compound **2-12**, which was the most potent analogue alone, had relatively strong IM activity at 16 μg/mL (Table 17). Four compounds (**2-16** - **2-19**) had no detectable IM activity at the highest concentration tested (>128 μg/mL). Of these, compound **2-17** was the most potent potentiator of linezolid (Table 17). Individual checkerboards are shown in supporting information.

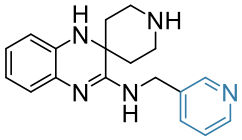
Table 17. Potentiation and inner membrane activity of Liproxstatin-1 analogues in E. coli BW25113



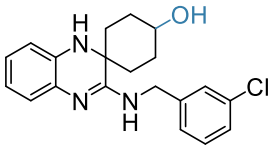
Liproxstatin-1: R = 3-Cl
2-13 R = 2-Cl
2-14 R = 4-Br
2-15 R = H
2-16 R = 3-F
2-17 R = 4-Me
2-18 R = 4-OMe
2-19 R = 4-F



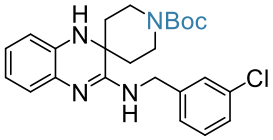
2-12



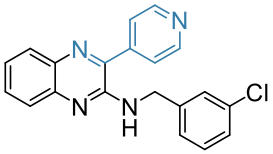
2-20



2-21



2-22



2-23

Compound	MIC (µg/ mL)	FICI	Linezolid [potentiation] (µg/ mL)	[Min] to observe IM activity (µg/ mL)
Liproxstatin-1	256	0.19	32	128
2-12	64	0.31	16	16
2-13	256	0.38	64	64
2-14	128	0.38	32	64
2-15	128	≤ 0.5	128	N/A
2-16	>256	≤0.38	128	>128
2-17	>256	≤0.25	64	>128
2-18	>256	≤0.38	128	>128
2-19	>256	≤0.38	128	>128
2-20	>256	≤0.75	N/A	N/A
2-21	>256	≤1.01	N/A	N/A
2-22	>256	≤1.01	N/A	N/A
2-23	>256	≥2	N/A	N/A

2.2.3. Conclusion

Out of a screen of approximately 140 000 chemically diverse synthetic compounds, it was found that liproxstatin-1 was able to potentiate the activity of the Gram-positive-targeting antibiotics linezolid, novobiocin, erythromycin, and rifampicin against various Gram-negative bacteria. This effect was caused by physical disruption of the outer membrane due to strong affinity for LPS, allowing these conventional antibiotics to accumulate in lethal concentrations inside the cell. Despite the disruption of the outer membrane, it was found that liprostatin-1 could spare the inner membrane, and can be considered a useful chemical probe compared to other cytotoxic membrane active compounds. Unfortunately, none of the synthesized analogs were able to improve the potentiation activity of the original liproxstatin-1 while also sparing the inner membrane, however, this investigation was a success as we demonstrated that the activity of the lead compound can be tuned with various structural changes.

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Supporting Information

Table of Contents

Nitrones Supplementary Information

Synthesis of N-Aryl Nitrones from Nitrosoarenes and Benzylic Alcohols

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Synthetic Experimental Procedures

General Information

Chemical shifts in ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million (ppm) relative to tetramethylsilane (TMS), with calibration of the residual solvent peaks according to values reported by Gottlieb et al. (chloroform: δ_H 7.26, δ_C 77.16; DMSO: δ_H 2.50, δ_C 39.52).[1] When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; sept., septet; dd, doublet of doublets; m, multiplet; br, broad; app., apparent; *gem*, geminal. ^{1}H NMR spectra were acquired at 700 MHz with a digital resolution (Brüker parameter: FIDRES) of 0.993 Hz/point and coupling constants reported herein therefore have uncertainties of ±0.2 Hz. Melting points (mp) are uncorrected. Reactions were carried out at room temperature (rt) if temperature is not specified. Reactions conducted at elevated temperature used an Anton Paar Monowave 50, a conventionally heated synthesis reactor (www.anton-paar.com). Compounds purified by normal-phase flash chromatography used Teledyne Combi*Flash* Rf+ and NextGen 300+ purification systems (www.teledyneisco.com) equipped with pre-packed silica cartridges (either 40–60 μM or 20–40 μM particle size). Reverse-phase chromatographic purifications used a Teledyne Combi*Flash* Rf with pre-packed columns of octadecyl-functionalized (C18) silica gel (40–60 μM particle size). Low-resolution mass spectral (LRMS) measurements were recorded on an Advion Expression CMS Compact Mass Spectrometer (Albany, NY). High-resolution mass spectrometric (HRMS) data was obtained using an Brüker micrOTOF II system with electrospray ionization (ESI) and paired with an Agilent HPLC and UV detector.

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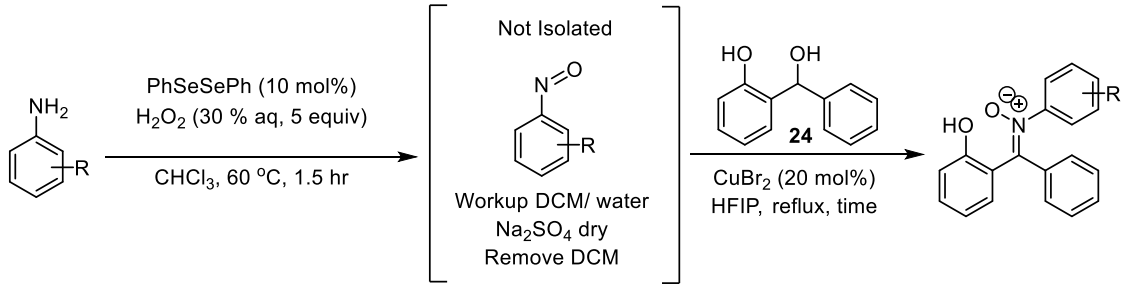
Table 1. Full Optimization of Reaction Conditions

Entry	Solvent	Lewis Acid	Acid Loading	Temp/ TIme	Yield (isolated)
LB.3.123	Toluene	$Sc(OTf)_3$	20 mol%	60 C/ 3 hrs	59
LB.3.124	Toluene	$Bi(OTf)_3$	20 mol%	60 C/ 3 hrs	46
LB.3.125	Toluene	$Zn(OTf)_2$	20 mol%	60 C/ 3 hrs	82
LB.3.126	Toluene	Ag(OTf)	20 mol%	60 C/ 3 hrs	80
LB.3.132	Toluene	$Yb(OTf)_2$	20 mol%	60 C/ 3 hrs	50
LB.3.133	Toluene	$ZnBr_2$	20 mol%	60 C/ 3 hrs	77
LB.3.134	Toluene	BF_3THF	20 mol%	60 C/ 3 hrs	NR
LB.3.139	Toluene	$Cu(OAc)_2$	20 mol%	60 C/ 3 hrs	NR
LB.3.140	Toluene	$FeCl_3$ $6H_2O$	20 mol%	60 C/ 3 hrs	74
LB.3.141	Toluene	$InBr_3$	20 mol%	60 C/ 3 hrs	84
LB.3.145	Toluene	$ZnBr_2$	1 eq	60 C/ 3 hrs	71
LB.3.146	Toluene	$Pd(OAc)_2$	1 eq	60 C/ 3 hrs	NR
LB.3.147	Toluene	$CuBr_2$	1 eq	60 C/ 3 hrs	84
LB.3.148	Toluene	CuBr	1 eq	60 C/ 3 hrs	NR
LB.3.149	Toluene	$AlMe_3$	1 eq	60 C/ 3 hrs	NR
LB.3.150	Toluene	$SnCl_4$	1 eq	60 C/ 3 hrs	36
LB.3.151	Toluene	$AlCl_3$	1 eq	60 C/ 3 hrs	NR
LB.3.152	Toluene	$Sc(OTf)_3$	10 mol%	60 C/ 3 hrs	74
LB.3.153	Toluene	$Zn(OTf)_2$	10 mol%	60 C/ 18 hrs	trace
LB.3.154	Toluene	Ag(OTf)	10 mol%	60 C/ 3 hrs	73
LB.3.155	Toluene	$FeCl_3 \bullet 6H_2O$	10 mol%	60 C/ 3 hrs	67
LB.3.156	Toluene	$InBr_3$	10 mol%	60 C/ 3 hrs	73
LB.3.157	Toluene	$ZnBr_2$	10 mol%	60 C/ 18 hrs	trace
LB.3.159	Toluene	CSA	20 mol%	60 C/ 3 hrs	43
LB.3.160	Toluene	p-TsOH	20 mol%	60 C/ 3 hrs	36
LB.3.161	Toluene	Meth. sulfonic	20 mol%	60 C/ 18 hrs	trace

LB.3.162	Toluene	TFA	20 mol%	60 C/ 18 hrs	trace
LB.3.163	Toluene	Acetic	20 mol%	60 C/ 18 hrs	trace
LB.3.164	Toluene	Phosphorus/ binap OH	20 mol%	60 C/ 18 hrs	trace
LB.3.165	DCE	Ag(OTf)	20 mol%	60 C/ 3 hrs	75
LB.3.166	DMF	Ag(OTf)	20 mol%	60 C/ 3 hrs	NR
LB.3.167	MeCN	Ag(OTf)	20 mol%	60 C/ 3 hrs	NR
LB.3.168	Dioxane	Ag(OTf)	20 mol%	60 C/ 3 hrs	trace
LB.3.169	THF	Ag(OTf)	20 mol%	60 C/ 3 hrs	trace
LB.3.170	DCM	Ag(OTf)	20 mol%	60 C/ 3 hrs	62
LB.3.171	Hexane	Ag(OTf)	20 mol%	60 C/ 3 hrs	NR
LB.3.172	HFIP	Ag(OTf)	20 mol%	60 C/ 3 hrs	80
LB.3.173	CHCl3	Ag(OTf)	20 mol%	60 C/ 3 hrs	82
LB.3.174	MeOH	Ag(OTf)	20 mol%	60 C/ 3 hrs	trace
LB.3.175-B	Toluene	$CuBr_2$	20 mol%	60 C/ 3 hrs	Trace
LB.3.176	DCM	$CuBr_2$	20 mol%	60 C/ 3 hrs	87
LB.3.177	DCE	$CuBr_2$	20 mol%	60 C/ 3 hrs	81
LB.3.178	CHCl3	$CuBr_2$	20 mol%	60 C/ 3 hrs	70
LB.3.179	HFIP	$CuBr_2$	20 mol%	60 C/ 3 hrs	84
LB.3.180	HFIP	Metal free	20 mol%	60 C/ 3 hrs	NR

One Pot Nitrone Synthesis from Anilines General Method A.



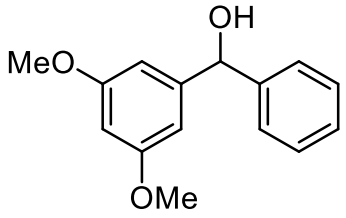
Aniline (0.36 mmol), and diphenyl diselenide (12.0 mg, 0.036 mmol) were dissolved in chloroform (2 mL) and 30% aqueous hydrogen peroxide (0.14 mL, 1.8 mmol) was added. This biphasic solution was stirred at 60 °C for 1 hour or until aniline had been consumed by TLC. Organic phase was removed from

the biphasic mixture, and aqueous was washed with DCM (4 x 2 mL), organics were combined, and dried over sodium sulfate, decanted and concentrated under reduced pressure. The dried residue was combined with benzyl alcohol **24** (60.0 mg, 0.3 mmol), Copper (II) bromide (14.0 mg, 0.06 mmol), taken up in HFIP (2 mL) and refluxed for 2.5 hours or until alcohol starting material was consumed by TLC. Reaction mixture was diluted with DCM (3 mL) and quenched with water (3 mL). The organic layer was separated and aqueous phase was washed with DCM (3 x 1 mL), organics were combined, concentrated and subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex).

One Pot Nitrone Synthesis from Anilines General Method B.

Aniline (0.6 mmol), and diphenyl diselenide (20.0 mg, 0.06 mmol) were dissolved in chloroform (3 mL) and 30% aqueous hydrogen peroxide (0.27 mL, 3 mmol) was added. This biphasic solution was stirred at 60 ^{o}C for 1 hour or until aniline had been consumed by TLC. Organic phase was removed from the biphasic mixture, and aqueous was washed with DCM (4 x 2 mL), organics were combined, and dried over sodium sulfate, decanted and concentrated under reduced pressure. The dried residue was combined with benzyl alcohol 24 (100.0 mg, 0.5 mmol), Copper (II) bromide (22.0 mg, 0.1 mmol), taken up in HFIP (3 mL) and refluxed for 2.5 hours or until alcohol starting material was consumed by TLC. Reaction mixture was diluted with DCM (3 mL) and quenched with water (3 mL). The organic layer was separated and aqueous phase was washed with DCM (3 x 2 mL), organics were combined, concentrated and subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex).

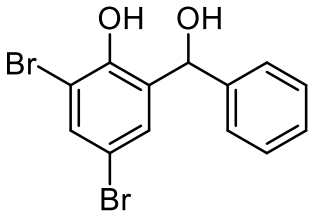
Compound 108



Aldehyde (256.5 mg, 1.5 mmol), was dissolved in 5 mL of dry THF and cooled in an ice bath as phenyl magnesium bromide (1.9 mL, 1.9 mmol) was added dropwise under argon atmosphere. Reaction warmed to room temperature overnight and continued stirring for 18 hours. Reaction mixture quenched with 10 mL aqueous HCl (1 M) and diluted with 10 mL DCM. Aqueous phase was washed with DCM (3 x 5 mL),

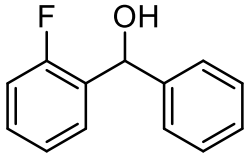
organics were combined and dried over sodium sulfate and concentrated under reduced pressure. Residue was subjected to normal-phase flash chromatography on silica gel (0→30% EtOAc/Hex). Product was isolated as a white solid (192.4 mg, 53% yield). R_f = 0.3 in 30% EtOAc/Hex, visualized with $KMnO_4$ stain. ^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.29 – 7.25 (m, 1H), 6.55 (d, *J* = 2.2 Hz, 2H), 6.36 (t, *J* = 2.3 Hz, 1H), 5.76 (s, 1H), 3.76 (s, 6H). ^{13}C NMR (176 MHz, Chloroform-*d*) δ 161.20, 146.62, 143.86, 128.82, 127.96, 126.85, 104.85, 99.74, 76.57, 55.66.

Compound 109



Aldehyde (274.3 mg, 0.98 mmol), was dissolved in 5 mL of dry THF and cooled in an ice bath as phenyl magnesium bromide (1.08 mL, 1.08 mmol) was added dropwise under argon atmosphere. Reaction warmed to room temperature overnight and continued stirring for 18 hours. Reaction mixture quenched with 10 mL aqueous HCl (1 M) and diluted with 10 mL DCM. Aqueous phase was washed with DCM (3 x 5 mL), organics were combined and dried over sodium sulfate and concentrated under reduced pressure. Residue was subjected to normal-phase flash chromatography on silica gel (0→30% EtOAc/Hex). Product was isolated as a white solid (270 mg, 77% yield). R_f = 0.1 in 20% EtOAc/Hex, visualized with $KMnO_4$ stain. ^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 2.4 Hz, 1H), 7.40 – 7.36 (m, 4H), 7.33 (dq, *J* = 6.1, 2.7 Hz, 1H), 7.24 (s, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 6.01 (s, 1H), 2.83 (s, 1H).

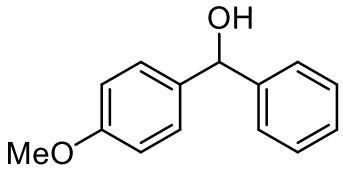
Compound 110



Aldehyde (264.6 mg, 2.1 mmol), was dissolved in 5 mL of dry THF and cooled in an ice bath as phenyl magnesium bromide (2.2 mL, 2.2 mmol) was added dropwise under argon atmosphere. Reaction warmed to room temperature overnight and continued stirring for 18 hours. Reaction mixture quenched with 10 mL aqueous HCl (1 M) and diluted with 10 mL DCM. Aqueous phase was washed with DCM (3 x 5 mL), organics were combined and dried over sodium sulfate and concentrated under reduced pressure. Residue

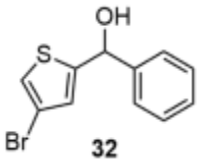
was subjected to normal-phase flash chromatography on silica gel (0→30% EtOAc/Hex). Product was isolated as a white solid (300.5 mg, 70% yield). R_f = 0.5 in 40% EtOAc/Hex, visualized with $KMnO_4$ stain.^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.42 (td, *J* = 7.6, 1.6 Hz, 1H), 7.33 – 7.30 (m, 2H), 7.25 (t, *J* = 7.7 Hz, 2H), 7.20 – 7.13 (m, 2H), 7.06 (td, *J* = 7.5, 1.0 Hz, 1H), 6.93 (ddd, *J* = 10.4, 8.2, 1.0 Hz, 1H), 6.04 (s, 1H), 2.52 – 2.34 (br, 1H). ^{13}C NMR (176 MHz, Chloroform-*d*) δ 160.91, 159.51, 143.14, 131.35 (d, *J* = 12.9 Hz), 129.43, 128.82, 128.02, 126.72, 124.63 (d, *J* = 3.7 Hz), 115.68 (d, *J* = 21.6 Hz), 70.32 (d, *J* = 3.2 Hz).

Compound 111



Aldehyde (260.4 mg, 1.9 mmol), was dissolved in 5 mL of dry THF and cooled in an ice bath as phenyl magnesium bromide (2.0 mL, 2.0 mmol) was added dropwise under argon atmosphere. Reaction warmed to room temperature overnight and continued stirring for 18 hours. Reaction mixture quenched with 10 mL aqueous HCl (1 M) and diluted with 10 mL DCM. Aqueous phase was washed with DCM (3 x 5 mL), organics were combined and dried over sodium sulfate and concentrated under reduced pressure. Residue was subjected to normal-phase flash chromatography on silica gel (0→30% EtOAc/Hex). Product was isolated as a white solid (287.4 mg, 71% yield). R_f = 0.35 in 30% EtOAc/Hex, visualized with $KMnO_4$ stain. ^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.39 – 7.37 (m, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.30 – 7.28 (m, 2H), 7.27 (d, *J* = 1.6 Hz, 1H), 6.88 – 6.86 (m, 2H), 3.79 (s, 3H). ^{13}C NMR (176 MHz, Chloroform-*d*) δ 159.07, 144.04, 136.20, 128.46, 127.93, 127.44, 126.42, 113.90, 75.83, 55.30.

Compound 113



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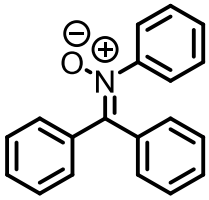
Aldehyde (446 mg, 2.3 mmol), was dissolved in 10 mL of dry THF and cooled in an ice bath as phenyl magnesium bromide (3.9 mL, 3.9 mmol) was added dropwise under argon atmosphere. Reaction warmed to room temperature overnight and continued stirring for 18 hours. Reaction mixture quenched with 10 mL aqueous HCl (1 M) and diluted with 20 mL DCM. Aqueous phase was washed with DCM (3 x 5 mL) and organics were combined and dried over sodium sulfate and concentrated under reduced pressure. Residue

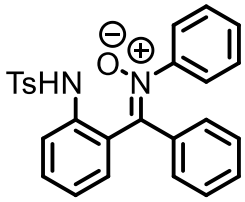
was subjected to normal-phase flash chromatography on silica gel (0→30% EtOAc/Hex). Product was isolated as a light pink oil that solidified on standing to puffy pink solid (578.5 mg, 93% yield). R_f = 0.45 in 30% EtOAc/Hex, visualized with $KMnO_4$ stain. ^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.44 – 7.42 (m, 2H), 7.40 – 7.37 (m, 2H), 7.36 – 7.33 (m, 1H), 7.16 (d, *J* = 1.5 Hz, 1H), 6.77 (s, 1H), 5.99 (s, 1H). ^{13}C NMR (176 MHz, Chloroform-*d*) δ 149.62, 142.67, 130.02, 129.11, 128.80, 127.71, 126.70, 122.90, 115.62, 109.59.

Compound 124



Alcohol (23.5 mg, 0.13 mmol), Nitrosobenzene (14.2 mg, 0.133 mmol), and Copper (II) bromide (6.0 mg, 0.027 mmol), refluxed in HFIP (2 mL) for 4 hours. Reaction mixture was diluted with DCM (3 mL) and quenched with water (3 mL). The organic layer was separated and aqueous phase was washed with DCM (3 x 1 mL), organics were combined, concentrated and subjected to normal phase flash chromatography on silica gel (0→50% EtOAc/Hex). Product was isolated as a white powder (31.6 mg, 89 % yield) R_f = 0.15 in 30% EtOAc/Hex visualized with PMA. ^{1}H NMR (700 MHz, Chloroform-*d*) δ 8.05 (dd, *J* = 6.8, 3.0 Hz, 1H), 7.40 (dd, *J* = 5.2, 2.0 Hz, 1H), 7.33 – 7.28 (m, 1H), 7.23 – 7.16 (m, 3H), 7.14 – 7.08 (m, 1H). ^{13}C NMR (176 MHz, Chloroform-*d*) δ 131.30, 130.67, 130.24, 128.84, 128.81, 128.62, 128.39, 128.07, 124.73.

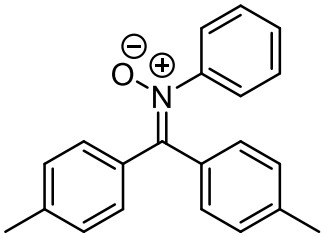
Compound 125



Alcohol (52.0 mg, 0.15 mmol), Nitrosobenzene (17.0 mg, 0.016), and Copper (II) bromide (6.3 mg, 0.028 mmol), refluxed in HFIP (2 mL) for 14 hours. Reaction mixture was diluted with DCM (3 mL) and quenched with water (3 mL). The organic layer was separated and aqueous phase was washed with DCM (3 x 1 mL), organics were combined, concentrated and subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex). Product was isolated as an off white powder (38.1 mg, 62 % yield) R_f = 0.35 in 30 % EtOAc/Hex visualized with PAA. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.44 (dtd, *J* = 9.6, 8.3, 1.3 Hz, 2H), 7.31 – 7.26 (m, 7H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 2H),

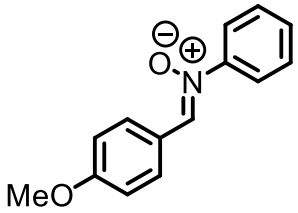
7.11 – 7.07 (m, 1H), 6.89 (dd, *J* = 7.9, 1.2 Hz, 1H), 6.85 – 6.82 (m, 2H), 2.44 (s, 3H). ^{13}C NMR (176 MHz, Chloroform-*d*) δ 153.22, 147.63, 143.66, 138.75, 138.11, 135.87, 133.36, 132.05, 131.39, 130.21, 130.00, 129.87, 129.68, 129.28, 128.53, 127.57, 126.52, 125.68, 125.06, 21.89.

Compound 126



Alcohol (88.0 mg, 0.41 mmol), Nitrosobenzene (47.9 mg, 0.46 mmol), and Copper (II) bromide (20.3 mg, 0.09 mmol), refluxed in HFIP (3 mL) for 1.5 hours. Reaction mixture was diluted with DCM (3 mL) and quenched with water (3 mL). The organic layer was separated and aqueous phase was washed with DCM (3 x 1 mL), organics were combined, concentrated and subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex). Product was isolated as an off white powder (90 mg, 75 % yield) R_f = 0.2 in 30 % EtOAc/Hex visualized with XX. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 8.4 Hz, 2H), 7.36 – 7.28 (m, 2H), 7.20 (dd, *J* = 7.4, 1.6 Hz, 5H), 6.98 (d, *J* = 2.5 Hz, 4H), 2.38 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 148.95, 140.75, 138.97, 133.10, 131.85, 131.35, 130.90, 129.21, 128.95, 128.85, 128.56, 124.93, 21.90, 21.57.

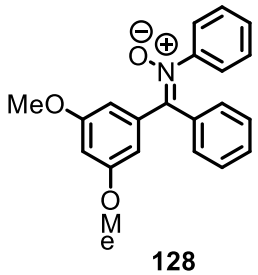
Compound 127



Alcohol (36.5 mg, 0.26 mmol), Nitrosobenzene (28.9 mg, 2.7 mmol), and Copper (II) bromide (11.4 mg, 0.05 mmol), refluxed in HFIP (2 mL) for 4 hours. Reaction mixture was diluted with DCM (3 mL) and quenched with water (3 mL). The organic layer was separated and aqueous phase was washed with DCM (3 x 1 mL), organics were combined, concentrated and subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex). Product was isolated as a white powder (43.1 mg, 78 % yield, 4.9 mg staring alcohol recovered) R_f = 0.2 in 30 % EtOAc/Hex visualized with PMA. ^{1}H NMR (700 MHz, Chloroform-*d*) δ 8.40 (d, *J* = 8.9 Hz, 2H), 7.85 (s, 1H), 7.79 – 7.73 (m, 2H), 7.52 – 7.40 (m, 3H), 6.98 (d,

J = 8.9 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (176 MHz, Chloroform-*d*) δ 161.80, 149.24, 134.43, 131.45, 129.90, 129.39, 124.06, 121.94, 114.32, 55.69.

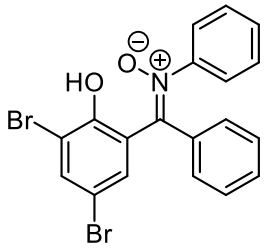
Compound 128



128

Alcohol (74.5 mg, 0.3 mmol), Nitrosobenzene (35.2 mg, 0.33 mmol), and Copper (II) bromide (14.5 mg, 0.065), refluxed in HFIP (2 mL) for 1.5 hours. Reaction mixture was diluted with DCM (3 mL) and quenched with water (3 mL). The organic layer was separated and aqueous phase was washed with DCM (3 x 1 mL), organics were combined, concentrated and subjected to normal phase flash chromatography on silica gel (0→ 50 0% EtOAc/Hex). *Product was isolated as a mixture of cis/trans isomers (approx. 1.5:1)* with the physical appearance of a white powder (65.3 mg, 65 % yield) R_f = 0.1 in 30 % EtOAc/Hex visualized with $KMnO_4$. ^{1}H NMR (700 MHz, Chloroform-*d*) δ 8.15 – 8.01 (m, 2H), 7.48 – 7.39 (m, 3H), 7.36 – 7.32 (m, 2H), 7.28 (dd, *J* = 8.1, 1.6 Hz, 3H), 7.25 – 7.22 (m, 2H), 7.22 – 7.20 (m, 3H), 7.20 – 7.17 (m, 3H), 7.12 – 7.09 (m, 1H), 6.54 (t, *J* = 2.3 Hz, 1H), 6.31 (t, *J* = 2.3 Hz, 1H), 6.24 (d, *J* = 2.3 Hz, 2H), 3.77 (s, 4H), 3.60 (s, 6H). ^{13}C NMR (176 MHz, Chloroform-*d*) δ 160.68, 160.43, 148.93, 147.83, 147.48, 137.54, 136.06, 135.81, 134.09, 131.43, 130.81, 130.44, 129.06, 129.00, 128.90, 128.82, 128.52, 128.23, 124.83, 124.58, 109.82, 108.99, 103.37, 101.28, 55.77, 55.68.

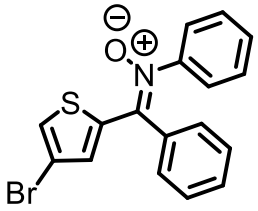
Compound 129



Alcohol (50.5 mg, 0.14 mmol), Nitrosobenzene (16.4 mg, 0.15 mmol), and Copper (II) bromide (6.1 mg, 0.027 mmol), refluxed in HFIP (2 mL) for 14 hours. Reaction mixture was diluted with DCM (3 mL) and quenched with water (3 mL). The organic layer was separated and aqueous phase was washed with DCM (3 x 1 mL), organics were combined, concentrated and subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex). *Product was isolated as a mixture of cis/trans isomers* (> 20:1) as a white

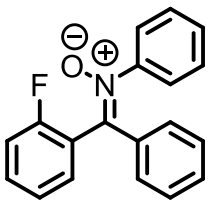
powder (44.9 mg, 72 % yield) R_f = 0.8 in 40 % EtOAc/Hex visualized with PMA. ^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 2.4 Hz, 1H), 7.42 – 7.32 (m, 1H), 7.31 – 7.27 (m, 6H), 7.20 – 7.14 (m, 1H), 7.14 – 7.05 (m, 2H), 6.89 (d, *J* = 2.3 Hz, 1H). ^{13}C NMR (176 MHz, Chloroform-*d*) δ 156.65, 155.47, 146.61, 139.00, 134.99, 134.41, 131.52, 130.88, 130.01, 129.38, 129.14, 125.26, 124.35, 117.13, 110.62.

Compound 130



Alcohol (50.0 mg, 0.19 mmol), Nitrosobenzene (23.1 mg, 0.22 mmol), and Copper (II) bromide (8.3 mg, 0.035 mmol), refluxed in HFIP (2 mL) for 3 hours. Reaction mixture was diluted with DCM (3 mL) and quenched with water (3 mL). The organic layer was separated and aqueous phase was washed with DCM (3 x 1 mL), organics were combined, concentrated and subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex). Product was isolated as a dull yellow powder (51.1 mg, 75 % yield) R_f = 0.5 in 30 % EtOAc/Hex visualized with PAA. ^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.47 (d, *J* = 1.4 Hz, 1H), 7.38 – 7.31 (m, 3H), 7.27 (d, *J* = 1.5 Hz, 2H), 7.25 (d, *J* = 2.5 Hz, 2H), 7.22 (dd, *J* = 5.2, 1.9 Hz, 3H), 7.02 (d, *J* = 1.5 Hz, 1H). ^{13}C NMR (176 MHz, Chloroform-*d*) δ 146.19, 142.63, 136.78, 134.21, 132.64, 130.89, 129.92, 129.29, 129.09, 128.99, 128.30, 125.08, 110.43. 51.1 mg (75% yield).

Compound 131



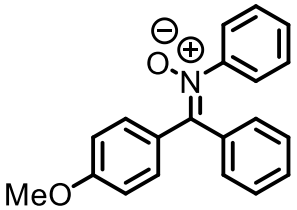
Alcohol (105.0 mg, 0.52 mmol), Nitrosobenzene (57.7 mg, 0.54 mmol), and Copper (II) bromide (22.4 mg, 0.1 mmol), refluxed in HFIP (3 mL) for 2 hours. Reaction mixture was diluted with DCM (3 mL) and quenched with water (3 mL). The organic layer was separated and aqueous phase was washed with DCM (3 x 2 mL), organics were combined, concentrated and subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex).

Isomer A (Top spot): Product was isolated as an off white powder (42.5 mg, 28 % yield) R_f = 0.3 in 30 % EtOAc/Hex visualized with $KMnO_4$. ^{1}H NMR (700 MHz, Chloroform-*d*) δ 8.15 (dd, *J* = 6.7, 3.1 Hz, 2H),

7.43 – 7.40 (m, 3H), 7.33 (d, *J* = 7.4 Hz, 2H), 7.29 – 7.27 (m, 1H), 7.21 (dt, *J* = 13.8, 7.0 Hz, 3H), 7.13 (td, *J* = 7.4, 1.8 Hz, 1H), 7.03 (td, *J* = 7.6, 1.1 Hz, 1H), 6.94 (ddd, *J* = 9.5, 8.4, 1.1 Hz, 1H). ^{13}C NMR (176 MHz, Chloroform-*d*) δ 160.35, 158.93, 148.53, 141.71, 133.00, 132.49, 130.40, 129.57, 128.79, 128.73, 128.17, 124.22 (d, *J* = 3.8 Hz), 116.04, 115.91. 42.5 mg (28% yield) isolated as an off white powder.

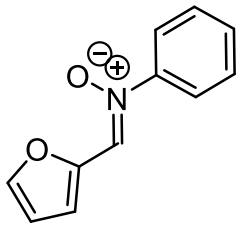
Isomer B (bottom spot): Product was isolated as an off white powder (67.4 mg, 45 % yield) R_f = 0.15 in 30 % EtOAc/Hex visualized with $KMnO_4$. ^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.45 – 7.39 (m, 4H), 7.28 (dd, *J* = 5.2, 1.9 Hz, 3H), 7.22 – 7.15 (m, 5H), 7.08 – 7.02 (m, 2H). ^{13}C NMR (176 MHz, Chloroform-*d*) δ 161.16, 159.72, 147.58, 143.25, 135.25, 131.47, 130.34, 129.23, 128.84, 128.74, 128.28, 125.00, 124.11, 123.55 (d, *J* = 14.0 Hz), 116.24 (d, *J* = 21.6 Hz).

Compound 132



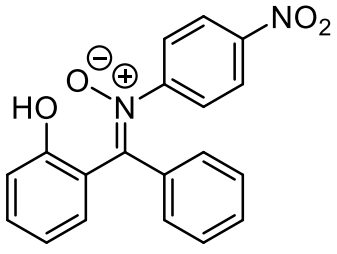
Alcohol (110 mg, 0.51 mmol), Nitrosobenzene (59.4 mg, 0.55 mmol), and Copper (II) bromide (22.5 mg, 0.1 mmol), refluxed in HFIP (3 mL) for 1.5 hours. Reaction mixture was diluted with DCM (3 mL) and quenched with water (3 mL). The organic layer was separated and aqueous phase was washed with DCM (3 x 1 mL), organics were combined, concentrated and subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex). *Product was isolated as a mixture of cis/trans isomers (approx. 2:1)* as an off white powder (120.7 mg, 82 % yield) R_f = 0.1 in 30 % EtOAc/Hex visualized with $KMnO_4$. ^{1}H NMR (700 MHz, Chloroform-*d*) δ 8.17 – 8.10 (m, 2H), 8.03 (dd, *J* = 7.6, 2.2 Hz, 1H), 7.39 (dd, *J* = 6.0, 1.6 Hz, 2H), 7.32 – 7.29 (m, 1H), 7.27 (d, *J* = 1.4 Hz, 1H), 7.23 (dd, *J* = 8.3, 6.7 Hz, 2H), 7.22 – 7.17 (m, 5H), 7.16 (d, *J* = 7.3 Hz, 1H), 7.11 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.00 (d, *J* = 8.9 Hz, 1H), 6.91 (d, *J* = 9.2 Hz, 2H), 6.72 – 6.70 (m, 1H), 3.85 (s, 3H), 3.75 (s, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 135.70, 134.48, 132.52, 131.15, 130.59, 129.94, 129.69, 128.72, 128.61, 128.32, 128.19, 127.85, 126.60, 124.60, 124.54, 113.67, 113.16, 55.33, 55.17.

Compound 134



Alcohol (71.0 mg, 0.7 mmol), Nitrosobenzene (80.0 mg, 0.75 mmol), and Copper (II) bromide (35.7 mg, 0.016 mmol), refluxed in HFIP (2 mL) for 5 hours. Reaction mixture was diluted with DCM (3 mL) and quenched with water (2 mL). The organic layer was separated and aqueous phase was washed with DCM (3 x 2 mL), organics were combined, concentrated and subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex). Product was isolated as a white powder (10.9 mg, 8 % yield) R_f = 0.6 in 30 % EtOAc/Hex visualized with PMA. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 (s, 1H), 8.01 (d, *J* = 3.5 Hz, 1H), 7.80 (dd, *J* = 8.1, 1.7 Hz, 2H), 7.58 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.54 – 7.42 (m, 3H), 6.64 (ddd, *J* = 3.6, 1.7, 0.7 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 147.53, 147.28, 144.75, 130.01, 129.23, 124.47, 121.09, 116.68, 112.78.

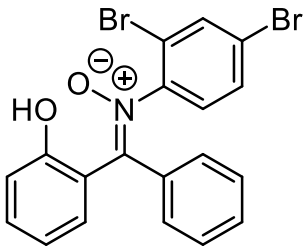
Compound 145



Alcohol (93 mg, 0.46 mmol), Nitrosobenzene (77 mg, 0.50 mmol), and Copper (II) bromide (24.5 mg, 0.11 mmol), refluxed in HFIP (3 mL) for 2.5 hours. Reaction mixture was diluted with DCM (4 mL) and quenched with water (4 mL). The organic layer was separated and aqueous phase was washed with DCM (3 x 2 mL), organics were combined, concentrated and subjected to normal phase flash chromatography on

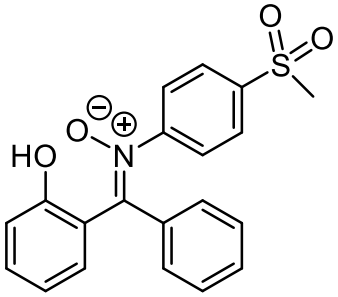
silica gel (0→ 50% EtOAc/Hex). Product was isolated as an off white powder (93.6 mg, 61 % yield) R_f = 0.5 in 30 % EtOAc/Hex visualized with PMA. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 – 8.09 (m, 2H), 7.54 – 7.49 (m, 3H), 7.40 – 7.36 (m, 1H), 7.29 (t, *J* = 7.7 Hz, 2H), 7.18 – 7.13 (m, 3H), 6.85 – 6.82 (m, 2H). ^{13}C NMR (176 MHz, Chloroform-*d*) δ 161.12, 151.35, 136.70, 135.00, 134.66, 133.90, 131.78, 131.18, 129.52, 129.29, 128.71, 126.70, 124.79, 121.54, 119.98.

Compound 146



Alcohol (64 mg, 0.32 mmol), Nitrosobenzene (99 mg, 0.37 mmol), and Copper (II) bromide (16 mg, 0.071 mmol), refluxed in HFIP (2 mL) for 2.5 hours. Reaction mixture was diluted with DCM (3 mL) and quenched with water (3 mL). The organic layer was separated and aqueous phase was washed with DCM (3 x 1 mL), organics were combined, concentrated and subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex). Product was isolated as an off white powder (36.6 mg, 26 % yield) R_f = 0.2 in 30 % EtOAc/Hex visualized with XX. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 2.0 Hz, 1H), 7.49 (ddd, *J* = 8.6, 5.2, 3.6 Hz, 1H), 7.40 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.35 – 7.32 (m, 3H), 7.31 – 7.27 (m, 2H), 7.25 (d, *J* = 6.7 Hz, 2H), 7.18 – 7.11 (m, 1H), 6.82 – 6.79 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.17, 159.09, 145.05, 136.46, 134.68, 134.06, 133.92, 131.67, 130.97, 130.86, 128.96, 128.74, 123.78, 121.45, 121.23, 119.68, 118.88.

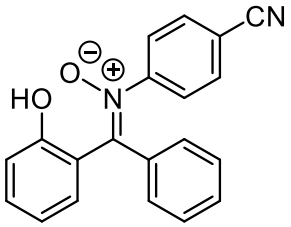
Compound 147



Alcohol (38 mg, 0.19), Nitrosobenzene (42.3 mg, 0.22 mmol), and Copper (II) bromide (10 mg, 0.045 mmol), refluxed in HFIP (2 mL) for 2.5 hours. Reaction mixture was diluted with DCM (3 mL) and quenched with water (3 mL). The organic layer was separated and aqueous phase was washed with DCM

(3 x 1 mL), organics were combined, concentrated and subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex). Product was isolated as an off white powder (31.7 mg, 46 % yield) R_f = 0.3 in 30 % EtOAc/Hex visualized with PMA. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 3H), 7.41 – 7.33 (m, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.19 – 7.10 (m, 4H), 6.85 – 6.81 (m, 2H), 2.98 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.67, 157.84, 150.50, 140.79, 134.59, 134.21, 133.58, 131.40, 130.80, 128.92, 128.52, 126.33, 121.35, 121.14, 119.64, 44.38.

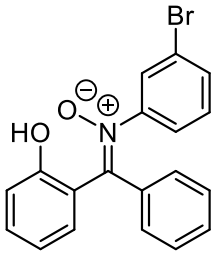
Compound 148/150



Using Synthesized Nitrosobenzene. Alcohol (39.0 mg, 0.20 mmol), Nitrosobenzene (30.4 mg, 0.23 mmol), and Copper (II) bromide (11.5 mg, 0.051 mmol), refluxed in HFIP (1 mL) for 2.5 hours. Reaction mixture was diluted with DCM (3 mL) and quenched with water (3 mL). The organic layer was separated and aqueous phase was washed with DCM (3 x 1 mL), organics were combined, concentrated and subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex). Product was isolated as a white powder (29.8 mg, 45 % yield) R_f = 0.45 in 30 % EtOAc/Hex visualized with PMA.

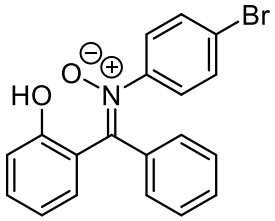
Following One Pot Method General procedure A: To a mixture of aniline (45.6 mg, 0.39 mmol), and diphenyl diselenide (12.0 mg, 0.038 mmol) in 2 mL chloroform, 30% aqueous hydrogen peroxide (0.14 mL, 1.8 mmol) was added. This biphasic solution was stirred at 60 ^{o}C for 1 hour, then worked up following the general procedure. The dried residue was combined with benzyl alcohol (57.5 mg. 0.29 mmol), Copper (II) bromide (14 mg, 0.063 mmol), taken up in HFIP (2 mL) and refluxed for 2.5 hours and worked up as described in the general procedure. Residue was subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex). Product was isolated as an off white powder (23.4 mg, 28 % yield) R_f = 0.45 in 30 % EtOAc/Hex visualized with PMA. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 (d, *J* = 8.8 Hz, 2H), 7.51 (ddd, *J* = 8.6, 5.4, 3.4 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.40 – 7.35 (m, 1H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.17 – 7.11 (m, 3H), 6.84 – 6.80 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.08, 157.83, 150.00, 134.84, 134.70, 133.85, 133.25, 131.73, 131.00, 129.19, 126.45, 121.65, 121.48, 119.88, 117.75, 113.37.

Compound 151



Following One Pot Method General procedure A: To a mixture of aniline (69.5 mg, 0.40 mmol), and diphenyl diselenide (15.0 mg, 0.048 mmol) in 2 mL chloroform, 30% aqueous hydrogen peroxide (0.14 mL, 1.8 mmol) was added. This biphasic solution was stirred at 60 °C for 1 hour then worked up following the general procedure. The dried residue was combined with benzyl alcohol (56.7 mg, 0.28 mmol), Copper (II) bromide (14.0 mg, 0.063 mmol), taken up in HFIP (2 mL) and refluxed for 2.5 hours and worked up as described in the general procedure. Residue was subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex). Product was isolated as a light brown powder (47.3 mg, 46 % yield) R_f = 0.6 in 30 % EtOAc/Hex visualized with PMA. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 (t, *J* = 1.9 Hz, 1H), 7.49 (ddd, *J* = 8.6, 5.4, 3.3 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.36 – 7.32 (m, 1H), 7.31 – 7.26 (m, 2H), 7.20 (ddd, *J* = 8.1, 2.1, 1.0 Hz, 1H), 7.16 – 7.13 (m, 3H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.83 – 6.79 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.63, 156.86, 147.54, 134.74, 134.13, 133.48, 132.40, 131.32, 130.29, 130.06, 128.67, 128.41, 123.78, 122.31, 121.56, 121.07, 119.37.

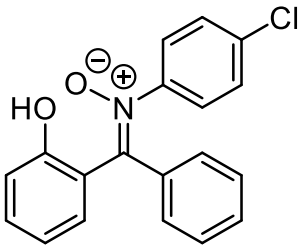
Compound 152



Following One Pot Method General procedure A: To a mixture of aniline (61.8 mg, 0.36 mmol), and diphenyl diselenide (12.7 mg, 0.04 mmol) in 2 mL chloroform, 30% aqueous hydrogen peroxide (0.14 mL, 1.8 mmol) was added. This biphasic solution was stirred at 60 °C for 1.5 hours then worked up following

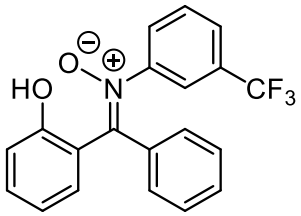
the general procedure. The dried residue was combined with benzyl alcohol (54.7 mg, 0.27 mmol), Copper (II) bromide (16.4 mg, 0.073 mmol), taken up in HFIP (2 mL) and refluxed for 3 hours and worked up as described in the general procedure. Residue was subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex). Product was isolated as light brown powder (33.8 mg, 34 % yield) R_f = 0.6 in 30 % EtOAc/Hex visualized with PMA. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 (ddd, *J* = 8.6, 4.8, 3.9 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.17 – 7.12 (m, 3H), 6.81 – 6.79 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.60, 156.64, 145.69, 134.89, 134.07, 133.45, 132.11, 131.33, 130.23, 128.71, 126.68, 123.16, 121.69, 121.07, 119.36.

Compound 153



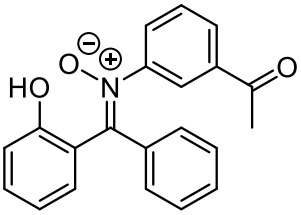
Following One Pot Method General procedure B: To a mixture of aniline (77.5 mg, 0.61 mmol), and diphenyl diselenide (20.6 mg, 0.066 mmol) in 2 mL chloroform, 30% aqueous hydrogen peroxide (0.27 mL, 3.4 mmol) was added. This biphasic solution was stirred at 60 ºC for 1.5 hours then worked up following the general procedure. The dried residue was combined with benzyl alcohol (98.3 mg, 0.49 mmol), Copper (II) bromide (25.0 mg, 0.11 mmol), taken up in HFIP (2 mL) and refluxed for 1.5 hours and worked up as described in the general procedure. Residue was subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex). Product was isolated as dark brown powder (56.3 mg, 38 % yield) R_f = 0.7 in 30 % EtOAc/Hex visualized with PMA. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 (ddd, *J* = 8.6, 5.0, 3.8 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.30 – 7.27 (m, 5H), 7.22 (d, *J* = 8.9 Hz, 2H), 7.17 – 7.11 (m, 3H), 6.80 (dd, *J* = 4.0, 0.9 Hz, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.57, 156.67, 145.17, 134.06, 133.45, 131.32, 130.20, 129.12, 128.68, 126.43, 123.92, 121.06, 119.35, 118.16, 115.84.

Compound 154



Following One Pot Method General procedure B: To a mixture of aniline (100 mg, 0.62 mmol), and diphenyl diselenide (25.3 mg, 0.08 mmol) in 2 mL chloroform, 30% aqueous hydrogen peroxide (0.27 mL, 3.4 mmol) was added. This biphasic solution was stirred at 60 °C for 2 hours then worked up following the general procedure. The dried residue was combined with benzyl alcohol (92.5 mg, 0.46 mmol), Copper (II) bromide (25.5 mg, 0.11 mmol), taken up in HFIP (2 mL) and refluxed for 1.5 hours and worked up as described in the general procedure. Residue was subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex). Product was isolated as dark brown powder (45.8 mg, 28 % yield) R_f = 0.6 in 30 % EtOAc/Hex visualized with PMA. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 (s, 1H), 7.51 (dtd, *J* = 8.7, 5.7, 2.9 Hz, 3H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.31 – 7.27 (m, 1H), 7.18 – 7.11 (m, 4H), 7.03 – 6.95 (m, 1H), 6.84 – 6.80 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.00, 157.50, 147.31, 135.68, 134.61, 133.81, 131.64, 130.70, 129.92, 129.40, 129.06, 128.70, 126.22 (d, *J* = 3.7 Hz), 122.82 (d, *J* = 4.1 Hz), 121.45, 119.77.

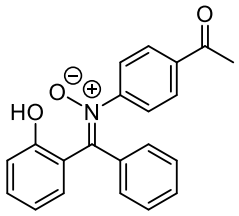
Compound 155



Following One Pot Method General procedure B: To a mixture of aniline (81.8 mg, 0.06 mmol), and diphenyl diselenide (22.4 mg, 0.072 mmol) in 2 mL chloroform, 30% aqueous hydrogen peroxide (0.27 mL, 3.4 mmol) was added. This biphasic solution was stirred at 60 °C for 1 hour or until aniline had been consumed by TLC then worked up following the general procedure. The dried residue was combined with benzyl alcohol (92 mg, 0.46 mmol), Copper (II) bromide (29.6 mg, 0.13 mmol), taken up in HFIP (2 mL) and refluxed for 1.5 hours and worked up as described in the general procedure. Residue was subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex). Product was isolated as off white powder (32.0 mg, 21 % yield) R_f = 0.3 in 30 % EtOAc/Hex visualized with PMA. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 (t, *J* = 1.9 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.55 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.49

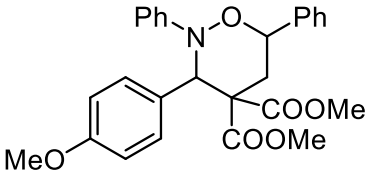
(ddd, *J* = 8.6, 5.9, 2.9 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 7.3 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.16 (ddd, *J* = 8.6, 5.0, 1.3 Hz, 3H), 6.83 – 6.80 (m, 2H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.14, 160.61, 147.00, 137.63, 134.86, 134.15, 133.45, 131.36, 130.24, 129.35, 128.68, 125.16, 121.59, 121.08, 119.39, 26.58.

Compound 157



Following One Pot Method General procedure A: To a mixture of aniline (51.2 mg, 0.38 mmol), and diphenyl diselenide (13 mg, 0.042 mmol) in 2 mL chloroform, 30% aqueous hydrogen peroxide (0.14 mL, 1.8 mmol) was added. This biphasic solution was stirred at 60 °C for 1 hour then worked up following the general procedure. The dried residue was combined with benzyl alcohol (58.0 mg, 0.29 mmol), Copper (II) bromide (14 mg, 0.063 mmol), taken up in HFIP (2 mL) and refluxed for 2.5 hours and worked up as described in the general procedure. Residue was subjected to normal phase flash chromatography on silica gel (0→ 50% EtOAc/Hex). Product was isolated as light brown powder (7.5 mg, 8 % yield) R_f = 0.3 in 30 % EtOAc/Hex visualized with PMA. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 8.7 Hz, 2H), 7.56 – 7.50 (m, 1H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.39 – 7.34 (m, 1H), 7.30 (d, *J* = 0.6 Hz, 1H), 7.26 (s, 1H), 7.21 – 7.15 (m, 4H), 6.84 (dd, *J* = 4.0, 0.7 Hz, 2H), 2.58 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.71, 157.09, 156.69, 151.58, 149.92, 137.09, 134.71, 134.23, 133.50, 131.41, 130.38, 129.07, 128.71, 125.49, 121.10, 119.42, 26.70.

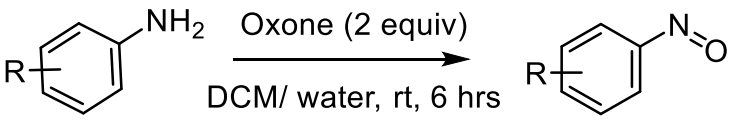
Compound 159



Full sequence in Scheme 25. Alcohol (51.8 mg, 0.37 mmol), Nitrosobenzene (41.6 mg, 0.39 mmol), and Copper (II) bromide (16 mg, 0.07 mmol), refluxed in HFIP (1.5 mL) for 4 hours. Reaction mixture was concentrated under reduced pressure and taken up in DCM (2 mL). Cyclopropane (92.8 mg, 0.4 mmol) and $Yb(OTf)_3$ (15 mg, 0.024 mmol) were added and mixture was stirred at rt for 18 hours. Crude reaction

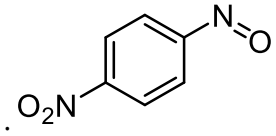
mixture was subjected to normal phase flash chromatography on silica gel (0→ 70% EtOAc/Hex). Product was isolated as a white powder (154.6 mg, 90 % yield) R_f = 0.3 in 20 % EtOAc/Hex visualized with PMA. ^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 7.2 Hz, 2H), 7.52 (d, *J* = 8.9 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.42 – 7.37 (m, 1H), 7.16 (dd, *J* = 8.8, 7.2 Hz, 2H), 7.10 (dd, *J* = 8.8, 1.3 Hz, 2H), 6.85 – 6.81 (m, 1H), 6.72 (d, *J* = 8.9 Hz, 2H), 5.76 (s, 1H), 5.03 (dd, *J* = 12.2, 2.6 Hz, 1H), 3.92 (s, 3H), 3.71 (s, 3H), 3.50 (s, 3H), 2.87 (dd, *J* = 14.4, 12.1 Hz, 1H), 2.81 – 2.75 (m, 1H). ^{13}C NMR (176 MHz, Chloroform-*d*) δ 170.18, 168.37, 159.15, 148.67, 139.50, 131.67, 128.67, 128.56, 128.35, 126.98, 126.54, 121.60, 115.86, 113.37, 78.80, 65.35, 55.00, 53.50, 52.70, 31.59.

General Method for Nitrosobenzene Synthesis.



Aniline (3 mmol) was dissolved in DCM (10 mL) and Added dropwise to a stirring solution of Oxone (3.7g, 6 mmol) dissolved in water (15 mL). After stirring for 6 h at rt, the DCM was removed and aqueous phase was washed with DCM (5x 5 mL) and organics were combined, concentrated under reduced pressure and subjected to normal-phase flash chromatography on silica gel (0→30% EtOAc/Hex) to provide the desired nitrosobenzenes.

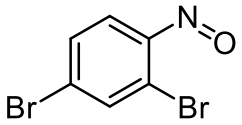
Compound 140



p- nitroaniline (424 mg, 3 mmol) was dissolved in DCM (10 mL) and Added dropwise to a stirring solution of Oxone (3.7g, 6 mmol), reaction mixture was worked up and purified as described in the nitrosobenzene synthesis general method. Product was isolated as an off white powder (149.3 mg, 33 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.51 (d, *J* = 8.9 Hz, 1H), 8.05 (d, *J* = 9.0 Hz, 1H). NMR

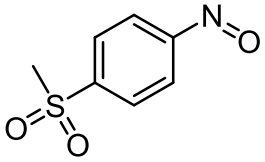
matches literature[77].

Compound 141



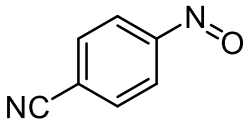
2,4-dibromoaniline (753 mg, 3 mmol) was dissolved in DCM (10 mL) and Added dropwise to a stirring solution of Oxone (3.7g, 6 mmol), reaction mixture was worked up and purified as described in the nitrosobenzene synthesis general method. Product was isolated as an off white powder (401.3 mg, 50 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 1.9 Hz, 1H), 7.42 (dd, *J* = 8.6, 1.9 Hz, 1H), 6.08 (d, *J* = 8.6 Hz, 1H). NMR matches literature[78].

Compound 142



p-(methylsulfonyl)aniline (514 mg, 3 mmol) was dissolved in DCM (10 mL) and Added dropwise to a stirring solution of Oxone (3.7g, 6 mmol), reaction mixture was worked up and purified as described in the nitrosobenzene synthesis general method. Product was isolated as an off white powder (64.2 mg, 12 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.42 (d, *J* = 8.9 Hz, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 3.12 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 129.64, 129.30, 124.96, 121.52, 44.61.

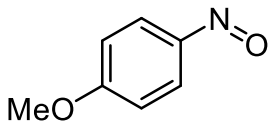
Compound 143



p-cyanoaniline (354 mg, 3 mmol) was dissolved in DCM (10 mL) and Added dropwise to a stirring solution of Oxone (3.7g, 6 mmol), reaction mixture was worked up and purified as described in the nitrosobenzene synthesis general method. Product was isolated as an off white powder (53.6 mg, 14 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.36 (d, *J* = 8.9 Hz, 2H), 7.89 (d, *J* = 8.9 Hz, 2H). NMR matches

literature[79].

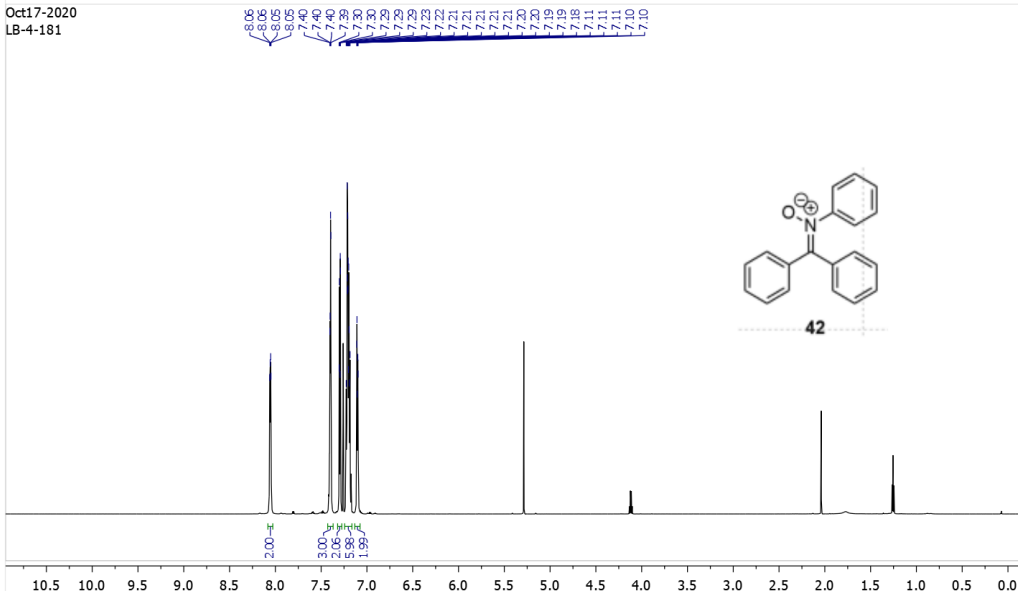
Compound 144



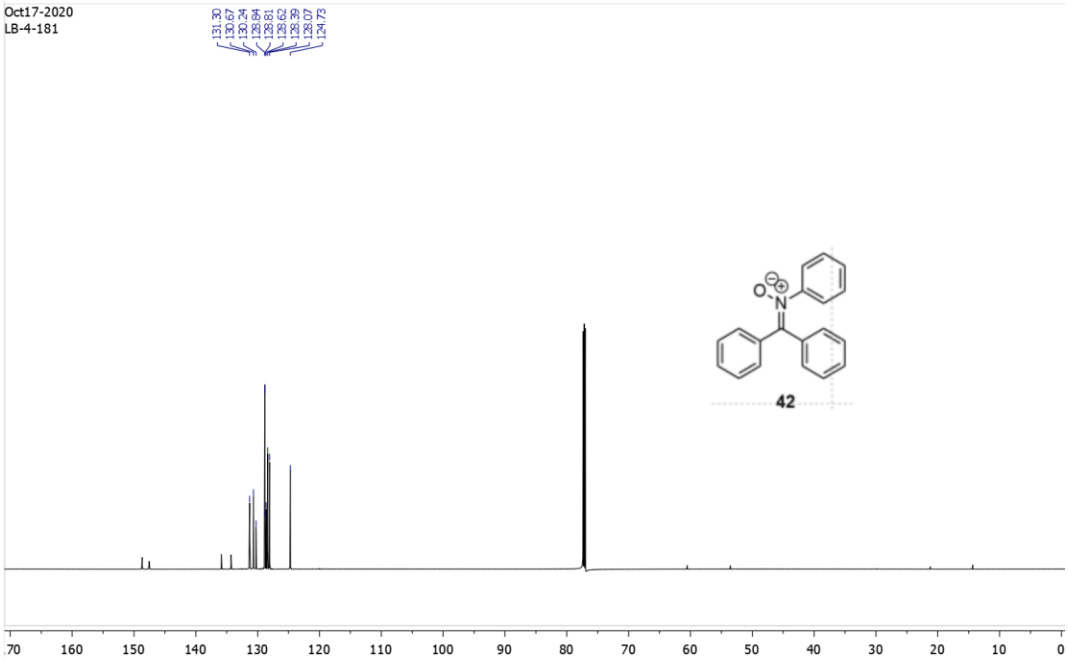
p-anisidine (370 mg, 3 mmol) was dissolved in DCM (10 mL) and Added dropwise to a stirring solution of Oxone (3.7g, 6 mmol), reaction mixture was worked up and purified as described in the nitrosobenzene synthesis general method. Product was isolated as an off white powder (243.5 mg, 60 % yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 9.3 Hz, 2H), 6.94 (d, *J* = 9.3 Hz, 2H), 3.89 (s, 3H). NMR matches literature[77].

NMR Spectra of Compounds

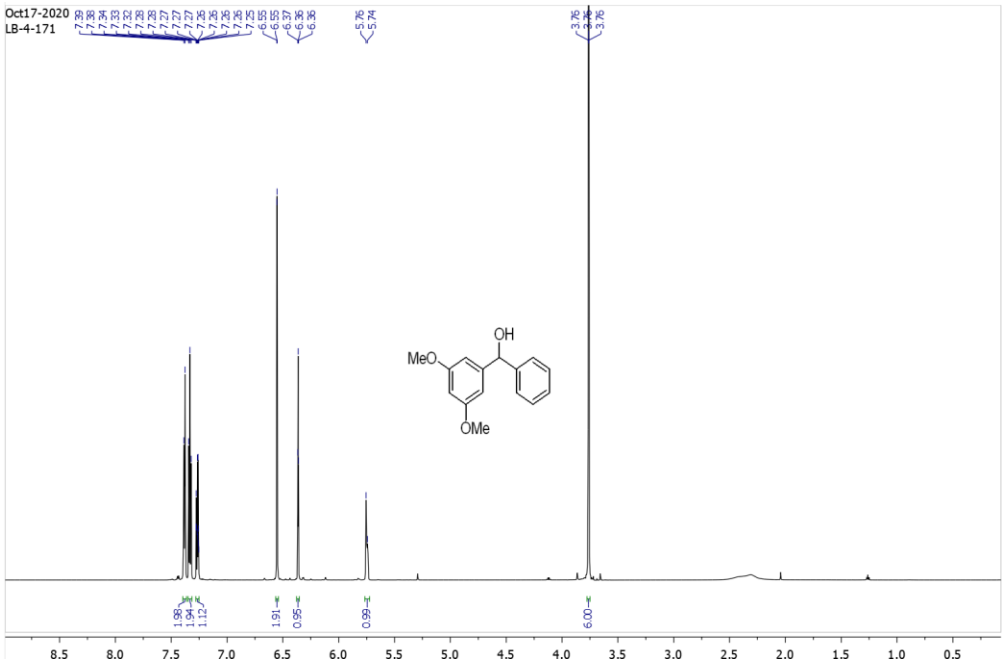
Compound 107 (^{1}H NMR; 700 MHz; Chloroform-*d*)



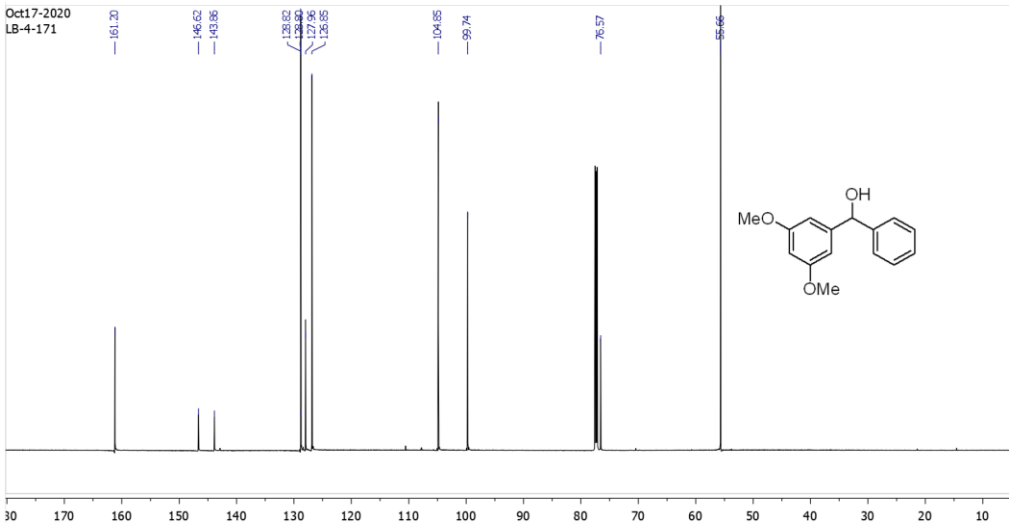
Compound 107 (^{13}C NMR; 176 MHz; Chloroform-*d*)



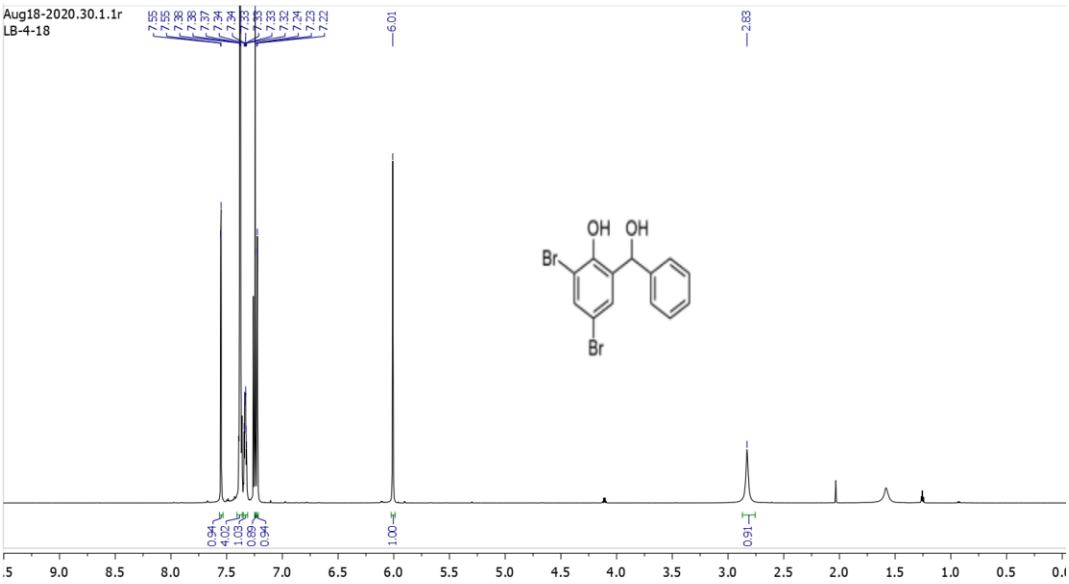
Compound 108 (^{1}H NMR; 700 MHz; Chloroform-*d*)



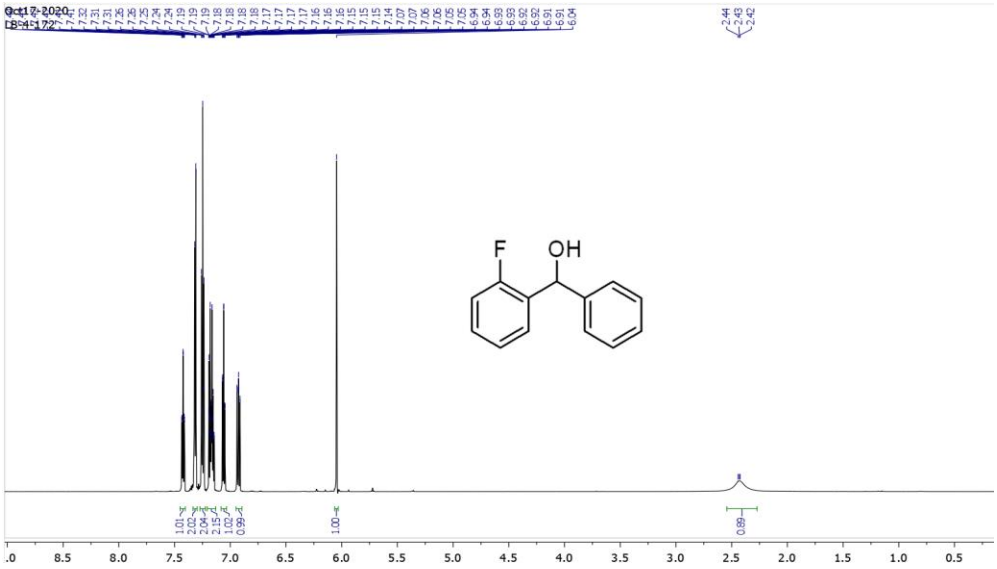
Compound 108 (^{13}C NMR; 176 MHz; Chloroform-*d*)



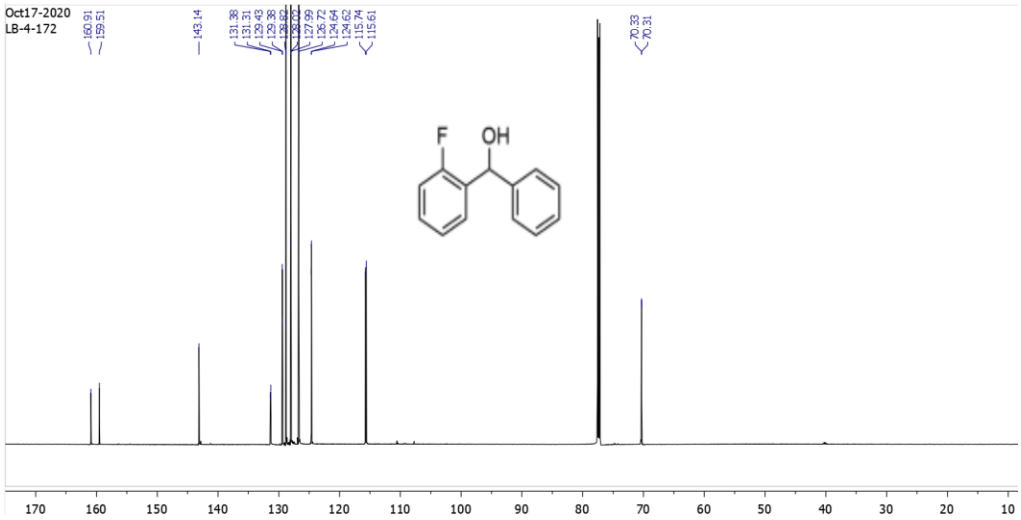
Compound 109 (^{1}H NMR; 700 MHz; Chloroform-*d*)



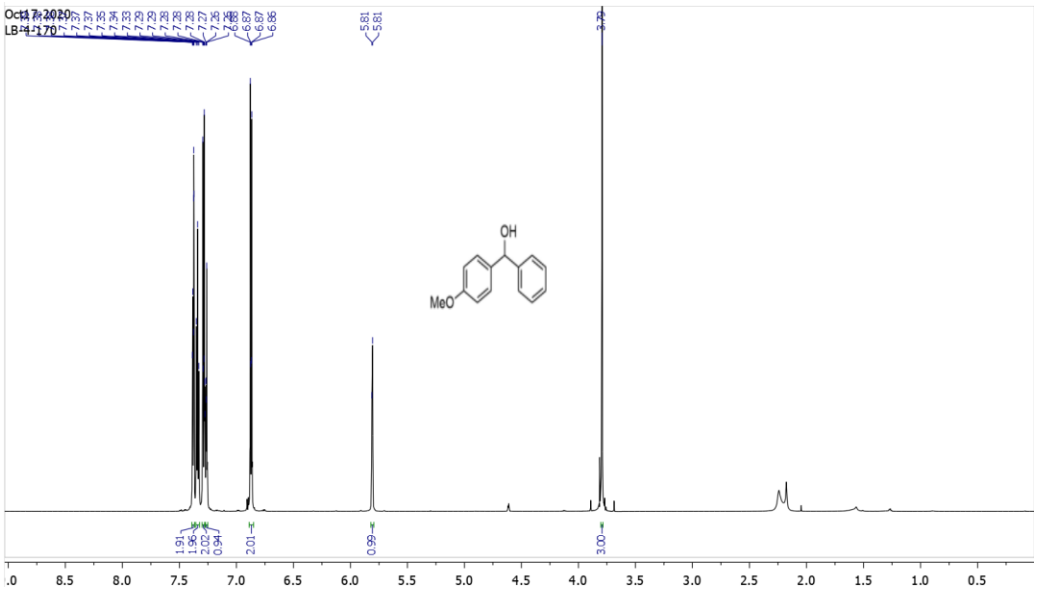
Compound 110 (^{1}H NMR; 700 MHz; Chloroform-*d*)



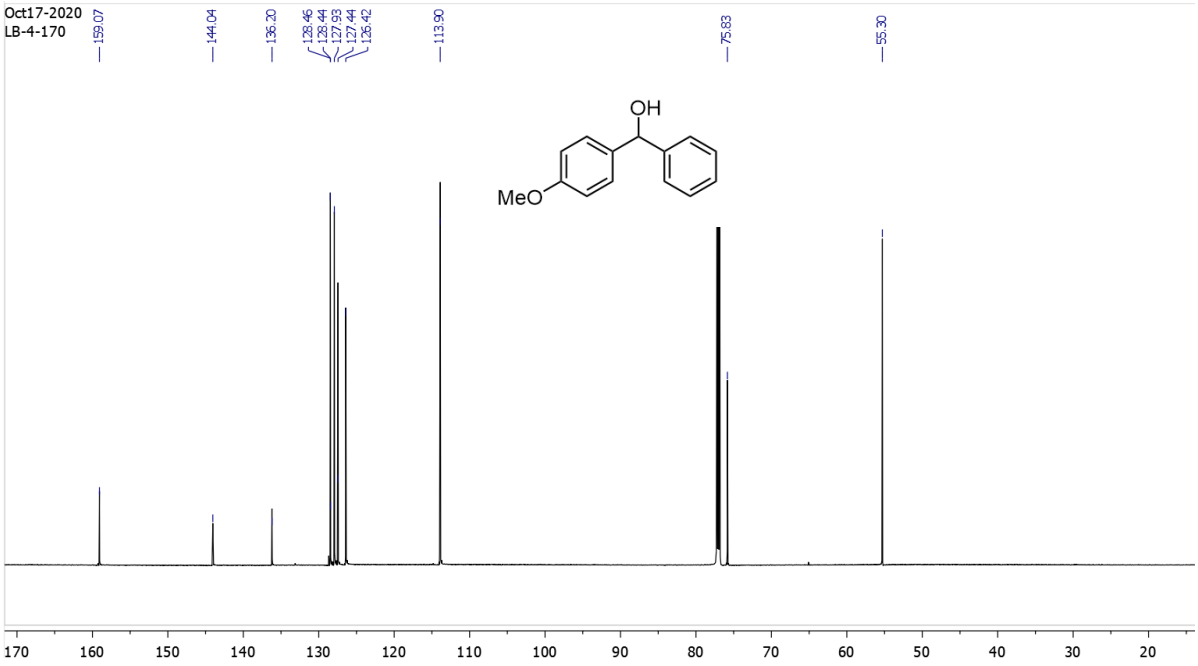
Compound 110 (^{13}C NMR; 176 MHz; Chloroform-*d*)



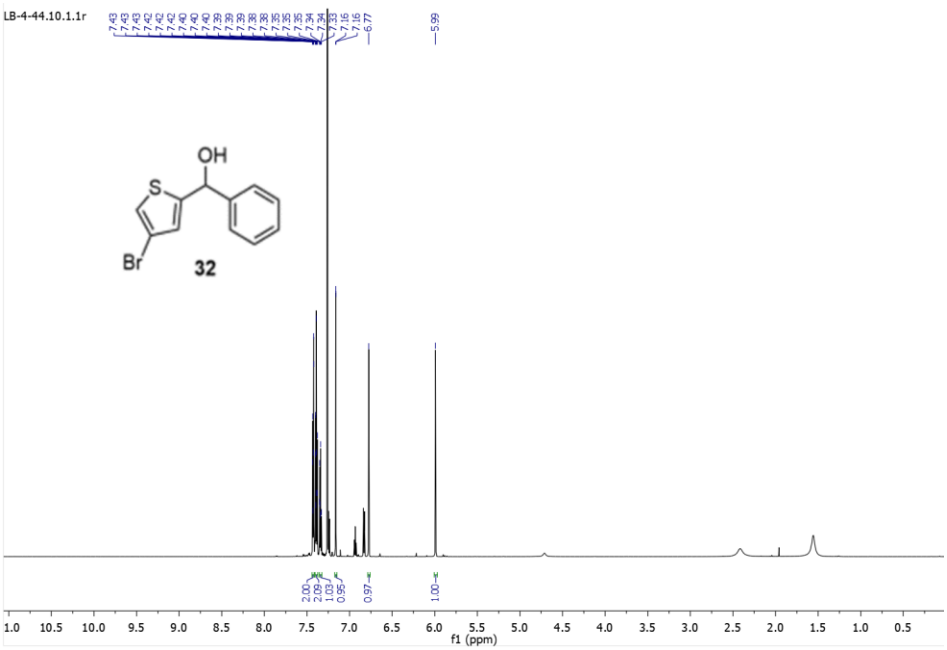
Compound 111 (^{1}H NMR; 700 MHz; Chloroform-*d*)



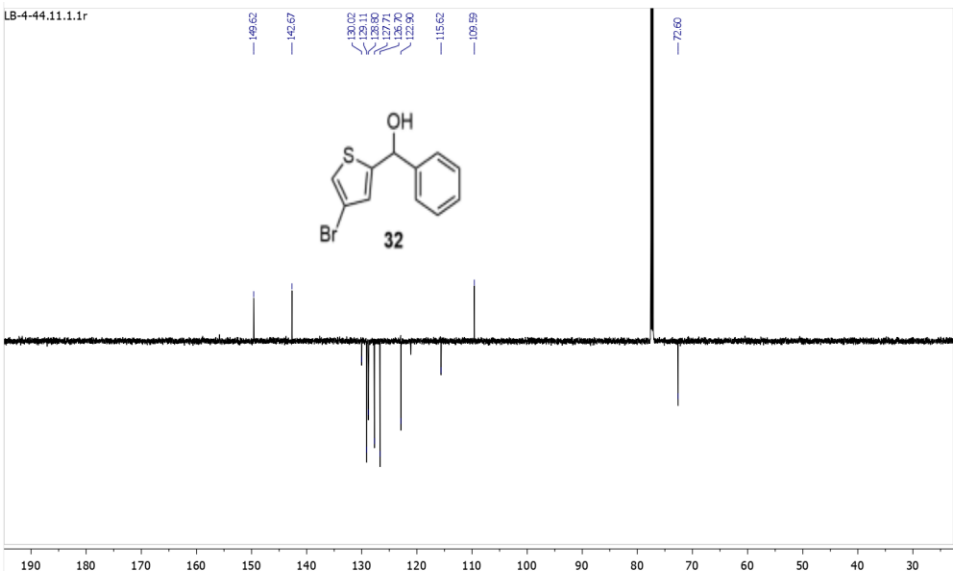
Compound 111 (^{13}C NMR; 176 MHz; Chloroform-*d*)



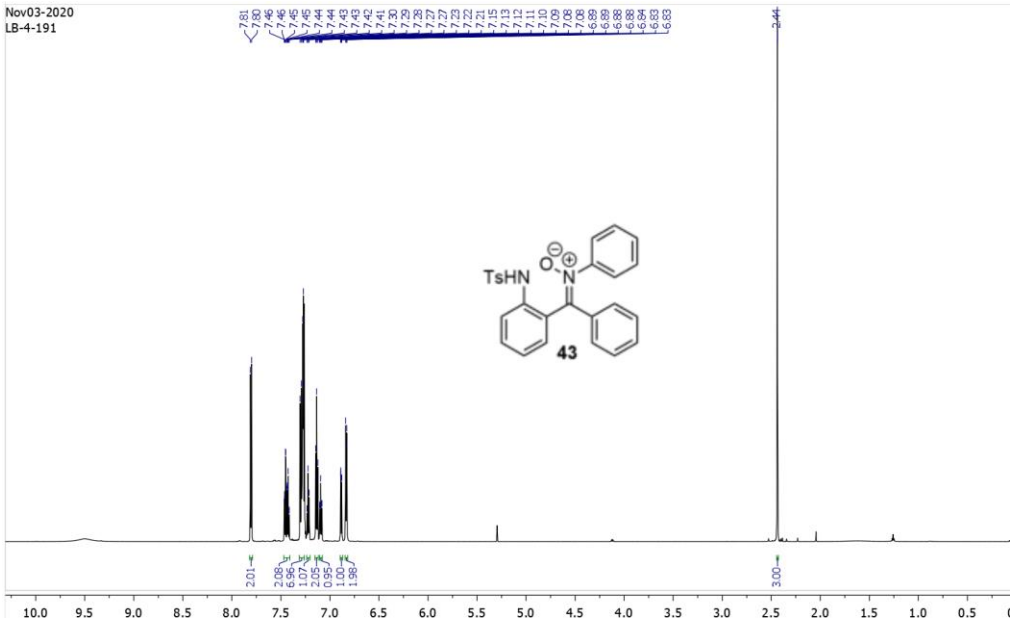
Compound 113 (^{1}H NMR; 700 MHz; Chloroform-*d*)



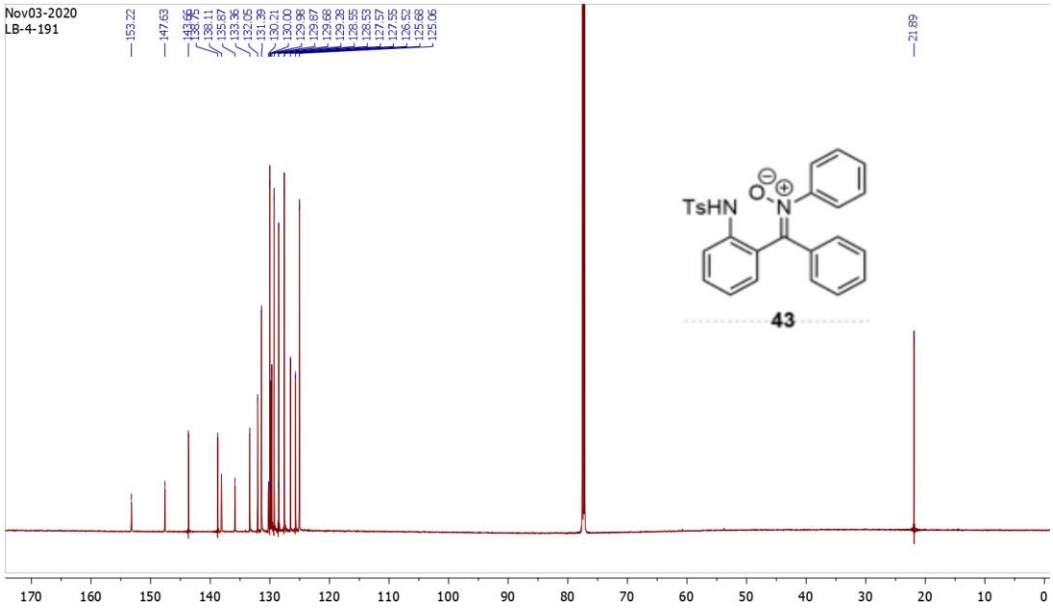
Compound 113 (^{13}C NMR; 176 MHz; Chloroform-*d*)



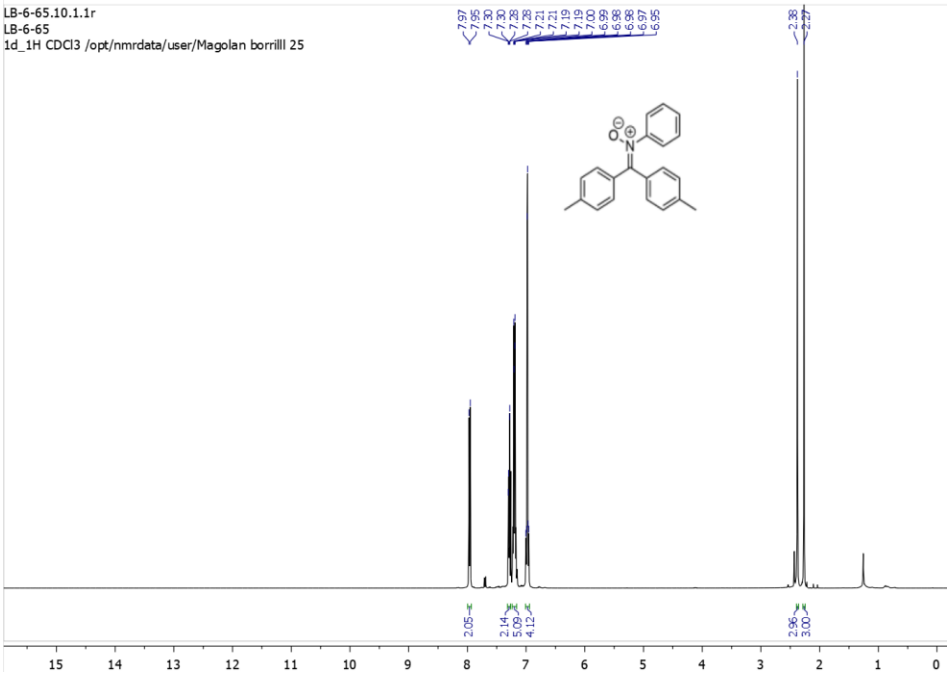
Compound **125** (^{1}H NMR; 700 MHz; Chloroform-*d*)



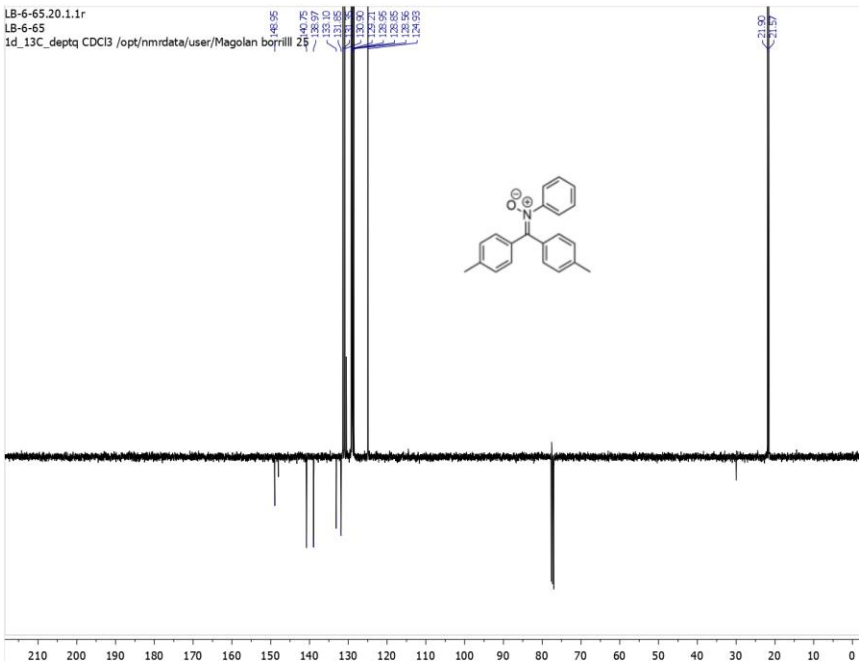
Compound **125** (^{13}C NMR; 176 MHz; Chloroform-*d*)



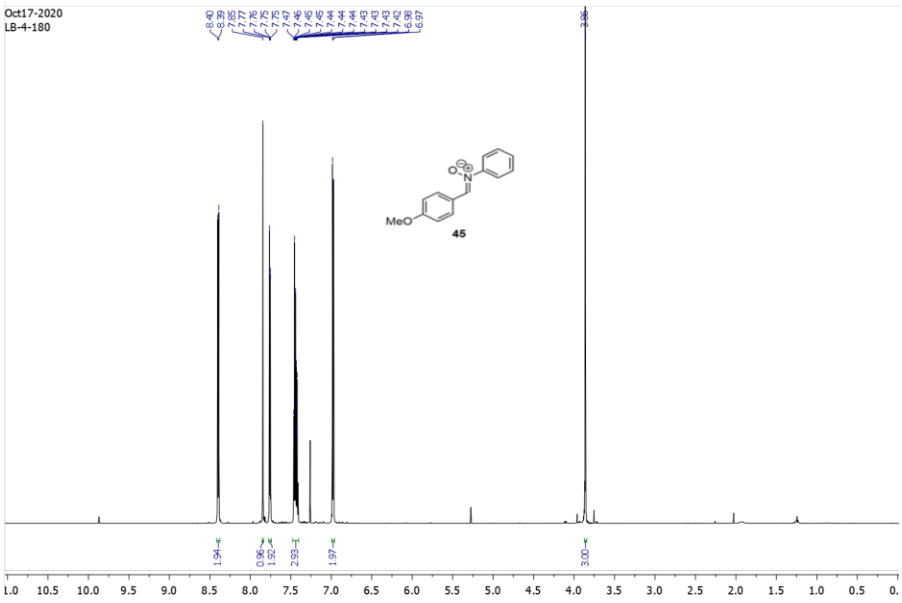
Compound **126** (^{1}H NMR; 400 MHz; Chloroform-*d*)



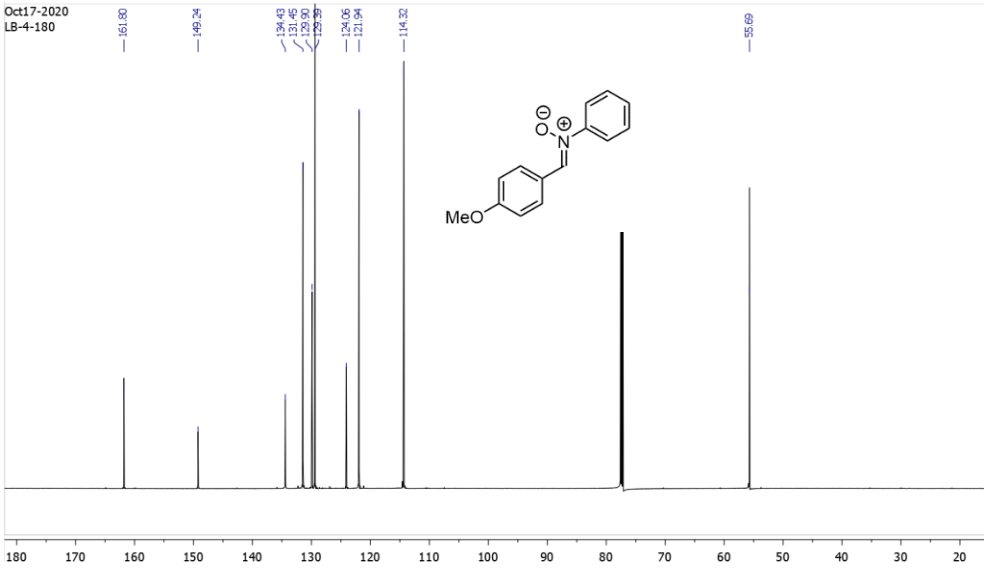
Compound **126** (^{13}C NMR; 100 MHz; Chloroform-*d*)



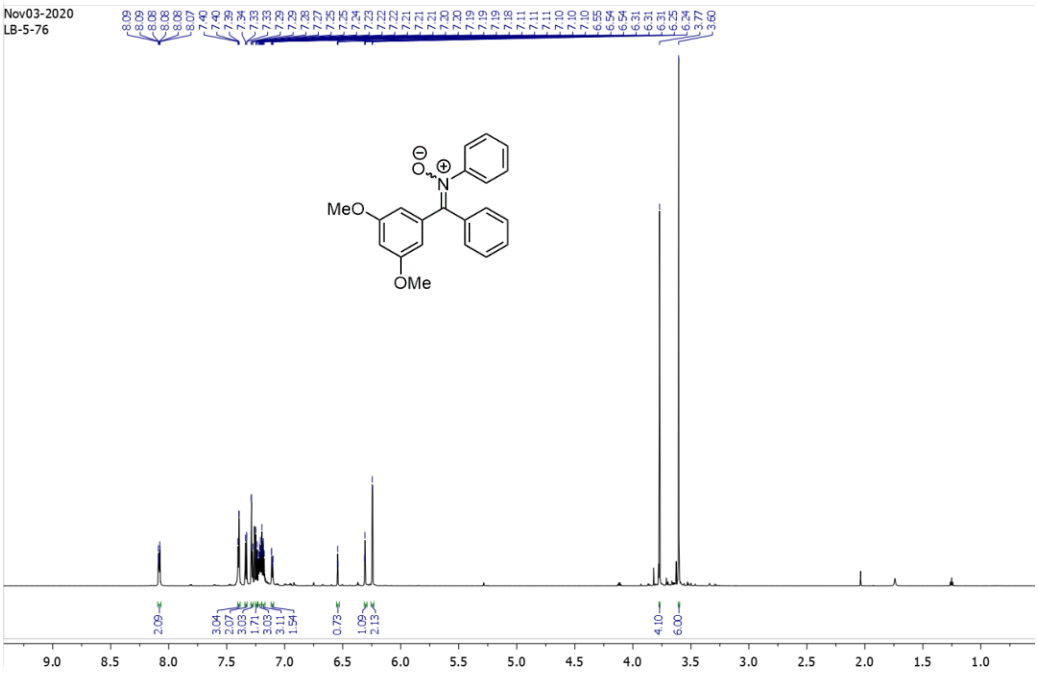
Compound **127** (^{1}H NMR; 700 MHz; Chloroform-*d*)



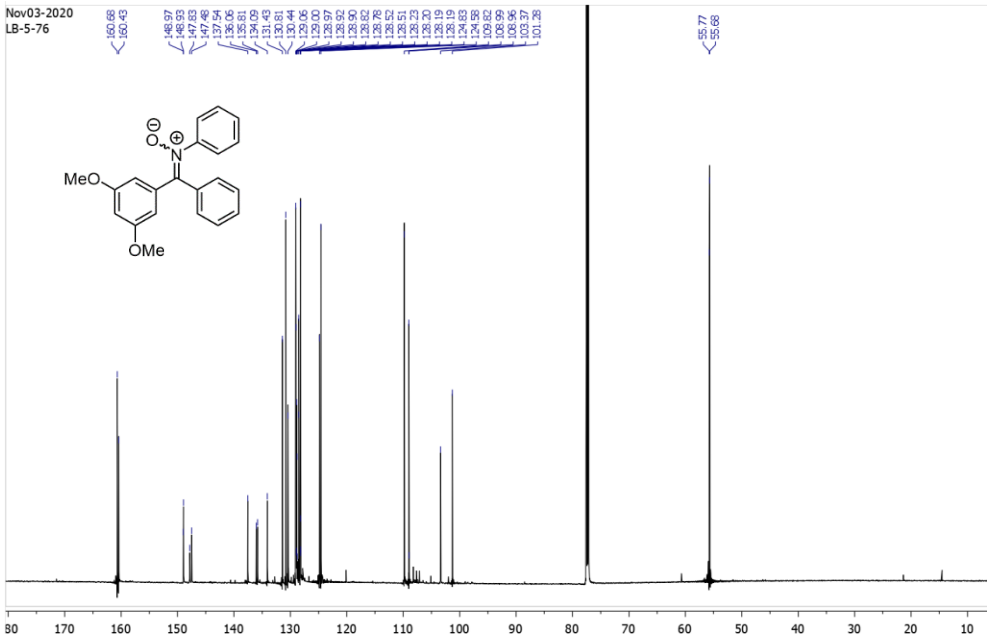
Compound **127** (^{13}C NMR; 176 MHz; Chloroform-*d*)



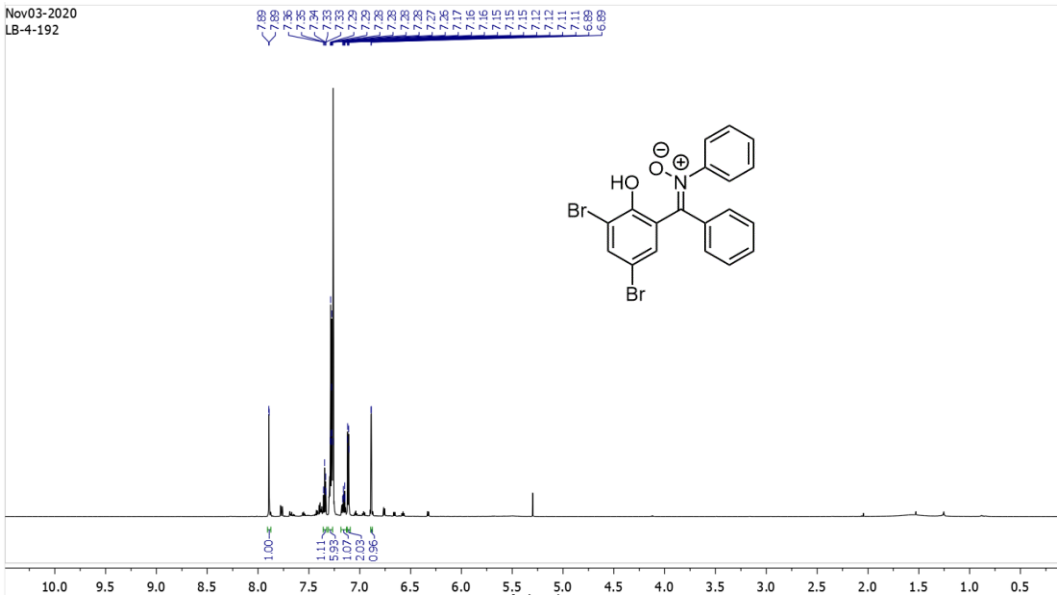
Compound **128** (^{1}H NMR; 700 MHz; Chloroform-*d*)



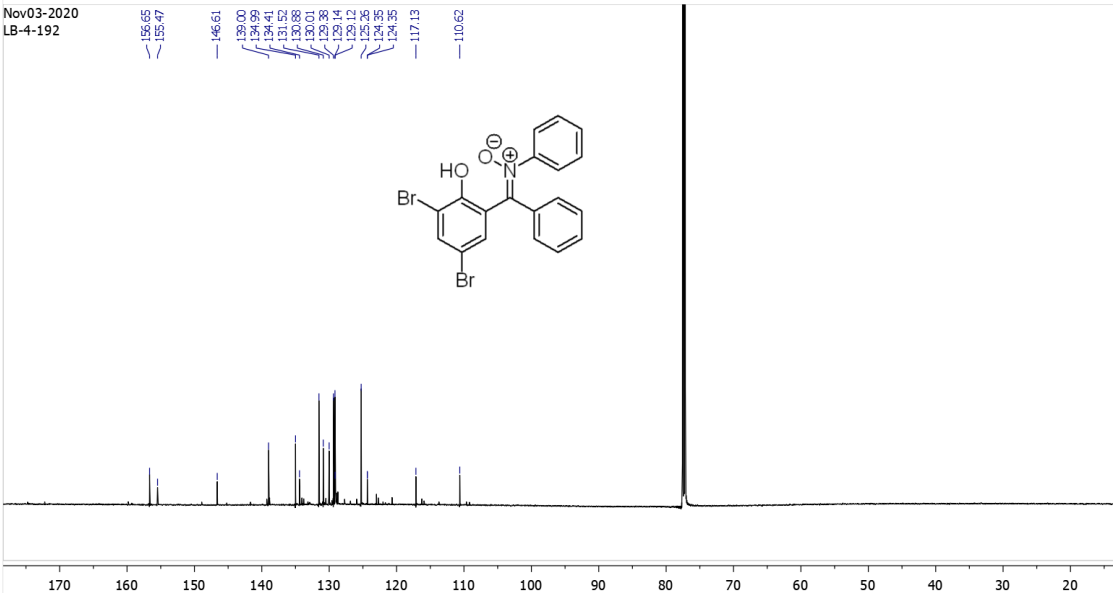
Compound **128** (^{13}C NMR; 176 MHz; Chloroform-*d*)



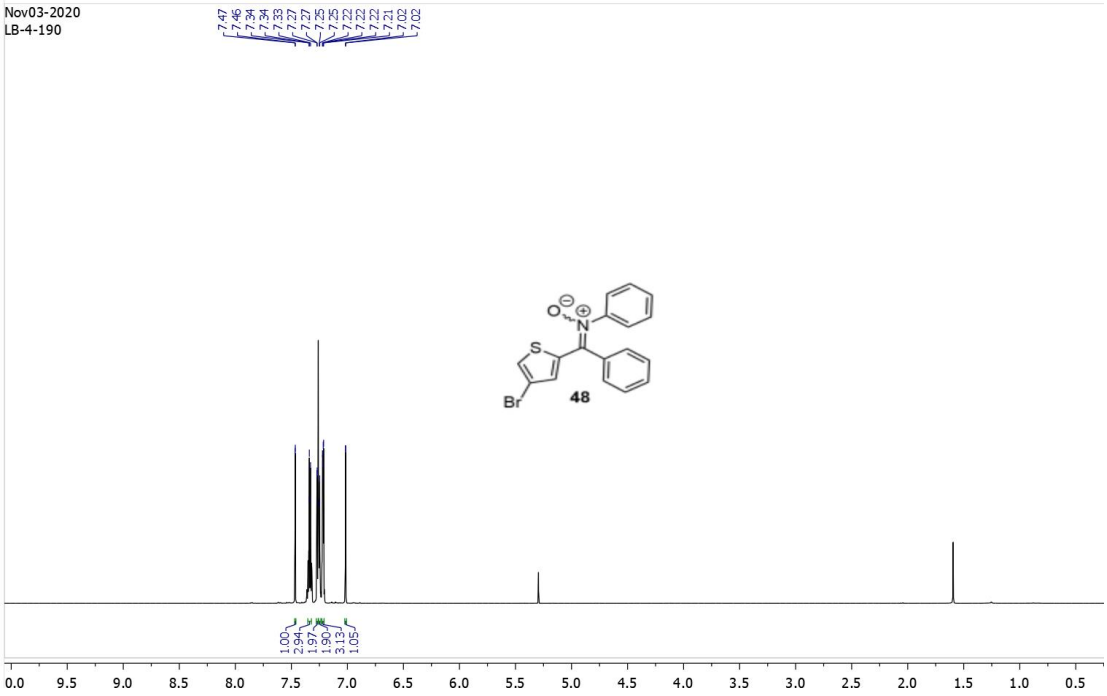
Compound **129** (^{1}H NMR; 700 MHz; Chloroform-*d*)



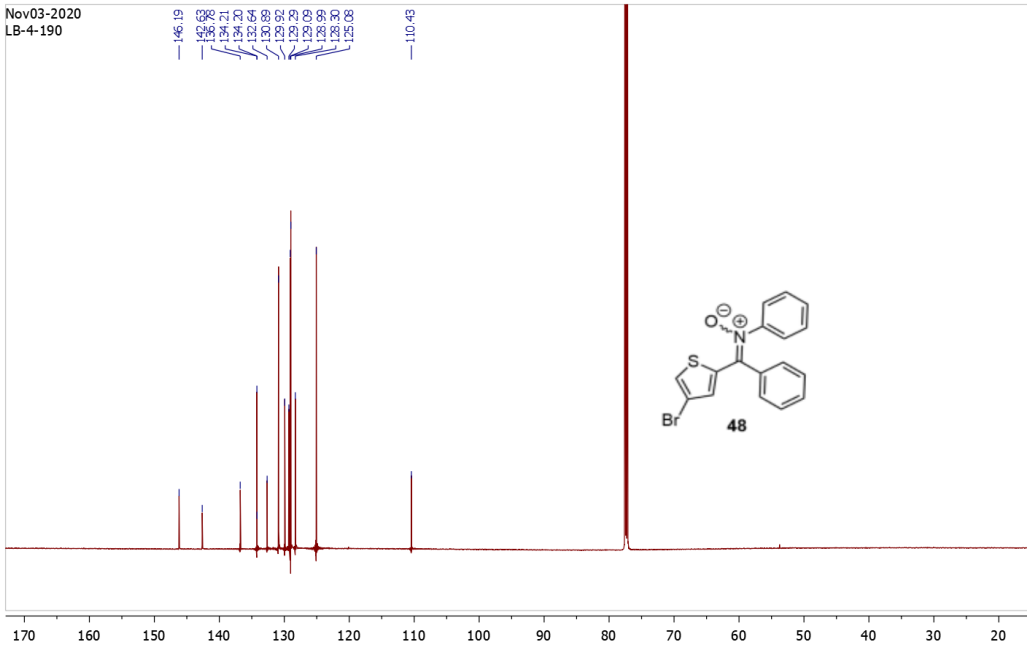
Compound **129** (^{13}C NMR; 176 MHz; Chloroform-*d*)



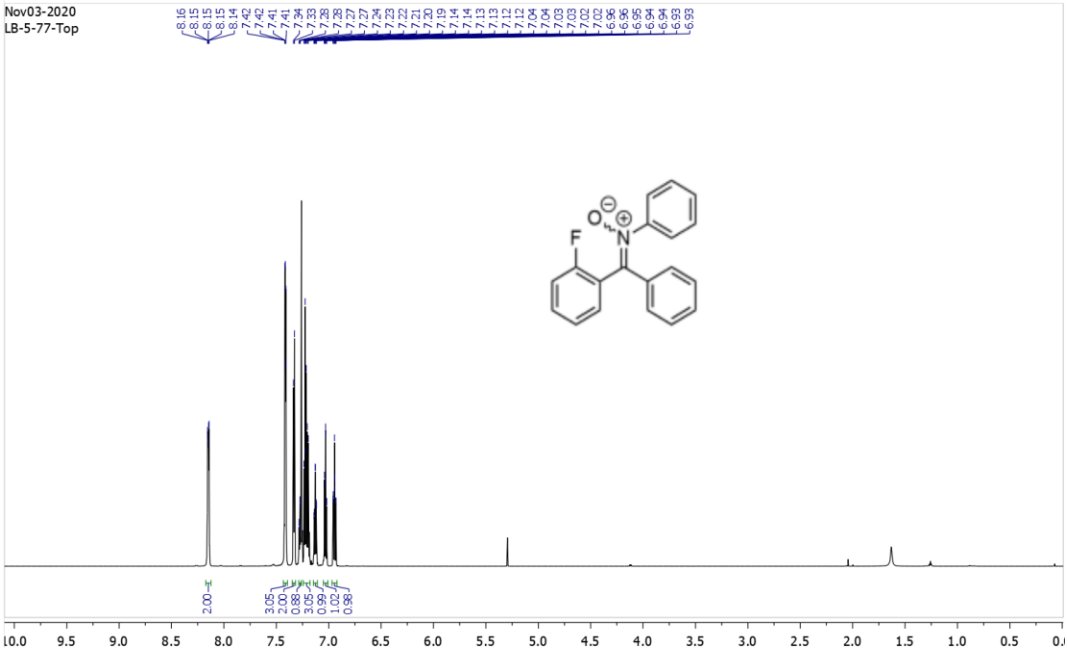
Compound **130** (^{1}H NMR; 700 MHz; Chloroform-*d*)



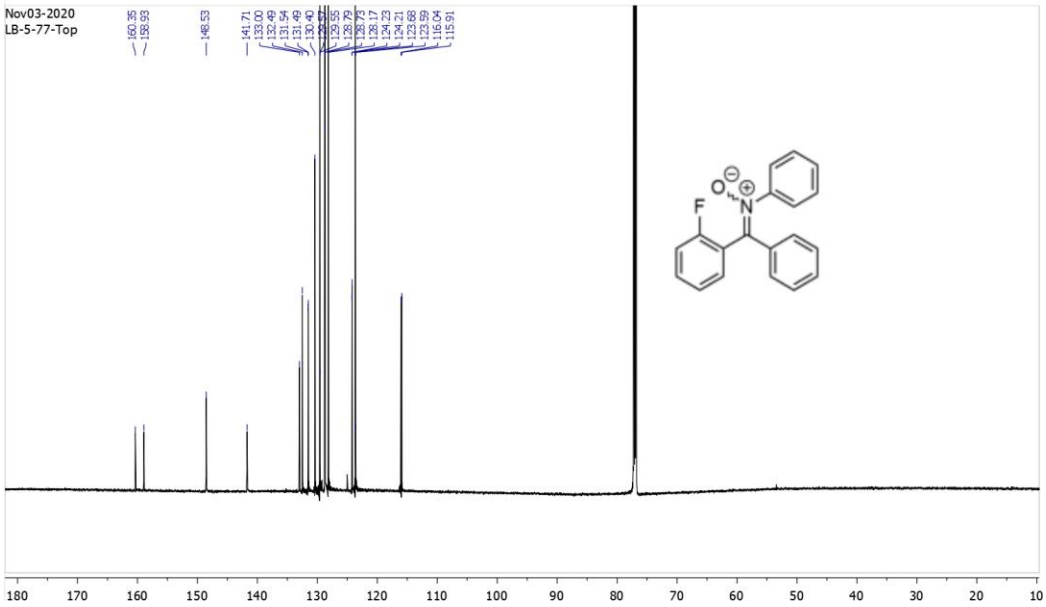
Compound **130** (^{13}C NMR; 176 MHz; Chloroform-*d*)



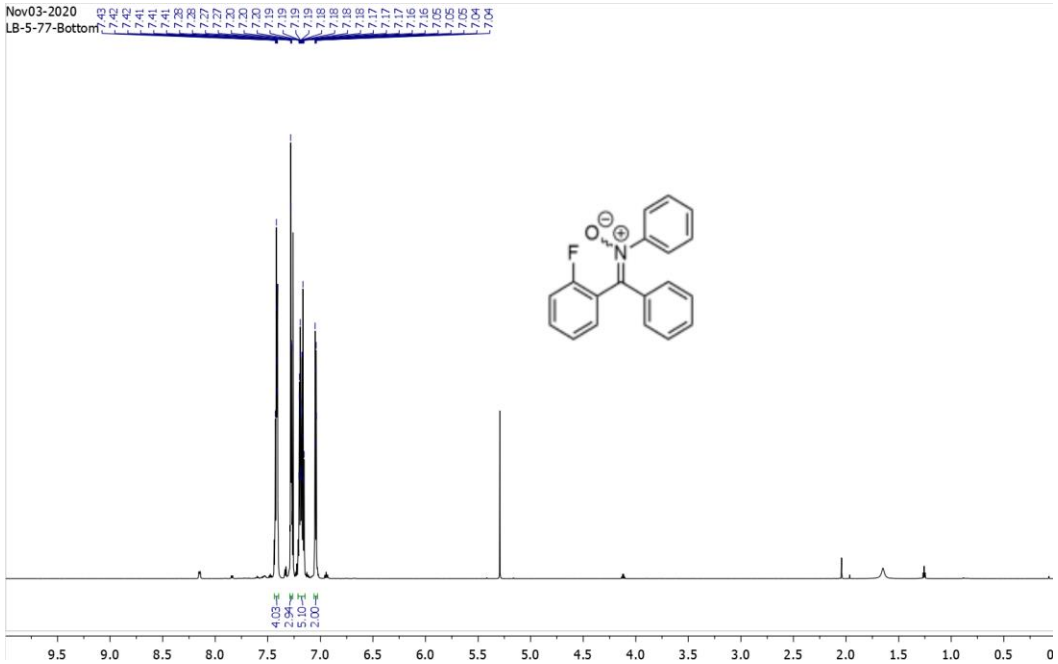
Compound **131** top (^{1}H NMR; 700 MHz; Chloroform-*d*)



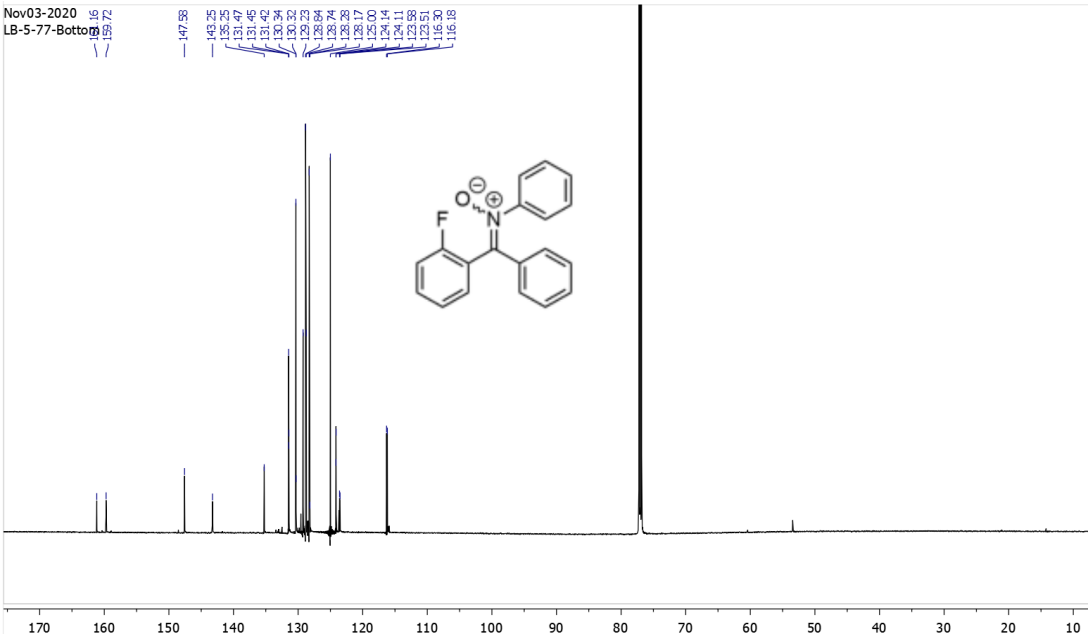
Compound **131** top (^{13}C NMR; 176 MHz; Chloroform-*d*)



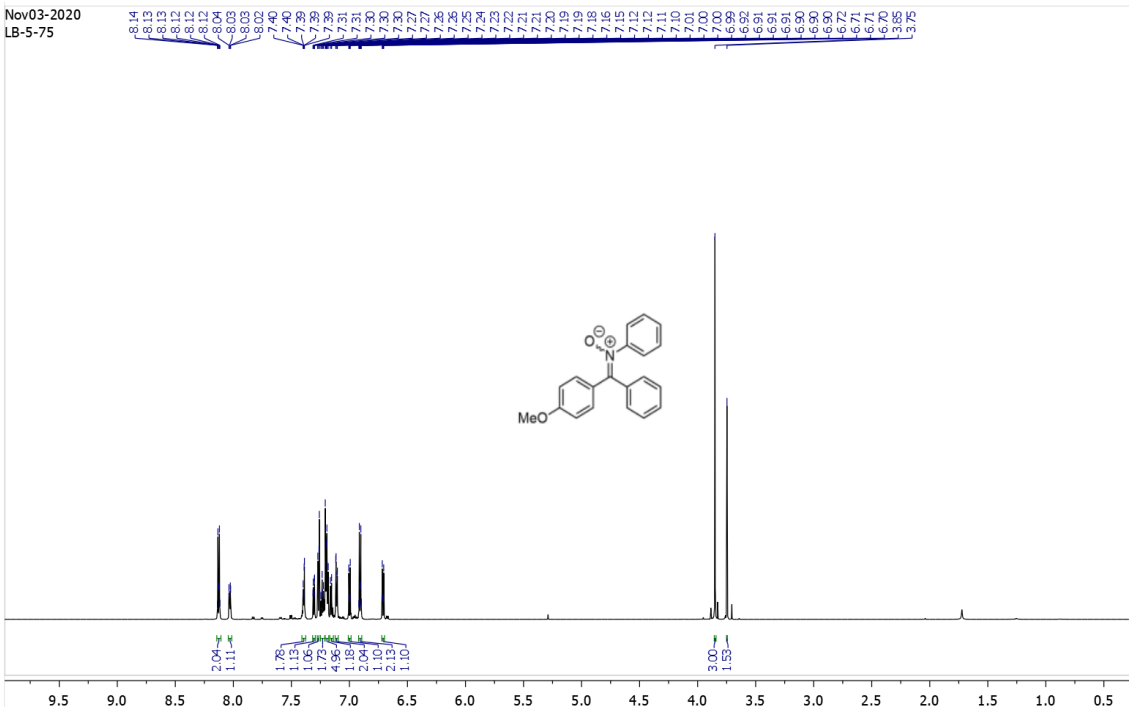
Compound **131** (^{1}H NMR; 700 MHz; Chloroform-*d*)



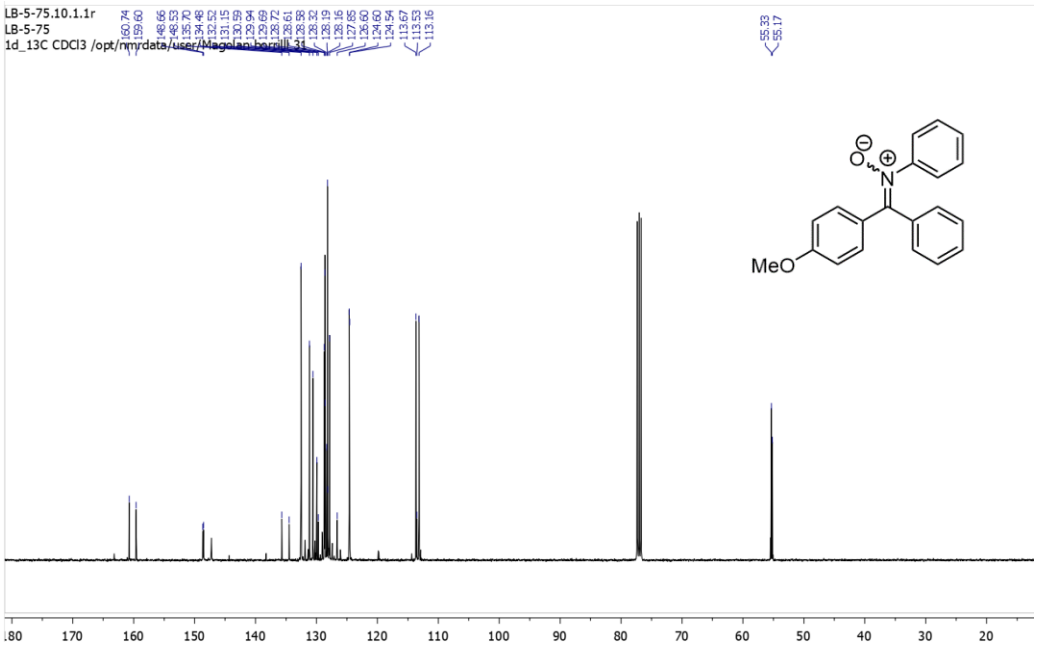
Compound **131** (^{13}C NMR; 700 MHz; Chloroform-*d*)



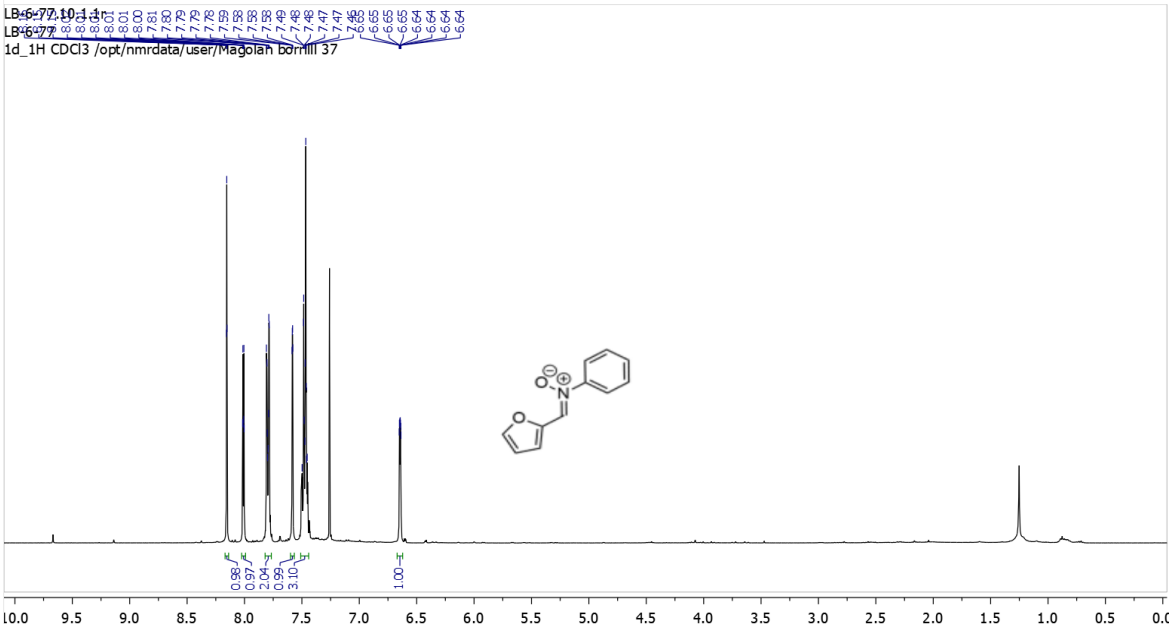
Compound **132** (^{1}H NMR; 700 MHz; Chloroform-*d*)



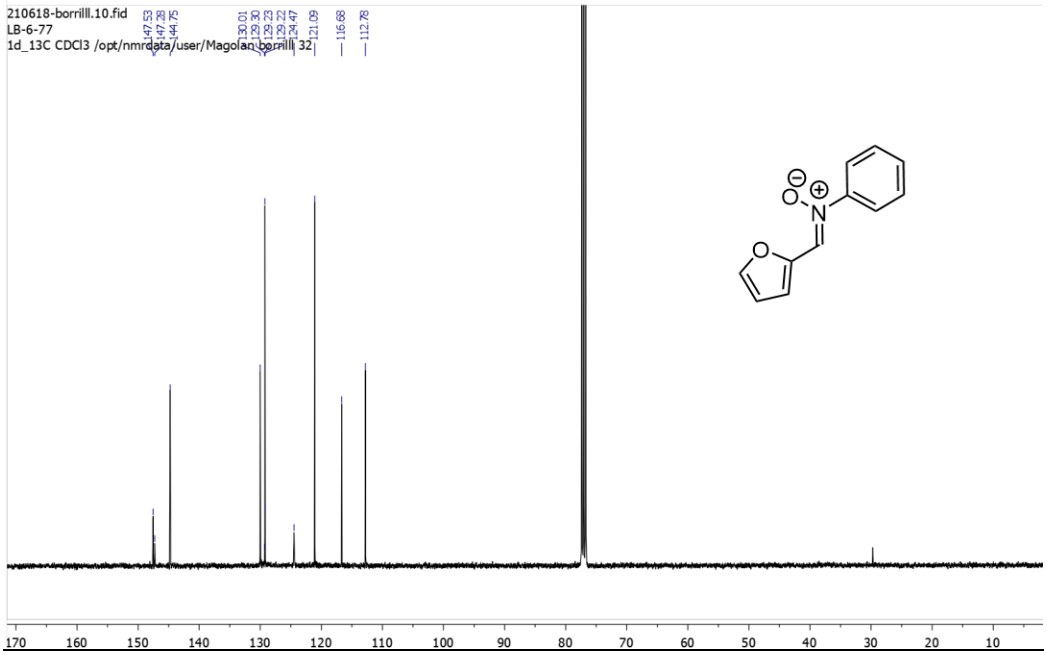
Compound **132** (^{13}C NMR; 176 MHz; Chloroform-*d*)



Compound **134** (^{1}H NMR; 400 MHz; Chloroform-*d*)



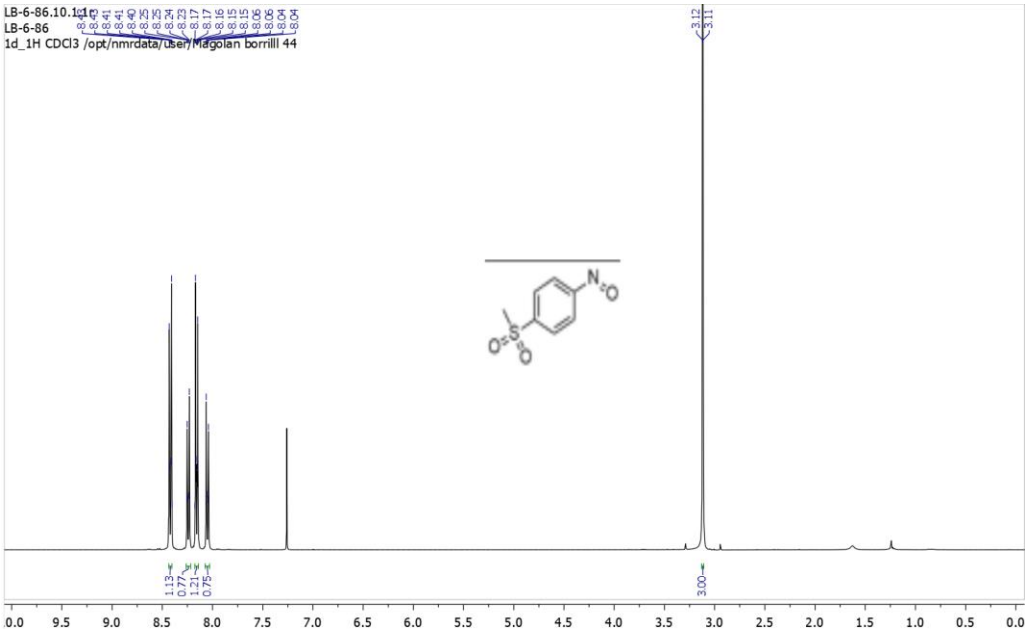
Compound **134** (^{13}C NMR; 100 MHz; Chloroform-*d*)



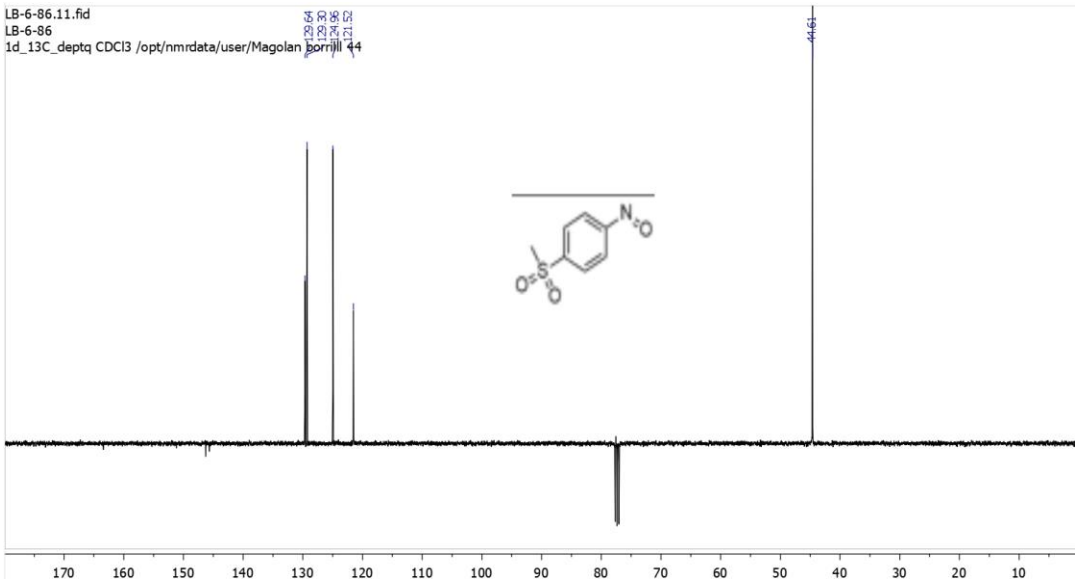
Compound 140 (^{1}H NMR; 400 MHz; Chloroform-*d*)

Compound 141 (^{1}H NMR; 400 MHz; Chloroform-*d*)

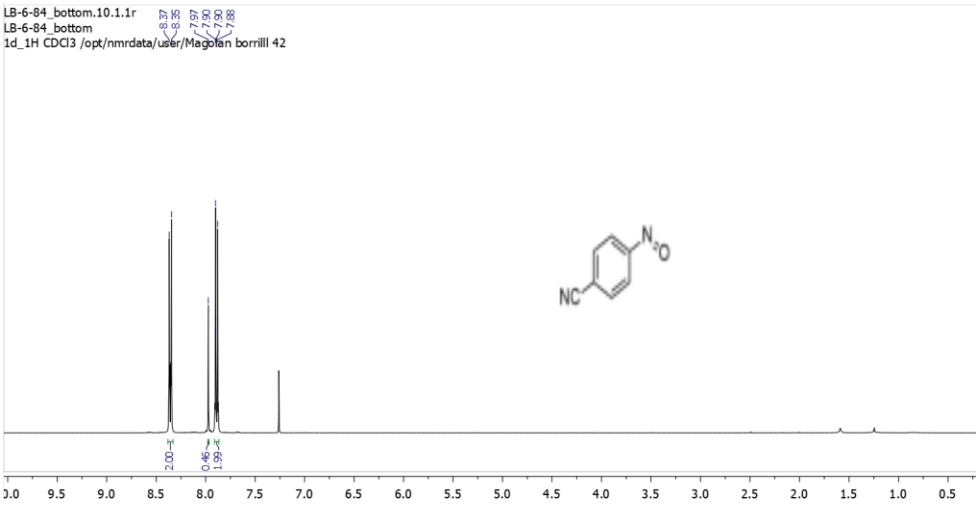
Compound 142 (^{1}H NMR; 400 MHz; Chloroform-*d*)



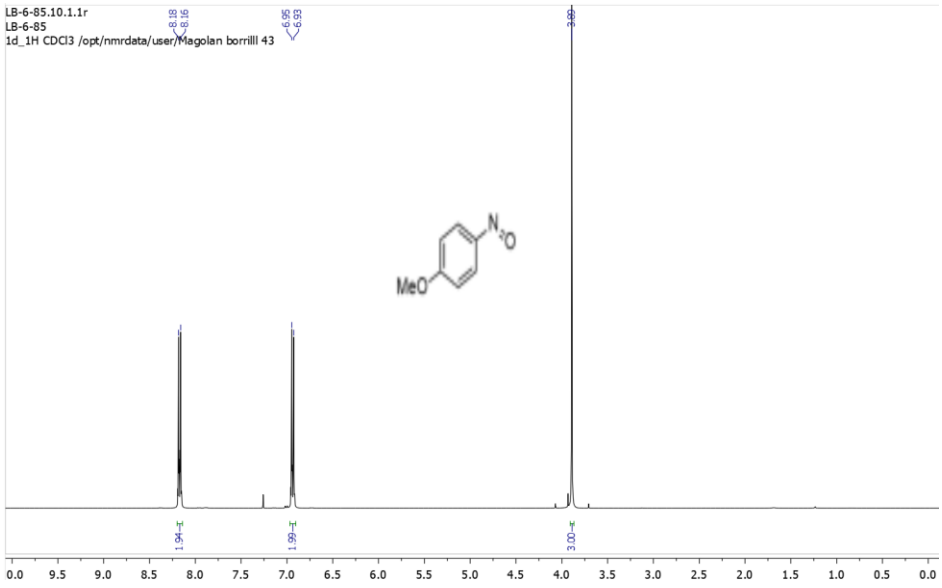
Compound 142 (^{13}C NMR; 100 MHz; Chloroform-*d*)



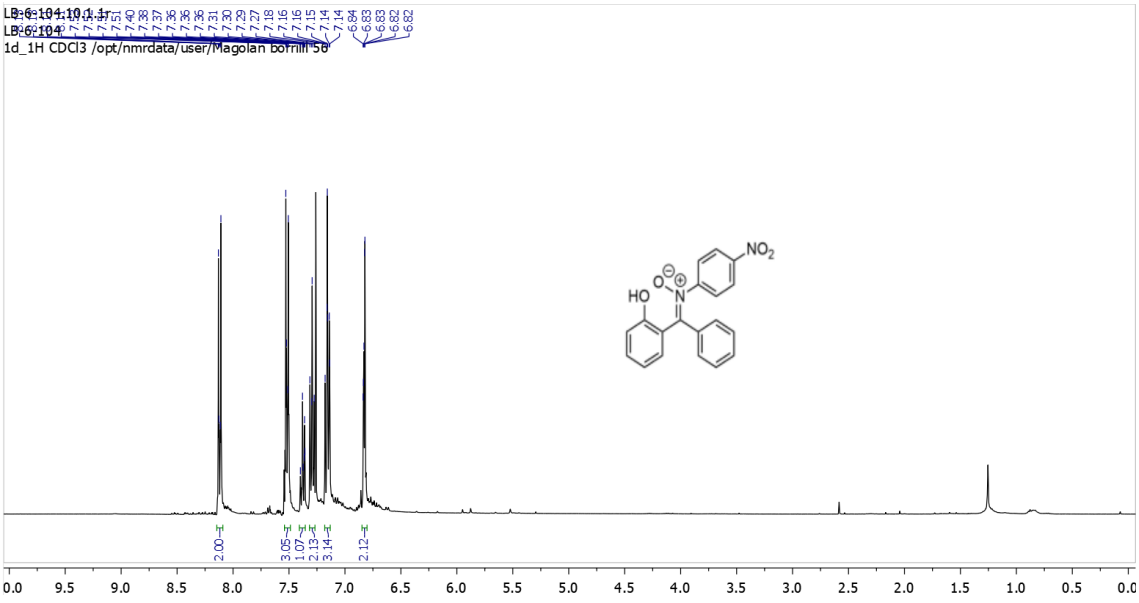
Compound 143 (^{1}H NMR; 400 MHz; Chloroform-*d*)



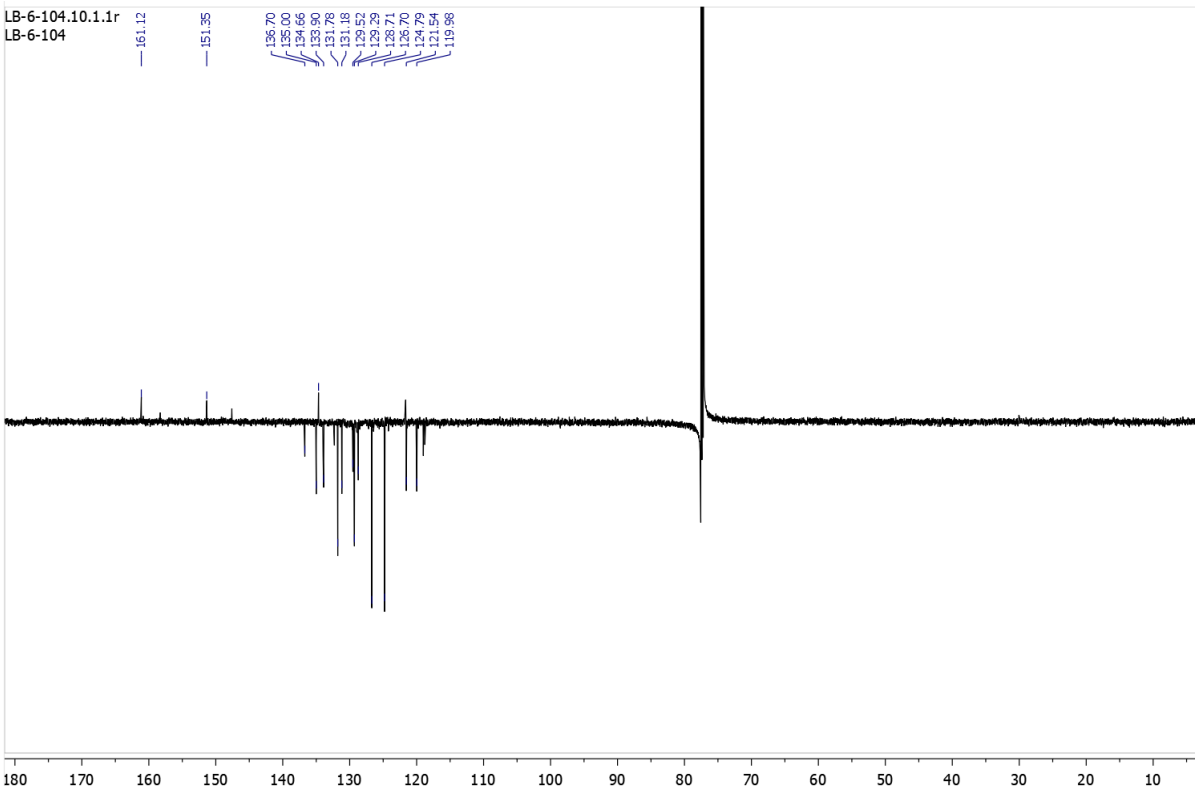
Compound 144 (^{1}H NMR; 400 MHz; Chloroform-*d*)



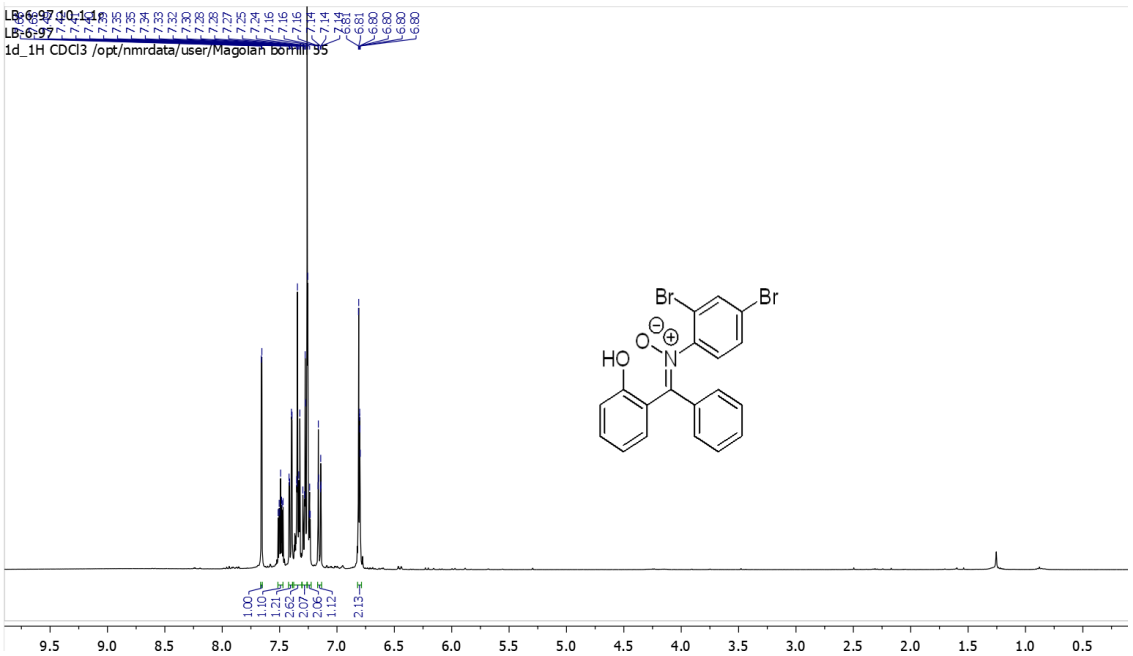
Compound 145 (^{1}H NMR; 400 MHz; Chloroform-*d*)



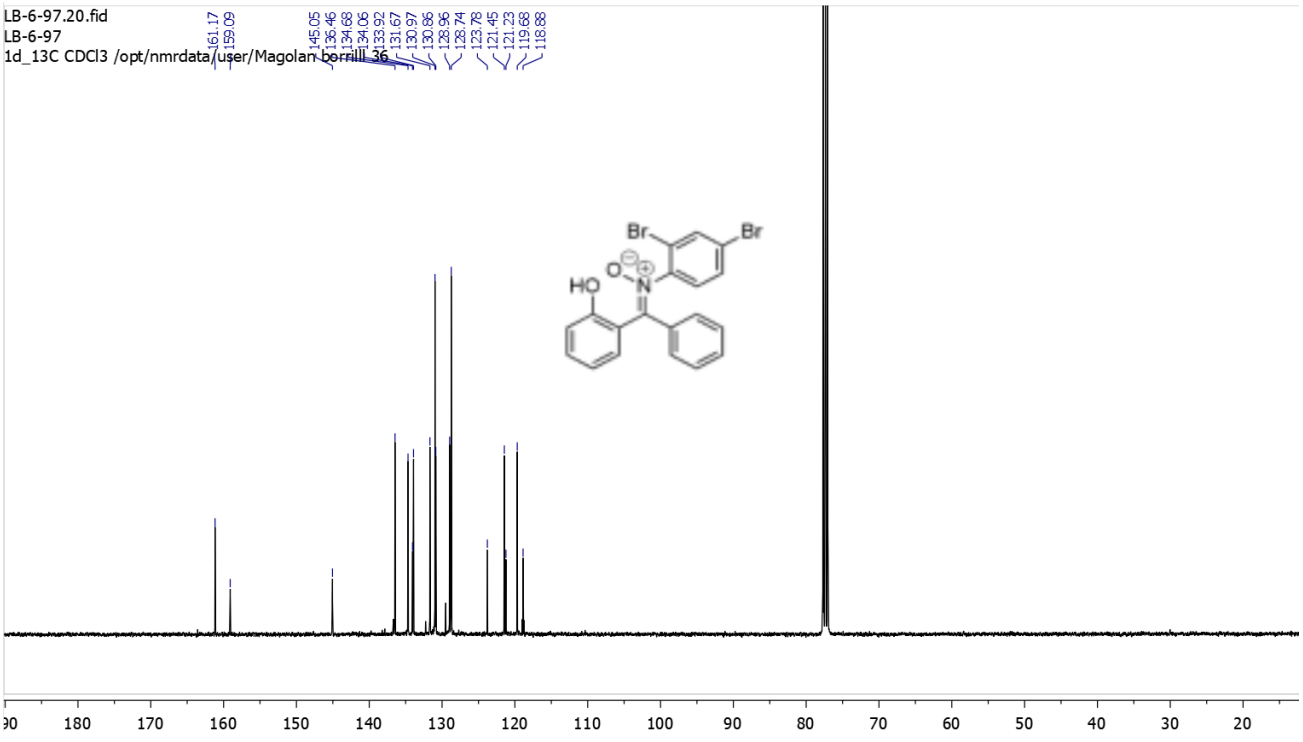
Compound 145 (^{13}C NMR; 100 MHz; Chloroform-*d*)



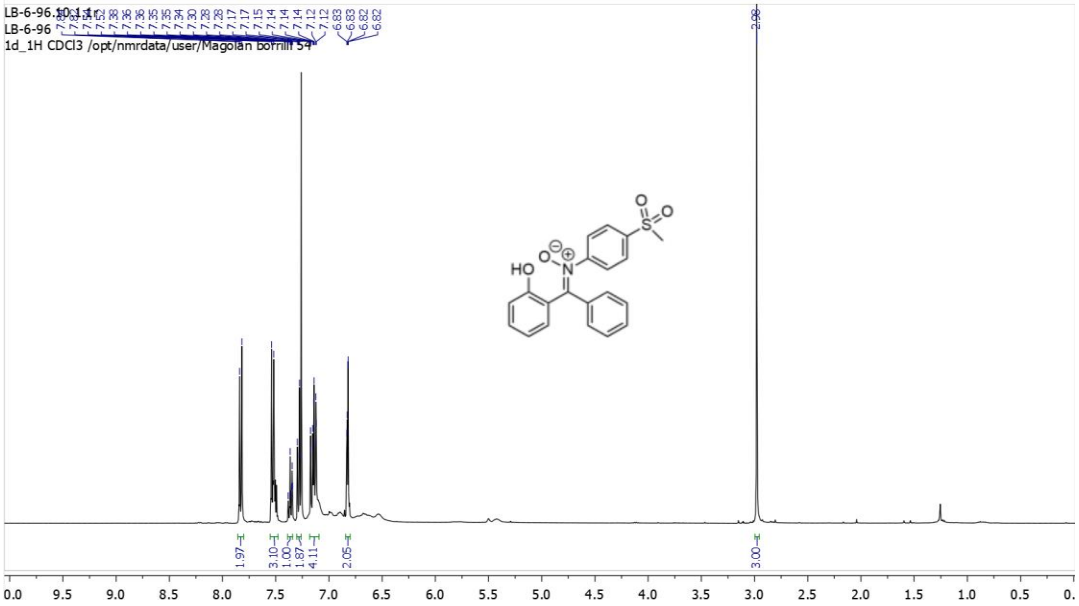
Compound 146 (^{1}H NMR; 400 MHz; Chloroform-*d*)



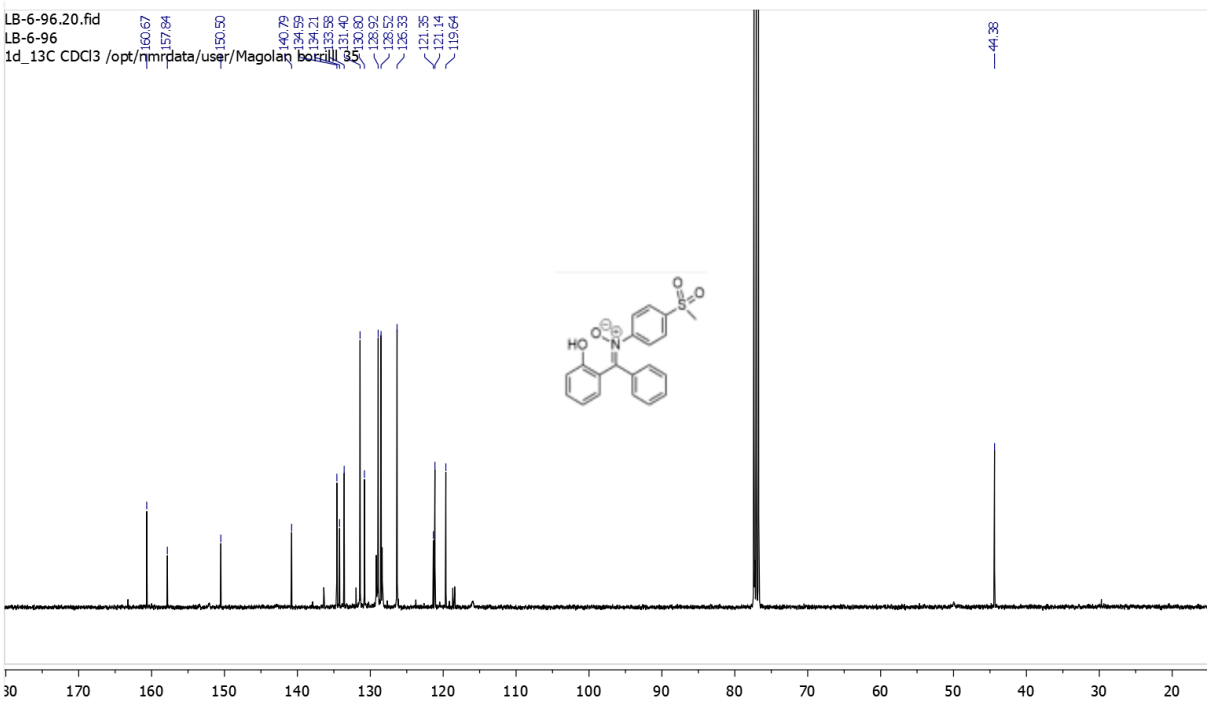
Compound 146 (^{13}C NMR; 100 MHz; Chloroform-*d*)



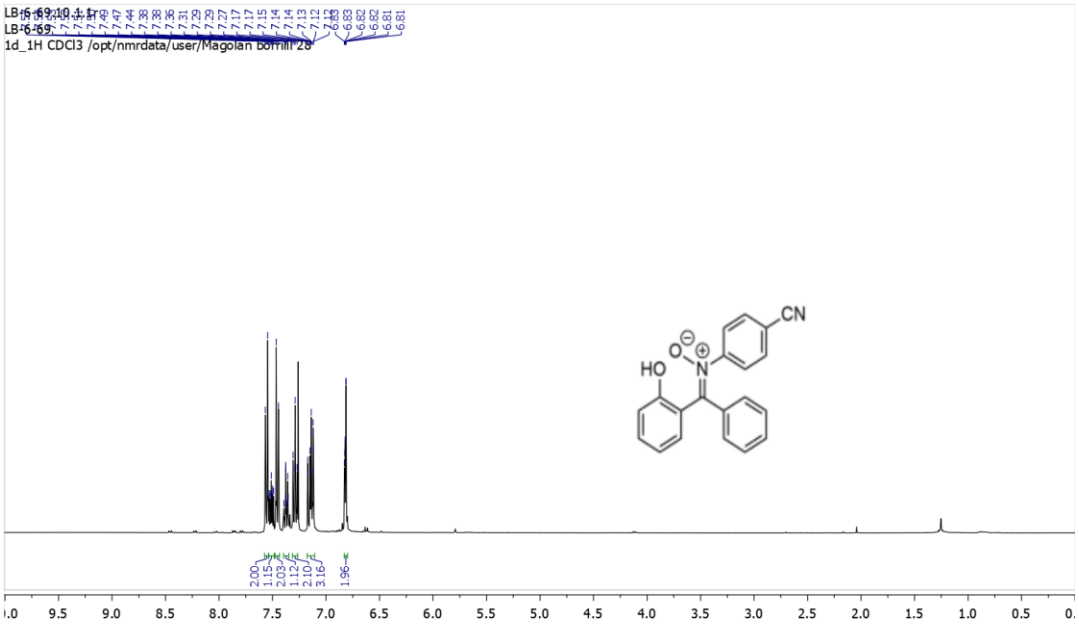
Compound 147 (^{1}H NMR; 400 MHz; Chloroform-*d*)



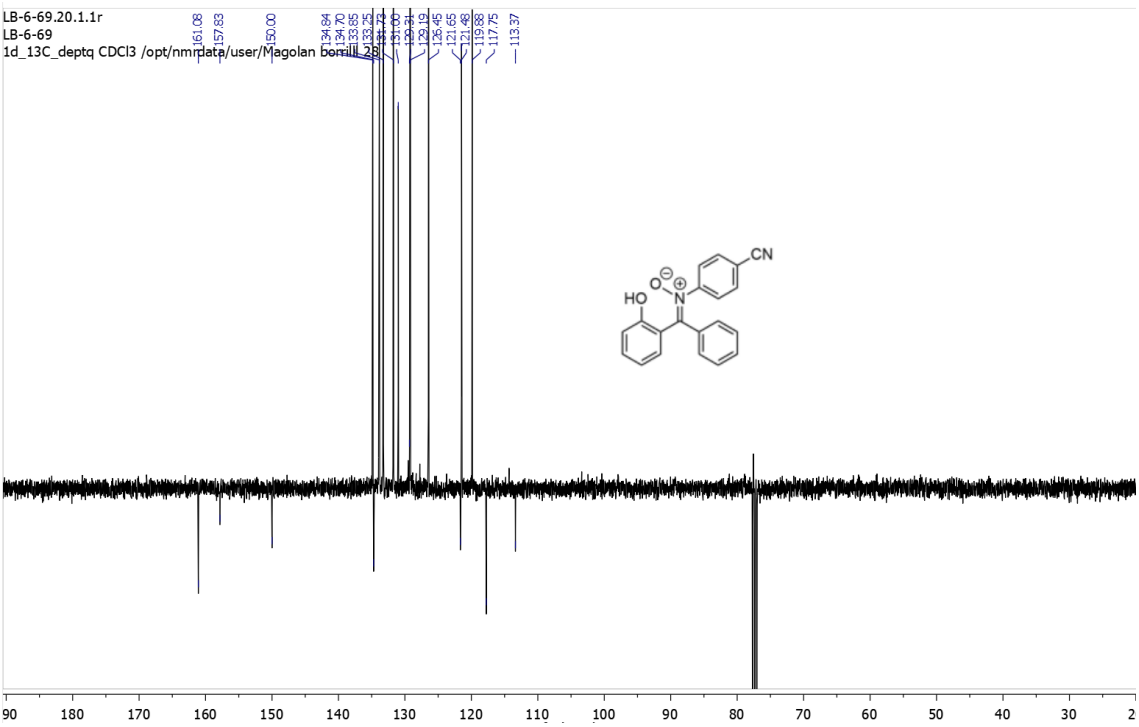
Compound 147 (^{13}C NMR; 100 MHz; Chloroform-*d*)



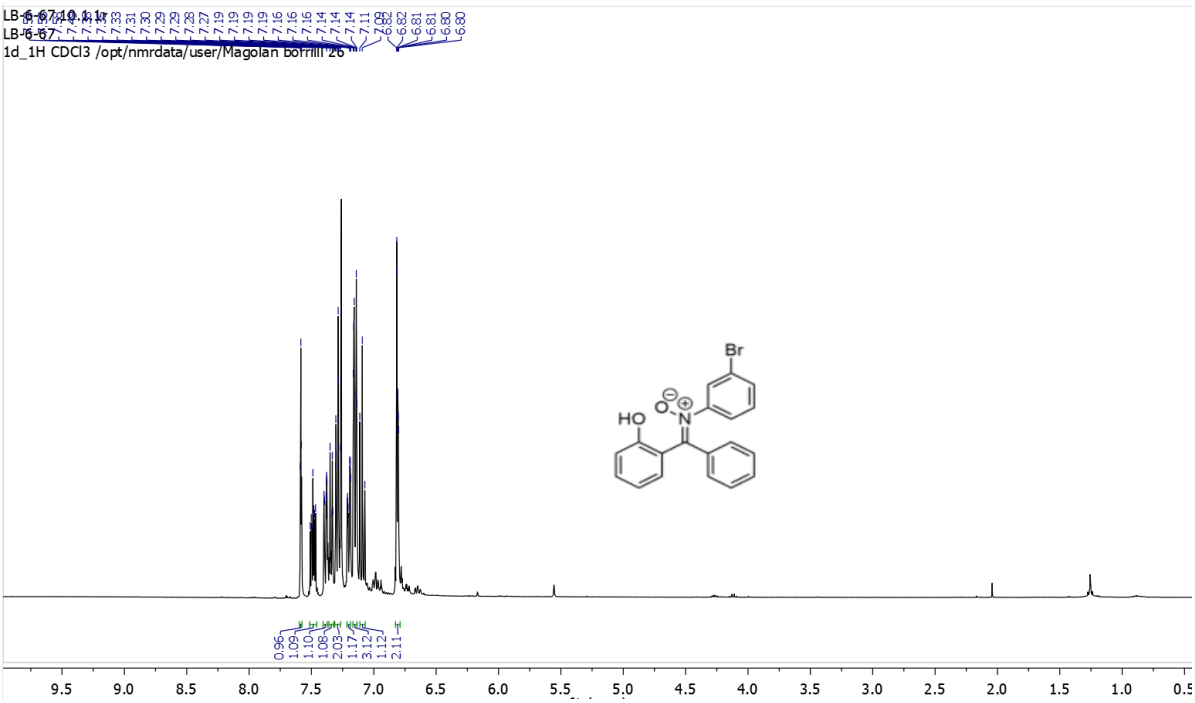
Compound 148/150 (^{1}H NMR; 400 MHz; Chloroform-*d*)



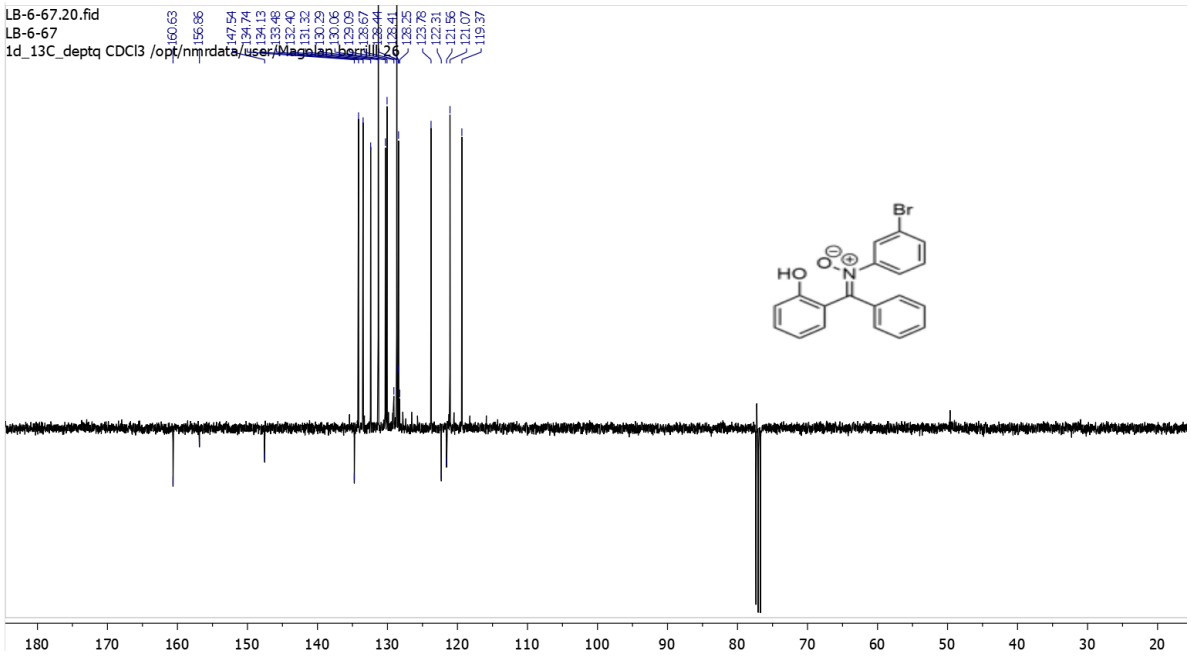
Compound 148/150 (^{13}C NMR; 100 MHz; Chloroform-*d*)



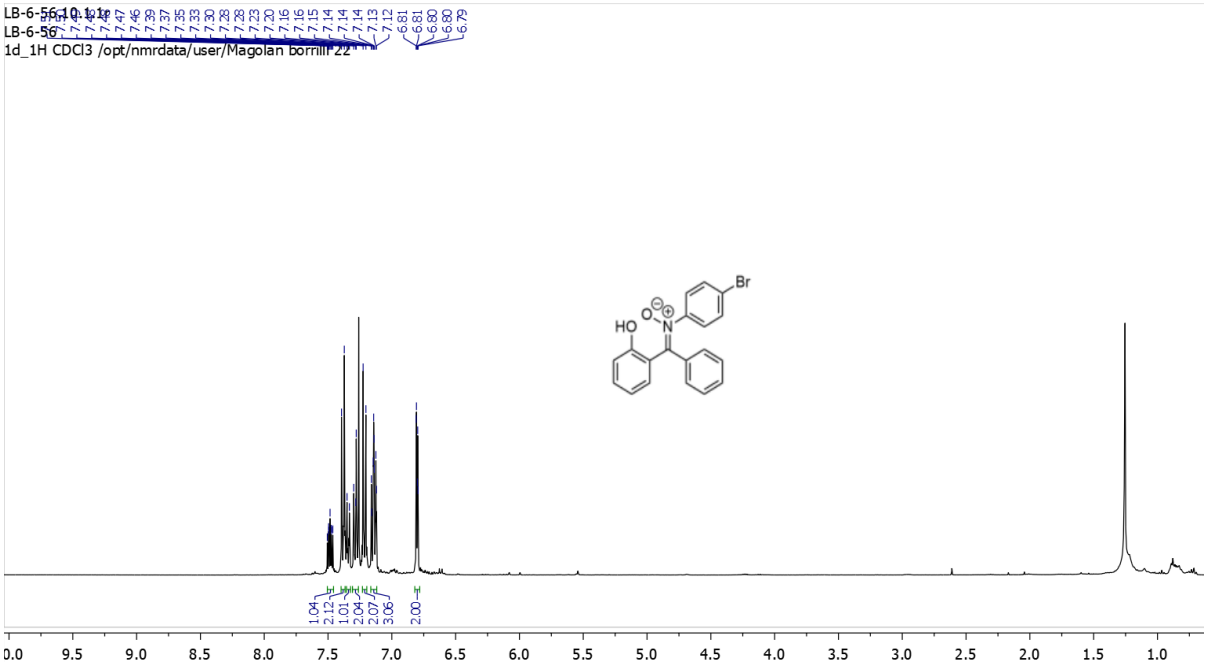
Compound 151 (^{1}H NMR; 400 MHz; Chloroform-*d*)



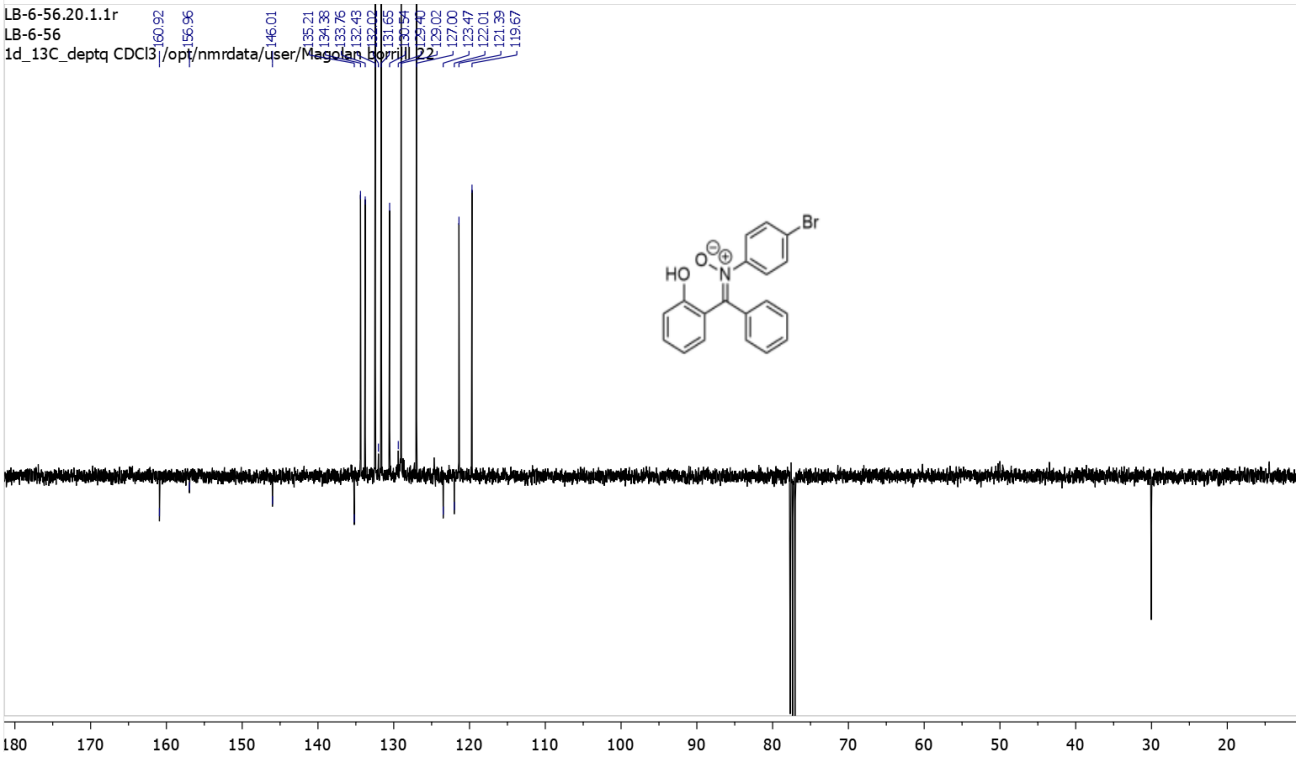
Compound 151 (^{13}C NMR; 100 MHz; Chloroform-*d*)



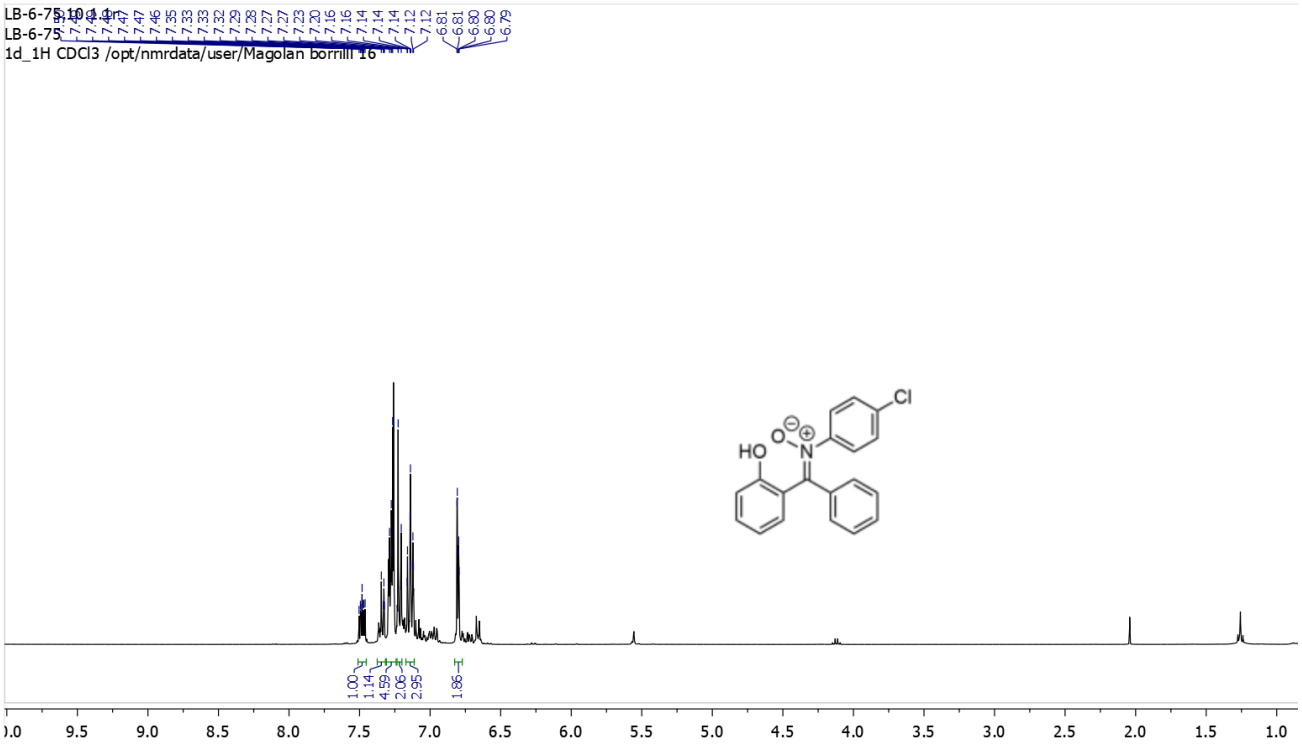
Compound 152 (^{1}H NMR; 400 MHz; Chloroform-*d*)



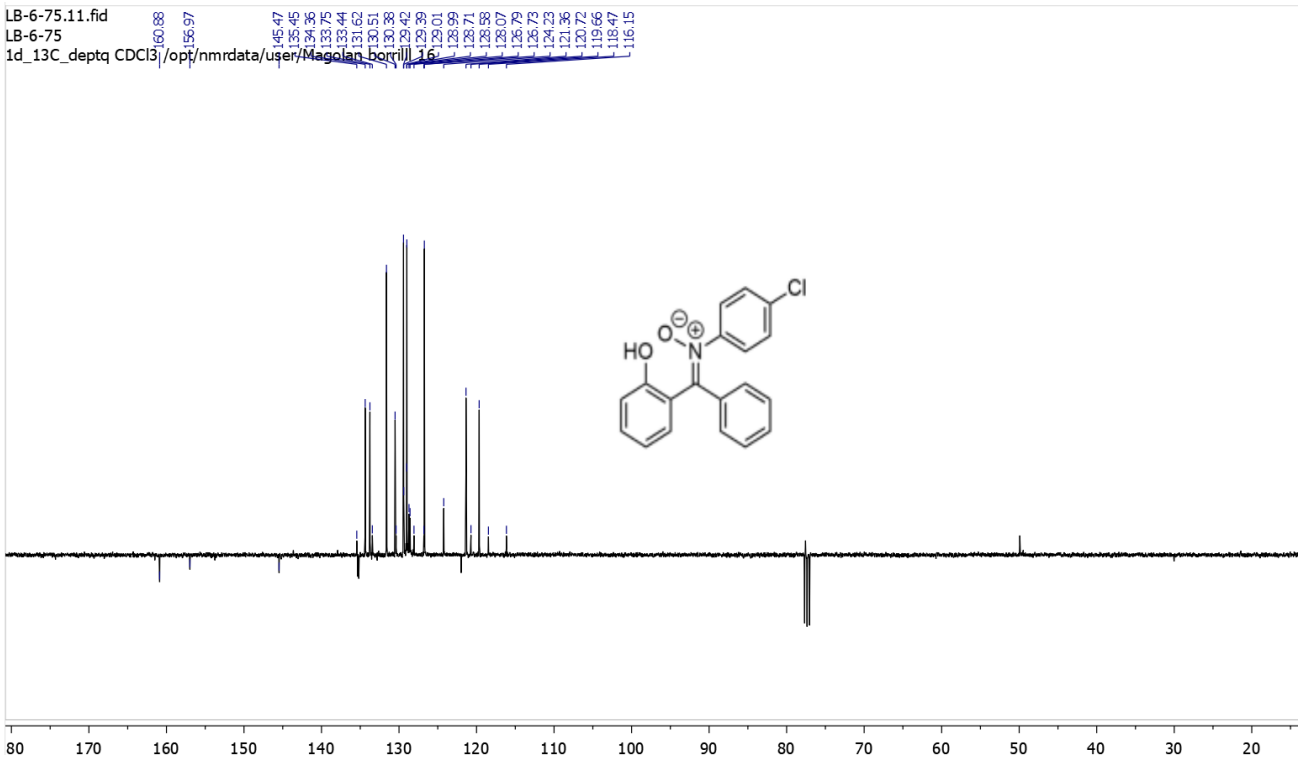
Compound 152 (^{13}C NMR; 100 MHz; Chloroform-*d*)



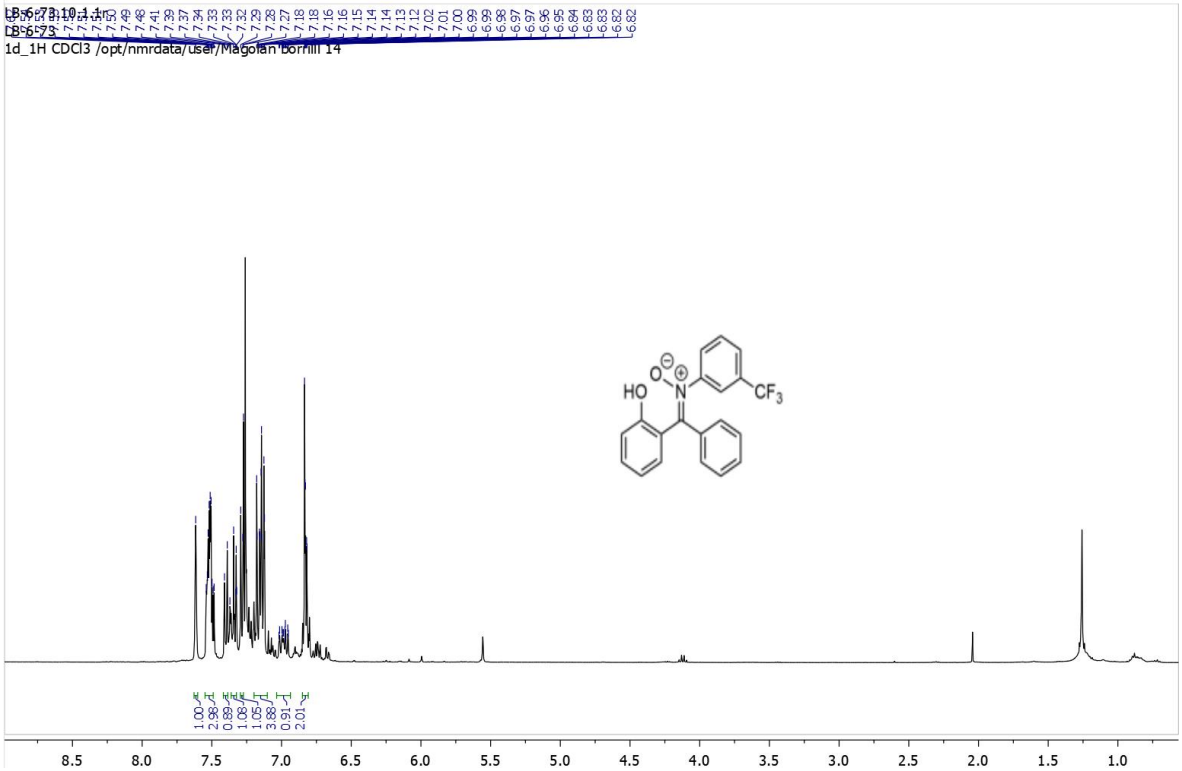
Compound 153 (^{1}H NMR; 400 MHz; Chloroform-*d*)



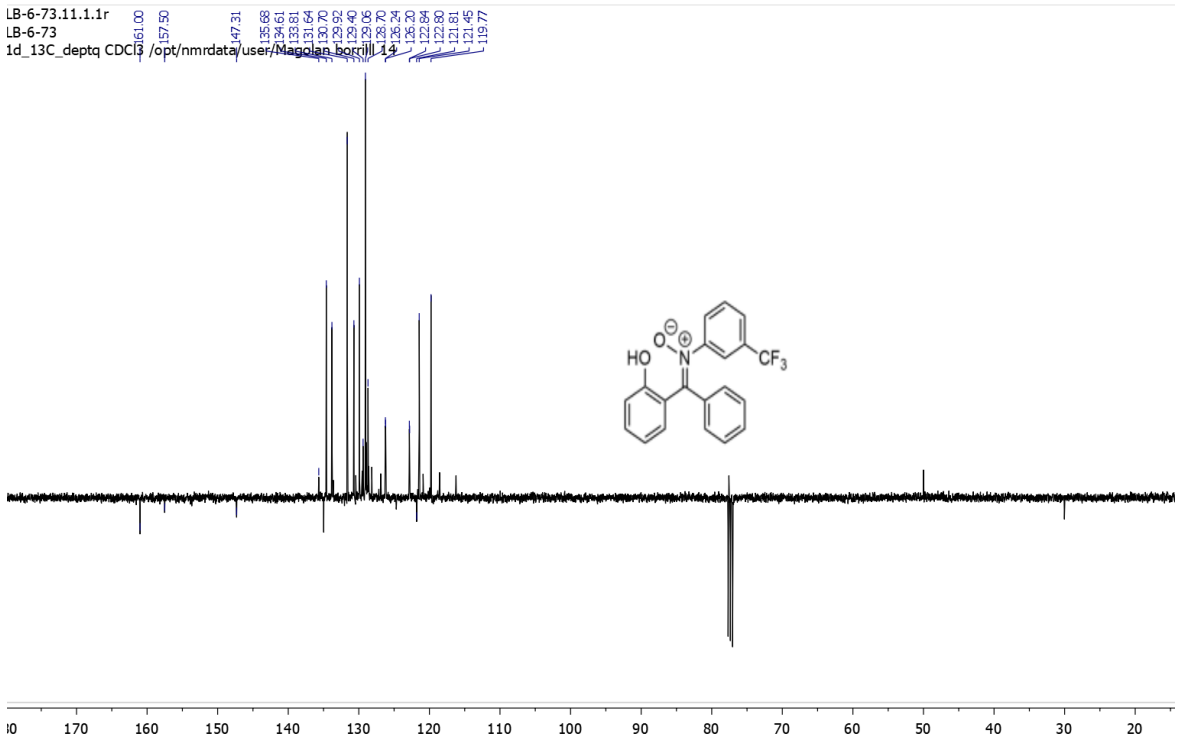
Compound 153 (^{13}C NMR; 100 MHz; Chloroform-*d*)



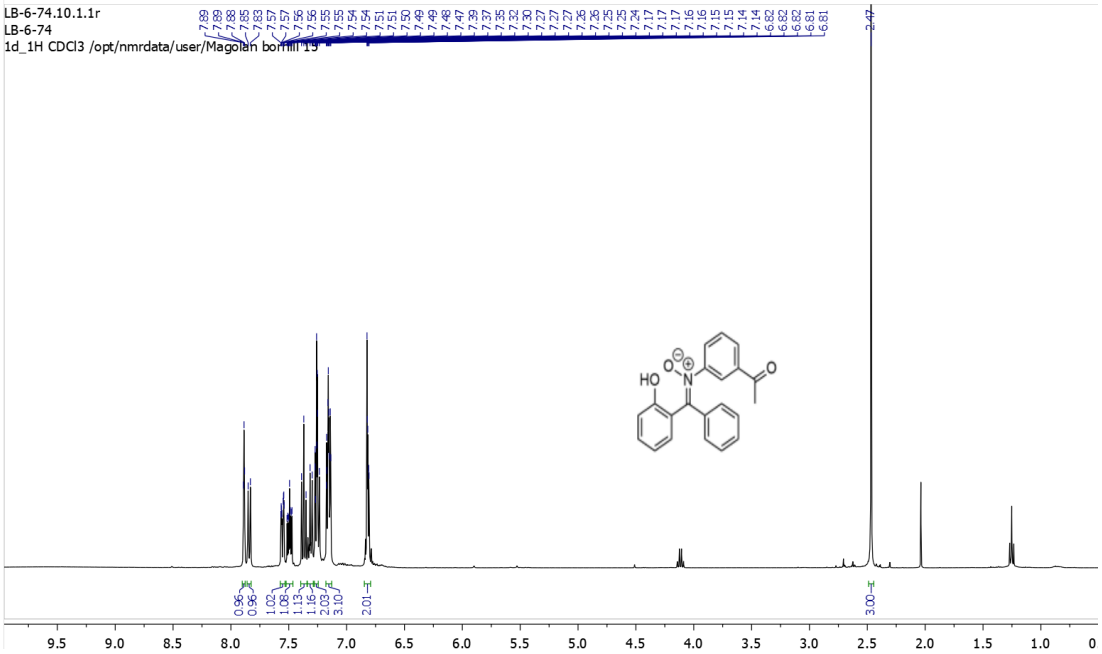
Compound 154 (^{1}H NMR; 400 MHz; Chloroform-*d*)



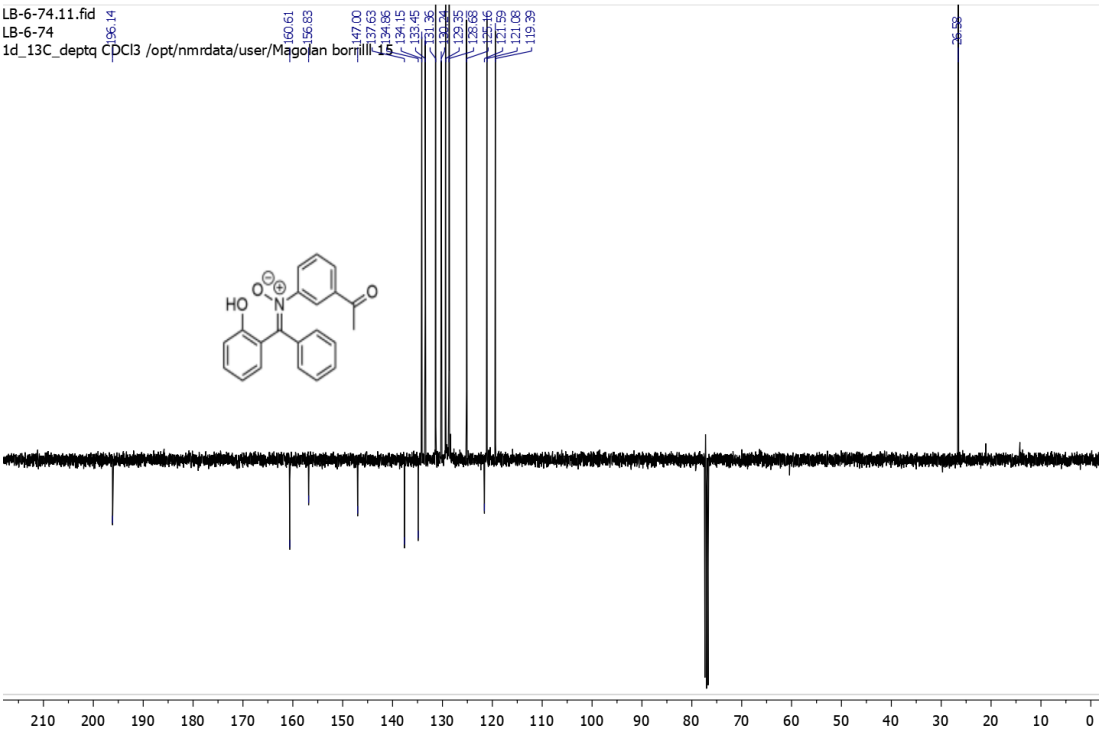
Compound 154 (^{13}C NMR; 100 MHz; Chloroform-*d*)



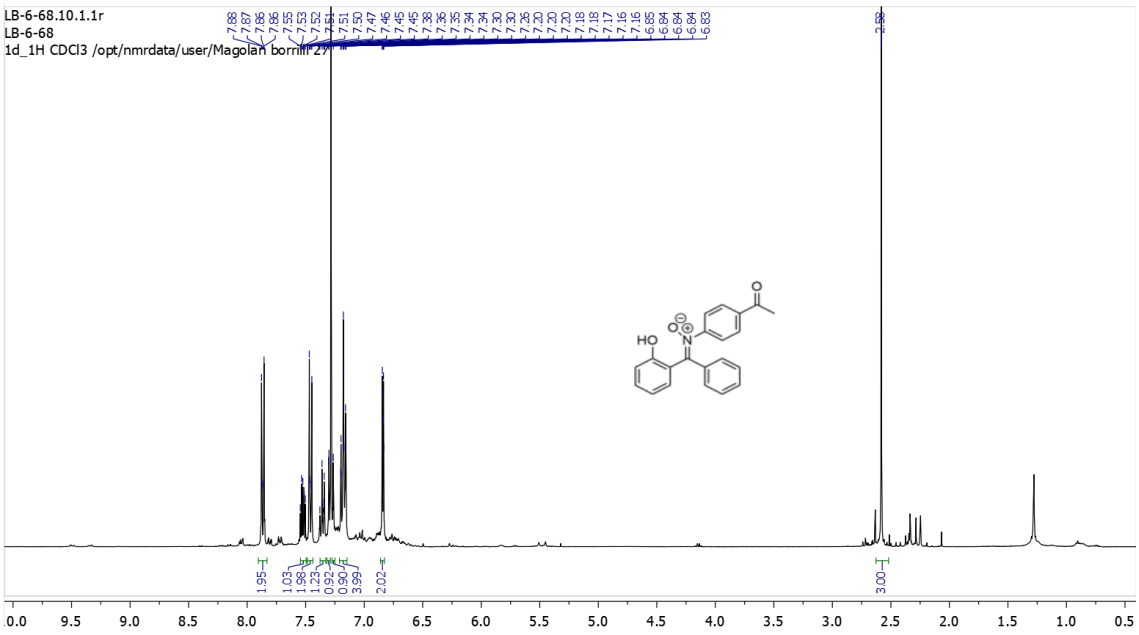
Compound 155 (^{1}H NMR; 400 MHz; Chloroform-*d*)



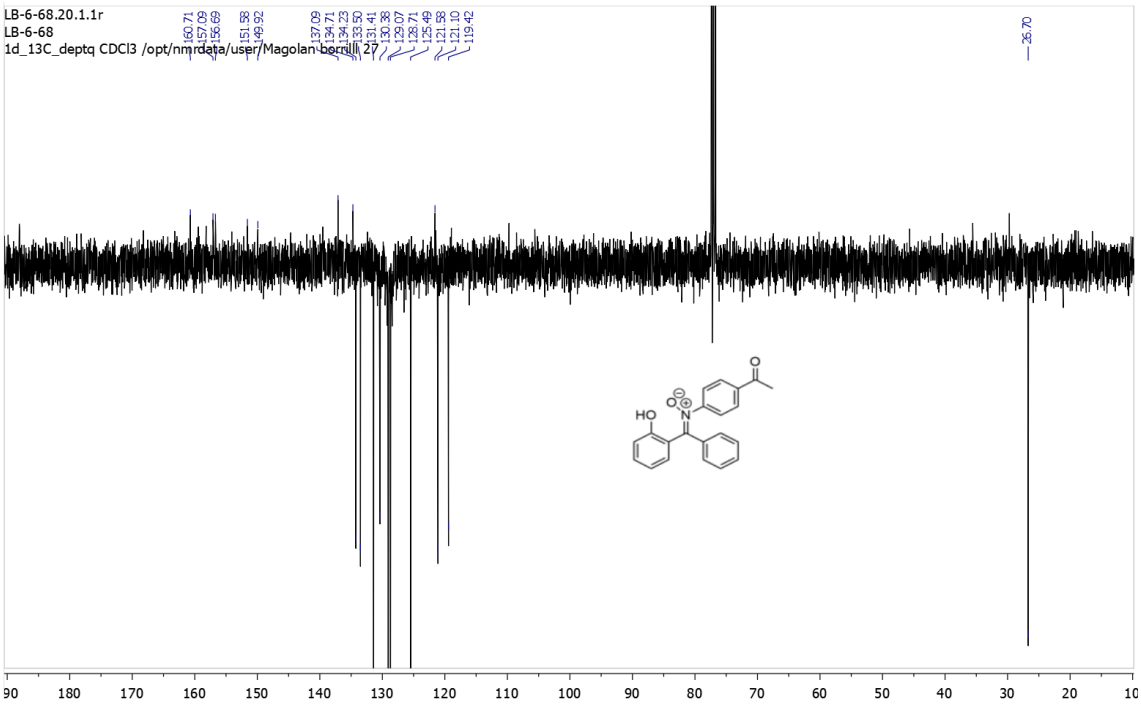
Compound 155 (^{13}C NMR; 100 MHz; Chloroform-*d*)



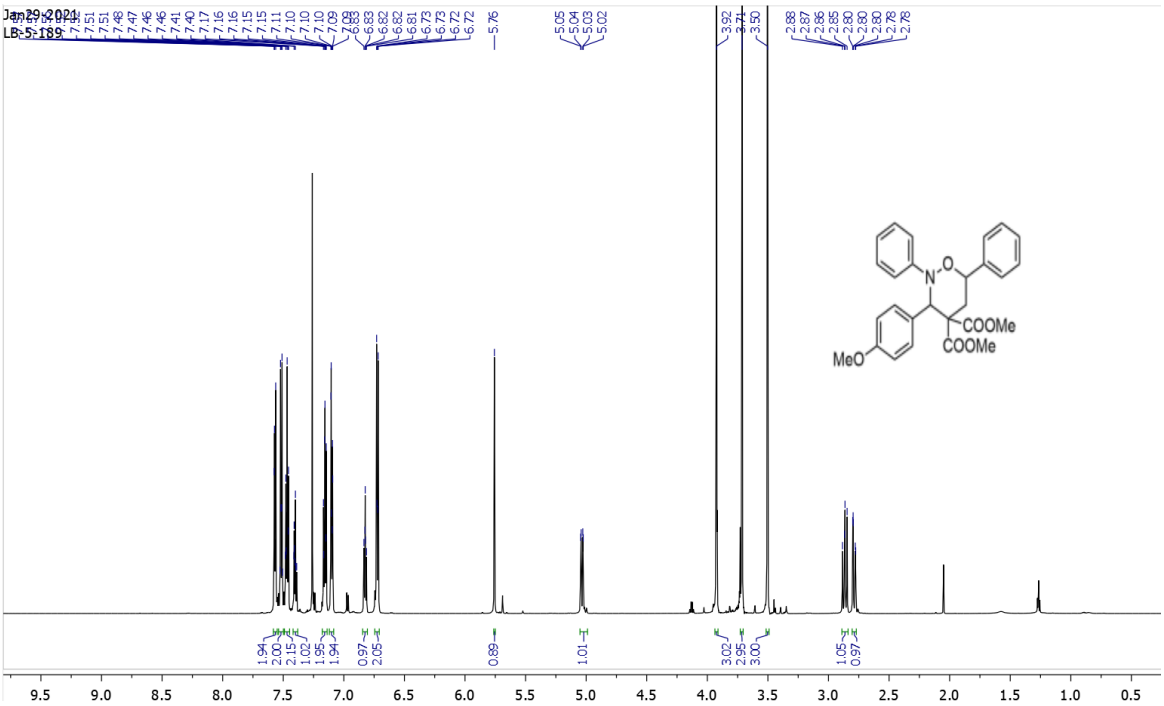
Compound 157 (^{1}H NMR; 400 MHz; Chloroform-*d*)



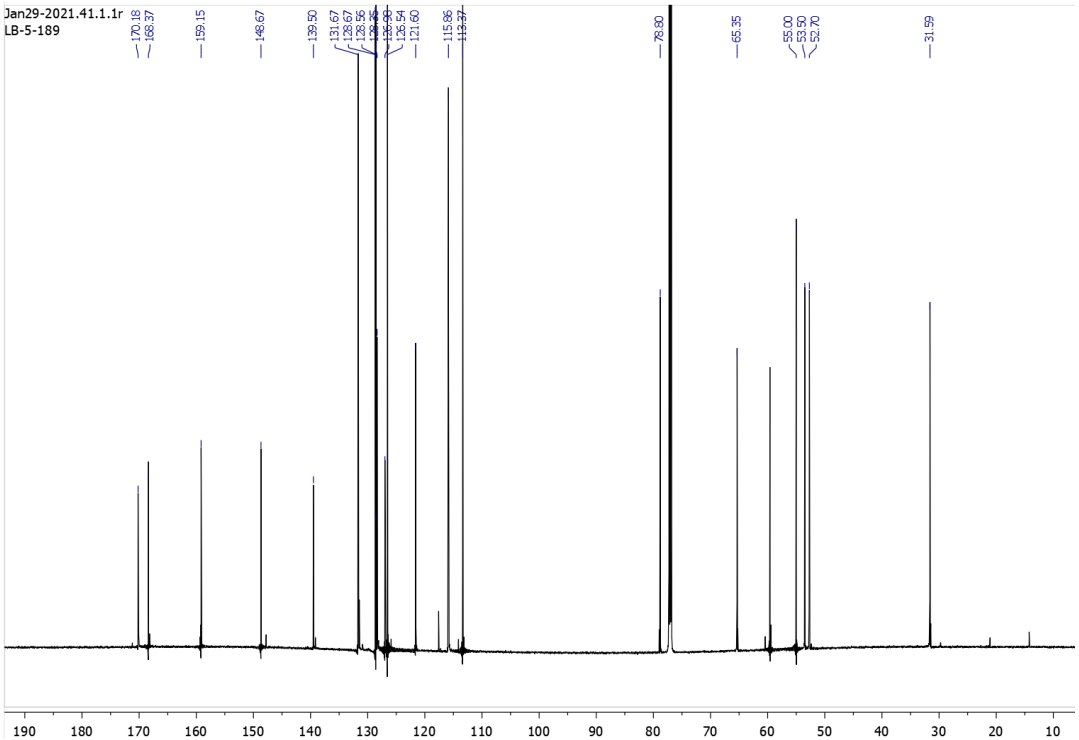
Compound 157 (^{13}C NMR; 100 MHz; Chloroform-*d*)



Compound 159 (^{1}H NMR; 700 MHz; Chloroform-*d*)



Compound 159 (^{13}C NMR; 400 MHz; Chloroform-*d*)



Liproxstatin-1 Supporting Information

A Chemical Screen for Vancomycin Antagonism Uncovers Probes of the Gram-Negative Outer Membrane

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[2] *Michael G. DeGroote Institute for Infectious Disease Research, McMaster University, Hamilton, Ontario, Canada.*
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[#] *These authors contributed equally*

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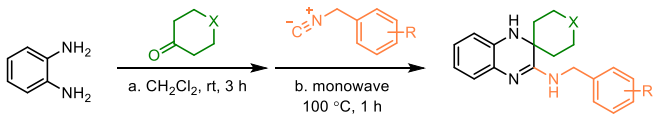
Synthetic Experimental Procedures

General

Chemical shifts in ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million (ppm) relative to tetramethylsilane (TMS), with calibration of the residual solvent peaks according to values reported by Gottlieb et al. (chloroform: δ_H 7.26, δ_C 77.16; DMSO: δ_H 2.50, δ_C 39.52).[2] When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; sept., septet; dd, doublet of doublets; m, multiplet; br, broad; app., apparent; *gem*, geminal. ^{1}H NMR spectra were acquired at 700 MHz with a digital resolution (Brüker parameter: FIDRES) of 0.993 Hz/point and coupling constants reported herein therefore have uncertainties of ±0.2 Hz. Melting points (mp) are uncorrected. Reactions were carried out at room temperature (rt) if temperature is not specified. Reactions conducted at elevated temperature used an Anton Paar Monowave 50, a conventionally heated synthesis reactor (www.anton-paar.com). Compounds purified by normal-phase flash chromatography used Teledyne Combi*Flash* Rf+ and NextGen 300+ purification systems (www.teledyneisco.com) equipped with pre-packed silica cartridges (either 40–60 μM or 20–40 μM particle size). Reverse-phase chromatographic purifications used a Teledyne Combi*Flash* Rf with pre-packed columns of octadecyl-functionalized (C18) silica gel (40–60 μM particle size). Low-resolution mass spectral (LRMS) measurements were recorded on an Advion Expression CMS Compact Mass Spectrometer (Albany, NY). High-resolution mass spectrometric (HRMS) data was obtained using an Brüker micrOTOF II system with electrospray ionization (ESI) and paired with an Agilent HPLC and UV detector.

General Method A



o-Phenylenediamine (59 mg, 0.55 mmol) and a ketone (0.5 mmol) were dissolved in CH_2Cl_2 (1.5 mL) and stirred in a 10-mL sealed tube equipped with a Teflon-lined cap. After stirring for 3 h at rt, the appropriate isocyanide (0.55 mmol) was added and the reaction vessel re-capped and stirred at 100 °C for 1 h in an Anton-Paar Monowave 50. The reaction mixture was concentrated under reduced pressure and subjected to normal-phase flash chromatography on silica gel (0→50% EtOAc/Hex) to provide a mixture of the dihydroquinoxaline product and imine intermediate. The quinoxaline product was purified by reverse-phase chromatography on C18-silica gel (5→50% MeOH/H_2O).

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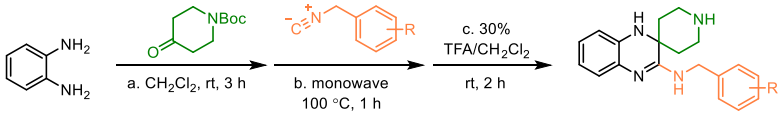
[2]. Gottlieb, H. G.; Kotlyar, V.; Nudelman, A. NMR Chemical Shifts of Common Laboratory Solvents as Trace Impurities. *J. Org. Chem.* **1997**, *62*, 7512–7515.

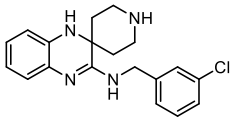
General Method B



o-Phenylenediamine (59 mg, 0.55 mmol) and a ketone (0.5 mmol) were dissolved in CH_2Cl_2 (1.5 mL) and stirred in a 10-mL sealed tube equipped with a Teflon-lined cap. After stirring for 3 h at rt, the appropriate isocyanide (0.55 mmol) was added and the reaction vessel re-capped and stirred at 100 °C for 1 h in an Anton-Paar Monowave 50. The reaction mixture was concentrated under reduced pressure and subjected to normal-phase flash chromatography on silica gel (0→50% EtOAc/Hex). Fractions containing the desired product were concentrated under reduced pressure and stirred in TFA/CH_2Cl_2 (30:70, 2 mL) at rt for 2 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated Na_2CO_3 (5 mL). The aqueous Na_2CO_3 was back-extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were combined and washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The desired dihydroquinoxaline product was obtained using normal-phase chromatography on silica gel (0→20% MeOH/CH_2Cl_2 with 0.1% NH_4OH), followed by reverse-phase chromatography on C18-silica gel (5→100% MeOH/H_2O).

Checker Board Assays of all Analogs:

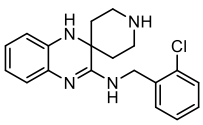
Liproxstatin-1



Liproxstatin-1

Prepared according to General Method B. Off-white solid (14.8 mg, 9%). Mp: 86–90 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.36–7.31 (m, 2H), 7.29–7.24 (m, 2H), 7.17–7.12 (brs, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 6.69 (d, *J* = 7.7 Hz, 1H), 6.66 (t, *J* = 7.7 Hz, 1H), 6.50 (t, *J* = 7.7 Hz, 1H), 5.94–5.83 (brs, 1H), 4.49 (d, *J* = 5.7 Hz, 2H), 2.93–2.84 (brs, 2H), 2.74–2.64 (brs, 2H), 1.76 (td, *J* = 12.2, 4.6 Hz, 2H), 1.46 (d, *J* = 12.2 Hz, 2H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 157.57, 143.28, 134.54, 134.42, 132.74, 129.90, 126.94, 126.23, 125.87, 122.66, 122.25, 118.08, 113.58, 49.87, 42.83, 38.71 (2C), 29.28 (2C). HRMS (ESI) *m/z*: $[M+H]^+$ 341.1527 calculated for $C_{19}H_{22}{}^{35}ClN_4$; 341.1543 observed.

Compound 2-13

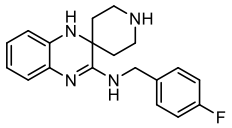


MAC-0549481

Prepared according to General Method B. Off-white solid (13.9 mg, 12%). Mp: 81–84 °C. ^{1}H NMR

(700 MHz, DMSO-d_6): δ 7.42 (d, J = 7.7 Hz, 1H), 7.32–7.27 (m, 2H), 7.25 (dt, J = 7.3, 2.0 Hz, 1H), 7.12–7.06 (brs, 1H), 6.82 (d, J = 7.6 Hz, 1H), 6.69–6.63 (m, 2H), 6.49 (t, J = 7.3 Hz, 1H), 5.94–5.90 (brs, 1H), 4.55 (d, J = 5.4 Hz, 2H), 2.92 (t, J = 11.9 Hz, 2H), 2.73 (d, J = 11.9 Hz, 2H), 1.88–1.80 (m, 2H), 1.53 (d, J = 12.3 Hz, 2H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 158.40, 137.30, 135.20, 134.58, 131.88, 128.90, 128.30, 128.06, 126.93, 122.50, 122.09, 117.66, 113.55, 50.94, 41.19, 39.92 (2C), 30.87 (2C). HRMS (ESI) *m/z*: 341.1527 calculated for $C_{19}H_{22}{}^{35}ClN_4$; 341.1540 observed.

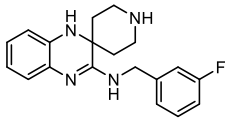
Compound 2-19



M1

Prepared according to General Method B. White solid (6.2 mg, 74%). Mp: 83–87 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.33 (dd, J = 8.6, $^4J_{HF}$ = 5.4 Hz, 2H), 7.08 (d, J = 7.5 Hz, 1H), 7.02 (appt, J = 8.6 Hz, $^3J_{HF}$ = 8.6 Hz, 2H), 6.88 (t, J = 7.5 Hz, 1H), 6.84 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 7.5 Hz, 1H), 4.58 (s, 2H), 4.10 (brs, 1H), 3.06–2.96 (m, 4H), 1.91–1.80 (m, 4H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 163.0, 162.33 (d, $^1J_{CF}$ = 246 Hz), 134.67 (2C), 132.97, 129.92 (d, $^3J_{CF}$ = 8.2 Hz, 2C), 123.41, 120.83, 115.64 ($^2J_{CF}$ = 21.5 Hz, 2C), 115.31 (2C), 50.75, 45.20, 40.90 (2C), 31.25 (2C). HRMS (ESI) *m/z*: $[M+H]^+$ 325.1823 calculated for $C_{19}H_{22}FN_4$; 325.1823 observed.

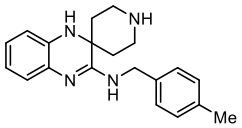
Compound 2-16



M2

Prepared according to General Method B. Off-white solid (11.1 mg, 64%). Mp: 82–85 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.29 (brq, J = 7.3 Hz, 2H), 7.14 (d, J = 7.5 Hz, 1H), 7.07 (d, $^3J_{HF}$ = 9.5 Hz, 1H), 7.05 (brd, J = 6.0 Hz, 1H), 6.95 (brt, J = 8.3 Hz, 1H), 6.91–6.85 (m, 2H), 6.79 (d, J = 7.0 Hz, 1H), 4.58 (s, 2H), 3.97–3.89 (brs, 1H), 3.93–3.16 (brs, 4H), 2.25–2.11 (m, 2H), 1.85 (d, J = 13.7 Hz, 2H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 162.19 (d, $^1J_{CF}$ = 243 Hz), 158.35, 143.81 (d, $^3J_{CF}$ = 7.3 Hz), 135.19, 134.74, 129.92 (d, $^3J_{CF}$ = 8.3 Hz), 123.12, 122.44, 122.00, 117.73, 113.68 (d, $^2J_{CF}$ = 21.7 Hz), 113.62, 113.02 (d, $^2J_{CF}$ = 21.0 Hz), 50.85, 42.74, 39.91 (2C), 31.71 (2C). HRMS (ESI) *m/z*: $[M+H]^+$ 325.1823 calculated for $C_{19}H_{22}FN_4$; 325.1838 observed.

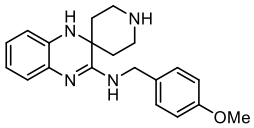
Compound 2-17



M3

Prepared according to General Method B. Off-white solid (19.7 mg, 93%). Mp: 55–61 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.25 (m, 2H), 7.16 (d, *J* = 7.5 Hz, 2H), 7.10 (d, *J* = 7.4 Hz, 1H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.83 (t, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 7.4 Hz, 1H), 4.57 (s, 2H), 4.16–4.09 (brs, 1H), 3.04–2.92 (m, 4H), 2.35 (s, 3H), 1.85–1.78 (m, 4H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 157.48, 137.39, 135.69, 133.19, 129.55 (2C), 128.28 (2C), 12328 (2C), 120.67, 115.05, 50.83, 45.76, 41.04 (2C), 31.56 (2C), 21.27. HRMS (ESI) *m/z*: $[M+H]^+$ 321.2073 calculated for $C_{20}H_{24}N_4$; 321.2065 observed.

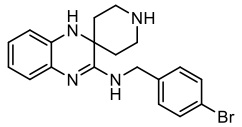
Compound 2-18



M4

Prepared according to General Method B. Brown oil (5.0 mg, 86%). ^{1}H NMR (700 MHz, DMSO-d_6): δ 10.19–9.84 (brs, 1H), 9.19–8.94 (s, 1H), 8.79–8.56 (s, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.15–7.01 (brs, 2H), 6.95 (d, *J* = 8.2 Hz, 2H), 6.91–6.73 (brs, 2H), 4.79–4.65 (brs, 2H), 3.74 (s, 3H), 3.32–3.15 (m, 4H), 2.23–2.11 (brs, 2H), 1.96–1.83 (brs, 2H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 157.96, 157.90, 134.89 (2C), 132.39, 128.47 (2C), 122.44, 121.87, 117.94, 113.66, 113.47 (2C), 54.99, 50.43, 42.71, 39.53 (2C), 30.86 (2C). HRMS (ESI) *m/z*: $[M+H]^+$ 337.2022 calculated for $C_{20}H_{25}N_4O$; 337.2038 observed.

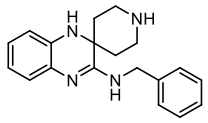
Compound 2-14



M5

Prepared according to General Method B. White solid (18.3 mg, 34%). Mp: 130–135 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.14–7.07 (brs, 1H), 6.81 (d, *J* = 7.5, 1H), 6.69 (d, *J* = 7.5 Hz, 1H), 6.65 (t, *J* = 7.5 Hz, 1H), 6.50 (t, *J* = 7.5 Hz, 1H), 5.89–5.84 (brs, 1H), 4.45 (d, *J* = 5.6 Hz, 2H), 2.88 (appt, *J* = 11 Hz, 2H), 2.68 (brd, *J* = 11 Hz, 2H), 1.80–1.71 (m, 2H), 1.46 (brd, *J* = 12.2 Hz, 2H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 158.36, 140.13, 135.19, 134.72, 130.87 (2C), 129.44 (2C), 122.43, 121.96, 119.25, 117.65, 113.52, 50.85, 42.69, 39.92 (2C), 31.79 (2C). HRMS (ESI) *m/z*: $[M+H]^+$ 385.1022 calculated for $C_{19}H_{21}{}^{79}BrN_4$ 385.1041 observed.

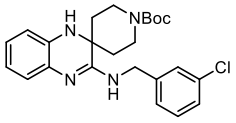
Compound 2-15



M6

Prepared according to General Method B. White solid (17.0 mg, 11%). Mp: 74–78 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.34–7.27 (m, 4H), 7.20 (t, J = 6.9 Hz, 1H), 7.11–7.05 (brs, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.74–6.69 (m, 1H), 6.66 (t, J = 7.4 Hz, 1H), 6.52 (t, J = 7.0 Hz, 1H), 5.92 (s, 1H), 4.51 (s, 2H), 2.95 (t, J = 12.2 Hz, 2H), 2.82–2.71 (m, 2H), 1.86–1.77 (m, 2H), 1.51 (t, J = 11.9 Hz, 2H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 158.19, 140.68, 135.06 (2C), 128.20 (2C), 127.24 (2C), 126.48, 122.53, 122.06, 118.05, 113.81, 50.73, 45.53, 43.33 (2C), 31.24 (2C). HRMS (ESI) *m/z*: $[M+H]^+$ 307.1917 calculated for $C_{19}H_{23}N_4$; 307.1933 observed.

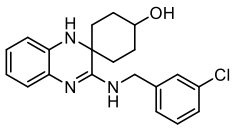
Compound 2-22



M7

Prepared according to General Method A. White solid (129.1 mg, 59%). Mp: 136–141 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.35 (s, 1H), 7.28–7.26 (m, 3H), 7.23–7.13 (brs, 1H), 6.90 (t, J = 7.5, 1.1 Hz, 1H), 6.84 (td, J = 7.5 Hz, 1H), 6.72 (d, J = 7.5 Hz, 1H), 4.72–7.52 (brs, 2H), 4.19–4.09 (brs, 1H), 4.10–3.92 (brs, 2H), 3.09–2.90 (s, 2H), 1.86–1.77 (brs, 2H), 1.77–1.66 (brs, 2H), 1.44 (s, 9H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 156.88, 154.72, 141.04, 134.60 (2C), 133.22, 130.11, 128.25, 127.76, 126.32, 123.57, 120.64 (2C), 114.93, 80.24, 50.92, 45.14, 38.97 (br), 38.01 (br), 31.23 (2C), 28.52 (3C). HRMS (ESI) *m/z*: $[M+H]^+$ 441.2051 calculated for $C_{24}H_{30}{}^{35}ClN_4O_2$; 441.2065 observed.

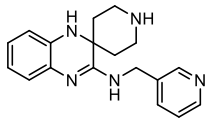
Compound 2-21



M8

Prepared according to General Method A. Off-white solid (24.8 mg, 14%). Mp: 208–212 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.36–7.30 (m, 1H), 7.29–7.23 (m, 1H), 7.10–7.03 (brs, 1H), 6.82 (d, J = 7.6 Hz, 1H), 6.69 (d, J = 7.4 Hz, 1H), 6.65 (appt, J = 7.3 Hz, 1H), 6.50 (appt, J = 7.3 Hz, 1H), 5.81–5.74 (brs, 1H), 4.68 (d, J = 3.1 Hz, 1H), 4.48 (d, J = 5.6 Hz, 2H), 3.42–3.38 (m, 1H), 1.73–1.65 (m, 2H), 1.65–1.54 (m, 6H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 158.61, 143.25, 135.20, 134.55, 132.75, 129.97, 126.98, 126.29, 125.87, 122.40, 122.12, 117.58, 113.54, 68.32, 51.16, 42.80, 29.92 (2C), 29.10 (2C). HRMS (ESI) *m/z*: $[M+H]^+$ 356.1524 calculated for $C_{20}H_{23}{}^{35}ClN_3O$; 356.1510 observed.

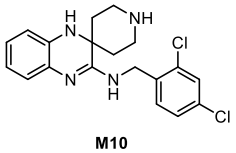
Compound 2-20



M9

Prepared according to General Method B. Yellow oil (11.3 mg, 7%). ^{1}H NMR (700 MHz, DMSO-d_6): δ 8.54 (s, 1H), 8.40 (d, *J* = 4.7 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.32 (dd, *J* = 7.6, 4.7 Hz, 1H), 7.19–7.14 (brs, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.51 (t, *J* = 7.5 Hz, 1H), 5.91–5.86 (brs, 1H), 4.49 (d, *J* = 5.1 Hz, 2H), 2.88 (appt, *J* = 12.0 Hz, 2H), 2.70 (brd, *J* = 11.3 Hz, 2H), 1.75 (m, 2H), 1.46 (d, *J* = 12.3 Hz, 2H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 158.28, 148.90, 147.61, 135.93, 135.18, 135.03, 134.68, 123.25, 122.48, 122.05, 117.71, 113.59, 50.81, 45.33, 41.09 (2C), 31.67 (2C), 15.09. HRMS (ESI) *m/z*: $[M+H]^+$ 308.1869 calculated for $C_{18}H_{22}N_5$; 308.1884 observed.

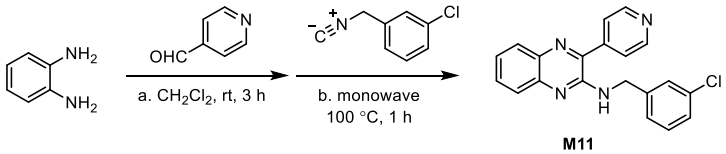
Compound 2-12



M10

Prepared according to General Method B. White solid (11.2 mg, 8%). Mp: 89–93 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 7.58 (t, *J* = 2.1 Hz, 1H), 7.39 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.13 (t, *J* = 5.8 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 6.69–6.63 (m, 2H), 6.49 (t, *J* = 7.3 Hz, 1H), 5.92 (s, 1H), 4.50 (d, *J* = 5.8 Hz, 2H), 2.90 (appt, *J* = 12.2 Hz, 2H), 2.71 (d, *J* = 12.2 Hz, 2H), 1.80 (dt, *J* = 12.4, 4.7 Hz, 2H), 1.51 (d, *J* = 12.4 Hz, 2H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 158.27, 136.61, 135.21, 134.45, 132.80, 131.62, 129.81, 128.33, 127.10, 122.57, 122.20, 117.64, 113.55, 50.94, 45.34, 40.94 (2C), 31.85 (2C). HRMS (ESI) *m/z*: $[M+H]^+$ 375.1137 calculated for $C_{19}H_{21}{}^{35}Cl_2N_4$; 375.1159 observed.

Compound 2-23



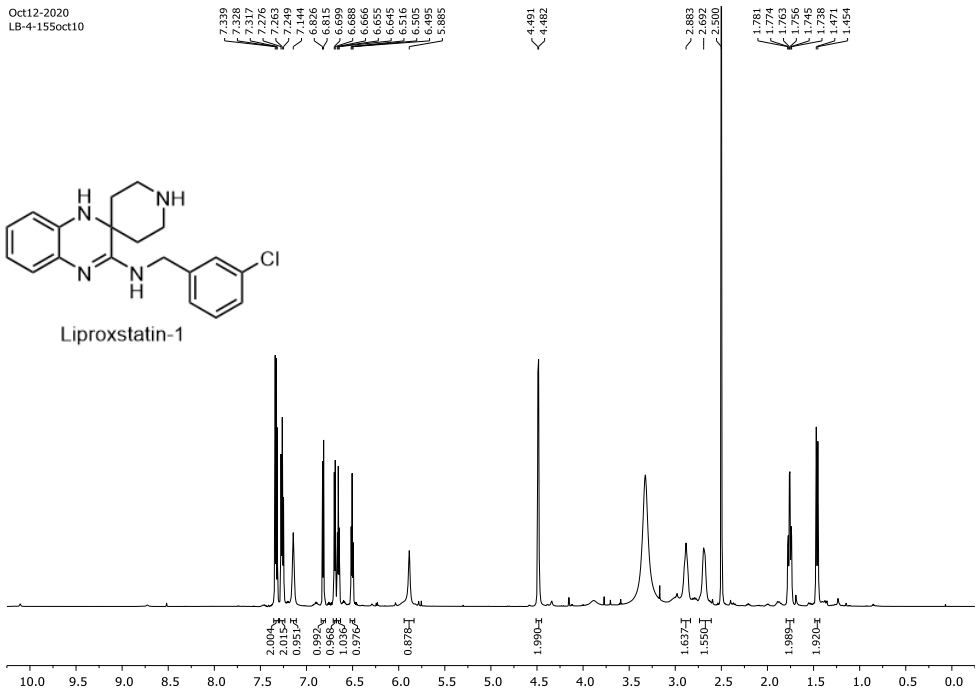
M11

o-Phenylenediamine (32 mg, 0.30 mmol) and 4-formylpyridine (31 mg, 0.30 mmol) were dissolved in CH_2Cl_2 (1.5 mL) and stirred with dry 4 Å molecular sieves in a 10-mL sealed tube equipped with a Teflon-lined cap. After stirring for 3 h at rt, the 3-chlorobenzyl isocyanide (46 mg, 0.30 mmol) was added and the reaction vessel re-capped and stirred at 100 °C for 1 h in an Anton-Paar monowave. The reaction mixture was concentrated under reduced pressure and subjected to normal-phase flash chromatography on silica gel (0→50% EtOAc/Hex) to provide a mixture of the quinoxaline product and imine intermediate. The quinoxaline product was purified by reverse-phase chromatography on C18-silica gel (5→50%

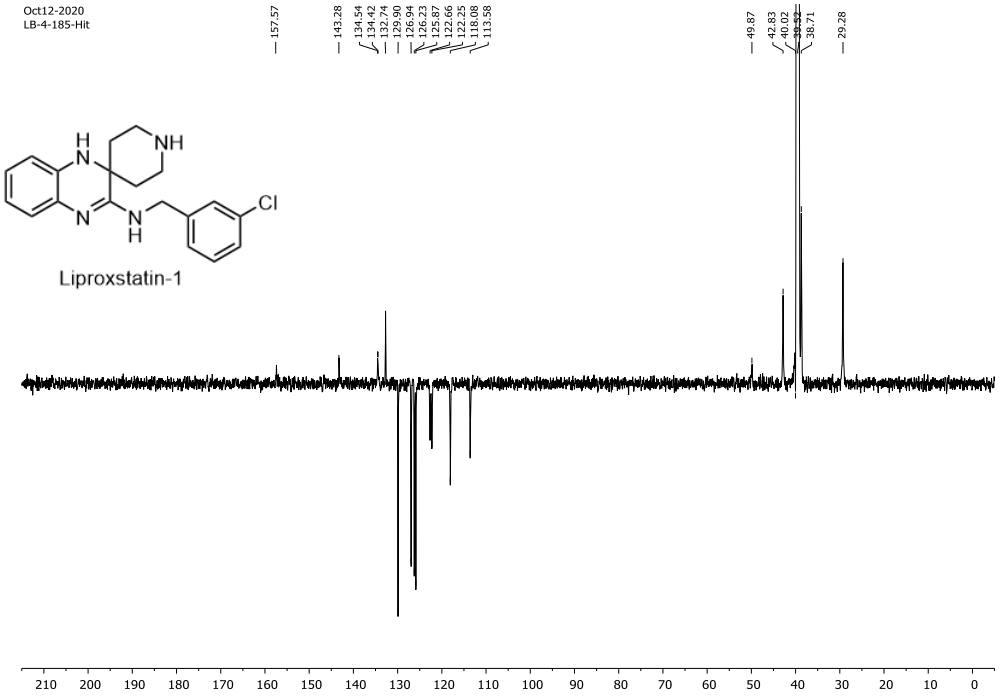
MeOH/H_2O) and isolated as an off-white solid (6.6 mg, 8%). Mp: 110–115 °C. ^{1}H NMR (700 MHz, DMSO-d_6): δ 8.78 (d, *J* = 5.9 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 5.4, 2H), 7.61–7.57 (m, 2H), 7.48–7.44 (m, 2H), 7.41–7.37 (m, 2H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 7.3 Hz, 1H), 4.63 (d, *J* = 5.9 Hz, 1H). ^{13}C NMR (176 MHz, DMSO-d_6): δ 150.19, 149.54, 144.36, 144.00, 142.57, 141.27, 136.23, 132.77, 130.30, 130.02, 128.58, 127.35, 126.49, 126.17, 125.65, 124.37, 123.32, 43.60. HRMS (ESI) *m/z*: $[M+H]^+$ 347.1058 calculated for $C_{20}H_{16}{}^{35}ClN_4$; 347.1046 observed.

^{1}H and ^{13}C NMR Spectra

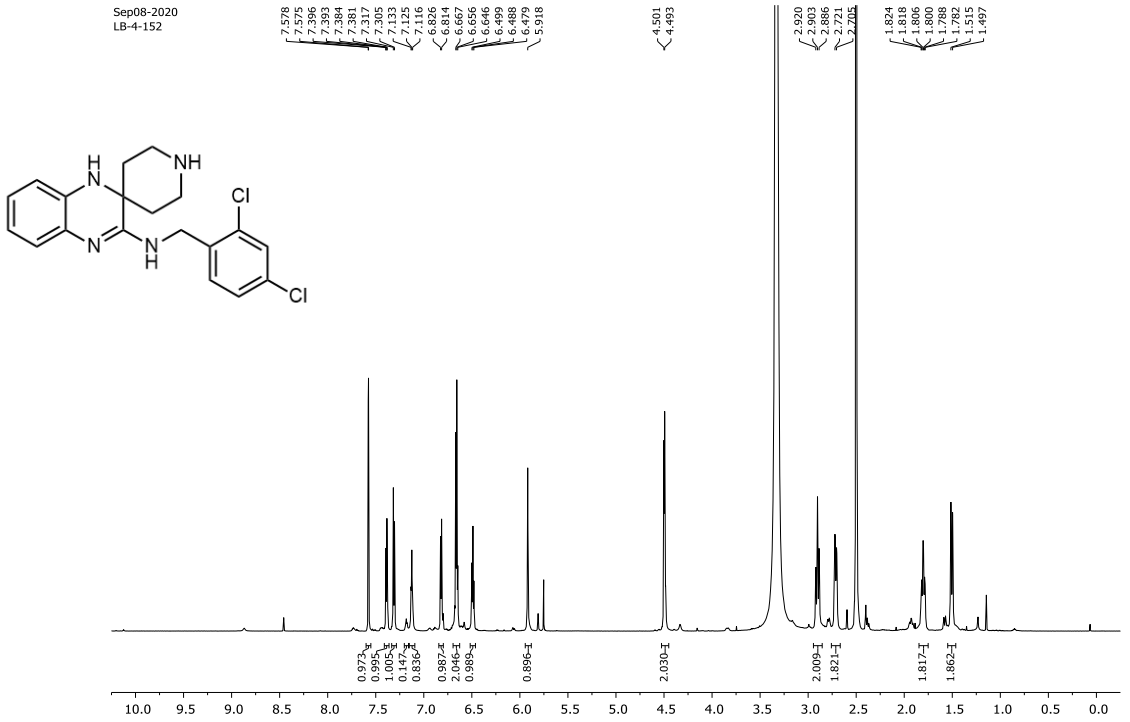
Liproxstatin-1 (^{1}H NMR; 700 MHz; DMSO-d_6)



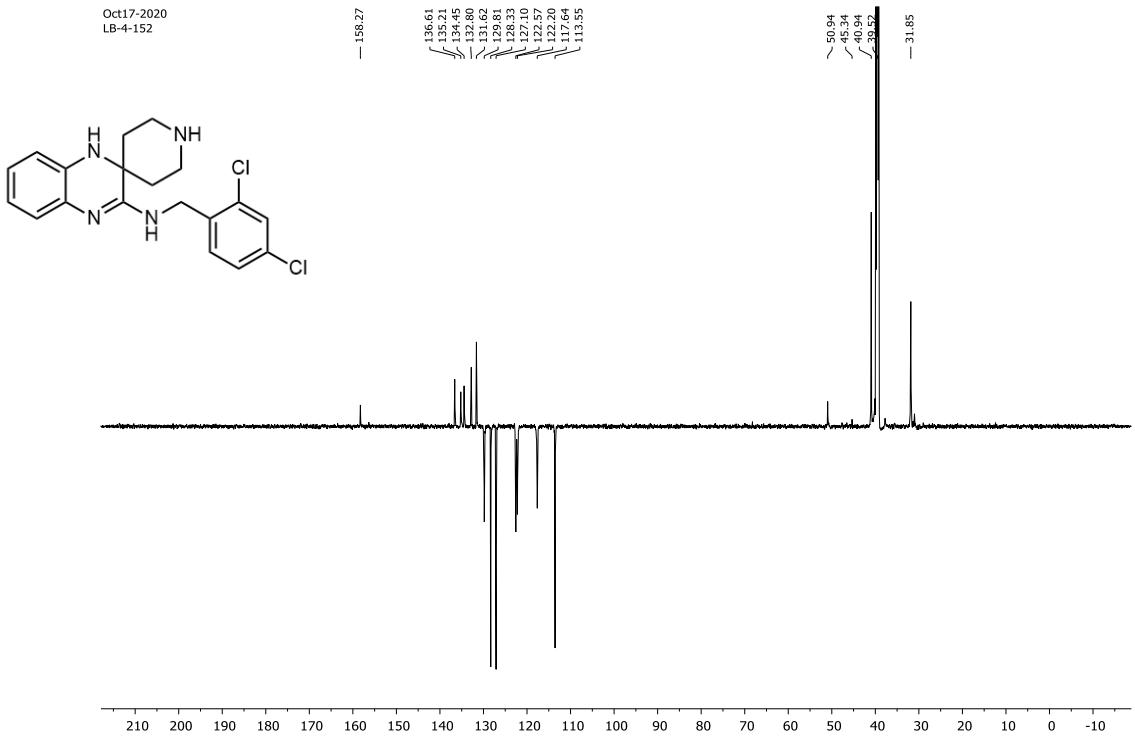
Liproxstatin-1 (^{13}C NMR; 176 MHz; DMSO-d_6)



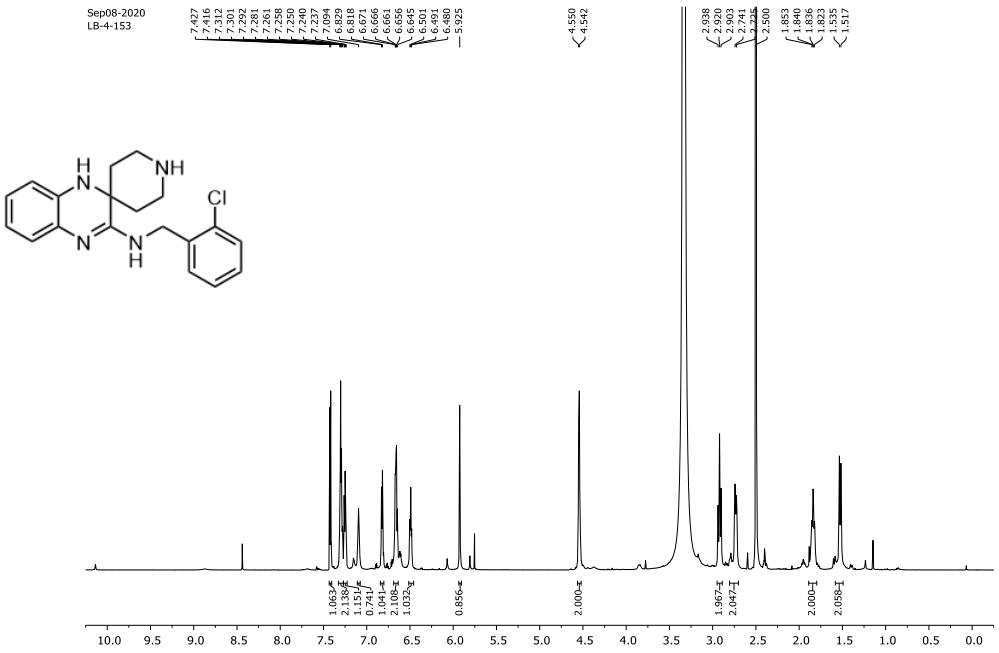
Compound 2-12 (^{1}H NMR; 700 MHz; DMSO-d_6)



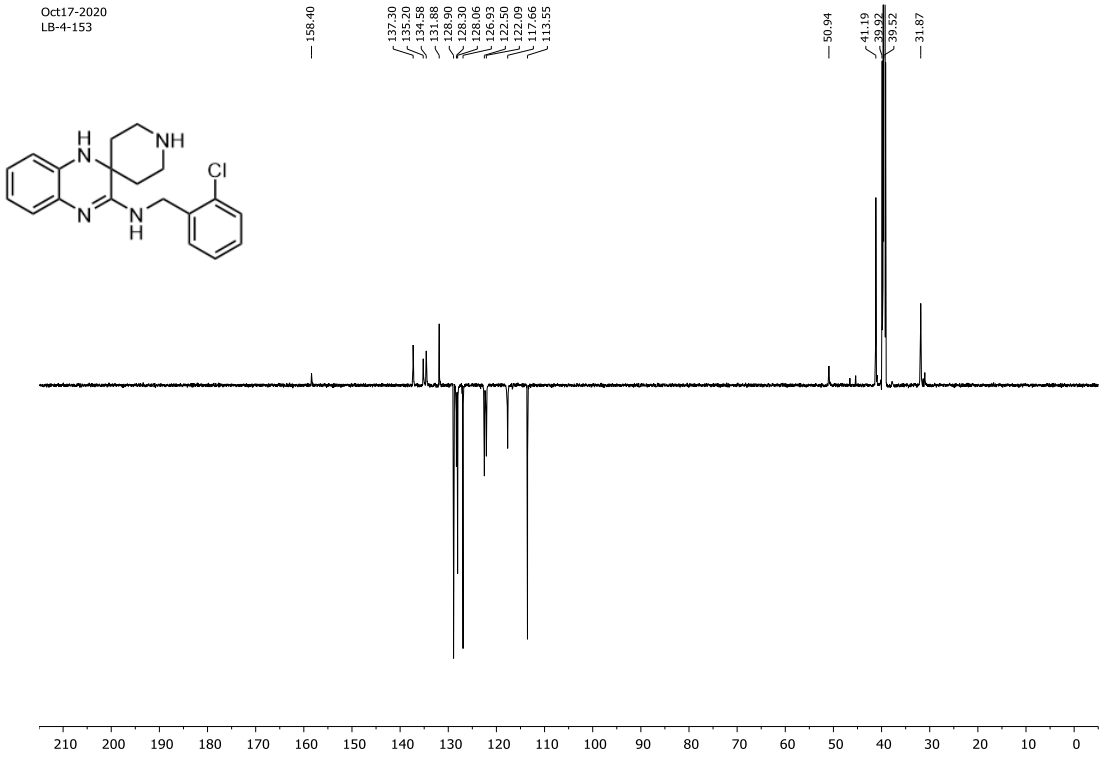
Compound 2-12 (^{13}C NMR; 176 MHz; DMSO-d_6)



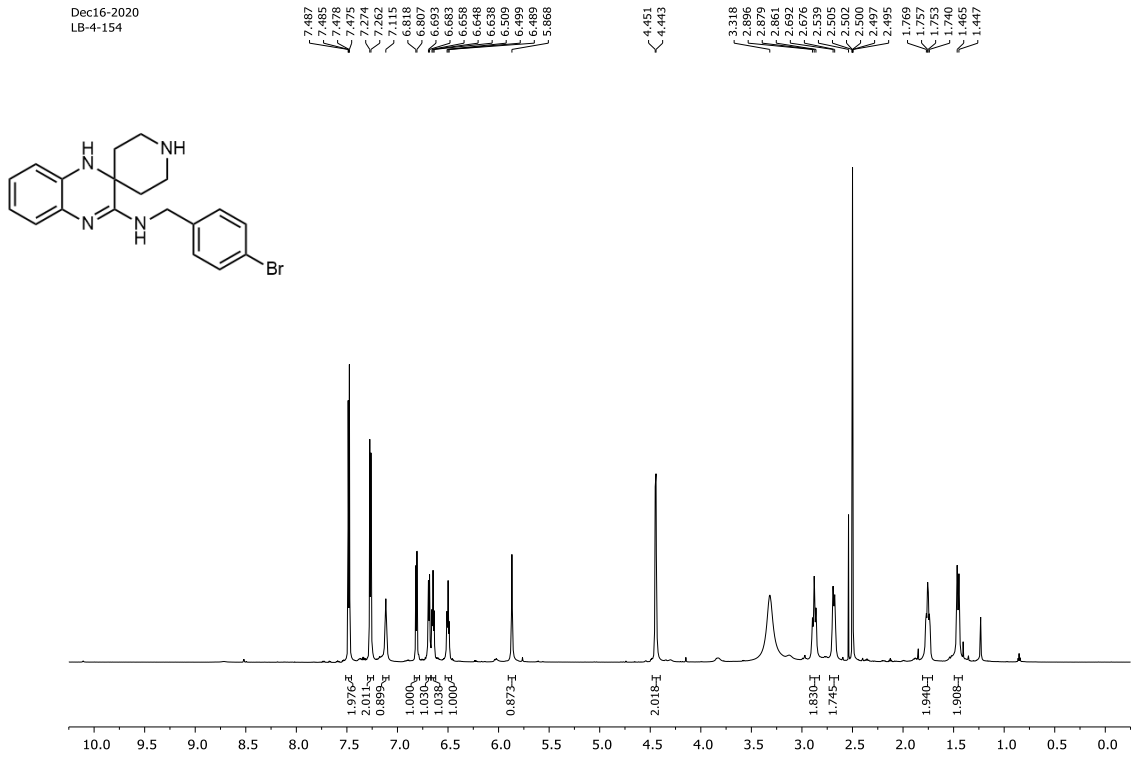
Compound 2-13 (^{1}H NMR; 700 MHz; DMSO-d_6)



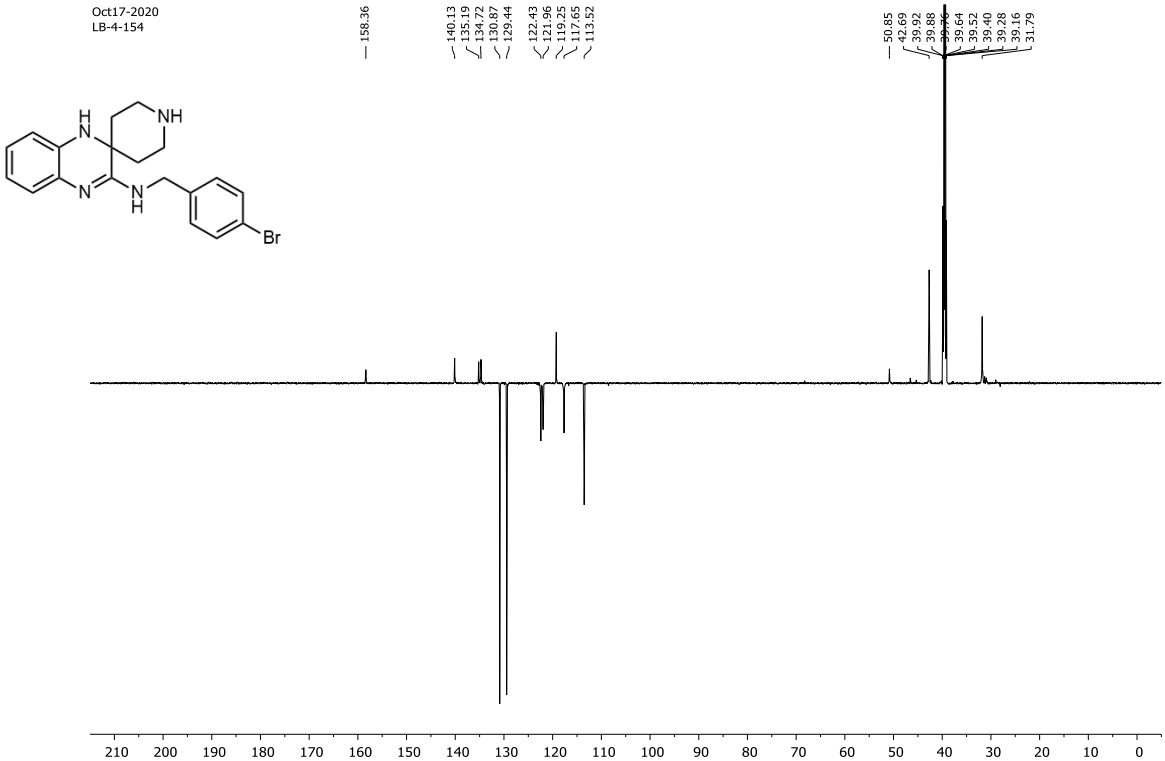
Compound 2-13 (^{13}C NMR; 176 MHz; DMSO-d_6)



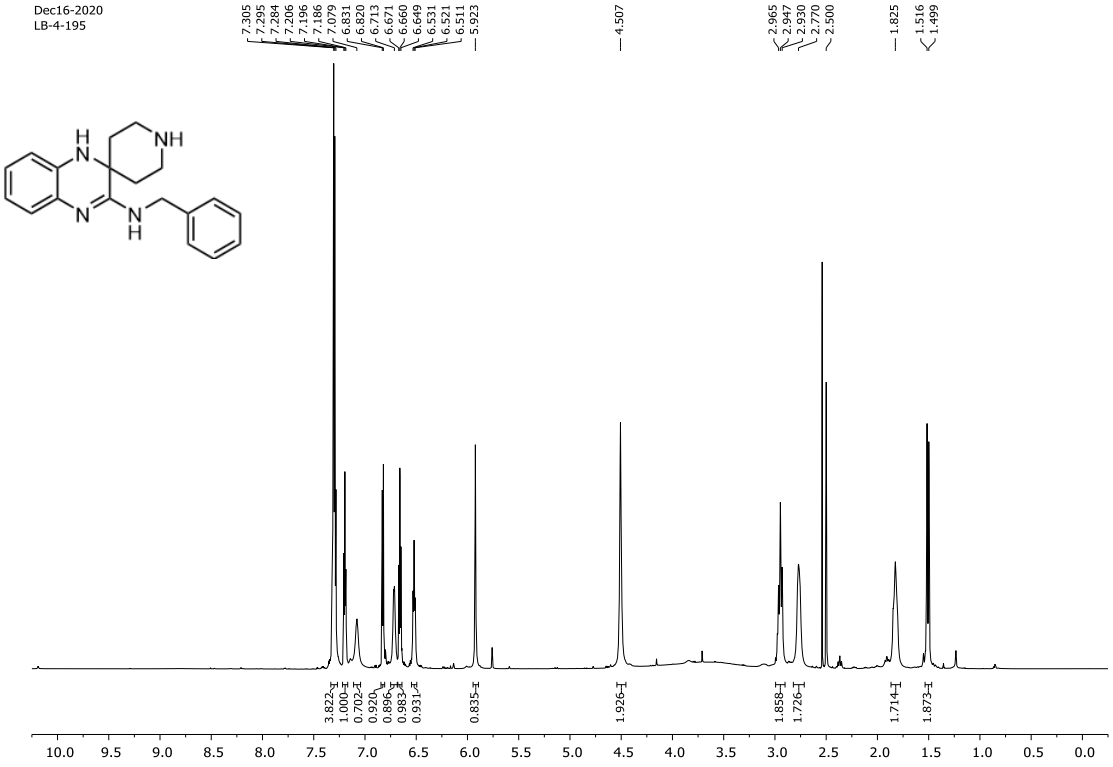
Compound 2-14 (^{1}H NMR; 700 MHz; DMSO-d_6)



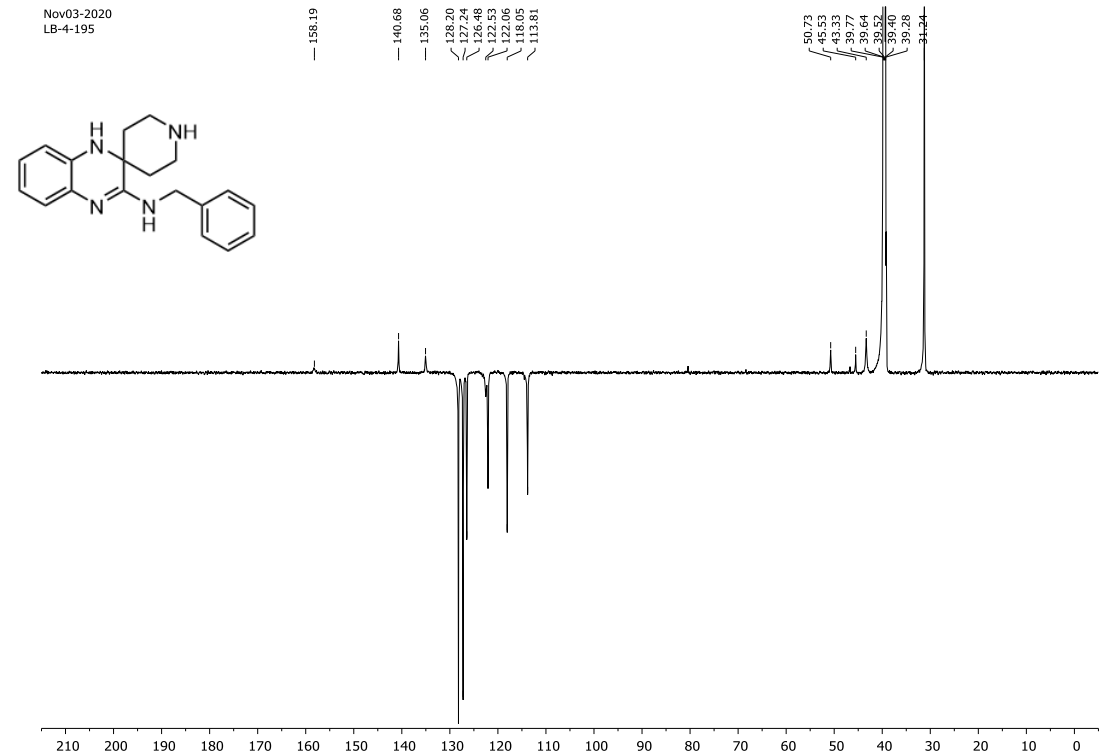
Compound 2-14 (^{13}C NMR; 176 MHz; DMSO-d_6)



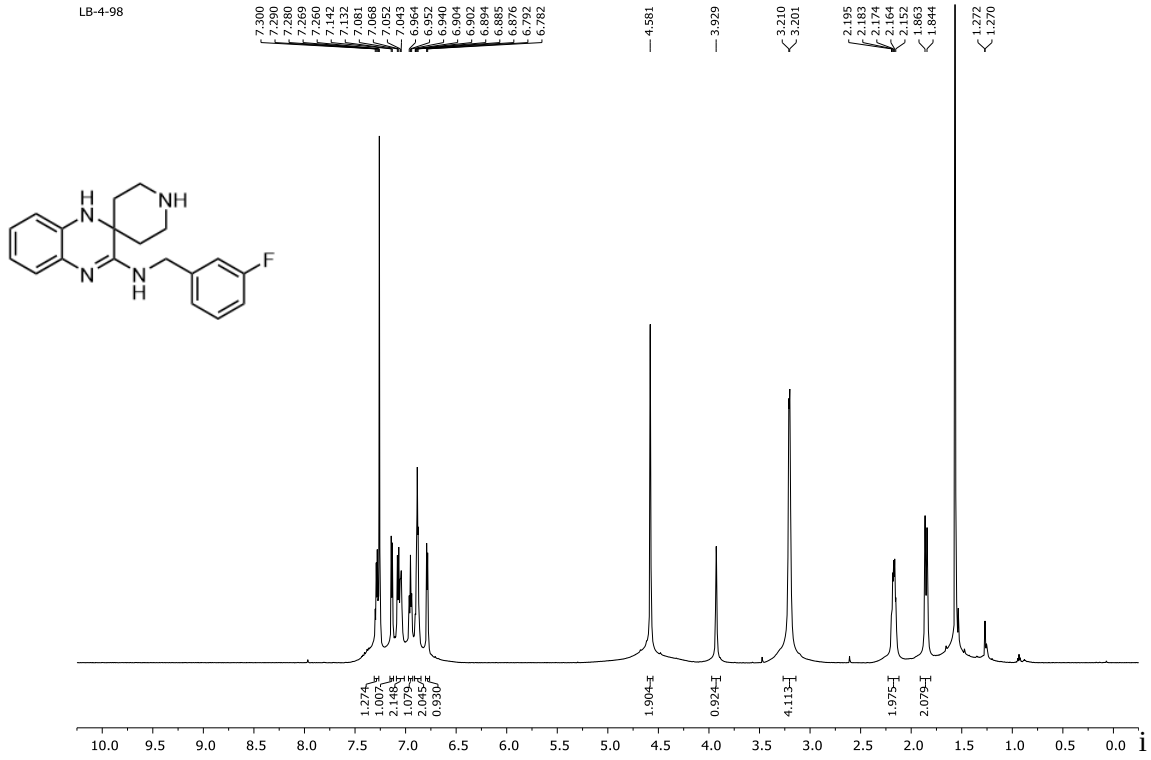
Compound 2-15 (^{1}H NMR; 700 MHz; DMSO-d_6)



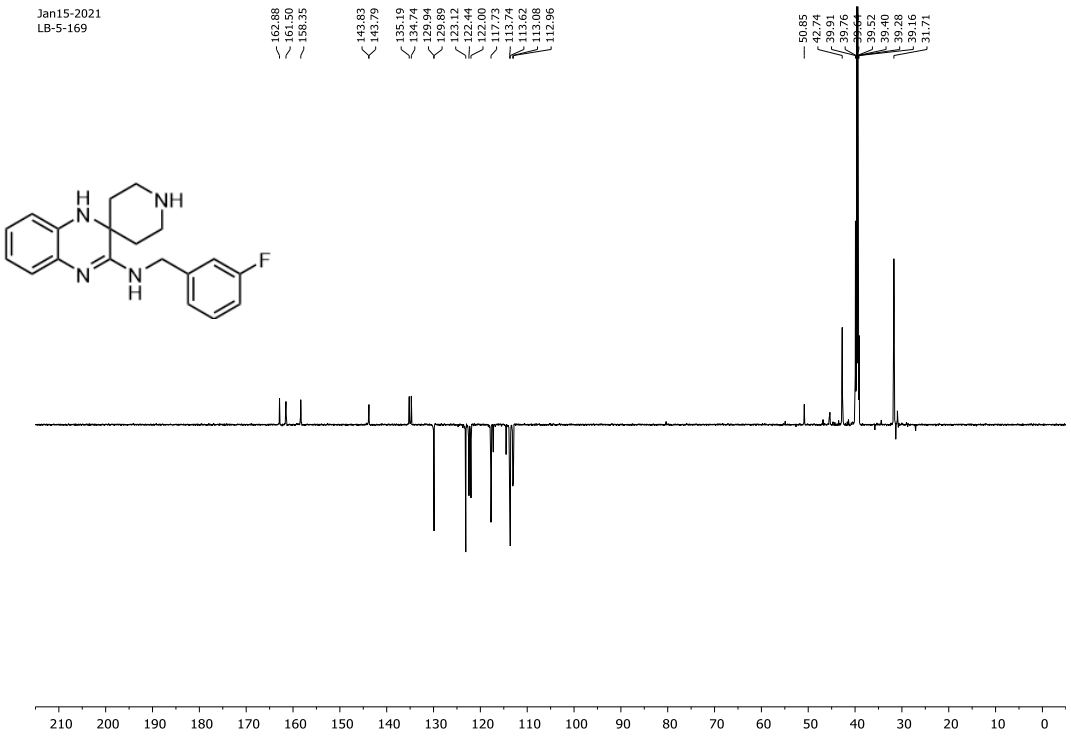
Compound 2-15 (^{13}C NMR; 176 MHz; DMSO-d_6)



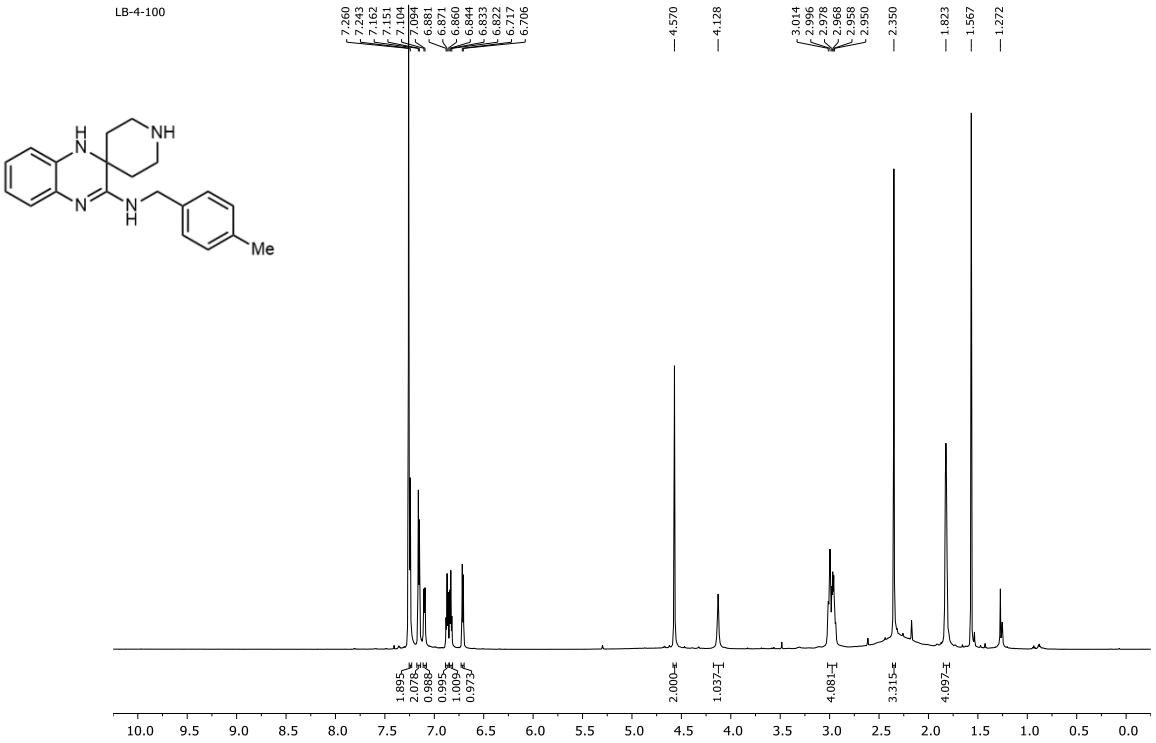
Compound 2-16 (^{1}H NMR; 700 MHz; $CDCl_3$)



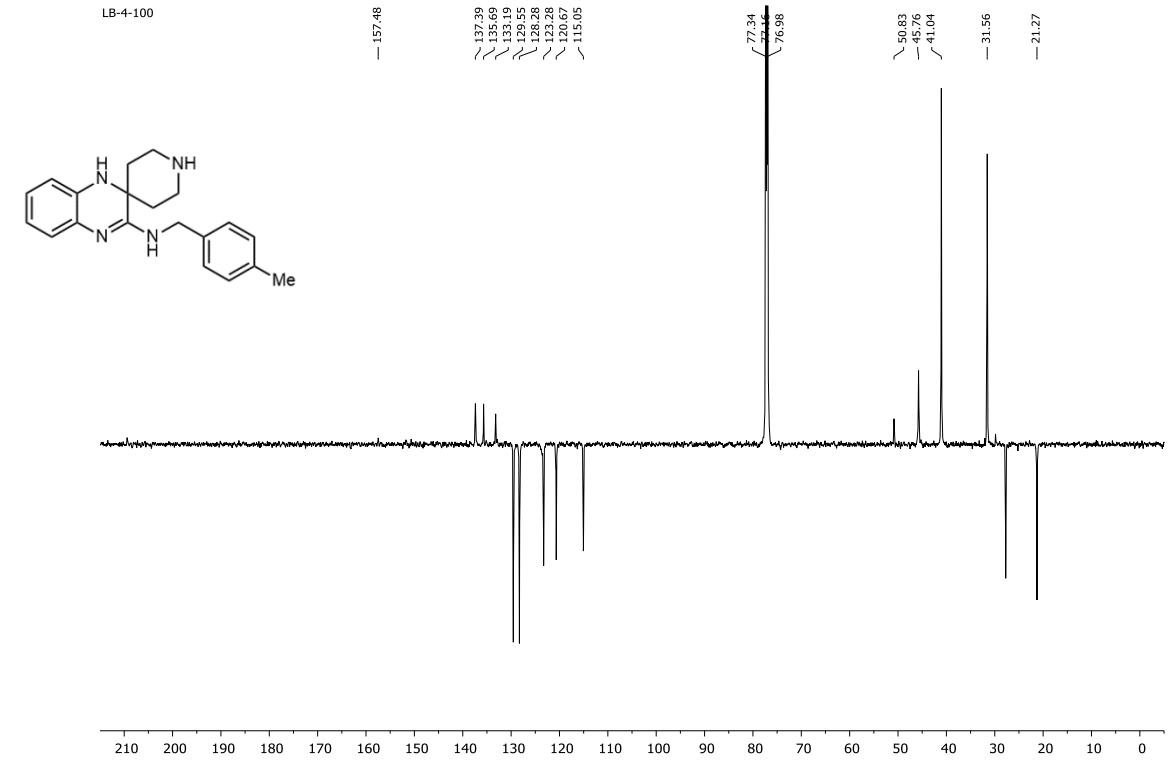
Compound 2-16 (^{13}C NMR; 176 MHz; DMSO-d_6)



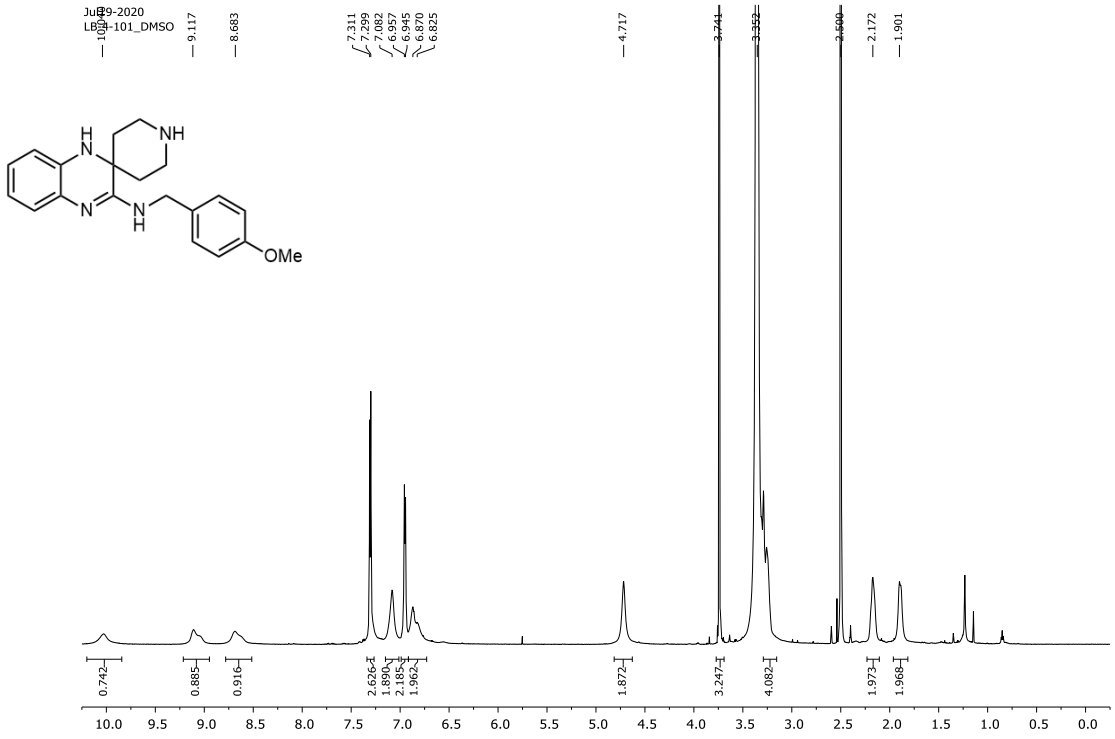
Compound 2-17 (^{1}H NMR; 700 MHz; DMSO-d_6)



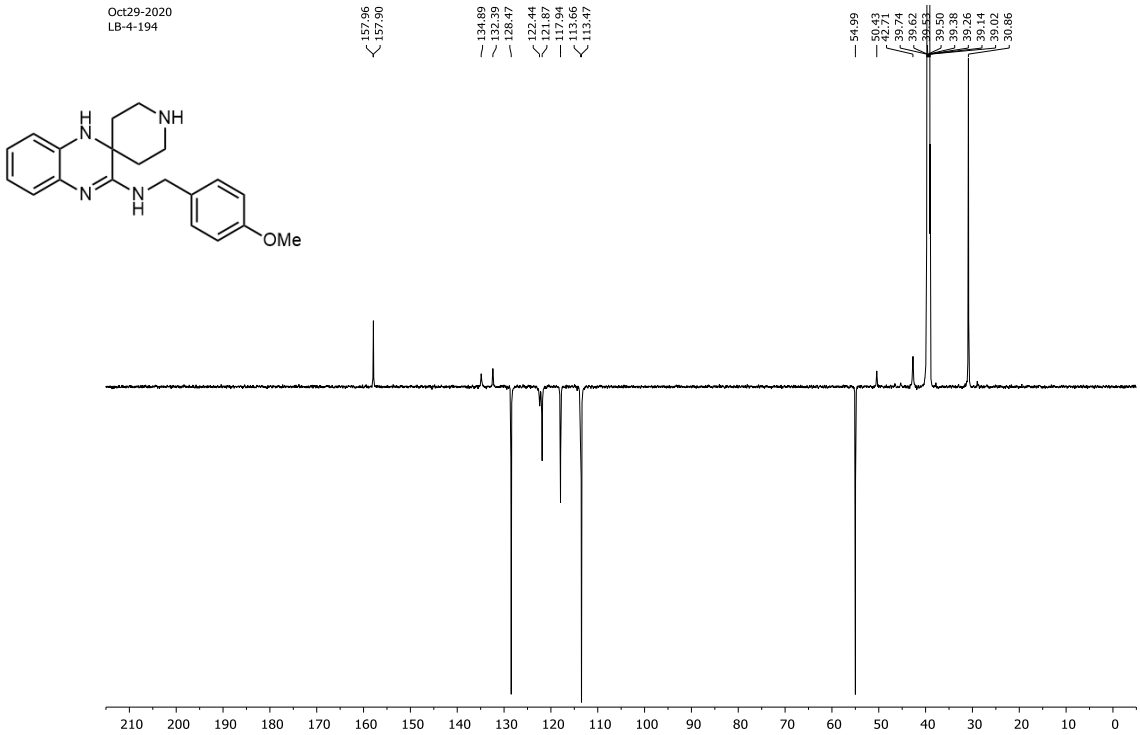
Compound 2-17 (^{13}C NMR; 176 MHz; $CDCl_3$)



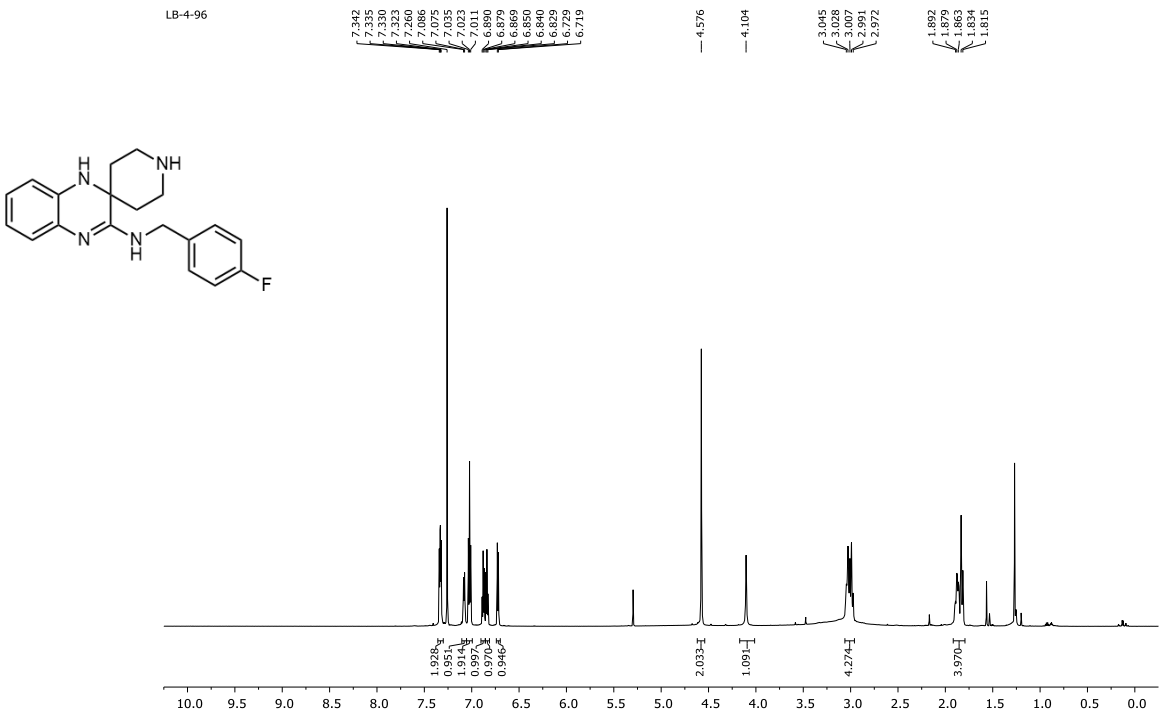
Compound 2-18 (^{1}H NMR; 700 MHz; DMSO-d_6)



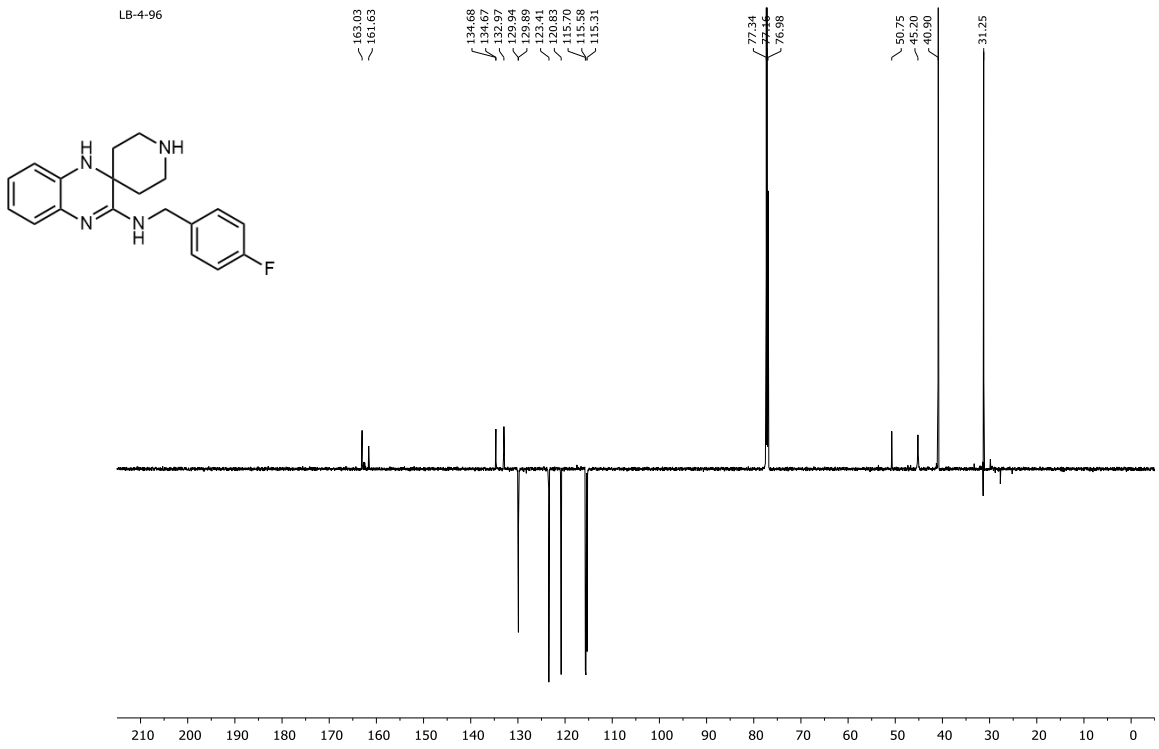
Compound 2-18 (^{13}C NMR; 176 MHz; DMSO-d_6)



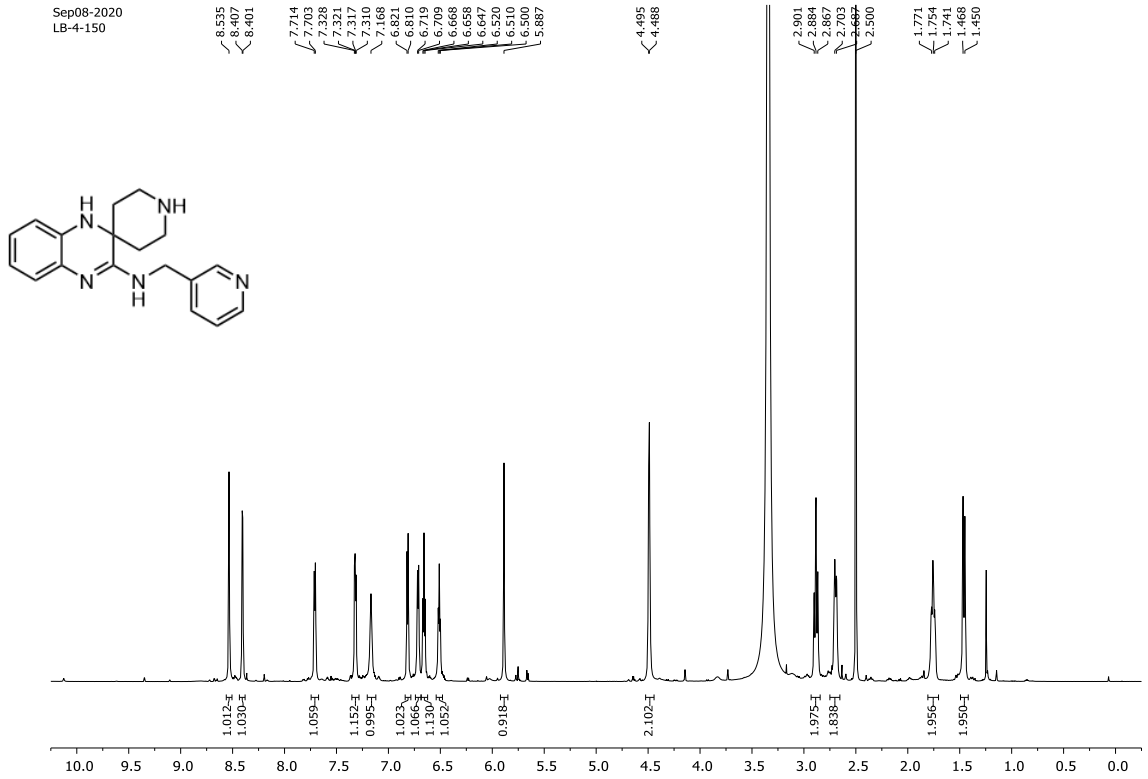
Compound 2-19 (^{1}H NMR; 700 MHz; $CDCl_3$)



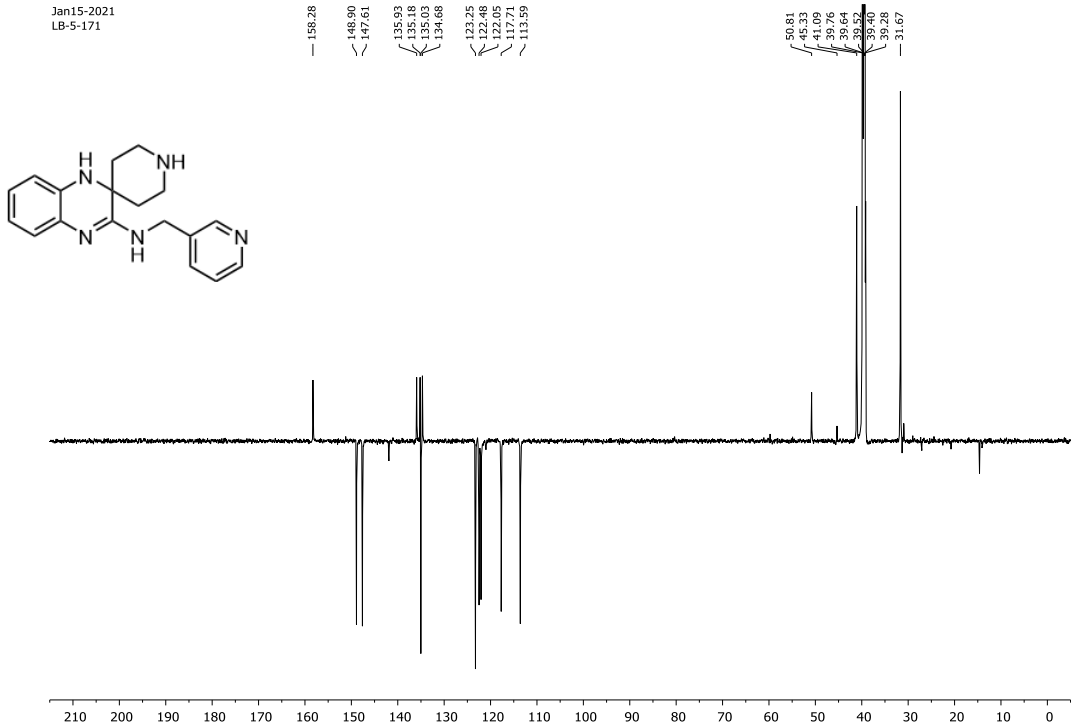
Compound 2-19 (^{13}C NMR; 176 MHz; $CDCl_3$)



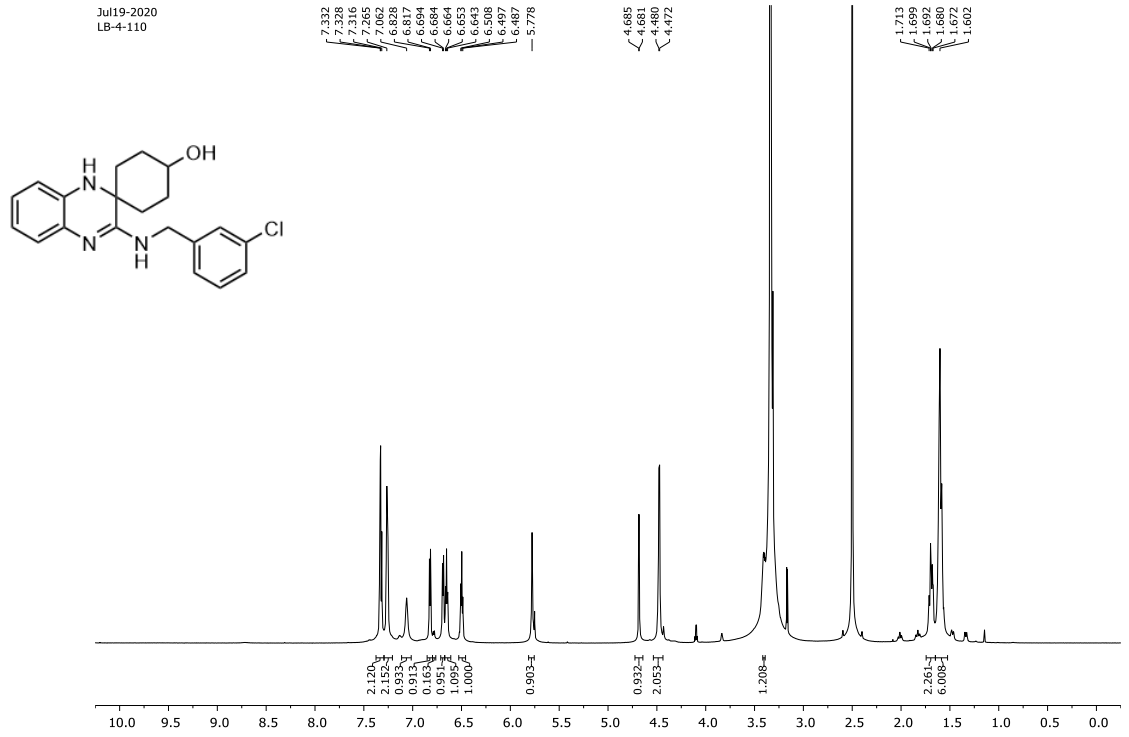
Compound 2-20 (^{1}H NMR; 700 MHz; DMSO-d_6)



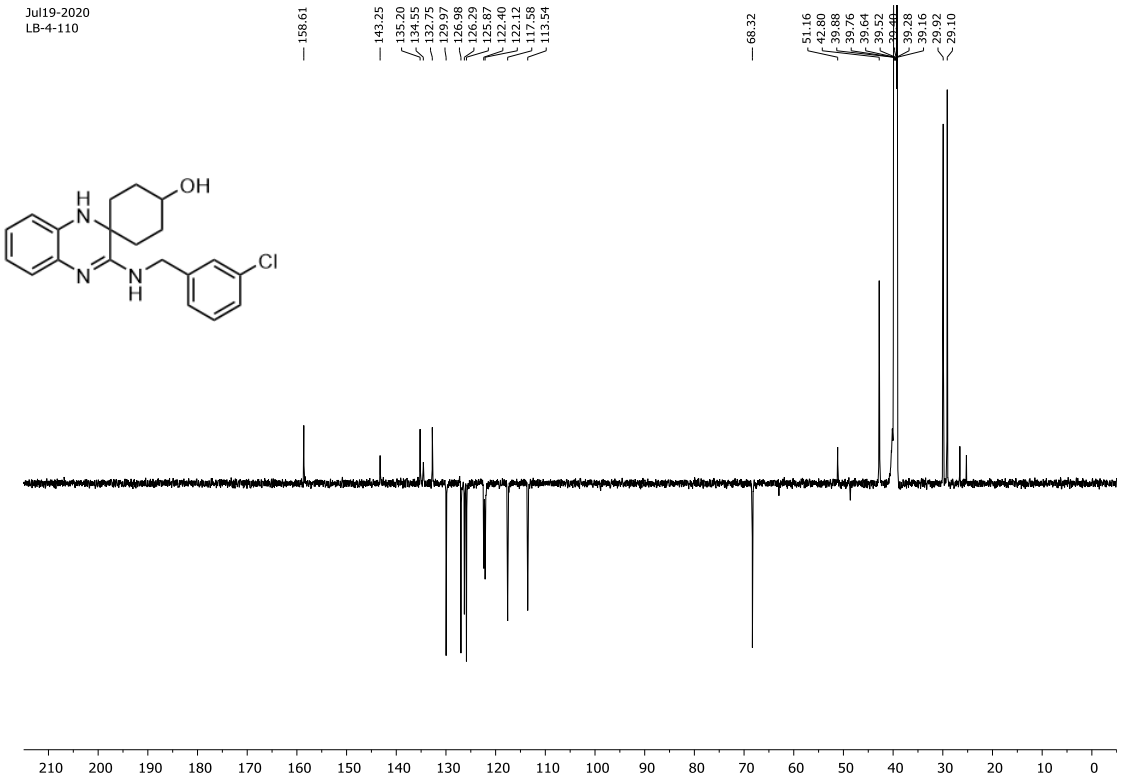
Compound 2-20 (^{13}C NMR; 176 MHz; DMSO-d_6)



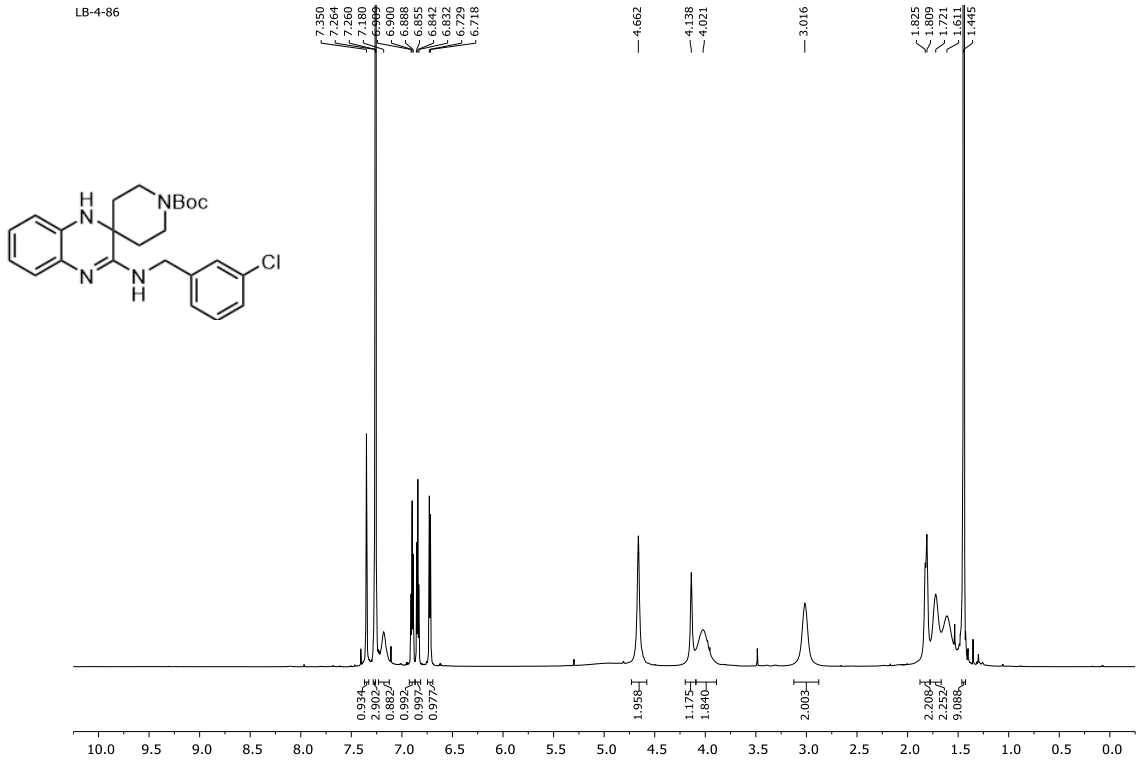
Compound 2-21 (^{1}H NMR; 700 MHz; DMSO-d_6)



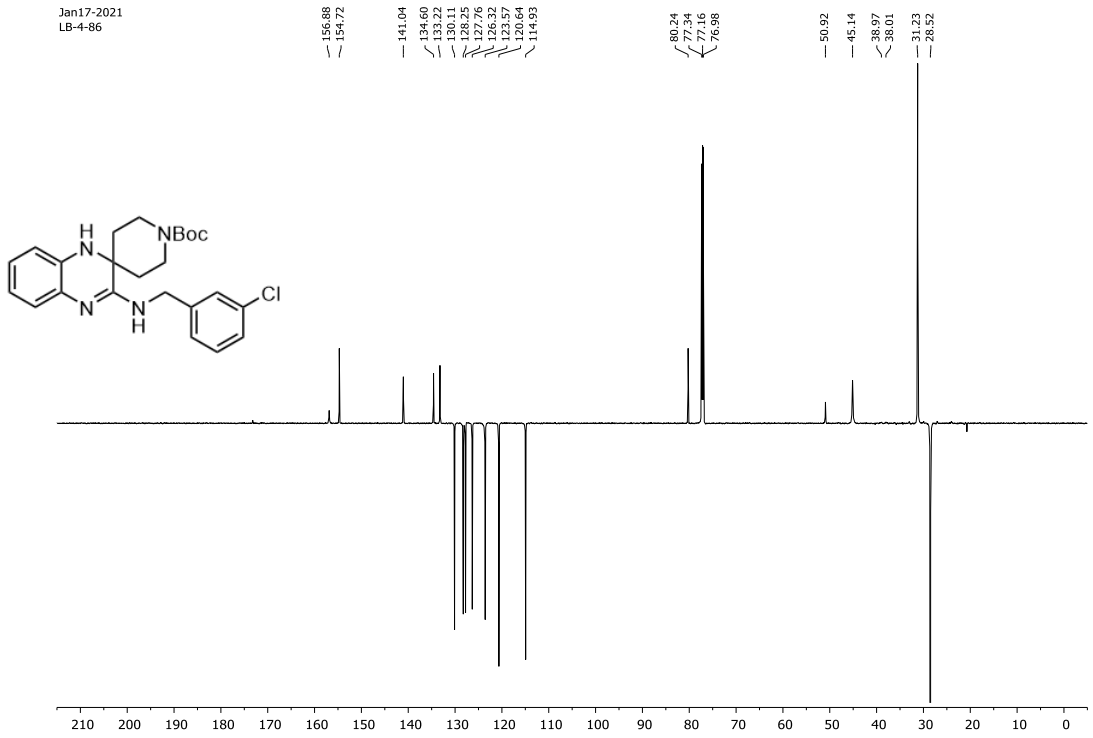
Compound 2-21 (^{13}C NMR; 176 MHz; DMSO-d_6)



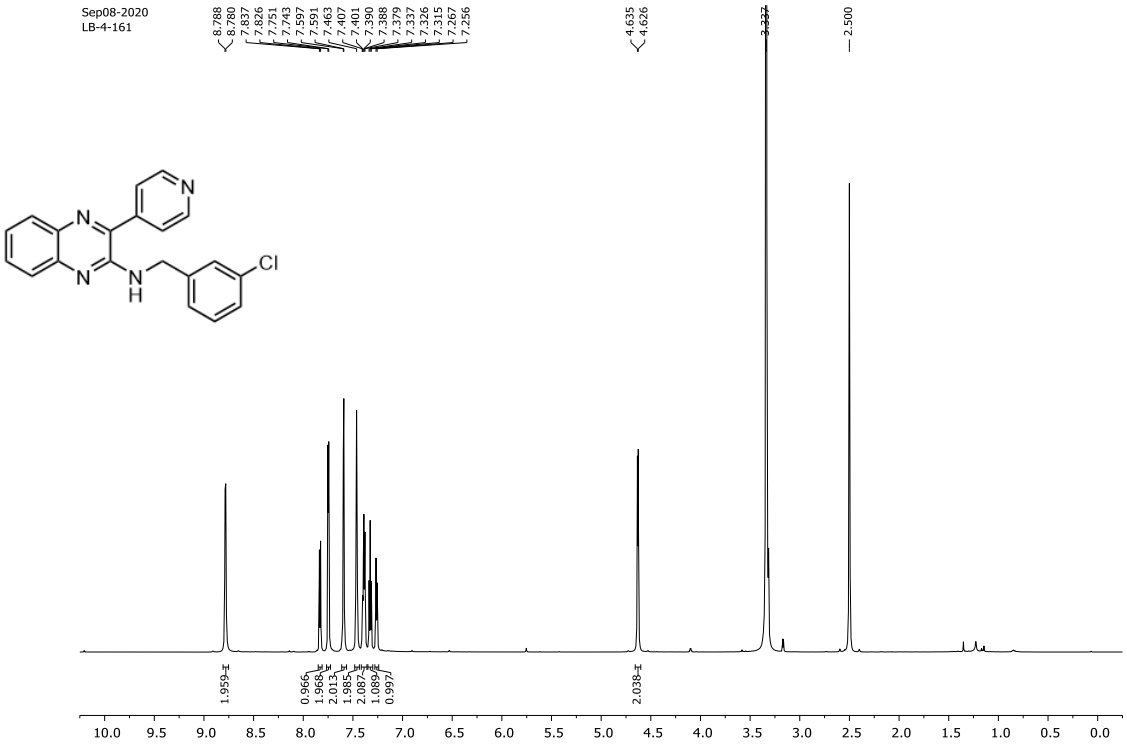
Compound 2-22 (^{1}H NMR; 700 MHz; $CDCl_3$)



Compound 2-22 (^{13}C NMR; 176 MHz; $CDCl_3$)



Compound 2-23 (^{1}H NMR; 700 MHz; DMSO-d_6)



Compound 2-23 (^{13}C NMR; 176 MHz; DMSO-d_6)

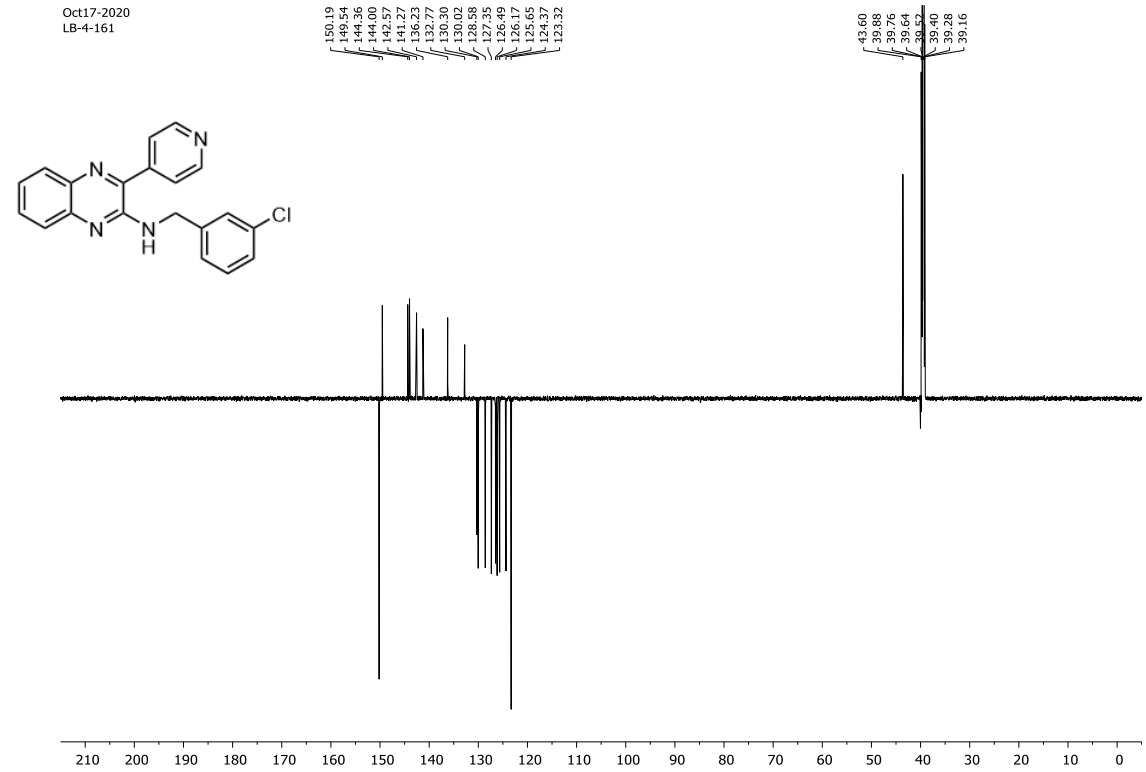
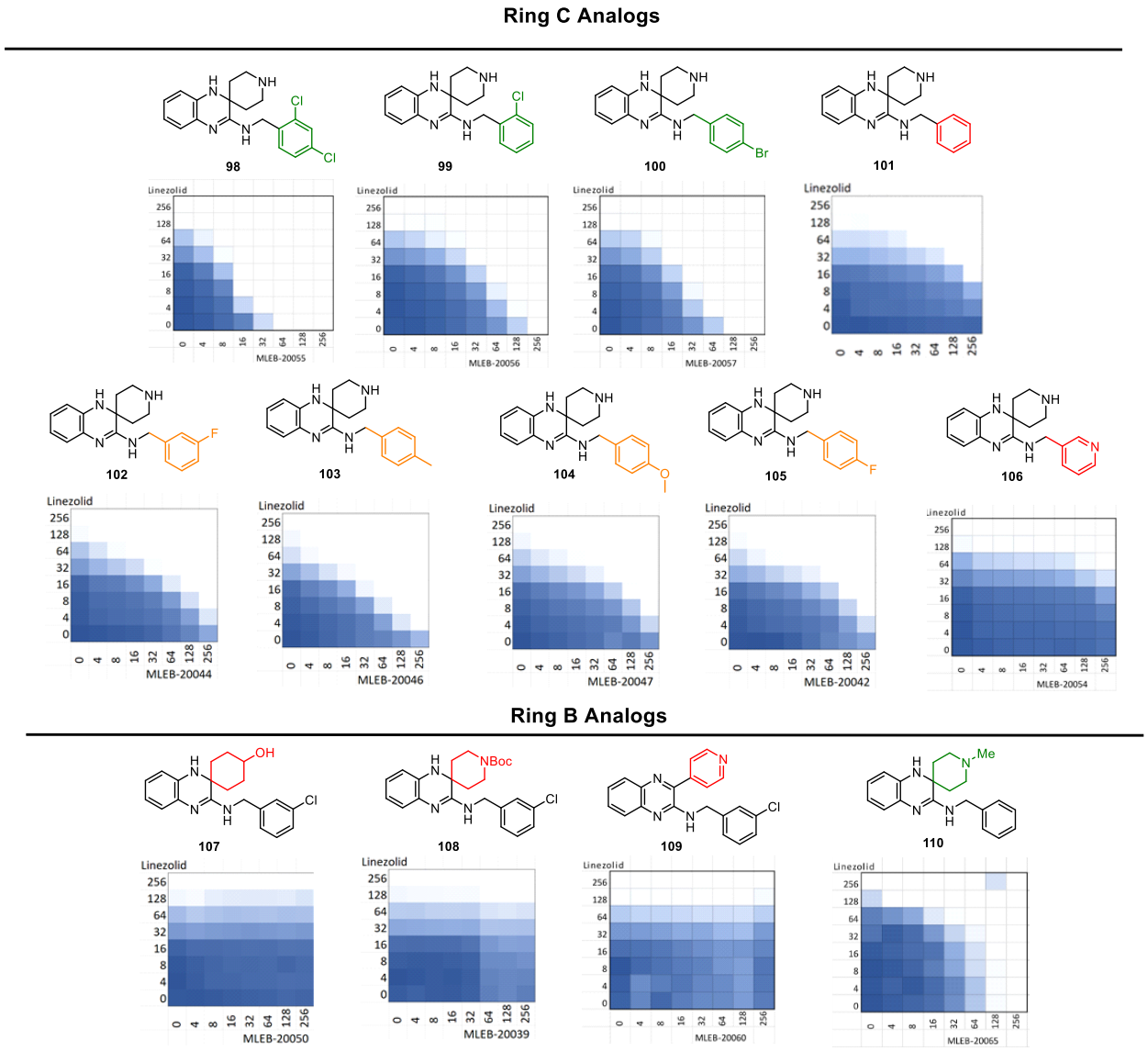


Table 2. Checkerboards of Liproxstatin-1 Analogs



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