Peroxide Promoted C-X (X = -O, -N) Bond Synthesis

By

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List of Publications arising from the thesis

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1. **Bose, A.**; Mal, P. Electrophilic aryl-halogenation using N-halosuccinimides under ball-milling. *Tetrahedron Lett.* **2014**, *55*, 2154-2156.
2. [#]**Bose, A.**; Mal, P. Cross Redox Coupling of Aryl-Aldehydes and p-Benzoquinone. *J. Org. Chem.* **2015**, *80*, 11219-11225.
3. Sahoo, P. K.; **Bose, A**.; Mal, P. Solvent-Free Ball-Milling Biginelli Reaction by Subcomponent Synthesis. *Eur. J. Org. Chem.* **2015**, *2015*, 6994-6998.
4. [#]**Bose, A.**; Mal, P. Using weak interactions to control C-H mono-nitration of indolines. *Chem. Commun.* **2017**, *53*, 11368-11371.
5. Maiti, S.; **Bose, A.**; Mal, P. Oxidative N-Arylation for Carbazole Synthesis by C–C Bond Activation. *J. Org. Chem.* **2018**, *83*, 8127-8138.
6. Achar, T. K.; **Bose, A**.; Mal, P. Mechanochemical synthesis of small organic molecules. *Beilstein J. Org. Chem.* **2017**, *13*, 1907-1931.
7. **Bose, A.**; Maiti, S.; and Mal, P. CHAPTER 9: Soft Forces in Organic Synthesis by C–N Coupling Reactions in *Noncovalent Interactions in Catalysis*, eds. K. T. Mahmudov, M. N. Kopylovich, M. F. C. Guedes da Silva and A. J. L. Pombeiro, The Royal Society of Chemistry, 2019, pp. 188-208.
8. [#] **Bose, A.**; Maiti, S.; Sau, S.; and Mal, P. *Chem. Commun.*, 2019, **55**, 2066-2069.
9. **Bose, A.**; Mal, P. *Beilstein J. Org. Chem.*, 2019, **15,** 881-900.

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4. RSC Publishing workshop at NISER, Bhubaneswar on 23rd September, 2016.
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Anima Bose

Anima Bose

To

My Parents

Mr. Ashok Kumar Bose

Mrs. Malati Bose

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…Anima Bose

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SYNOPSIS OF Ph. D. THESIS

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2. **Name of the Constituent Institution:** National Institute of Science Education and Research (NISER)
3. **Enrolment No. :** CHEM11201404001
4. **Title of the Thesis:** Peroxide Promoted C-X (X = -O, -N) Bond Synthesis
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SYNOPSIS

Introduction

The most common class of bonds found in any organic molecules is C-C and C-H bonds. Among the C-hetero bonds, C-O and C-N bonds are the most important due to their abundance in majority of the organic compounds present in nature. In addition, synthetically they are significant for the construction of many pharmaceuticals, biologically relevant scaffolds,

agrochemical, pesticides, functional materials, etc. Oxidative cross coupling reactions *via* transition metal catalyst are one of the essential methods for making these bonds. However, many of those transformations have drawbacks for example: (a) due to requirement of prefunctionalized substrates *i.e.*, preparation of aryl halides (or pseudohalides) or metal reagents prior to the bond formation (making overall transformation multistep in nature) (b) use of stoichiometric amounts of metal based oxidizing agent under harsh reaction condition. Therefore, direct couplings of diverse functional groups are particularly attractive because they do not necessitate preactivation of coupling partners, and atom and step economical. Recently, C-H activation[1] strategy has emerged as a powerful tool for direct incorporation various functional groups in a selective manner. Use of transition metal catalyst as well as metal based oxidant in C-X bond formation are well studied but these reagents find difficulties due to their expensive, toxic and environmentally hazardous nature. In search of environmentally benign and cost effective method for construction of C-X bonds, peroxides reagents became popular because of their low toxicity, high reactivity and environmentally benign nature.[2] Herein, we present the development of peroxide promoted C-O, C-N bond formation reactions for few synthetically challenging molecules. Mono-esters of hydroquinone have been synthesised in one step from quinone and aryl aldehydes using catalytic amount of copper salt and *tert*-butylhydroperoxide (TBHP) as oxidant *via* radical pathway. By accounting the cooperative multiple weak interactions, selective mono-nitration of indoline derivatives were achieved using metal nitrates as the nitro source and peroxide potassium peroxodisulfate. *meta*-Chloroperbenzoic (*m*CPBA) acid was also used successfully for *in situ* generation of iodine(III) reagent from iodobenzene to synthesize 1,2-disubstituted benzimidazole derivatives with 4H elimination occurring in one step. Water soluble iodide(I) reagent was used for *in situ* generation iodite(III) reagent with the

help of oxidant TBHP for functionalization of C(sp^3)-H bond towards construction of benzimidazole rings *via* iminium intermediate.

Scope and Organization of the Present Thesis

In this thesis, methods have been introduced for several C-O and C-N bond formation reactions using peroxides as one of the reagents. Scope of the reactions including mechanistic studies is also described. This thesis includes five Chapters with the following contents:

CHAPTER 1

What are Peroxides? and what do they do in C-X Bond Synthesis?

Oxidation reactions or oxidative transformations are considered as important synthetic methods in organic chemistry. However, harsh reaction condition, use of highly reactive oxidants and transition metal based oxidative systems makes the process unfriendly, thus restricted to be used in large scale synthesis. However, peroxides are one of the preferred oxidants due to their extraordinary reactivity, mild nature, safe and high oxidizing ability. The peroxides introduced as both inorganic and organic peroxides.

This Chapter mainly focuses on brief introduction about peroxides as oxidants, and their applications in C-O and C-N bond formation reactions. In the first part a concise discussion is made on the structural aspects, classification, physical properties and general reactivity of peroxides. In the second part, recent literature reports of C-O and C-N bond synthesis and ring forming reactions[3,4] promoted by peroxides have been discussed. Representative examples of

peroxide promoted reactions using both metal catalysed[5,6] and metal-free[7,8] approaches have been highlighted. Finally, this Chapter concludes with the approaches for C-X bond formation reactions to be followed in the present thesis.

CHAPTER 2

Cross Redox Coupling of Aryl aldehydes and *p*-Benzoquinone for the Synthesis of Hydroquinone mono-esters (A. Bose and P. Mal, *J. Org. Chem.* **2015**, *80*, 11219; Highlighted in *Org. Proc. Res. Dev.* **2015**, *19*, 1918).

Benzoquinones are one of the prevalent classes of core structure found in organic synthesis. These are popularly used in many research areas such as radical reactions, medicinal chemistry, molecular electronics, oxidation chemistry, etc. Nucleophilic addition of thiols and amines to quinones are the most common reactions to synthesis functionalized hydroquinone derivatives which follows Michael addition pathway. Recently, hypervalent iodine mediated or metal catalyzed C(sp^2)−H activation is another major development in synthesis of quinone derivatives. However, direct acylation of hydroquinone to get ester derivatives from quinone and any acylating reagents are very less explored in literature. Regio-selective mono-esterification of hydroquinone is synthetically challenging due to unavailability of properly activated acids and coupling reagents and probabilities of formation of diesters. In this Chapter an unique $Cu(OAc)_2 \cdot H_2O$ catalyzed Cross Redox Coupling (CRC)[9] reaction by has been discussed. Direct coupling of *p*-benzoquinone and aromatic aldehydes (or benzyl alcohols) led to selective formation of mono-esters of hydroquinone in the presence of catalytic amount of Cu(II) salt and

peroxide TBHP as oxidant. During the esterification reaction, aldehydic C−H bond of the aryl aldehyde was directly transformed to C−O bond of ester *via* an aroyl radical intermediate. This radical intermediate has been generated in presence of TBHP. Also the method has been successfully applied from benzyl alcohol oxidation state *via in situ* oxidation to aldehyde. Mechanistic investigation suggested a radical pathway for the conversion. In this reaction both atoms and electrons were well conserved.

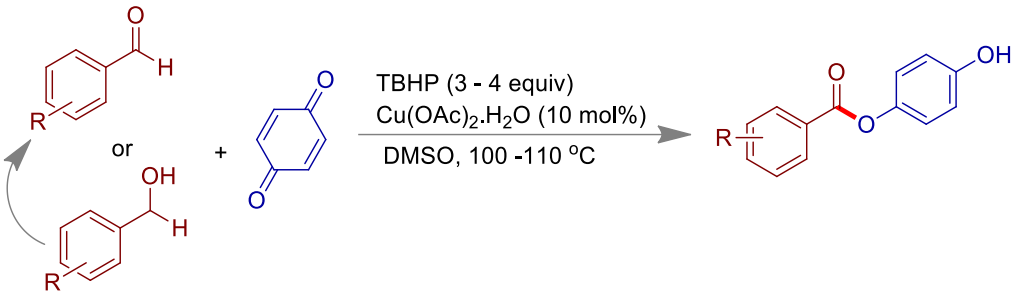

Fig. 1. Cu-TBHP promoted Cross Redox Coupling Reaction.

CHAPTER 3

Weak Interactions Assisted C–H mono-Nitration of Indolines (A. Bose and P. Mal, *Chem. Commun.* **2017**, *53*, 11368).

Nitroarenes are one of the essential classes of synthetic precursors which have potential application in a variety of industries like production of pharmaceuticals, agrochemicals, dyes, pesticides, and polymers. Developments of synthetic procedures for nitroarenes are one of the most comprehensively studied organic reactions. The high synthetic efficacy of nitroaryls is due to their straightforward conversion to other important aryl functionalities like halo arenes, phenol derivatives and organometallic arene groups via diazonium intermediates. Also, nitroglycerin is an important class of cardiac drug. In classical method nitration reaction uses conc. HNO_3 and

fuming H_2SO_4 to generate electrophilic nitronium ion species. Indoles and indolines are a privilege class of heterocyclic ring found in many natural products and drug molecules. Some of the nitro-substituted indoles having anti- tuberculosis properties are known in literature. Despite of the importance of nitro moieties, this reaction suffers from the demerits like over nitration as well as unwanted oxidation of the substrates. So development of milder condition for this transformation is always desirable. In supramolecular chemistry it is known that the surrounding of the chemical system can modify its reactivity in a controlled manner to furnish selectively a particular product. Various noncovalent or weak interactions for example different π-effects like anion–π or cation–π, hydrogen bonding effect, solvent effects are being widely studied for alteration of product formation in different chemical systems. This chapter focuses on a distinctive C(sp^2)–H nitration reaction of indolines[10] selectively at the $–C_5$ or $–C_7$ positions to give mono-nitro product under mild reaction condition. An effort has been made to utilize the simultaneous cooperative multiple weak interactions towards selective mono-nitration on the aromatic ring of the non-prefunctionalized indoline heterocycles. Nitration of non-prefunctionalized aromatic/heteroaromatic compounds are generally done in harsh condition and uncontrollable to selective mono-substitution. Only 20 mol % of trifluoroacetic acid (TFA) was used as catalyst and $Cu(NO_3)_2$ or $AgNO_3$ were the source of nitronium ion. Mechanistically, several nocovalent interactions like electronic effects, steric factors, cation-π, solvent polarity, etc. were helpful to achieve complete regio-selective electrophilic aromatic (EArS) mono-nitration. The electrophilic nitronium ion (NO_2^+) could be generated using an inorganic peroxide potassium peroxodisulfate ($K_2S_2O_8$) from metal nitrates as mild nitrating source.

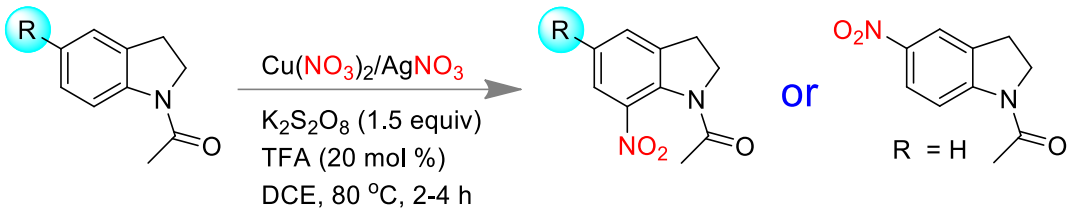

Fig. 2. C-H mono-nitration for non-prefunctionalized Indoline system under mild condition with 100% regio-selectivity.

CHAPTER 4

Organocatalytic Intramolecular Oxidative C(sp3)-H Imination Reaction for Benzimidazole Synthesis (**Bose, A.**; Maiti, S.; Sau, S.; and Mal, P. *Chem. Commun.*, 2019, **55**, 2066-2069).

C(sp3)-H bonds are considered to be less reactive than C(sp2)-H due to their high thermodynamic stability. Development of synthetic methodology for the conversion of unreactive C(sp3)-H bonds into other useful functionalities are of great significance in fundamental research but extremely challenging. N-containing heterocycles are widespread in synthetic pharmaceuticals and natural products. Intramolecular C-N bond formation reaction is one of the most targeted approaches in generating N-heterocycles. Dehydrogenative coupling between C-H and N-H bonds represent the state of art practice in C-N bond synthesis due to non-requisite of prefunctionalization of substrate. Major literature reports for C(sp3)-H amination reactions are based on transition metal catalysis. Compared to C(sp3)-H amination reactions, imination reactions are more challenging as formation of imine from the combination of $–CH_2$ and $–NH_2$ with 4H elimination is thermodynamically unfavorable. For oxidative C-N bond synthesis by C-H bond functionalization, hypervalent iodine(III) reagents gained high popularity

because of their low toxicity, environmentally benign nature and easy availability. Notably, iodine(III) mediated most of the C-H amination developments are based on 2H elimination and starting from secondary amines. However to the best of our knowledge, there is no literature precedence of hypervalent iodine(III) mediated intramolecular C(sp3)-H imination (4H elimination) reaction towards heteroaromatic ring synthesis. Herein, this chapter the discovery of an organocatalytic intramolecular oxidative C-H imination reaction under mild condition is discussed. The double dehydrogenative C-N coupling reaction between a free amine group and a *N*-methylene group was established under *in situ* generated hypervalent iodine(III) reagent. The iodine(III) condition was maintained using iodobenzene as catalyst and *meta*-Chloroperbenzoic acid (*m*CPBA) as oxidant. In a single step, 4H elimination was achieved to access 1,2-disubstituted benzimidazoles at room temperature open atmosphere condition. Mechanistic investigation says it goes via formation of iminium intermediated followed by dihydrobenzoimidazole which subsequently led to 1,2-disubstituted benzimidazoles.

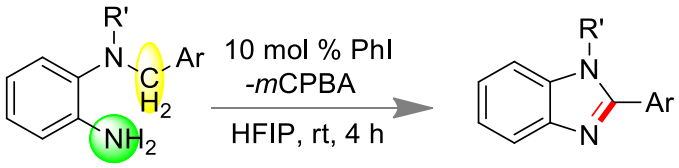

Fig. 3. Organocatalytic Intramolecular Oxidative C(sp3)-H and –NH_2 coupling.

CHAPTER 5

TBHP-TBAI Induced C(sp^3)-H Functionalization (**Bose, A.**; Sau, S.; and Mal, P. *Submitted*).

Oxidative transformation is one of the essential reactions in organic synthesis, which has remarkably progressed during the last few decades. However, a huge proportion of the known methods deal with the transition metals as catalysts. In light of metal free oxidants, iodide or

hypervalent iodine based reagents have gained huge attention to the organic chemists. More recently, the combination of tetrabutylammonium iodide (TBAI) as catalyst and TBHP as oxidant has received significant attention. However, the use of TBAI is advantageous because of its water solubility, economical, and high stability under ambient condition. This Chapter is dealing with functionalization of C(sp^3)-H bond by *in situ* generation of catalytic amount hypoiodite(I) or iodite(III) from TBAI-TBHP combination. This method is used to synthesize the 1,2-disubstituted benzimidazoles. Mechanistically shown that two step oxidation could be achieved with 4H elimination from a free amine (-NH_2) and benzylic –CH_2. Electronic effect of different benzylic center has also been discussed.

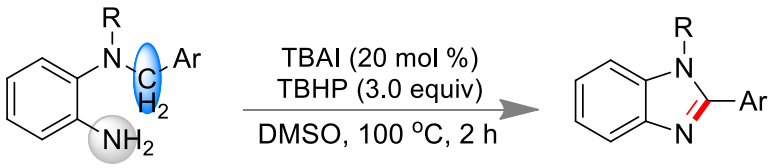

Fig. 4. C(sp3)-H Functionalization for 1,2-Disubstituted benzimidazole synthesis using TBHP-TBAI.

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List of Schemes

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List of Abbreviations Used

Å	Angstrom
Ac	Acetyl
AcOH	Acetic Acid
AcOOH	Peracetic acid
Anal.	Analytically
Anhyd	Anhydrous
aq	Aqueous
Bn	benzyl
bp	Boiling Point
br	Broad
Bz	Benzoyl
ºC	Degree Celcius
Calcd	Calculated
cm	Centimeter
Conc	Concentrated
Cp	Cyclopentadienyl
Cy	Cyclohexyl
d	Doublet
DCE	1,2-Dichloroethane
DCM	Dichloromethane
dd	Doublet of a Doublet
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
dil	Dilute
DMA	Dimethylacetamide
DMF	*N*,*N*-Dimethyl Formamide
DMSO	Dimethyl Sulfoxide
DTBP	Di-tert-butyl peroxide
equiv.	Equivalent
ESI-TOF	Electrospray ionization time-of-flight

Et	Ethyl
EtOAC	Ethyl Acetate
g	Grams
h	Hours
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HRMS	High-Resolution Mass Spectrometry
IR	Infrared
lit	Liter
m	Multiplet
*m*CPBA	*meta*-chloroperbenzoic acid
*m*CBA	*meta*-chlorobenzoic acid
M	Molar
MeCN	Acetonitrile
mp	Melting point
Me	Methyl
MHz	Mega Hertz
Min	Minutes
mL	Milliliter
mmol	Millimole
mol	Mole
MS	Mass Spectra
Ms	Methane sulfonyl
M/Z	Mass to charge ratio
N	Normal
nm	Nanometer
NMP	N-Methyl-2-pyrrolidine
NMR	Nuclear Magnetic Resonance
Piv	Pivaloyl
ppm	Parts per Million
Py	Pyridine
rt	Room Temperature

s	Singlet, Seconds
t	*tert*
TBHP	Tert-Butylhydroperoxide
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFE	2,2,2-Trifluoroethanol
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl
TFA	Trifluoroacetic acid
XRD	X-Ray Diffraction

Table of Contents

CHAPTER 1

What are Peroxides? And What do they do in C-X Bond Synthesis?

1.1 ABSTRACT

This section mainly focuses on brief introduction about peroxide reagents, oxidative carbon-hetero atom bond formation reactions and is divided in two parts: (1) structural aspects, physical properties, classification, and general reactivity, (2) application of this reagent in carbon-hetero atom bond formation reactions. The history and development of peroxide based bond formation reactions have also been highlighted along with collection of significant literature reports. Finally, this Chapter concludes with conferring the aim of present thesis for C-X (X= -O, -N) bond formation reactions to be followed.

1.2 INTRODUCTION

Peroxides are a class of chemical compounds where two oxygen atoms are bonded together by a single covalent bond. Chemically, peroxides contain an extra oxygen atom than required to fulfill its valency. Oxidation number of both the oxygen atom in a peroxide molecule is -1, which is a deviation from its normal oxidation state *i.e.* -2. Peroxides are used for several purposes like bleaching agent, disinfectant and as oxidant for chemical transformations, etc. Some peroxides like hydrogen peroxide in 3 – 6 wt % are also used as antiseptic in medical purpose. In addition, peroxides are found in biological system including human body. The simplest known peroxide is hydrogen peroxide having molecular formula H_2O_2. Alexander von Humboldt, in 1799 was the first person to synthesize one of the first peroxides, barium peroxide (BaO_2). In 1818 a French chemist, Louis-Jacques Thenard, was recognized to

synthesize hydrogen peroxide for the first time. It was believed for a quite long time that pure hydrogen peroxide was unstable, and could not be separated from water. But later, it was established that the instability was because of the trace of metal impurities present in it which could catalyze the decomposition of the hydrogen peroxide. In 1894, Richard Wolffenstein isolated pure hydrogen peroxide by vacuum distillation method. In its pure form, hydrogen peroxide is a clear pale blue liquid.

1.3 HYDROGEN PEROXIDE

The simplest peroxide molecule with chemical formula H_2O_2 is commonly called as "peroxide". It attains non-planar structure with *C2*-symmetry. The skewed non-planarity of the molecule is mainly due to the high energy of repulsion between the lone pair of electrons located on both the oxygen atoms which are adjacent to each other. In spite of having single bond between the two oxygen atoms, hydrogen peroxide shows atropisomerism due to high rotational energy barrier. Figure 1.1 shows the typical functional group of peroxide molecule and structural features of hydrogen peroxide.

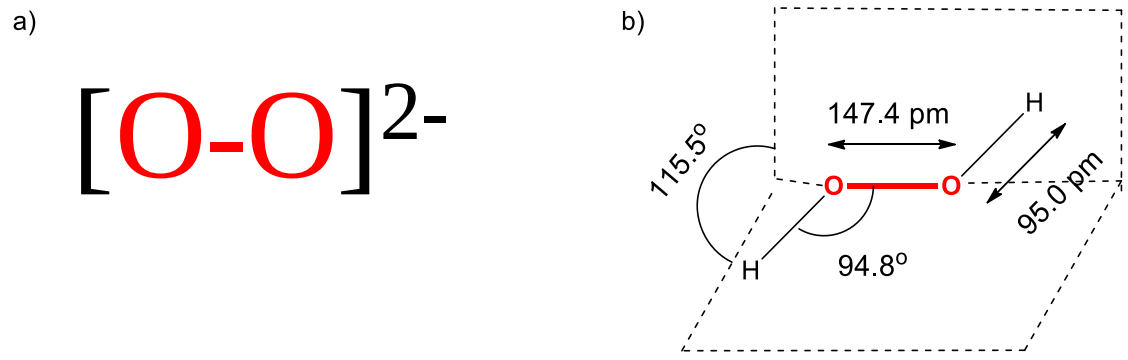


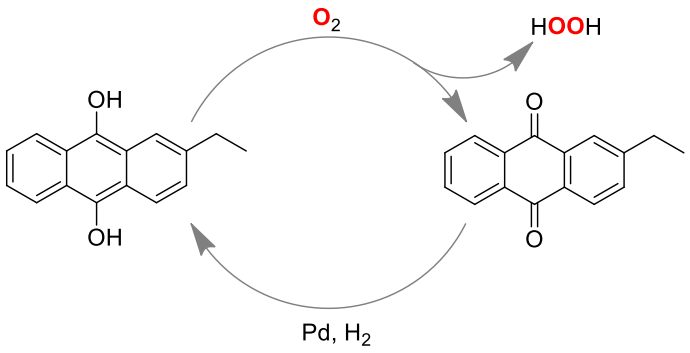
Figure 1.1 a) General structure of peroxide linkage. b) Structural feature of hydrogen peroxide.

The most important feature of peroxide is the weak O-O bond dissociation energy (142 kJ/mol) which makes the molecule highly labile, reactive and sensitive to heat and light. Table 1.1 represents a comparison among common bond dissociation energy found in organic molecules between oxygen and other atoms. This single weak bond between the oxygen atoms known as "peroxide linkage" makes the molecule thermodynamically unstable and the sole reason for the specific reactivity and spontaneous decomposition of the reagent.

Table 1.1 Comparison of bond energy between oxygen and other common atoms.

O-X Bond	**Bond Energy (kJ/mol)**
O=O	494
O-H	459
O-C	358
O-P	335
O-N	201
O-F	190
O-O	**142**

Since pure hydrogen peroxide (ca. above 68 wt %) is unstable and causes explosion, it is available in market as 3 – 6 wt % solution in water for medical purpose and commonly 30 wt % is being used for laboratory purpose. Anthraquinone process (Scheme 1.1) is one of the most widely used industrial processes which involve production of hydrogen peroxide. It is a transition metal catalysed process. Hydrogen peroxide acts as the precursor for other peroxides like hydroperoxide, metal peroxides, peroxy acids, etc.



Scheme 1.1 Anthraquinone process for synthesis of hydrogen peroxide.

1.4 CLASSIFICATION OF PEROXIDES

When hydrogen atoms of hydrogen peroxide are replaced with other groups it is converted to other peroxides. Depending up on the substitution it can be broadly classified into two categories, such as (i) organic peroxide and (ii) inorganic peroxides.

(i) Organic Peroxides: When one or both the hydrogens are replaced by other organic groups like alkyl, aryl, acyl, etc., then it is known as organic peroxides. Dialkyl peroxides, diacyl peroxides, alkyl hydroperoxides, aryl hydroperoxides, peroxy esters, peroxydicarbonates fall under this category. If both the hydrogens are substituted with an alkyl group, it is called peroxide. It has a general formula of R-O-O-R'. Di*tert*-butylperoxide, benzoyl peroxide, etc. fall under this category. When one of the hydrogen is only replaced with any alkyl group, it is called hydroperoxide having a common formula R-O-O-H. *tert*-Butylhydroperoxide, cuminhydroperoxide, etc. are common example of this class. In case, when one hydrogen is replaced with acyl group, it is known as peracids with general formula R(CO)-O-O-H. Peracetic acid and *meta*-chloroprbenzoic acid are very important examples of this class of peroxides. Figure 1.2 shows some representative examples of these classes.

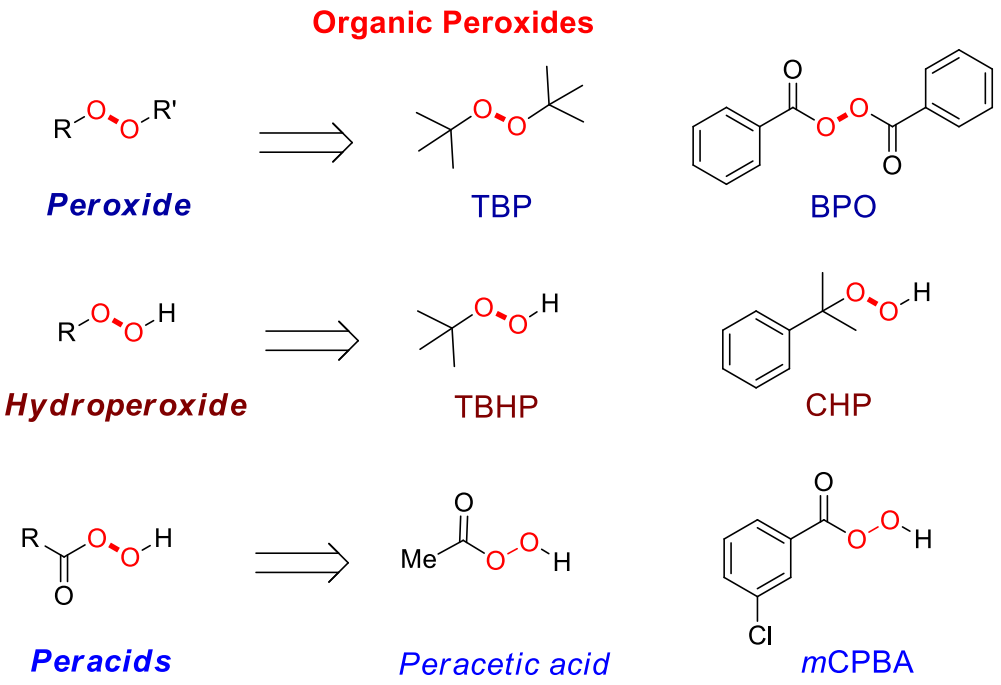


Figure 1.2 Some representative example of organic peroxides.

(ii) Inorganic Peroxide: Inorganic peroxides are compounds containing one element in its highest oxidation state or a peroxo linkage i.e. –O-O- in the structure. Metal peroxides like BaO_2, Na_2O_2, etc. are an important class of peroxides but these are less frequently used in routine organic synthesis. Peroxydisulfates are very vital which finds wide application in various bond formation reactions. Potassium peroxydisulfates, sodium peroxydisulfates, ammonium peroxydisulfates are some of the important entries for this class of peroxides. Potassium peroxymonosulfate, commonly known as "Oxone" (a triple salt with formula $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$)[1] is extensively used as an oxidizing agent and has huge synthetic application.

1.5 PEROXIDE IN ORGANIC CHEMISTRY

The most common classes of bonds found in any organic molecules are C-C and C-H bonds. Among the C-heteroatom bonds, C-O and C-N bonds are the most important due to their abundance in majority of the organic compounds present in nature. In addition, synthetically they are significant for the construction of many pharmaceuticals, biologically relevant scaffolds, agrochemical, pesticides, functional materials, etc. Oxidative cross coupling reactions *via* transition metal catalyst is one of the essential methods for making these bonds. However, many of those transformations have drawbacks for example: (a) due to requirement of prefunctionalized substrates *i.e.,* preparation of aryl halides (or pseudohalides) or metal reagents prior to the bond formation (making overall transformation multistep in nature) (b) use of stoichiometric amount of metal based oxidizing agent under harsh reaction condition. Therefore, direct couplings of diverse functional groups are particularly attractive because they do not necessitate preactivation of coupling partners, and is an atom and step economical. Recently, C-H activation[2] strategy has emerged as a powerful tool for direct incorporation of various functional groups in a selective manner. Use of transition metal catalyst as well as metal based oxidant in C-X bond formation reaction are well studied but these reagents find difficulties due to their expensive, toxic and environmentally hazardous nature. In search of environmentally benign and cost effective method for construction of C-X bond, peroxides reagents became popular because of their low toxicity, high reactivity and environmentally benign nature.[3] Oxidation reactions or oxidative transformations are considered as important synthetic methods in organic chemistry. However, harsh reaction condition, use of highly reactive oxidants and transition metal based oxidative systems makes the process unfriendly, thus restricted to be used in large scale synthesis. However, peroxides are one of the preferred oxidants due to their extraordinary reactivity, mild nature, safe and high oxidizing ability. Peroxides are used in synthetic chemistry since centuries. These reagents are extensively used as oxidizing agents as well as initiators for free-radical

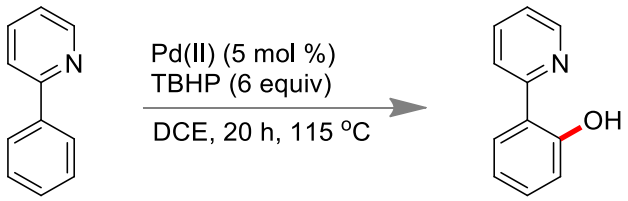
reactions and various rearrangement reactions in large scale production in industry and in academic research laboratory. In this section synthetic application of peroxides like *tert*-butylhydroperoxide, *meta*-chloroperbenzoicacid, and one of the important inorganic peroxide potassium peroxodisulfate in C-O and C-N bond formation reaction will be discussed.

1.6 *tert*-BUTYLHYDROPEROXIDE PROMOTED C-O AND C-N BOND SYNTHESIS

tert-Butylhydroperoxide is one of the widely used organic peroxide for various important bond formation in organic chemistry. Starting from the discovery of Sharpless epoxidation method in 1980, this reagent has been used for oxidation of alcohol, aldehydes, and benzylic methylene group functionalization. Recently, it has found application in C(sp^2)-H activation for C-O, C-N and incorporation of other groups like halogen, azide, nitro, etc. It is commonly used with transition metal catalyst such as Fe, Cu, Pd, etc.[4-8]

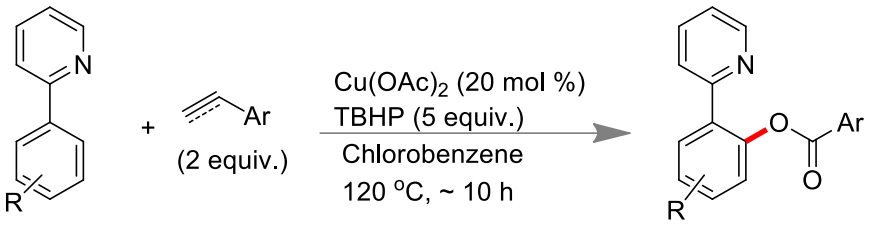
1.6.1 Metal catalysed approach for C-O bond synthesis mediated by TBHP

In 2015, Sun and his group[9] have reported an efficient method for synthesis of phenols *via* Pd-catalyzed C(sp^2)-H activation using pyridyl as the directing group and TBHP as the exclusive oxidant (scheme 1.2). Using 5 mol % of $Pd(OAc)_2$ and 6 equiv of TBHP they obtained phenol derivatives in 20 h reaction time in DCE solvent. The method was proved to be highly selective for *ortho*-hydroxylation and tolerable for both electron-rich as well as electron-deficient 2-arylpyridines giving moderate to good yield.



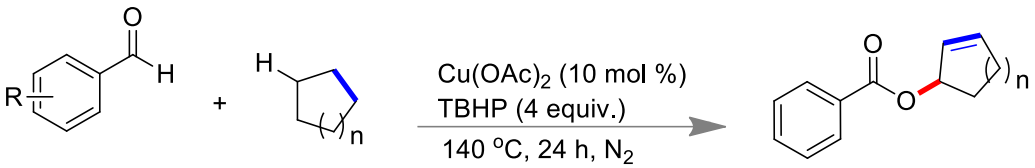
Scheme 1.2 Sun's Pd catalysed approach for C-O bond synthesis.

An efficient method for O-benzoxylation of 2-phenylpyridine derivatives has been reported by Patel and his group in 2014.[10] Using 10 mol % of $Cu(OAc)_2$ and 5 equiv. (Scheme 1.3) of TBHP they could achieve arylcarboxylation within 16 h where various styrenes and phenylacetylenes derivatives serve as the arylcarboxy surrogates.



Scheme 1.3 Patel's Cu catalysed benzoxylation approach for C-O bond synthesis.

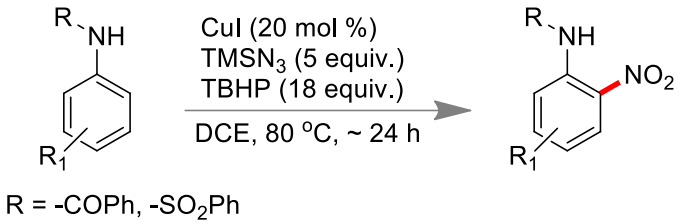
In 2014 Han's group reported a very interesting four C−H[11] bond activations using 10 mol % of $Cu(OAc)_2$ and 4 equiv. of TBHP as an oxidant via dehydrogenation−olefination followed by esterification to result in cycloallyl ester derivatives (Scheme 1.4). Aryl aldehydes along with cycloalkanes underwent the unprecedented transformation *via* radical pathway where formation of acyl radical was established in the mechanism.



Scheme 1.4 Han's Cu catalysed esterification approach for C-O bond synthesis.

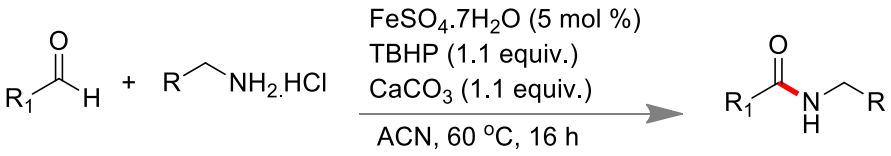
1.6.2 Metal catalysed approach for C-N bond synthesis mediated by TBHP

In 2017, Chandrasekharam and his group has functionalized *ortho* C-H bond of anilides with nitro group by using 20 mol % of CuI, 5 equiv. $TMSN_3$ and 18 equiv. of TBHP[12] as the oxidant (Scheme 1.5). Nitration was achieved *via* oxidation of azide group in presence of oxidant TBHP.



Scheme 1.5 Chandrasekharam's Cu catalysed nitration approach for C-N bond synthesis.

Amide bonds are one of the important functionality in the molecular world. An efficient method has been developed by Chen and his group for the synthesis of amides from aldehydes and amine hydrochloride salts.[13] Using catalytic amount of iron salt and 1.1 equiv. of TBHP they isolated good yield of amides at 60 °C in ACN solvent. (Scheme 1.6)



Scheme 1.6 Chen's Fe catalysed amidation approach for C-N bond synthesis.

1.6.3 TBAI catalysed C-O/N bond synthesis mediated by TBHP

Recently, in last two decades rapid progress in development of sustainable methods for organic transformation has been seen. As a result, green chemistry[14-16] has been highly appreciated by the chemists to replace transition metals with less toxic, inexpensive, milder and stable reagents. Tetrabutylammonium iodide[17] being stable, inexpensive and water soluble reagent has proved to be an efficient oxidative system with peroxides such as TBHP, H_2O_2, etc. In presence of oxidant peroxide, iodide (I^-) gets oxidized to the active iodine intermediates[18,19] like ammonium hypoiodite ($[n\text{-}Bu_4N]^+[IO]^-$) or iodite ($n\text{-}[Bu_4N]^+[IO_2]^-$) which are crucial for the desired transformation. After the desired transformation, the active catalyst goes back to its initial oxidation state to enter another cycle (Figure 1.3). Here some

of the important bond formations using the oxidative combination TBAI-TBHP has been discussed.

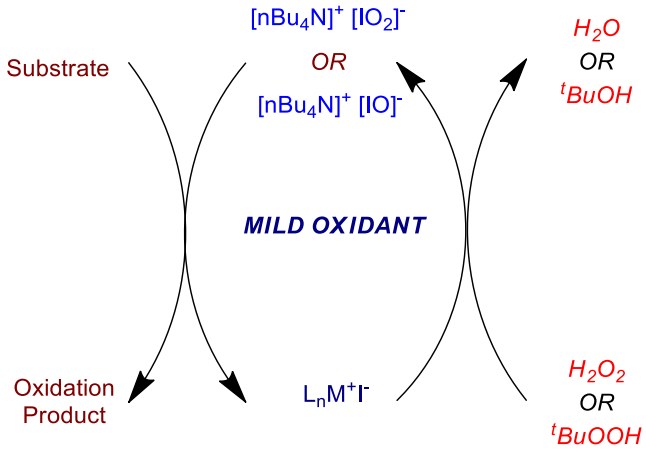
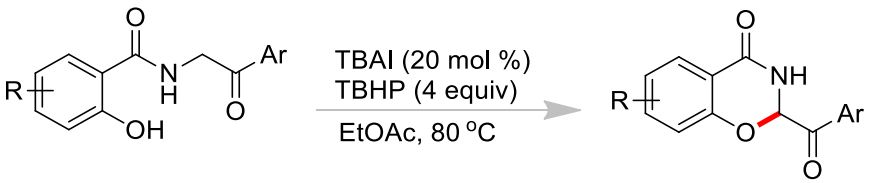


Figure 1.3 Catalytic use of inorganic iodine reagent with milder oxidant like TBHP.

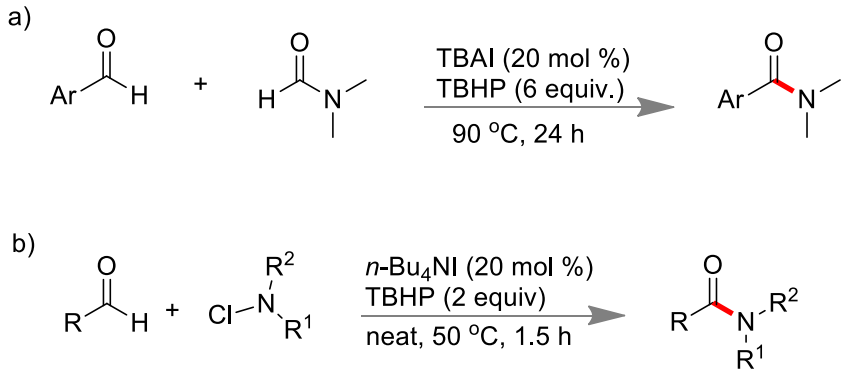
In 2015, Nachtsheim and his group has achieved α-phenoxylation of acetophenone derivatives by using 3 equiv. of TBHP as oxidant and catalytic amount of TBAI in ethyl acetate solvent at 80 °C.[20] C(sp^3)-O bond formation took place in a short span of twenty minutes with up to 92% yield (Scheme 1.7). From their mechanistic investigation formation of hypoiodite intermediate was proposed. This method was effectively applied to intramolecular synthesis of dihydro-4H-benzo[e][1,3]oxazin-4-ones.



Scheme 1.7 Nachtsheim's C(sp^3)-H functionalization for C-O bond synthesis.

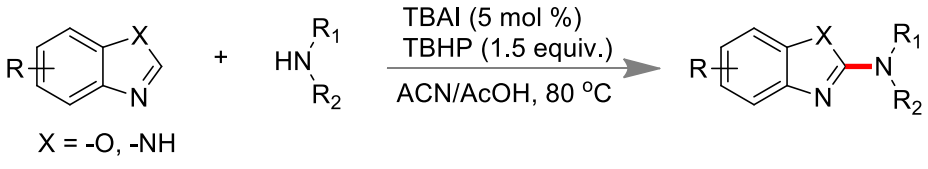
By replacing various transition metal catalysed amidation methods,[21] TBAI and other iodine[22-24] reagents have proved to be very efficient in oxidative amidation of aldehydes with

free amines as well as *N*-protected amines. In 2012 Wan's group have reported an amidation method from aldehyde using 20 mol % TBAI and 3 equiv. TBHP oxidative system (Scheme 1.8a) where DMF acted as the aminyl radical source.[25] This method has proved to be very efficient for electron donating as well as withdrawing substituent and good yields of amide derivatives were isolated at 90 ^{o}C in 24 h reaction time. Later in 2015, Mal's group have reported similar amidation from aldehyde and *N*-chloramine under solvent free neat condition[26] at 50 ^{o}C within a very short reaction time (Scheme 1.8b). This method was also very successful in mechano-milling condition.



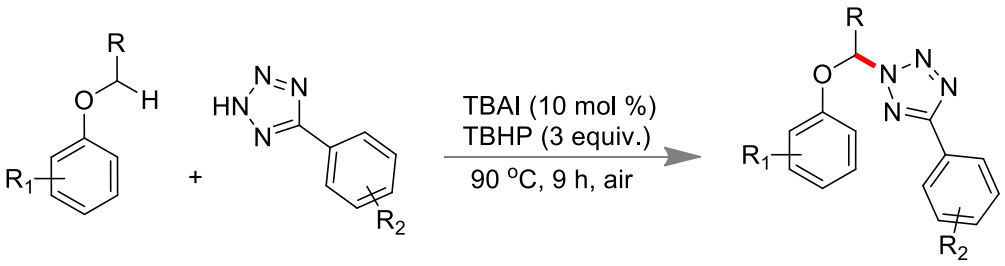
Scheme 1.8 Oxidative amidation method for C-N bond synthesis. a) Wan's approach using formamide. b) Mal's approach using *N*-chloramine derivatives.

In 2011, Nachtsheim and his group developed first iodine catalysed amination of benzoxazoles. Using only 5 mol % of tetrabutylammoniumiodide (TBAI) along with stoichimetric oxidant TBHP in ACN solvent at 80 ^{o}C they could achieve excellent yield of 2-aminobenzoxazoles (Scheme 1.9).[27] Mechanistic investigation by the authors propose formation of hypoiodite intermediate which plays the vital role in the conversion.



Scheme 1.9 Nachtsheim's oxidative amination method for C-N bond synthesis from secondary amine.

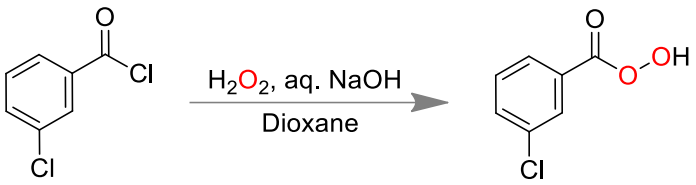
Patel and co-workers have reported a regioselective C(sp^3)-N bond synthesis using 3 equiv. of TBHP and only 10 mol % of TBAI as the catalyst by cross dehydrogenative coupling of aryl ethers and tetrazoles as the coupling partner.[28] Both electron donating and electron withdrawing aryl ethers worked well for this transformation giving excellent yield within 9 h of reaction time (Scheme 1.10). The authors have proposed formation of $[Bu_4N]^+[IO]^-$ species and radical pathway for the transformation.



Scheme 1.10 Patel's C(sp^3)-N bond synthesis from tetrazoles.

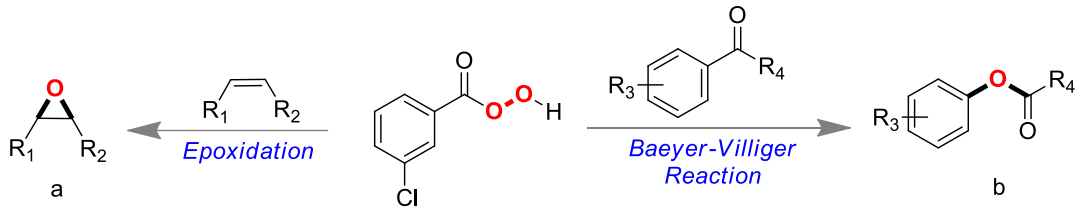
1.7 *meta*-CHLOROPERBENZOIC ACID IN ORGANIC TRANSFORMATION

Among peracids, *meta*-chloroperbenzoic acid (*m*CPBA)[3] is one of the efficient and useful reagents for various organic transformations like oxidation of carbonyl groups, active methylene groups, amines, several oxygen insertion rearrangement reactions. High reactivity, easy handling, inexpensive nature of this reagent has made it popular among synthetic chemists since last century. It can be prepared from the reaction of *m*-chlorobenzoyl chloride with H_2O_2 as the peroxide precursor (Scheme 1.11).



Scheme 1.11 Synthetic method for *m*CPBA.

Baeyer–Villiger oxidation, Rubottom oxidation, Dakin reaction, Nef reaction, epoxidation of alkene, etc. are some of the important contributions to *m*CPBA chemistry. Apart from these routine organic transformations, it is extensively used as a terminal oxidant for *in situ* generation of hypervalent iodine(III) species from iodine(I) reagent in reaction system.[29] Scheme 1.12 shows some common application of *m*CPBA like epoxidation of alkene and Baeyer-Villiger oxidation.



Scheme 1.12 Common synthetic application of *m*CPBA. a) Epoxidation of alkene. b) Baeyer–Villiger oxidation.

Recently iodine(III) reagent have gained huge consideration in oxidation chemistry because of its easy handling, low toxicity, selective reactivity, ready availability, and stability, etc.[30] For these advantages, a handful of reports have arose in last two decades on the development and application of this reagent in C-C and C-X (X = -N, -O, -S, etc.) bond synthesis.[31-35] But the major pitfalls of these iodine(III) reagents are their expensive nature, and production of equimolar amount of iodoarene which makes the process atom uneconomic. Hence, catalytic use of these reagents is highly desirable which can be cost effective as well as atom

economic. In figure 1.4 stoichimetric and organocatalytic use of iodine reagent has been pictorised. Here, some of the applications of *m*CPBA as terminal oxidant in organoiodine reagent and their application in C-O and C-N bonds have been discussed.

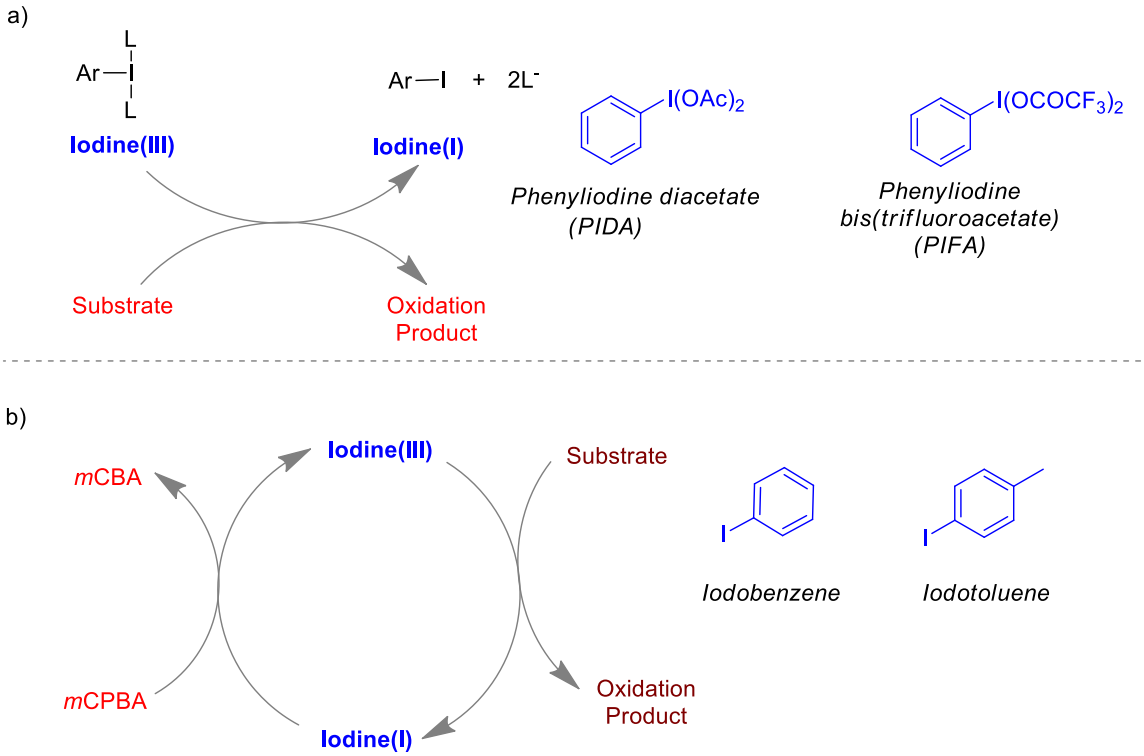
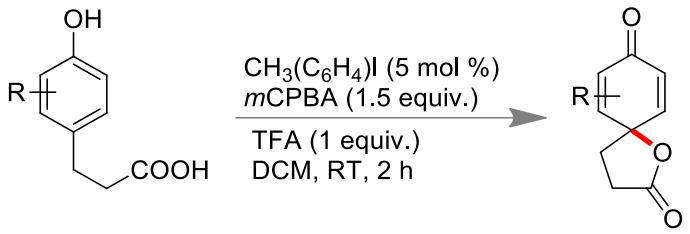


Figure 1.4 a) Stoichiometric use of iodine(III) reagent and common iodine(III) reagents. b) Catalytic use of iodine(III) reagent and common iodine(I) reagents.

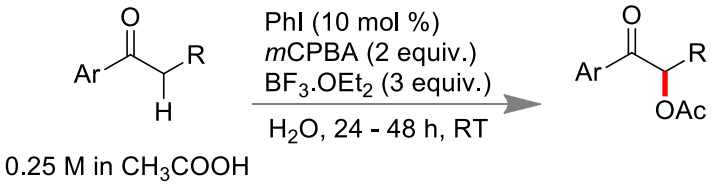
1.7.1 Organocatalytic C-O bond formation using *m*CPBA as terminal oxidant

In some of the early reports, Kita and his group reported C-O oxidative spirocyclization of phenol derivative using 5 mol % of iodotoluene, 1 equiv. of trifluoroacetic acid, and 1.5 equiv. of *m*CPBA as terminal oxidant which helped in the *in situ* generation of iodine(III) reagent in DCM solvent at room temperature condition (Scheme 1.13).[36] In this organocatalytic approach they isolated up to 91% of product in only 2 h.



Scheme 1.13 Kita's oxidative spirocyclization approach for C-O bond synthesis.

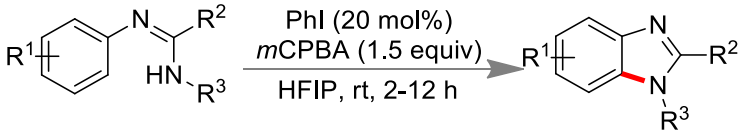
Ochiai's group have developed a method where using 10 mol % of iodobenzene as catalyst and 2 equiv. of *m*CPBA as a terminal oxidant they observed α-acetoxylation of ketones in aq. medium (Scheme 1.14).[37] Good to moderate yield of products were isolated although the reaction time was quite longer *i.e.* 24 h.



Scheme 1.14 Ochiai's α-acetoxylation approach for C-O bond synthesis.

1.7.2 Organocatalytic C-N bond formation using *m*CPBA as terminal oxidant

Intramolecular dehydrogenative C(sp^2)-N bond formation reaction of *N,N′*-disubstituted imines has been established by Punniyamurthy and co-workers by using *in situ* generated hypervalent iodine(III)[38] reagent from catalytic amount of iodobenzene in presence of co-oxidant *meta*-chloroperbenzoic acid in fluorinated alcohol as solvent (Scheme 1.15).



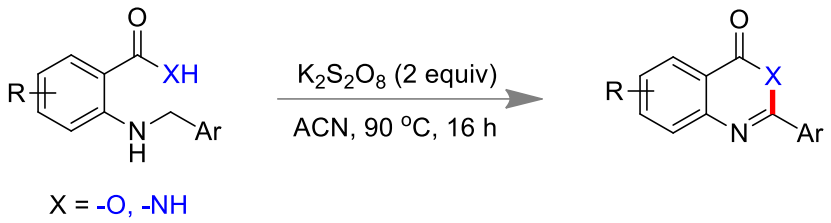
Scheme 1.15 Punniyamurthy's dehydrogenative coupling for C-N bond synthesis.

1.8 POTASSIUM PEROXODISULFATE IN ORGANIC SYNTHESIS

Among inorganic persulfates, Potassium persulfate ($K_2S_2O_8$) has proved to be one of the most efficient, inexpensive, stable, easy to handle inorganic oxidant for a broad collection of oxidative bond formations which can be applied to both laboratory and industrial preparations.[39] The peroxydisulfate ion ($S_2O_8^{2-}$) with standard redox potential 2.01 V is regarded as the most powerful oxidant in peroxygen group of compounds. Thermal or transition metal catalysed decomposition of $S_2O_8^{2-}$ generates sulfate radical anion ($SO4^{\bullet-}$) under ambient conditions. The sulfate radical anion is a very powerful single electron oxidant with a redox potential of 2.5−3.1 V. Starting from Minisci's developmental work, it has been used to oxidize many organic molecules, metal complexes, as well as anions and nucleophilic radicals.[40] In comparison to similar derivatives of this persulfates like $(NH_4)_2S_2O_8$ and $Na_2S_2O_8$, $K_2S_2O_8$ is more useful for organic transformations due to superior solubility of potassium salt in common organic solvent.

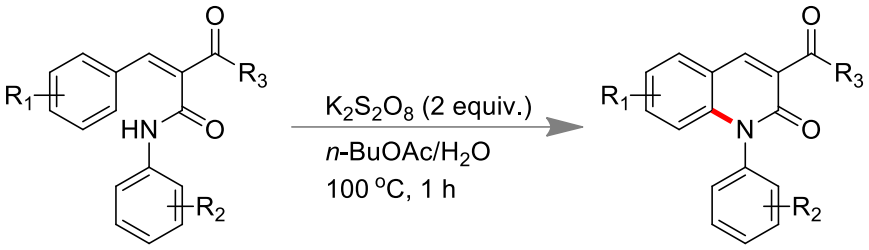
1.8.1 Thermal decomposition of $K_2S_2O_8$ for C(sp^3)-O/N bond synthesis

Laha and co-workers have reported a transition-metal-free, $K_2S_2O_8$-promoted intramolecular oxidative C(sp^3)−N and C(sp^3)−O bond formation followed by benzylic oxidation to afford heterocyclic ring like benzamidine or benzoxazine (Scheme 1.16).[41] Using 2 equiv. of $K_2S_2O_8$ in ACN solvent at 90 ^oC, they have made library of several important heterocyclic rings such as quinazolinones, benzoxazin-4-ones, benzimidazoles, benzoxazole, and their sulphur analogous with good to excellent yield of up to 96%. Detailed mechanistic investigation of the authors suggests a thermal decomposition of $K_2S_2O_8$ followed by formation of imine intermediate which undergoes intramolecular nucleophilic attack as the key step.



Scheme 1.16 Laha's heterocyclic ring formation for C-O/N bond synthesis.

Luo's group developed a metal free approach for the synthesis of *N*-aryl 2-quinolinones using 2 equiv. of $K_2S_2O_8$ in *n*-butylacetate and water mixture from 2-benzylidene-3-oxo-*N*-phenylbutanamide derivatives under reflux condition.[42] Their mechanistic investigation suggests an amidyl radical intermediate for the intramolecular C(sp^2)-H amidation reaction. Good yields of *N*-aryl 2-quinolinones were isolated in 1 h of reaction time (Scheme 1.17).

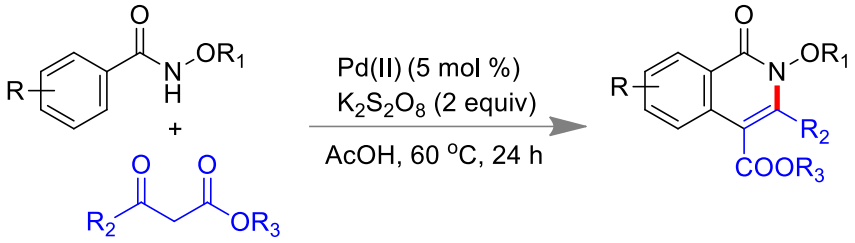


Scheme 1.17 Luo's intramolecular C(sp^2)-H amidation reaction.

1.8.2 Metal catalysed decomposition of $K_2S_2O_8$ for C(sp^3)-O/N bond synthesis

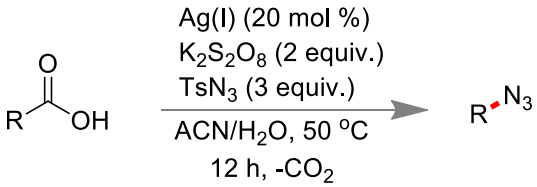
Huang's group developed a palladium catalysed cascade cross dehydrogenative coupling to form C-C bond between *N*-alkoxybenzamides and β-keto esters followed by annulation reaction to get C-N bond for the construction of isoquinolinone rings.[43] Using only 5 mol % of palladium triflate as the catalyst and 2 equiv. of $K_2S_2O_8$ as co-oxidant they obtained up to 87% of product (Scheme 1.18). From mechanistic investigation they have proposed a Pd

catalysed ortho C-H activation to form C-C bond followed by C-N bond formation to get the isoquinolinone rings.



Scheme 1.18 Huang's cascaded C-C and C-N bond synthesis.

Li and co-workers reported an azidation method using catalytic amount of silver salt to decompose $K_2S_2O_8$ for decarboxylation of aliphatic carboxylic acid under aq. ACN solvent in 12 h reflux condition at 50 °C (Scheme 1.19).[44] The method proved to be chemoselective for highly substituted carboxylic acid group.



Scheme 1.19 Li's decarboxylative azidation approach.

1.9 OBJECTIVE

Objective of the present thesis has been development of simpler methods for the synthesis of C-O and C-N bonds in important organic molecules. The present thesis focuses on three important peroxide such as *tert*-butylhydroperoxide, *meta*-chloroperbenzoic acid and potassium peroxydisulfte. New methods for C-O and C-N bond synthesis has been developed using this peroxides.

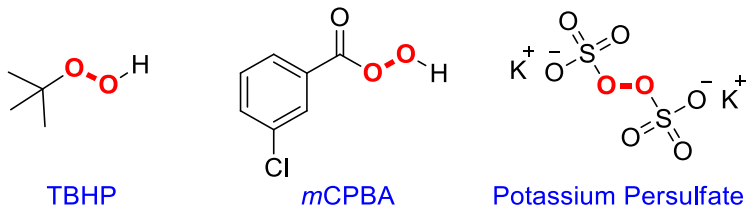


Figure 1.5 Peroxides on which thesis has been focused.

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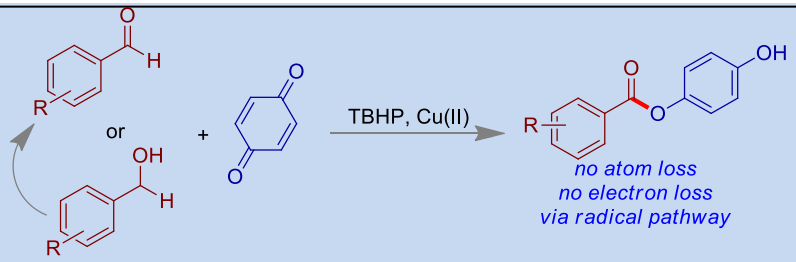
CHAPTER 2

Cross Redox Coupling of Aryl Aldehydes and *p*-Benzoquinones for synthesis of Hydroquinone mono-esters

2.1 ABSTRACT



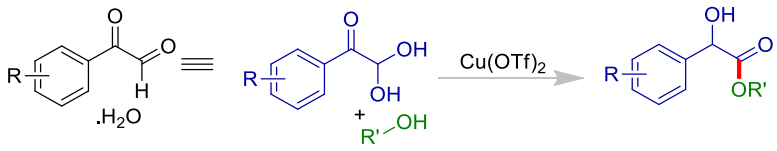
Here, in this chapter an exceptional Cross Redox Coupling (CRC) reaction mediated by *tert*-Butylhydroperoxide and catalytic amount of $Cu(OAc)_2$ has been discussed. Direct coupling of *p*-benzoquinone and aromatic aldehydes (or benzyl alcohols) led to selective formation of mono-esters of hydroquinone in presence of catalytic amount of Cu(II) salt and peroxide TBHP as oxidant. During the esterification reaction, C−H bond of the aryl aldehyde was directly transformed to C−O bond of ester *via* an aroyl radical intermediate.

2.2 INTRODUCTION

Benzoquinones are one of the prevalent classes of core structure found in organic synthesis.[1] These are popularly used in many research areas such as radical reactions, medicinal chemistry, molecular electronics, oxidation chemistry, etc.[2-5] Nucleophilic addition of thiols and amines to quinones are the most common reactions to synthesize functionalized hydroquinone derivatives which follows Michael addition[6] pathway. Recently, hypervalent iodine mediated[7] or metal catalyzed[8] C(sp^2)−H activation[9] is another major development in synthesis of quinone derivatives.[10,11] However, direct acylation of hydroquinone to get ester derivatives from quinone and any acylating reagents are very less explored in literature.[11]

Regio-selective mono-esterification of hydroquinone is synthetically challenging due to unavailability of properly activated acids and coupling reagents and probabilities of formation of diesters.[1]

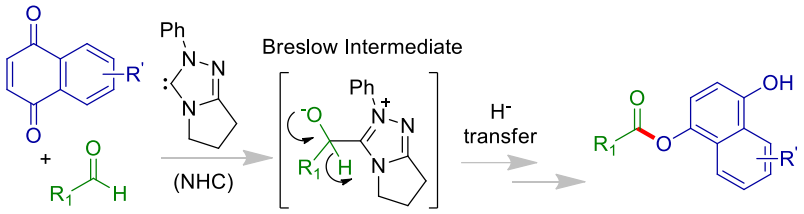
A redox coupling reaction is a transformation[12] where one of the substrate loses electron to get oxidized[13,14] at the expense another substrate accepts these electrons[15] and get reduced.[16] Various enzymatic processes undergo this mechanism for biochemical transformations. One such example is the reaction between lactate and NAD^+ where lactate undergoes oxidation to form pyruvate and NAD^+ gets reduced to NADH in presence of enzyme lactate dehydrogenase. Similarly, chemists are mimicking natural process in laboratory to get various chemical transformations.[17-21] Fischer indolization[14] is an example of redox reaction where oxidative C – C bond formation occurs as a consequence of reductive N – N bond cleavage. Similarly, a range of condensation reaction between similar or different carbonyl compounds such as Cannizzaro reaction,[22] aldol condensation, coupling of ketones and enolates[23] are well recognized in literature (Scheme 2.1). Although, these reactions are well explored the yields and purity of desired product is highly dependent on reaction condition such as concentration of base, temperature and solvent as well.



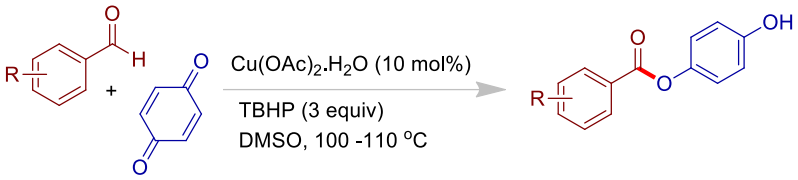
Scheme 2.1 Intramolecular Cannizzaro reaction approach for ester synthesis.

Traditionally, for synthesis of esters pre-activation of acids to various active synthons like acyl halides, anhydrides, and activated esters are necessary and the esterification with alcohols requires stoichiometric amount of bases or coupling reagent which makes the synthesis multistep.[24,25] The oxidative esterification between β-dicarbonyl compounds and

aldehydes, and synthesis of enol carbamates by direct C-H bond activation of formamides are reported.[26,27] Various transition metal as well as *N*-heterocyclic carbene (NHC)[10] catalyzed C-H esterification of aldehydes are reported. Mono-acylation of *p*-napthaquinones with aldehydes was observed by Csáky and coworkers in 2009 using catalytic amount of NHC *via* Breslow[28] intermediate (Scheme 2.2). We report here direct cross coupling reaction for esterification of two carbonyl compounds (*p*-benzoquinone and benzaldehyde derivatives) without activating any one of them (Scheme 2.3).



Scheme 2.2 *N*-Heterocyclic carbene (NHC) mediated monoacylation of 1,4-napthaquinopne using aldehyde *via* Breslow intermediate.



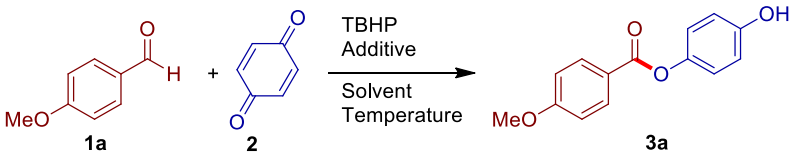
Scheme 2.3 Our approach for Cross Redox Coupling catalyzed by $Cu(OAc)_2$ and TBHP.

2.3 RESULTS AND DISCUSSIONS

Table 2.1 describes the screening of reaction condition to get the optimum reagents combinations and parameters for getting best yield of product transformation. Most appropriate condition (entry 5) was recognized for the combination of 1.0 equiv of **1a** (*p*-anisaldehyde), 1.5 equiv of **2** (*p*-benzoquinone), 3.0 equiv of *tert*-Butylhydroperoxide (TBHP) (*Caution!!*) and catalyst $Cu(OAc)_2.H_2O$ in 10 mol% of in DMSO at 100-110 °C

temperature. When temperature was below 100 °C the reaction gave poor yield of corresponding mono-ester. Addition of I_2 (entry 8) or KI-I_2 (entry 9) were not successful to improve the yield of product. When $CuCl_2$ (entry 11), $FeCl_3$ (entry 12), $Cu(OTf)_2$ (entry 13), etc. were used in place of $Cu(OAc)_2.H_2O$, the resulting reaction mixture was not conclusive and product formation could not occur. There was no significant improvement of yield when $K_2S_2O_8$ (entry 10) was added under standard condition. Solvents like ACN (entry 1), dimethyl formamide (entry 2), were also not successful for the transformation. Under solvent free neat condition (entry 14), yield was poor and no successful reaction could be observed under mechanochemical[29] ball-milling.

Table 2.1. Optimization of reaction condition for synthesis of **3a**.



Entry	TBHP[a] (equiv)	Additive[b] (mol%)	Solvent[c] (temp, °C)	Yield[d] (%)
1	2	$Cu(OAc)_2$	CH_3CN (90 °C)	< 5
2	2	$Cu(OAc)_2$	DMF (90 °C)	< 5
3	2	$Cu(OAc)_2$	DMSO (90 °C)	36
4	3	$Cu(OAc)_2$	DMSO	62
5	3	$Cu(OAc)_2$ (10)	DMSO	82
6	3	$Cu(OAc)_2$ (5)	DMSO	48
7	3	TBAI (20)	DMSO	30
8	3	I_2 (20)	DMSO	-- [e]
9	3	KI (50) + I_2 (20)	DMSO	-- [e]
10	2	$Cu(OAc)_2$ (10) + $K_2S_2O_8$ (20)	DMSO	50

11	3	$CuCl_2$ (20)	DMSO	--[f]
12	3	$FeCl_3$ (30)	DMSO	< 5
13	3	$Cu(OTf)_2$ (20)	DMSO	--[e]
14	3	$Cu(OAc)_2$	Neat	38[d]
15	3[g]	$Cu(OAc)_2$	DMSO	--[h]
16	3	CuI (20)	DMSO	--[h]

[a] 70% In water. [b] In all cases $Cu(OAc)_2$ used as $Cu(OAc)_2.H_2O$ and in 20 mol%, if not mentioned. [c] In DMSO, the reactions were done at 110 °C, if not shown. [d] Yield based on recovered starting material. [e] Not conclusive. [f] Sluggish reaction mixture. [g] 5-6 M TBHP in decane. [h] No reaction.

Several benzaldehyde derivatives were subjected to optimized condition (Table 2.1, entry 5), to verified the efficiency of the CRC methodology (Figure 2.1). Electron neutral unsubstituted benzaldehyde and electron rich derivatives yielded good amount of the product formation (**3a**, **3b**, **3c**, **3j**, **3k** and **3l**) ranging from 65 – 85%. Halogened benzaldehydes resulted the corresponding monoesters with reasonable yields (**3e** and **3f, 3i**). Sterically hindered *ortho*-substituted benzaldehydes (**3d**, **3g**, **3j** and **3m**) did not affect product formation. Similarly, hetero-aromatic aldehyde (**3o**) and polynuclear aromatic aldehyde (**3p**, **3q** and **3r**) underwent smooth transformation to monoesters to give up to 80% of yield. Over-oxidation of benzylic CH_3 to aldehydic or acidic group was not observed in presence of TBHP for methyl or ethyl substituted derivatives. The major pitfall of this methodology is that aldehydes having electron withdrawing group like $–NO_2$ or -CN were unsuccessful to provide the corresponding ester.

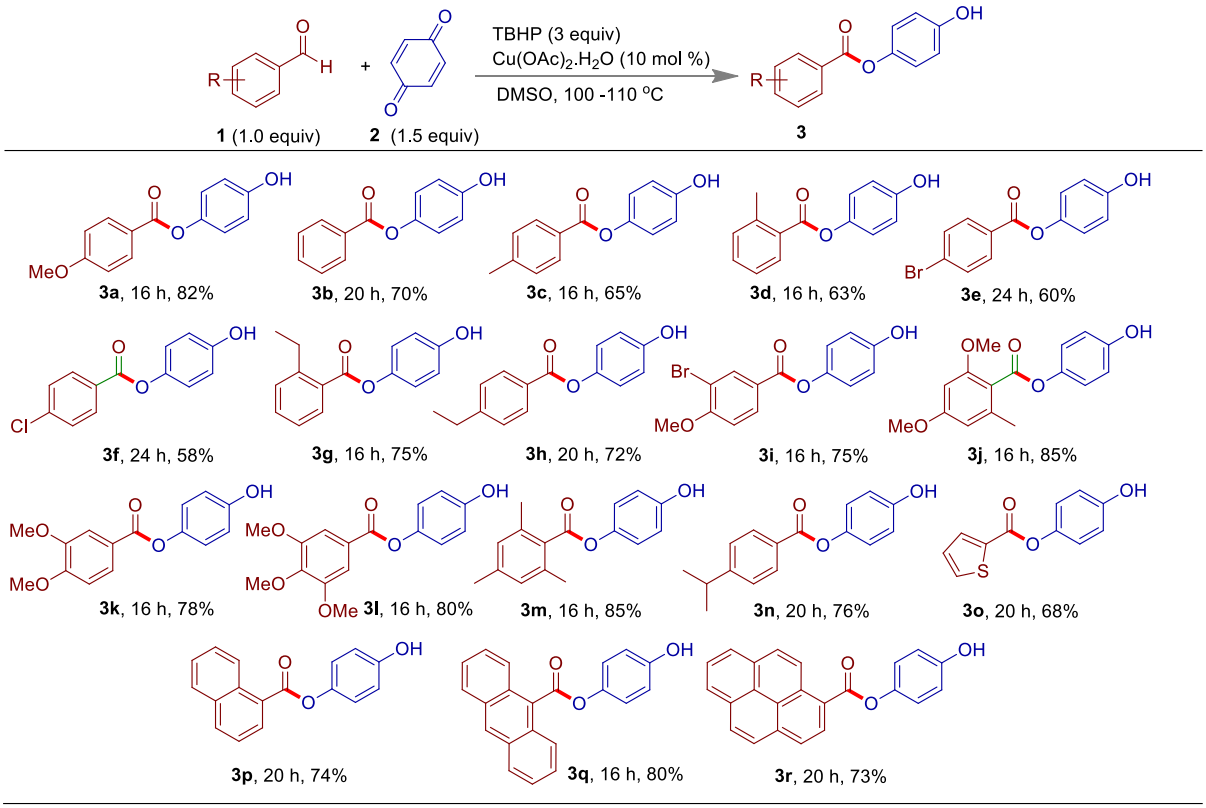


Figure 2.1. Mono esterification of *p*-Benzoquinone with benzaldehyde derivatives.

To further explore the effectiveness of the cross redox coupling reaction benzyl alcohols were directly used for *in situ* generation of benzaldehyde *via* oxidation in presence of TBHP. *In situ* generated aldehydes were also successful for the mono esterification reaction with *p*-benzoquinone to give up to 78% yield under standard condition although 4 equiv of TBHP were used which can attributed to the need for oxidation of alcohols to aldehydes (Figure 2.2). In this method also electron rich benzyl alcohols as well as halogen containing benzyl alcohols worked well. Also polynuclear benzyl alcohols gave 67 – 72% of mono esters.

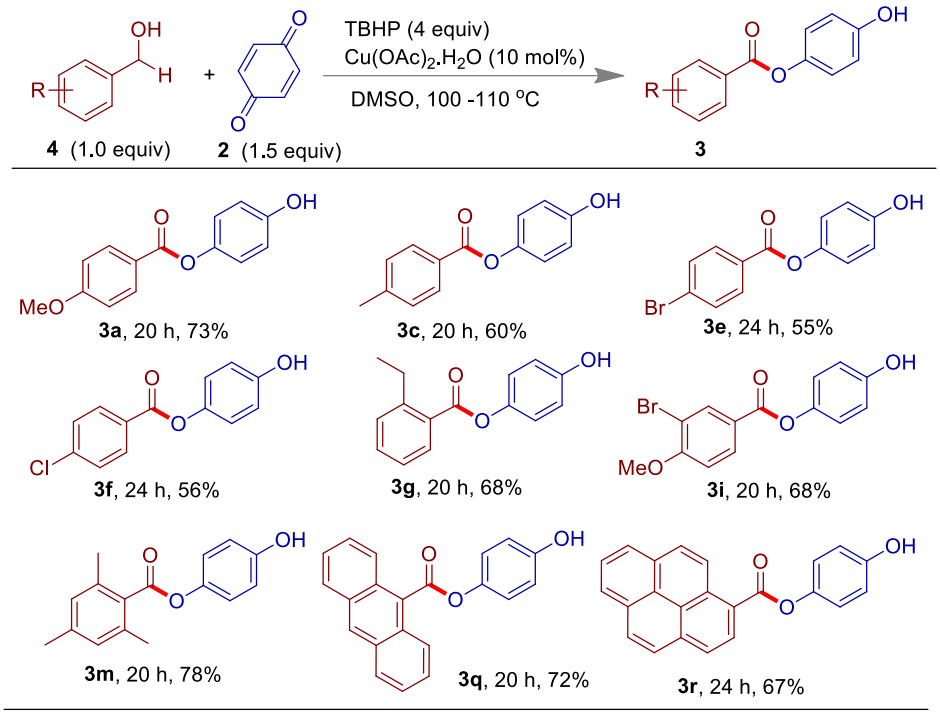


Figure 2.2. *In situ* generation of aldehydes; followed by cross redox coupling with *p*-benzoquinones.

To understand the reaction pathway several control experiments were performed (Figure 2.3). Radical scavenger experiment was done with substrate **1a** and 2 equiv of 2,2,6,6-Tetramethylpiperidin-1-yl-oxy radical (TEMPO)[30,31] under standard condition where 78% of TEMPO adduct of *p*-anisaldehyde (**5**, 78%) was observed (Figure 2.3a). Formation of adduct **5** concluded radical pathway for the esterification reaction and generation of benzoyl radical. Both the reagents TBHP and $Cu(OAc)_2$ were involved synergistically for the product formation since in absence of any of the component, the reaction failed to give esters (Figure 2.3b). Reaction between hydroquinone (**6**) and and *p*-anisic acid (**7**) under standard condition failed to give any ester which confirms that none of these **6** or **7** are intermediate in the reaction pathway. Again hydroquinone (**6**) and **1a** under optimized reaction condition resulted only trace amount of esters. On prolong heating of the reaction mixture for 48 h (Figure 2.3d), **3a'** was detected (~ 5%) which was due to C-aroylation of the resulting ester.

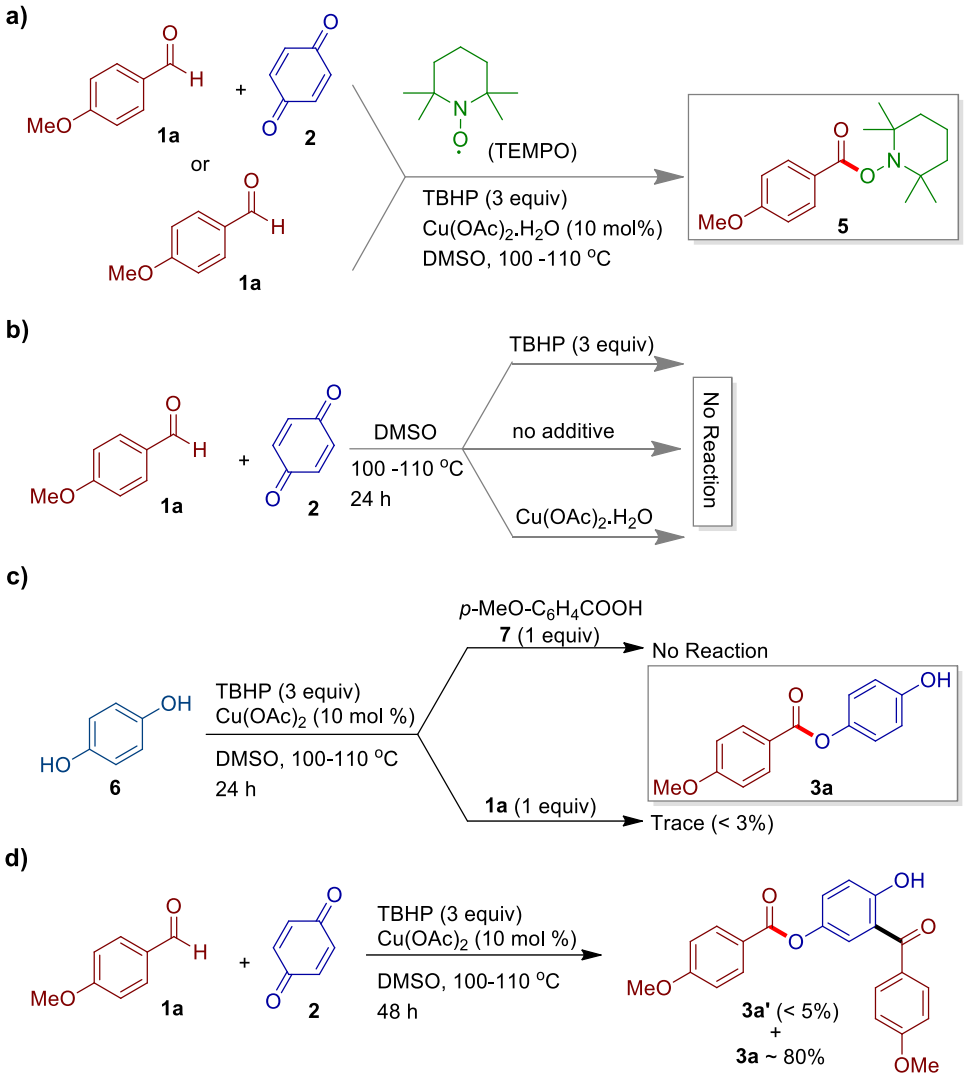


Figure 2.3. a) - d) Controlled experiments for mechanistic understanding of the CRC reaction.

Following the results of the controlled experiments the mechanism of the cross redox coupling reaction is portrayed in figure 2.4. Catalytic amount of $Cu(OAc)_2$ helped to generate *t*-butylperoxy radicals from TBHP along with hydrogen radical which converted to H^+ to reduce Cu(II) to Cu(I).[32,33] t-BuOO• or t-BuO• abstracted the aldehydic hydrogen[34,35] from benzaldehyde derivatives to generate aroyl radical **8**. Radical intermediate **8** underwent O-addition with *p*-benzoquinone[36] to give 4-(aroyloxy)phenoxide radical (**9**) which got reduced by Cu(I) to 4-(aroyloxy)phenolate anion (**10**) and Cu(II) was generated for the next catalytic

cycle. Anion **10** due to the presence of H_3O^+ in the reaction system led to ester **3** via proton abstraction.

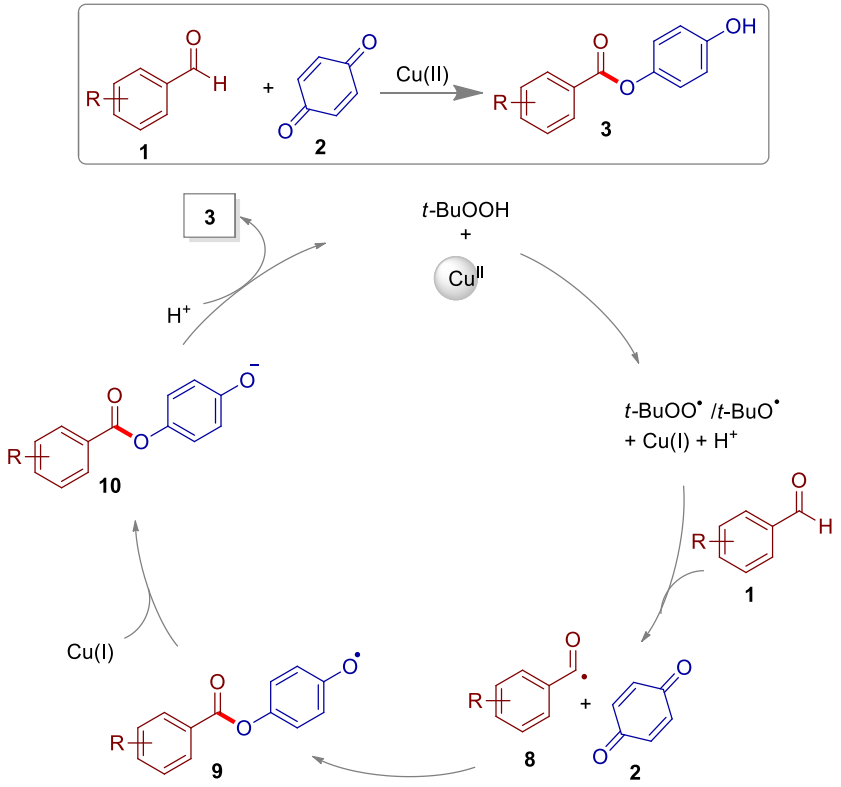


Figure 2.4 Plausible mechanistic cycle for Cu-TBHP mediated CRC reaction.

2.4 CONCLUSIONS

In conclusion, an unique Cu(II) catalyzed TBHP mediated cross redox coupling (CRC) reaction has been developed for regio-selective synthesis of monoesters of *p*-benzoquinone, using benzaldehyde or benzyl alcohol as the acylating without activation. Both the carbonyl groups were used directly without the necessity of activation prior to esterification. In this transformation both atoms as well as electrons were well conserved. Hence, we anticipate that our study may draw significant attention of chemists working on the development of synthetic methodologies as well as the researchers searching for better understanding of mechanistic organic chemistry.

2.5 EXPERIMENTAL SECTION

General Methods. Column chromatographic purifications of the compounds were performed using silica gel (mesh 100–200) and hexane – ethyl acetate mixtures as eluent, unless otherwise specified. NMR spectra were recorded on a 400 MHz instrument at 25 °C. The chemical shift values are reported in parts per million (ppm) with respect to residual dimethyl sulfoxide (2.50 ppm for ^{1}H and 40.00 for ^{13}C). The peak patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; td, triplet of doublets; br s, broad singlet. The coupling constants (*J*) are reported in Hertz (Hz). High-resolution mass spectra (HR-MS) were recorded on an ESI-TOF (time of flight) mass spectrometer. Infrared spectral data are reported in wave number (cm^{-1}). FT-IR spectra were recorded after making pellet of the compounds using anhydrous solid KBr. Melting points of the compounds were determined using a digital melting point apparatus and are uncorrected.

Caution. TBHP is a potential shock sensitive chemical.[31] Therefore, very high level of safety precautions should be exercised during reaction with TBHP. The precautions like PPEs (personal protective equipment) should be used while handling TBHP under neat condition. In this work, the TBHP was used as 70% in water. Use of blast shields is mandatory at all times during the reactions.

Yields (after column chromatography) were calculated based on recovered aldehydes. However, in parenthesis yields are calculated based on aldehydes used for the reaction.

Procedure for preparation of 4-hydroxyphenyl-4-methoxybenzoate (3a): To an oven-dried sealed tube charged with a magnetic stirring bar and **1a** (100 mg, 0.73 mmol, 1 equiv), $Cu(OAc)_2.H_2O$ (14.5 mg, 0.073 mmol, 10 mol %), and TBHP (0.3 mL, 2.2 mmol, 3 equiv, 70 % in water) in DMSO (2 mL) was added **2** (120 mg, 1.1 mmol, 1.5 equiv). The reaction

mixture was allowed to stir at 110 °C for 16 h. After cooling at room temperature, the reaction mixture washed with water and followed by extracted with ethyl acetate. Column purification using 15% ethyl acetate-hexane yielded **3a** 82% (117 mg, 66%) as pale yellow solid; R_f 0.20 (15% ethyl acetate/hexane); mp: 162-164 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (s, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.0, 164.0, 155.5, 143.2, 132.3, 123.0, 121.7, 116.0, 114.7, 56.1; IR (KBr) $\tilde{\nu}$ 3438, 2935, 1701, 1597, 1509, 1398, 1321, 1287, 1261, 1168, 1112, 1073, 994, 850, 767, 696 cm^{-1}; HRMS observed 245.0808 (calculated for $C_{14}H_{13}O_4$ $[M+H]^+$ 245.0814).

Procedure for in situ oxidation of benzyl alcohols to aldehydes and preparation of 4-hydroxyphenyl-4-methoxybenzoate (3a): To an oven-dried sealed tube charged with a magnetic stirring bar and **4a** (100 mg, 0.72 mmol, 1 equiv), $Cu(OAc)_2.H_2O$ (14.5 mg, 0.072 mmol, 10 mol %), and TBHP (0.4 mL, 2.8 mmol, 4 equiv, 70 % in water) in DMSO (2 mL) was added **2** (117 mg, 1.1 mmol, 1.5 equiv). The reaction mixture was allowed to stir at 110 °C for 20 h. After cooling at room temperature, the reaction mixture washed with water and followed by extracted with ethyl acetate. Column purification using 15% ethyl acetate-hexane yielded **3a** (104 mg, 73%) as pale yellow solid.

Trapping of acyl radical by TEMPO: TEMPO (228 mg, 1.46 mmol, 2 equiv) was added to an oven-dried sealed tube charged with a magnetic stirring bar and **1a** (100 mg, 0.73 mmol, 1 equiv). $Cu(OAc)_2.H_2O$ (14.5 mg, 0.073 mmol, 10 mol %), and TBHP (0.3 mL, 2.2 mmol, 3 equiv, 70 % in water) were added to the mixture in DMSO, and the sealed tube was kept at 100 °C. The reaction was monitored by TLC. After completion of the reaction, the mass was dissolved in dichloromethane and purified by column chromatography to obtain 2,2,6,6-

tetramethylpiperidin-1-yl-4-methoxybenzoate **(5)** . Yield 78% (166 mg); R_f 0.40 (2% diethyl ether/hexane); pale yellow liquid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 1.54 – 1.34 (m, 6H), 1.17 (s, 6H), 0.96 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.6, 163.6, 131.5, 121.6, 114.6, 60.1, 55.9, 39.2, 32.0, 20.8, 16.9; IR Neat $\tilde{\nu}$ 2974, 2937, 1740, 1601, 1503, 1458, 1364, 1319, 1245, 1172, 1074, 1033, 922, 849, 771, 686, 608 cm^{-1}; HRMS observed 292.1907 (calculated for $C_{17}H_{26}NO_3$ $[M+H]^+$ 292.1913).

Compound Characterization Data

4-Hydroxyphenylbenzoate (3b): R_f 0.20 (10% ethyl acetate/hexane); colorless solid; yield 70% (90 mg, 58%) ; mp: 160-162 °C (lit.[37] 161-165 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 8.10 (d, *J* = 8.0 Hz, 2H), 7.73 (t, *J* = 6.8 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.4, 155.6, 143.1, 134.3, 130.1, 129.6, 129.4, 123.0, 116.1; IR (KBr) $\tilde{\nu}$ 3455, 1714, 1596, 1508, 1398, 1338, 1281, 1209, 1188, 1112, 1066, 1000, 878, 816, 712 cm^{-1}; HRMS observed 215.0703 (calculated for $C_{13}H_{11}O_3$ $[M+H]^+$ 215.0709).

4-Hydroxyphenyl-4-methylbenzoate (3c): R_f 0.20 (10% ethyl acetate/hexane); off white solid; yield 65%, (93 mg, 49%); mp: 119-122 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 7.99 (d, *J* = 7.6 Hz, 2H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.79 (d, *J* = 8.0 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.3, 155.5, 144.7, 143.2, 130.1, 129.9, 126.8, 123.0, 116.0, 21.7; IR (KBr) $\tilde{\nu}$ 3331, 2919, 1721, 1709, 1601, 1507, 1395, 1286, 1181, 1114, 1080, 822, 747 cm^{-1}; HRMS observed 251.0677 (calculated for $C_{14}H_{12}O_3Na$ $[M+Na]^+$ 251.0679). .

4-Hydroxyphenyl-2-methylbenzoate (3d): R_f 0.20 (10% ethyl acetate/hexane); pale yellow solid; yield 63% (90 mg, 48%); mp: 114-116 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.2, 155.5, 143.1, 140.2, 133.1, 132.2, 131.0, 129.1, 126.6, 123.0, 116.0, 21.6; IR (KBr) $\tilde{\nu}$ 3436, 2962, 2929, 1719, 1593, 1507, 1446, 1392, 1249, 1209, 1180, 1053, 882, 824, 739, 596 cm^{-1}; HRMS observed 229.0887 (calculated for $C_{14}H_{13}O_3$ $[M+H]^+$ 229.0865).

4-Hydroxyphenyl-4-bromobenzoate (3e): R_f 0.20 (12% ethyl acetate/hexane); pale yellow solid; yield 60% (30 mg, 38%); mp: 126-127 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.9, 155.8, 143.2, 132.7, 132.2, 129.0, 128.5, 123.1, 116.2; IR (KBr) $\tilde{\nu}$ 3373, 2922, 1730, 1590, 1509, 1458, 1398, 1287, 1207, 1114, 1077, 1009, 867, 848, 814, 749 cm^{-1}; HRMS observed 292.9808 (calculated for $C_{13}H_{10}BrO_3$ $[M+H]^+$ 292.9813).

4-Hydroxyphenyl-4-chlorobenzoate (3f): R_f 0.20 (12% ethyl acetate/hexane); colorless solid; yield 58% (62 mg, 35%); mp: 117-119 °C (lit.[37] 117 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.6, 155.7, 143.0, 139.2, 132.0, 129.6, 128.5, 122.9, 116.1; IR (KBr) $\tilde{\nu}$ 3379, 2933, 1730, 1592, 1510, 1486, 1399, 1292, 1208, 1111, 1075, 917, 850, 752 cm^{-1}; HRMS observed 249.0313 (calculated for $C_{13}H_{10}ClO_3$ $[M+H]^+$ 249.0319).

4-Hydroxyphenyl-2-ethylbenzoate (3g): R_f 0.20 (8% ethyl acetate/hexane); off white solid; yield 75% (101 mg, 56%); mp: 128-130 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.42 - 7.36 (m, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 2.94 (q, *J* = 7.6 Hz, 2H), 1.19 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.4 , 155.6, 145.9, 143.1, 133.2, 130.9, 130.8, 129.0, 126.6, 123.0, 116.1, 27.2, 16.43; IR (KBr) $\tilde{\nu}$ 3466, 2960, 1705, 1598, 1520, 1446, 1397, 1254, 1180, 1066, 886, 820, 735, 587 cm^{-1}; HRMS observed 243.1016 (calculated for $C_{15}H_{15}O_3$ $[M+H]^+$ 243.1021).

4-Hydroxyphenyl-4-ethylbenzoate (3h): R_f 0.20 (8% ethyl acetate/hexane); off white solid; yield 72% (97 mg, 52%); mp: 120-122 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 2.71 (q, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.4, 155.6, 150.8, 143.2, 130.3, 128.8, 127.1, 123.0, 116.1, 28.7, 15.7; IR (KBr) $\tilde{\nu}$ 3448, 2971, 2932, 1710, 1599, 1508, 1443, 1397, 1280, 1212, 1175, 1112, 1085, 881, 851, 822 cm^{-1}; HRMS observed 265.0835 (calculated for $C_{15}H_{14}O_3Na$ $[M+Na]^+$ 265.0841).

4-Hydroxyphenyl-3-bromo-4-methoxybenzoate (3i): R_f 0.22 (20% ethyl acetate/hexane); pale yellow solid; yield 75%, (89 mg, 59%); mp: 174-177 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (s, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 8.10 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 160.1, 155.6, 143.1, 134.6, 131.8, 123.1, 123.0, 116.1, 113.1, 111.2, 57.3; IR (KBr) $\tilde{\nu}$ 3406, 2917, 2847, 1729, 1594, 1511, 1400, 1271, 1190, 1115, 1024, 1003, 829, 755 cm^{-1}; HRMS observed 322.9913 (calculated for $C_{14}H_{12}BrO_4$ $[M+H]^+$ 322.9919).

4-Hydroxyphenyl-2,4-dimethoxy-6-methylbenzoate (3j): R_f 0.24 (25% ethyl acetate/hexane); light orange solid; yield 85% (115 mg, 72%); mp: 112-114 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.52 (s,1H), 6.49 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.8, 161.8, 158.5, 155.5, 143.1, 138.0, 122.8, 116.1, 115.6, 107.5, 96.7, 56.4, 55.8, 19.8; IR (KBr) $\tilde{\nu}$ 3440, 2942, 2837, 1728, 1604, 1503, 1466, 1443, 1335, 1294, 1260, 1204, 1043, 746 cm^{-1}; HRMS observed 289.1071 (calculated for $C_{16}H_{17}O_5$ $[M+H]^+$ 289.1076).

4-Hydroxyphenyl-3,4-dimethoxybenzoate (3k): R_f 0.30 (25% ethyl acetate/hexane); light orange solid; yield 78% (103 mg, 63%); mp: 153-155 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H), 7.74 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.1, 155.5, 153.9, 149.0, 143.3, 124.3, 123.0, 121.6, 116.0, 112.5, 111.7, 56.2, 56.0; IR (KBr) $\tilde{\nu}$ 3440, 2917, 2847, 1740, 1601, 1510, 1417, 1274, 1191, 1139, 1078, 1012, 906, 755, 526 cm^{-1}; HRMS observed 275.0914 (calculated for $C_{15}H_{15}O_5$ $[M+H]^+$ 275.0919).

4-Hydroxyphenyl- 3,4,5-trimethoxybenzoate (3l): R_f 0.30 (30% ethyl acetate/hexane); light orange solid; yield 80% (98 mg, 64%); mp: 137-140 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (s, 1H), 7.37 (s, 2H), 7.04 (d, *J* = 8.8 , 2H), 6.80 (d, *J* = 8.8, 2H), 3.86 (s, 6H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.0, 155.6, 153.3, 143.2, 142.7, 124.6, 123.0, 116.1, 107.5, 60.7, 56.5; IR (KBr) $\tilde{\nu}$ 3415, 2928, 2852, 1728, 1593, 1509, 1463, 1417, 1398, 1337, 1215, 1192, 1112, 1025, 996, 763, 702, 618 cm^{-1}; HRMS observed 305.1020 (calculated for $C_{16}H_{17}O_6$ $[M+H]^+$ 305.1025).

4-Hydroxyphenyl-2,4,6-trimethylbenzoate (3m): R_f 0.20 (12% ethyl acetate/hexane); colorless powder; yield 85% (116 mg, 67%); mp: 130-132 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (s, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.98 (s, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 2.3 (s, 6H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.6, 155.7, 142.8, 139.8, 135.1, 130.5, 128.8, 122.8, 116.2, 21.2, 19.8; IR (KBr) $\tilde{\nu}$ 3469, 2928, 1723, 1596, 1508, 1444, 1398, 1264, 1207, 1177, 1112, 1066, 851, 809 cm^{-1}; HRMS observed 257.1192 (calculated for $C_{16}H_{17}O_3$ $[M+H]^+$ 257.1178).

4-Hydroxyphenyl-4-isopropylbenzoate (3n): R_f 0.22 (10% ethyl acetate/hexane); pale yellow solid; yield 76% (105 mg, 60%); mp: 115-119 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 8.02 (d, *J* = 8.4Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 3.00 (m,1H), 1.24 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.7, 155.7, 155.6, 143.5, 130.6, 127.6, 127.4, 123.3, 116.4, 34.3, 24.2; IR (KBr) $\tilde{\nu}$ 3375, 2962, 2933, 1713, 1593, 1509, 1397, 1276, 1193, 1112, 1075, 768, 705 cm^{-1}; HRMS observed 257.1203 (calculated for $C_{16}H_{17}O_3$ $[M+H]^+$ 257.1178).

4-Hydroxyphenyl-thiophene-2-carboxylate (3o): R_f 0.20 (10% ethyl acetate/hexane); brown solid; yield 68% (86 mg, 44%); mp: 109-111 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.06 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.98 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.29 (dd, *J* = 4.4, 3.6 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.9, 155.7, 142.8, 135.4, 135.3, 132.6, 129.1, 123.0, 116.1; IR (KBr) $\tilde{\nu}$ 3448, 2923, 2852, 1691, 1594, 1505, 1408, 1291, 1260, 1205, 1183, 1112, 1067, 994, 917, 855, 807, 728 cm^{-1}; HRMS observed 221.0267 (calculated for $C_{11}H_9O_3S$ $[M+H]^+$ 221.0272).

4-Hydroxyphenyl-2-naphthoate (3p): R_f 0.22 (12% ethyl acetate/hexane); pale yellow solid; yield 74% (98 mg, 58%); mp: 138-142 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 1H), 8.80 (d, *J* = 8.4 Hz, 1H), 8.39 (d, *J* = 7.2 Hz, 1H), 8.27 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.72 – 7.62 (m, 3H), 7.15 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.2, 155.7, 143.2, 134.5, 133.9, 131.2, 131.1, 129.3, 128.6, 127.0, 126.3, 125.5, 125.4, 123.1, 116.1; IR (KBr) $\tilde{\nu}$ 3412, 1696, 1592, 1505, 1433, 1401, 1343, 1282, 1245, 1128, 988, 882, 781 cm^{-1}; HRMS observed 265.0859 (calculated for $C_{17}H_{13}O_3$ $[M+H]^+$ 265.0865).

4-Hydroxyphenyl-anthracene-9-carboxylate (3q): R_f 0.30 (15% ethyl acetate/hexane); off white solid; yield 80% (110 mg, 71%); mp: 230-234 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1H), 8.87 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 2H), 8.17 (d, *J* = 8.8 Hz, 2H), 7.73-7.69 (m, 2H), 7.65 – 7.61 (m, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.3, 156.0, 143.0, 130.9, 130.3, 129.3, 128.3, 128.0, 126.9, 126.4, 124.8, 123.1, 116.4; IR (KBr) $\tilde{\nu}$ 3500, 2934, 1730, 1597, 1507, 1447, 1401, 1270, 1197, 1171, 1115, 984, 874, 788 cm^{-1}; HRMS observed 337.0835 (calculated for $C_{21}H_{14}O_3Na$ $[M+Na]^+$ 337.0841).

4-Hydroxyphenyl-pyrene-1-carboxylate (3r): R_f 0.30 (15% ethyl acetate/hexane); bright yellow solid; yield 73% (80 mg, 55%); mp: 210-213 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (s, 1H), 9.17 (d, *J* = 9.6 Hz, 1H), 8.84 (d, *J* = 8.4 Hz, 1H), 8.47-8.40(m, 5H), 8.32 (d, *J* = 9.6 Hz, 1H), 8.20 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.7, 155.8, 143.5, 134.8, 131.07, 131.06, 130.6, 130.4, 130.3, 129.3, 127.7, 127.4, 127.1, 125.1, 124.6, 124.5, 123.8, 123.32 (×2), 122.8, 116.3; IR

(KBr) $\tilde{\nu}$ 3432, 2927, 1683, 1586, 1500, 1440, 1324, 1226, 1174, 1129, 1076, 1035, 998, 889, 833, 709 cm^{-1}; HRMS observed 361.0835 (calculated for $C_{23}H_{14}O_3Na$ $[M+Na]^+$ 361.0841).

4-Hydroxy-3-(4-methoxybenzoyl)phenyl-4-methoxybenzoate (3a′): R_f 0.35 (8% ethyl acetate/hexane); pale yellow solid; yield 12 mg (<5%); mp: 188-191 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.06 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.28 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.15 (d, *J* = 2.8 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.8, 165.0, 164.2, 163.8, 153.9, 143.0, 132.5, 132.4, 130.2, 126.7, 126.1, 122.9, 121.5, 117.6, 114.7, 114.4, 56.18 , 56.13; IR (Neat) $\tilde{\nu}$ 3435, 2924, 2852, 1730, 1631, 1604, 1510, 1479, 1420, 1334, 1261, 1169, 1134, 1066, 1028, 970, 845, 785 cm^{-1}; HRMS observed 379.1184 (calculated for $C_{22}H_{18}O_6$ $[M+H]^+$ 379.1176).

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^{1}H and ^{13}C NMR spectra of the compounds

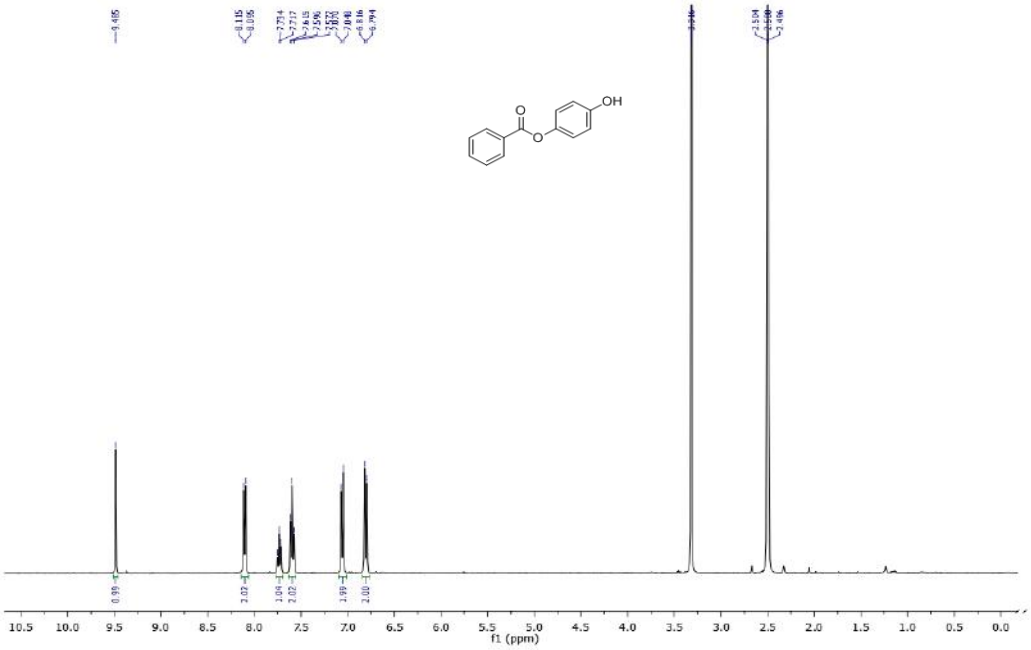


Figure 2.5. ^{1}H NMR spectrum of 4-Hydroxyphenyl benzoate (**3b**).

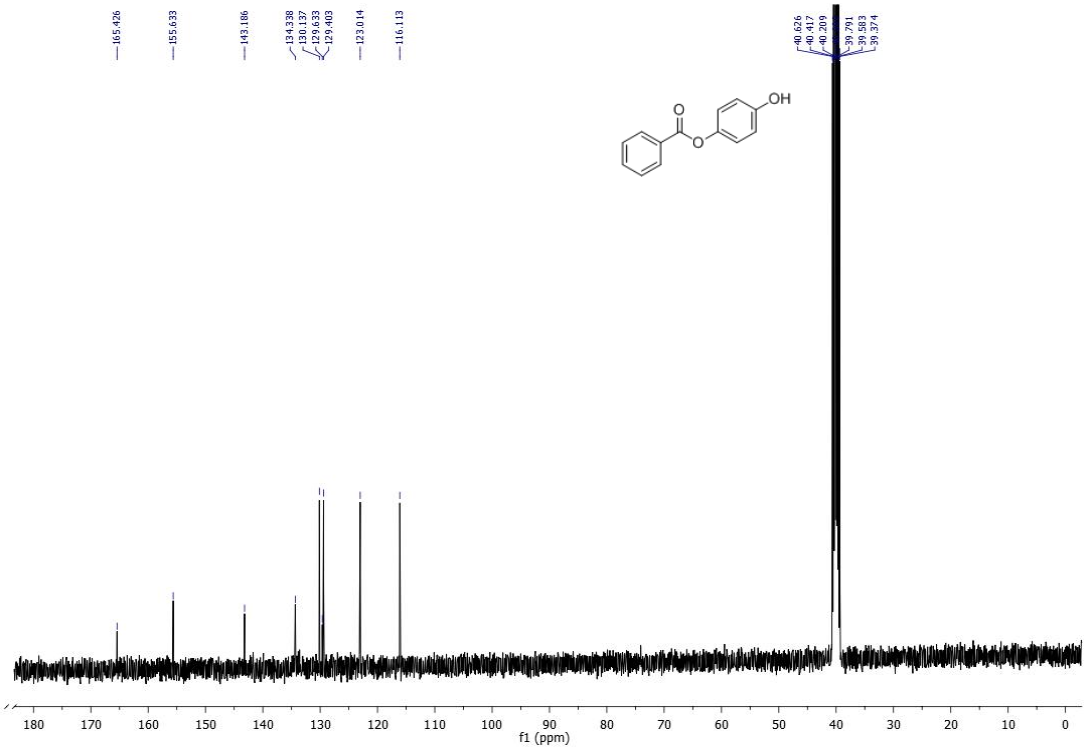


Figure 2.6. ^{13}C{^{1}H} NMR spectrum of 4-hydroxyphenyl benzoate (**3b**).

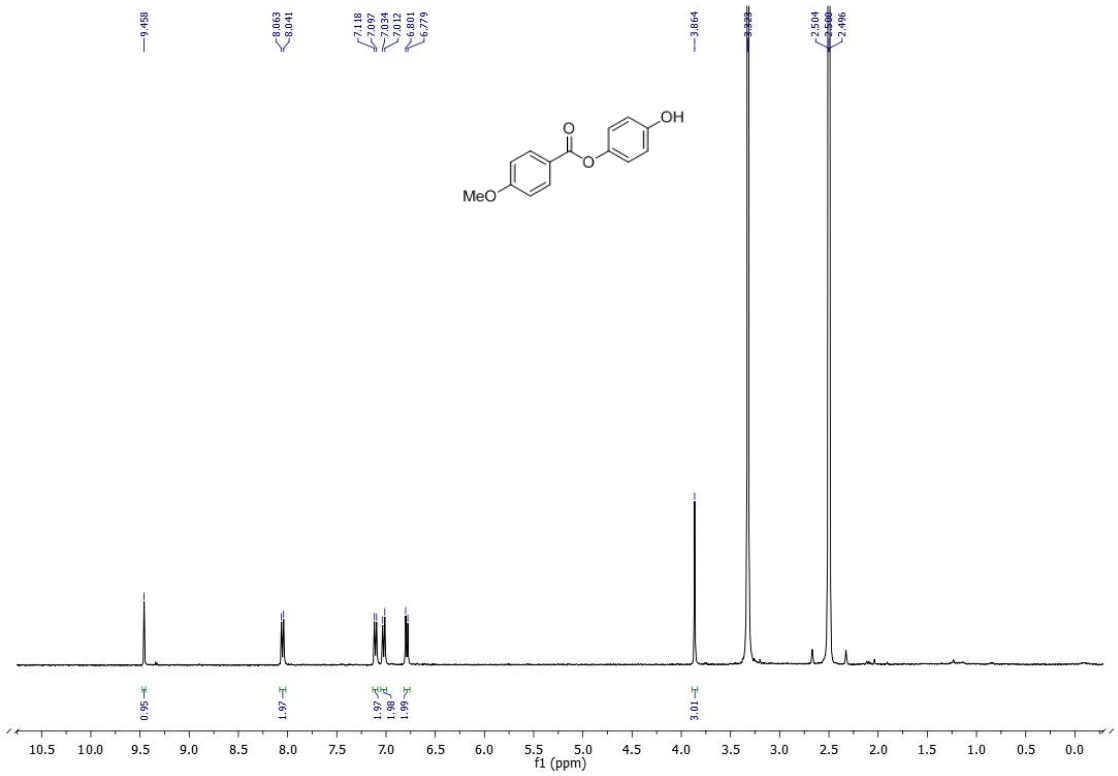


Figure 2.7. ^{1}H NMR spectrum of 4-hydroxyphenyl-4-methoxybenzoate (**3a**).

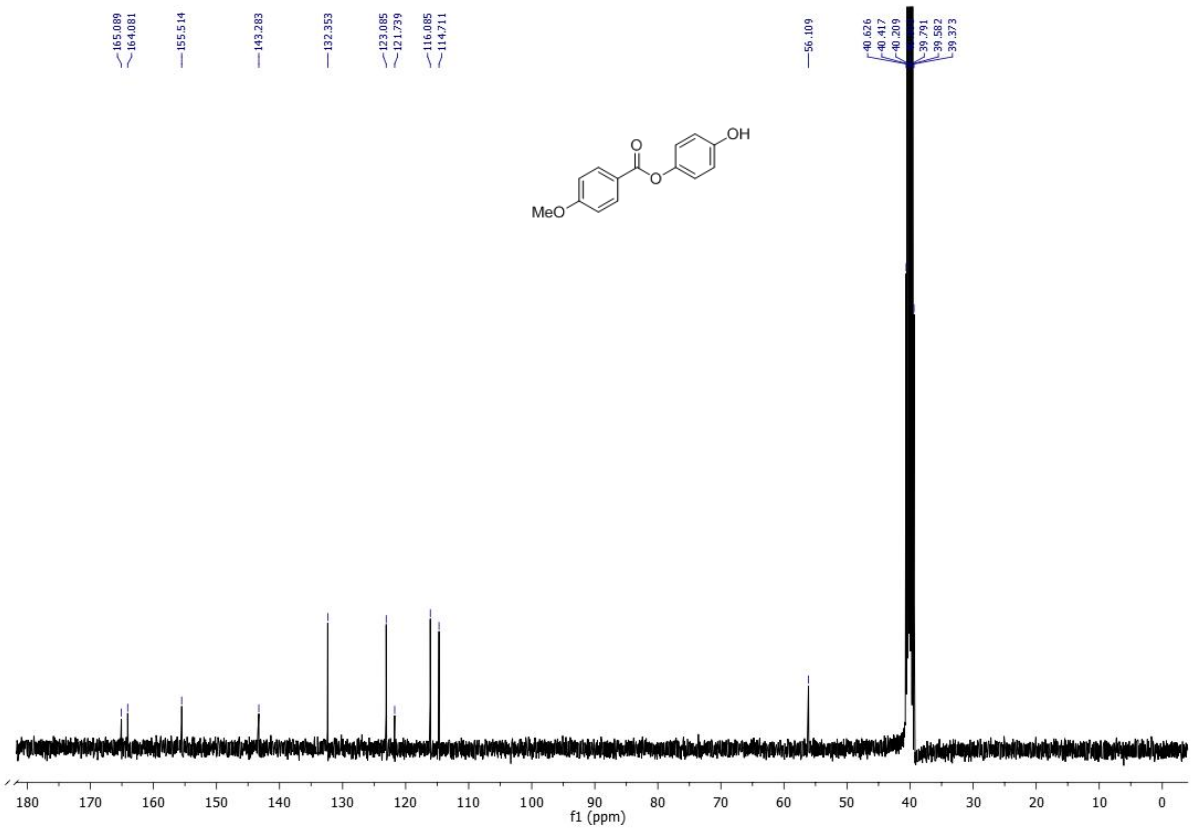


Figure 2.8. ^{13}C{^{1}H} NMR spectrum of 4-hydroxyphenyl-4-methoxybenzoate (**3a**).

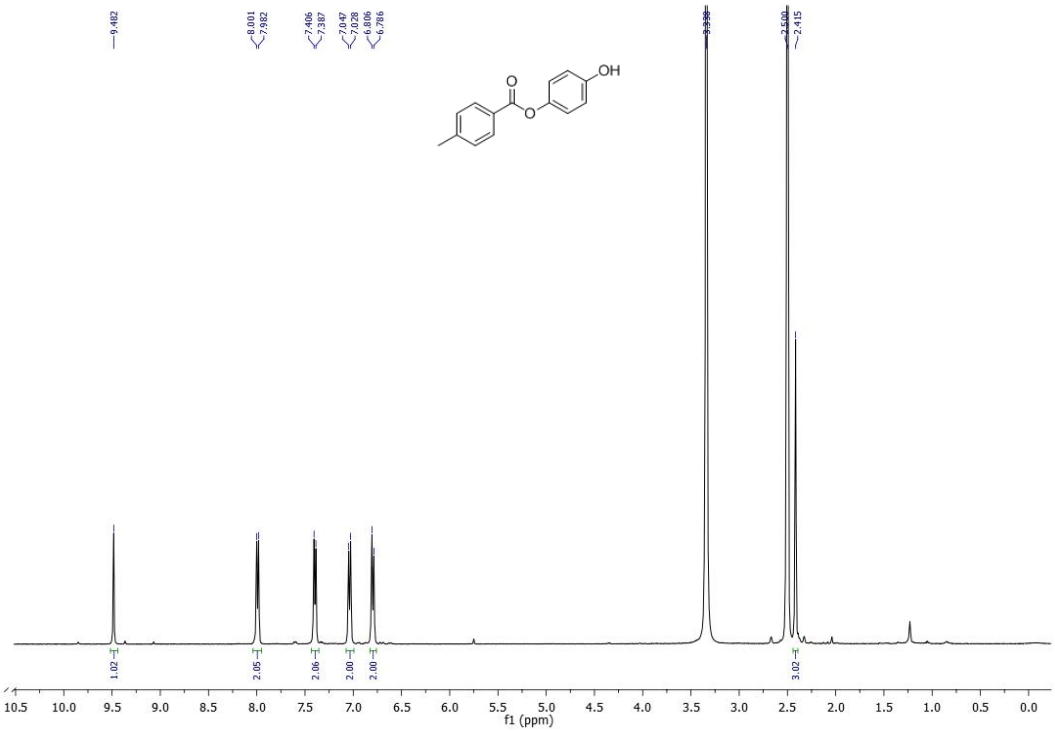


Figure 2.9. ^{1}H NMR spectrum of 4-hydroxyphenyl-4-methylbenzoate (**3c**).

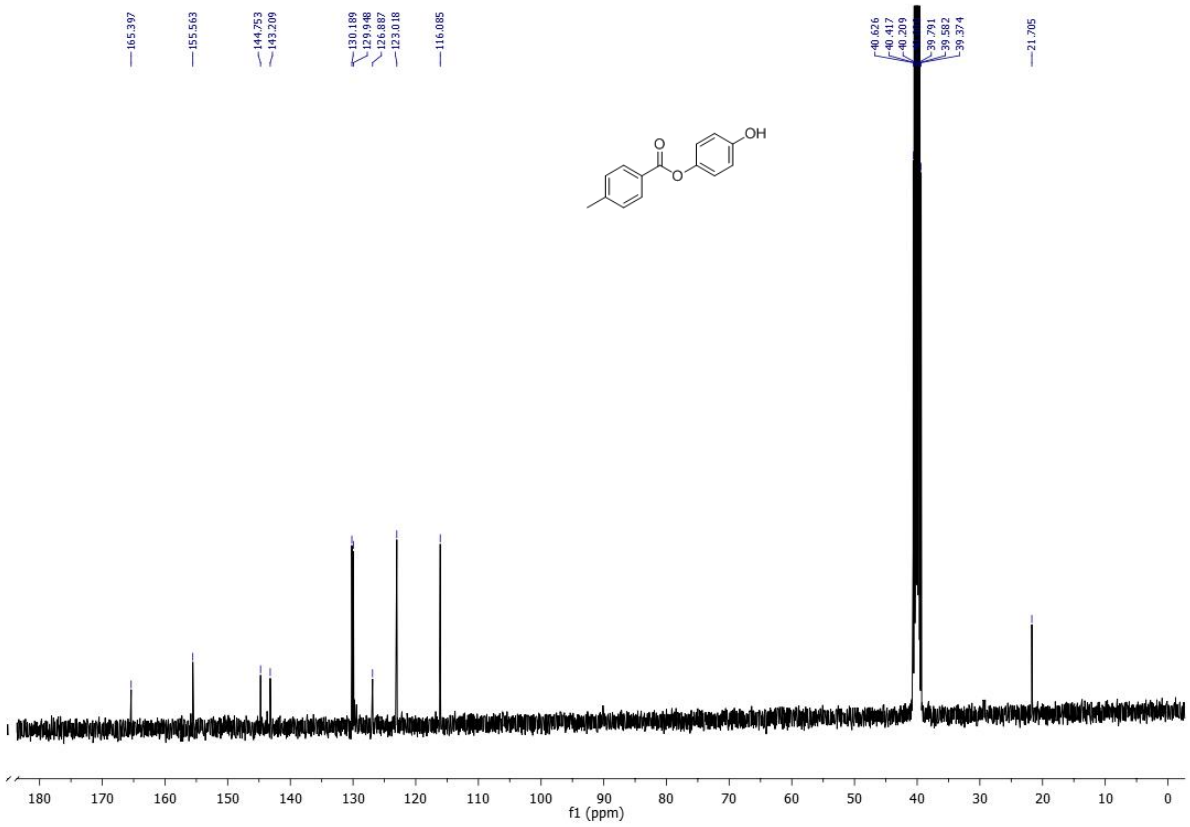


Figure 2.10. ^{13}C{^{1}H} NMR spectrum of 4-hydroxyphenyl-4-methylbenzoate (**3c**).

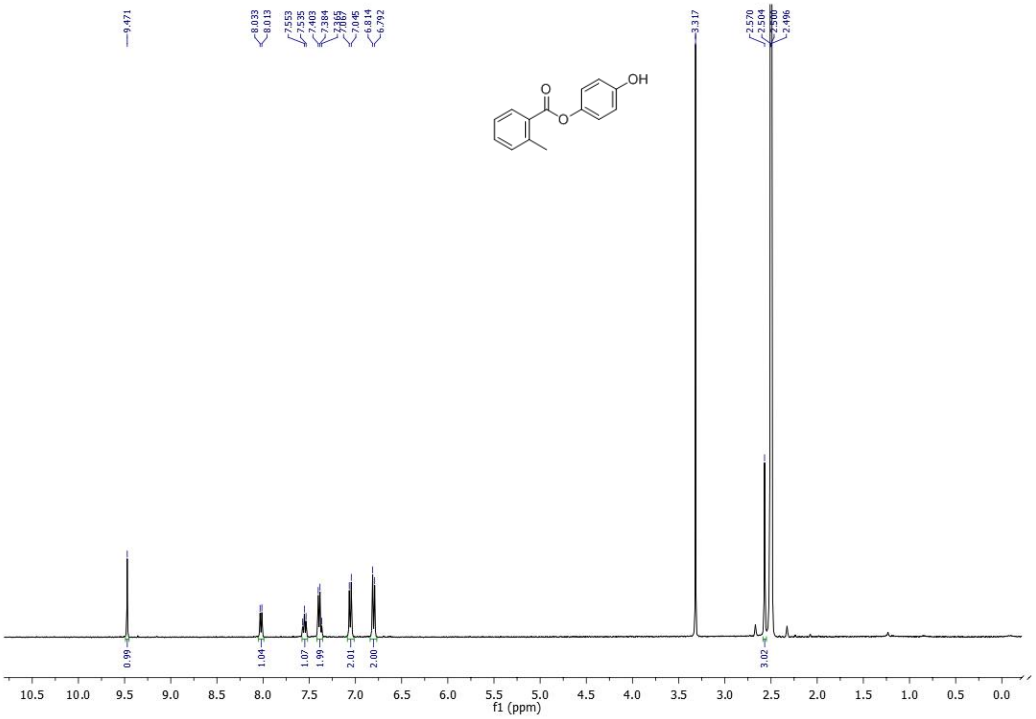


Figure 2.11. ^{1}H NMR spectrum of 4-hydroxyphenyl-2-methylbenzoate (**3d**).

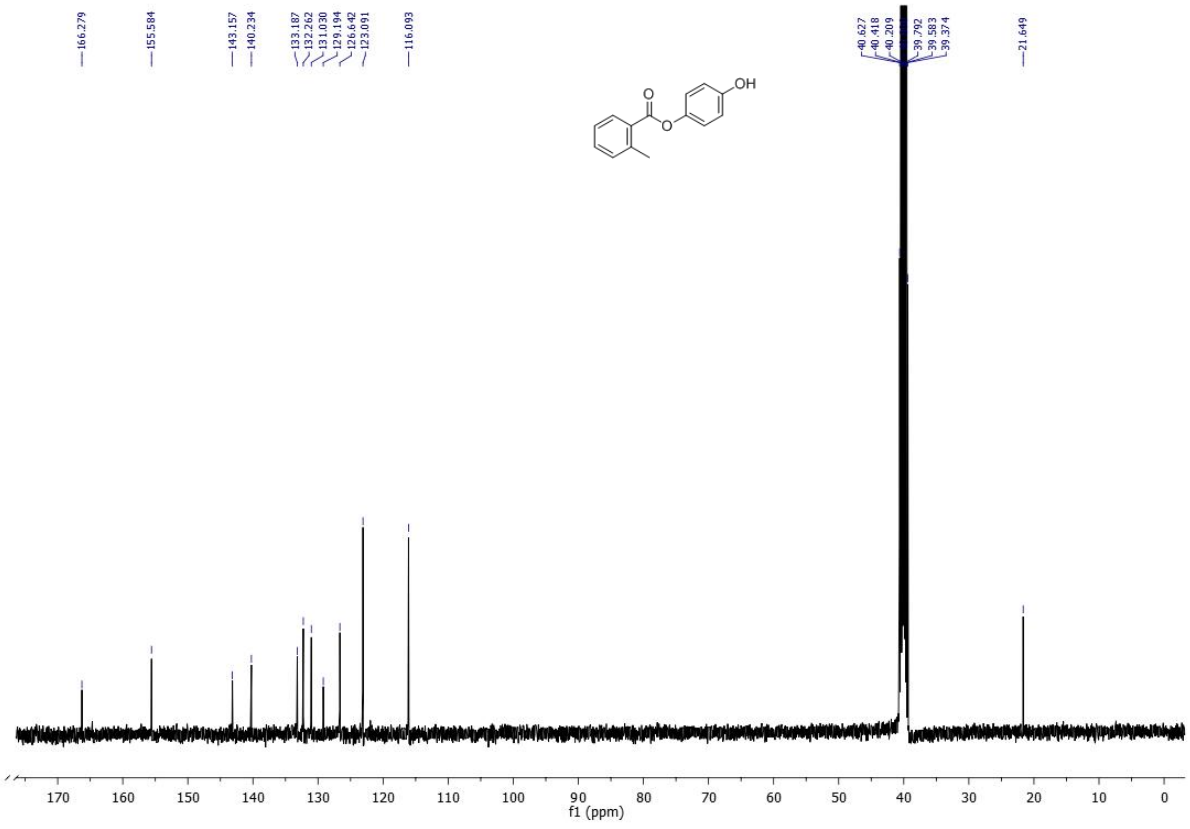


Figure 2.12 ^{13}C{^{1}H} NMR spectrum of 4-hydroxyphenyl-2-methylbenzoate (**3d**).

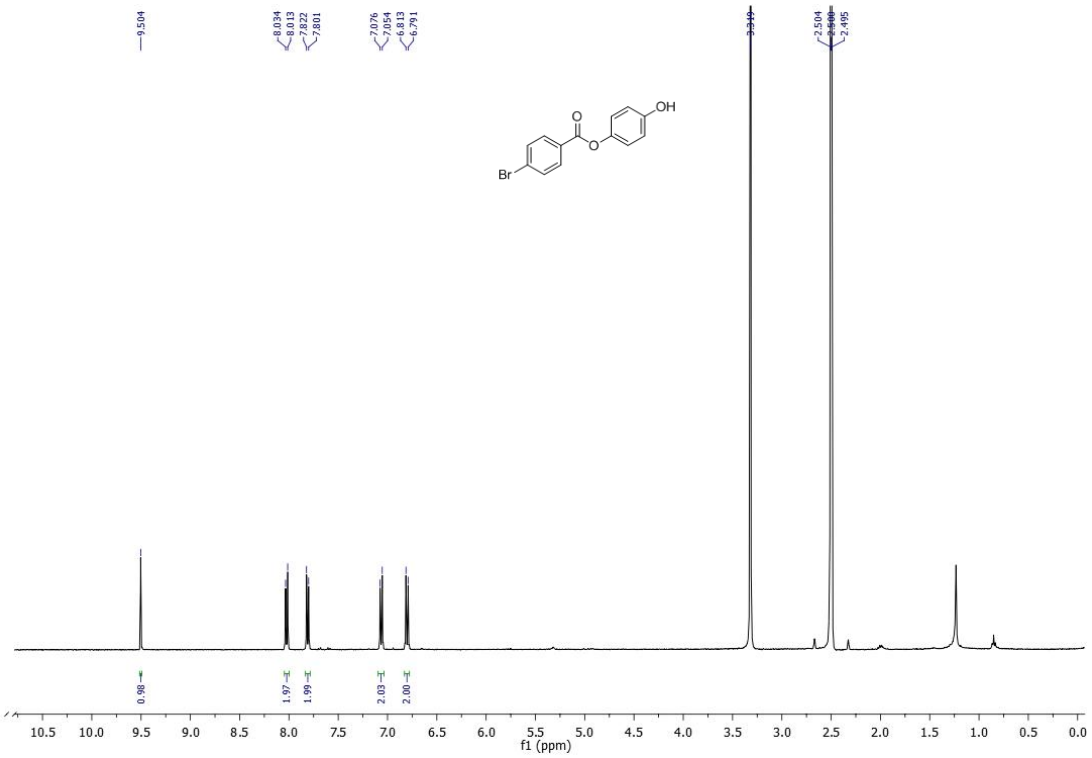


Figure 2.13. ^{1}H NMR spectrum of 4-hydroxyphenyl-4-bromobenzoate (**3e**).

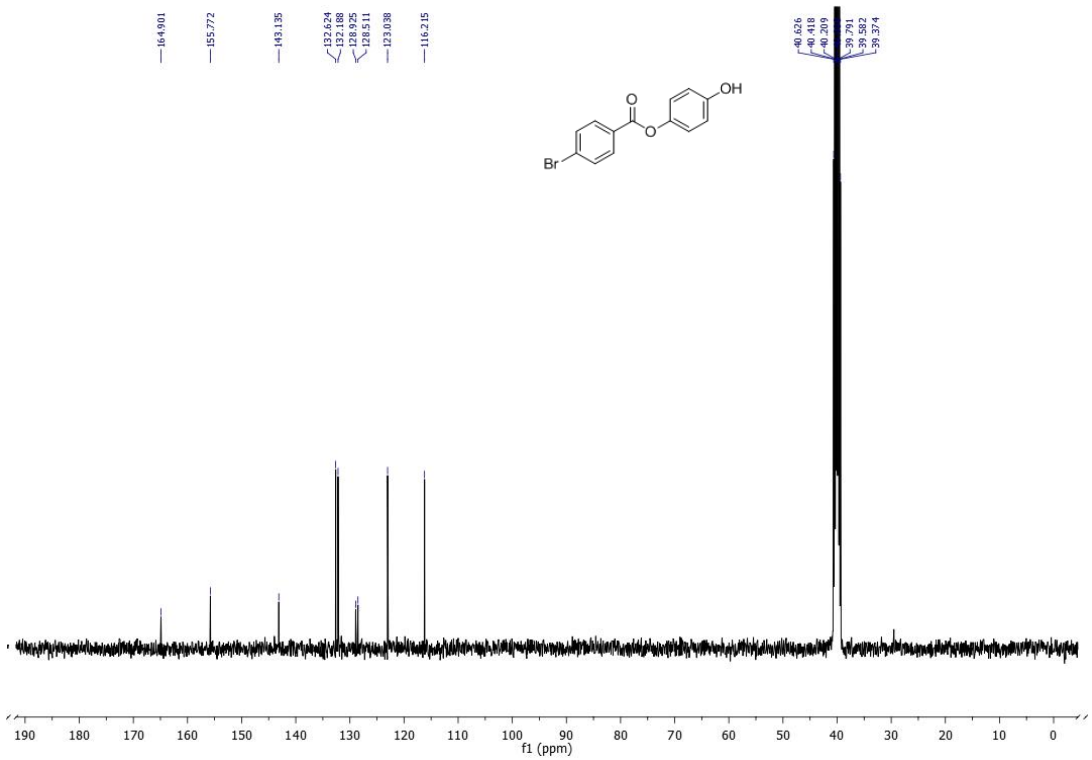


Figure 2.14. ^{13}C{^{1}H} NMR spectrum of 4-hydroxyphenyl-4-bromobenzoate (**3e**).

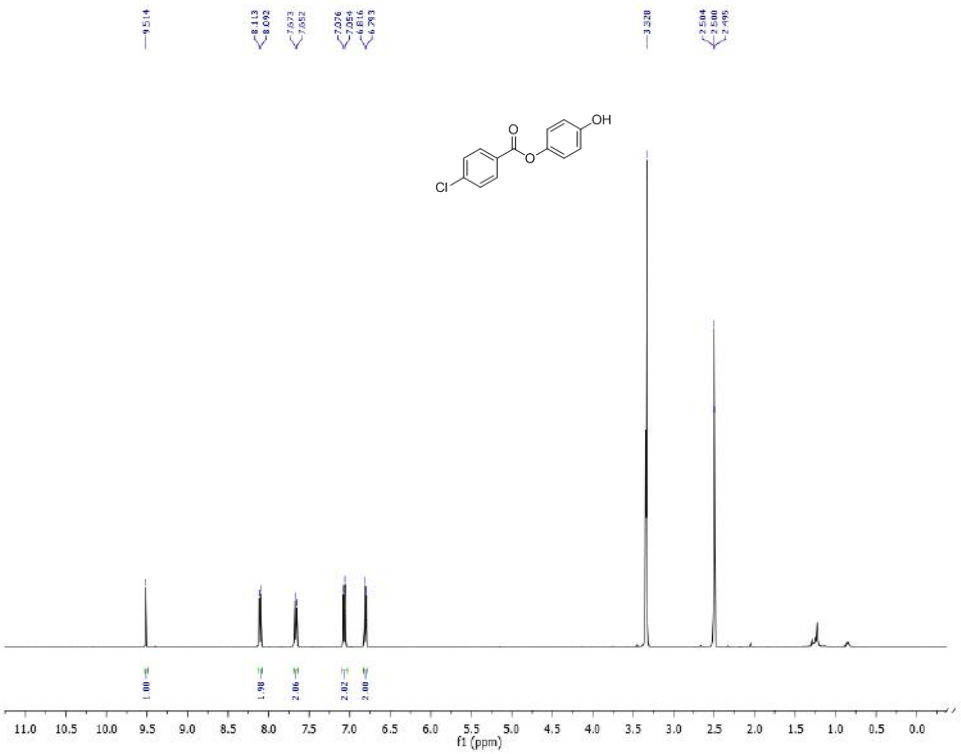


Figure 2.15. ^{1}H NMR spectrum of 4-hydroxyphenyl-4-chlorobenzoate (**3f**).

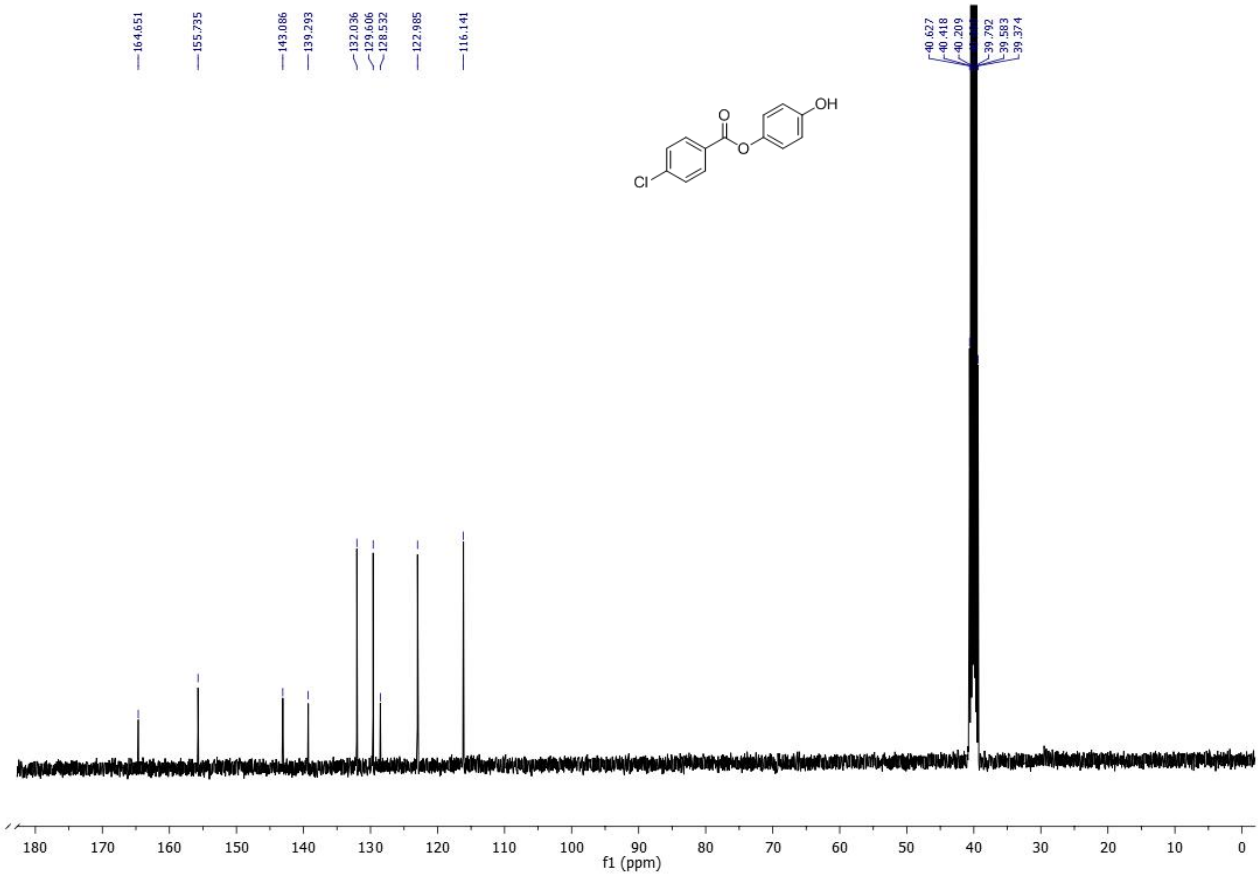


Figure 2.16 ^{13}C{^{1}H} NMR spectrum of 4-hydroxyphenyl-4-chlorobenzoate (**3f**).

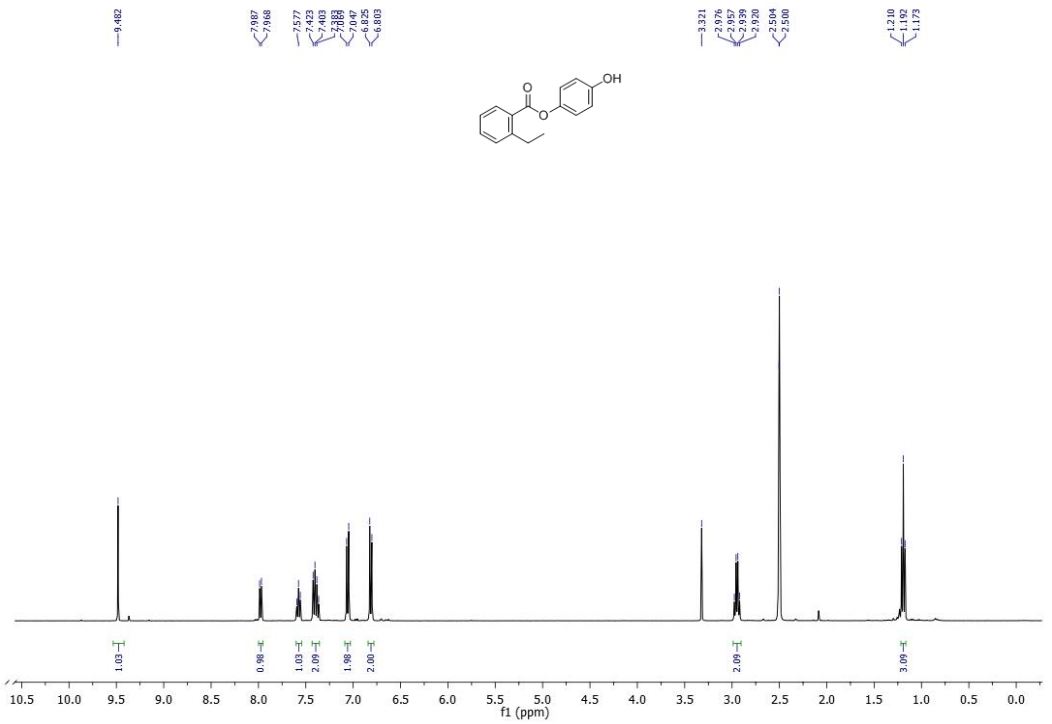


Figure 2.17. ^{1}H NMR spectrum of 4-hydroxyphenyl-2-ethylbenzoate (**3g**).

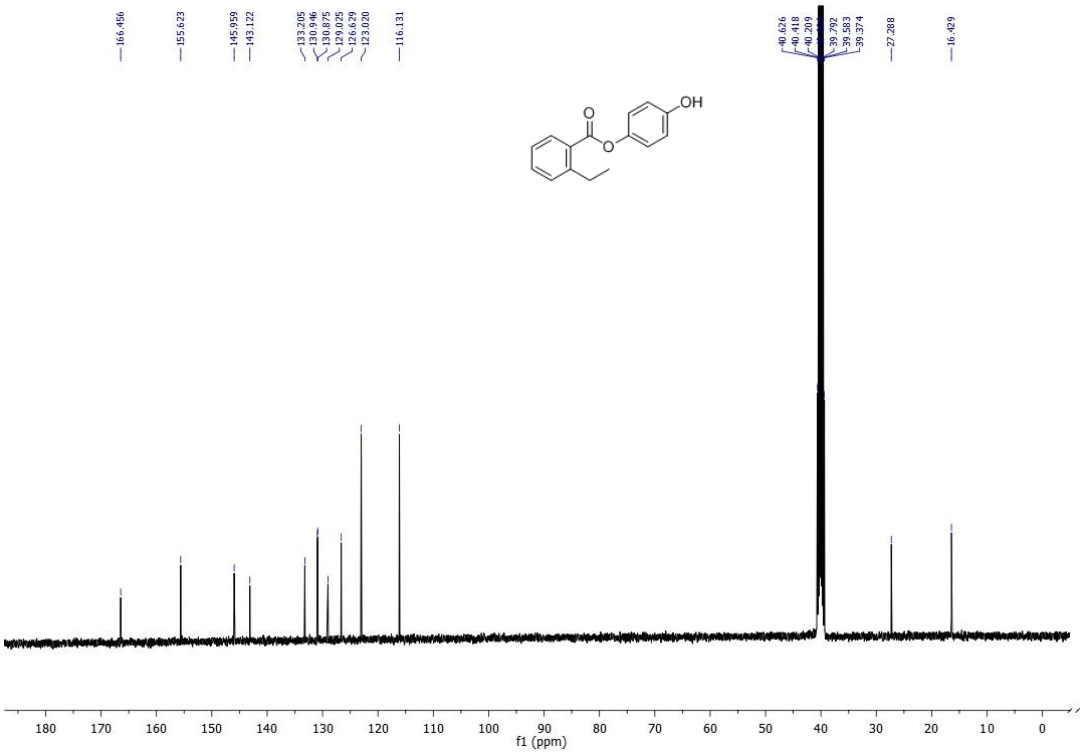


Figure 2.18. ^{13}C{^{1}H} NMR spectrum of 4-hydroxyphenyl-2-ethylbenzoate (**3g**).

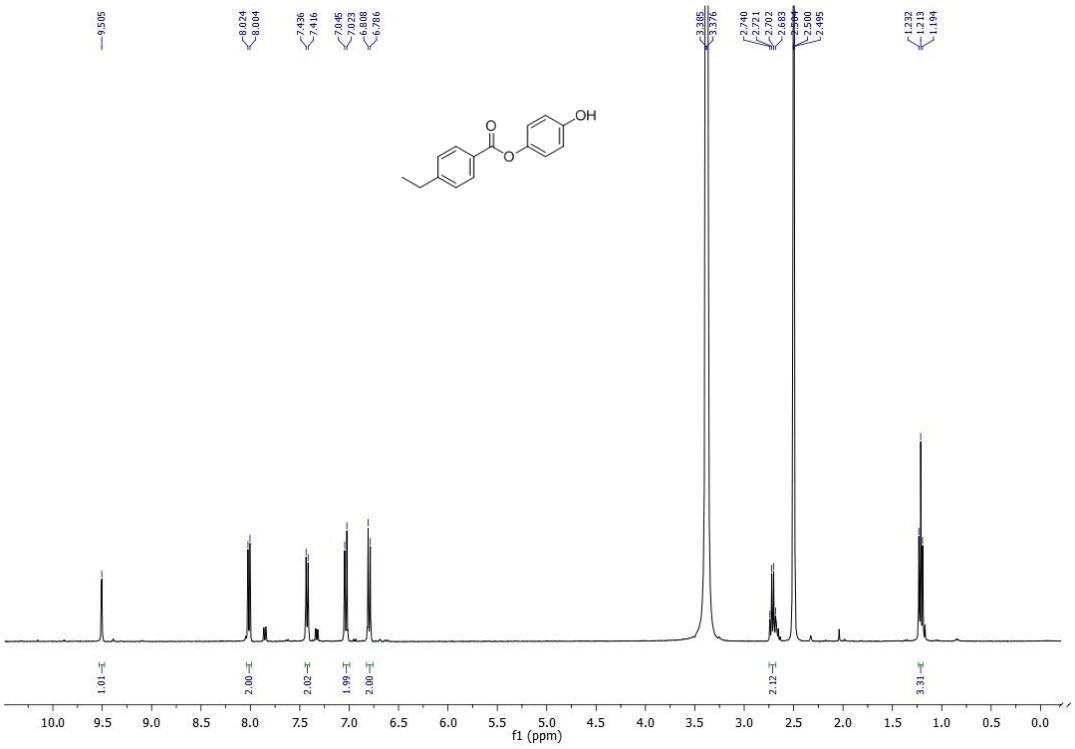


Figure 2.19. ^{1}H NMR spectrum of 4-hydroxyphenyl-4-ethylbenzoate (**3h**).

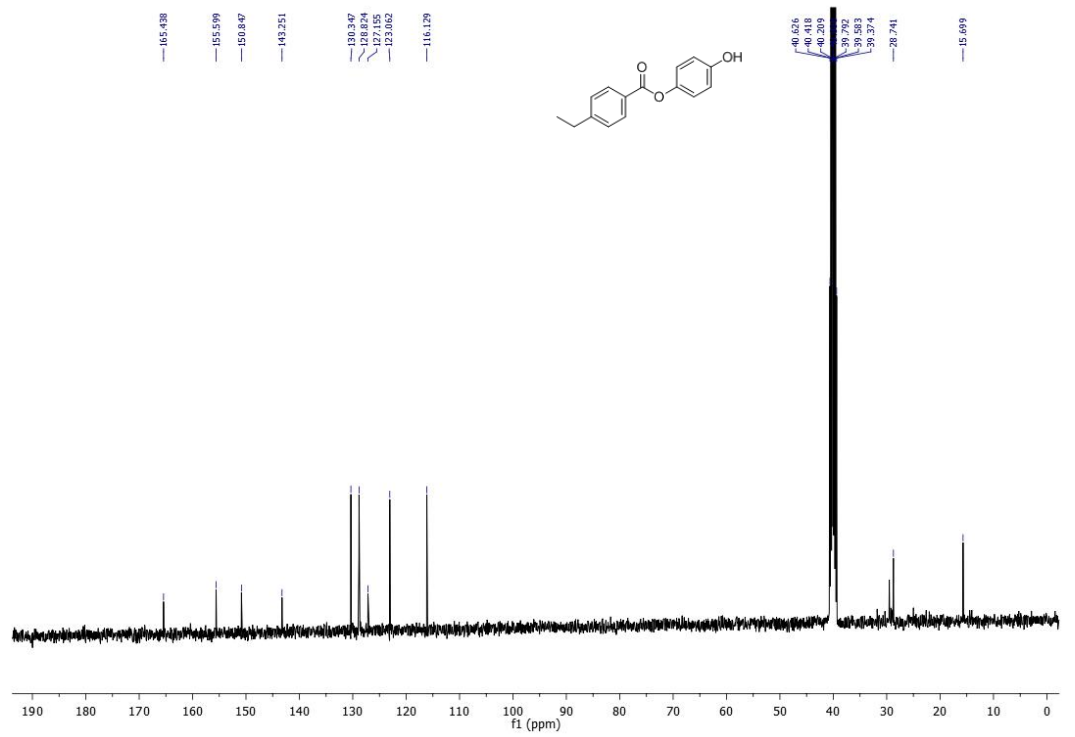


Figure 2.20. ^{13}C{^{1}H} NMR spectrum of 4-hydroxyphenyl-4-ethylbenzoate (**3h**).

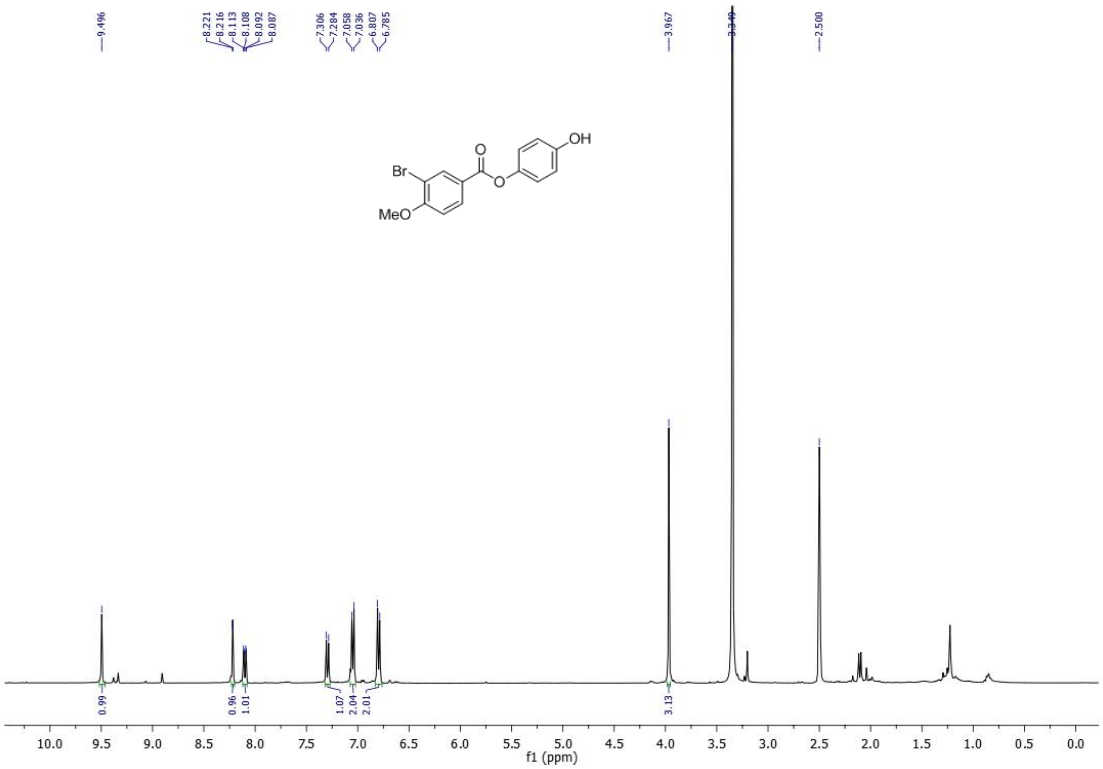


Figure 2.21. [1]HNMR spectrum of 4-hydroxyphenyl-3-bromo-4-methoxybenzoate (**3i**).

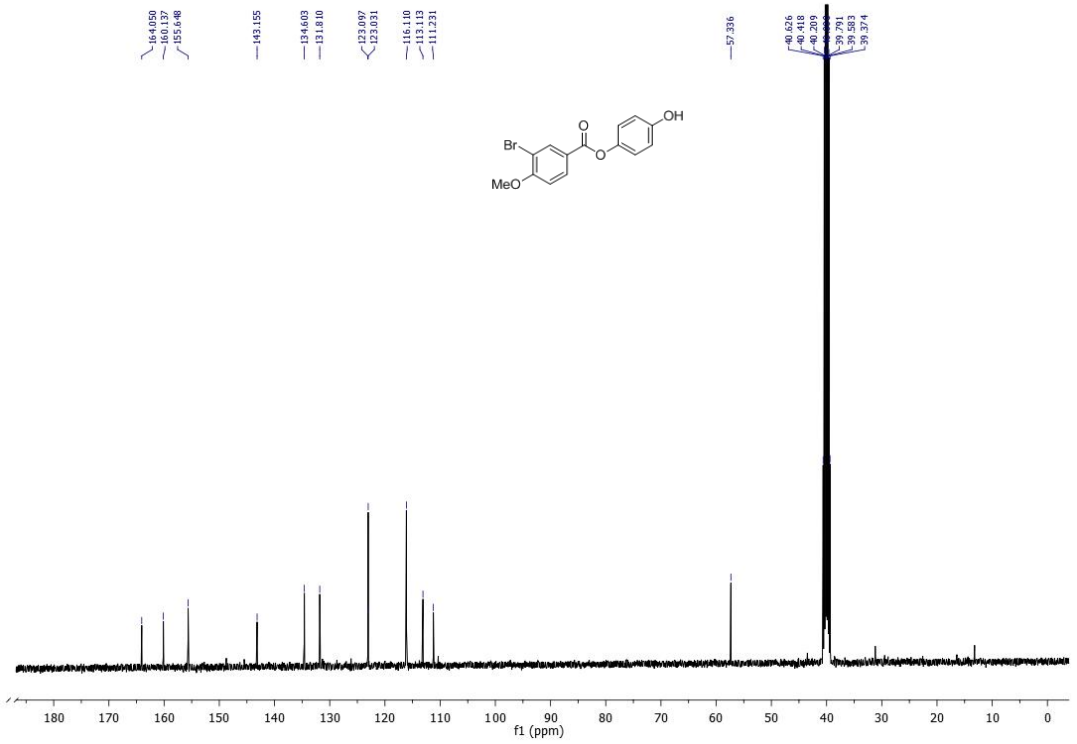


Figure 2.22. [13]C NMR{[1]H} spectrum of 4-hydroxyphenyl-3-bromo-4-methoxybenzoate (**3i**).

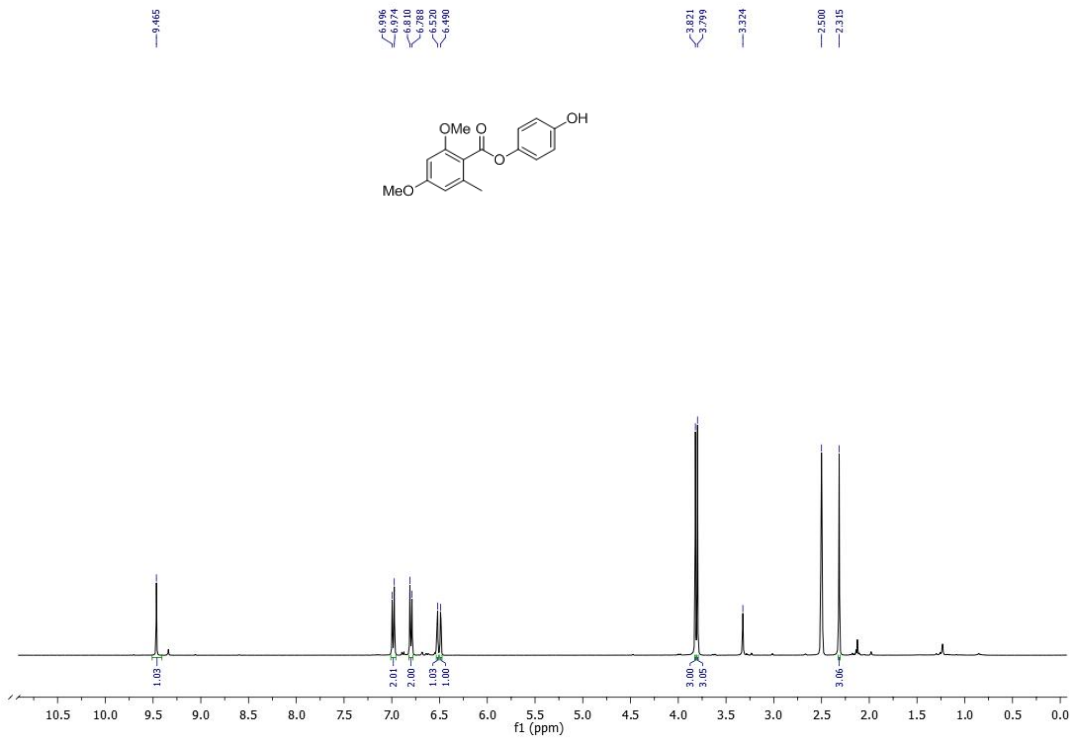


Figure 2.23. ^{1}H NMR spectrum of 4-hydroxyphenyl -2,4-dimethoxy-6-methylbenzoate (**3j**).

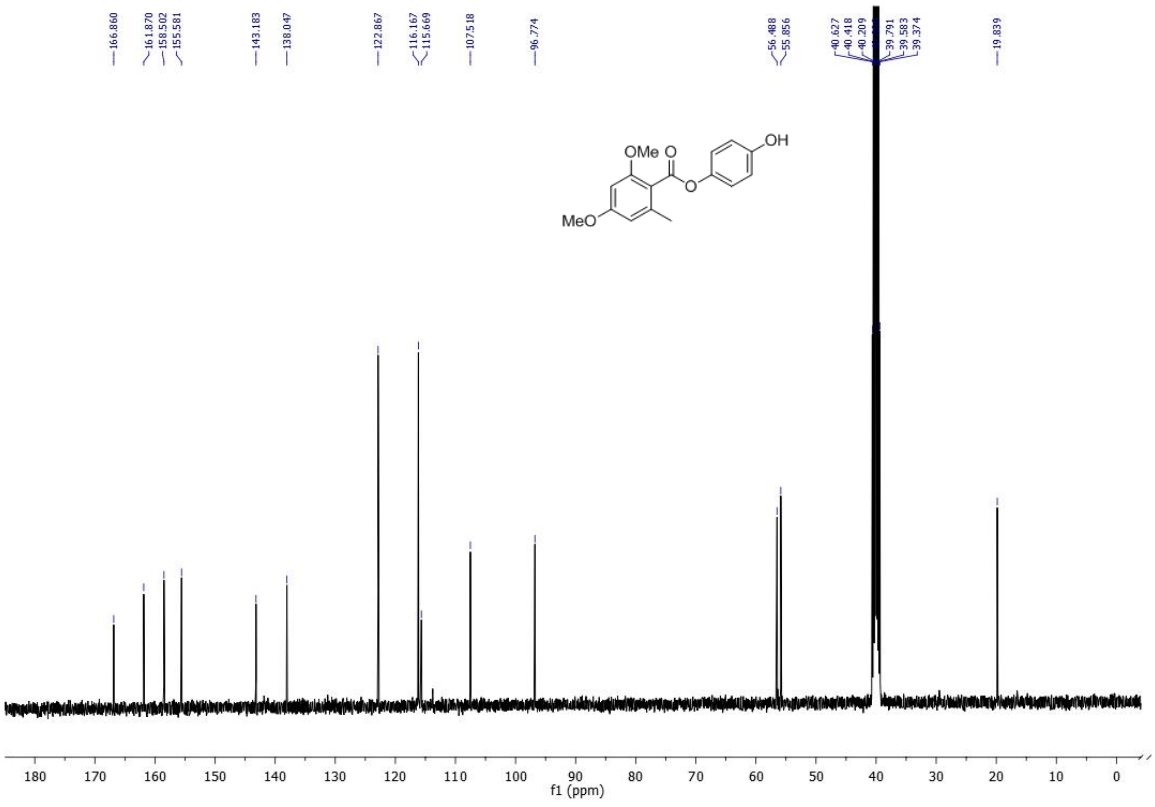


Figure 2.24. ^{13}C{^{1}H} NMR spectrum of 4-hydroxyphenyl-2,4-dimethoxy-6-methylbenzoate (**3j**).

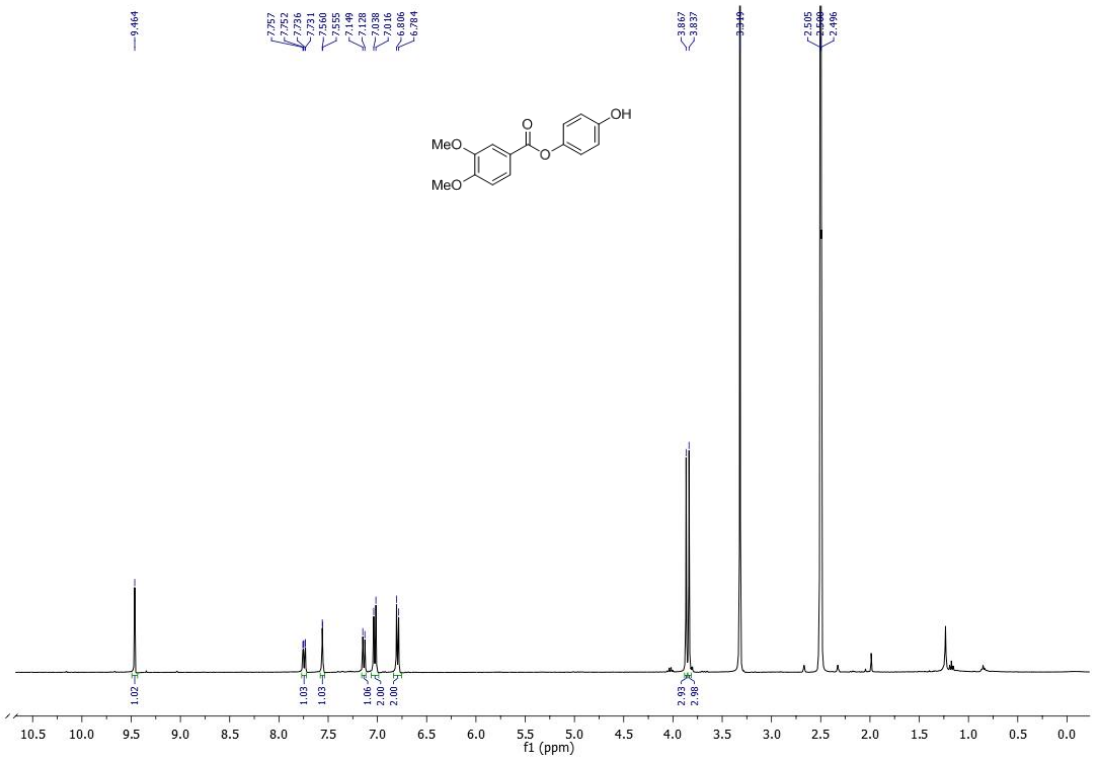


Figure 2.25. ^{1}H NMR spectrum of 4-hydroxyphenyl-3,4 dimethoxybenzoate (**3k**).

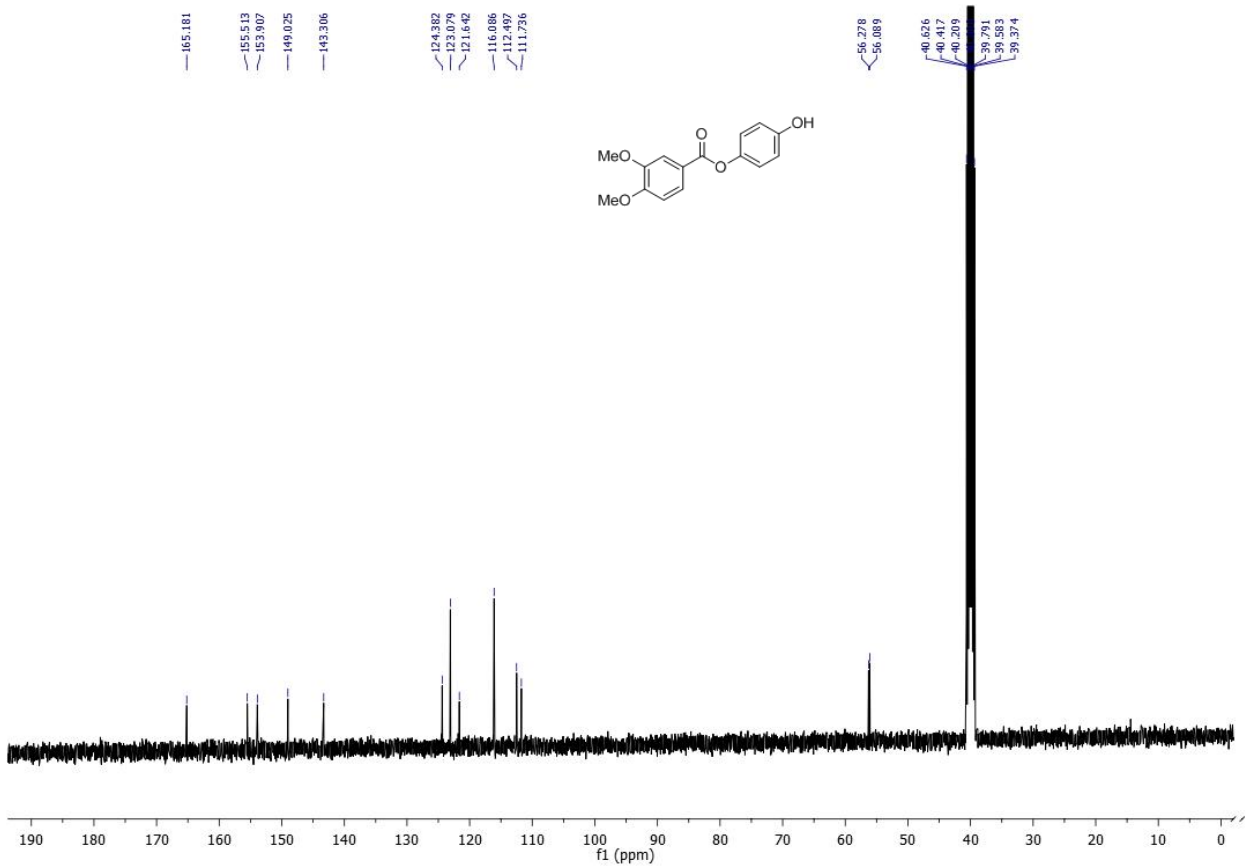


Figure 2.26. ^{13}C{^{1}H} NMR spectrum of 4-hydroxyphenyl-3,4-dimethoxybenzoate (**3k**).

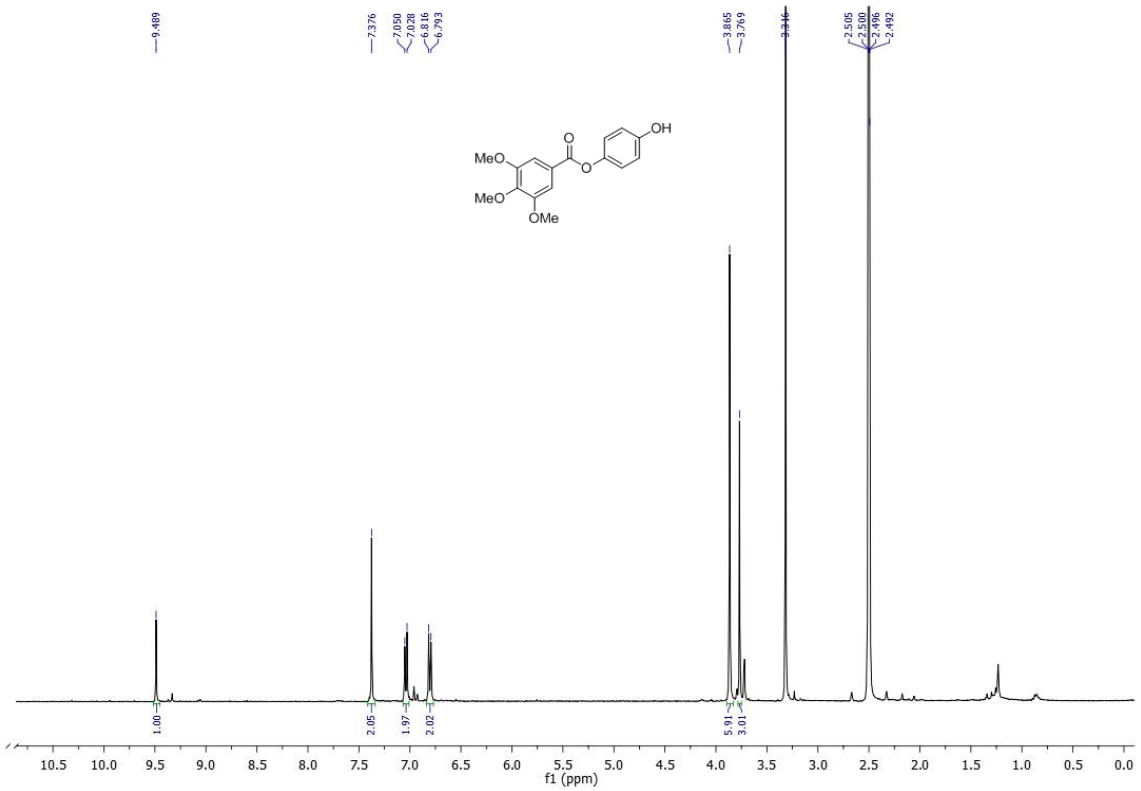


Figure 2.27. ^{1}H NMR spectrum of 4-hydroxyphenyl-3,4,5-trimethoxybenzoate (**3l**).

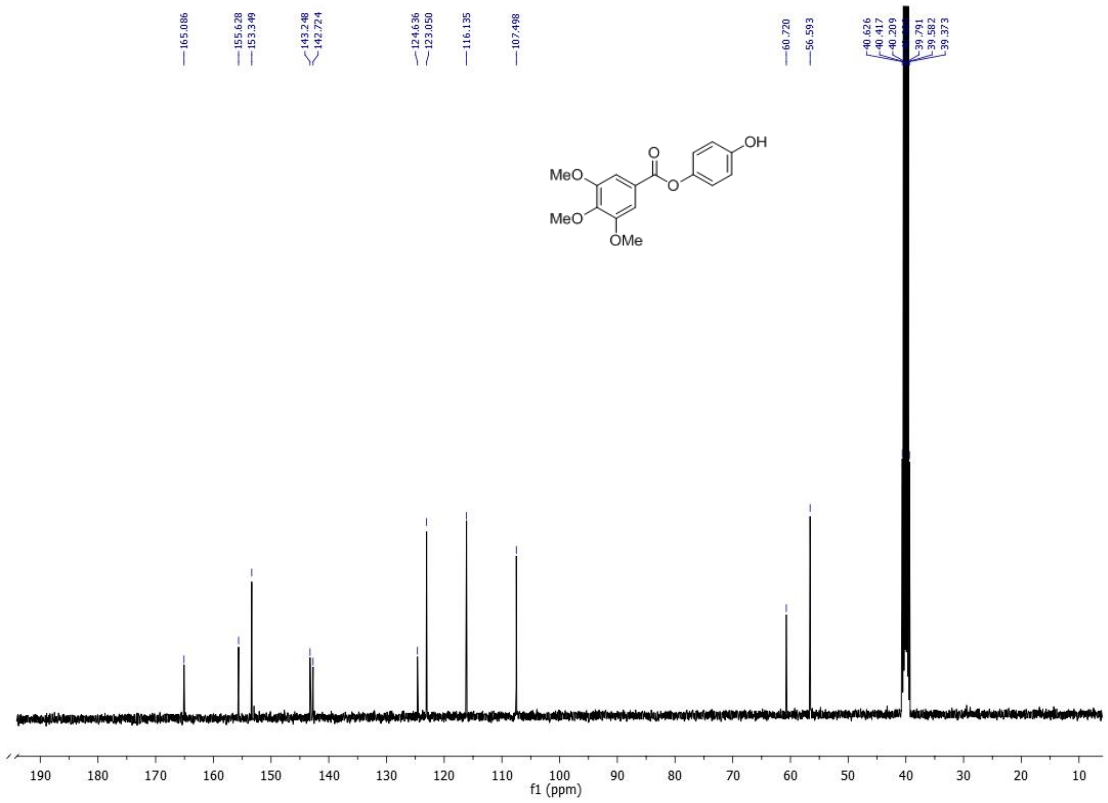


Figure 2.28. ^{13}C{^{1}H} NMR spectrum of 4-hydroxyphenyl-3,4,5-trimethoxybenzoate (**3l**).

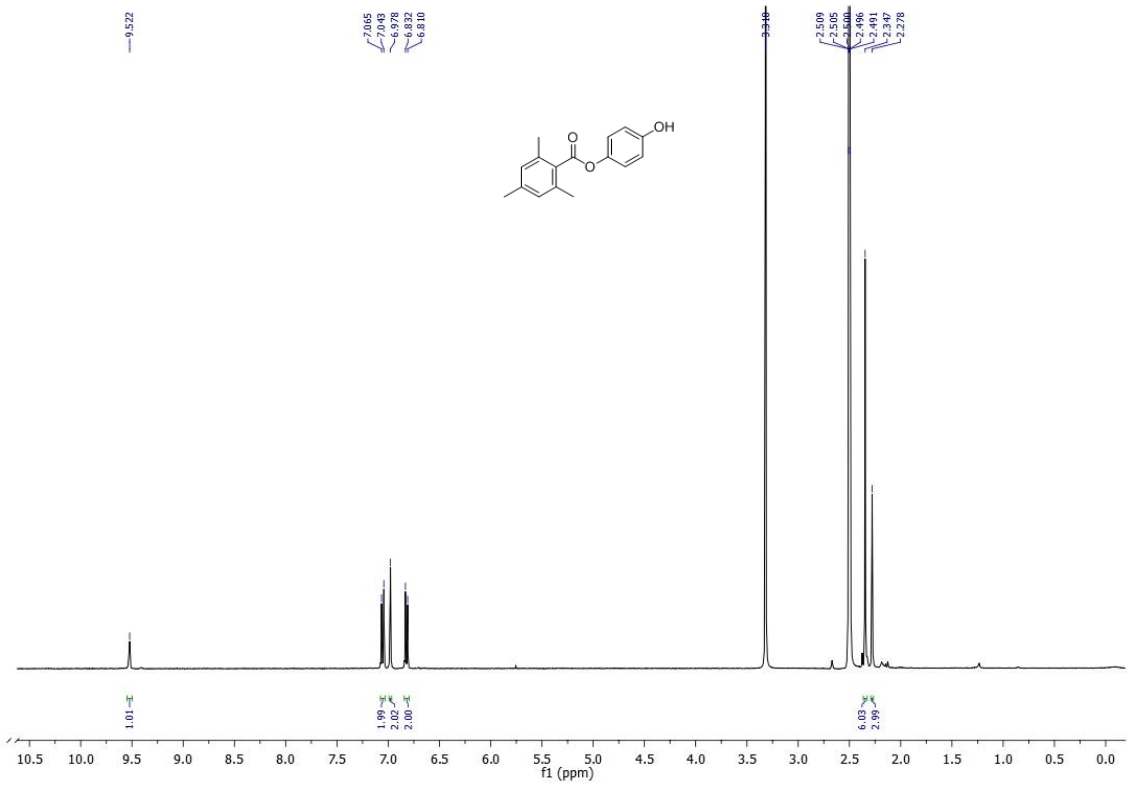


Figure 2.29. ^{1}H NMR spectrum of 4-hydroxyphenyl-2,4,6-trimethylbenzoate (**3m**).

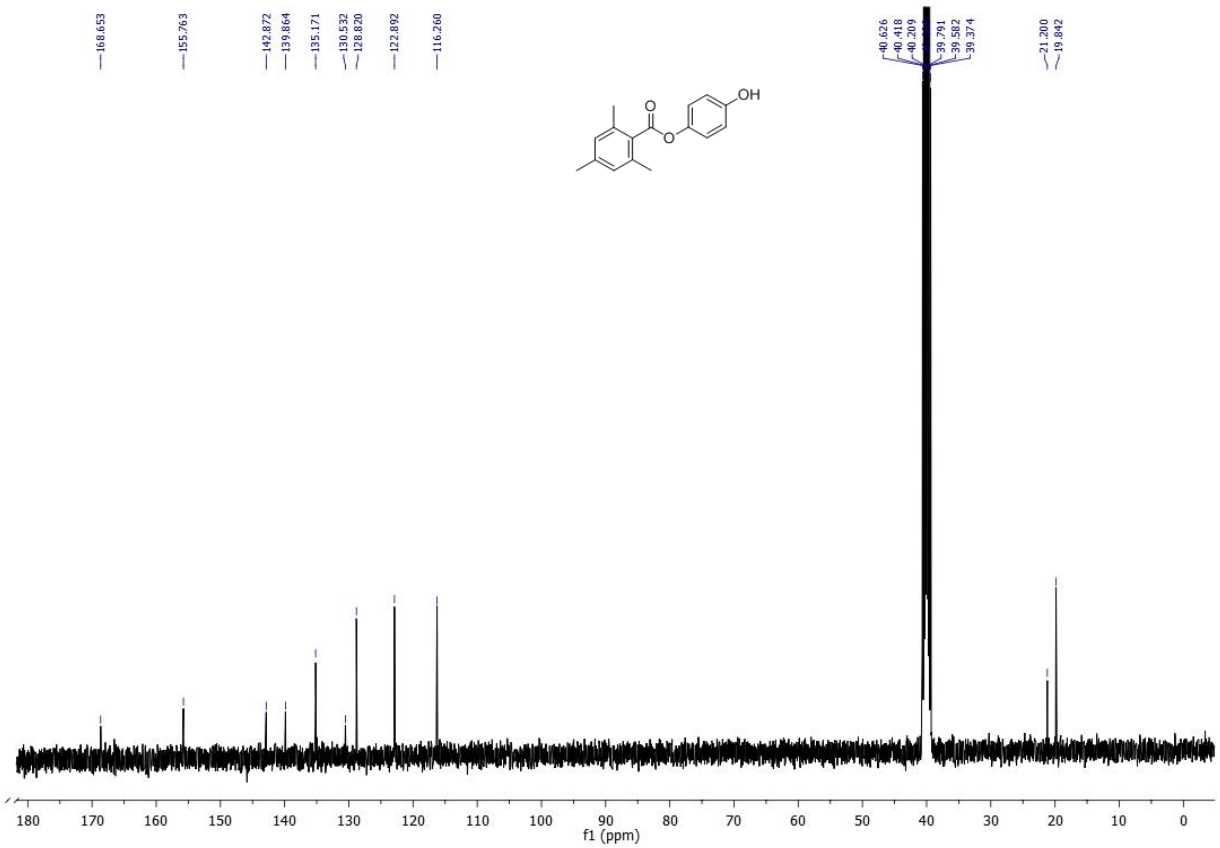


Figure 2.30. ^{13}C{^{1}H} NMR spectrum of 4-hydroxyphenyl-2,4,6-trimethylbenzoate (**3m**).

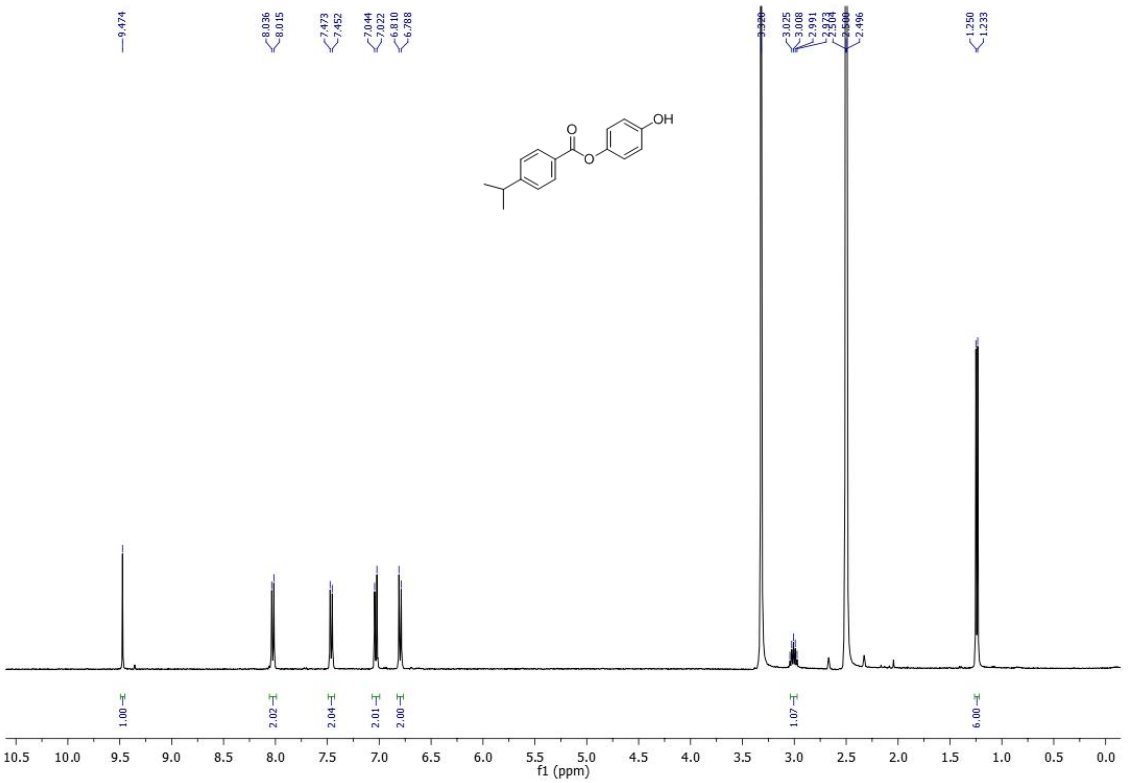


Figure 2.31. ^{1}H NMR spectrum of 4-hydroxyphenyl-4-isopropylbenzoate (**3n**).

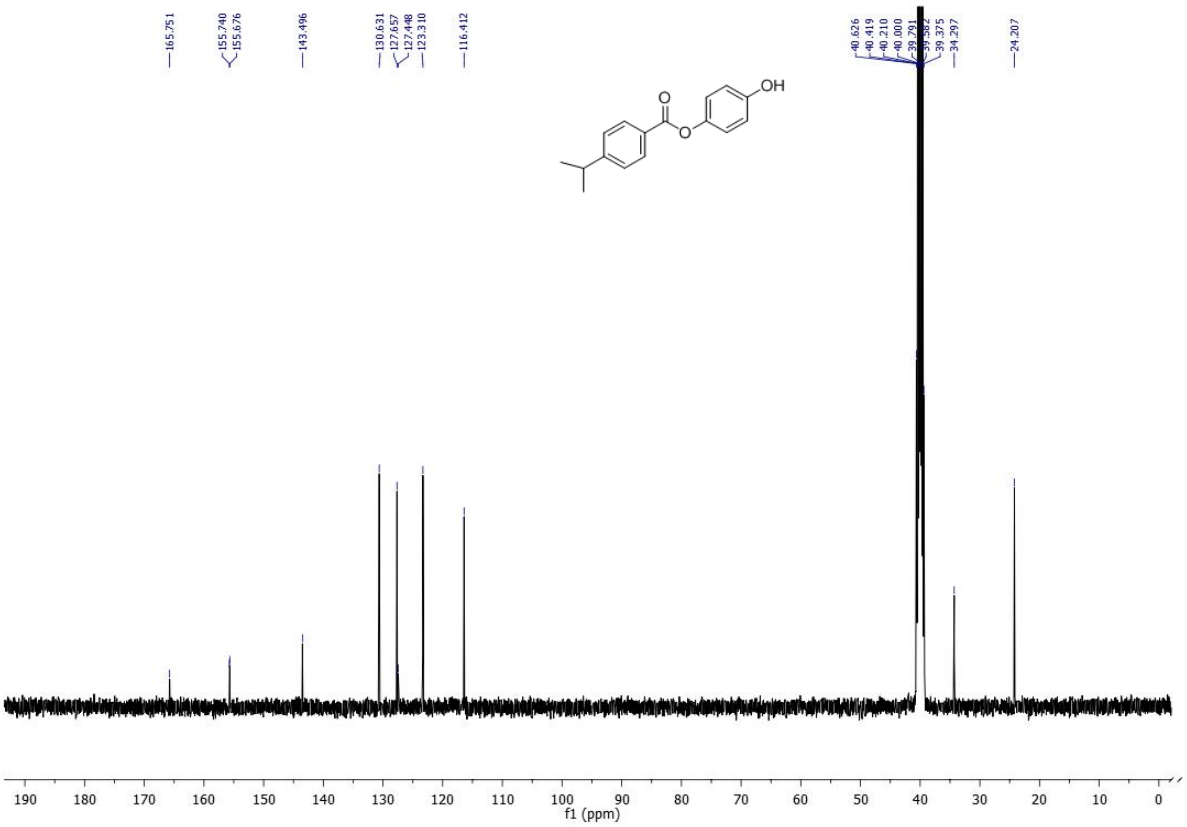


Figure 2.32. ^{13}C{^{1}H} NMR spectrum of 4-hydroxyphenyl-4-isopropylbenzoate (**3n**).

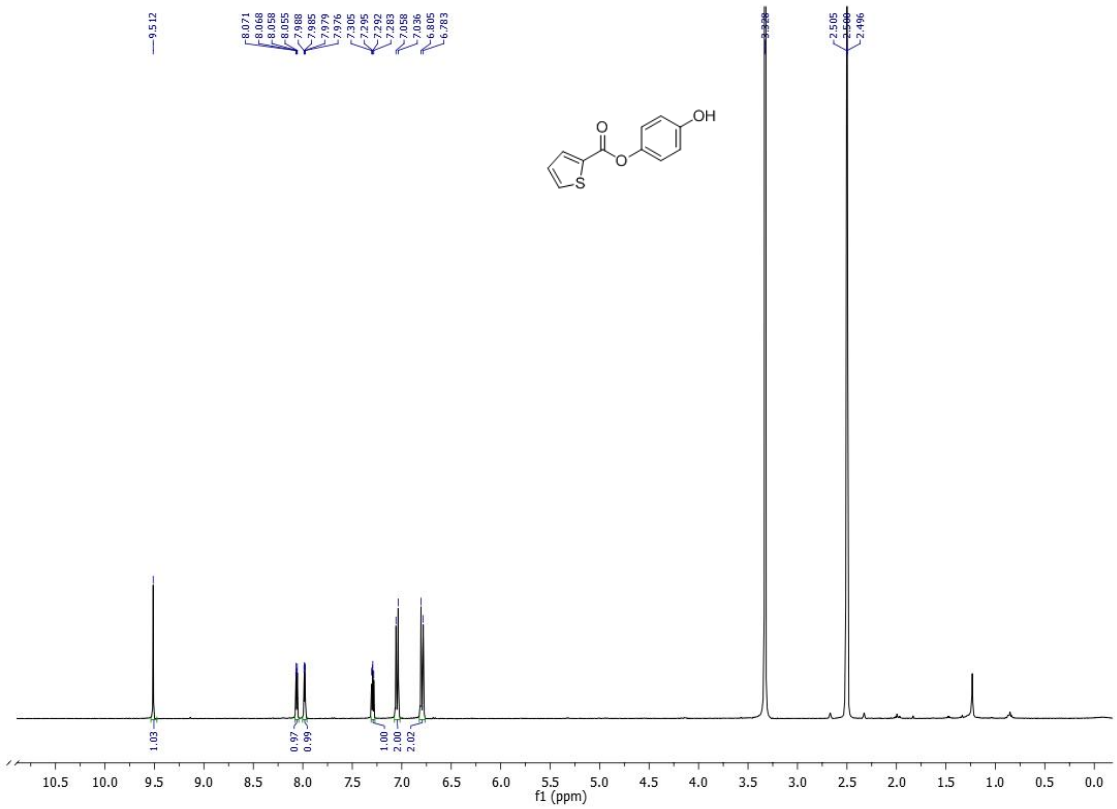


Figure 2.33. ^{1}H NMR spectrum of 4-hydroxyphenyl thiophene-2-carboxylate (**3o**).

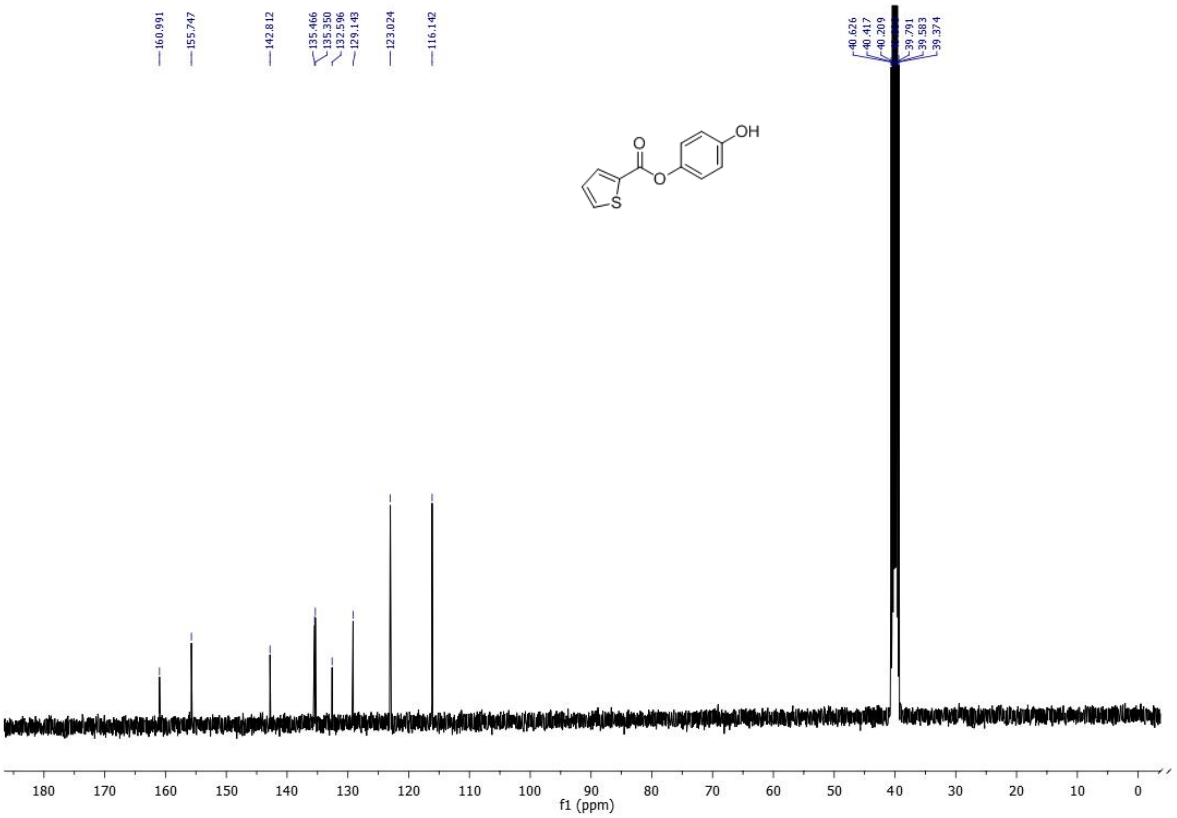


Figure 2.34. ^{13}C{^{1}H} NMR spectrum of 4-hydroxyphenyl thiophene-2-carboxylate (**3o**).

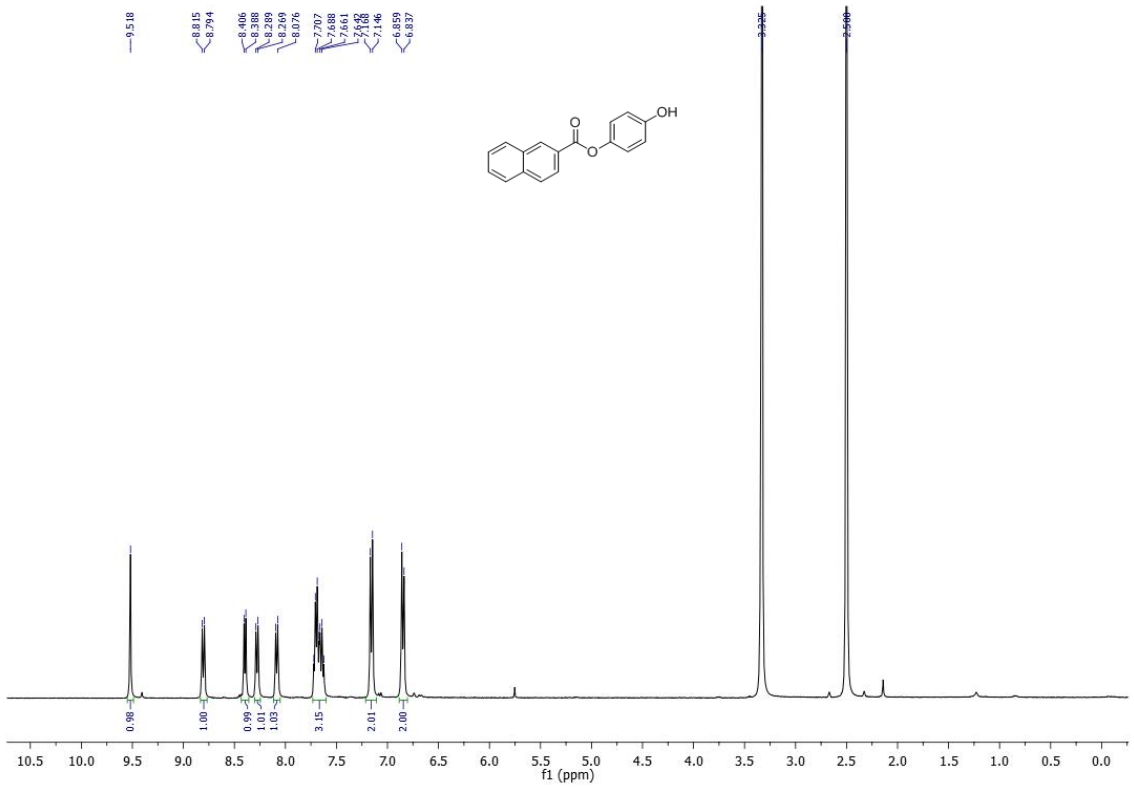


Figure 2.35. ^{1}H NMR spectrum of 4-hydroxyphenyl-2-naphthoate (**3p**).

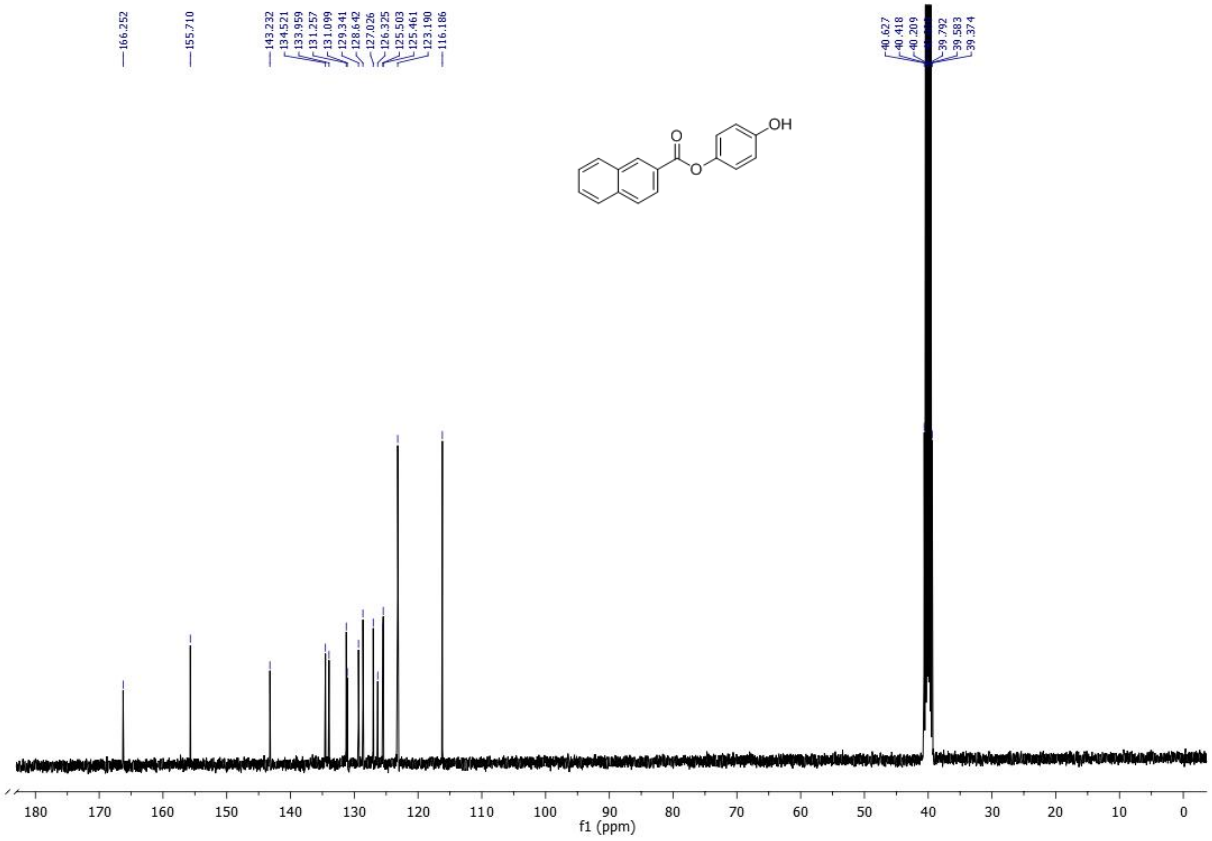


Figure 2.36. ^{13}C{^{1}H} NMR spectrum of 4-hydroxyphenyl-2-naphthoate (**3p**).

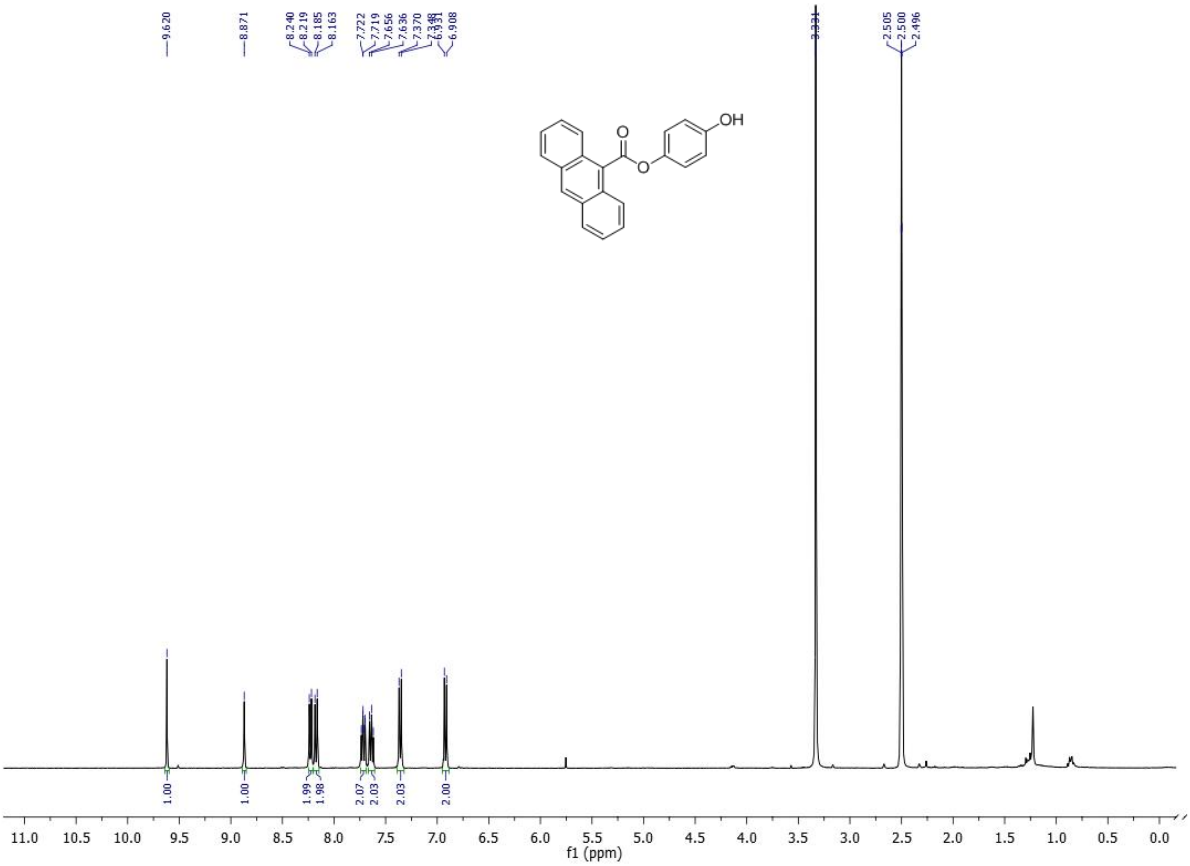


Figure 2.37. ^{1}H NMR spectrum of 4-hydroxyphenyl-anthracene-9-carboxylate (**3q**).

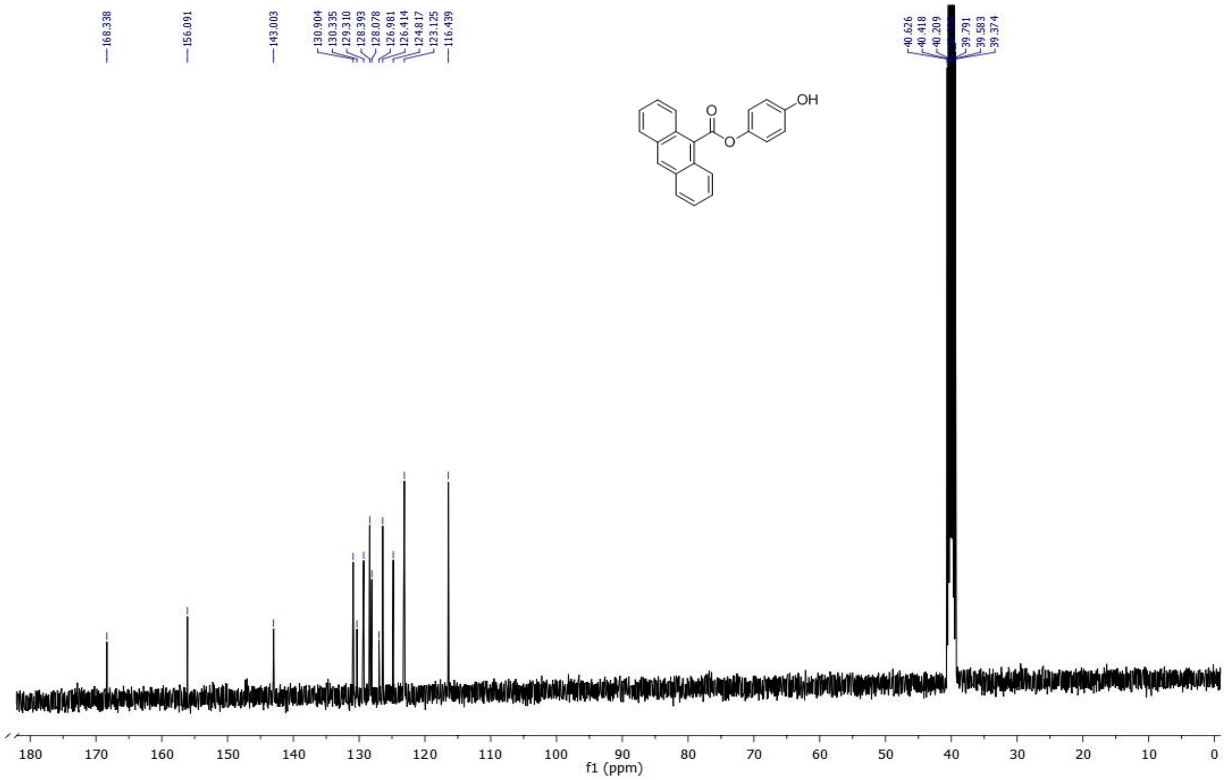


Figure 2.38. ^{13}C{^{1}H} NMR spectrum of 4-hydroxyphenyl-anthracene-9-carboxylate (**3q**).

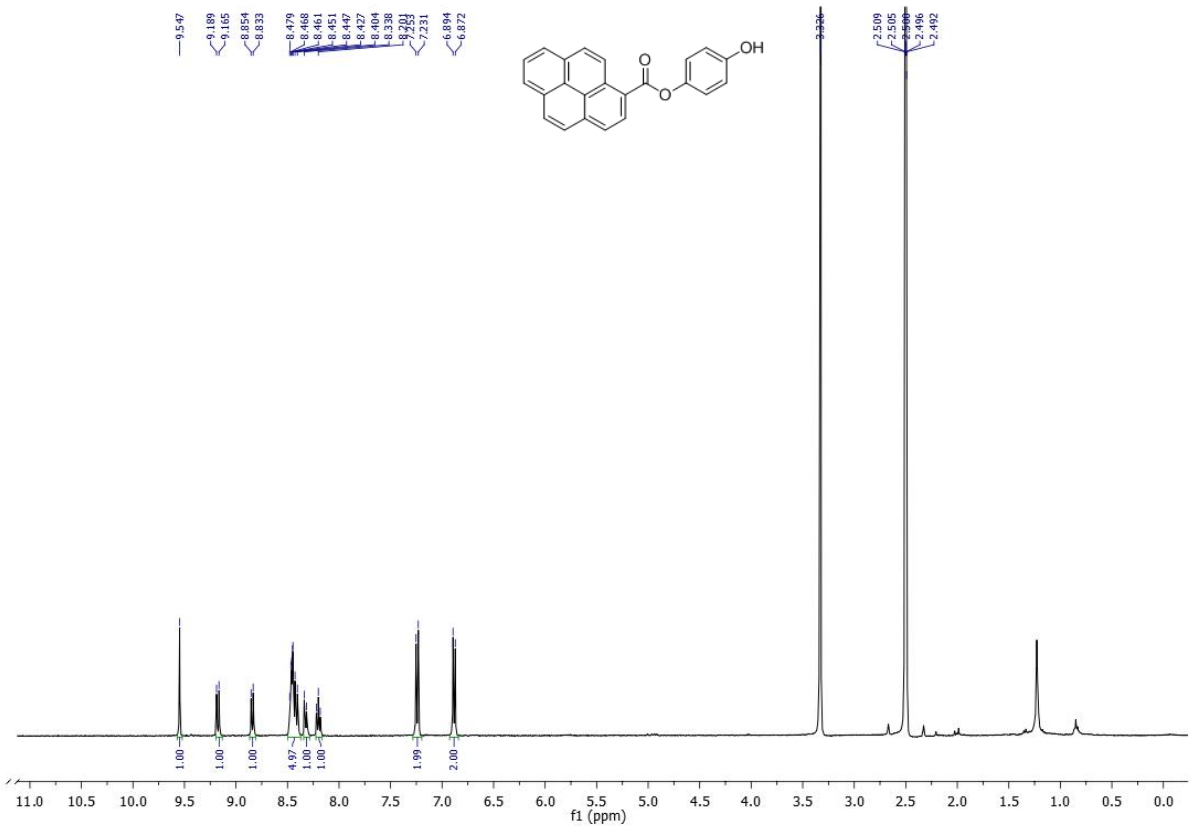


Figure 2.39. ^{1}H NMR spectrum of **4**-hydroxyphenyl-pyrene-1-carboxylate (**3r**).

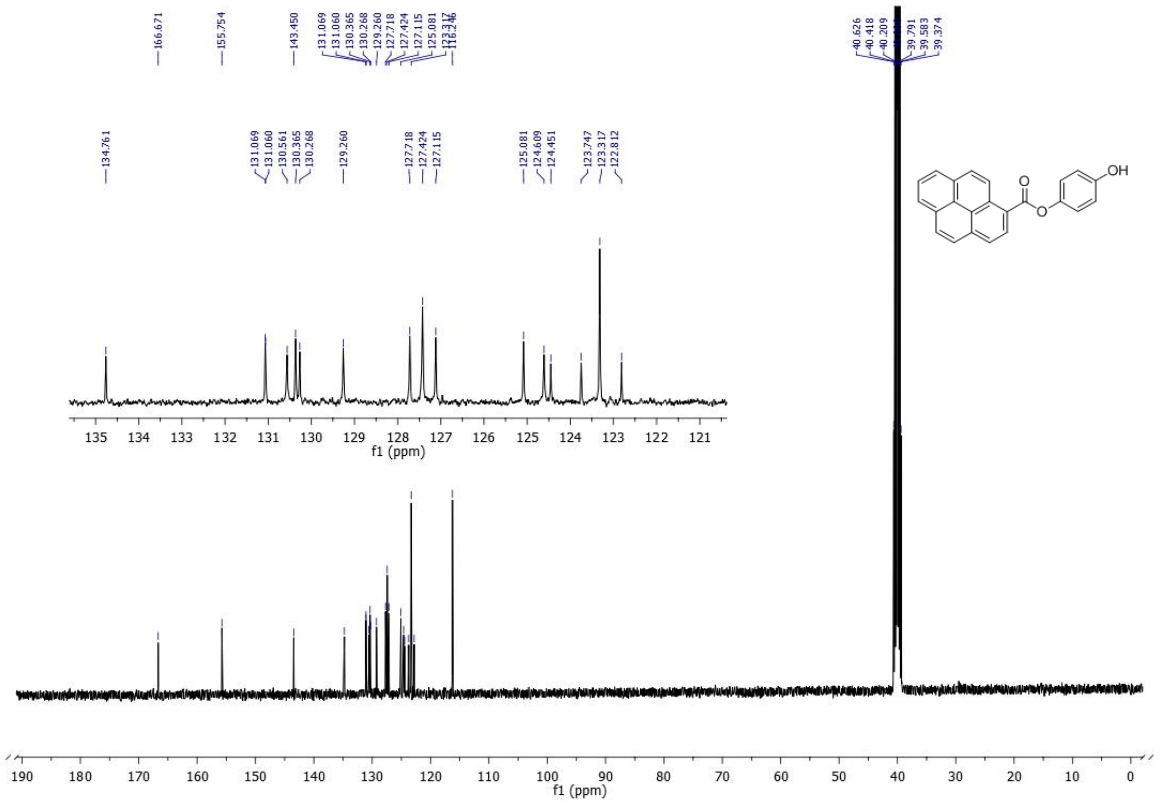


Figure 2.40. $^{13}C\{^{1}H\}$ NMR spectrum of 4-hydroxyphenyl-pyrene-1-carboxylate (**3r**).

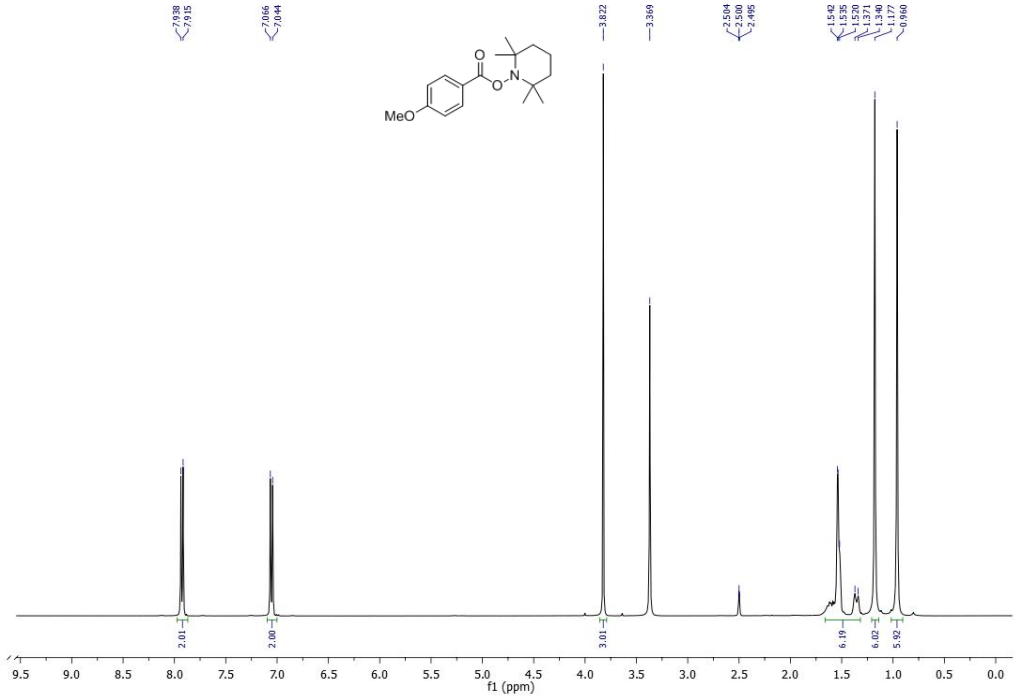


Figure 2.41. ^{1}H NMR spectrum of 2,2,6,6-tetramethylpiperidin-1-yl-4-methoxybenzoate (**5**).

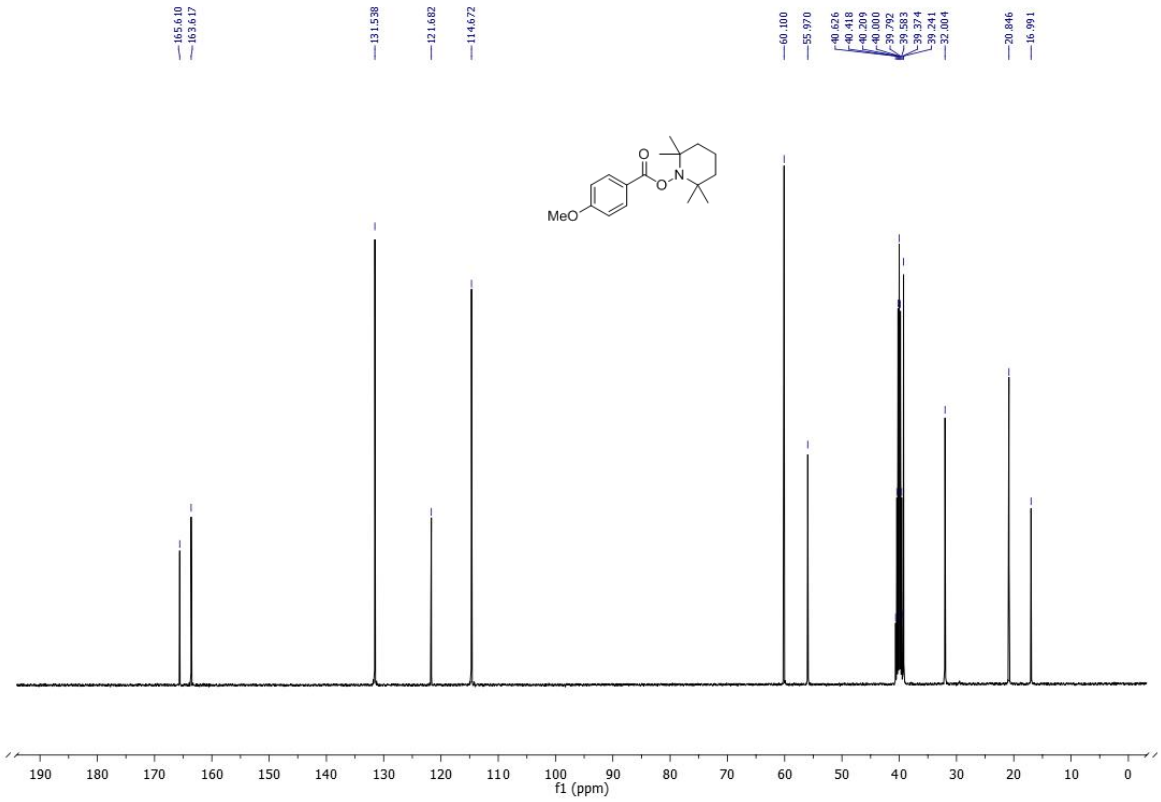


Figure 2.42. ^{13}C{^{1}H} NMR spectrum of 2,2,6,6-tetramethylpiperidin-1-yl-4-methoxybenzoate (**5**).

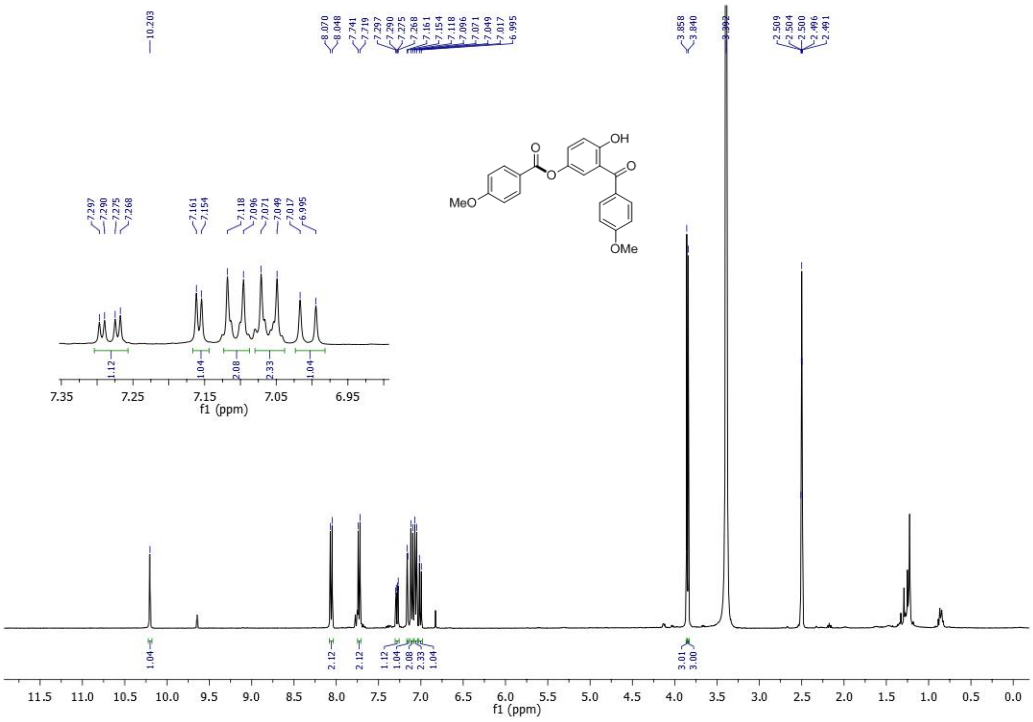


Figure 2.43. ^{1}H NMR spectrum of 4-Hydroxy-3-(4-methoxybenzoyl)phenyl-4-methoxybenzoate (**3a′**).

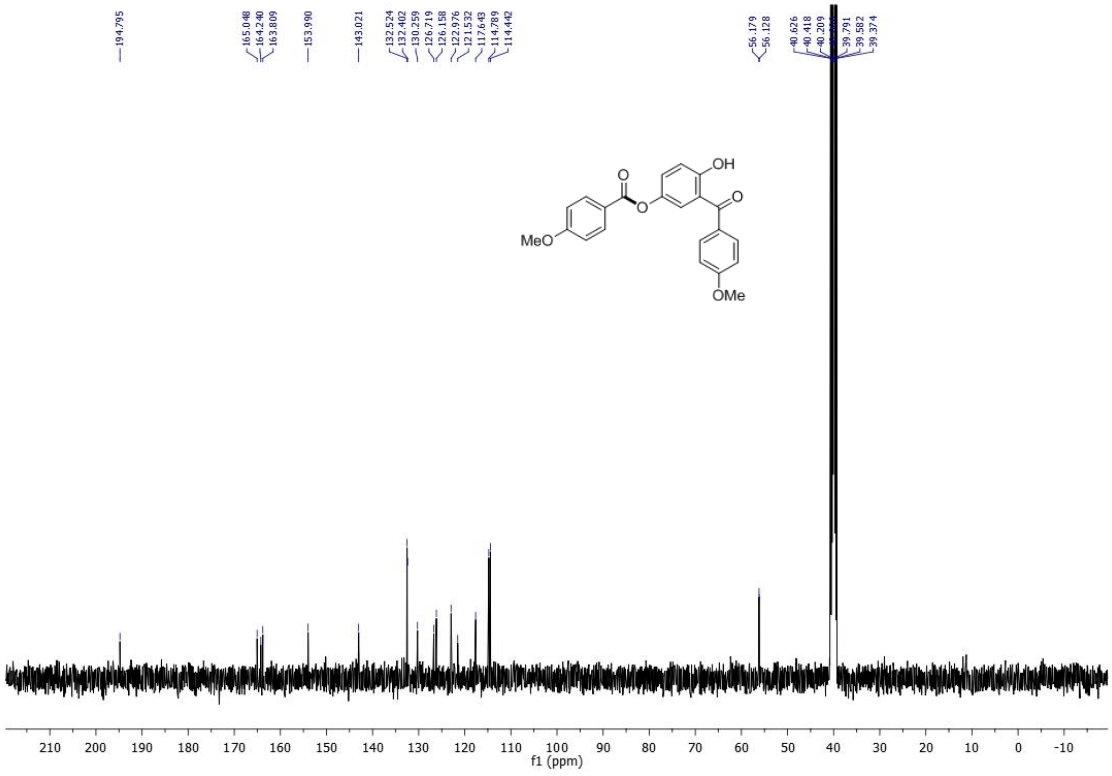
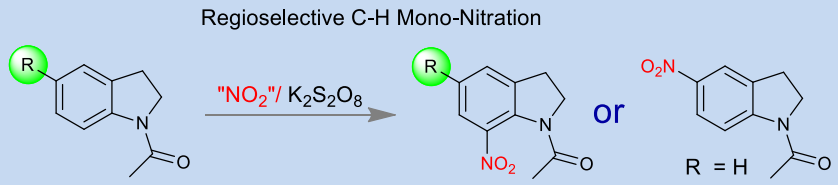


Figure 2.44. ^{13}C{^{1}H} NMR spectrum of 4-Hydroxy-3-(4-methoxybenzoyl)phenyl-4-methoxybenzoate (**3a′**).

CHAPTER 3

Weak Interactions Assisted C-H mono-Nitration of Indolines

3.1 ABSTRACT

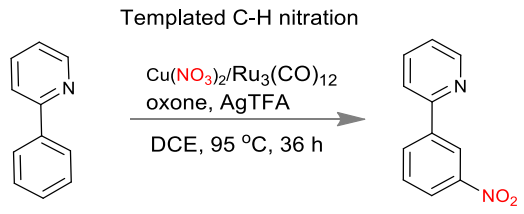


Under mild reaction condition a distinctive mononitration of indolines either at -C_5 or -C_7 positions is reported here. Various weak interactions like electronic effects, steric factors, solvent polarity, etc. were recognized as the cause for the exclusive regioselective electrophilic aromatic nitration by utilizing $Cu(NO_3)_2$ or $Ag(NO_3)_2$ as the nitro source.

3.2 INTRODUCTION

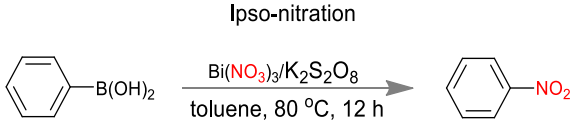
Nitroarenes are synthetically important moiety due to their potent application in different industries for example pharmaceutical, agrochemical, dyes, pesticides, etc. and also straightforward synthetic conversion to other functional groups like amino, diazo, etc. makes the molecule significant. Hence, easy and milder synthesis of these molecules is one of the most demanding organic reactions. Nitro group containing hetero-aromatic rings like indoline, indole, carbazole derivatives have compelling activity towards various diseases like *tuberculosis*.

Nitration of vital hetero arenes like indoles and indolines are advantageous and demanding due to their important pharmaceutical application in drug discovery but unavailability of appropriate methods[1-5] makes the process challenging. Most of the literature known procedures for electrophilic nitration of aromatic molecules uses harsh and toxic reaction conditions like conc. HNO_3-H_2SO_4,[6] conc. HNO_3-mixed anhydrides,[7] *N*-nitropyridinium salts, nitronium tetrafluoroborate,[8] $NaNO_3$-TFA,[9] etc.[10] These electrophilic nitration methods usually causes non-selective nitration[1] as well as over oxidized products. Also, some acid sensitive functional groups like –CN, -CHO may react under acidic medium which causes the purification process tedious.[11] Recently, C-H activation has emerged as a powerful tool for functionalization of non-functionalized substrates *via* metal template strategy.[12,13] Generally transition metals such as Fe,[14,15] Pd,[16] Rh, Ru,[17] etc. are used for C-H nitration reactions.[18,19] Zhang and his group have reported first *meta*-selective C-H nitration *via ortho*-metalation[20] approach by using Ru as the catalyst (Scheme 3.1).



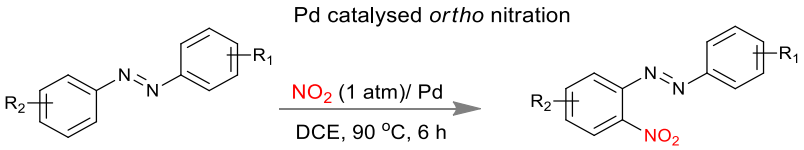
Scheme 3.1. Zhang's Ru- templated *meta*-selective C-H nitration approach.

Organometallic reagents[21,22] like aryl boronic acids, carboxylic acids,[23] aryl halides, aryl triflates, etc.[24,25] are proved to be efficient substrate for the synthesis of nitro derivatives via ipso substitution. A representative example of *ipso*-nitration on aryl boronic acids is shown in scheme 3.2 which is reported by Maiti and co-workers.



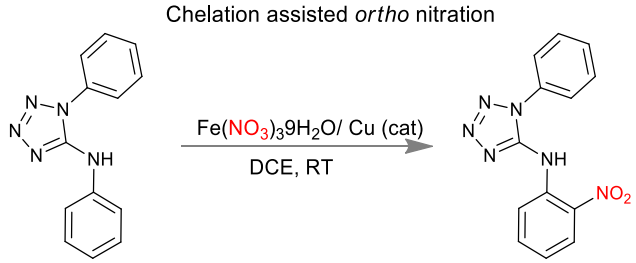
Scheme 3.2. Maiti's *ipso*-nitration on aryl boronic acids approach.

In 2014 Sun and his group reported a Pd catalysed ortho nitration of azoarenes using NO_2 gas as the nitro source.[26] Under 1 atm. pressure of NO_2 gas and 10 mol % of palladium acetate as catalyst under DCE solvent they have achieved good yield of ortho-nitro substituted product in 6 h (Scheme 3.3).



Scheme 3.3. Sun's Pd catalysed *ortho* nitration approach.

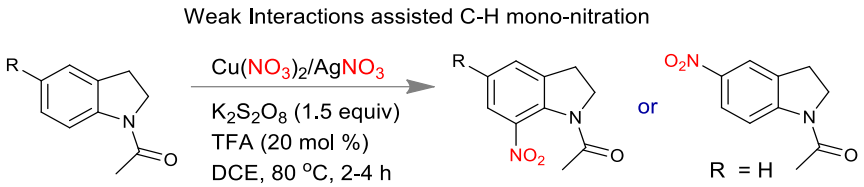
Punniyamurthy's group achieved a copper catalysed chelation assisted ortho nitration of *N*-phenyl-tetrazol-5-amine using $Fe(NO_3)_3 \cdot 9H_2O$ as the nitro source in DCE solvent at room temperature (Scheme 3.4).[19]



Scheme 3.4. Punniyamurthy's chelation assisted *ortho* nitration approach.

In system chemistry reactivity of a particular system can be altered by choosing suitable environment.[27-29] The weak secondary interactions or soft force[30] of low-energy non-covalent or weak interactions[31] like anion-π,[32] cation-π,[33,34] hydrophobic effect,[35] solvent effect, etc. are known to participate in selectivity of products in chemical systems.[36] Here in this work, secondary interactions have been utilized to achieve selective -C_7 or -C_5 aromatic

electrophilic (ArSE) nitration of indolines (Scheme 3.5) under a mild[37-39] reaction condition. The mechanism of the highly selective mono-nitration of non-prefunctionalized system is explained as an aromatic electrophilic substitution with the help of non-covalent interactions.



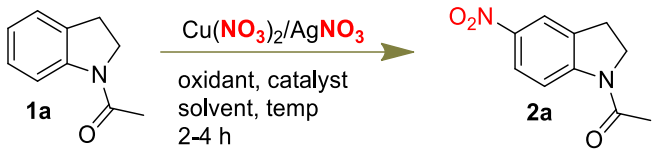
Scheme 3.5. Our weak interaction assisted C-H mono-nitration approach.

3.3 RESULT AND DISCUSSION

The standard condition of this nitration reaction was optimized (Table 3.1) for the transformation of *N*-acetyl indoline (**1a**) to 5-nitro-1-acetyl indoline (**2a**) using $Cu(NO_3)_2.3H_2O$ (1.1.equiv) or $AgNO_3$ (1.5 equiv) as $-NO_2$ (nitro) source, potassium persulfate ($K_2S_2O_8$, 1.5 equiv) as oxidizing agent and with catalytic amount of trifluoroacetic acid (TFA, 20 mol %) in 1,2-dichloroethane (DCE) at 80 ºC. The yield of **2a** was found to be up to 82% and 80%, respectively, using $Cu(NO_3)_2$ and $AgNO_3$. No product could be isolated by utilizing KNO_3 (entry 14) and $NaNO_3$ (entry 15) as the nitrating salts. Moreover, 23% of **2a** was obtained using $Bi(NO_3)_3$ (entry 16) and 54% of **2a** using $Fe(NO_3)_3$ although it took 8 h for complete consumption of starting indoline derivative. Among the other solvents examined, DCE was the most effective and the reaction failed in polar solvents like acetonitrile, DMSO, DMF, 1,4-dioxane, ethyl acetate, dichloromethane (entries 1-6) etc. Oxidizing agents e.g., oxone or phenyliodine diacetate (PIDA) were also inefficient (entries 17-19) to provide any promising results compared to $K_2S_2O_8$. Under oxygen atmosphere 48% of **2a** was isolated after 24 h. A representational example is shown in entry 7 (Table 3.1) that by

changing temperatures from 80 ºC did not have any positive impact in the improvement of yields.

Table 3.1. Optimization of reaction condition.



Entry	catalyst (equiv)	additive (equiv)	solvent	3aa (%)[b]
1	$Cu(NO_3)_2$ (1.0)	$K_2S_2O_8$ (3.0)	ACN, 90	--[b]
2	$Cu(NO_3)_2$ (1.0)	$K_2S_2O_8$ (3.0)	DMSO, 110	--
3	$Cu(NO_3)_2$ (1.2)	$K_2S_2O_8$ (3.0)	Dioxane, 90	--
4	$Cu(NO_3)_2$ (1.2)	$K_2S_2O_8$ (3.0)	DMF, 90	--
5	$Cu(NO_3)_2$ (1.2)	$K_2S_2O_8$ (3.0)	EtOAc, 90	--
6	$Cu(NO_3)_2$ (1.2)	$K_2S_2O_8$ (3.0)	DCM, 50	--
7	$Cu(NO_3)_2$ (1.0)	$K_2S_2O_8$ (3.0)	DCE, 90	58
8	$Cu(NO_3)_2$ (1.0)	$K_2S_2O_8$ (1.5)	DCE, 80	73
9[c]	$Cu(NO_3)_2$ (1.1)	$K_2S_2O_8$ (1.5)	DCE, 80	82
10	$AgNO_3$ (1.0)	$K_2S_2O_8$ (3.0)	DCE, 80	45
11[c]	$AgNO_3$ (1.5)	$K_2S_2O_8$ (1.5)	DCE, 80	80
12[d]	$AgNO_3$ (0.2), KNO_3 (2.0)	$K_2S_2O_8$ (3.0)	DCE, 80	18
13[d]	$AgNO_3$ (0.2), $NaNO_3$ (2.0)	$K_2S_2O_8$ (3.0)	DCE, 80	<10
14	KNO_3 (2.0)	$K_2S_2O_8$ (3.0)	DCE, 80	--
15	$NaNO_3$ (2.0)	$K_2S_2O_8$ (3.0)	DCE, 80	--
16[d]	$Bi(NO_3)_3.5H_2O$	$K_2S_2O_8$ (3.0)	DCE, 80	23
17[d]	$Cu(NO_3)_2$ (1.2)	Oxone (3.0)	DCE, 80	42
18[d]	$AgNO_3$ (1.5)	Oxone (3.0)	DCE, 80	30
19	$Cu(NO_3)_2$ (1.2)	PIDA (2.0)	DCE, 80	28

[a]$Cu(NO_3)_2$ used as $Cu(NO_3)_2.3H_2O$, [b]No reaction, [c]TFA 20 mol %. [d]Continued for16 h instead of 2 h.

A number of control experiments were done to understand the mechanistic pathway of the conversion. The radical scavenger 2,2,6,6-tetramethylpiperidin-1-yl)oxyl

(TEMPO) radical (1.0 equiv) was used under standard condition (Figure 3.1a) to check the radical nature of any intermediate. Isolation of 64% of **2a** under standard condition indicated that radicals are not involved in the reaction pathway. Similarly, no deuterium incorporation in the final product could rule out the metal template C-H activation mechanism while D_2O was used under optimized condition (Figure 3.1b). As in case of 1-methyl indoline and 1-H indoline no nitrated products (Figure 3.1c and d) were formed, carbonyl or sulfonyl substitution at N-centre of indoline was essential.

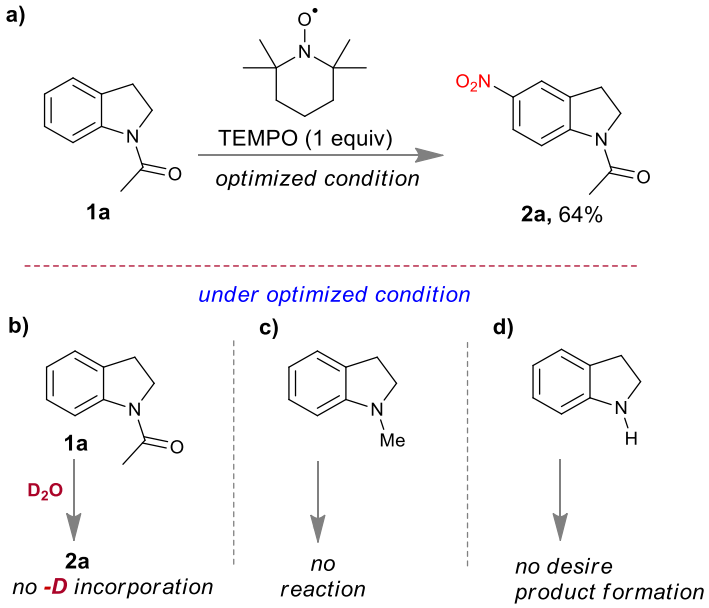


Figure 3.1. Control Experiments to the reaction mechanism.

From optimization (Table 3.1) and control (Figure 3.1) experiments a plausible mechanism of the mild and selective mono-nitration reaction of indolines is proposed (Figure 3.2). The electrophilic nitronium ion ($^{+}NO_2$) was supposed to generate from metal nitrate such as $Cu(NO_3)_2/AgNO_3$ in dichloroethane (DCE) solvent in the presence of catalytic amount of phase transfer catalyst TFA and oxidant $K_2S_2O_8$ (figure 3.2a). The nitrogen center of the indoline ring was expected to donate electron density towards aromatic ring *via* +R effect and the C_5- or C_7- positions were likely to be adequately electrophilic (figure 3.2b). Hence the necessity of π-acceptor protecting

groups (figure 3.2e) could be attributed to avoid protonation under mild acidic condition and also 1-methyl indoline and 1-H indoline underwent unsuccessful reaction due to protonation (figure 3.2d). Amongst several metal nitrates examined (Table 1), the soft Cu^{2+}/Ag^{+} ions in non-polar solvent like DCE best results was obtained. In polar solvents (DMSO, ACN, DMF, etc.) the weak interaction would not have been operative and hence no products were detected in high polar solvents. The C_5-H nitration was preferred over C_7-H nitration possibly due to the steric effect caused by *N*-acetyl group (figure 3.2c). When C_5-position of the indoline rings was blocked C_7-H nitration was the preferred consequently.

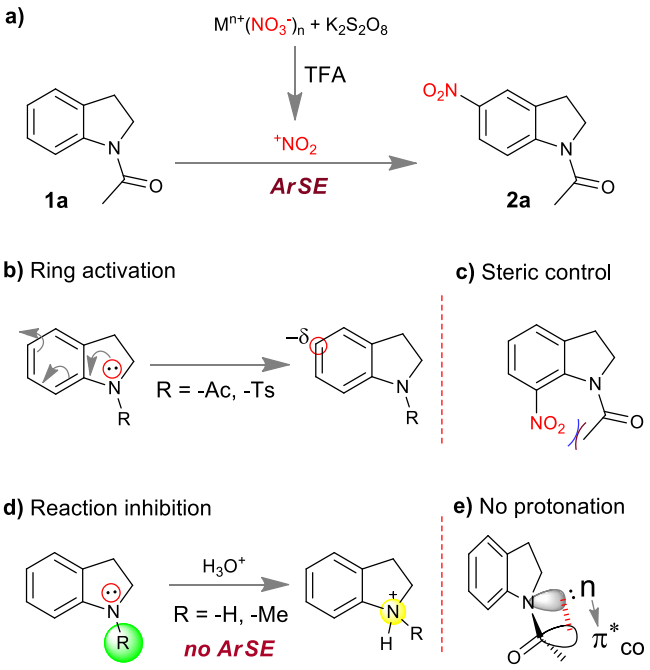


Figure 3.2. Plausible mehanism with the understanding of non-covalent interaction.

After finding the optimized condition the efficacy of the method was verified for a number of substrates to obtain C-H mono-nitration product (Figure 3.3). N-protected indoline moieties having substitution in the saturated pyrrolidine ring of indolines underwent regio-selective nitration reaction to give C_5-nitro substituted products in

reasonably good yields (Figure 3.3). Aryl substitution at C_2 position of indolines (**2f, 2g**) resulted in the preferred C_5 nitrated products in 58 - 70% yield. Apart from N-acyl indoline derivatives other π- accepter protecting groups like *N*-mesyl (**2d**), *N*-pivaloyl (**2e, 2f, 2g, 2h**), *N*-tosyl (**2i**) and *N*-benzoyl (**2j**) resulted in selective C_5-H nitrated products with 58 - 72% yield within 4 h.

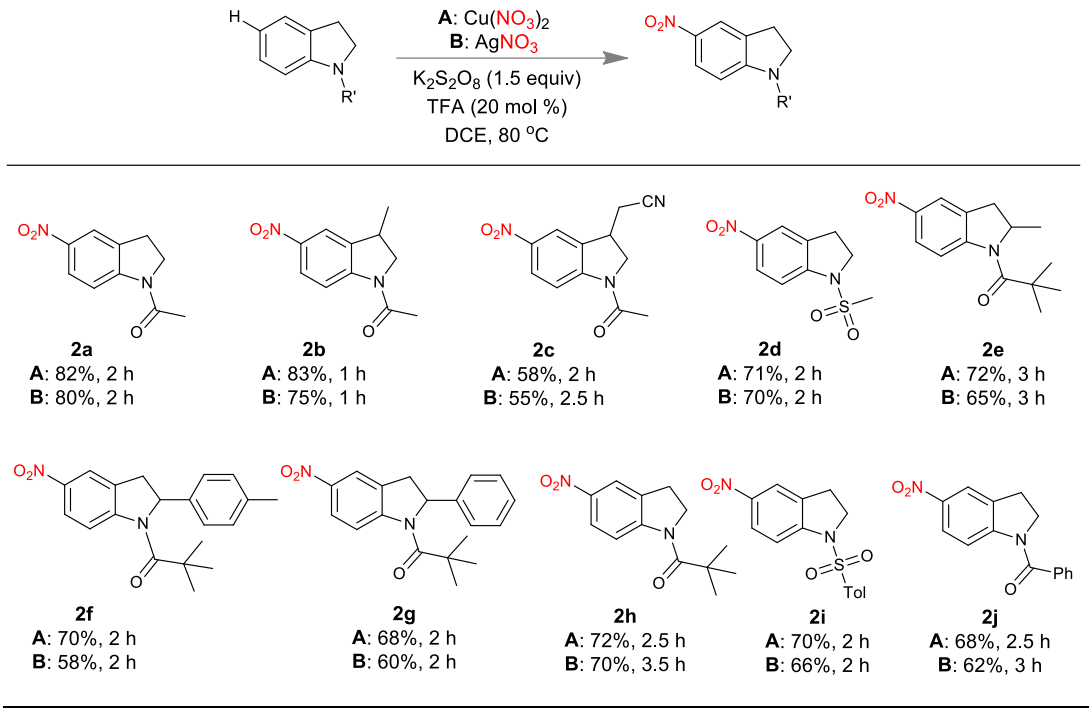


Figure 3.3. Substrate scope of C_5-Nitration of Indolines.

Substrates blocked at C_5 position with substitutions like bromo or aryl rings gave exclusive C_7-H nitrated products with good yield (figure 3.4). Interestingly under standard condition C_5-nitro indoline produced C_5,C_7-dinitro (**2k**) indoline derivative with 60% yield within 4 h. The substituted aryl groups at the C_5 position remain unaffected under reaction condition to give C_7-nitro product (**2p**, **2q**, **2r**, **2s**). C_5-bromo indoline also resulted in nitration product successfully (**2l**).

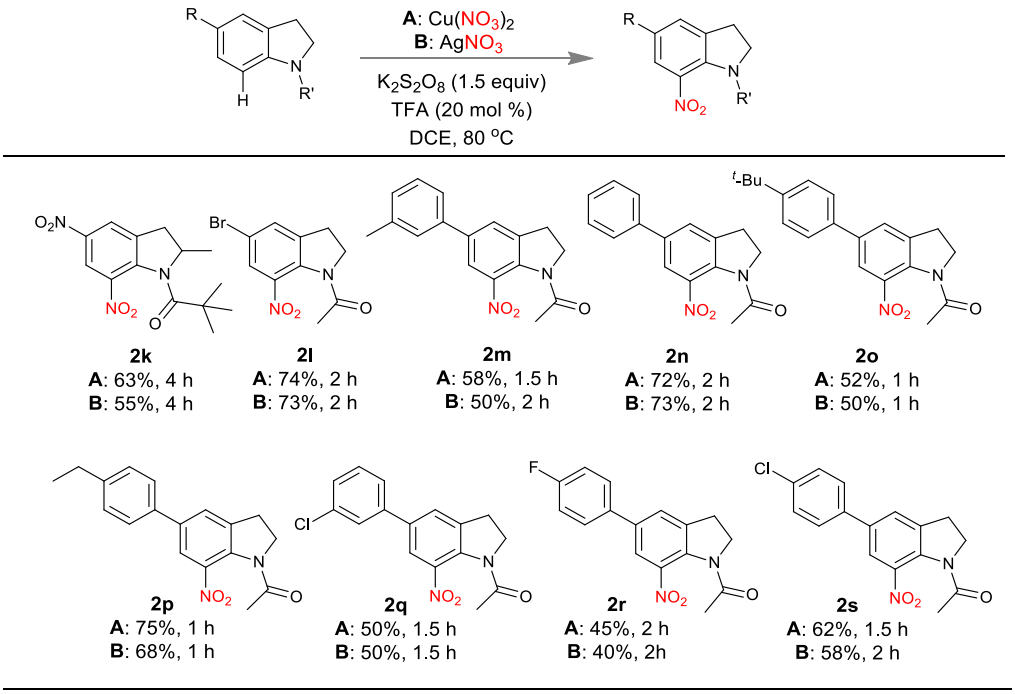


Figure 3.4. Substrate scope of C_7-Nitration of Indolines.

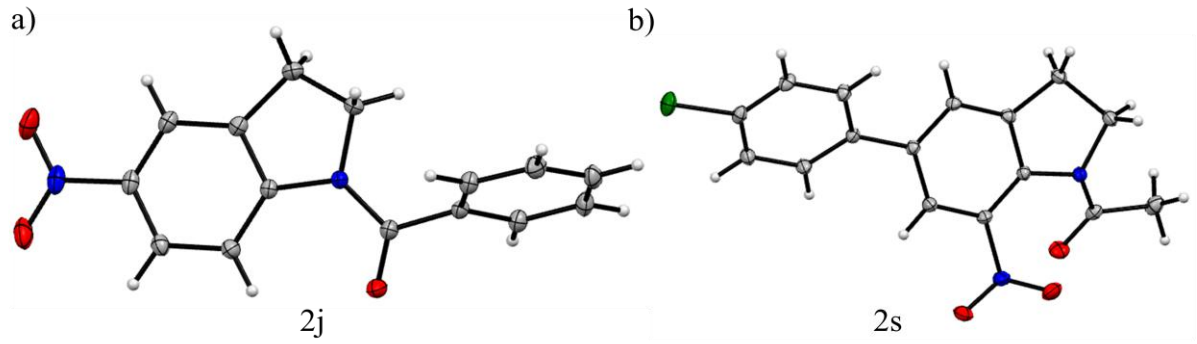


Figure 3.5. Crystal structure of compound **2j (CCDC: 1550269)** and **2s (CCDC: 1550265)**.

Compound **2j** and **2s** was also verified with single crystal X-ray analysis (Figure 3.5). After successful synthesis of several nitro derivatives utility of the method was tested for making various important molecules. Large scale preparation was done with compound **1a** and 74% of **2a** was isolated (Figure 3.5a) which says that the method can be applied in industrial purpose. Oxidation of 5-nitroindoline **2a** with DDQ gave

5-nitroindole (**3a**) with 70% yield (Figure 3.5b). Reduction of the nitro group of **2a** with Fe (powder)-HCl further produced the analogous amine **3b** with 80% yield (Figure 3.5c). Removal of the *N*-acetyl group under acidic condition by using 10 M HCl resulted in 5-nitroindoline **3c** in 4 h with 82% yield (Figure 3.5d). Under optimized condition nitration of *N*-acetyl tetrahydroquinoline (**4**, Figure 3.5e) resulted corresponding 6-nitrotetrahydroquinoline derivative (**5**) with 85% and 73% yields respectively in methods A and B.

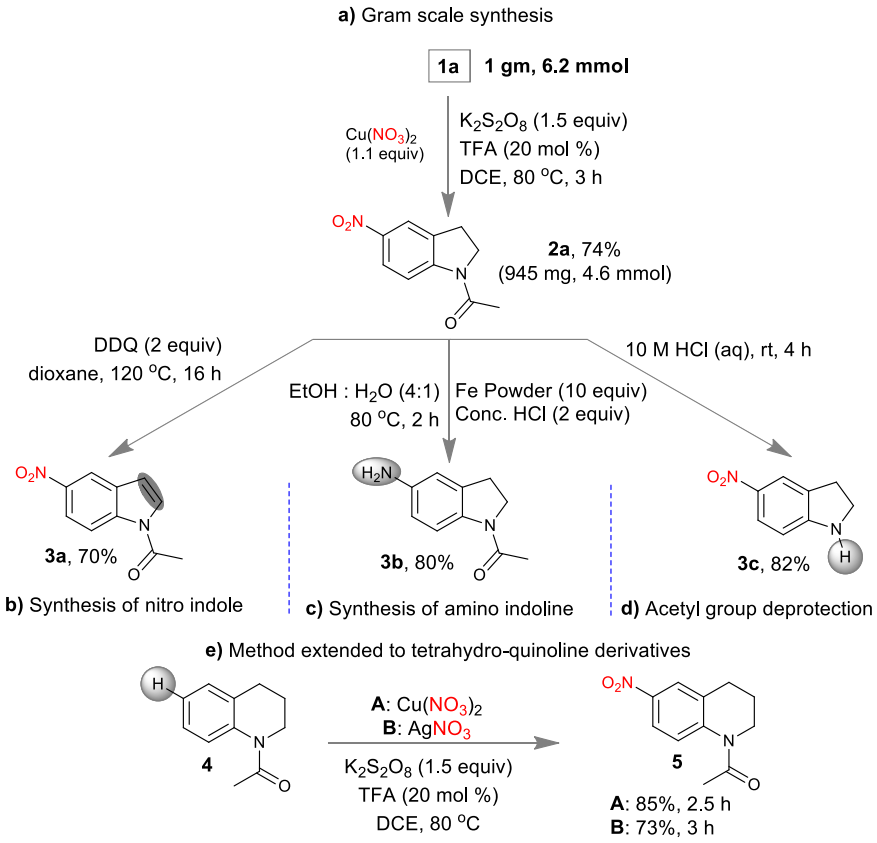


Figure 3.6. Post synthetic application. a) Gram scale synthesis of **2a**. b) Oxidation of nitroindoline to nitroindole. c) Reduction of nitro-indoline to amino-indoline. d) Acetyl group deprotection. e) Nitration of tetrahdroquinoline derivatives.

3.4 CONCLUSION

In summary, under a mild condition regio-selective aromatic nitration has been described with good yield and shorter reaction time. Strategically it is shown that by designing suitable reactive system complex conversion can also be done easily. Thus, a unique and regioselective method for mono-nitration at C_5 or C_7 of indolines has been achieved. This result may add a new aspect towards expansion of supramolecular catalysis in synthetic organic chemistry. The synthetic application of nitro-indolines towards formation of a range of valuable molecules is also reported. We anticipate this mild and selective nitration method can be used for straightforward synthesis of the functionalized heterocyclic molecules and could have a high impact for the development of pharmaceutically important molecules, biologically active moieties and synthons for natural product.

3.5 EXPERIMENTAL SECTION

Instrumentation and Chemicals. Column chromatographic purifications of the compounds were performed using silica gel (mesh 100–200) and hexane – ethyl acetate mixtures as eluent unless otherwise specified. FT-IR spectra were recorded after making pellet of the compounds using anhydrous solid KBr. NMR spectra were recorded on a 400 MHz or 700 MHz instrument at 25 °C. The chemical shift values are reported in parts per million (ppm) with respect to residual trichloromethane (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C) or dimethylsulfoxide (2.50 ppm for ^{1}H and 40.0 ppm for ^{13}C). The peak patterns are designated as follows: s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet; dd: doublet of doublets; td: triplet of doublets; br s broad singlet. The coupling constants (*J*) are reported in hertz (Hz). High-resolution mass spectra (HR-MS) were recorded on an ESI-TOF (time of flight) mass

spectrometer. The crystals data were collected with Bruker SMART D8 goniometer equipped with an APEX CCD detector and with an INCOATEC micro source (Cu-Kα radiation, λ = 0.71073 Å). SAINT+[40] and SADABS[41] were used to integrate the intensities and to correct the absorption respectively The structure was resolved by direct methods and refined on F^2 with SHELXL-97.[42] Infrared spectral data are reported in wave number (cm^{-1}). Melting points of the compounds were determined using a digital melting point apparatus and are uncorrected.

Representative procedure for preparation of 1-(5-nitroindolin-1-yl)ethanone (2a)

Method A. To an oven-dried sealed tube charged with a magnetic stirring bar and **1a** (100 mg, 0.62 mmol, 1 equiv), $Cu(NO_3)_2.3H_2O$ (165 mg, 0.68 mmol, 1.1 equiv), and $K_2S_2O_8$ (252 mg, 0.93 mmol, 1.5 equiv) in DCE (2 mL) was added TFA (10 μL, 0.12 mmol, 0.2 equiv). The reaction mixture was allowed to stir at 80 °C for 2 h. After cooling at room temperature, the reaction mixture washed with water and followed by extracted with dichloromethane. Column purification using 25% ethyl acetate-hexane yielded **2a** (105 mg, 82%) as pale yellow solid.

Method B. To an oven-dried sealed tube charged with a magnetic stirring bar and **1a** (100 mg, 0.62 mmol, 1 equiv), $AgNO_3$ (158 mg, 0.93 mmol, 1.5 equiv), and $K_2S_2O_8$ (252 mg, 0.93 mmol, 1.5 equiv) in DCE (2 mL) was added TFA (10 μL, 0.12 mmol, 0.2 equiv). The reaction mixture was allowed to stir at 80 °C for 2 h. After cooling at room temperature, the reaction mixture washed with water and followed by extracted with dichloromethane. Column purification using 25% ethyl acetate-hexane yielded **2a** (102 mg, 80%) as pale yellow solid.

Characterisation Data of Compounds

1-(5-Nitroindolin-1-yl)ethanone (2a):[43] R_f = 0.28 (25% ethyl acetate/hexane); pale yellow solid; yield A: 105 mg (82%), B: 102 mg (80%); mp: 175-178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.8 Hz, 1H), 8.11 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.03 (s, 1H), 4.19 (t, *J* = 8. 4 Hz, 2H), 3.28 (t, *J* = 8.4 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 148.4, 143.7, 132.4, 124.8, 120.4, 116.3, 49.5, 27.5, 24.4; IR (KBr) $\tilde{\nu}$ 2972, 2812, 2373, 1603, 1515, 1480, 1399, 1258, 1172, 1129, 1074, 1025, 994, 892, 843, 748, 624 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{10}H_{11}N_2O_3$ $[M+H]^+$ 207.0764, found 207.0765.

1-(3-Methyl-5-nitroindolin-1-yl)ethanone (2b): R_f = 0.4 (20% ethyl acetate/hexane); pale yellow solid; yield A: 106 mg (83%), B: 95 mg (75%); mp: 122-125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.8 Hz, 1H), 8.11 (dd, *J* = 8.8, 2.0 Hz, 1H), 8.00 (s, 1H), 4.33 (t, *J* = 10 Hz, 1H), 3.71 (dd, *J* = 10, 6.8 Hz, 1H), 3.57 (dm, 1H), 2.26 (s, 3H), 1.41 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 147.8, 143.8, 137.7, 124.9, 119.4, 116.3, 57.6, 34.4, 24.4, 20.3; IR (KBr) $\tilde{\nu}$ 2964, 2891, 2191, 1672, 1602, 1510, 1478, 1399, 1329, 1261, 1175, 1116, 1078, 1032, 1012, 916, 836, 787, 732, 620 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{11}H_{13}N_2O_3$ $[M+H]^+$ 221.0921, found 221.0909.

2-(1-Acetyl-5-nitroindolin-3-yl)acetonitrile (2c): R_f = 0.3 (40% ethyl acetate/hexane); off white solid; yield A: 71 mg (58%), B: 67 mg (55%); mp: 156-168 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1H), 8.20 (d, *J* = 1.6 Hz, 2H), 4.45 (t, *J* = 9.8 Hz, 1H), 4.00 (dd, *J* = 10.8, 5.6 Hz, 1H), 3.88 (dd, *J* = 9.2, 5.6 Hz, 1H), 3.09 (d, *J* = 6.0, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.4, 148.9, 143.2, 134.6, 126.1, 120.9, 119.3, 115.8, 54.6, 35.8, 24.6, 22.3; IR (KBr) $\tilde{\nu}$ 2995, 2872, 2254, 2128, 1758, 1659, 1551, 1501, 1484, 1338,

1266, 1049, 1025, 1002, 825, 764, 655 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{11}N_3O_3Na$ $[M+Na]^+$ 268.0693, found 268.0693.

1-(Methylsulfonyl)-5-nitroindoline (2d): R_f = 0.42 (25% ethyl acetate/hexane); pale yellow solid; yield A: 90 mg (71%), B: 88 mg (70%); mp: 142-145 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.07 (d, *J* = 2.0 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 4.13 (t, *J* = 8.8 Hz, 2H), 3.26 (t, *J* = 8.8 Hz, 2H), 2.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 143.9, 132.4, 125.2(2C), 121.4, 112.5, 51.0, 36.3, 27.3; IR (KBr) $\tilde{\nu}$ 2912, 2298, 20978, 1637, 1456, 1339, 1318, 1235, 1108, 1079, 958, 756, 635 cm^{-1}; HRMS (ESI-TOF) calcd for $C_9H_{11}N_2O_4S$ $[M+H]^+$ 243.0434, found 243.0433.

2,2-Dimethyl-1-(2-methyl-5-nitroindolin-1-yl)propan-1-one (2e): R_f = 0.57 (10% ethyl acetate/hexane); off white solid; yield A: 87 mg (72%), B: 79 mg (65%); mp: 157-160 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.8 Hz, 1H), 8.13 (dd, *J* = 8.8, 2.0 Hz, 1H), 8.08 (s, 1H), 4.99 – 4.93 (m, 1H), 3.37 (dd, *J* = 15.2, 7.6 Hz, 1H), 2.71 (d, *J* = 15.2 Hz, 1H), 1.40 (s, 9H), 1.29 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 148.9, 143.7, 131.8, 124.3, 120.5, 118.6, 57.1, 41.0, 36.3, 28.3, 22.0; IR (neat) $\tilde{\nu}$ 2975, 2931, 2874, 1696, 1655, 1599, 1514, 1435, 1298, 1160, 1118, 1066, 992, 754, 671 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{19}N_2O_3$ $[M+H]^+$ 263.1390, found 263.1372.

2,2-Dimethyl-1-(5-nitro-2-(p-tolyl)indolin-1-yl)propan-1-one (2f): R_f = 0.28 (6% ethyl acetate/hexane); yellow solid; yield A: 81 mg (70%), B: 67 mg (58%); mp: 142-145 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 9.2 Hz, 1H), 8.18 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.94 (s, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 5.91 (d, *J* = 8.8 Hz, 1H), 3.75 (dd, *J* = 15.2, 8.8 Hz, 1H), 3.00 (d, *J* = 15.2 Hz, 1H), 2.28 (s, 3H), 1.22 (s, 9H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 178.2, 150.5, 144.0, 139.6, 137.4, 130.4, 129.7, 124.7, 124.5, 120.5, 117.7, 63.8, 41.0, 39.2, 28.3, 20.9; IR (KBr) $\tilde{\nu}$ 3407, 2983, 2937, 2365, 1653, 1602, 1520, 1466, 1401, 1301, 1218, 1181, 1068, 970, 890, 754 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{23}N_2O_3$ $[M+H]^+$ 339.1703, found 339.1696.

2,2-Dimethyl-1-(5-nitro-2-phenylindolin-1-yl)propan-1-one (2g): R_f = 0.21 (8% ethyl acetate/hexane); pale yellow solid; yield A: 80 mg (68%), B: 70 mg (60%); mp: 160-164 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.8 Hz, 1H), 8.17 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.93 (s, 1H), 7.27 – 7.18 (m, 3H), 7.04 (d, *J* = 6.8 Hz, 2H), 5.93 (d, *J* = 8.4 Hz, 1H), 3.76 (dd, *J* = 15.6, 8.4 Hz, 1H), 3.01 (d, *J* = 15.6 Hz, 1H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 150.5, 144.0, 142.6, 130.3, 129.0, 127.7, 124.8, 124.6, 120.5, 117.7, 63.9, 41.0, 39.2, 28.3; IR (KBr) $\tilde{\nu}$ 2971, 2873, 1954, 1748, 1664, 1599, 1492, 1401, 1339, 1254, 1160, 1120, 1029, 936, 839, 754 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{19}H_{21}N_2O_3$ $[M+H]^+$ 325.1547, found 325.1572.

2,2-Dimethyl-1-(5-nitroindolin-1-yl)propan-1-one (2h): R_f = 0.42 (20% ethyl acetate/hexane); pale yellow solid; yield A: 88 mg (72%), B: 85 mg (70%); mp: 119-122 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.8 Hz, 1H), 8.12 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.05 (s, 1H), 4.36 (t, *J* = 8.4 Hz, 2H), 3.24 (t, *J* = 8.4 Hz, 2H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 150.5, 143.7, 132.1, 124.6, 120.0, 117.7, 50.3, 40.7, 28.8, 27.7; IR (KBr) $\tilde{\nu}$ 3056, 2977, 2879, 2307, 2156, 1656, 1515, 1402, 1313, 1160, 921, 835, 739, 703, 614 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{13}H_{17}N_2O_3$ $[M+H]^+$ 249.1234, found 249.1225.

5-Nitro-1-tosylindoline (2i): R_f = 0.28 (18% ethyl acetate/hexane); pale yellow solid; yield A: 82 mg (70%), B: 77 mg (66%); mp: 168-171 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd,

J = 8.8, 2.0 Hz, 1H), 7.92 (d, *J* = 1.2 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.28 – 7.23 (m, 2H), 4.00 (t, *J* = 8.8 Hz, 2H), 3.04 (t, *J* = 8.8 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 145.2, 143.8, 133.7, 132.6, 130.2, 127.3, 124.9, 121.1, 113.3, 50.6, 27.2, 21.7; IR (KBr) $\tilde{\nu}$ 2956, 2902, 2307, 2090, 1641, 1599, 1479, 1339, 1306, 1256, 1166, 1091, 1074, 972, 704, 665 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{15}N_2O_4S$ $[M+H]^+$ 319.0747, found 319.0744.

(5-Nitroindolin-1-yl)(phenyl)methanone (2j): R_f = 0.28 (15% ethyl acetate/hexane); yellow solid; yield A: 105 mg (68%), B: 102 mg (62%); mp: 197-200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.2 Hz, 1H), 7.58 – 7.46 (m, 5H), 7.26 (s, 1H), 4.19 (t, *J* = 8.4 Hz, 2H), 3.22 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 148.4, 143.9, 136.0, 133.7, 131.2, 128.9, 127.3, 124.5, 120.7, 116.5, 51.5, 27.7; IR (KBr) $\tilde{\nu}$ 3005, 2987, 2922, 2315, 2114, 1659, 1551, 1441, 1383, 1317, 1152, 833, 751, 699 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{13}N_2O_3$ $[M+H]^+$ 269.0921, found 269.0931.

2,2-Dimethyl-1-(2-methyl-5,7-dinitroindolin-1-yl)propan-1-one (2k): R_f = 0.42 (20% ethyl acetate/hexane); yellow solid; yield A: 74 mg (63%), B: 65 mg (55%); mp: 158-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.86 (s, 1H), 5.06 – 4.99 (m, 1H), 3.43 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.80 (d, *J* = 16.0 Hz, 1H), 1.39 (s, 9H), 1.33 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 148.1, 144.4, 137.0, 134.6, 121.6, 114.2, 57.6, 41.2, 36.4, 28.2, 22.1; IR (KBr) $\tilde{\nu}$ 2973, 2933, 2366, 1655, 1602, 1547, 1528, 1474, 1380, 1319, 1291, 1189, 1110, 1009, 993, 707 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{18}N_3O_5$ $[M+H]^+$ 308.1241, found 308.1243.

1-(5-Bromo-7-nitroindolin-1-yl)ethanone (2l):[43] R_f = 0.42 (20% ethyl acetate/hexane); yellow solid; yield A: 88 mg (74%), B: 86 mg (73%); mp: 196-198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.52 (s, 1H), 4.23 (t, *J* = 8.0 Hz, 2H), 3.22 (t, *J* = 8.0 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 140.9, 138.5, 133.7, 131.6, 125.4, 116.2, 50.1, 28.8, 23.2; IR (neat) $\tilde{\nu}$ 3055, 2988, 2686, 2411, 2306, 1686, 1596, 1542, 1458, 1421, 1384, 1331, 1265, 896, 737 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{10}H_{10}BrN_2O_4$ $[M+H]^+$ 284.9869, found 284.9876.

1-(7-Nitro-5-(m-tolyl)indolin-1-yl)ethanone (2m): R_f = 0.28 (6% ethyl acetate/hexane); yellow solid; yield A: 68 mg (58%), B: 59 mg (50%); mp: 198-200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.86 (s, 1H), 7.64 (s, 1H), 7.49 (d, *J* = 6.0 Hz, 2H), 4.29 (t, *J* = 8.0 Hz, 2H), 3.30 (t, *J* = 8.0 Hz, 2H), 2.67 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 148.6, 143.3, 141.1, 137.9, 135.6, 134.8, 131.2, 127.2, 125.8, 125.3, 121.8, 50.4, 29.1, 23.4, 20.9; IR (KBr) $\tilde{\nu}$ 3056, 2975, 2929, 2851, 2377, 2307, 1679, 1609, 1580, 1474, 1307, 1264, 1148, 1031, 982, 966, 739, 704 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{17}N_2O_3$ $[M+H]^+$ 297.1234, found 297.1257.

1-(7-Nitro-5-phenylindolin-1-yl)ethanone (2n): R_f = 0.28 (20% ethyl acetate/hexane); pale yellow solid; yield A: 86 mg (72%), B: 87 mg (73%); mp: 188 -190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 0.8 Hz, 1H), 7.63 (s, 1H), 7.54 (d, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.39 – 7.36 (m, 1H), 4.27 (t, *J* = 8.0 Hz, 2H), 3.27 (t, *J* = 8.0 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 141.1, 138.7, 138.4, 137.3, 133.6, 129.2, 128.2, 127.2, 127.0, 121.5, 50.4, 29.2, 23.4; IR (KBr) $\tilde{\nu}$ 2934, 2820, 1618, 1530, 1427, 1387, 1231, 1117, 1069, 1020, 882, 747, 693 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{15}N_2O_3$ $[M+H]^+$ 283.1077, found 283.1080.

1-(5-(4-(tert-Butyl)phenyl)-7-nitroindolin-1-yl)ethanone (2o): R_f = 0.28 (10% ethyl acetate/hexane); yellow solid; yield A: 60 mg (52%), B: 57 mg (50%); mp: 177-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.63 (s, 1H), 7.48 (d, *J* = 2.0 Hz, 4H), 4.27 (t, *J* = 8.0 Hz, 2H), 3.27 (t, *J* = 8.0 Hz, 2H), 2.28 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 151.5, 141.2, 138.4, 137.2, 135.8, 133.4, 127.0, 126.7, 126.2, 121.3, 50.4, 34.8, 31.4, 29.3, 23.4; IR (KBr) $\tilde{\nu}$ 3055, 2964, 2927, 2855, 2305, 1678, 1538, 1478, 1409, 1382, 1319, 1265, 1111, 836, 745 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{23}N_2O_3$ $[M+H]^+$ 339.1703, found 339.1679.

1-(5-(4-Ethylphenyl)-7-nitroindolin-1-yl)ethanone (2p): R_f = 0.28 (12% ethyl acetate/hexane); yellow solid; yield A: 88 mg (75%), B: 80 mg (68%); mp: 144-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.62 (s, 1H), 7.46 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 8 Hz, 2H), 4.27 (t, *J* = 8 Hz, 2H), 3.26 (t, *J* = 8 Hz, 2H), 2.69 (q, *J* = 7.6 Hz, 2H), 2.27 (s, 3H), 1.27 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 144.5, 141.1, 138.4, 137.2, 136.1, 133.3, 128.7, 126.97, 126.95, 121.1, 50.3, 29.2, 28.6, 23.4, 15.6; IR (KBr) $\tilde{\nu}$ 2967, 2931, 2365, 1609, 1567, 1498, 1389, 1288, 1116, 1072, 918, 896, 835, 707, 618 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{19}N_2O_3$ $[M+H]^+$ 311.1390, found 311.1375.

1-(5-(3-Chlorophenyl)-7-nitroindolin-1-yl)ethanone (2q): R_f = 0.42 (15% ethyl acetate/hexane); yellow solid; yield A: 58 mg (50%), B: 58 mg (50%); mp: 145- 148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.62 (s, 1H), 7.54 (s, 1H), 7.44 – 7.36 (m, 3H), 4.29 (t, *J* = 8.0 Hz, 2H), 3.29 (t, *J* = 8.0 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 141.1, 140.5, 137.6, 136.8, 135.2, 134.2, 130.5, 128.3, 127.16, 127.08, 125.2, 121.6, 50.4, 29.2, 23.5; IR (KBr) $\tilde{\nu}$ 2925, 2853, 2685, 2305, 2125, 1733, 1681, 1641, 1465, 1381,

1264, 1114, 1078, 895, 705 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{13}ClN_2O_3Na$ $[M+Na]^+$ 339.0507, found 339.0508.

1-(5-(4-Fluorophenyl)-7-nitroindolin-1-yl)ethanone (2r): R_f = 0.42 (12% ethyl acetate/hexane); yellow solid; yield A: 53 mg (45%), B: 47 mg (40%); mp: 153-156 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.58 (s, 1H), 7.50 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.14 (t, *J* = 8.8 Hz, 2H), 4.28 (t, *J* = 8.0 Hz, 2H), 3.28 (t, *J* = 8.0 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 164.2, 161.7, 141.1, 137.4 (d, $^1J_{F-C}$ = 7.8 Hz), 134.9 (d, $^1J_{F-C}$ = 3.1 Hz), 133.6, 128.7 (d, $^1J_{F-C}$ = 8.2 Hz), 127.0, 121.3, 116.2 (d, $^1J_{F-C}$ = 21.5 Hz), 50.4 , 29.2, 23.4; IR (KBr) $\tilde{\nu}$ 2959, 2927, 2854, 2305, 2114, 1640, 1543, 1512, 1467, 1381, 1265, 1169, 836, 745, 705 cm^{-1};
HRMS (ESI-TOF) calcd for $C_{16}H_{14}FN_2O_3$ $[M+H]^+$ 301.0983, found 301.0970.

1-(5-(4-Chlorophenyl)-7-nitroindolin-1-yl)ethanone (2s): R_f = 0.28 (18% ethyl acetate/hexane); pale yellow solid; yield A: 72 mg (62%), B: 67 mg (58%); mp: 149-152 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 1.6 Hz, 1H), 7.58 (d, *J* = 1.6 Hz, 1H), 7.47-7.44 (m , 2H), 7.41 – 7.39 (m, 2H), 4.27 (t, *J* = 8.0 Hz, 2H), 3.27 (t, *J* = 8.0 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 140.9, 137.4, 137.0, 136.8, 134.2, 133.7, 129.2, 128.0,126.7, 121.1, 50.2, 29.0, 23.3; IR (KBr) $\tilde{\nu}$ 2937, 2812, 2678, 2165, 1728, 1670, 1634, 1567, , 1256, 1109, 1085, 801, 734 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{13}ClN_2O_3Na$ $[M+Na]^+$ 339.0502, found 339.0502.

Post synthetic application of 1-(5-nitroindolin-1-yl)ethanone (2a)

Synthesis of nitro indole. To an oven-dried sealed tube charged with a magnetic stirring bar, a mixture of **2a** (50 mg, 0.24 mmol, 1 equiv) and DDQ (110 mg, 0.48 mmol, 2 equiv) was added and dissolved in 2 ml of 1,4-dioxane. The reaction mixture was allowed to stir at 120 °C for 16 h. After cooling at room temperature, the reaction mixture was washed with brine solution and followed by extracted with ethyl acetate. Column purification using 8% ethyl acetate-hexane yielded 1-(5-Nitro-1H-indol-1-yl)ethanone (**3a**)[44] as pale yellow solid; R_f = 0.28 (8% ethyl acetate/hexane); yield 35 mg (70%); mp: 173-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57(d, *J* = 9.2 Hz, 1H), 8.49 (d, *J* = 2.4 Hz, 1H), 8.24 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.59 (d, *J* = 4.0 Hz, 1H), 6.79 (d, *J* = 2.4 Hz, 1H), 2.69 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 144.4, 138.6, 130.4, 128.2, 120.6, 117.2, 116.9, 109.7, 24.1; IR (KBr) $\tilde{\nu}$ 2928, 2902, 2306, 2114, 1641, 1550, 1421, 1321, 1203, 896, 739, 706 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{10}H_8N_2O_3Na$ $[M+Na]^+$ 227.0427, found 227.0439.

Synthesis of amino indoline. To a mixture of **2a** (50 mg, 0.24 mmol, 1 equiv) and iron powder (134 mg, 2.4 mmol, 10 equiv) in a round bottom flask, 2 mL of EtOH and 0.5 ML of water was added along with 45 μL of conc. HCl. The resulting mixture was allowed to reflux at 80 ºC for 2 h. After cooling at room temperature, the reaction mixture was washed with $NaHCO_3$ solution and extracted with ethyl acetate. Column chromatographic purification using 40% ethyl acetate-hexane yielded 1-(5-Aminoindolin-1-yl)ethanone (**3b**)[45] as pale yellow solid; R_f = 0.21 (40% ethyl acetate/hexane); yield 34 mg (80%); mp: 180-183 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, *J* = 8.8 Hz, 1H), 6.45 (s, 1H), 6.32 (dd, *J* = 8.8, 2.0 Hz, 1H), 4.85 (s, 2H), 3.97 (t, *J* = 8.4 Hz, 2H), 2.99 (t, *J* = 8.4 Hz, 2H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.1, 145.2, 133.7, 133.0, 117.0, 112.3, 111.1, 48.5, 28.0, 24.1; IR (KBr) $\tilde{\nu}$ 3443, 3055, 2376, 2306, 2114, 1642, 1492, 1265, 895, 742, 700 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{10}H_{13}N_2O$ $[M+H]^+$ 177.1022, found 177.1032.

Deprotection of acetyl group. In a round bottom flask **2a** (50 mg, 0.24 mmol, 1 equiv) was taken and 2 ml of 10 M HCl was added to it. The solution was stirred at room temperature for 4 h. Then the reaction mixture was washed with saturated NaOH solution and extracted in dichloromethane. The organic layer was concentrated under reduced pressure and re-crystallised from ethanol to get orange solid of 5-nitroindoline (**3c**);[43] orange solid; yield 33 mg (82%); mp: 91-93 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.83 (s, 1H), 7.25 (s, 1H), 6.44 (d, *J* = 8.8 Hz, 1H), 3.65 (t, *J* = 8.4 Hz, 2H), 3.04 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.2, 136.8, 129.9, 126.9, 121.0, 105.7, 47.0, 27.9; IR (KBr) $\tilde{\nu}$ 3439, 3056, 2926, 1612, 1500, 1321, 1265, 1161, 1072, 897, 741 cm^{-1}; HRMS (ESI-TOF) calcd for $C_8H_9N_2O_2$ $[M+H]^+$ 165.0659, found 165.0648.

Method extended to the synthesis of 1-(6-nitro-3,4-dihydroquinolin-1(2H)-yl)ethanone (5) from 1-(3,4-dihydroquinolin-1(2H)-yl)ethanone 4[46]

1-(6-Nitro-3,4-dihydroquinolin-1(2H)-yl)ethanone (5): R_f = 0.28 (25% ethyl acetate/hexane); yellow solid; yield A: 107 mg (85%), B: 92 mg (73%); mp: 160-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.03 (m, 2H), 7.64 (d, *J* = 7.2 Hz, 1H), 3.80 (t, *J* = 6.4, 2H), 2.85 (t, *J* = 6. 4 Hz, 2H), 2.31 (s, 3H), 2.07 – 1.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 144.5, 143.9, 132.5, 124.8, 124.1, 121.8, 45.0, 27.5, 23.8, 23.5; IR (KBr) $\tilde{\nu}$ 2945, 2934, 2371, 1618, 1603, 1511, 1388, 1330, 1280, 1200, 1118, 1073, 1019, 994, 965, 919, 901, 751, 697 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{11}H_{13}N_2O_3$ $[M+H]^+$ 221.0921, found 221.0917.

Synthesis of starting materials

Synthesis of C2-substituted indole derivative. The corresponding C_2 substituted indole (for **2f, 2g**) derivatives were prepared by literature reported procedures.[47] In a sealed tube under air, a mixture of $Pd(OAc)_2$ (24.0 mg, 0.01 mmol, 5 mol %), dppm (41.0 mg, 0.01 mmol, 5 mol%), AcOK (630 mg, 6.3 mmol, 3.0 equiv), iodobenzene (522 mg, 2.52 mmol, 1.2 equiv) and indole (250 mg, 2.1 mmol, 1.0 equiv) in 5 mL H_2O was vigorously stirred at 110°C. After 24 h the reaction mixture was cooled to room temperature and washed with 1N HCl and ethyl acetate. The organic layer was extracted with ethyl acetate and were dried over $NaSO_4$, and concentrated under reduced pressure. Column purification using 10% ethyl acetate-hexane yielded 2-Phenylindole as white solid.

2-(p-Tolyl)-1H-indole (1f'):[48] R_f = 0.21 (8% ethyl acetate/hexane); white solid; yield 302 mg (68%); mp: 178-180 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.44 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.98 (t, *J* = 7. 4 Hz, 1H), 6.83 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 138.4, 137.6, 137.5, 130.1, 130.0, 129.3, 125.5, 122.0, 120.5, 119.9, 111.8, 98.7, 21.4; IR (KBr) $\tilde{\nu}$ 3433, 2366, 1627, 1398, 1276, 1122, 1069, 823, 791, 734, 511 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{14}N$ $[M+H]^+$ 208.1121, found 208.1096.

2-Phenyl-1H-indole (1g'):[47] R_f = 0.28 (10% ethyl acetate/hexane); white solid; yield 290 mg (70%); mp: 187-190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 138.0, 137.6, 132.6, 129.3, 129.0, 127.8, 125.4, 122.0, 120.5, 119.8, 111.7, 99.1; IR (KBr) $\tilde{\nu}$ 3448, 2366, 1617, 1400, 1299, 1230, 1116, 1073, 907, 764, 743, 689 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{12}N$ $[M+H]^+$ 194.0964, found 194.0944.

Synthesis of C5-substituted indole derivative. The corresponding C_5 substituted indole (for **2m, 2n, 2o, 2p, 2q, 2r, 2s)** derivatives were prepared by literature reported procedure.[49] To an oven-dried sealed tube charged with a magnetic stirring bar and 5-bromoindole (200 mg, 0.84 mmol, 1 equiv), phenylboronic acid (205 mg, 1.68 mmol, 2 equiv), $Pd(PPh_3)_4$ (48.5 mg, 0.04 mmol, 0.05 equiv), K_2CO_3 (175 mg, 1.26 mmol, 1.5 equiv) in 10 ml DMF, Ethanol, H_2O (1.5: 1.5: 1 v/v) mixture were stirred at 120 ^oC for 24 h. The reaction mixture was cooled to room temperature and washed with brine solution. The organic layer was extracted with ethyl acetate and were dried over Na_2SO_4, and concentrated under reduced pressure. Column purification using 3% ethyl acetate-hexane yielded 5-phenylindole as white solid.

5-(m-Tolyl)-1H-indole (1m'):[50] R_f = 0.42 (4% ethyl acetate/hexane); off white solid; yield 200 mg (75%); mp: 110-113 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.13 (s, 1H), 7.80 (s, 1H), 7.48-7.43 (m, 3H), 7.39 – 7.36 (m, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.48 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 142.3, 138.2, 135.9, 131.9, 129.1, 128.7, 127.9, 127.2, 126.4, 124.3, 120.8, 118.5, 112.2, 101.9, 21.6; IR (KBr) $\tilde{\nu}$ 2938, 2874, 1617, 1470, 1380, 1259, 1150, 1079, 1012, 978, 929, 772, 697 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{14}N$ $[M+H]^+$ 208.1121, found 208.1116.

5-Phenyl-1H-indole (1n'): R_f = 0.28 (5% ethyl acetate/hexane); white solid; yield 244 mg (82%); mp: 70-73 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.13 (s, 1H), 7.80 (s, 1H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.48 – 7.36 (m, 5H), 7.28 (t, *J* = 7.2 Hz, 1H), 6.48 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 142.5, 136.1, 132.0, 129.5, 128.9, 127.3, 126.8, 126.7, 121.0, 118.8, 112.5, 102.3; IR (KBr) $\tilde{\nu}$ 2920, 2882, 1613, 1601, 1468, 1399, 1276, 1174, 1089, 1073, 1035,

994, 916, 880, 780, 756, 738, 701 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{12}N$ $[M+H]^+$ 194.0964, found 194.0960.

5-(4-(tert-Butyl)phenyl)-1H-indole (1o'): R_f = 0.50 (5% ethyl acetate/hexane); white solid; yield 240 mg (75%); mp: 102-104 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (s, 1H), 7.78 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.45 (t, *J* = 6.8, 8.0 Hz, 3H), 7.36 (dd, *J* = 5.4, 2.2 Hz, 2H), 6.47 (s, 1H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.9, 139.5, 135.8, 131.7, 128.7, 126.7, 126.4, 125.9, 120.7, 118.3, 112.2, 101.9, 34.6, 31.6; IR (KBr) $\tilde{\nu}$ 2951, 2368, 1602, 1450, 1390, 1364, 1217, 1175, 1111, 1026, 994, 889, 807, 721, 613 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{20}N$ $[M+H]^+$ 250.1590, found 250.1579.

5-(4-Ethylphenyl)-1H-indole (1p'): R_f = 0.28 (6% ethyl acetate/hexane); white solid; yield 221 mg (78%); mp: 100-103 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (s, 1H), 7.77 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 5.2, 1.6 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 6.47 (s, 1H), 2.63 (q, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 142.1, 139.8, 135.8, 131.8, 128.7, 128.6, 127.0, 126.4, 120.7, 118.3, 112.2, 101.9 , 28.2, 16.1; IR (KBr) $\tilde{\nu}$ 2960, 2930, 2374, 1603, 1399, 1220, 1174, 1113, 1070, 995, 917, 888, 805, 764, 721, 617 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{16}N$ $[M+H]^+$ 222.1277, found 222.1253.

5-(3-Chlorophenyl)-1H-indole (1q'): R_f = 0.42 (8% ethyl acetate/hexane); off white solid; yield 217 mg (62%); mp: 94-97 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (s, 1H), 7.86 (s, 1H), 7.70 – 7.62 (m, 2H), 7.49 –7.32 (m, 5H), 6.49 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.6, 136.2, 134.0, 131.0, 130.2, 128.7, 126.8, 126.7, 126.4, 125.8, 120.7, 118.9, 112.4, 102.1; IR (KBr) $\tilde{\nu}$ 2935, 2369, 2345, 1598, 1458, 1399, 1342, 1251, 1178, 1112, 1074, 1032,

996, 917, 875, 775, 690 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{11}NCl$ $[M+H]^+$ 228.0575, found 228.0571.

5-(4-Fluorophenyl)-1H-indole (1r'):[51] R_f = 0.28 (7% ethyl acetate/hexane); white solid; yield 227 mg (70%); mp: 90-93 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.14 (s, 1H), 7.78 (s, 1H), 7.69 – 7.65 (m, 2H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.37 – 7.34 (m, 2H), 7.25 (t, *J* = 8.8 Hz, 2H), 6.48 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7 (d, *J* = 241.2 Hz), 138.9 (d, *J* = 3.0 Hz), 135.9, 130.9, 129.0 (d, *J* = 7.9 Hz), 128.8, 126.7, 120.9, 118.7, 116.0 (d, *J* = 21.0 Hz), 112.4, 102.1; IR (KBr) $\tilde{\nu}$ 2933, 2912, 2368, 1612, 1399, 1216, 1115, 1072, 917, 894, 838, 807, 763, 713cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{11}FN$ $[M+H]^+$ 212.0870, found 212.0854.

5-(4-Chlorophenyl)-1H-indole (1s'): R_f = 0.42 (8% ethyl acetate/hexane); off white solid; yield 248 mg (71%); mp: 89-91 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.17 (s, 1H), 7.80 (d, *J* = 1.6 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.47 (t, *J* = 8.4, 2.0 Hz, 3H), 7.39 – 7.36 (m, 2H), 6.48 (d, *J* = 0.8 Hz, 1H); ^{13}C NMR (176 MHz, DMSO-d_6) δ 141.2, 136.1, 131.5, 130.5, 129.2, 128.8, 128.7, 126.7, 120.7, 118.7, 112.4, 102.1; IR (KBr) $\tilde{\nu}$ 3105, 3029, 2924, 2130, 1712, 1599, 1466, 1263, 1091, 1010, 890, 803, 730, 603 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{11}ClN$ $[M+H]^+$ 228.0575, found 228.0561.

Representative procedure for reduction of indole to indoline derivatives.[52] The corresponding indoline derivatives were prepared by literature reported procedure from substituted indoles. In a round bottom flask 2-phenylindole (100 mg, 0.52 mmol, 1 equiv) was dissolved in 6 mL glacial acetic acid and $NaCNBH_3$ (228 mg, 3.6 mmol, 6 equiv) was added in small portions for 30 minutes at 10 °C. Temperature was raised to 20 °C and

reaction was monitored by TLC. After 3 h reaction was quenched with 1 M NaOH solution at 0 ^{o}C and organic layer was extracted with DCM. The combined organic layer was dried over $NaSO_4$ and concentrated under reduced pressure. The crude residue was directly used in next step without further column purification.

Representative procedure for synthesis of *N*-protected indoline derivatives.[53] In a round bottom flask indoline (250 mg, 2.1 mmol, 1 equiv) was dissolved in 10 ml DCM and Pyridine (216 mg, 2.7 mmol, 1.3 equiv) was added drop wise at 0 ^{o}C. Maintaining the temperature at 0 ^{o}C, acetyl chloride (198 mg, 2.25 mmol, 1.1 equiv) was added dropwise. Temperature was raised to RT and reaction was monitored by TLC. After 2 h reaction was quenched with saturated solution of ammonium chloride and organic layer was extracted with DCM. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was re- crystallised from ethanol to get pure *N*-Acylindoline.

1-(Indolin-1-yl)ethanone (1a): White solid; yield: 305 mg (90%); mp: 102-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.0 Hz, 1H), 7.20 – 7.15 (m, 2H), 7.00 (t, *J* = 8.0 Hz, 1H), 4.02 (t, *J* = 8. 4 Hz, 2H), 3.18 (t, *J* = 8.4 Hz, 2H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 142.9, 131.2, 127.6, 124.6, 123.6, 117.0, 48.8, 28.0, 24.3; IR (KBr) $\tilde{\nu}$ 2957, 2909, 2857, 1960, 1924, 1817, 1640, 1594, 1482, 1400, 1321, 1263, 1173, 1093, 1031, 1016, 988, 950, 922, 850, 769, 730, 652, 595 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{10}H_{12}NO$ $[M+H]^{+}$ 162.0913, found 162.0920.

1-(3-Methylindolin-1-yl)ethanone (1b):[54] White solid; yield: 276 mg (84%); mp: 72-76 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 4.20 (t, *J* = 10 Hz, 1H), 3.57 (dd, *J* = 10, 7.2 Hz, 1H),

3.50 (dd, *J* = 10, 7.2 Hz, 1H), 2.22 (s, 3H), 1.36 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 142.5, 136.4, 127.8, 123.8, 123. 5, 117.0, 57.1, 34.9, 24.3, 20.4; IR (KBr) $\tilde{\nu}$ 3121, 2928, 2832, 2369, 2345, 1602, 1399, 1217, 1114, 994, 918, 851, 762, 706 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{11}H_{14}NO$ $[M+H]^+$ 176.1070, found 176.1107.

2-(1-Acetylindolin-3-yl)acetonitrile (1c): Pale yellow solid; yield: 263 mg (82%); mp: 82-85 ^oC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.4 Hz, 1H), 7.29-7.25 (m, 2H), 7.06 (t, *J* = 7.4 Hz, 1H), 4.27 (t, *J*= 10 Hz, 1H), 3.85-3.81 (m, 1H), 3.78 – 3.75 (m, 1H), 2.71 – 2.57 (m, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 142.6, 130.9, 129.4, 124.2, 123.8, 117.7, 117.3, 54.1, 37.0, 24.3, 23.4; IR (KBr) $\tilde{\nu}$ 3055, 2986, 2413, 2306, 2249,1664, 1599, 1483, 1353, 1265, 1130, 1023, 738, 703 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{13}N_2O$ $[M+H]^+$ 201.1022, found 201.1043.

1-(Methylsulfonyl)indoline (1d):[55] Light pink solid; yield: 340 mg (88%); mp: 70-72 ^oC; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.7 Hz, 1H), 7.22 – 7.18 (m, 1H), 7.03 (t, *J* = 7.0 Hz, 1H), 3.97 (t, *J* = 8.4 Hz, 1H), 3.15 (t, *J* = 8.4 Hz, 1H), 2.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 131.3, 128.1 (2C), 125.5, 123.8, 113.8, 50.5, 34.4, 28.0; IR (KBr) $\tilde{\nu}$ 3010, 2914, 1600, 1477, 1417, 1325, 1293, 1200, 1102, 1034, 982, 758 cm^{-1}; HRMS (ESI-TOF) calcd for $C_9H_{12}NO_2S$ $[M+H]^+$ 198.0583, found 198.0578.

2,2-Dimethyl-1-(2-methylindolin-1-yl)propan-1-one (1e):[44] Colorless oil; yield: 296 mg (90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 2H), 7.02 (t, *J* = 8.0, 6.8 Hz, 1H), 4.84 (p, *J* = 8.0 Hz, 2H), 3.30 (dd, *J* = 14.8, 6. 4 Hz, 1H), 2.58 (d, *J* = 14.8 Hz, 1H), 1.38 (s, 9H), 1.25 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 143.3, 130.8, 127.2, 124.9, 123.9, 119.7, 56.1, 40.7, 36.9, 28.6, 21.9; IR (neat) $\tilde{\nu}$ 2969, 2931,

2875, 2563, 1793, 1643, 1475, 1462, 1401, 1324, 1278, 1222, 1162, 1062, 991, 759 cm-1; HRMS (ESI-TOF) calcd for $C_{14}H_{20}NO$ $[M+H]^+$ 218.1539, found 218.1569.

2,2-Dimethyl-1-(2-(p-tolyl)indolin-1-yl)propan-1-one (1f): White solid; yield: 283 mg (80%); mp: 122-125 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 7.6 Hz , 1H), 7.08 – 6.98 (m, 6H), 5.80 (d, *J* = 8.4 Hz, 1H), 3.70 (dd, *J* = 15.0, 8.4 Hz, 1H), 2.89 (d, *J* = 15.0 Hz, 1H), 2.27 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 145.0, 140.8, 136.7, 129.3, 129.1, 127.4, 125.0, 124.8, 124.1, 118.7, 62.9, 40.6, 39.8, 28.6, 20.9; IR (KBr) $\tilde{\nu}$ 3055, 2928, 2307, 2115, 1641, 1550, 1419, 1265, 896, 740, 705 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{24}NO$ $[M+H]^+$ 249.1852, found 294.1844.

2,2-Dimethyl-1-(2-phenylindolin-1-yl)propan-1-one (1g): White solid; yield: 296 mg (82%); mp: 128-130 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.0 Hz, 1H), 7.27 – 7.22 (m, 3H), 7.19-7.15 (m, 1H), 7.11 (d, *J* = 7.2 Hz, 2H), 7.07 (d, *J* = 7.4 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 5.83 (d, *J* = 8. 4 Hz, 1H), 3.73 (dd, *J* = 15.2, 8.8 Hz, 1H), 2.92 (d, *J* = 15.2 Hz, 1H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 145.1, 143.9, 129.1, 128.8, 127.6, 127.2, 125.3, 125.0, 124.3, 118.8, 63.2, 40.7, 39.8, 28.7; IR (KBr) $\tilde{\nu}$ 3015, 2909, 2119, 1635, 1520, 1401, 1237, 870, 735, 698 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{19}H_{22}NO$ $[M+H]^+$ 280.1701, found 280.1692.

1-(Indolin-1-yl)-2,2-dimethylpropan-1-one (1h):[44] Pale yellow solid; yield: 292 mg (92%); mp: 63-66 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.4 Hz, 1H), 7.20 – 7.16 (m, 2H), 7.01 (t, *J* = 7.4 Hz, 1H), 4.22 (t, *J* = 8.4 Hz, 2H), 3.13 (t, *J* = 8.4 Hz, 2H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 144.8, 130.9, 127.4, 124.3, 123.7, 118.5, 49.6, 40.3, 29.4,

27.8; IR (KBr) $\tilde{\nu}$ 2984, 2961, 1644, 1598, 1474, 1401, 1358, 1223, 1198, 1100, 1073, 761, 707 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{13}H_{18}NO$ $[M+H]^+$ 204.1383, found 204.1388.

1-Tosylindoline (1i):[56] Off white solid; yield: 510 mg (89%); mp: 134-136 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 6.96 (t, *J* = 7.2 Hz, 1H), 3.90 (t, *J* = 8.4 Hz, 2H), 2.87 (t, *J* = 8.4 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 142.1, 134.1, 131.8, 129.7, 127.8, 127.4, 125.2, 123.8, 115.1, 50.0, 28.0, 21.6; IR (KBr) $\tilde{\nu}$ 3393, 3031, 2935, 2874, 2853, 1599, 1508, 1460, 1308, 1239, 1152, 1090, 975, 754, 711, 659 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{16}NO_2S$ $[M+H]^+$ 274.0896, found 274.0902.

Indolin-1-yl(phenyl)methanone (1j):[57] White solid; yield: 480 mg (85%); mp: 114-117 ^oC; ^1H NMR (700 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.0 Hz, 2H), 7.49 – 7.43 (m, 3H), 7.21 (d, *J* = 7.0 Hz, 1H), 7.02 (s, 1H), 4.07 (s, 2H), 3.12 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 142.7, 137.0, 132.4, 130.3, 128.6, 127.1, 124.9, 123.9, 117.4, 50.6, 28.2; IR (KBr) $\tilde{\nu}$ 2945, 2931, 2864, 2370, 1637, 1594, 1482, 1296, 1113, 1073, 996, 862, 763cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{14}NO$ $[M+H]^+$ 224.1070, found 224.1092.

1-(5-Bromoindolin-1-yl)ethanone (1l):[58] White solid; yield: 275 mg (91%); mp: 120-123 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.2 Hz, 1H), 7.27-7.24 (m, 2H), 4.04 (t, *J* = 8.4 Hz, 2H), 3.16 (t, *J* = 8.4 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 142.1, 133.5, 130.5, 127.7, 118.3, 116.0, 48.9, 27.8, 24.2; IR (KBr) $\tilde{\nu}$ 2971, 2926, 1654, 1604, 1560, 1475, 1329, 1249, 1169, 1066, 994, 814, 706 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{10}H_{11}BrNO$ $[M+H]^+$ 240.0019, found 240.0044.

1-(5-(m-Tolyl)indolin-1-yl)ethanone (1m): Off white solid; yield: 230 mg (76%); mp: 132-135 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8. 4 Hz, 1H), 7.43 – 7.28 (m, 5H), 7.13 (d, *J* = 7.6 Hz, 1H), 4.10 (t, *J* = 8.8 Hz, 2H), 3.25 (t, *J* = 8.8 Hz, 2H), 2.41 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 142.3, 141.0, 138.4, 137.0, 131.8, 128.8, 127.8 (2 C), 126.7, 124.0, 123.3, 117.1, 49.1, 28.1, 24.3, 21.6; IR (KBr) $\tilde{\nu}$ 2945, 2908, 2136, 1603, 1528, 1398, 1216, 1114, 1072, 994, 918, 699, 618 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{17}NONa$ $[M+Na]^+$ 274.1202, found 274.1210.

1-(5-Phenylindolin-1-yl)ethanone (1n): White solid; yield: 221 mg (72%); mp: 183-185 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.44 – 7.39 (m, 4H), 7.31 (t, *J* = 7.2 Hz, 1H), 4.10 (t, *J* = 8.4 Hz, 2H), 3.26 (t, *J* = 8.4 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 142.5, 141.0, 136.9, 131.9, 128.9, 127.0, 126.9, 126.7, 123.3, 117.2, 49.2, 28.2, 24.3; IR (KBr) $\tilde{\nu}$ 2953, 2907, 2852, 1620, 1600, 1533, 1431, 1110, 1067, 1008, 964, 843, 825, cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{16}NO$ $[M+H]^+$ 238.1226, found 238.1229.

1-(5-(4-(tert-Butyl)phenyl)indolin-1-yl)ethanone (1o): White solid; yield: 215 mg (73%); mp: 144-147 ^{o}C; ^{1}H NMR (400 MHz, CDCl3) δ 8.24 (d, *J* = 8.4 Hz, 1H), 7.52 – 7.49 (m, 2H), 7.45 – 7.40 (m, 4H), 4.09 (t, *J* = 8.8 Hz, 2H), 3.24 (t, *J* = 8.8 Hz, 2H), 2.24 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 150.0, 142.2, 138.1, 136.7, 131.8, 126.6, 126.5, 125.8, 123.1, 117.1, 49.1, 34.6, 31.5, 28.1, 24.3; IR (KBr) $\tilde{\nu}$ 2968, 2922, 2217,1619, 1608, 1508, 1369, 1114, 1035, 994, 897, 707 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{24}NO$ $[M+H]^+$ 294.1852, found 294.1854.

1-(5-(4-Ethylphenyl)indolin-1-yl)ethanone (1p): White solid; yield: 228 mg (76%); mp: 144-147 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8. 4 Hz, 1H), 7.48 (d, *J* = 8 Hz, 2H), 7.41 (t, *J* = 8.4, 5.6 Hz, 2H), 7.25 (d, *J* = 6.8 Hz, 2H), 4.09 (t, *J* = 8.4 Hz, 2H), 3.25 (t, *J* = 8.4 Hz, 2H), 2.68 (q, *J* = 7.6 Hz, 2H), 2.24 (s, 3H), 1.27 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 143.2, 142.2, 138.4, 136.9, 131.8, 128.4, 126.9, 126.4, 123.1, 117.2, 49.1, 28.6, 28.2, 24.3, 15.7; IR (KBr) $\tilde{\nu}$ 2959, 2367, 1663, 1604, 1488, 1395, 1299, 1116, 1068, 993, 822, 700 cm^{-1};

HRMS (ESI-TOF) calcd for $C_{18}H_{20}NO$ $[M+H]^+$ 266.1539, found 266.1540.

1-(5-(3-Chlorophenyl)indolin-1-yl)ethanone (1q): White solid; yield: 202 mg (68%); mp: 136-138 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 2.0 Hz, 1H), 7.44 – 7.31 (m, 5H), 4.11 (t, *J* = 8.4 Hz, 2H), 3.26 (t, *J* = 8.4 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 142.0, 141.9, 134.4, 133.8, 131.1, 129.1, 126.1, 126.0, 125.7, 124.1, 122.3 , 116.3, 48.2, 27.1, 23.3; IR (KBr) $\tilde{\nu}$ 2959, 2927, 2366, 1655, 1606, 1468, 1394, 1355, 1111, 1073, 995, 841, 779, 688 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{15}ClNO$ $[M+H]^+$ 272.0837, found 272.0845.

1-(5-(4-Fluorophenyl)indolin-1-yl)ethanone (1r): White solid; yield: 211 mg (70%); mp: 156-158 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.4 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.38 – 7.35 (m, 2H), 7.10 (t, *J* = 8.8 Hz, 2H), 4.10 (t, *J* = 8.8 Hz, 2H), 3.25 (t, *J* = 8.8 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 163.6, 161.2, 142.4, 136.6 (d, $^{1}J_{F-C}$ = 124.6 Hz), 132.0, 128.5 (d, $^{1}J_{F-C}$ = 7.9 Hz), 126.6, 123.2, 117.3, 115.7 (d, $^{1}J_{F-C}$ = 21.4 Hz), 49.2, 28.2, 24.3; IR (KBr) $\tilde{\nu}$ 2962, 2902, 2363, 1653, 1508, 1488, 1392, 1235, 1159, 1035, 828, 627 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{15}FNO$ $[M+H]^+$ 256.1132, found 256.1138.

1-(5-(4-Chlorophenyl)indolin-1-yl)ethanone (1s): White solid; yield: 193 mg (65%); mp: 169-172 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.4 Hz, 1H), 7.49 – 7.46 (m, 2H), 7.38 (dd, *J* = 7.6, 5.8 Hz, 4H), 4.10 (t, *J* = 8.4 Hz, 2H), 3.25 (t, *J* = 8.4 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 142.7, 139.5, 135.6, 133.1, 132.1, 129.0, 128.2, 126.6, 123.1, 117.3, 49.1, 28.1, 24.3; IR (KBr) $\tilde{\nu}$ 2972, 2922, 1635, 1600, 1443, 1352, 1108, 998, 901, 863, 645 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{15}NOCl$ $[M+H]^+$ 272.0837, found 272.0834.

1-(3,4-Dihydroquinolin-1(2H)-yl)ethanone (4): Colorless oily liquid; yield: 303 mg (92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.08 (m, 4H), 3.78 (t, *J* = 6.4, 2.4 Hz, 2H), 2.71 (t, *J* = 6.4, 2.4 Hz, 2H), 2.22 (s, 3H), 1.95 (p, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 139.4, 128.5 (2 C), 126.1, 125.2, 124.7, 42.9, 26.9, 24.1, 23.2; IR (neat) $\tilde{\nu}$ 3028, 2948, 2081, 1634, 1645, 1580, 1488, 1385, 1294, 1176, 1094, 962, 760 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{11}H_{14}NO$ $[M+H]^+$ 176.1070, found 176.1088.

2.6 NOTES AND REFERENCES

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^{1}H and ^{13}C NMR spectra of synthesized compound

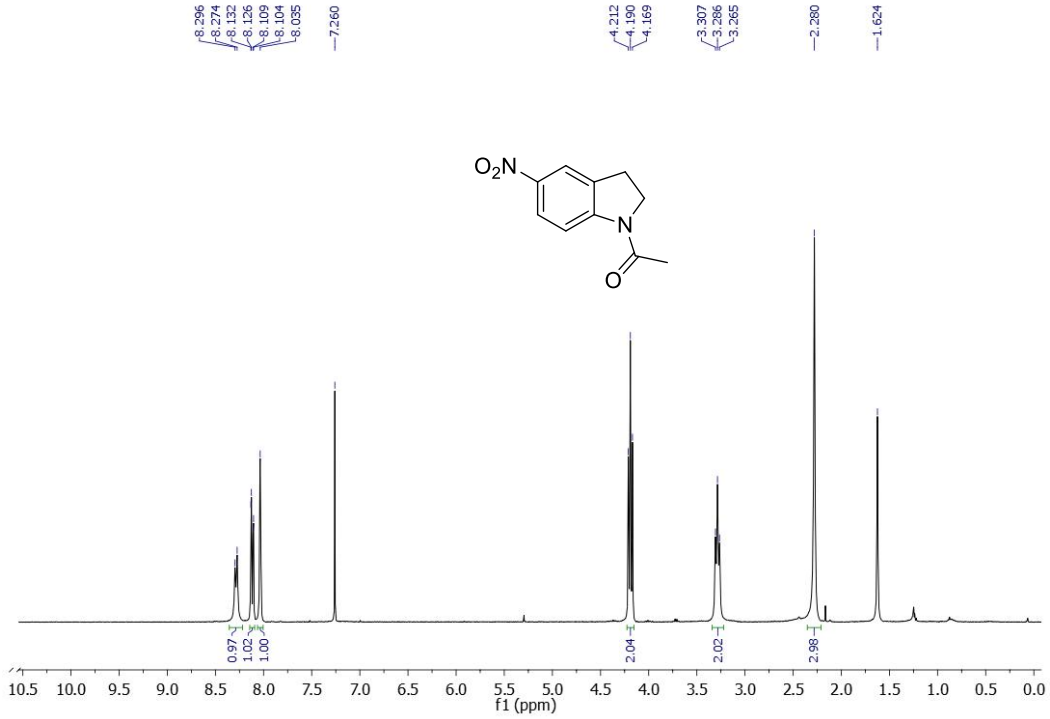

Figure 3.7. ^{1}H NMR spectrum of 1-(5-Nitroindolin-1-yl)ethanone **(2a).**

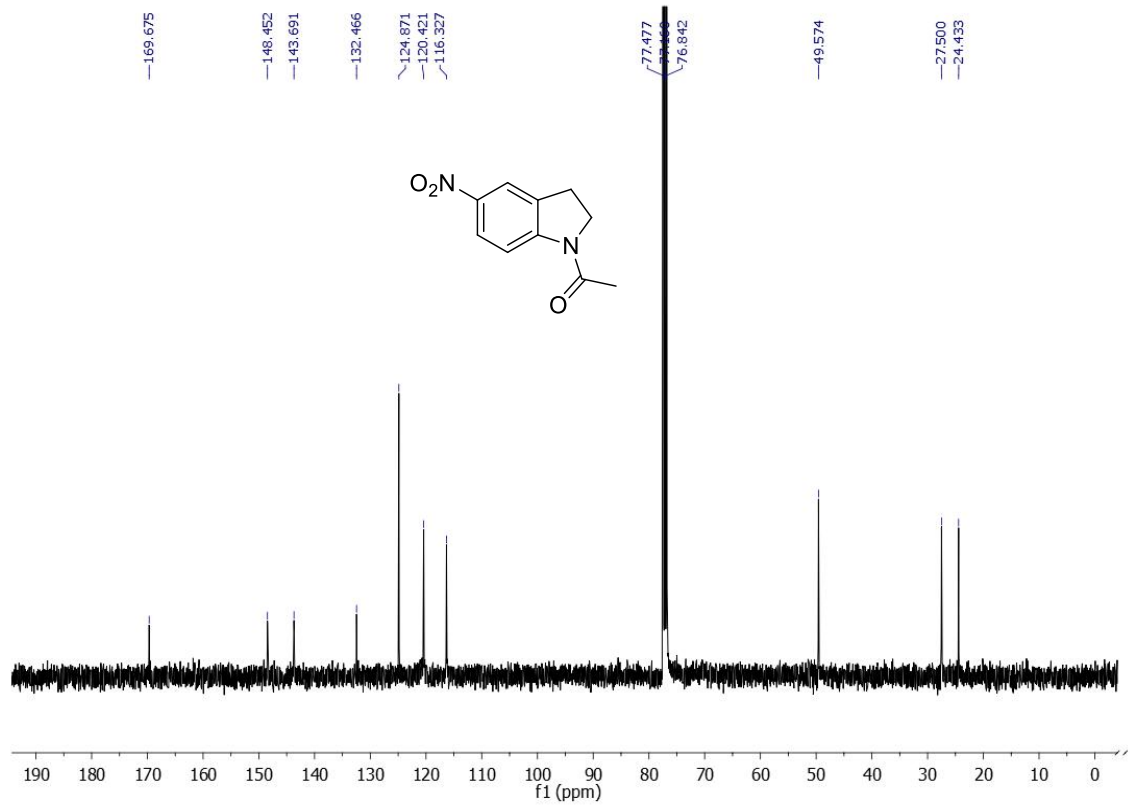

Figure 3.8. ^{13}C NMR spectrum of 1-(5-Nitroindolin-1-yl)ethanone **(2a).**

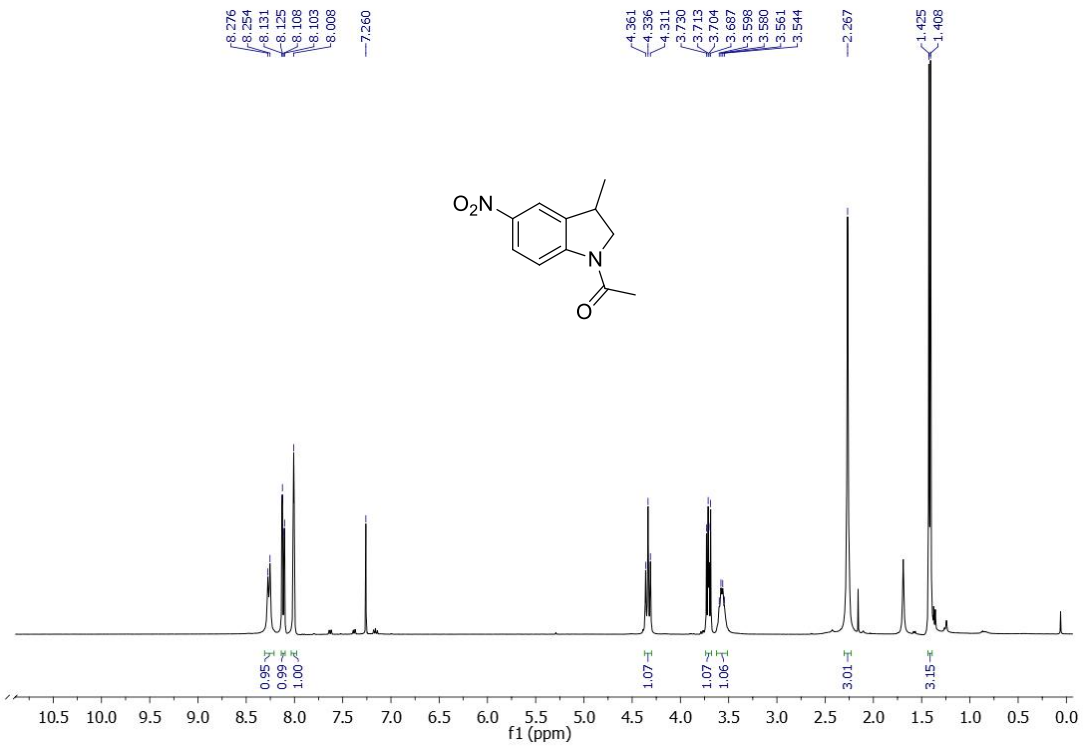

Figure 3.9. [1]H NMR spectrum of 1-(3-Methyl-5-nitroindolin-1-yl)ethanone **(2b).**

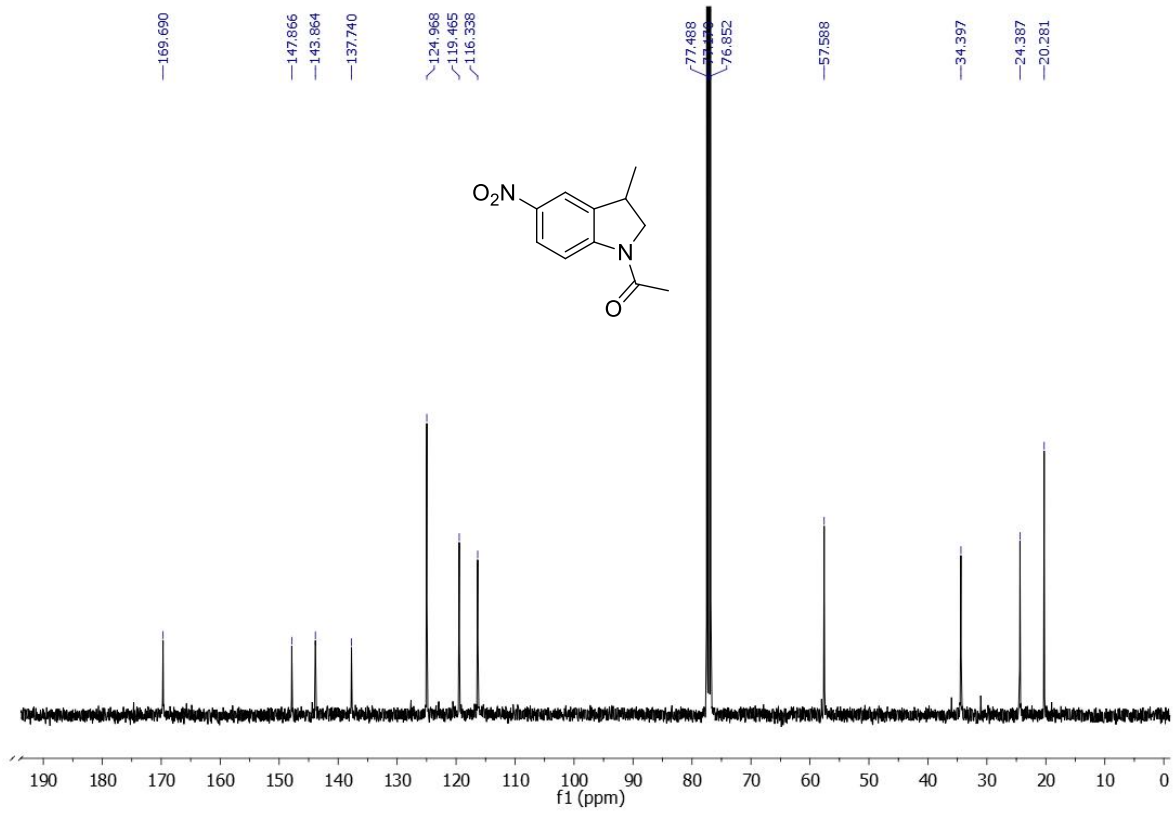

Figure 3.10. [13]C NMR spectrum of 1-(3-Methyl-5-nitroindolin-1-yl)ethanone **(2b).**

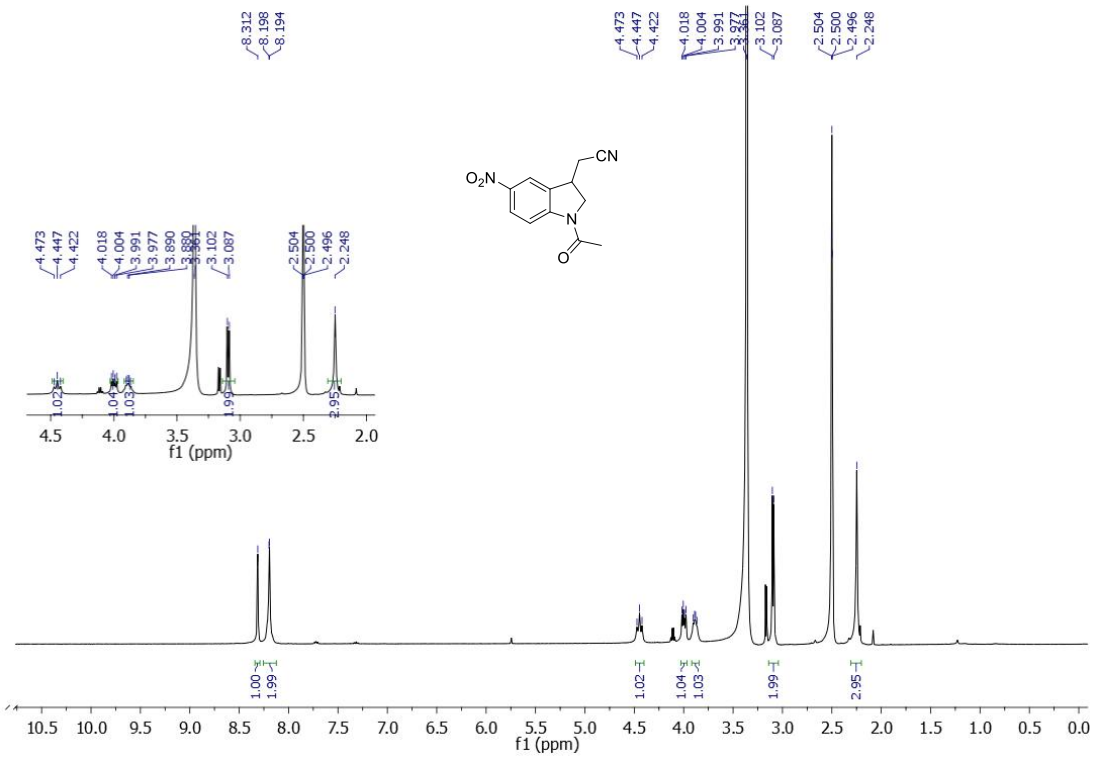

Figure 3.11. ^{1}H NMR spectrum of 2-(1-Acetyl-5-nitroindolin-3-yl)acetonitrile **(2c).**

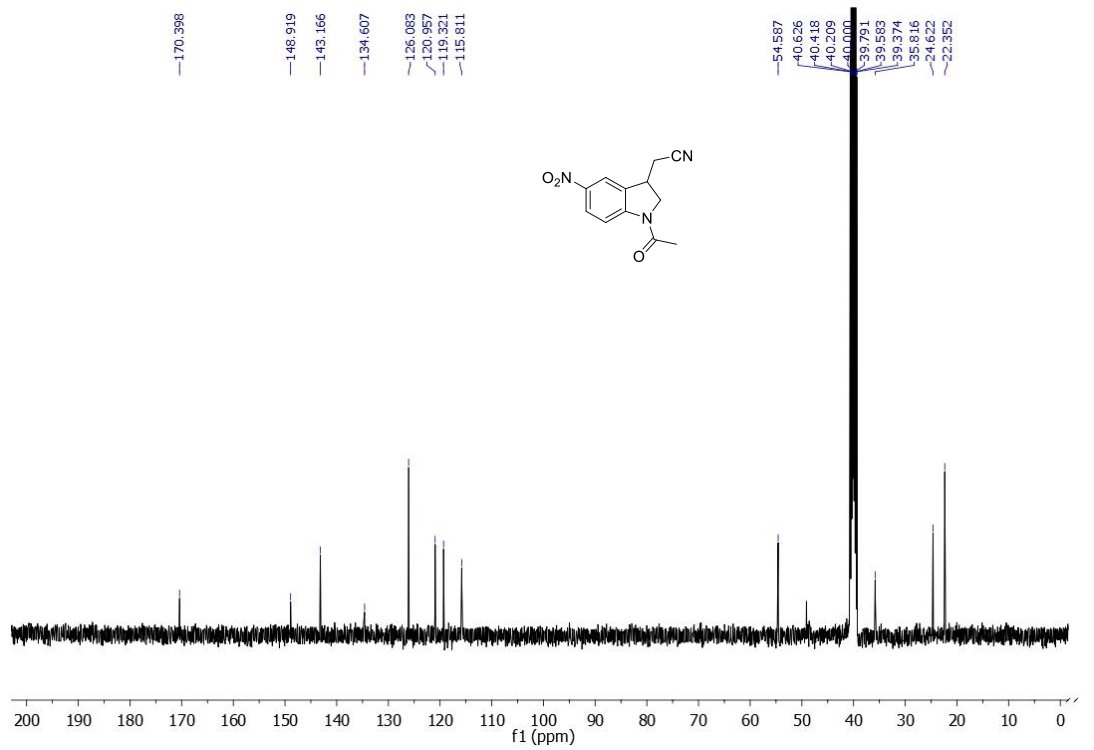

Figure 3.12. ^{13}C NMR spectrum of 2-(1-Acetyl-5-nitroindolin-3-yl)acetonitrile **(2c).**

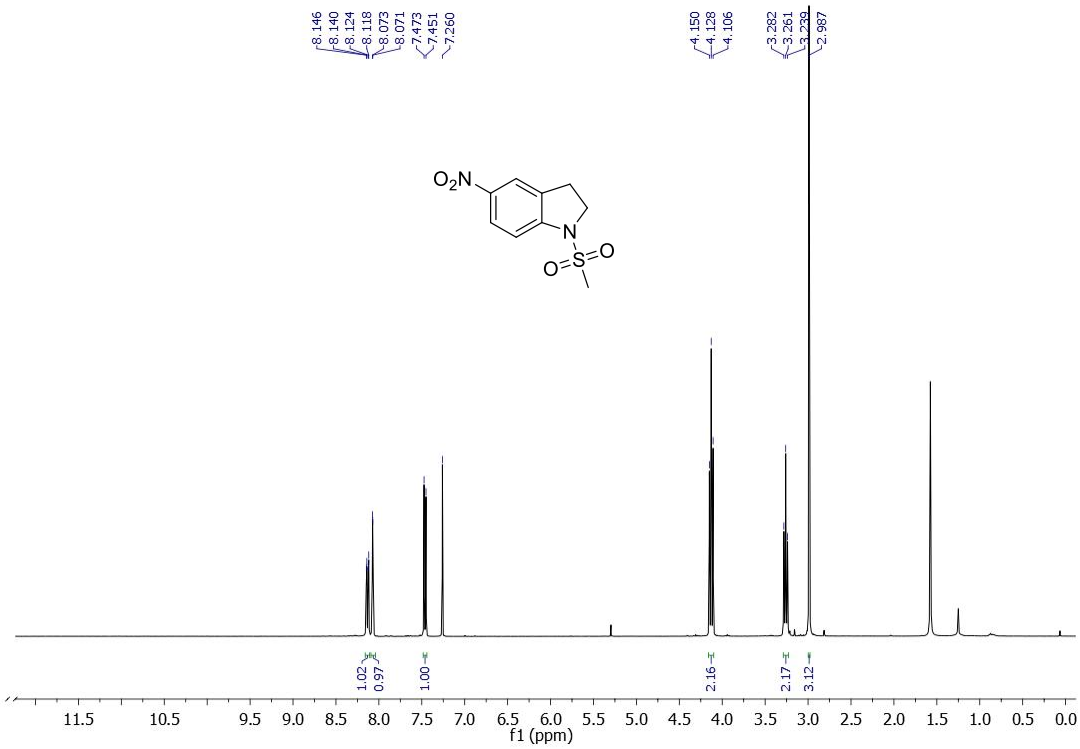

Figure 3.13. [1]H NMR spectrum of 1-(Methylsulfonyl)-5-nitroindoline **(2d).**

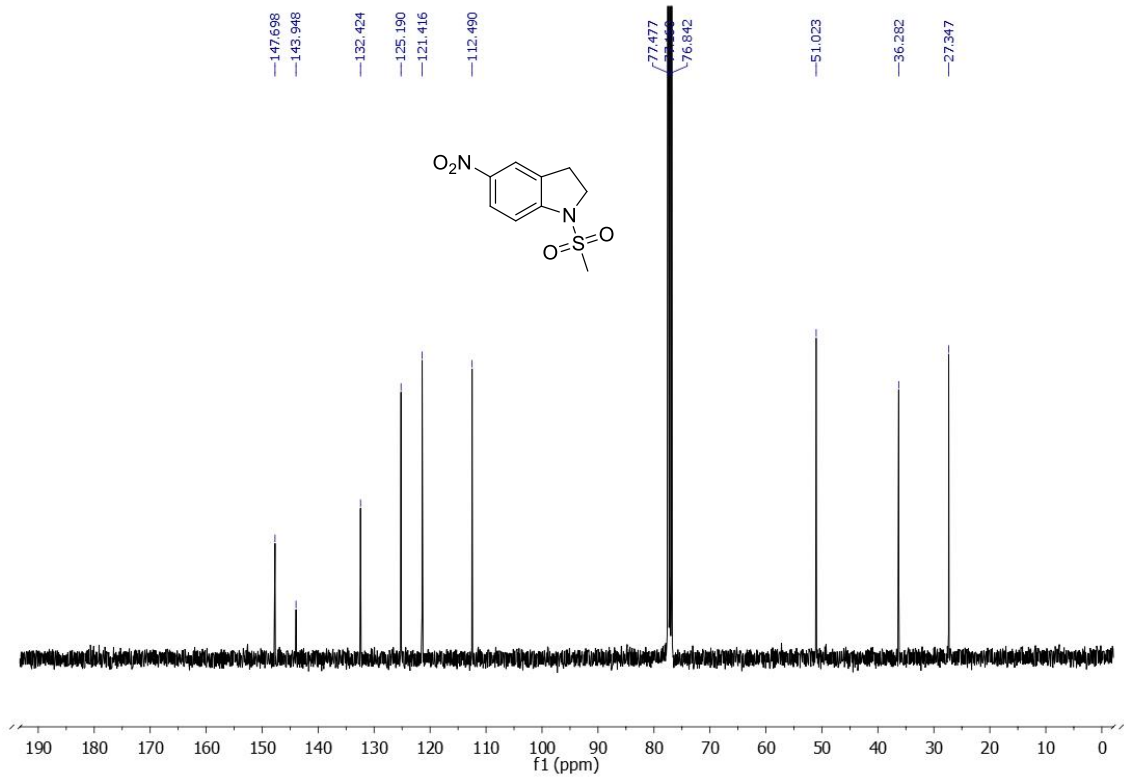

Figure 3.14. [13]C NMR spectrum of 1-(Methylsulfonyl)-5-nitroindoline **(2d).**

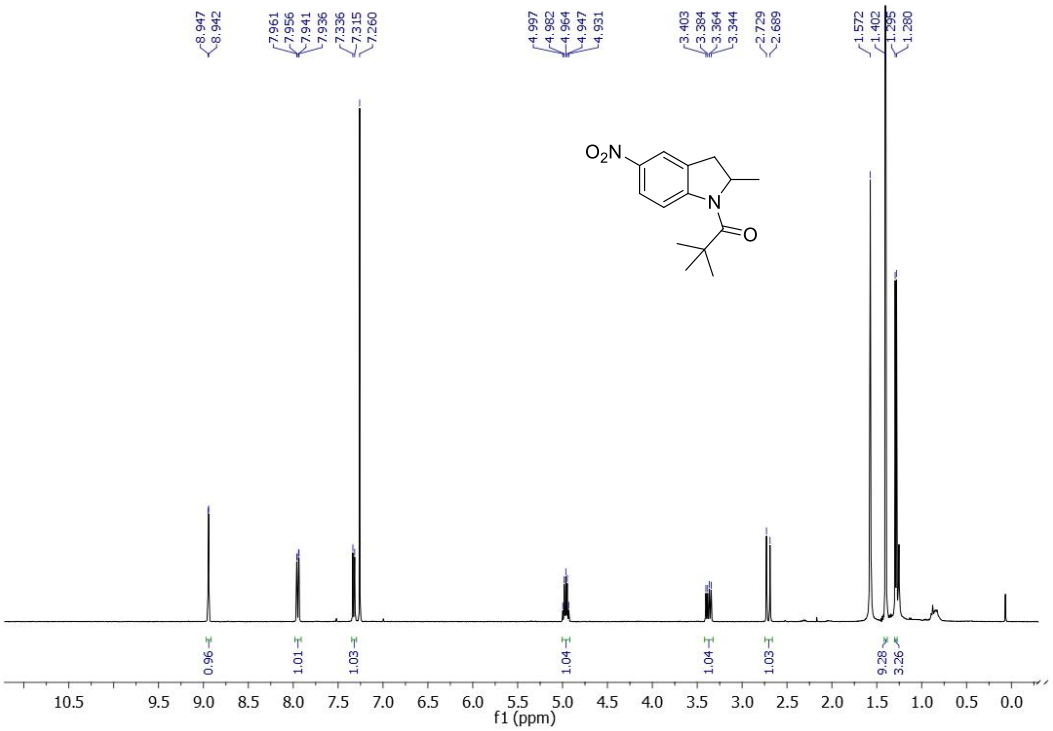

Figure 3.15. ^{1}H NMR spectrum of 2,2-Dimethyl-1-(2-methyl-5-nitroindolin-1-yl)propan-1-one **(2e).**

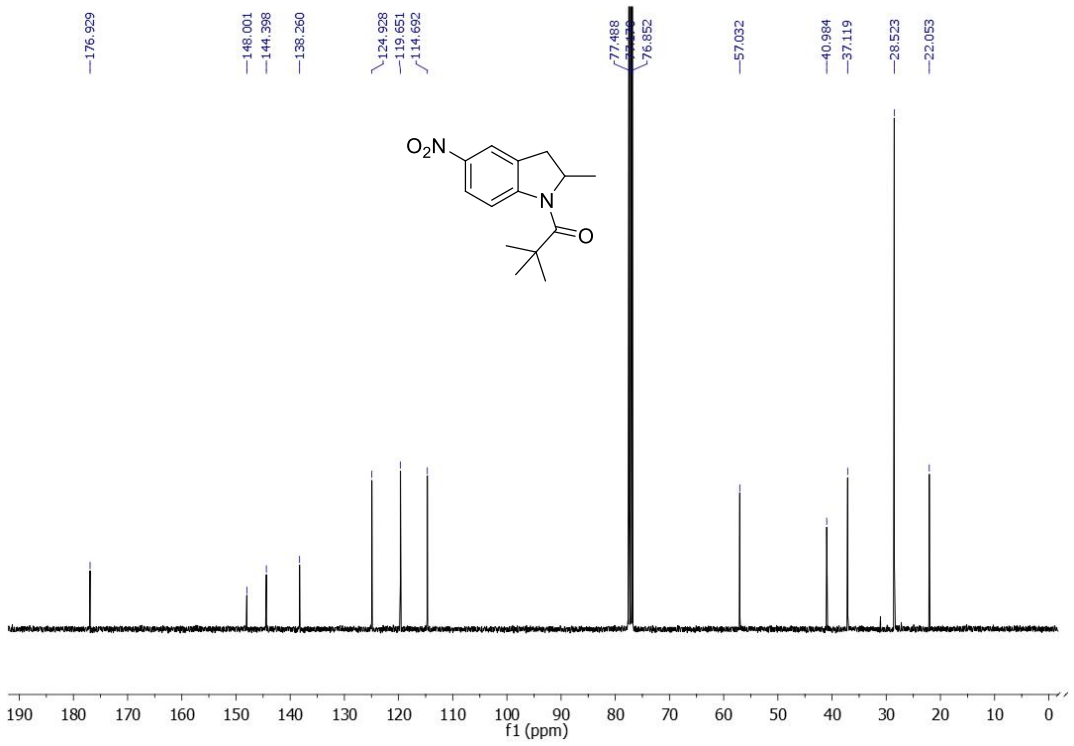

Figure 3.16. ^{13}C NMR spectrum of 2,2-Dimethyl-1-(2-methyl-5-nitroindolin-1-yl)propan-1-one **(2e).**

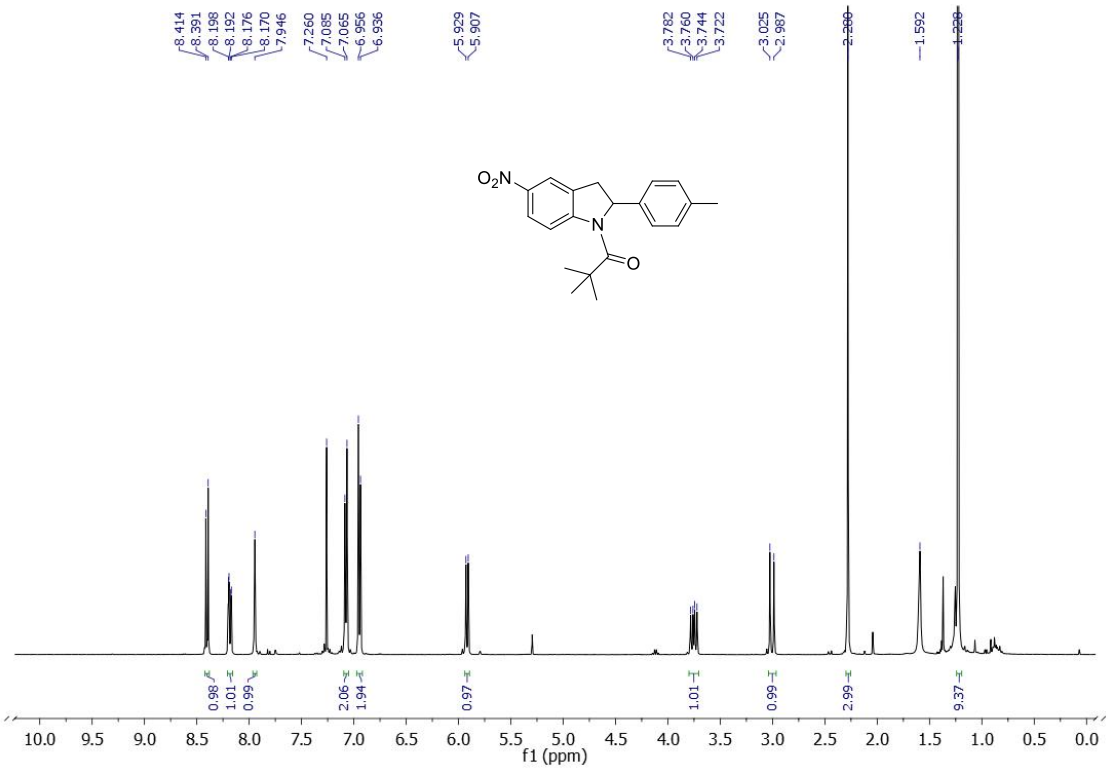

Figure 3.17. ^{1}H NMR spectrum of 2,2-Dimethyl-1-(5-nitro-2-(p-tolyl)indolin-1-yl)propan-1-one **(2f).**

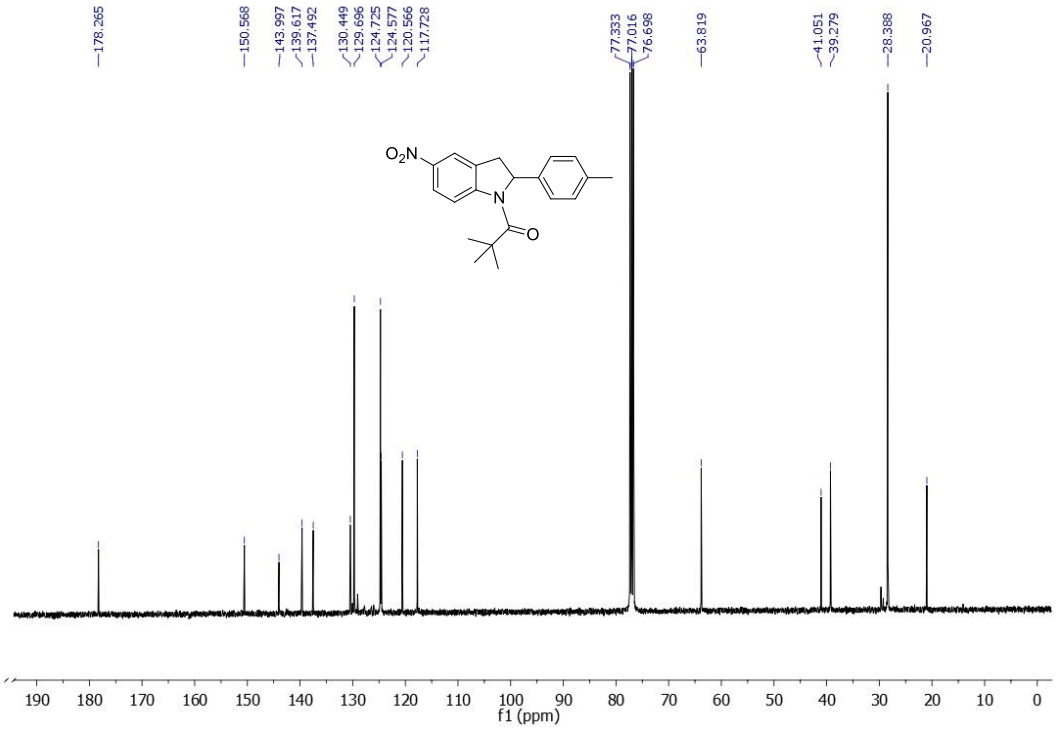

Figure 3.18. ^{13}C NMR spectrum of 2,2-Dimethyl-1-(5-nitro-2-(p-tolyl)indolin-1-yl)propan-1-one **(2f).**

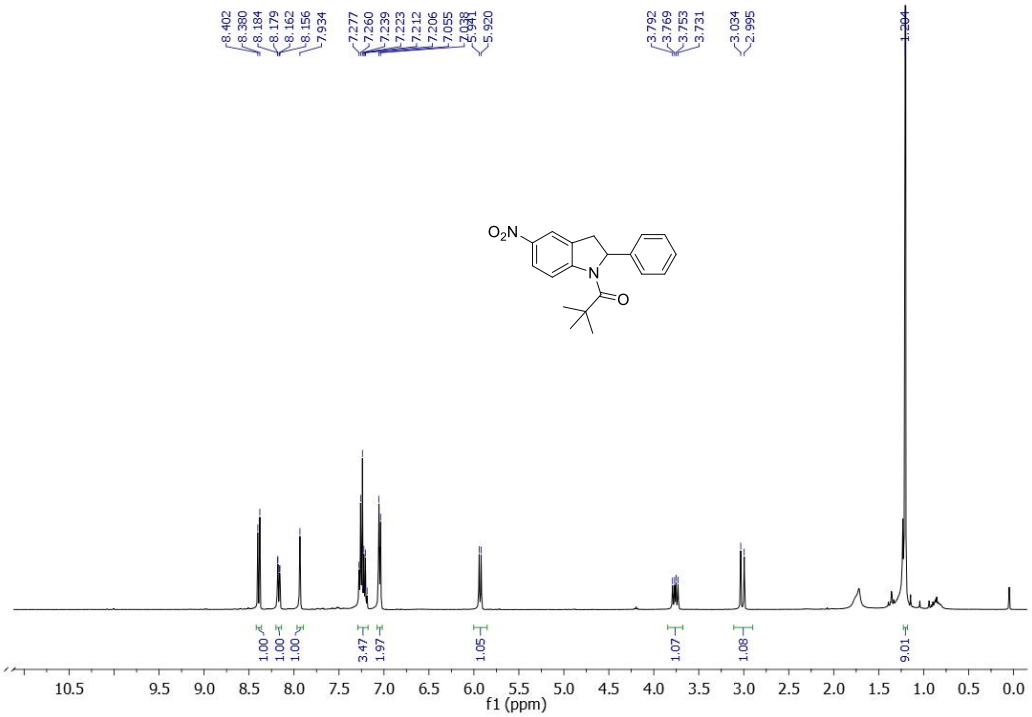

Figure 3.19. ^{1}H NMR spectrum of 2,2-Dimethyl-1-(5-nitro-2-phenylindolin-1-yl)propan-1-one **(2g).**

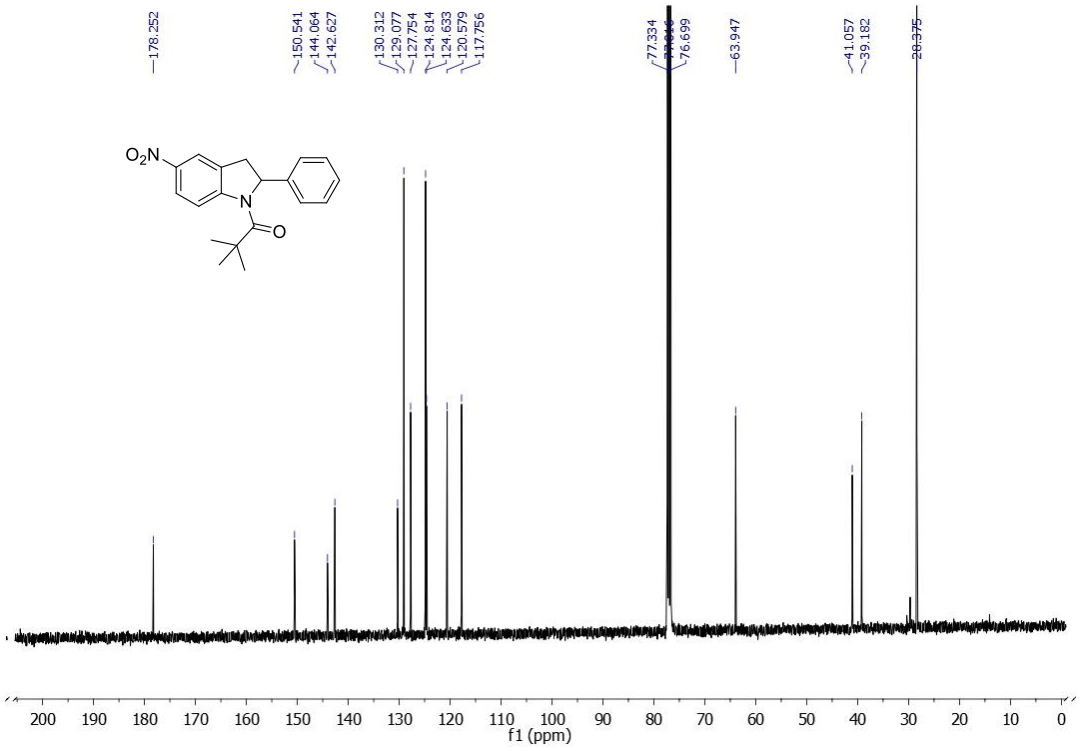

Figure 3.20. ^{13}C NMR spectrum of 2,2-Dimethyl-1-(5-nitro-2-phenylindolin-1-yl)propan-1-one **(2g).**

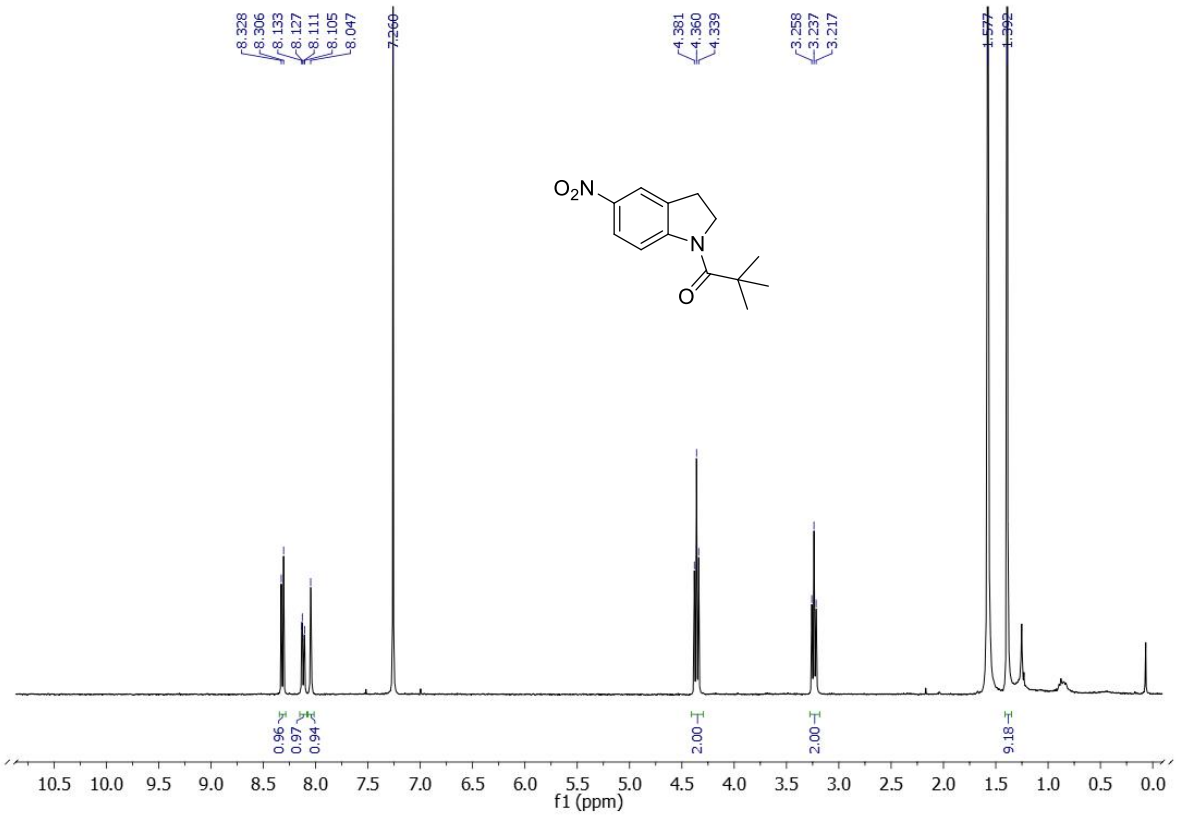

Figure 3.21. ^{1}H NMR spectrum of 2,2-Dimethyl-1-(5-nitroindolin-1-yl)propan-1-one **(2h).**

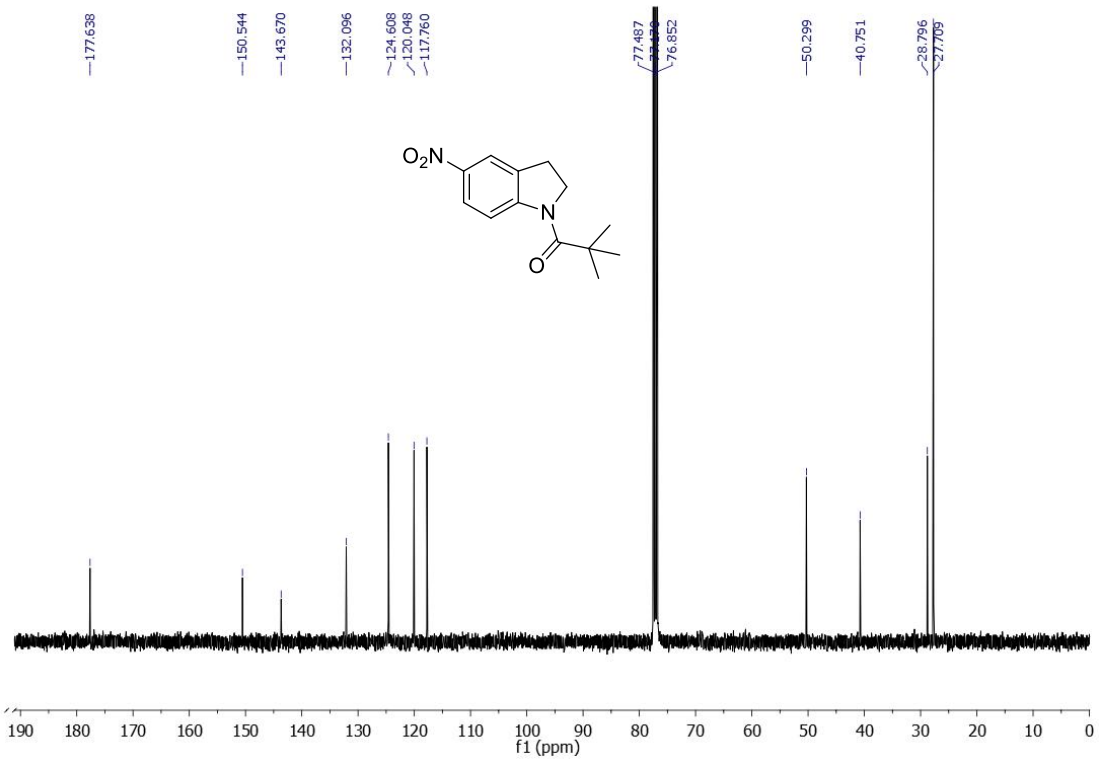

Figure 3.22. ^{13}C NMR spectrum of 2,2-Dimethyl-1-(5-nitroindolin-1-yl)propan-1-one **(2h).**

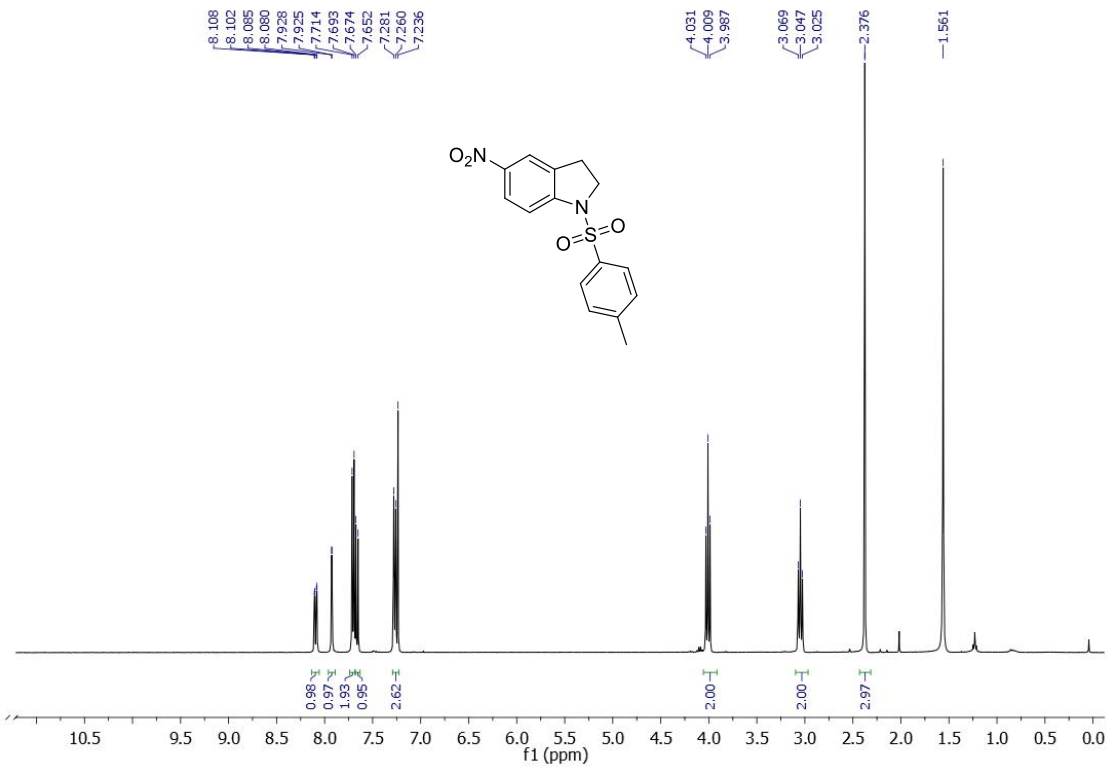

Figure 3.23. ^{1}H NMR spectrum of 5-Nitro-1-tosylindoline **(2i).**

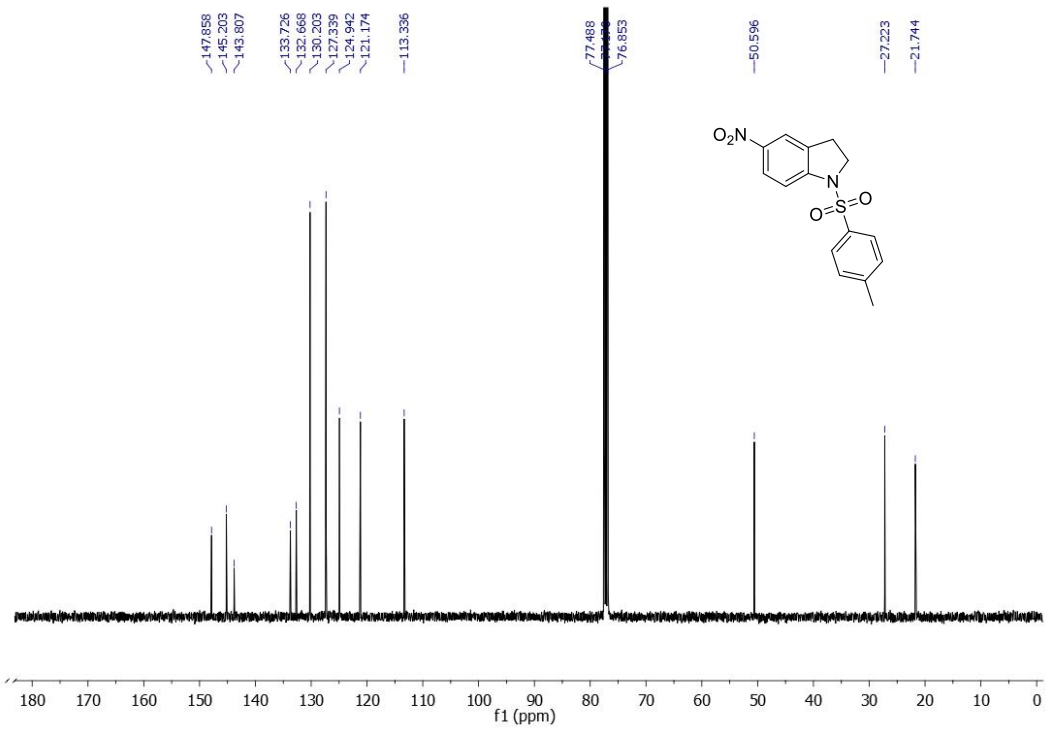

Figure 3.24. ^{13}C NMR spectrum of 5-Nitro-1-tosylindoline **(2i).**

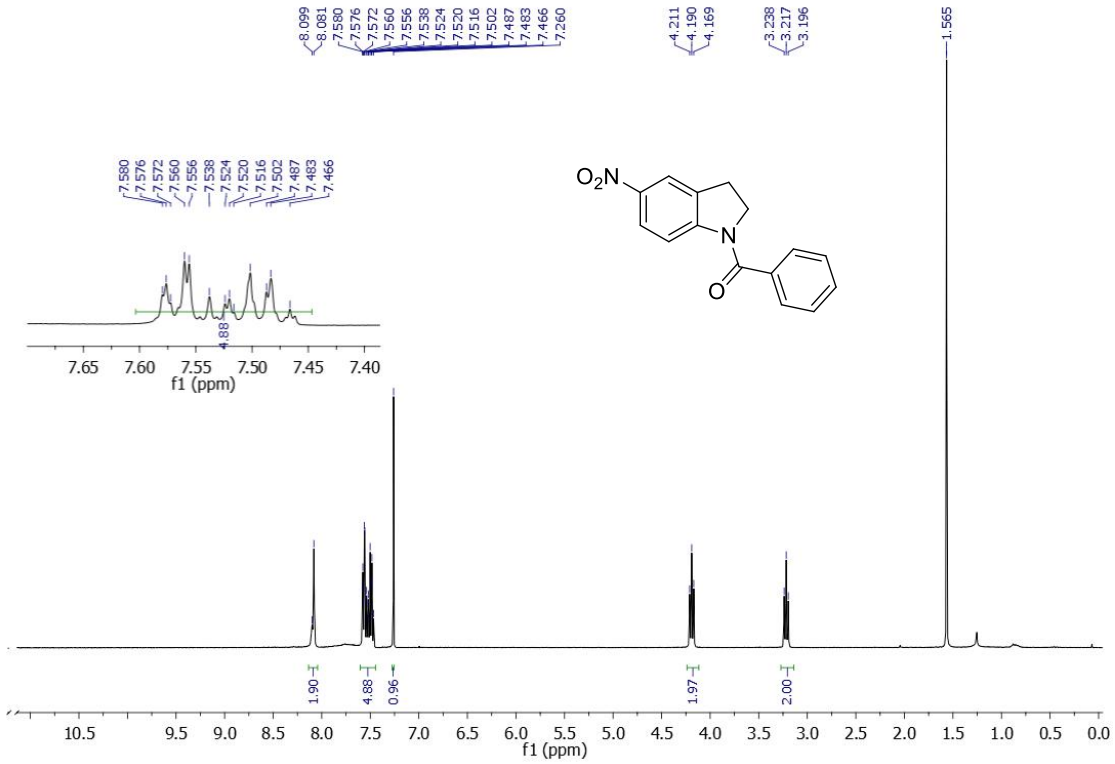

Figure 3.25. [1]H NMR spectrum of (5-Nitroindolin-1-yl)(phenyl)methanone **(2j).**

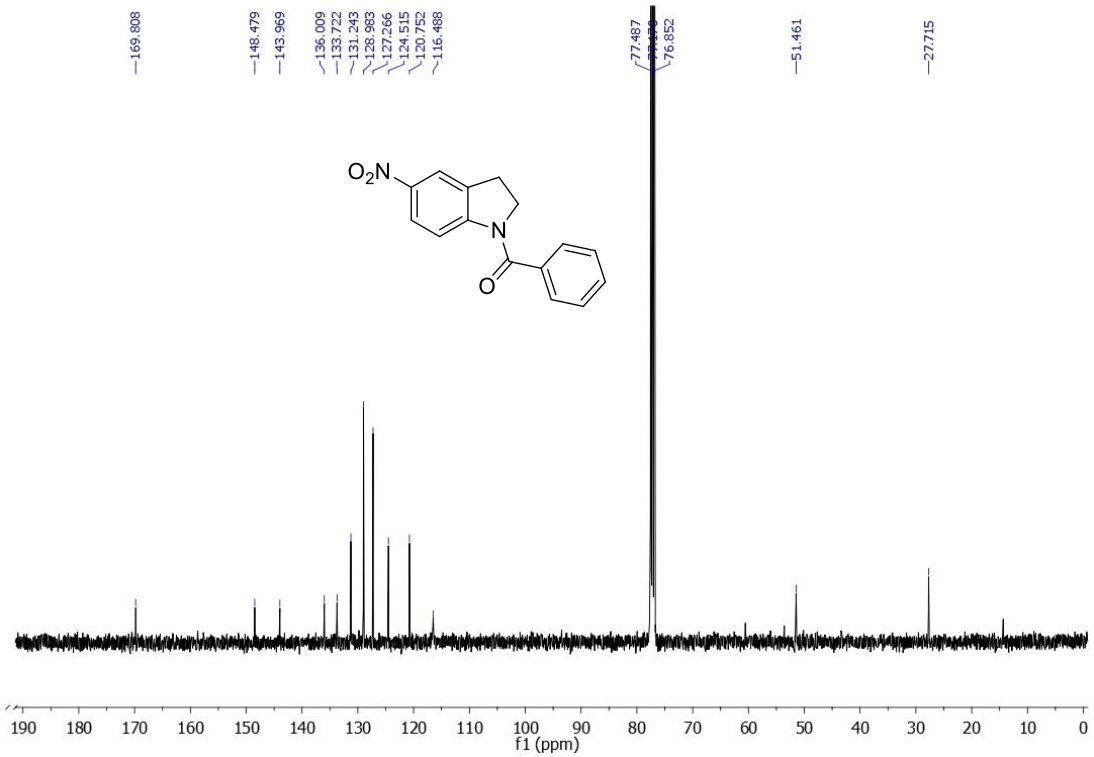

Figure 3.26. [13]C NMR spectrum of (5-Nitroindolin-1-yl)(phenyl)methanone **(2j).**

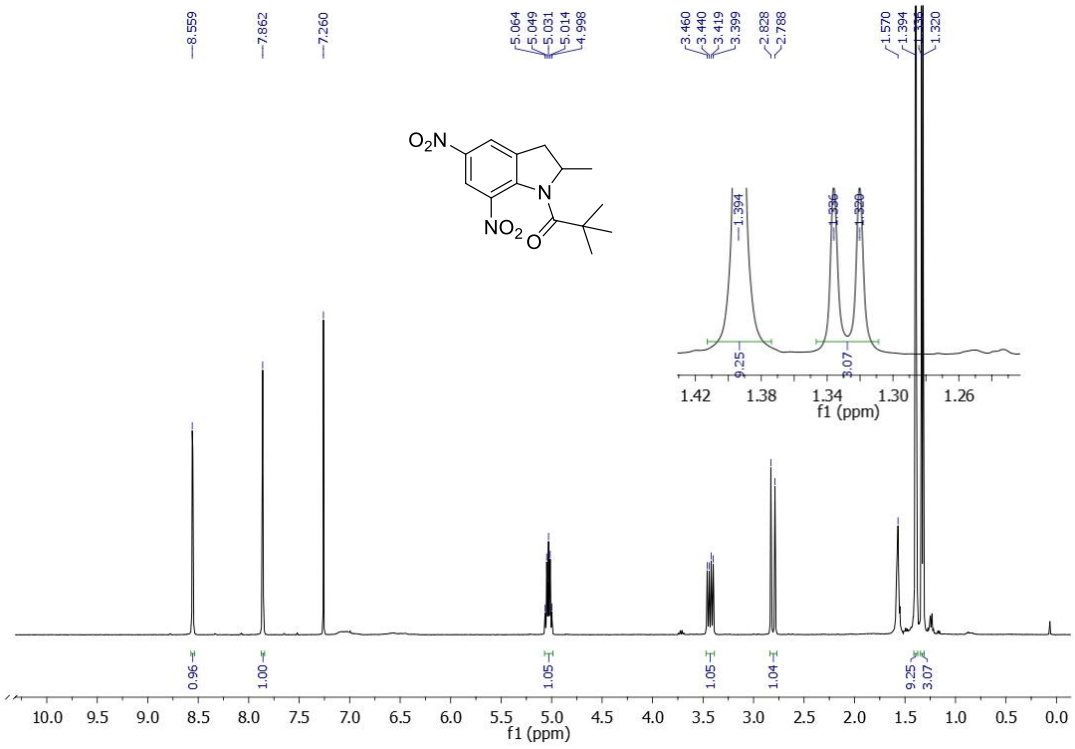

Figure 3.27. ^{1}H NMR spectrum of 2,2-Dimethyl-1-(2-methyl-5,7-dinitroindolin-1-yl)propan-1-one (**2k**).

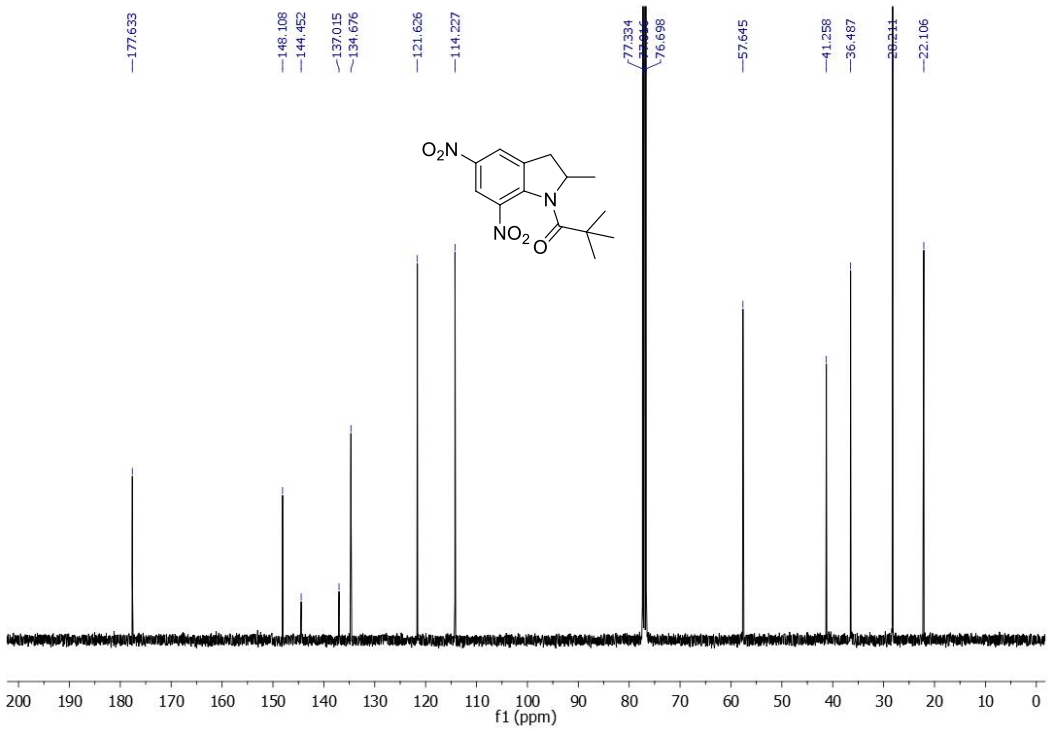

Figure 3.28. ^{13}C NMR spectrum of 2,2-Dimethyl-1-(2-methyl-5,7-dinitroindolin-1-yl)propan-1-one **(2k).**

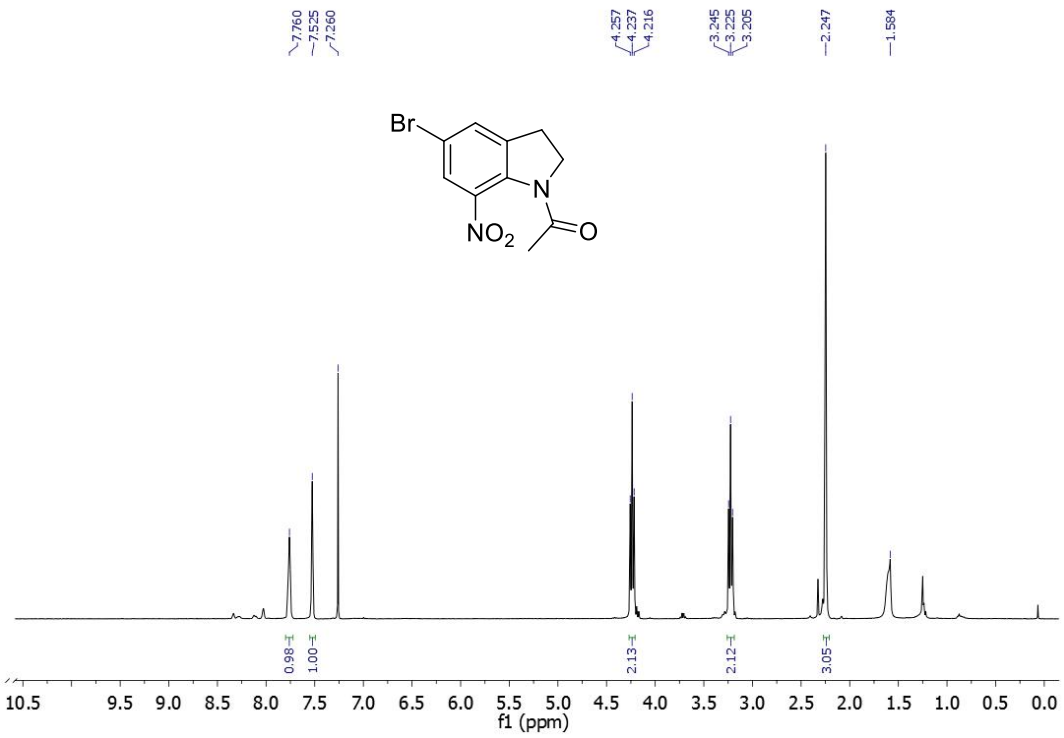

Figure 3.29. [1]H NMR spectrum of 1-(5-Bromo-7-nitroindolin-1-yl)ethanone **(2l).**

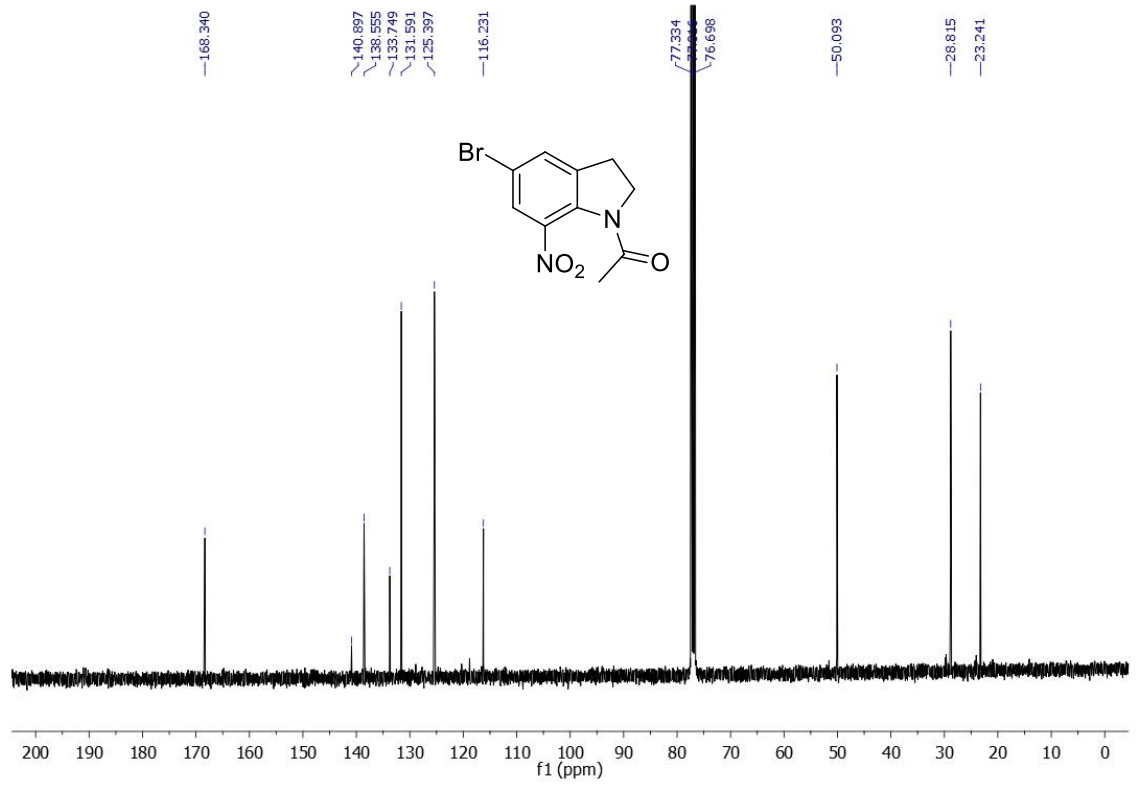

Figure 3.30. [13]C NMR spectrum of 1-(5-Bromo-7-nitroindolin-1-yl)ethanone **(2l).**

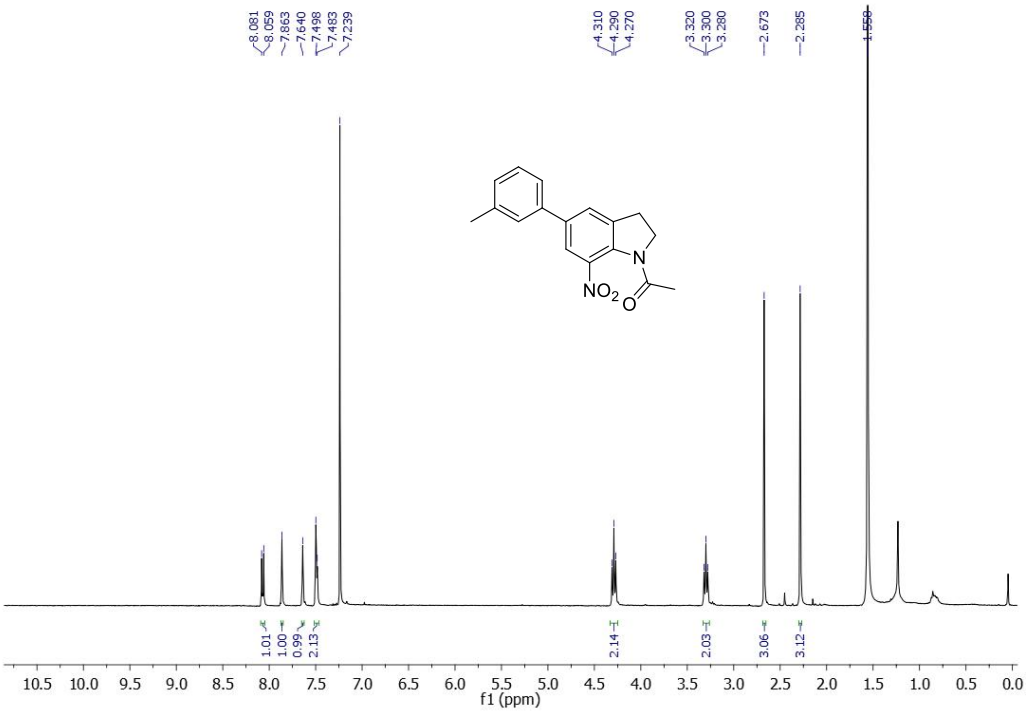

Figure 3.31. [1]H NMR spectrum of 1-(7-Nitro-5-(m-tolyl)indolin-1-yl)ethanone **(2m).**

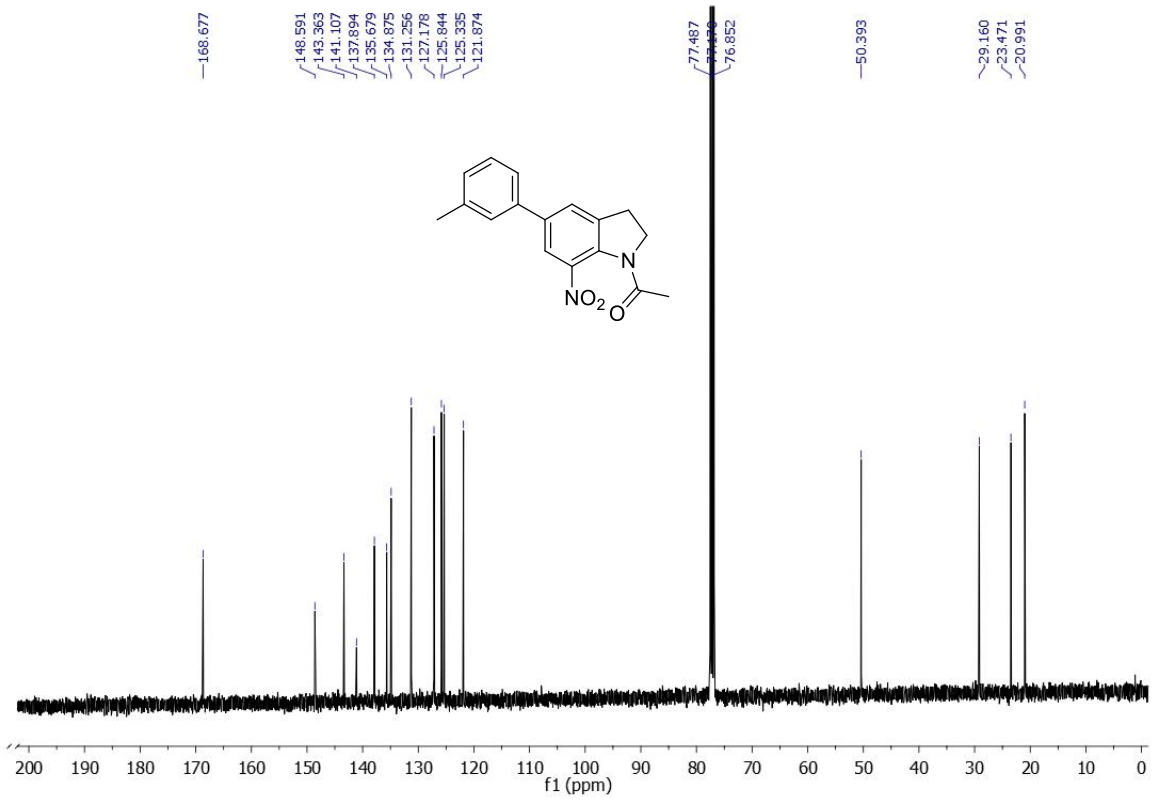

Figure 3.32. [13]C NMR spectrum of 1-(7-Nitro-5-(m-tolyl)indolin-1-yl)ethanone **(2m).**

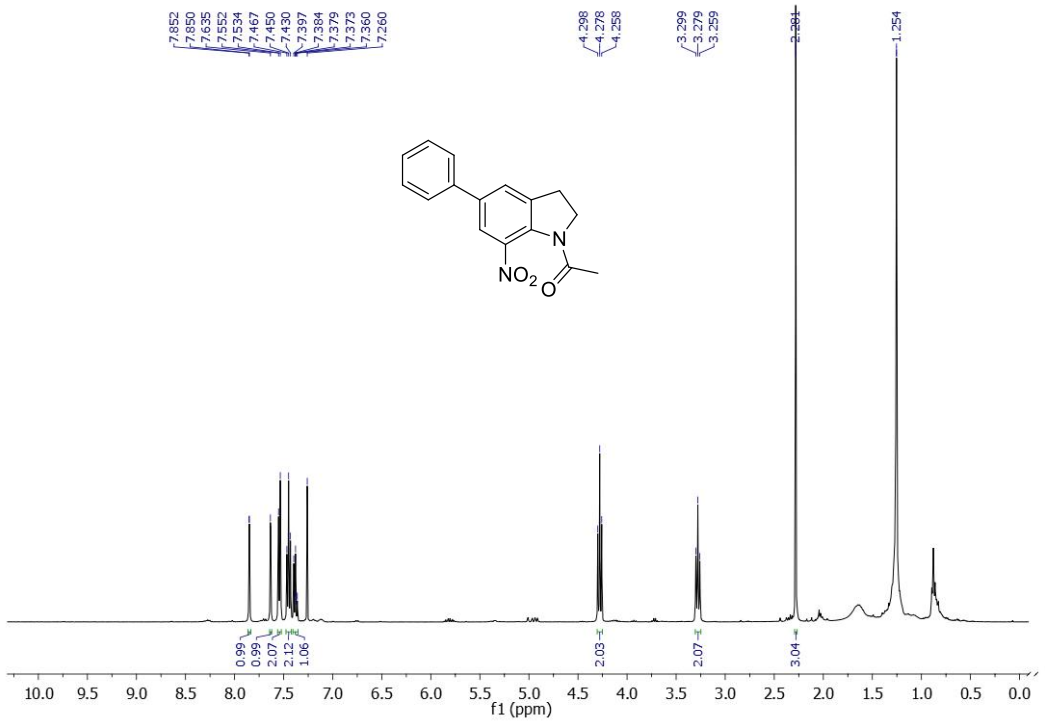

Figure 3.33. ^{1}H NMR spectrum of 1-(7-Nitro-5-phenylindolin-1-yl)ethanone **(2n).**

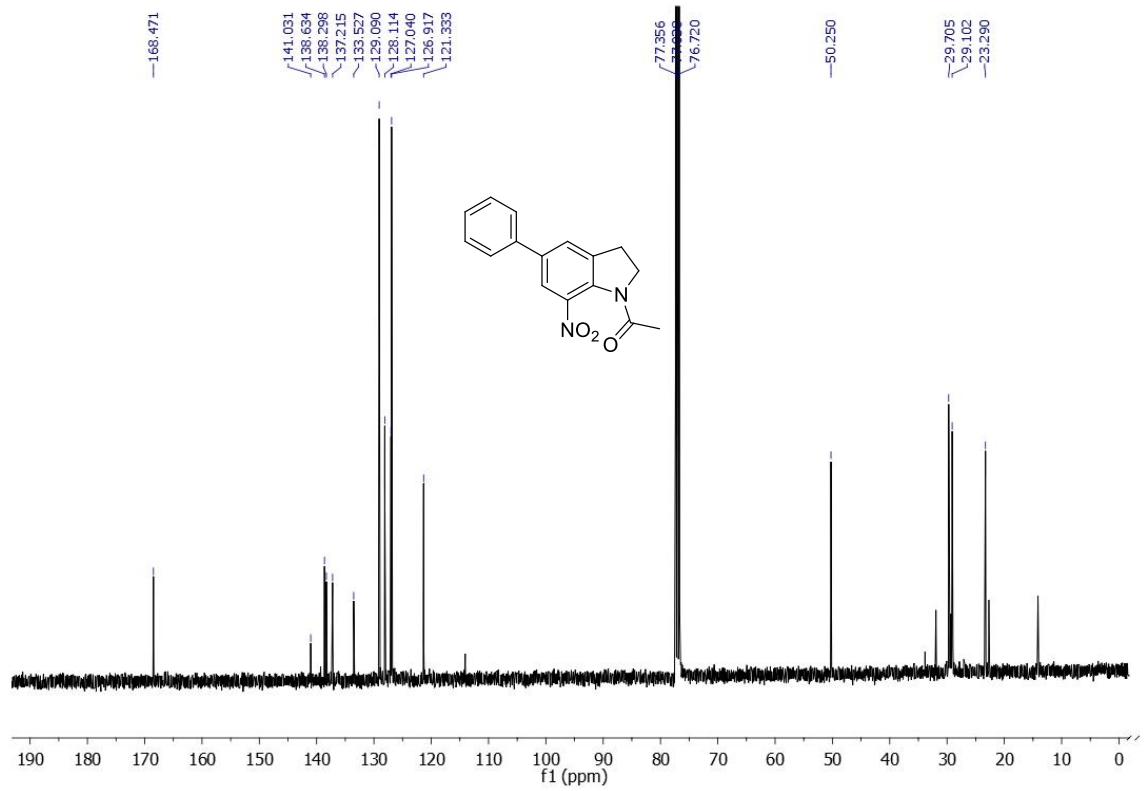

Figure 3.34. ^{13}C NMR spectrum of 1-(7-Nitro-5-phenylindolin-1-yl)ethanone **(2n).**

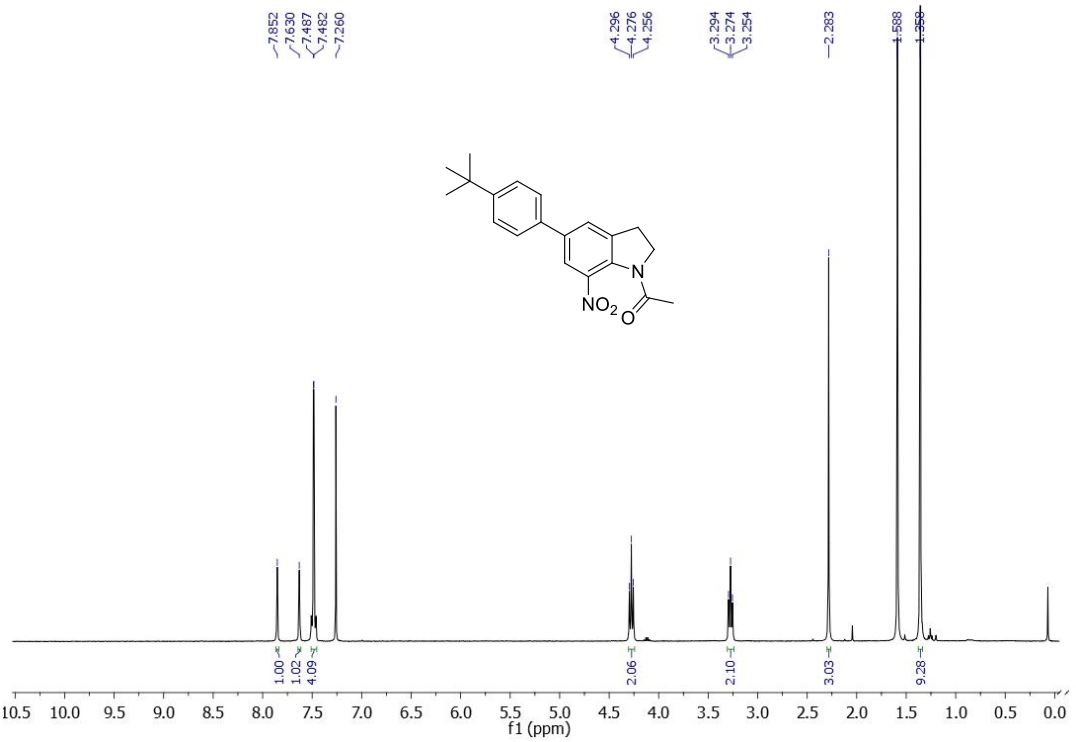

Figure 3.35. ^{1}H NMR spectrum of 1-(5-(4-(tert-Butyl)phenyl)-7-nitroindolin-1-yl)ethanone **(2o).**

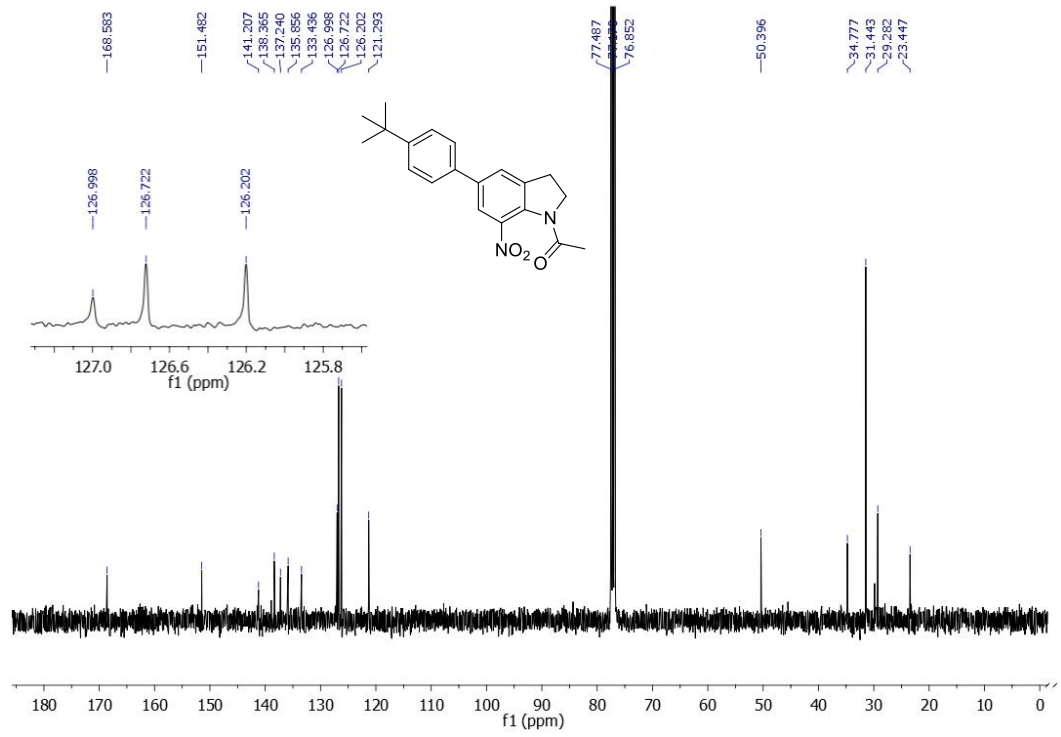

Figure 3.36. ^{13}C NMR spectrum of 1-(5-(4-(tert-Butyl)phenyl)-7-nitroindolin-1-yl)ethanone **(2o).**

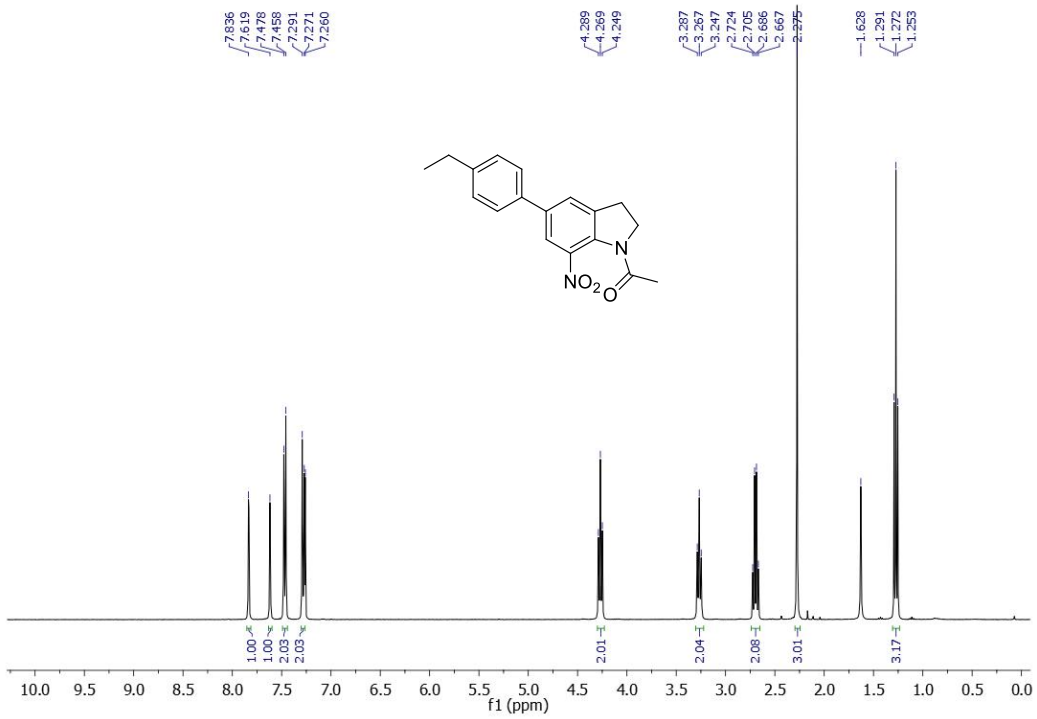

Figure 3.37. ^{1}H NMR spectrum of 1-(5-(4-Ethylphenyl)-7-nitroindolin-1-yl)ethanone **(2p).**

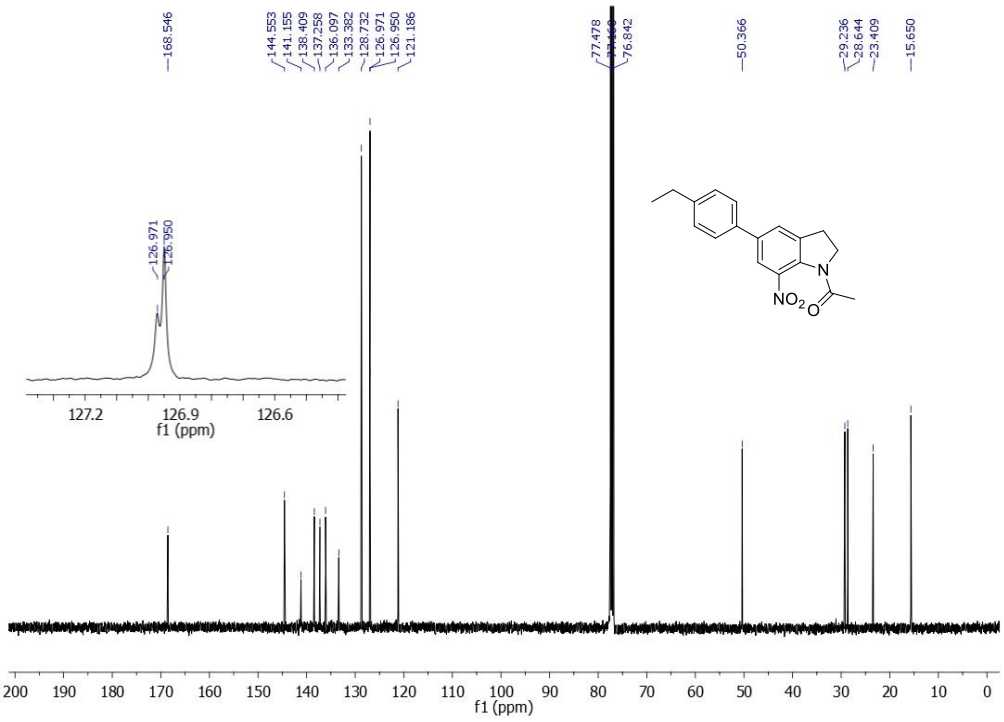

Figure 3.38. ^{13}C NMR spectrum of 1-(5-(4-Ethylphenyl)-7-nitroindolin-1-yl)ethanone **(2p).**

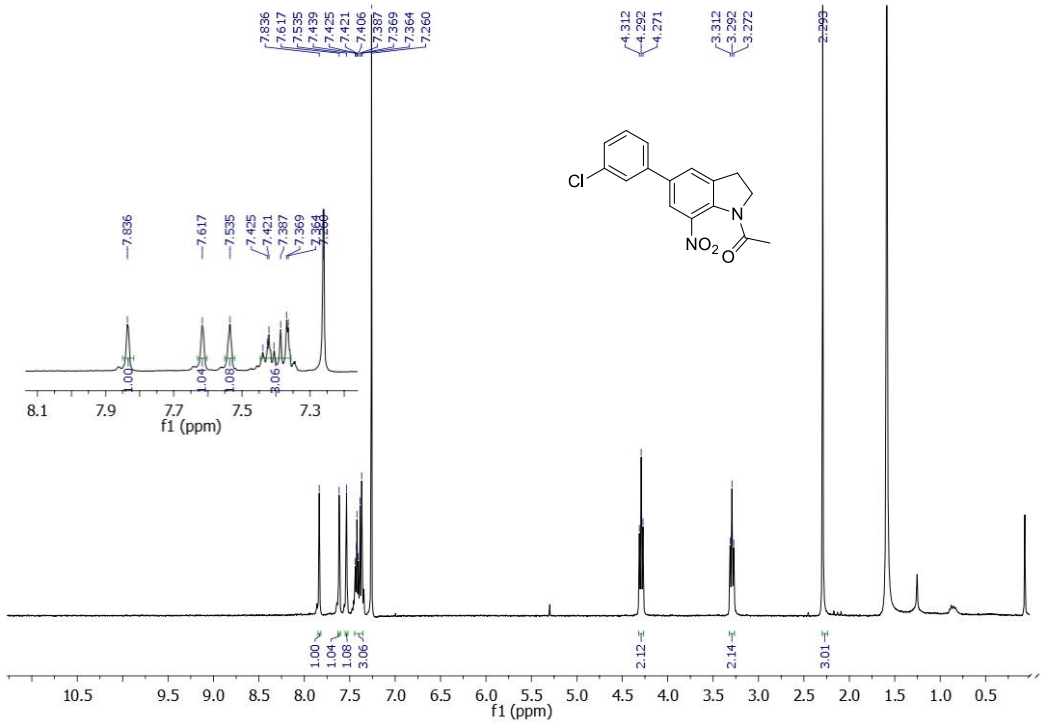

Figure 3.39. ^{1}H NMR spectrum of 1-(5-(3-Chlorophenyl)-7-nitroindolin-1-yl)ethanone **(2q).**

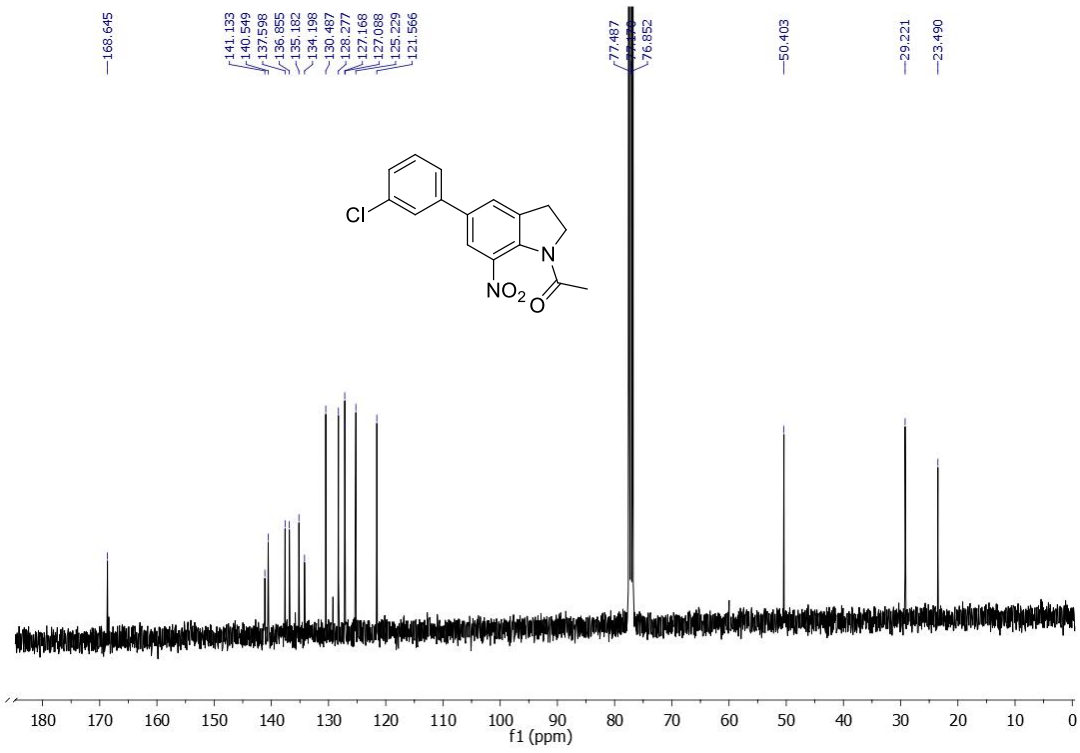

Figure 3.40. ^{13}C NMR spectrum of 1-(5-(3-Chlorophenyl)-7-nitroindolin-1-yl)ethanone **(2q).**

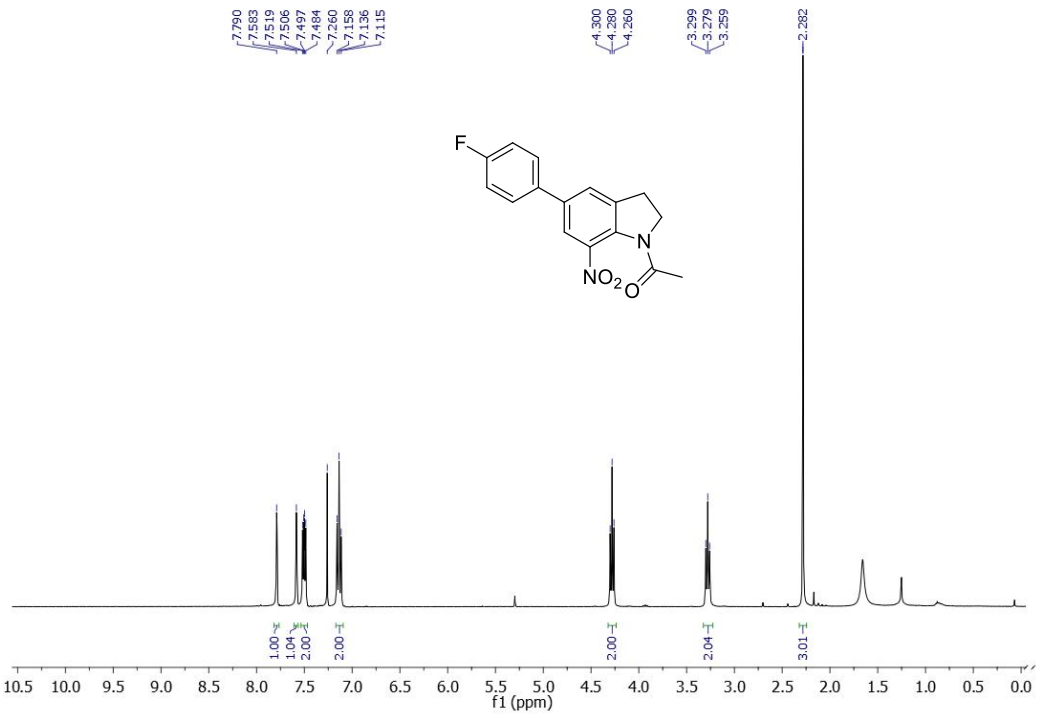

Figure 3.41. [1]H NMR spectrum of 1-(5-(4-Fluorophenyl)-7-nitroindolin-1-yl)ethanone **(2r).**

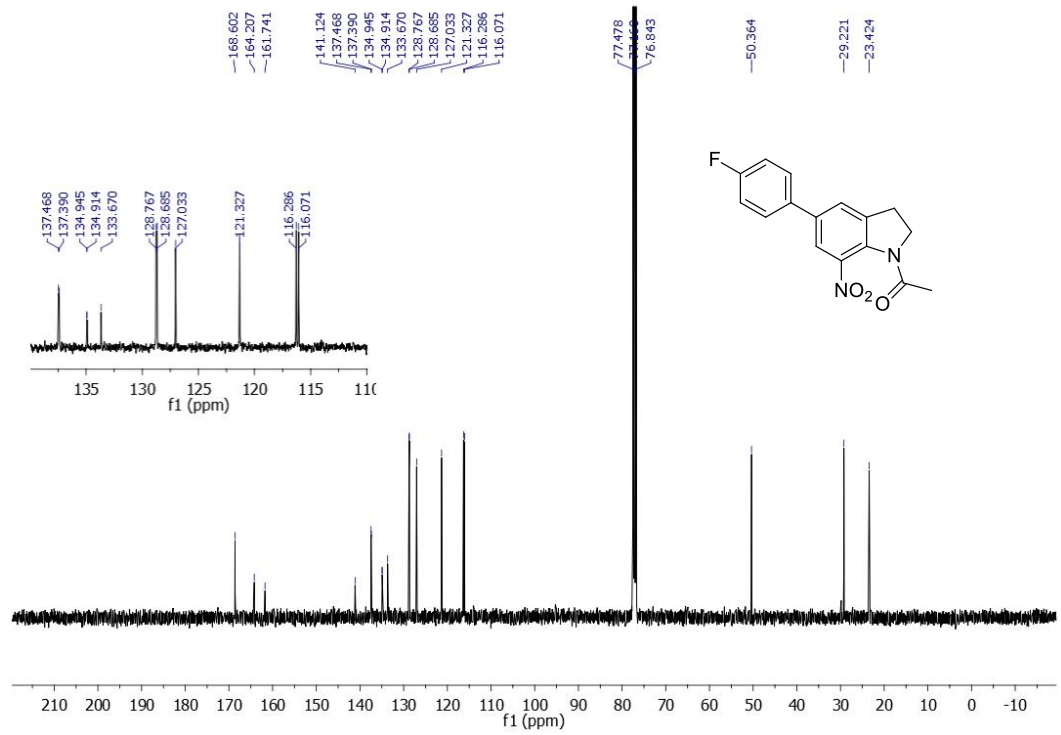

Figure 3.42. [13]C NMR spectrum of 1-(5-(4-Fluorophenyl)-7-nitroindolin-1-yl)ethanone **(2r).**

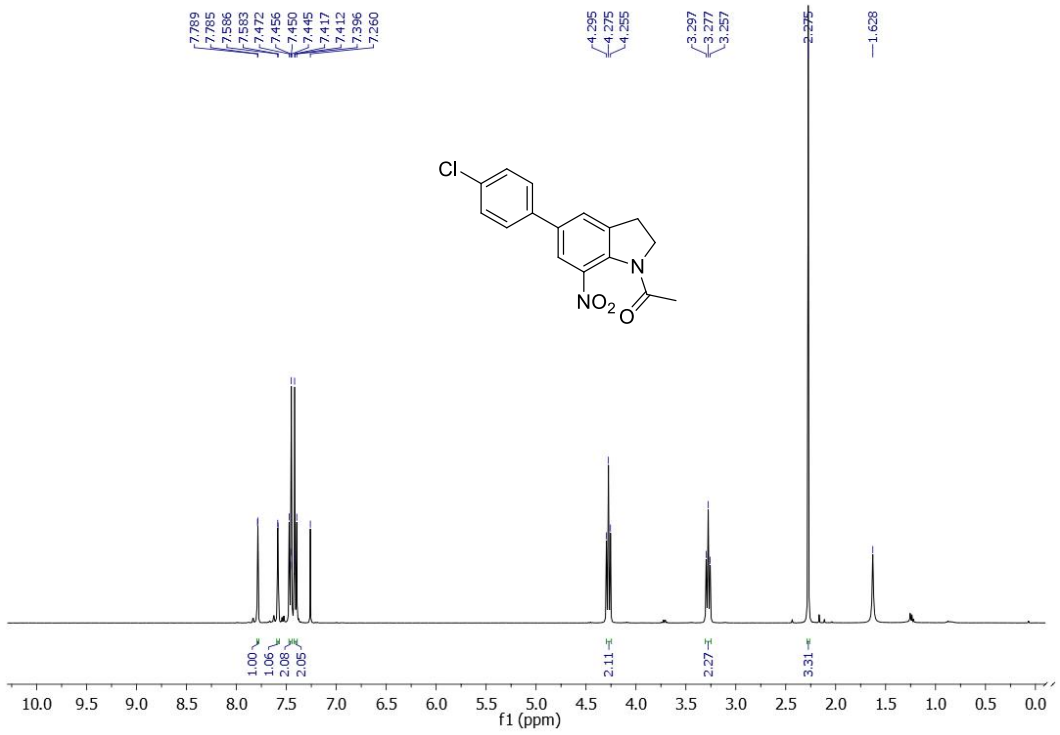

Figure 3.43. ^{1}H NMR spectrum of 1-(5-(4-Chlorophenyl)-7-nitroindolin-1-yl)ethanone **(2s).**

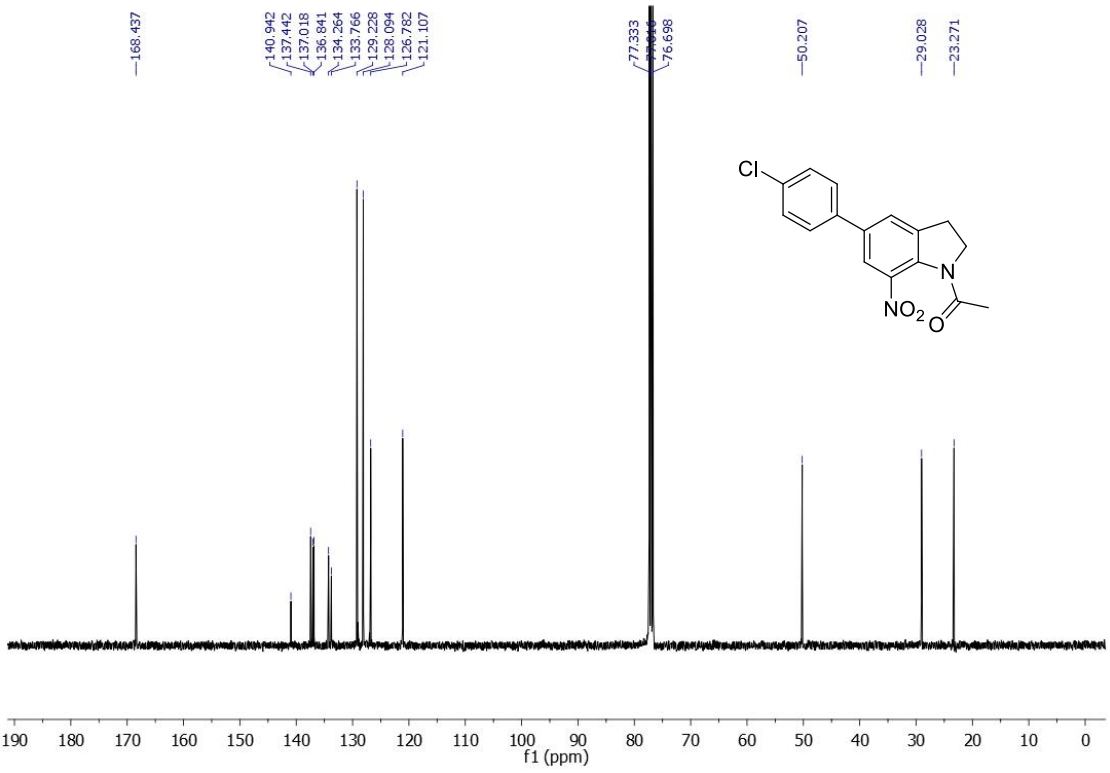

Figure 3.44. ^{13}C NMR spectrum of 1-(5-(4-Chlorophenyl)-7-nitroindolin-1-yl)ethanone **(2s).**

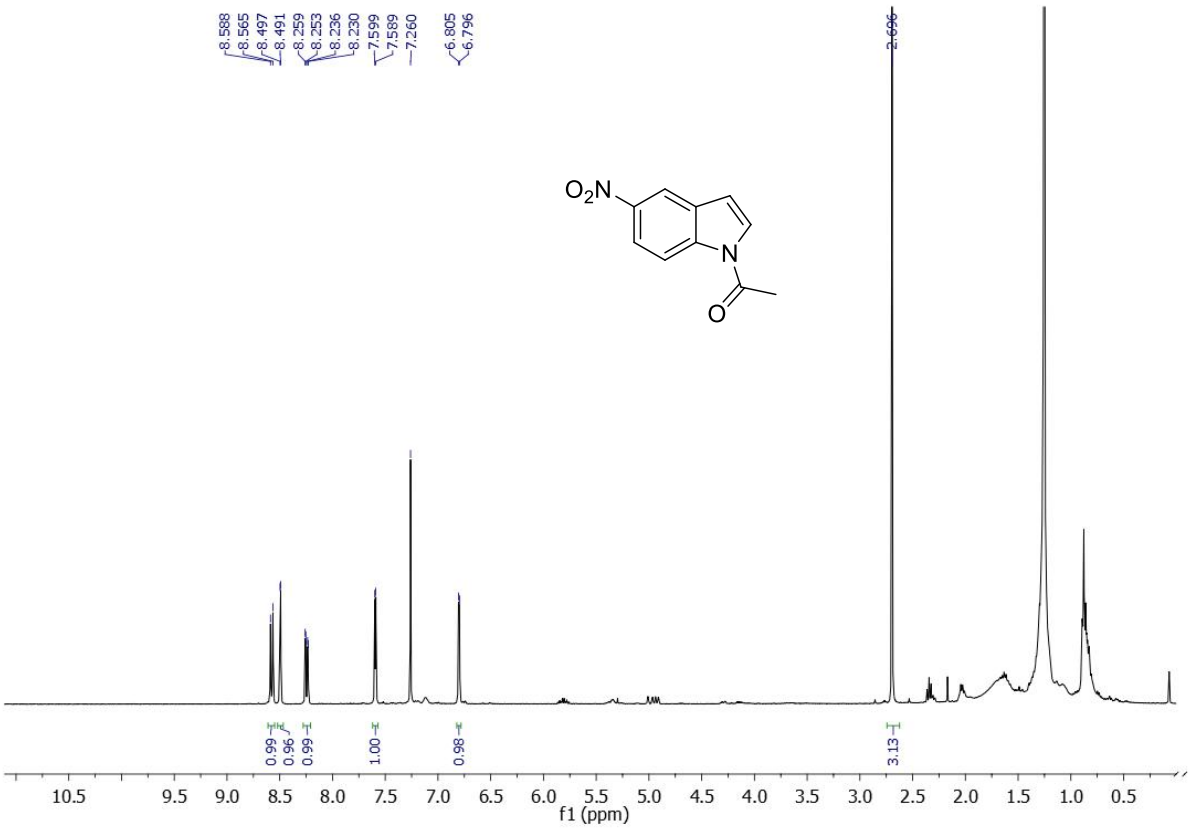

Figure 3.45. [1]H NMR spectrum of 1-(5-Nitro-1H-indol-1-yl)ethanone (**3a).**

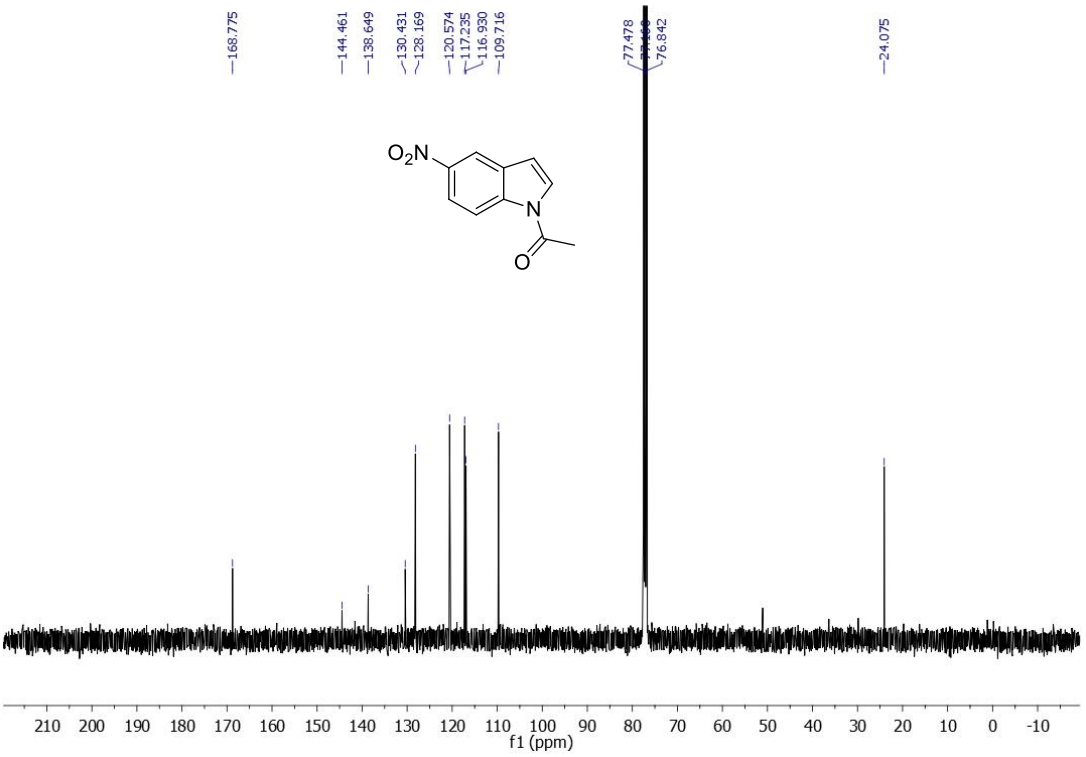

Figure 3.46. [13]C NMR spectrum of 1-(5-Nitro-1H-indol-1-yl)ethanone (**3a).**

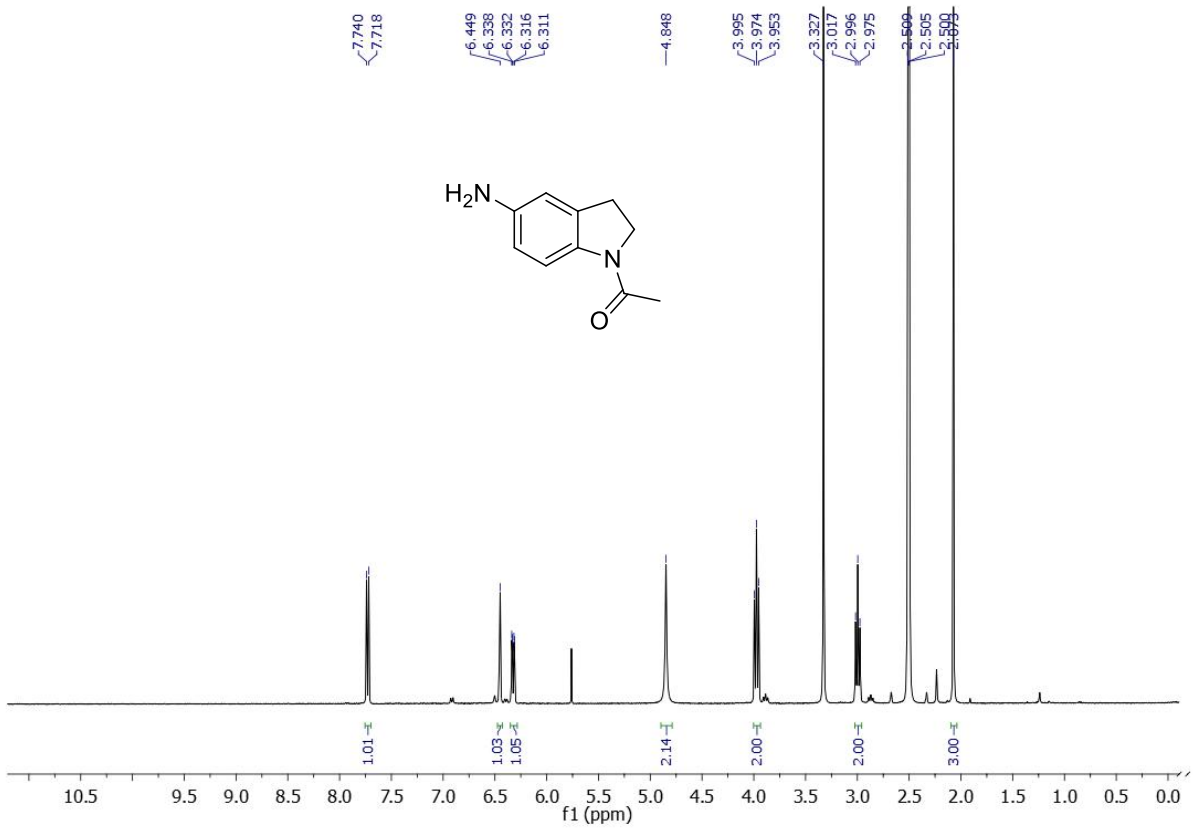

Figure 3.47. [1]H NMR spectrum of 1-(5-Aminoindolin-1-yl)ethanone **(3b).**

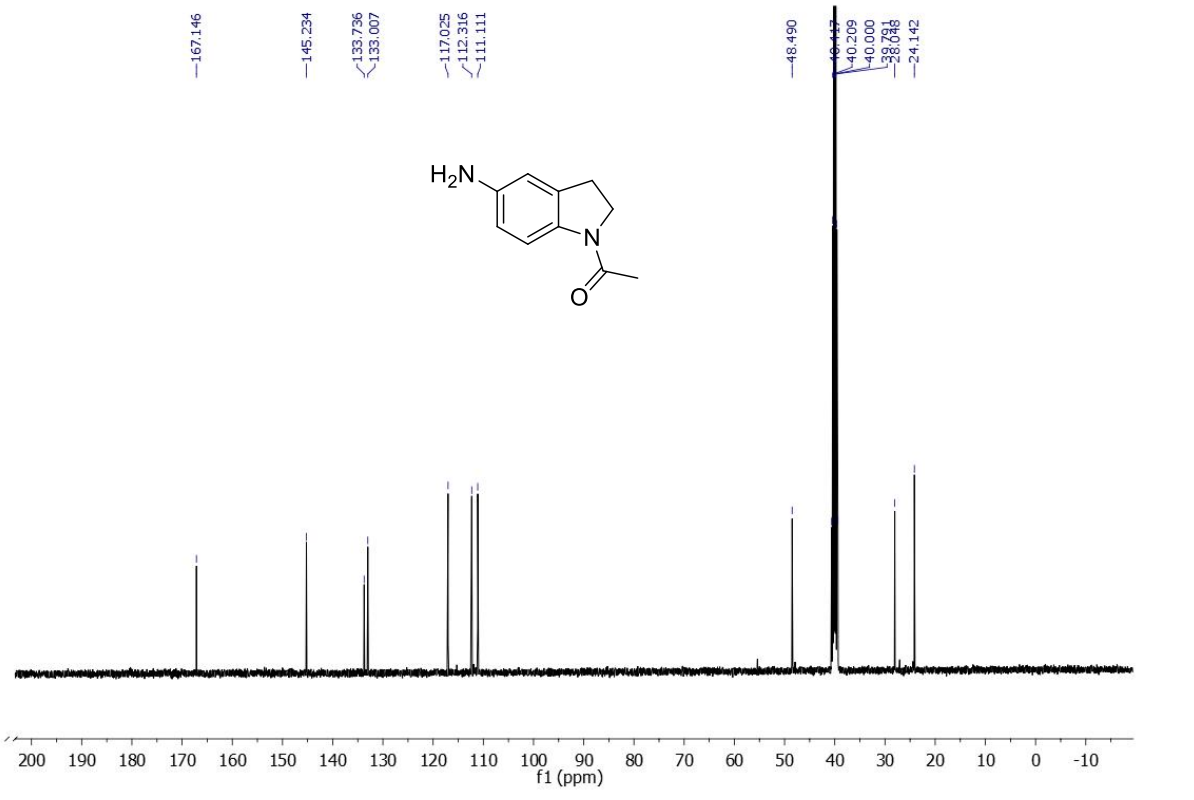

Figure 3.48. [13]C NMR spectrum of 1-(5-Aminoindolin-1-yl)ethanone **(3b).**

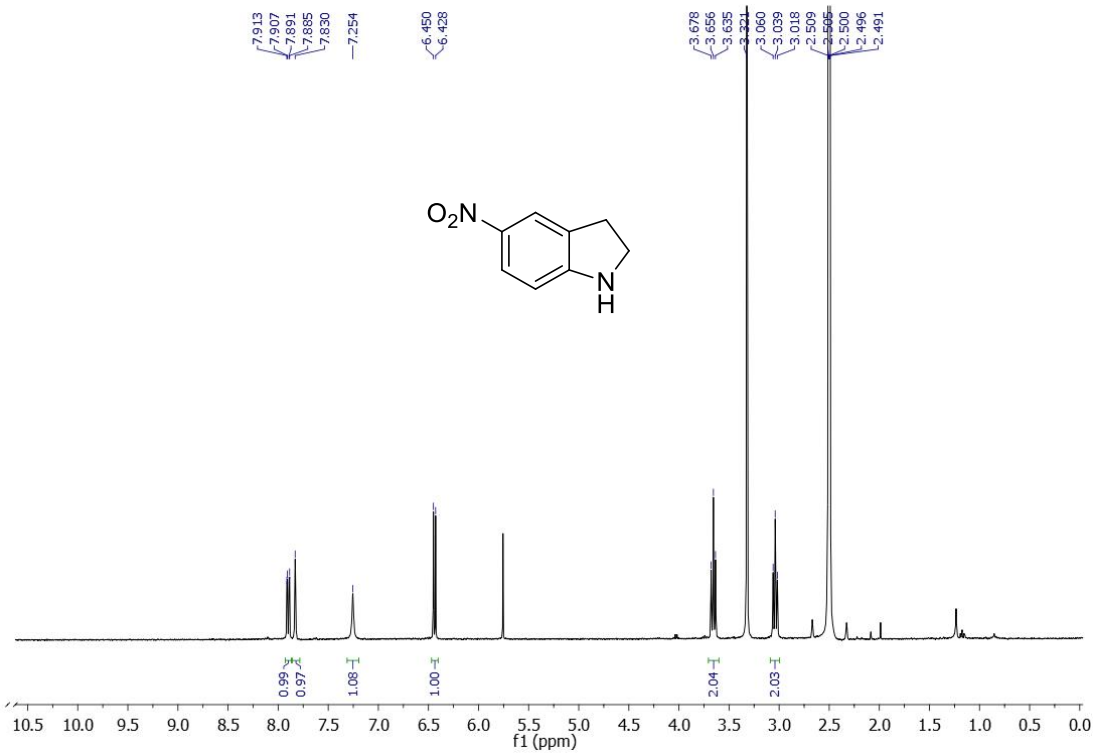

Figure 3.49. ^{1}H NMR spectrum of 5-Nitroindoline **(3c).**

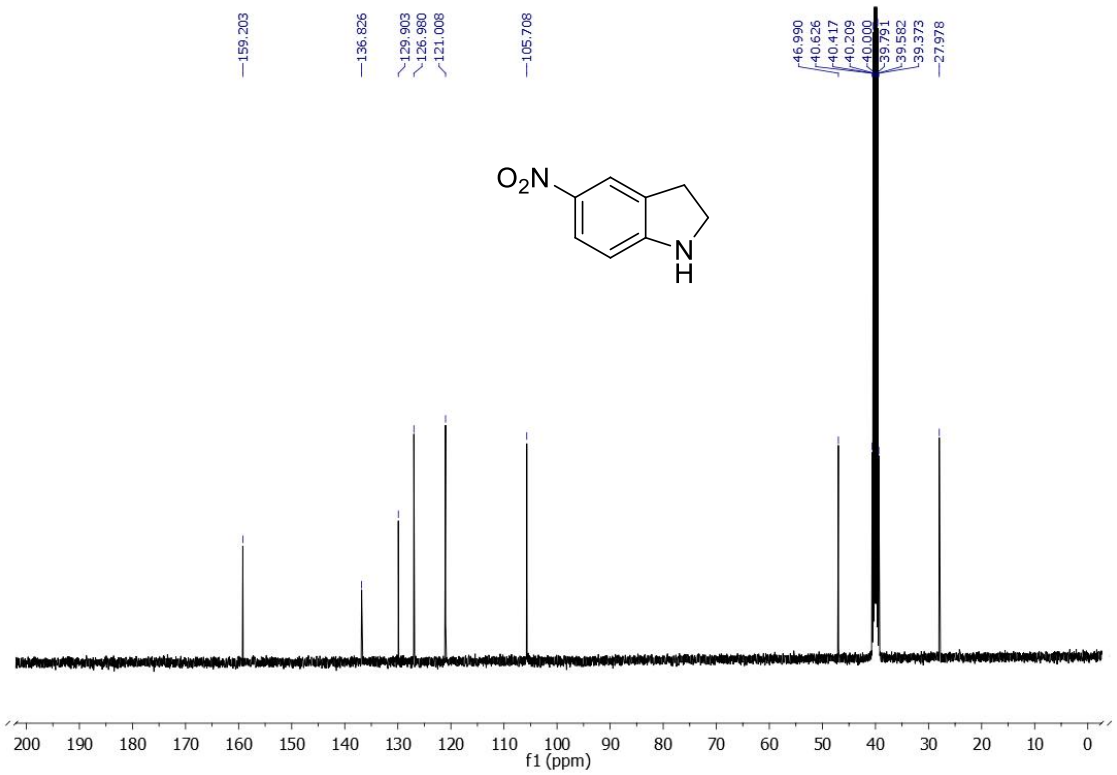

Figure 3.50. ^{13}C NMR spectrum of 5-Nitroindoline **(3c).**

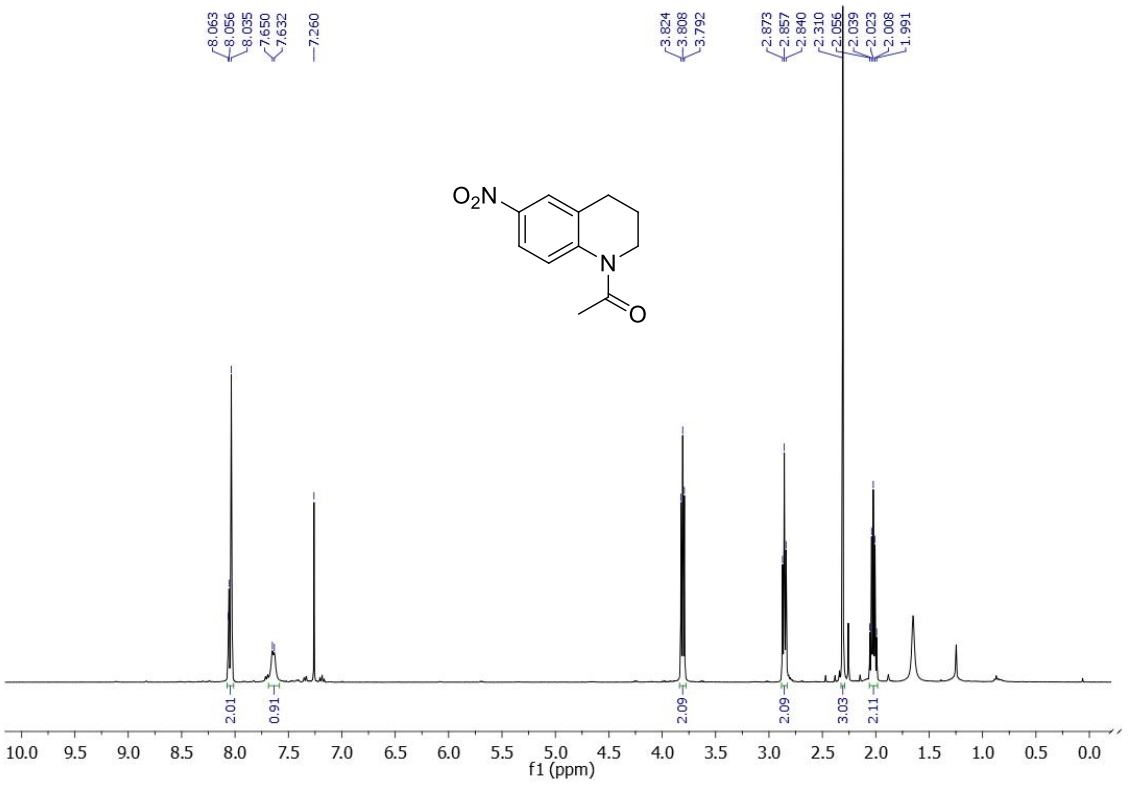

Figure 3.51. ^{1}H NMR spectrum of 1-(6-Nitro-3,4-dihydroquinolin-1(2H)-yl)ethanone **(5).**

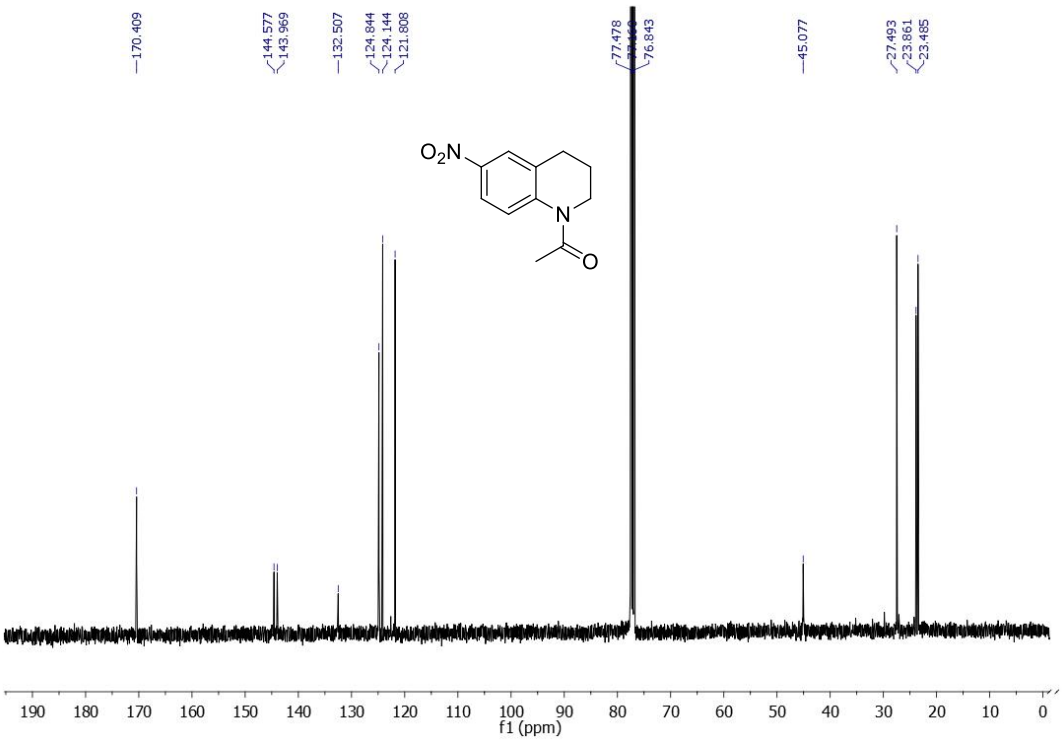

Figure 3.52. ^{13}C NMR spectrum of 1-(6-Nitro-3,4-dihydroquinolin-1(2H)-yl)ethanone **(5).**

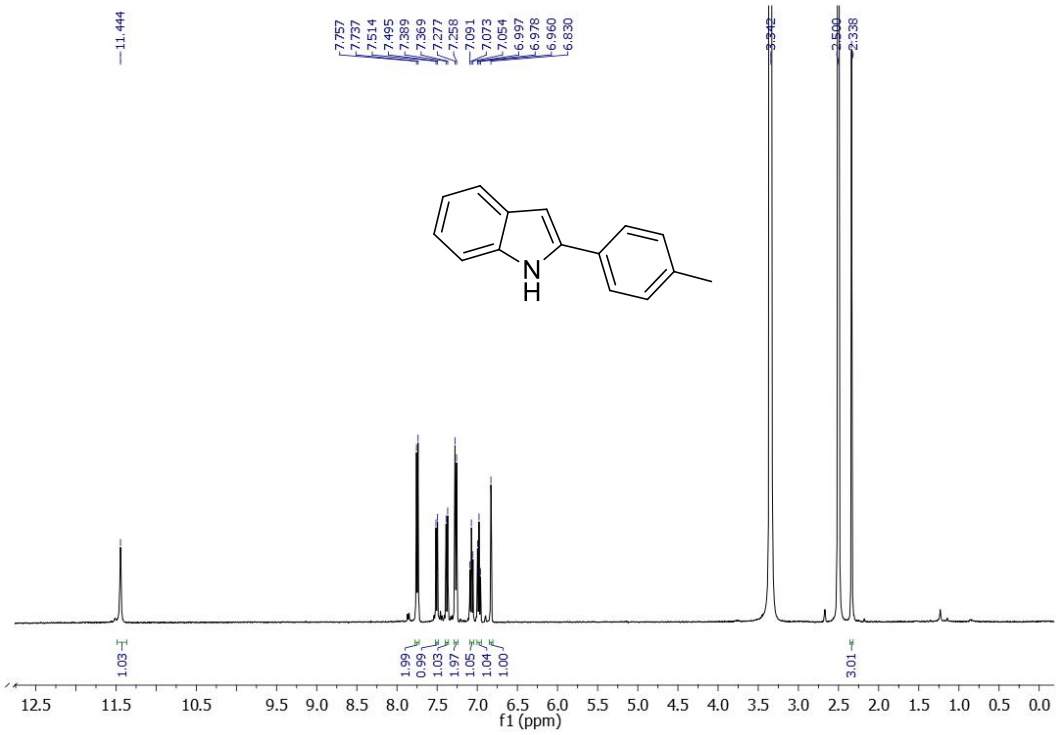

Figure 3.53. ^{1}H NMR spectrum of 2-(p-Tolyl)-1H-indole **(1f').**

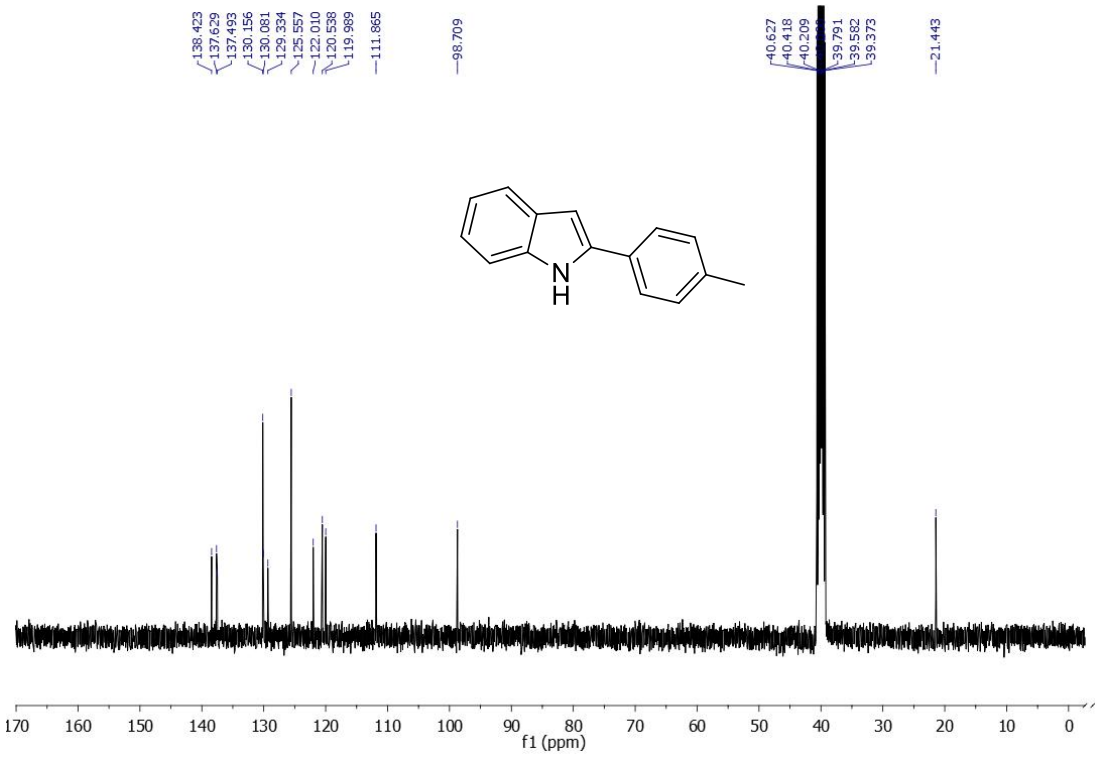

Figure 3.54. ^{13}C NMR spectrum of 2-(p-Tolyl)-1H-indole **(1f').**

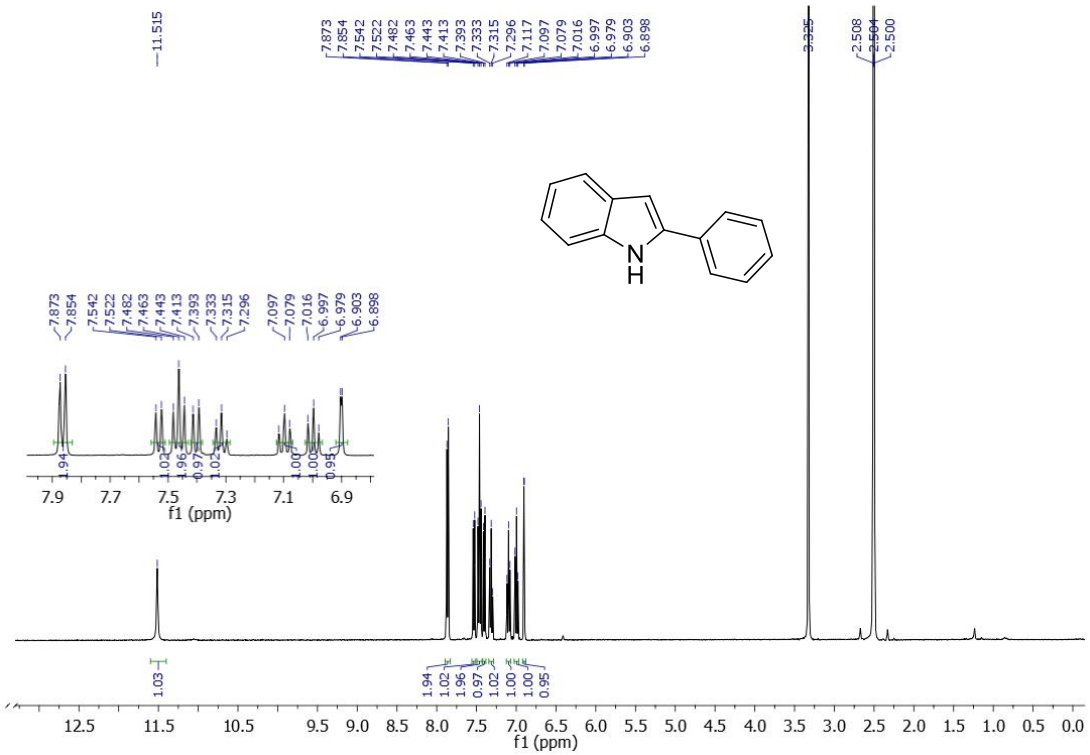

Figure 3.55. ^{1}H NMR spectrum of 2-Phenyl-1H-indole **(1g').**

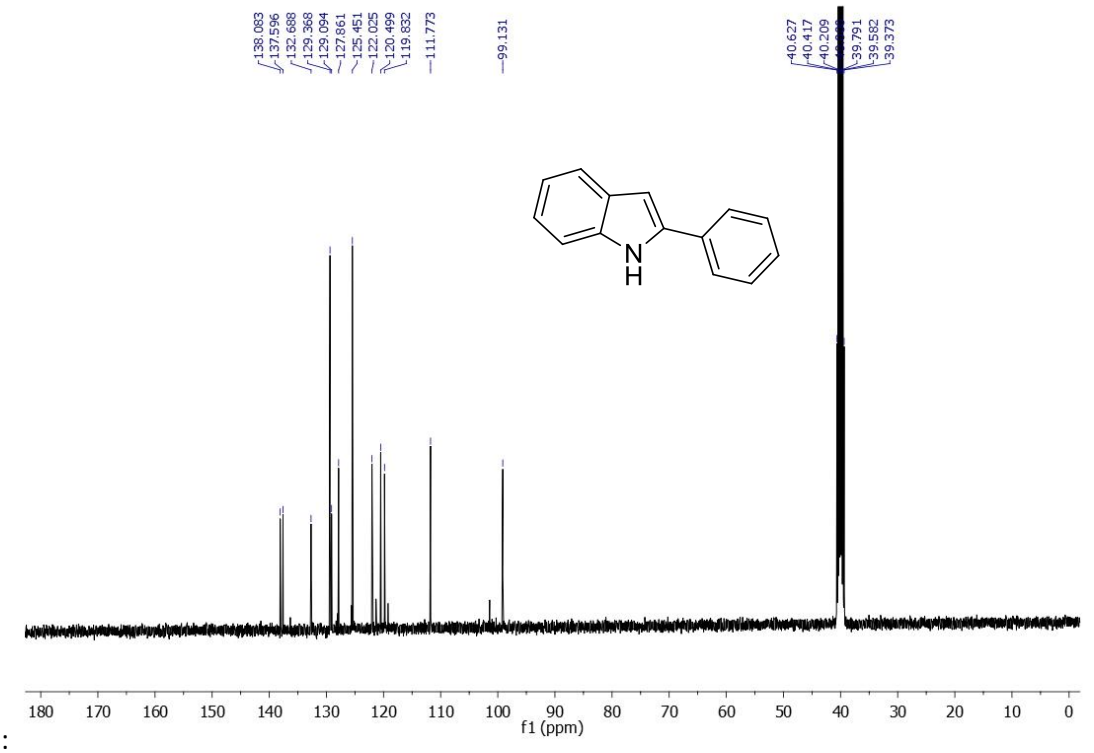

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Figure 3.56. ^{13}C NMR spectrum of 2-Phenyl-1H-indole **(1g').**

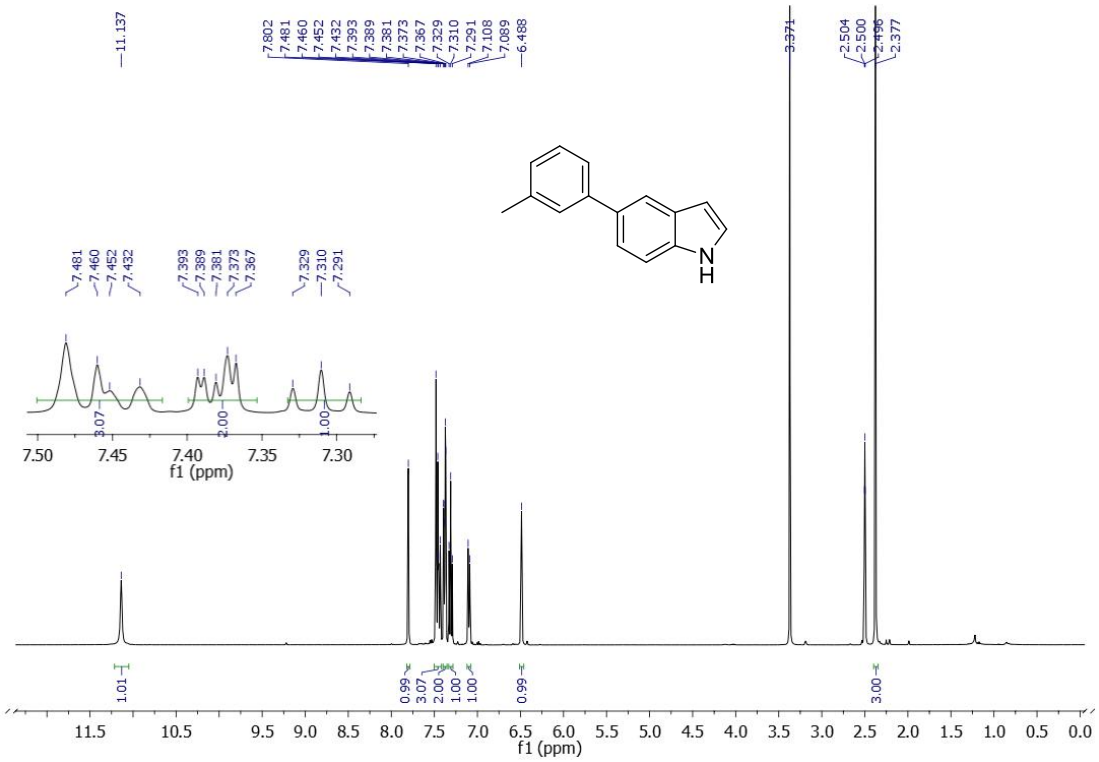


Figure 3.57. ^{1}H NMR spectrum of 5-(m-Tolyl)-1H-indole **(1m').**

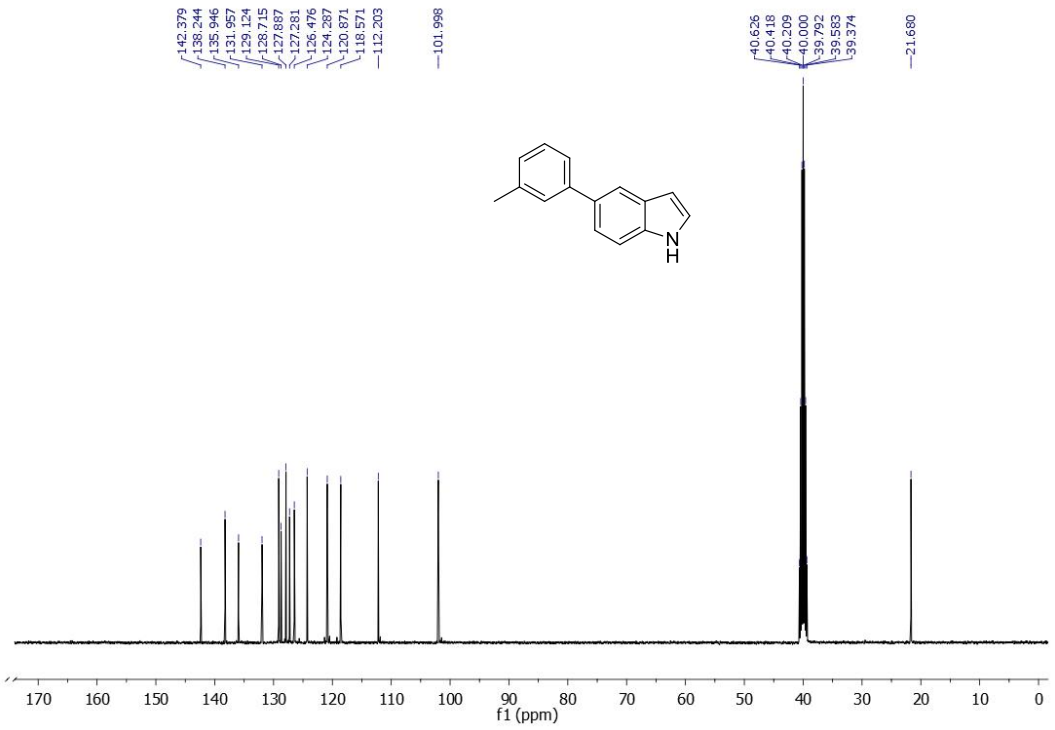


Figure 3.58. ^{13}C NMR spectrum of 5-(m-Tolyl)-1H-indole **(1m').**

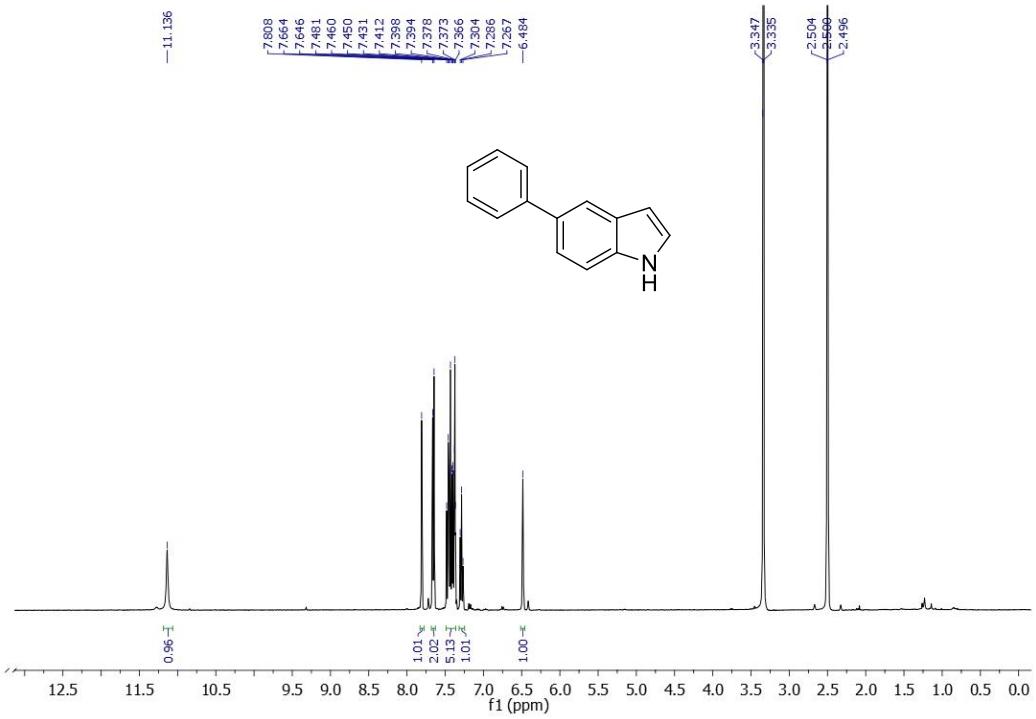


Figure 3.59. ^{1}H NMR spectrum of 5-Phenyl-1H-indole**(1n').**

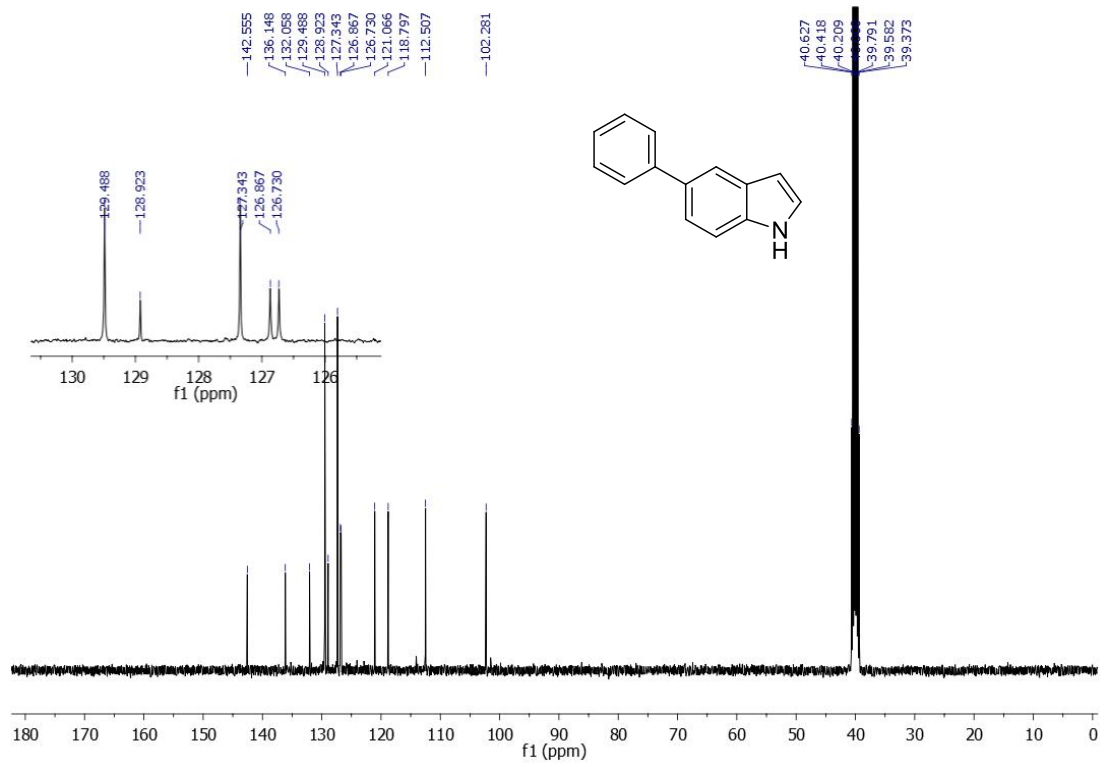


Figure 3.60. ^{13}C NMR spectrum of 5-Phenyl-1H-indole**(1n').**

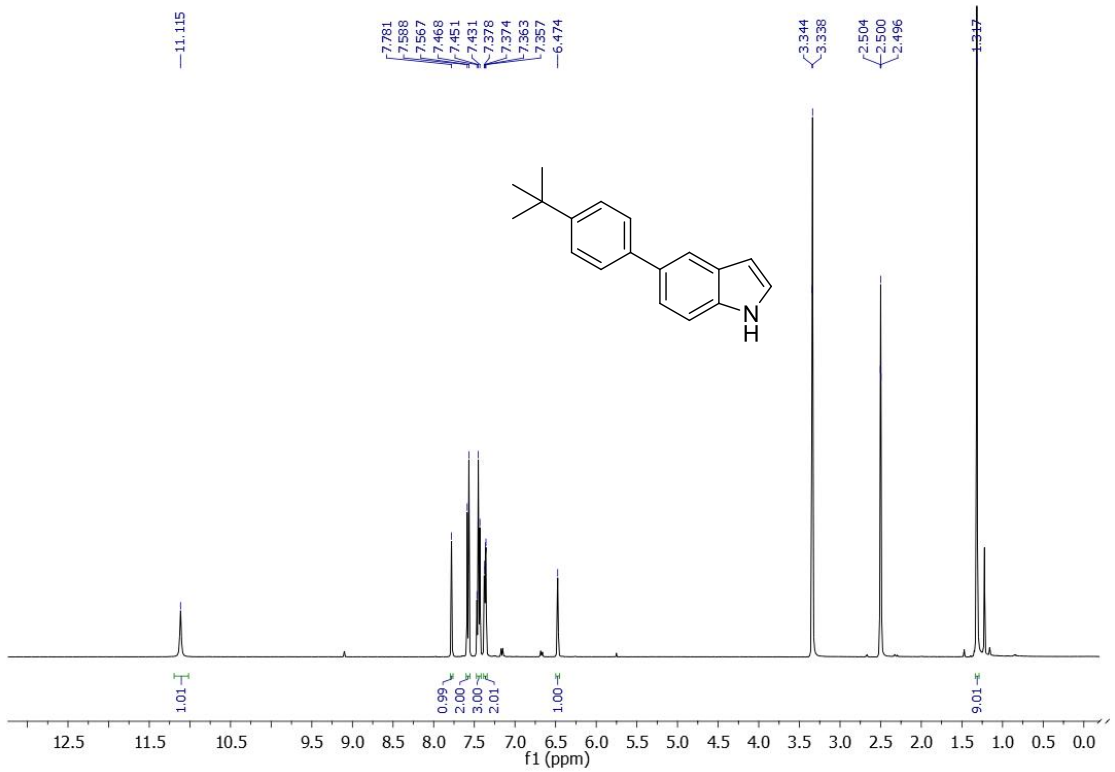


Figure 3.61. ^{1}H NMR spectrum of 5-(4-(tert-Butyl)phenyl)-1H-indole **(1o').**

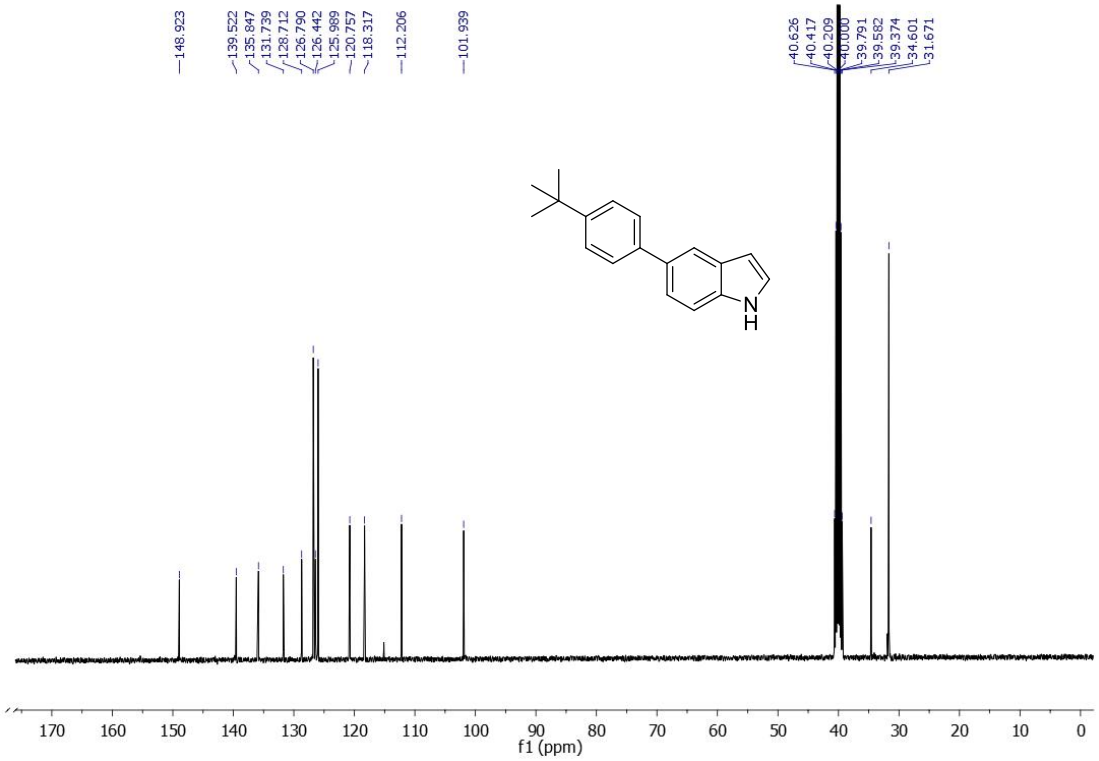


Figure 3.62. ^{13}C NMR spectrum of 5-(4-(tert-Butyl)phenyl)-1H-indole **(1o').**

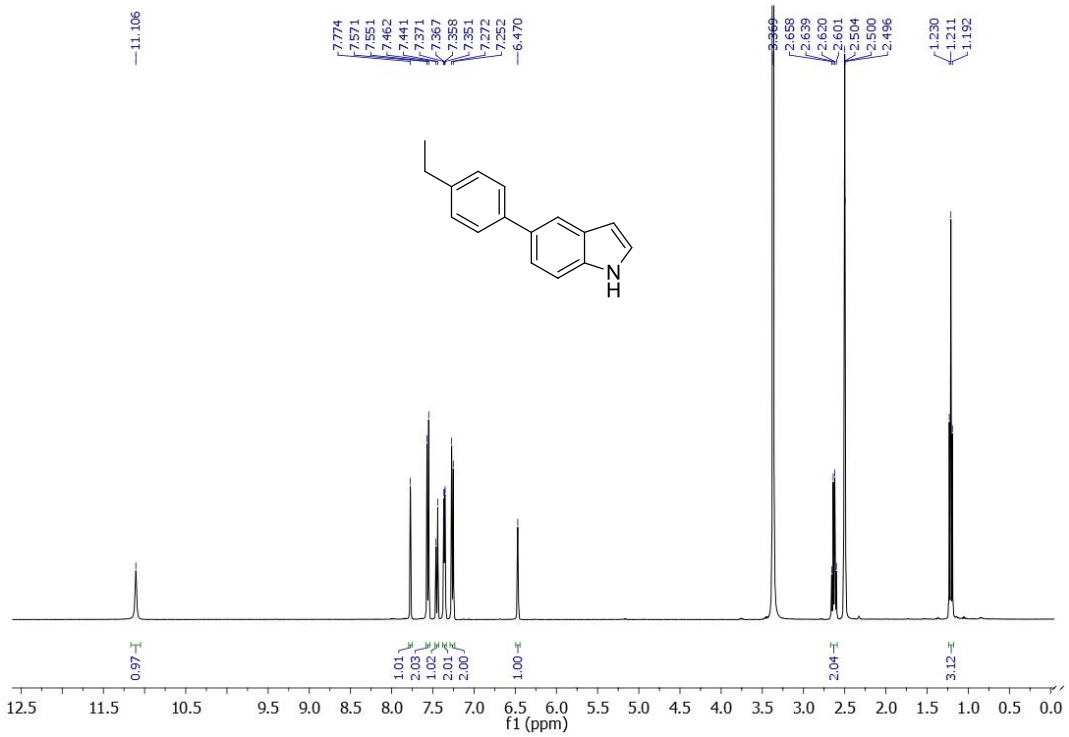


Figure 3.63. ^{1}H NMR spectrum of 5-(4-Ethylphenyl)-1H-indole **(1p').**

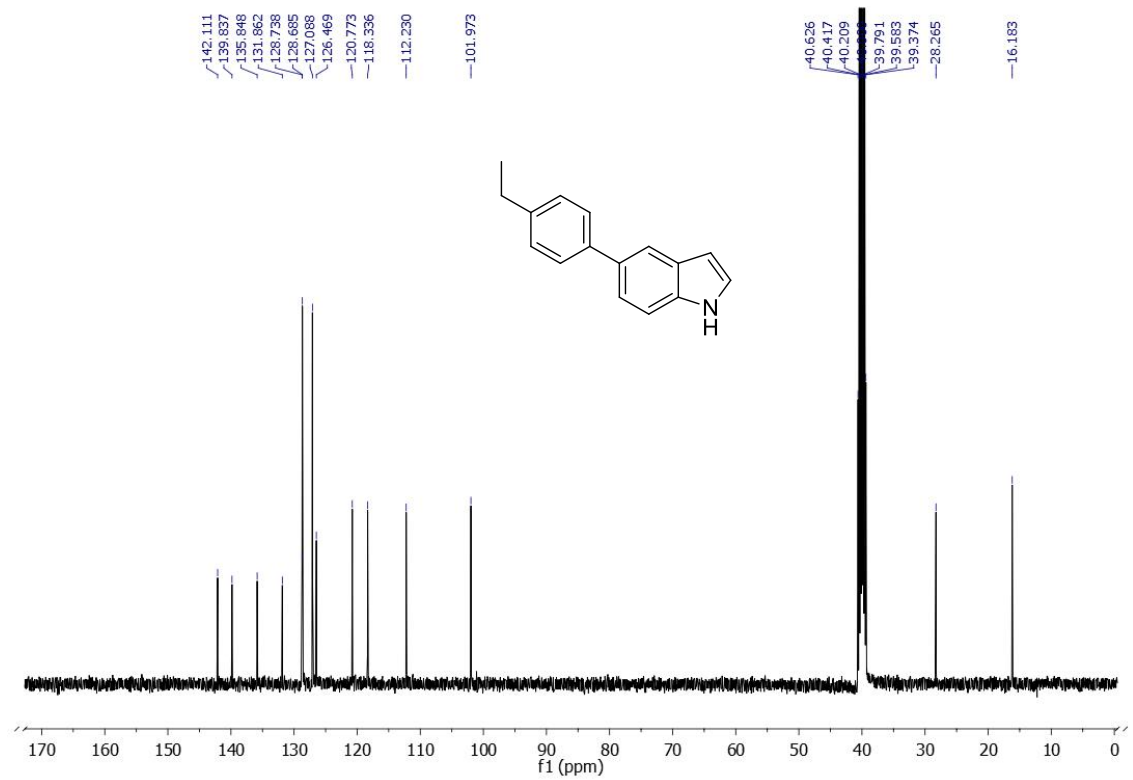


Figure 3.64. ^{13}C NMR spectrum of 5-(4-Ethylphenyl)-1H-indole **(1p').**

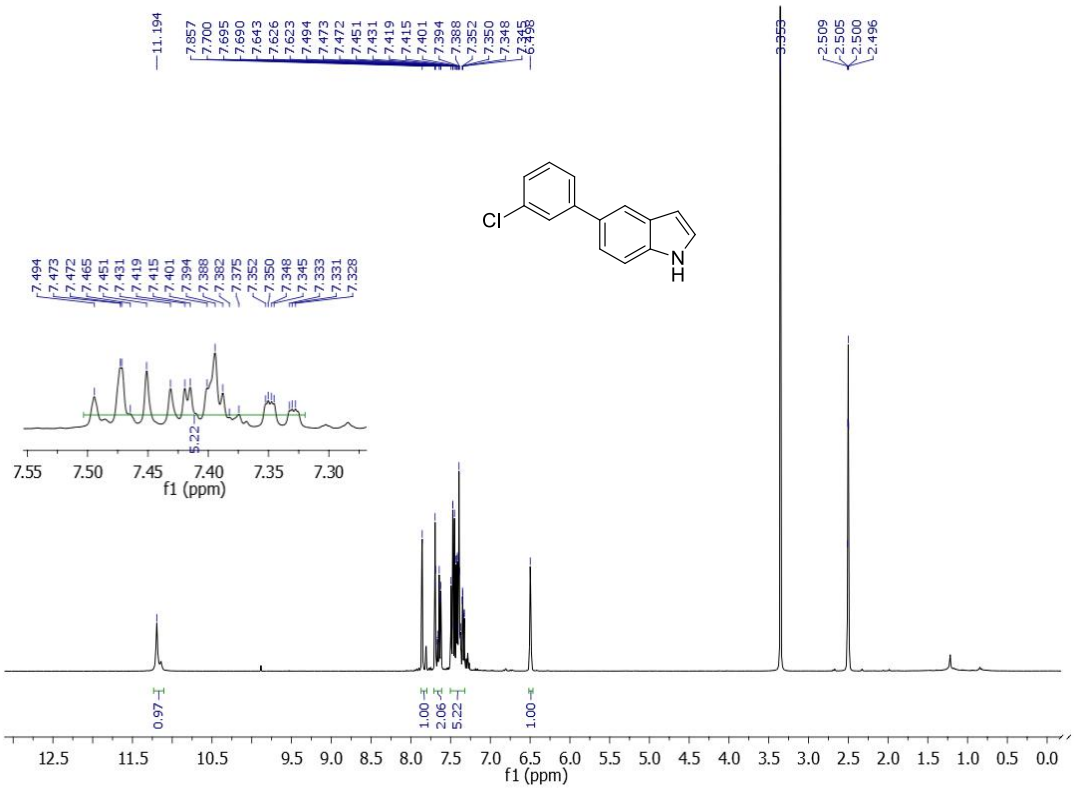


Figure 3.65. ^{1}H NMR spectrum of 5-(3-Chlorophenyl)-1H-indole **(1q').**

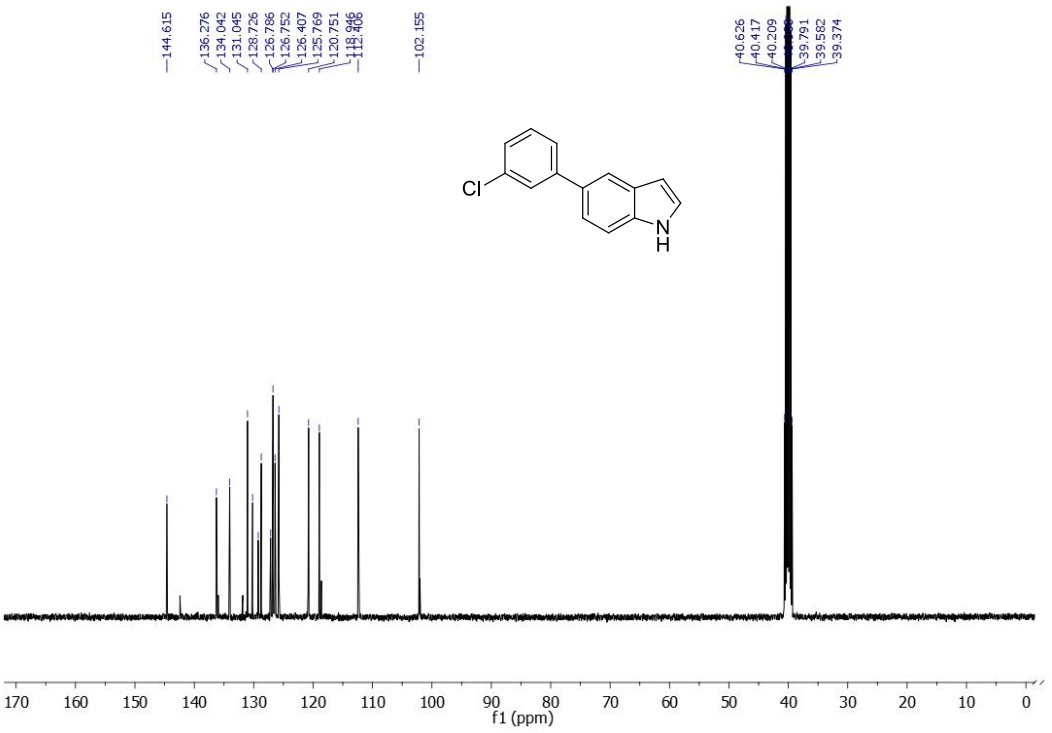


Figure 3.66. ^{13}C NMR spectrum of 5-(3-Chlorophenyl)-1H-indole **(1q').**

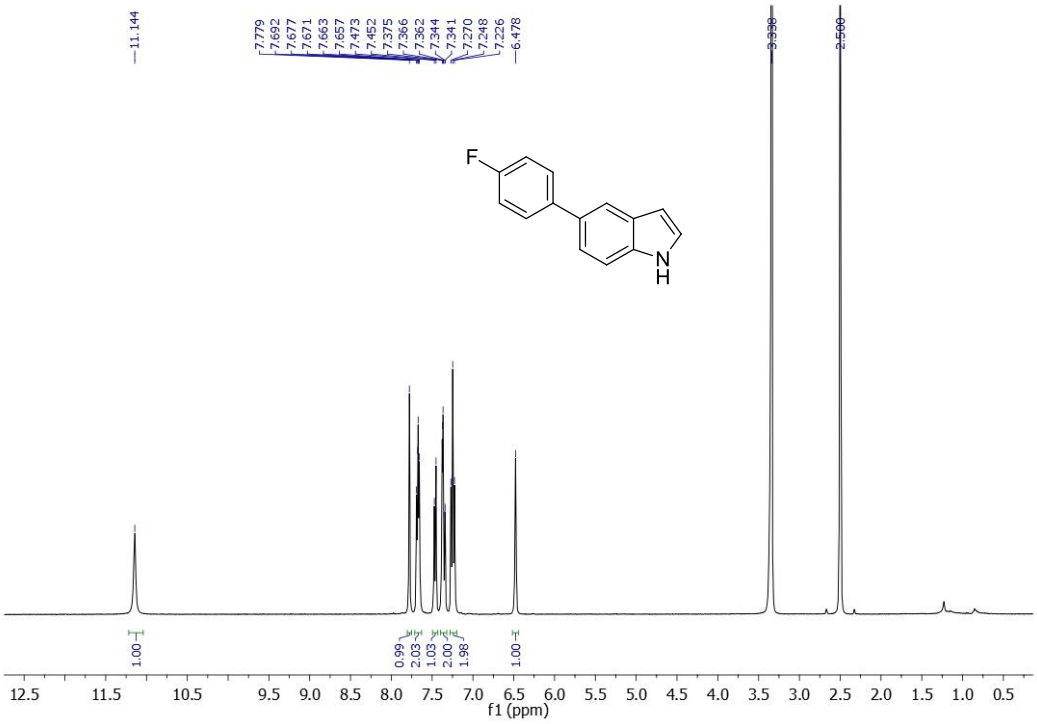


Figure 3.67. ^{1}H NMR spectrum of 5-(4-Fluorophenyl)-1H-indole **(1r').**

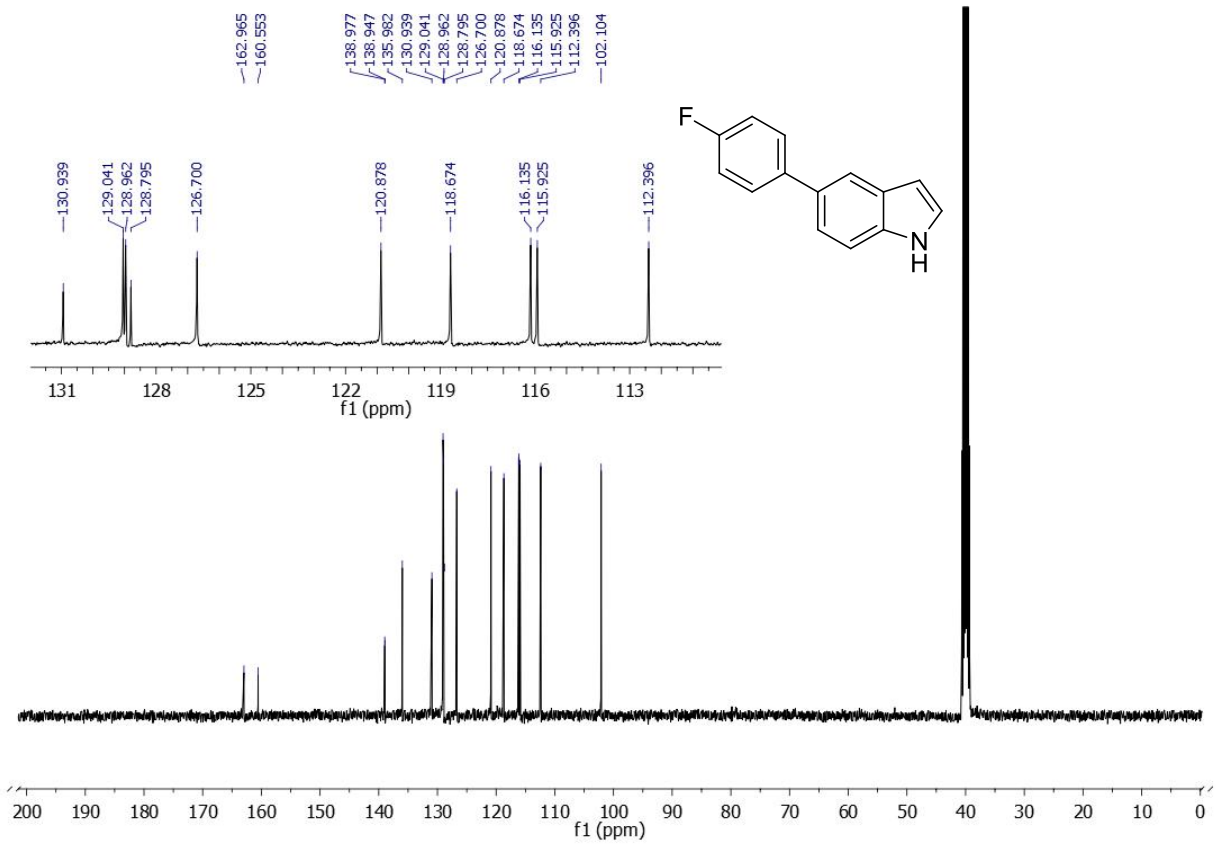


Figure 3.68. ^{13}C NMR spectrum of 5-(4-Fluorophenyl)-1H-indole **(1r').**

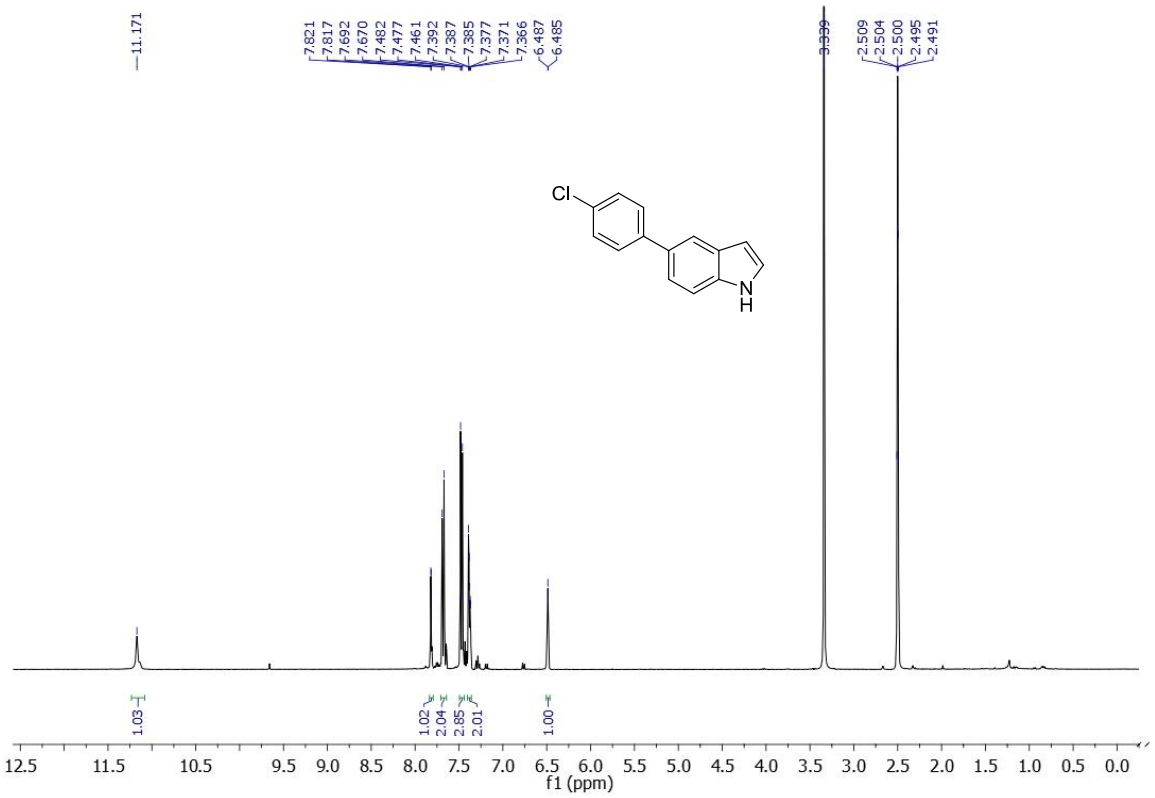


Figure 3.69. [1]H NMR spectrum of 5-(4-Chlorophenyl)-1H-indole **(1s').**

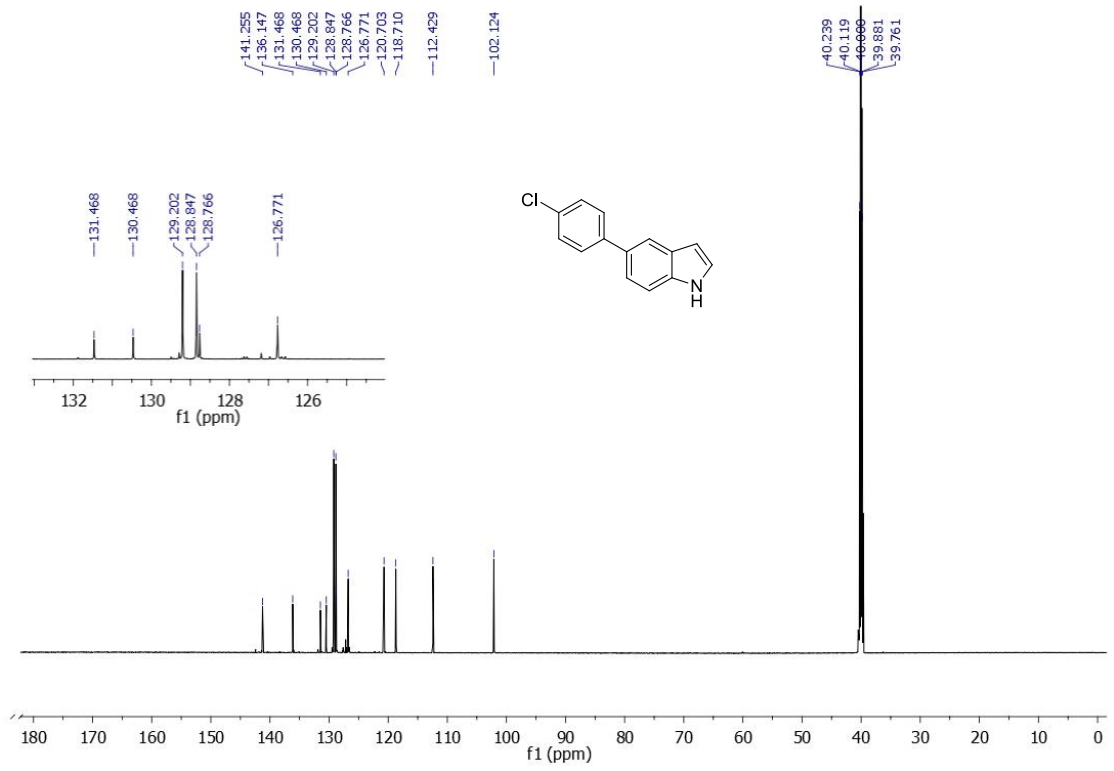


Figure 3.70. 13C NMR spectrum of 5-(4-Chlorophenyl)-1H-indole **(1s').**

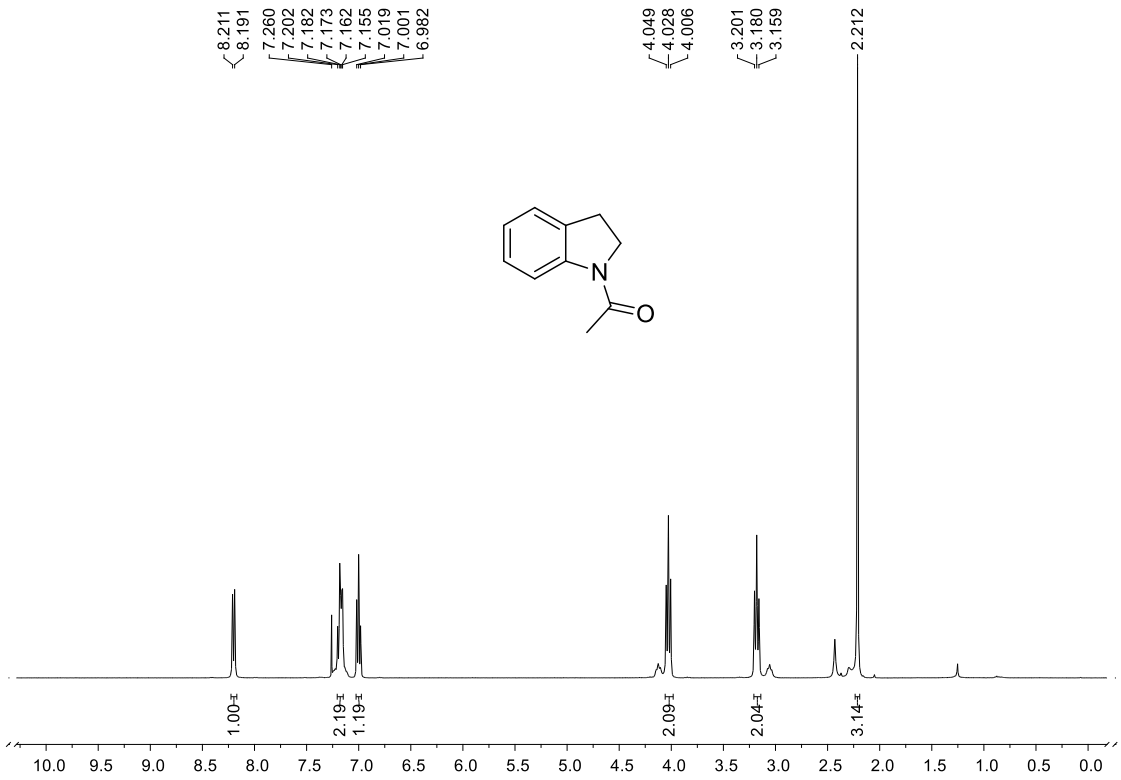


Figure 3.71. ^{1}H NMR spectrum of 1-(Indolin-1-yl)ethanone **(1a).**

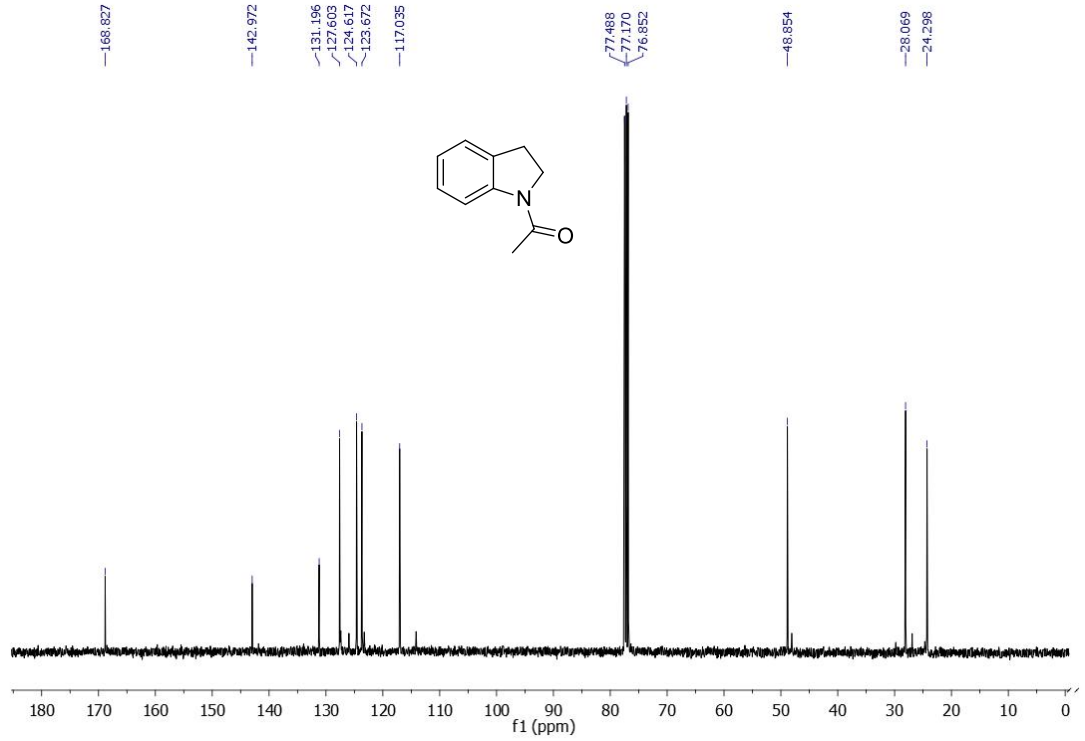


Figure 3.72. ^{13}C NMR spectrum of 1-(Indolin-1-yl)ethanone **(1a).**

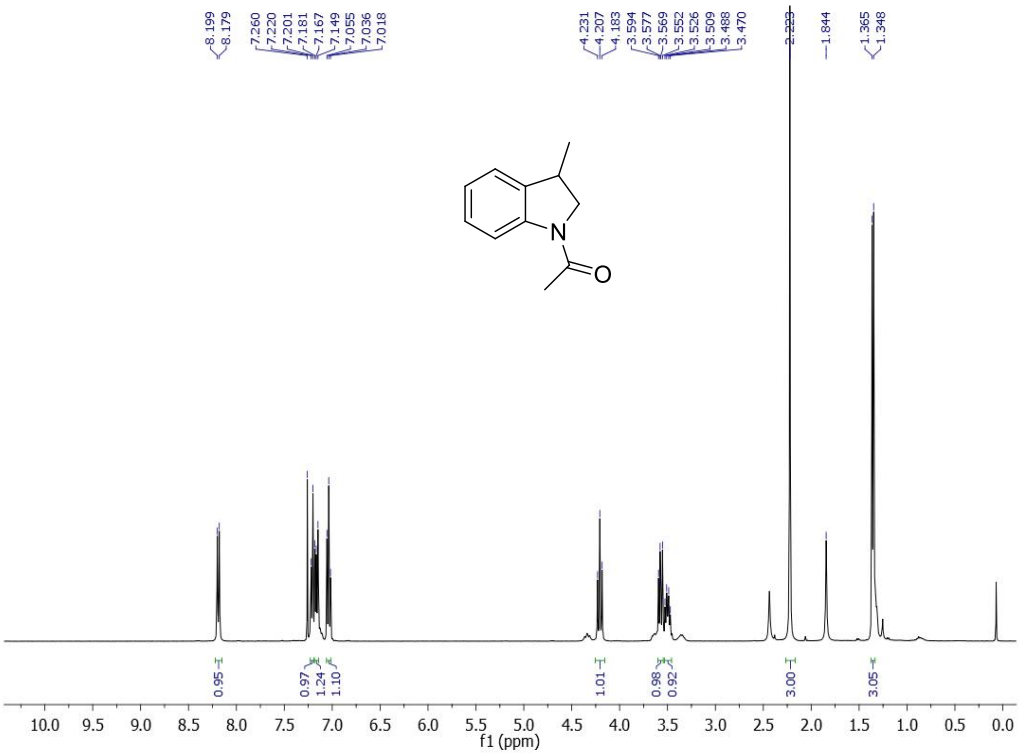


Figure 3.73. ^{1}H NMR spectrum of 1-(3-Methylindolin-1-yl)ethanone **(1b).**

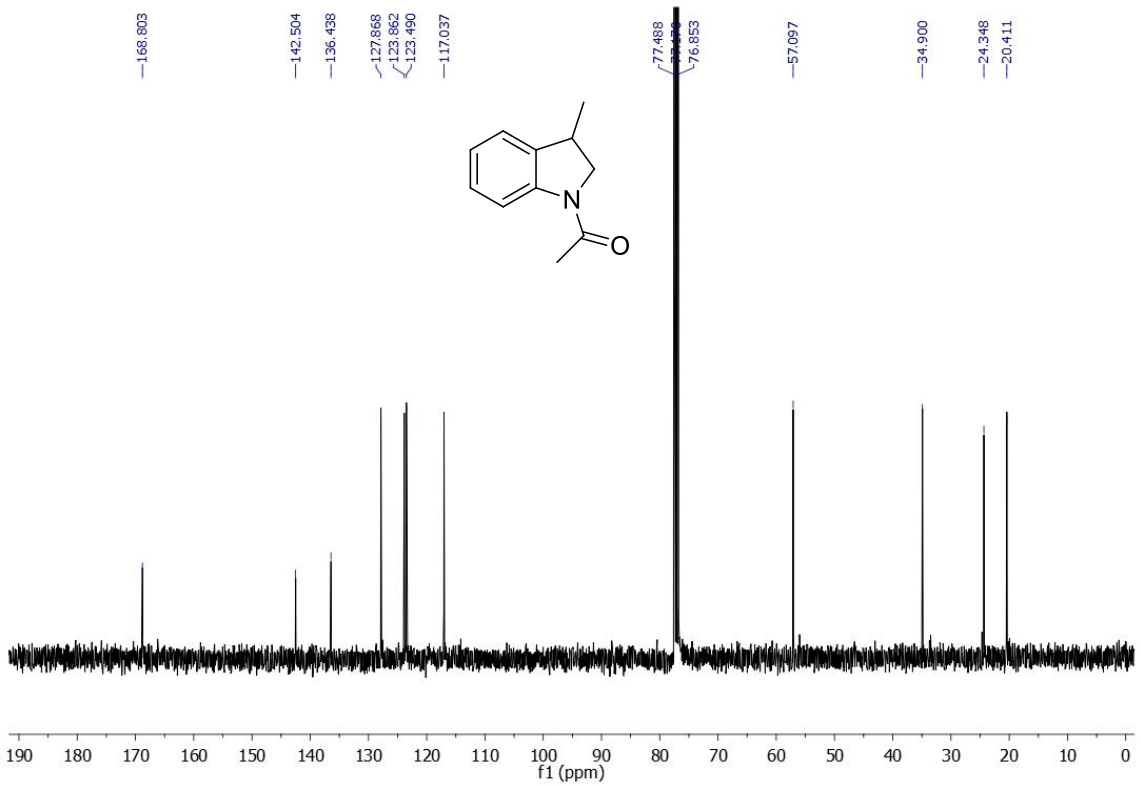


Figure 3.74: ^{13}C NMR spectrum of 1-(3-Methylindolin-1-yl)ethanone **(1b).**

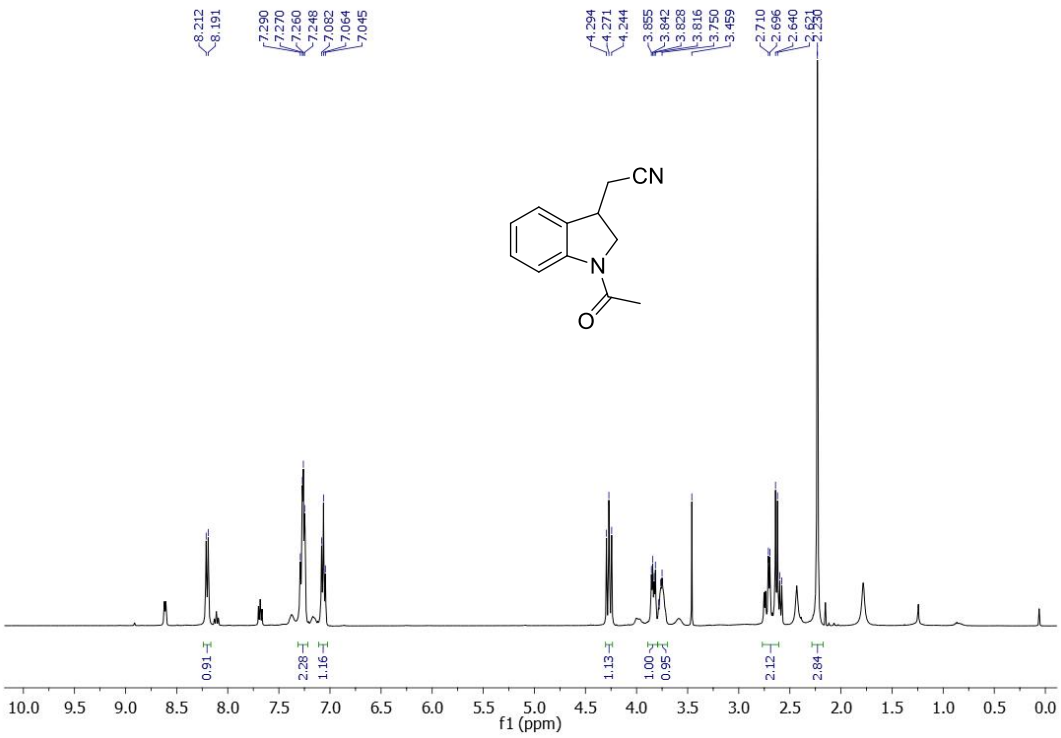


Figure 3.75. [1]H NMR spectrum of 2-(1-Acetylindolin-3-yl)acetonitrile **(1c).**

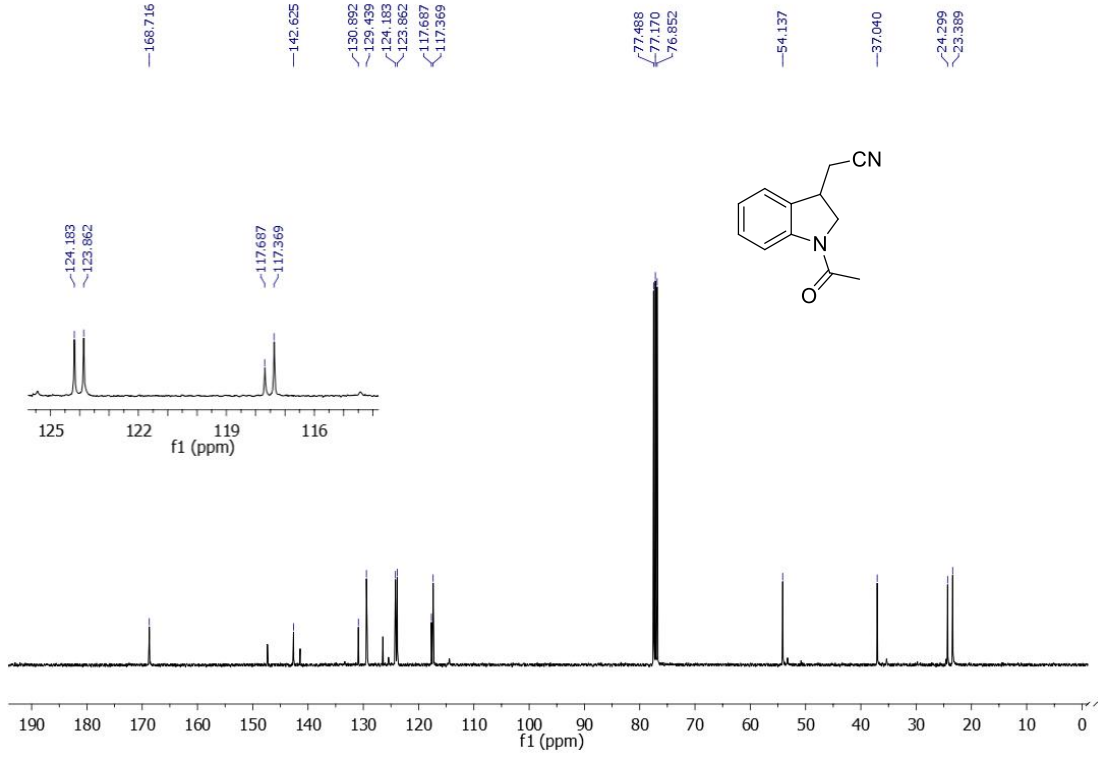


Figure 3.76. [13]C NMR spectrum of 2-(1-Acetylindolin-3-yl)acetonitrile **(1c).**

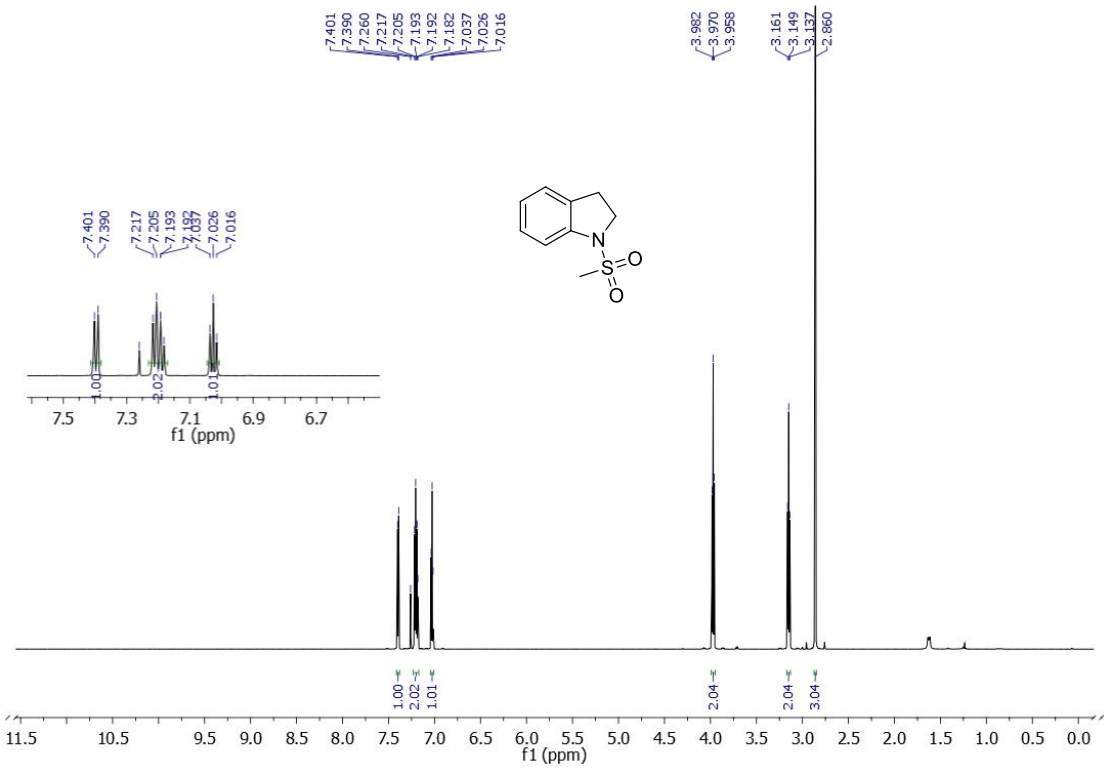


Figure 3.77. [1]H NMR spectrum of 1-(Methylsulfonyl)indoline **(1d).**

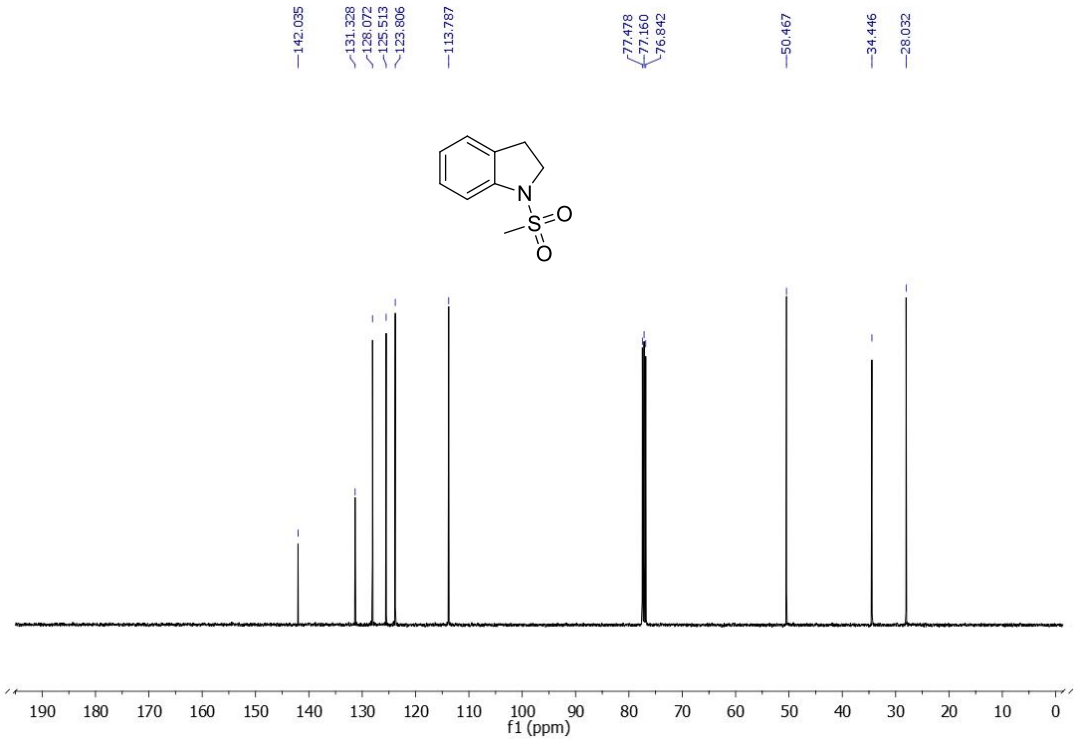


Figure 3.78. [13]C NMR spectrum of 1-(Methylsulfonyl)indoline **(1d).**

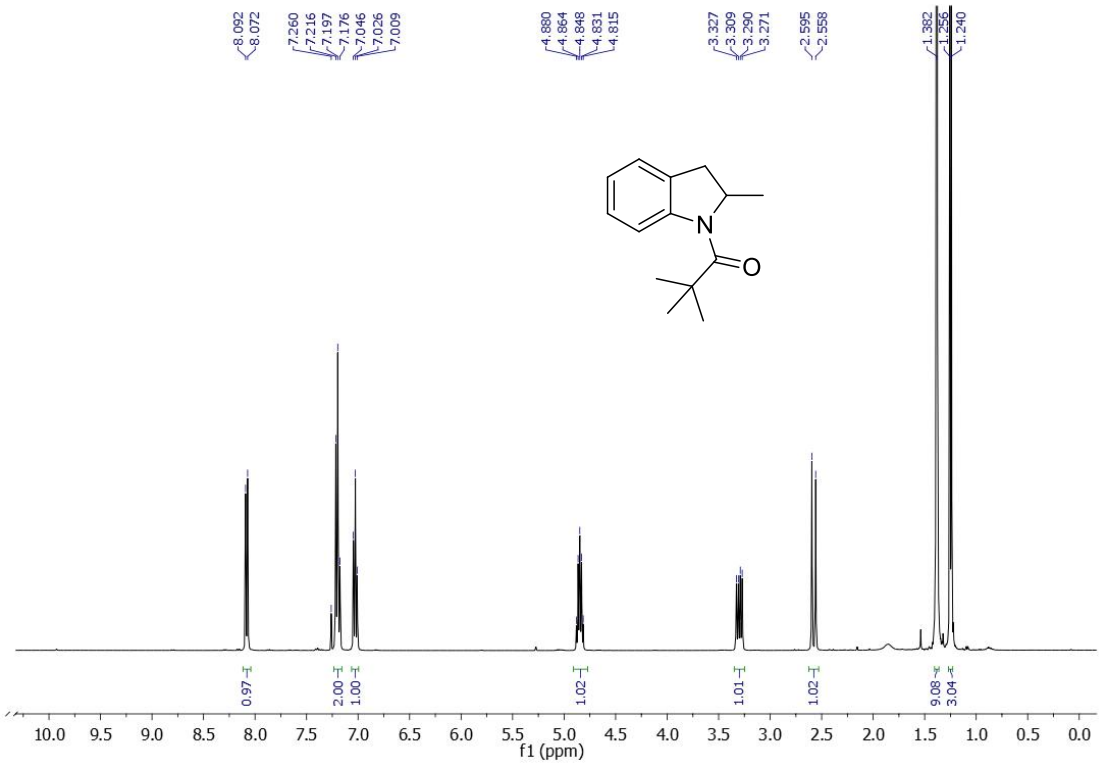


Figure 3.79. ^{1}H NMR spectrum of 2,2-Dimethyl-1-(2-methylindolin-1-yl)propan-1-one **(1e).**

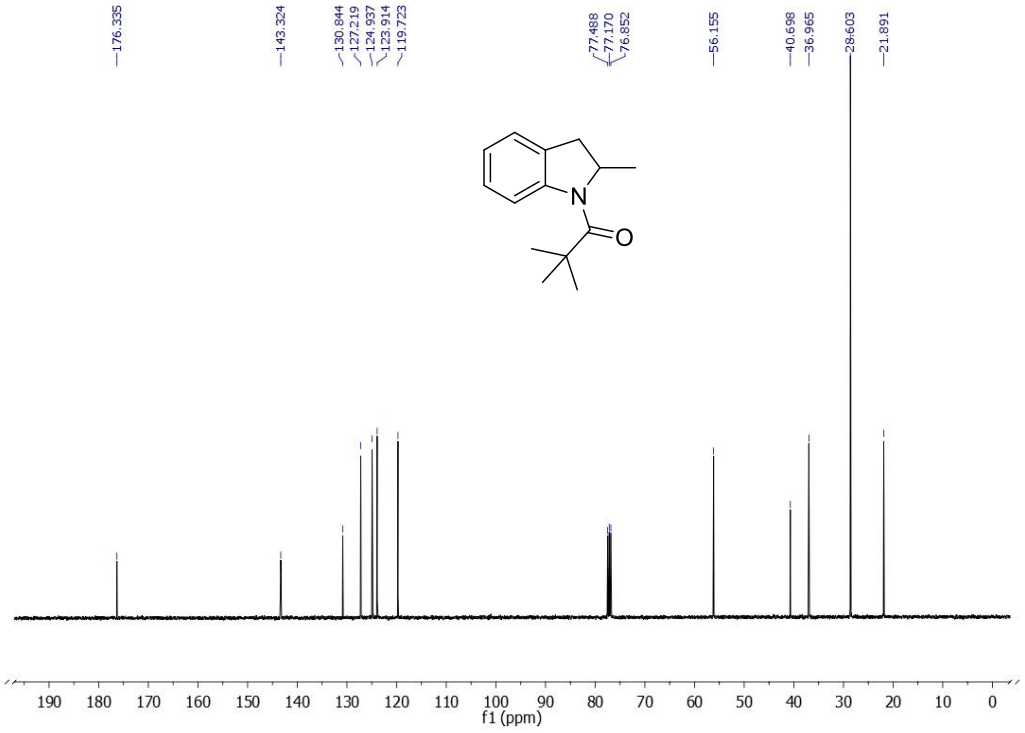


Figure 3.80. ^{13}C NMR spectrum of 2,2-Dimethyl-1-(2-methylindolin-1-yl)propan-1-one **(1e).**

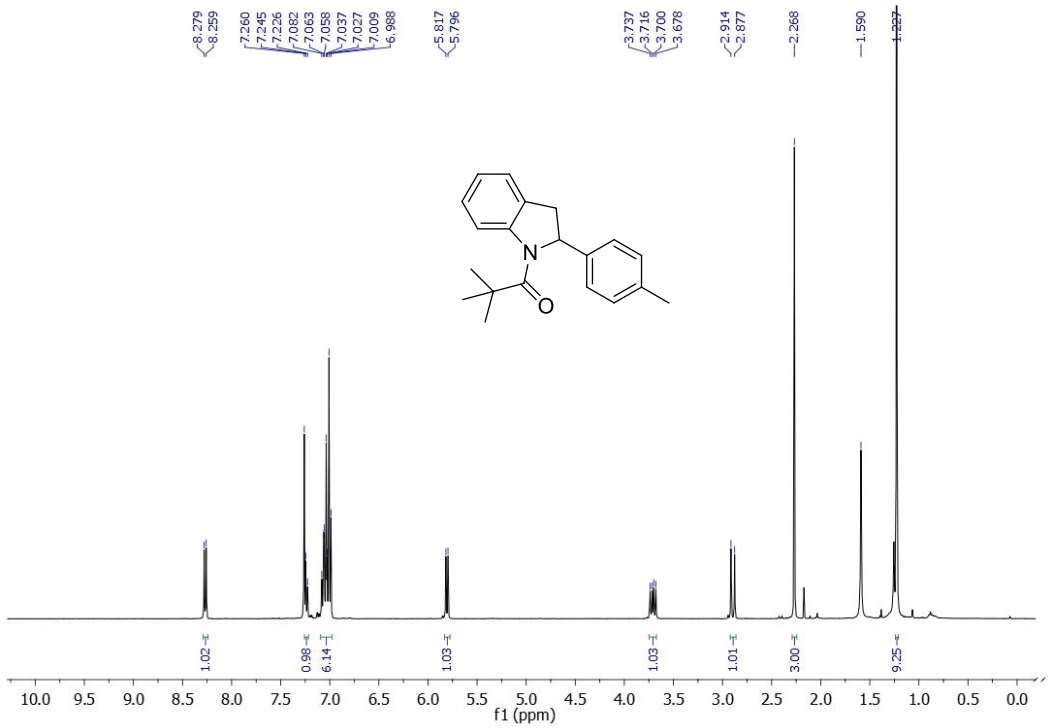


Figure 3.81. ^{1}H NMR spectrum of 2,2-Dimethyl-1-(2-(p-tolyl)indolin-1-yl)propan-1-one **(1f).**

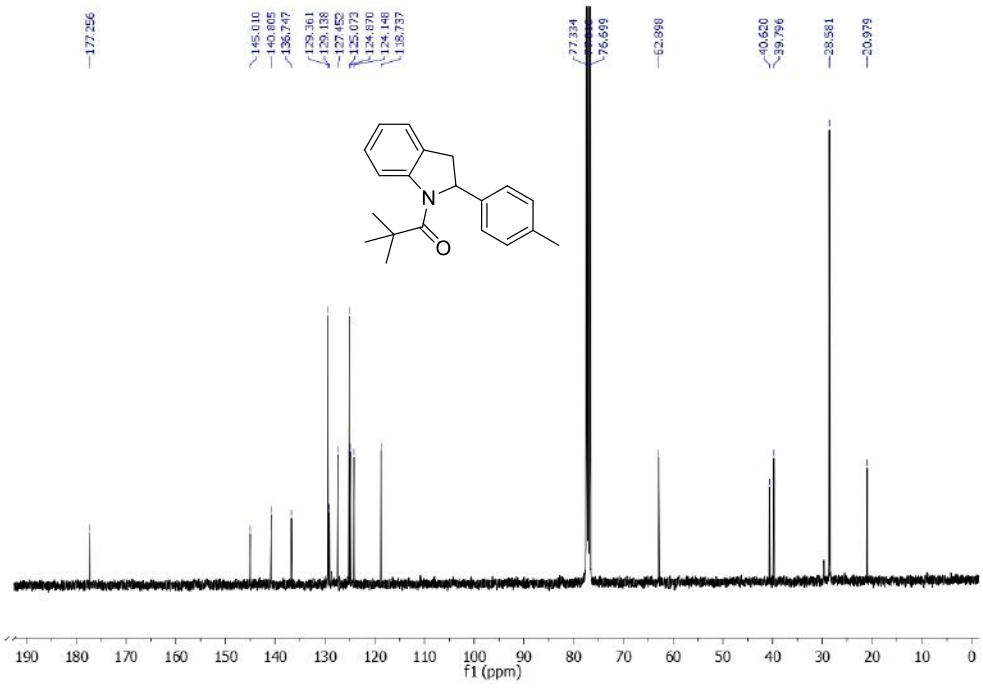


Figure 3.82. ^{13}C NMR spectrum of 2,2-Dimethyl-1-(2-(p-tolyl)indolin-1-yl)propan-1-one **(1f).**

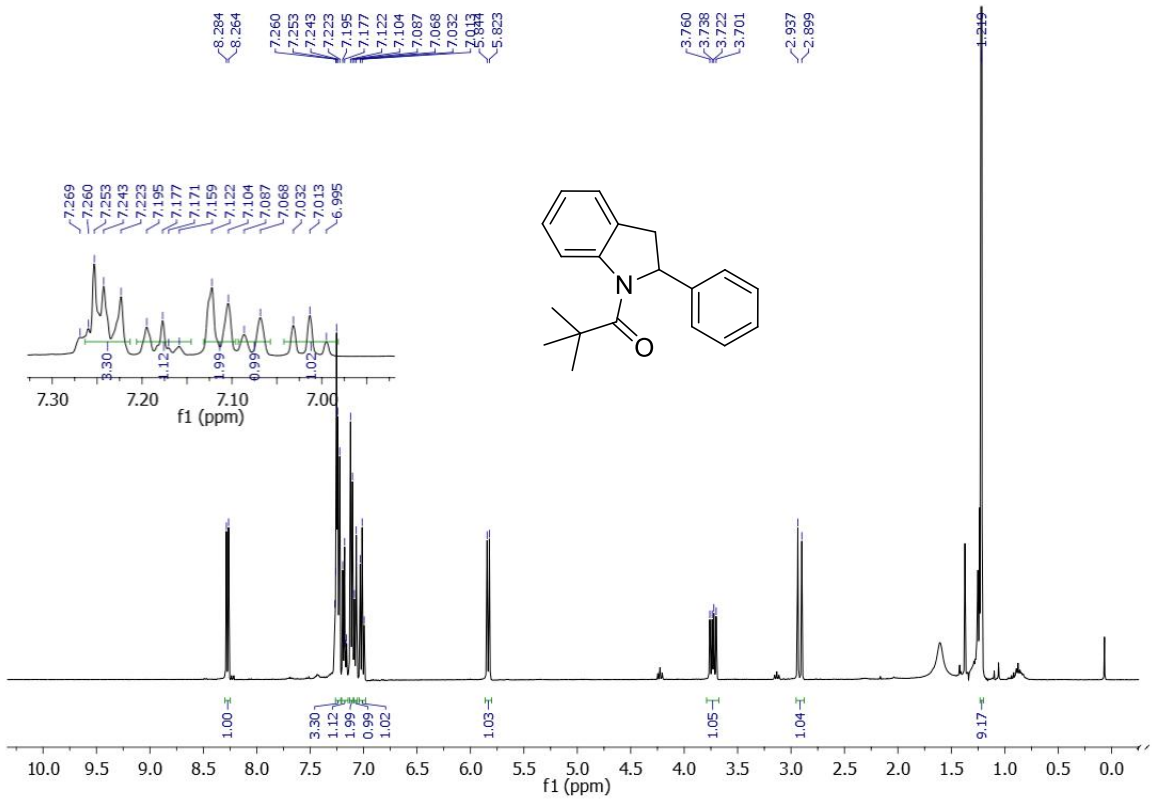


Figure 3.83. ^{1}H NMR spectrum of 2,2-Dimethyl-1-(2-phenylindolin-1-yl)propan-1-one **(1g).**

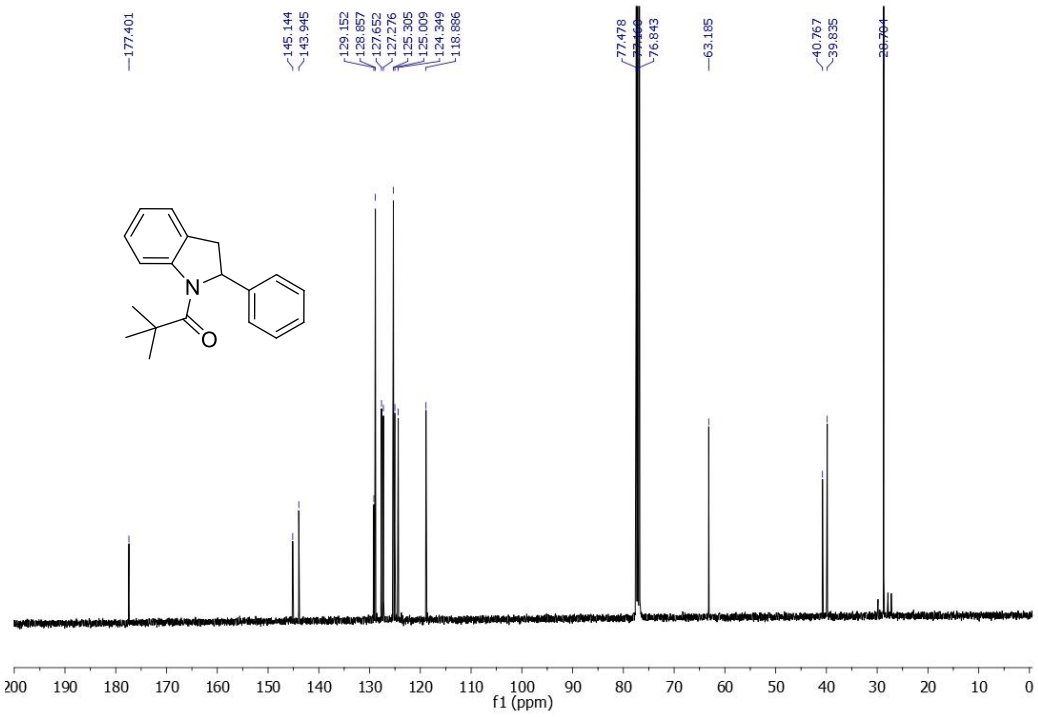


Figure 3.84. ^{13}C NMR spectrum of 2,2-Dimethyl-1-(2-phenylindolin-1-yl)propan-1-one **(1g).**

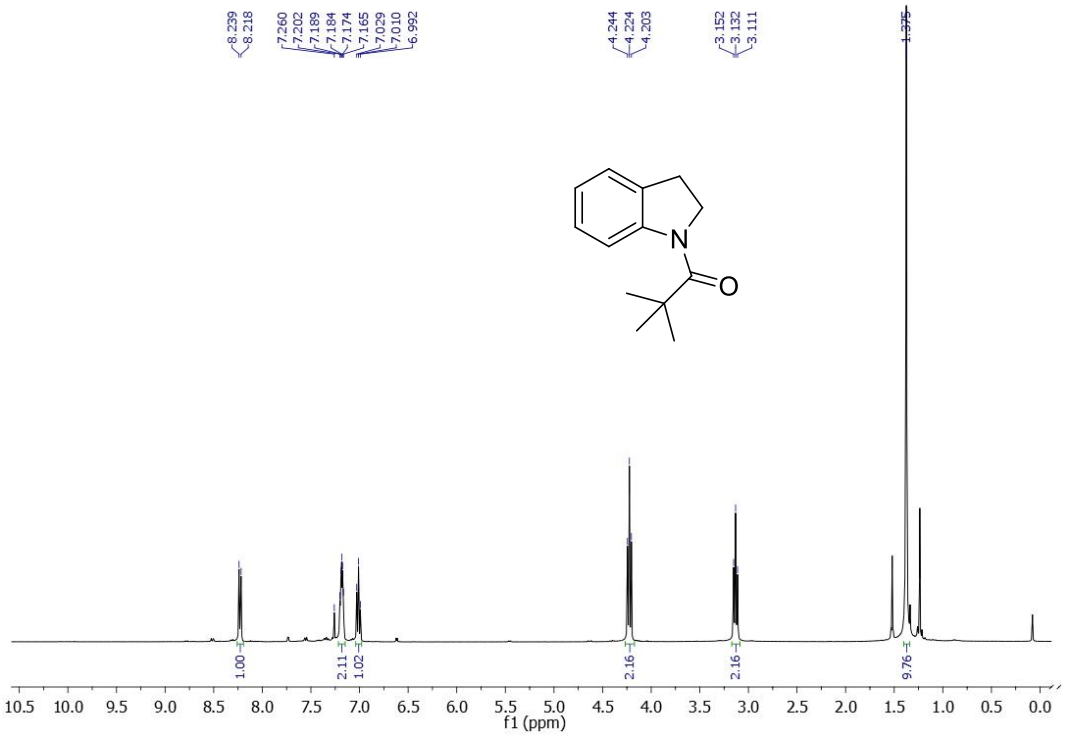


Figure 3.85. [1]H NMR spectrum of 1-(Indolin-1-yl)-2,2-dimethylpropan-1-one **(1h).**

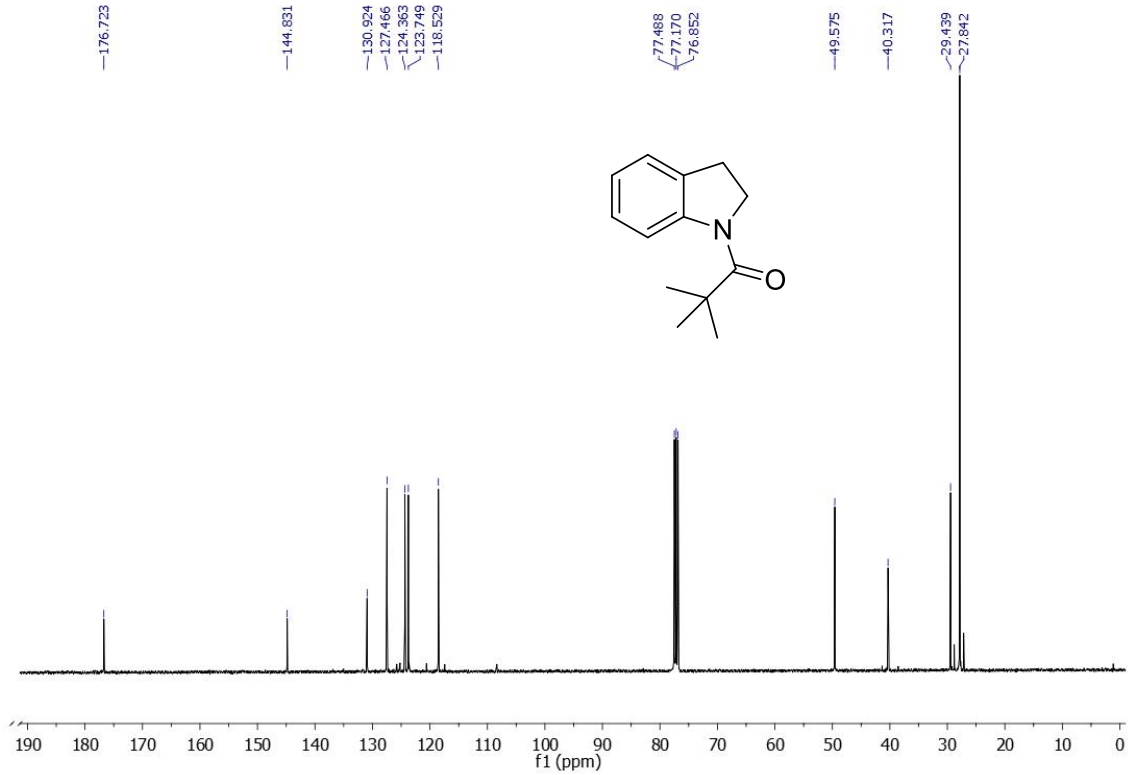


Figure 3.86. [13]C NMR spectrum of 1-(Indolin-1-yl)-2,2-dimethylpropan-1-one **(1h).**

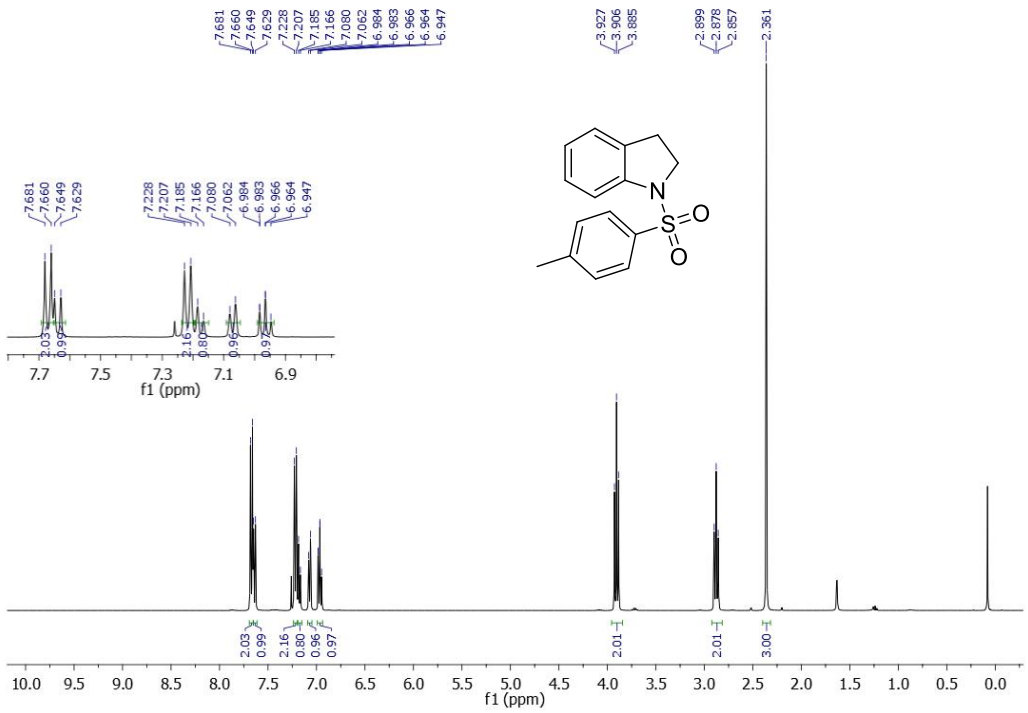


Figure 3.87. ^{1}H NMR spectrum of 1-Tosylindoline **(1i).**

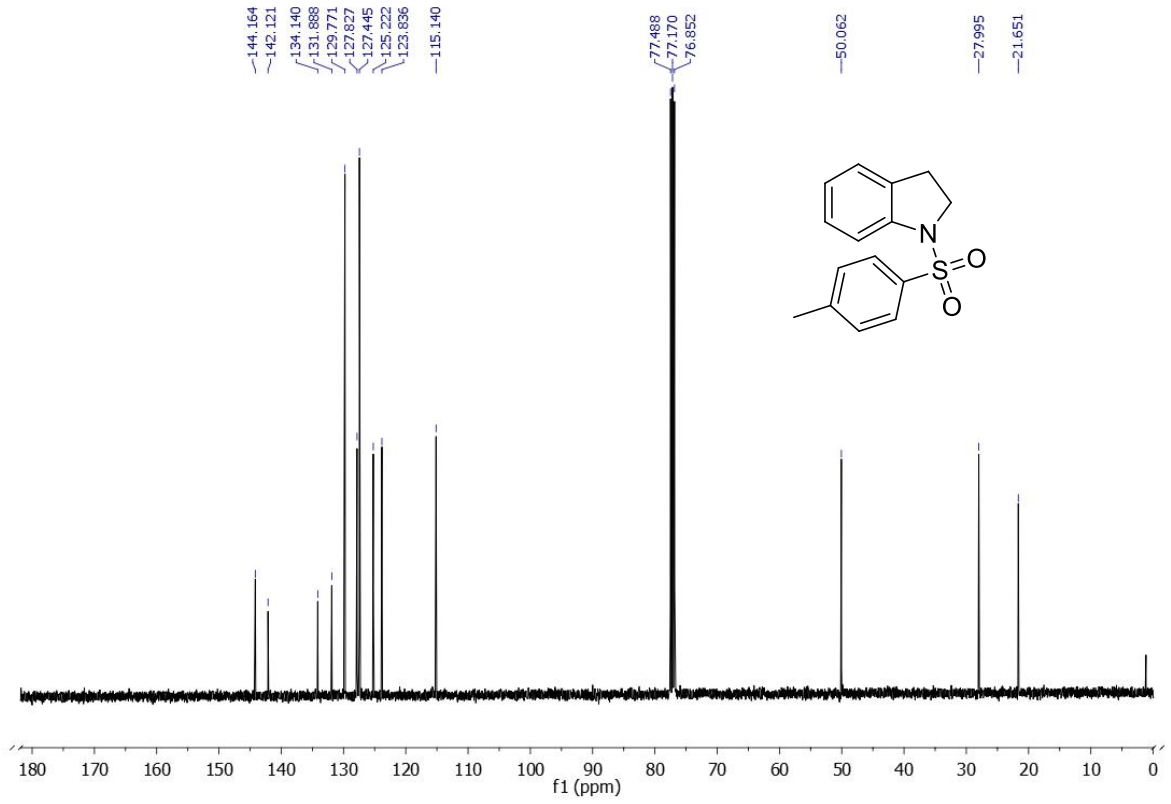


Figure 3.88. ^{13}C NMR spectrum of 1-Tosylindoline **(1i).**

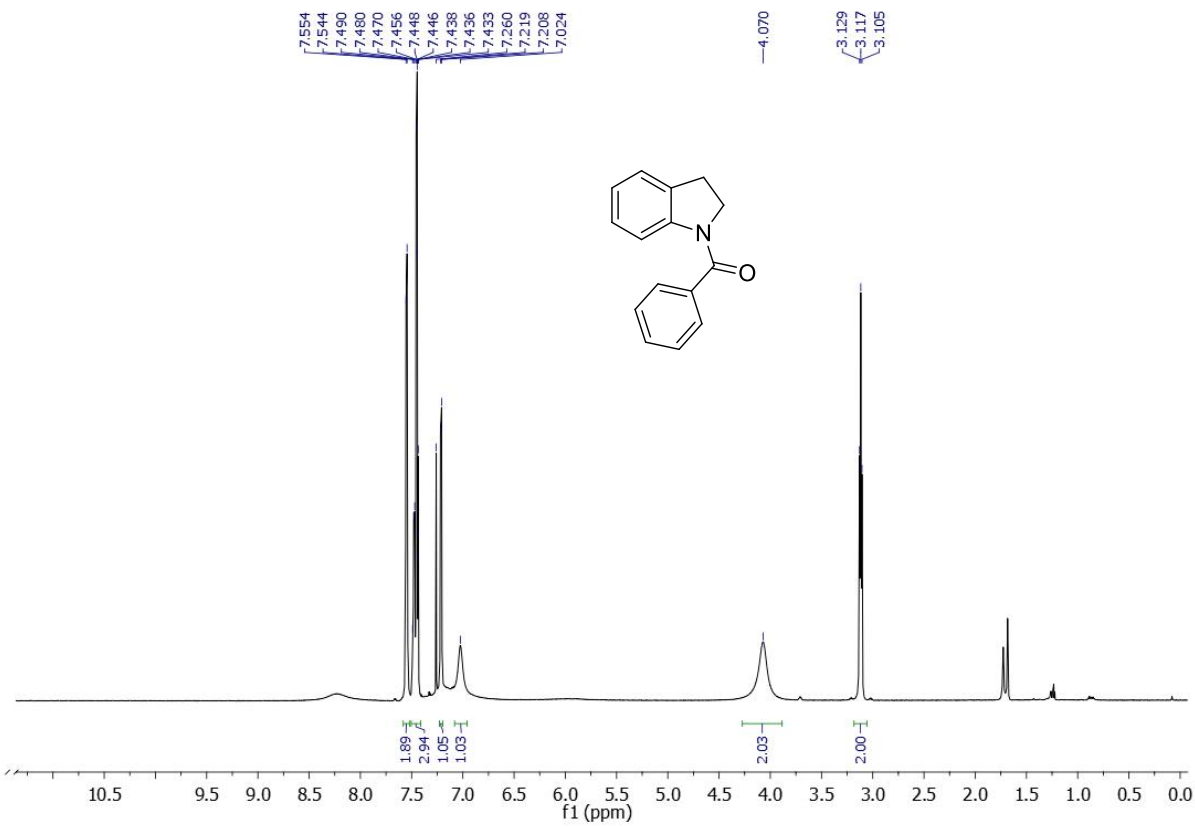


Figure 3.89. [1]H NMR spectrum of Indolin-1-yl(phenyl)methanone **(1j).**

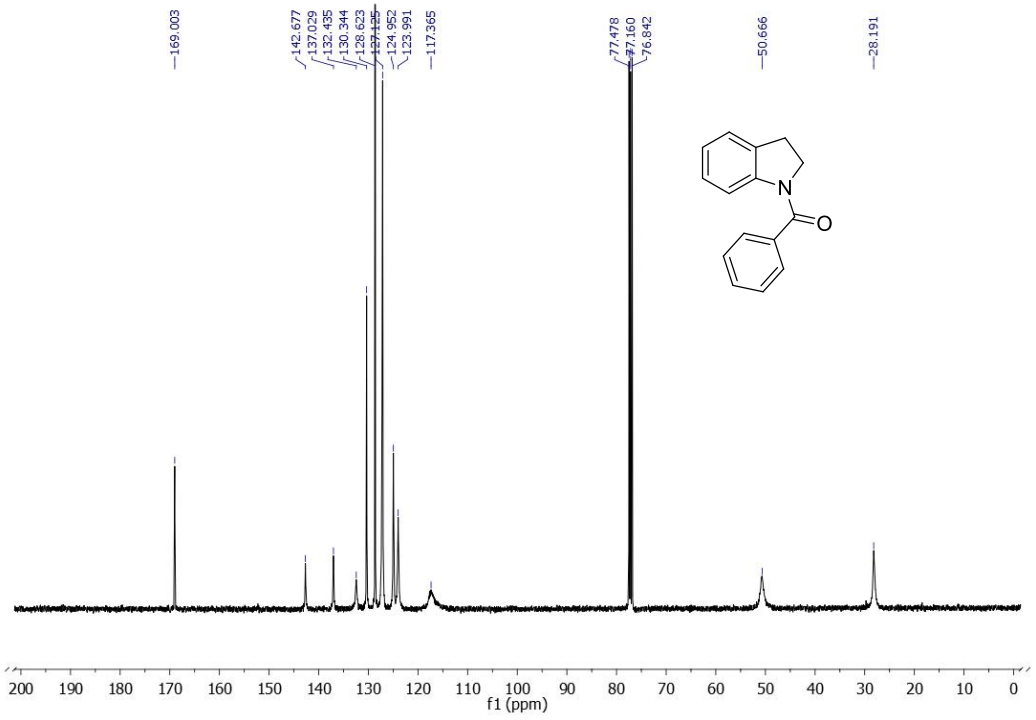


Figure 3.90. [13]C NMR spectrum of Indolin-1-yl(phenyl)methanone **(1j).**

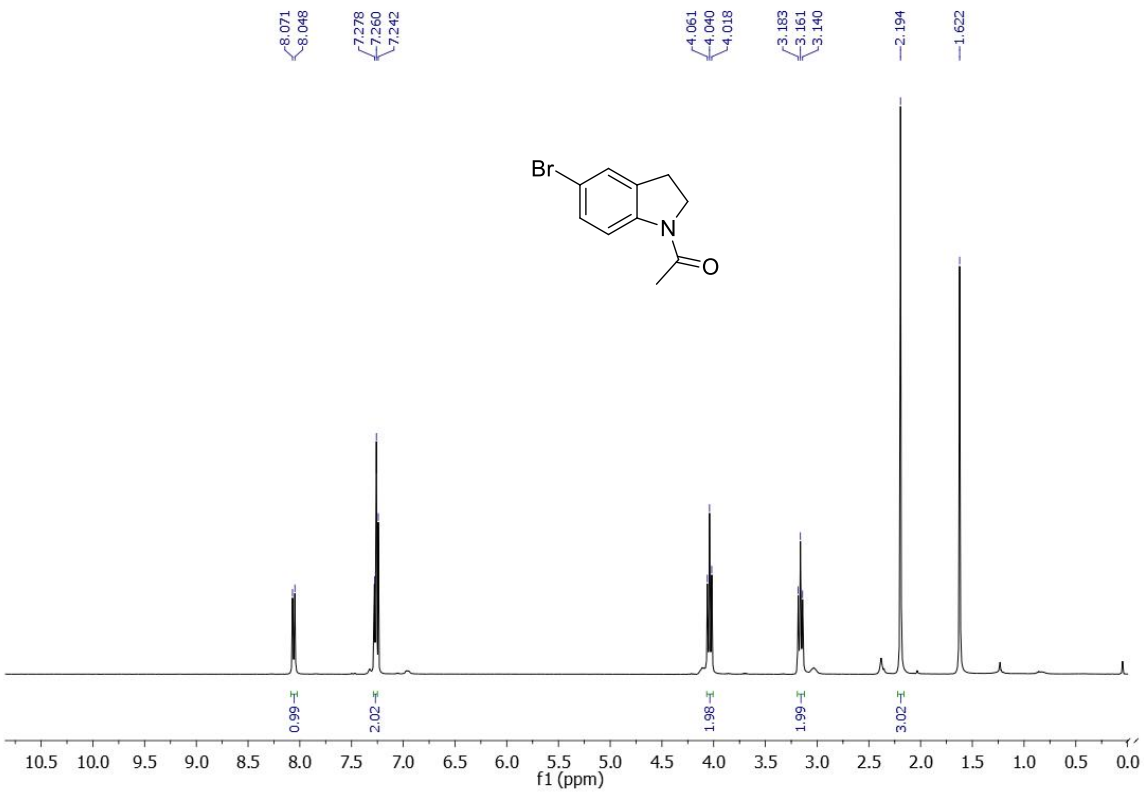


Figure 3.91. ^{1}H NMR spectrum of 1-(5-Bromoindolin-1-yl)ethanone **(1l).**

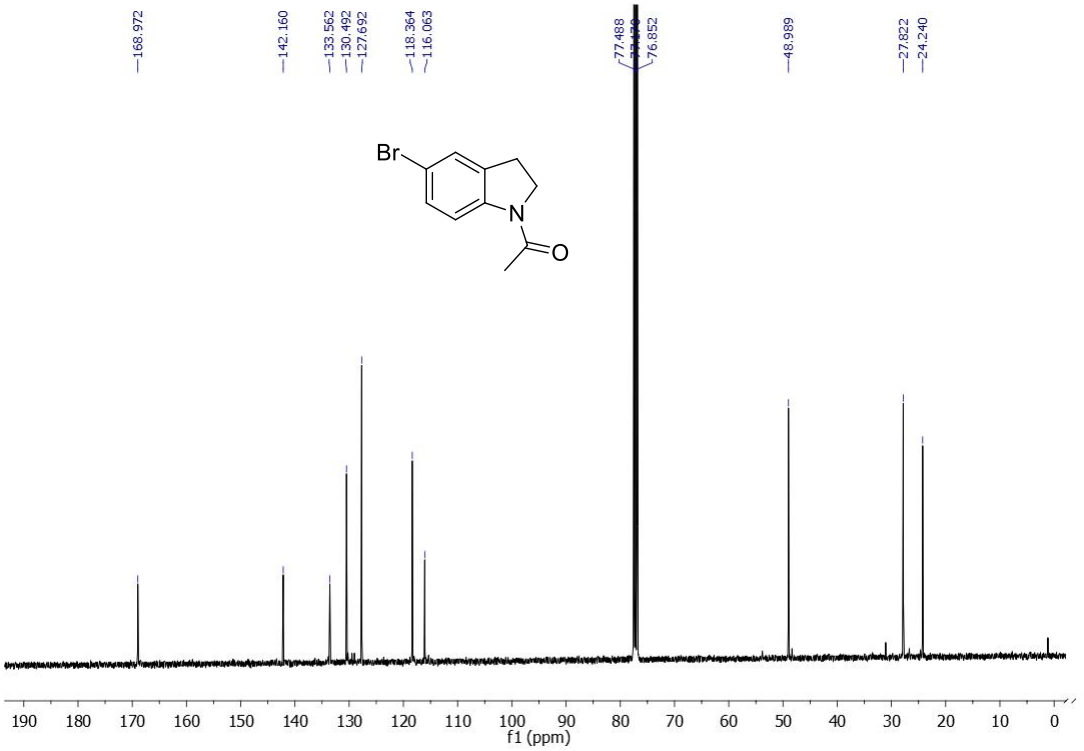


Figure 3.92. ^{13}C NMR spectrum of 1-(5-Bromoindolin-1-yl)ethanone **(1l).**

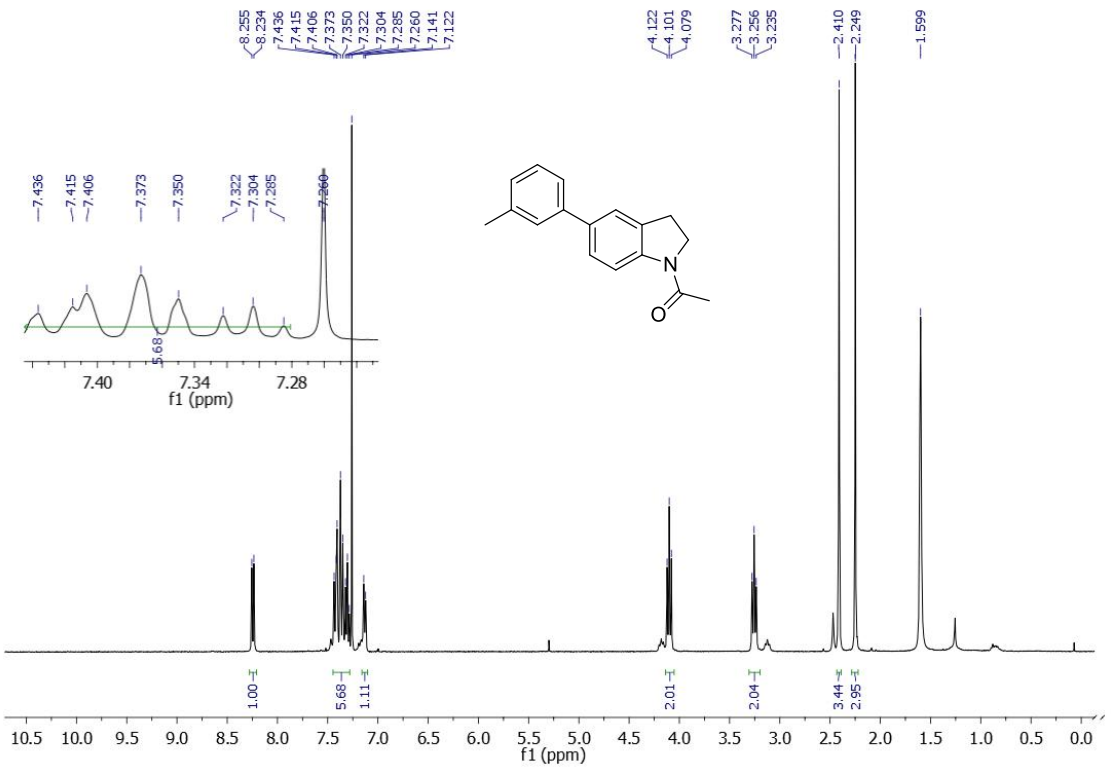


Figure 3.93. ^{1}H NMR spectrum of 1-(5-(m-Tolyl)indolin-1-yl)ethanone **(1m).**

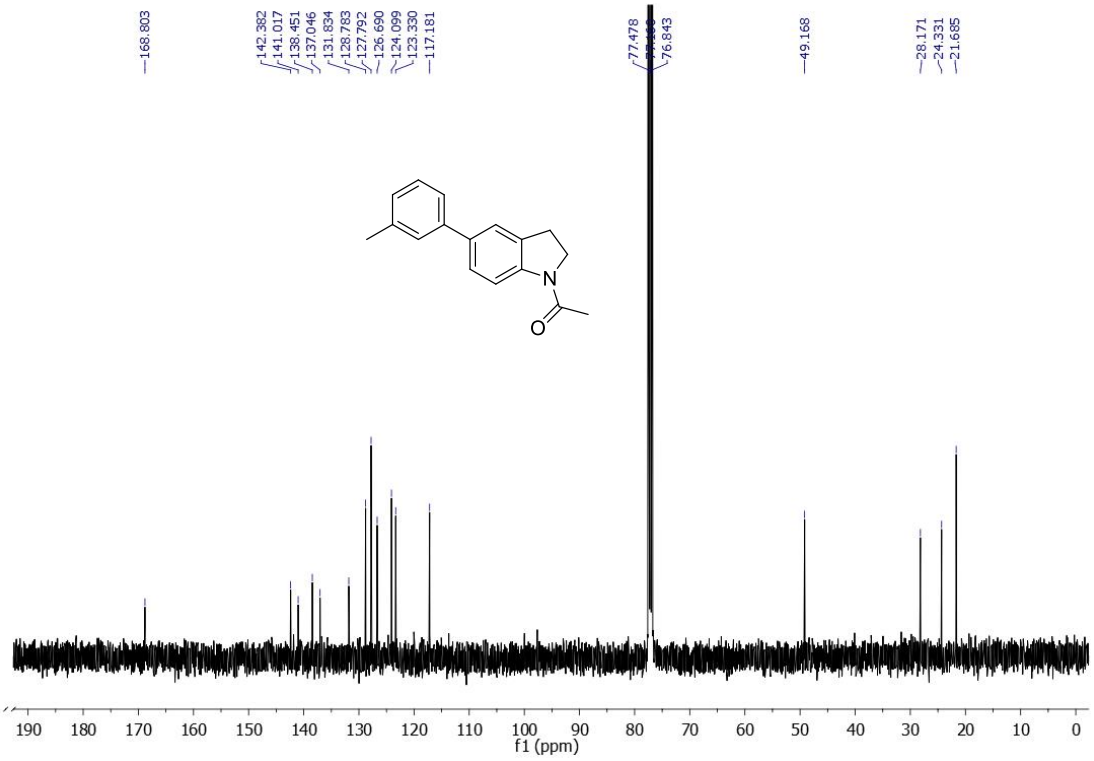


Figure 3.94. ^{13}C NMR spectrum of 1-(5-(m-Tolyl)indolin-1-yl)ethanone **(1m).**

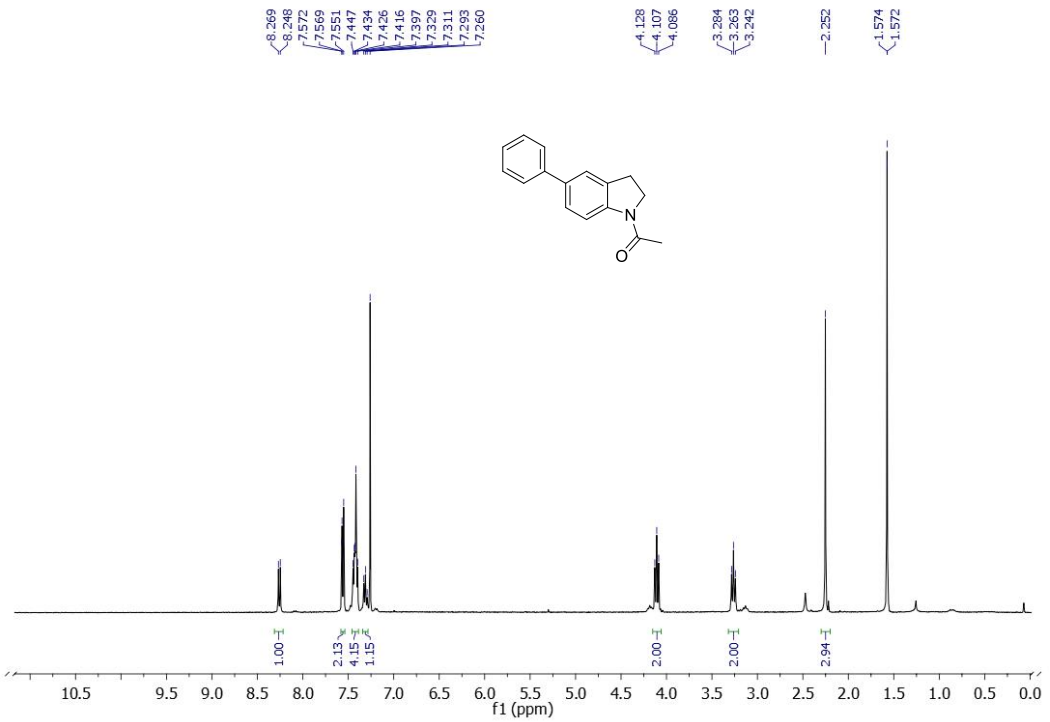


Figure 3.95. [1]H NMR spectrum of 1-(5-Phenylindolin-1-yl)ethanone **(1n).**

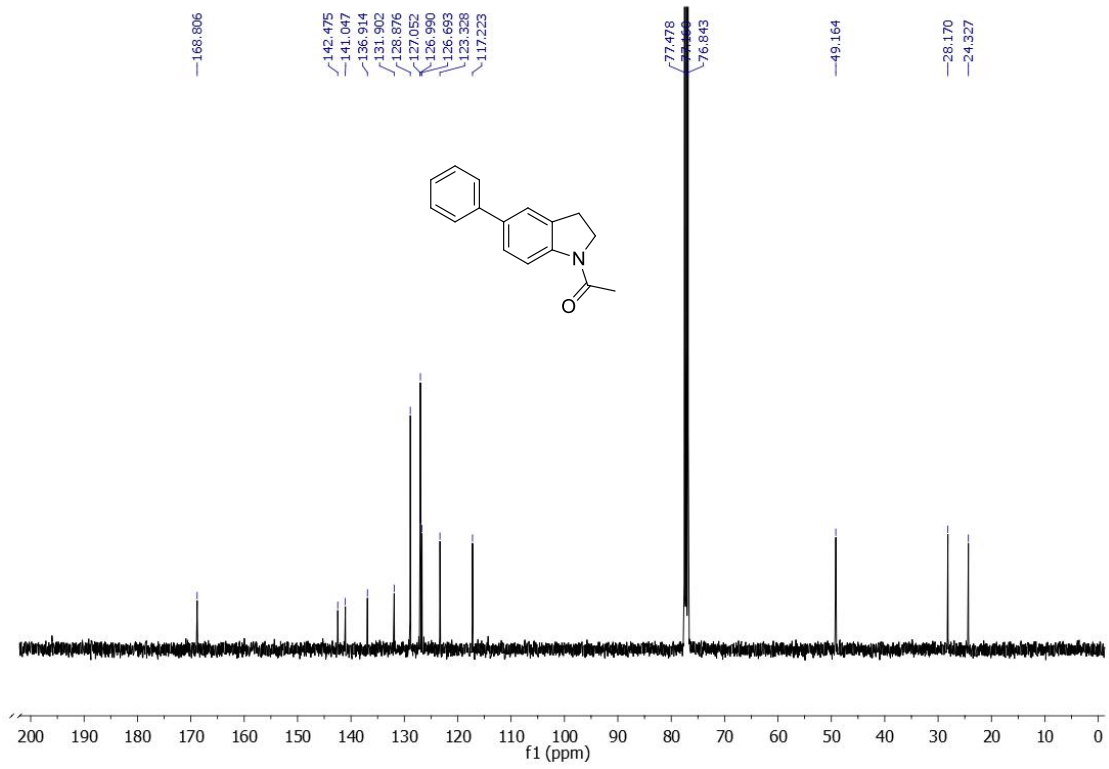


Figure 3.96. [13]C NMR spectrum of 1-(5-Phenylindolin-1-yl)ethanone **(1n).**

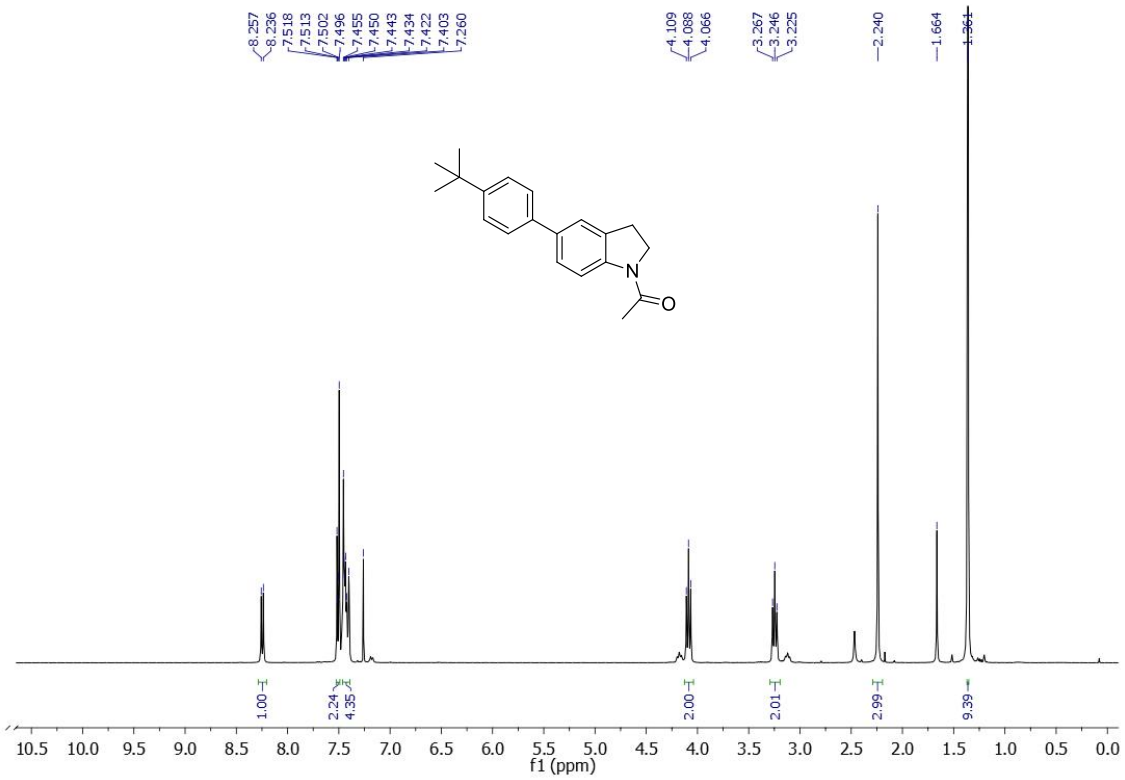


Figure 3.97. [1]H NMR spectrum of 1-(5-(4-(tert-Butyl)phenyl)indolin-1-yl)ethanone **(1o).**

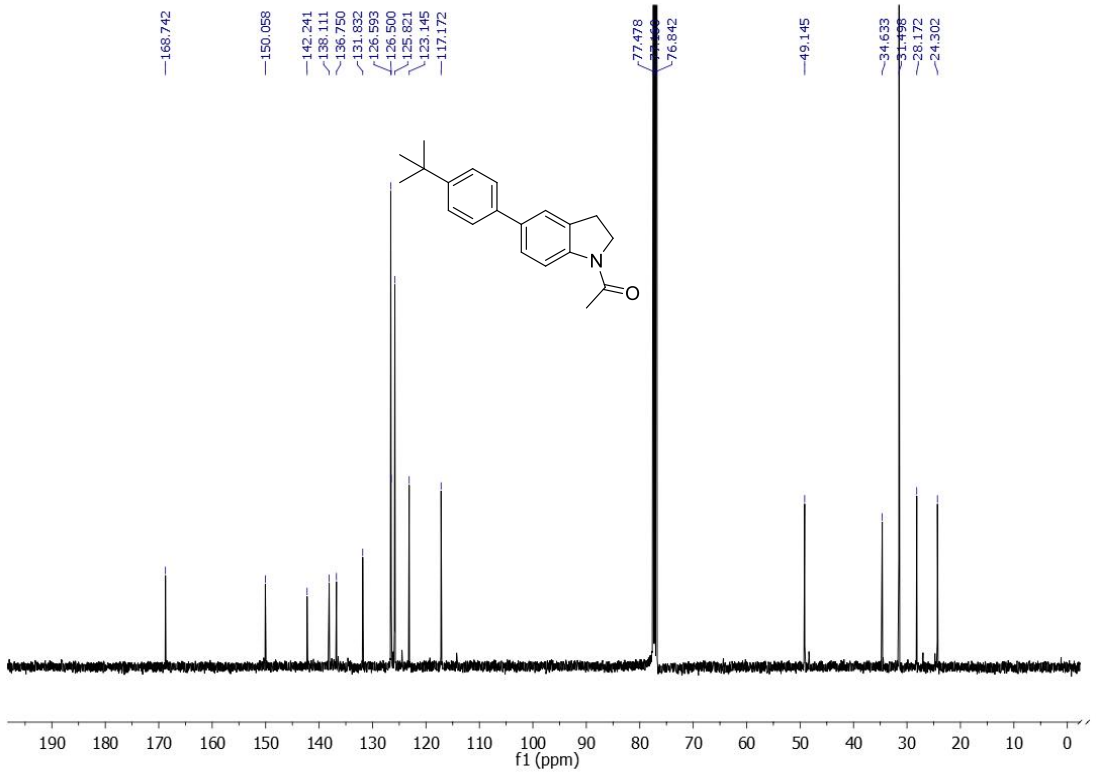


Figure 3.98. [13]C NMR spectrum of 1-(5-(4-(tert-Butyl)phenyl)indolin-1-yl)ethanone **(1o).**

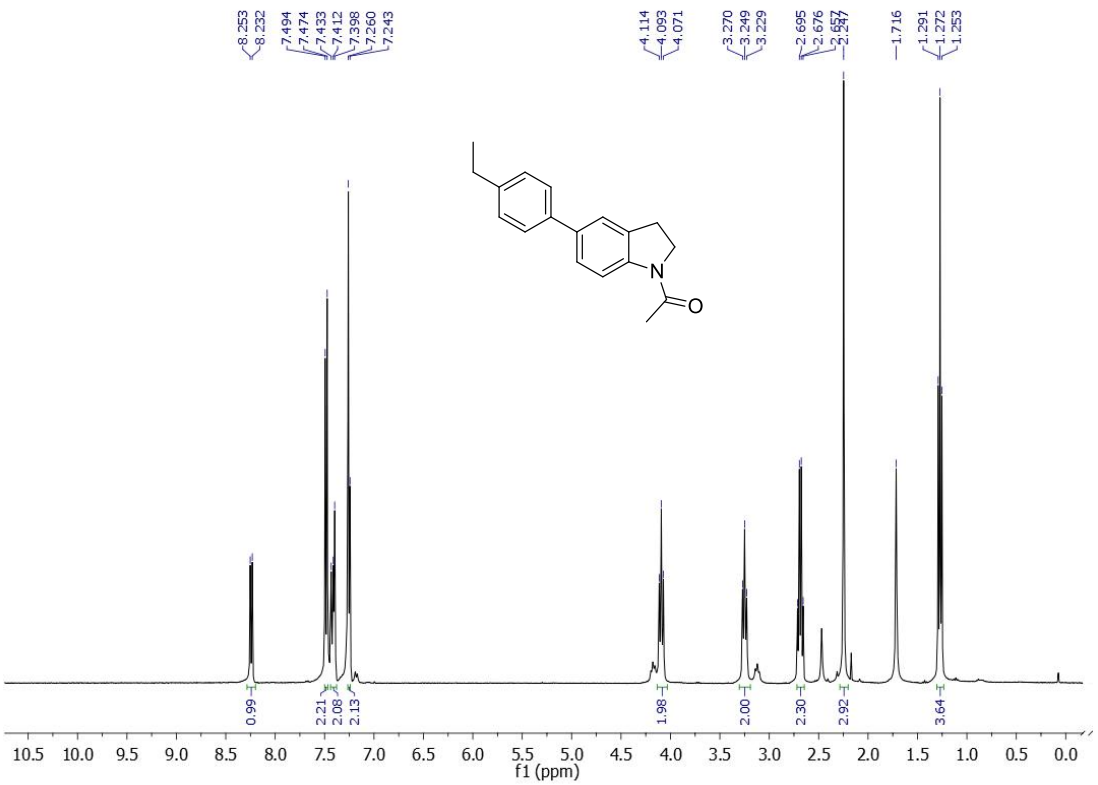


Figure 3.99. [1]H NMR spectrum of 1-(5-(4-Ethylphenyl)indolin-1-yl)ethanone **(1p).**

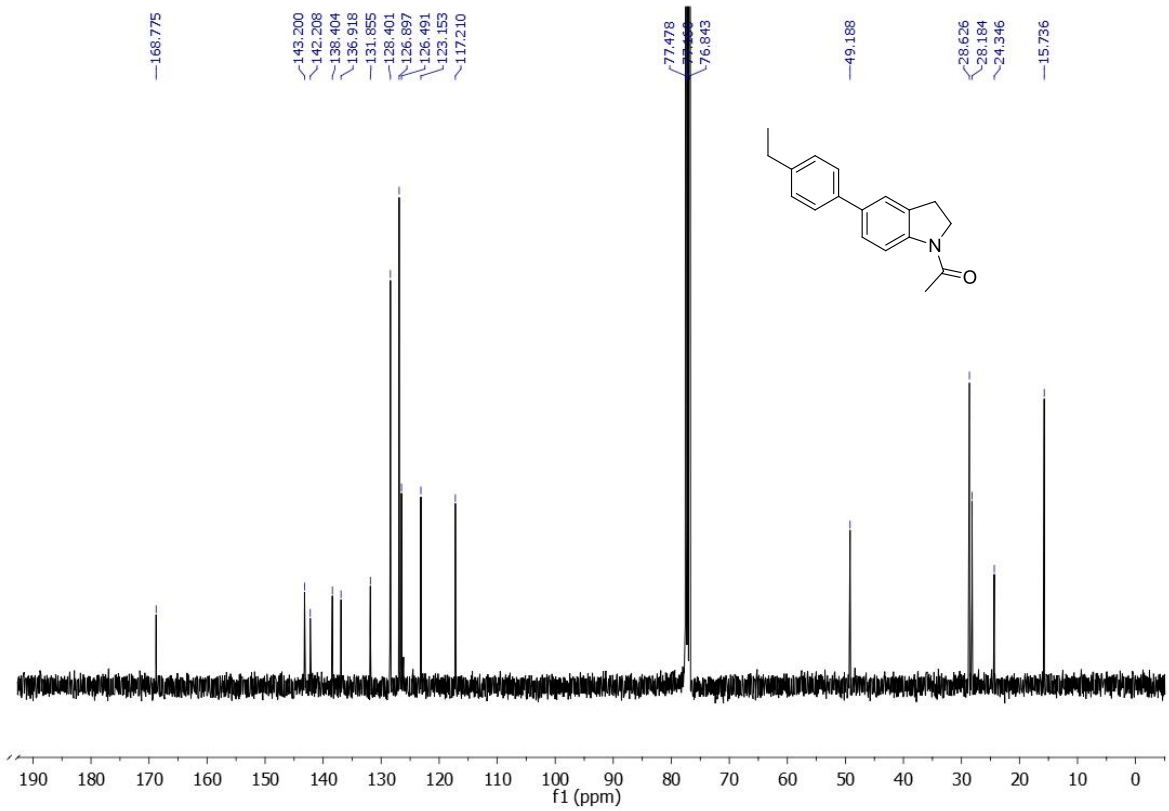


Figure 3.100. [13]C NMR spectrum of 1-(5-(4-Ethylphenyl)indolin-1-yl)ethanone **(1p).**

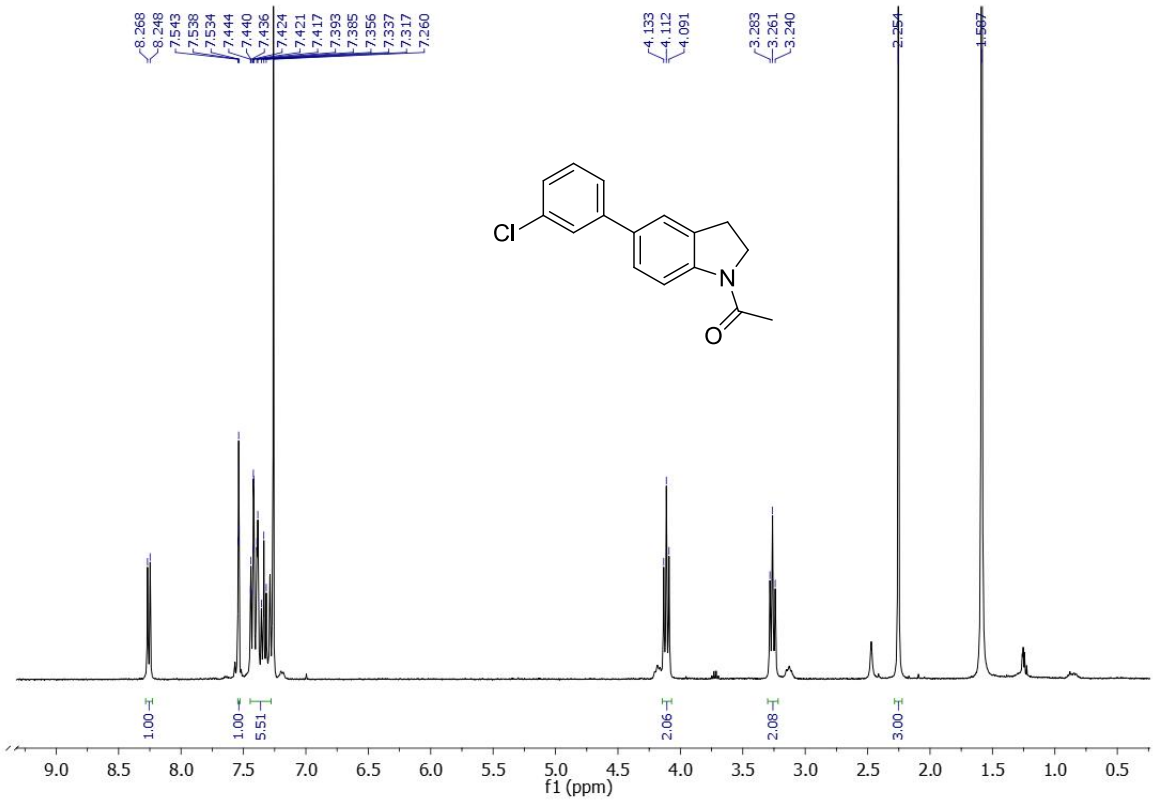


Figure 3.101. ^{1}H NMR spectrum of 1-(5-(3-Chlorophenyl)indolin-1-yl)ethanone **(1q).**

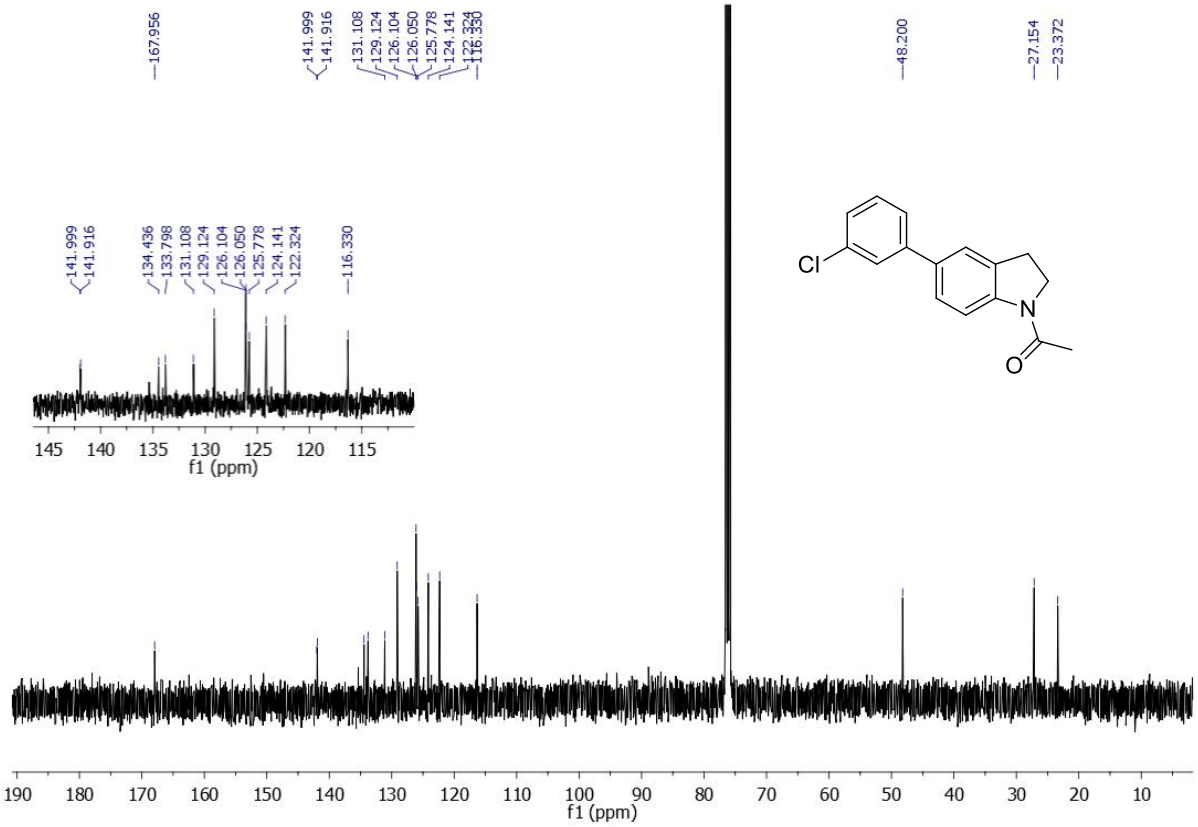


Figure 3.102. ^{13}C NMR spectrum of 1-(5-(3-Chlorophenyl)indolin-1-yl)ethanone **(1q).**

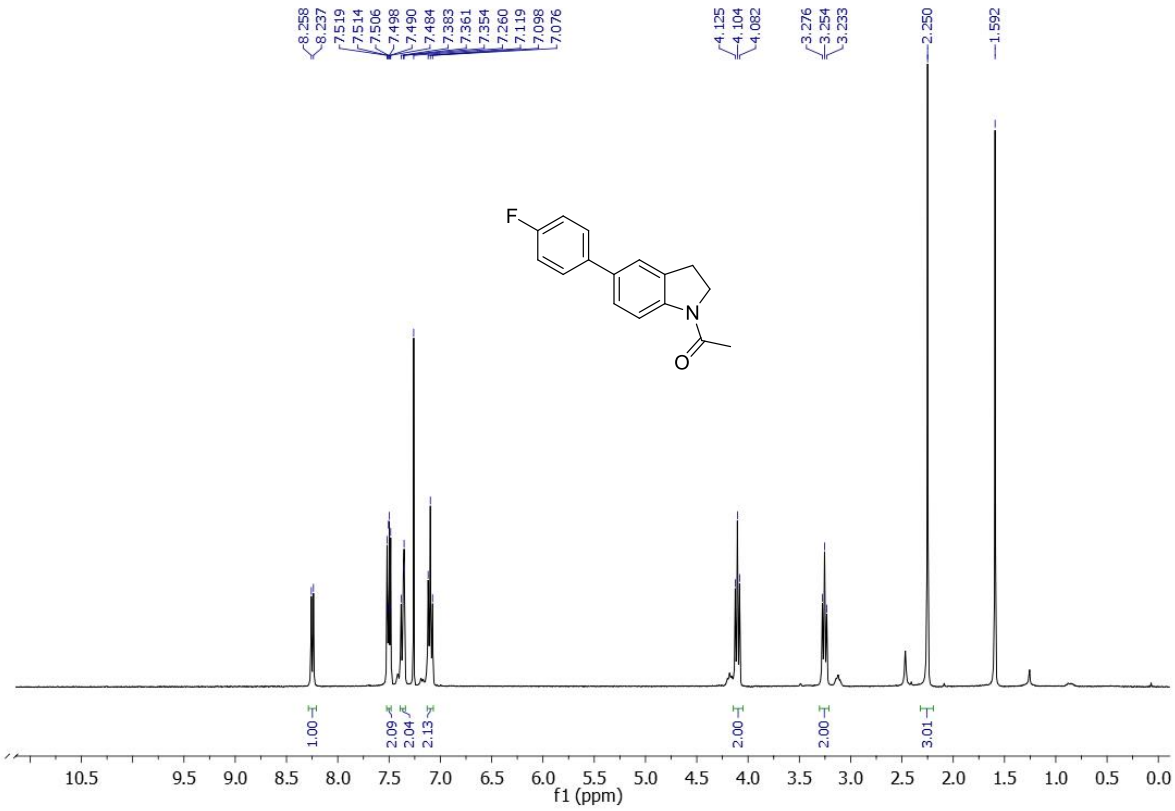


Figure 3.103. ^{1}H NMR spectrum of 1-(5-(4-Fluorophenyl)indolin-1-yl)ethanone **(1r).**

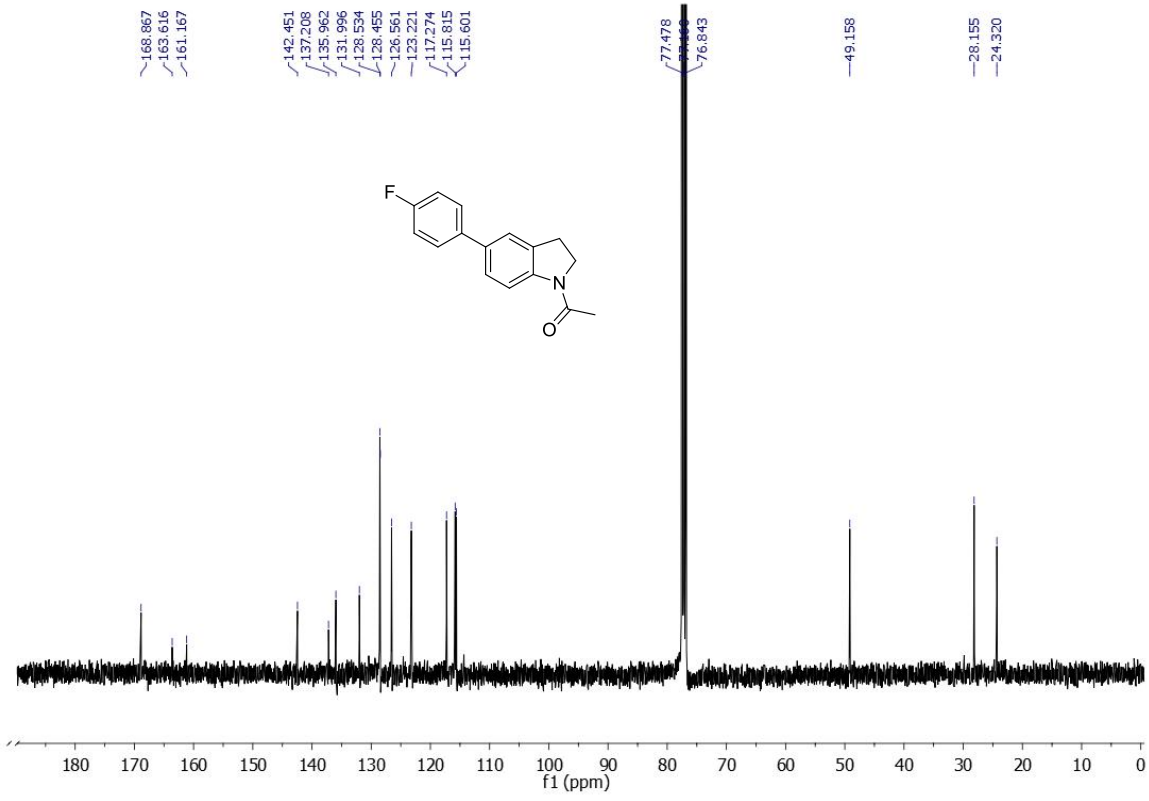


Figure 3.104. ^{13}C NMR spectrum of 1-(5-(4-Fluorophenyl)indolin-1-yl)ethanone **(1r).**

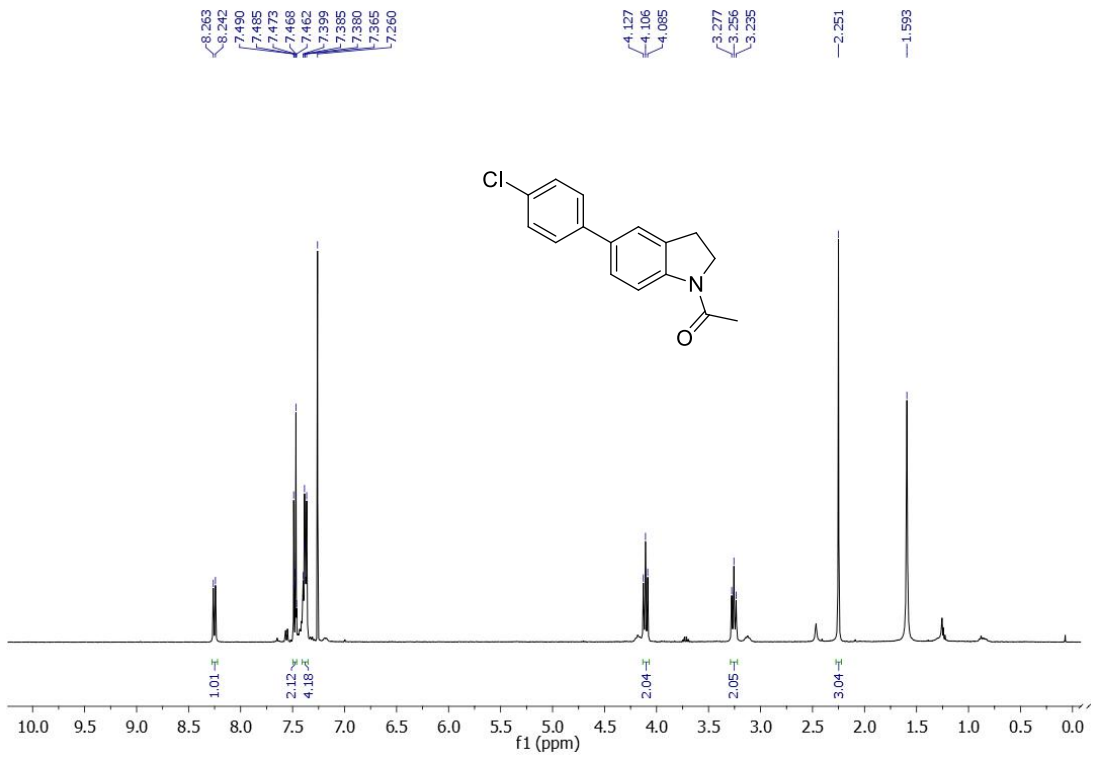


Figure 3.105. ^{1}H NMR spectrum of 1-(5-(4-Chlorophenyl)indolin-1-yl)ethanone **(1s).**

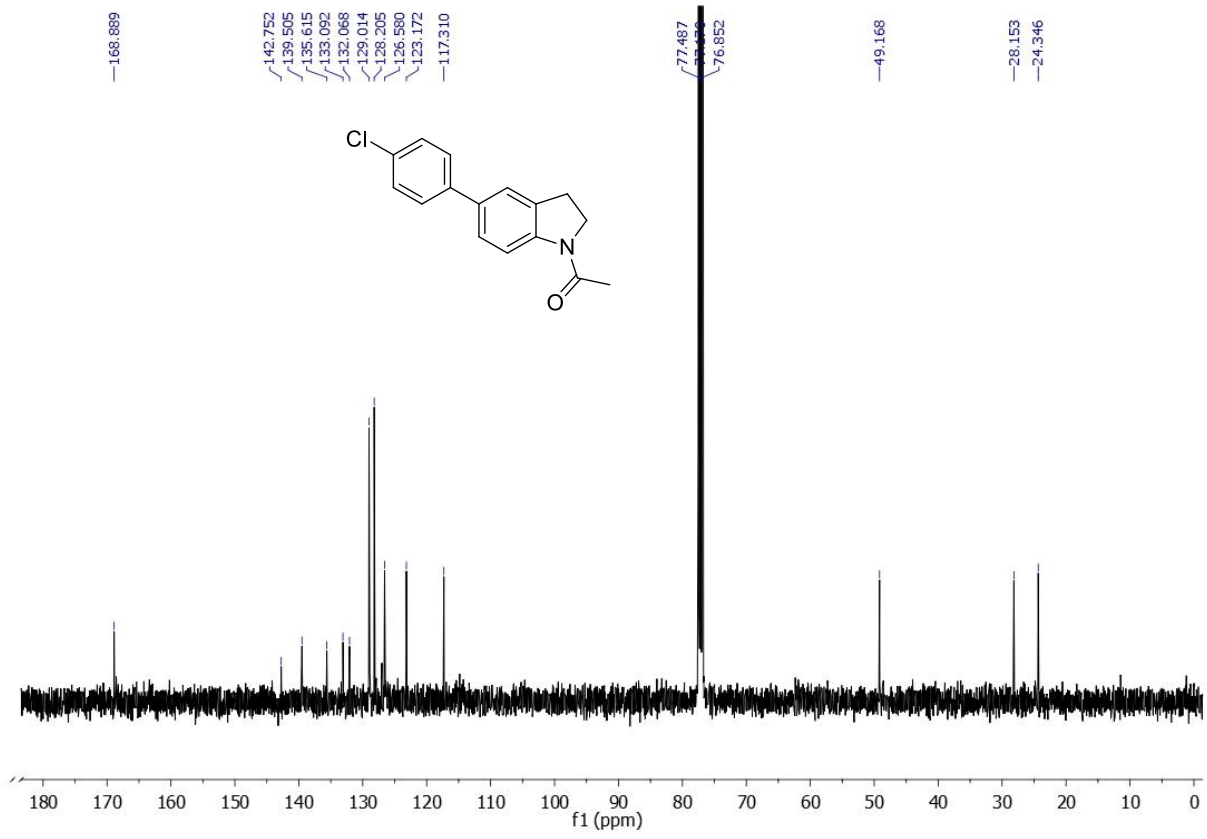


Figure 3.106. ^{13}C NMR spectrum of 1-(5-(4-Chlorophenyl)indolin-1-yl)ethanone **(1s).**

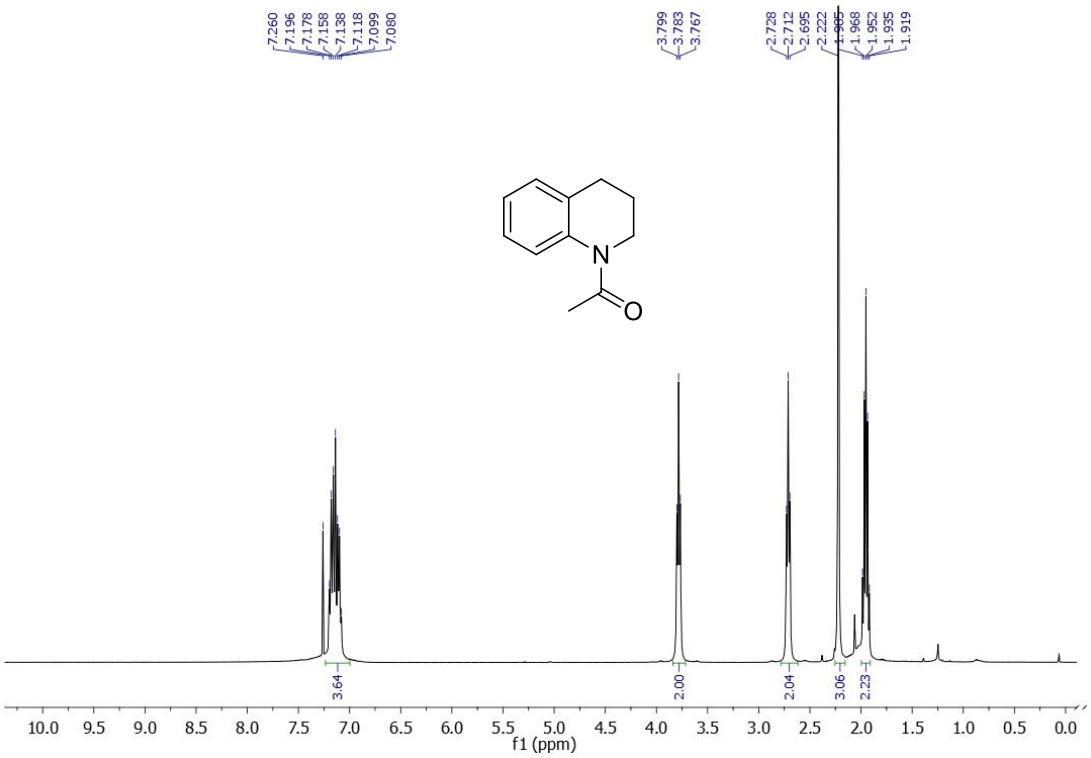


Figure 3.107. ^{1}H NMR spectrum of 1-(3,4-Dihydroquinolin-1(2H)-yl)ethanone **(4).**

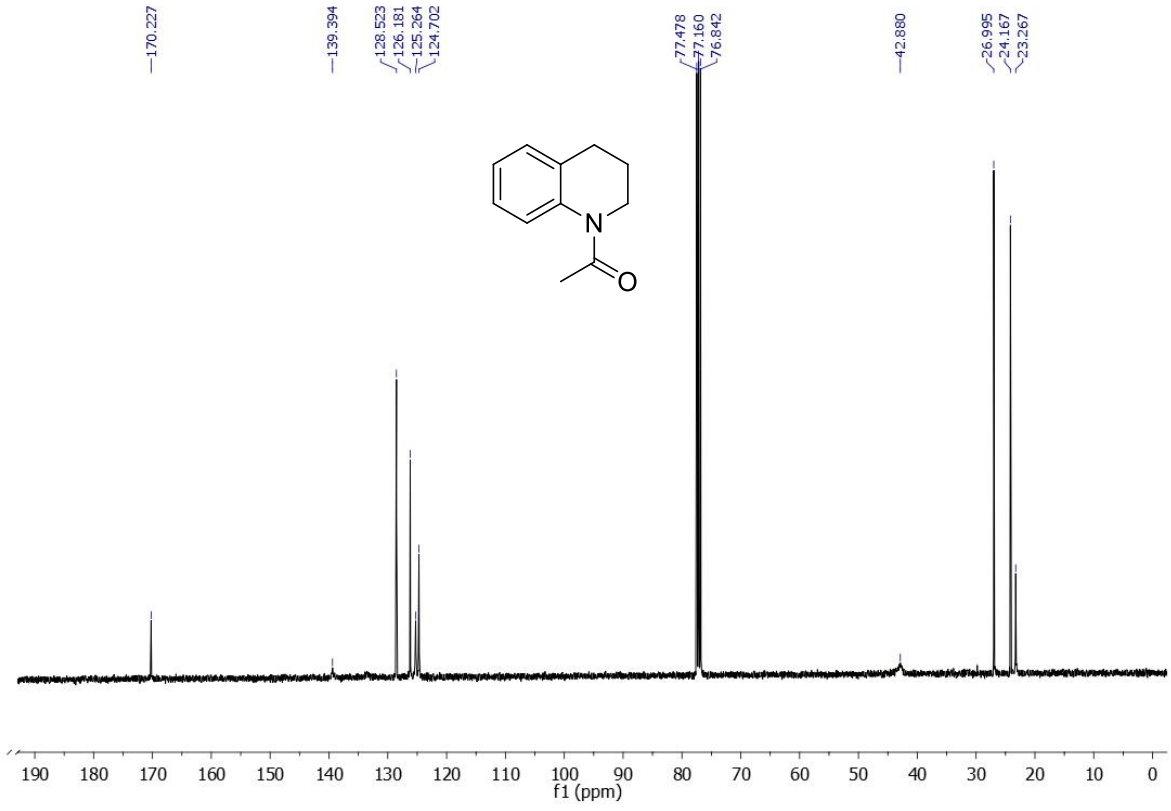
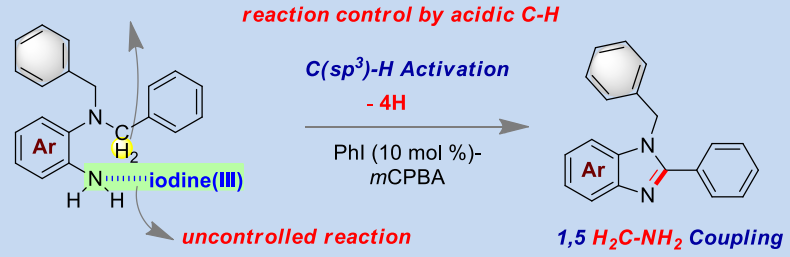


Figure 3.108. ^{13}C NMR spectrum of 1-(3,4-Dihydroquinolin-1(2H)-yl)ethanone **(4).**

CHAPTER 4

Organocatalytic Intramolecular Oxidative C(sp^3)-H Imination Reaction for Benzimidazole Synthesis

4.1 ABSTRACT

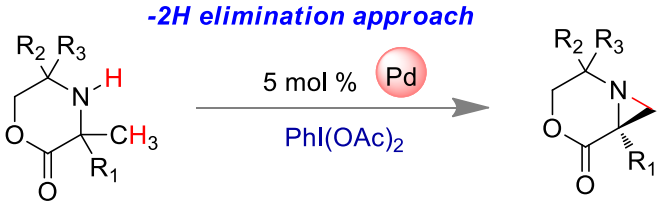


Development of sustainable methods for the activation of less reactive undirected C(sp^3)-H bonds is challenging but desirable in organic synthesis. Herein, successful reaction between highly exothermic primary amine - polyvalent iodine has been demonstared for a dehydrogenative C-H imination *via* selective activation of acidic C(sp^3)-H group by 4H elimination. At 1,5 distances C(sp^3)−H imination was voluntarily done *via* organocatalysis using simplest organoiodine reagent PhI (10 mol %)-*m*CPBA at normal reaction condition.

4.2 INTRODUCTION

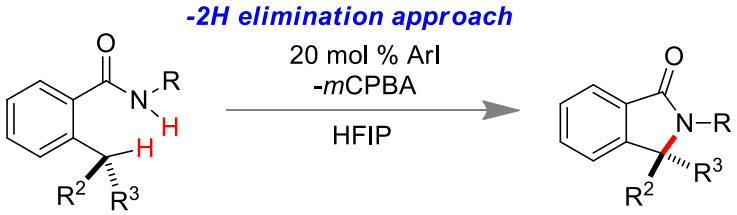
Many enzyme mediated selective oxidation of unactivated aliphatic C-H bonds are known in literature. However, it remains challenging to the synthetic chemists due to lack of suitable reagents.[1] The C(sp^3)-H bonds are comparitively less reactive than C(sp^2)-H because of their higher thermodynamic stability. Expansion of synthetic methods for the transformation of undirected C(sp^3)-H bonds into other valuable functionalities are of huge importance but remains challenging in research.[2] *N*-containing heterocycles are widespread in innumerable

synthetic pharmaceuticals and natural products. Intramolecular C-N bond formation reaction is one of the most targeted approaches in generating N-heterocycles. Major literature reports for C(sp^3)-H amination reactions are based on transition metal catalysis or by radical initiated pathway.[3-10] Due to their profusion in medicinally active molecules and bio-active products, it's difficult to overstress the importance of nitrogen-based heterocyclic rings. Therefore construction of C-N bonds has become a primary subject of research in organic chemistry. Dehydrogenative cross coupling (DCC) between N-H and C-H bonds signify one of the common methods in C-N bond synthesis due to non-requisite of prefunctionalization of substrate. One of the outstanding example is Pd(II)-catalyzed three membered strained heterocyclic synthesis by aliphatic C-H amination *via* 2H elimination, demonstrated by Gaunt and co-workers (Scheme 4.1).[11]



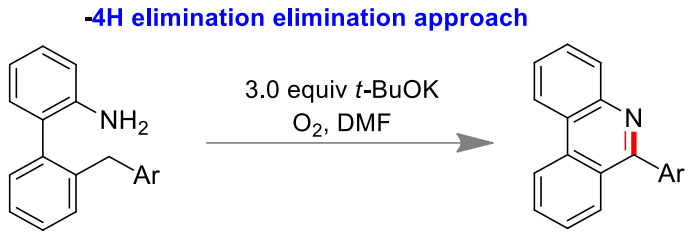
Scheme 4.1. Gaunt's Pd-catalyzed C-H amination approach.

Similarly towards development of 2H elimination methodology for the synthesis of γ-lactams, Shi and coworkers have shown intramolecular C-H amination reaction *via* iodoarene-catalysis (Scheme 4.2).[12]



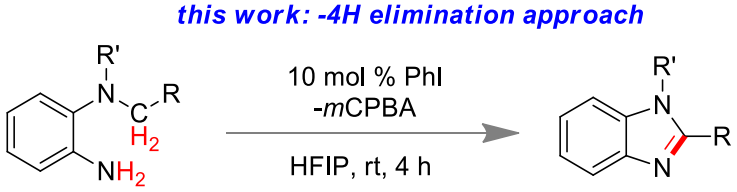
Scheme 4.2. Shi's intramolecular C-H amination approach.

In compared to C(sp^3)-H amination reactions, imination reactions are more difficult as formation of imine from the $–CH_2$ and $–NH_2$ containing groups with 4H elimination is thermodynamically unfavourable.[13,14] Alabugin with co-workers established a Fe(II)-catalyzed oxidative C-H imination reaction[15] *via* single electron transfer (SET). Later, they have established a transition metal-free method for similar kind of transformation by using strong base like ^{t}BuOK under aerobic condition (Scheme 4.3).[16] However, both the methods hold certain pitfalls such as the use of transition metal salts as catalysts, strong bases in excess amount, etc.



Scheme 4.3. Alabugin's intramolecular imination approach.

However, the present work is based on the direct functionalization of two aliphatic-C(sp^3)H and two aryl-N(sp^3)H at 1,5 positions for an imination reaction in absence of any metal or strong base using organocatalysis to achieve 4H elimination in a single step at room temperature (Scheme 4.4).



Scheme 4.4. Our 1,5 aliphatic-CH_2 - aryl-NH_2 imination approach using organocatalysis.

This unprecedented C-H imination reaction represents another unique addition towards our recent contribution in polyvalent iodine reagents in organic synthesis.[17-21] Thus an additive

free approach based on intramolecular C(sp3)-H imination reaction *via* organocatalysis is developed using PhI (10 mol%)-*m*CPBA.[22-24] Using simplest organoiodine reagent PhI as catalyst with only 10 mol % loading is the key improvement of this protocol.

4.3 RESULT AND DISCUSSION

Ammonia and iodine mixture is known to be *contact explosive* since it forms NI_3 which is explosive.[25] The hypervalent iodines reagents[26] are identified to undergo explosive reaction with amines.[27] Hence, synthetic transformations using primary or secondary amines and hypervalent iodines reacting together at room temperature is difficult.[28,29] in general, the uncontrolled reaction of primary amines are restricted by converting them into secondary amine with introduction of various protecting groups at *N*-center of amines. Here, the reactivity of unprotected primary amine with iodine(III) reagent has been controlled by introducing acidic hydrogens in the same molecule. Iodine(III) reagents were generated *in situ* using the iodobenzene (PhI)-*m*CPBA (*meta*-chloroperbenzoic acid) combinations.[30] Neither aniline nor *N,N*-dibenzylaniline reacted with iodine(III) reagents in a controlled manner to give any desired product at room temperature and no selectivity in product formation was observed (Figure 4.1a). N^1,N^1-dibenzylbenzene-1,2-diamine (Figure 4.1b) which is a combination of aniline and *N,N*-dibenzylaniline underwent successful reaction to give 1-benzyl-2-phenyl-benzo[d]imidazole under *in situ* generated iodine(III) environment. When the reacting components were allowed to come at maximum contact simply by neat mixing, similar observation like HFIP solvent system was made (Figure 4.1).[29] We foresee, that the explosive reaction of aniline could be controlled due to the presence of acidic hydrogens (CH_2) in the same molecule at benzylic position.

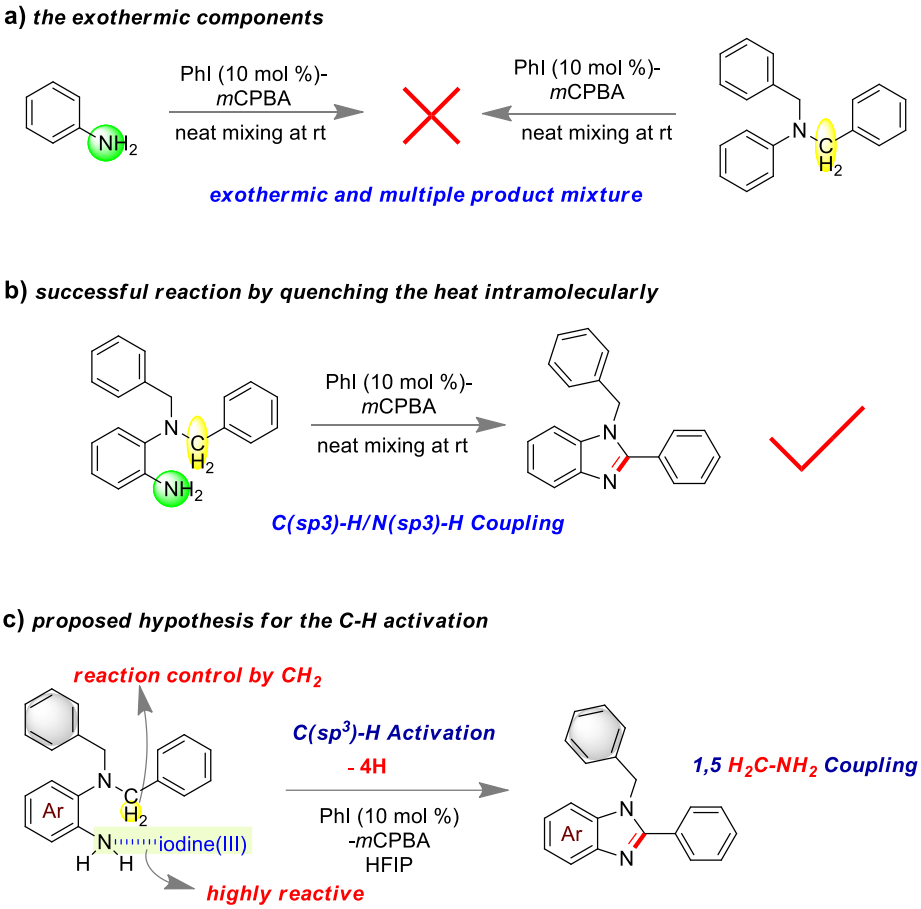
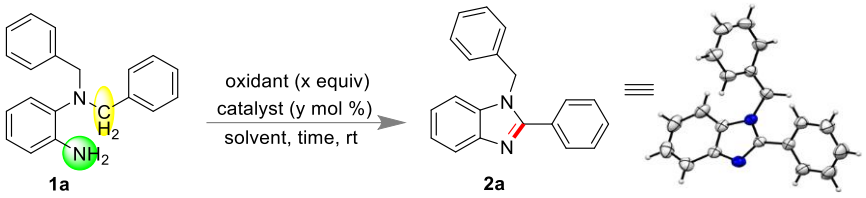


Figure 4.1. a) Observed exothermic reactions. b) The oxidative C-N bond formation by two aliphatic-C(sp^3)H and two aryl-N(sp^3)H imination. c) The hypothesis of acidic C-H functionalization.

To get the optimized condition (Table 4.1), N^1,N^1-dibenzylbenzene-1,2-diamine (**1a**) was treated with several reaction conditions. Successfully, 82% of 1-benzyl-2-phenyl-benzo[d]imidazole (**2a**) was obtained when N^1,N^1-dibenzylbenzene-1,2-diamine (**1a**) was reacted with 2.0 equiv of $PhI(OAC)_2$ (PIDA) in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP)[31] solvent, (entry 1) within 1.5 h at room temperature and open atmospheric condition. Further, the structure of **2a** was clearly confirmed by single crystal X-ray analysis. However, the reaction led to 72% of product formation in solvent trifluoroethanol (TFE) within 2 h (entry 2). Inferior results were obtained in other solvents like dichloromethane (DCM), acetonitrile (ACN) and dichloroethane (DCE), 1,4-dioxane gave (entry 3-6). Similarly the results with PIFA (bis(trifluoroacetoxy)iodobenzene) or $PhI(OPiv)_2$ (bis(tert-

butylcarbonyloxy)iodobenzene) were also not encouraging (entry 7-8). With further analysis it was found that, organocatalytic method was more successful than the stoichiometric iodine(III) reagent. Using iodobenzene (PhI) in presence of oxidizing agent like *meta*-chloroperbenzoic acid (*m*CPBA), organocatalytic version of iodine(III) reagent was generated *in situ* . Several condition of organocatalytic version was tried and it was found that 10 mol % PhI, 2.5 equiv of *m*CPBA and 4h reaction time was the optimum condition for the conversion (entry 13).

Table 4.1. Condition Optimization.



Entry	oxidant (equiv)	catalyst (mol %)	Solvent	time (h)	yield %[a]
1	PIDA (2)	---	HFIP	1.5	82
2	PIDA (2)	---	TFE	2	72
3	PIDA (2)	---	DCM	16	18
4	PIDA (2)	---	CAN	16	NR
5	PIDA (2)	---	DCE	16	NR
6	PIDA (2)	---	1,4-Dioxane	16	50
7	PIFA (2)	---	HFIP	1.5	55
8	$PhI(OPiv)_2$ (2)	---	HFIP	1	61
9	*m*CPBA (2.25)	PhI (20)	HFIP	1.5	75
10	*m*CPBA (2.5)	PhI (20)	HFIP	1.5	84
11	*m*CPBA (2.5)	PhI (20)	TFE	2	68
12	*m*CPBA (2.5)	PhI (20)	HFIP:DCM[b]	3	89

13	*m*CPBA (2.5)	PhI (10)	HFIP:DCM[b]	4	89

[a]isolated yield after column chromatographic purification. [b] HFIP:DCM ratio is 2:1

At the standard condition, the eficacy of the method was verified with a broad range of functional substrates (Figure 4.2). Electron donating methoxy (-OMe) group (**2b**, **2d**, **2g**, **2h**, **2l**) containing benzyl amines gave good yields of 1,2-disubstituted benzimidazoles up to 88-92%. Benzyl amine with electron withdrawing halide groups in benzene ring (**2j**, **2k**, **2m**) also did not affect much towards the yields of the reaction (75-80%). The exclusive chemoselectivity was observed in case of the substrates **2e**-**2h** and **2j**-**2m** where less acidic hydrogen containing methyl, ethyl or isopropyl groups were present. Complete regioselective product dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline (**2i**) was isolated in 78% yield form the corresponding 2-(3,4-dihydroisoquinolin-2-yl)aniline (**1i**).

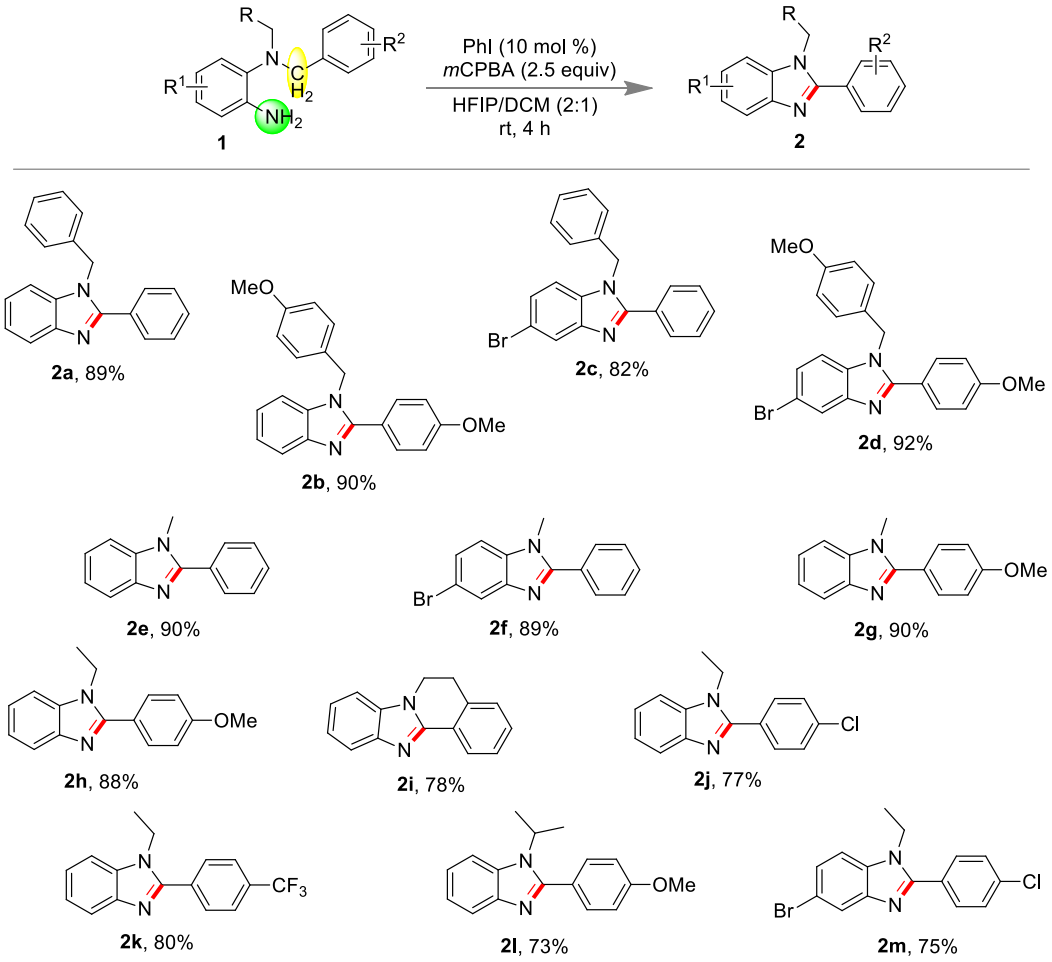


Figure 4.2. Scope of C-H imination reaction.

For substrates with symmetrical dibenzyl amines single product of benzimidazoles (**2a-2d**) were isolated in good yields (Figure 4.2). While dealing of unsymmetrical dibenzyl amines we could observe electronic effect of the substituent of aryl rings for product selectivity (Figure 4.3). Several substrates having electron donating as well as electron with drawing were tested under standard condition where major product was the imination at the benzylic carbon center containing with more electron rich arenes. Electron donating group containing derivatives (**2p-2r**) resulted in the formation of benzimidazoles with good to excellent overall yield (up to 91%). Electron withdrawing (**2u**) as well as sterically hindered *ortho* methyl substituted substrates (**2s**, **2t**) underwent smooth reaction to give 75-85% overall product formation.

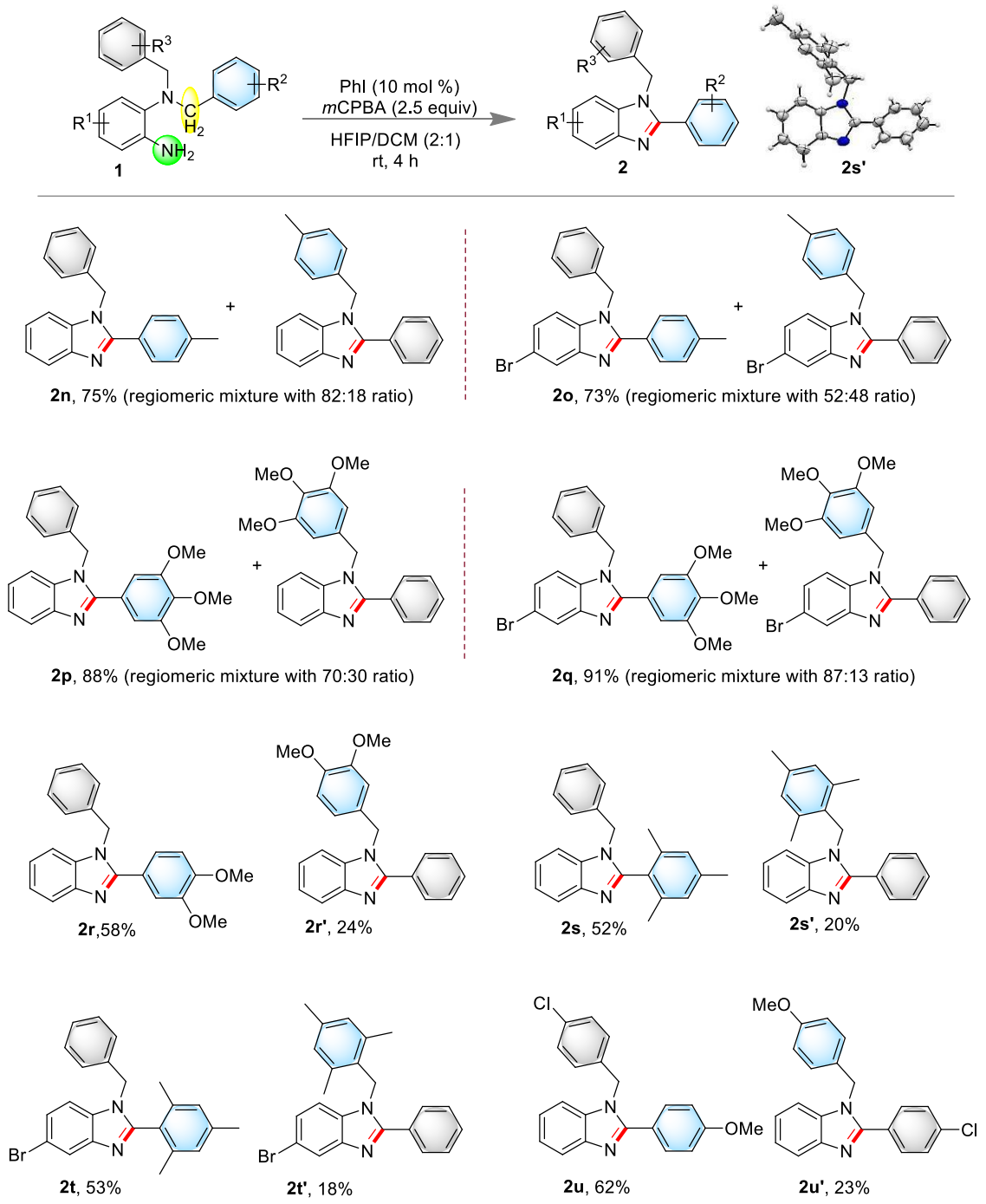


Figure 4.3. Electronic effects of *N*-alkyl substituents.

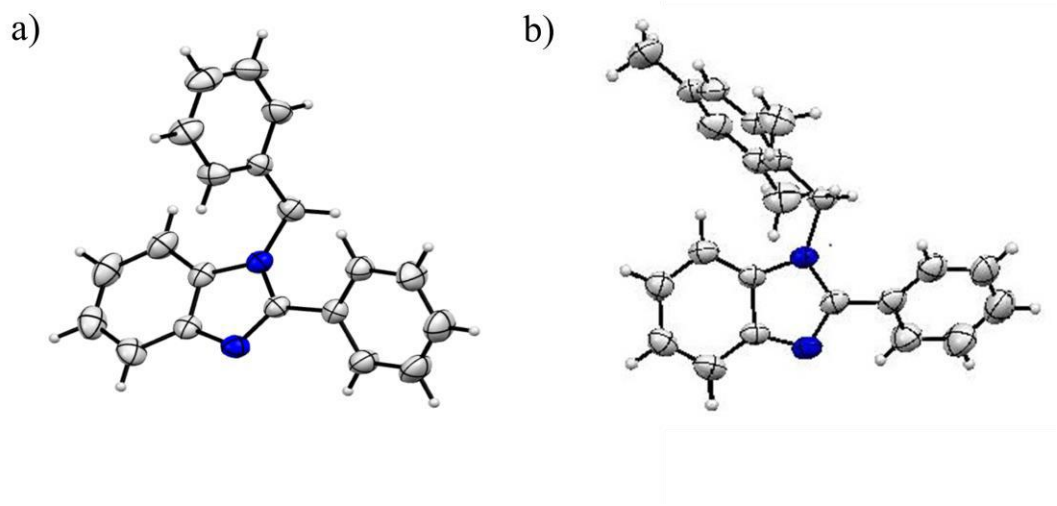


Figure 4.4. a) Crystal structure of compound **2a (CCDC: 1812137)**. b) Crystal structure of compound **2s' (CCDC: 1867630)**.

To get insight into the reaction mechanism several control experiments were performed Figure 4.5. When substrate **1a** was treated with 2.0 equiv of radical scavenger TEMPO (2,2,6,6- Tetramethylpiperidin-1-yl-oxyl) under standard condition, 74% of **2a** was isolated (Figure 4.5a). Formation of desired product with good amount ruled out probability of radical intermediate during the reaction. Also, the substrate **1a** was alkylated to obtain mono-butylated product *N*,*N*-dibenzyl-N-butylbenzene-1,2-diamine **3**. When this model substrate **3** was treated under standard condition, the formation of intermediate **4** (Figure 4.5b) was detected under ESI-MS (supporting information, Figure. 4.110). Intermediate **4** suggested the formation of dihydrobenzimidazole type intermediate in the reaction pathway which subsequently indicates iminium ion could be the key intermediate in the transformation.

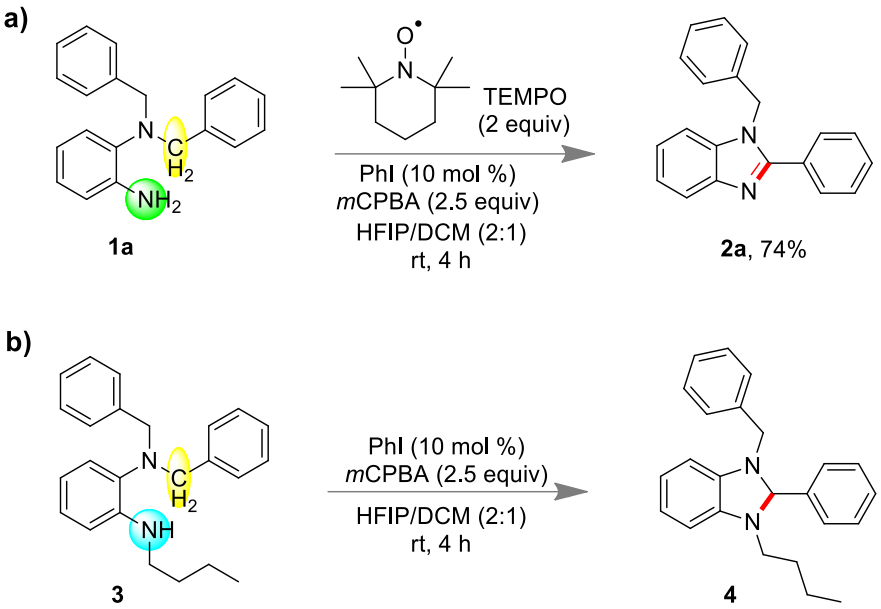


Figure 4.5. Control experiments.

A plausible mechanism for the imination reaction *via* 4H – elimination has been drawn from the observations made from control experiments and it is pictorised in Figure 4.6. At first iodine(III) species has been formed from iodobenzene with the help of oxidant *m*CPBA which itself gets reduced into *meta*-chlorobenzoic acid (*m*CBA). The tertiary amine group which is substituted with two electron donating alkyl groups is expected to have greater nucleophilicity towards iodine(III) reagent than free amine. Thus nucleophilic attack from electron rich tertiary amine nitrogen to iodine centre of *in situ* generated iodine(III) reagent produce intermediate **5**. The carboxylate ion abstract one alkyl proton to give iminium ion intermediate **6** with the reductive elimination of iodobenzene.[32] The monovalent iodobenzene is further oxidized by additional amount of *m*CPBA to generate iodine(III) again. Primary amine undergoes intramolecular nucleophilic addition to benzylic carbocation which results in the formation of cyclized intermediate **7**. Oxidation of intermediate **7** by iodine(III) oxidant help the aromatization to give 1,2-disubstituted benzimidazole **2** *via* another elimination of 2H.

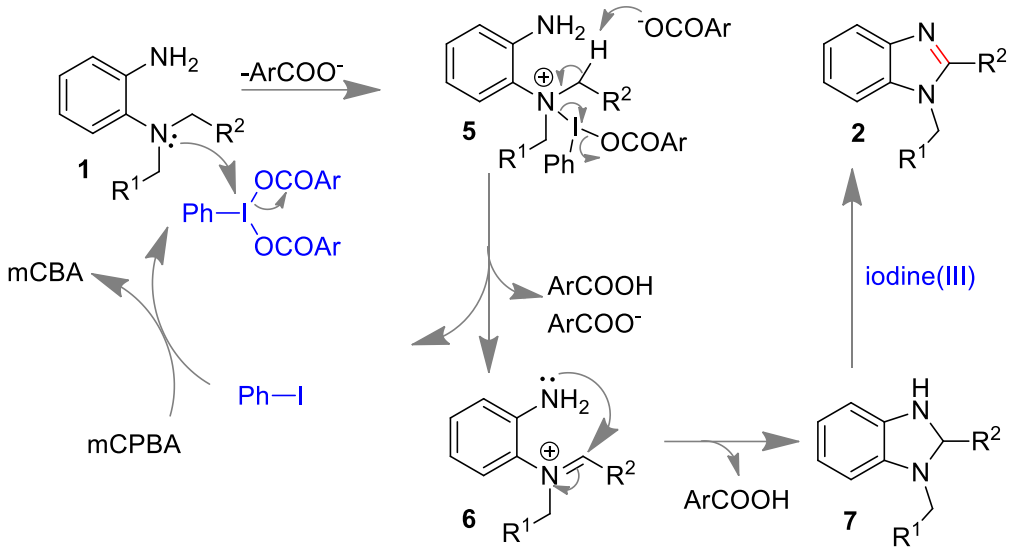


Figure 4.6 Plausible mechanism of the reaction.

4.4 CONCLUSION

In summary, an intramolecular benzylic C-H imination *via* 4H elimination which proceeds organocatalitycally is reported. The reactivity of unprotected primary amine to iodine(III) reaction has been controlled by the acidic hydrogens present within the molecule. Two C(sp^3)-H and N(sp^3)-H were directly converted to imine in a single step. By using simplest iodoarene PhI with 10 mol % of loading, inexpensive oxidant *m*CPBA, and ambient reaction condition like room temperature and open atmosphere are the major advantages for the method. The mechanistic understanding will facilitate certain methods of reactivity control of other non-directed C(sp^3)–H bonds for many heterocycle synthesis.

4.5 EXPERIMENTAL SECTION

Instrumentation and Chemicals: Column chromatographic purifications of the compounds were performed using silica gel (mesh 100–200 or mesh 230–400) and hexane – ethyl acetate mixtures as eluent unless otherwise specified. NMR spectra were recorded on a 400 MHz or 700 MHz instrument at 25 °C. The chemical shift values are reported in parts per million

(ppm) with respect to residual trichloromethane (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). The peak patterns are designated as follows: s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet; dd: doublet of doublets; td: triplet of doublets; br s: broad singlet. The coupling constants (*J*) are reported in hertz (Hz). High-resolution mass spectra (HR-MS) were recorded on an ESI-TOF (time of flight) mass spectrometer. Infrared spectral data are reported in wave number (cm^{-1}). The crystals data were collected with Bruker SMART D8 goniometer equipped with an APEX CCD detector and with an INCOATEC micro source (Cu-Kα radiation, λ = 0.71073 Å). SAINT+[33] and SADABS[34] were used to integrate the intensities and to correct the absorption respectively The structure was resolved by direct methods and refined on F^2 with SHELXL-97.[35] FT-IR spectra were recorded after making thin layer of the compounds on the surface of NaCl crystal using dichloromethane. Melting points of the compounds were determined using a digital melting point apparatus and are uncorrected.

Materials. $PhI(OAc)_2$ (PIDA), $PhI(OCOCF_3)_2$ (PIFA), $PhI(OPiv)_2$, mCPBA were purchased from commercial source and used without further purification. Solvents were commercially available and used without further purification.

Compound Characterization Data for Starting Materials:

***N*[1],*N*[1]-dibenzylbenzene-1,2-diamine (1a)[36]:** R_f = 0.7 (5% ethyl acetate/hexane); brown oily liquid; yield 315 mg (62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 10H), 6.92 – 6.87 (m, 2H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.64 (t, *J* = 7.6 Hz, 1H), 4.09 (br s, 2H), 4.05 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 138.4, 137.3, 129.1, 128.3, 127.1, 125.0, 123.4, 118.3, 115.4, 56.4; IR (neat) $\tilde{\nu}$ 3703, 2972, 1611, 1499, 1263, 1156, 775 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{20}N_2Na$ $[M+Na]^+$ 311.1524, found 311.1519.

***N*[1],*N*[1]-bis(4-methoxybenzyl)benzene-1,2-diamine (1b):** R_f = 0.7 (6% ethyl acetate/hexane); brown oily liquid; yield 345 mg (56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.4 Hz,

4H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 4H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.64 (t, *J* = 7.6 Hz, 1H), 4.08 (br s, 2H), 3.96 (s, 4H), 3.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 142.5, 137.4, 130.5, 130.3, 124.9, 123.6, 118.2, 115.4, 113.6, 55.5, 55.3; IR (neat) $\tilde{\nu}$ 3691, 2976, 1608, 1411, 1172, 755 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{24}N_2O_2Na$ $[M+Na]^+$ 371.1735, found 371.1730.

***N*^{1},*N*^{1}-dibenzyl-4-bromobenzene-1,2-diamine (1c):** R_f = 0.7 (4% ethyl acetate/hexane); pale yellow oily liquid; yield 265 mg (64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.19 (m, 10H), 6.83 (s, 1H), 6.71 (s, 2H), 4.13 (br s, 2H), 4.02 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 137.9, 136.0, 129.0, 128.4, 127.3, 124.9, 120.9, 118.0, 117.9, 56.4; IR (neat) $\tilde{\nu}$ 3756, 3035, 2966, 2305, 1603, 1494, 1156, 737 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{20}BrN_2$ $[M+H]^+$ 367.0810, found 367.0750.

4-Bromo-*N*^{1},*N*^{1}-bis(4-methoxybenzyl)benzene-1,2-diamine (1d): R_f = 0.7 (6% ethyl acetate/hexane); brown oily liquid; yield 345 mg (71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.4 Hz, 4H), 6.82 (d, *J* = 8.8 Hz, 5H), 6.73 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 4.14 (br s, 2H), 3.93 (s, 4H), 3.79 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 144.0, 136.1, 130.2, 129.9, 125.1, 120.8, 117.9, 117.8, 113.7, 55.5, 55.3; IR (neat) $\tilde{\nu}$ 3456, 3364, 3053, 2837, 1511, 1493, 1262, 896, 749 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{23}BrN_2O_2Na$ $[M+Na]^+$ 449.0841, found 449.0830.

***N*^{1}-benzyl-*N*^{1}-methylbenzene-1,2-diamine (1e):** R_f = 0.6 (5% ethyl acetate/hexane); brown oily liquid; yield 255 mg (68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 4H), 7.28 – 7.26 (m, 1H), 7.03 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.94 (dt, *J* = 8.0, 1.2 Hz, 1H), 6.77 – 6.72 (m, 2H), 4.08 (br s, 2H), 4.01 (s, 2H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 139.9, 138.8, 128.7, 128.3, 127.1, 124.6, 120.9, 118.5, 115.2, 60.0, 40.5; IR (neat) $\tilde{\nu}$ 3690, 2946, 2360, 1500, 1264, 746, 704 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{17}N_2$ $[M+H]^+$ 213.1392, found 213.1338.

***N*^{1}-benzyl-4-bromo-*N*^{1}-methylbenzene-1,2-diamine (1f):** R_f = 0.7 (4% ethyl acetate/hexane); brown oily liquid; yield 250 mg (75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 5H), 6.87 (d, *J* = 1.6 Hz, 1H), 6.84 – 6.80 (m, 2H), 4.12 (br s, 2H), 3.97 (s, 2H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 138.9, 138.4, 128.8, 128.5, 127.3, 122.6, 121.1, 117.8, 117.6, 59.9, 40.7; IR (neat) $\tilde{\nu}$ 3400, 2936, 1618, 1550, 1427, 1157, 896, 746 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{16}BrN_2$ $[M+H]^+$ 291.0497, found 291.0492.

***N*^{1}-(4-methoxybenzyl)-*N*^{1}-methylbenzene-1,2-diamine (1g):** R_f = 0.6 (6% ethyl acetate/hexane); colorless liquid; yield 295 mg (69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.76 – 6.72 (m, 2H), 4.07 (br s, 2H), 3.94 (s, 2H), 3.80 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 141.8, 140.1, 130.9, 130.0, 124.6, 121.1, 118.6, 115.3, 113.7, 59.4, 55.4, 40.5; IR (neat) $\tilde{\nu}$ 3443, 3048, 2972, 1608, 1511, 1172, 1034, 749 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{18}N_2NaO$ $[M+Na]^+$ 265.1317, found 265.1313.

***N*^{1}-ethyl-*N*^{1}-(4-methoxybenzyl)benzene-1,2-diamine (1h):** R_f = 0.7 (6% ethyl acetate/hexane); brown oily liquid; yield 192 mg (66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.4 Hz, 2H), 7.00 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.93 (td, *J* = 7.6, 1.2 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.71 (m, 2H), 4.08 (br s, 2H), 3.97 (s, 2H), 3.79 (s, 3H), 2.92 (q, *J* = 6.8 Hz, 2H), 0.97 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 143.3, 137.3, 131.1, 129.9, 124.9, 123.1, 118.1, 115.2, 113.5, 57.4, 55.2, 46.0, 12.2; IR (neat) $\tilde{\nu}$ 3600, 2976, 2836, 1607, 1499, 1247, 732 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{20}N_2NaO$ $[M+Na]^+$ 279.1473, found 279.1467.

2-(3,4-Dihydroisoquinolin-2-yl)aniline (1i)[36]: R_f = 0.5 (5% ethyl acetate/hexane); pale yellow solid; yield 302 mg (76%); mp: 124 - 126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.14 (m, 3H), 7.09 – 7.06 (m, 2H), 6.99 – 6.95 (m, 1H), 6.79 – 6.76 (m, 2H), 4.10 (s, 2H), 4.02 (br s, 2H), 3.25 (t, *J* = 5.6 Hz, 2H), 3.02 (t, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 141.9, 139.4, 135.6, 134.5, 129.1, 126.6, 126.4, 125.8, 124.9, 120.3, 118.8, 115.3, 53.9, 49.5, 30.0; IR (neat) $\tilde{\nu}$ 3689, 3054, 2986, 2305, 1421, 1264, 896, 745 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{17}N_2$ $[M+H]^+$ 225.1392, found 225.1387.

***N*¹-(4-chlorobenzyl)-*N*¹-ethylbenzene-1,2-diamine (1j):** R_f = 0.6 (5% ethyl acetate/hexane); colorless oily liquid; yield 325 mg (70%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 9.6 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.93 (t, *J* = 7.2 Hz, 1H), 6.74 – 6.68 (m, 2H), 4.06 (br s, 2H), 4.01 (s, 2H), 2.92 (q, *J* = 6.8 Hz, 2H), 0.98 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 137.6, 136.8, 132.7, 130.2, 128.4, 125.2, 123.1, 118.3, 115.4, 57.4, 46.6, 12.3; IR (neat) $\tilde{\nu}$ 3690, 3054, 2886, 2359, 1498, 1156, 748 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{18}ClN_2$ $[M+H]^+$ 261.1159, found 261.1150.

***N*¹-ethyl-*N*¹-(4-(trifluoromethyl)benzyl)benzene-1,2-diamine (1k):** R_f = 0.7 (6% ethyl acetate/hexane); brown oily liquid; yield 330 mg (63%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.00 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.95 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.76 – 6.68 (m, 2H), 4.11 (s, 2H), 4.08 (br s, 2H), 2.94 (q, *J* = 7.2 Hz, 2H), 1.00 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 143.3, 136.8, 129.0 (x2), 125.4, 125.28 (q, *J* = 7.6, 3.8 Hz), 123.1, 118.4, 115.5, 57.7, 46.9, 12.4; IR (neat) $\tilde{\nu}$ 3690, 3104, 2948, 1609, 1499, 1325, 1124, 1066, 748 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{18}F_3N_2$ $[M+H]^+$ 295.1422, found 295.1415.

***N*¹-isopropyl-*N*¹-(4-methoxybenzyl)benzene-1,2-diamine (1l):** R_f = 0.6 (5% ethyl acetate/hexane); brown oily liquid; yield 278 mg (58%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.86 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.66 – 6.62 (m, 2H), 4.08 (s, 2H), 4.00 (br s, 2H), 3.73 (s, 3H), 3.27 (sept, *J* = 6.8 Hz, 1H), 1.15 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 144.2, 136.4, 132.1, 129.6, 124.96, 124.92, 117.9, 115.3, 113.5, 55.3, 52.4, 50.8, 19.8; IR (neat) $\tilde{\nu}$ 3693, 2987,

1606, 1512, 1417, 1195, 749 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{22}N_2NaO$ $[M+Na]^+$ 293.1630, found 293.1621.

4-Bromo-*N*^{1}-(4-chlorobenzyl)-*N*^{1}-ethylbenzene-1,2-diamine (1m): R_f = 0.7 (5% ethyl acetate/hexane); brown oily liquid; yield 250 mg (65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.85 (s, 1H), 6.81 – 6.77 (m, 2H), 4.11 (br s, 2H), 3.97 (s, 2H), 2.90 (q, *J* = 7.2 Hz, 2H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 136.9, 135.6, 132.9, 130.2, 128.5, 124.7, 120.9, 118.2, 117.8, 57.2, 46.7, 12.3; IR (neat) $\tilde{\nu}$ 3564, 2949, 1612, 1493, 1287, 1154, 748 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{16}BrClN_2Na$ $[M+Na]^+$ 361.0083, found 361.0067.

***N*^{1}-benzyl-*N*^{1}-(4-methylbenzyl)benzene-1,2-diamine (1n):** R_f = 0.4 (3% ethyl acetate/hexane); brown oily liquid; yield 385 mg (72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 5H), 7.09 (dd, *J* = 8.0, 4.0 Hz, 4H), 6.92 – 6.86 (m, 2H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.63 (t, *J* = 6.8 Hz, 1H), 4.09 (br s, 2H), 4.04 (s, 2H), 4.00 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 138.5, 137.4, 136.7, 135.3, 129.1, 129.0, 128.9, 128.3, 127.1, 124.9, 123.4, 118.3, 115.4, 56.2, 56.1, 21.3; IR (neat) $\tilde{\nu}$ 3500, 3054, 2986, 1421, 1265, 892, 740 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{23}N_2$ $[M+H]^+$ 303.1861, found 303.1854.

***N*^{1}-benzyl-4-bromo-*N*^{1}-(4-methylbenzyl)benzene-1,2-diamine (1o):** R_f = 0.6 (4% ethyl acetate/hexane); pale yellow solid; yield 325 mg (76%); mp: 107 - 109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 3H), 7.22 (d, *J* = 6.8 Hz, 2H), 7.11 (s, 4H), 6.85 (d, *J* = 2.0 Hz, 1H), 6.75 – 6.69 (m, 2H), 4.16 (br s, 2H), 4.02 (s, 2H), 3.99 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 137.9, 136.8, 136.1, 134.7, 129.05, 129.0, 128.98, 128.3, 127.2, 124.9, 120.8, 117.9, 117.8, 56.2, 56.0, 21.2; IR (neat) $\tilde{\nu}$ 3680, 2926, 2831, 1621, 1493, 1272, 1188, 1028, 775 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{21}BrN_2Na$ $[M+Na]^+$ 403.0786, found 403.0780.

***N*^{1}-benzyl-*N*^{1}-(3,4,5-trimethoxybenzyl)benzene-1,2-diamine (1p):** R_f = 0.5 (8% ethyl acetate/hexane); orange sticky liquid; yield 410 mg (61%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 5H), 6.92 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.65 (t, *J* = 7.6 Hz, 1H), 6.36 (s, 2H), 4.07 (br s, 4H), 3.99 (s, 2H), 3.82 (s, 3H), 3.76 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 142.1, 138.4, 137.2, 136.9, 133.5, 128.9, 128.2, 127.1, 124.9, 123.4, 118.2, 115.3, 106.0, 60.9, 56.2, 56.0, 55.9; IR (neat) $\tilde{\nu}$ 3690, 3050, 2988, 1550, 1423, 1129, 746 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{26}N_2O_3Na$ $[M+Na]^+$ 401.1841, found 401.1853.

***N*^{1}-benzyl-4-bromo-*N*^{1}-(3,4,5-trimethoxybenzyl)benzene-1,2-diamine (1q):** R_f = 0.6 (8% ethyl acetate/hexane); yellow sticky liquid; yield 295 mg (57%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 5H), 6.86 (d, *J* = 2.0 Hz, 1H), 6.73 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.34 (s, 2H), 4.15 (br s, 2H), 4.03 (s, 2H), 3.95 (s, 2H), 3.82 (s, 3H), 3.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 143.7, 138.0, 137.1, 136.0, 133.2, 128.9, 128.4, 127.4, 125.0, 120.8, 118.0, 117.9, 106.0, 60.9, 56.3, 56.2, 56.1; IR (neat) $\tilde{\nu}$ 3692, 2996, 2305, 1602, 1256, 1129, 887 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{25}BrN_2O_3Na$ $[M+Na]^+$ 479.0946, found 479.0925.

***N*^{1}-benzyl-*N*^{1}-(3,4-dimethoxybenzyl)benzene-1,2-diamine (1r):** R_f = 0.5 (6% ethyl acetate/hexane); yellow oily liquid; yield 405 mg (66%); mp: 128 - 130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 5H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.81 – 6.74 (m, 3H), 6.67 (t, *J* = 7.6 Hz, 1H), 6.62 (s, 1H), 4.07 (s, 2H), 4.02 (s, 2H), 3.87 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 148.0, 142.2, 138.5, 137.2, 130.4, 129.0, 128.2, 127.1, 124.9, 123.5, 121.3, 118.2, 115.3, 112.5, 110.7, 56.1, 55.8, 55.7, 55.5; IR (neat) $\tilde{\nu}$ 3692, 2978, 2831, 1625, 1513, 1155, 1027, 749 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{24}N_2O_2Na$ $[M+Na]^+$ 371.1735, found 371.1742.

***N*^{1}-benzyl-*N*^{1}-(2,4,6-trimethylbenzyl)benzene-1,2-diamine (1s):** R_f = 0.6 (5% ethyl acetate/hexane); brown oily liquid; yield 425 mg (73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.20 – 7.15 (m, 5H), 6.89 (dt, *J* = 8.0, 2.0 Hz, 1H), 6.76 – 6.72 (m, 3H), 6.52 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.06 (s, 2H), 4.04 (s, 2H), 3.63 (br s, 2H), 2.22 (s, 3H), 2.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 139.1, 138.2, 138.1, 136.6, 131.9, 129.7, 129.1, 128.0, 127.1, 126.0, 124.9, 118.6, 115.7, 59.5, 53.8, 21.0; IR (neat) $\tilde{\nu}$ 3576, 2966, 1605, 1423, 1287, 896, 776 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{26}N_2Na$ $[M+Na]^+$ 353.1994, found 353.1989.

***N*^{1}-benzyl-4-bromo-*N*^{1}-(2,4,6-trimethylbenzyl)benzene-1,2-diamine (1t):** R_f = 0.6 (3% ethyl acetate/hexane); brown oily liquid; yield 240 mg (52%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.2 Hz, 3H), 7.16 (d, *J* = 8.0 Hz, 3H), 6.83 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.78 (s, 2H), 6.63 (d, *J* = 2.0 Hz, 1H), 4.04 (s, 2H), 4.03 (s, 2H), 3.69 (br s, 2H), 2.24 (s, 3H), 2.19 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 138.6, 137.9, 137.0, 136.8, 131.6, 129.6, 129.2, 128.1, 127.8, 127.2, 126.5, 121.1, 118.0, 59.5, 53.8, 21.0, 20.1; IR (neat) $\tilde{\nu}$ 3442, 3053, 2986, 1635, 1491, 1265, 737 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{26}BrN_2$ $[M+H]^+$ 409.1279, found 409.1261.

***N*^{1}-(4-chlorobenzyl)-*N*^{1}-(4-methoxybenzyl)benzene-1,2-diamine (1u):** R_f = 0.5 (8% ethyl acetate/hexane); yellow oily liquid; yield 450 mg (72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.4 Hz, 2H), 7.11 (dd, *J* = 8.0, 1.6 Hz, 3H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.85 – 6.80 (m, 3H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.63 (t, *J* = 7.6 Hz, 1H), 4.04 (br s, 2H), 4.00 (s, 2H), 3.96 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 142.4, 136.9, 132.8, 130.4, 130.3, 130.1, 130.0, 128.4, 125.2, 123.4, 118.3, 115.5, 113.7, 56.0, 55.4, 55.2; IR (neat) $\tilde{\nu}$ 3690, 2956, 2831, 1608, 1532, 1156, 1034, 775 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{21}ClN_2ONa$ $[M+Na]^+$ 375.1240, found 375.1233.

4-Bromo-N^1-(4-chlorobenzyl)-N^1-(4-methoxybenzyl)benzene-1,2-diamine (1v): R_f = 0.5 (7% ethyl acetate/hexane); light orange oily liquid; yield 332 mg (68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz, 2H), 7.09 (dd, *J* = 8.4, 2.0 Hz, 4H), 6.83 – 6.81 (m, 3H), 6.72 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 4.10 (br s, 2H), 3.96 (s, 2H), 3.92 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 143.9, 136.4, 135.7, 133.0, 130.4, 130.3, 129.6, 128.5, 125.0, 120.9, 118.2, 117.9, 113.8, 56.0, 55.4, 55.3; IR (neat) $\tilde{\nu}$ 3690, 3053, 2986, 2410, 1422, 1264, 896, 749 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{20}BrClN_2ONa$ $[M+Na]^+$ 453.0345, found 453.0361.

Representative procedure for the synthesis of 1-Benzyl-2-phenyl-benzo[d]imidazole (2a): To a round bottom flask charged with a magnetic stirring bar and N^1,N^1-dibenzylbenzene-1,2-diamine (1a) (60 mg, 0.208 mmol, 1.0 equiv), PhI (3 µl, 0.0208 mmol, 10 mol %) was added and mCPBA (90 mg, 0.52 mmol, 2.5 equiv) dissolved in 1,1,1,3,3,3-Hexafluoro-2-propanol and dichloromethane (1.5 ml, 2:1 v/v). The mixture was stirred under room temperature for 4 h. The completion of reaction was confirmed by TLC and afterwards it was evaporated to dryness under reduced pressure. The crude reaction mixture was purified by 230 – 400 mesh silica gel column chromatography using 18% ethyl acetate/hexane as eluent to get 1-Benzyl-2-phenyl-benzo[d]imidazole (**2a**) as white solid with 89% yield.

Compound Characterization Data:

1-Benzyl-2-phenyl-benzo[d]imidazole (2a)[37]: R_f = 0.5 (18% ethyl acetate/hexane); white solid; yield 52 mg (89%); mp: 139 - 141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 6.0 Hz, 2H), 7.46 (d, *J* = 6.8 Hz, 3H), 7.35 – 7.30 (m, 4H), 7.22 (t, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 7.2 Hz, 2H), 5.46 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 134.7, 133.5, 130.3, 129.9, 129.5, 129.2, 129.0, 128.4, 128.0, 126.1, 123.5, 123.2, 119.9,

110.8, 48.6; IR (KBr) ῡ 2927, 2854, 1605, 1453, 1160, 1028, 970, 737 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{17}N_2$ $[M+H]^+$ 285.1386, found 285.1366.

1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (2b)[38]: R_f = 0.5 (30% ethyl acetate/hexane); white solid; yield 53 mg (90%); mp: 128 - 130 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.31 – 7.27 (m, 1H), 7.21 (d, *J* = 2.0 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.38 (s, 2H), 3.85 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.0, 159.2, 154.2, 143.2, 136.2, 130.8, 128.6, 127.3, 122.9, 122.6, 122.5, 119.8, 114.5, 114.3, 110.5, 55.5, 55.4, 48.0; IR (KBr) ῡ 2912, 2839, 1696, 1514, 1265, 970, 748 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{21}N_2O_2$ $[M+H]^+$ 345.1598, found 345.1615.

1-Benzyl-5-bromo-2-phenyl-benzo[d]imidazole (2c)[39]: R_f = 0.5 (15% ethyl acetate/hexane); white solid; yield 48 mg (82%); mp: 156 - 158 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 1.6 Hz, 1H), 7.68 – 7.66 (m, 2H), 7.52 – 7.44 (m, 3H), 7.36 – 7.29 (m, 4H), 7.06 (d, *J* = 8.4 Hz, 3H), 5.44 (s, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 155.3, 144.6, 136.0, 135.1, 130.4, 129.7, 129.4, 129.3, 129.0, 128.1, 126.2, 126.0, 122.9, 115.8, 111.9, 48.6; IR (KBr) ῡ 2916, 2851, 1516, 1455, 1384, 1160, 923 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{16}BrN_2$ $[M+H]^+$ 363.0491, found 363.0506.

5-Bromo-1-(4-methoxybenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (2d): R_f = 0.5 (30% ethyl acetate/hexane); white solid; yield 54 mg (92%); mp: 136 - 138 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 1.6 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.30 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.98 (t, *J* = 8.0 Hz, 4H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.35 (s, 2H), 3.84 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 159.4, 155.2, 144.5, 135.1,

130.8, 128.0, 127.3, 125.8, 122.6, 121.9, 115.6, 114.6, 114.4, 111.8, 55.5, 55.4, 48.1; IR (KBr) ῡ 2927, 2831, 1611, 1461, 1293, 1173, 1028, 735 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{20}BrN_2O_2$ $[M+H]^+$ 423.0703, found 423.0712.

1-Methyl-2-phenyl-benzo[d]imidazole (2e)[40]: R_f = 0.5 (12% ethyl acetate/hexane); white solid; yield 53 mg (90%); mp: 100 - 102 °C; ^1H NMR (700 MHz, $CDCl_3$) δ 7.84 – 7.82 (m, 1H), 7.77 (dd, *J* = 7.6, 1.2 Hz, 2H), 7.55 – 7.50 (m, 3H), 7.41 – 7.39 (m, 1H), 7.34 – 7.30 (m, 2H), 3.87 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 153.9, 143.0, 136.7, 130.3, 129.9, 129.6, 128.8, 122.9, 122.6, 119.9, 109.7, 31.8; IR (KBr) ῡ 3009, 2981, 1612, 1384, 1175, 1027, 893 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{13}N_2$ $[M+H]^+$ 209.1073, found 209.1096.

5-Bromo-1-methyl-2-phenyl-benzo[d]imidazole (2f): R_f = 0.5 (10% ethyl acetate/hexane); white solid; yield 52 mg (89%); mp: 150 - 152 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 1.2 Hz, 1H), 7.73 (dd, *J* = 6.4, 3.2 Hz, 2H), 7.53 – 7.51 (m, 3H), 7.41 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.24 (d, *J* = 3.2 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 154.9, 144.3, 135.7, 130.2, 129.8, 129.6, 128.9, 125.9, 122.8, 115.6, 111.0, 31.9; IR (KBr) ῡ 3046, 2985, 1492, 1421, 1261, 895 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{12}BrN_2$ $[M+H]^+$ 287.0178, found 287.0155.

2-(4-Methoxyphenyl)-1-methyl-benzo[d]imidazole (2g): R_f = 0.5 (15% ethyl acetate/hexane); white solid; yield 53 mg (90%); mp: 122 - 124 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.79 (m, 1H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.37 – 7.35 (m, 1H), 7.31 – 7.28 (m, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 153.9, 143.0, 136.7, 130.9, 122.64, 122.60, 122.4, 119.7, 114.2, 109.6, 55.5, 31.8; IR

(KBr) ῡ 2925, 2843, 1610, 1462, 1379, 1250, 1179, 1023, 835 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{15}N_2O$ $[M+H]^+$ 239.1179, found 239.1162.

1-Ethyl-2-(4-methoxyphenyl)-benzo[d]imidazole (2h): R_f = 0.5 (15% ethyl acetate/hexane); white solid; yield 52 mg (88%); mp: 112 - 114 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 6.4, 2.8 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.41 (dd, *J* = 6.4, 2.8 Hz, 1H), 7.30 – 7.28 (m, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 1.47 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 160.9, 153.5, 143.2, 135.5, 130.8, 122.9, 122.6, 122.4, 119.8, 114.3, 109.9, 55.5, 39.7, 15.4; IR (KBr) ῡ 2939, 2838, 1614, 1455, 1249, 1028, 839 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{17}N_2O$ $[M+H]^+$ 253.1335, found 253.1341.

5,6-Dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline (2i)[41]: R_f = 0.5 (10% ethyl acetate/hexane); white solid; yield 46 mg (78%); mp: 148 - 150 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.29 (m, 1H), 7.84 – 7.80 (m, 1H), 7.44 – 7.36 (m, 3H), 7.33 – 7.27 (m, 3H), 4.33 (t, *J* = 6.8 Hz, 2H), 3.29 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 149.2, 144.0, 134.8, 134.4, 130.3, 128.2, 127.9, 126.8, 125.8, 122.8, 122.6, 119.9, 109.2, 40.5, 28.4; IR (KBr) ῡ 3058, 2992, 1615, 1433, 1268, 1037, 738 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{13}N_2$ $[M+H]^+$ 221.1073, found 221.1056.

2-(4-Chlorophenyl)-1-ethyl-benzo[d]imidazole (2j): R_f = 0.5 (14% ethyl acetate/hexane); white solid; yield 45 mg (77%); mp: 126 - 128 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.81 (m, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.44 (dd, *J* = 5.6, 3.2 Hz, 1H), 7.33 – 7.29 (m, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.47 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 152.4, 143.2, 136.2, 135.5, 130.7, 129.2, 129.1, 123.1, 122.7, 120.2, 110.1, 39.8,

15.4; IR (KBr) ῡ 3053, 2986, 1607, 1421, 1264, 1094, 895, 747 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{14}ClN_2$ $[M+H]^+$ 257.0840, found 257.0816.

1-Ethyl-2-(4-(trifluoromethyl)phenyl)-benzo[d]imidazole (2k): R_f = 0.5 (20% ethyl acetate/hexane); white solid; yield 47 mg (80%); mp: 127 - 130 °C; ^1H NMR (700 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.37 – 7.32 (m, 2H), 4.30 (q, *J* = 7.0 Hz, 2H), 1.49 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 151.9, 143.3, 135.6, 134.3, 131.8 (q, *J* = 32.8 Hz), 129.8, 125.9 (q, *J* = 3.6 Hz), 123.4, 122.9, 120.4, 110.2, 39.9, 15.5; IR (KBr) ῡ 2981, 2937, 1619, 1452, 325, 1115, 1071, 854 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{14}F_3N_2$ $[M+H]^+$ 291.1104, found 291.1099.

1-Isopropyl-2-(4-methoxyphenyl)-benzo[d]imidazole (2l): R_f = 0.4 (15% ethyl acetate/hexane); white solid; yield 43 mg (73%); mp: 150 - 152 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.80 (m, 1H), 7.62 – 7.57 (m, 3H), 7.29 – 7.23 (m, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 4.82 (sept, *J* = 6.8 Hz, 1H), 3.88 (s, 3H), 1.64 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 160.8, 153.7, 143.8, 133.6, 130.9, 123.4, 122.1, 122.0, 120.2, 114.2, 112.3, 55.5, 48.8, 21.5; IR (KBr) ῡ 2976, 2839, 1608, 1454, 1371, 1251,1176 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{19}N_2O$ $[M+H]^+$ 267.1492, found 267.1472.

5-Bromo-2-(4-chlorophenyl)-1-ethyl-benzo[d]imidazole (2m): R_f = 0.5 (15% ethyl acetate/hexane); white solid; yield 44 mg (75%); mp: 160 - 162 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 2.0 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.41 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 153.4, 144.5, 136.5, 134.5, 130.6, 129.3, 128.6,

126.1, 122.9, 115.6, 111.3, 39.9, 15.4; IR (KBr) ῡ 2981, 2933, 1599, 1405, 1326, 1087, 992 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{13}BrClN_2$ $[M+H]^+$ 334.9945, found 334.9944.

1-Benzyl-2-(p-tolyl)-benzo[d]imidazole and 1-(4-Methylbenzyl)-2-phenyl-benzo[d]imidazole (2n): R_f = 0.6 (10% ethyl acetate/hexane); white solid; yield 44 mg (75%); Two regio isomers with 82:18 Ratio; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.85 (d, J = 7.7 Hz, 1H), 7.70 (d, *J* = 7.0 Hz, 2H x 0.22), 7.58 (d, *J* = 8.4 Hz, 2H), 7.48 - 7.44 (m, 1H), 7.34 – 7.28 (m, 4H), 7.25 (d, *J* = 7.0 Hz, 3H), 7.23 – 7.19 (m, 2H), 7.13 (d, *J* = 7.7 Hz, 2H x 0.22), 7.11 (d, *J* = 7.7 Hz, 2H), 6.99 (d, *J* = 7.7 Hz, 2H x 0.22), 5.45 (s, 2H, major isomer), 5.42 (s, 2H x 0.22, minor isomer), 2.40 (s, 3H, major isomer), 2.33 (s, 3H x 0.22, minor isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 143.3, 140.2, 136.6, 136.2, 129.8, 129.6, 129.4, 129.3, 129.2, 128.9, 127.9, 127.3, 126.1, 126.0, 123.1, 123.0, 122.8, 122.7, 120.1, 120.0, 110.7, 110.6, 48.5, 48.3, 21.6, 21.2.

1-Benzyl-5-bromo-2-(p-tolyl)-benzo[d]imidazole and 5-Bromo-1-(4-methylbenzyl)-2-phenyl-benzo[d]imidazole (2o): R_f = 0.6 (12% ethyl acetate/hexane); white solid; yield 43 mg (73%); Two regio isomers with 52:48 Ratio; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.98 (d, *J* = 3.5 Hz, 2H), 7.67 (d, *J* = 7.7 Hz, 2H), 7.56 (d, *J* = 7.7 Hz, 2H), 7.49 – 7.44 (m, 3H), 7.33 – 7.28 (m, 5H), 7.25 (d, *J* = 7.7 Hz, 2H), 7.13 (d, *J* = 7.7 Hz, 2H), 7.06 – 7.02 (m, 4H), 6.95 (d, *J* = 7.7 Hz, 2H), 5.41 (s, 2H, major isomer), 5.38 (s, 2H, minor isomer), 2.40 (s, 4H, major isomer), 2.33 (s, 3H, minor isomer); ^{13}C NMR (175 MHz, $CDCl_3$) δ 155.5, 155.2, 144.51, 144.49, 140.6, 137.8, 136.1, 135.1, 132.9, 130.3, 129.9, 129.7, 129.3, 129.2, 128.9, 128.0, 126.7, 126.1, 125.98, 125.96, 125.92, 122.8, 122.7, 115.72, 115.70, 111.9, 111.8, 48.6, 48.4, 21.5, 21.2.

1-Benzyl-2-(3,4,5-trimethoxyphenyl)-benzo[d]imidazole[37] and 2-Phenyl-1-(3,4,5-trimethoxybenzyl)-benzo[d]imidazole (2p): R_f = 0.5 (35% ethyl acetate/hexane); white solid; yield 52 mg (88%); Two regio isomers with 70:30 Ratio; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.86 (s, 1H), 7.72 (dd, *J* = 7.2, 2.4 Hz, 1H), 7.49 – 7.47 (m, 2H), 7.37 – 7.27 (m, 7H), 7.15 (d, *J* = 7.2 Hz, 2H), 6.86 (s, 2H, major isomer), 6.29 (s, 2H x 0.43, minor isomer), 5.48 (s, 2H, major isomer), 5.38 (s, 2H x 0.43, minor isomer), 3.87 (s, 3H, major isomer), 3.82 (s, 3H x 0.43, minor isomer), 3.70 (s, 6H x 0.43, minor isomer), 3.64 (s, 6H, major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 154.2, 153.9, 153.4, 143.2, 143.0, 139.5, 137.5, 136.9, 136.5, 136.2, 132.2, 130.1, 129.4, 129.3, 128.9, 127.9, 125.8, 125.2, 123.4, 123.3, 123.0, 122.9, 120.1, 120.0, 110.6, 110.3, 106.5, 103.2, 61.1, 61.0, 56.2, 56.0, 48.6, 48.5.

1-Benzyl-5-bromo-2-(3,4,5-trimethoxyphenyl)-benzo[d]imidazole and 5-Bromo-2-phenyl-1-(3,4,5-trimethoxybenzyl)-benzo[d]imidazole (2q): R_f = 0.4 (30% ethyl acetate/hexane); white solid; yield 54 mg (91%); Two regio isomers with 87:13 Ratio; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 1.6 Hz, 1H), 7.70 – 7.68 (m, 2H x 0.15), 7.49 (d, *J* = 7.2 Hz, 3H x 0.15), 7.38 – 7.34 (m, 3H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.12 (t, *J* = 8.8 Hz, 3H), 6.84 (s, 2H, major isomer), 6.25 (s, 2H x 0.15, minor isomer), 5.45 (s, 2H, major isomer), 5.36 (s, 2H x 0.15, minor isomer), 3.87 (s, 3H, major isomer), 3.83 (s, 3H x 0.15, minor isomer), 3.70 (s, 6H x 0.15, minor isomer), 3.65 (s, 6H, major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 155.2, 153.9, 153.5, 144.5, 144.3, 139.7, 137.6, 136.4, 135.5, 135.2, 131.6, 130.4, 129.7, 129.3, 129.0, 128.1, 126.25, 126.20, 125.7, 124.7, 122.9, 122.8, 115.8, 111.8, 111.5, 106.4, 103.0, 61.0, 60.9, 56.2, 56.0, 48.7, 48.6.

1-Benzyl-2-(3,4-dimethoxyphenyl)-benzo[d]imidazole (2r)[37]: R_f = 0.4 (25% ethyl acetate/hexane); white solid; yield 34 mg (58%); mp: 144 - 146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.28 (m, 4H), 7.25 – 7.21 (m, 4H), 7.14 (d, *J* = 7.2 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 1H), 5.47 (s, 2H), 3.91 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 150.5, 149.1, 143.1, 136.8, 136.4, 129.2, 127.8, 125.9, 123.0, 122.8, 122.6, 121.9, 119.8, 112.3, 111.1, 110.3, 56.0, 55.8, 48.5; IR (KBr) ῡ 3016, 2856, 1643, 1417, 1134, 895, 670 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{21}N_2O_2$ $[M+H]^+$ 345.1598, found 345.1613.

1-(3,4-Dimethoxybenzyl)-2-phenyl-benzo[d]imidazole (2r'): R_f = 0.4 (22% ethyl acetate/hexane); white solid; yield 14 mg (24%); mp: 150 - 152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.71 (dd, *J* = 7.2, 2.4 Hz, 2H), 7.49 – 7.45 (m, 3H), 7.33 – 7.29 (m, 1H), 7.28 – 7.25 (m, 2H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.63 – 6.61 (m, 2H), 5.40 (s, 2H), 3.85 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 149.5, 148.7, 143.3, 136.2, 130.3, 130.0, 129.40, 128.9, 128.8, 123.1, 122.8, 120.1, 118.4, 111.6, 110.6, 109.3, 56.0, 55.9, 48.2; IR (KBr) ῡ 2933, 2830, 1592, 1515, 1460, 1237, 1139, 1025 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{21}N_2O_2$ $[M+H]^+$ 345.1598, found 345.1573.

1-Benzyl-2-mesityl-benzo[d]imidazole (2s): R_f = 0.6 (8% ethyl acetate/hexane); white solid; yield 31 mg (52%); mp: 140 - 142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.6 Hz, 1H), 7.32 – 7.25 (m, 3H), 7.23 – 7.21 (m, 3H), 6.97 (dd, *J* = 6.4, 2.8 Hz, 2H), 6.92 (s, 2H), 5.07 (s, 2H), 2.34 (s, 3H), 1.94 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 143.5, 139.6, 138.2, 135.9, 134.8, 128.8, 128.4, 127.9, 127.3, 126.9, 122.6, 122.2, 120.1, 110.6, 47.9, 21.4, 19.8; IR (KBr) ῡ 2916, 2851, 1613, 1449, 1374, 1170, 852 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{23}N_2$ $[M+H]^+$ 327.1856, found 327.1862.

2-Phenyl-1-(2,4,6-trimethylbenzyl)-benzo[d]imidazole (2s'): R_f = 0.6 (10% ethyl acetate/hexane); white solid; yield 12 mg (20%); mp: 204 - 206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.74 (m, 3H), 7.55 – 7.52 (m, 3H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.80 (s, 2H), 6.70 (d, *J* = 8.0 Hz, 1H), 5.45 (s, 2H), 2.24 (s, 3H), 2.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 143.3, 138.0, 137.3, 135.1, 131.0, 129.9, 129.8, 128.8, 128.4, 122.7, 122.2, 119.9, 111.4, 45.5, 21.1, 20.2; IR (KBr) ῡ 2912, 2847, 1692, 1518, 1423, 1015, 895 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{23}N_2$ $[M+H]^+$ 327.1856, found 327.1875.

1-Benzyl-5-bromo-2-mesityl-benzo[d]imidazole (2t): R_f = 0.6 (6% ethyl acetate/hexane); oily liquid; yield 32 mg (53%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 1.6 Hz, 1H), 7.35 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.23 (dd, *J* = 5.2, 1.2 Hz, 3H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 7.2 Hz, 4H), 5.04 (s, 2H), 2.34 (s, 3H), 1.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 144.8, 139.9, 138.1, 135.5, 133.8, 128.9, 128.5, 128.1, 127.2, 126.5, 125.7, 123.0, 115.3, 111.8, 48.0, 21.4, 19.8; IR (KBr) ῡ 2920, 2853, 1610, 1454, 1372, 1045, 853 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{22}BrN_2$ $[M+H]^+$ 405.0961, found 405. 0949.

5-Bromo-2-phenyl-1-(2,4,6-trimethylbenzyl)-benzo[d]imidazole (2t'): R_f = 0.6 (8% ethyl acetate/hexane); white solid; yield 11 mg (18%); mp: 190 - 192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 1.6 Hz, 1H), 7.76 – 7.74 (m, 2H), 7.55 – 7.54 (m, 3H), 7.08 (dd, *J* = 8.8, 1.6 Hz, 1H), 6.81 (s, 2H), 6.50 (d, *J* = 8.8 Hz, 1H), 5.42 (s, 2H), 2.25 (s, 3H), 2.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 144.7, 138.4, 137.3, 134.1, 130.5, 130.2, 129.9, 129.8, 128.9, 127.9, 125.8, 122.7, 115.3, 112.6, 45.7, 21.1, 20.2; IR (KBr) ῡ 2916, 2843, 1609, 1455, 1372, 1172, 1013, 844 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{22}BrN_2$ $[M+H]^+$ 405.0961, found 405. 0984.

1-(4-Chlorobenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (2u): R_f = 0.5 (14% ethyl acetate/hexane); white solid; yield 38 mg (62%); mp: 147 - 150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.33-7.30 (m, 3H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 5.40 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 154.2, 143.3, 136.0, 135.1, 133.7, 130.7, 129.4, 127.4, 123.0, 122.8, 122.3, 119.9, 114.4, 110.3, 55.5, 47.9; IR (KBr) ϑ 2935, 2825, 1612, 1513, 1248, 1094, 1033, 839 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{18}ClN_2O$ $[M+H]^+$ 349.1102, found 349.1083.

2-(4-Chlorophenyl)-1-(4-methoxybenzyl)-benzo[d]imidazole (2u'): R_f = 0.6 (16% ethyl acetate/hexane); white solid; yield 11 mg (14%); mp: 130 - 132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.33 – 7.30 (m, 1H), 7.25 (s, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.38 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 153.0, 143.2, 136.3, 136.2, 130.8, 129.2, 128.8, 128.3, 127.3, 123.4, 122.9, 120.2, 114.6, 110.7, 55.4, 48.0; IR (KBr) ϑ 2929, 2835, 1614, 1483, 1249, 1176, 1029, 837 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{18}ClN_2O$ $[M+H]^+$ 349.1102, found 349.1112.

5-Bromo-1-(4-chlorobenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (2v): R_f = 0.6 (10% ethyl acetate/hexane); white solid; yield 37 mg (65%); mp: 150 - 152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 1.0 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.33 - 7.30 (m, 3H), 7.03 – 6.96 (m, 5H), 5.38 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 155.3, 144.6, 134.9, 134.6, 133.9, 130.7, 129.5, 127.4, 126.0, 122.8, 121.7, 115.9, 114.5, 111.5, 55.5, 48.0; IR (KBr) ϑ 2929, 2839, 1613, 1469, 1247, 1176, 1034, 836 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{17}BrClN_2O$ $[M+H]^+$ 427.0207, found 427.0206.

5-Bromo-2-(4-chlorophenyl)-1-(4-methoxybenzyl)-benzo[d]imidazole (2v'): R_f = 0.6 (13% ethyl acetate/hexane); white solid; yield 13 mg (18%); mp: 123 - 125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 1.0 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.34 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.35 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 154.1, 144.5, 136.7, 135.2, 130.6, 129.3, 128.2, 127.7, 127.2, 126.4, 122.9, 115.9, 114.7, 111.9, 55.5, 48.2; IR (KBr) ϑ 3051, 2977, 2916, 1606,1469, 1264, 1176, 738 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{17}BrClN_2O$ $[M+H]^+$ 427.0207, found 427.0231.

Procedure for the radical scavenger experiment with 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl radical (TEMPO): To a round bottom flask charged with a magnetic stirring bar and *N*^{1},*N*^{1}-dibenzylbenzene-1,2-diamine (1a) (50 mg, 0.173 mmol, 1.0 equiv), PhI (3 µl, 0.0173 mmol, 10 mol %) was added and mCPBA (75 mg, 0.43 mmol, 2.5 equiv) dissolved in 1,1,1,3,3,3-Hexafluoro-2-propanol and dichloromethane (1.5 ml, 2:1 v/v). To it TEMPO (54 mg, 0.35 mmol, 2.0 equiv) was added. The mixture was stirred under room temperature for 4 h. The completion of reaction was confirmed by TLC and afterwards it was evaporated to dryness under reduced pressure. The crude reaction mixture was purified by 230 – 400 mesh silica gel column chromatography using 18% ethyl acetate/hexane as eluent to get 1-Benzyl-2-phenyl-benzo[d]imidazole (2a) as white solid with 74% yield.

Procedure for the synthesis of *N*^{1},*N*^{1}-dibenzyl-*N*^{2}-butylbenzene-1,2-diamine (3): To an oven-dried sealed tube charged with a magnetic stirring bar and *N*^{1},*N*^{1}-dibenzylbenzene-1,2-diamine (1a) (100 mg, 0.35 mmol, 1.0 equiv), K_2CO_3 (48 mg, 0.35 mmol, 1.0 equiv) was added[42]. To it 4 ml acetone was further added and n-Butyl Iodide (40 µl, 0.35 mmol, 1.0 equiv) was added drop wise. The resulting mixture was stirred at 70 °C for 2 h. After completion of the reaction the whole solution was transferred in to a round bottom flask and

evaporated to dryness. Then the crude material was washed with water and organic layer was extracted with dichloromethane. It was collected together and dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was purified by 230 – 400 mesh silica gel column chromatography using 1% ethyl acetate/hexane as eluent to get N^1,N^1-dibenzyl-N^2-butylbenzene-1,2-diamine (3) as colorless oily liquid with 54% yield.

***N*^{1},*N*^{1}-dibenzyl-*N*^{2}-butylbenzene-1,2-diamine (3):** R_f = 0.9 (1% ethyl acetate/hexane); colorless liquid; yield 64 mg (54%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 4H), 7.23 – 7.19 (m, 6H), 6.99 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.90 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.60 – 6.55 (m, 2H), 4.87 (s, 1H), 4.00 (s, 4H), 1.62 – 1.57 (m, 2H), 1.46 – 1.41 (m, 2H), 1.33 – 1.26 (m, 2H), 0.98 – 0.95 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 138.6, 136.7, 129.0, 128.3, 127.1, 125.4, 122.9, 116.0, 110.3, 56.8, 43.6, 31.9, 20.5, 14.1; IR (neat) $\tilde{\nu}$ 3433, 2962, 1601, 1454, 1146, 765 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{29}N_2$ $[M+H]^+$ 345.2331, found 345.2326.

Identification of Intermediate of the reaction pathway (1-Benzyl-3-butyl-2-phenyl-2,3-dihydro-benzo[d]imidazole, 4): Under standard condition when the model substrate N^1,N^1-dibenzyl-N^2-butylbenzene-1,2-diamine **3** was treated with PhI (10 mol %) and 2.5 equivalent mCPBA, intermediate **4** was observed (**Figure 4.110**) in ESI – TOF Mass spectrometer although it was not isolable through silica gel column chromatography.

Pictorial Presentation of Reactivity of Aniline Derivative with PhI and mCPBA:

a) b)

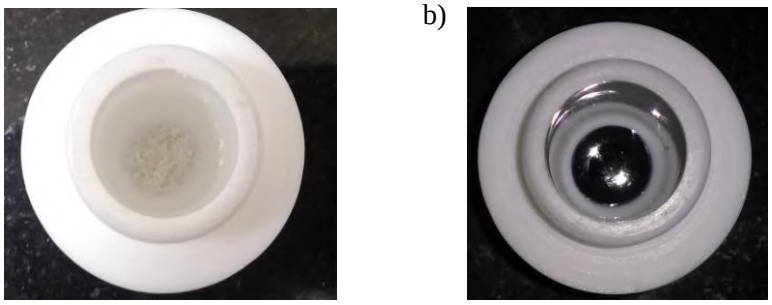


Figure 4.7. a) *p*-Bromoaniline before treatment with PhI and mCPBA. b) Color of reaction mixture of *p*-Bromoaniline and 10 mol % PhI and 1 equiv *m*CPBA.

Pictorial Presentation of Reactivity of Dibenzylamine with PhI and mCPBA:

c) d)

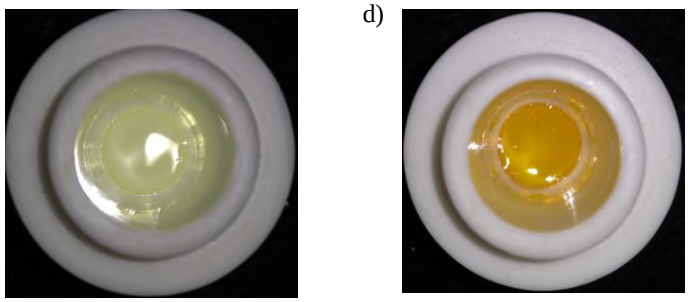


Figure 4.8. c) Dibenzylamine before treatment with PhI and mCPBA. d) Color of reaction mixture of dibenzylamine and 10 mol % PhI and 1 equiv *m*CPBA.

Pictorial Presentation of Reactivity of Substrate 1a with PhI and mCPBA:

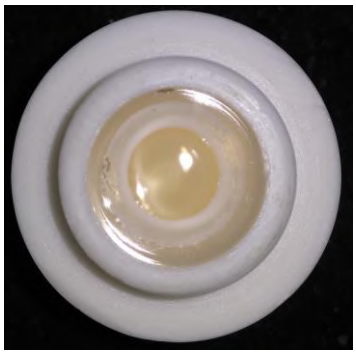
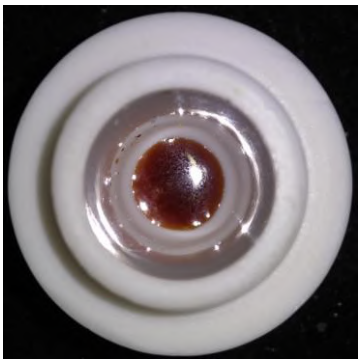
e)  f) 

Figure 4.9. e) Substrate **1a** before treatment with PhI and mCPBA. f) Color of reaction mixture of **1a** and 10 mol % PhI and 1 equiv *m*CPBA.

4.6. NOTES AND REFERENCE

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Copies of ^{1}H and ^{13}C NMR Spectra of Compounds

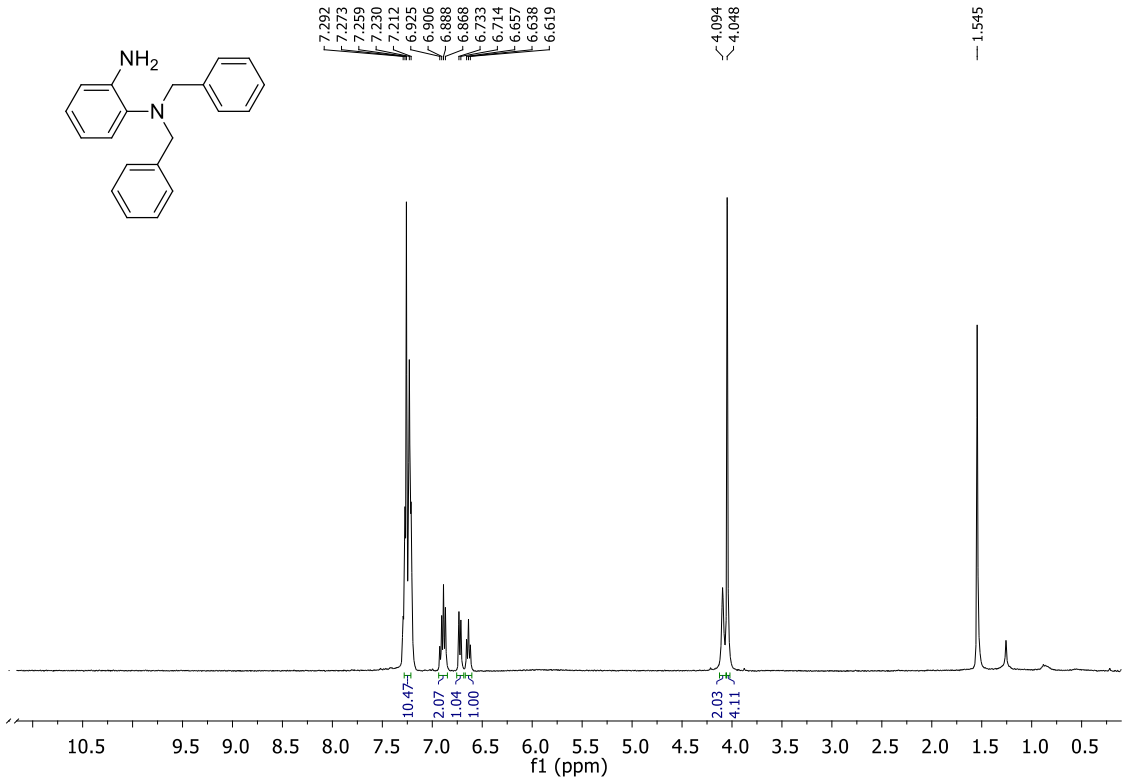


Figure 4.10. ^{1}H NMR of N^{1},N^{1}-dibenzylbenzene-1,2-diamine (**1a**)

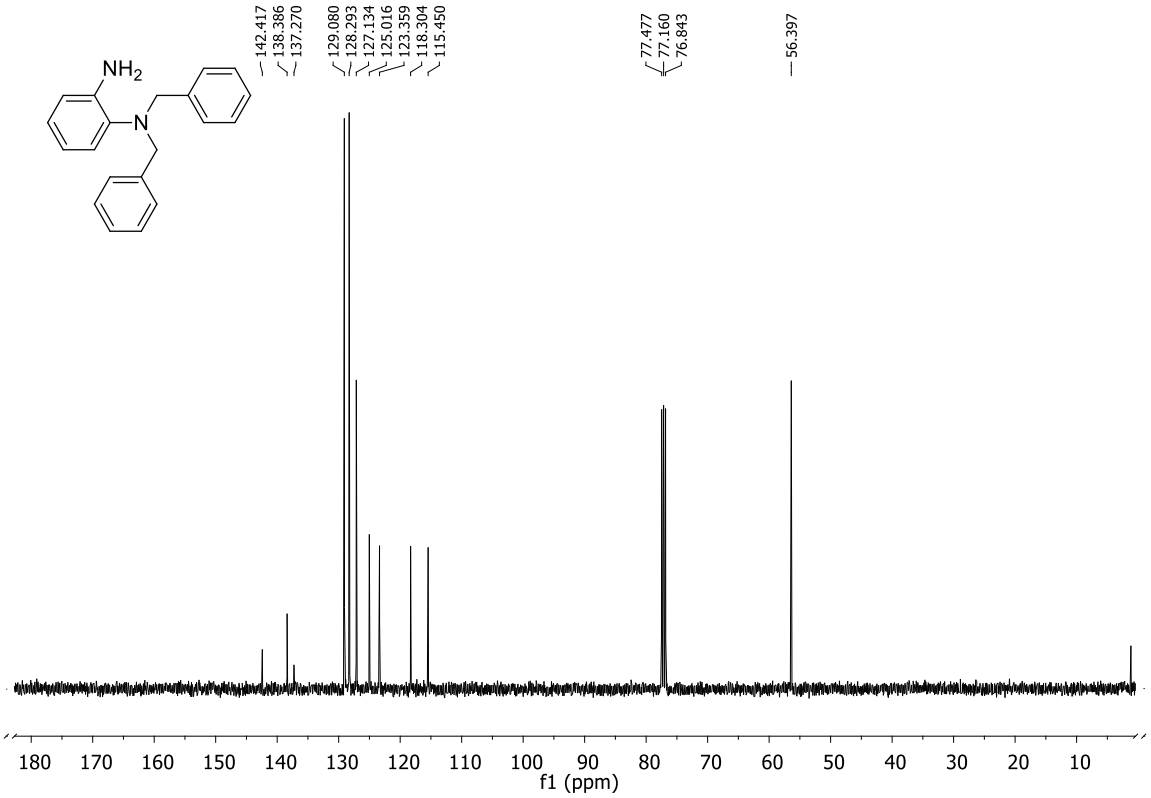


Figure 4.11. ^{13}C NMR of N^{1},N^{1}-dibenzylbenzene-1,2-diamine (**1a**)

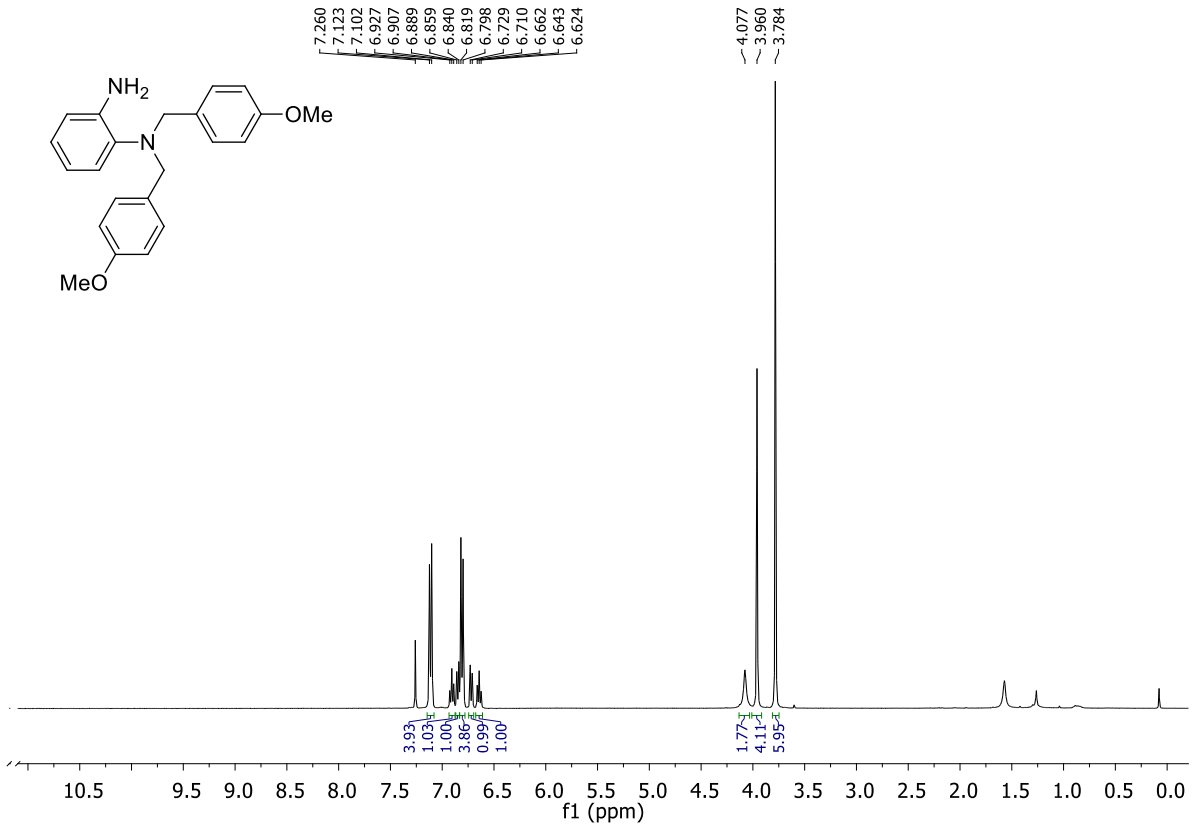


Figure 4.12. ^{1}H NMR of *N*^{1},*N*^{1}- bis(4-methoxybenzyl)benzene-1,2-diamine (**1b**)

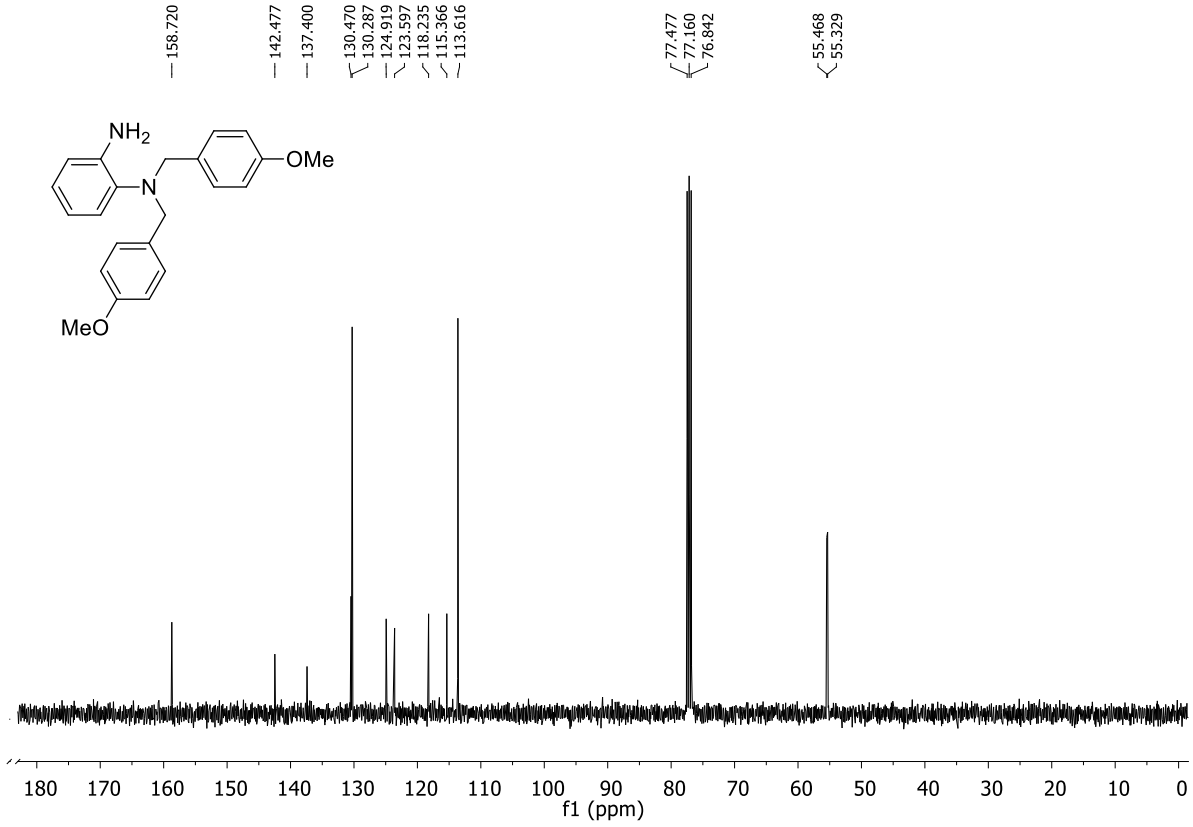


Figure 4.13. ^{13}C NMR of *N*^{1},*N*^{1}- bis(4-methoxybenzyl)benzene-1,2-diamine (**1b**)

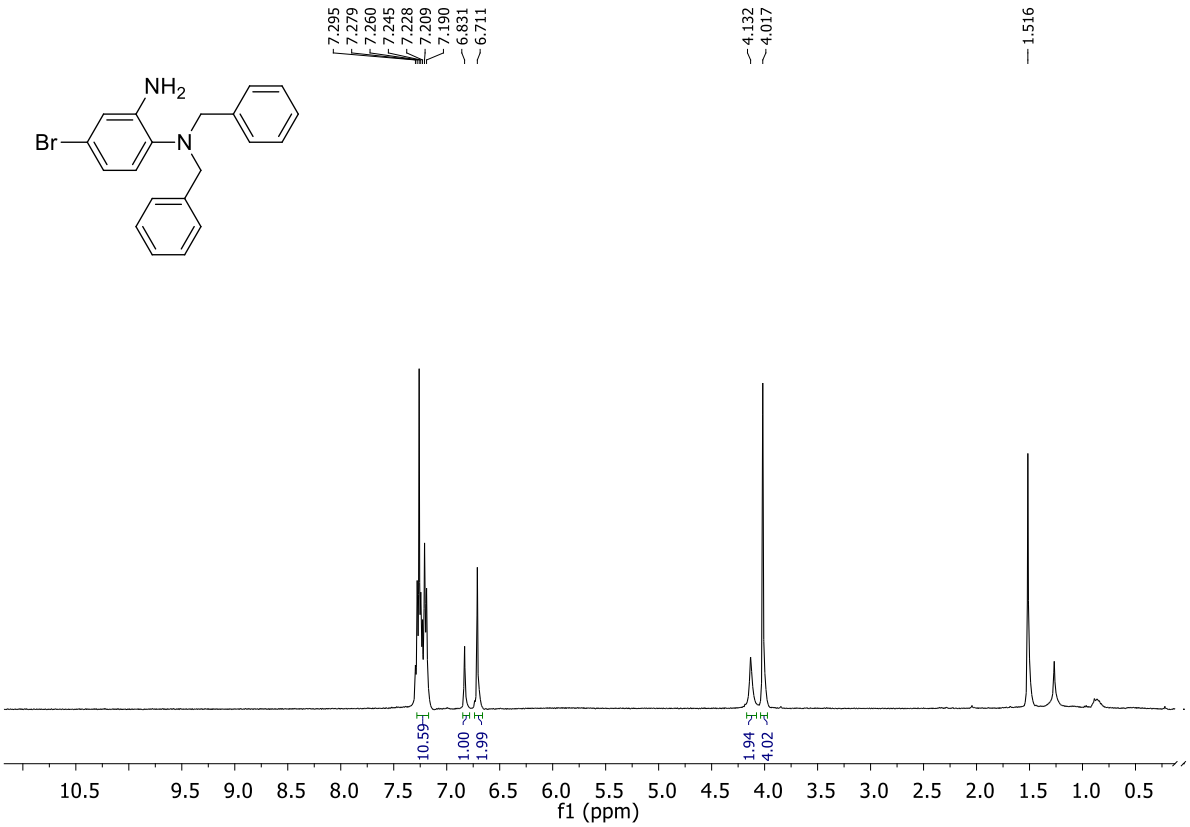


Figure 4.14. ^{1}H NMR of N^{1},N^{1}- dibenzyl-4-bromobenzene-1,2-diamine (**1c**)

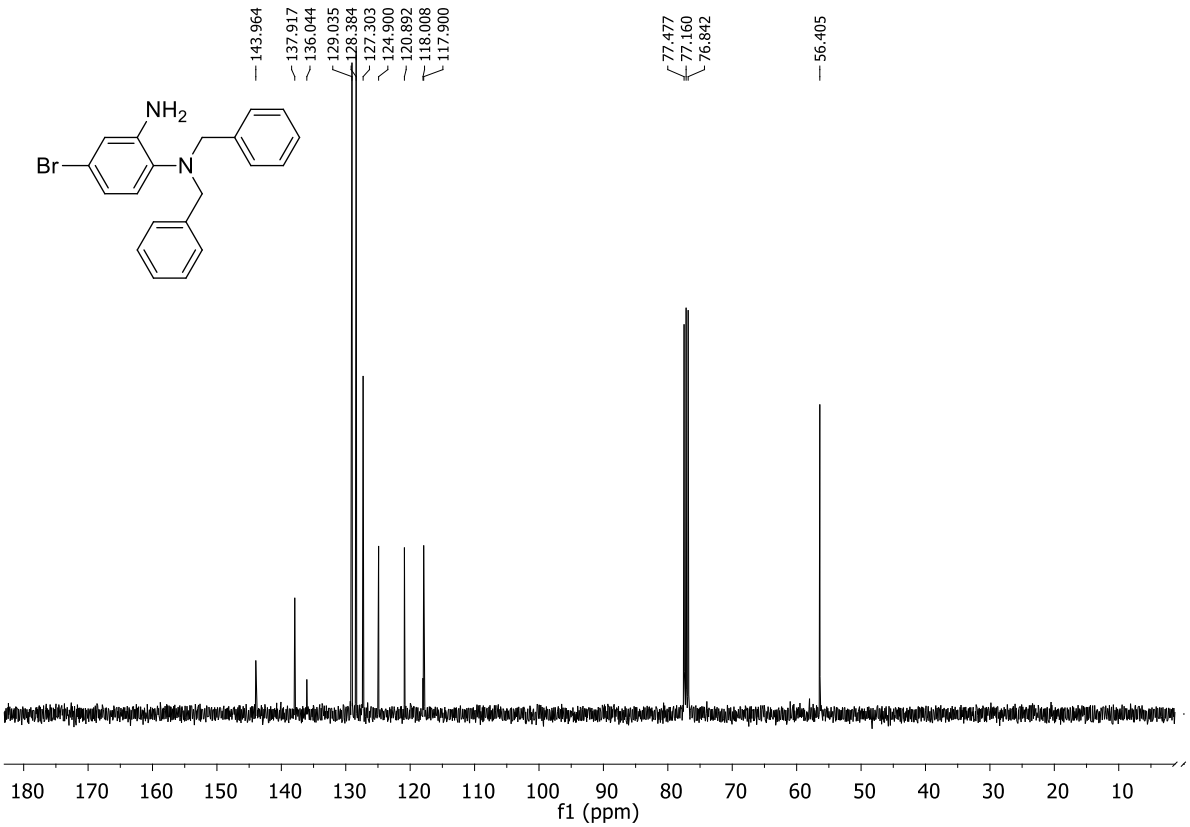


Figure 4.15. ^{13}C NMR of N^{1},N^{1}- dibenzyl-4-bromobenzene-1,2-diamine (**1c**)

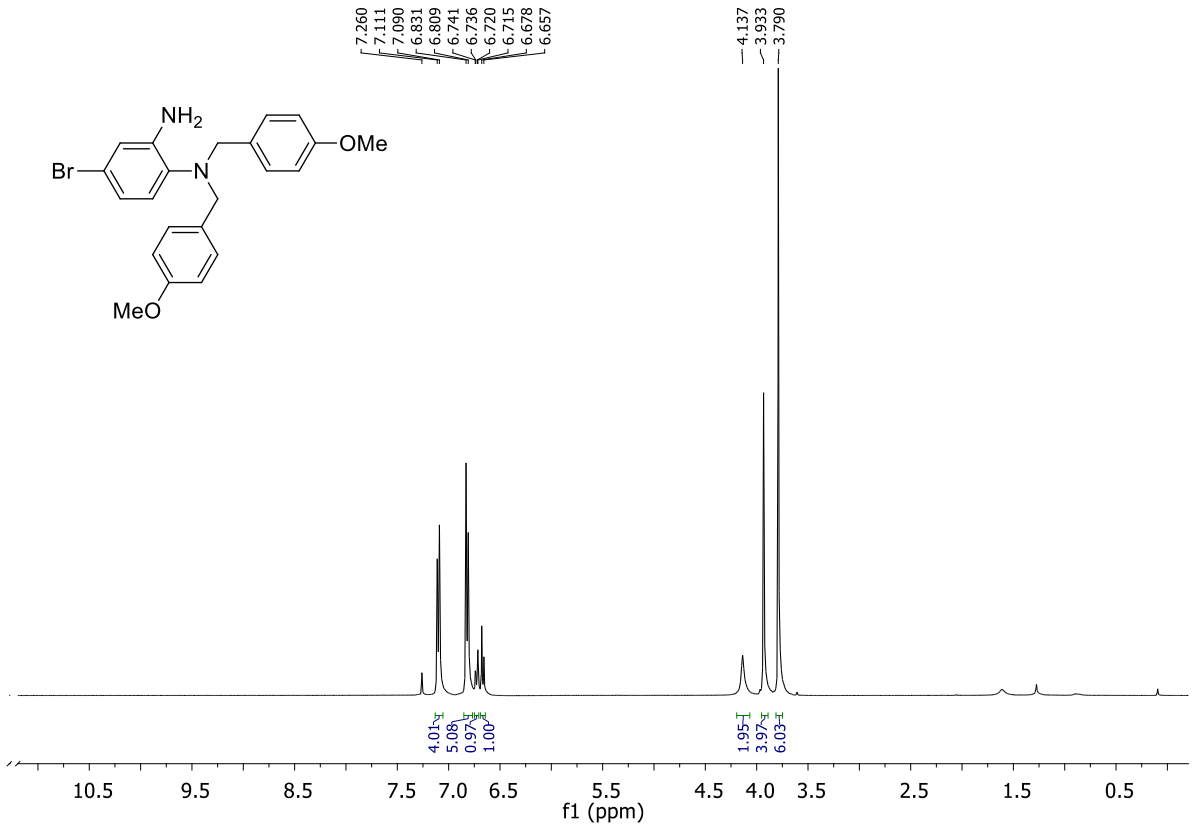


Figure 4.16. ^{1}H NMR of 4-Bromo-N^{1},N^{1}-bis(4-methoxybenzyl)benzene-1,2-diamine (**1d**)

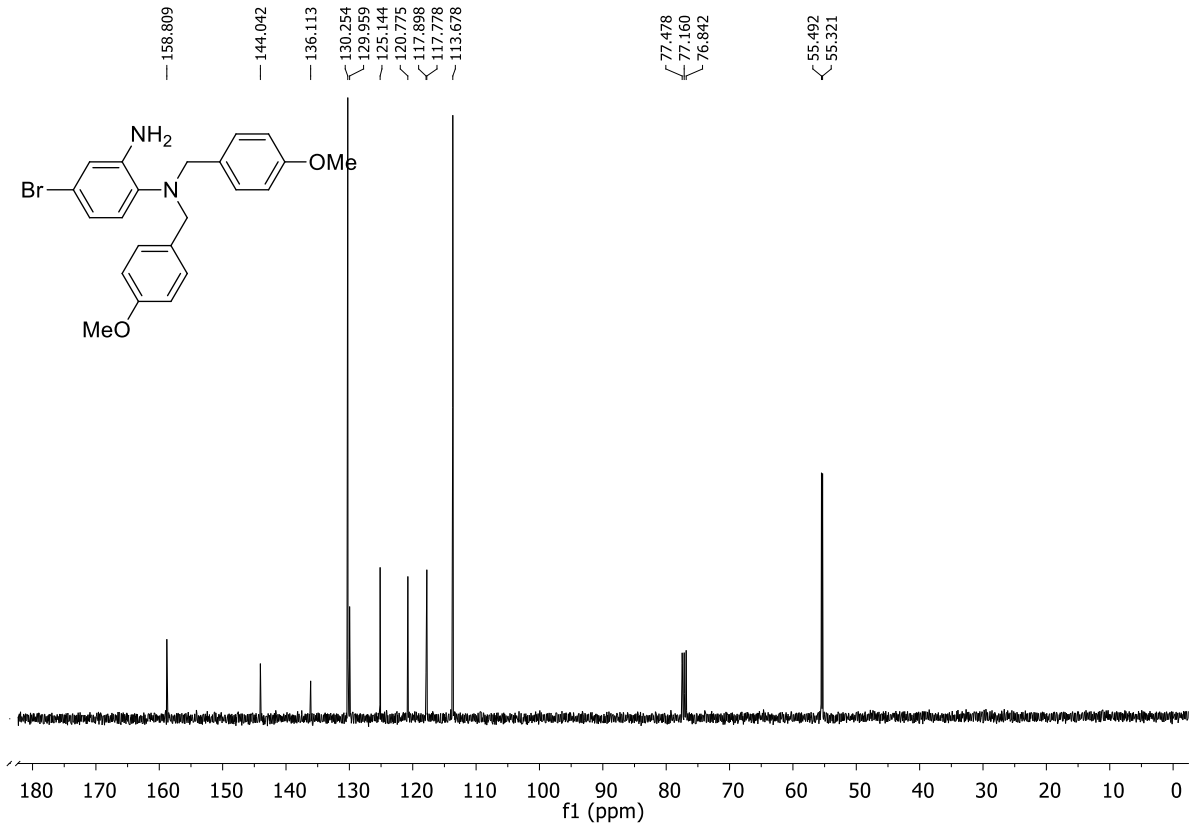


Figure 4.17. ^{13}C NMR of 4-Bromo-N^{1},N^{1}-bis(4-methoxybenzyl)benzene-1,2-diamine (**1d**)

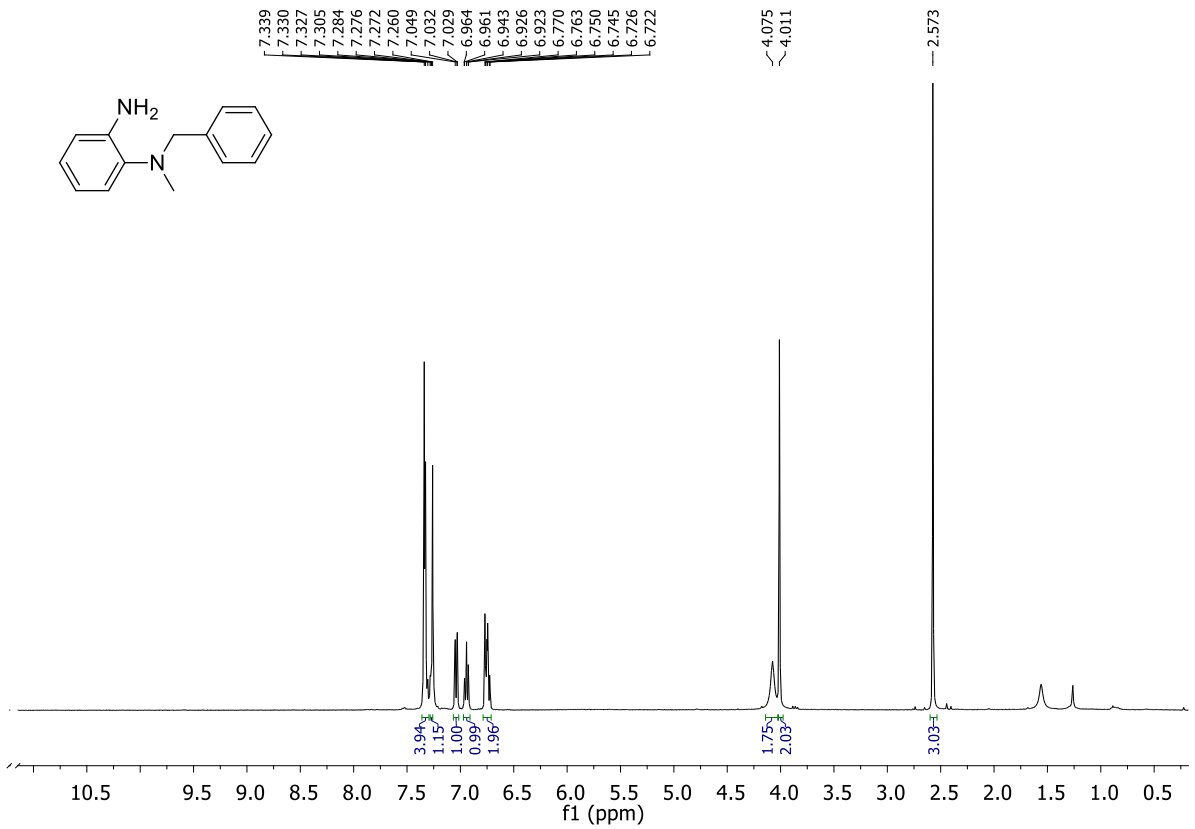


Figure 4.18. ^{1}H NMR of *N*^{1}-benzyl-*N*^{1}-methylbenzene-1,2-diamine (**1e**)

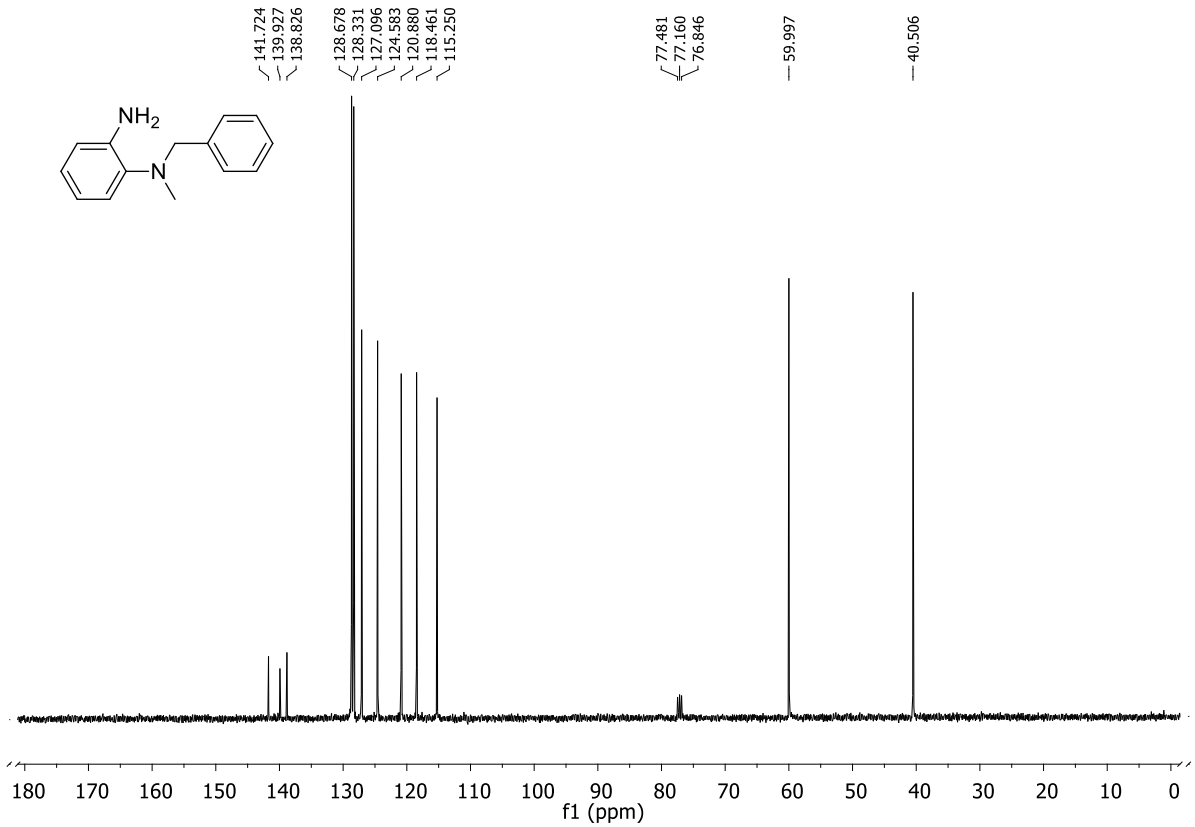


Figure 4.19. ^{13}C NMR of *N*^{1}-benzyl-*N*^{1}-methylbenzene-1,2-diamine (**1e**)

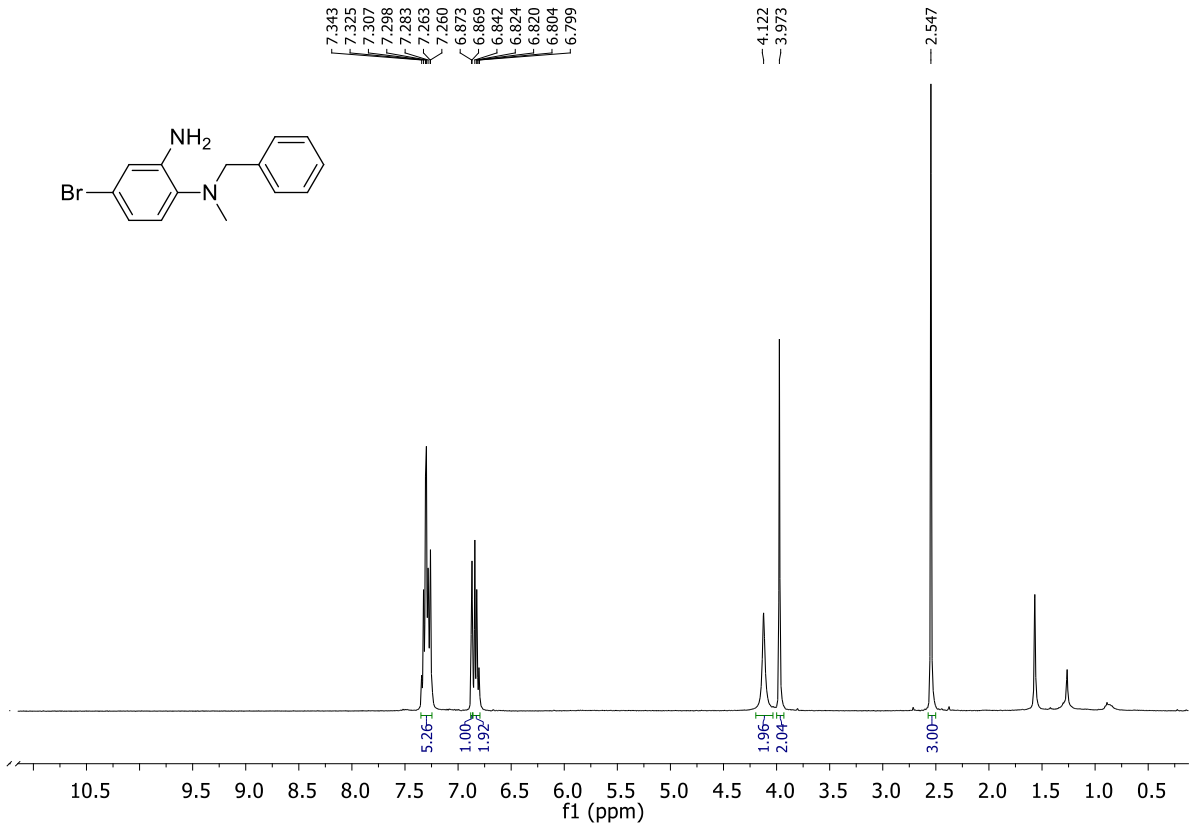


Figure 4.20. ^{1}H NMR of *N*^{1}-Benzyl-4-bromo-*N*^{1}-methylbenzene-1,2-diamine (**1f**)

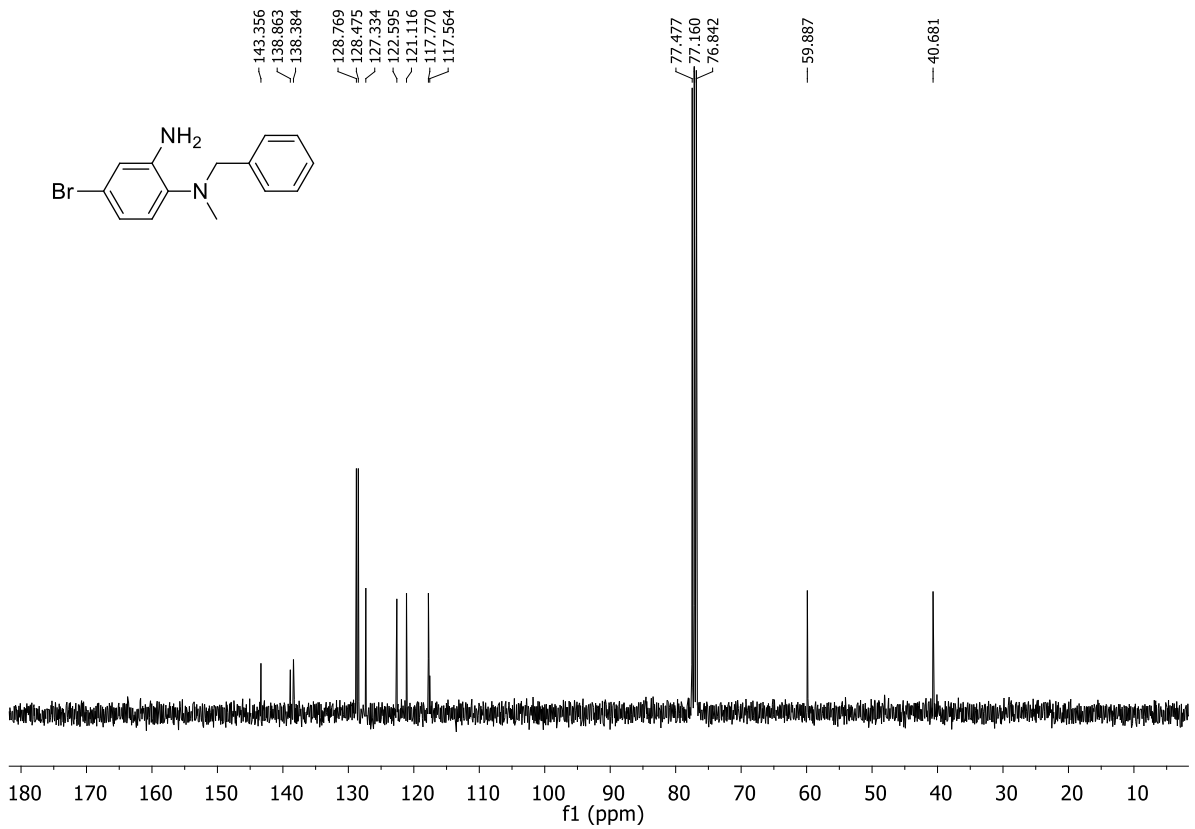


Figure 4.21. ^{13}C NMR of *N*^{1}-Benzyl-4-bromo-*N*^{1}-methylbenzene-1,2-diamine (**1f**)

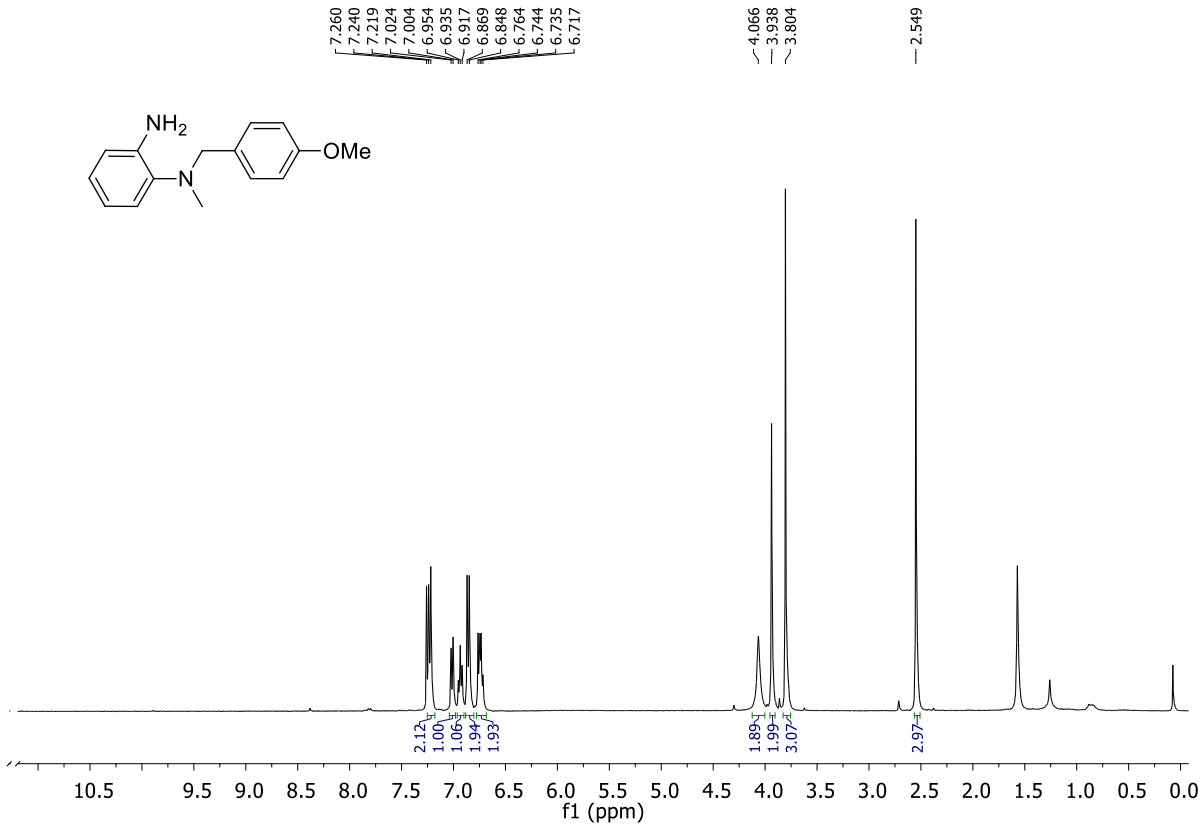


Figure 4.22. ^{1}H NMR of *N*^{1}-(4-methoxybenzyl)-*N*^{1}-methylbenzene-1,2-diamine (**1g**)

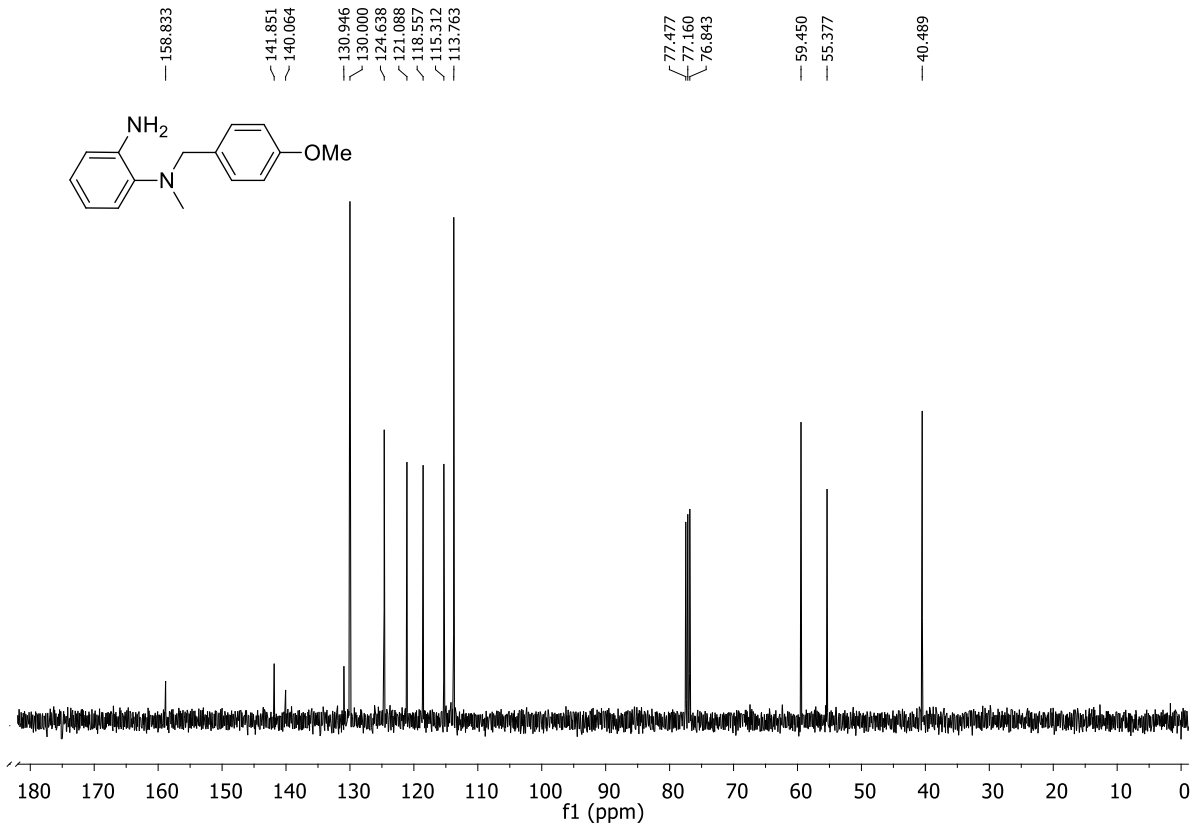


Figure 4.23. ^{13}C NMR of *N*^{1}-(4-methoxybenzyl)-*N*^{1}-methylbenzene-1,2-diamine (**1g**)

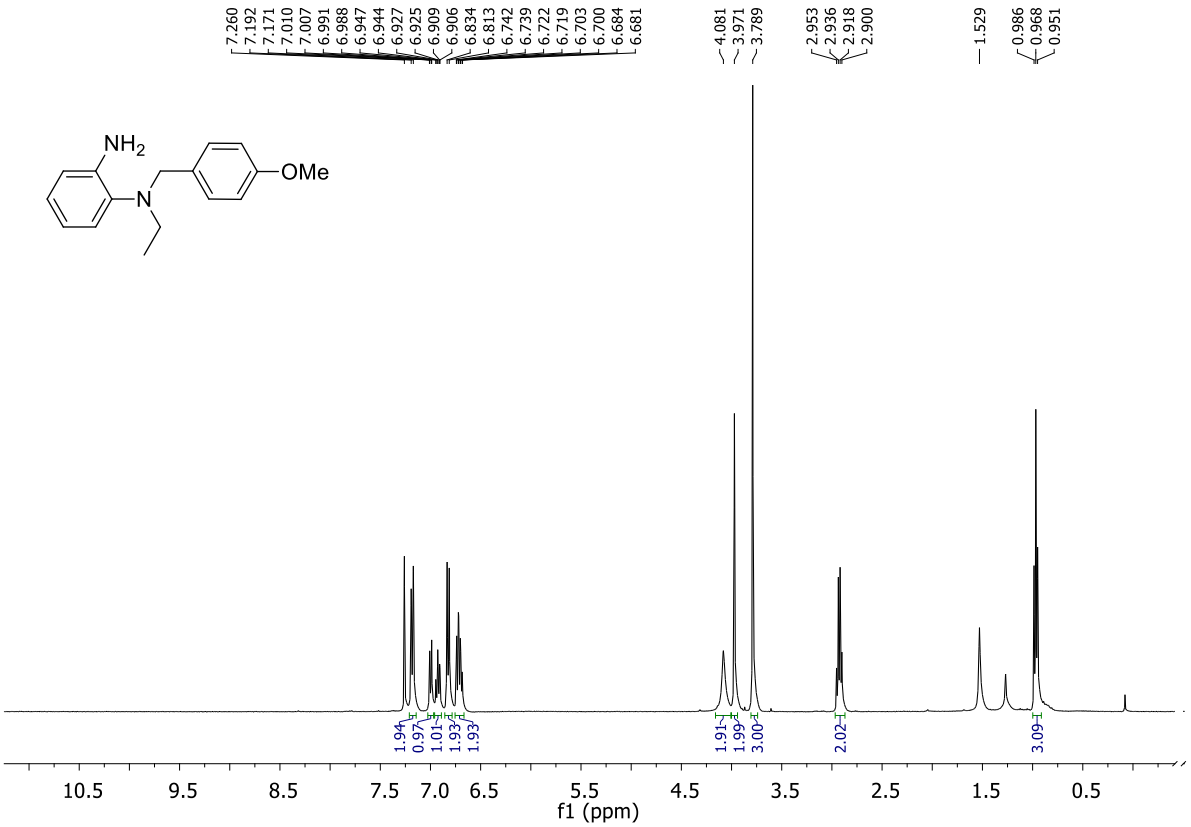


Figure 4.24. ^{1}H NMR of *N*^{1}-ethyl-*N*^{1}-(4-methoxybenzyl)benzene-1,2-diamine (**1h**)

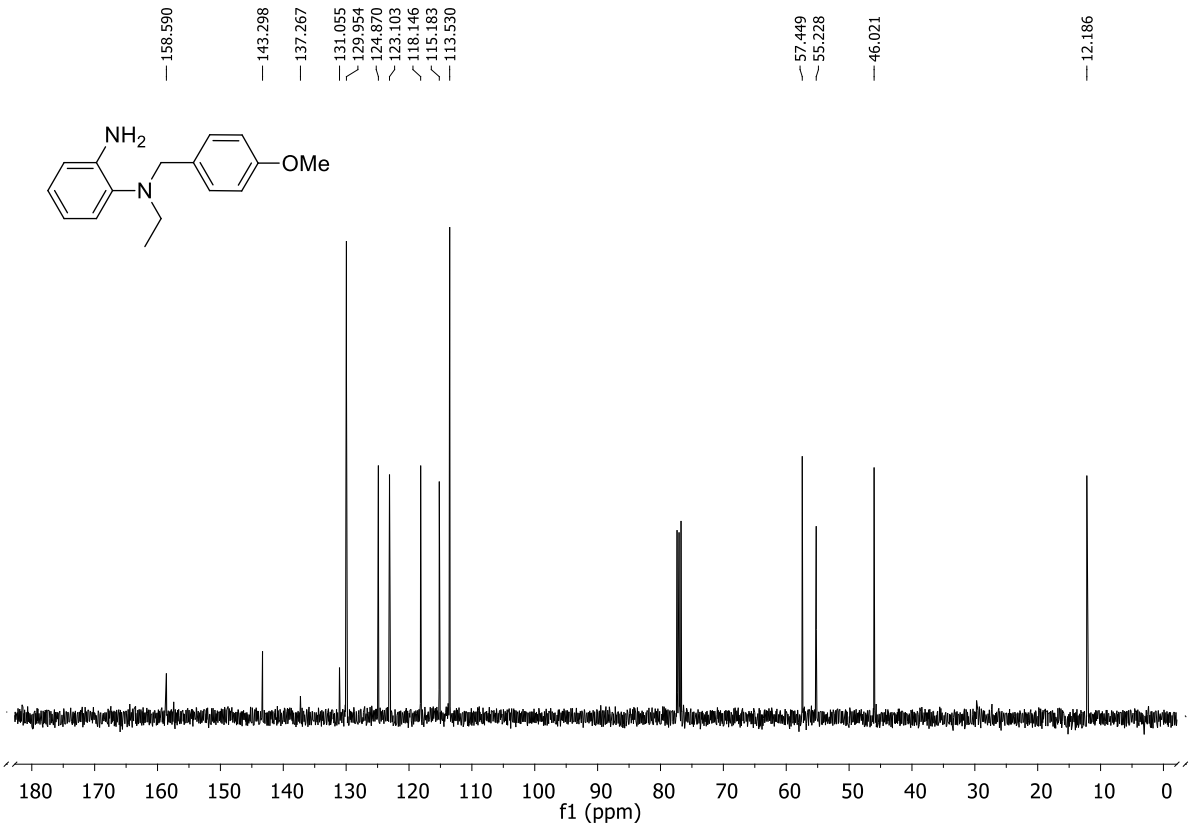


Figure 4.25. ^{13}C NMR of *N*^{1}-ethyl-*N*^{1}-(4-methoxybenzyl)benzene-1,2-diamine (**1h**)

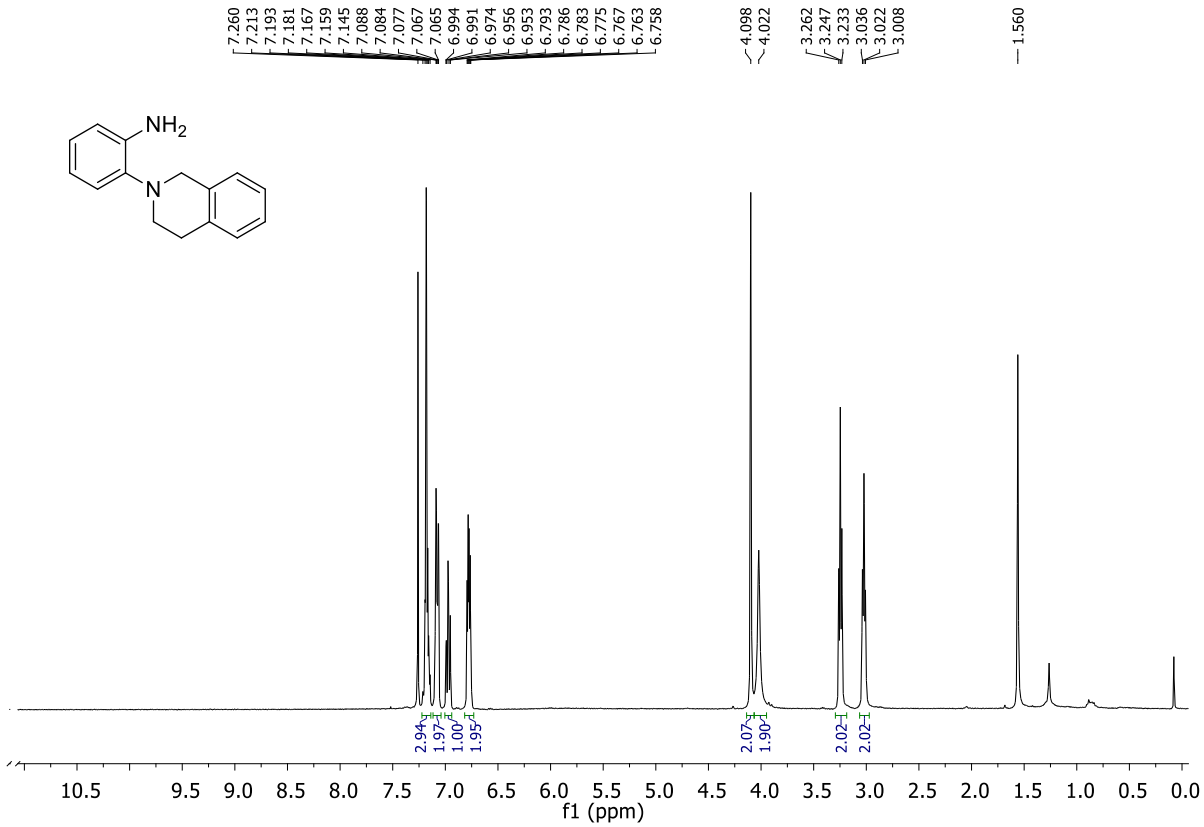


Figure 4.26. ^{1}H NMR of 2-(3,4-Dihydroisoquinolin-2-yl)aniline (**1i**)

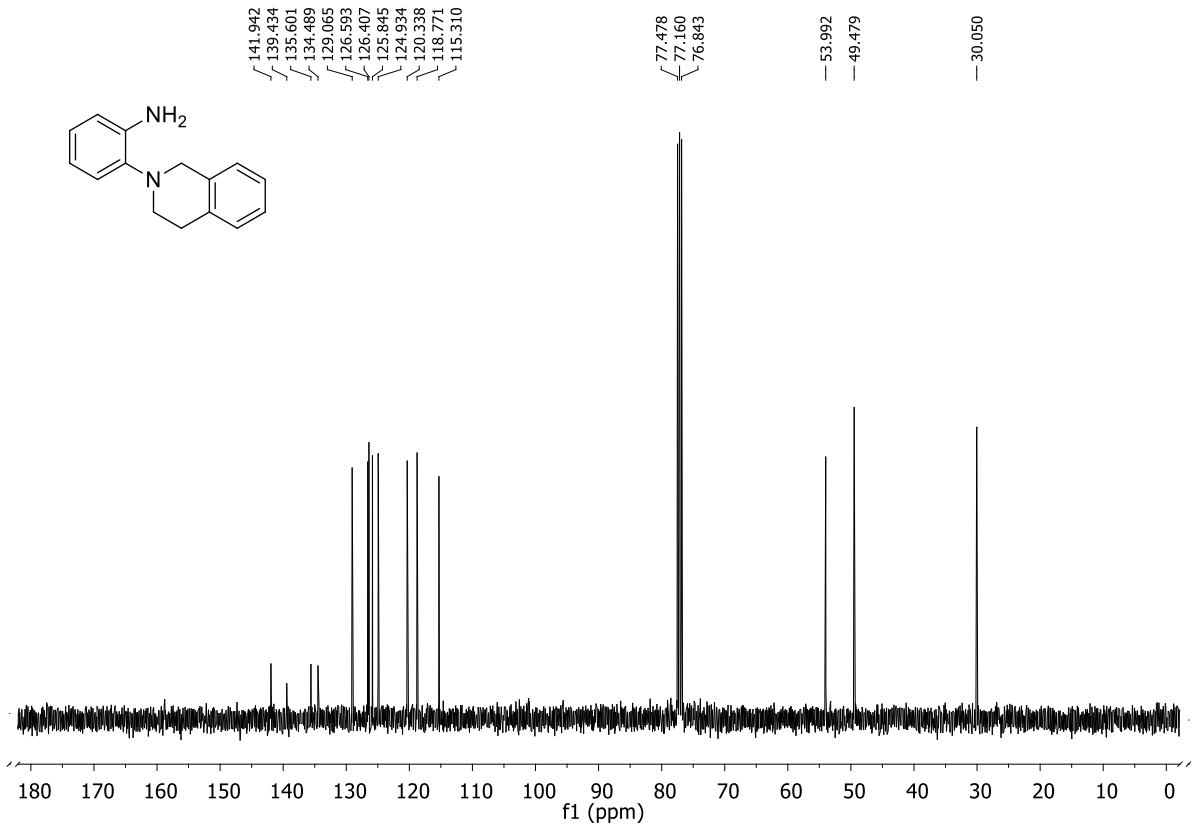


Figure 4.27. ^{13}C NMR of 2-(3,4-Dihydroisoquinolin-2-yl)aniline (**1i**)

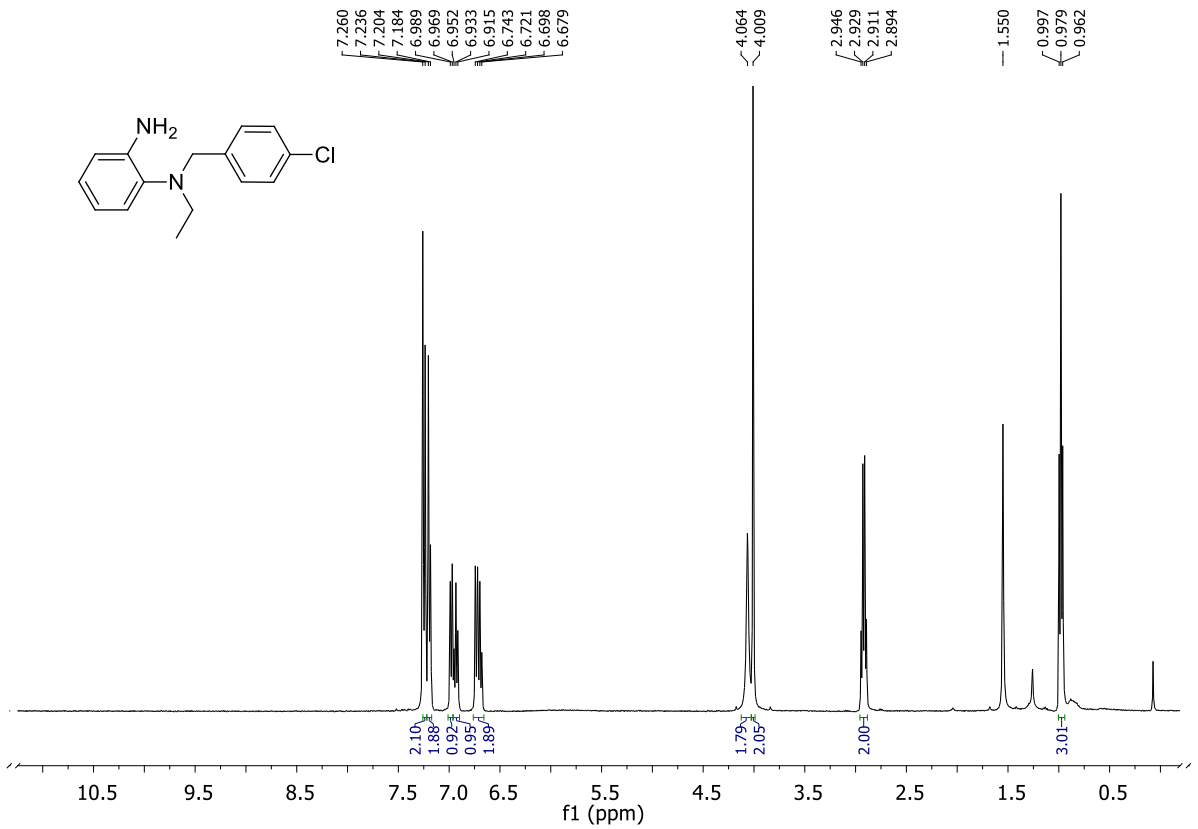


Figure 4.28. ^{1}H NMR of N^{1}-(4-chlorobenzyl)-N^{1}-ethylbenzene-1,2-diamine (**1j**)

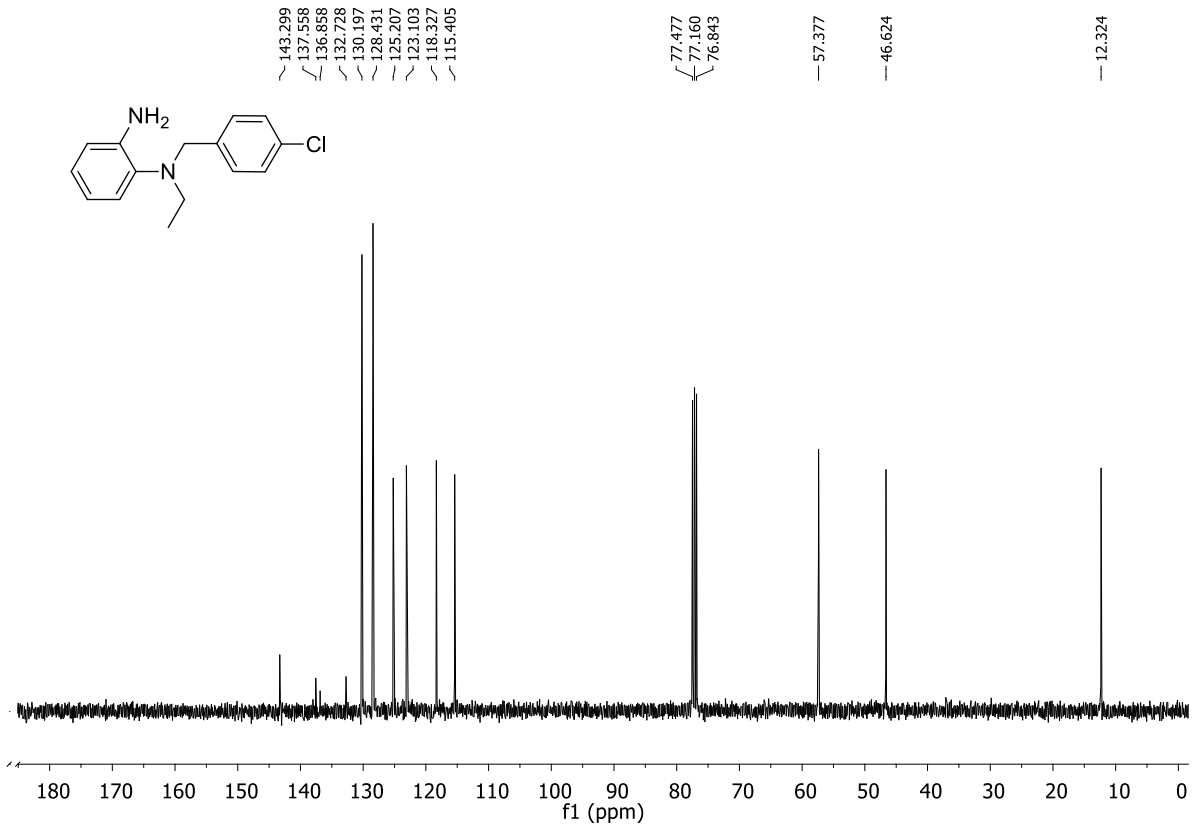


Figure 4.29. ^{13}C NMR of N^{1}-(4-chlorobenzyl)-N^{1}-ethylbenzene-1,2-diamine (**1j**)

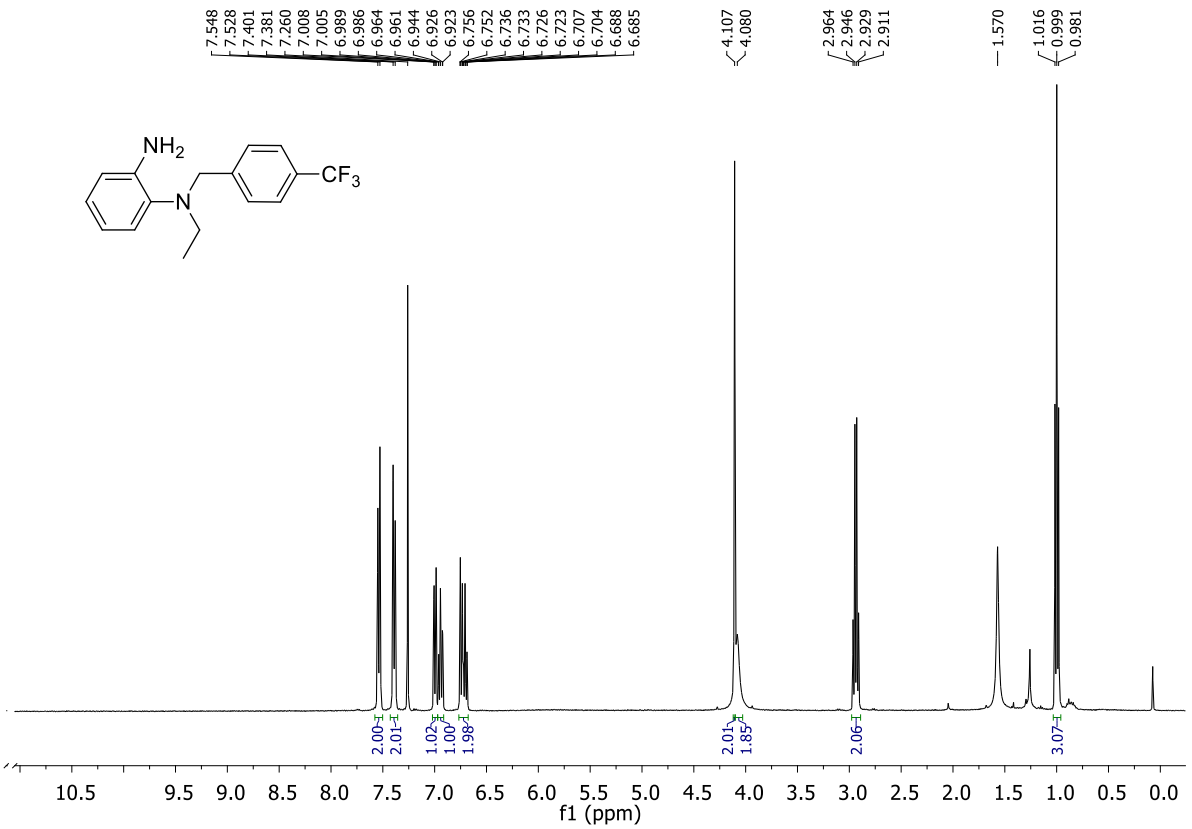


Figure 4.30. ^{1}H NMR of *N*^{1}-ethyl-*N*^{1}-(4-(trifluoromethyl)benzyl)benzene-1,2-diamine (**1k**)

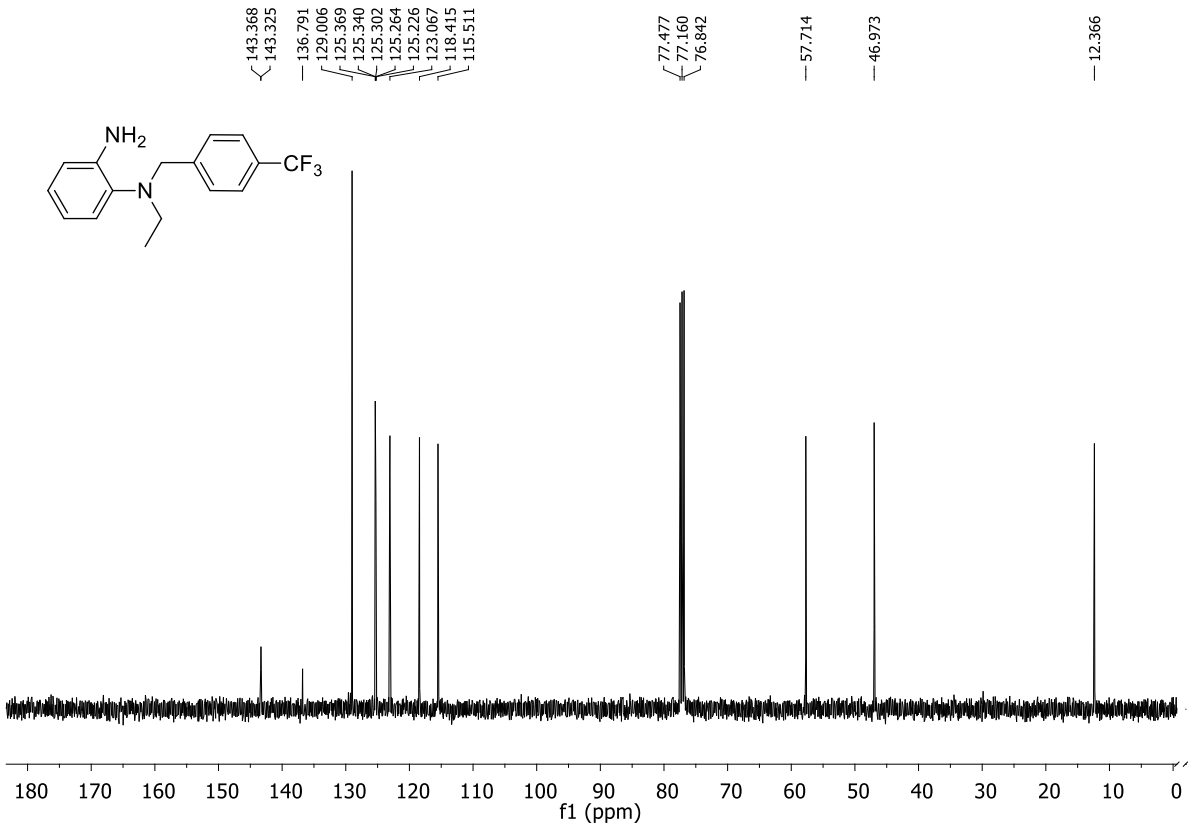


Figure 4.31. ^{13}C NMR of *N*^{1}-ethyl-*N*^{1}-(4-(trifluoromethyl)benzyl)benzene-1,2-diamine (**1k**)

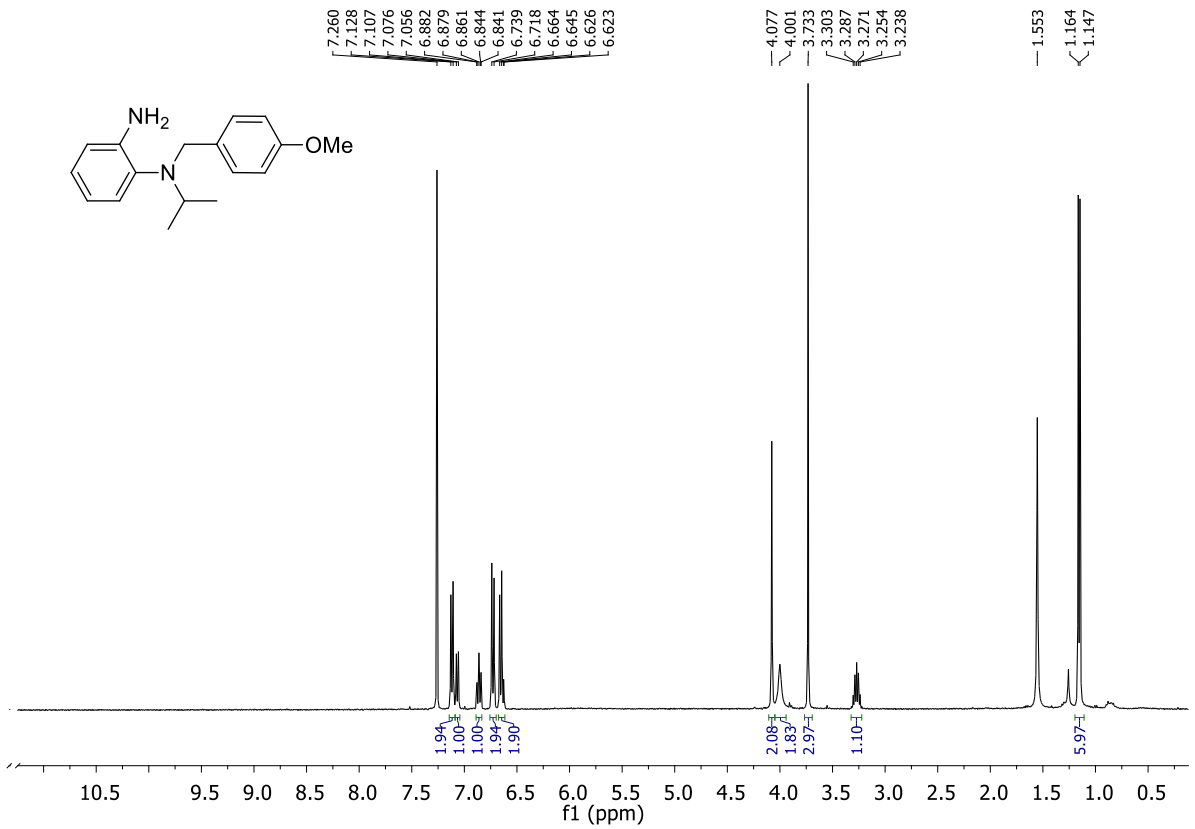


Figure 4.32. ^{1}H NMR of *N*^{1}-isopropyl-*N*^{1}-(4-methoxybenzyl)benzene-1,2-diamine (**1l**)

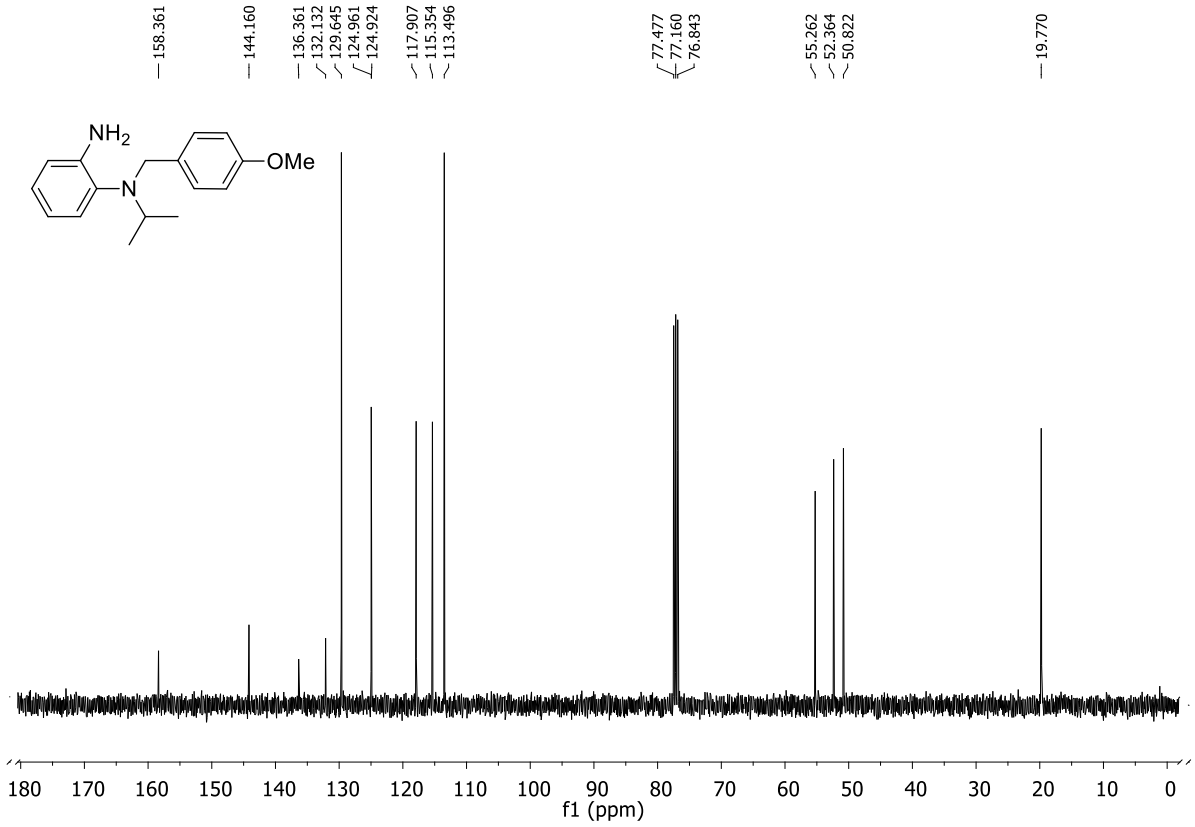


Figure 4.33. ^{13}C NMR of *N*^{1}-isopropyl-*N*^{1}-(4-methoxybenzyl)benzene-1,2-diamine (**1l**)

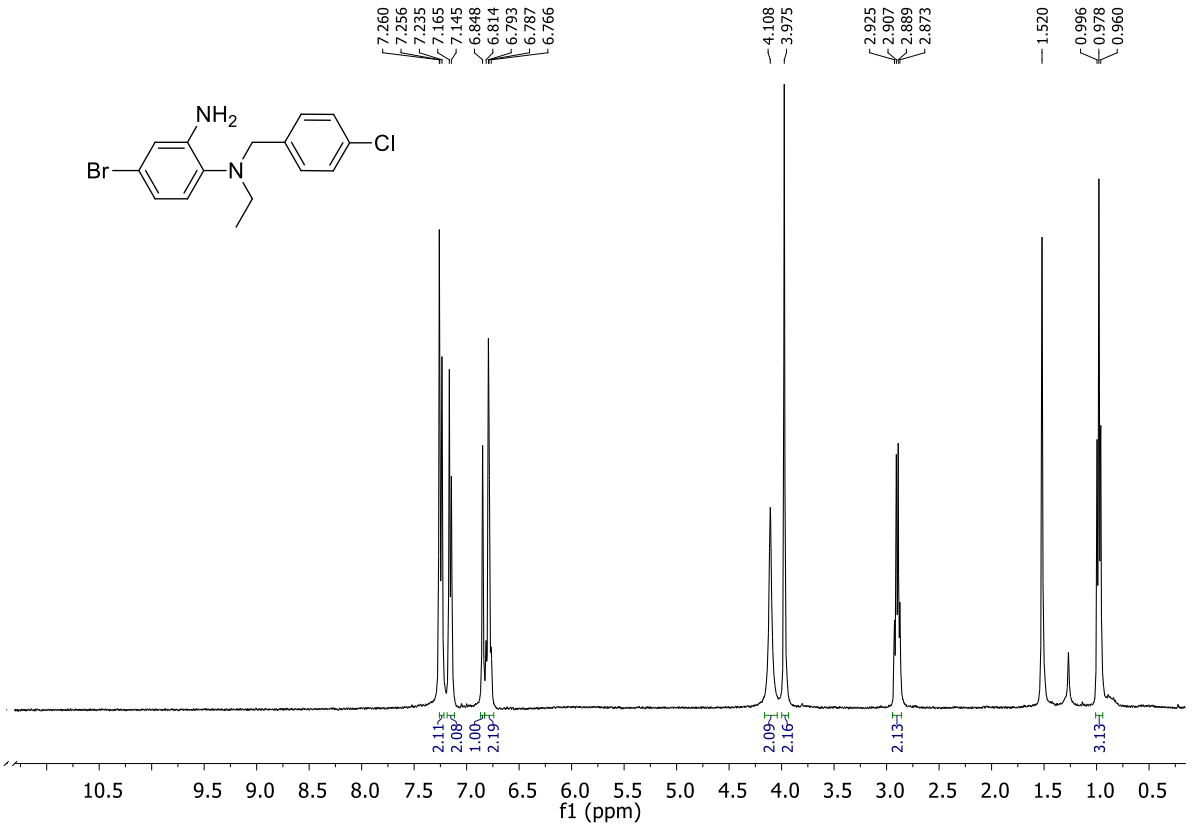


Figure 4.34. ^{1}H NMR of 4-Bromo-*N*^{1}-(4-chlorobenzyl)-*N*^{1}-ethylbenzene-1,2-diamine (**1m**)

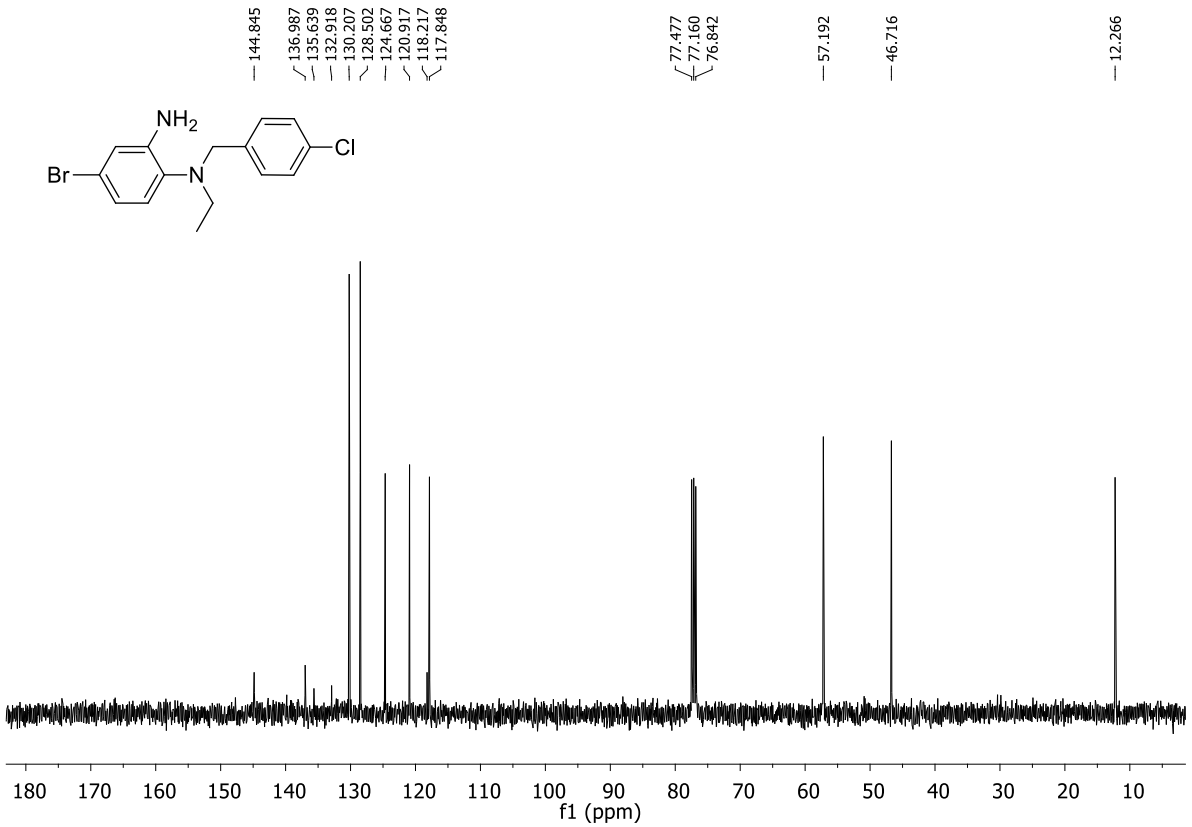


Figure 4.35. ^{13}C NMR of 4-Bromo-*N*^{1}-(4-chlorobenzyl)-*N*^{1}-ethylbenzene-1,2-diamine (**1m**)

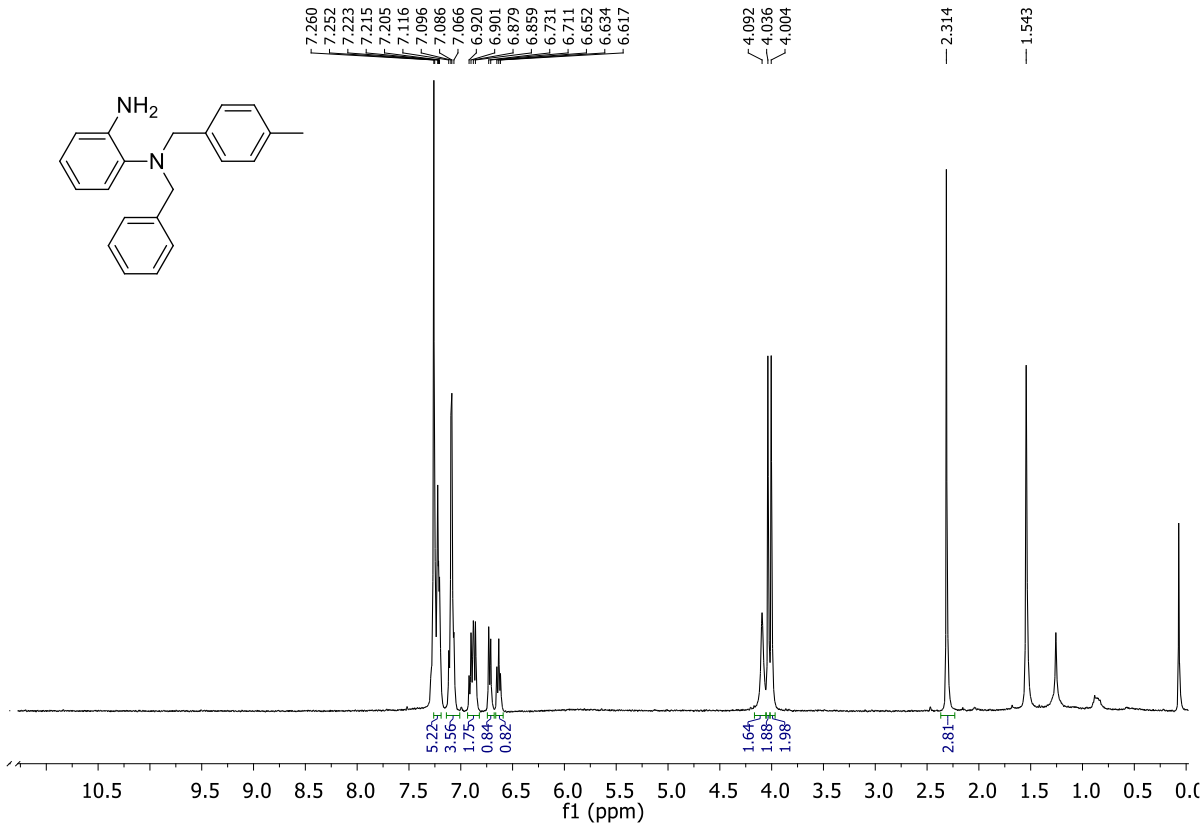


Figure 4.36. ^{1}H NMR of *N*^{1}-benzyl-*N*^{1}-(4-methylbenzyl)benzene-1,2-diamine (**1n**)

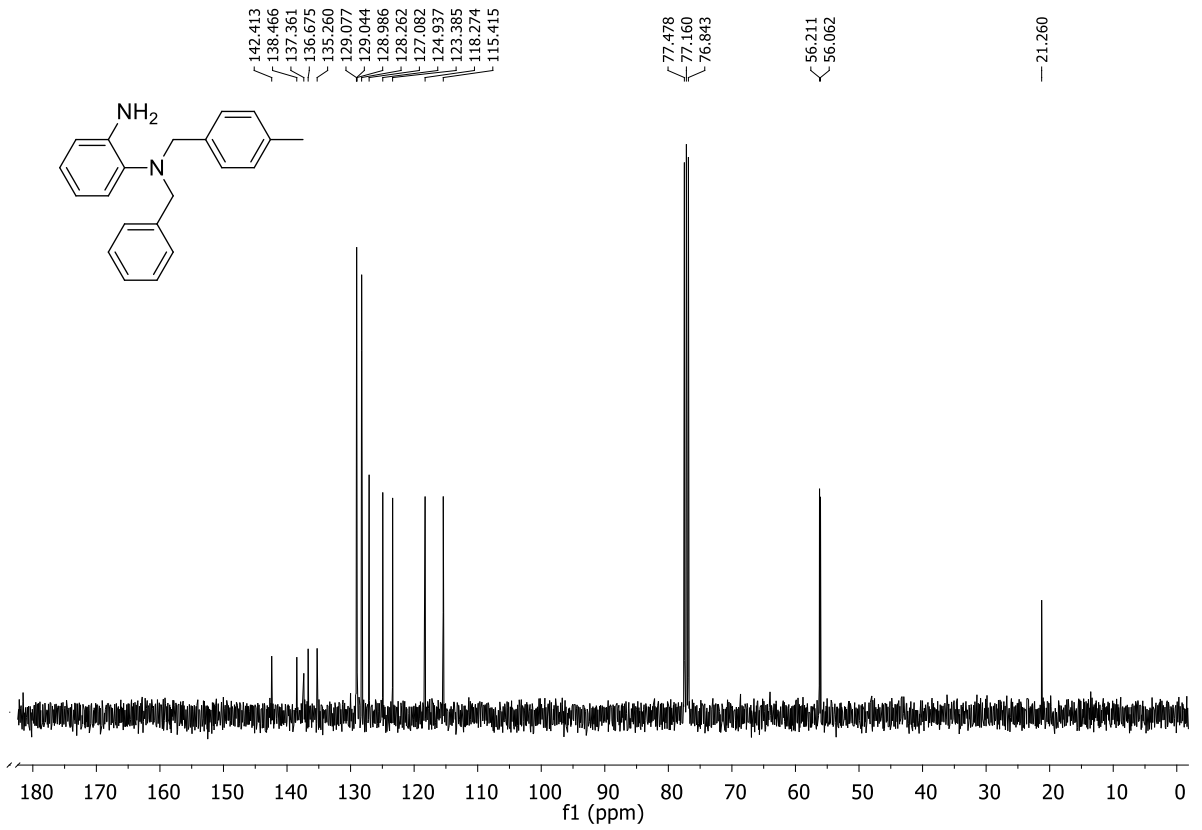


Figure 4.37. ^{13}C NMR of *N*^{1}-benzyl-*N*^{1}-(4-methylbenzyl)benzene-1,2-diamine (**1n**)

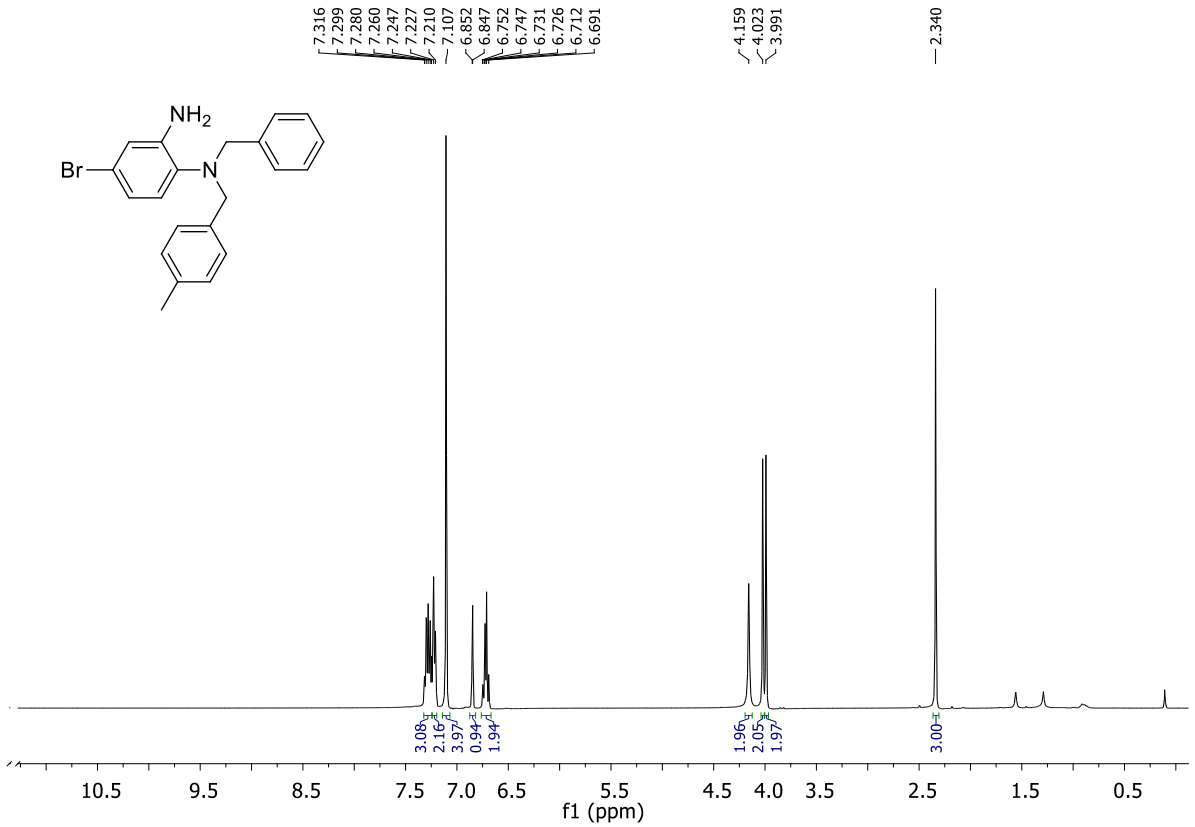


Figure 4.38. ^{1}H NMR of *N*^{1}-benzyl-4-bromo-*N*^{1}-(4-methylbenzyl)benzene-1,2-diamine (**1o**)

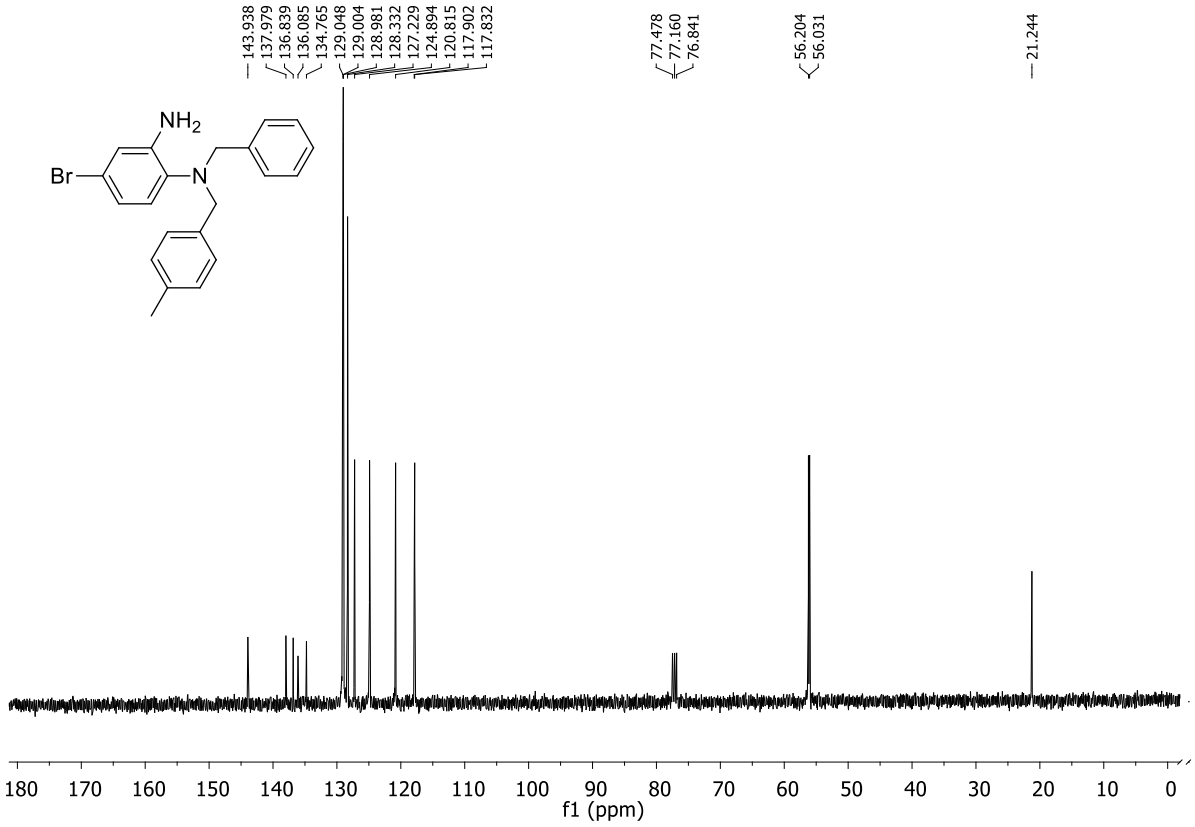


Figure 4.39. ^{13}C NMR of *N*^{1}-benzyl-4-bromo-*N*^{1}-(4-methylbenzyl)benzene-1,2-diamine (**1o**)

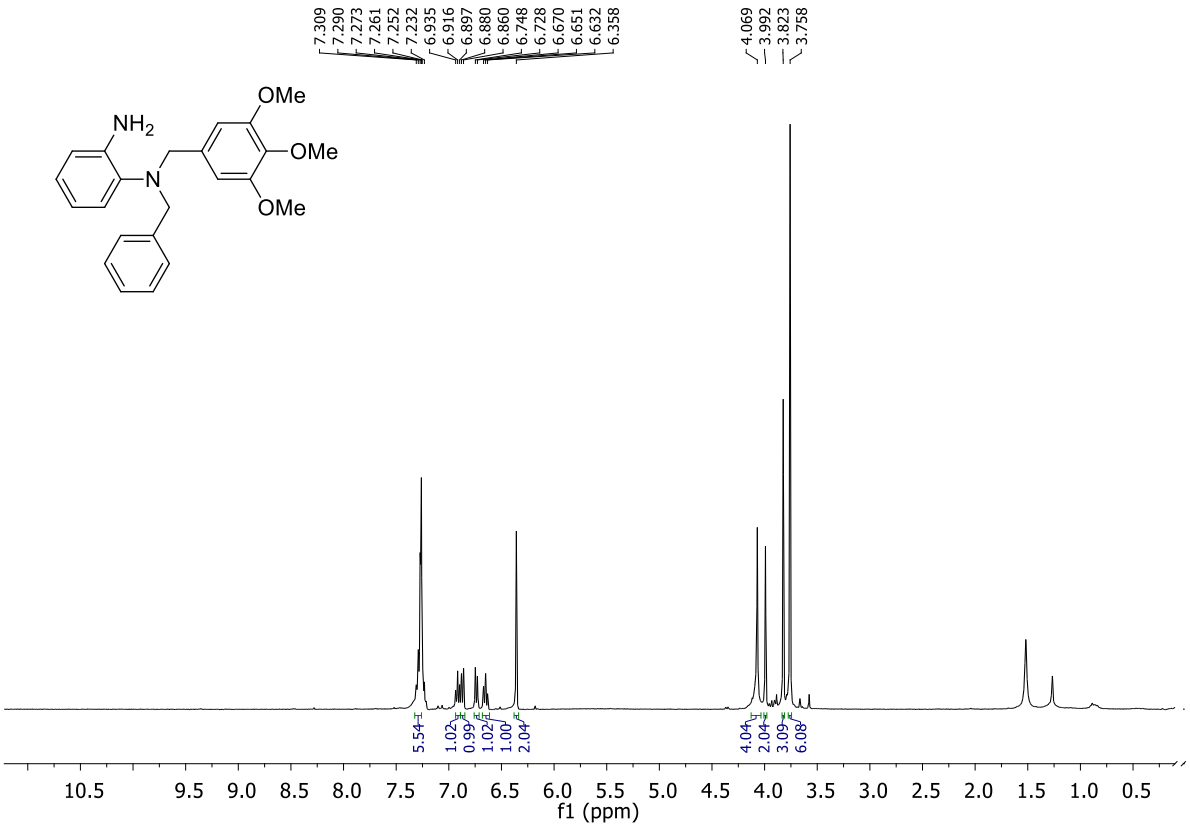


Figure 4.40. ^{1}H NMR of N^{1}-benzyl-N^{1}-(3,4,5-trimethoxybenzyl)benzene-1,2-diamine (**1p**)

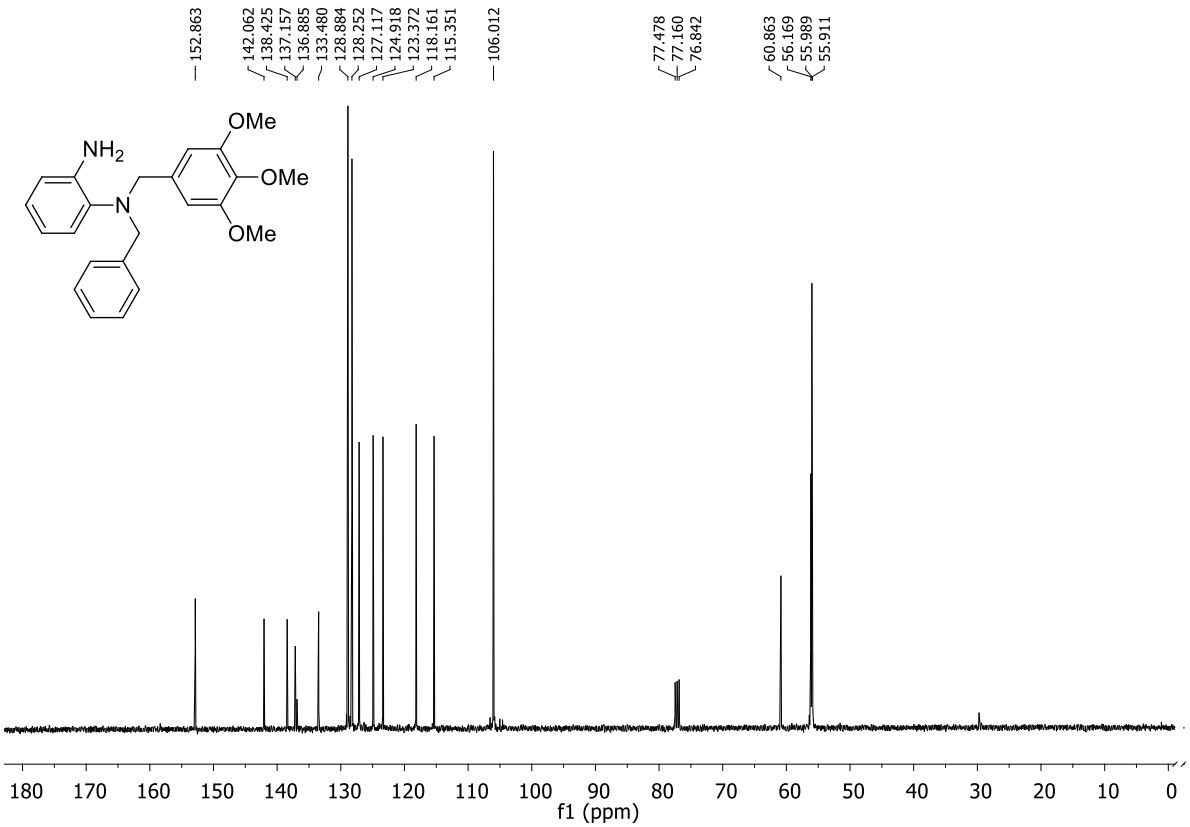


Figure 4.41. ^{13}C NMR of N^{1}-benzyl-N^{1}-(3,4,5-trimethoxybenzyl)benzene-1,2-diamine (**1p**)

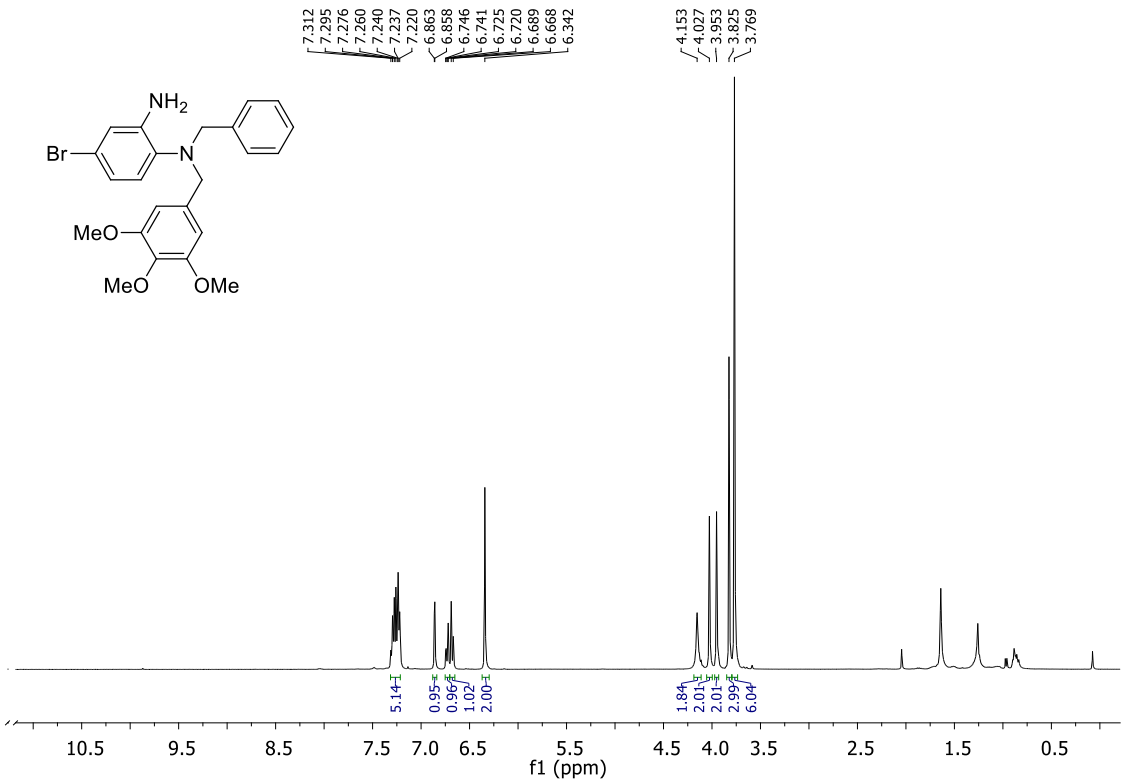


Figure 4.42. ^{1}H NMR of *N*^{1}-benzyl-4-bromo-*N*^{1}-(3,4,5-trimethoxybenzyl)benzene-1,2-diamine (**1q**)

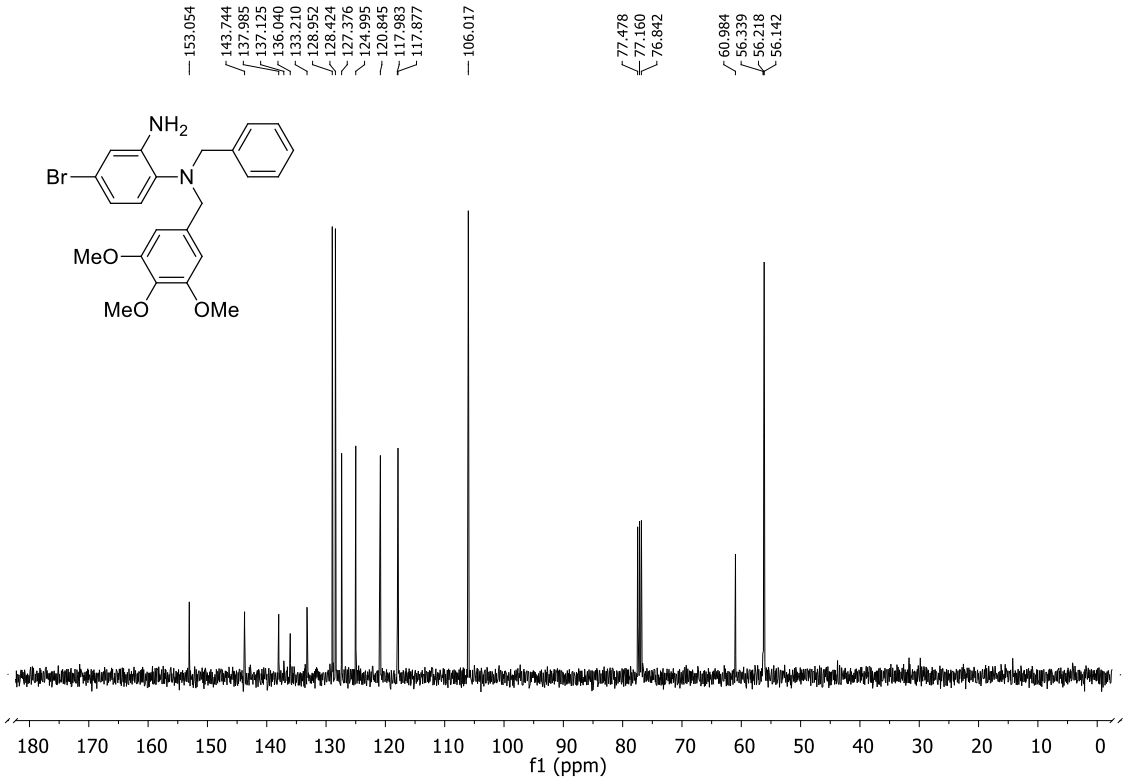


Figure 4.43. ^{13}C NMR of *N*^{1}-benzyl-4-bromo-*N*^{1}-(3,4,5-trimethoxybenzyl)benzene-1,2-diamine (**1q**)

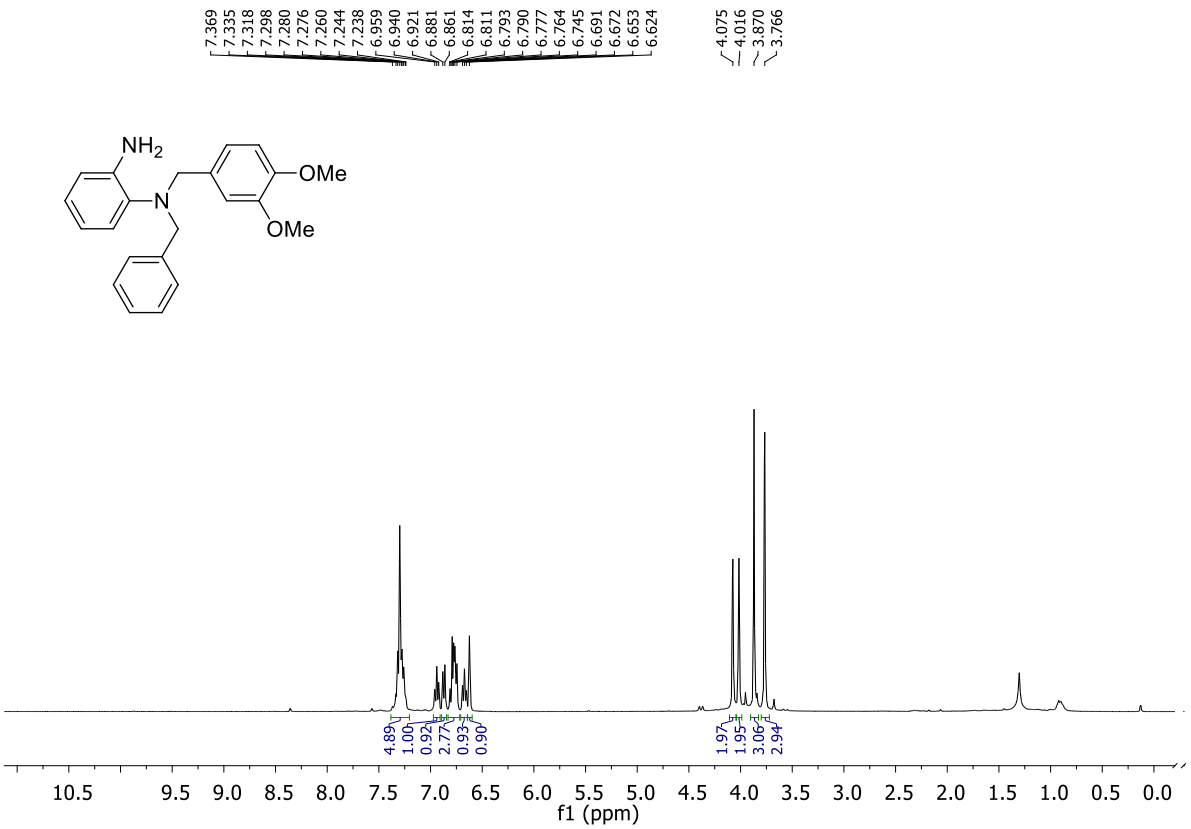


Figure 4.44. ^{1}H NMR of N^{1}-benzyl-N^{1}-(3,4-dimethoxybenzyl)benzene-1,2-diamine (**1r**)

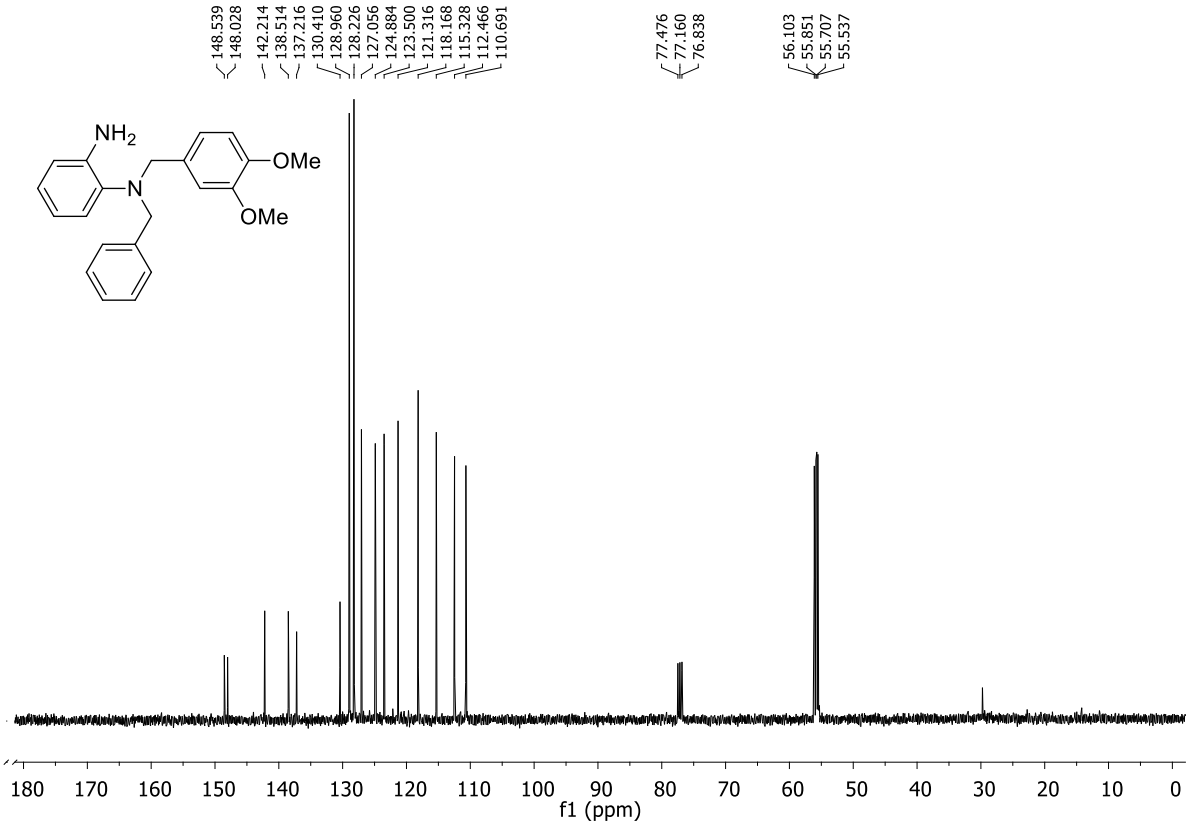


Figure 4.45. ^{13}C NMR of N^{1}-benzyl-N^{1}-(3,4-dimethoxybenzyl)benzene-1,2-diamine (**1r**)

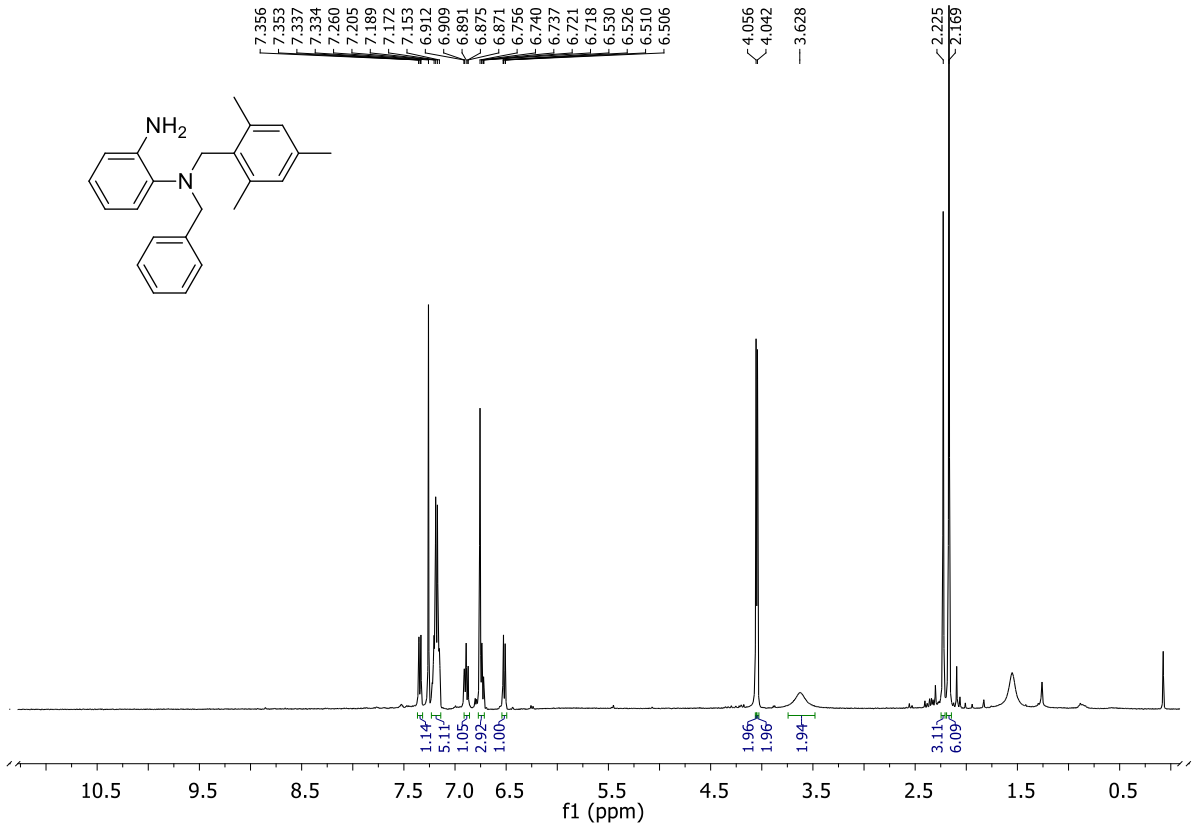


Figure 4.46. ^{1}H NMR of *N*^{1}-benzyl-*N*^{1}-(2,4,6-trimethylbenzyl)benzene-1,2-diamine (**1s**)

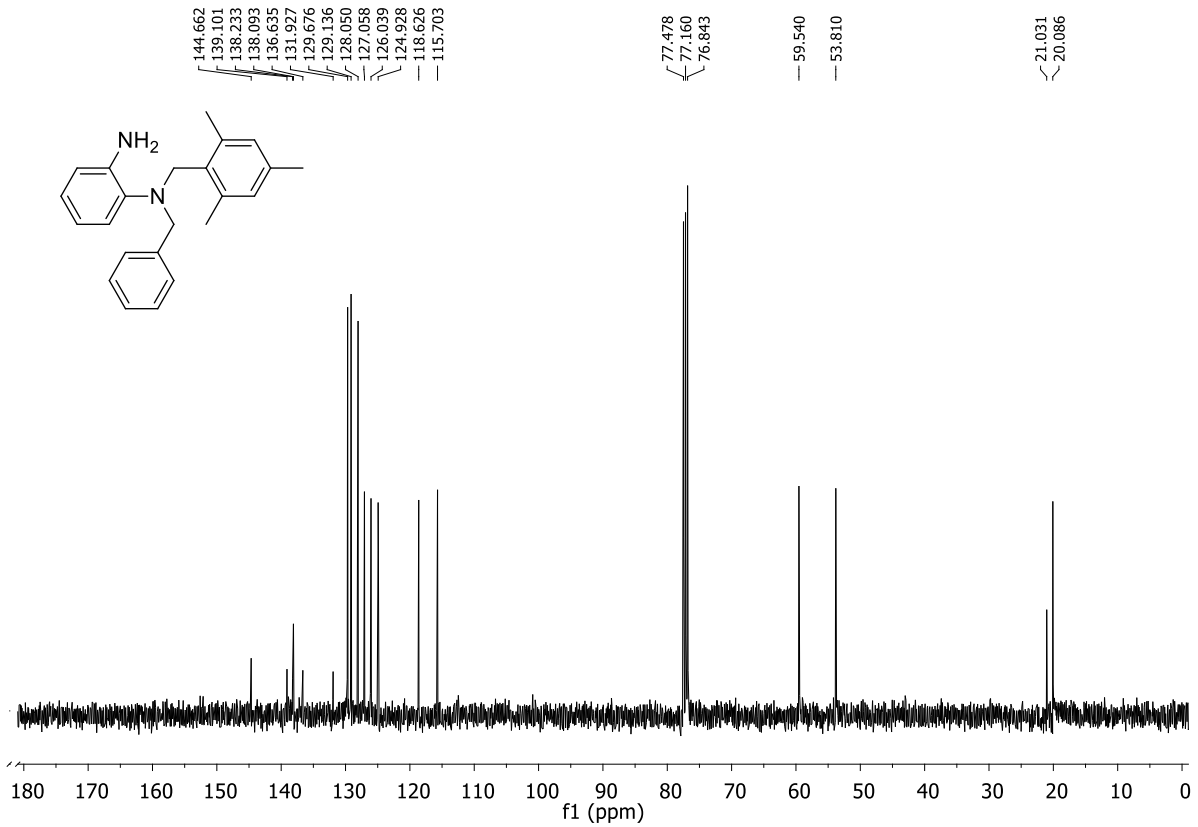


Figure 4.47. ^{13}C NMR of *N*^{1}-benzyl-*N*^{1}-(2,4,6-trimethylbenzyl)benzene-1,2-diamine (**1s**)

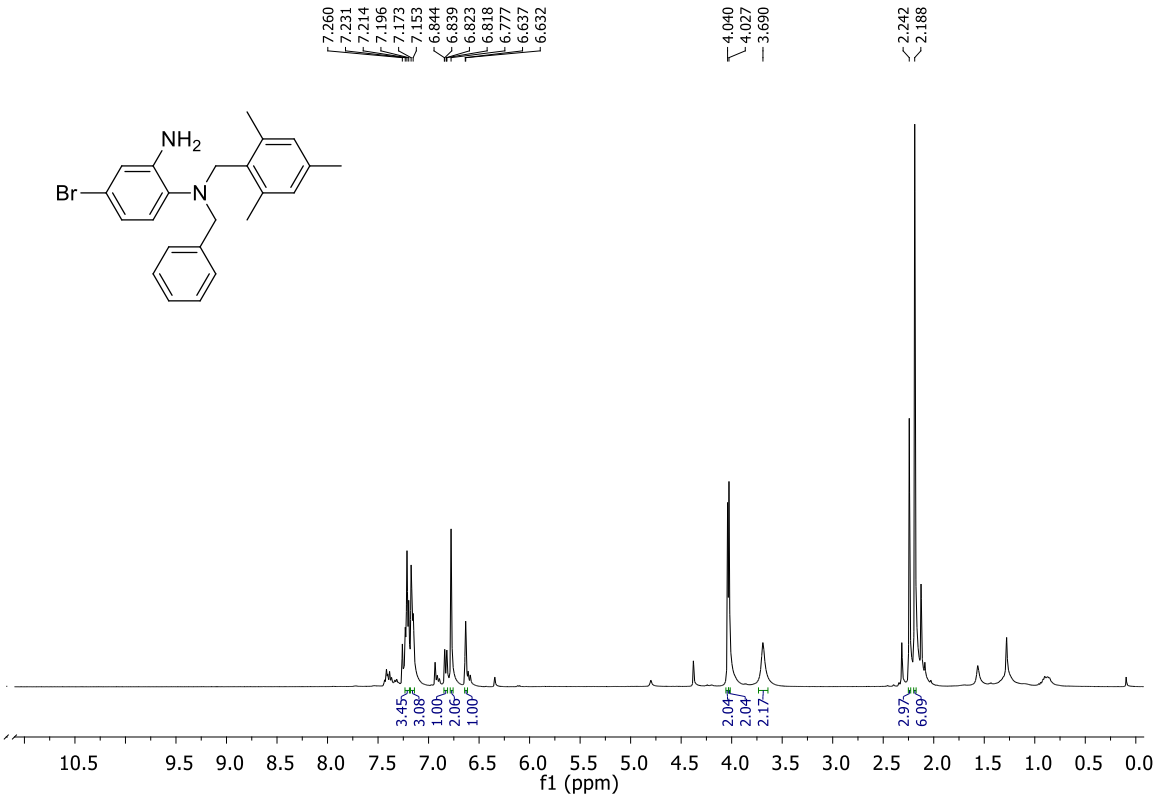


Figure 4.48. ^{1}H NMR of *N*^{1}-benzyl-4-bromo-*N*^{1}-(2,4,6-trimethylbenzyl)benzene-1,2-diamine (**1t**)

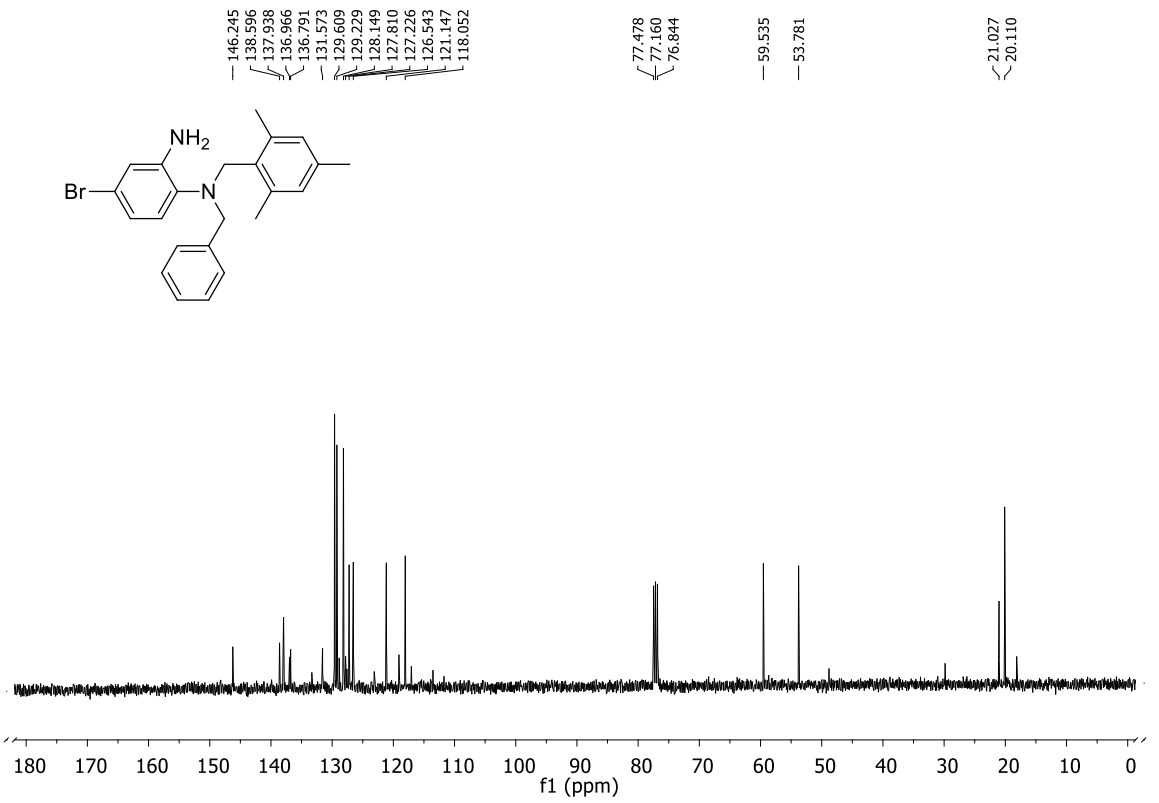


Figure 4.49. ^{13}C NMR of *N*^{1}-benzyl-4-bromo-*N*^{1}-(2,4,6-trimethylbenzyl)benzene-1,2-diamine (**1t**)

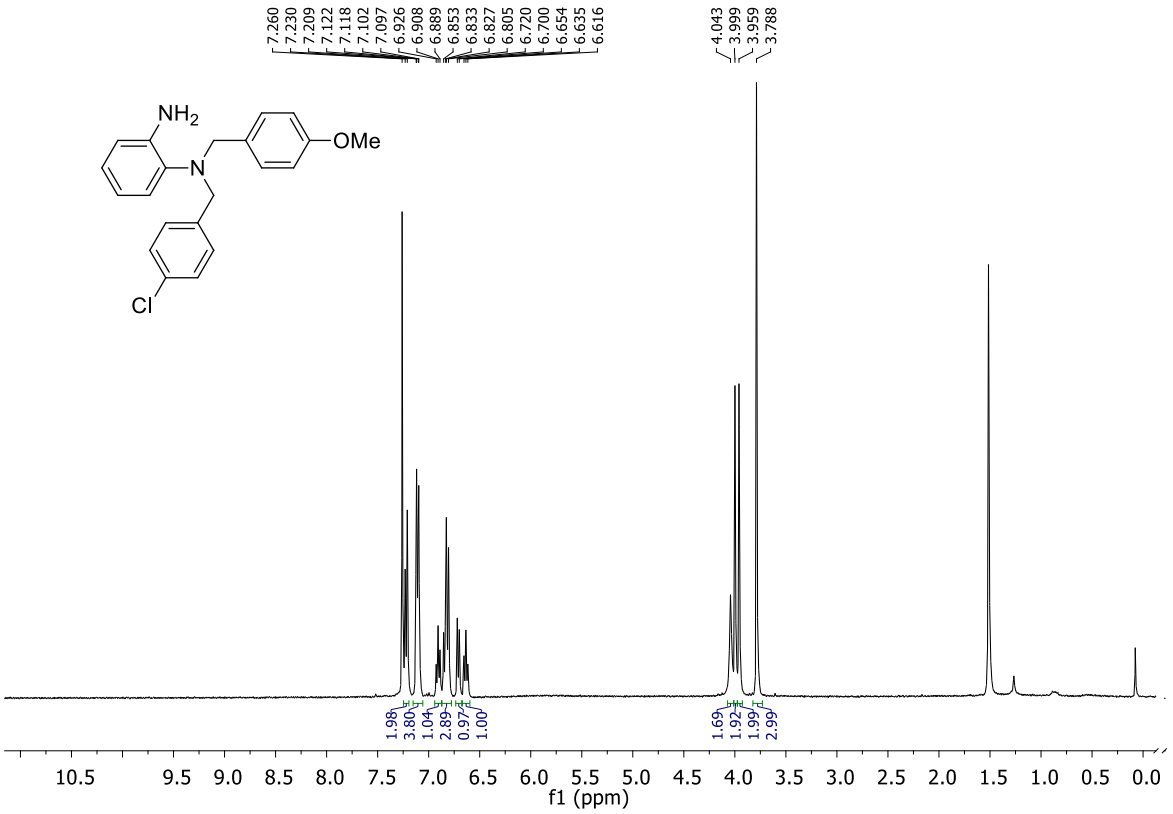


Figure 4.50. ^{1}H NMR of *N*^{1}-(4-chlorobenzyl)-*N*^{1}-(4-methoxybenzyl)benzene-1,2-diamine (**1u**)

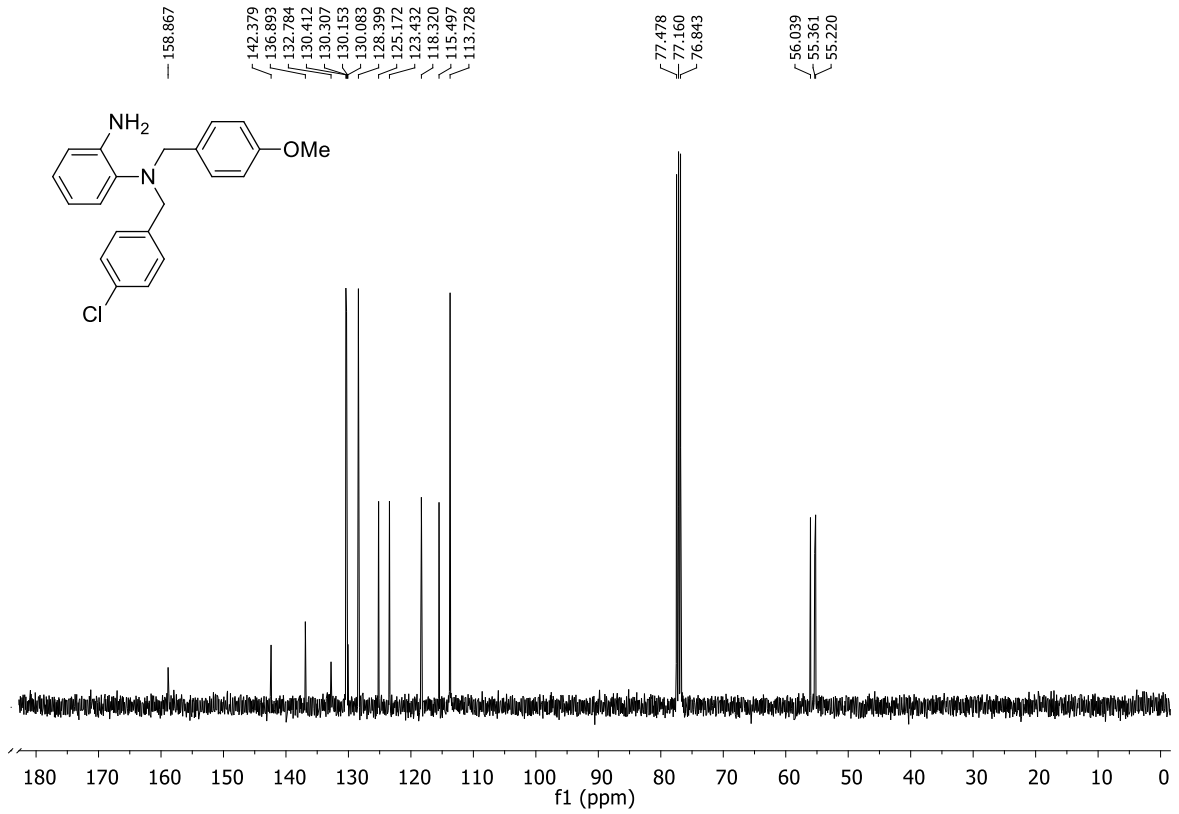


Figure 4.51. ^{13}C NMR of *N*^{1}-(4-chlorobenzyl)-*N*^{1}-(4-methoxybenzyl)benzene-1,2-diamine (**1u**)

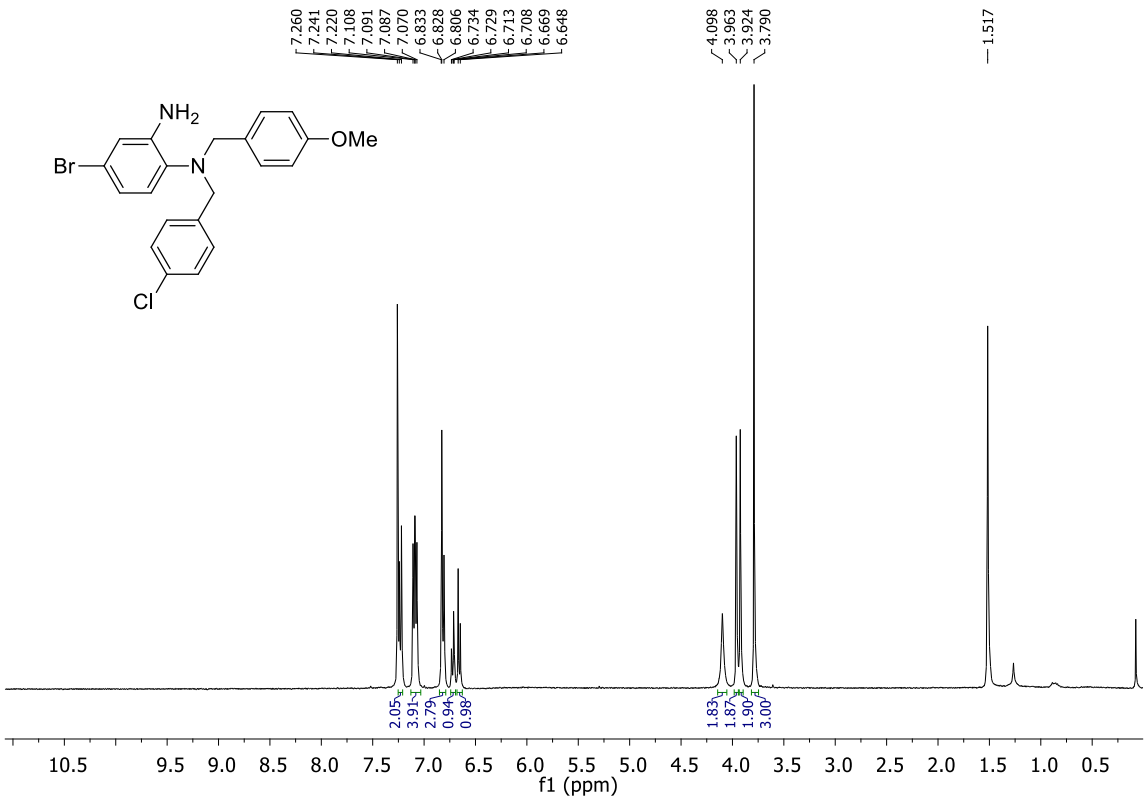


Figure 4.52. ^{1}H NMR of 4-Bromo-*N*^{1}-(4-chlorobenzyl)-*N*^{1}-(4-methoxybenzyl)benzene-1,2-diamine (**1v**)

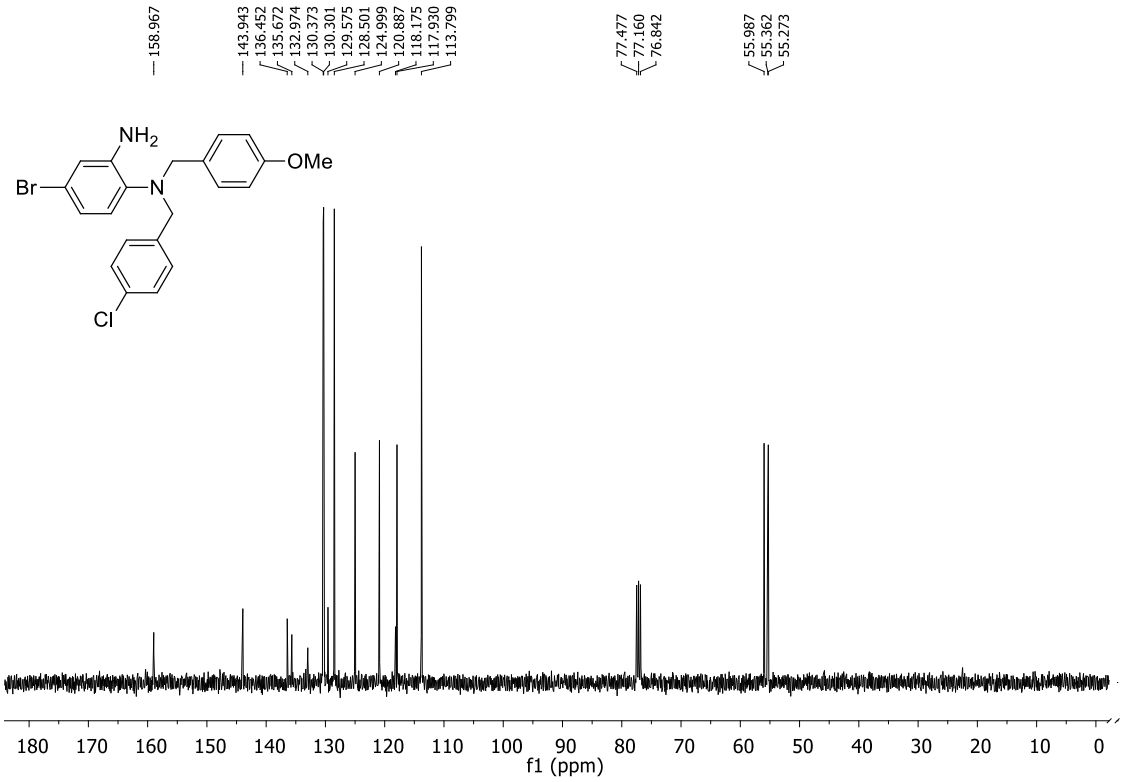


Figure 4.53. ^{13}C NMR of 4-Bromo-*N*^{1}-(4-chlorobenzyl)-*N*^{1}-(4-methoxybenzyl)benzene-1,2-diamine (**1v**)

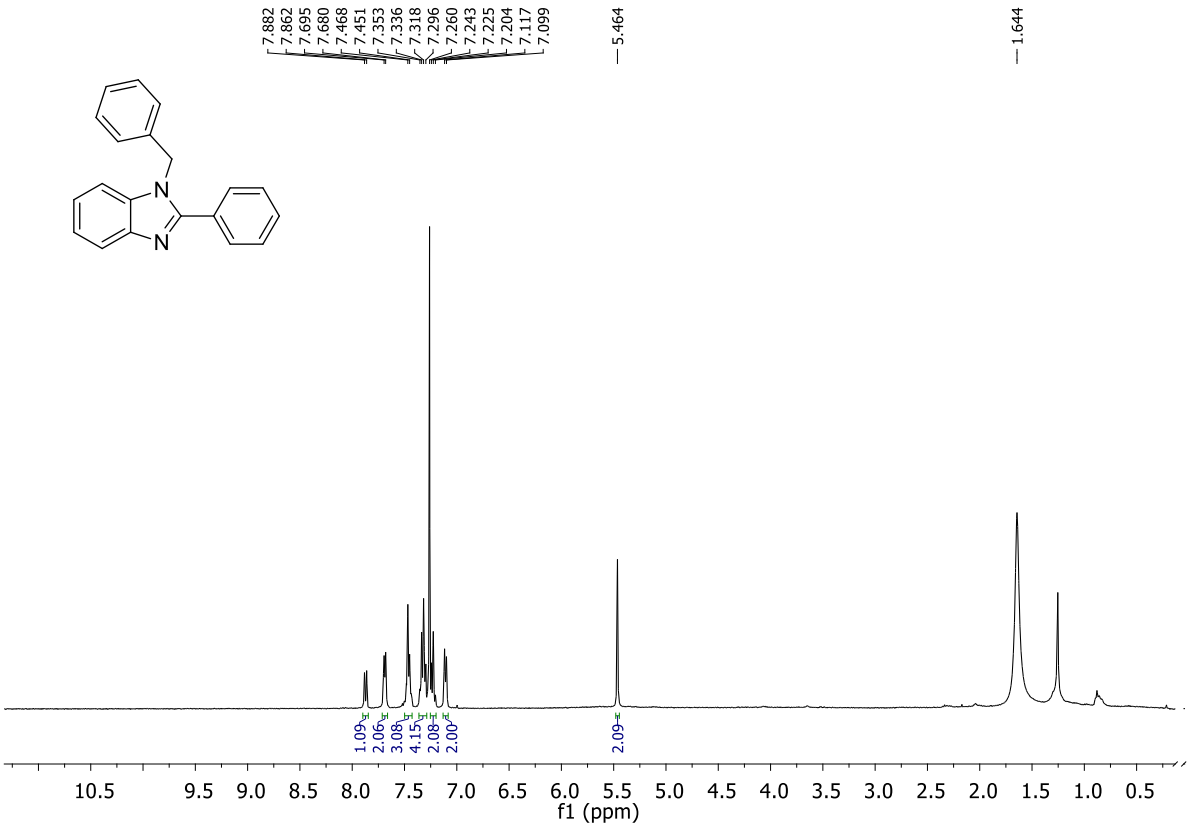


Figure 4.54. ^{1}H NMR of 1-Benzyl-2-phenyl-benzo[d]imidazole (**2a**)

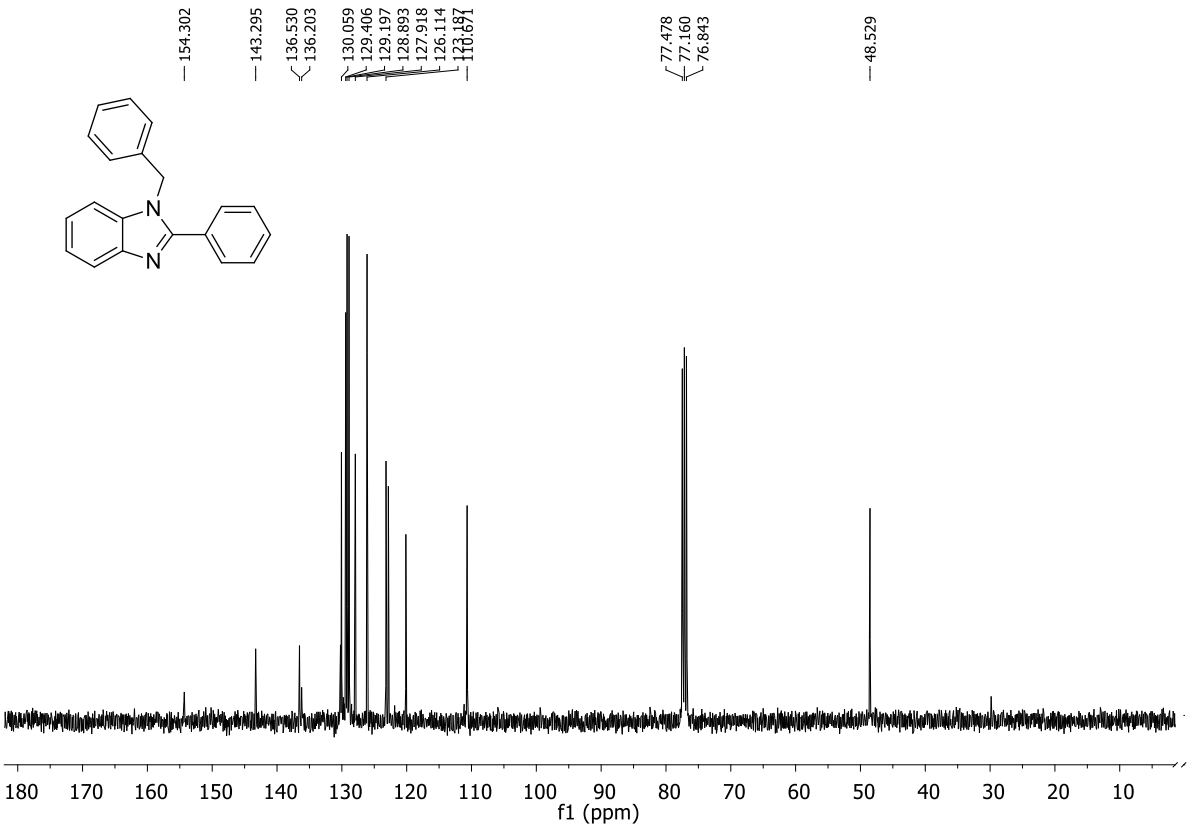


Figure 4.55. ^{13}C NMR of 1-Benzyl-2-phenyl-benzo[d]imidazole (**2a**)

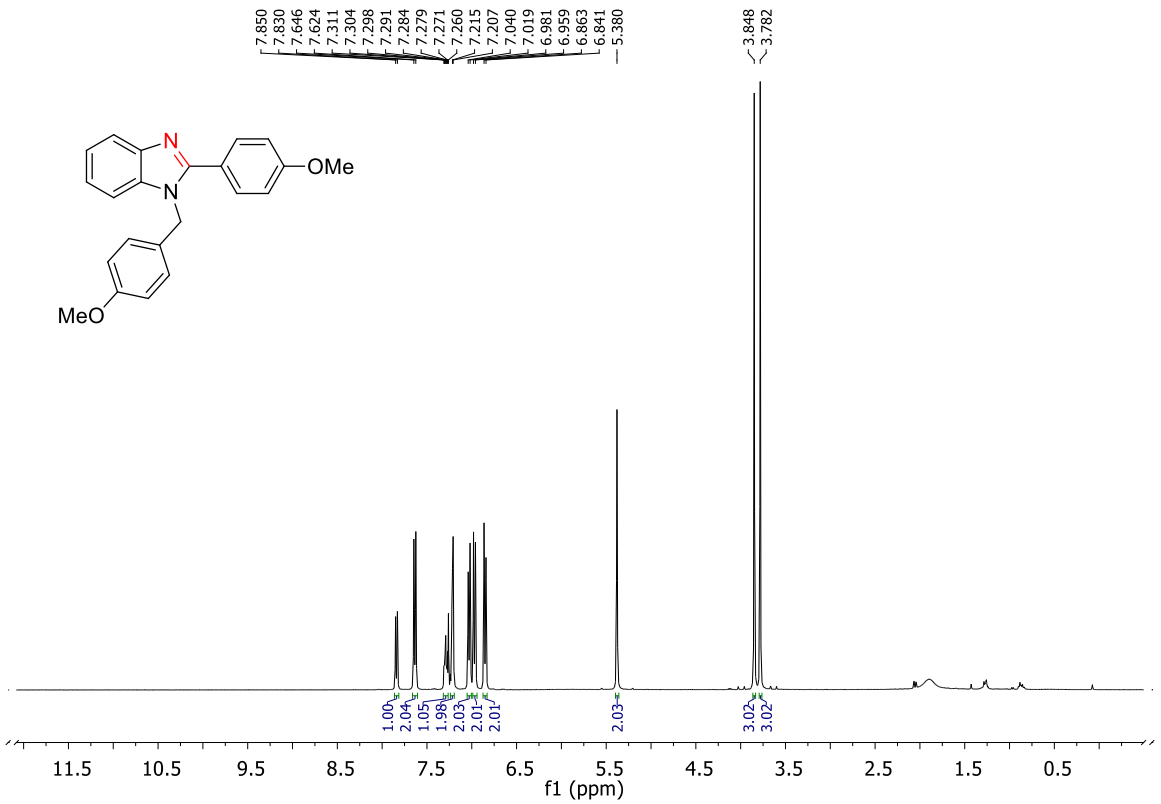


Figure 4.56. ^{1}H NMR of 1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (**2b**)

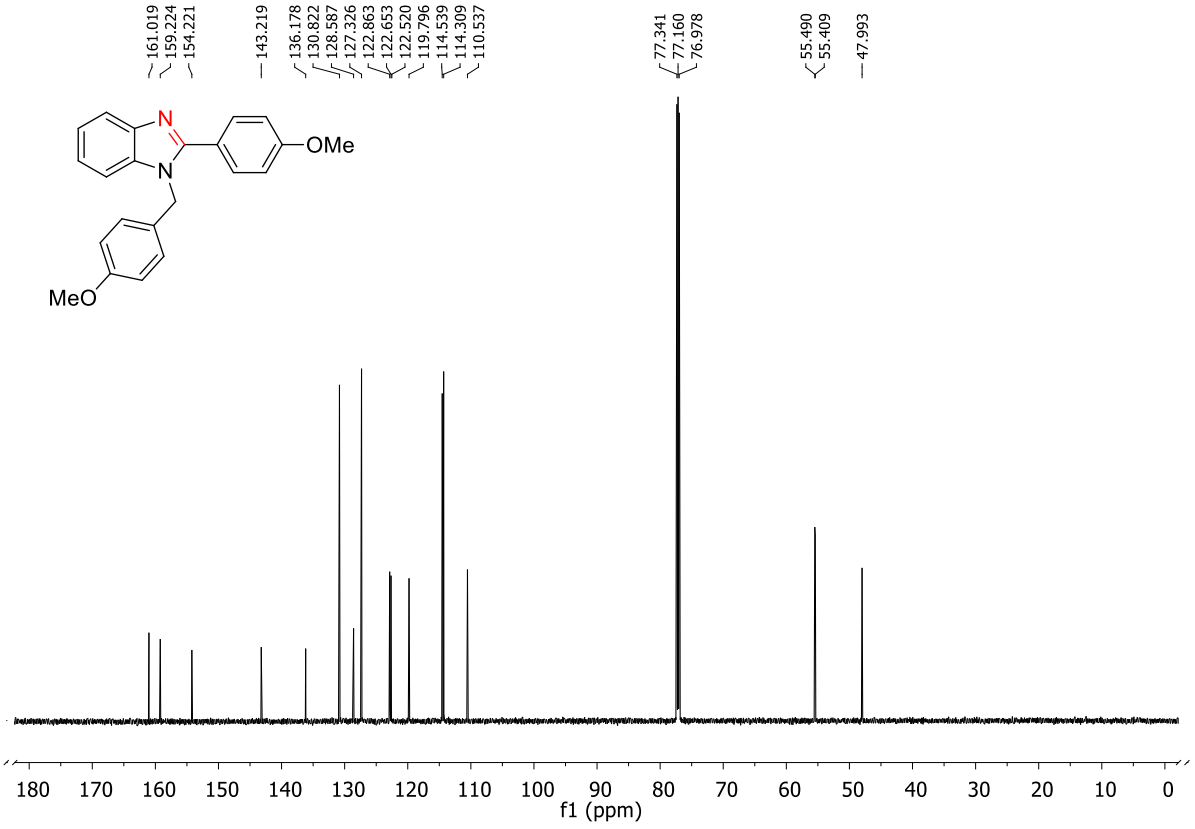


Figure 4.57. ^{13}C NMR of 1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (**2b**)

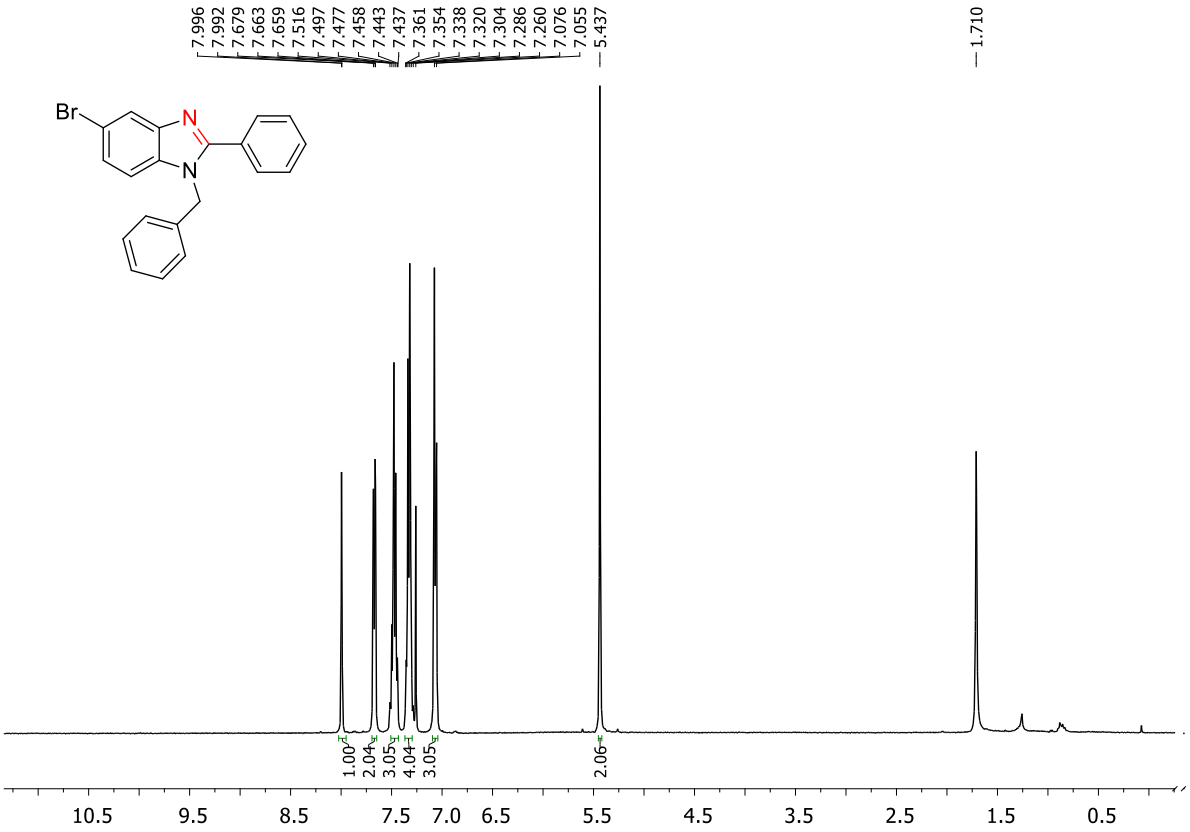


Figure 4.58. ^{1}H NMR of 1-Benzyl-5-bromo-2-phenyl-benzo[d]imidazole (**2c**)

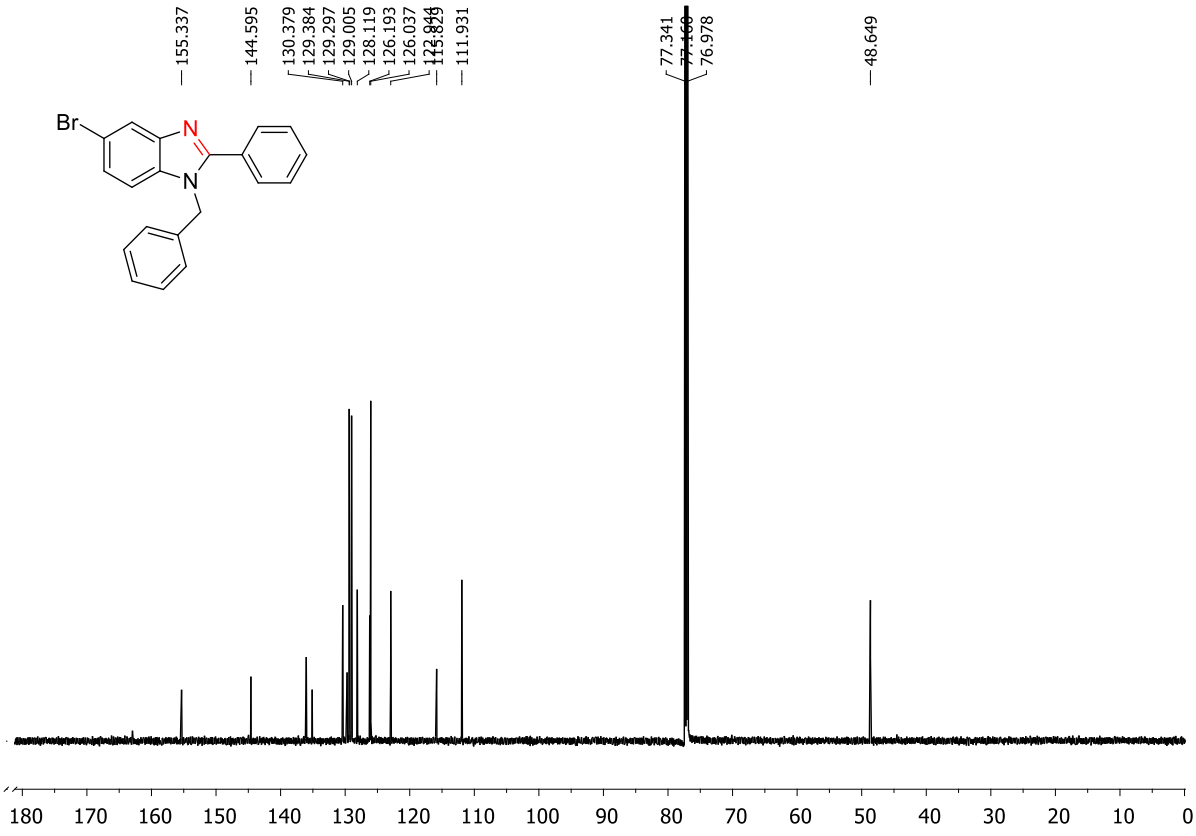


Figure 4.59. ^{13}C NMR of 1-Benzyl-5-bromo-2-phenyl-benzo[d]imidazole (**2c**)

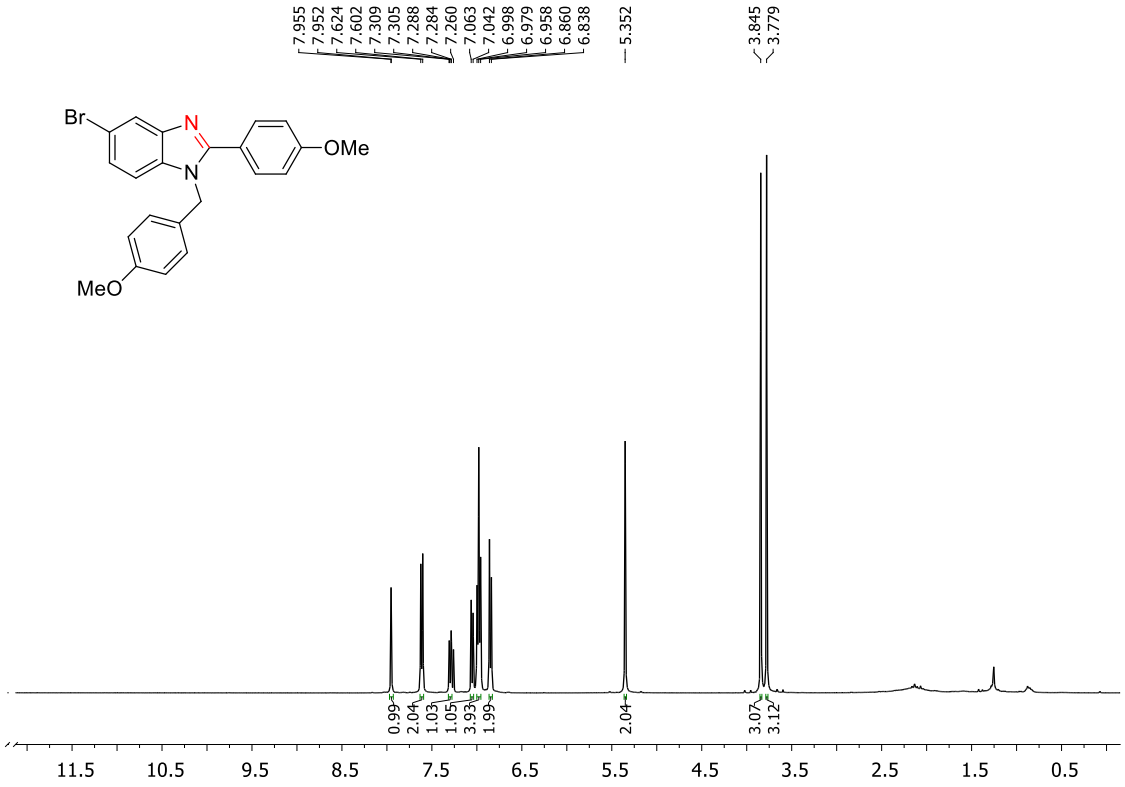


Figure 4.60. ^{1}H NMR of 5-Bromo-1-(4-methoxybenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (**2d**)

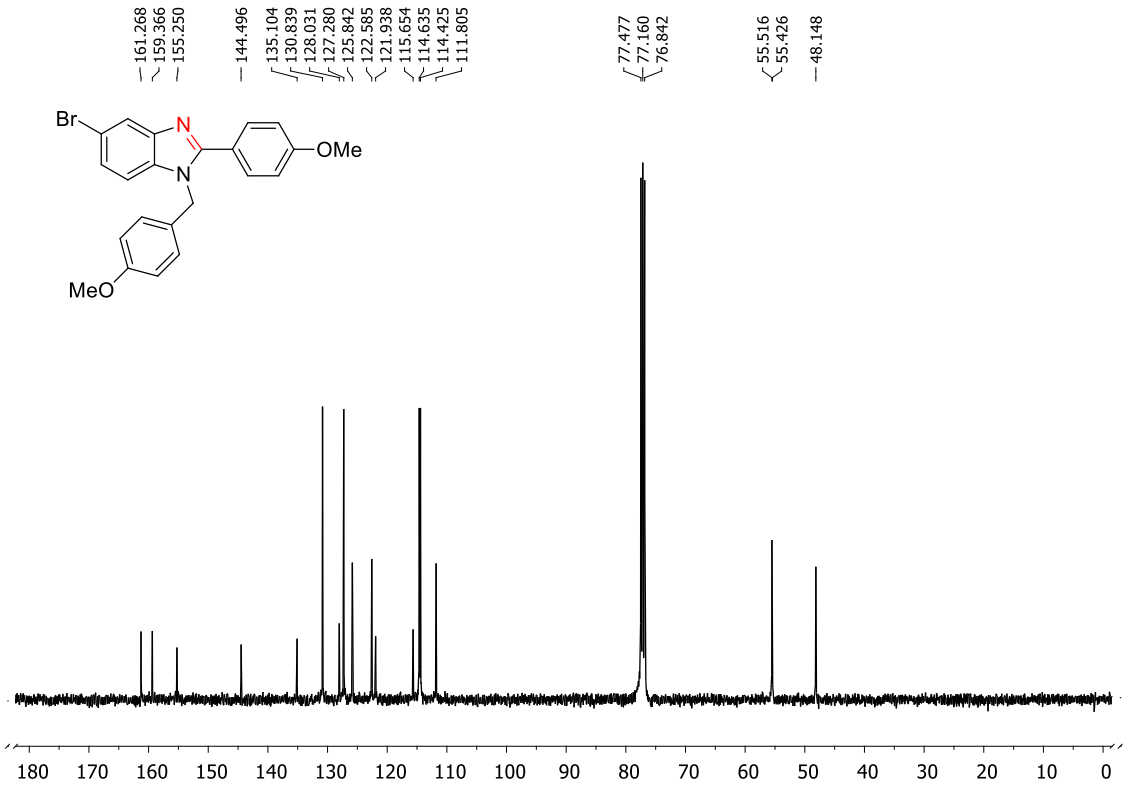


Figure 4.61. ^{13}C NMR of 5-Bromo-1-(4-methoxybenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (**2d**)

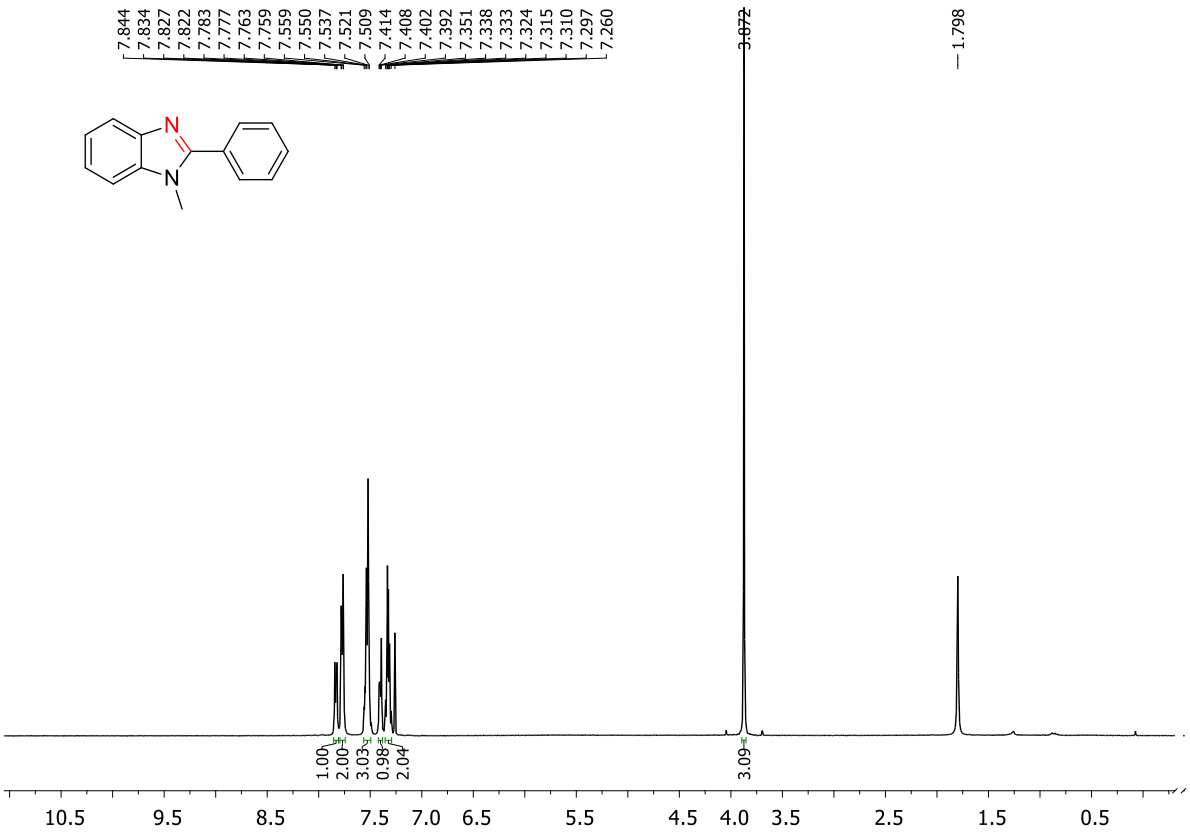


Figure 4.62. ^{1}H NMR of 1-Methyl-2-phenyl-benzo[d]imidazole (**2e**)

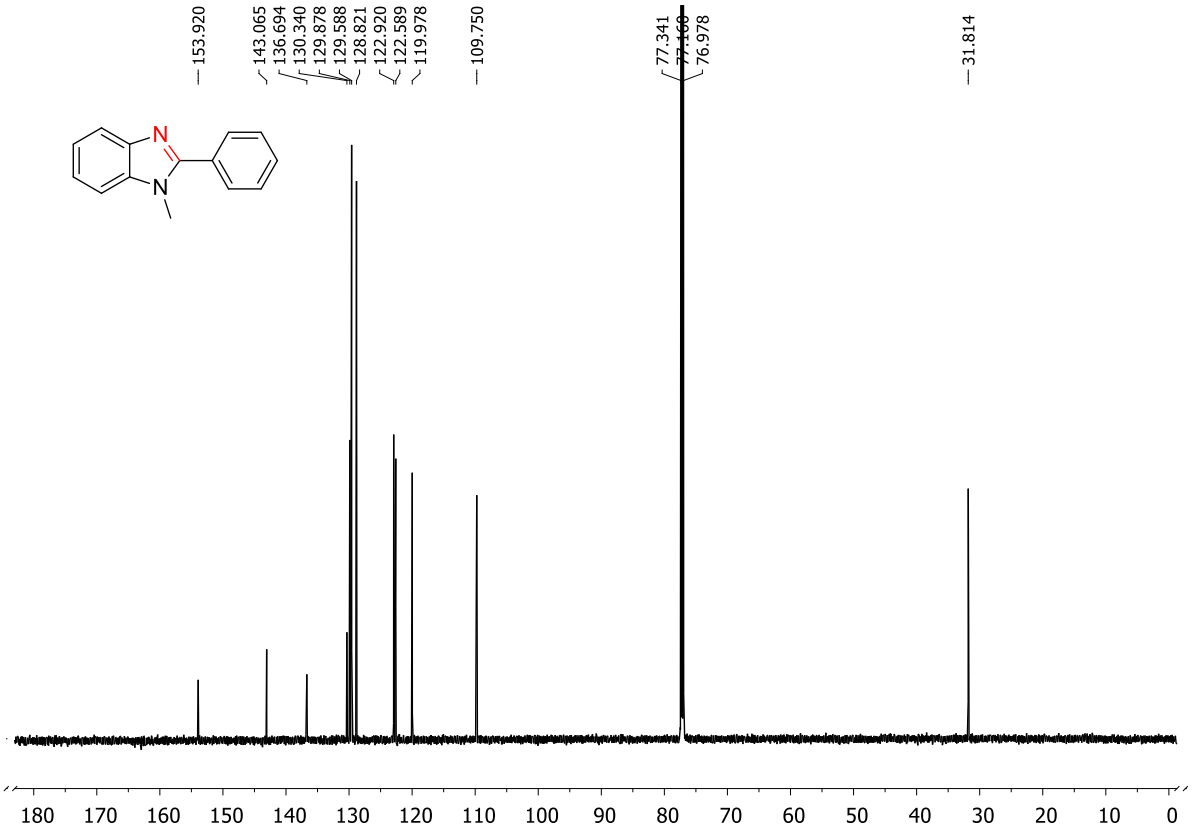


Figure 4.63. ^{13}C NMR of 1-Methyl-2-phenyl-benzo[d]imidazole (**2e**)

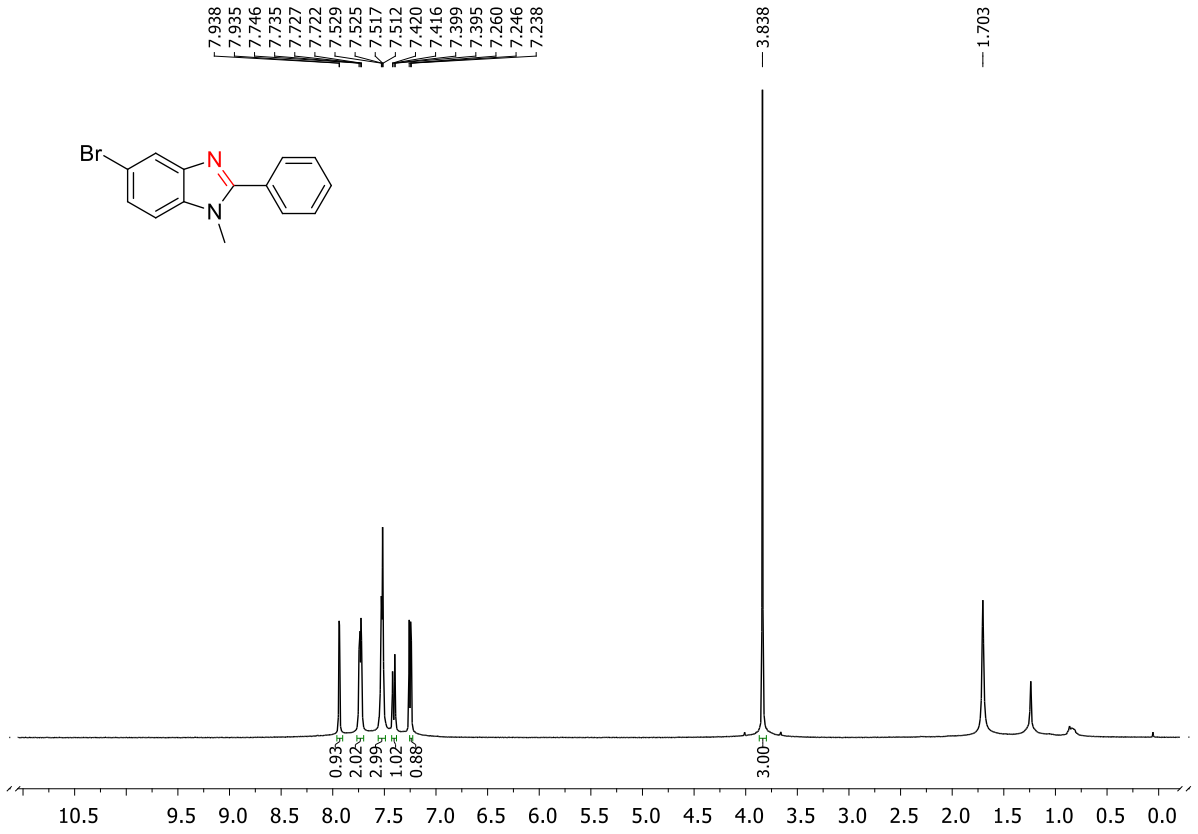


Figure 4.64. ^{1}H NMR of 5-Bromo-1-methyl-2-phenyl-benzo[d]imidazole (**2f**)

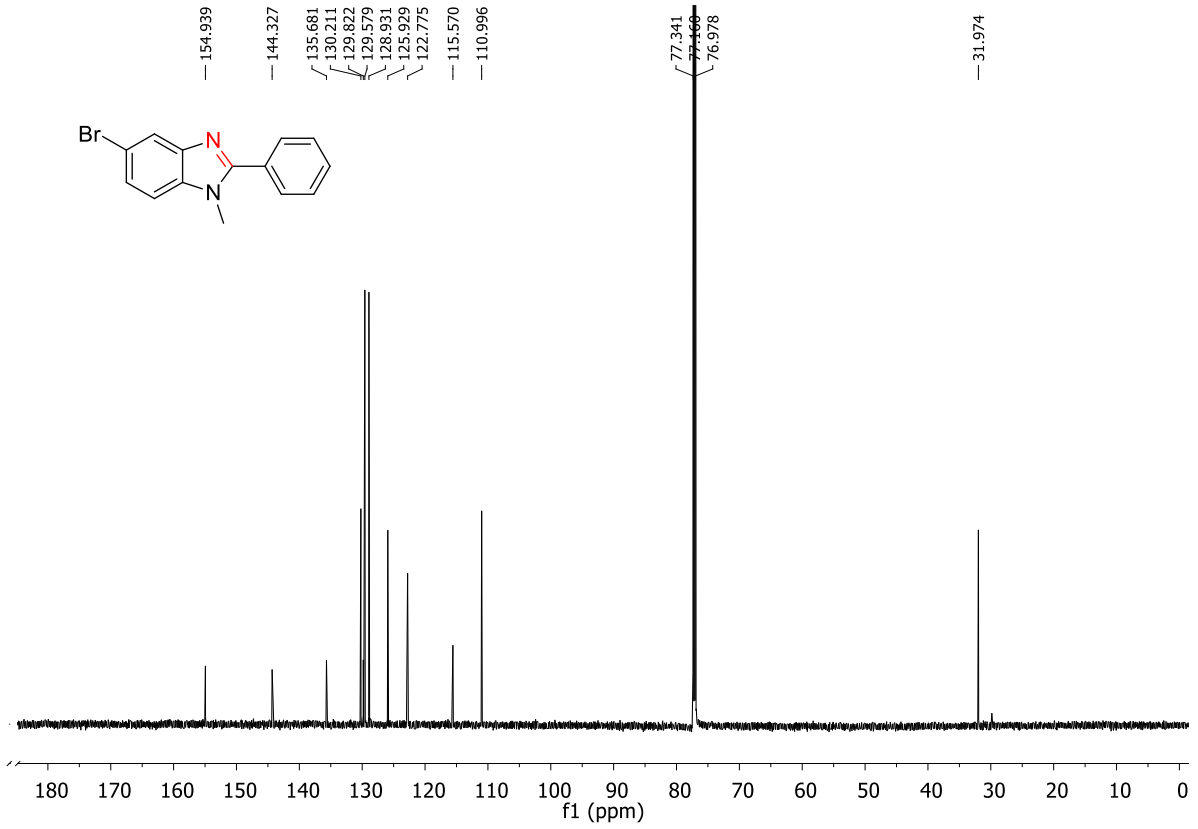


Figure 4.65. ^{13}C NMR of 5-Bromo-1-methyl-2-phenyl-benzo[d]imidazole (**2f**)

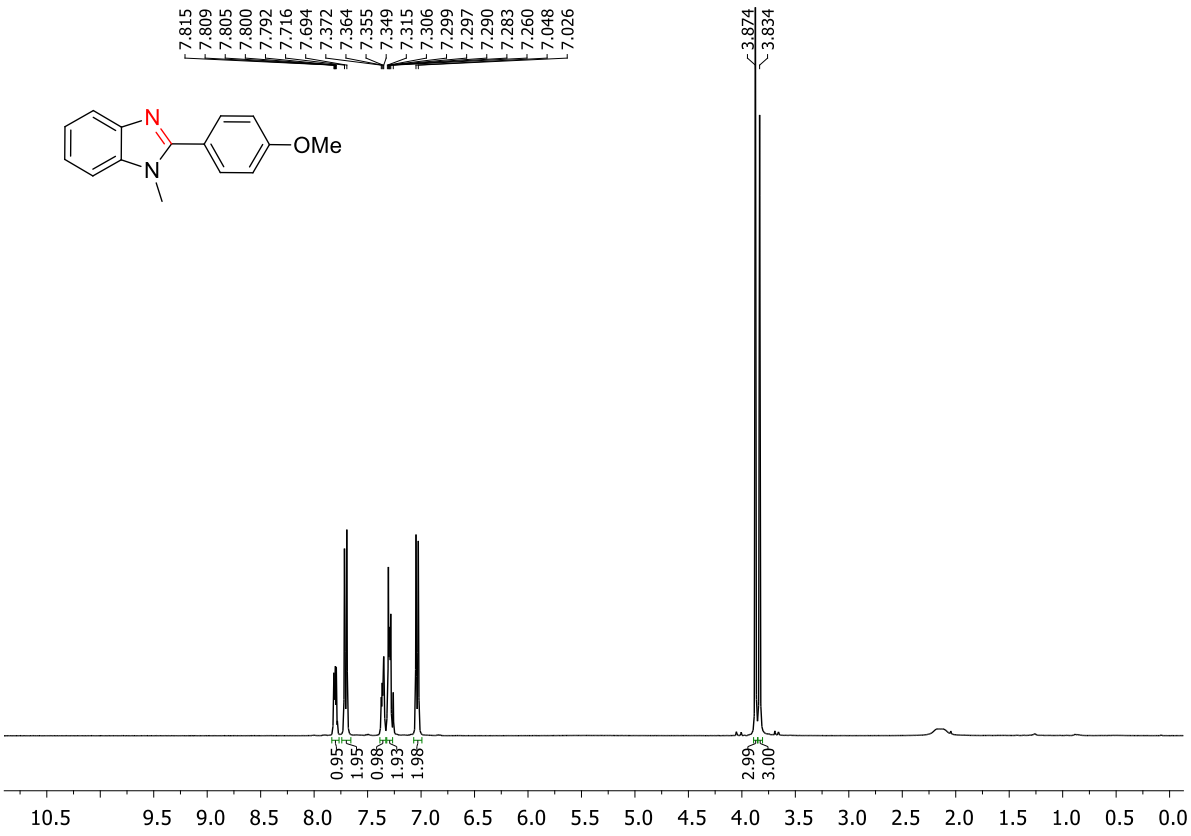


Figure 4.66. ^{1}H NMR of 2-(4-Methoxyphenyl)-1-methyl-benzo[d]imidazole (**2g**)

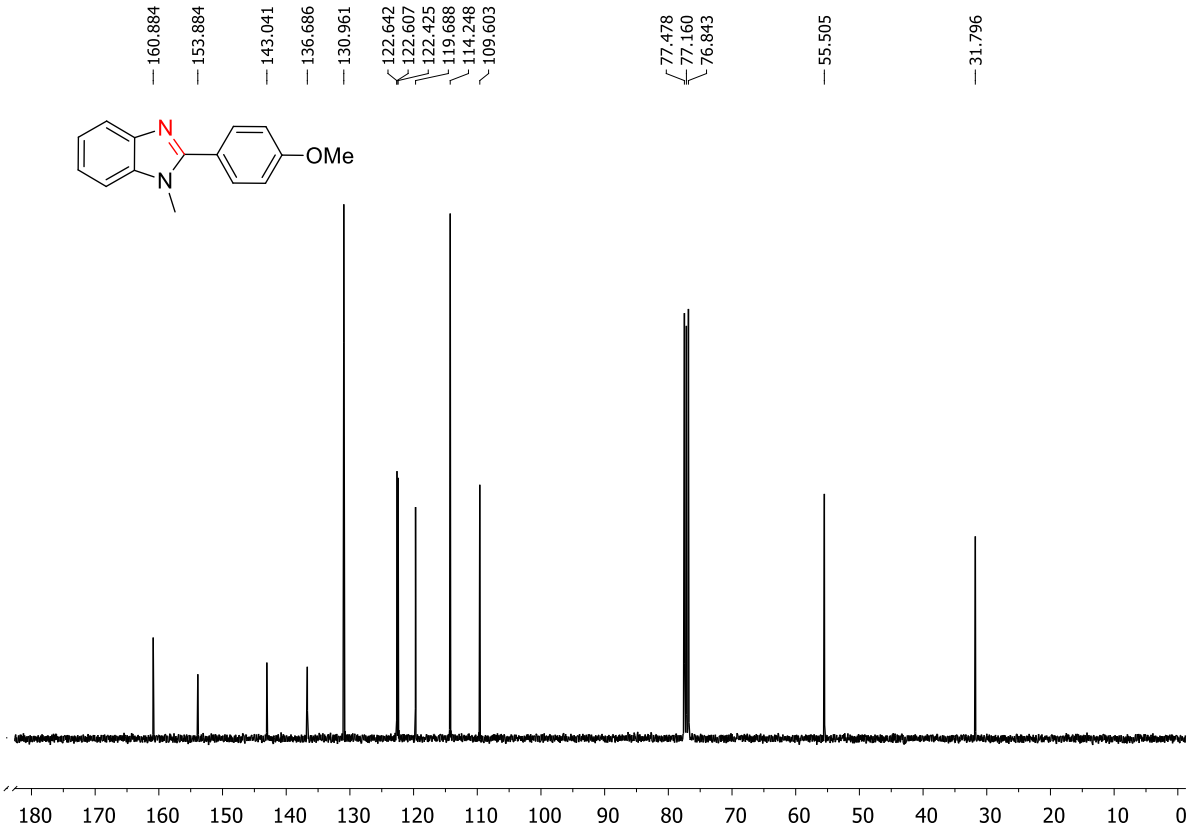


Figure 4.67. ^{13}C NMR of 2-(4-Methoxyphenyl)-1-methyl-benzo[d]imidazole (**2g**)

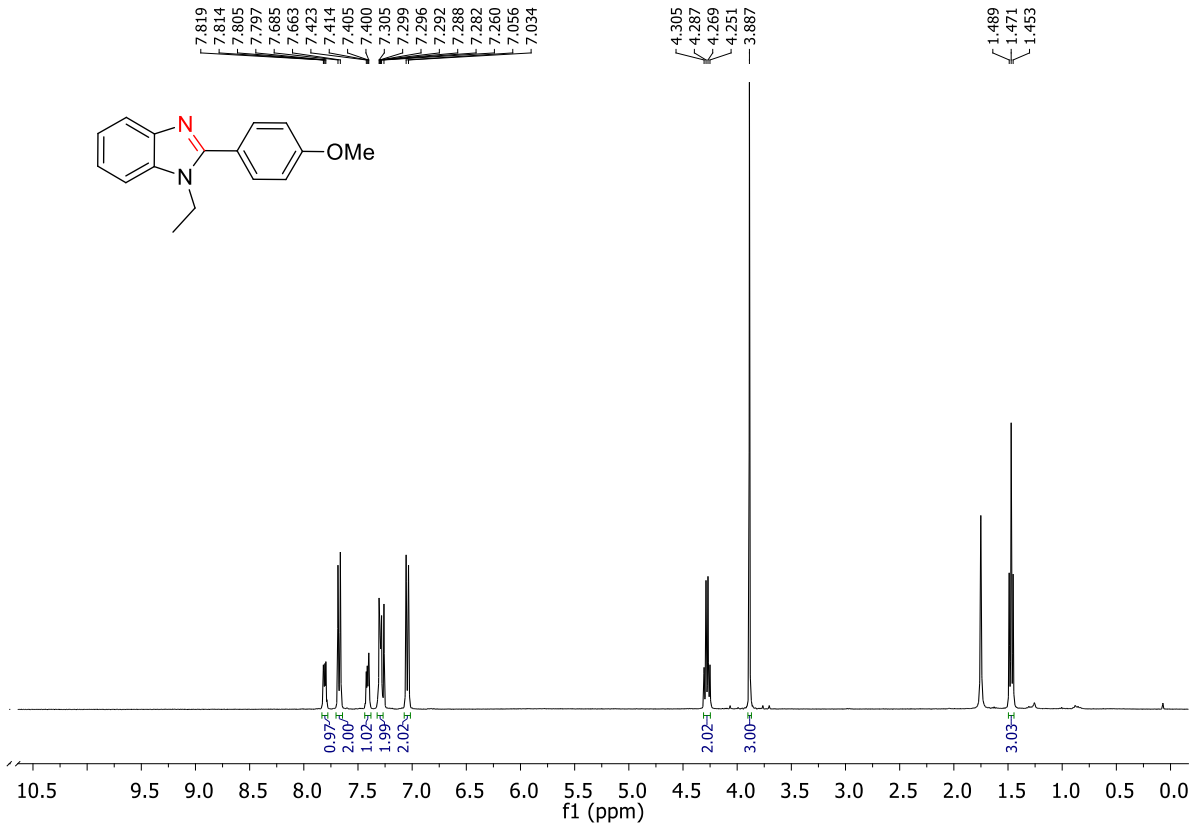


Figure 4.68. ^{1}H NMR of 1-Ethyl-2-(4-methoxyphenyl)-benzo[d]imidazole (**2h**)

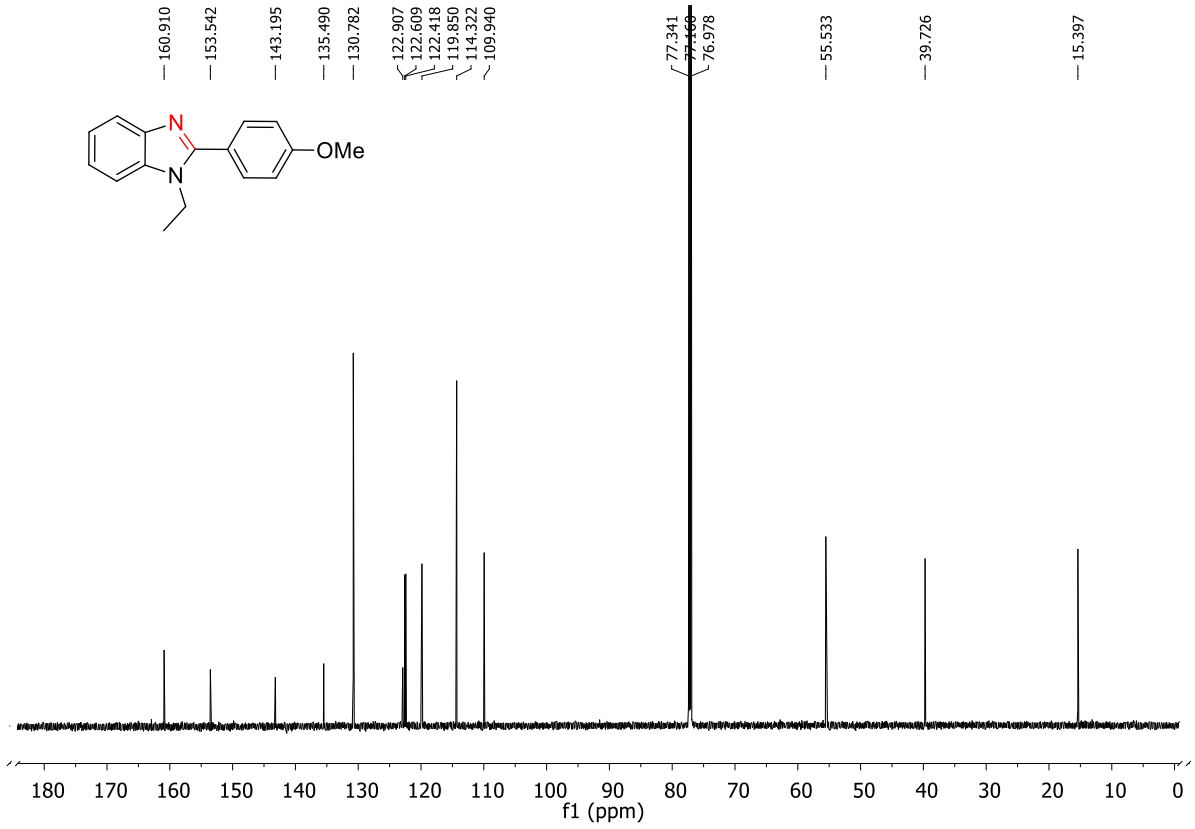


Figure 4.69. ^{13}C NMR of 1-Ethyl-2-(4-methoxyphenyl)-benzo[d]imidazole (**2h**)

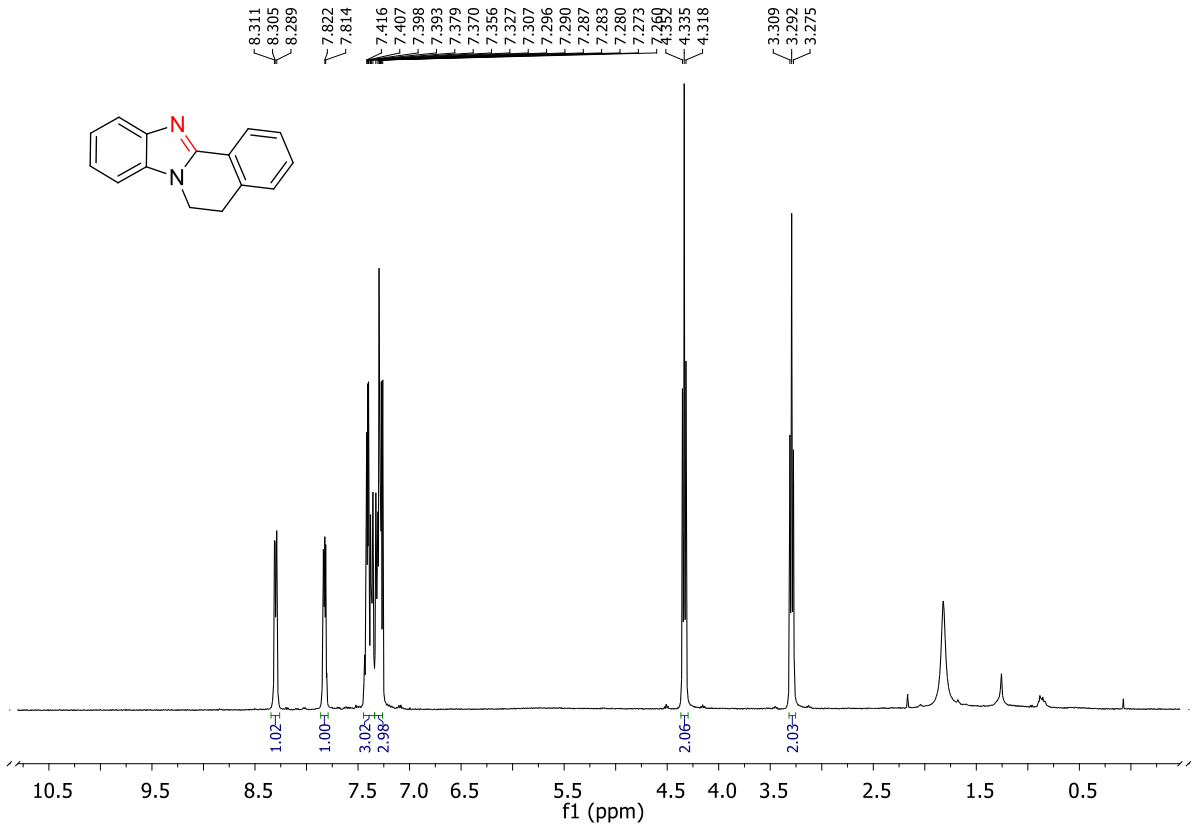


Figure 4.70. ^{1}H NMR of 5,6-Dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline (**2i**)

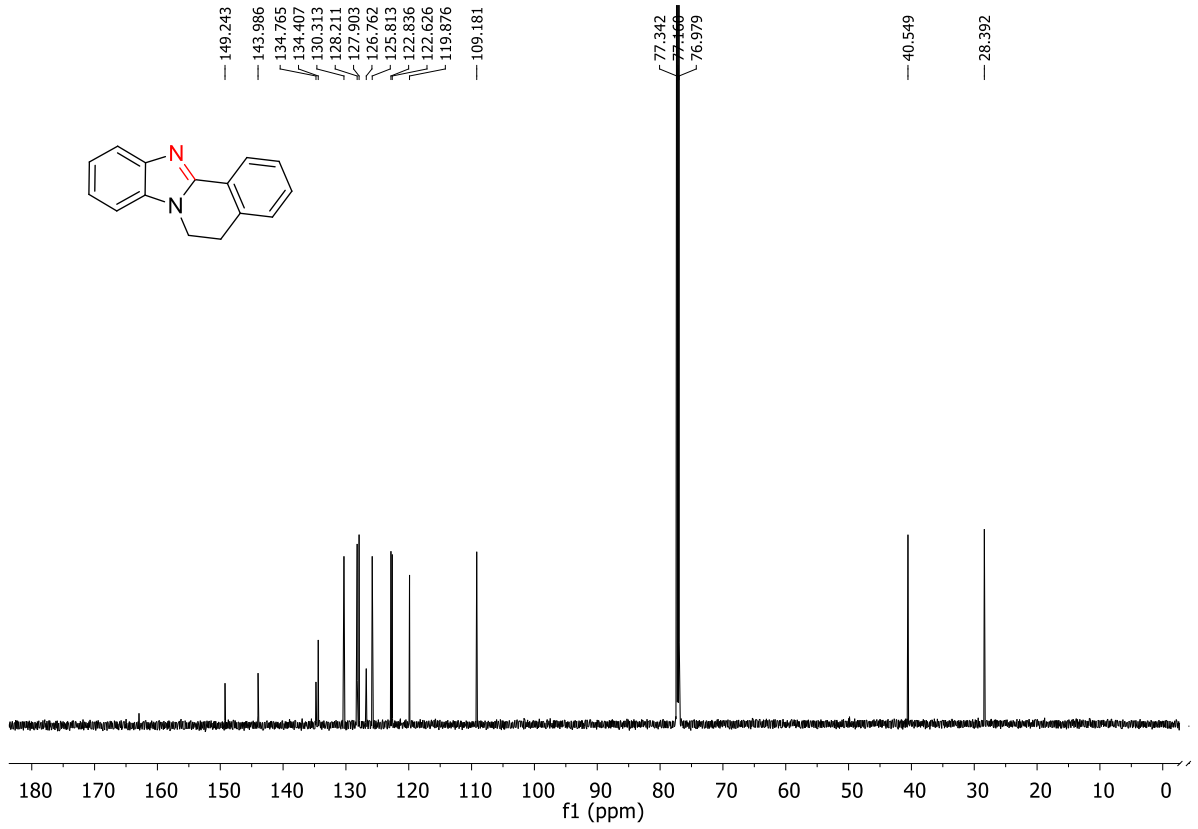


Figure 4.71. ^{13}C NMR of 5,6-Dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline (**2i**)

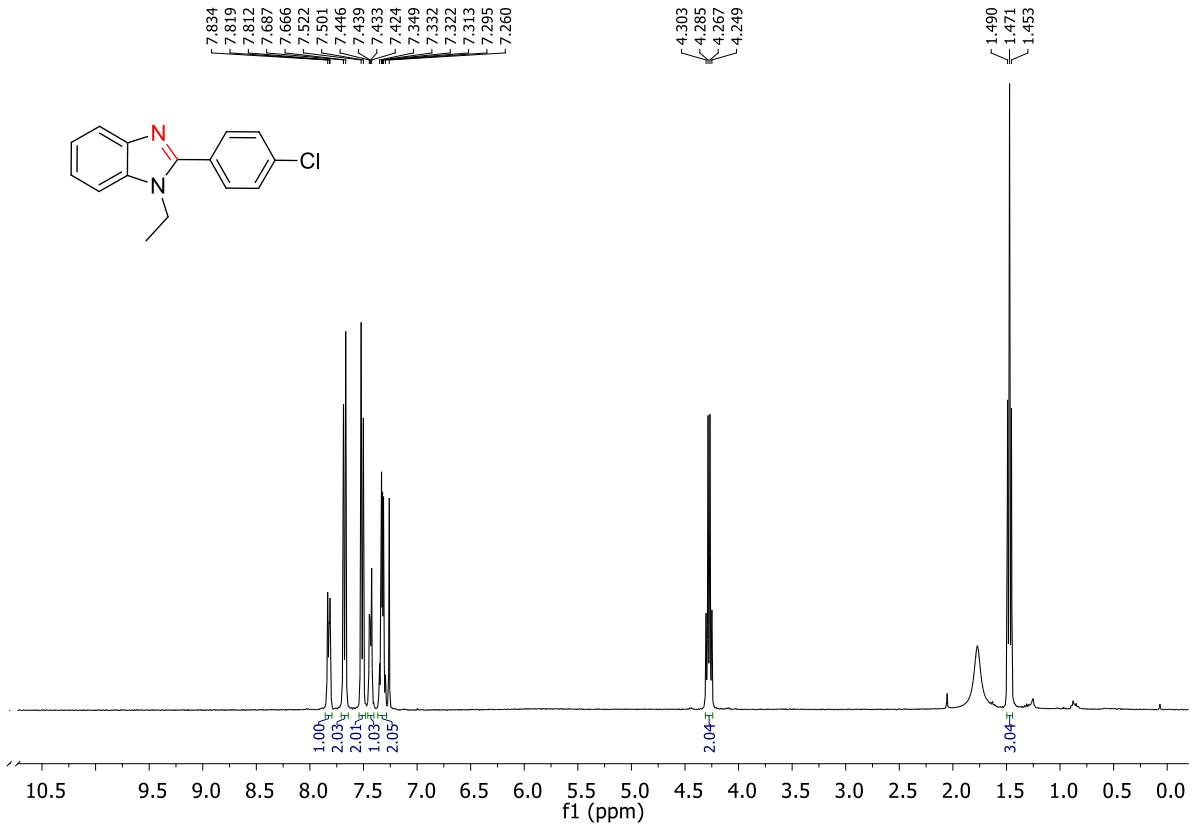


Figure 4.72. ^{1}H NMR of 2-(4-Chlorophenyl)-1-ethyl-benzo[d]imidazole (**2j**)

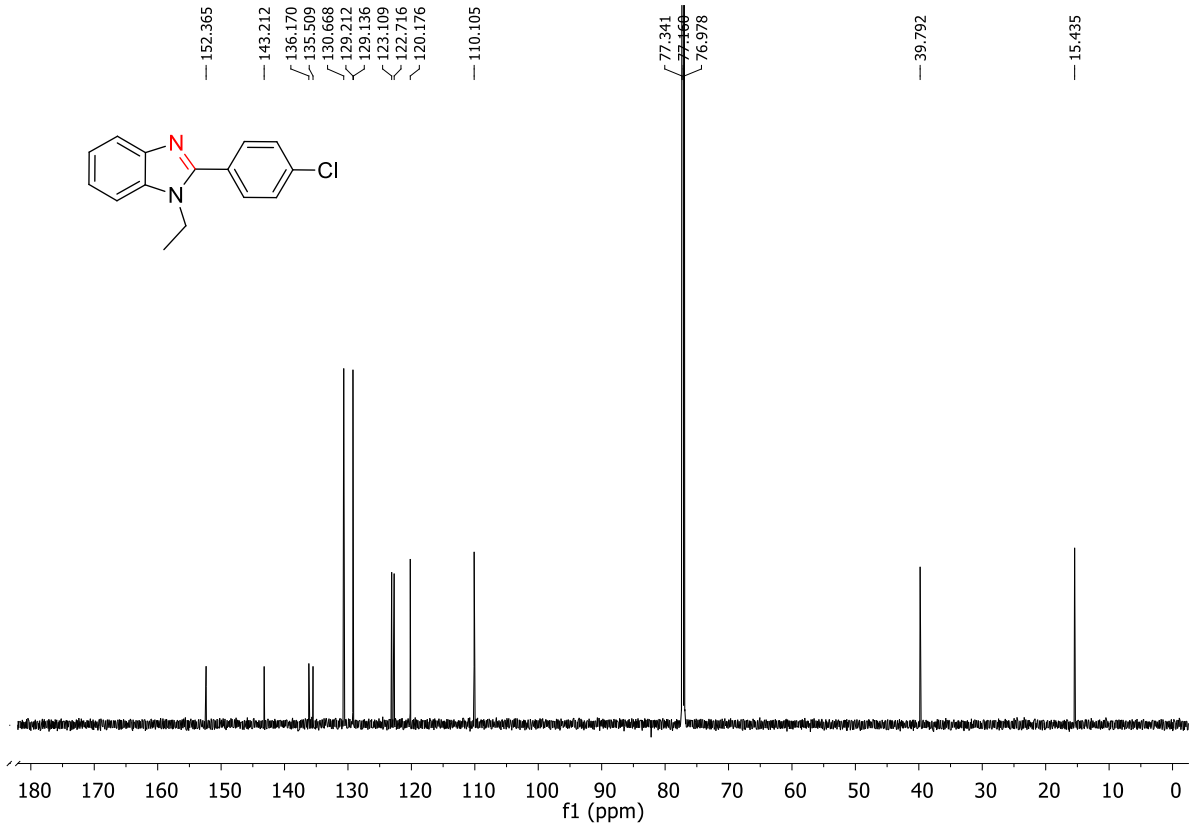


Figure 4.73. ^{13}C NMR of 2-(4-Chlorophenyl)-1-ethyl-benzo[d]imidazole (**2j**)

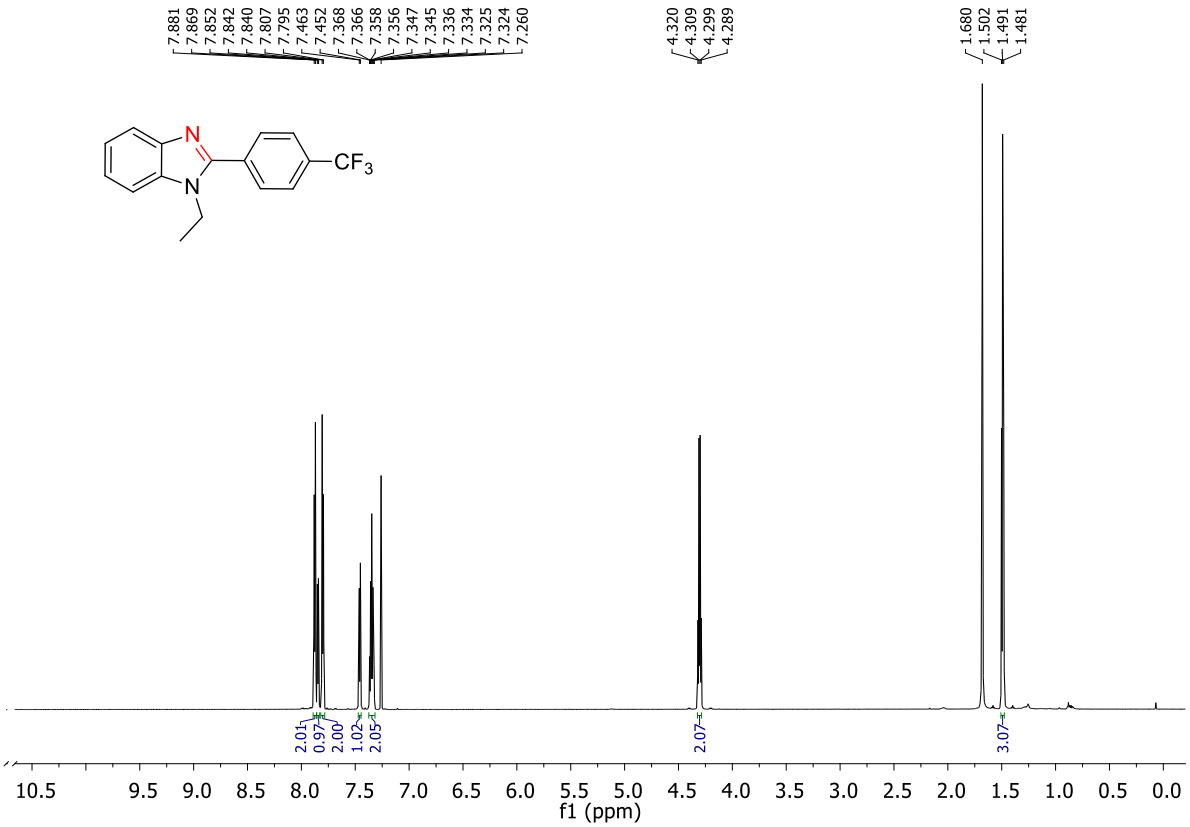


Figure 4.74. ^{1}H NMR of 1-Ethyl-2-(4-(trifluoromethyl)phenyl)-benzo[d]imidazole (**2k**)

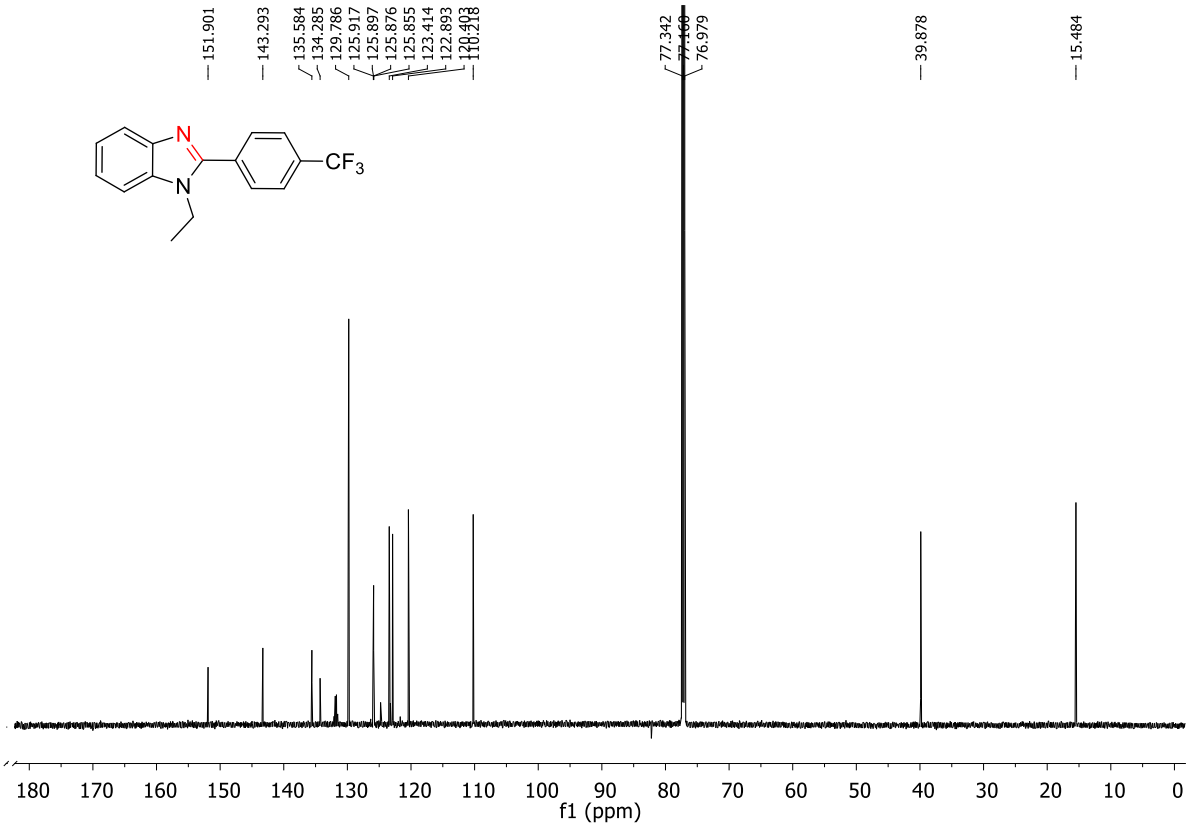


Figure 4.75. ^{13}C NMR of 1-Ethyl-2-(4-(trifluoromethyl)phenyl)-benzo[d]imidazole (**2k**)

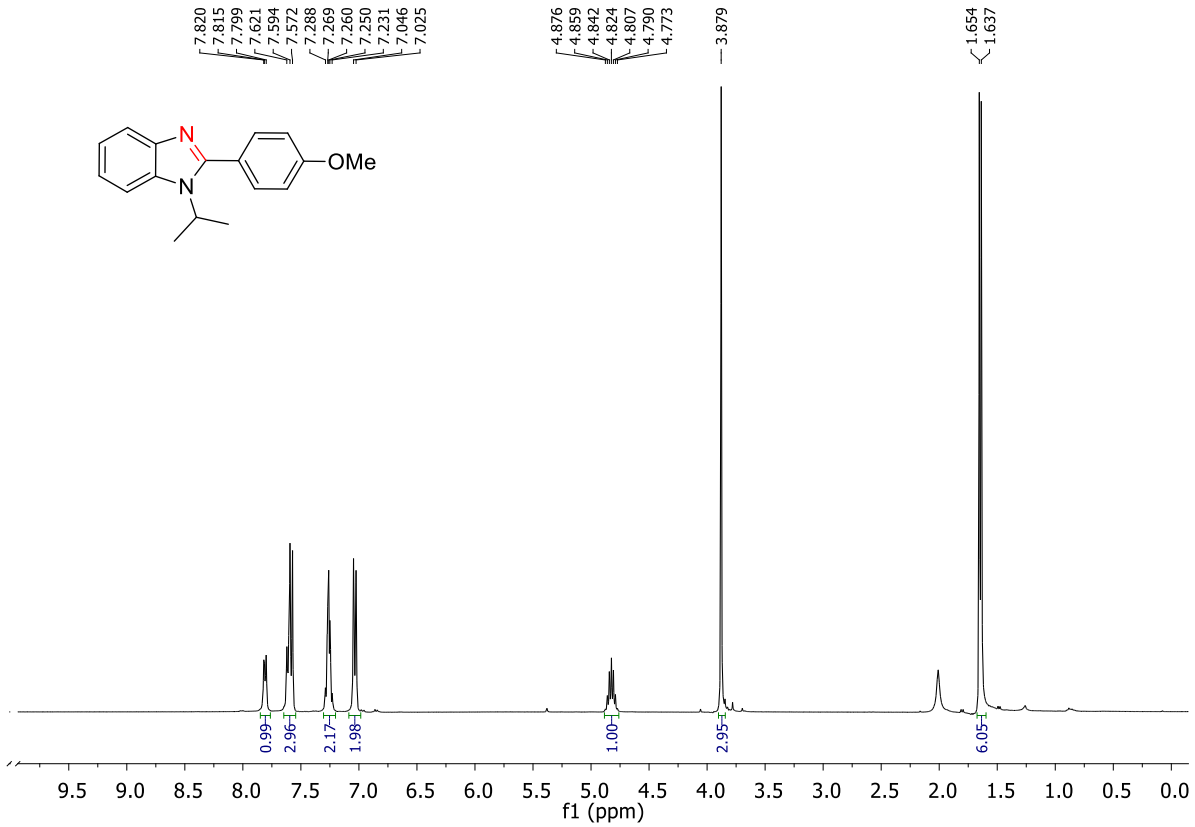


Figure 4.76. ^{1}H NMR of 1-Isopropyl-2-(4-methoxyphenyl)-benzo[d]imidazole (**2l**)

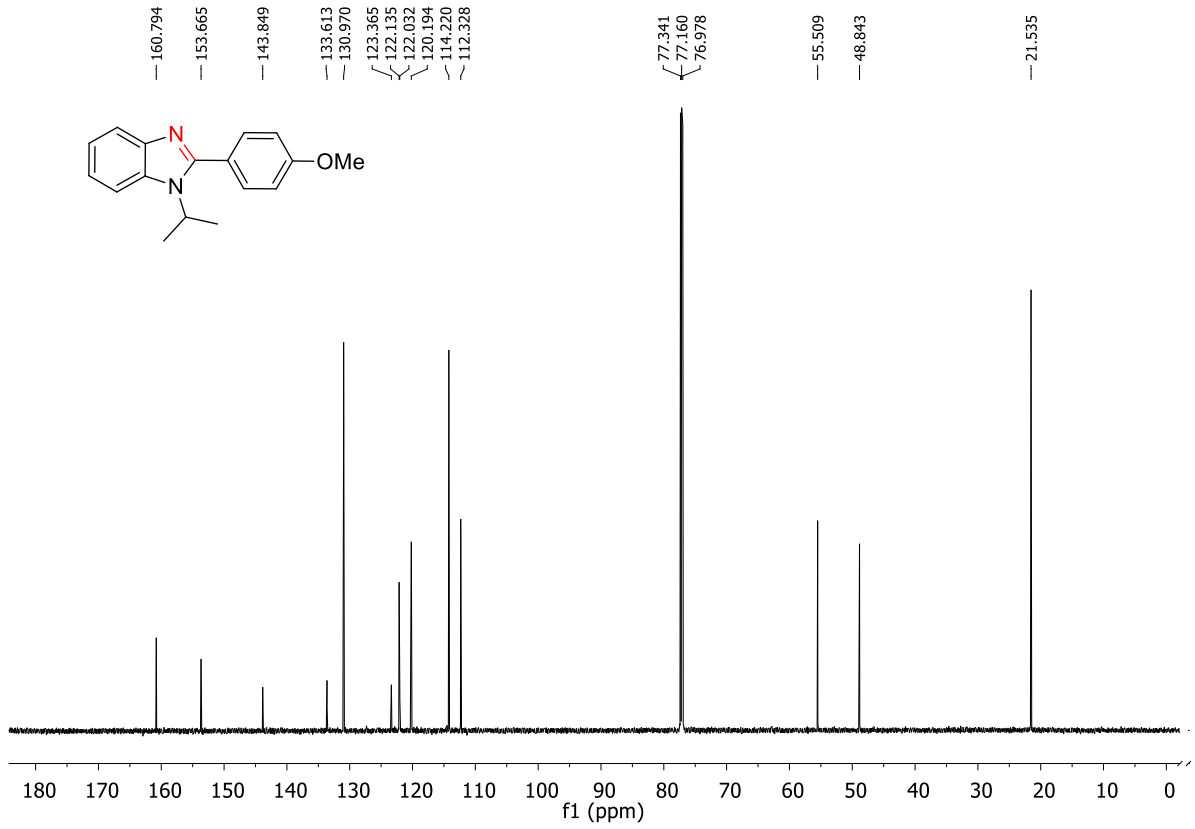


Figure 4.77. ^{13}C NMR of 1-Isopropyl-2-(4-methoxyphenyl)-benzo[d]imidazole (**2l**)

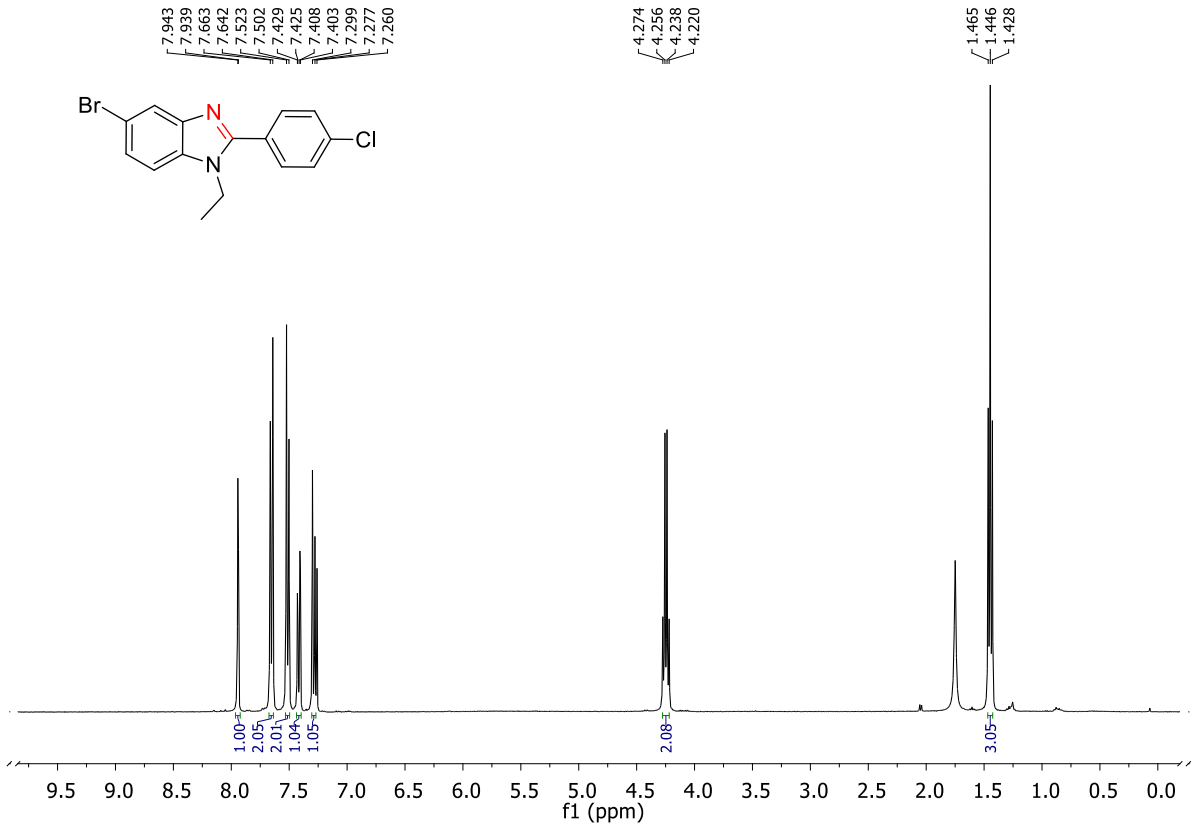


Figure 4.78. [1]H NMR of 5-Bromo-2-(4-chlorophenyl)-1-ethyl-benzo[d]imidazole (**2m**)

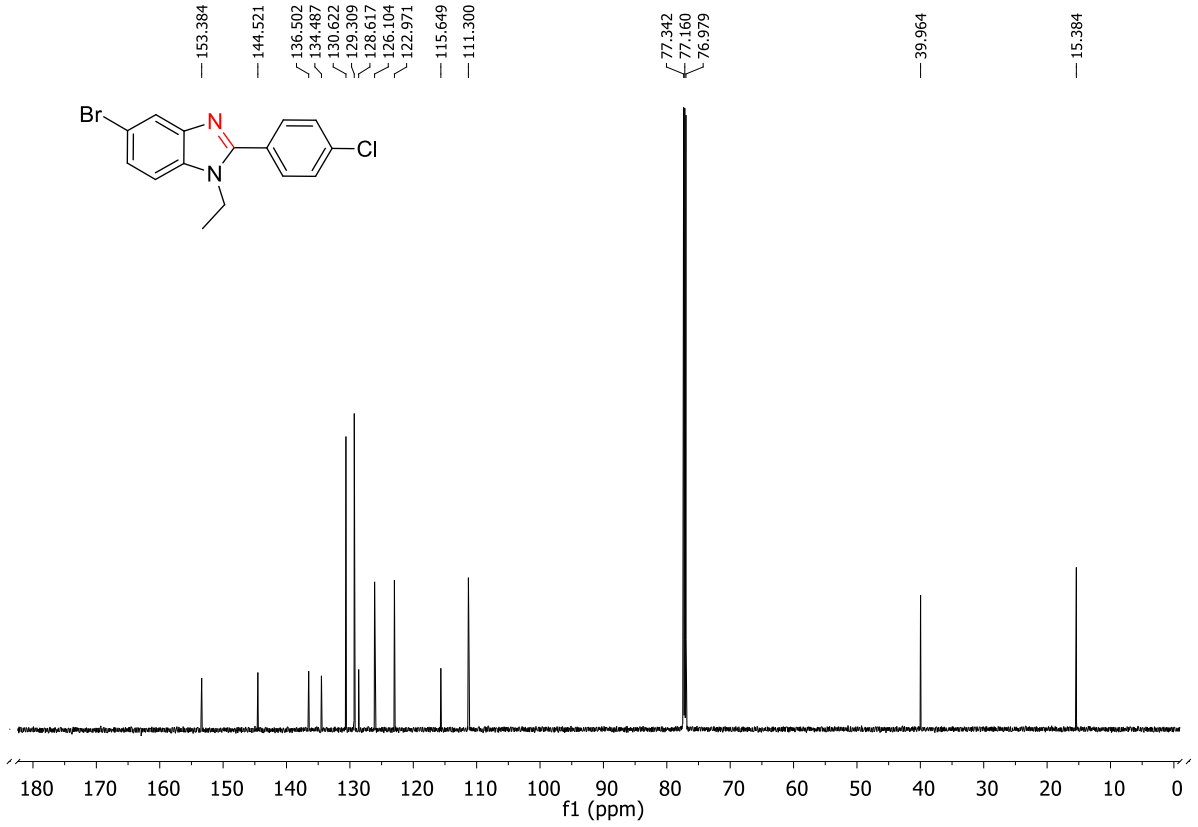


Figure 4.79. [13]C NMR of 5-Bromo-2-(4-chlorophenyl)-1-ethyl-benzo[d]imidazole (**2m**)

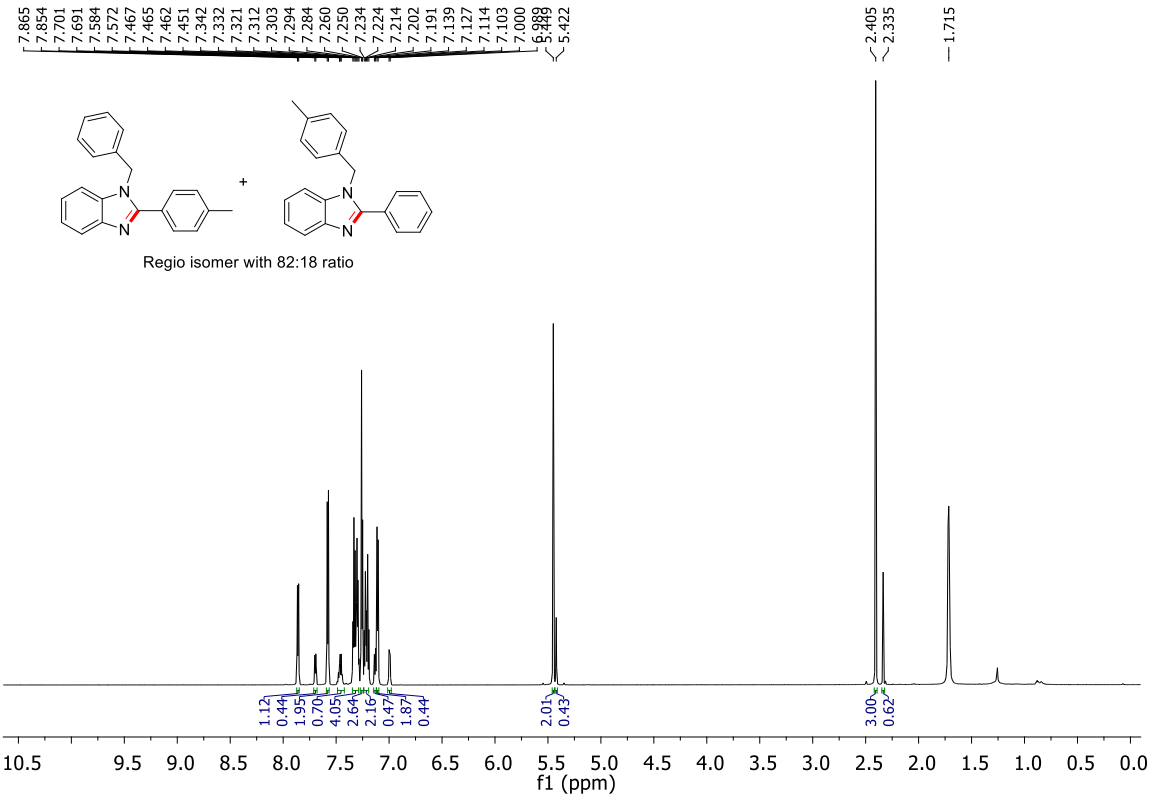


Figure 4.80. ^{1}H NMR of 1-Benzyl-2-(p-tolyl)-benzo[d]imidazole and 1-(4-Methylbenzyl)-2-phenyl-benzo[d]imidazole **(2n)**

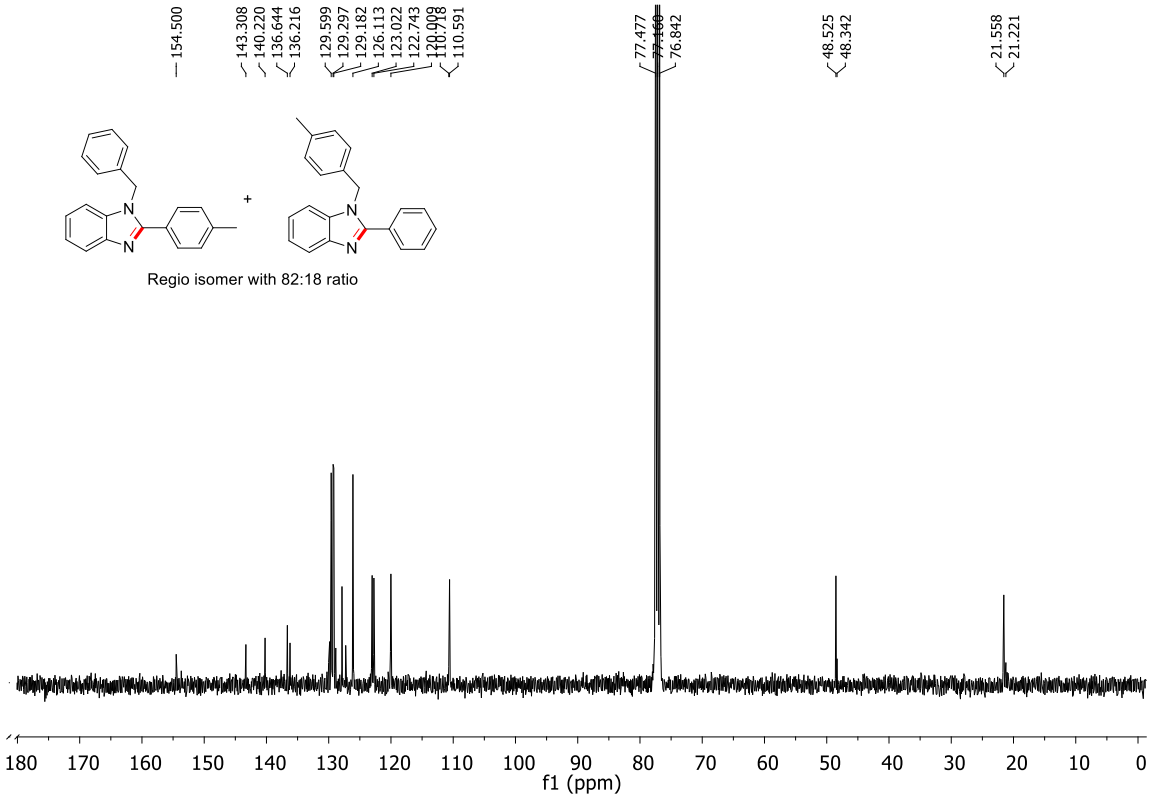


Figure 4.81. ^{13}C NMR of 1-Benzyl-2-(p-tolyl)-benzo[d]imidazole and 1-(4-Methylbenzyl)-2-phenyl-benzo[d]imidazole **(2n)**

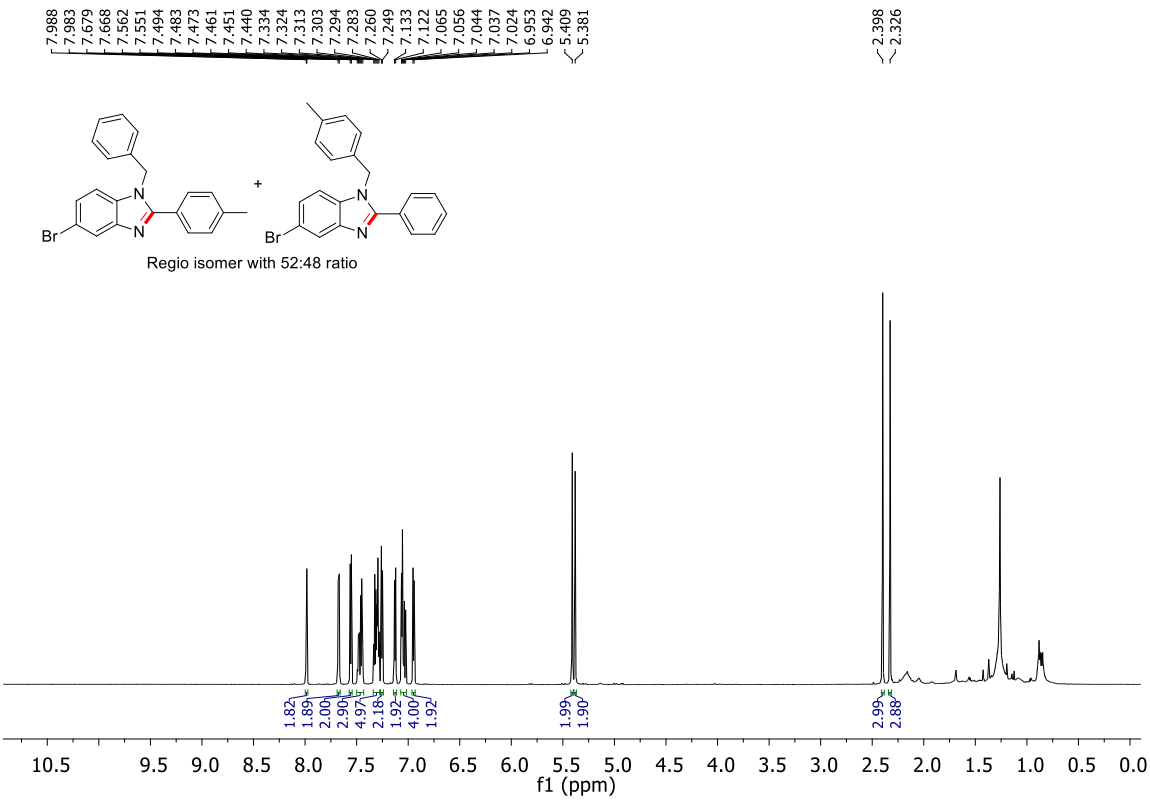


Figure 4.82. ^{1}H NMR of 1-Benzyl-5-bromo-2-(p-tolyl)-benzo[d]imidazole and 5-Bromo-1-(4-methylbenzyl)-2-phenyl-benzo[d]imidazole **(2o)**

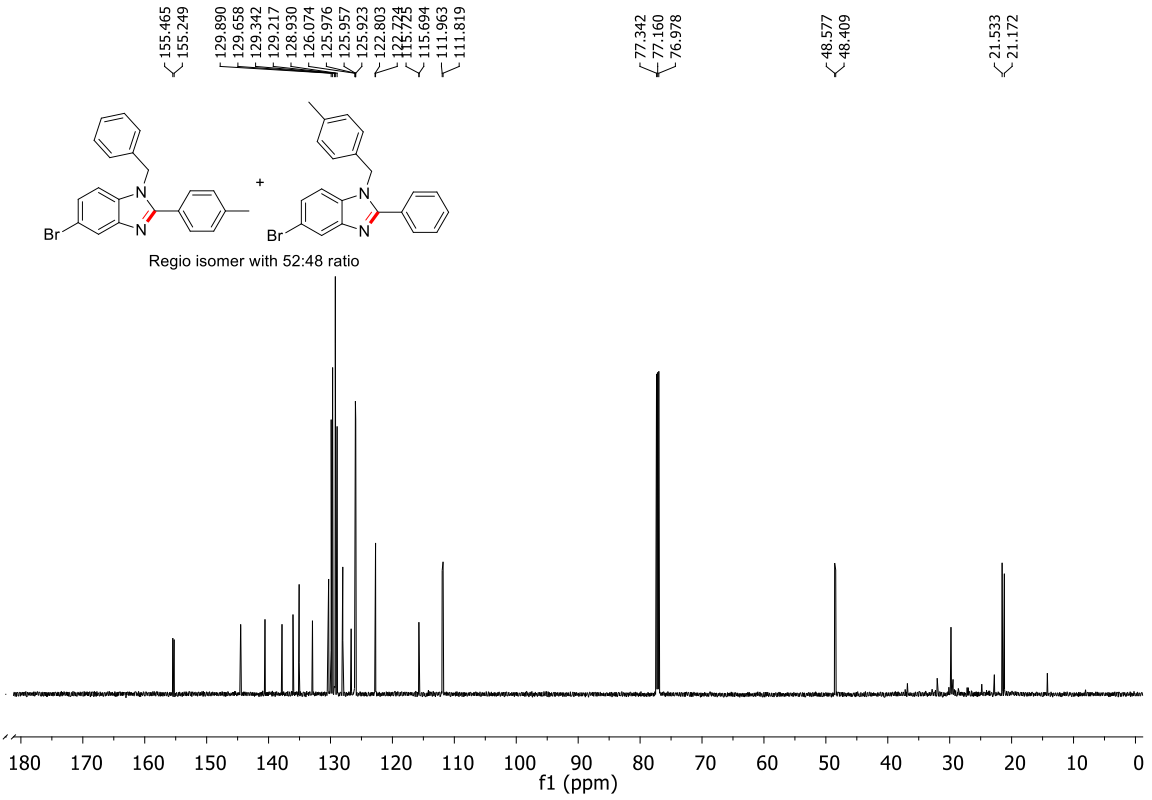


Figure 4.83. ^{13}C NMR of 1-Benzyl-5-bromo-2-(p-tolyl)-benzo[d]imidazole and 5-Bromo-1-(4-methylbenzyl)-2-phenyl-benzo[d]imidazole **(2o)**

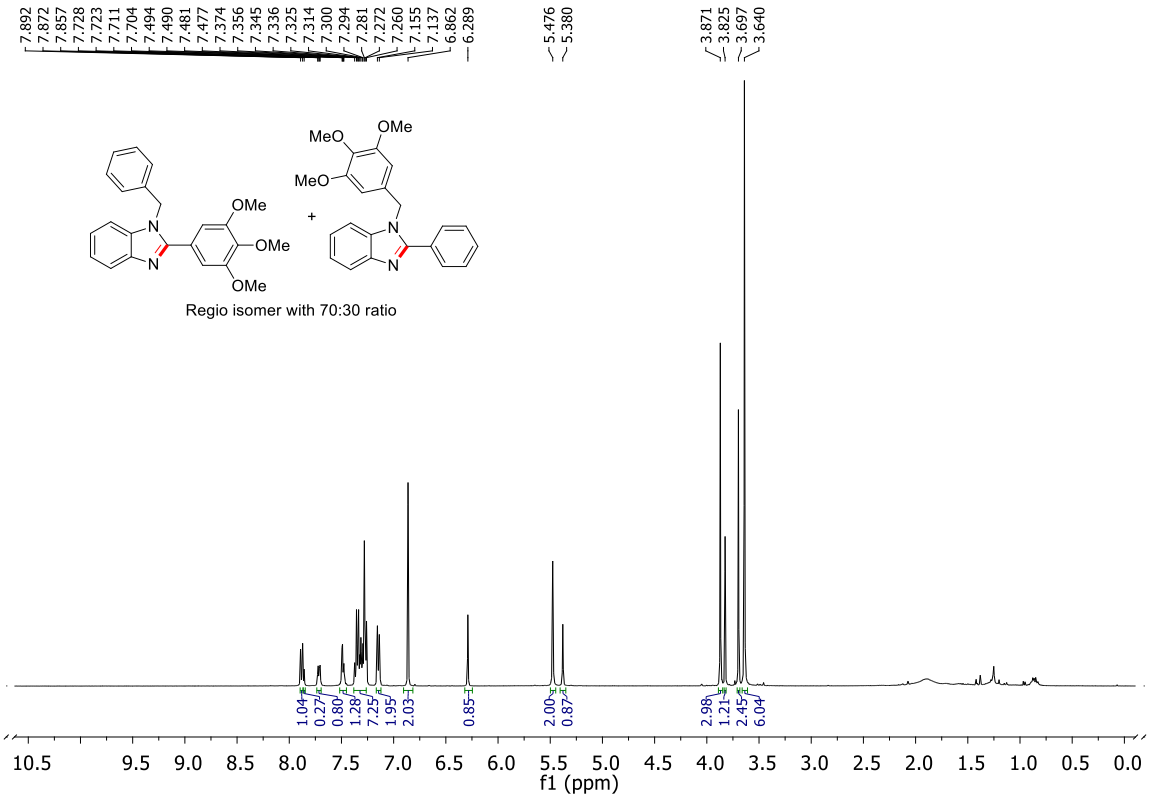


Figure 4.84. [1]H NMR of 1-Benzyl-2-(3,4,5-trimethoxyphenyl)-benzo[d]imidazole and 2-Phenyl-1-(3,4,5-trimethoxybenzyl)-benzo[d]imidazole **(2p)**

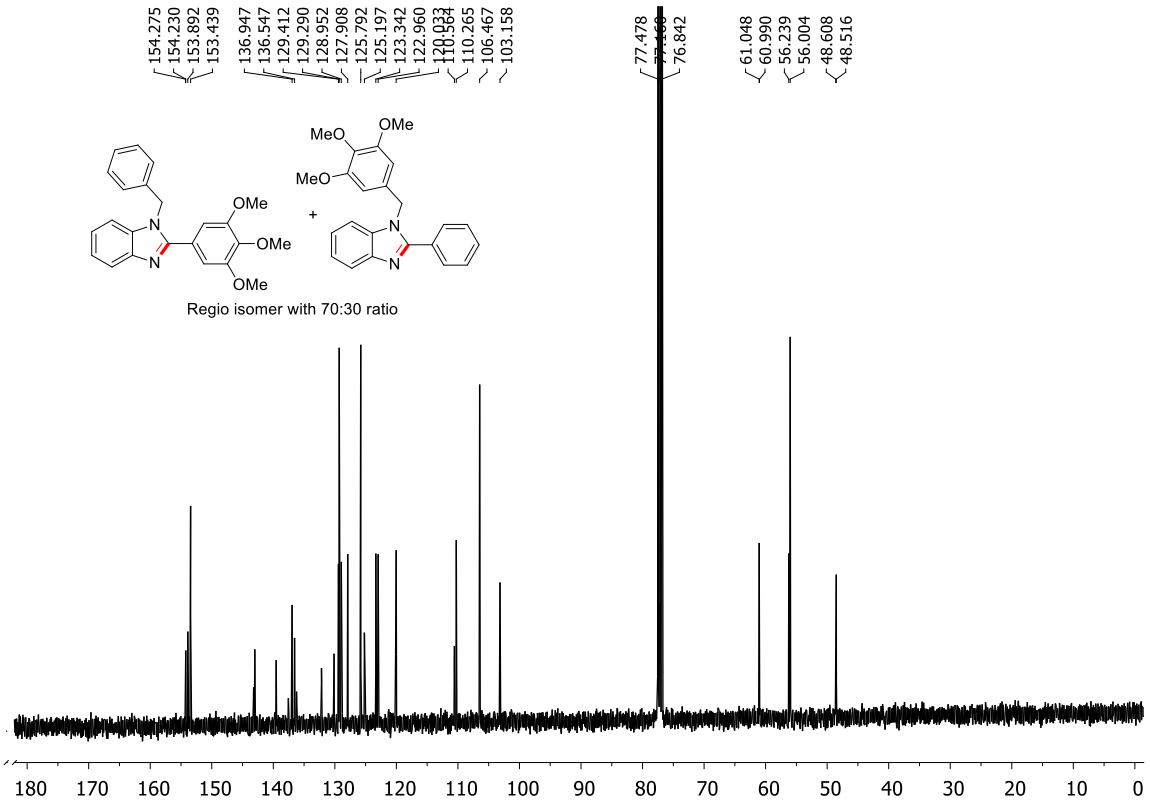


Figure 4.85. [1]H NMR of 1-Benzyl-2-(3,4,5-trimethoxyphenyl)-benzo[d]imidazole and 2-Phenyl-1-(3,4,5-trimethoxybenzyl)-benzo[d]imidazole **(2p)**

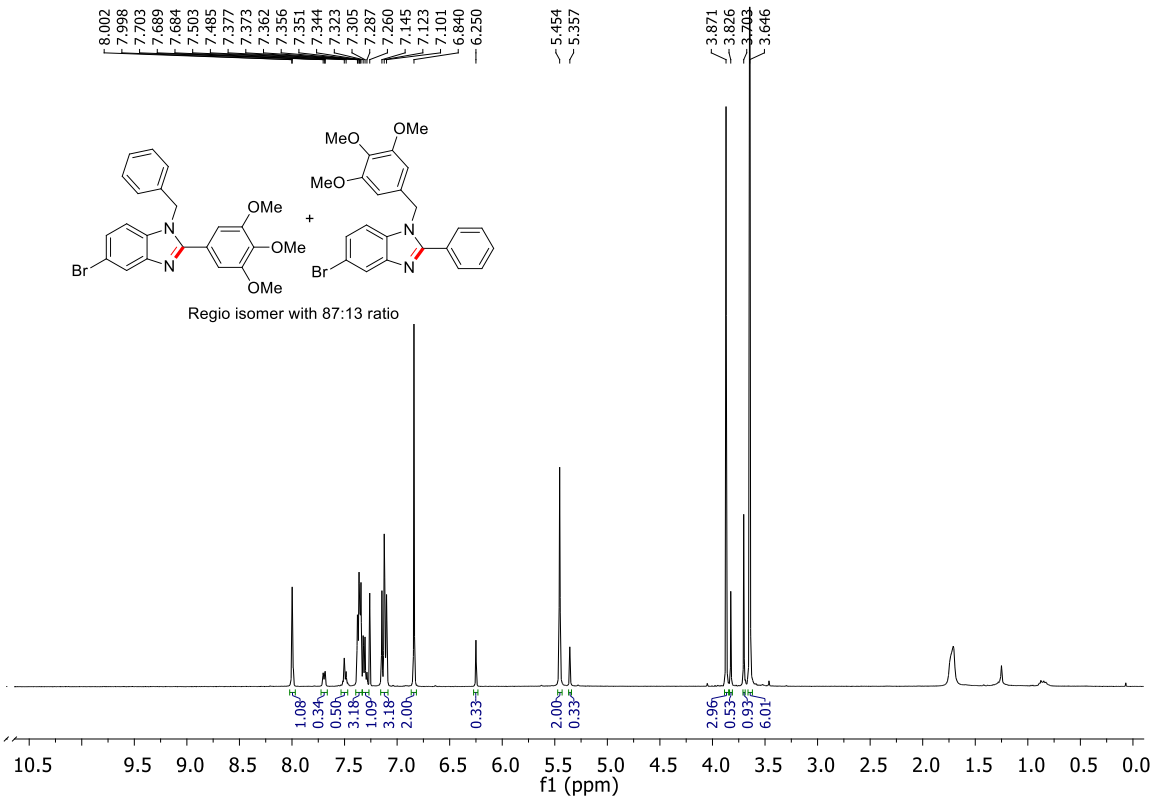


Figure 4.86. [1]H NMR of 1-Benzyl-5-bromo-2-(3,4,5-trimethoxyphenyl)-benzo[d]imidazole and 5-Bromo-2-phenyl-1-(3,4,5-trimethoxybenzyl)-benzo[d]imidazole **(2q)**

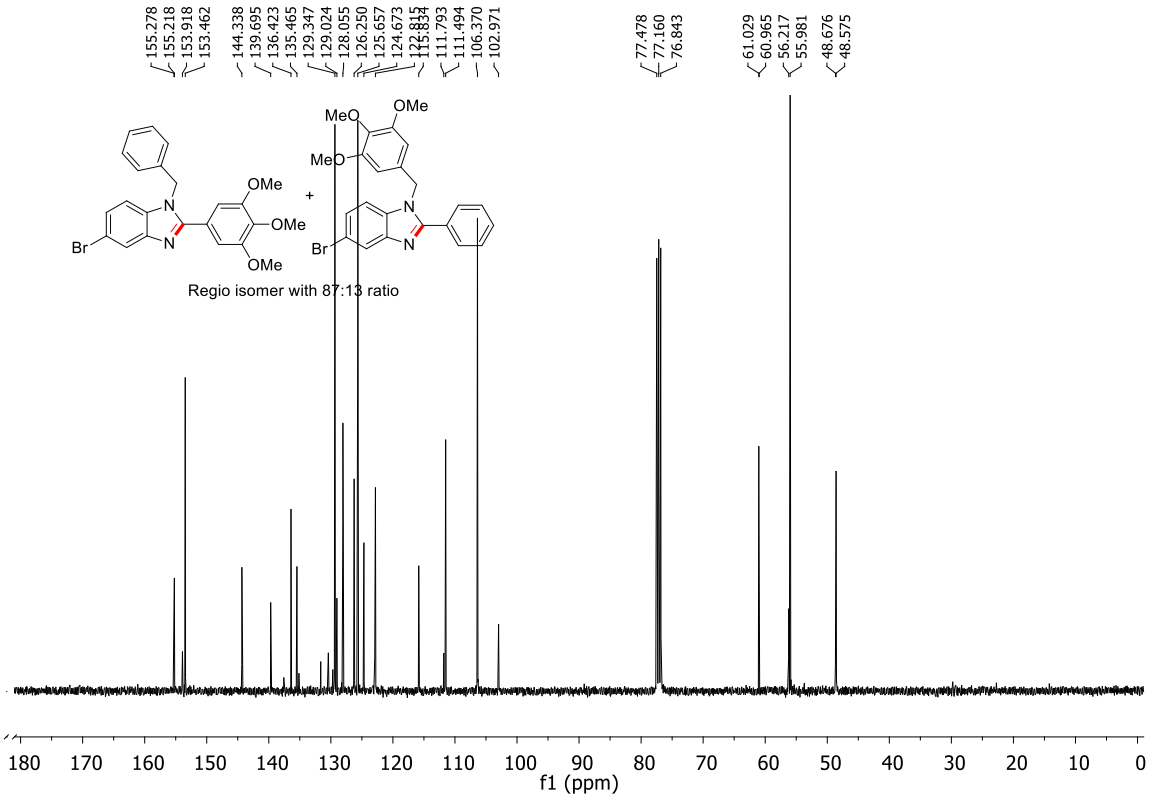


Figure 4.87. [13]C NMR of 1-Benzyl-5-bromo-2-(3,4,5-trimethoxyphenyl)-benzo[d]imidazole and 5-Bromo-2-phenyl-1-(3,4,5-trimethoxybenzyl)-benzo[d]imidazole **(2q)**

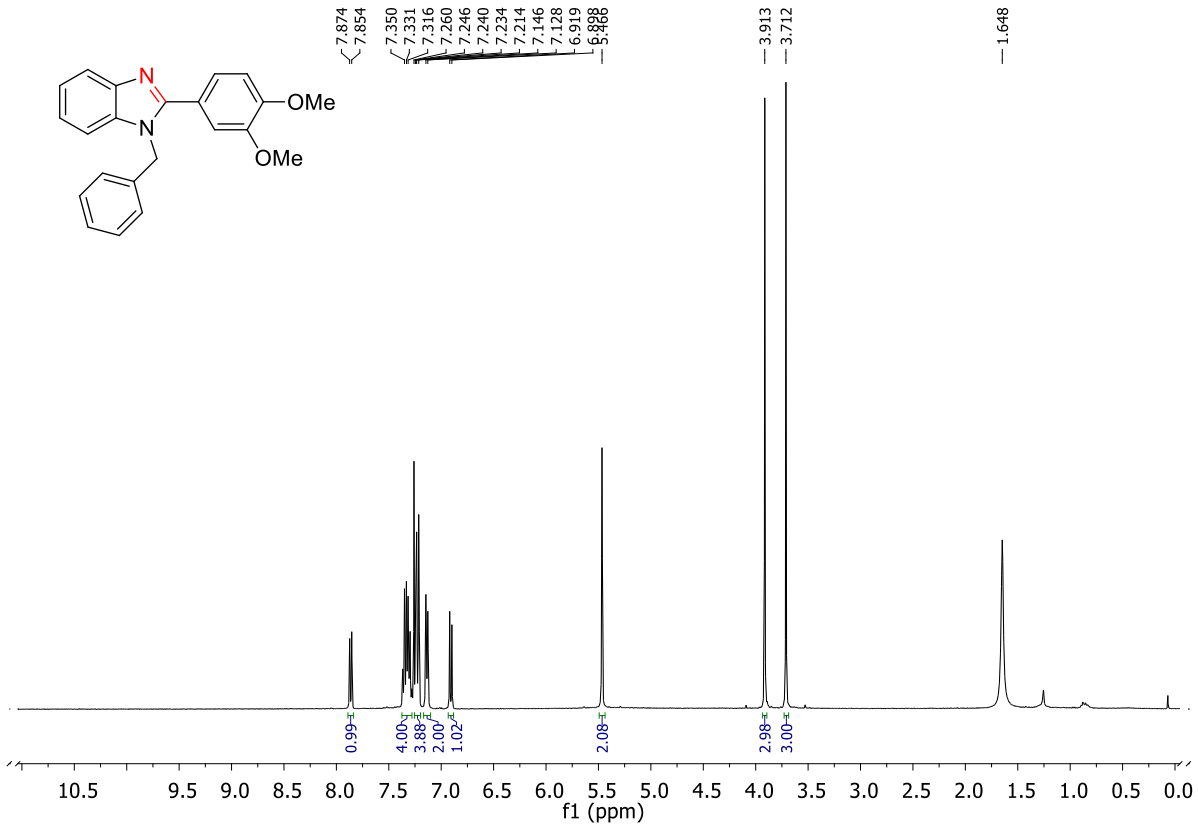


Figure 4.88. ^{1}H NMR of 1-Benzyl-2-(3,4-dimethoxyphenyl)-benzo[d]imidazole (**2r**)

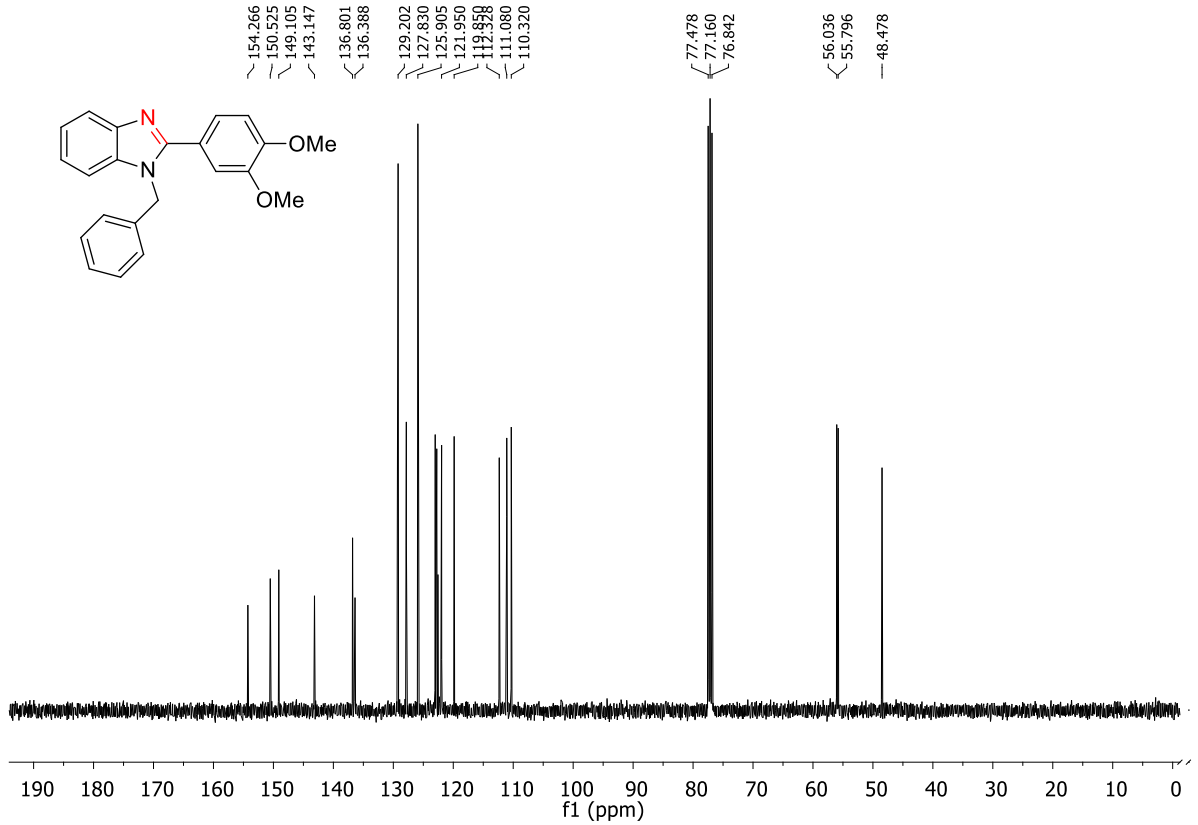


Figure 4.89. ^{13}C NMR of 1-Benzyl-2-(3,4-dimethoxyphenyl)-benzo[d]imidazole (**2r**)

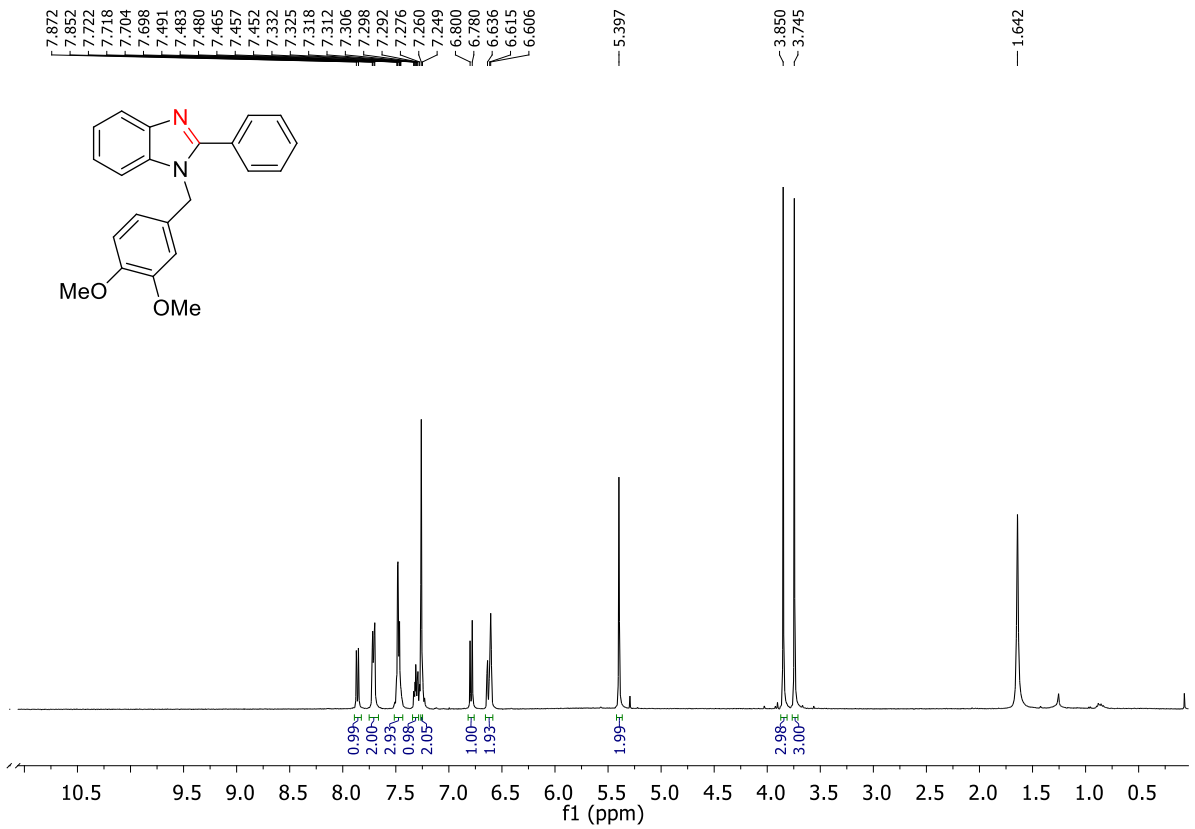


Figure 4.90. ^{1}H NMR of 1-(3,4-Dimethoxybenzyl)-2-phenyl-benzo[d]imidazole (**2r'**)

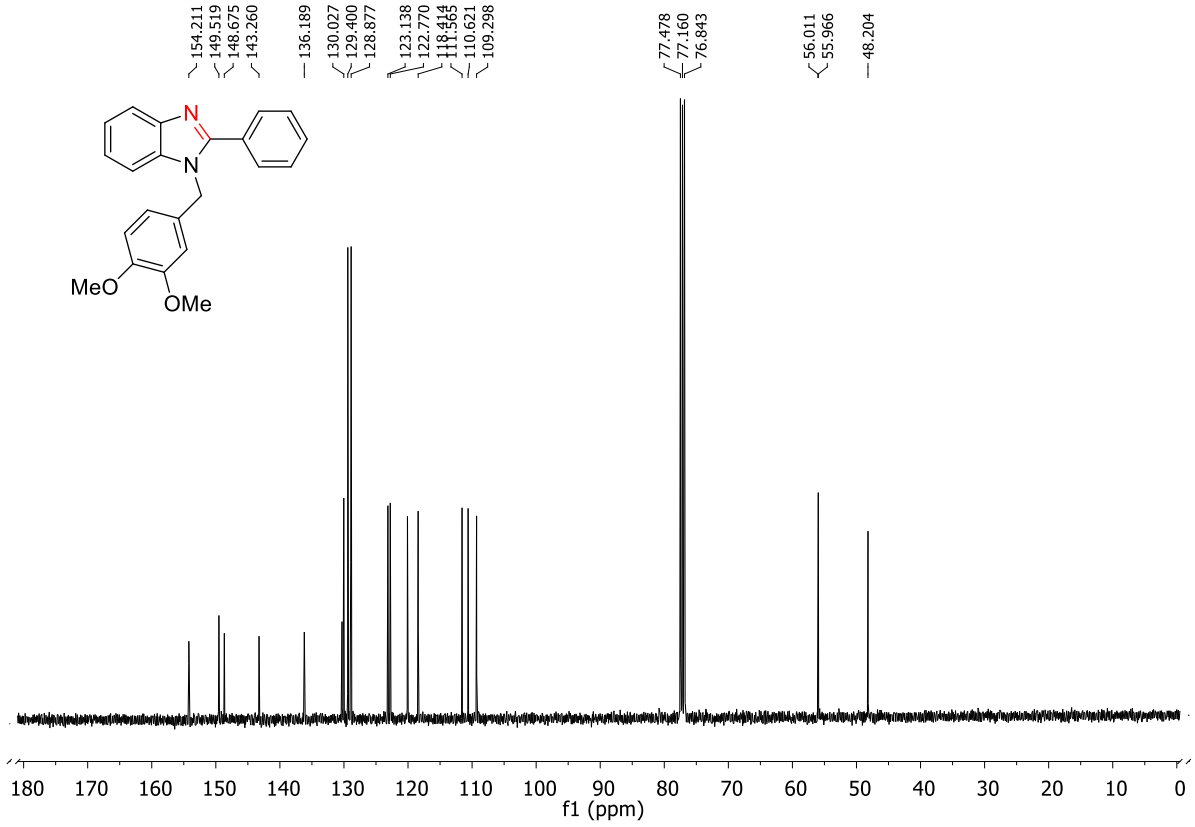


Figure 4.91. ^{13}C NMR of 1-(3,4-Dimethoxybenzyl)-2-phenyl-benzo[d]imidazole (**2r'**)

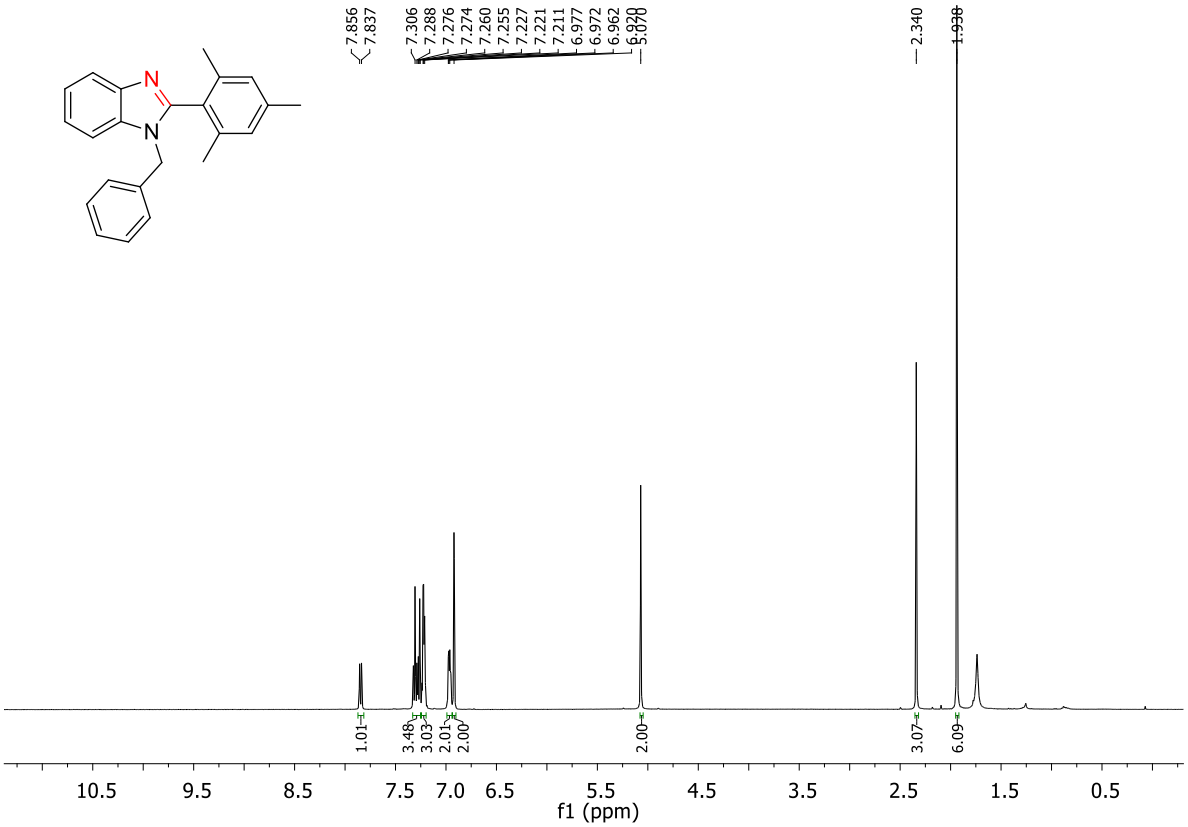


Figure 4.92. ^{1}H NMR of 1-Benzyl-2-mesityl-benzo[d]imidazole (**2s**)

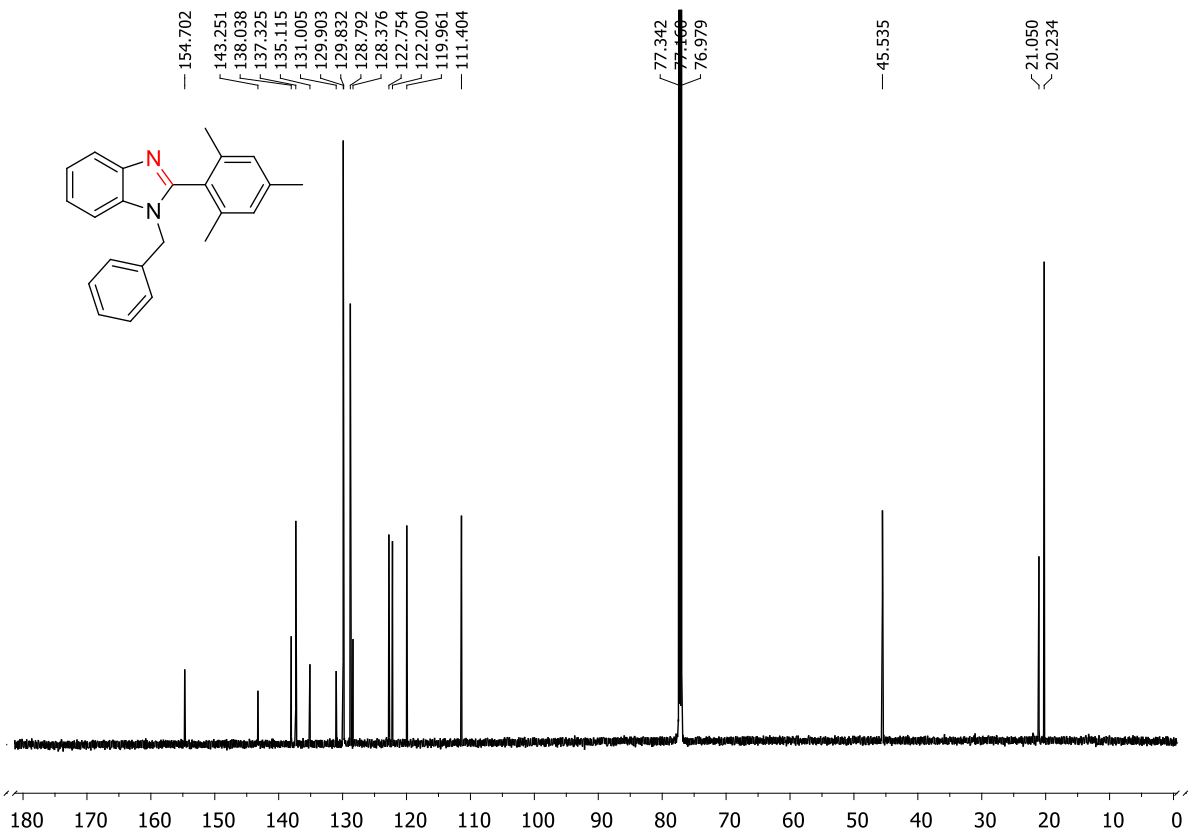


Figure 4.93. ^{13}C NMR of 1-Benzyl-2-mesityl-benzo[d]imidazole (**2s**)

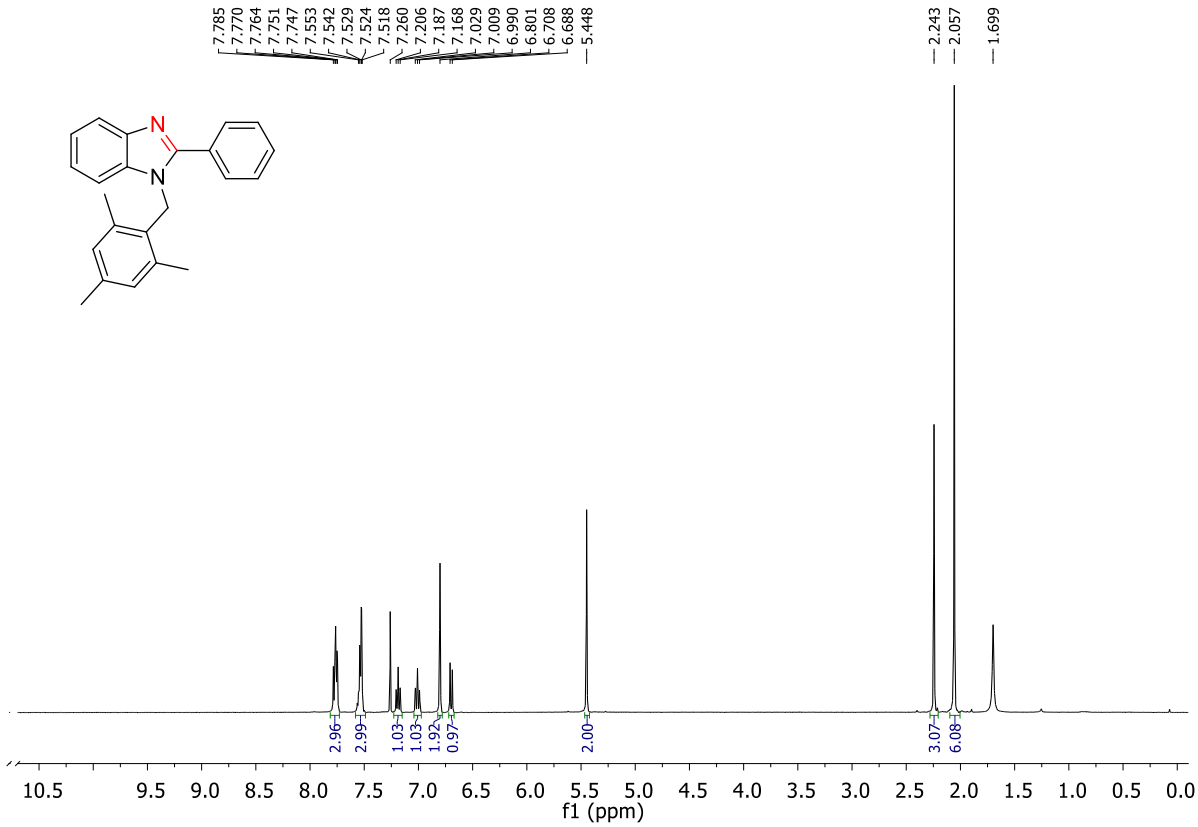


Figure 4.94. [1]H NMR of 2-Phenyl-1-(2,4,6-trimethylbenzyl)-benzo[d]imidazole (**2s'**)

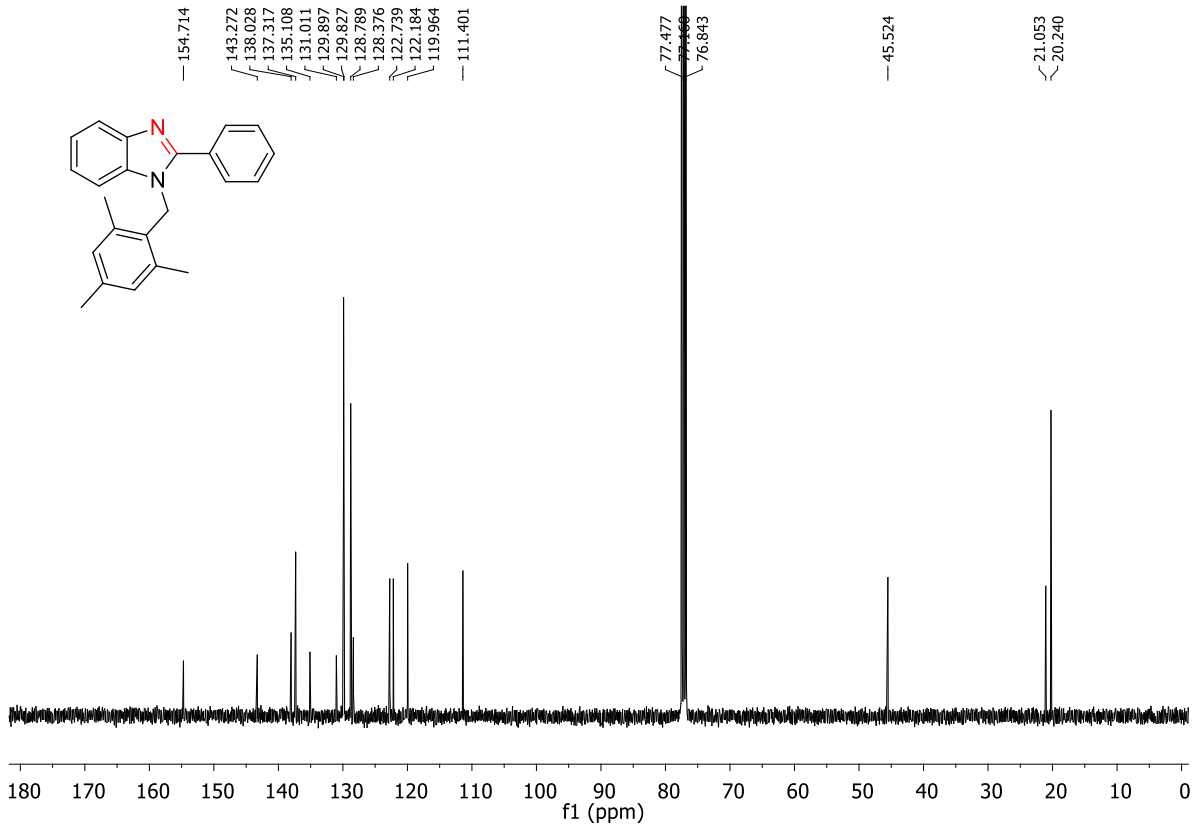


Figure 4.95. [13]C NMR of 2-Phenyl-1-(2,4,6-trimethylbenzyl)-benzo[d]imidazole (**2s'**)

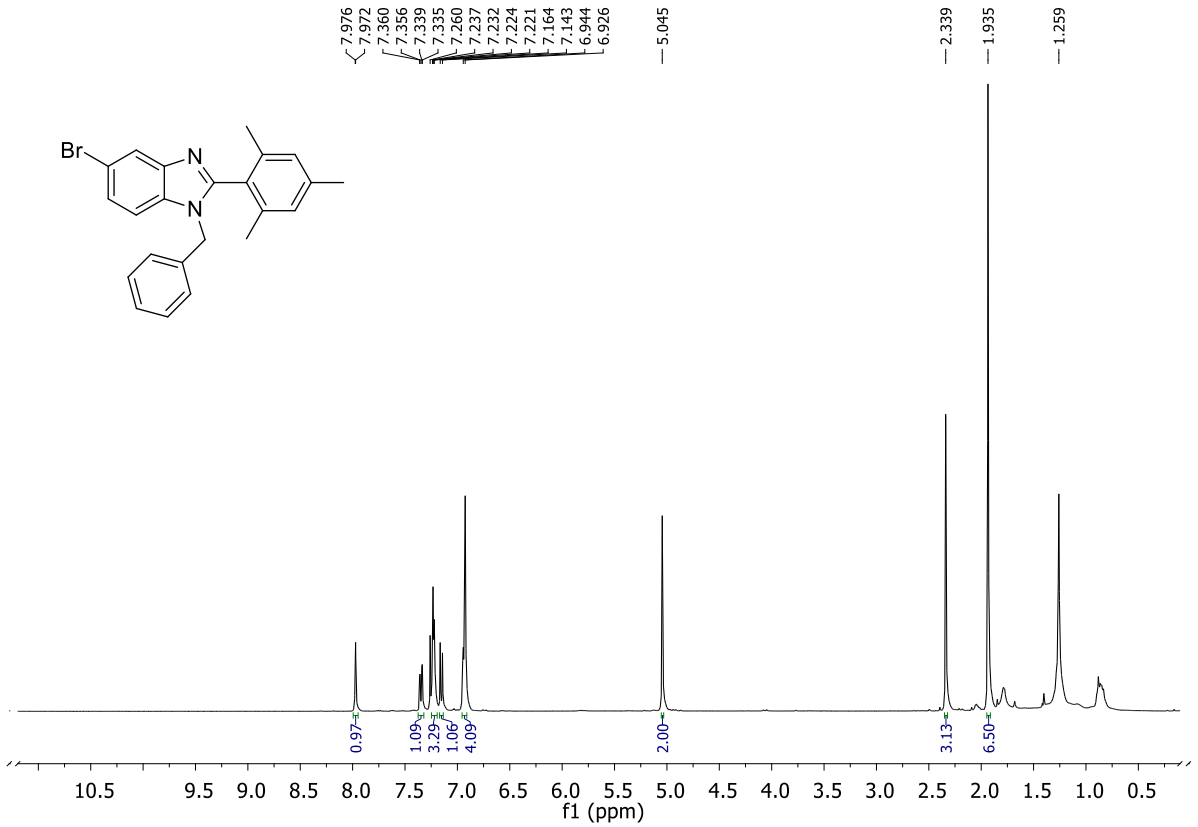


Figure 4.96. ^{1}H NMR of 1-Benzyl-5-bromo-2-mesityl-benzo[d]imidazole (**2t**)

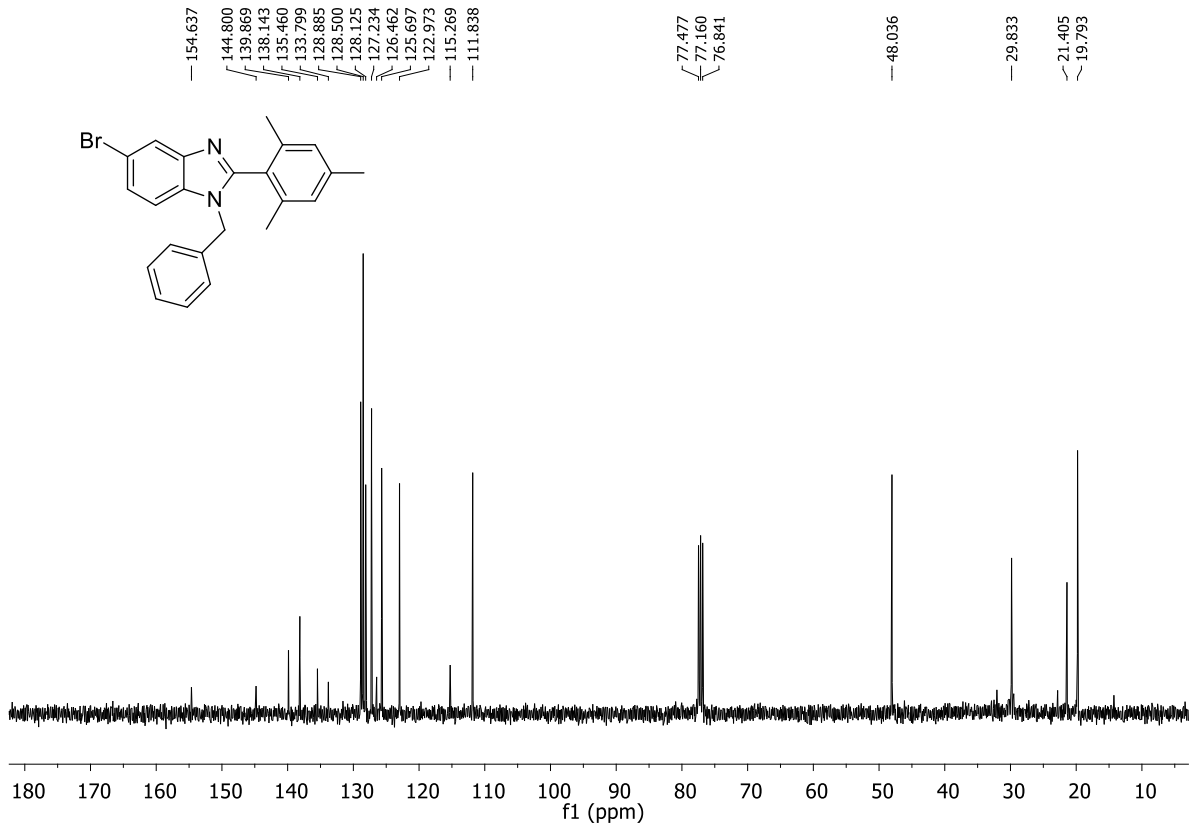


Figure 4.97. ^{13}C NMR of 1-Benzyl-5-bromo-2-mesityl-benzo[d]imidazole (**2t**)

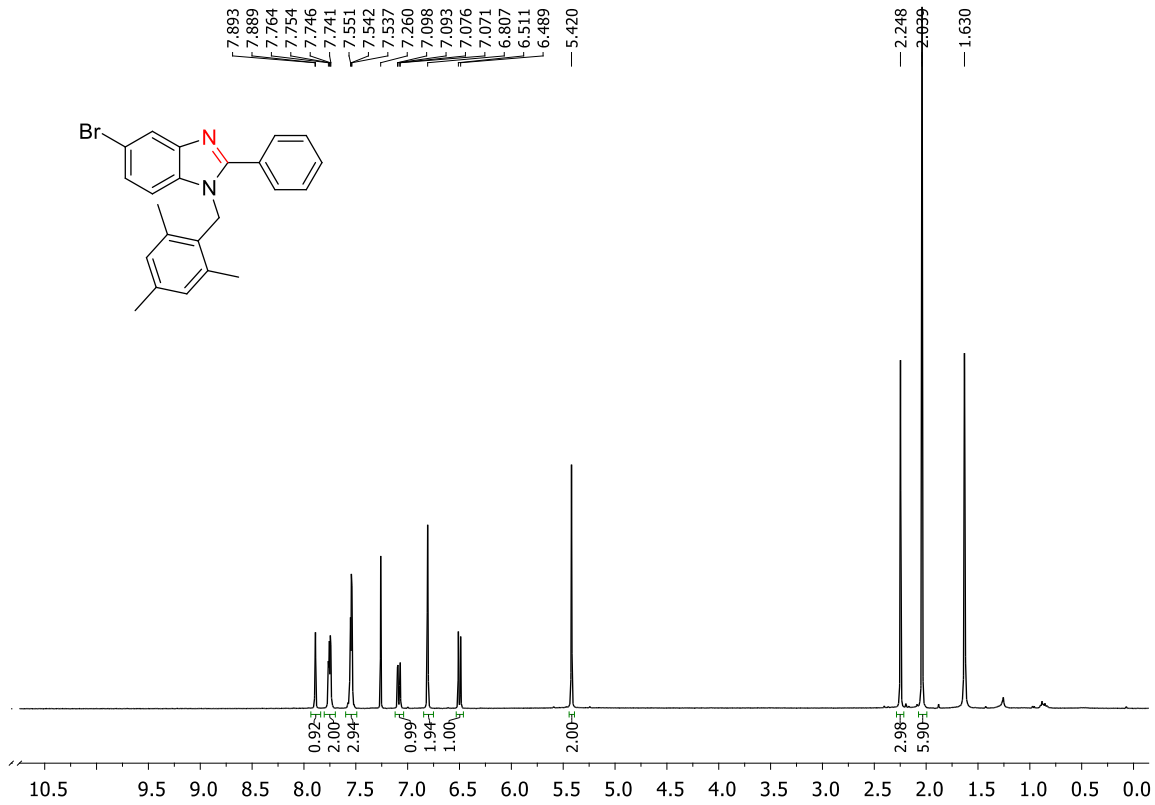


Figure 4.98. ^{1}H NMR of 5-Bromo-2-phenyl-1-(2,4,6-trimethylbenzyl)-benzo[d]imidazole (**2t'**)

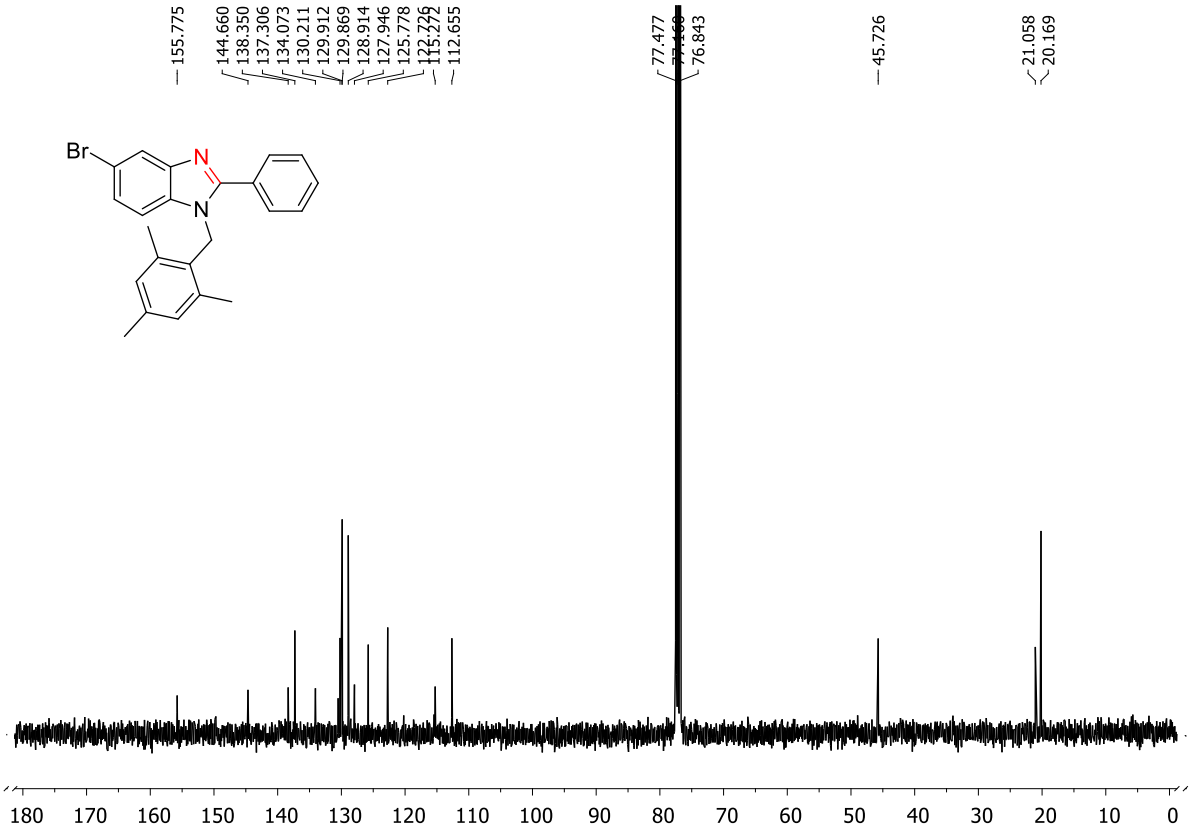


Figure 4.99. ^{13}C NMR of 5-Bromo-2-phenyl-1-(2,4,6-trimethylbenzyl)-benzo[d]imidazole (**2t'**)

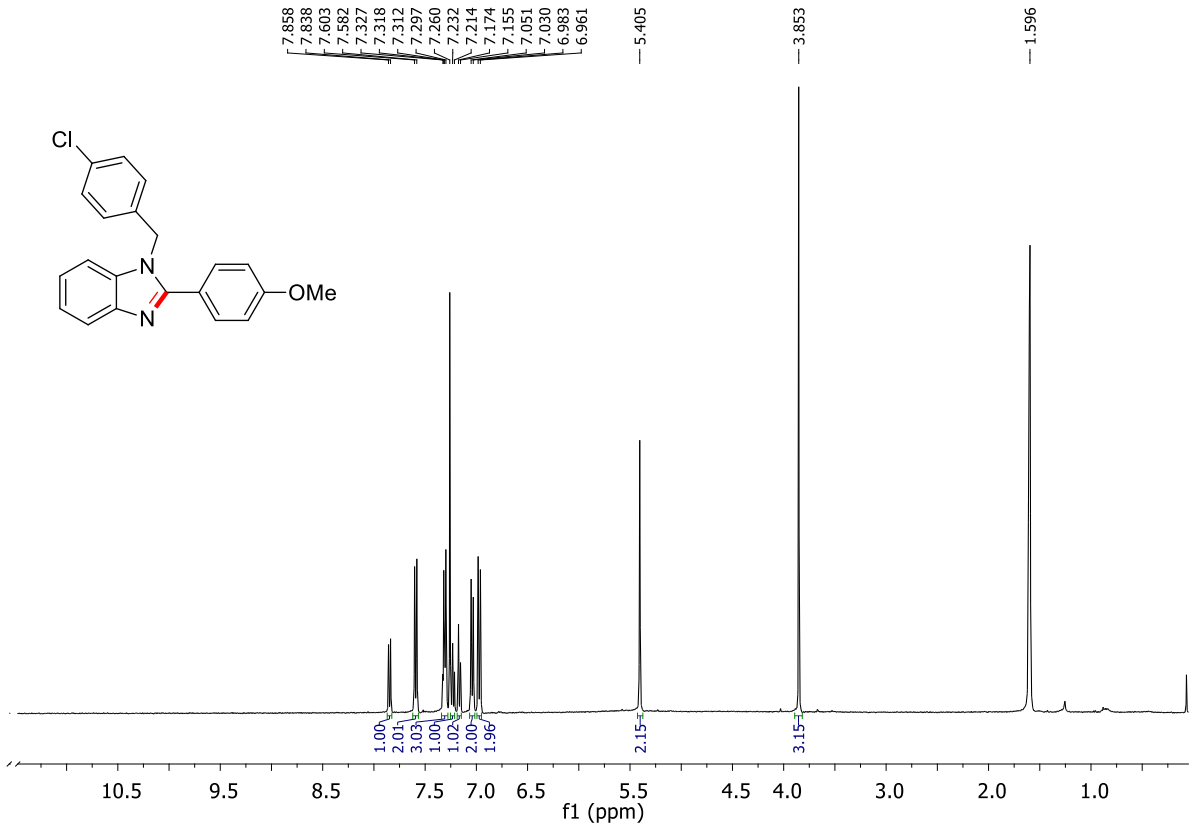


Figure 4.100. ^{1}H NMR of 1-(4-chlorobenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (**2u**)

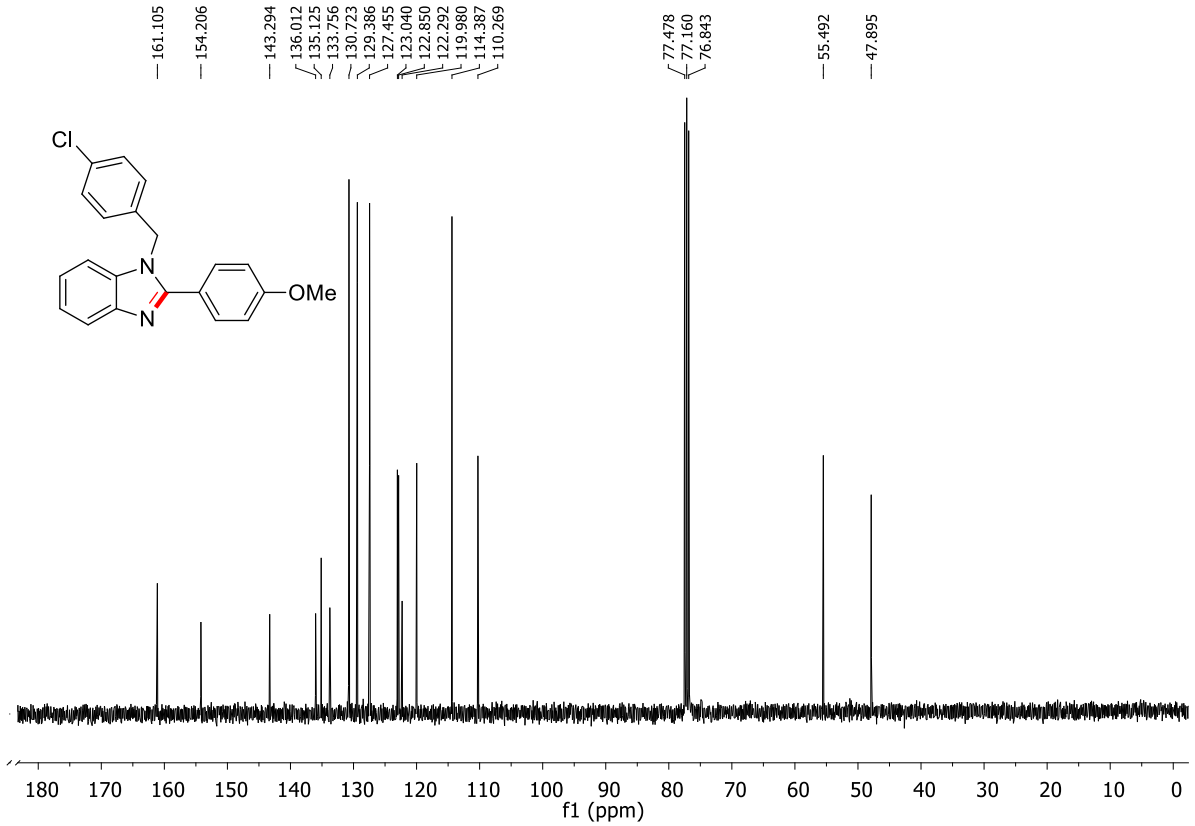


Figure 4.101. ^{13}C NMR of 1-(4-chlorobenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (**2u**)

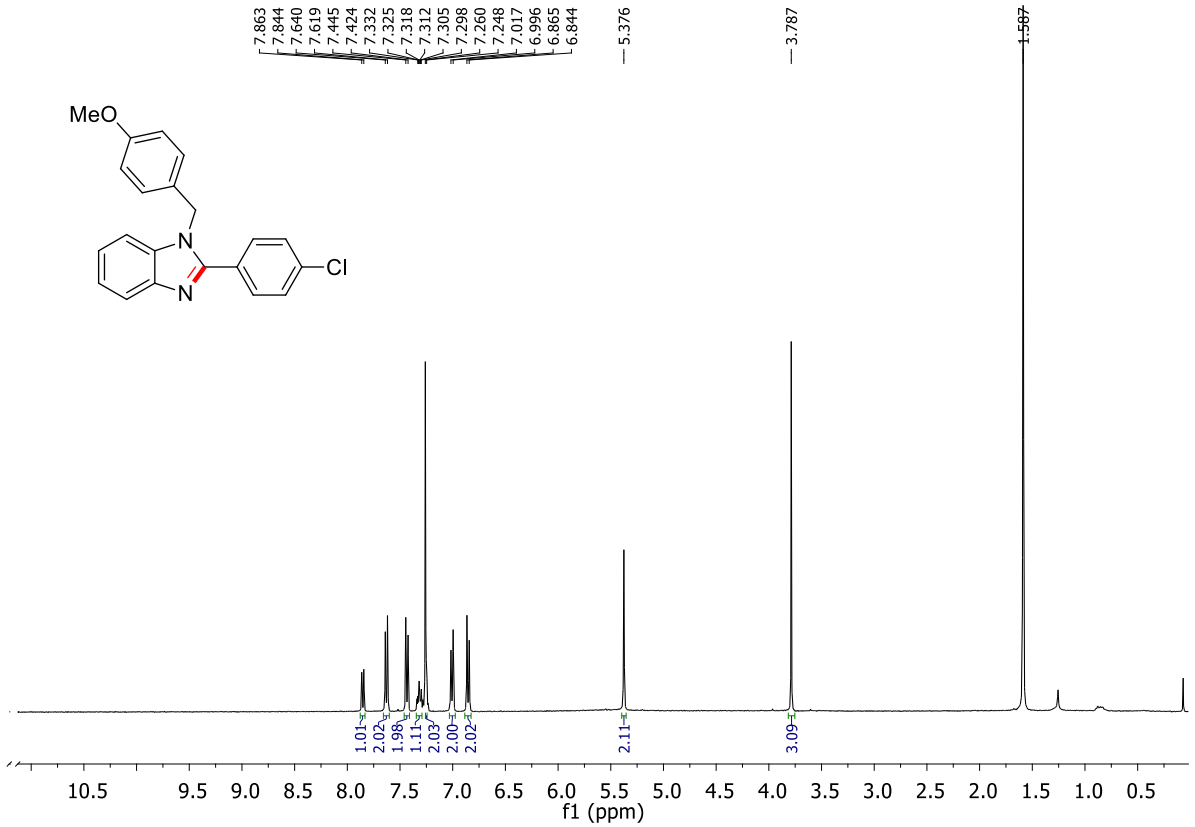


Figure 4.102. ^{1}H NMR of 2-(4-chlorophenyl)-1-(4-methoxybenzyl)-benzo[d]imidazole (**2u'**)

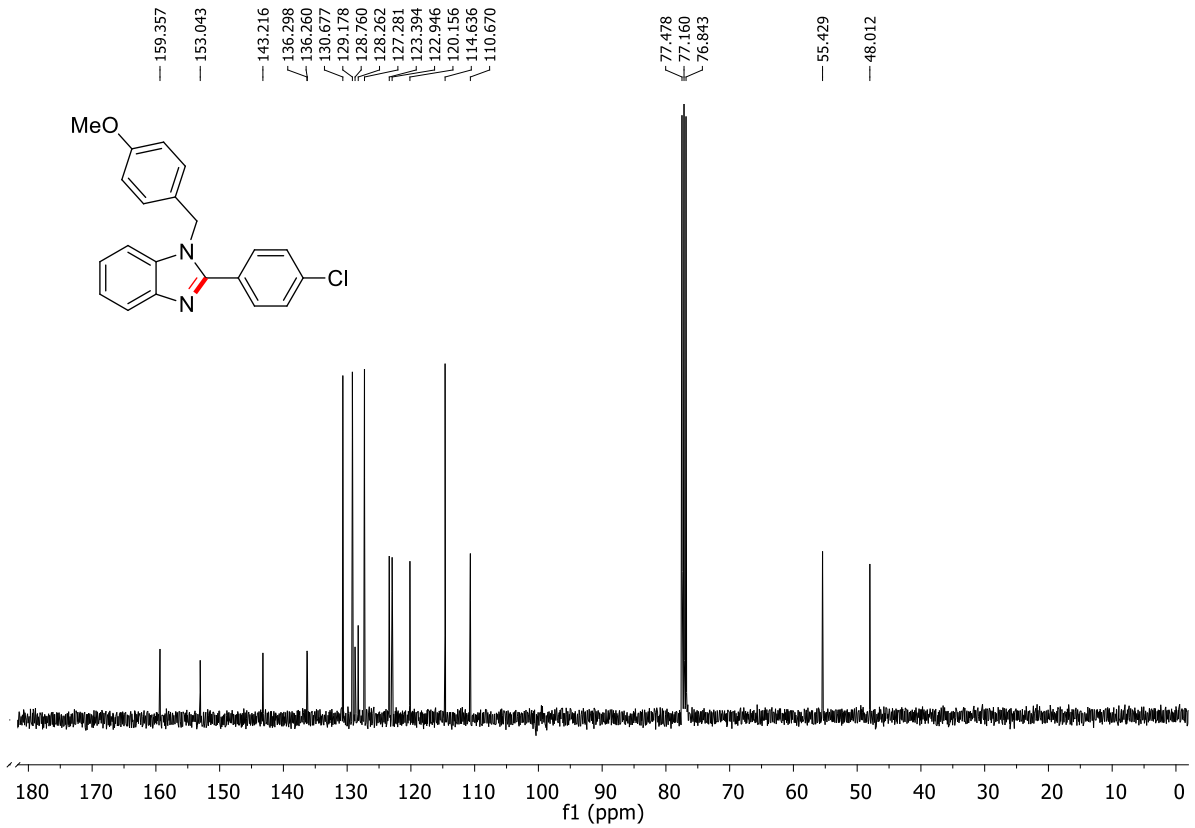


Figure 4.103. ^{13}C NMR of 2-(4-chlorophenyl)-1-(4-methoxybenzyl)-benzo[d]imidazole (**2u'**)

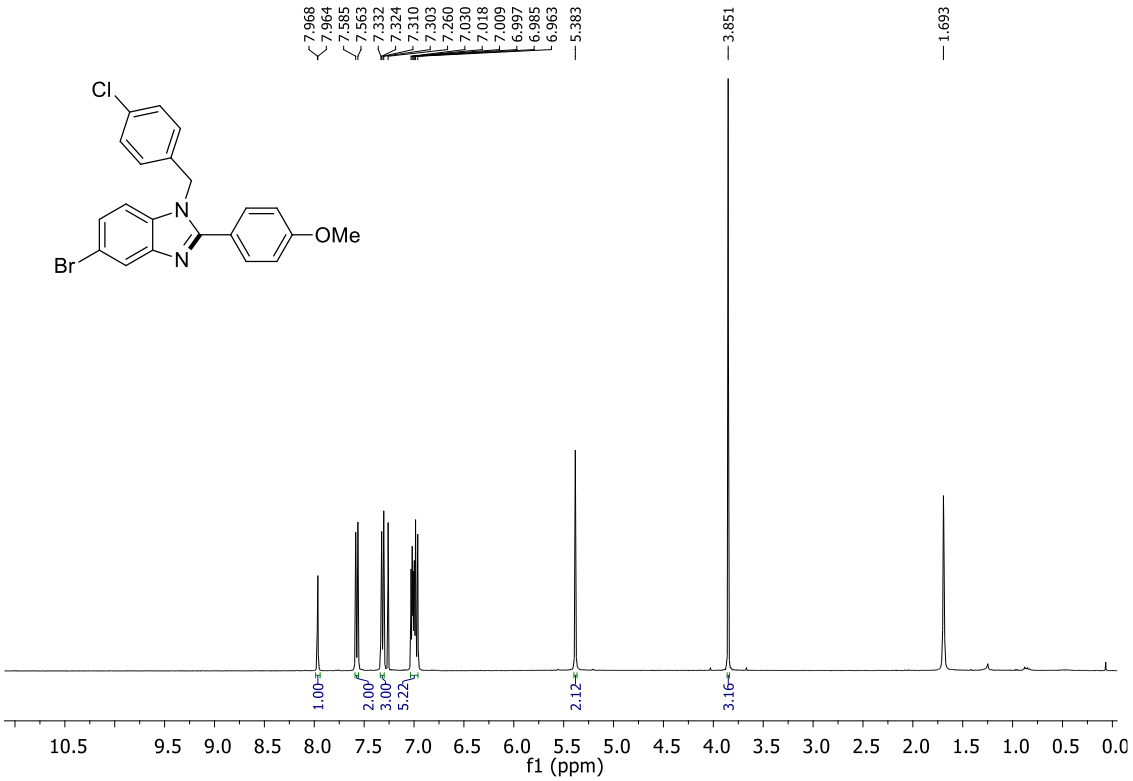


Figure 4.104. ^{1}H NMR of 5-Bromo-1-(4-chlorobenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (**2v**)

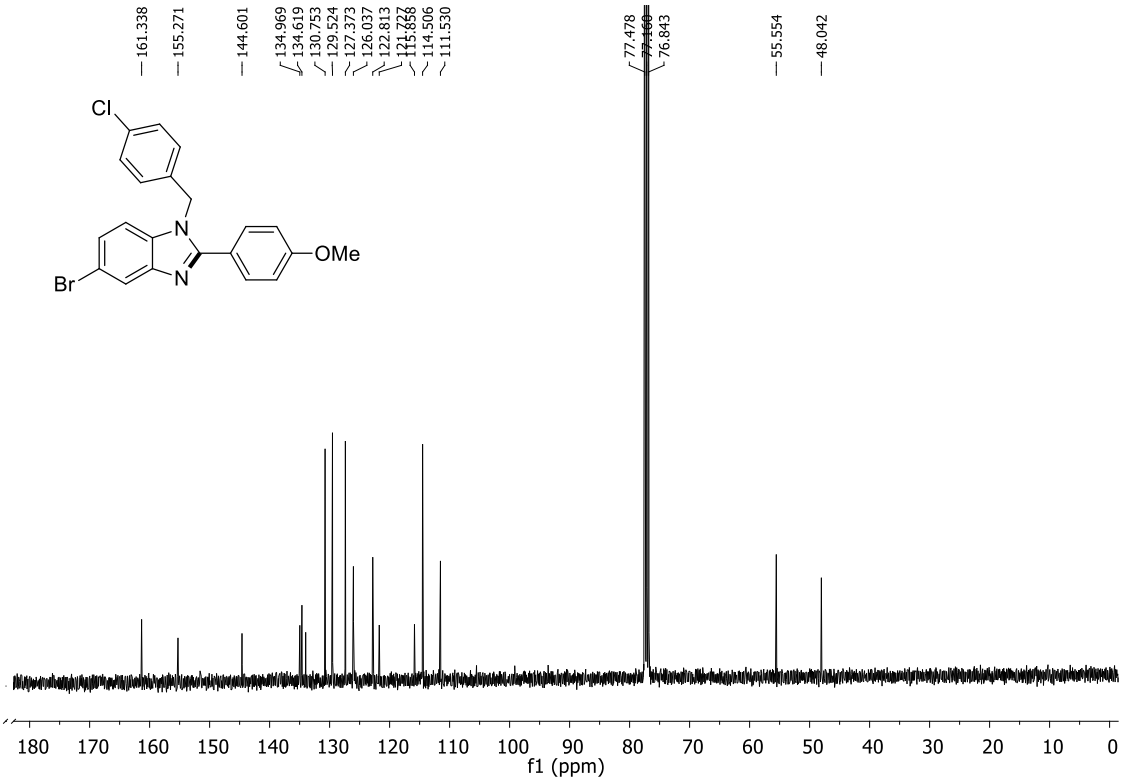


Figure 4.105. ^{13}C NMR of 5-Bromo-1-(4-chlorobenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (**2v**)

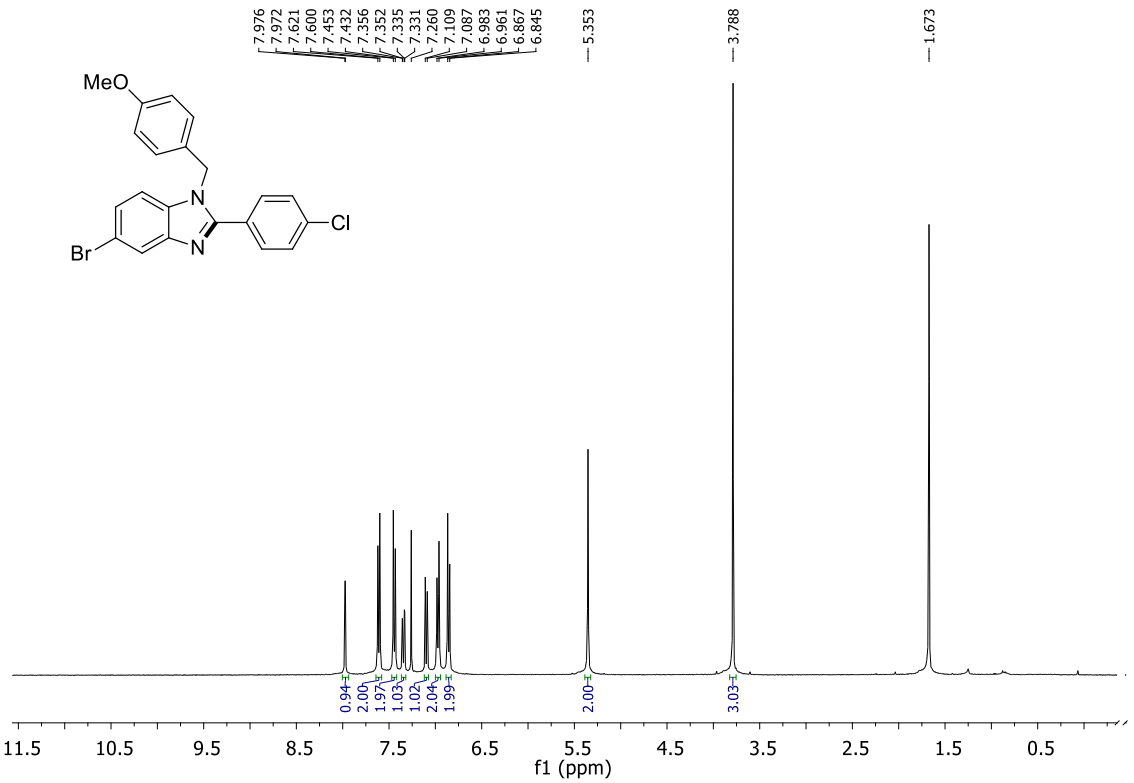


Figure 4.106. ^{1}H NMR of 5-Bromo-2-(4-chlorophenyl)-1-(4-methoxybenzyl)-benzo[d]imidazole (**2v'**)

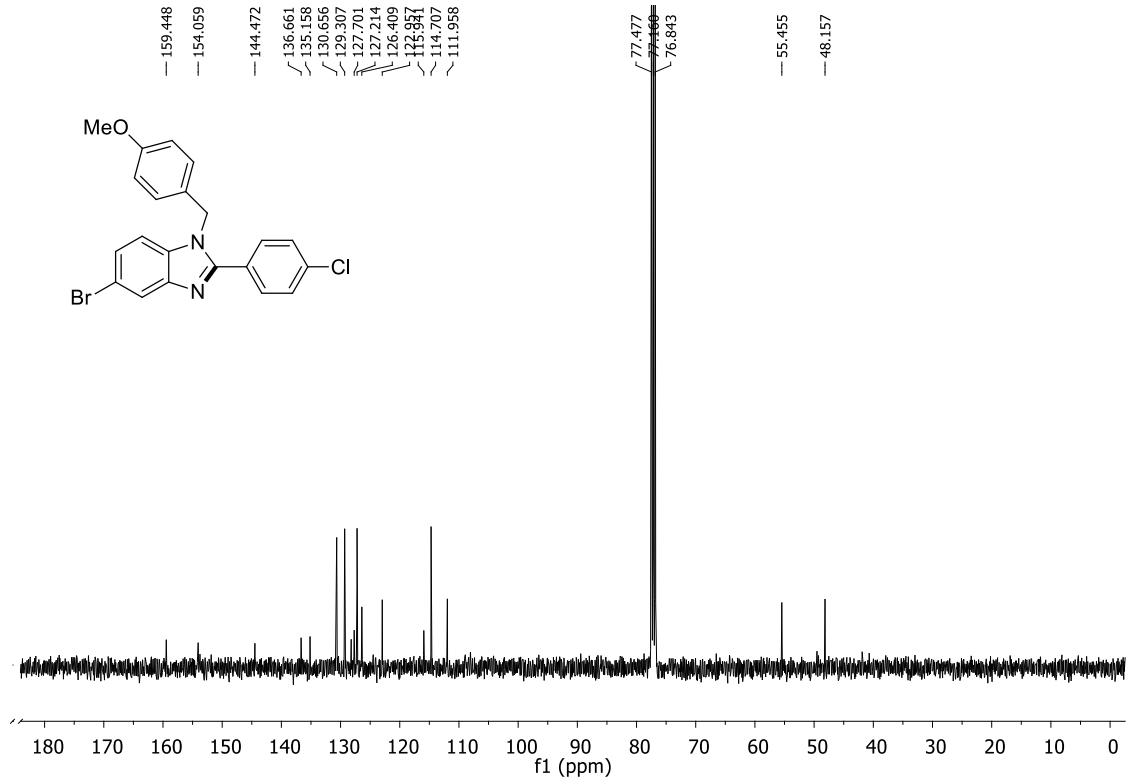


Figure 4.107. ^{13}C NMR of 5-Bromo-2-(4-chlorophenyl)-1-(4-methoxybenzyl)-benzo[d]imidazole (**2v'**)

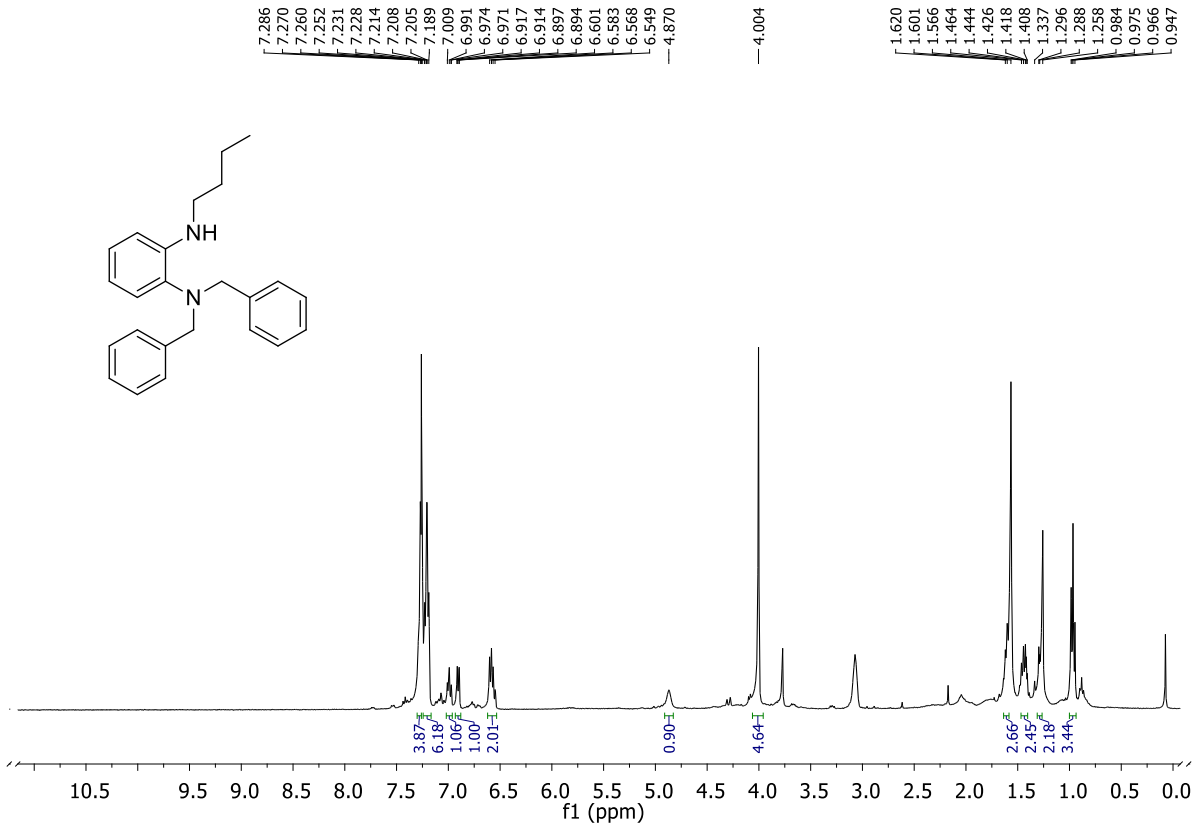


Figure 4.108. ^{1}H NMR of N^{1},N^{1}-dibenzyl-N^{2}-butylbenzene-1,2-diamine (**3**)

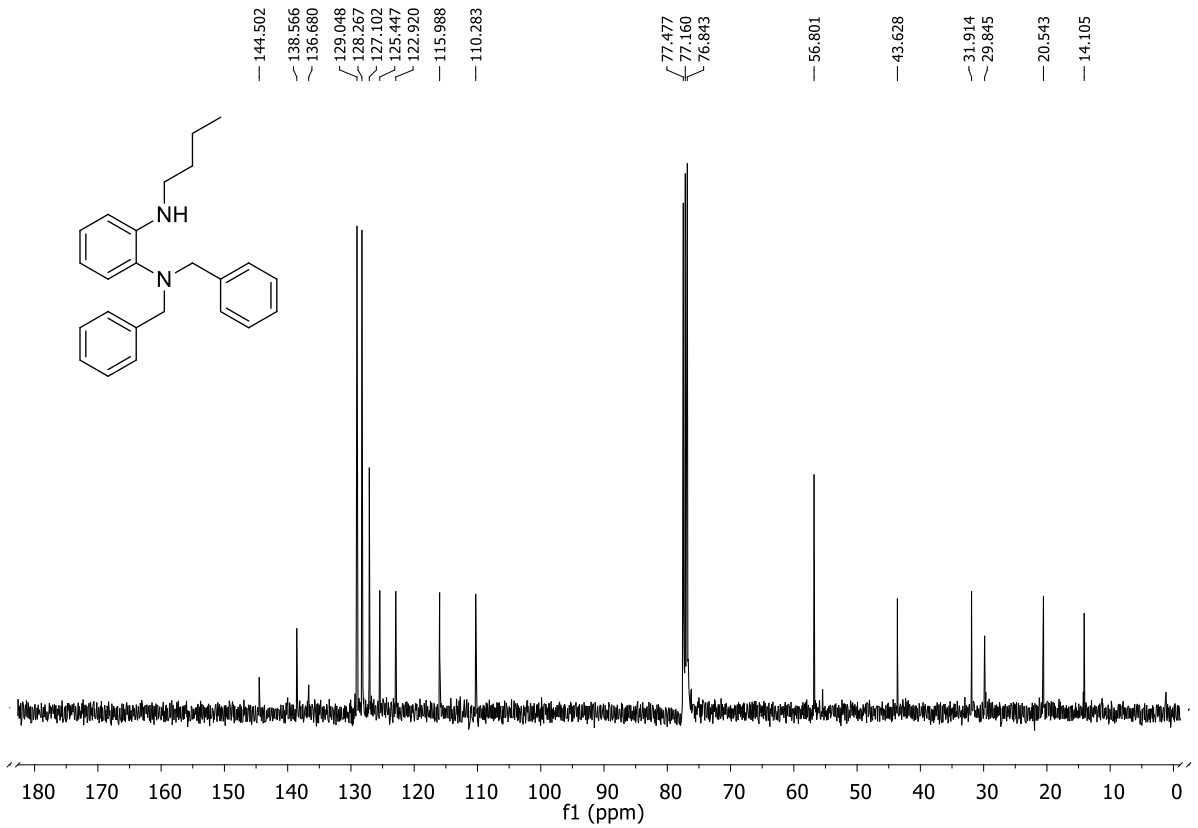


Figure 4.109. ^{13}C NMR of N^{1},N^{1}-dibenzyl-N^{2}-butylbenzene-1,2-diamine (**3**)

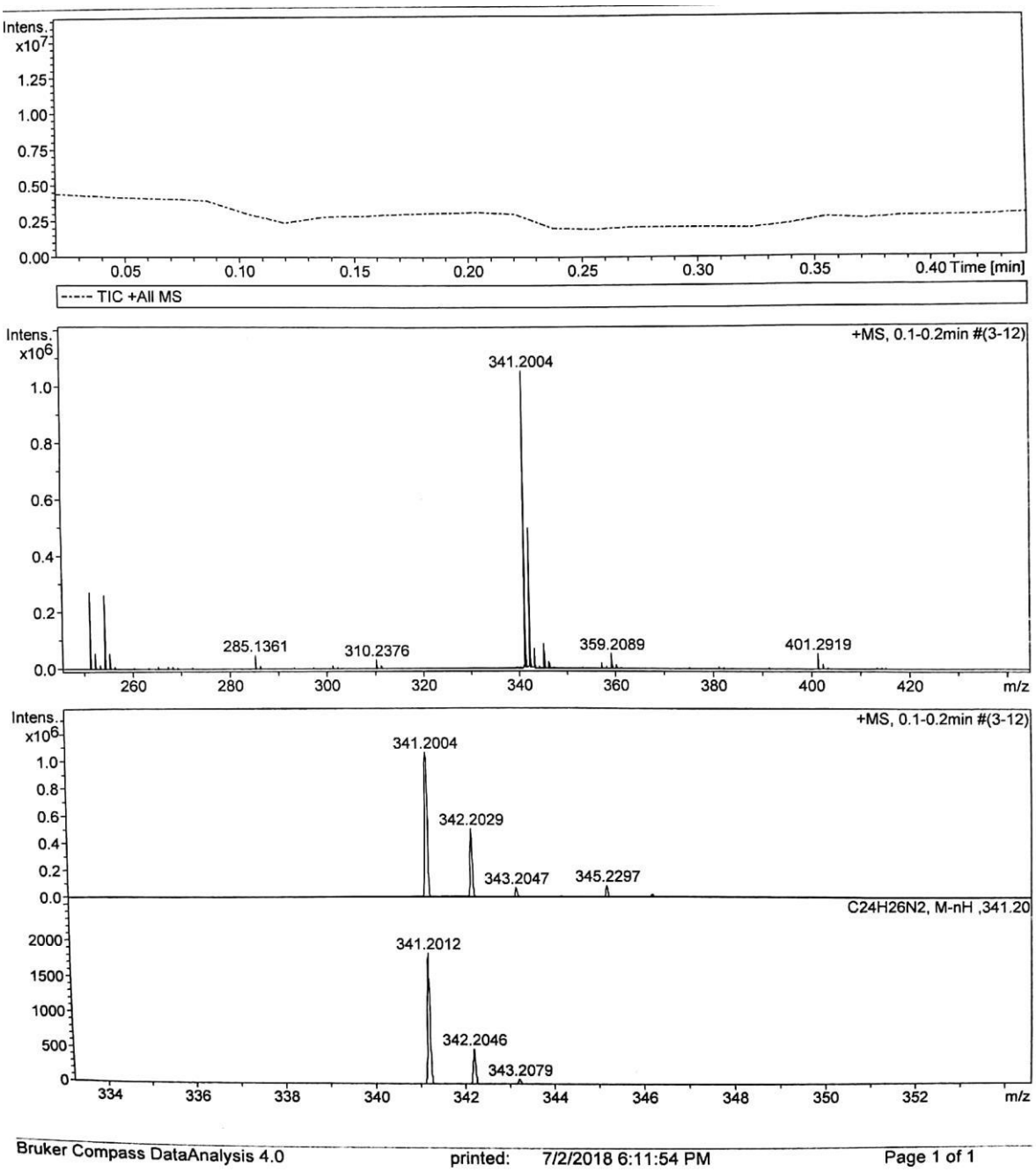
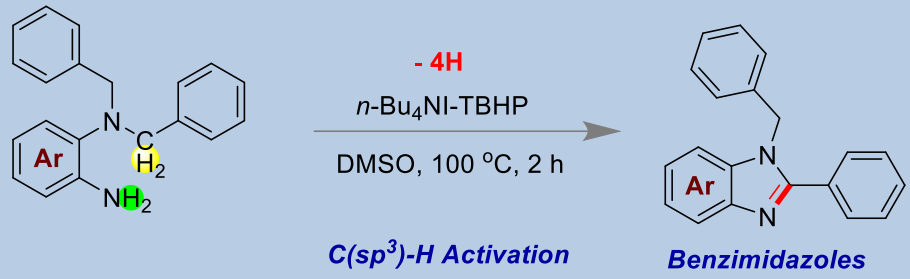


Figure 4.110. HRMS of 1-Benzyl-3-butyl-2-phenyl-2,3-dihydro-benzo[d]imidazole (**4**)

CHAPTER 5

TBAI-TBHP Mediated C(sp^3)-H Functionalization

5.1 ABSTRACT



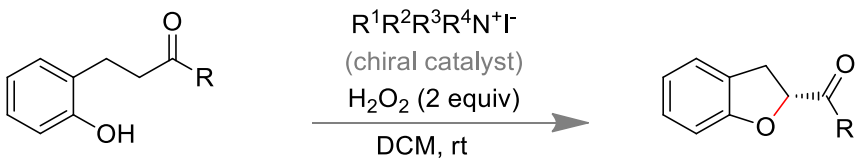
A sustainable and metal free method for an intramolecular oxidative C-H imination reaction is reported. The double dehydrogenative C-N coupling reaction between a free amine group and *N*-methylene group was established under TBAI-TBHP condition. Thus, in a single step, 4H elimination was achieved to access 1,2-disubstituted benzimidazoles.

5.2 INTRODUCTION

Selective oxidation of undirected aliphatic C-H bonds are mostly known *via* enzyme mediated methods, but, it remains challenging to the chemists because of unviability of appropriate reagents.[1] The C(sp^3)-H bonds are thermodynamically more stable and generally become less reactive than the C(sp^2)-H bonds. Advancement towards development of synthetic methods of functionalizing unactivated C(sp3)-H bonds to any useful functionalities are significantly important in fundamental research.[2] The methods developed based on dehydrogenative C(sp^3)−H amination on undirected C-H systems are well-known either as metal initiated or by radical mediated pathway.[3-10] The C(sp^3)-H imination reactions are more

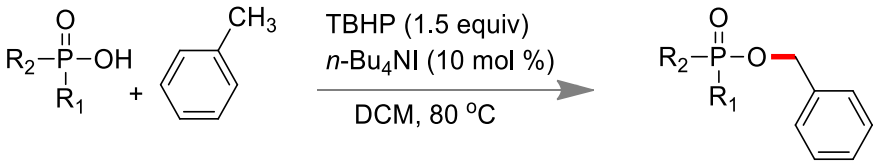
challenging than the amination reactions, because combining the $–CH_2$ and $–NH_2$ for 4H elimination can be thermodynamically unfavorable process.[11,12] Alabugin and co-workers established a Fe(II)-mediated oxidative C-H imination method[13] by single electron transfer (SET) pathway. Later, they have also established another approach which is transition metal-free and under aerobic condition for the same transformation using ^{t}BuOK.[14] However, the drawbacks associated with these methods are: the use of expensive transition metal catalyst makes the process uneconomical; most of the transformations required pre-activation of the substrates.

For oxidative C-N bond synthesis by C-H bond functionalization, hypervalent iodine reagents gained high popularity because of their low toxicity, environmentally benign nature and easy availability.[15-18] However, recently the methods based on *in situ* generation of reactive iodine reagent from lower valent iodine[19] compound with the help of inexpensive co-oxidant like *m*CPBA (*meta*-chloroperbenzoic acid),[20] H_2O_2 (hydrogen peroxide), TBHP (*tert*-butylhydroperoxide), etc.[19,21] have become popular for construction of various new bonds and important molecules. Simple organic molecule like iodobenzene, iodotoluene and inorganic iodide reagents have find practical application for this *in situ* generated method. The advantages with the inorganic reagents are water solubility, low-cost and can act as phase transfer catalyst. Various groups have demonstrated the use of tetrabutylammonium iodide (TBAI) in combination with mild oxidant like TBHP, H_2O_2 and other peroxide based oxidants.[22-24] Ishihara and co-workers reported enantioselective cycloetherification[25] of phenol derivative by using chiral tetraalkylammoniumiodide in combination with TBHP or H_2O_2 as co-oxidant.



Scheme 5.1 Ishihara's chiral catalyst for cycloetherification method.

These reagents have proved to be very efficient in cross dehydrogenative coupling for the construction of C – heteroatom bonds. Recently, Tang and his group developed a cross dehydrogenative coupling of C(sp3)-H bond of arenes with diarylphosphinic acid to construct C – P bond[26] by using catalytic amount of TBAI along with oxidant TBHP.



Scheme 5.2 Tang's approach for phosphorylation.

Benzimidazoles are an important class of heterocyclic molecule with broad range of application in material science and pharmaceutical chemistry. These moieties are well-known to have various medicinal properties like anti-depressant, anti-HIV, anti-cancer, anti-inflamatory, and anti-hepatitis B, etc. Some of the important benzimidazole containing drug molecules are represented in figure 5.1. The extensive application of these benzimidazole molecules has encouraged chemists to develop new efficient methods for the synthesis of these core structure and more precisely disubstituted benzimidazole rings.

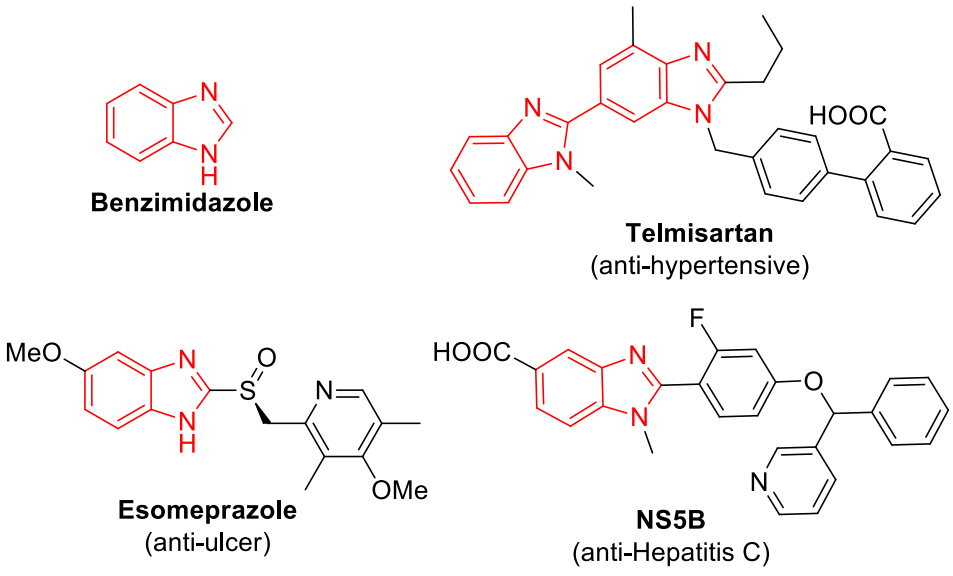
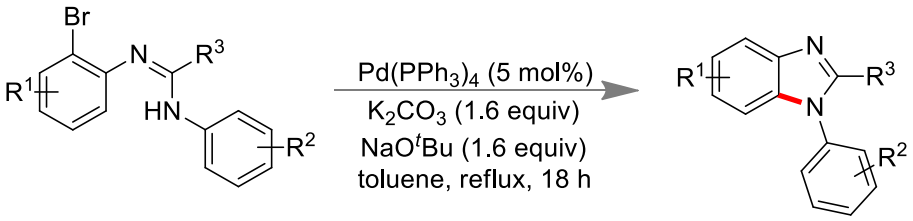


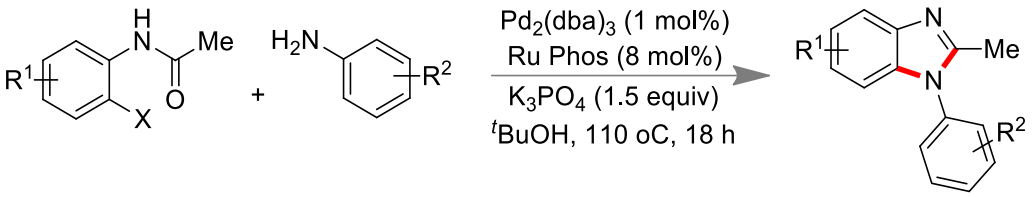
Figure 5.1 Some important drug molecules containing benzimidazole moiety.

Very limited methods exist for direct synthesis of *N*-substituted benzimidazoles. Brain and co-workers developed an intramolecular C(sp^2)-N bond formation protocol for the synthesis of *N*-substituted benzimidazoles from (o-bromophenyl)amidines using catalytic amount of palladium salt (Scheme 5.3).[27] Electron withdrawing as well as electron donating groups *para*- to the amidine bromo substituent were well tolerated.



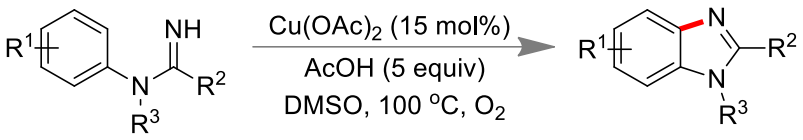
Scheme 5.3 Brain's Pd(II)-catalyzed C(sp^2)-N bond formation approach.

Buchwald's group established a Palladium catalyzed intermolecular tandem C(sp^2)-N bond formation reaction by the coupling between 2-haloacetaniolides and anilines for the synthesis of *N*-aryl benzimidazoles in regioisomerically pure form with good functional group tolerance (Scheme 5.4).[28]



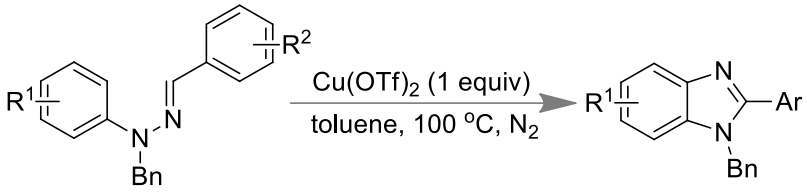
Scheme 5.4 Buchwald's Pd-catalyzed C(sp^2)-N bond formation approach.

Similar kind of disubstituted benzimidazoles were prepared by Buchwald and co-workers by Cu-catalyzed dehydrogenative C(sp^2)-N bond formation method for the synthesis of *N*-substituted benzimidazole in good yields from amidines (Scheme 5.5).[29]



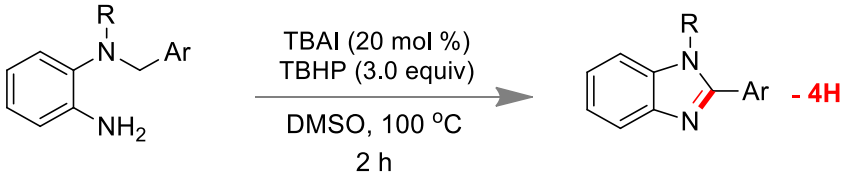
Scheme 5.5 Buchwald's Cu(II)-catalyzed C(sp^2)-N bond formation approach.

Punniyamurthy and co-worker developed a method for the conversion of *N*-benzylbisarylhydrazones to 2-aryl-*N*-benzylbenzimidazoles by using stoichiometric amount of Cu(II) *via* C-H functionalization and followed by C-N bond formation strategy (Scheme 5.6).[30]



Scheme 5.6 Punniyamurthy's Cu(II) mediated rearrangement approach.

Herein, we have demonstrated an intramolecular C(sp^3)-H functionalization for the imination reaction *via* 4H elimination in one pot and in one step. This methodology has been used successfully for the synthesis of highly substituted benzimidazole moieties. Using N^1,N^1-dibenzylbenzene-1,2-diamine as the precursor, 1-benzyl-2-phenyl-benzo[d]imidazole was synthesized efficiently by the reagent combination of 20 mol % of TBAI - 3.0 equiv of TBHP within 2 h with excellent yield.

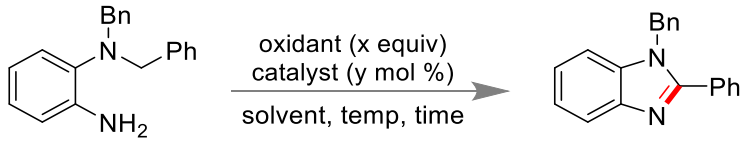


Scheme 5.7 Our TBAI catalyzed intramolecular C(sp^3)-H functionalization for C-N bond synthesis.

5.3 RESULTS AND DISCUSSION

Towards condition optimization (Table 5.1) the model substrate N^1,N^1-dibenzylbenzene-1,2-diamine (**1a**) was treated with 2 equiv of oxidant TBHP (used as 70% aq solution, *Caution!!*) and 10 mol % of TBAI. In dimethylsulfoxide (DMSO) at 80 ºC the desired 1-benzyl-2-phenyl-benzo[d]imidazole (**2a**) was obtained with 61% yield (entry 1) within 4 h of reaction time. However, within 2 h of reaction time 80% of the product was obtained when 3 equiv TBHP was used at 100 ºC (entry 2). The best result *i.e.*, 92% yield was obtained using 20 mol % of TBAI, 3 equiv TBHP and at 100 ºC (entry 3). Changing the solvents (entries 4-11) to acetonitrile, 1,4-dioxane, trifluoroethanol, dimethylformamide, dichloroethane, hexafluoroisopropanol did not furnish better results. Similarly, varying the catalysts (entries 12-16) oxidants (entries 17-18) were also not giving any encouraging results.

Table 5.1 Condition Optimization.



Entry	oxidant[a] (equiv)	catalyst (mol %)	solvent, temp (ºC)	time (h)	yield (%)
1	TBHP (2)	TBAI (10)	DMSO, 80	4	61
2	TBHP (3)	TBAI (10)	DMSO, 100	2	80
3	TBHP (3)	TBAI (20)	DMSO, 100	2	92
4	TBHP (3)	TBAI (20)	ACN, 80	10	58
5	TBHP (3)	TBAI (20)	1,4-Dioxane, 80	16	trace
6	TBHP (3)	TBAI (20)	TFE, 60	4	62
7	TBHP (3)	TBAI (20)	TFE, rt	10	42
8	TBHP (3)	TBAI (20)	DMF, 100	3	59
9	TBHP (3)	TBAI (20)	DCE, 80	10	38
10	TBHP (3)	TBAI (20)	EtOH, 80	16	trace

11	TBHP (3)	TBAI (20)	HFIP, 80	4	78
12	TBHP (3)	CuBr (20)	DMSO, 100	16	48
13	TBHP (3)	$Cu(OAc)_2$ (20)	DMSO, 100	16	51
14	TBHP (3)	TBAB (20)	DMSO, 100	4	30
15	TBHP (3)	NIS (50)	DMSO, 100	10	39
16	TBHP (3)	I_2 (50)	DMSO, 100	10	trace
17	TBHP in decane (3)	TBAI (20)	DMSO, 100	4	64
18	CHP	TBAI (20)	DMSO, 100	6	45

[a]If not indicated, TBHP used as 70% aq solution

Under optimized condition, substrate scope was explored for the imination reaction using various N^1,N^1-disubstituted benzene-1,2-diamines (Figure 5.2). Symmetrical dibenzyl substituted benzene-1,2-diamines resulted in 76 – 92% of the benzimidazoles. Electron donating methoxy (-OMe) group (**2b**: 90%, **2c**: 87%) worked well for this conversion. Bromo substitution at benzene-1,2-diamine part also yielded fairly the corresponding benzimidazoles (**2c**: 87%, **2d**: 83%). Single regio-isomeric products were observed (**2e-2m**) in case of N^1,N^1-benzylalkyl substituted benzene-1,2-diamines with 100% selectivity towards benzylic $–CH_2$ group. The *N*-methyl and *N*-ethyl substituted benzimidazoles were obtained up to 87%. Similarly, *p*-trifluoromethyl phenyl substituted benzimidazole **2l** was isolated in 70% yield. The 5,6-dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline (**2m**) was isolated exclusively with 72% of yield.

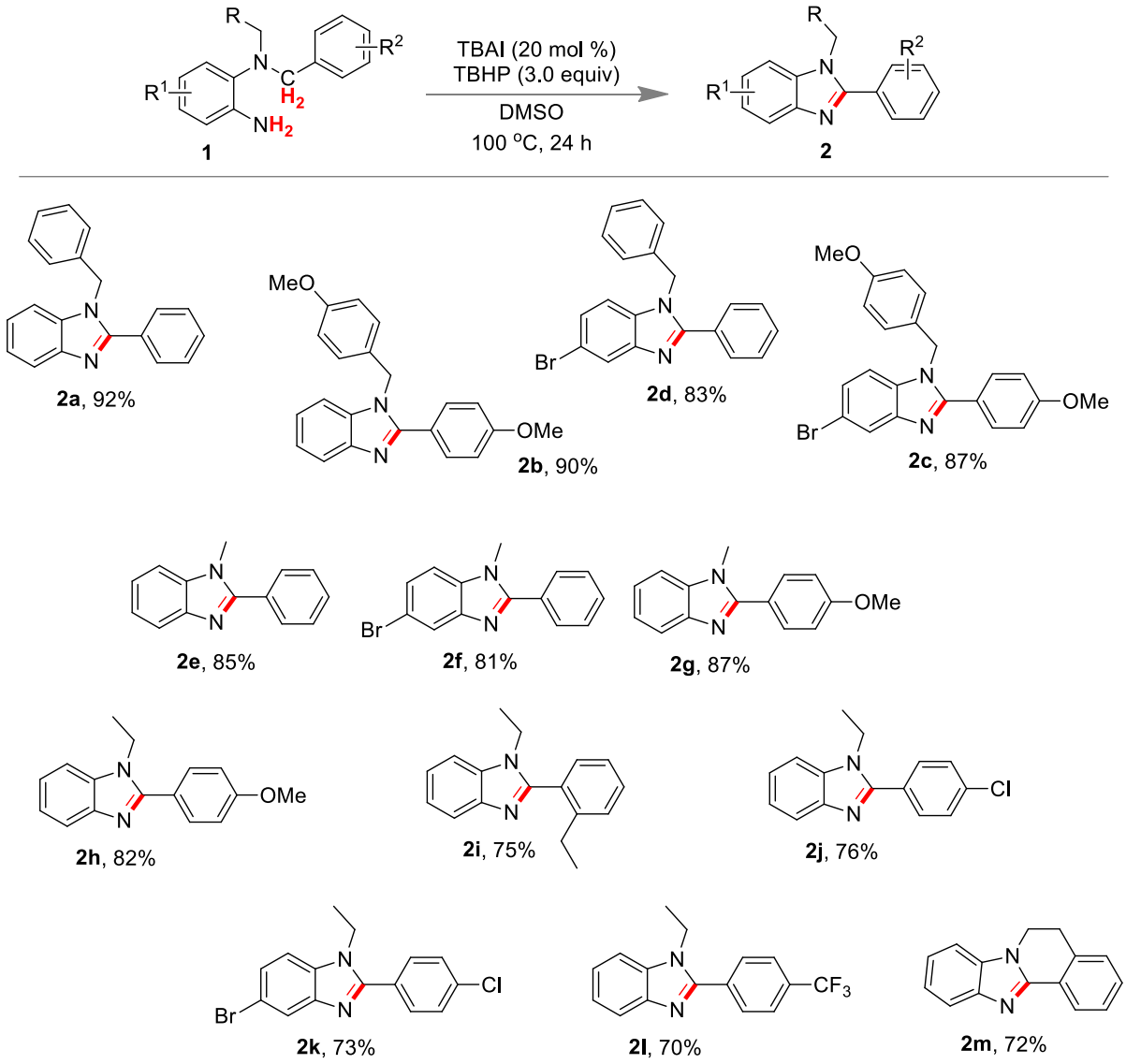


Figure 5.2 Substrate scope for C(sp^3)-H imination reaction.

As we have seen, the symmetrical dibenzyl amines led to single isomeric benzimidazoles. Conversely, unsymmetrical dibenzyl amines exhibited certain regioselectivity *via* electronic control (Figure 5.3). Interestingly, the major product among the mixture of isomers was the imination at the benzylic center substituted with relatively electron rich arenes. Substrate having both benzyl and tolyl group like N^1-benzyl-N^1-(4-methylbenzyl)benzene-1,2-diamine gave mixture of two regio-isomeric product with 80% yield as an inseparable mixture (**2n**, **2o**). Similarly, benzylic –CH_2 having electron donating –OMe group as well as electron

withdrawing halogen group at para position both participated in C(sp3)-H functionalization to produce corresponding benzimidazoles with up to 80% yield (**2p**, **2r**). Ortho substituted hindered mesitylene ring also participated in reaction giving 54% (**2q**) of corresponding benzimidazole along with its regio-isomer (**2q'**: 17%).

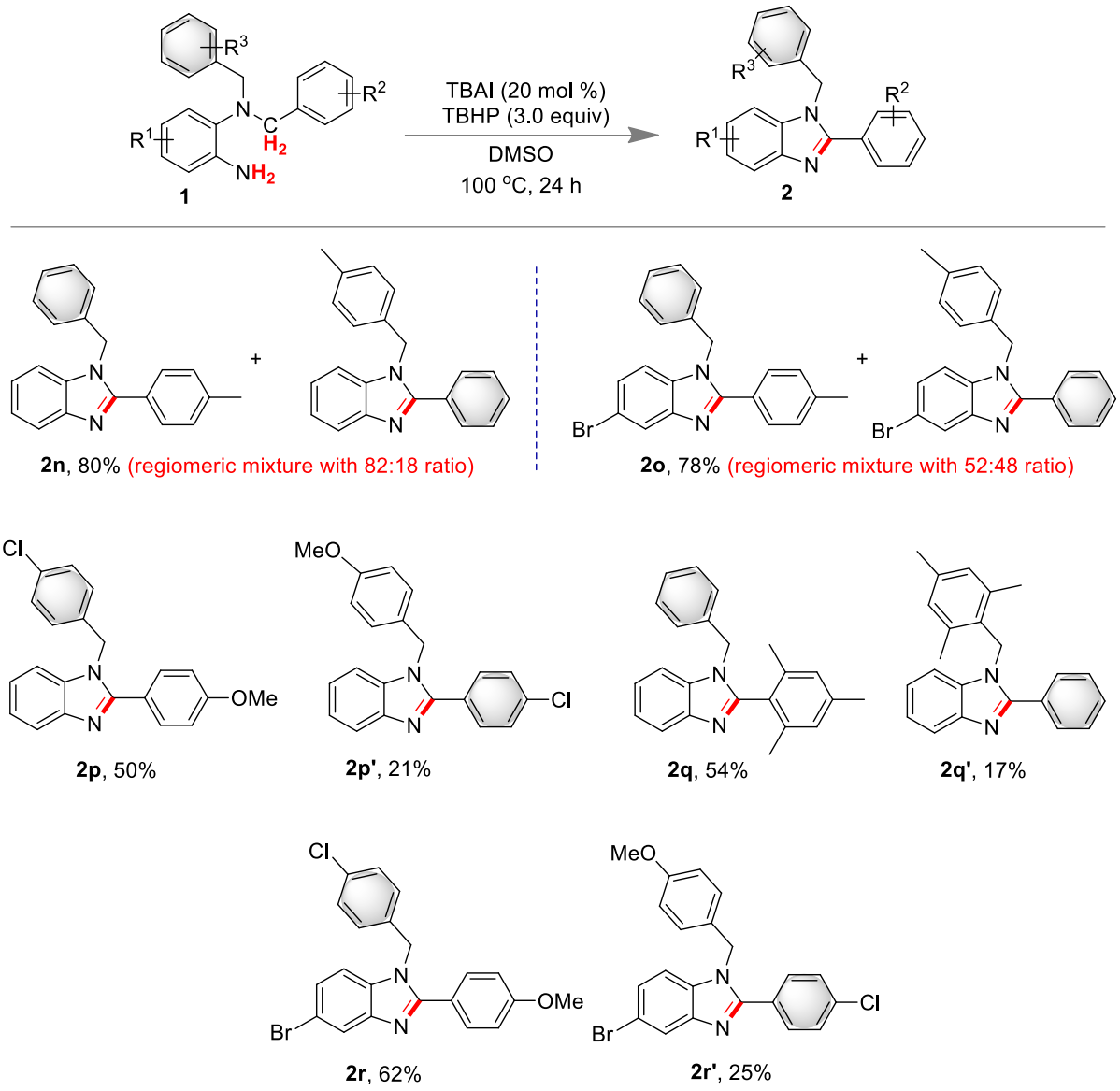


Figure 5.3 Investigation of electronic effects of *N*-alkyl substituents.

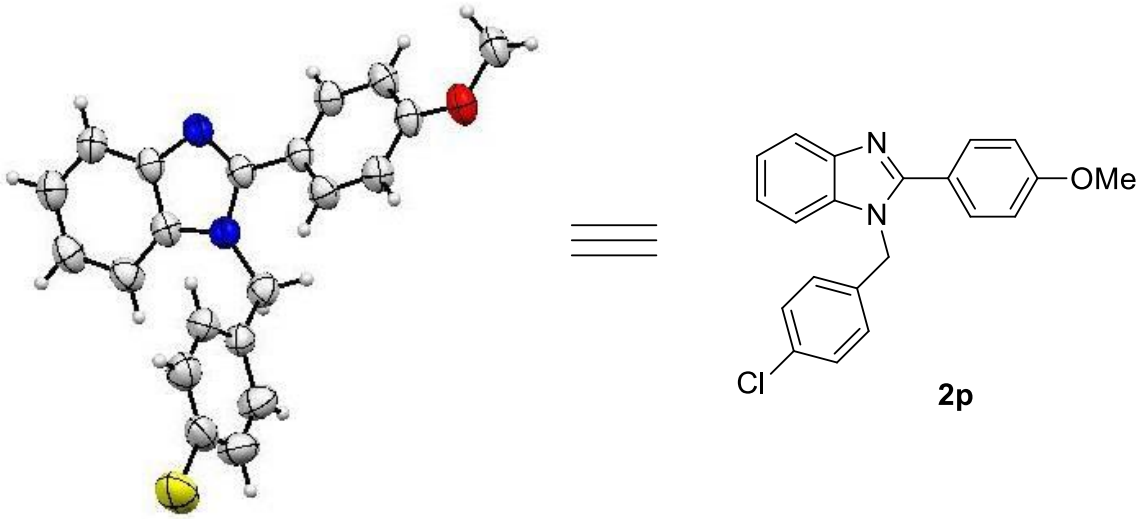


Figure 5.4 Crystal structure of compound **2p (CCDC: 1879241)**.

To understand the reaction pathway radical scavenger experiment was done using 2 equiv of 2,2,6,6-tetramethylpiperidine N-oxyl (TEMPO) under standard condition for the conversion of N^1,N^1-dibenzylbenzene-1,2-diamine (**1a**) to 1-benzyl-2-phenyl-benzo[d]imidazole (**2a**) where 87% of the desired product formation was observed within 2 h of time (Figure 5.5a). This experiment confirms that radical intermediates are not involved in the conversion. Based on the experimental observations and literature reports a plausible mechanism has been portrayed in figure 5.5b. In the first step tetrabutylammonium iodide (TBAI) in presence of tert-butylhydroperoxide (TBHP) oxidized to tetrabutylammonium hypoiodite ($[Bu_4N]^+[IO]^-$) which subsequently oxidized to tetrabutylammonium iodite ($[Bu_4N]^+[IO_2]^-$)[22,31] *in situ* which acts as the active catalyst for the transformation. Following the substrate **1** converted to iminium intermediate **3** in presence of the active catalyst and produced ammonium hydroxide and regenerated hypoiodite which acted as the catalyst for the next cycle. The iminium intermediate **3** might undergo intramolecular nuleophilic substitution to form intermediate **4**. This intermediate **4** being unstable and prone to oxidation, oxidized to the final compound **2** in presence of another 1 equivalent of TBHP.

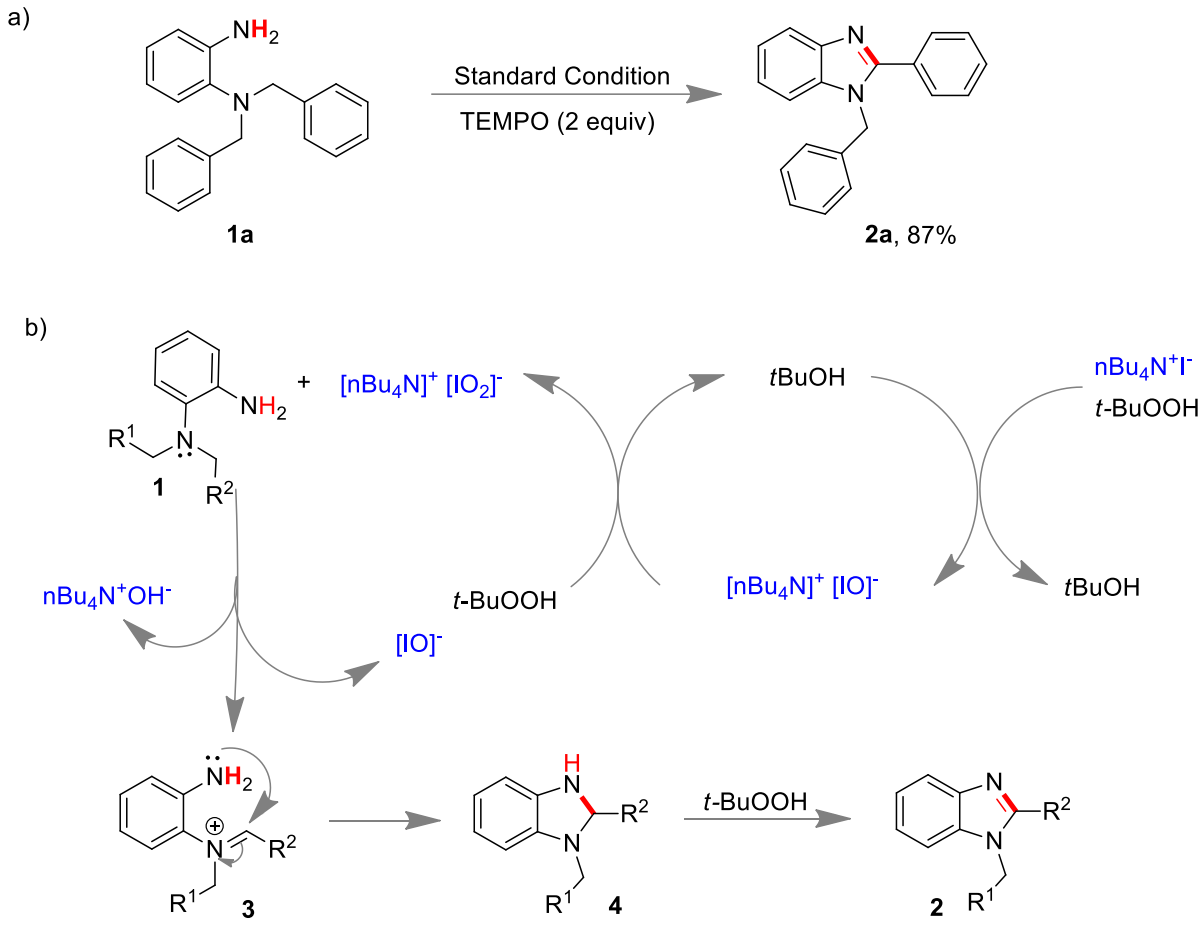


Figure 5.5 a) Radical scavenger experiment with TEMPO. b) Plausible reaction mechanism.

5.4 CONCLUSIONS

In summary, an efficient metal free approach for C(sp^3)-H imination reaction has been developed using the TBAI-TBHP combination and subsequently synthesis of 1,2-disubstituted benzimidazoles has been achieved with 4H elimination. This methodology avoids the use of expensive metal based catalyst and harsh reaction condition. Additionally, ambient condition, inexpensive oxidant, water soluble iodide reagent, functional group tolerance and shorter reaction time make the methodology more synthetically appealing towards construction of highly substituted benzimidazoles. We anticipate that this

organocatalyzed C-H imination approach can provide direct access to various heteroaromatic compounds and might have a major impact on the synthesis of complex structural motifs.

5.5 EXPERIMENTAL SECTION

Instrumentation and Chemicals: Column chromatographic purifications of the compounds were performed using silica gel (mesh 100–200 or mesh 230–400) and hexane – ethyl acetate mixtures as eluent unless otherwise specified. Solvents were commercially available and used without further purification. NMR spectra were recorded on a 400 MHz or 700 MHz instrument at 25 °C. The chemical shift values are reported in parts per million (ppm) with respect to residual trichloromethane (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). The peak patterns are designated as follows: s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet; dd: doublet of doublets; td: triplet of doublets; br s: broad singlet. The coupling constants (*J*) are reported in hertz (Hz). High-resolution mass spectra (HR-MS) were recorded on an ESI-TOF (time of flight) mass spectrometer. The crystals data were collected with Bruker SMART D8 goniometer equipped with an APEX CCD detector and with an INCOATEC micro source (Cu-Kα radiation, λ = 0.71073 Å). SAINT+[32] and SADABS[33] were used to integrate the intensities and to correct the absorption respectively The structure was resolved by direct methods and refined on F^2 with SHELXL-97.[34] Infrared spectral data are reported in wave number (cm^{-1}). FT-IR spectra were recorded after making thin layer of the compounds on the surface of NaCl crystal using dichloromethane. Melting points of the compounds were determined using a digital melting point apparatus and are uncorrected.

Representative procedure for the synthesis of 1-Benzyl-2-phenyl-benzo[d]imidazole (2a):

To an oven dried seal tube charged with a magnetic stirring bar and N^1,N^1-dibenzylbenzene-1,2-diamine (1a) (80 mg, 0.28 mmol, 1.0 equiv), TBAI (21 mg, 0.055 mmol, 20 mol %) was added and TBHP as 70% aq. solution (115 µl, 0.83 mmol, 3.0 equiv) dissolved in 2 ml dimethylsulfoxide. The mixture was stirred in a preheated oil bath of 100 ^{o}C temperature for 2 h. The completion of reaction was confirmed by TLC and afterwards it was cooled to room temperature. The reaction mixture was then washed with brine solution and organic layer extracted with ethyl acetate. The organic layers were collected and evaporated to dryness under reduced pressure. The crude reaction mixture was purified by 230 – 400 mesh silica gel column chromatography using 18% ethyl acetate/hexane as eluent to get 1-Benzyl-2-phenyl-benzo[d]imidazole (**2a**) as white solid with 92% yield.

Procedure for the radical scavenger experiment with 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl radical (TEMPO):

To an oven dried seal tube charged with a magnetic stirring bar and N^1,N^1-dibenzylbenzene-1,2-diamine (1a) (40 mg, 0.14 mmol, 1.0 equiv), TBAI (10 mg, 0.0275 mmol, 20 mol %) was added and TBHP as 70% aq. solution (58 µl, 0.42 mmol, 3.0 equiv) dissolved in 2 ml dimethylsulfoxide. To it TEMPO (43 mg, 0.28 mmol, 2.0 equiv) was added. The mixture was stirred in a preheated oil bath of 100 ^{o}C temperature for 2 h. The completion of reaction was confirmed by TLC and afterwards it was cooled to room temperature. The reaction mixture was then washed with brine solution and organic layer extracted with ethyl acetate. The organic layers were collected and evaporated to dryness under reduced pressure. The crude reaction mixture was purified by 230 – 400 mesh silica gel column chromatography using 18% ethyl acetate/hexane as eluent to get 1-Benzyl-2-phenyl-benzo[d]imidazole (**2a**) as white solid with 87% yield.

Compound Characterization Data:

1-Benzyl-2-phenyl-benzo[d]imidazole (2a): R_f = 0.5 (18% ethyl acetate/hexane); white solid; yield 72 mg (92%); mp: 139 - 141 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.49 – 7.43 (m, 3H), 7.35 – 7.28 (m, 4H), 7.25 – 7.20 (m, 2H), 7.11 (d, *J* = 7.7 Hz, 2H), 5.46 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 154.3, 143.3, 136.5, 136.2, 130.2, 130.1, 129.4, 129.2, 128.9, 127.9, 126.1, 123.2, 122.8, 120.1, 110.7, 48.5; IR (KBr) ῡ 2927, 2854, 1605, 1453, 1160, 1028, 970, 737 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{17}N_2$ $[M+H]^+$ 285.1386, found 285.1405.

1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (2b): R_f = 0.5 (30% ethyl acetate/hexane); white solid; yield 71 mg (90%); mp: 128 - 130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.31 – 7.27 (m, 1H), 7.21 (d, *J* = 1.6 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.38 (s, 2H), 3.85 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.0, 159.2, 154.2, 143.2, 136.2, 130.8, 128.6, 127.3, 122.9, 122.7, 122.5, 119.8, 114.5, 114.3, 110.5, 55.5, 55.4, 48.0; IR (KBr) ῡ 2912, 2839, 1696, 1514, 1265, 970, 748 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{21}N_2O_2$ $[M+H]^+$ 345.1598, found 345.1616.

1-Benzyl-5-bromo-2-phenyl-benzo[d]imidazole (2c): R_f = 0.5 (15% ethyl acetate/hexane); white solid; yield 65 mg (83%); mp: 156 - 158 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.99 (d, *J* = 1.4 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 2H), 7.51 – 7.45 (m, 4H),), 7.35 – 7.30 (m, 4H), 7.07 – 7.06 (m, 3H), 5.44 (s, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 155.3, 144.6, 136.0, 135.1, 130.4, 129.7, 129.4, 129.3, 129.0, 128.1, 126.2, 126.0, 122.9, 115.8, 111.9, 48.65; IR (KBr) ῡ 2916, 2851, 1516, 1455, 1384, 1160, 923 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{16}BrN_2$ $[M+H]^+$ 363.0491, found 363.0505.

5-Bromo-1-(4-methoxybenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (2d): R_f = 0.5 (30% ethyl acetate/hexane); white solid; yield 68 mg (87%); mp: 136 - 138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 1H), 6.98 (t, *J* = 7.8 Hz, 4H), 6.85 (d, *J* = 8.0 Hz, 2H), 5.35 (s, 2H), 3.85 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 159.4, 155.3, 144.6, 135.1, 130.8, 128.1, 127.3, 125.8, 122.6, 122.0, 115.6, 114.6, 114.4, 111.8, 55.5, 55.4, 48.2; IR (KBr) ῡ 2927, 2831, 1611, 1461, 1293, 1173, 1028, 735 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{22}H_{20}BrN_2O_2$ $[M+H]^+$ 423.0703, found 423.0722.

1-Methyl-2-phenyl-benzo[d]imidazole (2e): R_f = 0.5 (12% ethyl acetate/hexane); white solid; yield 67 mg (85%); mp: 100 - 102 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 7.0, 2.1 Hz, 1H), 7.77 (dd, *J* = 7.7, 1.4 Hz, 2H), 7.55 – 7.51 (m, 3H), 7.40 (dd, *J* = 7.0, 2.1 Hz, 1H), 7.34 – 7.30 (m, 2H), 3.87 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 153.9, 143.0, 136.7, 130.3, 129.9, 129.6, 128.8, 122.9, 122.6, 119.9, 109.7, 31.8; IR (KBr) ῡ 3009, 2981, 1612, 1384, 1175, 1027, 893 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{13}N_2$ $[M+H]^+$ 209.1073, found 209.1098.

5-Bromo-1-methyl-2-phenyl-benzo[d]imidazole (2f): R_f = 0.5 (10% ethyl acetate/hexane); white solid; yield 63 mg (81%); mp: 150 - 152 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.95 (d, *J* = 1.4 Hz, 1H), 7.75 – 7.74 (m, 2H), 7.55 – 7.52 (m, 3H), 7.43 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 154.9, 144.3, 135.7, 130.2, 129.8, 129.6, 128.9, 125.9, 122.8, 115.6, 111.0, 32.0; IR (KBr) ῡ 3046, 2985, 1492, 1421, 1261, 895 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{12}BrN_2$ $[M+H]^+$ 287.0178, found 287.0182.

2-(4-Methoxyphenyl)-1-methyl-benzo[d]imidazole (2g): R_f = 0.5 (15% ethyl acetate/hexane); white solid; yield 68 mg (87%); mp: 122 - 124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 6.4, 2.8 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.38 – 7.36 (m, 1H), 7.32 – 7.27 (m, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 153.9, 143.0, 136.7, 130.9, 122.6, 122.5, 119.7, 114.3, 109.6, 55.5, 31.8; IR (KBr) ῡ 2925, 2843, 1610, 1462, 1379, 1250, 1179, 1023, 835 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{15}N_2O$ $[M+H]^+$ 239.1179, found 239.1198.

1-Ethyl-2-(4-methoxyphenyl)-benzo[d]imidazole (2h): R_f = 0.5 (15% ethyl acetate/hexane); white solid; yield 65 mg (82%); mp: 112 - 114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 6.4, 2.8 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.41 (dd, *J* = 5.2, 2.8 Hz, 1H), 7.31 – 7.28 (m, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 1.47 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 160.9, 153.6, 143.3, 135.5, 130.8, 123.0, 122.6, 122.4, 119.9, 114.3, 109.9, 55.5, 39.7, 15.4; IR (KBr) ῡ 2939, 2838, 1614, 1455, 1249, 1028, 839 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{17}N_2O$ $[M+H]^+$ 253.1335, found 253.1356.

1-Ethyl-2-(2-ethylphenyl)-benzo[d]imidazole (2i): R_f = 0.5 (12% ethyl acetate/hexane); white solid; yield 57 mg (75%); mp: 106 - 108 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 6.3, 1.4 Hz, 1H), 7.47 (td, *J* = 7.7, 1.4 Hz, 1H), 7.44 (dd, *J* = 7.0, 2.1 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.35 – 7.30 (m, 4H), 4.04 (q, *J* = 7.7 Hz, 2H), 2.57 (q, *J* = 7.7 Hz, 2H), 1.30 (t, *J* = 7.7 Hz, 3H), 1.11 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 153.2, 144.3, 143.3, 134.4, 130.1, 129.8, 128.9, 125.8, 122.6, 122.2, 120.2, 109.9, 39.2, 26.4, 15.3, 15.1; IR (KBr) ῡ 3040, 2986, 1610, 1440, 1270, 1065, 890, 745 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{19}N_2$ $[M+H]^+$ 251.1548, found 251.1561.

2-(4-Chlorophenyl)-1-ethyl-benzo[d]imidazole (2j): R_f = 0.5 (14% ethyl acetate/hexane); white solid; yield 59 mg (76%); mp: 126 - 128 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.0 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.34 – 7.30 (m, 2H), 4.28 (q, *J* = 7.0 Hz, 2H), 1.47 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 152.4, 143.2, 136.1, 135.5, 130.7, 129.2, 129.17, 123.1, 122.7, 120.2, 110.1, 39.8, 15.4; IR (KBr) ῡ 3053, 2986, 1607, 1421, 1264, 1094, 895, 747 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{14}ClN_2$ $[M+H]^+$ 257.0840, found 257.0863.

5-Bromo-2-(4-chlorophenyl)-1-ethyl-benzo[d]imidazole (2k): R_f = 0.5 (15% ethyl acetate/hexane); white solid; yield 57 mg (73%); mp: 160 - 162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 2.0 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.42 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 153.4, 144.5, 136.5, 134.5, 130.6, 129.3, 128.6, 126.1, 123.0, 115.6, 111.3, 40.0, 15.4; IR (KBr) ῡ 2981, 2933, 1599, 1405, 1326, 1087, 992 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{13}BrClN_2$ $[M+H]^+$ 334.9945, found 334.9962.

1-Ethyl-2-(4-(trifluoromethyl)phenyl)-benzo[d]imidazole (2l): R_f = 0.5 (20% ethyl acetate/hexane); white solid; yield 55 mg (70%); mp: 127 - 130 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.86 – 7.83 (m, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 7.3 Hz, 1H), 7.38 – 7.32 (m, 1H), 4.30 (q, *J* = 7.3 Hz, 1H), 1.49 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 151.9, 143.3, 135.6, 134.3, 131.8 (q, *J* = 32.6 Hz), 129.8, 125.9 (q, *J* = 3.6 Hz), 123.4, 122.9, 120.4, 110.2, 39.9, 15.5; IR (KBr) ῡ 2981, 2937, 1619, 1452, 325, 1115, 1071, 854 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{16}H_{14}F_3N_2$ $[M+H]^+$ 291.1104, found 291.1109.

5,6-Dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline (2m): R_f = 0.5 (10% ethyl acetate/hexane); white solid; yield 57 mg (72%); mp: 148 - 150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.23 (m, 1H), 7.82 (dd, *J* = 5.6, 3.2 Hz, 1H), 7.44 – 7.27 (m, 6H), 4.34 (t, *J* = 6.8 Hz, 2H), 3.29 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 149.3, 144.0, 134.8, 134.4, 130.3, 128.2, 127.9, 126.8, 125.8, 122.8, 122.6, 119.9, 109.2, 40.6, 28.4; IR (KBr) ῡ 3058, 2992, 1615, 1433, 1268, 1037, 738 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{13}N_2$ $[M+H]^+$ 221.1073, found 221.1060.

1-Benzyl-2-(p-tolyl)-benzo[d]imidazole and 1-(4-Methylbenzyl)-2-phenyl-benzo[d]imidazole (2n): R_f = 0.6 (10% ethyl acetate/hexane); white solid; yield 63 mg (80%); Two regio isomers with 89:11 Ratio; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.7 Hz, 1H), 7.7 (d, *J* = 7.0 Hz, 2H x 0.12), 7.58 (d, *J* = 8.4 Hz, 2H), 7.48 – 7.44 (m, 4H x 0.12), 7.35 – 7.29 (m, 4H), 7.28 (s, 1H x 0.12), 7.25 – 7.19 (m, 4H), 7.13 (d, *J* = 7.7 Hz, 2H x 0.12), 7.11 (d, *J* = 7.0 Hz, 2H), 6.99 (d, *J* = 7.7 Hz, 2H x 0.12), 5.45 (s, 2H, major isomer), 5.42 (s, 2H x 0.12, minor isomer), 2.40 (s, 3H, major isomer), 2.33 (s, 3H x 0.12, minor isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 143.3, 140.2, 136.6, 136.2, 129.8, 129.6, 129.4, 129.3, 129.2, 128.9, 127.9, 127.3, 126.1, 126.0, 123.1, 123.0, 122.8, 122.7, 120.1, 120.0, 110.7, 110.6, 48.5, 48.3, 21.6, 21.2.

1-Benzyl-5-bromo-2-(p-tolyl)-benzo[d]imidazole and 5-Bromo-1-(4-methylbenzyl)-2-phenyl-benzo[d]imidazole (2o): R_f = 0.6 (12% ethyl acetate/hexane); white solid; yield 61 mg (78%); Two regio isomers with 51:49 Ratio; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.98 (d, *J* = 3.5 Hz, 2H), 7.68 (d, *J* = 7.0 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.49 (t, *J* = 7.0 Hz, 1H), 7.46 (t, *J* = 7.0 Hz, 2H), 7.35 – 7.30 (m, 5H), 7.27 (d, *J* = 6.3 Hz, 2H), 7.14 (d, *J* = 7.7 Hz, 2H), 7.08 – 7.04 (m, 4H), 6.96 (d, *J* = 7.7 Hz, 2H), 5.42 (s, 3H, major isomer), 5.40 (s, 3H, minor

isomer), 2.41 (s, 3H, major isomer), 2.34 (s, 3H, minor isomer); ^{13}C NMR (175 MHz, $CDCl_3$) δ 155.5, 155.3, 144.62, 144.60, 140.6, 137.9, 136.1, 135.1, 133.0, 130.3, 129.9, 129.8, 129.7, 129.4, 129.3, 129.0, 128.1, 126.8, 126.1, 126.03, 126.01, 125.9, 122.9, 122.8, 115.8, 115.7, 112.0, 111.8, 48.6, 48.5, 21.6, 21.2.

1-(4-Chlorobenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (2p): R_f = 0.5 (14% ethyl acetate/hexane); white solid; yield 41 mg (50%); mp: 147 - 150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 3H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.39 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 154.2, 143.1, 135.9, 135.0, 133.8, 130.7, 129.4, 128.5, 127.5, 123.1, 122.9, 119.9, 114.4, 110.3, 55.5, 47.9; IR (KBr) ῡ 2935, 2825, 1612, 1513, 1248, 1094, 1033, 839 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{18}ClN_2O$ $[M+H]^+$ 349.1102, found 349.1126.

2-(4-Chlorophenyl)-1-(4-methoxybenzyl)-benzo[d]imidazole (2p'): R_f = 0.6 (16% ethyl acetate/hexane); white solid; yield 22 mg (21%); mp: 130 - 132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.34 – 7.28 (m, 1H), 7.25 (d, *J* = 4.8 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.37 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 153.1, 143.2, 136.3, 136.2, 130.7, 129.2, 128.7, 128.3, 127.3, 123.4, 122.9, 120.2, 114.6, 110.7, 55.4, 48.0; IR (KBr) ῡ 2929, 2835, 1614, 1483, 1249, 1176, 1029, 837 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{18}ClN_2O$ $[M+H]^+$ 349.1102, found 349.1110.

1-Benzyl-2-mesityl-benzo[d]imidazole (2q): R_f = 0.6 (8% ethyl acetate/hexane); white solid; yield 43 mg (54%); mp: 140 - 142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.0

Hz, 1H), 7.32 – 7.25 (m, 3H), 7.21 (dd, *J* = 6.4, 4.0 Hz, 3H), 6.97 – 6.95 (m, 2H), 6.92 (s, 2H), 5.07 (s, 2H), 2.34 (s, 3H), 1.94 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 143.5, 139.6, 138.2, 135.9, 134.9, 128.8, 128.4, 127.9, 127.3, 127.0, 122.6, 122.2, 120.1, 110.6, 47.9, 21.4, 19.8; IR (KBr) ῡ 2916, 2851, 1613, 1449, 1374, 1170, 852 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{23}N_2$ $[M+H]^+$ 327.1856, found 327.1826.

2-Phenyl-1-(2,4,6-trimethylbenzyl)-benzo[d]imidazole (2q'): R_f = 0.6 (10% ethyl acetate/hexane); white solid; yield 14 mg (17%); mp: 204 - 206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (t, *J* = 7.2 Hz, 1H), 7.53 (d, *J* = 5.0 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.7 Hz, 1H), 6.80 (s, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 5.45 (s, 1H), 2.25 (s, 1H), 2.06 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 143.3, 138.0, 137.3, 135.1, 131.0, 129.9, 129.8, 128.8, 128.4, 122.7, 122.2, 119.9, 111.4, 45.5, 21.0, 20.2; IR (KBr) ῡ 2912, 2847, 1692, 1518, 1423, 1015, 895 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{23}N_2$ $[M+H]^+$ 327.1856, found 327.1829.

5-Bromo-1-(4-chlorobenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (2r): R_f = 0.6 (10% ethyl acetate/hexane); white solid; yield 47 mg (62%); mp: 150 - 152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 3H), 7.03 – 6.96 (m, 5H), 5.38 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 161.4, 155.3, 144.6, 135.0, 134.6, 134.0, 130.8, 129.5, 127.4, 126.0, 122.8, 121.7, 115.9, 114.5, 111.5, 55.5, 48.1; IR (KBr) ῡ 3051, 2977, 2916, 1606,1469, 1264, 1176, 738 cm^{-1}; IR (KBr) ῡ 2929, 2839, 1613, 1469, 1247, 1176, 1034, 836 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{17}BrClN_2O$ $[M+H]^+$ 427.0207, found 427.0233.

5-Bromo-2-(4-chlorophenyl)-1-(4-methoxybenzyl)-benzo[d]imidazole (2r'): R_f = 0.6 (13% ethyl acetate/hexane); white solid; yield 24 mg (25%); mp: 123 - 125 °C; ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.97 (d, *J* = 2.0 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.35 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.35 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.5, 154.1, 144.5, 136.7, 135.2, 130.7, 129.3, 128.2, 127.7, 127.2, 126.4, 123.0, 116.0, 114.7, 112.0, 55.5, 48.2; HRMS (ESI-TOF) calcd for $C_{21}H_{17}BrClN_2O$ $[M+H]^+$ 427.0207, found 427.0223.

5.6 NOTES AND REFERENCE

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Copies of ^{1}H and ^{13}C NMR Spectra of Compounds

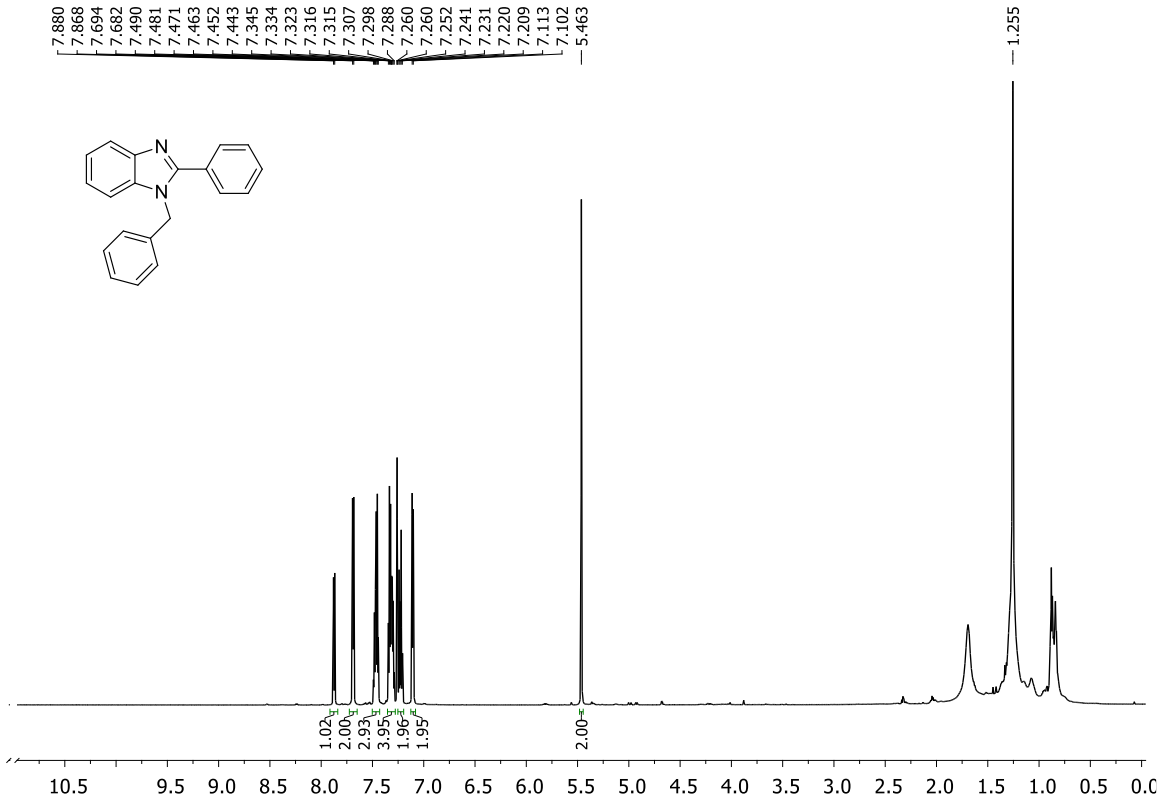


Figure 5.6 ^{1}H NMR of 1-Benzyl-2-phenyl-benzo[d]imidazole (**2a**)

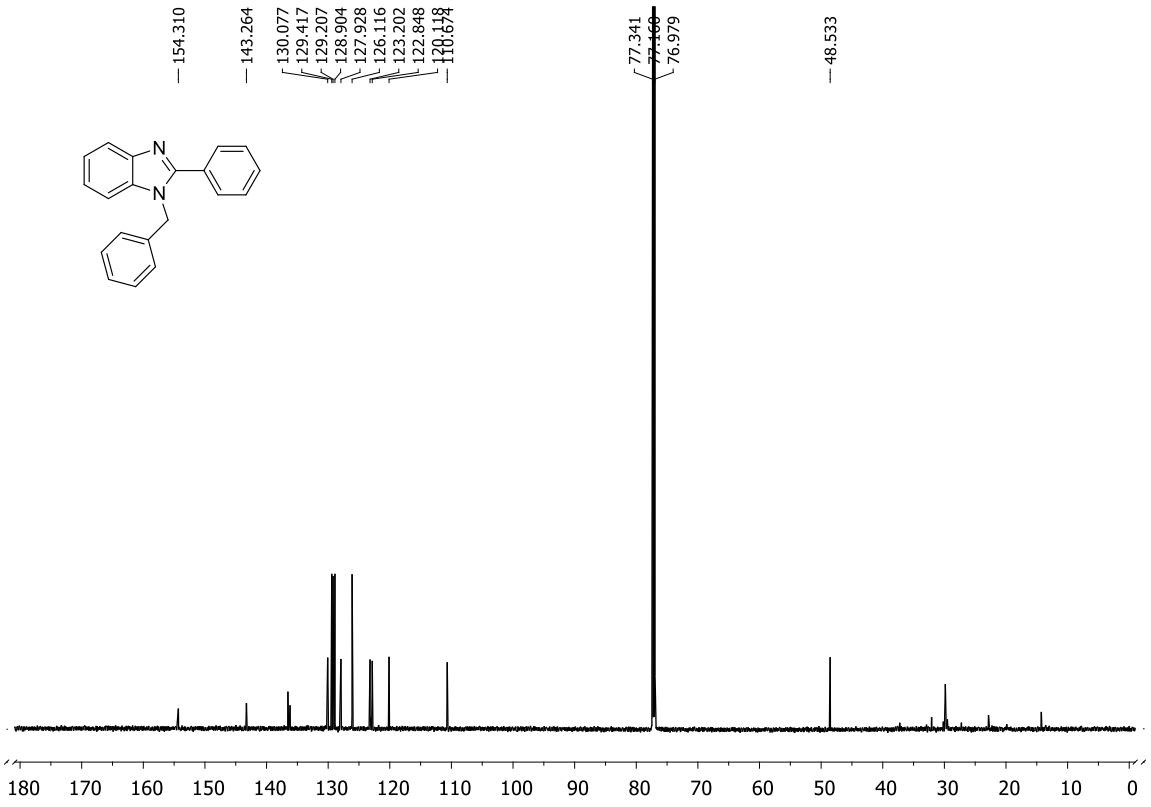


Figure 5.7 ^{13}C NMR of 1-Benzyl-2-phenyl-benzo[d]imidazole (**2a**)

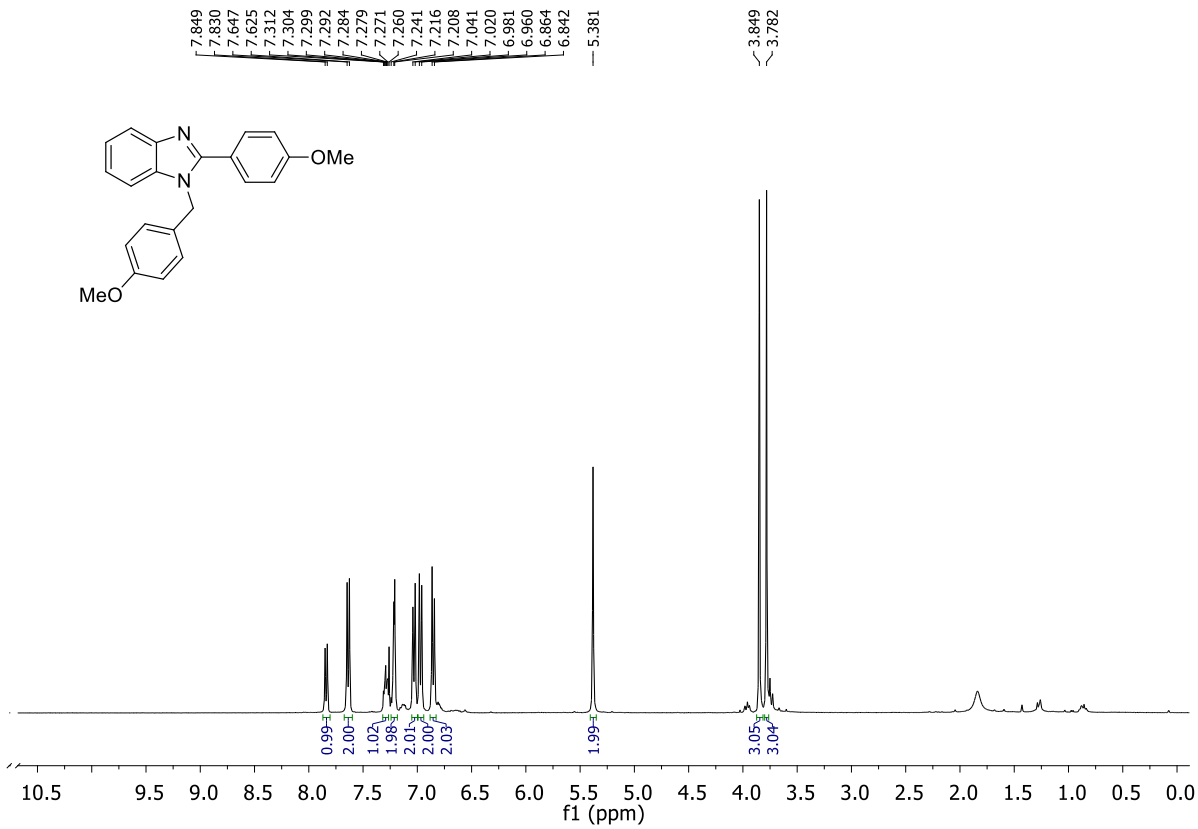


Figure 5.8 ^{1}H NMR of 1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (**2b**)

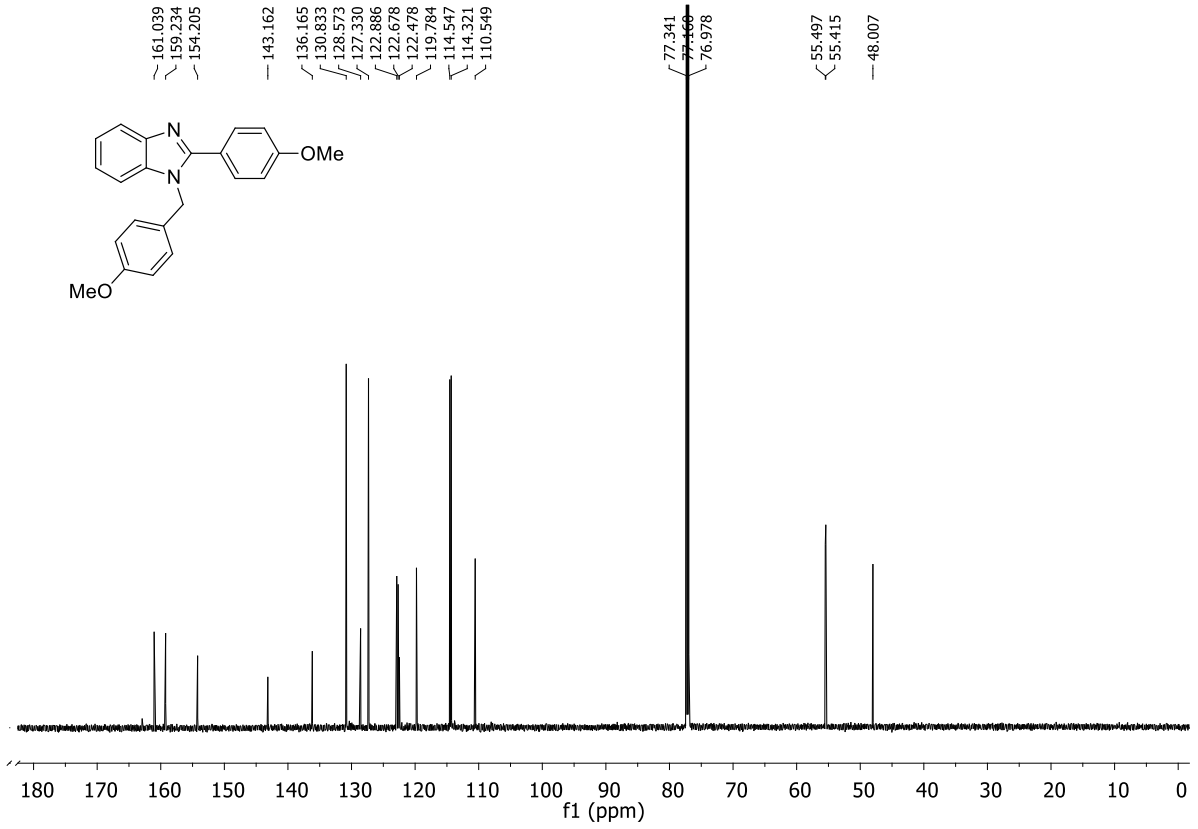


Figure 5.9 ^{13}C NMR of 1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (**2b**)

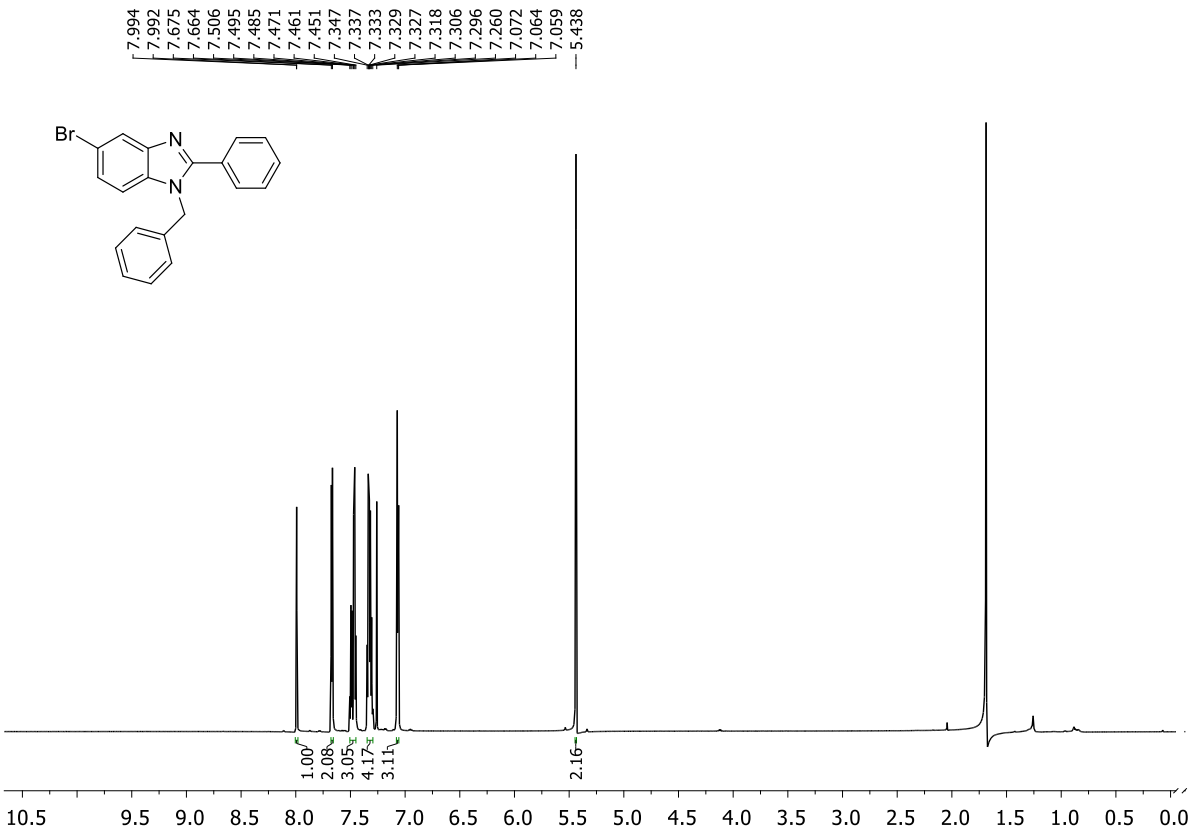


Figure 5.10 ^{1}H NMR of 1-Benzyl-5-bromo-2-phenyl-benzo[d]imidazole (**2c**)

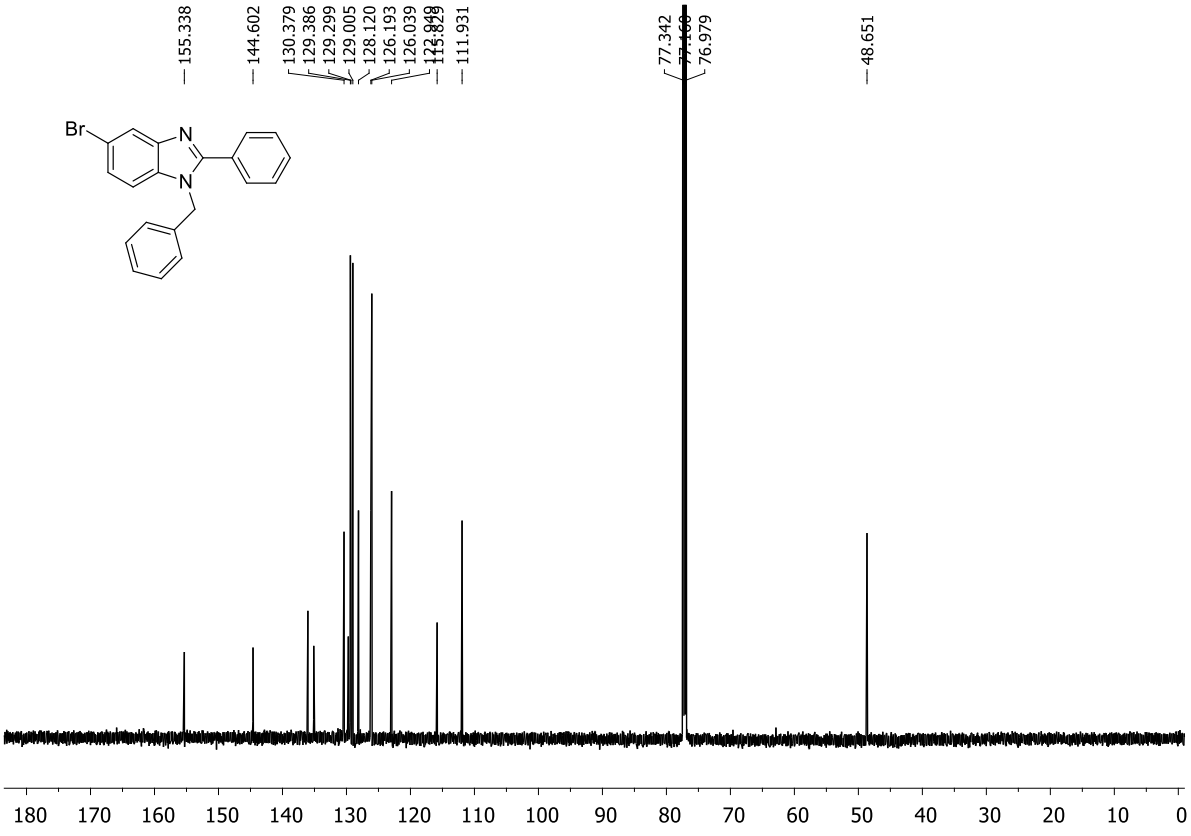


Figure 5.11 ^{13}C NMR of 1-Benzyl-5-bromo-2-phenyl-benzo[d]imidazole (**2c**)

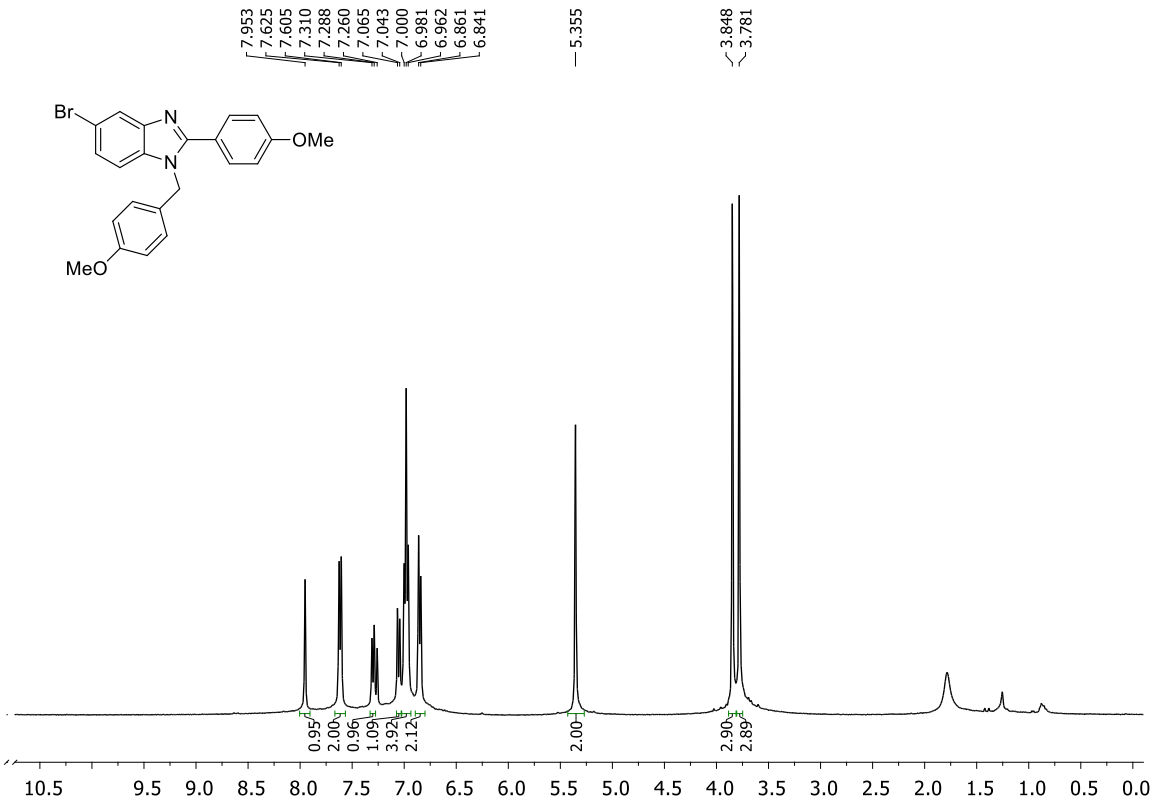


Figure 5.12 ^{1}H NMR of 5-Bromo-1-(4-methoxybenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (**2d**)

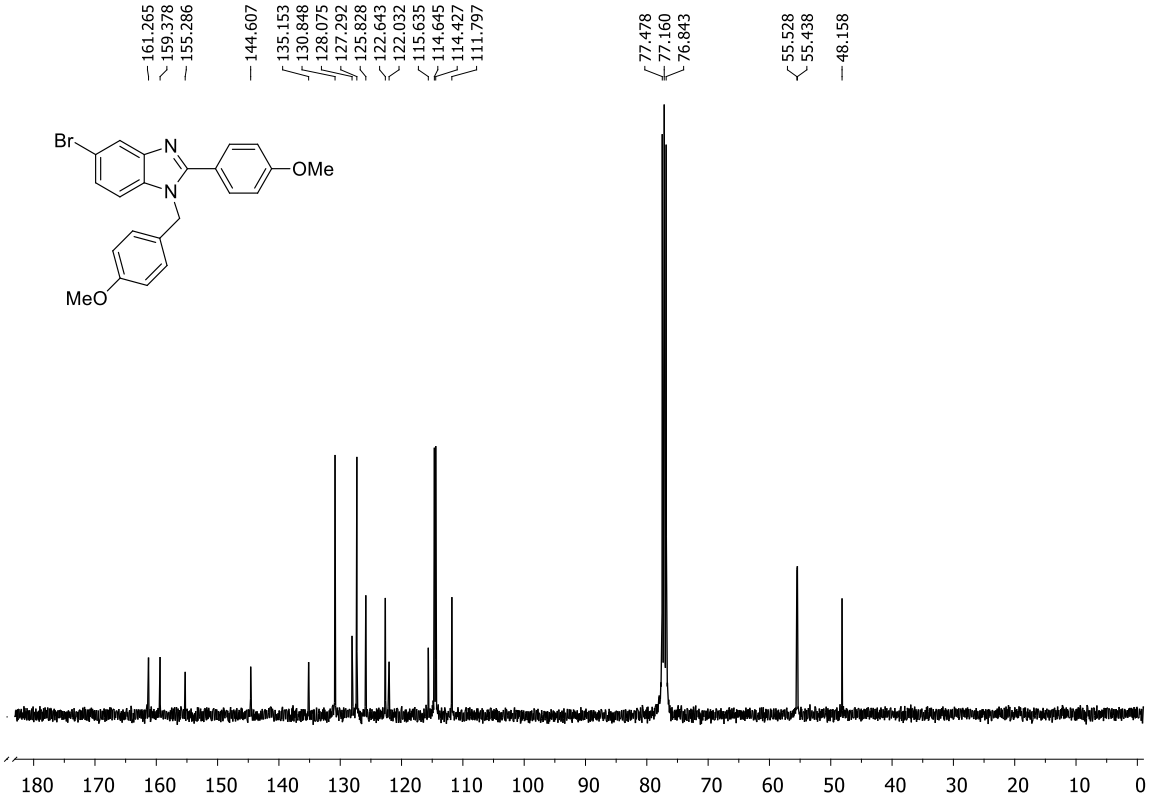


Figure 5.13 ^{13}C NMR of 5-Bromo-1-(4-methoxybenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (**2d**)

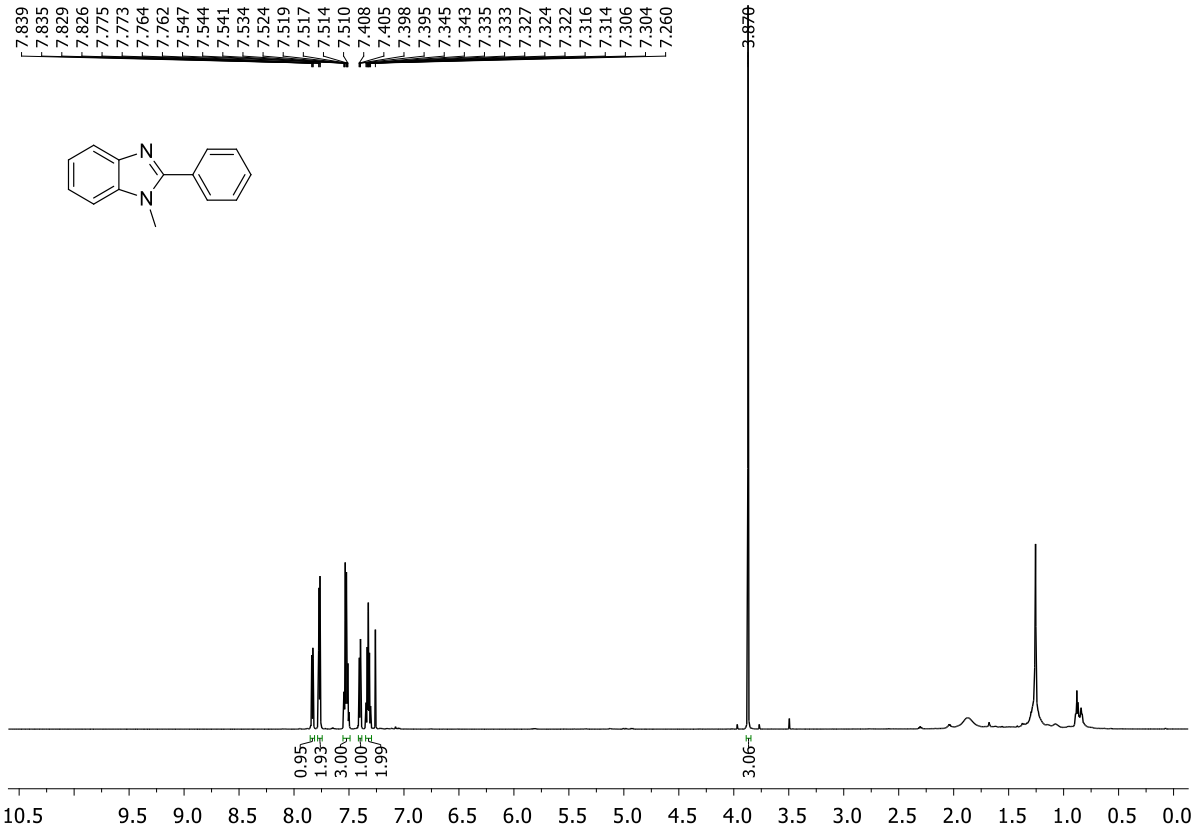


Figure 5.14 ^{1}H NMR of 1-Methyl-2-phenyl-benzo[d]imidazole (**2e**)

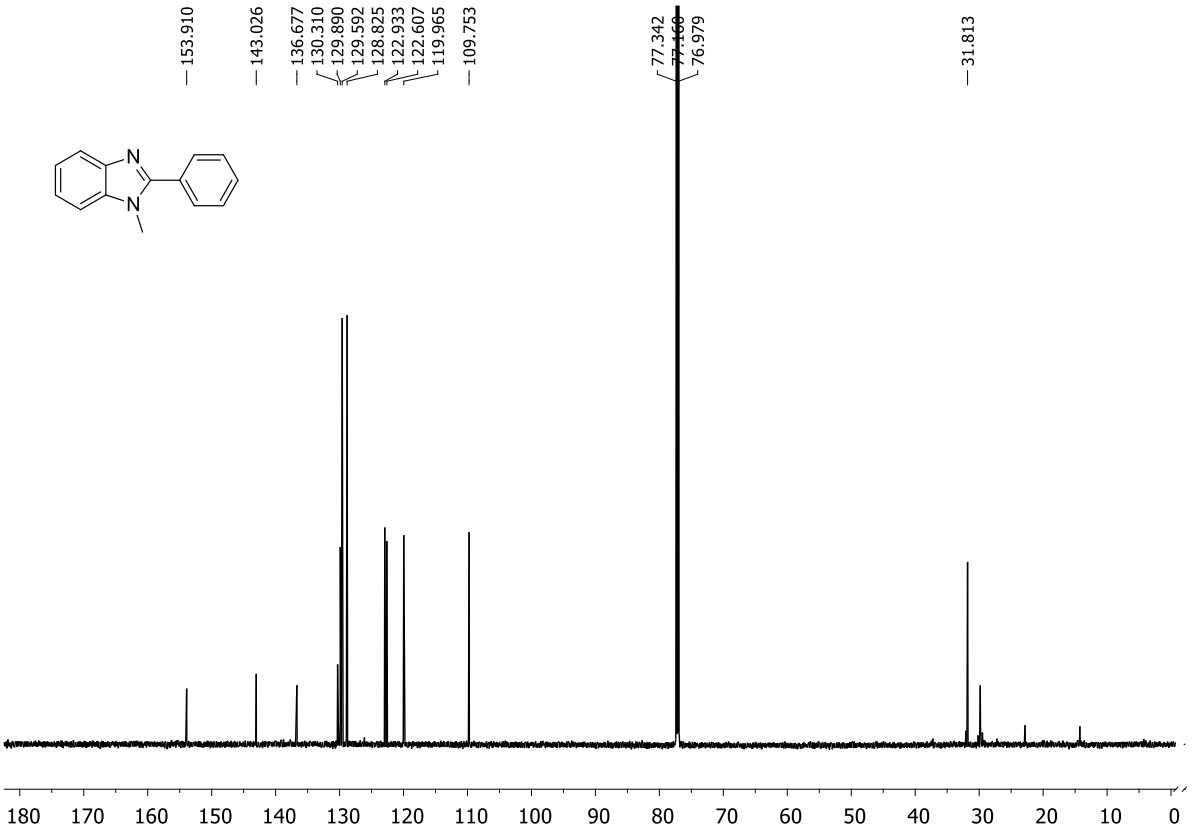


Figure 5.15 ^{13}C NMR of 1-Methyl-2-phenyl-benzo[d]imidazole (**2e**)

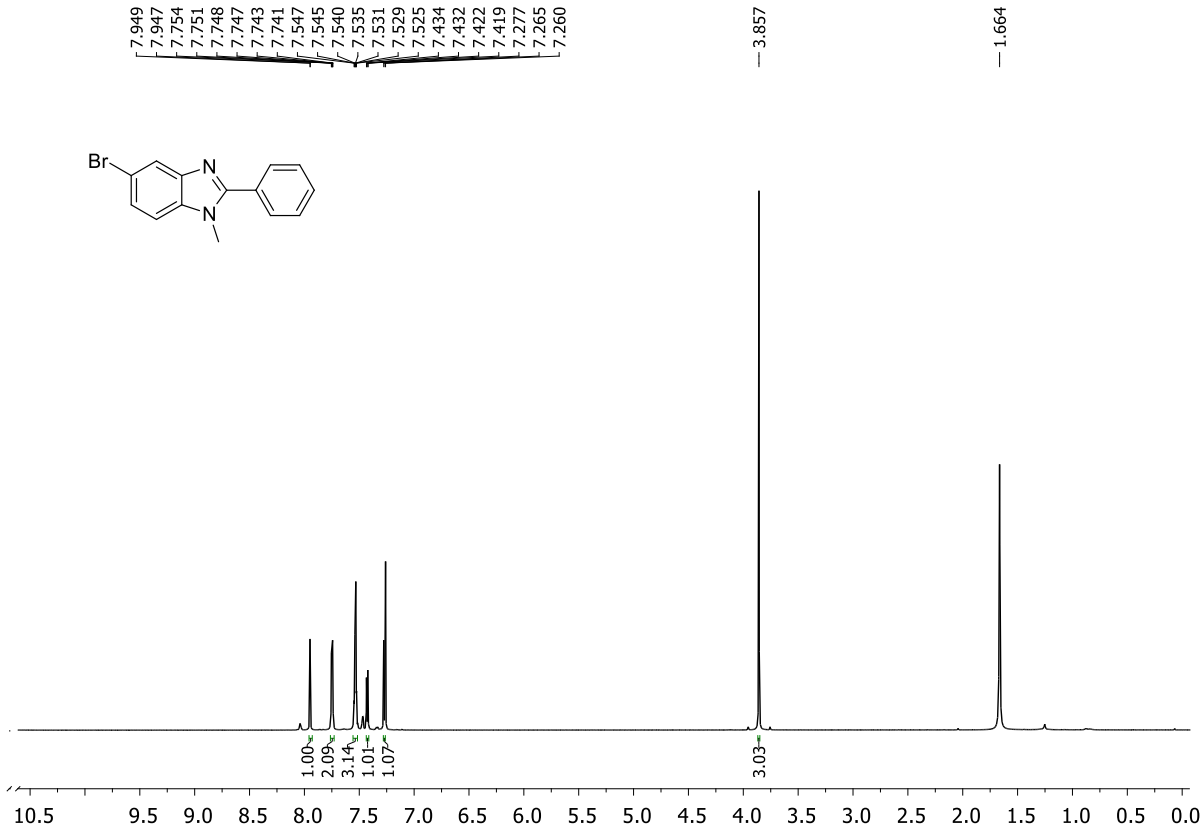


Figure 5.16 ^{1}H NMR of 5-Bromo-1-methyl-2-phenyl-benzo[d]imidazole (**2f**)

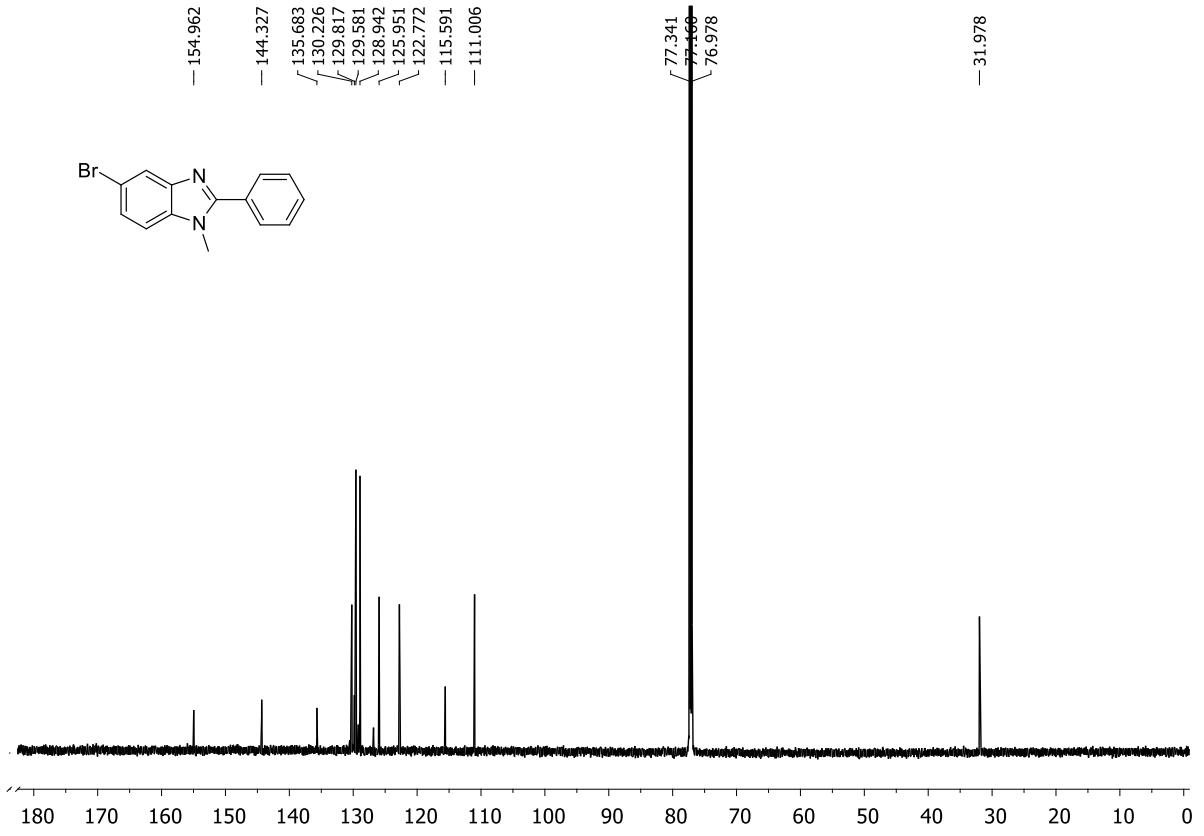


Figure 5.17 ^{13}C NMR of 5-Bromo-1-methyl-2-phenyl-benzo[d]imidazole (**2f**)

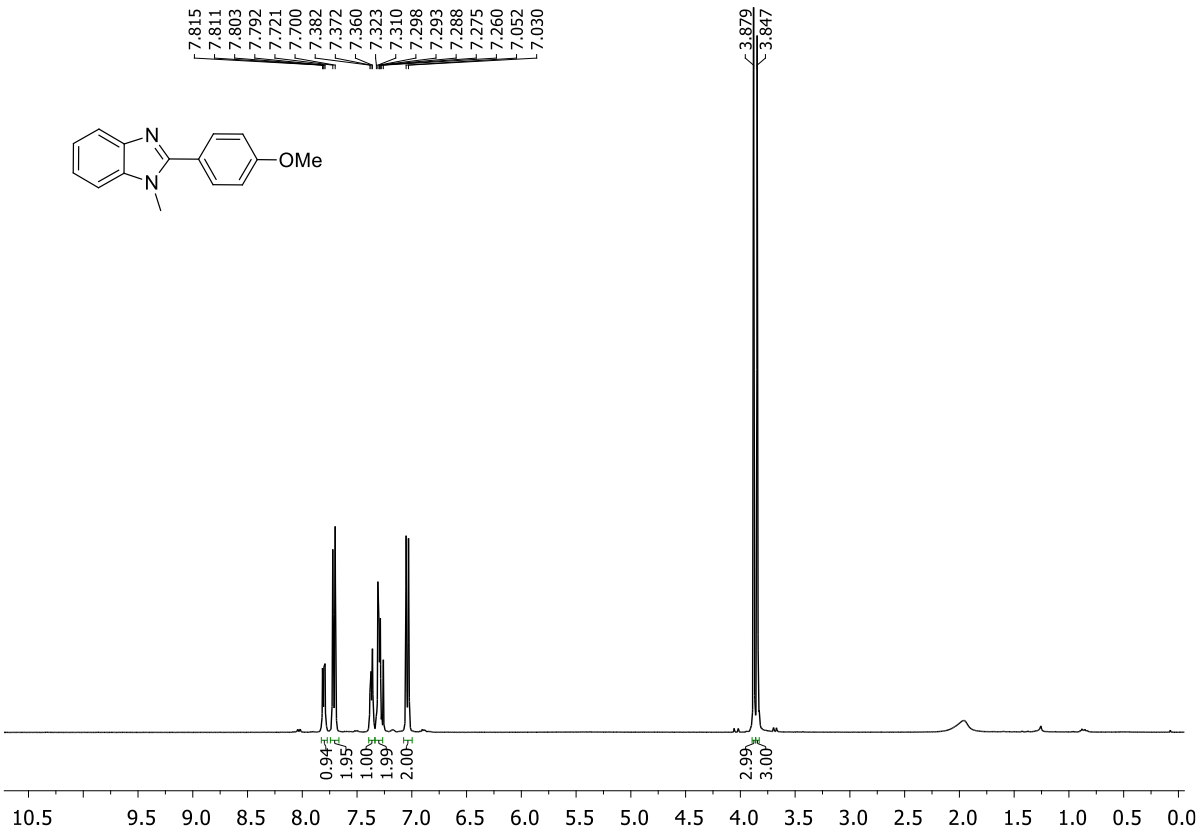


Figure 5.18 ^{1}H NMR of 2-(4-Methoxyphenyl)-1-methyl-benzo[d]imidazole (**2g**)

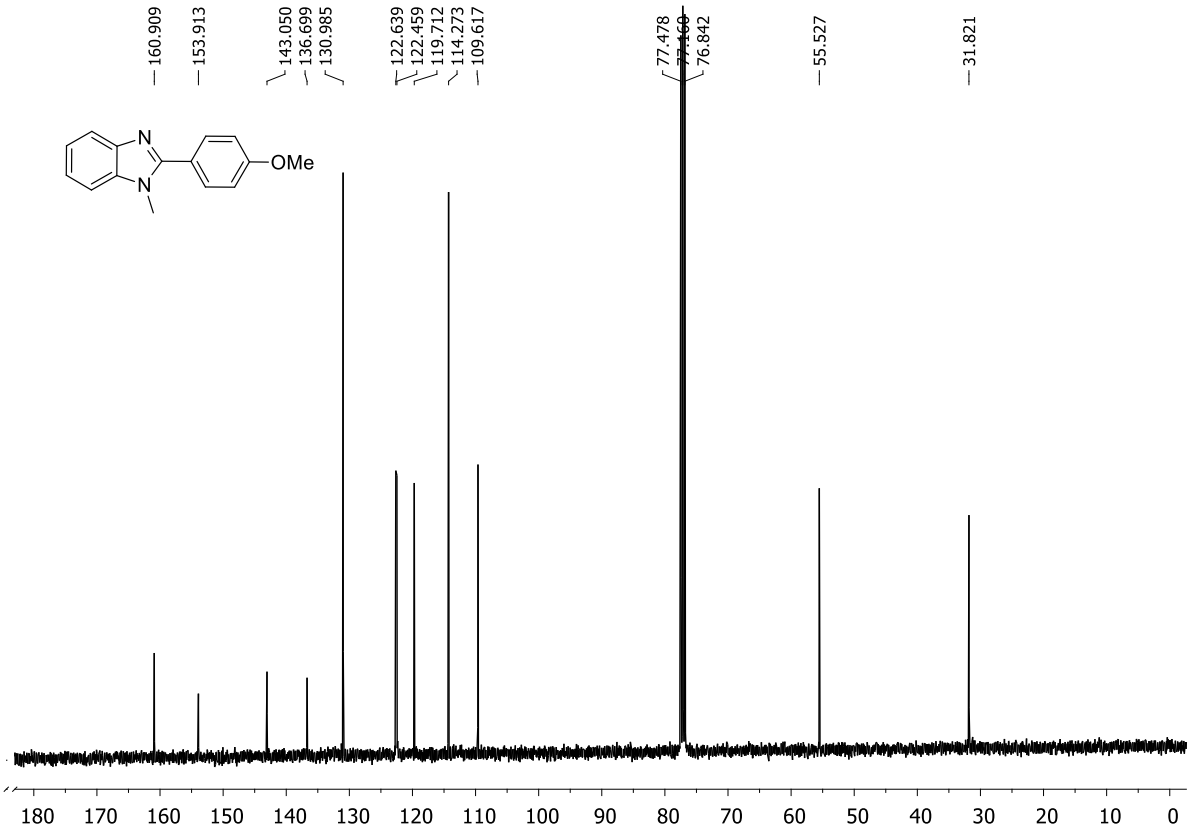


Figure 5.19 ^{13}C NMR of 2-(4-Methoxyphenyl)-1-methyl-benzo[d]imidazole (**2g**)

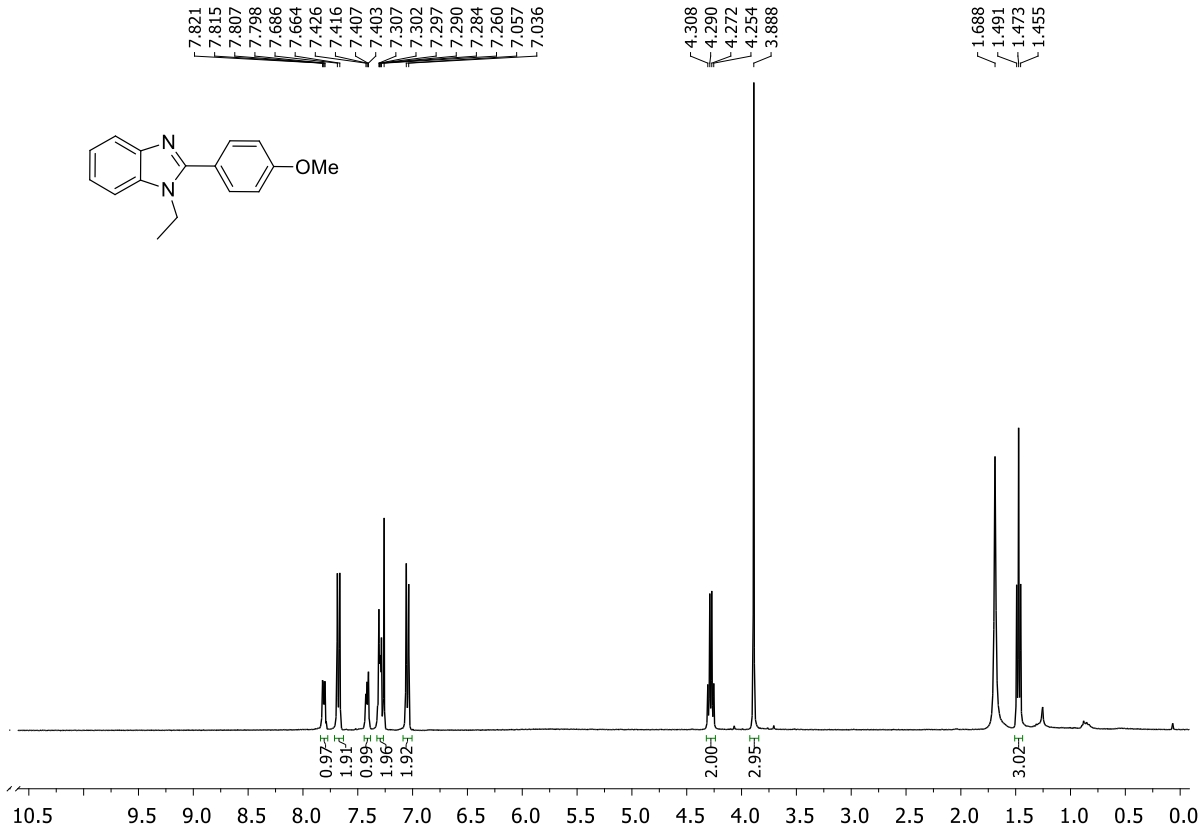


Figure 5.20 ^{1}H NMR of 1-Ethyl-2-(4-methoxyphenyl)-benzo[d]imidazole (**2h**)

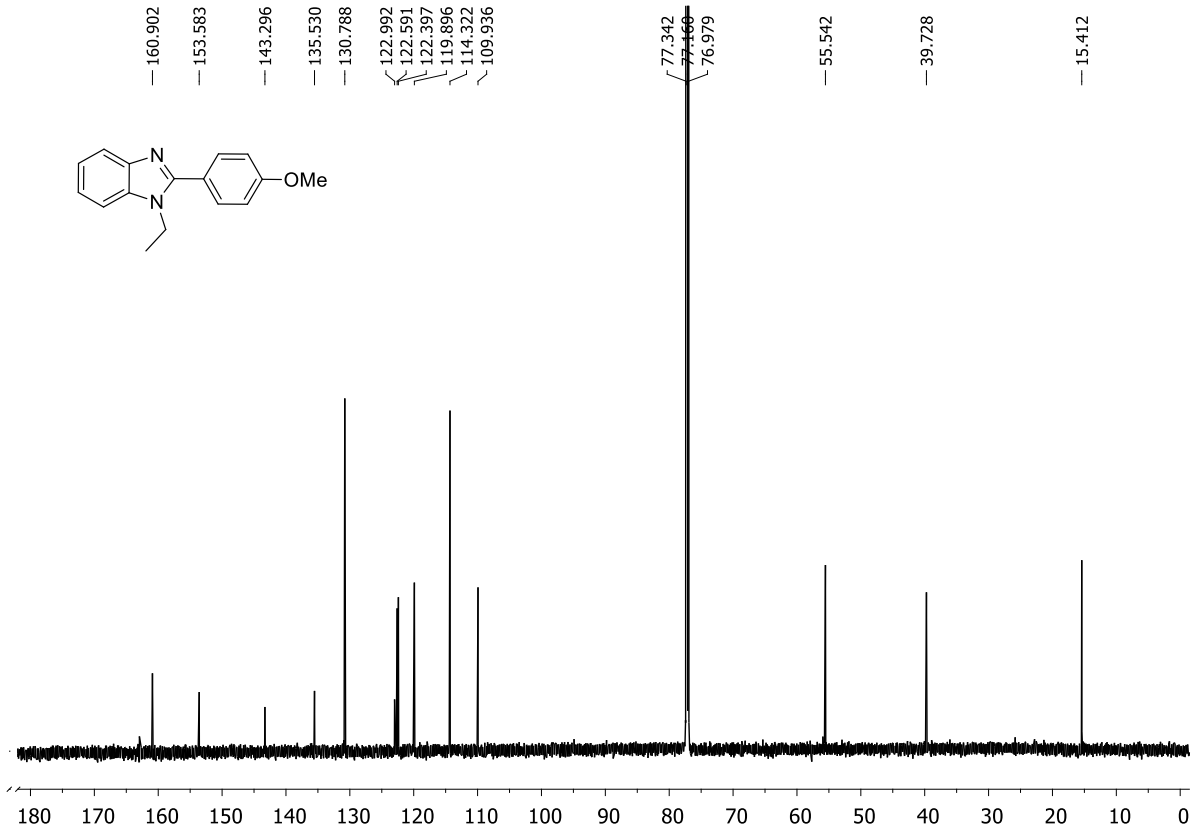


Figure 5.21 ^{13}C NMR of 1-Ethyl-2-(4-methoxyphenyl)-benzo[d]imidazole (**2h**)

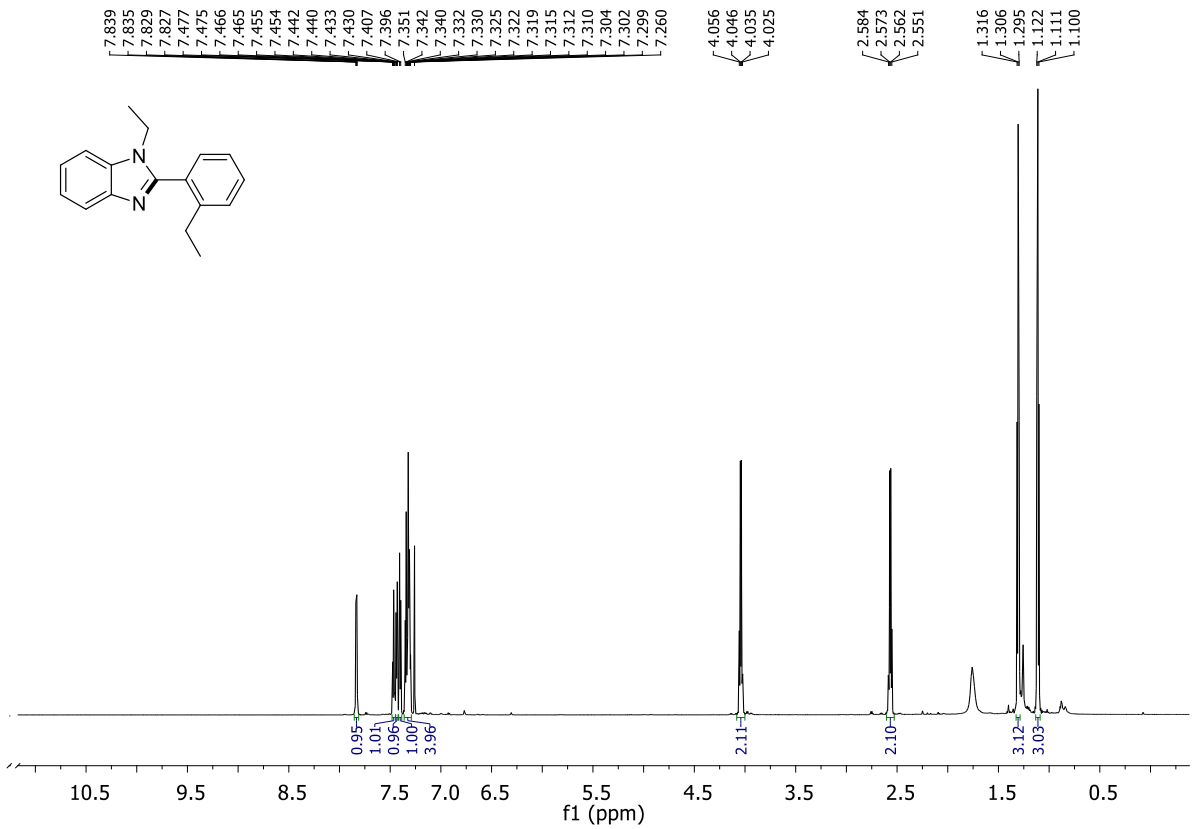


Figure 5.22 ^{1}H NMR of 1-Ethyl-2-(2-ethylphenyl)-benzo[d]imidazole (**2i**)

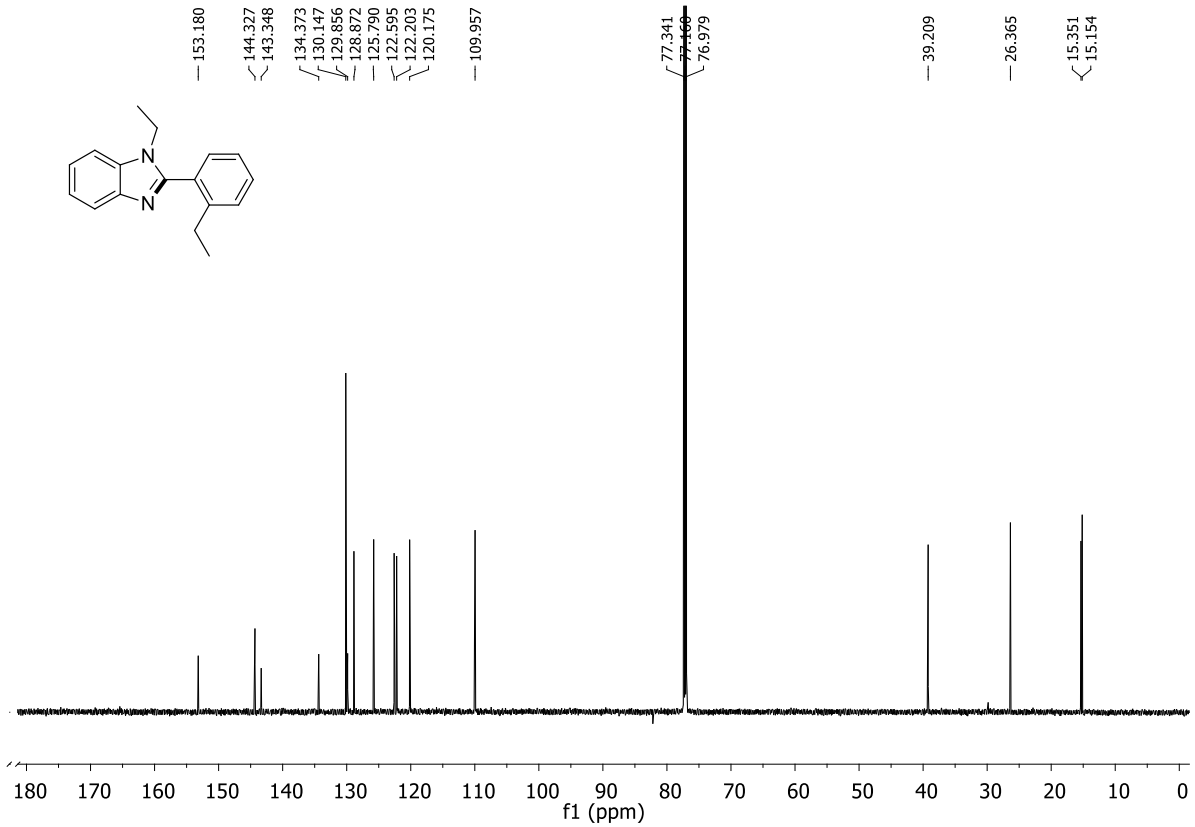


Figure 5.23 ^{13}C NMR of 1-Ethyl-2-(2-ethylphenyl)-benzo[d]imidazole (**2i**)

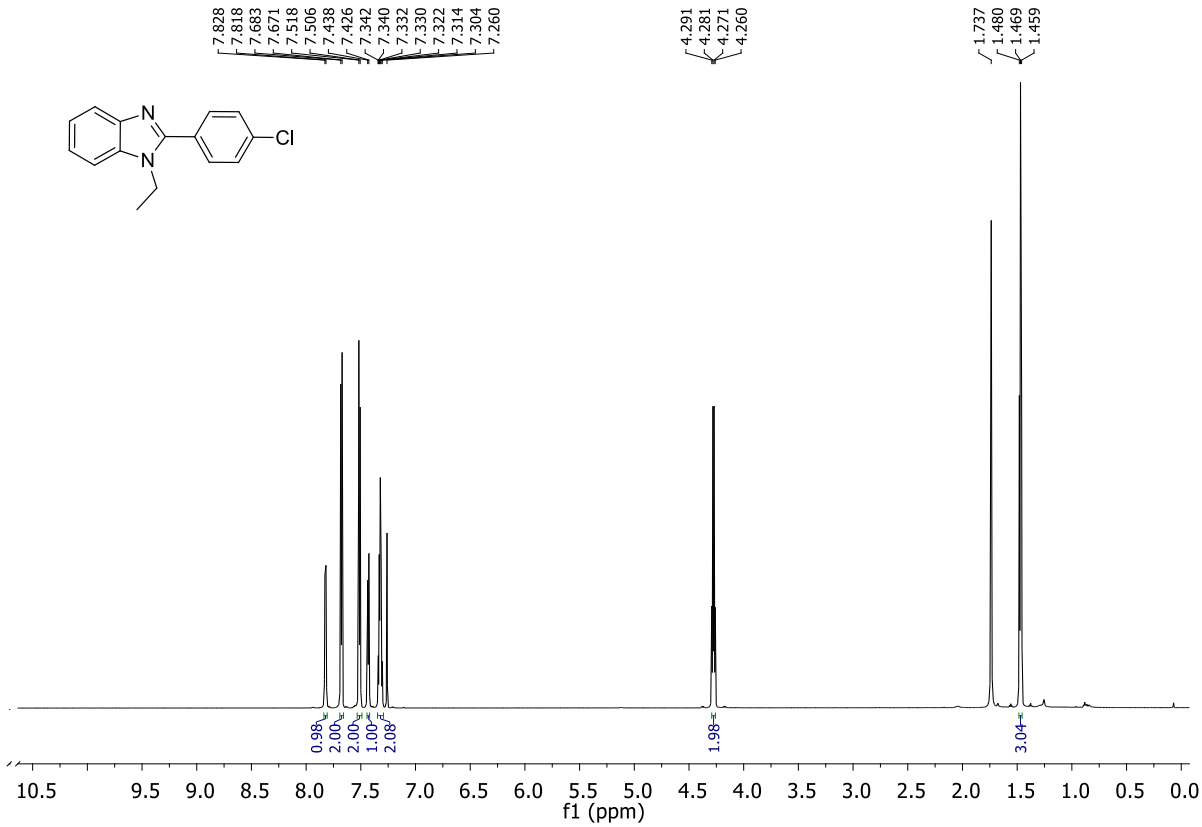


Figure 5.24 ^{1}H NMR of 2-(4-Chlorophenyl)-1-ethyl-benzo[d]imidazole (**2j**)

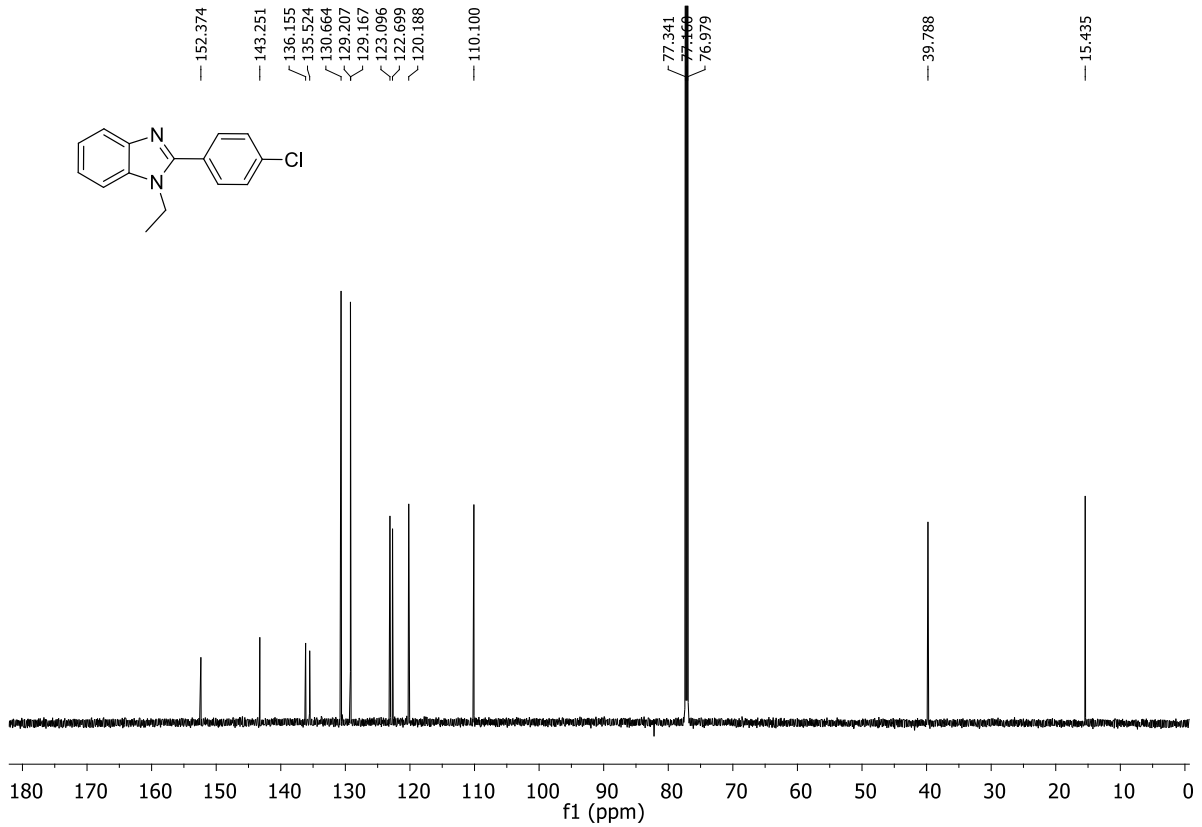


Figure 5.25 ^{13}C NMR of 2-(4-Chlorophenyl)-1-ethyl-benzo[d]imidazole (**2j**)

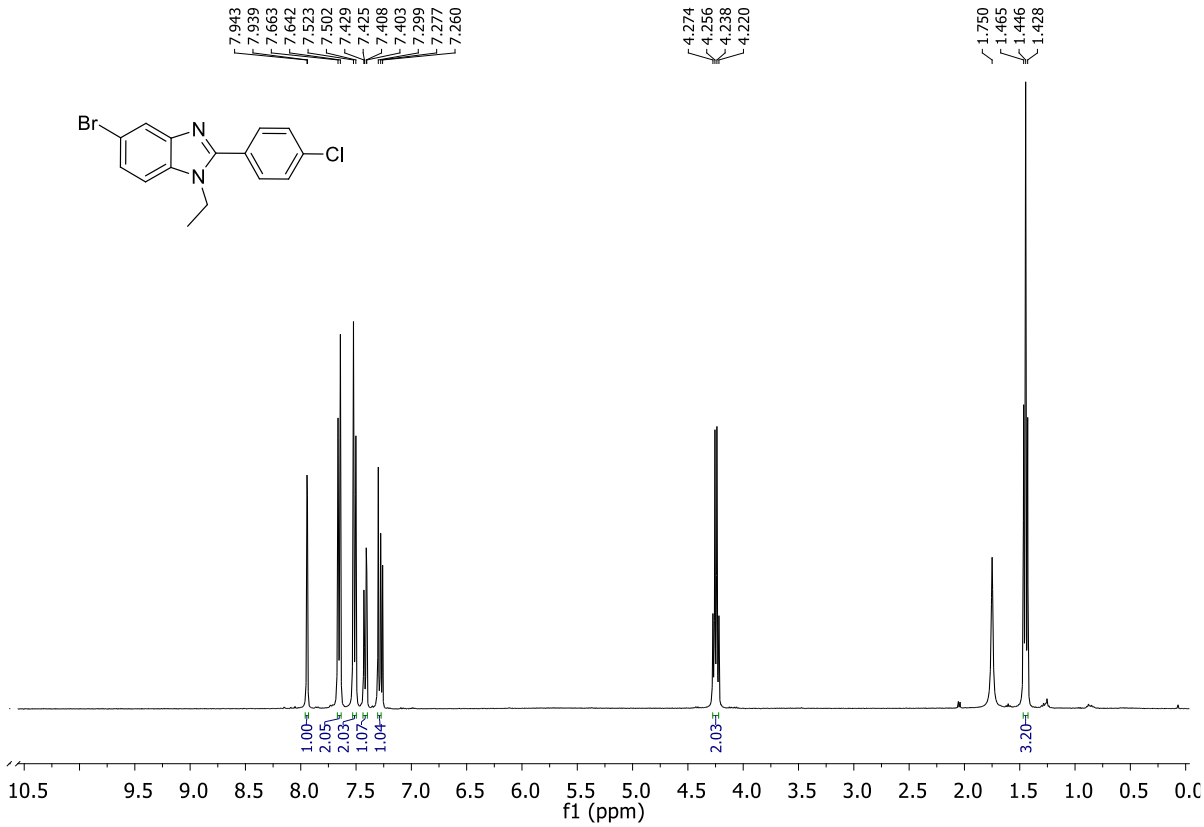


Figure 5.26 ^{1}H NMR of 5-Bromo-2-(4-chlorophenyl)-1-ethyl-benzo[d]imidazole (**2k**)

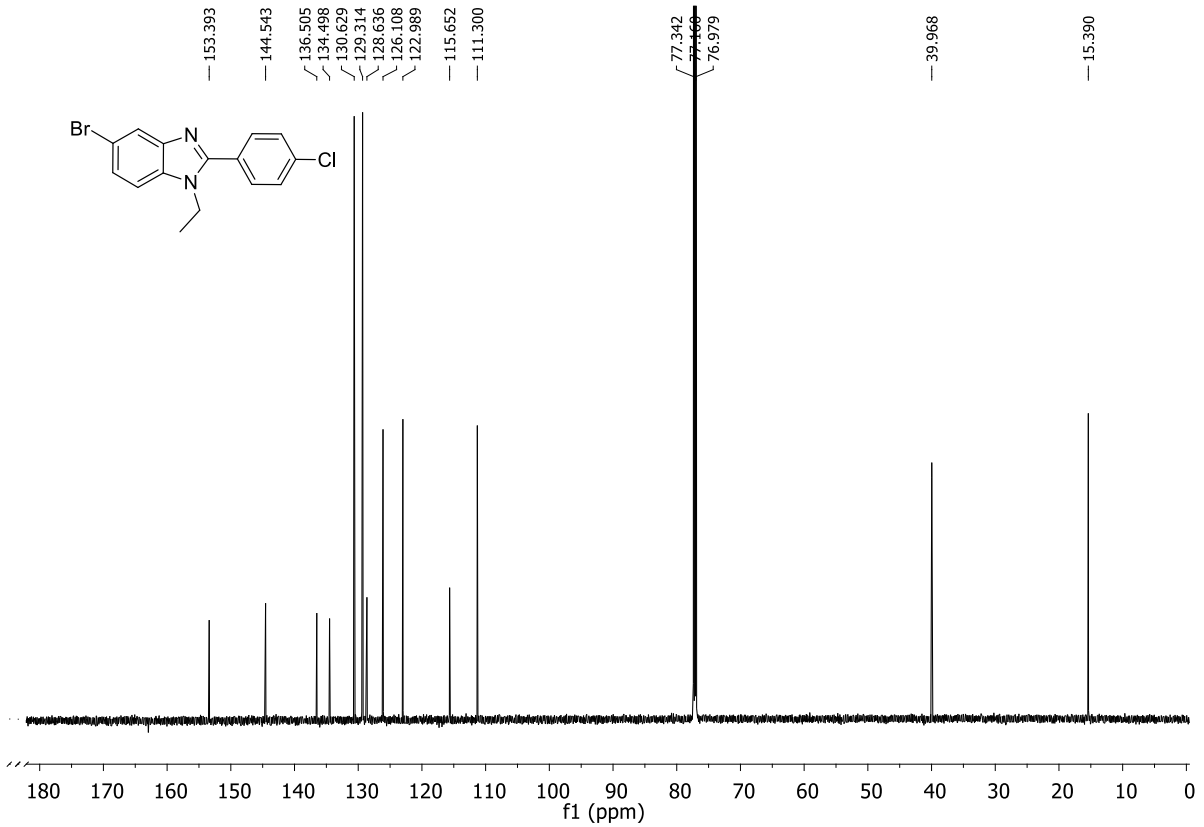


Figure 5.27 ^{13}C NMR of 5-Bromo-2-(4-chlorophenyl)-1-ethyl-benzo[d]imidazole (**2k**)

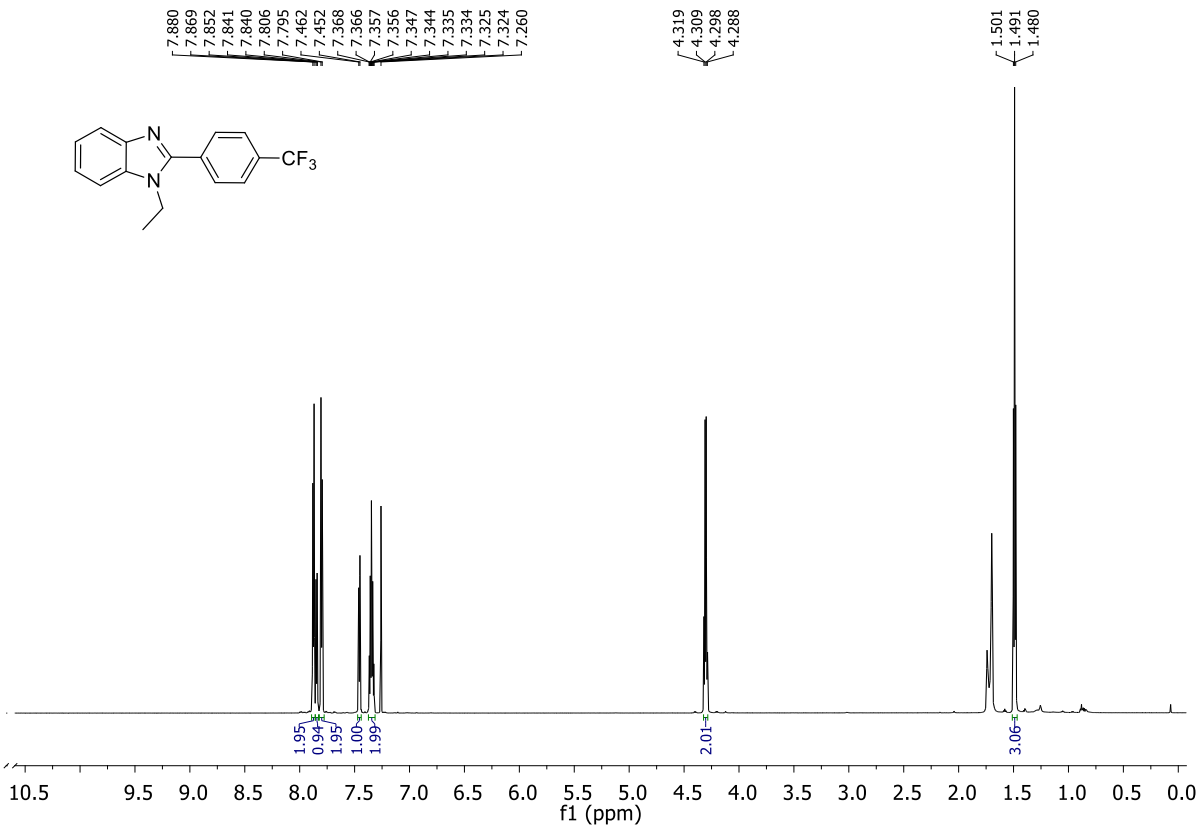


Figure 5.28 ^{1}H NMR of 1-Ethyl-2-(4-(trifluoromethyl)phenyl)-benzo[d]imidazole (**2l**)

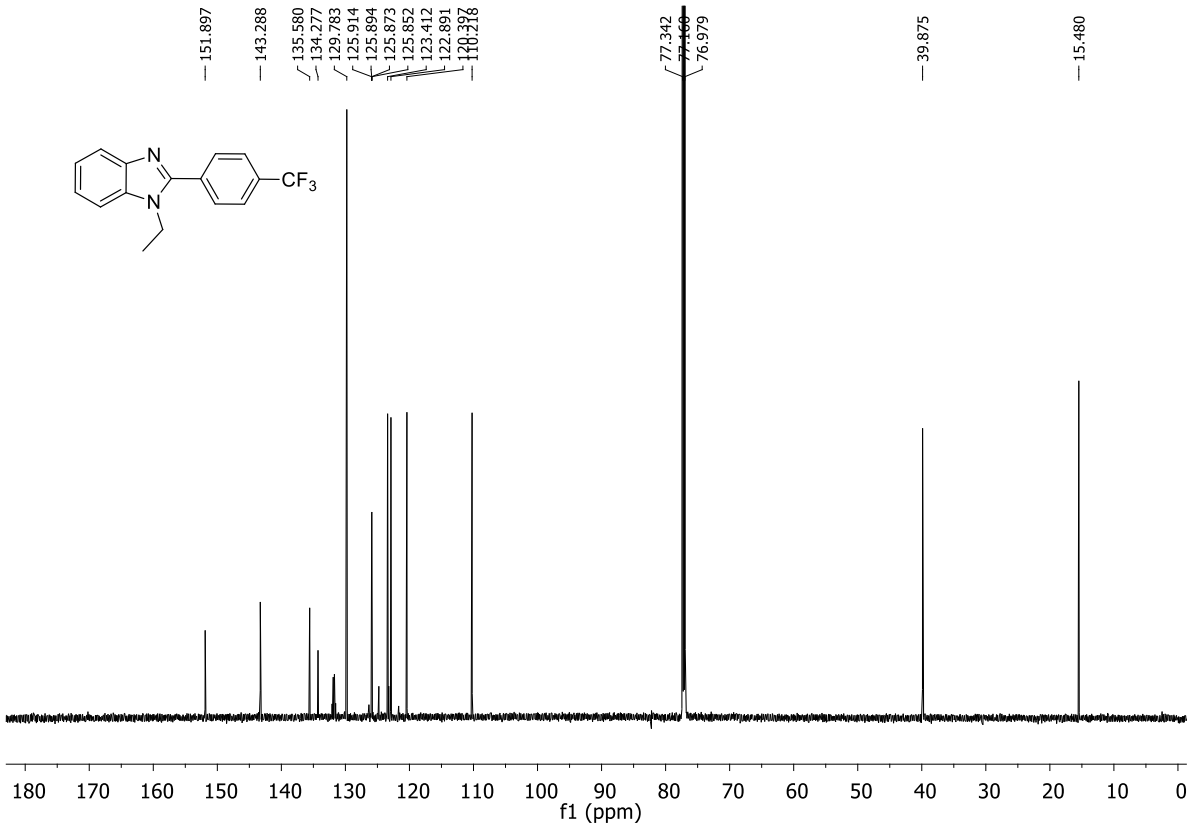


Figure 5.29 ^{13}C NMR of 1-Ethyl-2-(4-(trifluoromethyl)phenyl)-benzo[d]imidazole (**2l**)

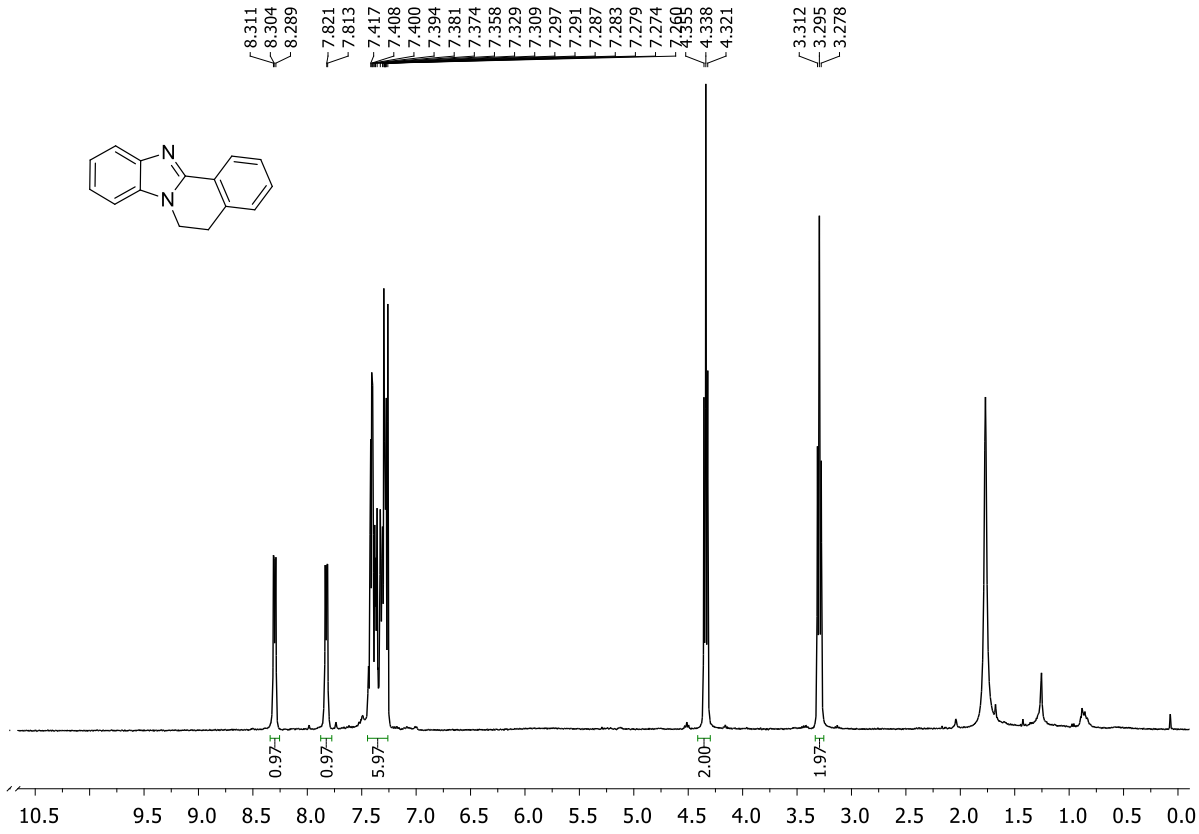


Figure 5.30 ^{1}H NMR of 5,6-Dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline (**2m**)

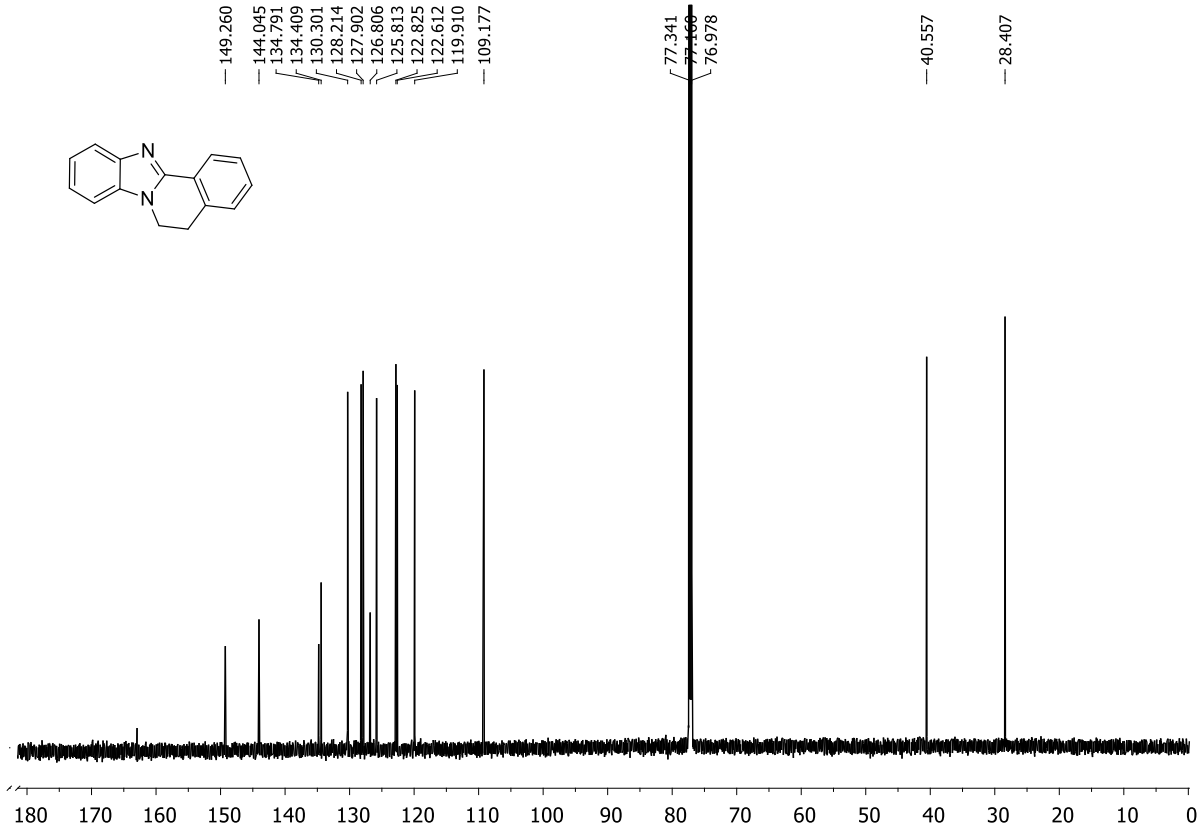


Figure 5.31 ^{13}C NMR of 5,6-Dihydrobenzo[4,5]imidazo[2,1-a]isoquinoline (**2m**)

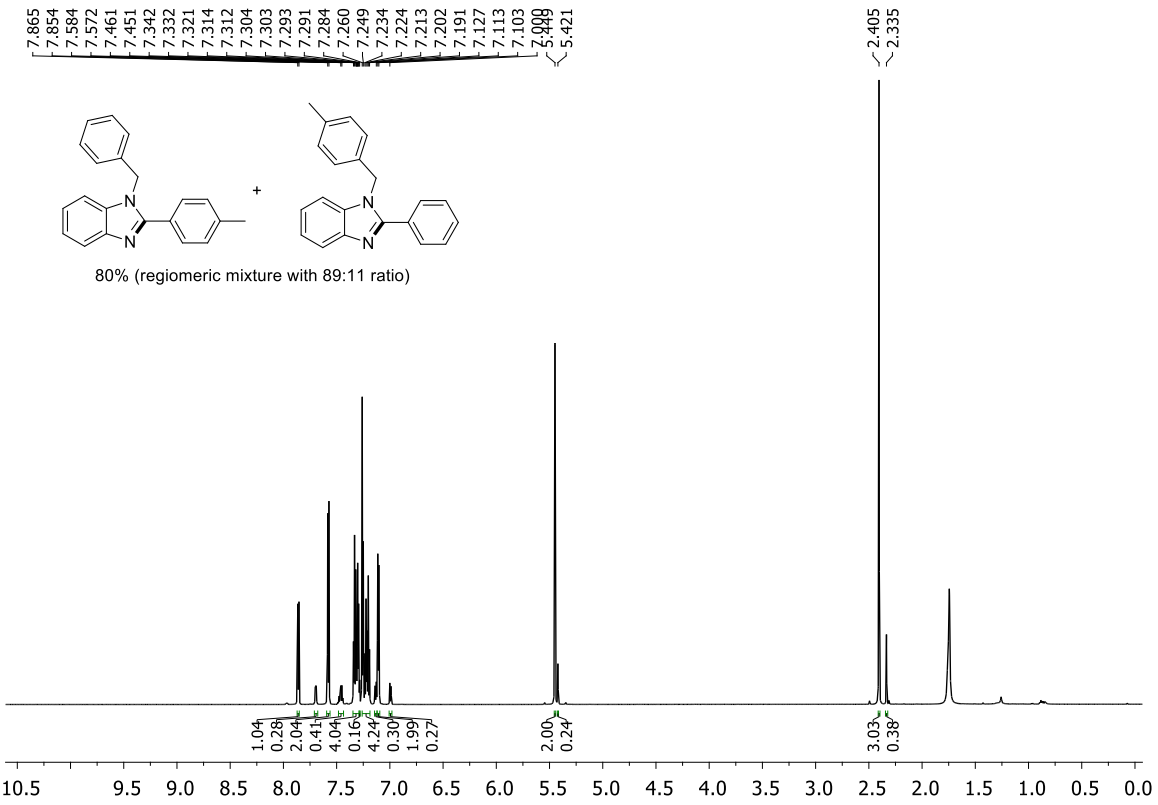


Figure 5.32 ^{1}H NMR of 1-Benzyl-2-(p-tolyl)-benzo[d]imidazole and 1-(4-Methylbenzyl)-2-phenyl-benzo[d]imidazole **(2n)**

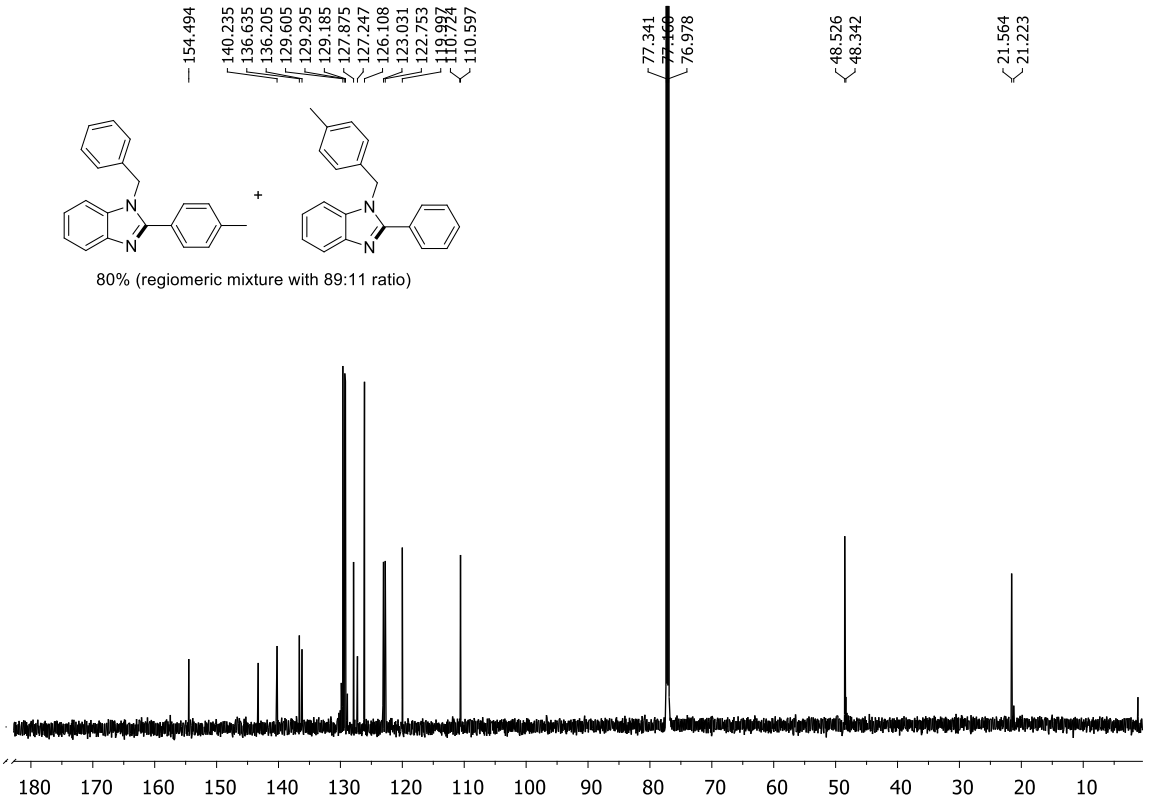


Figure 5.33 ^{13}C NMR of 1-Benzyl-2-(p-tolyl)-benzo[d]imidazole and 1-(4-Methylbenzyl)-2-phenyl-benzo[d]imidazole **(2n)**

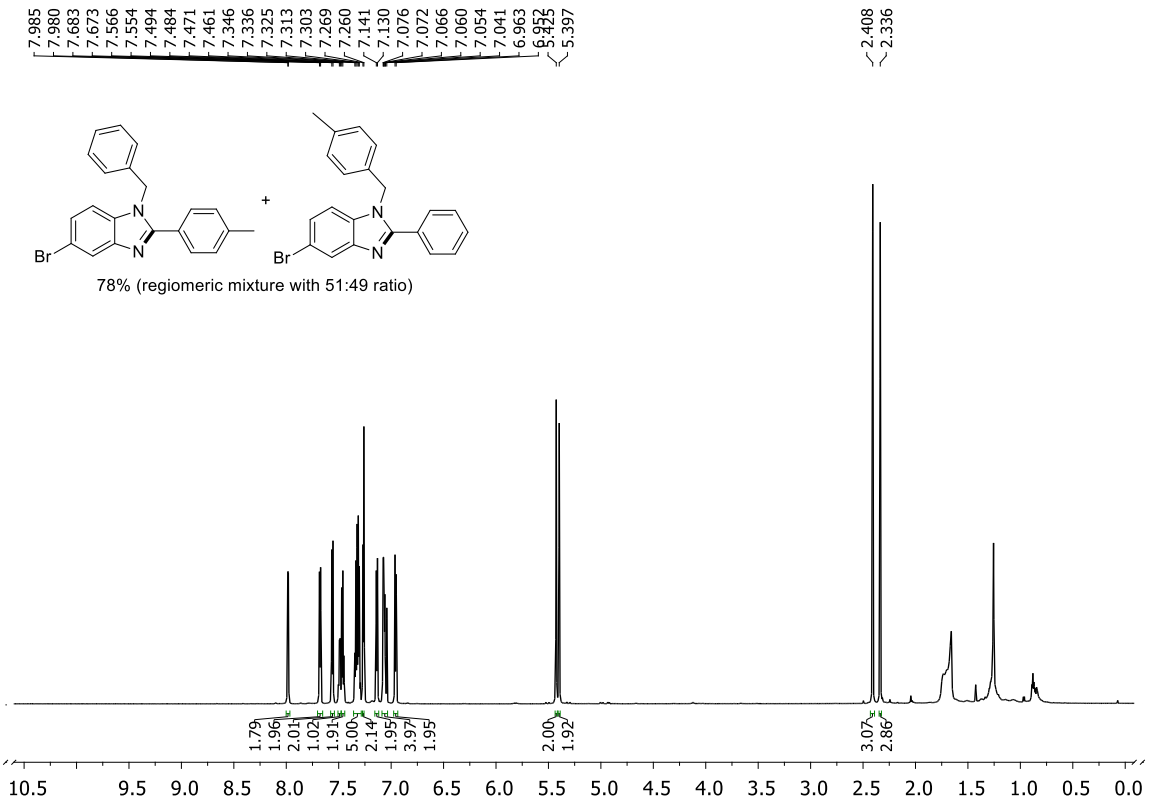


Figure 5.34 ^{1}H NMR of 1-Benzyl-5-bromo-2-(p-tolyl)-benzo[d]imidazole and 5-Bromo-1-(4-methylbenzyl)-2-phenyl-benzo[d]imidazole **(2o)**

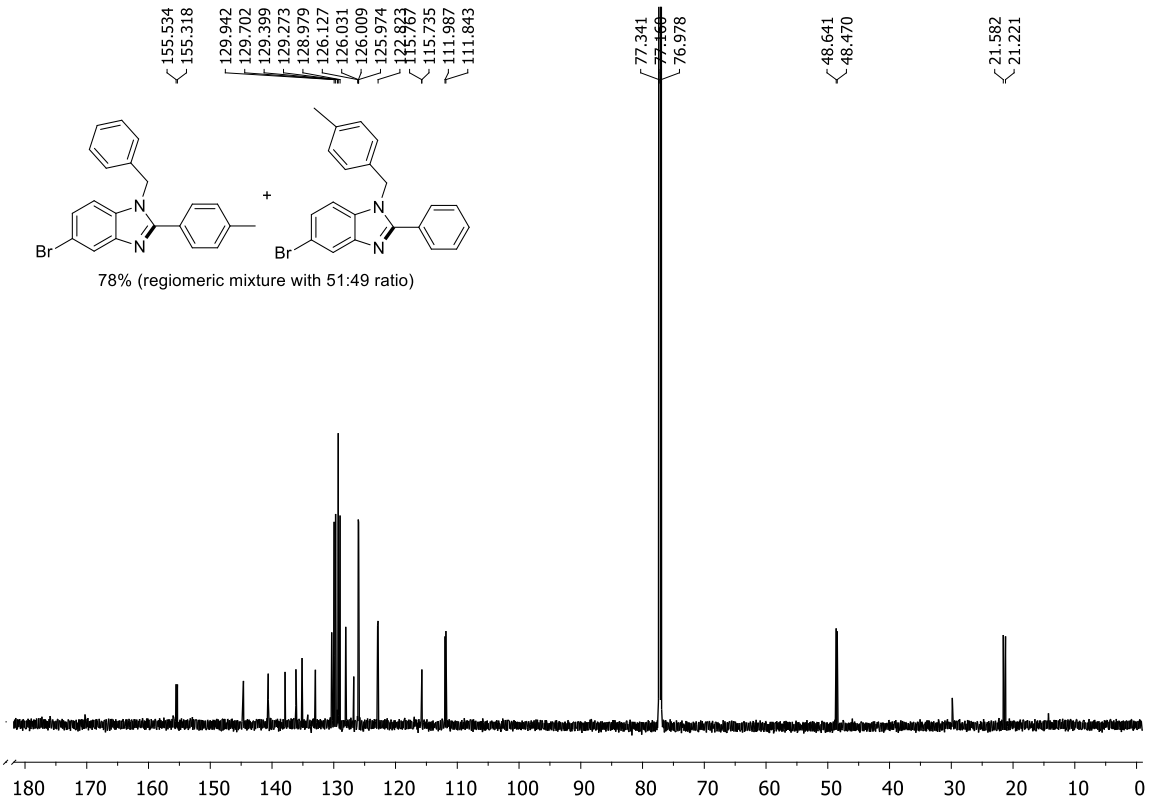


Figure 5.35 ^{13}C NMR of 1-Benzyl-5-bromo-2-(p-tolyl)-benzo[d]imidazole and 5-Bromo-1-(4-methylbenzyl)-2-phenyl-benzo[d]imidazole **(2o)**

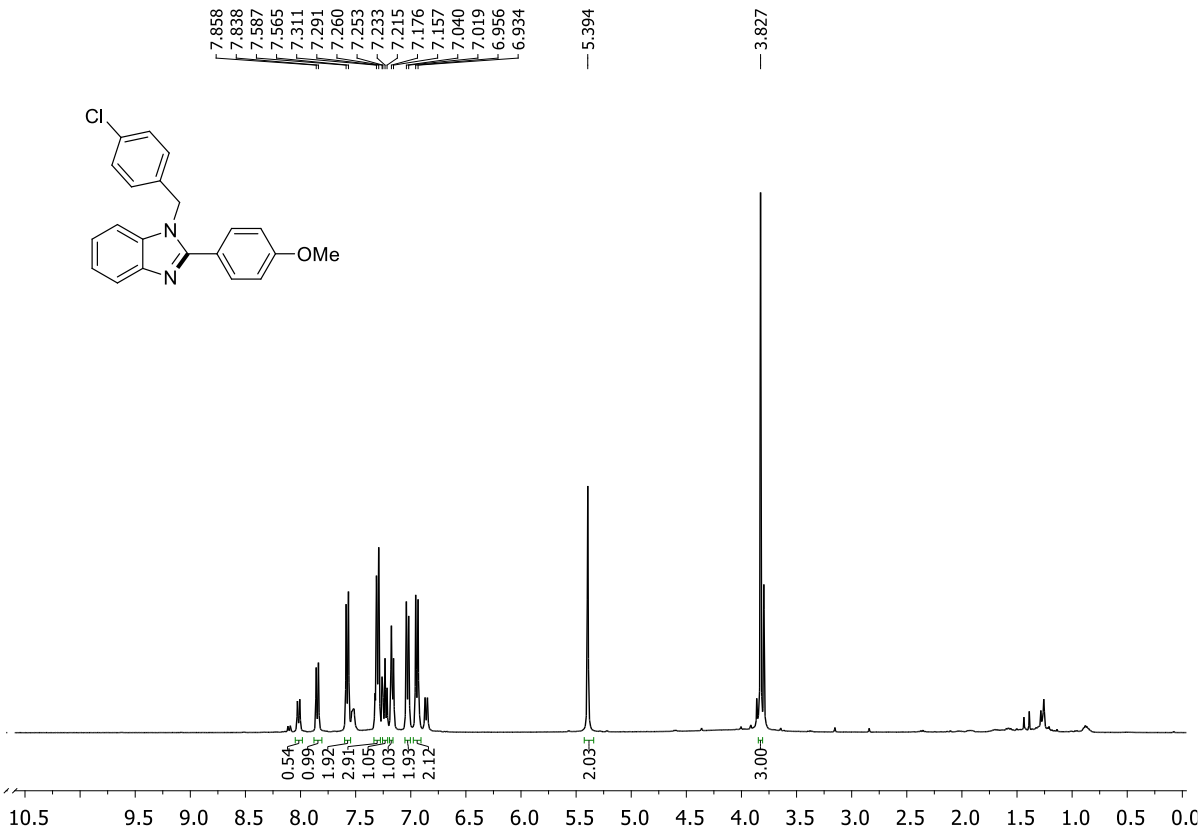


Figure 5.36 ^{1}H NMR of 1-(4-chlorobenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (**2p**)

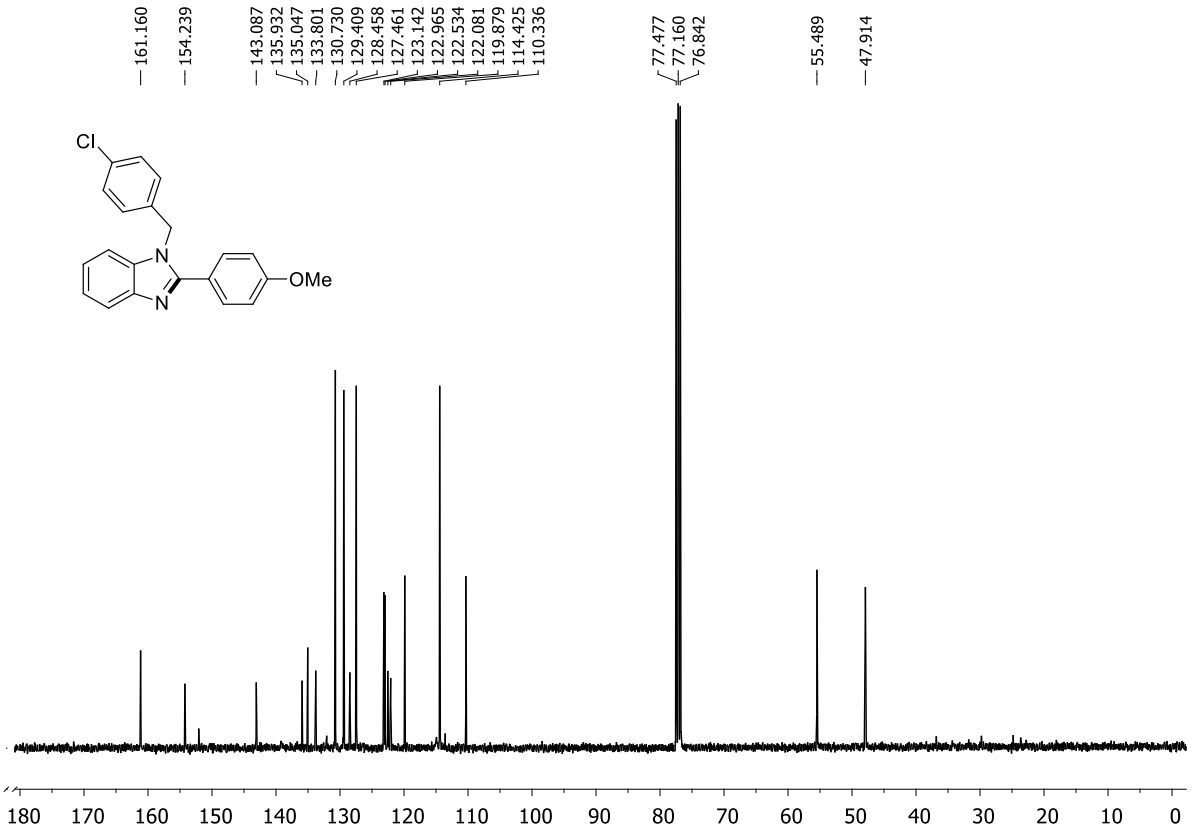


Figure 5.37 ^{13}C NMR of 1-(4-chlorobenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (**2p**)

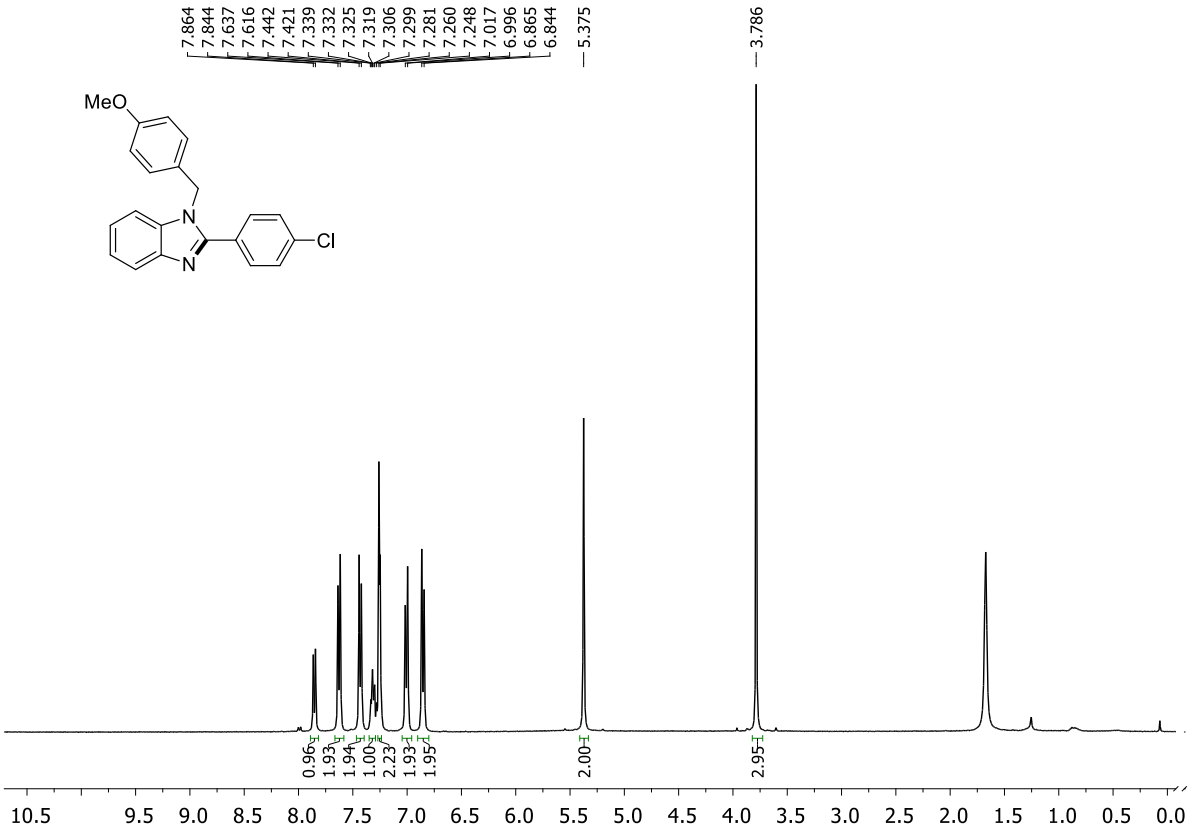


Figure 5.38 ^{1}H NMR of 2-(4-chlorophenyl)-1-(4-methoxybenzyl)-benzo[d]imidazole (**2p'**)

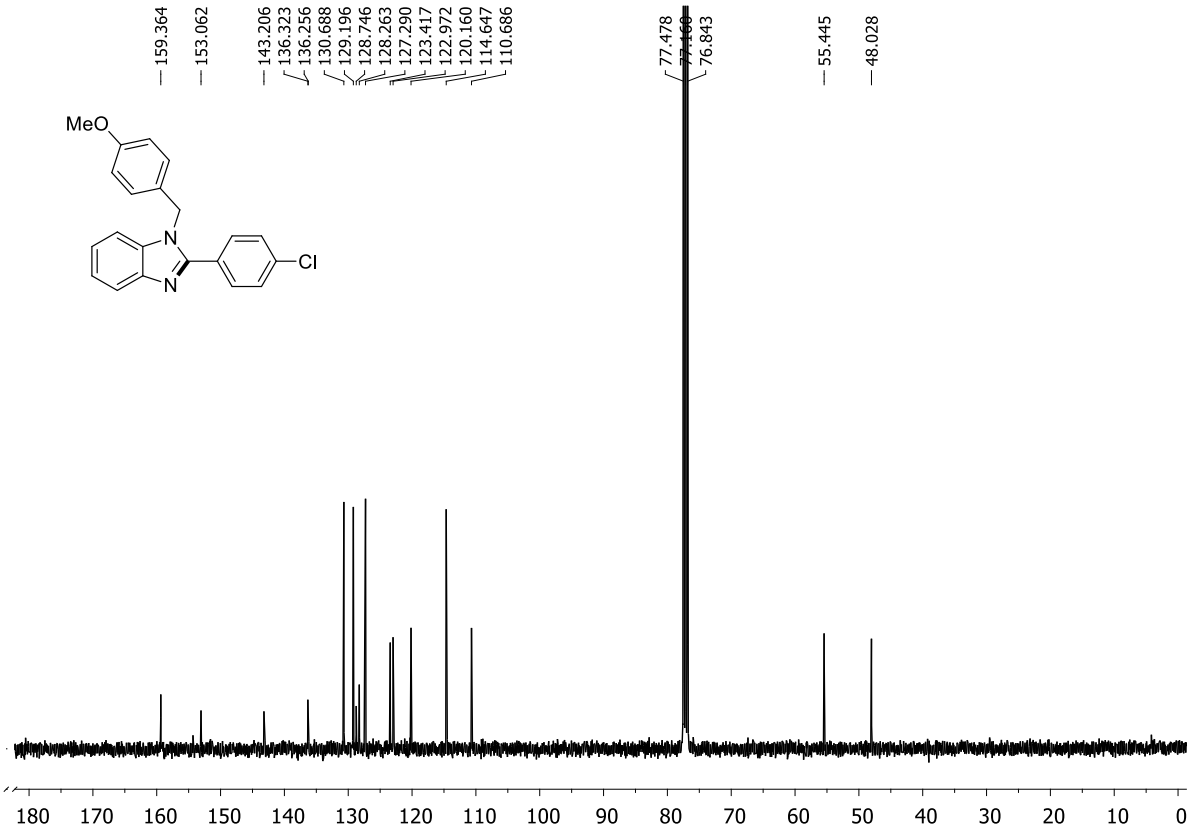


Figure 5.39 ^{13}C NMR of 2-(4-chlorophenyl)-1-(4-methoxybenzyl)-benzo[d]imidazole (**2p'**)

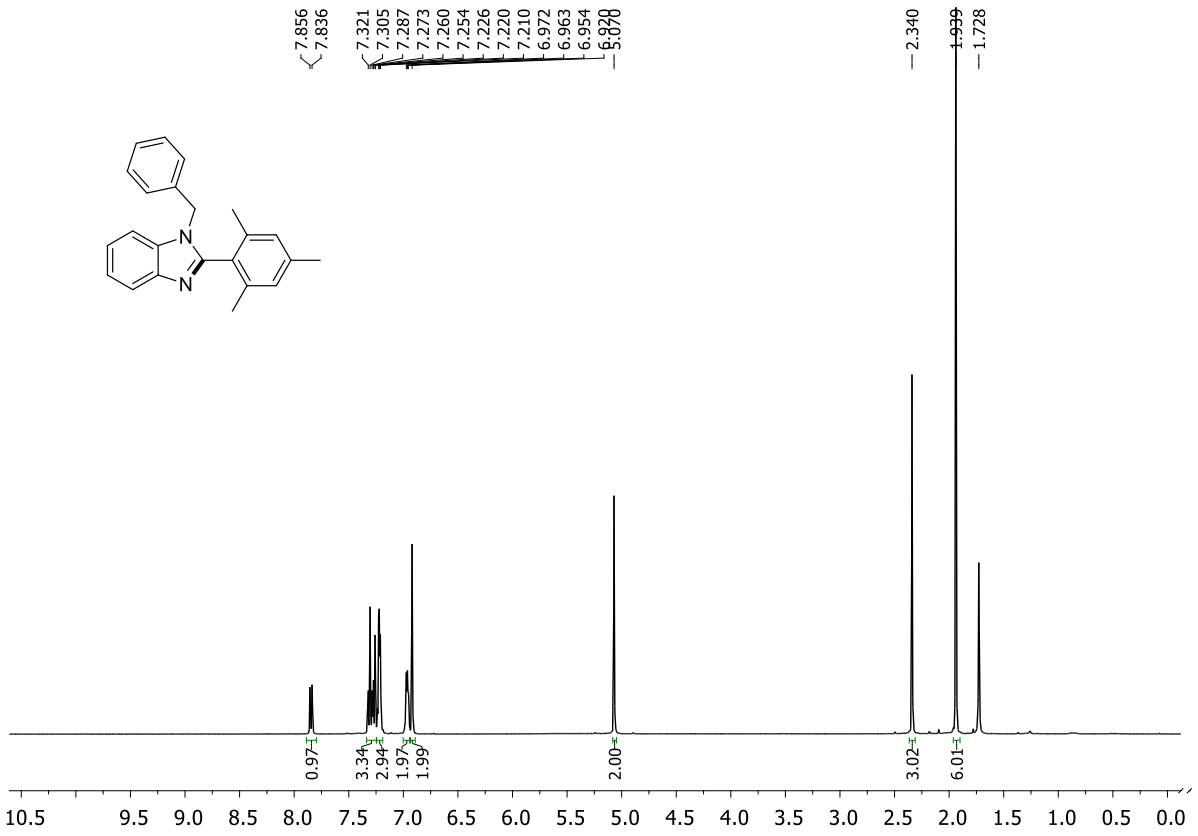


Figure 5.40 ^{1}H NMR of 1-Benzyl-2-mesityl-benzo[d]imidazole (**2q**)

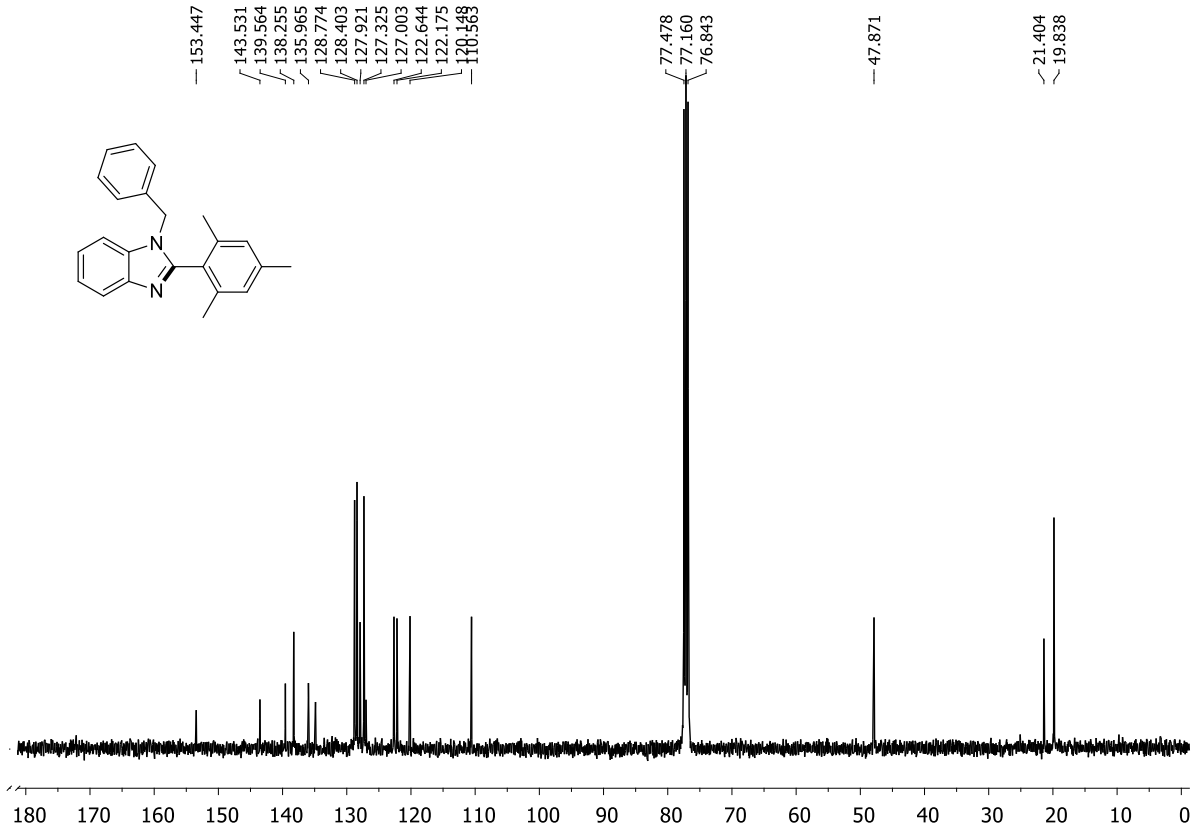


Figure 5.41 ^{13}C NMR of 1-Benzyl-2-mesityl-benzo[d]imidazole (**2q**)

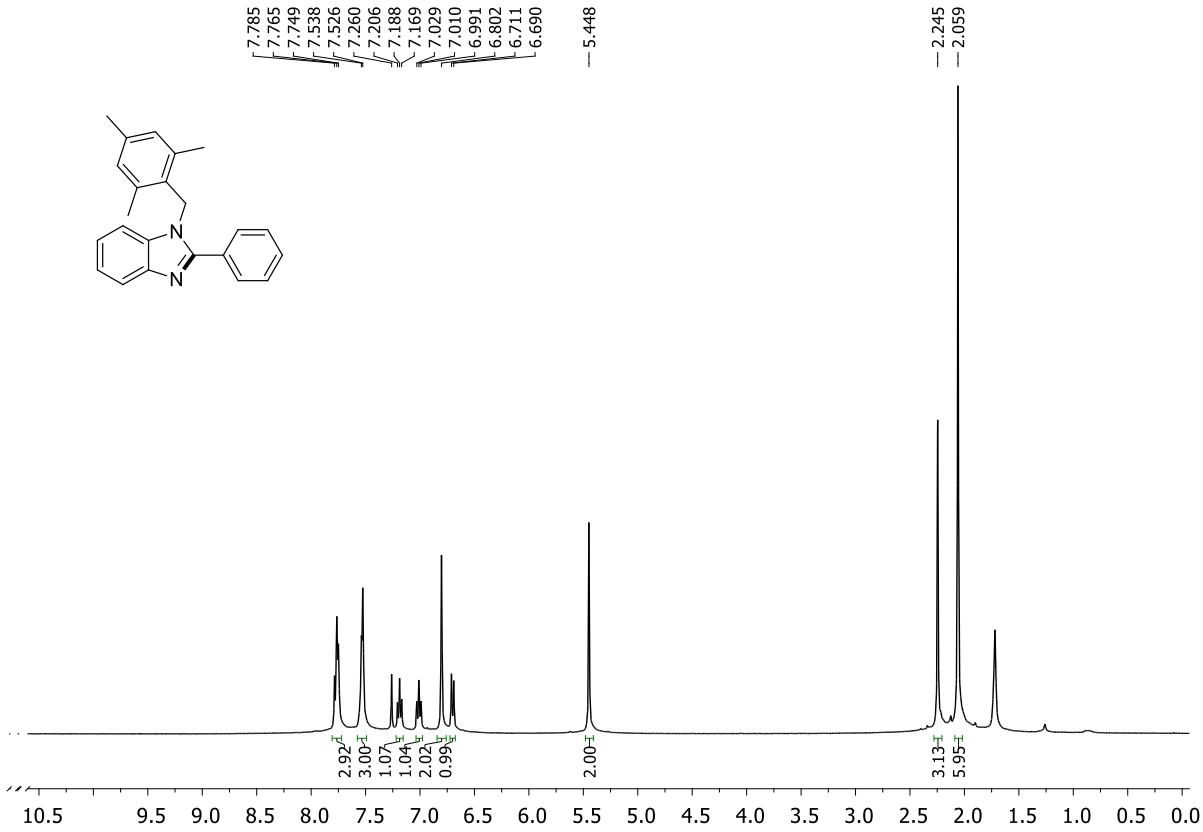


Figure 5.42 ^{1}H NMR of 2-Phenyl-1-(2,4,6-trimethylbenzyl)-benzo[d]imidazole (**2q'**)

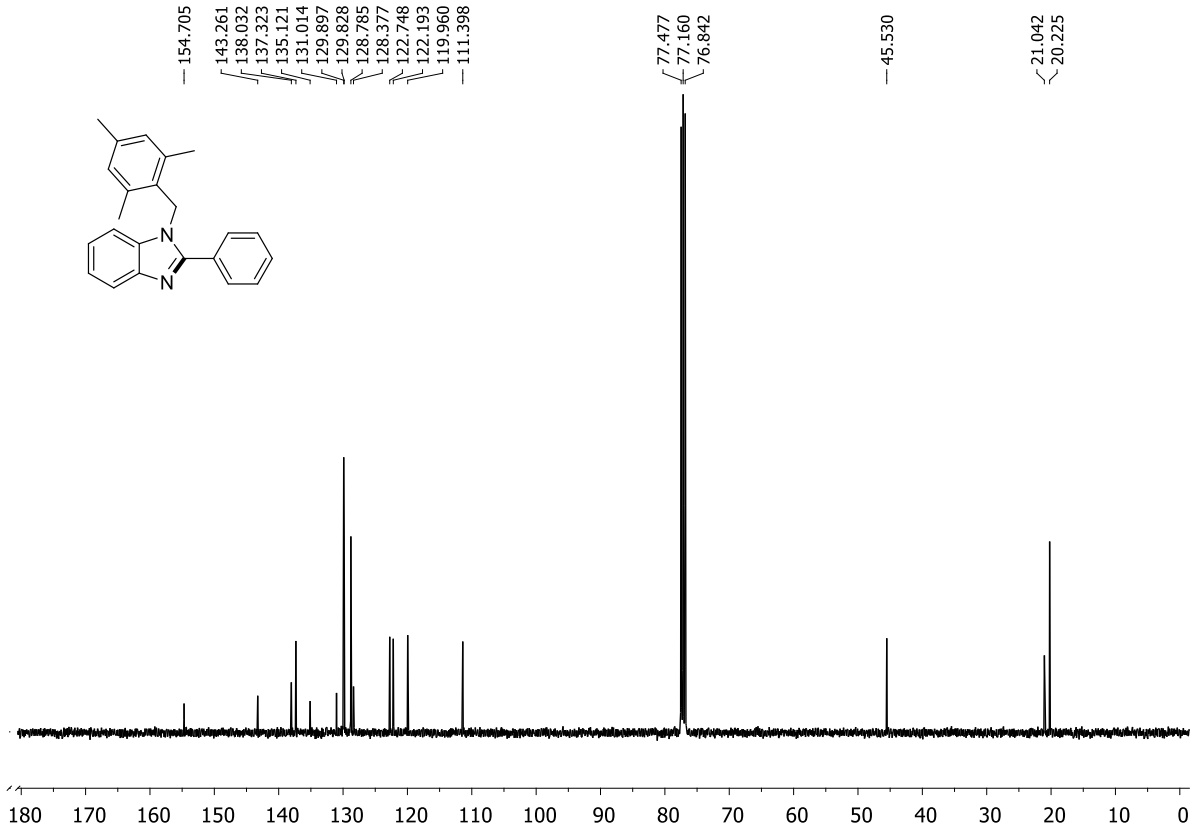


Figure 5.43 ^{13}C NMR of 2-Phenyl-1-(2,4,6-trimethylbenzyl)-benzo[d]imidazole (**2q'**)

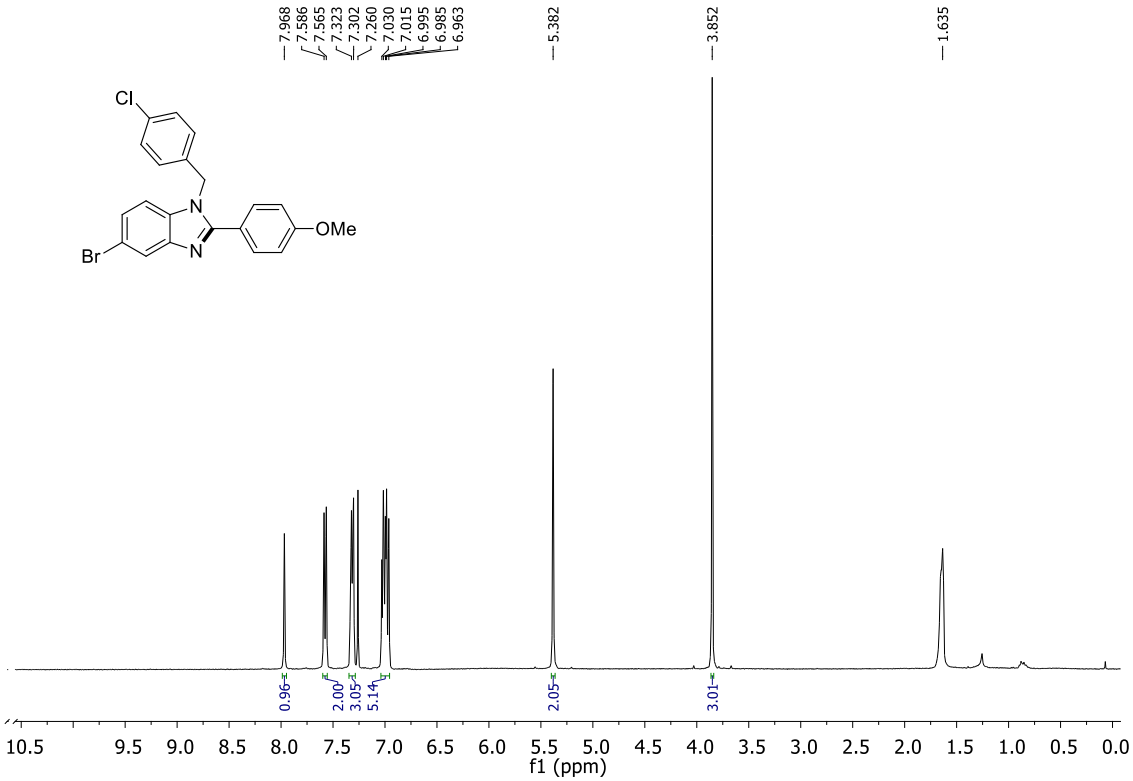


Figure 5.44 ^{1}H NMR of 5-Bromo-1-(4-chlorobenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (**2r**)

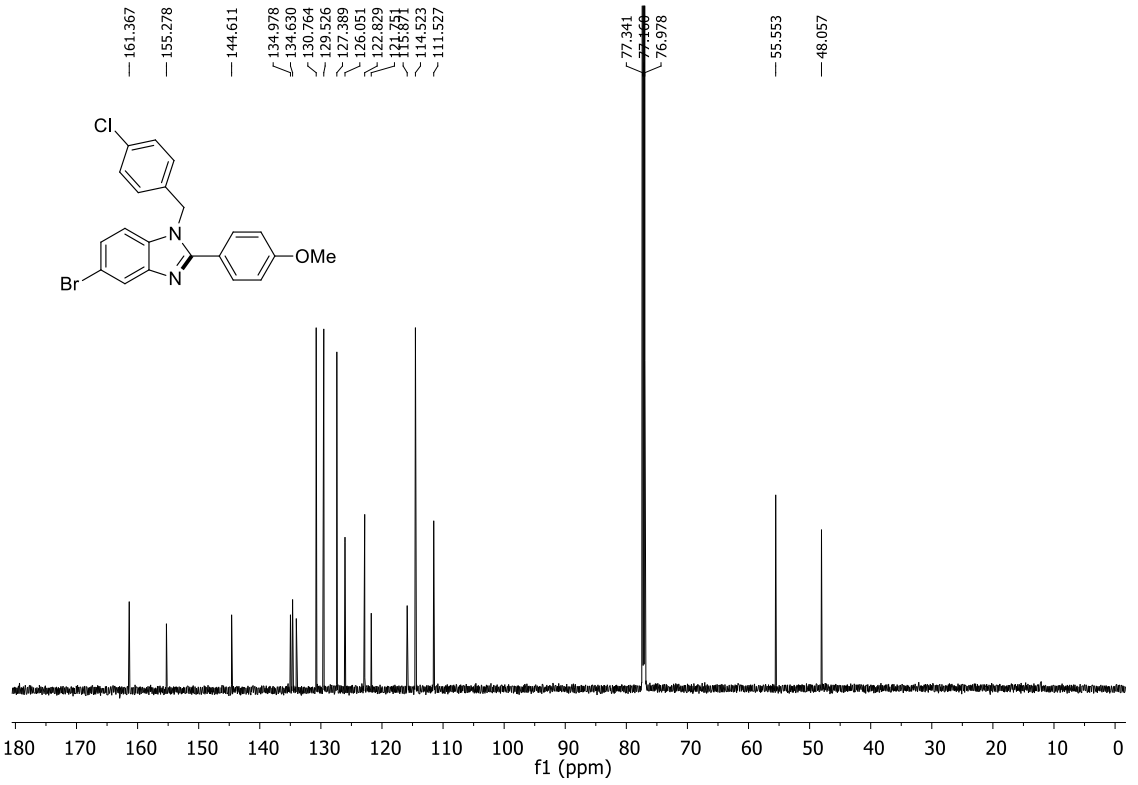


Figure 5.45 ^{13}C NMR of 5-Bromo-1-(4-chlorobenzyl)-2-(4-methoxyphenyl)-benzo[d]imidazole (**2r**)

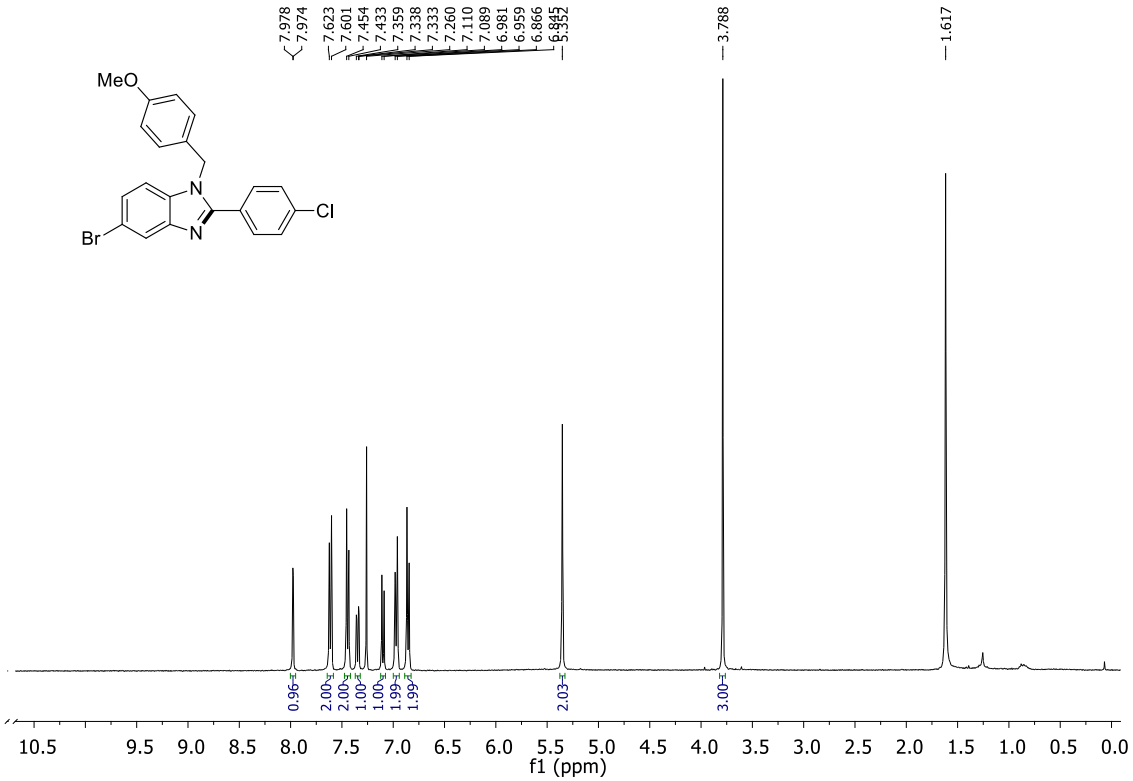


Figure 5.46 ^{1}H NMR of 5-Bromo-2-(4-chlorophenyl)-1-(4-methoxybenzyl)-benzo[d]imidazole (**2r'**)

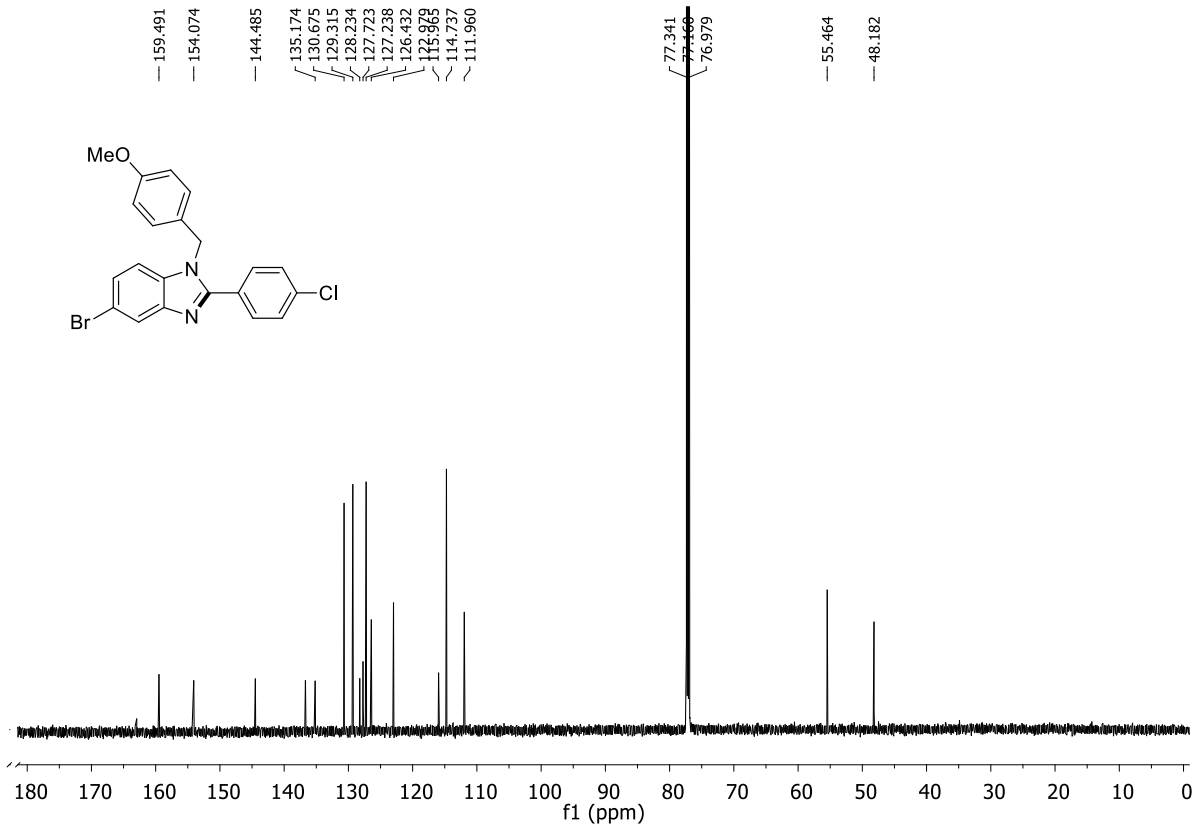
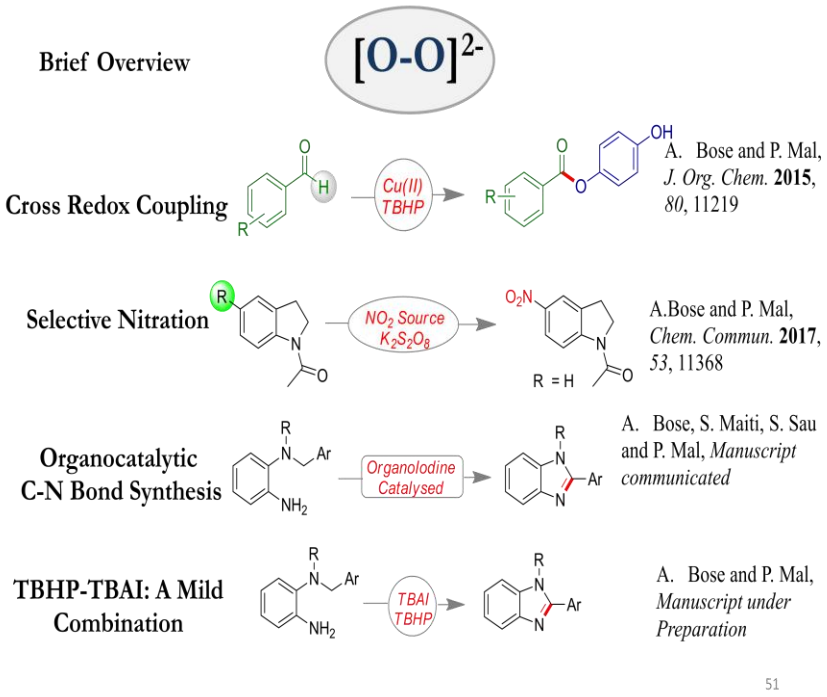


Figure 5.47 ^{13}C NMR of 5-Bromo-2-(4-chlorophenyl)-1-(4-methoxybenzyl)-benzo[d]imidazole (**2r'**)

Conclusion


Brief Overview
[O-O]2-
Cross Redox Coupling
Cu(II)
TBHP
A. Bose and P. Mal, J. Org. Chem. 2015, 80, 11219
Selective Nitration
NO2 Source
K2S2O8
R = H
A.Bose and P. Mal, Chem. Commun. 2017, 53, 11368
Organocatalytic
C-N Bond Synthesis
Organolodine
Catalysed
A. Bose, S. Maiti, S. Sau and P. Mal, Manuscript communicated
TBHP-TBAI: A Mild
Combination
TBAI
TBHP
A. Bose and P. Mal, Manuscript under Preparation
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Note

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Cross Redox Coupling of Aryl-Aldehydes and *p*-Benzoquinone

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Supporting Information

ABSTRACT: Herein, we report an unprecedented **C**ross **R**edox **C**oupling (CRC) reaction catalyzed by $Cu(OAc)_2·H_2O$. As a proof-of-concept, direct coupling of aromatic aldehydes (or alcohols) and *p*-benzoquinone led to an ester in the presence of the Cu(II)−TBHP combination. During the coupling process, the C−H bond of the aldehydes was converted directly to a C−O bond. Mechanistically, we propose that the reaction proceeded via a radical pathway. In addition, atom and electron economies were well-conserved during this CRC reaction.

A redox coupling reaction[1] is known in Fischer indolization reaction[2,3] in which a C−C single bond is oxidatively created[4] at the expense of the reductive cleavage of a N−N bond. Overall, indolization reaction could be rationalized as dehydrogenative α-cross-coupling of two ketones to a 1,4-diketone.[5] Similarly, various cross-condensation reactions between two carbonyl compounds are well-documented in the literature, e.g., cross-aldol condensation,[6] Cannizzaro reaction,[7] coupling of ketones and carboxylate enolates,[5] etc. Undesirably, most of these traditional procedures require strong basic conditions and higher temperature and produce unwanted side products.

Benzoquinone and its derivatives[8] are prevalent in organic synthesis. Also, they have versatile use in many research fields such as molecular electronics,[9] oxidation chemistry,[10] medicinal chemistry,[11,12] radical reactions,[13,14] etc. The most common reactions of quinones are nucleophilic addition of thiols and amines to derive substituted hydroquinone derivatives via Michael addition[15] and metal[16,17] or hypervalent iodine catalyzed[18] C−H activation.[19−24] However, examples of acylation of hydroquinone directly from quinone with acylating agents are very few, if any.[25] In synthesis, monoesterification of hydroquinone is challenging because of the unavailability of suitably activated acid or coupling reagents[8] and uncontrollable diesterification reactions.

We report here direct cross-coupling reaction for esterification of two carbonyl compounds (*p*-benzoquinone and benzaldehyde derivatives) (Figure 1). To the best of our knowledge, coupling reaction between two carbonyls via a radical pathway is unprecedented (this work). Nevertheless, cross-coupling of α-alkoxymethyl-trifluoroborates with aryl- and heteroaryl bromides has recently been demonstrated using iridium photoredox catalyst and Ni catalyst.[26] Generally, esters are synthesized using preactivated acid derivatives (e.g., anhydrides, acyl halides, activated esters, etc.) and alcohols in the presence of stoichiometric amounts of bases by multistep processes.[27−31] Besides, few modified esterification approaches are oxidative esterification of aldehydes with β-dicarbonyl compounds,[32] C−O coupling by direct C−H bond activation of formamides for synthesis of enol carbamates,[33] Pd catalyzed oxidative cross-esterifications,[34] *N*-heterocyclic carbene (NHC)[35] catalyzed esterifications of *p*-napthaquinones using aldehydes via a Breslow intermediate (Figure 1d),[36] etc.

Table 1 represents the optimization of the reaction conditions. The most suitable condition (entry 5) was identified using 1.0 equiv of **1b** (*p*-anisaldehyde), 1.5 equiv of **2** (*p*-benzoquinone), 3.0 equiv of TBHP (***Caution!***; see Caution paragraph in the Experimental Section), and 10 mol % of $Cu(OAc)_2·H_2O$ in DMSO at 100−110 °C. At high temperature (ca. 110 °C), TBHP is known to undergo decomposition. Therefore, excess TBHP (3 equiv, 70% aqueous solution) was required for the reaction. The reaction led to poor yields when the temperature was <100 °C and failed in the presence of additives like I_2 (entry 8) or KI-I_2 (entry 9). A sluggish mixture was obtained in the presence of $CuCl_2$ (entry 11), $Cu(OTf)_2$ (entry 13), $FeCl_3$ (entry 12), etc. Addition of $K_2S_2O_8$ (entry 10) to $Cu(OAc)_2·H_2O$ did not lead to any improvement of yield. Reaction was also unsuccessful with solvents like acetonitrile (entry 1) and dimethylformamide (entry 2). Conversely, it was poor yielding (ca. 38%) under neat conditions (entry 14) and a failure under solvent-free ball-milling conditions.[37]

Under optimized conditions (Table 1, entry 5), we verified the substrates scope for benzoylation of *p*-benzoquinone (Figure 2). Benzaldehyde and its derivative with electron-

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Using weak interactions to control C–H mono-nitration of indolines†

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An unprecedented C–H mononitration of indolines either at the $-C_5$ or $-C_7$ positions under mild condition is reported here. The roles of multiple weak interactions and factors such as steric factors, electronic effects, cation–π interactions, and solvent polarity were established, and we achieved a 100% regioselective electrophilic aromatic (EArS) nitration using $Cu(NO_3)_2$ or $AgNO_3$.

Nitroarenes are important synthetic precursors used in various industries such as those involving agrochemicals, pesticides, pharmacology, dyes, and polymers, and the syntheses of nitroarenes are among the most extensively studied chemical reactions.[1] The high synthetic utility of nitroaryl moieties is due to their abundance and easy synthetic transformation to other functional groups such as amino and diazo groups.[1,2] In literature, few of the nitro-substituted indoles known to have potent activity towards tuberculosis.[3]

Regioselective nitration reactions of pharmaceutically important indolines are desirable but challenging due to the unavailability of suitable methods.[4] Aromatic electrophilic nitration (EArS) reactions are generally performed under harsh conditions[5] using conc. HNO_3–H_2SO_4,[6] nitronium tetrafluoroborate,[7] conc. HNO_3-mixed anhydrides,[8] *N*-nitropyridinium salts, $NaNO_3$–TFA,[9] as well as other reagents.[10] Therefore, EArS reactions may cause non-selective nitration of starting materials[4a] or overoxidation of the products. Also, under highly acidic conditions, some functional groups such as –CN and –CHO might be over-oxidised and hence make the isolation procedure tedious.[11] However, selective EArS C–H nitrations are carried out by following transition metal-template strategies.[12] For example, transition metals commonly used in the C–H nitrations[13] include Fe,[14] Pd,[15] Rh, Ru,[16] *etc.* Zhang and co-workers have developed the first *meta*-selective Ru-catalysed C–H nitration using an *ortho*-metalation template strategy (Fig. 1b).[16] Also, using organometallic reagents,[17] *ipso*-nitrations have been reported for systems including aryl boronic acids, carboxylic acids,[18] aryl halides, aryl triflates, *etc.*[19] A reported example by Maiti and co-workers is shown in Fig. 1c for the *ipso*-nitration of aryl boronic acids.[17b]

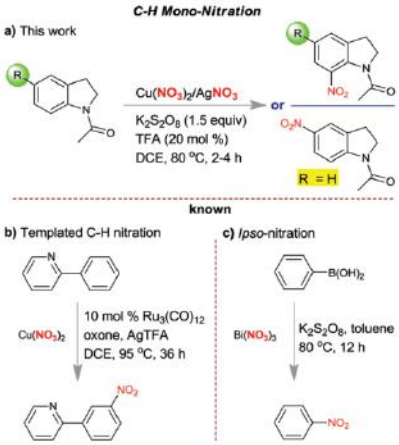

Fig. 1 C–H mono-nitration. (a) Our mono-nitration approach for non-prefunctionalized systems under mild conditions with 100% selectivity. (b) Zhang's Ru-templated *meta*-selective C–H nitration using an *ortho*-metalation template strategy.[16] (c) Maiti's *ipso*-nitration of aryl boronic acids.[17b]

The extents of reactivity of chemical systems have been shown to be altered by the environment.[20] Soft forces[21] of several cooperative noncovalent or weak interactions[22] such as hydrophobic,[23] anion–π,[24] and cation–π[25] interactions are being extensively explored in chemical systems.[26] In the current work, we exploited weak interactions to carry out the $-C_7$– or $-C_5$-selective EArS C–H mono-nitration of indolines (Fig. 1a) using an easy, convenient, and mild[27] approach. To explain the highly selective nature of the mono-nitration reaction, we derived a mechanism of the reaction based on noncovalent interactions and that can be related to the concept of supramolecular catalysis.[28]

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† Electronic supplementary information (ESI) available. CCDC 1550269 and 1550265. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7cc06267b

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Oxidative *N*-Arylation for Carbazole Synthesis by C−C Bond Activation

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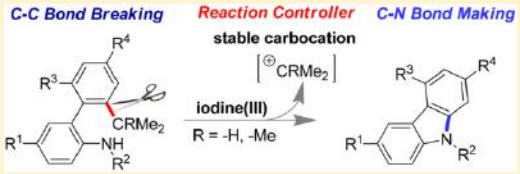
Supporting Information

ABSTRACT: Activation of strong C−C σ-bonds is quite challenging. We report here an intramolecular oxidative *N*-arylation method of biarylsulfonamides via cleavage of C−C bonds toward synthesis of heterocycle carbazoles. The stability of generated carbocations could control the reactivity of a nitrenium ion for the C−N bond formations at the *ipso*-carbon via a retro-Friedel−Crafts-type reaction using hypervalent iodine(III) reagent PhI(OAc)$_2$.



INTRODUCTION

The environmentally benign methods[1−3] for C−N bond synthesis are important in synthetic organic chemsitry.[4−6] Compared to metal-mediated C−N coupling reactions,[7] metal-free C−H amination reactions are more popular.[8,9] Hence, iodine(III)-based reagents are considered as highly efficient oxidants due to their low toxicity and economic viability.[10,11] Many cross-dehydrogenative coupling (CDC) or oxidative cross C−N coupling reactions are reported[12−14] using hypervalent iodine(III) reagents for the construction of numerous heterocyclic scaffolds by C−H and N−H bond functionalization.[10−12,15]

The concept of systems chemistry of small molecules has gained popularity in simplifying difficult chemical reactions.[16] Generally, this approach offers primary insight into the development of techniques to prepare complex supramolecules using weak or noncovalent interactions[17] but is less explored in organic synthesis.[18] Thus, as anticipated, understanding of the thermodynamic and kinetic parameters during chemical transformations may help to design desirable chemical reactions.[19] Also, the stability of certain intermediates like carbocation,[20] formed during the progress of a reaction, can be a reaction-controlling factor. For example, in the Beckmann rearrangement the product selectivity is dependent upon the stability of the group which is anti to the leaving group.[21,22]

Carbazole heterocycles are extensively found in biologically active natural products, pharmaceutical chemistry, and material science.[23] Therefore, considerable attention has been given to develop methods for the efficient synthesis of various carbazoles. However, most of them are based on intramolecular *N*-arylation via C−halogen or C−H bond functionalization reactions. Interestingly, the oxidative C−N coupling reaction for carbazole synthesis at the expense of a C−C bond is possibly unknown. Also, the C−C bond cleavage reactions using iodine(III) reagents have not been explored much.[24]

RESULTS AND DISCUSSION

Herein we demonstrate a C−C bond-breaking method to achieve oxidative C−N bond coupling using phenyliodine diacetate (PhI(OAc)$_2$ or PIDA) as the sole reagent. In general, dealkylation from aromatic rings is achieved through reverse- or retro-Friedel−Crafts (FC) alkylation[25,26] catalyzed by Lewis acids and/or proton.[27] Moreover, the *tert*-butyl group is cleaved more easily than isopropyl or other alkyl groups due to higher stability of the *tert*-butyl carbocation (3° carbocation). In the FC dealkylation reaction, the generated *tert*-butyl group is required to be trapped by another aromatic ring for the follow-up alkylation purpose. In contrast, no dealkylation protocol has ever been used for construction of a C−N bond toward carbazole synthesis. In this work, no external nucleophile was added to stabilize the carbocation for the N−H arylation.

This work was developed based on an intramolecular C−C bond fragmentation reaction which leads to the synthesis of carbazoles from sulfonamides using hypervalent iodine(III) reagent PhI(OAc)$_2$. Thus, synthesis of a C(sp^2)−N(sp^3) bond by replacement of a C(sp^2)−C(sp^3) bond was achieved by an intramolecular oxidative *N*-arylation method. The reactivity of the PIDA-mediated reaction system was probably determined by the stability of the carbocation generated via a nitrenium ion (Figure 1a).[28] Cleavage of *tert*-butyl (^{t}Bu) and isopropyl (^{i}Pr) groups from the aromatic ring was achieved to favor the coupling reaction.

Initially, the reaction of *N*-(5-bromo-2′,4′-di-*tert*-butyl-6′-methyl-[1,1′-biphenyl]-2-yl)methane-sulfonamide (**1a**) and PIDA was performed. The model substrate **1a** was synthesized by dehydrogenative coupling between *N*-(4-bromophenyl)-methanesulfonamide and 1,3-di-*tert*-butyl-5-methylbenzene using 1.0 equiv of PIDA in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) at room temperature.[29] Following, **1a** was treated with

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Electrophilic aryl-halogenation using N-halosuccinimides under ball-milling

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Solvent free

ABSTRACT

We report here a methodology of chemo- and regio-selective aryl bromination and iodination using respective N-halosuccinimides at room temperature in the absence of any solvents, catalyst/additives under ball-milling condition. However, for chlorination ceric ammonium nitrate was used as additive. The coupled product succinimide, produced from the reactions, was recycled via regeneration of NBS. This methodology works with the electron-donor substituted or unsubstituted arenes.

It is essential to minimize the usage of chemicals, solvents and catalysts in routine organic synthesis to do chemical reactions in greener way.[1,2] Aryl halides are well known synthetic intermediates towards the synthesis of natural or pharmaceutical products.[3] The aryl halogenation methodologies are well known over a century but still need modifications because of high demand for better methodologies. For example, bromination reactions using elemental bromine may lead to unwanted side reactions at harsh conditions[4] and chlorination reagents are generally non-eco-friendly. We did focus on a few literature known halogenation procedures relevant to our studies (a) brominations using NBS[5] (N-bromosuccinimide): NBS–acetonitrile,[6] NBS–H_2SO_4–TFA,[7] NBS–BF_3–H_2O,[8] NBS–Al_2O_3 (solvent free condition[9] and Vilsmeier–Haack bromination[10] (b) for chlorinations: NCS (N-chlorosuccinimide)–acetonitrile,[11] NCS–CuCl[12] and NCS–BF_3–H_2O[8] (c) iodinations: NIS (N-iodosuccinimide)–TFA,[13] NIS–In(OTf)$_3$[14] NIS–BF_3–H_2O[8] and NO_2–I_2[15] etc.

We report a synthetic methodology for electrophilic aryl halogenations under ball-milling[16–18] conditions and solvent-free conditions at room temperature. To the best of our knowledge, only one example of aryl-bromination under ball-milling condition using oxone–NaBr is known in literature.[19,20]

Herein, we have demonstrated the bromination and iodination reactions using NBS and NIS, respectively. This methodology works in the absence of any catalyst or additives. However, chlorination was done using NCS–CAN (ceric ammonium nitrate) combination. Interestingly, the coupled product succinimide, obtained from the reaction, was reprocessed for preparation of NBS. It has been found that this newly generated NBS works efficiently without losing its activity. This is an unprecedented example in the literature where NBS and NIS work efficiently in the absence of any additive/catalyst.

The results of aryl brominations are presented in Figure 1. Brominated products were obtained in very good to excellent yield for the derivatives of anilines, anisoles, benzaldehydes, nitrobenzene, alkyl benzenes etc. Taking a few examples into consideration, we are now examining the efficiency of our methodology. As shown in Figure 1, **2h** was prepared in **2 h** using only NBS under ball-milling condition compared to a literature reported procedure in which the bromination was done for 18 h using NBS–TFA–H_2SO_4.[21] We have successfully done the bromination of alkyl benzenes (**2c**–**2f**, Fig. 1) in the absence of hazardous molecular bromine.[4] The ring brominations of anisole derivatives are generally performed in toxic acetonitrile solvent and NBS.[6] However, the synthesis of **2m** was done at 45 min at ambient temperature under ball-milling rather than 24 h at reflux condition (Table 1).[6] In a similar manner we have made a few comparisons with literature reported data and our method (ball milling). These data are shown in Table 1.

The reactions were done under ball-milling condition (frequency 21 Hz), in solid state and at room temperature. The progress of the reactions was monitored by either TLC (thin layer

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SHORT COMMUNICATION

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Solvent-Free Ball-Milling Biginelli Reaction by Subcomponent Synthesis

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Keywords: Synthetic methods / Multicomponent reactions / Mechanochemistry / Biginelli reaction / Ball mill

We report here an understanding of systems chemistry on small molecules through covalent mechanochemistry. As a proof-of-concept, the multicomponent Biginelli reaction by subcomponent synthesis was considered as a model system. Reactions were performed under solvent-free, metal-free, mechanochemical (ball milling) and ambient laboratory conditions. Br^+-catalyzed oxidation of benzyl alcohols led to the product benzaldehydes and byproduct H^+ which were further promoted as component and catalyst, respectively, for a cascade transformation to dihydropyrimidones within the same reaction pot. Remarkably, in solution, the reaction system could not be reproduced at room temperature even after 24 h.

Introduction

Many cascading chemical reactions are involved in the process of haemostasis[1] which causes bleeding to stop. These kinds of biological processes are examples of self-sorting methodologies[2] in systems biology.[3] However, the study of systems chemistry[4] offers a primary understanding into the self-sorting principles[5] of molecular networks that eventually assist us to gain new systems[6] with functions and properties unlike any conventional materials.[7] Also, a subcomponent self-assembly approach[8] under systems chemistry, is a synthetic method in which ligands of metallo-supramolecular complexes are produced in situ from their subcomponents. This systems chemistry method has been established to be a promising technique for the synthesis of high-purity metal complexes from complex mixtures of reactants with a minimum number of reaction steps[9] and possibly unexplored in organic synthesis.

With rising public concern over alternative energy and global warming, it is important to decrease the usage of chemicals in routine chemical synthesis. Essentially, developing recyclable methodology and eliminating waste are important aspects for doing reactions in a greener fashion.[10] Recently, ball-milling mechanochemistry,[11] as a solvent-free method for synthetic transformations has become an area of research interest due to its benefits over solution-based methods.[12] Many advantages are associated during synthesis by mechanochemistry.[11d] This method has huge importance for green processes due to time efficiency, environmentally friendliness and inexpensive synthesis. High yielding reactions, fewer byproducts and minimum purification add extra significance to this method in organic synthesis.[13] Organic synthesis of small molecules by mechanochemistry has been considerably explored,[13a] including multistep synthesis, olefin metathesis,[14] amongst others. In addition, we have also recently explored the research area under mechanochemistry.[9b,10,15] Therefore, we anticipated that ball-milling methodology could possibly be used for the supply of mechanical energy and reactions might be done in environmentally benign way.

Considering these aspects, we are demonstrating here a unique example of a covalent (metal-free) approach in systems chemistry in which subcomponent and catalyst were

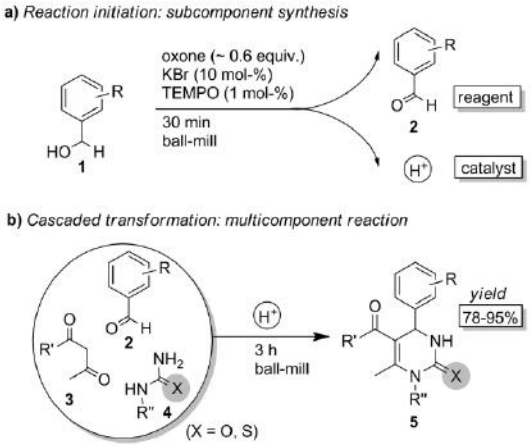

Figure 1. System chemistry model. a) Subcomponent synthesis and b) multicomponent transformation.

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Mechanochemical synthesis of small organic molecules

Tapas Kumar Achar, Anima Bose and Prasenjit Mal*

Review

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Abstract

With the growing interest in renewable energy and global warming, it is important to minimize the usage of hazardous chemicals in both academic and industrial research, elimination of waste, and possibly recycle them to obtain better results in greener fashion. The studies under the area of mechanochemistry which cover the grinding chemistry to ball milling, sonication, etc. are certainly of interest to the researchers working on the development of green methodologies. In this review, a collection of examples on recent developments in organic bond formation reactions like carbon–carbon (C–C), carbon–nitrogen (C–N), carbon–oxygen (C–O), carbon–halogen (C–X), etc. is documented. Mechanochemical syntheses of heterocyclic rings, multicomponent reactions and organometallic molecules including their catalytic applications are also highlighted.

Introduction

The field of organic synthesis has experienced recently significant changes towards achieving the goal of more efficient and sustainable processes [1]. Thus, a new branch of chemistry termed as "Green Chemistry" has become a part of research interest by the chemists [2-4]. Green chemistry covers a wide range of research areas and generally deals with 12 principles [5,6] and few of them are: avoiding the use of volatile and toxic solvents, reducing the quantity of catalyst and reagents, using environmentally benign chemicals, atom-economical synthesis, minimization of chemical-waste/energy, etc. Non-conventional energy sources for chemical reactions such as microwave, mechanical mixing, visible-light and ultrasound are becoming surge of interest to the chemist as alternative energy sources in laboratories [7]. By imposing these techniques innumerable chemical transformations have been documented and thereby developing many existing protocols with superior results are further anticipated [8,9].

To address one of the major issues of green chemistry, i.e., minimizing chemical-waste/energy, solvent-free syntheses have become a popular research topic [8]. The mechanochemical techniques like ball-milling or hand grinding are considered to be promising candidates in solvent-free synthesis [10,11]. Mechanochemical methods deal with chemical transformations induced by mechanical energy, such as compression, shear, or friction [12]. Wilhelm Ostwald, a Russian-German chemist who

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An intramolecular C(sp^3)–H imination using PhI–*m*CPBA†

Anima Bose, ‡ Saikat Maiti, ‡ Sudip Sau and Prasenjit Mal *

Herein, a highly exothermic primary amine–polyvalent iodine reaction has been used successfully for selective functionalization of acidic C(sp^3)–H groups for a dehydrogenative C–H imination reaction by 4H elimination. Overall, C(sp^3)–H imination at 1,5 distances was readily done *via* organocatalysis using PhI (10 mol%)–*m*CPBA under ambient conditions.

Enzyme-mediated selective oxidation of unactivated aliphatic C–H bonds has been well-known since time immemorial. However, it remains a challenge for synthetic chemists due to the unavailability of suitable reagents.[1] C(sp^3)–H bonds are considered to be less reactive than C(sp^2)–H bonds because of their higher thermodynamic stability. Development of synthetic methods for the conversion of undirected C(sp^3)–H bonds to suitable functionalities are of great importance in fundamental research.[2] Therefore, chemists have investigated selective catalysts for functionalization of C–H bonds to C–N bonds *via* a dehydrogenative pathway. The approaches for dehydrogenative C(sp^3)–H amination of non-prefunctionalized systems are mainly known either using a metal catalyzed or by a radical initiated pathway.[3] Compared to C(sp^3)–H aminations, imination reactions are more challenging since the formation of imines from $-CH_2$ and $-NH_2$ combination with 4H elimination is thermodynamically unfavorable.[4] In 2016, Alabugin and co-workers reported a Fe(II)-catalyzed oxidative C–H imination reaction[5] through single electron transfer (SET). Later, the same group established a transition metal-free approach for a similar transformation using ^{t}BuOK under aerobic conditions.[6] Nevertheless, these methods have certain limitations like the use of transition metals as catalysts, strong bases in excess amount, *etc.*

Due to their abundance in pharmaceutically active compounds and natural products, it is hard to exaggerate the significance of nitrogen-based heterocycles. As a result, efforts towards synthesis of C–N bonds have become a fundamental subject of study in organic chemistry.

Dehydrogenative coupling between C–H and N–H bonds represent the state of the art practice in C–N bond synthesis due to non-requirement of prefunctionalization of substrates. Gaunt and co-workers established the synthesis of three membered strained heterocycle aziridine *via* aliphatic C–H amination using a Pd(II)-catalyst (Fig. 1a).[7] Similarly, for the synthesis of γ-lactams by 2H elimination, Shi and co-workers have shown intramolecular C–H amination reaction *via* iodoarene-catalysis (Fig. 1b).[8] Moreover, the present work is based on 4H elimination for direct functionalization of two aliphatic-C(sp^3)H and two aryl-N(sp^3)H intramolecularly at the 1,5 positions. This single step imination protocol works in the absence of any metal or strong base *via* organocatalysis at room temperature (Fig. 1c). Thus an additive-free approach based on intramolecular C(sp^3)–H imination

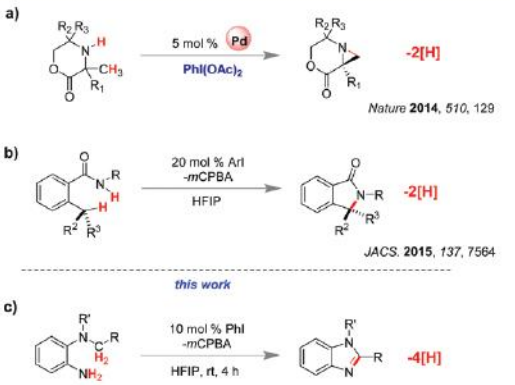

Fig. 1 Iodine(III) in intramolecular aliphatic C–H amination reactions. (a) Gaunt's Pd-catalyzed C–H amination method.[7] (b) Shi's intramolecular C–H amination reaction.[8] (c) Our 1,5-aliphatic-CH_2–aryl-NH_2 imination approach using organocatalysis.

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CHAPTER 9

Soft Forces in Organic Synthesis by C–N Coupling Reactions

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9.1 Introduction

When considering controlling the reactivity of chemical systems *via* soft force relay, it is necessary to understand the functions of living systems or generate novel structures with functions. Importantly, the reactivity of chemical systems is known to be altered by the surroundings.[1–6] Therefore, the soft forces[7,8] of several low-energy and low-level multiple cooperative noncovalent or weak interactions[9] such as charge transfer,[10] hydrophobic effect,[11] anion–π,[12] cation–π[13–15] and halogen bonding[16,17] are undergoing considerable exploration in chemical[18,19] and biological systems[20] in the research area of supramolecular organic chemistry.[21–25]

These noncovalent interactions are important in understanding the structure and functions of biomacromolecules such as DNA, RNA and proteins.[26]

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Mechanochemistry of supramolecules

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Review

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Abstract

The urge to use alternative energy sources has gained significant attention in the eye of chemists in recent years. Solution-based traditional syntheses are extremely useful, although they are often associated with certain disadvantages like generation of waste as by-products, use of large quantities of solvents which causes environmental hazard, etc. Contrastingly, achieving syntheses through mechanochemical methods are generally time-saving, environmentally friendly and more economical. This review is written to shed some light on supramolecular chemistry and the synthesis of various supramolecules through mechanochemistry.

Introduction

In living systems an important aspect is to create complex functional molecules from simpler units by following biomolecular mechanisms [1]. The biological assemblies for living beings are developed from processes of spontaneous self-assembly with a high degree of compartmentalization [2]. In addition, the same building units are often used across an enormous number of structures in a reversible fashion through thermodynamic control [3]. Conversely, small-molecule synthesis is generally performed under kinetically controlled reaction conditions through covalent approaches. By using common synthetic methodologies chemists are able to proficiently synthesize a variety of both natural and unnatural molecular scaffolds [4-6].

The era of supramolecular chemistry began with the introduction of coordination theory by Alfred Werner in 1893 [7] followed by the lock-and-key concept of Emil Fischer in 1894 [8]. Weak or non-covalent interactions had been used systematically in the early 1960s by Lehn, Cram and Pederson to create targeted supramolecular architectures [9]. Small molecules, anions or cations could be assembled spontaneously to form supramolecular structures through self-assembly processes by exploiting the weak or non-covalent interactions [10]. Self-assembly is a kinetically reversible process which is more efficient than traditional stepwise synthesis concerning large molecules. Some recent developments in supramolecular chemistry are dynamic combinatorial chemistry [11], subcomponent self-assembly approach [12-14], and systems chemistry [15-18], etc.

There also has been growing interest towards exploration of nontraditional energy sources like visible light [19,20], micro-