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THESIS

PRACTICAL ONE POT METHODOLOGY FOR CARBON-HETEROATOM BOND FORMATION MEDIATED BY PHOSPHORUS REAGENTS AND SYNTHESIS OF CHIRAL BIQUINOLYLS AS PRECURSORS FOR POLYDENTATE AUXILIARIES

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Parinthorn Temyarasilp 2014: Practical One Pot Methodology for Carbon-Heteroatom Bond Formation Mediated by Phosphorus Reagents and Synthesis of Chiral Biquinolyls as Precursors for Polydentate Auxiliaries. Doctor of Philosophy (Chemistry), Major Field: Chemistry, Department of Chemistry. Thesis Advisor: Assistant Professor Wanchai Pluempanupat, Ph.D. 373 pages.

A new and convenient method for carbon-heteroatom bond formation using trivalent phosphorus reagents in one pot reaction was disclosed.

The oxidation-reduction condensation between various nucleophiles and alkyl diphenylphosphites, generated *in situ* from alcohols and chlorodiphenyl-phosphine ($ClPPh_2$), proceeded smoothly in the presence of camphorquinone to furnish the corresponding products in low to high yields.

The halogenation of alcohols, carboxylic acid and phenol derivatives utilizing a new combination of triphenylphosphine (PPh_3) and halogenating agents smoothly converted into the corresponding alkyl halides, acid halides and halobenzene derivatives, respectively in good yields. Moreover, nucleophilic substitution of alkyl halides and acid halides, generated *in situ* from alcohols and carboxylic acids, could be reacted with various nitrogen, oxygen and sulfur nucleophiles to afford the corresponding products in moderate to high yields.

In addition, 7,7'-Dihydroxy-8,8'-biquinolyl (azaBINOL) and its derivatives, which used as a substrate for the preparation of chiral phosphinite catalysts were prepared from 7-hydroxyquinoline *via N,N*-dimethyl *O*-quinol-7-yl carbamate by directed *ortho* metallation (DoM) followed by $FeCl_3$ oxidative coupling or Ullmann coupling of 8-iodoquinolin-7-yl dimethylcarbamate and hydrolysis of the resulting dicarbamate. Moreover, the preparation of 2,2'-disubstituted derivatives of 8,8'-biquinolyl and adding the oxide or alkyl group at *N* position were also tried.

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Student's signature Thesis Advisor's signature

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LIST OF ABBREVIATIONS

Ac	=	Acetyl
Ar	=	Aryl
Bn	=	Benzyl
DBU	=	1, 8-Diazabicyclo[5.4.0]undec-7-ene
DCM	=	Dichloromethane
DDQ	=	2,3-Dichloro-5,6-dicyanobenzoquinone
DMAP	=	*N*, *N*-Dimethylpyridine
DMF	=	*N*, *N*-Dimethylformamide
Ph	=	Phenyl
TBDMS	=	*tert*-Butyldimethylsilyl
THF	=	Tetrahydrofuran
δ	=	Chemical shift (ppm)
J	=	Coupling constant
m	=	Multiplet
s	=	Singlet
t	=	Triplet
q	=	Quartet
d	=	Doublet
dd	=	Doublet of doublets
ddd	=	Doublet of doublet of doublets
Hz	=	Hertz
EI	=	Electron impact
HRMS	=	High resolution mass spectroscopy
m/z	=	A value of mass divided by charge
NMR	=	Nuclear magnetic resonance
H	=	Hour

PRACTICAL ONE POT METHODOLOGY FOR CARBON-HETEROATOM BOND FORMATION MEDIATED BY PHOSPHORUS REAGENTS AND SYNTHESIS OF CHIRAL BIQUINOLYLS AS PRECURSORS FOR POLYDENTATE AUXILIARIES

INTRODUCTION

Phosphorus Chemistry

The phosphorus organic chemistry is based on the existence of numerous stable functional groups containing at least carbon-phosphorus bond. Phosphorous is an extremely versatile element, located below nitrogen in the periodic table in the group V elements and it has general application in a diverse range of reactions in organic synthesis.

Consequently, phosphorus atom shows several stable oxidation states including +3, +5 and +6 whereby the substituents can be both organic and inorganic in nature. The advantage of phosphorus reagents in organic synthesis stems from the elements' ability to progress from the lowest to highest coordination number and occasionally in the reverse direction. Key features of phosphorus include high nucleophilicity of tervalent phosphorus towards electrophiles, strong P=O bonds that are readily formed (also to S, N and the halogens) and the capability of phosphorus to stabilize adjacent anions. Phosphorus displays an important role in all organisms, it provides the stable macro molecular backbone for DNA and RNA, as well as interacting almost biochemical pathways *via* phosphorylation *etc*. Phosphorus polymers could be used as fire and smoke retardants in electrical devices. Moreover, phosphorus compounds are widely used as reagents for organic synthesis in the last century that has revolutionized the number of compounds available to organic chemists.

1. Organophosphorus Chemistry

Organophosphorus chemistry is the corresponding science exploring the properties and reactivity of organophosphorus compounds (Vereshchagina, 2005). Common phosphorus funtionalities are shown in Figure 1.

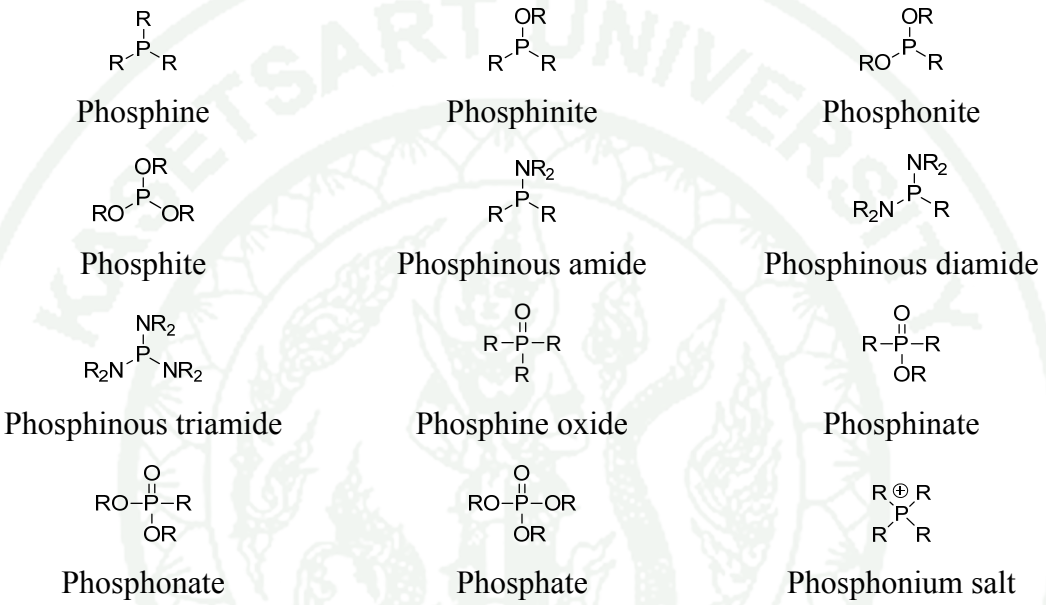


Figure 1 The examples of organophosphorus compounds.

The thermal stability of the C-P bond is quite high. The heat of dissociation of the 4-coordinated C-P bond is generally accepted to be about 65 kcal/mol, and there is never any difficulty in handling most alkyl and aryl phosphorus compounds even at elevated temperatures (Quin, 2000).

2. Uses of Organophosphorus Compounds

Organophosphorus compounds, have widespread use throughout the world, mainly in agriculture as insecticides, herbicides, and plant growth regulators (Moraies – Rojas, 2002). They have also been used as nerve agents in chemical warfare and as therapeutic agents, such as ecothiopate used in the treatment of glaucoma (Kovacie, 2003). In many research, the organophosphorus compounds are found important

application in stoichiometric organic synthesis such as Wittig reaction, Mitsunobu, Staudinger reaction, as well as in organocatalysis, etc. The use of organophosphorus compounds as achiral or chiral ligands for transition metal catalyzed transformations is also rapidly growing in both laboratory synthesis and industrial production (Tang, 2003). Furthermore, organo-phosphorus compounds can be used as flame retardants for fabrics and plastic plasticising and stabilising agents in the plastics industry, selective extractants for metal salts from ores, additives for petroleum products and corrosion inhibitors.

2.1 Agricultural Applications

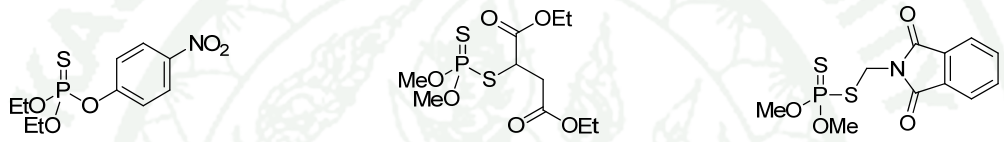
Over the years, many organophosphorus compounds have been synthesized and used in very large quantities in agriculture, not only as insecticides but also later as herbicides and in other applications. Phosphorus compounds have distinct advantages in the pesticides market; they are relatively easy to make, and they biodegrade readily by hydrolysis, so that the problems of residual activity, so serious with the chlorinated hydrocarbon pesticides, are avoided. The active compounds are normally esters, amides, or thiol derivatives of phosphoric or phosphonic acid (Figure 2).

Phosphoric acid derivative Phosphonic acid derivative

Figure 2 Structure of derivatives of phosphoric or phosphonic acid

Substituents R_1 and R_2 are usually simple alkyl or aryl groups, both of which may be bonded directly to phosphorus (in phosphinates), or linked via *O*, or *S* (in phosphates), or R_1 may be bonded directly and R_2, bonded via one of the above groups (phosphonates).

Parathion **(1)** was one of the first commercially produced insecticides. Its toxicity (LD_{50}) is 55 mg/Kg, which is rather low but still requires careful handling and application in the farmland. It was very popular in 1960s, but after this period the interest in Parathion has greatly declined with the introduction of safer agents. Definitely, many compounds are now produced that are relatively harmless to humans yet with excellent toxicity to insects; for example, the well-known garden insecticide Malathion **(2)** and Phosmet **(3)** with LD_{50} up 4000 mg/Kg. On the other hand, the phosphorus compounds were late entries in the fields of organic herbicides, and to this date only a few compounds have attained major commercial importance.



(1) **(2)** **(3)**

Figure 3 Examples of some insecticides and herbicides based on organophosphorus compounds.

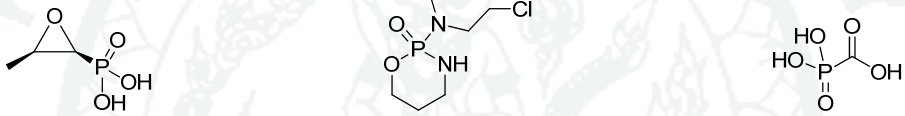
2.2 Organophosphorus Compounds in Medicine

A source of organophosphorus compounds from natural origin was first recognized by Hendlin in 1969. From the products in a fermentation broth of the bacterium *Streptomyces fradiae* a new phosphoric acid was isolated that exhibited antibacterial activity. This isolated compound was Fosfomycin **(4)** and its discovery was a milestone in the field of phosphorus chemistry (Quin, 2000). Phosphorus compounds have been largely ignored by medicinal chemists seeking new agents against infectious disease. Fosfomycin **(4)** is active against both Gram-positive and Gram-negative bacteria, and its effectiveness is comparable to that of the well-known antibiotics Tetracycline.

High-level anticancer activity has been found in a large number of phosphorus compounds of quite different structural types, and there is much current

research in this field. Probably the first organophosphorus compound to receive acclaim as a valuable chemotherapeutic agent is the anticancer drug cyclophosphamide **(5)**. Its activity was discovered by Arnold in 1958 and remains in clinical use until nowadays.

Phosphorus compounds have also displayed antiviral activity. The first active compound, trisodium phosphonoformiate was discovered by Helgstand in 1978.This compound is still used in clinic under the name Foscarnet **(6)**. It can inhibit viral DNA polymerase, and it is a useful agent in the treatment of Herpes and is also active against HIV.



(**4**) (**5**) (**6**)

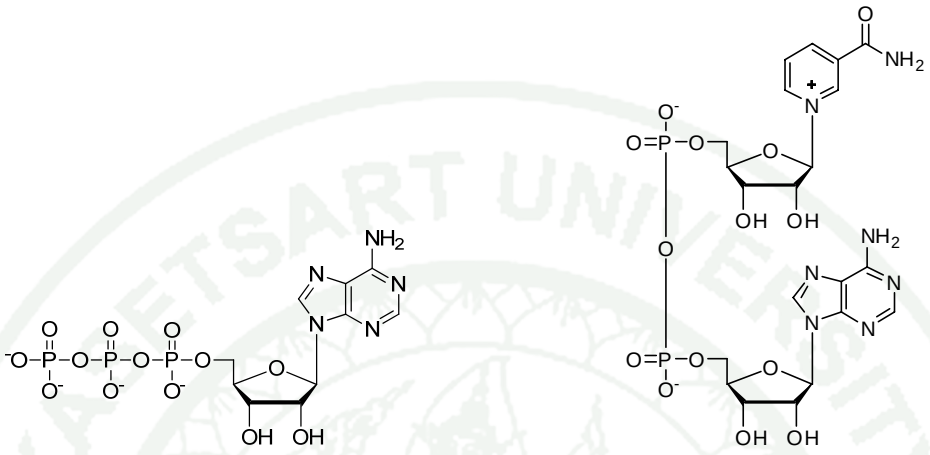
Figure 4 Organophophorus compounds in medicine.

2.3 Biological Compounds containing Phosphorus

Phosphorus is present in both animals and plants. In the animals, it is a component of fundamental bioactive compounds. It is found in complex organic compounds in the blood, muscles, and nerves, and in calcium phosphate, the principal material in teeth and bones. Especially, phosphoric acid is an essential in building block nucleotides, nucleic acids, phospholipids and sugar phosphates.

Nucleotides are monomers consisting of a phosphate group, a five carbon sugar (either ribose or deoxyribose) and a heterocyclic base. The genetic material (DNA) is a polymer of four different nucleotides. The genetic information is coded in the sequence of nucleotides in a DNA molecule. Nucleotides and related compounds are also important "energy carrying" compounds. Among the ones

commonly encountered are Adenosine triphosphate, ATP **(7)**, and Nicotinamide adenine dinucleotide, NADH **(8)** (Voet, 1995).



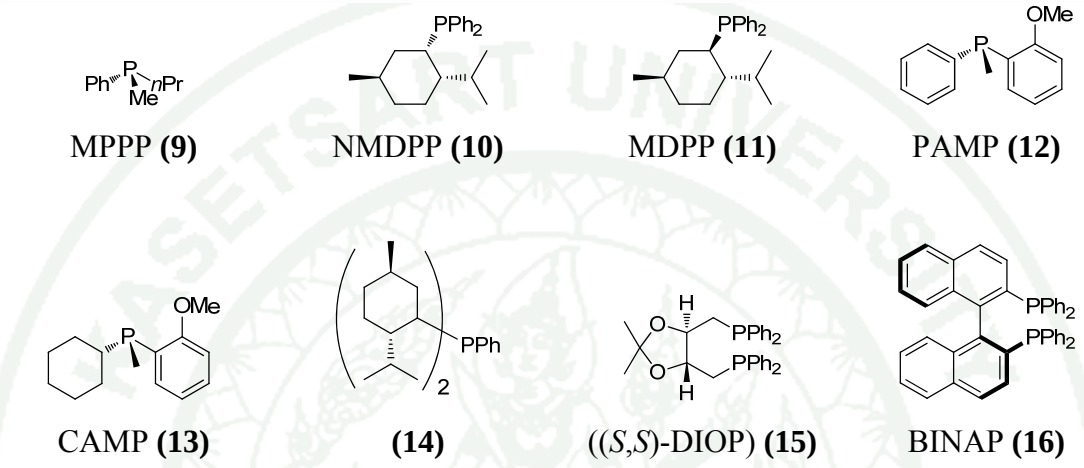
(7) **(8)**

Figure 5 Structure of ATP and NADH.

2.4 Catalysis

Between various types of enantiomerically pure ligands used for catalytic asymmetric reactions, chiral tertiary phosphines are established as the most effective ligands for most homogeneous transition-metal catalyses. The homogeneous asymmetric hydrogenation was started by using (*S*)-methyl (phenyl)(propyl) phosphine **(9)** (MPPP) as ligand by Horner (1968). In 1971, Morrison prepared neomenthyldiphenylphosphine **(10)** (NMDPP) and methyldiphenyl phosphine **(11)** (MDPP) and they also published synthesis and application of methylphenyl-*O*-anisyl phosphine **(12)** (PAMP) and methylcycohexyl-*O*-anisylphosphine **(13)** (CAMP) in 1974. At the same time, Bogdanović (1972) used dimenthylphenylphosphine **(14)** as ligand of nickel complexes. Dang (1971) and Bogdanović (1973) demonstrated that a bidentate chelating chiral C2-symmetric diphosphine, (−)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane, ((*S*,*S*)-DIOP) **(15)** was an excellent enantioselective catalyst. A multitude of chelating diphosphines are presently known, some of them are patented because of industrial applications (Lagasse, 2000). One of

the most effective chiral biphosphine ligands is 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) **(16)** (Noyori, 1990), which has exhibited high enantioselectivity in many asymmetric reactions including rhodium- or ruthenium-catalyzed hydrogenation.



MPPP **(9)** NMDPP **(10)** MDPP **(11)** PAMP **(12)**

CAMP **(13)** **(14)** ((*S*,*S*)-DIOP) **(15)** BINAP **(16)**

Figure 6 Examples of ligands for homogeneous catalysis.

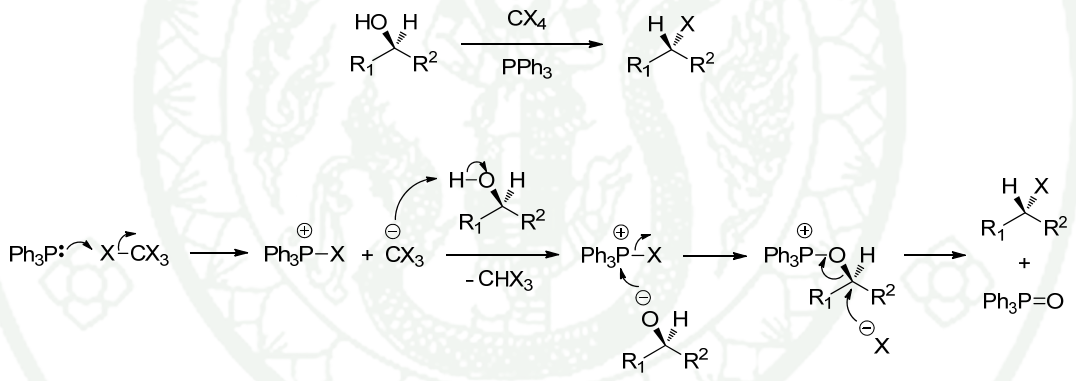
2.5 Functional Group Interconversion in Organic Synthesis with Participated of Phosphorus

The Functional Group Interconversion (FGI) was defined by Stuart Warren (2008) as "the process of converting one functional group into another by substitution, addition, elimination, oxidation or reduction and the reverse process used in (retrosynthetic) analysis". In many organic reactions, the organophosphorus compounds participated as the intermediate such as Wittig reaction, Mitsunobu reaction, Staudinger reaction or as auxiliaries and ligands in organo- and transition metal catalysis.

2.5.1 Appel Reaction

The Appel reaction, credited to Rolf Appel (1975), is used for converting an alcohol to an alkyl halide using a tetrahalomethane (CX_4) and triphenylphosphine (PPh_3).

The reaction begins with the halogenation of PPh_3 followed by the formation of the alkoxide from starting alcohol. The alkoxide subsequently attacks the phosphorous, releasing the halide leaving group. Then, the halide attacks the carbon stereocenter to give the corresponding product with inverted stereochemistry and triphenylphosphine oxide ($Ph_3P{=}O$) is obtained as by–product. The formation of the strong P=O double bond is a driving force for this reaction (Scheme 1).

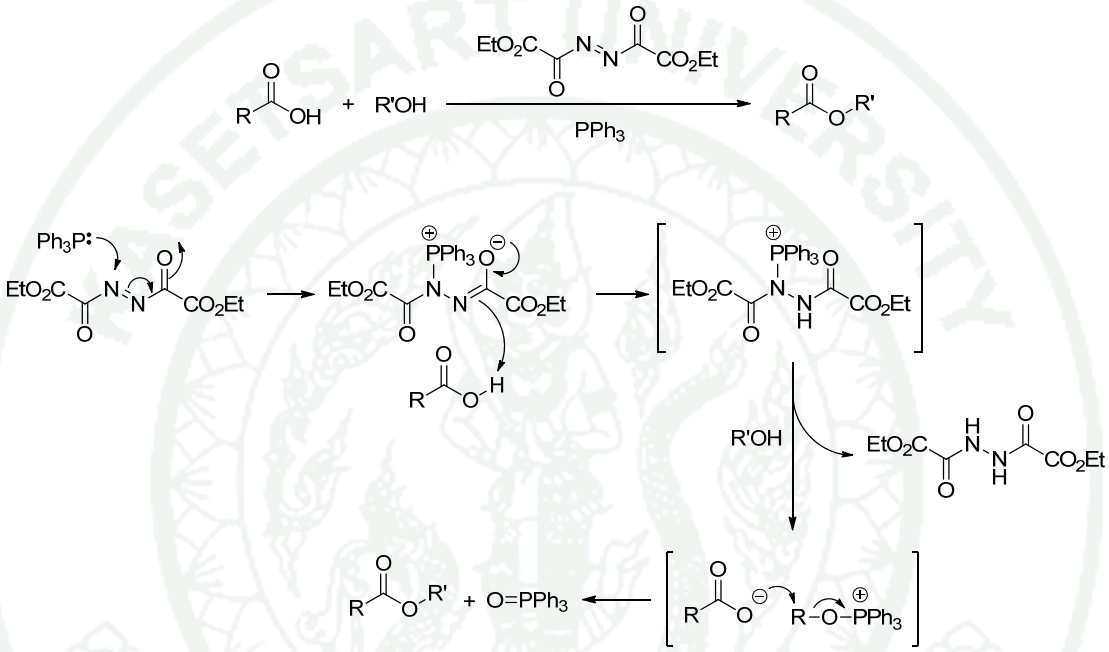


Scheme 1 Reaction and mechanism of Appel reaction

2.5.2 Mitsunobu Reaction

The Mitsunobu reaction, discovered by Oyo Mitsunobu (1967), is an important organic reaction used for converting primary and secondary alcohols into a variety of compounds using the combination between triphenylphosphine (PPh_3) and azodicarboxylate such as diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD).

The mechanism begins with attack of PPh_3 on DEAD which forms a betaine intermediate which deprotonates the carboxylic acid to form the anionic nucleophile. The alcohol then binds to the phosphonium ion and the nucleophile performs a S_N2 attack to yield the desired product with inversion of configurtion (Scheme 2).



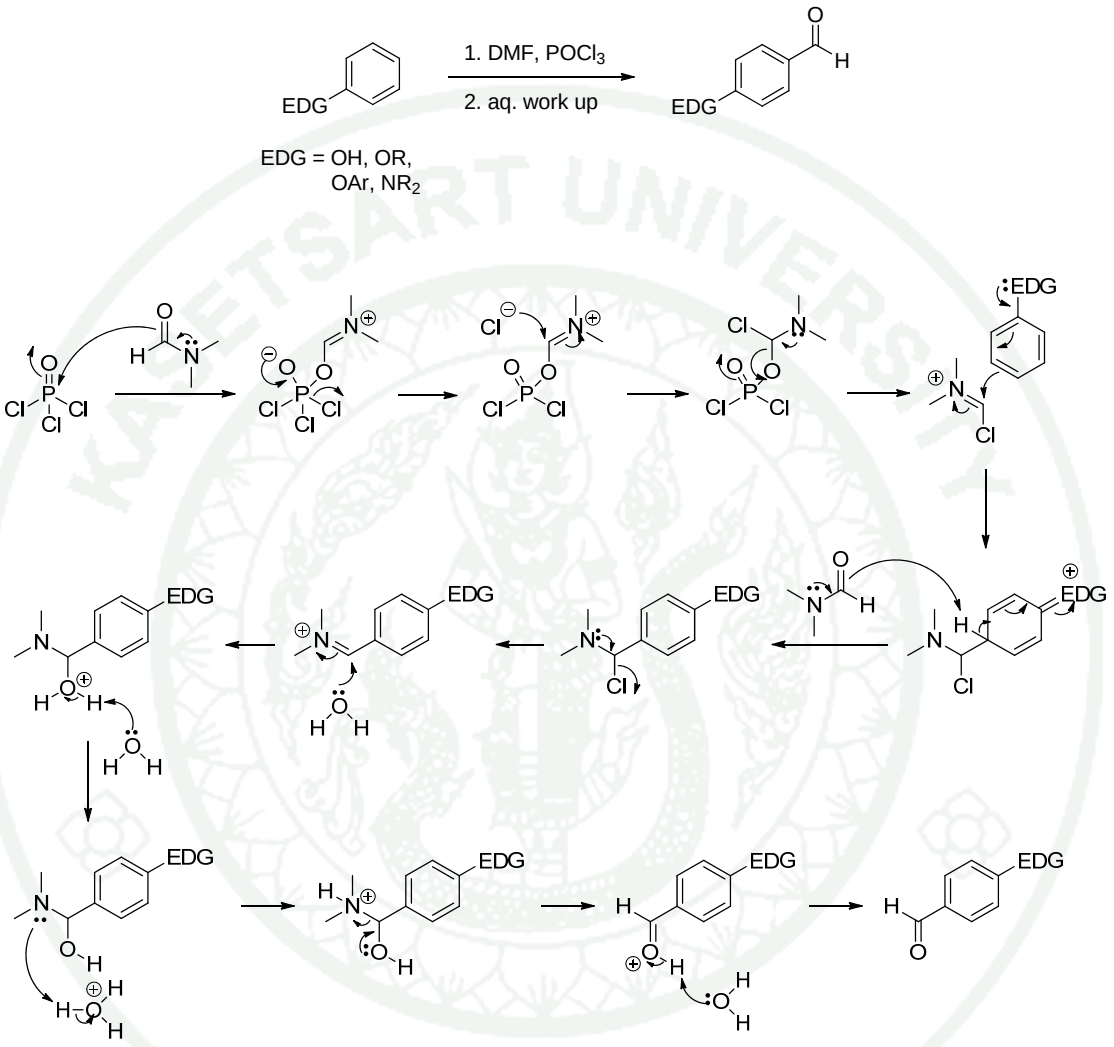
Scheme 2 Reaction and mechanism of Mitsunobu reaction

2.5.3 Vilsmeier-Haack Reaction

The Vilsmeier-Haack reaction is used for the preparation of aryl aldehyde from electron rich aromatic compound using DMF and $POCl_3$. The reaction is named after Anton Vilsmeier and Albrecht Haack discovered (1927).

The mechanism begins with the reaction of DMF with $POCl_3$ to form an iminium salt known as the "Vilsmeier reagent". The electron rich aromatic compound then attacks the iminium ion with loss of aromaticity. A rearomatization step, which is followed by the release of a chloride ion to form another iminium

intermediate. Aqueous work-up then leads to the corresponding aryl aldehyde (Scheme 3).

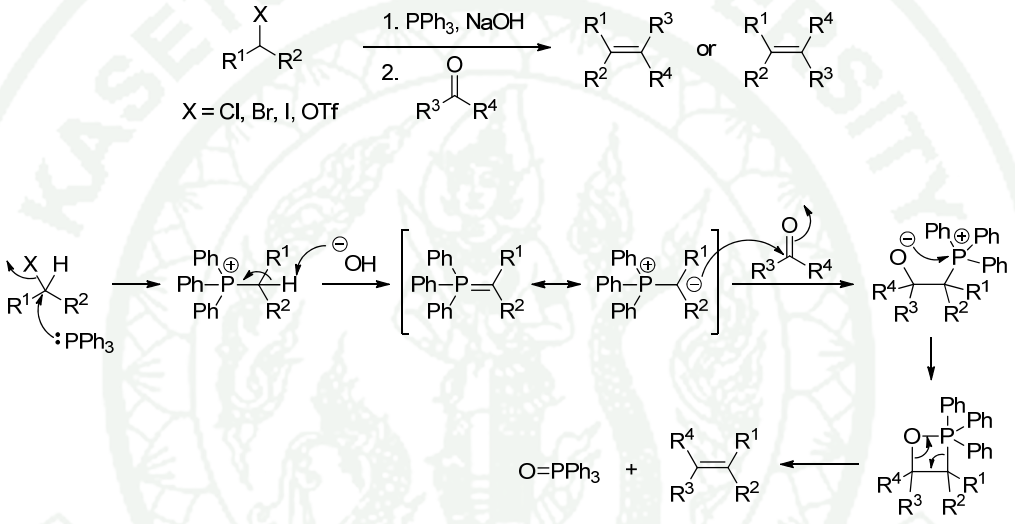


Scheme 3 Reaction and mechanism of Vilsmeier-Haack reaction

2.5.4 Wittig Reaction

The Wittig reaction was discovered in 1955 by George Wittig. It is widely used in organic synthesis for the preparation of alkenes. Wittig reaction iscommonly used to couple aldehyde or ketone to mono substituted phosphorus ylide. In the case of unstabilized ylide, the produced were obtainedalmost exclusively with *Z*-geometry.

The mechanism beings with attack of PPh_3 on alkyl halide which releases halide anion and forms phosphonium salt intermediate. The base then deprotonates at the alpha position to obtain phosphonium ylide. The ylide subsequently attacks carbonyl group of aldehyde or ketone to form a zwitterion intermediate where the oxygen anion then attacks the phosphonium cation to form an oxaphosphetane. A rearrangement then generates the corresponding olefin product and $Ph_3P=O$ **(Scheme 4).**



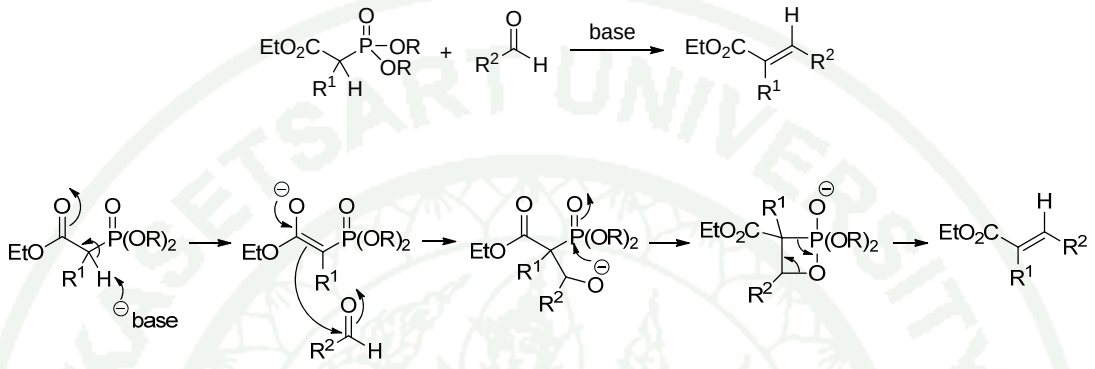
Scheme 4 Reaction and mechanism of Wittig reaction

2.5.5 Horner-Wadworth-Emmons Reaction

The Horner-Wadworth-Emmons reaction is used for the conversion of an aldehyde and β-alkoxy carbonyl phosphonated into alkene using base such as sodium hydride (NaH) or sodium alokoxide (NaOR). In 1959, Leopold Hornor reported the modified Wittig reaction using phosphonate stabilized carbanions. Then, William Wadsworth and William Emmons further suggested the mechanism in 1961.

The mechanism starts with α-deprotonation of the phosphonate ester with base to give the phosphonate carbanion. Then, nucleophilic addition of the

carbanion to aldehyde or ketone affords the enolate anion that can attack the phosphorus atom to generate four-membered ring intermediate. A rearrangement then generates the corresponding olefin product and releases dialkylphosphate as by-product (Scheme 5).

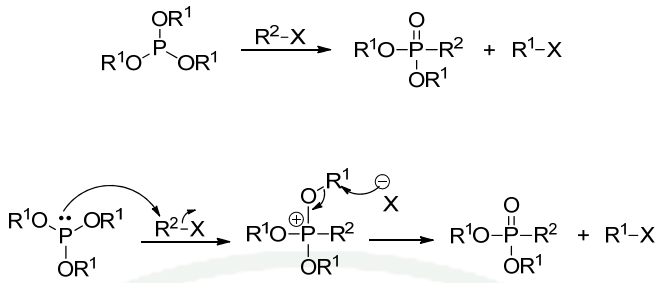


Scheme 5 Reaction and mechanism of Horner-Wadworth-Emmons reaction

2.5.6 Michaelis-Arbusov Reaction

The Michaelis-Arbusov reaction is applied for the transformation of triphenylphosphite into phosphonate. The reaction was discovered by August Michaelis in 1898 and greatly explored by Aleksandr Arbusov. Modifications are also applied to synthesize various phosphinates and phosphine oxides.

According to the mechanism, phosphite reacts with alkyl halide to give phosphonium intermediate. Then, halide anion attacks alkoxy substituent of the phosphonium intermediate to give the desired phosphonate via S_N2 displacement (Scheme 6).

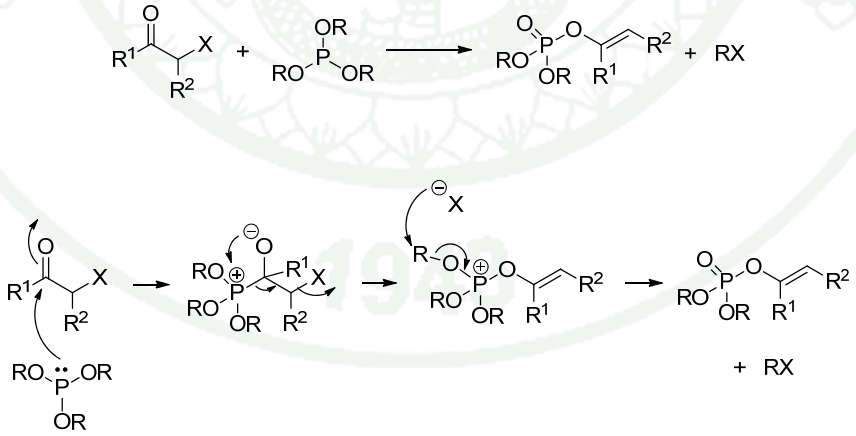


Scheme 6 Reaction and mechanism of Michaelis-Arbusov reaction

2.5.7 The Perkow Reaction

The Perkow reaction was developed by Werner Perkow in 1954. Trialkylphosphite ester reacts with a haloketone to afford dialkyl vinyl phosphate.

The mechanism is initiated by nucleophilic addition of phosphite at carbonyl carbon to form zwitterionic intermediate. This intermediate can rearrange to obtain phosphonium salt. Then dealkylation of phosphonium salt by attacking of halide anion affords enol phosphate (Scheme 7).



Scheme 7 Reaction and mechanism of Perkow reaction

As demonstrated through the above reactions, phosphorus reagents are essential role for functional group interconversion in organic synthesis. However, some reactions still remain problematic giving side reaction or low yield. A new methodology which could solve those problems is therefore still desired and represents a responsible task for organic chemists. The aim of this research is to study and to develop a new methodology for carbon-heteroatom bond formation by using phosphorus reagent.

OBJECTIVES

1. To study the effect of carbon-heteroatom bond formation by oxidation-reduction condensation using a new combination of alkyl diphenylphosphinites, generated from alcohol, nucleophiles and 1,2-dicarbonyl compounds.

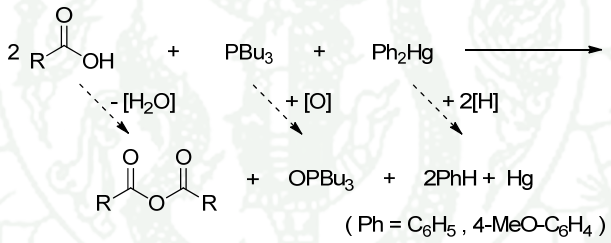
2. To study the effect of carbon-heteroatom bond formation by nucleophilic substitution and nucleophilic aromatic substitution using a combination of halogen compounds, generated from alcohol, carboxylic acid or phenol derivatives reacted with halogenating agents in the presence of phosphorus compound and nucleophiles

3. To synthesize 7,7'-dihydroxy-8,8'-biquinolyl (azaBINOL) as a precursor for the preparation of chiral phosphinite catalyst

LITERATURE REVIEW

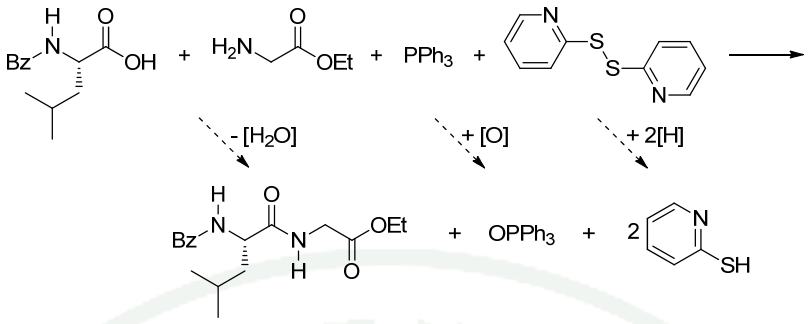
1. Synthetic Methodology for Carbon-Carbon and Carbon-Heteroatom Bond Formation by Oxidation-Reduction Condensation

The oxidation-reduction condensation concept is dehydration between two molecules by removing H_2O as 2[H] and [O] using a combination of reductant and oxidant. This reaction proceeds under mild and neutral conditions without any assistance of promoters. The first reaction of this concept was published by Mukaiyama in 1963 reporting that two molecules of carboxylic acids were dehydrated to form the corresponding acid anhydrides in high yields by using diphenyl- or bis(4-methoxyphenyl)mercury (Ph_2Hg) (oxidant) and tributylphosphine (*n*-Bu_3P) (reductant) as shown in Scheme 8.



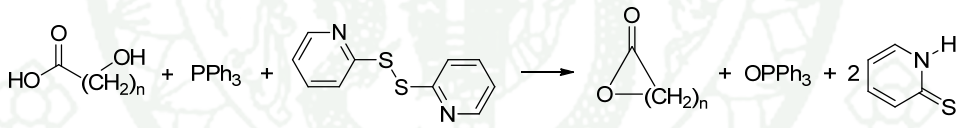
Scheme 8 The oxidation-reduction condensation of 2 moles of carboxylic acid in the presence of Ph_2Hg and PBu_3

In 1970, Mukaiyama also reported that the condensation reaction between Bz-L-Leu-OH and H-Gly-OEt proceeding smoothly in the presence of triphenylphosphine (PPh_3) and di(2-pyridyl)disulfide (PySSPy) to afford dipeptide, Bz-L-Leu-Gly-OEt, in high yield (Scheme 9).



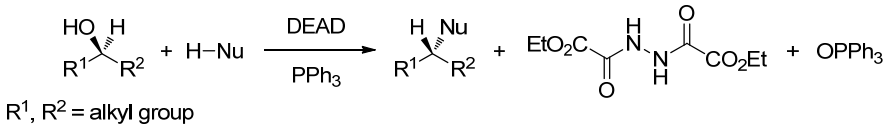
Scheme 9 The oxidation-reduction condensation of Bz-L-Leu-OH and H-Gly-OEt in the presence of PPh_3 and PySSPy

Later, Corey *et al* (1974) reported an effective method for a macrocyclic lactone synthesis by treating a ω-hydroxycarboxylic acid with PPh_3 and PySSPy (Scheme 10). The developed reaction could be used to synthesize macrocyclic compounds such as Erythronolide B (1975a), Vermiculine (1975b) and Enterobactin (1977).



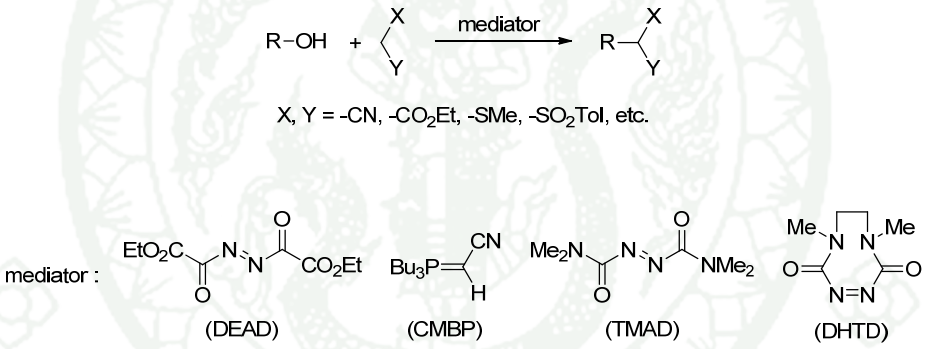
Scheme 10 The oxidation-reduction condensation of a ω-hydroxycarboxylic acid in the presence of PPh_3 and PySSPy

This concept was applied by Mitsunobu *et al.* (1967a) for the preparation of phosphoric esters by treating of allyl diethyl phosphite with PPh_3 and DEAD in the presence of alcohols. Later, they also applied this concept to develop an efficient dehydration condensation between alcohols and carboxylic acids to give esters using the combination of PPh_3 and DEAD (1967b) as shown in Scheme 11. To investigated scope and limits of this reaction, it was extended to various nucleophiles such as phenols, imides, hydrogen azides, active methylene compounds, and thiols (Mitsunobu, 1981; Hughes, 1992; Dembinski, 2004). It was found that all reactions proceeded smoothly to give the corresponding products in good yields.



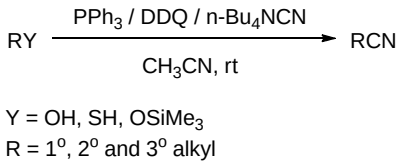
Scheme 11 The condensation reaction between alcohols and various nucleophiles using the combination of PPh_3 and DEAD.

In 1995, Tsunoda also demonstrated dehydration reactions by using azodicarboxylic acid derivative reagents such as cyanomethylenetributylphosphorane (CMBP), *N,N,N',N'*-tetramethylazodicarboxamide (TMAD) and 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHTD), which were applied to use with various active methylene compounds (Scheme 12).



Scheme 12 The condensation reaction between alcohols and various active methylene compounds using the combination of PPh_3 and azodicarboxylic acid.

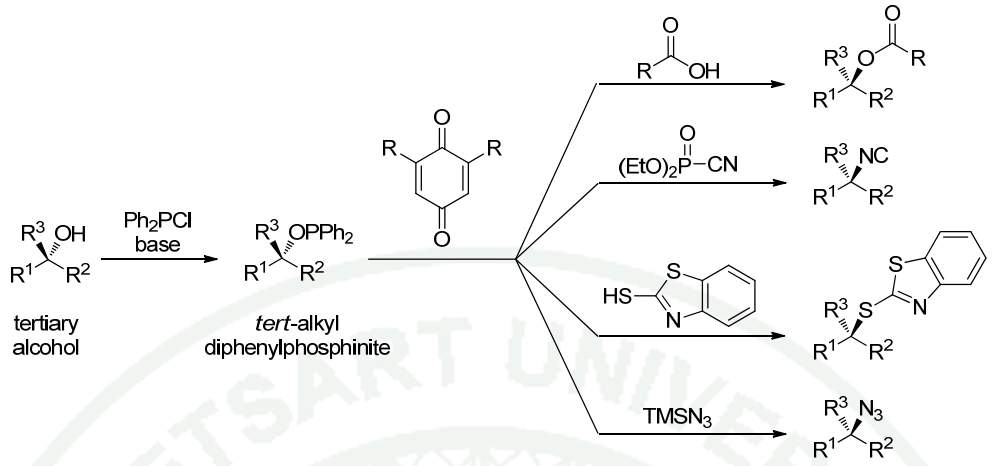
Iranpoor (2004) reported on the application of PPh_3/DDQ/*n*-Bu_4NCN for the conversion of alcohols, thiols and their derivatives into the corresponding alkyl cyanides in good to excellent yields at room temperature **(**Scheme 13**)**.



Scheme 13 The conversion of alcohols, thiols and their derivatives into the alkyl cyanides using the combination of PPh_3, DDQ and *n*-Bu_4NCN

After the efforts on these condensation reactions, however, a challenging problem still remained when bulky secondary or tertiary alcohols were used as a substrate because the formation of a key reaction intermediate, alkoxyphosphonium salt, was strongly interfered by steric hindrance of alcohols.

The search for new and suitable combinations of reductants and oxidants for oxidation-reduction condensation has been a matter of continued interest. For example, Mukaiyama reported that a new type of oxidation-reduction condensation using alkyl diphenylphosphinites ($ROPPh_2$), prepared from the corresponding alcohols and chlorodiphenylphosphine ($ClPPh_2$) proceeded with various nucleophiles (NuH) in the presence of benzoquinone could be proceeded to give the corresponding products. Interestingly, chiral *tert*-alkyl diphenylphosphinites could be converted into the corresponding chiral products with complete or nearly complete inversion of configuration when various nucleophiles such as carboxylic acid (Mukaiyama, 2003a; Shintou, 2004), diethyl cyanophosphonate (Mukaiyama, 2004a; Matsutani, 2006), 2-sulfanyl-1,3-benzo-thiazole (Ikegai 2005 and 2006), and trimethylsilylazide (Kuroda 2006 and 2007) were used (Scheme 14).

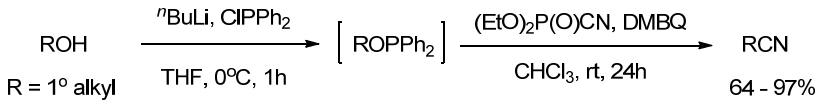


Scheme 14 The oxidation-reduction condensation using $ROPPh_2$, prepared from alcohols and $ClPPh_2$ with various nucleophiles in the presence of benzoquinones

In the next chapter, the literature reviews are given disclosing the preparation of carbon-carbon and carbon-heteroatom bond formations by oxidation-reduction condention using the combination of alkyl diphenylphosphinites and 1,4-benzoquinone derivatives.

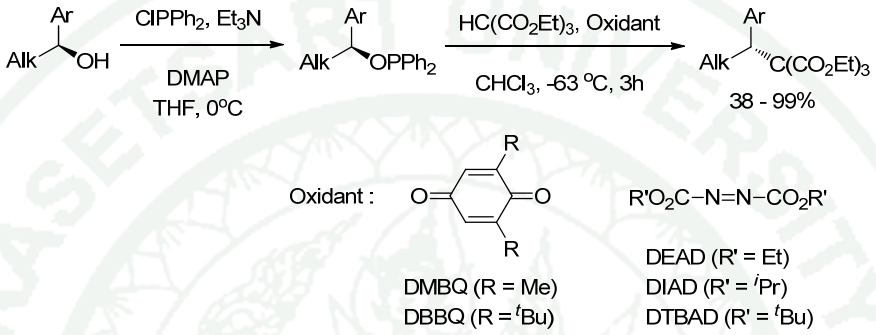
1.1 Carbon-Carbon Bond Formation

Mukaiyama (2004) reported the cyanation of alkoxydiphenyl-phosphines, prepared *in situ* from ^{n}BuLi and various primary alcohols, with 2,6-dimethyl-1,4-benzoquinone (DMBQ) and diethyl cyanophosphonate. The reactions provided the corresponding nitriles in high yields (Scheme 15).



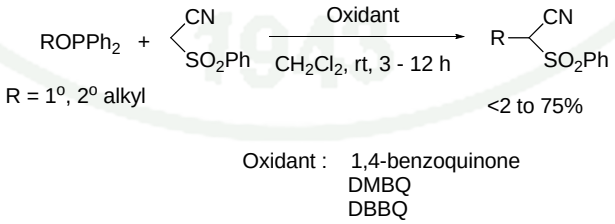
Scheme 15 The cyanation of $ROPPh_2$ with DMBQ and diethyl cyanophosphonate.

Mukaiyama (2005a) published the oxidation–reduction condensation reactions between alkyl diphenylphosphinites derived from chiral alkyl aryl alcohols and triethyl methanetricarboxylate in the presence of 1,4-benzoquinones. The reactions afforded the corresponding condensation products in good yields with inversion of stereochemistry (Scheme 16).



Scheme 16 The oxidation-reduction condensation using $ROPPh_2$, derived from chiral alcohols and $ClPPh_2$ with triethyl methanetricarboxylate in the presence of benzoquinones

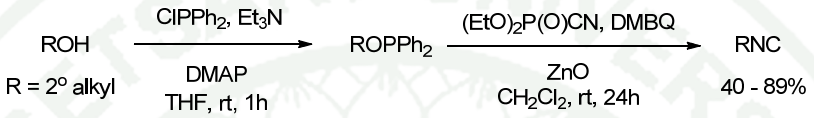
Mukaiyama (2005b) reported the 1,4-benzoquinone-mediated condensation of primary or secondary $ROPPh_2$ with (phenylsulfonyl)acetonitrile. The reactions proceeded smoothly at room temperature to form the corresponding alkylated products in good to high yields (Scheme 17).



Scheme 17 1,4-Benzoquinone-mediated condensation of primary or secondary $ROPPh_2$ with (phenylsulfonyl)acetonitrile

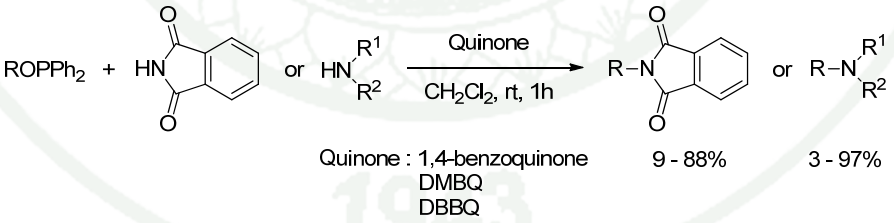
1.2 Carbon-Nitrogen Bond Formation

Masutani (2005) described the isocyanation of alkoxydiphenyl-phosphines with 2,6-dimethyl-1,4-benzoquinone (DMBQ) and diethyl cyanophosphonate in the presence of ZnO. The reactions provided the corresponding isonitriles in good to high yields (Scheme 18).



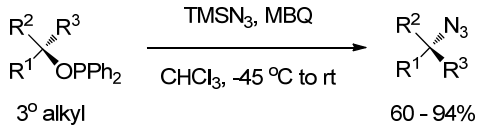
Scheme 18 The isocyanation of alkoxydiphenyl-phosphines with 2,6-dimethyl-1,4-benzoquinone (DMBQ) and diethyl cyanophosphonate in the presence of ZnO

Mukaiyama (2005b) reported the *N*-alkylation by using the condensation of alkyl diphenylphosphinites with phthalimide and various amines in the presence of 1,4-benzoquinone derivatives. The reactions yielded give the desired *N*-benzylation products in good to high yields (Scheme 19).



Scheme 19 The condensation of $ROPPh_2$ with phthalimide or various amines in the presence of 1,4-benzoquinone

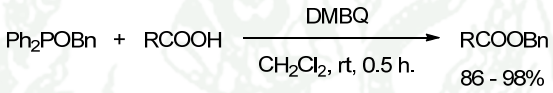
Kuroda (2006) reported an efficient method for the preparation of *tert*-alkyl azides from *tert*-alkyl phosphinites and trimethyl-silylazide ($TMSN_3$) in the presence of methoxybenzoquinone (MBQ). The reactions afforded the azide products in good to high yields with complete inversion of configuration (Scheme 20).



Scheme 20 The preparation of *tert*-alkyl azides from *tert*-alkyl phosphinites and $TMSN_3$ in the presence of MBQ.

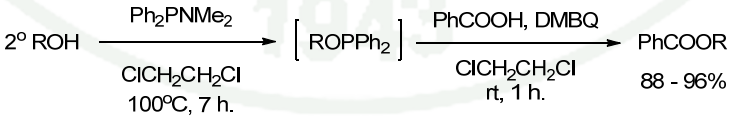
1.3 Carbon-Oxygen Bond Formation

Mukaiyama (2002) published the preparation of esters using a combination of benzyloxydiphenylphosphine (BDPP) with various carboxylic acids in the presence of DMBQ under mild and neutral conditions (Scheme 21).



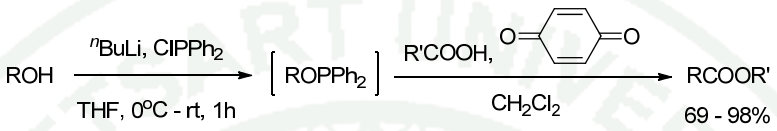
Scheme 21 Benzylation of carboxylic acid with BDPP and DMBQ

Mukaiyama (2003b) described a new-type oxidation-reduction condensation by using DMBQ, carboxylic acids and alkoxydiphenylphosphines, generated *in situ* from alcohols and Ph_2PNMe_2. The corresponding esters were isolated in good to high yields (Scheme 22).



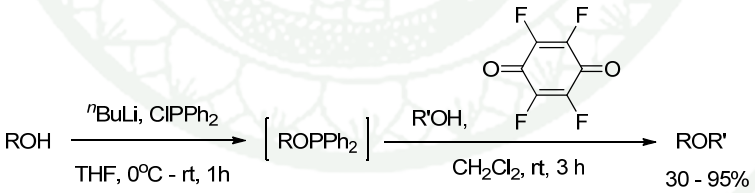
Scheme 22 Esterification of benzoic acid using Ph_2PNMe_2 and various secondary alcohols.

Shintou (2003a) reported a new and efficient method for the preparation of alkyl carboxylates from the corresponding alcohols by using alkoxydiphenyl phosphines and carboxylic acids in the presence of 1,4-benzoquinone. The results were found that secondary and tertiary alcohols could be proceeded to obtain the desired products in high yields under mild and neutral conditions (Scheme 23).



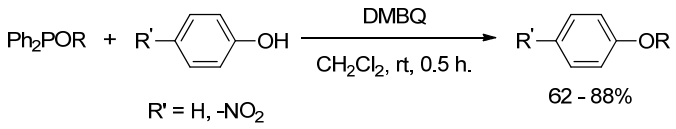
Scheme 23 Esterification of various carboxylic acids using several alkoxydiphenyl phosphine in the presence of 1,4-benzoquinone

Shintou (2003b) published a new type of oxidation–reduction condensation using tetrafluoro-1,4-benzoquinone (fluoranil), alcohols and alkoxydiphenylphosphines, formed *in situ* from ^{n}BuLi-treated alcohols and $ClPPh_2$, to afford the corresponding symmetrical or unsymmetrical ethers in good to high yields (Scheme 24).



Scheme 24 Etherification using fluoranil, variousalcohols and alkoxydiphenyl phosphines in situ formed alcohols, $ClPPh_2$ and n-BuLi

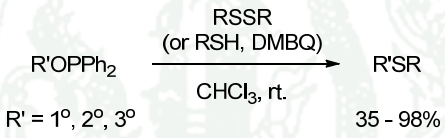
Shintou (2003c) reported the preparation of alkyl phenyl ethers in high yields using the combination of alkoxydiphenylphosphine and phenols in the presence of DMBQ under mild condition as shown in Scheme 25.



Scheme 25 Alkylation of phenol and 4-nitrophenol with several alkoxydiphenyl-phosphines and DMBQ.

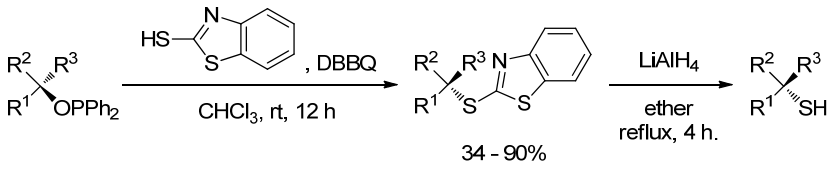
1.4 Carbon-Sulfur Bond Formation

Mukaiyama (2004b) reported a new method for the preparation of alkyl aryl sulfides from alcohol *via* alkoxydiphenylphosphines by oxidation-reduction condensation. Moreover, various primary, secondary and tertiary alcohols were successfully converted into the corresponding sulfides in moderate to high yields (Scheme 26).



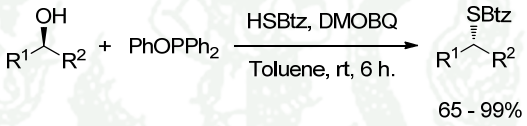
Scheme 26 Thioetherification of various alcohol via alkoxydiphenylphosphines by employing the disulfide and DMBQ.

Ikegai (2005) reported a two-step procedure for the formation of carbon-sulfur bond from *tert*-alcohols. Alkyl diphenylphosphinites were easily prepared in excellent yields from *tert*-alcohols and $ClPPh_2$ by the combined use of Et_3N and a catalytic amount of DMAP. Subsequent condensation of alkyl diphenylphosphinites with thiol smoothly proceeded in the presence of 1,4-benzoquinone derivatives to afford the corresponding *tert*-alkyl sulfides in good to high yields via S_N2 displacement. Moreover, removal of benzothiazol-2-yl group was also achieved with $LiAlH_4$ to afford the desired chiral thiol (Scheme 27).



Scheme 27 DBBQ-mediated condensation of *tert*-alkyl phosphinite with HSBtz using DBBQ and deprotection of benzothiol-2-yl group

Kuroda (2008) reported a method for the preparation of alkyl aryl sulfides from alcohol and HSBtz using phenyl diphenylphosphinite and 2,6-dimethoxy-1,4-benzoquinone (DMOBQ). In addition, the chiral alcohols could be converted into the corresponding chiral sulfides with clean inversion of the configuration under mild and neutral conditions (Scheme 28).



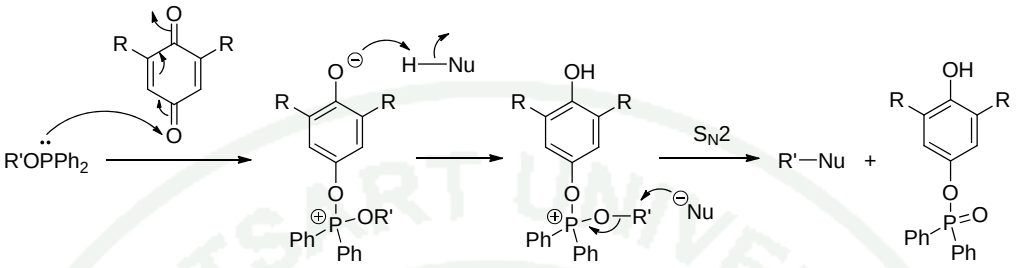
Scheme 28 Thoetherification of various alcohol using alkoxydiphenylphosphines by employing the HSBtz and DMOBQ

1.5 Mechanism of the oxidation-reduction condensation

The proposed mechanism of the oxidation-reduction condensation for carbon-carbon and carbon-heteroatom bond formation from using the combination of alkyl diphenylphosphinites and nucleophiles in the presence of 1,4-benzoquinone derivatives is addressed in Scheme 29.

In the first step, alkyl diphenylphosphinite reacted with the less hindered oxo group of 1,4-benzoquinone derivative to form a phenoxide anion. After that, the anion adduct abstracted a proton from an acidic nucleophile to give the phosphonium intermediate. Then, nuclophilic substitution at a carbon atom adjacent to oxygen atom

of the alkoxy group afforded the corresponding product and 4-hydroxyphenyl diphenylphosphinate as the by-product.



Scheme 29 The mechanism of the oxidation-reduction condensation using the combination of alkyl diphenylphosphinites and nucleophiles in the presence of 1,4-benzoquinone

2. Synthetic Methodology for Carbon-Carbon and Carbon-Heteroatom Bond Formation by Nucleophilic Substitution of Alkyl Halides and Acyl Halide

Alkyl halides (also known as halogenoalkanes or haloalkanes) are a group of chemical compounds containing one or more halogens and are derived from alkanes. Alkyl halides are widely used such as flame retardants, fire extinguishants, refrigerants, propellants, solvents, and pharmaceuticals.

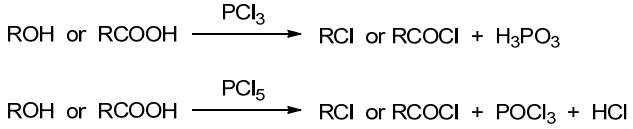
Acyl halides (also known as acid halides) are a group of chemical compounds derived from carboxylic acid by replacement of hydroxyl group with halogen. There are often used as intermediates in organic synthesis because they are generally more reactive than carboxylic acid.

Alkyl halides and acyl halides are important for using as intermediates to convert into many other functional groups as summarized in the Table 1.

Usually, alkyl halides and acyl halides could be prepared from alcohols and carboxylic acids by using phosphorus reagents which can be summarized as follows:

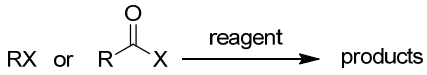
2.1 Phosphorus-halogen compounds

Both coordination number 3 and 5 compounds containing phosphorus-halogen bonds are commonly used as halogenating agents. In organic chemistry, PX_3 and PX_5 have been used for the conversion of C-OH into C-X (where X = Cl, Br). The examples of the conversion of alcohol or carboxylic acid into haloalkane or acid halide, using phosphorus halide were shown in Scheme 30.



Scheme 30 The preparation of haloalkane or acid halide using phosphorus halide

Table 1 Conversion of alkyl halides and acyl halides.



Reaction of	Reagent	Product	Product functional group
Alkyl halide	^-OH	ROH	Alcohol
	H_2O	ROH	Alcohol
	RO^-	ROR	Ether
	$RC{\equiv}C^-$	RC≡CR	Alkyne
	$ArH + AlX_3$	ArR	Alkyl benzene
	^-CN	RCN	Nitrile
	Mg, ether	RMgX	Grignard reagent
	$RCOO^-$	RCOOR	Ester
	NH_3	RNH_2	Amine
	HS^-	RSH	Thiol
	RS^-	RSR	Thioether
	base	C=C	Alkene
Acyl halide	H_2O	RCOOH	Carboxylic acid
	$ArH + AlX_3$	ArR	Acyl benzene
	ROH	RCOOR	Ester
	NH_3	$RCONH_2$	Amide
	$LiAlH_4$	RCH_2OH	Alcohol
	R'MgX	RCOR'	Ketone

Source: Mcmurry (2012)

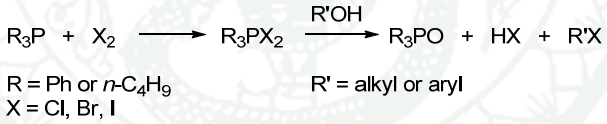
2.2 Phosphorus compound used for preparation of halogenated products

PPh_3 in combination with chlorinating agents such as CCl_4, Cl_3CCCl_3, Cl_3CCN, Cl_3CCONH_2, *N*-chlorosuccinimide (NCS) or with brominating agents such as CBr_4, Br_3CCO_2Et or *N*-bromosuccinimide (NBS) have been reported as reagents for the conversion of alcohols into alkyl halides and the conversion of carboxylic into acyl halide.

The followings are the interesting literature reviews highlighting the preparation of alkyl halides and acyl halides by nucleophilic substitution using the combination of PPh_3 and halogenating agent.

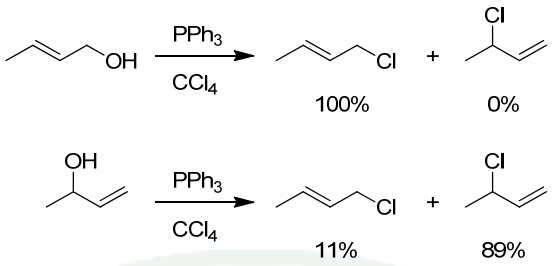
2.2.1 Preparation of alkyl halide

Wiley (1964) reported the preparation of a variety of alkyl and aryl halides in high yields using phosphorus reagents of the type R_3PX_2 (Scheme 31).



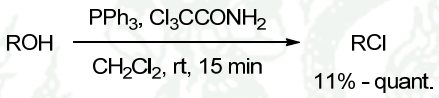
Scheme 31 The preparation of a variety of alkyl and aryl halides using phosphorus reagents of the type R_3PX_2

Snyder (1972) reported the conversion of primary allylic alcohols to their chlorides without isomerization by using PPh_3 and CCl_4 but the secondary could be achieved to the high stability (Scheme 32).



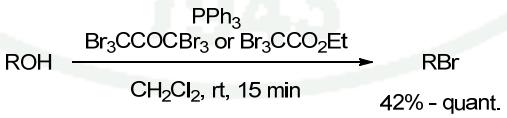
Scheme 32 The conversion of allylic alcohols to their chlorides using Ph_3P-CCl_4

Pluempanupat (2006) reported the chlorination of alcohols by using the combination of PPh_3 and Cl_3CCONH_2. The alcohols could be converted into the corresponding alkyl chloride in high yield under mild and neutral conditions (Scheme 33).



Scheme 33 Chlorination of alcohols with PPh_3/Cl_3CCONH_2

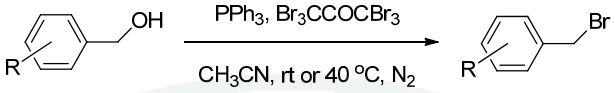
Tongkate (2008) reported the bromination of alcohols by using the combination of PPh_3 and $Br_3CCOCBr_3$ or Br_3CCO_2Et. The alcohols could be converted into the corresponding alkyl bromide in high yield under mild and neutral conditions (Scheme 34).



Scheme 34 Chlorination of alcohols with $PPh_3/Br_3CCOCBr_3$ or PPh_3/Br_3CCO_2Et

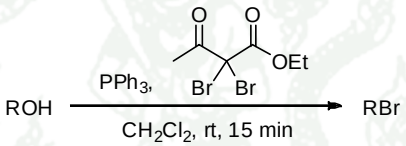
Joseph (2011) reported a series of benzyl bromides which prepared from the corresponding alcohols with $Br_3CCOCBr_3$ / PPh_3 at low temperature and under mild and neutral conditions. Moreover, the protocol could be

applied to the heterocyclic analogues and to the synthesis of precursor of the drug (Scheme 35).



Scheme 35 Bromination of benzyl alcohols with $PPh_3/Br_3CCOCBr_3$

Cui (2014) introduced α,α-dibromoacetoacetate as bromination agent for the conversion of primary and secondary alcohols to the alkyl bromides under neutral conditions **(**Scheme 36**)**.



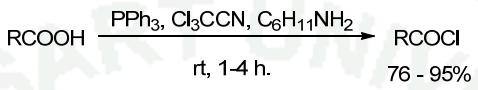
Scheme 36 Bromination of variuos alcohols with PPh_3 and ethyl α,α-dibromo acetoacetate

2.2.2 Preparation of acyl halide

Lee (1966) reported alkyl chloride by using trialkylacyl-oxyphosphonium halides that prepared from the corresponding carboxylic acid and PPh_3 in the presence of CCl_4. The reaction produced acetyl chloride, triphenylphosphine oxide and $CHCl_3$ in good yield (Scheme 37).

Scheme 37 Preparation of acid chloride from carboxylic acid using PPh_3/CCl_4

Jang (1999) reported the conversion of carboxylic acids to the corresponding acid chlorides by using trichloroacetonitrile and PPh_3 in CH_2Cl_2. The reaction showed that the aryl acids were higher reactivity than alkyl acids. Moreover , the reaction could be applicable for the synthesis of (-)-Captopril, which is being used in the treatment of hypertension (Scheme 38).

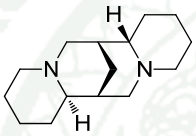


Scheme 38 Formation of various acid chloride with PPh_3/Cl_3CCN

3. Synthesis of 7,7'-dihydroxy-8,8'-biquinolyl (azaBINOL) and its derivatives

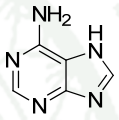
3.1 Heterocyclic biaryl molecules

Heterocyclic molecules represent a highly diverse and important class of organic compound and offer an abundance of opportunities for exploration and application (Gupta, 1998). Heterocyclic compounds are constituents of many pharmaceutical agents and natural product molecules that giving often distinguished properties and biological activity such as Sparteine **(17)** and Adenine **(18)**.



(17)

(used as ligand)

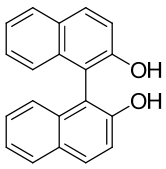


(18)

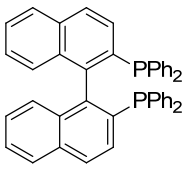
(DNA constituent)

Figure 7 The examples of heterocyclic compounds.

Another class of compounds that has received a great deal of attention in the current evolution of asymmetric catalysis is the group of biaryl molecules. Families of biaryls have been applied as the enantioselective catalyst and chiral auxiliaries such as particularly 2,2'-disubstituted-1,1'-binaphthyl such as [1,1'-binaphthalene]-2,2'-diol, BINOL **(19)** (Brunol, 2005 and Brunol, 2007) and 2,2'-bis(diphenyl phosphino)-1,1'-binaphthalene, BINAP **(16)** (Walsh, 2003).



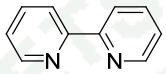
(19)



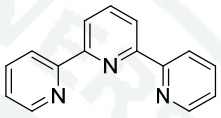
(16)

Figure 8 The examples of biaryl molecules.

Biaryl compounds with various structural features and properties have been used in many applications for organic synthesis, especially ligands in organometallic chemistry. The inclusion of heterocyclic structures into the biaryl groups provides a subclass of heteroaromatic biaryl compounds. Well known examples are bipyridyl compounds such as 2,2'-bipyridyl **(20)** (Cepanec, 2004) and 2,2',2''-tripyridyl **(21)** (Chelucci, 2002) (Figure 9).



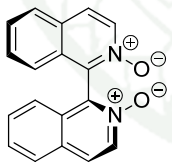
(20)



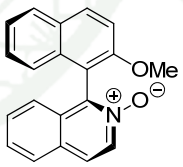
(21)

Figure 9 The examples of heteromatic polyaryl compounds.

Furthermore, the funtionalization of heteroaromatic biaryl molecules can provide compounds with configurationally atropisomerism, such as *N*-oxides (shown in Figure 10) obtained from bipyridyl compounds by treatment with peroxide such as *m*-CPBA. They are most stable than non-oxidized counterparts (Dalko, 2007).



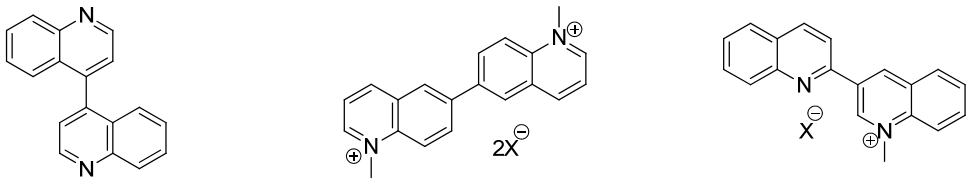
(S)-[1,1'-biisoquinoline] 2,2'-dioxide **(22)**



(S)-1-(2-methoxynaphthalen-1-yl) isoquinoline 2-oxide **(23)**

Figure 10 The examples of configurationally stable biquinolyl molecules.

A number of different biquinolyl compounds can be envisioned, however the heterocyclic biaryl compounds have been payed in the little attention. Reported examples are limited to 4,4'-biquinolyls **(24)**, 6,6'- biquinolyls **(25)** or 2,3'-biquinolyls **(26)** as shown in Figure 11 (Crawford, 1971).

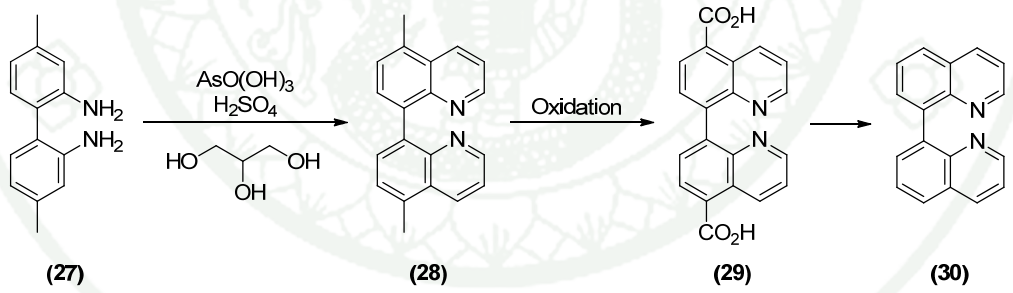


(24) **(25)** **(26)**

Figure 11 The examples of biquinolyl molecules.

3.2 Synthesis of 8,8'-biquinolyl compounds

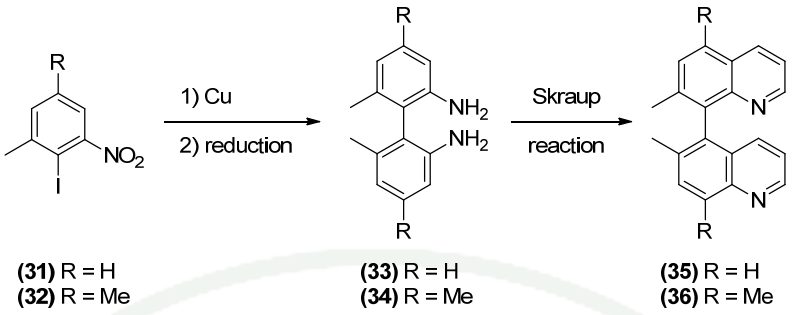
The earliest synthesis of a 8,8'-biquinolyl compound was reported by Niementowski and Seifert in 1905. They employed a double Skraup reaction to afford 5,5'-dimethyl-8,8'-biquinoline **(28)** from 4,4'-dimethyl-[1,1'-biphenyl]-2,2'-diamine **(27).** Then, Niementowski demonstrated further functionalization and converted 5,5'-dimethyl-8,8'-biquinoline **(28)** to [8,8'-biquinoline]-5,5'-dicarboxylic acid **(29)** and 8,8'-biquinoline **(30)**, respectively as shown in Scheme 39.



(27) **(28)** **(29)** **(30)**

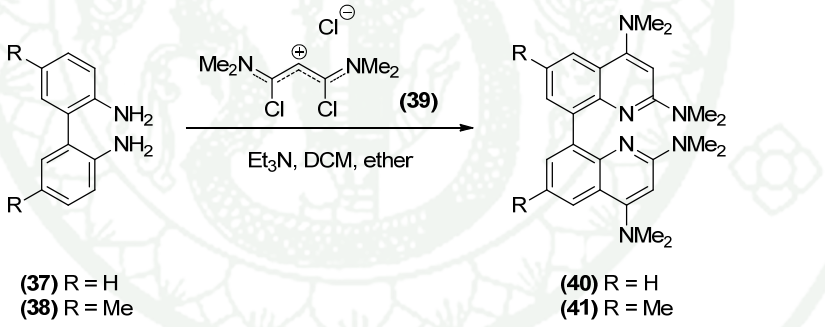
Scheme 39..Preparation of 8,8'-biquinoline **(30)** from 4,4'-dimethyl-[1,1'-biphenyl]-2,2'-diamine **(27)**

Ward and Waring (1932) reported the preparation of 7,7'-dimethyl-8,8'-biquinoline **(35)** and 5,5',7,7'-tetramethyl-8,8'-biquinoline **(36)** using double Skraup reaction as shown in Scheme 40. The intermediates for the Skraup reaction **(33)** and **(34)** were prepared from the corresponding iodobenzene compound **(31)** and **(32)** *via* Ullmann coupling.



Scheme 40 The preparation of 7,7'-dimethyl-8,8'-biquinoline **(35)** and 5,5',7,7'-tetramethyl-8,8'-biquinoline **(36)** using double Skraup reaction

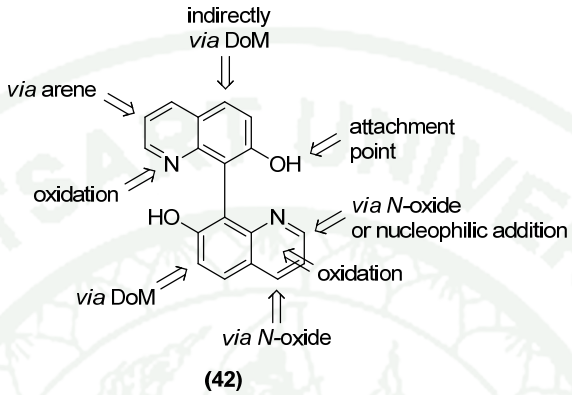
In 1976, the Viehe group reported that substituted 8,8'-biquinolyl compounds **(40)** and **(41)**, as shown in Scheme 41, that these compounds can be prepared from the bianiline, **(37)** and **(38)**, in a cyclocondensation reaction with 1,3-dichloro-trimethinecyanines **(39).**



Scheme 41 Preparation of substituted 8,8'-biquinolyl compounds from bianiline

From the opportunities for research into 8,8'-biquinolyl compounds, we would extend our phosphorus research to asymmetrical reaction using chiral 8,8'-biquinolyl phosphinites as a catalyst (X). These compounds could synthesize from 7,7'-dihydroxy-8,8'-biquinoline, azaBINOL **(42)**. For the first time, azaBINOL was functionalized in any position by methods in the literatures as depicted in Scheme 42.

According to the literatures, azaBINOL derivatives could be synthesized from the 7,7'-dihydroxy-8,8'-biquinoline, azaBINOL **(42)** by functionalization in any position as shown in Scheme 42.

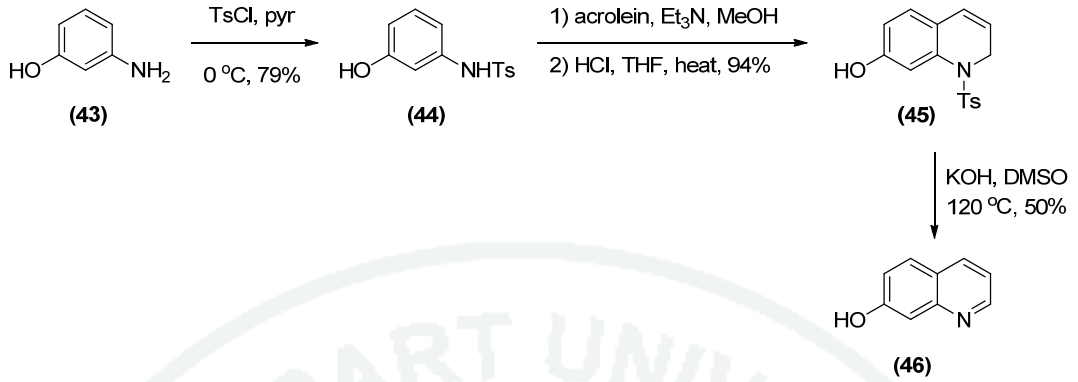


Scheme 42 The functionalization of azaBINOL

3.3 Synthesis of 7,7'-dihydroxy-8,8'-biquinoline (azaBINOL)

3.3.1 Synthesis of 7-hydroxy quinoline (46)

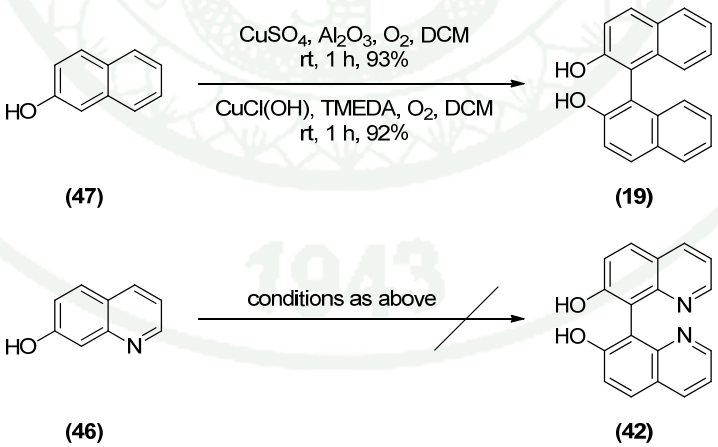
Tokuyama (2001) developed a four step protocol for the synthesis of 7-hydroxy quinoline **(46)** as shown in Scheme 43. The process involved the activation of amine **(43)** to form *N*-tosylamine **(44)**, reacting with acrolein to give compound **45** by cyclodehydration. The last step was removal of Ts group of compound **45** to afford the desired product **(46)**.



Scheme 43 Synthesis of 7-hydroxy quinoline

3.3.2 The formation of 8,8'-biquinolyl compound

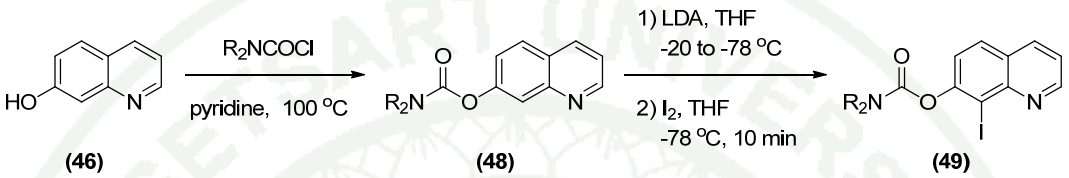
The methods for the direct oxidative coupling of 2-naphthol **(47)** to afford BINOL **(19)** are described in many publications. Examples are shown in Scheme 44 (Noji, 1994 and Love, 2002). Furthermore, Blakemore (2005, 2006 and 2007) reported that direct coupling of 7-hydroxyquinoline **(46)** to form 7,7'-dihydroxy-8,8'-biquinoline **(42)** were unsuccessful.



Scheme 44 Formation of 8,8'-biquinolyl compound

In addition, the alternative route for synthesis of 8,8'-biquinolines was developed by directed *ortho* metallation (D*o*M), a well known process

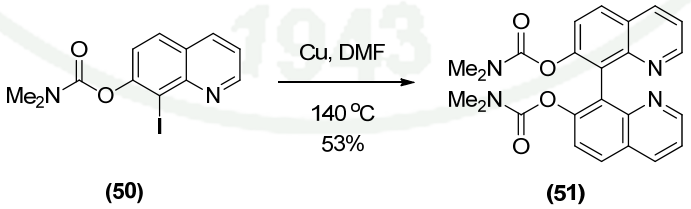
investigated by Snickus (1990), Wang (1992) and Whisler (2004). To allow the D*o*M, the hydroxyl group of 7-hydroxyquinoline **(46)** was protected as a carbamate **(48)** as shown in Scheme 45. Iodo intermediate, the 8-iodoquinolyl carbamate **(49)**, was protected by metallation of carbamate **(48)** with LDA and subsequent treatment with iodine, yielding **(49)**.



Scheme 45 Preparation of 8-iodoquinolyl carbamate

The Ullmann coupling represents a traditional way for reductive dimerization to form biaryl compounds from the aryl halides (Ley, 2003). Ullmann (1901) reported the reaction for C-C bond formation between two aromatic rings in a typical ratio 2:1 of aryl halide and copper. The reaction has been optimized and used for the preparation of various symmetrical biaryl molecules.

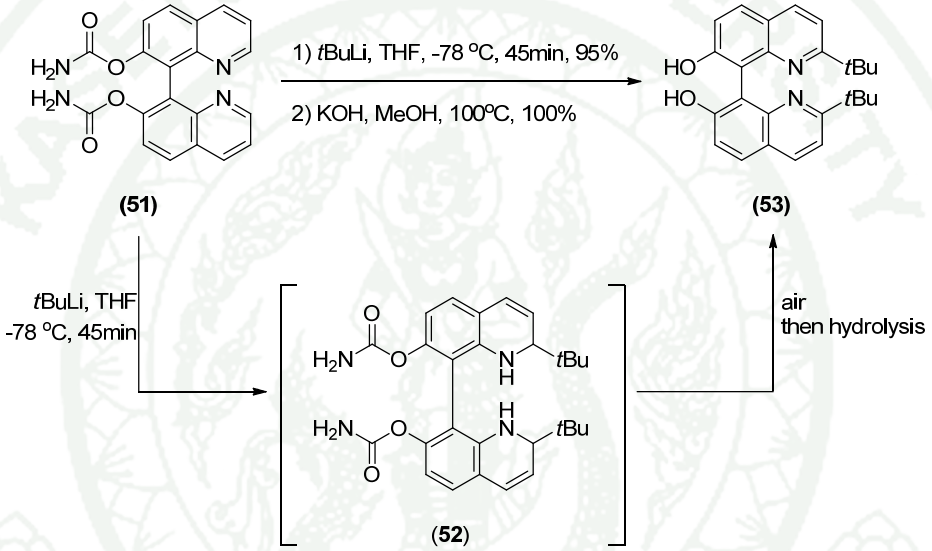
The Ullmann reaction was also applied for the synthesis of [8,8'-biquinoline]-7,7'-diyl bis(dimethyl carbamate) **(51)** from 8-iodoquinolyl methyl carbamate **(50)** (Blackmore, 2005) as shown in Scheme 46.



Scheme 46 The Ullmann coupling reaction of 8-iodoquinolyl methyl carbamate

3.3.3 Synthesis of 2,2'-disubstituted derivatives of 8,8'-biquinoline

Nucleophilic aromatic substitution of [8,8'-biquinoline]-7,7'-diyl-bis(di methylcarbamate) **(51)** with *tert*-BuLi afforded 2,2'-di-*tert*-butyl-1,1',2,2'-tetrahydro-[8,8'-biquinoline]-7,7'-diyl bis(dimethylcarbamate) **(52)**. This compound was re-aromatized by exposure to the air and converted to fully oxidized form of 2,2'-di-*tert*-butyl-[8,8'-biquinoline]-7,7'-diol **(53)** after saponification of the carbamate group (Blackmore, 2007) as shown in Scheme 47.



Scheme 47 Synthesis of 2,2'-di-*tert*-butyl-[8,8'-biquinoline]-7,7'-diol

MATERIALS AND METHODS

Materials

The following instrumentation, chromatographic system and chemical reagents were used throughout in all of work.

1. Instrumentation

Proton nuclear magnetic resonance (^{1}H NMR) spectra, carbon nuclear magnetic resonance (^{13}C NMR) spectra and phosphorus nuclear magnetic resonance (^{31}P NMR) spectra were recorded on a VARIAN^{UTITY} INOVA NMR spectrometer at 400 MHz at the Department of Chemistry, Faculty of Science, Kasetsart University and a Bruker AVIII400 NMR spectrometer at 400 MHz at Institute of Organic Chemistry, Faculty of Chemistry, University of Vienna. Chemical shifts δ are given in ppm relatively to the residual peaks of the deuterated solvent used. ^{1}H and ^{13}C NMR spectrums were measured in $CDCl_3$, DMSO and CD_3OD. The all of solvent residual peaks are shown in Table 2.

Table 2 The solvent peak

NMR Data	Solvent		
	$CDCl_3$	DMSO	CD_3OD
^{1}H	7.26 Hz	2.50 Hz	3.31 Hz
^{13}C	77.16 Hz	39.52 Hz	49.00 Hz

Source : Gottlieb (1997)

The coupling constants (*J*) are given in Hz, and the patterns are designated as s (singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of doublet), t (triplet), q (quartet), quin (quintet), sex (sextet), m (multiplet) and b (board).

Accurated mass in High Resolution Mass Spectrometry (HRMS) were measured on ESI-Qq ao TOF mass spectrometer (Bruker) at Institute of Organic Chemistry, Faculty of Chemistry, University of Vienna.

2. Chromatographic system

Analytical thin layer chromatography (TLC) was conducted on aluminum-backed 0.2 mm thick silica gel F254 plates (Merck). The Chromatograms were visualized under a 254 nm UV lamp.

Preparative thin layer chromatography (PTLC) was prepared by using silica gel 60 PF254 for preparative thin layer chromatography (Merck) that coating 500 μm thick on the mirror (20 cm x 20 cm).

3. Chemical reagents

All chemicals used in this research were obtained from commercial sources and used directly without purification. Furthermore the solvents were distilled freshly.

Methods

1. Synthetic Methodology for Carbon-Carbon and Carbon-Heteroatom Bond Formation by Oxidation-Reduction Condensation

1.1 Preparation of alkyl diphenylphosphinites

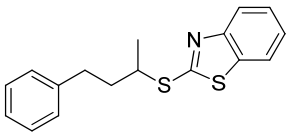
To a solution of alcohol 4-phenyl-2-butanol **(54)** and base in $CDCl_3$ was added base and chlorodiphenylphosphine ($ClPPh_2$). After the mixture was stirred, the slurry was filtered through a pack of celite-alumina in a pasteur pipette and washed with $CDCl_3$. Next, the crude reaction was monitored as fast as possible for determining the yield of alcohol transformation to alkyl diphenylphosphinite by ^1H NMR.

1.2 General procedure for using sulfer nucleophile

To a stirred solution of alcohol in dry CH_2Cl_2 or $CHCl_3$ was successively added triethylamine, NEt_3, (1.2 eq) and $ClPPh_2$ (1.2 eq), respectively and stirred at room temperature under nitrogen or argon atmosphere for 2 hours. After that, the sulfur nucleophile and camphorquinone were added to the mixture, respectively and stirred for 9 – 20 hours at room temperature. Then, the mixture was extracted with CH_2Cl_2/H_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel to afford the desired product.

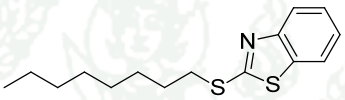
1.2.1 Using benzo[d]thiazole-2-thiol as a nucleophile

1.2.1.1 2-((4-Phenylbutan-2-yl)thio)benzo[d]thiazole **(58)**



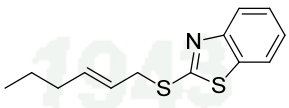
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.93 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.37 – 7.22 (m, 6H), 4.05 (sex, *J* = 8.0 Hz, 1H), 2.88 (t, *J* = 8.0 Hz, 2H), 2.19 – 2.07 (m, 2H), 1.61 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.6, 153.3, 141.4, 135.3, 128.6, 126.2, 124.5, 121.7, 121.1, 44.2, 38.6, 33.4, 21.7.

1.2.1.2 2-(Octylthio)benzo[d]thiazole **(60)**



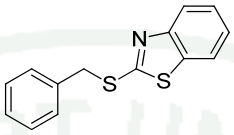
Colorless oil. ^{1}H NMR (400 MHz, CDCl3) : δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 3.34 (t, *J* = 8.0 Hz, 1H), 1.82 (quin, *J* = 8.0 Hz, 2H), 1.48 (quin, *J* = 8.0 Hz, 2H), 1.32 – 1.28 (m, 8H), 0.88 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, CDCl3) : δ 167.5, 153.5, 135.3, 126.1, 124.2, 121.6, 121.0, 33.8, 31.9, 29.3, 29.3, 29.2, 28.9, 22.8, 14.2.

1.2.1.3 (E)-2-(hex-2-en-1-ylthio)benzo[d]thiazole **(62)**



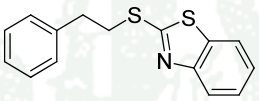
Colorless oil. ^{1}H NMR (400 MHz, CDCl3) : δ = 7.88 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 5.82 – 5.77 (m, 1H), 5.67 – 5.59 (m, 1H), 3.96 (d, *J* = 8.0 Hz, 2H), 2.02 (q, *J* = 8.0 Hz, 2H), 1.41 – 1.33 (m, 2H), 0.87 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, CDCl3) : δ 166.8, 153.4, 136.3, 135.5, 126.1, 124.3, 123.9, 121.7, 121.1, 36.1, 34.5, 22.3, 13.7. HRMS (ESI) Calcd for $C_{13}H_{15}NNaS_2$ 272.0544 $[M + Na]^+$, Found 272.0539 $[M + Na]^+$.

1.2.1.4 2-(Benzylthio)benzo[d]thiazole **(64)**



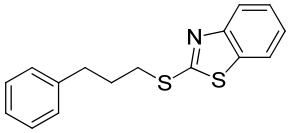
Colorless oil. ^{1}H NMR (400 MHz, CDCl3) : δ 7.92 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.48 – 7.41 (m, 3H), 7.36 – 7.29 (m, 4H), 4.62 (s, 2H). ^{13}C NMR (100 MHz, CDCl3) : δ 166.6, 153.2, 136.2, 135.4, 129.3, 128.8, 127.9, 126.2, 124.4, 121.6, 121.1, 37.9.

1.2.1.5 2-(Phenethylthio)benzo[d]thiazole **(66)**



Colorless oil. ^{1}H NMR (400 MHz, CDCl3) : δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.39–7.20 (m, 6H), 3.56 (t, *J* = 8.0 Hz, 2H), 3.11 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, CDCl3) : δ 166.8, 153.4, 139.8, 135.4, 128.8, 128.7, 126.8, 126.1, 124.3, 121.7, 121.1, 35.8, 34.9.

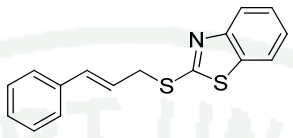
1.2.1.6 2-((3-Phenylpropyl)thio)benzo[d]thiazole **(68)**



Colorless oil. ^{1}H NMR (400 MHz, CDCl3) : δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.33 – 7.20 (m, 6H), 3.37 (t, *J* = 8.0 Hz, 2H), 2.83 (d, *J* = 8.0 Hz, 2H), 2.19 (quin, *J* = 8.0 Hz, 2H). ^{13}C NMR

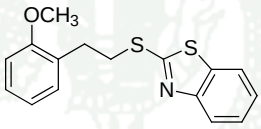
(100 MHz, CDCl3) : δ 167.2, 153.3, 141.0, 135.2, 128.6, 128.6, 126.2, 126.2 124.3, 121.6, 121.1, 34.8, 33.0, 30.9.

1.2.1.7 2-(Cinnamylthio)benzo[d]thiazole **(70)**



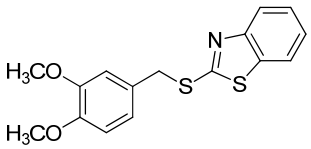
Colorless oil. ^{1}H NMR (400 MHz, CDCl3) : δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.44 – 7.21 (m, 7H), 6.71 (d, *J* = 16.0 Hz, 1H), 6.42 – 6.35 (m, 1H), 4.18 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, CDCl3) : δ 166.3, 153.4, 136.5, 135.5, 134.4, 128.7, 128.0, 126.6, 126.2, 124.4, 123.7, 121.7, 121.1, 36.2.

1.2.1.8 2-(2-Methoxyphenethylthio)benzo[d]thiazole **(72)**



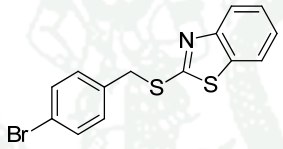
Colorless oil. ^{1}H NMR (400 MHz,CDCl3) : δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.76 d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 8. Hz, 2H), 6.94 – 6.87 (m, 2H), 3.86 (s, 3H), 3.60 (t, *J* = 8.0 Hz, 2H), 3.16 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (400 MHz,CDCl3) : δ 167.4, 157.7, 153.6, 135.4, 130.6, 128.2, 128.0, 126.1, 124.2, 121.6, 121.0, 120.6, 110.5, 55.4, 33.6, 30.7. HRMS (ESI) Calcd for $C_{16}H_{15}NOS_2Na$ $[M + Na]^+$ 324.0493. Found : 324.0491 $[M + Na]^+$.

1.2.1.9 2-(3,4-Dimethoxybenzylthio)benzo[d]thiazole **(74)**



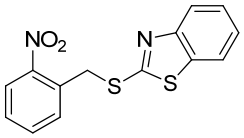
Colorless oil. ^{1}H NMR (400 MHz,$CDCl_3$) : δ 7.90 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.32 – 7.26 (m, 1H), 7.00 (m, 2H), 6.81 (d, J = 8.0 Hz, 1H), 4.49 (s, 2H), 3.78 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (100 MHz,$CDCl_3$) : δ 166.6, 153.3, 149.2, 148.8, 135.5, 128.7, 126.2, 124.4, 121.6, 121.6, 121.2, 112.4, 111.4, 56.4, 56.0, 38.0. HRMS (ESI) Calcd for $C_{16}H_{15}NO_2S_2Na$ 340.0442 $[M + Na]^+$. Found : 340.0430 $[M + Na]^+$.

1.2.1.10 2-(4-Bromobenzylthio)benzo[d]thiazole **(76)**



Colorless oil. ^{1}H NMR (400 MHz,$CDCl_3$) : δ 7.90 (d, *J* = 7.0 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.46 – 7.41 (m, 3H), 7.35 – 7.28 (m, 3H), 4.55 (s, 2H). ^{13}C NMR (400 MHz,$CDCl_3$) : δ = 165.9, 153.2, 135.7, 135.5, 131.9, 130.9, 126.3, 124.5, 121.8, 121.7, 121.2, 37.0. HRMS (ESI) Calcd for $C_{14}H_{10}BrNS_2Na$ 357.9336 $[M + Na]^+$. Found: 357.9330 $[M + Na]^+$.

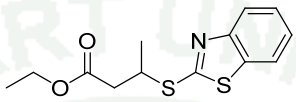
1.2.1.11 2-(2-Nitrobenzylthio)benzo[d]thiazole **(78)**



Colorless oil. ^{1}H NMR (400 MHz,$CDCl_3$) : δ 8.06 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.6, 1H), 7.44 – 7.40 (m, 2H), 7.30 (t, J = 7.2 Hz, 1H), 4.96 (s, 2H).

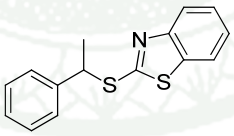
^{13}C NMR (400 MHz,$CDCl_3$) : δ 165.8, 153.1, 148.6, 135.7, 133.7, 133.5, 132.9, 128.9, 126.2, 125.4, 124.5, 121.7, 121.2, 34.3. HRMS (ESI) Calcd for $C_{14}H_{10}N_2O_2S_2Na$ 325.0081 $[M + Na]^+$. Found :325.0071 $[M + Na]^+$.

1.2.1.12 Ethyl 3-(benzo[d]thiazol-2-ylthio)butanoate **(80)**



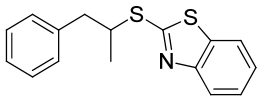
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7. 89 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 4.41 – 4.32 (m, 1H), 4.17 (q, *J* = 8.0 Hz, 2H), 2.99 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.72 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.58 (d, *J* = 8.0 Hz, 3H), 1.27 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 171.0, 165.4., 153.4, 135.5, 126.1, 124.5, 121.9, 121.1, 60.9, 41.6, 40.1, 21.0, 14.3. HRMS (ESI) Calcd for $C_{13}H_{16}NO_2S_2$ 282.0622 $[M + H]^+$, Found 282.0609 $[M + H]^+$.

1.2.1.13 2-(1-Phenylethylthio)benzo[d]thiazole **(82)**



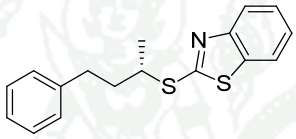
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.28 – 7.18 (m, 4H), 5.08 (q, *J* = 8.0 Hz, 1H), 1.78 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.0, 153.4, 142.0, 135.6, 128.8, 127.9, 127.5, 126.1, 124.5, 121.9, 121.1, 47.7, 22.8. HRMS (ESI) Calcd for $C_{15}H_{13}NS_2Na$ 294.0387 $[M + Na]^+$. Found : 294.0376 $[M + Na]^+$.

1.2.1.14 2-((1-Phenylpropan-2-yl)thio)benzo[d]thiazole **(84)**



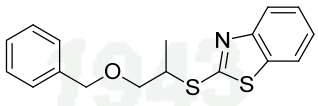
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.92 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.35 – 7.24 (m, 6H), 7.28 – 7.19 (m, 1H), 3.30 (dd, *J* = 16.0, 8.0 Hz, 2H), 2.88 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.45 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.5, 153.3, 138.7, 135.3, 129.5, 128.5, 126.8, 126.2, 124.5, 121.7, 121.1, 45.3, 43.2, 20.2

1.2.1.15 (S)-2-((4-phenylbutan-2-yl)thio)benzo[d]thiazole **(86)**



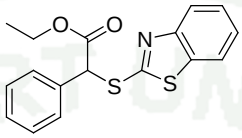
Characterization data, ^{1}H and ^{13}C NMR, were imitated as 2-((4-phenyl butan-2-yl)thio)benzo[d]thiazole (54). % ee by HPLC (DAICEL CHIRALCEL OD-H column, hexane : i-PrOH = 250 : 1, (1.0 mL/min) : 78% *ee*.

1.2.1.16 2-((1-(Benzyloxy)propan-2-yl)thio)benzo[d]thiazole **(88)**



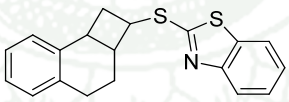
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.40 – 7.27 (m, 6H), 4.60 (s, 2H), 4.28 – 4.14 (m, 1H), 3.82 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.68 (dd, *J* = 8.0, 4.0 Hz, 1H), 1.56 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.1, 153.5, 138.2, 135.5, 128.5, 127.8, 127.7, 126.1, 124.4, 121.8, 73.8, 73.3, 43.5, 18.3. HRMS (ESI) Calcd for $C_{17}H_{17}NOS_2Na$ 338.0649 $[M + Na]^+$. Found : 338.0637 $[M + Na]^+$.

1.2.1.17 Ethyl 2-(benzothiazol-2-ylthio)-2-phenylacetate **(90)**



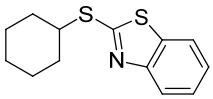
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.44 – 7.28 (m, 5H), 5.80 (s, 1H), 4.34 – 4.14 (m, 2H), 1.26 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 169.7, 164.6, 153.1, 135.7, 134.5, 129.1, 129.0, 128.7, 126.2, 124.6, 121.9, 121.2, 62.4, 54.8, 14.2. HRMS (ESI) Calcd for $C_{17}H_{15}NO_2S_2Na$ 352.0442 $[M + Na]^+$. Found : 352.0440 $[M + Na]^+$.

1.2.1.18 2-((1,2,2a,3,4,8b-Hexahydrocyclobuta[a]naphthalen-2-yl)thio)benzo[d]thiazole **(92)**



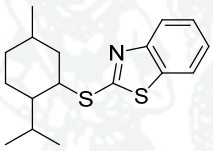
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.78 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.13 – 7.06 (m, 3H), 7.00 (d, *J* = 8.0 Hz, 1H), 4.16 (q, *J* = 8.0 Hz, 1H), 3.69 (td, *J* = 8.0, 4.0 Hz, 1H), 2.98 – 2.90 (m, 2H), 2.75 – 2.60 (m, 2H), 2.50 – 2.43 (m, 1H), 2.01 – 1.94 (m, 1H), 1.78 – 1.70 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.6, 153.5, 139.4, 137.2, 128.9, 128.5, 126.6, 126.0, 125.9, 124.2, 121.7, 120.9, 42.1, 41.5, 37.3, 33.2, 27.0. 25.0. HRMS (ESI*)* Calcd for $C_{19}H_{17}NS_2Na$ 346.0700 $[M + Na]^+$. Found : 346.0686 $[M + Na]^+$.

1.2.1.19 2-(Cyclohexylthio)benzo[d]thiazole **(94)**



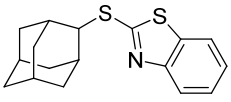
Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 3.93 – 3.88 (m, 1H), 2.22 – 2.18 (m, 2H), 1.83 – 1.77 (m, 2H), 1.68 – 1.32 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) : δ 167.2, 154.5, 137.7, 126.3, 125.5, 121.3, 120.7, 48.7, 33.4, 25.8, 25.5

1.2.1.20 2-((2-Isopropyl-5-methylcyclohexyl)thio)benzo[d] thiazole **(96)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.27 (t, *J* = 8.0 Hz, 1H), 4.56 (s, 1H), 2.27 – 2.22 (m, 1H), 1.90 – 1.86 (m, 2H), 1.82 – 1.77 (m, 1H), 1.69 – 1.62 (m, 1H), 1.47 – 1.39 (m, 1H), 1.31 – 1.24 (m, 1H), 1.16 – 1.06 (m, 1H), 1.01 – 0.89 (m, 10 H). ^{13}C NMR (500 MHz, $CDCl_3$) : δ 169.5, 151.6, 134.1, 126.6, 124.7, 121.1, 121.1, 51.7, 48.6, 41.4, 35.1, 30.8, 27.8, 27.0, 22.1, 21.2, 20.9.

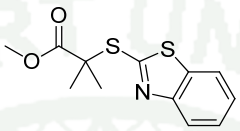
1.2.1.21 2-(Adamantan-2-ylthio)benzo[d]thiazole **(98)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 4.37 (s, 1H), 2.27 (s, 1H), 2.13 (d, *J* = 16.0 Hz, 1H), 1.98 – 1.93 (m, 6H), 1.80 (s,

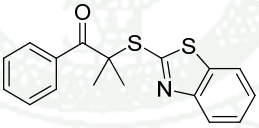
1H), 1.69 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 167.4, 153.6, 135.3, 126.0, 124.2, 121.7, 121.0, 109.9, 56.2, 38.6, 37.6, 33.5, 32.8, 27.6, 27.3. HRMS (ESI) Calcd for $C_{17}H_{19}NS_2$ 302.1037 ($[M + H]^+$), Found 302.1025 ($[M + H]^+$).

1.2.1.22 Methyl 2-(benzo[d]thiazol-2-ylthio)-2-methyl-propanoate **(100)**



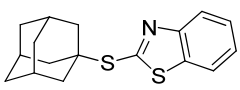
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.93 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 3.75 (s, 3H), 1.75 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 174.0, 161.2, 153.5, 136.7, 126.3, 125.2, 122.7, 121.1, 54.1, 53.1, 26.5.

1.2.1.23 2-(Benzo[d]thiazol-2-ylthio)-2-methyl-1-phenyl propan-1-one **(102)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.10 (d, *J* = 8.0 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.48 – 7.26 (m, 5H), 1.87 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 200.6, 161.5, 153.2, 136.8, 136.4, 131.9, 129.2, 128.1, 126.2, 125.1, 122.6, 121.1, 58.2, 27.5.

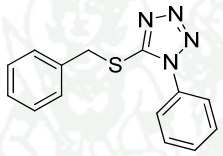
1.2.1.24 2-((3s,5s,7s)-Adamantan-1-ylthio)benzo[d]thiazole **(104)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 3.36 (d, *J* = 8.0 Hz, 1H), 2.17 – 2.10 (m, 9H), 1.72 – 1.71 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 162.0, 153.7, 137.0, 126.1, 125.1, 122.9, 121.0, 53.1, 43.7, 36.2, 30.4.

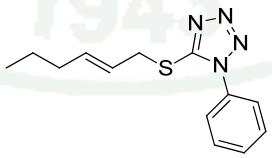
1.2.2 Using 1-phenyl-1H-tetrazole-5-thiol as a nucleophile

1.2.2.1 5-(Benzylthio)-1-phenyl-1H-tetrazole **(116)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.48 – 7.41 (m, 5H), 7.36 – 7.33 (m, 2H), 7.27 – 7.21 (3H), 4.55 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 153.9, 135.3, 133.7, 130.1, 129.8, 129.3, 128.9, 128.2, 123.8, 37.7. HRMS (ESI) Calcd for $C_{14}H_{12}N_4SNa$ 291.0680 ($[M + Na]^+$), Found 291.0673 ($[M + Na]^+$).

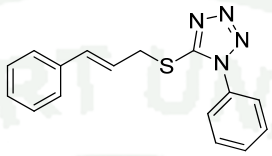
1.2.2.2 (*E*)-5-(Hex-2-en-1-ylthio)-1-phenyl-1H-tetrazole **(117)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.58 – 7.49 (m, 5H), 5.84 – 5.77 (m, 1H), 5.63 – 5.55 (m, 1H), 3.99 (d, *J* = 8.0 Hz, 2H), 1.99 (q, *J* = 8.0 Hz, 2H), 1.36 (sex, *J* = 8.0 Hz, 2H), 0.85 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : 154.1, 137.3, 136.6, 133.9, 130.2, 129.9, 124.0, 123.0, 122.1,

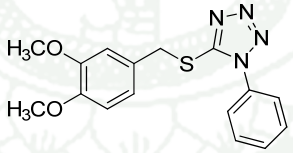
35.8, 34.4, 22.2, 13.7. HRMS (ESI) Calcd for $C_{13}H_{16}N_4SNa$ 283.0993 $[M + Na]^+$. Found 283.0987 $[M + Na]^+$.

1.2.2.3 5-(Cinnamylthio)-1-phenyl-1H-tetrazole **(118)**



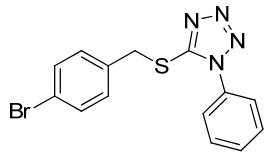
Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) : δ 7.48 – 7.43 (m, 5H), 7.27 – 7.15 (m, 5H), 6.62 (d, *J* = 16.0 Hz, 1H), 6.30 – 6.22 (m, 1H), 4.12 (dd, *J* = 8.0, 4.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 153.9, 136.2, 135.3, 133.8, 130.2, 129.9, 128.7, 128.3, 126.7, 124.0, 122.6, 36.0. HRMS (ESI) Calcd for $C_{16}H_{14}N_4SNa$ 317.0837 $[M + Na]^+$. Found 317.0837 $[M + Na]^+$.

1.2.2.4 5-((3,4-Dimethoxybenzyl)thio)-1-phenyl-1H-tetrazole **(119)**



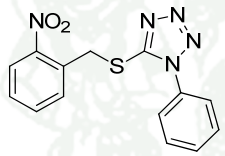
Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) : δ 7.54 – 7.50 (m, 5H), 6.97 – 6.95 (m, 2H), 6.80 (d, *J* = 8.0 Hz, 1H), 4.59 (s, 2H), 3.86 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 154.0, 149.3, 149.2, 133.8, 130.6, 130.2, 129.9, 127.8, 124.0, 123.6, 121.9, 112.4, 111.4, 56.1, 38.0. HRMS (ESI) Calcd for $C_{16}H_{16}N_4O_2SNa$ 351.0892 $[M + Na]^+$. Found 351.0892 $[M + Na]^+$.

1.2.2.5 5-((4-Bromobenzyl)thio)-1-phenyl-1H-tetrazole **(120)**



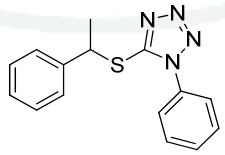
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.56 – 7.48 (m, 5H), 7.45 – 7.41 (m, 2H), 7.32 – 7.28 (m, 2H), 4.55 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 153.6, 134.7, 133.6, 132.0, 131.0, 130.3, 129.9, 123.9, 122.3, 37.0. HRMS (ESI) Calcd for $C_{14}H_{11}BrN_4SNa$ 370.9765 ($[M + Na]^+$), Found 370.9759 ($[M + Na]^+$).

1.2.2.6 5-((2-Nitrobenzyl)thio)-1-phenyl-1H-tetrazole **(121)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.13 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.64 – 7.47 (m, 7H), 4.97 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 134.2, 133.6, 133.5, 132.8, 130.7, 130.3, 130.1, 130.0, 129.5, 125.7, 124.1, 123.9, 35.3. HRMS (ESI) Calcd for $C_{14}H_{11}N_5O_2SNa$ 336.0531 [M + Na]$^+$. Found 336.0531 [M + Na]$^+$.

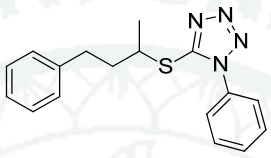
1.2.2.7 1-Phenyl-5-((1-phenylethyl)thio)-1H-tetrazole **(122)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.54 – 7.46 (m, 5H), 7.42 – 7.39 (m, 2H), 7.34 – 7.27 (m, 3H), 5.21 (d, *J* = 8.0 Hz, 1H), 1.88 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) : 153.8, 141.0, 134.0, 130.2, 129.8,

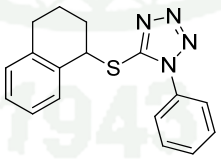
129.0, 128.4, 127.4, 124.2, 48.1, 22.4. HRMS (ESI) Calcd for $C_{15}H_{14}N_4SNa$ 305.0837 $[M + Na]^+$. Found 305.0837 $[M + Na]^+$.

1.2.2.8 1-Phenyl-5-((4-phenylbutan-2-yl)thio)-1H-tetrazole **(123)**



Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) : δ 7.59 – 7.52 (m, 5H), 7.30 – 7.26 (m, 2H), 7.21 – 7.16 (m, 3H), 4.11 – 4.03 (m, 1H), 2.83 – 2.74 (m, 2H), 2.17 – 2.04 (m, 2H), 1.56 (d, J = 4.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 153.9, 140.9, 133.8, 130.1, 129.7, 128.5, 128.3, 126.2, 124.1, 44.4, 38.3, 33.2, 21.5. HRMS (ESI) Calcd for $C_{17}H_{18}NSNa$ 333.9765 $[M + Na]^+$, Found 333.1143 $[M + Na]^+$.

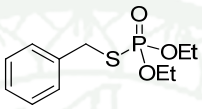
1.2.2.9 1-Phenyl-5-((1,2,3,4-tetrahydronaphthalen-1-yl)thio)-1H-tetrazole **(125)**



Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) : δ 7.59 – 7.49 (m, 5H), 7.40 (d, J = 8.0 Hz, 1H), 7.21 – 7.09 (m, 3H), 2.84 – 2.79 (m, 2H), 2.47 – 2.42 (m, 1H), 2.31 – 2.23 (m, 1H), 2.08 – 2.03 (m, 1H), 1.92 – 1.88 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 154.2, 138.1, 133.8,133.3, 130.8, 130.0, 129.7, 129.5, 128.1, 126.2, 123.9, 48.4, 29.4, 28.9, 19.0. HRMS (ESI) Calcd for $C_{17}H_{16}N_4SNa$ 331.0993 $[M + Na]^+$. Found 331.0972 $[M + Na]^+$.

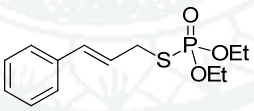
1.2.3 Using *O*,*O*-diethyl S-hydrogen phosphorothioate as a nucleophile

1.2.3.1 *S*-Benzyl *O*,*O*-diethyl phosphorothioate **(126)**



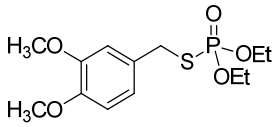
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.37 – 7.24 (m, 5H), 4.17 – 3.97 (m, 6H), 1.29 (d, J = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 137.7 (d, J = 5.0 Hz), 129.0, 128.8, 127.7, 63.6 (d, J = 6.0 Hz), 35.1 (d, J = 4.0 Hz), 16.1 (t, J = 8.0 Hz). ^{32}P NMR (162 MHz, $CDCl_3$) : δ 26.7. HRMS (ESI) Calcd $C_{11}H_{17}O_3PSNa$ 283.0534 $[M + Na]^+$. Found 283.0524 $[M + Na]^+$.

1.2.3.2 *S*-Cinnamyl *O*,*O*-diethyl phosphorothioate **(128)**



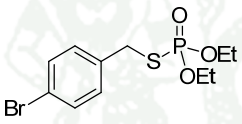
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.38 – 7.22 (m, 5H), 6.60 (d, J = 16.0 Hz, 1H), 6.30 – 6.23 (m, 1H), 4.22 – 4.13 (m, 4H), 3.69 – 3.63 (m, 2H), 1.34 (t, J = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 136.6, 133.6, 128.8, 128.1, 126.6 125.1 (d, J = 5.0 Hz), 63.7 (d, J = 6.0 Hz), 33. 6 (d, J = 4.0 Hz), 16.2 (d, J = 7.0 Hz). ^{32}P NMR (162 MHz, $CDCl_3$) : δ 27.1 HRMS (ESI) Calcd for $C_{13}H_{19}O_3PSNa$ $[M + Na]^+$ 309.3690. Found 309.3691 $[M + Na]^+$.

1.2.3.3 *S*-3,4-Dimethoxybenzyl *O,O*-diethyl phosphorothioate **(129)**



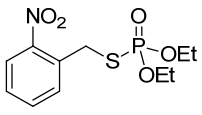
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 6.91 – 6.89 (m, 2H), 6.81 – 6.79 (m, 1H), 4.18 – 4.00 (m, 6H), 3.88 (d, *J* = 8.0 Hz, 6H), 1.31 (t, *J* = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 149.1, 145.2, 130.2, 121.4, 112.2, 111.3, 63.7 (d, *J* = 5.0 Hz), 56.1 (d, *J* = 3.0 Hz), 35.2 (d, *J* = 4.0 Hz), 16.1 (d, *J* = 7.0 Hz). ^{32}P NMR (162 MHz, $CDCl_3$) : δ 26.9. HRMS (ESI) Calcd for $C_{13}H_{21}O_5PSNa$ 343.0745 $[M + Na]^+$. Found 343.0736 $[M + Na]^+$.

1.2.3.4 *S*-4-Bromobenzyl *O,O*-diethyl phosphorothioate **(130)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.47 – 7.43 (m, 2H), 7.24 – 7.22 (m, 2H), 4.16 – 3.96 (m, 6H), 1.29 (t, *J* = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 136.9 (d, *J* = 5.0 Hz), 131.9, 130.8, 121.7, 63.8 (d, *J* = 5.0 Hz), 34.5 (d, *J* = 4.0 Hz), 16.1 (d, *J* = 7.0 Hz, 1H). ^{32}P NMR (162 MHz, $CDCl_3$) : δ 26.3. HRMS (ESI) Calcd $C_{11}H_{16}BrO_3PSNa$ 362.9168 $[M + Na]^+$. Found 362.9623 $[M + Na]^+$.

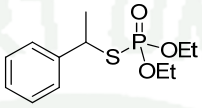
1.2.3.5 *O,O*-Diethyl *S*-2-nitrobenzyl phosphorothioate **(131)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.49 – 7.44 (m, 1H), 4.39 (d, *J* = 16.0 Hz, 2H), 4.13 – 3.95 (m, 4H), 1.26 (t, *J* = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 157.9,

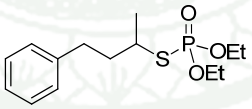
153.3, 133.8, 133.0, 129.1, 125.5, 63.9 (d, J = 6.0 Hz), 32.6, 16.1 (d, J = 7.0 Hz). ^{32}P NMR (162 MHz, $CDCl_3$) : δ 26.3. HRMS (ESI) Calcd for $C_{11}H_{16}NO_5PSNa$ 328.0384 $[M + Na]^+$. Found 328.0376 $[M + Na]^+$.

1.2.3.6 *O,O*-Diethyl *S*-(1-phenylethyl) phosphorothioate **(132)**



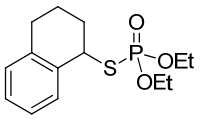
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.39 – 7.23 (m, 5H), 4.51 – 4.46 (m, 1H), 4.14 – 3.89 (m, 4H), 1.75 (d, J = 8.0 Hz, 3H), 1.26 – 1.22 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 143.7 (d, J = 5.0 Hz), 128.7, 127.2, 127.1, 63.5 (d, J = 5.0 Hz), 46.0 (d, J = 3.0 Hz), 24.8 (d, J = 8.0 Hz), 16.0 (d, J = 7.0 Hz). ^{32}P NMR (162 MHz, $CDCl_3$) : δ 25.9. HRMS (ESI) Calcd for $C_{12}H_{19}O_3PSNa$ $[M + Na]^+$ 297.0690. Found 297.0682 $[M + Na]^+$.

1.2.3.7 *O,O*-Diethyl *S*-(4-phenylbutan-2-yl)phosphorothioate **(133)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.30 – 7.27 (m, 2H), 7.20 – 7.17 (m, 3H), 4.22 – 4.08 (m, 4H), 3.39 – 3.34 (m, 1H), 2.80 – 2.73 (m, 2H), 2.02 – 1.93 (m, 2H), 1.49 (d, J = 4.0 Hz, 3H), 1.37 – 1.32 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 141.4, 128.6, 128.5, 126.2, 63.6, 42.7, 40.2 (d, J = 8.0 Hz), 33.3, 23.7 (d, J = 4.0 Hz), 16.2. ^{32}P NMR (162 MHz, $CDCl_3$) : δ 27.3 *HRMS (ESI)* Calcd for $C_{14}H_{23}O_3PSNa$ 325.1003 $[M + Na]^+$. Found 325.0996 $[M + Na]^+$.

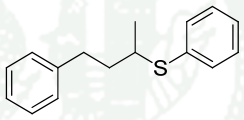
1.2.3.8 *O,O*-Diethyl *S*-(1,2,3,4-tetrahydronaphthalen-1-yl) phosphorothioate **(134)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.43 – 7.41 (m, 1H), 7.16 – 7.13 (m, 2H), 7.07 – 7.05 (m, 1H), 4.80 – 4.76 (m, 1H), 4.27 – 4.13 (m, 4H), 2.84 – 2.75 (m, 2H), 2.29 – 2.28 (m, 1H), 2.22 – 2.11 (m, 2H), 1.91 – 1.87 (m, 1H), 1.41 – 1.36 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 137.3, 136.0, 130.56, 129.5, 127.6, 126.2, 63.7 (dd, *J* = 11.0, 6.0 Hz), 46.4 (d, *J* = 3.0 Hz), 31.8, 28.9, 19.1, 16.2 (d, *J* = 7.0 Hz). ^{32}P NMR (162 MHz, $CDCl_3$) : δ 26.9. HRMS (ESI) Calcd for $C_{14}H_{21}O_3PSNa$ 323.0847 $[M + Na]^+$. Found 323.0838 $[M + Na]^+$.

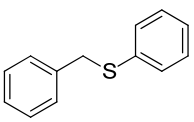
1.2.4 Using diphenyl disulfide as a nucleophile

1.2.4.1 Phenyl(4-phenylbutan-2-yl)sulfane **(135)**



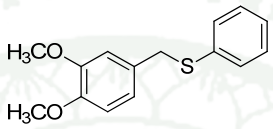
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ ^{1}H NMR (400 MHz,$CDCl_3$) : δ = 7.52 – 7.49 (m, 1H), 7.38 – 7.35 (m, 2H), 7.32 – 7.16 (m, 7H), 3.24 – 3.16 (m, 1H), 2.85 – 2.73 (m, 2H), 1.98 – 1.78 (m, 2H), 1.32 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz,$CDCl_3$) : δ = 132.2, 129.2, 128.9, 128.6, 128.5, 127.7, 127.3, 126.9, 126.0, 42.7, 38.4, 33.3, 21.4. HRMS (ESI) Calcd for $C_{16}H_{18}SNa$ 265.1027 $[M + Na]^+$. Found 265.1029 $[M + Na]^+$.

1.2.4.2 Benzyl(phenyl)sulfane **(136)**



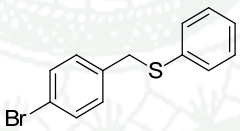
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.57 – 7.13 (m, 10H), 4.08 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 137.6, 136.5, 130.0, 129.5, 129.0, 128.6, 127.3, 126.5, 39.2. HRMS (ESI) Calcd for $C_{13}H_{12}SNa$ 223.0557 $[M + Na]^+$. Found 223.0560 $[M + Na]^+$.

1.2.4.3 (3,4-Dimethoxybenzyl)(phenyl)sulfane **(137)**



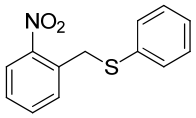
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.33 – 7.30 (m, 2H), 7.28 – 7.24 (m, 2H), 7.21 – 7.17 (M, 1H) 6.83 – 6.76 (m, 3H), 4.07 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 149.0, 148.4, 136.5, 130.3, 130.1, 129.0, 126.6, 121.1, 112.1, 111.2, 56.0,55.9, 39.2. HRMS (ESI) Calcd for $C_{15}H_{16}O_2SNa$ 283.0769 $[M + Na]^+$. Found 283.0774 $[M + Na]^+$.

1.2.4.4 (4-Bromobenzyl)(phenyl)sulfane **(138)**



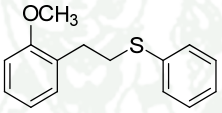
Colorless oil. ^{1}H NMR (400 MHz,$CDCl_3$) : δ = 7.41 – 7.38 (m, 2H), 7.31 – 7.18 (m, 5H), 7.16 – 7.13 (m, 2H), 4.05 (s, 2H). ^{13}C NMR (100 MHz,$CDCl_3$) : δ = 136.5, 135.8, 131.7, 130.6, 130.5, 129.1, 126.8, 121.1, 38.8. HRMS (ESI) Calcd for $C_{13}H_{11}NO_2SNa$ 300.9663 $[M + Na]^+$. Found 300.9668 $[M + Na]^+$.

1.2.4.5 (2-Nitrobenzyl)(phenyl)sulfane **(139)**



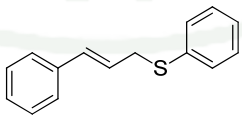
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.96 (d, *J* = 8.0 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.29 – 7.21 (M, 6H), 4.42 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 148.6, 134.8, 133.6, 133.1, 132.0, 131.9, 129.1, 128.3, 127.5, 125.4, 37.3. HRMS (ESI) Calcd for $C_{13}H_{11}NO_2SNa$ 268.0408 $[M + Na]^+$. Found 268.0402 $[M + Na]^+$.

1.2.4.6 (2-Methoxyphenethyl)(phenyl)sulfane **(141)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.40 – 7.37 (m, 2H), 7.31 – 7.27 (m, 2H), 7.24 – 7.12 (m, 3H), 6.91 – 6.85 (m, 2H), 3.83 (s, 3H), 3.18 – 3.14 (m, 2H), 2.97 – 2.93 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 157.6, 136.9, 130.3, 128.8, 128.6, 128.6, 127.8, 125.5, 120.5, 110.3, 55.2, 33.0, 31.0. HRMS (ESI) Calcd for $C_{15}H_{16}OSNa$ 267.0820 $[M + Na]^+$. Found 267.0815 $[M + Na]^+$.

1.2.4.7 Cinnamyl(phenyl)sulfane **(142)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.47 – 7.45 (m, 1H), 7.36 – 7.33 (m, 2H), 7.28 – 7.13 (m, 7H), 6.39 (d, *J* = 16.0 Hz, 1H), 6.25 – 6.17 (m, 1H), 3.67 (d, *J* = 18.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ

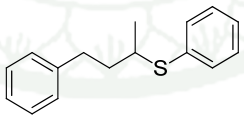
136.9, 136.1, 132.9, 130.4, 129.2, 128.7, 127.7, 126.6, 126.5, 125.2, 37.3. HRMS (ESI) Calcd for $C_{15}H_{14}SNa$ 226.0816 $[M + Na]^+$. Found 226.0819 $[M + Na]^+$.

1.3 General procedure for using other nucleophiles

To a stirred solution of 4-phenyl-2-butanol **(54)** in dry CH_2Cl_2 was successively added NEt_3 (1.2 eq) and $ClPPh_2$ (1.2 eq), respectively and stirred at room temperature under nitrogen atmosphere for 2 h. After that, selected nucleophile and camphorquinone were added to the mixture, respectively and stirred for 9 – 12 h at room temperature. Then, the mixture was extracted with CH_2Cl_2/H_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel to afford the corresponding products.

1.3.1 Using benzenethiol as a sulfur nucleophile

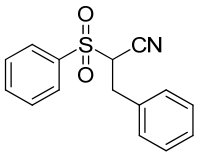
1.3.1.1 Phenyl(4-phenylbutan-2-yl)sulfane **(135)**



Characterization data, ^1H and ^{13}C NMR, were previously given in oxidation-reduction condensation using diphenyl disulfide as a nucleophile.

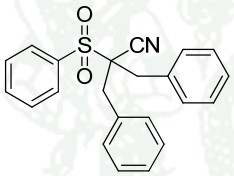
1.3.2 Using 2-(phenylsulfonyl)acetonitrile as a carbon nucleophile

1.3.2.1 3-Phenyl-2-(phenylsulfonyl)propanenitrile **(169)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.08 – 8.05 (m, 2H), 7.81 – 7.77 (m, 1H), 7.69 – 7.65 (m, 2H), 7.35 – 7.26 (m, 5H), 4.07 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.60 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.10 (dd, *J* = 16.0, 12.0 Hz, 1H). (Mukayama, 2005b)

1.3.2.2 2-Benzyl-3-phenyl-2-(phenylsulfonyl)propanenitrile **(170)**



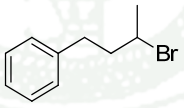
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.03 – 8.00 (m, 4H), 7.97 – 7.92 (m, 1H), 7.83 – 7.74 (m, 3H), 7.66 – 7.61 (m, 4H), 7.54 – 7.40 (m 2H), 7.34 – 7.29 (m, 1H), 4.10 (s, 4H). (Mukayama, 2005b)

2. Synthetic Methodology for Carbon-Heteroatom Bond Formation by Nucleophilic Substitution

2.1 Nucleophilic Substitution of Alkyl Halides

2.1.1 Preparation of (3-bromobutyl)benzene **(171)**

To a stirred solution of 4-phenyl-2-butanol **(54)** in dry CH_2Cl_2 was successively added triphenylphosphine (PPh_3) and ((tribromomethyl)sulfonyl)-benzene ($PhSO_2CBr_3$), respectively and stirred at room temperature under N_2 atmosphere for 30 minutes. Then, the mixture was extracted with CH_2Cl_2/H_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel to afford the desired product.

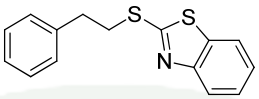


Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.36 – 7.18 (m, 5H), 4.14 – 4.06 (m, 1H), 2.93 – 2.74 (m, 2H), 2.21 – 2.03 (m, 2H), 1.76 (d, J = 4.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 141.0, 126.4, 128.6, 126.2, 51.0, 42.8, 34.1, 26.6.

2.1.2 Preparation of 2-(Phenethylthio)benzo[d]thiazole **(66)**

A stirred solution of (2-bromoethyl)benzene in dry CH_2Cl_2 was added bases and HSBtz. Then, the mixture was extracted with CH_2Cl_2/H_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated

in vacuo. The residue was purified by preparative TLC on silica gel to afford the desired product.

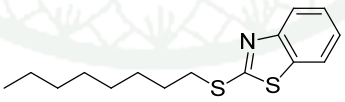


Characterization data, ^{1}H and ^{13}C NMR, were previously given in oxidation-reduction condensation using benzo[d]thiazole-2-thiol as a nucleophile.

2.1.3 General procedure for nucleophilic substitution of alkyl halides

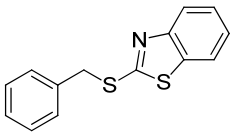
To a stirred solution of alcohol in dry CH_2Cl_2 (1 M) was successively added NEt_3 (1.4 eq) and $ClPPh_2$ (1.1 eq), respectively and stirred at room temperature under N_2 atmosphere for 30 minutes. After that, the HSBtz and NEt_3 were added to the mixture, respectively and stirred for 6 hours at room temperature. Then, the mixture was extracted with CH_2Cl_2/H_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel to afford the desired product.

2.1.3.1 2-(Octylthio)benzo[d]thiazole **(60)**



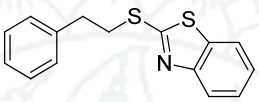
Characterization data, ^{1}H and ^{13}C NMR, were previously given in oxidation-reduction condensation using benzo[d]thiazole-2-thiol as a nucleophile.

2.1.3.2 2-(Benzylthio)benzo[d]thiazole **(64)**



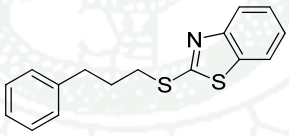
Characterization data, ^{1}H and ^{13}C NMR, were previously given in oxidation-reduction condensation using benzo[d]thiazole-2-thiol as a nucleophile.

2.1.3.3 2-(Phenethylthio)benzo[d]thiazole **(66)**



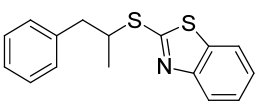
Characterization data, ^{1}H and ^{13}C NMR, were previously given in oxidation-reduction condensation using benzo[d]thiazole-2-thiol as a nucleophile.

2.1.3.4 2-((3-Phenylpropyl)thio)benzo[d]thiazole **(68)**



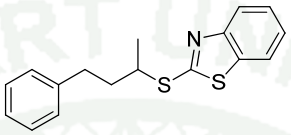
Characterization data, ^{1}H and ^{13}C NMR, were previously given in oxidation-reduction condensation using benzo[d]thiazole-2-thiol as a nucleophile.

2.1.3.5 2-((1-Phenylpropan-2-yl)thio)benzo[d]thiazole **(84)**



Characterization data, ^{1}H and ^{13}C NMR, were previously given in oxidation-reduction condensation using benzo[d]thiazole-2-thiol as a nucleophile.

2.1.3.6 2-((4-Phenylbutan-2-yl)thio)benzo[d]thiazole **(58)**



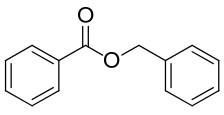
Characterization data, ^{1}H and ^{13}C NMR, were previously given in oxidation-reduction condensation using benzo[d]thiazole-2-thiol as a nucleophile.

2.2 Nucleophilic Substitution of Acid Halides

2.2.1 General procedure

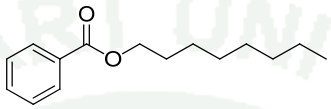
To a stirred solution of carboxylic acid in dry CH_2Cl_2 was successively added PPh_3 (1.4 eq) and halogenating agent (1.1 eq), respectively and stirred at room temperature under N_2 atmosphere for 30 minutes. After that, selected nucleophile (alcohol or amine) and NEt_3 were added to the mixture, respectively and stirred for 6 hours at room temperature. Then, the mixture was extracted with CH_2Cl_2/H_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel to afford the desired product.

2.2.1.1 Benzyl benzoate **(175)**



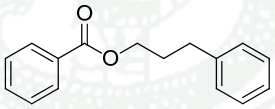
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.11 – 8.08 (m, 2H), 7.59 – 7.55 (m, 1H), 7.48 – 7.33 (m, 7H), 5.38 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.5, 163.1, 133.1, 130.2, 129.8, 128.7, 128.5, 128.3, 128.2, 66.8.

2.2.1.2 Octyl benzoate **(176)**



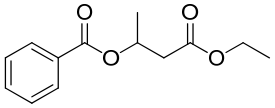
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.05 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.56 – 7.52 (m, 1H), 7.45 – 7.40 (m, 2H), 4.32 (t, *J* = 8.0 Hz, 2H), 1.80 – 1.73 (m, 2H), 1.45 – 1.28 (m, 10H), 0.89 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.8, 132.9, 130.7, 129.6, 128.4, 65.2, 31.9, 29.4, 29.3, 28.9, 26.2, 22.8, 14.8.

2.2.1.3 3-Phenylpropyl benzoate **(177)**



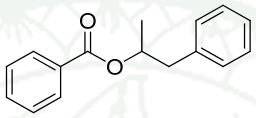
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.09 – 8.06 (m, 2H), 7.61 – 7.57 (m, 1H), 7.49 – 7.45 (m, 2H), 7.35 – 7.31 (m, 2H), 7.27 – 7.21 (m, 3H), 4.38 (t, *J* = 8.0 Hz, 2H), 2.83 (t, *J* = 8.0 Hz, 2H), 2.18 – 2.11 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 165.7, 140.3, 132.0, 129.5, 128.7, 127.6, 127.5, 127.5, 125.1, 63.4, 31.4, 29.4.

2.2.1.4 4-Ethoxy-4-oxobutan-2-yl benzoate **(178)**



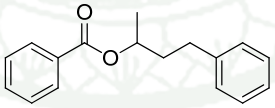
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.03 – 8.00 (m, 2H), 7.56 – 7.52 (m, 1H), 7.52 – 7.40 (m, 2H), 5.56 – 5.48 (m, 1H), 4.13 (q, *J* = 8.0 Hz, 2H), 2.79 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.63 (dd, *J* = 16.0, 4.0 Hz, 1H), 1.43 (d, *J* = 8.0 Hz, 3H), 1.20 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 169.3, 164.8, 132.0, 129.5, 128.7, 127.4, 67.2, 59.8, 40.2, 19.1, 13.3.

2.2.1.5 1-Phenylpropan-2-yl benzoate **(179)**



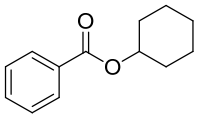
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.03 – 8.01 (m, 2H), 7.55 – 7.51 (m, 2H), 7.44 – 7.40 (m, 2H), 7.32 – 7.18 (m, 5H), 5.38 (sex, *J* = 8.0 Hz, 1H), 3.08 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.90 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.35 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 165.1, 136.6, 131.9, 129.8, 128.6, 127.5, 127.4, 125.6, 109.0, 71.2, 41.4, 18.6.

2.2.1.6 4-Phenylbutan-2-yl benzoate **(180)**



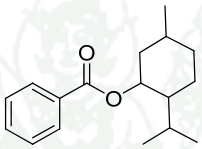
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.11 – 8.08 (m, 2H), 7.61 – 7.56 (m, 1H), 7.49 – 7.45 (m, 2H), 7.33 – 7.29 (m, 2H), 7.24 – 7.20 (m, 3H), 5.27 – 5.22 (m, 1H), 2.81 – 2.74 (m, 2 H), 2.15 – 2.09 (m, 1H), 2.03 – 1.98 (m, 1H), 1.43 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 165.2, 140.6, 131.9, 129.9, 128.6, 127.5, 127.4, 125.0, 70.3, 36.9, 31.0, 19.2.

2.2.1.7 Cyclohexyl benzoate **(181)**



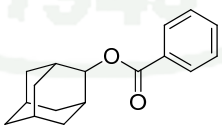
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.07 – 8.04 (m, 2H), 7.56 – 7.52 (m, 1H), 7.45 – 7.41 (m, 2H), 5.07 – 5.01 (m, 1H), 1.98 – 1.92 (m, 2H), 1.84 – 1.76 (m, 2H), 1.64 -1.54 (m, 3H), 1.50 – 1.30 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.1, 132.8, 131.1, 129.6, 128.4, 73.2, 31.8, 25.6, 23.8.

2.2.1.8 2-Isopropyl-5-methylcyclohexyl benzoate **(182)**



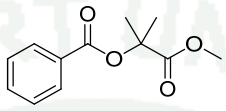
White solid. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.06 – 8.04 (m, 2H), 7.56 – 7.52 (m, 1H), 7.46 – 7.42 (m, 2H), 4.97 – 4.91 (m, 1H), 2.16 – 2.11 (m, 1H), 2.01 – 1.93 (m, 1H), 1.77 – 1.70 (m, 2H), 1.60 – 1.52 (m, 2H), 1.19 – 1.06 (m, 2H), 0.94 – 0.91 (m, 7H), 0.80 (d, J = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.2, 132.8, 131.0, 129.7, 128.4, 47.4, 41.1, 34.5, 31.6, 26.7, 23.8, 22.2, 20.9, 16.7.

2.2.1.9 Adamantan-2-yl benzoate **(183)**



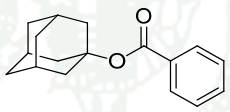
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.11 – 8.09 (m, 2H), 7.57 – 7.53 (m, 1H), 7.47 – 7.42 (m, 2H), 2.19 – 2.15 (m, 4H), 1.92 – 1.78 (m, 9H), 1.66 – 1.62 (2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 165.9, 132.8, 131.2, 129.6, 128.4, 37.5, 36.5, 32.1, 27.4, 27.1.

2.2.1.10 1-Methoxy-2-methyl-1-oxopropan-2-yl benzoate **(184)**



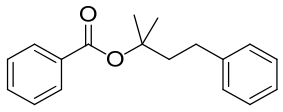
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.05 – 8.02 (m, 2H), 7.58 – 7.54 (m, 1H), 7.46 – 7.41 (m, 2H), 3.74 (s, 3H), 1.69 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 173.2, 165.5, 133.2, 130.1, 129.9, 128.5, 78.8, 52.6, 24.9.

2.2.1.11 Adamantan-1-yl benzoate **(185)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.01 – 7.98 (m, 2H), 7.53 – 7.49 (m, 1H), 7.43 – 7.38 (m, 2H), 2.27 – 2.22 (m, 10H), 1.76 – 1.68 (5H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 165.6, 132.5, 132.2, 129.5, 128.2, 81.1, 41.6, 36.4, 31.0.

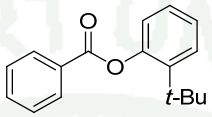
2.2.1.12 2-Methyl-4-phenylbutan-2-yl benzoate **(186)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.03 – 8.00 (m, 2H), 7.57 – 7.52 (m, 1H), 7.45 – 7.42 (m, 2H), 7.31 – 7.27 (m, 2H), 7.25 –

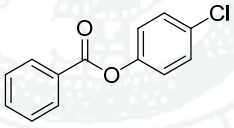
7.17 (m, 3H), 2.78 – 2.74 (m, 2H), 2.25 – 2.21 (m, 2H), 1.67 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 165.8, 142.2, 132.6, 132.0, 129.5, 128.5, 128.4, 128.3, 125.9, 82.8, 43.2, 30.6, 26.3.

2.2.1.13 2-(*tert*-Butyl)phenyl benzoate **(188)**



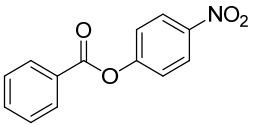
White solid. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.28 – 8.25 (m, 2H), 7.69 – 7.65 (m, 1H), 7.57 – 7.54 (m, 2H), 7.48 – 7.46 (m, 1H), 7.32 – 7.27 (m, 1H), 7.25 – 7.23 (m, 1H), 7.13 - 7.11 (m, 1H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 165.6, 149.6, 141.5, 133.7, 130.4, 130.0, 128.8, 127.4, 121.1, 126.0, 124.3, 34.7, 30.5.

2.2.1.14 4-Chlorophenyl benzoate **(190)**



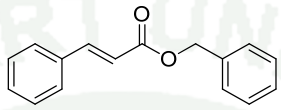
White solid. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.21 – 8.18 (m, 2H), 7.67 – 7.63 (m, 1H), 7.54 – 7.50 (m,2H), 7.42 – 7.38 (m, 2H), 7.19 – 7.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 165.1, 149.6, 133.9, 131.4, 130.3, 129.7, 129.3, 128.8, 123.3.

2.2.1.15 4-Nitrophenyl benzoate **(192)**



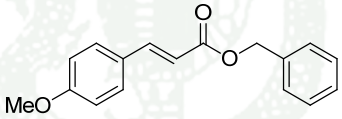
White solid. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.21 – 8.19 (m, 2H), 7.68 – 7.63 (m, 1H), 7.55 – 7.50 (m,2H), 7.42 – 7.38 (m, 2H), 7.20 – 7.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 165.0, 149.6, 133.9, 131.4, 130.3, 129.6, 129.3, 128.7, 123.2.

2.2.1.16 Benzyl cinnamate **(196)**



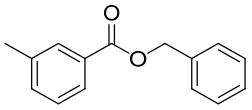
White solid. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.76 (d, *J* = 16.0 Hz, 1H), 7.55 – 7.38 (m, 10H), 6.52 (dd, *J* = 16.0, 1.2 Hz), 5.28 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.8, 145.3, 136.2, 134.5, 130.4, 129.0, 128.7, 128.4, 128.2, 118.0, 117.9, 66.4.

2.2.1.17 Benzyl-(*E*)-4-methoxy cinnmate **(198)**



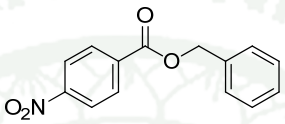
White solid. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.70 (d, *J* = 16.0 Hz, 1H), 7.49 – 7.37 (m, 7H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.37 (d, *J* = 16.0 Hz, 1H), 5.26 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 167.2, 161.5, 144.9, 136.3, 129.9, 129.8, 128.7, 128.3, 127.2, 115.4, 114.4, 66.3, 55.4.

2.2.1.18 Benzyl-3-methylbenzoate **(202)**



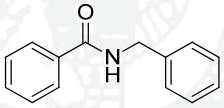
White solid. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.49 – 7.34 (m, 7H), 5.39 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 166.3, 138.2, 136.2, 133.9, 130.3, 130.2, 128.7, 128.4, 128.3, 128.3, 127.0, 66.7, 21.4.

2.2.1.19 Benzyl-4-nitrobenzoate **(206)**



White solid. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.29 – 8.22 (m, 4H), 7.47 – 7.26 (m, 5H), 5.41 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 164.4, 150.5, 135.4, 135.2, 130.7, 128.7, 128.6, 128.3, 123.5, 67.6.

2.2.1.20 *N*-Benzylbenzamide **(209)**



White solid. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.12 (d, *J* = 8.0 Hz, 2H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.50 – 7.37 (m, 7H), 6.42 (br s, 1H), 5.40 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) : δ 167.7, 138.3, 134.3, 131.5, 128.7, 128.5, 127.8, 127.5, 127.1, 44.0.

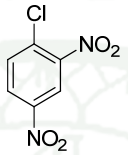
2.3 Nucleophilic Aromatic Substitution of Phenol Derivatives

2.3.1 General procedure

To a stirred solution of phenol derivatives in dry toluene was successively added PPh_3 and trichloroacetonitrile (Cl_3CCN), respectively and stirred at refluxed temperature under N_2 atmospher. After that, the mixture was extracted

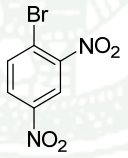
with CH_2Cl_2/H_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel to afford the desired product.

2.3.1.1 1-Chloro-2,4-dinitrobenzene **(221)**



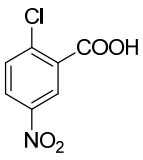
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.73 (d, *J* = 2.4 Hz, 1H), .8.39 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H). (Aridoss, 2011 and Barbero, 2011)

2.3.1.2 1-Bromo-2,4-dinitrobenzene **(222)**



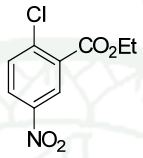
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.73 (d, *J* = 2.4 Hz, 1H), .8.29 (dd, *J* = 8.0, 4.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H). (Barbero, 2011)

2.3.1.3 2-Chloro-5-nitrobenzoic acid **(225)**



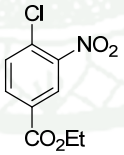
White solid. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.80 (d, *J* = 4.0 Hz, 1H), 8.48 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H). (Rupe, 1897)

2.3.1.4 Ethyl 2-chloro-5-nitrobenzoate **(229)**



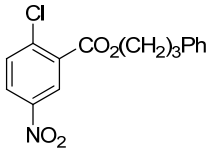
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.68 (d, *J* = 4.0 Hz, 1H), 8.26 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 4.45 (q, *J* = 8.0 Hz, 2H), 1.43 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, CDCl3) : δ 163.7, 146.3, 140.8, 132.4, 131.6, 126.8, 126.6, 62.6, 14.3. HRMS (ESI) Calcd for $C_9H_9ClO_4$ 230.0220 $[M + H]^+$. Found 230.0475 $[M + H]^+$.

2.3.1.5 Ethyl 4-chloro-3-nitrobenzoate **(231)**



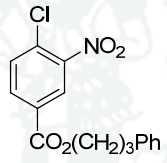
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.49 (d, *J* = 2.0 Hz, 1H), 8.16 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 4.42 (q, *J* = 8.0 Hz, 2H), 1.41 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, CDCl3) : δ 163.8, 148.2, 133.7, 132.2, 131.6, 130.6, 126.7, 62.3, 14.4. HRMS (ESI) Calcd for $C_9H_9ClO_4$ 230.0220 $[M + H]^+$. Found 230.0478 $[M + H]^+$.

2.3.1.6 3-Phenylpropyl 2-chloro-5-nitrobenzoate **(233)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.66 (d, *J* = 2.8 Hz, 1H), 8.27 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.32 – 7.16 (m, 5H), 4.42 (t, *J* = 8.0 Hz, 2H), 2.80 (t, *J* = 8.0 Hz, 2H), 2.15 (quin, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, CDCl3) : δ 163.8, 146.3, 140.9, 140.7, 132.4, 131.5, 128.7, 128.5, 126.9, 126.7, 126.3, 66.0, 32.4, 30.2. HRMS (ESI) Calcd for $C_{16}H_{14}ClO_4Na$ 342.0509 $[M + Na]^+$. Found 342.0516 $[M + Na]^+$.

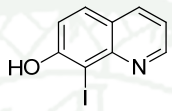
2.3.1.7 3-Phenylpropyl 4-chloro-3-nitrobenzoate **(235)**



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.40 (d, *J* = 4.0 Hz, 1H), 8.10 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.31 – 7.17 (m, 5H), 4.40 (t, *J* = 8.0 Hz, 2H), 2.79 (t, *J* = 8.0 Hz, 2H), 2.15 (quin, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, CDCl3) : δ 163.8, 148.0, 141.0, 133.6, 132.2, 131.6, 130.3, 128.6, 128.5, 126.5, 126.2, 65.7, 32.5, 30.0. . HRMS (ESI) Calcd for $C_{16}H_{14}ClO_4Na$ 342.0509 $[M + Na]^+$. Found 342.0505 $[M + Na]^+$.

3. Synthetic the 7,7'-dihydroxy-8,8'-biquinolyl (azaBINOL) and its derivatives

3.1 8-Iodoquinolin-7-ol **(236)**



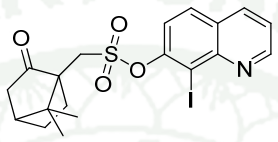
Method A : A solution of quinoline-7-ol (1.45 g, 10.0 mmol) in methanol (500 mL) was added to $NaClO_2$ (904 mg, 10.0 mmol) and NaI (3.0 g, 10.0 mmol) in water (500 mL) followed by 12 M HCl (60 mmol) and the mixture was stirred at rt. After the reaction was completed (2 h), the mixture was diluted with H_2O (500 mL) and extracted with EtOAc. The combined organic layers were washed with a saturated solution of sodium chloride containing $Na_2S_2O_3$ (10 g/L) to remove excess iodine, dried over Na_2SO_4 and taken to dryness under reduced pressure to give the crude. The reaction mixture was purified by column chromatography to afford the desired product (1.089 g, 4.02 mmol, 40%).

Method B : A stirred solution of quinoline-7-ol (145 mg, 1.0 mmol) in anhydrous DMF (2.0 mL) at rt was treated with NIS (225 mg, 1.0 mmol) and the resulting suspension stirred at rt for overnight. The mixture was washed with EtOAc and H_2O. The layers were separated and the aqueous phase extracted with EtOAc. The combined organic extracts were washed successively with H_2O and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was further purified by column chromato-graphy to afford the desired product (109 mg, 0.40 mmol, 40%).

Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.94 (dd, J = 8.8, 1.6 Hz, 1H), 8.07 (dd, J = 8.0, 1.6 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H), 7.33 (dd, J = 8.0, 4.4 Hz, 1H), 6.12 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.5,

151.8, 148.1, 136.5, 129.9, 124.4, 120.8, 119.8, 117.5. HRMS (ESI) *m/z*: C_9H_6INO $[M+H]^+$, calcd 271.9574, found 271.9571.

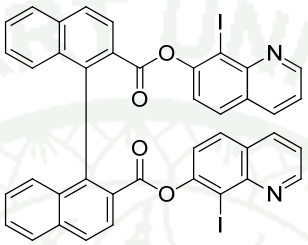
3.2 8-Iodoquinolin-7-yl (7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl) methane-sulfonate **(240)**



A solution of 8-iodoquinolin-7-ol (135 mg, 0.50 mmol) in DCM (3 mL) was added to a mixture of sulfonyl chloride (126 mg, 0.50 mmol), Et_3N (140 μL, 2.0 mmol) and 4 drops of DMF in DCM (10 mL) at 0 ^oC. Then the mixture was stirred at rt for overnight. After that, the mixture was worked up with H_2O and extracted with DCM. The combined organic layers were washed with brine and dried over $MgSO_4$ and taken to dryness under reduced pressure to give the crude. The reaction mixture was purified by column chromatography to afford the desired product (164 mg, 0.34 mmol, 68%).

Pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.04 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.16 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.49 (dd, *J* = 8.8, 4.4 Hz, 1H), 4.08 (d, *J* = 14.8 Hz, 1H), 3.58 (d, *J* = 14.8 Hz, 1H), 2.56 (ddd, *J* = 14.8, 11.6, 4.0 Hz, 1H), 2.43 (dt, *J* = 18.4, 4.4 Hz, 1H), 2.16 (t, *J* = 4.4 Hz, 1H), 2.134 – 2.06 (m, 1H), 1.98 (d, *J* = 18.4 Hz, 1H), 1.80 (ddd, *J* = 14.0, 9.2, 4.8 Hz, 1H), 1.48 (ddd, *J* = 12.8, 9.2, 4.0 Hz, 1H), 1.19 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.8, 152.4, 151.8, 148.4, 136.8, 130.0, 127.3, 122.4, 122.2, 99.0, 58.5, 50.7, 48.2, 43.1, 42.6, 27.1, 25.5, 20.2, 19.9. HRMS (ESI) *m/z*: $C_{19}H_{20}INO_4S$ $[M+Na]^+$, calcd 508.0058, found 508.0054.

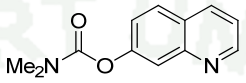
3.3 Bis(8-iodoquinolin-7-yl) [1,1'-binaphthalene]-2,2'-dicarboxylate **(242)**



A solution of [1,1'-binaphthalene]-2,2'-dicarboxylic acid (171 mg, 0.5 mmol) and DMF 2 drops in DCM (5 mL) at 0 °C was treated with the similarly cooled solution of $(COCl)_2$ (215 μL, 2.5 mmol) in DCM (1 mL) and stirred for 1 h. The resulting solution was kept in 4 ^{o}C overnight. Then, the solvent of solution was removed and after that the solid was dissolved with DCM (5 mL). The solution of diacid chloride was stirred at 0 °C and then to a similarly cooled solution of iodine (298 mg, 1.1 mmol) in anhydrous DCM (5 mL). The resulting mixture was stirred for 2 h at 0 °C. The reaction mixture was quenched with H_2O and sat. aq. $NaHCO_3$, DCM was added and the layers well shaken and separated. The organic phase was extracted with H_2O and the combined organic extracts were dried with $MgSO_4$ and concentrated *in vacuo*. The reaction mixture was purified by column to afford the desired product (208 mg, 0.25 mmol, 49%).

Pale yellow solid. ^{1}H NMR (400 MHz, DMSO) δ: 8.95 (dd, J = 4.4, 1.6 Hz, 2H), 8.49 (d, J = 8.8, 2H), 8.36 (dd, J = 8.4, 1.6 Hz, 2H), 8.29 (d, J = 8.8 Hz, 2H), 8.15 (d, J = 8.0 Hz, 2H), 7.95 (d, J = 9.2 Hz, 2H), 7.69 (t, J = 8.0 Hz, 2H), 7.58 (dd, J = 8.0, 4.0 Hz, 2H), 7.45 (t, J = 8.0 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ: 163.8, 152.7, 152.2, 147.3, 140.2, 136.8, 135.0, 132.3, 129.8, 128.7, 128.6, 128.2, 127.6, 126.9, 126.4, 125.8, 125.7, 122.1, 99.0. HRMS (ESI) *m/z*: $C_{40}H_{22}N_2O_4I_2[M+Na]^+$, calcd 870.9567, found 870.9556.

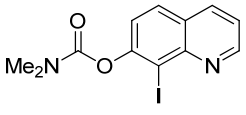
3.4 Quinolin-7-yl dimethylcarbamate **(243)**



A stirred solution of 7-hydroxyquinoline (9.81 g, 67.6 mmol) in pyridine (60 mL) at rt was treated with dimethyl-aminocarbonyl chloride (12.4 mL, 135.0 mmol). The resulting brown solution was heated to 100 °C and stirred for 52 h. After this time the mixture was allowed to cool to rt and partitioned between EtOAc (300 mL) and H_2O (150 mL). The pH of the aqueous layer was adjusted to 9 by the addition of 5% w/v aq. NaOH and the layers were shaken and separated. The aqueous phase was extracted with EtOAc and the combined organic extracts washed with H_2O, dried with Na_2SO_4 and concentrated *in vacuo*. The crude was further purified by column chromatography to yield the desired product (9.31 g, 43.05 mmol, 64%).

Pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.90 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.13 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.81 (d, *J* = 2.8 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.39 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.35 (dd, *J* = 8.4, 4.4 Hz, 1H), 3.16 (s, 3H), 3.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.7, 152.3, 151.0, 149.1, 135.9, 128.7, 126.1, 122.8, 120.7, 120.3, 36.9, 36.7. HRMS (ESI) *m/z*: $C_{12}H_{12}N_2O_2[M+H]^+$, calcd 217.0979, found 217.0981

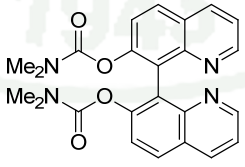
3.5 8-Iodoquinolin-7-yl dimethylcarbamate **(50)**



A solution of *i*-Pr_2NH (1.7 mL, 12.15 mmol) in THF (15 mL) at –20 °C was treated dropwise with *n*-BuLi (7.5 mL, 1.6 M, 12 mmol) and stirred for 5 min. The resulting solution of LDA was further cooled to -78 °C and quinolin-7-yl dimethylcarbamate (2.08 g, 9.62 mmol) in THF (15 mL) added carefully over 5 min down the cold flask side-wall. The dark brown solution of lithiated quinoline was stirred for 1 h at –78 °C and then added *via* cannula over 5 min to a similarly cooled solution of iodine (28.86 mmol) in anhydrous THF (30 mL). The resulting mixture was stirred for 5 min at –78 °C and the cooling bath was removed. The reaction mixture was allowed to stir vigorously for a further 5 min while slowly warming and then quenched with sat. aq. $Na_2S_2O_3/NH_4Cl$ (1:1). EtOAc was added and the layers well shaken and separated. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with sat. aq. $Na_2S_2O_3$, dried with Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography to yield the desired product (1.915 g, 5.60 mmol, 58%).

Pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.00 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.11 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.41 (dd, *J* = 8.4, 4.0 Hz, 1H), 3.28 (s, 3H), 3.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.0, 153.7, 151.8, 148.4, 136.6, 129.1, 126.7, 123.3, 121.5, 98.5, 37.1. HRMS (ESI) *m/z*: $C_{12}H_{11}N_2O_2I[M+H]^+$, calcd 342.9945, found 342.9952

3.6 [8,8'-Biquinoline]-7,7'-diyl bis(dimethylcarbamate) **(51)**



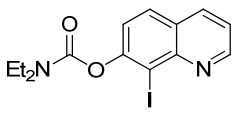
Method A : A solution of *i*-Pr_2NH (0.86 mL, 6.1 mmol) in THF (7.5 mL) at –20 °C was treated with *n*-BuLi (3.5 mL, 1.6 M, 5.55 mmol) and stirred for 5 min. The resulting solution of LDA was further cooled to –78 °C and the quinolin-7-yl dimethyl carbamate (0.75 g, 4.63 mmol) in THF (7.5 mL) added carefully over 5

min down the cold flask side-wall. The dark brown solution of lithiated quinoline was stirred for 30 min at –78 °C and then a chilled suspension of $FeCl_3$ (1.0 g, 4.63 mmol) in THF (10 mL) was added over 15 min. The resulting dark purple mixture was allowed to warm to 0 °C over 11 h and then sat. aq. NH_4Cl (50 mL) was added. The mixture was further diluted with H_2O and EtOAc and the layers were well shaken and separated. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by column chromatography to yield the desired product (410 mg, 0.95 mmol, 41%).

Method B : A stirred solution of iodide (1.04 g, 3.04 mmol) in DMF (10 mL) at rt was treated with freshly prepared copper (772 mg, 12.16 mmol) in one portion and the resulting suspension heated to 130 °C (bath temp.) and stirred for 3 h. The mixture was allowed to cool and partitioned between EtOAc and NH_4OH. The layers were separated and the aqueous phase extracted with EtOAc. The combined organic extracts were washed successively with H_2O, brine, dried Na_2SO_4 and concentrated *in vacuo*. The crude residue was further purified by column chromatography to yield the desired product (439 mg, 1.02 mmol,67%)

Coloress solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.79 (dd, J = 4.0, 1.6 Hz, 2H), 8.21 (dd, J = 8.0, 1.6 Hz, 2H), 7.92 (d, J = 9.2 Hz, 2H), 7.74 (d, J = 8.8 Hz, 2H), 7.33 (dd, J = 8.0, 4.0 Hz, 2H), 2.72 (s, 6H), 2.09 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.0, 150.5, 150.4, 148.1, 136.0, 128.2, 126.1, 125.7, 123.8, 120.3, 36.5, 35.5. HRMS (ESI) *m/z*: $C_{24}H_{24}N_4O_4[M+H]^+$, calcd 431.1721, found 431.1730

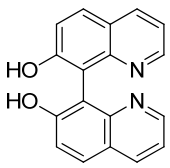
3.7 8-iodoquinolin-7-yl diethylcarbamate **(245)**



A solution of *i*-Pr_2NH (0.7 mL, 5.0 mmol) in THF (7.5 mL) at –20 °C was treated dropwise with *n*-BuLi (1.6 M., 3.1 mL, 5.0 mmol) and stirred for 5 min. The resulting solution of LDA was further cooled to -78 °C and quinolin-7-yl diethyl carbamate (1.0 g, 4.1 mmol) in THF (7.5 mL) added carefully over 5 min down the cold flask side-wall. The dark brown solution of lithiated quinoline was stirred for 1 h at –78 °C and then added *via* cannula over 5 min to a similarly cooled solution of iodine (4.7 g., 12.3 mmol) in anhydrous THF (14 mL). The resulting mixture was stirred for 5 min at –78 °C and the cooling bath was removed. The reaction mixture was allowed to stir vigorously for a further 5 min while slowly warming and then quenched with sat. aq. $Na_2S_2O_3/NH_4Cl$ (1:1). EtOAc was added and the layers well shaken and separated. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with sat. aq. $Na_2S_2O_3$, dried with Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (eluting with 30 to 50% EtOAc in hexanes) to afford 8- the desired product (729 mg, 1.97 mmol, 48%).

Yellow brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.00 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.12 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.44 (d, *J* = 9.2 Hz, 1H), 7.42 (dd, *J* = 8.0, 4.4 Hz, 1H), 3.63 (q, *J* = 7.2 Hz, 2H), 3.45 (q, *J* = 7.2 Hz, 2H), 1.4 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.1, 153.0, 151.8, 148.4, 136.6, 129.0, 126.7, 123.4, 121.4, 98.5, 42.5, 42.4, 14.6, 13.5. HRMS (ESI) *m/z*: $C_{14}H_{15}IN_2O_2$ $[M+H]^+$, calcd 371.0258, found 371.0259.

3.8 **[8,8'-biquinoline]-7,7'-diol (42)**



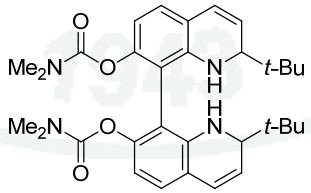
Method A : The solution of [8,8'-biquinoline]-7,7'-diyl bis(diethylcarbamate) (48.7 mg, 0.1 mmol) in 10 wt.% methanolic KOH (1 mL) was stirred at reflux

for 24 h. The resulting yellow solution was allowed to cool to rt. The residue was dissolved in H_2O (10 mL) and the pH adjusted to 7 by 3 M aq. HCl. The aqueous phase was saturated with NaCl and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to yield the desired product (14.9 mg, 0.052 mmol, 52%)

Method B : A stirred solution [8,8'-biquinoline]-7,7'-diyl bis(dimethyl carbamate) (226 mg, 0.525 mmol) in 10 wt.% methanolic KOH (5 mL) was heated at reflux for 18 h. The resulting red solution was allowed to cool to rt and concentrated *in vacuo*. The residue was taken up in H_2O (and neutralized (with 3 M aq. HCl), and the resulting mixture extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to yield the desired product (129 mg, 0.447 mmol, 85%).

Pale yellow solid. ^{1}H NMR (400 MHz, DMSO) δ: 9.29 (s, 2H), 8.47 (dd, J = 8.0, 4.0 Hz, 2H), 8.22 (dd, J = 8.0, 4.0 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.21 (dd, J = 8.0, 4.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ: 157.3, 149.1, 148.8, 135.3, 127.4, 122.1, 119.9, 118.5, 117.2. HRMS (ESI) *m/z*: $C_{18}H_{12}N_2O_2$ $[M+H]^+$, calcd 289.0979, found 289.0981.

3.9 2,2'-di-tert-butyl-1,1',2,2'-tetrahydro-[8,8'-biquinoline]-7,7'-diyl-bis (dimethyl carbamate) **(52)**

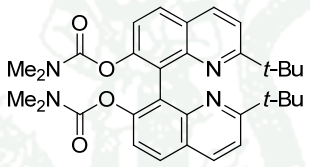


A stirred solution of [8,8'-biquinoline]-7,7'-diyl bis(dimethylcarbamate) (77 mg, 0.18 mmol) in THF (4.0 mL) at –78 °C, was treated with *t*-BuLi (0.27 mL, 1.7 M in hexane, 0.45 mmol). The resulting solution was stirred for 45 min and then sat. aq. NH_4Cl added immediately. The quenched biphasic mixture was allowed to warm to rt in the presence of air and partitioned between H_2O and EtOAc. The layers

were separated and the pH of the aqueous phase adjusted to 13 (with aq. NaOH). The basified aqueous phase was extracted with EtOAc and the combined organic phases dried with Na_2SO_4 and concentrated *in vacuo*. The residue was puried by column chromatography to yield the desired product (84 mg, 0.154 mmol, 86%)

Pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.81 (d, *J* = 8.0 Hz, 2H), 6.50 (d, *J* = 8.0 Hz, 2H), 6.42 (dd, *J* = 12.0, 1.2 Hz, 2H), 5.53 (m, 2H), 3.98 (s, 2H), 3.84 (d, *J* = 8.0 Hz, 2H), 2.82 (s, 6H), 2.64 (s, 6H), 0.76 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.4, 150.4, 143.8, 126.8, 126.6, 121.7, 116.7, 110.4, 107.5, 62.0, 38.5, 30.1, 24.7.

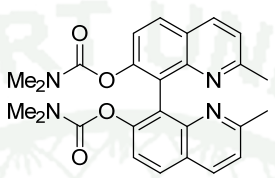
3.10 2,2'-di-tert-butyl-[8,8'-biquinoline]-7,7'-diyl bis(dimethylcarbamate) **(248)**



A stirred solution of 2,2'-di-tert-butyl-1,1',2,2'-tetrahydro-[8,8'-biquinoline]-7,7'-diyl-bis(dimethyl carbamate) (82 mg, 0.15 mmol) in DCM (4.0 mL) at rt, was treated with DDQ (41 mg, 0.18 mmol) for 1 night (or 1 week standing in the air). The reaction was partitioned by H_2O and EtOAc. The aqueous phase was extracted with EtOAc and the combined organic phases dried with Na_2SO_4 and concentrated *in vacuo*. The residue was puried by column chromatography to yield the desired product (46 mg, 0.084 mmol, 57%).

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, *J* = 8.0, 2H), 7.80 (d, *J* = 8.0, 2H), 7.67 (d, *J* = 8.0, 2H), 7.37 (d, *J* = 8.0, 2H), 2.74 (s, 6H), 2.22 (s, 6H), 1.07 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.1, 154.3, 150.1, 147.0, 135.4, 126.8, 126.0, 123.5, 121.9, 116.7, 38.1, 36.5, 35.7, 29.9.HRMS (ESI) *m/z*: $C_{32}H_{38}N_4O_4$ $[M+H]^+$, calcd 543.2973, found 543.2980

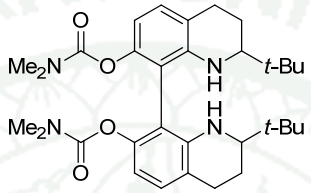
3.11 2,2'-di-methyl-[8,8'-biquinoline]-7,7'-diyl bis(dimethylcarbamate) **(249)**



A stirred solution of [8,8'-biquinoline]-7,7'-diyl bis(dimethylcarbamate) (153 mg, 0.36 mmol) in THF (7.0 mL) at –78 °C, was treated with MeLi (0.56 mL, 1.6 M in ether, 0.90 mmol). The resulting solution was stirred for 45 min and then sat. aq. NH_4Cl added immediately. The quenched biphasic mixture was allowed to warm to rt in the presence of air and partitioned between H_2O and EtOAc. The layers were separated and the pH of the aqueous phase adjusted to 13 (with aq. NaOH). The basified aqueous phase was extracted with EtOAc and the combined organic phases dried with Na_2SO_4 and concentrated *in vacuo*. After that, the crude mixture was react with DDQ (82 mg, 0.36 mmol) in DCM (3.0 mL) at rt for overnight. The mixture was diluted with H_2O and DCM and the layers were separated. The aqueous phase was extracted with DCM and the combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The residue was puried by column chromato graphy to yield the desired product (45 mg, 0.098 mmol, 27%).

Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (d, J = 8.0, 2H), 7.84 (d, J = 8.0, 2H), 7.67 (d, J = 12.0, 2H), 7.18 (d, J = 8.0, 2H), 2.70 (s, 6H), 2.51 (s, 6H), 1.93 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.0, 153.9, 150.7, 147.5, 135.9, 127.5, 125.1, 124.1, 122.7, 120.9, 36.4, 35.1, 25.4. HRMS (ESI) *m/z*: $C_{26}H_{26}N_4O_4$ $[M+H]^+$, calcd 459.2034, found 459.2039.

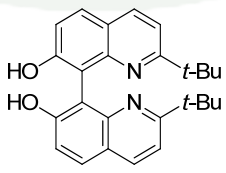
3.12 2,2'-Di-tert-butyl-1,1',2,2',3,3',4,4'-octahydro-[8,8'-biquinoline]-7,7'-diyl bis(dimethylcarbamate) **(251)**



A stirred solution of 2,2'-di-tert-butyl-1,1',2,2'-tetrahydro-[8,8'-biquinoline]-7,7'-diyl bis(dimethylcarbamate) (25 mg, 0.046 mmol) in methanol (3.0 mL) at rt, was treated with excess 5% Pt/C under H_2 pressure and stirred overnight at rt. The mixture was filtered by celite. The filtrate was concentrated *in vacuo.* The residue was puried by column chromatography to yield the desired product (9 mg, 0.016 mmol, 35%).

Pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.90 (d, J = 8.0 Hz, 2H), 6.41 (d, J = 8.0 Hz, 2H), 4.00 (s, 2H), 2.81 – 2.65 (m, 18H), 1.91 – 1.87 (m, 2H), 1.55 – 1.49 (m, 2H), 0.78 (s, 18H).

3.13 2,2'-di-tert-Butyl-[8,8'-biquinoline]-7,7'-diol **(53)**

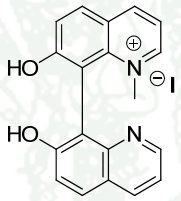


A stirred solution of 2,2'-di-tert-butyl-[8,8'-biquinoline]-7,7'-diyl bis (dimethylcarbamate) (50mg, 0.092 mmol) in 10 wt.% methanolic KOH (1.0 mL) was heated at reflux for 17 h. The resulting red solution was allowed to cool and

concentrated *in vacuo*. The residue was taken up in H_2O (and neutralized (with 3 M aq. HCl), and the resulting mixture extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo.* The residue was puried by column chromatography to yield the desired product (31 mg, 0.077 mmol, 84%).

Yellow solid. ^{1}H NMR (400 MHz, DMSO) δ: 9.17 (s, 2H), 8.10 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 0.97 (s, 18H). ^{13}C NMR (100 MHz, DMSO) δ: 166.4, 155.6, 147.4, 135.5, 126.9, 120.3, 118.2, 118.0, 114.0, 37.5, 29.5. HRMS (ESI) *m/z*: $C_{26}H_{28}N_2O_2$ $[M+H]^+$, calcd 401.2231, found 401.2232.

3.14 7,7'-dihydroxy-1-methyl-[8,8'-biquinolin]-1-ium iodide **(258)**



A solution of the [8,8'-biquinoline]-7,7'-diol (45 mg, 0.156 mmol) and excess MeI (5 drops) in MeCN (2 mL) was refluxed for 2 nights. The solvent was evaporated under reduced pressure, and residue was subjected to vacuum to remove excess MeI. The residue was puried by column chromatography to yield the product, (17 mg, 0.026 mmol, 17%).

Yellow solid. ^{1}H NMR (400 MHz, MEOD) δ: 8.56 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.53 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.31 – 8.27 (m, 2H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.33 – 7.29 (m, 2H), 7.22 (dd, *J* = 8.0, 6.4 Hz, 1H), 3.47 (s, 3H). HRMS (ESI) *m/z*: $C_{19}H_{15}N_2O_2I$ $[M+H]^+$, calcd 431.0258, found 431.0264.

RESULTS AND DISCUSSION

1. Carbon-Heteroatom Bond Formation by Oxidation-Reduction Condensation

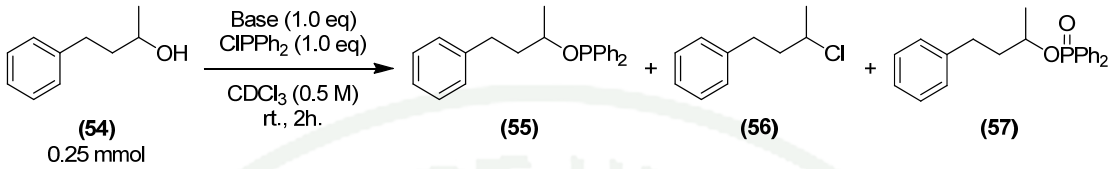
1.1 Preparation of Alkyl Diphenylphosphinites

In the first place, the alkyl diphenylphosphinite was prepared by taking the reaction of 4-phenyl-2-butanol **(54)** as a model compound to avoid a benzylic effect, in the presence of $ClPPh_2$ and base such as DMAP, pyridine, 4-picoline, piperidine and Et_3N (Table 3). Furthermore, the other variable parameters including the ratio of base and $ClPPh_2$ and the amount of solvent were also examined. The reaction could be proceeded in $CDCl_3$ within 2 hours at room temperature. The %yield of the desired product was determined by ^1H NMR.

The reaction could not be performed in the absence of base (Entry 1) whereas the quantity of 4-phenyl-2-butyl diphenylphosphinite **(55)** was significantly affected by the nature of the base. The most effective results were achieved when Et_3N was used (Entry 6). Nonetheless, the reaction did not proceed completely because the remaining of 4-phenyl-2-butanol **(54)** and the undesired products including 4-phenyl-2-butyl chloride **(56)** and 4-phenyl-2-butyl diphenyl phosphine oxide **(57)**, were detected.

Probably, the alkyl chloride **(56)**, and the alkyl diphenylphosphine oxide **(57)** were generated from chlorination and oxidation of alkyl diphenylphosphinite, respectively (Scheme 48 and 49).

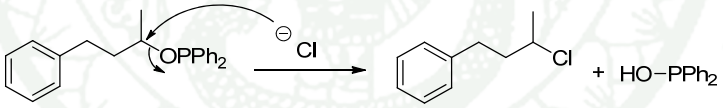
Table 3 Effect of the type of base for the preparation of 4-phenyl-2-butyl diphenylphosphinite



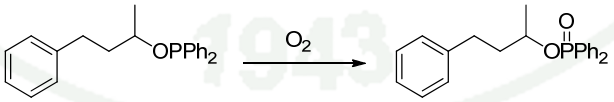
(54) 0.25 mmol **(55)** **(56)** **(57)**

Entry	Base	Yield[a] (%)			% Recovery[a]
		(55)	**(56)**	**(57)**	**(54)**
1	None	0	79	2	20
2	DMAP	54	9	2	35
3	Pyridine	22	31	6	41
4	4-Picoline	42	6	2	51
5	Piperidine	24	34	2	40
6	Et_3N	76	4	4	16

[a] Determined by ^1H NMR.



Scheme 48 Chlorination of 4-phenyl-2-butyl diphenylphosphinite

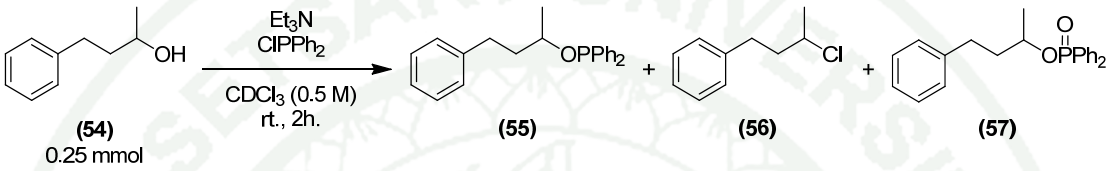


Scheme 49 Oxidation of 4-phenyl-2-butyl diphenylphosphinite

Next, the quantities of Et_3N and $ClPPh_2$ were also varied in order to find the most suitable stoichiometric ratio to provide the maximum possible yield of 4-phenyl-2-butyl diphenylphosphinite **(55)** (Table 4). Increasing the amounts of Et_3N and $ClPPh_2$ from 1 to 1.2 equivalents afforded the highest yield of the desired product

(Entry 2). On the other hand, yield was decreased when 0.1 eq of DMAP was added (Entry 3). Similar result was obtained when amount of Et_3N and $ClPPh_2$ was used in greater excess (1.3 and 1.4 equivalents, Entries 4 and 5).

Table 4 Effect of the equivalent of NEt_3 and chlorodiphenylphosphine for the preparation of 4-phenyl-2-butyl diphenylphosphinite



(54) 0.25 mmol **(55)** **(56)** **(57)**

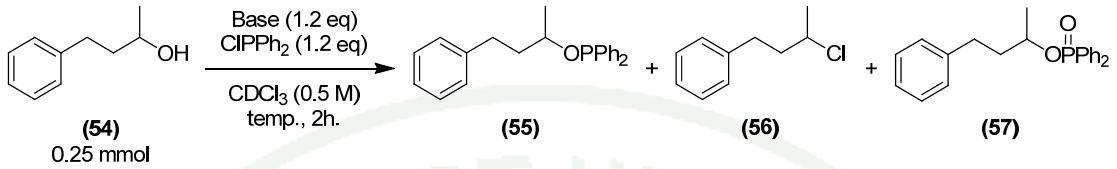
Entry	NEt_3 (eq)	$ClPPh_2$ (eq)	Yield[a] (%)			% Recovery[a]
			(55)	**(56)**	**(57)**	**(54)**
1	1.0	1.0	76	4	4	16
2	1.2	1.2	76	1	9	13
3	1.2	1.2	68	4	3	28
4	1.3	1.3	75	10	5	11
5	1.4	1.4	63	15	4	17

[a] Determined by ^1H NMR.

[b] 0.1 Equivalent of DMAP was added.

The effect of temperature on the reaction was further investigated (Table 5). As the result, it was noted that the temperature did not show a significant effect between room temperature (Entry 1) and reflux temperature (Entry 2).

Table 5 Effect of the temperature for the preparation of 4-phenyl-2-butyl diphenyl phosphinite



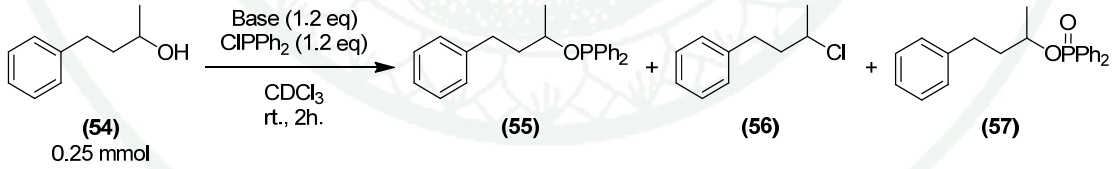
(54) 0.25 mmol **(55)** **(56)** **(57)**

Entry	Temperature	Yield[a] (%)			% Recovery[a]
		(55)	**(56)**	**(57)**	**(54)**
1	RT	76	1	9	13
2	Reflux	78	4	6	12

[a] Determined by ^{1}H NMR

The variation of reaction concentration was also determined (Table 6). It was found that the reaction concentration did not significantly affect to the yield.

Table 6 Effect of the reaction concentration for the preparation of 4-phenyl-2-butyl diphenylphosphinite



(54) 0.25 mmol **(55)** **(56)** **(57)**

Entry	Concentration (M)	Yield[a] (%)			% Recovery[a]
		(55)	**(56)**	**(57)**	**(54)**
1	0.5	76	1	9	13
2	1.0	77	2	8	13

[a] Determined by ^{1}H NMR

From the above results, we summarized that the optimized conditions for the preparation of 4-phenyl-2-butyl diphenylphosphinite **(55)** were 1.2 equivalents of $ClPPh_2$ and Et_3N in 1M $CDCl_3$ at room temperature for 2 hours.

The example of ^{1}H NMR spectrum of reaction mixture is shown in Figure 12. The proton signals at 4.58 – 4.45, 4.05 – 3.94, 3.94 – 3.85 and 3.76 – 3.68 were assigned to four methine protons of phosphine oxide **(57)**, phosphinite product **(55)**, alkyl chloride **(56)** and remaining alcohol **(54),** respectively.

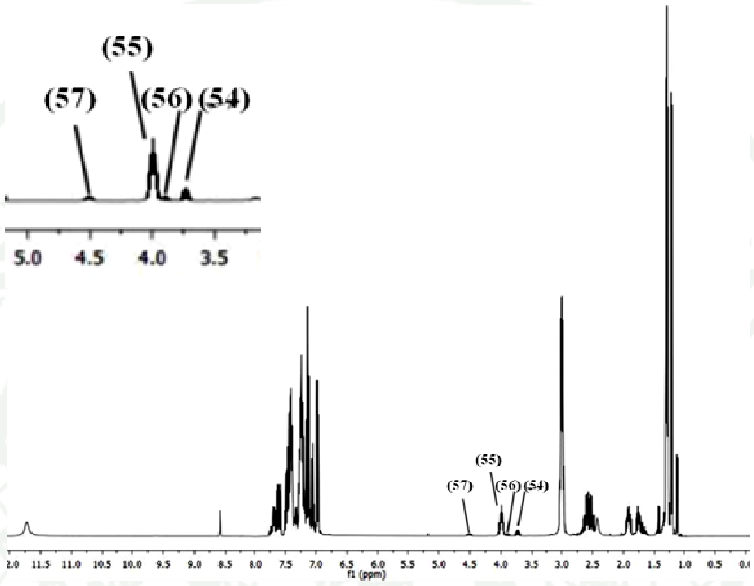


Figure 12 ^{1}H NMR spectrum of reaction mixture from the preaparation of 4-phenyl-2-butanyl diphenylphosphinite

1.2 Carbon-Sulfur Bond Formation

From the literature reviews, the oxidation-reduction condensation of alkyl diphenylphosphinites and HSBtz in the presence of oxidant has been reported. This reaction could proceed to give the corresponding sulfides in good yields *via* the S_N2 displacement. However, the alkyl diphenylphosphinite are unstable compounds because easily oxidized by oxygen in the air to afford alkyl diphenylphosphine oxides. Therefore, this research would devote for the exploration of a practical and convenient protocol for carbon-sulfur bond formation. Moreover, a new and efficient oxidant to utilize in our protocol was also studied. Thus, 1,2-dicarbonyl compounds were chosen to study for their efficiency as an oxidant in the condensation with alkyl diphenylphosphinites and HSBtz.

Next, the exploration of optimum conditions for the preparation of carbon-sulfur bond formation from alkylphosphinite, generated *in situ* from alcohol, sulfur nucleophile and selected oxidant was examined. Variable parameters studied included type of oxidant, molar ratio of oxidants and nucleophile, reaction time and reaction temperature.

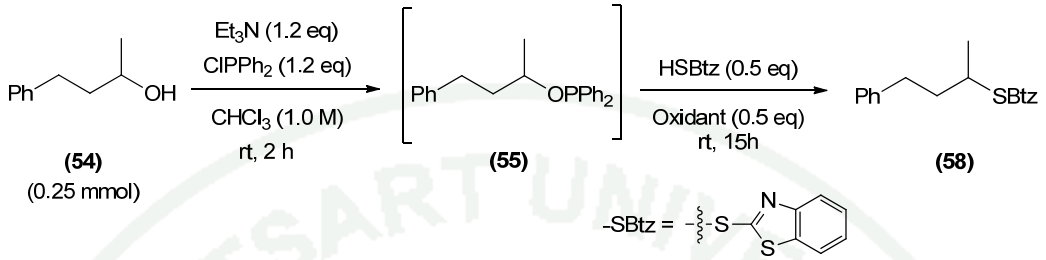
1.2.1 Using benzothiazole-2-thiol (HSBtz) as a nucleophile

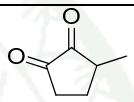
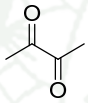
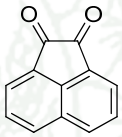
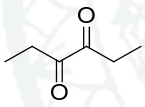
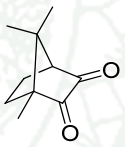
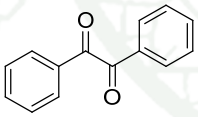
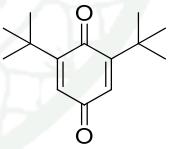
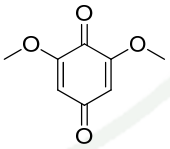
1.2.1.1 Effect of the oxidants

In order to find the most suitable oxidant, the various 1,2-dicarbonyl compounds were examined in the first by taking the condensation reaction of 4-phenyl-2-butyl diphenylphosphinite **(55),** derived *in situ* from 4-phenyl-2-butanol **(54)** and HSBtz (Table 7).

In the absence of an oxidant, 2-((4-Phenylbutan-2-yl)thio)benzo[d]thiazole **(58)** was not obtained indicating that the oxidant was crucial for this reaction (Entry 1). In the presence of 2,3-butanedione, 3,4-hexanedione, benzil, and acenaphthenequinone, the desired product was obtained only in trace amounts (Entries 2 – 4 and 7) whereas the use of 1,2-cyclohexanedione and 3-methyl-1,2-cyclopentanedione did not yield the desired product (Entries 5 and 6). A reaction using camphorquinone (CQ) afforded the desired product **(58)** in 84% yield (Entry 8). Under the newly developed conditions, it was found that camphorquinone could afford the desired product **(58)** in higher yield that compared with 2,6-di-*tert*-butyl-1,4-benzoquinone (DBBQ) and 2,6-dimethoxy-1,4-benzoquinone (DMOBQ) (Entries 9 and 10).

Table 7 Effect of the oxidants for preparation of 2-((4-phenylbutan-2-yl)thio) benzo[d]thiazole



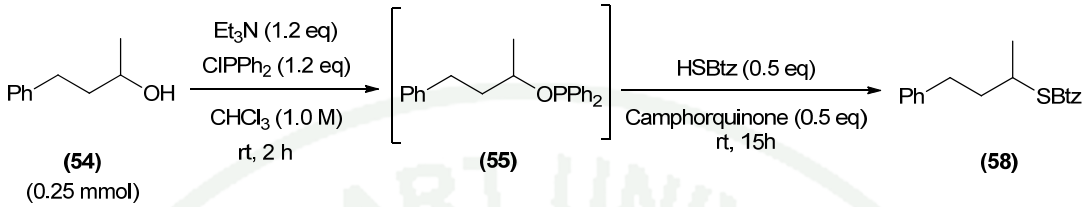
Entry	Oxidant	Yield (%)[a]	Entry	Oxidant	Yield (%)[a]
1	None	0	6		0
2		Trace	7		Trace
3		Trace	8		84
4		Trace	9		69
5		0	10		75

[a] Isolated yield.

1.2.1.2 **Effect of solvent**

Thioetherification of the 4-phenyl-2-butanol **(54)** using various solvents was further investigated in order to determine the most appropiate type of solvent (Table 8).

Table 8 Effect of the solvents for preparation 2-((4-phenylbutan-2-yl)thio)benzo[d] thiazole



Entry	Solvent	Yield (%)[a]	Entry	Solvent	Yield (%)[a]
1	Neat	40	5	Toluene	28
2	$CHCl_3$	84	6	$ClCH_2CH_2Cl$	59
3	CH_2Cl_2	81	7	CH_3CN	74
4	THF	17			

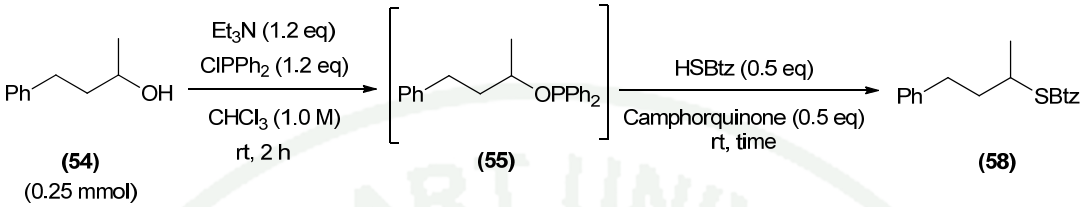
[a] Isolated yield.

According to above results, $CHCl_3$ was the preferred medium for use in this reaction because it can dissolve both of the substrate and reagent. Therefore, the effect of replacing $CHCl_3$ with alternate solvents was examined. It was found that the reaction performed in CH_2Cl_2 (Entry 3) led to a similar yield in comparison to $CHCl_3$. In contrast, the isolated yields of desired product dropped to 17%, 28%, 59% and 74% when THF, toluene, $ClCH_2CH_2Cl$ and CH_3CN were used, respectively (Entries 4 – 7). Also, the reactions in absence of solvent afforded the products in the lower yields (Entry 1).

1.2.1.3 Effect of reaction time

Taking the above results into consideration, reaction time was also determined (Table 9).

Table 9 Effect of the reaction time for preparation 2-((4-phenylbutan-2-yl)thio) benzo[d]thiazole



Entry	Time (h)	Yield (%)[a]	Entry	Time (h)	Yield (%)[a]
1	6.0	64	4	15.0	84
2	9.0	83	5	24.0	61
3	12.0	81			

[a] Isolated yield.

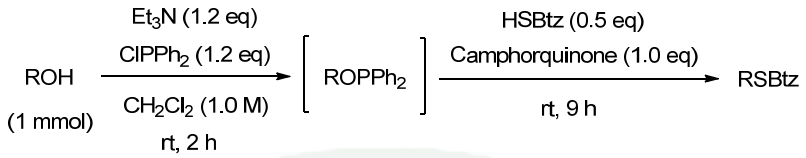
This reaction could afford the corresponding product in good yield when the reaction time was 15 hours (Entry 4). However, similar results were obtained in the case of reaction time as 9 and 12 hours. (Entries 2 and 3). Thus, 9 hours was a suitable time for our developed thioetherification.

1.2.1.4 Thioetherification of various alcohols

Next, thioetherification of the various alcohols was studied in order to examine the scope of this developed reaction (Table 10).

Almost primary and secondary alcohols could be converted to the corresponding sulfides, 2-(alkylthio)benzo[*d*]thiazole, in moderate to high yields (Entries 1 – 20). Moreover, tertiary alcohols that having the carbonyl group (ester and ketone) at quaternary carbon (Entries 21 and 22) were converted to the corresponding sulfides in moderate yields. On the other hand, tertiary alcohols with alkyl substituent at quaternary carbon (Entries 24 – 28) did not afford the corresponding sulfides, except in the case of 1-adamentanol (Entry 23).

Table 10 Thioetherification of alcohols with 1,3-benzothiazole-2-thiol



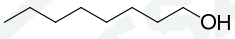
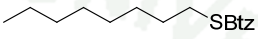
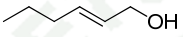
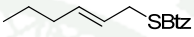
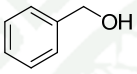
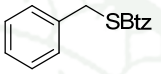
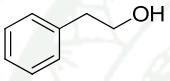
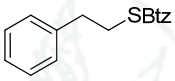
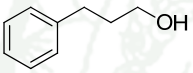
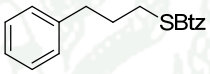
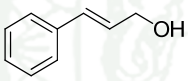
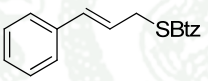
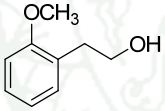
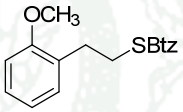
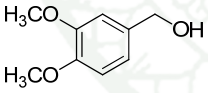
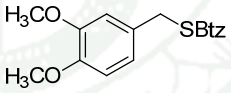
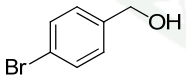
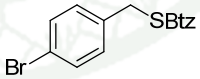
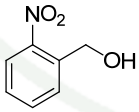
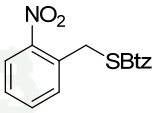
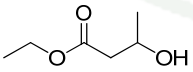
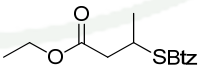
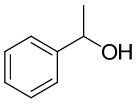
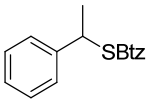
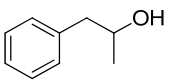
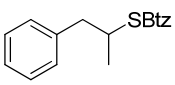
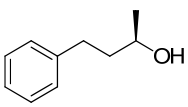
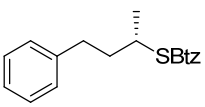
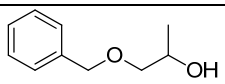
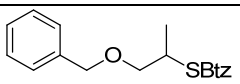
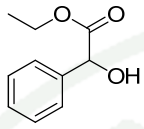
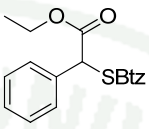
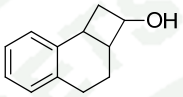
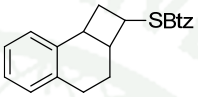
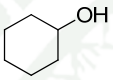
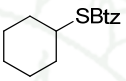
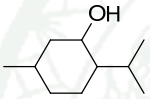
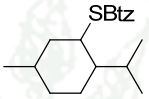
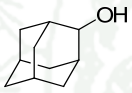
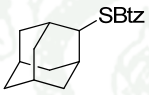
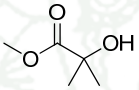
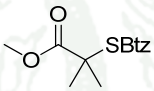
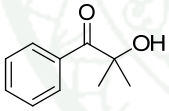
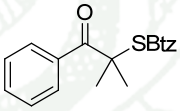
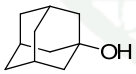
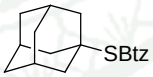
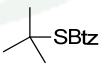
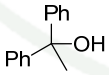
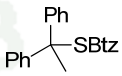
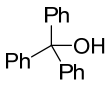
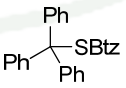
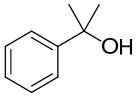
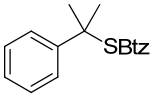
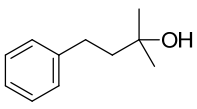
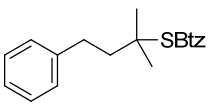
Entry	Substrate		Product		Yield (%)[a]
1		**(59)**		**(60)**	77
2		**(61)**		**(62)**	90
3		**(63)**		**(64)**	86
4		**(65)**		**(66)**	74
5		**(67)**		**(68)**	75
6		**(69)**		**(70)**	55
7		**(71)**		**(72)**	87
8		**(73)**		**(74)**	50
9		**(75)**		**(76)**	88
10		**(77)**		**(78)**	77
11		**(79)**		**(80)**	69
12		**(81)**		**(82)**	25
13		**(83)**		**(84)**	78
14		**(85)**		**(86)**	78

Table 10 (Continued)

Entry	Substrate		Product		Yield (%)[a]
15		**(87)**		**(88)**	74
16		**(89)**		**(90)**	73
17		**(91)**		**(92)**	47
18		**(93)**		**(94)**	32
19		**(95)**		**(96)**	44
20		**(97)**		**(98)**	58
21		**(99)**		**(100)**	50
22		**(101)**		**(102)**	58
23		**(103)**		**(104)**	38
24		**(105)**		**(106)**	ND.[b]
25		**(107)**		**(108)**	ND.[b]
26		**(109)**		**(110)**	ND.[b]
27		**(111)**		**(112)**	ND.[b]
28		**(113)**		**(114)**	ND.[b]

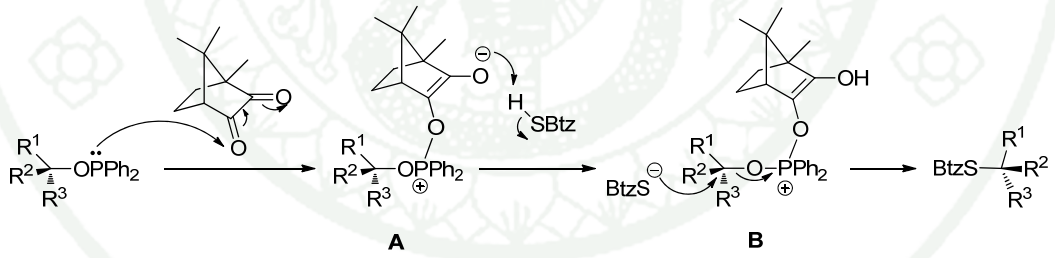
[a] Isolated yield. [b] Not detected.

Effect of stereochemistry where also investigated by using enantiomerically pure substrate, 99% ee of (*R*)- 4-phenylbutan-2-ol (Entry 14). After purification, (*S*)-2-((4-phenylbutan-2-yl)thio)benzo[d]thiazole was afforeded in 78% ee.

From above results, it was concluded that the carbon-sulfur bond formation by oxidation-reduction condensation using our developed conditions proceeded *via* S_N2 mechanism. However, the incomplete inversion of chirality is indicative that a minor fraction of the phosphonium salt intermediate is not transformed *via* the expected S_N2 attack of the nucleophile.

1.2.1.5 The proposed mechanism

A proposed mechanism for the carbon-sulfur bond formation using the combination of alkyl diphenylphosphinite and HSBtz in the presence of camphorquinone is shown in Scheme 50.



Scheme 50 The mechanism of the oxidation-reduction condensation using the combination of alkyl diphenylphosphinite and HSBtz in the presence of camphorquinone

The first step, alkyl diphenylphosphinite, prepared by the corresponding alcohol in the presence of $ClPPh_2$ and NEt_3, reacted with oxo group of camphorquinone to form the phosphonium salt intermediate **A**. Then, the acidic proton of HSBtz was trapped by the oxo anion of the zwitter ion to generate the phosphonium intermediate **B**. The last step, SBtz anion attacked to the carbon atom

adjacent to oxygen atom of the alkoxy group of phosphonium intermediate **B** to afford the desired product *via* S_N2 displacement.

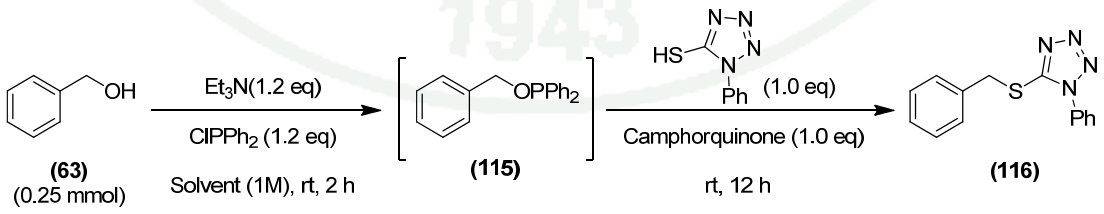
1.2.2 Using 1-phenyl-1H-tetrazole-5-thiol as a nucleophile

In this experimental, the exploration of optimum conditions was examined for the preparation of 5-(alkylthio)-1-phenyl-1H-tetrazole from alkyl diphenylphosphinite and 1-phenyl-1H-tetrazole-5-thiol as a nucleophile in the presence of camphorquinone. Variable parameters including the types of solvents, the mole ratio of 1-phenyl-1H-tetrazole-5-thiol and camphorquinone, reaction time and reaction temperature were studied.

1.2.2.1 Effect of solvent

According to previous studies, CH_2Cl_2 is the most suitable solvent for our protocol. It may be because this solvent could dissolve all of substrate and reagents. However, we would try to confirm the result thus the other solvents were selected to examine using condensation of benyzl diphenylphosphinite that derived *in situ* from benzyl alcohol **(63)** and 1-phenyl-1H-tetrazole-5-thiol as a sulfur nucleophile (Table 11).

Table 11 Effect of the solvent for preparation 5-(benzylthio)-1-phenyl-1H-tetrazole



(63) (0.25 mmol) **(115)** **(116)**

Entry	Solvent	Yield (%)[a]	Entry	Solvent	Yield (%)[a]
1	CH_2Cl_2	63	3	Toluene	31
2	$ClCH_2CH_2Cl$	48			

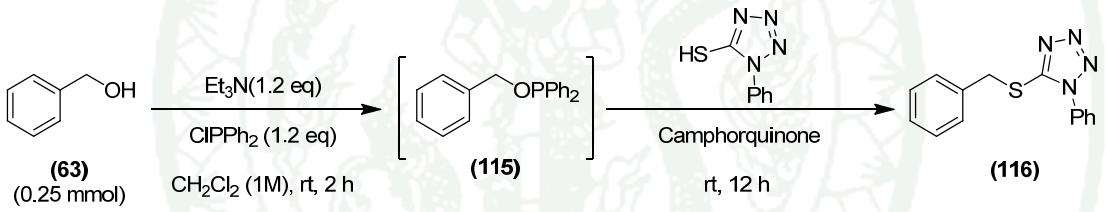
[a] Isolated Yield

We found that CH_2Cl_2 was the best solvent for our reaction because the desired product was obtained in the best %yield (Entry 1), whereas the use of $ClCH_2CH_2Cl$ and toluene gave the product in 48% and 31%, respectively (Entries 2 and 3).

1.2.2.2 Effect of the molar ratio

Later, the ratio of using 1-phenyl-1H-tetrazole-5-thiol to camphorquinone was examined (Table 12).

Table 12 Effect of the molar ratio of 1-phenyl-1H-tetrazole-5-thiol and camphorquinone for preparation 5-(benzylthio)-1-phenyl-1H-tetrazole



Entry	1-Phenyl-1H-tetrazole-5-thiol (eq)	Camphorquinone (eq)	Yield (%)[a]
1	0.5	-	12 (24)[b]
2	0.5	1.0	33 (66)[b]
3	1.0	1.0	63

[a] Isolated Yield.

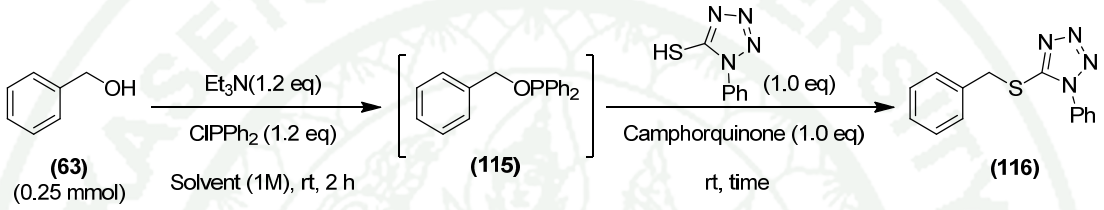
[b] Yield based on quivalent of nucleophile.

The results were showed that the best of molar ratio of 1-phenyl-1H-tetrazole-5-thiol to camphorquinone was 1.0 and 1.0 equivalent, respectively (Entry 3) while decreasing the ratio of 1-phenyl-1H-tetrazole-5-thiol from 1.0 to 0.5 equivalent afforded the desired product in lower yield (Entries 1 and 2).

1.2.2.3 Effect of reaction time

Next, the reaction time was further examined. The results are shown in Table 13.

Table 13 Effect of the reaction time for preparation 5-(benzylthio)-1-phenyl-1H-tetrazole



Entry	Time (h)	Yield (%)[a]	Entry	Time (h)	Yield (%)[a]
1	12	63	2	20	73

[a] Isolated Yield.

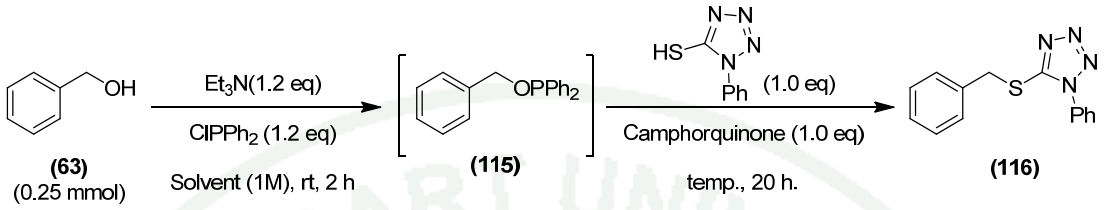
According to the results, it was found that the best reaction time was 20 hours (Entry 2).

1.2.2.4 Effect of temperature

Effect of reaction temperature was also examined at room temperature and reflux. The results are shown in Table 14.

The results showed that the highest %yield was obtained when the reaction was performed at room temperature.

Table 14 Effect of the reaction temperature for preparation 5-(benzylthio)-1-phenyl-1H-tetrazole



Entry	Temperature	Yield (%)[a]	Entry	Temperature	Yield (%)[a]
1	Rt	63	2	Reflux	25

[a] Isolated Yield.

1.2.2.5 Thioetherification of various alcohols

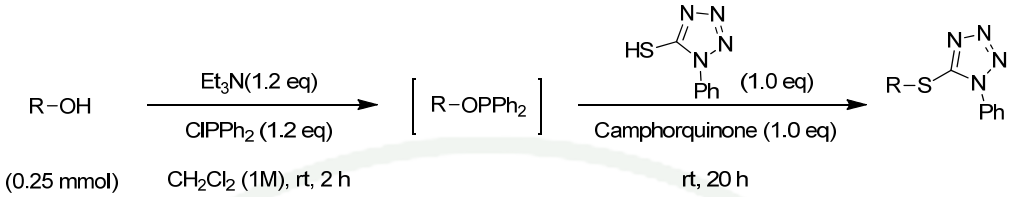
Later, various alcohols were investigated in order to examine the scope of this thioetherification under the optimized conditions (Table 15).

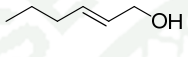
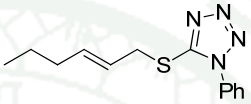
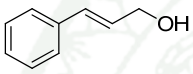
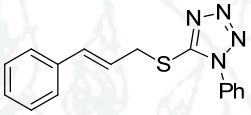
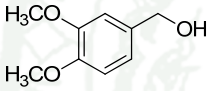
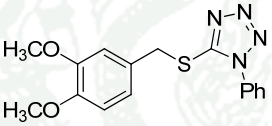
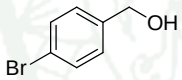
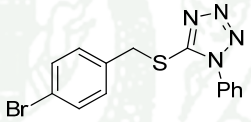
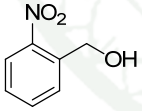
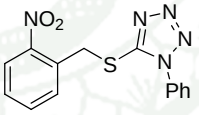
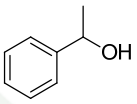
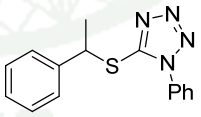
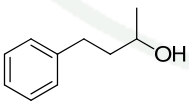
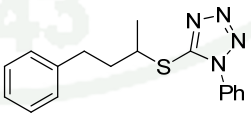
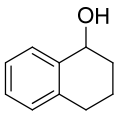
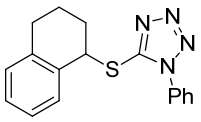
Based on this results, it turned on that primary alcohols could be converted to the corresponding sulfides **(117 – 121)** in moderate yields (Entries 1 – 5) whereas secondary alcohols did not proceed to afford the corresponding products in satisfactory yield. It may be caused through to hindrance of alcohol.

1.2.2.6 The proposed mechanism

The mechanism is similar to the mechanism of the carbon-sulfur bond formation using the combination of alkyl diphenylphosphinite and camphorquinone with HSBtz (Scheme 50), just only change the sulfur nucleophile.

Table 15 Thioetherification of alcohols with 1-phenyl-1H-tetrazole-5-thiol



Entry	Substrate		Product		Yield (%)[a]
1		**(61)**		**(117)**	55
2		**(69)**		**(118)**	50
3		**(73)**		**(119)**	49
4		**(75)**		**(120)**	65
5		**(77)**		**(121)**	56
6		**(81)**		**(122)**	31
7		**(54)**		**(123)**	18
8		**(124)**		**(125)**	23

[a] Isolated Yield.

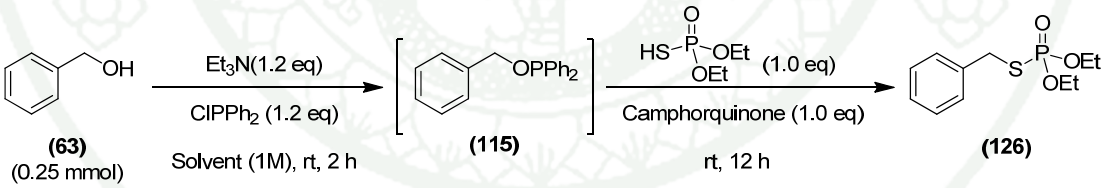
1.2.3 Using *O*,*O*-diethyl *S*-hydrogen phosphorothioate as a nucleophile

In this research, the exploration of optimum conditions was applied for the preparation of *O*,*O*-diethyl *S*-alkyl phosphorothioate from alkyl diphenylphosphinite and *O*,*O*-diethyl *S*-hydrogen phosphorothioate as a nucleophile in the presence of camphorquinone. Variable parameters including the types of solvents, the molar ratio of substate to *O*,*O*-diethyl *S*-hydrogen phosphorothioate and camphorquinone, reaction time and reaction temperature were studied.

1.2.3.1 Effect of solvent

Based on the above successful results, CH_2Cl_2 was chosen as the solvent to study the substitution reaction of benzyl diphenylphosphinite that derived *in situ* from benzyl alcohol **(63)** with *O*,*O*-diethyl *S*-hydrogen phosphorothioate as a sulfur nucleophile (Table 16).

Table 16 Effect of the solvent for preparation *S*-benzyl *O*,*O*-diethyl phosphorothioate



Entry	Solvent	Yield (%)[a]	Entry	Solvent	Yield (%)[a]
1	CH_2Cl_2	49	3	Toluene	22
2	$ClCH_2CH_2Cl$	40			

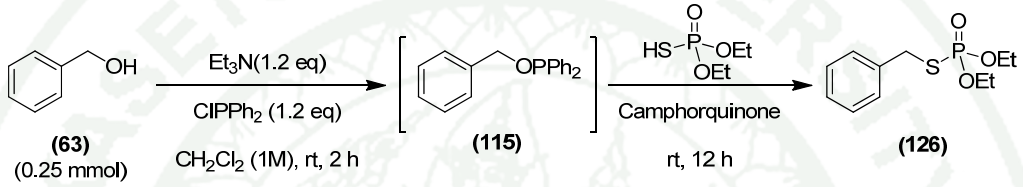
[a] Isolated Yield

We found that CH_2Cl_2 still be the best solvent for our reaction because the yield of the product was obtained in the highest %yield (Entry 1), whereas the use of $ClCH_2CH_2Cl$ and toluene gave only in 40% and 22%, respectively (Entries 2 and 3).

1.2.3.2 Effect of the molar ratio

Later, the ratio of using *O*,*O*-diethyl *S*-hydrogen phosphorothioate and camphorquinone was examined (Table 17).

Table 17 Effect of the molar ratio of *O*,*O*-diethyl *S*-hydrogen phosphorothioate and camphorquinone for preparation *S*-benzyl *O*,*O*-diethyl phosphorothioate



Entry	*O*,*O*-diethyl *S*-hydrogen phosphorothioate (eq)	Camphorquinone (eq)	Yield (%)[a]
1	0.5	-	17 (34)[b]
2	0.5	1.0	23 (46)[b]
3	1.0	1.0	49

[a] Isolated Yield.

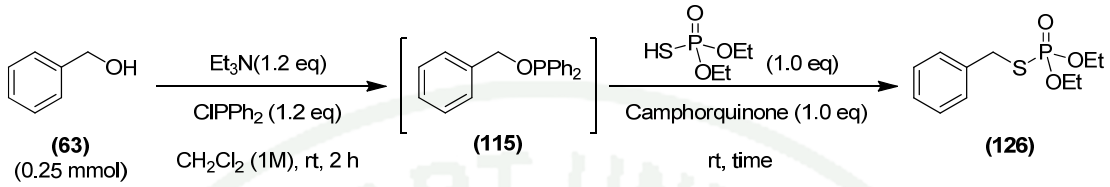
[b] Yield based on quivalent of nucleophile.

The results were found that the best of mole ratio of *O*,*O*-diethyl *S*-hydrogen phosphorothioate and camphorquinone was 1.0 and 1.0 equivalent, respectively (Entry 3) while decreasing the ratio of *O*,*O*-diethyl *S*-hydrogen phosphorothioate from 1.0 to 0.5 equivalent afforded the desired product in lower yield (Entries 1 and 2).

1.2.3.3 **Effect of reaction ime**

Next, the reaction time was further examined. The results are shown in Table 18.

Table 18 Effect of the reaction time for preparation *S*-benzyl *O,O*-diethyl phosphorothioate



Entry	Time (h)	Yield (%)[a]	Entry	Time (h)	Yield (%)[a]
1	12	49	2	20	58

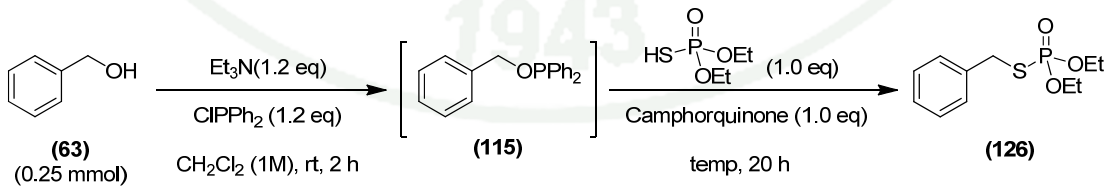
[a] Isolated Yield.

It was found that the suitable reaction time was 20 hours (Entry 2) because this time could performed to obtain %yield in higher than 12 hours.

1.2.3.4 Effect of Temperature

Effect of reaction temperature was also examined at room temperature and reflux. The results are shown in Table 19.

Table 19 Effect of the reaction temperature for preparation *S*-benzyl *O,O*-diethyl phosphorothioate



Entry	Temperature	Yield (%)[a]	Entry	Temperature	Yield (%)[a]
1	RT	58	2	Reflux	20

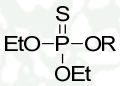
[a] Isolated Yield.

The results were showed that the highest %yield was obtained at room temperature.

1.2.3.5 Thioetherification of various alcohols

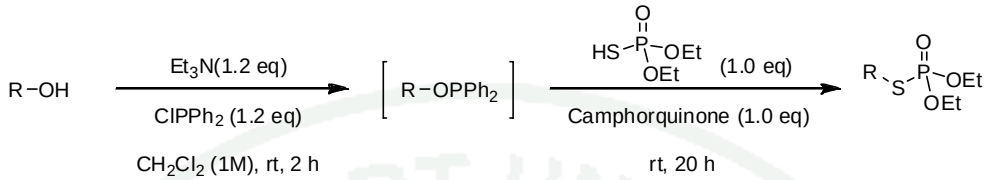
Various alcohols were tried in order to examine the scope of this thioetherification under the optimized conditions (Table 20).

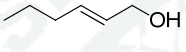
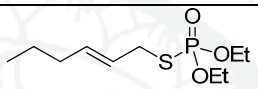
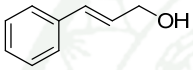
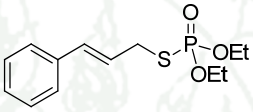
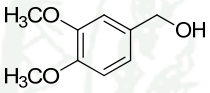
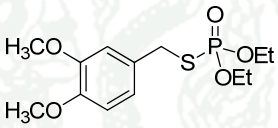
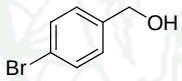
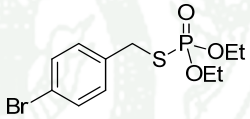
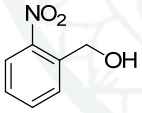
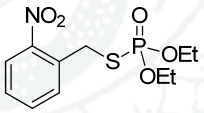
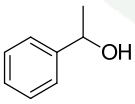
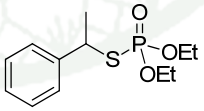
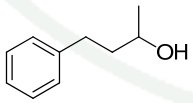
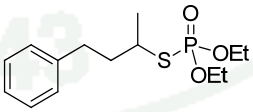
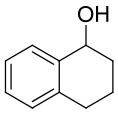
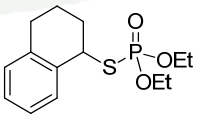
The alcohols could not be converted to the corresponding sulfides, *S*-alkyl *O*,*O*-diethyl phosphorothioate, products in satisfactory yield (Entries 1 – 8) It may be because the reaction generated an undesired product, *O*-alkyl *O*,*O*-diethyl phosphorothioate could be completed (Scheme 51).



Scheme 51 Structure of *O*-alkyl *O*,*O*-diethyl phosphorothioate

Table 20 Thioetherification of alcohols with *O,O*-diethyl *S*-hydrogen phosphorothioate



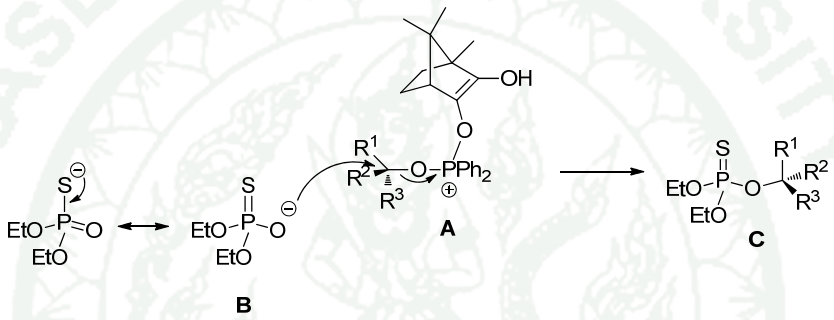
Entry	Substrate		Product		Yield (%)[a]
1		**(61)**		**(127)**	ND[b]
2		**(69)**		**(128)**	11
3		**(73)**		**(129)**	11
4		**(75)**		**(130)**	15
5		**(77)**		**(131)**	13
6		**(81)**		**(132)**	15
7		**(54)**		**(133)**	5
8		**(124)**		**(134)**	11

[a] Isolated Yield.

[b] Not Detected

1.2.3.6 The proposed mechanism

The mechanism for causing the desired product is similar to the mechanism of the carbon-sulfur bond using the combination of alkyl diphenylphosphinite and camphorquinone with HSBtz (Scheme 50), with the only exception of different the sulfur nucleophile. On the other hand, the mechanism that could explain the reason why the undesired product was detected is shown in Scheme 52.



Scheme 52 The mechanism for explanation why the carbon–oxygen bond was occurred when using *O*,*O*-diethyl *S*-hydrogen phosphorothioate as a nucleophile

After oxide anion of the adduct deprotonated the proton of *O*,*O*-diethyl *S*-hydrogen phosphorothioate to generate the phosphonium cation intermediate **A**, the lone pair electron of sulfur atom could delocalized to oxygen atom to give oxygen anion **B**. Then this compound could react with phosphonium cation intermediate to afford the undesired product, *O*-alkyl *O*,*O*-diethyl phosphorothioate **C.**

1.2.4 Using 1,2-diphenyldisulfane as a nucleophile

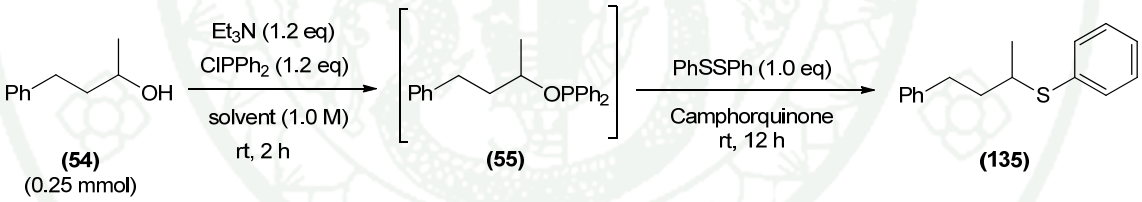
In this experiment, the exploration of optimum conditions for the preparation of 1-alkyl-2-phenyldisulfane from alkyl diphenylphosphinite and 1,2-diphenyldisulfane as a nucleophile in the presence of camphorquinone was examined.

Various parameters including the molar ratio of 1,2-diphenyldisulfane and camphorquinone and reaction time were also studied.

1.2.4.1 Effect of the mole ratio

According to Mukaiyama result (2004b), the oxidation-reduction condensation of alkyl diphenylphosphinites and diaryl disulfide was reported. The literature showed that an oxidant was unnecessary for transformation into the product. However, we need to study this so the equivalent of camphorquinone was also examined by taking the condensation reaction of 4-phenyl-2-butyl diphenylphosphinite **(55)** that derived *in situ* from 4-phenyl-2-butanol **(54)** and 1,2-diphenyldisulfane as a sulfur nucleophile (Table 21).

Table 21 Effect of the mole ratio of camphorquinone for preparation phenyl(4-phenylbutyl-2-yl)sulfane



Entry	Camphorquinone (eq)	Yield (%)[a]	Entry	Camphorquinone (eq)	Yield (%)[a]
1	1.0	26	2	None	30

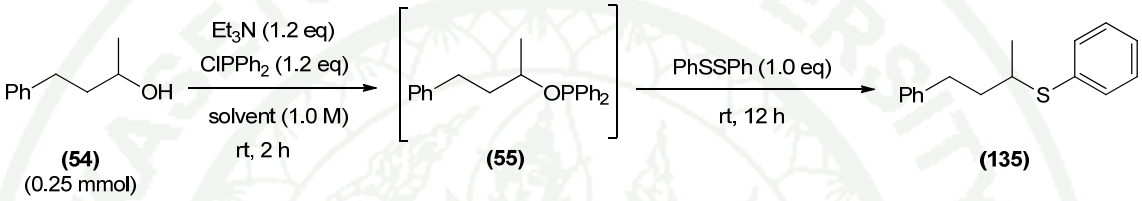
[a] Isolated Yield.

The results did not show a significant between the absence and the present of camphorquinone. Thus, the absence of camphorquinone was chosen to further study.

1.2.4.2 Effect of the reaction time

Taking the above results into consideration, reactions time was next tried to examine **(Table 22)**.

Table 22 Effect of the reaction time for preparation preparation phenyl(4-phenylbutan-2-yl)sulfane



(54) (0.25 mmol) **(55)** **(135)**

Entry	Time (h)	Yield (%)[a]	Entry	Time (h)	Yield (%)[a]
1	9	28	3	20.0	20
2	12.0	30			

[a] Isolated yield.

The thioetherification was performed under optimized standardcondition. The corresponding products were isolated in the best yield when the reaction time was 12 hours (Entry 2). However, similar results were obtained in the case of 9 hours (Entry 1). Thus, 9 hours was a optimized time for our reaction.

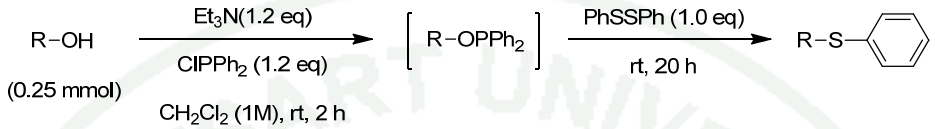
1.2.4.3 Thioetherification of various alcohols

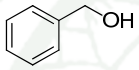
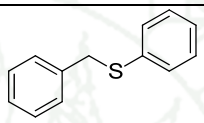
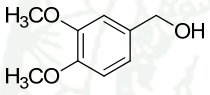
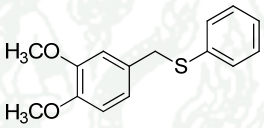
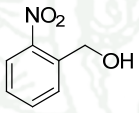
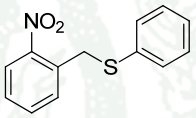
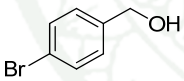
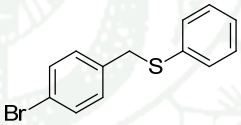
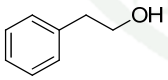
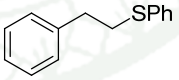
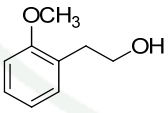
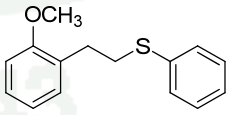
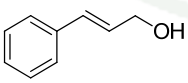
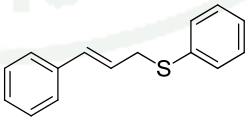
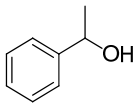
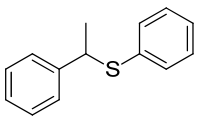
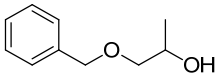
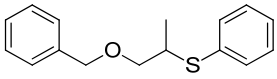
Thioetherification of various alcohols was investigated next in order to study the scope of this reaction **(Table 23)**.

Primary alcohols could be converted to the corresponding sulfides, 1-alkyl-2-phenyldisulfane, in moderate to high yields (entries 1 – 4 and 6 – 7) except in the case of 2-phenylethanol (entry 5) whereas secondary

alcohols did not proceed to afford the corresponding products (entries 8 and 9). It may be because of the hindrance of alcohol.

Table 23 Thioetherification of alcohols with 1,2-diphenyldisulfane

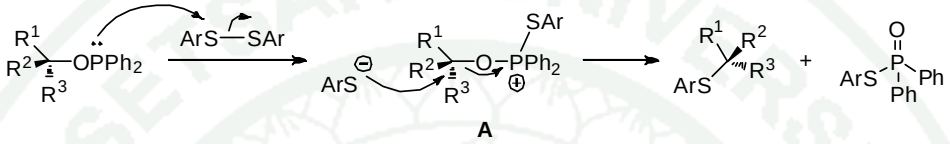


Entry	Substrate		Product		Yield (%)[a]
1		**(63)**		**(136)**	85
2		**(73)**		**(137)**	49
3		**(75)**		**(138)**	64
4		**(77)**		**(139)**	83
5		**(65)**		**(140)**	ND.[b]
6		**(71)**		**(141)**	46
7		**(69)**		**(142)**	57
8		**(75)**		**(143)**	ND.[b]
9		**(77)**		**(144)**	ND.[b]

[a] Isolated Yield. [b] Not Determined

1.2.4.4 The proposed mechanism

A proposed mechanism for the carbon-sulfur bond formation using the combination of alkyl diphenylphosphinite, generated *in situ* from alcohol, and 1-alkyl-2-phenyldisulfane in the absence of camphorquinone is shown in **Scheme 53**.



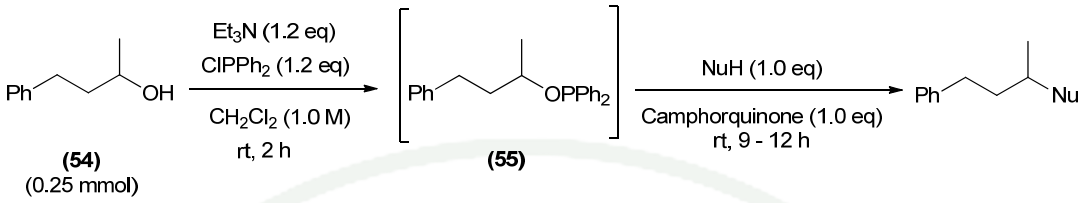
Scheme 53 The mechanism of the oxidation-reduction condensation using the combination of alkyl diphenylphosphinite and PhSSPh

The first step, alkyl diphenylphosphinite reacted with sulfur atom of 1,2-diphenyldisulfane to form the phosphorus intermediate **A** and benzenethiolate. Next, *S*-alkylation of benzenethiolate attacked the carbon atom adjacent to oxygen atom of the alkoxy group of phosphonium cation intermediate to afford the sulfide and phosphinate derivative *via* S_N2 displacement.

1.3 Using other nucleophiles

In addition, synthetic methodology for carbon-carbon, carbon-nitrogen and carbon-oxygen bond formations by oxidation-reduction condensation was further studied to assess the efficiency of our protocols. We then performed camphorquinone mediated oxidation-reduction condensation on 4-phenyl-2-butanol with various nucleophiles under the optimized conditions (Table 24).

Table 24 The reaction of 4-phenyl-2-butanol with other nucleophile



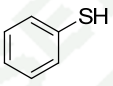
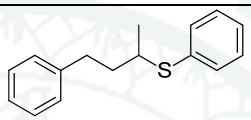
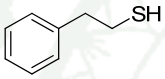
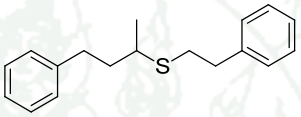
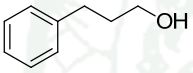
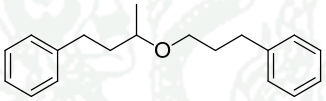
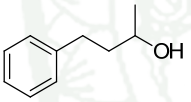
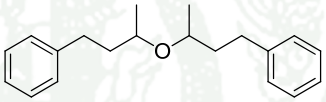
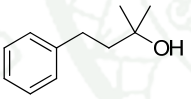
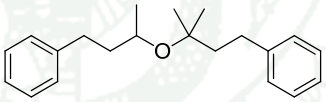
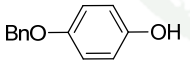
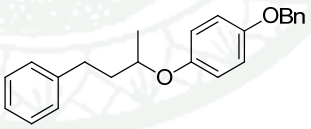
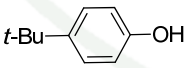
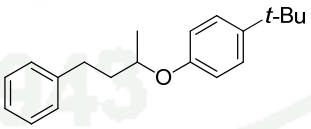
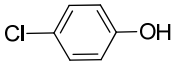
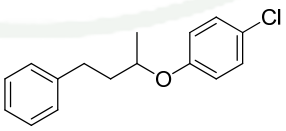
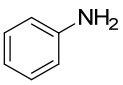
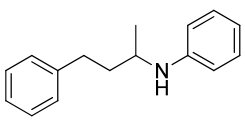
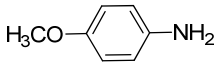
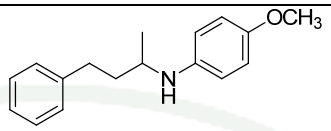
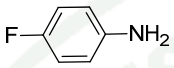
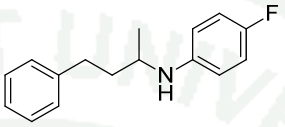
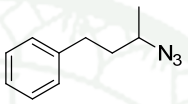
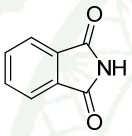
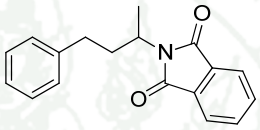
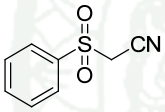
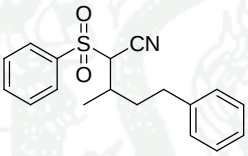
Entry	Nucleophile		Product		Yield (%)[a]
1		**(145)**		**(135)**	39
2		**(146)**		**(147)**	ND.[b]
3		**(67)**		**(148)**	ND.[b]
4		**(54)**		**(149)**	ND.[b]
5		**(113)**		**(150)**	ND.[b]
6		**(151)**		**(152)**	ND.[b]
7		**(153)**		**(154)**	ND.[b]
8		**(155)**		**(156)**	ND.[b]
9		**(157)**		**(158)**	ND.[b]

Table 24 (Continued)

Entry	Nucleophile		Product		Yield (%)[a]
10		**(159)**		**(160)**	ND.[b]
11		**(161)**		**(162)**	ND.[b]
12		**(163)**		**(164)**	ND.[b]
13		**(165)**		**(166)**	ND.[b]
14		**(167)**		**(168)**	ND.[b]

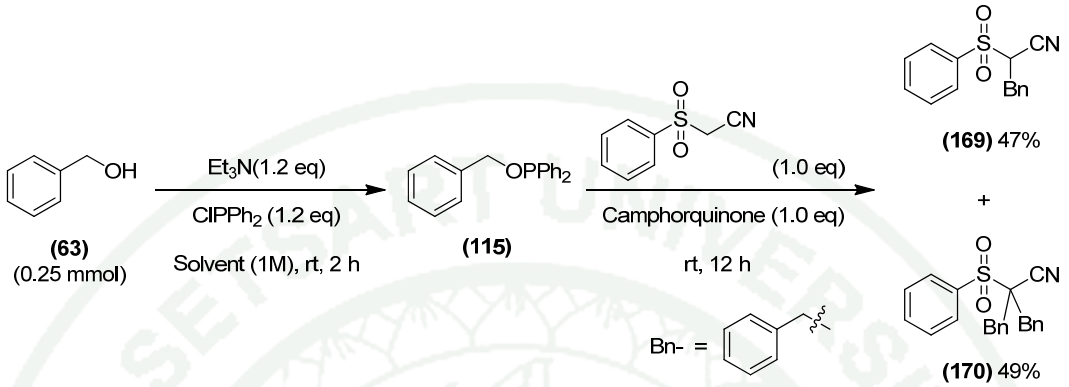
[a] Isolated Yield.

[b] Not Detected

From above results, the case of *O*-nucleophile could not be performed to afford the corresponding product (Entries 3 – 5). This was probably because these alcohols as weak acidic nucleophiles could not be employed to protonate the alkoxide adduct. Similarly, the reactions using phenol derivatives and aniline derivatives (Entries 6 – 11) as nucleophiles could not be proceeded to give the desired products. In the case of using azidotrimethylsilane (Entry 12), phthalimide (Entry 13) and 2-(phenylsulfonyl)acetonitrile (Entry 14), the reaction did not proceed to afford the desired product. This may be due to the steric hindrance in the nucleophile structure.

Next, the use of (phenylsulfonyl)acetonitrile as a nucleophile was also studied (Scheme 54).

Interestingly, the use of benzyl alcohol afforded mono- and di-alkylated products.

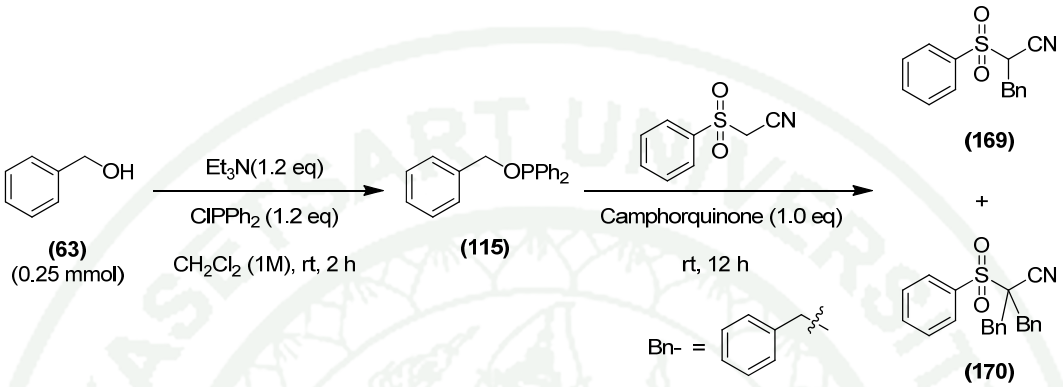


Scheme 54 Preparation of mono- and di-alkylated products of benzyldiphenyl phosphinite using (phenylsulfonyl)acetonitrile as a nuleophile

According to the literature reviews, Mukaiyama reported that the amount of active methylene showed an important factor towards the selectivity of products. Thus, study of mole ratio of (phenylsulfonyl)acetonitrile was first tried to study the optimum conditions (Table 25).

From the results in the Table 25, decreasing the amount of (phenylsulfonyl)acetonitrile from 1.5 to 1.0 equivalent significantly elevated the yield of mono-alkylated product (Entry 1). Furthermore, we found that reaction time did not effect to obtain the %yield of di-alkylated product **(170)** (Entries 3 and 4). However, the results were not clear for control the selectivity of the alkylated product. More study should be cautiously investigated in the future work.

Table 25 Effect of mole ratio of (phenylsulfonyl)acetonitrile for preparation 3-phenyl-2-(phenylsulfonyl)propanenitrile and 2-benzyl-3-phenyl-2-(phenylsulfonyl)propanenitrile



Entry	(phenylsulfonyl)acetonitrile (eq)	Yield (%)[a]	
		mono-alkylated **(169)**	di-alkylated **(170)**
1	1.0	47	49
2	1.5	ND[b]	98
3[c]	1.5	10	88
4[d]	1.5	10	90

[a] Isolated Yield.

[b] Not Detected.

[c] The reaction time was 3 hours.

[d] The reaction time was 6 hours.

2. Carbon-Heteroatom Bond Formation by Nucleophilic Alkyl Substitution and Nucleophilic Aromatic Substitution.

From the literature reviews, the methodology for the preparation of alkyl halides, acid halides, sulfonyl halides and halobenzenes by the halogenation of alcohols, carboxylic acids, sulfonic acids and phenols has been reported. Therefore, our research would extend this concept for developing a new combination of phosphorus and halogenating agents and optimization the conditions for the preparation of alkyl halides, acid halides, sulfonyl halides and halobenzene.

Moreover, the preparation of carbon-heteroatom bond formation such as ester or amide from halogen compounds, generated *in situ* from alcohol and oxygen or nitrogen nucleophile was also examined.

2.1 Nucleophilic Substitution of Alkyl Halides

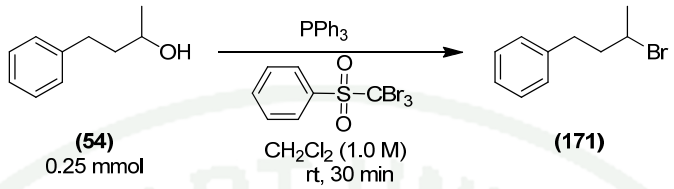
2.1.1 Preparation of Alkyl Halide

In the first place, the method for the preparation of alkyl halides from alcohols was studied by using 4-phenyl-2-butanol **(54)** as a model in the presence of PPh_3 and tribromomethylsulfonylbenzene ($PhSO_2CBr_3$) as halogenating agent. The mole ratio of PPh_3 and $PhSO_2CBr_3$ and reaction time were also varied to find out for providing the best yield of (3-bromobutyl)benzene.

2.1.1.1 Effect of molar ratio

Firstly, the use of PPh_3 and $PhSO_2CBr_3$ in 1.0:1.0 equivalent could furnish (3-bromobutyl)benzene in moderate yield. Then, increasing the amount of PPh_3 and $PhSO_2CBr_3$ was further examined (Table 26).

Table 26 Effect of the equivalent of PPh_3 and $PhSO_2CBr_3$ for the preparation of (3-bromobutyl)benzene



Entry	PPh_3 (eq)	$PhSO_2CBr_3$ (eq)	Yield[a] (%)
1	1.0	1.0	61
2	1.2	1.2	67
3	1.3	1.1	76
4	1.3	1.2	77
5	1.4	1.1	Quant.
6	1.4	1.2	Quant.
7	1.5	1.0	75
8	1.5	1.1	Quant.
9	1.5	1.2	Quant.

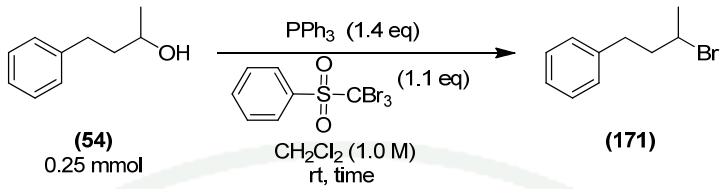
[a] Isolated yield.

From the above results, increasing the amount of both reagents over one eq significantly elevated the yield of the desired product. The quantitative yield was accomplished when 1.4 equivalents of PPh_3 and 1.1 equivalents of $PhSO_2CBr_3$ were used (Entry 5).

2.1.1.2 Effect of reaction time

Moreover, the short reaction time could be possible for preparation of (3-bromobutyl)benzene in the quantitative yield within 15 minutes (Entry 2) as shown in Table 27.

Table 27 Effect of time for the preparation of (3-bromobutyl)benzene



Entry	Time (min)	Yield (%)[a]	Entry	Time (min)	Yield (%)[a]
1	30	Quant.	2	15.0	Quant.

[a] Isolated yield.

2.1.2 Preparation of thioether

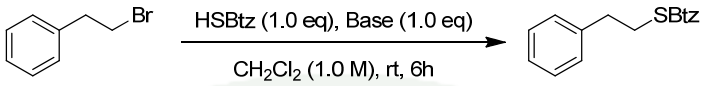
In this experimental, the study of optimum conditions for the preparation of carbon-sulfur bond formation from alkyl halide were examined. Variable parameters studied included types of bases, ratio of base and nucleophile, reaction time and reaction temperature.

2.1.2.1 Effect of the type of base

The effect of base on the reaction was examined using (2-bromoethyl)benzene as the model and HSBtz as sulfur nucleophile (Table 28).

The results were found that the reaction afforded the desired product in low yields in the case of absence of base or using base as $NaHCO_3$, NaH, 4-picoline and pyridine (Entries 1 – 5). The desired product was obtained by using piperidine and NEt_3 in fair to good yield (Entries 6 – 8). However, the best yield of the desired product was achieved when Et_3N was used as base (Entry 7).

Table 28 Effect of the type of base for the preparation of 2-(phenethylthio) benzo[d]thiazole



(172)
0.25 mmol

(66)

Entry	Base	Yield (%)[a]	Entry	Base	Yield (%)[a]
1	None	7	5	Pyridine	3
2	$NaHCO_3$	ND.[b]	6	Piperidine	46
3	NaH	ND.[b]	7	Et_3N	86
4	4-Picoline	4			

[a] Isolated yield.

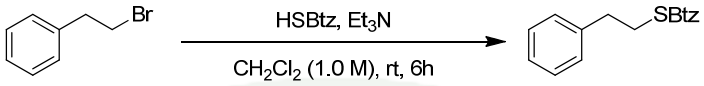
[b] Not determined

2.1.2.2 Effect of the mole ratio

Later, the ratio of Et_3N and HSBtz was examined to find the most suitable stoichiometric ratio to obtain the best %yield (Table 29).

The best result was obtained with a molar ratio of substrate, Et_3N and HSBtz of 1:1.1:0.9 equivalents, respectively (Entry 6) while decreasing the amout of both reagents afforded the desired product in lower yield (Entries 1 – 5).

Table 29 Effect of the mole ratio of NEt_3 and HSBtz for the preparation of 2-(phenethylthio) benzo[d]thiazole



(172)
0.25 mmol

(66)

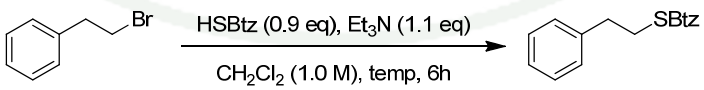
Entry	Et_3N (eq)	HSBtz (eq)	Yield (%)[a]
1	1.0	1.0	86
2	1.1	1.1	93
3	1.1	1.2	88
4	1.2	1.1	88
5	1.2	1.2	88
6	1.1	0.9	Quant

[a] Isolated yield.

2.1.2.3 Effect of reaction temperature

Effect of reaction temperature was also examined at room temperature and refluxing temperature. The results are shown in Table 30.

Table 30 Effect of the reaction temperatute for the preparation of 2-(phenethylthio) benzo[d]thiazole



(172)
0.25 mmol

(66)

Entry	Temperature	Yield (%)[a]	Entry	Temperature	Yield (%)[a]
1	Rt	Quant.	2	Reflux	71

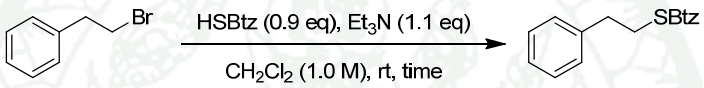
[a] Isolated yield.

The results were showed that the highest %yield was obtained when the reaction proceeded at room temperature.

2.1.2.4 Effect of reaction time

Next, the reaction time was further examined to disclose the optimum conditions. The results are shown in Table 31.

Table 31 Effect of the reaction time for the preparation of 2-(phenethylthio) benzo[d]thiazole



(172)
0.25 mmol

(66)

Entry	Time (h)	Yield (%)[a]	Entry	Time (h)	Yield (%)[a]
1	3	95	3	9	Quant.
2	6	Quant.	4	12	Quant.

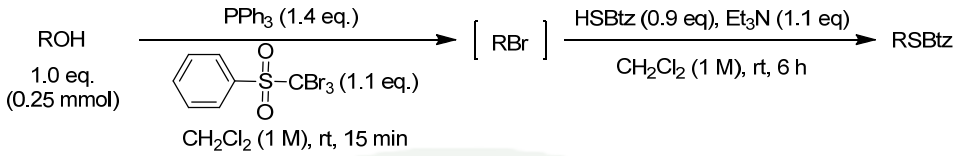
[a] Isolated yield.

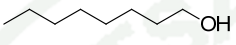
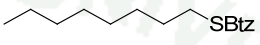
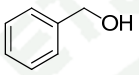
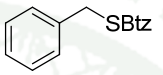
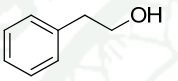
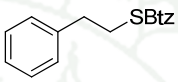
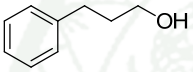
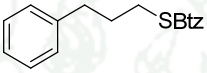
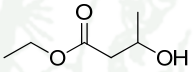
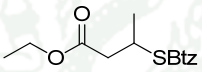
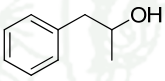
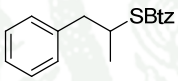
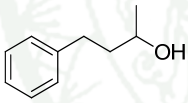
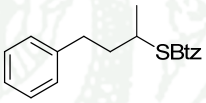
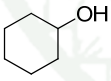
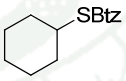
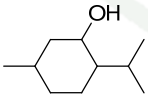
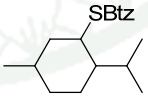
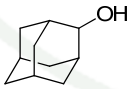
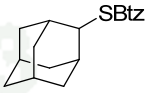
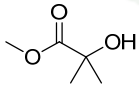
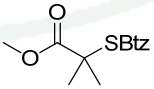
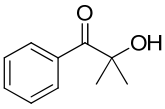
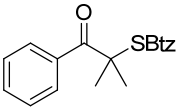
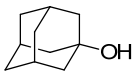
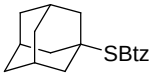
The thioetherification could afford the corresponding product in good yield when the reaction time was 6 hours (Entry 2). However, similar results were obtained in the case of 9 and 12 hours. (Entries 2 and 3). Thus, 6 hours was a suitable time for our developed method.

2.1.3 Thioetherification of various alcohols

Next, thioetherification of the various alcohols was tried in order to study the scope of this developed reaction (Table 32).

Table 32 Thioetherification of alcohols with 1,3-benzothiazole-2-thiol



Entry	Substrate		Product		Yield (%)[a]
1		**(59)**		**(60)**	89
2		**(63)**		**(64)**	82
3		**(65)**		**(66)**	75
4		**(67)**		**(68)**	75
5		**(79)**		**(80)**	ND.[b]
6		**(83)**		**(84)**	38[c]
7		**(54)**		**(58)**	54, 67[c]
8		**(93)**		**(94)**	ND.[b]
9		**(95)**		**(96)**	ND.[b]
10		**(97)**		**(98)**	ND.[b]
11		**(99)**		**(100)**	ND.[b]
12		**(101)**		**(102)**	ND.[b]
13		**(103)**		**(104)**	ND.[b]

[a] Isolated yield. [b] Not Determined.

[c] Using 1.0 mmol of alcohol

Primary and some secondary alcohols could be converted to the corresponding sulfides, 2-(alkylthio)benzo[*d*]thiazole, in moderate to high yields (entries 1 – 4 and 8 – 9). On the other hand, cyclic and tertiary alcohols did not proceed to give the corresponding sulfide products (entries 5 – 7 and 10 – 13). This was clearly explained that the steric hindrance of substituent group could affect on the rate of the substitution by nucleophile.

2.1.4 The exploration of optimum conditions for preparation 2-((4-phenylbutan-2-yl)thio)benzo[d]thiazole

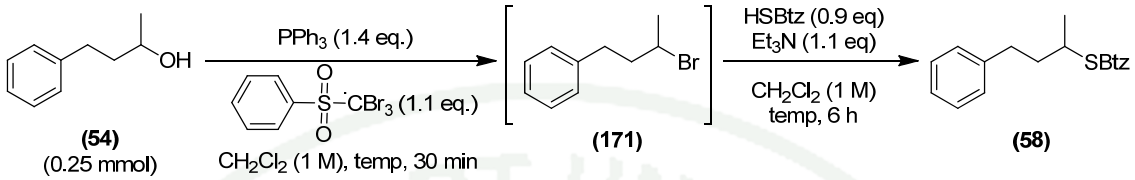
From the unsatisfactory yield of 2-((4-phenylbutan-2-yl)thio)benzo[d] thiazole **(58)** (Table 32). Concluded that our developed conditions may not be suitable conditions for this preparation. Thus, the conditions were tried to optimize again. Four parameters including the reaction temperature and reaction time were chosen to study.

2.1.4.1 Effect of reaction temperature

Both reaction temperatures in the first and the second step for generating 2-((4-phenylbutan-2-yl)thio)benzo[d]thiazole **(58)** were examined between 0 ^{o}C and room temperature as shown in Table 33.

From the results, the reaction proceeded to afford the desired product in the highest yield at 0^{o}C of both steps (Entry 1). However, it did not show a strong significant when compared with the proceeded reaction at room temperature (Entry 4). Thus, room temperature was chosen due to reaction simpler and more convenient.

Table 33 Effect of the reaction temperature for the preparation of 2-((4-phenylbutan-2-yl)thio)benzo[d]thiazole



(54) (0.25 mmol) **(171)** **(58)**

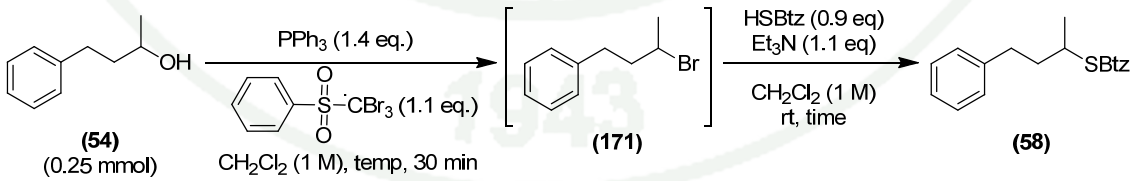
Entry	Temperature 1st step	Temperature 2nd step	Yield (%)[a]	Entry	Temperature 1st step	Temperature 2nd step	Yield (%)[a]
1	0	0	57	3	RT	0	50
2	0	RT	56	4	RTt	RT	54

[a] Isolated yield.

2.1.4.2 Effect of reaction time

Next, the reaction time of the second step was examined. The results are shown in Table 34.

Table 34 Effect of the reaction time of second step for the preparation of 2-((4-phenylbutan-2-yl)thio)benzo[d]thiazole



(54) (0.25 mmol) **(171)** **(58)**

Entry	Time (h)	Yield (%)[a]	Entry	Time (h)	Yield (%)[a]
1	6	52	3	12	53
2	9	53			

[a] Isolated yield.

The reaction proceeded to obtain the desired product in similar yield when the reaction time was compared at 6, 9 or 12 hours. Therefore, 6 hours was still a suitable time for the developed method.

2.2 Nucleophilic Substitution of Acid Halides

Acid halides have been playing an important role as intermediates for the synthesis of esters, amides and the other carboxylic derivatives. A variety reagents have been also used for the formation of these compounds from carboxylic acid directly. In this research, we developed a practical method for the preparation of esters and amides from acid halides that generated *in situ* from carboxylic acids using a new and efficient combination of triphenylphosphine (PPh_3) and halogenating agents under mild and neutral conditions.

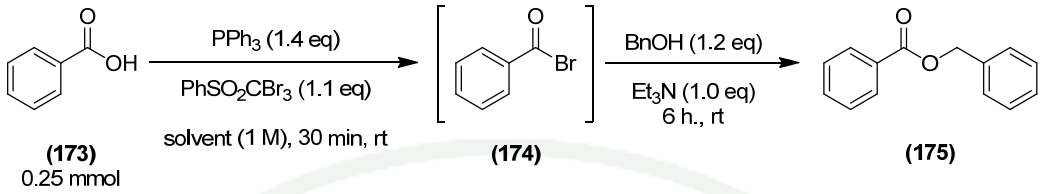
2.2.1 Optimization of the condition of the first step

2.2.1.1 Effect of solvents

According to literature reviews, CH_2Cl_2 is the most suitable solvent for this reaction. It may be because this solvent could dissolve all of substrate and reagents. However, other solvents should be investigated to examine by taking the esterification of benzoyl bromide **(174)** that derived *in situ* from benzoic acid **(173)** using triphenylphosphine and tribromomethylsulfonylbenzene ($PhSO_2CBr_3$) as a brominating agent and benzyl alcohol as a nucleophile (Table 35).

We found that CH_2Cl_2 was still the best solvent for the developed protocol because the desired product was obtained in the highest yield (Entry 1).

Table 35 Effect of solvents for the preparation of benzyl benzoate



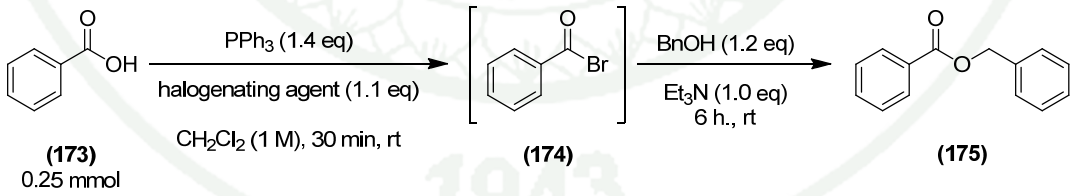
Entry	Solvent	Yield (%)[a]	Entry	Solvent	Yield (%)[a]
1	CH_2Cl_2	87	3	Toluene	77
2	$CHCl_3$	59			

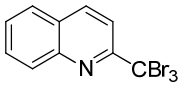
[a] Isolated Yield

2.2.1.2 Effect of halogenating agents

Significant differences in the reactivities of acid halides were mainly caused from the type of halogenating agents. To observe this assumption, selected halogenating agents was studied and the results are described in Table 36.

Table 36 Effect of halogenating agents for the preparation benzyl benzoate



Entry	Halogenating Agent	Yield (%)[a]	Entry	Halogenating Agent	Yield (%)[a]
1	$PhSO_2CBr_3$	87	5	CBr_4	79
2	Cl_3CCOCl_3	57	6	Br_3CCOOH	71
3	Cl_3CCN	50	7		49
4	Cl_3CCONH_2	63			

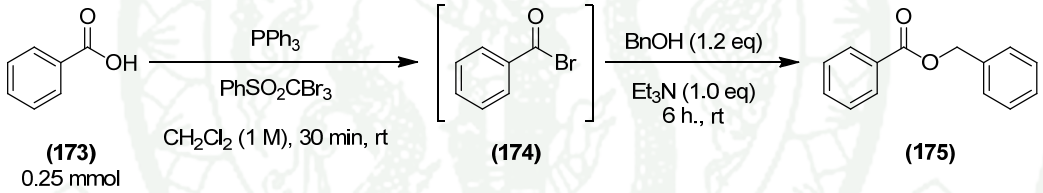
[a] Isolated Yield

According to above results, they concluded that $PhSO_2CBr_3$ could provide the desired product in the highest %yield (Entry 1). Based on the results obtained, $PhSO_2CBr_3$ was considered as the most proper halogenating agent for further study because it has not been addressed, more stable than $Cl_3CCOCCl_3$ and commercially available inexpensive reagent.

2.2.1.3 Effect of PPh_3 and $PhSO_2CBr_3$ mole ratio

The ratios of PPh_3 and $PhSO_2CBr_3$ for the synthesis of benzyl benzoate were further examined (Table 37).

Table 37 Effect of mole ratio of PPh_3 and $PhSO_2CBr_3$ for the preparation of benzyl benzoate



Entry	PPh_3 (eq)	$PhSO_2CBr_3$ (eq)	Yield (%)[a]
1	1.4	0.5	50
2	1.4	0.8	61
3	1.4	1.1	87
4	1.4	1.1	67[b]
5	1.4	1.2	67
6	1.8	1.1	72
7	1.8	1.2	65
8	2.0	2.0	64
9	2.5	2.5	30

[a] Isolated yield.

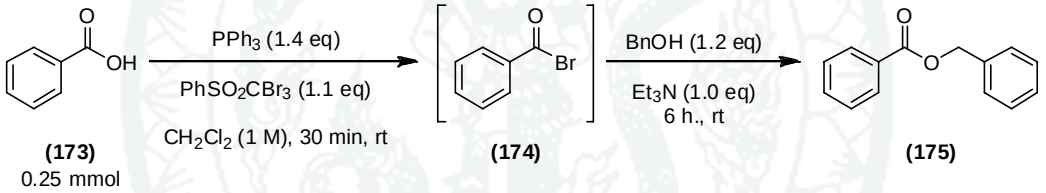
[b] The concentration of reaction was 0.5 M.

From the above results, the highest yield was accomplished when using 1.4 equivalents of PPh_3 and 1.1 equivalents of $PhSO_2CBr_3$ (Entry 3). Increasing the amount of PPh_3 and $PhSO_2CBr_3$ afforded the the desired product in moderate yields (Entries 5 – 9). It may be because of the excess reagent could converted benzyl alcohol into undesired product, benzyl bromide.

2.2.1.4 Effect of reaction time

Taking the above results into consideration, reaction time was also studied to optimize the conditions (Table 38).

Table 38 Effect of reaction time for the preparation of benzyl benzoate



(173) 0.25 mmol **(174)** **(175)**

Entry	Time (min)	Yield (%)[a]	Entry	Time (min)	Yield (%)[a]
1	15	62	3	60	76
2	30	87			

[a] Isolated Yield

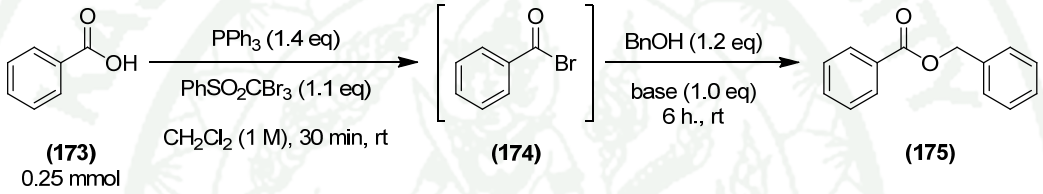
The esterification proceeded smoothly to afford the corresponding product in good yield when the reaction time was 30 minutes (Entry 2).

2.2.2 Optimization of the condition in the second step

2.2.2.1 Effect of type of bases

Et_3N is the most suitable base for our protocol This effect was studied to find out for the most suitable base that provided the maximum yield of the desired product. The results are shown in Table 39.

Table 39 Effect of the type of base for preparation benzyl benzoate



Entry	Base	Yield (%)[a]	Entry	Base	Yield (%)[a]
1	None	78	4	Pyridine	75
2	Et_3N	87	5	Piperidine	51
3	4-Picoline	59			

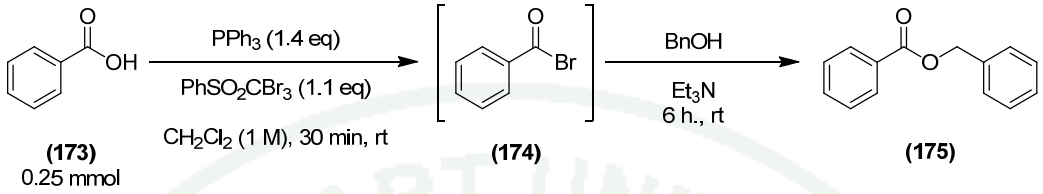
[a] Isolated Yield

From the results, the reaction could perform to give the desired product in the highest %yield in the use of Et_3N, whereas the yield decreased when three bases including 4-picoline, pyridine and piperidine were used (Entries 3 – 5).

2.2.2.2 Effect of BnOH and Et_3N mole ratio

Next, the ratios of BnOH and Et_3N for the preparation of benzyl benzoate were examined (Table 40).

Table 40 Effect of the molar ratio of BnOH and Et_3N for the preparation of benzyl benzoate



Entry	BnOH (eq)	Et_3N (eq)	Yield (%)[a]
1	1.0	1.0	85, 90[b]
2	1.0	3.0	73
3	1.2	1.0	88
4	1.2	1.2	67
5	1.2	3.0	76
6	1.5	1.0	72
7	1.5	1.2	70
8	1.2	3.0	76

[a] Isolated yield.

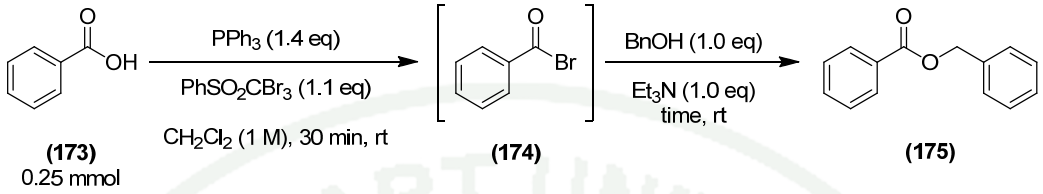
[b] 0.5 mmol of benzoic acid was used.

The results were showed that the best of mole ratio of BnOH and Et_3N was 1.0 and 1.0 equivalent, respectively (Entry 1). On the other hand, the yields were slightly decreased when both compounds were used in greater excess (Entries 2 – 7).

2.2.2.3 Effect of reaction time

Taking the above results into consideration, reactions time was also studied to find out for the optimized conditions that provided the maximum yield of benzyl benzoate (Table 41).

Table 41 Effect of the reaction time in the second step for preparation benzyl benzoate



Entry	Time (h)	Yield (%)[a]	Entry	Time (h)	Yield (%)[a]
1	3	64	3	9	87
2	6	85, 90[b]	4	12	87

[a] Isolated yield.

[b] 0.5 mmol of benzoic acid was used.

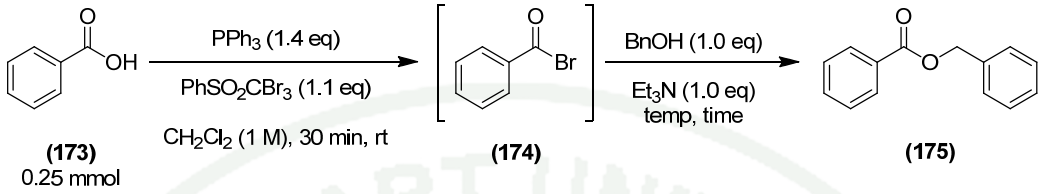
It was found that the estererification could perform to afford the desired product in good yield when the reaction time was 6 hours (Entry 2). However, longer reaction time did not effect to %yield of the desired product (Entries 3 and 4).

2.2.2.4 Effect of the reaction temperature

From the above results, the reaction temperature was further studied to find out for the optimized conditions (Table 42).

From the results, the desired product was obtained in good yield when the reaction temperature was room temperature for 6 hours (Entry 1). However, the result was similarly obtained in the case of refluxing temperature for 3 hours (Entry 4).

Table 42 Effect of the reaction temperature in second step for preparation benzyl benzoate



Entry	Temperature	Time (h)	Yield[a] (%)
1	RT	6	85, 90[b]
2	Reflux	1	80[b]
3	Reflux	2	81[b]
4	Reflux	3	88[b]

[a] Isolated yield.

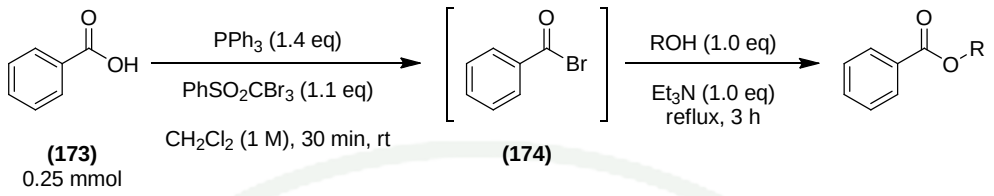
[b] 0.5 mmol of benzoic acid was used.

2.2.3 Esterification of benzoic acid and various alcohols

Next, one pot esterification of carboxylic acids and alcohols via acid bromides was tried in order to examine the scope of this developed protocol (Table 43).

Primary and secondary alcohols could be converted to the corresponding esters in moderate to high yields (Entries 1 – 5). Similar results were obtained in the case of cyclic alcohols (Entries 6 – 8) whereas tertiary alcohols were transformed to the desired product in moderate yields (Entries 9 – 11). Moreover, the case of phenols containing electron donating group afforded the corresponding products in higher yield than phenols containing electron withdrawing group (Entries 12 – 14).

Table 43 Esterification of benzoic acid and various alcohols



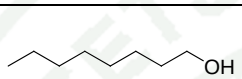
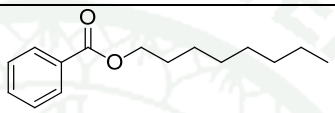
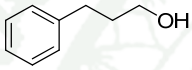
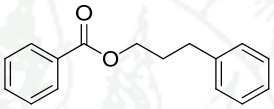
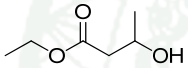
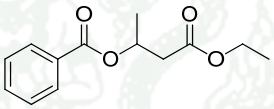
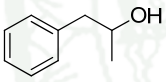
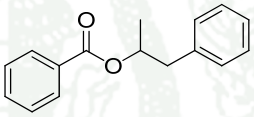
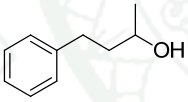
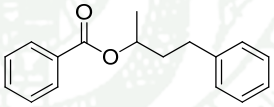
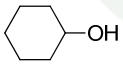
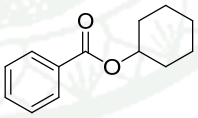
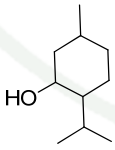
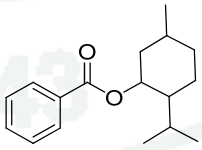
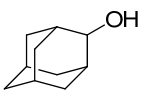
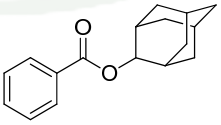
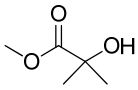
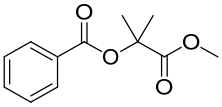
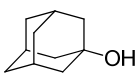
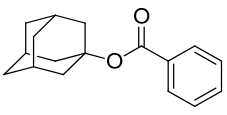
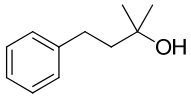
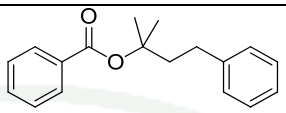
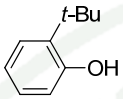
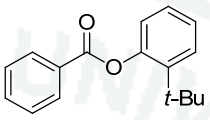
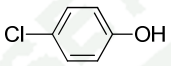
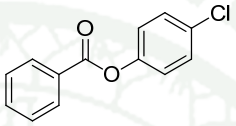
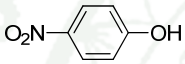
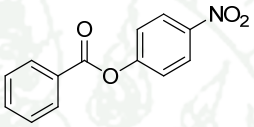
Entry	Substrate		Product		Yield (%)[a]
1		**(59)**		**(176)**	80, 84[b]
2		**(67)**		**(177)**	85, 87[b]
3		**(79)**		**(178)**	67
4		**(81)**		**(179)**	71, 76[b]
5		**(54)**		**(180)**	76, 85[b]
6		**(93)**		**(181)**	72, 97[b]
7		**(95)**		**(182)**	78, 80[b]
8		**(97)**		**(183)**	61, 77[b]
9		**(99)**		**(184)**	56
10		**(103)**		**(185)**	50, 66[b]

Table 42 (Continued)

Entry	Substrate		Product		Yield (%)[a]
11		**(113)**		**(186)**	46, 48[b]
12		**(187)**		**(188)**	91, 92[b]
13		**(189)**		**(190)**	60
14		**(191)**		**(192)**	56[b]

[a] Isolated Yield.

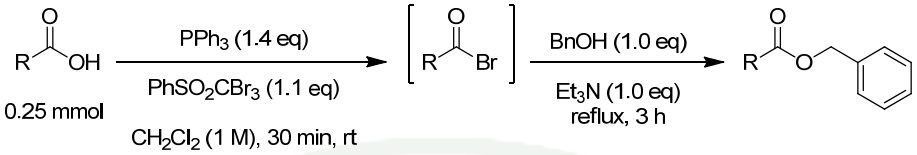
[b] 0.5 mmol of benzoic acid was used.

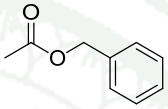
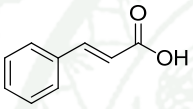
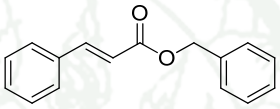
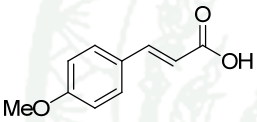
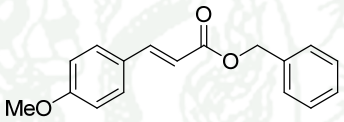
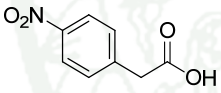
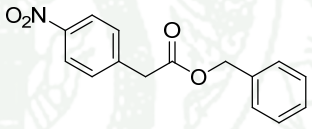
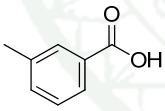
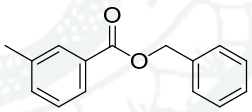
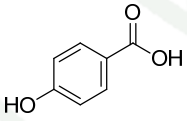
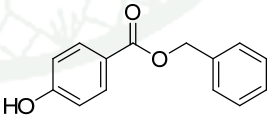
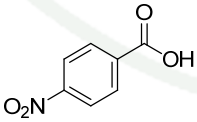
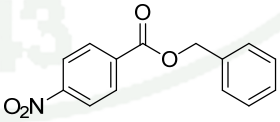
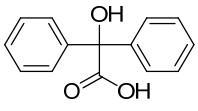
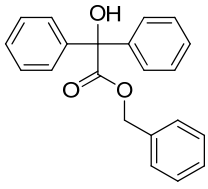
2.2.4 Esterification of various carboxylic acids and benzyl alcohol

Esterification of various carboxylic acids under the optimized conditions was also examined. The results are summarized in Table 44.

Almost carboxylic acids could be converted to the corresponding esters in good yields. However, the case of acetic acid and carboxylic acids containing hydroxyl group did not proceed to obtain the corresponding products (Entries 1, 6 and 8).

Table 44 Esterification of various carboxylic acids and benzyl alcohol



Entry	Substrate		Product		Yield (%)[a]
1		**(193)**		**(194)**	ND[b]
2		**(195)**		**(196)**	75
3		**(197)**		**(198)**	72
4		**(199)**		**(200)**	ND[b]
5		**(201)**		**(202)**	94
6		**(203)**		**(204)**	ND[b]
7		**(205)**		**(206)**	57
8		**(207)**		**(208)**	ND[b]

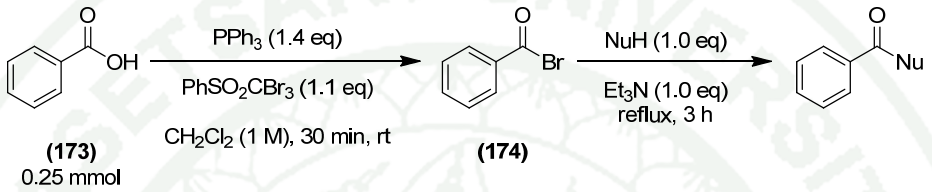
[a] Isolated Yield.

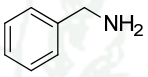
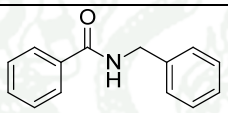
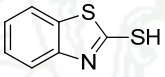
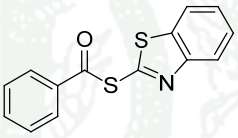
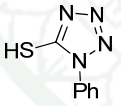
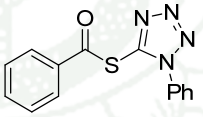
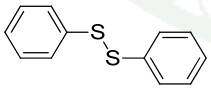
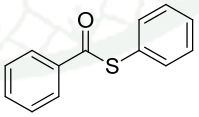
[b] Not detected

2.2.5 Reaction of benzyl bromide with other nucleophiles

The reaction of benzoic acid with other nucleophiles was also tried to study the scope of nucleophiles under the present conditions (Table 45).

Table 45 Reaction of benzyl bromide with other nucleophiles



Entry	Nucleophile	Product		Yield (%)[a]
1			**(209)**	85
2			**(210)**	ND[b]
3			**(211)**	ND[b]
4			**(212)**	ND[b]

[a] Isolated Yield.

[b] Not detected

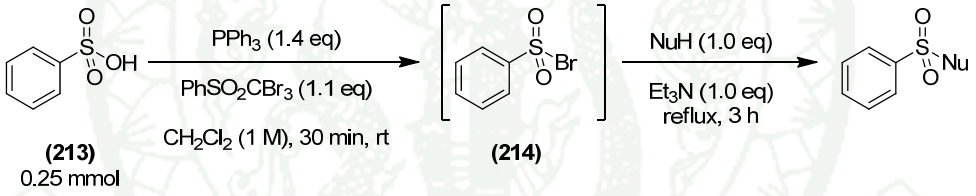
Unfortunately, the desired product did not obtain when three sulfur nucleophiles were applied under standard conditions. It was postulated that sulfur nucleophile could react with the combination reagents to give the unidentified product (Entries 2 – 4). However, the reaction of carboxylic acid and benzylamine as a nitrogen nucleophile could proceed to give the corresponding product in 85% yield (Entry 1).

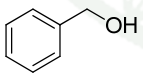
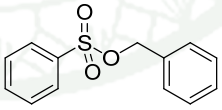
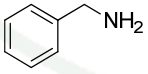
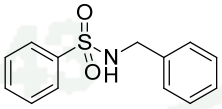
2.2.6 Using phenylsulfonic acid as a substrate

The organosulfonic aic derivatives are one of the most familiar compounds which have several pharmaceutical applications at present such as using as effective drugs against malaria or infections in patients with AIDS discoid lupus erythematosus. Thus, this research topic would extend our protocol to be applied for the sulfonylation with various nucleophiles such as alcohols or amines.

For this study, benzenesulfonic acid was chosen as a model substrate for esterification and amidation with benzyl alcohol and benzylamine, respectively as a nucleophile under the developed conditions (Table 46).

Table 46 The reaction of benzenesulfonic acid with benzyl alcohol and benzylamine



Entry	Nucleophile	Product		Yield (%)[a]
1			**(215)**	ND[b]
2			**(216)**	ND[b]

[a] Isolated Yield.

[b] Not detected.

The results were found that the reaction of benzenesulfonic acid with benzyl alcohol or benzylamine could not afford the corresponding products under the developed protocol.

2.3 Nucleophilic Aromatic Substitution of Phenol Derivatives

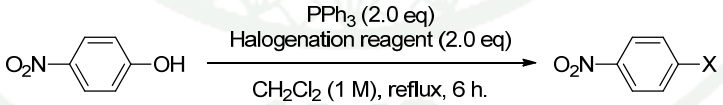
From the literature reviews, phenol and derivatives could be converted to halobenzenes by nucleophilic aromatic substitution (S_NAr) using halogenating agent such as PCl_3, $POCl_3$ or PBr_3. However, the use of triphenylphosphine and halogenating agents has not been reported to date. Therefore, the combination reagents were further studied for their efficiency for halogenation of phenol derivatives.

In this study, phenol with nitro substituent was used as a model substrate for halogenations because the non-electron-deficient benzene derivatives are intrinsically reluctant to participate in S_NAr reactions.

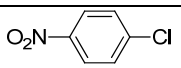
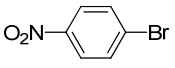
2.3.1 Reaction of 4-nitrophenol with PPh_3 and halogenating agent

In the first place, PPh_3 and halogenating agent was examined to convert 4-nitrophenol to the corresponding halobenzenes. The results are shown in Table 47.

Table 47 Reaction of 4-nitrophenol with PPh_3 and halogenating agent



(217)
0.25 mmol

Entry	Halogenating agent	Product		Recovery Phenol (%)[a]	%Yield [a]
1	Cl_3CCN		**(218)**	95	NR[b]
2	CBr_4		**(219)**	82	NR[b]

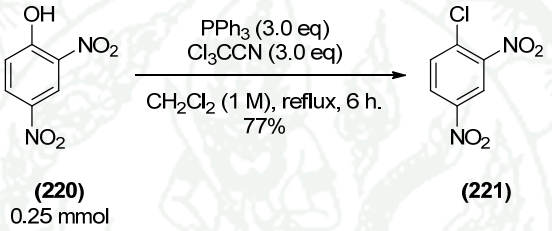
[a] Isolated Yield.

[b] No reaction.

Surprisingly, the both reactions did not proceed to detect the corresponding products when reactions were done under the developed conditions.

2.3.2 Reaction of 2,4-dinitrophenol with halogenating agent

According to the aforementioned results, 2,4-dinitrophenol was chosen as a substrate instead of 4-nitrophenol. Under same conditions, the chlorination could perform to afford the desired product in 77 %yield as shown in the Scheme 55.



Scheme 55 Preparation of 2,4-dinitrochlorobenzene from 2,4-dinitrophenol

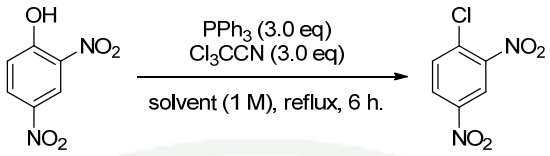
Next, Variable parameters for the halogenation of 2,4-dinitrophenol including type of solvent, reaction temperature, type of halogenating agents, mole ratio of PPh_3 and halogenating agent and reaction time were optimized as follows.

2.3.2.1 Effect of solvent

Common solvents were chosen to examine whether they could proceed in this halogenation. The results are presented in Table 48.

The results were found that the desire product was obtained in the highest yield in the case of toluene (Entry 4). In contrast, the %yields of the desired product were decreased when CH_2Cl_2, DMF, $ClCH_2CH_2Cl$, THF and CH_3CN were used (Entries 1– 3, 5 and 6).

Table 48 Effect of the solvent for preparation 2,4-dinitro chlorobenzene



(220)
0.25 mmol

(221)

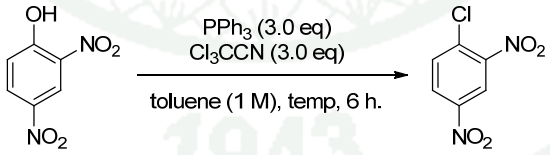
Entry	Solvent	Yield (%)[a]	Entry	Solvent	Yield (%)[a]
1	CH_2Cl_2	77	4	Toluene	94
2	DMF	39	5	THF	84
3	$ClCH_2CH_2Cl$	85	6	CH_3CN	75

[a] Isolated Yield

2.3.2.2 Effect of reaction temperature

Effect of reaction temperature was further examined at room temperature and refluxing temperature. The results are shown in Table 49.

Table 49 Effect of the temperature for preparation 2,4-dinitro chlorobenzene



(220)
0.25 mmol

(221)

Entry	Temperature	Yield (%)[a]	Entry	Temperature	Yield (%)[a]
1	Reflux	94	2	Rt	33

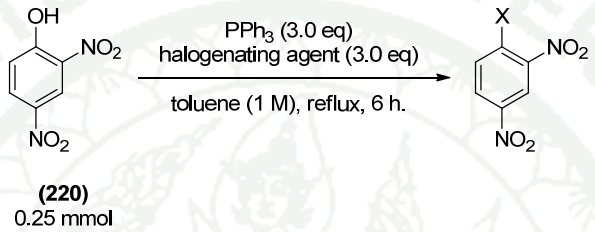
[a] Isolated Yield.

It was found that this chlorination still required high temperature because the highest %yield was obtained at refluxing temperature.

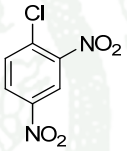
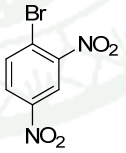
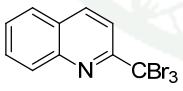
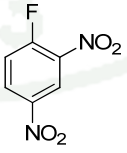
2.3.2.3 Effect of halogenating agent

The efficiency of halogenating agents in combination with PPh_3 for the conversion of 2,4-dinitrophenol into 2,4-dinitro halobenzene was examined (Table 50).

Table 50 Effect of halogenating agents for preparation 2,4-dinitro halobenzene



(220)
0.25 mmol

Entry	Halogenating agent	Product		Yield (%)[a]
1	Cl_3CCN		**(221)**	94
2	$Cl_3CCOCCl_3$			93
3	Cl_3CCONH_2			21
4	Cl_3CCOOH			14
5	Br_3CCOOH			9
6	CBr_4		**(222)**	69
7				58
8	$PhSO_2CBr_3$			21
9	F_3CCOCF_3		**(223)**	0

[a] Isolated yield.

[b] Not detected.

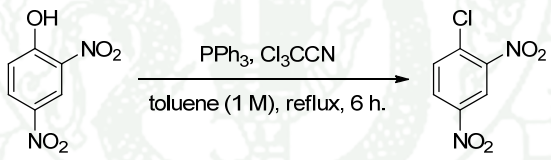
Using a ratio of alcohol:PPh_3:halogenating agent of 1:3:3 equivalents, the efficiency of chlorinating agent greatly depended on the type of chlorinating agent. The reagents that bearing electron withdrawing groups, -CN and

-$COCCl_3$ (Entries 1 and 2) gave the desired product in high yields while Cl_3CCONH_2 and Cl_3CCOOH (Entries 3 – 4) gave low yields. In the case of bromination, carbontetrabromide (Entry 6) and 2-(tribromomethyl)quinoline (Entry 7) gave the desired product in the moderate yields whereas the use of Br_3CCOOH and $PhSO_2CBr_3$ (Entries 5 – 8) did not give the good results. In addition, F_3CCOCF_3 as a fluorinating agent was also tried to study, however, the fluorination did not proceed (Entry 9).

2.3.2.4 Effect of PPh_3 and Cl_3CCN ratio

The quantities of PPh_3 and Cl_3CCN were varied to find a suitable ratio to provide the maximum yield of 2,4-dinitrochlorophenol **(221)** as shown in Table 51.

Table 51 Effect of PPh_3 and Cl_3CCN ratio for preparation of 2,4-dinitrochlorophenol



(220)
0.25 mmol

(221)

Entry	PPh_3 (eq)	Cl_3CCN (eq)	Yield[a] (%)
1	1.0	1.0	39
2	1.0	1.5	49
3	1.0	2.0	61
4	1.2	1.2	44
5	1.5	1.5	54
6	2.0	1.2	90
7	2.0	1.5	93, 97[b]
8	2.0	2.0	69, 79[b]
9	2.5	2.0	82

Table 51 (Continued)

Entry	PPh_3 (eq)	Cl_3CCN (eq)	Yield[a] (%)
10	2.5	2.5	74, 86[b]
11	3.0	2.5	92
12	3.0	3.0	94

[a] Isolated yield.

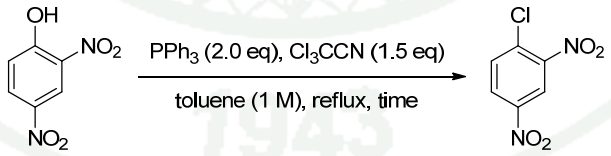
[b] Used 1.0 mmol of 2,4-dinitrophenol

The use of PPh_3 and Cl_3CCN in a 1:1 ratio furnished the desired product in moderate yield (Entry 1). Increasing the amount of PPh_3 and Cl_3CCN over 1 equivalent elevated the yield. The appropriate ratio of PPh_3:Cl_3CCN was 2.0:1.5 (Entry 7).

2.3.2.5 Effect of reaction time

Next, the reaction time was further examined. The results are shown in Table 52.

Table 52 Effect of the reaction time for preparation 2,4-dinitrochlorophenol



(220)
0.25 mmol

(221)

Entry	Time (h)	Yield (%)[a]	Entry	Time (h)	Yield (%)[a]
1	3	88	3	9	94
2	6	93			

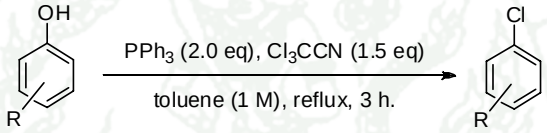
[a] Isolated Yield.

The chlorination could proceed to the desired product in the highest yield when the reaction time was set to 9 hours (Entry 3). However, the result was similarly as obtained in the case of 6 hours (Entry 2). Therefore, 6 hours was a suitable time for next study.

2.3.2.6 Electrophilic aromatic substitution of phenol derivatives

This optimized reaction conditions were utilized in a study on the scope of the conversion of various 2,4-disubstituted phenols (Table 53).

Table 53 Reaction of phenol derivatives with PPh_3 and Cl_3CCN



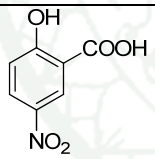
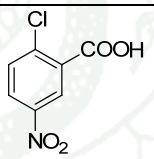
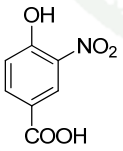
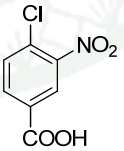
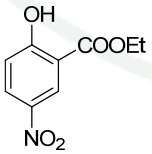
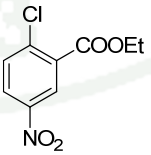
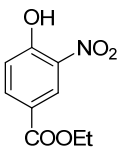
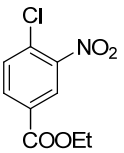
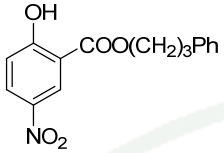
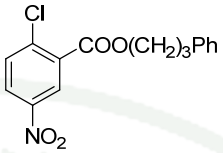
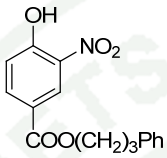
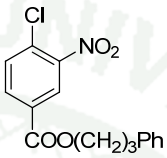
Entry	Substrate		Product		Yield (%)[a]
1		**(224)**		**(225)**	44
2		**(226)**		**(227)**	ND[b]
3		**(228)**		**(229)**	67
4		**(230)**		**(231)**	72

Table 53 (Continued)

Entry	Substrate		Product		Yield (%)[a]
5		**(232)**		**(233)**	53
6		**(234)**		**(235)**	49

[a] Isolated yield.

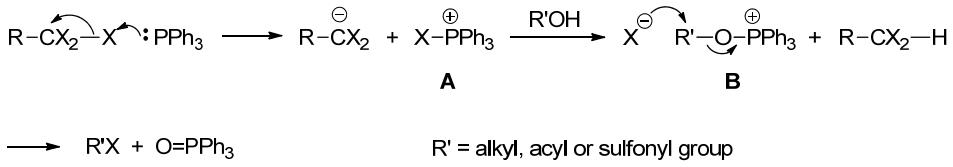
[b] Not detected

From the above results, the protected carboxyl group phenol derivatives (Entries 3 – 6) could be converted into the corresponding products in moderate to high yields. However, the phenols containing carboxyl substituent on the aromatic ring gave the desired product in very low yield (Entries 1 and 2). It may be because of side reaction that the carboxyl group could react with PPh_3 and Cl_3CCN to give the corresponding acid chloride.

2.4 Proposed the mechanism

2.4.1 The proposed mechanism of halogenation of alcohols, carboxylic acids and sulfonic acids with PPh_3 and halogenating agents

The proposed mechanism for the conversion of alcohols, carboxylic acids and sulfonic acids into their corresponding halides using PPh_3 and halogenating agent is shown in Scheme 56.

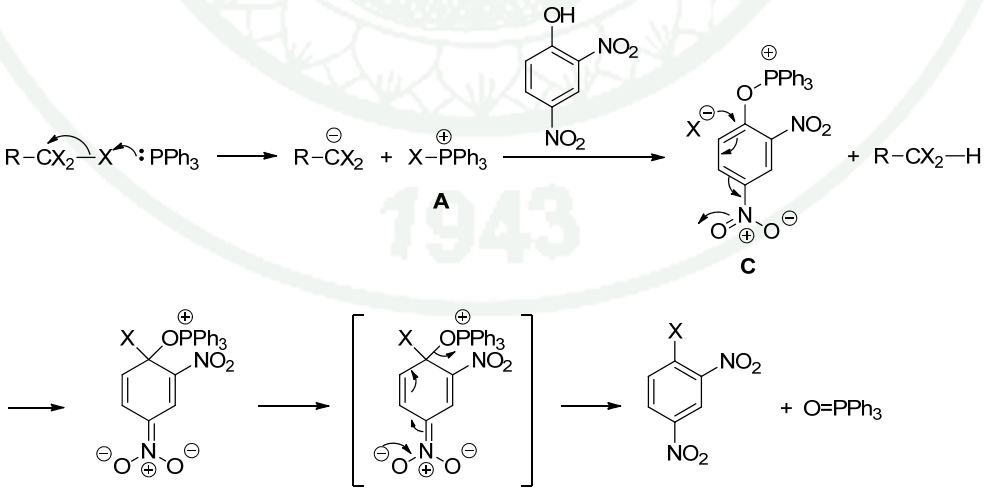


Scheme 56 The mechanism of halogenation of alcohols, carboxylic acids and sulfonic acids with PPh_3 and halogenating agents

The initial step is the reaction between PPh_3 and halogenating agent to form the intermediate **A** which subsequently reacted with hydroxyl group of alcohols, carboxylic acids or sulfonic acids yielding a phosphonium salt **B**, the latter then transformed to the corresponding halide by nucleophilic substitution.

2.4.2 The proposed mechanism of nucleophilic aromatic substitution of phenol derivatives with PPh_3 and halogenating agent

The proposed mechanism for the conversion of electron deficient phenol derivatives into their corresponding halobenzene using PPh_3 and halogenating agent is shown in Scheme 57.



Scheme 57 The proposed mechanism of nucleophilic aromatic substitution of phenol derivatives

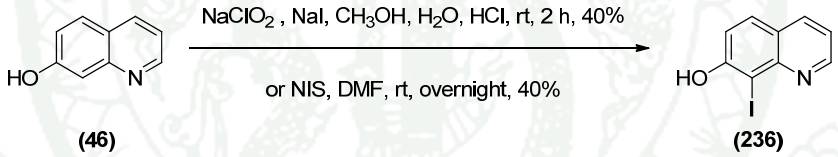
The initial step is the reaction between PPh_3 and halogenating agent to form the intermediate **A** which subsequently reacted with phenol derivatives yielding an arylphosphonium salt **C**. After that, the addition of the halide formed a resonance-stabilized carbanion with a new carbon-halogen bond with three resonance structures. Finally, loss of the triphenylphosphine oxide re-formed the aromatic ring.

3. Synthesis the 7,7'-dihydroxy-8,8'-biquinoline (azaBINOL) and its derivatives

3.1 Synthesis the 7,7'-dihydroxy-8,8'-biquinoline (azaBINOL)

As seen in the introduction, the synthesis of Skraup quinoline represents an effective commercial method for preparation of many quinolines (Bradford, 1947). Due to the limited commercial availability of 7-hydroxyquinoline **(46)**, its synthesis *via* Skraup reaction was explored as shown in Scheme 43, however, the 7-hydroxy quinoline was commercially available.

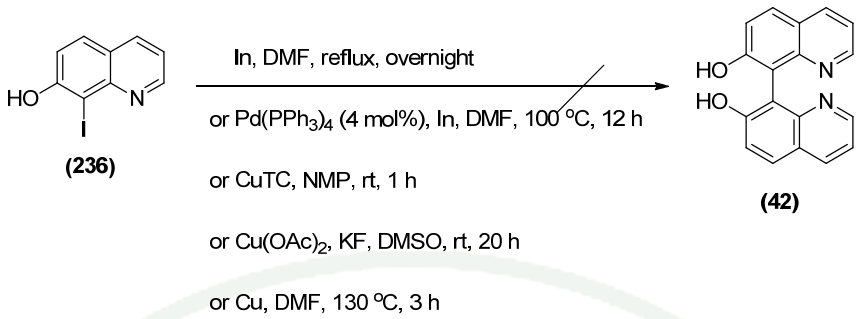
From this, the synthesis of 7-hydroxy-8-iodoquinoline **(236)** from 7-hydroxy quinoline **(46)** was tried by using $NaClO_2$/NaI or NIS (Scheme 57) because we attempt to prepare 7,7'-dihydroxy-8,8'-biquinoline **(42)** by using Ullmann coupling reaction.



(46) **(236)**

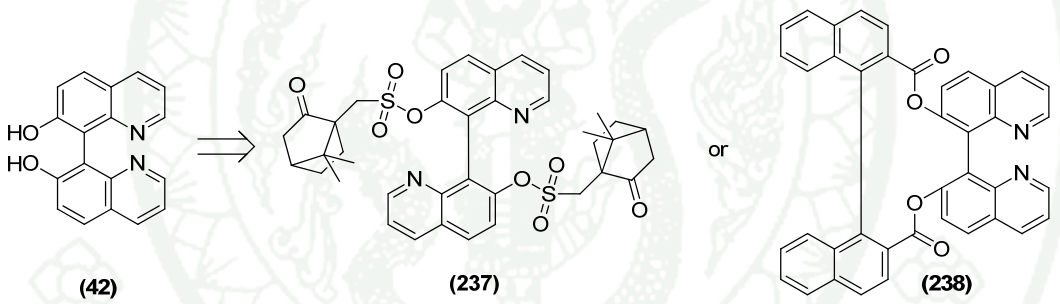
Scheme 58 Preparation of 7-hydroxy-8-iodoquinoline **(236)**

Accordingly, synthesis of 7,7'-dihydroxy-8,8'-biquinoline **(42)** was tried by using various reagents such as In (Ranu, 1998), $Pd(PPh_3)_4$/In (Chang, 2005), Copper(I)-thiophene-2-carboxylate with *N*-Methyl-2-pyrrolidone (CuTC/NMP) (Zhang, 1997), $Cu(OAc)_2$/KF (Qiang, 2012) and Cu (Blakemore, 2005) (Scheme 58). Unfortunately, the coupling reactions using the reagents as above-mentioned did not proceed to give the desired product there may be due to the interference from the basic quinoline nitrogen atom and the known difficulties associated with oxidizing electron-deficient phenols in the desired manner.



Scheme 59 The failure reaction for synthesis of 7,7'-dihydroxy-8,8'-biquinoline

Moreover, preparation of azaBINOL **(42)** was also attempted by cleavage the hydroxyl protecting group for separation the diastereomer. In our protocol, we used menthylsulfonyl and binaphthyl macrocylcic groups (Scheme 60).

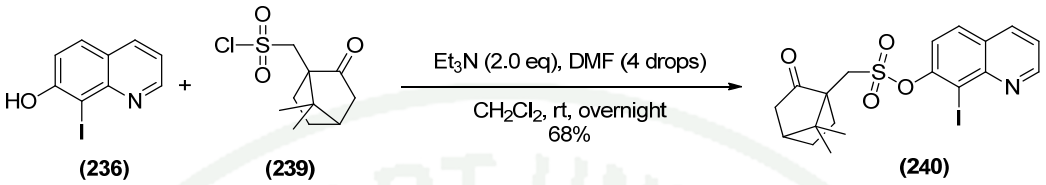


Scheme 60 Retrosynthesis for preparation azaBINOL (42) from menthylsulfonyl derivative and binapthyl macrocyclic group

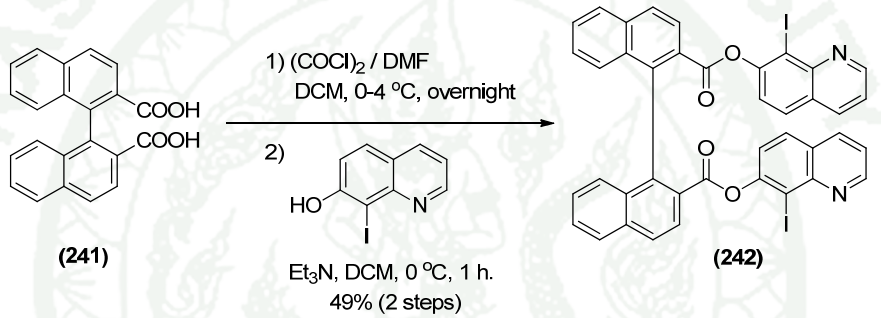
In the first, the [8,8'-biquinoline]-7,7'-diyl bis((7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonate) **(237)** and dinaphtho[2',1':8,9;1",2":10,11][1,6]dioxacyclododecino[2,3-h:5,4-h'] diquinoline-12,25-dione **(238)**, were tried to synthesize for being the substrate for optical resolution procedure.

The preparations of menthylsulfonyl derivative **(237)** and binapthyl macrocyclic group **(238)** were started by preparing their precursor including the 8-iodoquinolin-7-yl (7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonate

(240) and bis(8-iodoquinolin-7-yl) [1,1'-binaphthalene]-2,2'-dicarboxylate **(242)**, respectively (Scheme 61 and 62).

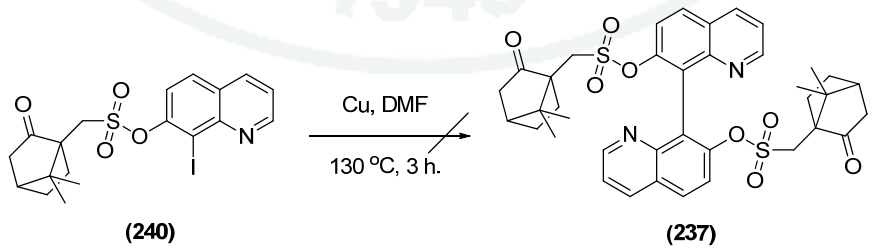


Scheme 61 Preparation of precursor for synthesizing the menthylsulfonyl derivative

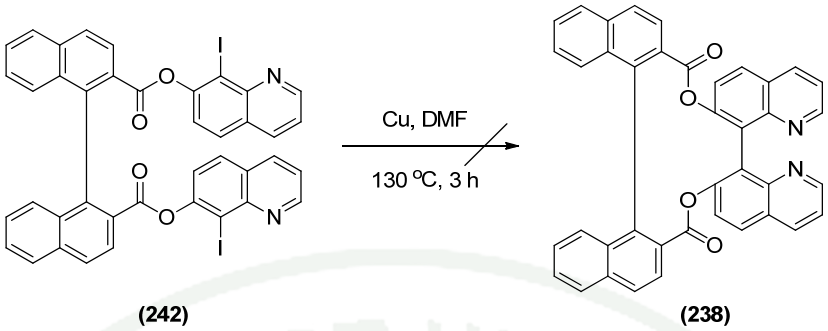


Scheme 62 Preparation of precursor of for synthesizing the binapthyl macrocyclic group

Unfortunately, the desired product **(237)** and **(238)** were not detected when the Ullmann coupling condition was applied. This may be due to the steric hindrance of menthyl and binapthyl macrocyclic groups (Scheme 63 and 64).



Scheme 63 Preparation of menthylsulfonyl derivative

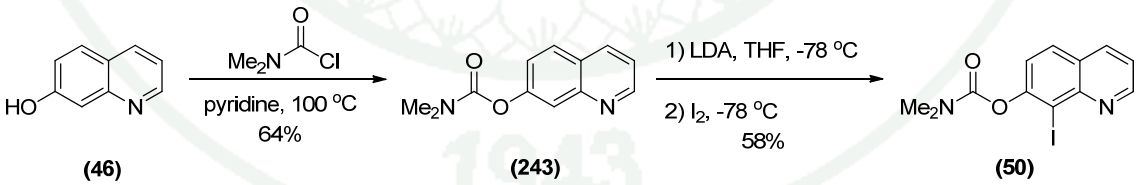


(242) (238)

Scheme 64 Preparation of binapthyl macrocyclic group

The failure to produce azaBINOL **(42)** under the above conditions showed that the properties and chemistry between BINOL **(19)** and azaBINOL **(42)** are entirely different. It led to the development by other routes for the synthesis. The directed *ortho* metallation (DoM) is a well known process in the literatures (Sniekus, 1990)

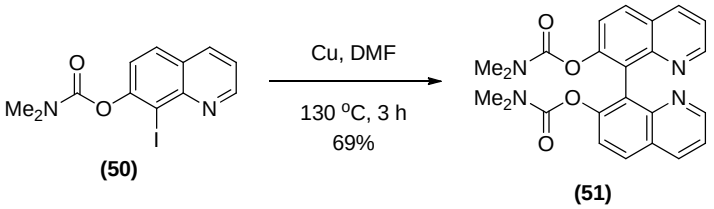
To perform the DoM, the hydroxyl group in 7-hydroxyquinoline **(46)** was protected as carbamate **(243)**. After that, it was transformed into 8-iodoquinolin-7-yl-dimethylcarbamate **(50)** by metalation with LDA and subsequent treatment with iodide (Scheme 65).



(46) (243) (50)

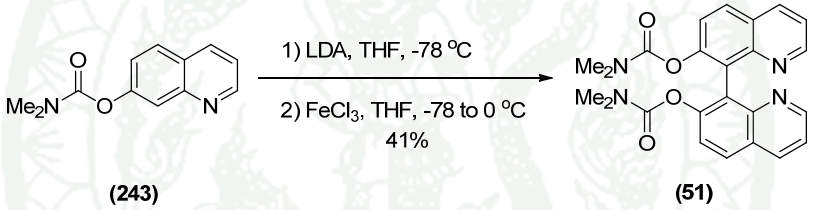
Scheme 65 Preparation of 8-iodoquinolin-7-yl-dimethylcarbamate

Next, the Ullmann coupling reaction condition using copper at high temperature was applied to 8-iodoquinolin-7-yl dimethylcarbamate **(50)**. The reaction could proceed to form [8,8'-biquinoline]-7,7'-diyl bis(dimethylcarbamate) **(51)** in 68 %yield (Scheme 66).



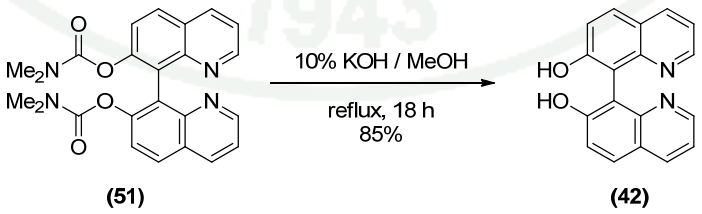
Scheme 66 Preparation of [8,8'-biquinoline]-7,7'-diyl bis(dimethylcarbamate) under Ullmann coupling condition

Moreover, the bis(dimethylcarbamate) **(51)** could be prepared directly from *N,N*-dimethyl *O*-(quinol-7-yl) carbamate **(243)** by using *in situ* oxidative coupling of the 8-lithio intermediate with $FeCl_3$ (Scheme 67).



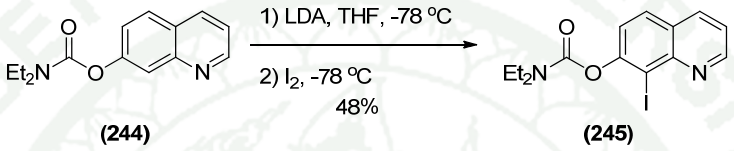
Scheme 67 Preparation of [8,8'-biquinoline]-7,7'-diyl bis(dimethylcarbamate) under oxidative coupling condition

Then, hydrolysis of bis(dimethylcarbamate) **(51)** using methanolic potassium hydroxide proceeded to yield the azaBINOL **(42)** as shown in Scheme 68.

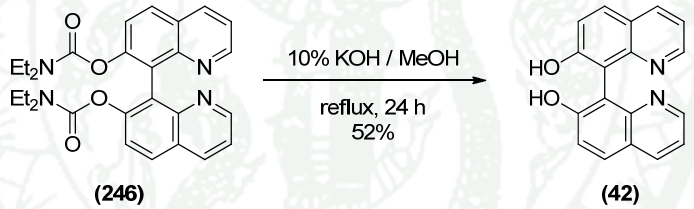


Scheme 68 Hydrolysis of bis(dimethylcarbamate)

Accordingly, the preparation of 8-iodoquinolin-7-yl diethylcarbamate **(245)** prepared from *N,N*-diethyl *O*-(quinol-7-yl) carbamate **(244)** and hydrolysis of [8,8'-biquinoline]-7,7'-diyl bis(diethylcarbamate) **(246)** were also tried to synthesize the azaBINOL**(42)** because we need to compare that which one was the best method. However, using [8,8'-biquinoline]-7,7'-diyl bis(diethyl carbamate) **(246)** afforded the corresponding products in lower yield. This may be because of the steric hindrance from the ethyl group (Scheme 69 and 70).



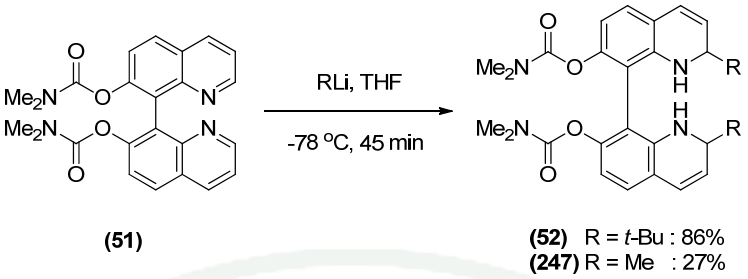
Scheme 69 Preparation of 8-iodoquinolin-7-yl-diethylcarbamate



Scheme 70 Hydrolysis of bis(diethylcarbamate)

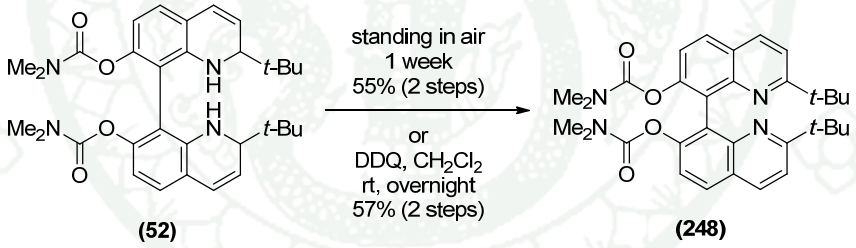
3.2 Synthesis of 7,7'-dihydroxy-8,8'-biquinoline (azaBINOL) derivatives

Introduction of substituents to C2 position of quinoline is easily achieved by nucleophilic addition of an organolithium reagent and followed by oxidative re-aromatization of the resulting dihydroquinoline. Accordingly, *t*-BuLi and MeLi were added to bis(dimethylcarbamate) **(51)** to afford 2,2'-di-*tert*-butyl-1,1',2,2'-tetrahydro-[8,8'-biquinoline]-7,7'-diyl bis(dimethylcarbamate) **(52)** and 2,2'-dimethyl-1,1',2,2'-tetrahydro-[8,8'-biquinoline]-7,7'-diyl bis(dimethylcarbamate) **(247)**, respectively (Scheme 71). However, the dihydroquinoline products were not completely oxidized.

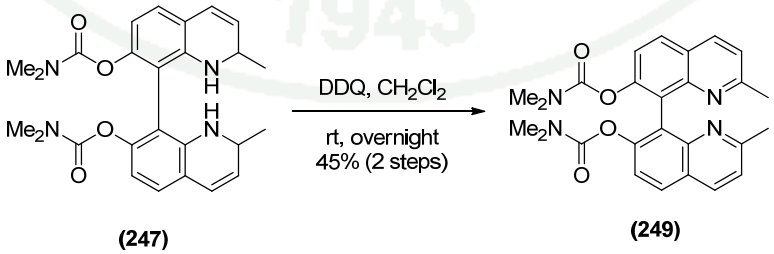


Scheme 71 Introduction of *t*-Bu or Me group to C2 position of bis(dimethyl carbamate) **(51)**

Then, dihydroquinolines **52** and **247** was re-aromatized to the completely biquinoline, 2,2'-di-*tert*-butyl-[8,8'-biquinoline]-7,7'-diyl bis(dimethyl carbamate) **(248)** and 2,2'-dimethyl-[8,8'-biquinoline]-7,7'-diyl bis(dimethyl carbamate) **(249)**, respectively by standing in air or reacting with DDQ (Scheme 72 and Scheme 73).

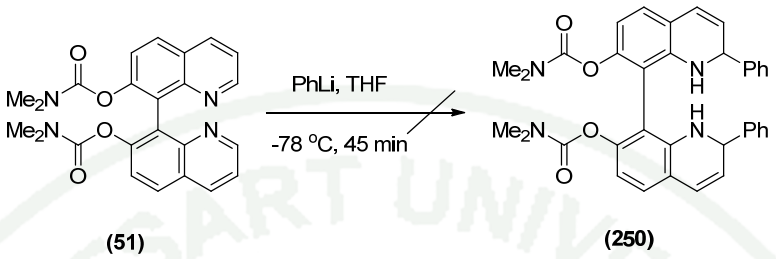


Scheme 72 Re-aromatized of dihydroquinolines **(52)**



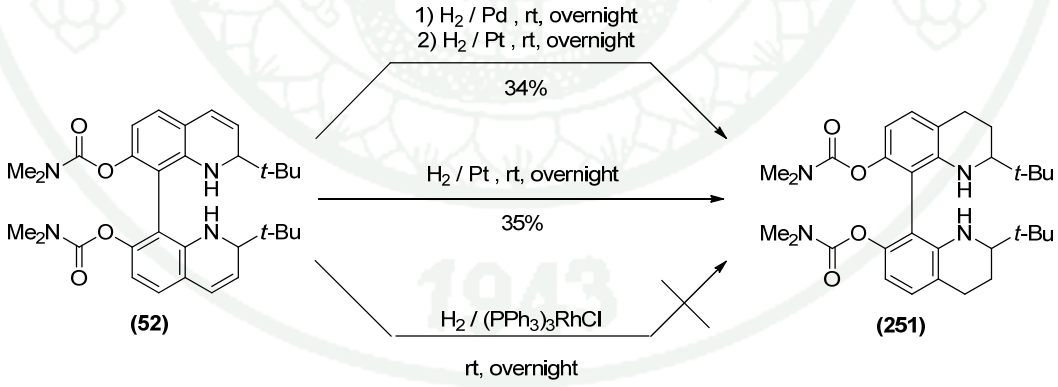
Scheme 73 Re-aromatized of dihydroquinolines **(247)**

In contrast, the desired product was not detected when PhLi was used instead of *t*-BuLi and MeLi (Scheme 74).



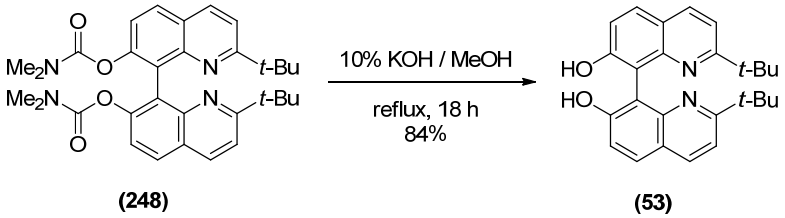
Scheme 74 The failure reaction for introduction of phenyl group to C2 position of bis(dimethylcarbamate) **(51)**

Then, 2,2'-di-*ter*t-butyl-1,1',2,2'-tetrahydro-[8,8'-biquinoline]-7,7'-diyl bis (dimethylcarbamate) **(52)** could be reduced in the presence of H_2/Pt to give the bistetrahydroquinoline **(251)**. Furthermore, this starting compound was also tried to reduce by using Wilkinson's catalyst, however, the reaction was unsuccessful (Scheme 75).



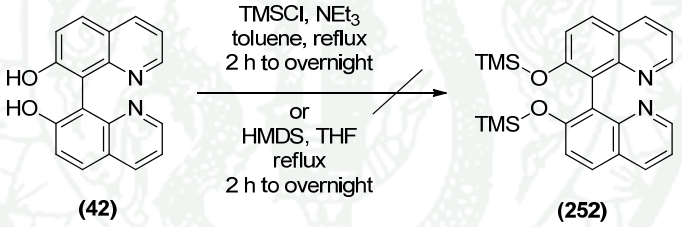
Scheme 75 Hydrogenation of tetrahydroquinolyl carbamate **(52)**

Basic hydrolysis of bis(dimethylcarbamate) **(248)** was further examined to cleave the carbomoyl group to obtain the azaBINOL derivative, 2,2'-di-*tert*-butyl-[8,8'-biquinoline]-7,7'-diol **(53)** in good yield (Scheme 76).

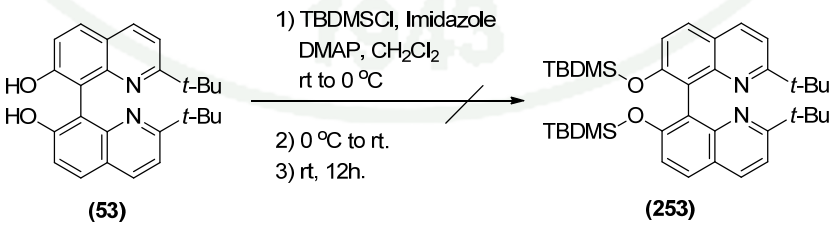


Scheme 76 Basic hydrolysis of bis(dimethylcarbamate) **(248)**

In addition, two hydroxyl groups of azaBINOL **(42)** were tried to protect with TMS group using TMSCl (Assié, 2010) or HMDS (Peña, 2000) as shown in Scheme 77 while 2,2'-di-*tert*-butyl-[8,8'-biquinoline]-7,7'-diol **(53)** was also tried using TBDMSCl (Baker, 2011) as shown in Scheme 78. Unfortunately, the desired products from both reactions were not obtained. Because of only the starting material was recovered.

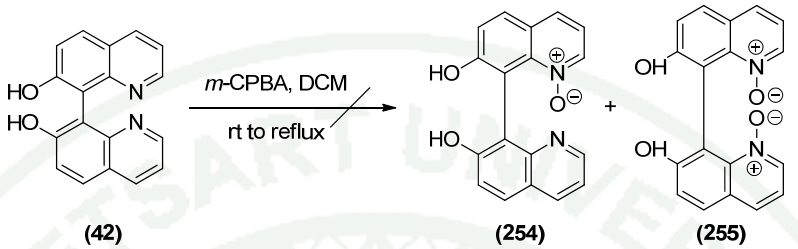


Scheme 77 The failure reaction for protecting the hydroxygroup of azaBINOL **(42)** with TMS or HMDS groups



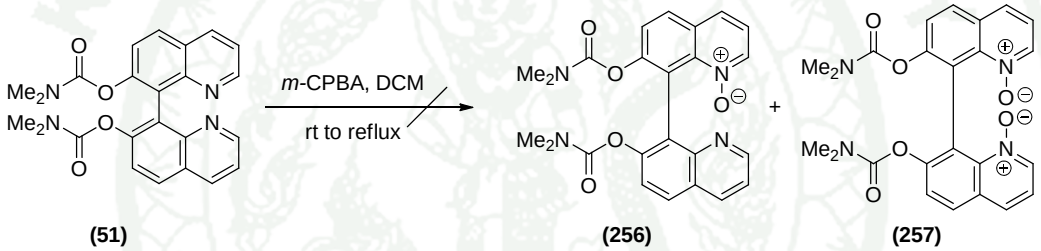
Scheme 78 The failure for protecting the hydroxygroup of 2,2'-di-*tert*-butyl-[8,8'-biquinoline]-7,7'-diol **(53)** with TBDMS group

Furthermore, the azaBINOL **(42)** and the bis(dimethylcarbamate) **(51)** were also tried to convert into *N*-oxide compounds but the both reactions were unsuccessful (Scheme 79 and 80).



(42) **(254)** **(255)**

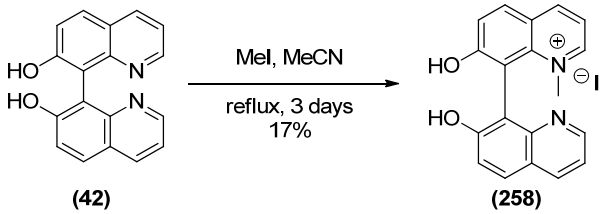
Scheme 79 The failure reaction for converting azaBINOL **(42)** to *N*-oxide



(51) **(256)** **(257)**

Scheme 80 The failure reaction for converting bis(dimethylcarbamate) **(51)** to *N*-oxide

This failure could be explained by effect of steric hindrance and the repulsive nature of the lone pair on the two neighboring nitrogen atom, which prevented the oxidation. It is also possible that the reaction required harsher conditions as quaterization with CH_3I required 3 days to afford the mono-salt (258) in low yield and *N*-bis methylation could not be achieved (Scheme 81).



(42) **(258)**

Scheme 81 The iodo-*N*-methylation of azaBINOL **(42)**

CONCLUSIONS

This research is to investigate and to develop the new and efficient one pot methodology for carbon-heteroatom bond formation mediated by phosphorus reagents. They were used as a wide variety of useful reagents which can be summarized as follows:

1. One Pot Methodology for Carbon-Heteroatom Bond Formation by Oxidation-Reduction Condensation

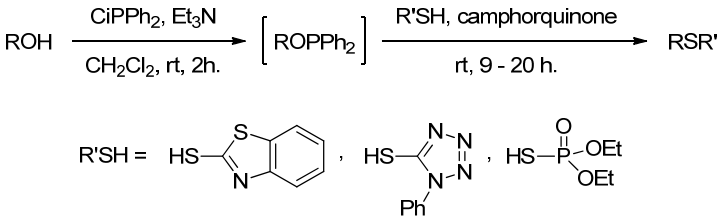
1.1 Preparation of Alkyl Diphenylphosphinites

The preparation of alkyl diphenylphosphinite could be acheived from various alcohols and chlorodiphenylphosphine at room temperature. In this experiment, the alkyl diphenylphosphinite need not be isolated because preventing to be oxidixed from air and transformed to alkyl diphenylphosphine oxide. According to this problem, we have optimized the convenient method for the preparation of alkyl diphenylphosphinites generated *in situ* from alcohols.

1.2 Carbon-Sulfur Bond Formation

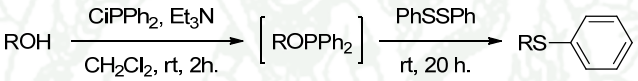
A practical one-pot protocol for the preparation of various sulfides from alcohols and sulfur nucleophiles including benzothiazole-2-thiol (HSBtz), 1-phenyl-1H-tetrazole-5-thiol and *O*,*O*-diethyl *S*-hydrogen phosphorothioate from alcohol utilizing the camphorquinone-mediated oxidation-reduction condensation is disclosed as shown in Scheme 82**.**

The condensation between sulfur nucleophiles and alkyl diphenylphosphinites proceeded smoothly in the presence of camphorquinone to furnish the corresponding sulfides in moderate to high yields *via* S_N2 mechanism.



Scheme 82 Thioetherification of alkyldiphenylphosphinites generated *in situ* from alcohol using sulfur nucleophile in the presence of camphorquinone

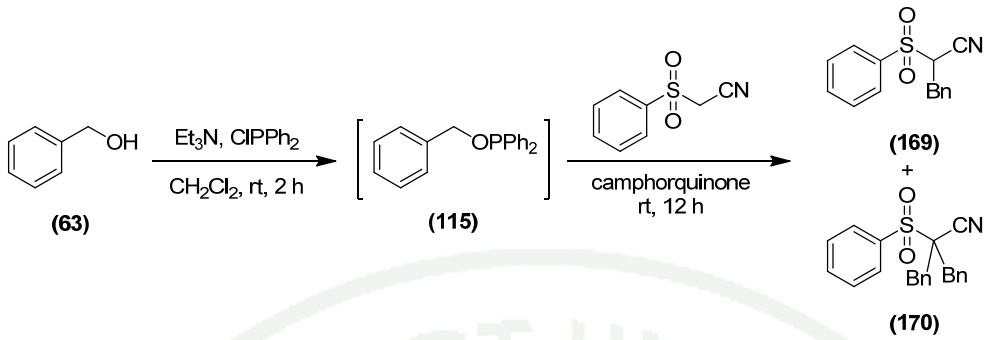
In the use of 1,2-diphenyldisulfane as a nucleophile, the reaction could afford the desired products in the absence of camphorquinone in moderate to high yields (Scheme 83).



Scheme 83 Thioetherification of alkyldiphenylphosphinites generated *in situ* from alcohol using diphenyldisulfane

1.3 Using other nucleophiles

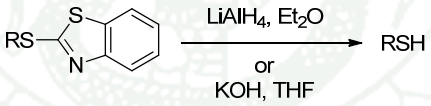
(Phenylsulfonyl)acetonitrile was allowed to react with benzyl diphenylphosphenite in the presence of camphorquinone to give mixture of mono- and di-alkylated products as shown in Scheme 84.



Scheme 84 Preparation of mono- and di-alkylated products of benzyldiphenyl phosphinite using (phenylsulfonyl)acetonitrile as a nuleophile

1.4 The proposal for the future work

The developed method for the preparation of sulfides (Btz products) will be further examined to afford the corresponding thiols by treatment with reducing agent such as $LiAlH_4$ (Ikegai, 2005) or hydrolyzing with base such as KOH (Han, 2010) in one pot synthesis **(**Scheme 85**)**.

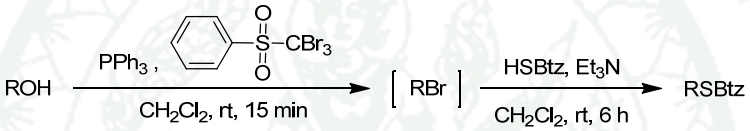


Scheme 85 Future plan for preparation of thiol by reducing the sulfide.

2. One Pot Methodology for Carbon-Heteroatom Bond Formation by Nucleophilic Substitution and Nucleophilic Aromatic Substitution using Alkyl, Acyl and Aryl Bromo Intermediate, respectively.

2.1 Nucleophilic Substitution of Alkyl Halide

A convenient one-pot procedure for the preparation of sulfides from alkyl halides, generated *in situ* from alcohols using a combination of PPh_3 and $PhSO_2CBr_3$, and sulfur nucleophiles including benzothiazole-2-thiol (HSBtz) is disclosed as shown in Scheme 86**.**

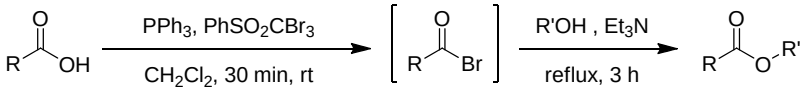


Scheme 86 Preparation of sulfide from alkyl halides

The nucleophilic substitution between HSBtz and alkyl halides from primary and secondary alcohols furnished the corresponding sulfides in fair to high yields. On the other hand, the steric hindrance with the bulky secondary and tertiary alcohols gave the products in low yields.

2.2 Nucleophilic Substitution of Carboxylic Acid

Esters were prepared from acid halides, generated *in situ* from carboxylic acids using a combination of PPh_3 and $PhSO_2CBr_3$. Oxygen nucleophiles such as alcohols and phenols were investigated as shown in Scheme 87.



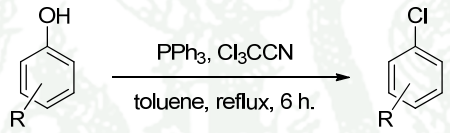
Scheme 87 Esterification of acid bromide with alcohol or phenol

Primary and secondary alcohols could be converted to esters in moderate to high yields whereas tertiary alcohol showed lower yields.

Under the optimized conditions, the reaction proceeded with amine to afford amides. Moreover, sulfonyl esters and sulfonamides were also prepared from phenylsulfonic acid under the same conditions. However, the desired products were obtained in low yields.

2.3 Nucleophilic Aromatic Substitution of Phenol Derivatives

A new and efficient procedure for the preparation of chlolobenzene derivatives from phenol containing electron withdrawing groups was also developed using the combination of PPh_3 and Cl_3CCN as shown in Scheme 88.

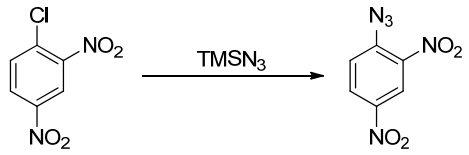


Scheme 88 Preparation of chlolobenzene derivatives from phenol

Under the optimized conditions, phenol derivatives could be transformed into the halobenzenes in moderate to high yields.

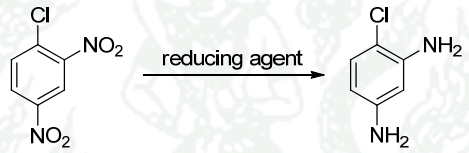
2.4 The proposal for the future work

The extension of the protocol to other nucleophiles such as trimethylsilyl azide ($TMSN_3$) will be attempted (Scheme 89).



Scheme 89 Future plan for preparation of phenyl azide derivatives from chlorobenzene

Subsequent transformation of 2,4-dinitro-chlorobenzene will be further studied to find the optimum conditions for conversion to 2,4-diamino-chlorobenzene by treatment with reducing agent after chlorination. In the case, a convenient one-pot protocol should be developed (Scheme 90).

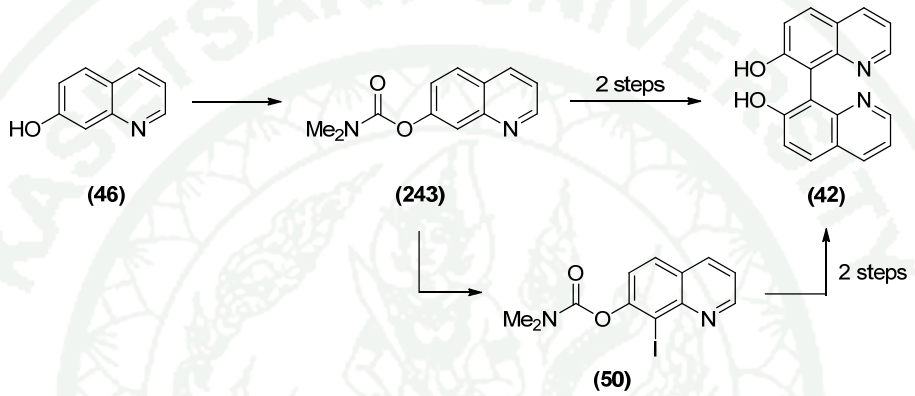


Scheme 90 Future plan for reduction of 2,4-dinitro-chlorobenzene

3. Synthesis the 7,7'-dihydroxy-8,8'-biquinoline (azaBINOL) and its derivatives

3.1 Synthesis the 7,7'-dihydroxy-8,8'-biquinoline (azaBINOL)

The pathway for synthesis the 7,7'-dihydroxy-8,8'-biquinoline (azaBINOL) is summarized in Scheme 91.

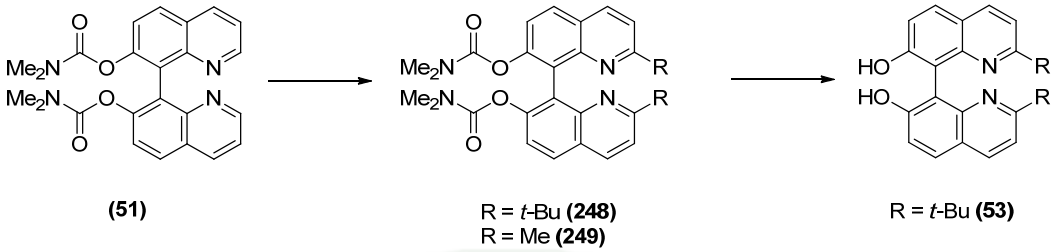


Scheme 91 The pathway for synthesis the azaBINOL

The *N,N*-dimethyl *O*-(quinol-7-yl) carbamate **(243)** was prepared from 7-hydroxyquinoline **(46)** and it could be used as a substrate for preparation the azaBINOL **(42)** *via* $FeCl_3$-mediated coupling reaction of carbamate **(243)** or Ullmann coupling reaction 8-iodoquinolin **(50)** and followed by the hydrolysis reaction.

3.2 Synthesis of 7,7'-dihydroxy-8,8'-biquinoline (azaBINOL) derivatives

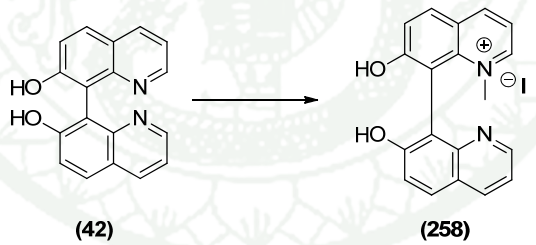
The 2,2'-disubstituted derivatives of azaBINOL were summarized in the Scheme 92.



Scheme 92 Introduction of substituents to C2 position of bis(dimethylcarbamate) and cleavage of the carbamate group

The 2,2'-di-*tert*-butyl-[8,8'-biquinoline]-7,7'-diol **(53)** was prepared from [8,8'-biquinoline]-7,7'-diyl-bis(di methylcarbamate) **(51)** which reacted with *tert*-BuLi followed by re-aromatizing by standing in the air or reacted with DDQ and the hydrolysis reaction of the dicarbamate **(248)**.

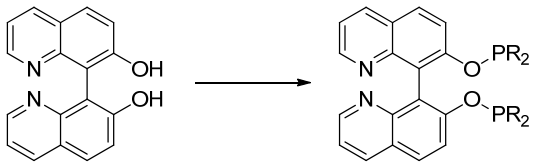
Moreover, mono-quaternarized salt **(258)** was isolated when azaBINOL **(42)** was heated in methyliodide as shown in **Scheme 93.**



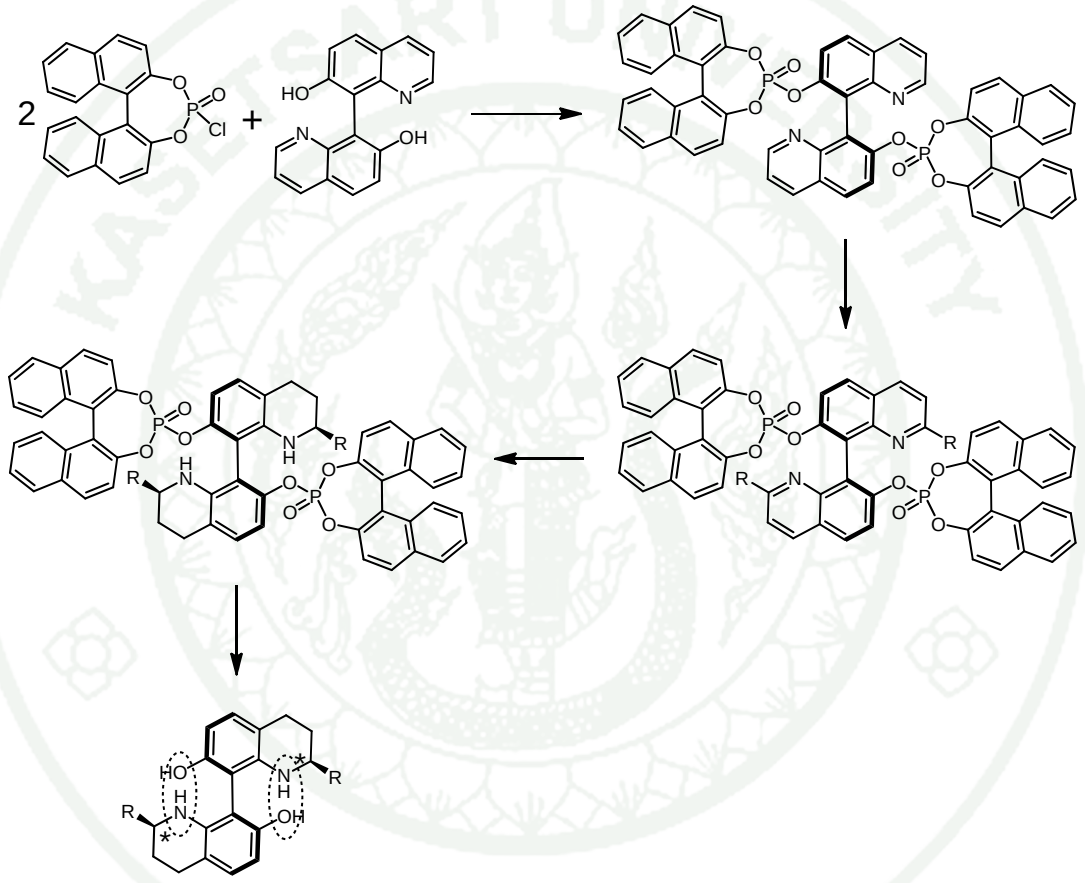
Scheme 93 The iodo-*N*-methylation of azaBINOL

3.3 The proposal for the future work

The synthetic access to azaBINOL and 8,8'-biquinolyl derivatives have been investigated and in part improved. It is anticipated that this work can be the bases to prepare new 8,8'-biquinolyls useful asymmetric synthesis such as chiral phosphinite (Scheme 94) or chiral phosphate catalysts (Scheme 95).



Scheme 94 Future plan for preparation of a chiral phosphinite



Scheme 95 Future plan for preparation of chiral phosphate catalysts

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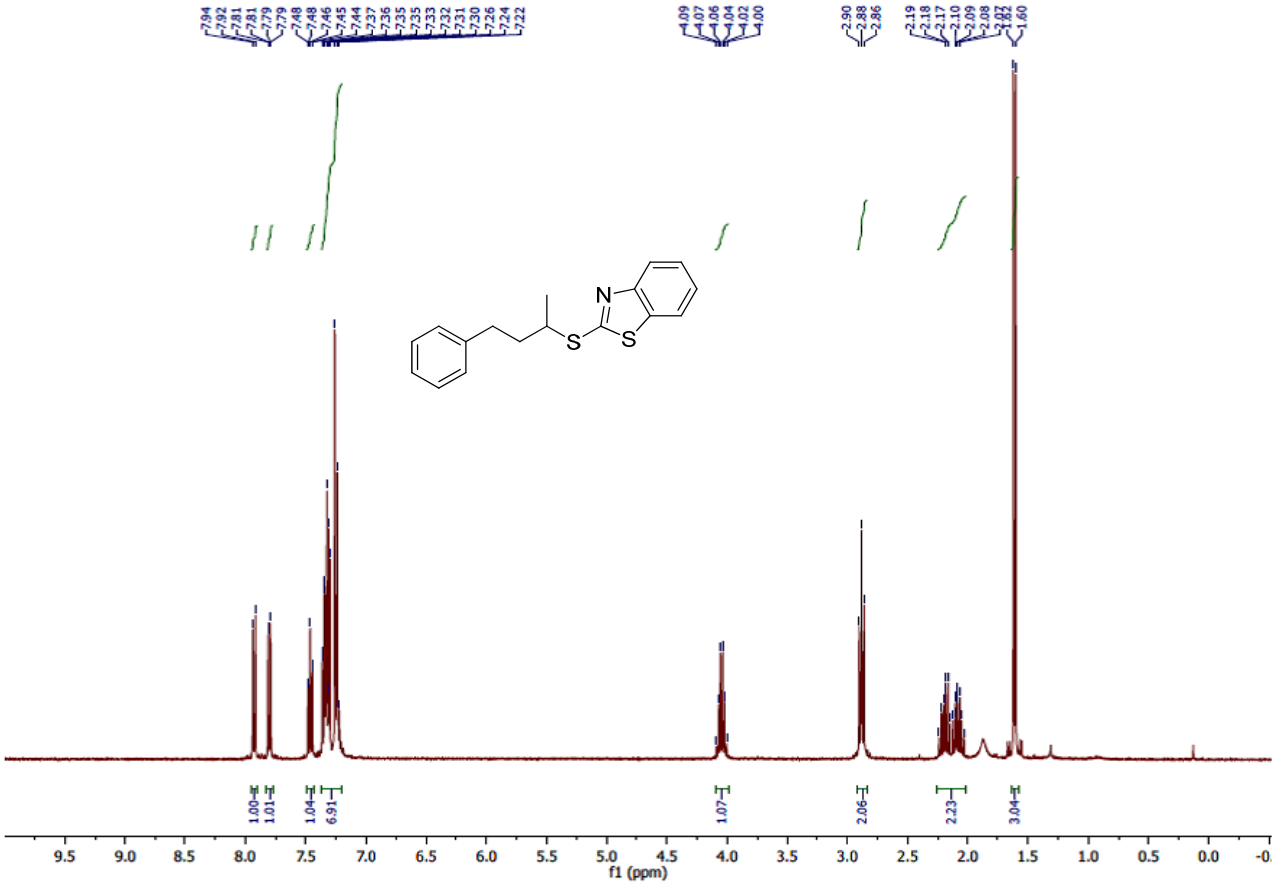
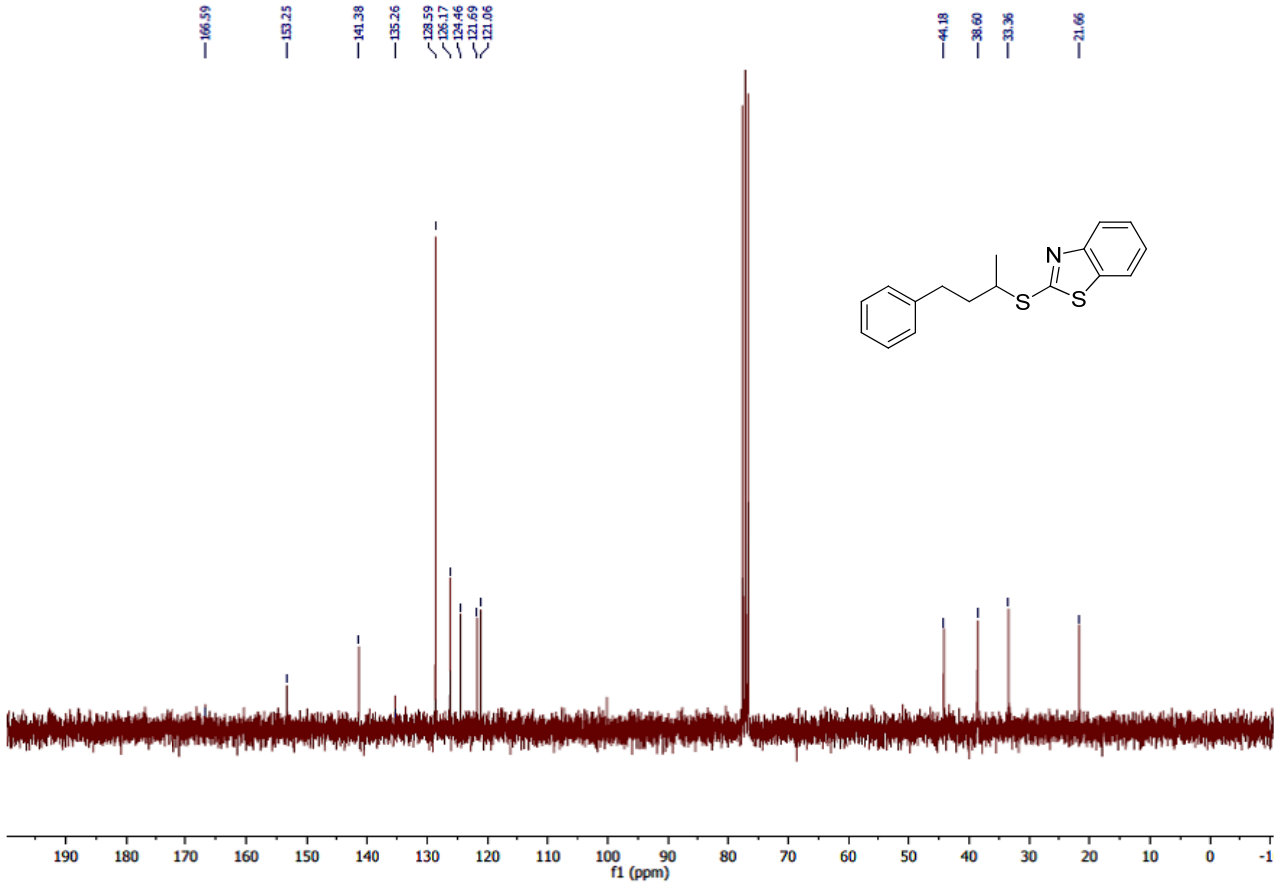
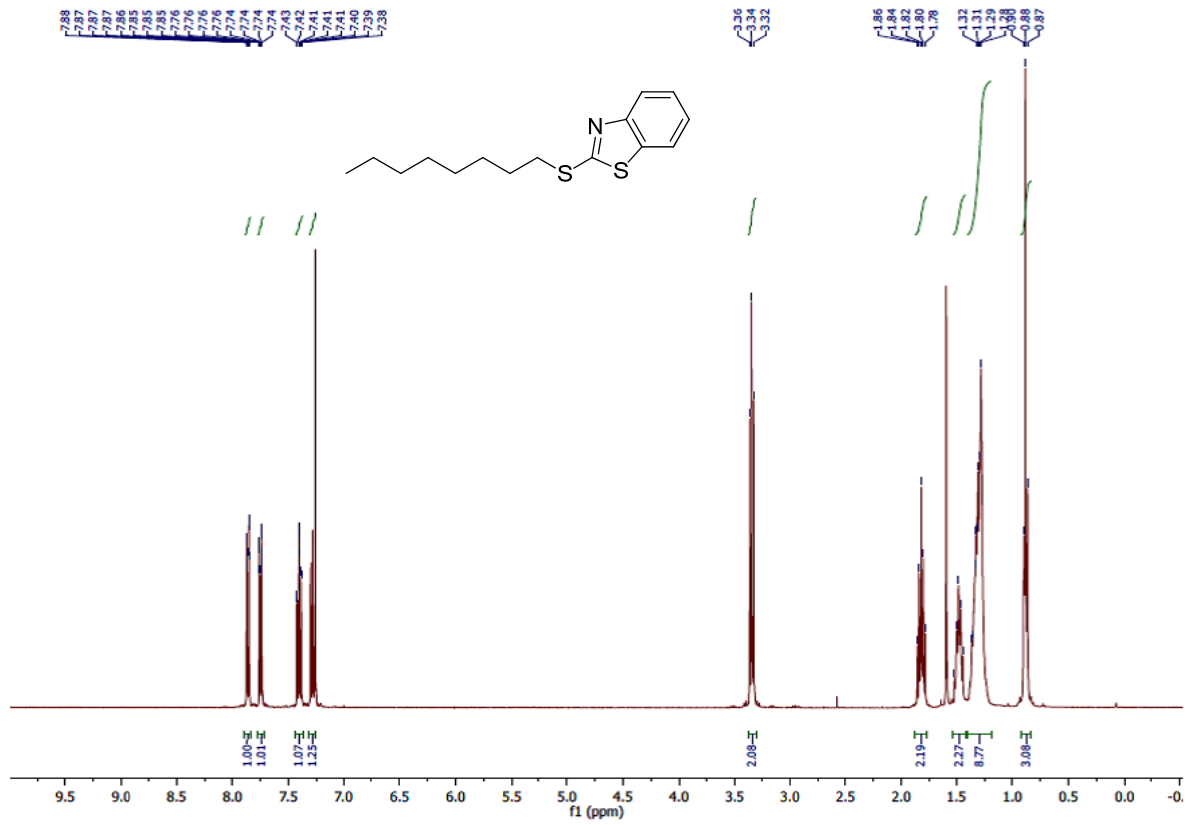
APPENDIX



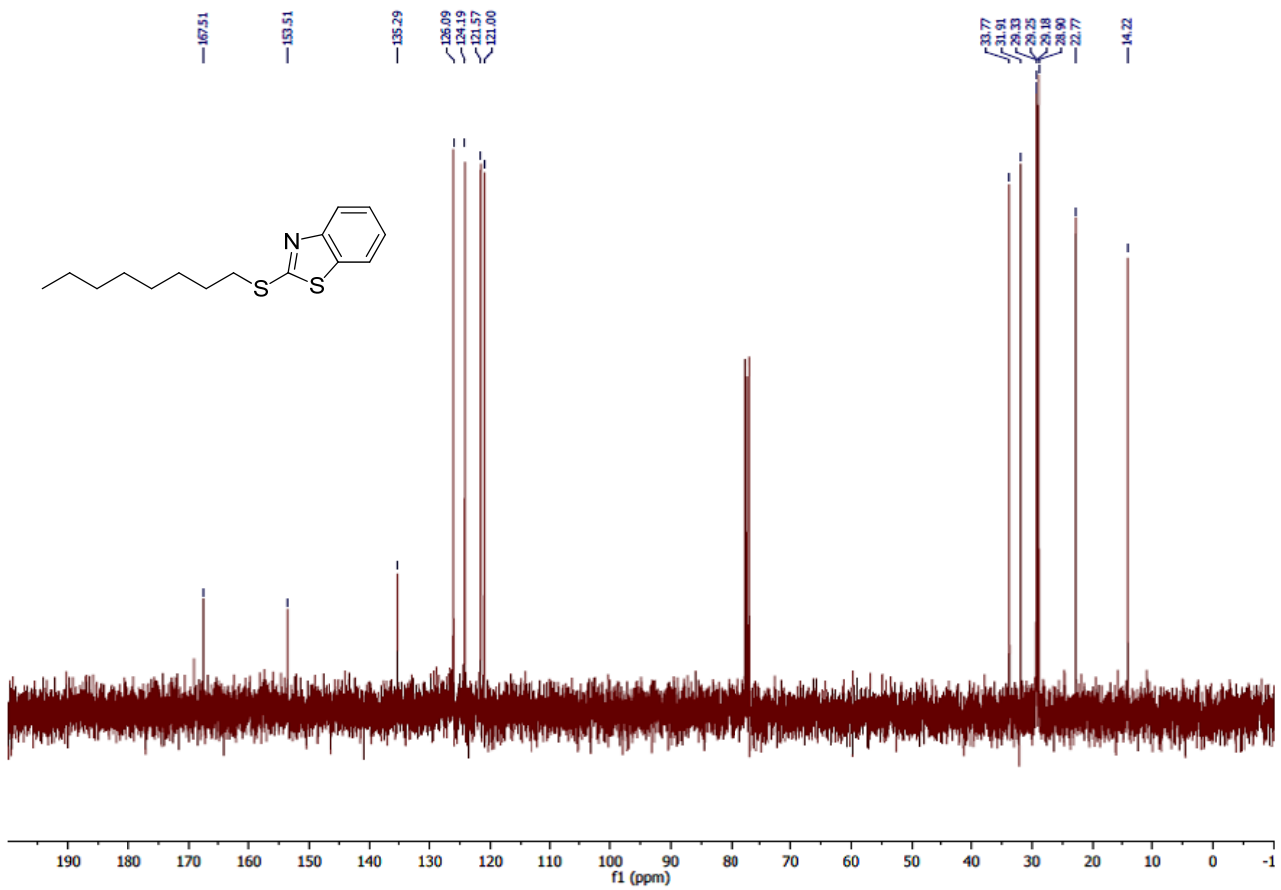
Appendix Figure 1 400 MHz ^{1}H NMR spectrum of 2-((4-phenylbutan-2-yl)thio)benzo[d]thiazol **(58)**



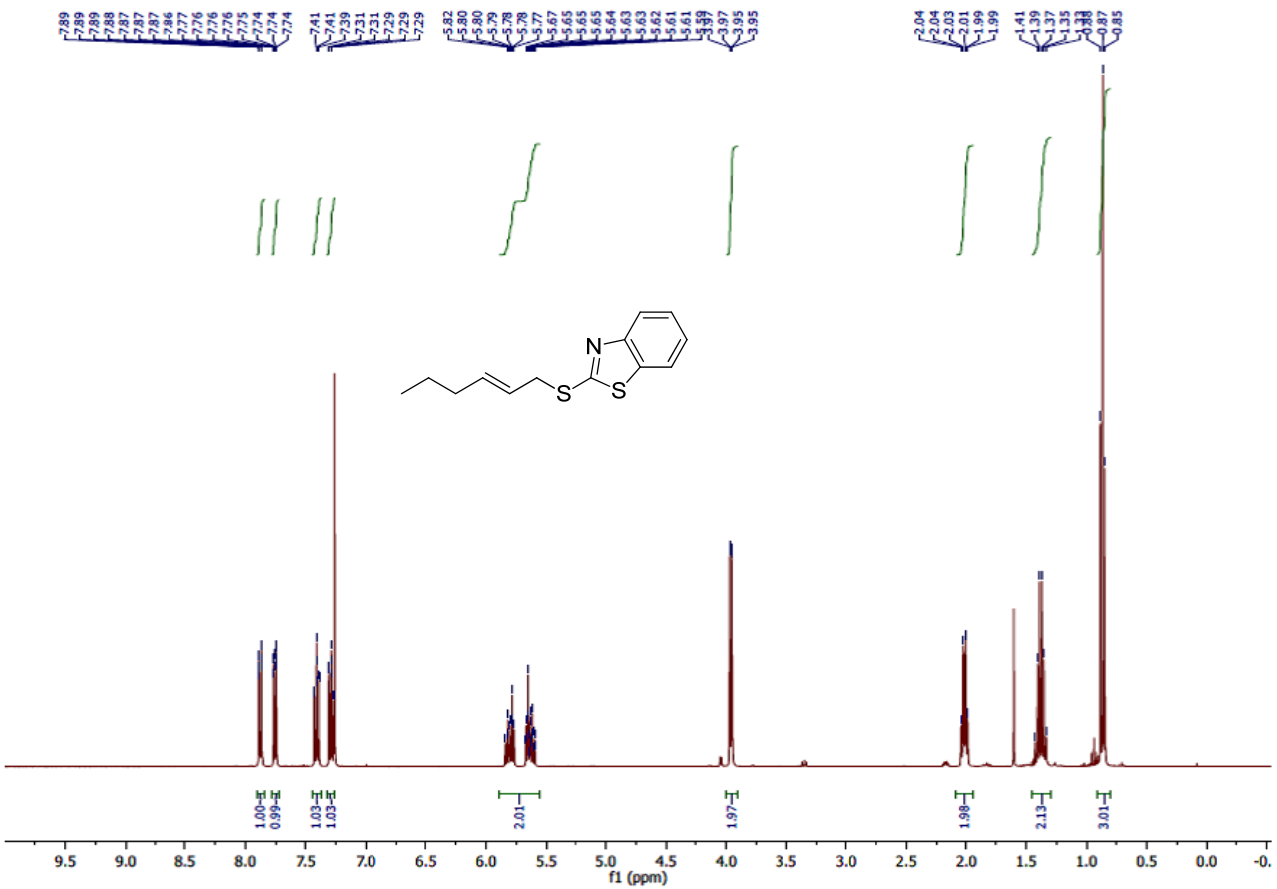
Appendix Figure 2 100 MHz ^{13}C NMR spectrum of 2-((4-phenylbutan-2-yl)thio)benzo[d]thiazol **(58)**



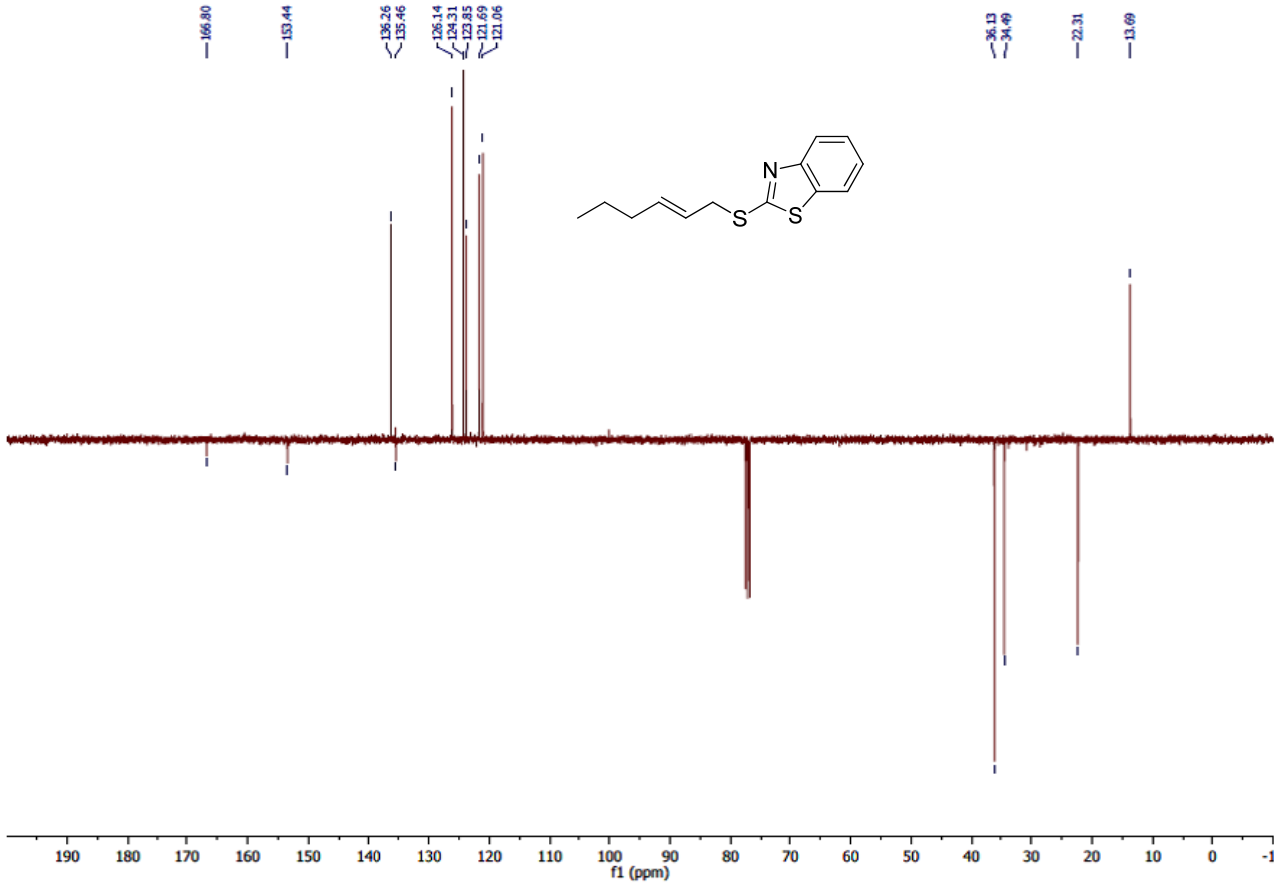
Appendix Figure 3 400 MHz ^{1}H NMR spectrum of 2-(octylthio)benzo[d]thiazole **(60)**



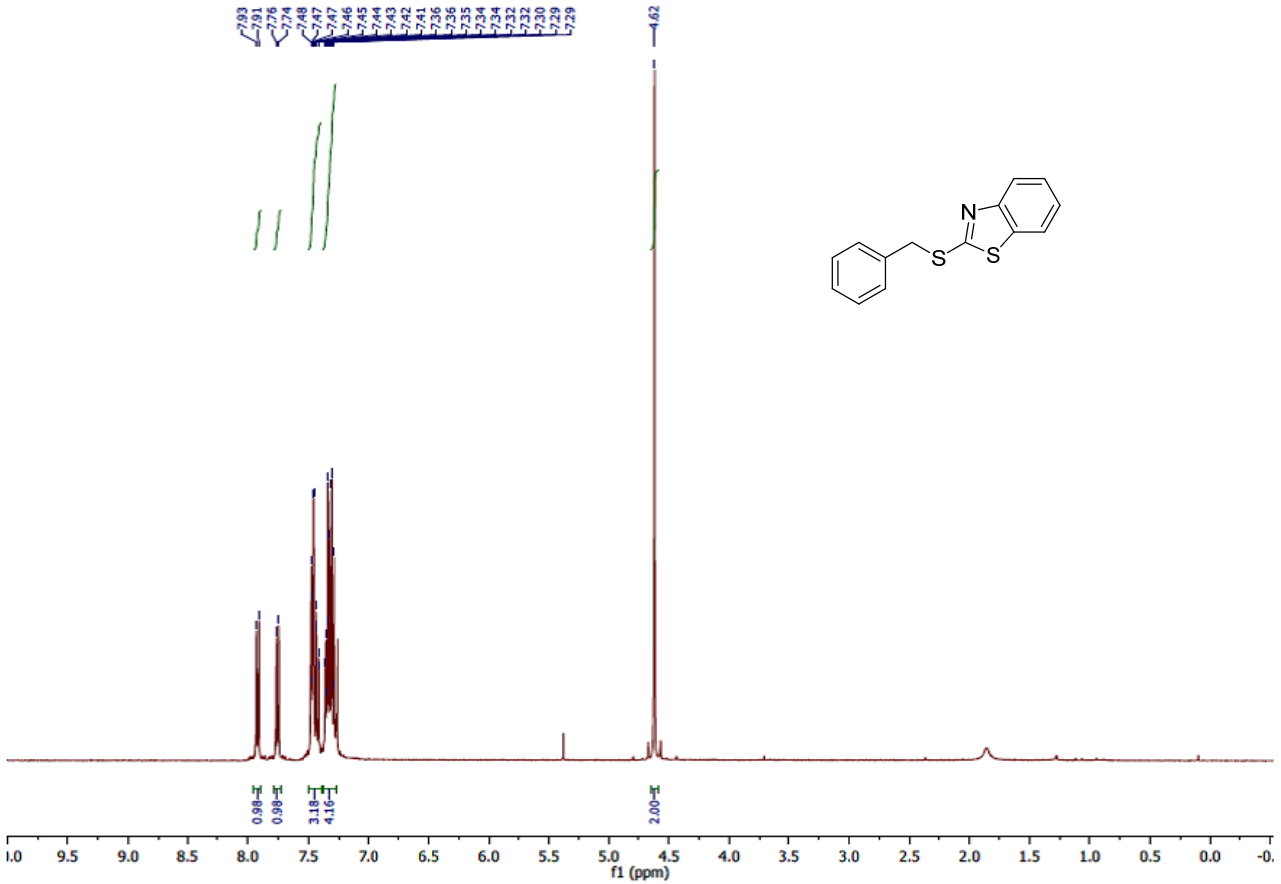
Appendix Figure 4 100 MHz ^{13}C NMR spectrum of 2-(octylthio)benzo[d]thiazole **(60)**



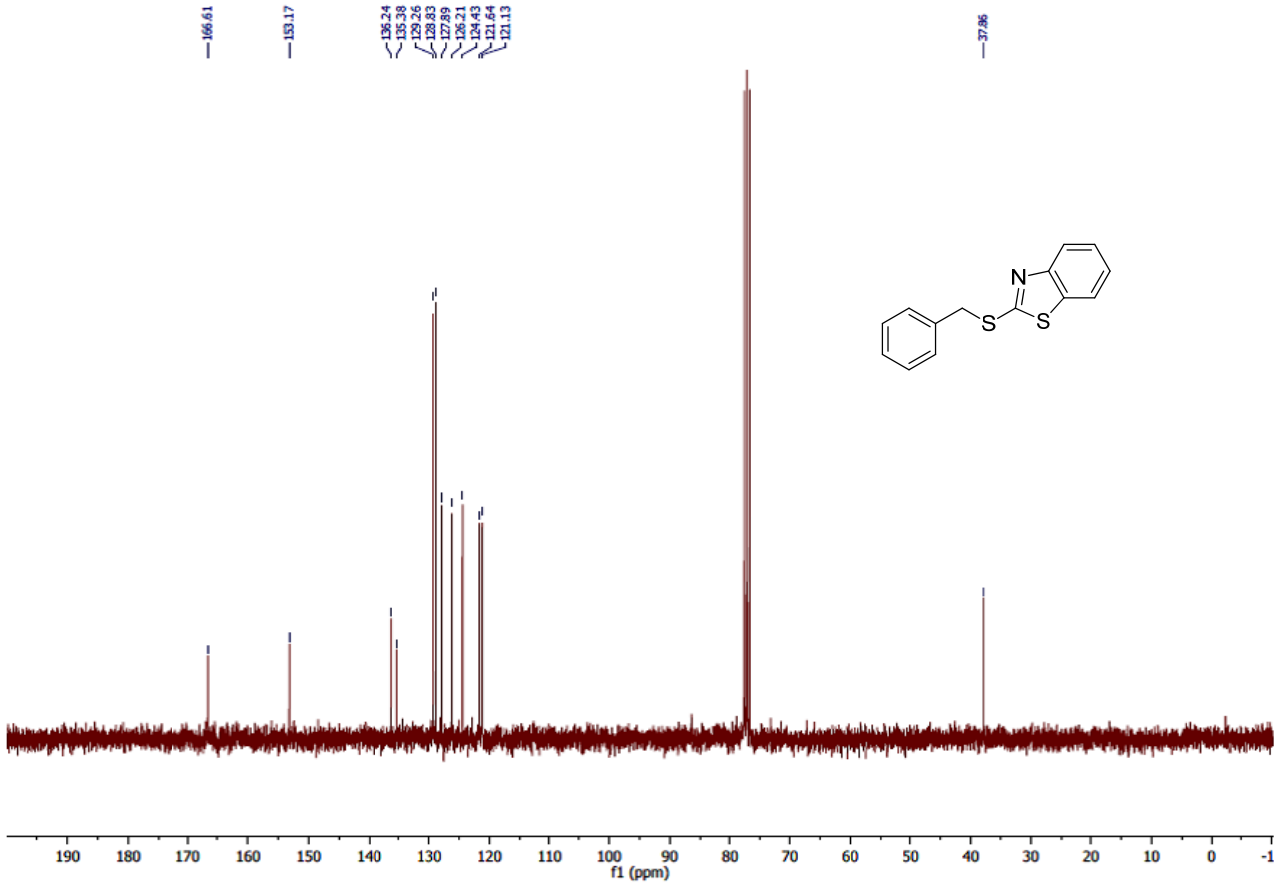
Appendix Figure 5 400 MHz ^{1}H NMR spectrum of (*E*)-2-(hex-2-en-1-ylthio)benzo[d]thiazole **(62)**



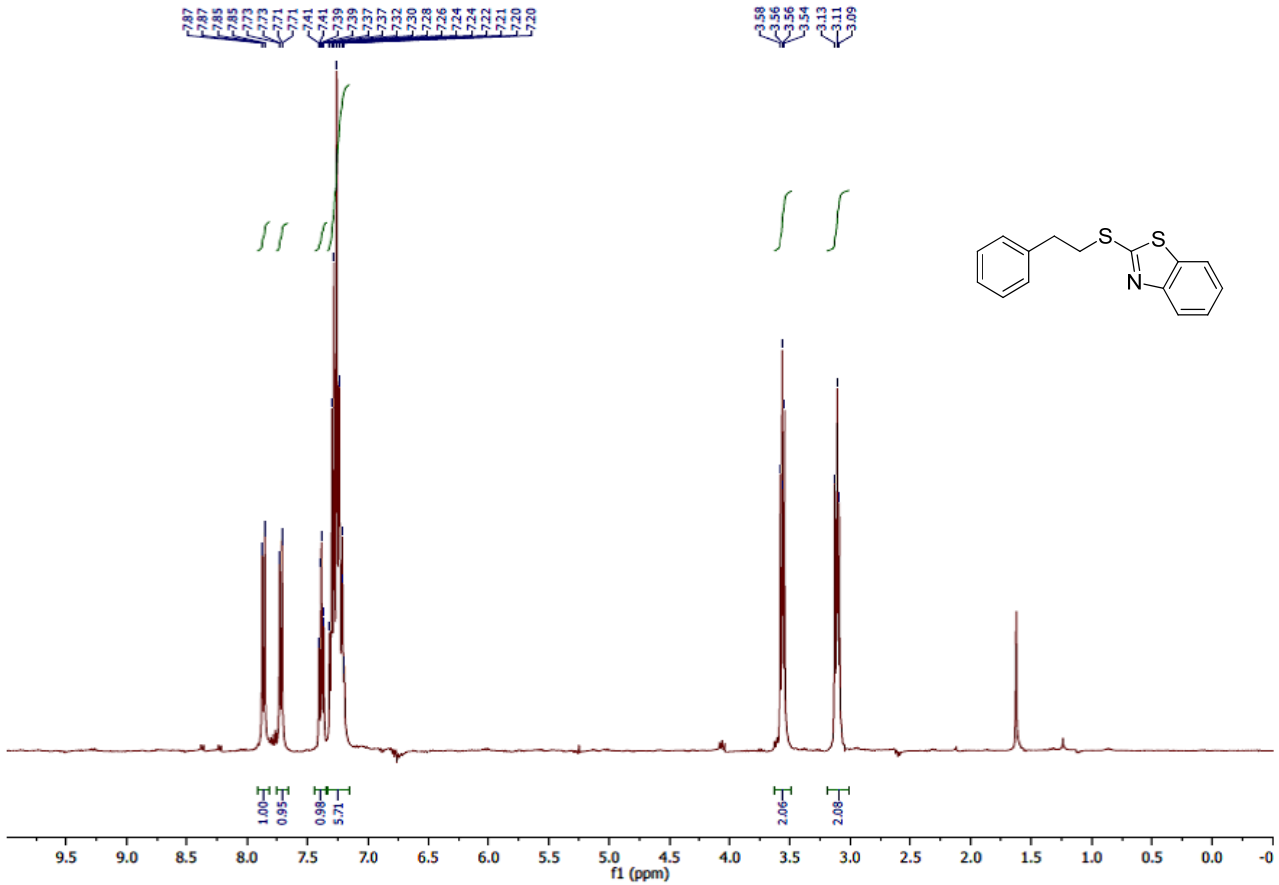
Appendix Figure 6 100 MHz ^{13}C NMR spectrum of (*E*)-2-(hex-2-en-1-ylthio)benzo[d]thiazole **(62)**



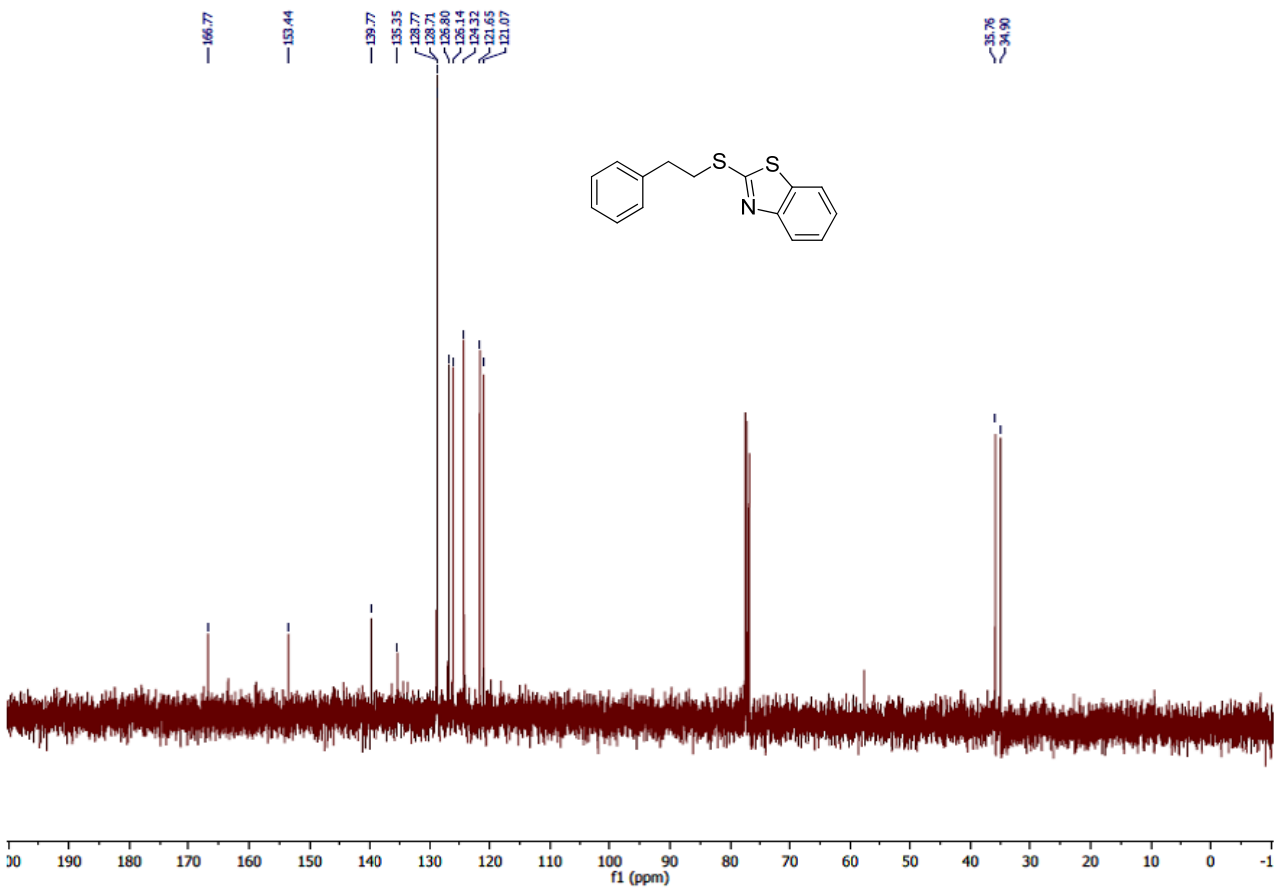
Appendix Figure 7 400 MHz ^{1}H NMR spectrum of 2-(benzylthio)benzo[d]thiazole **(64)**



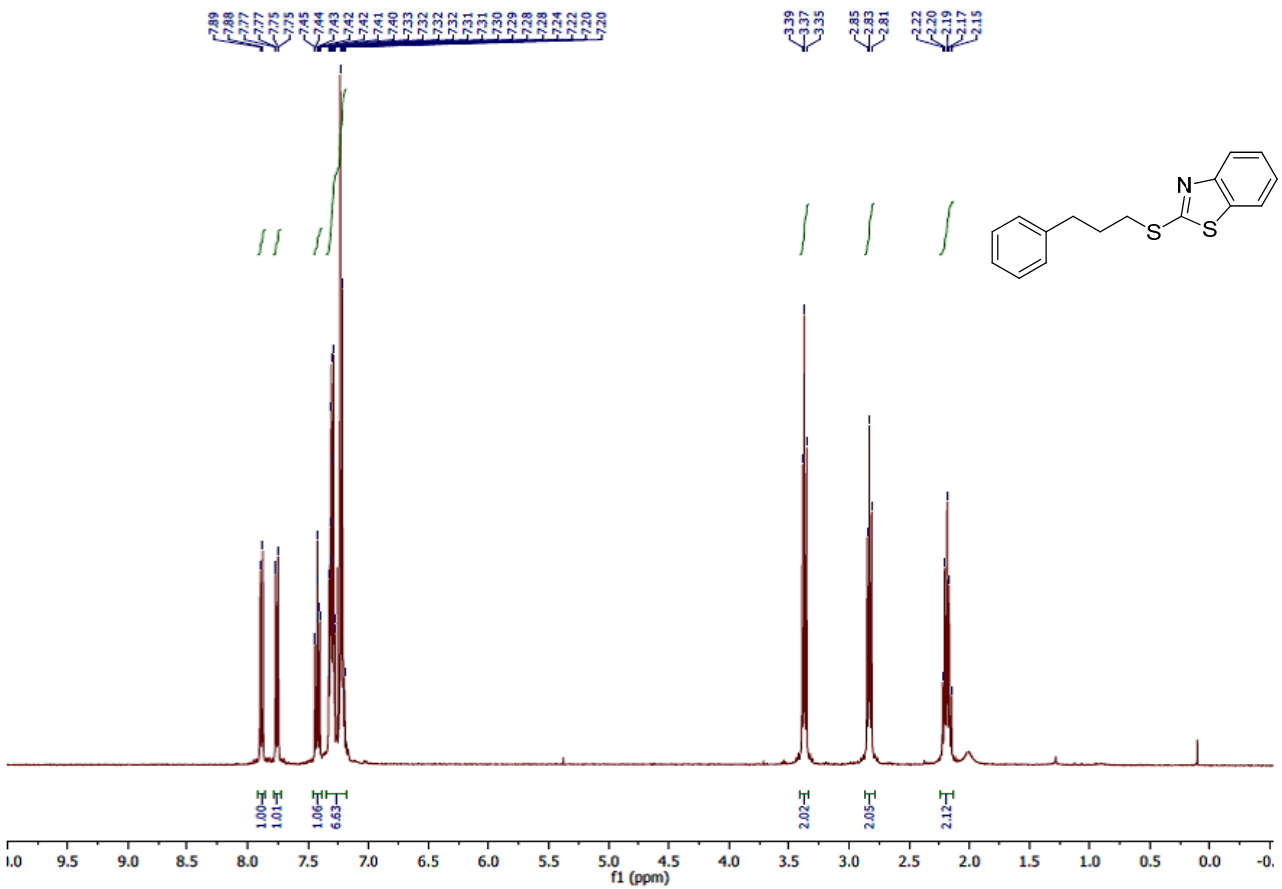
Appendix Figure 8 100 MHz ^{13}C NMR spectrum of 2-(benzylthio)benzo[d]thiazole **(64)**



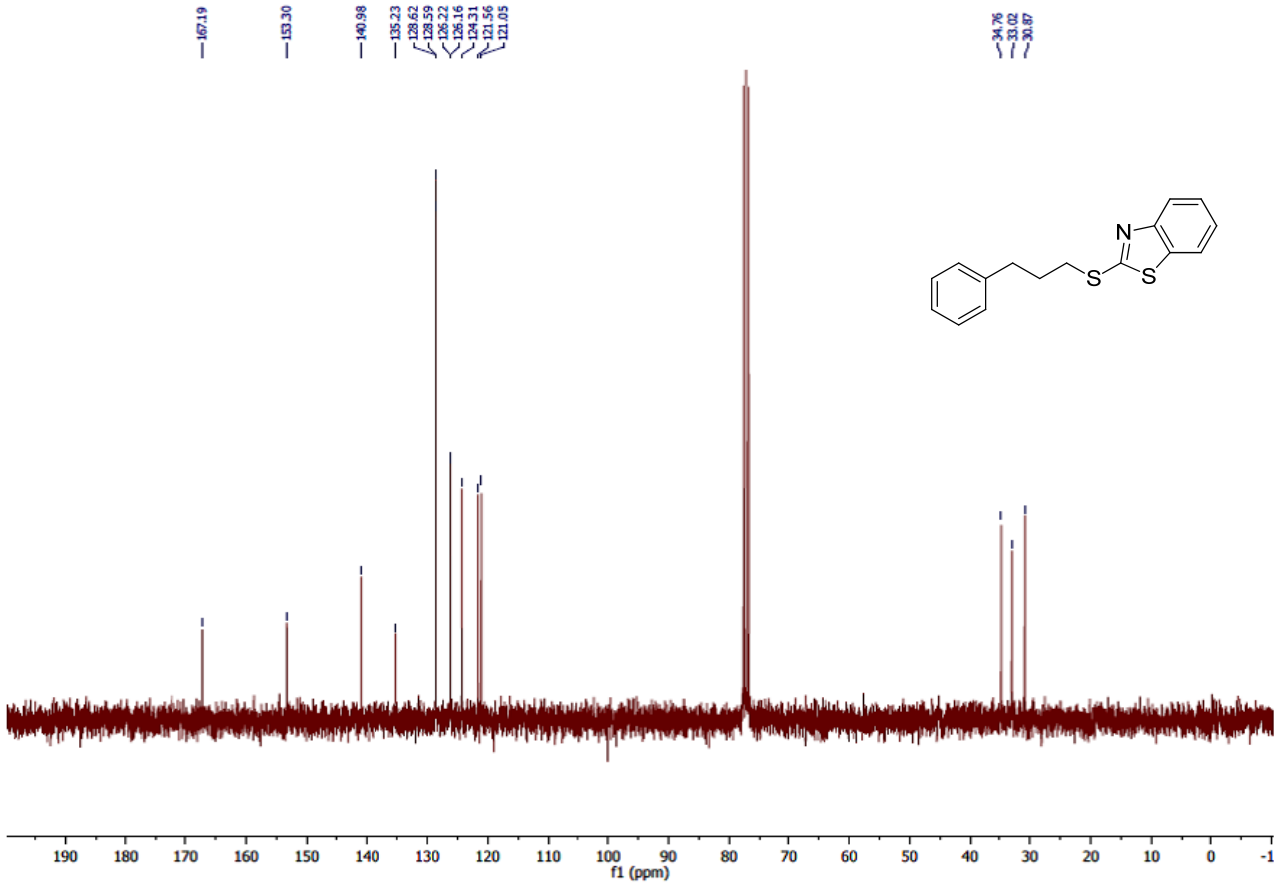
Appendix Figure 9 400 MHz ^{1}H NMR spectrum of 2-(phenethylthio)benzo[d]thiazole **(66)**



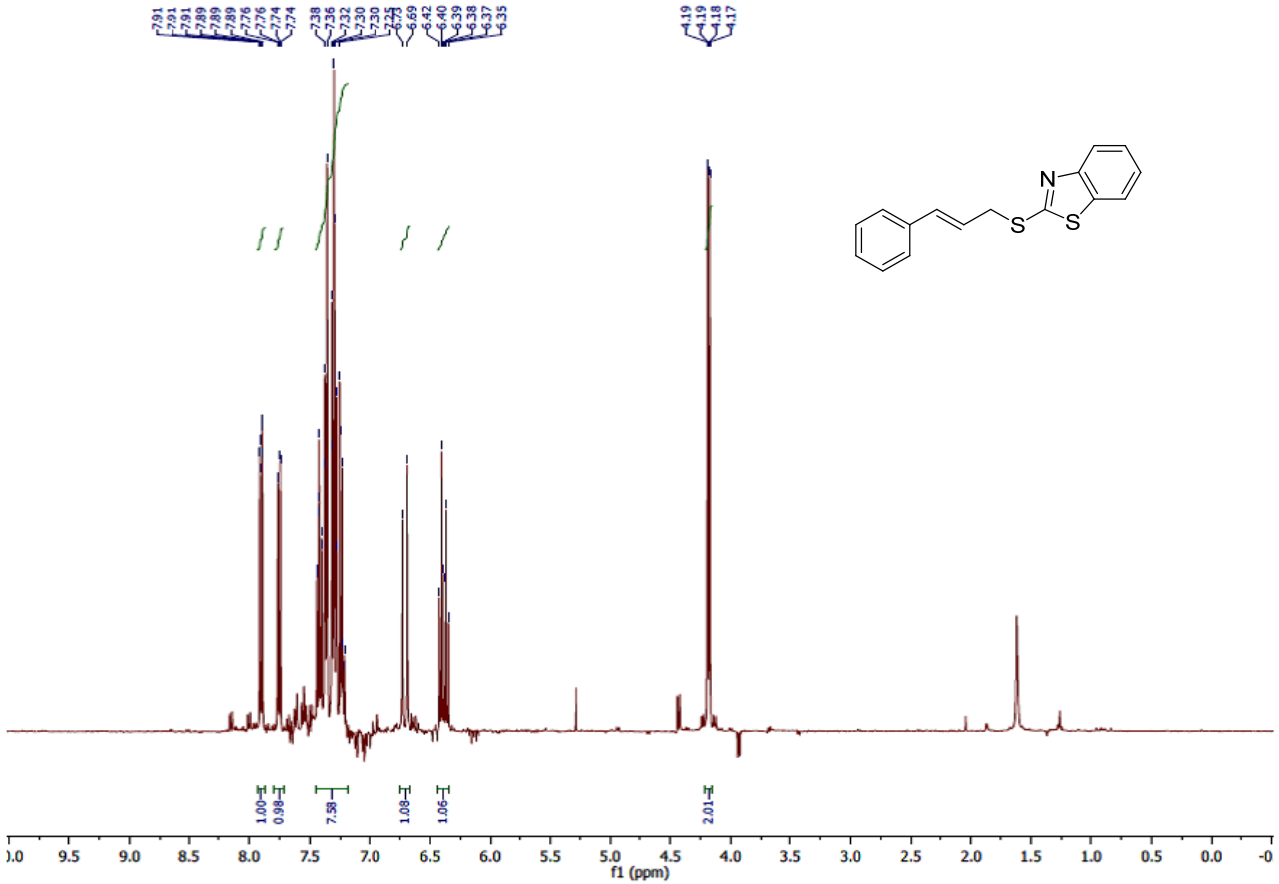
Appendix Figure 10 100 MHz ^{13}C NMR spectrum of 2-(phenethylthio)benzo[d]thiazole **(66)**



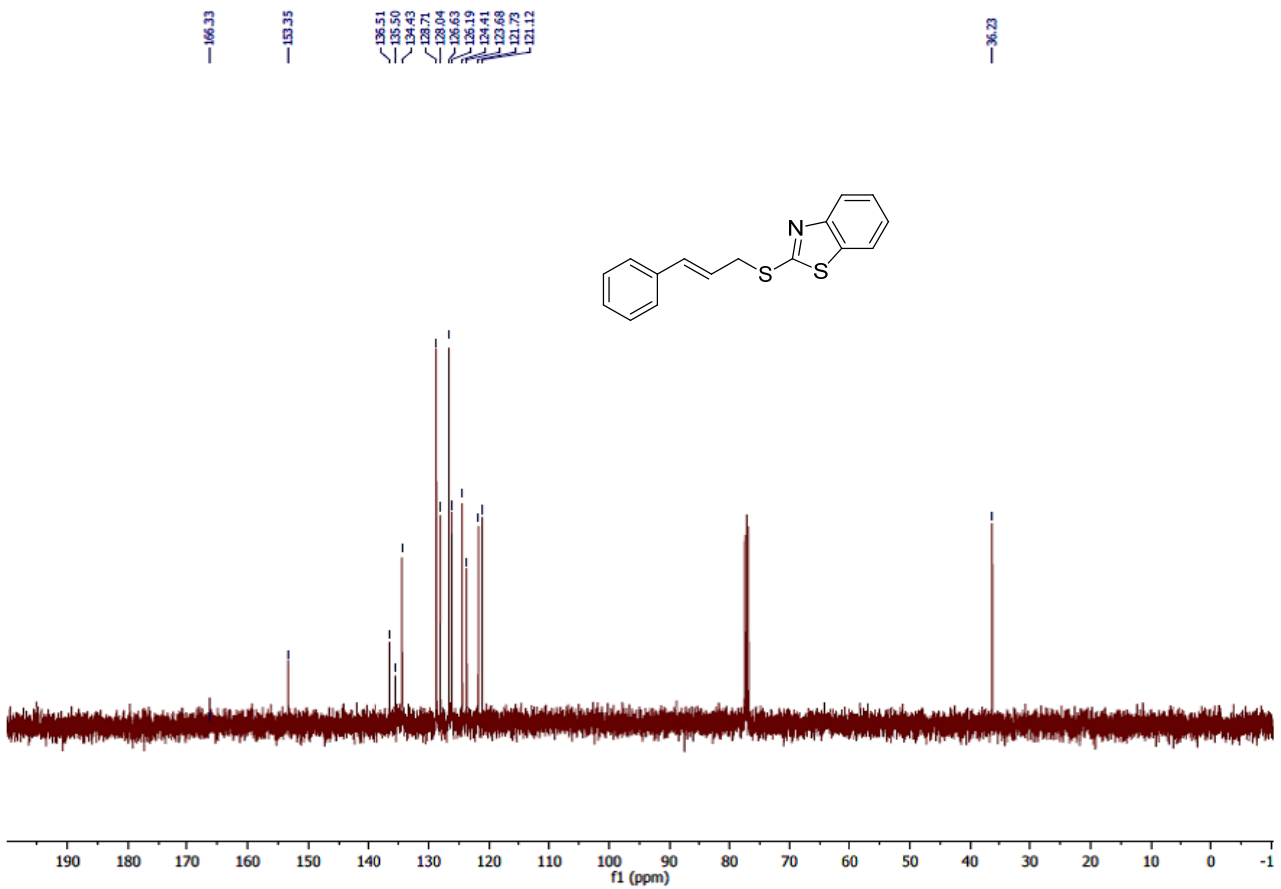
Appendix Figure 11 400 MHz ^{1}H NMR spectrum of 2-((3-phenylpropyl)thio)benzo[d]thiazole **(68)**



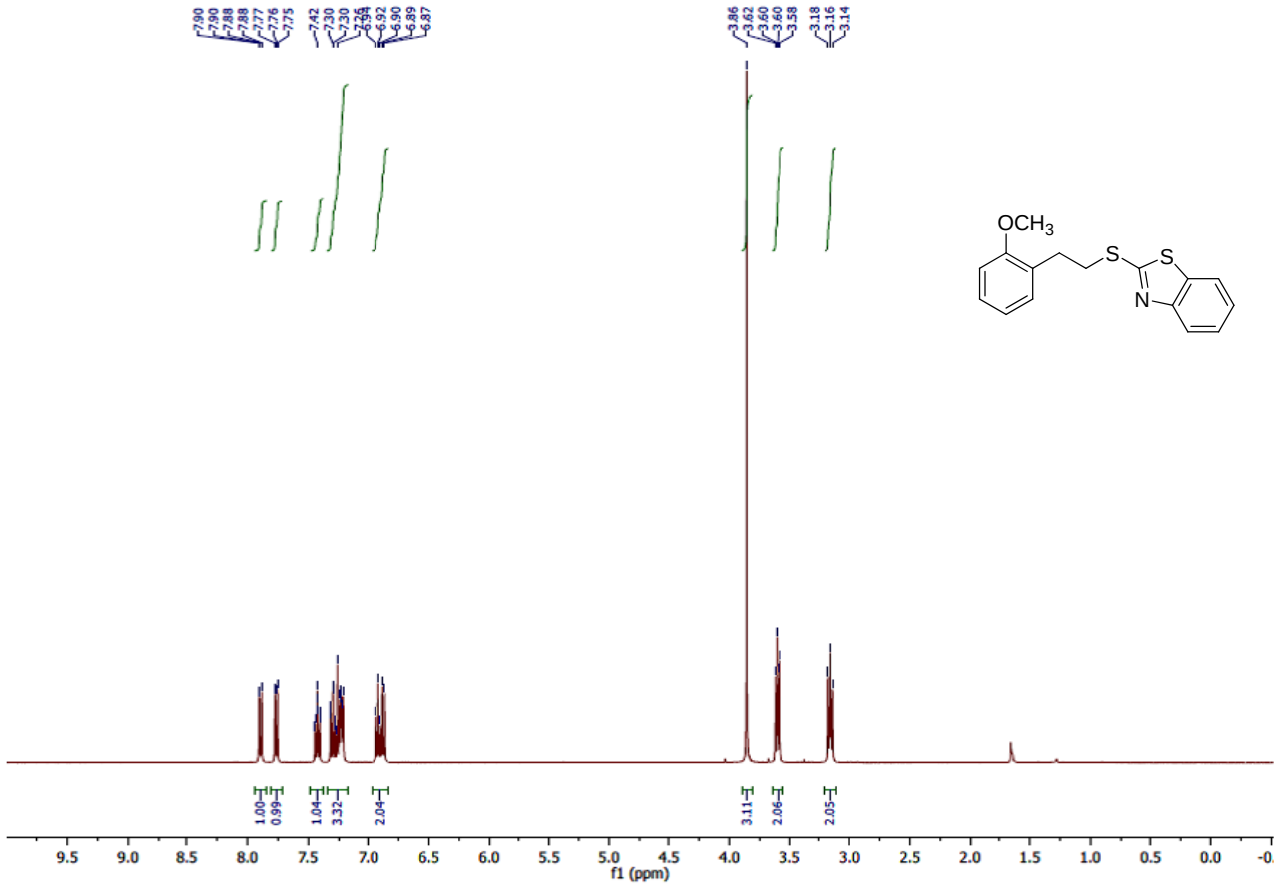
Appendix Figure 12 100 MHz ^{13}C NMR spectrum of 2-((3-phenylpropyl)thio)benzo[d]thiazole **(68)**



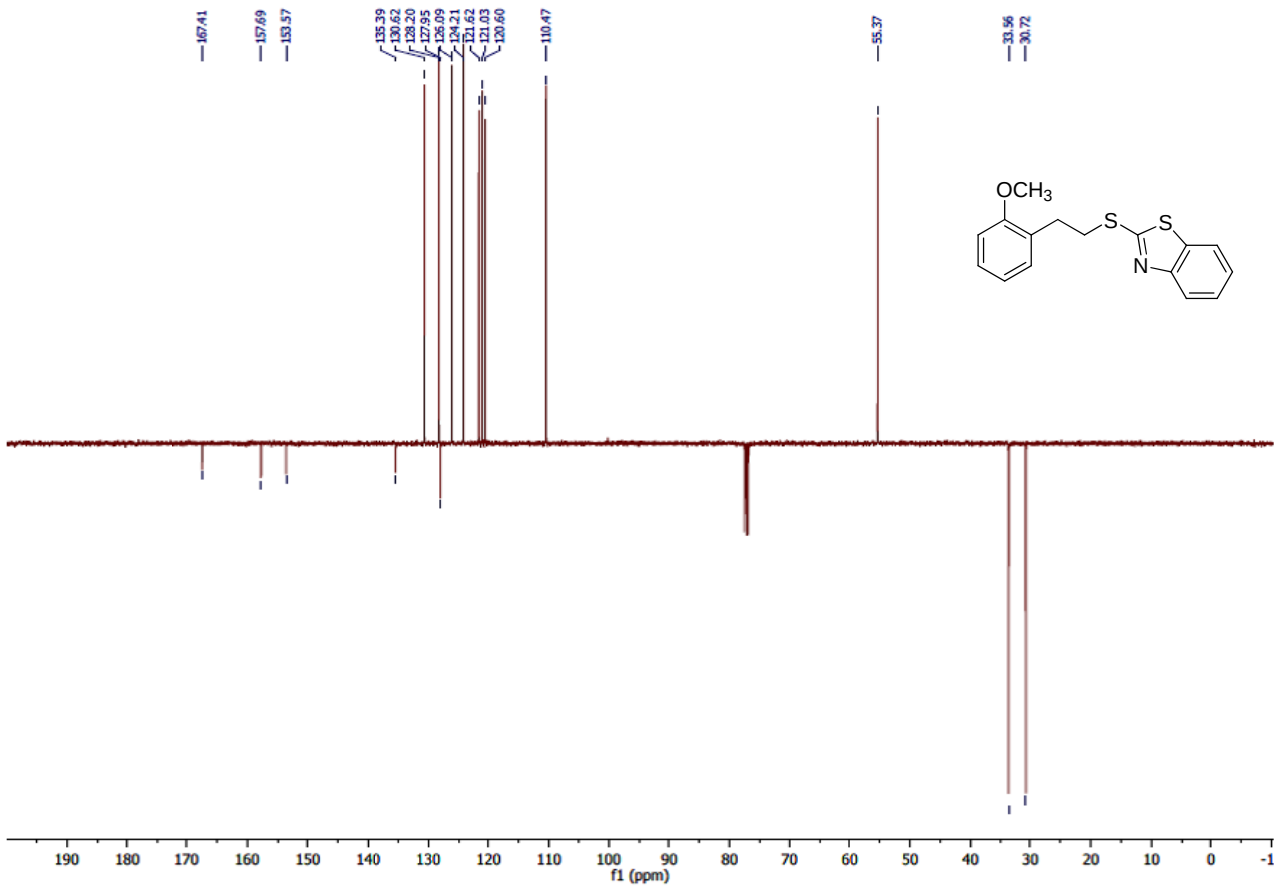
Appendix Figure 13 400 MHz ^{1}H NMR spectrum of 2-(cinnamylthio)benzo[d]thiazole **(70)**



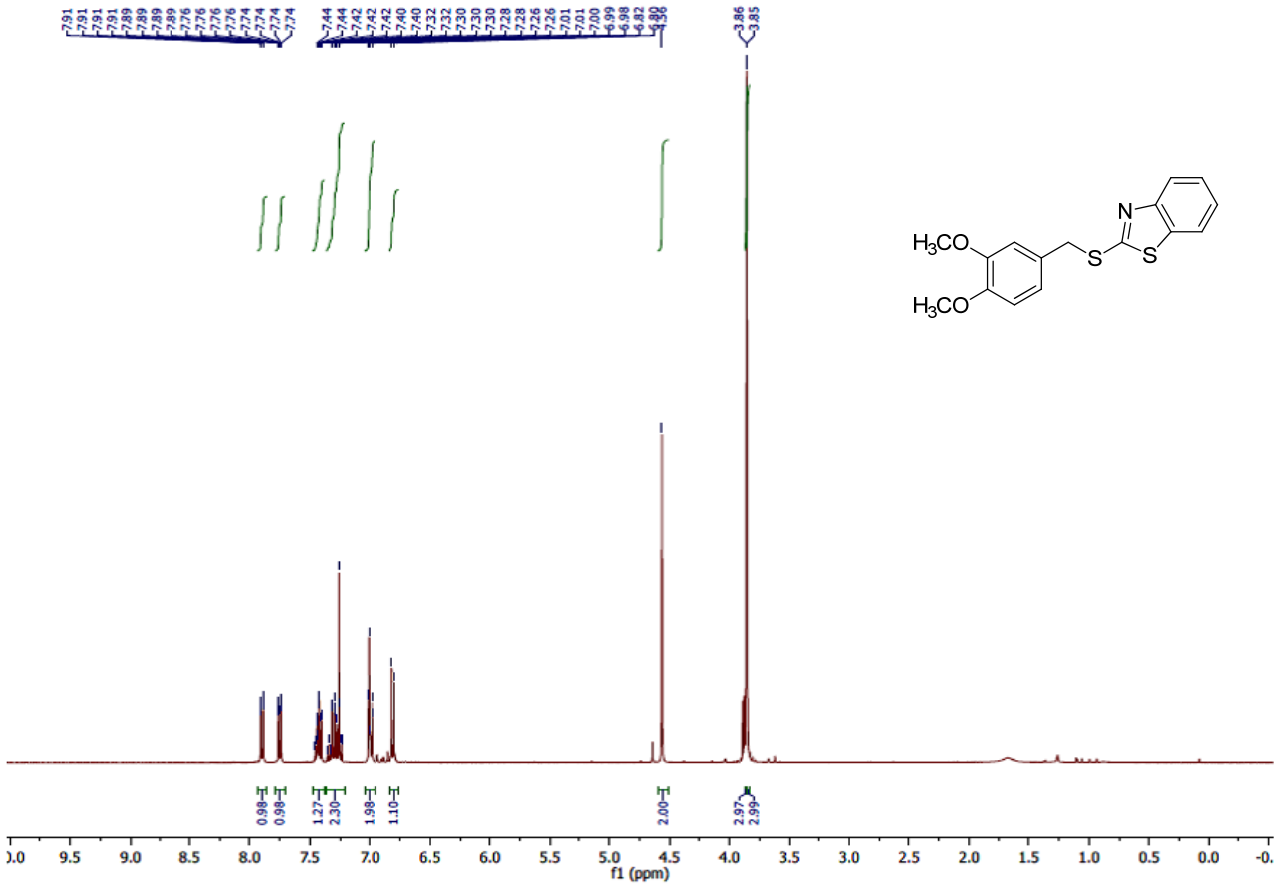
Appendix Figure 14 100 MHz ^{13}C NMR spectrum of 2-(cinnamylthio)benzo[d]thiazole **(70)**



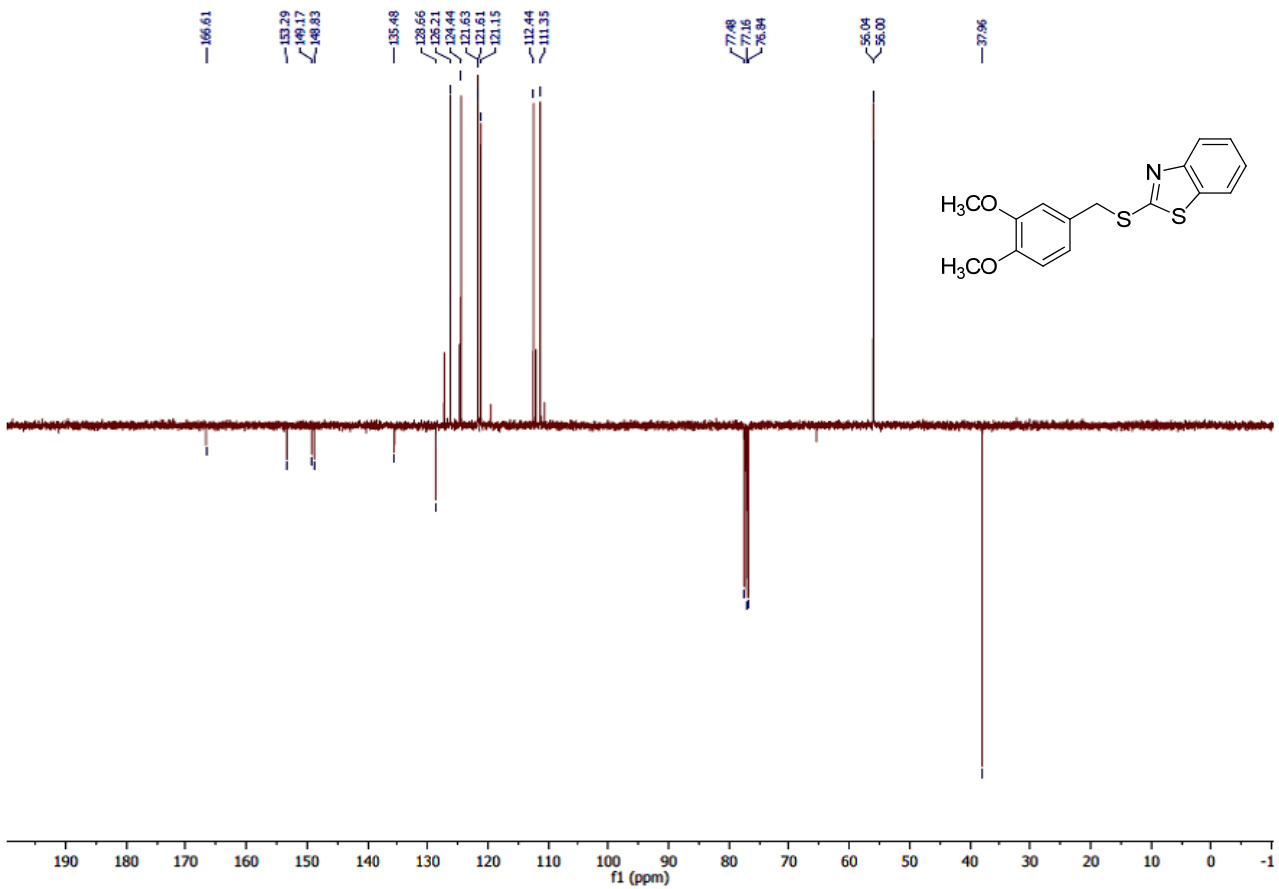
Appendix Figure 15 400 MHz ^{1}H NMR spectrum of 2-(2-methoxyphenethylthio)benzo[d]thiazole **(72)**



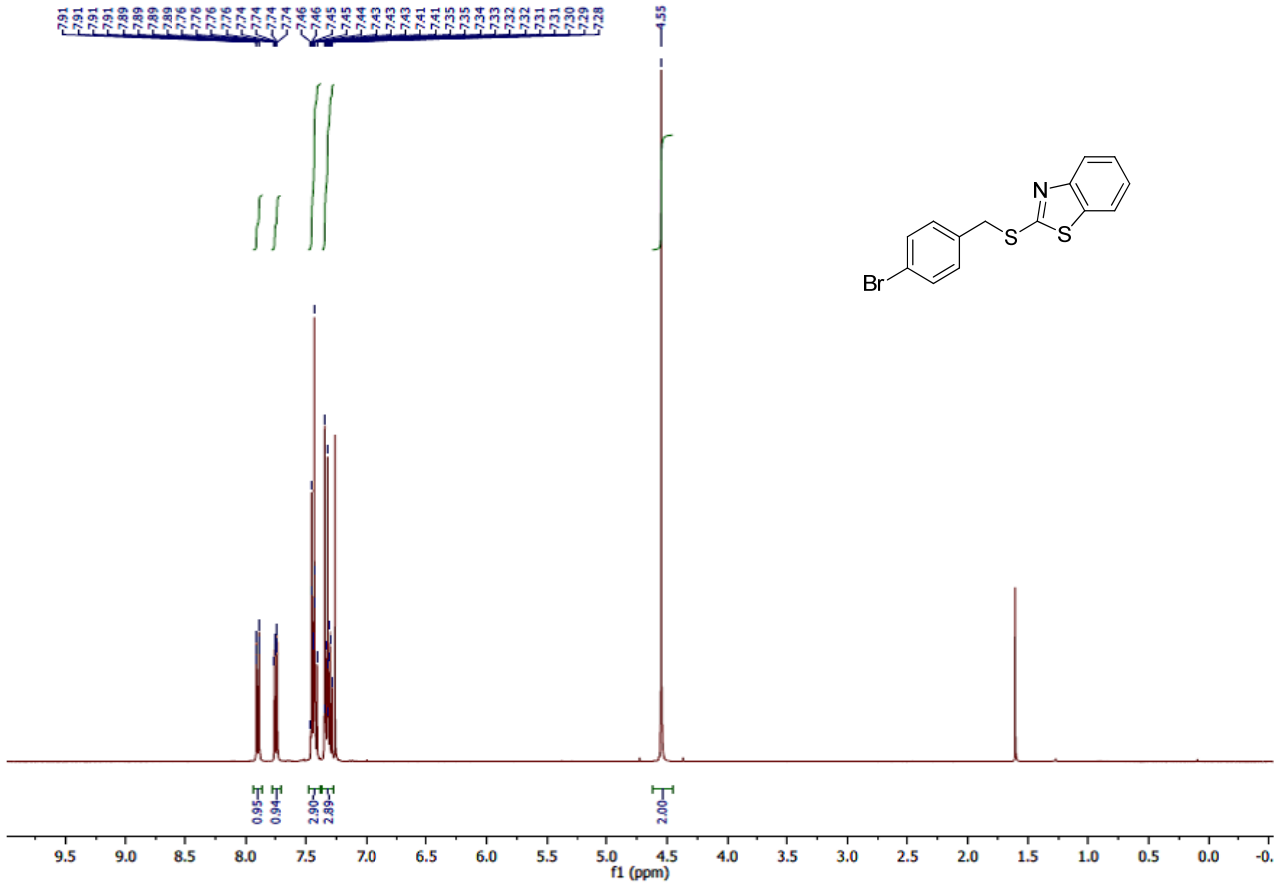
Appendix Figure 16 100 MHz ^{13}C NMR spectrum of 2-(2-methoxyphenethylthio)benzo[d]thiazole **(72)**



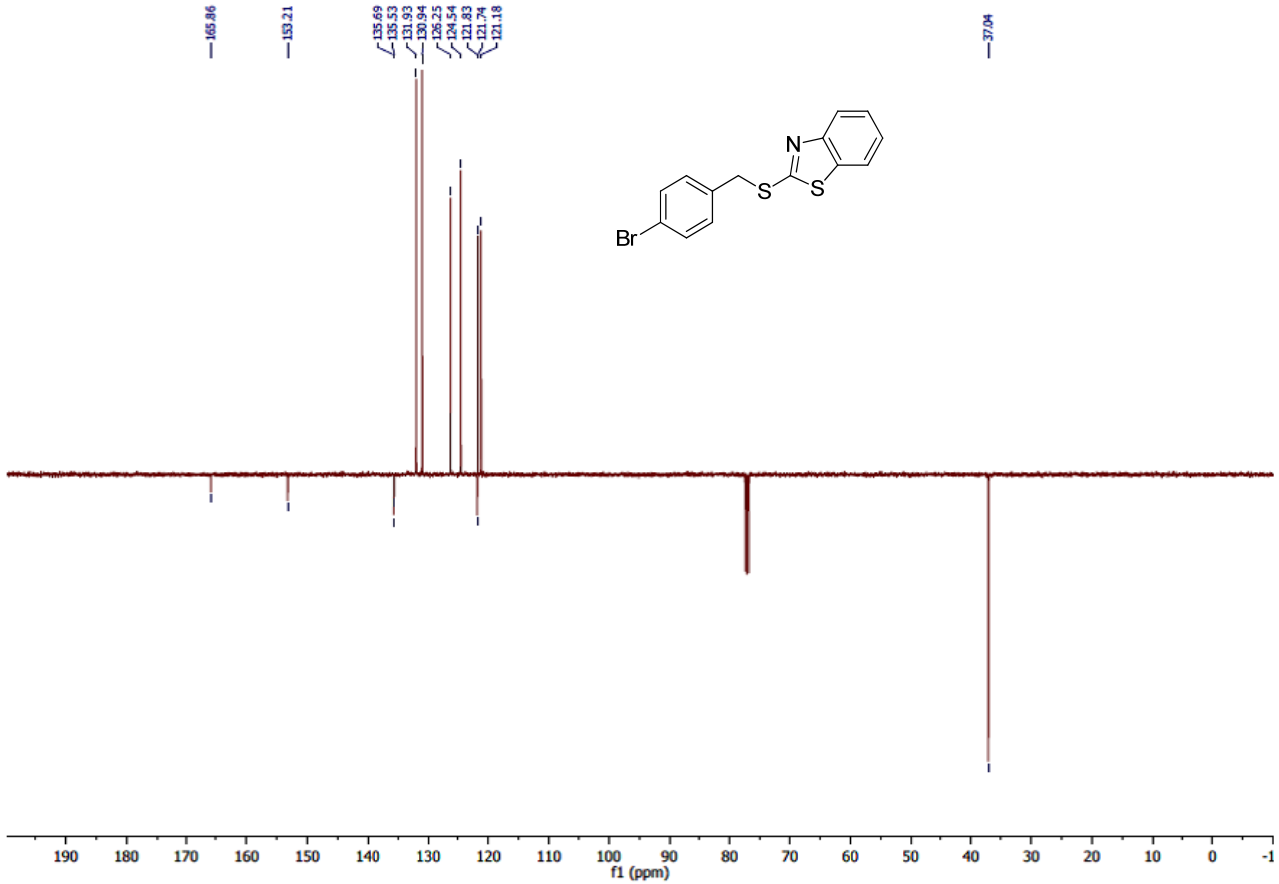
Appendix Figure 17 400 MHz ^{1}H NMR spectrum of 2-(3,4-dimethoxybenzylthio)benzo[d]thiazole **(74)**



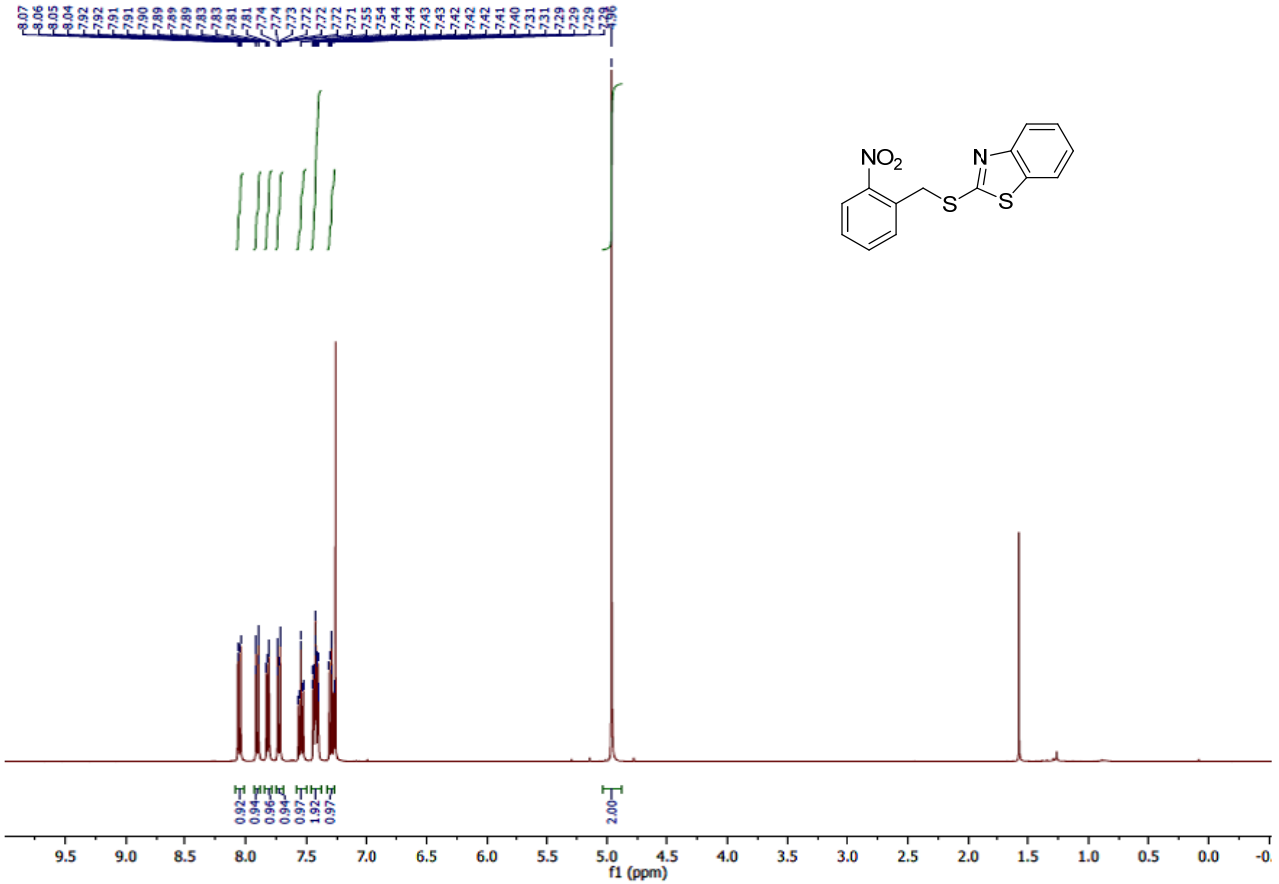
Appendix Figure 18 100 MHz ^{13}C NMR spectrum of 2-(3,4-dimethoxybenzylthio)benzo[d]thiazole **(74)**



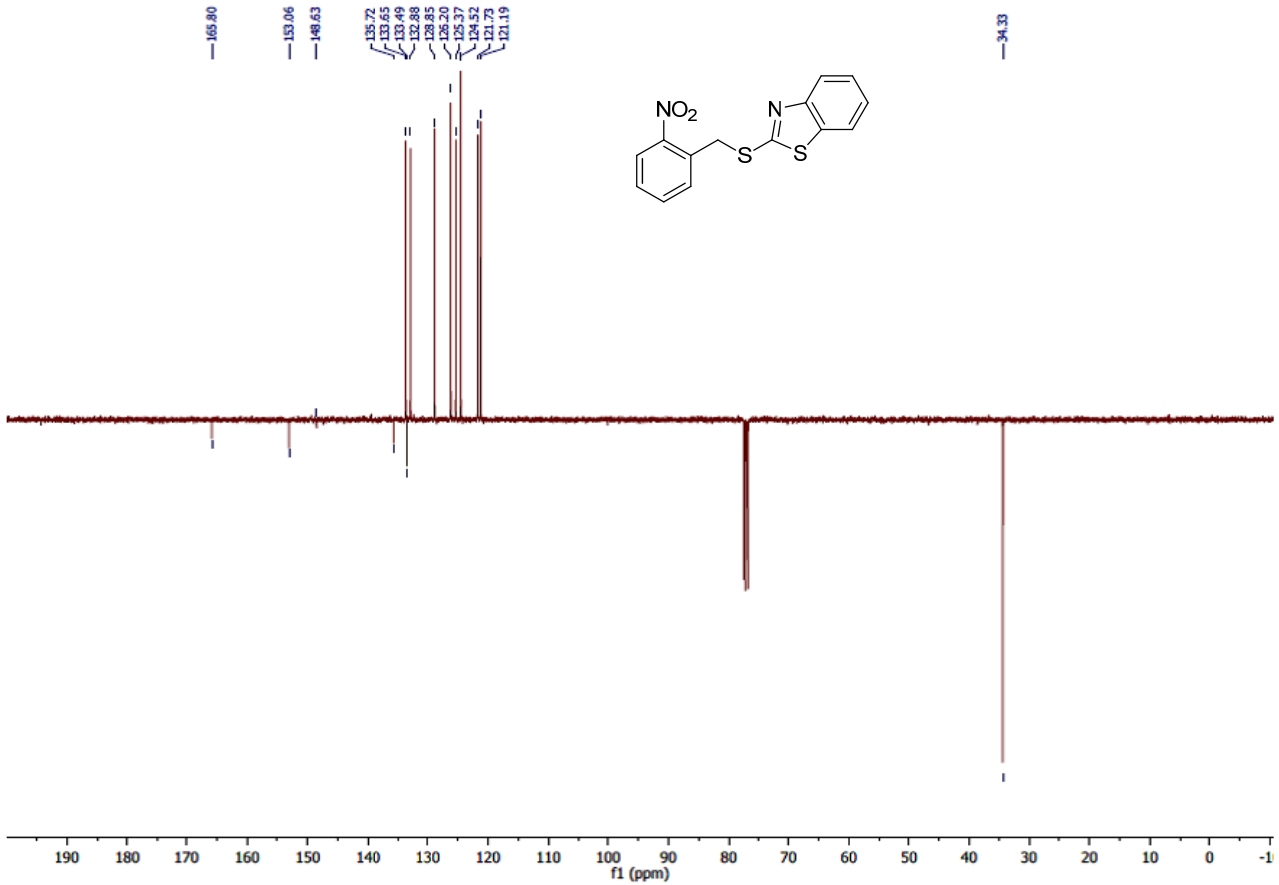
Appendix Figure 19 400 MHz ^{1}H NMR spectrum of 2-(4-bromobenzylthio)benzo[d]thiazole **(76)**



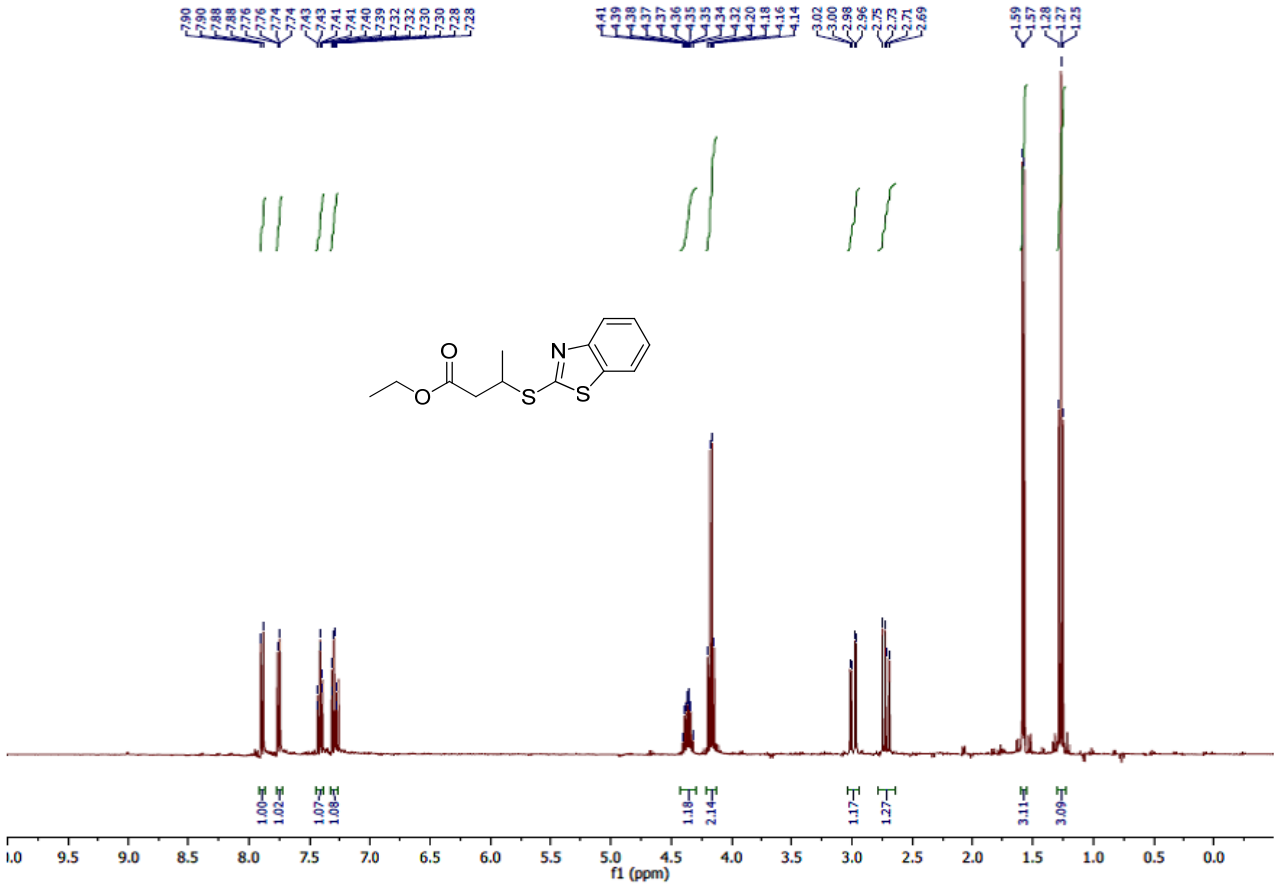
Appendix Figure 20 100 MHz ^{13}C NMR spectrum of 2-(4-bromobenzylthio)benzo[d]thiazole **(76)**



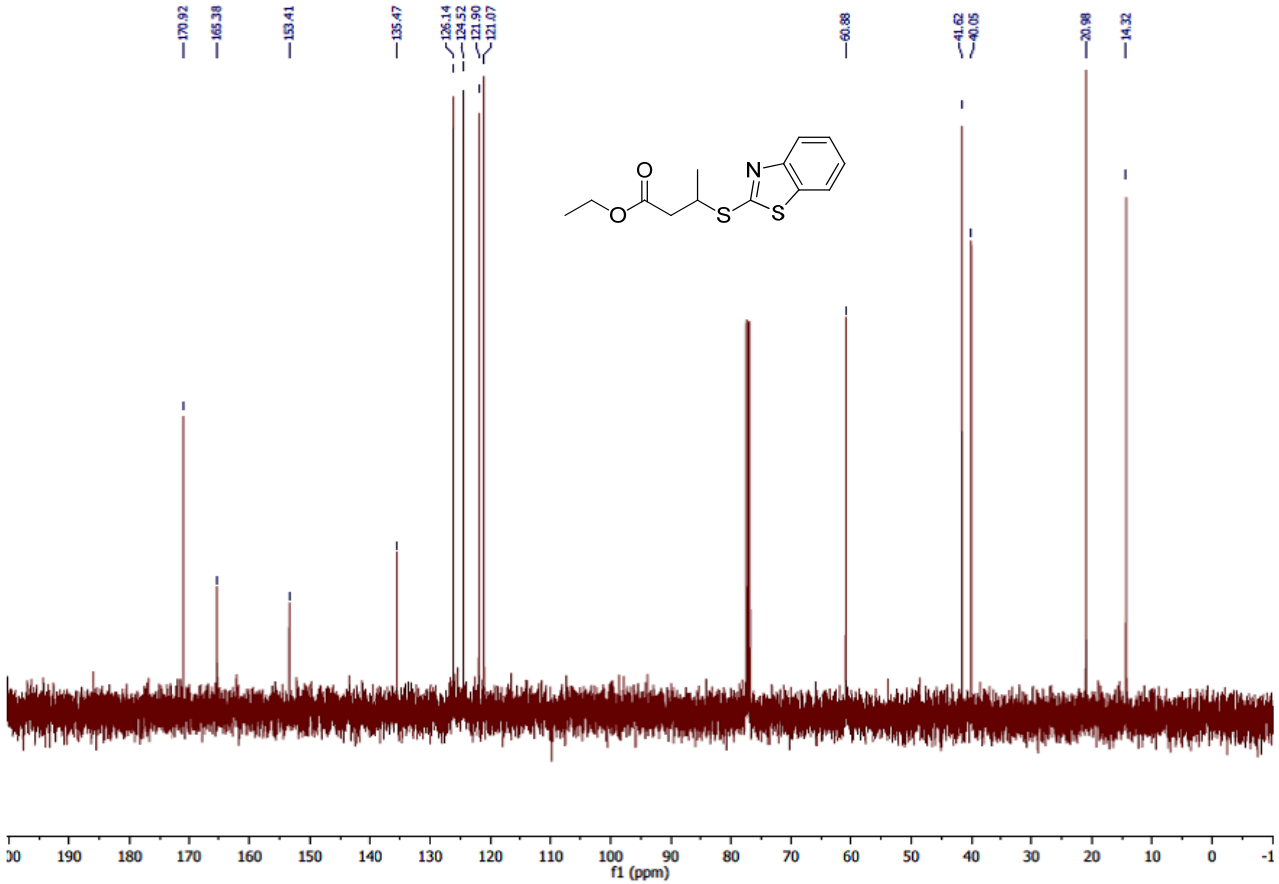
Appendix Figure 21 400 MHz ^{1}H NMR spectrum of 2-(2-nitrobenzylthio)benzo[d]thiazole **(78)**



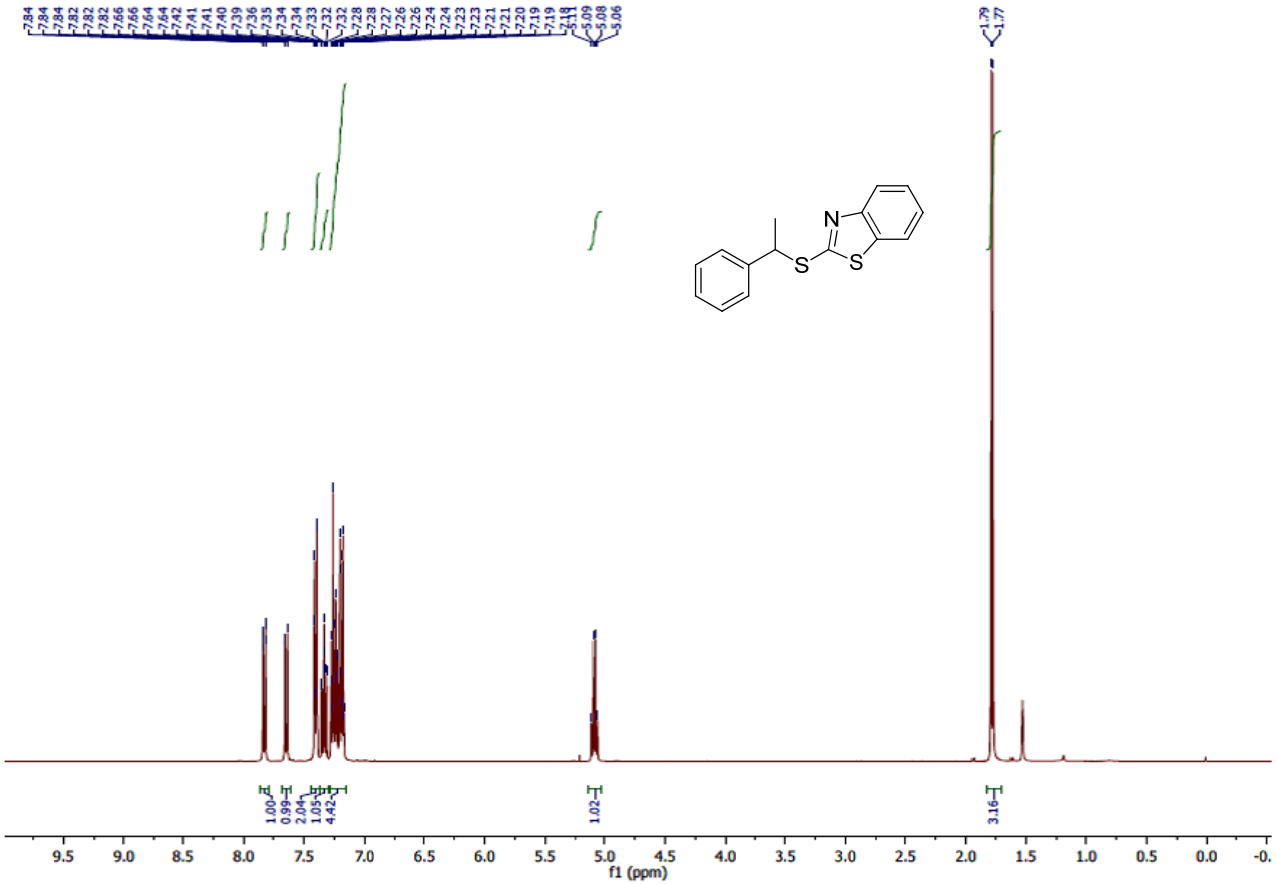
Appendix Figure 22 100 MHz ^{13}C NMR spectrum of 2-(2-nitrobenzylthio)benzo[d]thiazole **(78)**



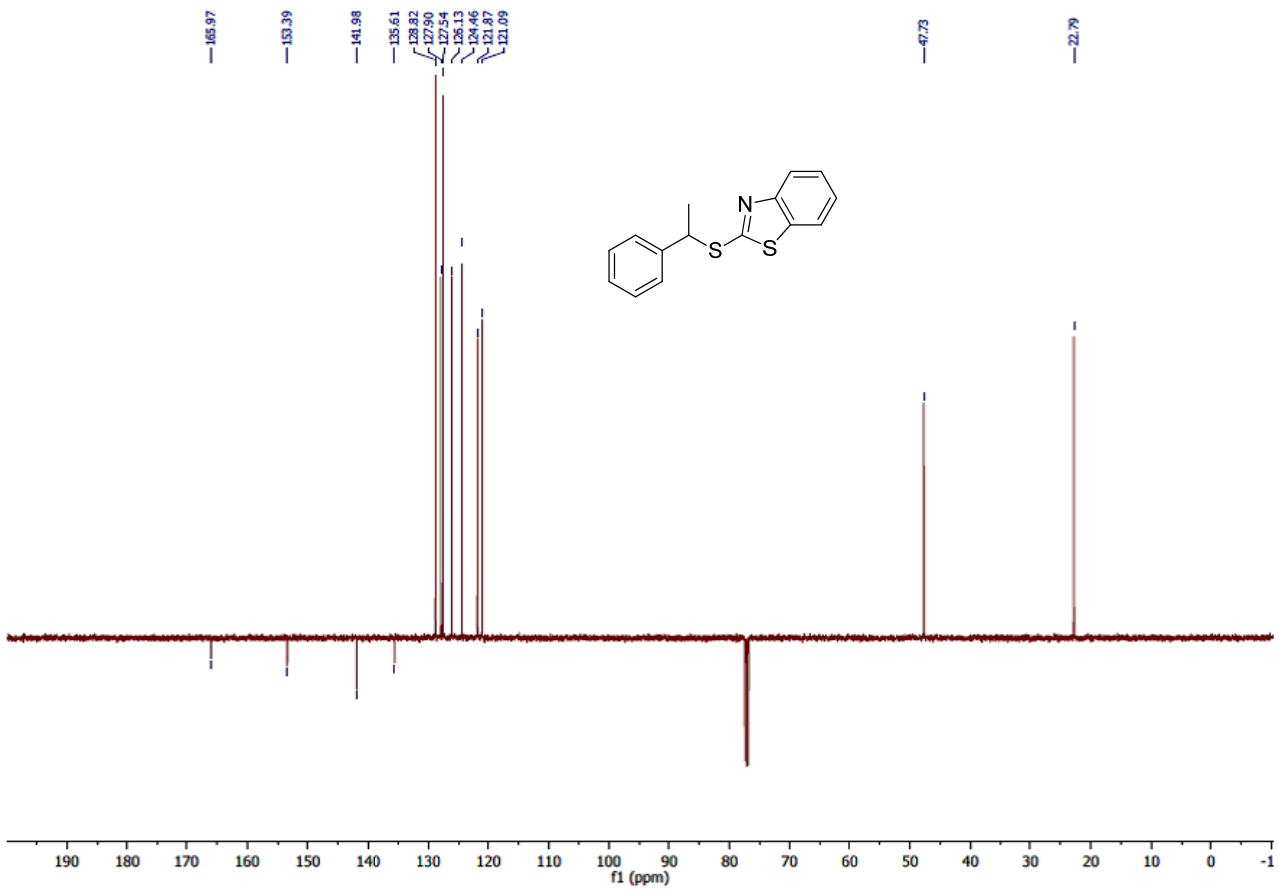
Appendix Figure 23 400 MHz ^{1}H NMR spectrum of ethyl 3-(benzo[d]thiazol-2-ylthio)butanoate **(80)**



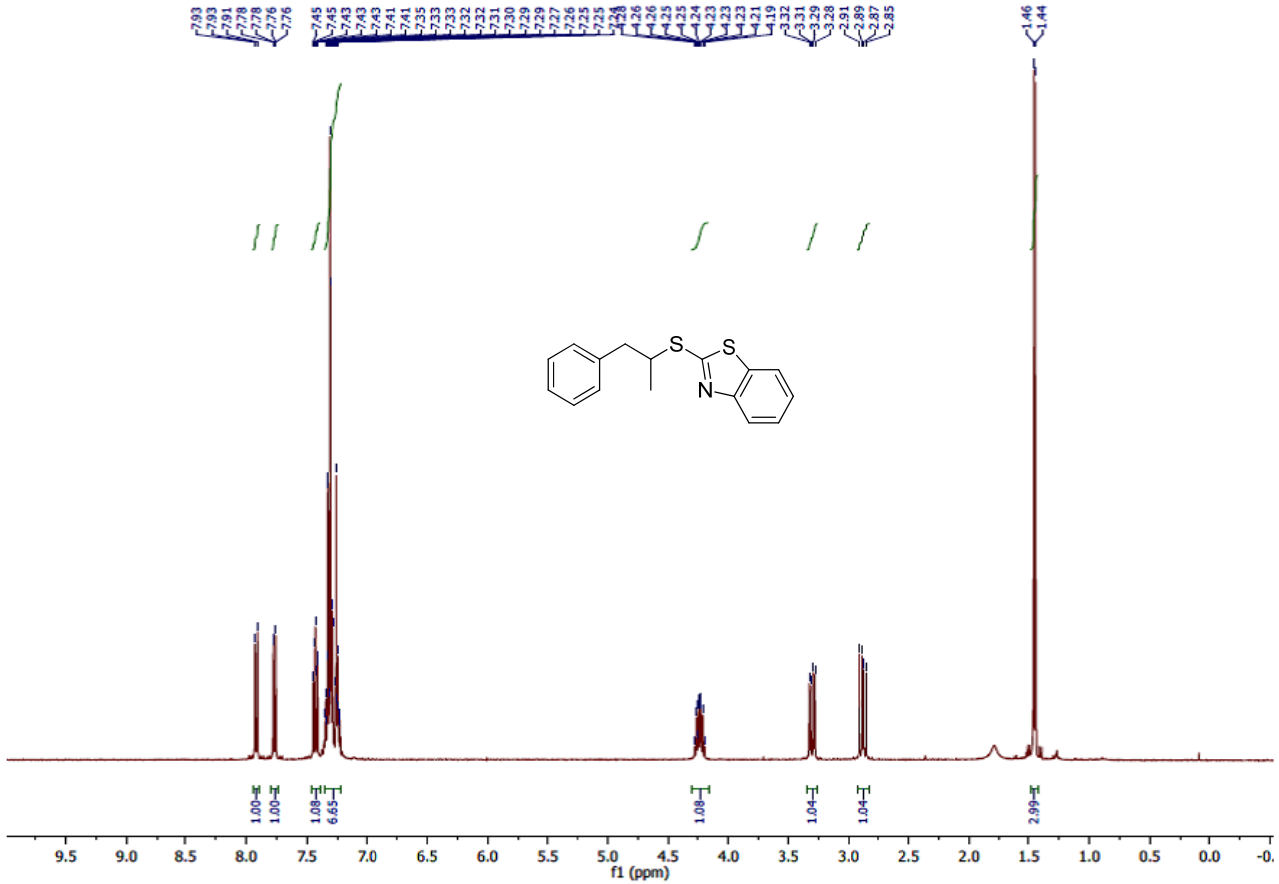
Appendix Figure 24 100 MHz ^{13}C NMR spectrum of ethyl 3-(benzo[d]thiazol-2-ylthio)butanoate **(80)**



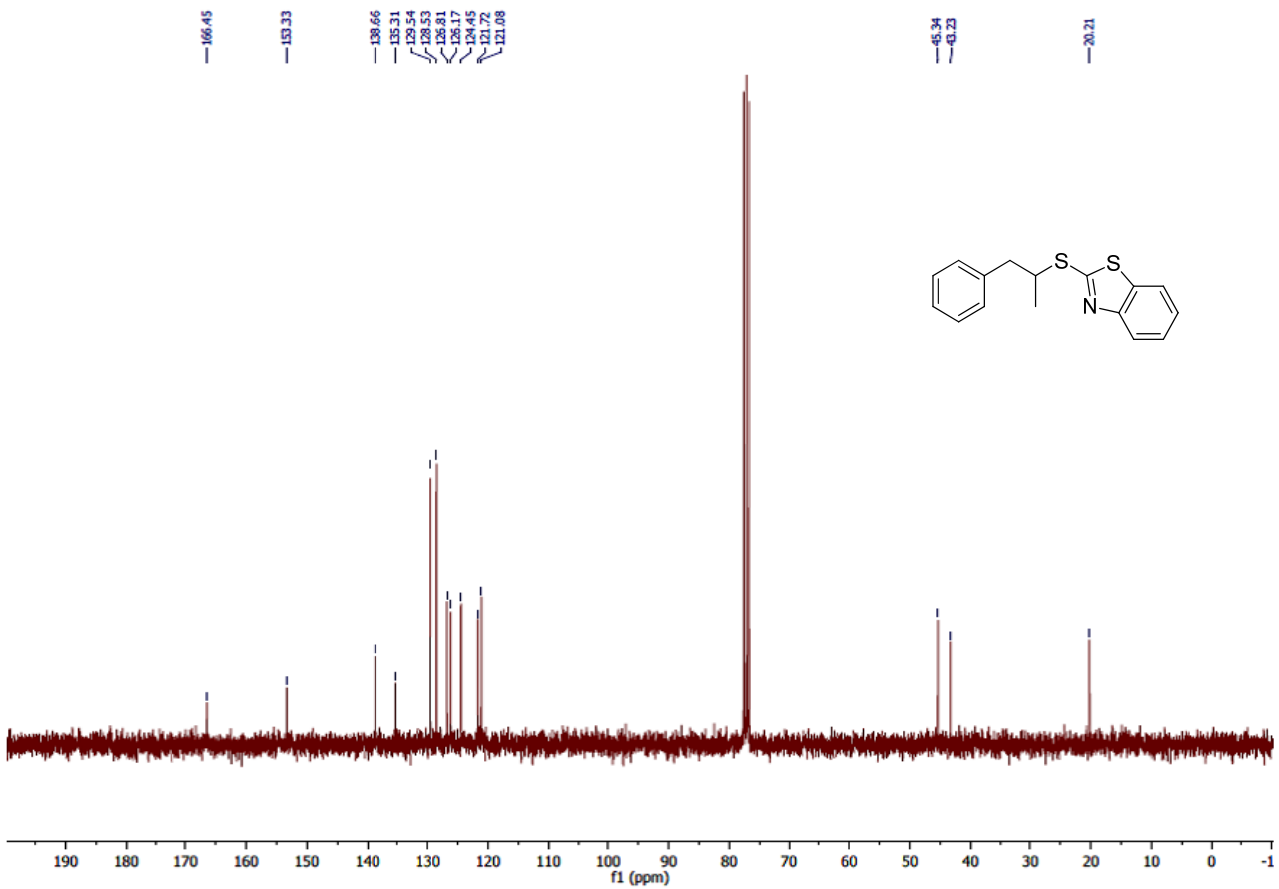
Appendix Figure 25 400 MHz ^{1}H NMR spectrum of 2-(1-phenylethylthio)benzo[d]thiazole **(82)**



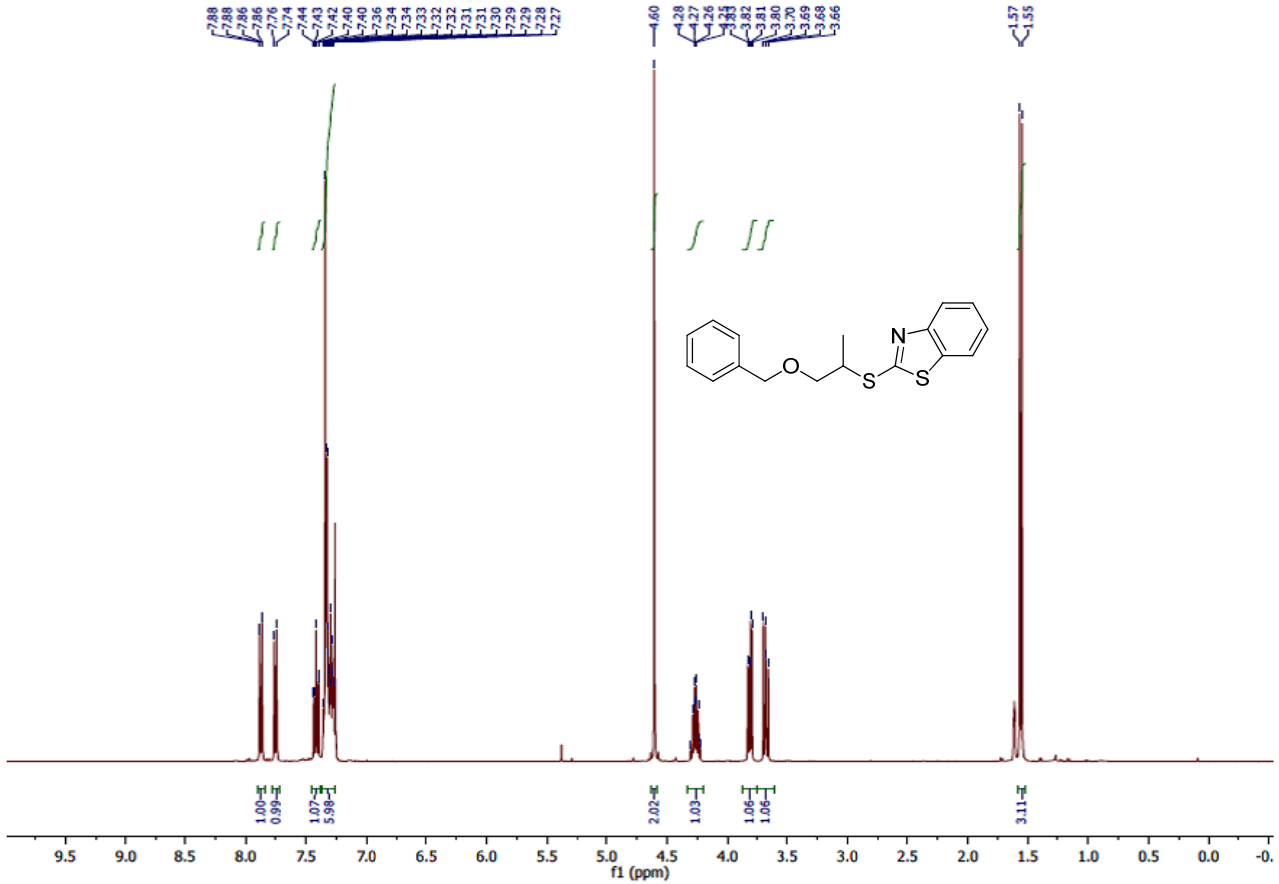
Appendix Figure 26 100 MHz ^{13}C NMR spectrum of 2-(1-phenylethylthio)benzo[d]thiazole **(82)**



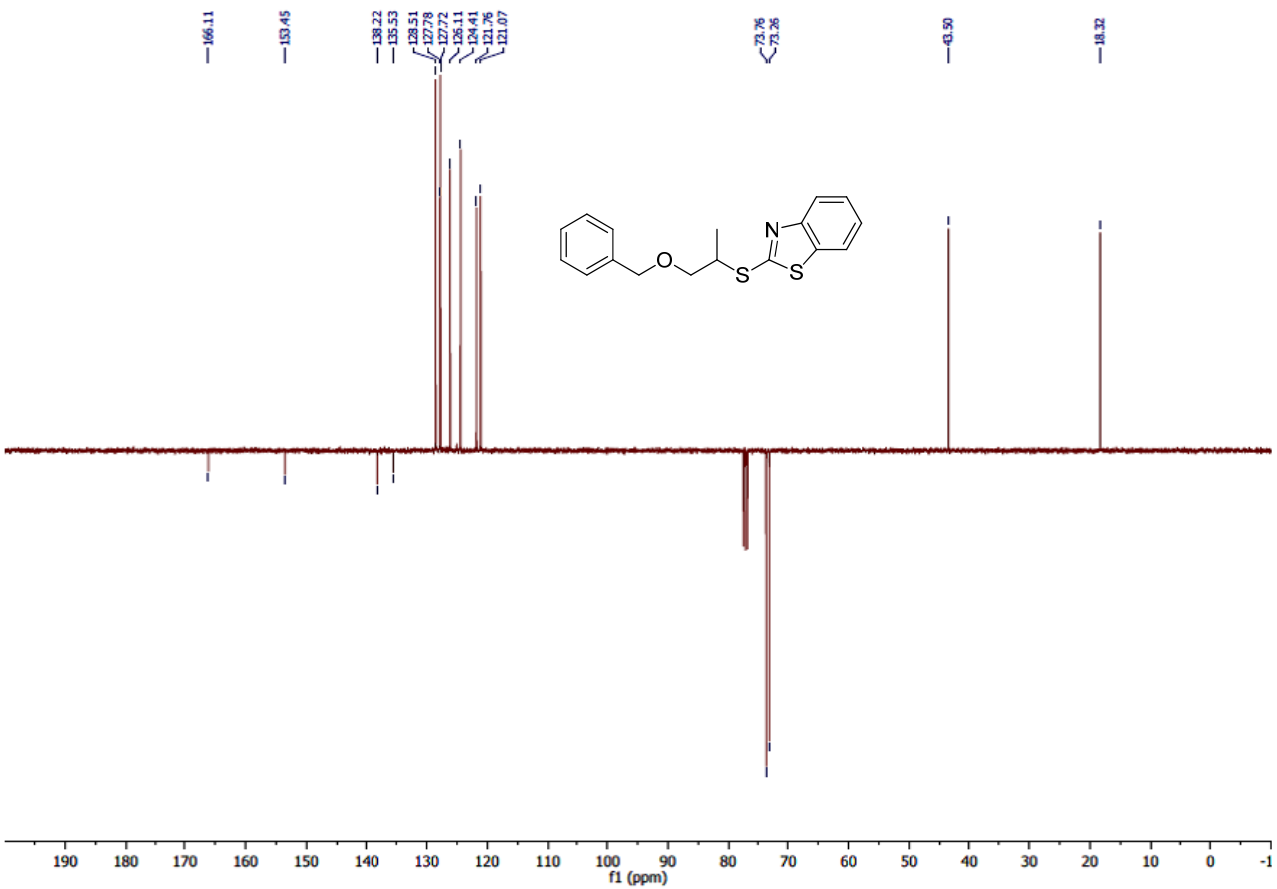
Appendix Figure 27 400 MHz ^{1}H NMR spectrum of 2-((1-phenylpropan-2-yl)thio)benzo[d]thiazole **(84)**



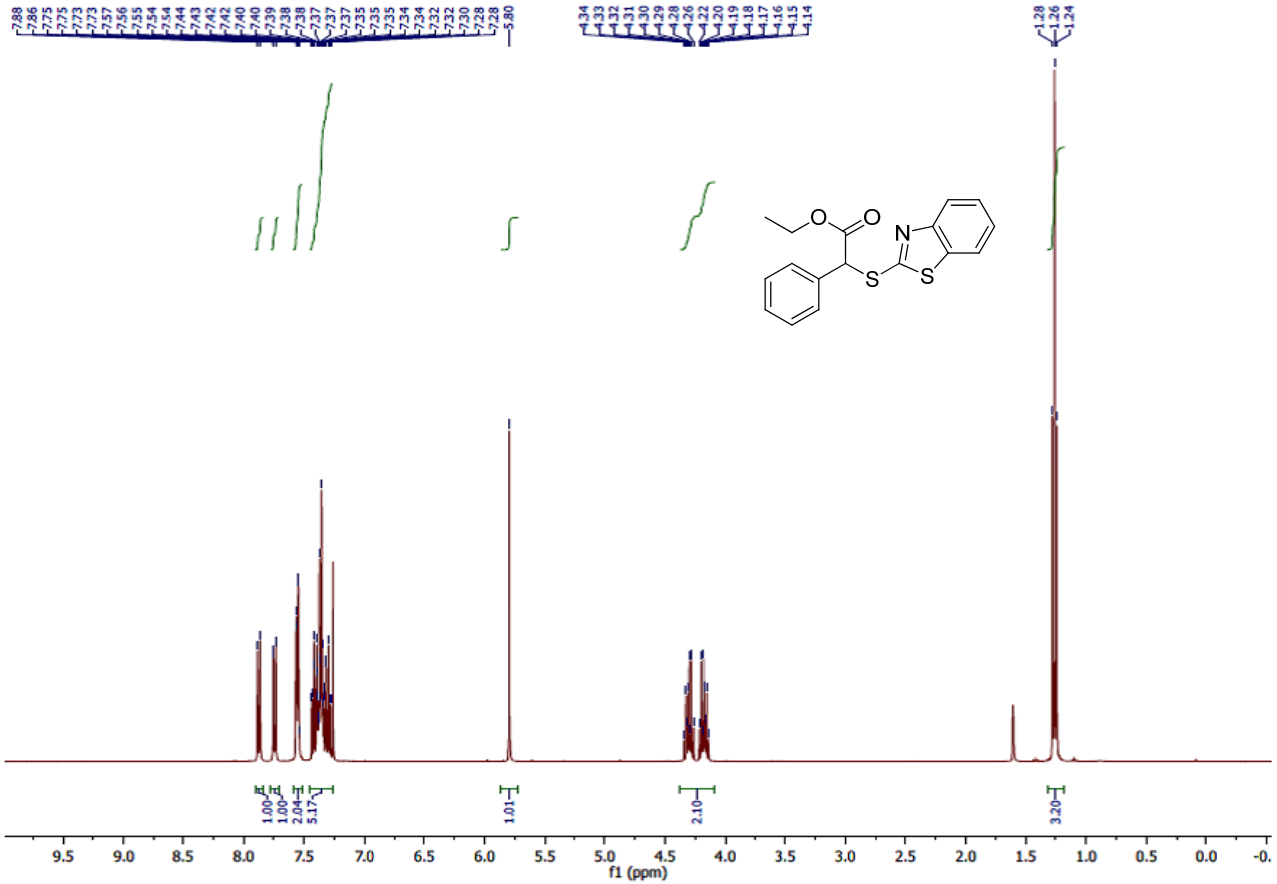
Appendix Figure 28 100 MHz ^{13}C NMR spectrum of 2-((1-phenylpropan-2-yl)thio)benzo[d]thiazole **(84)**



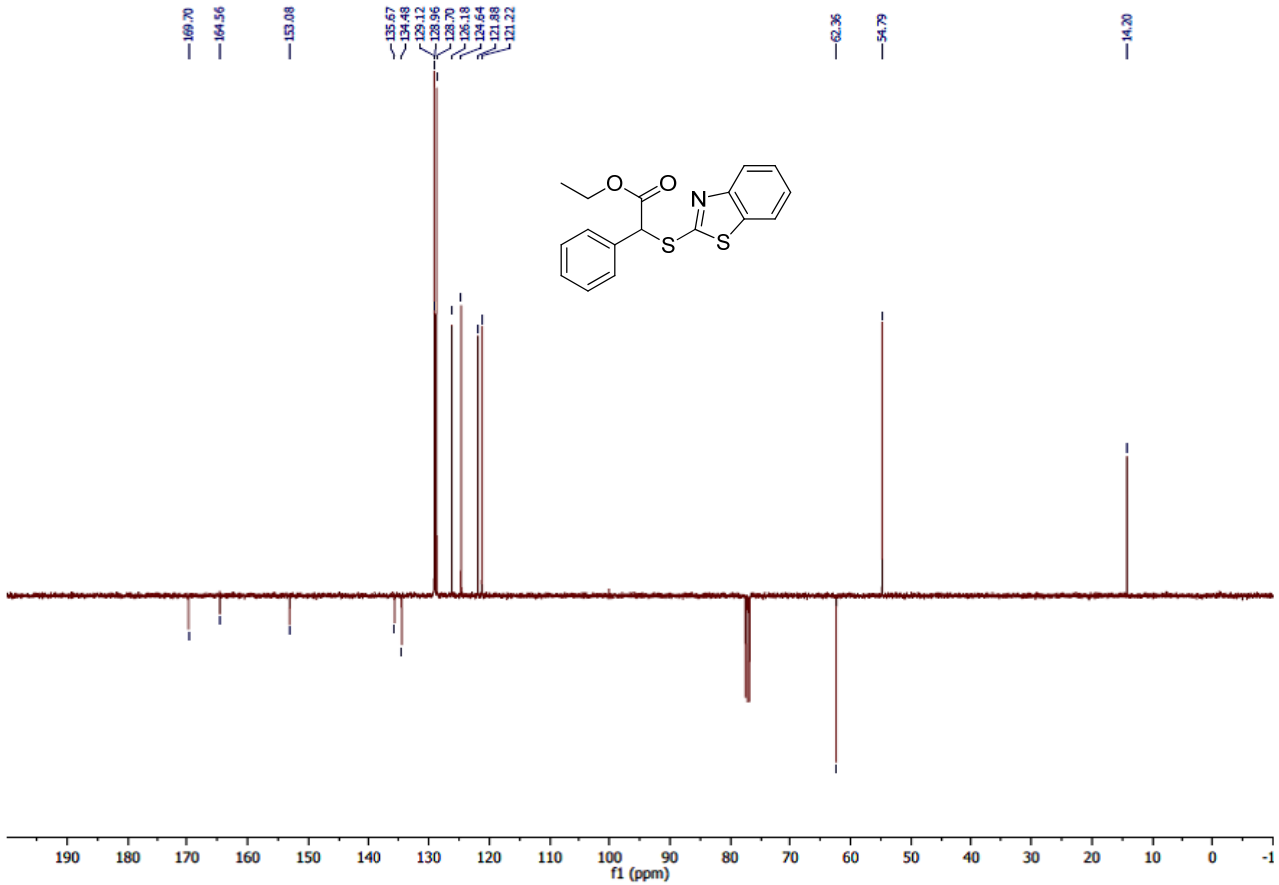
Appendix Figure 29 400 MHz ^{1}H NMR spectrum of 2-((1-(benzyloxy)propan-2-yl)thio)benzo[d]thiazole **(88)**



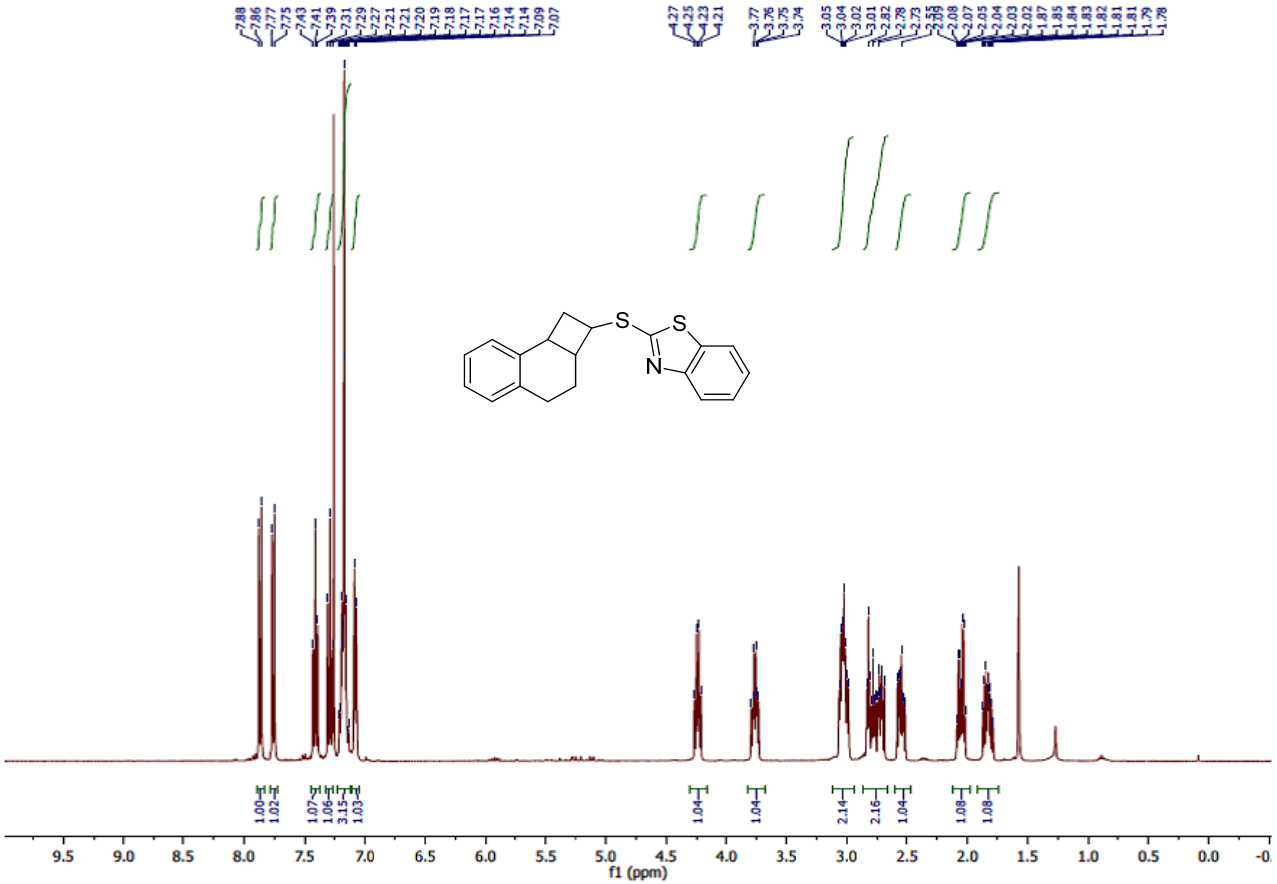
Appendix Figure 30 100 MHz ^{13}C NMR spectrum of 2-((1-(benzyloxy)propan-2-yl)thio)benzo[d]thiazole **(88)**



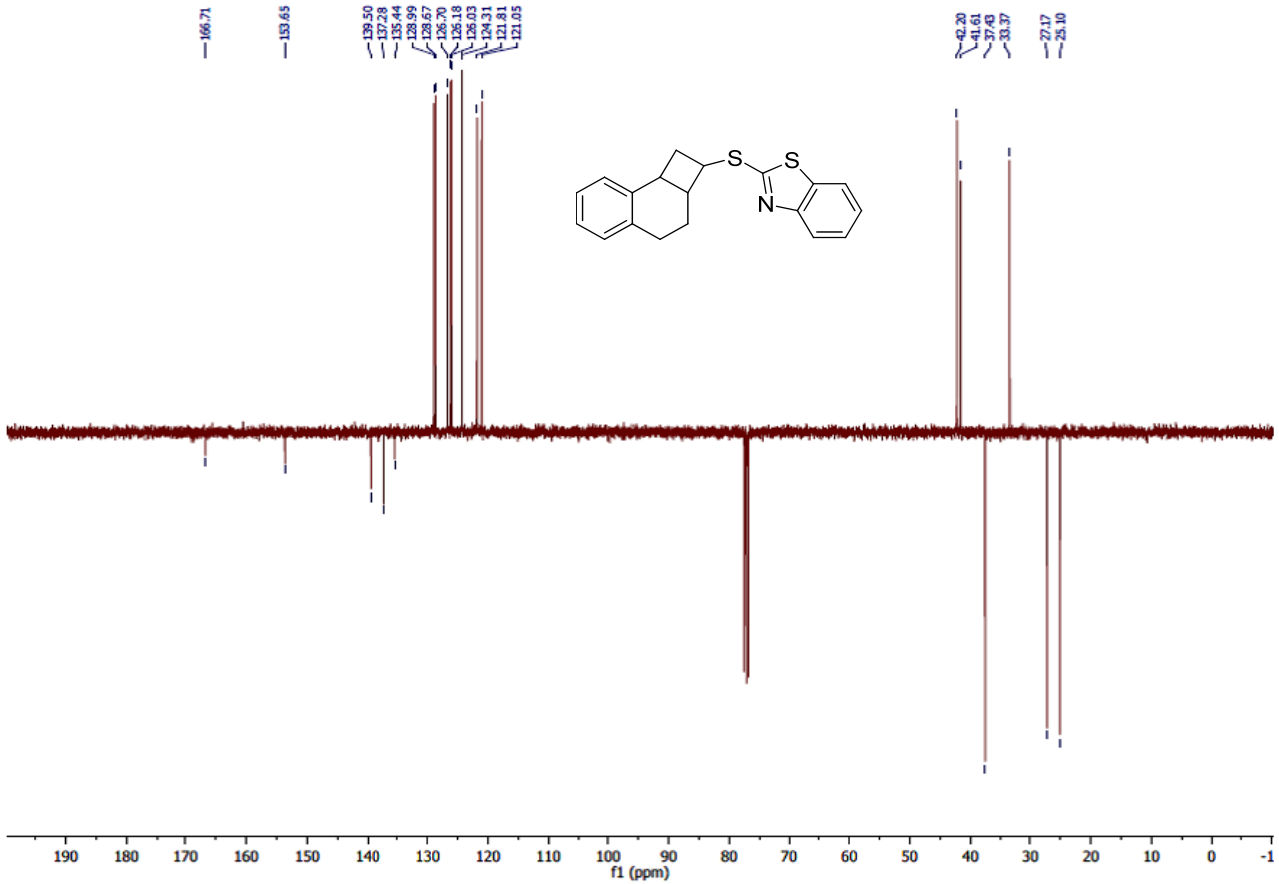
Appendix Figure 31 400 MHz ^{1}H NMR spectrum of ethyl 2-(benzothiazol-2-ylthio)-2-phenylacetate **(90)**



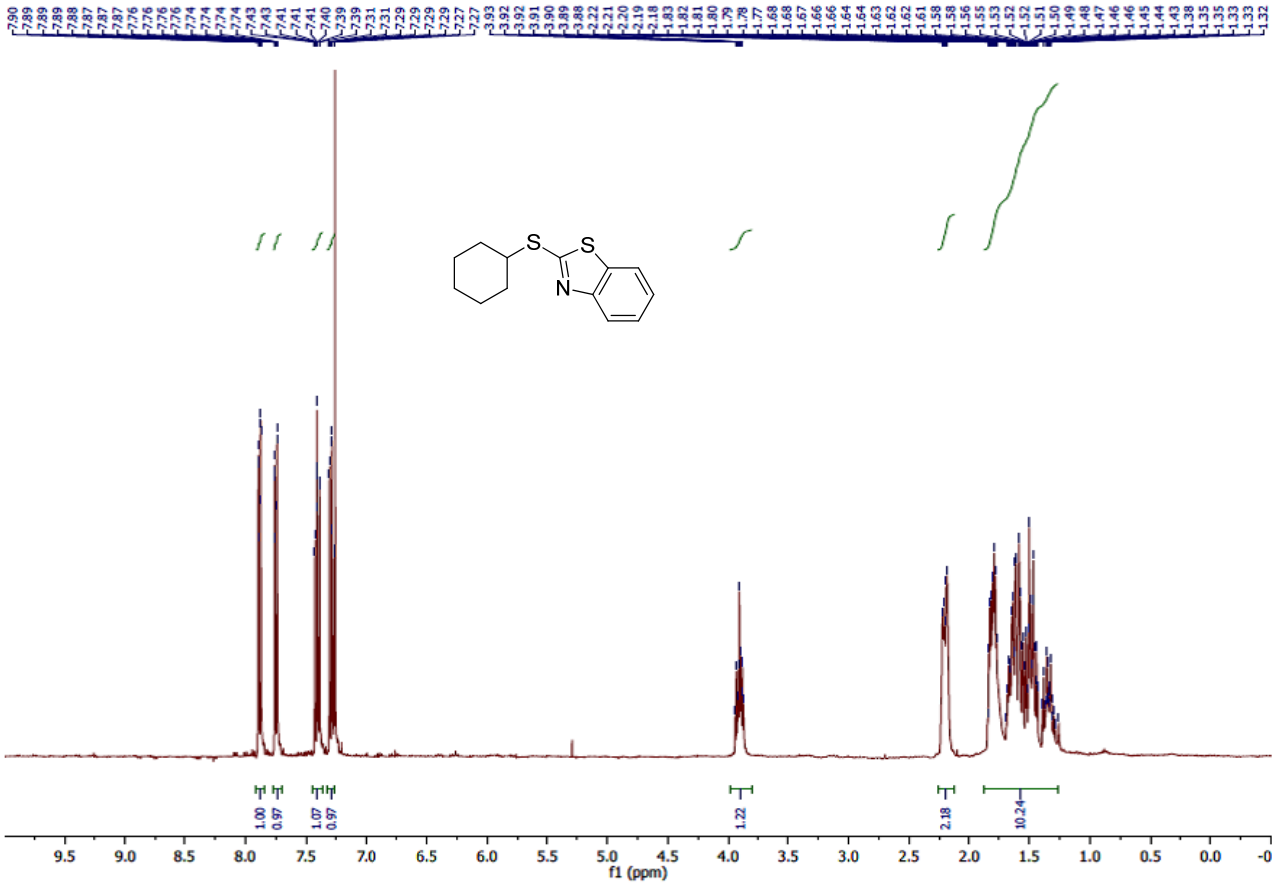
Appendix Figure 32 100 MHz ^{13}C NMR spectrum of ethyl 2-(benzothiazol-2-ylthio)- 2-phenylacetate **(90)**



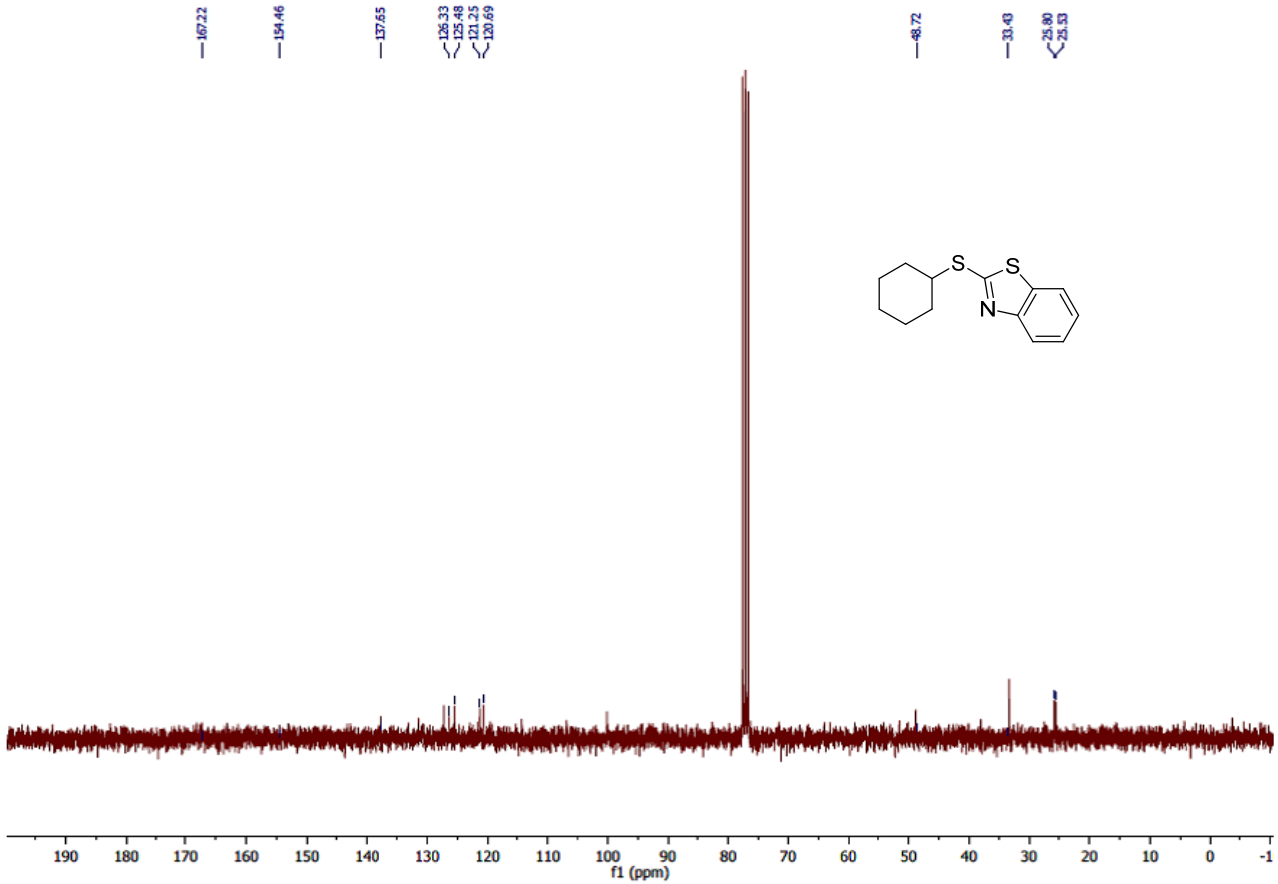
Appendix Figure 33 400 MHz ^{1}H NMR spectrum of 2-((1,2,2a,3,4,8b-hexahydro-cyclobuta[a]naphthalene-2-yl)thio) benzo[d]thiazole **(92)**



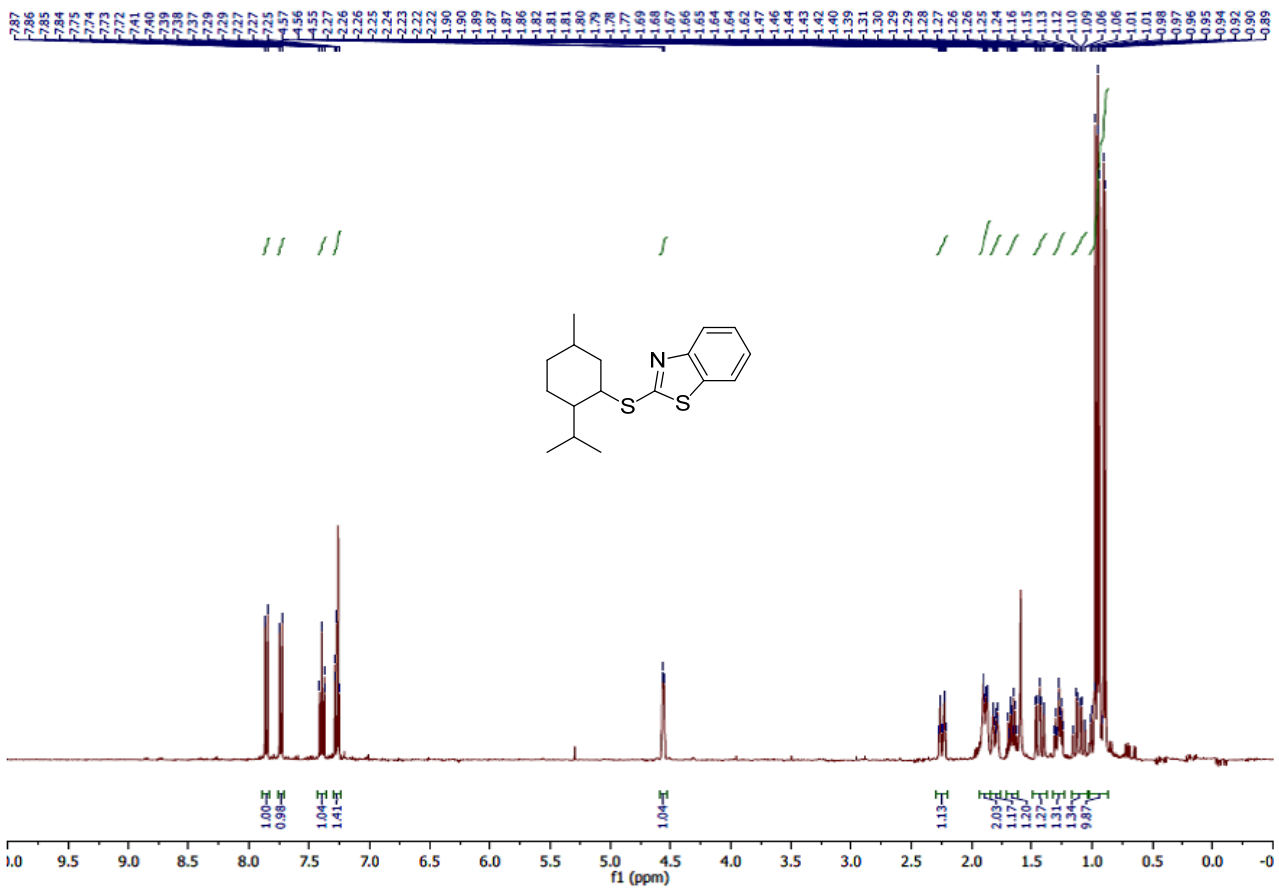
Appendix Figure 34 100 MHz ^{13}C NMR spectrum of of 2-((1,2,2a,3,4,8b-hexahydro- cyclobuta[a]naphthalene-2-yl)thio) benzo[d]thiazole **(92)**



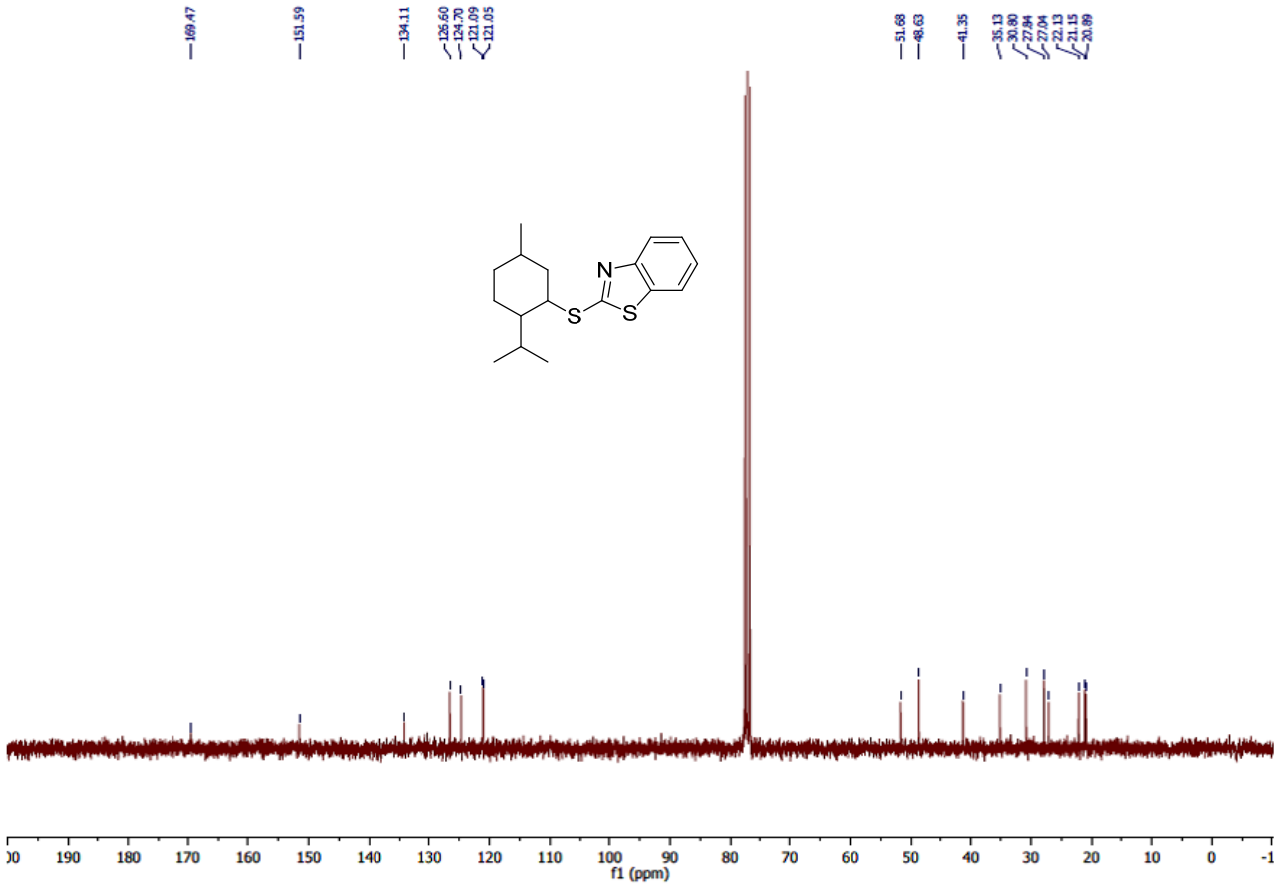
Appendix Figure 35 400 MHz ^{1}H NMR spectrum of 2-(cyclohexylthio)benzo[d]thiazole **(94)**



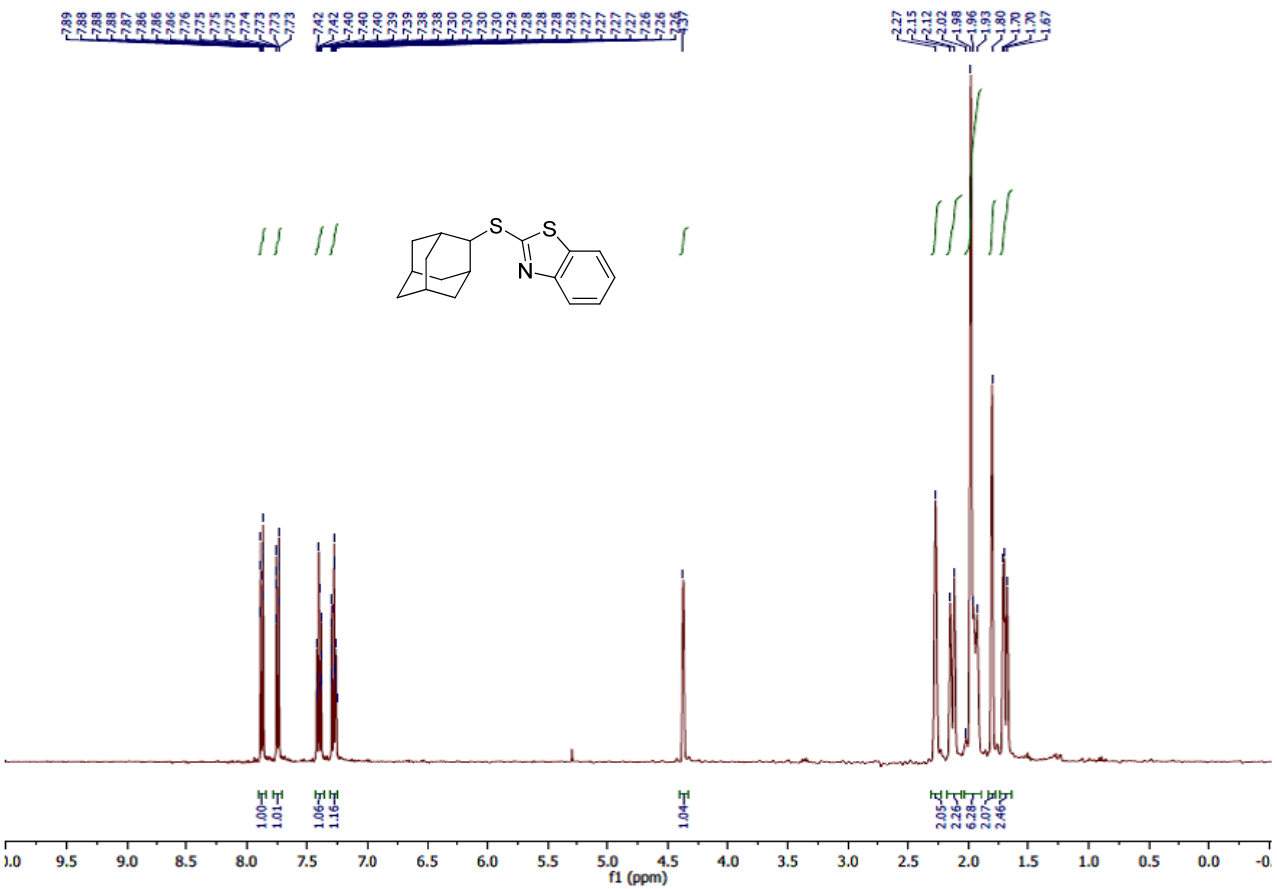
Appendix Figure 36 100 MHz ^{13}C NMR spectrum of 2-(cyclohexylthio)benzo[d]thiazole **(94)**



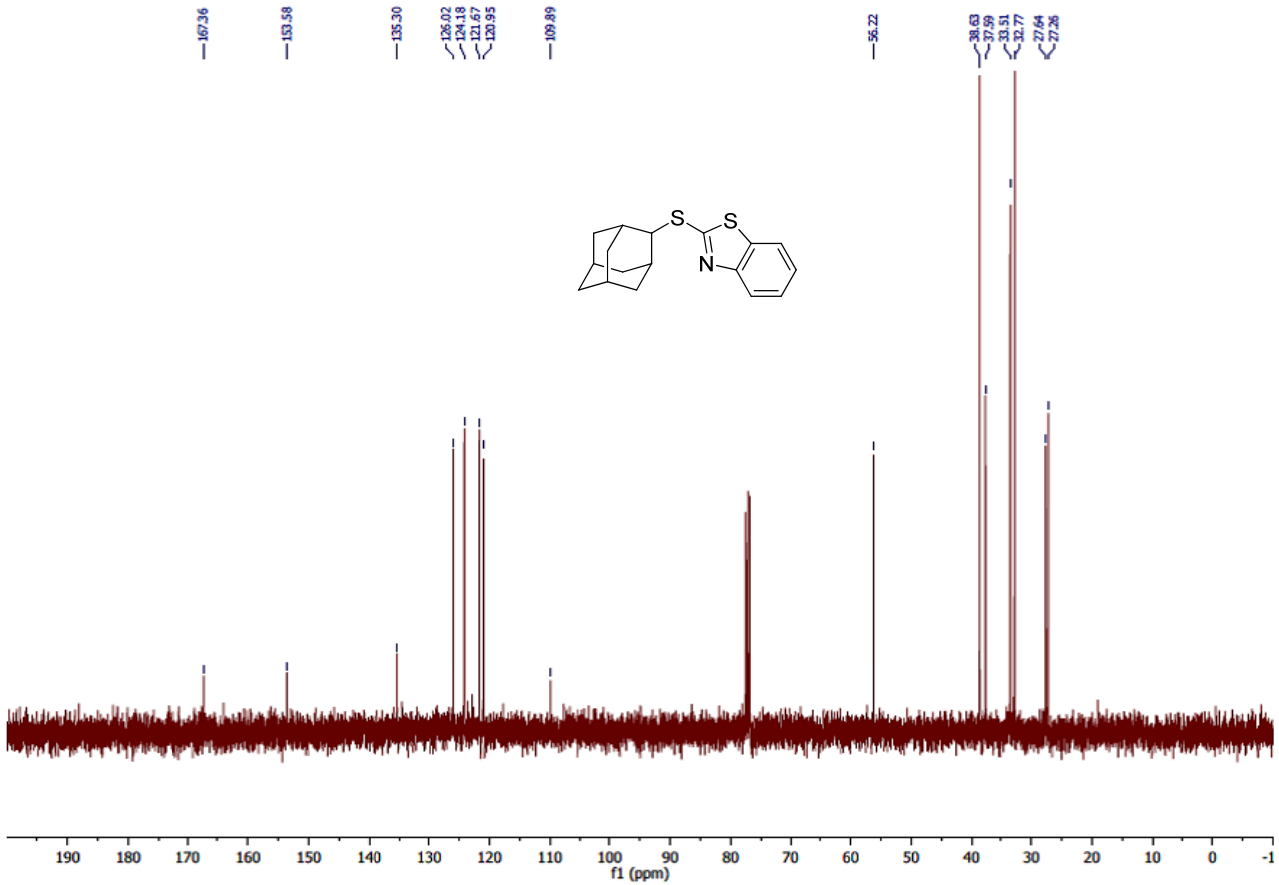
Appendix Figure 37 400 MHz ^{1}H NMR spectrum of 2-((2-isopropyl-5-methylcyclohexyl)thio)thiazole **(96)**



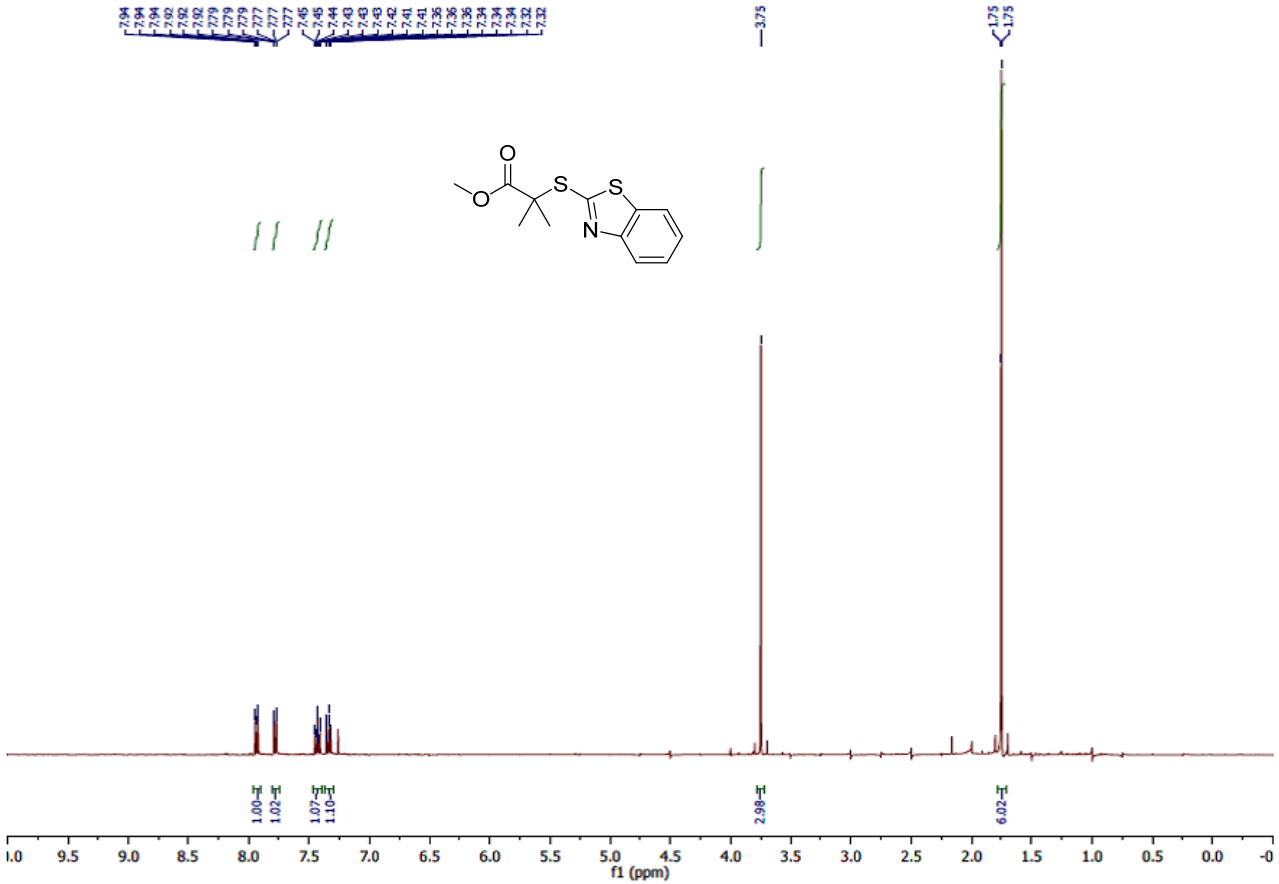
Appendix Figure 38 100 MHz ^{13}C NMR spectrum of 2-((2-isopropyl-5-methylcyclohexyl)thio)thiazole **(96)**



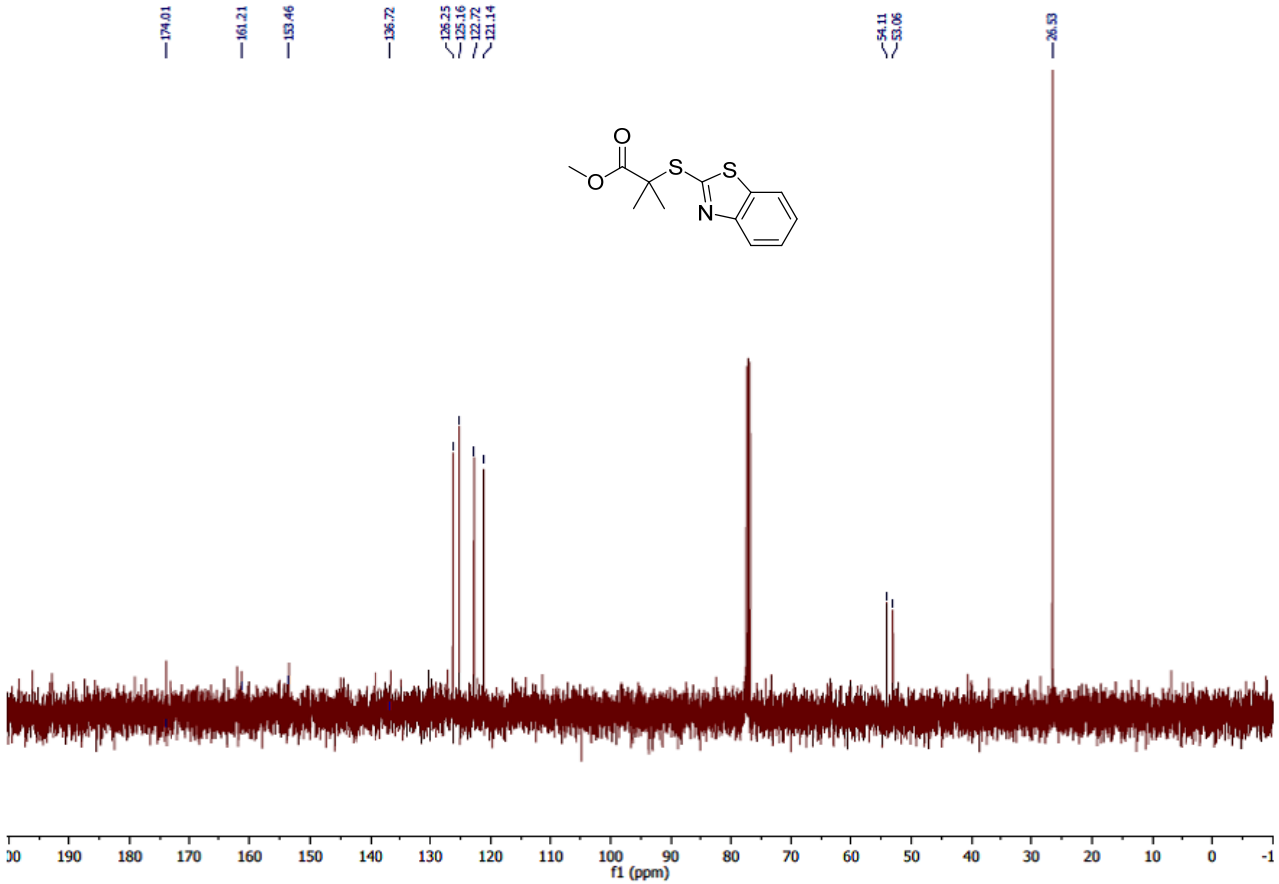
Appendix Figure 39 400 MHz ^{1}H NMR spectrum of 2-(adamantan-2-ylthio)benzo[d]thiazole **(98)**



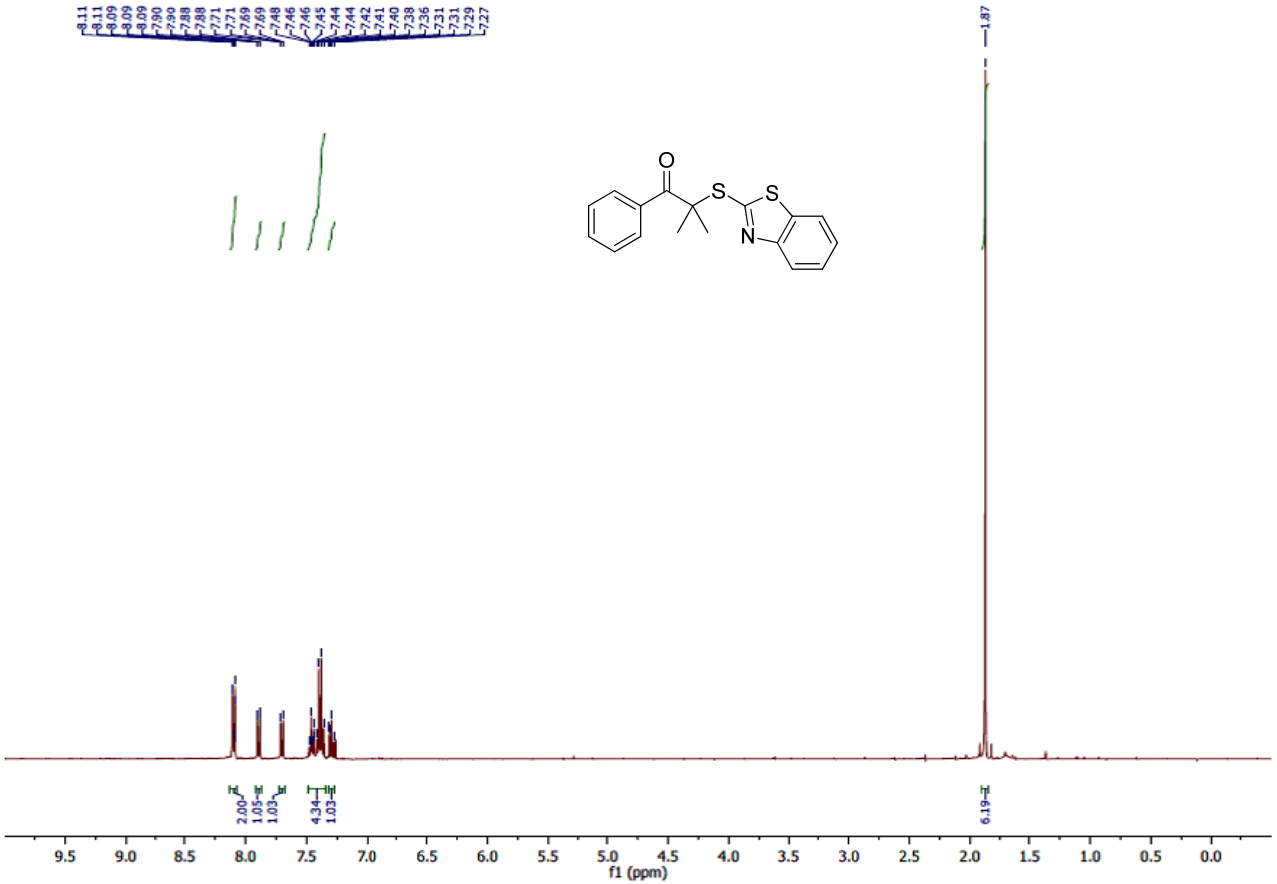
Appendix Figure 40 100 MHz ^{13}C NMR spectrum of 2-(adamantan-2-ylthio)benzo[d]thiazole **(98)**



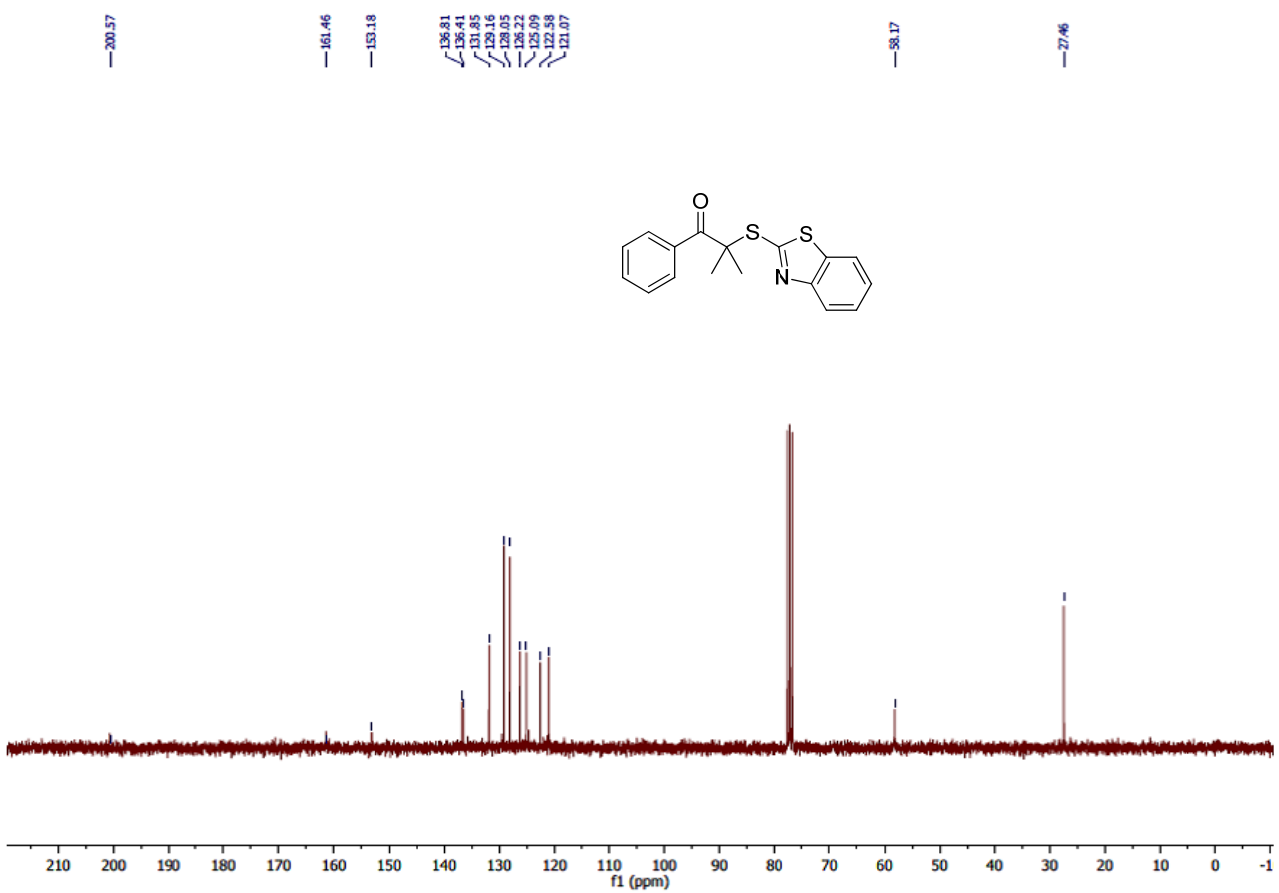
Appendix Figure 41 400 MHz ^{1}H NMR spectrum of methyl 2-(benzo[d]thiazol-2-ylthio)-2methyl-propanoate **(100)**



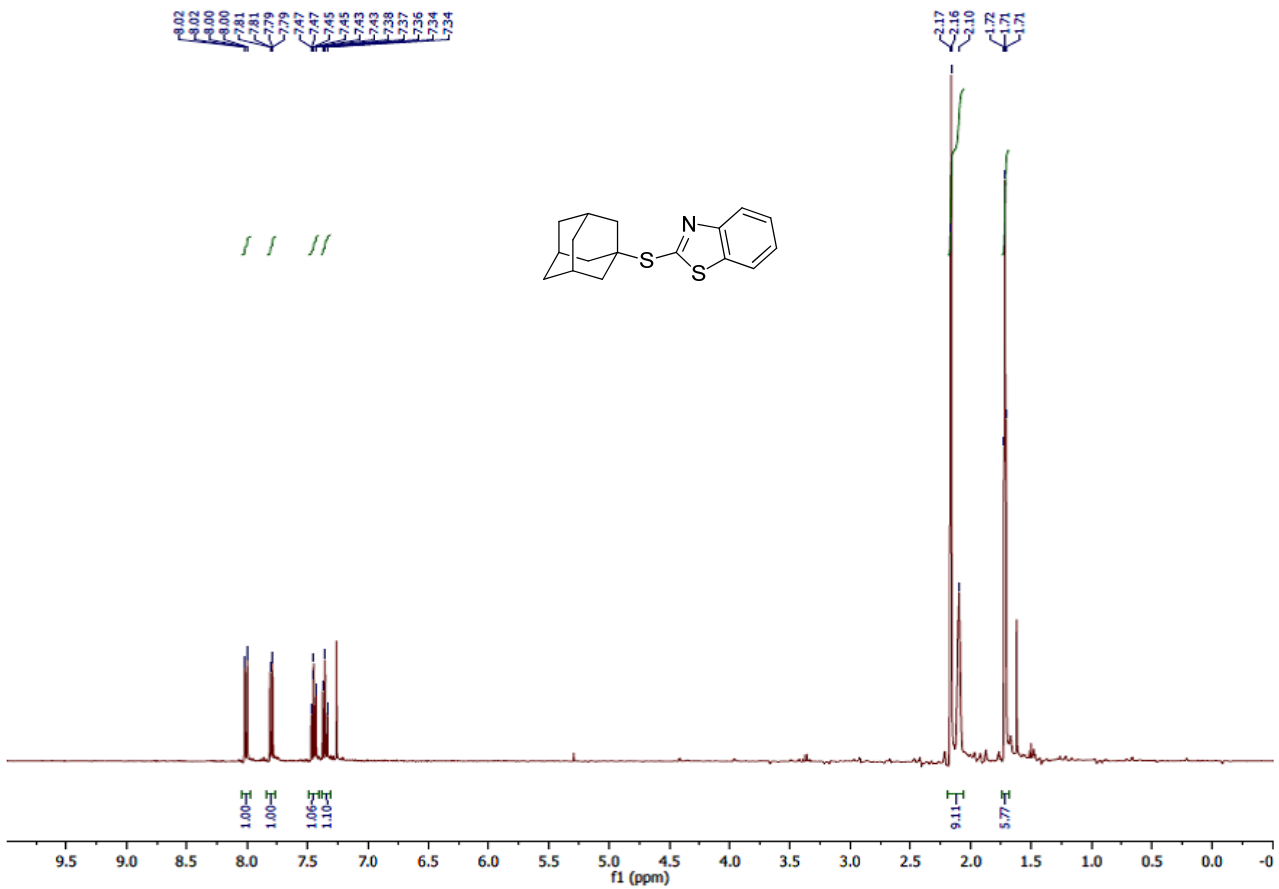
Appendix Figure 42 100 MHz ^{13}C NMR spectrum of methyl 2-(benzo[d]thiazol-2-ylthio)-2methyl-propanoate **(100)**



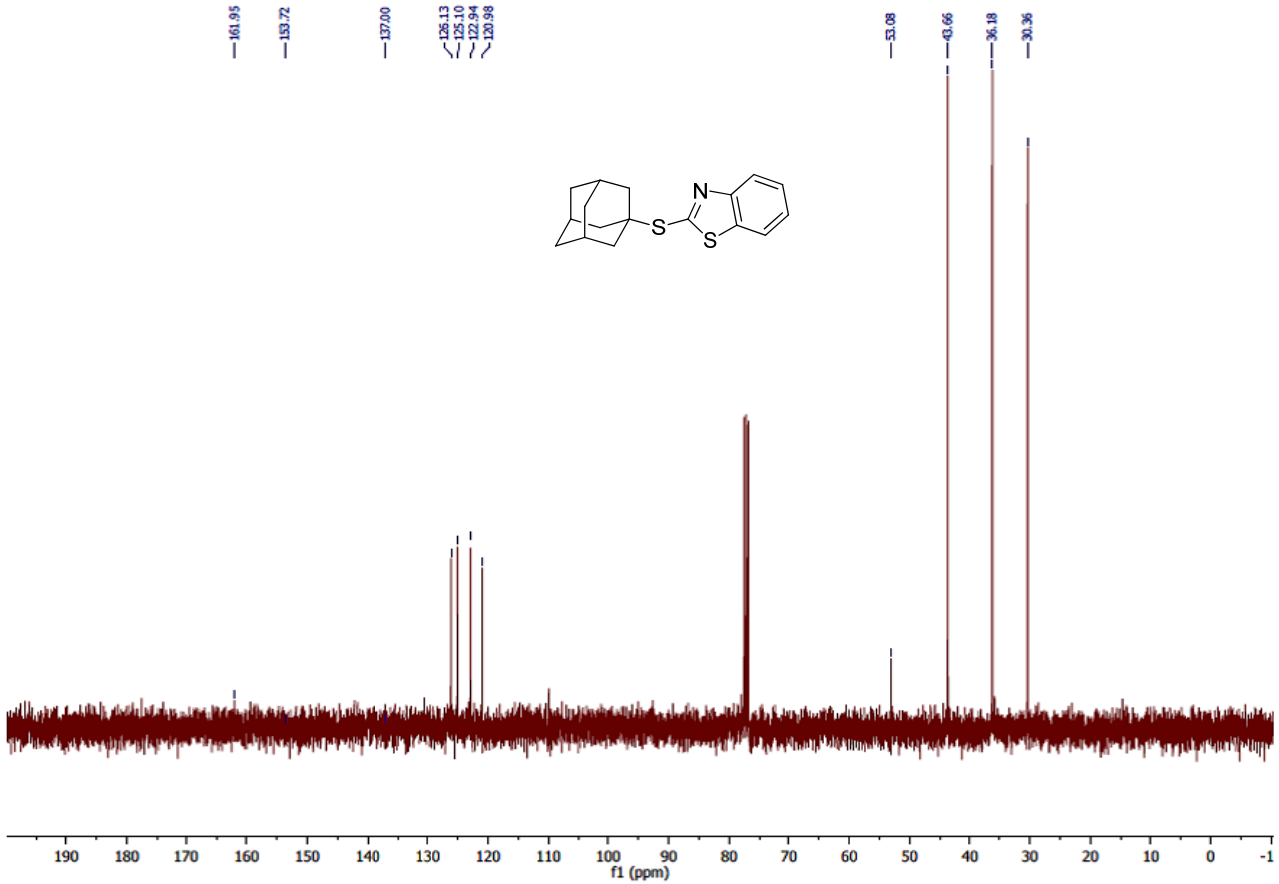
Appendix Figure 43 400 MHz ^{1}H NMR spectrum of 2-(benzo[d]thiazol-2-ylthio)-2-methyl-1-phenylpropan-1-one **(102)**



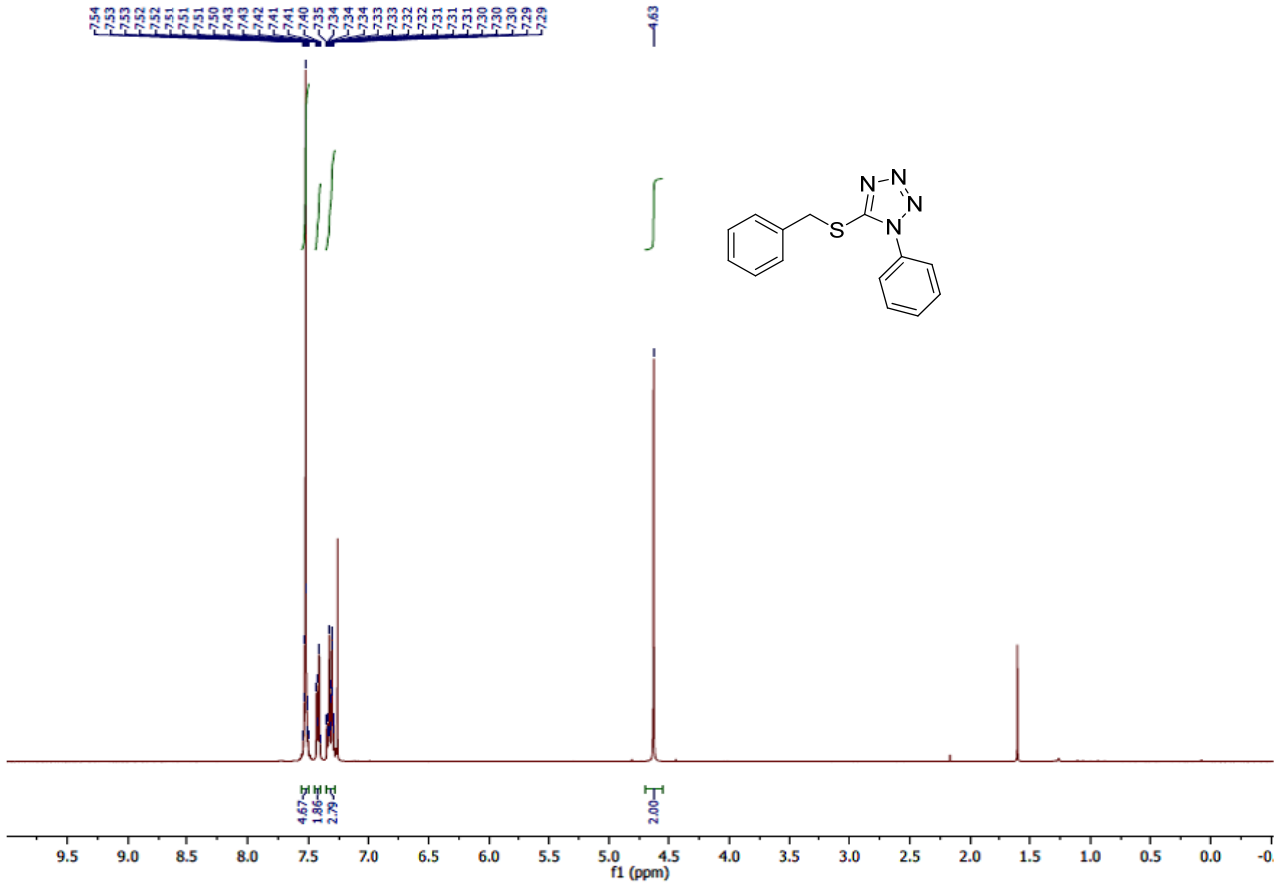
Appendix Figure 44 100 MHz ^{13}C NMR spectrum of 2-(benzo[d]thiazol-2-ylthio)-2-methyl-1-phenylpropan-1-one **(102)**



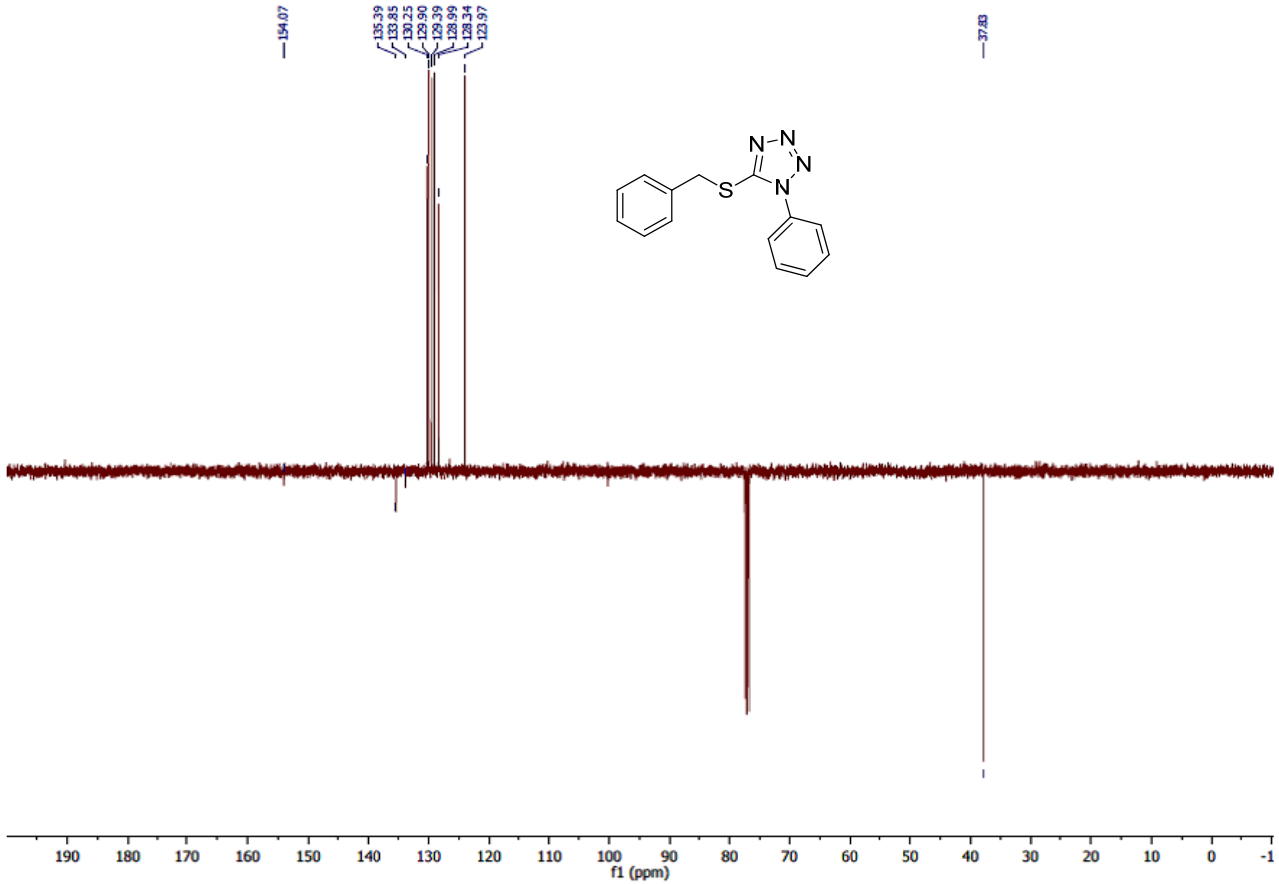
Appendix Figure 45 400 MHz ^{1}H NMR spectrum of 2-((3s,5s,7s)-adamantan-1-ylthio)benzo[d]thiazole **(104)**



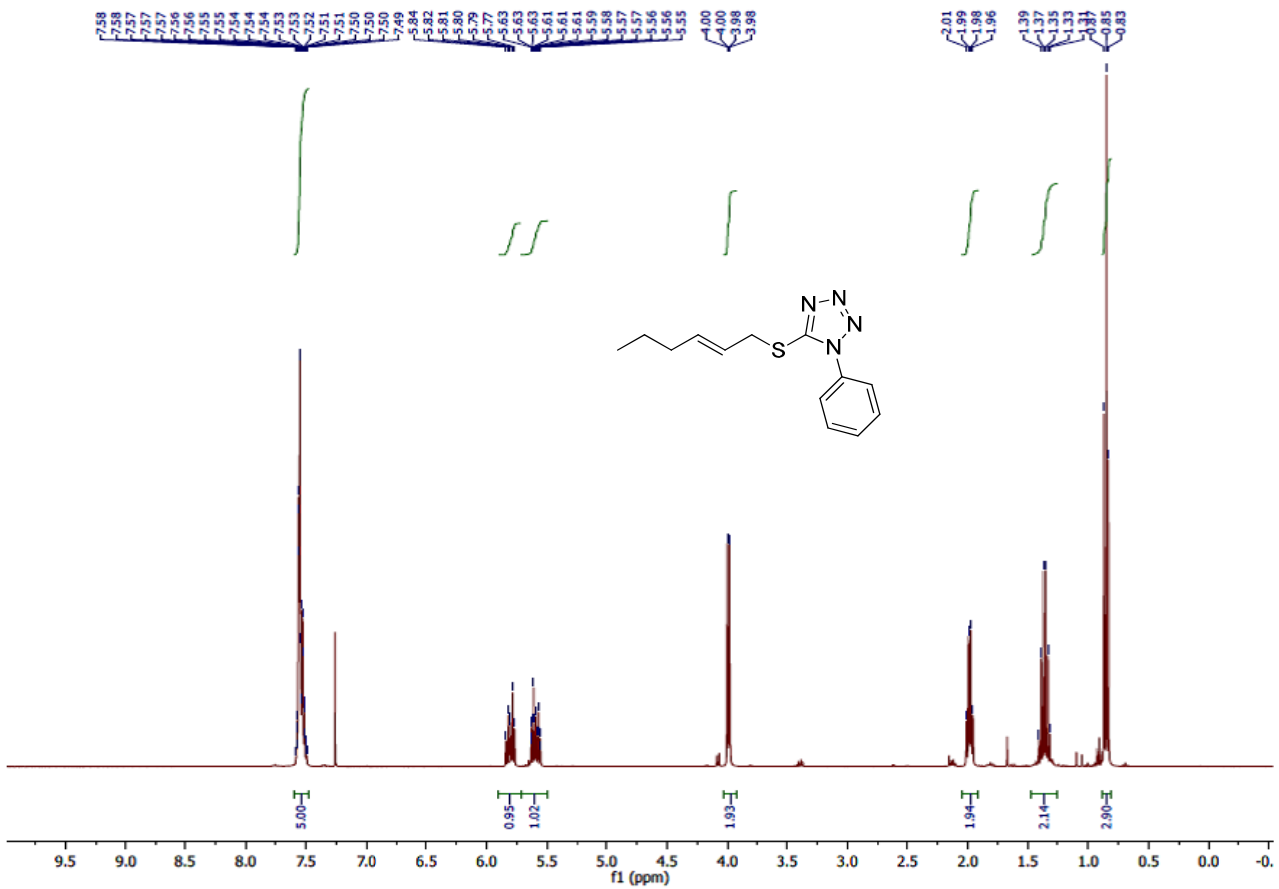
Appendix Figure 46 100 MHz ^{13}C NMR spectrum of 2-((3s,5s,7s)-adamantan-1-ylthio)benzo[d]thiazole **(104)**



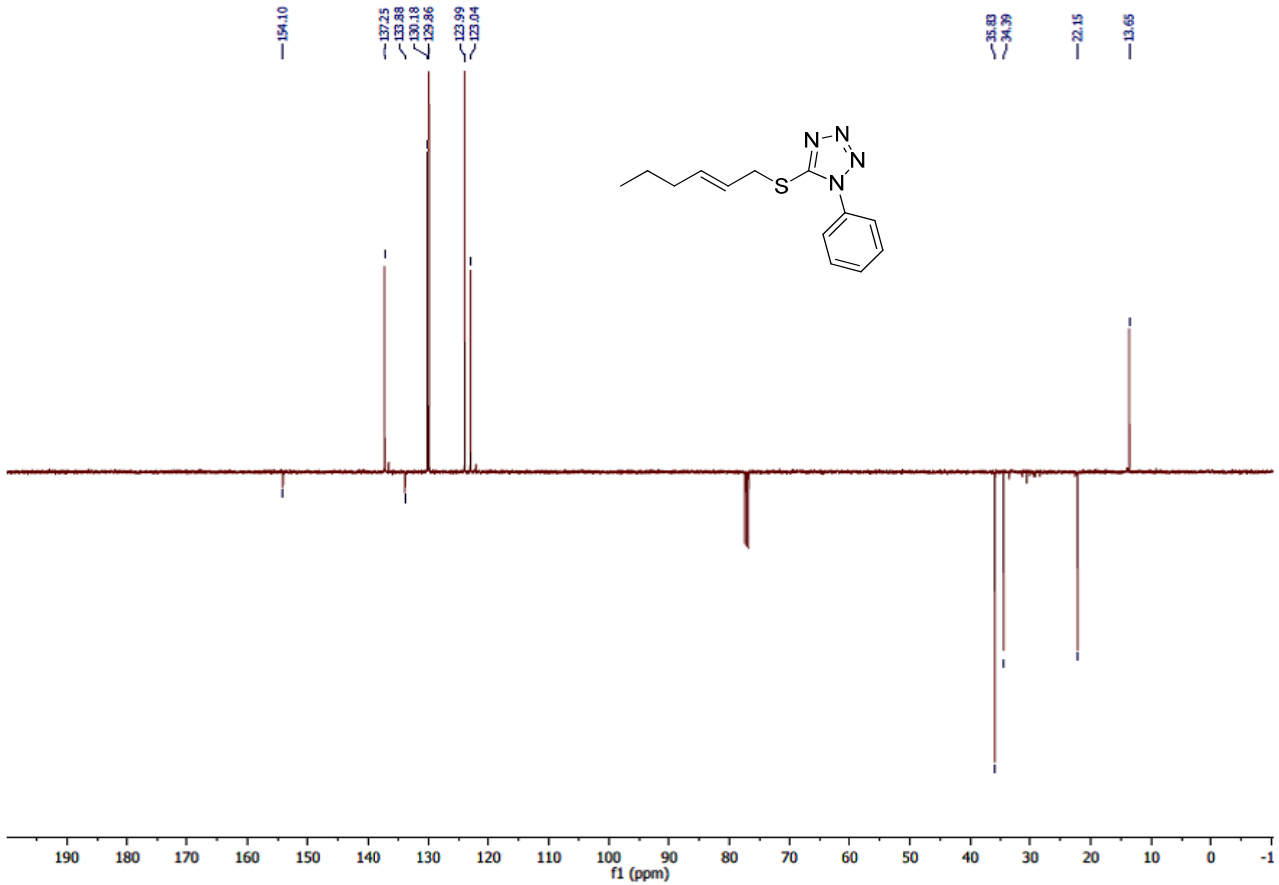
Appendix Figure 47 400 MHz ^{1}H NMR spectrum of 5-(benzylthio)-1-phenyl-1H-tetrazole **(116)**



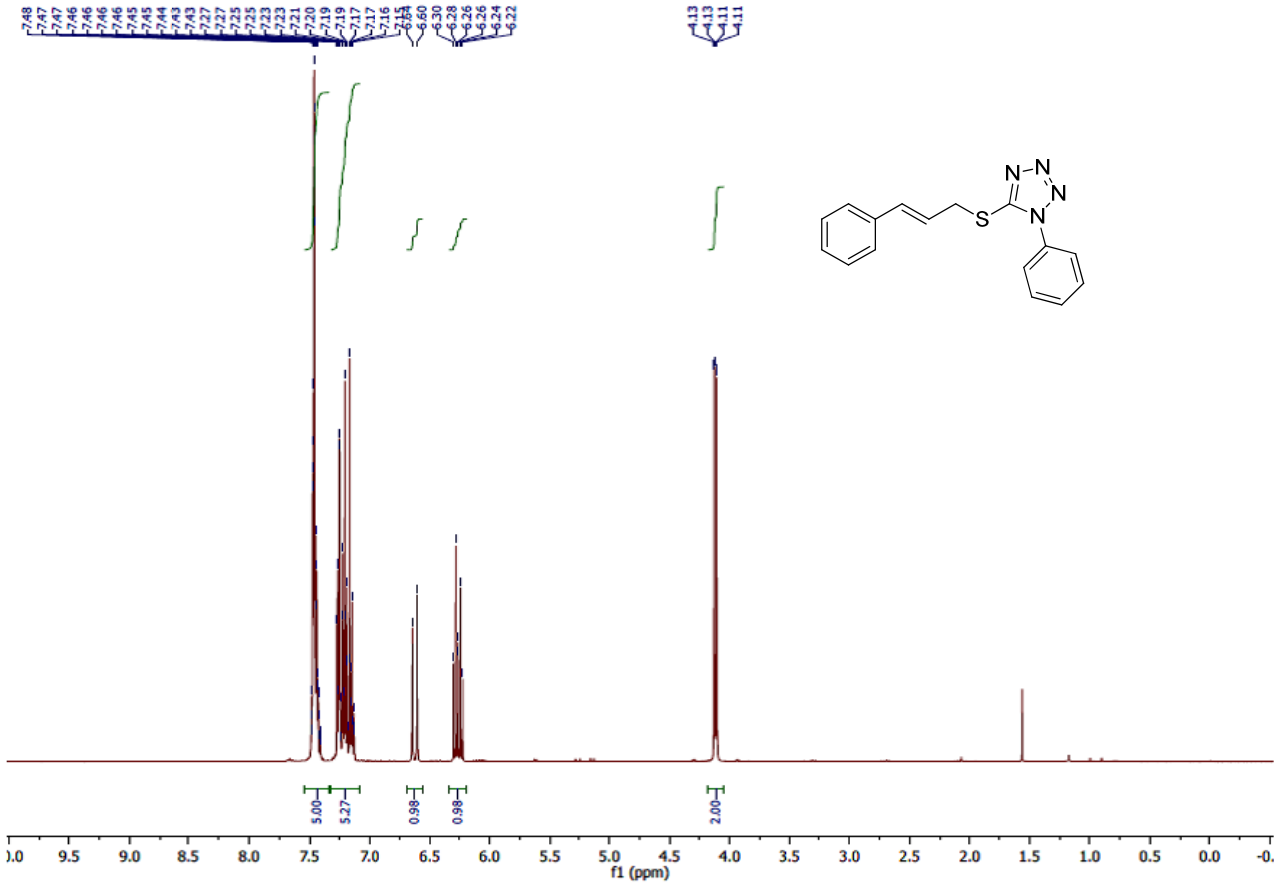
Appendix Figure 48 100 MHz ^{13}C NMR spectrum of 5-(benzylthio)-1-phenyl-1H-tetrazole **(116)**



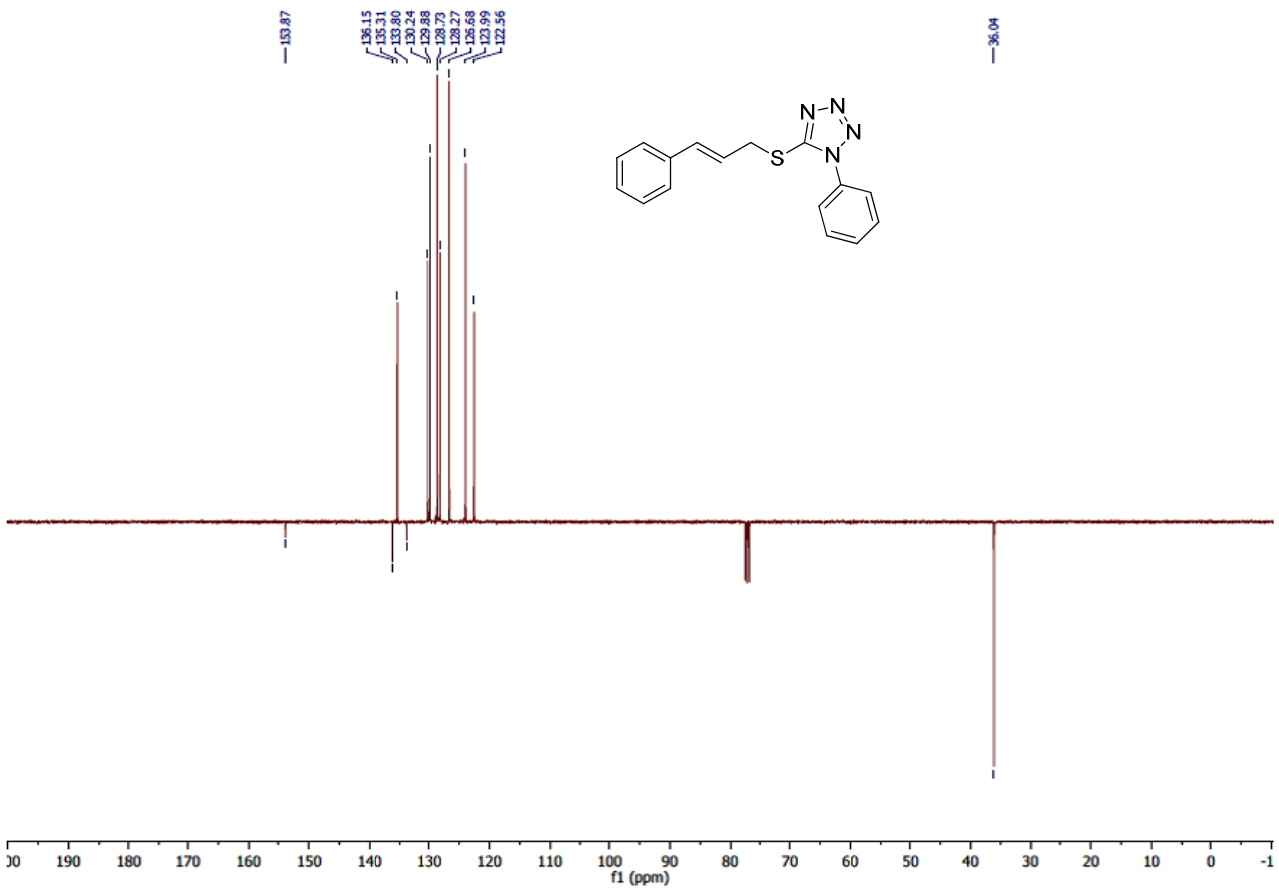
Appendix Figure 49 400 MHz ^{1}H NMR spectrum of (*E*)-5-(hex-2-en-1-ylthio)-1-phenyl-1H-tetrazole **(117)**



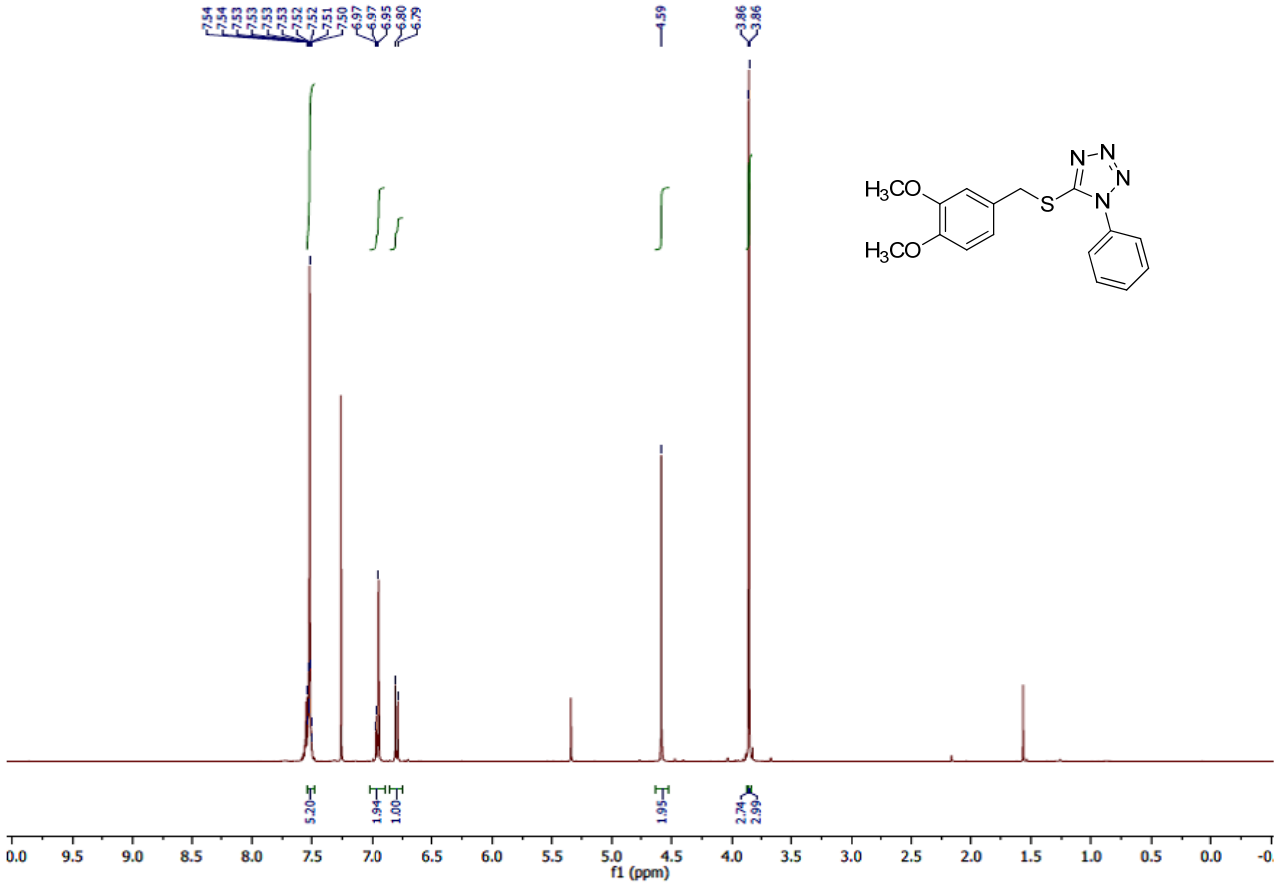
Appendix Figure 50 100 MHz ^{13}C NMR spectrum of (*E*)-5-(hex-2-en-1-ylthio)-1-phenyl-1H-tetrazole **(117)**



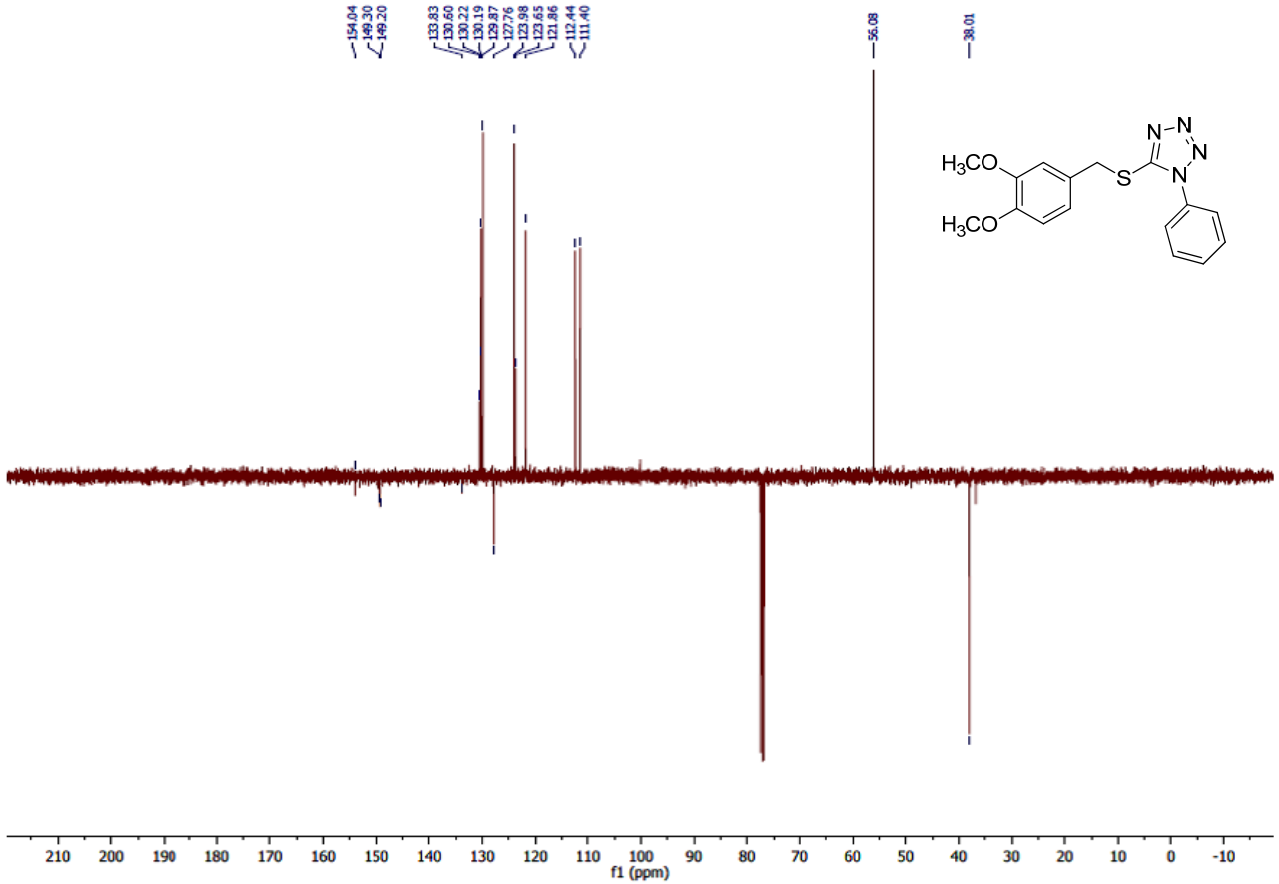
Appendix Figure 51 400 MHz ^{1}H NMR spectrum of 5-(cinnamylthio)-1-phenyl-1H-tetrazole **(118)**



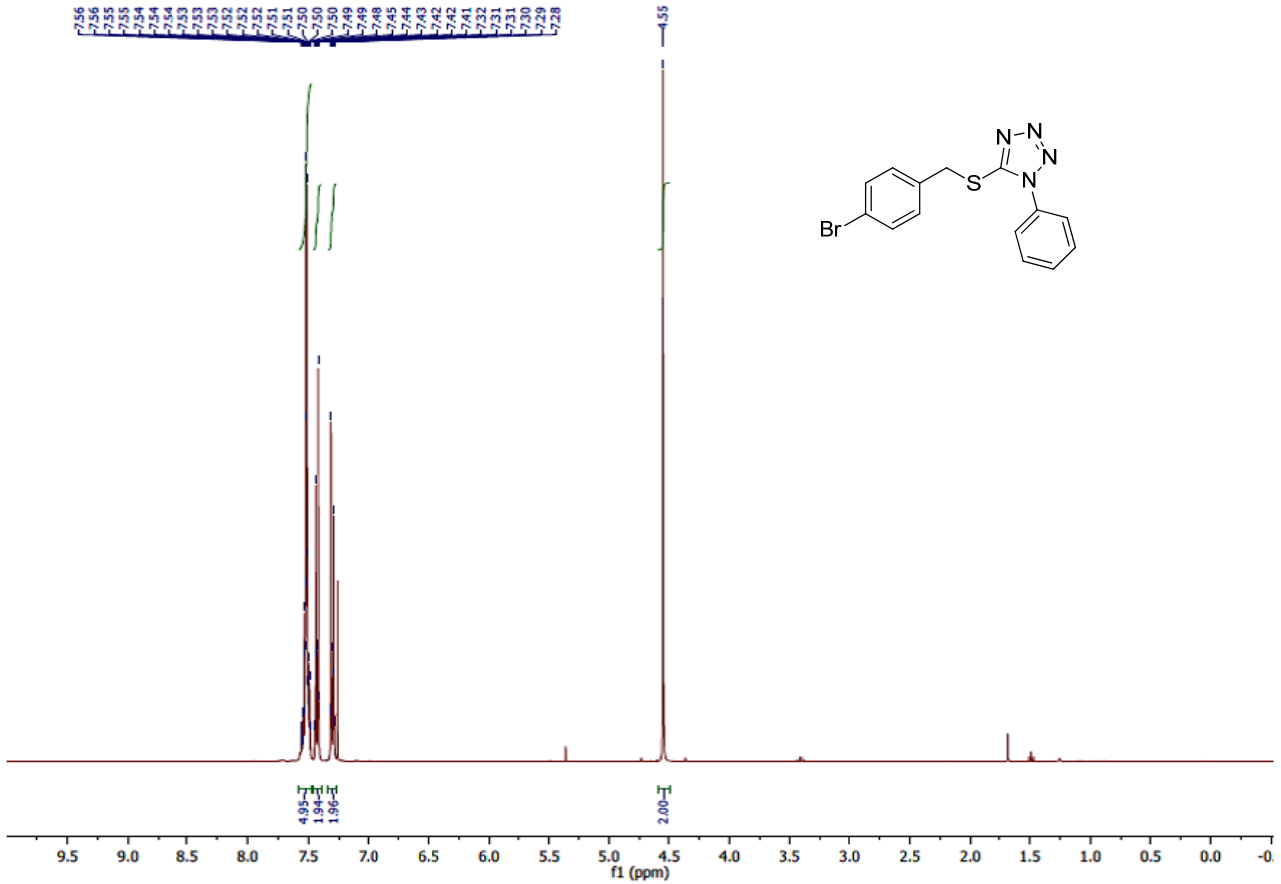
Appendix Figure 52 100 MHz ^{13}C NMR spectrum of 5-(cinnamylthio)-1-phenyl-1H-tetrazole **(118)**



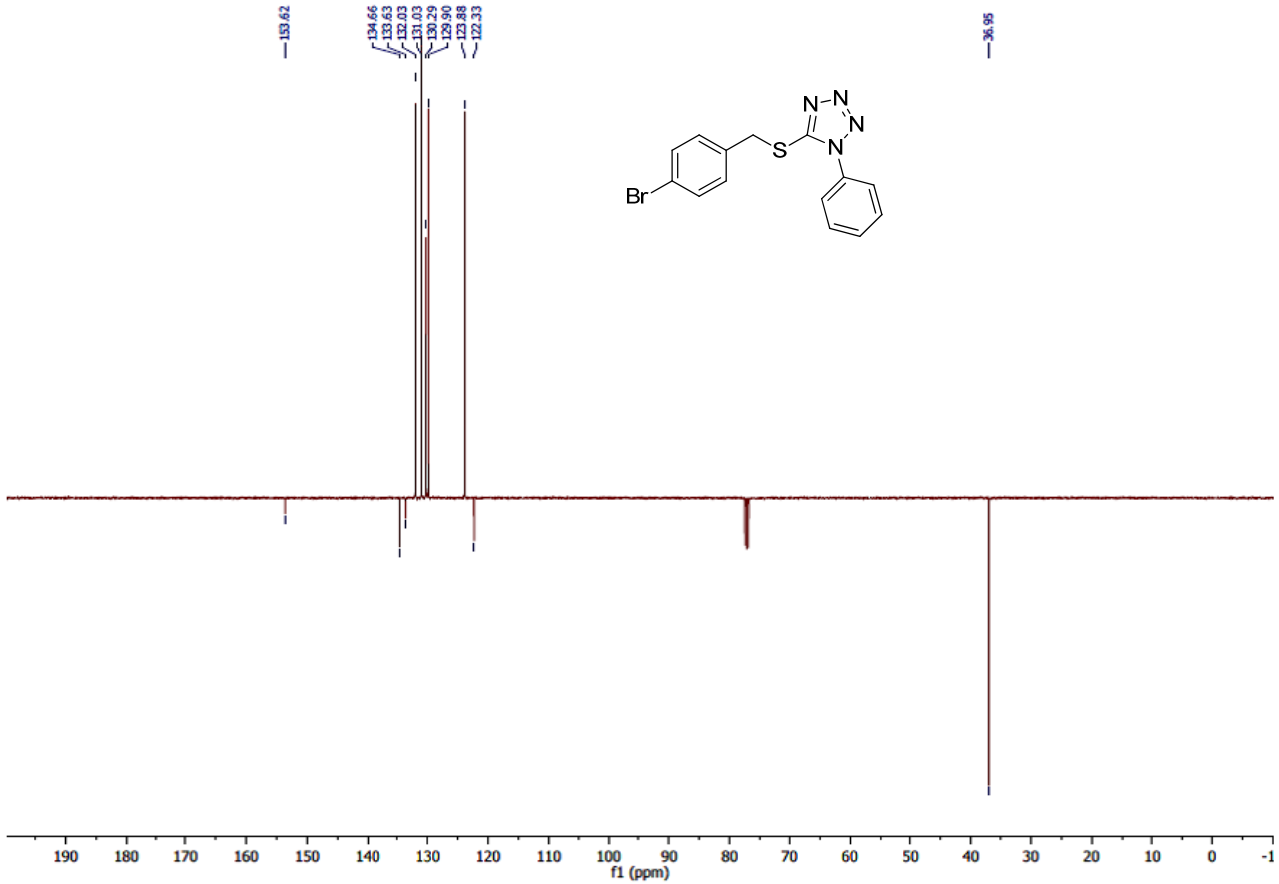
Appendix Figure 53 400 MHz ^{1}H NMR spectrum of 5-((3,4-dimethoxybenzyl)thio)-1-phenyl-1H-tetrazole **(119)**



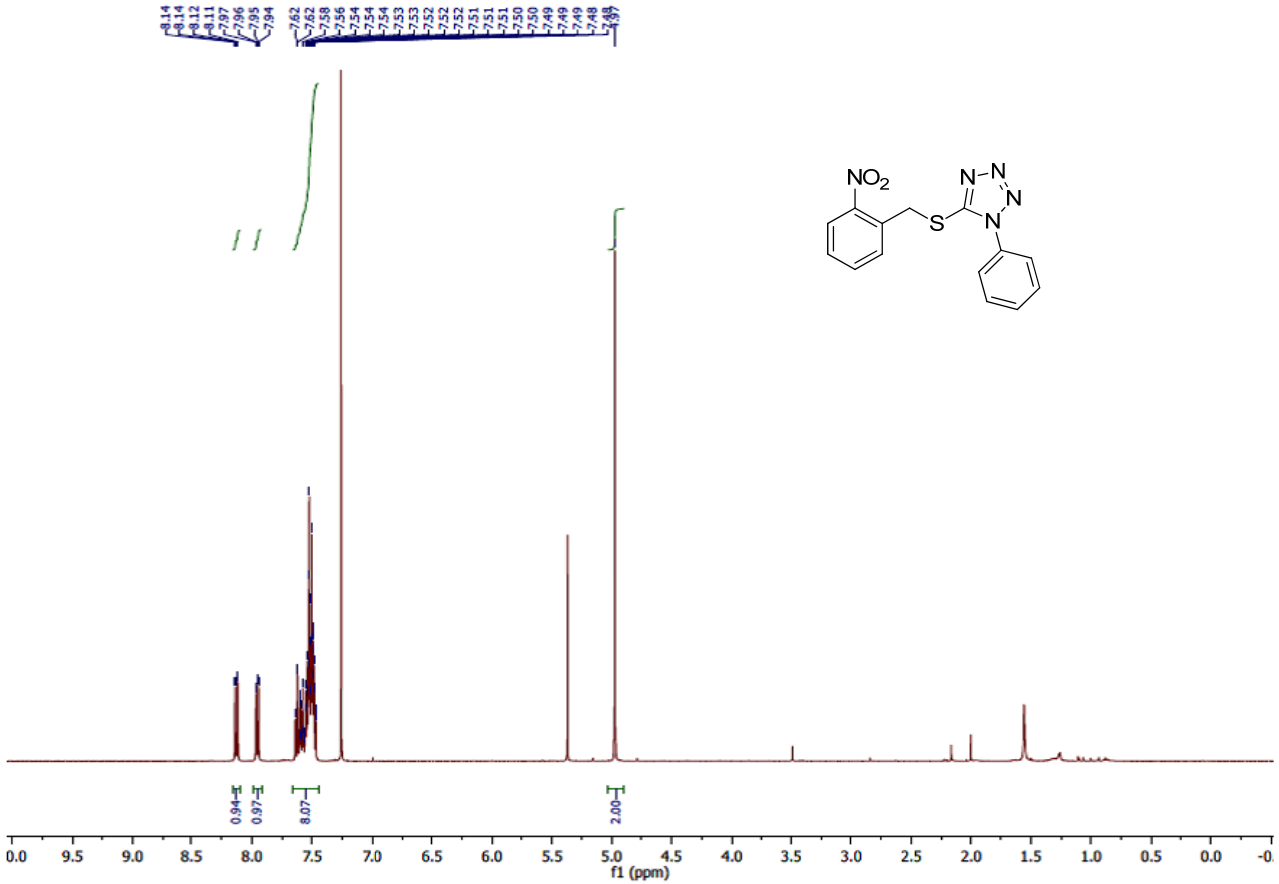
Appendix Figure 54 100 MHz ^{13}C NMR spectrum of 5-((3,4-dimethoxybenzyl)thio)-1-phenyl-1H-tetrazole **(119)**



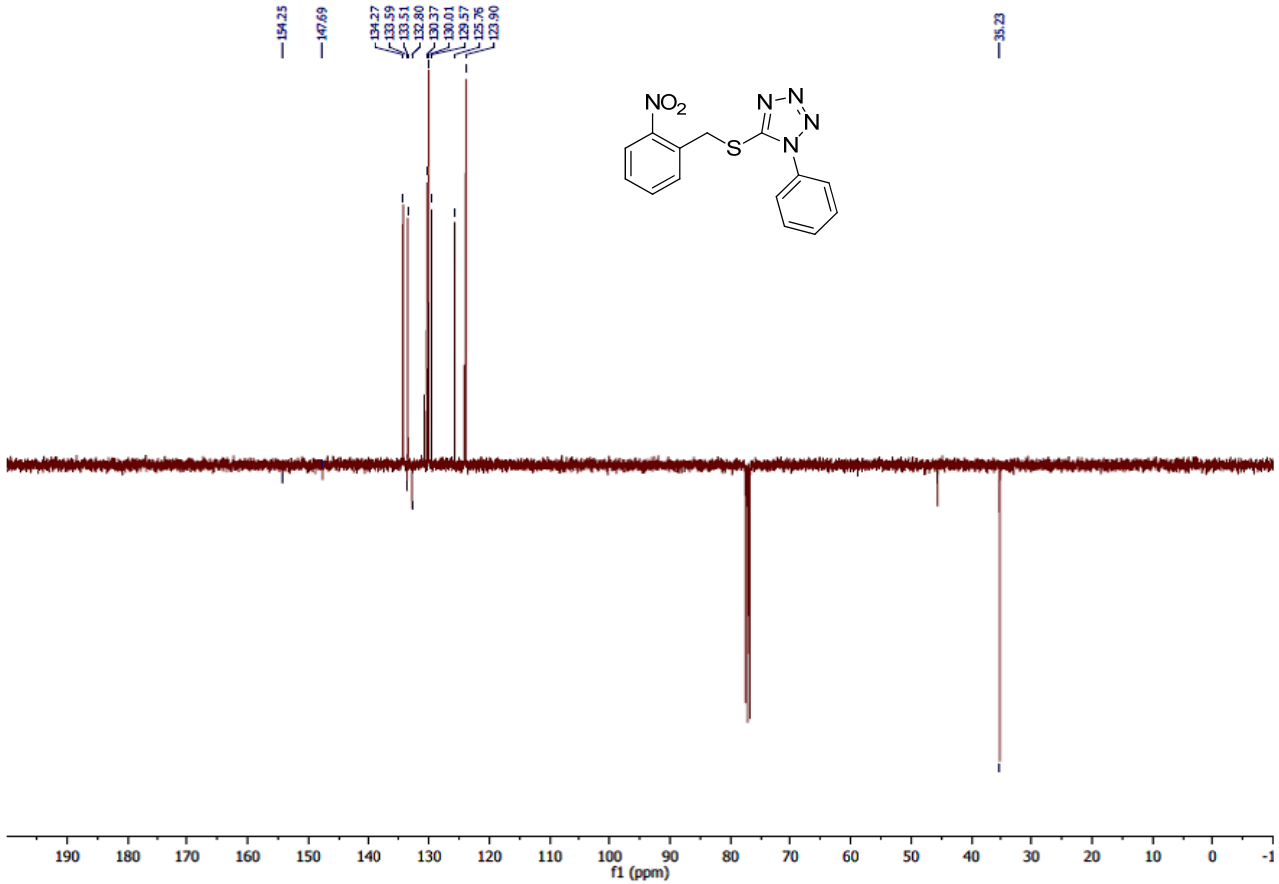
Appendix Figure 55 400 MHz ^{1}H NMR spectrum of 5-((4-bromobenzyl)thio)-1-phenyl-1H-tetrazole **(120)**



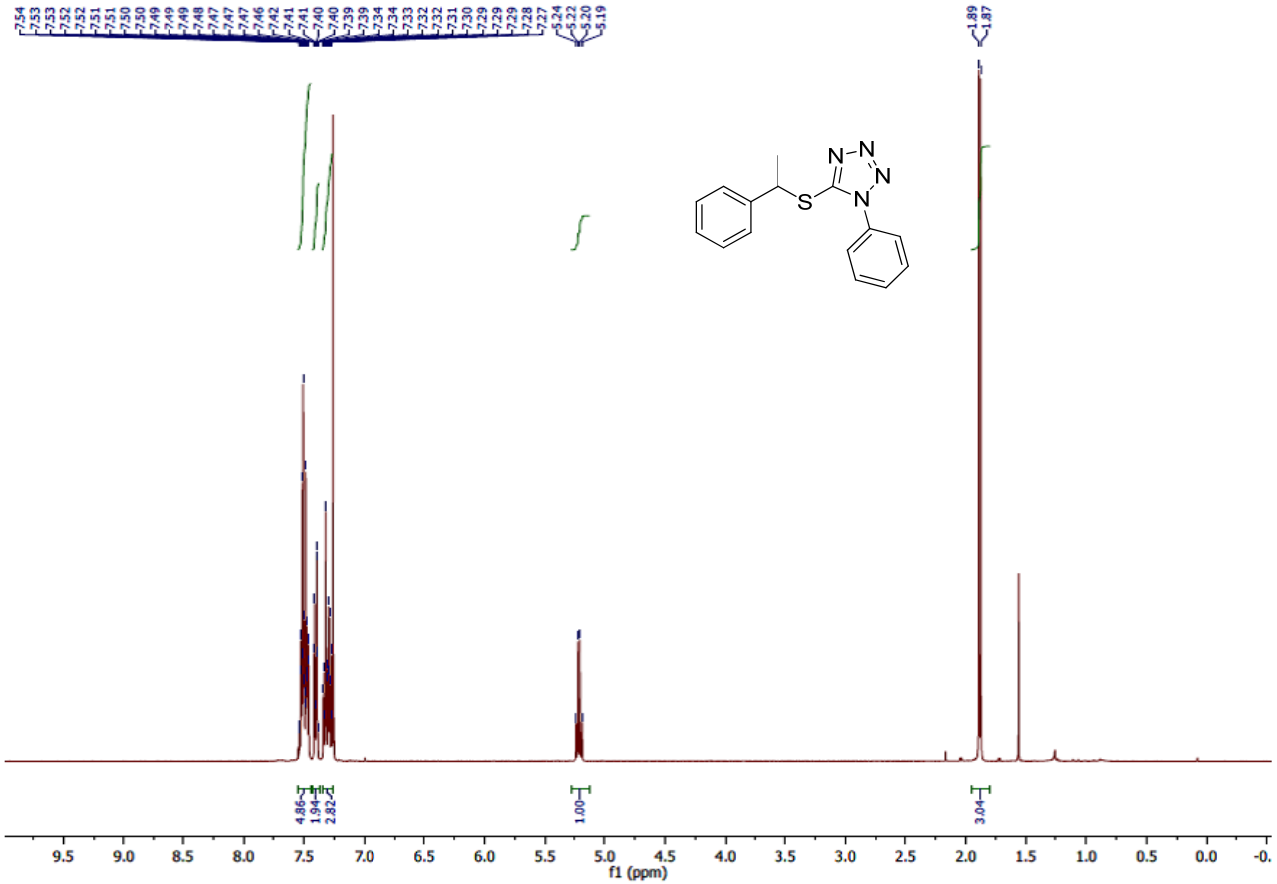
Appendix Figure 56 100 MHz ^{13}C NMR spectrum of 5-((4-bromobenzyl)thio)-1-phenyl-1H-tetrazole **(120)**



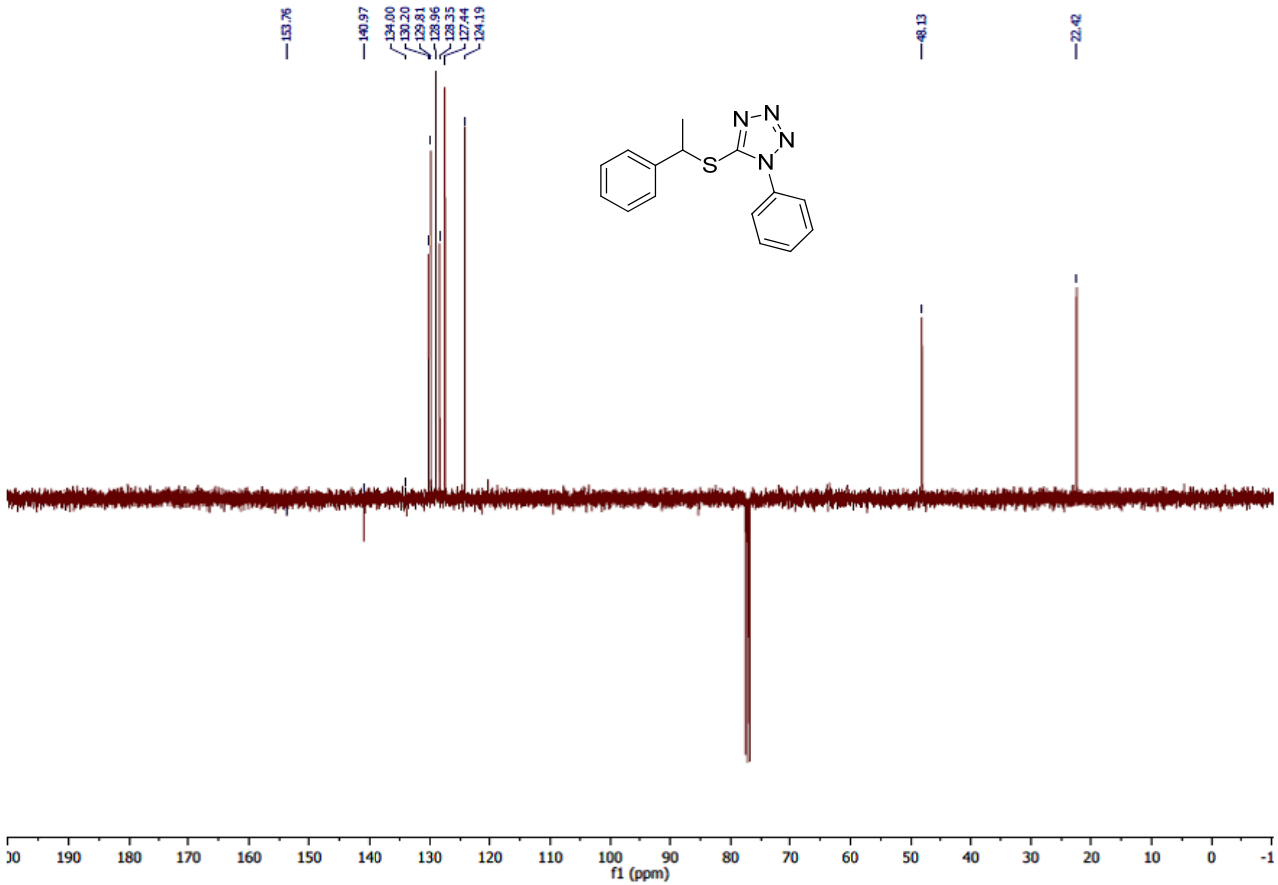
Appendix Figure 57 400 MHz ^{1}H NMR spectrum of 5-((2-nitrobenzyl)thio)-1-phenyl-1H-tetrazole **(121)**



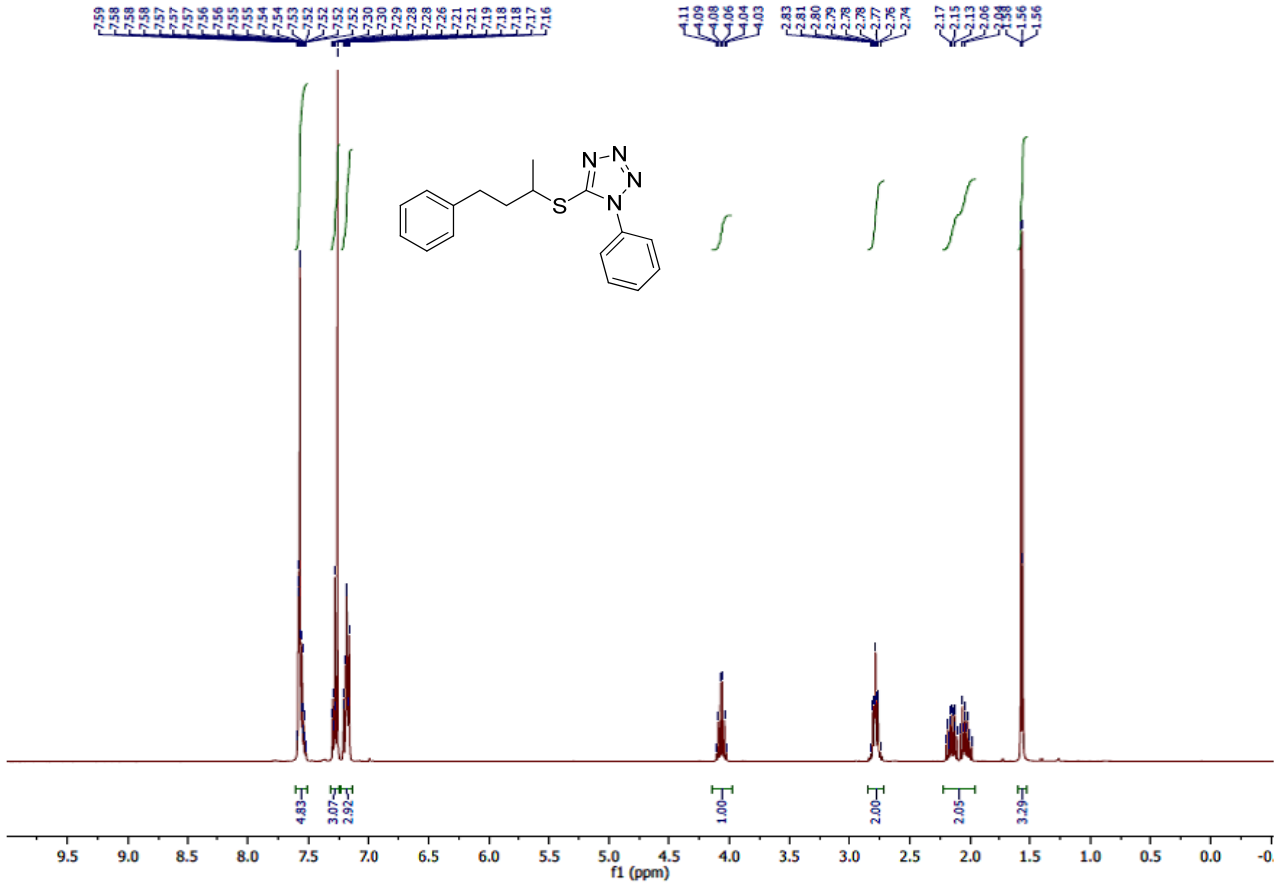
Appendix Figure 58 100 MHz ^{13}C NMR spectrum of 5-((2-nitrobenzyl)thio)-1-phenyl-1H-tetrazole **(121)**



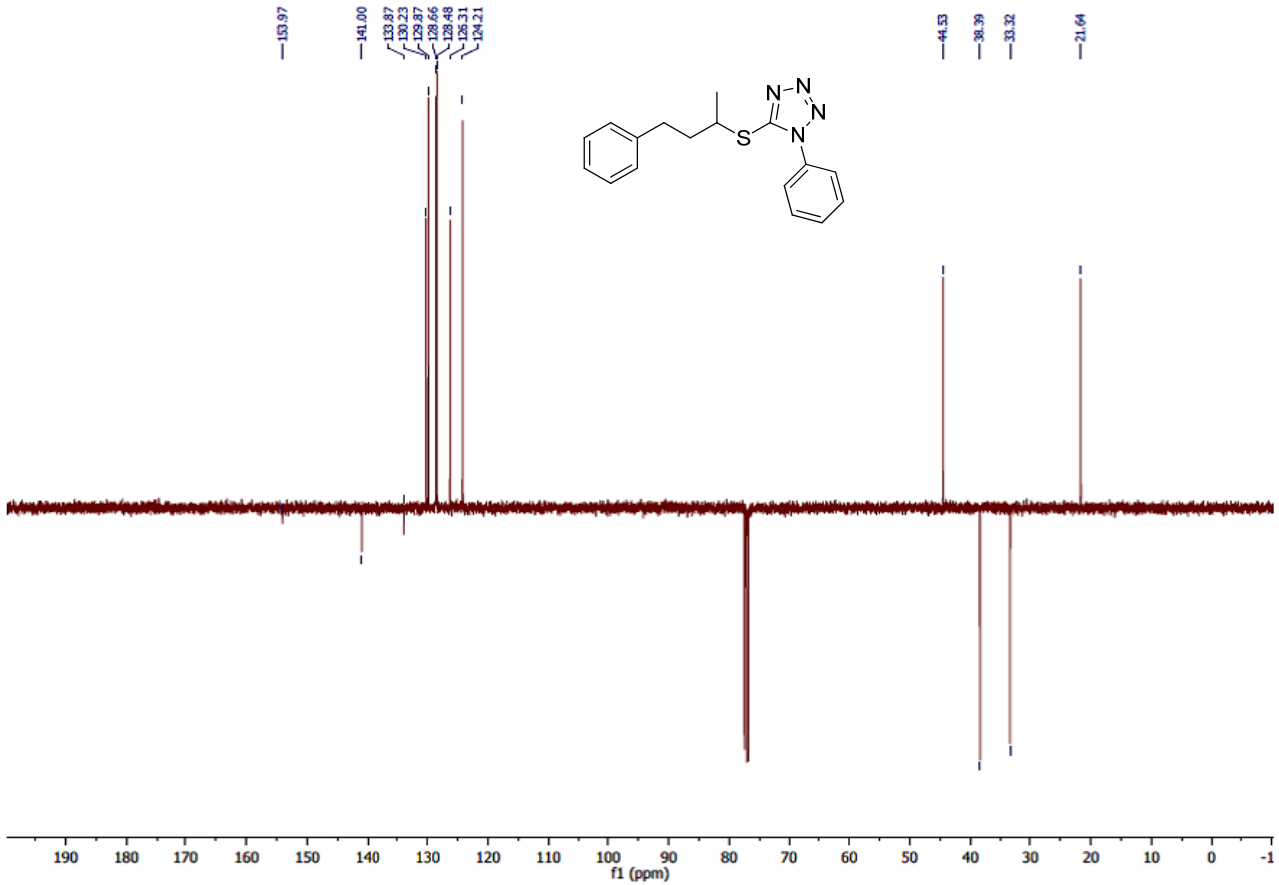
Appendix Figure 59 400 MHz ^{1}H NMR spectrum of 1-phenyl-5-((1-phenylethyl)thio)-1H-tetrazole **(122)**



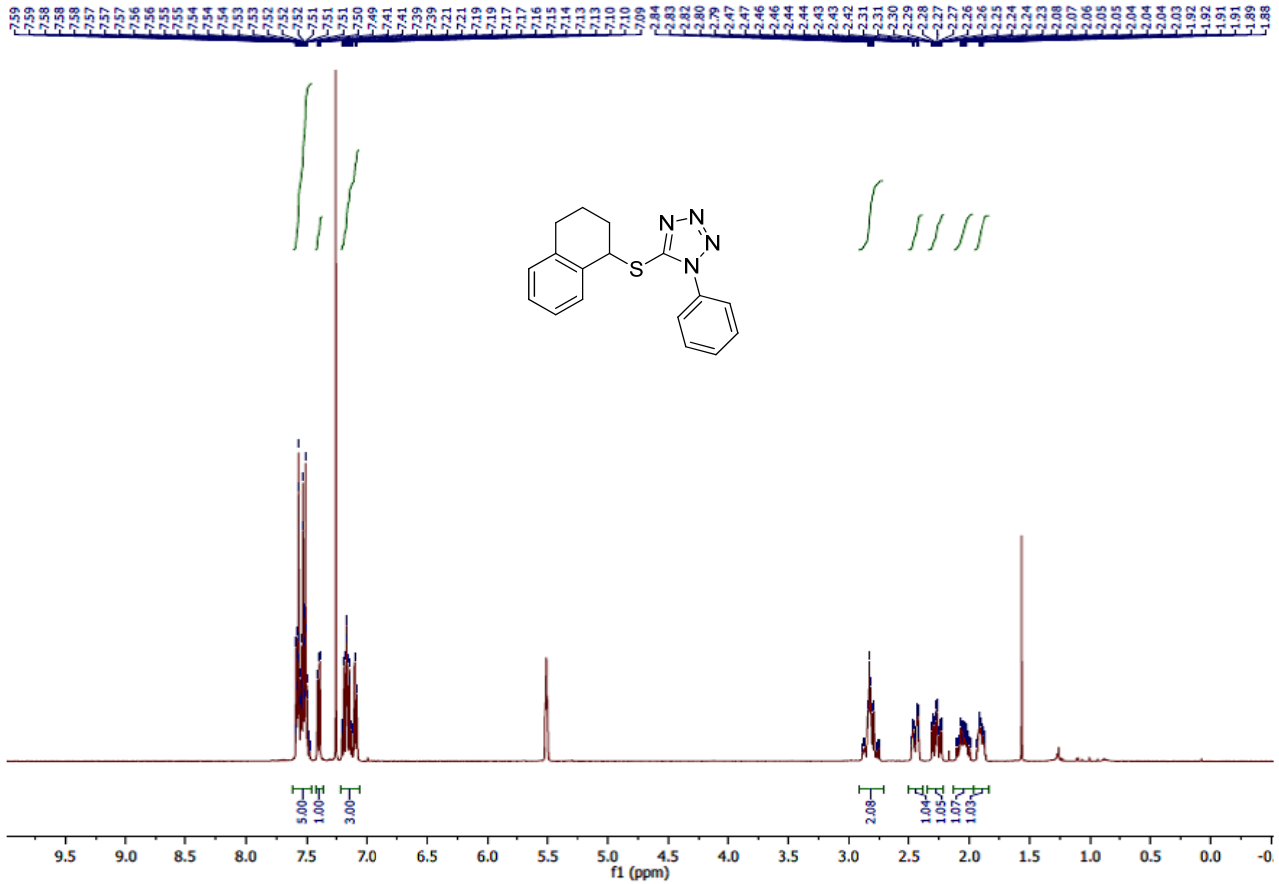
Appendix Figure 60 100 MHz ^{13}C NMR spectrum of of 1-phenyl-5-((1-phenylethyl)thio)-1H-tetrazole **(122)**



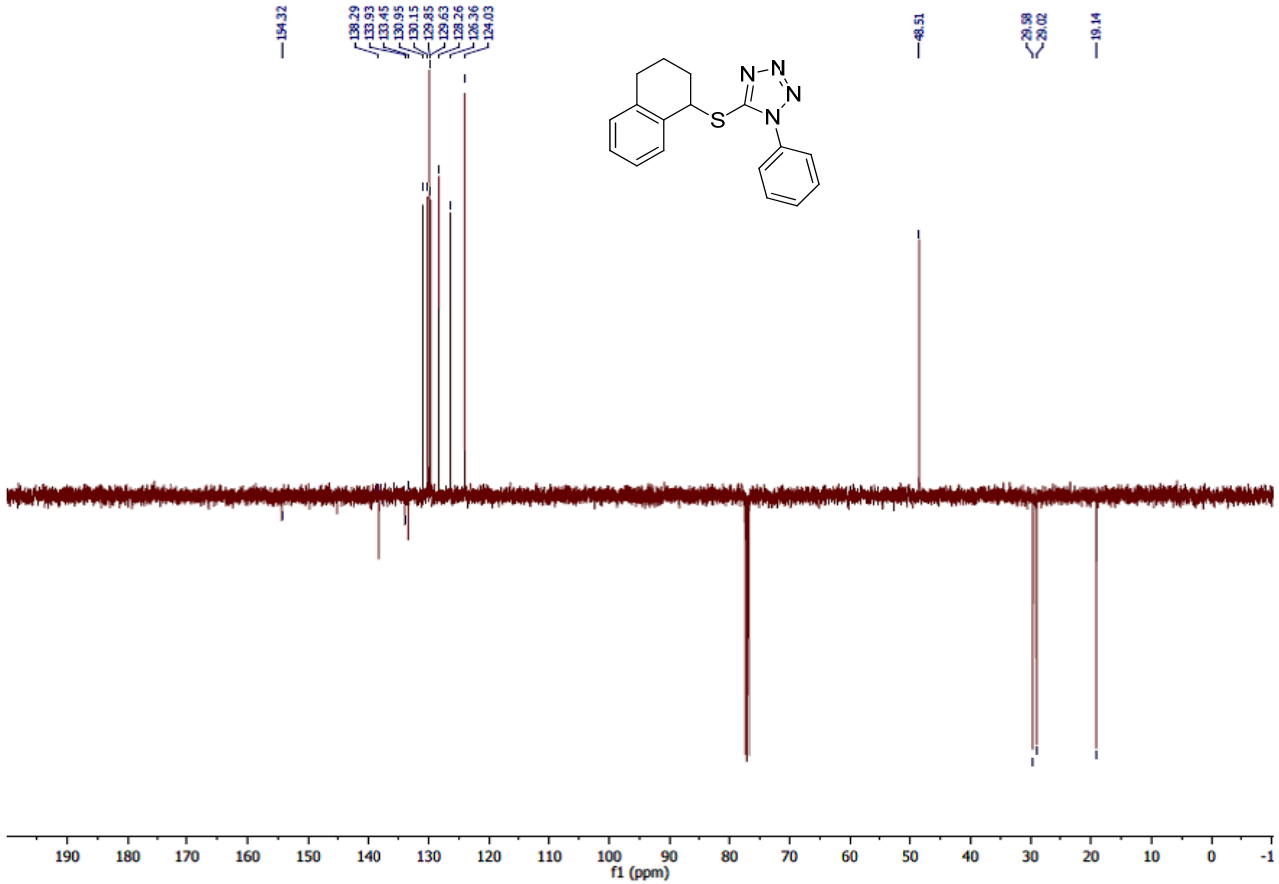
Appendix Figure 61 400 MHz ^{1}H NMR spectrum of 1-phenyl-5-((4-phenylbutan-2-yl)thio)-1H-tetrazole **(123)**



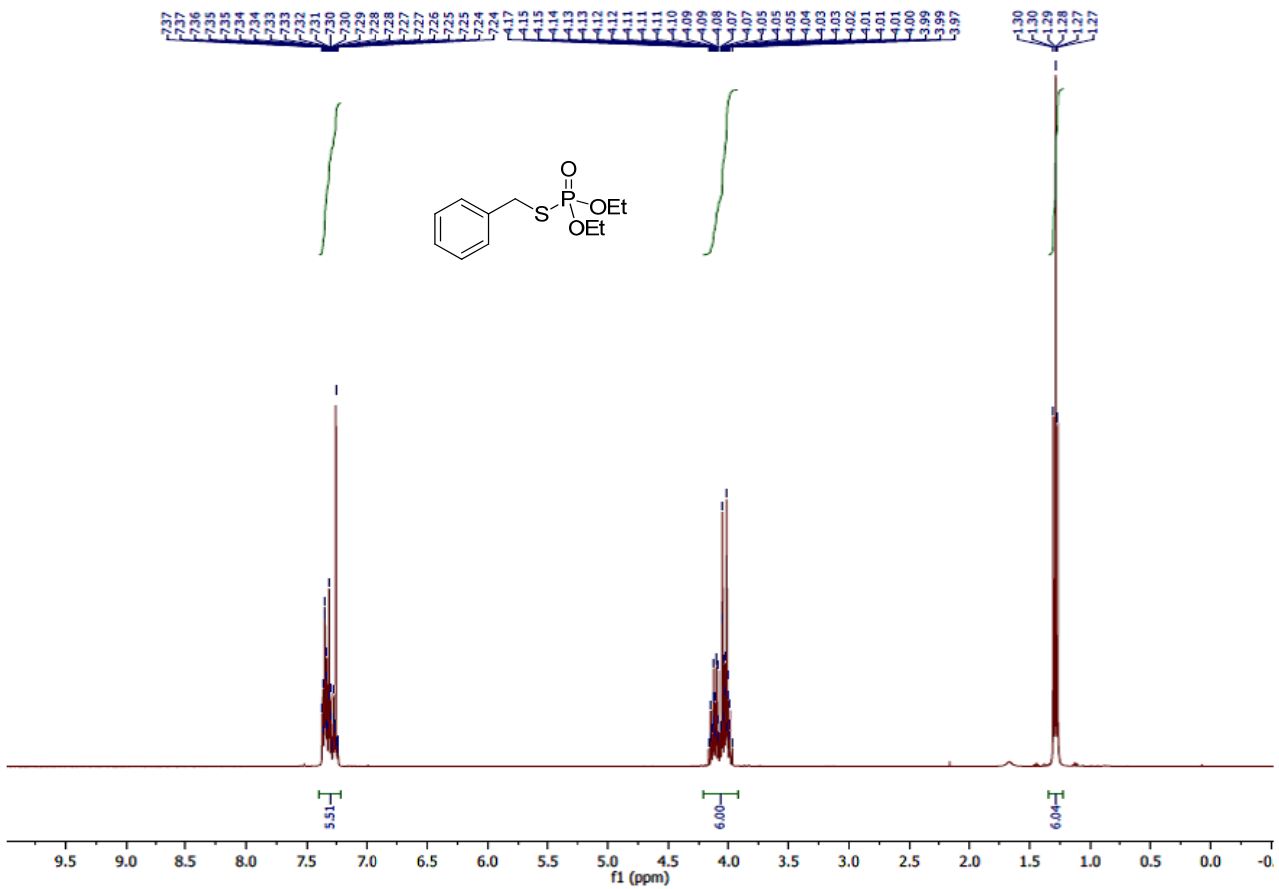
Appendix Figure 62 100 MHz ^{13}C NMR spectrum of 1-phenyl-5-((4-phenylbutan-2-yl)thio)-1H-tetrazole **(123)**



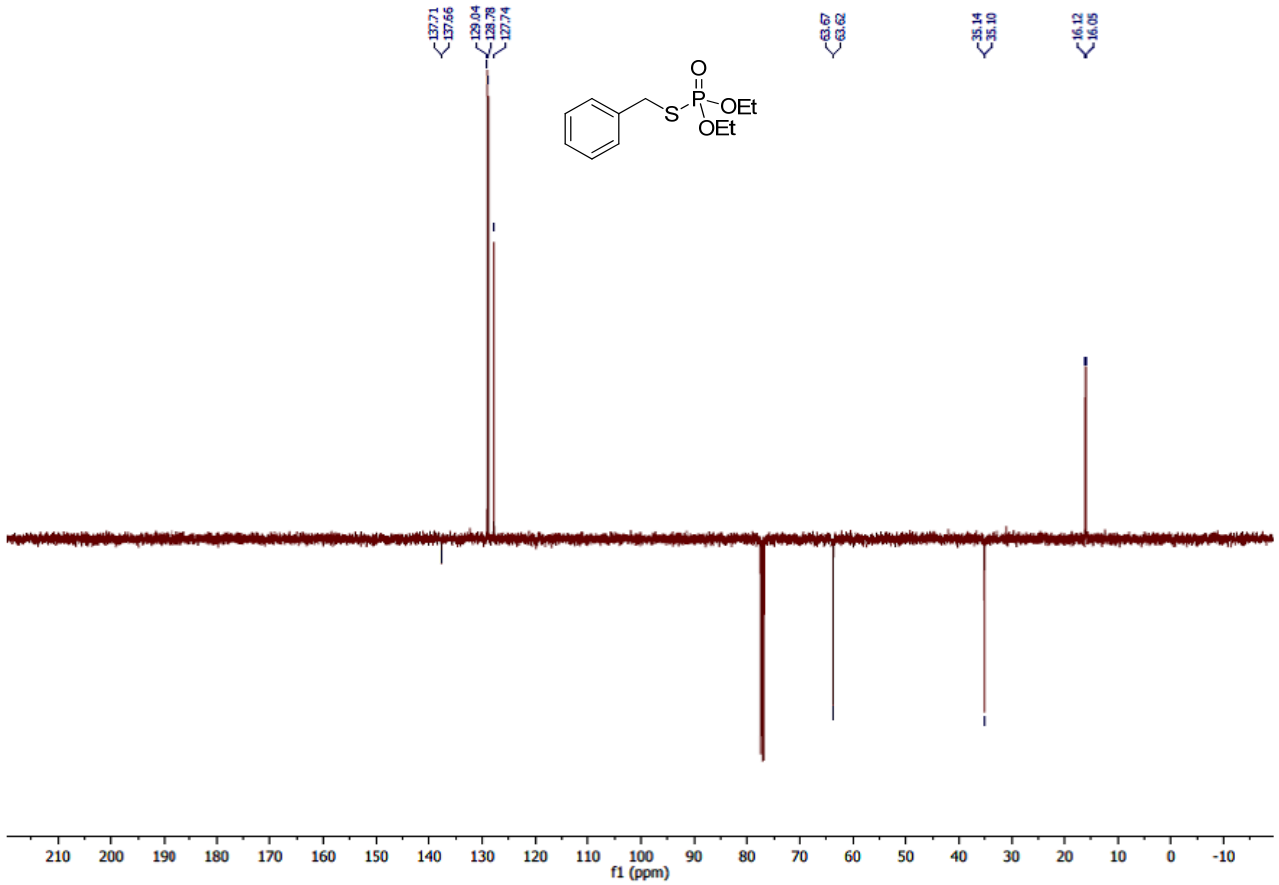
Appendix Figure 63 400 MHz ^{1}H NMR spectrum of 1-phenyl-5-((1,2,3,4-tetrahydronaphthalen-1-yl) thio)-1H-tetrazole **(125)**



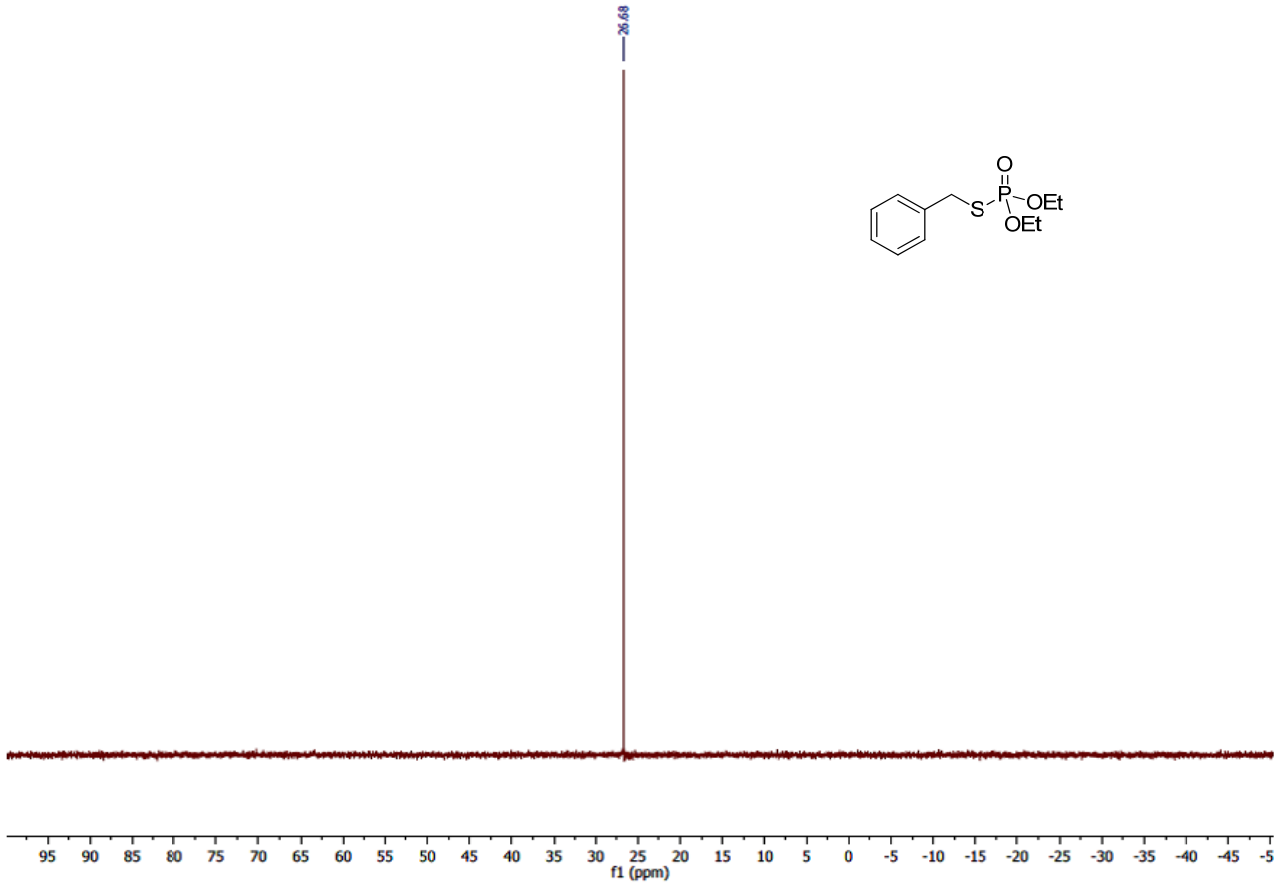
Appendix Figure 64 100 MHz ^{13}C NMR spectrum of 1-phenyl-5-((1,2,3,4-tetrahydronaphthalen-1-yl)thio)-1H-tetrazole **(125)**



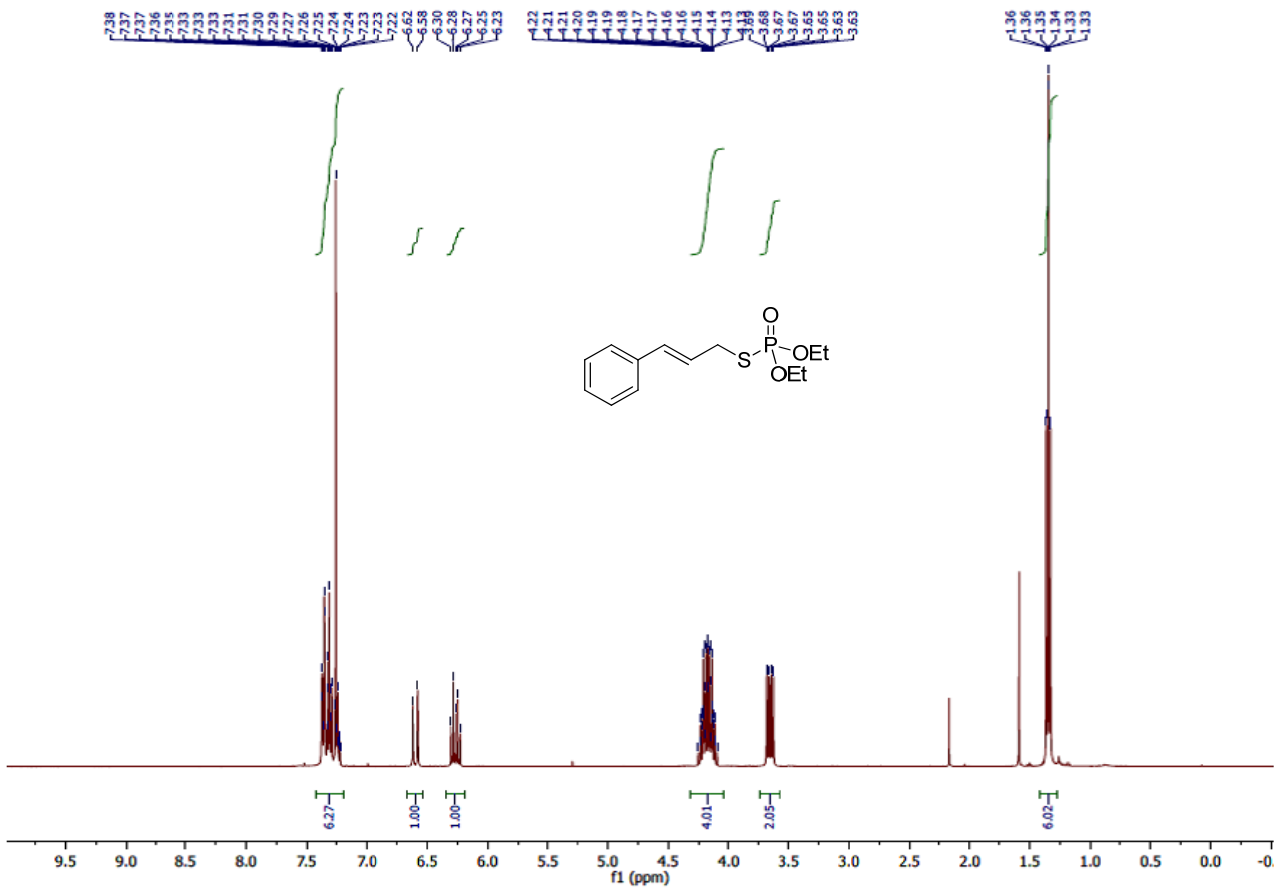
Appendix Figure 65 400 MHz ^{1}H NMR spectrum of *S*-benzyl *O,O*-diethylphosphorothioate **(126)**



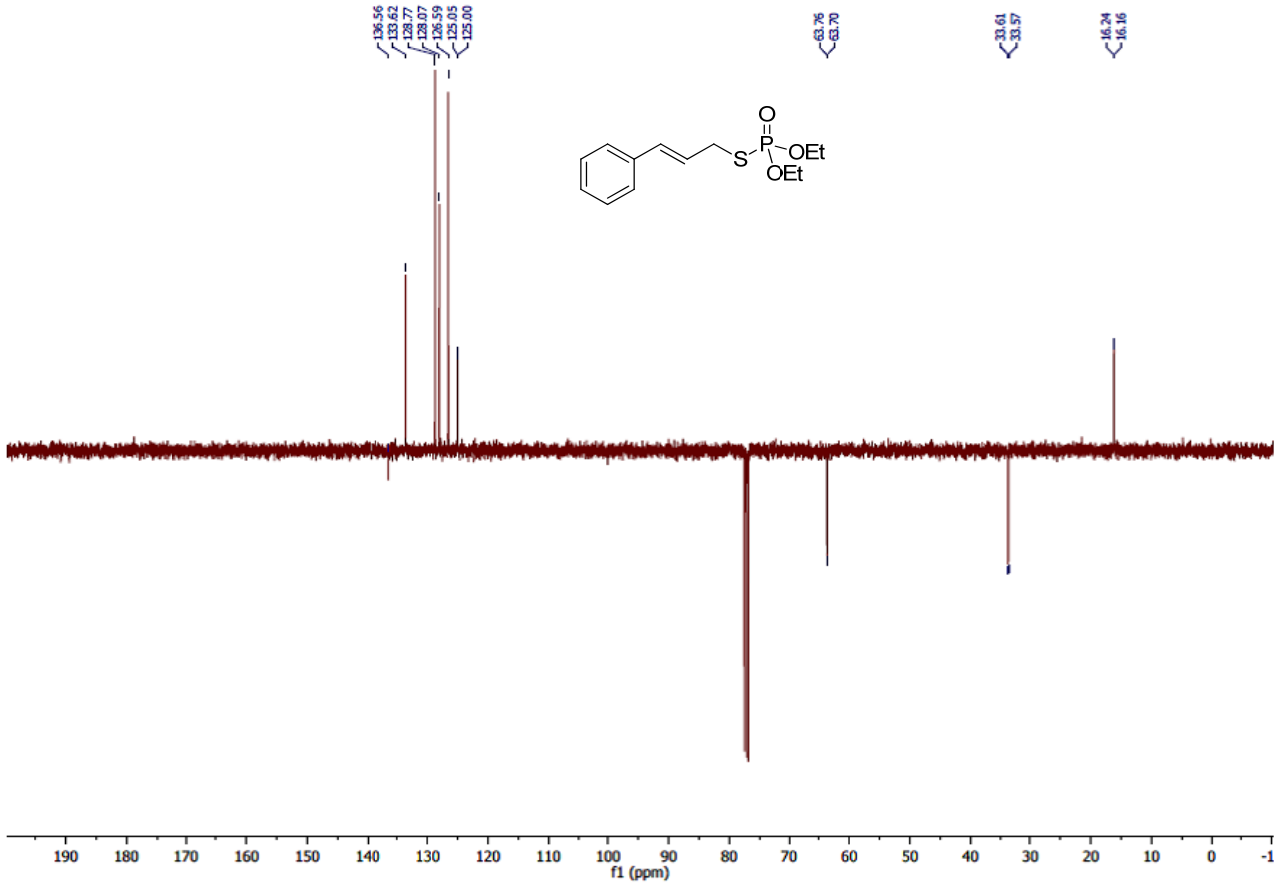
Appendix Figure 66 100 MHz ^{13}C NMR spectrum of *S*-benzyl *O,O*-diethylphosphorothioate **(126)**



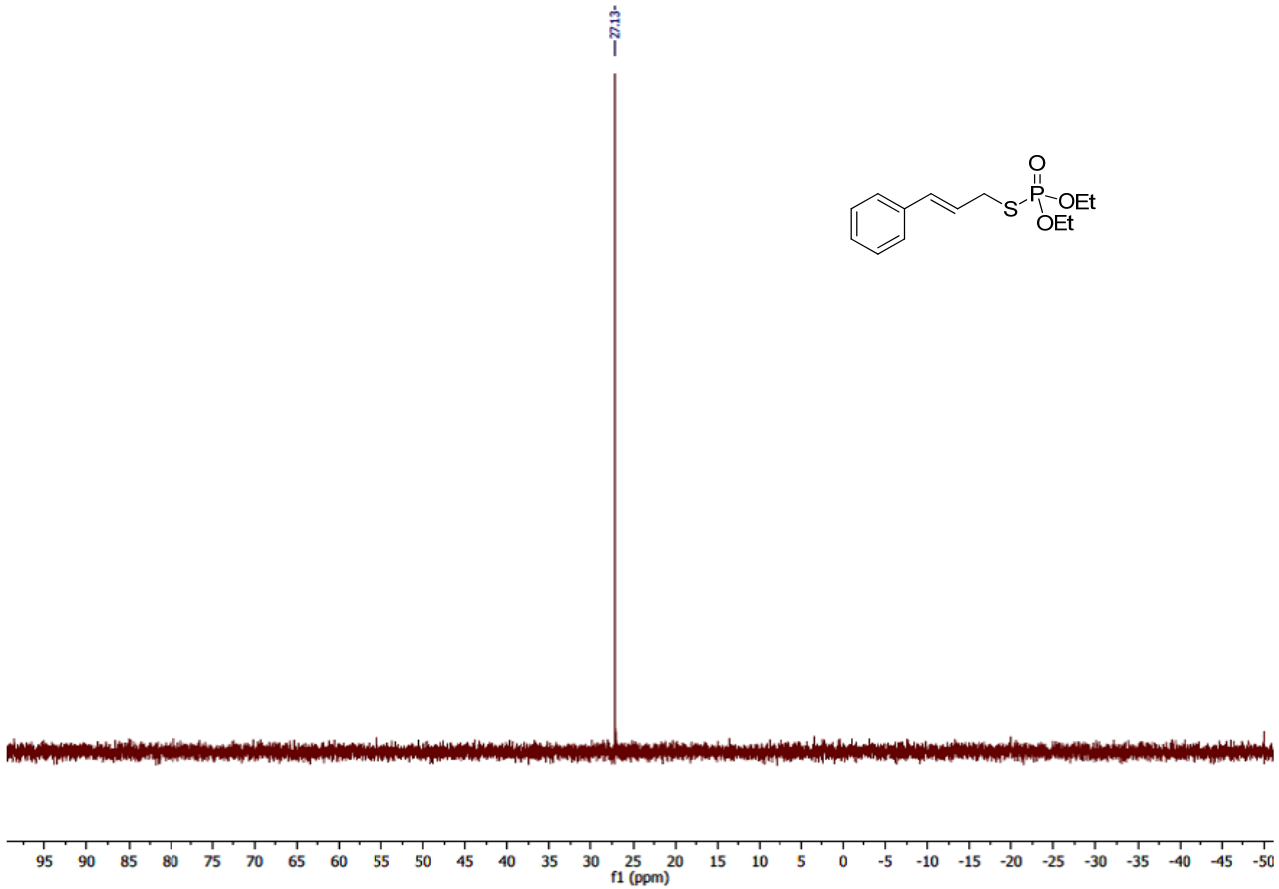
Appendix Figure 67 162 MHz ^{32}P NMR spectrum of *S*-benzyl *O,O*-diethylphosphorothioate **(126)**



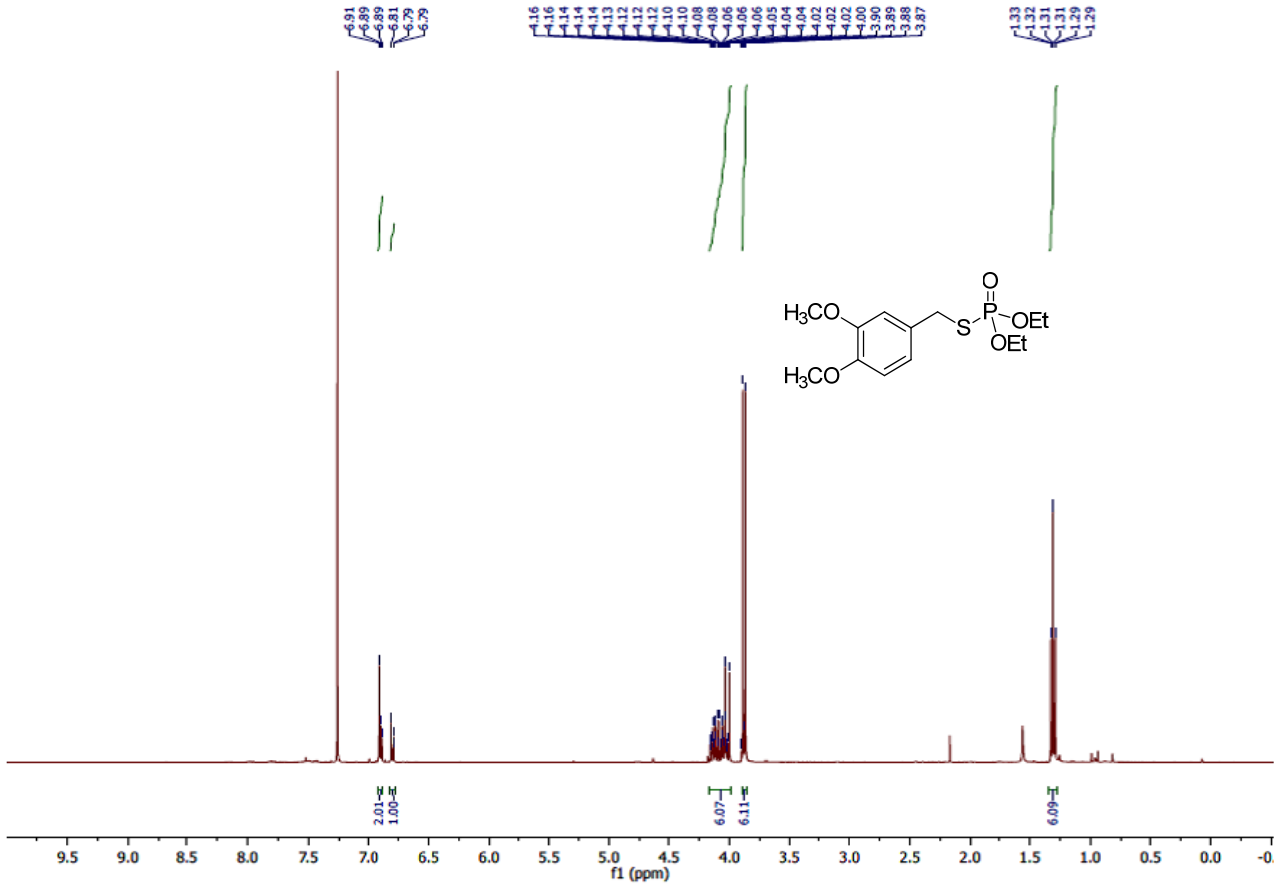
Appendix Figure 68 400 MHz ^{1}H NMR spectrum of *S*-cinnamyl *O,O*-diethylphosphorothioate **(128)**



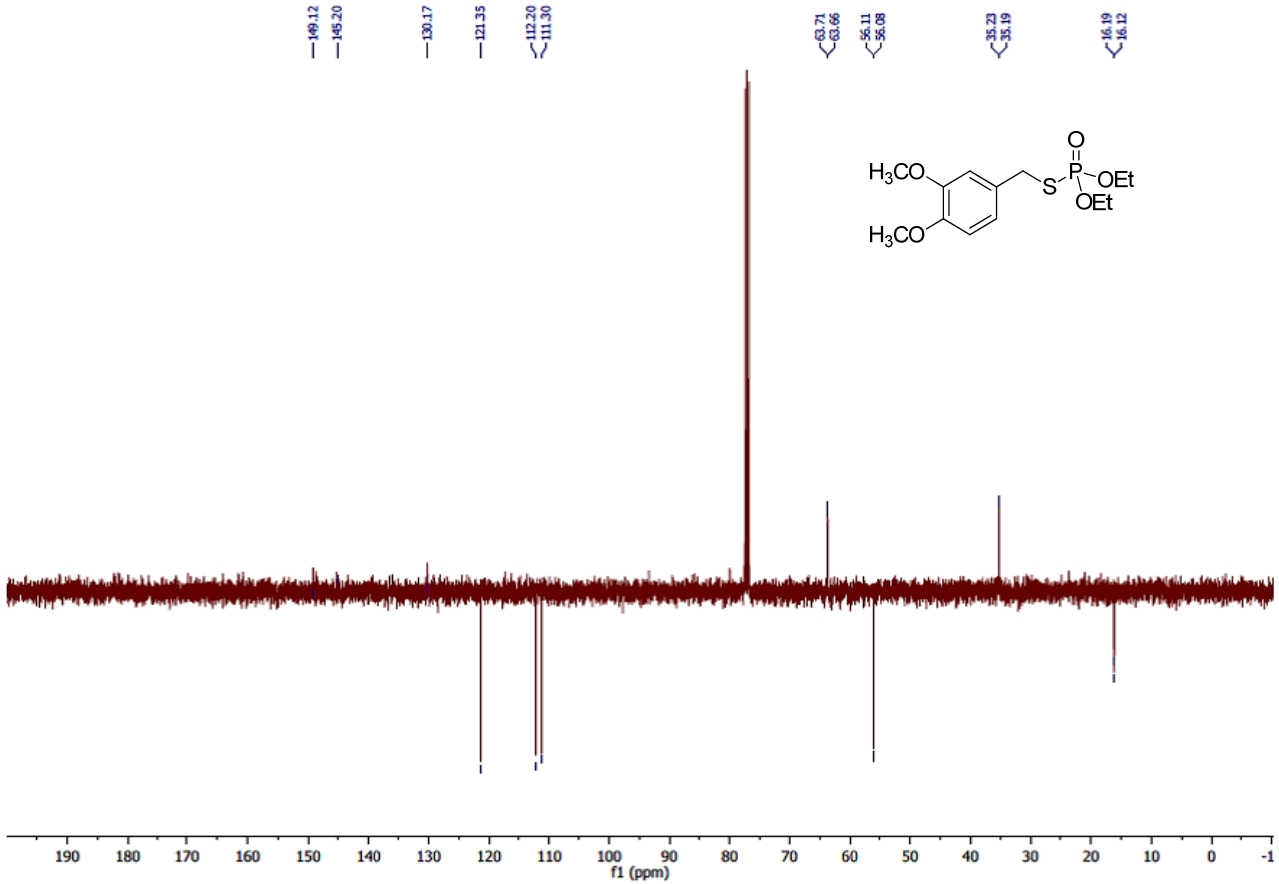
Appendix Figure 69 100 MHz ^{13}C NMR spectrum of *S*-cinnamyl *O,O*-diethylphosphorothioate **(128)**



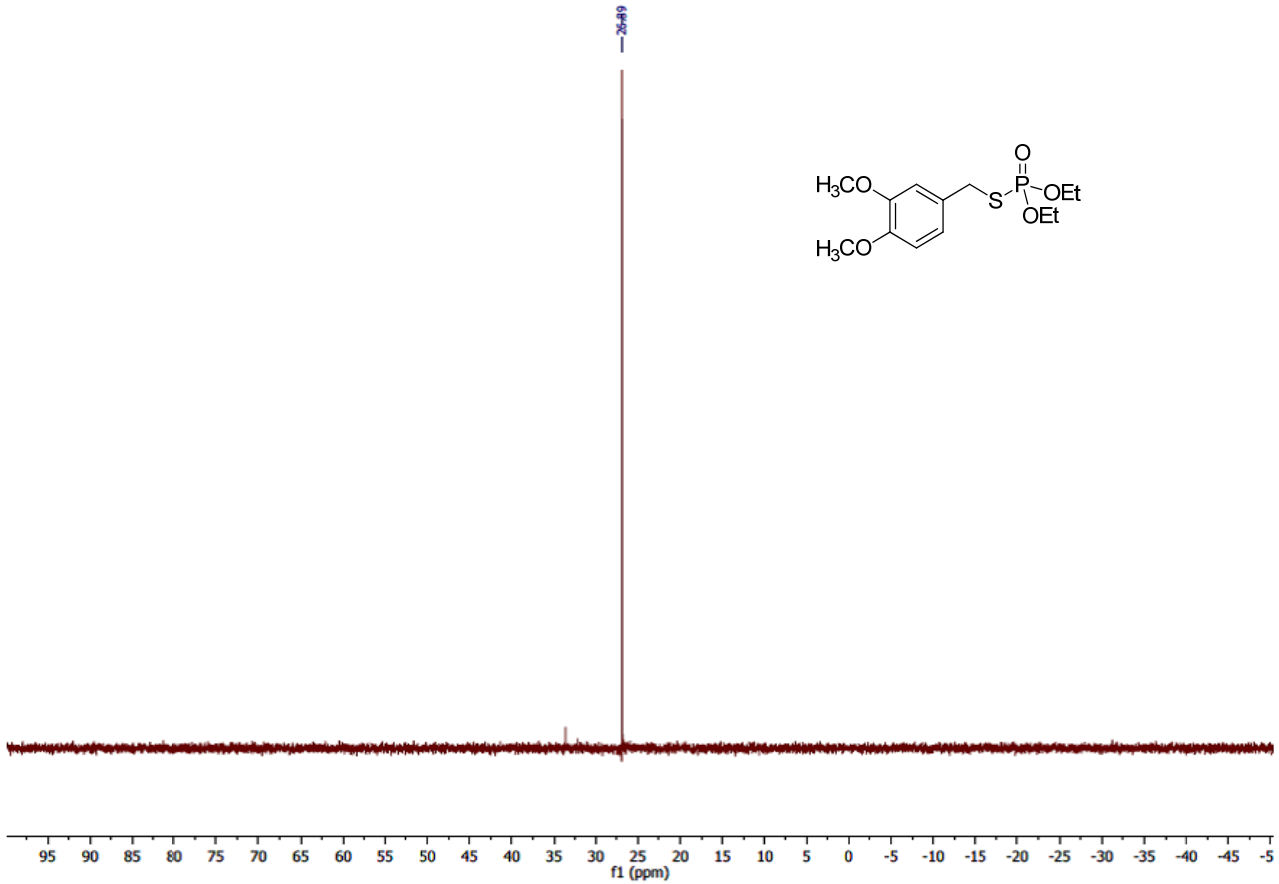
Appendix Figure 70 162 MHz ^{32}P NMR spectrum of *S*-cinnamyl *O,O*-diethylphosphorothioate **(128)**



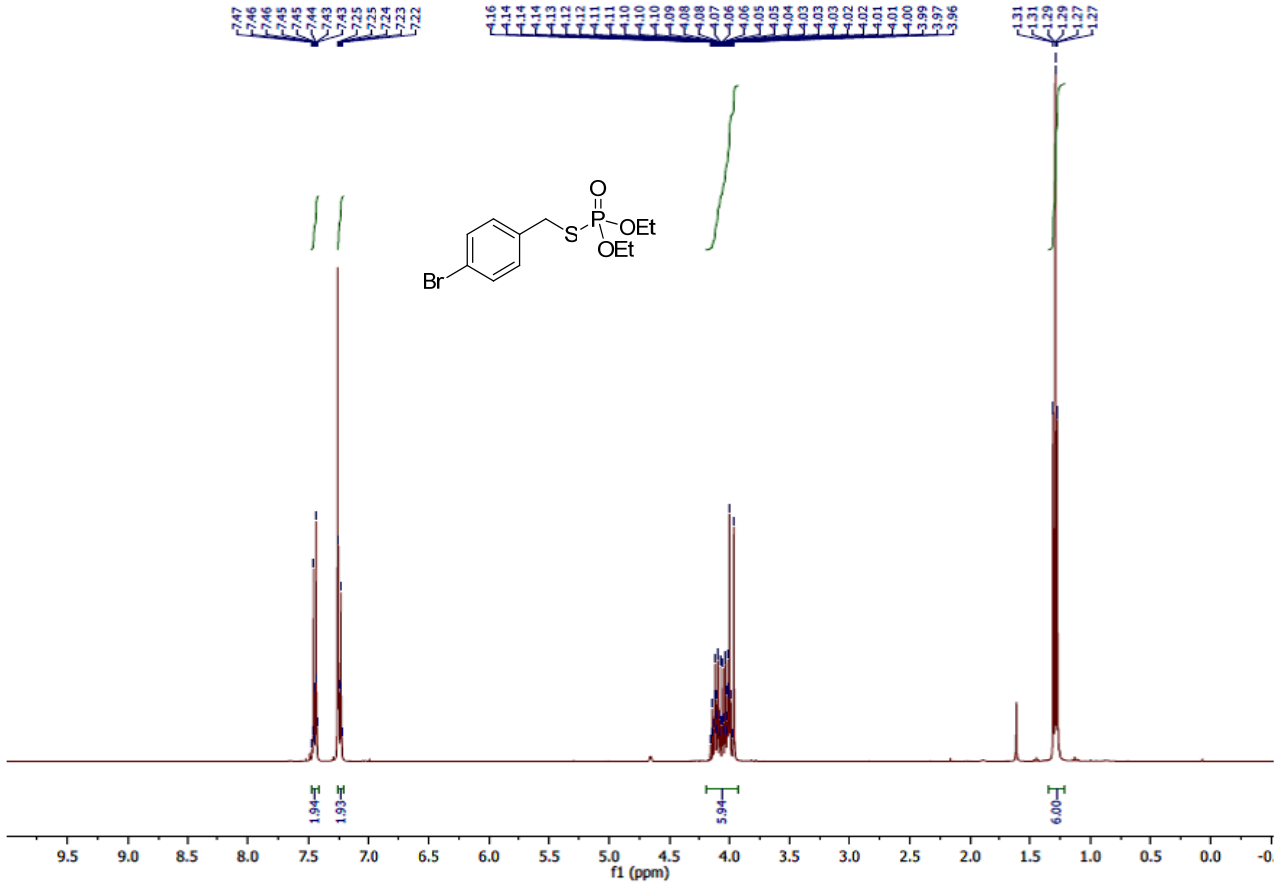
Appendix Figure 71 400 MHz ^{1}H NMR spectrum of *S*-3,4-dimethoxybenzyl *O,O*-diethyl phosphorothioate **(129)**



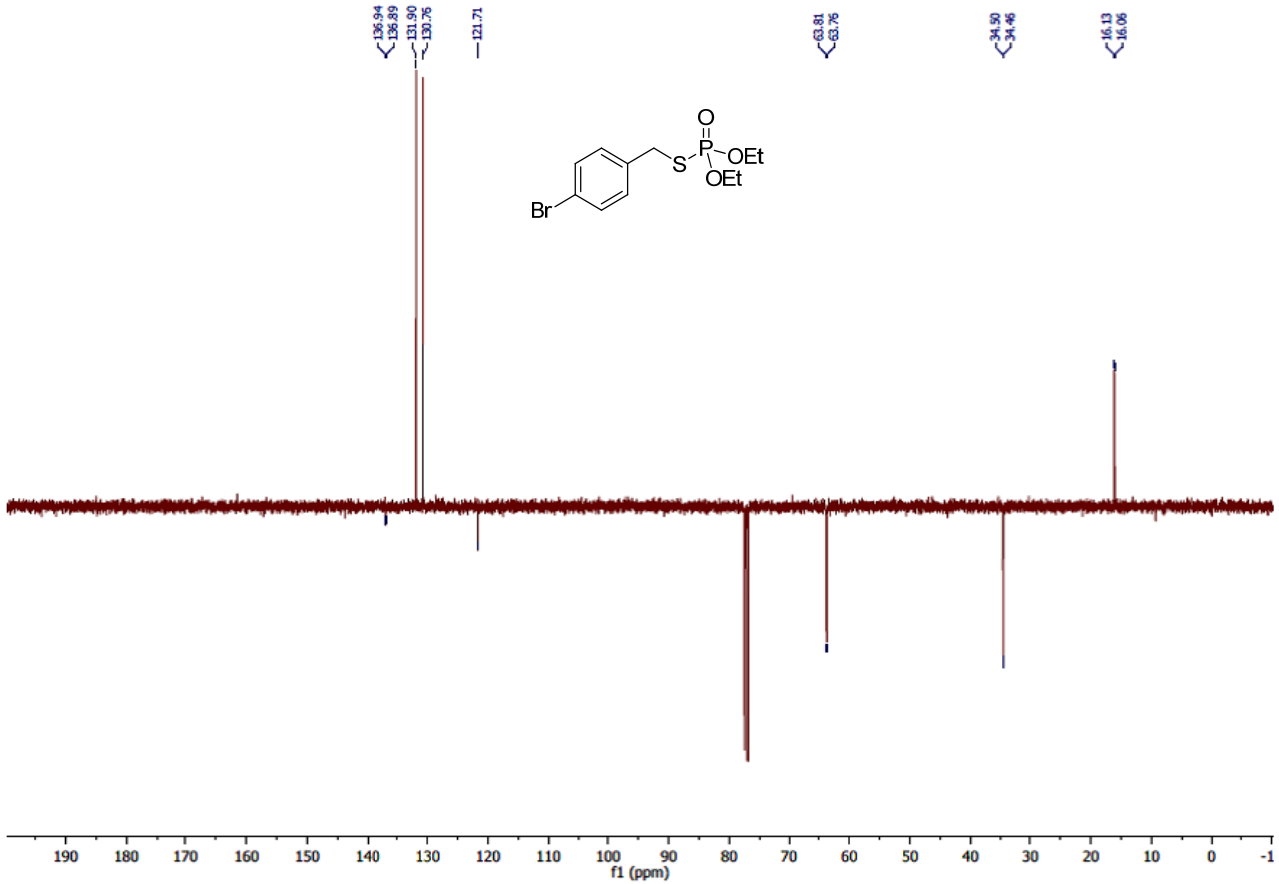
Appendix Figure 72 100 MHz ^{13}C NMR spectrum of of *S*-3,4-dimethoxybenzyl *O,O*- diethyl phosphorothioate **(129)**



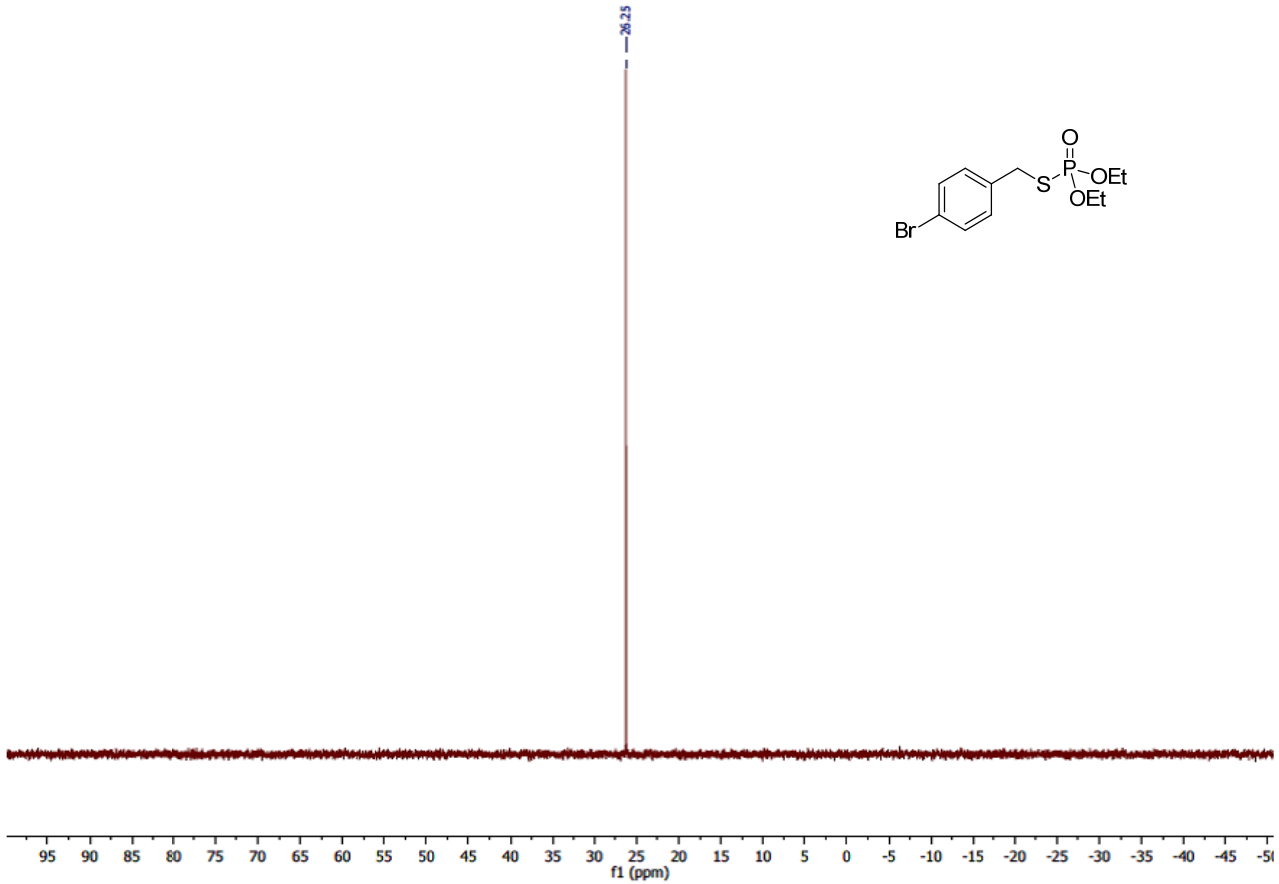
Appendix Figure 73 162 MHz ^{32}P NMR spectrum of *S*-3,4-dimethoxybenzyl *O,O*-diethyl phosphorothioate **(129)**



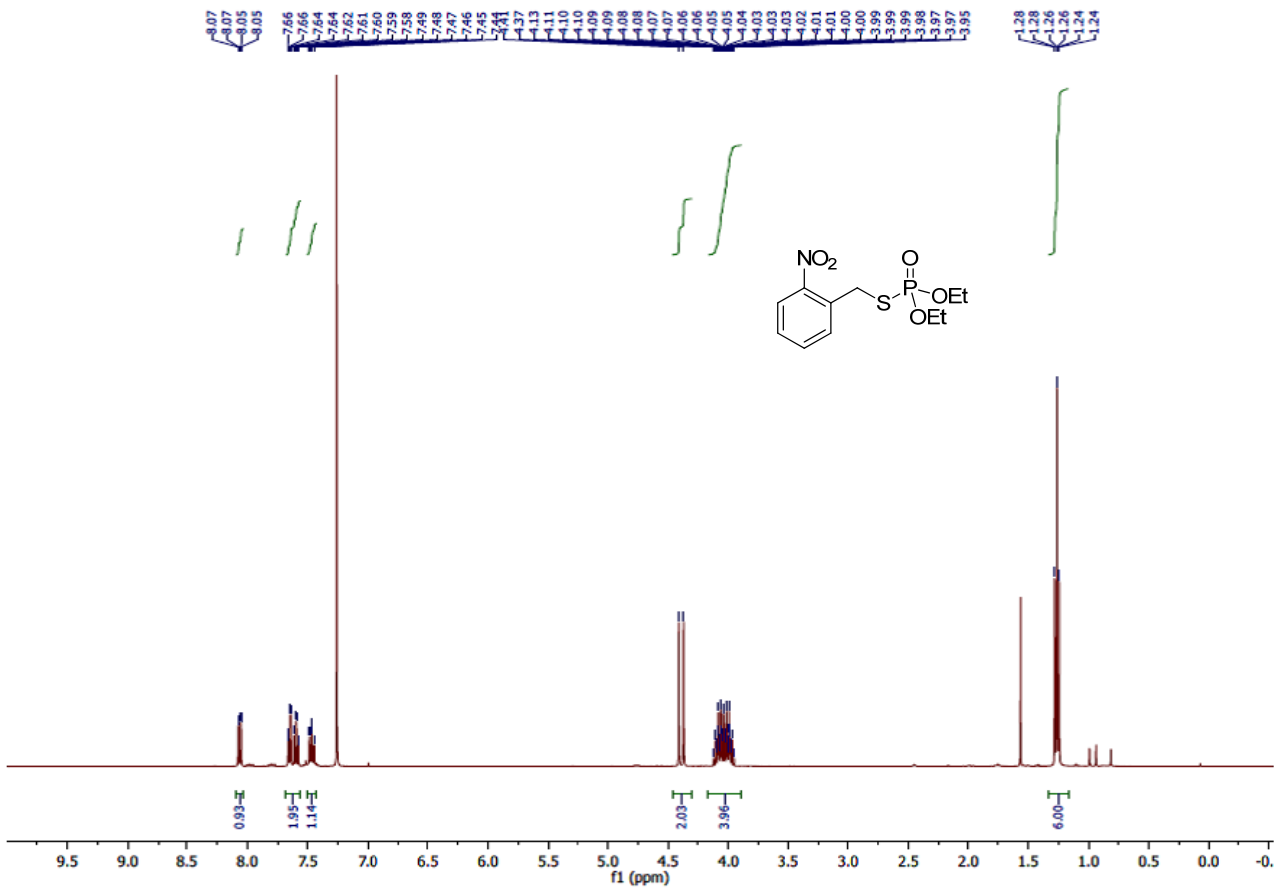
Appendix Figure 74 400 MHz ^{1}H NMR spectrum of *S*-4-bromobenzyl *O,O*-diethylphosphorothioate **(130)**



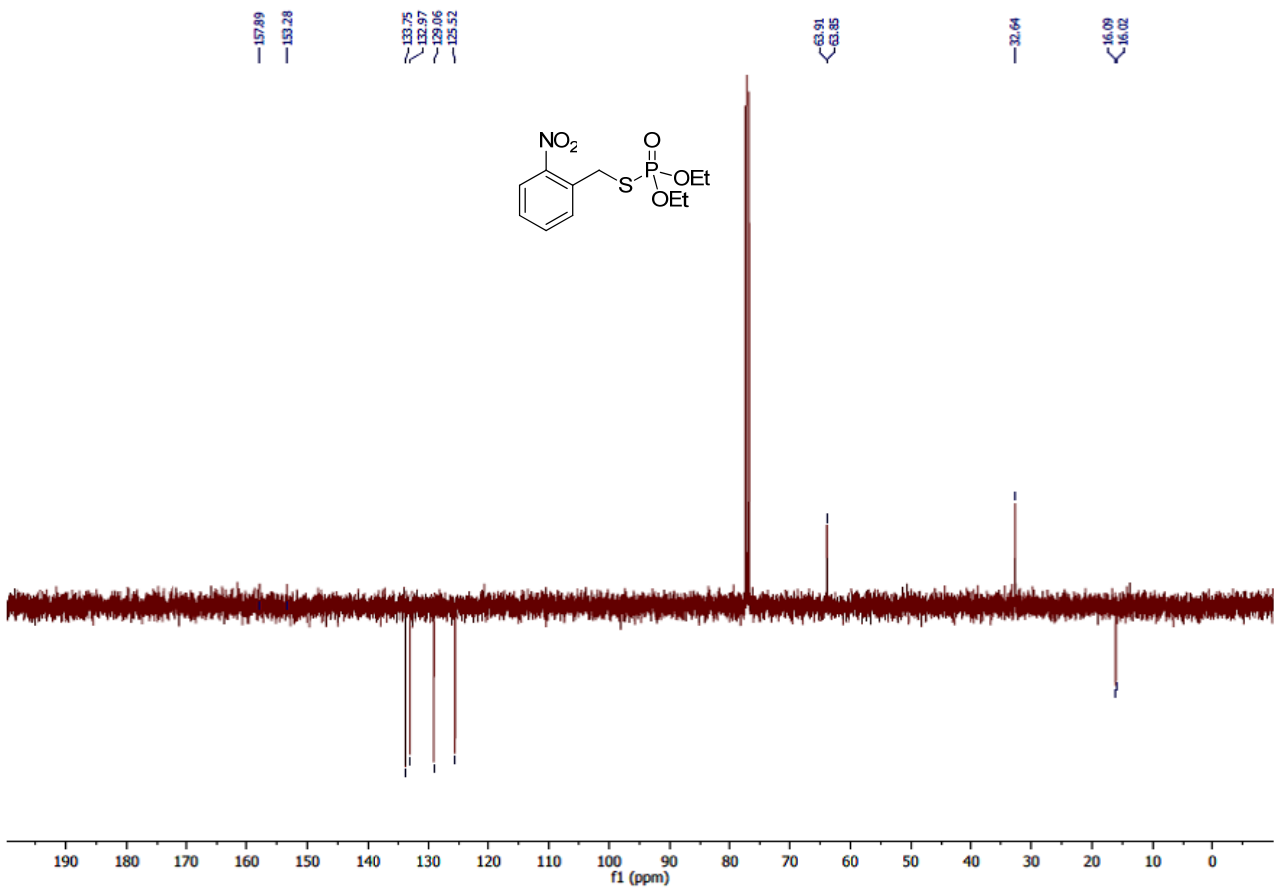
Appendix Figure 75 100 MHz ^{13}C NMR spectrum of *S*-4-bromobenzyl *O,O*-diethylphosphorothioate **(130)**



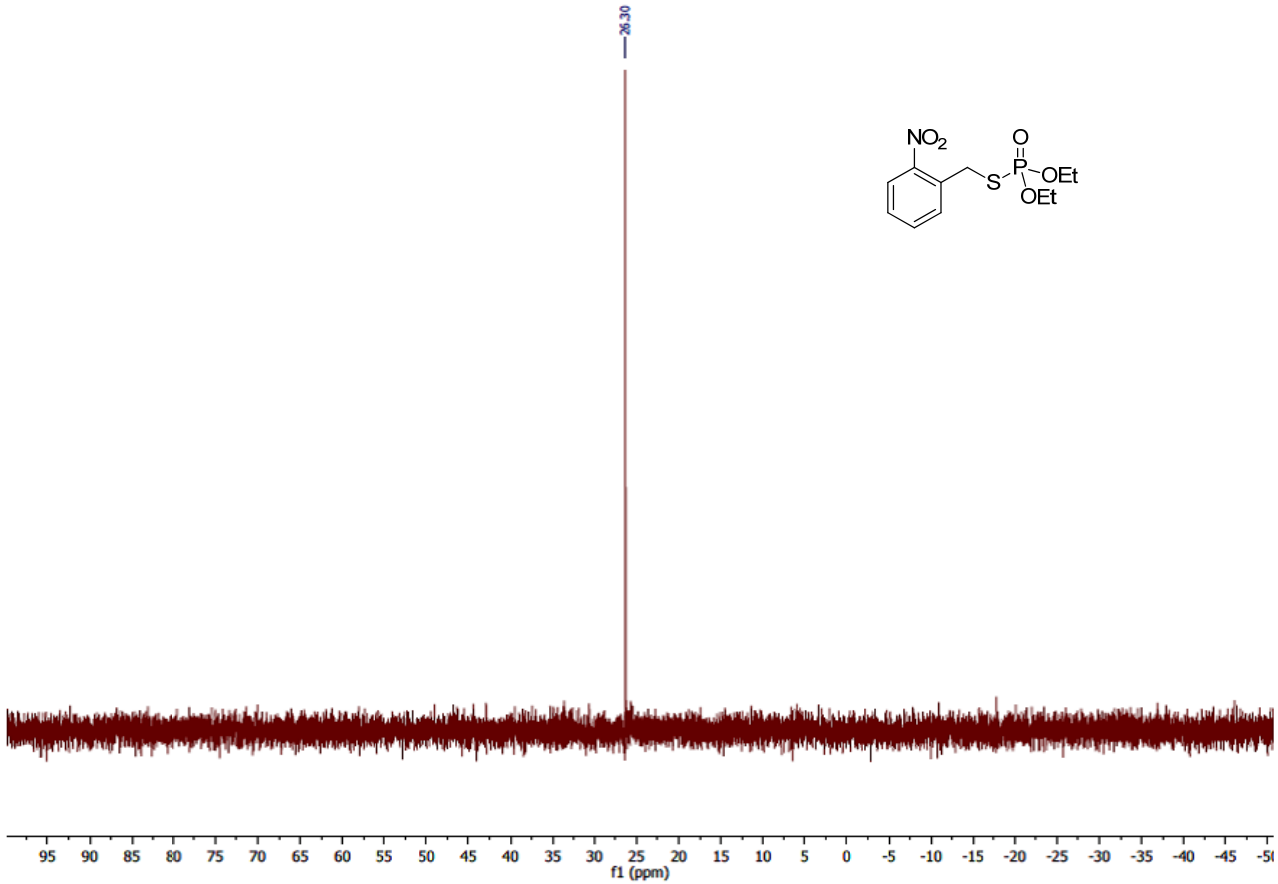
Appendix Figure 76 162 MHz ^{32}P NMR spectrum of *S*-4-bromobenzyl *O,O*-diethylphosphorothioate **(130)**



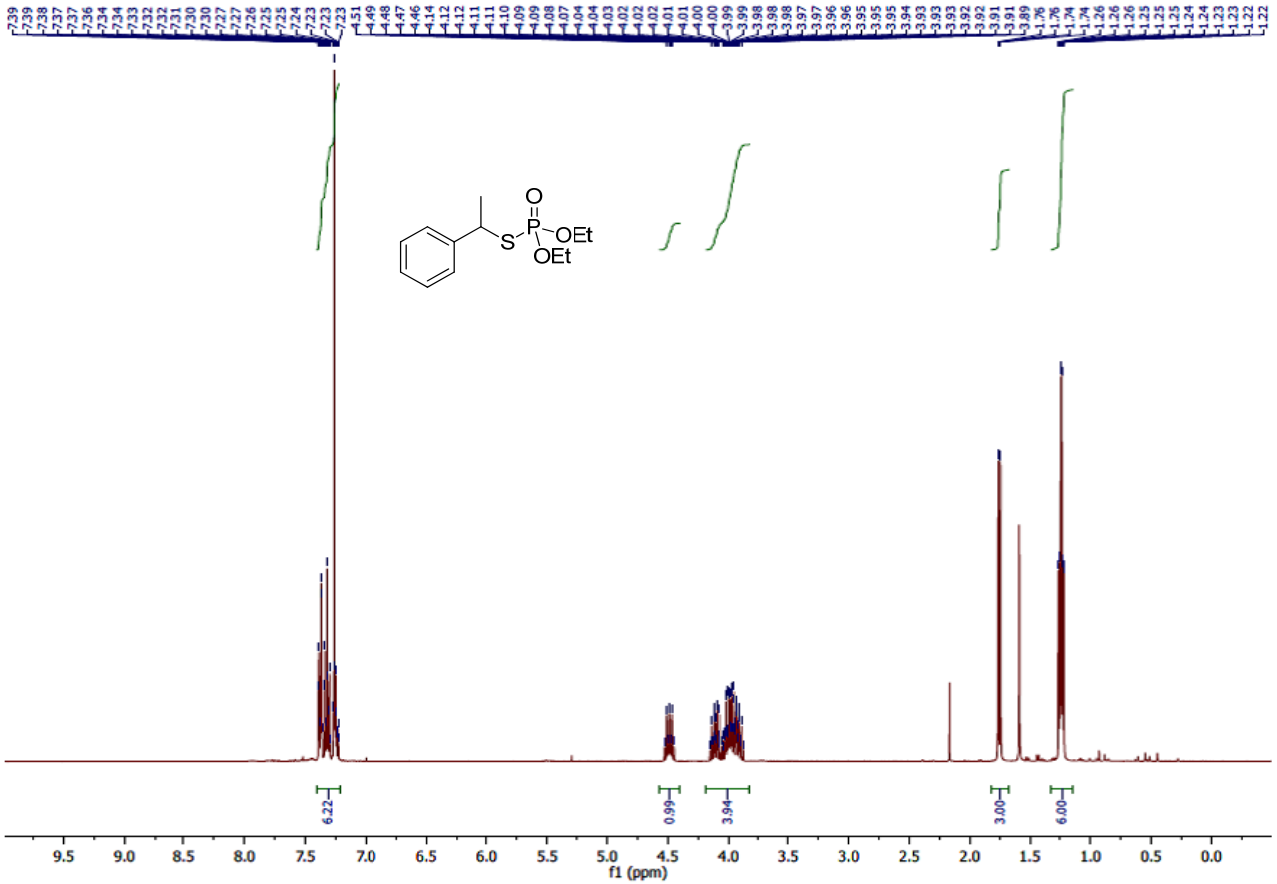
Appendix Figure 77 400 MHz ^{1}H NMR spectrum of *O,O*-diethyl-*S*-2-nitrobenzyl phosphorothioate **(131)**



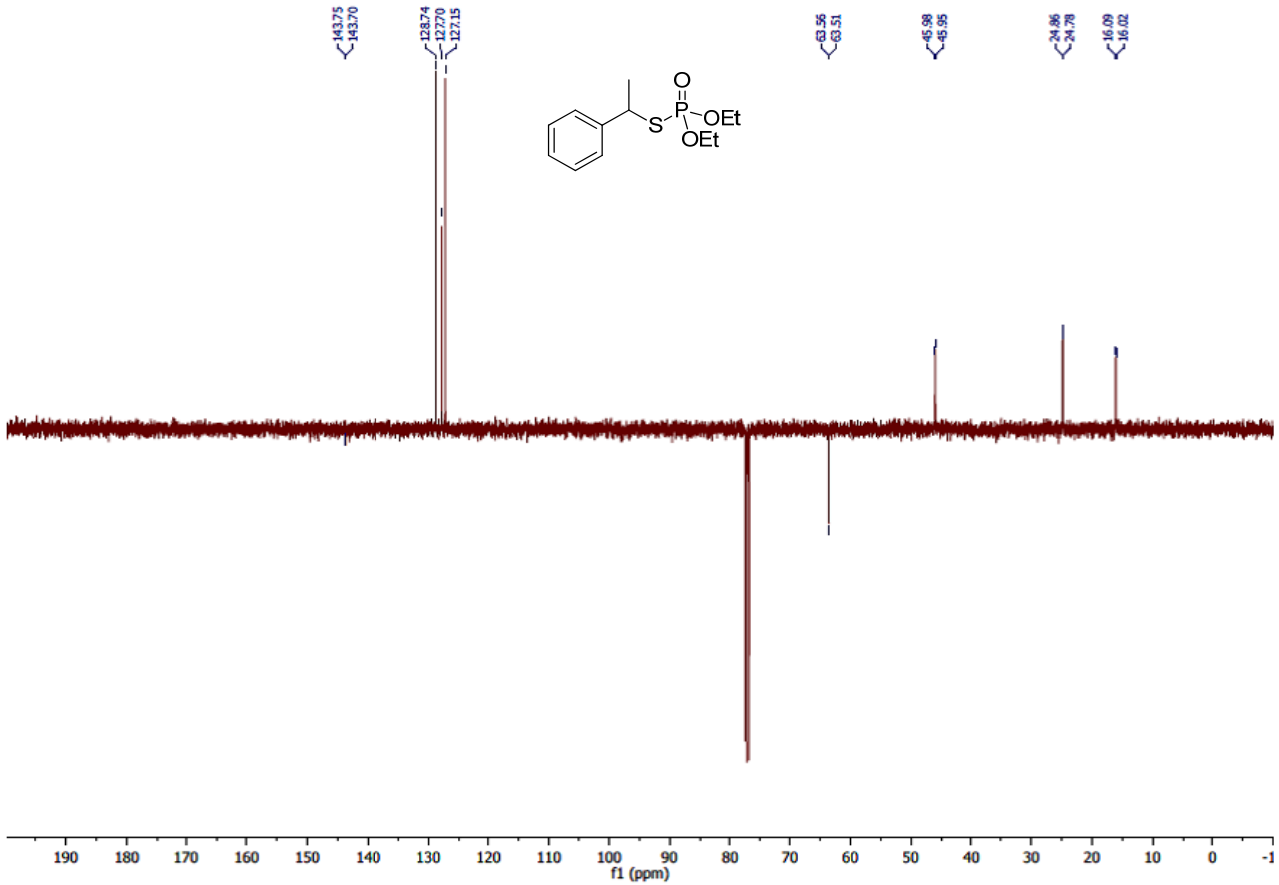
Appendix Figure 78 100 MHz ^{13}C NMR spectrum of *O,O*-diethyl-*S*-2-nitrobenzyl phosphorothioate **(131)**



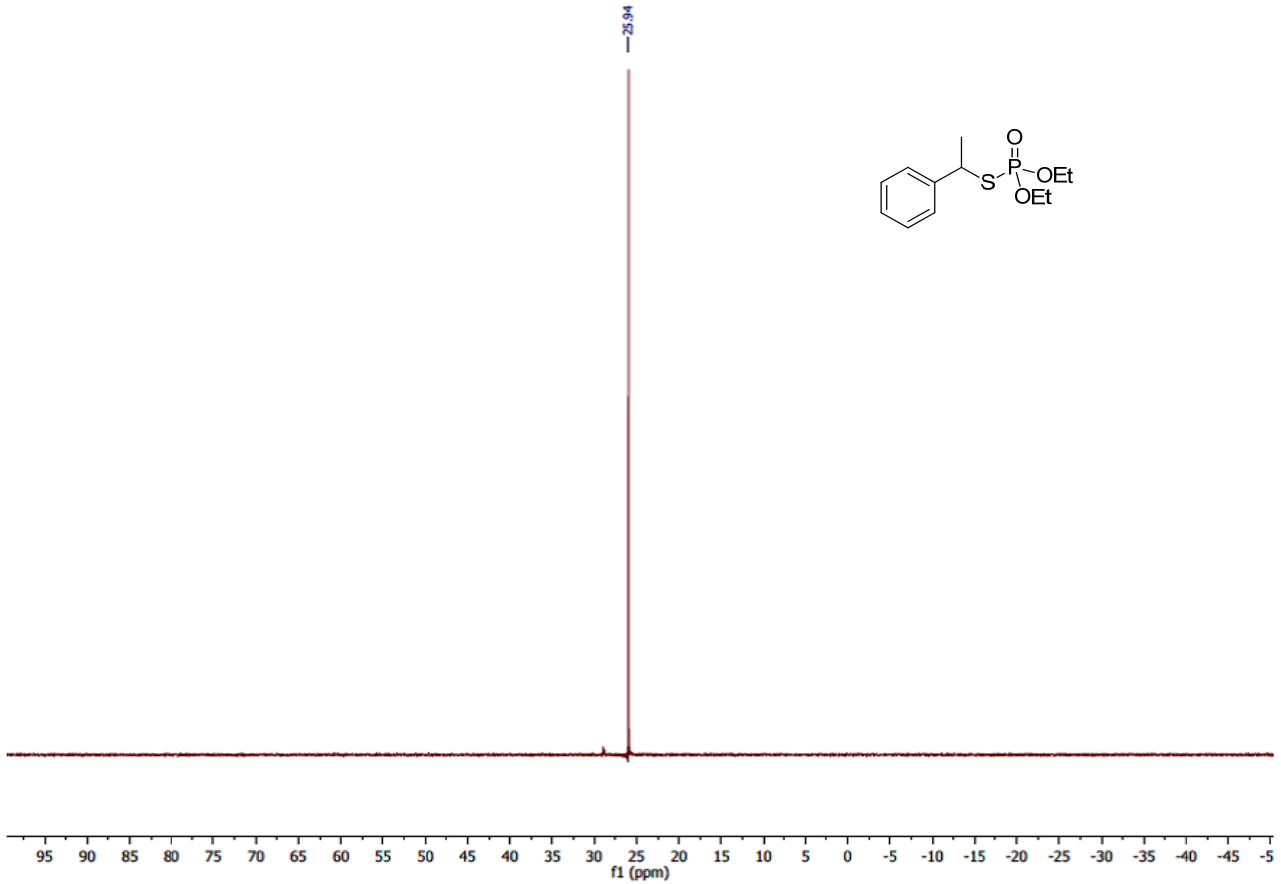
Appendix Figure 79 162 MHz ^{32}P NMR spectrum of *O,O*-diethyl-*S*-2-nitrobenzyl phosphorothioate **(131)**



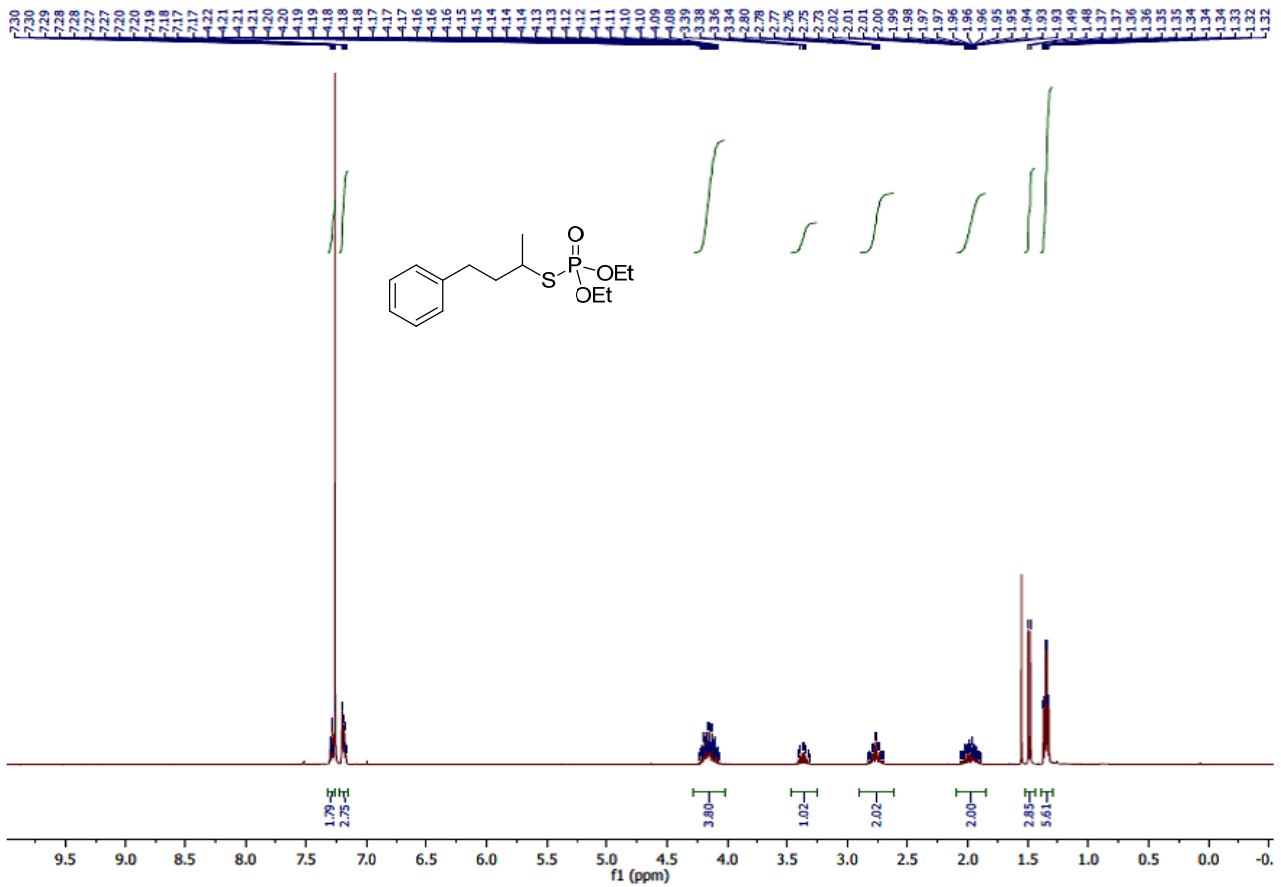
Appendix Figure 80 400 MHz ^{1}H NMR spectrum of *O,O*-diethyl-*S*-(1-phenylethyl) phosphorothioate **(132)**



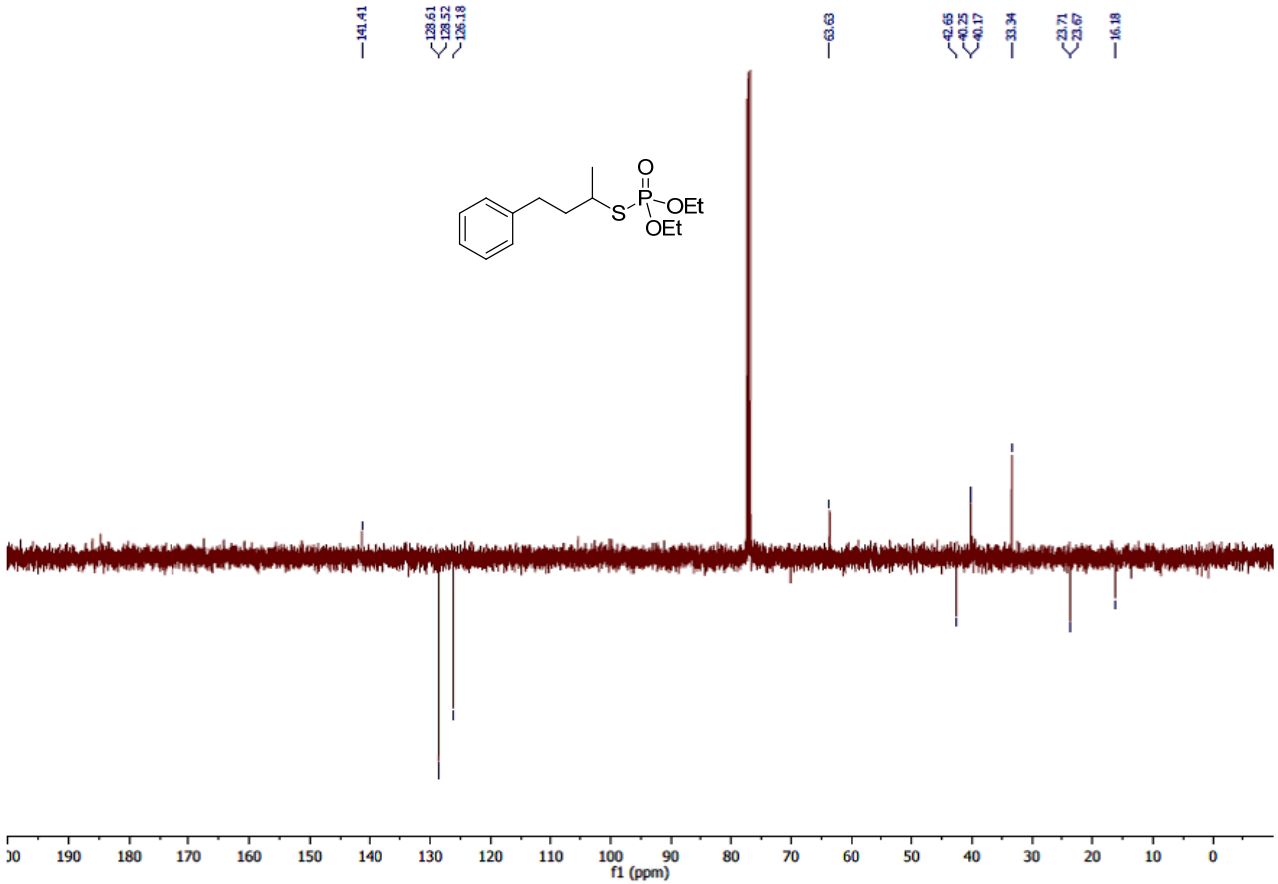
Appendix Figure 81 100 MHz ^{13}C NMR spectrum of *O,O*-diethyl-*S*-(1-phenylethyl) phosphorothioate **(132)**



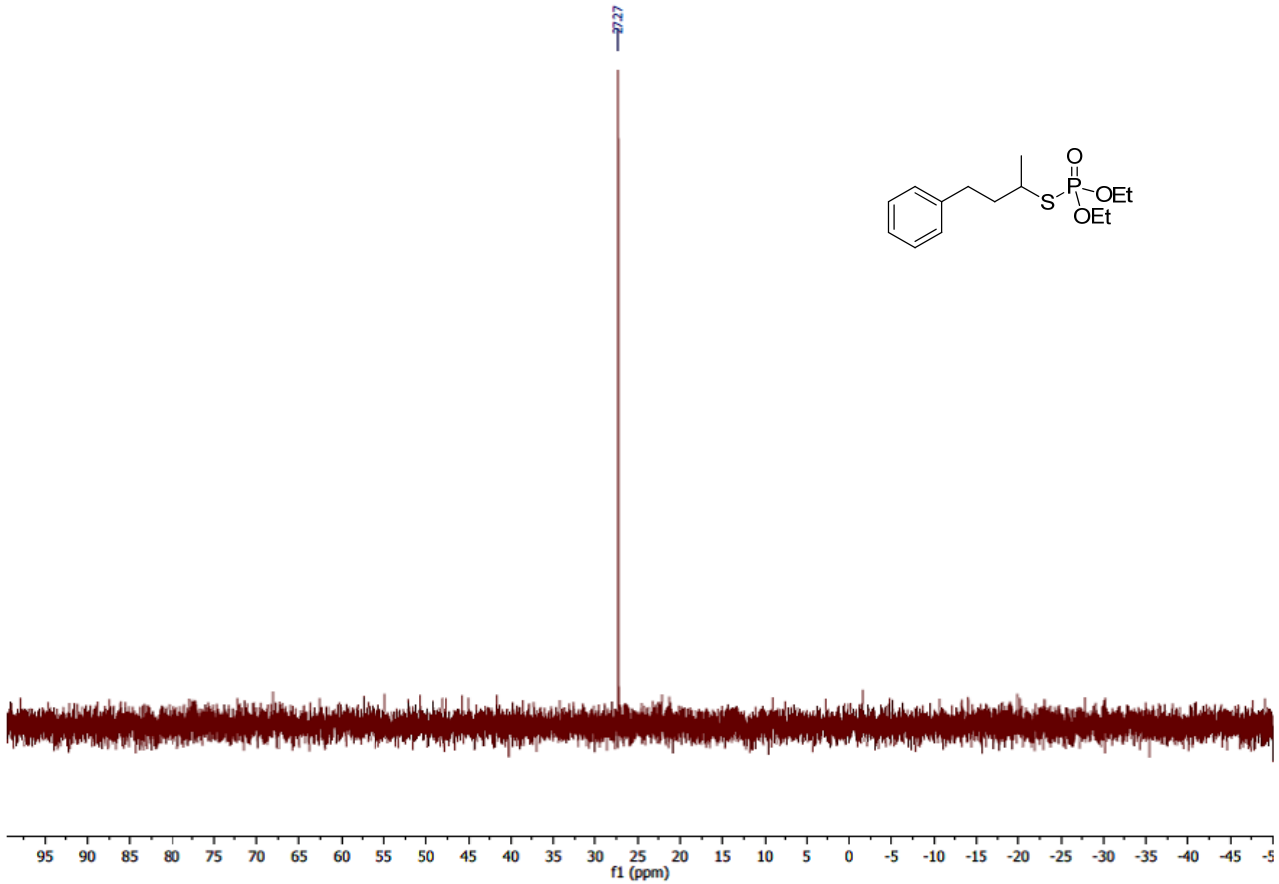
Appendix Figure 82 162 MHz ^{32}P NMR spectrum of *O,O*-diethyl-*S*-(1-phenylethyl) phosphorothioate **(132)**



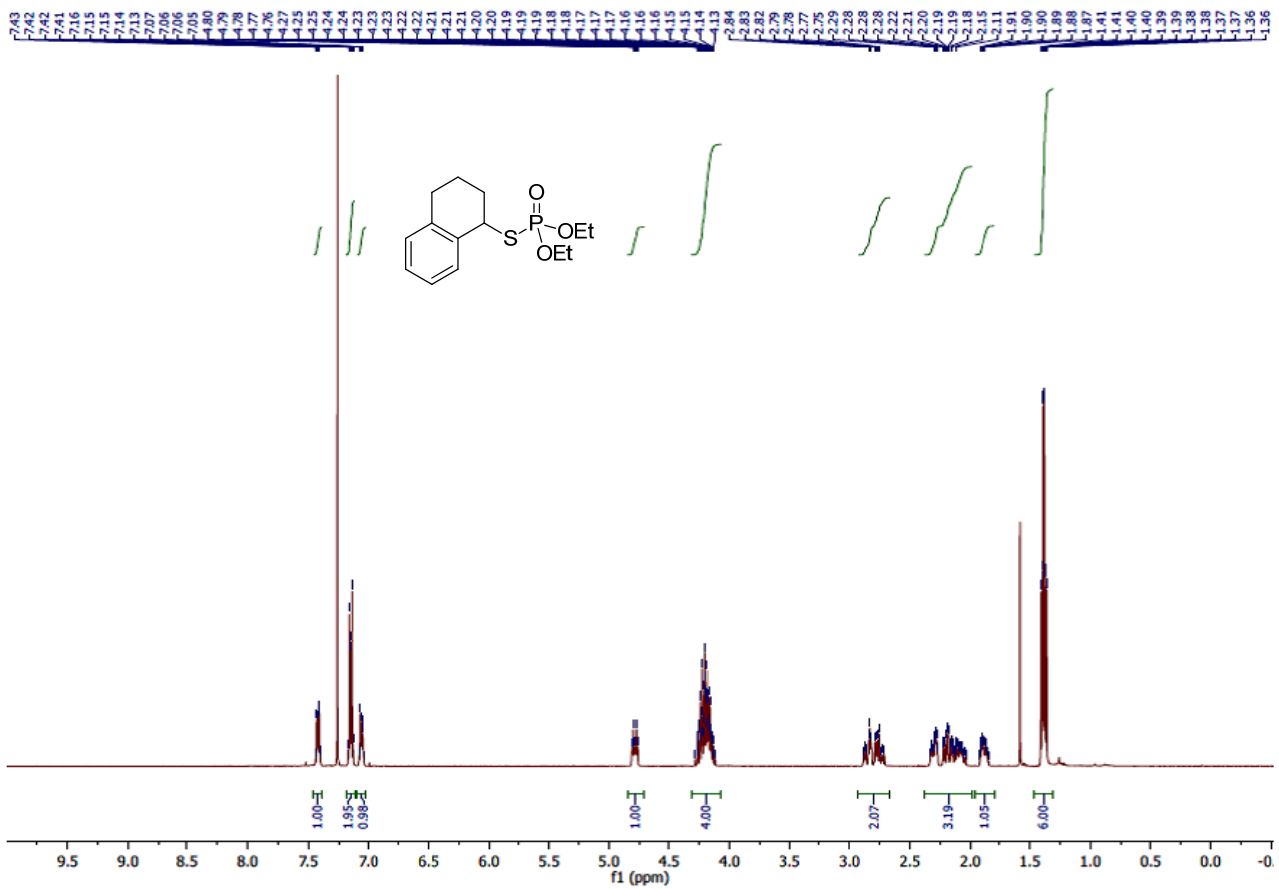
Appendix Figure 83 400 MHz ^{1}H NMR spectrum of *O,O*-diethyl-*S*-(4-phenyl butan-2-yl) phosphorothioate **(133)**



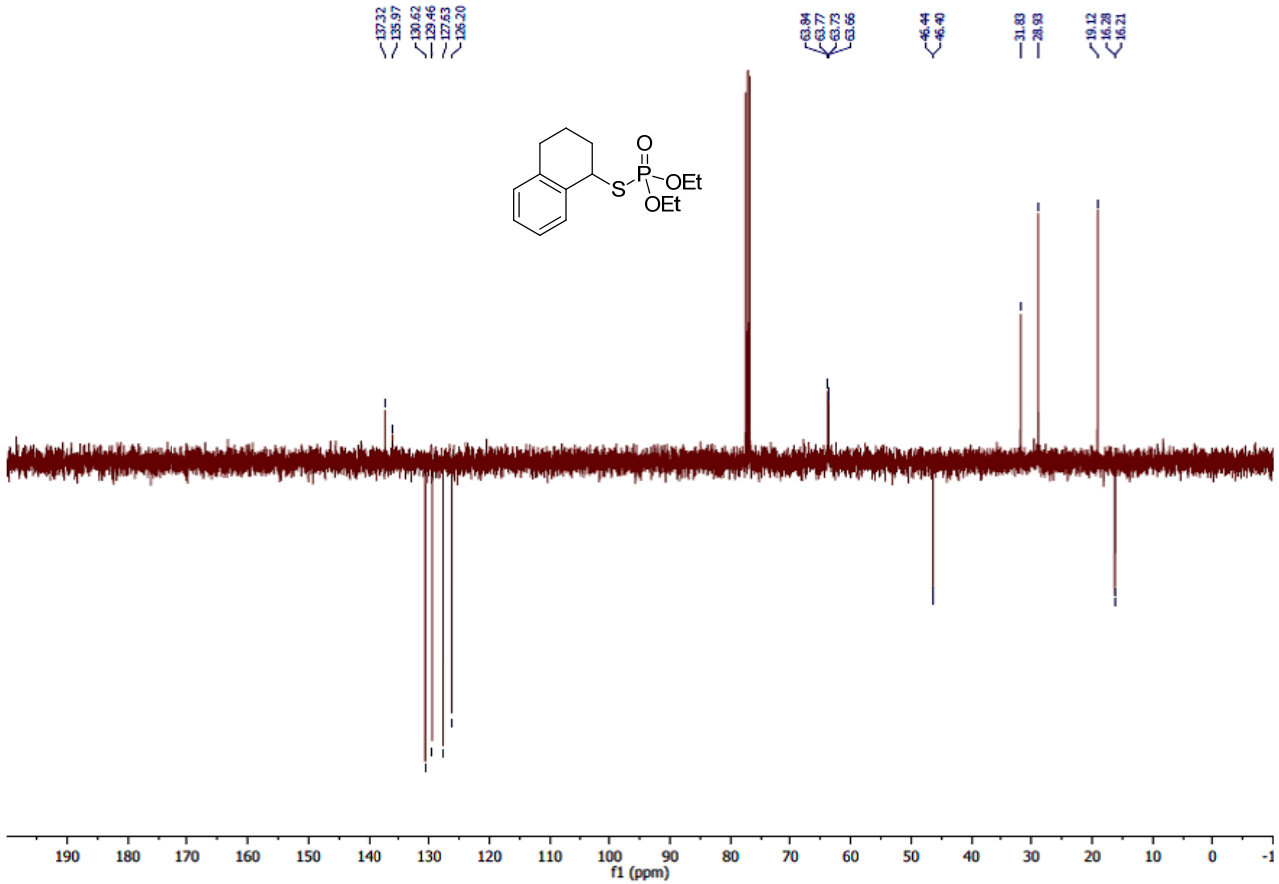
Appendix Figure 84 100 MHz ^{13}C NMR spectrum of *O,O*-diethyl-*S*-(4-phenyl butan-2-yl) phosphorothioate **(133)**



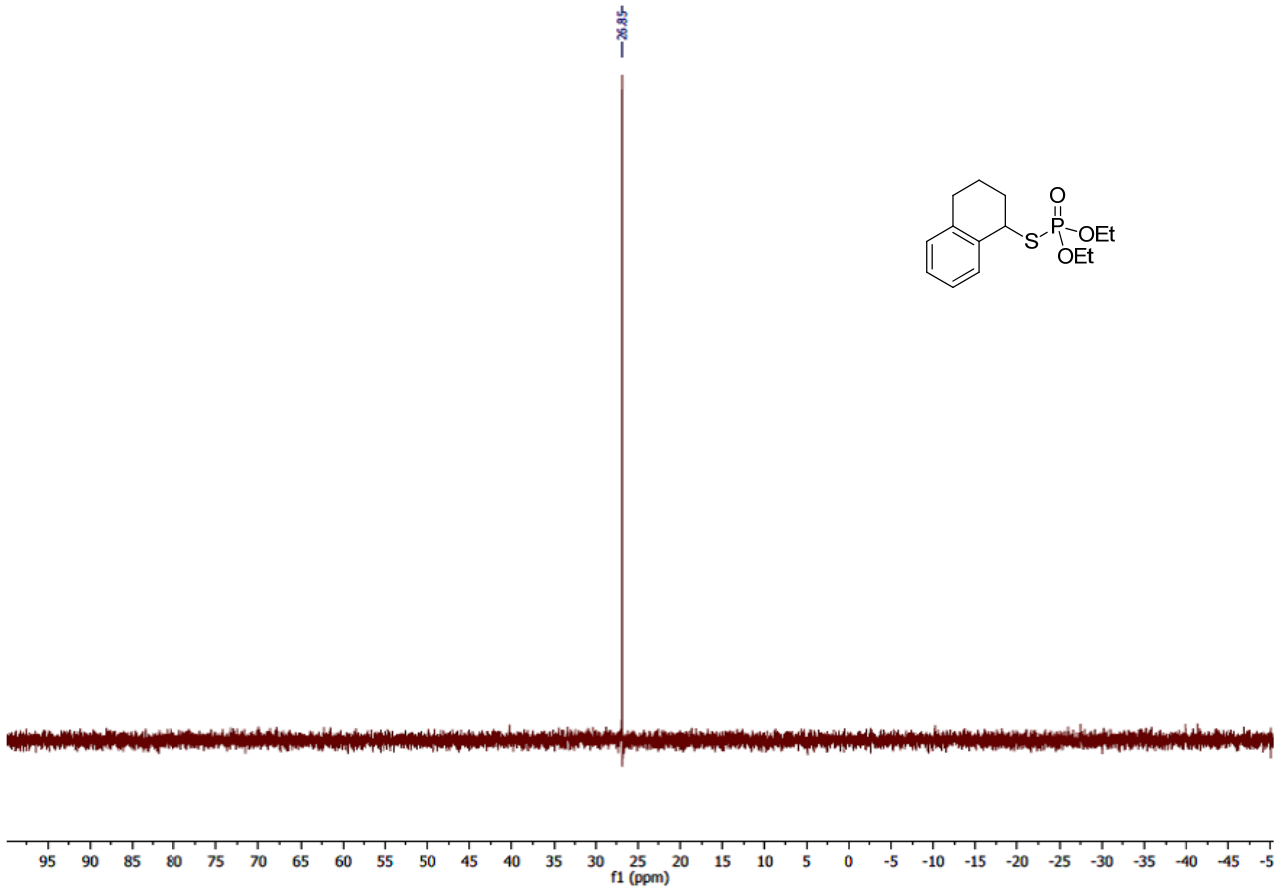
Appendix Figure 85 162 MHz ^{32}P NMR spectrum of *O,O*-diethyl-*S*-(4-phenyl butan-2-yl) phosphorothioate **(133)**



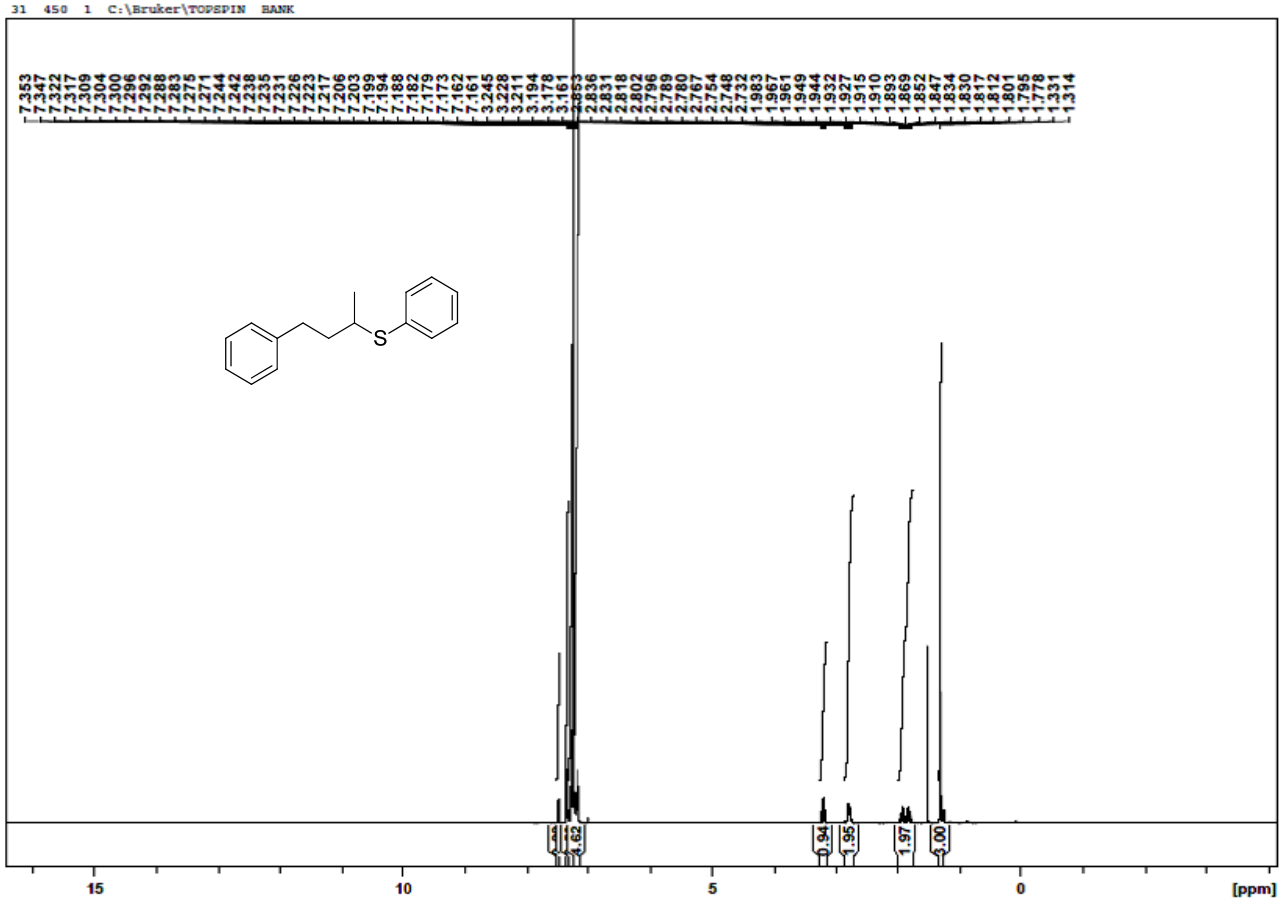
Appendix Figure 86 400 MHz ^{1}H NMR spectrum of *O,O*-diethyl *S*-(1,2,3,4-tetrahydronaphthalen-1-yl) phosphorothioate **(134)**



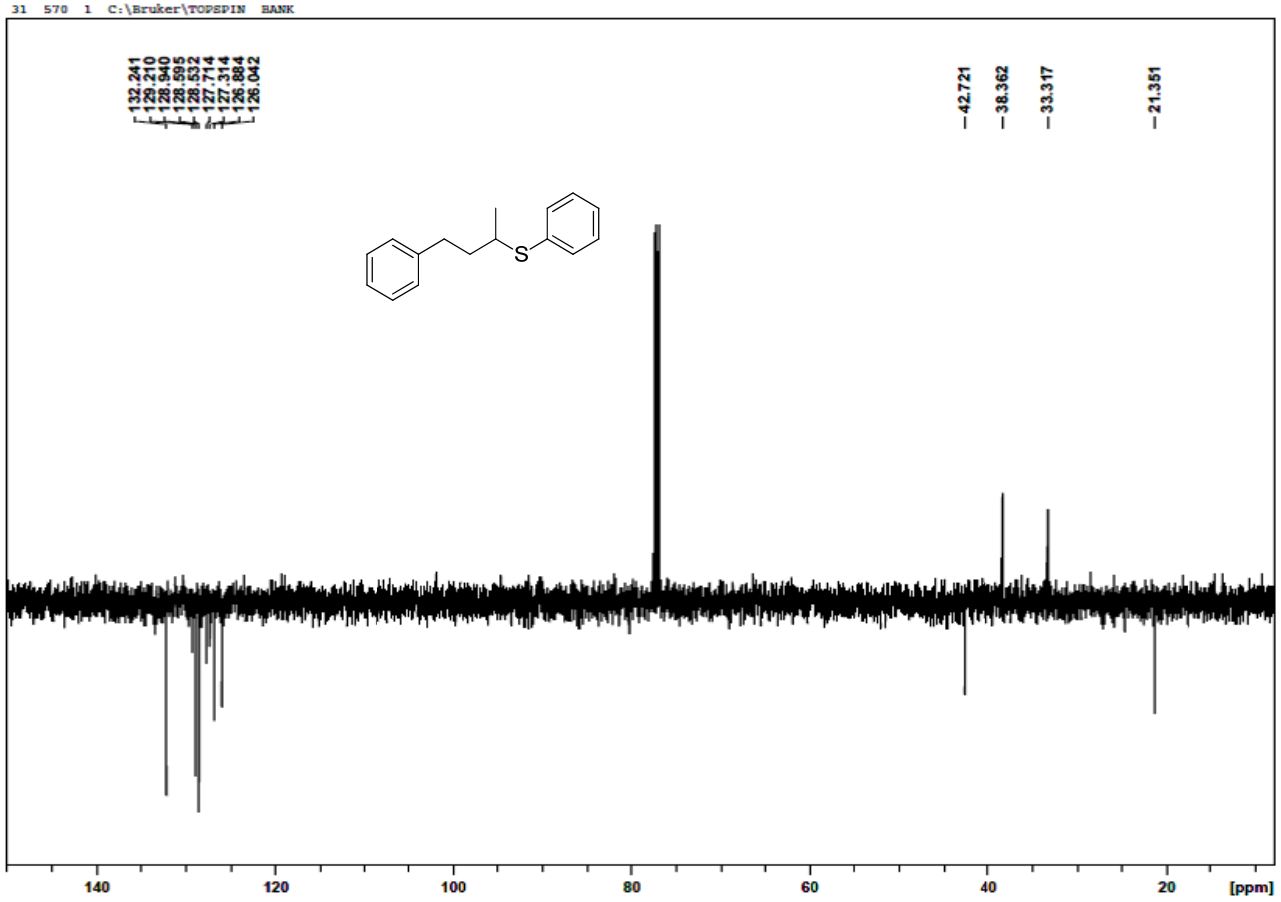
Appendix Figure 87 100 MHz ^{13}C NMR spectrum of *O,O*-diethyl *S*-(1,2,3,4-tetrahydronaphthalen-1-yl) phosphorothioate **(134)**



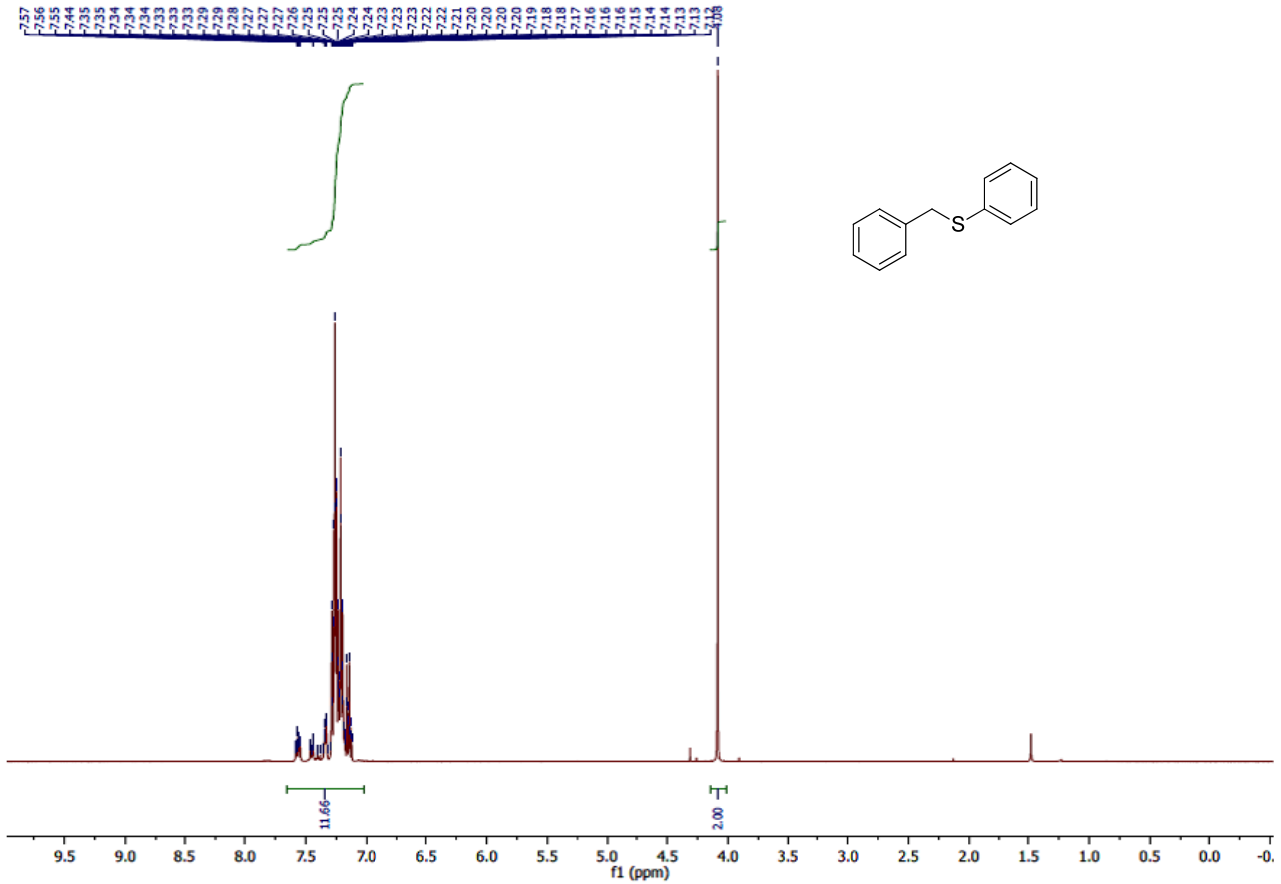
Appendix Figure 88 162 MHz ^{32}P NMR spectrum of *O,O*-diethyl *S*-(1,2,3,4-tetrahydronaphthalen-1-yl) phosphorothioate **(134)**



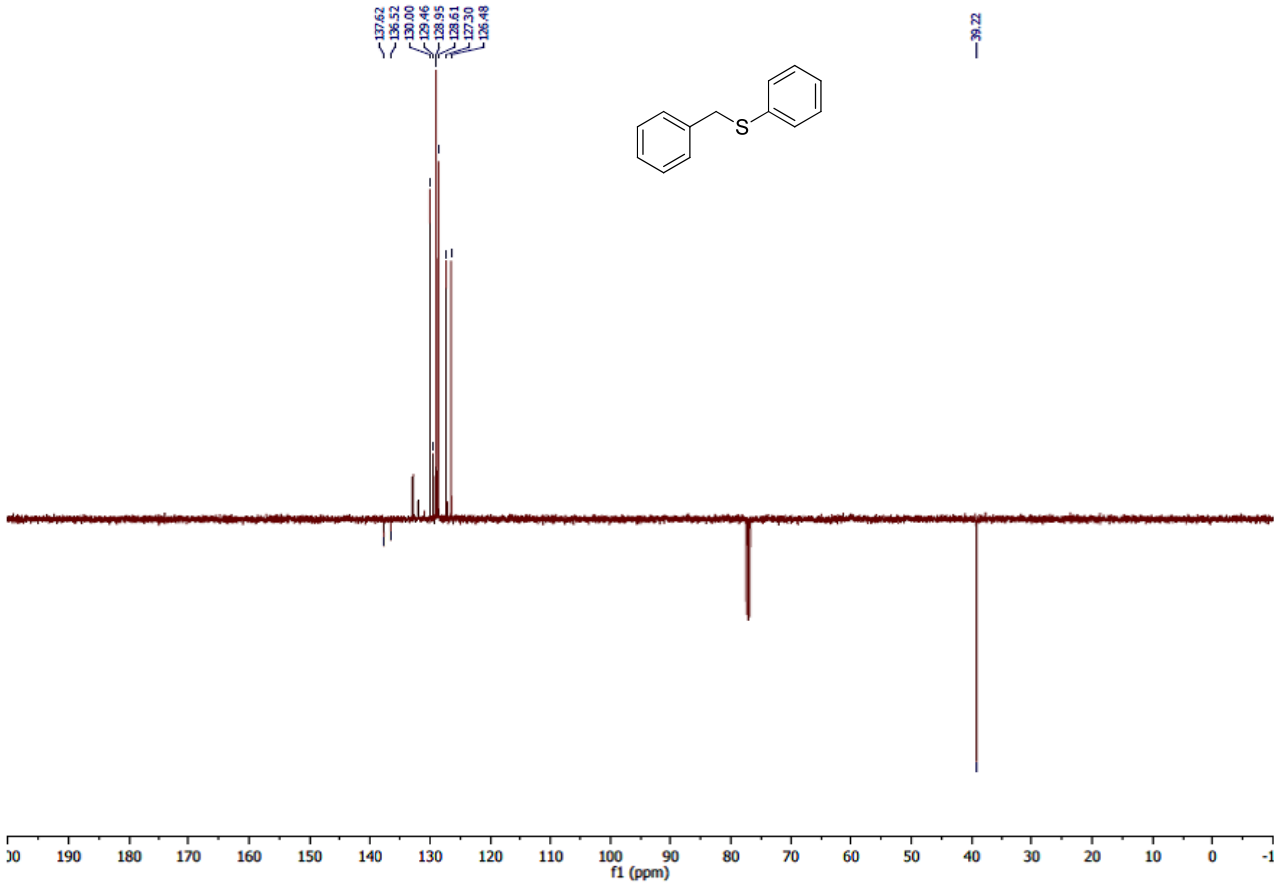
Appendix Figure 89 400 MHz ^{1}H NMR spectrum of phenyl(4-phenylbutan-2-yl)sulfane **(135)**



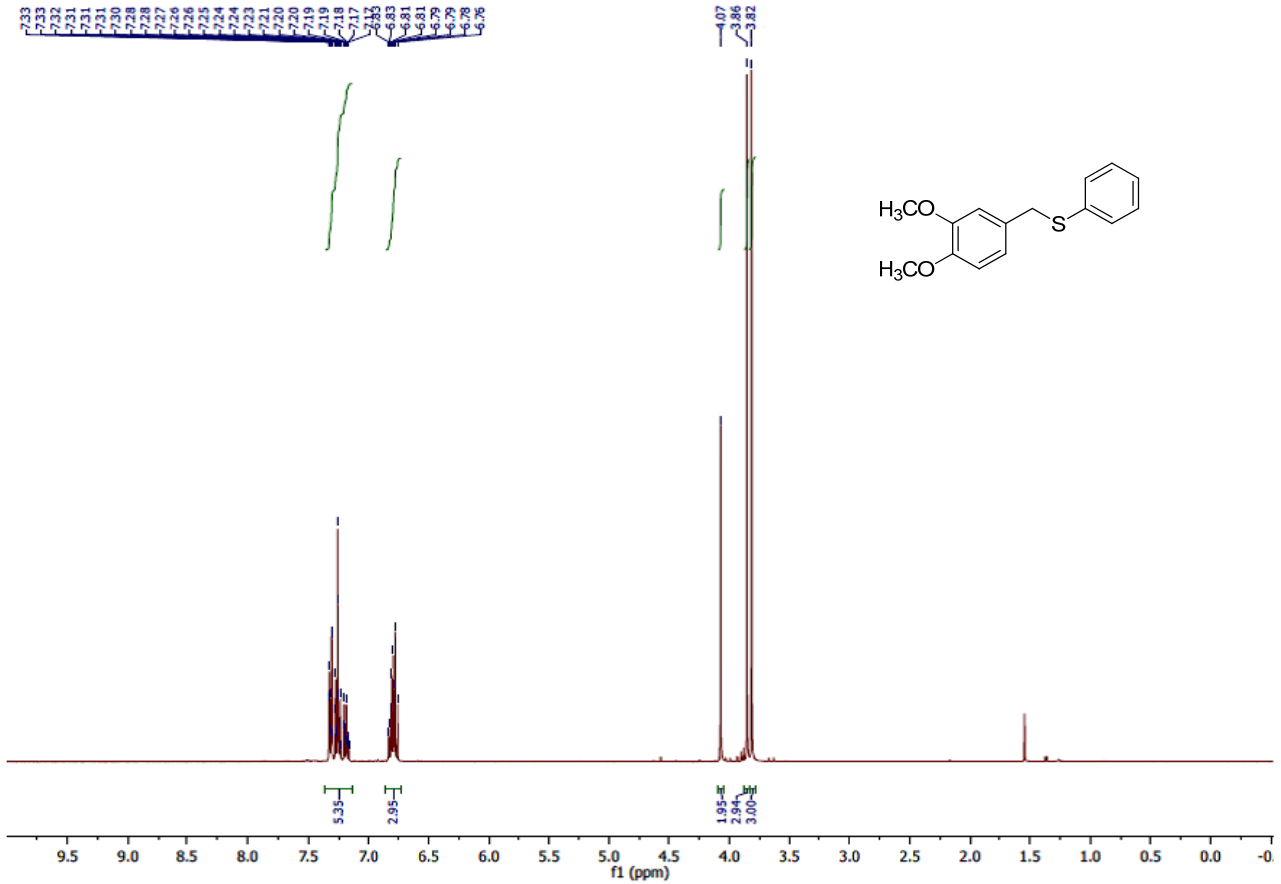
Appendix Figure 90 100 MHz ^{13}C NMR spectrum of phenyl(4-phenylbutan-2-yl)sulfane **(135)**



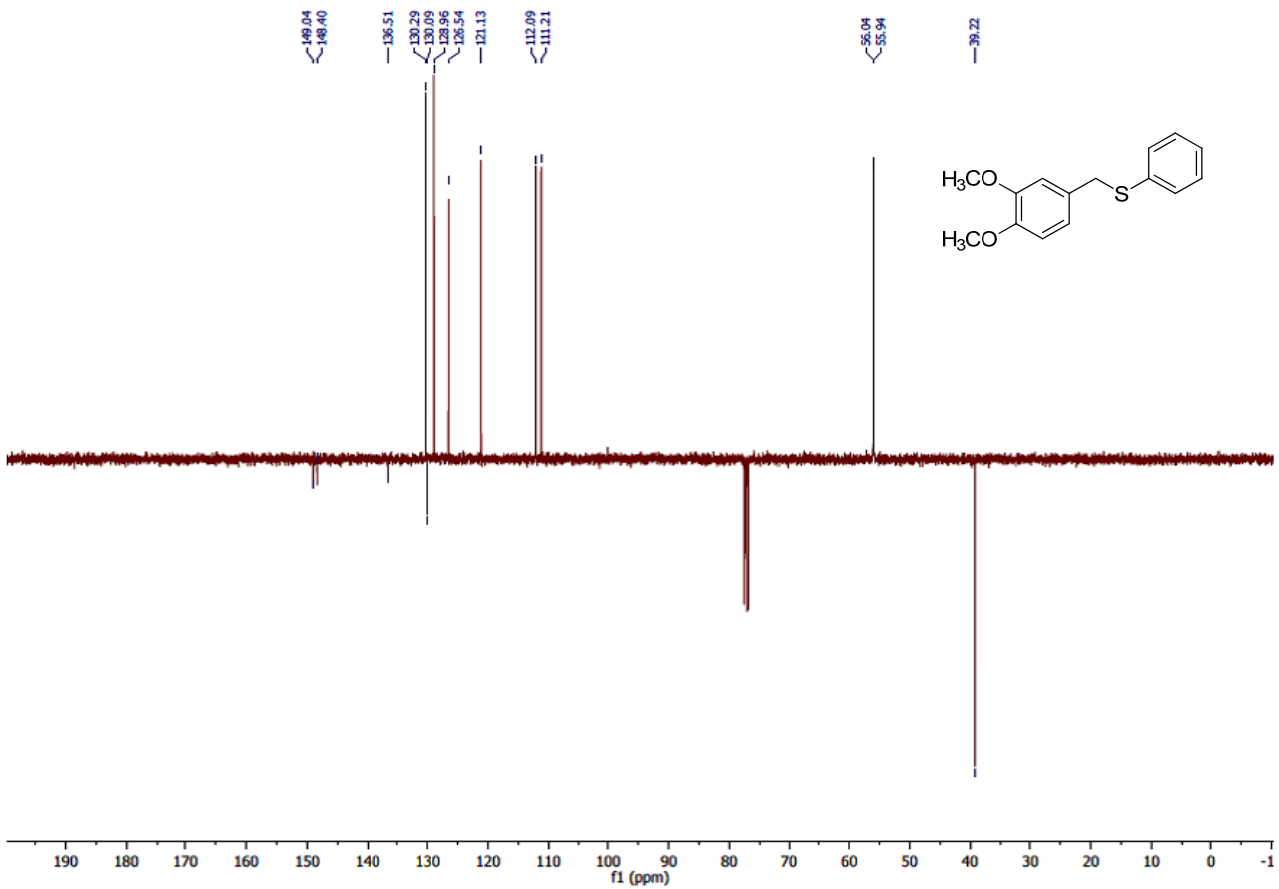
Appendix Figure 91 400 MHz ^{1}H NMR spectrum of benzyl(phenyl)sulfane **(136)**



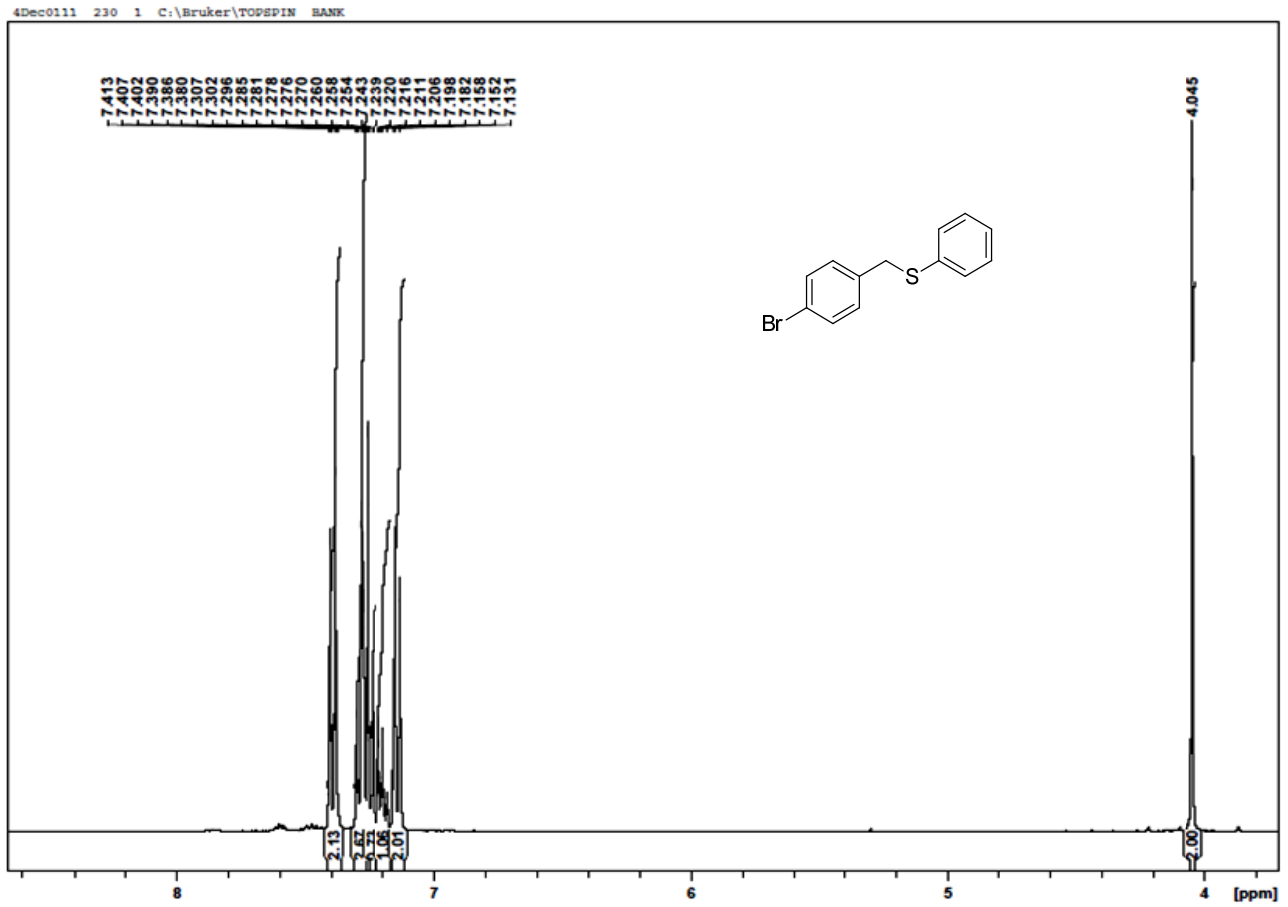
Appendix Figure 92 100 MHz ^{13}C NMR spectrum of benzyl(phenyl)sulfane **(136)**



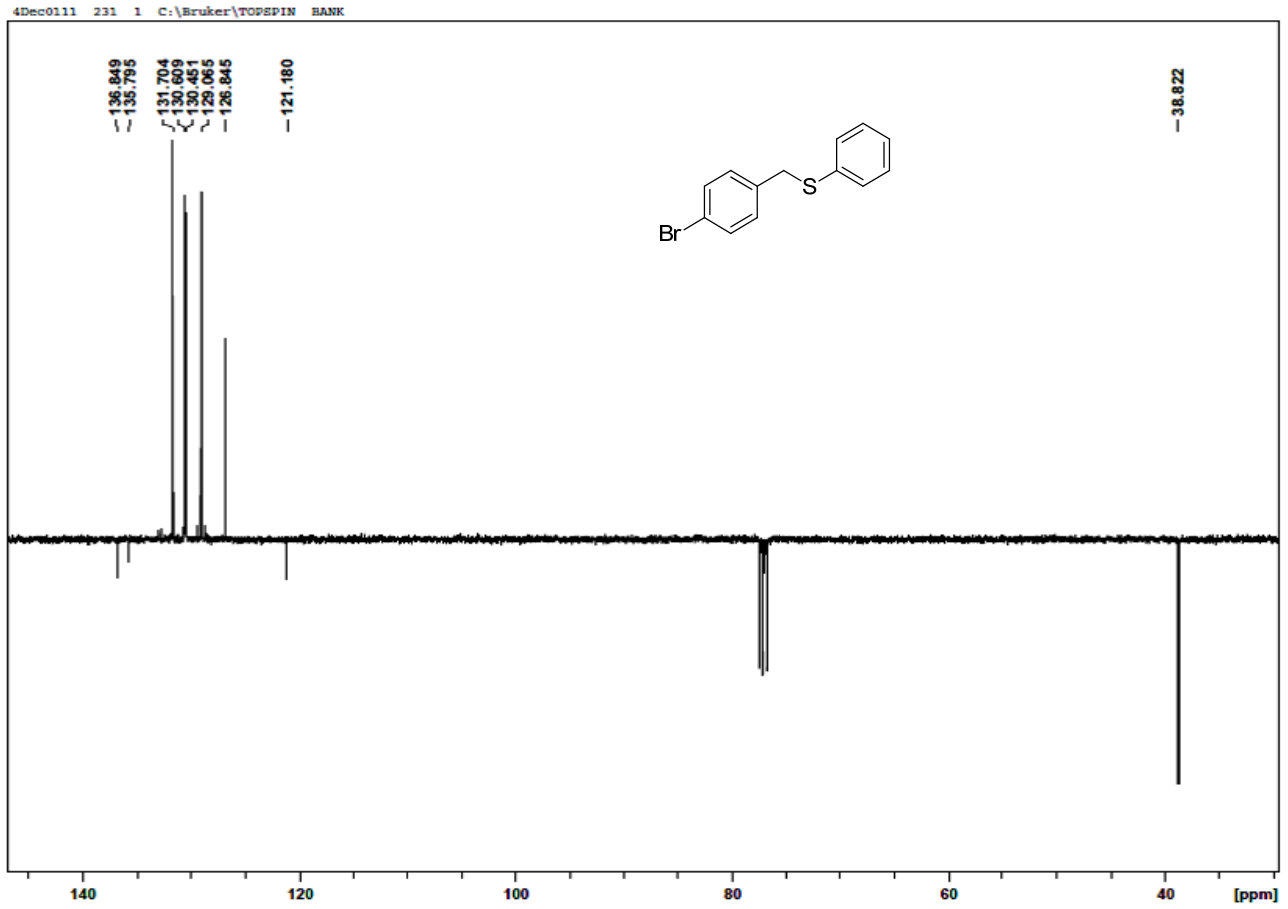
Appendix Figure 93 400 MHz ^{1}H NMR spectrum of (3,4-dimethoxybenzyl)(phenyl)sulfane **(137)**



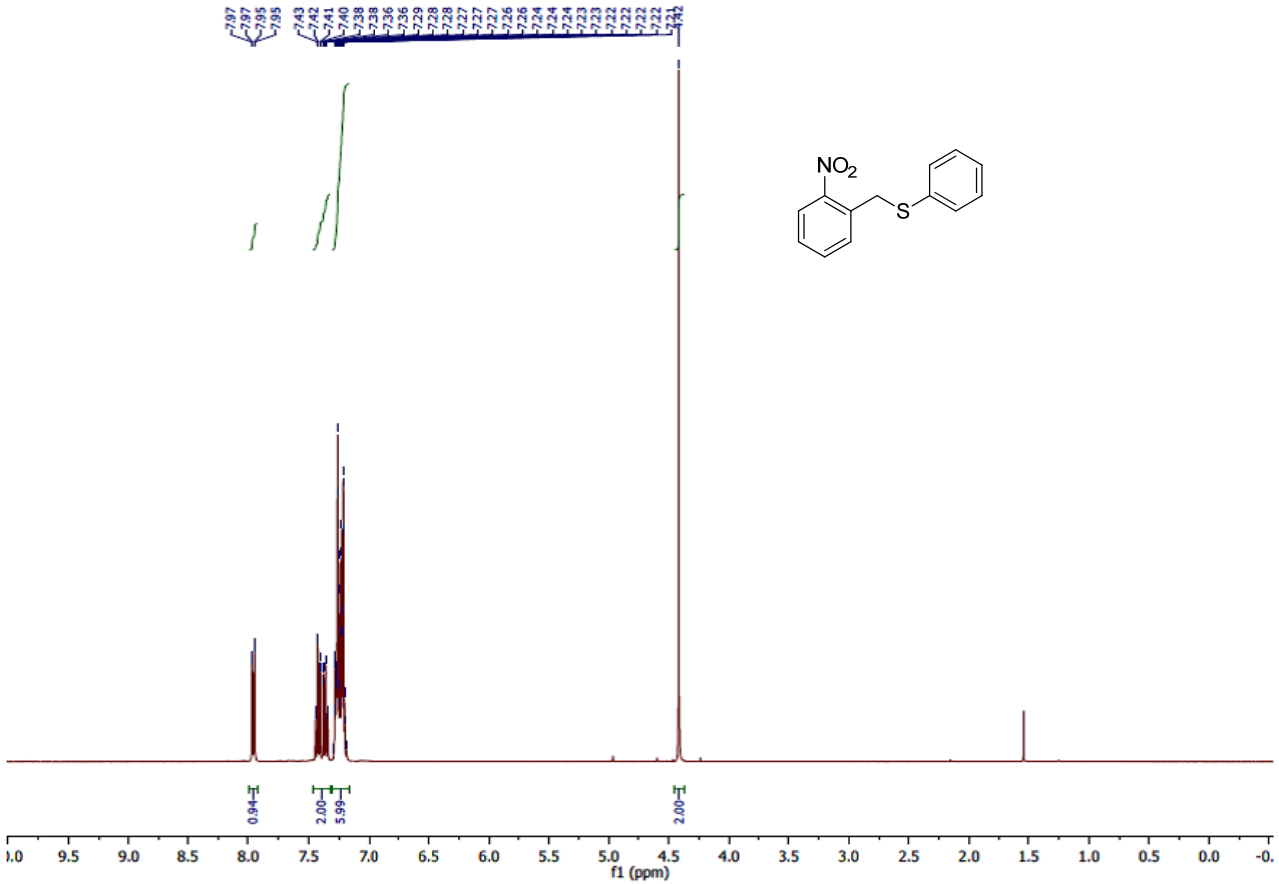
Appendix Figure 94 100 MHz ^{13}C NMR spectrum of (3,4-dimethoxybenzyl)(phenyl)sulfane **(137)**



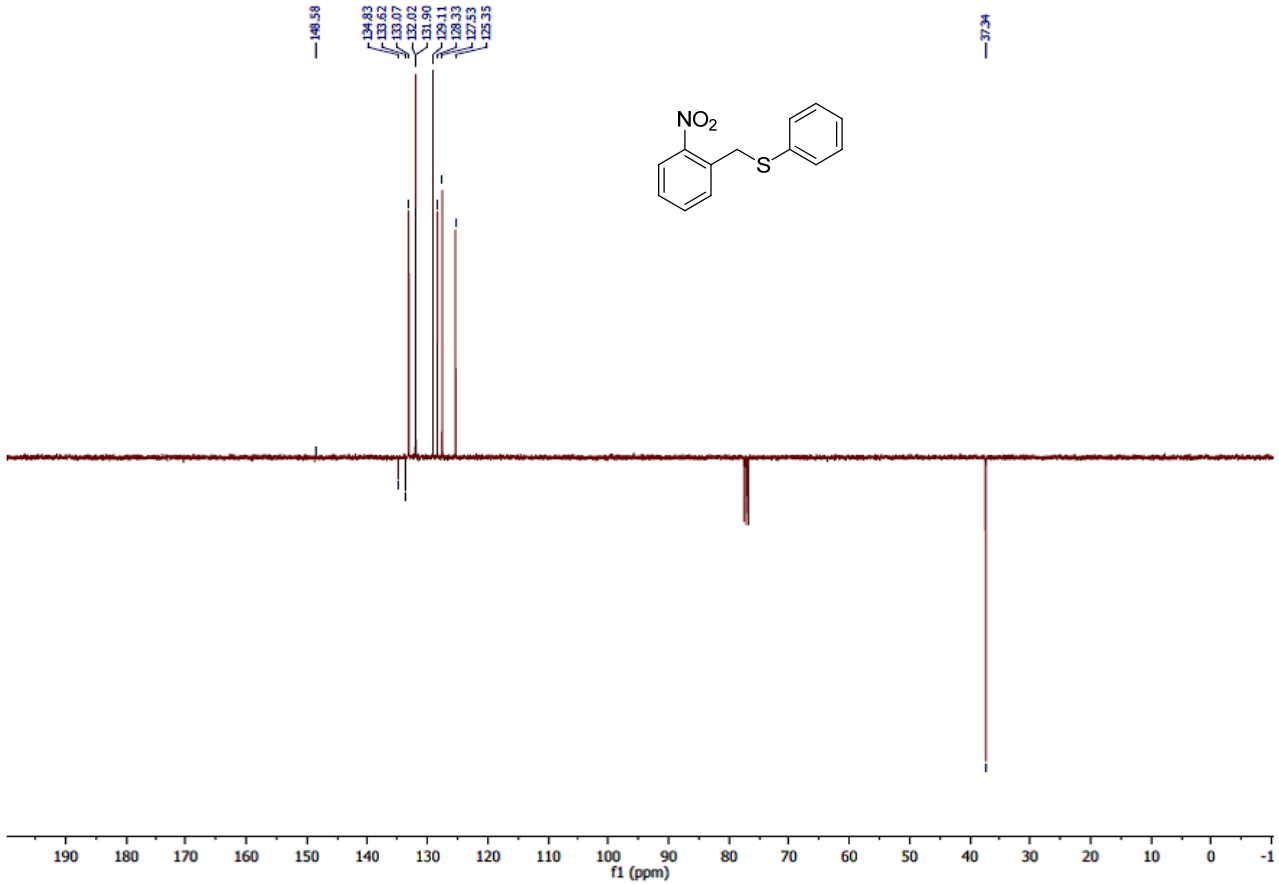
Appendix Figure 95 400 MHz ^{1}H NMR spectrum of (4-bromobenzyl)(phenyl)sulfane **(138)**



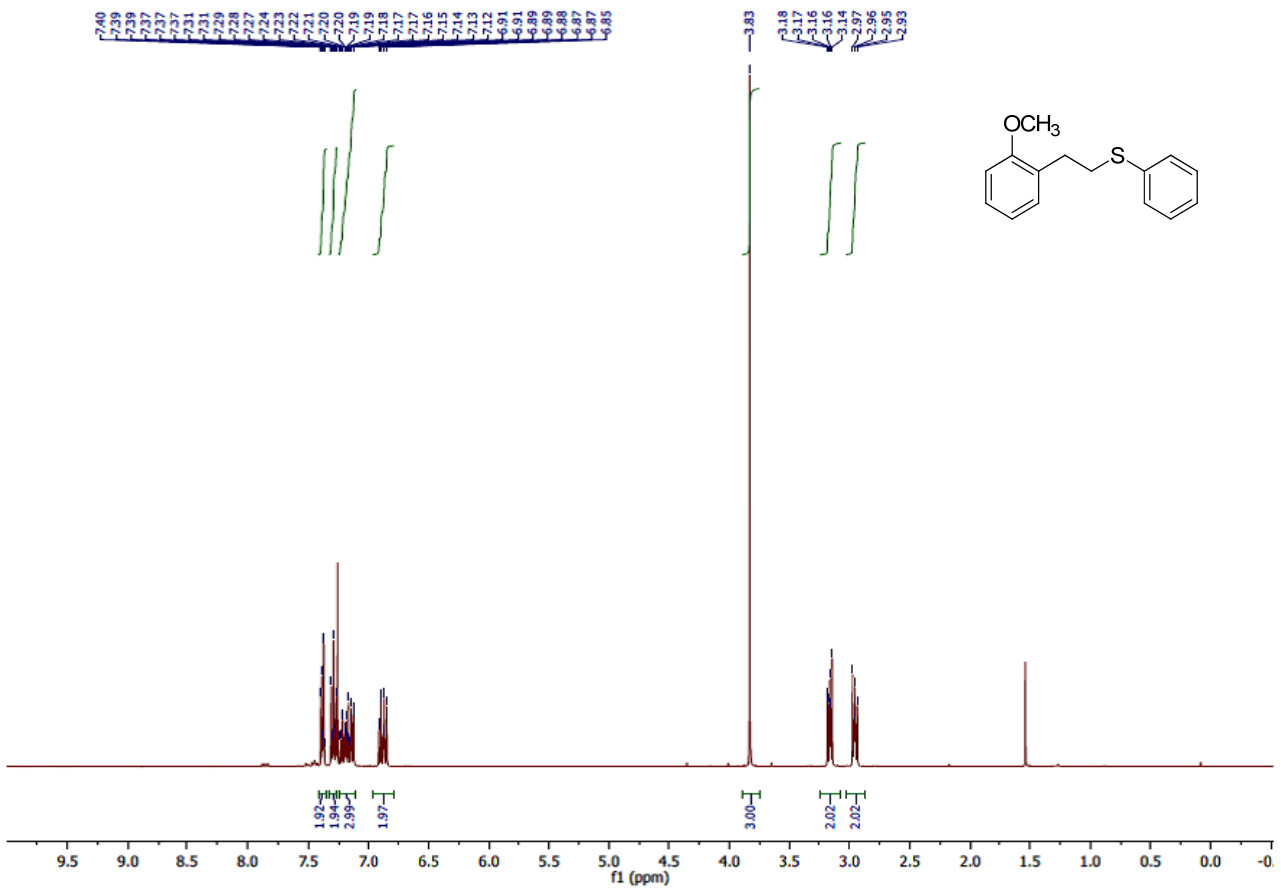
Appendix Figure 96 100 MHz ^{13}C NMR spectrum of (4-bromobenzyl)(phenyl)sulfane **(138)**



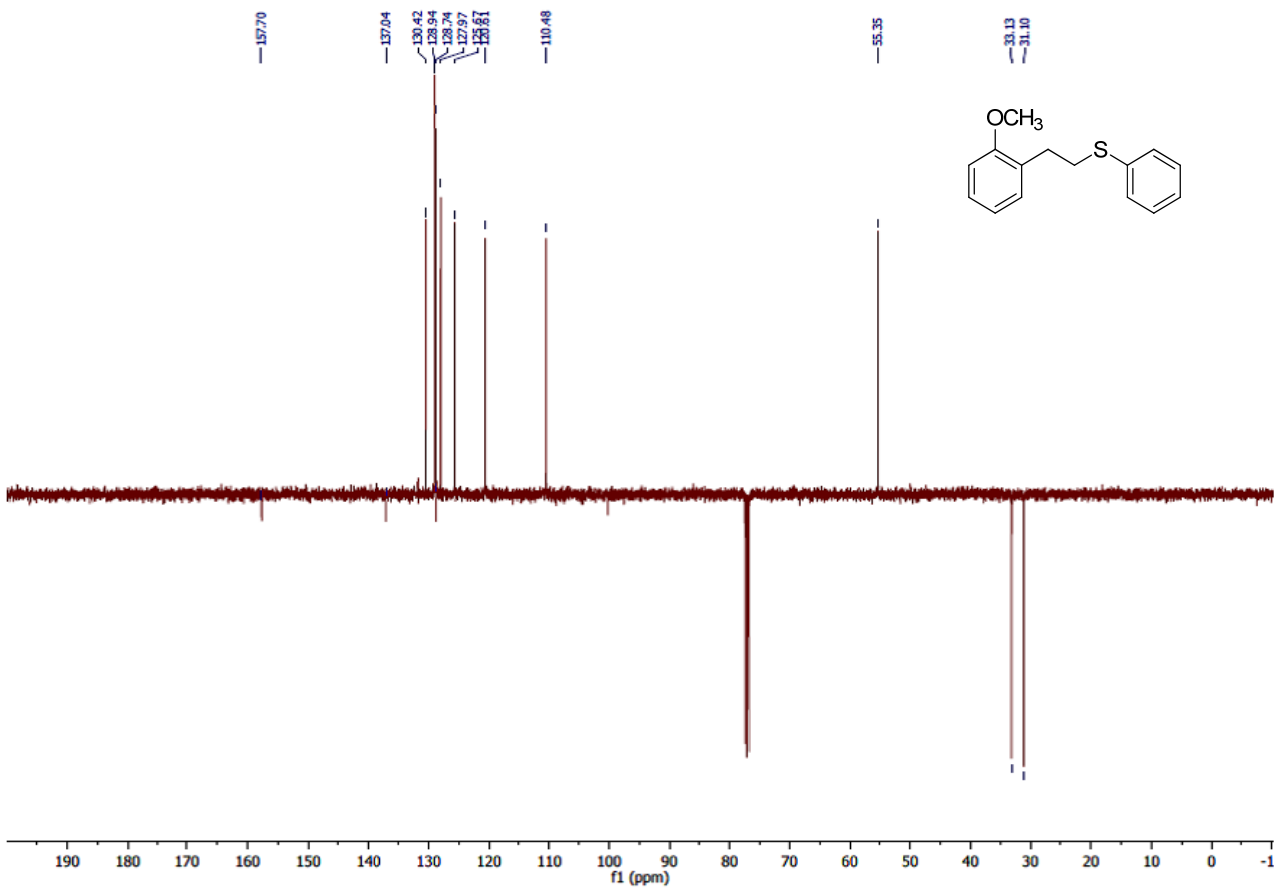
Appendix Figure 97 400 MHz ^{1}H NMR spectrum of (2-nitrobenzyl)(phenyl)sulfane **(139)**



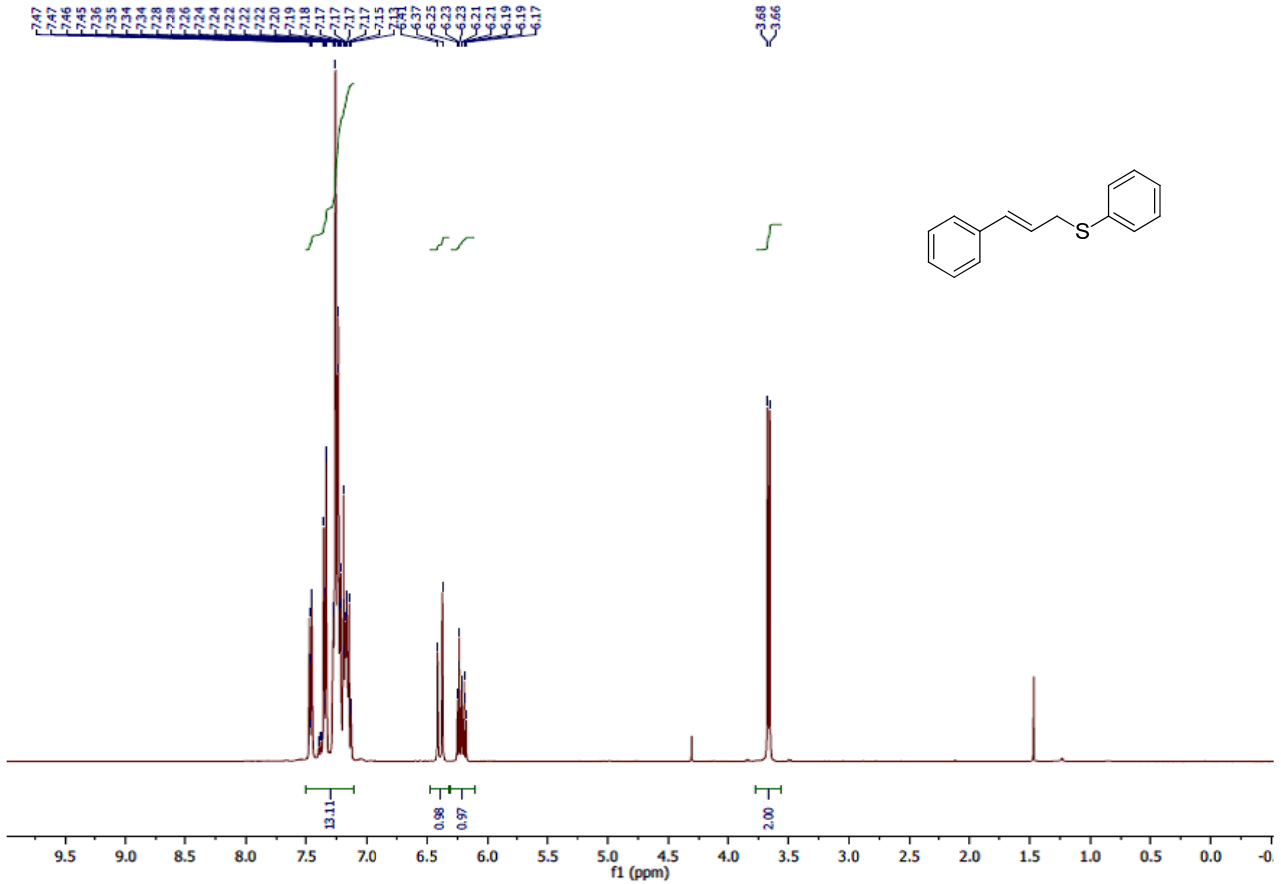
Appendix Figure 98 100 MHz ^{13}C NMR spectrum of (2-nitrobenzyl)(phenyl)sulfane **(139)**



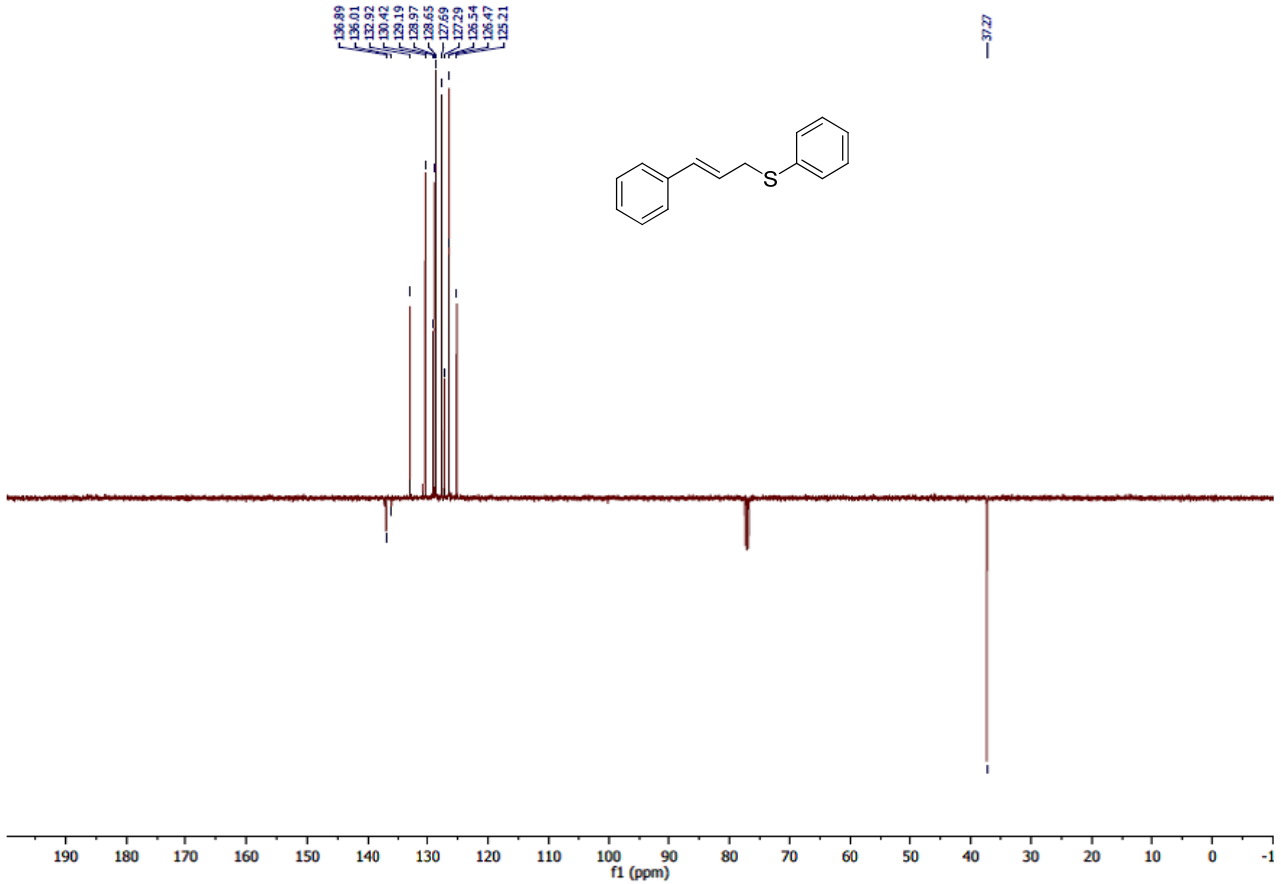
Appendix Figure 99 400 MHz ^{1}H NMR spectrum of (2-methoxyphenethyl)(phenyl)sulfane **(141)**



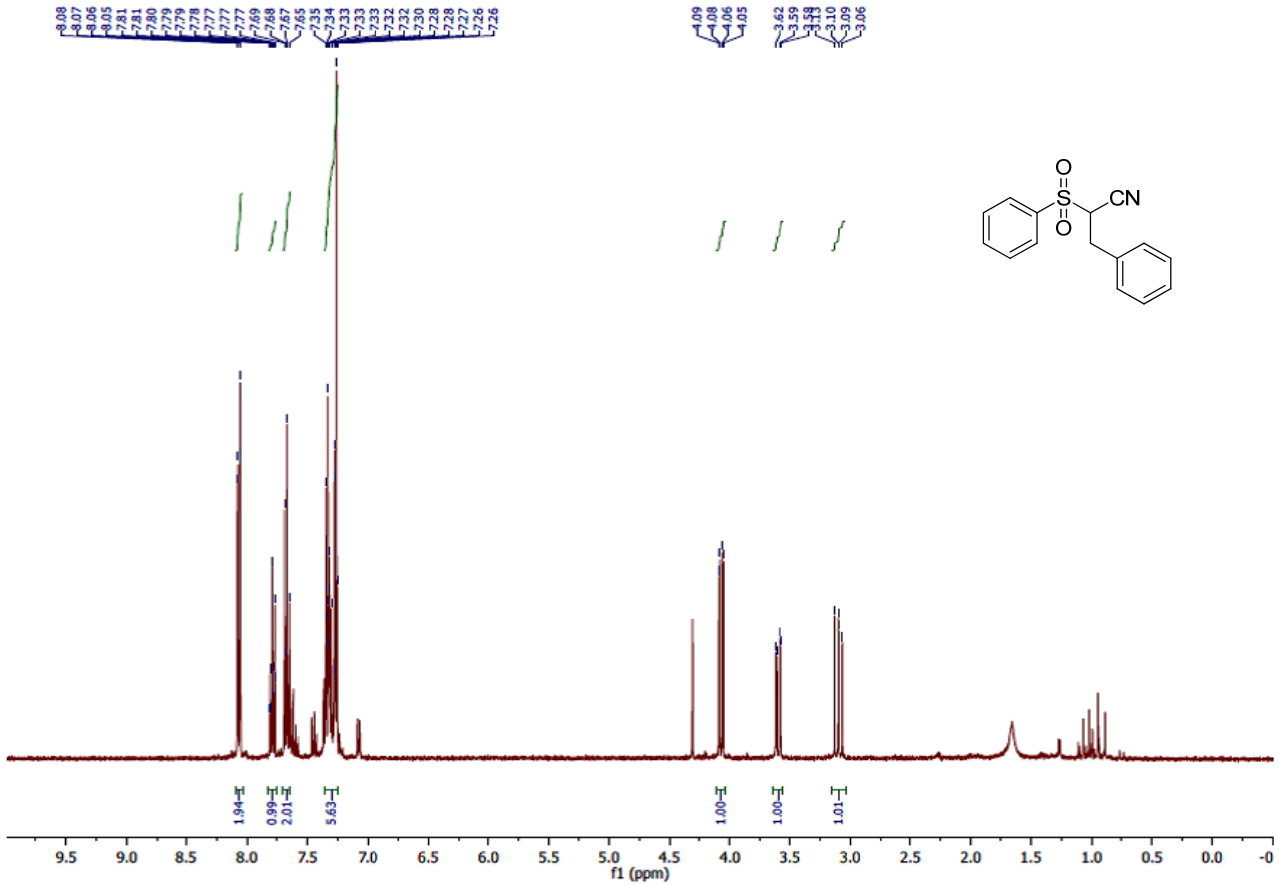
Appendix Figure 100 100 MHz ^{13}C NMR spectrum of (2-methoxyphenethyl)(phenyl)sulfane **(141)**



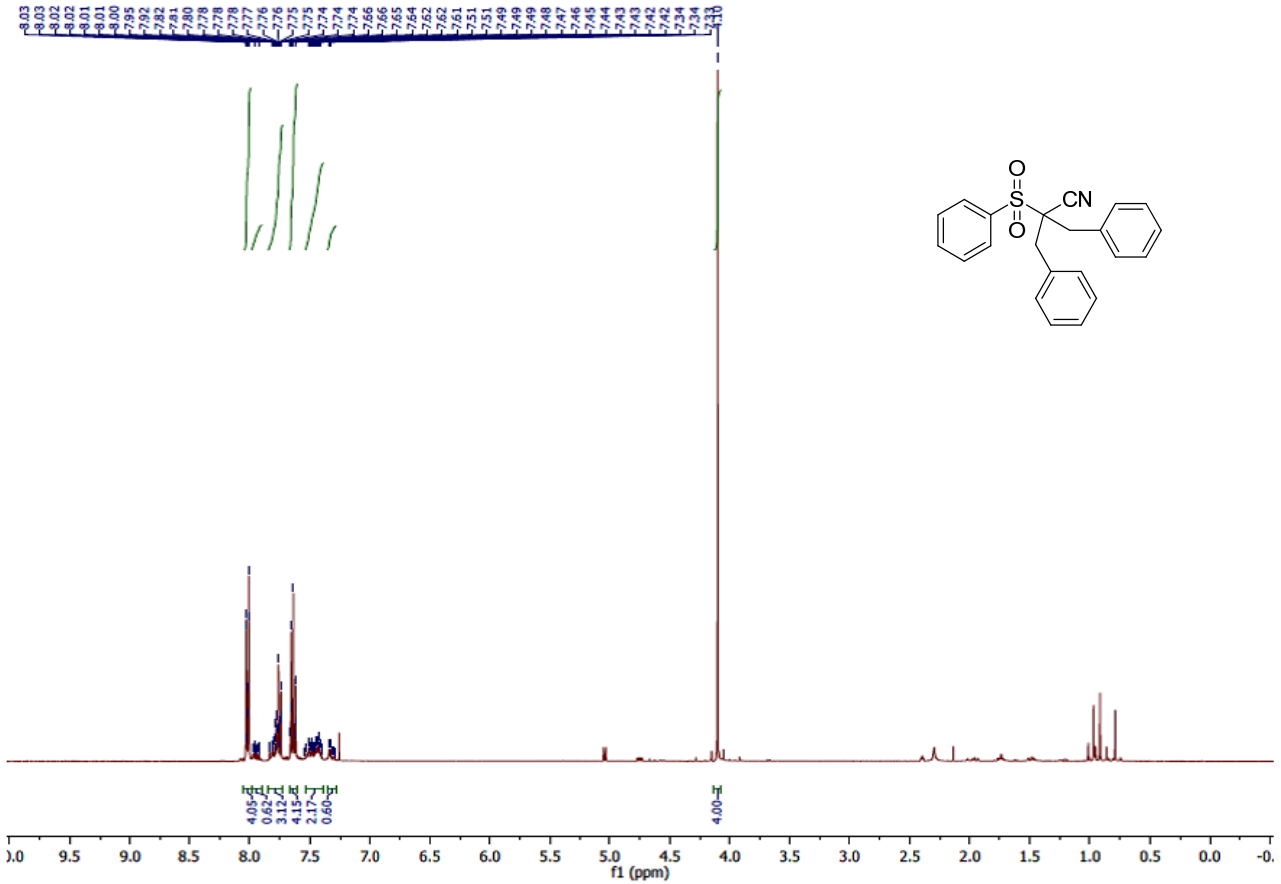
Appendix Figure 101 400 MHz ^{1}H NMR spectrum of cinnamyl(phenyl)sulfane **(142)**



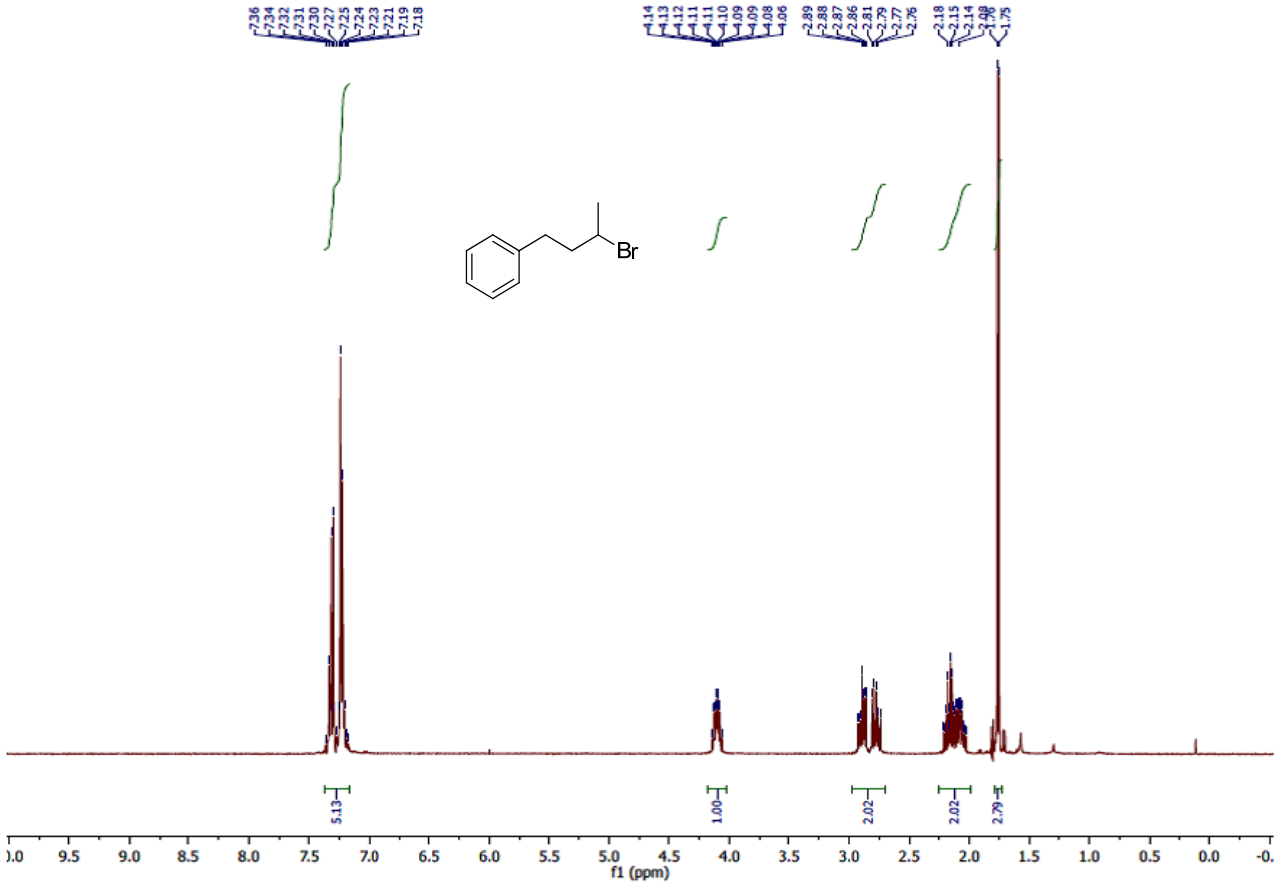
Appendix Figure 102 100 MHz ^{13}C NMR spectrum of cinnamyl(phenyl)sulfane **(142)**



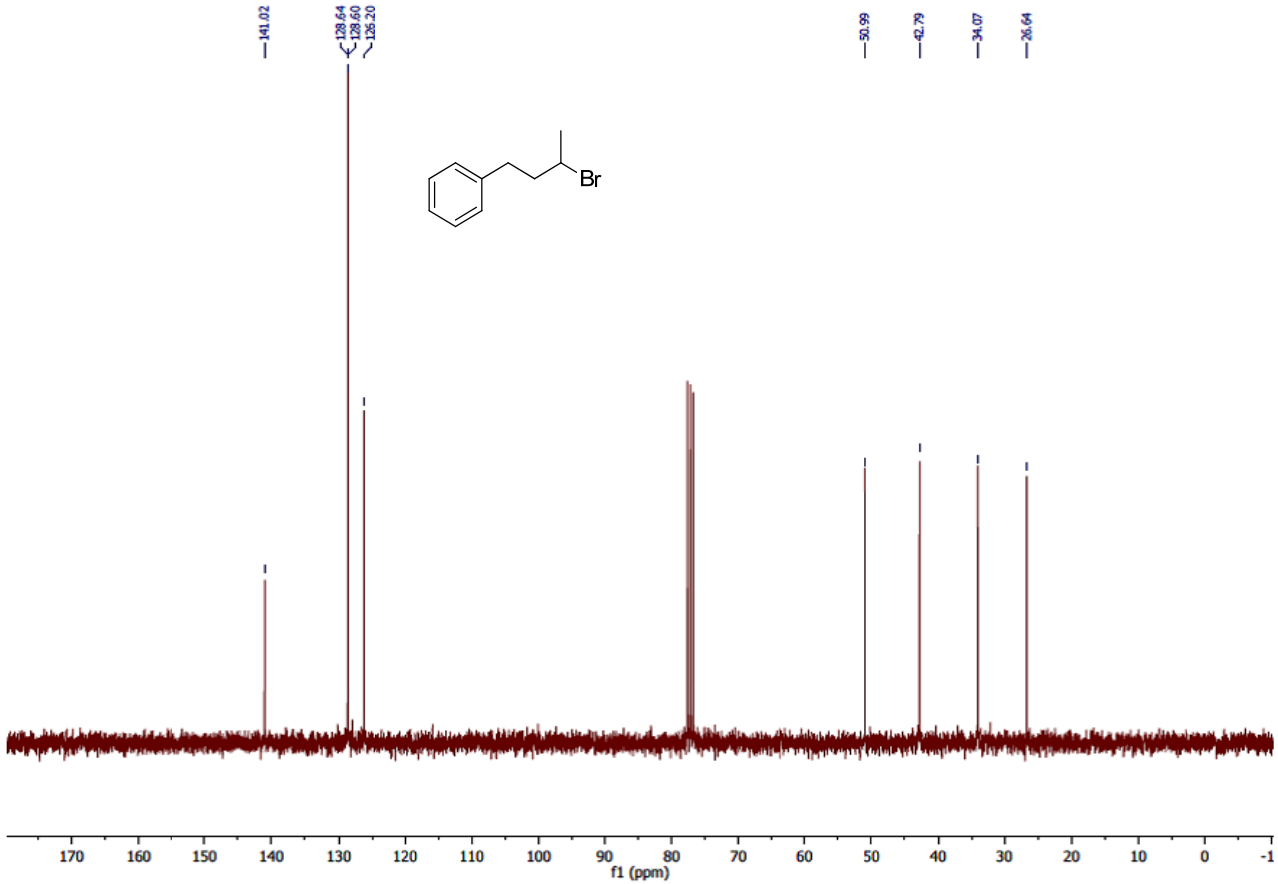
Appendix Figure 103 400 MHz ^{1}H NMR spectrum of 3-phenyl-2-(phenylsulfonyl)propanenitrile **(169)**



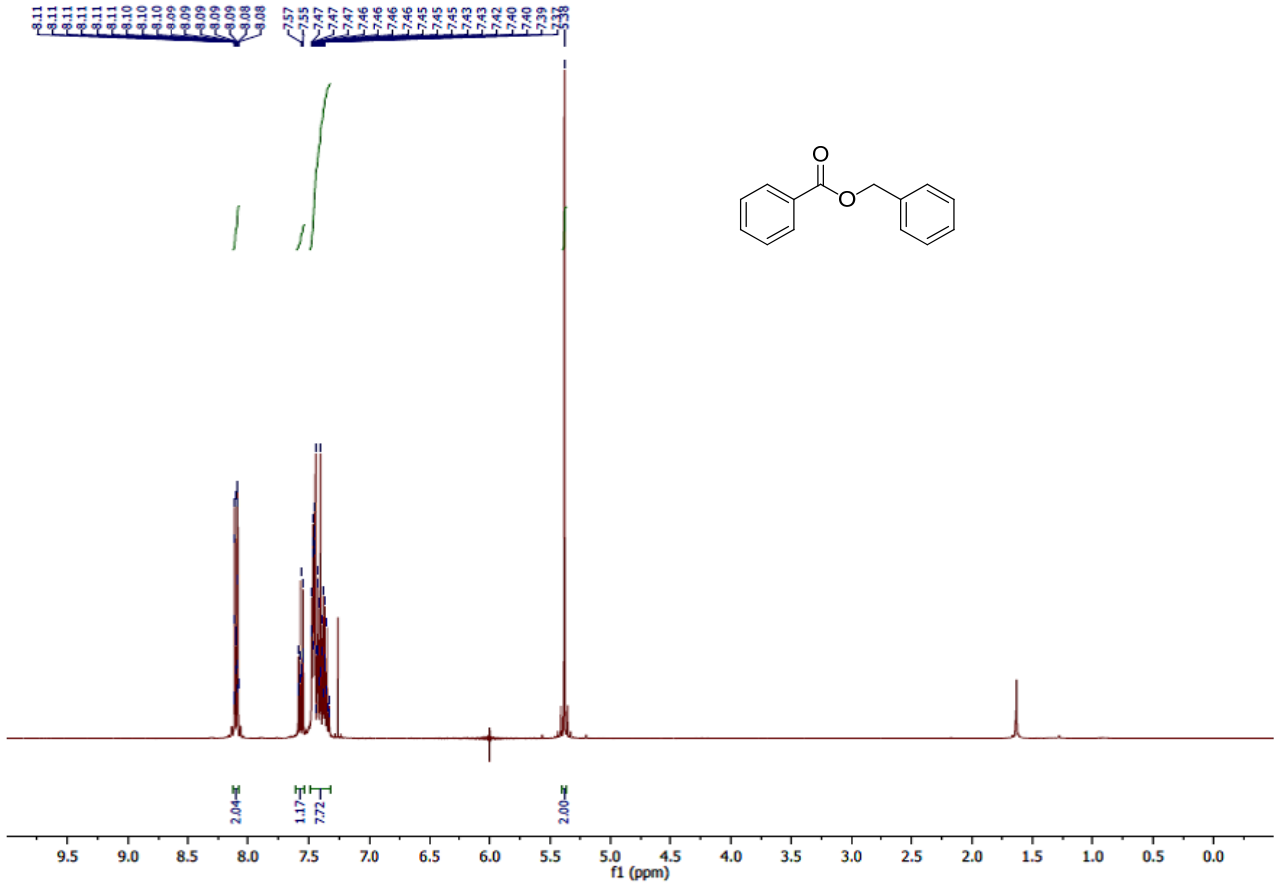
Appendix Figure 104 400 MHz ^{1}H NMR spectrum of 2-benzyl-3-phenyl-2-(phenylsulfonyl)propanenitrile **(170)**



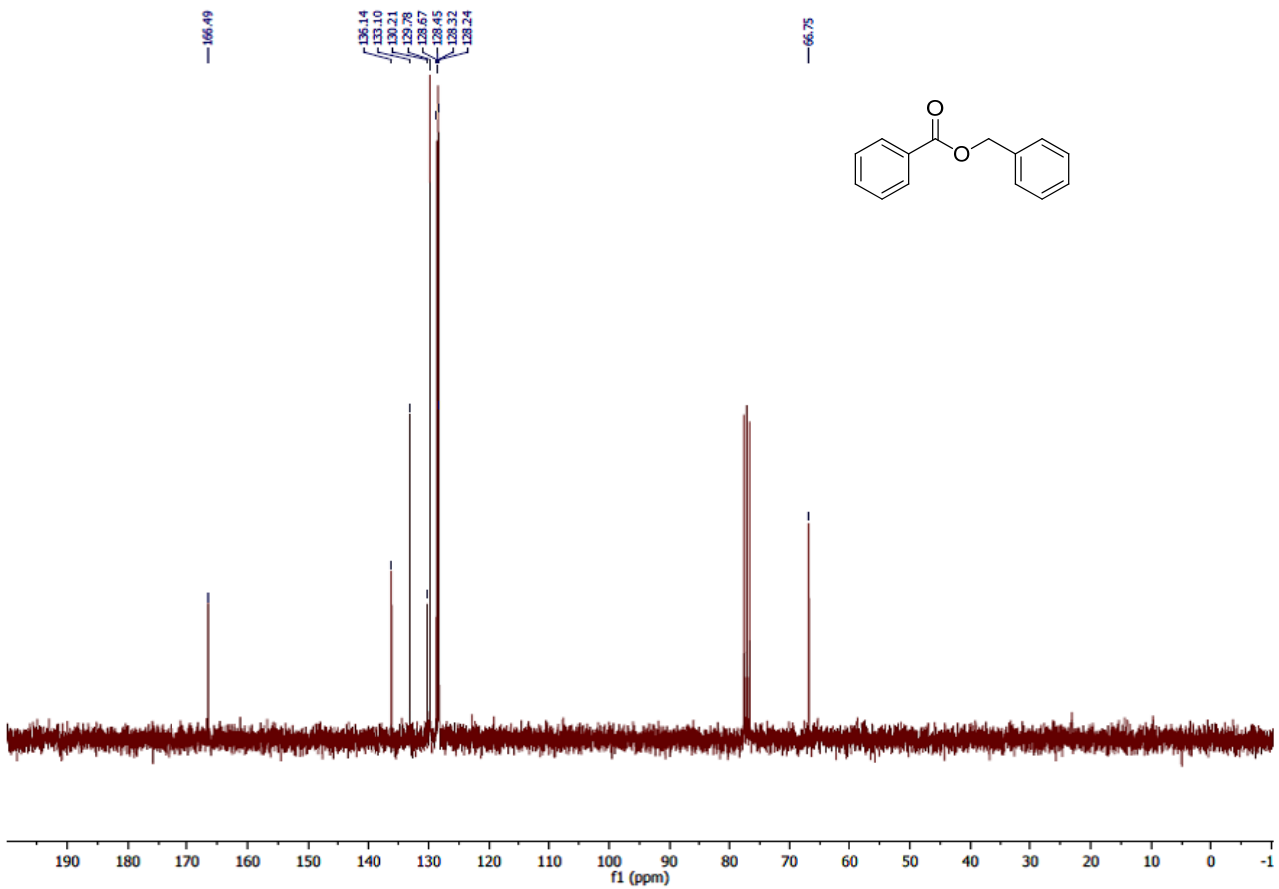
Appendix Figure 105 400 MHz ^{1}H NMR spectrum of (3-bromobutyl)benzene **(171)**



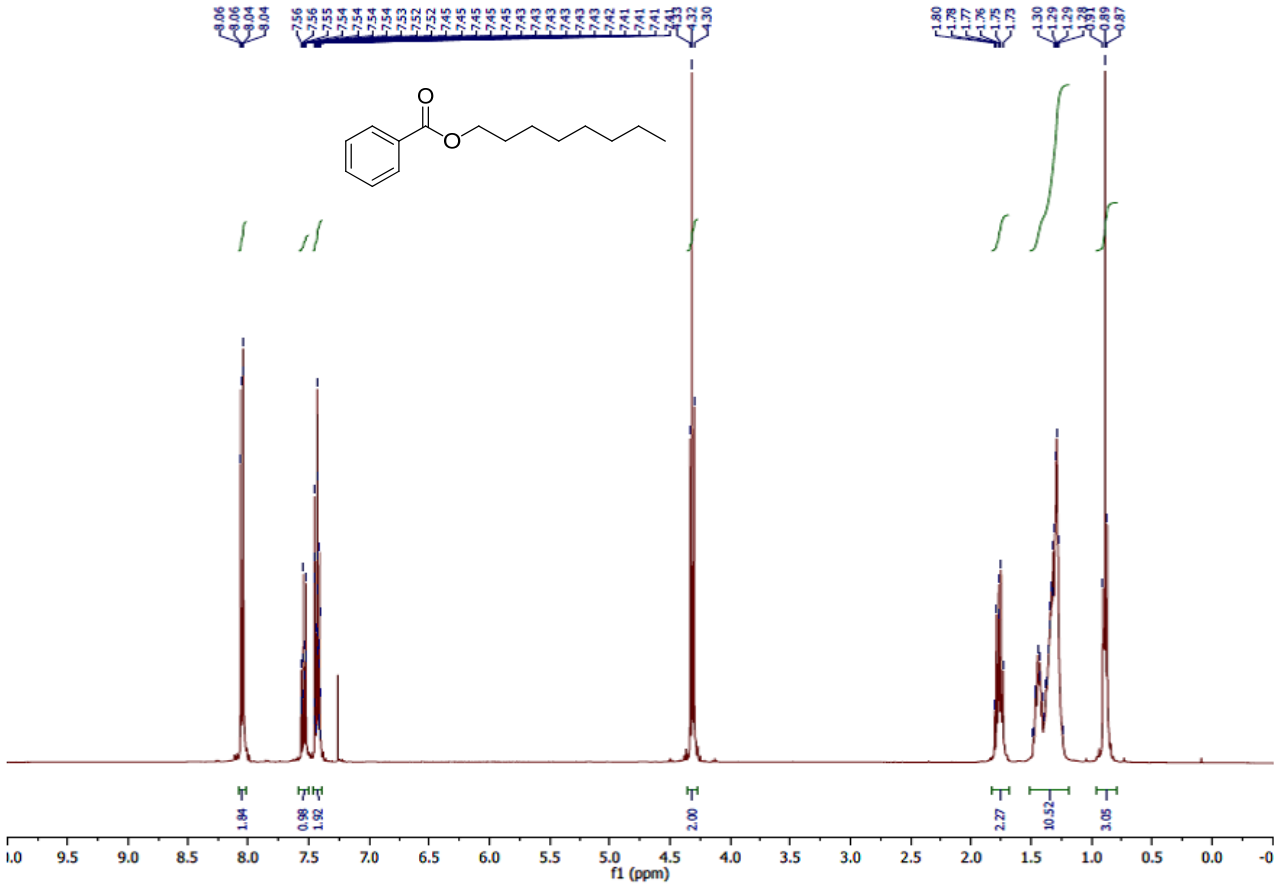
Appendix Figure 106 100 MHz ^{13}C NMR spectrum of (3-bromobutyl)benzene **(171)**



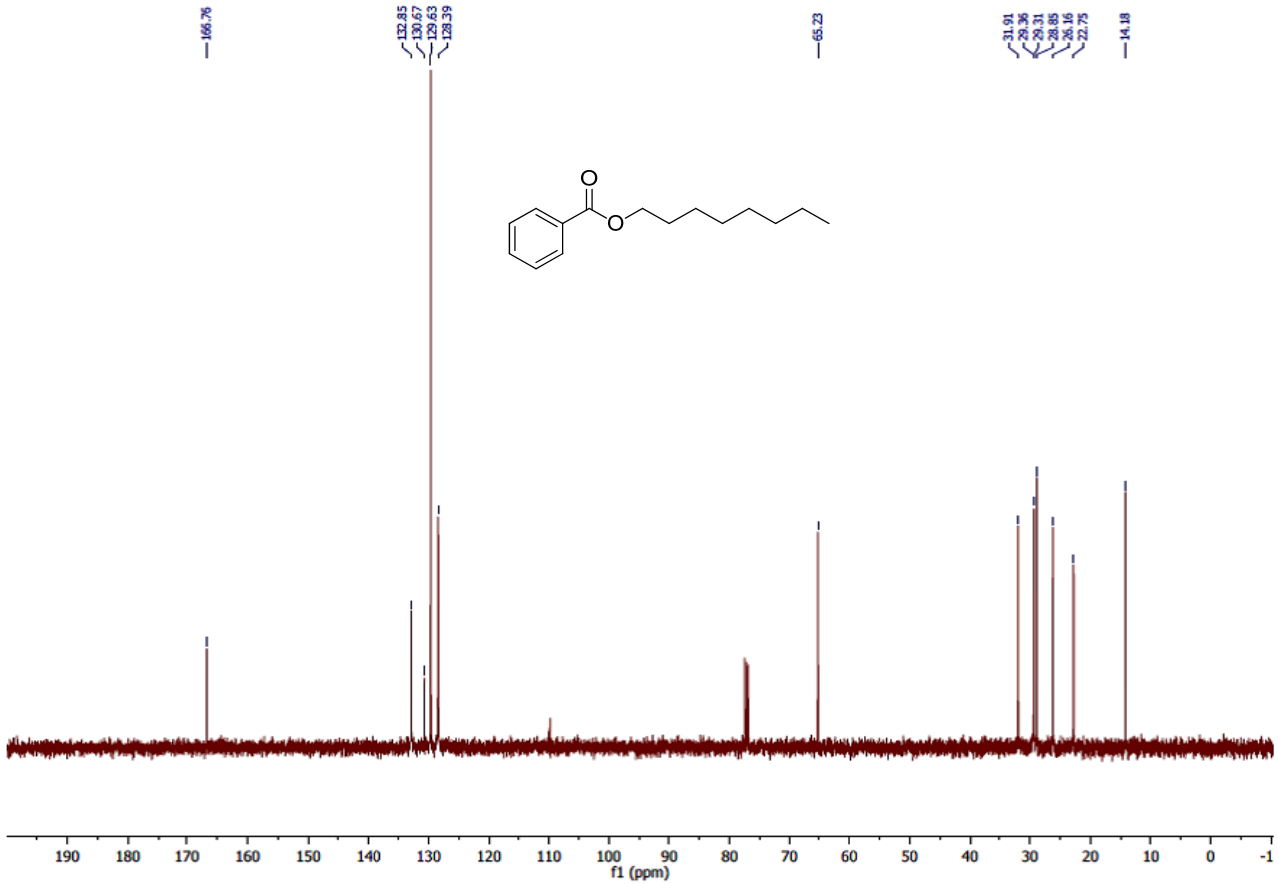
Appendix Figure 107 400 MHz ^{1}H NMR spectrum of benzyl benzoate **(175)**



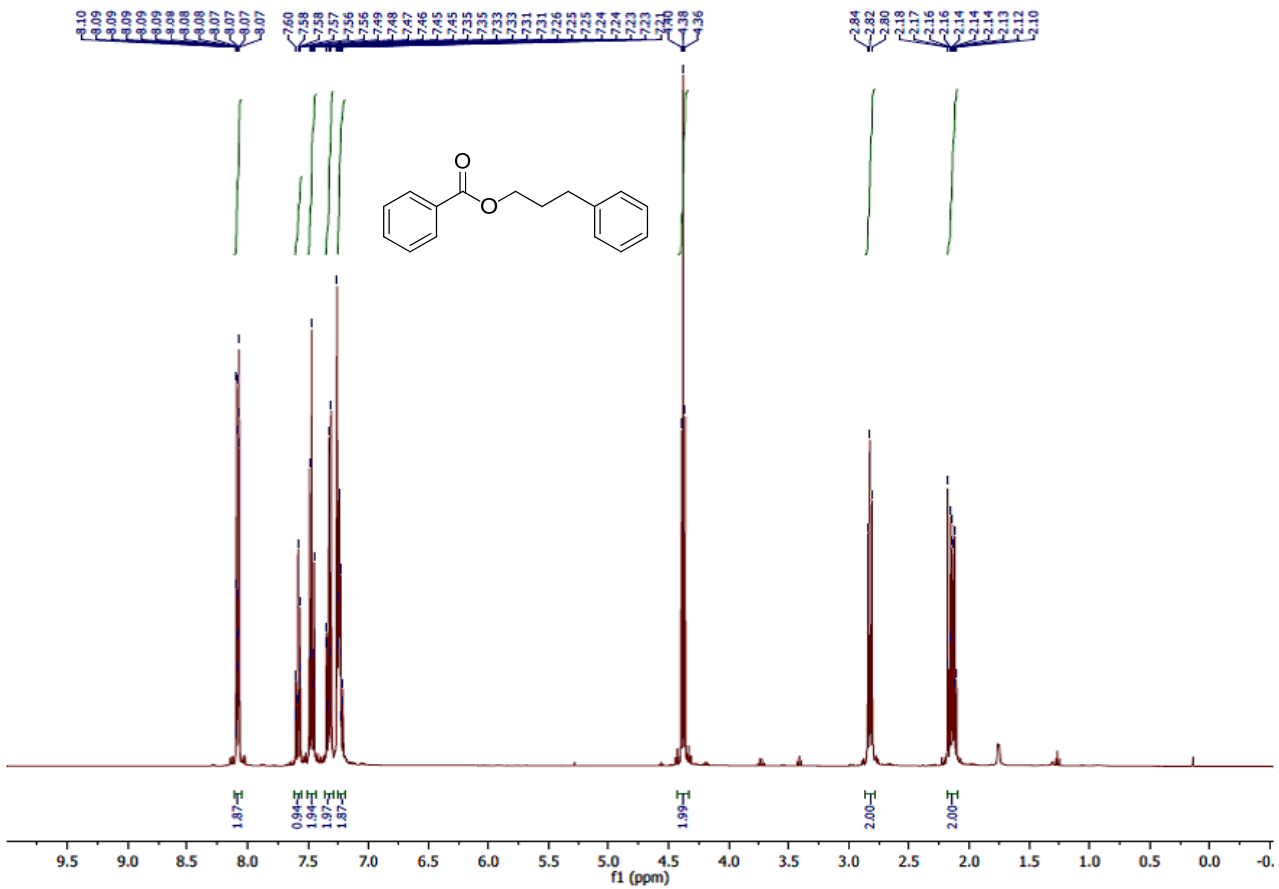
Appendix Figure 118 100 MHz ^{13}C NMR spectrum of benzyl benzoate **(175)**



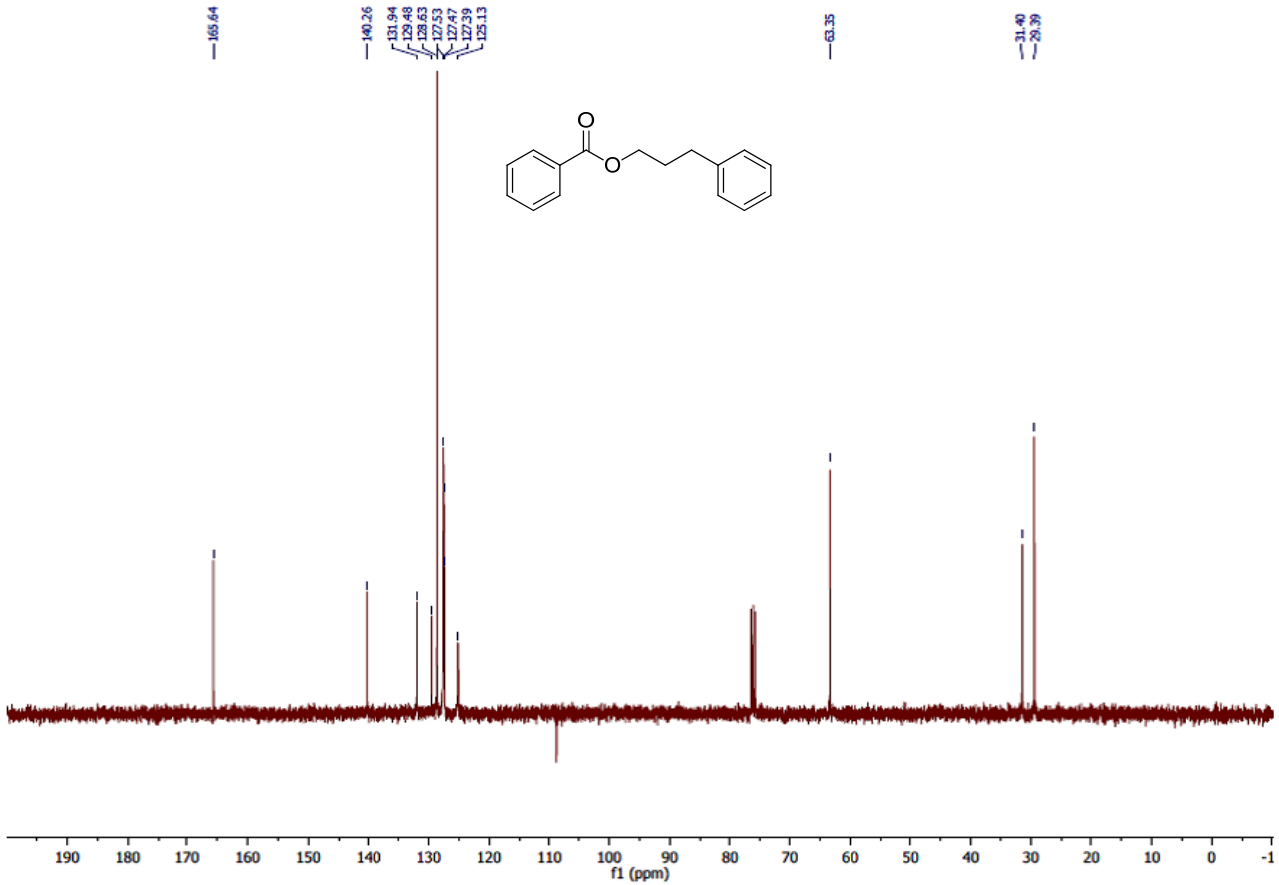
Appendix Figure 109 400 MHz ^{1}H NMR spectrum of octyl benzoate **(176)**



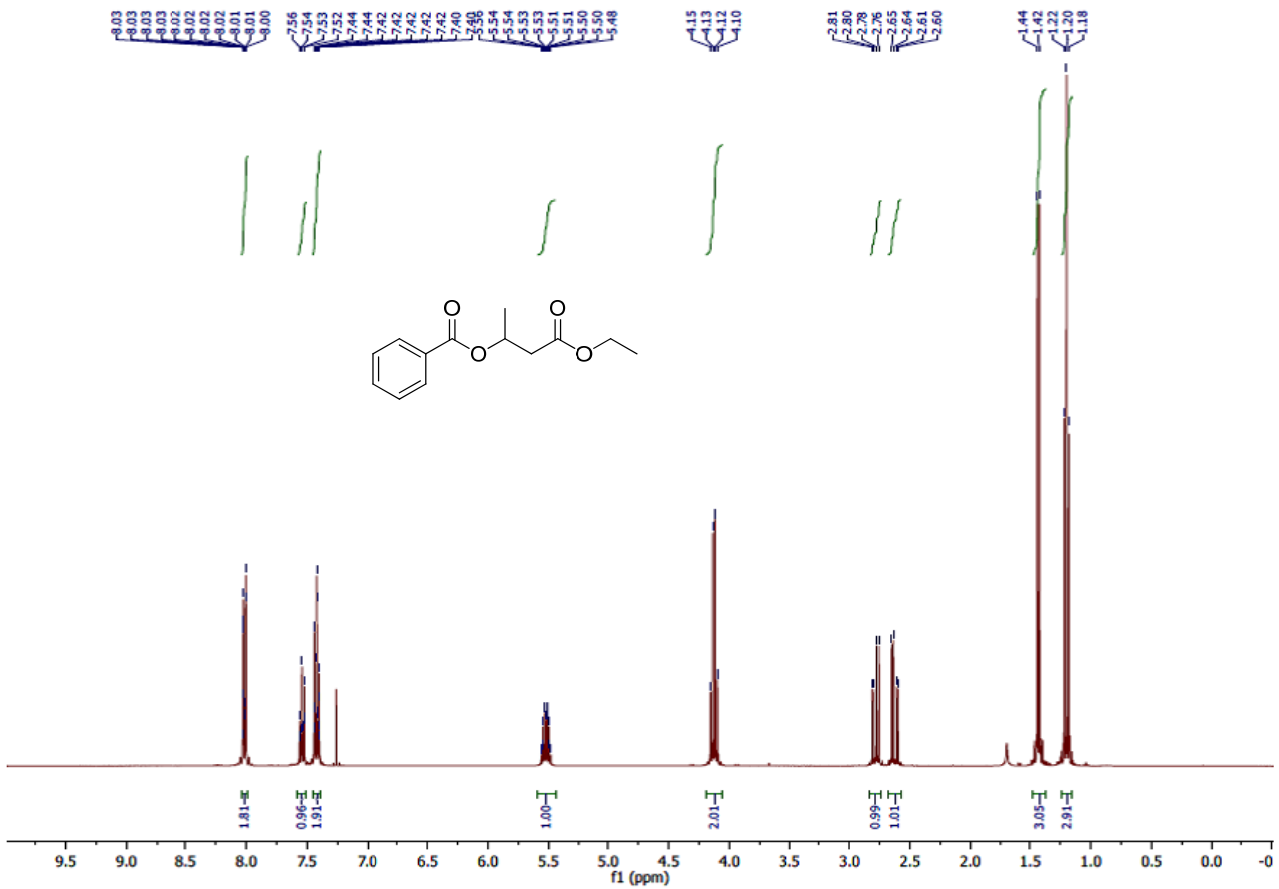
Appendix Figure 110 100 MHz ^{13}C NMR spectrum of octyl benzoate **(176)**



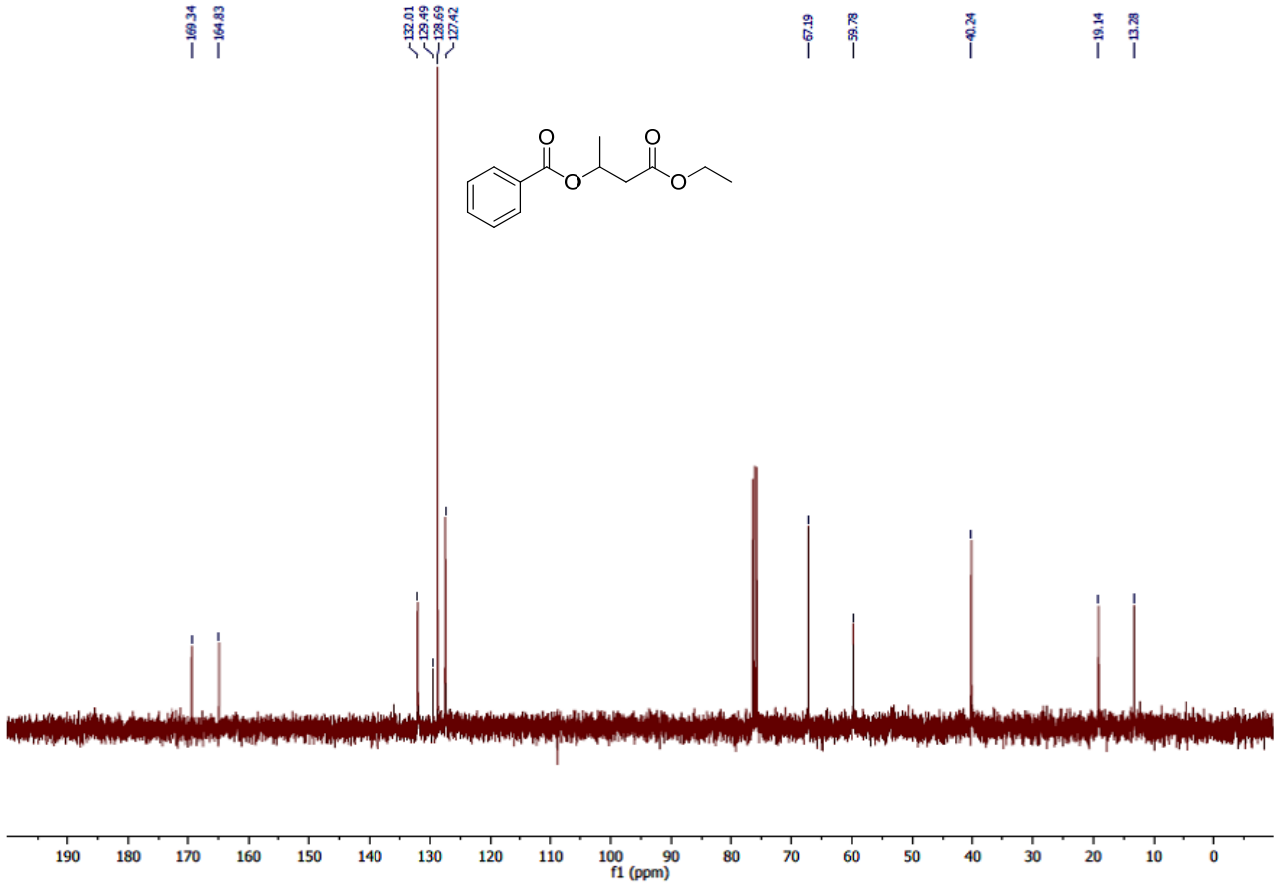
Appendix Figure 111 400 MHz ^{1}H NMR spectrum of 3-phenylpropyl benzoate **(177)**



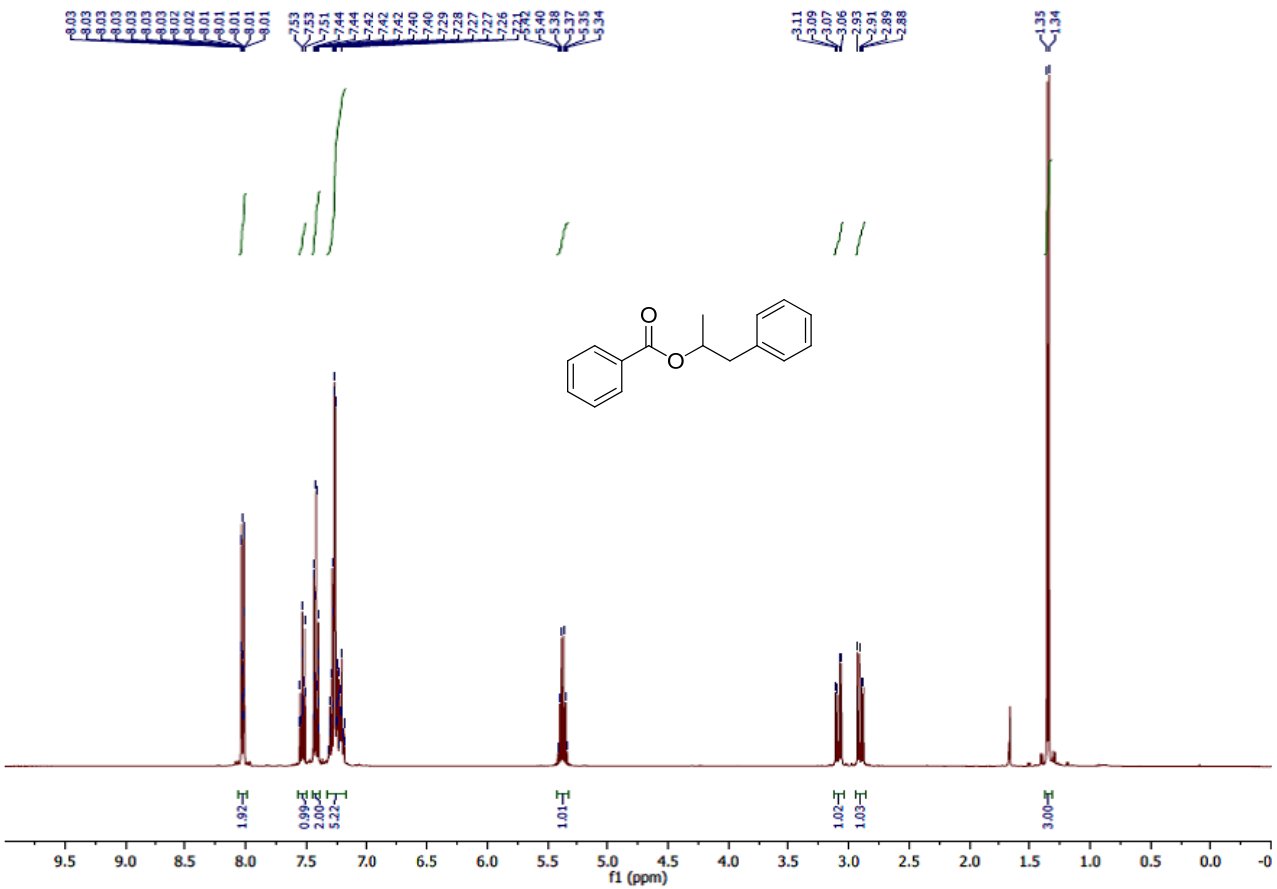
Appendix Figure 112 100 MHz ^{13}C NMR spectrum of 3-phenylpropyl benzoate **(177)**



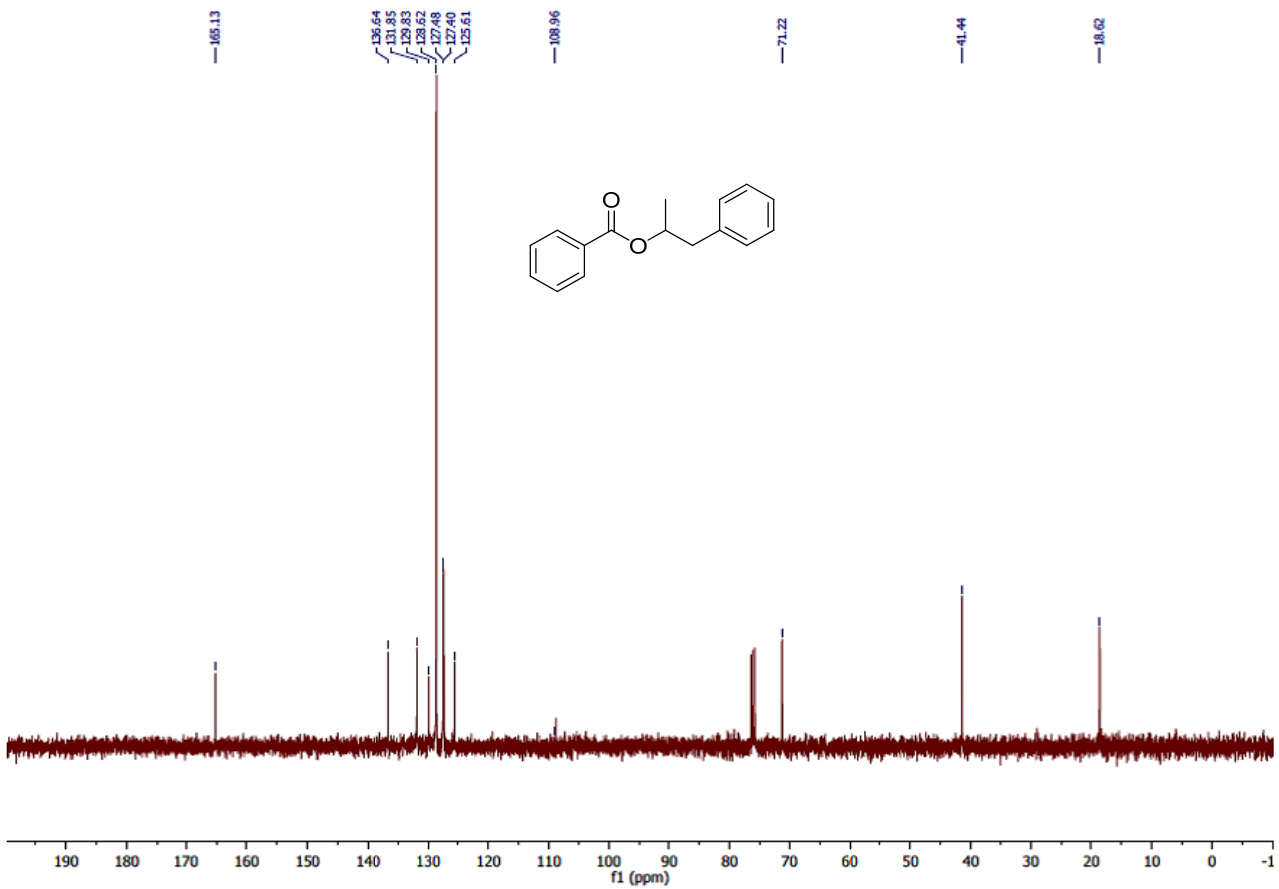
Appendix Figure 113 400 MHz ^{1}H NMR spectrum of 4-ethoxy-4-oxobutan-2-yl benzoate **(178)**



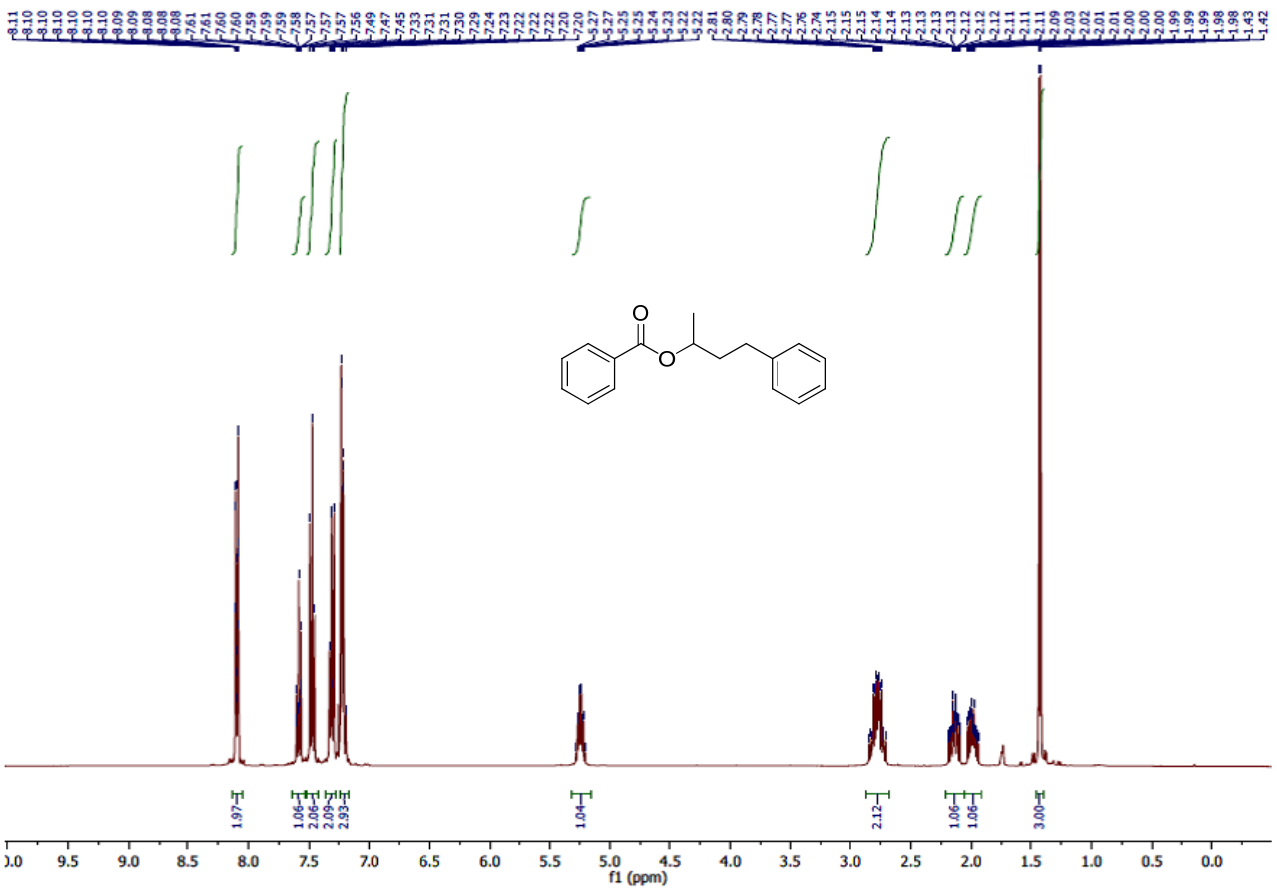
Appendix Figure 114 100 MHz ^{13}C NMR spectrum of of 4-ethoxy-4-oxobutan-2-yl benzoate **(178)**



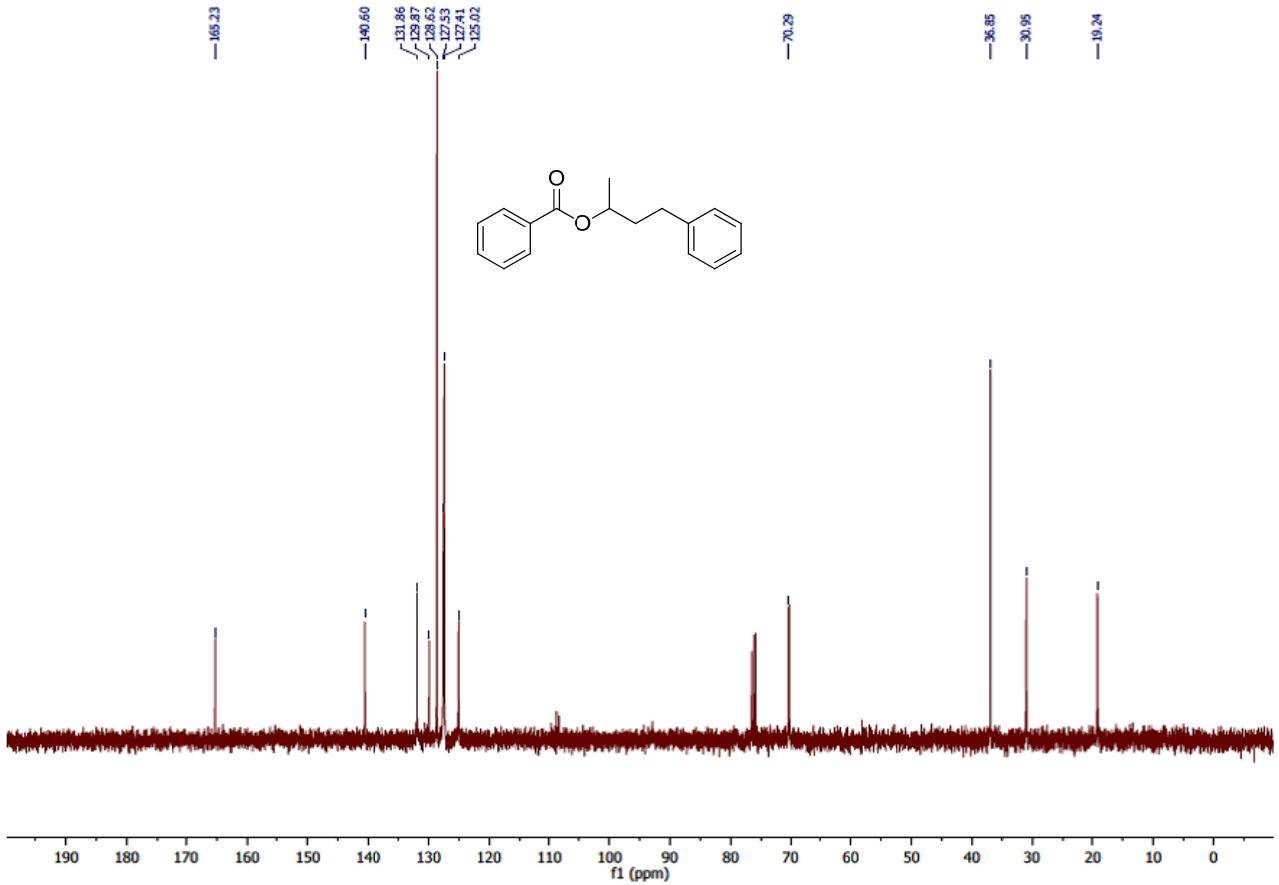
Appendix Figure 115 400 MHz ^{1}H NMR spectrum of 1-phenylpropan-2-yl benzoate **(179)**



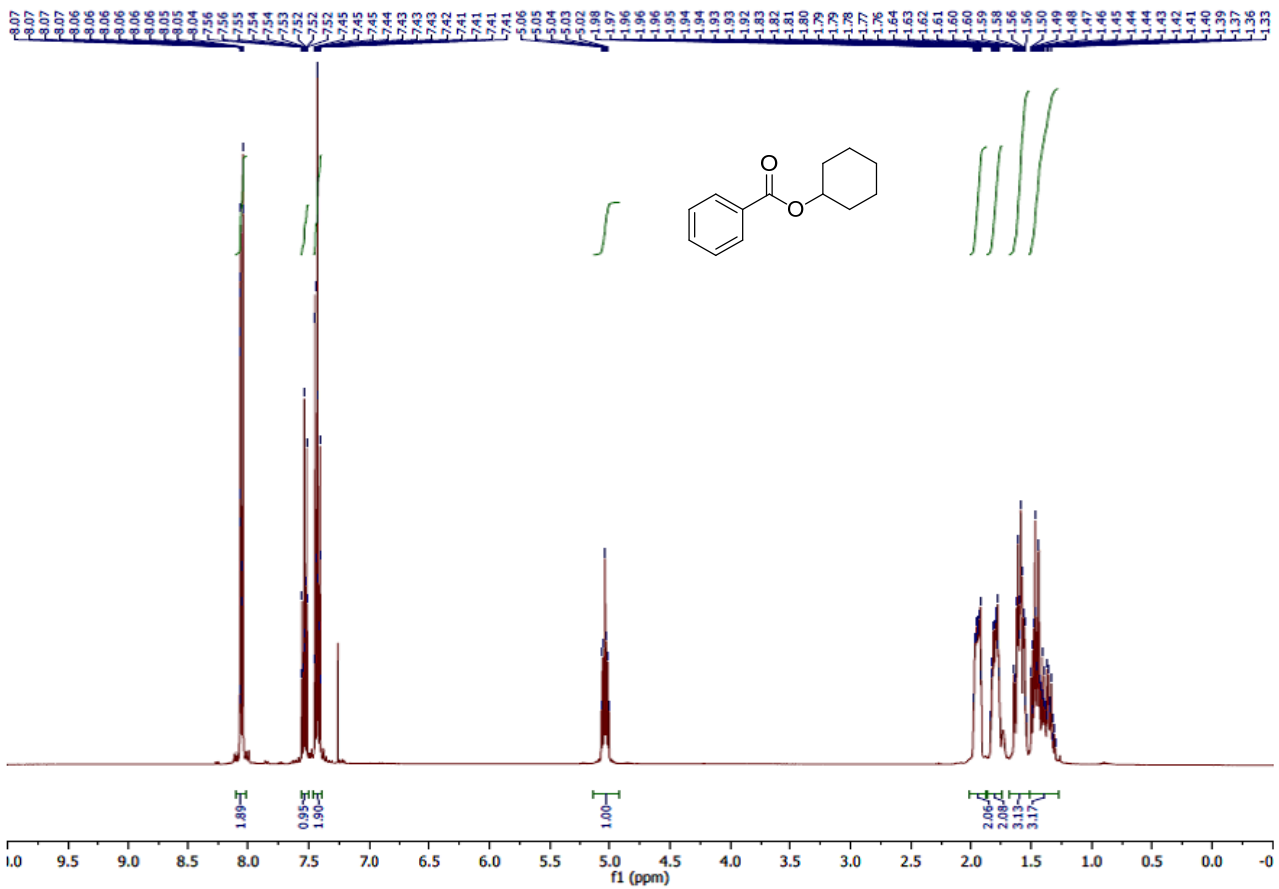
Appendix Figure 116 100 MHz ^{13}C NMR spectrum of 1-phenylpropan-2-yl benzoate **(179)**



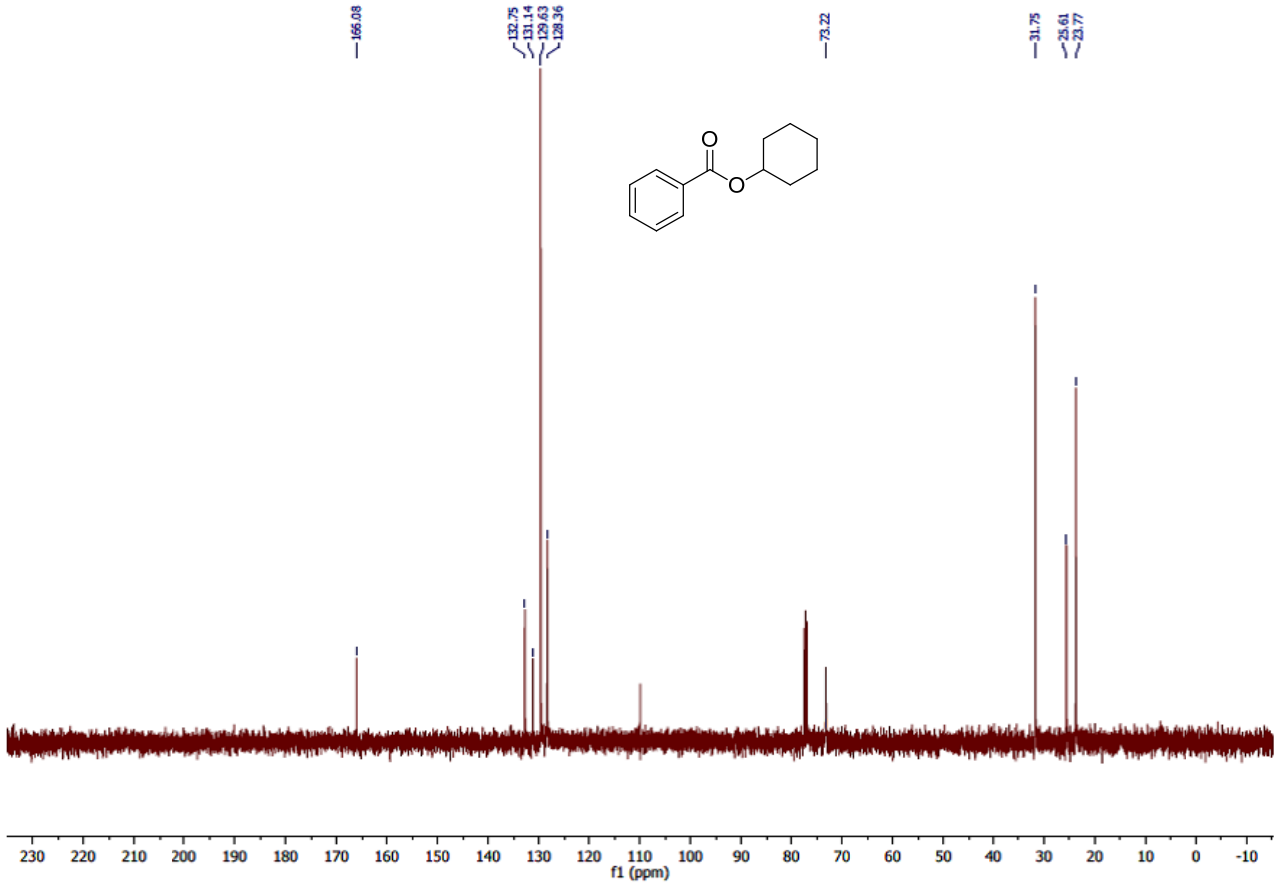
Appendix Figure 117 400 MHz ^{1}H NMR spectrum of 4-phenylbutan-2-yl benzoate **(180)**



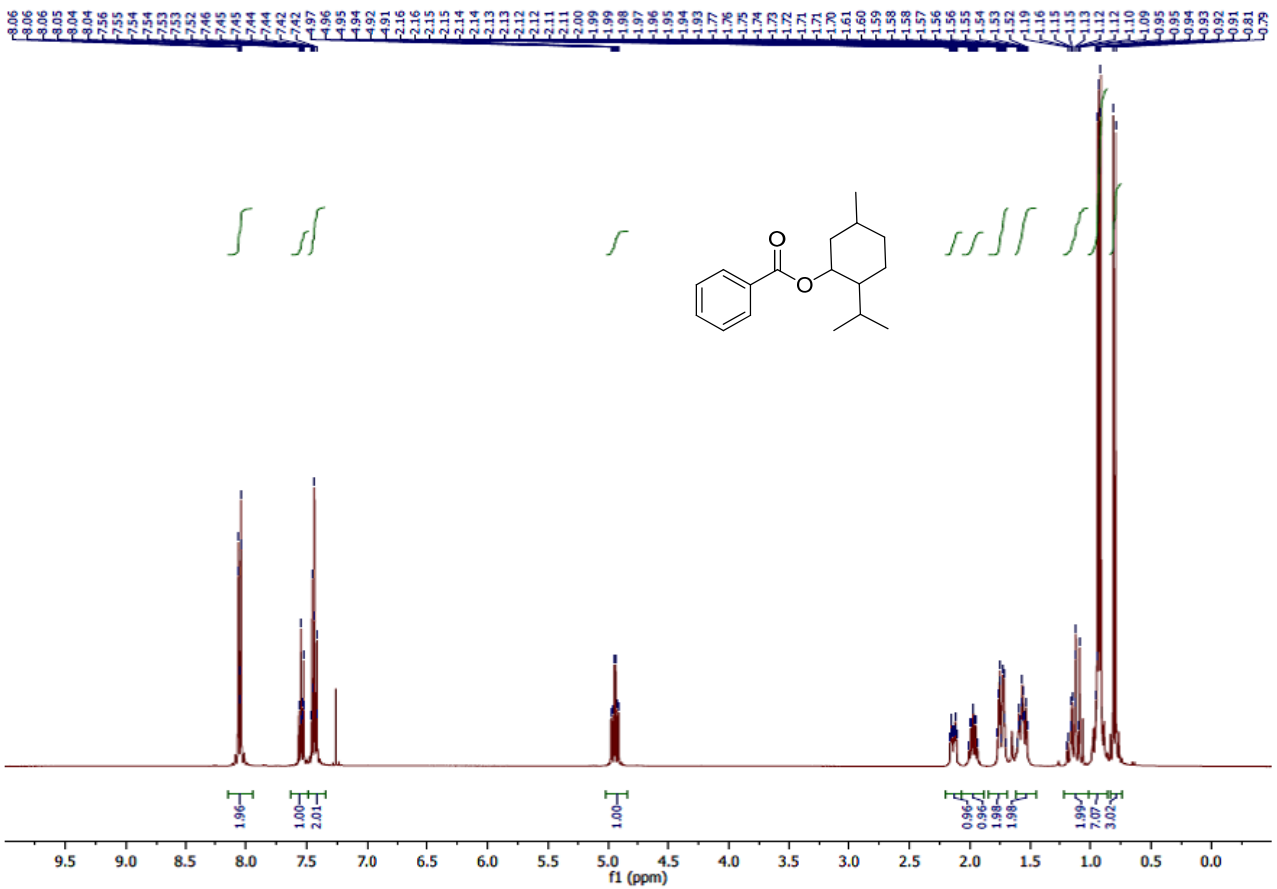
Appendix Figure 118 100 MHz ^{13}C NMR spectrum of 4-phenylbutan-2-yl benzoate **(180)**



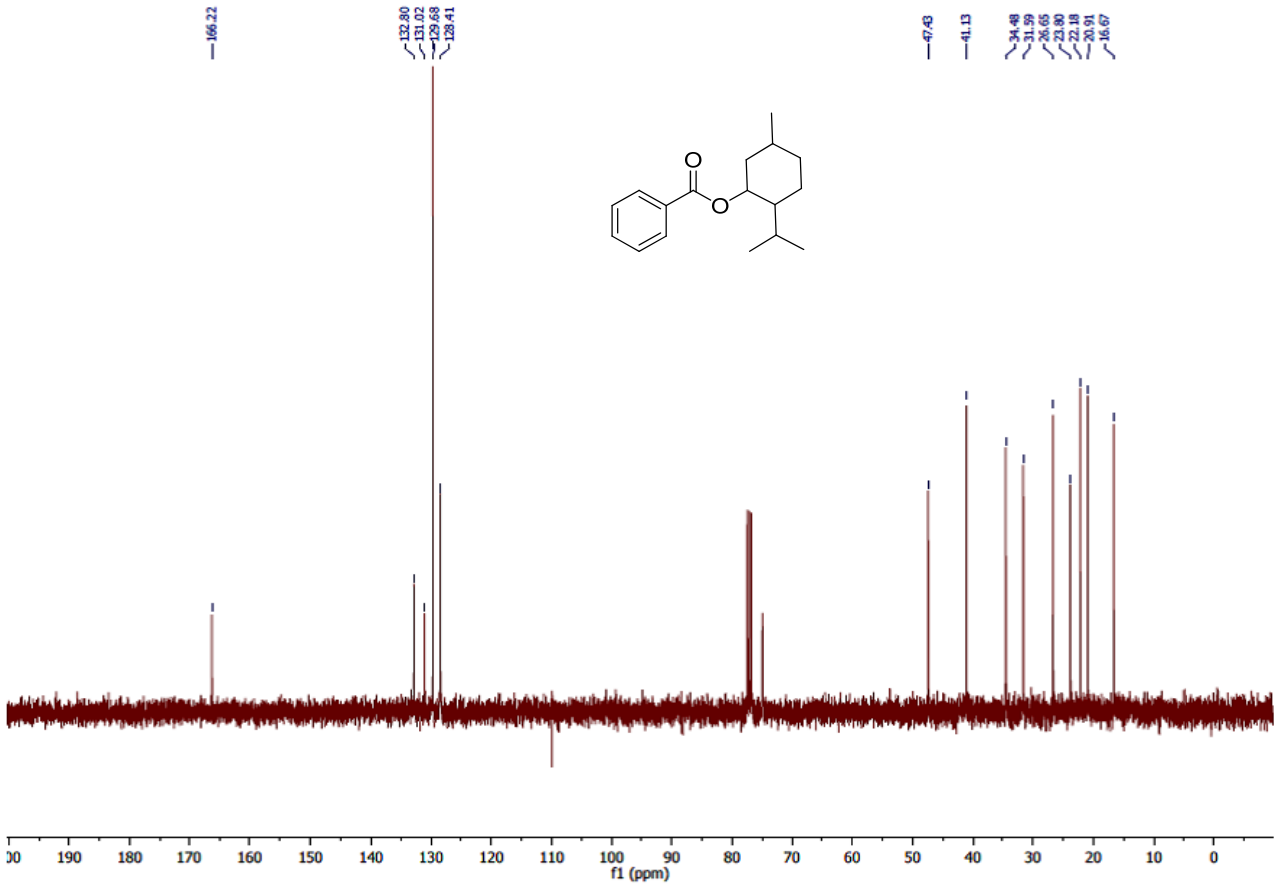
Appendix Figure 119 400 MHz ^{1}H NMR spectrum of cyclohexyl benzoate **(181)**



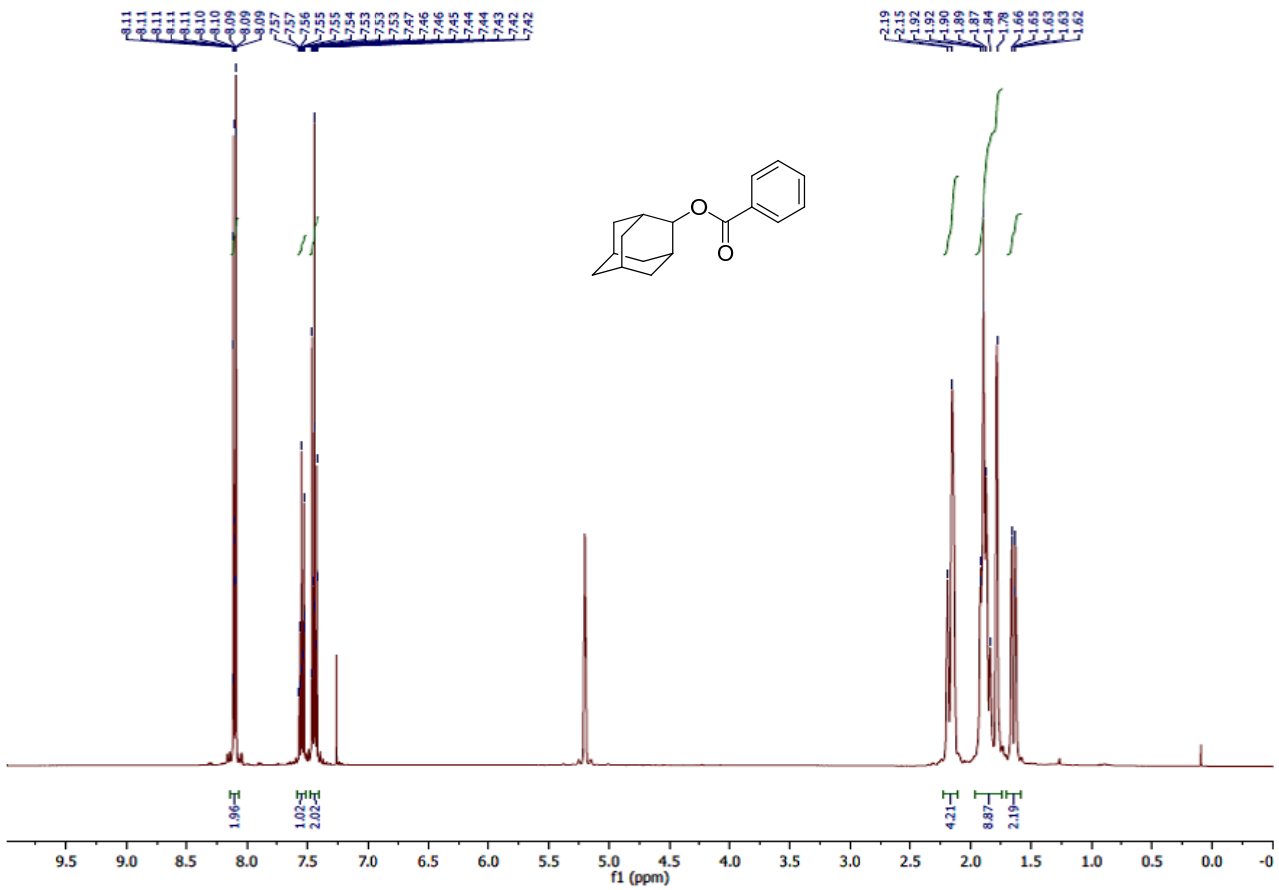
Appendix Figure 120 100 MHz ^{13}C NMR spectrum of cyclohexyl benzoate **(181)**



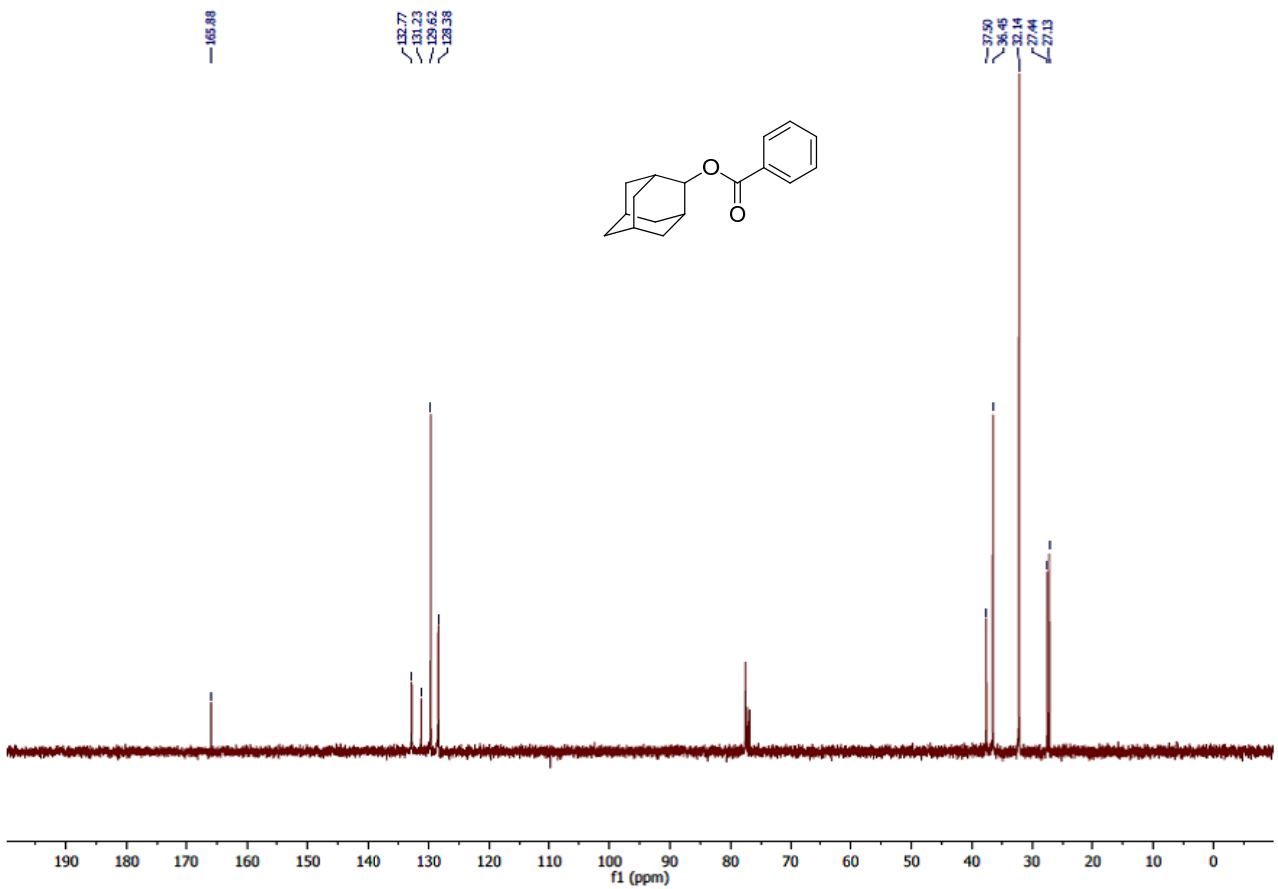
Appendix Figure 121 400 MHz ^{1}H NMR spectrum of 2-Isopropyl-5-methylcyclohexyl benzoate **(182)**



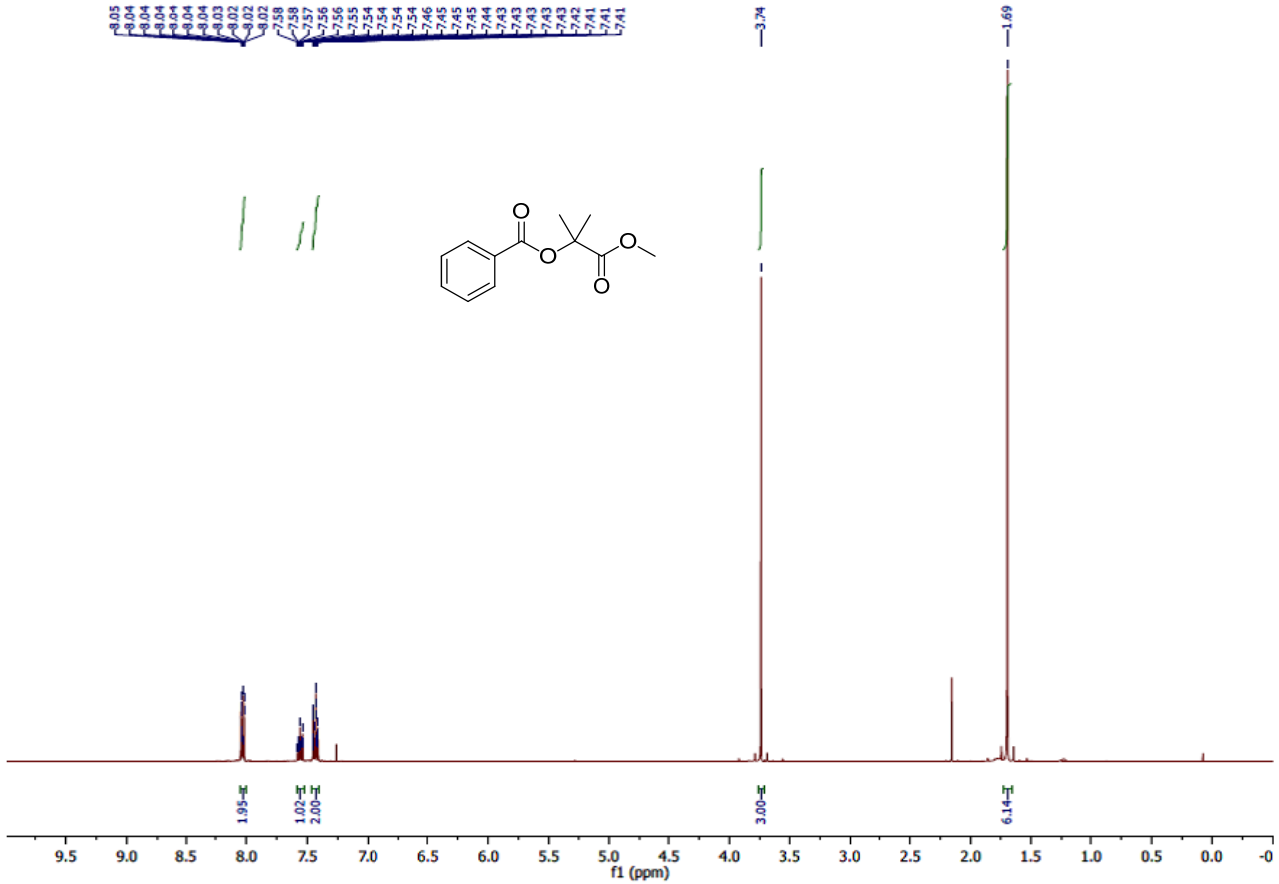
Appendix Figure 122 100 MHz ^{13}C NMR spectrum of 2-Isopropyl-5-methylcyclohexyl benzoate **(182)**



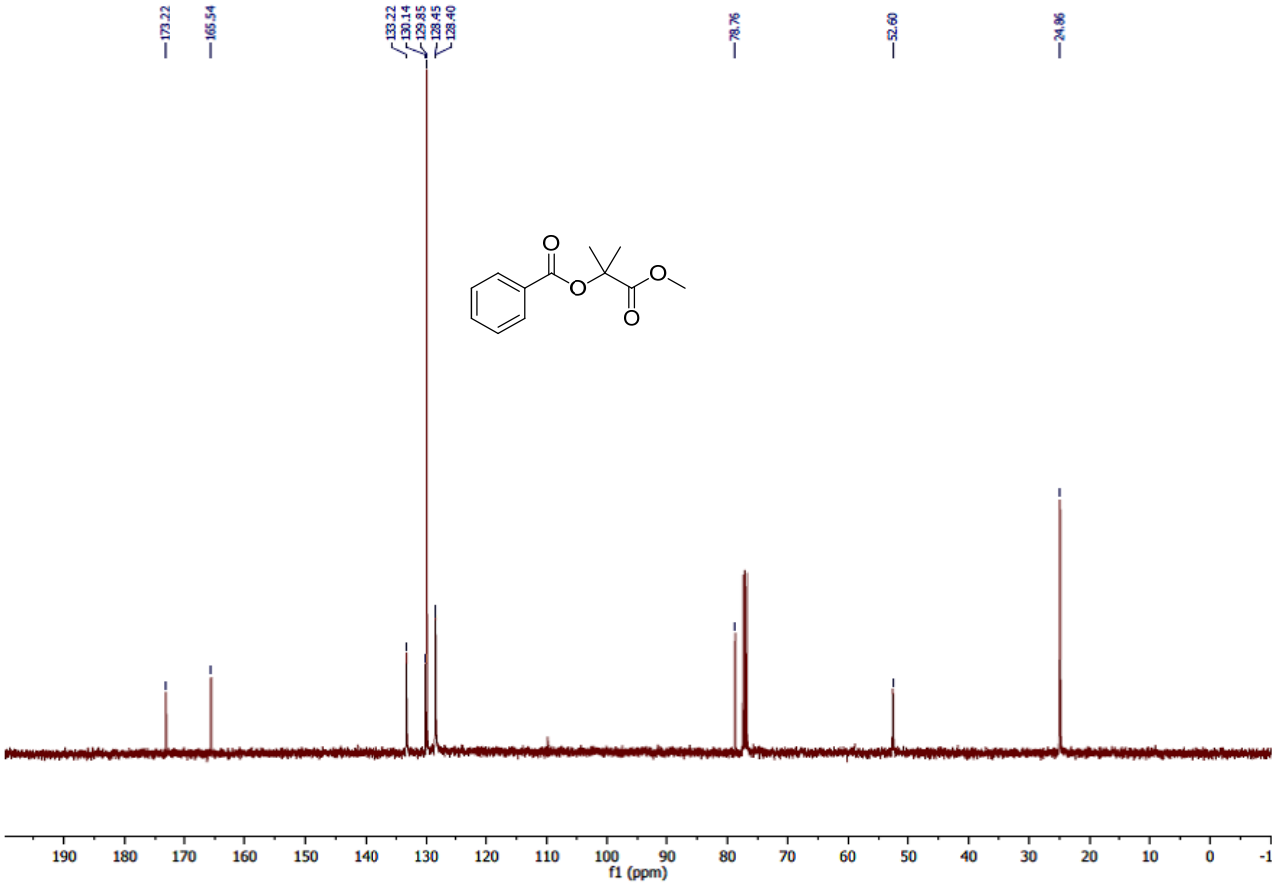
Appendix Figure 123 400 MHz ^{1}H NMR spectrum of adamantan-2-yl benzoate **(183)**



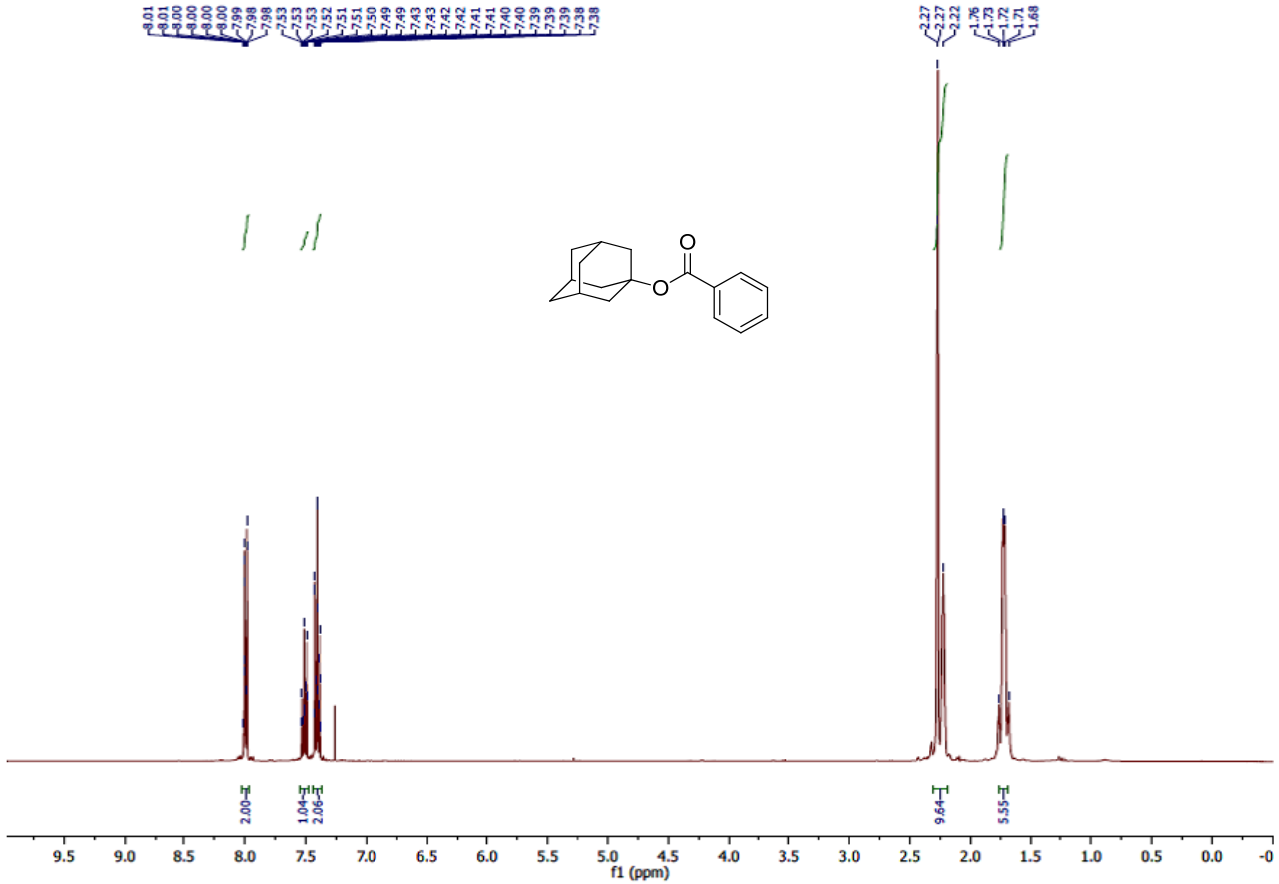
Appendix Figure 124 100 MHz ^{13}C NMR spectrum of adamantan-2-yl benzoate **(183)**



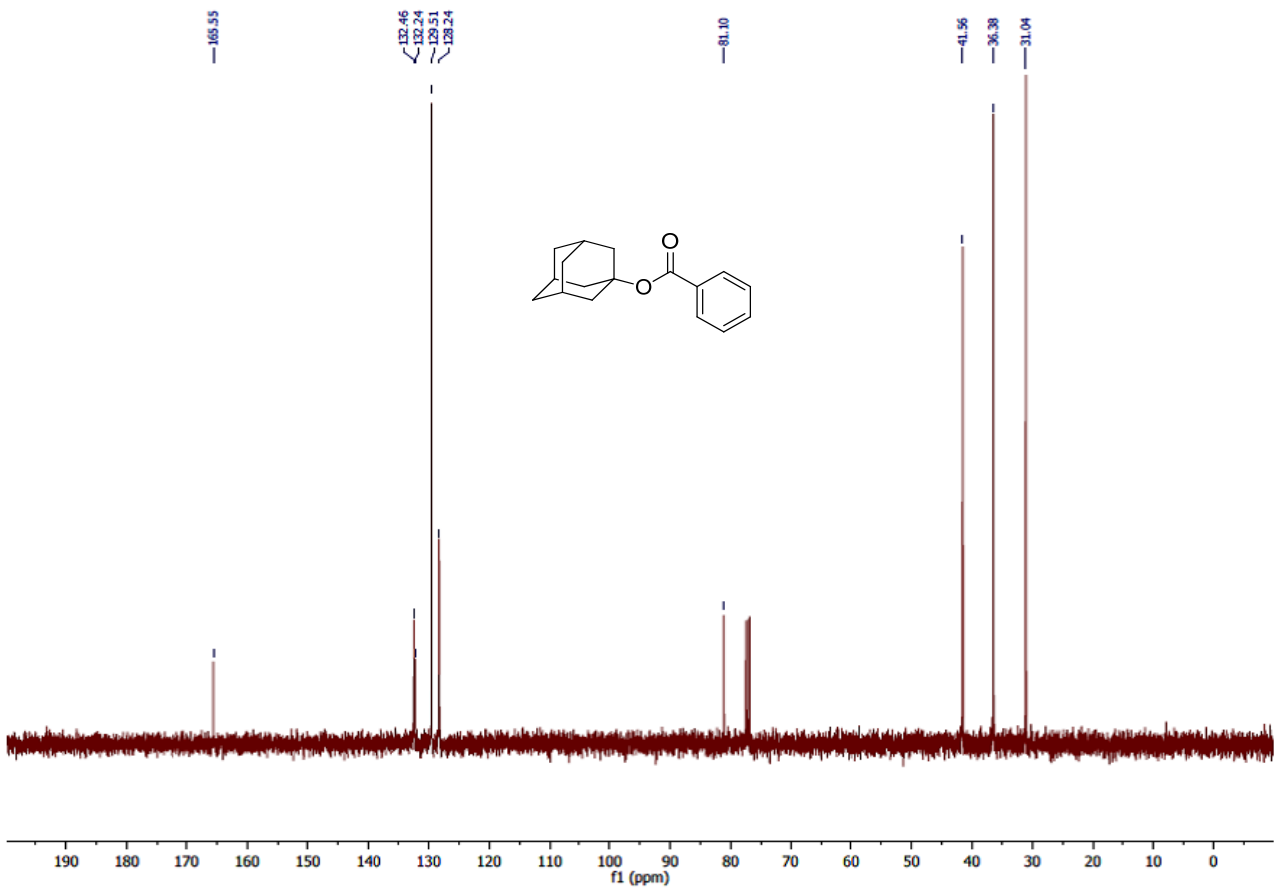
Appendix Figure 125 400 MHz ^{1}H NMR spectrum of 1-methoxy-2-methyl-1-oxopropan-2-yl benzoate **(184)**



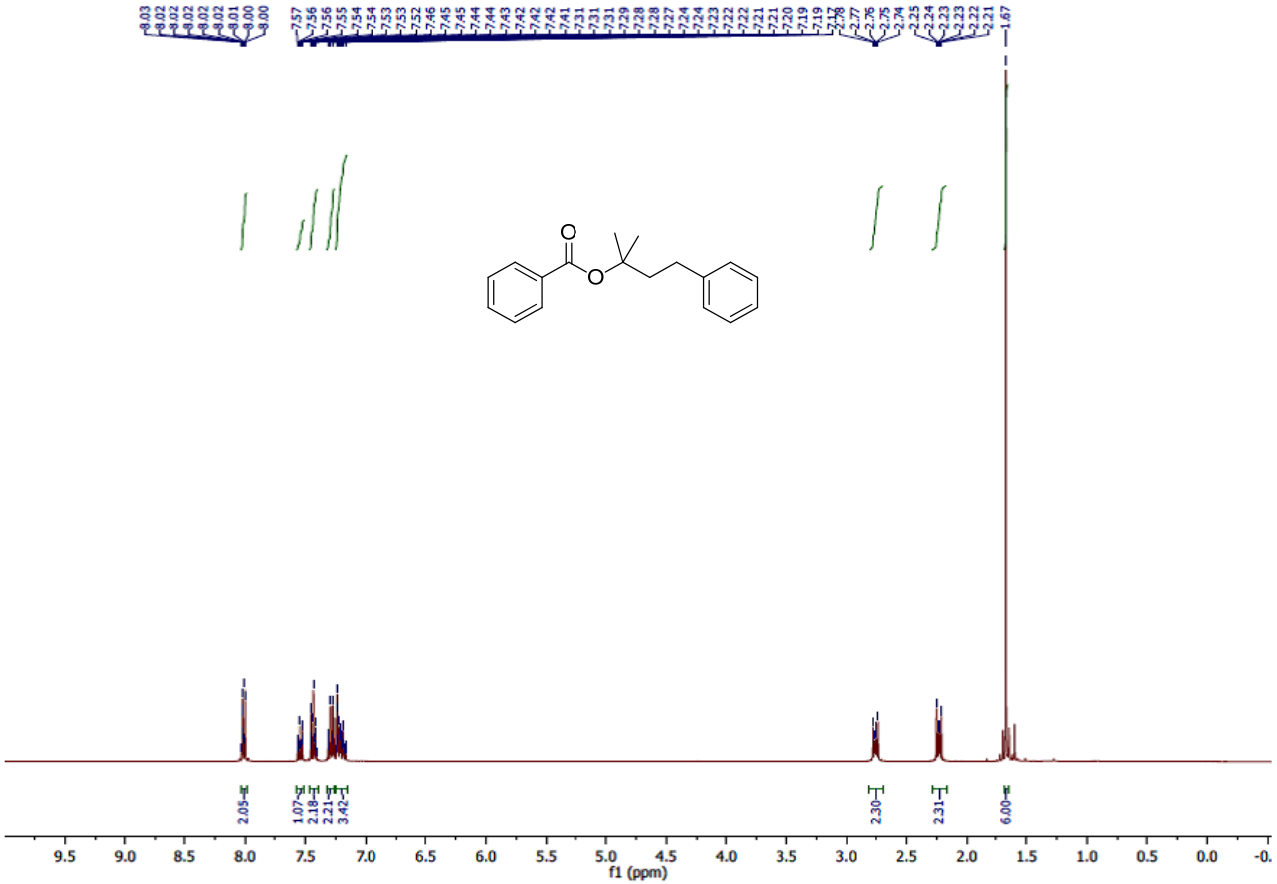
Appendix Figure 126 100 MHz ^{13}C NMR spectrum of 1-methoxy-2-methyl-1-oxopropan-2-yl benzoate **(184)**



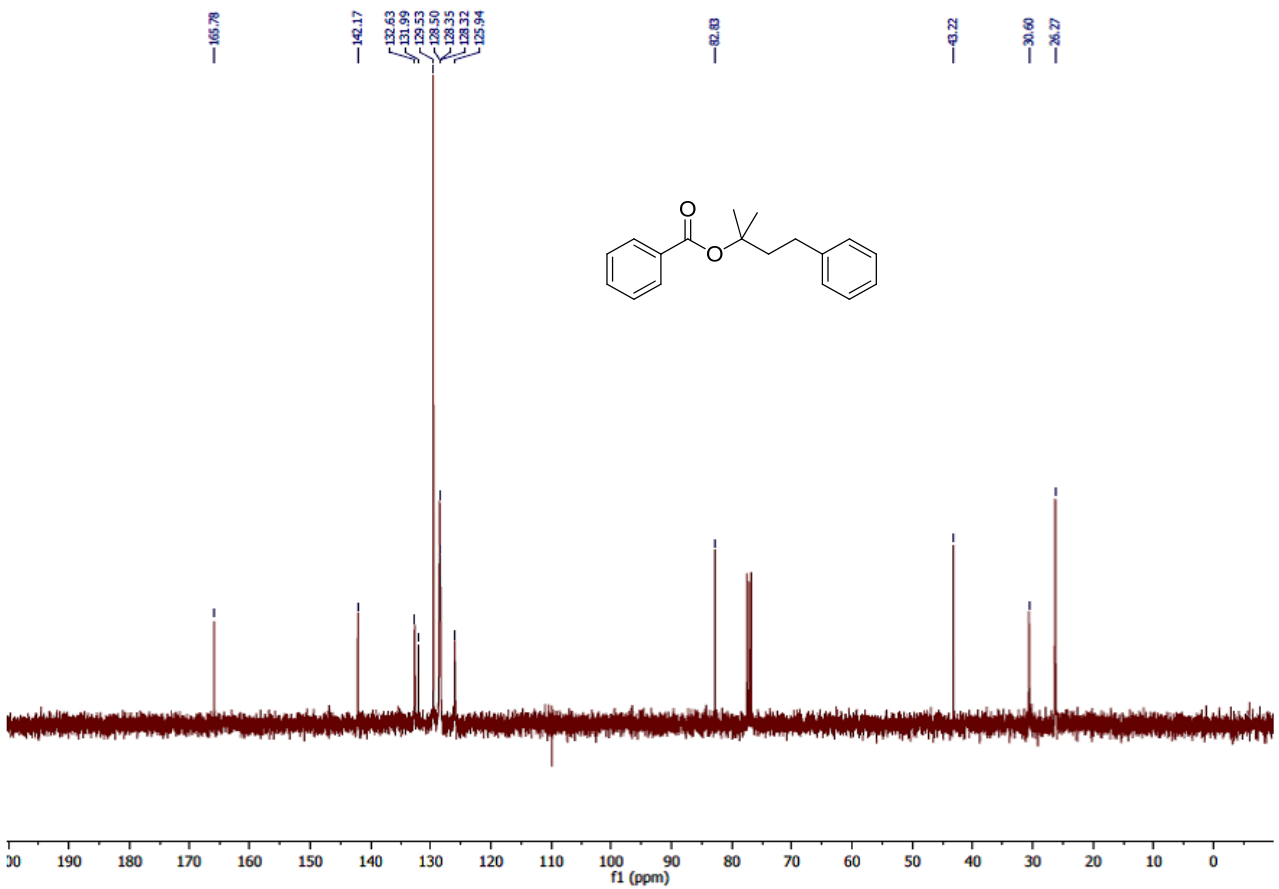
Appendix Figure 127 400 MHz ^{1}H NMR spectrum of adamantan-1-yl benzoate **(185)**



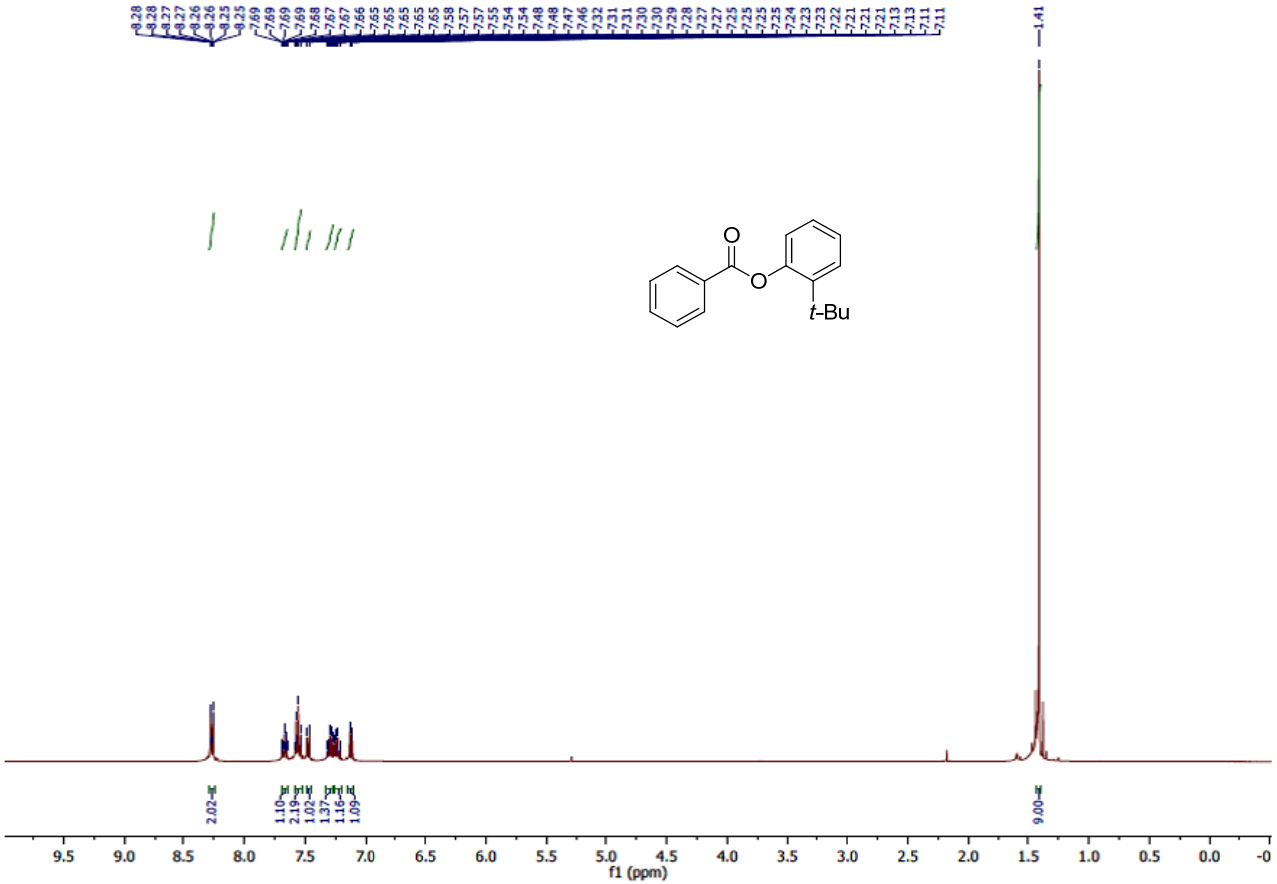
Appendix Figure 128 100 MHz ^{13}C NMR spectrum of adamantan-1-yl benzoate **(185)**



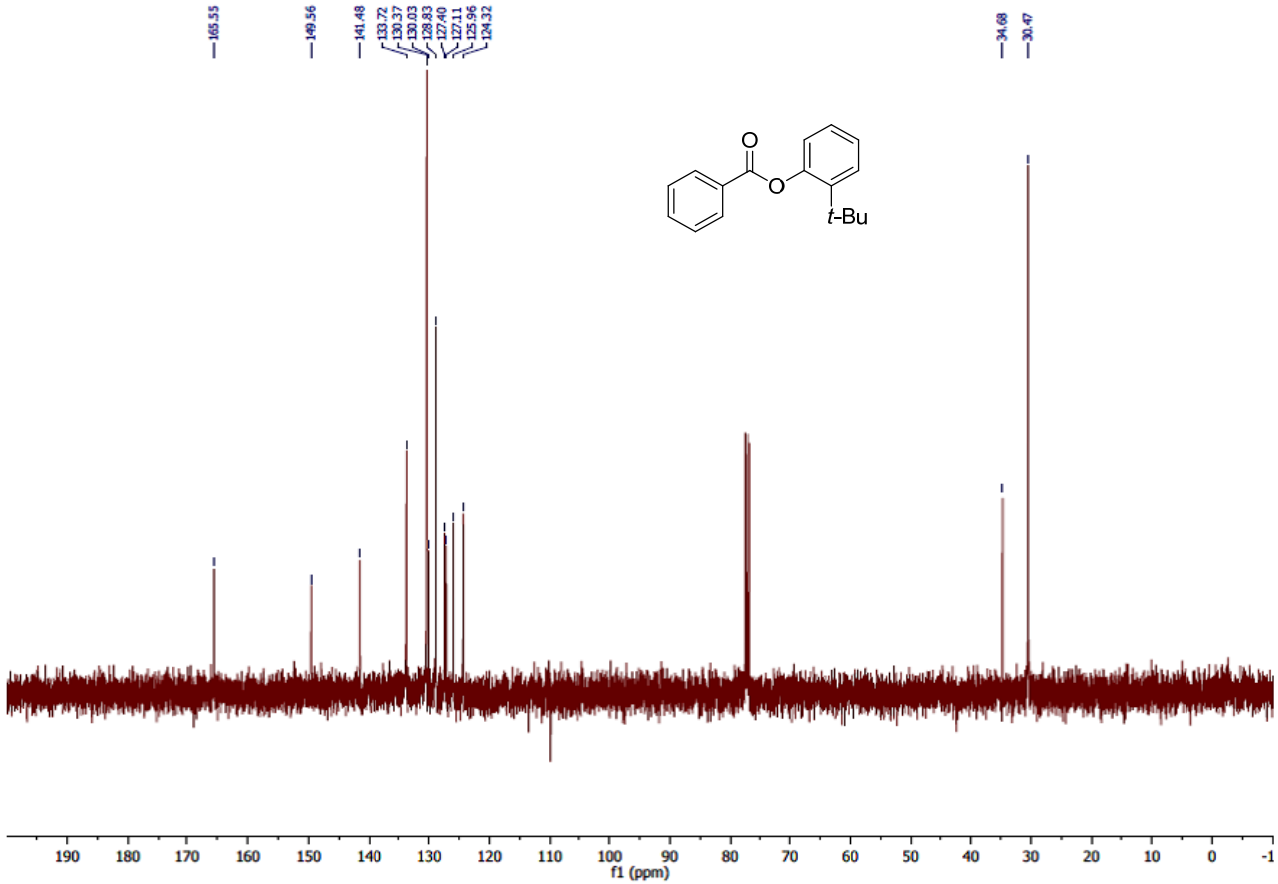
Appendix Figure 129 400 MHz ^{1}H NMR spectrum of 2-methyl-4-phenylbutan-2-yl benzoate **(186)**



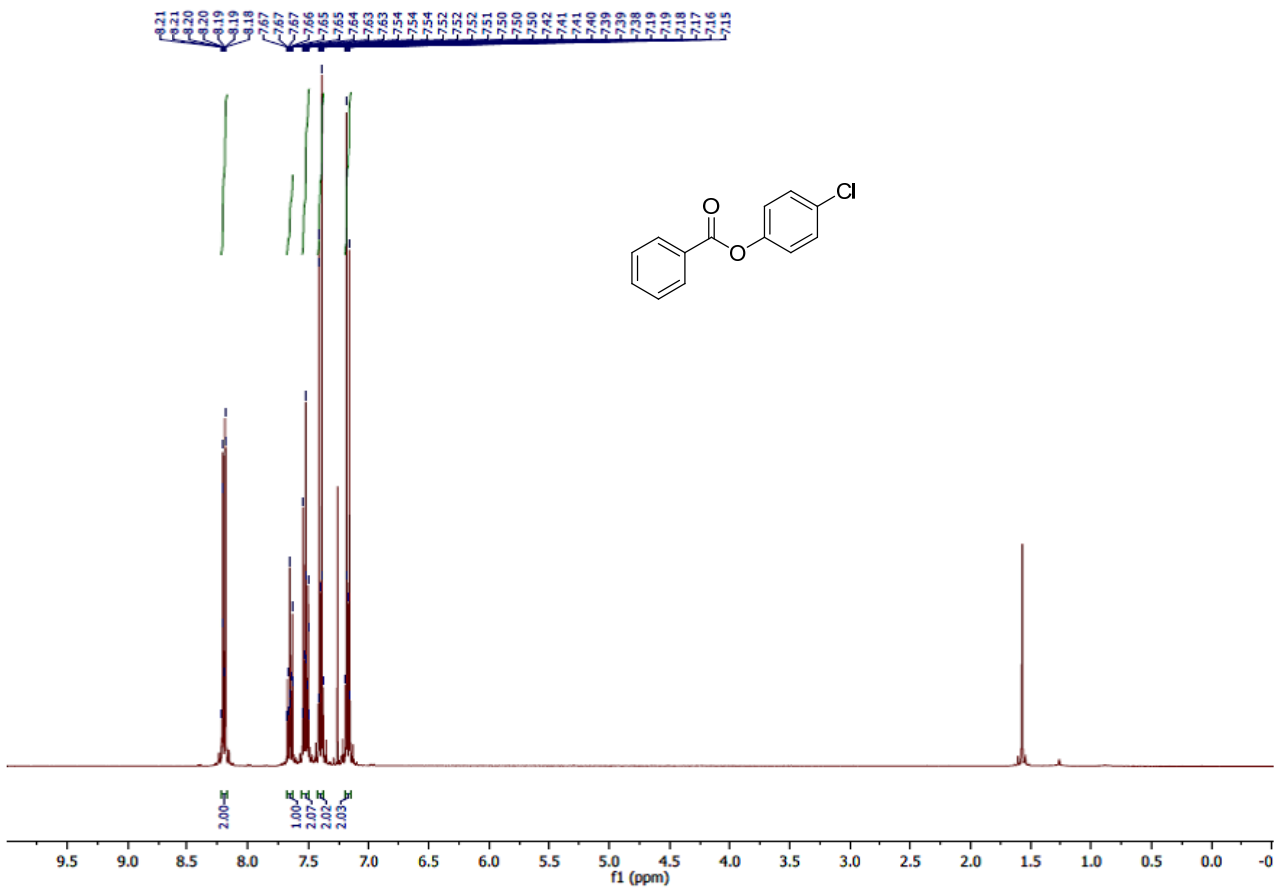
Appendix Figure 130 100 MHz ^{13}C NMR spectrum of 2-methyl-4-phenylbutan-2-yl benzoate **(186)**



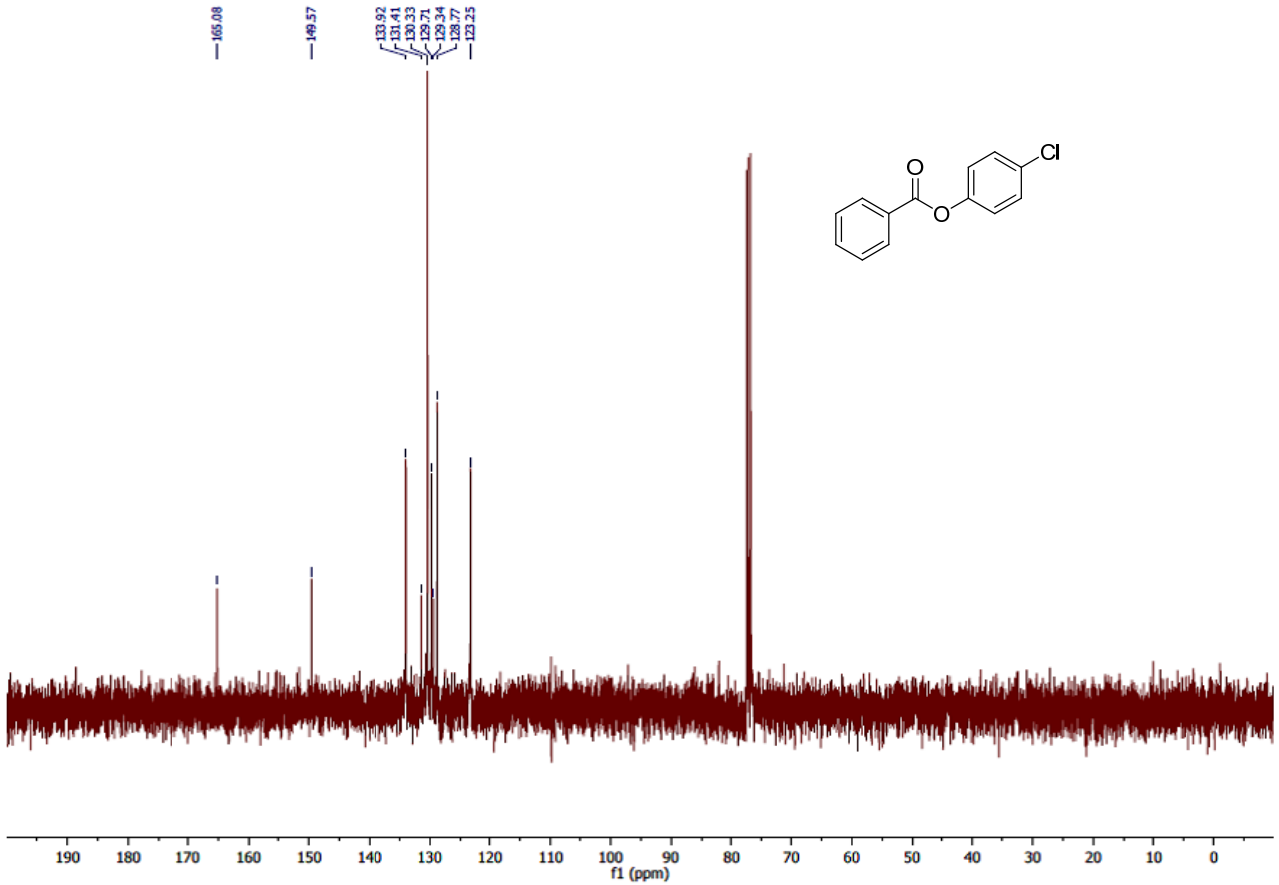
Appendix Figure 131 400 MHz ^{1}H NMR spectrum of 2-(*tert*-butyl)phenyl benzoate **(188)**



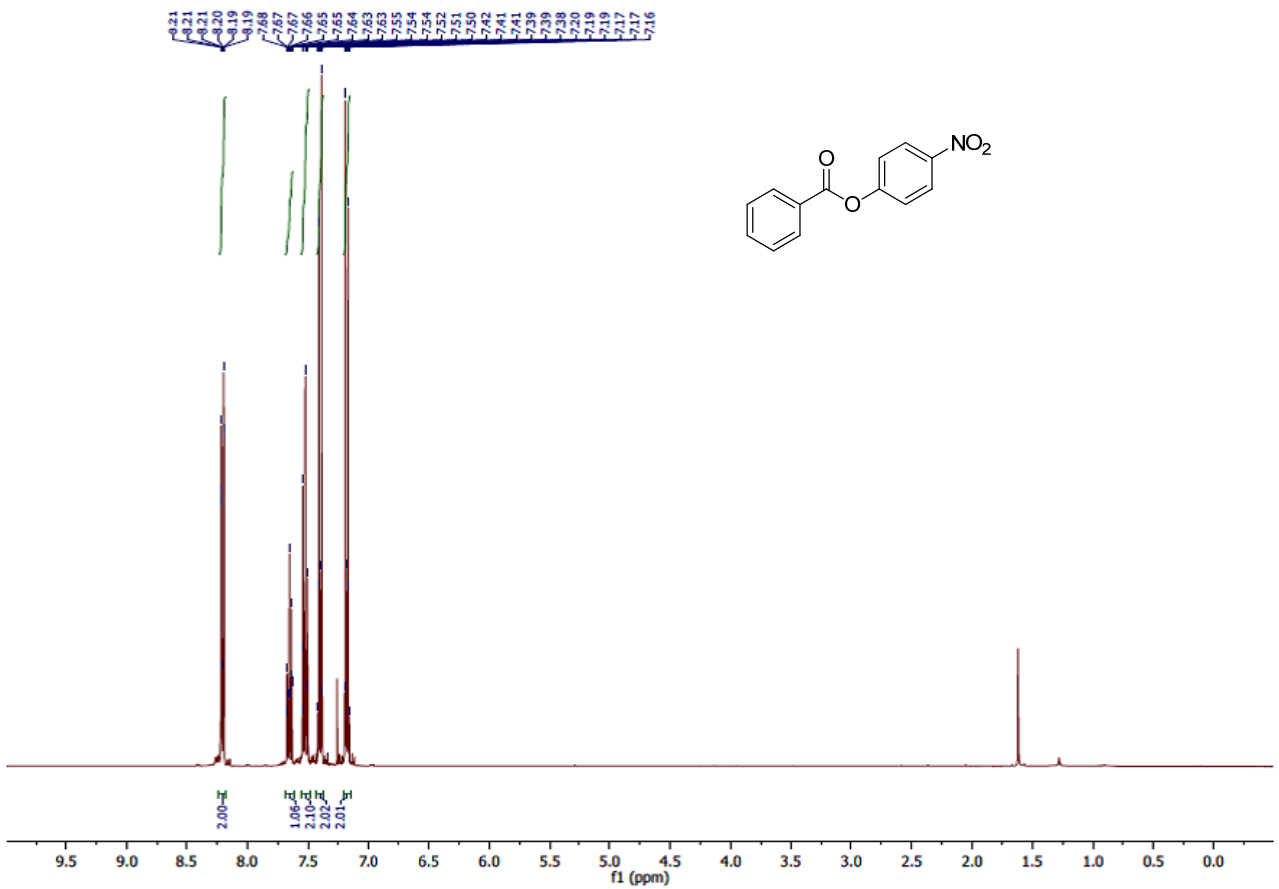
Appendix Figure 132 100 MHz ^{13}C NMR spectrum of 2-(*tert*-butyl)phenyl benzoate **(188)**



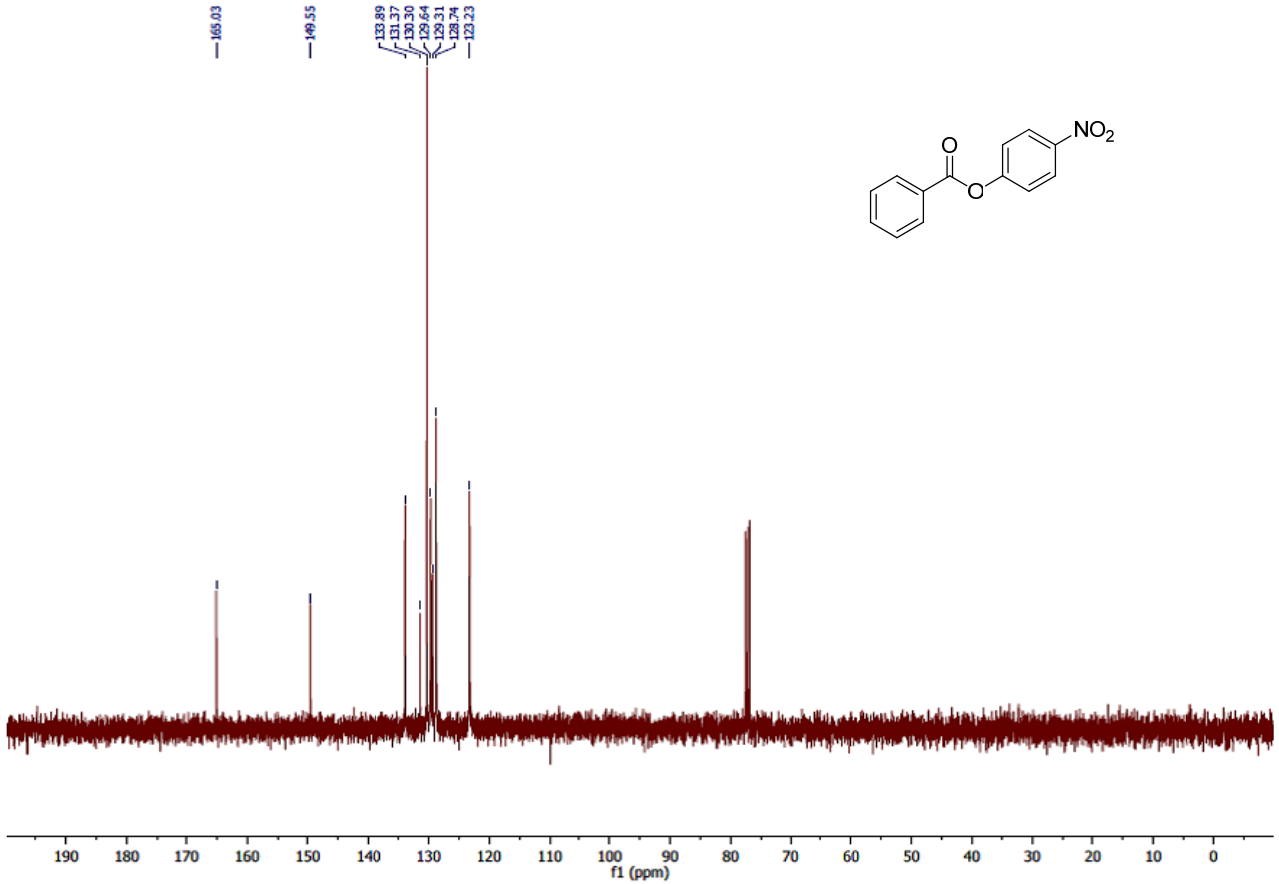
Appendix Figure 133 400 MHz ^{1}H NMR spectrum of 4-chlorophenyl benzoate **(190)**



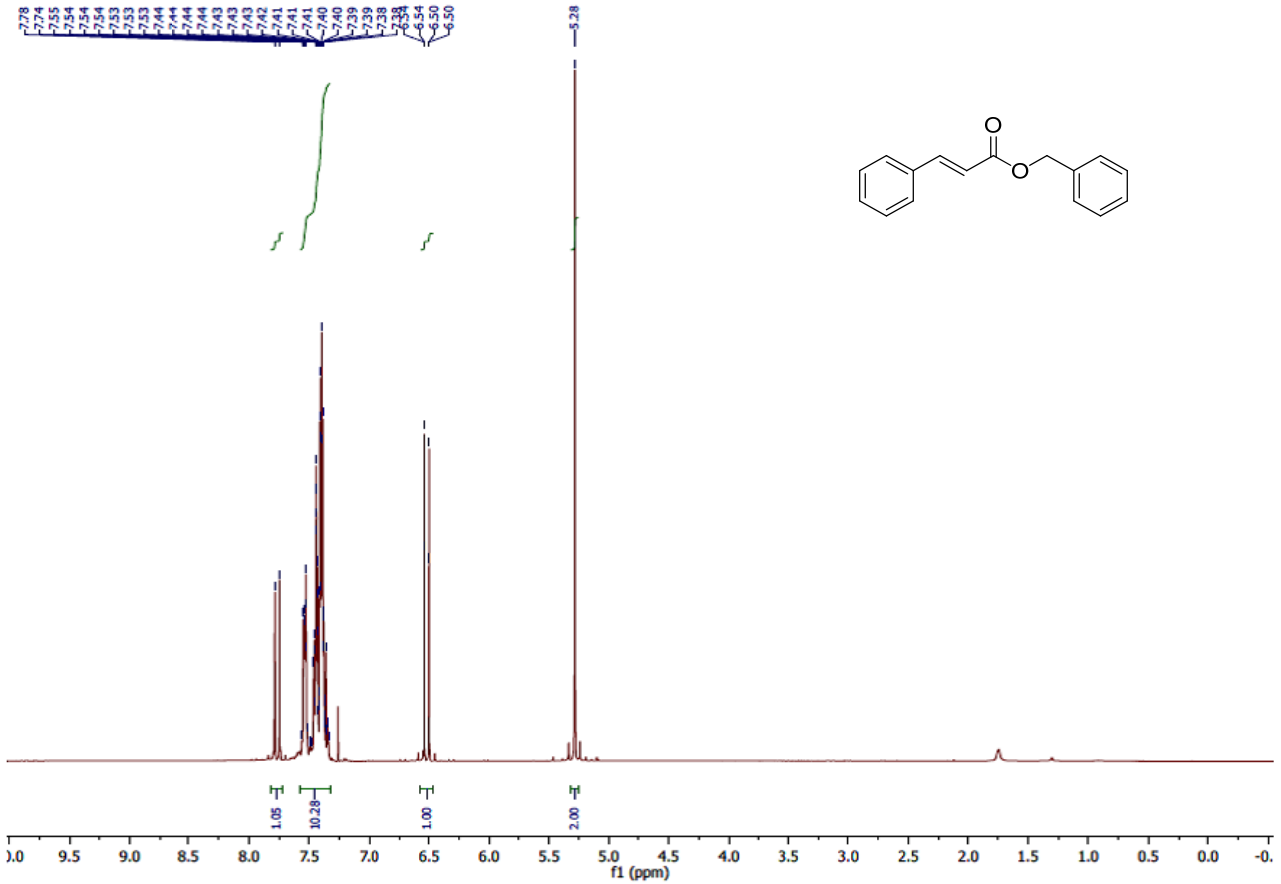
Appendix Figure 134 100 MHz ^{13}C NMR spectrum of 4-chlorophenyl benzoate **(190)**



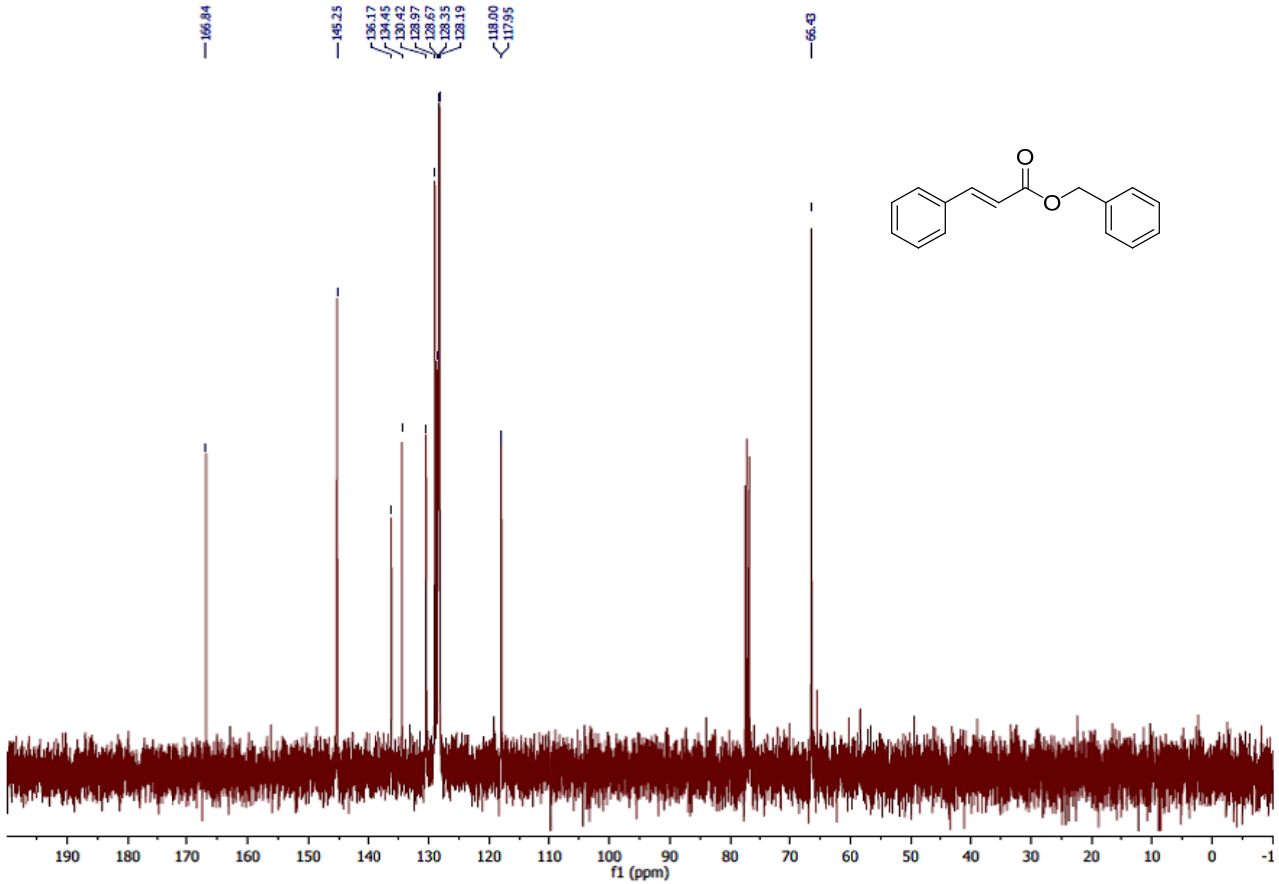
Appendix Figure 135 400 MHz ^{1}H NMR spectrum of 4-nitrophenyl benzoate **(192)**



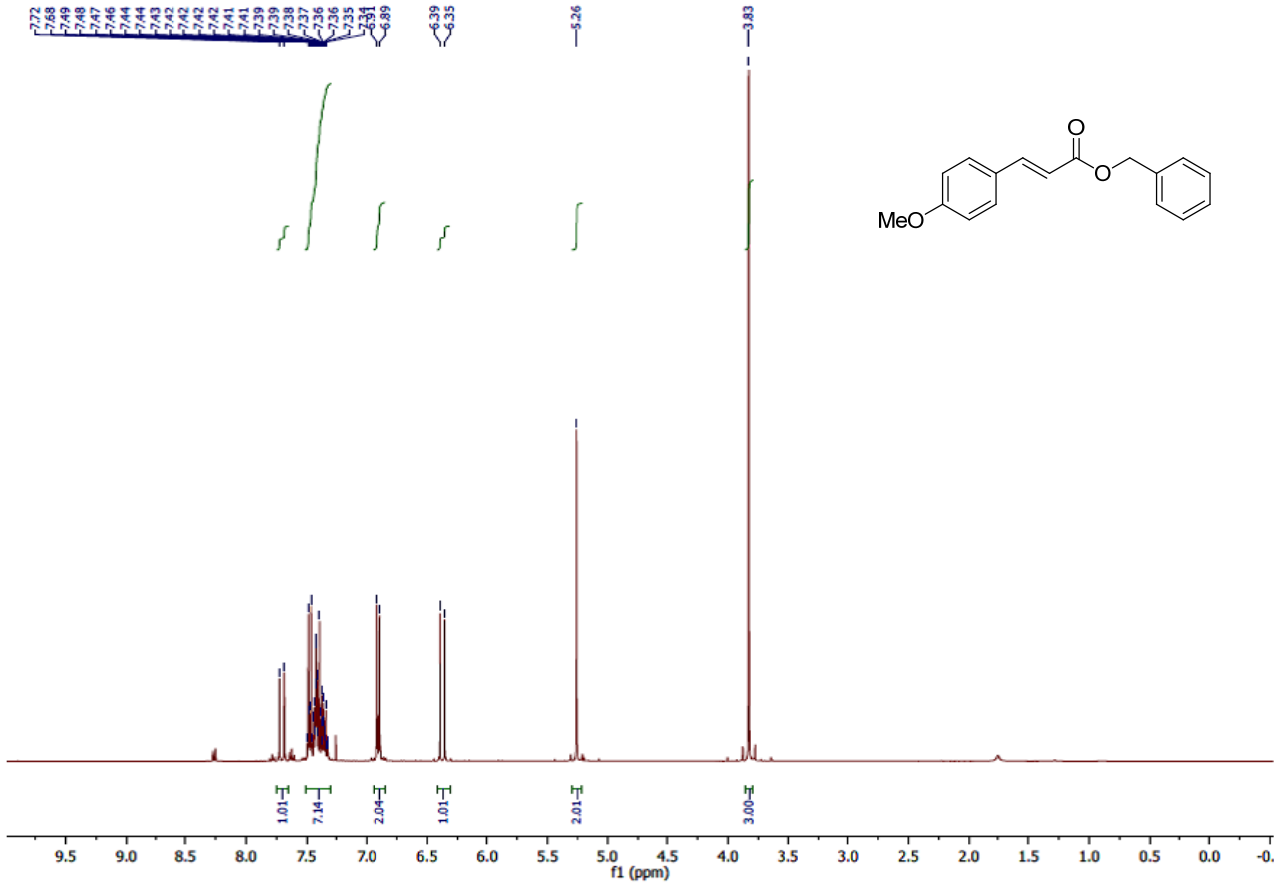
Appendix Figure 136 100 MHz ^{13}C NMR spectrum of 4-nitrophenyl benzoate benzoate **(192)**



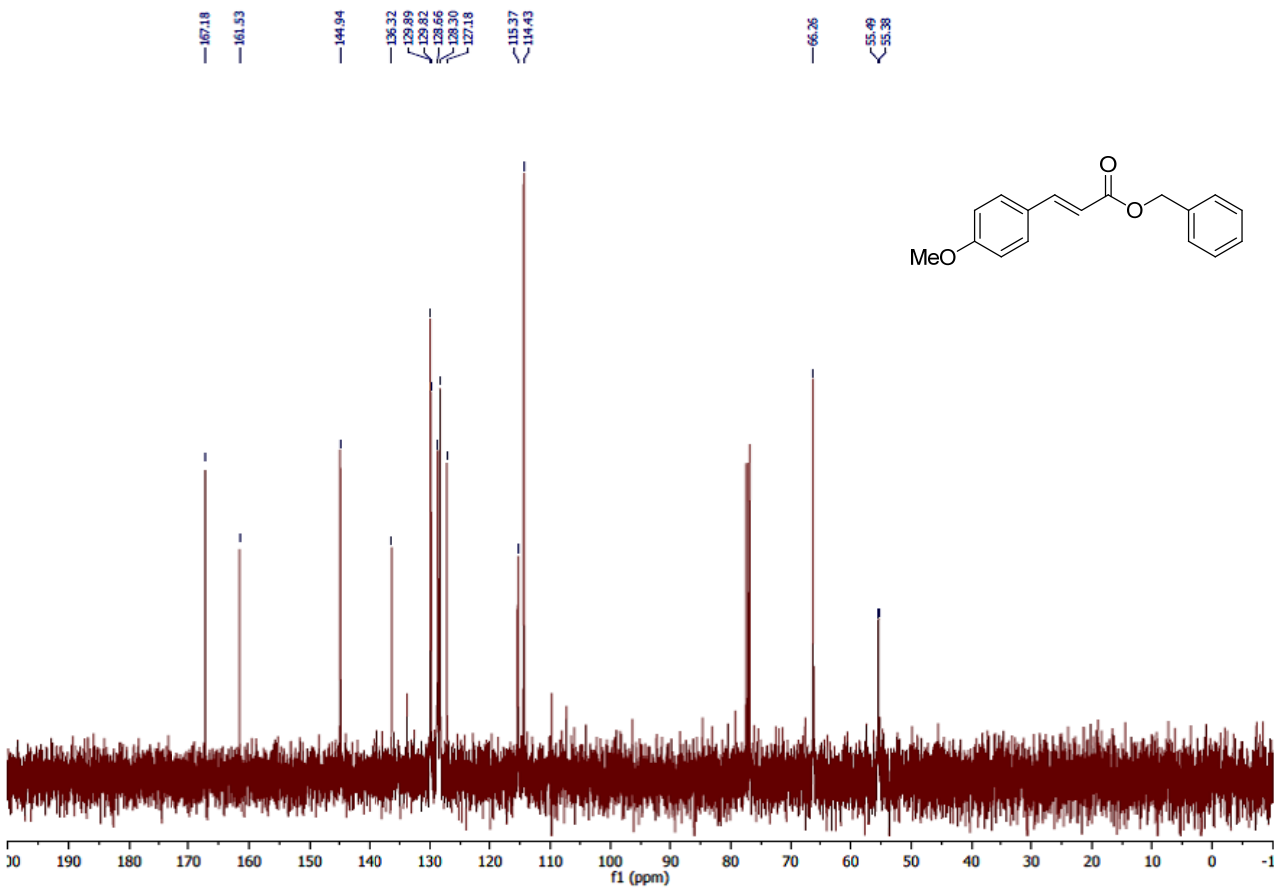
Appendix Figure 137 400 MHz ^{1}H NMR spectrum of benzyl cinnamate **(196)**



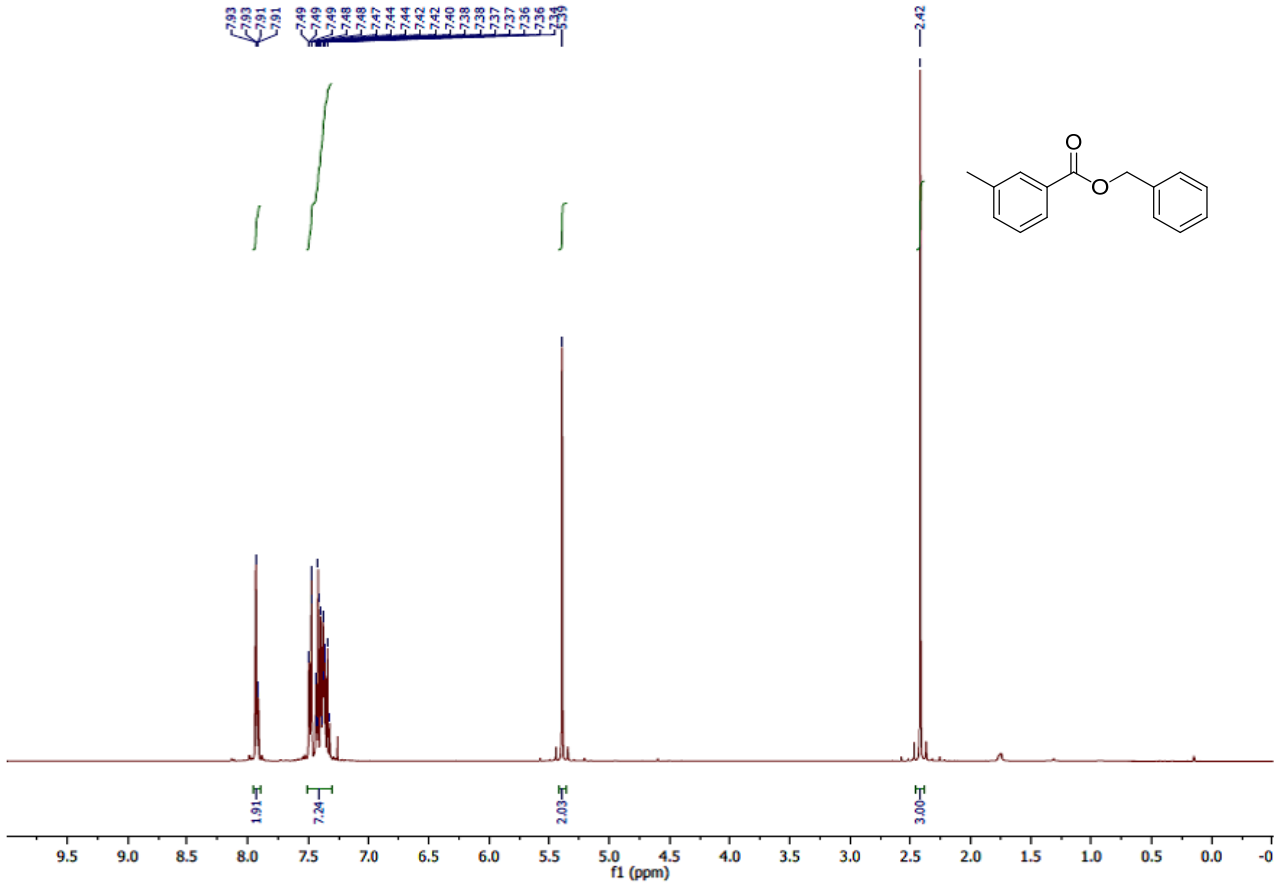
Appendix Figure 138 100 MHz ^{13}C NMR spectrum of benzyl cinnamate **(196)**



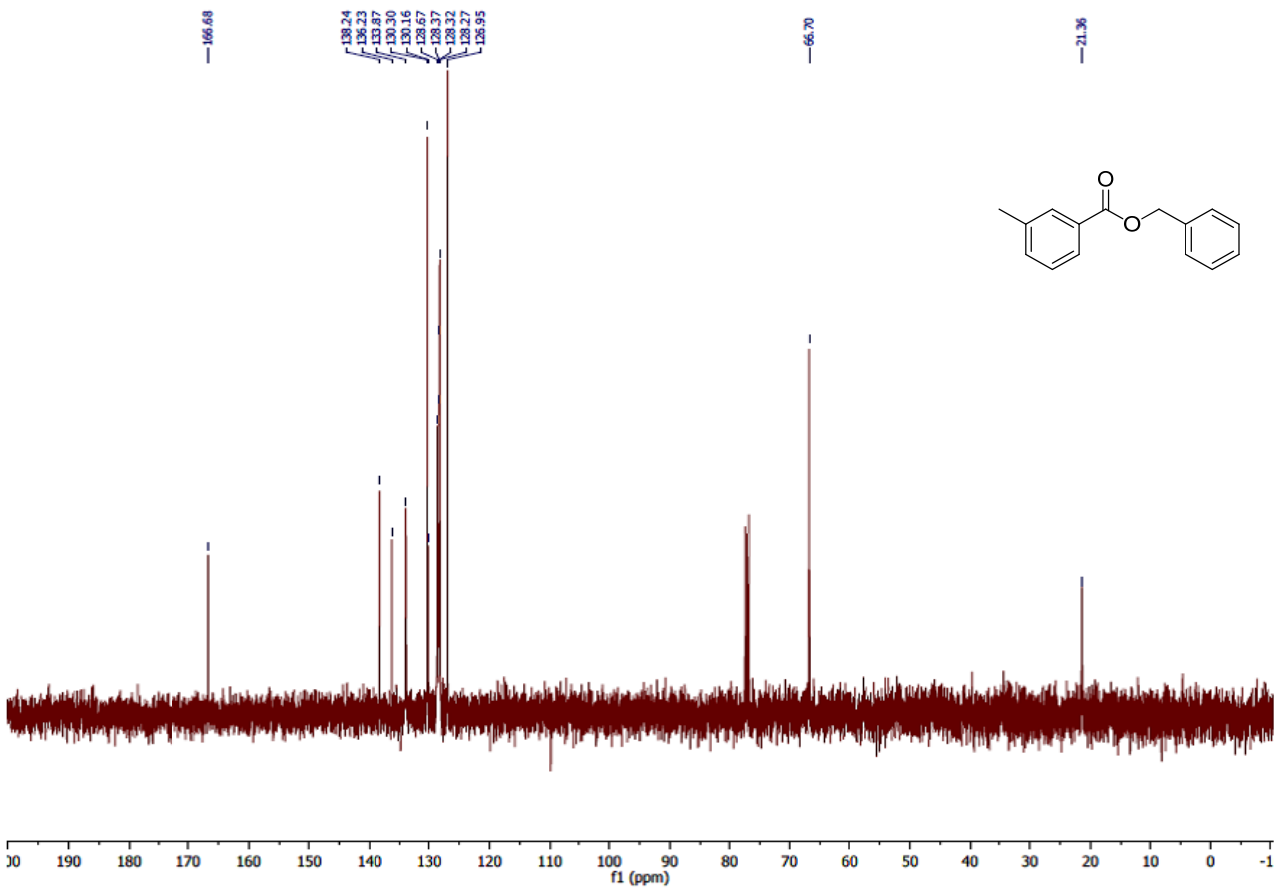
Appendix Figure 139 400 MHz ^{1}H NMR spectrum of benzyl-(*E*)-4-methoxy cinnamate **(198)**



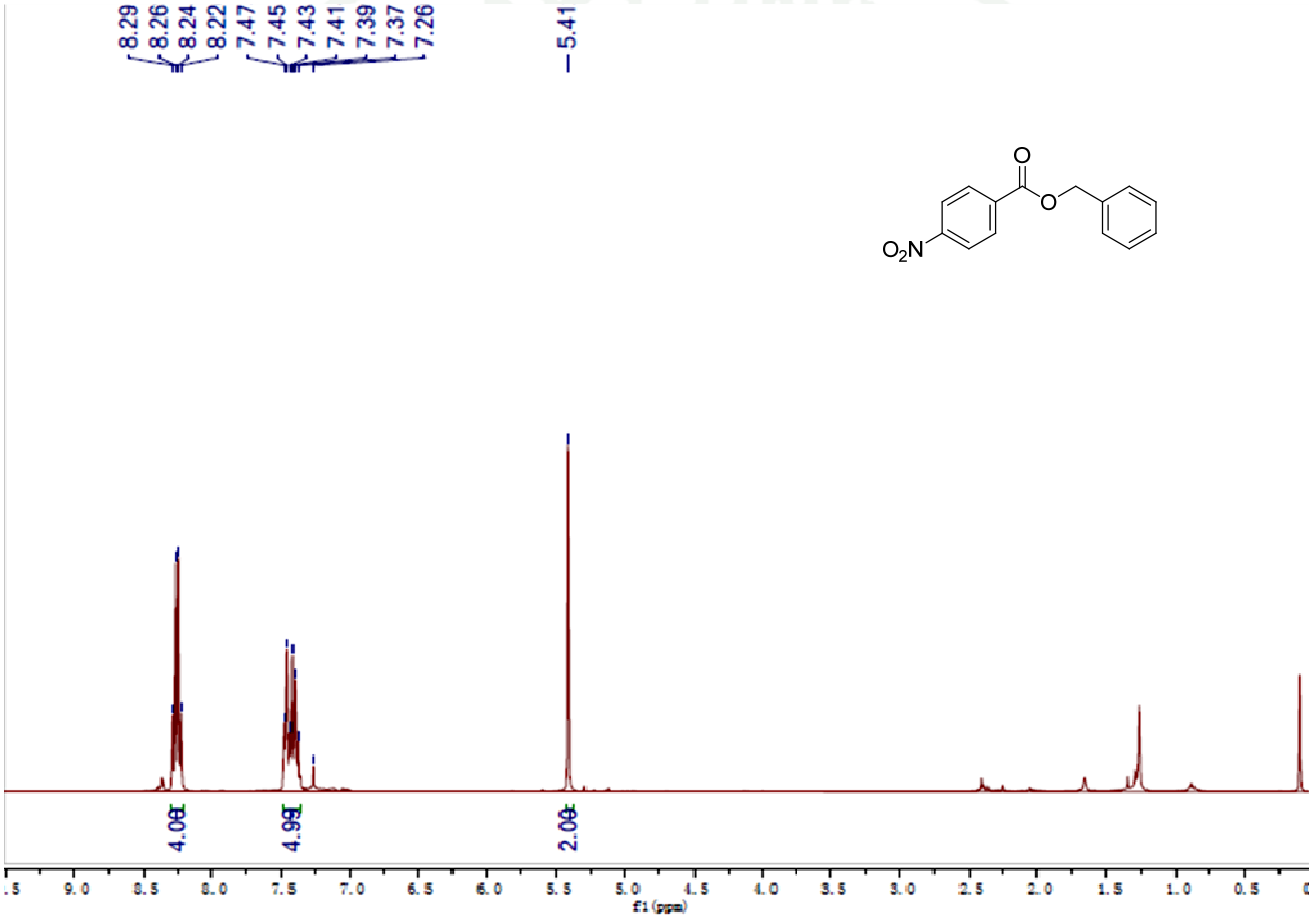
Appendix Figure 140 100 MHz ^{13}C NMR spectrum of benzyl-(*E*)-4-methoxy cinnamate **(198)**



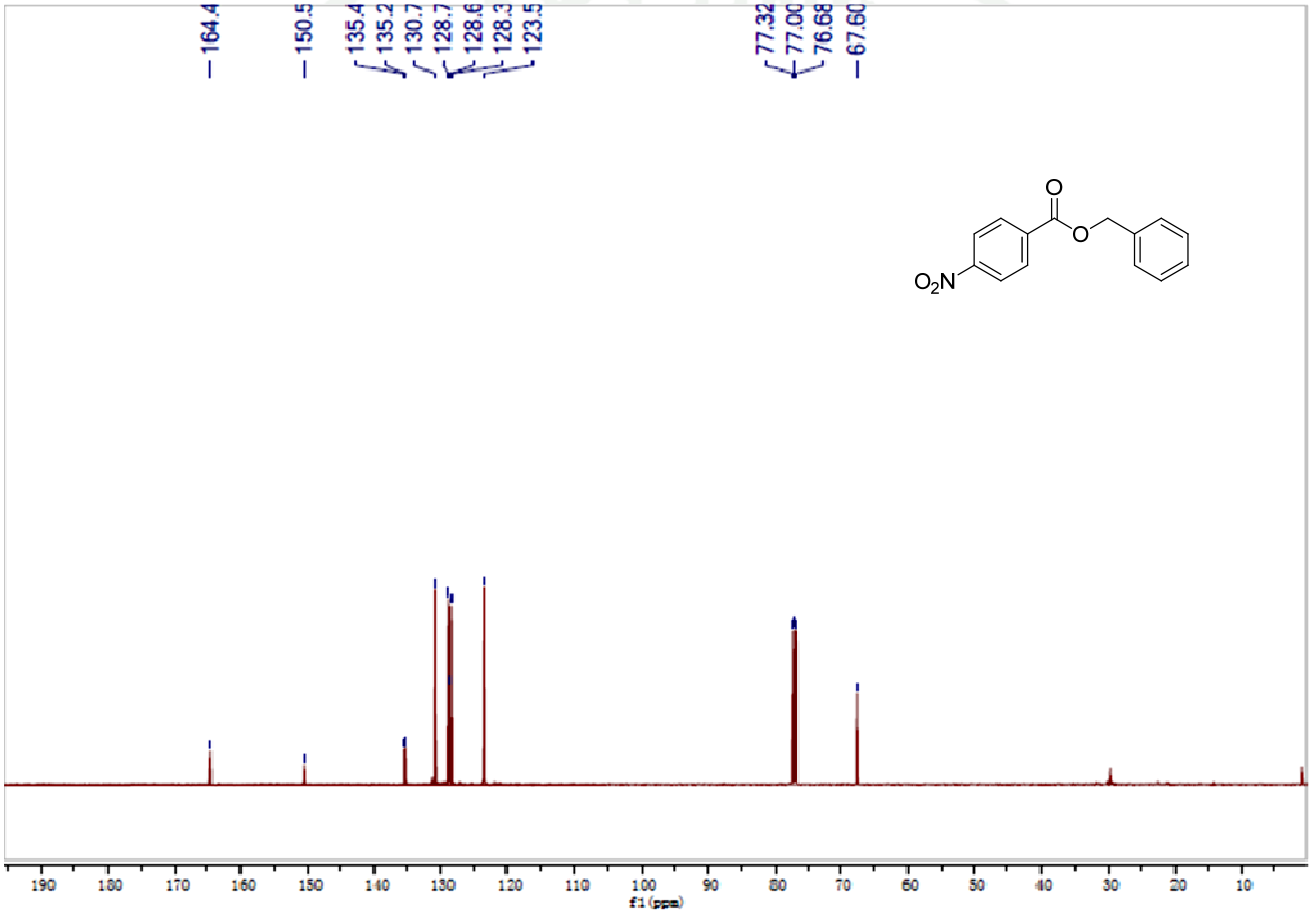
Appendix Figure 141 400 MHz ^{1}H NMR spectrum of benzyl-3-methyl benzoate **(202)**



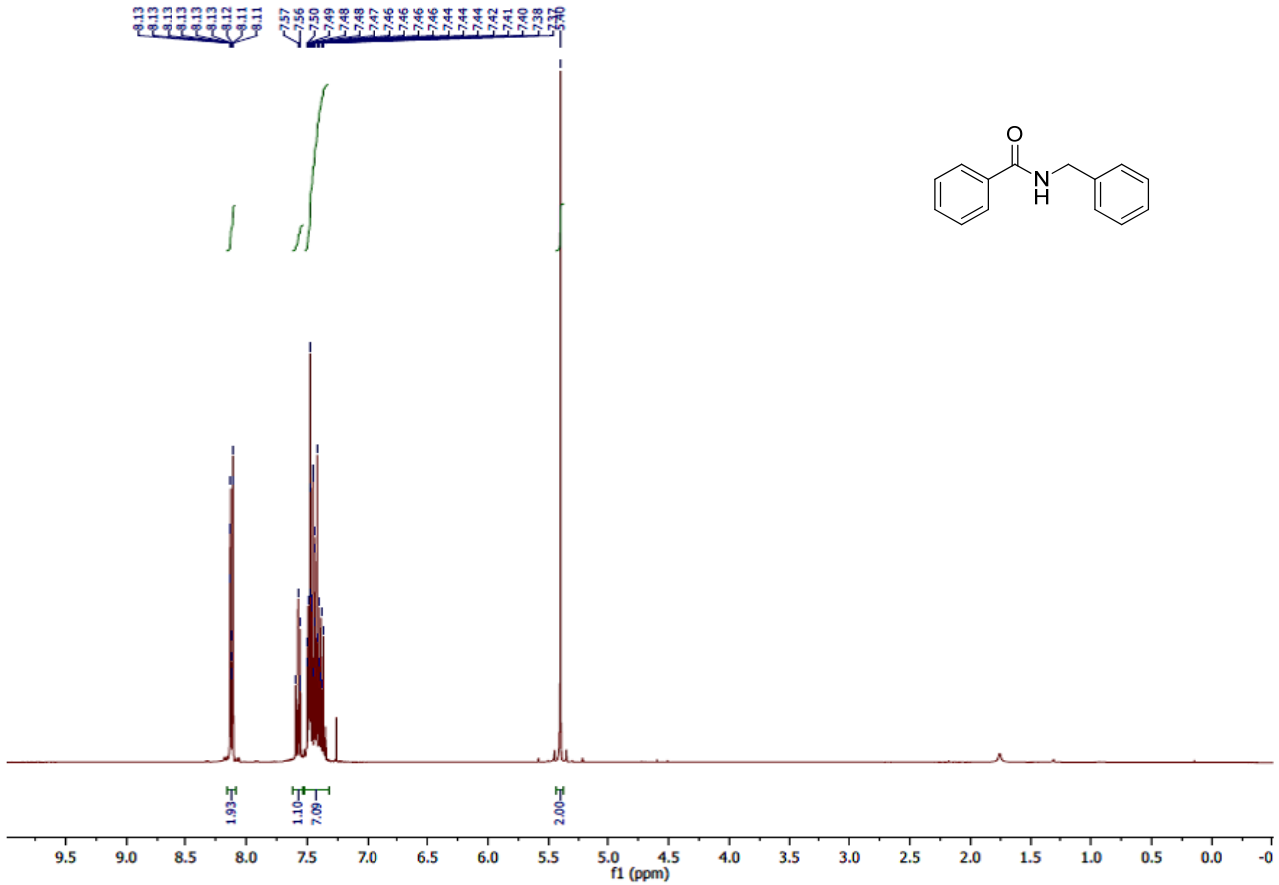
Appendix Figure 142 100 MHz ^{13}C NMR spectrum of benzyl-3-methyl benzoate **(202)**



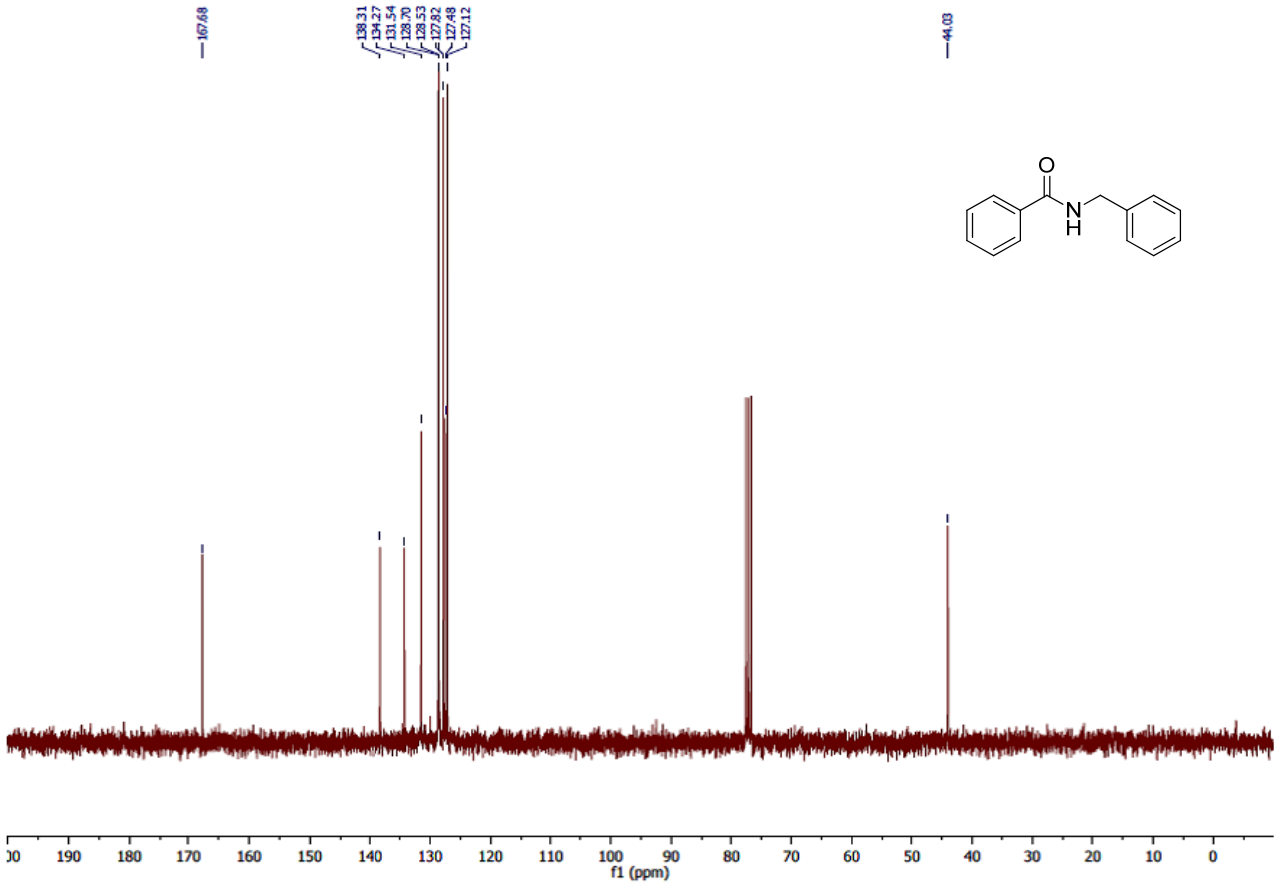
Appendix Figure 143 400 MHz ^{1}H NMR spectrum of benzyl-4-nitro benzoate **(206)**



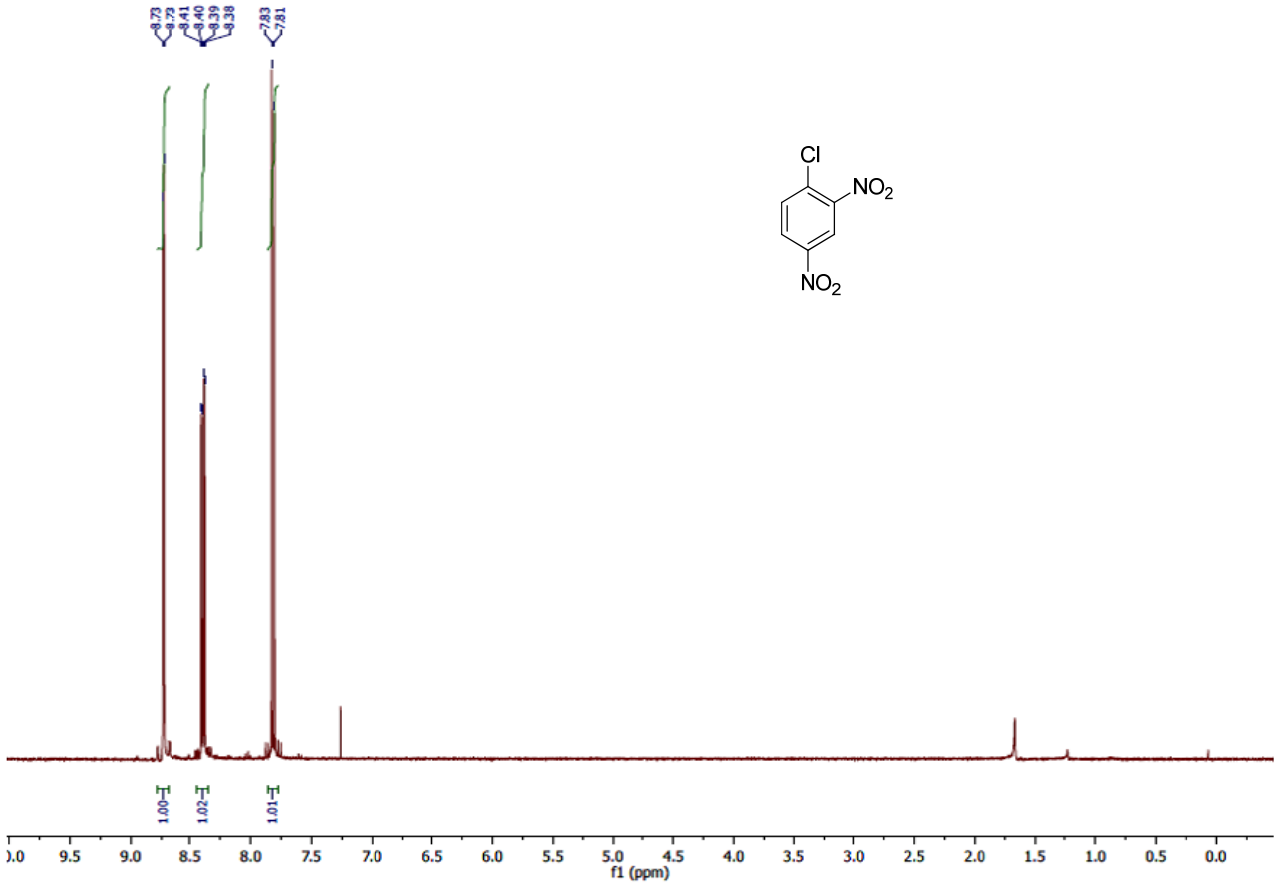
Appendix Figure 144 100 MHz ^{13}C NMR spectrum of benzyl-4-nitro benzoate **(206)**



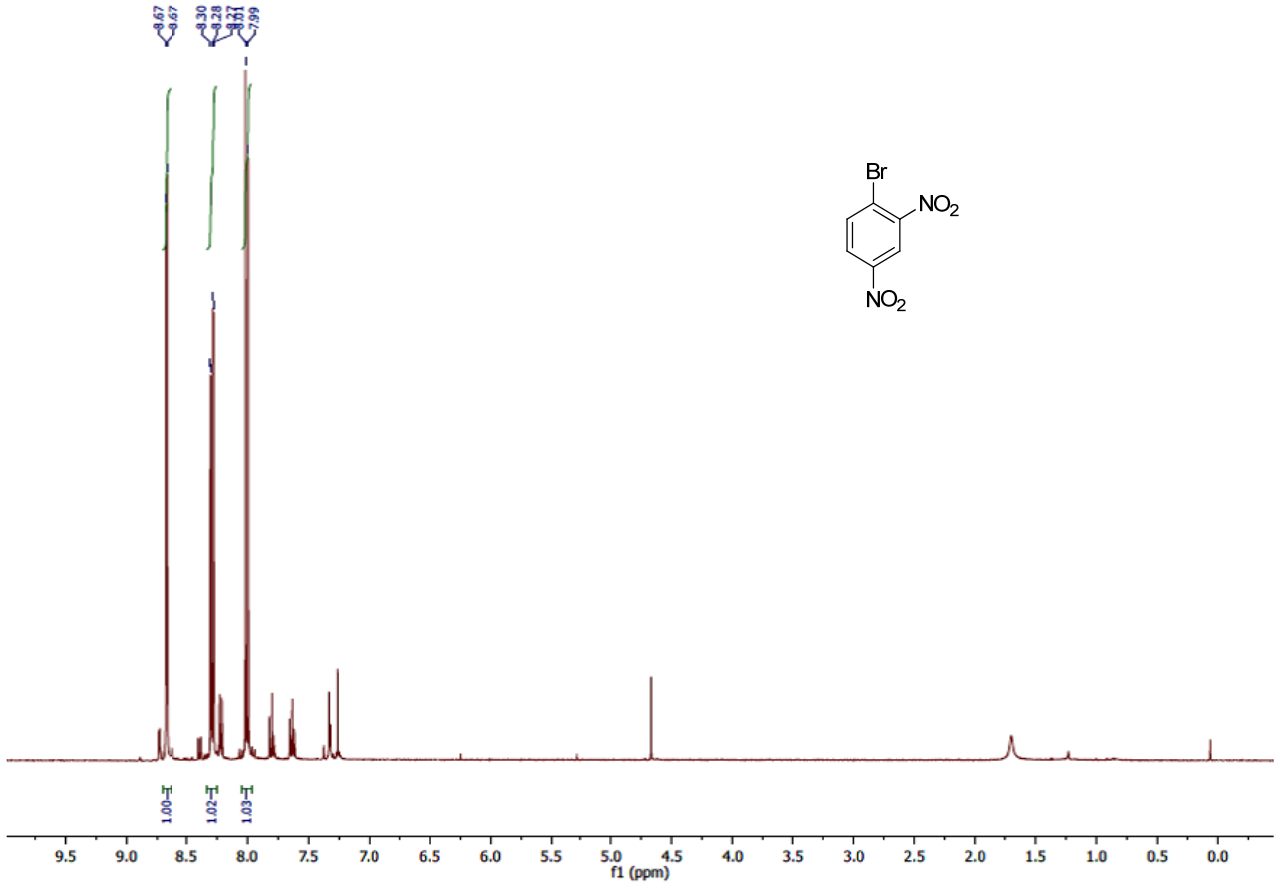
Appendix Figure 145 400 MHz ^{1}H NMR spectrum of *N*-benzylbenzamide **(209)**



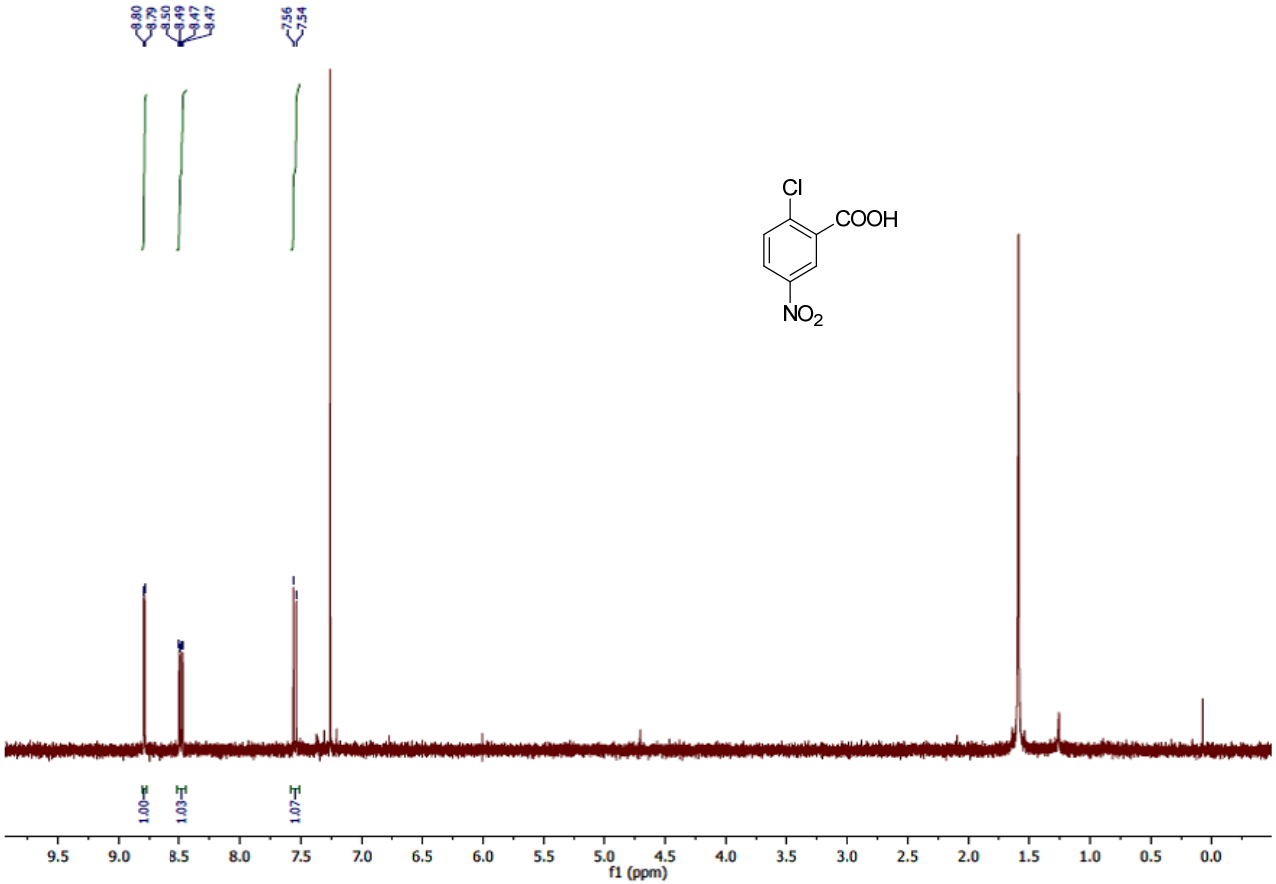
Appendix Figure 146 100 MHz ^{13}C NMR spectrum of *N*-benzylbenzamide **(209)**



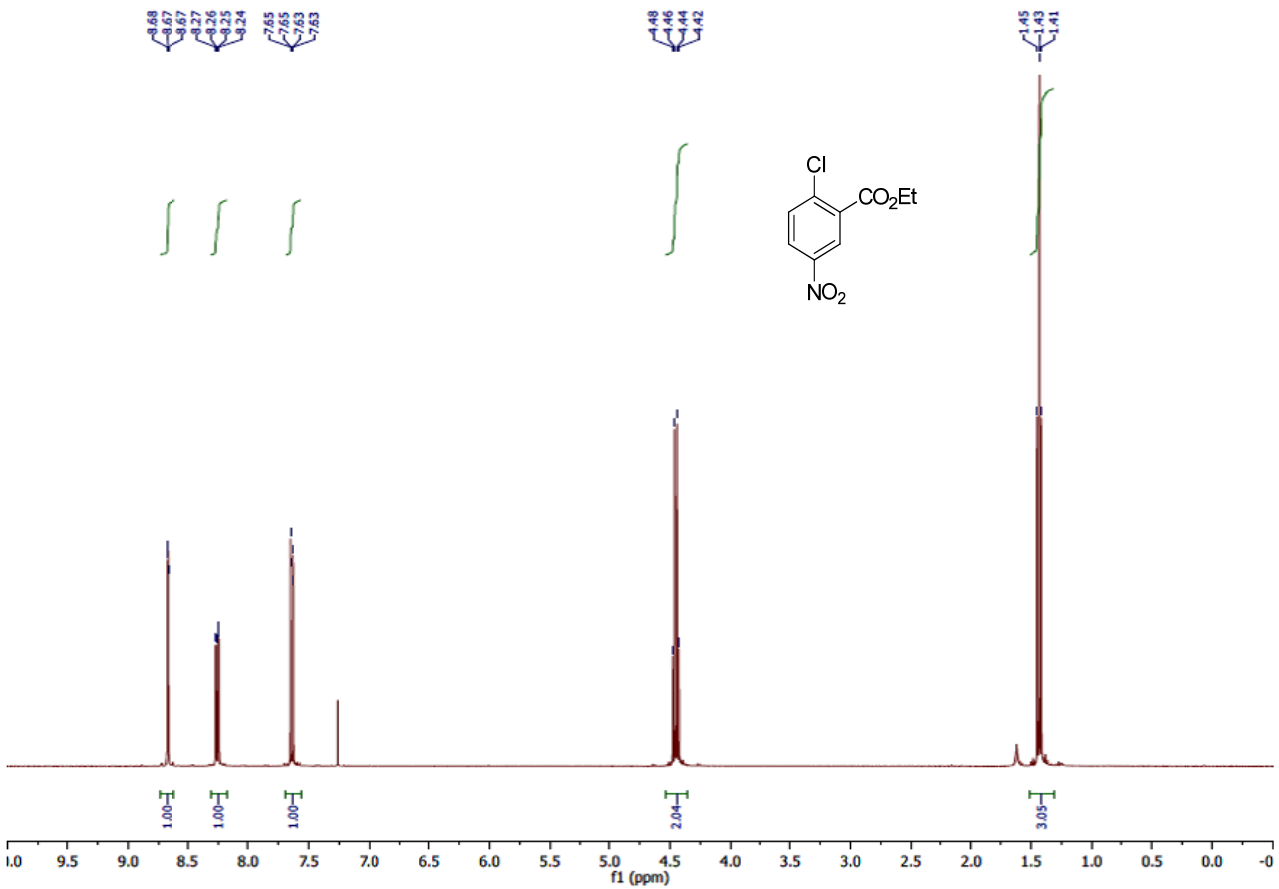
Appendix Figure 147 400 MHz ^{1}H NMR spectrum of 1-chloro-2,4-dinitrobenzene **(221)**



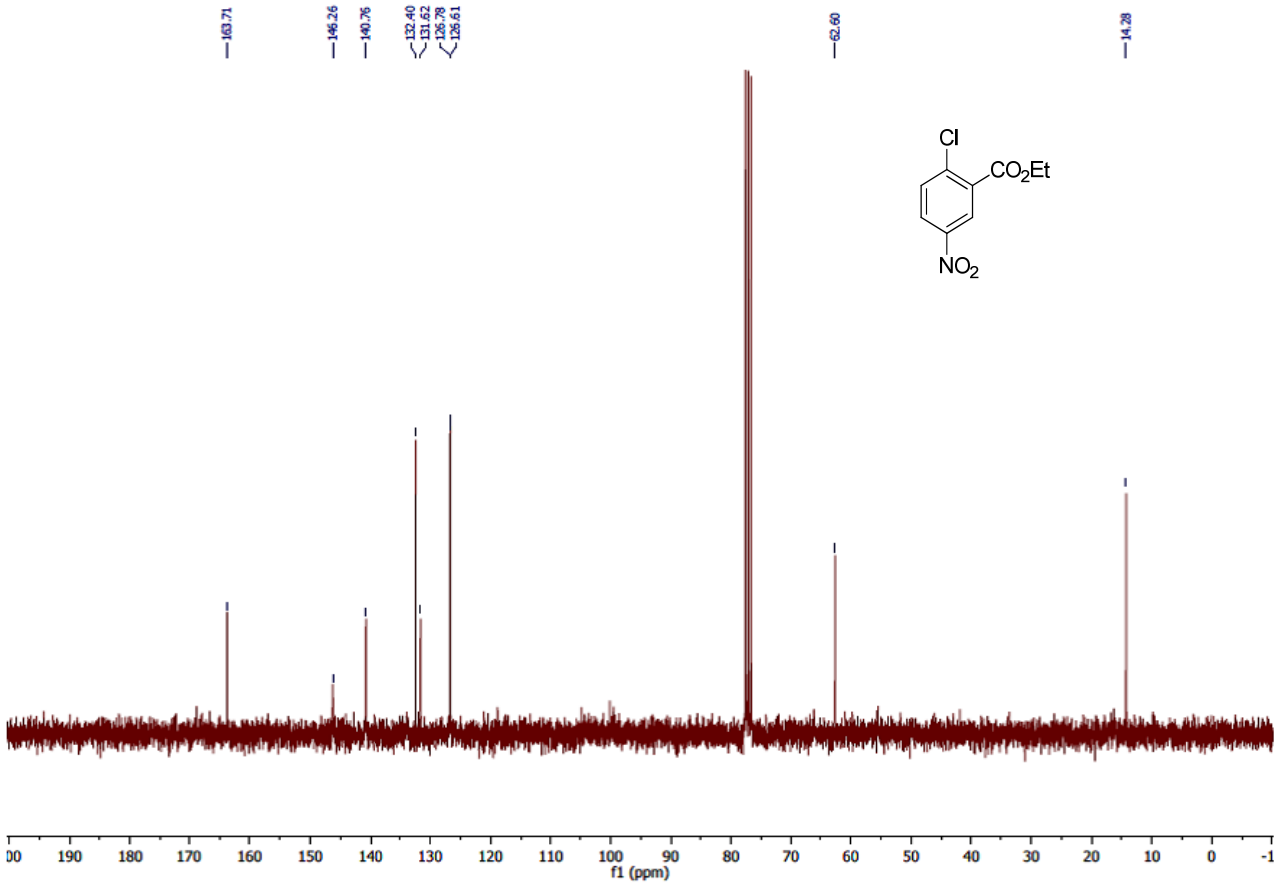
Appendix Figure 148 400 MHz ^{1}H NMR spectrum of 1-bromo-2,4-dinitrobenzene **(222)**



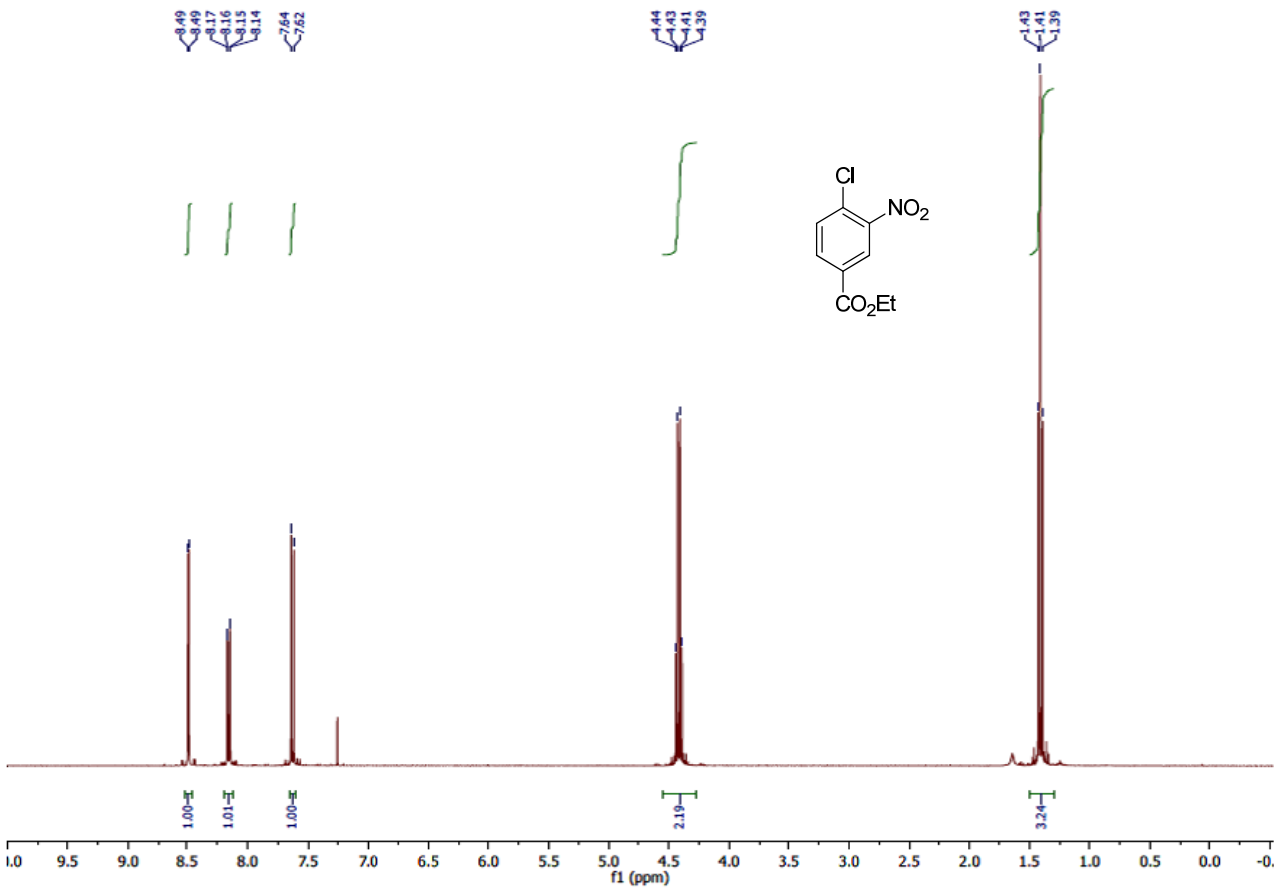
Appendix Figure 149 400 MHz ^{1}H NMR spectrum of 2-chloro-5-nitrobenzoic acid **(225)**



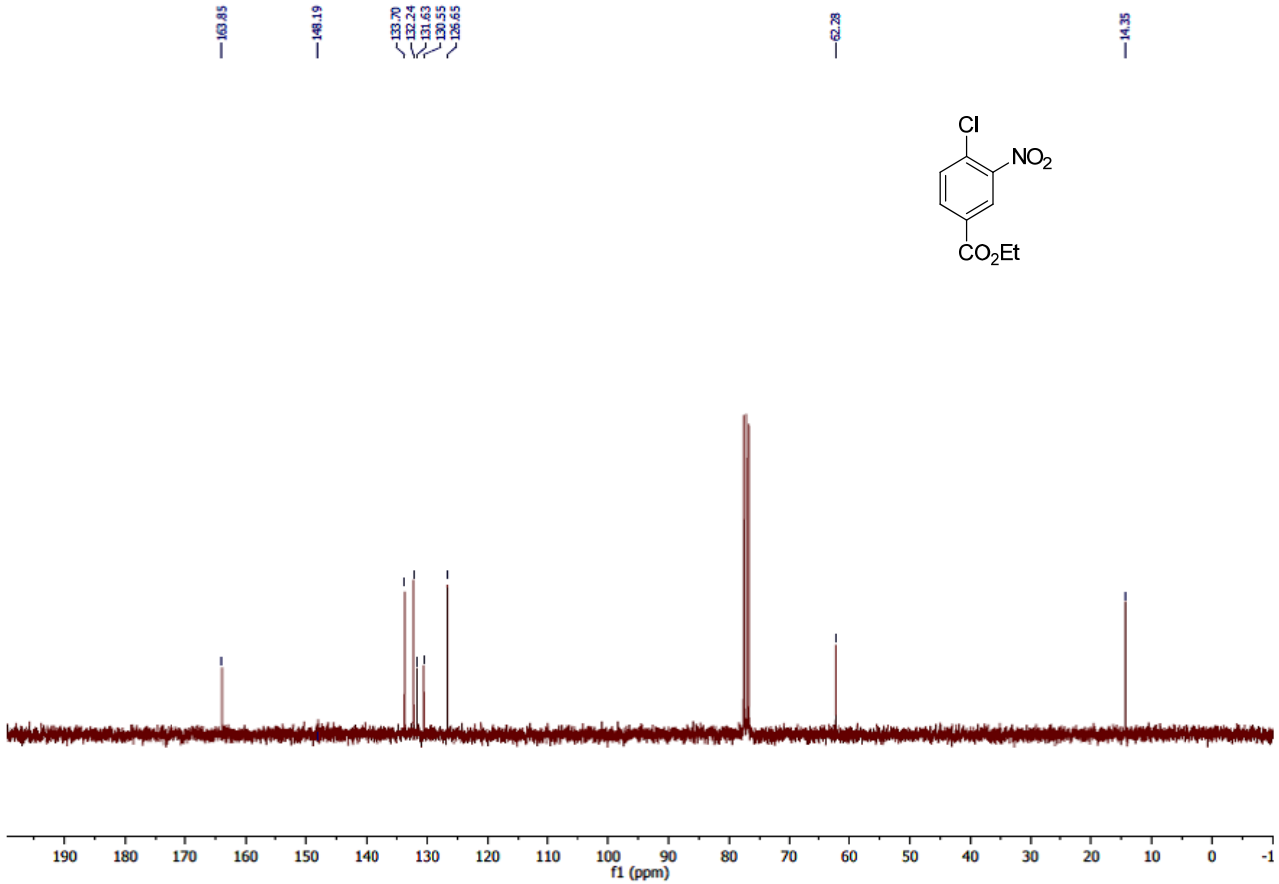
Appendix Figure 150 400 MHz ^{1}H NMR spectrum of ethyl 2-chloro-5-nitrobenzoate **(229)**



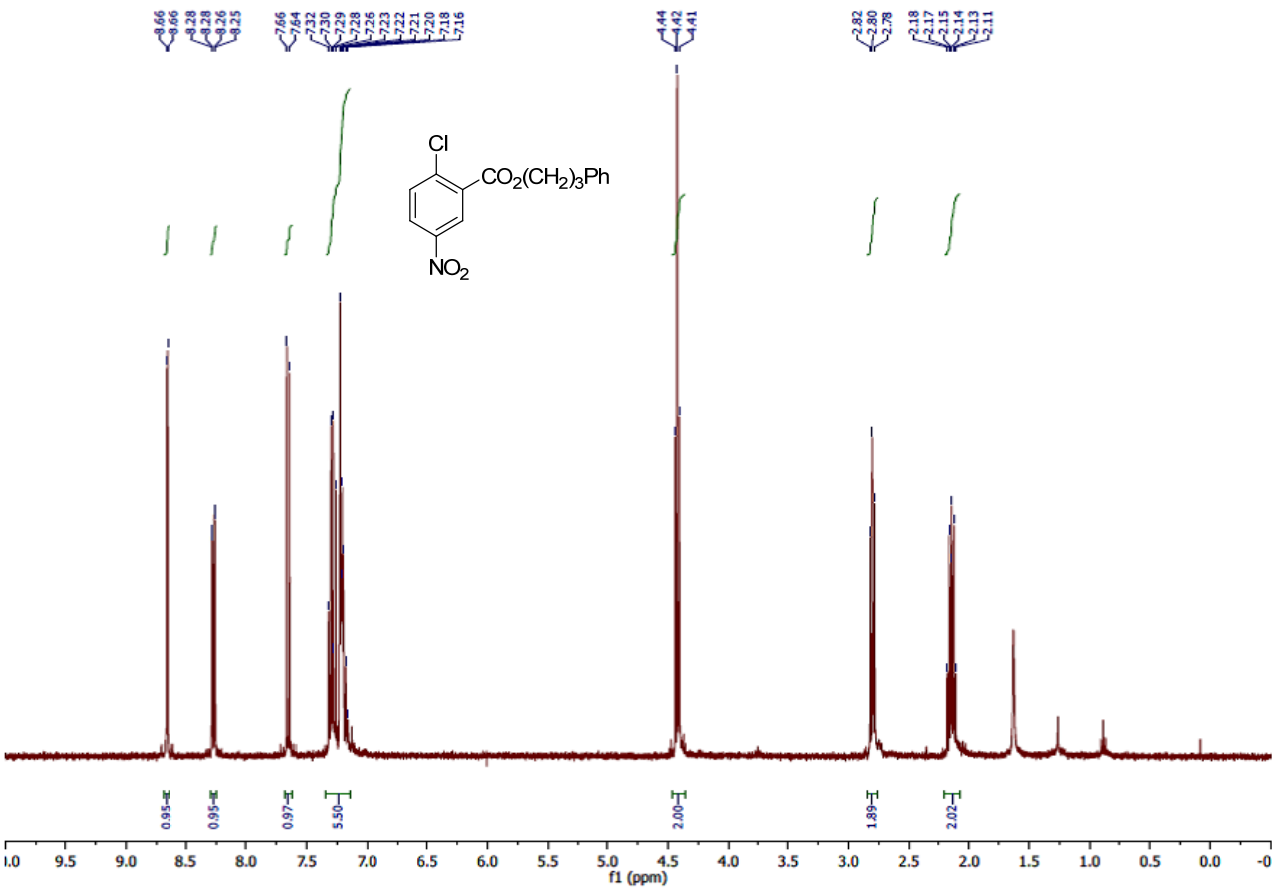
Appendix Figure 151 100 MHz ^{13}C NMR spectrum of ethyl 2-chloro-5-nitrobenzoate **(229)**



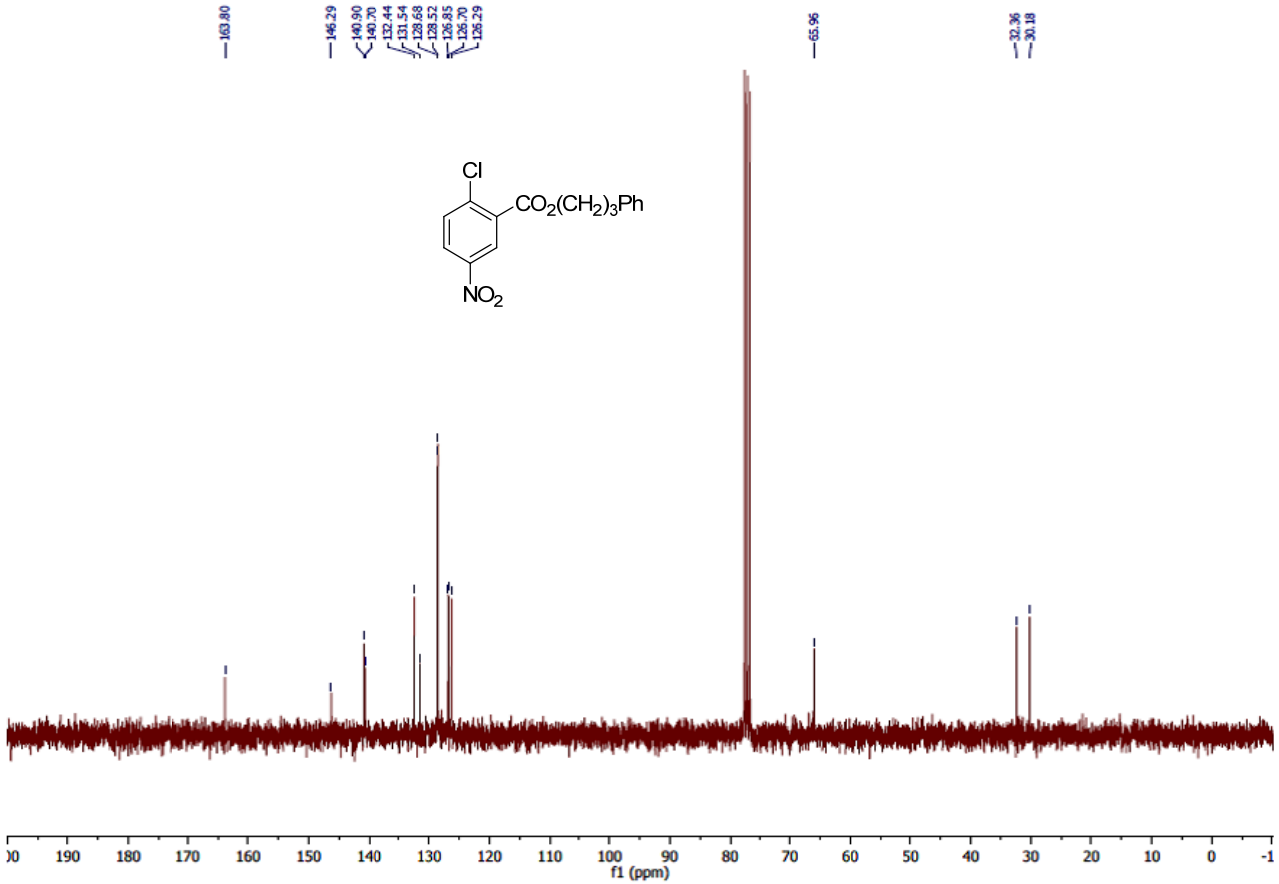
Appendix Figure 152 400 MHz ^{1}H NMR spectrum of ethyl 4-chloro-3-nitrobenzoate **(231)**



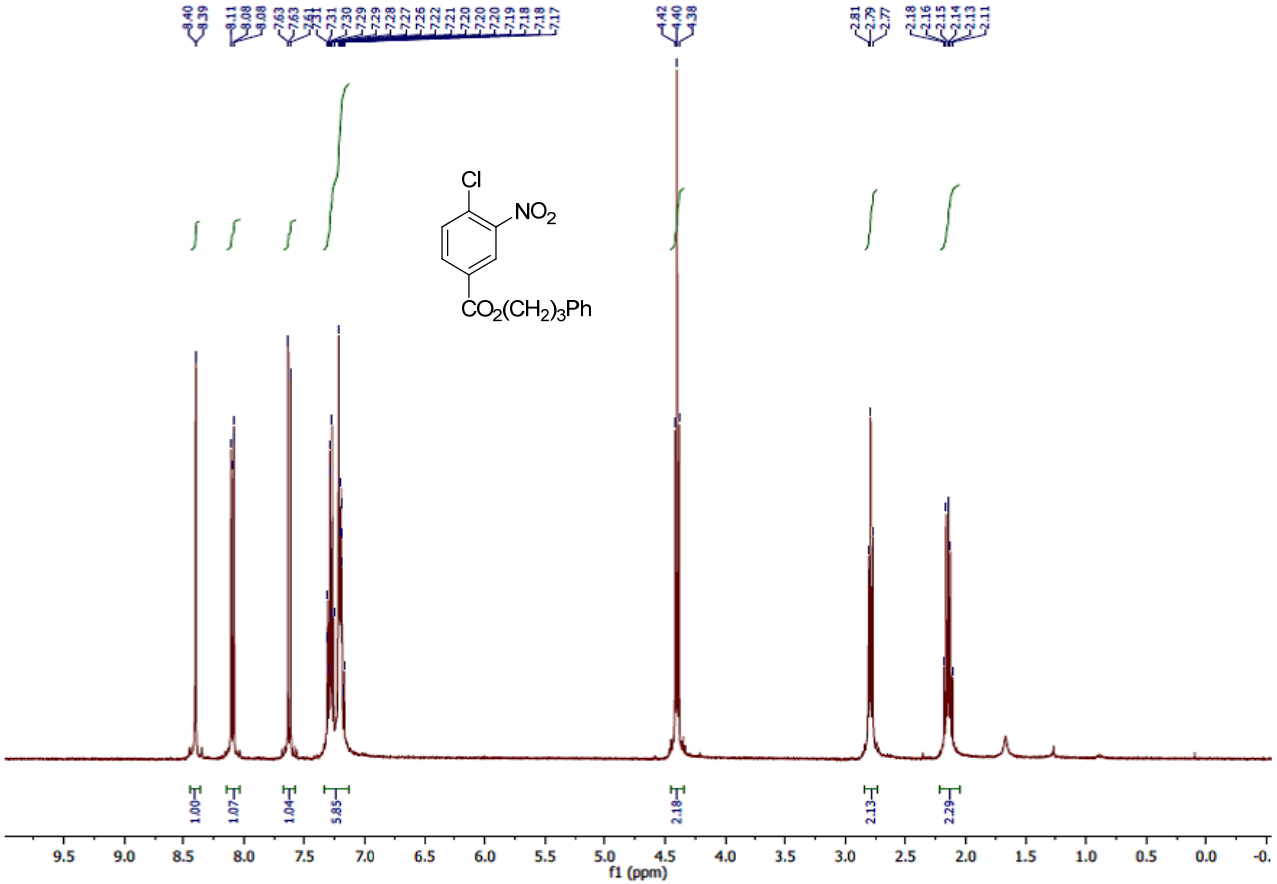
Appendix Figure 153 100 MHz ^{13}C NMR spectrum of ethyl 4-chloro-3-nitrobenzoate **(231)**



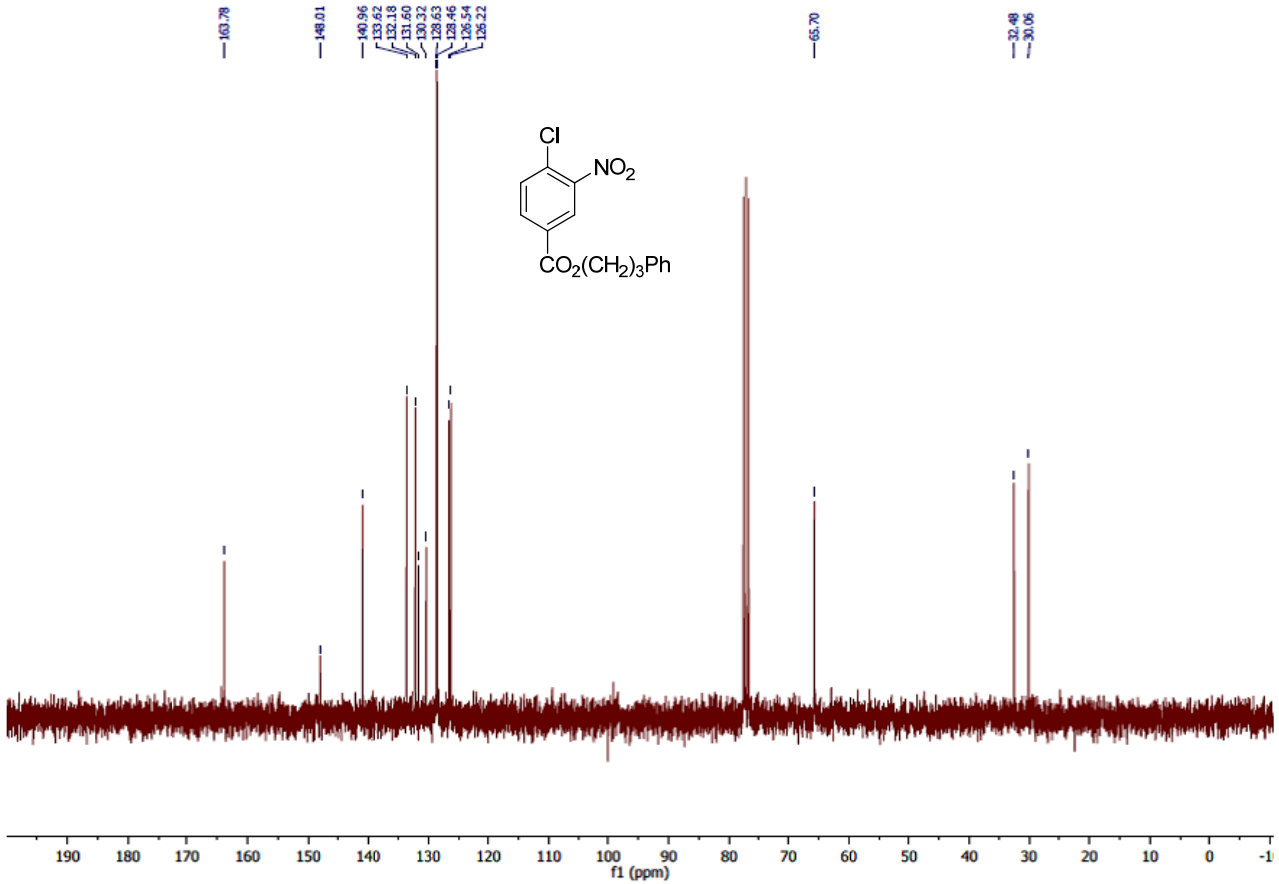
Appendix Figure 154 400 MHz ^{1}H NMR spectrum of 3-phenylpropyl 2-chloro-5-nitrobenzoate **(233)**



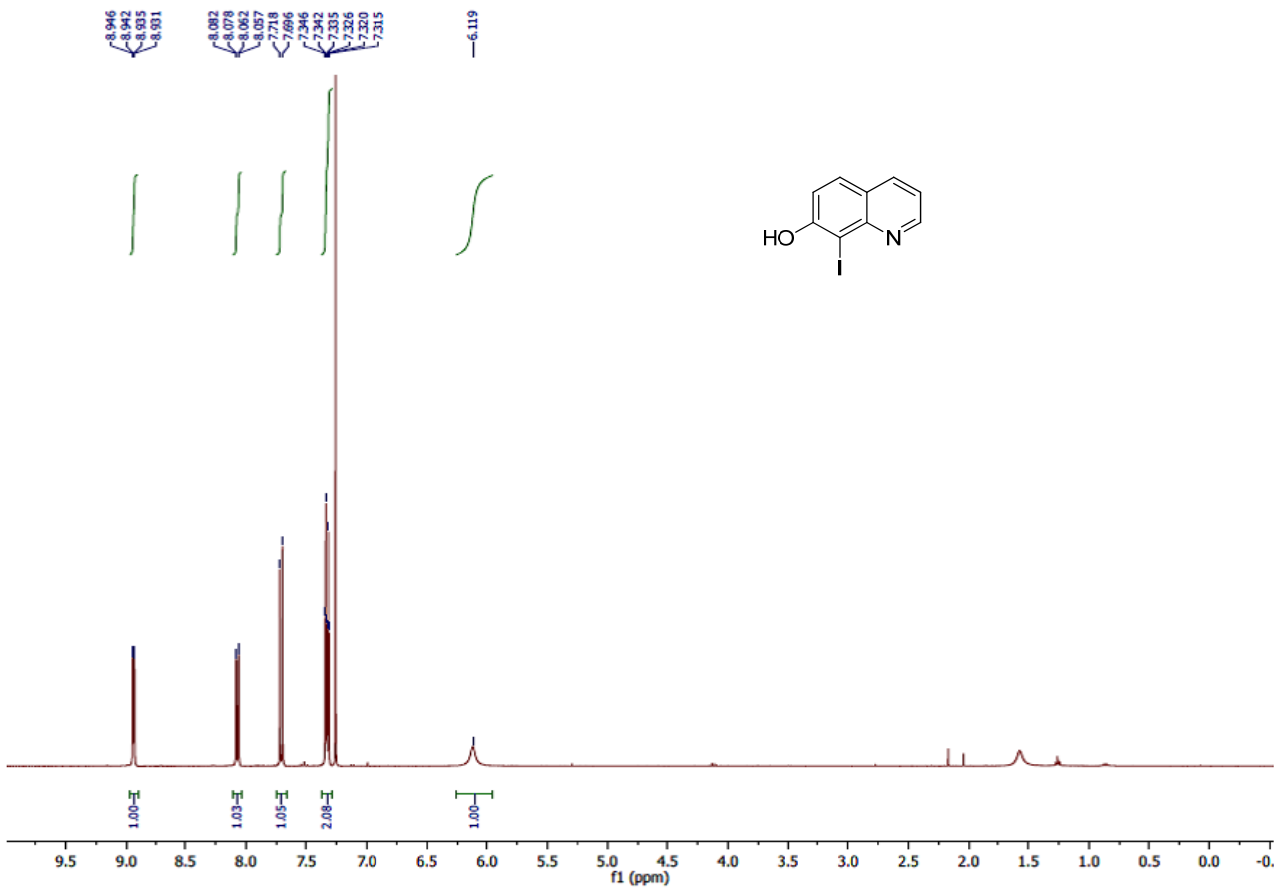
Appendix Figure 155 100 MHz ^{13}C NMR spectrum of 3-phenylpropyl 2-chloro-5-nitrobenzoate **(233)**



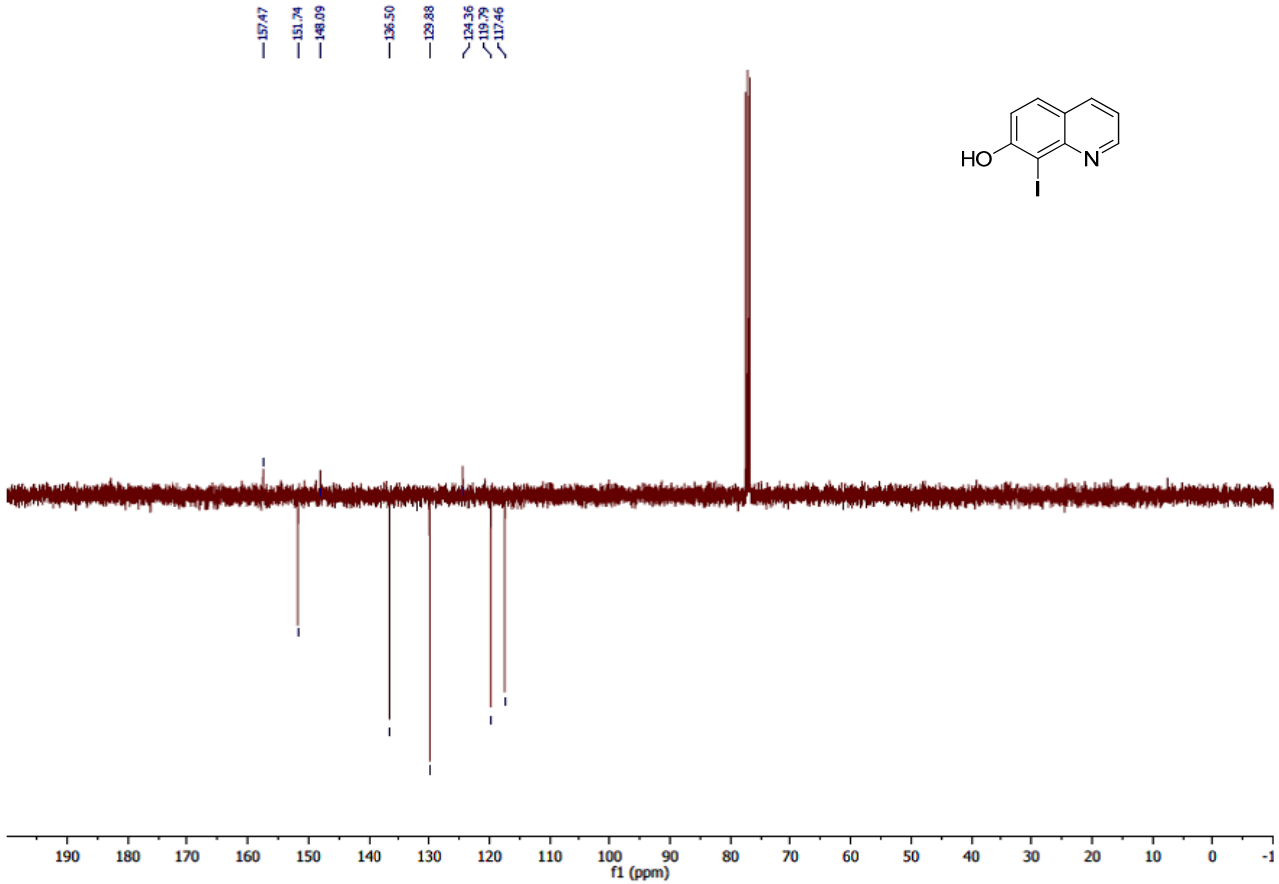
Appendix Figure 156 400 MHz ^{1}H NMR spectrum of 3-phenylpropyl 4-chloro-3-nitrobenzoate **(235)**



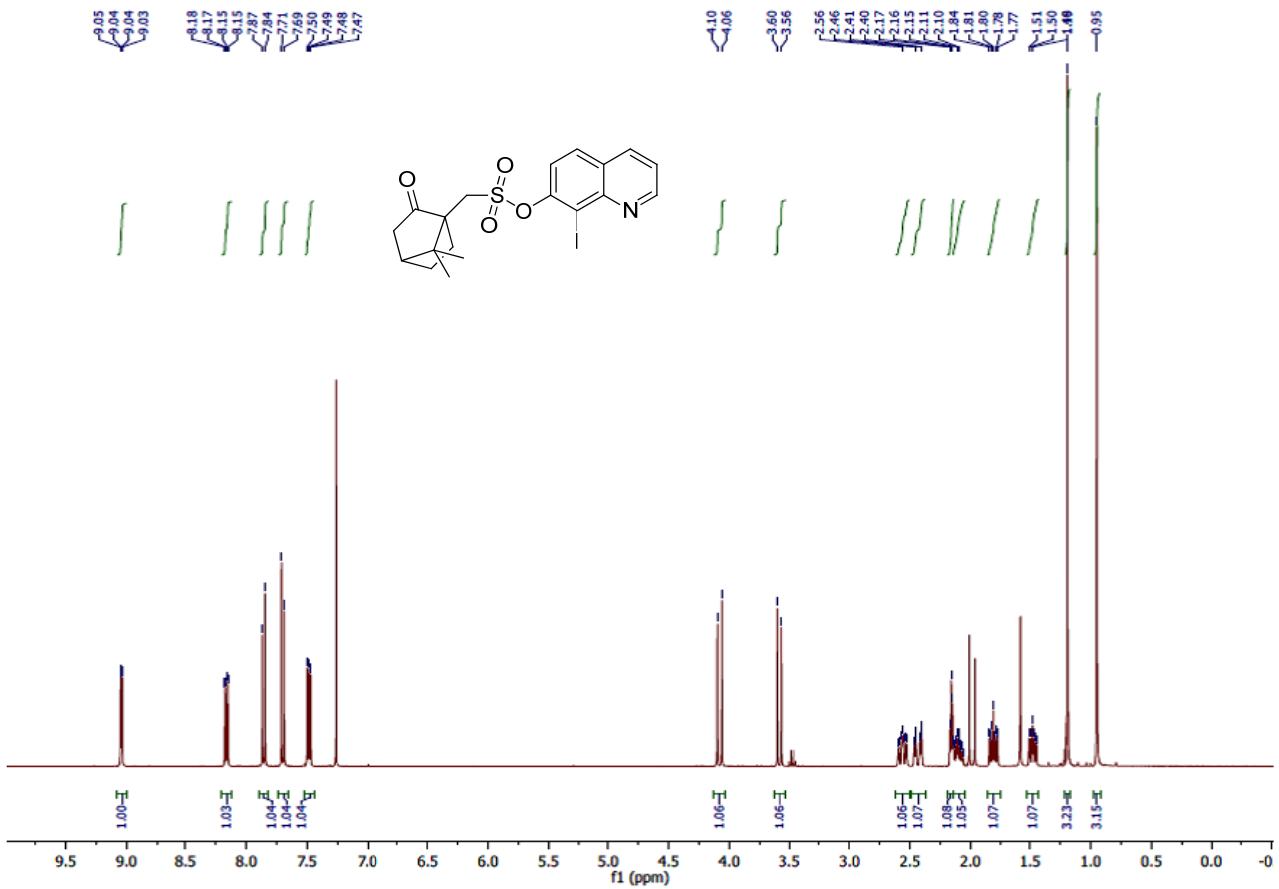
Appendix Figure 157 100 MHz ^{13}C NMR spectrum of 3-phenylpropyl 4-chloro-3-nitrobenzoate **(235)**



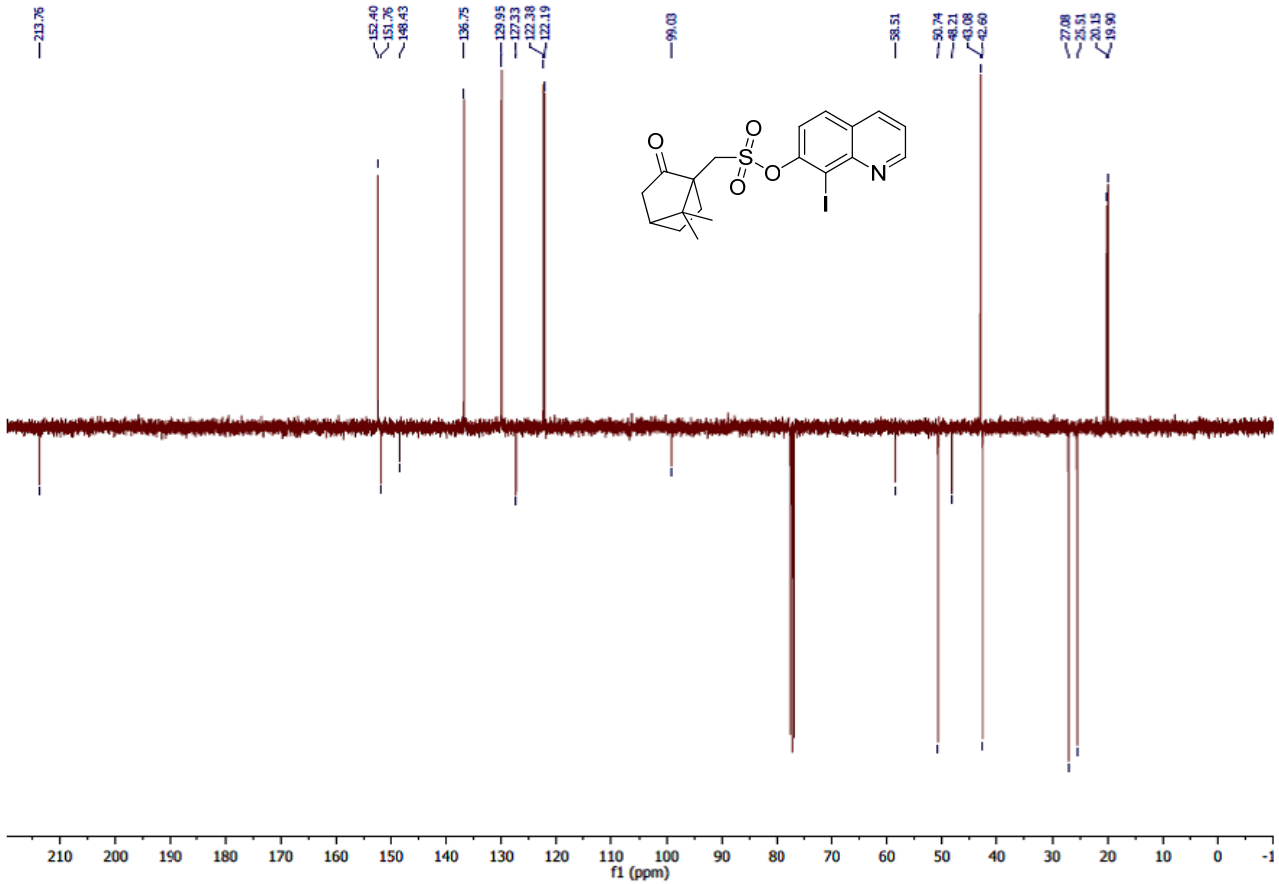
Appendix Figure 158 400 MHz ^{1}H NMR spectrum of 8-iodoquinolin-7-ol **(236)**



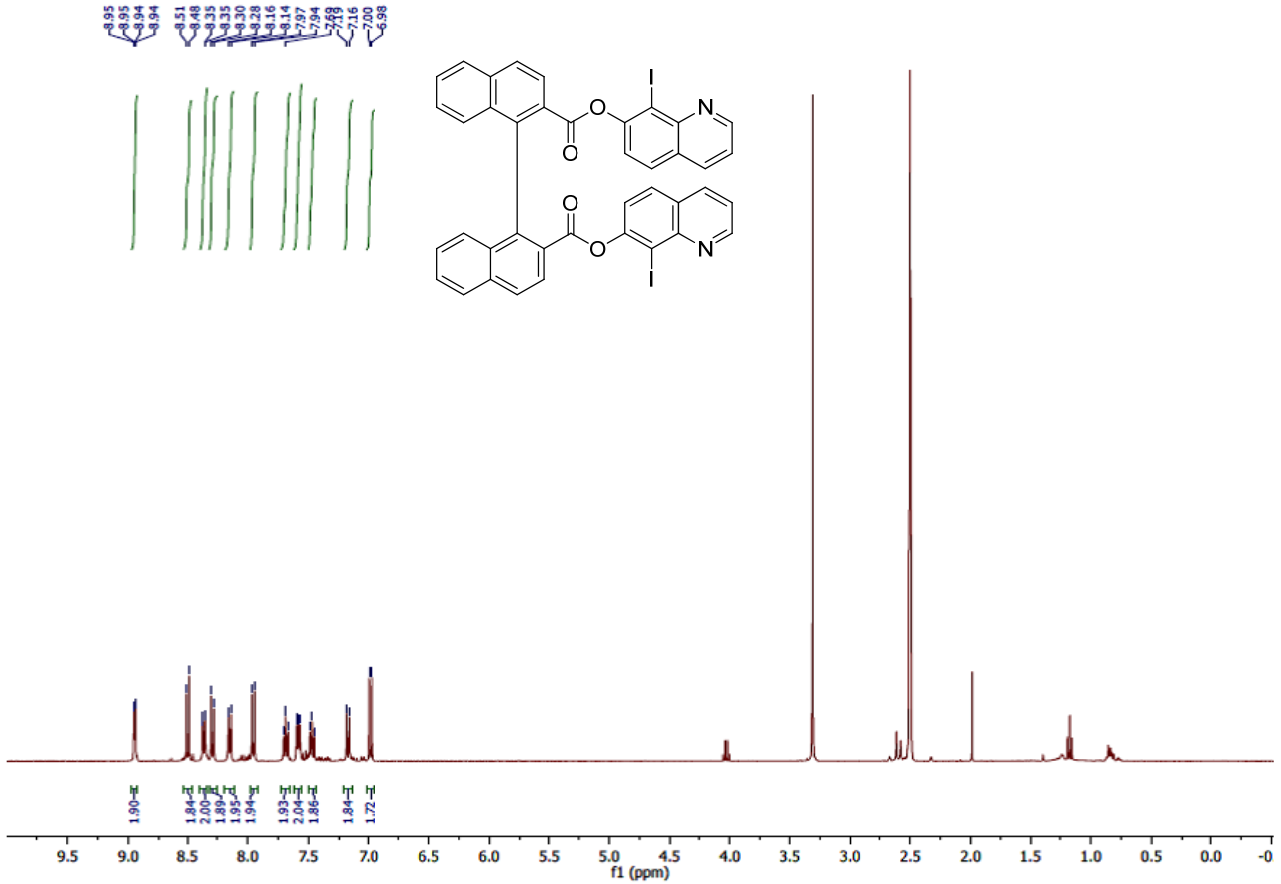
Appendix Figure 159 100 MHz ^{13}C NMR spectrum of 8-iodoquinolin-7-ol **(236)**



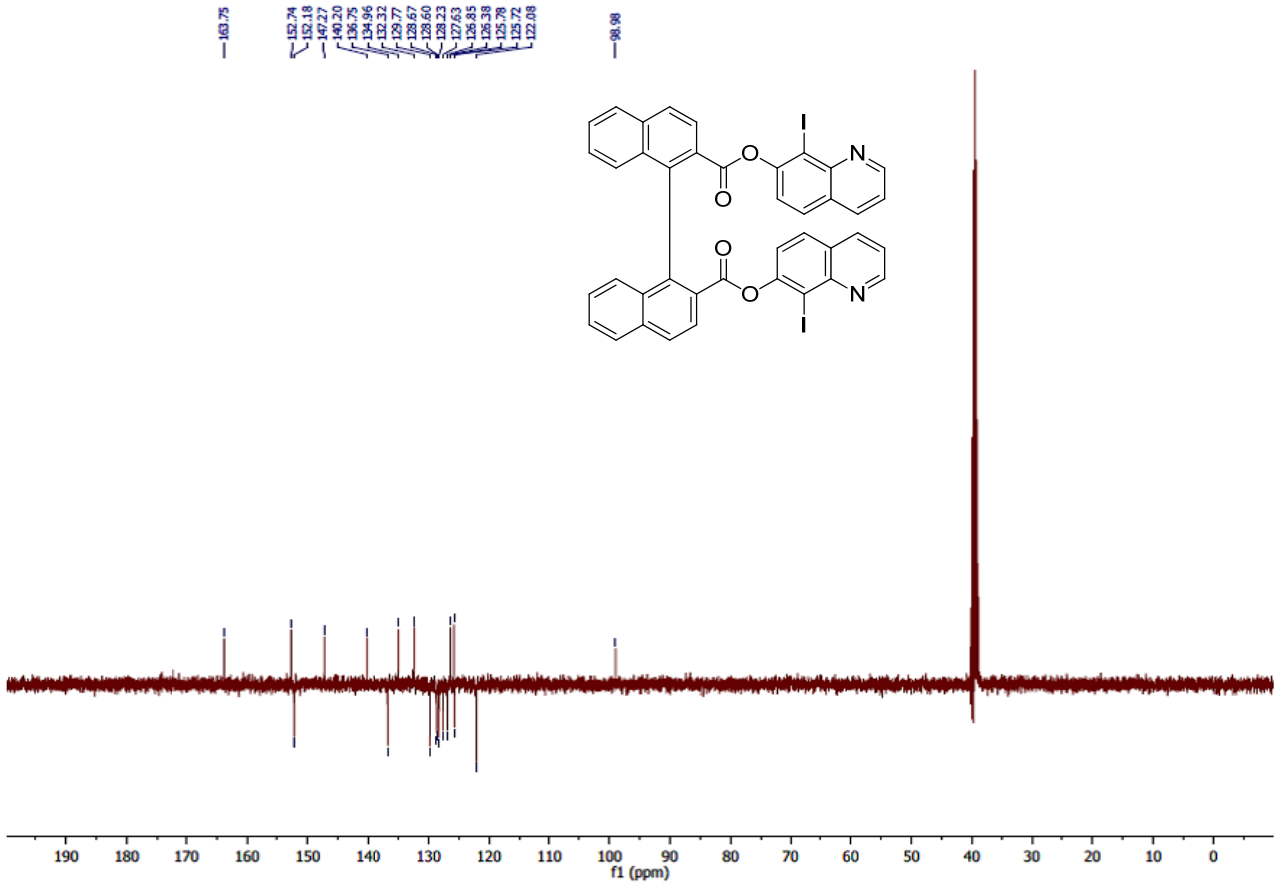
Appendix Figure 160 400 MHz ^{1}H NMR spectrum of 8-iodoquinolin-7-yl (7,7- dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl) methane sulfonate **(240)**



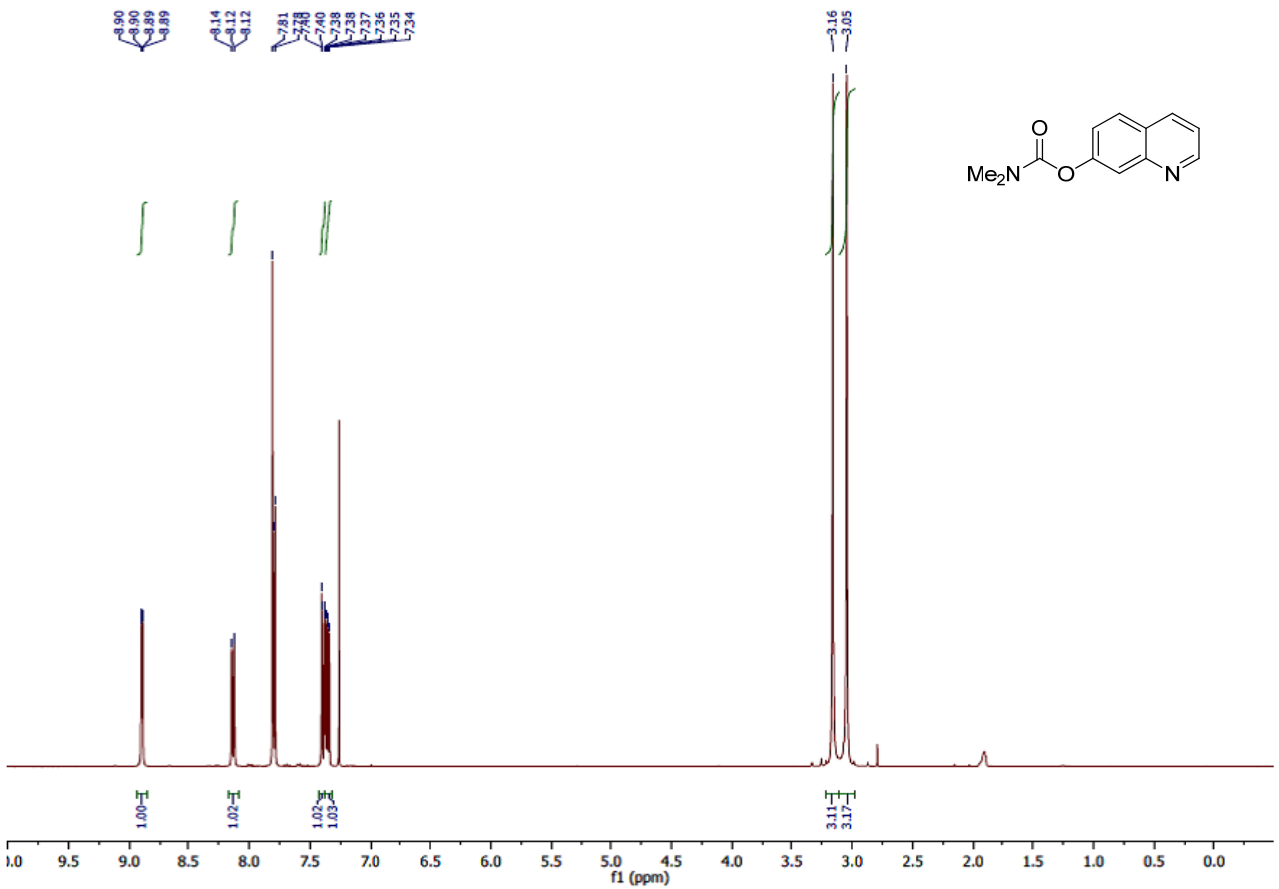
Appendix Figure 161 100 MHz ^{13}C NMR spectrum of 8-iodoquinolin-7-yl (7,7- dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl) methane sulfonate **(240)**



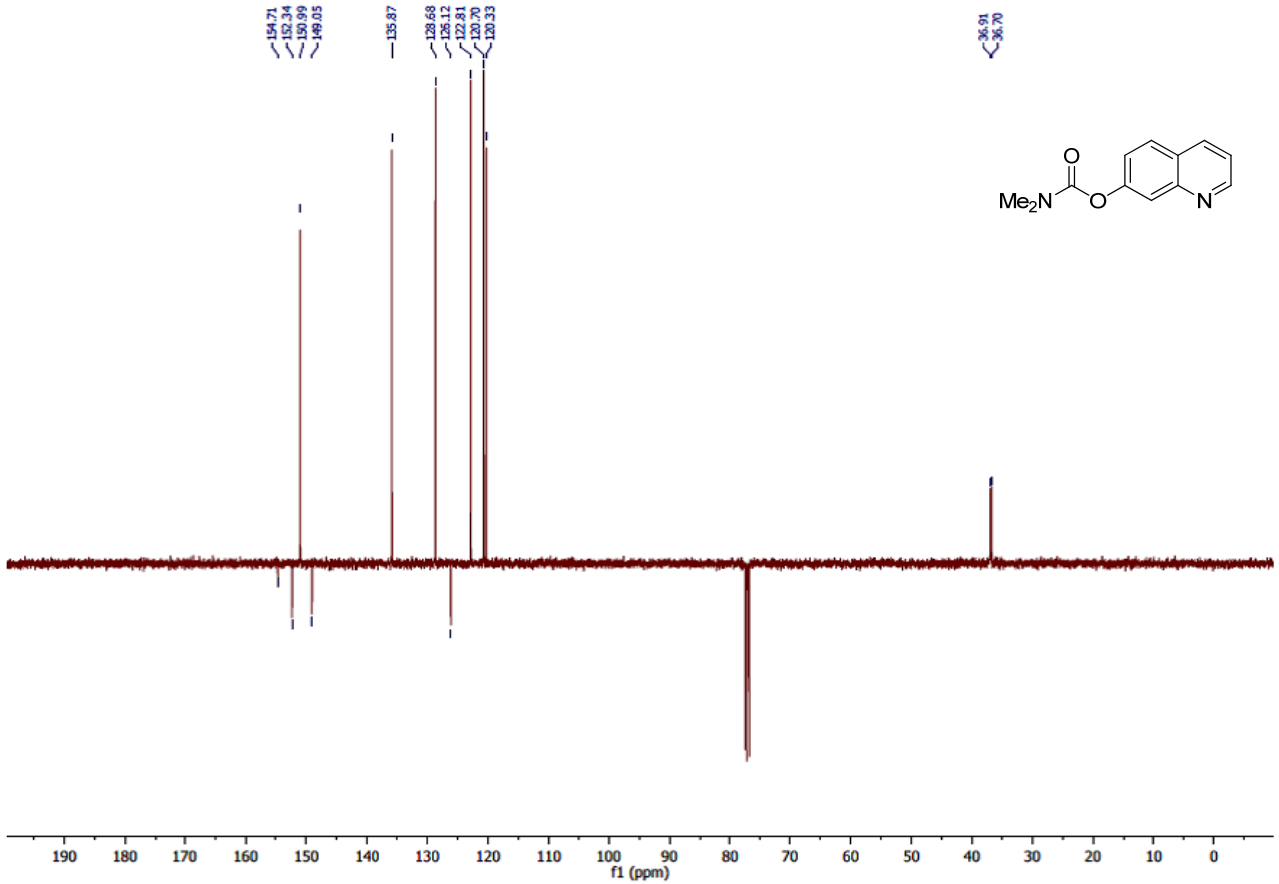
Appendix Figure 162 400 MHz ^{1}H NMR spectrum of bis(8-iodoquinolin-7-yl)[1,1'-binaphthalene]-2,2'-dicarboxylate **(242)**



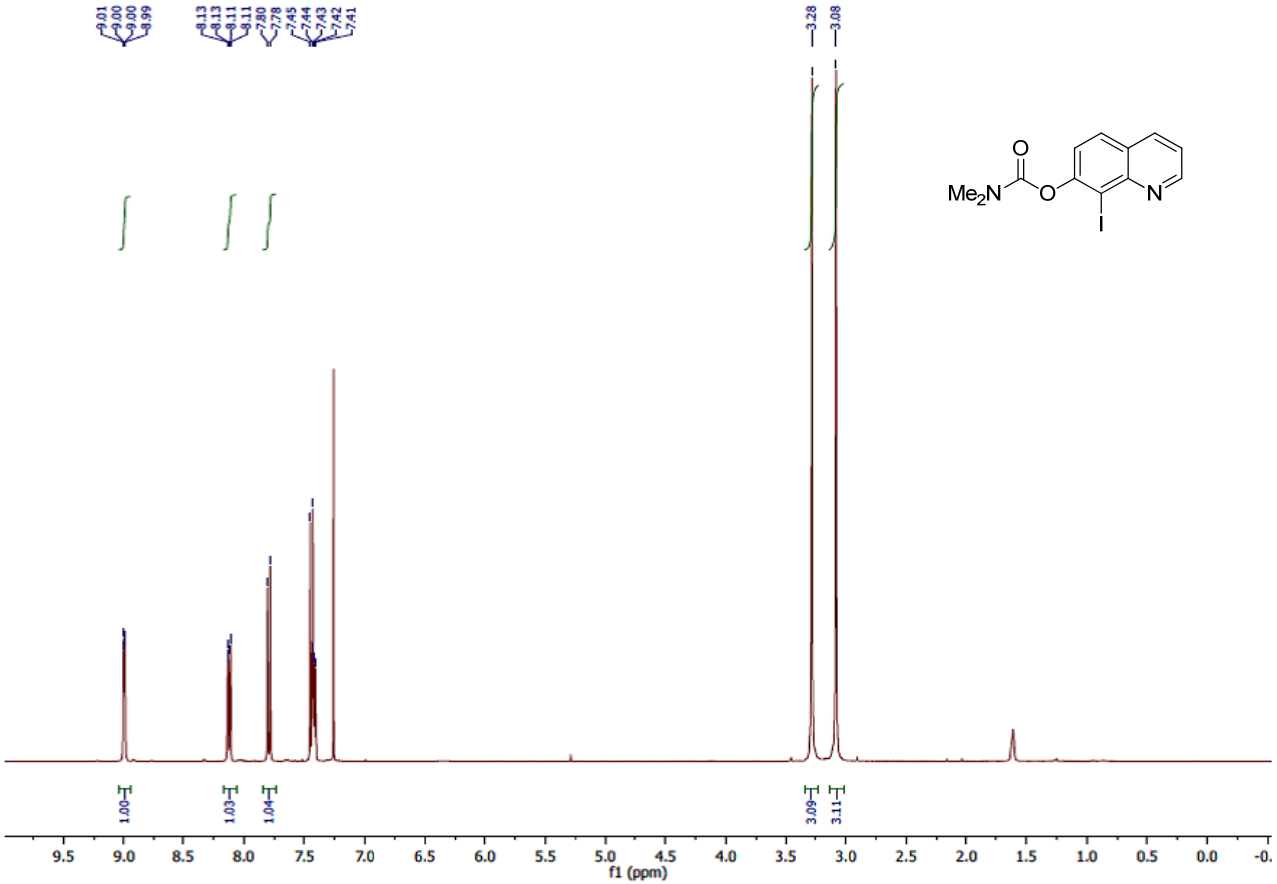
Appendix Figure 163 100 MHz ^{13}C NMR spectrum of bis(8-iodoquinolin-7-yl)[1,1'-binaphthalene]-2,2'-dicarboxylate **(242)**



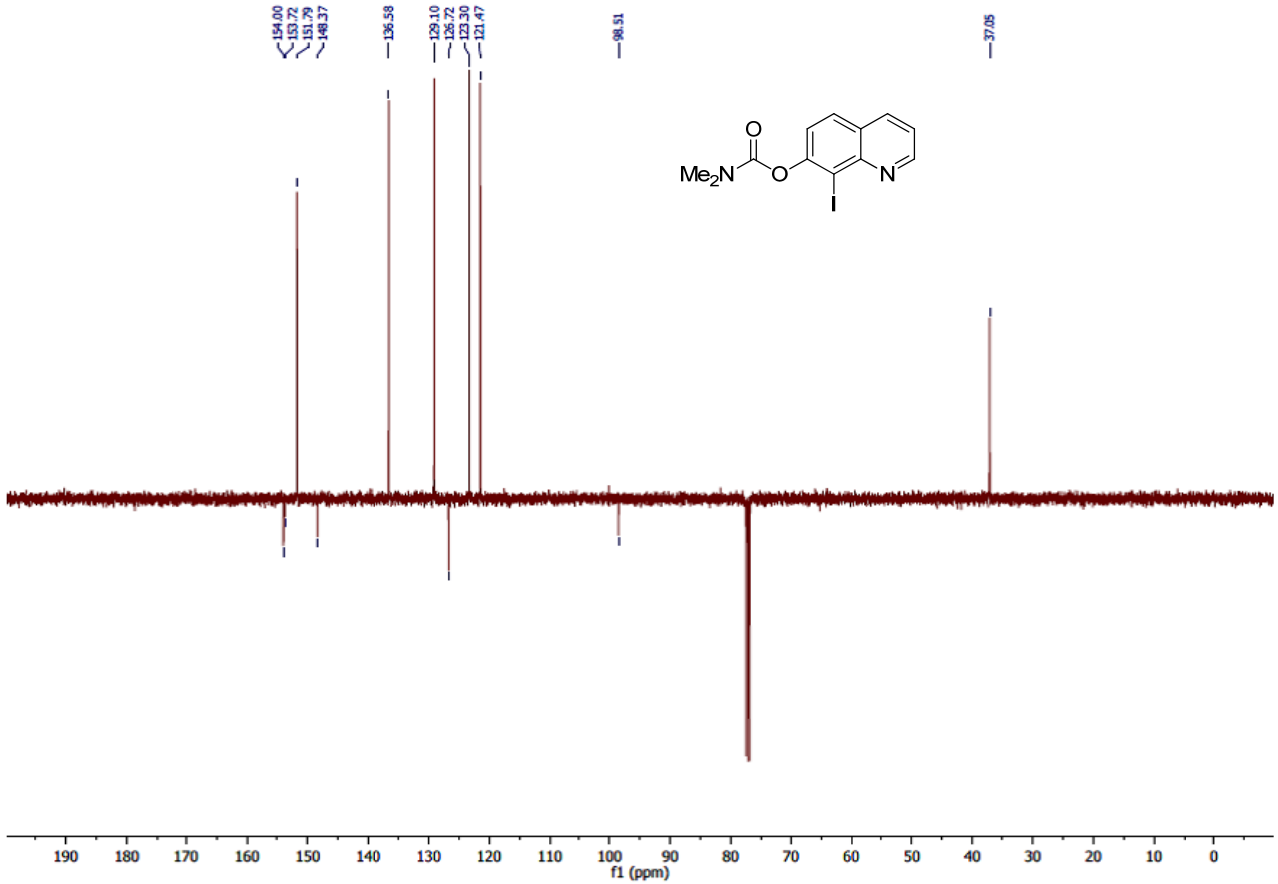
Appendix Figure 164 400 MHz ^{1}H NMR spectrum of quinolin-7-yl dimethyl carbamate **(243)**



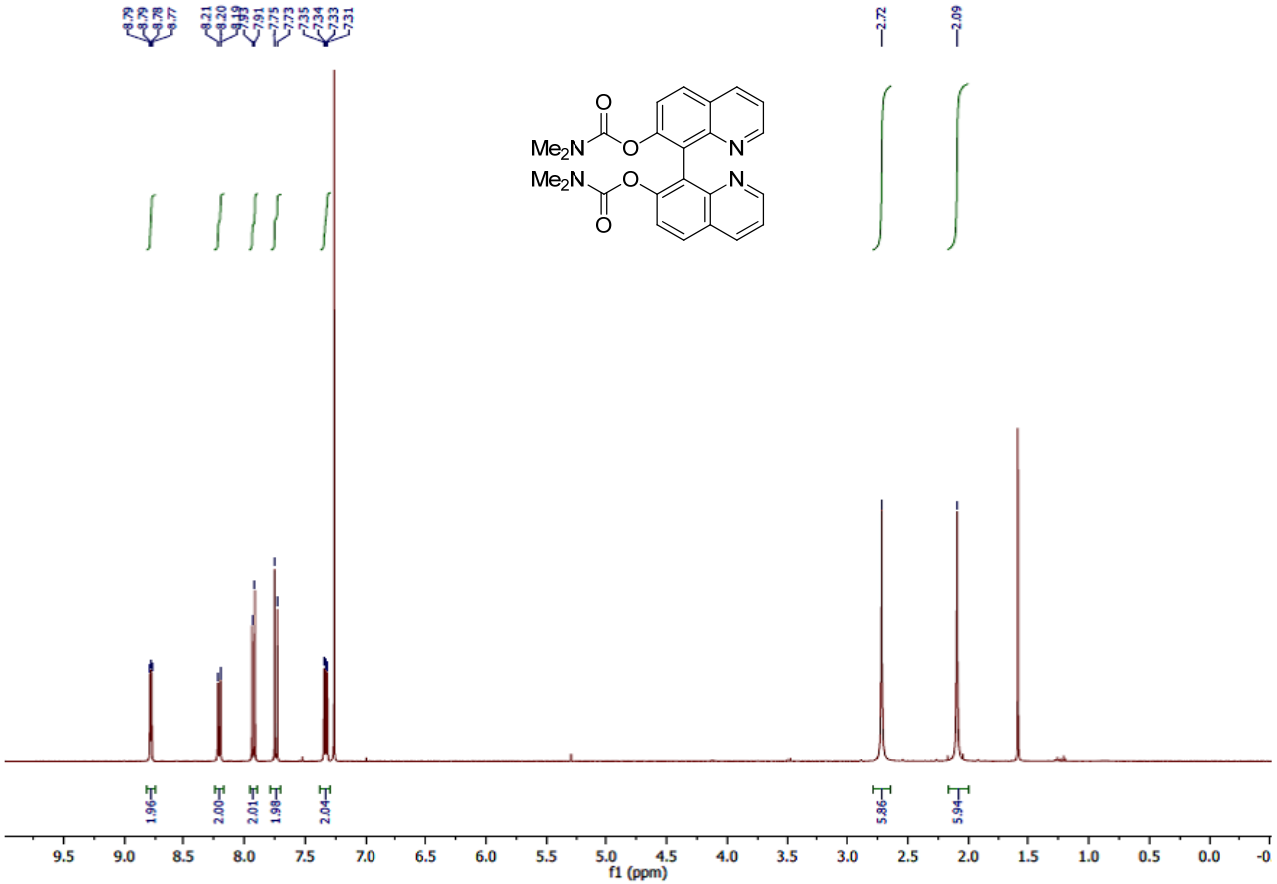
Appendix Figure 165 100 MHz ^{13}C NMR spectrum of quinolin-7-yl dimethyl carbamate **(243)**



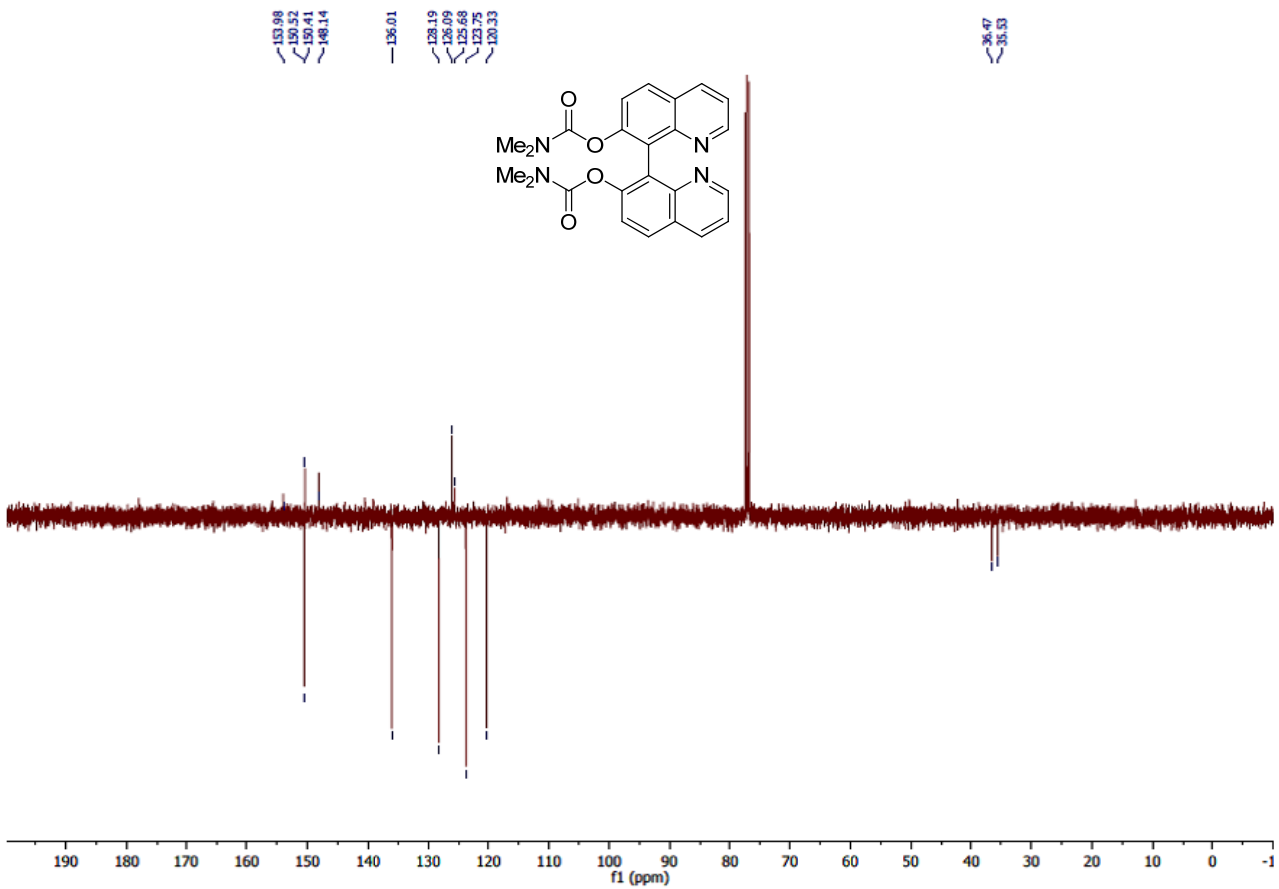
Appendix Figure 166 400 MHz ^{1}H NMR spectrum of 8-iodoquinolin-7-yl dimethylcarbamate **(50)**



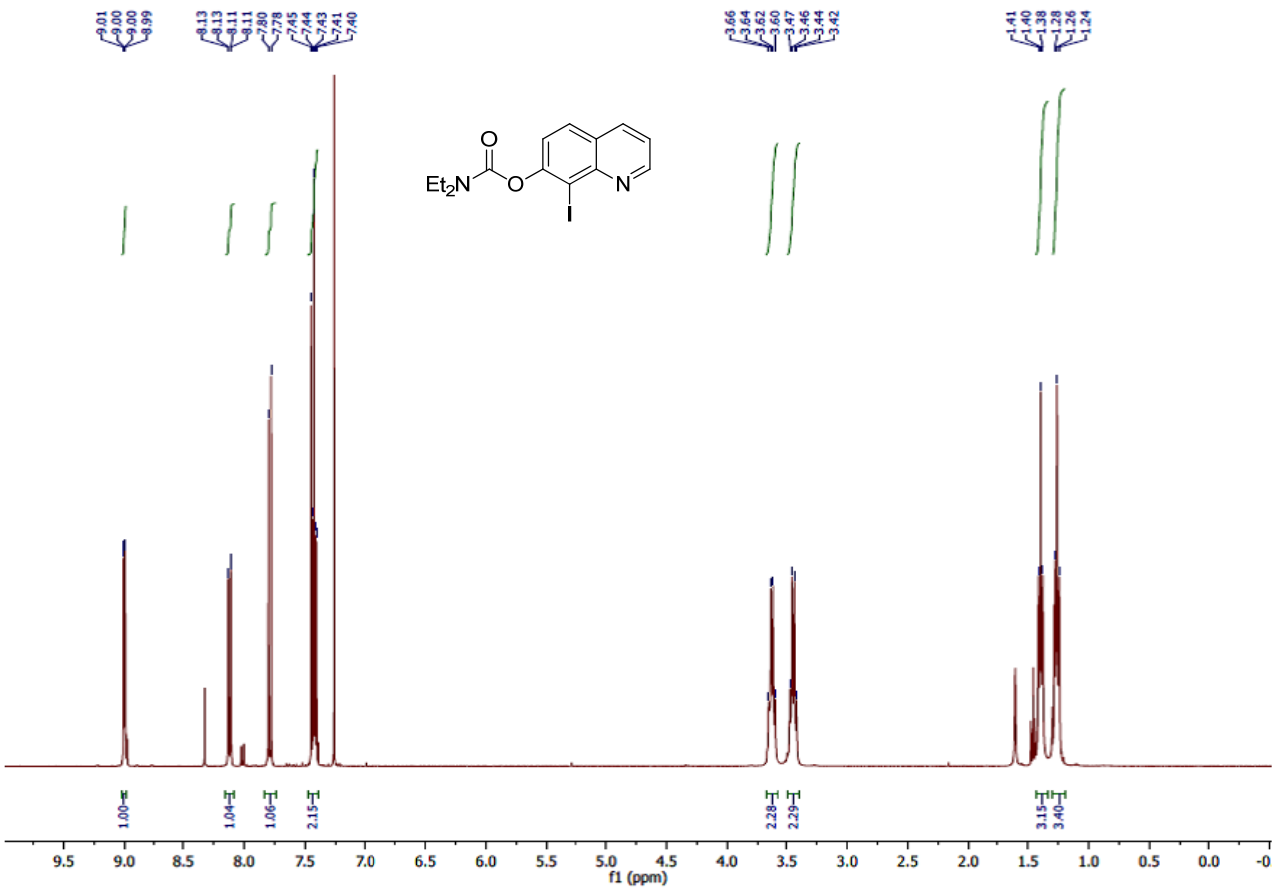
Appendix Figure 167 100 MHz ^{13}C NMR spectrum of 8-iodoquinolin-7-yl dimethylcarbamate **(50)**



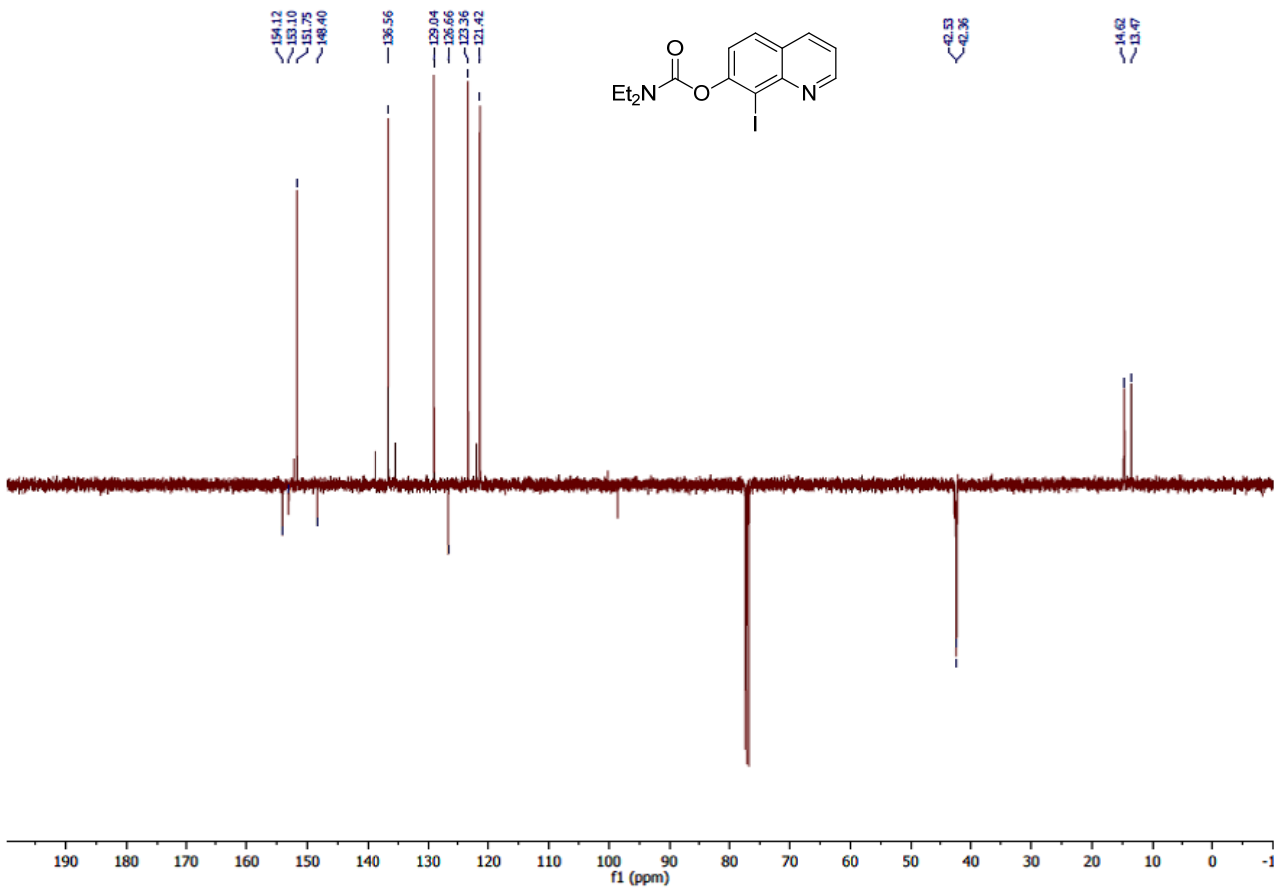
Appendix Figure 168 400 MHz ^{1}H NMR spectrum of [8,8'-biquinoline]-7,7'-diyl bis(dimethylcarbamate) **(51)**



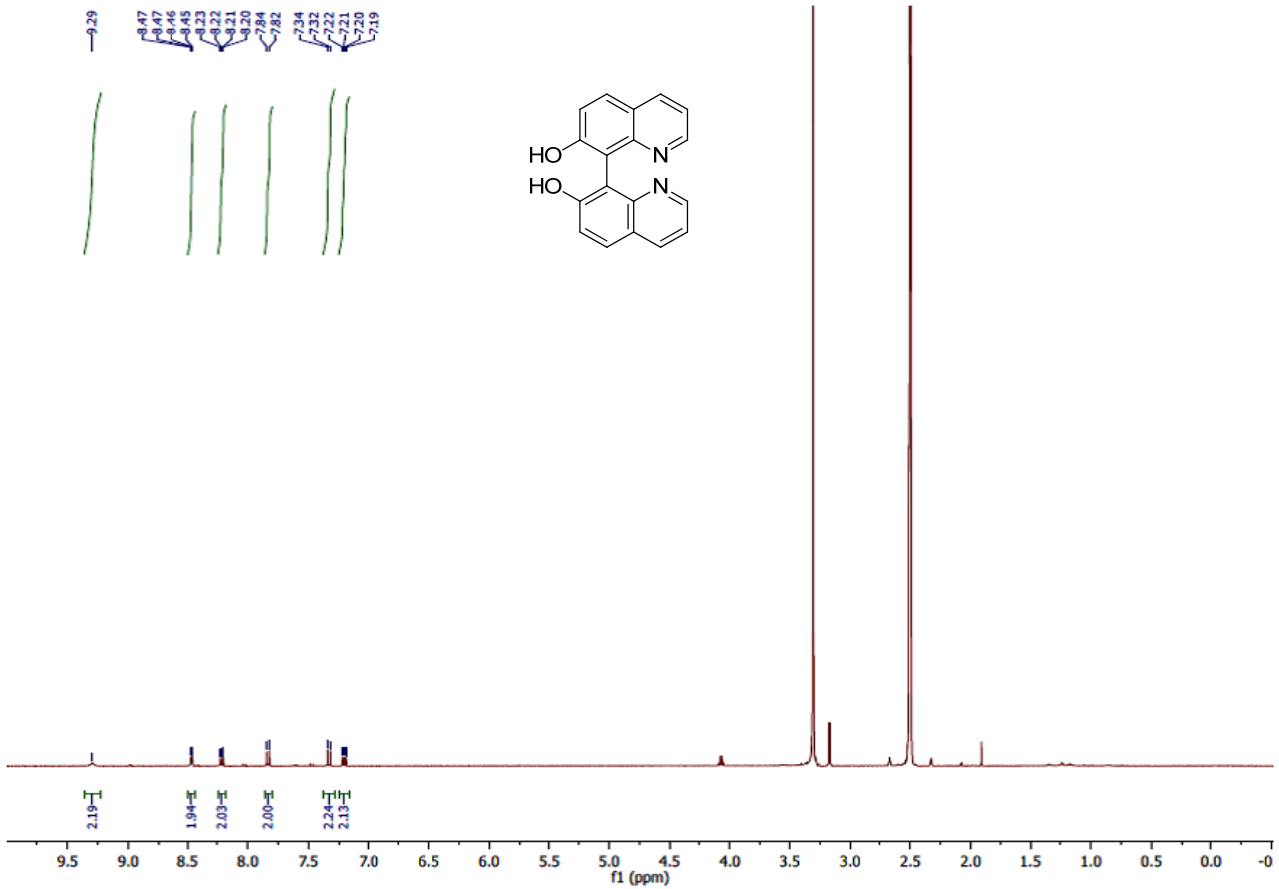
Appendix Figure 169 100 MHz ^{13}C NMR spectrum of [8,8'-biquinoline]-7,7'-diyl bis(dimethylcarbamate) **(51)**



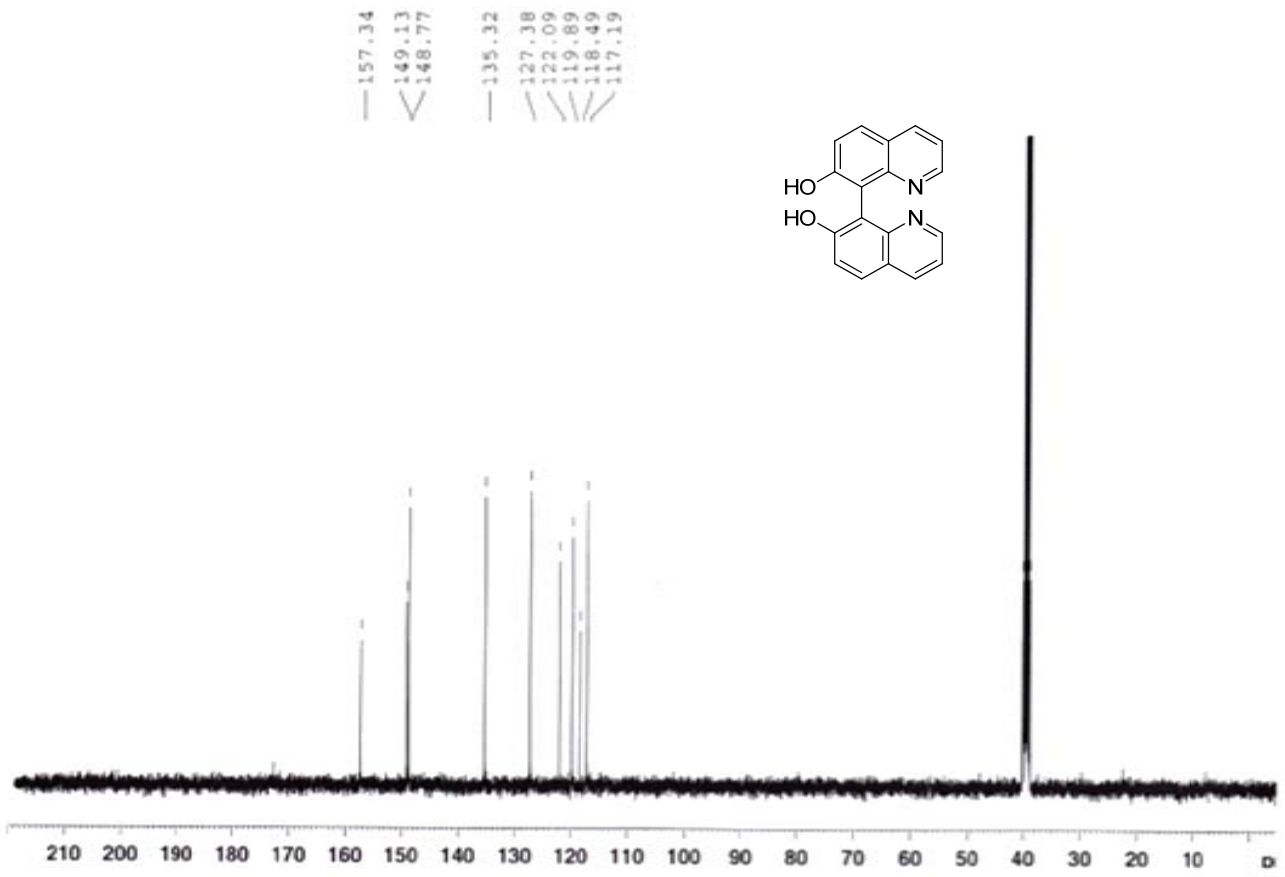
Appendix Figure 170 400 MHz ^{1}H NMR spectrum of 8-iodoquinolin-7-yl diethylcarbamate **(245)**



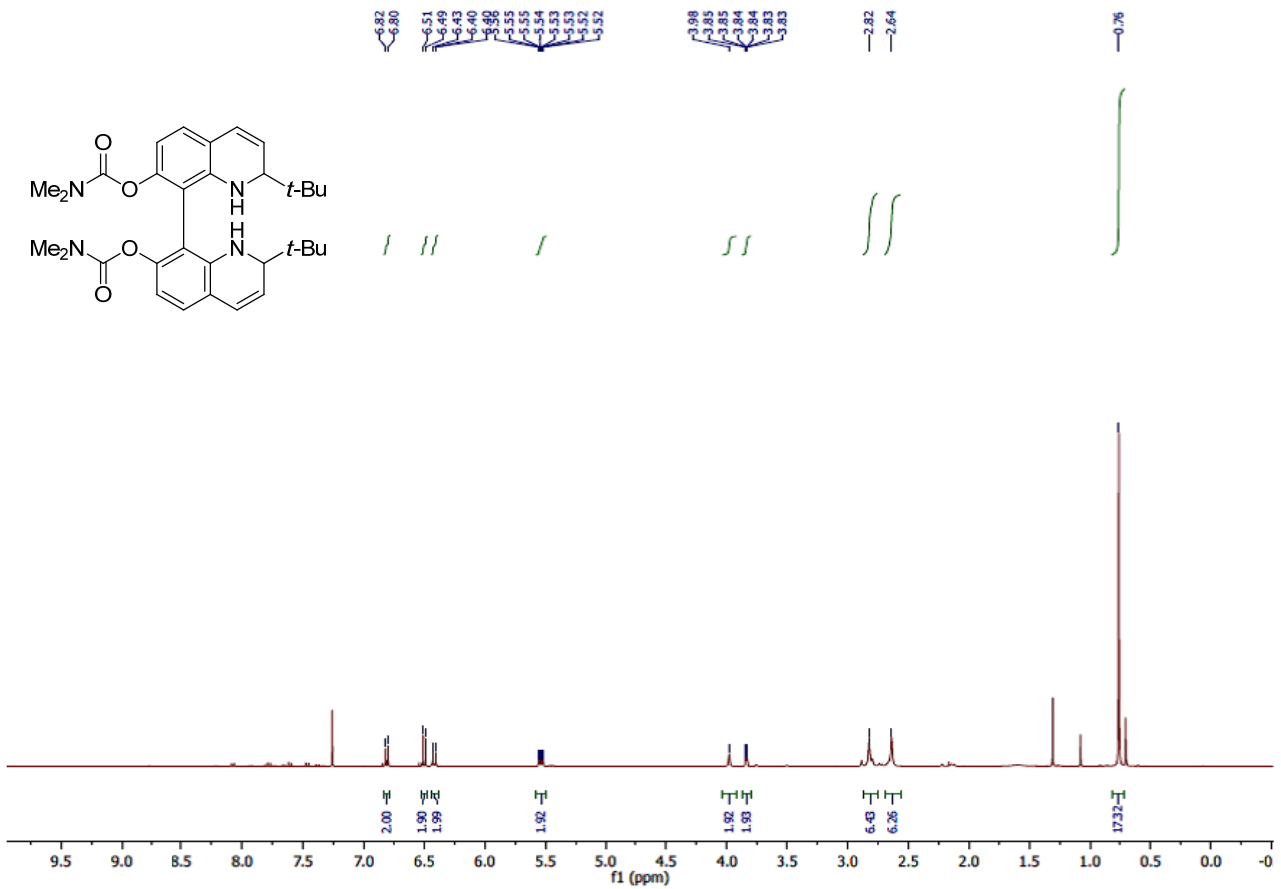
Appendix Figure 171 100 MHz ^{13}C NMR spectrum of 8-iodoquinolin-7-yl diethylcarbamate **(245)**



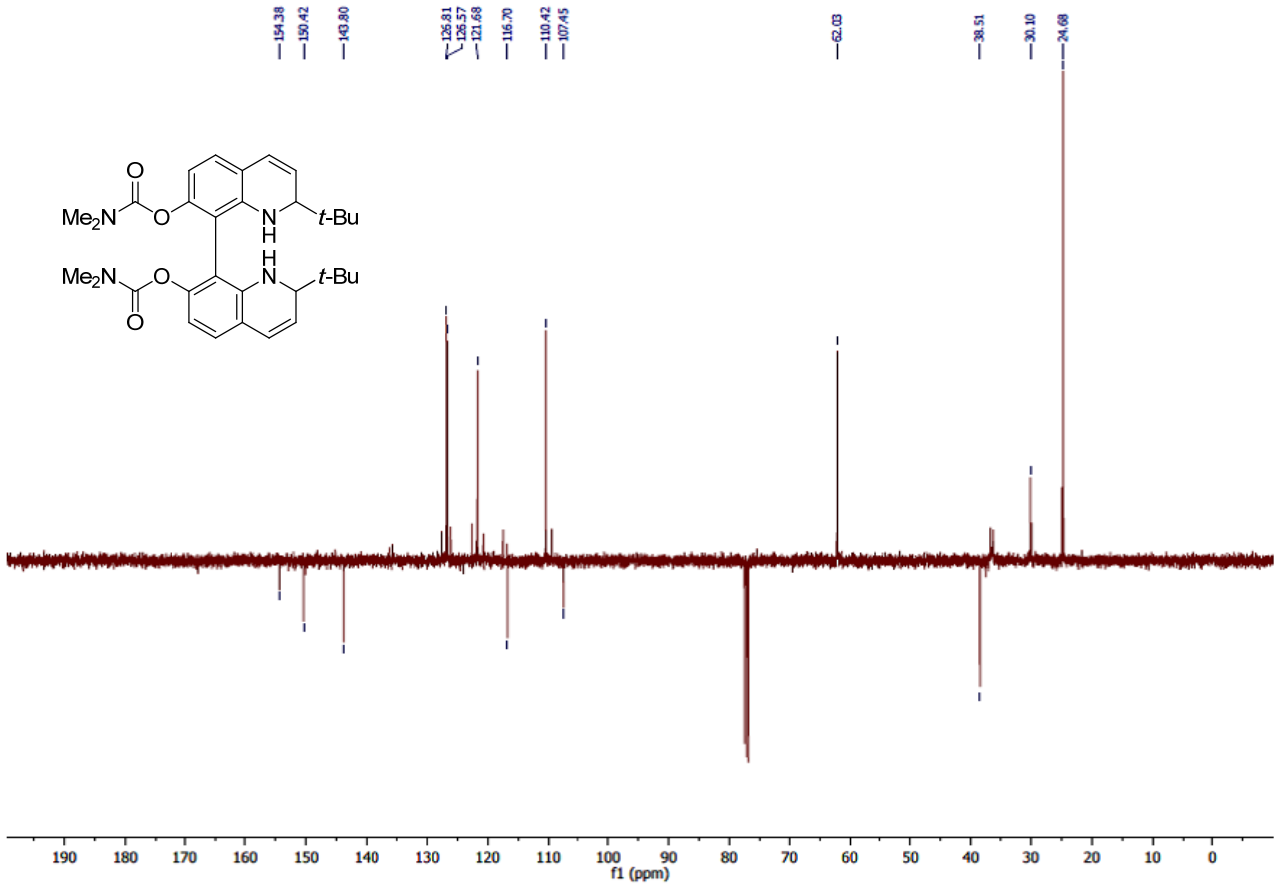
Appendix Figure 172 400 MHz ^{1}H NMR spectrum of [8,8'-biquinoline]-7,7'-diol **(42)**



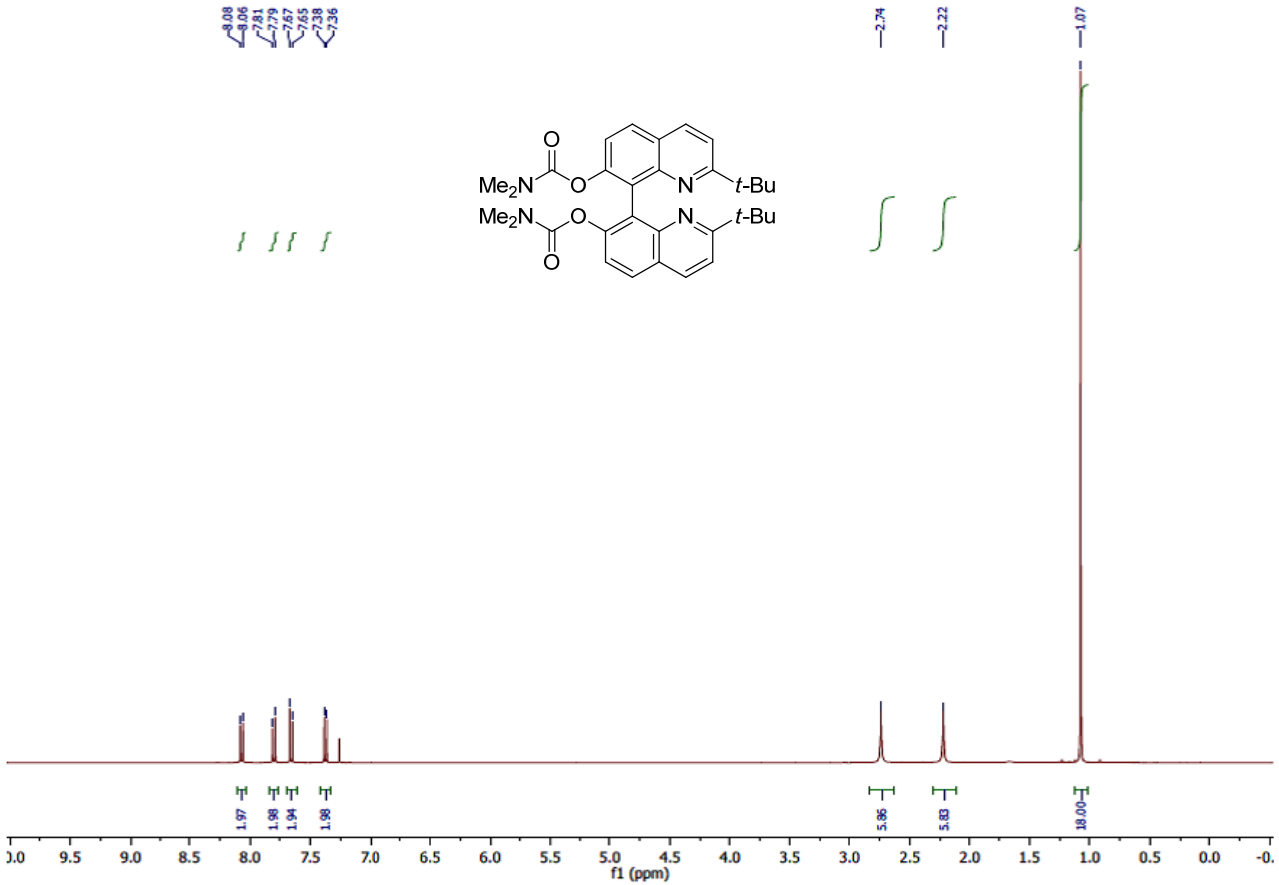
Appendix Figure 173 100 MHz ^{13}C NMR spectrum of [8,8'-biquinoline]-7,7'-diol **(42)**



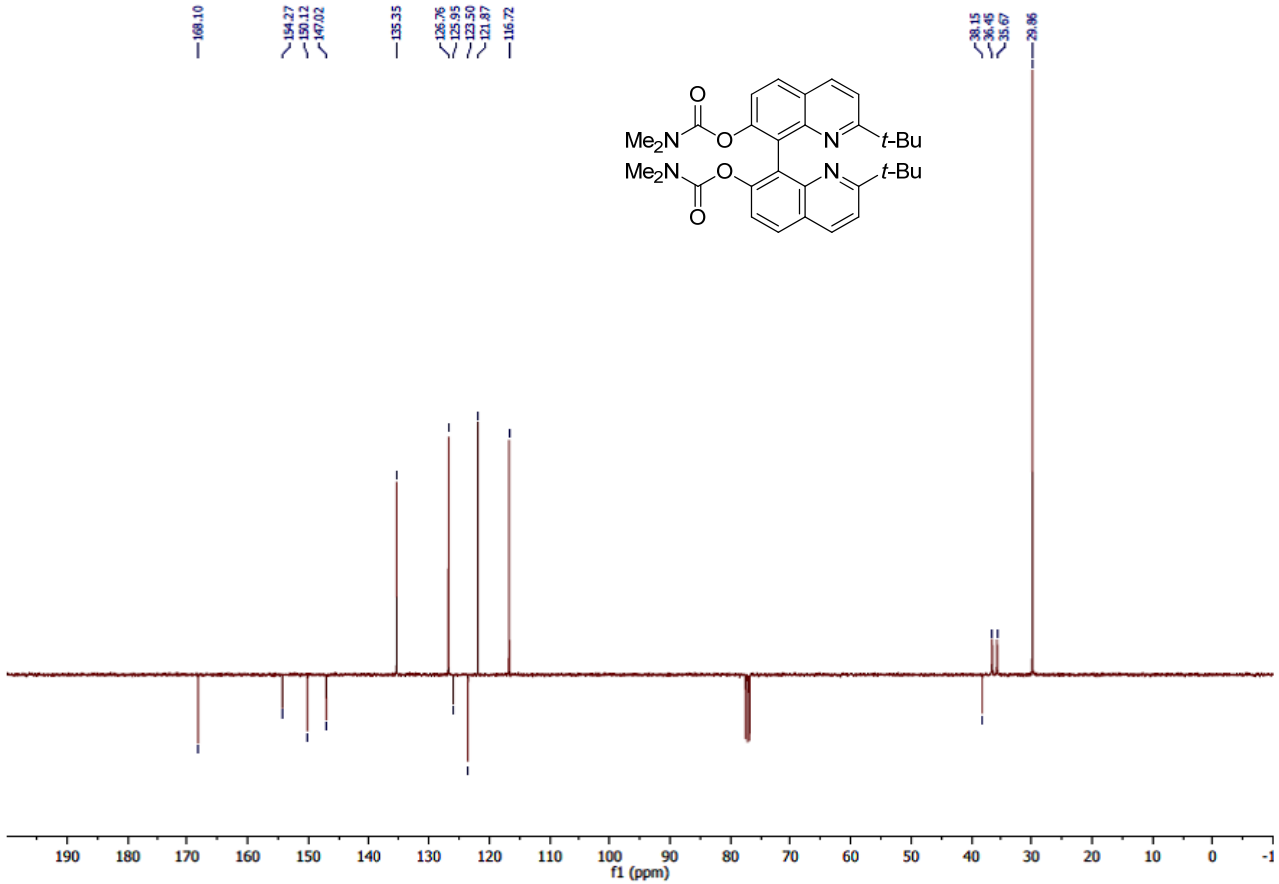
Appendix Figure 174 400 MHz ^{1}H NMR spectrum of 2,2'-di-tert-butyl-1,1',2,2'-tetrahydro-[8,8'-biquinoline]-7,7'-diyl-bis(dimethylcarbamate) **(52)**



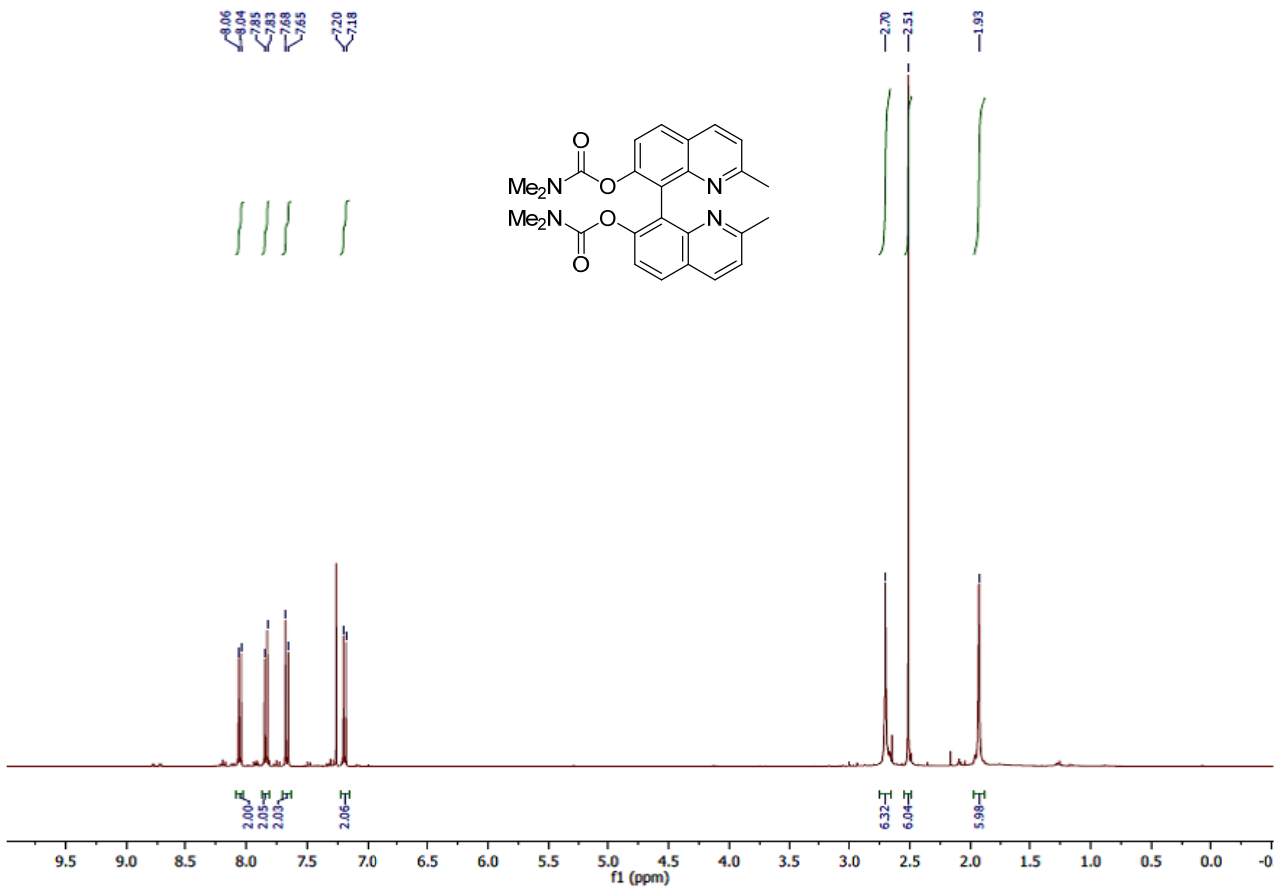
Appendix Figure 175 100 MHz ^{13}C NMR spectrum of 2,2'-di-tert-butyl-1,1',2,2'-tetrahydro-[8,8'-biquinoline]-7,7'-diyl-bis(dimethylcarbamate) **(52)**



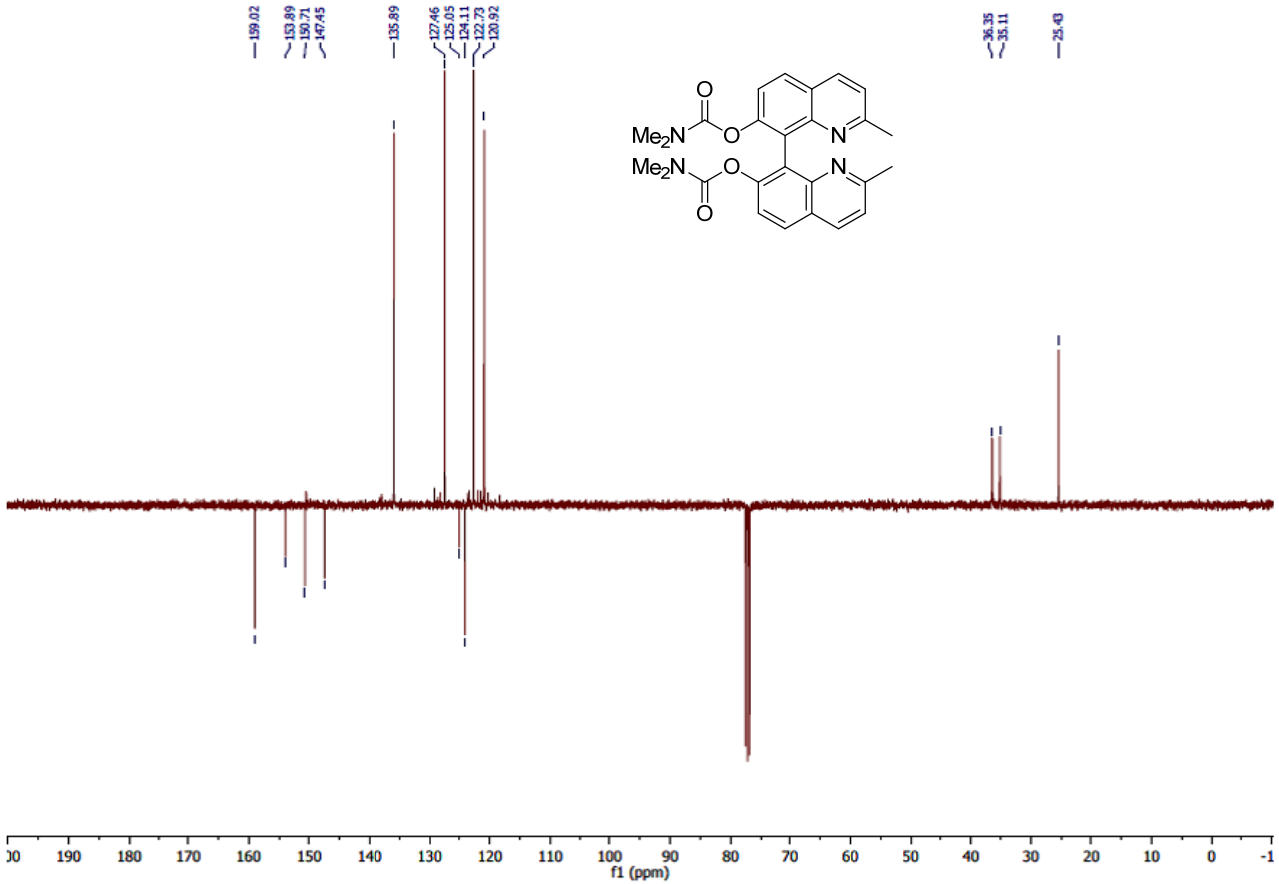
Appendix Figure 176 400 MHz ^{1}H NMR spectrum of 2,2'-di-tert-butyl-[8,8'-biquinoline]-7,7'-diyl bis(dimethylcarbamate) **(248)**



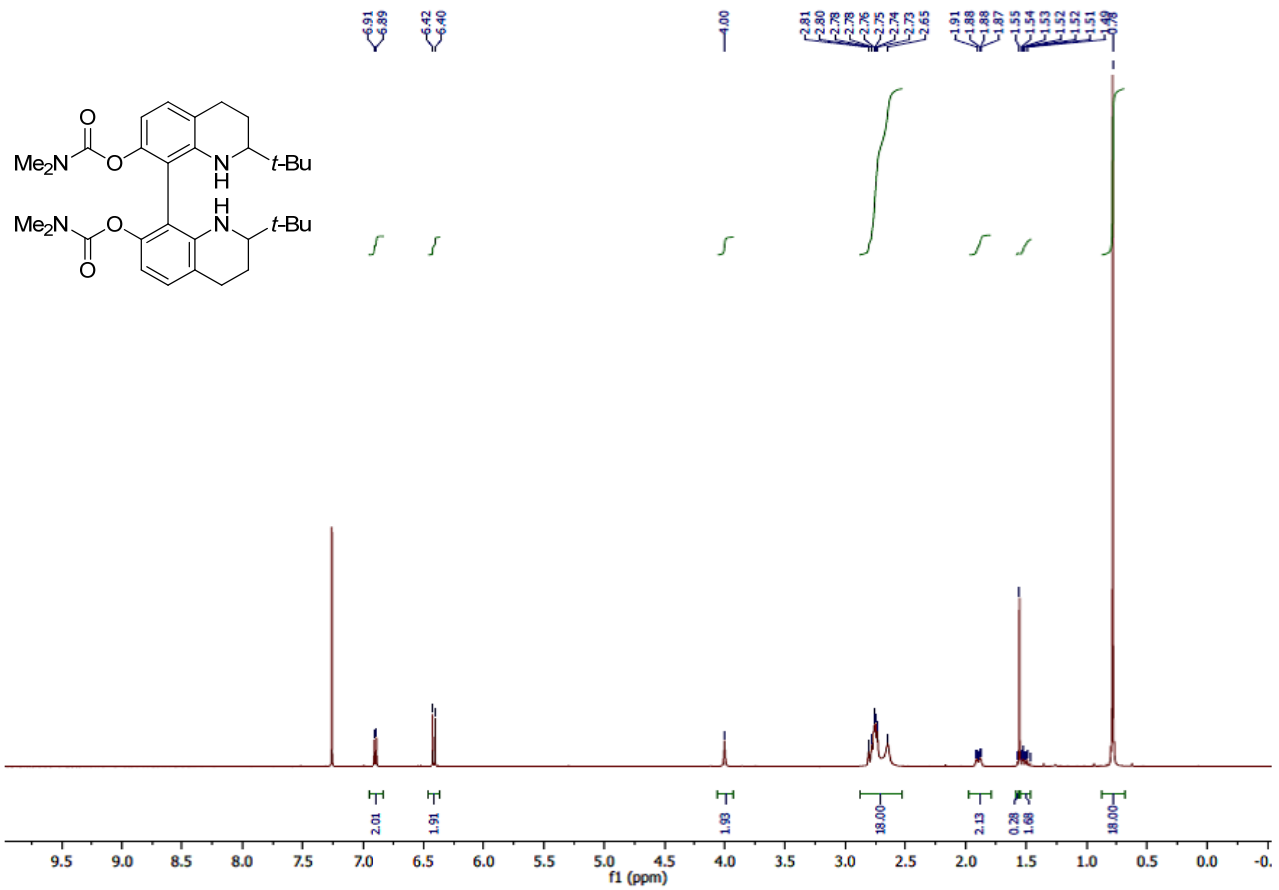
Appendix Figure 177 100 MHz ^{13}C NMR spectrum of 2,2'-di-tert-butyl-[8,8'-biquinoline]-7,7'-diyl bis(dimethylcarbamate) **(248)**



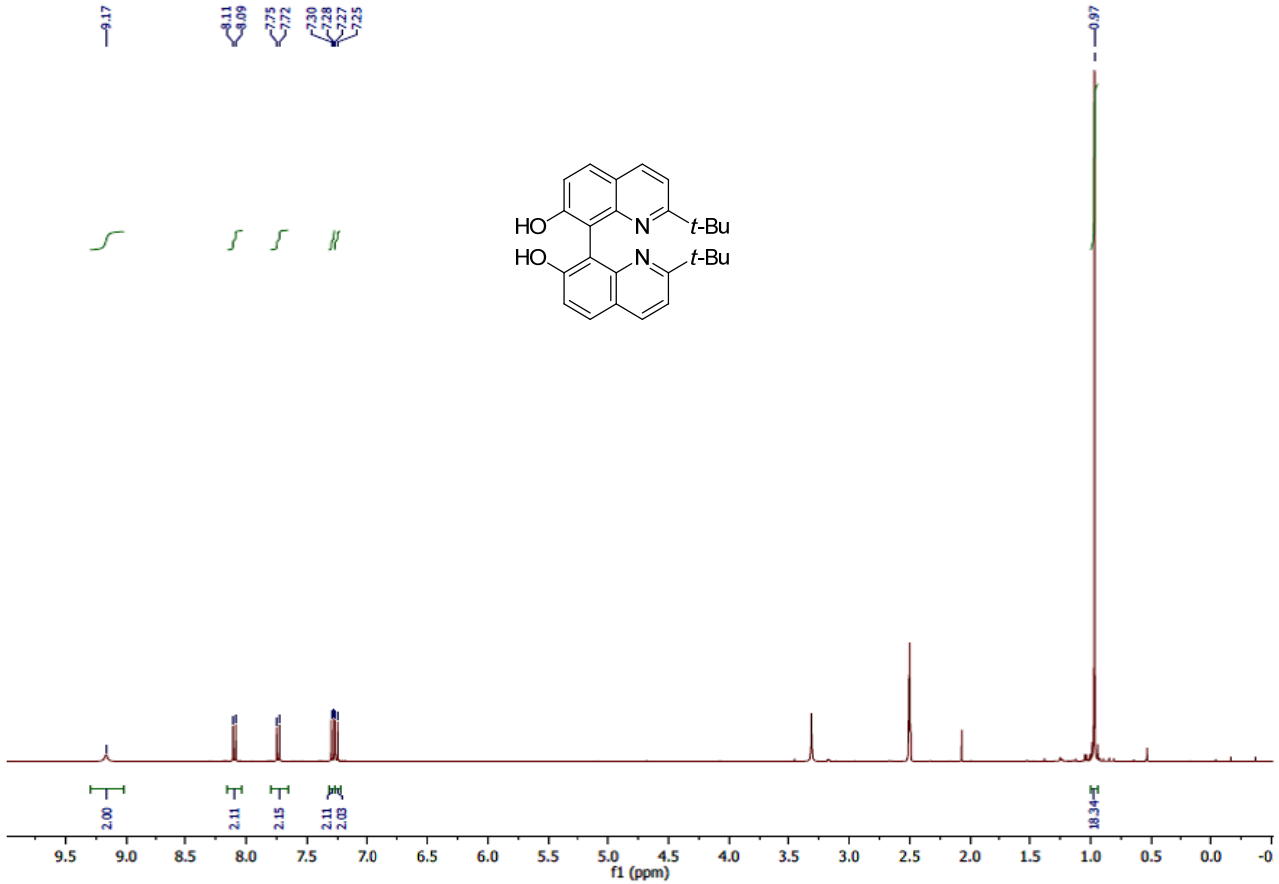
Appendix Figure 178 400 MHz ^{1}H NMR spectrum of 2,2'-di-methyl-[8,8'-biquinoline]-7,7'-diyl bis(dimethylcarbamate) **(249)**



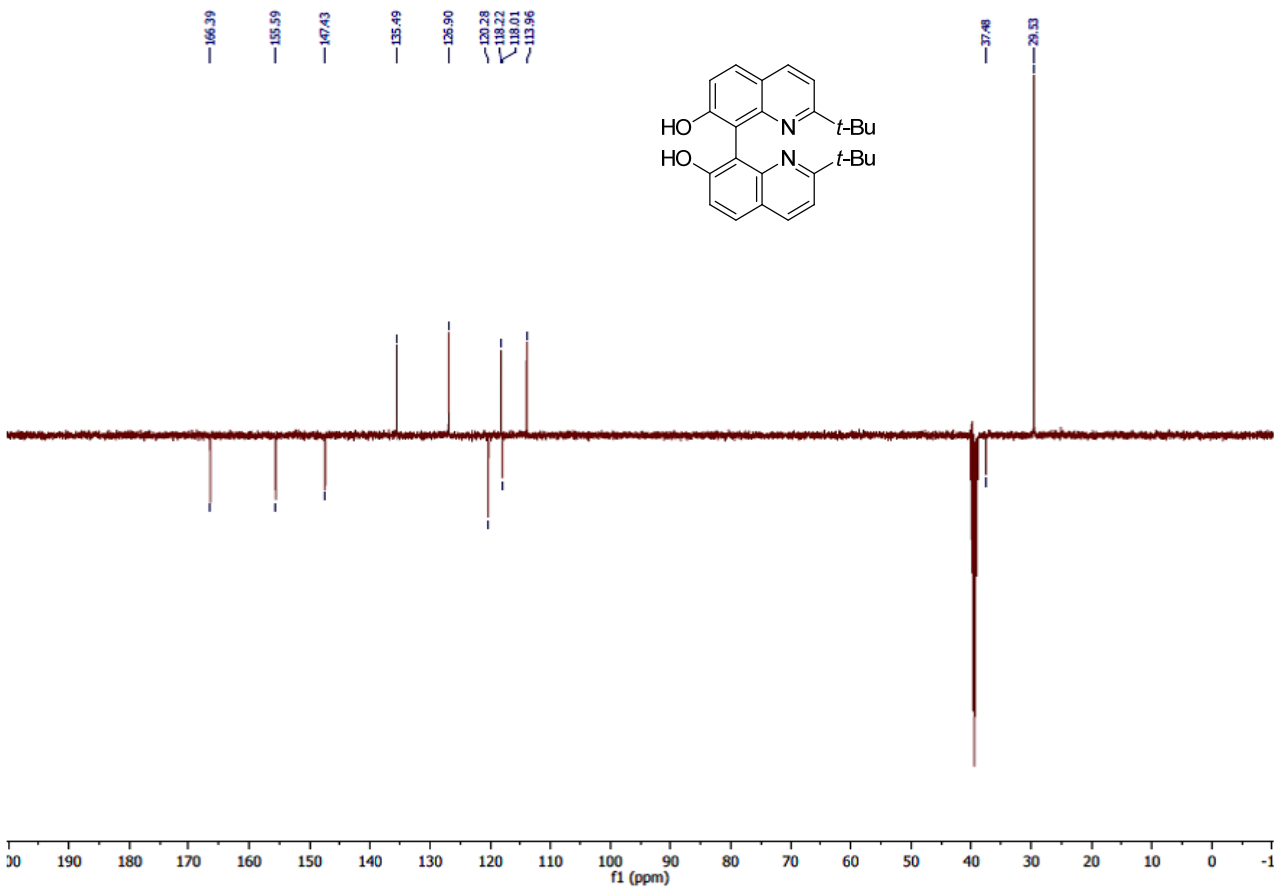
Appendix Figure 179 100 MHz ^{13}C NMR spectrum of 2,2'-di-methyl-[8,8'-biquinoline]-7,7'-diyl bis(dimethylcarbamate) **(249)**



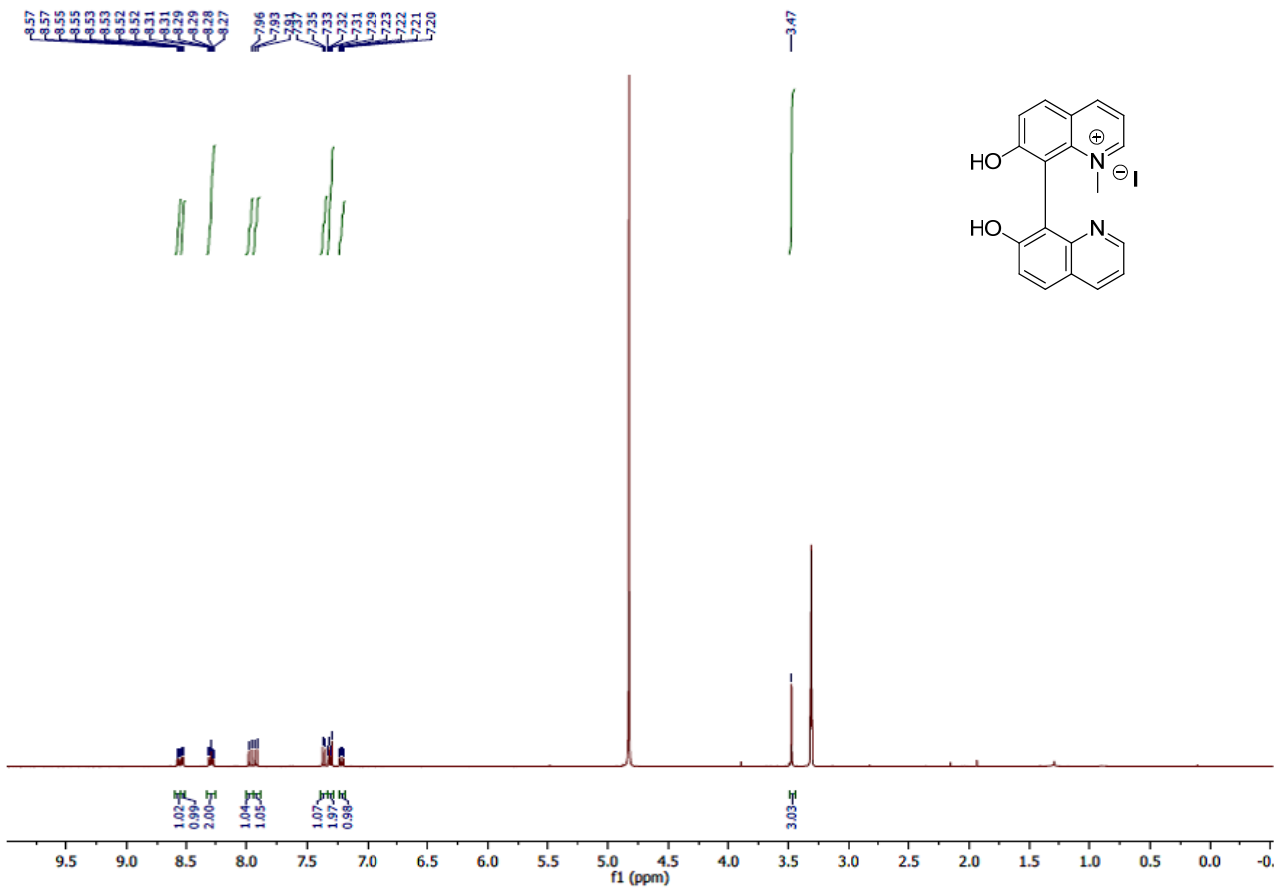
Appendix Figure 180 400 MHz ^{1}H NMR spectrum of 2,2'-Di-tert-butyl-1,1',2,2',3,3',4,4'- octahydro-[8,8'-biquinoline]-7,7'- diyl bis(dimethylcarbamate) **(251)**



Appendix Figure 181 400 MHz ^{1}H NMR spectrum of 2,2'-di-tert-butyl-[8,8'-biquinoline]-7,7'-diol **(53)**



Appendix Figure 182 100 MHz ^{13}C NMR spectrum of 2,2'-di-tert-butyl-[8,8'-biquinoline]-7,7'-diol **(53)**



Appendix Figure 183 400 MHz ^{1}H NMR spectrum of 7,7'-dihydroxy-1-methyl-[8,8'- biquinolin]-1-ium iodide **(258)**

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EDUCATION :

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2002	Kasetsart University	B.S. (Chemistry)

RESEARCH TOPICS

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: M.S.
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: B.S.
Recovery of Chromium (VI) from Chromium Waste

WORKING EXPERIENCES

: Lecturer (February – May 2009); Department of Chemistry, Faculty of Science, Kasetsart University.

: Scientist (August 2002 – May 2004); Secretary Office, Faculty of Science, Kasetsart University.

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TEACHING EXPERIENCES

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- Laboratory in General Chemistry
- Laboratory in Fundamental of General Chemistry
- Basic Chemistry Laboratory
- Laboratory in Organic Chemistry
- Laboratory in Chemistry for Veterinary Medicine

: Teaching Assistant (2007 - 2008); Department of Chemistry, Faculty of Science and Technology, Thammasart University.

- Fudamental Chemical Laboratory

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GRANTS and SCHOLARSHIPS

: ASEA – UNINET, ÖeAD (2013)
: BRC (2011)
: ASEA – UNINET, ÖeAD (2011)
: PERCH – CIC (2010 – 2012)
: Teacher Assistant (2007)
: Thai Plastic and Chemical Public Co., Ltd. (1998 – 2002)

CONFERENCE PRESENTATIONS

: JICCEOCA-4; November 28 – 30, 2014
: PERCH – CIC Congress VIII; May 5 – 8, 2013
: ChPGS II; March 27, 2013
: PACCON Congress 2013; January 23 – 25, 2013
: PERCH – CIC Congress VII; May 3 – 6, 2011
: 32nd Congress on Science and Technology of Thailand; October 10 – 12, 2006.

PUBLICATION : Pluempanupat, W., P. Temyarasilp, M. Widhalm and W. Chavasiri. 2014. Camphorquinone: a new and efficient oxidant for the preparation of 2-thio-substituted benzothiazoles from alcohols by oxidation-reduction condensation. **J. Sulfur Chem.** 35: 418 – 430.