# Synthesis of Deuterated and Novel Heterocyclic Compounds *via* Metal Mediated Organic Transformations

*BY*

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***For the degree of***

**DOCTOR OF PHILOSOPHY**
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**MANOJKUMAR JANNI**

# DECLARATION

I, hereby declare that the investigation presented in the thesis has been carried out by me. The work is original and has not been submitted earlier as a whole or in part for a degree / diploma at this or any other Institution / University.

**MANOJKUMAR JANNI**

# List of Publications

**Papers Published**:

1. *Trideuteromethoxylation of Aryl and Heteroaryl Halides*
   Pragyanditi Dash, Manojkumar Janni and S. Peruncheralathan,
   *Eur. J. Org. Chem.*, **2012**, 4914.
2. *Catalytic Selective Deuteration of Halo(hetero)arenes*
   Manojkumar Janni and S. Peruncheralathan,
   *Org. Biomol. Chem.* **2016**, *14*, 3091 - 3097.
3. *Double heteroannulation of S,N-acetals: a facile access to quinolone derivatives*
   Manojkumar Janni, Sahil Arora and S. Peruncheralathan,
   *Org. Biomol. Chem.* **2016**, *14*, 8781 - 8788.

**Manuscript Under Preparation**:

1. Palladium Catalyzed Tandem Intramolecular Cyclizations: A Facile Access to Thieno[1,2-*b*]quinolone Derivatives.

2. Copper Catalyzed Tandem C—S & C—N Cross-Coupling Reactions: A Facile Access to Thioanalogoues of Cryptolepine Derivatives.

3. Chemoselective Copper Catalzed Thiolation of *S*-Arylation at Ambient temperature: A facile Access to 2-Aminobenzo[*b*]thiophenes

## Conferences Attended

1. Participated in **Royal Society of Chemistry Publishing Workshop** held on 23rd September, 2016, NISER-Bhubaneswar, India.

2. Poster (*Metal-Free Regioselective Intramolecular Amination of α-Oxo Ketene N,S-Acetals: A Facile Access to 4-Quinolones and Its Derivatives*) (**PP-84**) presented in **XI-JNOST** Conference for Research Scholars (**J-NOST**) held on (14-17)th December 2015, NISER-Bhubaneswar, India.

3. Poster (*Room Temperature Copper Catalyzed C—S Cross-coupling Reaction: A Facile Access to 2-Aminobenzo[b]thiophenes*) (**PP-60**) presented in **X-JNOST** Conference for Research Scholars (**J-NOST**) held on (4-6)th December 2014, IIT-Madras, India.

4. Poster (*Copper Catalyzed Tandem C—S & C—N Cross-coupling Reactions: A Facile Access to Thioanalogous of Cryptolepine Derivatives*) presented in **Indo-French Symposium on Metal Organic Frameworks** held on (24-26)th February 2014, NISER-Bhubaneswar, India.

5. Oral presentation (*Deuteration of Aryl and Heteroaryl Halides)* given in **VIII-JNOST** Conference for Research Scholars (**J-NOST**) held on (15-17)th December, 2012, IIT-Guwahati, India.

6. Attended the **Indo-European Symposium** on Frontiers in Chemistry (10-12 Nov, 2011), NISER, Bhubaneswar, India.

7. Attended the National Seminar on **Frontiers in Chemistry** (11-14 Nov, 2010), NISER, Bhubaneswar, India.

**MANOJKUMAR JANNI**

*Dedicated to*

*My Parents*

*&*

*My wife*

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***Above all, Thank You GOD for everything…..***

*Manojkumar Janni*

# CONTENTS

# SYNOPSIS

Name of Student: **Manojkumar Janni**

Degree for which submitted: **Ph.D**

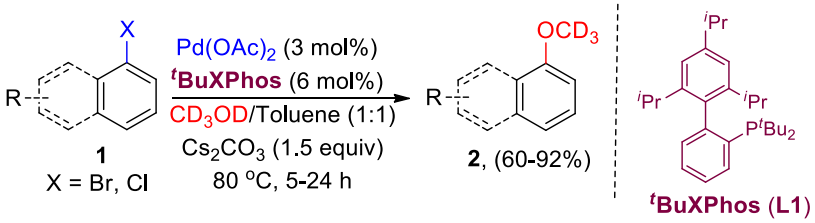
Title of the Thesis: "**Synthesis of Deuterated and Novel Heterocyclic Compounds *via* Metal Mediated Organic Transformations**"

Name of Thesis Supervisor: **Dr. S. Peruncheralathan**

The thesis has been divided into five chapters.

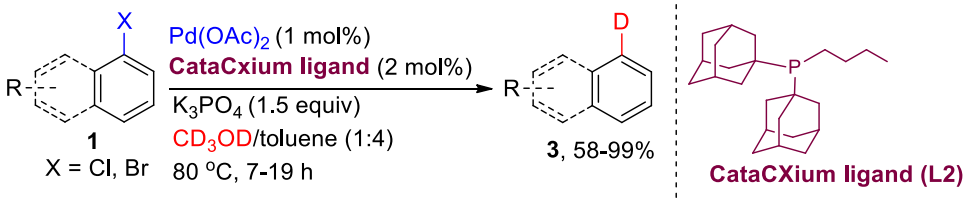
In the **first chapter** of the thesis, a brief description of C—N bond forming reactions and tandem cross-coupling reactions of functionalized haloarenes has been discussed.

The **second chapter** of the thesis describes the synthesis of trideuteromethoxylated and deuterated compounds by using palladium catalysts. Initially, the C—O cross coupling reaction of 1-bromonaphthalene (**1a**) with $CD_3OD$ was investigated as a model system in the presence of 5 mol % $Pd(OAc)_2$ and various commercially available phosphane ligands (10 mol%). Gratifyingly, the experiment performed in the presence of $^t$BuXPhos (**L1**) ligand provided corresponding trideuteromethoxylated naphthalene (**2a**) with very good yield (83%). We also screened different metal salts & bases and found that those were less beneficial when compared with $Pd(OAc)_2$ and $Cs_2CO_3$. Interestingly, we observed that preactivation of $Pd(OAc)_2$ (3 mol%) and **L1** (6 mol%) in toluene at 80 °C followed by subsequent addition of 1-bromonaphthalene (**1a**) in $CD_3OD$ gave an improved yield (90%). With the optimized conditions, we examined several activated and non-activated aryl/heteroaryl bromides and chlorides **1**. These bromides and chlorides **1** were effectively coupled with $CD_3OD$ affording the corresponding trideuteromethoxylated products **2** in moderate to excellent yields (Scheme 1).




**Scheme 1**

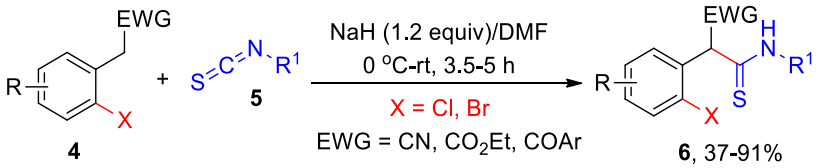
During this study, we observed that few ligands gave a mixture of deutero and trideuteromethoxy aromatic compounds. To accomplish an exclusive deuterated product, we started the optimization studies with commercially available phosphane ligands for deuteration of aryl halides. The reaction of 2-bromonaphthalene (**1b**) with $CD_3OD$ was investigated as a model system in the presence of 5 mol% $Pd(OAc)_2$ and 5-10 mol% ligands. In most of the cases, the reaction was completed within 12 hours; however yield of the product **3a** was ranging from 45 to 72%. When an experiment performed in the presence of cataCXium®A (**L2**) ligand provided an improved yield of 94%. For further fine tuning of this process, other palladium precursors such as $PdCl_2(MeCN)_2$, $PdCl_2(PPh_3)_2$ and $Pd_2(dba)_3$ were screened and found to be less beneficial when compared with $Pd(OAc)_2$. However, in case of bases, $K_3PO_4$ gave better yield as compared with KOH, $Et_3N$, $K_2CO_3$ and $Cs_2CO_3$. Interestingly, we obtained quantitative yield of **3a** when the catalyst loading was reduced from 5 mol% to 1 mol% and reaction was completed within 16 hours. With the optimized conditions, we screened several activated and non-activated aryl/heteroaryl bromides and chlorides **1**. These bromides and




**Scheme 2**

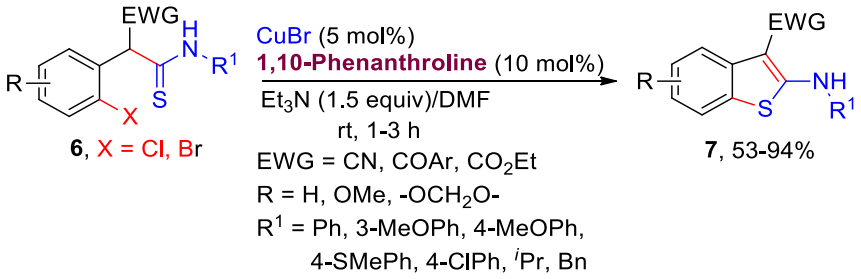
chlorides **1** were effectively deuterated and furnishing the corresponding deutero compounds **3** in 58-99% yields with >98% deuterium incorporation (Scheme 2).

The **third chapter** of the thesis deals with copper catalyzed facile room temperature intramolecular C—S coupling of thioamides **6** for synthesis of 2-aminobenzo[*b*]thiophenes **7**. The required thioamides **6** were prepared from the 2-halobenzyl derivatives **4** in moderate to very good yields (Scheme 3).




**Scheme 3**

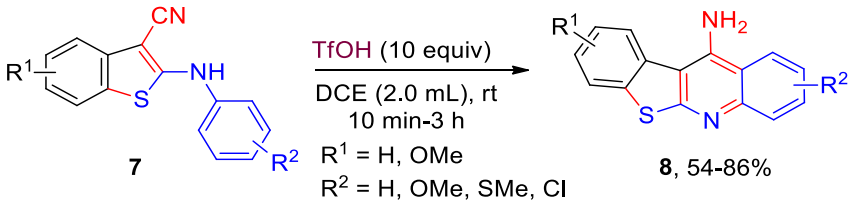
First, we studied 2-(2-bromophenyl)-2-cyano-*N*-phenylthioacetamide [$R^1$ = H, $R^2$ = Ph, X = Br, EWG = CN] (**6a**) as a model system for C—S coupling reaction. Our choice was CuI and 1,10–phenanthroline (**L3**). When we performed intramolecular C—S coupling under this reaction conditions, 2-aminobenzo[*b*]thiophene **7a** was obtained in 84% yield. To improve the




**Scheme 4**

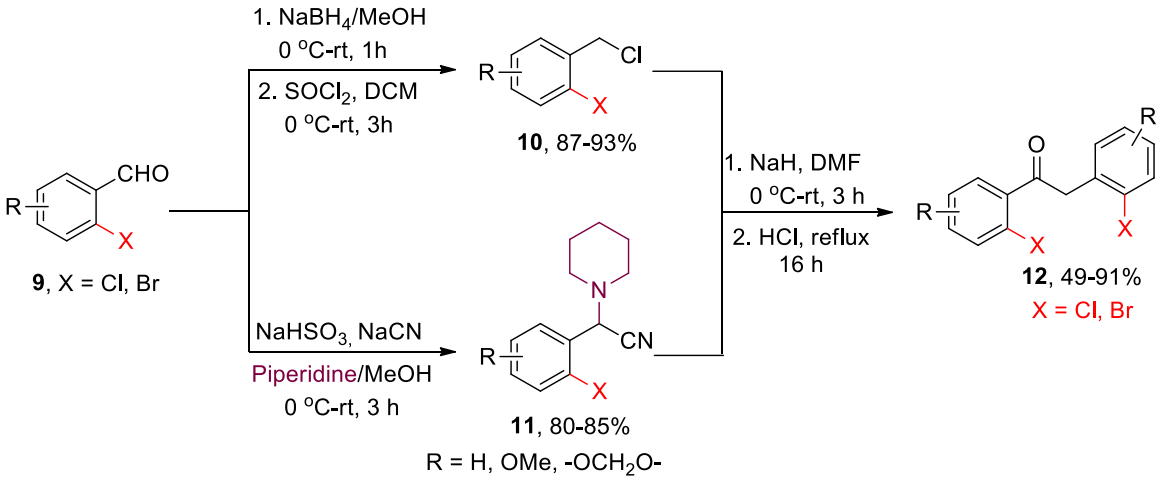
yield of the product **7a**, various conditions were screened by combining metal salts, ligands, bases & solvents. We found that CuBr (5 mol%), 1,10–phenanthroline (**L3**) (10 mol%), $Et_3N$ and DMF were the best combination to accelerate the C—S coupling at room temperature and yielded 88% of the isolated product **7a**. Without ligand, the yield of the product **7a** was dropped drastically (13%). With the optimized combination, we have synthesized various 2-aminobenzo[*b*]thiophenes **7** in 53-94% yields (Scheme 4).

Next, we turned our attention towards functionalization of 2-aminobenzo[*b*]thiophene derivatives **7**. Our initial interest was activation of nitrile by brønsted acid and followed by intramolecular Friedel-Craft reaction to synthesis benzothieno quinolines **8**. In this context, various brønsted acids were screened and TfOH was found to be effective for Friedel-Craft type cyclization. Thus, 2-aminobenzo[*b*]thiophenes **7** were easily transformed into benzothieno quinolines **8** in 54-86% yields (Scheme 5). *This core of heterocyclic compound is unknown in literature*.

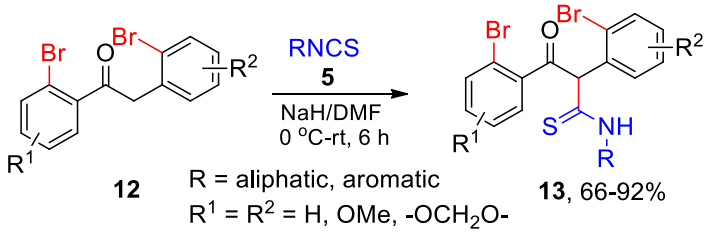



**Scheme 5**

The **fourth chapter** of the thesis describes a highly controlled tandem coupling reaction of dihalo substituted *β*-ketothioamide derivatives **13**. Designing a new tandem reaction is a challenging task. Especially, a selective carbon-hetero bond formation is always important for synthesis of newer heterocyclic cores with diversed structural and functional groups. We designed a new class of *β*-ketothioamides **13** where multiple carbon-hetero bonds can be formed in a single synthetic operation. The challenging task of the present chapter is a controlled carbon-hetero bond coupling reaction. The synthetic protocols for designed *β*-ketothioamides **13** were depicted in Schemes 6 & 7. We have synthesized handful amount of various *β*-ketothioamides **13** for tandem coupling reactions. All newly synthesized thioamides **13** were characterized by Spectruml and analytical data.



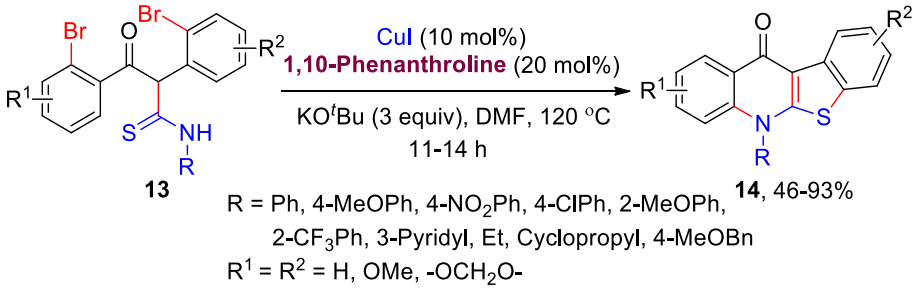

**Scheme 6**




**Scheme 7**

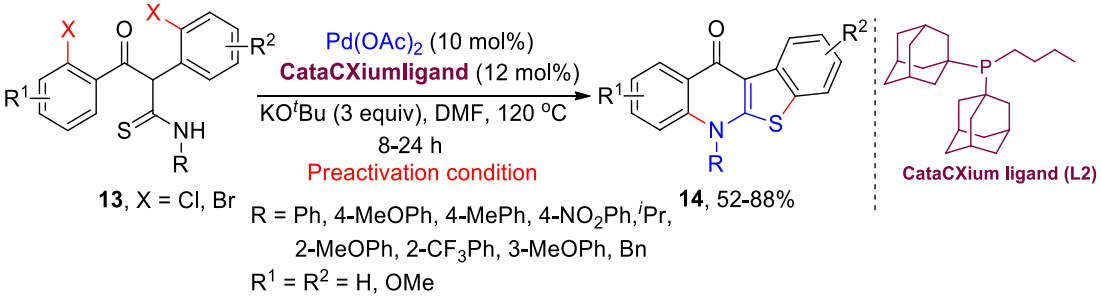
The 2,3-bis(2-bromophenyl)-3-oxo-*N*-phenylpropanethioamide [R = Ph, $R^1$ = $R^2$ = H] (**13a**) was choosen as model system for present tandem reaction. Thus, thioamide **13a** was treated with CuI (10 mol%), 1,10-phenanthroline (**L3**) (20 mol%) and KO$^t$Bu (3 equiv) in DMF at room temperature. After several hours, the reaction mixture gave multiple products formation. Therefore, we performed reaction in various temperatures for our initial optimization studies. Gratifyingly, at 120 °C the reaction mixture was yield a single product and characterized as benzo[*b*]thiopheno fused quinolone **14a**. The structure of the compound **14a** was confirmed by single crystal X-ray analysis. Other conditions such as ligands, metal salts, bases & solvents were screened. We found that $Cs_2CO_3$ and DMF were turned to be the best. Absence of ligand, yield of the product was decreased by 60%. With the optimized conditions in our hand, various benzo[*b*]thiopheno fused quinolones **14** were synthesized from

respective *β*-ketothioamides **13**. To best of our knowledge, benzo[*b*]thiopheno fused quinolone skeleton **14** is not reported in literature.



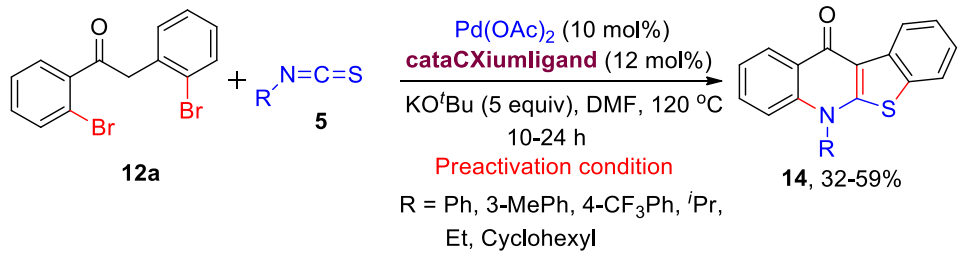

**Scheme 8**

We also examined tandem coupling reaction of thioamides **13** under palladium catalyst. Initially, we screened various phosphene based ligands, palladium salts, bases & solvents at 120 °C. We found that $Pd(OAc)_2$ (10 mol%), cataCXium®A (**L2**) ligand (12 mol%) and KO*t*Bu were the best combination for tandem coupling and yield the expected product **14a** in 88%. To best of our knowledge cataCXium®A (**L2**) ligand is never been used for C—S & C—N coupling reaction. The optimized conditions were suitable for other thioamides **13**. Several benzo[*b*]thiopheno fused quinolones **14** were synthesized under similar conditions.



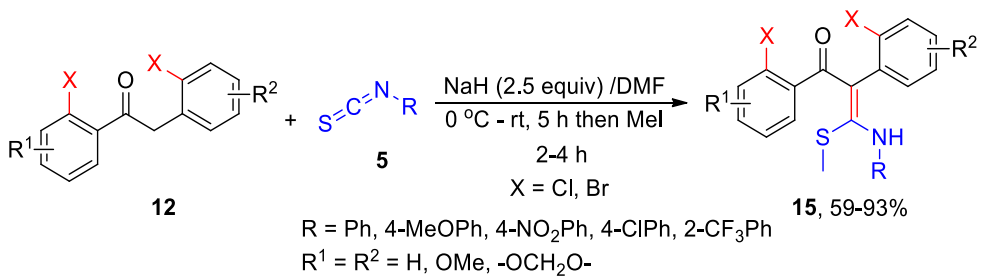

**Scheme 9**

Interestingly, a two component tandem reaction was also studied under optimized conditions. Although the yield of the reaction was lower, one synthetic step was minimized. The results were shown in Scheme 10.



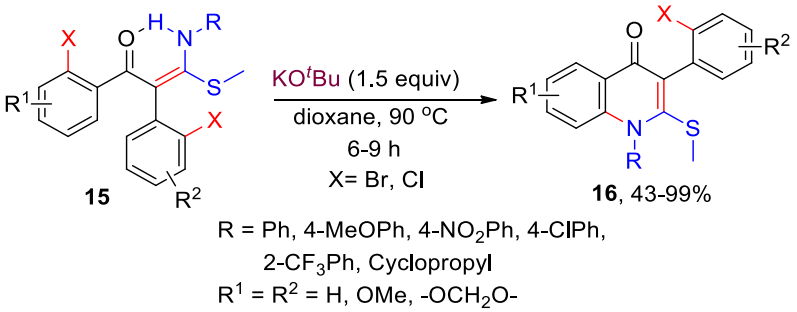

**Scheme 10**

The **fifth chapter** of the thesis describes the synthesis of 4-quinolones **16** *via* a metal-free regioselective intramolecular amination of *α*-(2-haloaroyl)ketene *N,S*-acetals **15**. The synthetic precursors **15** were synthesized from deoxybenzoins **12** and isothiocyanates **5** (Scheme 11).



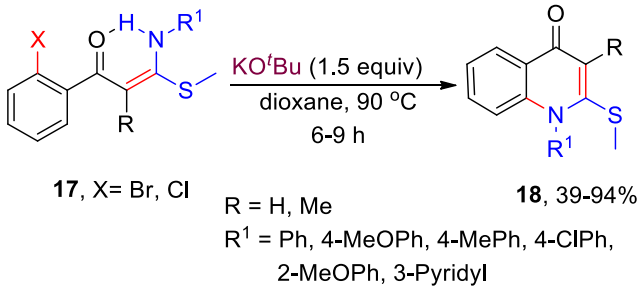

**Scheme 11**

We took 1,2-bis(2-bromophenyl)-3-(methylthio)-3-(phenylamino)prop-2-en-1-one [R = Ph, $R^1 = R^2 = H$, X = Br)] (**15a**) as a standard system and KO$^t$Bu as a base for a regioselective intramolecular amination process. Our initial optimization, we screened different solvents. Among them, dioxane was the best and 90% of 4-quinolone **16a** was isolated. No other product was formed. We also examined various bases. However, results were not satisfactory. Interestingly, we performed the reaction in a sealed tube, the quinolone **16a** was obtained in a quantitative yield. With the optimized conditions we synthesized various 4-quinolones **16** from the respective *α*-(2-haloaroyl)ketene *N,S*-acetals **15** (Scheme 12).



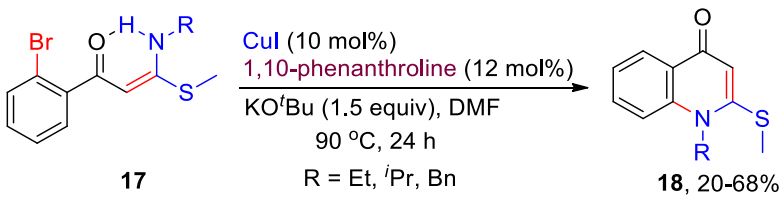

**Scheme 12**

We also studied the scope of the intramolecular amination process with other substrates **17**. The most of case yield of products **18** were moderate to excellent. The results were described in Scheme 13.



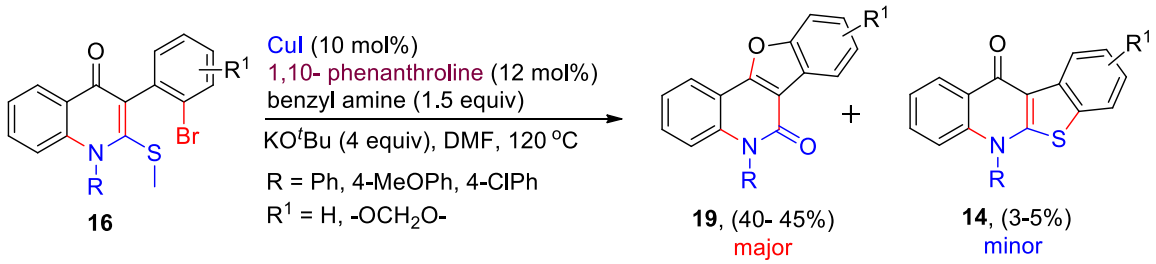

**Scheme 13**

However, alkyl substituted amines did not give the expected quinolone products. This may be due to aryl groups play a crucial role in intramolecular amination process. This problem was solved when we used CuI/1,10-phenanthroline (**L3**) combination. The aliphatic substituted *α*-oxo ketene *N,S*-acetals **17** were also converted into their corresponding 4-quinolones **18** (Scheme 14).




**Scheme 14**

When we attempted to replace SMe group by benzylamine under copper catalyzed conditions, we found two interesting products. One product was major and other one was minor. The minor one was characterized as benzothiopheno fused quinolone **14** which was synthesized in previous chapter. The major product was characterized as benzofurano fused quinolone **19** (Scheme 15). The proposed structure was further confirmed by single crystal X-ray analysis.




**Scheme 15**

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# List of Schemes

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# List of Abbreviations

| | |
|---|---|
| Ac | Acetyl |
| AIBN | 2,2′-Azobis(2-methylpropionitrile) |
| Anhyd | Anhydrous |
| Ar | Aryl |
| Bn | Benzyl |
| BrettPhos | 2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′biphenyl |
| Bz | Benzoyl |
| (*R*)-BINOL | *(R)*-(+)-1,1′- Binaphthyl-2,2′-diol |
| (*R*)-BINAM | (*R*)-(+)-1,1′-Binaphthyl-2,2′-diamine |
| (±)-BINAP | Racemic-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene |
| Boc | Tertiary butoxy carbonyl |
| CAN | Ceric ammonium nitrate |
| *cataCXium®A* | Di-(1-adamantyl)-*n*-butyl phosphine |
| Cp | Cyclopentyl |
| Cy | Cyclohexyl |
| Cbz | Carboxybenzyl |
| DABCO | 1,4-Diazabicyclo[2.2.2]octane |
| *DavePhos* | Dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl |
| dba | Dibenzylideneacetone |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DCC | *N,N′*-Dicyclohexylcarbodiimide |
| DCM | Dichloromethane |
| DDQ | 2,3-Dichloro-5,6-dicyanobenzoquinone |
| DIPEA | *N,N′*-Diisopropylethylamine |
| DIPP | *N,N*-Diisopropyl phosphoamino |
| DMA | *N,N′*-Dimethylacetamide |
| DMAP | 4-(Dimethylamino)pyridine |
| DMB | 2,4-Dimethoxybenzyl |
| DMEDA | *N,N′*-Dimethylethylenediamine |

| | |
|---|---|
| DME | Dimethoxyethane |
| DMF | *N,N*-Dimethylformamide |
| DMSO | Dimethyl sulfoxide |
| DpePhos | Bis[(2-diphenylphosphino)phenyl] ether |
| *dppf* | Bis(diphenylphosphino)ferrocene |
| dppe | 1,2-Bis(diphenylphosphino)ethane |
| dppp | 1,3-Bis(diphenylphosphino)propane |
| *dr* | Diastereomeric ratio |
| dtbdppf | 1-Di-tert-butyl-1′-diphenylphosphino ferrocene |
| DTBB | 4,4′-Di-tert-butylbiphenyl |
| *ee* | Enantiomeric excess |
| equiv | Equivalents |
| Et | Ethyl |
| EWG | Electron withdrawing group |
| h | Hours |
| (Het)Ar | Heteroaryl |
| $^{i}$Bu | Isobutyl |
| $^{i}$Pr | Isopropyl |
| KIE | Kinetic isotope effect |
| LiHMDS | Lithium bis(trimethylsilyl)amide |
| LDA | Lithium diisopropylamide |
| Me | Methyl |
| Me-Phos | 2-Dicyclohexylphosphino-2′-methylbiphenyl |
| min | Minutes |
| MOM | Methoxymethyl ether |
| Ms | Mesyl |
| MW | Microwave |
| (±)-MOP | Racemic-2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl |
| NaHMDS | Sodium bis(trimethylsilyl)amide |
| $^{n}$Bu | *n*-Butyl |
| $^{n}$Pr | *n*-Propyl |

| | |
|---|---|
| NMP | *N*-Methyl -2-pyrrolidone |
| OMe | Methoxy |
| PEG | Polyethylene glycol |
| PEPPSI-IPr | [1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloro pyridyl)palladium(II) dichloride |
| Ph | Phenyl |
| 1,10-phen | 1,10-Phenanthroline |
| PMP | *p*-Methoxy phenyl |
| PPA | Polyphosphoric acid |
| rt | Room Temperature |
| $S_NAr$ | Aromatic substitution reaction |
| S-Phos | Dicyclohexyl(2′,6′-dimethoxybiphenyl-2-yl)phosphine |
| $^t$Bu | Tertiary butyl |
| $^t$BuBrettPhos | 2-(Di-*tert*-butylphosphino)-2′,4′,6′-triisopropyl-3,6-dimethoxy-1,1′-biphenyl |
| *$^t$BuXPhos* | 2-Di-t-butylphosphino-2',4',6'-*tri*-i-propyl-1,1'-biphenyl |
| *trippyPhos* | 1-[2-[Bis(*tert*-butyl)phosphino]phenyl]-3,5-diphenyl-1*H*-pyrazole |
| TEMPO | 2,2,6,6-Tetramethylpiperidine 1-oxyl |
| TFA-$d_1$ | Deuterated trifluoracetic acid |
| TFE | Tetrafluoroethylene |
| THF | Tetrahydrofuran |
| TMEDA | *N*,*N*,*N*′,*N*′-Tetramethylethane-1,2-diamine |
| TMG | 1,1,3,3-Tetramethylguanidine |
| TMS | Tetramethylsilane |
| Tf | Triflyl |
| Ts | Tosyl |
| *TrixiePhos* | Racemic-2-di-t-butylphosphino-1,1'-binaphthyl |
| Xantphos | 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene |
| W | Watts |
| wt | Weight |

# General Introduction of C—N Bond Formation and Tandem Cross-Coupling Reactions

## 1.1 Introduction

Chemistry is in part an illustrative science, which allows the discovery and the fundamental understanding of natural phenomena. But the most exciting part of chemical sciences is a creative experimental science. Indeed, chemical synthesis provides unique possibilities to create highly valuable substances.[1] In early 19th century, the synthesis of C—C bonds was typically done by either pericyclic reactions or by reactions of reactive nucleophiles and electrophiles. Further, copper mediated homo coupling reactions such as Glaser, Ullmann

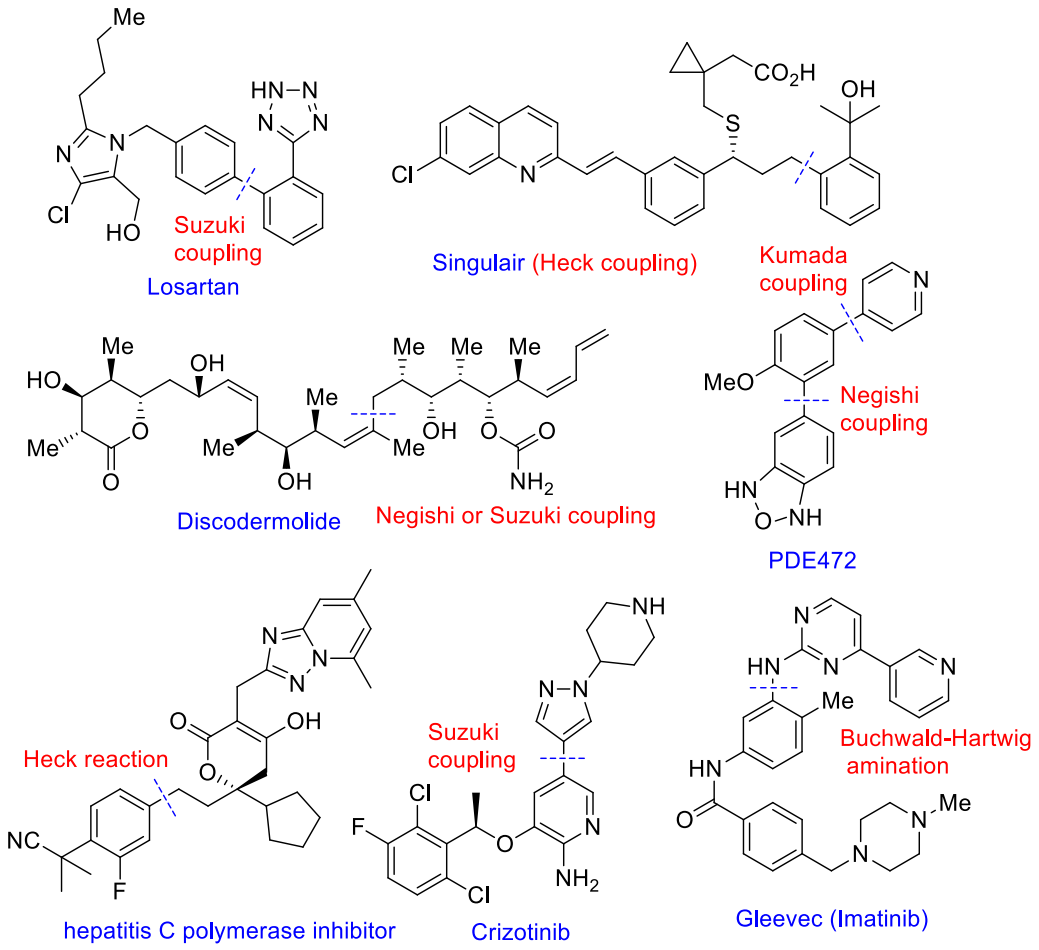
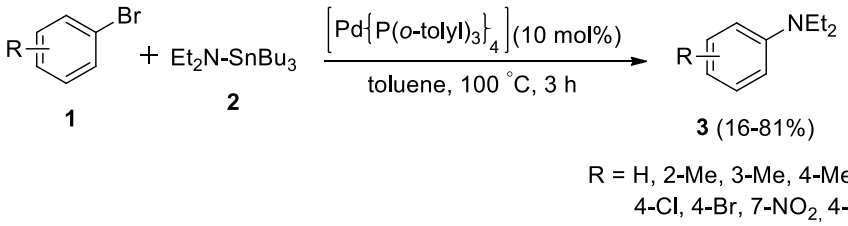



**Figure 1.1**: *Coupling Reactions in Selected Natural Products and Drug Synthesis*

and Kharasch reactions are also used for C—C bond formations. After decades of extensive research on transition metal promoted reactions, nowadays, these reactions have emerged as very powerful tools for the construction of C—C and C—Y (Y = O, N, S, etc) bonds in organic synthesis. Especially palladium catalyzed cross-coupling reactions such as Suzuki, Heck, Negishi, Stille, Sonogashira have created a fascinating history to make complex natural products and molecules in a simple and highly efficient manner. In 2010, Suzuki, Heck, Negishi received the noble prize in chemistry for their discovery of palladium catalyzed cross-couplings in organic synthesis. Several natural products and drugs were synthesized by palladium catalyzed cross-coupling reactions, among them selected one shown in Figure 1.1.[2] This chapter describes a general introduction of copper and palladium catalyzed carbon-heteroatom cross-coupling reactions with special emphasis on tandem reactions.

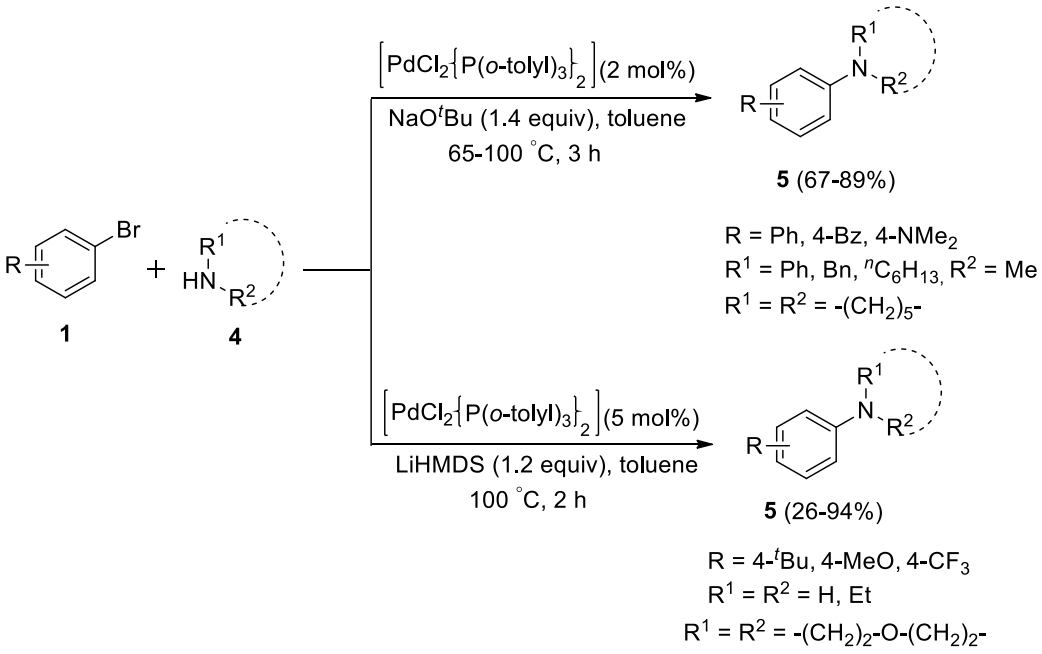
In 1983, Migita and co-workers reported the first palladium catalyzed C—N bond formation of arylbromides **1** by using toxic and moisture sensitive *N,N*-diethylamino-tributyltin (**2**) as amine equivalent (Scheme 1.1).[3] Due to lack potential utility and cost of the coupling partner, chemists devoted time to develop conditions which allowed to use simple amine as coupling partner.




**Scheme 1.1**: *The Migita Amination of Aryl Bromides **1***

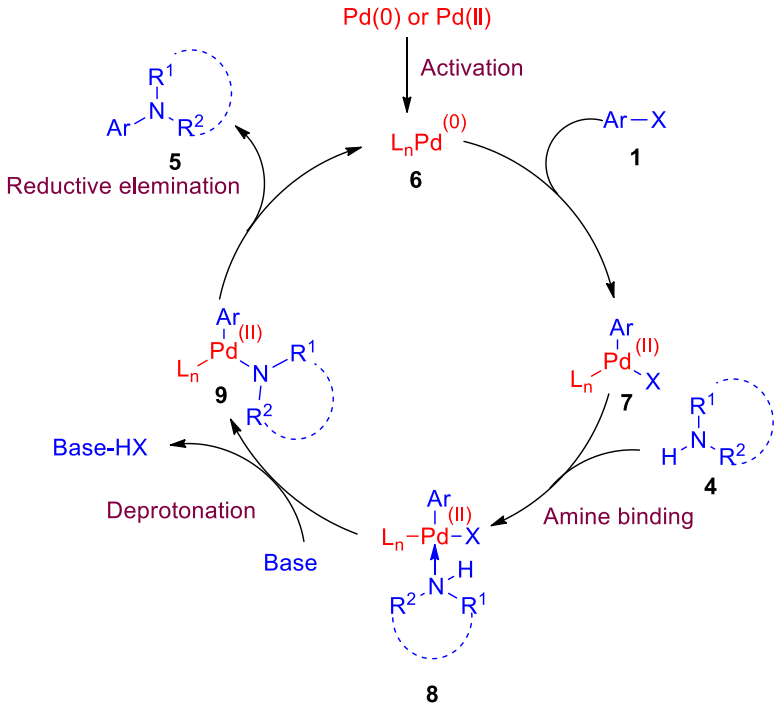
After 12 years, Buchwald[4] and Hartwig[5] independently reported the cross-coupling reactions of aryl halides with free amine by using a strong base such as LiHMDS or NaO$^t$Bu in the presence of a catalytic amount of $PdCl_2(o\text{-}tol_3P)_2$ (Scheme 1.2). These methods replaced

the Migita amidotin reagent. After these reports, the C—N coupling reactions have received noteworthy attention among synthetic chemists. Rapidly, new conditions were developed for practical C—N coupling reactions. Further these results led to the establishment of the C—O bond forming cross-coupling processes, replacing the Ullmann reaction.[6] Furthermore, these reactions together with C—S and C—P cross coupling reactions are regularly used in chemical synthesis.[7]




**Scheme 1.2**: *Buchwald–Hartwig C—N bond Forming Reaction*

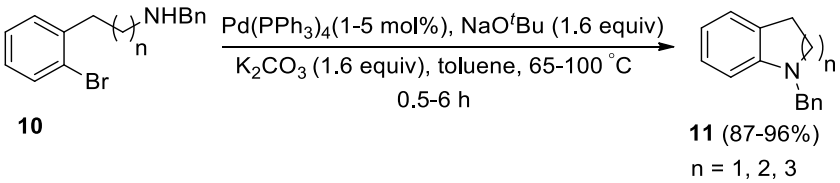
The general mechanism for C—N bond formation is given in Scheme 1.3. The precatalyst forms a Pd(0)−ligand complex **6** that undergoes oxidative addition with the aryl halide **1**. In the next step, the amine nucleophile **4** is coordinated to the metal and deprotonated by the base. The catalytic cycle is closed by reductive elimination, yielding the final arylated amine **5** product while regenerating the active catalyst **6** (Scheme 1.3).




**Scheme 1.3**: *Catalytic Cycle for Buchwald-Hartwig Amination*

## 1.2 Methods for the Synthesis of Fused Heterocycles *via* Intramolecular Amination and Amidation Processes

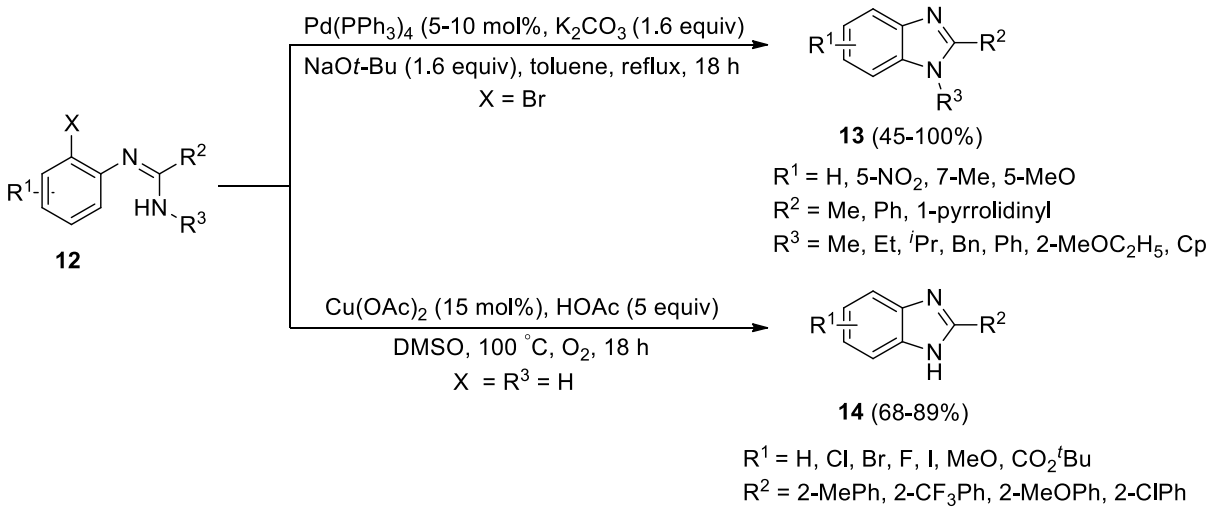
In 1996, Buchwald group reported a method for the palladium catalyzed intramolecular aryl amination of aryl halides. While screening the various palladium catalysts and bases, they found that the combination of $Pd(PPh_3)_4$ and a mixture of bases $KO^tBu/K_2CO_3$ were suitable for the intramolecular cylization of amino arylhalides **10** to form five, six and seven membered heterocycles (Scheme 1.4).[8]




**Scheme 1.4**: *Palladium Catalyzed Intramolecular Amination of Aryl Bromides **10***

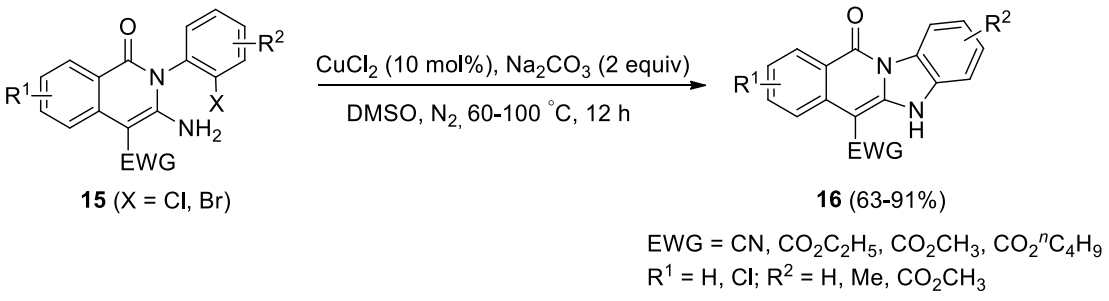
Early 2002, Brain and Brunton demonstrated a novel synthesis of benzimidazoles **13** from (2-bromoaryl)amidine precursors **12** (Scheme 1.5).[9] After six years, Buchwald and

Brasche synthesized benzimidazoles **14** from aryl amidines **12** through a copper catalyzed C—H functionalization/C—N bond-forming process. The method was applicable to wide range of functional groups and provides the substituted benzimidazoles **14** with up to 89 % yield (Scheme 1.5).[10]



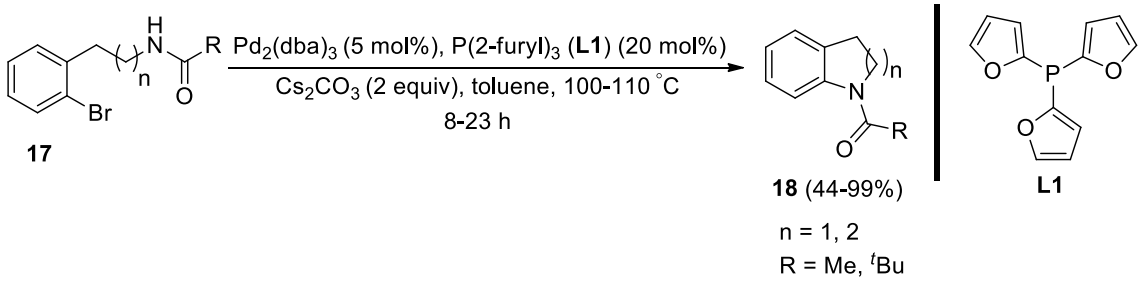

**Scheme 1.5***: Palladium & Copper Catalyzed Intramolecular Aryl Aminations*

Fu and co-workers described an efficient copper catalyzed intramolecular amination process for the synthesis of benzimidazo[1,2-*b*]isoquinolin-11-one derivatives **16** from 3-amino-isoquinolone derivatives **15** (Scheme 1.6),[11] which is formed by the reaction of 2-halo-*N*-(2-haloaryl)benzamide derivatives with alkyl 2-cyanoacetates or malononitrile under mild reaction conditions.



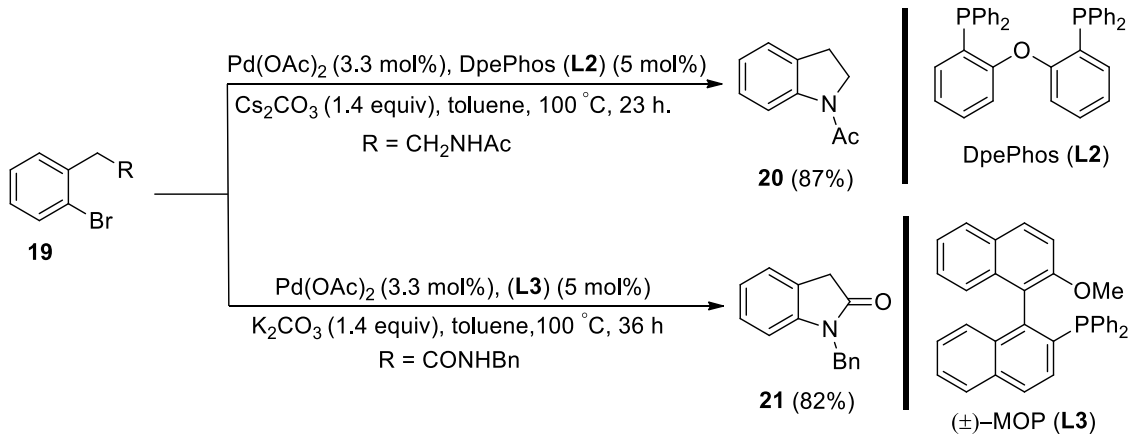

**Scheme 1.6**: *Copper Catalyzed Intramolecular Amination of Aryl Halides*

In 1996, Buchwald developed a new method for the palladium catalyzed intramolecular cyclization of amides **17** (Scheme 1.7).[8] After screening the various ligands and bases, they found that the catalyst obtained from the $Pd_2(dba)_3$ and P(2-furyl)$_3$ (**L1**) was more efficient for the intramolecular amidation process of bromo substituted amides **17** affording indoline derivatives **18**.




**Scheme 1.7**: *Palladium Catalyzed Cyclization of Amides **17***

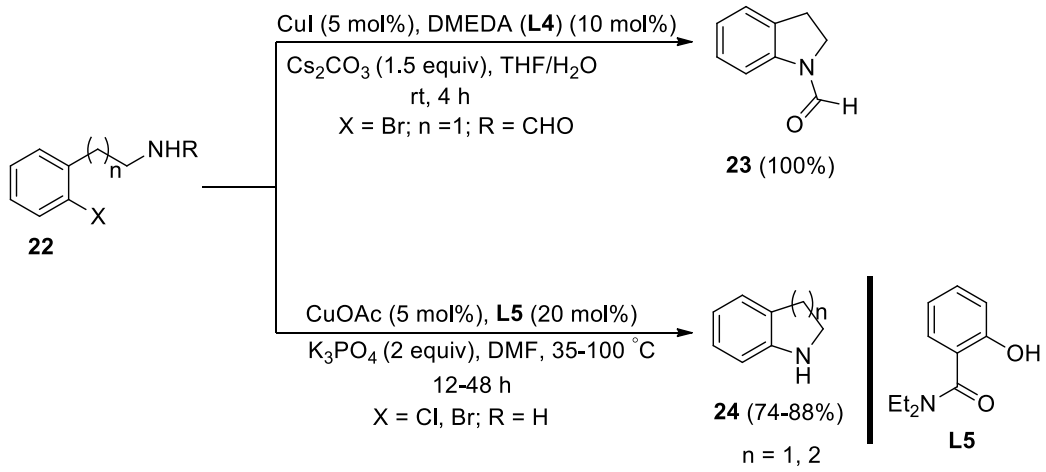
The same group also established another efficient protocol for the palladium catalyzed cyclizations of secondary amides and carbamates (Scheme 1.8).[12] This process resulted from the fine tuning of several palladium catalysts, ligands, and bases. Thus, the proper choice of metal salt, ligand and base are crucial for intramolecular amination process.




**Scheme 1.8**: *Palladium Catalyzed Cyclizations of Secondary Carbamates and Amides*

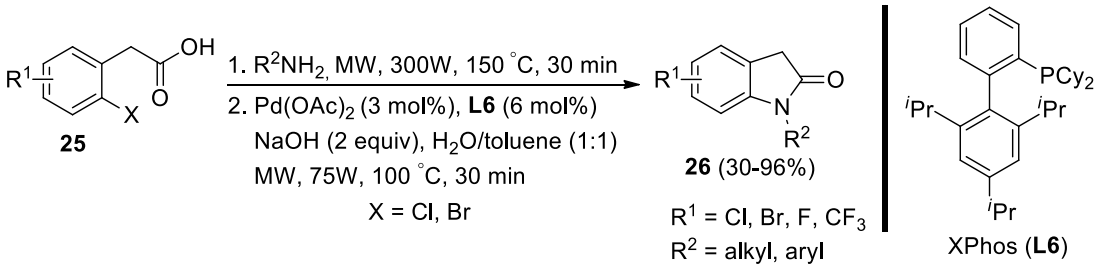
After continuous research on the amidation processes, Buchwald and his co-workers also developed an operationally simple and inexpensive catalyst system such as CuI/DMEDA

(**L4**) for the amidation of haloarenes (Scheme 1.9).[13] Further a copper catalyzed intramolecular amination of aryl halides **22** with commercially available diethylsalicylamide ligand (**L5**) was also reported (Scheme 1.9).[14]



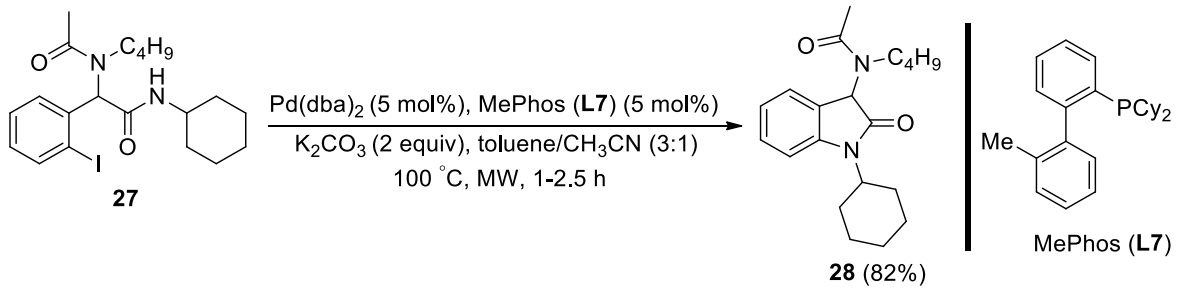

**Scheme 1.9**: *Copper Catalyzed Intramolecular Aryl Amidation and Amination*

Recently, Poondra and Turner demonstrated a general method for the synthesis of *N*-substituted oxindoles **26**. This method involves two steps. The first step is microwave assisted intermolecular amidation of 2-halo-arylacetic acids **25** with alkyl/aryl amines. The second step is palladium catalyzed intramolecular amidation under aqueous condition (Scheme 1.10).[15]



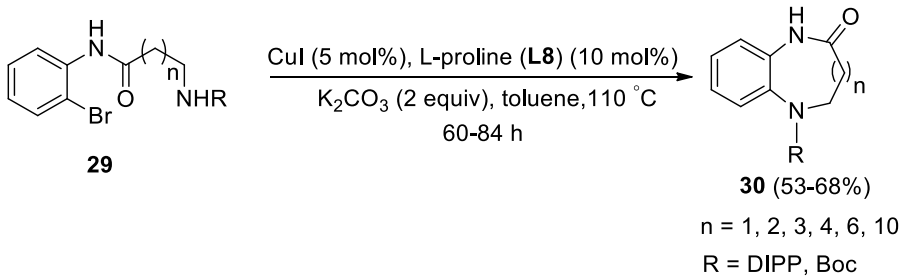

**Scheme 1.10**: *MW-Assisted Sequential Amide bond Formation and Intramolecular Amidation*

Bonnaterre *et al.* also studied a microwave assisted intramolecular Buchwald-Hartwig amidation process to rapid synthesis of functionalized oxindoles **28** (Scheme 1.11).[16] The combination of $Pd(dba)_2$/MePhos (**L7**) gave better results for the construction of oxindoles **28** by intramolecular amidation process.



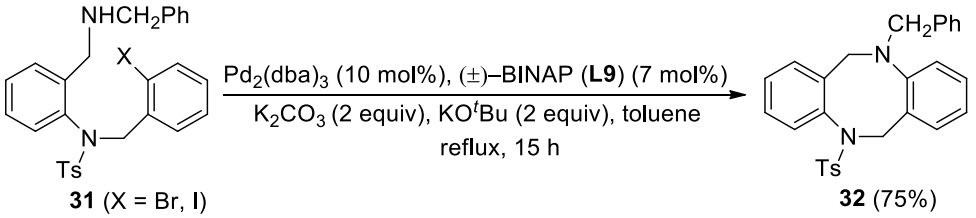

**Scheme 1.11**: *MW-Assisted Intramolecular Buchwald-Hartwig Amidation*

Yang *et al.* reported an efficient method for the construction of medium- and large-sized nitrogen heterocycles **30** *via* copper catalyzed intramolecular *N*-arylation of phosphoramidates and carbamates **29**. They have also proved that the introduction of the phosphoryl group or *tert*-butoxycarbonyl at *N*-termini can improve intramolecular cyclization under these conditions (Scheme 1.12).[17]



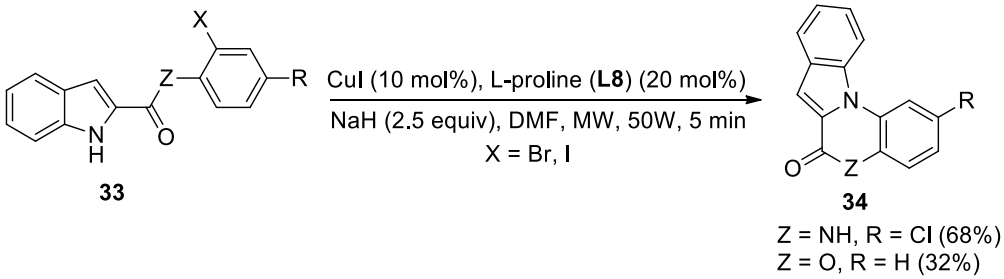

**Scheme 1.12**: *Copper Catalyzed Synthesis of Medium and Large-Sized Nitrogen-Heterocycles **30***

In recent years, chemists are interested in synthesizing of potential biologically important molecules by intramolecular amination process. From this point of view, Adhikary and Chattopadhyay showed synthesis of dibenzodiazocine derivatives **32** by using palladium catalyzed intramolecular amination of aryl bromides and iodides **31** (Scheme 1.13).[18] While tuning the different bulky biaryl phosphane ligands, it was found that BINAP (**L9**) acted as a suitable ligand for the coupling process.




**Scheme 1.13**: *Synthesis of Dibenzodiazocine Derivative **32** via Palladium Catalyzed Amination*

Martin and co-workers demonstrated a method for the preparation of indole quinoxalinone and oxazinone derivatives **34** by using copper catalyzed intramolecular *N*-arylation of indole carboxamides and carboxylates linked with a pendant haloarene **33** (Scheme 1.14).[19] The amination reaction gave the best results under microwave heating as compare to the conventional heating.

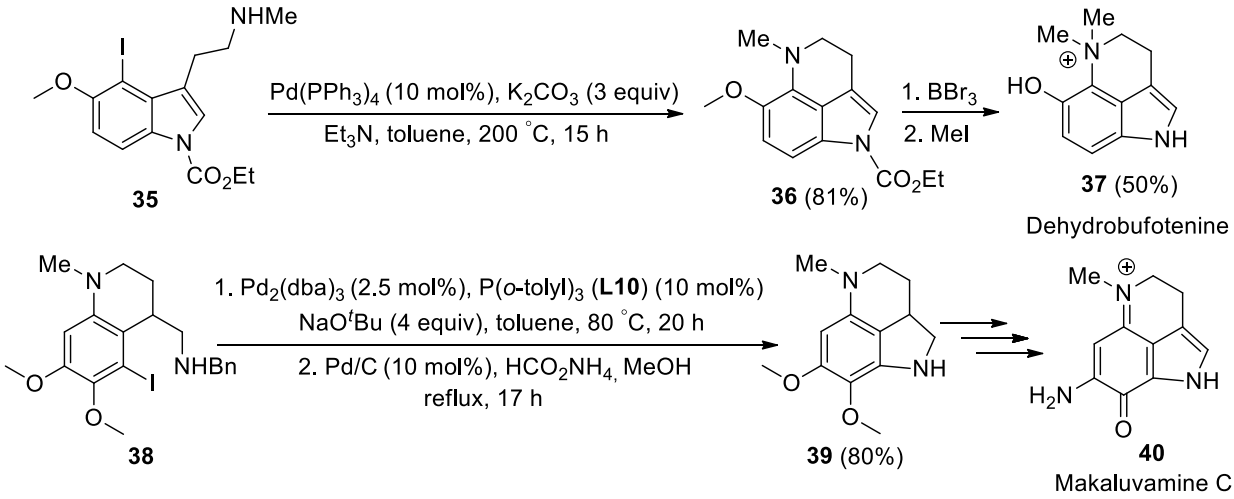



**Scheme 1.14**: *Synthesis of Quinoxalinones **34** via Copper Catalyzed Intramolecular N-Arylation*

## 1.3 Importance of C—N bond formation in Total Synthesis

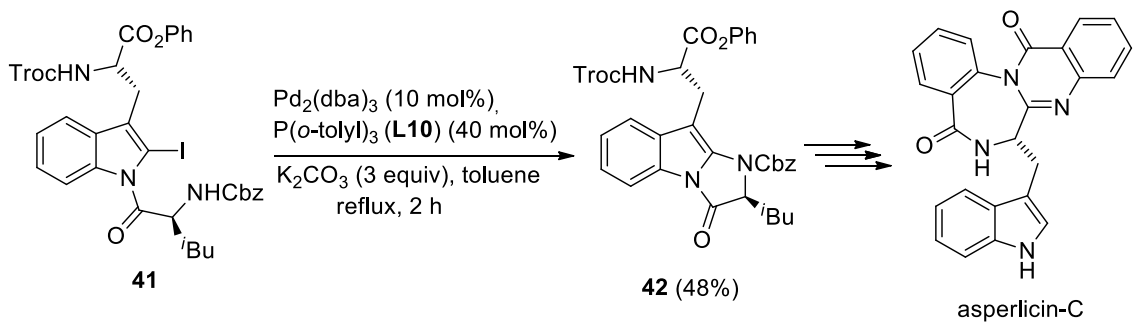
Transition metal catalyzed cross-coupling reaction has played a vital role in synthesizing complex natural products. Selected examples of natural product syntheses are described in Schemes 15-18. Dehydrobufotenine (**37**) and makaluvamine-C (**40**) have received considerable attention due to the exhibition of potent *in vitro* cytotoxicity against human tumor cell lines and their action as DNA topoisomerase inhibitors. Therefore, Buchwald devised two strategies to synthesize marine alkaloids **37** & **40** through palladium-catalyzed amination of hetero aryl compounds. Thus, in the first strategy, intramolecular C—N coupling reaction of

4-iodoindole derivatives **35** affords **36**, which was further transformed into **37** (Scheme 1.15).[20] The second strategy, 5-iodo-tetrahydroquinoline **38** was subjected to amination process followed by deprotection of benzyl group leading to the compound **39**, which is a key intermediate for synthesis of makaluvamine C **40** (Scheme 1.15).[20]



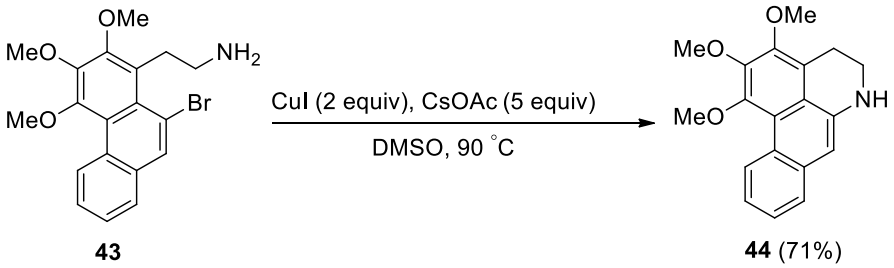

**Scheme 1.15**: *Synthesis of Tetrahydropyrroloquinolines **36** & **39** by Palladium Catalyzed Aryl Amination*

The Snider group cleverly utilized palladium catalyzed intramolecular C—N bond formation for the construction of key intermediate **42** in total synthesis of asperlicin-C (Scheme 1.16).[21]



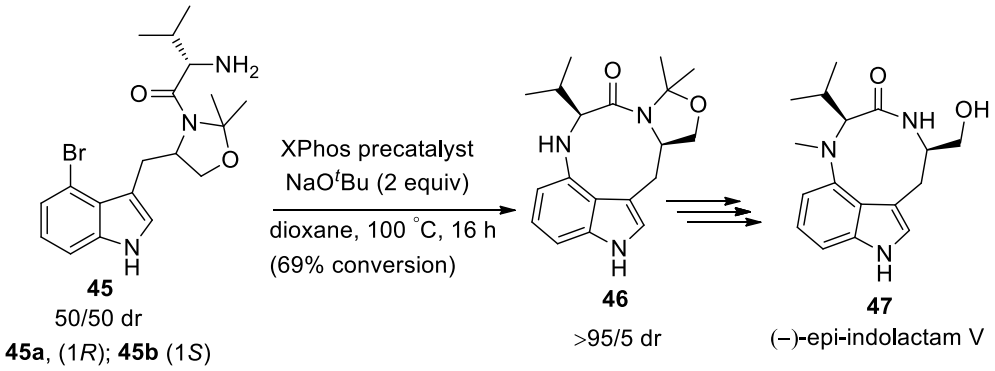

**Scheme 1.16**: *Synthesis of Key Intermediate **42** for Asperlicin via Amidation*

Fuerstner and Mamane used amination reaction to complete the first total synthesis of *O*-methyldehydroisopiline (**44**) from 9-bromo-4-ethylaminophenanthrene derivative **43** (Scheme 1.17).[22]




**Scheme 1.17**: *Synthesis of the Aporphine Alkaloid O-Methyldehydroisopiline **44***

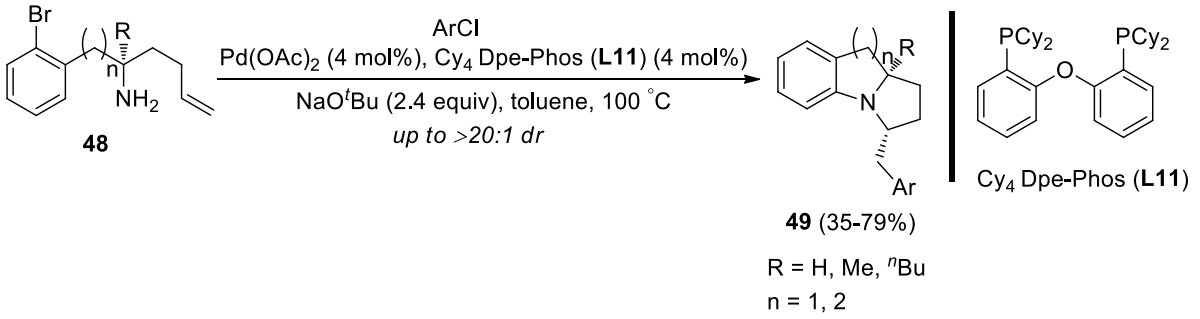
Recently, the group of Piersanti studied palladium catalyzed intramolecular cross-coupling reaction of 4-bromo substituted tryptophan derivatives **45**. The bromo compound **45** gave expected cyclization product **46** in presence of XPhos precatalyst. Further, the compound **46** converted into one of the possible stereoisomers of (−)-indolactam V (**47**) by *N*-methylation of secondary amino group followed by acidic cleavage of acetonide group (Scheme 1.18).[23]




**Scheme 1.18**: *Palladium Catalyzed Intramolecular N-Arylation towards Synthesis of (-)-Epi-indolactam **47***

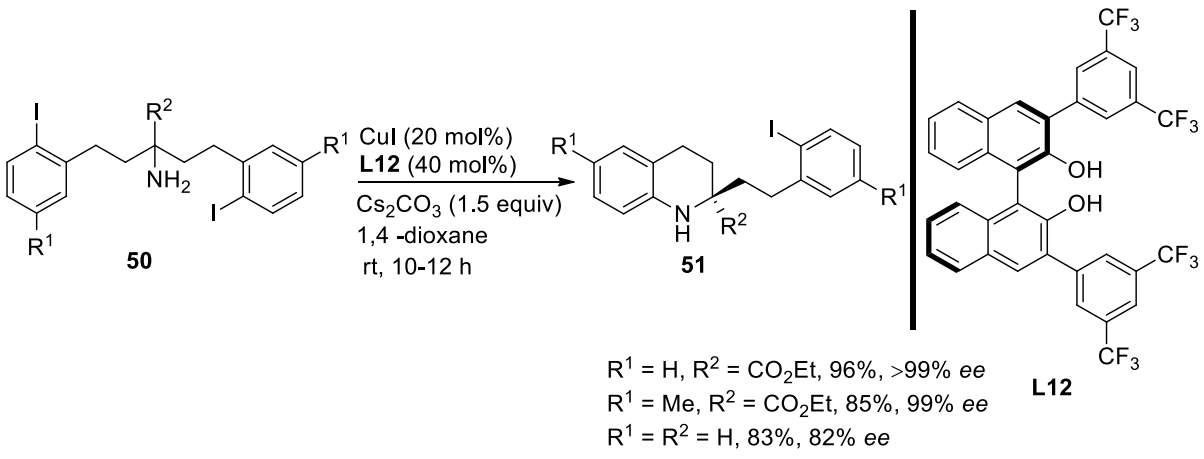
## 1.4 Importance of C—N bond Formation in Enantioselective Reactions

The stereoselective synthesis of tetrahydropyrroloindoles **49** was reported by Wolfe and Lemen. They obtained these products through cascade palladium catalyzed coupling reactions between aryl chlorides and unsaturated amine substrates. The highlight of the work was a single catalyst effects an intramolecular *N*-arylation reaction followed by an intermolecular alkene carboamination reaction to generate two rings, three bonds, and one stereo center with good chemoselectivity, diastereoselectivity, and chemical yield (Scheme 1.19).[24]




**Scheme 1.19**: *Stereoselective Synthesis of Tetrahydropyrroloindoles **49** and Hexahydropyrroloquinolines*

In 2012, Cai and his co-workers, demonstrated the first highly enantioselective copper-catalyzed intramolecular desymmetric Ullmann C—N coupling reaction of **50** for the

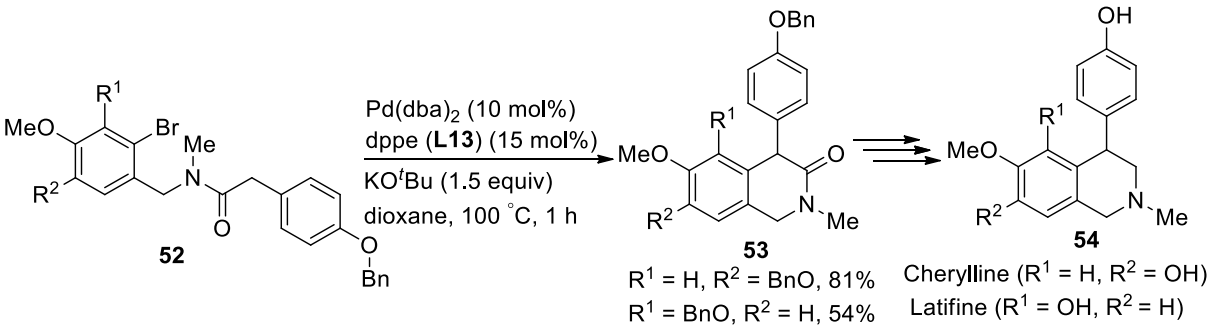



**Scheme 1.20**: *Intramolecular Desymmetric Ullmann C—N Coupling Reaction*

enantioselective synthesis of tetra-1,2,3,4-hydroquinolines **51** (Scheme 1.20).[25] The 3,3′-diaryl substituted BINOL **L12** used as a chiral ligand.

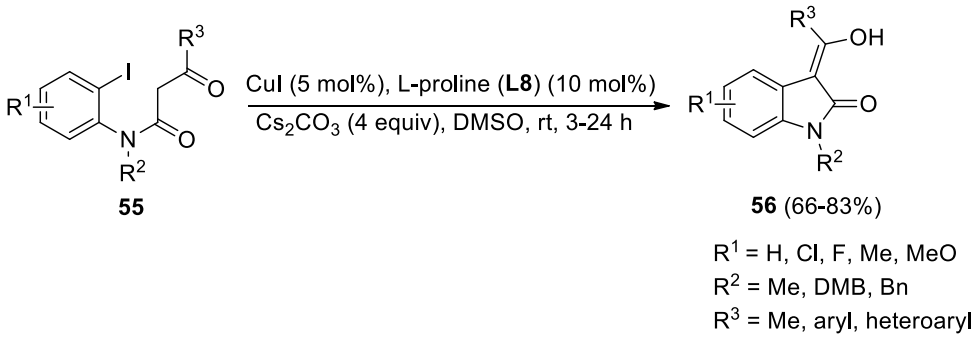
## 1.5 Methods for the Synthesis of Fused Heterocycles *via* C—C and C—N bond Formation

Early 2001, Honda and his co-workers accomplished 4-arylisoquinoline derivatives **53** by the palladium─catalyzed intramolecular carbon─carbon bond formation between aryl halides and amide-enolates (Scheme 1.21).[26] The isoquinoline derivatives **53** were transformed into natural products cherylline and latifine.



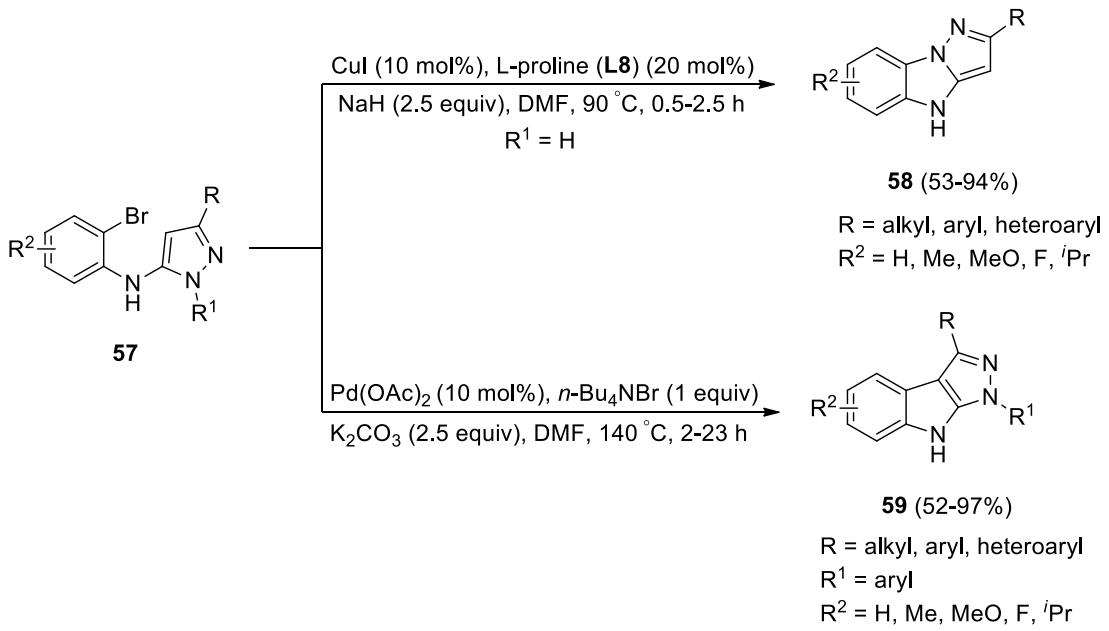

**Scheme 1.21**: *Intramolecular C—C bond Formation of Aryl Halides and Amide-Enolates*

Lu and Ma studied CuI/L-proline catalyzed intramolecular coupling of *β*-keto 2-iodoanilides **55** affording substituted 3-acyloxindoles **56** in good to excellent yields. The electronic effects on the aromatic ring was also studied (Scheme 1.22).[27]



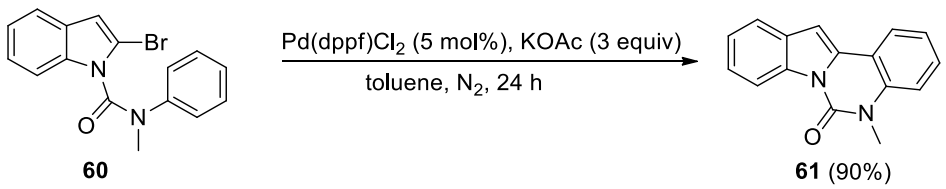

**Scheme 1.22**: *Copper Catalyzed Intramolecular Arylation of β-Keto Amides **55***

In 2009, Ila group reported an efficient synthetic routes for the construction of two new classes of heterocyclic frame works such as pyrazolo[3,4-*b*]indoles **59** and pyrazolo[1,5-*a*]benzimidazoles **58** from a common synthetic precursor **57** *via* intramolecular palladium and copper catalyzed C—C and C—N bond formation reactions respectively (Scheme 1.23).[28]




**Scheme 1.23**: *Palladium & Copper Catalyzed Intramolecular C—C and C—N bond Formation*

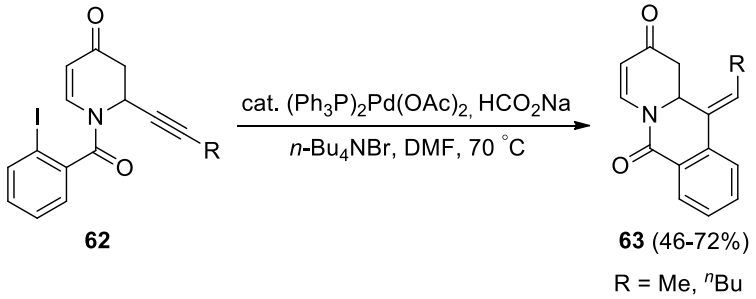
Bao group developed a convenient method for the synthesis of pyrimido[1,6-*a*]indol-1(2*H*)-one derivatives **61** through palladium catalyzed intramolecular direct arylation process (Scheme 1.24).[29]




**Scheme 1.24**: *Palladium Catalyzed Intramolecular Direct Arylation*

## 1.6 Methods for the Synthesis of Fused Heterocycles *via* Heck Reaction Conditions

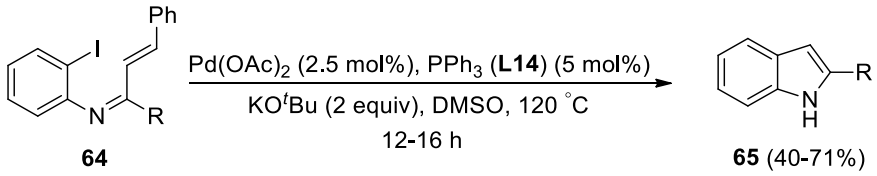
Recently, *N*-acyl-2,3-dihydro-4-pyridones **62** have shown to be considerable utility for alkaloid synthesis. Comins *et al* studied regio and stereoselective intramolecular Heck reaction of *N*-acyl-2,3-dihydro-4-pyridones **62** (Scheme 1.25).[30] In these reactions the amide carbonyl group plays an important role; in the absence of carbonyl group under similar conditions deiodination occurs.




**62** **63** (46-72%)
R = Me, $^{n}$Bu

**Scheme 1.25**: *Palladium Catalyzed Regioselective Intramolecular Heck Reaction*

Recently, Sun and his co-workers achieved 2-substituted indoles **65** from **64** through a palladium catalyzed domino Heck and dealkylation reaction (Scheme 1.26).[31] The starting precursors *ortho*-iodo-*N*-allylimines **64** were prepared by condensation of chalcones with 2-iodoaniline.



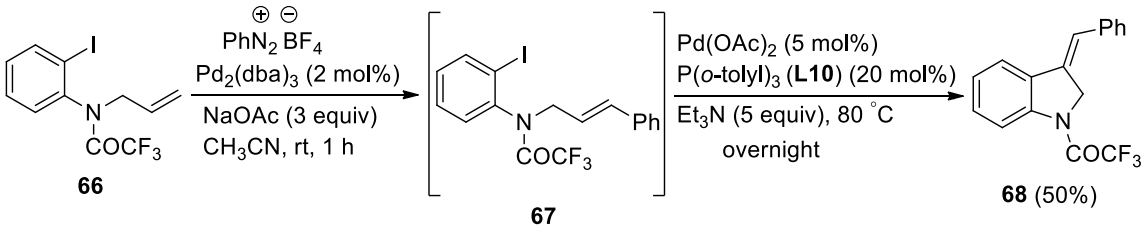

**64** **65** (40-71%)

R = H, Ph, 4-MePh, 4-MeOPh, 4-ClPh, 4-BrPh
4-FPh, 4-$CF_3$Ph, 4-$NO_2$Ph, 2-thienyl

**Scheme 1.26**: *Palladium Catalyzed Domino Heck reaction and Dealkylation*

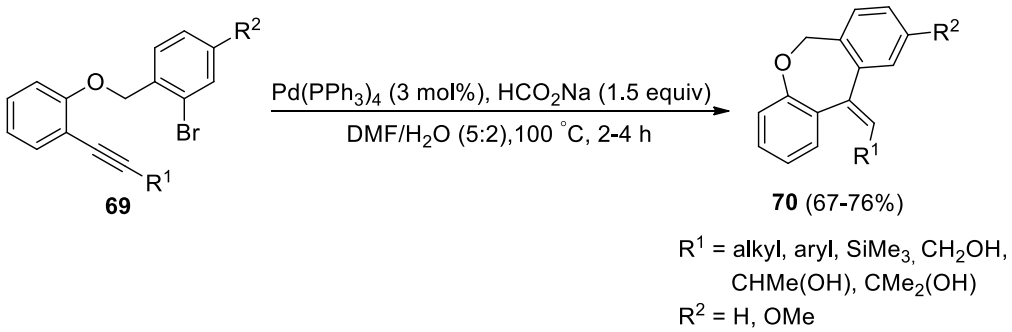
The novel palladium catalyzed Heck reaction of arenediazonium salts with *N*,*N*-diprotected allylamines **66** was described by Cacchi *et al.* (Scheme 1.27).[32] The typical

alkylidene indoline **68** was prepared by the reaction of arenediazonium tetrafluoroborates with *ortho*-iodo-*N*-allyl-trifluoroacetanilide **66**. They noticed that *β*-hydride elimination is unfavourable. Therefore, benzyl group is eliminated.



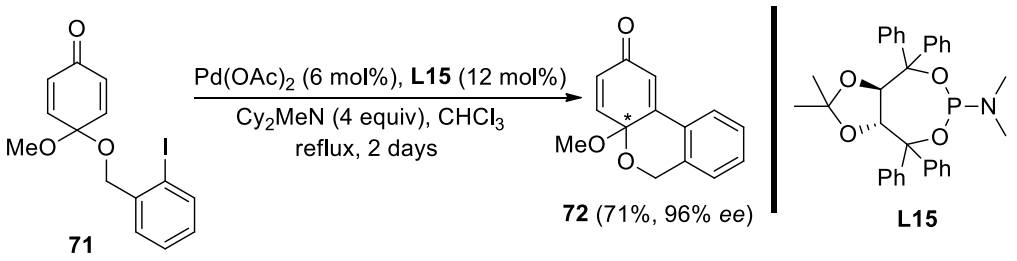

**Scheme 1.27**: *Heck Reaction of Arenediazonium Salt with N-Protected Allylamine **66***

Many of the natural products possess a seven membered oxepin ring in their frame work. Moreover, this ring is highly biological active. Because of the importance of this core, the group of Majumdar synthesized dibenzo[*b,e*]oxepine **70** framework *via* palladium-mediated reductive Mizoroki–Heck reaction of **69** (Scheme 1.28).[33]




**Scheme 1.28***: Palladium Catalyzed Reductive Mizoroki–Heck Reactions*

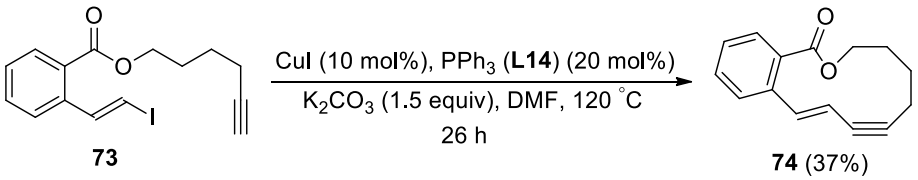
Feringa group developed a highly enantioselective intramolecular Heck reaction of cyclohexadienones **71** by using readily available and modular TADDOL-based mono- and bidentate phosphoramidites chiral ligands (Scheme 1.29).[34] They achieved enantioselectivities up to 96% *ee*. It was the first report where the high enantioselectivity was observed in Heck reaction by using monodentate ligands.




**Scheme 1.29**: *Enantioselective Intramolecular Heck Reaction with a Monodentate Ligand*

## 1.7 Synthesis of Macrocycles *via* Intramolecular C—C bond Formation

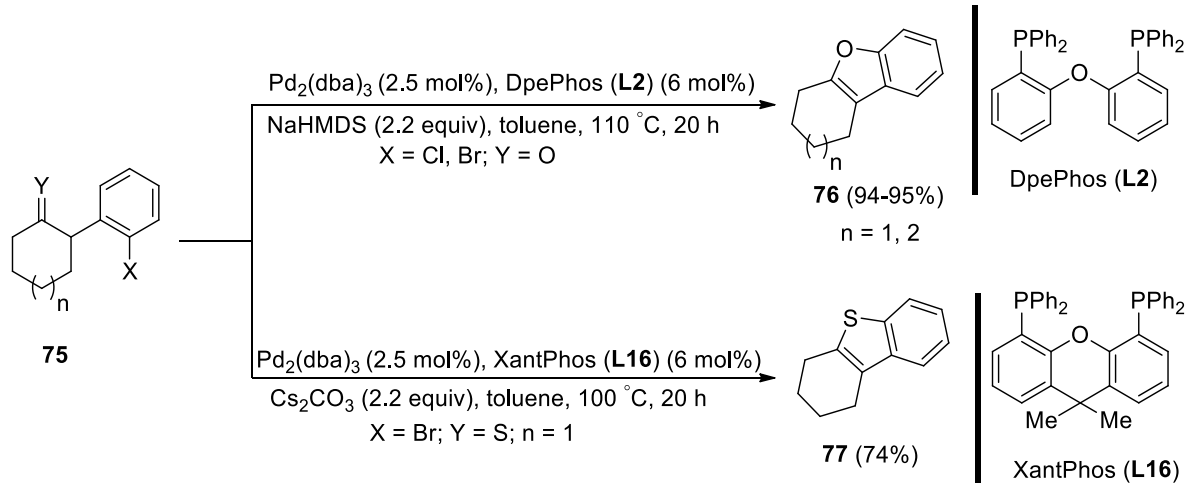
Coleman and Garg reported a method for the construction of the 12-membered diene lactone from **74**. The compound **74** was prepared from ester intermediate **73** by Castro-Stephens coupling (Scheme 1.30).[35] Initially, this reaction was attempted under Sonogashira coupling conditions, however, failed to give **74**. Further, this macrocyclic molecule **74** is structurally very closed to the antitumor agent oximidine.




**Scheme 1.30**: *Macrocycle Formation via Intramolecular Castro-Stephens Coupling*

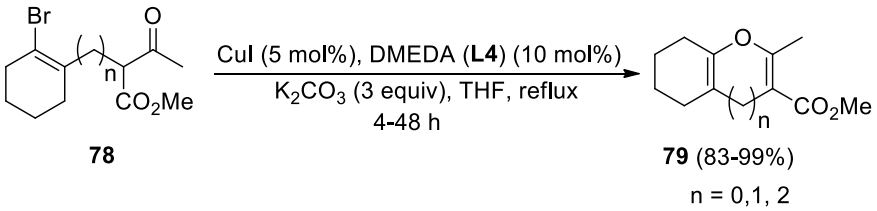
## 1.8 Synthesis of Fused Heterocycles *via* Intramolecular C—O, C—N, C—S bond Formation

In 2004, Willis *et al* described a synthetic protocol for synthesis of benzo[*b*]furans **76** and benzo[*b*]thiophenes **77** (Scheme 1.31).[36] They used a catalyst generated from $Pd_2(dba)_3$/ligand DPEphos (**L2**) which was more effective for the intramolecular C—O bond formation between enolates and aryl halides. In the similar way, they have also constructed C—S bond between thioenolates and arylhalides by using XantPhos (**L16**) ligand.




**Scheme 1.31**: *Palladium Catalyzed Intramolecular O-Arylation and S-Arylation of Enolates*

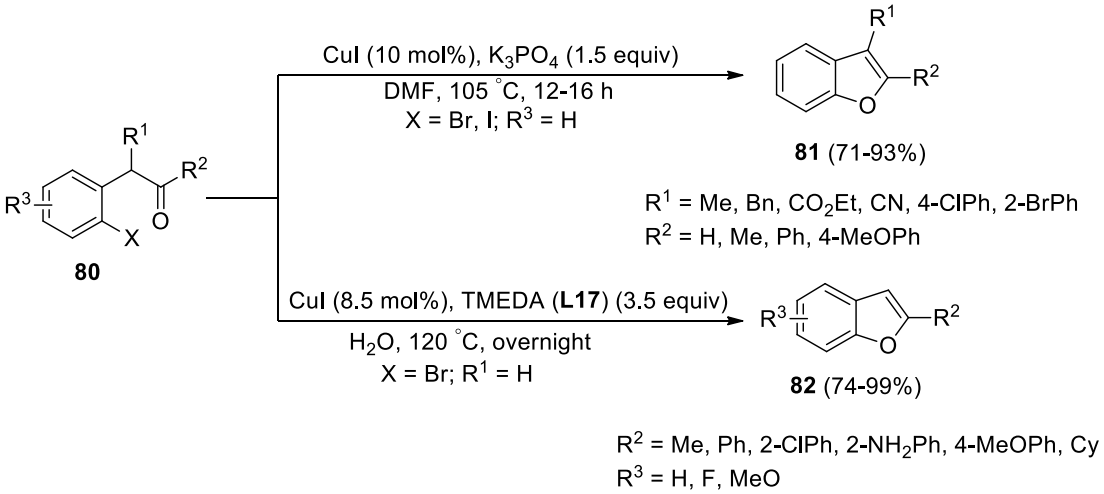
Fang and Li found an efficient protocol for the first copper-catalyzed intramolecular *O*-vinylation of carbonyl compounds with vinyl bromides **78** (Scheme 1.32).[37] This method provides 5-, 6- and even 7-membered cyclic alkenyl ether derivatives **79**.




**Scheme 1.32**: *Intramolecular O-Vinylation of Carbonyl Compounds*

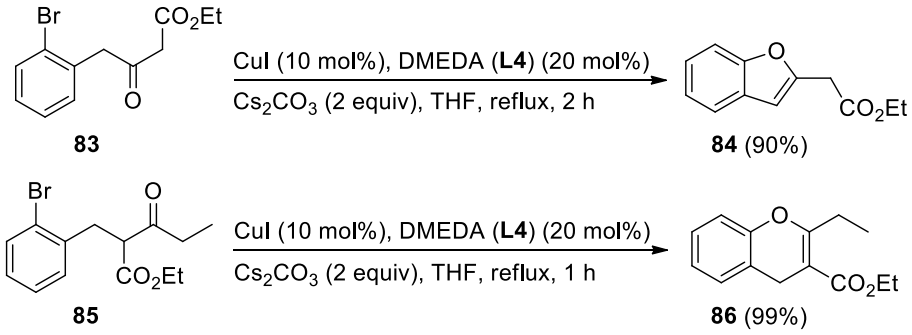
After intensive research on the C—O cross-coupling reactions, in 2005, Chen and Dormer studied an intramolecular enolate *O*-arylation process for synthesis of benzo[*b*]furans **81** (Scheme 1.33).[38] Thus, a wide variety of benzo[*b*]furans **81** were prepared efficiently through a CuI catalyzed ring closure of substituted 2-haloaromatic ketones **80**. Further, they extended this methodology to different functional group substituted halo ketones **80** (R = CN, $CO_2Et$) affording the corresponding benzo[*b*]furans **81** in 72-99% yields. Later, Dominguez research group reported a more sustainable protocol for synthesis of various 2-alkyl and 2-aryl

substituted benzo[*b*]furans **82** by using copper-TMEDA complex in aqueous media (Scheme 1.33).[39]




**Scheme 1.33**: *Copper Catalyzed Synthesis of Benzo[b]furans **81** & **82***

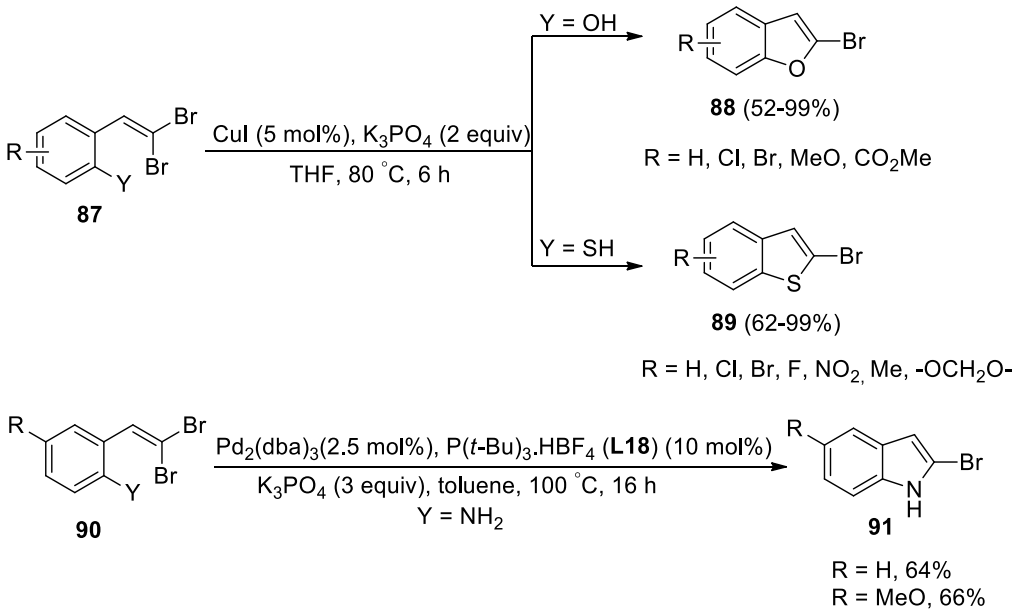
Inspired by aforementioned work (Scheme 1.32), Fang and Li also developed a new methodology for accomplished five and six-membered ring closure products **84**, **86** *via* the copper catalyzed intramolecular coupling of aryl bromides with 1,3-dicarbonyls (Scheme 1.34).[40]



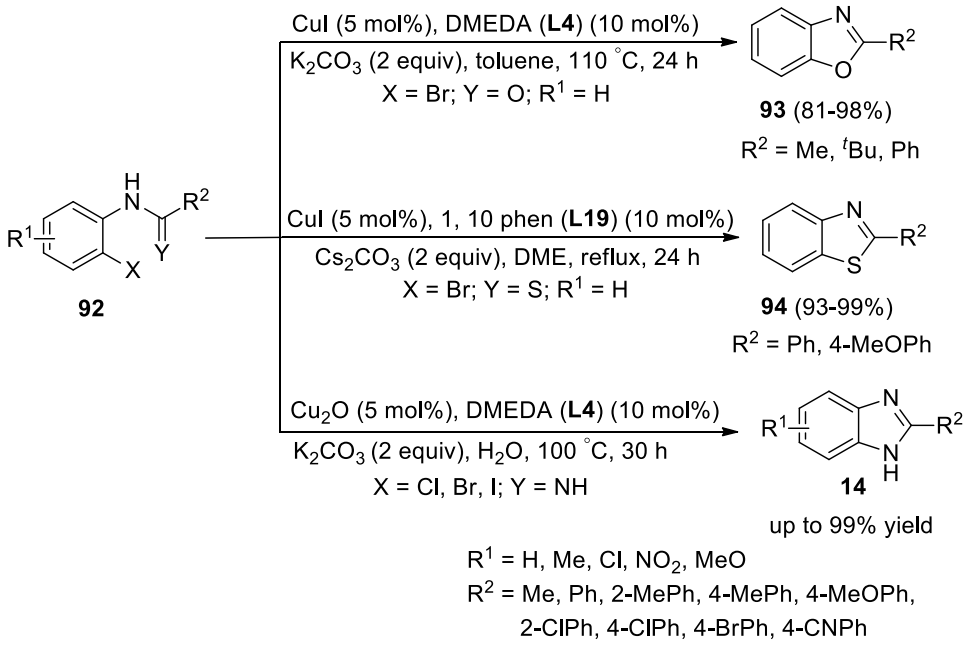

**Scheme 1.34**: *Intramolecular O-Arylation of Aryl Bromides with Carbonyl Compounds*

In particular, halogenated heterocycles have great demand in the synthesis of natural and unnatural products, because of their reactivity and ease of derivitazation. Thus, the group of Lautens focused on the synthesis of highly useful halogenated benzo[*b*]furans **88**,

benzo[*b*]thiophenes **89** and indoles **91**. They successfully achieved their target molecules by using copper and palladium catalyzed cross-coupling reactions of readily available *gem*-dibromoolefins **87**, **90** (Scheme 1.35).[41]




**Scheme 1.35**: *Intramolecular Cross-Coupling of gem-Dibromoolefins **87** & **90***




**Scheme 1.36**: *Copper Catalyzed Intramolecular O-, S-, N-Arylations*

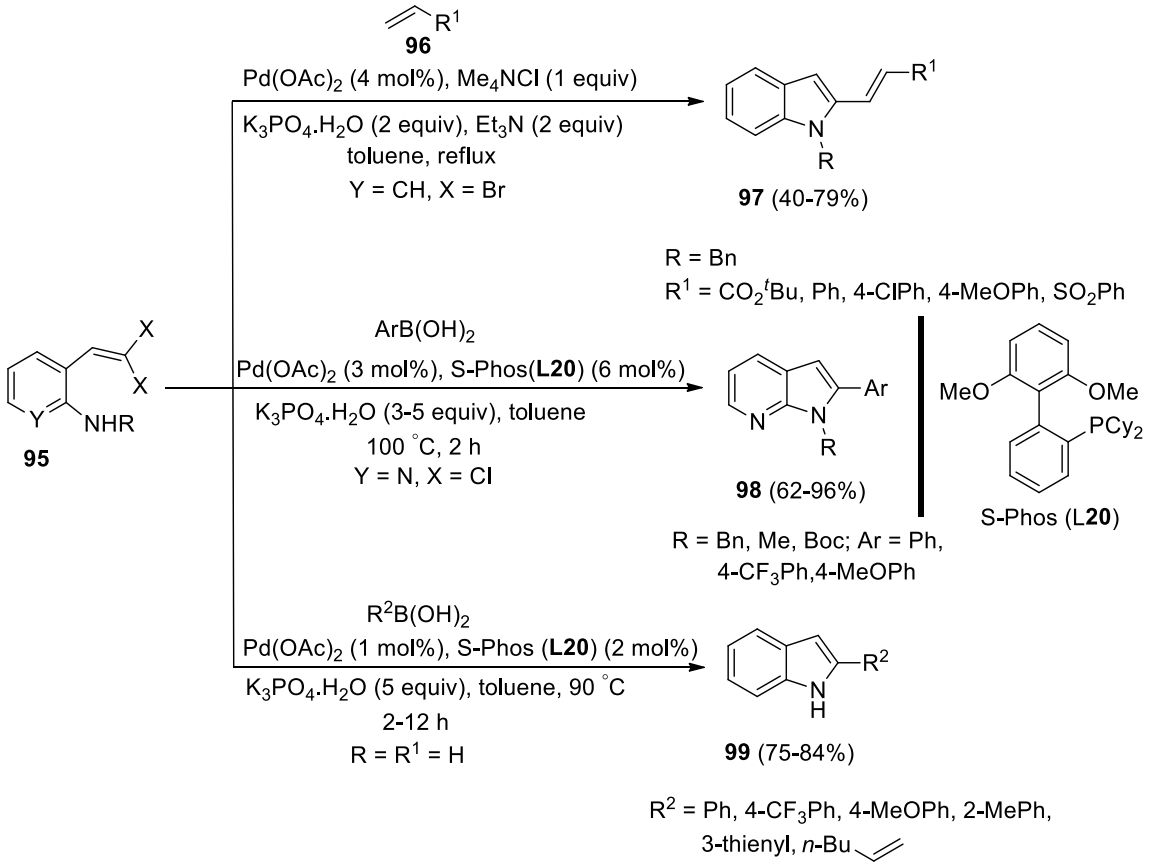
So far, we discussed the methods involved in the preparation of molecules containing one-hetero atom like benzofuran, benzothiophene and Indoles. Several other methods were also developed for the construction of compounds containing two hetero atoms such as benzoxazoles, benzothiazoles, benzimidazoles. The Glorius,[42] Batey[43] and Peng[44] research groups individually developed new copper catalyzed protocols for the construction of fused heterocycles **93**, **94**, **14** from *ortho*-halobenzene derivatives **92** (Scheme 1.36).

## 1.9 Methods for the Synthesis of Fused Heterocycles *via* Tandem Reactions

One method for increasing the efficiency of a synthetic sequence is to carry out more than one transformation in a 'one-pot' process without isolating any of the intermediates called a tandem or cascade reaction. Tandem reactions always lead to an increase in molecular complexity by combining a multiple reactions in one synthetic operation.[45] A modern synthetic approach mainly demands the need to develop high efficiency in terms of decreasing the multiple synthetic operations and increasing the molecular complexity. Earlier, scientists used cycloaddition sequences, tandem radical reactions and tandem anionic processes to build the natural products.[46] But those methods have their own advantages and disadvantages. Later, tandem metal catalysis was introduced to overcome all these challenges. In the beginning, the scope of tandem metal catalysis was limited to simple oxidation and reduction chemistry. Now it has been extended to cover all the carbon—carbon, carbon—hydrogen, and carbon—heteroatom bond formations.[47] In this chapter we have discussed recent works on tandem reactions for the synthesis of heterocycles.

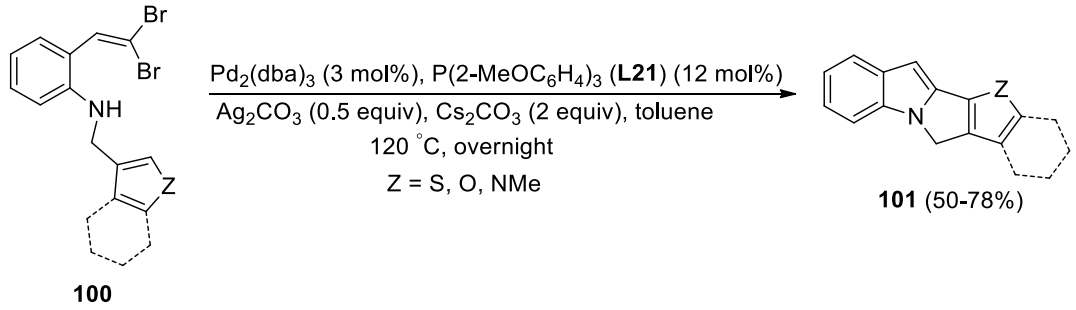
*gem*-Dihalovinyl compounds **95** are versatile synthons because these compounds are having two reactive halo groups, which can be easily functionalized. Especially, these synthons **95** are used for synthesis of various heterocycles and carbocycles.

Recently, Lautens and co-workers have shown that *gem*-dihalovinyl compounds **96** can be used to synthesize 2-vinyl substituted indoles **97** (Scheme 1.37).[48a] The first step of the reaction is Buchwald-Hartwig amination reaction followed by intramolecular Heck reaction (Scheme 1.37). The overall yield of the reaction is moderate to very good with excellent functional group tolerance. A similar strategy was extended to synthesize 2-aryl azaindoles **98** via intramolecular Suzuki-Miyaura coupling reaction.[48b] It was further extended to synthesize 2-arylindoles **99**.[48c]



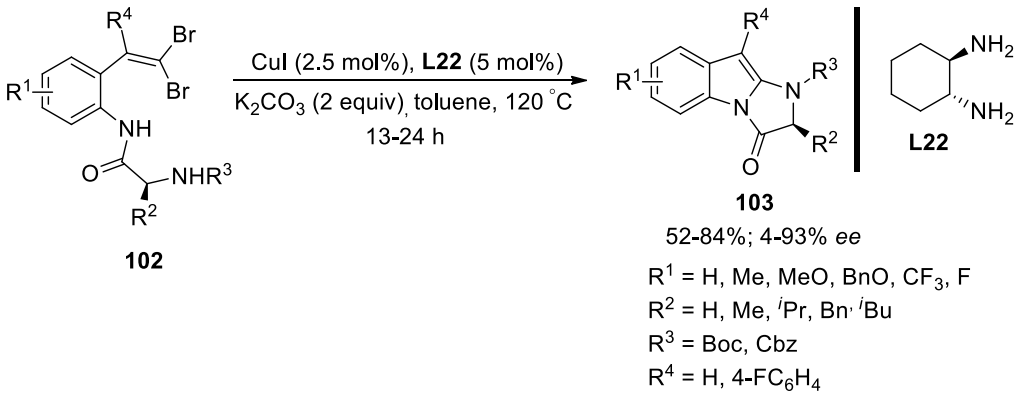

**Scheme 1.37**: *Palladium Catalyzed Tandem Coupling Reactions*

In 2008, novel tetracyclic and pentacyclic indole derivatives **101** from *gem*-dibromovinylaniline derivatives **100** were reported. This reaction proceeds through a palladium catalyzed domino Buchwald-Hartwig amination/intramolecular arylation (Scheme 1.38).[49]



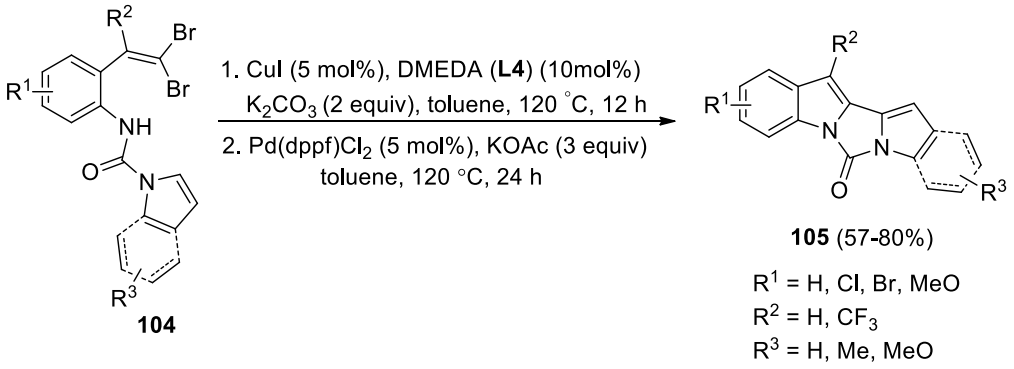

**Scheme 1.38**: *Palladium Catalyzed Domino Buchwald-Hartwig Amination/Direct Arylation Reaction*

So far, the construction of indole derivatives from *gem*-dihalovinyl compounds *via* palladium catalyzed tandem reactions was discussed. However, these catalytic transformations are also performed in the presence of copper. Thus, Lauten *et al.* reported the first example of a CuI-catalyzed tandem intramolecular amidation process (Scheme 1.39).[50] Several substituted imidazoindolones **103** were synthesized from readily accessible *ortho* gem-dibromovinylanilines **102**. Imidazoindolone core is one of the key structural motifs in the family of antifungals, fumiquinazolines, and the antagonist asperlicin.



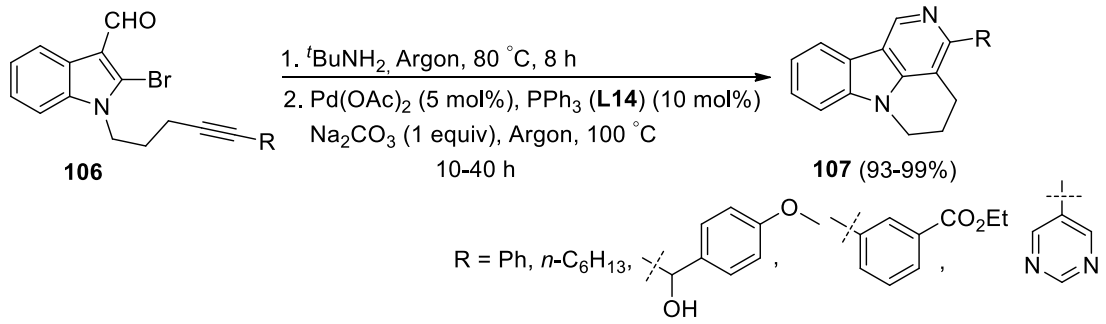

**Scheme 1.39**: *CuI-Catalyzed Tandem Intramolecular Amidation*

Recently, Bao and his group described a one-pot synthesis of 2,2′-bisindolyl derivatives **105** from *gem*-dibromo vinyl precursors **104**. This reaction involves a copper catalyzed *N*-arylation followed by palladium catalyzed direct arylation (Scheme 1.40).[51]



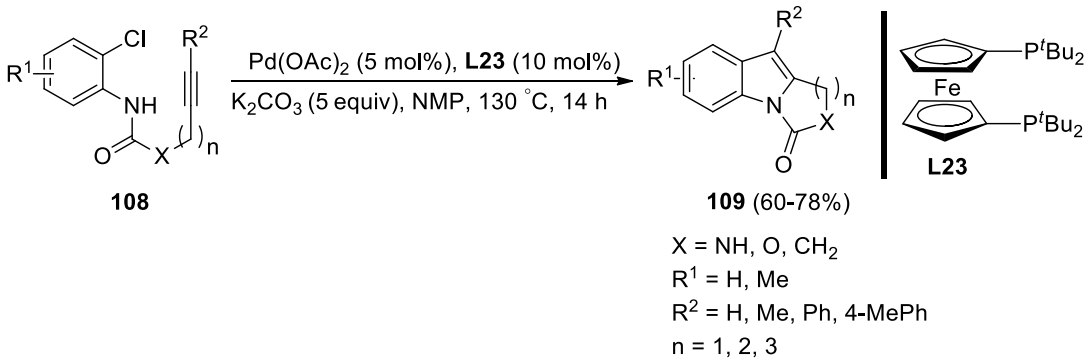

**Scheme 1.40**: *Copper Catalyzed N-Arylation/Palladium Catalyzed Direct Arylation Sequential Process*

Zhang and Larcok developed various annulated *γ*-carbolines **107** with the palladium catalyzed intramolecular iminoannulation of **106**, which was prepared from the *tert*-butylimines of starting precursors *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehydes **106** (Scheme 1.41).[52]



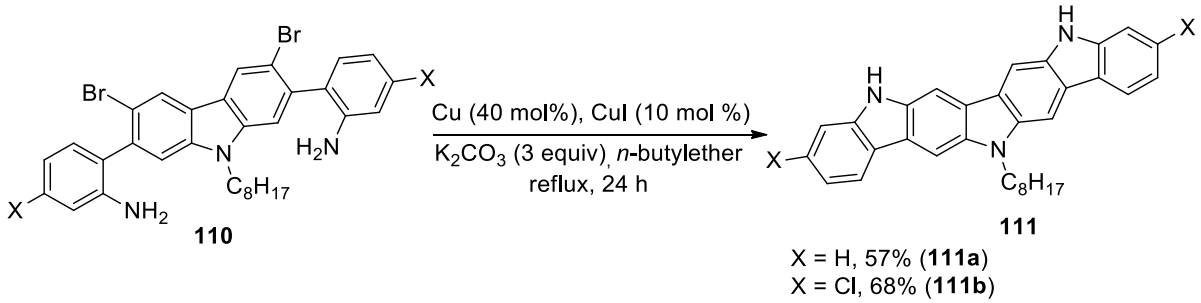

**Scheme 1.41**: *Synthesis of Annulated γ-Carbolines by Palladium Catalyzed Intramolecular Iminoannulation*

Later, Lu and co-workers also utilized the similar kind of approach to get a variety of polycyclic indole skeletons **109**. They used a robust one-pot consecutive sequence of hydroamidation followed by palladium catalyzed annulation of inexpensive 2-chloroanilines bearing tethered acetylenes **108** for the synthesis of polycyclic indole skeletons **109** (Scheme 1.42).[53]




**Scheme 1.42**: *Tandem Intramolecular Hydroamidation/Palladium Catalyzed Annulation Process*

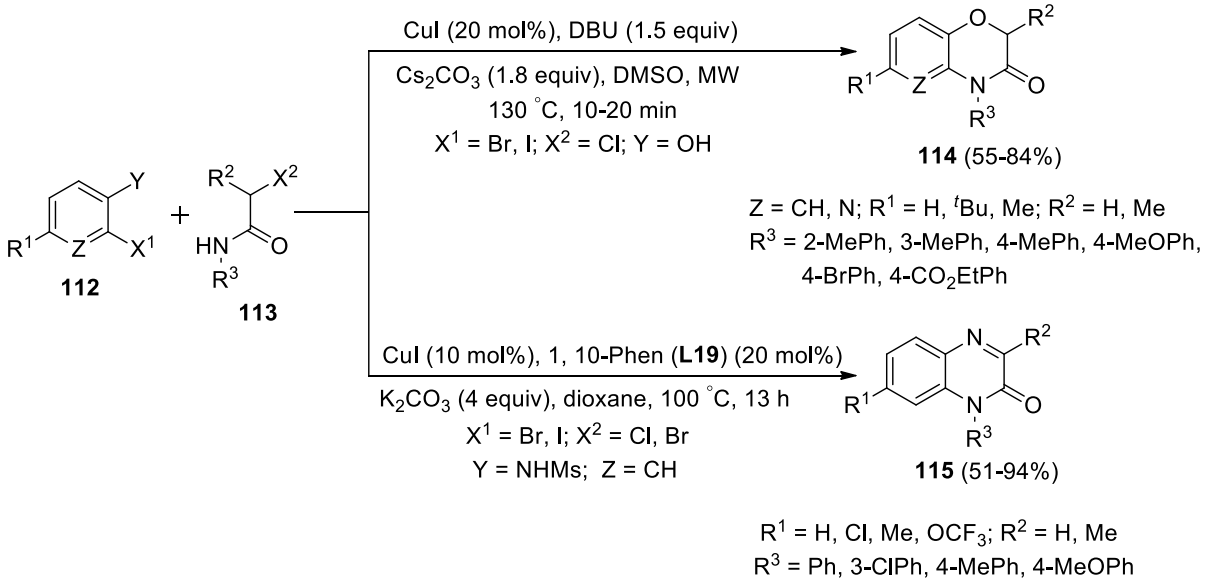
Leclerc research group synthesized symmetric bisindolocarbazoles **111** by using a double-intramolecular cyclization reaction of *N*-alkyl-3,6-dibromo-2,7-bis(2′aminophenyl)carbazole derivatives **110** (Scheme 1.43).[54] The indolocarbazole derivatives **111** were used for synthesis of thin films and semi ladder polymers.



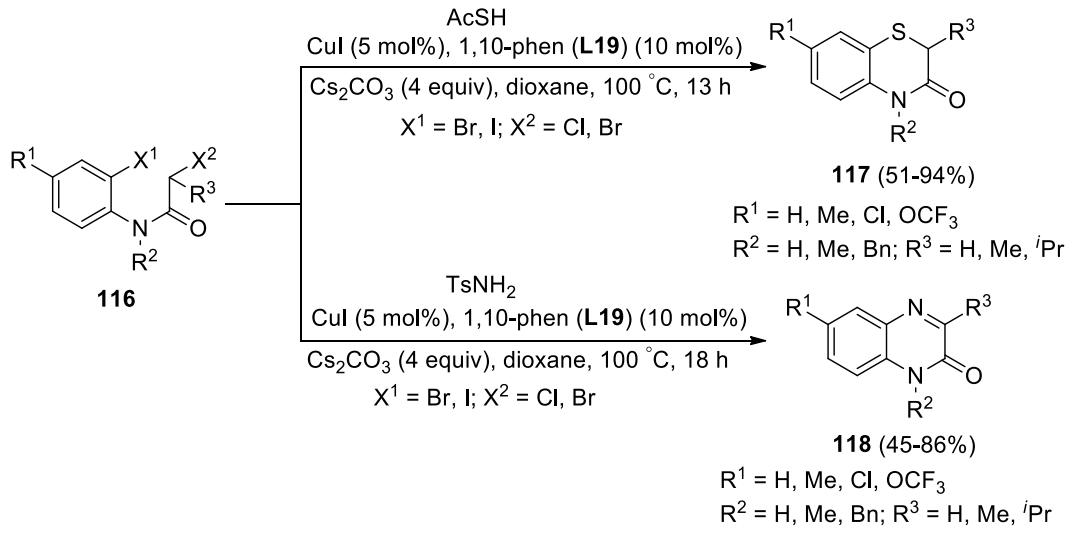

**Scheme 1.43**: *Synthesis of Diindolocarbazoles **111** by Ullmann Reaction*

We have discussed a series of tandem reactions which are involved C—N and C—C bond formations (Schemes 1.37-1.42). In following discussion, we have described some representative examples where C—N bond formation followed by C—O, C—S and C—N bond forming reactions occured. Liu and his co-workers developed an efficient and convenient strategy for preparing *N*-substituted 2*H*-1,4-benzoxazin-3-(4*H*)-ones **114** from 2-halophenols **112** (Scheme 1.44).[55a] Initially, the reaction started with nucleophilic substitution of 2-chloroacetamides **113** with 2-halophenols **112** followed by a CuI-catalyzed coupling

cyclization. This method was very attractive because of simple reaction conditions, a short reaction time, and a broad substrate scope. After this report, Chen and Bao published similar kind of structural motifs quinoxalin-2-(1*H*)-one derivatives **115** with the help of domino $S_NAr$/coupling/demesylation reaction of *N*-(2-halophenyl)methylsulfonamides **112** with 2-halo amides **113** (Scheme 1.44).[55b]



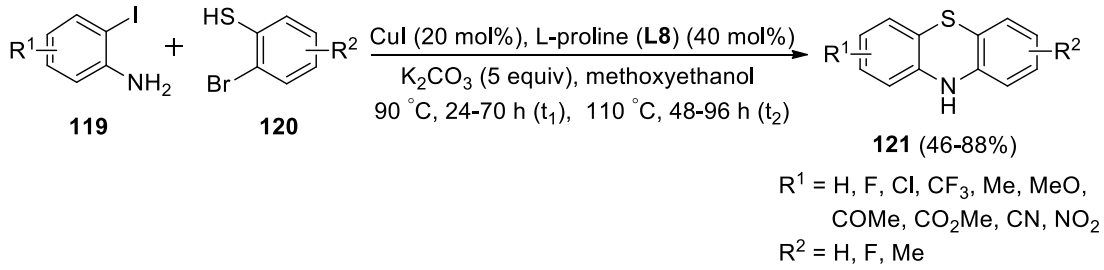

**Scheme 1.44**: *CuI-Catalyzed Synthesis of N-substituted 2H-1,4-benzoxazin-3-(4H)-ones and quinoxalin-2(1H)-ones derivatives*




**Scheme 1.45**: *Copper Catalyzed Cascade Synthesis of 2H-benzo[b][1,4]thiazin-3(4H)-ones **117** and Quinoxalin-2(1H)-ones **118***

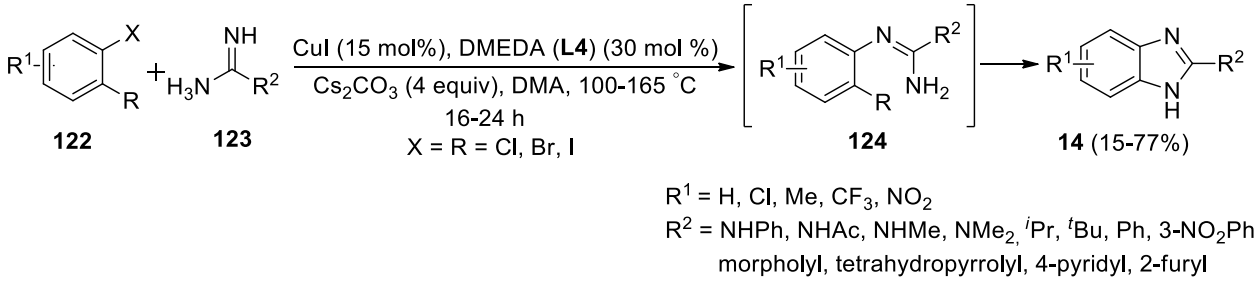
A new copper catalyzed cascade strategy ''$S_N2$/deacetylation/coupling'' process was developed for synthesis of 2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-ones **117** from 2-halo-*N*-(2-haloaryl)-acetamides **116**. Similar strategy was used for synthesis of quinoxalin-2(1*H*)-ones **118** (Scheme 1.45).[56]

Recently, Ma *et al* reported a new approach to construct functionalized phenothiazines **121** starting from substituted 2-iodoanilines **119** and 2-bromobenzene thiols **120**. This protocol is based on a sequentially controlled CuI/L-proline catalyzed tandem process. The efficiency and substituent tolerance of this procedure were also demonstrated (Scheme 1.46).[57]




**Scheme 1.46**: *Sequentially Controlled Copper-Catalyzed Cascade C—S and C—N Bond Formation*

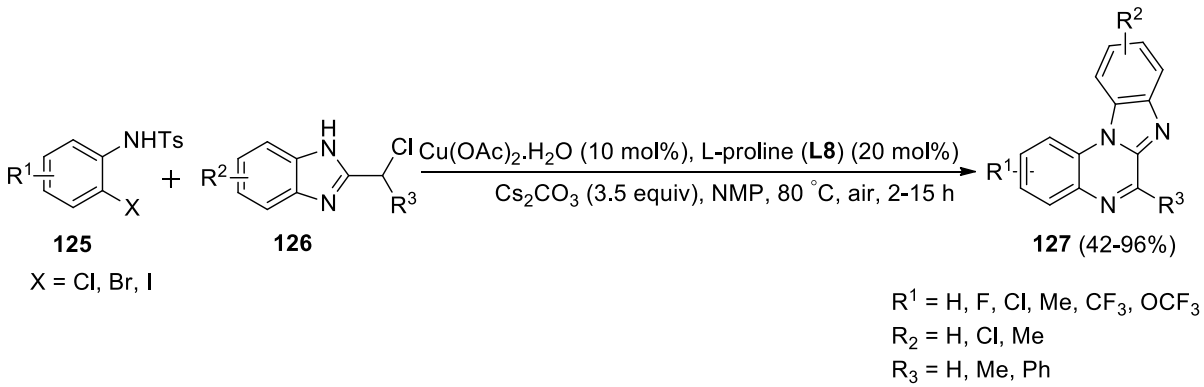
In 2009, Deng and his co-workers found that the combination of CuI with *N,N′*-dimethylethylenediamine to be an efficient catalyst system for the amination of arylhalides **122** with guanidines **123**. They also utilized the same catalyst system to the one-step synthesis of




**Scheme 1.47**: *Copper Catalyzed Tandem Aminations of 1,2-Dihaloarenes*

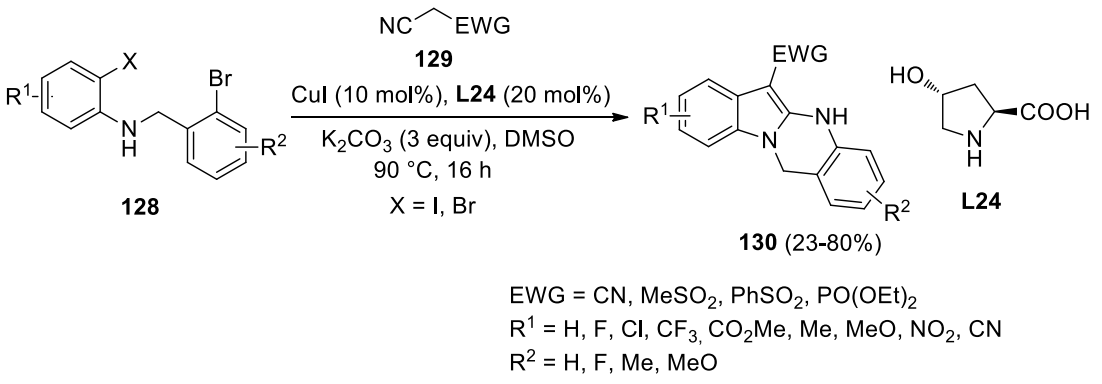
1-*H*-2-aminobenzimlizeidazoles **14** through tandem aminations of 1,2-dihaloarenes **122** (Scheme 1.47).[58]

Very recently, Ma group described a copper catalyzed one-pot process for the preparation of benzo[4,5]imidazo[1,2-*a*]quinoxalines **127** from *N*-tosyl-2-haloaniliines **125** and benzimadazole derivatives **126** under air (Scheme 1.48).[59] Various aryl chlorides, aryl bromides, and aryl iodides were also examined for synthesis of imidazo[1,2-*a*]quinoxaline derivatives **127**.




**Scheme 1.48**: *Copper Catalyzed Domino Process for the Construction of Benzo[4,5]imidazo[1,2-a]quinoxalines*

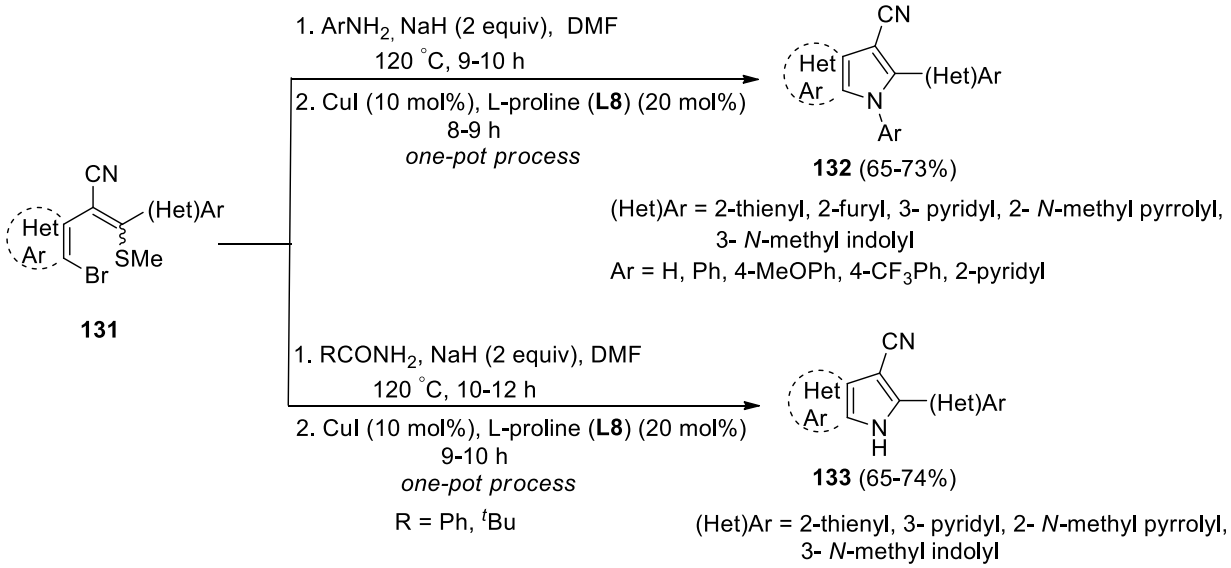
Early 2012, Zhao and his co-workers demonstrated a domino synthesis of 5,12-dihydroindolo[2,1-*b*]quinazoline derivatives **130** by using copper catalyzed Ullmann-type




**Scheme 1.49**: *Copper Catalyzed Ullmann-Type Intermolecular C—C and Intramolecular C—N Couplings*

intermolecular C—C and intramolecular C—N couplings (scheme 1.49).[60] They have also studied the substrate scope and limitations of the reactions.

In 2014, Ila research group identified a novel, efficient route to substituted 1-*N*-(het)aryl/NH-2-(het)aryl-3-cyanoindoles **132**, **133** and related pyrrolo-fused heterocycles (scheme 1.50).[61] The general strategy involves sequential cycloamination of readily available 2-[2-bromo(het)aryl]-3-(het)aryl-3-(methylthio)acrylonitrile **131** precursors with primary amines or amides through two key C—N bond-forming processes. In this approach, initially base-mediated intermolecular C—N bond formation occurs, further the intermediate was converted into their corresponding products **132** & **133** by copper catalyzed intramolecular arylamination process.




**Scheme 1.50**: *Synthesis of N-Functionalized/NH-Multisubstituted Indoles **132** & **133***

## 1.10 References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# Palladium Catalyzed Coupling Reaction of Aryl/Heteroaryl Halides with Deuterated Methanol: A facile Access of Deuterated Organic Compounds

## 2.1 Introduction

Deuterium is one of the naturally-occurring, stable and non-radioactive isotopes of hydrogen and obtained from the $D_2O$ (heavy water). Selective incorporation of deuterium in place of hydrogen leads to the retaining the pharmacologic profile of physiologically active compounds while, in certain instances, positively impacting their metabolic fate to considerably alter their overall therapeutic profile. In comparison with hydrogen, heavier molecular weight of the deuterium leads to formation of stronger molecular bonds and facilitates more stable resulting drugs. Due to the greater atomic mass of deuterium, C—D bonds are generally about six to ten times stronger than the corresponding C—H bonds. It helps to slow the rate of bond cleavage (kinetic isotope effect). The KIE of deuterium concerns the biological fate of many drugs that are metabolized by pathways involving C—H bond cleavage.[1]

Selective incorporation of deuterium in place of hydrogen is a powerful tool in medicinal chemistry.[2] Deuterated compounds are effectively utilized in studying reaction mechanism (Kinetic Isotopic Effects), catalysts pathways, for elucidation of biosynthetic pathways, as analytical standards, and for altering selectivity in total synthesis.[3] Further, these compounds are realized as potential drug candidates because of their unique ability of altering the therapeutic profile and metabolic fate of the drug thereby retaining its biochemical potency and selectivity.[4] For example, deuterated analogues[5] of paroxetine (CTP-347; antidepressant drug), [$D_9$]-and [$D_{22}$]-etacrynic acid *n*-hexylamides (diuretic drug), venlafaxine (SD-254; serotonin-norepinephrine reuptake inhibitor), and Atazanavit (CTP-518; HIV protease inhibitor), tetrabenazine (SD-809; chorea

associated with Huntingdon's disease), lisofylline (CTP-499; diabetic nephropathy) have entered in clinical trials.[2a,6-7] Selected deuterated compounds are shown in Figure 2.1.[8]

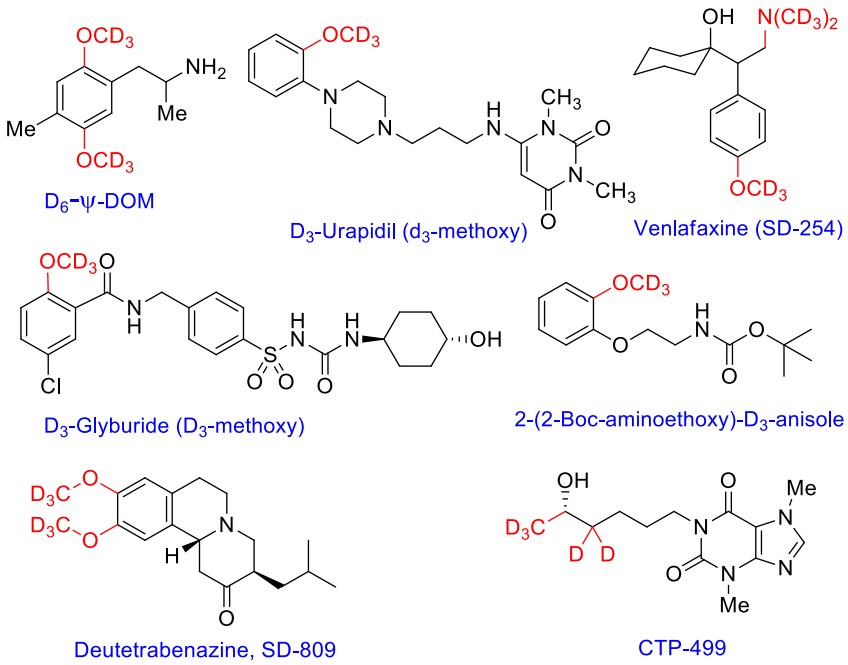



**Figure 2.1**: *Selected C—OCD₃ and C—D bond Containing Structural Motifs*

Very recently, DeWitt *et al.* found that differentiation of anti-inflammatory and anti-tumorigenic properties of deuterium stabilized enantiomers of thalidomide analogues (CC-122) in *in vitro* and *in vivo* efficacy models (Figure 2.2).[9] These findings open up a new window to improve therapeutic properties of other racemic drugs.[9] Hence, the deuterated drugs are increasingly in high demand in pharmaceutical industries.[10] Therefore, deuteration of organic compounds especially drugs have a great potential to

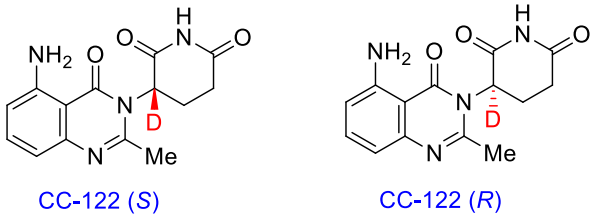



**Figure 2.2**: *Deuterated Enantiomers of Thalidomide Analogues*

generate new drugs with high therapeutic values. In this chapter, we discussed about a short literature survey of deuterated organic compounds synthesis.

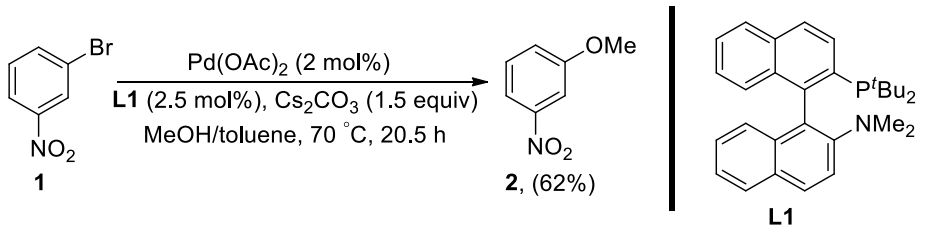
## 2.2 Methoxylation/Trideuteromethoxylation of Halo(hetero)arenes by C—O Cross-Coupling Reactions

The C—O bond forming reactions are interesting in organic synthesis due to presence of these bonds in numerous natural products, biological compounds, pharmaceuticals, fragrances, cosmetics and polymers.[11] In recent years, palladium and copper catalyzed cross-coupling reactions have become useful tools for the synthesis of aryl/alkyl (hetero)aryl ethers.[12] Due to the presence of ether bonds in numerous biologically important molecules, further developments of efficient C—O bond forming reactions are of continuing interest for organic chemists. Interestingly, deuterium labeled alkyl aryl ethers have the potential to alter the therapeutic profile and biological fate of the drugs, especially if these entities are metabolized through pathways involving C—H bond cleavage (Figure 2.1).[13] Most of the deuterated organic compounds are prepared by pH dependent and metal catalyzed H/D exchange reactions which require drastic conditions. Hence attempts to synthesize deuterated methyl aryl ethers by C—O bond forming reactions in relatively mild conditions would open an unprecedented plethora of synthetic scopes and clinical studies.

In general, alkyl (hetero)aryl ethers are synthesized through the classical method of *O*-alkylation by using strong alkylating agents (MeI, $Me_2SO_4$) that are often carcinogenic.[14] Further, traditional Williamson ether synthesis carried out at higher temperatures (300 °C) leads to low functional group tolerance.[15] Therefore, transition-metal catalyzed cross-coupling methodologies[16] have become an efficient and versatile tool for the synthesis of alkyl (hetero)-aryl ethers. Especially, palladium catalyzed C—O cross-coupling reactions are well developed with phenol and primary, secondary, and tertiary alcohols under comparably mild conditions.[17] During the last decade, Buchwald,[18] Hartwig,[19] Singer[20] and Beller[21] have designed a series of

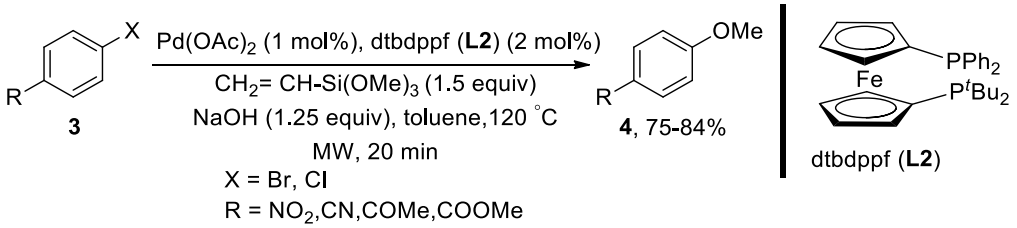
phosphane ligands that facilitate the palladium catalyzed C—O cross-coupling of various (hetero)aryl halides with different types of alcohols. Each of these individual protocols has its own limitations including the cumbersome synthesis of ligands, low selectivity of alcohols, low substrate scope, and unwanted formation of reduced arenes. In addition, simple methanol or its deuterated analogue was very difficult to couple with (hetero)aryl halides because of competing *β*- hydride elimination.

In 2001, the group of Buchwald described ligand effects in palladium catalyzed intermolecular C—O coupling of primary alcohols and aryl halides (Scheme 2.1).[22] During this process they studied the scope of reaction by changing the ligands with different *meta*-substituted aryl halides and alcohols. Synthesis of anisole derivative **2** from aryl bromide **1** was also reported in the presence of binaphthyl ligand **L1** under similar reaction conditions.



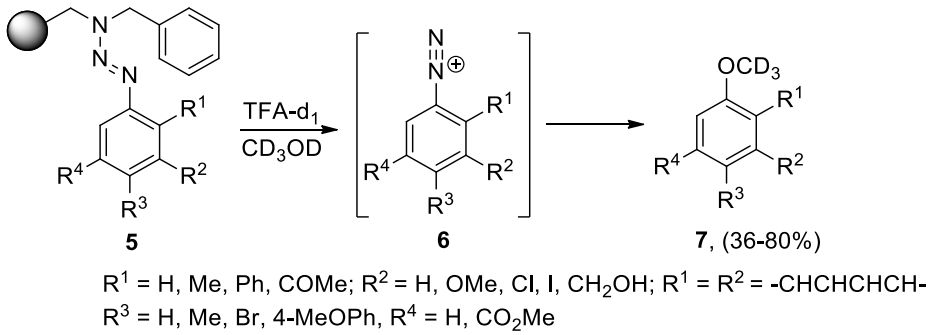

**Scheme 2.1**: *Methoxylation of 1-Bromo-3-nitrobenzene **1***

Clarke and co-workers observed the palladium catalyzed synthesis of aryl alkyl ethers **4** by using alkoxysilanes as nucleophiles in presence of sodium hydroxide as an activator and dtbdppf (1-di-tert-butyl-1′-diphenylphosphino ferrocene) (**L2**) as a ligand (Scheme 2.2).[23] However, this method has disadvantage due to cumbersome synthesis of the alkoxysilane precursors.



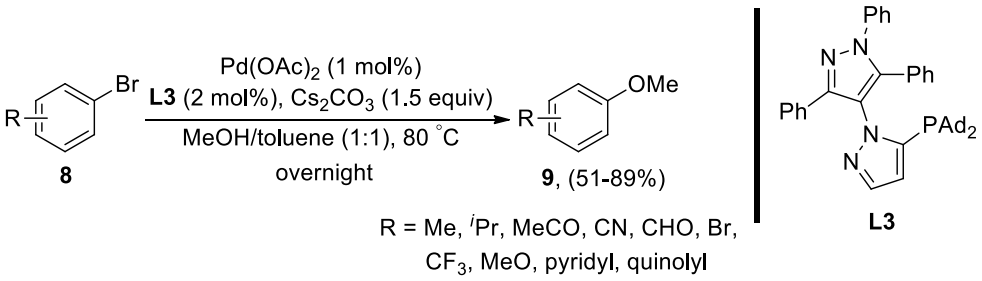

**Scheme 2.2**: *Coupling of Vinyl trimethoxysilane with Aryl Halides* ***3***

In 2011, Bräse group reported the solid phase synthesis of $D_3CO$-substituted arenes**7** by using immobilized triazenes **5** as precursors and deuterated methanol (Scheme 2.3).[24] However, excess deuterated methanol was used in the process and scaling up of the reactions was a practical problem.




**Scheme 2.3**: *Generation of* $D_3CO$*-Substituted Arenes* ***7*** *from Triazene Resins* ***5*** *in* $CD_3OD$

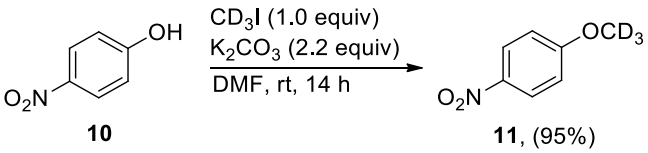
Recently, Beller came up with the first palladium catalyzed cross-coupling reaction of aryl halides **8** with methanol by using a novel air-stable adamantyl based phosphine ligand **L3**




**Scheme 2.4**: *Palladium Catalyzed Coupling Reactions of (Hetero)Aryl Halides with Methanol*

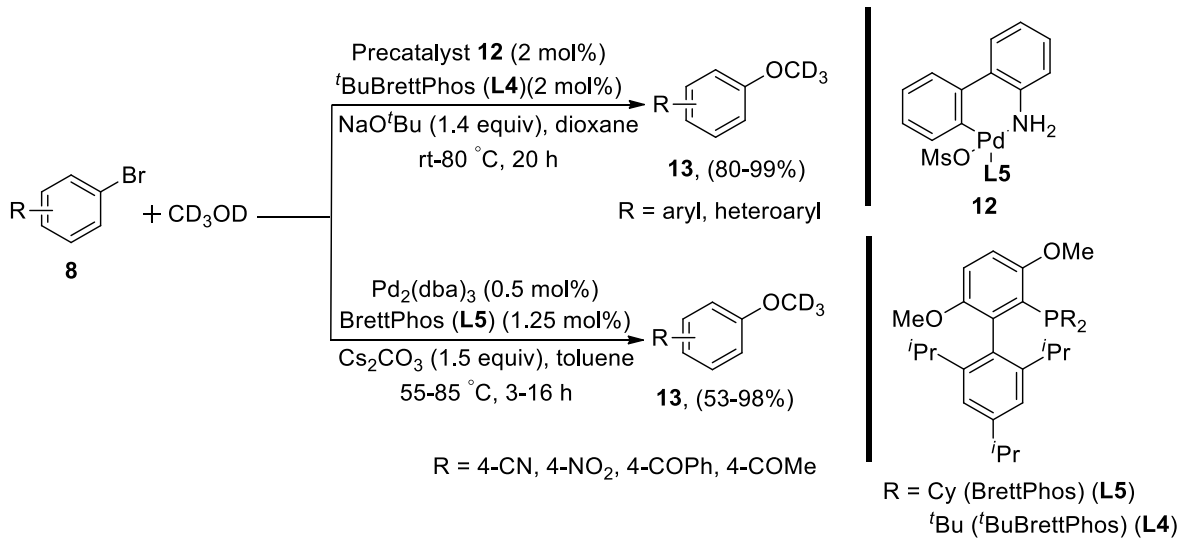
(Scheme 2.4).[25] The same protocol was also extended for synthesis of deuterated aryl methyl ethers.

Sando and co-workers reported the synthesis of 4-deuteromethoxy nitrobenzene **11** through classical method of *O*-alkylation by using strong alkylating agent $CD_3I$ (Scheme 2.5),[26] which is often carcinogenic.



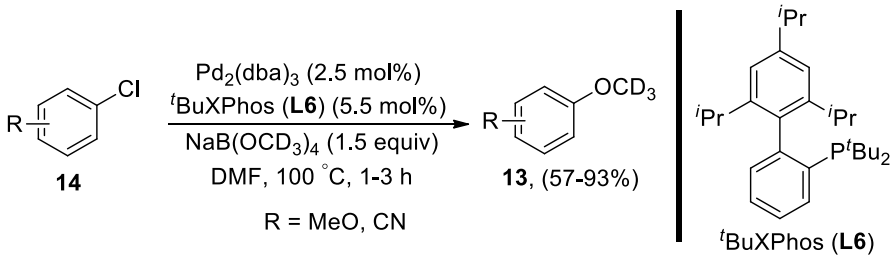

**Scheme 2.5**: *Synthesis of $D_3$-p-Nitromethoxybenzene **11***

Recently, Buchwald and Cheung reported a method for the synthesis of deuterated aryl ethers **13** in high yields under mild reaction conditions by using wide range of aryl and heteroaryl bromides **8** (Scheme 2.6).[27] Later, Rangarajan *et al.* described a simple and efficient palladium/BrettPhos-catalyzed C—O cross-coupling reaction of activated aryl bromides **8** with $CH_3OH/CD_3OD$ (Scheme 2.6).[28]




**Scheme 2.6**: *Palladium Catalyzed Deuteromethoxylation of Aryl and Heteroaryl Halides **8***

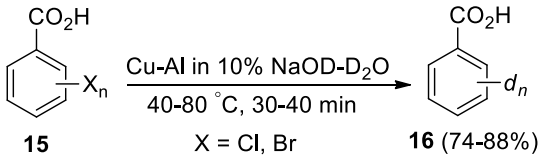
In 2014, Novak and his group disclosed a new and efficient synthetic protocol for the construction of trideuteromethoxylated compounds **13** by using palladium catalysed transformation of aromatic chlorides **14** with tetramethoxyborate salts (Scheme 2.7).[29]




**Scheme 2.7**: *Trideuteromethoxylation of Aryl Chlorides **14***

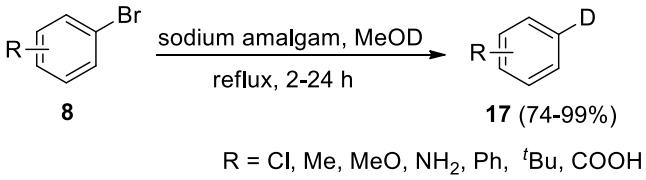
## 2.3 Deuteration of Aryl and Heteroaryl Halides

In 1983, Tashiro and Nakayama prepared all the possible ring deuteriated benzoic acids **16** by treatment of the corresponding bromobenzoic acids **15** with Raney Cu-Al alloy in 10% NaOD-$D_2O$ solution (Scheme 2.8).[30]



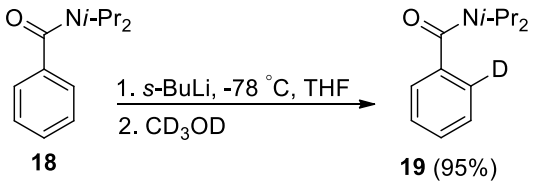

**Scheme 2.8**: *Deuteration of Halogenobenzoic Acids **15***

Miura and *et al.* utilized reductive debromination method of bromoarenes **8** with sodium amalgam/$CH_3OD$ to form the corresponding deuterated arenes **17** with high isotopic purities in high yields (Scheme 2.9).[31]



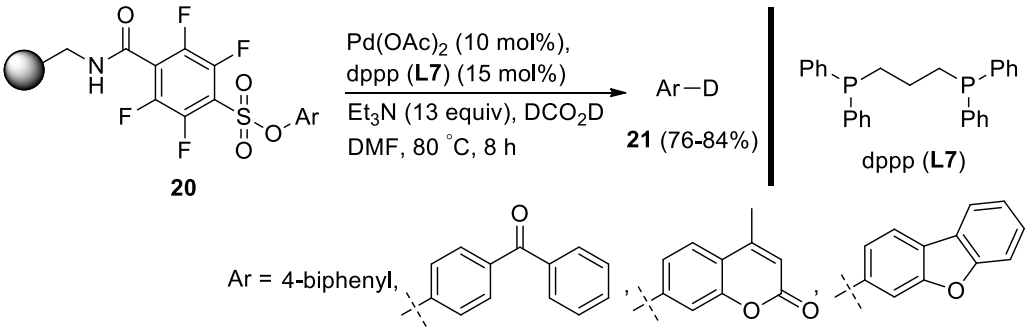

**Scheme 2.9**: *Deuteration of Bromo Aromatic Compounds **8** by Reductive Debromination*

Clayden *et al.* studied 'controlling the regioselectivity of lithiation' by using kinetic isotope effects of deuterium (Scheme 2.10).[32] For that *ortho*-deuteraion of amide **19** was carried out by using *S*-BuLi and $CD_3OD$.



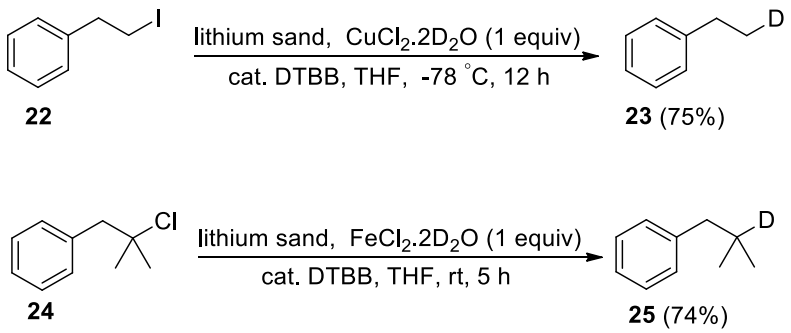

**Scheme 2.10**: *ortho-Deuteration of Benzamides **18***

Revell and Ganesan efficiently cleaved a tetrafluoroarylsulfonate solid-phase linker **20** in a traceless manner to the deoxygenated aromatic by Pd(0)-catalyzed transfer hydrogenation. Additionally they carried out the similar reaction of different sulfonate resins **20** with deuterated formic acid, and found to be equally successful as hydrogenation (Scheme 2.11).[33]



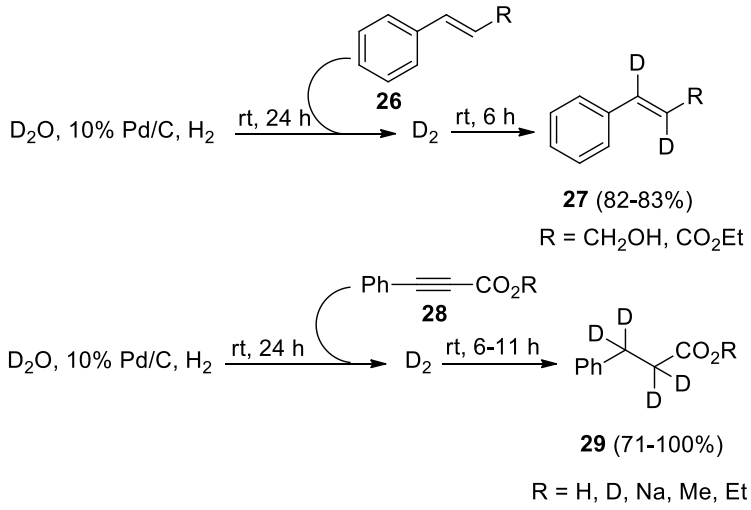

**Scheme 2.11**: *Deuteration of Polystyrene-Tetrafluoroarylsulfonate Linkers **20***

Yus and co-workers disclosed a hydrodehalogenation method of alkyl and aryl halides by using a reducing systems composed of $CuCl_2 \cdot 2H_2O$ and $FeCl_2.4H_2O$ with excess of lithium sand and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) as electron carrier, in tetrahydrofuran at room temperature (Scheme 2.12).[34] They also examined few substrates for deuterodehalogenation.



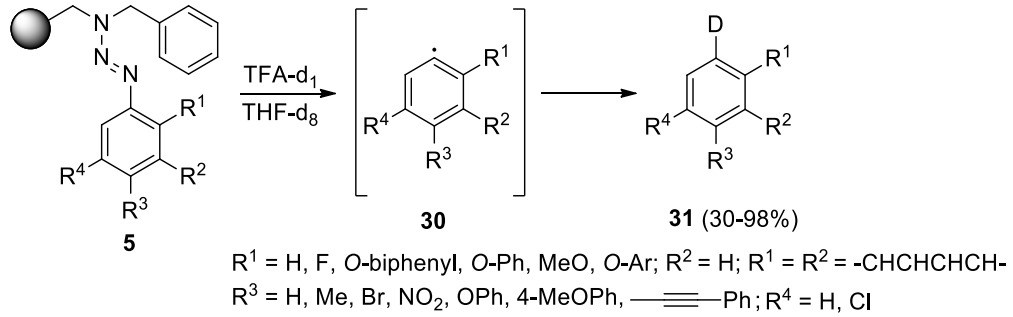

**Scheme 2.12**: *DeuteroDehalogenation of Organic Halides **22** & **24***

Further, the group of Sajiki described an *in situ* generated deuterium gas ($D_2$) which is obtained by the Pd/C-catalyzed $H_2$–$D_2$ exchange reaction using a $H_2$–$D_2O$ combination for the reductive deuteration of various reducible functionalities and the chemoselective one-pot deuterogenation of olefins **26** and acetylenes **28** (Scheme 2.13).[35]



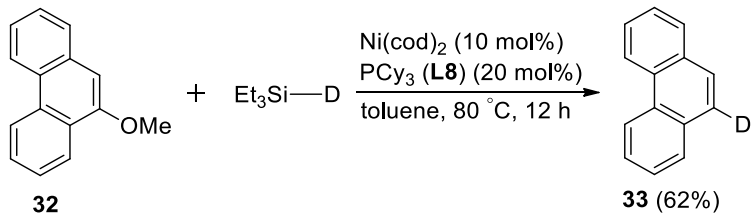

**Scheme 2.13**: *Catalytic Deuteration of Olefins **26** and Acetylenes **28***

Bräse and co-workers also studied selective D-incorporation into arenes from immobilized triazene precursors **5** (Scheme 2.14).[24] However, this method suffers with multi-step synthetic process of starting precursors **5**.



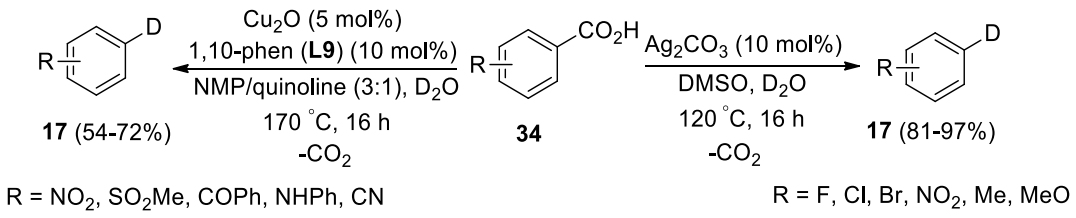

**Scheme 2.14**: *Cleavage of Monodeuterated Arenes **31** from Triazene Resins **5***

Tobisu *et al.* developed a nickel catalysed reductive deoxygenation of alkyl aryl ethers **32** (Scheme 2.15).[36] During this study they tried a deuterium labeling experiment for the reductive cleavage of a methoxy group by using $DSiEt_3$ as a reducing agent.




**Scheme 2.15**: *Nickel Catalyzed Reductive Cleavage of Aryl–Oxygen Bonds with Deuterosilanes*

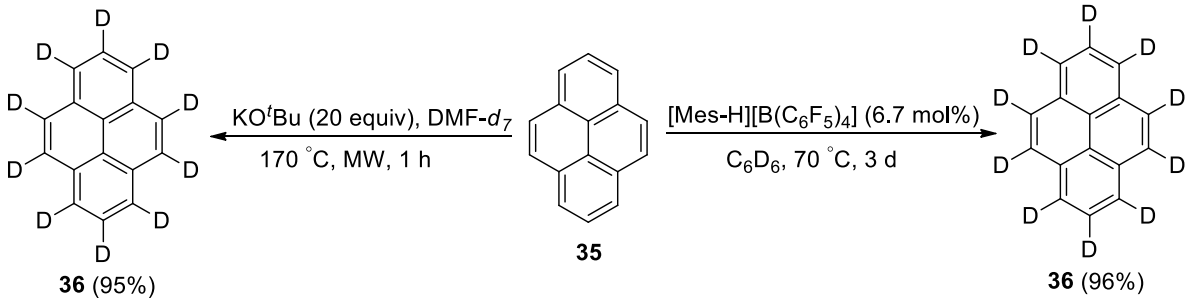
In 2012, Gooßen and Larrosa individually developed copper and silver catalysed practical, mild and highly selective protocols for the monodeuteration of a variety of arenes




**Scheme 2.16**: *Copper and Silver Catalyzed Deutero-Decarboxylation*

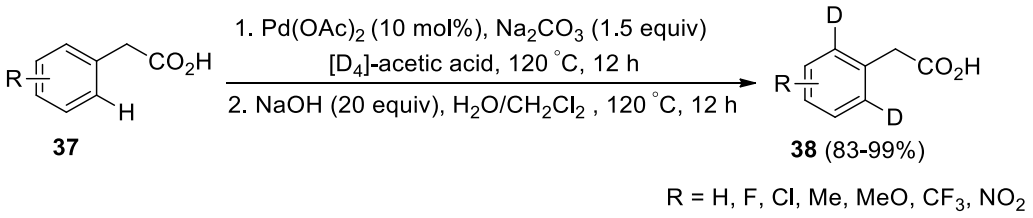
and heteroarenes **17** from aromatic carboxylic acids **34** (Scheme 2.16).[37]

Scott and Siegel individually developed two new protocols for the deuteration of polycyclic aromatic hydrocarbons **35** (Scheme 2.17).[38] Scott synthesized various deuterated polycyclic aromatic hydrocarbons **36** under microwave irradiation of **35** in a solution of KO$^t$Bu/DMF-$d_7$. On the other hand, Siegel showed arenium acid [mesitylene−H]+ was an extraordinarily active H/D exchange catalyst for the perdeuteration of polycyclic aromatic hydrocarbons **35**.




**Scheme 2.17**: *Deuteration of Polycyclic Aromatic Hydrocarbons **35***

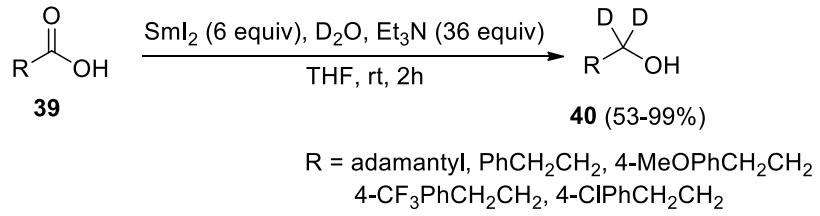
Yu and co-workers disclosed a protocol for the palladium catalysed *ortho*-deuteration of arenes **37** bearing weakly coordinated directing groups. They have shown phenylacetic acids **37** are suitable substrates for this reaction (Scheme 2.18).[39]




**Scheme 2.18**: *Palladium Catalyzed ortho-Deuteration of Phenylacetic Acids **37***

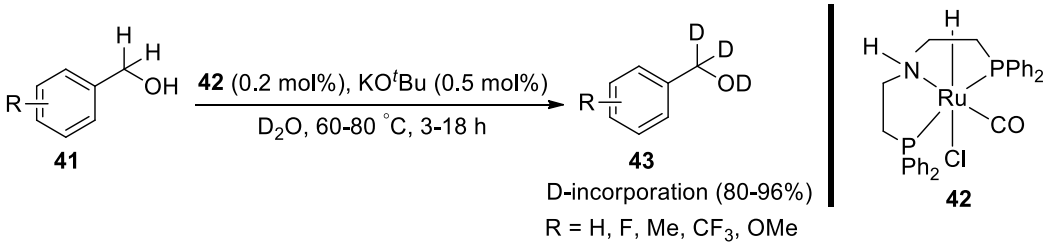
Recently, Procter and his group reported the first general method for the chemoselective synthesis of $\alpha,\alpha$-dideuterio alcohols **40** from feedstock carboxylic acids **39** by using $SmI_2$

(Scheme 2.19).[40] This process proceeds through the activation of Sm(II) with a Lewis base at room temperature.




**Scheme 2.19**: *Synthesis of α,α-Dideuterio Alcohols **40***

Very recently, Gunanathan *et al.* reported a highly selective ruthenium catalysed *α*-deuteration of primary alcohols **41** (Scheme 2.20).[41] They used deuterium oxide ($D_2O$) as a source of deuterium and reaction solvent.




**Scheme 2.20**: *Selective α-Deuteration of Aryl Methanols **41***

Despite excellent selectivities and high D-incorporation, each of these individual protocols has its own limitations owing to multi-step synthesis of starting materials, use of large excess deuterated solvents, excess of metal salts, higher catalyst loading & less heterocyclic substrates. Therefore, developing a simple and catalytic method for synthesis of deuterated compounds is always needed.

Overall, no general methodology is available for the simple palladium catalyzed cross-coupling reaction of (hetero)aryl halides with $CH_3OH/CD_3OD$ in presence of air-stable readily available ligand. Moreover, due to the underlying importance of methyl/$d_3$-methyl aryl ethers in biologically important molecules and increasing demand for stable deuterium labelled

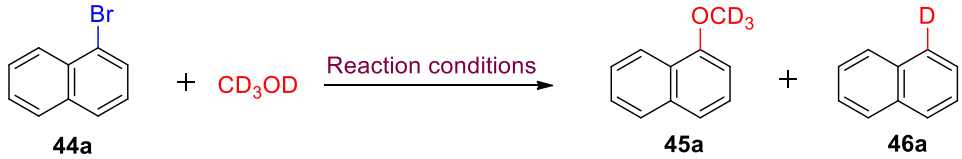
compounds, their synthesis remains a big challenge for the chemists. After seeing the literature methods, we were interested in investigating the cross-coupling reactions of aryl/hetero aryl halides with methanol/deuterated methanol which pose challenges because of the low boiling point of methanol and formation of reduced arenes. Further, commercially available ligands are more attractive than synthesis of new ligands for this process.

## 2.4 Results and Discussions

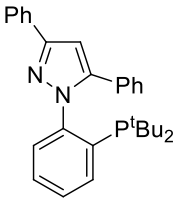
### 2.4.1 Trideuteromethoxylation of Halo(hetero)arenes

Over the last ten years, commercially available Buchwald diaryl phosphine ligands have drawn interest in the development of palladium catalyzed cross-coupling reactions thereby meeting both academic and industrial needs.[42] Therefore, we decided to investigate bulky ligands for the palladium catalyzed C—O cross-coupling reaction of aryl halides with $CD_3OD$-a difficult coupling partner. Initially, the reaction of 1-bromonaphthalene (**44a**) with $CD_3OD$ was investigated as a model system in the presence of 5 mol % $Pd(OAc)_2$ and ligands **L6**, **L10**-**L14**. In the absence of ligands **L6**, **L10**-**L14** only the well-known side product dehalogenated naphthalene **46a** was observed. However, the use of the bulky mono-*trippyPhos* (**L10**) ligand under similar conditions gave a negligible amount of desired 1-[$D_3$]-methoxynaphthalene (**45a**) along with a considerable amount of reduced product **46a** (Table 2.1, entry 1). The results were even more disappointing with the commercially available ferrocene-based *dppf* (**L11**) ligand. On the other hand, experiments performed in the presence of *DavePhos* (**L12**) provided a better yield than that obtained with ligands **L10** and **L11** but gave only 11% yield of **45a**. On the basis of this result, we started screening with known bisnaphthyl ligand *TrixiePhos* (**L13**), which afforded expected product **45a** in 75%yield. Unfortunately, the use of this ligand in the absence of a co-solvent resulted in a decrease in the yield by 45%.

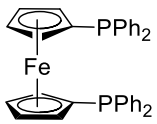
**Table 2.1**: **Screening of Ligands for Trideuteromethoxylation**[a]



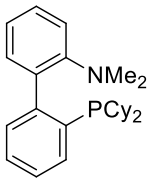

**44a** **45a** **46a**



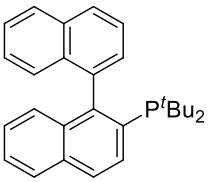
**L10** (49)
**45a** = 1%
**46a** = 28%



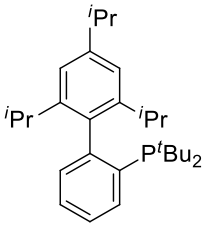
**L11** (83)
**45a** = 1%
**46a** = 54%



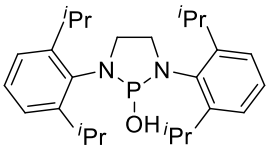
**L12** (100)
**45a** = 11%,
**46a** = 74%



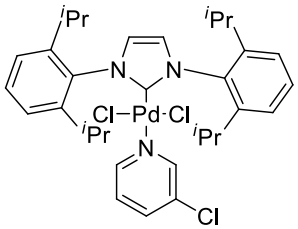
**L13** (100)
**45a** = 75%,
**46a** = 12%



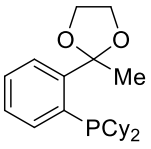
**L6** (100)
**45a** = 83%
**46a** = traces



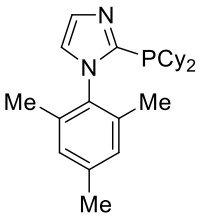
**L14** (40)
**45a** = <1%,
**46a** = 10%



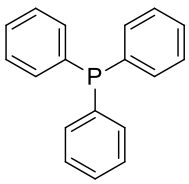
**PEPPSI-IPr** (100)
**45a** = 0%
**46a** = 65%



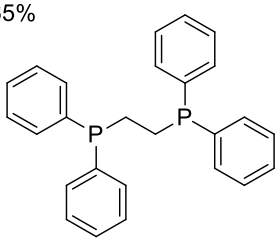
**L15** (80)
**45a** =1%
**46a** = 57%



**L16** (85)
**45a** = 0%
**46a** = 48%



**L17** (60)
**45a** = 0%
**46a** = 41%



**L18** (40)
**45a** = 0%,
**46a** = 25%

*[a] Reaction Conditions: 1-Bromonaphthalene (**44a**) (0.5 mmol), $CD_3OD$ (0.5 mL), $Pd(OAc)_2$ (5 mol%), **L6**, **L10-L18** (10 mol%), $Cs_2CO_3$ (1.5 mmol), Toluene (0.5 mL), 80 °C, 8 h. [b] Conversions are inside the parenthesis. [c] GC yield.[d] Without any co-solvent.*

Gratifyingly, when the experiment was performed in the presence of commercially available *$^t$BuXPhos* (**L6**) ligand, the yield improved to 83%. To further improve the yield, we examined different ligands (Table 2.1, **L14**-**L18**); however, bulky monodentate ligand **L6** turned out to be the best for this model reaction. These results once again emphasized the

importance of bulky diarylphosphane ligands for cross-coupling reactions of aryl halides with alcohols.

To our delight, the use of $^t$BuXPhos (**L6**) gave rise to an 85% yield of desired 1-[$D_3$]-methoxynaphthalene (**45a**) as a bench mark reaction. For further fine-tuning of this process, other palladium precursors such as $PdCl_2(MeCN)_2$, $PdCl_2(PPh_3)_2$ and $Pd_2(bda)_3$ were screened and found to be less beneficial when compared with $Pd(OAc)_2$ (Table 2.2). The coupling process was further optimized by varying bases such as KOH, $Et_3N$, $K_2CO_3$, and $Cs_2CO_3$ and the best results were obtained by using $Cs_2CO_3$ (Table 2.3). Interestingly, we observed that

**Table 2.2**: **Palladium Sources Screening of Trideuteromethoxylation Reactions**[a,b]

| Entry | Palladium Sources | Conversion | **45a** (%Yield) | **46a** (% Yield) |
|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | 40[c] | - | 19 |
| 2 | $PdCl_2(PPh_3)_2$ | 83 | 49 | 15 |
| 3 | $Pd_2(dba)_3$ | 100 | 70 | 20 |
| 4 | $PdCl_2(MeCN)_2$ | 100 | 78 | 4 |

*[a] Reaction Conditions: 1-Bromonaphthalene (**44a**)(0.5 mmol), $Pd(OAc)_2$(5 mol%), **L6**(10 mol%), $Cs_2CO_3$ (1.5 mmol), Toluene (0.5 mL), $CD_3OD$ (0.5 mL), 80 °C, 8 h. [b] GC yield. [c] Without co-solvent.*

**Table 2.3**: **Bases Screening of Trideuteromethoxylation Reactions**[a,b]

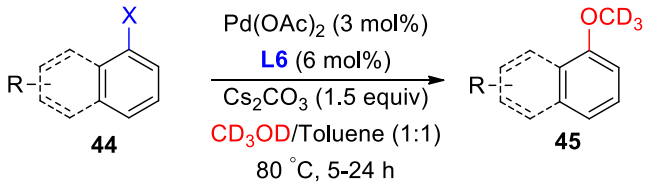
| Entry | Bases | Conversion | **45a** (% Yield) | **46a** (% Yield) |
|---|---|---|---|---|
| 1 | KOH | 100 | 72 | 4 |
| 2 | $K_2CO_3$ | 100 | 78 | 5 |
| 3 | $Et_3N$ | 30 | - | 15 |
| 4 | $Cs_2CO_3$ | 100 | 90 (85)[c,d] | - |

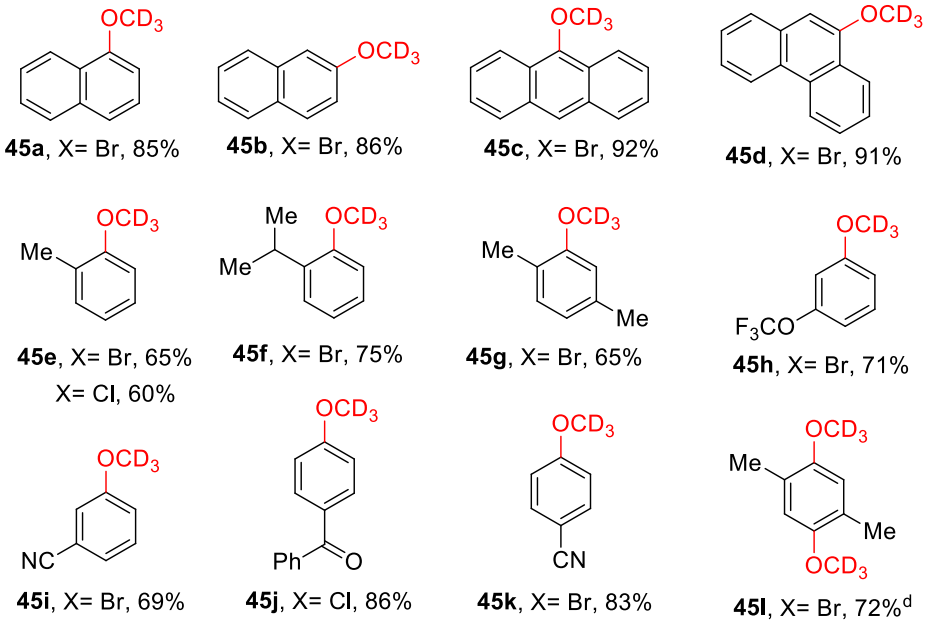
*[a] Reaction Conditions: 1-Bromonaphthalene (**44a**) (0.5 mmol), $Pd(OAc)_2$ (5 mol%), **L6**(10 mol%), $Cs_2CO_3$ (1.5 mmol), Toluene (0.5 mL), $CD_3OD$ (0.5 mL), 80 °C, 8 h. [b] GC yield. [c] Pre-activation protocol. [d] Isolated yield is inside the parenthesis.*

preactivation of $Pd(OAc)_2$ (3 mol% ) and **L6** (6 mol%) in toluene at 80 °C followed by subsequent addition of 1-bromonaphthelene (**44a**) in $CD_3OD$ gave an improved yield (90%, GC yield).

With the optimized conditions in our hand, we examined a series of polyaromatic bromides. These bromides were effectively coupled with $CD_3OD$ to furnish the corresponding [$D_3$]-methoxypolyaromatic compounds in excellent yields (Table 2.4, **45a-d**). Next, we performed the coupling of *ortho*-bromotoluene and the corresponding chloride with $CD_3OD$ and both of them were smoothly converted into the corresponding ether in moderate yield (65 and 60% respectively, Table 2.4, **45e**). Similarly, the sterically hindered substrate 1-bromo-2-

**Table 2.4**: **Palladium Catalyzed Coupling Reactions of Aryl Halides with Deuterated Methanol**[a,c]



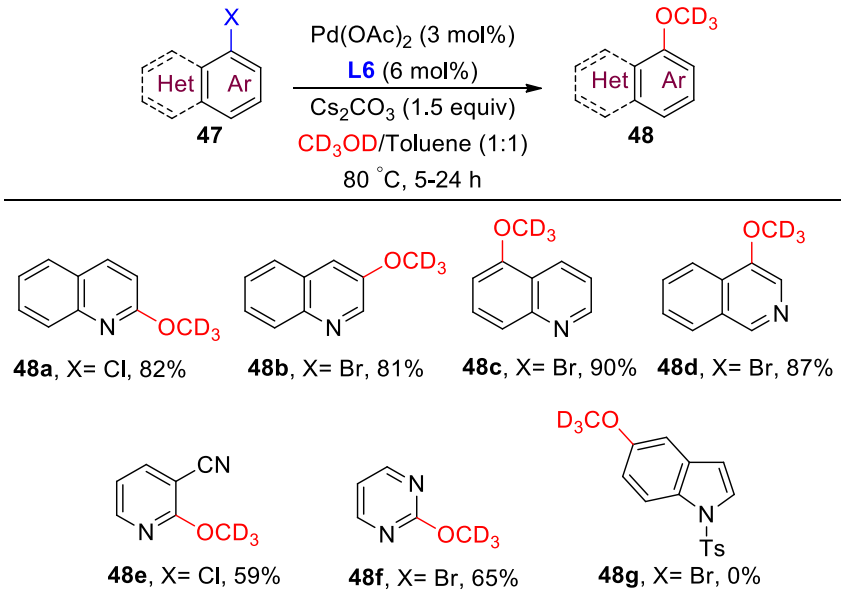




[a] *Reaction Conditions: 1-Bromonaphthalene (**44a**) (0.5 mmol), $CD_3OD$ (0.5 mL), $Pd(OAc)_2$ (3 mol%), **L6** (6 mol%), $Cs_2CO_3$ (1.5 mmol), Toluene (0.5 mL), 80 °C, 8 h.* [b] *Isolated yield.* [c] *Complete consumption of starting material as monitored by TLC and GC/MS analysis.* [d] *$Pd(OAc)_2$ (6 mol%) and **L6** (12 mol%) were used.*

isopropylbenzene gave the corresponding ether in 75% yield (Table 2.4, **45f**). On the other hand, substrats possessing an electron-withdrawing group at either the *meta*- or *para*-position (CN, $OCF_3$, and COPh) were coupled successfully with $CD_3OD$ to afford the products in moderate to very good yields (Table 2.4, **45h-k**). Interestingly, 2,5-dibromo-*p*-xylene was transformed into corresponding ether product **45l** in 72% yield. The reaction takes place *via* di-[$D_3$]-methoxylation in [$D_4$]-methanol as described in the reaction conditions.

We next turned our attention towards the synthesis of [$D_3$]-methoxylated heterocycles by applying our established synthetic methodology. Unfortunately, this coupling reaction was not explored in substrates such as activated and non-activated quinoline, isoquinoline, pyrimidine, and indole. Thus, 2-chloroquinoline was rapidly coupled with $CD_3OD$ to afford 2-[$D_3$]-methoxy-quinoline in very good yield (82%; Table 2.5, **48a**). In addition, non-activated

**Table 2.5**: **Palladium Catalyzed Coupling Reactions of Heteroaryl Halides with $CD_3OD$**[a]



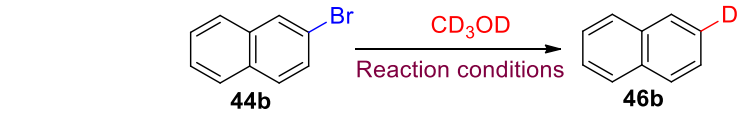

[a] *Reaction Conditions:* ***47*** *(0.5 mmol),* $CD_3OD$ *(0.5 mL),* $Pd(OAc)_2$ *(3 mol%),* ***L6*** *(6 mol%),* $Cs_2CO_3$ *(1.5 mmol), Toluene (0.5 mL), 80 °C, 8 h.* [b] *Isolated yield.* [c] *Complete consumption of starting material as monitored by TLC and GC/MS analysis.*

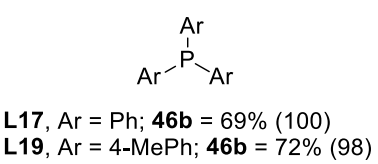
substrates like 3- and 5-bromoquinolines were smoothly converted into the corresponding coupled products in excellent yields (Table 2.5, **48b-c**). This process could also be successfully applied to the more challenging substrate 4-bromoisoquinoline (**47d**) to give **48d** in 87% yield. Further, other heteroaryl halides like 2-chloro-3-cyanopyridine (**47e**) and 2-bromopyrimidine (**47f**) proved to be suitable substrates for this process and delivered the products in moderate yields (Table 2.5, **48e** and **48f**). Unfortunately, 5-bromo-*N*-tosylindole (**47g**) gave only detosylated indole, and desired product **48g** was not detected in the reaction mixture.

### 2.4.2 Catalytic Selective Deuteration of Halo(hetero)arenes

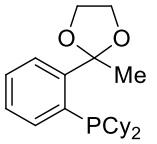
During our trideuteromethoxylation studies,[43] we observed that few ligands (**L12** and **L13**, Table 2.1) gave a mixture of deutero and trideuteromethoxy aromatic compounds. To accomplish an exclusive deuterated product, we started the optimization studies with a set of commercially available ligands for the deuteration of aryl halides (Table 2.6). Thus, the reaction of 2-bromonaphthalene (**44b**) with $CD_3OD$ was investigated as a model system in the presence of 5 mol% $Pd(OAc)_2$ and 5-10 mol% ligands (Table 2.6). In most of the cases, the reaction was completed within 12 hours, however yield of the product **46b** was ranging from 45 to 72%. Gratifyingly, an experiment performed in the presence of *cataCXium®A* (**L21**) ligand provided an improved yield of 94%. On the other hand, with *PEPPSI,* a carbene based ligand, a lower yield was obtained compared to ligand **L21**.For further fine tuning of this process, other palladium precursors such as $PdCl_2(MeCN)_2$, $PdCl_2(PPh_3)_2$ and $Pd_2(dba)_3$were screened and found to be less beneficial when compared with $Pd(OAc)_2$. However, in the case of bases, $K_3PO_4$ gave a better yield compared with KOH, $Et_3N$, $K_2CO_3$ and $Cs_2CO_3$. Interestingly, we obtained quantitative yield of **46b** when the catalyst loading was reduced from 5 mol% to 1 mol% and the reaction was completed within 16 hours.

**Table 2.6**: **Ligand Screening for Deuteration of 2-Bromonaphthalene**[a-e]

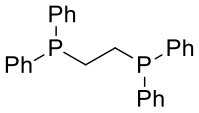


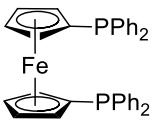
**L17**, Ar = Ph; **46b** = 69% (100)
**L19**, Ar = 4-MePh; **46b** = 72% (98)
**L20**, Ar = 2-Furyl; **46b** = 45% (100)



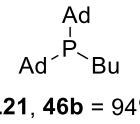
**L15**, **46b** = 46% (65)



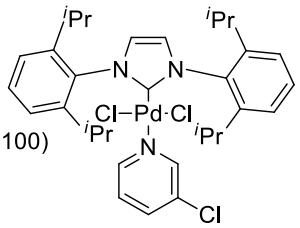
**L18**, **46b** = 62% (100)[d]



**L11**, **46b** = 70% (100)[d]



**L21**, **46b** = 94% (100)

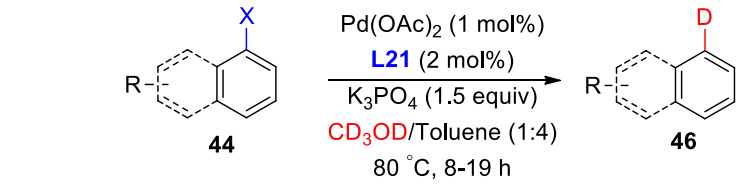


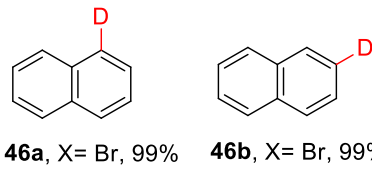
*PEPPSI*, **46b** = 67% (99)[e]

[a] *Reaction Conditions: 2-Bromonaphthalene (**44b**) (0.5 mmol), $Pd(OAc)_2$ (5 mol%), **L15**, **L17, L19-L21** (10 mol%), $Cs_2CO_3$ (0.75 mmol), $CD_3OD$/Toluene (1:4), 80 °C, 12 h;* [b] *Conversions are inside the parenthesis;* [c] *GC yield;* [d] ***L11*** *and **L18** (5 mol%);* [e] *Without $Pd(OAc)_2$.*

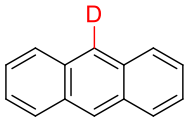
With the optimized conditions in our hand, we examined a series of polyaromatic bromides for the deuteration reaction. These bromides were effectively deuterated furnishing the corresponding deuteropolyaromatic compounds **46a-d** in excellent yields (Table 2.7, **46a-d**). Next, we performed the deuteration of the aryl halides having an electron withdrawing group at the *para*-position. Thus, 4-cyano and 4-nitro bromobenzenes gave the corresponding deuterated 4-nitro and 4-cyanobenzenes only in moderated yields (Table 2.7, **46e-f**). On the other hand, benzoyl substituted phenyl chloride was smoothly converted to 4-deuterobenzophenone (**46g**) in excellent yield whereas the alkoxy substituted bromide **44h** gave only 66% of deuterated compound **46h**. However, *ortho*-substituted bromide **44i** afforded the corresponding product **46i** in excellent yield (90%). Similarly, the deuteration of sterically hindered substrate 1-bromo-2,4,6-tri-*t*-butylbenzene gave the corresponding deuterated product **46j** in 85% yield. Interestingly, 6,6′-dibromo-MOM-protected *R*-BINOL **44k** was transformed into the corresponding deuterated product **46k** in 90% yield (Table 2.7).

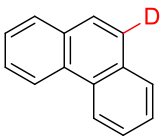
**Table 2.7: Catalytic Deuteration of Aryl Halides**[a]

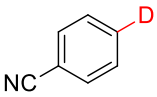


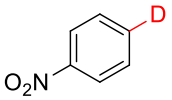


**46a**, X= Br, 99%

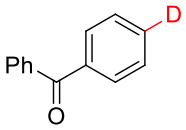

**46b**, X= Br, 99%

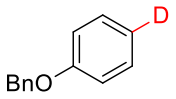

**46c**, X= Br, 99%

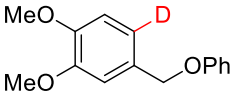

**46d**, X= Br, 94%

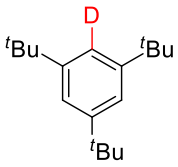

**46e**, X= Br, 58%

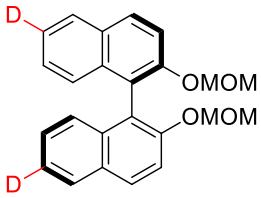

**46f**, X= Br, 64%


**46g**, X= Cl, 96%


**46h**, X= Br, 66%


**46i**, X= Br, 90%

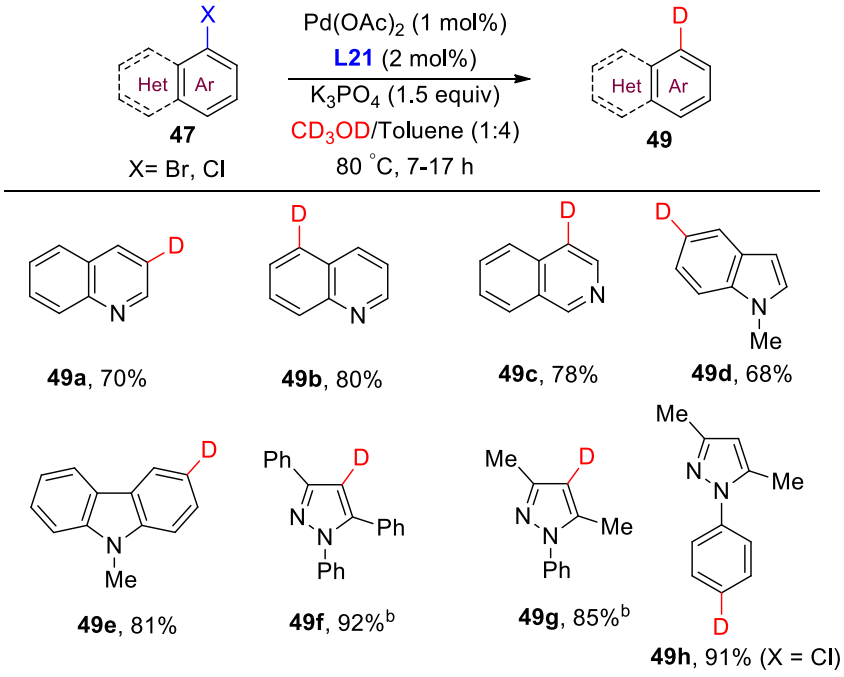

**46j**, X= Br, 85%[b]


**46k**, X= Br, 90%

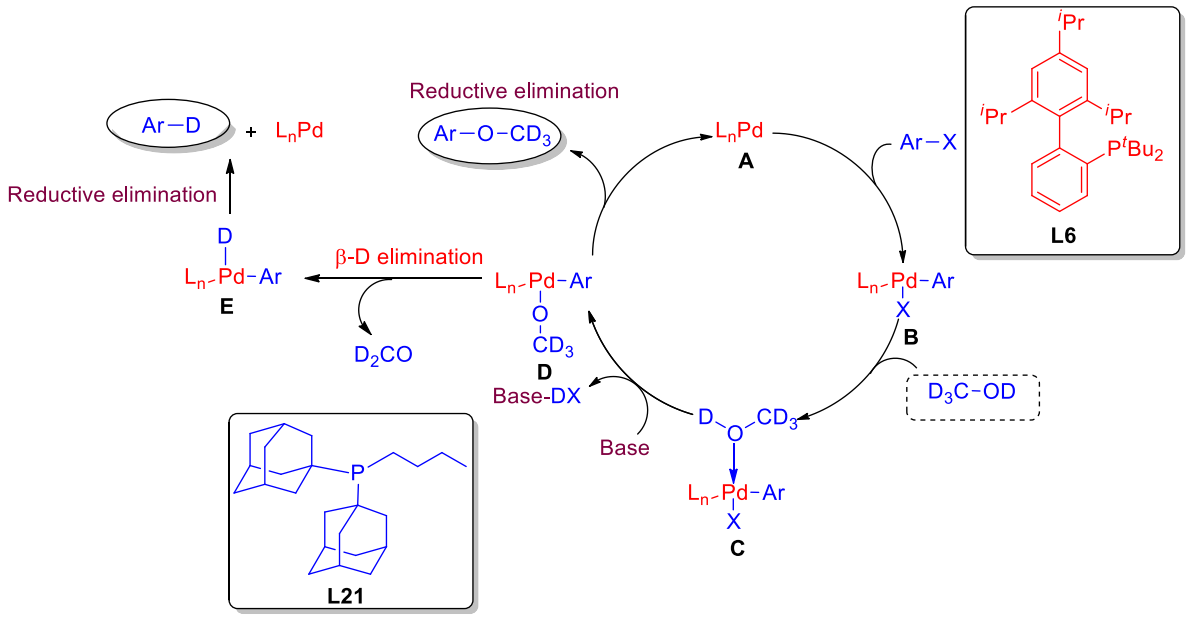
[a] *Isolated yields;* [b] *5 mol% Pd(OAc)$_2$ & 10 mol%* ***L21*** *were used.*

We next turned our attention towards the synthesis of deuterated heterocycles by applying our established synthetic methodology. Thus, 3- and 5-bromoquinolines were smoothly converted into the corresponding deuterated quinolines in good to very good yields (Table 2.8, **49a-b**). This process could also be successfully applied to 4-bromoisoquinoline (**47c**) yielding 78% of **49c**. Further, other heteroaryl bromides like 5-bromo-*N*-methylindole and 4-bromo-*N*-methylcarbazole proved to be suitable substrates for this process to deliver deuterated products in 68% & 81% yields respectively (Table 2.8, **49d-e**). Interestingly, bromo and chloro substituted pyrazoles **47f-h** were transformed into the corresponding deuterated products **49f-h** in very good to excellent yields (Table 2.8).

**Table 2.8**: **Catalytic Deuteration of Heteroaryl Bromides**[a]




[a] *Isolated yields;* [b] *5 mol% $Pd(OAc)_2$ & 10 mol%* ***L21*** *were used.*

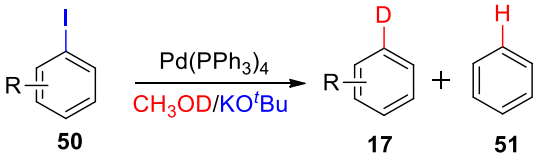



**Scheme 2.21**: *Proposed Mechanism for Palladium-Catalytic Cycle*

As shown in Scheme 2.21, we propose a mechanism which involves a palladium catalytic cycle. The first-step is the $Pd(OAc)_2$ in the presence of strong $\sigma$-donating ligand **L6**

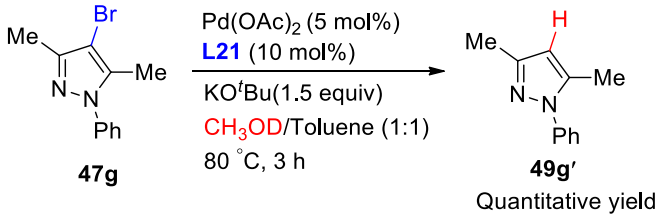
or **L21**, accelerating the oxidative addition of the catalyst **A** to form **B**. This step is most commonly believed to be the rate determining step. Next step is base-assisted displacement of the halide from **C**, followed by *β*-D-elimination of $D_2CO$ and reductive elimination of Ar–D to regenerate the Pd(0) species (**A**). On the other hand, if the reaction proceeds through the reductive elimination of **D**, alkylaryl ethers are the final products.

Recently, McIndoe *et al.* studied mechanistic investigation of deuterodehalogenation of aryl iodide **50** in the presence of $CH_3OD$ and KO$^t$Bu (Scheme 2.22)[44]. They obtained a mixture of deuterated and dehalogenated products **17** & **51**. According to his investigation under strong basic conditions hydrogen and deuterium exchange will takes place before the reductive elimination process.



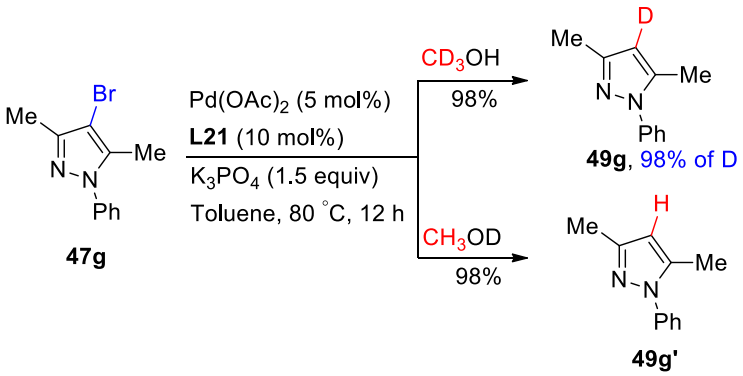

**Scheme 2.22**: *H/D Exchange and Formation of a Mixture of Products*

To understand the catalytic cycle, we performed a similar experiment with bromo pyrazole **47g** and $CH_3OD$. Under strong basic condition also we did not find trace amounts of deuterated product **49g**. Interestingly, our methodology provides quantitative yield of dehalogenated product **49g′** (Scheme 2.23).



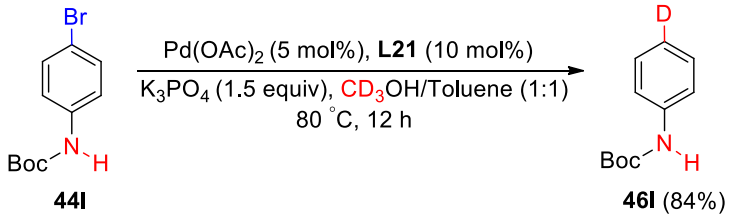

**Scheme 2.23**: *Controlled Experiment for Dehalogenation*

Our methodology provides a highly selective product depending upon methanol ($CD_3OH$ *vs* $CH_3OD$). To validate the proposed cycle, we performed two separate experiments with $CD_3OH$ and $CH_3OD$ respectively (Scheme 2.24). The first experiment gave exclusively deuterated product **49g** whereas the second experiment did not give a trace amount of **49g**, instead formed **49g′** (Scheme 2.24). These experiments clearly support that the D/H transfer occurs from the $CD_3/CH_3$.




**Scheme 2.24**: *Deuteration of 4-Bromopyrazole **47g** with $CD_3OH$ & $CH_3OD$*

To see if this methodology is reasonable, we performed an experiment with Boc-protected 4-bromoaniline **441**. We obtained exclusively 4-deuteroaniline **46l** without the exchange of acidic proton (Scheme 2.25). Hence, we believe that there is no H/Dexchange during the reaction and deuterium incorporation occurs from the reductive elimination process.

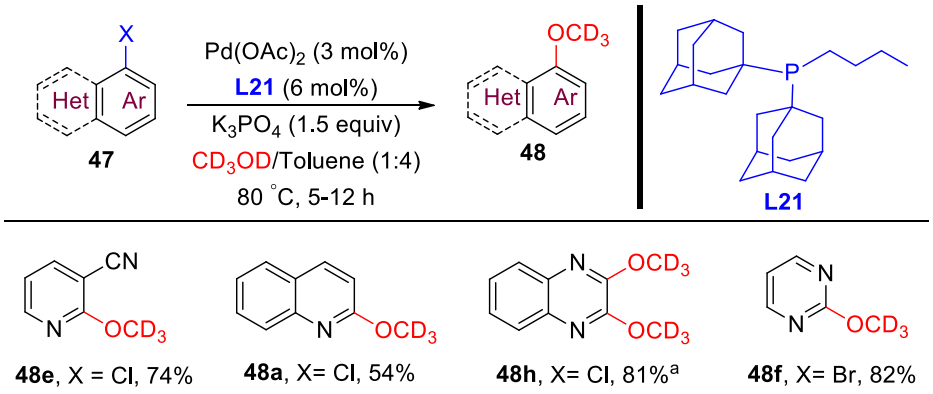



**Scheme 2.25**: *Selective Deuteration of 4-Bromoaniline **44l** with $CD_3OH$*

Further, we extended this methodology to highly activated heteroaryl halides **47**. In the case of highly activated substrates we found deuteromethoxylated products **48** instead of

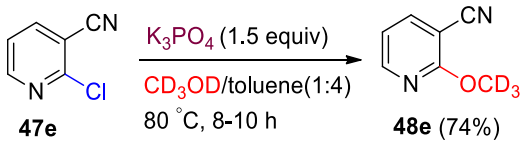
deuterated products **49**. More activated 2-chloro3-cyano pyridine (**47e**) gave better yield of trideuteromethoxylated product **48e** as compare to the 2-chloroquinoline (**47a**). Interestingly, dichloro substituted quinoxaline **47h** was transformed into corresponding deuterated anisole **48h** product with 81% yield. However, 2-bromopyrimidine (**47f**) also converted into 2-$d_3$-Methoxypyrimidine (**48f**) with very good yield (Table 2.9). These results were quite surprising to us.

**Table 2.9**: **Palladium Catalyzed C—O Cross-Coupling Reactions of Activated Heteroaryl Halides**



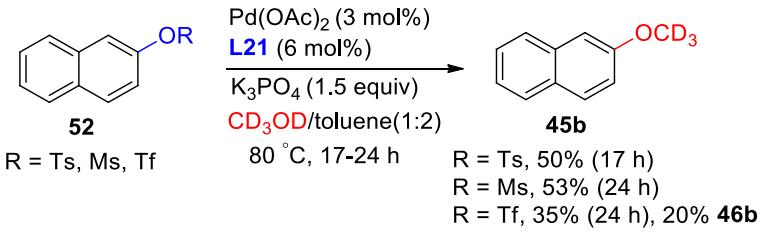

[a] *5 mol% $Pd(OAc)_2$, 10 mol% **L21**, $K_3PO_4$ (3 equiv.), $CD_3OD$/Toluene (1:4), 80 °C,12 h.*

To understand the reaction process, we performed a controlled experiment in the absence of ligand and catalyst. Interestingly, in this case also we observed trideuteromethoxylated product **48e**. From this experiment we confirmed that activated substrates under goes nucleophilic aromatic substitution reaction with $CD_3OD$ (Scheme 2.26).




**Scheme 2.26**: *Controlled Experiment for Trideuteromethoxylation*

We also studied the scope of reaction with different tosyl, mesyl and triflate based arenes. 2-tosyl and mesylated naphthalenes (**52a**) & (**52b**) provided corresponding deuterated anisole product **45b** with 50-53% yields. Whereas, in the case of triflate substituted naphthalene **52c**, mixture of trideuteromethoxylated and deuterated products **45b** & **46b** were obtained with 35% and 20% yields respectively. In all the cases we observed deuterated anisole derivatives. Especially, in the case of triflates we have obtained mixture of trideuteromethoxylated and deuterated compounds. The results are shown in Scheme 2.27.




**Scheme 2.27**: *Synthesis of Deuterated Anisoles*

**2.5 Conclusion**:

In summary, we have demonstrated the first general and efficient method for trideuteromethoxylation of aryl/heteroaryl halides with $CD_3OD$ using a commercial available $^t$BuXPhos ligand from moderate to excellent yields. The synthesis adopted here is simple, straight forward, and avoids any additional additives and argon atmosphere. In addition, we found that $^t$BuXPhos is highly effective at suppressing $\beta$-hydride elimination occurring in C—O coupling reactions involving alcohols like $CD_3OD$ and methanol.

We have also described the first general catalytic method for the deuteration of aryl and heteroaryl halides with 1 mol% of $Pd(OAc)_2$/2 mol% of $Ad_2P^nBu$ (**L21**). The present protocol is simple and straightforward providing a variety of deuterium labeled aryl/heteroaryl compounds in good to excellent yields with 98% deuterium purities from readily available

reagents. The potential application of the protocol was also demonstrated by the bromoaniline without H/D exchange in the amino N—H group.

## 2.6 Experimental Section:

### 2.6.1 Reagents

All reactions were performed by using standard *via*l technique with rubber septum. All solids were weighed in air. $CD_3OD$, $CD_3OH$ and $CH_3OD$ used as received (without adding any drying agent) from Acros. Toluene, $Cs_2CO_3$, $K_3PO_4$, KOH, $K_2CO_3$ and $Et_3N$ were purchased from Aldrich, Acros, Merck or Alfa-Aesar and used as received. $PdCl_2(PPh_3)_2$, $Pd_2(dba)_3$, $Pd(PPh_3)_4$, $Pd(CH_3CN)_2Cl_2$and $Pd(OAc)_2$ were purchased from Aldrich. Aryl and heteroaryl bromides and chlorides were purchased from Aldrich, Acros, Afla-Aesar and Spectrochem. 1-[2-[Bis(tert-butyl)phosphino]phenyl]-3,5-diphenyl-1*H*-pyrazole (**L10**), 1,1'-bis(diphenylphosphino)ferrocene (**L11**), dicyclohexylphosphino-2'-(*N,N*-dimethylamino) biphenyl **(L12**), racemic-2-di-*t*-butylphosphino-1,1'-binaphthyl (**L13**), 2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl (**L6**), 1,3-bis-(2,6-diisopropylphenyl)-[1,3,2]diazaphospholidine 2-oxide (**L14**), [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride (PEPPSI-*i*Pr), 2′-(dicyclohexylphosphino) acetophenone ethylene ketal (**L15**), 2-(dicyclohexylphosphino)-1-(2,4,6-trimethyl-phenyl)-1*H*-imidazole (**L16**), triphenylphosphine (**L17**), and 1,3-bis(diphenylphosphino)ethane (**L18**) were purchased from Aldrich. Tri-(*o*-tolyl)-phosphine (**L19**),tri-(2-furyl)-phosphine (**L20**), di-(1-adamantyl)-*n*-butyl phosphine (**L21**) were purchased from Aldrich. All other reagents were purchased from common suppliers and used without further purification. Flash chromatography was performed using Merck Silica gel (230-400 mesh). Fractions were monitored by thin-layer chromatography on precoated silica gel 60 F254 plates (Merck & co.) and were visualized by UV.

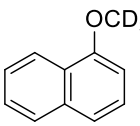
### 2.6.2Analytical Methods

NMR data were recorded on Bruker ARX 400 spectrometers. $^{13}C$ and $^{1}H$ NMR spectra were recorded in $CDCl_3$ and were referenced accrording to signals of deutero solvent. Gas chromatography analysis was performed on ThermoFisher ITQ 900 instrument with a FID detector and HP-5 capillary column (polydimethylsiloxane with 5% phenyl groups, 30 m, 0.32 mm i.d., 0.25 μm film thickness) using helium as carrier gas. Gas chromatography-Mass analysis was carried out on ThermoFisher ITQ 900 instrument (EI) and TG-SQC capillary column using helium carrier gas. ESI HR-MS measurements were performed on Bruker micro TOF-Q-II mass-spectrometer.

### 2.6.3 General Procedure for the Palladium Catalyzed Intermolecular Coupling of Aryl Halides with $d_4$-Methanol *via* Pre-Activation Protocol

An oven-dried 8 mL reaction vial was charged with $Pd(OAc)_2$ (3 mol%), ligand **L6** (6mol%) and $Cs_2CO_3$ (0.75 mmol) in toluene (0.5 mL) and was stirred at 80 °C for 5 min. Then it was cooled and respective aryl halide (0.5 mmol) in $d_4$-methanol (0.5 mL) was added. The reaction mixture was stirred at 80 °C and was monitored by TLC or GC/MS analysis. After the starting material had been completely consumed, the reaction mixture was then cooled to room temperature and was purified by flash chromatography.

**1-$d_3$-Methoxynaphthalene (45a)**




Reaction time: 6 h.

Yield: 85%, as a pale yellow oil.

$R_f$: 0.39 in pure hexane

IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3339, 3054, 2220, 2070, 1939, 1583, 1401, 1275, 1114.

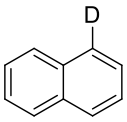
$^{1}H$ NMR (400 MHz, $CDCl_3$) δ = 8.23 – 8.27 (m, 1H), 7.78 – 7.79 (m, 1H), 7.36 – 7.47 (m, 4H), 6.78 (dd, *J* = 7.4, 1.2 Hz, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 155.5, 134.6, 127.6, 126.5, 125.9, 125.7, 125.3, 122.1, 120.3, 103.8, 54.5 – 55.2 (m, $OCD_3$).

MS (EI, 70eV): m/z (%) = 161 (90), 142 (25), 115 (100).

HR-MS (ESI): calcd. for $C_{11}H_7D_3O$ [M+H]: 162.09927, Found: 162.09611.

**1-Deuteronaphthalene (46a)**




As a colourless solid

Melting point: 71 –73 ºC

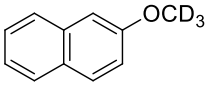
$R_f$: 0.50 in pure hexane

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.85 – 7.88 (m, 3H), 7.48 – 7.52 (m, 4H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 133.57, 133.5, 128.01, 127.97, 127.7 (t, *J* = 23 Hz), 125.9, 125.8.

MS (EI, 70eV): m/z (%) = 129 (100).

**2-$d_3$-Methoxynaphthalene (45b)**




Reaction time: 5 h

Yield: 86%, as a colourless solid.

Melting point: 64–65 ºC

$R_f$: 0.40 in pure hexane

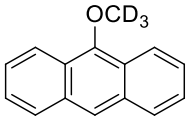
IR (KBr): ν ($cm^{-1}$) = 3436, 3055, 2924, 2362, 2222, 2069, 1630, 1600, 1470, 1390, 1263, 1222, 1184, 1109.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.41 –7.44 (m, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.14 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.11 (d, *J* = 2.0 Hz, 1H).

$^{13}$CNMR (100 MHz, $CDCl_3$) δ = 157.7, 134.7, 129.5, 129.0, 127.7, 126.8, 126.4, 123.7, 118.8, 105.8, 54.1 – 55.0 (m, $OCD_3$).

HR-MS (ESI): calcd. for $C_{11}H_7D_3O$ [M+H]: 162.09927, Found: 162.09780.

**9-d$_3$-Methoxyanthracene (45c)**




Reaction time: 12 h

Yield: 92% as a colourless solid.

Melting point: 162– 163 ºC

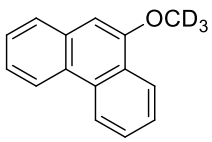
$R_f$: 0.30 in pure hexane

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.29 – 8.31 (m, 2H), 8.20 (s, 1H), 7.96– 7.98 (m, 2H), 7.42 – 7.49 (m, 4H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 152.4, 132.6, 128.6, 125.6, 125.3, 124.6, 122.4, 122.3, 61.9 – 62.8 (m, $OCD_3$).

MS (EI, 70eV): m/z (%) = 211 (100), 193 (20), 165 (90).

**9-d$_3$-Methoxyphenanthrene (45d)**




Reaction time: 12 h

Yield: 91%, as a colourless solid.

Melting point: 183– 184 ºC

$R_f$: 0.34 in pure hexane

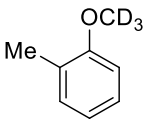
IR (KBr): ν ($cm^{-1}$) = 3448, 3054, 2926, 2369, 2224, 2070, 1600, 1451, 1399, 1318, 1239, 1202, 1151, 1124, 1103.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.65 (d, *J* = 8.0 Hz, 1H), 8.58 (d, *J* = 8.0 Hz, 1H), 8.36 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.76 – 7.78 (m, 1H), 7.65 – 7.69 (m, 1H), 7.59 – 7.63 (m, 1H), 7.47 –7.55 (m, 2H), 6.98 (s, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 153.6, 133.0, 131.4, 127.4 127.2, 126.9, 126.7, 126.6, 126.5, 124.3, 122.63, 122.62, 122.60, 101.9, 54.2 – 55.1 (m, $OCD_3$).

HR-MS (ESI): calcd. for $C_{15}H_9D_3O$ [M+H]: 212.1149, Found: 212.1116.

**2-d$_3$-Methoxytoluene (45e)**




Reaction time: 6 h

Yield: 65%, as a colourless liquid.

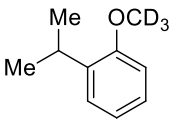
$R_f$: 0.64 in pure *n*-pentane

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.16– 7.18 (m, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 2.22 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 157.8, 130.7, 126.9, 126.7, 120.3, 110.0, 54.1 – 54.9 (m, $OCD_3$), 16.1.

MS (EI, 70eV): m/z (%) = 125 (100), 92 (30).

**2-d$_3$-Methoxy-1-isopropyl benzene (45f)**




Reaction time: 6 h

Yield: 75%, as a colourless oil.

$R_f$: 0.62 in pure *n*-pentane

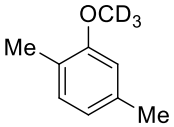
IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3423, 2963, 2217, 2065, 1600, 1490, 1248, 1113.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.21 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.15 (dt, *J* = 8.0, 2.0, 1H), 6.92 (dt, *J* = 7.4, 1.2 Hz, 1H), 6.83 (dd, *J* = 8.2, 1.2 Hz, 1H), 3.32 (hept, *J* = 6.8 Hz, 1H), 1.21(d, *J* = 6.8 Hz, 6H).

$^{13}$CNMR (100 MHz, $CDCl_3$) δ = 156.8, 137.1, 126.6, 126.1, 120.6, 110.4, 54.2 – 55.1 (m, $OCD_3$), 26.8, 22.8.

MS (EI, 70eV): m/z (%) = 153 (50), 138 (100).

**2-d$_3$-Methoxy-1,4-dimethylbenzene (45g)**




Reaction time: 8 h

Yield: 65%, as a colourless oil.

$R_f$: 0.60 in pure *n*-pentane

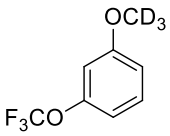
IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3436, 2925, 1586, 1272, 1112.

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.00 (d, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.64 (s, 1H), 2.32 (s, 3H), 2.17 (s, 3H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 157.7, 136.7, 130.4, 123.5, 120.8, 111.1, 54.3 – 54.9 (m, $OCD_3$), 21.57, 15.91.

MS (EI, 70eV): m/z (%) = 139 (100), 124 (40), 91 (45).

**1-$d_3$-Methoxy-3-(trifluoromethoxy)benzene (45h)**




Reaction time: 10 h

Yield: 71%, as a pale yellow oil.

$R_f$: 0.66 in pure *n*-pentane

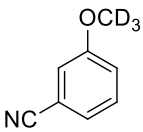
IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3394, 3052, 2934, 2857, 1604, 1495, 1431, 1384, 1295, 1178.

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.27 (t, *J* = 8.0 Hz, 1H), 6.79 – 6.83 (m, 2H), 6.75 (d, *J* =0.4 Hz, 1H).

$^{13}C$NMR (100 MHz, $CDCl_3$) δ = 160.8, 150.3 (q, *J* = 1.6 Hz), 130.3, 120.6 (q, *J* = 257.0 Hz), 112.9, 112.5, 107.2, 54.1 – 55.3 (m, $OCD_3$).

MS (EI, 70eV): m/z (%) = 195 (100), 163 (20).

**3-$d_3$-Methoxy-benzonitrile (45i)**




Reaction time: 12 h

Yield: 69%, as a pale yellow oil.

$R_f$: 0.50 in 25% ether in *n*-pentane

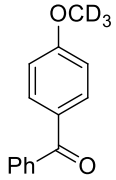
IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3435, 2927, 2212, 2066, 1601, 1226, 1110, 1014.

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.35 – 7.39 (m, 1H), 7.23 – 7.27 (m, 1H), 7.12 – 7.14 (m, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 159.7, 130.4, 124.6, 119.4, 118.8, 116.9, 113.3, 54.4 –55.2 (m, $OCD_3$).

HR-MS (ESI): calcd. for $C_8H_4D_3NO$ [M+H]: 137.0788, Found: 137.0783.

**4-d$_3$-Methoxy-benzophenone (45j)**




Reaction time: 10 h

Yield: 86%, as a colourless oil.

$R_f$: 0.25 in 20% ethyl acetae in petroleum ether

IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3464, 3062, 2224, 2072, 1651, 1600, 1506, 1446, 1304, 1269, 1174, 1149, 1105.

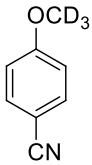
$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.81 – 7.84 (m, 2H), 7.74 – 7.77 (m, 2H), 7.54 – 7.59 (m, 1H), 7.46 – 7.49 (m, 2H), 6.94 – 6.98 (m, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 195.7, 163.4, 138.4, 132.7, 132.0, 130.3, 129.9, 128.3, 113.7, 54.6 – 55.0 (m, $OCD_3$).

HR-MS (ESI): calcd. for $C_{14}H_9D_3O_2$[M+H]: 216.1098, Found: 216.1097.

calcd. for $C_{14}H_9D_3O_2$[M+Na]: 238.0917, Found: 238.0918.

**4-d$_3$-Methoxy-benzonitrile (45k)**




Reaction time: 12 h

Yield: 83%, as a colourless solid.

Melting point: 48– 50 ºC

$R_f$: 0.21 in 16% ether in hexane

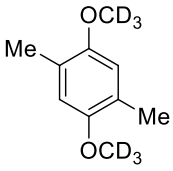
IR (KBr): ν ($cm^{-1}$) = 3461, 2218, 2075, 1606, 1509, 1272, 1177, 1100, 991.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.57 – 7.60 (m, 2H), 6.93 – 6.97 (m, 2H).

$^{13}$C NMR (400 MHz, $CDCl_3$) δ = 162.9, 134.0, 119.3, 114.8, 104.0, 54.2 – 55.3 (m, $OCD_3$).

HR-MS (ESI): calcd. for $C_8H_4D_3NO$ [M+H]: 137.0788, Found: 137.0786.

**2,5-d$_3$-Dimethoxy-1,4-dimethylbenzene (45l)**




Reaction time: 24 h

Yield: 72%, as a colourless solid.

Melting point: 75– 76 ºC

$R_f$: 0.41 in 12% ether in hexane

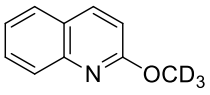
IR (KBr): ν ($cm^{-1}$) = 3435, 2927, 2212, 2066, 1601, 1226, 1110, 1014.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 6.64 (s, 2H), 2.20 (s, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 151.5, 124.3, 113.7, 54.7 – 55.8 (m, $OCD_3$), 16.2.

HR-MS (ESI): calcd. for $C_{10}H_8D_6O_2$[M+H]: 173.1443, Found: 173.1432.

**2-d$_3$-Methoxyquinoline (48a)**




Reaction time: 5 h

Yield: 82%, as a light brown oil.

$R_f$: 0.38 in 20% ethyl acetate in petroleum ether

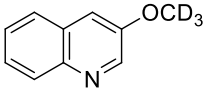
IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3425, 3052, 2927, 2242, 2075, 1948, 1606, 1425, 1285, 1097,976.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.86 (t, *J* = 8.0 Hz, 2H), 7.63 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.56–7.59 (m, 1H), 7.29 – 7.33 (m, 1H), 6.85 (d, *J* = 8.8 Hz, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 162.4, 146.6, 138.6, 129.5, 127.4, 127.3, 125.1, 124.0, 113.0, 51.9 – 53.3 (m, $OCD_3$).

HR-MS (ESI): calcd. for $C_{10}H_6D_3NO$ [M+H]: 163.0945, Found: 163.0933.

**3-d$_3$-Methoxyquinoline (48b)**




Reaction time: 6 h

Yield: 81%, as a pale yellow oil.

$R_f$: 0.50 in 20% ethyl acetate in petroleum ether

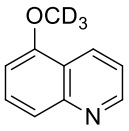
IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3402, 3063, 2221, 2070, 1603, 1464, 1425, 1383, 1349, 1279, 1218, 1106, 1003.

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 8.67 (d, *J* = 2.8 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.72 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.52 – 7.57 (m, 1H), 7.48 – 7.50 (m, 1H), 7.36 (d, *J* = 2.8 Hz, 1H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 153.2, 144.6, 143.5, 129.2, 128.9, 127.2, 126.79, 126.77, 112.3, 54.3 – 55.2 (m, $OCD_3$).

HR-MS (ESI): calcd. for $C_{10}H_6D_3NO$ [M+H]: 163.0945, Found: 163.0938.

**5-$d_3$-Methoxyquinoline (48c)**




Reaction time: 8 h

Yield: 90%, as a colourless oil.

$R_f$: 0.30 in 25% ether in hexane

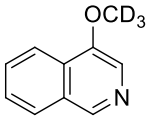
IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3393, 3070, 2223, 2126, 2071, 1931, 1614, 1589, 1499, 1469, 1403, 1317, 1273, 1204, 1172, 1145, 1145, 1110, 969.

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 8.89 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.58 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.37 (dd, *J* = 8.4, 4.2 Hz, 1H), 6.85 (d, *J* =7.7 Hz, 1H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 155.2, 150.4, 148.8, 131.25, 129.69, 121.32, 120.95, 120.25, 104.38, 54.6 – 55.5 (m, $OCD_3$).

HR-MS (ESI): calcd. for $C_{10}H_6D_3NO$ [M+H]: 163.0945, Found: 163.0954.

**4-$d_3$-Methoxyisoquinoline (48d)**




Reaction time: 8 h

Yield: 87%, as a slight brown solid.

Melting point: 62– 65 ºC

$R_f$: 0.30 in petroleum ether in ethyl acetate

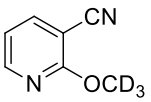
IR (KBr): ν ($cm^{-1}$) = 3449, 2926, 2070, 1580, 1397, 1330, 1294, 102, 973.

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 8.90 (s, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.07 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.68 – 7.72 (m, 1H), 7.60 – 7.64 (m, 1H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 150.7, 145.1, 129.7, 129.1, 128.3, 127.8, 127.0, 122.8, 121.2, 54.8 – 55.7 (m, $OCD_3$).

HR-MS (ESI): calcd. for $C_{10}H_6D_3NO$ [M+H]: 163.0945, Found: 163.0947.

**2-d$_3$-Methoxy-3-cyanopyridine (48e)**




Reaction time: 12 h

Yield: 59%, as a slight brown colour solid.

Melting point: 73–74 ºC

$R_f$: 0.39 in 20% ethyl acetae in hexane

IR (KBr): ν ($cm^{-1}$) = 3448, 2925, 2373, 2228, 1590, 1448, 1322, 1256, 1189, 1114, 1089, 986.

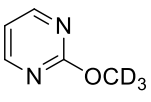
$^1H$ NMR (400 MHz, $CDCl_3$) δ = 8.36 – 8.37 (m, 1H), 7.90 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.00(dd, *J* = 7.5, 5.0 Hz, 1H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 164.2, 151.4, 142.9, 116.5, 115.2, 96.8, 53.1 – 54.4 (m, $OCD_3$).

HR-MS (ESI): calcd. for $C_7H_3D_3N_2O$ [M+H]: 138.0741, Found: 138.0724.

calcd. for $C_7H_3D_3N_2O$ [M+Na]: 160.0560, Found: 160.0525.

**2-d$_3$-Methoxypyrimidine (48f)**




Reaction time: 10 h

Yield: 65% as a pale yellow oil.

$R_f$: 0.30 in 25% ether in *n*-pentane

IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3394, 3052, 2934, 2857, 1604, 1495, 1431, 1384, 1295, 1178.

$^{1}$H NMR (400 MHz, $CDCl_3$) δ = 8.53 (d, *J* = 4.8 Hz, 2H), 6.95 (t, *J* = 4.8 Hz, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 165.6, 159.3, 114.9, 53.7 – 54.6 (m, $OCD_3$).

HR-MS (ESI): calcd. for $C_5H_3D_3N_2O$ [M+H]: 114.0741, Found: 114.0734.

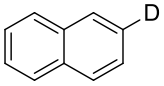
### 2.6.4 Procedure for the Optimization of Palladium Catalyzed Deuteration of 2-Bromonaphthalene (44b) with $CD_3OD$

An oven-dried 8 mL reaction vial was charged with $Pd(OAc)_2$ (5 mol%), ligand (10mol%), base (1.5 equiv), 2-bromonaphthalene (**44b**) (0.5 mmol), hexadecane (50 mg) and toluene (1.0 mL). The reaction mixture was stirred at 80 °C for 12 h. The reaction was monitored by TLC or GC/MS analysis. The yield and conversion of the reactions were calculated from GC using hexadecane as internal standard.

### 2.6.5 General Procedure for the Palladium Catalyzed Deuteration of Aryl Halides and Heteroaryl Halides with $CD_3OD$

An oven-dried 8 mL reaction vial was charged with $Pd(OAc)_2$ (1-5 mol%), ligand **L21** (2-10mol%) and $K_3PO_4$ (0.75 mmol), respective aryl/heteroaryl halide (0.5 mmol) in $CD_3OD$ (0.25 mL) and toluene (2.0 mL) was stirred at 80 °C for 7-19 h. The reaction mixture was stirred at 80 °C and was monitored by TLC or GC/MS analysis. After the starting material had been completely consumed, the reaction mixture was then cooled to room temperature and was purified by flash chromatography.

**2-Deuteronaphthalene (46b)**




Reaction time: 16 h

Yield: 99%, as a white colour solid.

Melting point: 64 – 66 °C

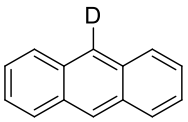
$R_f$: 0.40 in petroleum ether

$^{1}$H NMR (400 MHz, $CDCl_3$) δ = 7.89 – 7.87 (m, 4H), 7.52 – 7.49 (m, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 133.6, 128.0, 127.9, 125.95, 125.8, 125.7 (t, *J* = 24 Hz).

MS (EI, 70eV): m/z (%) = 129 (100).

**9-Deuteroanthracene (46c)**



Reaction time: 16 h

Yield: 99%, as a white colour solid.

Melting point: 198 – 201 ºC

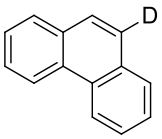
$R_f$: 0.32 in petroleum ether

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.44 (s, 1H), 8.03 – 8.01 (m, 4H), 7.49 – 7.47 (m, 4H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 131.8, 131.7, 128.3, 128.2, 126.3, 126.00 (t, *J* = 24 Hz), 125.5 (2C).

HR-MS (APCI): Calcd. for $C_{14}H_9D$ [M+H]: 180.0918, Found: 180.0928.

**9-Deuterophenanthrene (46d)**



Reaction time: 16 h

Yield: 94%, as a white colour solid.

Melting point: 88 – 90 ºC

$R_f$: 0.30 in petroleum ether

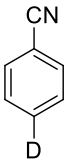
IR (KBr): ν ($cm^{-1}$) = 3050, 2925, 2368, 1638, 1428, 1006, 771, 754.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.72 (d, *J* = 8.2 Hz, 2H), 7.92 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.76 (s, 1H), 7.70– 7.60 (m,4H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 132.2, 132.1, 130.4, 128.71, 128.66, 126.9, 126.74 (t, *J* = 24 Hz), 126.70, 122.8.

HR-MS (APCI): Calcd. for $C_{14}H_9D$ [M+H]: 180.0918, Found: 180.0926.

**4-Deuterobenzonitrile (46e)**



Reaction time: 10.5 h

Yield: 58%, as a colourless oily liquid.

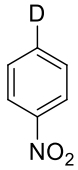
$R_f$: 0.36 in 10% diethyl ether in Petroleum ether

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.66 – 7.64 (m, 2H), 7.49 (d, *J* = 8.4 Hz, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 132.6 (t, *J* = 25 Hz), 132.2, 129.1, 118.9, 112.5.

MS (EI, 70eV): m/z (%) = 104 (100), 77 (20).

**4-Deuteronitrobenzene (46f)**



Reaction time: 18 h

Yield: 64%, as a brown colour oily liquid.

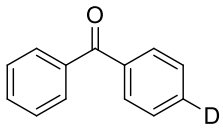
$R_f$: 0.32 in 5% ethyl acetate in petroleum ether

IR (as film in $CCl_4$): ν ($cm^{-1}$) = 2921, 2360, 1657, 1310, 1276, 938.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.24 – 8.21 (m, 2H), 7.55 (dd, *J* = 7.6, 0.8 Hz, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 148.3, 134.4 (t, *J*= 25 Hz), 129.3, 123.6.

**4-Deuterobenzophenone (46g)**



Reaction time: 10.5 h

Yield: 96%, as a pale yellow oily liquid.

$R_f$: 0.35 in 10% diethyl ether in petroleum ether

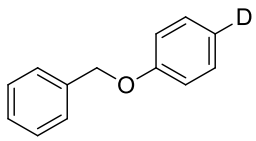
IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3060, 2920, 2423, 2264, 1659, 1651, 1599, 1513, 1472, 1447, 1408, 1311, 1277, 1175, 1149, 1108, 1076, 1026.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.82 – 7.80 (m, 4H), 7.61 – 7.57 (m, 1H), 7.50 – 7.46 (m, 4H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 196.8, 137.7, 132.5, 132.2 (t, *J* = 25 Hz), 130.2, 128.4, 128.3.

HR-MS (APCI): Calcd. for $C_{13}H_9DO$ [M+H]: 184.0867, Found: 184.0870.

**4-Benzyloxy-1-deuterobenzene (46h)**



Reaction time: 8 h

Yield: 66%, as a white colour solid.

Melting point: 36 – 38 ºC

$R_f$: 0.29 in hexane

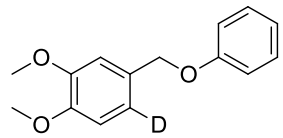
IR (KBr): ν ($cm^{-1}$) = 3035, 2907, 2867, 2373, 1590, 1467, 1377, 1293, 1245, 1170, 1107, 1022.

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.48 – 7.46 (m, 2H), 7.44 – 7.40 (m, 2H), 7.37 – 7.33 (m, 3H), 7.03 – 7.00 (m, 2H), 5.09 (s, 2H).

$^{13}C$ NMR (100 MHz, $CDCl_3$)δ = 158.9, 137.2, 129.5, 128.7, 128.1, 127.6, 120.8 (t, *J* = 24 Hz), 114.9, 70.0.

MS (EI, 70eV): m/z (%) = 185 (25), 91(100).

**6-Benzyloxy-3,4-dimethoxy-1-deuterobenzene (46i)**



Reaction time: 8 h

Yield: 90%, as a pale yellow colour solid.

Melting point: 67 – 70 ºC

$R_f$: 0.33 in 20% ethyl acetate in hexane

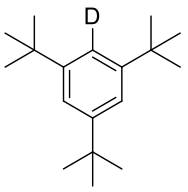
IR (KBr): ν ($cm^{-1}$) = 2997, 2961, 2937, 2835, 1595, 1508, 1402, 1376, 1340, 1229, 1159, 1080.

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.34 – 7.28 (m, 2H), 7.02 – 6.96 (m, 4H), 6.88 (s, 1H), 5.00 (s, 2H), 3.90 (s, 3H), 3.89 (s, 3H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 158.8, 149.2, 148.9, 129.5, 129.47, 120.9, 120.0 (t, *J* = 25 Hz), 114.9, 111.0 (2C), 69.9, 55.96, 55.90.

HR-MS (ESI): Calcd. for $C_{15}H_{15}DO_3$ [M+H]: 245.1157, Found: 245.1166.

**2,4,6-Tri-*t*-butyldeuterobenzene (46j)**



Reaction time: 18 h

Yield: 85%, asa colourless solid.

Melting point: 55 – 58 ºC

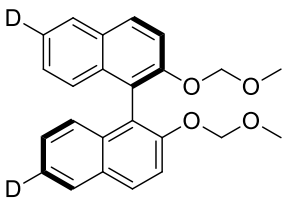
$R_f$: 0.71 in *n*-Pentane

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.26 (s, 2H), 1.34 (s, 27H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 150.1, 150.0, 119.6, 35.1, 31.7

MS (EI, 70eV): m/z (%) = 247 (25), 232 (100), 204 (20), 176 (5), 57 (15).

**6,6'-Dibromo-2,2'-bis (methoxymethoxy)-1,1'-binaphthalene (46k)**



Reaction time: 19 h

Yield: 94%, as a white colour solid.

Melting point: 93 – 96 ºC

$R_f$: 0.27 in 20% diethyl ether in petroleum ether

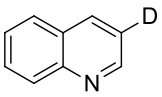
IR (KBr): ν ($cm^{-1}$) = 3055, 3026, 2998, 2952, 2901, 2846, 2824, 1620, 1586, 1499, 1463, 1347, 1298, 1241, 1196, 1147, 1094, 1075, 1039, 1026.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 8.8 Hz, 2H), 7.88 (s, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.18 (dd, *J* = 8.4, 0.4 Hz, 2H), 5.09 (d, *J*= 6.8 Hz, 2H), 4.99 (dd, *J* = 6.8, 0.4 Hz, 2H), 3.158 (s, 3H), 3.156 (s,3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 152.8, 134.2, 130.0, 129.5, 127.9, 126.3, 125.7, 123.9 (t, *J* = 23 Hz) 121.4, 117.4, 95.3, 55.9.

HR-MS (ESI): Calcd. for $C_{24}H_{20}D_2O_4$ $[M]^+$: 376.1638, Found: 376.1640.

**3-Deuteroquinoline (49a)**



Reaction time: 7 h

Yield: 70%, as a brown colour oily liquid.

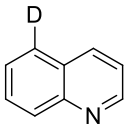
$R_f$: 0.26 in 20% diethyl ether in petroleum ether

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.91 (s, 1H), 8.15 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.74 – 7.69 (m, 1H), 7.56 – 7.52 (m, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 150.3, 148.2, 136.2, 129.6, 129.4, 128.4, 127.9, 126.7, 120.9 (t, *J* = 25 Hz).

HR-MS (ESI): Calcd. for $C_9H_6DN$ [M+H]: 131.0714, Found: 131.0716.

**5-Deuteroquinoline (49b)**



Reaction time: 8 h

Yield: 80%, as a colourless liquid.

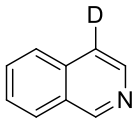
$R_f$: 0.24 in 10% ethyl acetate in hexane

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.89 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.14 – 8.09 (m, 2H), 7.70 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.52 (dd, *J* = 6.8, 0.8 Hz, 1H), 7.37 (dd, *J* = 8.2, 4.0 Hz, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 150.4, 148.2, 136.2, 129.6, 129.4, 128.3, 127.5 (t,*J* = 25 Hz), 126.5, 121.1.

HR-MS (ESI): Calcd. for $C_9H_6DN$ [M+H]: 131.0714, Found: 131.0725.

**4-Deuteroisoquinoline (49c)**



Reaction time: 17 h

Yield: 78%, as a brown colour oily liquid.

$R_f$: 0.28 in 20% ethyl acetate in petroleum ether

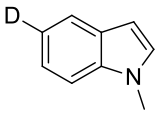
IR (as film in $CCl_4$): ν ($cm^{-1}$) = 2926, 2345, 2372, 1626, 1583, 1493, 1381, 1260, 1230, 1162, 941

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 9.24 (s, 1H), 8.51 (s, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.81 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.70 – 7.66 (m, 1H), 7.61 – 7.57 (m, 1H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 152.5, 142.9, 135.8, 130.5, 128.7, 127.7, 127.4, 126.5, 120.3 (t,*J* = 25 Hz).

HR-MS (APCI): Calcd. for $C_9H_6DN$ [M+H]: 131.0714, Found: 131.0732.

**5-Deutero-*N*-methylindole (49d)**




Reaction time: 7 h

Yield: 68%, as a colourless oily liquid.

$R_f$: 0.32 in 5% ethyl acetate inpetroleum ether

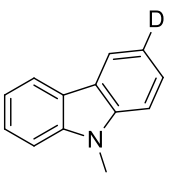
IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3100, 3046, 2943, 2816, 2264, 1870, 1610, 1513, 1471, 1442, 1422, 1382, 1333, 1288, 1243, 1194, 1148, 1107, 1079, 1018.

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.69 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.09 – 7.08 (m, 1H), 6.55 – 6.54 (m, 1H), 3.82 (s, 3H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 136.8, 128.9, 128.6, 121.5, 120.9, 119.1 (t, *J* = 24 Hz), 109.3, 100.9, 32.9.

HR-MS (APCI): Calcd. for $C_9H_8DN$ [M+H]: 133.0871, Found: 133.0887.

**3-Deutero-9-methyl-9*H*-carbazole (49e)**




Reaction time: 16 h

Yield: 81%, as a white colour solid.

Melting point: 80 – 83 °C

$R_f$: 0.41 in 3% ethyl acetate in hexane

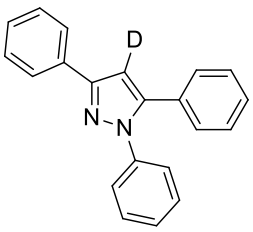
IR (KBr): ν ($cm^{-1}$) = 3049, 2888, 2823, 2352, 2320, 2267, 1623, 1596, 1476, 1457, 1423, 1350, 1331, 1285, 1246, 1142.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.15 – 8.13 (m, 2H), 7.54 – 7.50 (m, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.28 (m, 1H), 3.86 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 141.1, 125.8, 125.7, 122.9, 120.4, 120.3, 118.9,118.7 (t,*J* = 24 Hz), 108.5, 29.1.

HR-MS (ESI): Calcd. for $C_{13}H_{10}DN$ $[M]^+$: 182.0949, Found: 182.0923.

**4-Deutero-1,3,5-triphenyl-1*H*-pyrazole (49f)**




Reaction time: 10.5 h

Yield: 92%, as a white colour solid.

Melting point: 132 – 136 ºC

$R_f$: 0.38 in 10% diethyl ether in Petroleum ether

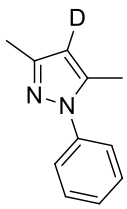
IR (KBr): ν ($cm^{-1}$) = 3061, 2352, 2332, 1596, 1498, 1479, 1455, 1366, 1358, 1311, 1178, 1159, 1001.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.96 – 7.93 (m, 2H), 7.47 – 7.43 (m, 2H), 7.41– 7.28 (m, 11H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 152.0, 144.5, 140.2, 133.1, 130.7, 129.0, 128.9, 128.8, 128.6, 128.4, 128.1, 127.6, 125.9, 125.4, 105.1(t, *J* = 25 Hz).

HR-MS (ESI): Calcd. for $C_{21}H_{15}DN_2$ [M+H]: 298.1449, Found: 298.1440.

**4-Deutero-3,5-dimethyl-1-phenyl-1*H*-pyrazole (49g)**




Reaction time: 8 h

Yield: 85%, as a pale yellow liquid.

$R_f$: 0.35 in 10% ethyl acetate in hexane

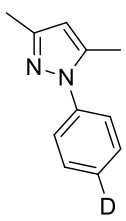
IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3067, 2926, 2362, 1598, 1542, 1504, 1458, 1415, 1381, 1364, 1140, 1072, 1047, 1024, 911.

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.45 – 7.40 (m, 4H), 7.36 – 7.30 (m, 1H), 2.30 (s, 3H), 2.29 (s, 3H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 148.9, 139.9, 139.3, 129.0, 127.3, 124.8, 106.7 (t, *J* = 26 Hz), 13.5, 12.4.

HR-MS (APCI): Calcd. for $C_{11}H_{11}DN_2$ [M+H]: 174.1136, Found: 174.1132.

**1-(4-Deuterophenyl)-3,5-dimethyl-1*H*-pyrazole (49h)**




Reaction time: 10.5 h

Yield: 91%, as a pale yellow liquid.

$R_f$: 0.40 in 10% ethyl acetate in petroleum ether

IR (as film in $CCl_4$): ν ($cm^{-1}$) = 2924, 2367, 1595, 1556, 1500, 1415, 1382, 1366, 1133, 1104, 1025, 977.

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.46 – 7.41 (m, 4H), 6.00 (s, 1H), 2.30 (s, 3H), 2.30 (s, 3H).

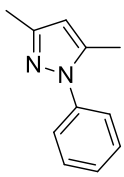
$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 149.0, 139.9, 139.5, 128.9, 127.0 (t, *J* = 25 Hz), 124.9, 107.0, 13.6, 12.5.

HR-MS (APCI): Calcd. for $C_{11}H_{11}DN_2$ [M+H]: 174.1136, Found: 174.1154.

### 2.6.6 Procedure for the Palladium Catalyzed Deuteration of 4-Bromopyrazole/4-Bromoaniline derivatives with $CD_3OH$ or $CH_3OD$

An oven-dried 8 mL reaction vial was charged with $Pd(OAc)_2$ (5 mol%), **L21** (10mol%) and $K_3PO_4$/KO$^t$Bu (1.5 equiv), bromo derivative (0.5 mmol) in $CD_3OH$/$CH_3OD$ (0.5 mL) in toluene (0.5 mL). The reaction mixture was stirred at 80 °C for 3-12 h. The reaction mixture was monitored by TLC or GC/MS analysis. After the starting material had been completely consumed, the reaction mixture was then cooled to room temperature and was purified by flash chromatography.

**3,5-Dimethyl-1-phenyl-1*H*-pyrazole (49g')**



Reaction time: 3-12 h

Yield: 98%, as a pale yellow liquid.

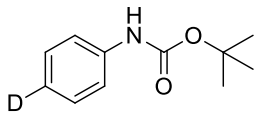
$R_f$: 0.30 in 10% ethyl acetate in hexane

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.45 – 7.41 (m, 4H), 7.36 – 7.31 (m, 1H), 5.99 (s, 1H), 2.30 (s, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 148.99, 139.97, 139.46, 129.05, 127.30, 124.82, 106.98, 13.56, 12.42.

HR-MS (ESI): calcd. for $C_{11}H_{12}N_2$[M+H]: 173.1073, Found: 173.1085.

***N*-Boc-4-deuterophenylamine (46l)**



Reaction time: 10 h

Yield: 84%, as a white colour solid.

Melting point: 124 – 126 $^o$C

$R_f$: 0.40 in 10% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3305, 2984, 2372, 1689, 1522, 1407, 1312, 1297, 1243, 1155, 1060.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.36 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J*= 8.4 Hz, 2H), 6.51 (s, 1H), 1.52 (s, 9H).

$^1$H NMR (400 MHz, $CDCl_3$) ($D_2O$ shake) δ = 7.35 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 1.52 (s, 9H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 152.9, 138.5, 128.9, 122.9(t, *J* = 25 Hz), 118.7, 80.6, 28.5.

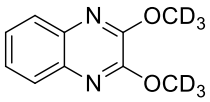
HR-MS (ESI): Calcd. for $C_{11}H_{14}DNO_2$ $[M]^+$: 194.1160, Found: 194.1134.

### 2.6.7 Procedure for the Palladium Catalyzed trideuteromethoxylation of Highly Activated Heteroaryl Halides with $CD_3OD$

An oven-dried 8 mL reaction vial was charged with $Pd(OAc)_2$ (3 mol%), **L21** (6mol%) and $K_3PO_4$ (1.5 equiv), activated heteroaryl halide **47** (0.5 mmol) in $CD_3OD$ (0.5 mL) in toluene (0.5 mL). The reaction mixture was stirred at 80 °C for 5-24 h. The reaction mixture was monitored by TLC or GC/MS analysis. After the starting material had been completely consumed, the reaction mixture was then cooled to room temperature and was purified by flash chromatography.

Data of the Compounds **48a**, **48e and 48f** as described in section **2.6.3**

#### 2,3-$d_3$-Dimethoxy-quinoxaline (48h)




Reaction time: 8 h

Yield: 81%, as a white colour solid.

Melting point: 86 – 88 ºC

$R_f$: 0.32 in 20% ethyl acetate in petroleum ether

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.79 – 7.45 (m, 2H), 7.50 – 7.46 (m, 2H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 150.1, 137.4, 126.8 (2C), 126.5 (2C), 54.6 – 55.0 (m, $OCD_3$).

HR-MS (ESI): Calcd. for $C_{10}H_4D_6N_2O_2$ [M+H]: 197.1119, Found: 197.1192.

### 2.6.8 Procedure for the Palladium Catalyzed Trideuteromethoxylation of Tosyl, Mesyl and Triflate based arenes 50 with $CD_3OD$

An oven-dried 8 mL reaction vial was charged with Pd $(OAc)_2$ (3 mol%), **L21** (6mol%) and $K_3PO_4$ (1.5 equiv), **50** (0.5 mmol) in $CD_3OD$ (0.5 mL) in toluene (1.0 mL). The reaction mixture was stirred at 80 °C for 17-24 h. The reaction mixture was monitored by TLC or GC/MS analysis. After the starting material had been completely consumed, the reaction mixture was then cooled to room temperature and was purified by flash chromatography.

Data of the compound **45b** as described in Section **2.6.3**

## 2.7 Copies of Selected $^{1}H$ & $^{13}C$ NMR Spectra

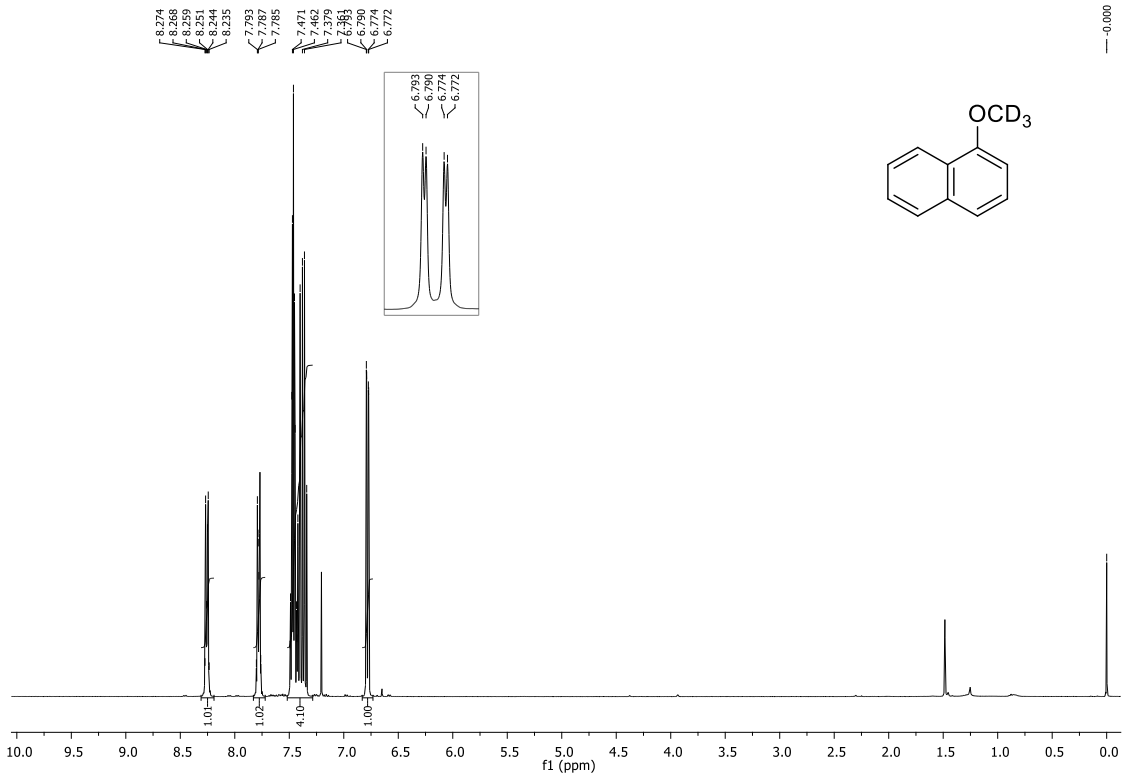



**Figure 2.3a**: $^{1}H$ NMR Spectrum of **45a**

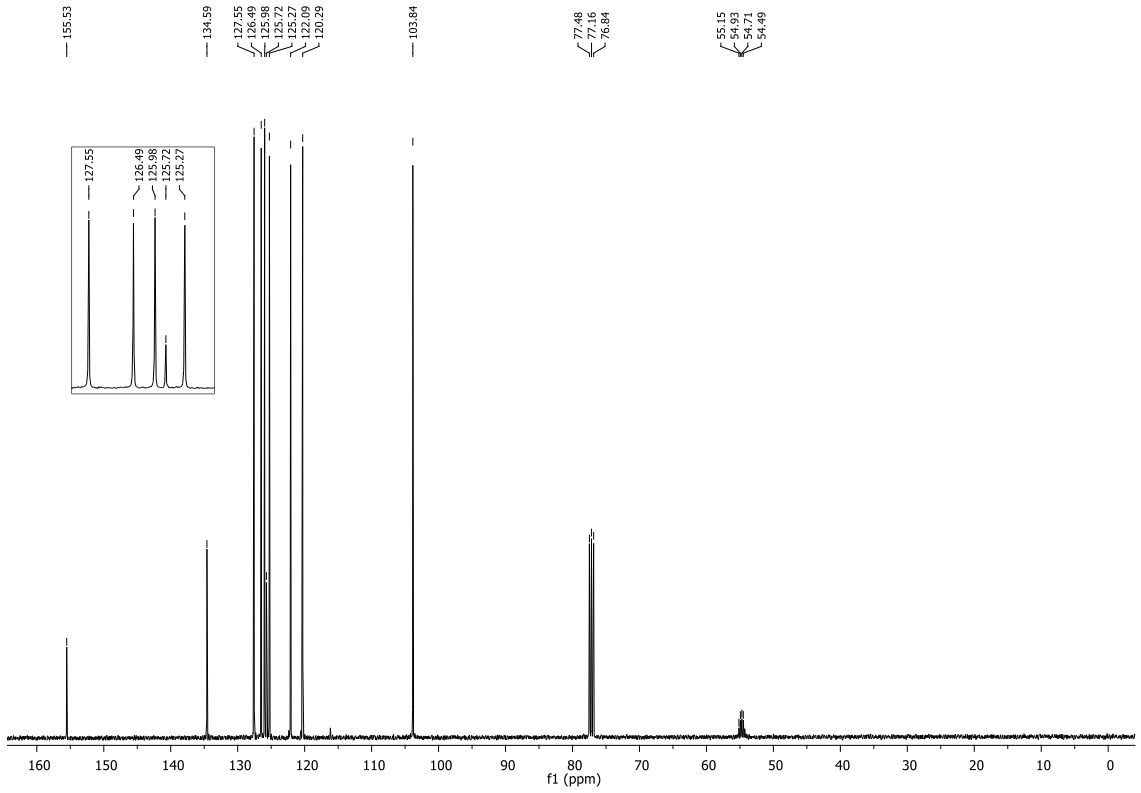



**Figure 2.3b**: $^{13}C$ NMR Spectrum of **45a**

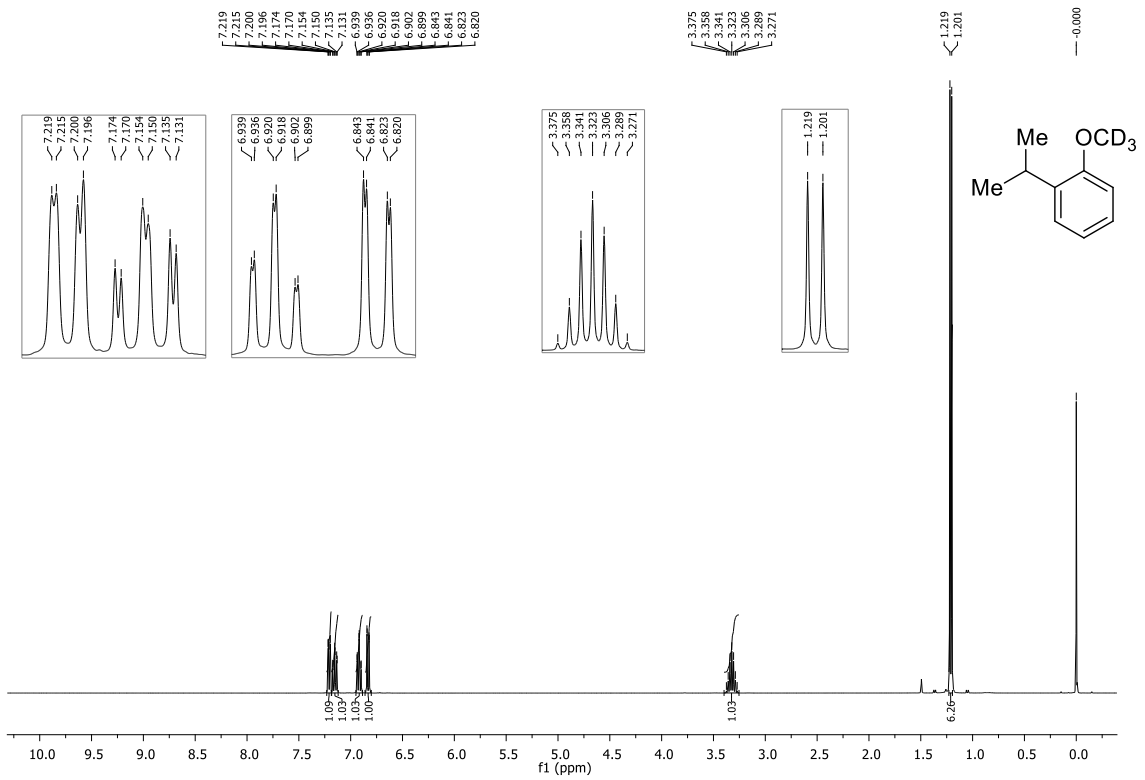



**Figure 2.4a**: $^{1}$H NMR Spectrum of **45f**

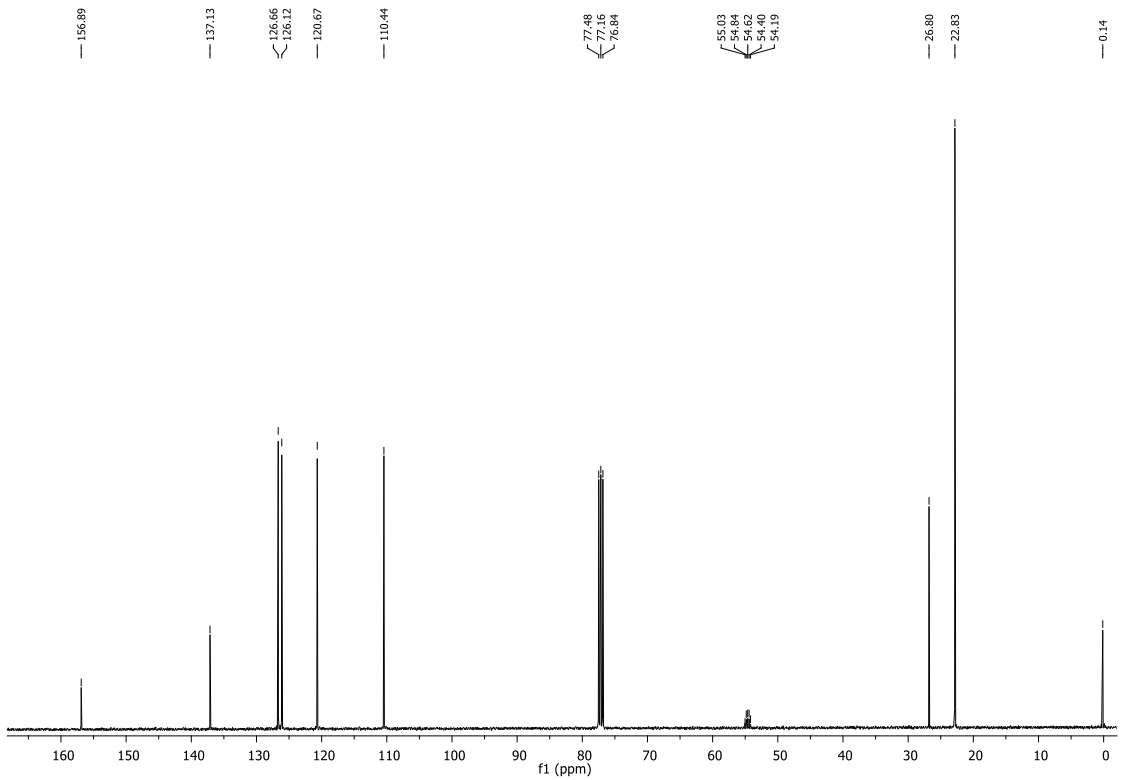



**Figure 2.4b**: $^{13}$C NMR Spectrum of **45f**

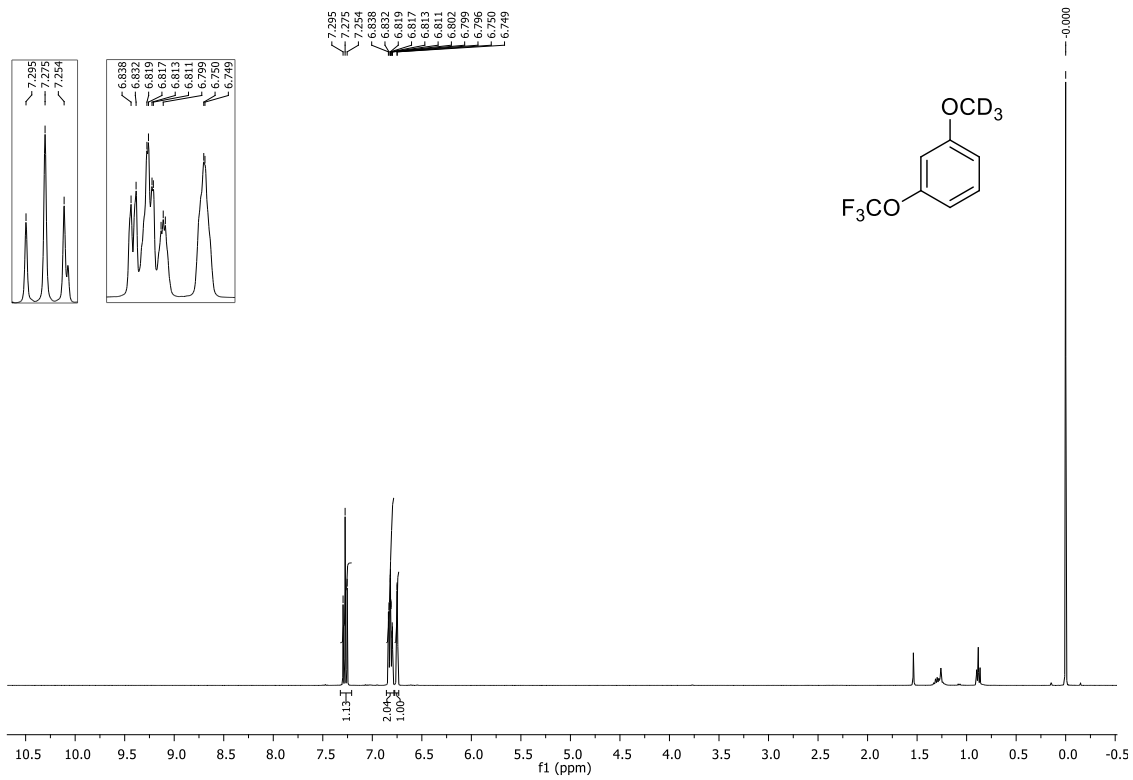



**Figure 2.5a**: $^{1}$H NMR Spectrum of **45h**

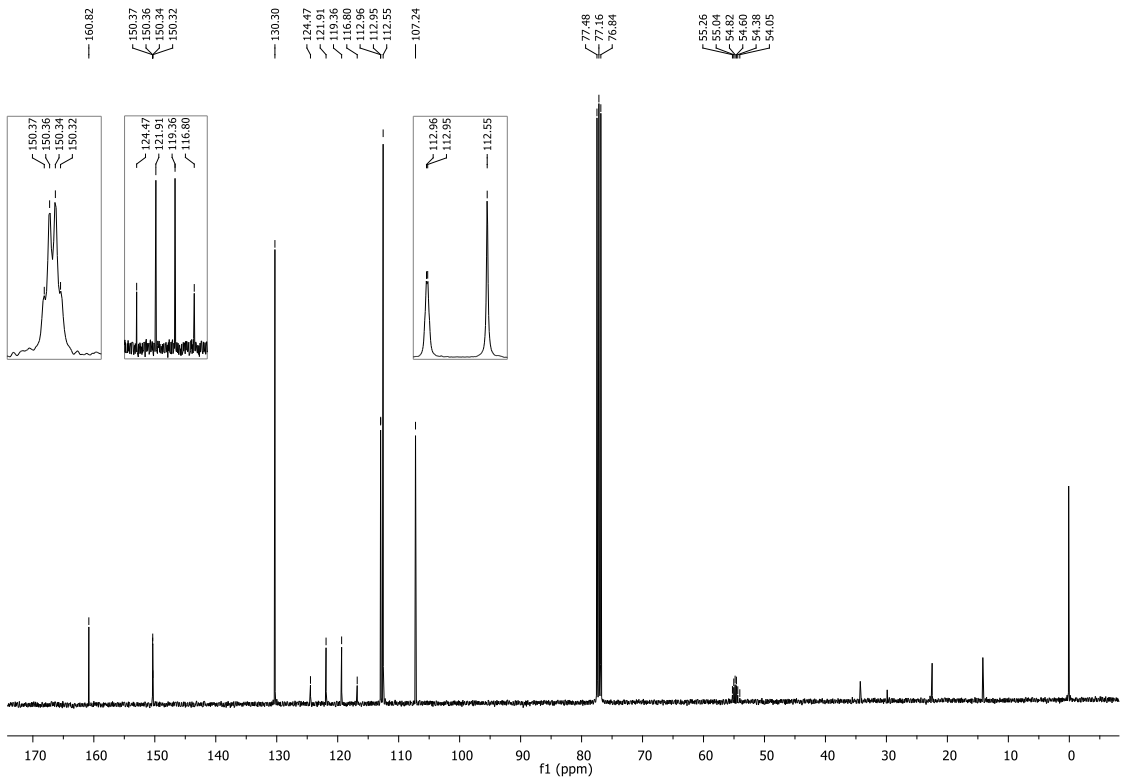



**Figure 2.5b**: $^{13}$C NMR Spectrum of **45h**

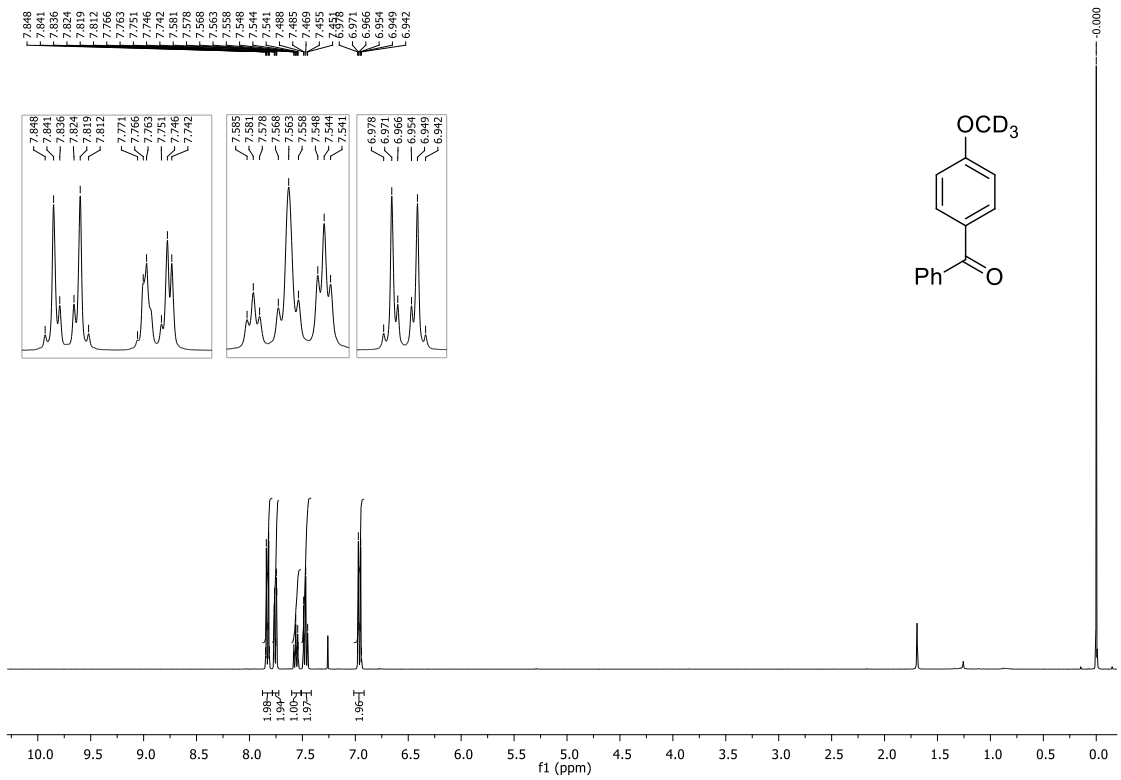



**Figure 2.6a**: $^{1}$H NMR Spectrum of **45j**

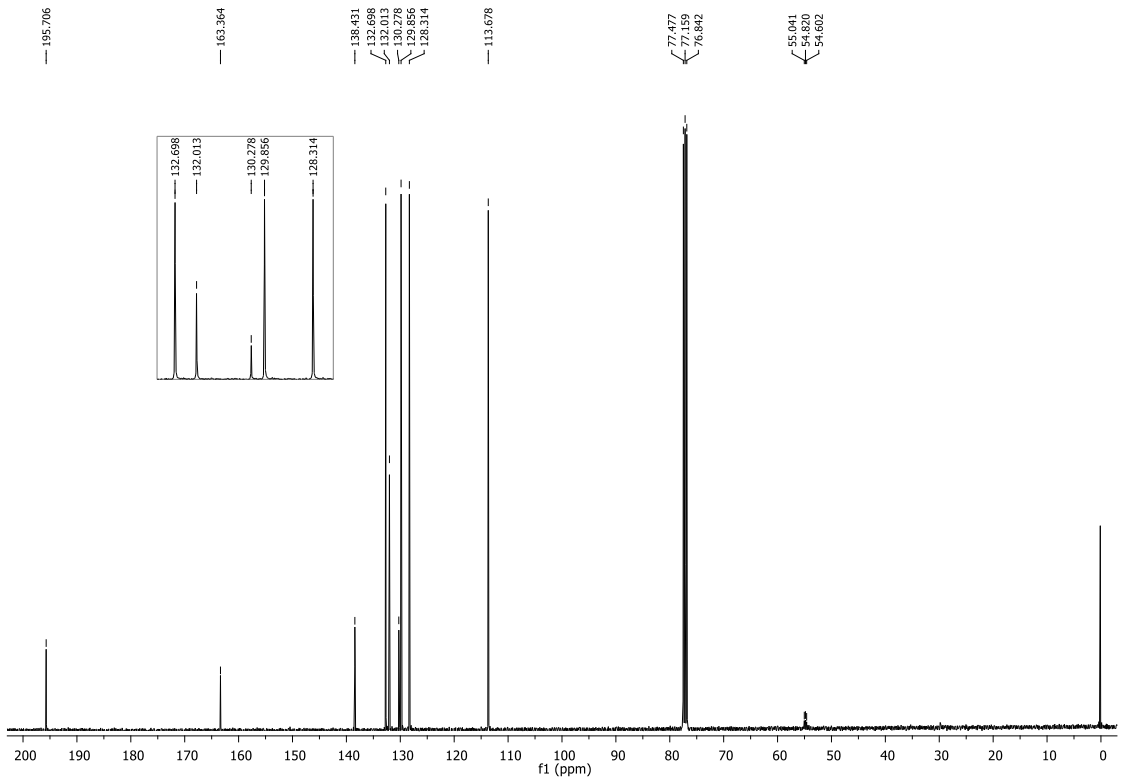



**Figure 2.6b**: $^{13}$C NMR Spectrum of**45j**

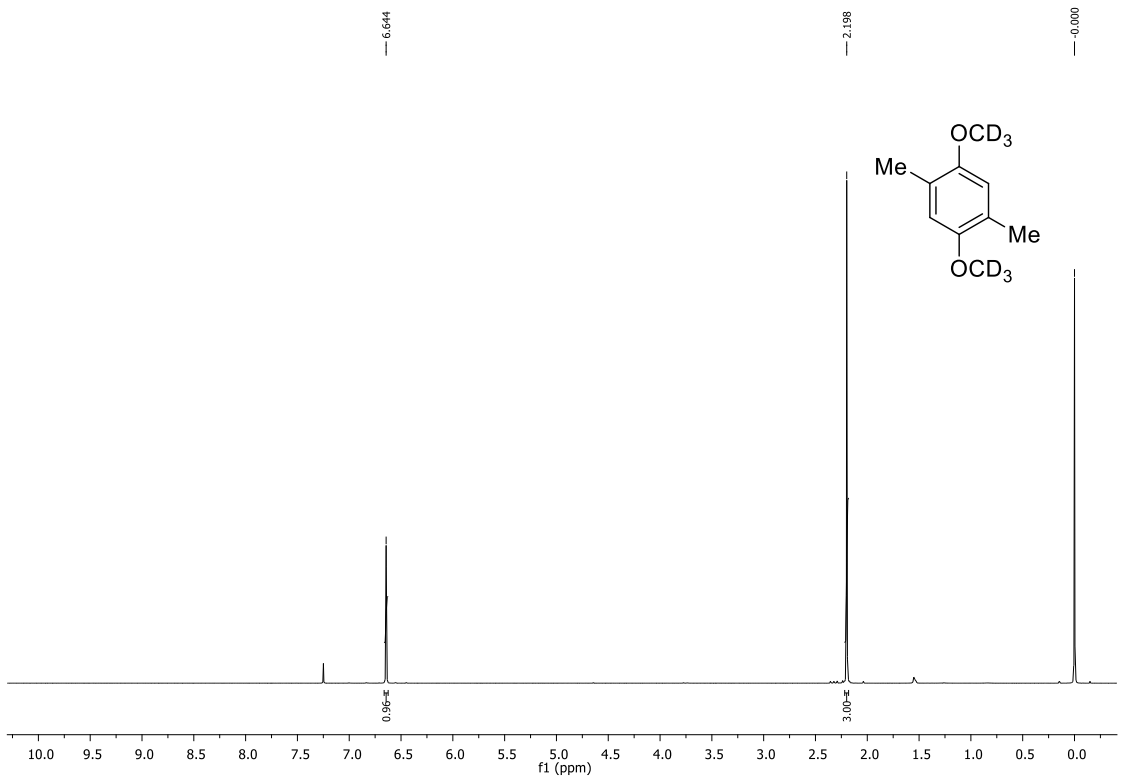



**Figure 2.7a**: $^{1}$H NMR Spectrum of **45l**

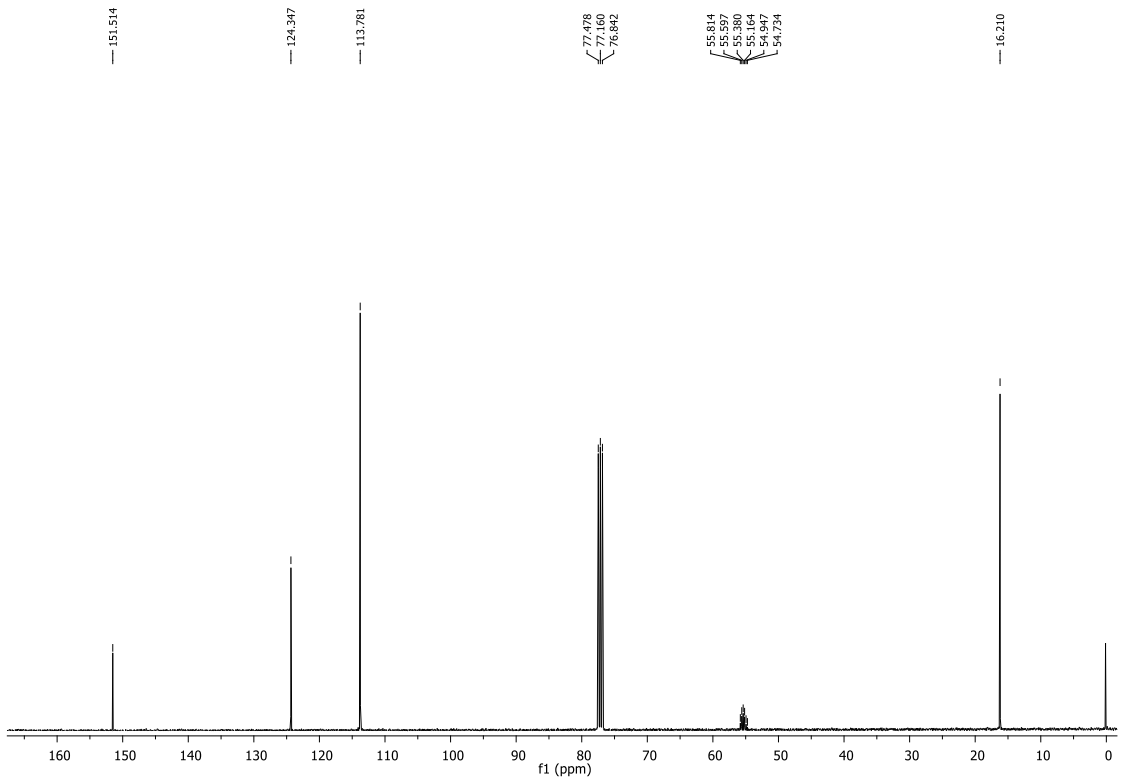



**Figure 2.7b**: $^{13}$C NMR Spectrum of **45l**

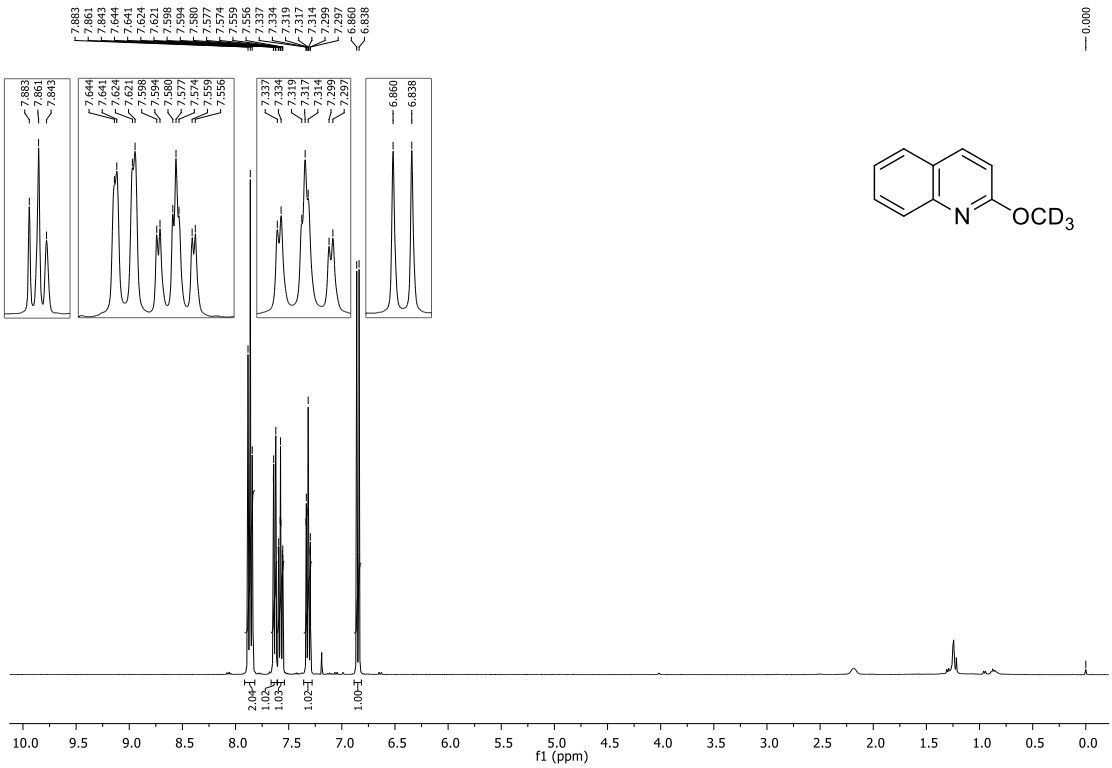



**Figure 2.8a**: $^{1}$H NMR Spectrum of **48a**

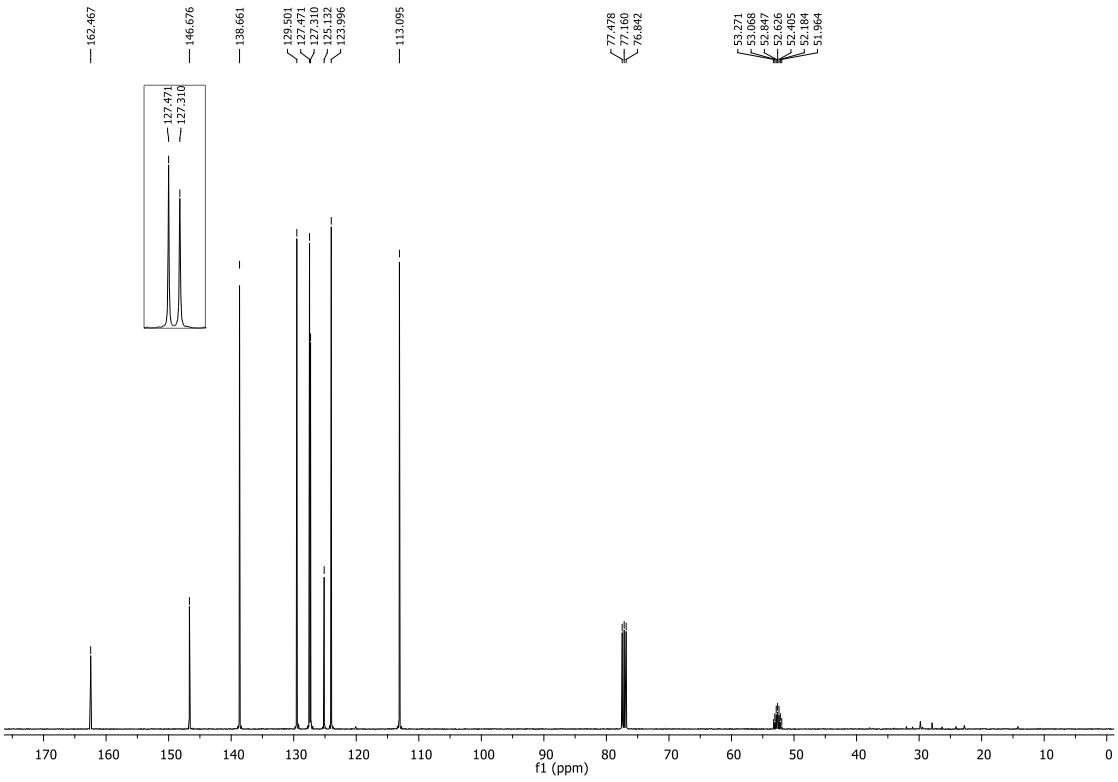



**Figure 2.8b**: $^{13}$C NMR Spectrum of **48a**

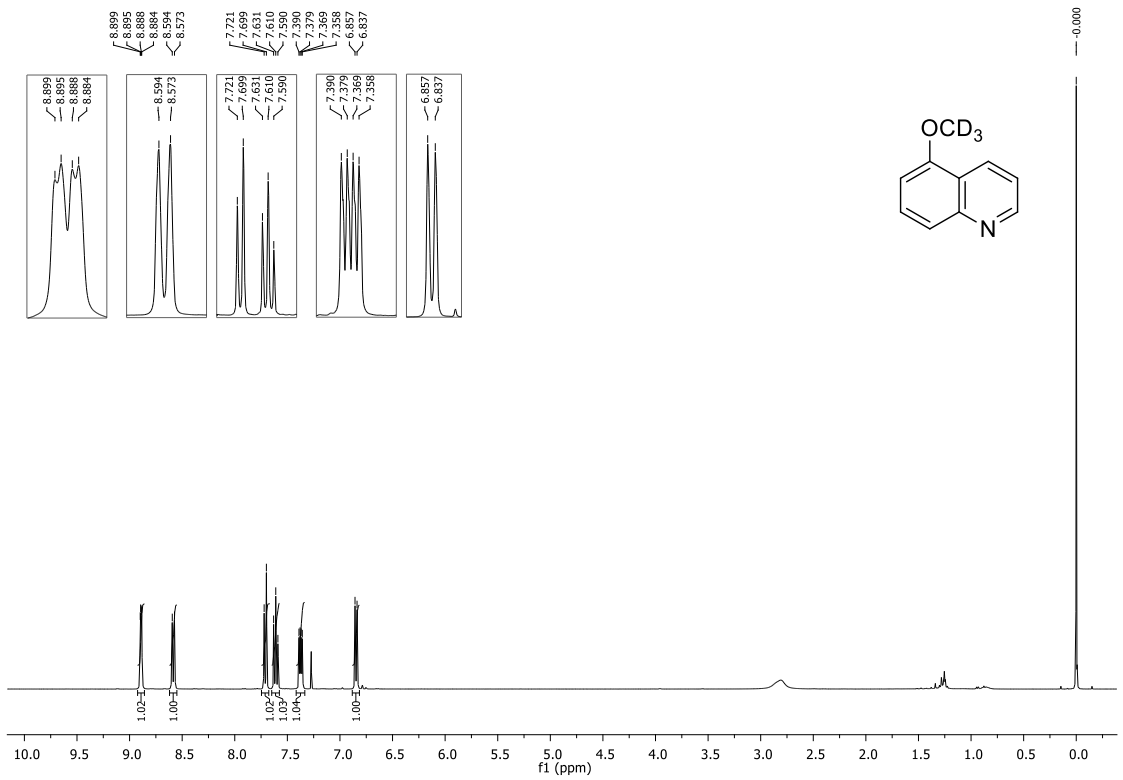



**Figure 2.9a**: $^{1}$H NMR Spectrum of **48c**

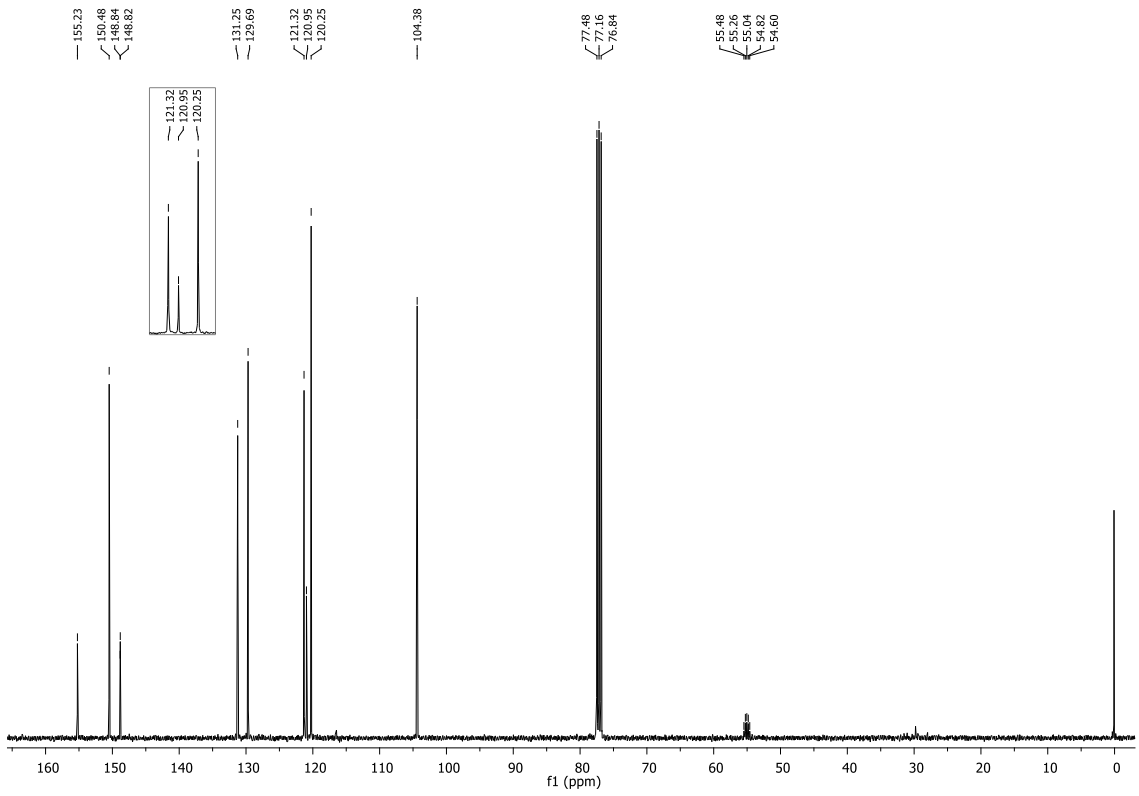



**Figure 2.9b**: $^{13}$C NMR Spectrum of **48c**

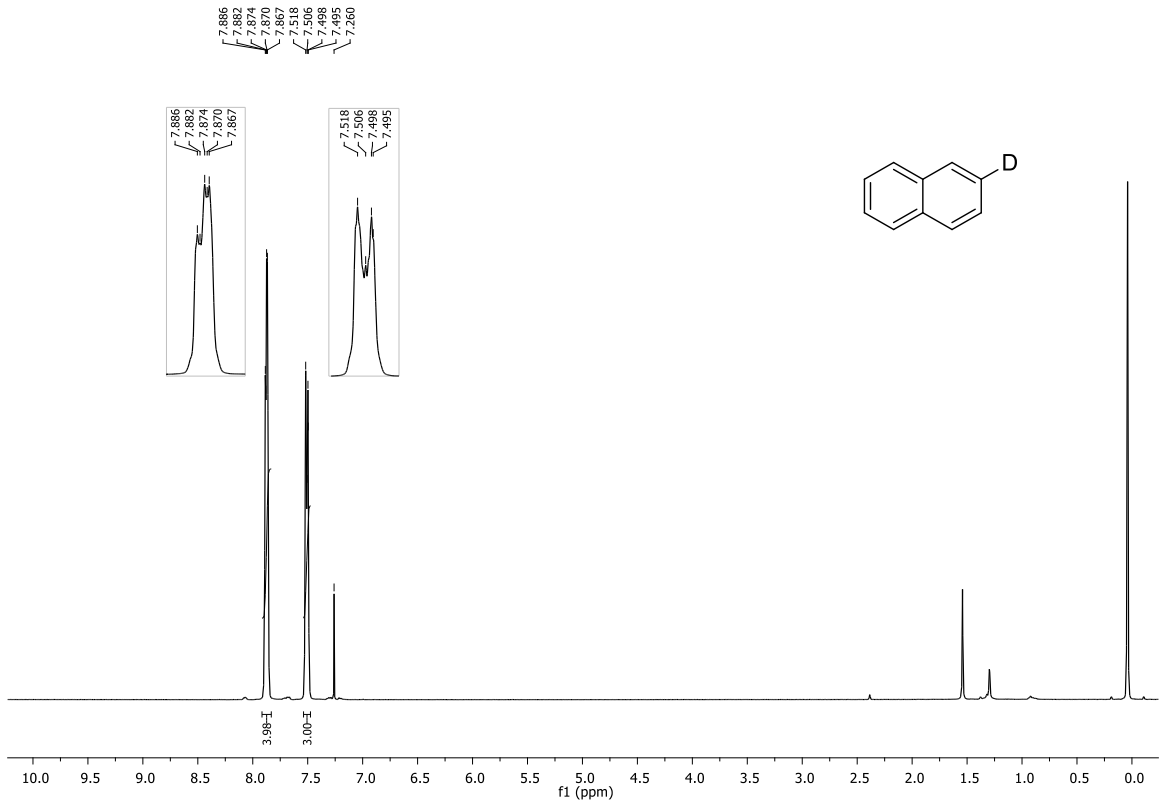



**Figure 2.10a**: $^{1}$H NMR Spectrum of **46a**

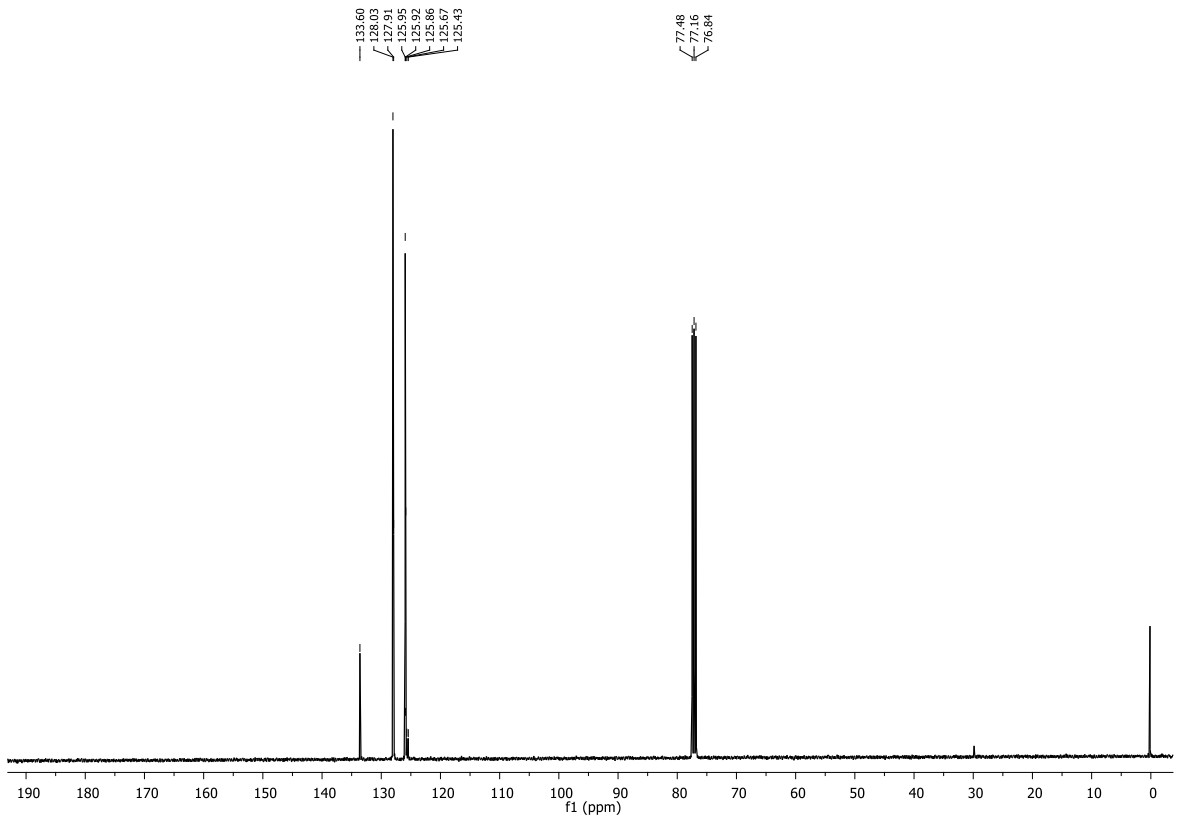



**Figure 2.10b**: $^{13}$C NMR Spectrum of **46a**

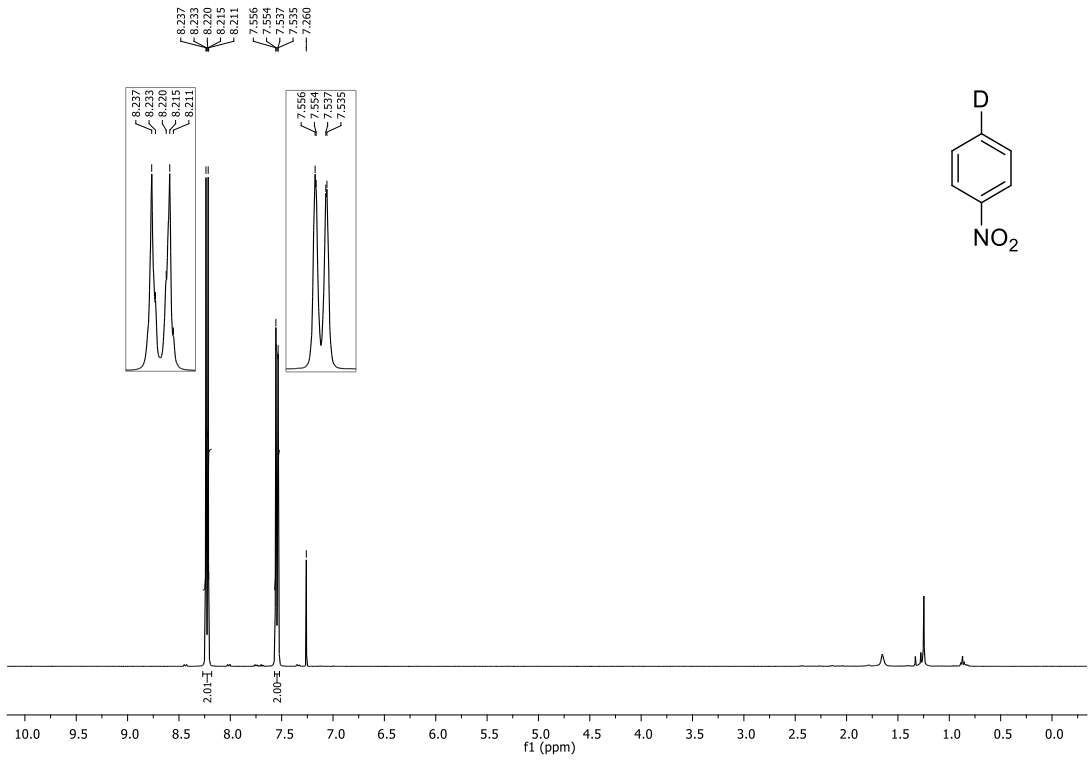



**Figure 2.11a**: $^{1}$H NMR Spectrum of **46f**

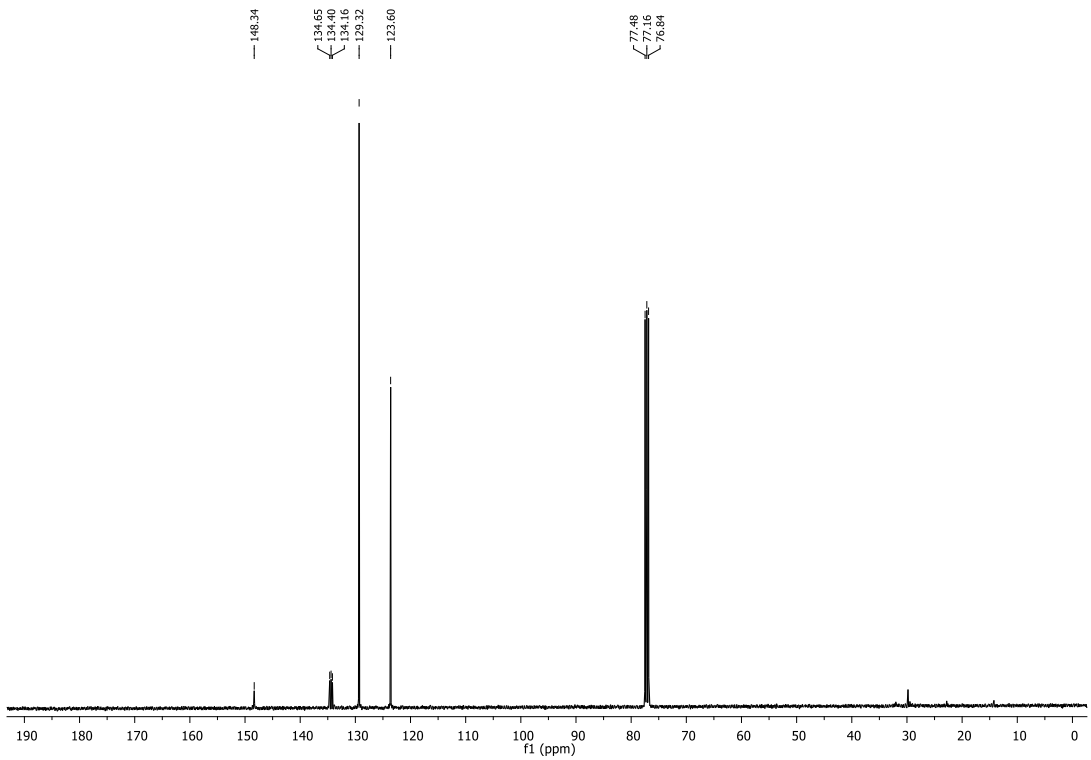



**Figure 2.11b**: $^{13}$C NMR Spectrum of **46f**

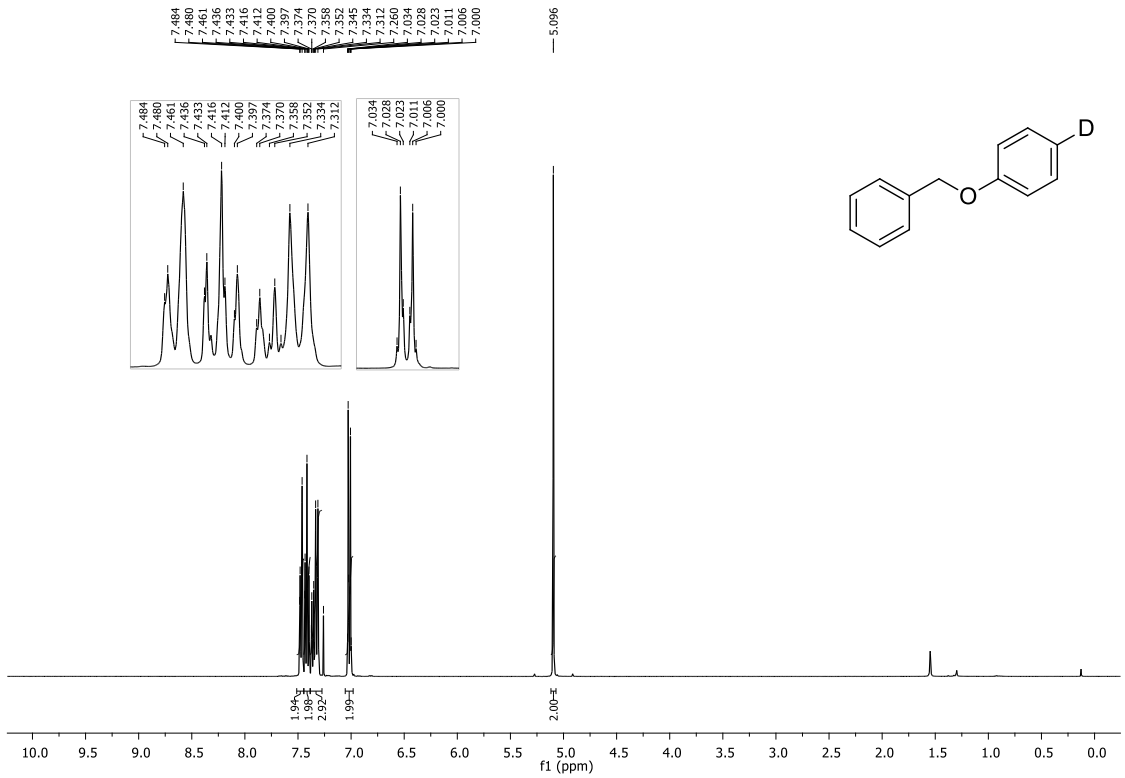



**Figure 2.12a**: $^{1}$H NMR Spectrum of **46h**

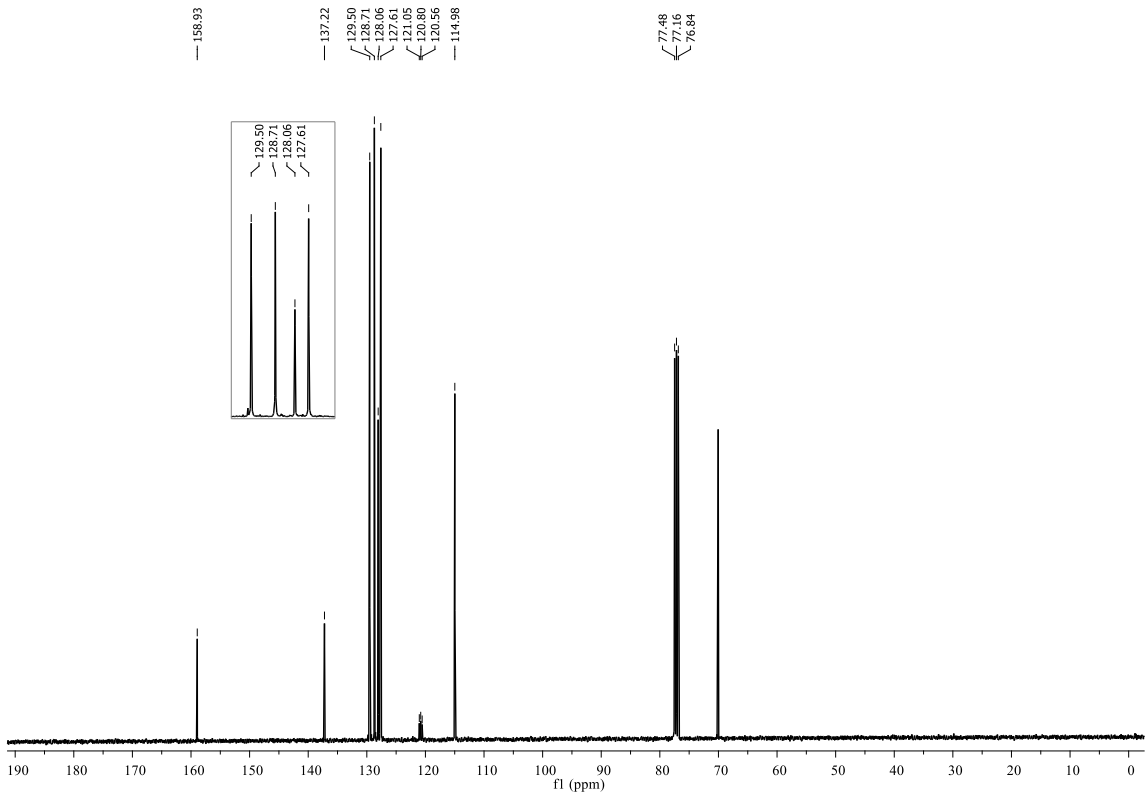



**Figure 2.12b**: $^{13}$C NMR Spectrum of **46h**

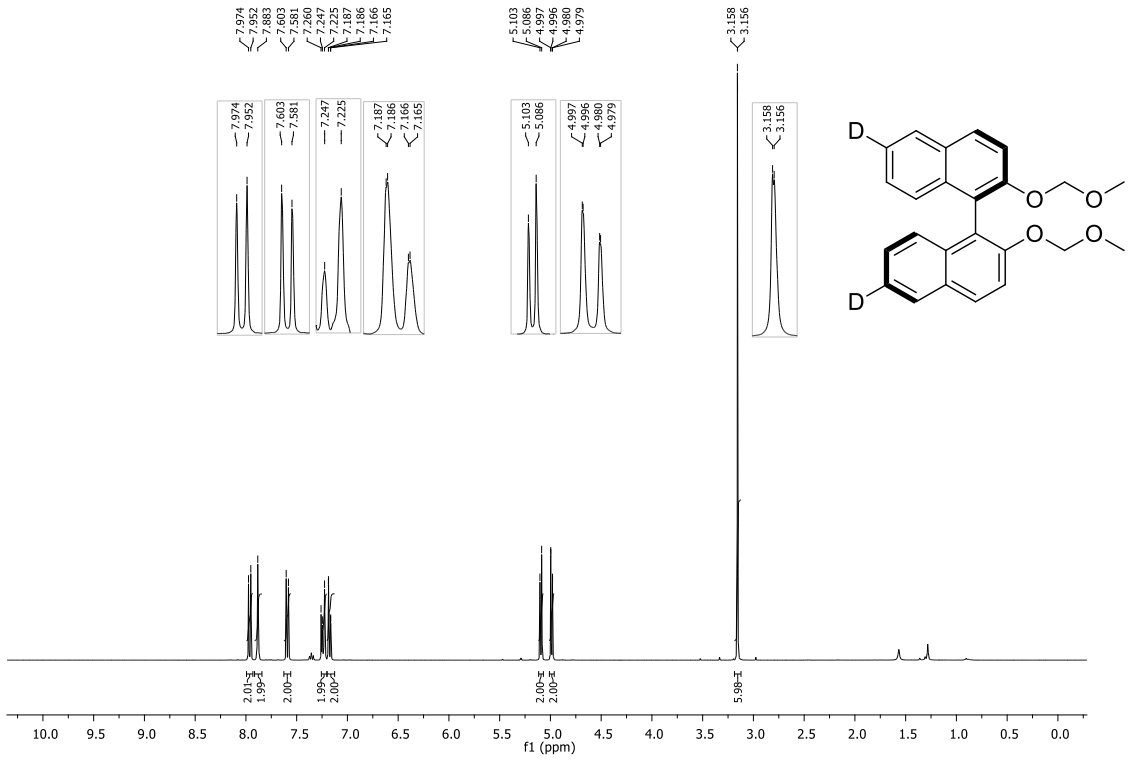



**Figure 2.13a**: $^{1}$H NMR Spectrum of **46k**

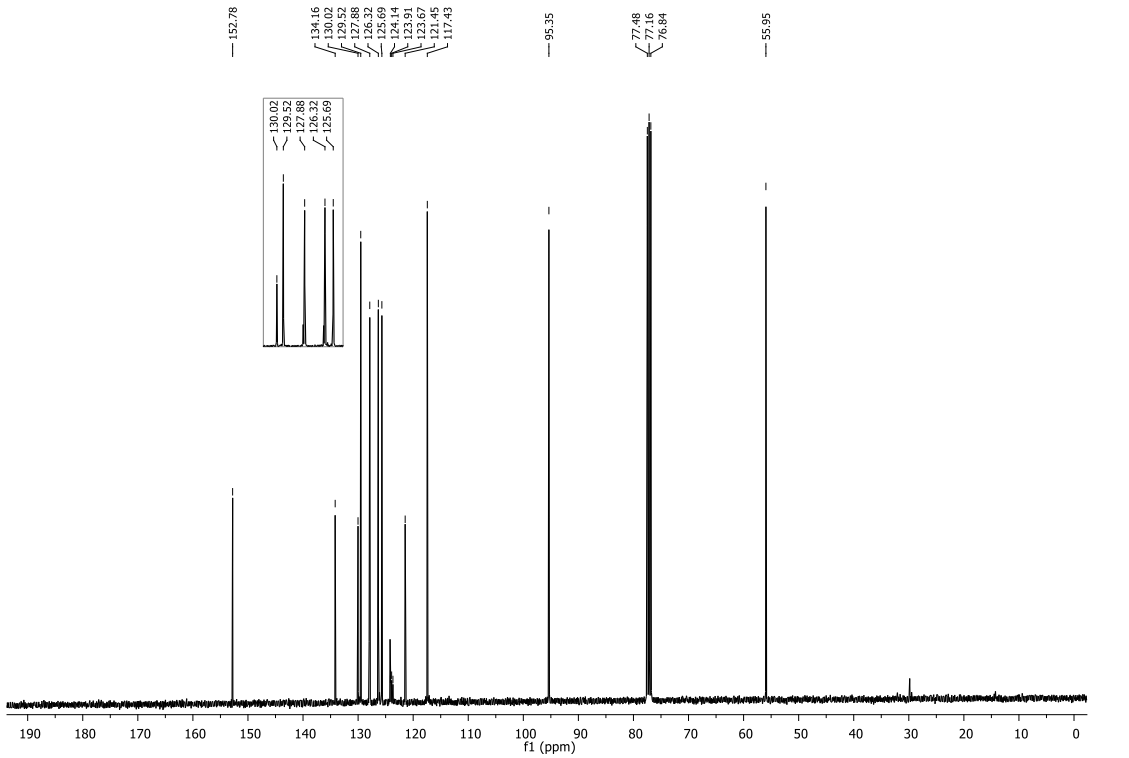



**Figure 2.13b**: $^{13}$C NMR Spectrum of **46k**

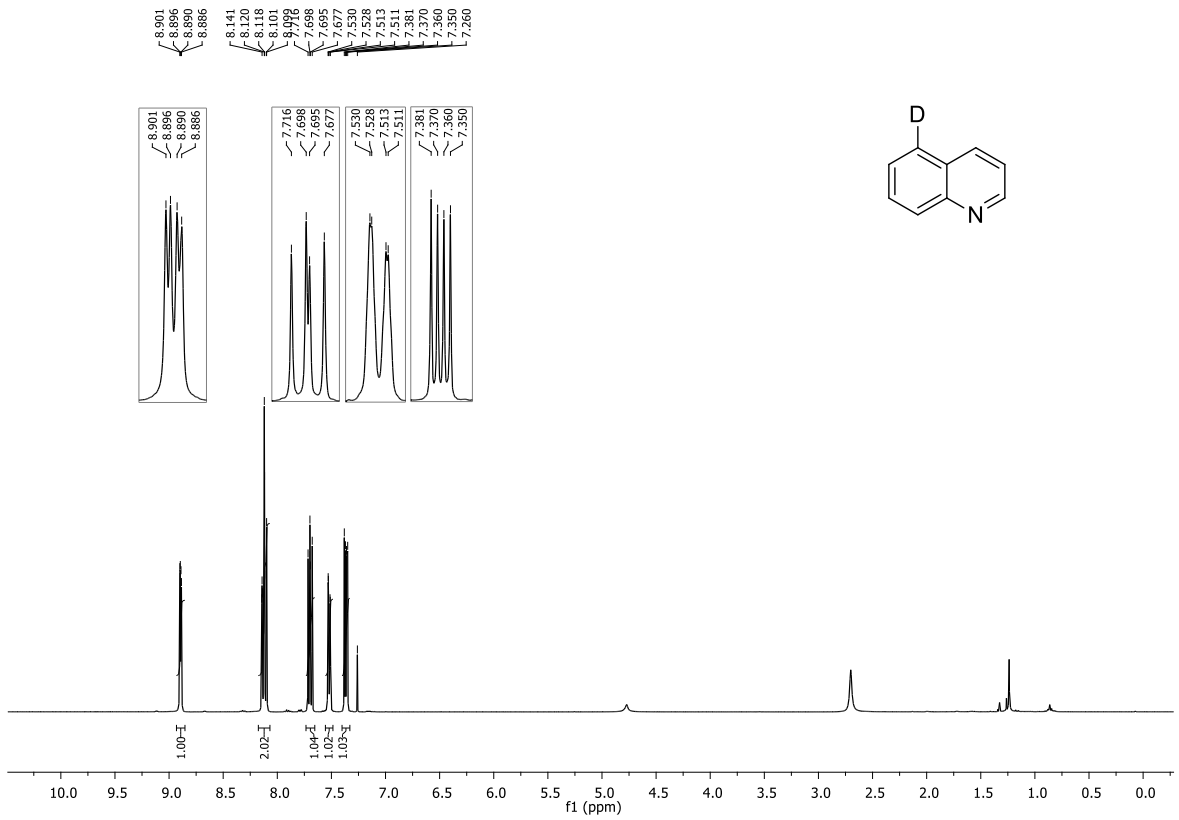



**Figure 2.14a**: $^{1}$H NMR Spectrum of **49b**

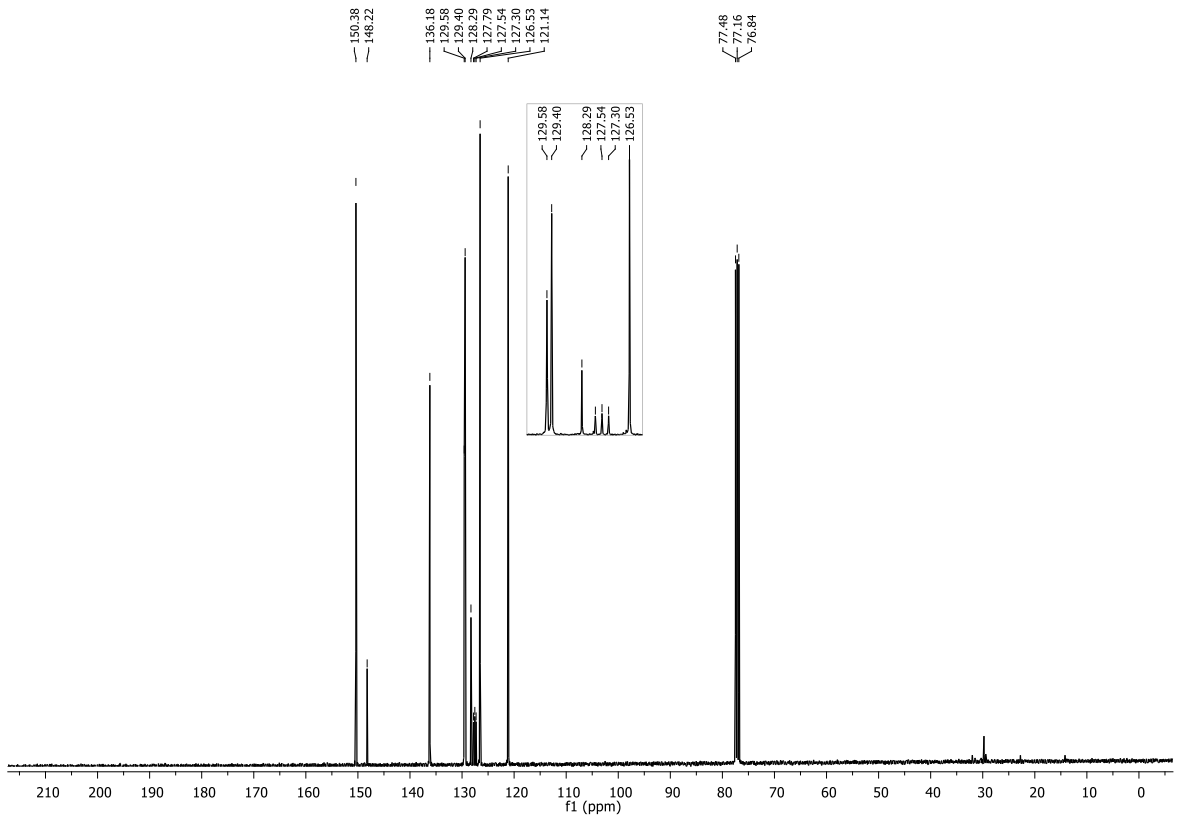



**Figure 2.14b**: $^{13}$C NMR Spectrum of **49b**

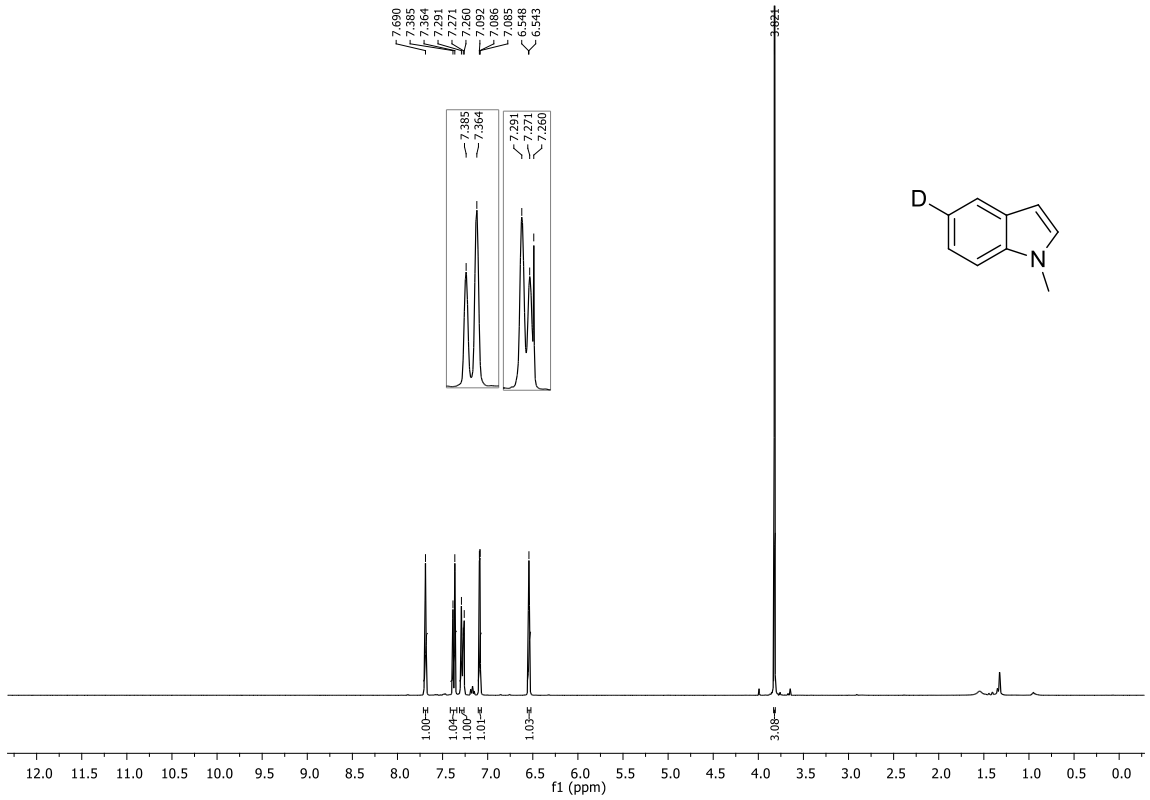



**Figure 2.15a**: $^{1}$H NMR Spectrum of **49d**

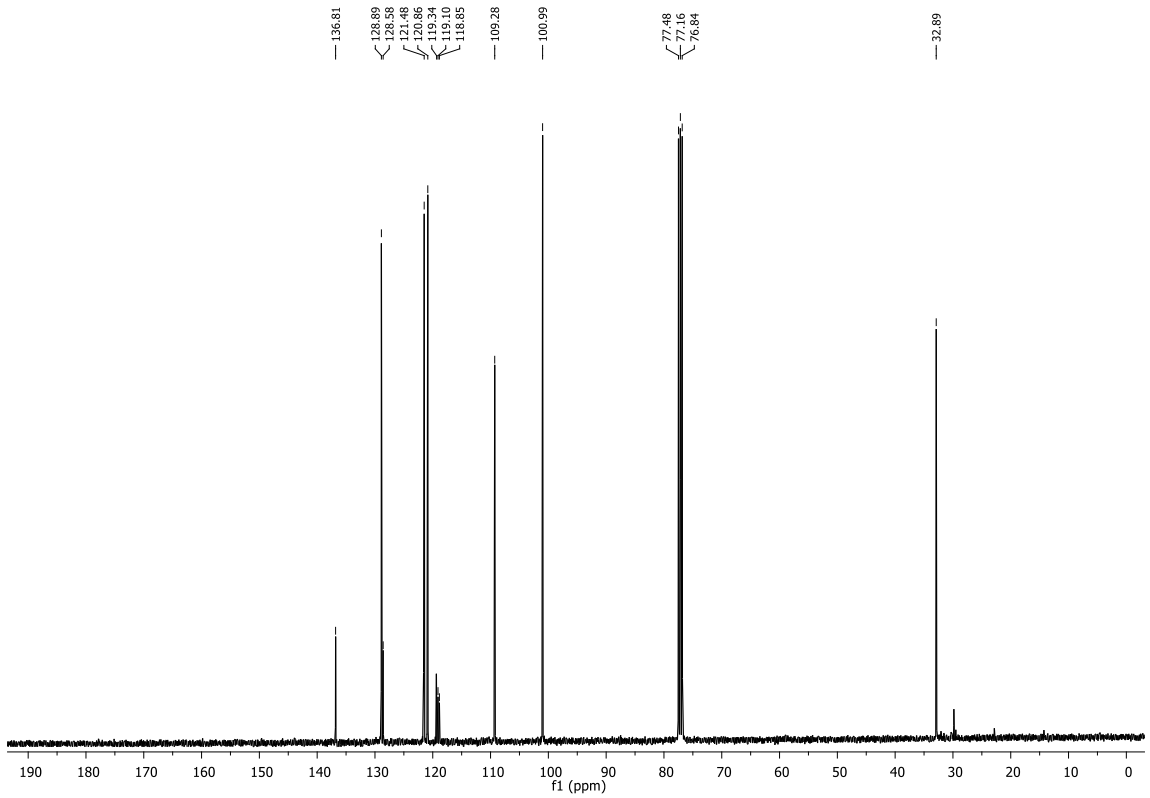



**Figure 2.15b**: $^{13}$C NMR Spectrum of **49d**

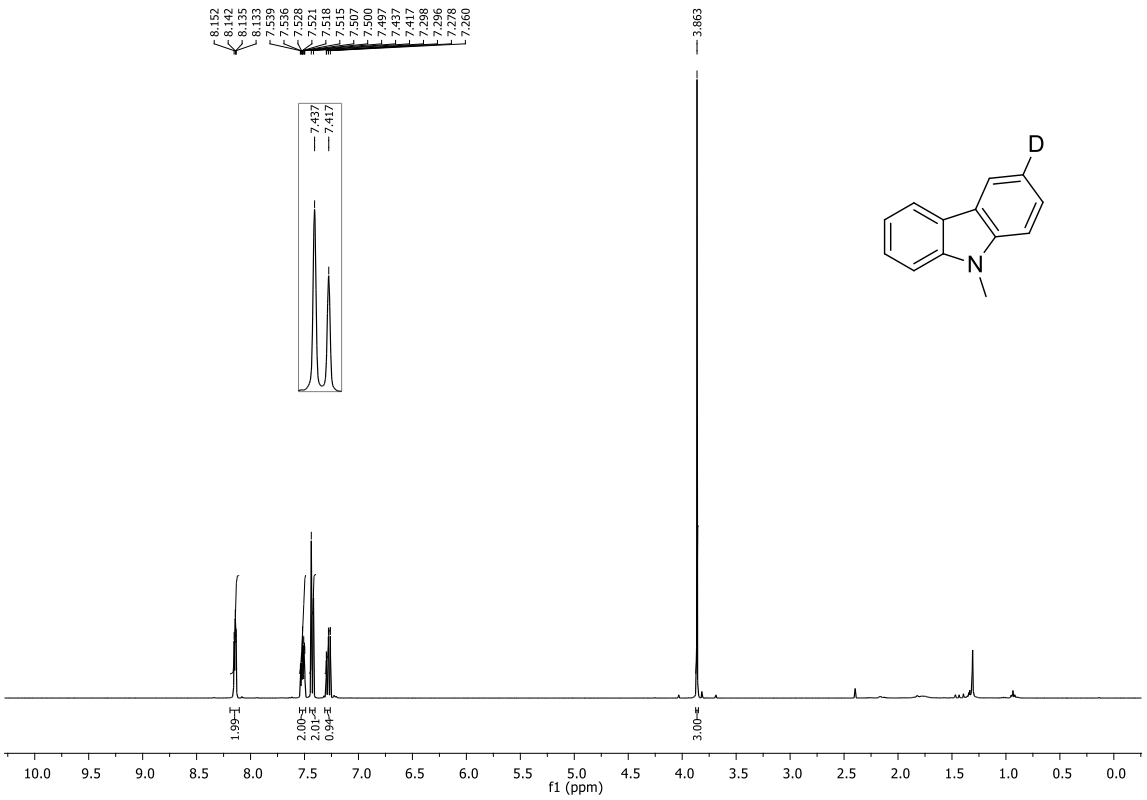



**Figure 2.16a**: $^{1}$H NMR Spectrum of **49e**

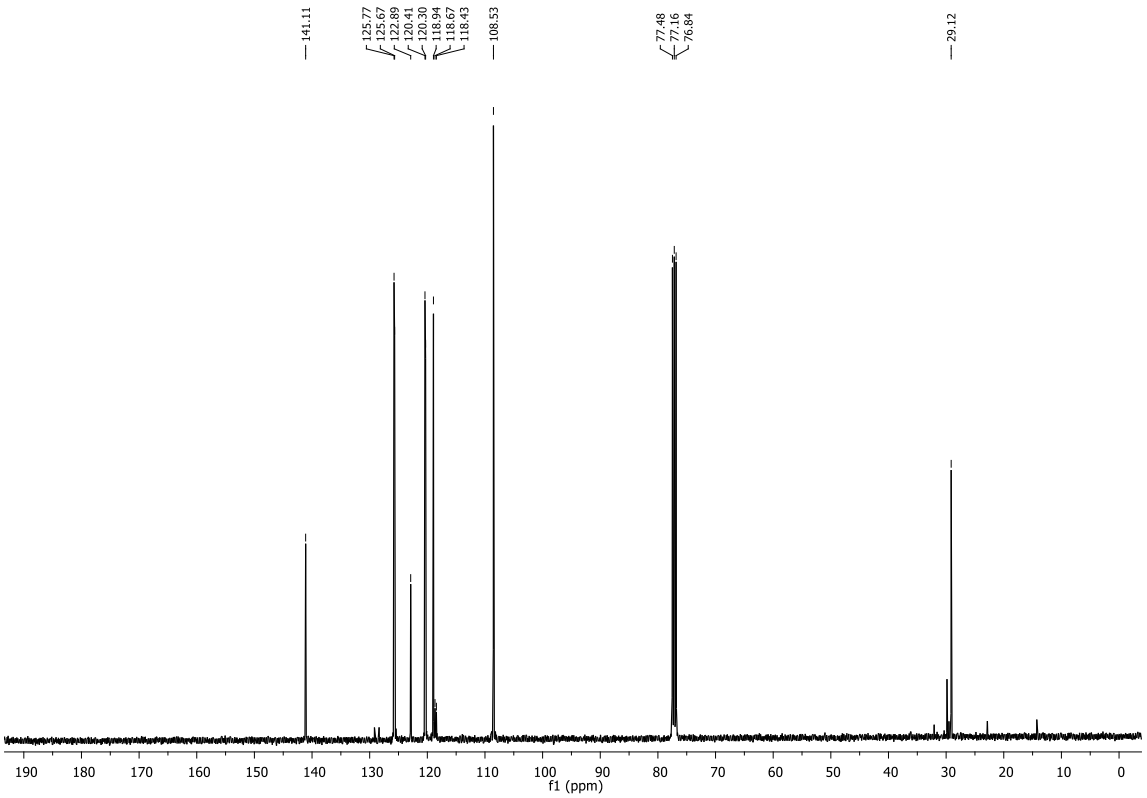



**Figure 2.16b**: $^{13}$C NMR Spectrum of **49e**

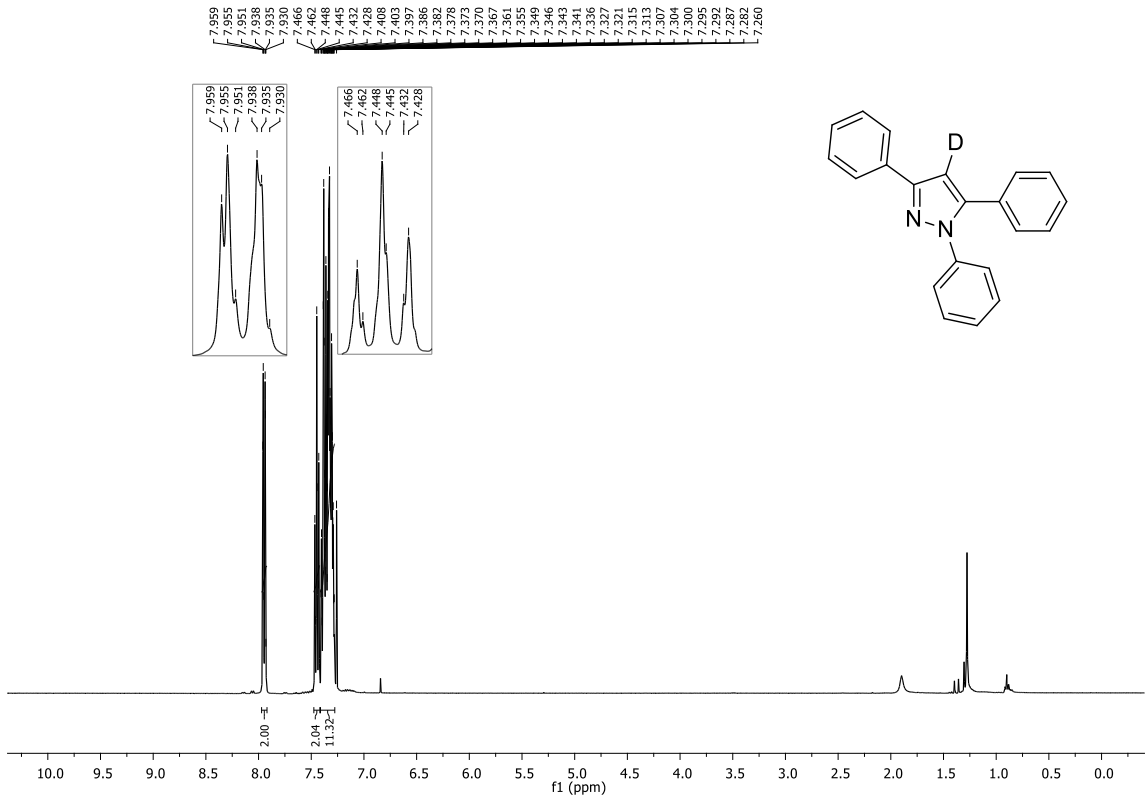



**Figure 2.17a**: $^{1}$H NMR Spectrum of **49f**

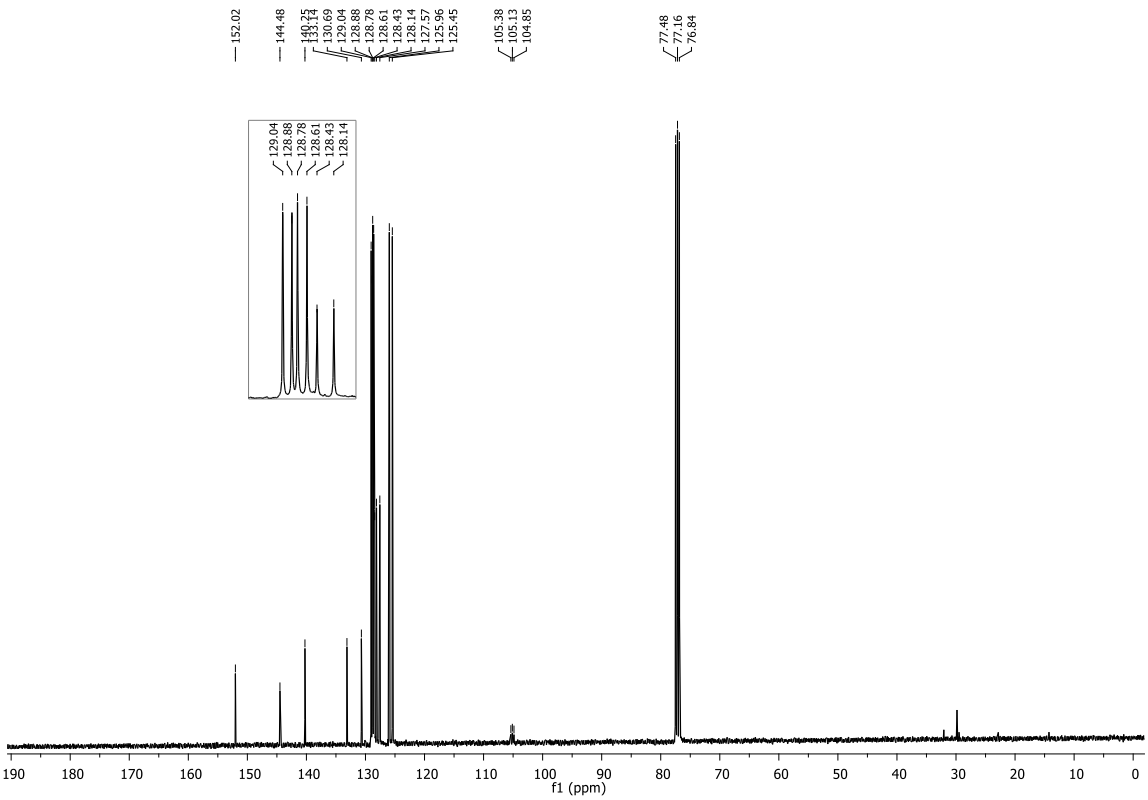



**Figure 2.17b**: $^{13}$C NMR Spectrum of **49f**

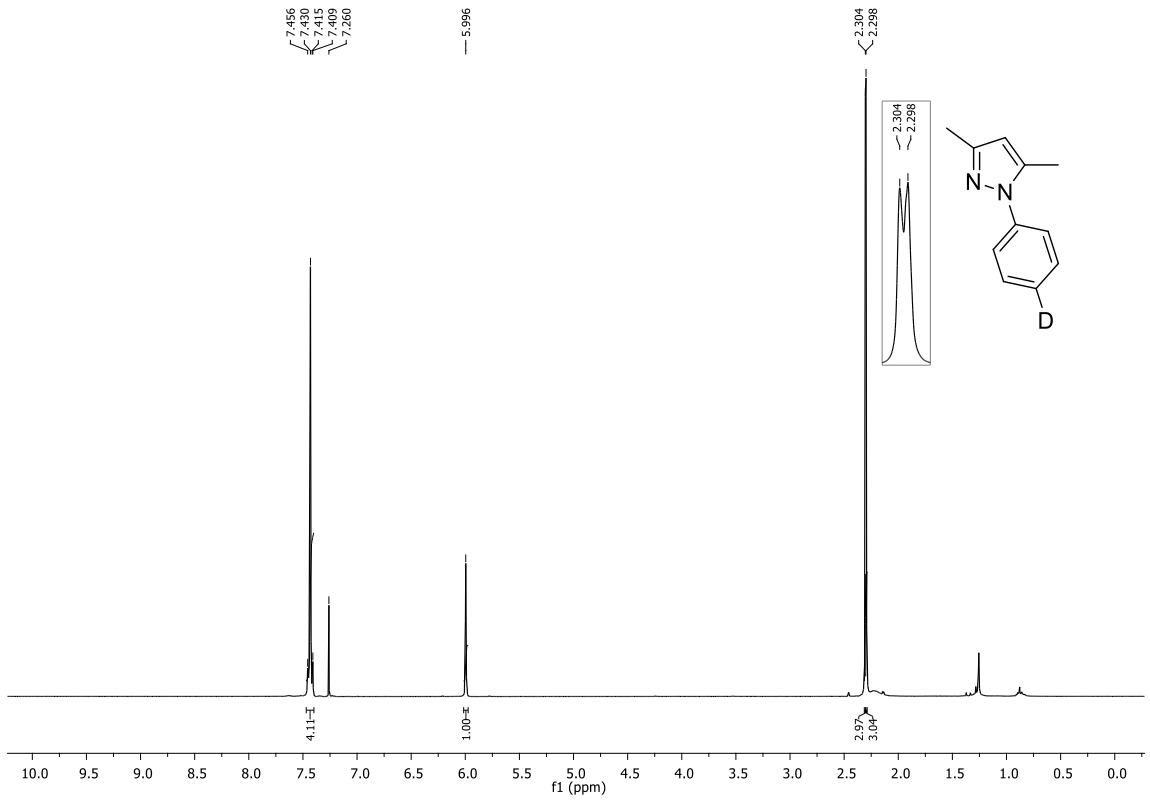



**Figure 2.18a**: $^{1}$H NMR Spectrum of **49h**

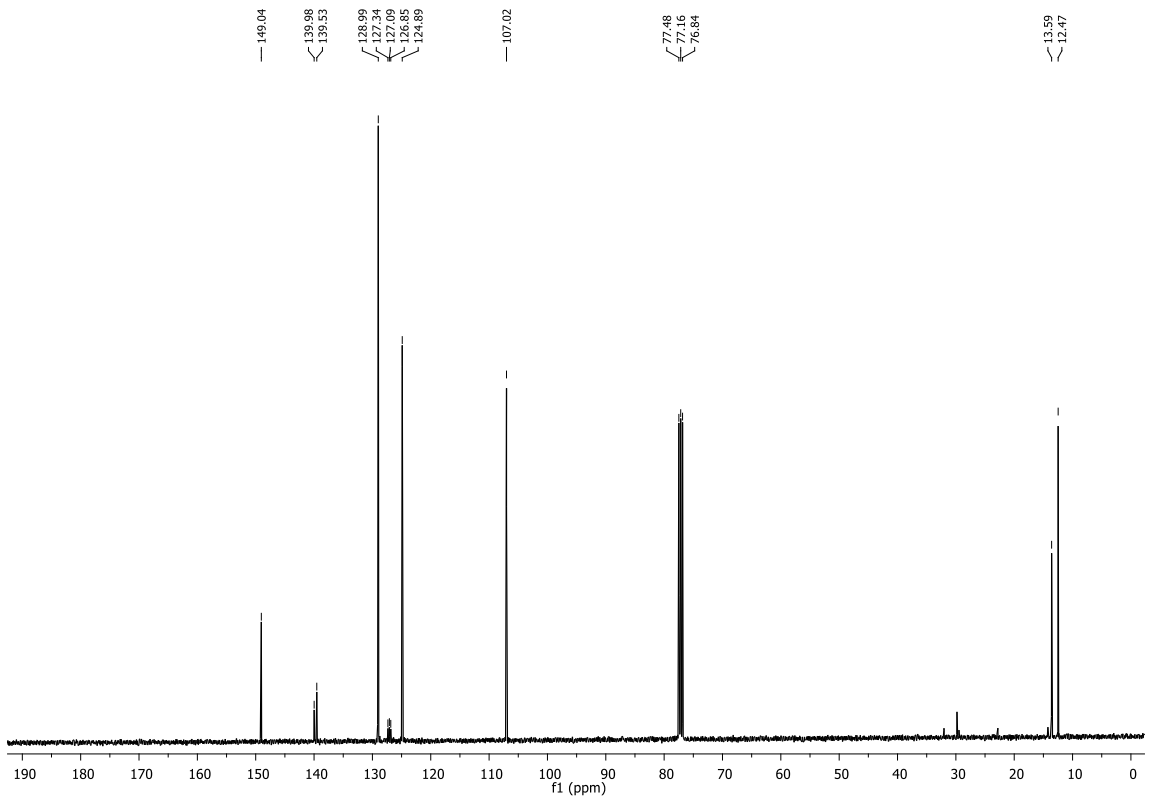



**Figure 2.18b**: $^{13}$C NMR Spectrum of **49h**

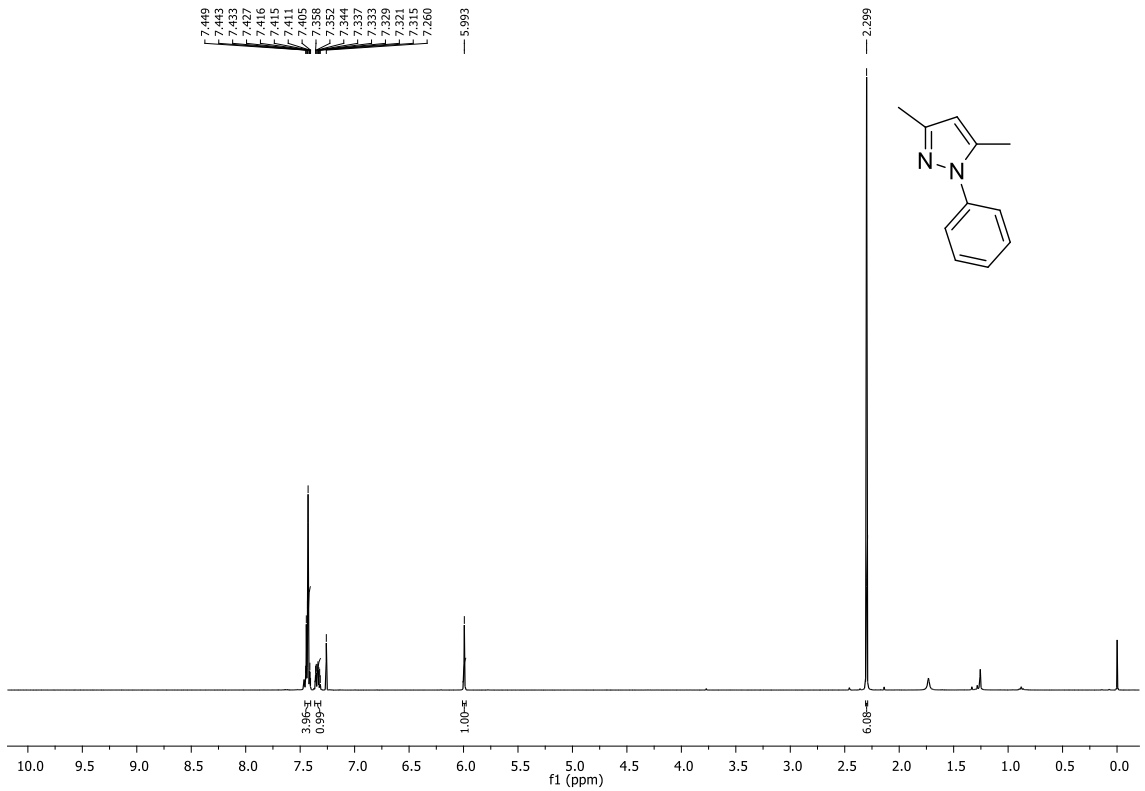



**Figure 2.19a**: $^{1}$H NMR Spectrum of **49g'**

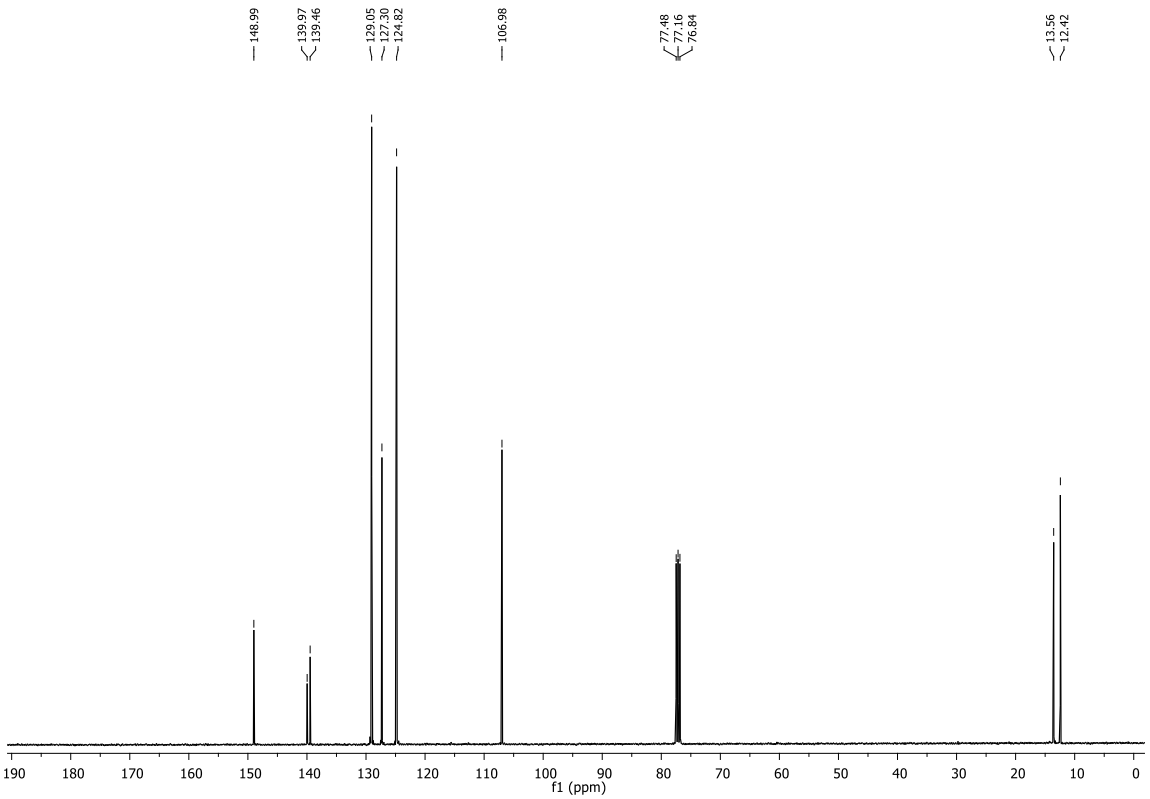



**Figure 2.19b**: $^{13}$C NMR Spectrum of **49g'**

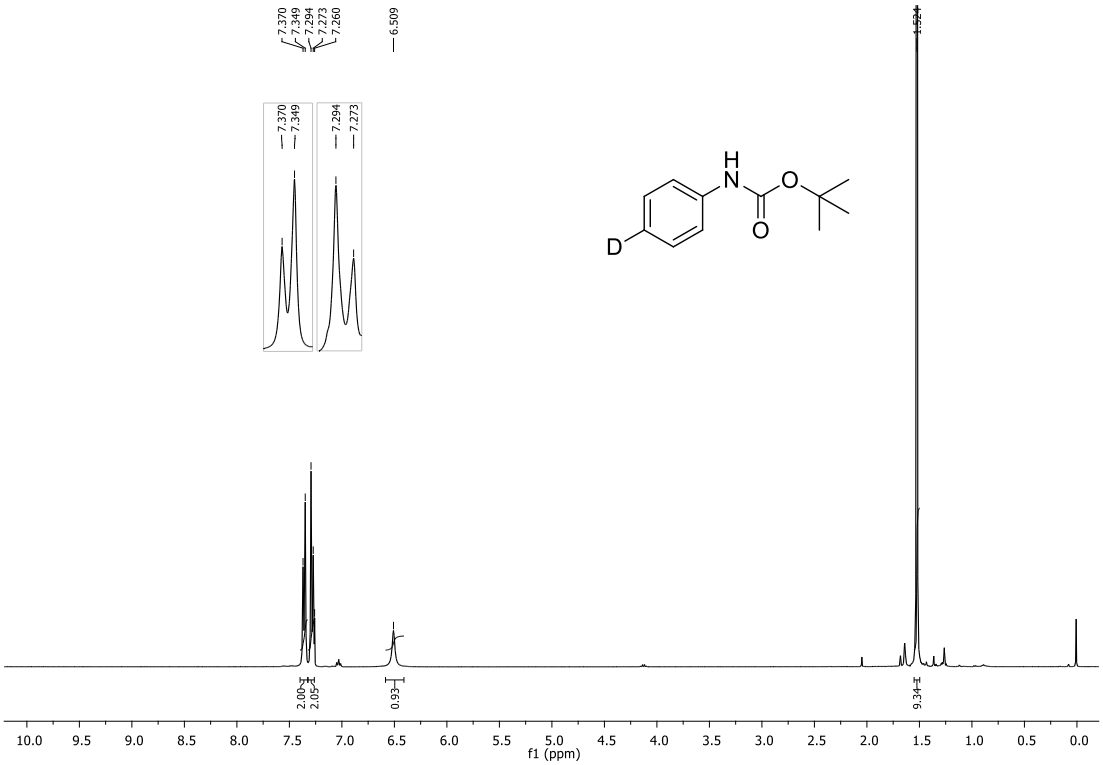



**Figure 2.20a**: $^{1}$H NMR Spectrum of **46i**

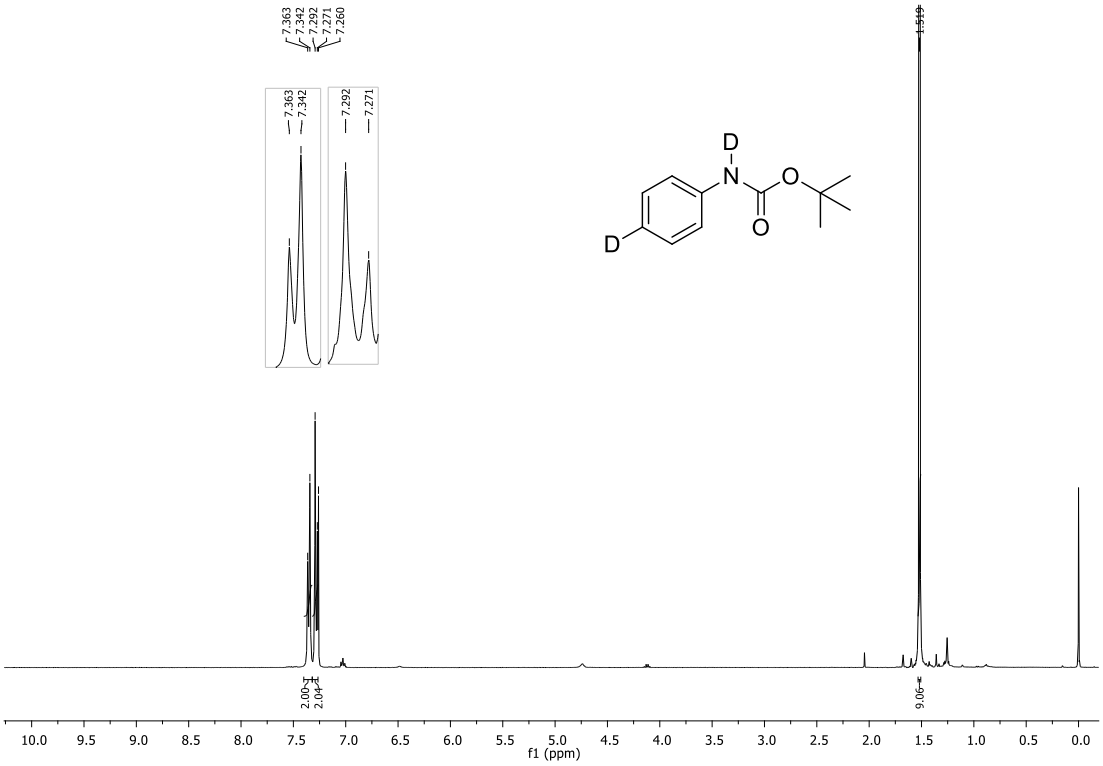



**Figure 2.20a'**: $^{1}$H NMR Spectrum of **46i** after $D_2O$ exchange

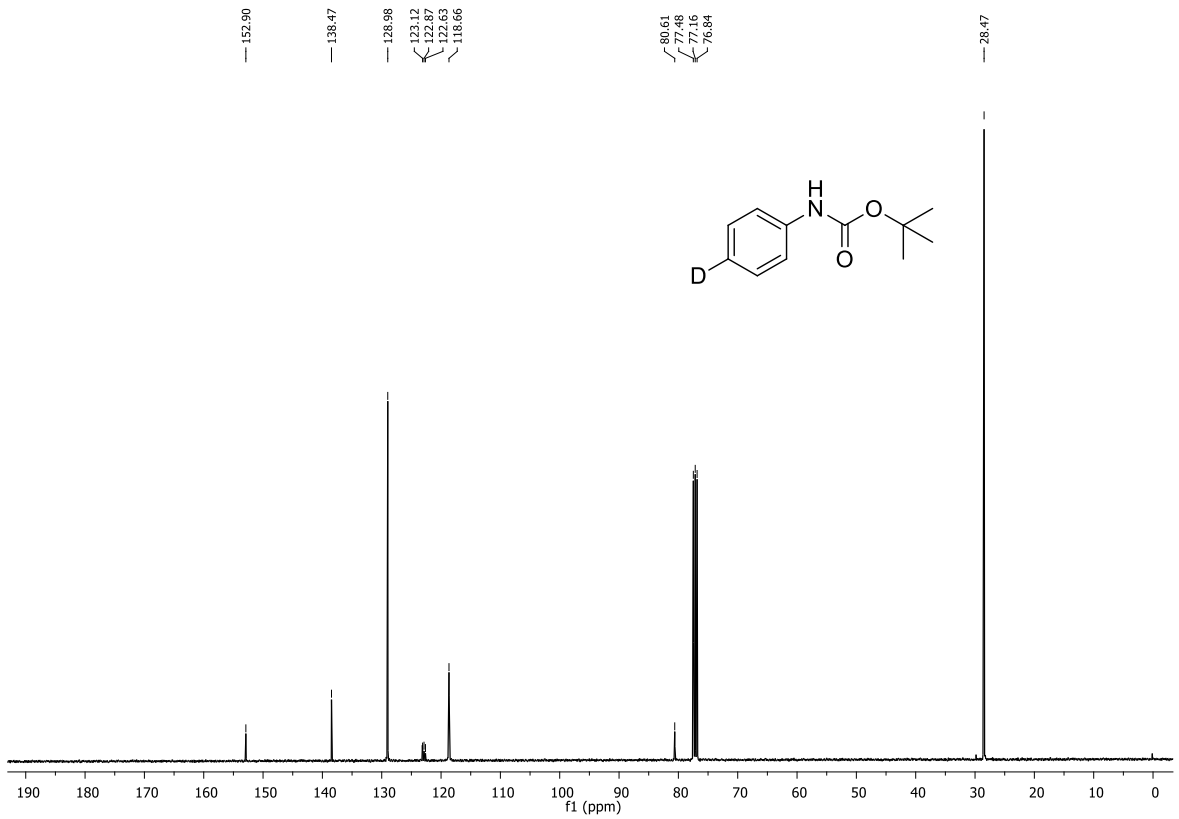



**Figure 2.20b**: $^{13}C$ NMR Spectrum of **46i**

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# Chemoselective Thiolation of Thioamides at Room Temperature: Synthesis of 2-Aminobenzo[*b*]thiophenes and Thieno[1,2-*b*]quinoline Derivatives

## 3.1 Introduction

Transition metal catalyzed carbon-heteroatom bond formation is one of the key breakthrough in modern organic chemistry, which mainly discloses the various methodologies to synthesize large number of heterocycles, which have significant role in biological, natural products and drugs.[1,2,3]

The different kinds of carbon-heteroatom bond formation reactions includes C—N, C—O, C—S and C—Se, among them, C—N bond formation has gained great attention to synthesize various nitrogen heterocycles which include indoles, carbazoles, pyrazoles, imidazoles, quinolones, oxazoles, thiazoles (Chapter 1).[4] After the C—N bond forming reactions, synthetic chemists were attracted towards C—O bond formation reactions to develop new strategies for synthesis of various kinds of oxygen heterocycles which include benzo[*b*]furans, oxazoles, isoxazole derivatives (Chapter 2).[5]

In the chemistry of carbon-heteroatom bond formation reactions, C—S bond formation reactions are less explored compared to the former. Unlike the past, from the last half decade C—S bond construction received much attention due to the high demand in the pharmaceutical industries and extensive application in material science.[6] The key advantage of the C—S bond is construction of various sulphur containing heterocycles including benzo[*b*]thiophene, thiazoles with diverse functional groups.[7] In those heterocycles, benzo[*b*]thiophene core is privileged structure and found in many natural products as well as synthetically designed drug

molecules.[8] Unlike its analogues indole and benzo[*b*]furan, synthesis of benzo[*b*]thiophene was explored very less although it is very important in various drugs (Figure 3.1).

The derivatives of the benzo[*b*]thiophene served as estrogen receptor modulators,[9] microtubule polymerization inhibitors,[10] potent acetyl-CoA carboxylase inhibitors,[11] HIV-1 reverse transcriptase inhibitors,[12] antimitotic agents, antifungal, anticancer, antiallergy, antiinflammatory agents and clinically important drugs such as zileuton, arzoxifene and raloxifene (Figure 3.1).[13]

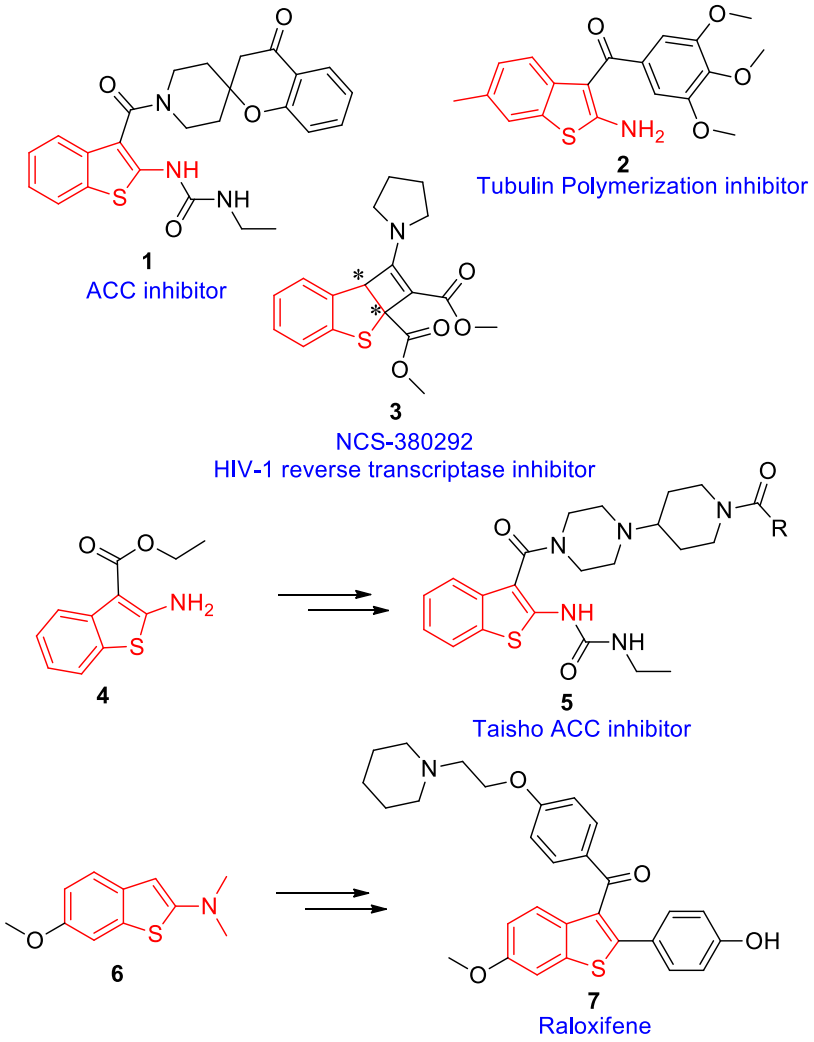
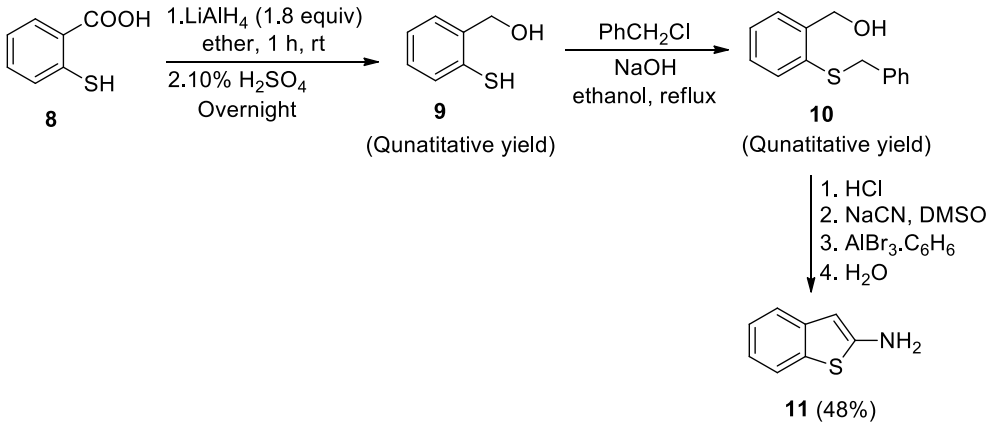



**Figure 3.1**: *Selected Bioactive Benzo[b]thiophene Derivatives*

Among the class of benzo[*b*]thiophenes, 2-aminobenzo[*b*]thiophene is an interesting core. This finds many applications in biological and pharmaceutical such as potent inhibitory activity in enzyme assay, inhibitors of tubulin polymerization, especially it is also key intermediate in the synthesis of bioactive rolaxifene and its analogues (Figure 3.1).[14,15] The versatile applications associated with the 2-aminobenzo[*b*]thiophene core is motivating one to develop new methods for synthesis of 2-aminobenzo[*b*]thiophenes by simple and mild reaction conditions. Although, few methods were known to access benzo[*b*]thiophene derivatives, synthesis of 2-aminobenzo[*b*]thiophenes is not studied well. In this chapter we described methods involved in the synthesis of 2-aminobenzo[*b*]thiophenes and their derivatives. Further, our approach to synthesize 2-aminobenzo[*b*]thiophene derivatives by using milder reaction conditions was discussed.

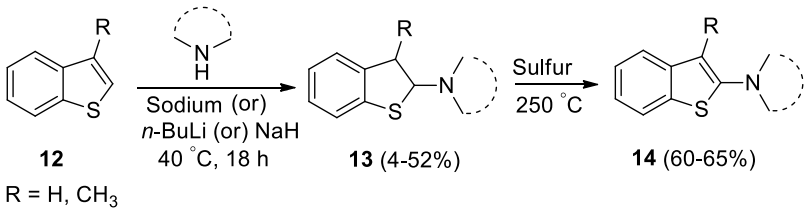
### 3.2 Previous Reports for Synthesis of 2-Aminobenzo[*b*]thiophenes

The first synthesis of 2-aminobenzo[*b*]thiophene (**11**) was reported in 1965 by G. W. Stacy *et al*, from thiosalicylic acid (**8**) as a precursor. They converted thiosalicylic acid (**8**) to alcohol **9**, followed by selective benzylation of thiol. Further, thioether **10** was converted into 2-aminobenzo[*b*]thiophene (**11**) by overall yield of 48% (Scheme 3.1).[16]



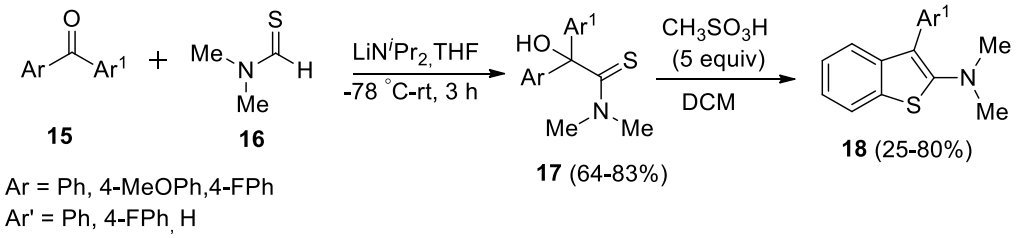

**Scheme 3.1**: *First Report of the Synthesis of 2-Aminobenzo[b]thiophene **11***

The second report of synthesis of 2-aminobenzo[*b*]thiophene came in 1978 by A. L. Combier and co-workers. Their approach depends on the metal catalyzed addition of primary and secondary amines to benzo[*b*]thiophene derivatives **12** in presence of strong base leading to formation of amino substituted 2,3-dihydrobenzo[*b*]thiophene **13**, which aromatized further by heating at 250 °C in presence of elemental sulphur affording 2-aminobenzo[*b*]thiophene derivatives **14** in 60-65% yield (Scheme 3.2).[17]




**Scheme 3.2**: *Synthesis of 2-Aminobenzo[b]thiophene **14** from Benzo[b]thiophene **12** through Addition/Rearomatization Protocol*

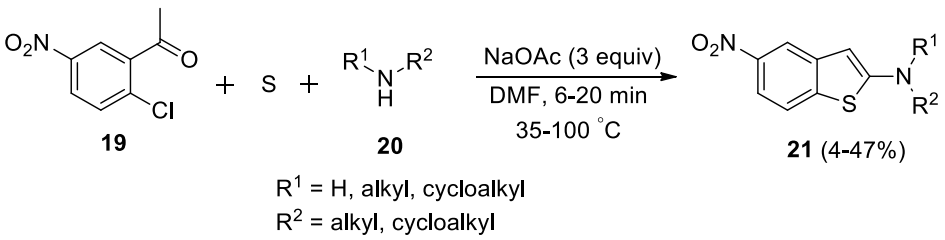
F. J. Albenas *et al* reported the synthesis of 3-aryl-2-aminobenzo[*b*]thiophene **18** from dimethyl thioformamide (**16**) and carbonyl compounds **15** by using non nucleophilic base, Lithium diisopropyl amide (LDA). The first step is generation of carbanion of thioamide by LDA which undergoes addition to ketone yielding adduct **17**. The adduct **17** undergo acid catalyzed cyclization leads to formation of benzo[*b*]thiophene derivative **18** in 25-80% yield (Scheme 3.3).[18]




**Scheme 3.3**: *Acid Catalyzed Cyclization of Hydroxy Thioamides* **17**

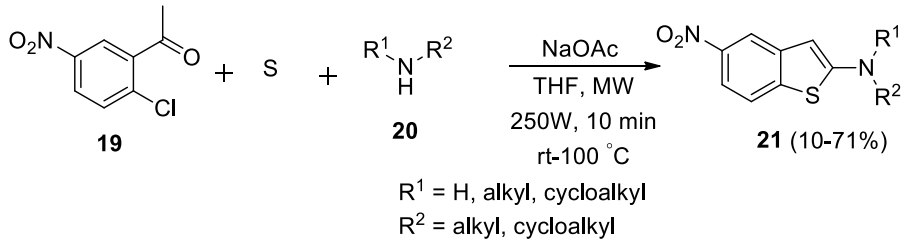
After two decades, in 2007, D. C. Neckers and co-workers reported one-pot synthesis of 5-nitro-2-aminobenzo[*b*]thiophene derivatives **21**. 2-Chloro-5-nitroacetophenone (**19**)

undergoes Willgerodt-Kindler reaction in the presence of primary and secondary amines **20** and base, followed by displacement of the chlorine on the aromatic ring resulting 2-aminobenzo[*b*]thiophene derivatives **21** through a simple, efficient three-component one-pot reaction (Scheme 3.4).[19]



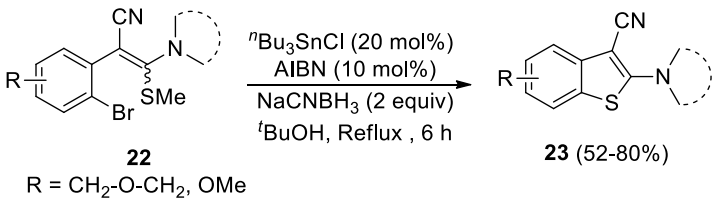

**Scheme 3.4**: *Three Components One-Pot Synthesis of Substituted 2-Aminobenzo[b]thiophenes **21***

Ed Biehl and co-workers reported the same reaction under microwave conditions with slightly better yields than conventional heating (Scheme 3.5).[20]



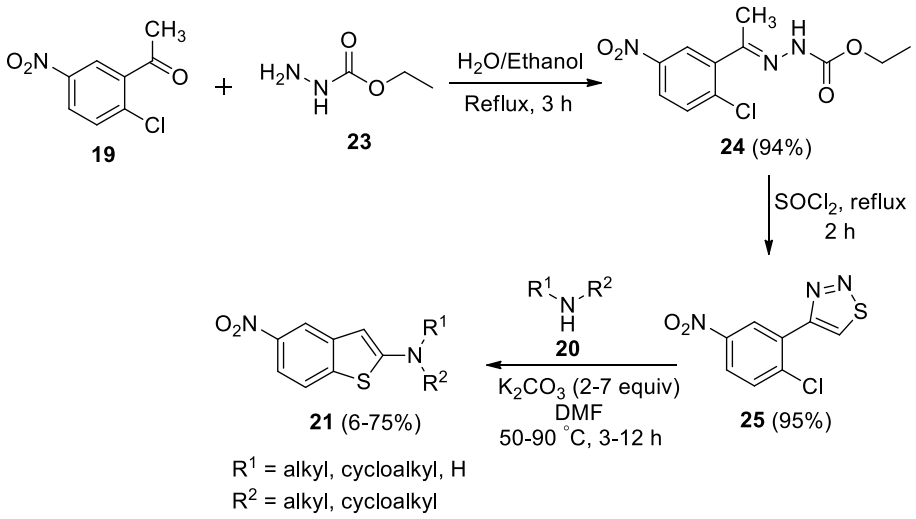

**Scheme 3.5**: *Microwave Assisted One-Pot Synthesis of Substituted 2-Aminobenzo[b]thiophenes **21***

In 2009, Ila and co-workers came up with a novel route to synthesize 2-amino-3-cyanobenzo[*b*]thiophenes **23** by intramolecular radical cyclization of polarized ketene *S,N*-acetals **22** which derived from *ortho*-bromoarylacetonitriles and primary & secondary amines (Scheme 3.6).[21]



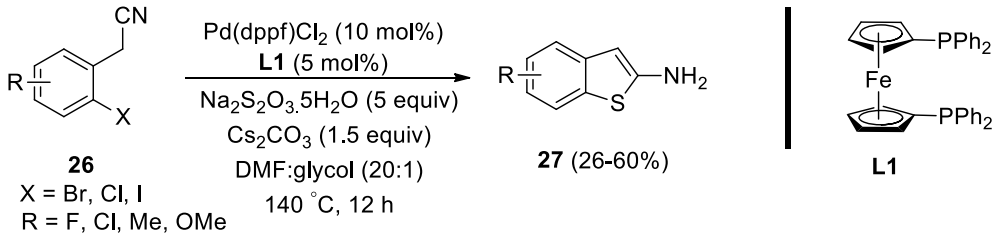

**Scheme 3.6**: *Synthesis of 2-Amino-3-cyanobenzo[b]thiophenes **23** by Radical Cyclization*

In 2010, D. A. Androsov and co-workers synthesized 1,2,3-thiadiazoles **25** from hydrazones of the methyl ketones **24** and thionyl chloride (Scheme 3.7). These 1,2,3-thiadiazoles **25** transformed to 2-aminobenzo[*b*]thiophenes **21** in the presence of base and amine (Scheme 3.7).[22]




**Scheme 3.7**: *Unusual Base-induced Transformation of 1,2 and 3- Thiadiazoles **25** to 2-Aminobenzo[b]thiophenes **21***

Very recently, Yang and co-workers disclosed a novel strategy for the synthesis of various 2-aminobenzo[*b*]thiophenes **27** from 2-haloaryl acetonitriles **26**. The reactions involved the palladium catalyzed C—S bond formation in the presence of dppf ligand (**L1**) and cheap sulphur source i.e., $Na_2S_2O_3$ at high temperature (Scheme 3.8).[23]

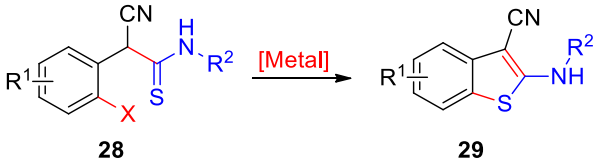



**Scheme 3.8**: *Synthesis of 2-Aminobenzo[b]thiophenes* **27** *via Palladium Catalyzed Carbon—Sulfur bond Formation Using* $Na_2S_2O_3$

Our literature survey clearly shows that each report has its own advantages and limitations. Most of them are suffering from low to moderate yields, limited substrate scope, expensive and harmful metal salts and harsh conditions. Some of the methods are required with multistep processes to reach 2-aminobenzo[*b*]thiophene derivatives. In other words, the methods reported are not suitable for industrial applications. Therefore, a general and practical method is required for synthesis of 2-aminobenzo[*b*]thiophene derivatives.

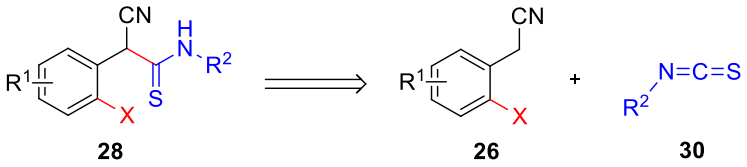
### 3.3 Results and Discussion

We envisioned a general strategy for the synthesis of 2-aminobenzo[*b*]thiophene derivatives **29** from thioamides **28** by chemoselective intramolecular thiolation reaction (Scheme 3.9). Further we are also interested in studying chemoselectivity of carbon-heteroatom bond forming reactions of thioamide **28**.




**Scheme 3.9**: *Our Strategy for Synthesis of 2-Aminobenzo[b]thiophene Derivatives* ***29***

The thioamide derivatives **28** can be synthesized from 2-haloaryl acetonitriles **26** and substituted isothiocyanates **30** (Scheme 3.10).[24]

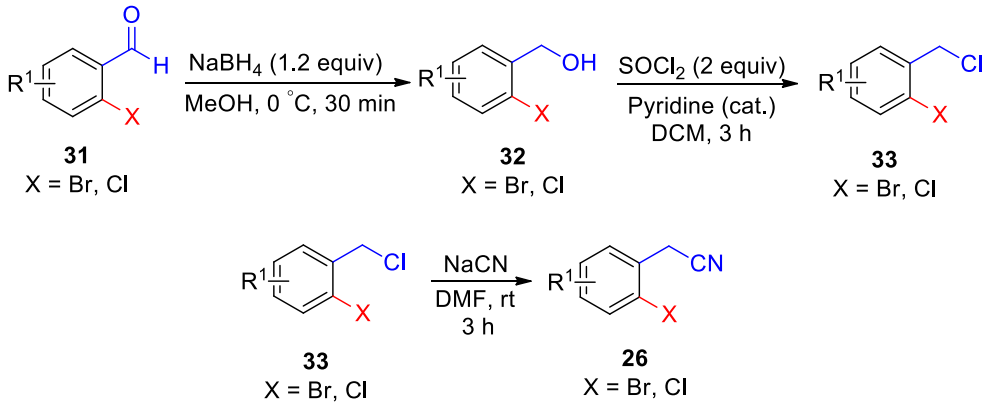


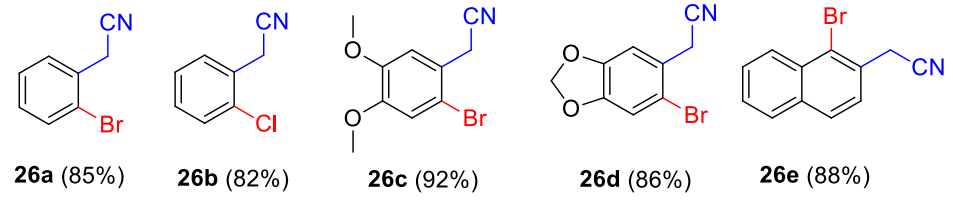

**Scheme 3.10**: *Retrosynthesis of Thioamide Derivatives* **28**

### 3.3.1 Synthesis of 2-Haloaryl Acetonitriles 26

The 2-haloaryl acetonitriles **26** synthesized from the corresponding 2-halo arylaldehydes **31**. Thus, the aldehydes **31** were reduced by $NaBH_4$ affording the respective alcohols **32** in quantitative yields. These alcohols **32** were transformed into the chloro derivatives **33** which were directly converted into 2-haloaryl acetonitriles **26** by cyanation (Table 3.1).[25]

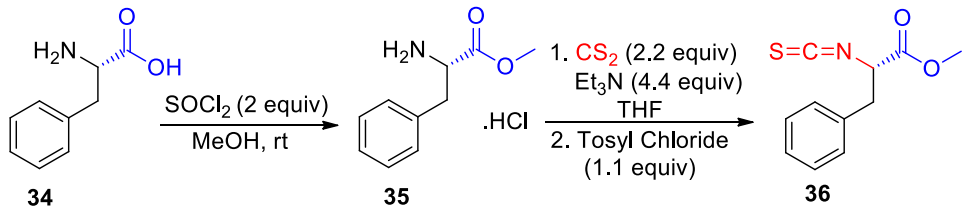
**Table 3.1**: **Synthesis of 2-Haloaryl Acetonitriles 26**



### 3.3.2 Synthesis Isothiocyanate 36 Derived from Aminoacids 34

Several isothiocyanates are commercially available. However, amino acid derived isothiocyante is not available. Hence, it was prepared by known literature method.[26] Thus phenyl alanine (**34**) was esterified in the presence of thionyl chloride and MeOH. The amine group of the amino acid ester **35** converted into dithiocabomate salt in presence of $CS_2$ and $Et_3N$. This dithiocarbomate salt was decomposed in the presence of tosyl chloride generated isothiocyanate derivative **36** (Scheme 3.11).

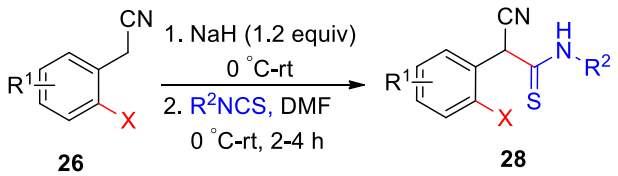



**Scheme 3.11**: *Synthesis of Isothiocyanate* **36** *from Phenyl Alanine*

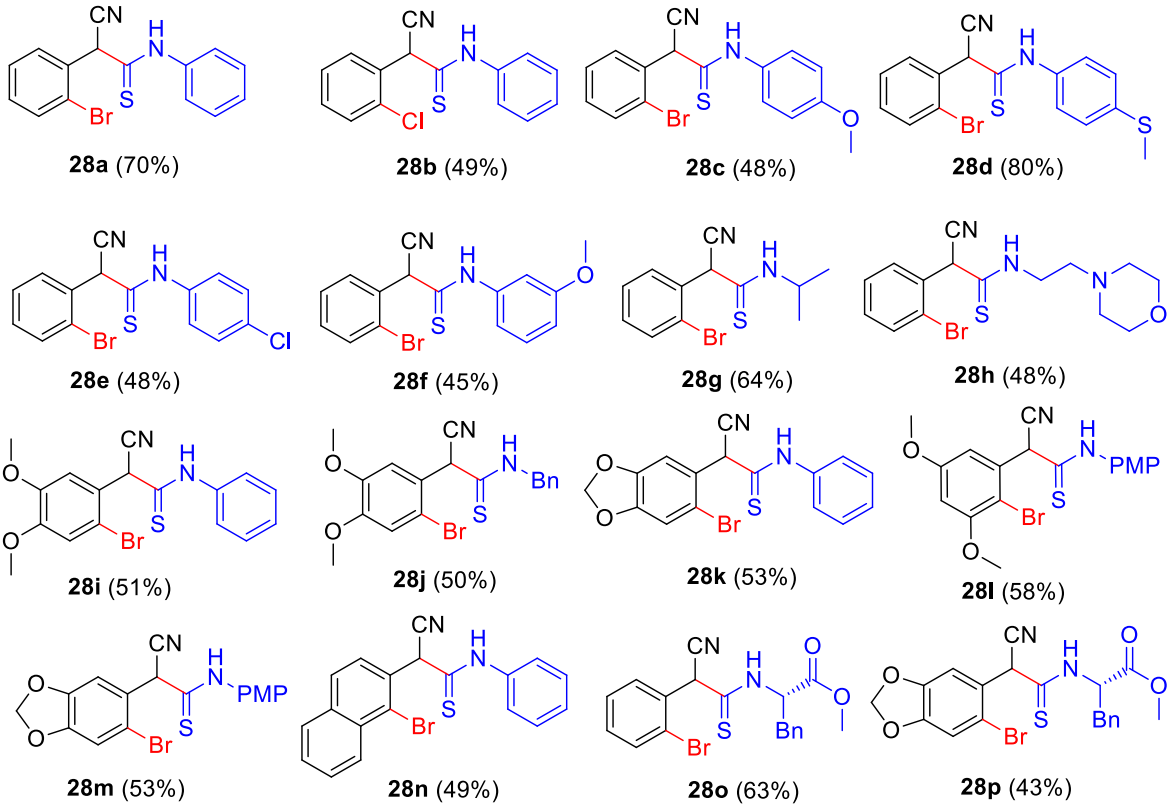
### 3.3.3 Synthesis of Thioamides 28

The required thioamides **28** were synthesized by reported procedure.[24] Thus 2-haloaryl acetonitrile **26** was treated with NaH in DMF at 0 $^oC$ to generate anion of acetonitrile **26** which was quenched with isothiocyanate **30** affording the thioamides **28** in 45-70% yield. The thioamides were characterized by Spectrum and analytical data (Table 3.2).

**Table 3.2: Synthesis of Thioamides 26 from 2-Halo Arylacetonitriles 26 and Isothiocyanates 36**




**26** **28**

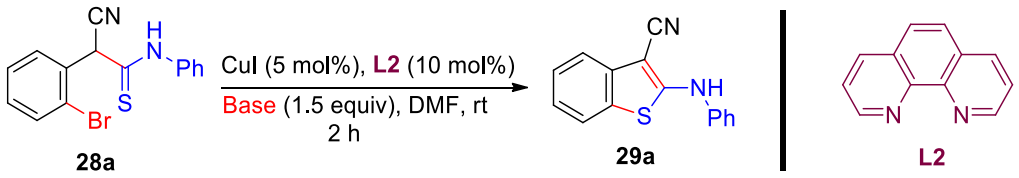



### 3.3.4 Optimization of Thiolation Reaction

We selected thioamide **28a** as the standard substrate for thiolation reaction. We treated thioamide **28a** with CuI (5 mol%), KO$^t$Bu (1.5 equiv) in DMF at room temperature for 2 h. The GC analysis showed that very poor conversion of product **29a** (Table 3.3, Entry 1). However, the same experiment was performed with 1,10-phenanthroline ligand **L2** (10 mol%) within 2 h, there is no starting material detected in GC and 72% of expected benzo[*b*]thiophene **29a** was isolated (Table 3.3, Entry 2). The structure of **29a** was confirmed by Spectruml and analytical data. The chemoselective carbon-heteroatom bond formation further confirmed by single crystal analysis (Figure 3.2). These results encouraged us to investigate fine tuning of

this process. Thus, we screened different bases (Table 3.3, Entries 3-7) for the thiolation process in the presence of 1,10-phenanthroline ligand. $Cs_2CO_3$ gave only 65% yield of the product **29a** (Table 3.3, Entry 3). Whereas $K_2CO_3$ and KOH are equally effective for thiolation (Table 3.3, Entries 4 and 5). Interestingly, when we used DMAP as a base, benzo[*b*]thiophene **29a** was obtained in 84% yield (Table 3.3, Entry 6). Gratifyingly, benzo[*b*]thiophene **29a** was isolated in 88% when $Et_3N$ was used as a base (Table 3.3, Entry 7). Compared to DMAP, $Et_3N$ is a milder and cheaper, we decided to proceed further thiolation reaction with $Et_3N$ as a base.

**Table 3.3**: **Base Screening of Intramolecular Thiolation of Thioamide 28a**




| Entry | Base | 29a (% Yield)[a] |
|---|---|---|
| 1 | KO$^t$Bu | 13 (79)[b,c] |
| 2 | KO$^t$Bu | 72 |
| 3 | $Cs_2CO_3$ | 65 |
| 4 | $K_2CO_3$ | 73 |
| 5 | KOH | 76 |
| 6 | DMAP | 84 |
| 7 | $Et_3N$ | 88 |

[a] *Reaction Conditions:* ***29a*** *(0.5 mmol), CuI (5 mol%), Ligand* ***L2*** *(10 mol%), Base (0.75 mmol), DMF (2 mL), rt, 2h.* [b] *Reaction was done without ligand.* [c] *Recovered thioamide* ***29a*** *in the parenthesis*

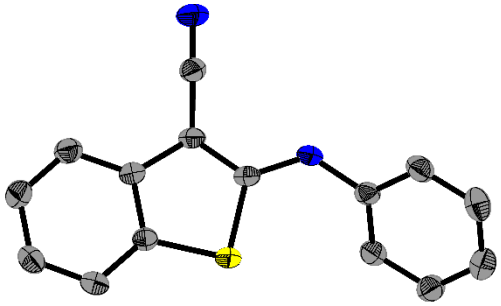
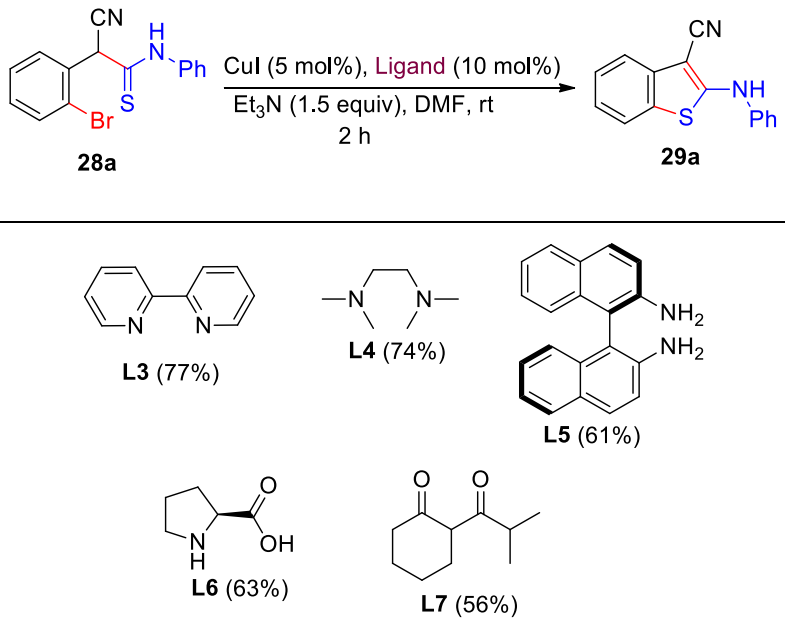


**Figure 3.2**: *Single Crystal X-ray of 2-Aminobenzo[b]thiophene* **29a**

Next we turned our attention towards the ligand effect of thiolation. Aforementioned, without ligand the reaction did not proceed well (Table 3.3, Entry 1). Thus, we selected series of ligands **L3-7** for intramolecular thiolation process. The results are summarized in the Table 3.4. We found that electron rich nitrogen centred ligands (**L3-L4**) gave very good yields (Table 3.4, **L3-4**) whereas BINAM (**L5**) and L-proline (**L6**) gave only 61-63% yield of the product **29a** (Table 3.4, **L5-6**). On the other hand, oxygen based ligand (**L7**) gave only 56% of the

**Table 3.4**: **Ligand Screening of Thiolation Reaction**

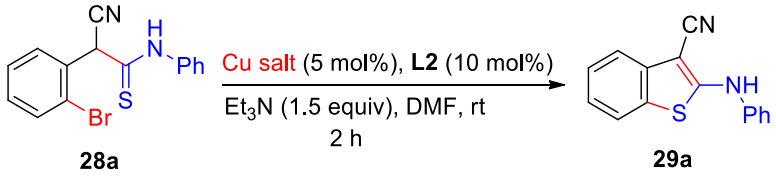



[a] *Reaction Conditions:* **28a** *(0.5 mmol), CuI (5 mol%), Ligand (10 mol%), $Et_3N$ (0.75 mmol), DMF (2 mL), rt, 2h, yield of the isolated product* **29a** *showed in parenthesis*

product **29a** within 2 h (Table 3.4, **L7**). These results clearly indicated that 1,10-phenanthroline is suitable for the chemoselective intramolecular thiolation of thioamides **28a**.

We also studied various copper salts to find suitable one for thiolation process. The results are summarized in Table 3.5. CuBr was equally effective as CuI (Table 3.4, Entry 1 vs Table 3.5, Entry 2). However, CuCl and $Cu(OAc)_2$ gave10% of the lower yield of the product **29a** (Table 3.5, Entries 1 & 3). CuBr is cheaper compared to CuI. Therefore CuBr was chosen for further studies.

**Table 3.5**: **Cu Salts Effect on Thiolation Reaction**[a]



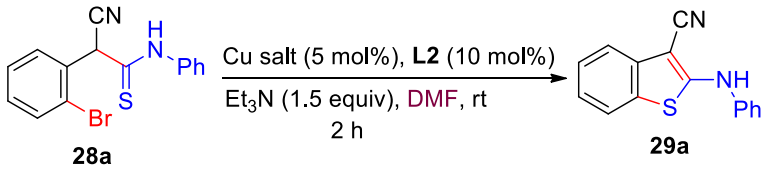

**28a** **29a**

| Entry | Cu salts | 29a (% Yield)[b] |
|---|---|---|
| 1 | CuCl | 77 |
| 2 | CuBr | 88 |
| 3 | $Cu(OAc)_2$ | 79 |

[a] *Reaction Conditions:* ***29a*** *(0.5 mmol), Cu salts (5 mol%), Ligand* ***L2*** *(10 mol%),* $Et_3N$ *(0.75 mmol), DMF (2 mL), rt, 2h.* [b] *Isolated yields.*

Finally, the solvent effect on thiolation was examined with DMSO, $CH_3CN$ and Toluene (Table 3.6). Among them DMSO was comparable with DMF interms of conversion and yields of benzo[*b*]thiophene **29a** (Table 3.6, Entry 1). However, acetonitrile gave 63% yield of the product **28a** (Table 3.6, Entry 2). On the other hand, in the case of toluene 64% of the starting material **28a** was recovered from the reaction along with only 15% of the thiophene product **29a** (Table 3.6, Entry 3).

**Table 3.6**: **Solvent Screening on Thiolation Reaction**



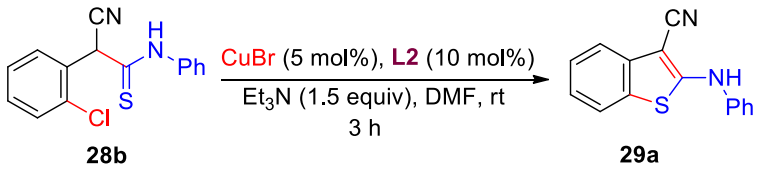

| Entry | Solvent | 29a (% Yield)[a,b] |
|---|---|---|
| 1 | DMSO | 84 |
| 2 | $CH_3CN$ | 63 |
| 3 | Toluene | 15 |

[a] *Reaction Conditions:* ***29a*** *(0.5 mmol), CuBr (5 mol%), Ligand* ***L2*** *(10 mol%), $Et_3N$ (0.75 mmol), Solvent (2 mL), rt, 2h.* [b] *Isolated yields.*

Overall our studies show that 5 mol% CuBr, 10 mol% 1,10-phenanthroline, DMF, $Et_3N$ (1.5 equiv) at room temperature are found to be effective condition for the chemoselective thiolation of thioamide **28a**.

### 3.3.5 Substrate Scope

With the optimization conditions in our hand, we studied various thioamides **28b-p** for intramolecular thiolation reaction. First the halogen effect of thiolation was examined. Thus, thioamide **28b** was treated with CuBr under optimized conditions, affording 66% of

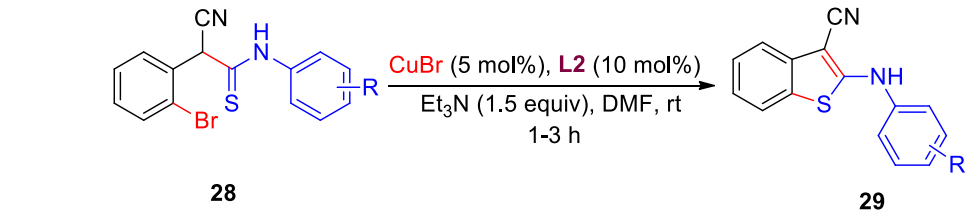



**Scheme 3.12**: *Chemoselective Intramolecular Thiolation of Chloro Thioamide* ***28b***

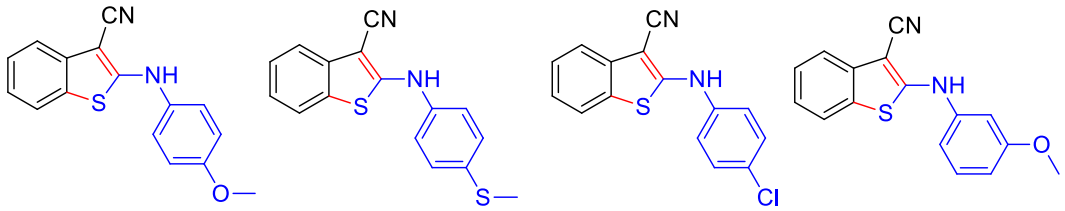
benzo[*b*]thiophene **29a** in 3 h. This results showed that bromo derivative is more effective compared with chloro derivative in terms of conversion rate as well as yield (Scheme 3.12).

Next, we studied *N*-aryl substituted thioamides **28c-f** for intramolecualr thiolation reaction (Table 3.7). Thus, 4-methoxy substituted *N*-phenyl thioamide derivative **28c** was smoothly transformed to 2-(4-anisidinyl)-3-cyanobenzo[*b*]thiophene (**29c**) in 78% yield (Table 3.7). Similarly 2-(4-thioanisidinyl)-3-benzo[*b*]thiophene (**29d**) was obtained from the corresponding thioamide **28d** in excellent yield of 94% (Table 3.7). However, 4-chloro substituted *N*-phenyl thioamide **28e** gave only 66% yield of the product (Table 3.8, **29e**). On the other hand, 3-methoxy substituted *N*-phenyl thioamide **28f** was converted to 2-(3-anisidinyl)-3-cyanobenzo[*b*]thiophene (**29f**) in very good yields (Table 3.7).

**Table 3.7**: **Synthesis of *N*-Aryl Substituted Benzo[*b*]thiophenes**



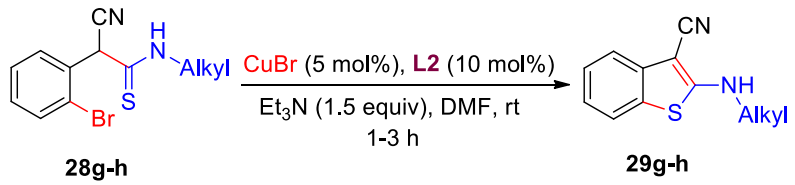

**28** **29**



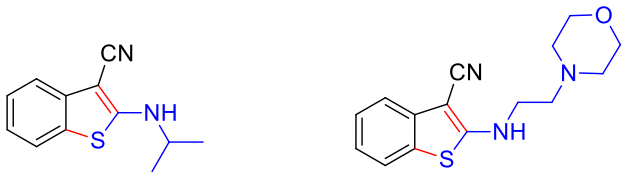

**29c** (78%) **29d** (94%) **29e** (66%) **29f** (82%)

Further, we extended this methodology to *N*-alkyl substituted thioamides **28g-h** for synthesis of 2-alkylamino-3-cyanobenzo[*b*]thiophenes **29g-h** (Table 3.8). Thus, *N*-isopropyl substituted thioamide **28g** gave excellent yield of benzo[*b*]thiophene **29g** (Table 3.8). Interestingly, 2-[2-(*N*-morpholine)ethylamino]-3-cyano-benzo[*b*]thiophene (**29h**) was prepared from thioamide **28h** in 78% yield by similar reaction conditions (Table 3.8).

**Table 3.8: Synthesis of *N*-Alkyl Substituted Benzo[*b*]thiophenes**



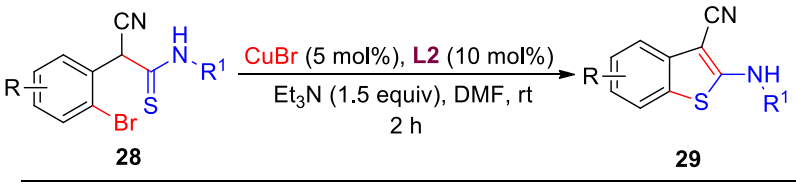

**28g-h** **29g-h**



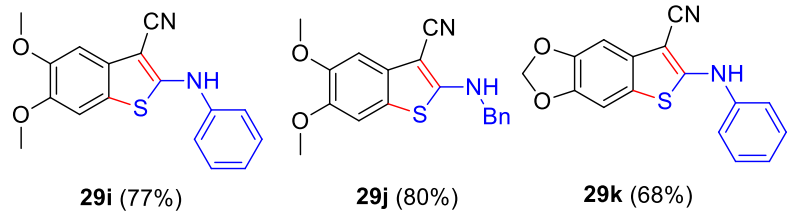

**29g** (88%) **29h** (78%)

We also studied the effect of electron donating substituents at 2-bromoaryl group of thioamide on the thiolation reaction. Thus, thioamides having dimethoxy group at aryl group, **28i-j** gave 77-80% yield of benzo[*b*]thiophenes **29i-j** (Table 3.9). Whereas, thioamide containing methylene dioxy, **28k** gave 68% yield of the product **29k** (Table 3.9). *N*-4-Methoxy

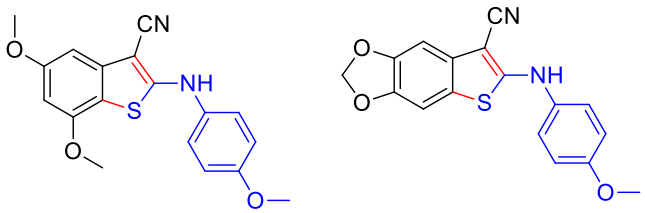
**Table 3.9**: **Synthesis of Electron Donating Group Containing Benzo[*b*]thiophenes 29**




**28** **29**



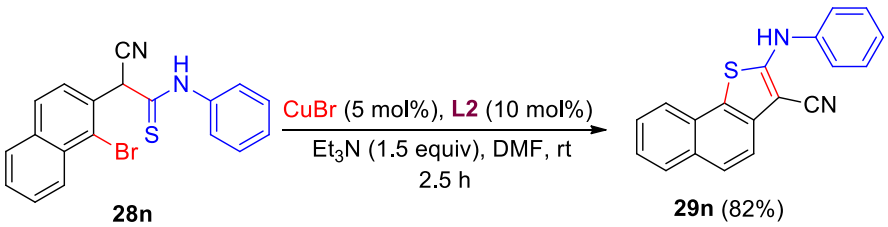

**29i** (77%) **29j** (80%) **29k** (68%)




**29l** (79%) **29m** (53%)

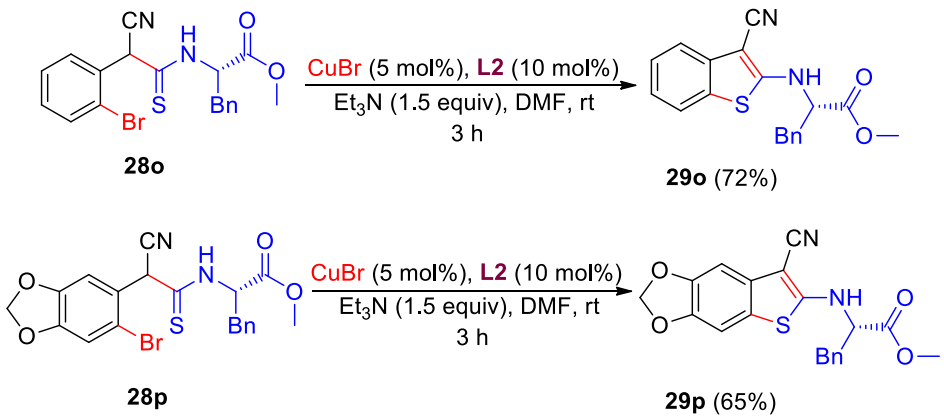
group substituted thioamides **28l-m** were also examined for thiolation reaction. Thus, 3,5-dimethoxy substituted bromo derivative **28l** gave the product **29l** in 79% yield, whereas, methylene dioxy group **28m** gave only 53% yield of product **29m** (Table 3.9).

The *α*-cyano-*α*-(1-bromo-2-naphthyl)-thioamide **28n** was transformed to the (2-phenylamino)naphtha[1,2-*b*]thiophene-3-carbonitrile (**29n**) in 82% yield under optimized reaction conditions (Scheme 3.13).




**Scheme 3.13**: *Synthesis of Naphtha Fused Benzo[b]thiophene Derivative **29n***

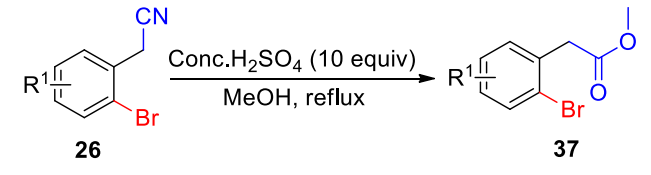
We also synthesized amino acid substituted benzo[*b*]thiophenes **29o-p** (Scheme 3.14). Thus, the amino acid substituted thioamides **28o-p** were subjected under identical reaction conditions, affording the corresponding benzo[*b*]thiophene derivatives **29o-p** in 72% and 65% yields respectively. Interestingly, no racemization was observed during reaction conditions (Scheme 3.14).

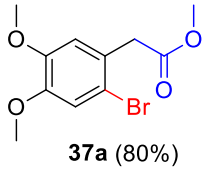



**Scheme 3.14**: *Synthesis of Amino Acid Substituted Benzo[b]thiophene Derivatives **29o-p***

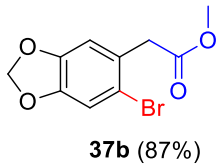
Next, we extended this methodology to other functional groups such as esters and carbonyl groups. The required methyl $\alpha$-(2-bromoaryl) acetates and deoxybenzoins were prepared according to the literature procedure (Tables 10 and 12).[27] Thus, 2-haloaryl acetonitriles were hydrolysed and *in situ* esterified affording esters **37a-b**.

**Table 3.10**: **Synthesis of Esters 37 from 2-Haloaryl Acetonitriles 26**



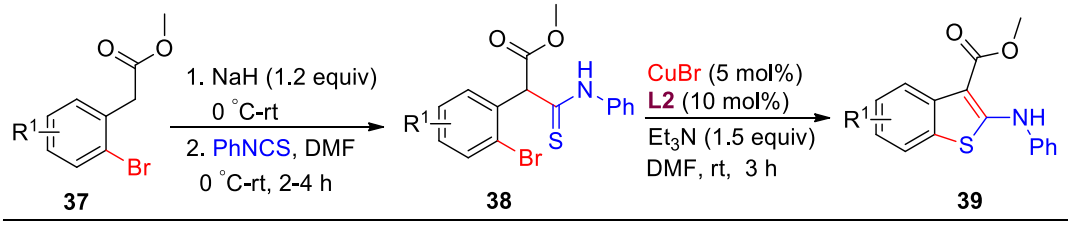



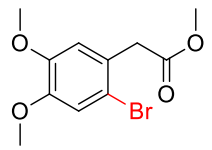
**37a** (80%)



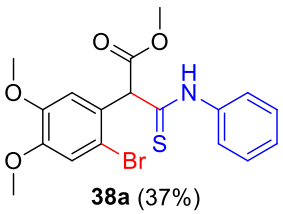
**37b** (87%)

**Table 3.11**: **Synthesis of Ester Substituted Benzo[*b*]thiophenes 39**

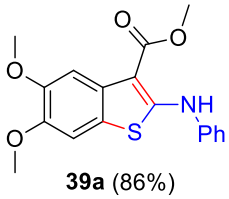


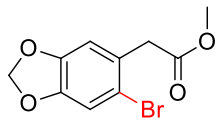
**37a** (80%)



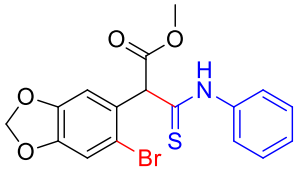
**38a** (37%)



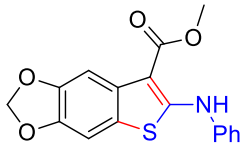
**39a** (86%)



**37b** (87%)



**38b** (57%)

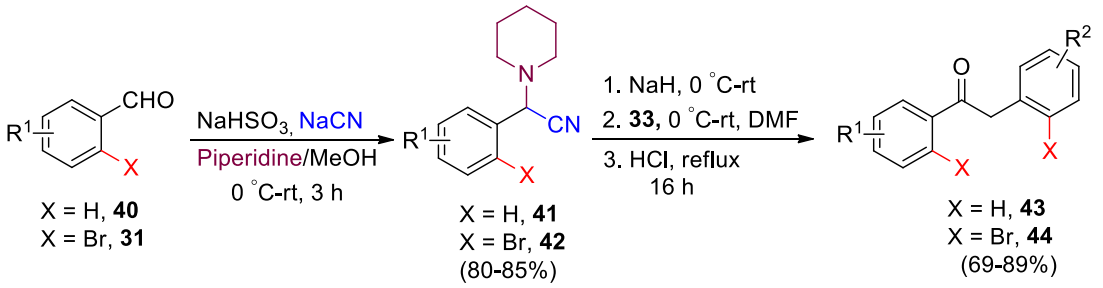


**39b** (88%)

These esters **37a-b** were converted into the respective thioamides **38a-b** by earlier conditions (Table 3.11). The thioamides **38a-b** derived from ester were smoothly transformed into the 3-ester substituted benzo[*b*]thiophenes **39a-b** in excellent yields (Table 3.11).

Next, we paid our attention towards synthesis of aroyl substituted benzo[*b*]thiophenes from α-(aroyl)-α-(2-bromoaryl)thioamides **45a-b** (Table 3.13). These thioamides could be prepared by reaction of deoxybenzoins with respective isothiocyanates (Table 3.13). The synthesis of deoxybenzoins **43a-b** and **44a-c** is shown in Table 3.12. The deoxybenzoin synthesis involves 3 steps. The first step is synthesis of aminonitriles **41**- **42**. These aminonitriles **41** - **42** were alkylated with substituted benzyl chlorides **33** and hydrolysis affording deoxybenzoins **43-44** in good to excellent yields (Table 3.12).[28]

**Table 3.12**: **Synthesis of Deoxybenzoins 43-44**



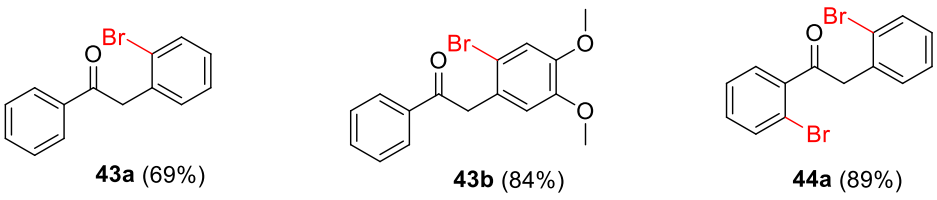
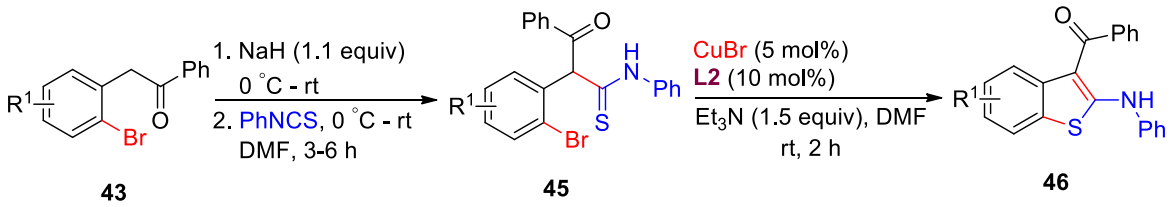
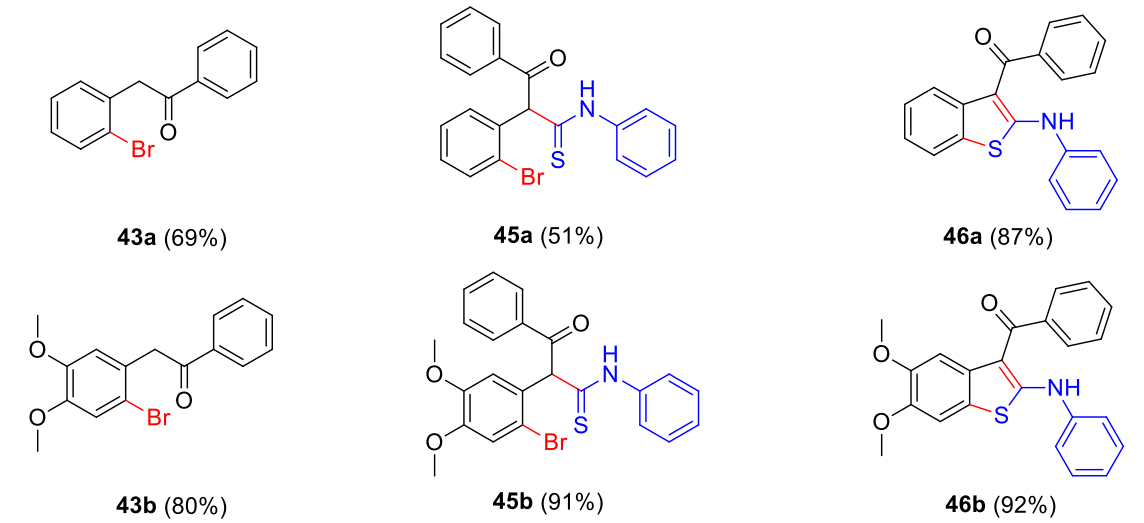



**Table 3.13**: **Synthesis of 3-Aroyl Substituted Benzo[*b*]thiophenes 46**



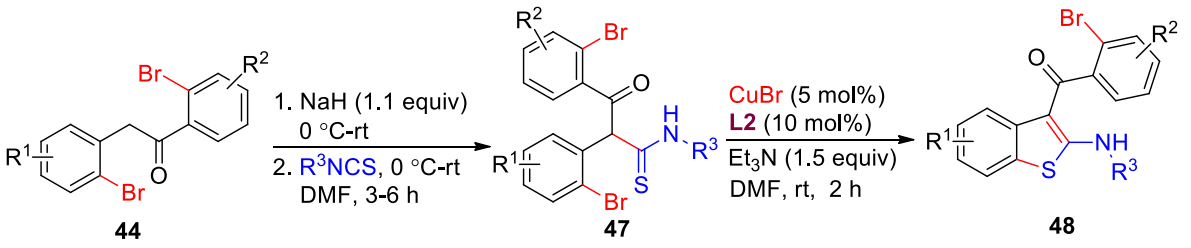



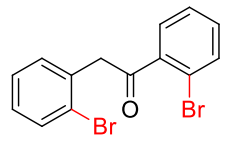

The deoxybenzoins **43-44** are in our hand, we converted those deoxybenzoins **43a-b** into the corresponding thioamides **45a-b** in good to excellent yields. Next, these thioamides **45a-b** were subjected to the optimized reaction conditions affording the respective 3-aroyl substituted benzo[*b*]thiophenes **46a-b** in excellent yields (Table 3.13).

Then we moved to chemo and regioselective synthesis of benzo[*b*]thiophene derivatives. Here we synthesized α-(2-bromoaroyl)-α-(2-bromoaryl) thioamides **47a-c** from deoxybenzoins **44a-c** and respective isothiocyanates (Table 3.14). These thioamides **47a-c** having two reactive halides can give four kinds of heterocyclic compounds, which are 2-aminobenzo[*b*]thiophene, indolo-2-thiol, quinolone, thiochromone derivatives. Gratifyingly, when we applied our optimized conditions to the thioamide **47a**, we observed exclusively one product i.e., 2-aminobenzo[*b*]thiophene **48a** with 83% yield. Other thioamides **47b-c** were also converted into

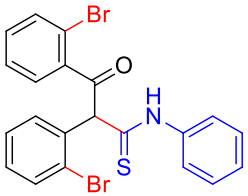
benzo[*b*]thiophenes **48b-c** with an excellent yield through highly chemoselective manner (Table 3.14).

**Table 3.14**: **Synthesis of Thioamides from Dihalo Substituted Deoxybenzoin and Chemo and Regioselective Studies of C—S bond Formation**

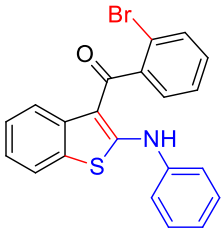


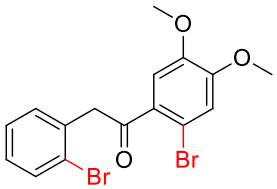
**44a** (89%)



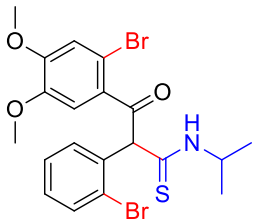
**47a** (77%)



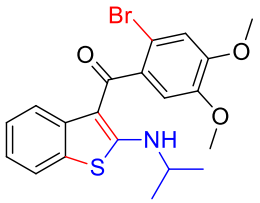
**48a** (83%)



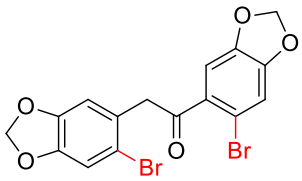
**44b** (80%)



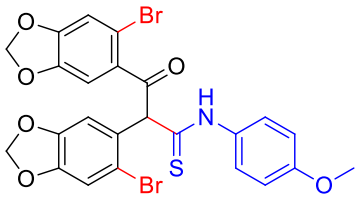
**47b** (72%)



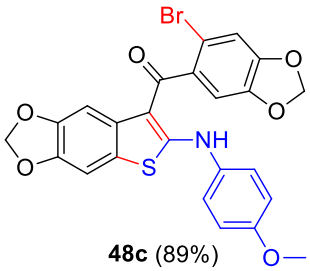
**48b** (88%)



**44c** (83%)



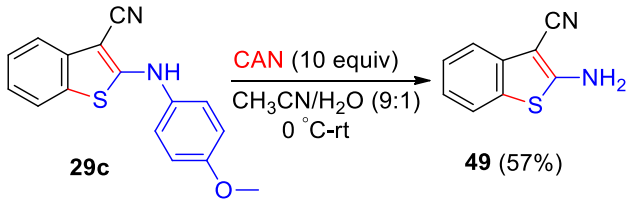
**47c** (71%)



**48c** (89%)

### 3.3.6 Cleavage of PMP Group of Benzo[*b*]thiophene 29c

We showed that cleavage of PMP group by CAN conditions. Thus, 2-*p*-anisidinyl-3-cyano benzo[*b*]thiophene (**30c**) was treated with CAN in $CH_3CN/H_2O$ affording the aminobenzo[*b*]thiophene **49** in 57% yield (Scheme 3.15).[29]

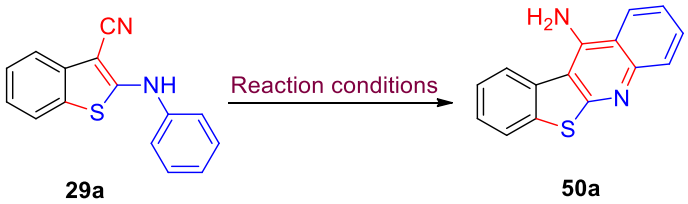



**Scheme 3.15**: *Cleavage of p-Methoxy Phenyl group of* **29c**

### 3.3.7 Synthetic Utility of 2-Aminobenzo[*b*]thiophenes

After successful study of the substrate scope, we turned our attention to explore the synthetic utility of the cyano group of 2-aminobenzo[*b*]thiophenes **29**. The cyano group can be activated by either lewis acid or bronsted acid.[30] This activation provides the construction of

**Table 3.15**: **Optimization of Reaction condition for Lewis acid/Bronsted acid catlyzed Nitrile Cyclization**



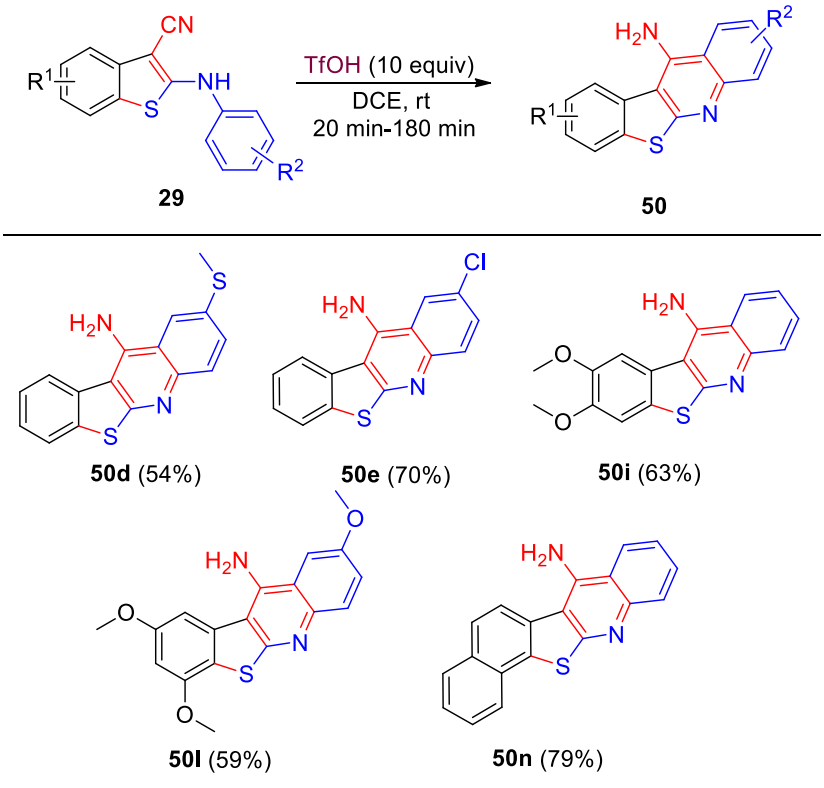

| Entry | Acid | Solvent | Temp | Time | 50a (% Yield)[a] |
|---|---|---|---|---|---|
| 1. | $Cu(OTf)_2$ (10 mol%) | DCE | 80 °C | 15 h | No reaction |
| 2. | $TiCl_4$ (10 equiv) | DCE | 80 °C | 15 h | No reaction |
| 3. | TFA (10 equiv) | DCE | 80 °C | 40 h | 24[b] |
| 4. | TfOH (10 equiv) | DCE | 80 °C | 3 h | 87 |
| 5. | TfOH (10equiv) | DCE | rt | 20 min | 86 |

[a] *Isolated yield.* [b] ***50a*** *was isolated as -*$COCF_3$ *amide derivative*

quinolone ring over the benzo[*b*]thiophene through Friedel-Craft reaction.[31] Thus, benzo[*b*]thiophene **29a** was treated with 10 mol% $Cu(OTf)_2$ in DCE at room temperature. After

several hours, there is no change in the reaction mixture. Hence, the reaction mixture was heated at 80 °C for 15 h. However, only starting material was detected from GC analysis (Table 3.15, Entry 1). Then we tried the similar reaction with excess of $TiCl_4$ at 80 °C. However, the result was similar with the previous one (Table 3.15, Entry 2). Interestingly, when the benzo[*b*]thiophene derivative **29a** was treated with excess TFA, a bronsted acid, and heated at 80 °C for 40 h, we observed a new product and characterized it as amide derivative of cyclized product in 24% yield (Table 3.15, Entry 3). Delightfully, when we used triflic acid, it gave an exclusively cyclized product **50a** in 87% yield within 3 h (Table 3.15, entry 4). Further, an experiment performed at room temperature gave the desired product **50a** in 86% yield in short time (Table 3.15, Entry 5).

**Table 3.16**: **Synthesis of Thieno[1,2-*b*]quinolones *via* Friedel-Craft Cyclization of 29**




The optimized conditions in our hand, several benzo[*b*]thiophene derivatives **29** were transformed into the corresponding benzothiopheno[2,3-*b*]quinolones **50d-e, 50i, 50l & 50n** in

moderate to very good yields (Table 3.16). To the best our knowledge this core is not reported in literature.

### 3.4 Biological Screening

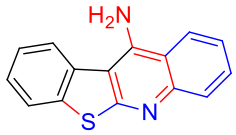
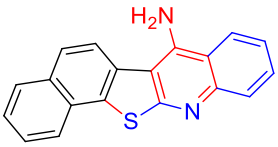
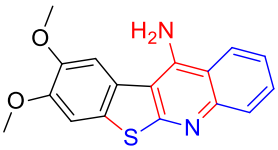
Newly synthesized thieno[1,2-b]quinolines were tested for various biological activities such as anti-bacterial, anti-fungal and anti-inflammatory.

#### 3.4.1 Anti-Bacterial Screening

The compounds are test in 50µg/mL concentration. We followed Mueller Hinton Broth method for analysis. Gentamcyin & Norfloxacin were used for reference. Seven bacteria were used. The results are summarized in Table 3.17.

These compounds were not shown any significant activities against the following the bacteria E.Coli (ATCC 9637) (**1**), Pseudomonas aeruginosa (ATCC BAA-427) (**2**), Staphylococcus aureus (ATCC 25923) (**3**); Staphylococcus aureus (ATCC 700699 methicillin resistant) (**4**); Staphylococcus aureus (ATCC 29213) (**5**); Staphylococcus aureus (ATCC 33592 gentamcyin resistant) (**6**); Klebsiella pneumonia (ATCC 27736) (**7**).

**Table 3.17**: **Anti- Bacterial Screening of Compounds**

| Structure of the Compounds | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
|  **50a** | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
|  **50n** | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
|  **50i** | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
| Gentamycin (1 mg/mL) | 3.12 | 0.78 | 0.78 | >50 | 1.56 | >50 | 1.56 |
| Norfloxacin | 0.05 | 1.56 | 0.78 | >50 | 1.56 | 0.78 | 0.19 |

*1. E.Coli (ATCC 9637); 2. Pseudomonas aeruginosa (ATCC BAA-427); 3. Staphylococcus aureus (ATCC 25923); 4. Staphylococcus aureus (ATCC 700699 methicillin resistant); 5. Staphylococcus aureus (ATCC 29213); 6. Staphylococcus aureus (ATCC 33592 gentamcyin resistant); 7. Klebsiella pneumonia (ATCC 27736)*

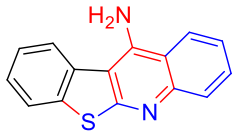
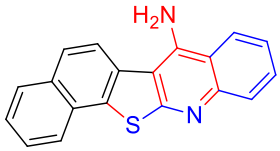
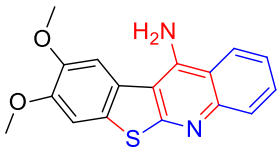
### 3.4.2 Anti-Fungal Screening

The compounds are test in 50µg/mL concentration. We used NCCLS method in RPMI 1640 medium.Fluonazole&Amphotericin B were used for reference. Six fungi were used for the screening. The results are summarized in Table 3.18.

These compounds were not shown any significant activities against the following the fungai Candida Albicans (**1**), Crptococcus neoformans (**2**), Sporothrix schenckii (**3**),

Trichophyton mentagrophytes (**4**), Aspergillus fumigatus (**5**), Candida parapsilosis (ATCC-2201900 (**6**).

**Table 3.18**: **Anti-Fungal Screening of Compounds**

| Structure of the Compounds | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
|  **50a** | >50 | >50 | >50 | >50 | >50 | >50 |
|  **50n** | >50 | >50 | >50 | >50 | >50 | >50 |
|  **50i** | >50 | >50 | >50 | >50 | >50 | >50 |
| Fluonazole | 1.00 | 2.00 | 2.00 | >32.00 | >32.00 | 2.00 |
| Amphotericin B | 0.02 | 0.13 | 0.25 | 0.25 | 0.50 | 0.02 |

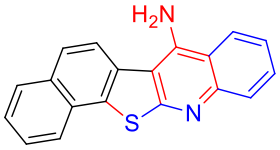
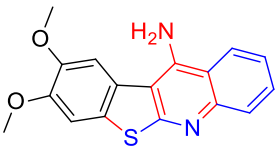
*1. Candida Albicans; 2. Crptococcus neoformans; 3. Sporothrix schenckii; 4. Trichophyton mentagrophytes; 5. Aspergillus fumigatus; 6. Candida parapsilosis (ATCC-22019).*

### 3.4.3 Anti-inflammatory:

The compounds are test in 10µg/mL concentration. Human monocytic leukemia THP-1 cells are pretreated for 12 h with the compounds and standard compound Dexamethasone (1µg/mL). Subsequently, pretreated cells were stimulated with LPS-50 ng> ML for 4 h. After

treatments, cell supernatant was collected for TNF measurement using ELISA. The results are summarized in Table 3.19.The compound showed a slightly less anti-inflammatory activity (64.7%) as compared with Dexamethasone (75%).

**Table 3.19**: **Anti-Inflammatory Activity**

| Structure of the Compounds | % Inhibition |
|---|---|
|  **50n** | 15.87 |
|  **50i** | 64.70 |
| **Dexamethasone** | 75.00 |

### 3.5 Conclusion

In this chapter, we demonstrated mild and highly chemoselective thiolation of thioamides at room temperature by inexpensive copper catalysis. Several 2-aminobenzo[*b*]thiophene derivatives were synthesized in high yields. This catalyst provides a highly regioselective thiolation, no racemization in amino acids. Further, we demonstrated the synthesis of novel class of thieno[1,2-*b*]quinolones through a bronsted acid mediated Friedel-Craft type cyclization. These derivatives were examined for various biological studies.

## 3.6 Experimental Section

### 3.6.1 Reagents

All reactions were performed by using standard *via*l technique with rubber septum. All solids were weighed in air. Toluene, $CH_3CN$, DMF, DMSO, $Cs_2CO_3$, KOH, $K_2CO_3$, DMAP, KOtBu and $Et_3N$ were purchased from Aldrich, Acros, Merck, Spectrochem or Alfa-Aesar and used as received. CuI, CuBr, CuCl and $Cu(OAc)_2$ were purchased from Aldrich. All isothiocyanates were purchased from Aldrich and few isothiocyanates were synthesized from the corresponding amines. Tetramethylethylenediamine, (*R*)-(+)-1,1'-binaphthyl-2,2'-diamine, 2,2'-bipyridine, L-proline, 2-isobutyrylcyclohexanone and 1,10-phenanthroline were purchased from Aldrich. All other reagents were purchased from common suppliers and used without further purification. Flash chromatography was performed using Merck Silica gel (230-400 mesh). Fractions were monitored by thin-layer chromatography on precoated silica gel 60 F254 plates (Merck & co.) and were visualized by UV.

### 3.6.2 Analytical Methods

As described in Section **2.6.2** (Chapter-2).

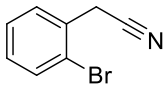
The X-ray quality crystals for the compound **29a** was grown by slow diffusion of *n*-hexane over $CH_2Cl_2$ solution. Single-crystal X-ray diffraction data of **29a** was collected in a Bruker KAPPA APEX-II, four angle rotation system, Mo-Kα radiation (0.71073 Å).

### 3.6.3 General Procedure for Preparation of 2- Bromoarylacetonitriles

To a stirred solution of 2-Bromobenzyl chlorides (10 mmol) in dry DMF (20 mL), NaCN (0.98 g, 20 mmol) was added at room temperature. The reaction mixture was stirred for 3 h (monitored by TLC). The reaction mixture was then poured into ice cold water and

extracted with DCM (3 x 50 mL), washed with brine solution (100 mL) and dried over $Na_2SO_4$. The solvent was evaporated under reduced pressure to give viscous oil which was passed through small filter silica gel column using hexane/EtOAc as eluent to give white crystal solid.

**2-(2-Bromophenyl)acetonitrile (26a)**



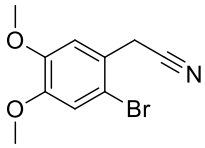
Yield: 85% as a yellowish liquid

$R_f$: 0.33 in pure hexane

IR (KBr): ν ($cm^{-1}$) = 2251 $cm^{-1}$ (CN)

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.61 (dd, *J* = 8.0 Hz, 1.1 Hz, 1H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.40 – 7.34 (m, 1H), 7.24 – 7.20 (m, 1H), 3.84 (s, 2H).

**2-(2-Bromo-4,5-dimethoxyphenyl)acetonitrile (26c)**



Yield: 2.346g (92%) as a light yellow crystalline solid

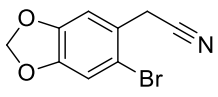
Melting point: 86 ˚C

$R_f$: 0.40 in 25% ethyl acetate in hexane.

IR (KBr): ν ($cm^{-1}$) = 2253 $cm^{-1}$ (CN)

$^1$H-NMR (400 MHz, $CDCl_3$) δ = 7.04 (s, 1H), 6.97 (s, 1H), 3.90 (s, 3H), 3.78 (s, 3H), 3.78 (s, 2H)

**2-(6-Bromo-4,5-methylenedioxyphenyl)acetonitrile (26d)**



Yield: 2.92g (86%) as a colourless crystalline solid

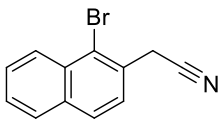
Melting point: 66 ˚C

$R_f$ : 0.30 in 10% ethyl acetate in hexane.

IR (KBr): ν ($cm^{-1}$) = 2250$cm^{-1}$ (CN)

$^1$H-NMR (400 MHz, $CDCl_3$) δ = 7.03 (s, 1H), 6.98 (s, 1H), 6.0 (s, 2H), 3.74 (s, 2H).

**2-(1-Bromonaphthalen-2-yl)acetonitrile (26e)**




Yield: 88% as a light white crystalline solid

Melting point: 180-182 ˚C; $R_f$: 0.25 in pure hexane

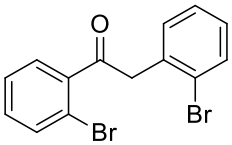
IR (KBr): ν ($cm^{-1}$) = 2255 $cm^{-1}$ (CN)

$^1$H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.86 (dd, *J* = 8.1 Hz, 3.8 Hz, 2H), 7.64-7.58 (m, 3H), 4.09 (s, 2H).

### 3.6.4 General Procedure for the Synthesis of Deoxybenzoins 44

To a stirring suspension of NaH (60% suspension in mineral oil) (20 mmol) in dry DMF (15 mL) under $N_2$ atmosphere was added drop wise a solution of aminonitrile (10 mmol) in dry DMF (10 mL). The resulting red colour suspension was stirred for 1 h at room temperature. After being cooled this suspension to 0 ºC, the corresponding benzyl chloride (10 mmol) in dry DMF (5 mL) was added over 10 min. This reaction mixture was stirred for 2 h at room temperature and monitored by TLC. After the starting materials had been completely consumed, the excess NaH was destroyed with methanol (20 mL) and the solvent was removed under reduced pressure. The resulting yellowish oil was refluxed in conc. HCl/MeOH (1:1) for 16 h and quenched the reaction mixture with saturated $NaHCO_3$ solution and extracted with dichloromethane. The combined organic layer washed with water (3 x 50 mL) & brine (3 x 50 mL), dried over anhyd. $Na_2SO_4$ and concentrated under reduced pressure. The crude products were purified by flash chromatography.

**1,2-Bis(2-Bromophenyl)ethanone (44a)**




Reaction time: 19 h.

Yield: 89%, as a pale yellow colour solid.

Melting point: 41 – 43 ºC

$R_f$: 0.32 in 5% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 2886, 2818, 1686, 1588, 1564, 1509, 1472, 1432, 1406, 1310, 1278, 1264, 1170, 1147, 1117, 1047, 1028, 990, 957, 902, 811, 791, 742, 685.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.50 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.34 – 7.28 (m, 3H), 7.18 – 7.13 (m, 1H), 4.42 (s, 2H).

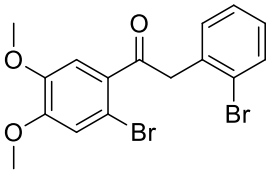
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 200.0, 141.4, 134.2, 133.8, 132.9, 132.1, 131.8, 129.1, 128.8, 127.7, 127.5, 125.3, 118.8, 49.8.

HR-MS (ESI): Calcd. for $C_{14}H_{10}Br_2O$ [M+H]: 352.9171, Found: 352.9001.

[M+H]: 354.9151, Found: 352.9147.

[M+H]: 356.9131, Found: 356.9128.

**1-(2-Bromo-4,5-dimethoxyphenyl)-2-(2-bromophenyl)ethanone (44b)**




Reaction time: 19 h.

Yield: 80%, white colour solid.

Melting point: 78 – 80 ºC

$R_f$: 0.28 in 10% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 2993, 2930, 2847, 1677, 1587, 1567, 1508, 1468, 1435, 1407, 1372, 1334, 1258, 1214, 1160, 1061, 1027, 1016, 919, 893, 860, 843, 795, 768, 753, 712, 697.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 8.0 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.16 – 7.14 (m, 1H), 7.12 (s, 1H), 7.06 (s, 1H), 4.46 (s, 2H), 3.91 (s, 3H), 3.86 (s, 3H).

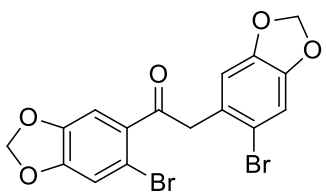
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 198.0, 151.5, 148.1, 134.9, 132.7, 132.2, 131.9, 128.8, 127.5, 125.0, 116.4, 112.5, 111.2, 56.3, 56.1, 49.3.

HR-MS (ESI): Calcd. for $C_{16}H_{14}Br_2O_3$ [M+H]: 412.9382, Found: 412.9370.

[M+H]: 414.9363, Found: 414.9357.

[M+H]: 416.9342, Found: 416.9332.

**1,2-Bis(6-bromobenzo[*d*][1,3]dioxol-5-yl)ethanone (44c)**



Reaction time: 19 h.

Yield: 83%, as white colour solid.

Melting point: 115– 118 ºC

$R_f$: 0.35 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 2984, 2900, 2887, 1687, 1612, 1504, 1484, 1403, 1385, 1343, 1252, 1227, 1174, 1156, 1124, 1114, 1035, 1019, 964, 933, 866, 838.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.05 (s, 1H), 7.02 (s, 1H), 7.01 (s, 1H), 6.78 (s, 1H), 6.04 (s, 2H), 5.97 (s, 2H), 4.28 (s, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 198.8, 150.4, 147.9, 147.6, 147.5, 134.3, 127.4, 115.6, 113.9, 112.9, 111.5, 111.4, 109.2, 102.6, 102.0, 49.4.

HR-MS (ESI): Calcd. for $C_{16}H_{10}Br_2O_5$ [M+H]: 440.8968, Found: 440.8940.

[M+H]: 442.8948, Found: 442.8901.

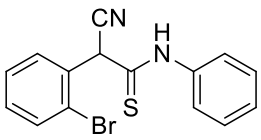
[M+H]: 444.8928, Found: 444.8893.

### 3.6.5 General Procedure for the Synthesis of Thioamides/*β*-Ketothioamides

To a stirring suspension of NaH (60% suspension in mineral oil) in (5.0 mL) of DMF at 0 ºC was added drop wise the corresponding 2-haloaryl acetonitrile/Methyl 2-(2-bromoaryl) acetate/deoxybenzoin (3.0 mmol) in (3.0 mL) of DMF. After being further stirred for 1 h at room temperature, a solution of isothiocyanate (3.0 mmol) in (2.0 mL) of DMF was added to the reaction mixture at 0 ºC and followed by further stirring for 2.5-5 h at room temperature. After complete consumption of the starting materials (monitored by TLC), the reaction mixture was quenched with saturated $NH_4Cl$ solution and extracted with EtOAc. The combined organic layer washed with water (3 x 25 mL) & brine (3 x 25 mL), dried over anhyd. $Na_2SO_4$ and

concentrated under reduced pressure. The crude products were purified by flash chromatography.

**2-(2-Bromophenyl)-2-cyano-*N*-phenylethanethioamide (28a)**




Reaction time: 4 h.

Yield: 70%, as a pale yellow colour viscous liquid.

$R_f$: 0.32 in 25% ethyl acetate in hexane

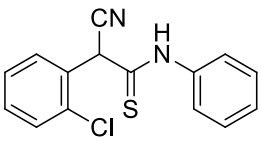
IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3272, 3058, 2933, 2360, 2340, 2251, 2202, 1597, 1496, 1469, 1409, 1275, 1204, 1089, 1027, 763, 739.

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 9.24 (s, 1H), 7.80 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.66 – 7.61 (m, 3H), 7.47 – 7.43 (m, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.33 – 7.28 (m, 2H), 5.73 (s, 1H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 190.1, 138.0, 133.8, 132.0, 131.5, 130.9, 129.3, 129.1, 127.8, 123.9, 123.7, 116.7, 53.8.

HR-MS (ESI): Calcd. for $C_{15}H_{11}BrN_2S$ [M+H]: 330.9899, Found: 330.9896.
[M+H]: 332.9879, Found: 332.9885.

**2-(2-Chlorophenyl)-2-cyano-*N*-phenylethanethioamide (28b)**




Reaction time: 4 h.

Yield: 49%, as a yellow colour viscous liquid.

$R_f$: 0.38 in 25% ethyl acetate in hexane

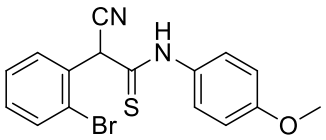
IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3273, 3139, 3062, 2252, 2198, 1596, 1495, 1472, 1443, 1409, 1278, 1206, 1091, 1051, 1039, 908, 860, 740, 695.

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 9.05 (s, 1H), 7.79 – 7.77 (m, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.50 – 7.48 (m, 1H), 7.43 – 7.38 (m, 4H), 7.29 (t, *J* = 7.6 Hz, 1H), 5.69 (s, 1H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 190.2, 138.0, 133.4, 131.3, 130.7, 130.5, 130.3, 129.2, 128.4, 127.8, 123.8, 116.6, 51.4.

HR-MS (ESI): Calcd. for $C_{15}H_{11}ClN_2S$ [M+H]: 287.0404, Found: 287.0405.

**2-(2-Bromophenyl)-2-cyano-*N*-(4-methoxyphenyl)ethanethioamide (28c)**



Reaction time: 4 h.

Yield: 48%, as a yellow colour viscous liquid.

$R_f$: 0.40 in 33% ethyl acetate in hexane

IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3274, 2923, 2365, 2340, 2247, 2190, 1605, 1509, 1467, 1439, 1405, 1300, 1249, 1027, 832, 752.

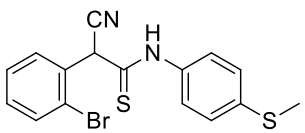
$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.98 (s, 1H), 7.80 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.49 – 7.45 (m, 3H), 7.35 – 7.31 (m, 1H), 6.90 (d, *J* = 9.2 Hz, 2H), 5.71 (s, 1H), 3.80 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 190.1, 158.8, 133.8, 132.1, 131.4, 130.94, 130.89, 129.0, 125.5, 123.9, 116.8, 114.4, 55.6, 53.4.

HR-MS (ESI): Calcd. for $C_{16}H_{13}BrN_2OS$ [M+Na]: 382.9824, Found: 382.9833.

[M+Na]: 384.9804, Found: 384.9831.

**2-(2-Bromophenyl)-2-cyano-*N*-(4-(methylthio)phenyl)ethanethioamide (28d)**



Reaction time: 4 h.

Yield: 80%, as a yellow colour viscous liquid.

$R_f$: 0.32 in 25% ethyl acetate in hexane

IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3275, 2916, 2363, 2344, 2251, 1589, 1492, 1389, 1202, 1178, 1093, 1026, 815, 736.

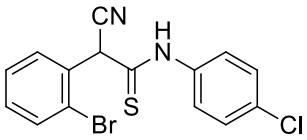
$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.98 (s, 1H), 7.80 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.67 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.47 (td, *J* = 7.6, 1.2 Hz, 1H), 7.33 (td, *J* = 7.8, 1.6 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 2H), 5.70 (s, 1H), 2.47 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 189.8, 138.5, 135.0, 133.8, 131.9, 131.5, 130.9, 129.0, 126.8, 124.1, 123.9, 116.7, 53.6, 15.8.

HR-MS (ESI): Calcd. for $C_{16}H_{13}BrN_2S_2$ [M+H]: 376.9776, Found: 376.9782.

[M+H]: 378.9756, Found: 378.9759.

**2-(2-Bromophenyl)-*N*-(4-chlorophenyl)-2-cyanoethanethioamide (28e)**




Reaction time: 4 h.

Yield: 48%, as a yellow colour viscous liquid.

$R_f$: 0.30 in 20% ethyl acetate in hexane

IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3277, 2924, 2361, 2340, 2251, 2198, 1593, 1491, 1470, 1417, 1392, 1265, 1200, 1091, 1027, 1014, 830, 739, 703.

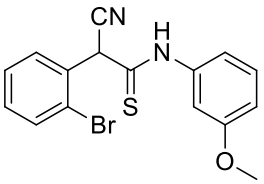
$^1$H NMR (400 MHz, $CDCl_3$) δ = 9.26 (s, 1H), 7.77 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.47 – 7.43 (m, 1H), 7.33 – 7.29 (m, 3H), 5.71 (s, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 190.4, 136.4, 133.7, 132.8, 131.6, 131.4, 130.8, 129.2, 128.8, 125.0, 123.8, 116.8, 53.3.

HR-MS (ESI): Calcd. for $C_{15}H_{10}BrClN_2S$ [M+Na]: 386.9329, Found: 386.9312.

[M+Na]: 388.9308, Found: 388.9286.

**2-(2-Bromophenyl)-2-cyano-*N*-(3-methoxyphenyl)ethanethioamide (28f)**




Reaction time: 3.5 h.

Yield: 45%, as a yellow colour viscous liquid.

$R_f$: 0.30 in 25% ethyl acetate in hexane

IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3292, 2923, 2851, 2365, 2340, 2251, 2194, 1607, 1548, 1490, 1467, 1403, 1265, 1158, 1089, 1046, 850, 736.

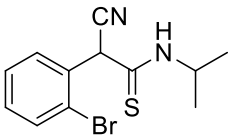
$^1$H NMR (400 MHz, $CDCl_3$) δ = 9.25 (s, 1H), 7.81 (d, *J* = 7.2 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.44 (s, 1H), 7.33 – 7.27 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.83 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.73 (s, 1H), 3.79 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 189.8, 160.1, 139.1, 133.8, 132.0, 131.5, 130.8, 130.0, 129.0, 123.9, 116.7, 115.6, 113.4, 109.2, 55.6, 53.9.

HR-MS (ESI): Calcd. for $C_{16}H_{13}BrN_2OS$ [M+H]: 361.0005, Found: 361.0022.

[M+H]: 362.9984, Found: 363.0008.

**2-(2-Bromophenyl)-2-cyano-*N*-isopropylethanethioamide (28g)**




Reaction time: 3.5 h.

Yield: 64%, as a brown colour viscous liquid.

$R_f$: 0.30 in 25% ethyl acetate in hexane

IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3285, 3057, 2973, 2933, 2250, 2186, 1523, 1458, 1438, 1367, 1165, 1126, 1075, 1027, 751, 736.

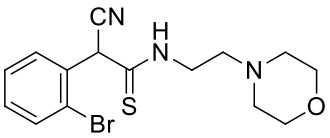
$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.68 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.63 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.43 (td, *J* = 7.6, 1.2 Hz, 1H), 7.39 (s, 1H), 7.29 (td, *J* = 7.8, 1.6 Hz, 1H), 5.49 (s, 1H), 4.61 – 4.53 (m, 1H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.22 (d, *J* = 6.8 Hz, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 190.0, 133.6, 132.0, 131.2, 130.7, 128.8, 123.8, 116.7, 52.5, 48.6, 20.99, 20.98.

HR-MS (ESI): Calcd. for $C_{12}H_{13}BrN_2S$ [M+H]: 297.0056, Found: 297.0083.

[M+H]: 299.0035, Found: 299.0065.

**2-(2-Bromophenyl)-2-cyano-*N*-(2-morpholinoethyl)ethanethioamide (28h)**




Reaction time: 5 h.

Yield: 48%, as a yellow colour solid.

Melting point: 100 – 102 °C

$R_f$: 0.25 in 50% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3448, 3242, 2931, 2869, 2819, 2372, 2345, 2251, 1521, 1458, 1389, 1294, 1276, 1223, 1129, 1113, 1068, 1017, 852, 819, 800, 757.

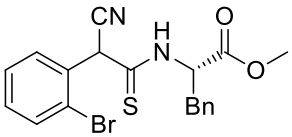
$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.30 (s, 1H), 7.75 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.66 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.47 (td, *J* = 7.6, 0.8 Hz, 1H), 7.33 (td, *J* = 7.6, 1.6 Hz, 1H), 5.60 (s, 1H), 3.67 – 3.59 (m, 2H), 3.54 (brs, 4H), 2.60 – 2.52 (m, 2H), 2.40 – 2.33 (m, 4H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 190.9, 133.8, 131.8, 131.3, 130.8, 128.9, 124.1, 116.8, 66.8, 54.7, 52.9, 52.6, 42.4.

HR-MS (ESI): Calcd. for $C_{15}H_{18}BrN_3OS$ [M+H]: 368.0427, Found: 368.0430.

[M+H]: 370.0406, Found: 370.0412.

**Methyl 2-(2-(2-bromophenyl)-2-cyanoethanethioamido)-3-phenylpropanoate (28i)**




Reaction time: 4 h.

Yield: 63%, as a yellow colour viscous liquid.

$R_f$: 0.30 in 20% ethyl acetate in hexane

IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3326, 3058, 3030, 2952, 2362, 2336, 2250, 1741, 1513, 1470, 1438, 1409, 1349, 1218, 1084, 1027, 739, 702.

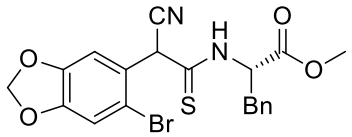
$^1$H NMR (400 MHz, $CDCl_3$ [*dr* (1 : 0.80)]) δ = 7.82 (brs, 2H), 7.71 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.64 – 7.59 (m, 3H), 7.44 – 7.38 (m, 2H), 7.33 – 7.28 (m, 3H), 7.254 – 7.249 (m, 1H), 7.18 – 7.12 (m, 4H), 7.02 – 7.00 (m, 2H), 6.78 – 6.76 (m, 2H), 5.62 (s, 1H), 5.57 (s, 1H), 5.28 – 5.22 (m, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 3.42 – 3.35 (m, 2H), 3.19 (dd, *J* = 14.0, 5.8 Hz, 1H), 3.11 (dd, *J* = 14.0, 4.8 Hz, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$ [*dr* (1 : 0.80)])) δ = 191.6, 191.4, 170.6, 170.5, 134.9, 134.6, 133.7, 131.7, 131.5, 131.3, 130.6, 130.4, 129.2, 129.1 (2C), 129.0, 128.95, 128.87, 128.85 (2C), 127.6, 127.5, 123.94, 123.92, 116.6, 116.5, 59.1, 59.0, 52.94, 52.88, 52.4, 52.3, 36.0, 35.6.

HR-MS (ESI): Calcd. for $C_{19}H_{17}BrN_2O_2S$ [M+H]: 417.0267, Found: 417.0251.

[M+H]: 419.0247, Found: 419.0235.

**Methyl-2-(2-(6-bromobenzo[1,3]dioxol-5-yl)-2-cyanoethanethioamido)-3-phenyl propanoate (28j)**



Reaction time: 5 h.

Yield: 43%, as a yellow colour viscous liquid.

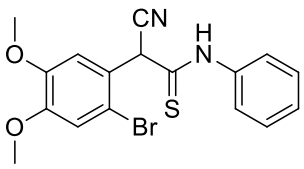
$R_f$: 0.30 in 25% ethyl acetate in hexane

IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3327, 3030, 2918, 2361, 2340, 2251, 2202, 1740, 1504, 1479, 1436, 1350, 1244, 1120, 1083, 1036, 929, 864, 737, 702.

HR-MS (ESI): Calcd. for $C_{20}H_{17}BrN_2O_4S$ [M+H]: 461.0165, Found: 461.0165.

Both the $^1H$ and $^{13}C$ Spectrums are not clean. We proceeded next step without purification.

**2-(2-Bromo-4,5-dimethoxyphenyl)-2-cyano-*N*-phenylethanethioamide (28k)**



Reaction time: 4 h.

Yield: 51%, as a pale yellow colour solid.

Melting point: 161 – 163 ºC

$R_f$: 0.40 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3270, 2962, 2914, 1592, 1504, 1458, 1401, 1377, 1329, 1267, 1204, 1184, 1162, 1083, 1020, 950, 871, 812, 748, 698.

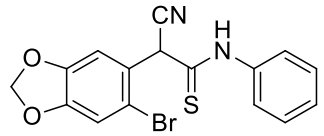
$^1H$ NMR (400 MHz, $CDCl_3$) δ = 8.90 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.26 (s, 1H), 7.08 (s, 1H), 5.63 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 190.6, 150.9, 149.6, 138.0, 129.2, 127.7, 123.6, 123.4, 117.0, 115.7, 114.1, 112.3, 56.5 (2C), 53.7.

HR-MS (ESI): Calcd. for $C_{17}H_{15}BrN_2O_2S$ [M+H]: 391.0110, Found: 391.0149.

[M+H]: 393.0090, Found: 393.0129.

**2-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)-2-cyano-*N*-phenylethanethioamide (28l)**



Reaction time: 4 h.

Yield: 53%, as a yellow colour solid.

Melting point: 58 – 60 ºC

$R_f$: 0.30 in 25% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3273, 2917, 2361, 2344, 2251, 2201, 1597, 1501, 1478, 1410, 1245, 1120, 1036, 930, 862, 757.

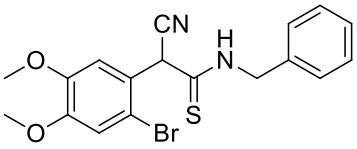
$^1H$ NMR (400 MHz, $CDCl_3$) δ = 9.14 (s, 1H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.40 – 7.37 (m, 3H), 7.29 – 7.27 (m, 1H), 7.06 (s, 1H), 6.05 (d, *J* = 6.0 Hz, 2H), 5.66 (s, 1H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 190.4, 149.8, 148.6, 138.0, 129.2, 127.7, 124.8, 123.7, 116.9, 114.9, 113.2, 110.0, 102.8, 53.4.

HR-MS (ESI): Calcd. for $C_{16}H_{11}BrN_2O_2S$ [M+H]: 374.9797, Found: 374.9728.

[M+H]: 376.9777, Found: 376.9710.

***N*-Benzyl-2-(2-bromo-4,5-dimethoxyphenyl)-2-cyanoethanethioamide (28m)**



Reaction time: 4 h.

Yield: 50%, as a pale yellow colour solid.

Melting point: 116 – 118 ºC

$R_f$: 0.32 in 33% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3306, 2935, 2843, 1600, 1505, 1455, 1379, 1340, 1265, 1227, 1166, 1028, 946, 860, 815, 737, 700.

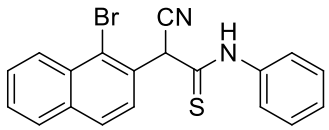
$^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.68 (s, 1H), 7.36 – 7.29 (m, 3H), 7.25 – 7.23 (m, 2H), 7.15 (s, 1H), 7.02 (s, 1H), 5.52 (s, 1H), 4.87 (dd, *J* = 15.0, 5.2 Hz, 1H), 4.75 (dd, *J* = 15.0, 5.2 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 192.2, 150.7, 149.5, 135.3, 129.1, 128.5, 128.1, 123.4, 117.0, 115.6, 114.1, 112.3, 56.45, 56.42, 52.1, 50.8.

HR-MS (ESI): Calcd. for $C_{18}H_{17}BrN_2O_2S$ [M+Na]: 427.0086, Found: 427.0092.

[M+Na]: 429.0066, Found: 429.0073.

**2-(1-Bromonaphthalen-2-yl)-2-cyano-*N*-phenylethanethioamide (28n)**




Reaction time: 4 h.

Yield: 49%, as a yellow colour solid.

Melting point: 101 – 103 ºC

$R_f$: 0.30 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3448, 3306, 2924, 2370, 2345, 2243, 2186, 1544, 1492, 1399, 1283, 1196, 1113, 1026, 962, 813, 754.

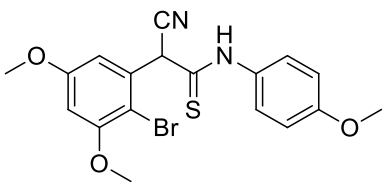
$^1$H NMR (400 MHz, $CDCl_3$) δ = 9.07 (s, 1H), 8.33 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.71 – 7.67 (m, 1H), 7.65 – 7.61 (m, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.29 – 7.25 (m, 1H), 6.10 (s, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 190.2, 138.0, 134.7, 132.4, 130.0, 129.7, 129.2, 128.8, 128.6, 128.2, 128.1, 127.7, 126.0, 125.2, 123.8, 116.9, 54.8.

HR-MS (ESI): Calcd. for $C_{19}H_{13}BrN_2S$ [M+H]: 381.0056, Found: 381.0060.

[M+H]: 383.0035, Found: 383.0041.

**2-(2-Bromo-3,5-dimethoxyphenyl)-2-cyano-*N*-(4 –methoxyphenyl)ethanethioamide (28o)**




Reaction time: 4 h.

Yield: 58%, as a yellow colour viscous liquid.

$R_f$: 0.32 in 33% ethyl acetate in hexane

IR (as film in $CCl_4$): ν ($cm^{-1}$) = 3282, 3007, 2938, 2839, 2360, 2340, 2250, 2198, 1589, 1510, 1455, 1331, 1300, 1251, 1205, 1167, 1085, 1026, 929, 832, 737,702.

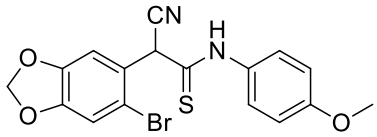
$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.84 (s, 1H), 7.44 (d, *J* = 9.2 Hz, 2H), 6.97 (d, *J* = 2.8 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.55 (d, *J* = 2.4 Hz, 1H), 5.77 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 190.1, 160.7, 158.7, 157.5, 133.3, 130.9, 125.5, 117.0, 114.3, 106.4, 104.5, 101.1, 56.7, 56.0, 55.6, 53.9.

HR-MS (ESI): Calcd. for $C_{18}H_{17}BrN_2O_3S$ [M+H]: 421.0216, Found: 421.0250.

[M+H]: 423.0196, Found: 423.0229.

**2-(6-Bromobenzo[*d*][1,3]dioxol-5yl)-2-cyano-*N*-(4-methoxyphenyl)ethanethioamide (28p)**




Reaction time: 4 h.

Yield: 53%, as a pale yellow colour viscous liquid.

$R_f$: 0.28 in 33% ethyl acetate in hexane

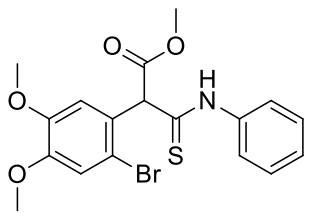
$^1$H NMR (400 MHz, $CDCl_3$) δ = 9.15 (s, 1H), 7.49 – 7.45 (m, 2H), 7.24 (s, 1H), 7.03 (s, 1H), 6.89 – 6.85 (m, 2H), 6.05 (dd, *J* = 6.0, 1.2 Hz, 2H), 5.60 (s, 1H), 3.78 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 190.3, 158.8, 149.8, 148.7, 130.9, 125.5, 124.8, 116.9, 115.0, 114.4, 113.2, 110.0, 102.8, 55.6, 53.2.

HR-MS (ESI): Calcd. for $C_{17}H_{13}BrN_2O_3S$ [M+H]: 404.9903, Found: 404.9866.

[M+H]: 406.9883, Found: 406.9848.

**2-(2-Bromo-4,5-dimethoxyphenyl)-3-(phenylamino)-3-thioxopropanoate (38a)**




Reaction time: 3.5 h.

Yield: 37%, as a white colour solid.

Melting point: 138 – 140 °C

$R_f$: 0.38 in 33% ethyl acetate in hexane

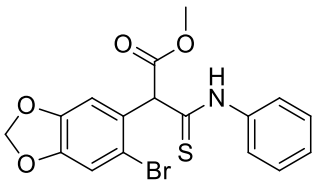
IR (KBr): ν ($cm^{-1}$) = 3287, 2951, 2842, 2360, 2341, 1738, 1598, 1505, 1436, 1402, 1380, 1263, 1208, 1164, 1027, 860, 759, 700.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 9.91 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.41 – 7.39 (m, 2H), 7.29 – 7.27 (m, 1H), 7.22 (s, 1H), 7.08 (s, 1H), 5.62 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 195.7, 171.0, 149.9, 149.0, 138.4, 129.8, 129.1, 127.3, 126.3, 125.4, 123.7, 115.9, 115.6, 112.0, 64.7, 56.34, 56.32, 53.2.

HR-MS (ESI): Calcd. for $C_{18}H_{18}BrNO_4S$ [M+H]: 424.0213, Found: 424.0243.
[M+H]: 426.0193, Found: 426.0221.

**Methyl 2-(6-bromobenzo[*d*][1,3]dioxol-5-yl)-3-(phenylamino)-3-thioxopropanoate (38b)**



Reaction Time: 4 h.

Yield: 57%, as a yellow colour viscous liquid.

$R_f$: 0.28 in 20% ethyl acetate in hexane

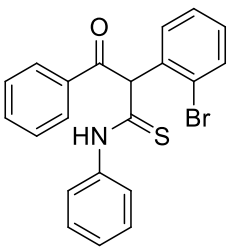
IR (KBr): ν ($cm^{-1}$) = 3348, 2912, 1724, 1599, 1556, 1499, 1479, 1405, 1286, 1261, 1240, 1110, 1033,`1016, 927, 763, 692.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 10.10 (s, 1H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.15 (s, 1H), 7.08 (s, 1H), 6.01 (s, 2H), 5.64 (s, 1H), 3.82 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 195.3, 171.1, 148.8, 148.1, 138.4, 129.1, 127.7, 127.3, 123.7, 116.2, 113.3, 109.1, 102.4, 64.5, 53.3.

HR-MS (ESI): Calcd. for $C_{17}H_{14}BrNO_4S$ [M+H]: 407.9900, Found: 407.9916.
[M+H]: 409.9880, Found: 409.9906.

**2-(2-Bromophenyl)-3-oxo-*N*, 3-diphenylpropanethioamide (45a)**



Reaction Time: 4 h.

Yield: 51%, as a yellow colour solid.

Melting point: 119 – 121 ºC

$R_f$: 0.33 in 20% ethyl acetate in hexane

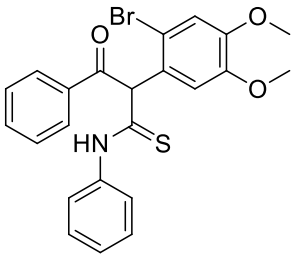
$^{1}$H NMR (400 MHz, $CDCl_3$) [enol : keto (1 : 1.4)] δ = 15.67 (s, 1H), 9.76 (s, 1H), 8.14 – 8.12 (m, 2H), 7.75 (s, 1H), 7.70 – 7.68 (m, 3H), 7.64 – 7.56 (m, 4H), 7.51 – 7.47 (m, 2H), 7.42 – 7.33 (m, 6H), 7.31 – 7.27 (m, 2H), 7.25 – 7.21 (m, 4H), 7.21 – 7.19 (m, 1H), 7.17 – 7.16 (m, 1H), 7.17 – 7.13 (m, 3H), 6.89 (s, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) [enol : keto (1 : 1.4)] δ = 197.3, 195.2, 191.1, 172.4, 138.5, 137.7, 137.0, 136.2, 135.2, 134.9, 134.4, 134.3, 133.7, 130.4, 130.3, 129.5, 129.4, 129.3, 129.2, 129.1, 129.09, 129.08, 128.8, 128.6, 128.5, 128.2, 128.1, 127.8, 127.6, 127.3, 126.4, 125.7, 123.7, 119.1, 112.9, 68.3.

HR-MS (ESI): calcd. for $C_{21}H_{16}BrNOS$ [M+Na]: 432.0028, Found: 432.0041.

[M+Na]: 434.0008, Found: 434.0023.

**2-(2-Bromo-4,5-dimethoxyphenyl)-3-oxo-*N*,3-diphenylpropanethioamide (45b)**




Reaction time: 2.5 h.

Yield: 91%, as a yellow colour solid.

Melting point: 154 – 156 °C

$R_f$: 0.28 in 25% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3448, 3277, 2931, 2367, 2345, 1684, 1579, 1501, 1460, 1445, 1376, 1319, 1259, 1204, 1167, 1027, 831, 781, 693.

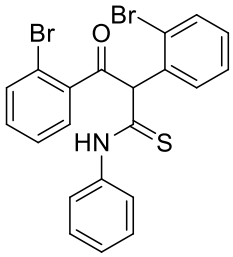
$^{1}$H NMR (400 MHz, $CDCl_3$) [keto : enol (1 : 1.06)] δ = 15.65 (s, 1H), 9.71 (s, 1H), 8.11 – 8.09 (m, 2H), 7.96 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.42 – 7.36 (m, 6H), 7.29 – 7.25 (m, 4H), 7.22 – 7.15 (m, 3H), 7.13 (s, 1H), 7.08 (s, 1H), 7.06 (s, 1H), 6.77 (s, 1H), 6.61 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.63 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) [keto : enol (1 : 1.06)] δ = 197.5, 196.2, 190.9, 172.5, 149.97, 149.93, 149.2, 149.1, 138.5, 137.7, 137.0, 136.3, 134.3, 129.3, 129.20 129.12, 129.10, 129.0, 128.5, 127.91, 127.87, 127.5, 127.3, 126.2, 126.0, 123.8, 118.2, 116.9, 116.6, 116.1, 115.7, 112.8, 111.7, 67.41, 56.4 (2C), 56.29, 56.26.

HR-MS (ESI): Calcd. for $C_{23}H_{20}BrNO_3S$ [M+H]: 470.0420, Found: 470.0422.

[M+H]: 472.0400, Found: 472.0405.

**2,3-Bis(2-bromophenyl)-3-oxo-*N*-phenylpropanethioamide (47a)**




Reaction time: 4.5 h.

Yield: 77%, as a pale yellow colour solid.

Melting point: 168 – 170 ºC

$R_f$: 0.35 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3444, 3322, 2370, 2345, 1572, 1498, 1466, 1309, 1229, 1190, 1087, 1024, 924, 797, 752, 695.$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.56 (s, 1H), 7.76 (s, 1H), 7.57 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.47 – 7.45 (m, 2H), 7.42 – 7.36 (m, 4H), 7.32 – 7.25 (m, 2H), 7.17 (td, *J* = 7.5, 1.2 Hz, 1H), 7.10 – 7.01 (m, 3H).

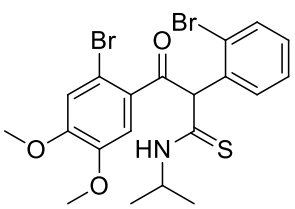
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 191.2, 171.0, 137.8, 137.5, 136.2, 133.7, 133.4, 132.7, 130.6, 130.3, 129.1, 128.6, 127.7, 127.2, 127.0, 126.2, 126.1, 121.3, 113.8.

HR-MS (ESI): Calcd. for $C_{21}H_{15}Br_2NOS$ [M+H]: 487.9314, Found: 487.9297.

[M+H]: 489.9294, Found: 489.9285.

[M+H]: 491.9273, Found: 491.9258.

**3-(2-Bromo-4,5-dimethoxyphenyl)-2-(2-bromophenyl)-*N*-isopropyl-3-oxopropanethioamide (47b)**




Reaction time: 4 h.

Yield: 72%, as a white colour solid.

Melting point: 141 – 143 ºC

$R_f$: 0.32 in 25% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3345, 2971, 2835, 1601, 1585, 1381, 1252, 1160, 1020, 941, 888, 855, 792, 772.

$^{1}$H NMR (400 MHz, $CDCl_3$) δ = 15.33 (s, 1H), 7.52 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.28 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.15 (td, *J* = 7.4, 1.2 Hz, 1H), 7.07 (td, *J* = 7.4, 1.6 Hz, 1H), 6.86 (s, 1H), 6.74 (s, 1H), 6.06 (d, *J* = 7.6 Hz, 1H), 4.70 – 4.61 (m, 1H), 3.76 (s, 3H), 3.67 (s, 3H), 1.18 (d, *J* = 6.4 Hz, 3H), 1.09 (d, *J* = 6.4 Hz, 3H).

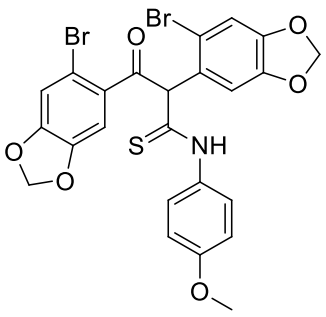
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 188.8, 169.1, 149.4, 147.7, 136.6, 133.9, 133.0, 130.5, 130.2, 128.6, 126.9, 115.1, 113.2, 111.7, 111.3, 56.1, 56.0, 45.6, 21.6, 21.2.

HR-MS (ESI): Calcd. for $C_{20}H_{21}Br_2NO_3S$ [M+H]: 513.9682, Found: 513.9668.

[M+H]: 515.9662, Found: 515.9660.

[M+H]: 517.9641, Found: 517.9629.

**2,3-Bis(6-bromobenzo[*d*][1,3]dioxol-5yl)-*N*-(4-methoxyphenyl)-3-oxopropanethioamide (47c)**




Reaction time: 4 h.

Yield: 71%, as a yellow colour solid.

Melting point: 188 – 190 °C

$R_f$: 0.37 in 33% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3452, 3346, 2895, 2366, 2345, 1596, 1511, 1500, 1474, 1329, 1249, 1169, 1117, 1028, 934, 835.

$^{1}$H NMR (400 MHz, $CDCl_3$) δ = 15.46 (s, 1H), 7.79 (s, 1H), 7.26 (s, 1H), 7.24 (s, 1H), 7.02 (s, 1H), 6.94 – 6.90 (m, 4H), 6.80 (s, 1H), 5.97 – 5.91(m, 4H), 3.81 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 191.4, 170.4, 158.8, 149.1, 148.7, 148.1, 146.9, 131.2, 130.2, 128.8, 127.7, 118.0, 114.3, 113.3, 113.1, 112.8, 112.5, 112.3, 108.1, 102.4, 102.1, 55.6.

HR-MS (ESI): Calcd. for $C_{24}H_{17}Br_2NO_6S$ [M+H]: 605.9216, Found: 605.9224.

[M+H]: 607.9197, Found: 607.9215.

[M+H]: 609.9176, Found: 609.9193.

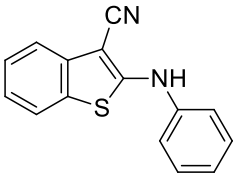
### 3.6.6 Procedure for the Optimization of Copper Catalyzed Synthesis of 2-Aminobenzo[*b*]thiophenes

An oven-dried 8 mL reaction vial was charged with copper-salt (1-5 mol%), ligand **L1**-**L6** (2-10 mol%) and base (0.75 mmol), respective thioamide (0.5 mmol) in solvent (2.0 mL) was stirred at room temperature for 2-3.5 h. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was purified by flash chromatography.

### 3.6.7 General Procedure for the Synthesis of 2-Aminobenzo[*b*]thiophenes

An oven-dried 8 mL reaction vial was charged with CuI (5 mol%), 1,10-Phenanthroline (10 mol%) and $Et_3N$ (0.75 mmol), respective thioamide (0.5 mmol) in DMF (2.0 mL) was stirred at room temperature for 1-3 h. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was purified by flash chromatography.

**2-(Phenylamino)benzo[*b*]thiophene-3-carbonitrile (29a)**




Reaction time: 2 h. (X = Br), 3 h. (X = Cl)

Yield: 88% (X = Br), 66% (X = Cl), as a white colour solid.

Melting point: 134 – 136 °C

$R_f$: 0.42 in 20% ethyl acetate in hexane

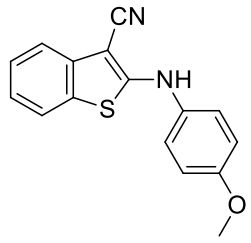
IR (KBr): ν ($cm^{-1}$) = 3436, 3263, 2211, 1602, 1561, 1426, 1081, 792, 744.

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 7.61 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.51 (s, 1H), 7.44 – 7.36 (m, 5H), 7.25 – 7.19 (m, 2H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 160.7, 140.1, 136.6, 129.9, 129.1, 126.2, 125.2, 123.8, 122.0, 120.3, 119.8, 115.4, 83.8.

HR-MS (ESI): Calcd. for $C_{15}H_{10}N_2S$ [M+H]: 251.0637, Found: 251.0655.

**2-((4-Methoxyphenyl)amino)benzo[*b*]thiophene-3-carbonitrile (29c)**




Reaction time: 2 h.

Yield: 78%, as a pale yellow colour solid.

Melting point: 193 – 195 ºC

$R_f$: 0.34 in 10% ethyl acetate in hexane

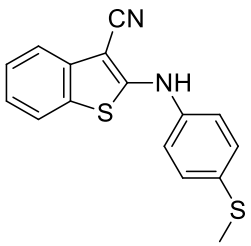
IR (KBr): ν ($cm^{-1}$) = 3440, 3261, 2210, 2202, 1598, 1566, 1513, 1466, 1438, 1247, 1027, 751.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.05 (s, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 163.0, 158.1, 137.1, 132.9, 128.9, 126.2, 124.1, 123.4, 121.1, 119.7, 115.1 (2C), 81.8, 55.7.

HR-MS (ESI): Calcd. for $C_{16}H_{12}N_2OS$ [M+H]: 281.0743, Found: 281.0778.

**2-((4-(Methylthio)phenyl)amino)benzo[*b*]thiophene-3-carbonitrile (29d)**




Reaction time: 2.5 h.

Yield: 94%, as a white colour solid.

Melting point: 182 – 184 ºC

$R_f$: 0.39 in 20% ethyl acetate in hexane

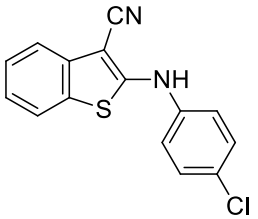
IR (KBr): ν ($cm^{-1}$) = 3432, 3254, 2914, 2207, 1602, 1555, 1497, 1465, 1435, 1319, 1096, 825, 748.

$^1$H NMR (400 MHz, DMSO) δ = 10.22 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 2.48 (s, 3H).

$^{13}$C NMR (100 MHz, DMSO) δ = 160.8, 138.2, 137.0, 133.7, 128.5, 127.4, 126.1, 123.4, 122.5, 121.4, 118.6, 115.0, 82.0, 15.3.

HR-MS (ESI): Calcd. for $C_{16}H_{12}N_2S_2$ [M+H]: 297.0515, Found: 297.0531.

**2-((4-Chlorophenyl)amino)benzo[*b*]thiophene-3-carbonitrile (29e)**




Reaction time: 2.5 h.

Yield: 66%, as a pale yellow colour solid.

Melting point: 240 – 242 ºC

$R_f$: 0.42 in 20% ethyl acetate in hexane

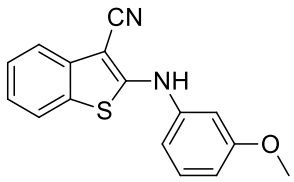
IR (KBr): ν ($cm^{-1}$) = 3449, 3246, 2213, 1565, 1439, 1088, 822, 743.

$^1$H NMR (400 MHz, DMSO) δ = 10.31 (s, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.46 – 7.39 (m, 5H), 7.27 (t, *J* = 7.2 Hz, 1H).

$^{13}$C NMR (100 MHz, DMSO) δ = 159.9, 139.9, 136.8, 129.4, 128.8, 127.9, 126.2, 123.8, 122.6, 121.7, 118.9, 114.8, 83.5.

HR-MS (ESI): Calcd. for $C_{15}H_9ClN_2S$ [M+H]: 285.0248, Found: 285.0209.

**2-((3-Methoxyphenyl)amino)benzo[*b*]thiophene-3-carbonitrile (29f)**




Reaction time: 2.5 h.

Yield: 82%, as a yellow colour solid.

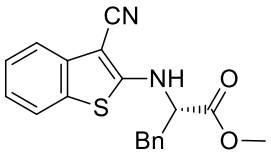
Melting point: 149 – 151 ºC

$R_f$: 0.40 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3428, 3282, 2953, 2197, 1596, 1558, 1292, 1163, 1053, 774, 751.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.61 (s, 1H), 7.59 – 7.53(m, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 7.2 Hz, 1H), 6.95 (s, 1H), 6.93 (brs, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 3.85 (s, 3H).

**Methyl 2-((3-cyanobenzo[*b*]thiophen-2-yl)amino)-3-phenylpropanoate (29i)**




Reaction time: 3 h.

Yield: 72%, as a white colour solid.

Melting point: 110 – 112 ºC

$R_f$: 0.37 in 20% ethyl acetate in hexane

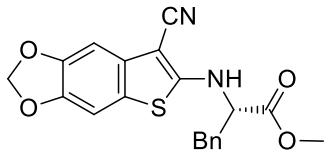
IR (KBr): ν ($cm^{-1}$) = 3428, 3316, 2927, 2200, 1725, 1559, 1384, 1288, 1175, 1115, 748.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.55 – 7.52 (m, 2H), 7.38 – 7.27 (m, 4H), 7.20 – 7.16 (m, 3H), 5.68 (d, *J* = 8.8 Hz, 1H), 4.52 – 4.47 (m, 1H), 3.77 (s, 3H), 3.31 (dd, *J* = 13.8, 5.6 Hz, 1H), 3.22 (dd, *J* = 13.8, 6.0 Hz, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 170.9, 162.7, 137.7, 134.9, 129.4, 129.0, 128.9, 127.8, 126.3, 123.3, 121.9, 119.8, 115.2, 81.0, 60.9, 52.9, 38.8.

HR-MS (ESI): Calcd. for $C_{19}H_{16}N_2O_2S$ [M+H]: 337.1005, Found: 337.1029.

**Methyl 2-((7-cyanothieno[2′,3′:4,5]benzo[1,2-*d*][1,3]dioxol-6-yl)amino)-3-phenyl propanoate (29j)**




Reaction time: 2.5 h.

Yield: 65%, as a white colour solid.

Melting point: 148 – 150 ºC

$R_f$: 0.38 in 20% ethyl acetate in hexane

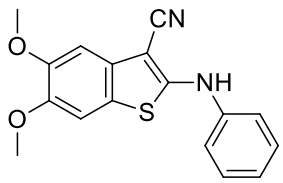
IR (KBr): ν ($cm^{-1}$) = 3441, 3311, 2953, 2373, 2346, 2202, 1727, 1555, 1485, 1283, 1220, 1082, 939, 841, 701.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.34 – 7.27 (m, 3H), 7.17 – 7.15 (m, 2H), 6.99 (s, 1H), 6.95 (s, 1H), 5.98 (s, 2H), 5.49 (brs, 1H), 4.42 (brs, 1H), 3.76 (s, 3H), 3.27 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.19 (dd, *J* = 14.0, 6.0 Hz, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 171.1, 161.6, 147.8, 145.3, 135.0, 131.8, 129.4, 129.0, 127.7, 120.9, 115.2, 102.0, 101.5, 100.2, 81.7, 60.9, 52.9, 38.8.

HR-MS (ESI): Calcd. for $C_{20}H_{16}N_2O_4S$ [M+H]: 381.0904, Found: 381.0901.

**5, 6-Dimethoxy-2-(phenylamino)benzo[*b*]thiophene-3-carbonitrile (29k)**




Reaction time: 2 h.

Yield: 77%, as a light brown colour solid.

Melting point: 180 – 182 °C

$R_f$: 0.32 in 25% ethyl acetate in hexane

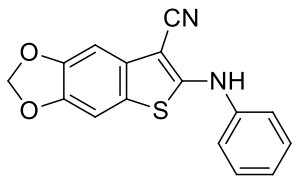
IR (KBr): ν ($cm^{-1}$) = 3272, 2993, 2963, 2199, 1601, 1562, 1491, 1474, 1461, 1435, 1402, 1298, 1246, 1208, 1173, 1083, 1033, 960, 836, 762, 700, 621.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.41 – 7.37 (m, 2H), 7.31 – 7.29 (m, 2H), 7.18 – 7.14 (m, 1H), 7.09 (s, 1H), 7.06 (s, 1H), 7.04 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 158.6, 149.5, 147.6, 140.4, 129.9, 129.8, 124.6, 121.1, 119.4, 115.5, 104.6, 102.4, 85.1, 56.5, 56.3.

HR-MS (ESI): Calcd. for $C_{17}H_{14}N_2O_2S$ [M+H]: 311.0849, Found: 311.0890.

**6-(Phenylamino)thieno[2′,3′:4,5]benzo[1,2-*d*][1,3]dioxole-7-carbonitrile (29l)**




Reaction time: 2.5 h.

Yield: 68%, as a brown colour solid.

Melting point: 222 – 225 °C

$R_f$: 0.37 in 20% ethyl acetate in hexane

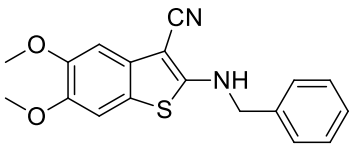
IR (KBr): ν ($cm^{-1}$) = 3441, 3255, 2371, 2345, 2204, 1561, 1474, 1295, 1052, 945, 823, 695.

$^1$H NMR (400 MHz, DMSO) δ = 9.97 (s, 1H), 7.41 (s, 1H), 7.39 – 7.34 (m, 4H), 7.10 (t, *J* = 5.6 Hz, 1H), 6.99 (s, 1H), 6.07 (s, 2H).

$^{13}$C NMR (100 MHz, DMSO) δ = 158.9, 147.3, 145.2, 141.4, 130.7, 129.4, 123.6, 121.2, 119.4, 114.9, 102.7, 101.4, 98.9, 84.3.

HR-MS (ESI): Calcd. for $C_{16}H_{10}N_2O_2S$ [M+H]: 295.0536, Found: 295.0565.

**2-(Benzylamino)-5,6-dimethoxybenzo[*b*]thiophene-3-carbonitrile (29m)**




Reaction time: 1 h.

Yield: 97%, as a pale yellow colour solid.

Melting point: 168 – 170 ºC

$R_f$: 0.32 in 33% ethyl acetate in hexane

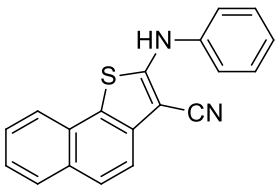
IR (KBr): ν ($cm^{-1}$) = 3304, 2923, 2193, 1570, 1489, 1401, 1292, 1241, 1204, 1169, 1038, 829.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.38 – 7.33 (m, 5H), 7.00 (s, 1H), 6.98 (s, 1H), 5.64 (brs, 1H), 4.50 (d, *J* = 5.2 Hz, 2H), 3.93 (s, 3H), 3.87 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 164.2, 149.3, 146.6, 136.5, 130.9, 129.1, 128.4, 127.8, 120.1, 116.2, 104.9, 102.1, 79.2, 56.5, 56.3, 51.5.

HR-MS (ESI): Calcd. for $C_{18}H_{16}N_2O_2S$ [M+H]: 325.1005, Found: 325.1047.

**2-(Phenylamino)naphtha[1,2-*b*]thiophene-3-carbonitrile (29n)**




Reaction time: 2 h.

Yield: 82%, as a brown colour solid.

Melting point: 204 – 207 ºC

$R_f$: 0.40 in 20% ethyl acetate in hexane

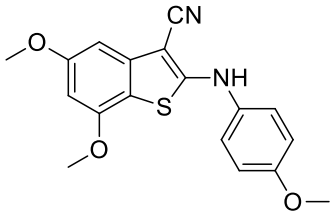
IR (KBr): ν ($cm^{-1}$) = 3432, 3261, 2927, 2209, 1560, 1086, 804, 695.

$^1$H NMR (400 MHz, DMSO) δ = 10.30 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.51 – 7.48 (m, 1H), 7.47 – 7.41 (m, 4H), 7.19 – 7.16 (m, 1H).

$^{13}$C NMR (100 MHz, DMSO) δ = 159.8, 141.2, 134.7, 130.0, 129.6, 129.1, 127.6, 127.6, 127.1, 125.2, 124.3, 123.6, 122.4, 120.0, 118.0, 114.9, 85.0.

HR-MS (ESI): Calcd. for $C_{19}H_{12}N_2S$ [M+H]: 301.0794, Found: 301.0810.

**5,7-Dimethoxy-2-((4-methoxyphenyl)amino)benzo[*b*]thiophene-3-carbonitrile (29o)**




Reaction time: 2 h.

Yield: 79%, as a pale brown colour solid.

Melting point: 188 – 189 ºC

$R_f$: 0.36 in 25% ethyl acetate in hexane

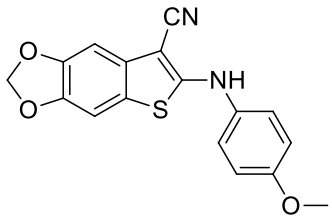
IR (KBr): ν ($cm^{-1}$) = 3448, 3254, 2926, 2373, 2208, 1577, 1549, 1513, 1437, 1297, 1248, 1203, 1148, 1105, 1027, 833, 804.

$^1$H NMR (400 MHz, DMSO) δ = 10.01 (s, 1H), 7.32 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.54 (s, 1H), 6.44 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H).

$^{13}$C NMR (100 MHz, DMSO) δ = 163.3, 160.2, 156.8, 154.0, 138.9, 133.8, 123.6, 115.3, 114.6, 107.2, 94.6, 94.4, 80.6, 55.9, 55.5, 55.3.

HR-MS (ESI): Calcd. for $C_{18}H_{16}N_2O_3S$ [M+H]: 341.0954, Found: 341.0964.

**6-((4-Methoxyphenyl)amino)thieno[2′,3′:4,5]benzo[1,2-*d*][1,3]dioxole-7-carbonitrile (29p)**




Reaction time: 3 h.

Yield: 53%, as a brown colour solid.

Melting point: 207 – 210 ºC

$R_f$: 0.35 in 25% ethyl acetate in hexane

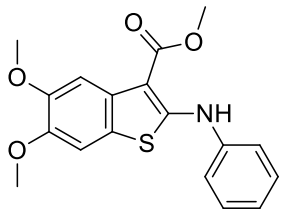
IR (KBr): ν ($cm^{-1}$) = 3408, 3293, 2371, 2345, 2197, 1597, 1406, 1291, 1257, 1036, 930, 831.

$^1$H NMR (400 MHz, DMSO) δ = 9.80 (s, 1H), 7.34 – 7.28 (m, 3H), 7.09 – 6.84 (m, 3H), 6.03 (s, 2H), 3.75 (s, 3H).

$^{13}$C NMR (100 MHz, DMSO) δ = 161.6, 156.6, 147.2, 144.7, 134.2, 131.3, 123.2, 120.4, 115.3, 114.7, 102.8, 101.4, 98.7, 81.0, 55.4.

HR-MS (ESI): Calcd. for $C_{17}H_{12}N_2O_3S$ [M+H]: 325.0641, Found: 325.0674.

**Methyl 5,6-dimethoxy-2-(phenylamino)benzo[*b*]thiophene-3-carboxylate (39a)**



Reaction time: 3 h.

Yield: 86%, as a pale yellow colour solid.

Melting point: 140 – 142 ºC

$R_f$: 0.32 in 20% ethyl acetate in hexane

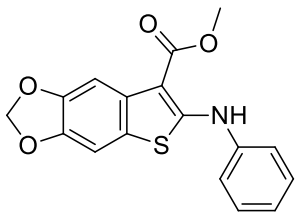
IR (KBr): ν ($cm^{-1}$) = 3432, 2953, 1654, 1594, 1559, 1496, 1388, 1291, 1253, 1202, 1075, 854, 751.

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 10.37 (s, 1H), 7.70 (s, 1H), 7.41 – 7.36 (m, 4H), 7.16 – 7.13 (m, 1H), 7.02 (s, 1H), 4.00 (s, 3H), 3.96 (s, 3H), 3.89 (s, 3H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 167.0, 160.9, 148.6, 146.5, 140.5, 130.0, 129.7, 124.3, 120.21, 120.20, 105.7, 104.1, 100.5, 56.3, 56.2, 51.4.

HR-MS (ESI): Calcd. for $C_{18}H_{17}NO_4S$ [M+H]: 344.0951, Found: 344.1007.

**Methyl 6-(phenylamino)thieno[2′,3′:4,5]benzo[1,2-*d*][1,3]dioxole-7-carboxylate (39b)**



Reaction time: 2 h.

Yield: 88%, as a white colour solid.

Melting point: 134 – 136 ºC

$R_f$: 0.43 in 20% ethyl acetate in hexane

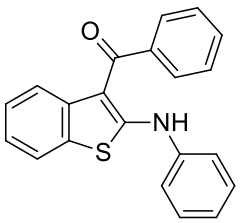
IR (KBr): ν ($cm^{-1}$) = 2949, 2920, 1658, 1593, 1569, 1500, 1433, 1393, 1287, 1251, 1225, 1206, 1032, 941, 917, 844, 826, 733.

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 10.42 (s, 1H), 7.63 (s, 1H), 7.41 – 7.34 (m, 4H), 7.14 (t, *J* = 6.8 Hz, 1H), 6.95 (s, 1H), 5.97 (s, 2H), 3.97 (s, 3H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 167.1, 160.8, 147.3, 144.4, 140.5, 130.8, 129.7, 124.3, 120.6, 120.2, 103.0, 101.4, 101.2, 100.8, 51.3.

HR-MS (ESI): Calcd. for $C_{17}H_{13}NO_4S$ [M+H]: 328.0638, Found: 328.0597

**Phenyl(2-phenylamino)benzo[*b*]thiophen-3yl)methanone (46a)**



Reaction time: 2 h.

Yield: 87%, as a yellow colour solid.

Melting point: 93 – 95 ºC

$R_f$: 0.32 in 5% ethyl acetate in hexane

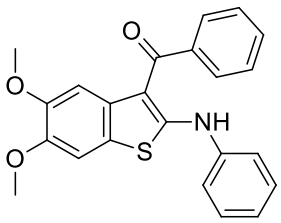
IR (KBr): ν ($cm^{-1}$) = 3057, 2354, 1586, 1538, 1455, 1351, 1255, 1232, 1197, 1174, 1054, 1022, 897, 849, 799, 752, 723, 696.7

$^1$H NMR (400 MHz, $CDCl_3$) δ = 12.08 (s, 1H), 7.65 – 7.63 (m, 2H), 7.58 – 7.53 (m, 2H), 7.50 – 7.43 (m, 6H), 7.25 – 7.21 (m, 1H), 7.09 (td, *J* = 7.2, 1.2 Hz, 1H), 7.03 – 6.99 (m, 1H), 6.72 – 6.70 (m, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 192.2, 164.2, 141.4, 140.1, 136.9, 131.0, 129.8, 129.1, 128.7, 127.9, 125.3, 125.1, 122.7, 122.0, 121.7, 121.1, 110.2.

HR-MS (ESI): Calcd. for $C_{21}H_{15}NOS$ [M+H]: 330.0947, Found: 330.0913.

**(5,6-Dimethoxy-2-(phenylamino)benzo[*b*]thiophen-3-yl)(phenyl)methanone (46b)**



Reaction time: 2 h.

Yield: 92%, as a yellow colour solid.

Melting point: 159 – 161 ºC

$R_f$: 0.31 in 20% ethyl acetate in hexane

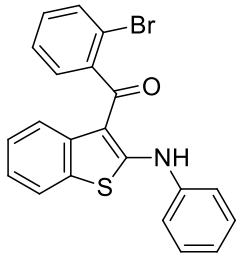
IR (KBr): ν ($cm^{-1}$) = 3448, 1595, 1582, 1555, 1496, 1404, 1265, 1207, 1050, 1028, 851, 793, 750.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 12.10 (s, 1H), 7.63 – 7.61 (m, 2H), 7.55 – 7.49 (m, 3H), 7.47 – 7.41 (m, 4H), 7.22 – 7.17 (m, 1H), 6.99 (s, 1H), 6.13 (s, 1H), 3.86 (s, 3H), 3.37 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 191.7, 163.3, 147.8, 146.4, 141.5, 140.2, 130.6, 130.1, 129.8, 128.7, 127.7, 124.9, 120.6, 120.4, 110.5, 105.2, 104.2, 56.3, 55.3.

HR-MS (ESI): Calcd. for $C_{23}H_{19}NO_3S$ [M+H]: 390.1158, Found: 390.1137.

**(2-Bromophenyl)(2-(phenylamino)benzo[*b*]thiophen-3-yl)methanone (48a)**




Reaction time: 1 h.

Yield: 83%, as a yellow colour solid.

Melting point: 126 – 128 $^oC$

$R_f$: 0.40 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3428, 2927, 2373, 1560, 1384, 1276, 1182, 1029, 760.

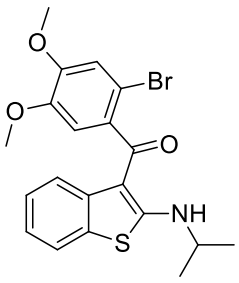
$^1H$ NMR (400 MHz, $CDCl_3$) δ = 12.62 (s, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.52 – 7.45 (m, 6H), 7.41 – 7.35 (m, 2H), 7.28 – 7.25 (m, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 6.99 (t, *J* = 7.2 Hz, 1H), 6.27 (d, *J* = 8.0 Hz, 1H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 189.4, 166.1, 142.9, 139.8, 136.2, 133.4, 130.8, 129.9, 129.0, 128.2, 128.0, 125.8 (2C), 123.1, 121.9, 121.5, 120.5, 119.2, 109.9.

HR-MS (ESI): Calcd. for $C_{21}H_{14}BrNOS$ [M+H]: 408.0052, Found: 408.0062.

[M+H]: 410.0032, Found: 410.0047.

**(2-Bromo-4,5-dimethoxyphenyl)(2-(isopropylamino)benzo[*b*]thiophen-3yl)methanone (48b)**




Reaction time: 2 h.

Yield: 88%, as a yellow colour solid.

Melting point: 130 – 132 $^oC$

$R_f$: 0.30 in 25% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3422, 2971, 2932, 2840, 1577, 1538, 1506, 1466, 1408, 1332, 1254, 1209, 1162, 1098, 1032, 775, 751.

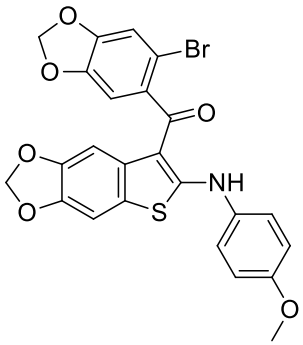
$^1H$ NMR (400 MHz, $CDCl_3$) δ = 10.52 (d, *J* = 8.0 Hz, 1H), 7.50 – 7.47 (m, 1H), 7.13 (s, 1H), 7.04 – 6.96 (m, 2H), 6.80 (s, 1H), 6.32 – 6.30 (m, 1H), 3.96 (s, 3H), 3.80 (s, 3H), 3.77 – 3.69 (m, 1H), 1.44 (d, *J* = 1.6 Hz, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 187.8, 169.6, 150.0, 149.0, 137.3, 135.3, 128.9, 125.7, 122.3, 121.8, 120.4, 115.8, 110.6, 109.6, 107.4, 56.4, 56.2, 50.5, 22.7.

HR-MS (ESI): Calcd. for $C_{20}H_{20}BrNO_3S$ [M+H]: 434.0420, Found: 434.0475.

[M+H]: 436.0400, Found: 436.0452.

**(6-Bromobenzo[*d*][1,3]dioxol-5-yl)(6-((4-methoxyphenyl)amino)thieno[2′,3′:4,5]benzo [1,2-*d*][1,3]dioxol-7-yl)methanone (48c)**



Reaction time: 2 h.

Yield: 89%, as a yellow colour solid.

Melting point: 223 – 226 °C

$R_f$: 0.32 in 25% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3402, 3120, 2905, 1559, 1502, 1472, 1427, 1384, 1287, 1244, 1186, 1037, 936, 820.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 12.10 (s, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.12 (s, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.90 (s, 1H), 6.79 (s, 1H), 6.07 (s, 2H), 5.94 (s, 1H), 5.89 (s, 2H), 3.85 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 188.1, 167.2, 157.9, 149.3, 148.1, 147.1, 144.5, 136.0, 132.9, 130.7, 124.0, 120.7, 115.00, 113.5, 110.3, 109.6, 107.9, 102.3, 101.9, 101.3, 101.2, 55.7.

HR-MS (ESI): Calcd. for $C_{24}H_{16}BrNO_6S$ [M+H]: 525.9954, Found: 525.9976.

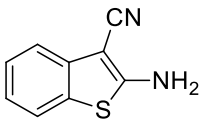
[M+H]: 527.9935, Found: 527.9958.

### 3.6.8 General Procedure for the Cleavage of *p*-Methoxyphenyl (PMP) group

To the solution of 2-((4-Methoxyphenyl)amino)benzo[*b*]thiophene-3-carbonitrile (0.35 mmol) in $CH_3CN/H_2O$ (9 : 1) at 0 °C was added portion wise of Ceric ammonium nitrate (CAN) (4 equiv) and the reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was monitored by TLC. After complete consumption of the starting material, the reaction mixture quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic layer washed with (3 x 5 mL) & brine (3 x 5 mL), dried over anhyd. $Na_2SO_4$ and concentrated

under reduced pressure. The crude products were purified by flash chromatography using EtOAc/hexanes as eluent.

**2-Aminobenzo[*b*]thiophene-3-carbonitrile (49)**




Reaction time: 3 h.

Yield: 57%, as a brown colour solid.

Melting point: 150 – 154 $^{o}$C

$R_f$: 0.30 in 25% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3415, 3325, 3220, 2371, 2345, 2210, 1633, 1544, 1457, 735, 716.

$^{1}$H NMR (400 MHz, MeOD) δ = 7.52 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.12 – 7.08 (m, 1H).

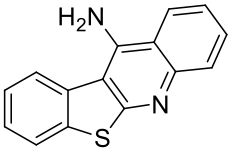
$^{13}$C NMR (100 MHz, MeOD) δ = 166.7, 139.4, 130.5, 126.7, 123.6, 122.8, 119.4, 116.5, 79.1.

HR-MS (ESI): Calcd. for $C_9H_6N_2S$ [M+H]: 175.0324, Found: 175.0317.

### 3.6.9 General Procedure for the Synthesis of Thieno[1,2-*b*]quinolines *via* Friedel-Craft Cyclization

An oven-dried 8 mL reaction vial was charged with respective 2-aminobenzo[*b*]thiophene (0.5 mmol) in dry DCE (2.0 mL) was added triflic acid (10 equiv) drop wise at room temperature. The reaction mixture was stirred at room temperature and monitored by TLC. After complete consumption of the starting material, the reaction mixture quenched with saturated $NaHCO_3$ solution and extracted with DCM. The combined organic layer washed with (3 x 5 mL) & brine (3 x 5 mL), dried over anhyd. $Na_2SO_4$ and concentrated under reduced pressure. The crude products were purified by flash chromatography using EtOAc/hexanes as eluent.

**Benzo[4,5]thieno[2,3-*b*]quinolin-11-amine (50a)**



Reaction time: 20 min.

Yield: 86%, as a white colour solid.

Melting point: 260 – 262 ºC

$R_f$: 0.30 in 33% ethyl acetate in hexane

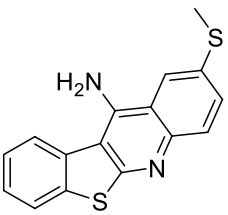
IR (KBr): ν ($cm^{-1}$) = 3495, 3307, 3146, 2372, 2345, 1648, 1578, 1560, 1429, 1264, 1068, 950.

$^1$H NMR (400 MHz, DMSO) δ = 8.55 (d, *J* = 8.4 Hz, 1H), 8.50 (d, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 7.6Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.53 – 7.46 (m, 3H), 7.42 (s, 2H).

$^{13}$C NMR (100 MHz, DMSO) δ = 163.3, 147.8, 147.4, 134.7, 133.6, 129.8, 127.5, 125.7, 125.0, 123.5, 123.1, 123.0, 122.8, 116.2, 108.4.

HR-MS (ESI): Calcd. for $C_{15}H_{10}N_2S$ [M+H]: 251.0637, Found: 251.0663.

**9-(Methylthio)benzo[4,5]thieno[2,3-*b*]quinolin-11-amine (50d)**



Reaction time: 1.5 h.

Yield: 54%, as a brown colour solid.

Melting point: 222 – 224 ºC

$R_f$: 0.30 in 33% ethyl acetate in hexane

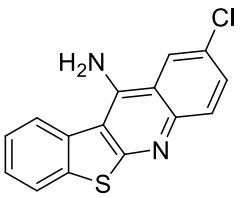
IR (KBr): ν ($cm^{-1}$) = 3448, 2921, 2372, 2345, 1640, 1554, 1423, 1257, 1133, 1020, 944, 815.

$^1$H NMR (400 MHz, DMSO) δ = 8.51 (d, *J* = 7.6 Hz, 1H), 8.29 (d, *J* = 1.2 Hz, 1H), 7.94 (d, *J* = 7.2 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.60 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.48 – 7.44 (m, 1H), 7.42 (s, 2H), 2.65 (s, 3H).

$^{13}$C NMR (100 MHz, DMSO) δ = 162.4, 146.8, 145.5, 134.7, 133.5, 132.9, 129.1, 128.0, 125.7, 124.9, 123.5, 122.7, 118.8, 116.6, 108.7, 15.5.

HR-MS (ESI): Calcd. for $C_{16}H_{12}N_2S_2$ [M+H]: 297.0514, Found: 297.0534.

**9-Chlorobenzo[4,5]thieno[2,3-*b*]quinolin-11-amine (50e)**




Reaction time: 1.5 h.

Yield: 70%, as a brown colour solid.

Melting point: 292 – 294 ºC

$R_f$: 0.37 in 33% ethyl acetate in hexane

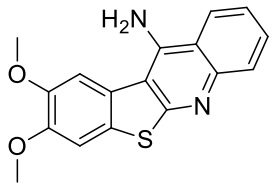
IR (KBr): ν ($cm^{-1}$) = 3468, 3308, 3191, 2920, 1633, 1573, 1494, 1434, 1257, 1091, 816, 718.

$^1$H NMR (400 MHz, DMSO) δ = 8.72 (s, 1H), 8.52 (d, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.56 – 7.44 (m, 4H).

$^{13}$C NMR (100 MHz, DMSO) δ = 163.7, 147.0, 145.8, 134.7, 133.2, 130.0, 129.6, 127.5, 125.9, 125.0, 123.7, 122.8, 122.1, 116.9, 108.8.

HR-MS (ESI): Calcd. for $C_{15}H_9ClN_2S$ [M+H]: 285.0248, Found: 285.0250.

**2,3-Dimethoxybenzo[4,5]thieno[2,3-*b*]quinolin-11-amine (50i)**




Reaction time: 20 min.

Yield: 63%, as a brown colour solid.

Melting point: 228 – 230 ºC

$R_f$: 0.26 in 50% ethyl acetate in hexane

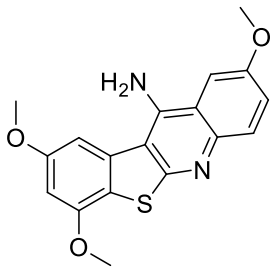
IR (KBr): ν ($cm^{-1}$) = 3364, 3226, 2919, 2347, 1634, 1576, 1403, 1308, 1272, 1210, 1079, 1038, 833, 803, 743.

$^1$H NMR (400 MHz, DMSO) δ = 8.53 (d, *J* = 8.4 Hz, 1H), 7.90 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.67(t, *J* = 7.2 Hz, 1H), 7.59 (s, 1H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.21 (s, 2H), 3.98 (s, 3H), 3.87 (s, 3H).

$^{13}$C NMR (100 MHz, DMSO) δ = 163.6, 148.3, 147.3, 146.7, 146.5, 129.1, 127.5, 126.9, 126.0, 122.8 (2C), 116.2, 109.5, 108.2, 106.0, 56.6, 55.8.

HR-MS (ESI): Calcd. for $C_{17}H_{14}N_2O_2S$ [M+H]: 311.0849, Found: 311.0862.

**2,4,9-Trimethoxybenzo[4,5]thieno[2,3-*b*]quinolin-11-amine (50l)**



Reaction time: 3 h.

Yield: 59%, as a light brown colour solid.

Melting point: 190 – 193 ºC

$R_f$: 0.41 in 33% hexane in ethylacetate.

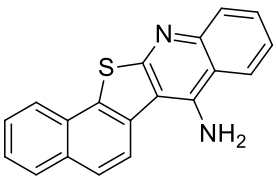
IR (KBr): ν ($cm^{-1}$) = 3446, 3324, 3197, 2998, 2931, 2833, 1646, 1575, 1505, 1450, 1419, 1357, 1328, 1282, 1236, 1206, 1165, 1140, 1108, 1033, 983, 940, 819, 729.

$^1$H NMR (400 MHz, DMSO) δ = 7.85 (d, *J* = 2.4 Hz, 1H), 7.73 (d, *J* = 9.2 Hz, 1H), 7.61 (d, *J* = 1.6 Hz, 1H), 7.36 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.22 (s, 2H), 6.79 (d, *J* = 1.2 Hz, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 3.94 (s, 3H).

$^{13}$C NMR (100 MHz, DMSO) δ = 161.4, 159.2, 155.4, 153.8, 147.2, 143.2, 134.7, 129.0, 121.7, 116.4, 113.9, 109.2, 101.9, 101.7, 96.2, 56.0, 55.9, 55.8.

HR-MS (ESI): Calcd. for $C_{18}H_{16}N_2O_3S$ [M+H]: 341.0954, Found: 341.0966.

**Naphtho[2′,1′:4,5]thieno[2,3-*b*]quinolin-7-amine (50n)**



Reaction time: 20 min.

Yield: 79%, as a brown colour solid.

Melting point: 284 – 286 ºC

$R_f$: 0.28 in 33% ethyl acetate in hexane

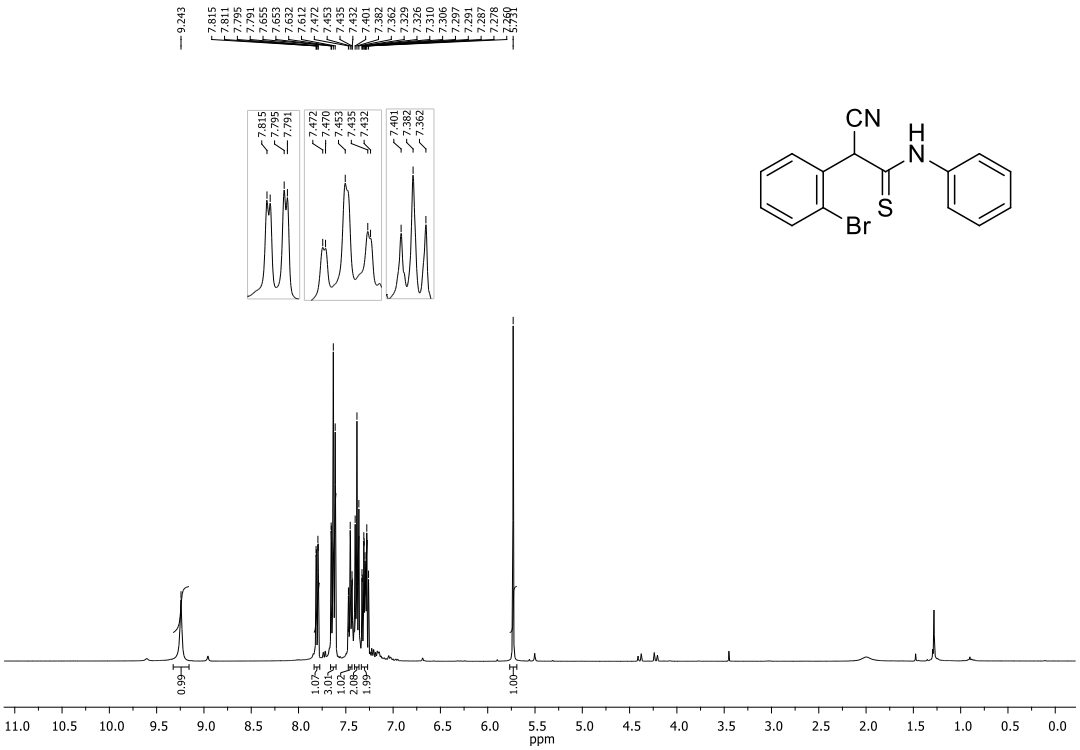
IR (KBr): ν ($cm^{-1}$) = 3489, 3298, 3135, 2372, 2345, 1638, 1571, 1444, 1279, 1117, 1019, 952, 900, 795, 758.

$^1$H NMR (400 MHz, DMSO) δ = 8.67 (d, *J* = 8.8 Hz, 1H), 8.59 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 8.08 – 8.04 (m, 2H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.74 – 7.67 (m, 2H), 7.64 – 7.61 (m, 1H), 7.51(s, 2H), 7.50 – 7.47 (m, 1H).

$^{13}$C NMR (100 MHz, DMSO) δ = 163.0, 148.0, 147.2, 131.4, 130.9, 130.8, 129.7, 128.7, 127.7, 127.6, 127.1, 126.2, 125.4, 124.1, 123.1, 123.0, 121.9, 116.1, 109.9.

HR-MS (ESI): Calcd. for $C_{19}H_{12}N_2S$ [M+H]: 301.0794, Found: 301.0813.

## 3.7 Copies of Selected $^{1}H$ and $^{13}C$ NMR Spectra




$^{1}H$ **Figure 3.3a**: $^{1}HNMR$ Spectrum of **28a**

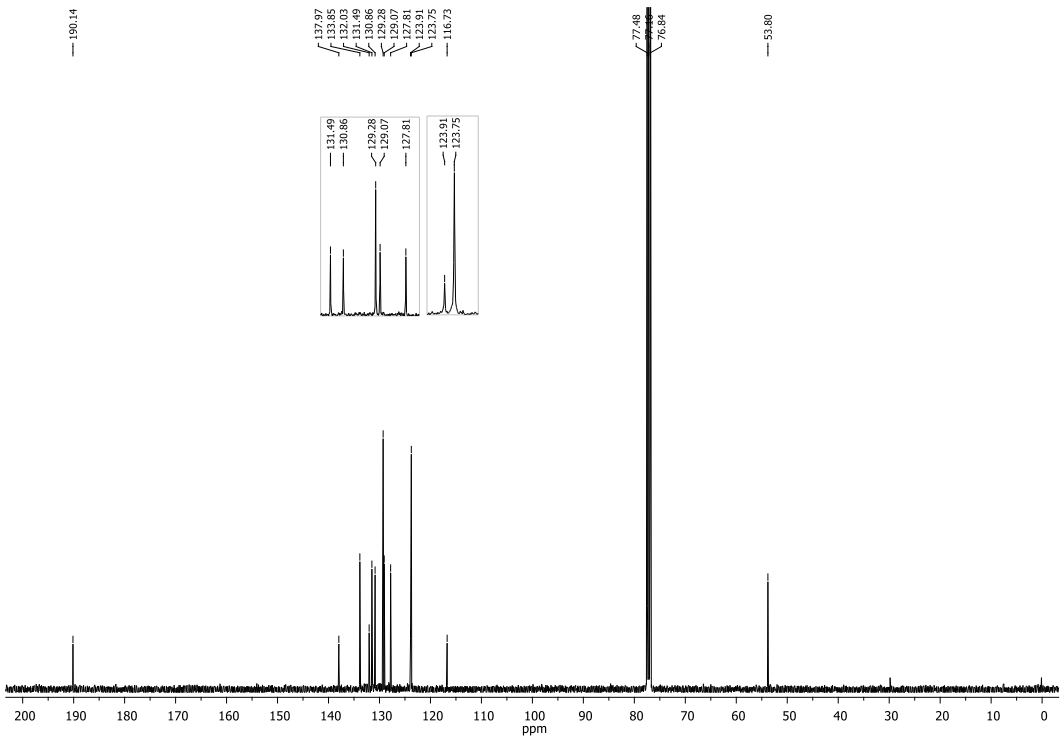



**Figure 3.3b**: $^{13}C$ NMR Spectrum of **28a**

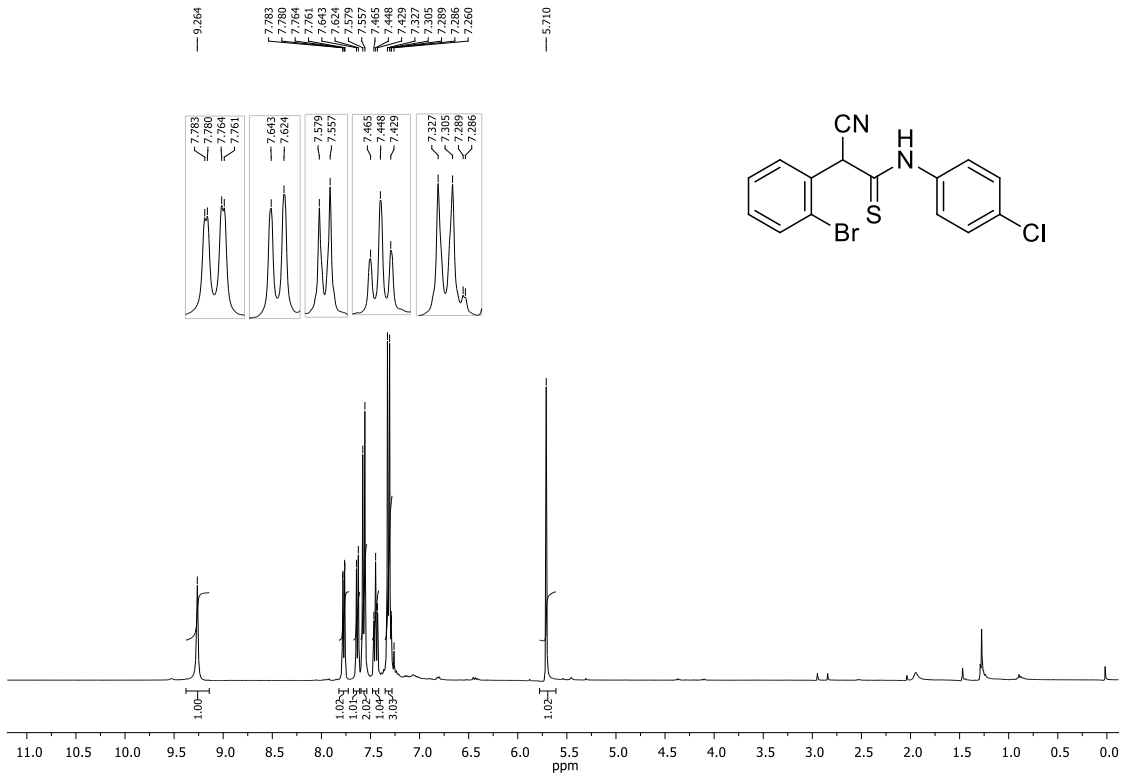



**Figure 3.4a**: $^{1}$HNMR Spectrum of **28e**

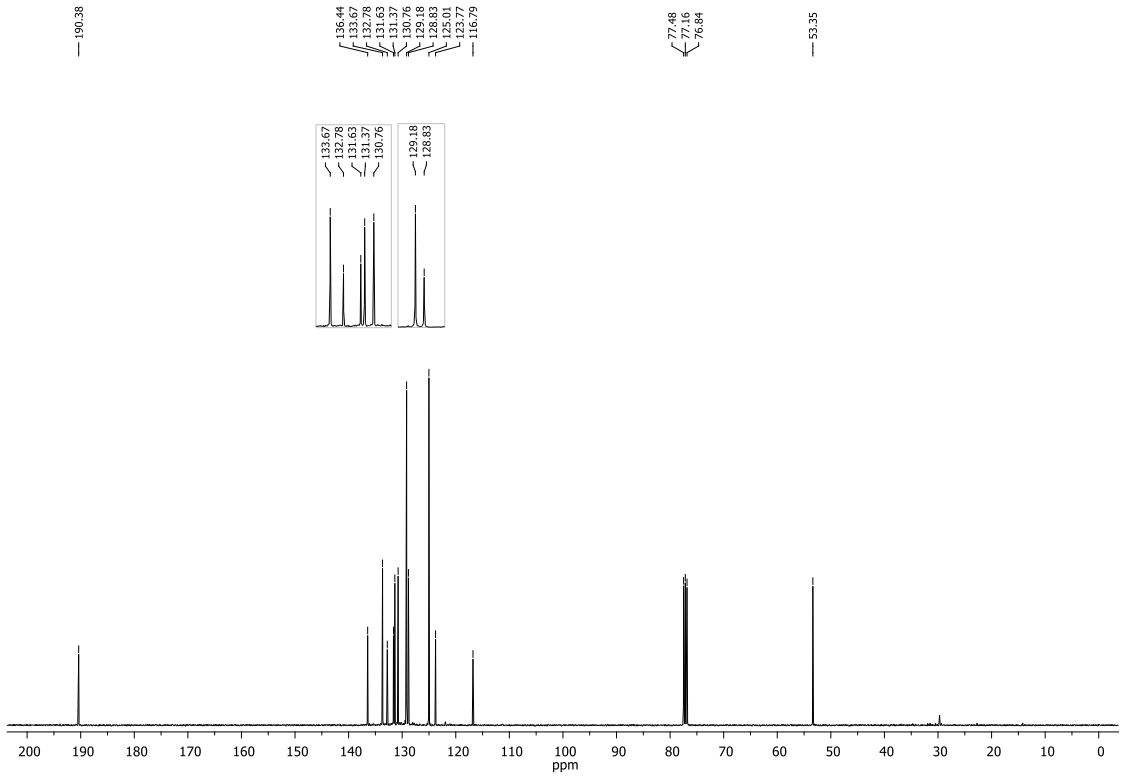



**Figure 3.4b**: $^{13}$C NMR Spectrum of **28e**

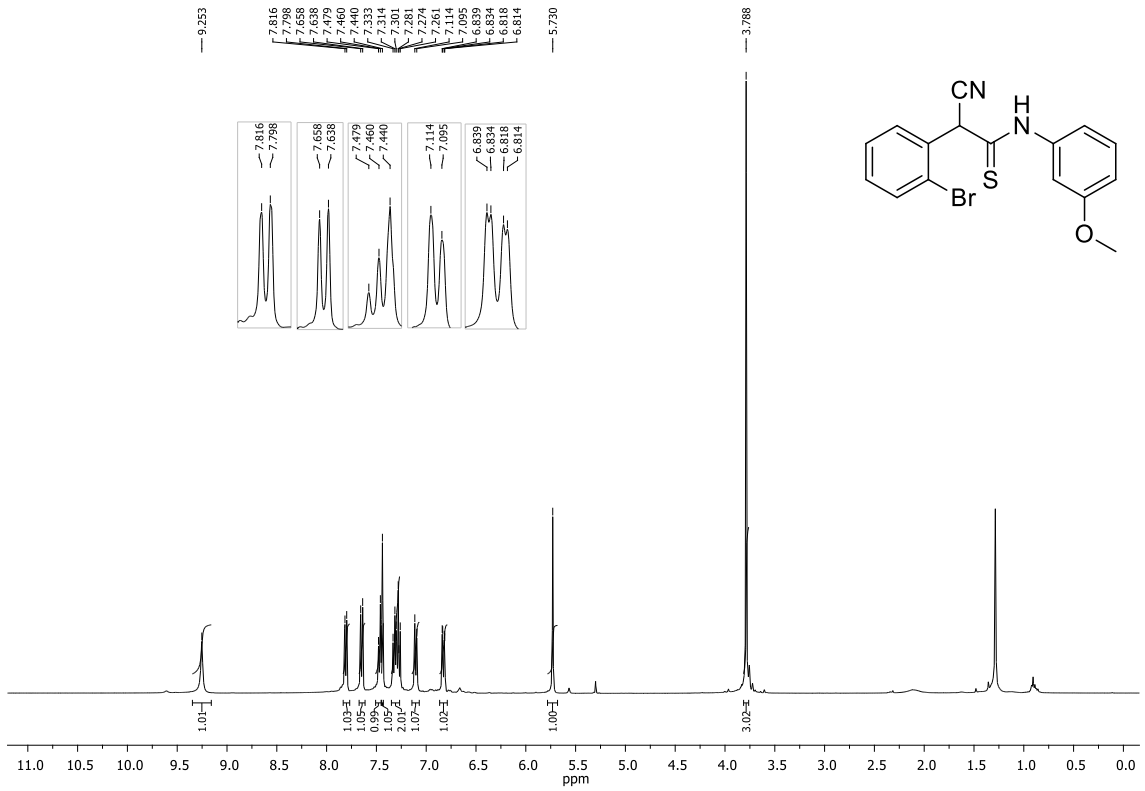



**Figure 3.5a**: $^{1}$H NMR Spectrum of **28f**

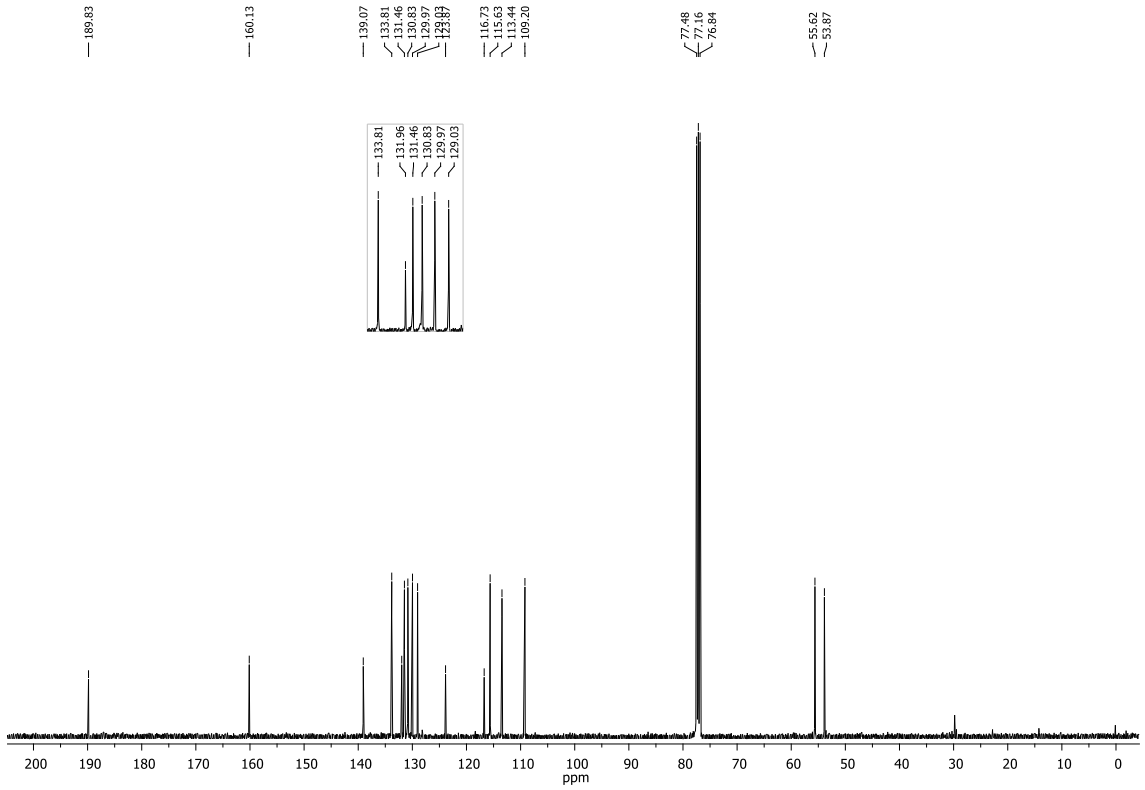



**Figure 3.5b**: $^{13}$C NMR Spectrum of **28f**

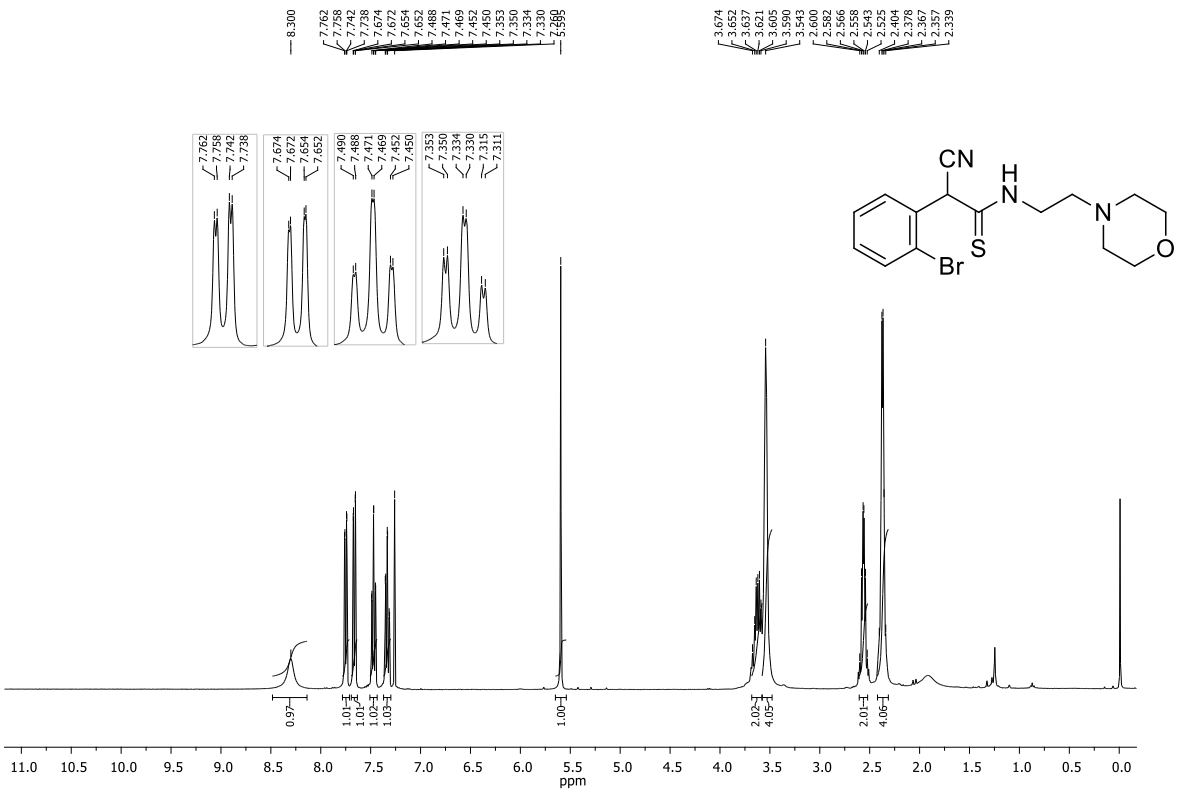



**Figure 3.6a**: $^{1}$H NMR Spectrum of **28h**

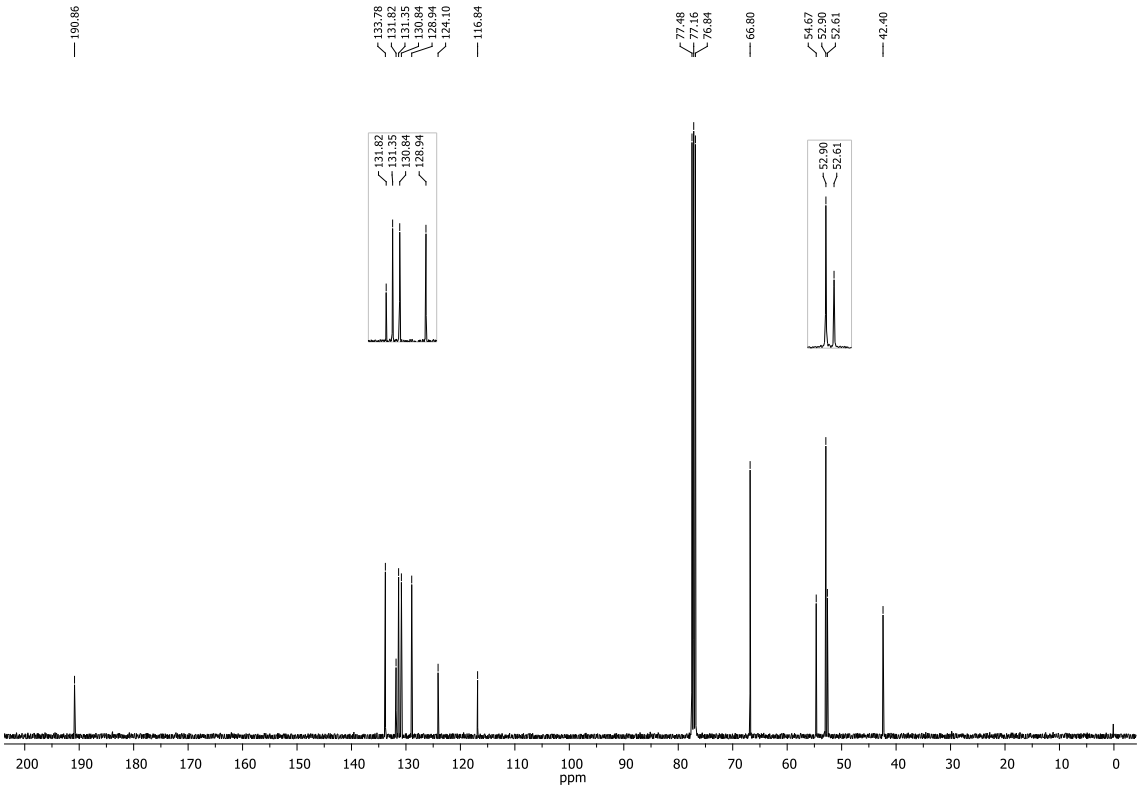



**Figure 3.6b**: $^{13}$C NMR Spectrum of **28h**

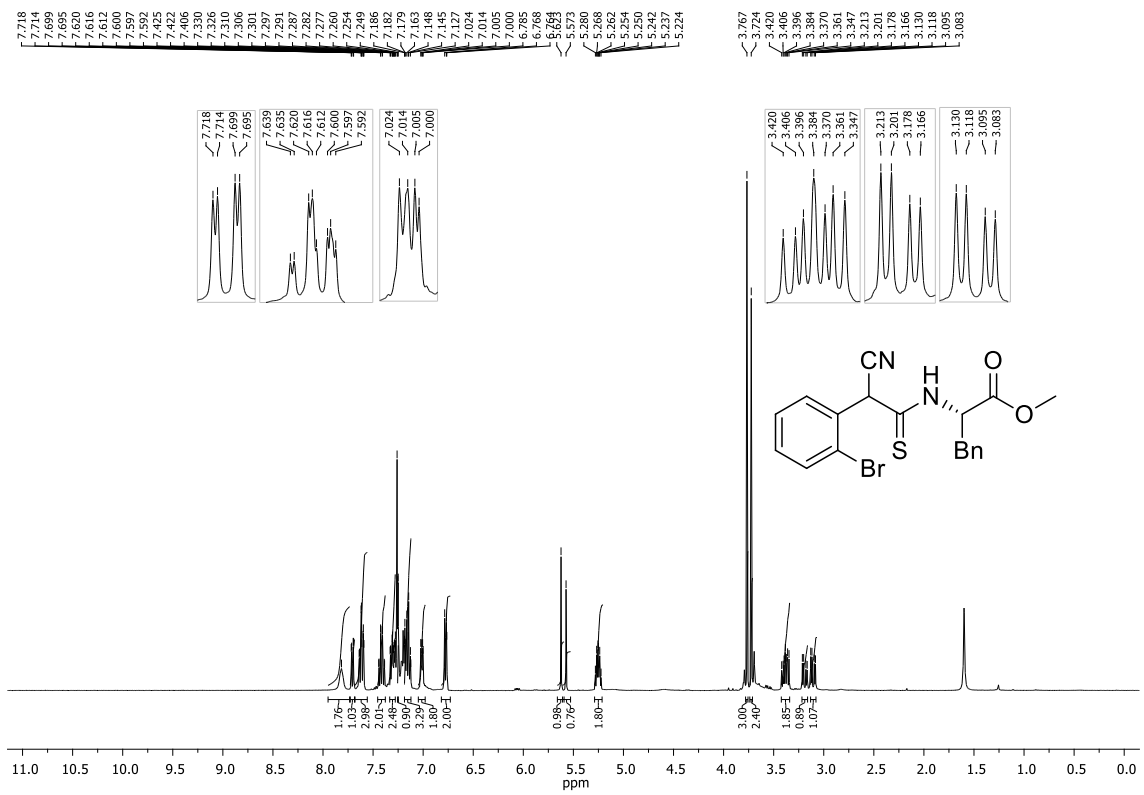



**Figure 3.7a**: $^{1}$H NMR Spectrum of **28i**

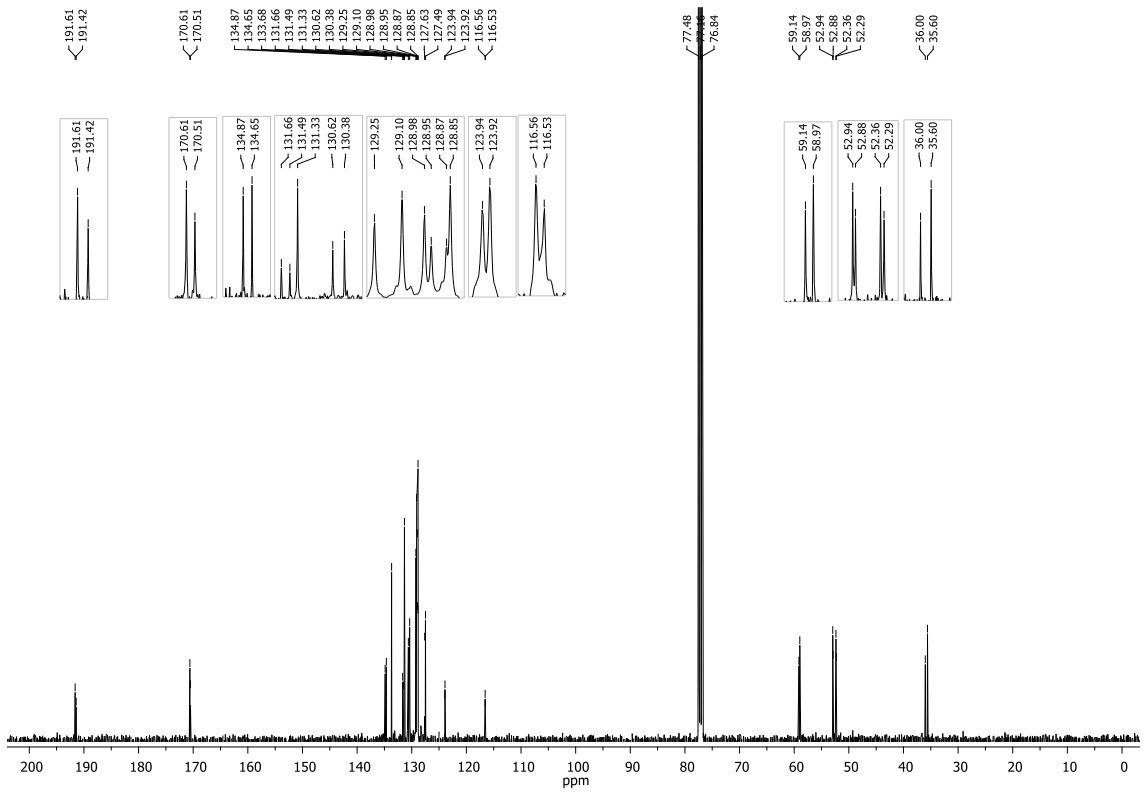



**Figure 3.7b**: $^{13}$C NMR Spectrum of **28i**

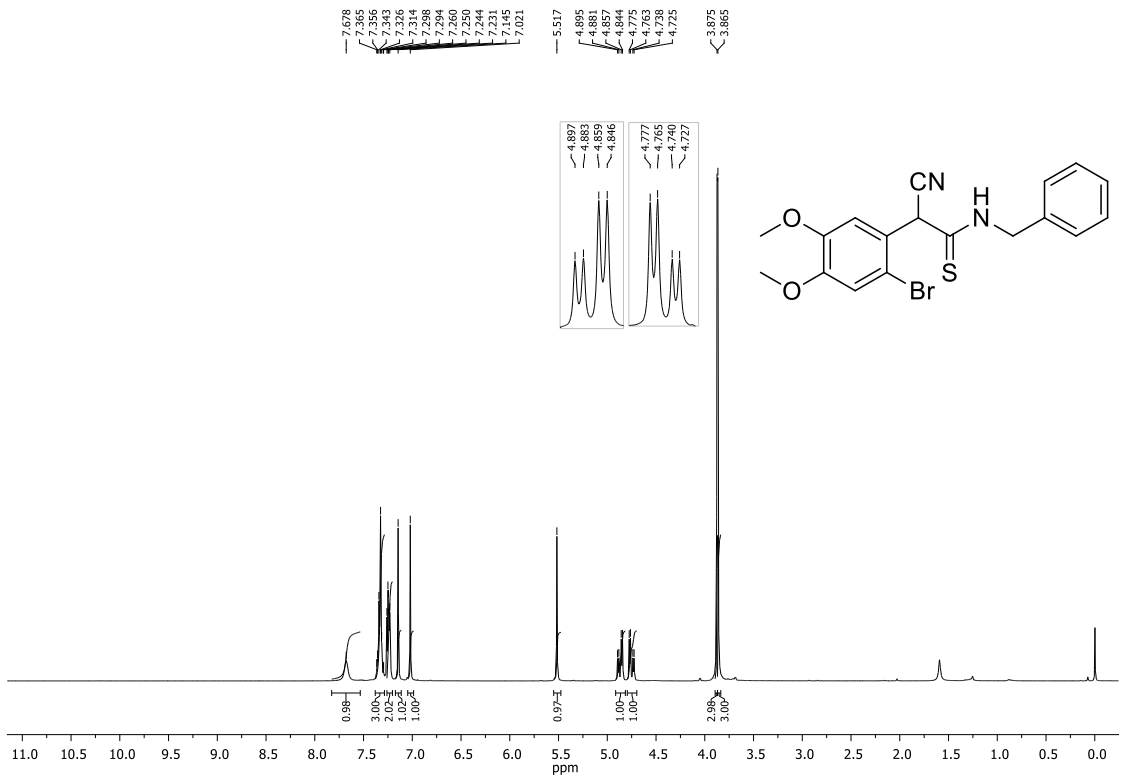



**Figure 3.8a**: $^{1}$H NMR Spectrum of **28j**

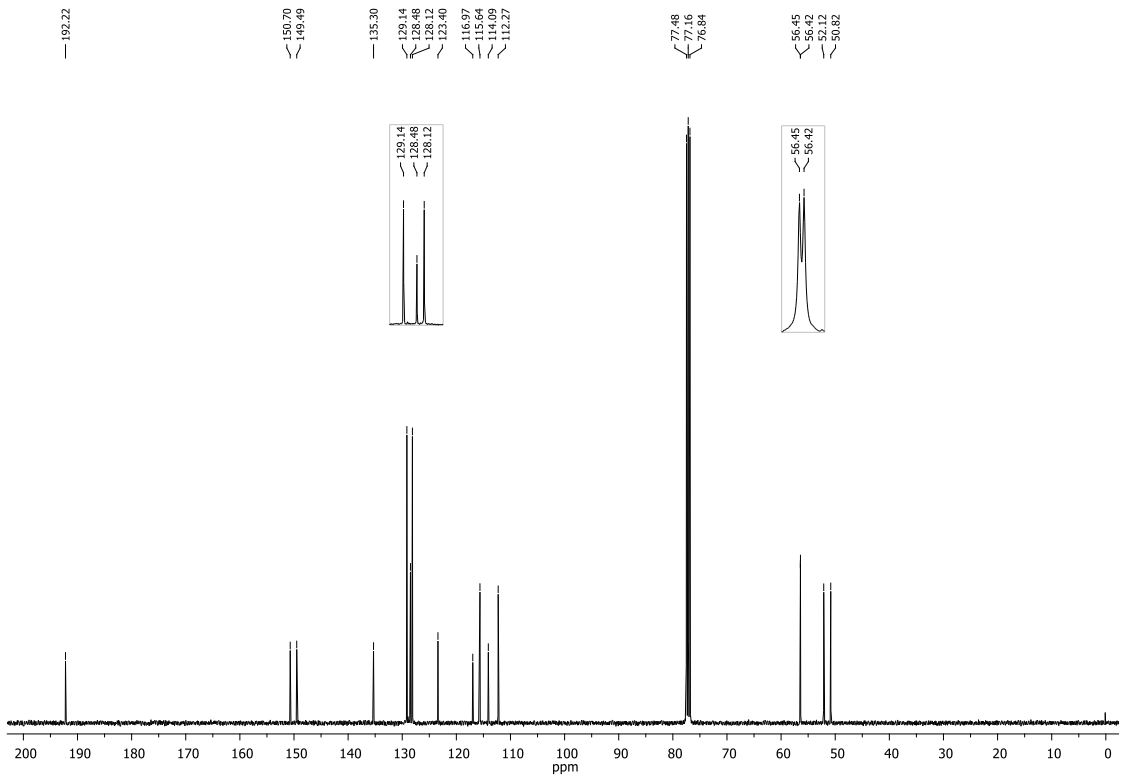



**Figure 3.8b**: $^{13}$CNMR Spectrum of **28j**

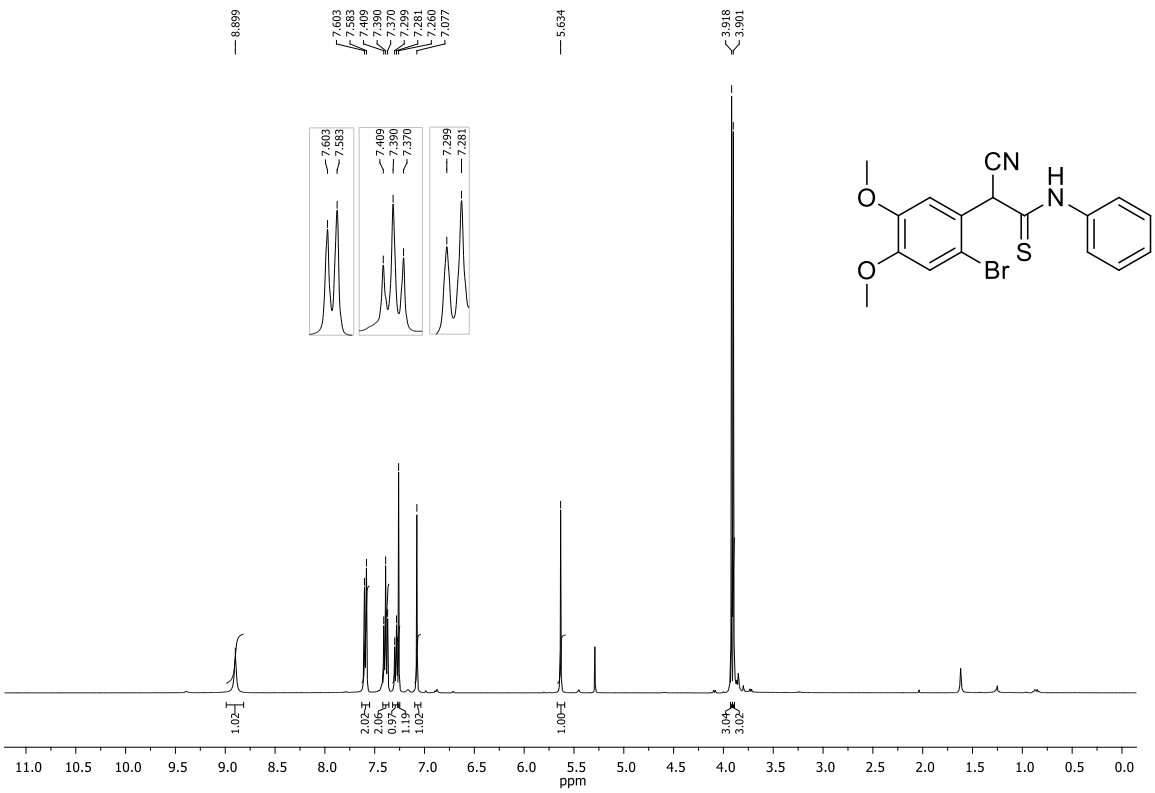



**Figure 3.9a**: $^{1}$H NMR Spectrum of **28k**

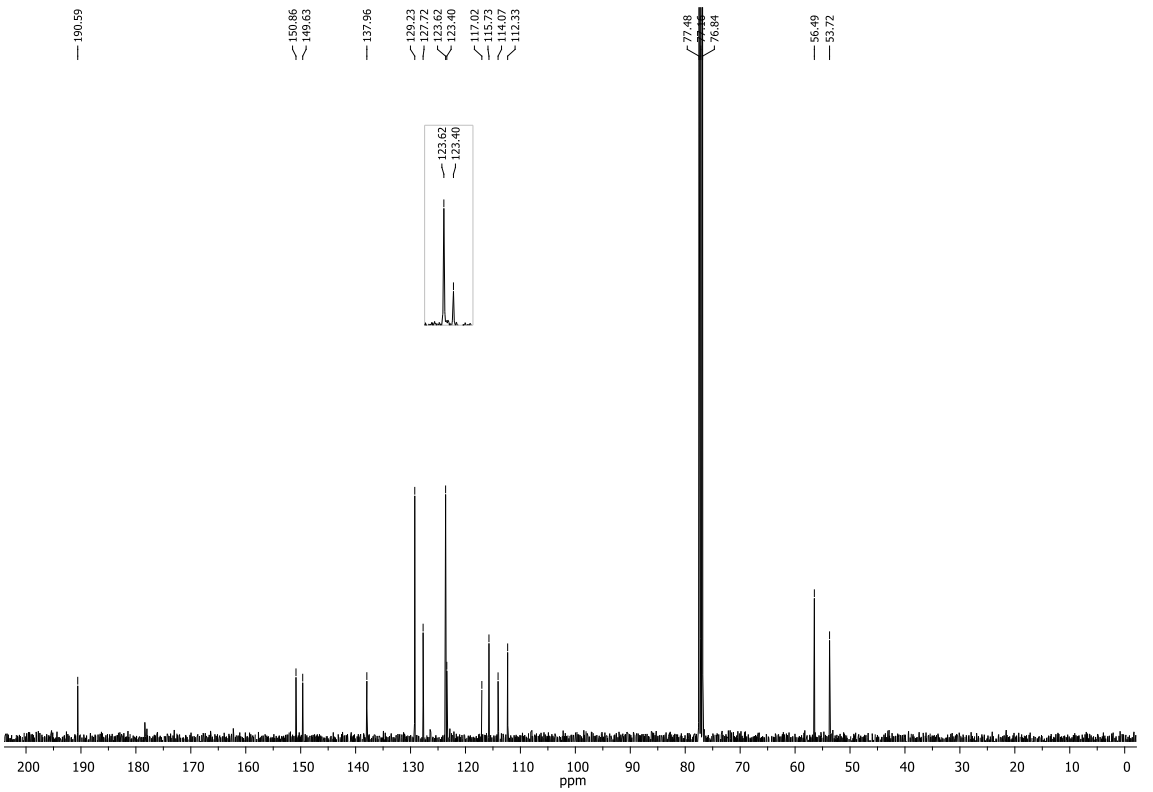



**Figure 3.9b**: $^{13}$C NMR Spectrum of **28k**

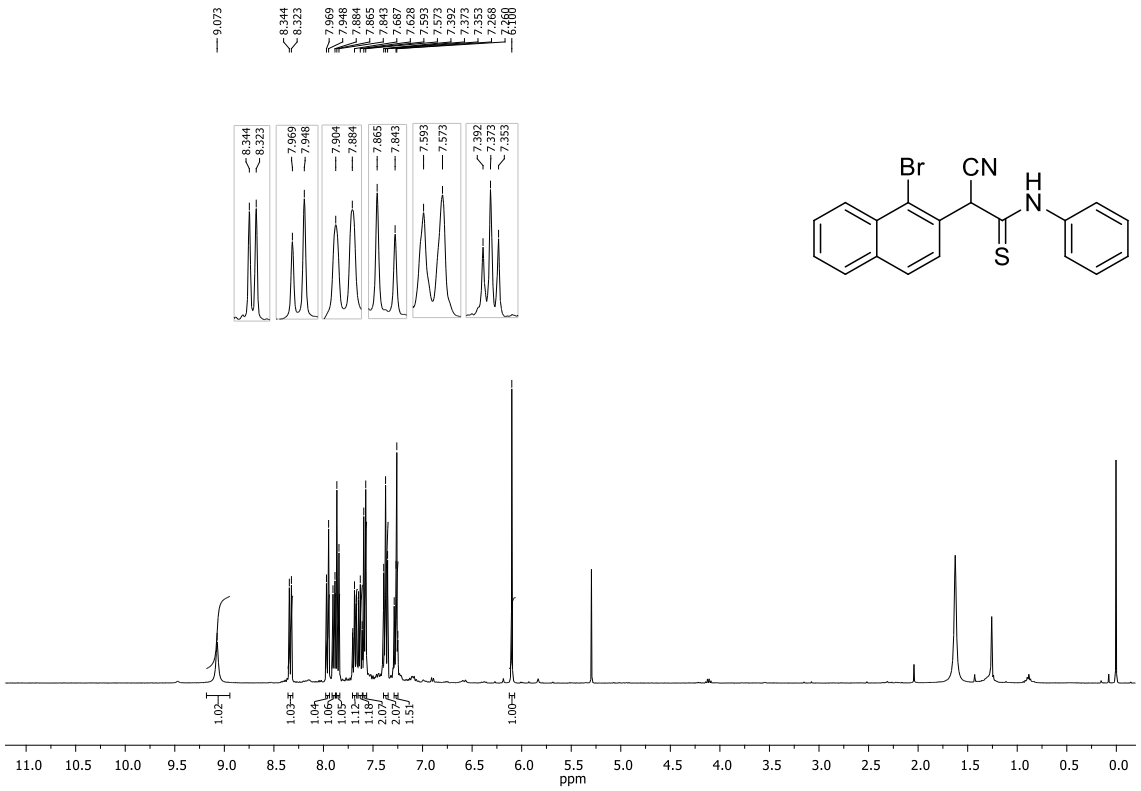



**Figure 3.10a**: $^{1}$H NMR Spectrum of **28n**

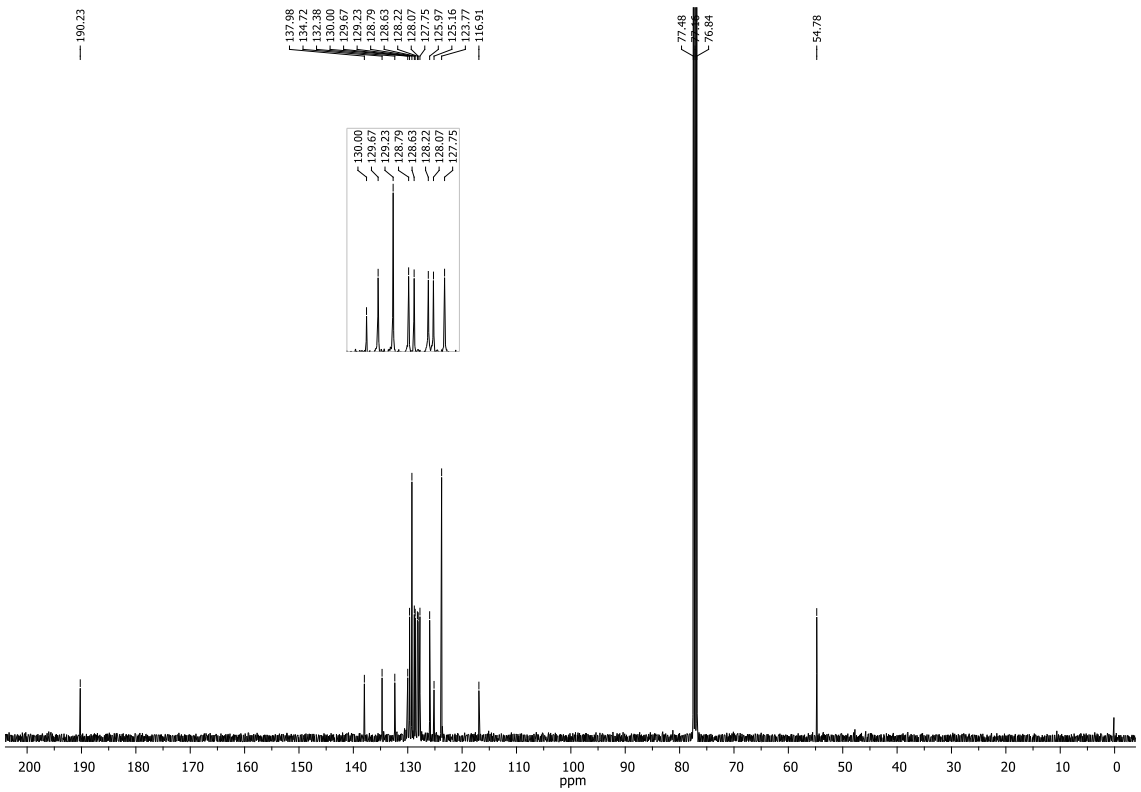



**Figure 3.10b**: $^{13}$C NMR Spectrum of **28n**

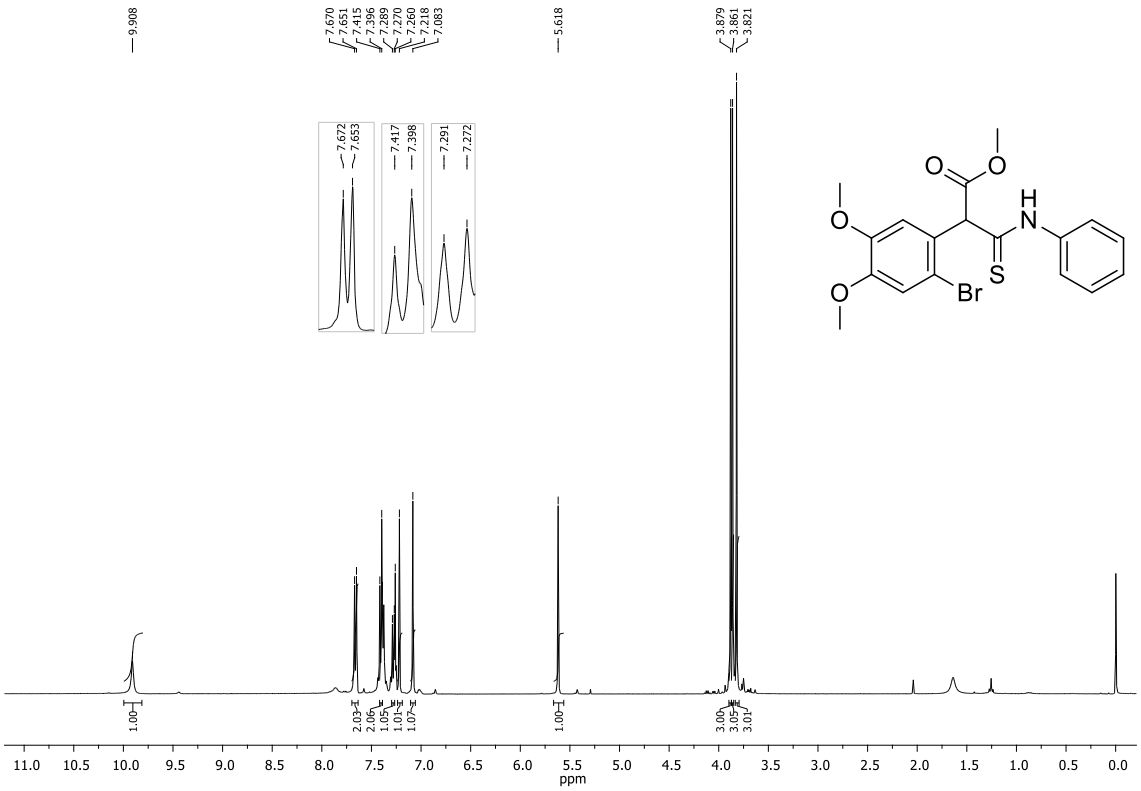



**Figure 3.11a**: $^{1}$H NMR Spectrum of **38a**

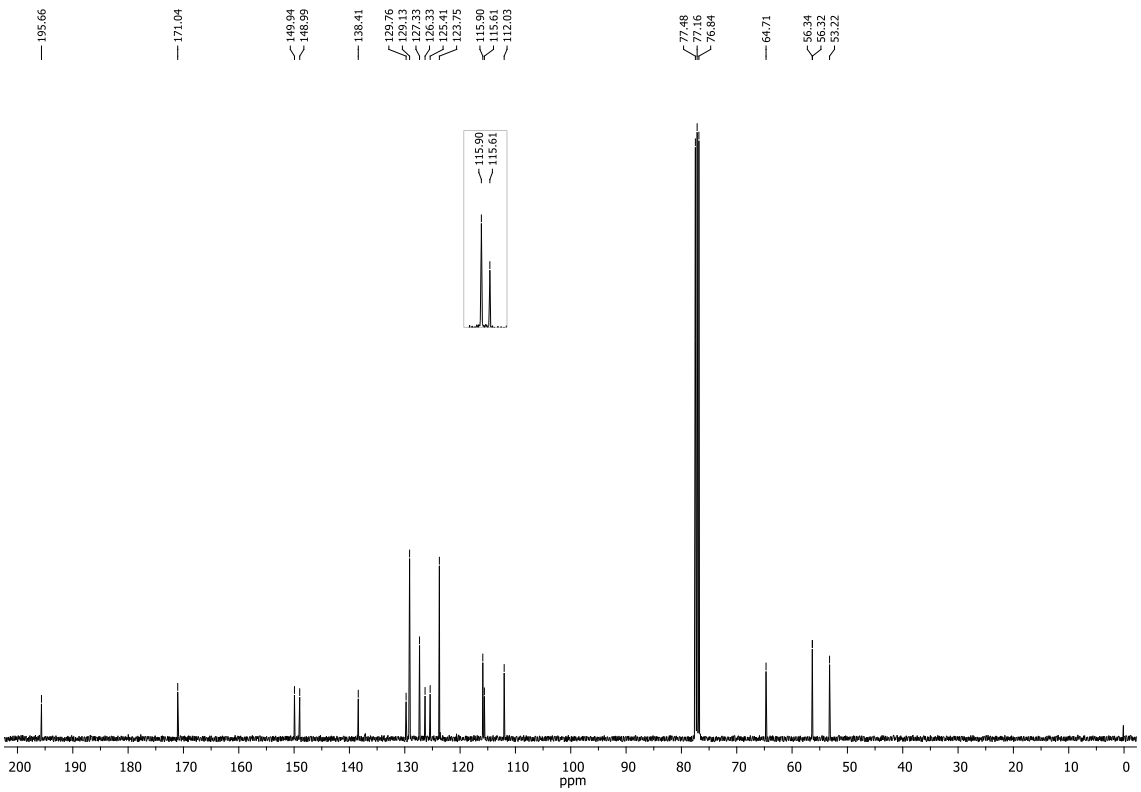



**Figure 3.11b**: $^{13}$C NMR Spectrum of **38a**

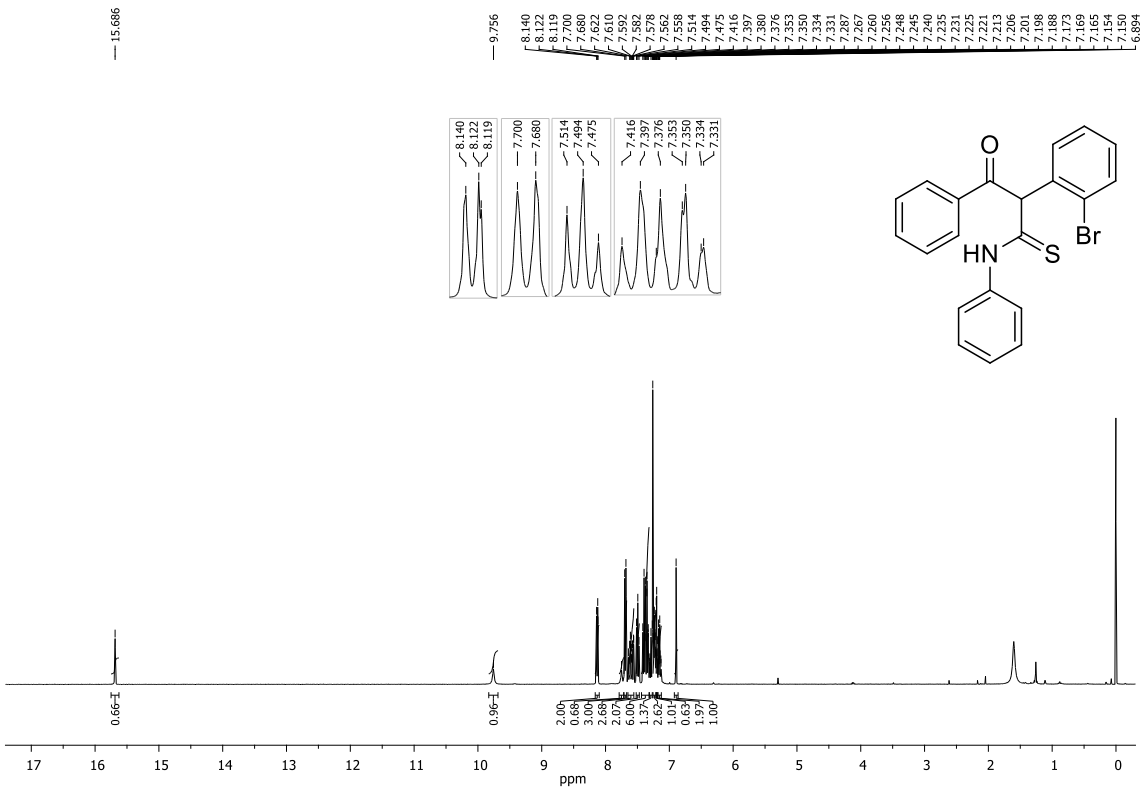



**Figure 3.12a**: $^{1}$H NMR Spectrum of **45a**

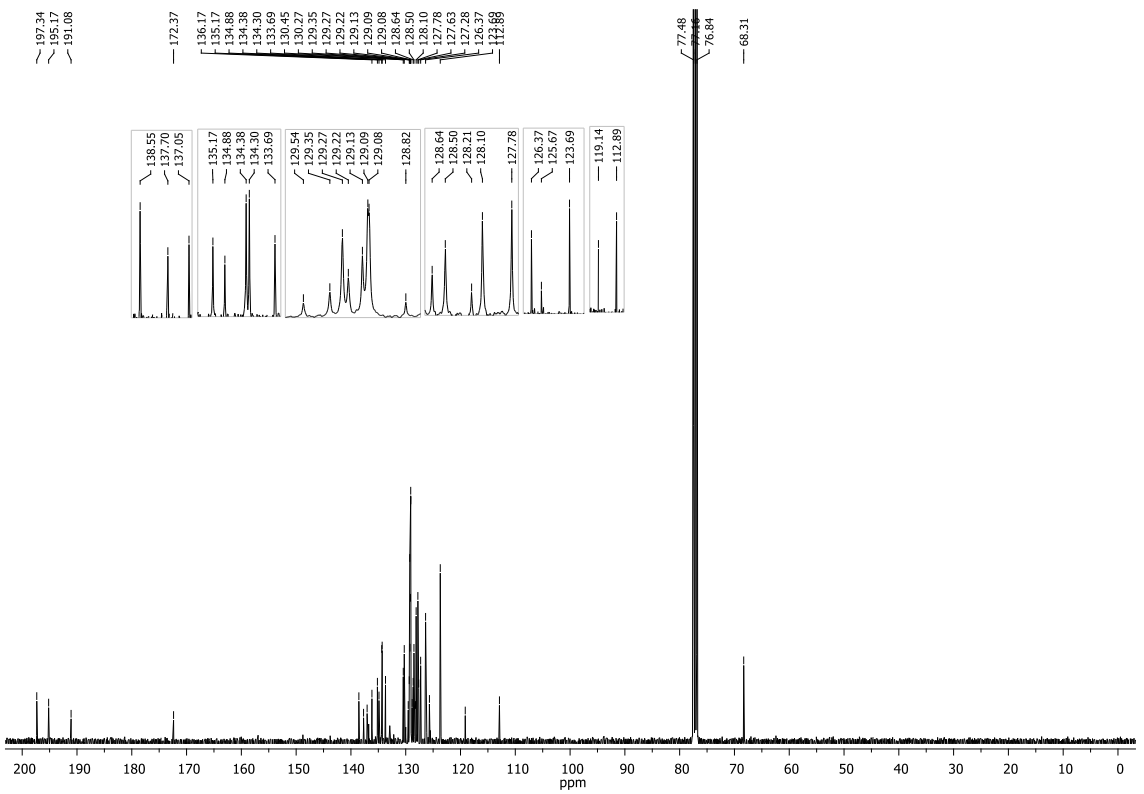



**Figure 3.12b**: $^{13}$C NMR Spectrum of **45a**

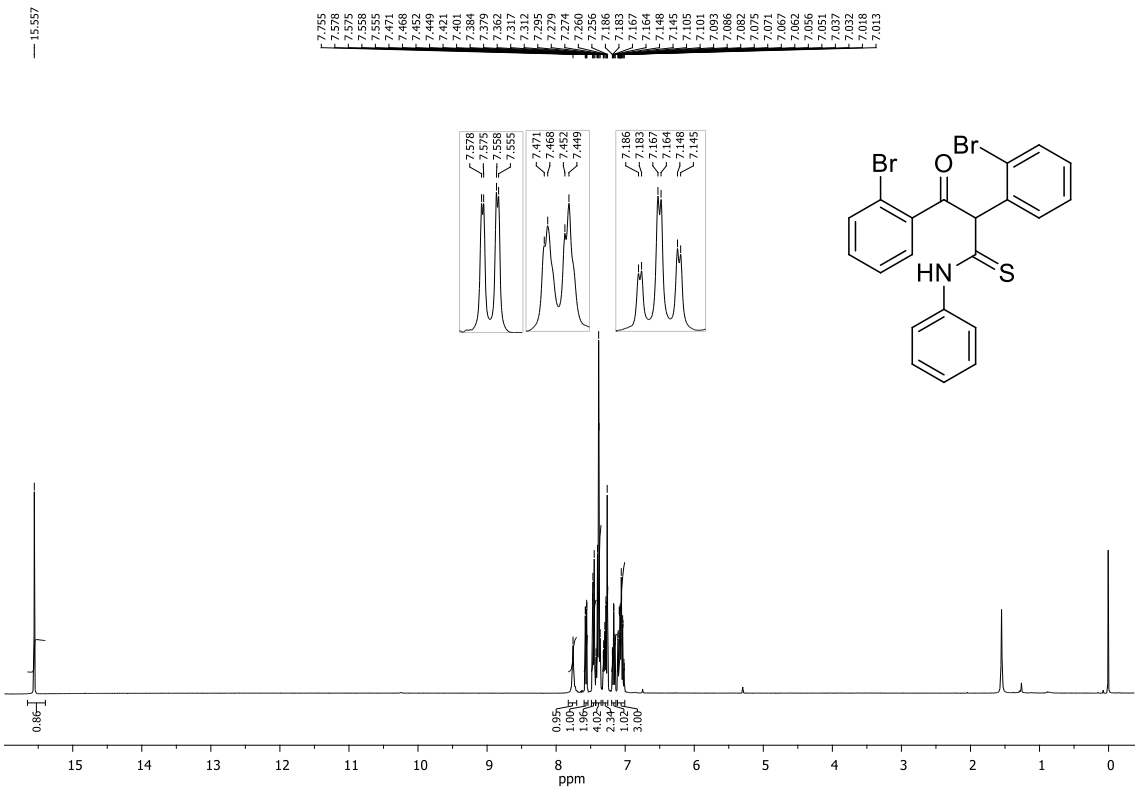



**Figure 3.13a**: $^{1}$H NMR Spectrum of **47a**

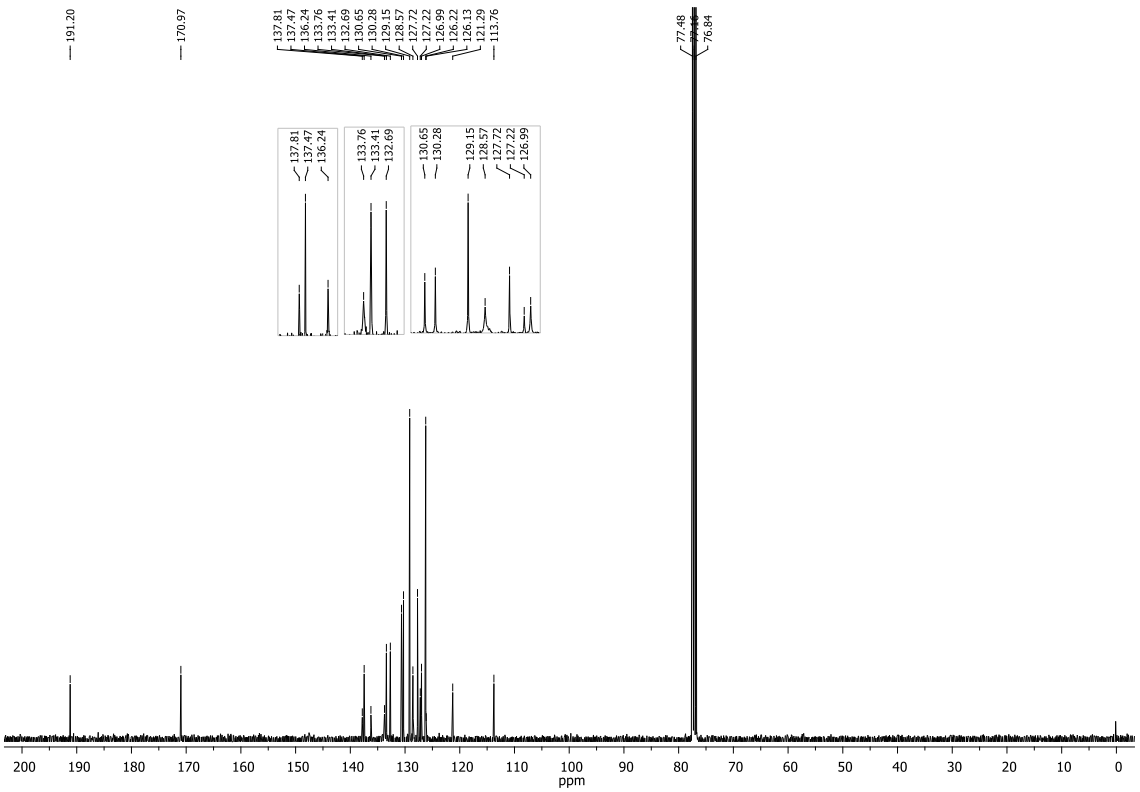



**Figure 3.13b**: $^{13}$C NMR Spectrum of **47a**

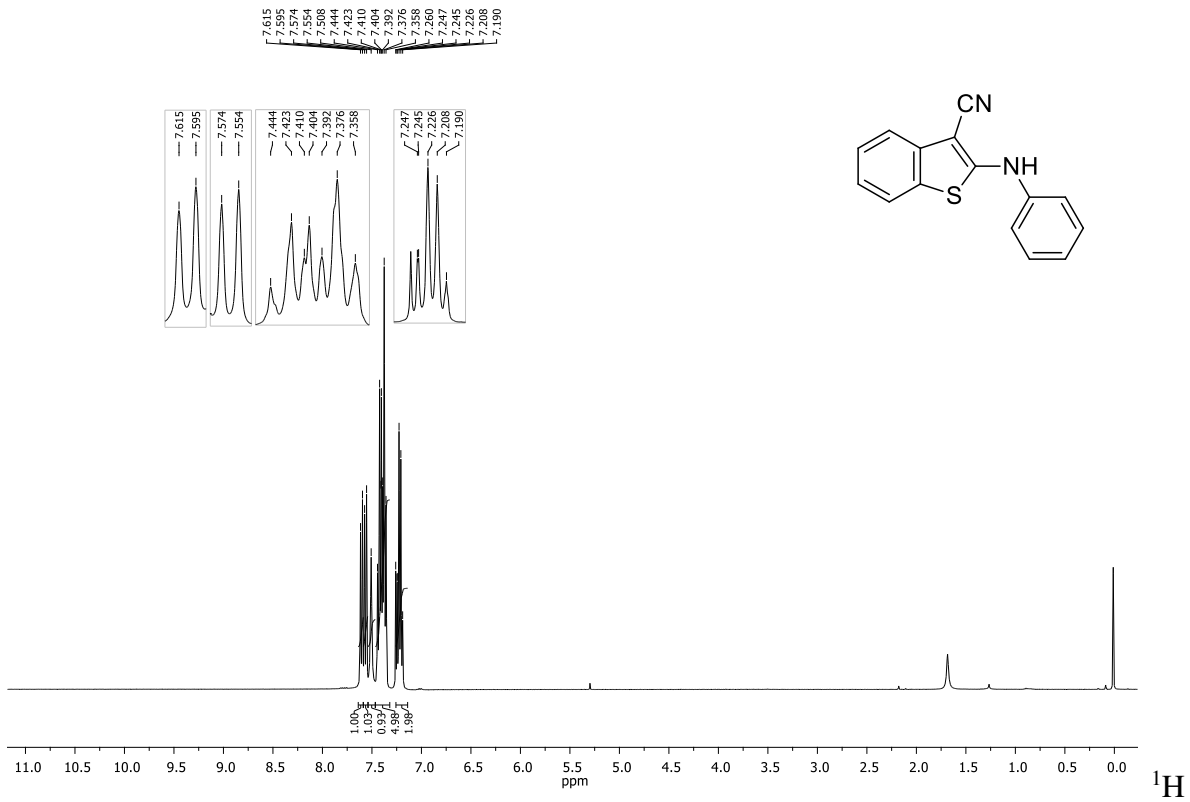



**Figure 3.14a**: $^1$H NMR Spectrum of **29a**

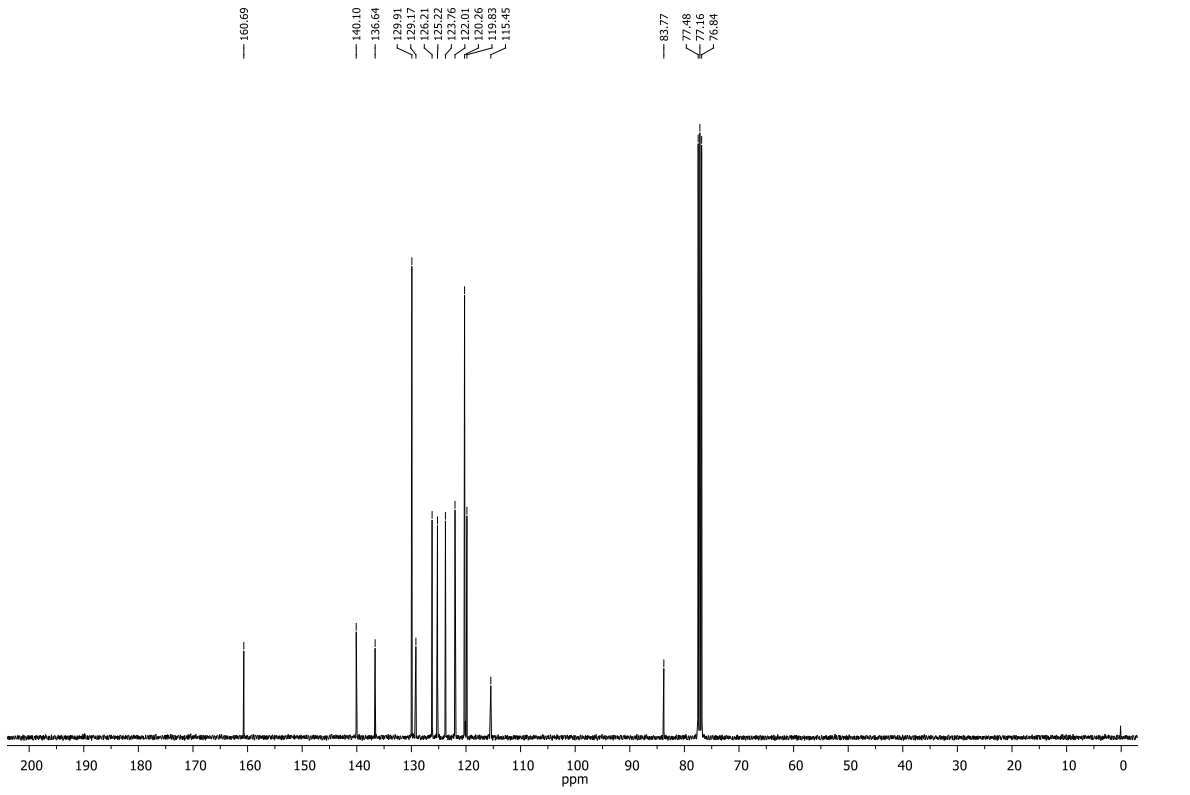



**Figure 3.14b**: $^{13}$C NMR Spectrum of **29a**

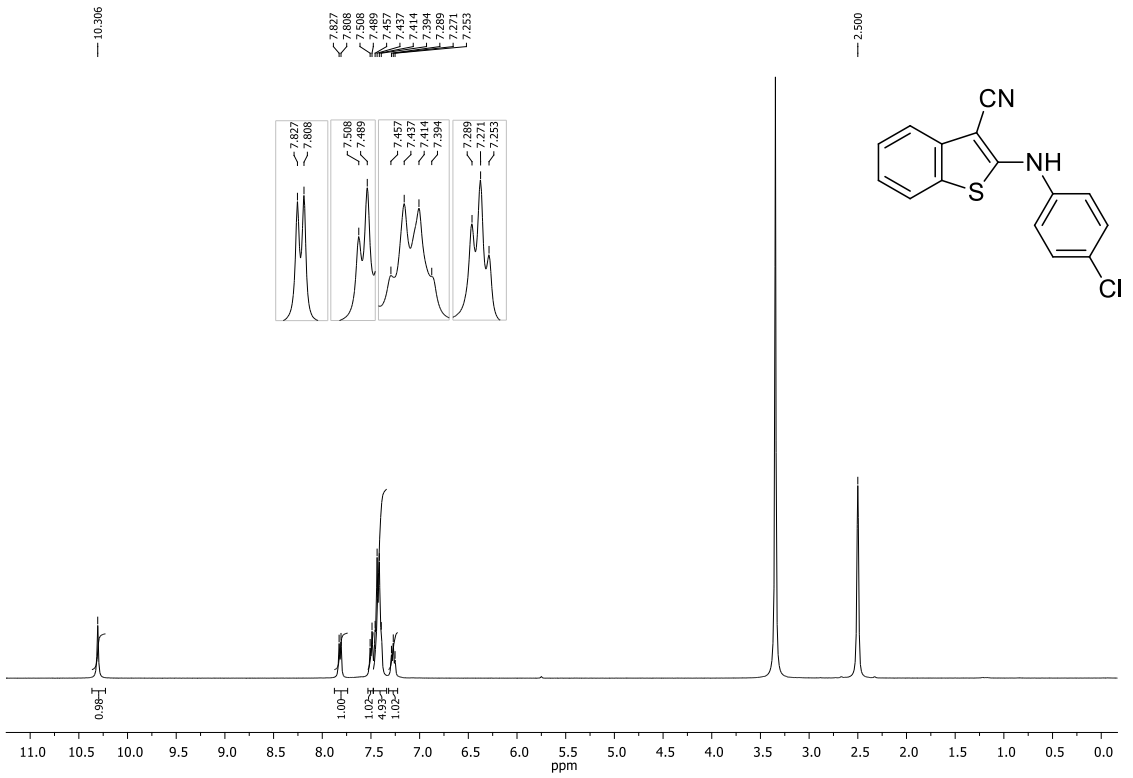



**Figure 3.15a**: $^{1}$H NMR Spectrum of **29e**

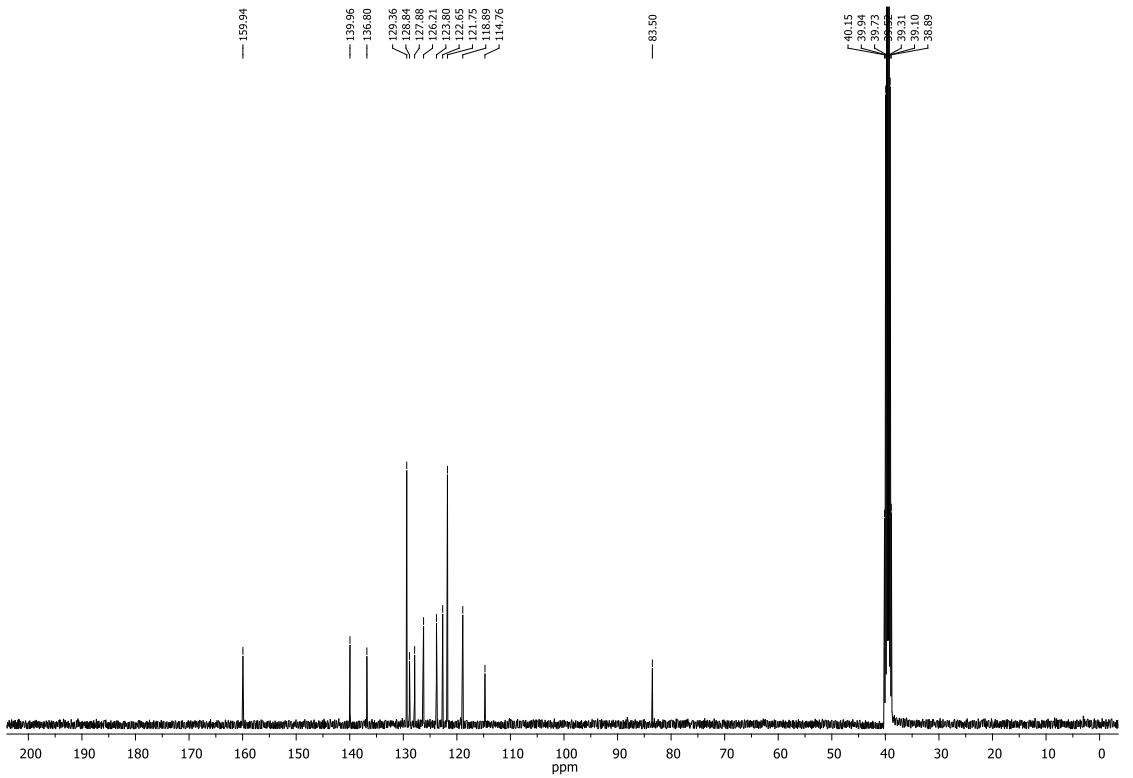



**Figure 3.15b**: $^{13}$C NMR Spectrum of **29e**

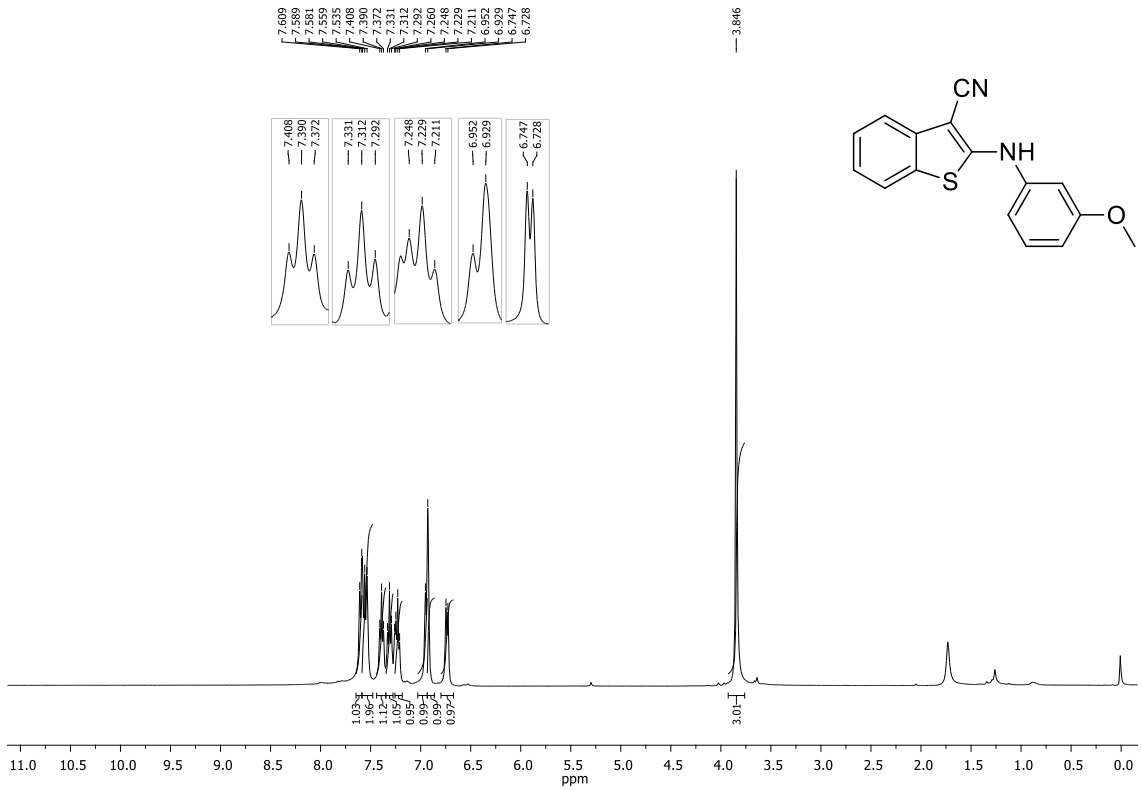



**Figure 3.16a**: $^{1}$H NMR Spectrum of **29f**

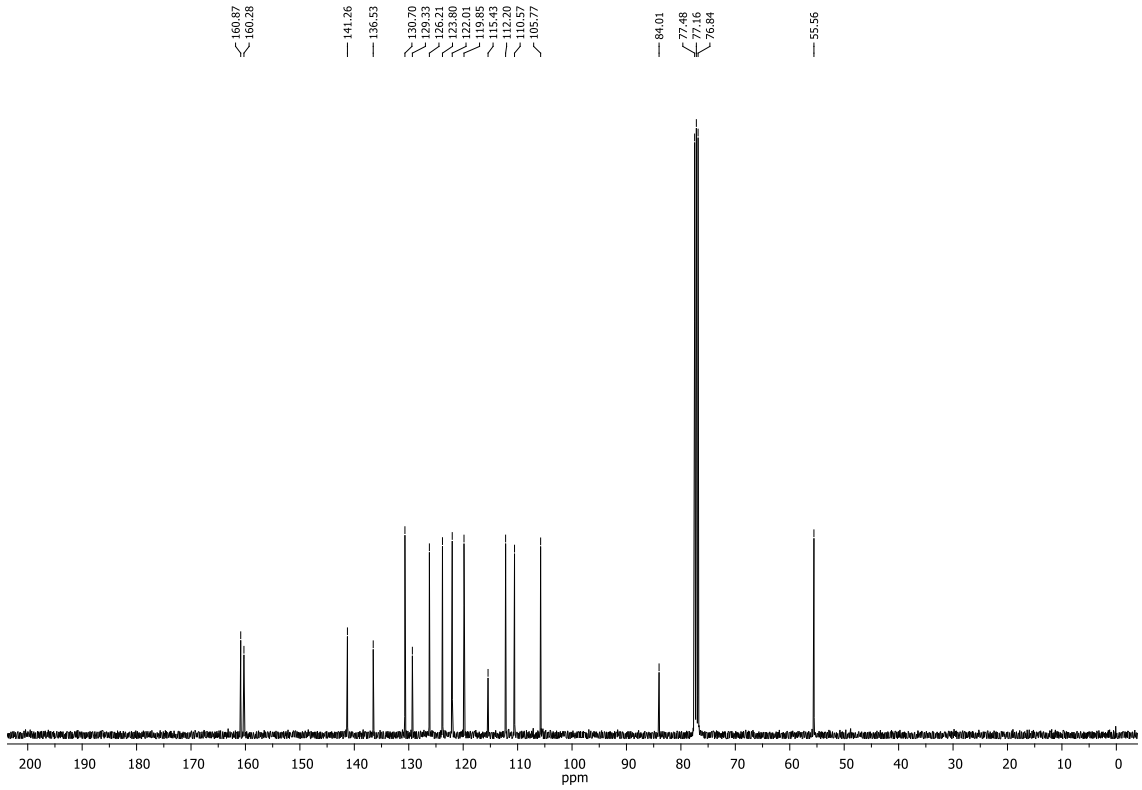



**Figure 3.16b**: $^{13}$C NMR Spectrum of **29f**

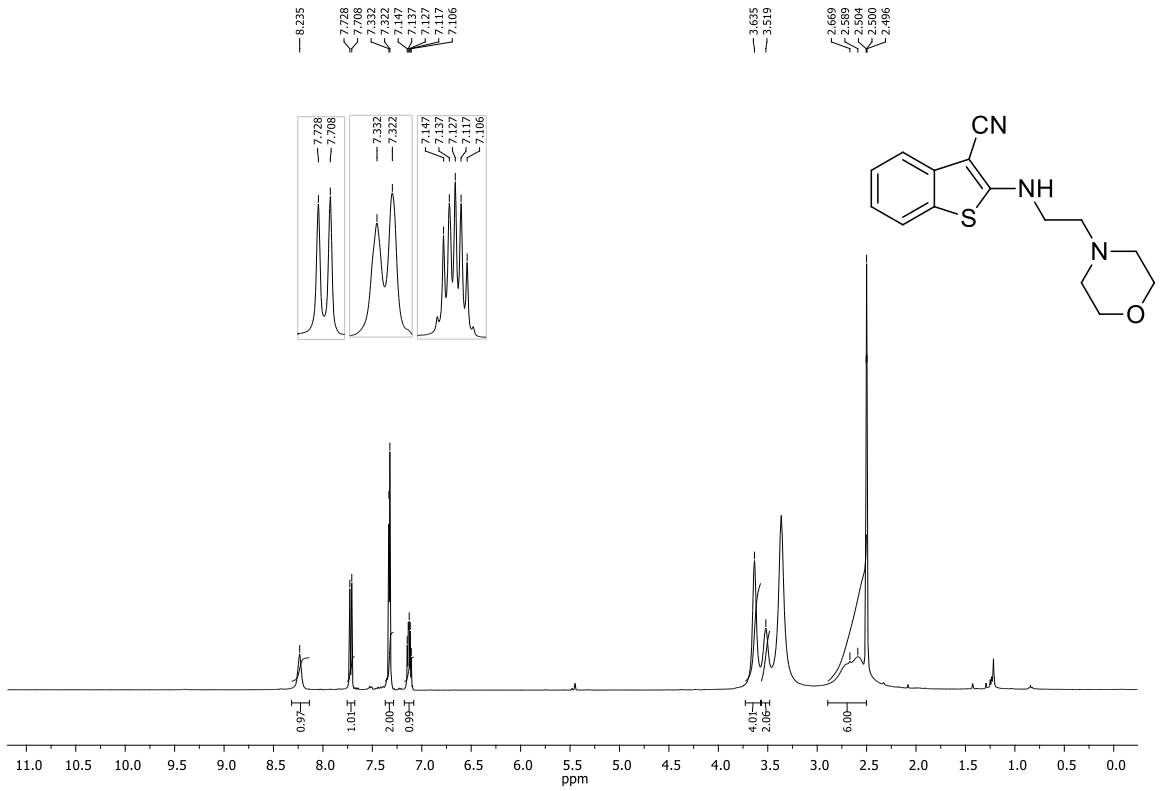



**Figure 3.17a**: $^{1}$H NMR Spectrum of **29h**

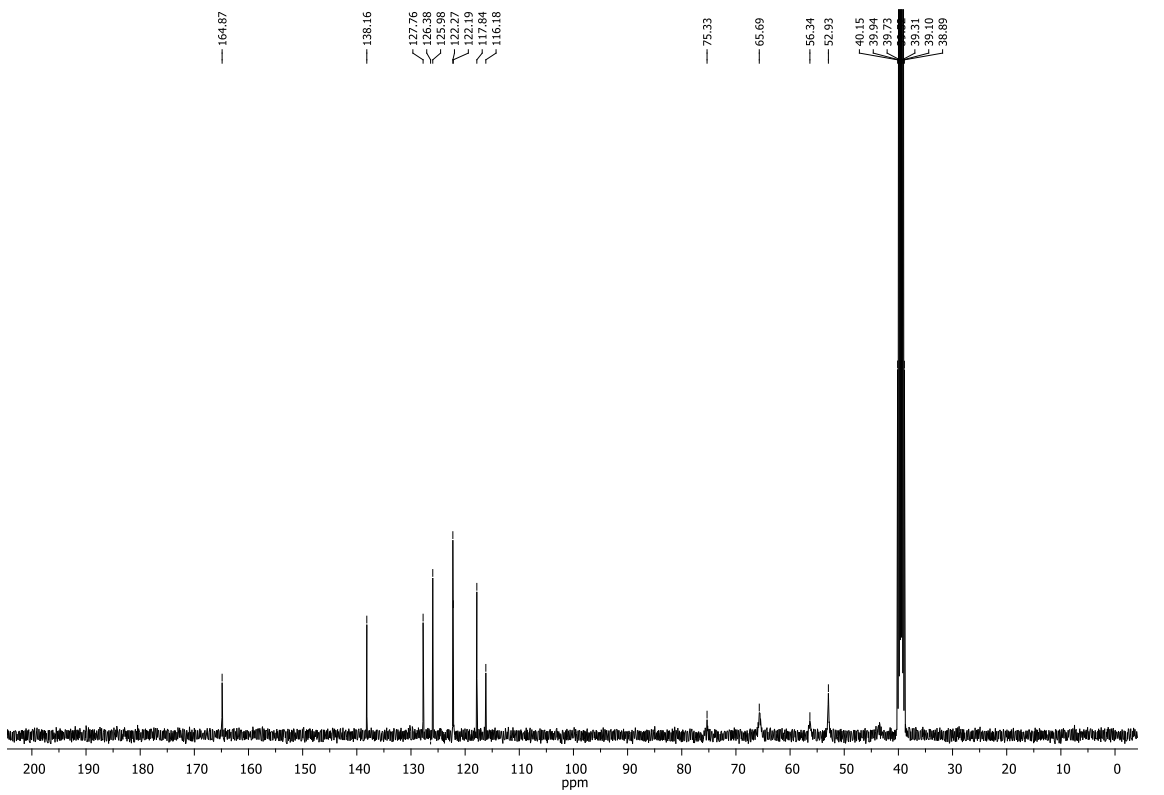



**Figure 3.17b**: $^{13}$C NMR Spectrum of **29h**

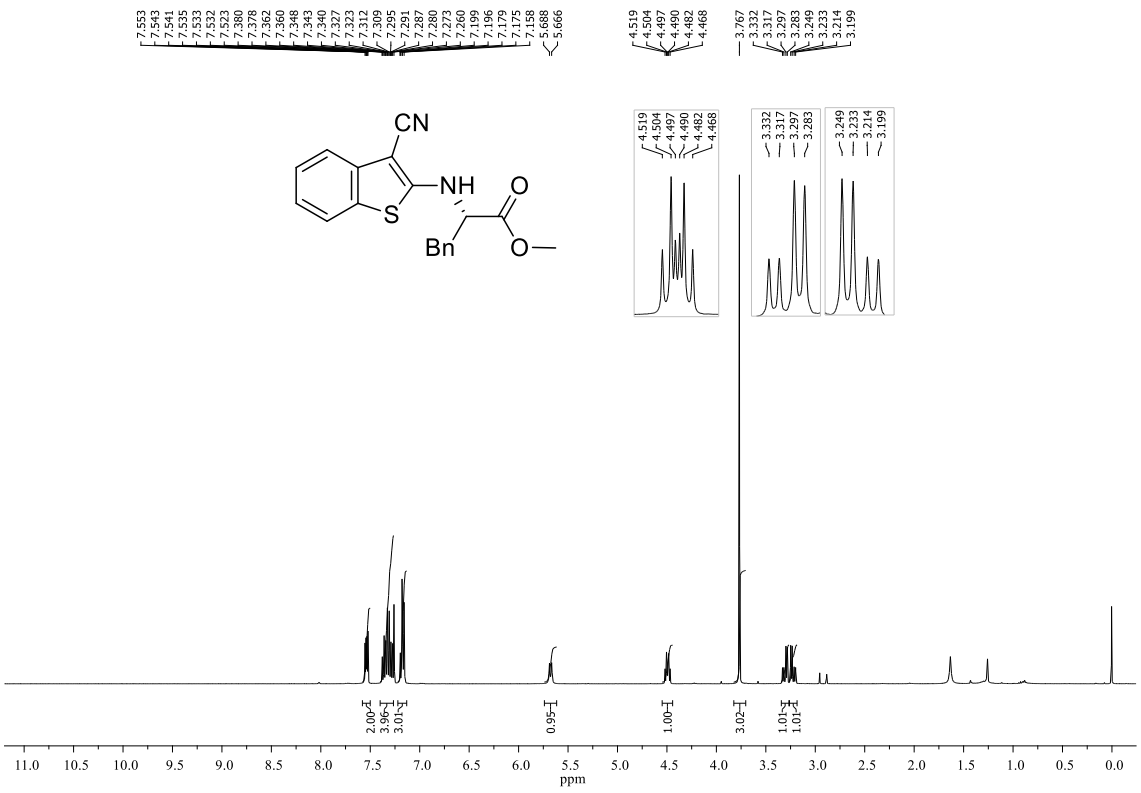



**Figure 3.18a**: $^{1}$H NMR Spectrum of **29i**

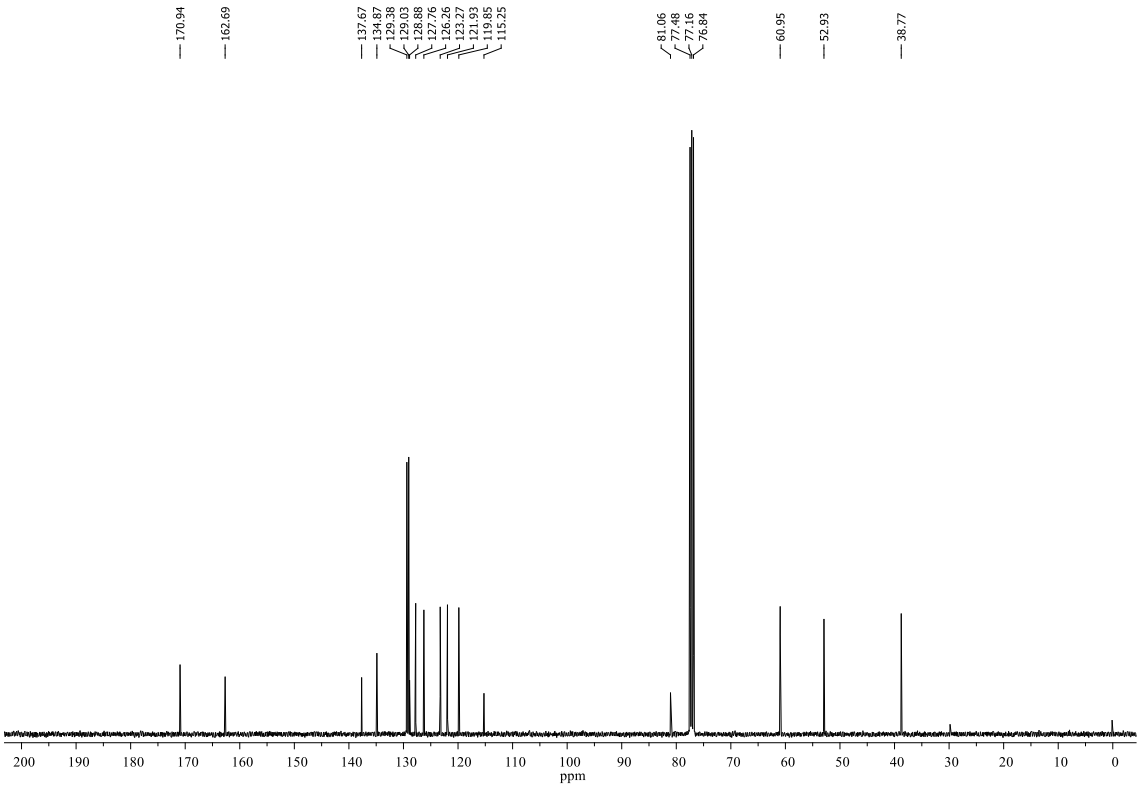



**Figure 3.18b**: $^{13}$C NMR Spectrum of **29i**

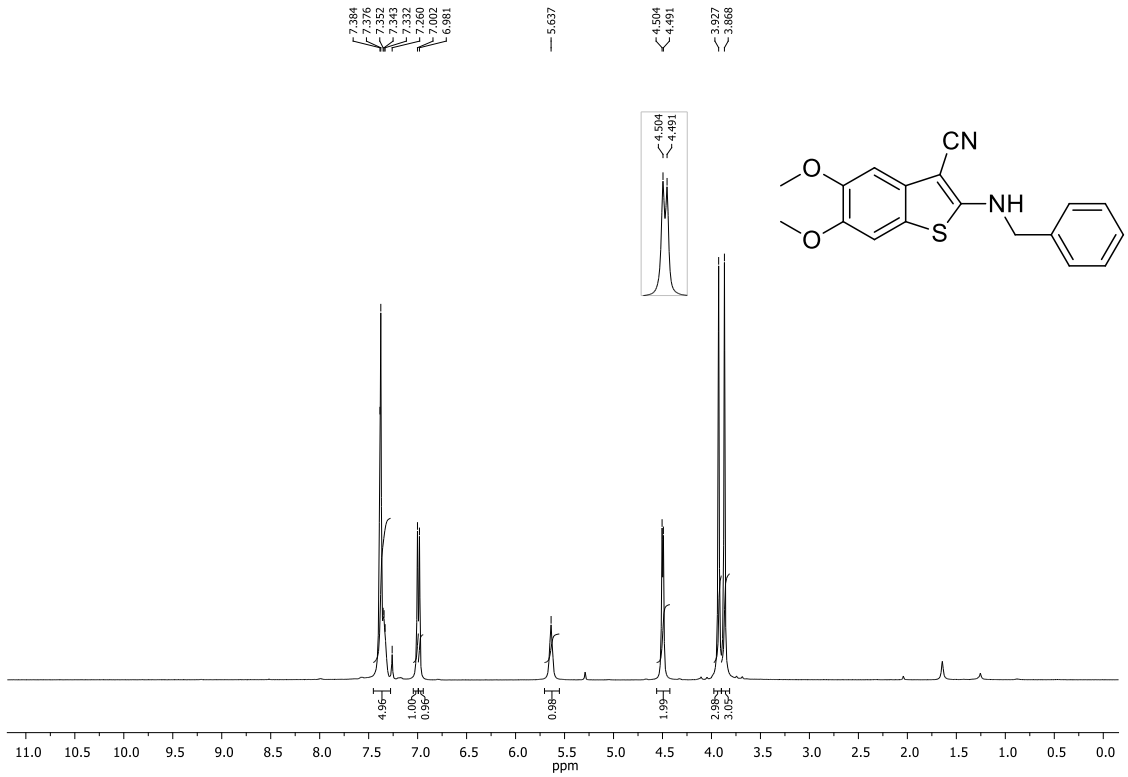



**Figure 3.19a**: $^{1}$H NMR Spectrum of **29j**

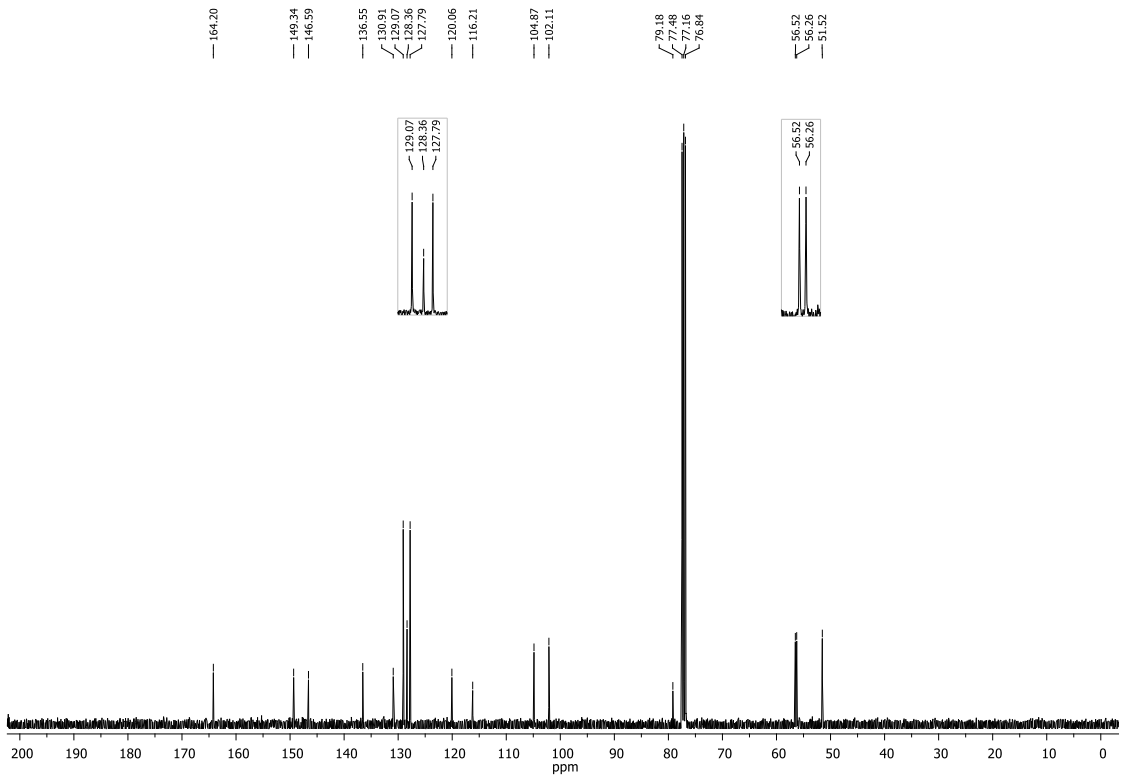



**Figure 3.19b**: $^{13}$C NMR Spectrum of **29j**

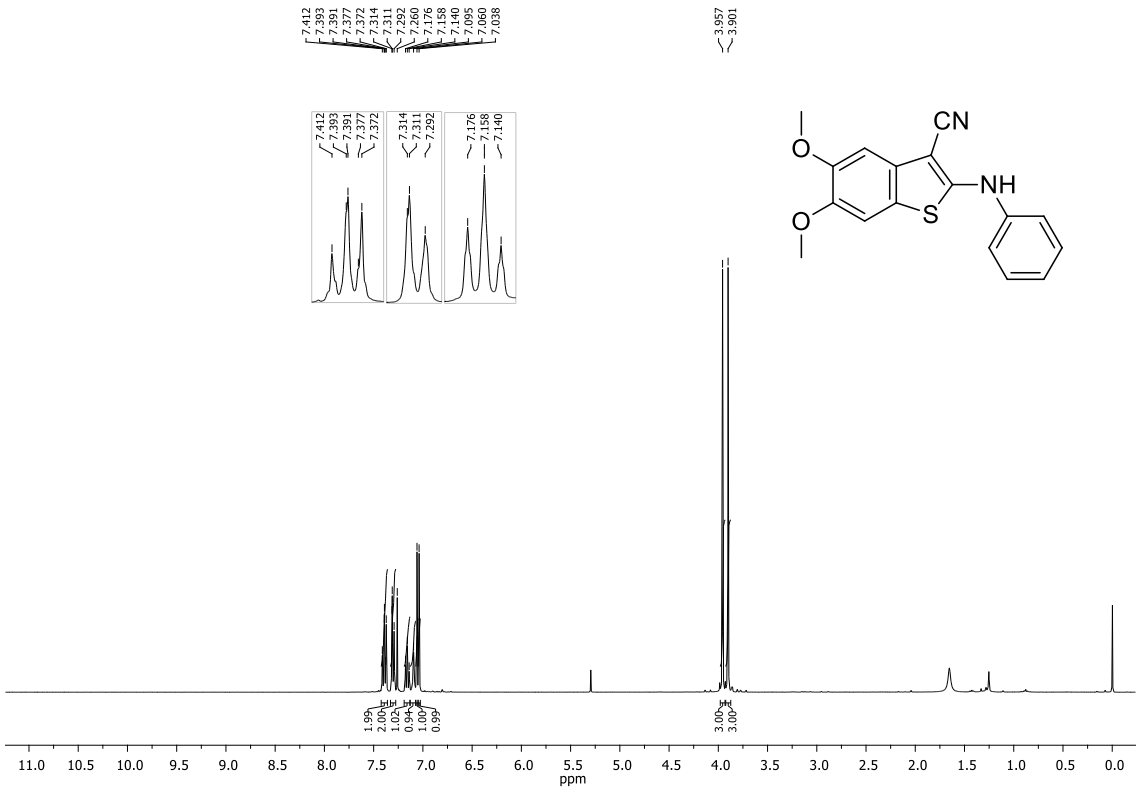



**Figure 3.20a**: $^{1}$H NMR Spectrum of **29k**

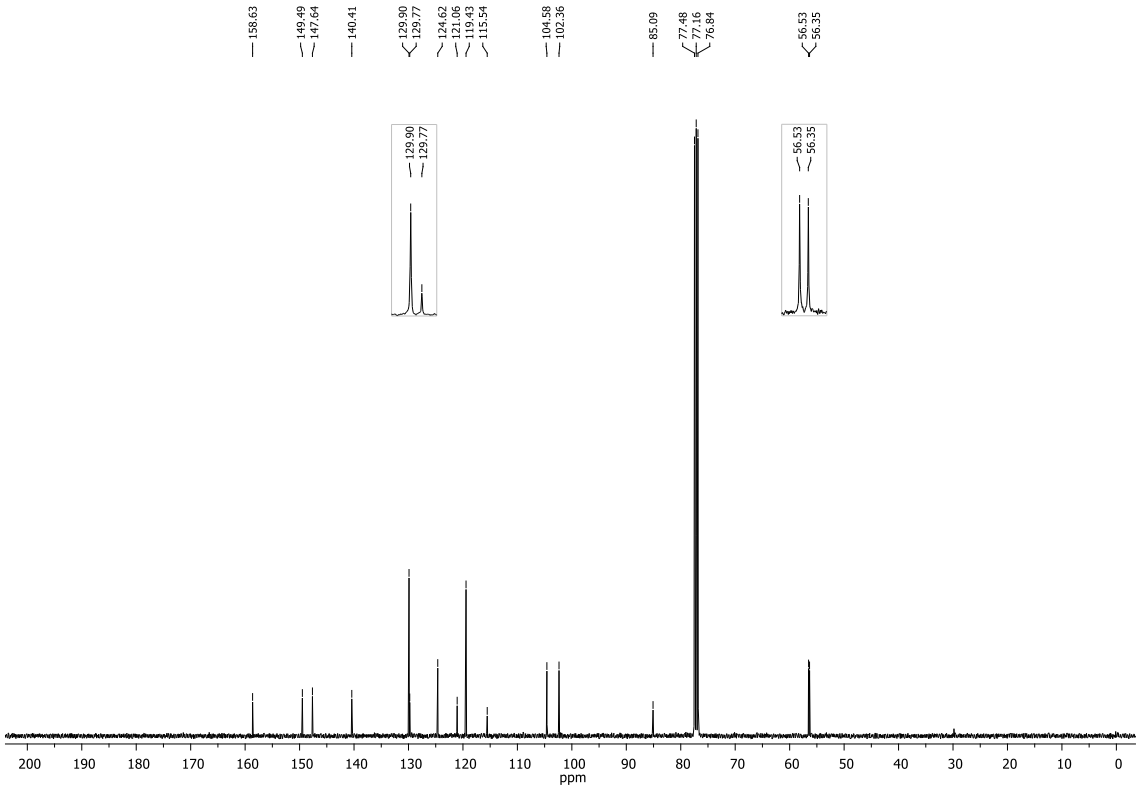



**Figure 3.20b**: $^{13}$C NMR Spectrum of **29k**

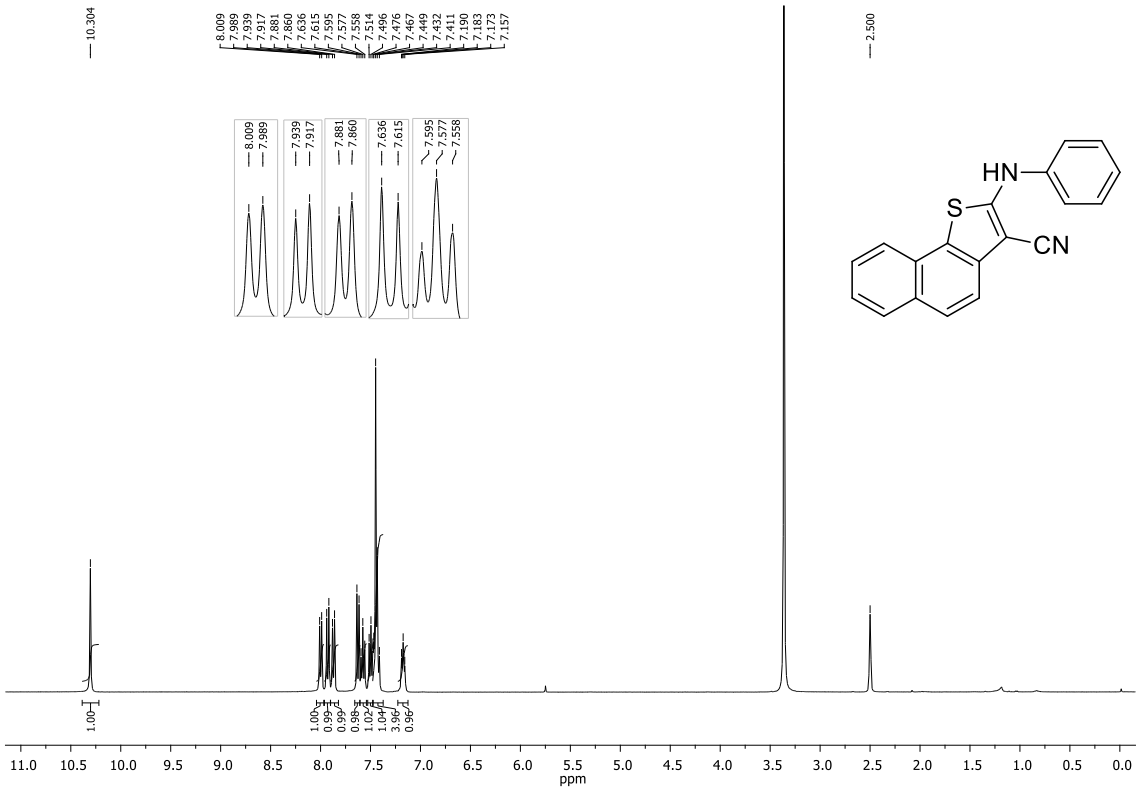



**Figure 3.21a**: $^{1}$H NMR Spectrum of **29n**

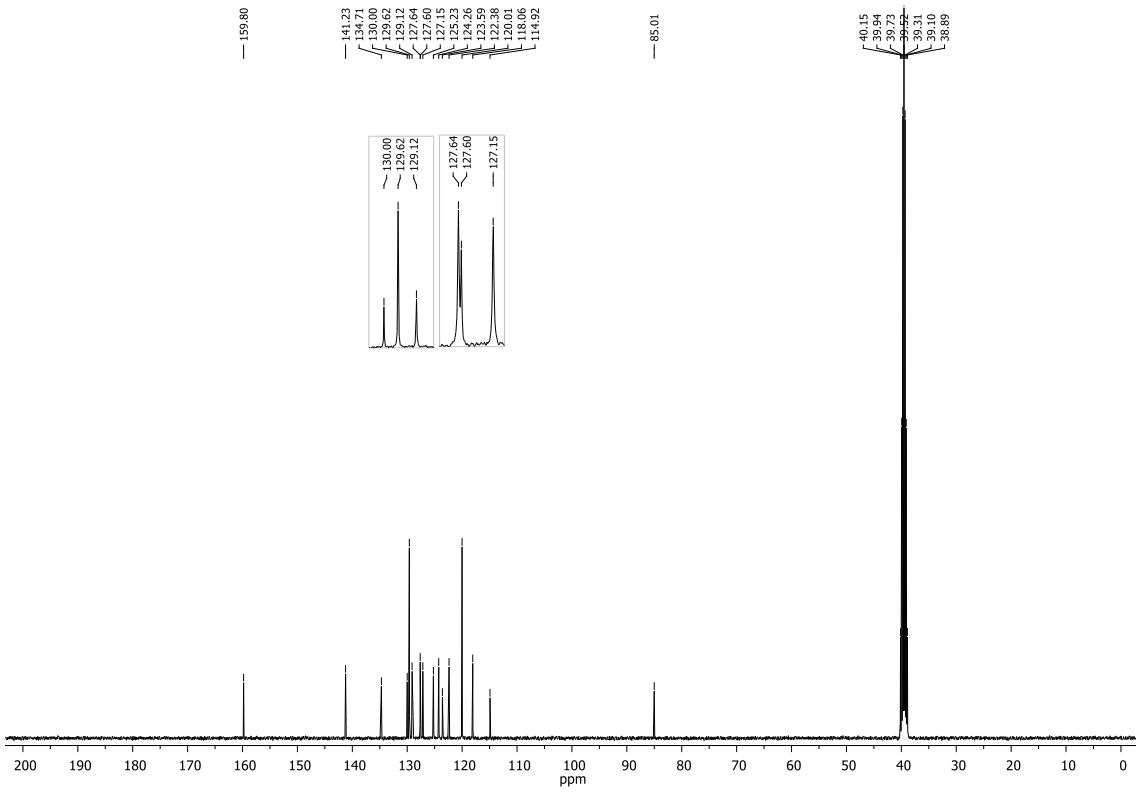



**Figure 3.21b**: $^{13}$C NMR Spectrum of **29n**

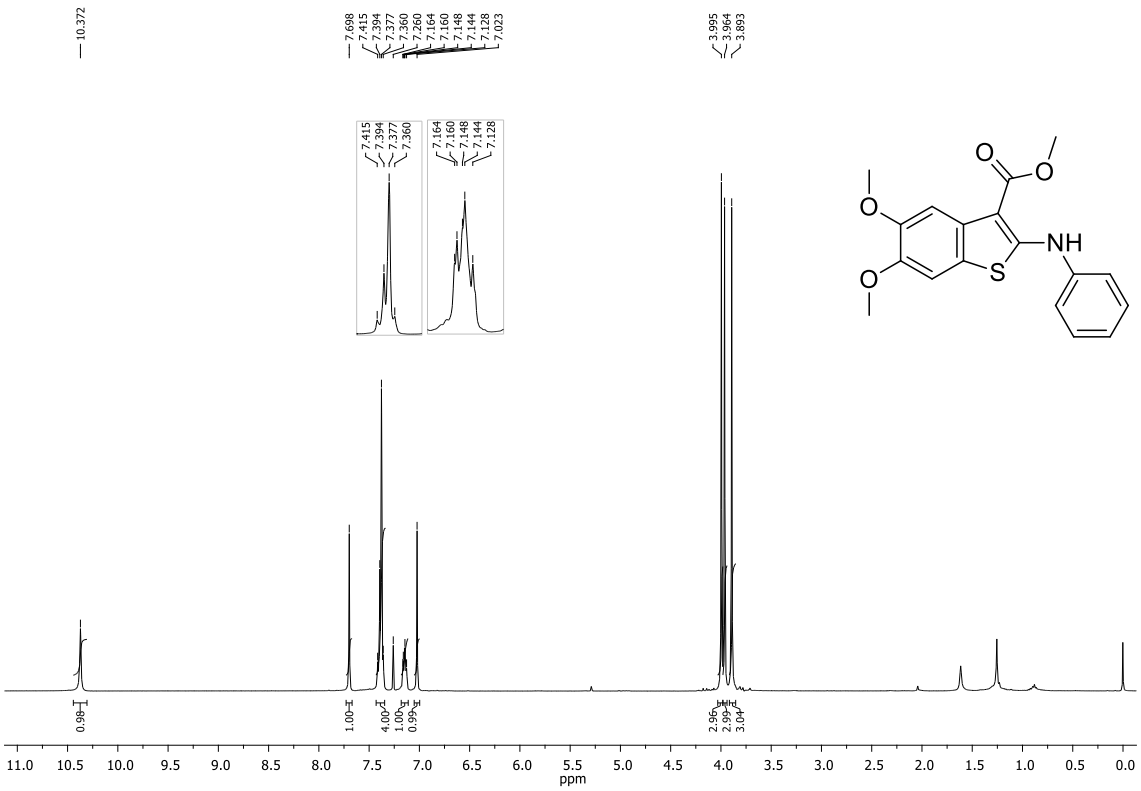



**Figure 3.22a**: $^{1}$H NMR Spectrum of **39a**

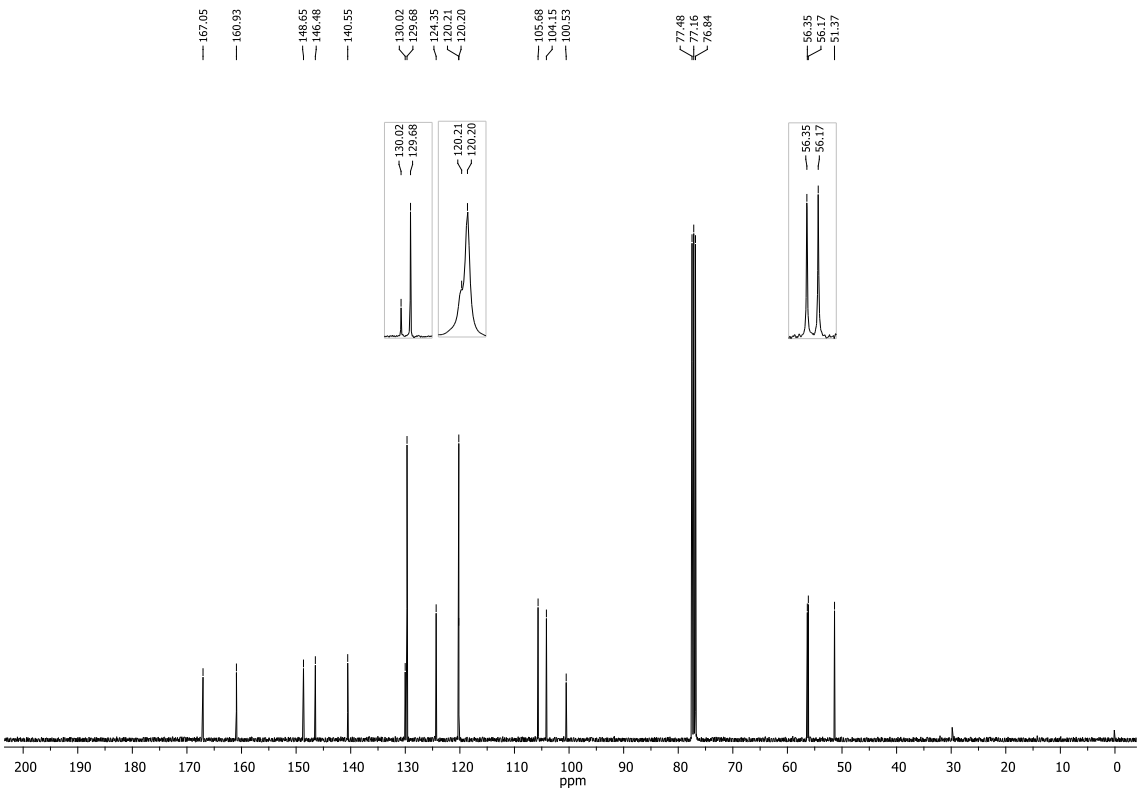
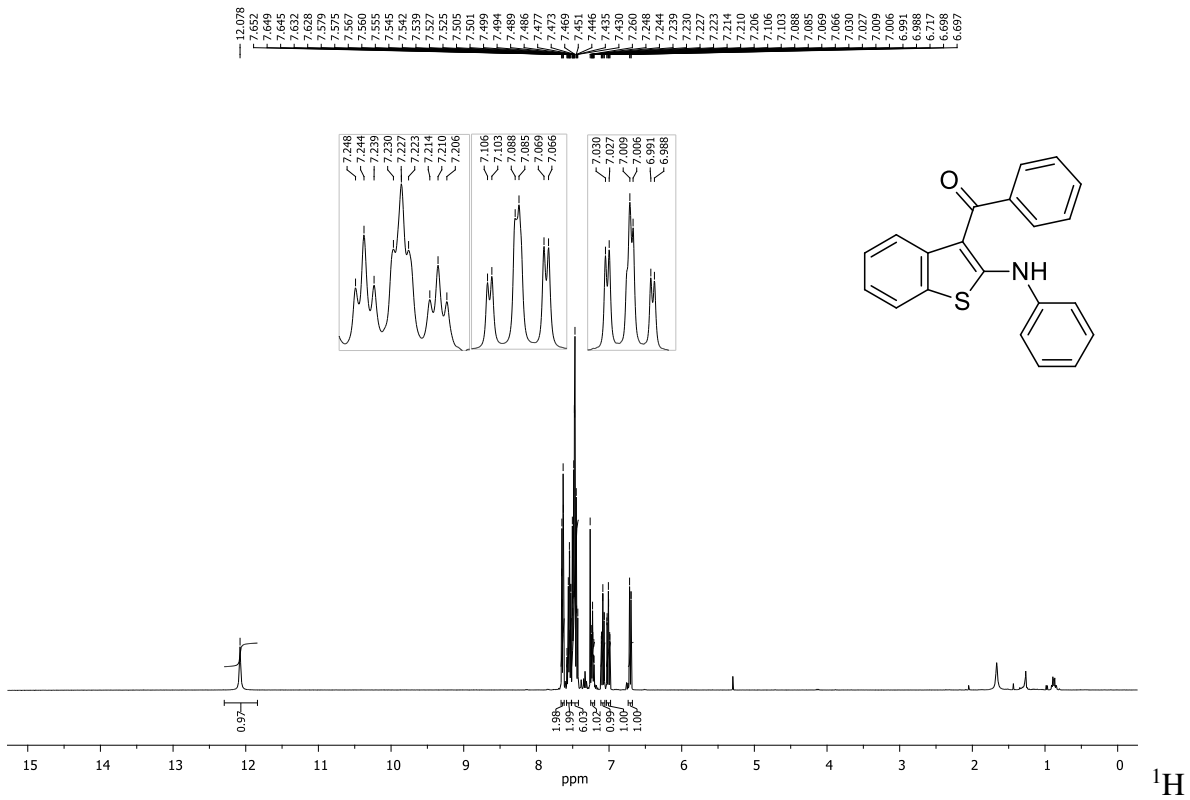



**Figure 3.22b**: $^{13}$C NMR Spectrum of **39a**




$^{1}H$

**Figure 3.23a**: $^{1}$HNMR Spectrum of **46a**

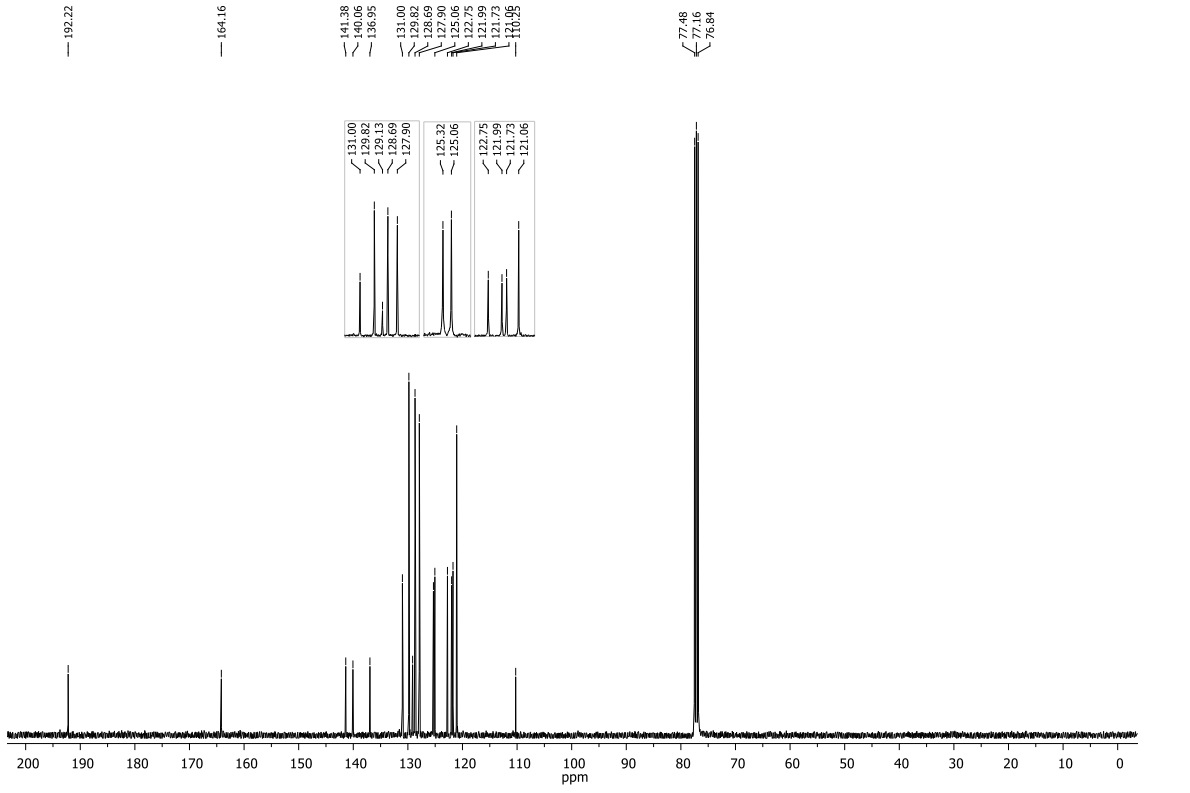



**Figure 3.23b**: $^{13}$C NMR Spectrum of **46a**

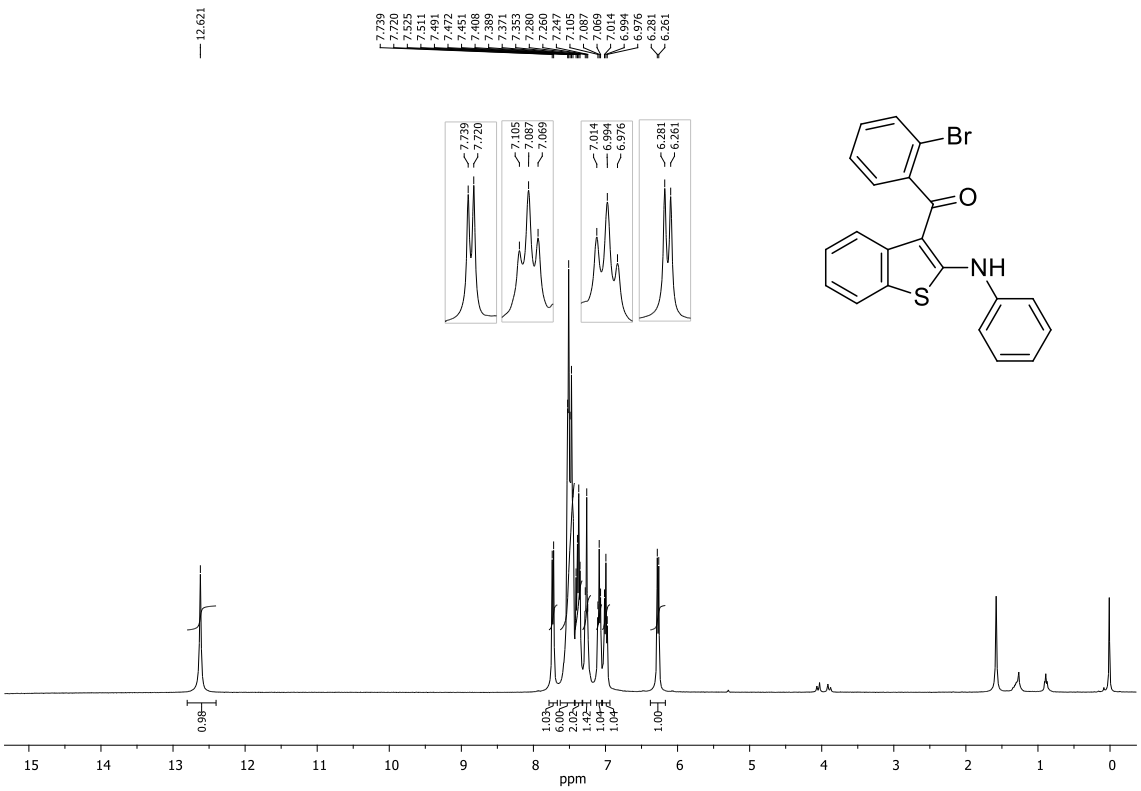



**Figure 3.24a**: $^{1}$H NMR Spectrum of **48a**

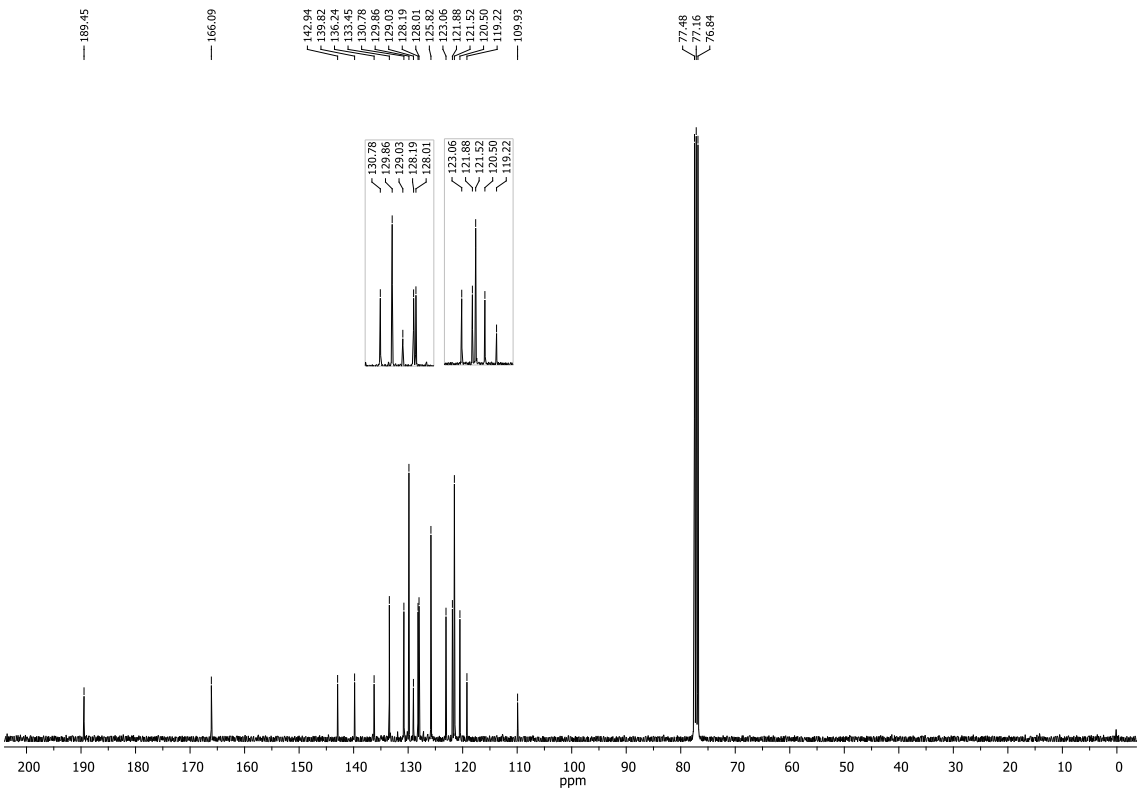



**Figure 3.24b**: $^{13}$C NMR Spectrum of **48a**

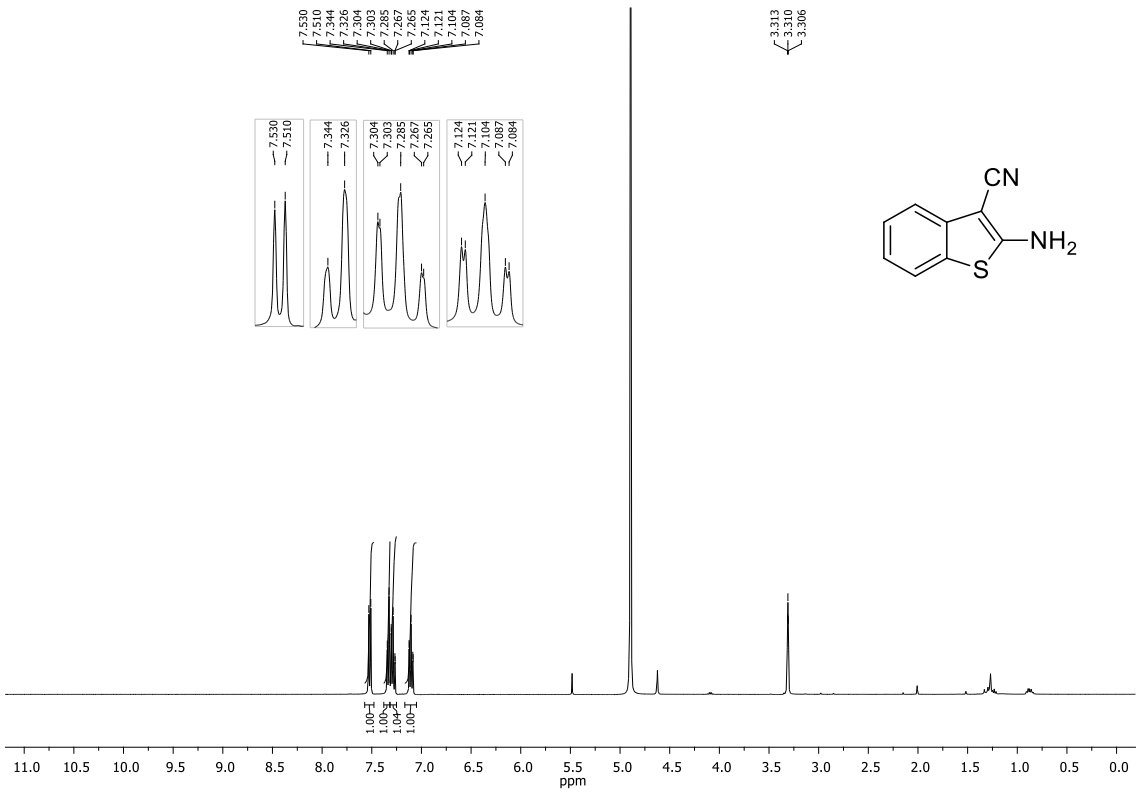



**Figure 3.25a**: $^{1}$H NMR Spectrum of **49**

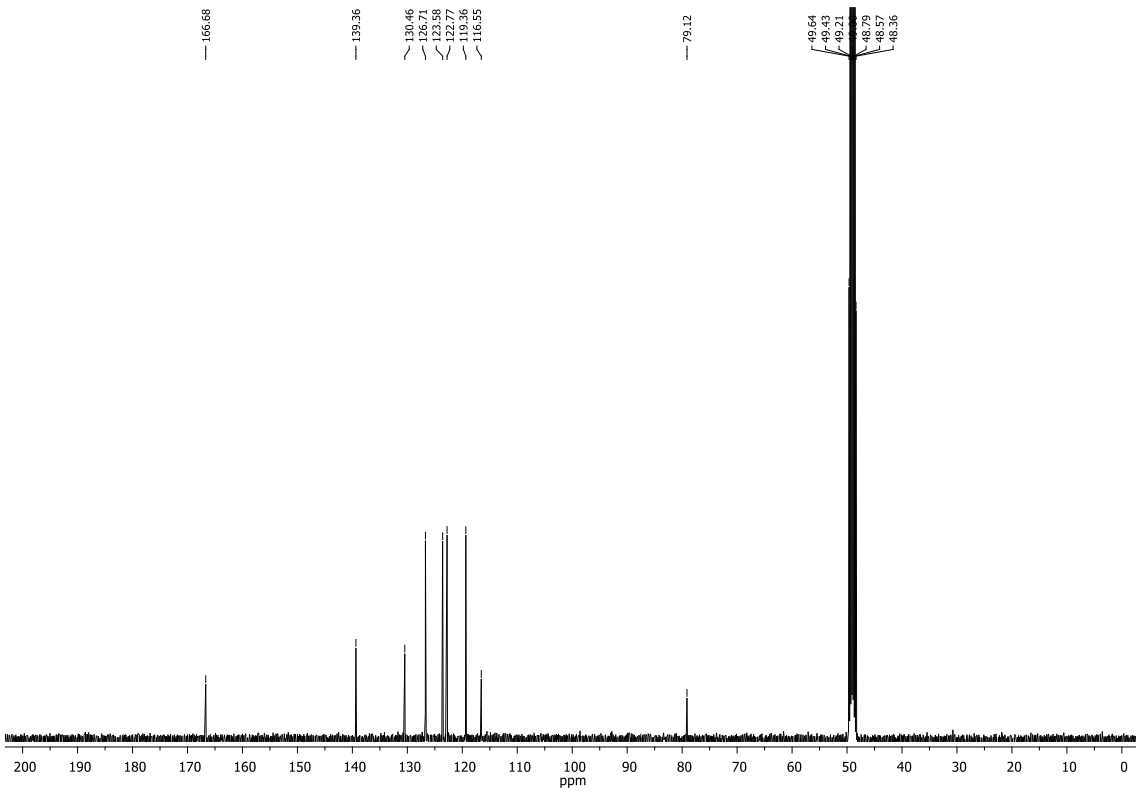



**Figure 3.25b**: $^{13}$C NMR Spectrum of **49**

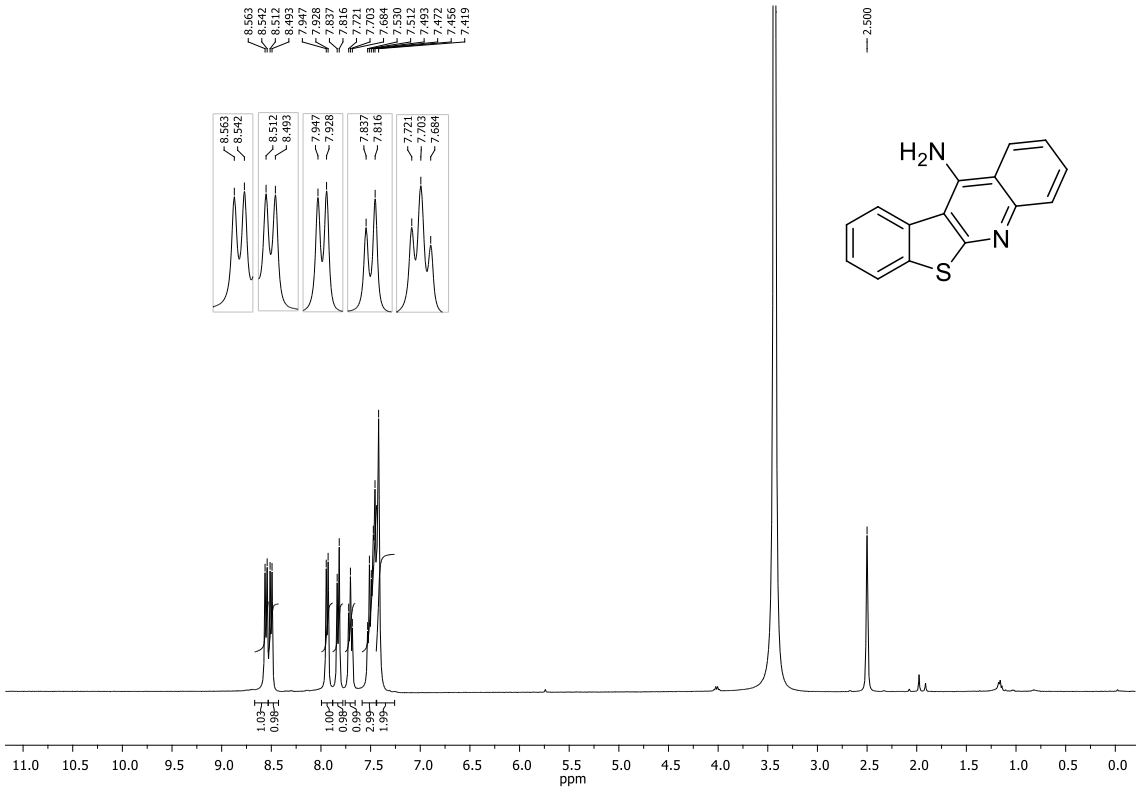



**Figure 3.26a**: $^{1}$H NMR Spectrum of **50a**

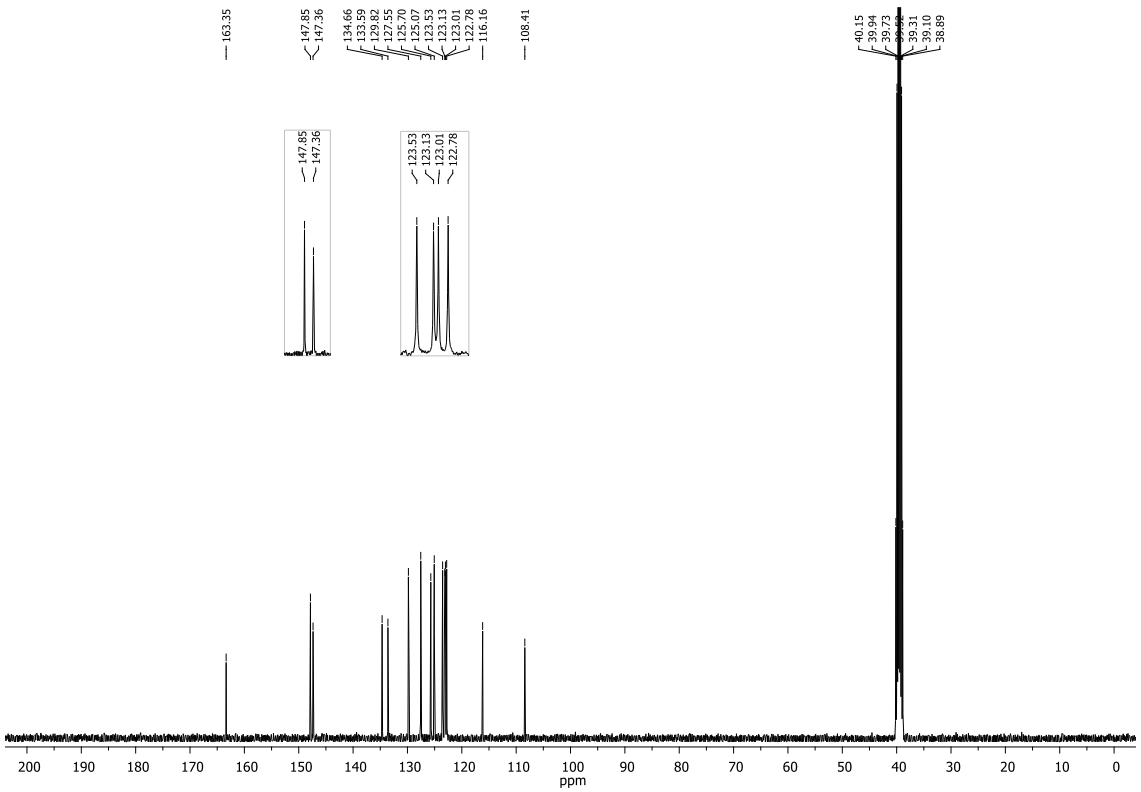



**Figure 3.26b**: $^{13}$C NMR Spectrum of **50a**

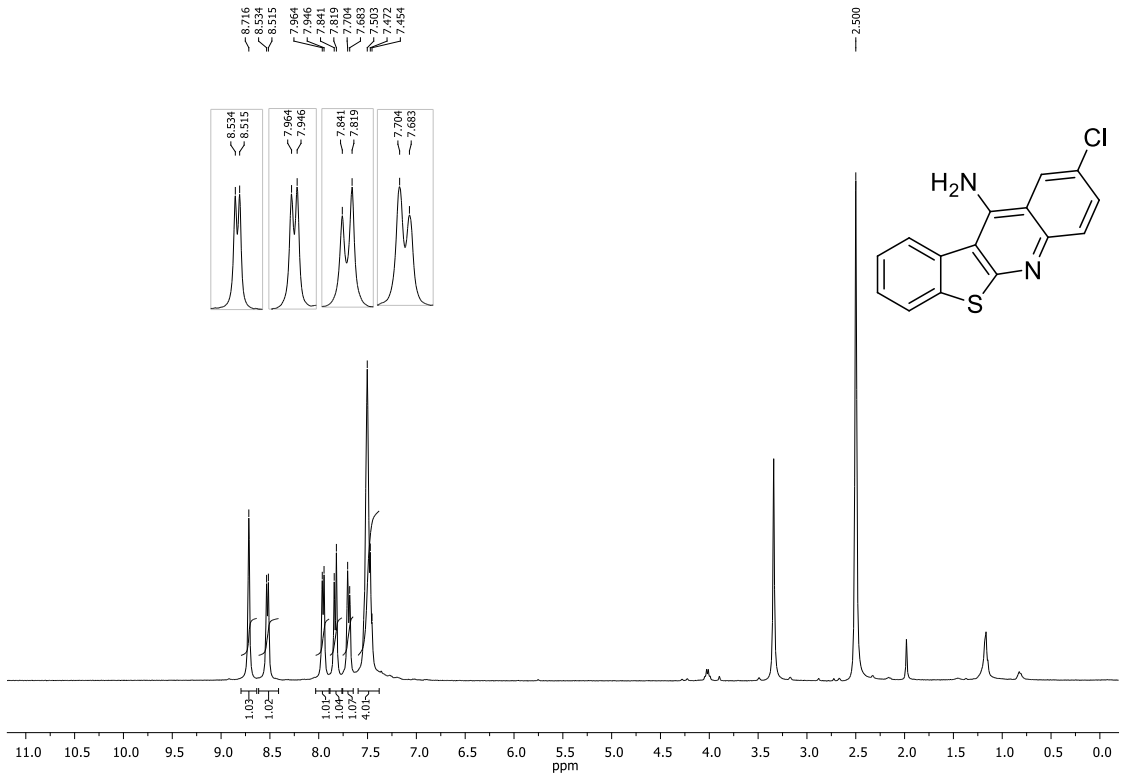



**Figure 3.27a**: $^{1}$H NMR Spectrum of **50e**

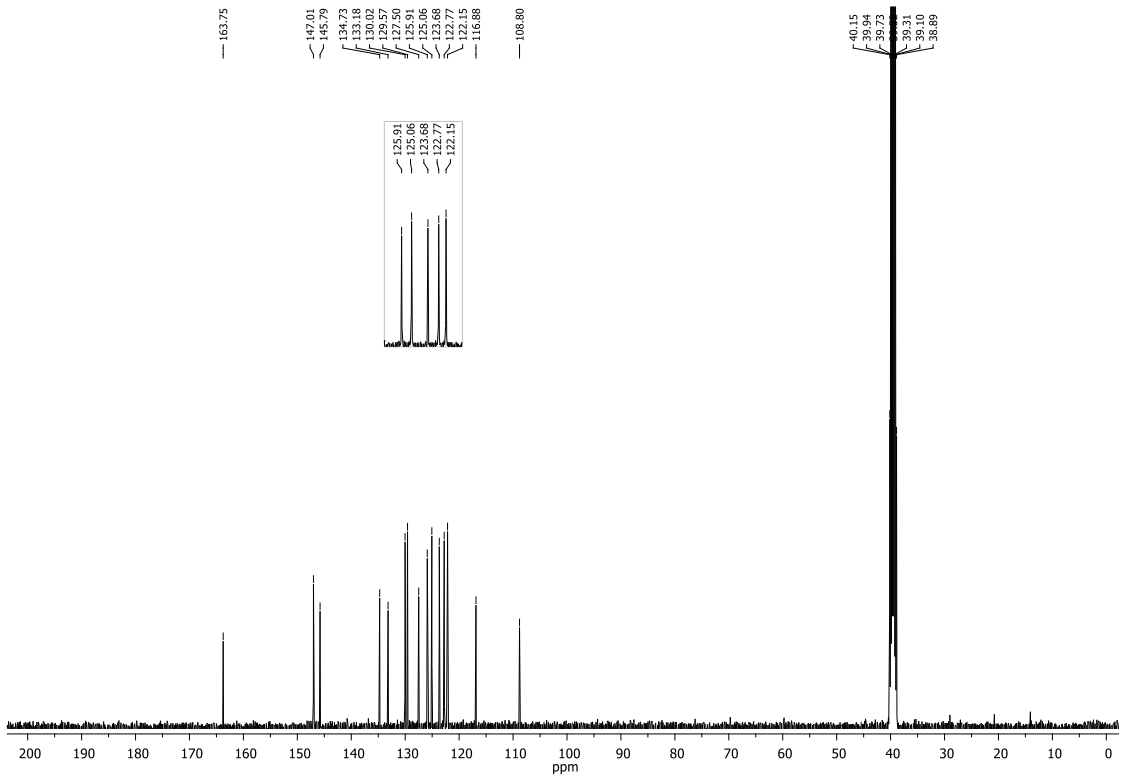



**Figure 3.27b**: $^{13}$C NMR Spectrum of **50e**

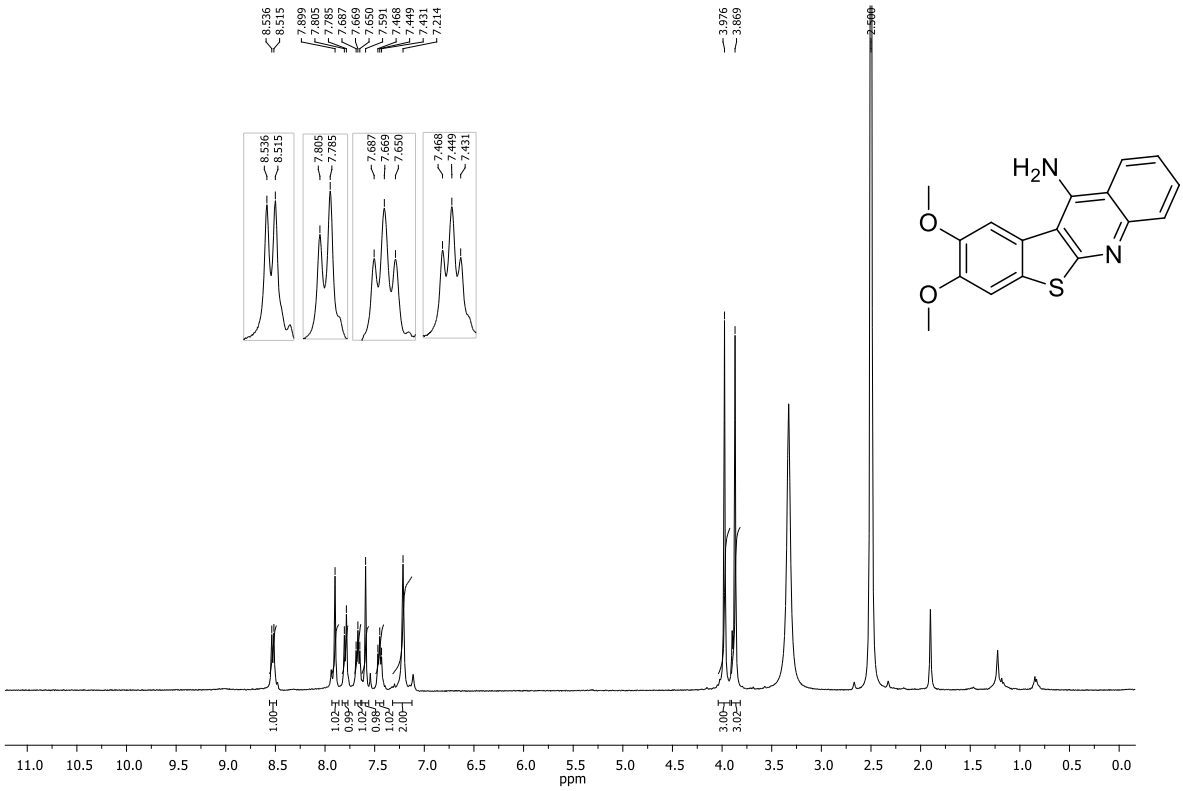



**Figure 3.28a**: $^{1}$H NMR Spectrum of **50i**

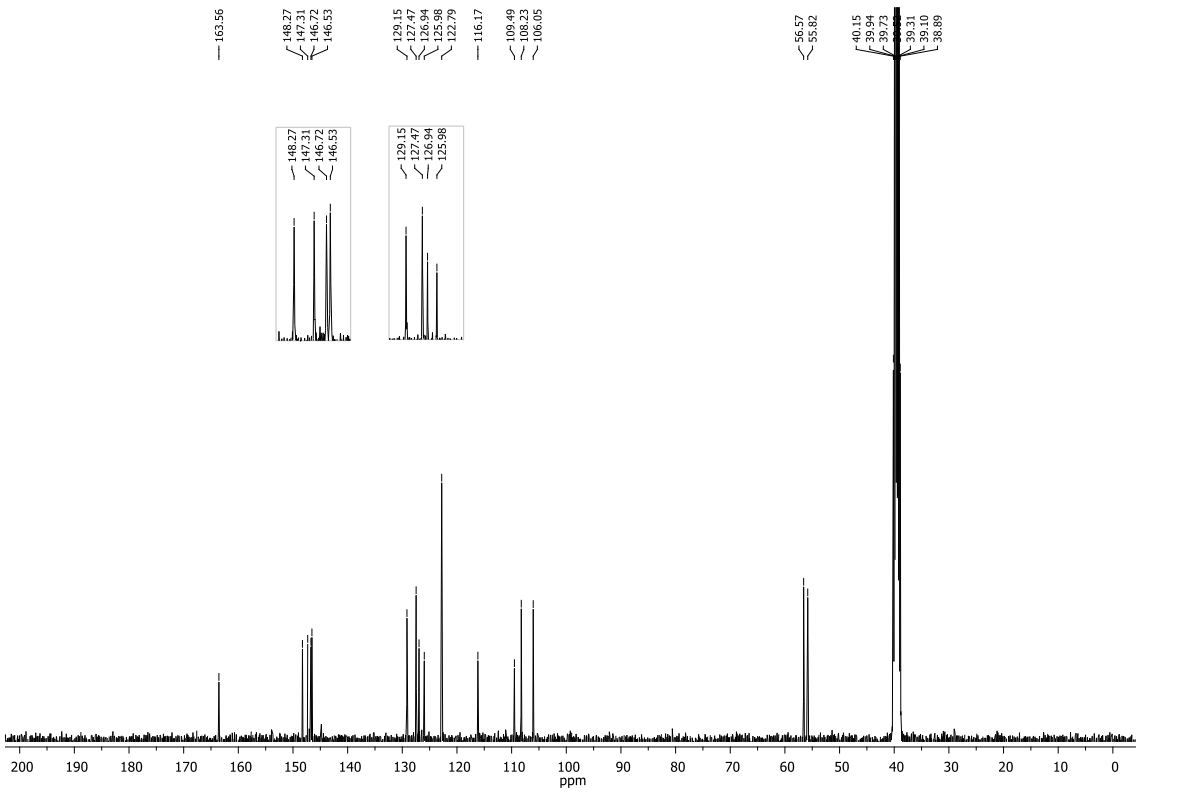



**Figure 3.28b**: $^{13}$C NMR Spectrum of **50i**

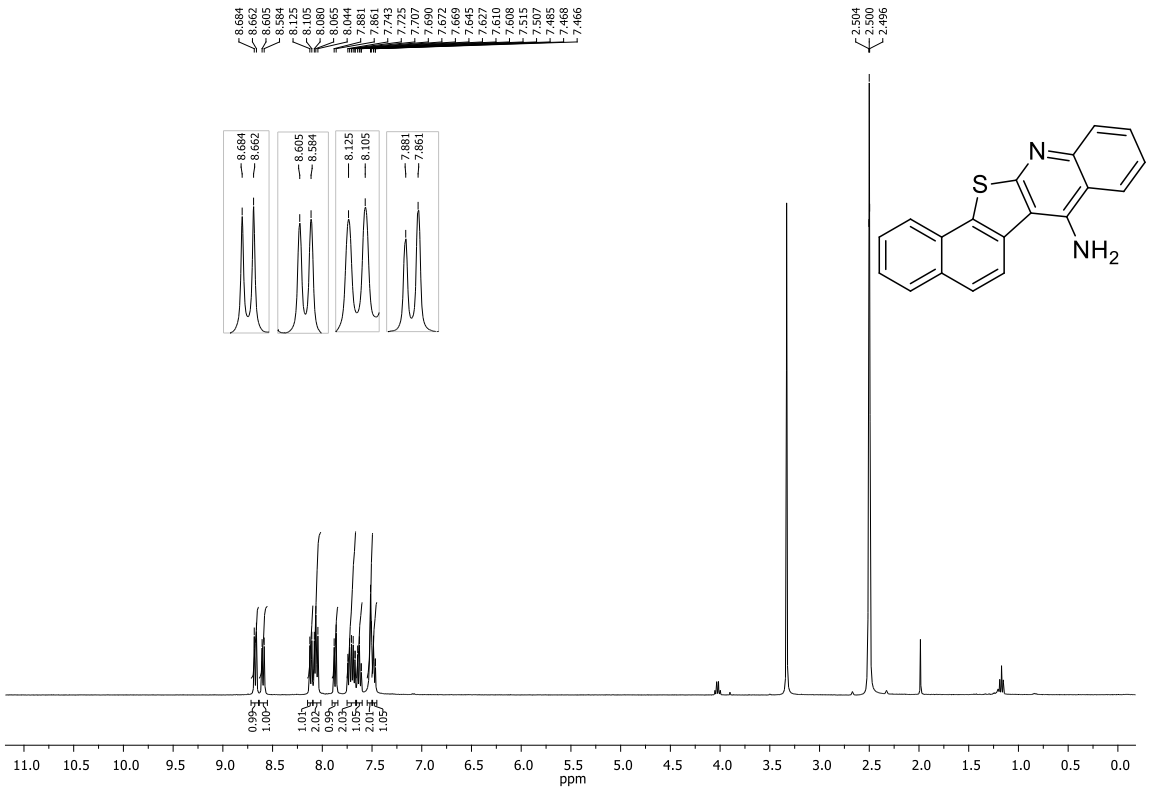



**Figure 3.29a**: $^{1}$H NMR Spectrum of **50n**

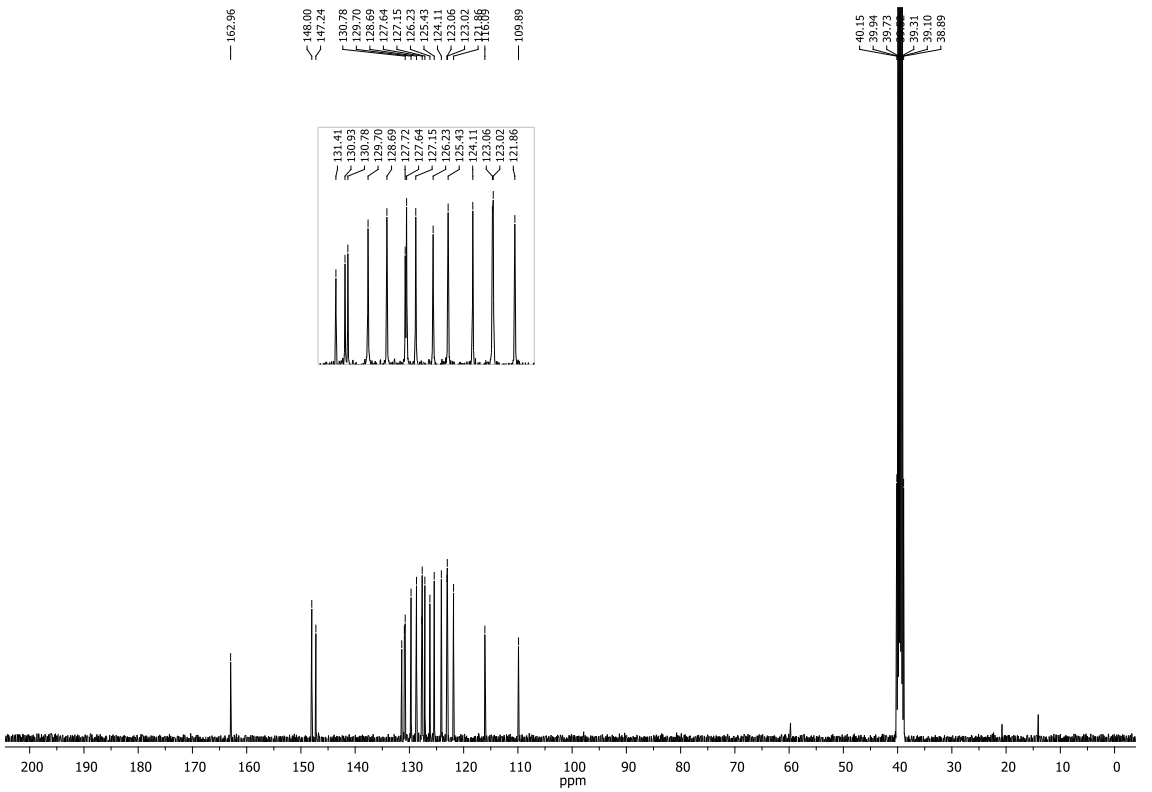



**Figure 3.29b**: $^{13}$C NMR Spectrum of **50n**

### 3.8 Crystal Data

Crystallographic data of **29a** in $CH_2Cl_2$/n-hexane: $C_{15}H_{10}N_2S$, Mw = 250.31, monoclinic, space group P21, a = 3.905 (5) Å, b = 12.317 (5) Å , c = 13.486 (5) Å , $\alpha$ = 74.773 (5) $^o$, $\beta$ = 83.574 (5) $^o$, $\gamma$ = 81.477(5) $^o$, $V$ = 617.2(9) Å 3 , $Z$ = 2, $D$calc = 1.347 mg/m3, $T$ = 293(2) K, R1 = 0.0448 {I > 2σ (I)}, R2w = 0.1369, GOF = 1.072.

**3.9 References:**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# Design, Synthesis and Tandem Reactions of New Class of *α*-(2-Haloaryl)-*α*-(2-haloaroyl)-*N*-substituted Thioamides

## 4.1 Introduction

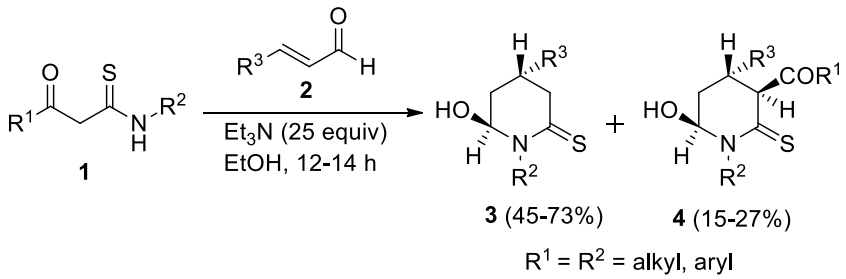
Over the past decades, synthetic organic chemistry created a fascinating history to make complex molecules. Several protocols are developed for synthesizing more complex molecules with an excellent regio-, chemo-, diastereo- and enantio-selectivities. However, these methods often suffer from chemical wastes, intermediates purifications, involving multi-steps, time and cost efficiencies. In general, the construction of complex organic molecules involves a step-wise bond formation. Thus, a target molecule can be synthesized by multi-step processes. An ideal synthesis would be making two or more than two bonds in a single synthetic operation without isolating intermediates and adding additional reagents/changing reaction conditions. This process often called as tandem synthesis or domino synthesis.[1] A molecular complexity in a single synthetic operation is considerable interest among the synthetic organic chemists, because, designing a substrate for such process is a very challenging task. However, several tandem/domino reactions involving pericyclic, radical, photochemical, biochemical, and transition metal mediated reactions have been developed.[1]

Developing a selective transition metal mediated tandem process is a formidable task. Especially, a substrate is having multiple reactive centers. Hence, the tandem precursors are clearly designed based on their reactivity profile. In this chapter, we discussed about design and development of new class of *α*-(2-bromoaroyl)-*α*-(2-bromoaryl)-thioamides as tandem precursors for synthesis of fused heterocycles.

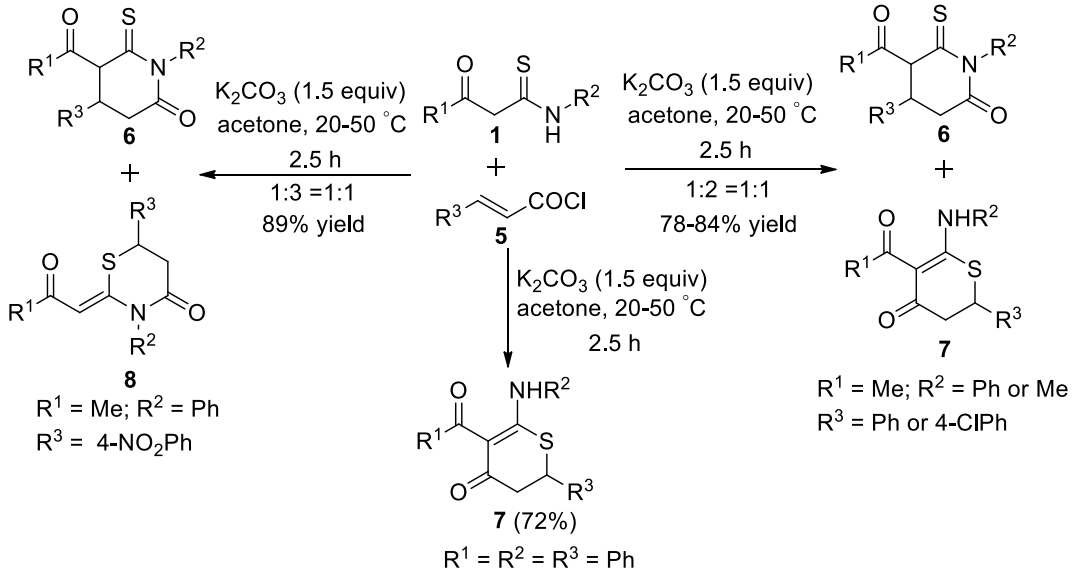
## 4.2 Previous Reports for the Applications of *β*-Ketothioamides in Synthesis of Heterocycles

In recent years, *β*-ketothioamides are proved to be useful synthons for the construction of various heterocycles.[2] We presented here a brief literature survey of *β*-ketothioamides in heterocycles synthesis.

Jagodziński *et al.* synthesized mixtures of 3-benzoylated and 3-unsubstituted 6-hydroxypiperidine-2-thione derivatives **3**-**4** by the reaction of benzoylthioacetamides **1** with *α,β*-unsaturated aldehyde **2** in presence of triethylamine (Scheme 4.1).[3]



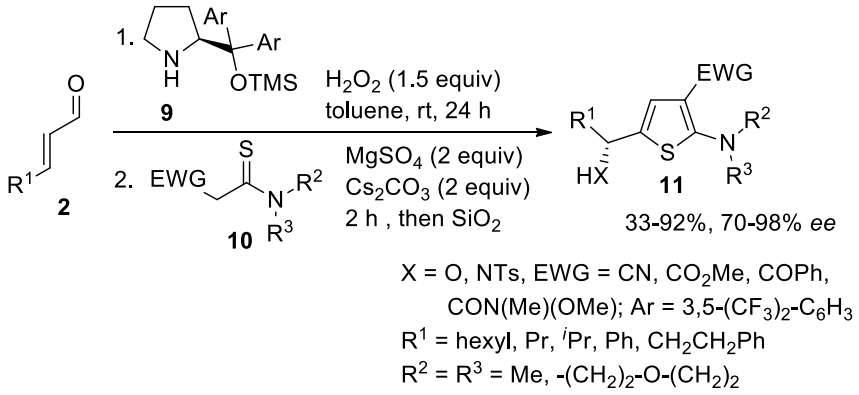

**Scheme 4.1**: *Synthesis of Piperidine-2-thiones **3** & **4***




**Scheme 4.2**: *Synthesis of Heterocycles from β*-Ketothioamides **1** *with 3-Aryl-2-propenoyl chlorides **5***

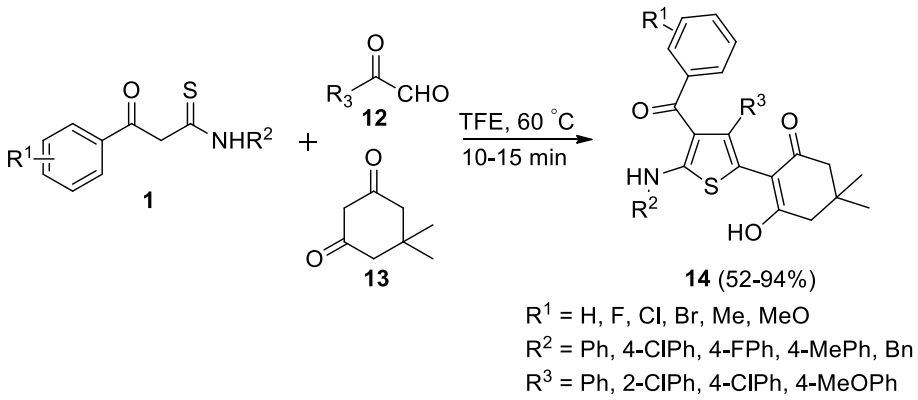
In 2006, Britsun and co-workers demonstrated a reaction of *β*-ketothioamides **1** and 3-aryl-2-propenoyl chlorides **5** in presence of $K_2CO_3$/acetone (Scheme 4.2).[4] Due to the several reaction centers in *β*-ketothioamides **1**, they obtained mixture of products **6-8** and the ratios were different when changing the substituents of the starting materials. Interestingly, in the case of 3-oxo-3-phenyl-*N*-phenylpropanethioamide (**1**, $R^1 = R^2 = Ph$) only one product **7** was formed.

Early 2012, Jørgensen and his co-workers demonstrated a general methodology for the synthesis of trisubstituted optically active thiophenes **11** by an organocatalytic one-pot cascade reaction (Scheme 4.3).[5] They isolated the target products **11** in good yields (up to 92%) with excellent enantioselectivities (up to 98% *ee*).



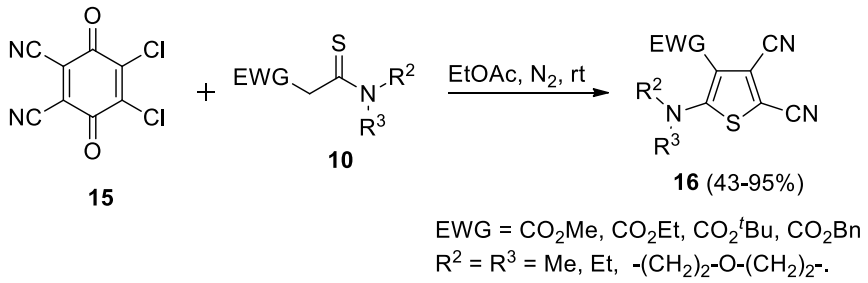

**Scheme 4.3**: *Synthesis of Optically Active Thiophenes **11***

Ming Li group developed a rapid and highly efficient method for the regioselective synthesis of thiophene derivatives **14**. The key step of this reaction was annulation of *β*-ketothioamides **1** with arylglyoxals **12** and 5,5-dimethyl-1,3-cyclohexanedione **13** in $CF_3CH_2OH$ within 15 min (Scheme 4.4).[6] This protocol involved with high regioselectivity, short period of reaction time, and easy purification. This strategy provides an alternative approach for easy access to tetrasubstituted thiophenes *via* a one-pot cascade approach without other additives.



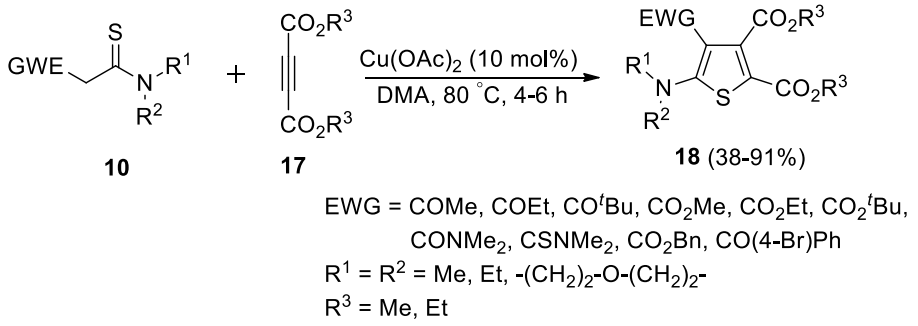

**Scheme 4.4**: *Regioselective Synthesis of Tetrasubstituted Thiophenes **14***

Recently, Deng and co-workers synthesized fully substituted thiophenes **16** by a facile oxidative coupling of $\alpha$-carbonyl radicals of $\beta$-keto thioamides **10** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) **15** (Scheme 4.5).[7]




**Scheme 4.5**: *Synthesis of 2,3-Dicyanothiophenes **16** via DDQ Mediated Oxidative-Coupling*

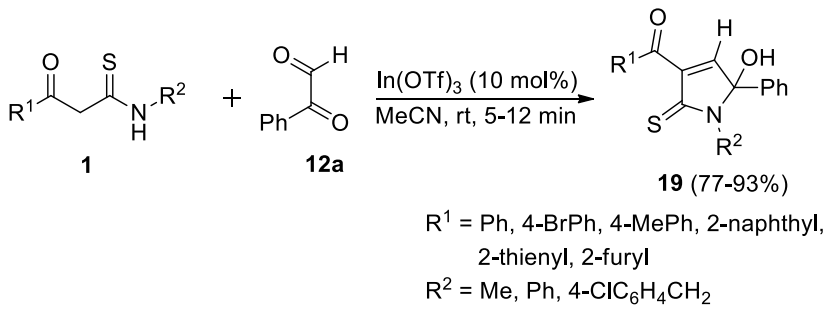
They also developed a facile and direct synthetic protocol for the transformation of $\beta$-ketothioamides **10** into structurally important 2-aminothiophenes **18** in moderate to excellent




**Scheme 4.6**: *Synthesis of 2-Aminothiophenes **18***

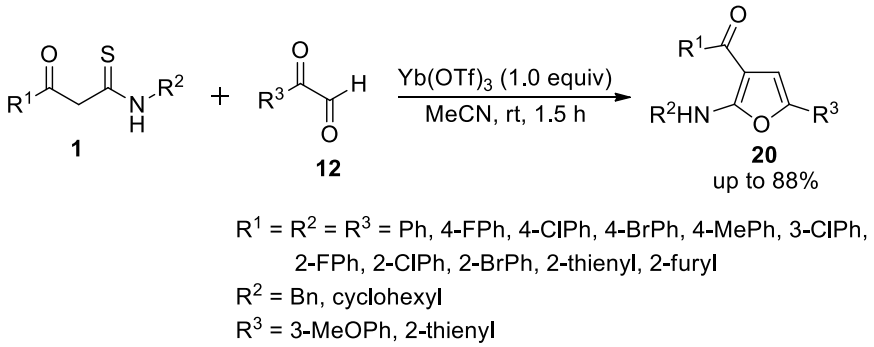
yields (Scheme 4.6).[8] The method was initiated with Cu(II)-catalyzed addition followed by oxidative cyclization of readily available thioamides **10** with alkynoates **17** under an air atmosphere.

Recently, Singh group developed a method to synthesize diversely functionalized pyrrol-2-thiones **19** using indium triflate mediated dehydrative annulation of *β*-ketothioamides **1** with phenylglyoxal (**12a**) by one-pot domino Knoevenagel condensation/cyclization cascade (Scheme 4.7).[9] The most attractive feature of this reaction was the formation of two new (C–C and C–N) bonds in a single synthetic operation.




**Scheme 4.7**: *Synthesis of Diversely Functionalized Pyrrol-2-thiones **19***

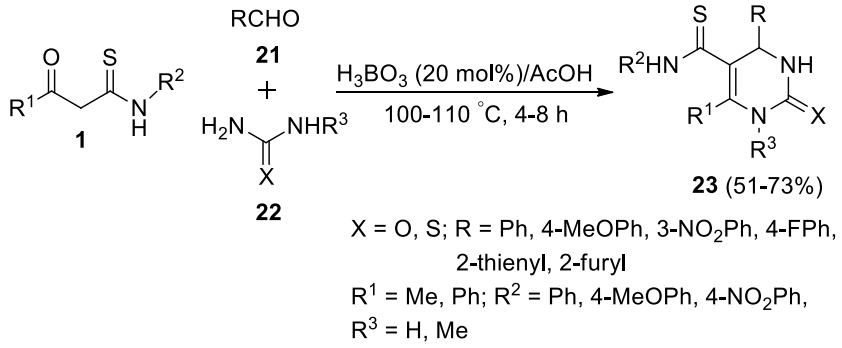
Very recently, the research group of Ming Li reported $Yb(OTf)_3$ promoted a mild and straightforward synthetic strategy for preparation of a furan skeleton **20** from *β*-ketothioamides




**Scheme 4.8**: *$Yb(OTf)_3$ Mediated Synthesis of Furans **20***

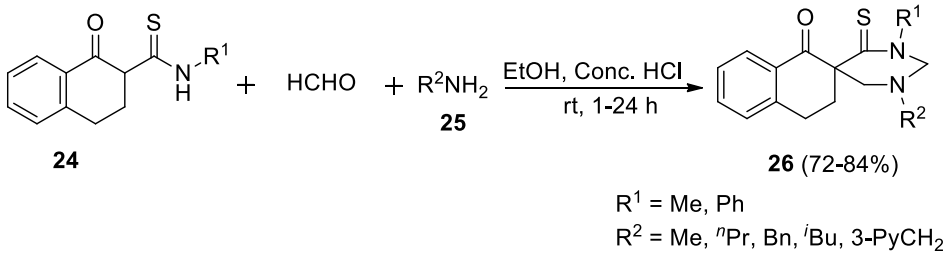
**1** and arylglyoxals **12** at room temperature (Scheme 4.8).[10] Interestingly, this strategy involves a tandem sequence that includes aldol condensation, *N*-cyclization, ring opening, *O*-cyclization, *S*-cyclization, and Eschenmoser sulfide contraction.

Early 2014, the group of Britsun reported the first Bignelli type reaction to synthesize tetrahydropyrimidine-5-carbothioamides **23** through *β*-ketothioamide **1**, aryl aldehyde **21** and ureas or thioureas **22** (Scheme 4.9).[11] It was shown that the reaction did not proceed in the absence of boric acid.




**Scheme 4.9**: *Synthesis of Tetrahydropyrimidine-5-carbothioamides **23***

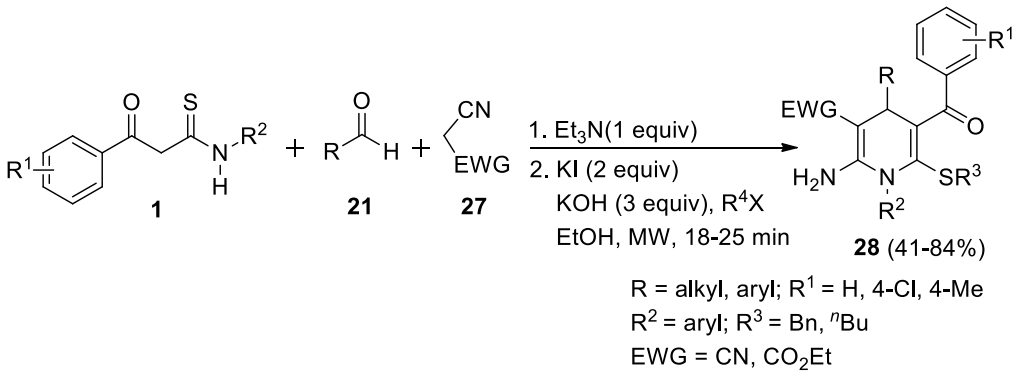
Jagodziński and Westerlich obtained spirohexahydropyrimidines **26** through alcoholic hydrogen chloride catalyzed one pot three-component Mannich type reaction of the tetralone-derived thioamides **24**, amines **25** and formaldehyde (Scheme 4.10).[12]




**Scheme 4.10**: *Synthesis of Spirohexahydropyrimidines **26** by Mannich Type Reaction*

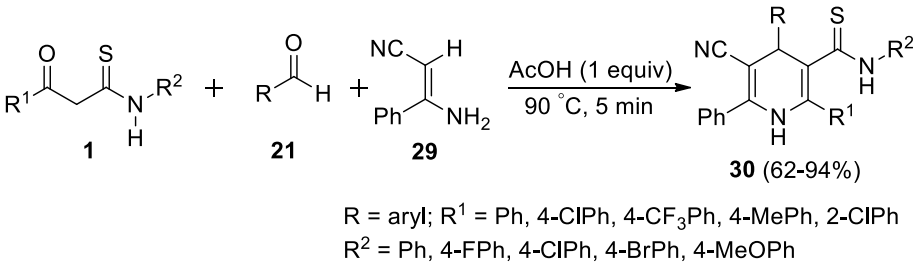
The research group of Ming Li developed a microwave-assisted sequential one-pot two-step methodology for synthesis of hexa-substituted 1,4-dihydropyridines **28** (Scheme 4.11).[13]

The three-component reactions of *β*-aroylthioamides **1** with aldehydes **21** and acetonitrile derivatives **27** proceeded through a Knoevenagel condensation-Michael addition-cyclocondensation-rearrangement-$S_N2$ reaction sequence. This approach was complementary to the classical Hantzsch type synthesis.




**Scheme 4.11**: *Microwave-Assisted Synthesis of Hexa-Substituted 1,4-Dihydropyridines **28***

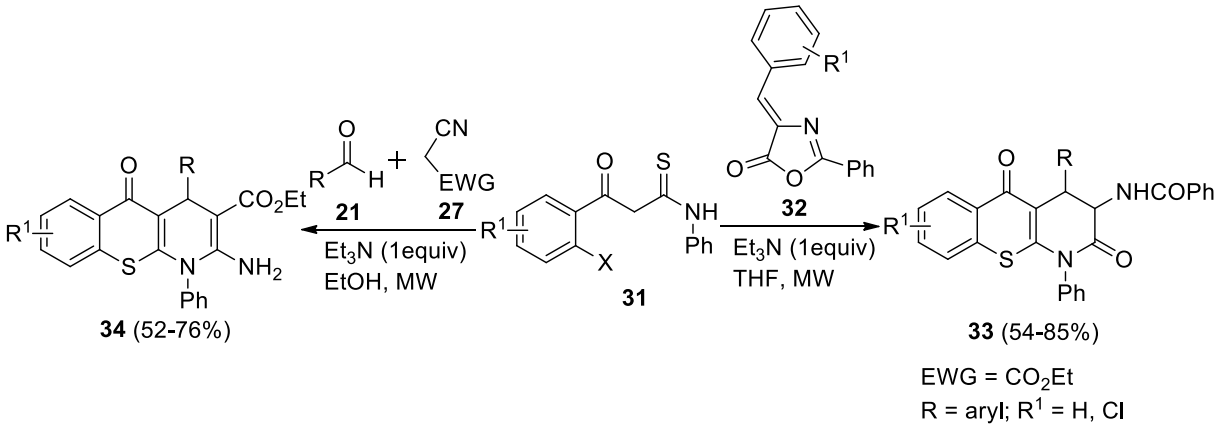
They also described the synthesis of 1,4-dihydropyridines **30** in the presence of AcOH under solvent-free conditions within 5 min (Scheme 4.12).[14] *β*-Ketothioamides **1** act as an excellent building block with aldehydes **21** and *β*-enaminonitriles to produce the corresponding 1,4-dihydropyridines **30**. The advantages of this method were high chemoselectivity, mild reaction conditions and easily available substrates.




**Scheme 4.12**: *Acid Promoted Synthesis of 1,4-Dihydropyridines **30***

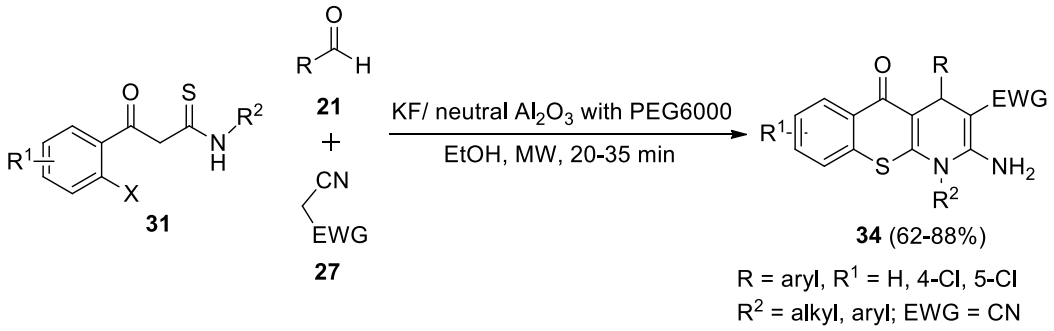
In 2009, Ming Li group derived a microwave assisted tandem [3 + 3] annulation and $S_NAr$ of *β*-(2-chloroaroyl) thioacetanilides **31** with activated 4-arylidene-2-phenyloxazol-5-

(4*H*)-ones **32** or aromatic aldehydes **21** and ethyl 2-cyanoacetate **27** (EWG = $CO_2Et$) to synthesize an unusual fused tricyclic thiochromeno[2,3-*b*]pyridines **33**-**34** (Scheme 4.13).[15]




**Scheme 4.13**: *MW-Assisted Synthesis of Tricyclic thiochromeno[2,3-b]pyridines **33** & **34***

They also constructed a series of new functionalized thiochromeno[2,3-*b*]pyridine derivatives **34** by using a sequence of Knoevenagel condensation, Michael addition, cyclization, and intramolecular nucleophilic substitution reaction (Scheme 4.14).[16]

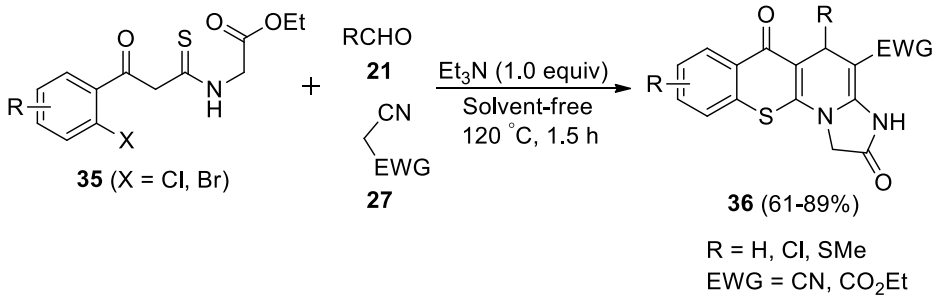



**Scheme 4.14**: *KF/neutral $Al_2O_3$ Catalyzed Synthesis of Thiochromeno[2,3-b]pyridines **34***

The reaction was first catalyzed by KF/neutral $Al_2O_3$ cooperated with PEG 6000 under microwave irradiation.

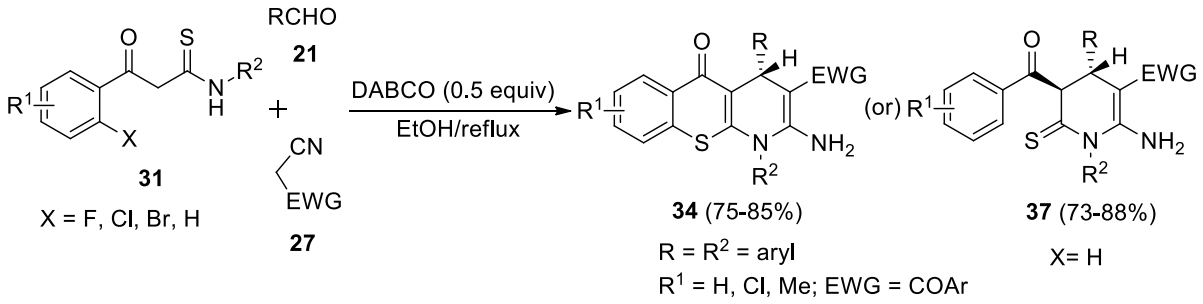
Further, they demonstrated a three-component cascade reaction under solvent-free conditions to prepare imidazo[1,2-*a*]thiochromeno[3,2-*e*]pyridines **36**. In this one-pot process

without using any transition metal catalysts they constructed three new C—C bonds, two C—N bonds, one C—S bond, and three new rings (Scheme 4.15).[17]



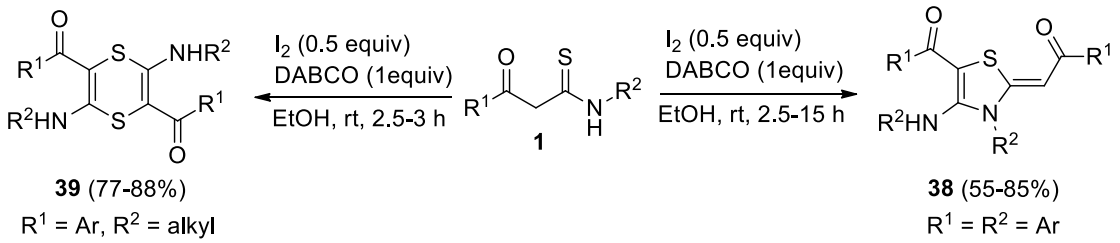

**Scheme 4.15**: *Synthesis of Imidazo[1,2-a]thiochromeno[3,2-e]pyridines* ***36***

Furthermore, they also developed an efficient and straightforward three-component synthetic protocol to synthesize 1,2,3,4-tetrahydropyridine derivatives **37** or thiochromeno[2,3-*b*]pyridine derivatives **34** from *β*-aroylthioacetanilides **1** or *β*-(2-haloaroyl)-thioacetanilides **31**, aldehydes, and aroyl acetonitriles **27** by using DABCO promoted tandem [3 + 2 + 1] annulation and nucleophilic aromatic substitution reaction ($S_NAr$). In this domino reaction up to three covalent bonds and one functionalized pyridine ring were generated (Scheme 4.16).[18]



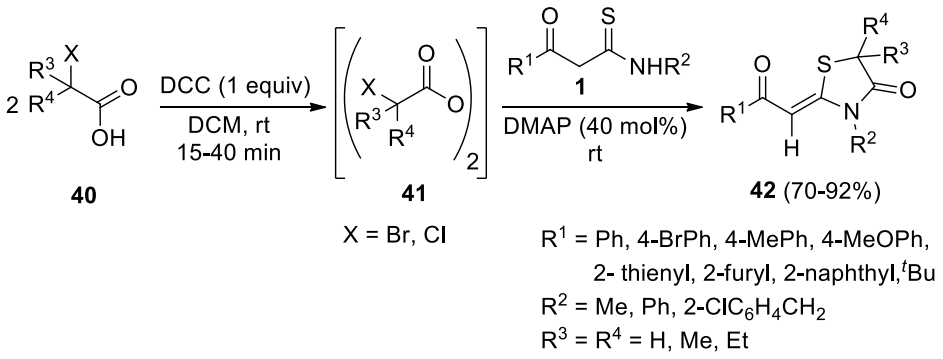

**Scheme 4.16**: *Synthesis of Tetrahydropyridines* ***37****/Thiochromeno[2,3-b]pyridines* ***34***

In 2014, the research group of Ming Li constructed various thiazolylidenes **38** and 1,4-dithiines **39** by using an efficient iodine promoted [3+2] or [3+3] cyclocondensation of *β*-ketothioamides **1** in a one-pot process (Scheme 4.17).[19]



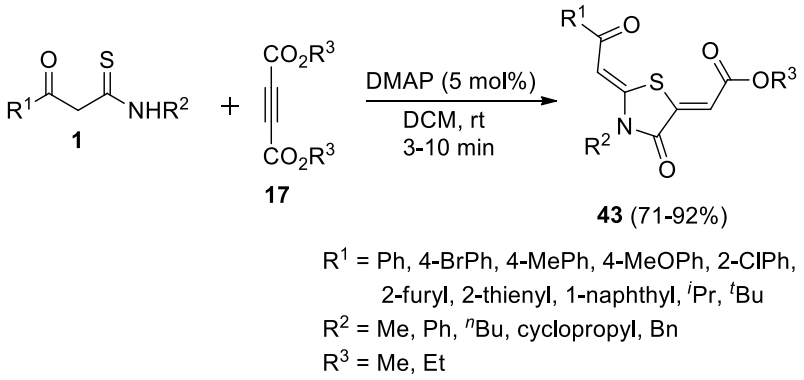

**Scheme 4.17**: *Iodine Catalyzed Synthesis of Thiazolylidenes **38** and 1,4-Dithiines **39***

Later, Singh and his co-workers exhibited an operationally simple and efficient one-pot straightforward method for the construction of 1,3-thiazolidin-4-ones **42** (Scheme 4.18).[20] This process mainly involved in cyclocondensation of *β*-ketothioamides **1** and an *in situ* generated acid anhydride **41** from *α*-halocarboxylic acid **40** in the presence of DCC at room temperature. The main advantages of this method were metal-free mild reaction conditions, short reaction time, and efficacy of forming consecutive C—S and C—N bonds and one ring in a single synthetic operation.




**Scheme 4.18**: *Synthesis of 1,3-Thiazolidin-4-ones **42***

The same group also developed DMAP-mediated rapid and efficient one-pot regioselective process to functionalized 1,3-thiazolidin-4-ones **43** by using annulation of *β*-ketothioamides **1** with internal alkynes **17** under mild reaction conditions (Scheme 4.19).[21] This domino protocol is highlighted because of its operational simplicity, short reaction time, tolerance of a large variety of functional groups, and more effectively producing two new bonds (C–S and C–N) and one thiazolidine ring.




**Scheme 4.19**: *Domino Annulation of β-Ketothioamides **1** with Internal Alkynes **17***

Our literature revealed that *β*-ketothioamides were used for construction of various heterocycles. However, these substrates are rarely explored in metal catalyzed domino reactions. We envisioned a new class of *β*-ketothioamides **44** having multiple reactive centers (Figure 4.1) for transition metal mediated organic transformations, especially for developing a tandem reaction for fused heterocycles with biological importances.

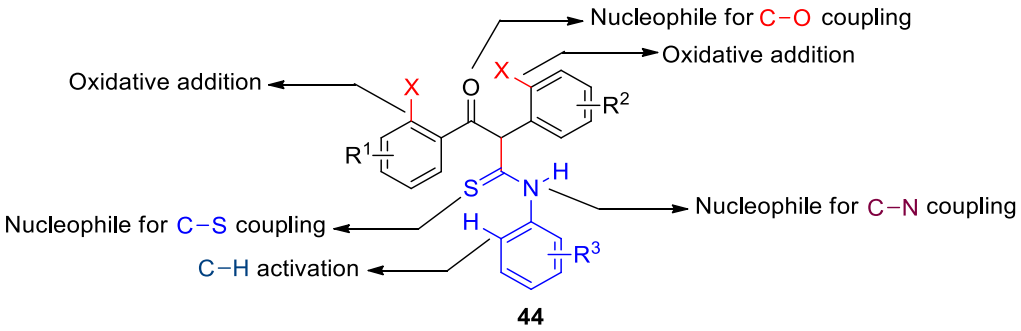



**Figure 4.1**: *Possible Reactive Centers of **44** & their Respective Reactions by Transition Metals*

## 4.3 Results and Discussions

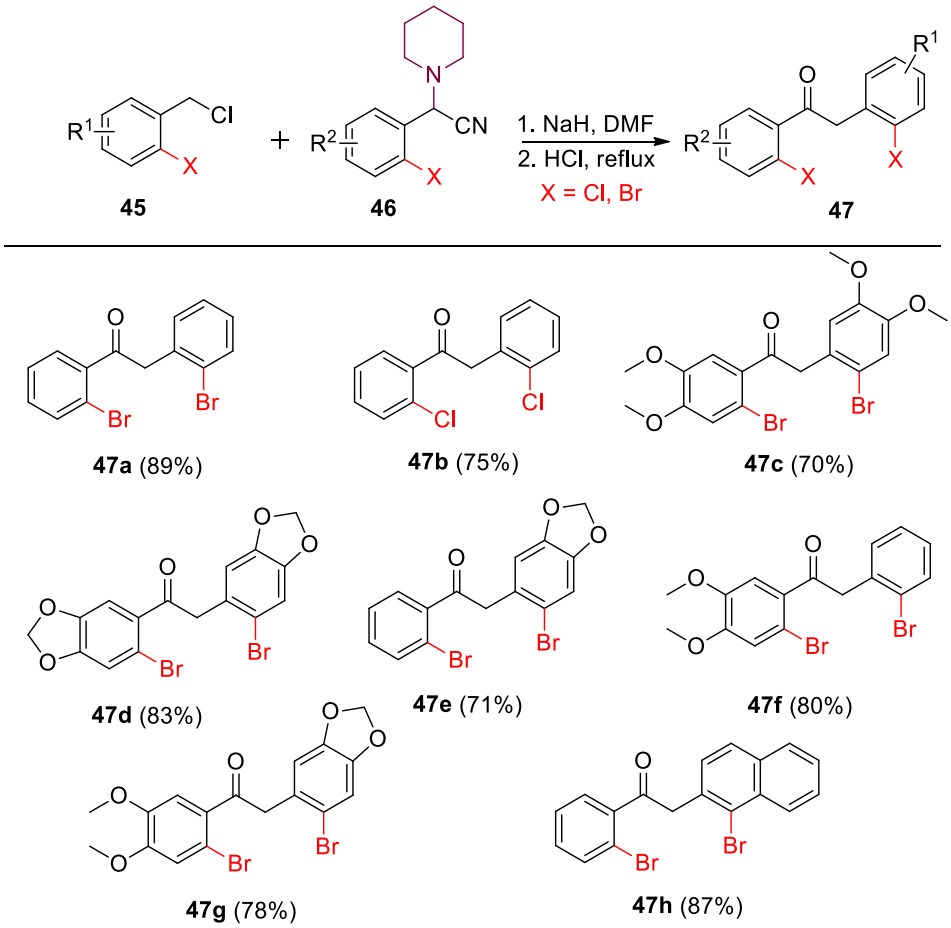
Designing a new tandem precursor is a challenging task. Thus, we designed *β*-ketothioamides **44** as tandem precursors, which can be prepared from deoxybenzoins **47** &

isothiocyanates **48** (Chapter-3, Table 3.12 & 3.14). The *β*-ketothioamide reactivities are well known.

### 4.3.1 Synthesis of Deoxybenzoins 47

We synthesized several deoxybenzoins **47** in three steps (Table 4.1, **47a-h**) as described in Chapter-3, Table 3.12. The newly synthesized deoxybenzoins **47c-h** were characterized by Spectrul and analytical data. The known deoxybenzoins **47a-b** are compared with reported ones.[22]

**Table 4.1**: **Synthesis of Various Dihalo Substituted Deoxybenzoins 4**

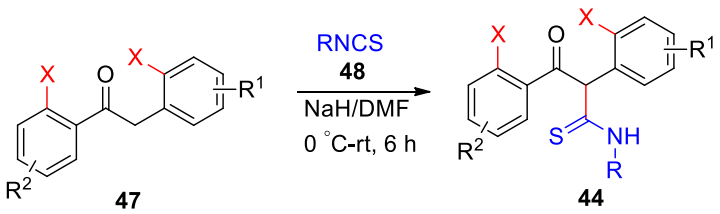



*Reaction conditions:* [a] *o-Bromo substituted benzyl chlorides* ***45*** *(1 equiv), Amino nitriles* ***46*** *(1 eq uiv), NaH (2 equiv), DMF, 0 °C-rt,* [b] *Conc. HCl, reflux.*

### 4.3.2 Synthesis of Thioamides 44

The synthesized deoxybenzoins **47** were further transformed into the corresponding *β*-ketothioamides **44** by the reaction with different isothiocyanates **48**.

**Table 4.2**: **Synthesis of *α*-(2-Halophenyl)-*α*-(2-halobenzoyl)-*N*-aryl thioamides**




**47** **44**

**44a** (77%) **44b** (58%) **44c** (75%) **44d** (68%)

**44e** (53%) **44f** (44%) **44g** (78%) **44h** (69%)

**44i** (56%) **44j** (61%) **44k** (67%)

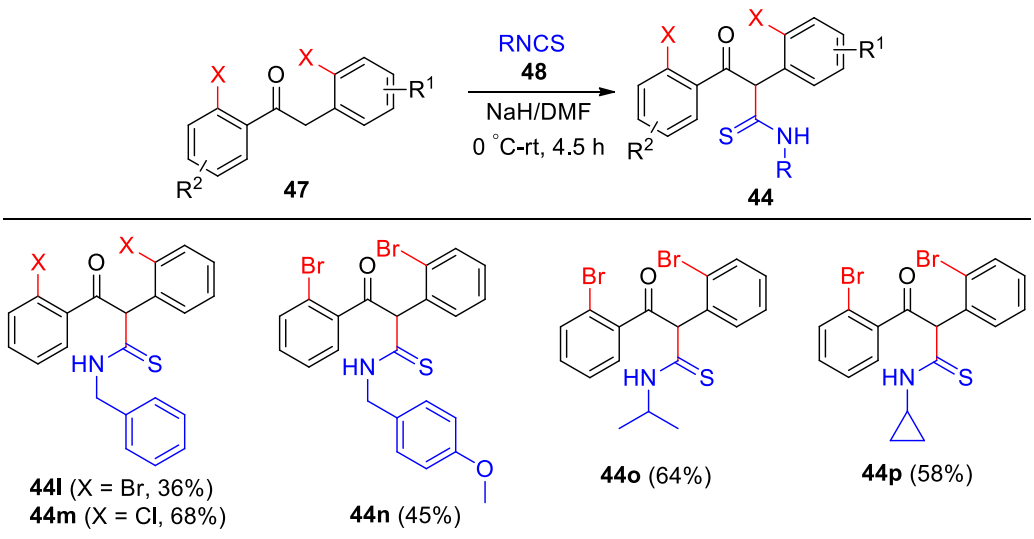
*Reaction conditions: Deoxybenzoin **47** (1 equiv), Isothiocyanate **48** (1.2 equiv) NaH (1.2 equiv), DMF, 0 °C-rt*

Initially, we focused on the synthesis of *β*-ketothioamides **44a-k** without substituents on the aryl rings. The bromo and chloro substituted deoxybenzoins **47a-b** were converted into the

corresponding thioamides **44a-b** in 77% and 58% yields respectively. Similarly, 4-methoxyphenyl isothiocyanate was reacted with deoxybenzoins **47a-b** affording the respective thioamides **44c-d** in 75% and 68% yields respectively. Further, isothiocyanates having electron donating and withdrawing groups on nitrogen atom were reacted with deoxybenzoins **47e-j** affording the respective thioamides **44e-j** in moderate to good yields. Interestingly, deoxybenzoin **47a** smoothly reacted with 3-pyridyl isothiocyanate (**48k**) and obtained thioamide **44k** in 67% yield (Table 4.2).

We also synthesized various *N*-alkyl substituted thioamides **44l-p**. In case of benzyl substituted thioamides **44l-m** dichlorodeoxybenzoin **47b** gave better yield as compared to the dibromodeoxybenzoin **47a**. Further, deoxybenzoin **47a** was also reacted with 4-methoxybenzyl isothiocyanate affording thioamide **44n** in 45% yield.

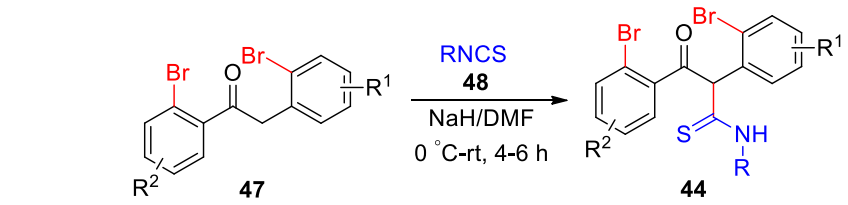
**Table 4.3**: **Synthesis of *N*-Alkyl Substituted *β*-Ketothioamides**

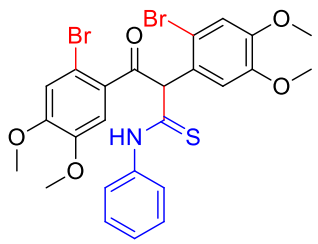



On the other hand, isopropyl and cyclopropyl isothiocyanates (**48o-p**) were also reacted with deoxybenzoin **47a** affording the moderate yields of corresponding thioamides **44o-p** (Table 4.3).

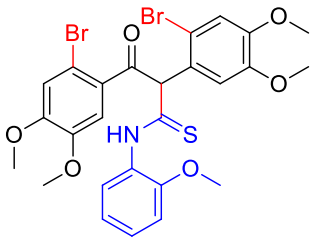
Further, we synthesized symmetrical electron rich aryl and aroyl substituted thioamides **44q-v**. Thus, deoxybenzoins **47c-d** were reacted with phenyl isothiocyanate to afford the corresponding thioamides **44q** & **44t** in 79-80% yields (Table 4.4).

**Table 4.4**: **Synthesis of Electron rich Symmetrical *α*-(Bromoaryl)-*α*-(bromoaroyl)-*N*-alkyl/aryl thioamides**

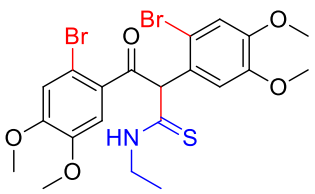


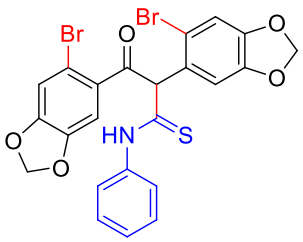
**44q** (80%)



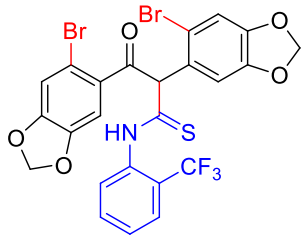
**44r** (92%)



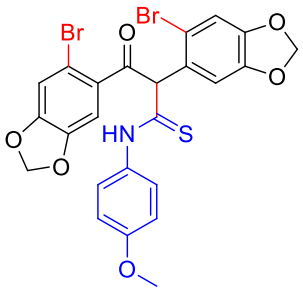
**44s** (79%)



**44t** (79%)



**44u** (73%)

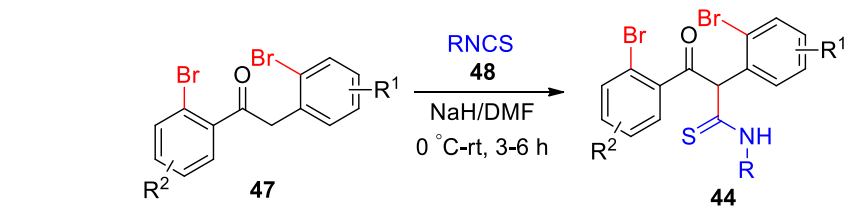


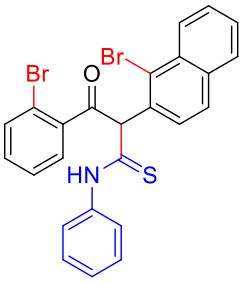
**44v** (71%)

2-Methoxyphenyl isothiocyanate was treated with anion of deoxybenzoin **47c** gave 92% of *β*-ketothioamide **44r** (Table 4.4). Whereas reaction of ethyl isothiocyanate with deoxybenzoin **47c** afforded only 79% of respective thioamide **44s**. Similarly, *N*-aryl substituted isothiocyanates gave good yields of *β*-ketothioamides **44u-v** under identical reaction conditions (Table 4.4).

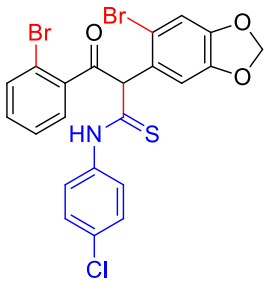
Futhermore, we prepared unsymmetrical aryl and aroyl substituted thioamides **44w-z** and **44aa** (Table 4.5). Thus, the deoxybenzoin **47h** was reacted with phenyl isothiocyanate affording excellent yield of unsymmetrical *α*-aryl-*α*-aroyl thioamide **44w** (Table 4.5, 95%). Similarly, *N*-aryl substituted thioamides **44x-y** were prepared from the respective deoxybenzoins & isothiocyanates (Table 4.5, **44x-y**). *N*-alkyl substituted thioamides **44z** & **44aa** were also synthesized under similar conditions (Table 4.5).

**Table 4.5**: **Synthesis of Electron rich Unsymmetrical *α*-(Bromoaryl)-*α*-(bromoaroyl)-*N*-alkyl/aryl Thioamides**

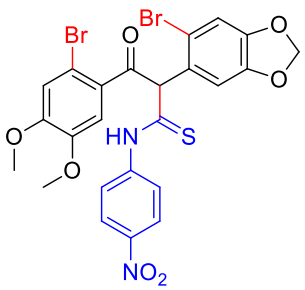


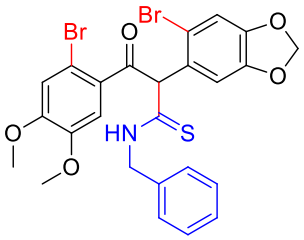
**44w** (95%)



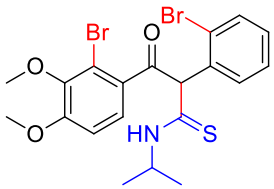
**44x** (80%)



**44y** (70%)



**44z** (66%)

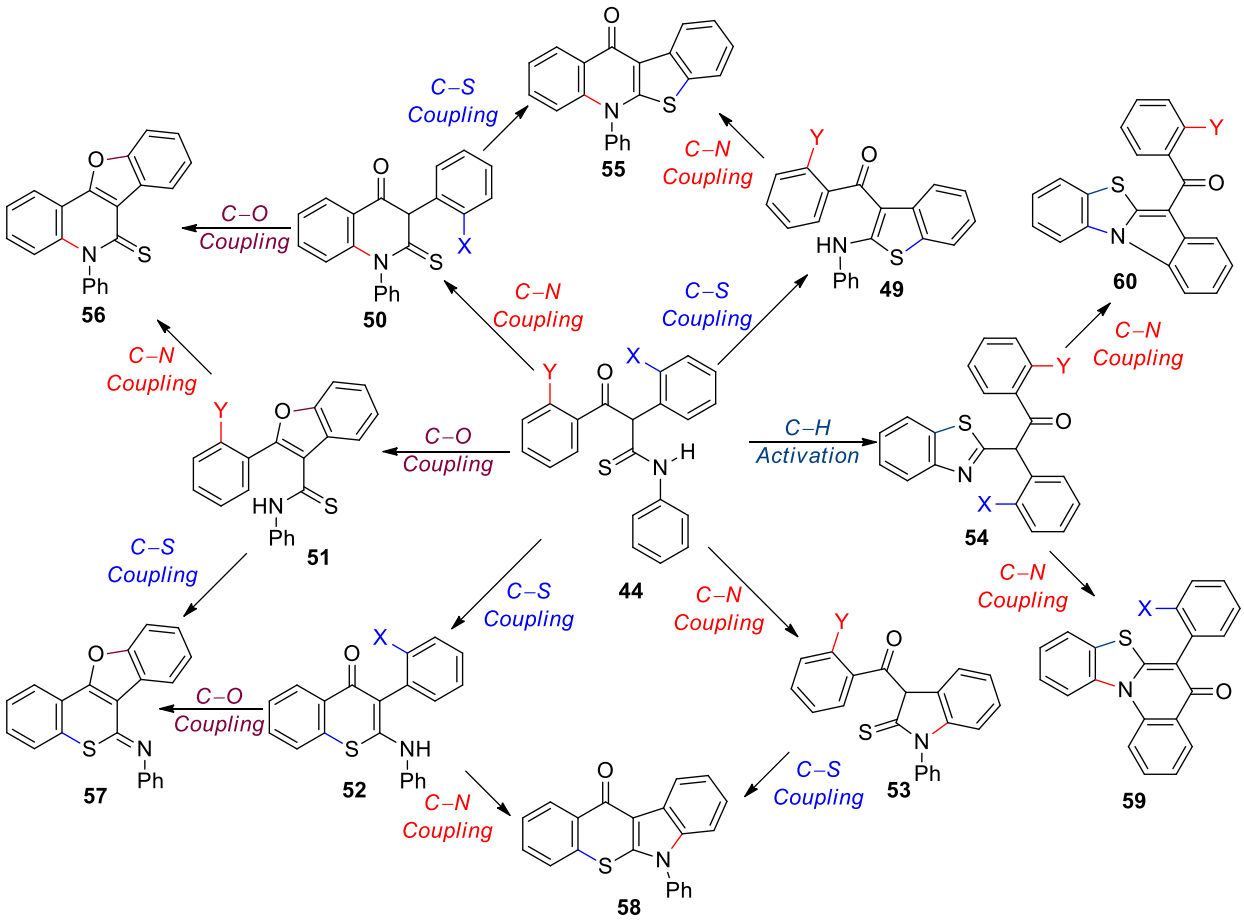


**44aa** (72%)

### 4.3.3 Optimization of Tandem Intramolecular Cross-Coupling of *β*-Ketothioamides 44

Aforementioned *β*-ketothioamides **44** is having a multiple reactive centers, when these *β*-ketothioamides **44** are subjected under transition metal catalyzed conditions, one would expect different kinds of heterocycles **49-60** (Scheme 4.20). These products **49-60** would be

derived from various coupling reactions and C—H activations. The first step would be oxidative addition of either C—X bond or C—Y of thioamide **44**. Depending upon oxidative addition of a particular carbon—halo bond (C—X bond oxidation) gives either five membered heterocycles **49**, **51**, **53** or six membered heterocycles **50**, **52** (C—Y bond oxidation). These heterocycles **49-52** will undergo further intramolecular cross-coupling of available carbon—halo bond and hetero atom gives fused heterocycles **55-58**. Whereas, thioamide **44**




**Scheme 4.20**: *Possible Intramolecular Cross-Coupling of β-Ketothioamides **44***

can also undergo C—H activation giving rise to **54** which further cross-coupled with either C—X or C—Y bonds affords fused heterocycles **59** & **60**. The former process could be most likely than later. The challenging task in this chapter is to get a single product from **49-60**. However, we discussed in Chapter-3, thioamide **44** was transformed into a single product **49**

under copper-phenanthroline combination in the presence of $Et_3N$ at room temperature. This condition ruled out for formation of other five possible products such as **50-54**. Further, the product **49** is very selective; which can only undergo intramolecular C—N cross-coupling reaction. Thus, heterocycle **55** is only possible product to yield out of 12 products (**49-60**). Based on these predictions, we started our optimization studies on tandem intramolecular cross-coupling of *β*-ketothioamides **44**.

The-(2-bromophenyl)-*α*-(2-bromobenzoyl)-*N*-phenyl thioamide (**44a**) was choosen as model substrate for tandem reaction. Thus, thioamide **44a** was heated with 10 mol% CuI, 20 mol% 1,10-phenanthroline (**L1**), 3 equiv of KO$^t$Bu in DMF at 120 $^o$C for 24 h. Gratifyingly, as per our prediction 82% of benzo[*b*]thieno[1,2-*b*]-quinol-11-one **55a** was isolated as a sole product. The product **55a** was confirmed by Spectral and analytical data. It was further confirmed by single crystal X-ray analysis (Figure 4.2). The result was summarized in Table 4.6. Further we examined various ligands. Thus, L-proline (**L2**), bipyridine (**L3**) gave 61 and 63% yield of **55a** respectively. Whereas (*R*)-BINAM (**L4**) was afforded only 46% of **55a**. However, TMEDA (**L5**) was effective for tandem reaction, thieno[1,2-*b*]-quinolone **55a** was isolated in 70% yield. However, 1,10-phenanthroline (**L1**) was best among the other ligands **L2-L5** (Table 4.6).

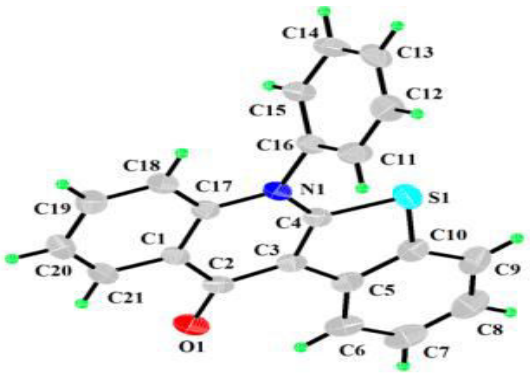
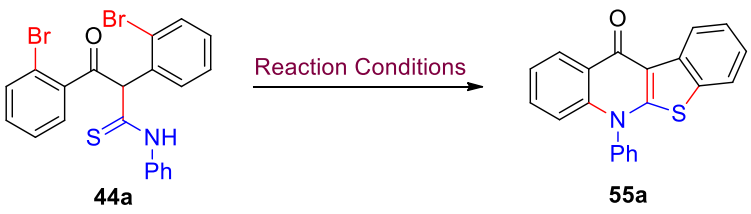
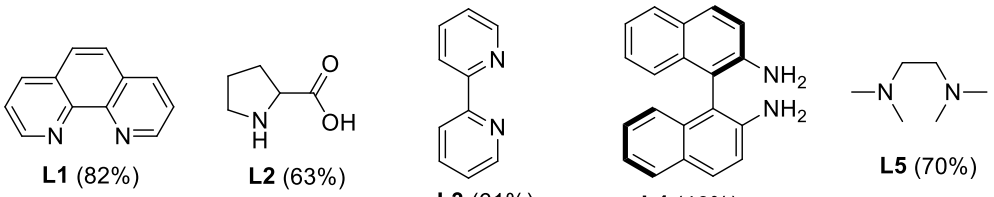



**Figure 4.2**: Single Crystal X-Ray of Compound **55a**

**Table 4.6**: **Screening of Ligands for synthesis of Benzothieno[2,3-*b*]quinolones**




**44a** **55a**




**L1** (82%) **L2** (63%) **L3** (61%) **L4** (46%) **L5** (70%)

*Reaction conditions: Thioamide (**44a**) (0.5 m.mol), CuI (10 mol%), **L1-L5** (20 mol%), KO$^t$Bu (3 equiv), DMF, 120 °C, 24 h*

For further fine-tuning of this process, other copper salts such as CuBr, CuCl and $Cu(OAc)_2$ were screened and found to be less beneficial when compared with CuI (Table 4.7).

**Table 4.7**: **Screening of Copper Salts for synthesis of Benzothieno[2,3-*b*]quinolones**

| Entry | Ligand | Metal Salt | Base | Solvent | **55a** (% Yield)[b] |
|---|---|---|---|---|---|
| 1 | **L1** | CuBr | KO$^t$Bu | DMF | 58 |
| 2 | **L1** | CuCl | KO$^t$Bu | DMF | 54 |
| 3 | **L1** | $Cu(OAc)_2$ | KO$^t$Bu | DMF | 70 |

[a] *Reaction conditions: Thioamide **44a** (0.5 mmol), Cu salt (10 mol%), **L1** (20 mol%), KO$^t$Bu (3 equiv), DMF (2.0 mL).* [b] *Isolated yields.*

Next, we optimized the solvents for this tandem reaction. DMSO & NMP gave 62% and 60% of **55a**. However, DMA and toluene were not effective as compared with DMF (Table 4.8). Finally, we screened various bases such as $K_2CO_3$, KOH, $Cs_2CO_3$ and NaOAc. Except $Cs_2CO_3$, other bases gave the products in the range of 51-60% (Table 4.9, Entries 1-3). Whereas $Cs_2CO_3$ was found to be equally effective as compared with KO$^t$Bu (Table 4.9, Entry 4). Interestingly, when catalyst loading was reduced to 5 mol%, tandem reaction proceeded well and without compromising yield of the product (Table 4.9, Entry 5).

**Table 4.8**: **Screening of Solvents for synthesis of Benzothieno[2,3-*b*]quinolones**

| Entry | Ligand | Base | Solvent | **55a** (% Yield)[b] |
|---|---|---|---|---|
| 1 | **L1** | KO$^t$Bu | DMSO | 62 |
| 2 | **L1** | KO$^t$Bu | NMP | 60 |
| 3 | **L1** | KO$^t$Bu | DMA | 45 |
| 4 | **L1** | KO$^t$Bu | Toluene | 55 |

*[a] Reaction conditions: Thioamide **44a** (0.5 mmol), CuI (10 mol%), **L1** (20 mol%), KO$^t$Bu (3 equiv), Solvent (2.0 mL). [b] Isolated yields.*

**Table 4.9**: **Screening of Bases for synthesis of Benzothieno[2,3-*b*]quinolones**

| Entry | Ligand | Base | Solvent | **55a** (% Yield)[b] |
|---|---|---|---|---|
| 1 | **L1** | $K_2CO_3$ | DMF | 64 |
| 2 | **L1** | KOH | DMF | 81 |
| 3 | **L1** | NaOAc | DMF | 60 |
| 4 | **L1** | $Cs_2CO_3$ | DMF | 82 |
| 5 | **L1** | $Cs_2CO_3$ | DMF | 82[c] |

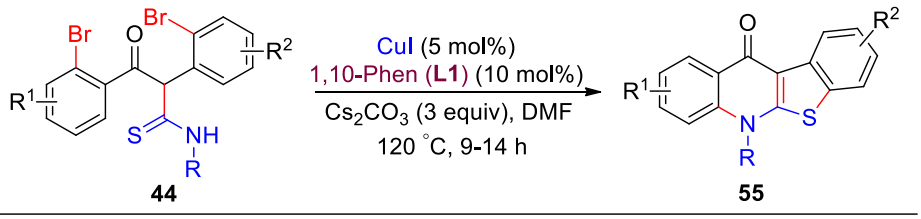
*[a] Reaction conditions: Thioamide **44a** (0.5 mmol), CuI (10 mol%), **L1** (20 mol%), KO$^t$Bu (3 equiv), Solvent (2.0 mL). [b] Isolated yields. [c] CuI (5 mol%), 1,10-Phenanthroline (10 mol%)*

The optimized tandem reaction conditions in our hand, we examined a series of *α*-(2-halophenyl)-*α*-(2-halobenzoyl)-*N*-aryl/alkyl thioamides **44** for synthesis of thieno[1,2-*b*]quinolones **55**. Thus, *N*-4-methoxyphenyl substituted thioamide **44c** gave excellent yield of **55c** (Table 4.10). Whereas 4-chloro and 4-nitro substituted *N*-phenyl thioamide gave only 73-74% yield of the products. Interestingly, alkyl substituted thioamides **45n** & **45p** gave expected compounds **55n** & **55p** (Table 4.10). Further, *N*-3-pyridyl substituted thioamide is also equally effective for this tandem coupling reactions.

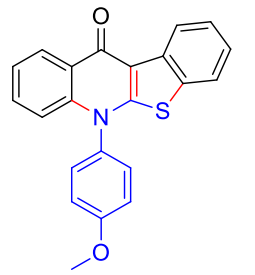
Next, we paided our attention towards *α*-(2-bromo-4,5-dimethoxy phenyl)-*α*-(2-bromo-4,5-dimethoxy benzoyl)-*N*-substituted thioamides and *α*-(2-bromo-4,5-methylenedioxy phenyl)-*α*-(2-bromo-4,5-methylenedioxy benzoyl)-*N*-aryl thioamides for synthesis of thieno[1,2-*b*]quinolones **55** through copper catalyzed tandem intramolecular C—S & C—N coupling reactions. Thioamide **44q** was transformed to **55q** in 61% yield. Whereas other substituted N-aryl thioamide **44r** gave excellent yield of thieno[1,2-*b*]quinolone **55r**.

### 4.3.4 Substrate Scope for the Synthesis of Benzothieno[2,3-*b*]quinolones

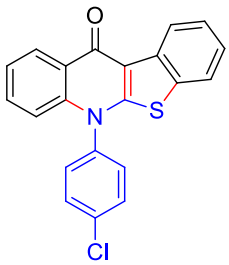
**Table 4.10**: **Copper Catalyzed Synthesis of benzothieno[2,3-*b*]quinolones 55 by Using Symmetrical Thioamides**



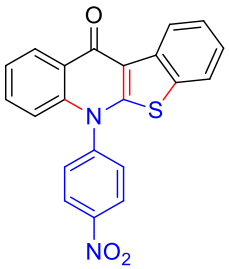

**44** **55**



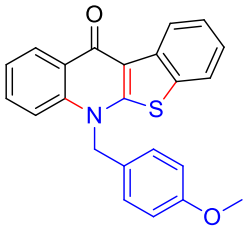

**55c** (90%)



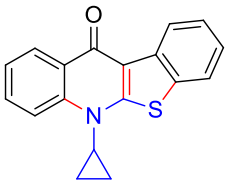

**55f** (74%)



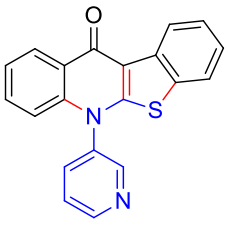

**55g** (73%)




**55n** (85%)




**55p** (85%)



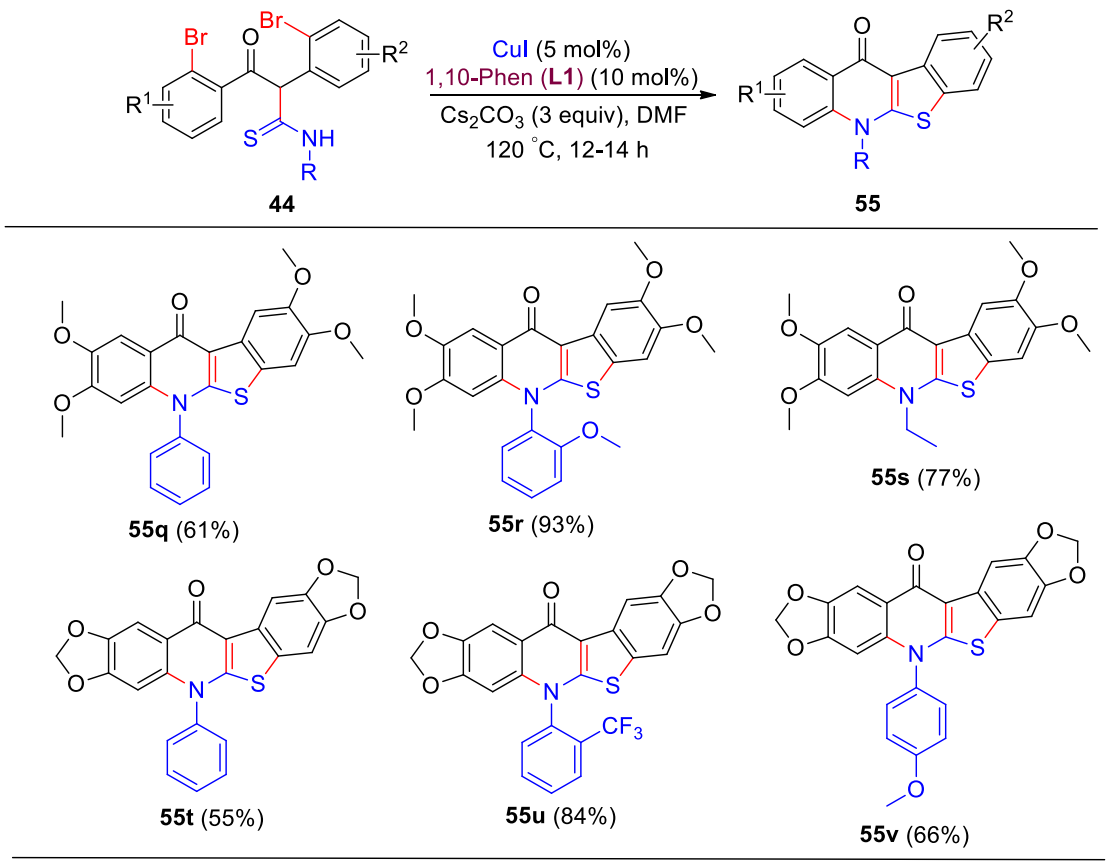

**55k** (87%)

However, *N*-alkyl thioamide **44s** was transformed into quinolone **55s** in 77% yield. Whereas *N*-phenyl & *N*-PMP substituted thioamides **44t** & **44v** gave moderate to good yield of the fused

quinolones **55t** & **55v** (Table 4.11). Interestingly, *ortho*-substituted *N*-aryl derivative gave excellent yield of **55u** under optimized conditions (Table 4.11).

Finally, we studied unsymmetrical *α*-(2-haloaryl)-*α*-(2-haloaroyl)-*N*-substituted thioamides **44w-z** and **44aa** for thieno[1,2-*b*]quinolone synthesis (Table 4.12). Thus, thioamide **44w** gave only 51% yield of **55w**. Whereas **55x-y** were synthesized from **44x-y** in 69-70% yields under optimized reaction conditions (Table 4.12). The *N*-benzyl substituted thioamide

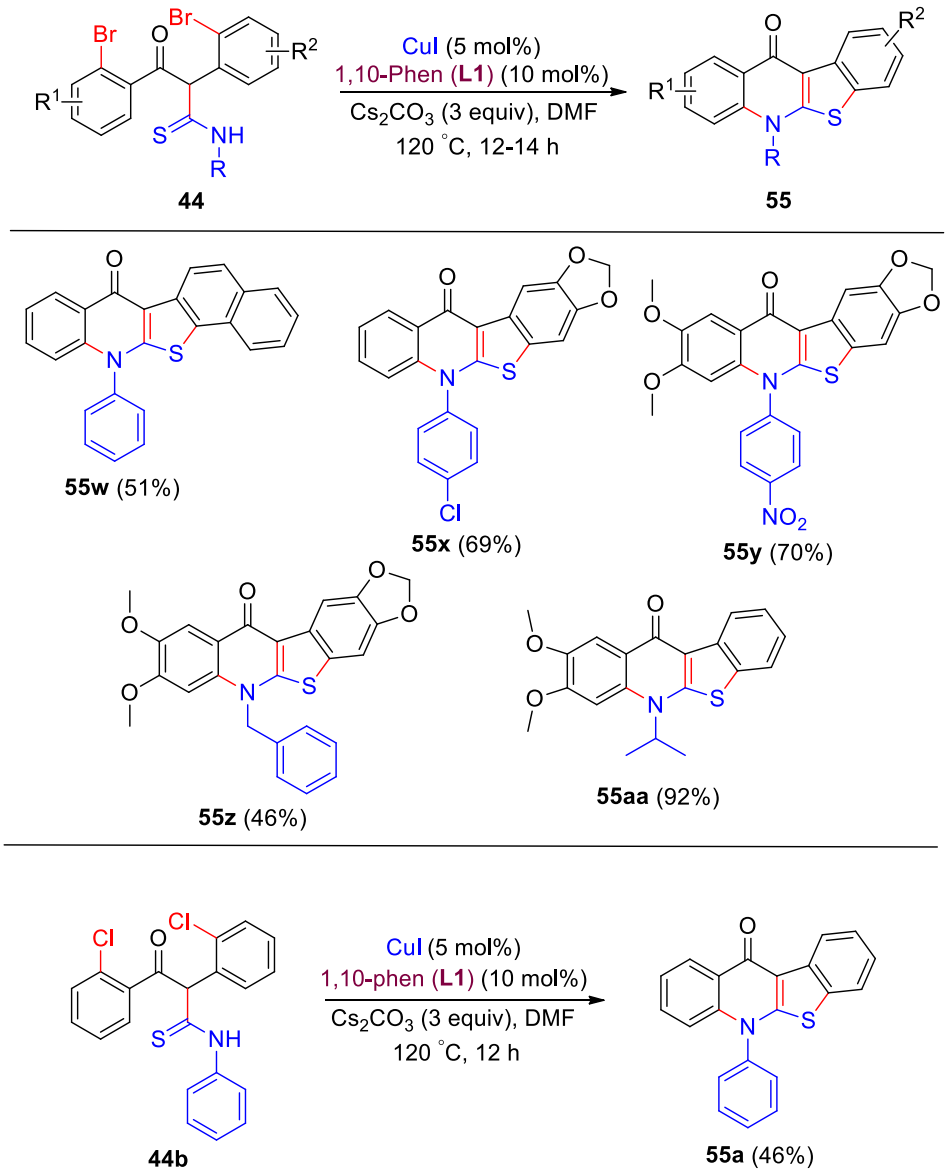
**Table 4.11**: **Copper Catalyzed Synthesis of benzothieno[2,3-*b*]quinolones 55 by Using Electron rich Symmetrical *β*-Ketothioamides**




**44z** gave moderate yield of thieno[1,2-*b*]quinolone **55z** (Table 4.12). Whereas *N*-isopropyl substituted thioamide **44aa** was smoothly transformed to quinolone **55aa** in 92% yield. The optimized tandem reactions were effective only for dibromo substituted thioamides. Where *α*-

(2-chlorophenyl)-*α*-(2-chlorobenzoyl)-*N*-phenyl thioamide **44b** gave only 46% of thieno[1,2-*b*]quinolone **55a** (Scheme 4.21).

**Table 4.12**: **Copper Catalyzed Synthesis of benzothieno[2,3-*b*]quinolones 55 by Using Electron rich Unsymmetrical *β*-Ketothioamides**




**Scheme 4.21**: *Reaction of α-(2-Chlorophenyl)-α-(2-chlorobenzoyl)-N-phenyl thioamide*

As compared with bromo aldehydes, which are starting materials for synthesis of deoxybenzoin derivative, chloro aldehydes much cheaper. Therefore we were interested in finding an alternative transition metal for tandem intramolecular cross-coupling reactions. As

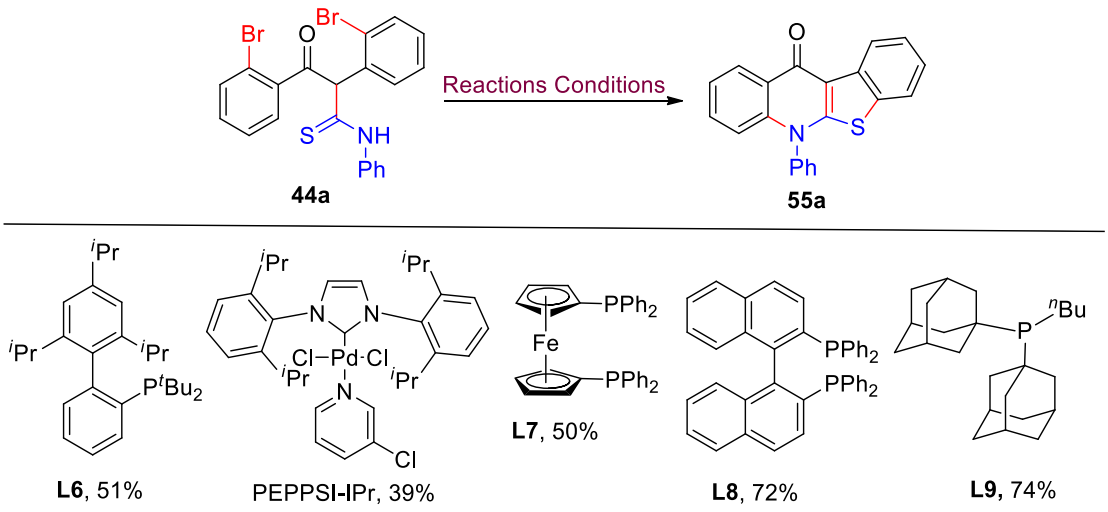
we discussed in Chapter-2, we identified a simple catalyst comprised of commercially available $^{t}$BuXPhos ligand/$Pd(OAc)_2$, which was effectively used for C—O cross-coupling reactions. Thus, we started our investigation with $Pd(OAc)_2$ and $^{t}$BuXPhos ligand (**L6**) KO$^{t}$Bu in DMF at 120 ºC for 24 h. To our surprise this system gave tandem product **55a** in 51% yield slightly higher than copper (Table 4.14). Further it gave only single sole product. For fine tuning of this process, various phosphine ligands **L6-L8** were screened. The most of the ligands afford the

**Table 4.13**: **Optimization of Reactions Conditions for Palladium Catalyzed Tandem Reaction**

| Entry | Catalyst | Ligand | Base | Solvent | Temp. (ºC) | **55a** (%Yield)[a, e] |
|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | **L9** | KO$^{t}$Bu | dioxane | 90 | 57[c] (12 h) |
| 2 | $Pd(OAc)_2$ | **L9** | $Cs_2CO_3$ | toluene | 90 | 41[b] (23 h) |
| 3 | $Pd(OAc)_2$ | **-** | KO$^{t}$Bu | dioxane | 90 | 46 (22 h) |
| 4 | $Pd(PPh_3)_4$ | - | KO$^{t}$Bu | DMF | 120 | 78 (22 h) |
| 5 | $Pd(OAc)_2$ | **L9** | KO$^{t}$Bu | DMF | 120 | 86[b, d] (24 h) |

*[a] Isolated yields. [b] $Pd(OAc)_2$ (10 mol%), CataCXium ligand (**L9**) (12 mol%), base (3 equiv. [c] $Pd(OAc)_2$ (5 mol%), CataCXium ligand (**L9**) (6 mol%), base (3 equiv). [d] Pre-activation condition. [e] Reaction times are given in parenthesis.*

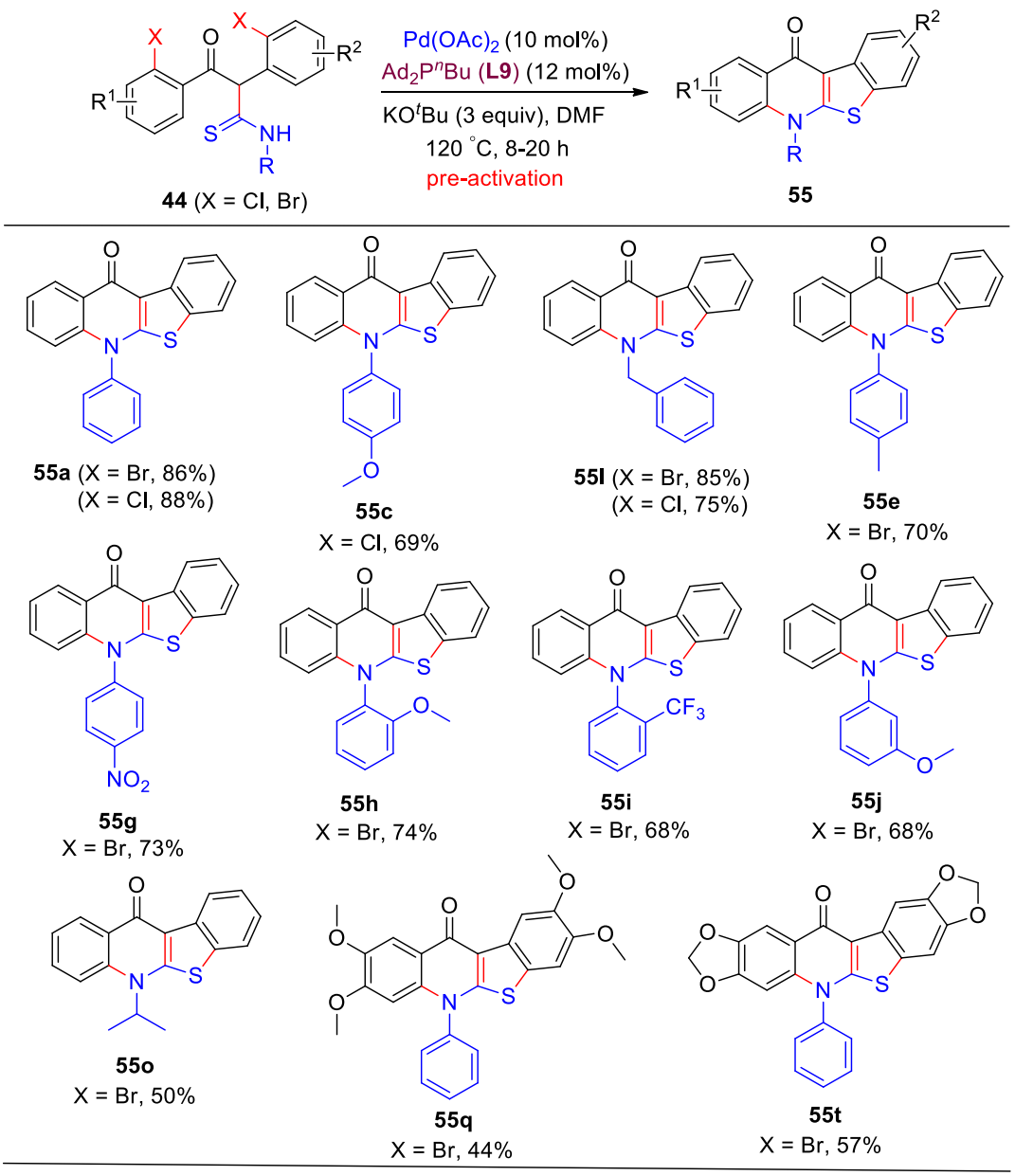
**Table 4.14**: **Screening of Ligands for Palladium Catalyzed Tandem Reaction**




*Reaction conditions: Thioamide **44a**, $Pd(OAc)_2$ (10 mol%), ligands **L6-L9** (12 mol%), KO$^{t}$Bu (3 equiv) DMF, 120 °C, 24 h*

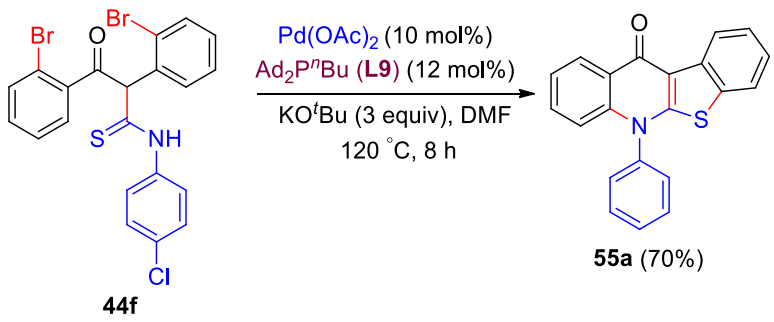
expected product in range of 39-72% (Table 4.14). Gratifyingly, $Ad_2P^nBu$ ligand (**L9**) gave 74% of thieno[1,2-*b*]quinolone **55a** with a very clean reaction. At similar condition the bromo derivative **44a** gave identical results (Table 4.15). Other solvents dioxane and toluene was not effective for tandem reaction (Table 4.13). Similarly, even $Cs_2CO_3$ did not give any significant

**Table 4.15**: **Palladium Catalyzed Synthesis of benzothieno[2,3-*b*]quinolones**




improvement in reaction (Table 4.13, Entry 2). Pd(0) complex of $Pd(PPh_3)_4$ also gave the expected product **55a** in 78% (Table 4.13, Entry 4). Thus, we performed an experiment under

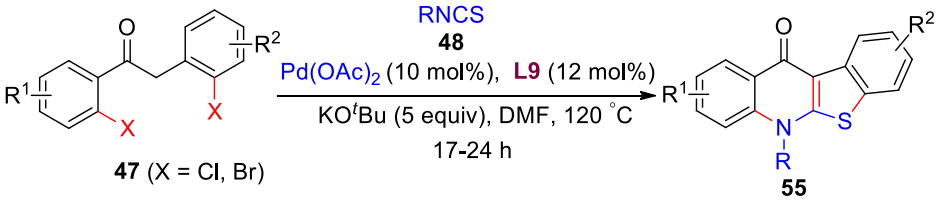
pre-activation condition, which gave 86% yield of the product **55a** (Table 4.13, Entry 5).the corresponding fused quinolone derivatives **55e** & **55g** in 70% & 73% yields respectively. *ortho*-Substituted *N*-aryl derivatives **44h-i** gave the corresponding thieno[1,2-*b*]quinolones **55h-i** in 74% and 68% yields. *N*-3-Methoxyphenyl-thieno[1,2-*b*]quinolone **55j** was prepared in 68% yield from thioamide **44j** under similar reaction conditions. However, *N*-aliphatic substituted thioamide **44o** afforded only 50% yield of the respective fused quinolone derivative **55o** (Table 4.15). Unfortunately, *N*-4-chloropheyl thioamide **44f** gave thieno[1,2-*b*]quinolone **55a** in 70% yield (Scheme 4.22). During this condition 4-chlorophenyl derivative underwent dechlorination.

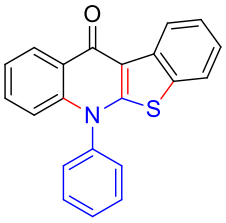



**Scheme 4.22**: *Tandem Reaction Followed by Dechlorination Reaction of β-Ketothioamide*

In the last part of this chapter, we investigated palladium catalyzed two components reaction. Thus, deoxybenzoin **47b** and phenyl isothiocyanate were heated in the presence of optimized catalyst [$Pd(OAc)_2$ & cataCXium (**L9**)] and KO$^t$Bu for 24 h. Gratifyingly, thieno[1,2-*b*]quinolone **55a** was isolated in 54% yield. It was interesting to note that, the described conditions allowed three bonds such as C—C, C—S & C—N and two rings were formed in a single synthetic operation. We also tested 3-methylphenyl isothiocyanate, that gave thieno[1,2-*b*]quinolone **55ab** in 59% yield. However, isopropyl & cyclohexyl isothiocyanates gave only 32-40% yield of quinolones **55o** & **55ac**. Whereas ethyl & cyclopropyl isothiocyanates afforded 56% & 60% yields of respective thieno[1,2-*b*]quinolones **55ad** & **55p** (Table 4.16).

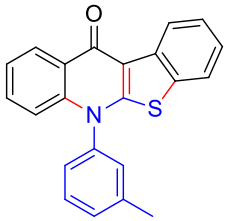
**Table 4.16**: **One-Pot Palladium Catalyzed Tandem Process to Synthesis of benzothieno[2,3-*b*]quinolones**



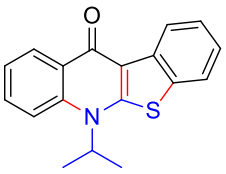
**55a**

X = Br, 54%



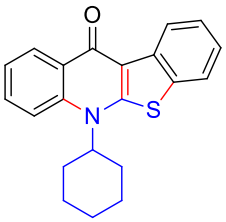
**55ab**

X = Cl, 59%



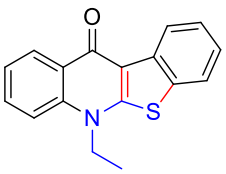
**55o**

X = Br, 40%



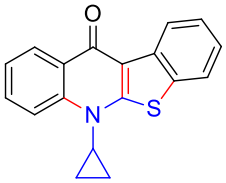
**55ac**

X = Cl, 32%



**55ad**

X = Br, 56%



**55p**

X = Cl, 60%

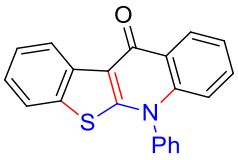
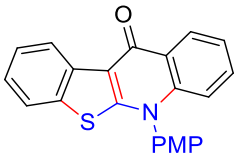
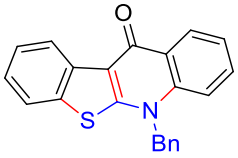
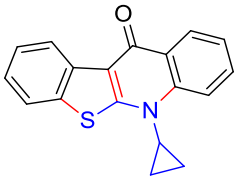
## 4.4 Biological Screening

Newly synthesized thieno[1,2-*b*]quinolines were tested for various biological activities such as anti-bacterial, anti-fungal and anti-inflammatory.

### 4.4.1 Anti-Bacterial Screening

The compounds are test in 50 µg/mL concentration. We followed Mueller Hinton Broth method for analysis. Gentamcyin & Norfloxacin were used for reference. Seven bacteria were used. The results are summarized in Table 4.17.

**Table 4.17**: **Anti-Bacterial Screening of Compounds**

| Structure of the Compounds | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
|  **55a** | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
|  **55c** | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
|  **55l** | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
|  **55p** | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
| Gentamycin (1 mg/mL) | 3.12 | 0.78 | 0.78 | >50 | 1.56 | >50 | 1.56 |
| Norfloxacin | 0.05 | 1.56 | 0.78 | >50 | 1.56 | 0.78 | 0.19 |

*1. E.Coli (ATCC 9637); 2. Pseudomonas aeruginosa (ATCC BAA-427); 3. Staphylococcus aureus (ATCC 25923); 4. Staphylococcus aureus (ATCC 700699 methicillin resistant); 5. Staphylococcus aureus (ATCC 29213); 6. Staphylococcus aureus (ATCC 33592 gentamcyin resistant); 7. Klebsiella pneumonia (ATCC 27736)*

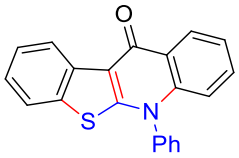
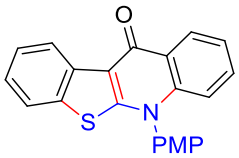
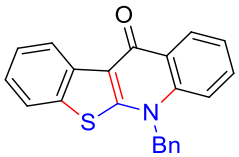
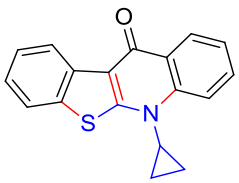
These compounds were not shown any significant activities against the following the bacteria E.Coli (ATCC 9637) (**1**), Pseudomonas aeruginosa (ATCC BAA-427) (**2**), Staphylococcus aureus (ATCC 25923) (**3**); Staphylococcus aureus (ATCC 700699 methicillin

resistant) (**4**); Staphylococcus aureus (ATCC 29213) (**5**); Staphylococcus aureus (ATCC 33592 gentamcyin resistant) (**6**); Klebsiella pneumonia (ATCC 27736) (**7**).

### 4.4.2 Anti-Fungal Screening:

The compounds are test in 50 µg/mL concentration. We used NCCLS method in RPMI 1640 medium. Fluonazole & Amphotericin B were used for reference. Six fungi were used for the screening. The results are summarized in Table 4.18.

**Table 4.18**: **Anti-Fungal Screening**

| Structure of the Compounds | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
|  **55a** | >50 | >50 | >50 | >50 | >50 | >50 |
|  **55c** | >50 | >50 | >50 | >50 | >50 | >50 |
|  **55l** | >50 | >50 | >50 | >50 | >50 | >50 |
|  **55p** | >50 | >50 | >50 | >50 | >50 | >50 |
| Fluonazole | 1.00 | 2.00 | 2.00 | >32.00 | >32.00 | 2.00 |
| Amphotericin B | 0.02 | 0.13 | 0.25 | 0.25 | 0.50 | 0.02 |

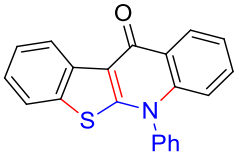
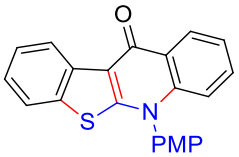
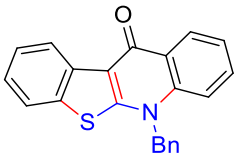
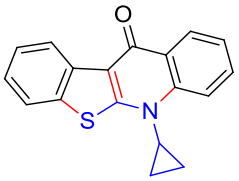
1. *Candida Albicans; 2. Crptococcus neoformans; 3. Sporothrix schenckii; 4. Trichophyton mentagrophytes; 5. Aspergillus fumigatus; 6. Candida parapsilosis (ATCC-22019).*

These compounds were not shown any significant activities against the following the fungai Candida Albicans (**1**), Crptococcus neoformans (**2**), Sporothrix schenckii (**3**), Trichophyton mentagrophytes (**4**), Aspergillus fumigatus (**5**), Candida parapsilosis (ATCC-2201900 (**6**)

### 4.4.3 Anti-inflammatory Screening:

The compounds are test in 10µg/mL concentration. Human monocytic leukemia THP-1 cells are pretreated for 12 h with the compounds and standard compound Dexamethasone (1µg/mL). Subsequently, pretreated cells were stimulated with LPS-50 µg/mL for 4 h.

**Table 4.19**: **Anti-Inflammatory Activity**

| Structure of the Compounds | % Inhibition |
|---|---|
|  **55a** | 32.41 |
|  **55c** | 54.70 |
|  **55l** | 26.90 |
|  **55p** | 51.75 |
| Dexamethasone | 75.00 |

After treatments, cell supernatant was collected for TNF measurement using ELISA. The results are summarized in Table 4.19.

These compounds showed no significant anti-inflammatory activity as compared with Dexamethasone (75%).

## 4.5 Conclusion

We designed and developed a new class of thioamides **44** which is having a multiple reactive centers. We demonstrated that chemo & regioselective copper catalyzed tandem intramolecular cross coupling of these *β*-ketothioamides **44**. We showed that *α*-(2-haloaryl)-*α*-(2-haloaroyl)-*N*-substituted thioamide **44** as a tandem precursor gave rise to a sole heterocycle i.e. thieno[1,2-*b*]quinolone **55** from 12 possible heterocycles. The tandem reaction was also studied with palladium; however, copper is the best for this process. Selected thieno[1,2-*b*]quinolones **55** were studied for anti-bacterial, anti-fungal, anti-inflammatory activities.

## 4.6 Experimental Section

### 4.6.1 Reagents

All reactions were performed by using standard vial technique with rubber septum. All solids were weighed in air. 2-Bromo benzaldehyde, *N*-bromosuccininide, sodium cyanide, piperidine, sodium bisulphite were purchased from Aldrich, Merck, Spectrochem and used as received. CuI, CuBr, CuCl and $Cu(OAc)_2$, $Pd(OAc)_2$ and $Pd(PPh_3)_4$ were purchased from Aldrich. Toluene, dioxane, DMF, DMSO, DMA, NMP, $Cs_2CO_3$, $K_2CO_3$, KO$^t$Bu, KOH and NaOAc, were purchased from Merck, Acros, Aldrich. 1,10-phenanthroline (**L1**), L-proline (**L2**), 2,2'-bipyridine (**L3**), (*R*)-(+)-1,1'-binaphthyl-2,2'-diamine (**L4**), *N,N,N′,N′*-Tetramethylethylenediamine (**L5**), 2-di-*t*-butylphosphino-2′,4′,6′-tri-isopropyl-1,1′-biphenyl (**L6**), 1,1′-bis(diphenylphosphino)ferrocene (**L7**), (*R*)-(+)-2,2′-Bis(diphenylphosphino)-1,1′-

binaphthyl **(L8),** [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride (PEPPSI-$^{i}$Pr), di-(1-adamantyl)-*n*-butyl phosphine (cataCXium®A) (**L9**) were purchased from Aldrich. All other reagents were purchased from common suppliers and used without further purification. Flash chromatography was performed using Merck Silica gel 60 (230-400 mesh). Fractions were monitored by thin-layer chromatography on precoated silica gel 60 F254 plates (Merck & co.) and were visualized by UV.

### 4.6.2 Analytical Methods

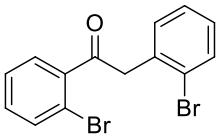
As described in Section **2.6.2** (Chapter-2).

The X-ray quality crystals for the compound **55a** was grown by slow diffusion of *n*-hexane over $CH_2Cl_2$ solution. Single-crystal X-ray diffraction data of **55a** was collected in a Bruker KAPPA APEX-II, four angle rotation system, Mo-Kα radiation (0.71073 Å).

### 4.6.3 General Procedure for the Synthesis of Deoxybenzoins

As described in Section **3.5.3** (Chapter-3)

**1,2-Bis(2-Bromophenyl)ethanone (47a)**




Reaction time: 19 h

Yield: 89%, as a pale yellow colour solid.

Melting point: 41 – 43 °C

$R_f$: 0.42 in 5% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 2886, 2818, 1686, 1588, 1564, 1509, 1472, 1432, 1406, 1310, 1278, 1264, 1170, 1147, 1117, 1047, 1028, 990, 957, 902, 811, 791, 742, 685.

$^{1}$H NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.50 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.34 – 7.28 (m, 3H), 7.18 – 7.13 (m, 1H), 4.42 (s, 2H).

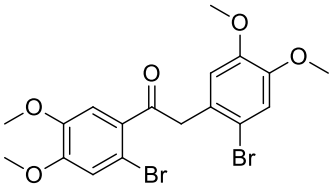
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 200.0, 141.4, 134.2, 133.8, 132.9, 132.1, 131.8, 129.1, 128.8, 127.7, 127.5, 125.3, 118.8, 49.8.

HR-MS (ESI): Calcd. for $C_{14}H_{10}Br_2O$ [M+H]: 352.9171, Found: 352.9001.

[M+H]: 354.9151, Found: 352.9147.

[M+H]: 356.9131, Found: 356.9128.

**1,2-Bis(2-bromo-4,5-dimethoxyphenyl)ethanone (47c)**




Reaction time: 19 h

Yield: 70%, as a white colour solid.

Melting point: 132 – 134 ºC

$R_f$: 0.35 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3003, 2980, 2953, 2906, 2834, 1689, 1592, 1567, 1512, 1459, 1429, 1406, 1383, 1368, 1335, 1311, 1257, 1228, 1218, 1192, 1163, 1056, 1030, 965, 921, 911, 850, 824, 795, 726.

$^{1}$H NMR (400 MHz, $CDCl_3$) δ = 7.10 (s, 1H), 7.04 (s, 1H), 7.01 (s, 1H), 6.79 (s, 1H), 4.36 (s, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H).

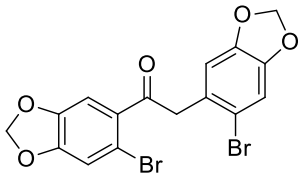
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 198.8, 151.6, 148.9, 148.6, 148.2, 132.4, 126.7, 116.5, 115.5, 115.0, 114.1, 112.5, 111.4, 56.4, 56.34, 56.27, 56.2, 48.9.

HR-MS (ESI): Calcd. for $C_{18}H_{18}Br_2O_5$ [M+H]: 472.9594, Found: 472.9564.

[M+H]: 474.9574, Found: 474.9543.

[M+H]: 476.9554, Found: 476.9528.

**1,2-Bis(6-bromobenzo[*d*][1,3]dioxol-5-yl)ethanone (47d)**



Reaction time: 19 h

Yield: 83%, as a white colour solid.

Melting point: 115 – 118 ºC

$R_f$: 0.35 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 2984, 2900, 2887, 1687, 1612, 1504, 1484, 1403, 1385, 1343, 1252, 1227, 1174, 1156, 1124, 1114, 1035, 1019, 964, 933, 866, 838.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.05 (s, 1H), 7.02 (s, 1H), 7.01 (s, 1H), 6.78 (s, 1H), 6.04 (s, 2H), 5.97 (s, 2H), 4.28 (s, 2H).

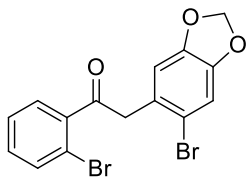
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 198.8, 150.4, 147.9, 147.6, 147.5, 134.3, 127.4, 115.6, 113.9, 112.9, 111.5, 111.4, 109.2, 102.6, 102.0, 49.4.

HR-MS (ESI): Calcd. for $C_{16}H_{10}Br_2O_5$ [M+H]: 440.8968, Found: 440.8940.

[M+H]: 442.8948, Found: 442.8901.

[M+H]: 444.8928, Found: 444.8893.

**2-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)-1-(2-bromophenyl)ethanone (47e)**



Reaction time: 19 h

Yield: 71%, as a white colour solid.

Melting point: 56 – 58 ºC

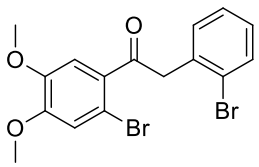
$R_f$: 0.30 in 10% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3053, 2954, 2924, 2854, 1681, 1613, 1594, 1581, 1562, 1504, 1482, 1432, 1409, 1392, 1298, 1248, 1216, 1165, 1114, 1032, 977, 961, 950, 925, 880, 837, 786, 760, 742.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.61 (d, *J* = 8.0 Hz, 1H), 7.47 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.01 (s, 1H), 6.80 (s, 1H), 5.96 (s, 2H), 4.30 (s, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 200.2, 147.9, 147.6, 141.4, 133.7, 131.8, 128.7, 127.5, 126.9, 118.7, 115.7, 112.8, 111.4, 101.9, 49.6.

**1-(2-Bromo-4,5-dimethoxyphenyl)-2-(2-bromophenyl)ethanone (47f)**



Reaction time: 19 h

Yield: 80%, as a white colour solid.

Melting point: 78 – 80 ºC

$R_f$: 0.28 in 10% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 2993, 2930, 2847, 1677, 1587, 1567, 1508, 1468, 1435, 1407, 1372, 1334, 1258, 1214, 1160, 1061, 1027, 1016, 919, 893, 860, 843, 795, 768, 753, 712, 697.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 8.0 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.16 – 7.14 (m, 1H), 7.12 (s, 1H), 7.06 (s, 1H), 4.46 (s, 2H), 3.91 (s, 3H), 3.86 (s, 3H).

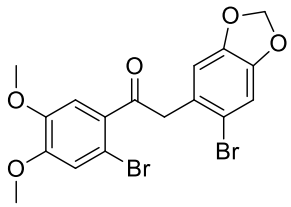
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 198.0, 151.5, 148.1, 134.9, 132.7, 132.2, 131.9, 128.8, 127.5, 125.0, 116.4, 112.5, 111.2, 56.3, 56.1, 49.3.

HR-MS (ESI): Calcd. for $C_{16}H_{14}Br_2O_3$ [M+H]: 412.9382, Found: 412.9370.

[M+H]: 414.9363, Found: 414.9357.

[M+H]: 416.9342, Found: 416.9332.

**1-(2-Bromo-4,5-dimethoxyphenyl)-2-(6-bromobenzo[*d*][1,3]dioxol-5-yl)ethanone (47g)**



Reaction time: 19 h

Yield: 78%, as a white colour solid.

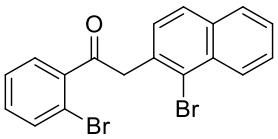
$R_f$: 0.32 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 2973, 2936, 2911, 2896, 2844, 1697, 1623, 1595, 1569, 1503, 1475, 1440, 1417, 1378, 1332, 1313, 1261, 1243, 1224, 1202, 1186, 1165, 1149, 1113, 1060, 1037, 1017, 966, 935, 917, 866, 857, 845, 829, 813, 782, 748.

$^{1}$H NMR (400 MHz, $CDCl_3$) δ = 7.10 (s, 1H), 7.05 (s, 1H), 7.01 (s, 1H), 6.78 (s, 1H), 5.96 (s, 2H), 4.35 (s, 2H), 3.91 (s, 3H), 3.87 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 198.6, 151.6, 148.2, 147.8, 147.6, 132.4, 127.7, 116.5, 115.4, 112.8, 112.5, 111.34, 111.33, 101.9, 56.4, 56.3, 49.2.

**2-(1-Bromonaphthalen-2-yl)-1-(2-bromophenyl)ethanone (47h)**




Reaction time: 19 h

Yield: 49%, as a white colour solid.

Melting point: 120 – 122 ºC

$R_f$: 0.35 in 5% ethyl acetate in hexane

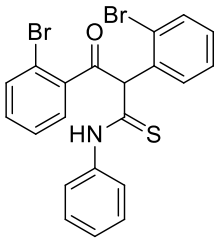
$^{1}$H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, *J* = 8.8 Hz, 1H), 7.83 – 7.78 (m, 2H), 7.64 – 7.57 (m, 2H), 7.54 – 7.50 (m, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.37 –7.34 (m, 1H), 7.31 – 7.27 (m, 1H), 4.67 (s, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 200.0, 141.4, 133.79, 133.76, 132.5, 132.4, 131.8, 128.8, 128.7, 128.2, 127.9, 127.6, 127.5 (2C), 126.6, 125.4, 118.8, 51.0.

### 4.6.4 General Procedure for the Synthesis of *β*-Ketothioamides 44

As described in section **3.6.5** (Chapter-3)

**2,3-Bis(2-bromophenyl)-3-oxo-*N*-phenylpropanethioamide (44a)**




Reaction time: 4.5 h

Yield: 77%, as a pale yellow colour solid

Melting point: 168 – 170 ºC

$R_f$: 0.35 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3444, 3322, 2370, 2345, 1572, 1498, 1466, 1309, 1229, 1190, 1087, 1024, 924, 797, 752, 695.

$^{1}$H NMR (400 MHz, $CDCl_3$) δ = 15.55 (s, 1H), 7.75 (s, 1H), 7.56 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.46 – 7.44 (m, 2H), 7.42 – 7.36 (m, 4H), 7.31 – 7.25 (m, 2H), 7.16 (td, *J* = 7.6, 1.2 Hz, 1H), 7.10 – 7.01 (m, 3H).

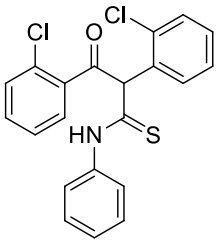
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 191.2, 171.0, 137.8, 137.5, 136.2, 133.7, 133.4, 132.7, 130.6, 130.3, 129.1, 128.6, 127.7, 127.2, 127.0, 126.2, 126.1, 121.3, 113.8.

HR-MS (ESI): Calcd. for $C_{21}H_{15}Br_2NOS$ [M+H]: 487.9314, Found: 487.9297.

[M+H]: 489.9294, Found: 489.9285.

[M+H]: 491.9273, Found: 491.9258.

**2,3-Bis(2-chlorophenyl)-3-oxo-*N*-phenylpropanethioamide (44b)**




Reaction time: 6 h

Yield: 58%, as a pale yellow colour solid.

Melting point: 168 – 170 ºC

$R_f$: 0.35 in 20% ethyl acetate in hexane

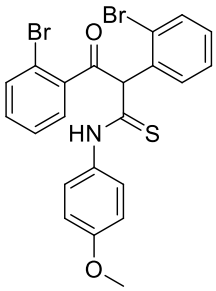
IR (KBr): ν ($cm^{-1}$) = 3463, 3337, 3060, 3028, 2927, 2738, 1605, 1594, 1577, 1498, 1466, 1432, 1413, 1332, 1308, 1255, 1231, 1193, 1156, 1123, 1094, 1056, 947, 923, 889, 799, 755, 743, 709.

$^{1}$H NMR (400 MHz, $CDCl_3$) δ = 15.57 (s, 1H), 7.77 (s, 1H), 7.42 – 7.35 (m, 6H), 7.30 (d, *J* = 6.7 Hz, 1H), 7.27 (d, *J* = 6.0 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.2 Hz, 2H), 7.03 (t, *J* = 7.4 Hz, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 191.1, 170.3, 137.4, 136.1, 135.8, 134.1, 133.6, 131.8, 130.6, 130.2, 130.1, 129.4, 129.1, 128.5, 127.8, 127.7, 126.4, 126.1, 112.1.

HR-MS (ESI): Calcd. for $C_{21}H_{15}Cl_2NOS$ [M+H]: 400.0324, Found: 400.0360.

**2,3-Bis(2-bromophenyl)-*N*-(4-methoxyphenyl)-3-oxopropanethioamide (44c)**




Reaction time: 5 h

Yield: 75%, as a yellow colour solid

Melting point: 148 – 150 ºC

$R_f$: 0.30 in 25% ethyl acetate in hexane

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.54 (s, 1H), 7.69 (s, 1H), 7.56 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.47 – 7.43 (m, 2H), 7.27 – 7.25 (m, 3H), 7.16 (td, *J* = 7.6, 1.2 Hz, 1H), 7.10 – 7.01 (m, 3H), 6.93 – 6.89 (m, 2H), 3.81 (s, 3H).

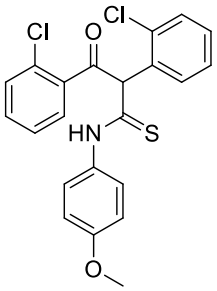
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 191.4, 170.6, 158.9, 137.8, 136.3, 133.7, 133.4, 132.7, 130.6, 130.2 (2C), 130.2, 128.5, 127.7, 127.2, 127.0, 121.3, 114.4, 113.6, 55.6.

HR-MS (ESI): Calcd. for $C_{22}H_{17}Br_2NO_2S$ [M+H]: 517.9420, Found: 517.9440.

[M+H]: 519.9400, Found: 519.9423.

[M+H]: 521.9379, Found: 521.9402.

**2,3-Bis(2-chlorophenyl)-*N*-(4-methoxyphenyl)-3-oxopropanethioamide (44d)**




Reaction time: 4 h

Yield: 68%, as a yellow colour solid.

Melting point: 62 – 64 ºC

$R_f$: 0.43 in 20% ethyl acetate in hexane

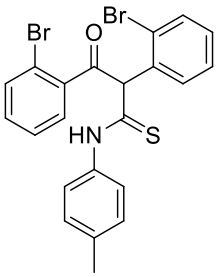
IR (KBr): ν ($cm^{-1}$) = 3349, 3054, 2933, 2836, 1607, 1576, 1510, 1466, 1434, 1298, 1247, 1092, 1057, 1033, 830, 810, 762.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.55 (s, 1H), 7.69 (s, 1H), 7.36 (d, *J* = 7.7 Hz, 2H), 7.27 – 7.20 (m, 4H), 7.18 – 7.15 (m, 1H), 7.12 – 7.09 (m, 2H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 191.4, 170.0, 158.9, 136.1, 135.8, 134.2, 133.7, 131.9, 130.5, 130.13 (2C), 130.10, 129.4, 128.6, 127.8, 127.7, 126.4, 114.3, 111.9, 55.6.

HR-MS (ESI): Calcd. for $C_{22}H_{17}Cl_2NO_2S$ [M+H]: 430.0430, Found: 430.0453.

**2,3-Bis(2-bromophenyl)-3-oxo-*N*-(*p*-tolyl)propanethioamide (44e)**




Reaction time: 3.5 h

Yield: 53%, as a yellow colour solid.

Melting point: 180 – 182 ºC

$R_f$: 0.30 in 10% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3446, 3341, 3054, 3024, 2925, 2852, 1603, 1572, 1512, 1485, 1464, 1430, 1411, 1334, 1305, 1255, 1194, 1090, 1047, 1023, 909, 798, 767, 757, 746.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.54 (s, 1H), 7.70 (s, 1H), 7.56 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.46 – 7.43 (m, 2H), 7.27 – 7.25 (m, 2H), 7.23 – 7.18 (m, 3H), 7.15 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.09 – 7.02 (m, 3H), 2.35 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 191.1, 170.7, 137.8, 137.7, 136.2, 134.8, 133.73, 133.70, 133.3, 132.6, 130.6, 130.2, 129.7, 128.5, 127.2, 127.0, 126.1, 121.3, 113.6, 21.3.

HR-MS (ESI): Calcd. for $C_{22}H_{17}Br_2NOS$ [M+H]: 501.9470, Found: 501.9410.

[M+H]: 503.9451, Found: 503.9411.

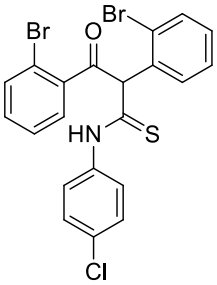
[M+H]: 505.9430, Found: 505.9399

**2,3-Bis(2-bromophenyl)-*N*-(4-chlorophenyl)-3-oxopropanethioamide (44f)**

Reaction time: 4 h

Yield: 44%, as a pale yellow colour solid.

Melting point: 168 – 170 ºC



$R_f$: 0.46 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3450, 3323, 3050, 2923, 1602, 1570, 1494, 1465, 1427, 1330, 1304, 1230, 1194, 1088, 1047, 1015, 947, 917, 797, 765, 753.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.49 (s, 1H), 7.68 (s, 1H), 7.57 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.45 (td, *J* = 7.2, 1.2 Hz, 2H), 7.36 – 7.29 (m, 4H), 7.24 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.17 (td, *J* = 7.4, 1.0 Hz, 1H), 7.11 – 7.01 (m, 3H).

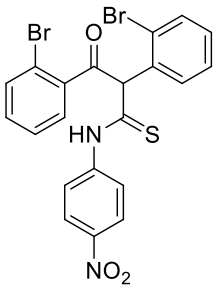
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 191.4, 171.3, 137.7, 136.0, 135.9, 133.7, 133.4, 133.2, 132.7, 130.7, 130.3, 129.3, 128.6, 128.4, 127.6, 127.1, 127.0, 121.2, 113.8.

HR-MS (ESI): Calcd. for $C_{21}H_{14}Br_2ClNOS$ [M+H]: 521.8924, Found: 521.8882.

[M+H]: 523.8903, Found: 523.8888.

[M+H]: 525.8883, Found: 525.8867.

**2,3-Bis(2-bromophenyl)-*N*-(4-nitrophenyl)-3-oxopropanethioamide (44g)**



Reaction time: 4 h

Yield: 78%, as a yellow colour solid.

Melting point: 180 – 182 ºC

$R_f$: 0.31 in 25% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3446, 3332, 3076, 2931, 2852, 1559, 1535, 1509, 1467, 1389, 1337, 1305, 1288, 1185, 1111, 1084, 1023, 853, 755.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.46 (s, 1H), 8.24 (d, *J* = 9.2 Hz, 2H), 7.84 (s, 1H), 7.63 (d, *J* = 9.2 Hz, 2H), 7.61 – 7.58 (m, 1H), 7.48 – 7.44 (m, 2H), 7.25 – 7.23 (m, 1H), 7.19 (td, *J* = 7.4, 1.0 Hz, 1H), 7.15 – 7.05 (m, 3H).

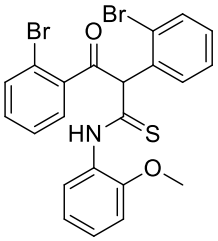
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 191.2, 172.5, 145.8, 143.2, 137.4, 135.6, 133.7, 133.5, 132.7, 131.0, 130.5, 128.8, 128.3, 127.0, 125.6, 124.6, 121.0, 114.5.

HR-MS (ESI): Calcd. for $C_{21}H_{14}Br_2N_2O_3S$ [M+H]: 532.9165, Found: 532.9105.

[M+H]: 534.9145, Found: 534.9077.

[M+H]: 536.9124, Found: 536.9049.

**2,3-Bis(2-bromophenyl)-*N*-(2-methoxyphenyl)-3-oxopropanethioamide (44h)**




Reaction time: 3.5 h

Yield: 69%, as a yellow colour solid.

Melting point: 176 – 178 °C

$R_f$: 0.38 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3446, 3322, 3046, 3021, 2935, 2838, 1605, 1570, 1522, 1463, 1432, 1410, 1351, 1319, 1289, 1249, 1191, 1162, 1113, 1083, 1047, 1027, 951, 908, 800, 769, 747.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.51 (s, 1H), 8.68 (d, *J* = 8.0 Hz, 1H), 8.45 (s, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.46 (t, *J* = 6.7 Hz, 2H), 7.34 (d, *J* = 7.0 Hz, 1H), 7.20 – 6.97 (m, 6H), 6.81 (d, *J* = 8.2 Hz, 1H), 3.59 (s, 3H).

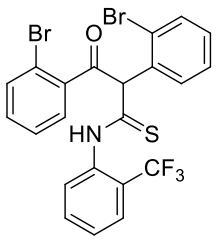
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 188.4, 169.9, 150.6, 137.9, 136.4, 133.7, 133.1, 132.6, 130.3, 130.2, 128.5, 128.2, 127.7, 127.5, 126.9, 126.8, 123.0, 121.3, 120.4, 114.9, 110.7, 55.9.

HR-MS (ESI): calcd. for $C_{22}H_{17}Br_2NO_2S$ [M+H]: 517.9420, Found: 517.9402.

[M+H]: 519.9400, Found: 519.9403.

[M+H]: 521.9379, Found: 521.9383.

**2,3-Bis(2-bromophenyl)-3-oxo-*N*-(2-trifluoromethyl)phenyl)propanethioamide (44i)**




Reaction time: 4 h

Yield: 56%, as a pale yellow colour solid.

Melting point: 150 – 152 °C

$R_f$: 0.32 in 10% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3450, 3343, 3068, 2923, 2848, 1604, 1572, 1500, 1465, 1407, 1315, 1294, 1169, 1136, 1059, 1031, 952, 919, 813, 759.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.45 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.74 (s, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.50 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.37 (d, *J* = 6.4 Hz, 1H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.11 – 7.02 (m, 3H).

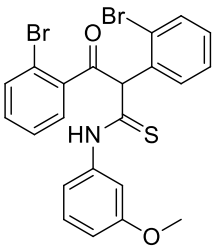
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 192.3, 171.5, 137.5, 135.6, 135.47, 135.46, 133.6, 133.4 (2C), 132.7, 132.3, 130.8 (2C), 130.4, 130.1, 128.5, 127.7, 127.4, 126.9, 126.6 (q, *J* = 5.1 Hz), 125.6 (q, *J* = 30.2 Hz), 123.3 (q, *J* = 273.3 Hz), 121.2, 114.2

HR-MS (ESI): Calcd. for $C_{22}H_{14}Br_2F_3NOS$ [M+H]: 555.9188, Found: 555.9202.

[M+H]: 557.9168, Found: 557.9181.

[M+H]: 559.9147, Found: 559.9156.

**2,3-Bis(2-bromophenyl)-*N*-(3-methoxyphenyl)-3-oxopropanethioamide (44j)**




Reaction time: 3.5 h

Yield: 61%, as a pale yellow colour solid.

Melting point: 121 – 123 $^o$C

$R_f$: 0.37 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3450, 3341, 3068, 3015, 2935, 2835, 1603, 1588, 1572, 1495, 1463, 1430, 1408, 1299, 1283, 1256, 1193, 1153, 1089, 1045, 1025, 947, 918, 868, 758, 744, 705.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.53 (s, 1H), 7.68 (s, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.42 – 7.40 (m, 2H), 7.24 (s, 1H), 7.23 – 7.20 (m, 1H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.06 – 6.97 (m, 4H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.79 (dd, *J* = 8.3, 2.1 Hz, 1H), 3.76 (s, 3H).

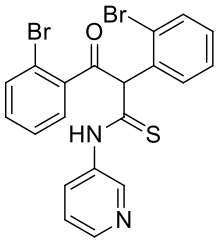
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 191.0, 171.0, 160.1, 138.5, 137.8, 136.2, 133.7, 133.4, 132.7, 130.7, 130.3, 129.8, 128.6, 128.5, 127.2, 127.0, 121.3, 118.1, 113.8, 113.4, 111.8, 55.6.

HR-MS (ESI): Calcd. for $C_{22}H_{17}Br_2NO_2S$ [M+H]: 517.9420, Found: 517.9397.

[M+H]: 519.9400, Found: 519.9431.

[M+H]: 521.9379, Found: 521.9420.

**2,3-Bis(2-bromophenyl)-3-oxo-N-(pyridine-3-yl)propanethioamide (44k)**




Reaction time: 4.5 h

Yield: 67%, as a pale yellow colour solid.

Melting point: 154 – 156 ºC

$R_f$: 0.28 in 50% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3343, 3054, 2926, 1599, 1588, 1567, 1482, 1463, 1427, 1398, 1322, 1291, 1256, 1244, 1187, 1090, 1047, 1027, 950, 917, 889, 792, 755, 739.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.46 (s, 1H), 8.50 – 8.46 (m, 2H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.77 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.47 – 7.45 (m, 2H), 7.36 –7.33 (m, 1H), 7.25 – 7.23 (m, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.11 – 7.03 (m, 3H).

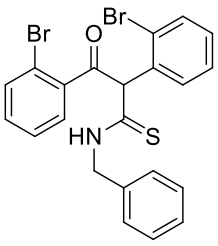
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 192.2, 172.1, 146.9, 146.0, 137.5, 135.8, 135.3, 134.9, 133.8, 133.5, 132.7, 130.9, 130.5, 128.7, 128.4, 127.1, 127.0, 123.9, 121.1, 114.1.

HR-MS (ESI): Calcd. for $C_{20}H_{14}Br_2N_2OS$ [M+H]: 488.9266, Found: 488.9260.

[M+H]: 490.9246, Found: 490.9258.

[M+H]: 492.9226, Found: 492.9236.

***N*-Benzyl-2,3-bis(2-bromophenyl)-3-oxopropanethioamide (44l)**




Reaction time: 4 h

Yield: 36%, as a white colour solid.

Melting point: 92 – 94 ºC

$R_f$: 0.38 in 10% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3450, 3356, 3054, 3028, 2918, 1603, 1571, 1509, 1472, 1454, 1425, 1400, 1308, 1269, 1185, 1104, 1047, 1024, 911, 890, 806, 757, 735.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.32 (s, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 7.4 Hz, 1H), 7.32 – 7.22 (m, 6H), 7.10 (d, *J* = 7.3 Hz, 1H), 7.07 – 6.98 (m, 3H), 6.57 (s, 1H), 4.98 (dd, *J* = 15.4, 5.7 Hz, 1H), 4.66 (dd, *J* = 15.4, 4.8 Hz, 1H).

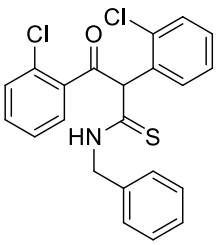
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 190.8, 169.3, 137.7, 136.1, 136.0, 133.5, 133.2, 132.6, 130.5, 130.2, 128.9, 128.5, 128.4, 128.0, 127.8, 127.1, 126.9, 121.3, 113.2, 48.4.

HR-MS (ESI): Calcd. for $C_{22}H_{17}Br_2NOS$ [M+H]: 501.9470, Found: 501.9461.

[M+H]: 503.9451, Found: 503.9449.

[M+H]: 505.9430, Found: 505.9417.

**_N_-Benzyl-2,3-bis(2-chlorophenyl)-3-oxopropanethioamide (44m)**




Reaction time: 4 h

Yield: 68%, as a white colour solid.

Melting point: 124 – 126 ºC

$R_f$: 0.38 in 10% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3371, 3063, 3028, 2922, 1605, 1577, 1513, 1469, 1310, 1255, 1188, 1057, 1033, 912, 759, 740.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.35 (s, 1H), 7.34 – 7.27 (m, 5H), 7.24 – 7.20 (m, 4H), 7.11 (t, *J* = 7.1 Hz, 2H), 7.07 – 7.00 (m, 2H), 6.61 (s, 1H), 4.99 (dd, *J* = 15.5, 5.7 Hz, 1H), 4.68 (dd, *J* = 15.5, 4.8 Hz, 1H).

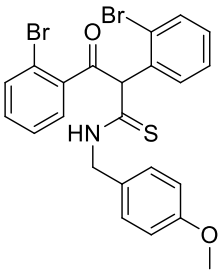
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 190.8, 168.7, 136.1, 136.0, 135.7, 133.9, 133.5, 131.9, 130.4, 130.1, 129.9, 129.4, 128.9, 127.9 (2C), 127.7, 127.6, 126.3, 111.5, 48.2.

HR-MS (ESI): Calcd. for $C_{22}H_{17}Cl_2NOS$ [M+H]: 414.0481, Found: 414.0441.

**2,3-Bis(2-bromophenyl)-_N_-(4-methoxybenzyl)-3-oxopropanethioamide (44n)**

Reaction time: 5 h

Yield: 45%, as a pale yellow colour solid.



Melting point: 150 – 152 °C

$R_f$: 0.36 in 20% ethyl acetate in hexane

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.31 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.43 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.32 (d, *J* = 6.8 Hz, 1H), 7.24 – 7.21 (m, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.09 – 6.97 (m, 4H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.48 (s, 1H), 4.89 (dd, *J* = 15.2, 5.6 Hz, 1H), 4.57 (dd, *J* = 15.2, 4.8 Hz, 1H), 3.77 (s, 3H).

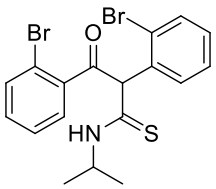
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 190.4, 169.2, 159.3, 137.7, 135.9, 133.5, 133.1, 132.6, 130.4, 130.2, 129.2, 128.5, 128.4, 128.0, 127.0, 126.9, 121.3, 114.3, 113.2, 55.4, 48.1.

HR-MS (ESI): Calcd. for $C_{23}H_{19}Br_2NO_2S$ [M+H]: 531.9576, Found: 531.9529.

[M+H]: 533.9557, Found: 533.9506.

[M+H]: 535.9536, Found: 535.9491.

**2,3-Bis(2-bromophenyl)-*N*-isopropyl-3-oxopropanethioamide (44o)**



Reaction time: 4 h

Yield: 64%, as a white colour solid; Melting point: 128 – 130 °C

$R_f$: 0.38 in 10% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3454, 3346, 3050, 2975, 2927, 2870, 1608, 1578, 1523, 1459, 1419, 1355, 1308, 1255, 1202, 1159, 1045, 1024, 963, 913, 767, 751.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.36 (s, 1H), 7.52 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.42 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.33 – 7.31 (m, 1H), 7.20 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.13 – 7.10 (m, 1H), 7.07 – 6.98 (m, 3H), 6.08 (d, *J* = 6.1 Hz, 1H), 4.73 – 4.61 (m, 1H), 1.19 (d, *J* = 6.5 Hz, 3H), 1.10 (d, *J* = 6.5 Hz, 3H).

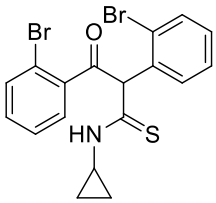
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 188.9, 169.0, 137.9, 136.2, 133.7, 133.2, 132.6, 130.4, 130.1, 128.5, 128.4, 127.0, 126.9, 121.4, 113.0, 45.6, 21.6, 21.2.

HR-MS (ESI): Calcd. for $C_{18}H_{17}Br_2NOS$ [M+Na]: 475.9290, Found: 475.930.

[M+Na]: 477.9270, Found: 477.9281.

[M+Na]: 479.9249, Found: 479.9263.

**2,3-Bis(2-bromophenyl)-*N*-cyclopropyl-3-oxopropanethioamide (44p)**




Reaction time: 5 h

Yield: 58%, as a pale yellow colour solid.

Melting point: 100 – 102 °C

$R_f$: 0.44 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3056, 3007, 1602, 1563, 1487, 1462, 1429, 1411, 1358, 1325, 1287, 1252, 1229, 1194, 1161, 1118, 1091, 1079, 1051, 1025, 983, 901, 874, 803, 788, 772, 755, 738.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.47 (s, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.18 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.10 (t, *J* = 7.3 Hz, 1H), 7.06 – 6.98 (m, 3H), 6.33 (s, 1H), 3.07 – 3.03 (m, 1H), 0.97 – 0.84 (m, 2H), 0.62 – 0.56 (m, 1H), 0.51 – 0.44 (m, 1H).

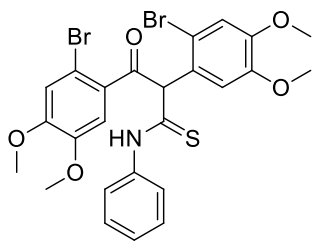
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 192.7, 169.2, 137.8, 136.1, 133.6, 133.2, 132.6, 130.4, 130.1 (2C), 128.5, 128.37, 126.9, 121.4, 112.9, 27.5, 7.9, 7.8.

HR-MS (ESI): Calcd. for $C_{18}H_{15}Br_2NOS$ [M+H]: 451.9314, Found: 451.9282.

[M+H]: 453.9294, Found: 453.9279.

[M+H]: 455.9273, Found: 455.9242.

**2,3-Bis(2-bromo-4,5-dimethoxyphenyl)-3-oxo-*N*-phenylpropanethioamide (44q)**




Reaction time: 4 h

Yield: 80%, as a pale yellow colour solid.

Melting point: 210 – 212 °C

$R_f$: 0.45 in 33% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3449, 3273, 3076, 3050, 3016, 2958, 2932, 2838, 1607, 1582, 1560, 1499, 1459, 1439, 1420, 1371, 1324, 1298, 1255, 1216, 1190, 1166, 1099, 1048, 1033, 988, 872, 839, 779, 755.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.48 (s, 1H), 7.95 (s, 1H), 7.40 – 7.39 (m, 4H), 7.32 – 7.27 (m, 1H), 6.97 (s, 1H), 6.94 (s, 1H), 6.88 (s, 1H), 6.83 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H).

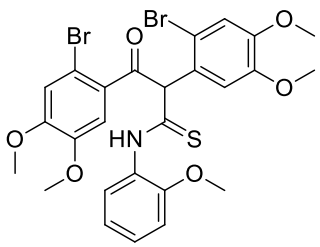
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 190.8, 171.4, 150.0, 149.7, 149.0, 147.9, 137.5, 130.4, 129.1, 128.1, 127.6, 126.0, 116.9, 115.7, 115.2, 114.9, 113.8, 111.3, 56.25, 56.18, 56.16, 56.10.

HR-MS (ESI): Calcd. for $C_{25}H_{23}Br_2NO_5S$ [M+H]: 607.9736, Found: 607.9772.

[M+H]: 609.9717, Found: 609.9764.

[M+H]: 611.9697, Found: 611.9746.

**2,3-Bis(2-bromo-4,5-dimethoxyphenyl)-*N*-(2-methoxyphenyl)-3-oxopropanethioamide (44r)**




Reaction time: 4 h

Yield: 92%, pale yellow colour solid

Melting point: 180 – 182 ºC

$R_f$: 0.28 in 40% ethyl acetate in hexane

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.43 (s, 1H), 8.63 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.57 (s, 1H), 7.16 (td, *J* = 8.0, 1.2 Hz, 1H), 7.01 – 6.99 (m, 1H), 6.97 (br s, 2H), 6.92 (s, 1H), 6.87 (s, 1H), 6.83 (dd, *J* = 8.4, 0.8 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.64 (s, 3H).

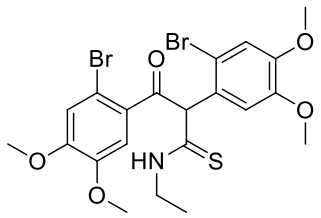
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 188.3, 170.3, 150.7, 149.8, 149.6, 148.8, 147.9, 130.5, 128.3, 127.5, 126.8, 123.2, 120.4, 117.5, 115.6, 115.0, 114.95, 114.90, 111.4, 111.3, 110.8, 56.23, 56.22, 56.15, 56.13, 55.9.

HR-MS (ESI): Calcd. for $C_{26}H_{25}Br_2NO_6S$ [M+H]: 637.9842, Found: 637.9776.

[M+H]: 639.9823, Found: 639.9778.

[M+H]: 641.9802, Found: 641.9763.

**2,3-Bis(2-bromo-4,5-dimethoxyphenyl)-*N*-ethyl-3-oxopropanethioamide (44s)**



Reaction time: 5 h

Yield: 79%, as a white colour solid

Melting point: 188 – 191 ºC

$R_f$: 0.34 in 50% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3471, 3380, 3077, 3001, 2978, 2933, 2912, 2839, 1606, 1583, 1566, 1499, 1461, 1422, 1382, 1356, 1325, 1284, 1214, 1154, 1083, 1052, 1026, 987, 904, 868, 849, 837, 795, 775, 742.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.26 (s, 1H), 6.94 (s, 1H), 6.86 (s, 1H), 6.84 (s, 1H), 6.80 (s, 1H), 6.50 (t, *J* = 5.0 Hz, 1H), 3.93 – 3.85 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H), 3.56 – 3.46 (m, 1H), 1.19 (t, *J* = 7.2 Hz, 3H).

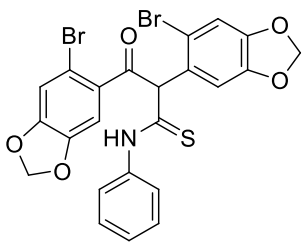
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 190.0, 169.3, 149.7, 149.5, 148.8, 147.9, 130.4, 128.1, 116.8, 115.6, 115.0, 114.9, 113.1, 111.41, 111.39, 56.2, 56.12 (2C), 56.06, 39.2, 13.3.

HR-MS (ESI): Calcd. for $C_{21}H_{23}Br_2NO_5S$ [M+H]: 559.9736, Found: 559.9749.

[M+H]: 561.9717, Found: 561.9731.

[M+H]: 563.9696, Found: 563.9712.

**2,3-Bis(6-bromobenzo[*d*][1,3]dioxol-5-yl)-3-oxo-*N*-phenylpropanethioamide (44t)**



Reaction time: 5 h

Yield: 79%, as a yellow colour solid

Melting point: 163 – 165 ºC

$R_f$: 0.30 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3339, 2900, 1578, 1499, 1474, 1448, 1328, 1298, 1236, 1116, 1036, 932, 878, 758, 695.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.46 (s, 1H), 7.86 (s, 1H), 7.42 – 7.36 (m, 4H), 7.32 – 7.27 (m, 1H), 7.03 (s, 1H), 6.95 (s, 1H), 6.93 (s, 1H), 6.81 (s, 1H), 5.98 – 5.96 (m, 2H), 5.93 (dd, *J* = 12.0, 1.2 Hz, 2H).

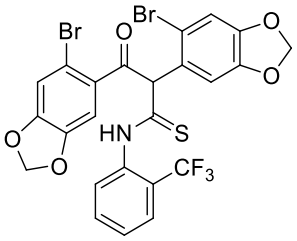
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 191.2, 170.7, 149.1, 148.7, 148.2, 146.9, 137.4, 131.1, 129.1, 128.7, 127.7, 126.2, 118.0, 113.5, 113.2, 112.8, 112.5, 112.3, 108.1, 102.4, 102.1.

HR-MS (ESI): Calcd. for $C_{23}H_{15}Br_2NO_5S$ [M+Na]: 597.8930, Found: 597.8911.

[M+Na]: 599.8911, Found: 599.8911.

[M+Na]: 601.8890, Found: 601.8895.

**2,3-Bis(6-bromobenzo[*d*][1,3]dioxol-5-yl)-3-oxo-*N*-(2-(trifluoromethyl)phenyl)propane thioamide (44u)**




Reaction time: 6 h

Yield: 75%, as a brown colour solid.

Melting point: 197 – 199 °C

$R_f$: 0.28 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3339, 3080, 3049, 3007, 2889, 2772, 1606, 1578, 1499, 1476, 1466, 1385, 1372, 1317, 1286, 1235, 1195, 1166, 1118, 1072, 1056, 1033, 995, 956, 937, 928, 883, 862, 816, 783, 762.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.36 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.01 (s, 1H), 6.97 (s, 1H), 6.93 (s, 1H), 6.90 (s, 1H), 5.98 – 5.93 (m, 4H).

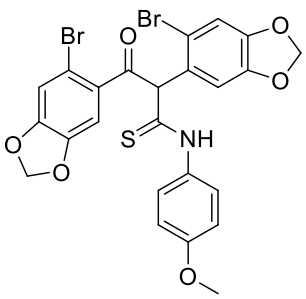
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 192.4, 171.3, 149.2, 148.9, 148.1, 146.9, 135.53, 135.51, 132.3, 130.9, 130.1, 128.2, 127.7, 126.7 (q, *J* = 5.1 Hz), 125.7 (q, *J* = 30.1 Hz), 123.3 (q, *J* = 273.5 Hz), 118.4, 114.0, 113.2, 112.9, 112.5, 112.2, 108.2, 102.4, 102.1.

HR-MS (ESI): Calcd. for $C_{24}H_{14}Br_2F_3NO_5S$ [M+Na]: 665.8804, Found: 665.8847.

[M+Na]: 667.8785, Found: 667.8828.

[M+Na]: 669.8764, Found: 669.8813.

**2,3-Bis(6-bromobenzo[*d*][1,3]dioxol-5-yl)-*N*-(4-methoxyphenyl)-3-oxopropanethioamide (44v)**



Reaction time: 4 h

Yield: 71%, as a yellow colour solid.

Melting point: 188 – 190 $^oC$

$R_f$: 0.37 in 33% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3452, 3346, 2895, 2366, 2345, 1596, 1511, 1500, 1474, 1329, 1249, 1169, 1117, 1028, 934, 835.

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 15.46 (s, 1H), 7.79 (s, 1H), 7.26 (s, 1H), 7.24 (s, 1H), 7.02 (s, 1H), 6.92 (t, *J* = 8.4 Hz, 4H), 6.80 (s, 1H), 5.97 – 5.91(m, 4H), 3.81 (s, 3H).

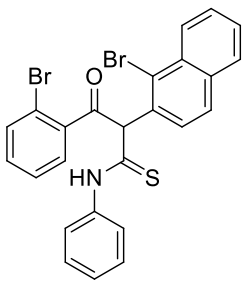
$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 191.4, 170.4, 158.8, 149.1, 148.7, 148.1, 146.9, 131.2, 130.2, 128.8, 127.7, 118.0, 114.3, 113.3, 113.1, 112.8, 112.5, 112.3, 108.1, 102.4, 102.1, 55.6.

HR-MS (ESI): Calcd. for $C_{24}H_{17}Br_2NO_6S$ [M+H]: 605.9216, Found: 605.9224.

[M+H]: 607.9197, Found: 607.9215.

[M+H]: 609.9176, Found: 609.9193.

**2-(1-Bromonaphthalen-2-yl)-3-(2-bromophenyl)-3-oxo-*N*-phenylpropanethioamide (44w)**



Reaction time: 4 h

Yield: 95%, as a pale yellow colour solid.

Melting point: 142 – 144 $^oC$

$R_f$: 0.32 in 10% ethyl acetate in hexane

$^{1}$H NMR (400 MHz, $CDCl_3$) δ = 15.67 (s, 1H), 8.33 (d, *J* = 8.4 Hz, 1H), 7.84 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.55 – 7.52 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.38 – 7.26 (m, 6H), 6.95 – 6.93 (m, 2H).

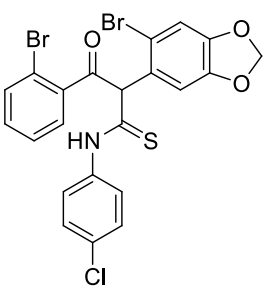
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 191.1, 170.8, 137.7, 137.4, 134.3, 134.1, 132.7, 132.4, 130.3, 129.5, 129.0 (2C), 128.5, 128.3, 128.1, 127.9, 127.8, 127.64, 127.62, 127.0, 126.2, 121.2, 114.7.

HR-MS (ESI): Calcd. for $C_{25}H_{17}Br_2NOS$ [M+H]: 537.9470, Found: 537.9455.

[M+H]: 539.9451, Found: 539.9466.

[M+H]: 541.9430, Found: 541.9453.

**2-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)-3-(2-bromophenyl)-*N*-(4-chlorophenyl)-3-oxo propanethioamide (44x)**




Reaction time: 6 h

Yield: 80%, as a yellow colour solid.

Melting point: 177 – 179 $^{o}$C

$R_f$: 0.32 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3446, 3334, 2978, 2909, 1599, 1585, 1567, 1539, 1501, 1488, 1474, 1429, 1401, 1393, 1375, 1332, 1301, 1236, 1198, 1131, 1083, 1075, 1036, 1013, 984, 929, 891, 869, 826, 817, 784, 767, 720.

$^{1}$H NMR (400 MHz, $CDCl_3$) δ = 15.46 (s, 1H), 7.81 (br s, 1H), 7.50 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.38 – 7.28 (m, 5H), 7.16 – 7.08 (m, 2H), 6.99 (s, 1H), 6.91 (s, 1H), 5.93 (d, *J* = 1.2 Hz, 1H), 5.90 (d, *J* = 1.2 Hz, 1H).

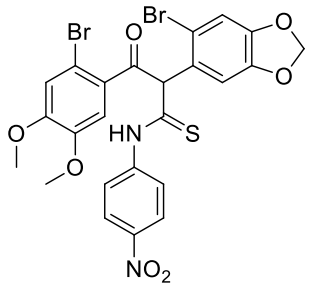
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 191.4, 171.4, 149.2, 148.1, 137.6, 135.9, 133.1, 132.7, 130.4, 129.2, 128.5, 128.3, 127.6, 127.1, 121.1, 118.1, 113.4, 113.1, 112.4, 102.3.

HR-MS (ESI): Calcd. for $C_{22}H_{14}Br_2ClNO_3S$ [M+H]: 565.8822, Found: 565.8810.

[M+H] 567.8801, Found: 567.8806.

[M+H]: 569.8781, Found: 569.8783.

**3-(2-Bromo-4,5-dimethoxyphenyl)-2-(6-bromobenzo[*d*][1,3]dioxol-5-yl)-*N*-(4-nitro phenyl)-3-oxopropanethioamide (44y)**




Reaction time: 3 h

Yield: 70%, as a yellow colour solid.

Melting point: 130 – 133 °C

$R_f$: 0.35 in 40% ethyl acetate in hexane

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.41 (s, 1H), 8.24 (d, *J* = 8.4 Hz, 2H), 7.99 (s, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.03 (s, 1H), 6.94 (s, 1H), 6.86 (s, 1H), 6.81 (s, 1H), 5.97 (d, *J* = 4.8 Hz, 2H), 3.84 (s, 3H), 3.74 (s, 3H).

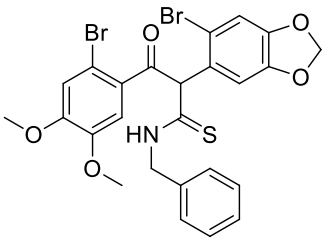
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 191.14, 172.72, 149.75, 149.50, 148.48, 147.84, 145.72, 143.25, 129.65, 128.57, 125.60, 124.54, 117.93, 115.32, 114.33, 112.98, 112.56, 111.38, 110.89, 102.53, 77.48, 77.16, 76.84, 56.23, 56.04.

HR-MS (ESI): Calcd. for $C_{24}H_{18}Br_2N_2O_7S$ [M+H]: 636.9274, Found: 636.9168.

[M+H]: 638.9255, Found: 638.9209.

[M+H]: 640.9234, Found: 640.9229.

***N*-Benzyl-3-(2-bromo-4,5-dimethoxyphenyl)-2-(6-bromobenzo[*d*][1,3]dioxol-5-yl)-3-oxopropanethioamide (44z)**




Reaction time: 4 h

Yield: 66%, as a pale yellow colour solid.

Melting point: 174 – 176 °C

$R_f$: 0.30 in 30% ethyl acetate in hexane

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.29 (s, 1H), 7.36 – 7.28 (m, 5H), 6.93 (s, 1H), 6.92 (s, 1H), 6.85 (s, 1H), 6.77 (s, 1H), 6.71 (br s, 1H), 5.91 (d, *J* = 1.5 Hz, 2H), 5.01 (dd, *J* = 15.4, 5.8 Hz, 1H), 4.66 (dd, *J* = 15.4, 4.8 Hz, 1H), 3.83 (s, 3H), 3.75 (s, 3H).

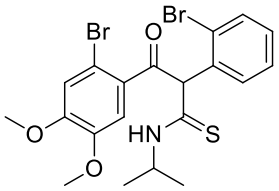
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 190.6, 169.5, 149.4, 149.0, 148.0, 147.7, 136.2, 129.9, 128.8, 127.9 (2C), 127.8, 117.8, 115.2, 113.0, 112.7, 112.4, 111.5, 111.1, 102.2, 56.1, 56.0, 48.3.

HR-MS (ESI): Calcd. for $C_{25}H_{21}Br_2NO_5S$ [M+H]: 605.9580, Found: 605.9568.

[M+H]: 607.9561, Found: 607.9586.

[M+H]: 609.9540, Found: 609.9577.

**3-(2-Bromo-4,5-dimethoxyphenyl)-2-(2-bromophenyl)-*N*-isopropyl-3-oxopropane thioamide (44aa)**




Reaction time: 4 h

Yield: 72%, as a white colour solid.

Melting point: 141 – 143 ºC

$R_f$: 0.32 in 25% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3345, 2971, 2835, 1601, 1585, 1381, 1252, 1160, 1020, 941, 888, 855, 792, 772.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 15.33 (s, 1H), 7.52 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.28 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.14 (td, *J* = 7.5, 1.1 Hz, 1H), 7.07 (td, *J* = 7.6, 1.0 Hz, 1H), 6.86 (s, 1H), 6.74 (s, 1H), 6.06 (d, *J* = 7.5 Hz, 1H), 4.70 – 4.61 (m, 1H), 3.76 (s, 3H), 3.67 (s, 3H), 1.18 (d, *J* = 6.4 Hz, 3H), 1.09 (d, *J* = 6.4 Hz, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 188.8, 169.1, 149.4, 147.7, 136.6, 133.9, 133.0, 130.5, 130.2, 128.6, 126.9, 115.1, 113.2, 111.7, 111.3, 56.1, 56.0, 45.6, 21.6, 21.2.

HR-MS (ESI): Calcd. for $C_{20}H_{21}Br_2NO_3S$ [M+H]: 513.9682, Found: 513.9668.

[M+H]: 515.9662, Found: 515.9660.

[M+H]: 517.9641, Found: 517.9629.

### 4.6.5 Procedure for the Optimization of Copper Catalyzed Tandem Intramolecular C—S and C—N bond Formation

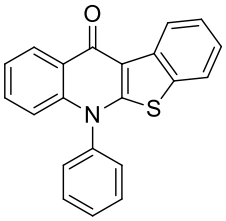
An oven-dried 8 mL reaction vial was charged with copper salt (5-10 mol%), ligand **L1**-**L5** (10-20 mol%) base (1.5 mmol) and *β*-Ketothioamide **44a** (0.5 mmol) in solvent (2.0

mL) was stirred at 120 ºC for 24 h. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was purified by flash chromatography.

### 4.6.6 General Procedure for the Copper Catalyzed Tandem Intramolecular Cross-Coupling of *β*-Ketothioamides

An oven-dried 8 mL reaction vial was charged with CuI (5 mol%), 1,10-phenanthroline (**L5**) (10 mol%), $Cs_2CO_3$ (1.5 mmol) and respective *β*-Ketothioamide **44** (0.5 mmol) in DMF (2.0 mL) was stirred at 120 ºC for 9-14 h. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was then cooled to room temperature and was purified by flash chromatography.

**6-Phenylbenzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55a)**




Reaction time: 13 h

Yield: 82%, as a white colour solid.

Melting point: 256 – 258 ºC

$R_f$: 0.32 in 25% ethyl acetate in hexane

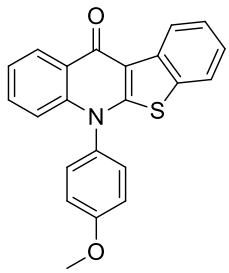
IR (KBr): ν ($cm^{-1}$) = 3048, 2923, 2852, 1618, 1589, 1520, 1483, 1442, 1340, 1288, 1184, 1091, 1018, 798, 760, 730, 702.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 9.00 (d, *J* = 7.6 Hz, 1H), 8.66 (d, *J* = 7.6 Hz, 1H), 7.73 – 7.71 (m, 3H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.54 – 7.49 (m, 4H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 173.8, 157.8, 141.7, 139.9, 136.5, 132.1, 131.8, 131.2, 130.8, 128.8, 127.0, 126.2, 125.5, 125.0, 123.4, 121.2, 117.0, 116.4.

HR-MS (ESI): Calcd. for $C_{21}H_{13}NOS$ [M+H]: 328.0791, found: 328.0792.

**6-(4-Methoxyphenyl)benzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55c)**



Reaction time: 11 h

Yield: 90%, as a white colour solid.

Melting point: 268 – 270 ºC

$R_f$: 0.30 in 25% ethyl acetate in hexane

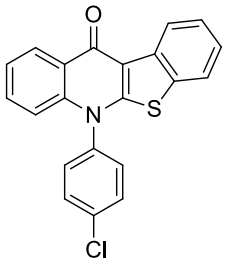
IR (KBr): ν ($cm^{-1}$) = 3050, 2953, 2927, 2835, 1618, 1594, 1515, 1479, 1406, 1285, 1252, 1024, 839, 750, 730.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.99 (d, *J* = 7.6 Hz, 1H), 8.65 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.51 (dd, *J* = 12.4, 6.5 Hz, 2H), 7.43 – 7.32 (m, 4H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 3.96 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 173.8, 161.1, 158.5, 142.0, 136.6, 132.5, 132.2, 131.8, 129.9, 127.0, 126.1, 125.5, 125.0, 124.9, 123.3, 121.2, 116.9, 116.4, 116.2, 55.9.

HR-MS (ESI): Calcd. for $C_{22}H_{15}NO_2S$ [M+H]: 358.0896, found: 358.0930.

**6-(4-Chlorophenyl)benzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55f)**



Reaction time: 11 h

Yield: 74%, as a white colour solid.

Melting point: 290 – 292 ºC

$R_f$: 0.40 in 20% ethyl acetate in hexane

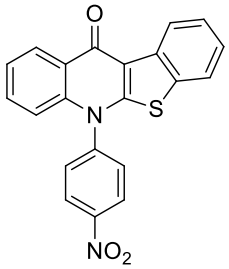
IR (KBr): ν ($cm^{-1}$) = 3043, 3029, 2982, 1617, 1593, 1571, 1558, 1519, 1482, 1456, 1441, 1408, 1337, 1288, 1253, 1188, 1089, 1058, 1031, 1015, 979, 891, 851, 835, 799, 753, 729, 715.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.98 (d, *J* = 8.0 Hz, 1H), 8.66 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.72 – 7.69 (m, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.55 – 7.51 (m, 2H), 7.50 – 7.47 (m, 2H), 7.43 – 7.39 (m, 1H), 7.38 – 7.34 (m, 1H), 6.90 (d, *J* = 8.4 Hz, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 173.8, 141.9, 141.5, 138.2, 137.0, 136.4, 133.2, 132.0, 131.6, 130.3, 127.1, 126.3, 125.5, 125.1, 125.0, 123.6, 121.3, 117.1, 116.1.

HR-MS (ESI): Calcd. for $C_{21}H_{12}ClNOS$ [M+H]: 362.0401, found: 362.0427.

**6-(4-Nitrophenyl)benzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55g)**




Reaction time: 10 h

Yield: 73%, as a yellow colour solid.

Melting point: 304 – 306 ºC

$R_f$: 0.40 in 33% ethyl acetate in hexane

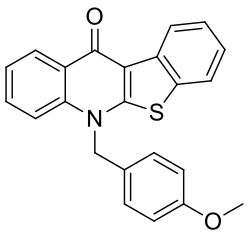
IR (KBr): ν ($cm^{-1}$) = 3056, 3032, 2927, 2852, 1618, 1593, 1521, 1490, 1410, 1349, 1313, 1290, 1253, 1190, 1105, 977, 838, 749, 730.

$^1$H NMR (400 MHz, DMSO) δ = 8.82 (d, *J* = 8.4 Hz, 1H), 8.64 (d, *J* = 9.2 Hz, 2H), 8.48 (d, *J* = 9.2 Hz, 1H), 8.14 (d, *J* = 9.2 Hz, 2H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.68 (t, *J* = 8.4 Hz, 1H), 7.58 – 7.49 (m, 2H), 7.42 (t, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 1H).

$^{13}$C NMR (100 MHz, DMSO) δ = 172.6, 156.7, 148.7, 144.4, 141.0, 135.7, 132.4, 131.5, 130.9, 126.6, 126.1, 126.0, 125.0, 124.6, 123.6, 123.5, 122.2, 116.5, 115.8.

HR-MS (ESI): Calcd. for $C_{21}H_{12}N_2O_3S$ [M+H]: 373.0641, found: 373.0627.

**6-(4-Methoxybenzyl)benzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55n)**




Reaction time: 11 h

Yield: 85%, as a white colour solid.

Melting point: 168 – 170 ºC

$R_f$: 0.30 in 33% ethyl acetate in hexane

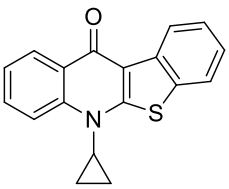
IR (KBr): ν ($cm^{-1}$) = 3065, 2925, 2835, 1620, 1595, 1558, 1539, 1514, 1491, 1442, 1418, 1361, 1305, 1280, 1247, 1196, 1173, 1135, 1076, 1021, 987, 864, 815, 802, 756, 731.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 9.01 (d, *J* = 8.0 Hz, 1H), 8.64 (d, *J* = 7.2 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.39 – 7.35 (m, 3H), 7.09 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 5.49 (s, 2H), 3.74 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 173.5, 159.5, 157.0, 140.0, 136.6, 132.1, 131.2, 127.4, 127.2, 126.2, 125.9, 125.7, 124.9, 124.8, 123.2, 121.3, 117.0, 115.1, 114.7, 55.4, 54.5.

HR-MS (ESI): Calcd. for $C_{23}H_{17}NO_2S$ [M+H]: 372.1053, found: 372.1032.

**6-Cyclopropylbenzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55p)**



Reaction time: 11 h

Yield: 85%, as a white colour solid.

Melting point: 206 – 208 ºC

$R_f$: 0.29 in 20% ethyl acetate in hexane

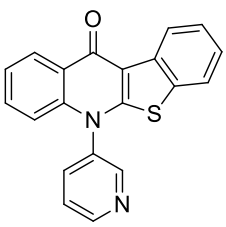
IR (KBr): ν ($cm^{-1}$) = 3055, 2995, 2923, 2848, 1619, 1593, 1571, 1519, 1492, 1458, 1441, 1412, 1357, 1342, 1287, 1255, 1170, 1095, 1044, 944, 841, 796, 751, 729.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.97 (d, *J* = 8.0 Hz, 1H), 8.62 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.69 – 7.65 (m, 1H), 7.53 – 7.49 (m, 1H), 7.42 – 7.35 (m, 2H), 3.51 – 3.45 (m, 1H), 1.54 – 1.49 (m, 2H), 1.34 – 1.30 (m, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 173.6, 157.9, 141.3, 136.1, 132.1, 131.4, 127.0, 125.8, 125.7, 124.7, 124.6, 123.1, 121.0, 117.0, 116.1, 32.2, 11.3.

HR-MS (ESI): Calcd. for $C_{18}H_{13}NOS$ [M+H]: 292.0791, found: 292.0792.

**6-(Pyridin-3-yl)benzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55k)**



Reaction time: 9 h

Yield: 87%, as a white colour solid.

Melting point: 282 – 284 ºC

$R_f$: 0.30 in 5% methanol in dichloromethane.

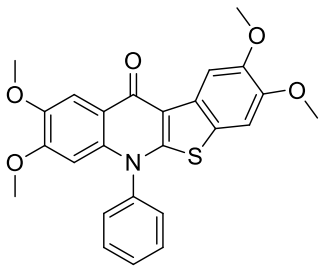
IR (KBr): ν ($cm^{-1}$) = 3041, 2925, 2852, 1620, 1595, 1573, 1542, 1524, 1483, 1445, 1425, 1344, 1293, 1256,1189, 1130, 1029, 977, 825, 793, 747, 727, 717.

$^1$H NMR (400 MHz, $CD_2Cl_2$ + TFA-d) δ = 9.57 (s, 1H), 9.46 (d, *J* = 5.6 Hz, 1H), 8.95 (d, *J* = 8.0 Hz, 1H), 8.87 (d, *J* = 8.0 Hz, 1H), 8.77 (d, *J* = 8.4 Hz, 1H), 8.59 – 8.56 (m, 1H), 7.88 (t, *J* = 7.8 Hz, 1H), 7.83 – 7.76 (m, 2H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 1H).

$^{13}$C NMR (100 MHz, $CD_2Cl_2$ + TFA-d) δ = 173.9, 158.4, 147.9, 145.8, 144.6, 140.7, 139.3, 134.5, 134.2, 132.1, 130.8, 127.3, 127.0, 126.3, 125.6, 124.9, 123.6, 122.2, 117.8, 115.6.

HR-MS (ESI): Calcd. for $C_{20}H_{12}N_2OS$ [M+H]: 329.0743, found: 329.0741.

**2,3,8,9-Tetramethoxy-6-phenylbenzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55q)**



Reaction time: 12 h

Yield: 61%, as a brown colour solid.

Melting point: 246 – 248 °C

$R_f$: 0.30 in 2% methanol in dichloromethane

IR (KBr): ν ($cm^{-1}$) = 2920, 1586, 1498, 1416, 1310, 1274, 1210, 1053, 1035, 865, 821, 700.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.56 (s, 1H), 7.95 (s, 1H), 7.72 – 7.70 (m, 3H), 7.57 (d, *J* = 6.0 Hz, 2H), 7.01 (s, 1H), 6.21 (s, 1H), 4.04 (s, 3H), 4.01 (s, 3H), 3.89 (s, 3H), 3.67 (s, 3H).

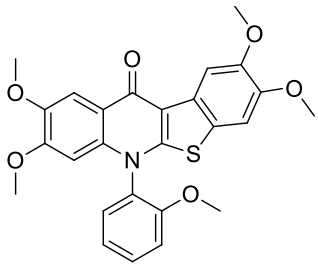
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 172.6, 155.5, 153.0, 148.6, 147.8, 146.7, 140.0, 137.3, 131.1, 130.8, 129.8, 128.7, 123.9, 118.9, 116.7, 106.9, 105.8, 103.6, 97.9, 56.3 (2C), 56.1, 55.9.

HR-MS (ESI): Calcd. for $C_{25}H_{21}NO_5S$ [M+H]: 448.1213, found: 448.1247.

**2,3,8,9-Tetramethoxy-6-(2-methoxyphenyl)benzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55r)**

Reaction time: 12 h

Yield: 93%, as a white colour solid.



Melting point: 247 – 249 ºC

$R_f$: 0.35 in 50% ethyl acetate in hexane

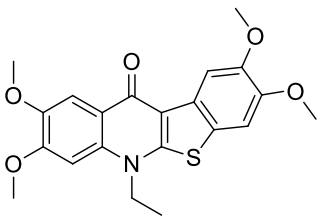
IR (KBr): ν ($cm^{-1}$) = 2996, 2943, 2838, 1624, 1600, 1498, 1466, 1438, 1415, 1317, 1277, 1253, 1212, 1190, 1139, 1091, 1054, 1026, 1003, 871, 818, 784, 760.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.61 (s, 1H), 8.01 (s, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.26 – 7.25 (m, 1H), 7.22 (d, *J* = 8.0 Hz, 1H),7.06 (s, 1H), 6.22 (s, 1H), 4.06 (s, 3H), 4.03 (s, 3H), 3.90 (s, 3H), 3.71 (s, 3H), 3.69 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 172.9, 156.0, 155.7, 153.1, 148.7, 147.7, 146.7, 137.2, 132.5, 130.2 (2C), 128.0, 123.8, 122.1, 119.1, 116.7, 113.5, 107.0, 106.0, 103.8, 97.6, 56.35, 56.30, 56.2, 56.1, 56.0.

HR-MS (ESI): Calcd. for $C_{26}H_{23}NO_6S$ [M+H]: 478.1319, found: 478.1369.

**6-Ethyl-2,3,8,9-tetramethoxybenzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55s)**



Reaction time: 12 h

Yield: 77%, as a white colour solid.

Melting point: 255 – 257 ºC

$R_f$: 0.38 in pure dichloromethane

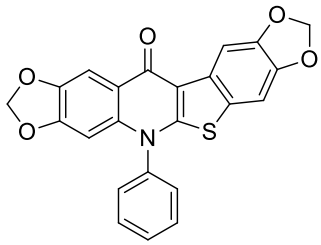
IR (KBr): ν ($cm^{-1}$) = 2998, 2946, 2841, 1622, 1592, 1566, 1508, 1475, 1457, 1443, 1413, 1337, 1288, 1255, 1209, 1185, 1086, 1045, 1023, 1007, 977, 869, 839, 824, 773, 756, 725.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.58 (s, 1H), 7.99 (s, 1H), 7.08 (s, 1H), 6.67 (s, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 4.06 (s, 3H), 4.03 (s, 3H), 3.97 (s, 3H), 3.92 (s, 3H), 1.49 (t, *J* = 7.2 Hz, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 172.2, 153.5, 153.3, 148.7, 147.7, 146.4, 134.8, 130.2, 122.9, 119.7, 116.7, 106.9, 106.5, 103.6, 95.9, 56.3 (2C), 56.24, 56.23, 46.7, 12.7.

HR-MS (ESI): Calcd. for $C_{21}H_{21}NO_5S$ [M+H]: 400.1213, found: 400.1210.

**6-Phenyl-[1,3]dioxolo[4'',5'':4',5']benzo[1',2':4,5]thieno[2,3-*b*][1,3]dioxolo[4,5-g]quinolin-12(6*H*)-one (55t)**



Reaction time: 12 h

Yield: 55% (X = Br), as a yellow colour solid.

Melting point: > 340 °C

$R_f$: 0.47 in pure dichloromethane

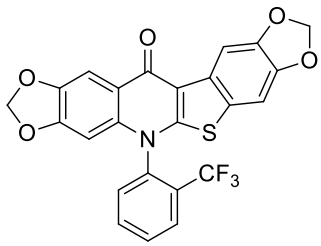
IR (KBr): ν ($cm^{-1}$) = 3046, 2962, 2905, 2773, 1616, 1586, 1561, 1531, 1498, 1474, 1443, 1313, 1263, 1159, 1123, 1053, 1036, 929, 866, 831, 750.

$^1$H NMR (400 MHz, $CDCl_3$ + TFA-d) δ = 8.07 (s, 1H), 8.04 (s, 1H), 7.84 – 7.83 (m, 3H), 7.50 – 7.48 (m, 2H), 7.07 (s, 1H), 6.55 (s, 1H), 6.19 (s, 2H), 6.05 (s, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$ + TFA-d) δ = 159.0, 154.9, 148.7, 148.4, 148.2, 140.0, 138.7, 132.6, 132.0, 127.0, 126.9, 126.4, 116.8, 116.4, 113.6, 105.9, 104.0, 102.4, 101.9, 100.9, 96.4.

HR-MS (ESI): Calcd. for $C_{23}H_{13}NO_5S$ (M): 415.0509, found: 415.0540.

**6-(2-(Trifluoromethyl)phenyl)-[1,3]dioxolo[4'',5'':4',5']benzo[1',2':4,5]thieno[2,3-*b*][1,3]dioxolo[4,5-g]quinolin-12(6*H*)-one (55u)**



Reaction time: 14 h

Yield: 84%, as a brown colour solid.

Melting point: 330 – 332 °C

$R_f$: 0.37 in 2% methanol in dichloromethane

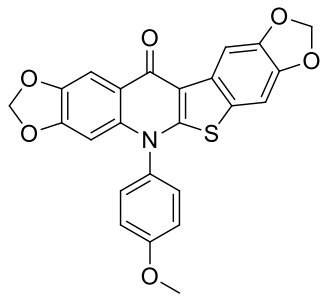
IR (KBr): ν ($cm^{-1}$) = 3037, 3010, 2916, 1617, 1596, 1571, 1529, 1474, 1456, 1446, 1309, 1295, 1265, 1234, 1179, 1160, 1141, 1111, 1051, 1035, 953, 929, 883, 836, 812, 781, 723.

$^1$H NMR (400 MHz, $CDCl_3$ + TFA-d) δ = 8.18 (s, 1H), 8.14 (dd, *J* = 7.2, 1.2 Hz, 1H), 8.10 (s, 1H), 8.08 – 8.02 (m, 2H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.12 (s, 1H), 6.39 (s, 1H), 6.22 (d, *J* = 6.4 Hz, 2H), 6.10 (s, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 164.1, 159.7, 155.4, 149.1, 148.8, 148.6, 140.5, 136.0, 135.29, 135.27, 133.5, 130.1, 129.9 (q, *J* = 4.5 Hz), 127.9 (q, *J* = 32.8 Hz), 126.9, 126.1, 122.1 (q, *J* = 280.0 Hz), 117.0, 115.0, 106.2, 104.3, 102.5 (2C), 102.1, 100.7, 96.4.

HR-MS (ESI): Calcd. for $C_{24}H_{12}F_3NO_5S$ [M+H]: 484.0461, found: 484.0481.

**6-(4-Methoxyphenyl)-[1,3]dioxolo[4'',5'':4',5']benzo[1',2':4,5]thieno[2,3-*b*][1,3]dioxolo [4,5-g]quinolin-12(6*H*)-one (55v)**



Reaction time: 12 h

Yield: 66%, as a white colour solid.

Melting point: > 340 ºC

$R_f$: 0.34 in pure dichloromethane

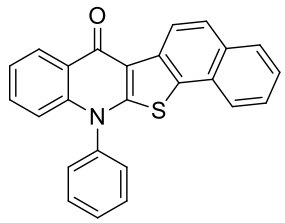
IR (KBr): ν ($cm^{-1}$) = 3062, 2997, 2965, 2897, 2837, 1621, 1594, 1570, 1530, 1497, 1487, 1472, 1313, 1299, 1266, 1252, 1236, 1180, 1160, 1112, 1036, 1025, 1006, 954, 927, 891, 876, 847.

$^1$H NMR (400 MHz, $CDCl_3$ + TFA-d) δ = 8.13 (s, 1H), 7.98 (s, 1H), 7.39 – 7.27 (m, 4H), 7.13 (s, 1H), 6.66 (s, 1H), 6.22 (s, 2H), 6.12 (s, 2H), 4.00 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 162.4, 160.1, 155.2, 149.0, 148.7, 148.4, 140.6, 131.0, 128.2, 127.2, 126.2, 117.0 (2C), 116.7, 115.0, 106.14, 104.16, 102.5, 102.0, 100.3, 96.6, 56.1.

HR-MS (ESI): Calcd. for $C_{24}H_{15}NO_6S$ [M+H]: 446.0693, found: 446.0687.

**12-Phenylnaphtho[2',1':4,5]thieno[2,3-*b*]quinolin-7(12*H*)-one (55w)**



Reaction time: 14 h

Yield: 51%, as a white colour solid.

Melting point: > 300 ºC

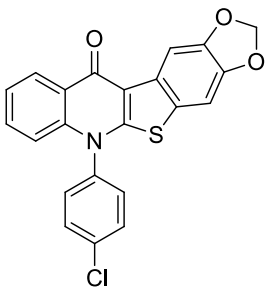
$R_f$: 0.42 in 33% ethyl acetate in hexane

$^1$H NMR (400 MHz, $CD_2Cl_2$) δ = 9.03 (d, *J* = 8.8 Hz, 1H), 8.63 (d, *J* = 7.6 Hz, 1H), 7.98 – 7.94 (m, 2H), 7.85 – 7.78 (m, 4H), 7.60 – 7.51 (m, 5H), 7.43 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H).

$^{13}$C NMR (100 MHz, $CD_2Cl_2$) δ = 174.4, 157.7, 142.3, 140.5, 135.1, 132.3, 131.83, 131.78, 131.3, 129.5, 129.3, 128.9, 128.4, 127.3, 127.23, 127.19, 126.0, 125.9, 123.7, 123.5, 123.4, 118.5, 117.0.

HR-MS (ESI): Calcd. for $C_{25}H_{15}NOS$ [M+H]: 378.0947, found: 378.0913.

**6-(4-Chlorophenyl)-[1,3]dioxolo[4'',5'':4',5']benzo[1',2':4,5]thieno[2,3-*b*]quinolin-11 (6*H* )-one (55x)**




Reaction time: 14 h

Yield: 69%, as a pale pink colour powder.

Melting point: > 340 ºC

$R_f$: 0.52 in pure dichloromethane

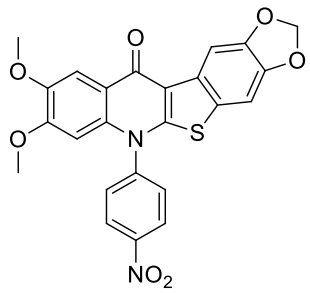
IR (KBr): ν ($cm^{-1}$) = 3041, 3028, 2979, 2893, 2776, 1617, 1591, 1570, 1521, 1490, 1460, 1440, 1421, 1333, 1316, 1287, 1260, 1202, 1182, 1088, 1080, 1044, 1008, 943, 866, 850, 786, 749.

$^1$H NMR (400 MHz, $CDCl_3$ + TFA-d) δ = 8.66 (d, *J* = 8.4 Hz, 1H), 8.27 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.05 (s, 1H), 6.04 (s, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$ + TFA-d) δ = 170.7, 160.1, 148.0, 147.9, 140.9, 138.2, 137.2, 133.7, 132.0, 129.4, 128.2, 126.5, 125.7, 125.6, 122.1, 117.7, 116.8, 105.6, 102.1, 101.7.

HR-MS (ESI): Calcd. for $C_{22}H_{12}ClNO_3S$ [M+H]: 406.0299, found: 406.0262.

**8,9-Dimethoxy-6-(4-nitrophenyl)-[1,3]dioxolo[4'',5'':4',5']benzo[1',2':4,5]thieno[2,3-*b*] quinolin-11(6*H*)-one (55y)**



Reaction time: 14 h

Yield: 65%, as a brown colour solid.

Melting point: 308 – 310 ºC

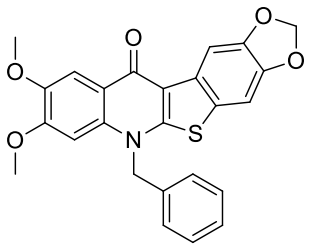
$R_f$: 0.33 in 50% ethyl acetate in hexane

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.73 (d, *J* = 6.8 Hz, 2H), 8.20 (s, 1H), 8.09 (s, 1H), 7.84 (d, *J* = 7.2 Hz, 2H), 7.16 (s, 1H), 6.44 (s, 1H), 6.14 (s, 2H), 4.08 (s, 3H), 3.82 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 158.4, 156.9, 150.2, 150.1, 149.5, 149.02, 148.98, 143.2, 138.2, 129.2, 127.6, 126.6, 126.2, 117.1, 113.4, 106.4, 103.4, 102.8, 102.1, 97.4, 57.0, 56.8.

HR-MS (ESI): Calcd. for $C_{24}H_{16}N_2O_7S$ (M): 476.0673, found: 476.0709.

**6-Benzyl-8,9-dimethoxy-[1,3]dioxolo[4'',5'':4',5']benzo[1',2':4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55z)**



Reaction time: 12 h

Yield: 46%, as a white colour solid.

Melting point: 261 – 264 ºC

$R_f$: 0.38 in 33% ethyl acetate in hexane

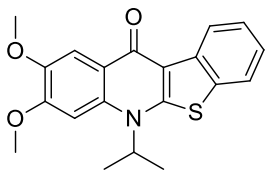
IR (KBr): ν ($cm^{-1}$) = 3019, 2997, 2929, 1618, 1591, 1574, 1507, 1471, 1437, 1327, 1287, 1253, 1207, 1158, 1064, 1038, 1016, 945, 850, 811, 768.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.49 (s, 1H), 7.94 (s, 1H), 7.30 – 7.17 (m, 5H), 7.06 (s, 1H), 6.62 (s, 1H), 6.04 (s, 2H), 5.45 (s, 2H), 4.00 (s, 3H), 3.75 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 172.3, 154.5, 153.1, 147.3, 146.4, 146.2, 135.5, 134.2, 131.0, 129.4, 128.5, 126.2, 123.8, 119.4, 116.8, 106.3, 104.9, 101.5, 101.2, 97.2, 56.3, 56.1, 55.4.

HR-MS (ESI): Calcd. for $C_{25}H_{19}NO_5S$ [M+H]: 446.1057, found: 446.1081.

**6-Isopropyl-8,9-dimethoxybenzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55aa)**



Reaction time: 12 h

Yield: 92%, as a white colour solid.

Melting point: 218 – 220 $^{o}$C

$R_f$: 0.29 in 50% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3058, 2969, 2934, 2848, 1624, 1590, 1502, 1458, 1442, 1376, 1324, 1271, 1238, 1203, 1154, 1116, 1084, 1026, 880, 827, 790, 777, 751, 729.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 9.02 (d, *J* = 7.6 Hz, 1H), 8.08 (s, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.16 (s, 1H), 4.96 (br s, 1H), 4.045 (s, 3H), 4.038 (s, 3H), 1.88 (d, *J* = 6.8 Hz, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 172.3, 155.2, 151.9, 146.0, 136.4, 134.4, 130.8, 130.7, 125.5, 124.4 (2C), 120.6, 116.3, 106.5, 98.5, 59.1, 56.0, 55.9, 20.4.

HR-MS (ESI): Calcd. for $C_{20}H_{19}NO_3S$ [M+H]: 354.1158, found: 354.1163.

### 4.6.7 Procedure for the Optimization of Palladium Catalyzed Tandem Intramolecular C—S and C—N bond Formation

An oven-dried 8 mL reaction vial was charged with $Pd(OAc)_2$ (5-10 mol%), ligand **L6**-**L9** (6-12 mol%) base (1.5 mmol) and respective *β*-ketothioamide **44** (0.5 mmol) in solvent (2.0 mL) was stirred at 90-120 $^{o}$C for 12-24 h. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was purified by flash chromatography.

### 4.6.8 General Procedure for the Palladium Catalyzed Tandem Intramolecular Cross-Coupling of *β*-Ketothioamides *via* Pre-Activation Protocol

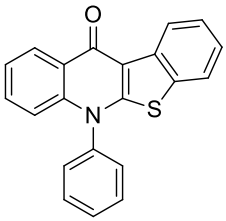
An oven-dried 8 mL reaction vial was charged with $Pd(OAc)_2$ (10 mol%), di-(1-adamantyl)-*n*-butyl phosphine ligand (**L9**) (12 mol%) and KO$^t$Bu (0.75 mmol) in DMF (1.0 mL) was stirred at 90 $^{o}$C for 5 min. Then it was cooled and respective thioenolate anion

generated from the *β*-ketothioamide **44** (0.5 mmol) in presence of KO$^t$Bu (0.75 mmol) in DMF (1.0 mL) under another an oven-dried 8 mL reaction vial was added at room temperature. The reaction mixture was stirred at 120 $^o$C and it was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was then cooled to room temperature and purified by flash chromatography.

### 4.6.9 General Procedure for the One-pot Palladium Catalyzed Tandem Intramolecular C—S and C—N bond Formation

An oven-dried 8 mL reaction vial was charged with deoxybenzoin **47**, KO$^t$Bu (1.5 mmol) in DMF (1.0 mL) was stirred at room temperature for 1h. Another reaction vial equipped with $Pd(OAc)_2$ (10 mol%), di-(1-adamantyl)-*n*-butyl phosphine ligand (**L9**) (12 mol%) and KO$^t$Bu (1.5 mmol) in DMF (1.0 mL) was stirred at 80 $^o$C for 3 min. Further, this pre-catalyst was added to the above reaction mixture at room temperature and stirred at 120 $^o$C. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was then cooled to room temperature and purified by flash chromatography.

**6-Phenylbenzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55a)**

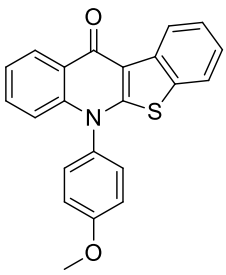



Reaction time: 8 h (X = Br), 16 h (X = Cl), 17 h (X = Br, one-pot).

Yield: 86% (X = Br), 88% (X = Cl), 54% (X = Br, one-pot), as a white colour solid.

Melting point, $R_f$, IR, Spectral data and HR-MS as described in Section **4.6.5**

**6-(4-Methoxyphenyl)benzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55c)**

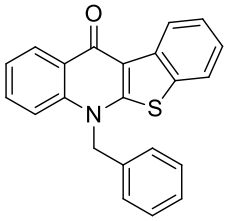


Reaction time: 16 h

Yield: 69% (X = Cl), as a white colour solid.

Melting point, $R_f$, IR, Spectral data and HR-MS as described in Section **4.6.5**

**6-Benzylbenzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55l)**



Reaction time: 8 h (X = Br), 16 h (X = Cl).

Yield: 85% (X = Br), 75% (X = Cl), as a brown colour solid.

Melting point: 214 – 216 ºC

$R_f$: 0.34 in 20% ethyl acetate in hexane

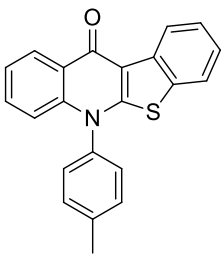
IR (KBr): ν ($cm^{-1}$) = 3059, 2923, 1616, 1581, 1522, 1489, 1438, 1277, 1138, 758, 729.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.72 (d, *J* = 7.9 Hz, 1H), 8.33 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.24 – 7.19 (m, 2H), 7.07 – 6.97 (m, 6H), 6.85 – 6.83 (m, 2H), 5.20 (s, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 173.5, 157.0, 140.0, 136.7, 133.9, 132.1, 131.2, 129.3, 128.3, 127.3, 126.2, 126.0, 125.9, 125.0, 124.9, 123.3, 121.3, 117.1, 115.1, 54.9

HR-MS (ESI): Calcd. for $C_{22}H_{15}NOS$ [M+H]: 342.0947, found: 342.0966.

**6-(*p*-Tolyl)benzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55e)**



Reaction time: 9 h

Yield: 70% (X = Br), as a white colour solid.

Melting point: 250 – 252 ºC

$R_f$: 0.32 in 20% ethyl acetate in hexane

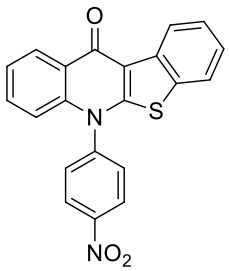
IR (KBr): ν ($cm^{-1}$) = 3041, 2918, 1617, 1595, 1481, 1406, 1284, 1184, 1029, 750, 728.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.99 (d, *J* = 7.9 Hz, 1H), 8.65 (d, *J* = 7.9 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.53 – 7.47 (m, 4H), 7.39 – 7.31 (m, 4H), 6.93 (d, *J* = 8.4 Hz, 1H), 2.55 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 173.8, 158.0, 141.8, 141.1, 137.3, 136.5, 132.1, 131.8, 131.7, 128.4, 126.9, 126.1, 125.5, 124.91, 124.87, 123.3, 121.2, 116.9, 116.4, 21.6.

HR-MS (ESI): Calcd. for $C_{22}H_{15}NOS$ [M+H]: 342.0947, found: 342.0947.

**6-(4-Nitrophenyl)benzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55g)**

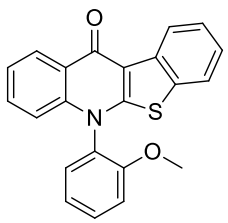



Reaction time: 10 h

Yield: 73% (X = Br), as a yellow colour solid.

Melting point, $R_f$, IR, Spectral data and HR-MS as described in section **4.6.5**

**6-(2-Methoxyphenyl)benzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55h)**




Reaction time: 8 h

Yield: 74% (X = Br), as a white colour solid.

Melting point: 234 – 236 ºC

$R_f$: 0.31 in 20% ethyl acetate in hexane

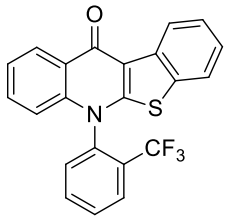
IR (KBr): ν ($cm^{-1}$) = 2971, 2927, 2835, 1612, 1588, 1480, 1338, 1278, 1248, 1015, 757, 724.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 9.00 (d, *J* = 7.9 Hz, 1H), 8.67 (d, *J* = 7.8 Hz, 1H), 7.68 – 7.61 (m, 2H), 7.52 – 7.50 (m, 2H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.26 – 7.22 (m, 2H), 6.89 (d, *J* = 8.3 Hz, 1H), 3.71 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 173.9, 158.4, 155.7, 141.5, 136.7, 132.5, 132.1, 131.8, 130.2, 127.8, 126.9, 126.0, 125.5, 124.85, 124.78, 123.3, 122.1, 121.2, 116.9, 116.0, 113.5, 56.0.

HR-MS (ESI): Calcd. for $C_{22}H_{15}NO_2S$ [M+H]: 358.0896, found: 358.0868.

**6-(2-(Trifluoromethyl)phenyl)benzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55i)**



Reaction time: 20 h

Yield: 68% (X = Br), as a white colour solid.

Melting point: 224 – 226 $^{o}$C

$R_f$: 0.38 in 20% ethyl acetate in hexane

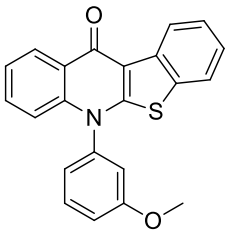
IR (KBr): ν ($cm^{-1}$) = 3071, 3040, 3006, 2923, 2861, 1617, 1590, 1519, 1483, 1457, 1443, 1409, 1369, 1340, 1319, 1192, 1167, 1157, 1138, 1120, 1064, 1036, 884, 817, 785, 757, 729.

$^{1}$H NMR (400 MHz, $CDCl_3$) δ = 9.00 (d, *J* = 8.0 Hz, 1H), 8.65 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.94 (t, *J* = 7.4 Hz, 1H), 7.86 (t, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 2H), 7.55 – 7.48 (m, 2H), 7.42 – 7.34 (m, 2H), 6.69 (d, *J* = 8.4 Hz, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 173.9, 157.7, 141.9, 137.03, 137.02, 136.3, 135.1, 132.2, 132.0, 131.8, 131.6, 129.7 (q, *J* = 31.0 Hz), 129.1 (q, *J* = 4.7 Hz), 127.0, 126.2, 125.3, 125.0 (2C), 123.6, 122.5 (q, *J* = 273.0 Hz), 121.3 (2C), 117.2, 116.4.

HR-MS (ESI): Calcd. for $C_{22}H_{12}F_3NOS$ [M+H]: 396.0664, found: 396.0674.

**6-(3-Methoxyphenyl)benzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55j)**



Reaction time: 9 h

Yield: 68% (X = Br), as a pale yellow colour solid.

Melting point: 212 – 214 $^{o}$C

$R_f$: 0.30 in 25% ethyl acetate in hexane

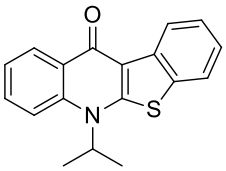
IR (KBr): ν ($cm^{-1}$) = 3065, 2835, 1618, 1588, 1521, 1482, 1340, 1243, 1172, 1040, 794, 752, 728.

$^{1}$H NMR (400 MHz, $CDCl_3$) δ = 8.98 (d, *J* = 8.0 Hz, 1H), 8.64 (d, *J* = 7.7 Hz, 1H), 7.63 – 7.59 (m, 2H), 7.53 – 7.48 (m, 2H), 7.39 – 7.31 (m, 2H), 7.22 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 7.05 (s, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 3.89 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 173.8, 161.7, 157.6, 141.5, 140.8, 136.4, 132.1, 131.9, 131.8, 126.9, 126.1, 125.4, 124.9 (2C), 123.4, 121.2, 120.5, 116.9, 116.7, 116.4, 113.9, 55.8.

HR-MS (ESI): Calcd. for $C_{22}H_{15}NO_2S$ [M+H]: 358.0896, found: 358.0898.

**6-Isopropylbenzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55o)**



Reaction time: 10 h (X = Br), 18 h (X = Br, one-pot)

Yield: 50%, 40% (one-pot), as a white colour solid.

Melting point: 150 – 152 ºC

$R_f$: 0.39 in 20% ethyl acetate in hexane

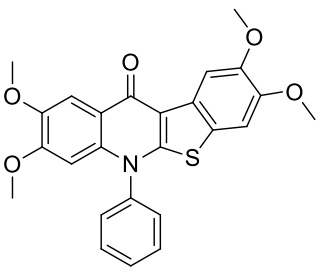
IR (KBr): ν ($cm^{-1}$) = 3063, 3015, 2971, 2931, 2865, 1618, 1592, 1517, 1497, 1331, 1258, 1166, 1127, 1083, 1018, 794, 754, 746.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 9.03 (d, *J* = 8.0 Hz, 1H), 8.70 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.68 – 7.64 (m, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.43 – 7.36 (m, 2H), 4.99 (br s, 1H), 1.86 (d, *J* = 7.1Hz, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 173.5, 139.1, 136.7, 131.2, 131.0, 127.8, 126.8, 126.1, 124.88 (2C), 124.86 (2C), 122.9, 120.9, 116.4, 59.6, 20.5.

HR-MS (ESI): Calcd. for $C_{18}H_{15}NOS$ [M+H]: 294.0947, found: 294.0974.

**2,3,8,9-Tetramethoxy-6-phenylbenzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55q)**

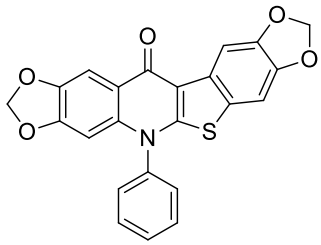


Reaction time: 10 h

Yield: 44% (X = Br), as a yellow colour solid.

Melting point, $R_f$, IR, Spectral data and HR-MS as described in section **4.6.5**

**6-Phenyl-[1,3]dioxolo[4'',5'':4',5']benzo[1',2':4,5]thieno[2,3-*b*][1,3]dioxolo[4,5-*g*] quinolin-12(6*H*)-one (55t)**

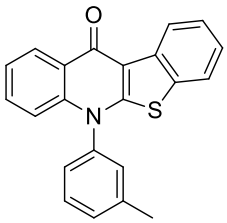


Reaction time: 10 h

Yield: 57% (X = Br), as a yellow colour solid.

Melting point, $R_f$, IR, Spectral data and HR-MS as described in section **4.6.5**

**6-(*m*-Tolyl)benzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55ab)**



Reaction time: 24 h (one-pot)

Yield: 59% (X = Cl), as a white colour solid.

Melting point: 216 – 218 $^oC$

$R_f$: 0.48 in 20% ethyl acetate in hexane

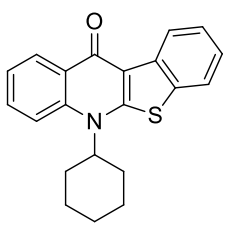
IR (KBr): ν ($cm^{-1}$) = 3048, 2918, 2852, 1619, 1594, 1516, 1489, 1441, 1337, 1292, 1168, 1091, 1019, 794, 748, 727.

$^1H$ NMR (400 MHz, $CDCl_3$) δ = 9.00 (d, *J* = 8.0 Hz, 1H), 8.68 (d, *J* = 7.9 Hz, 1H), 7.62 – 7.58 (m, 2H), 7.54 – 7.49 (m, 3H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.31 – 7.30 (m, 2H), 6.94 (d, *J* = 8.5 Hz, 1H), 2.51 (s, 3H).

$^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 173.8, 157.9, 141.7, 141.6, 139.8, 136.5, 132.1, 131.8, 131.5, 130.9, 129.0, 127.0, 126.1, 125.6, 125.4, 125.0, 124.9, 123.4, 121.2, 116.9, 116.5, 21.5.

HR-MS (ESI): Calcd. for $C_{22}H_{15}NOS$ [M+H]: 342.0947, found: 342.0955.

**6-Cyclohexylbenzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55ac)**



Reaction time: 24 h (one-pot)

Yield: 32% (X = Cl), as a white colour solid.

Melting point: 162 – 164 $^oC$

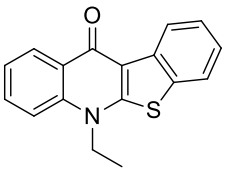
$R_f$: 0.34 in 33% ethyl acetate in hexane

$^1$H NMR (400 MHz, $CDCl_3$) δ = 9.03 (d, *J* = 7.9 Hz, 1H), 8.73 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.89 (brs, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.44 – 7.37 (m, 2H), 2.69 – 2.66 (m, 2H), 2.11 – 2.07 (m, 4H), 1.94 – 1.87 (m, 2H), 1.64 – 1.53 (m, 2H), 1.47 – 1.39 (m, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 173.6, 140.9, 131.1, 127.8, 126.9, 126.2, 125.02 (2C), 125.00 (2C), 124.0, 123.0, 120.9, 117.0, 116.7, 30.1, 26.8 (2C), 25.3.

HR-MS (ESI): Calcd. for $C_{21}H_{19}NOS$ [M+H]: 334.1260, found: 334.1260.

**6-Ethylbenzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55ad)**




Reaction time: 23 h (one-pot)

Yield: 56% (X = Br), as a white colour solid.

Melting point: 176 – 178 °C

$R_f$: 0.28 in 33% ethyl acetate in hexane

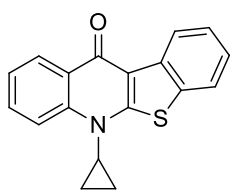
IR (KBr): ν ($cm^{-1}$) = 3063, 3041, 2979, 2923, 2861, 1612, 1587, 1515, 1492, 1466, 1442, 1413, 1364, 1275, 1145, 1083, 847, 799, 762, 734.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.99 (d, *J* = 8.0 Hz, 1H), 8.65 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.68 (t, *J* = 7.9 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 7.42 – 7.35 (m, 2H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.55 (t, *J* = 7.2 Hz, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 173.3, 155.8, 139.2, 136.7, 132.0, 131.1, 127.5, 126.1, 126.0, 124.83, 124.81, 123.0, 121.2, 116.9, 114.2, 46.6, 12.6.

HR-MS (ESI): Calcd. for $C_{17}H_{13}NOS$ [M+H]: 280.0791, found: 280.0798.

**6-Cyclopropylbenzo[4,5]thieno[2,3-*b*]quinolin-11(6*H*)-one (55p)**




Reaction time: 24 h (one-pot)

Yield: 60% (X = Cl), as a white colour solid.

Melting point, $R_f$, IR, Spectral data and HR-MS as described in Section **4.6.5**

## 4.7 Copies of Selected $^{1}H$ & $^{13}C$ NMR Spectra

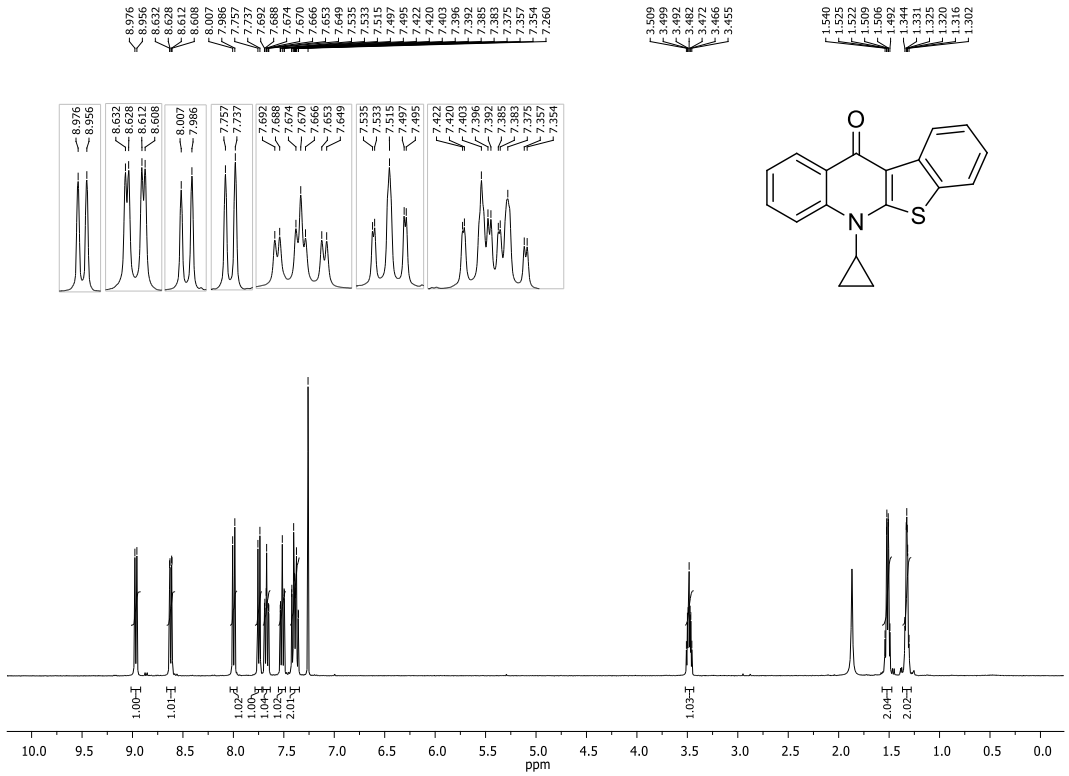



**Figure 4.3a**: $^{1}H$ NMR Spectrum of **55p**

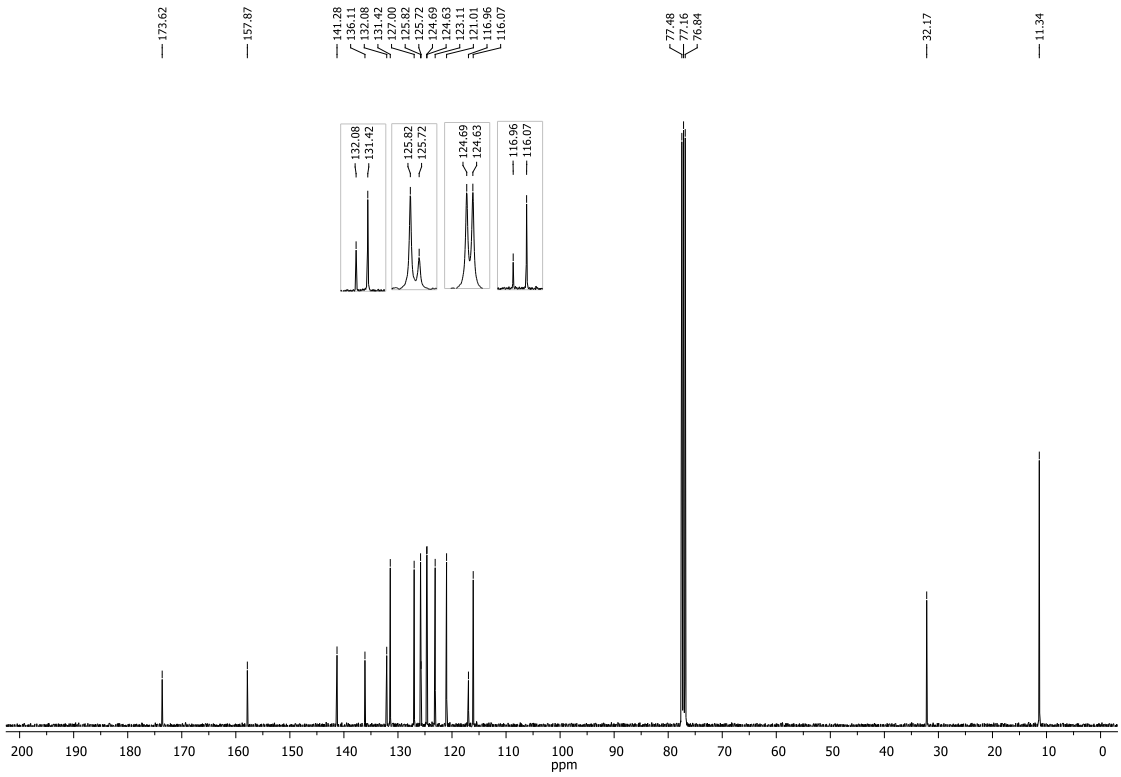



**Figure 4.3b**: $^{13}C$ NMR Spectrum of **55p**

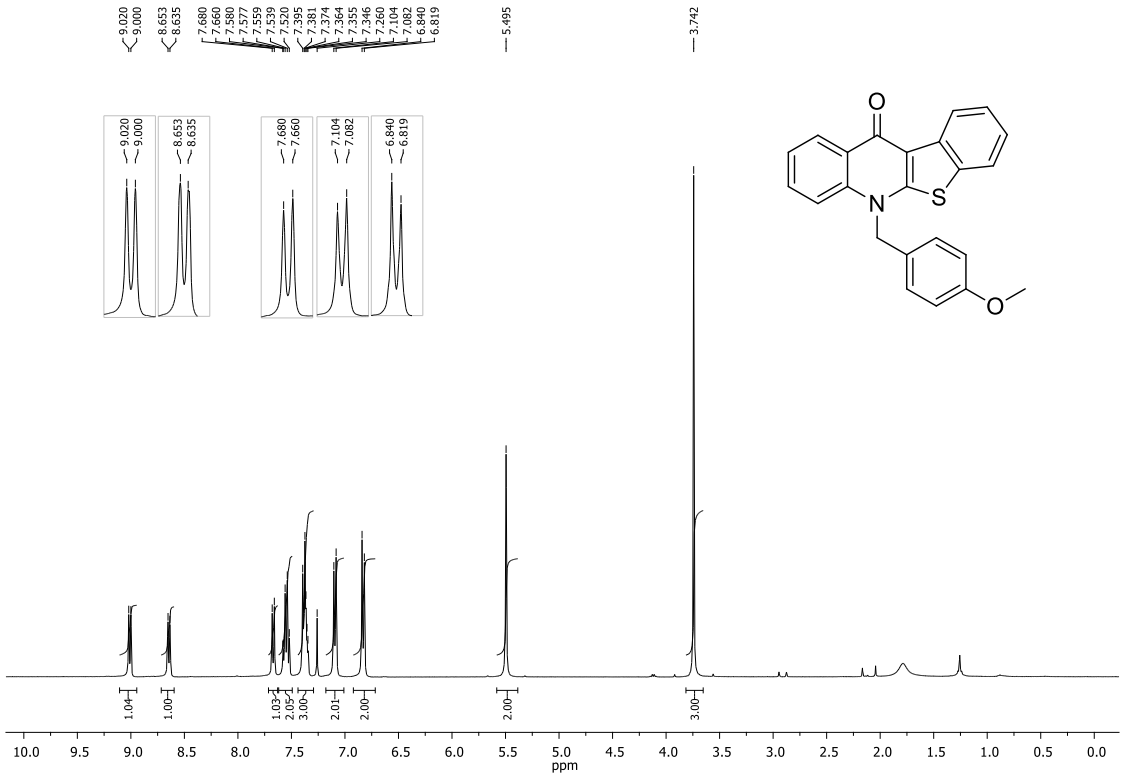



**Figure 4.4a**: $^{1}$H NMR Spectrum of **55n**

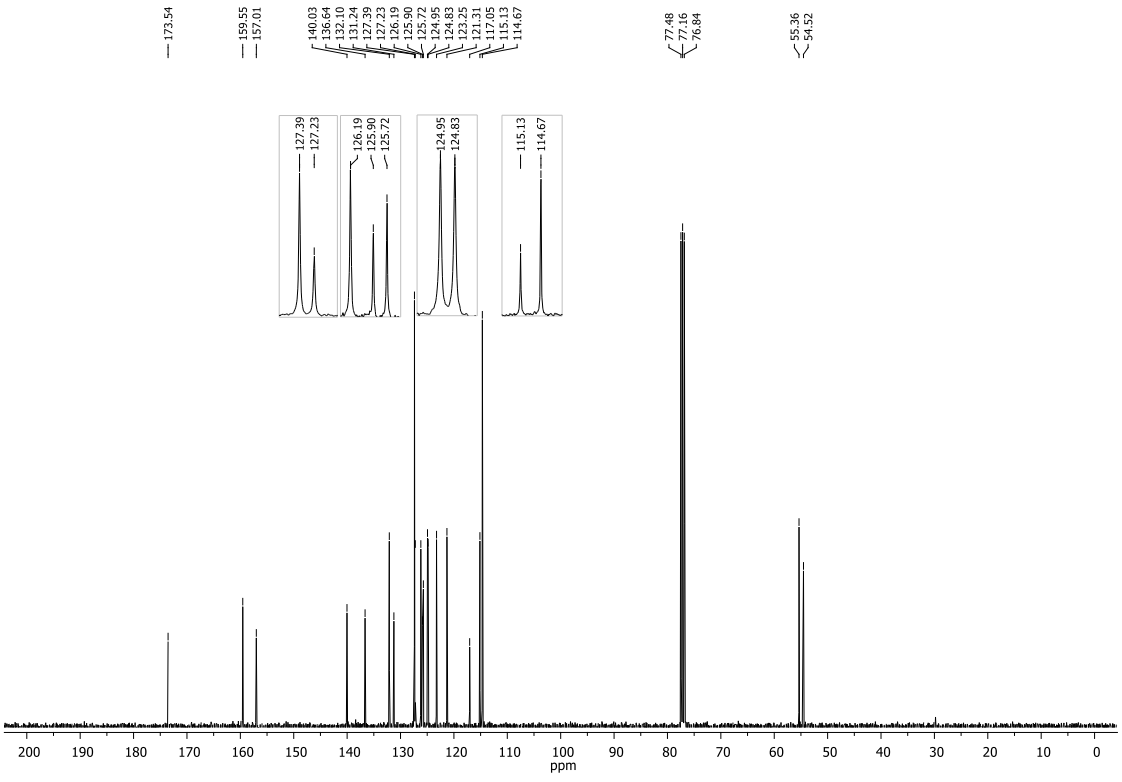



**Figure 4.4b**: $^{13}$C NMR Spectrum of **55n**

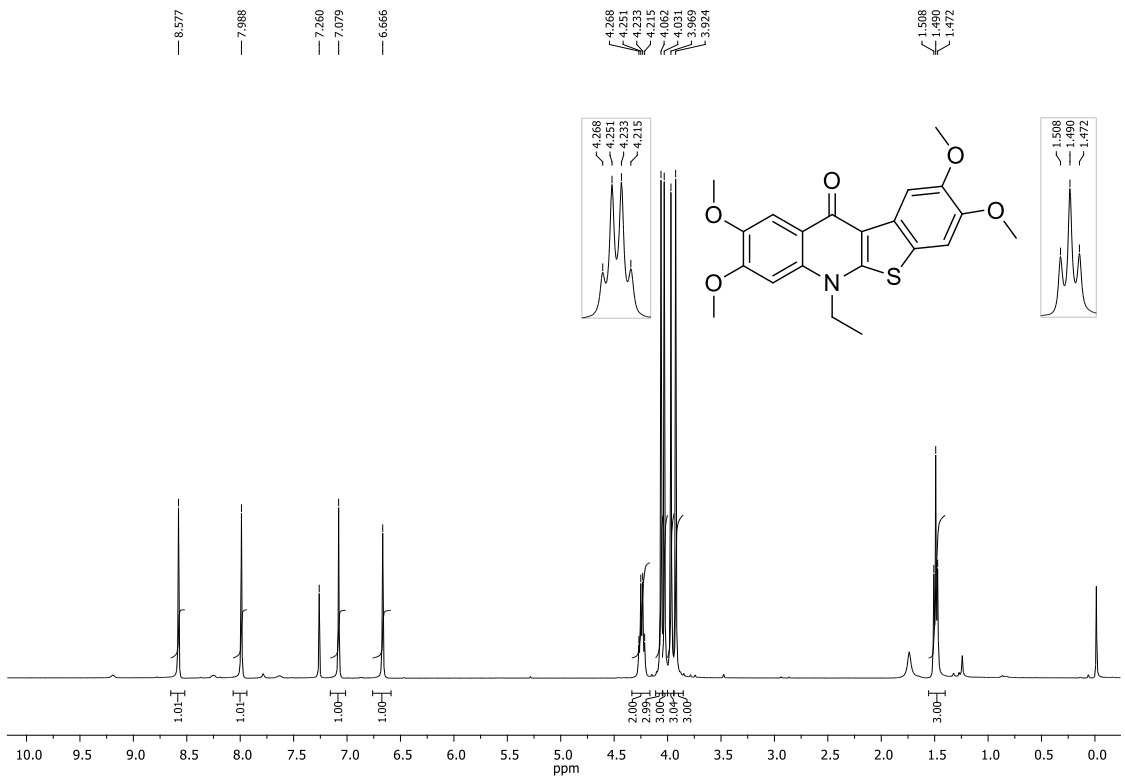



**Figure 4.5a**: $^{1}$H NMR Spectrum of **55s**

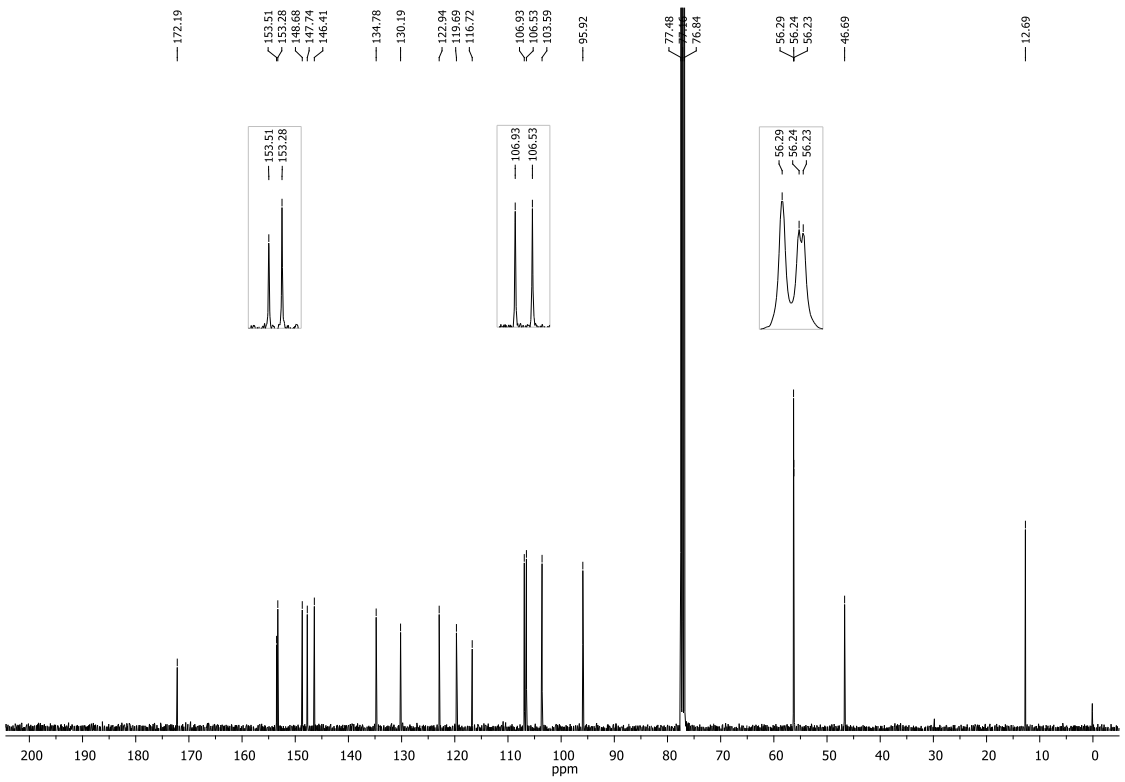



**Figure 4.5b**: $^{13}$C NMR Spectrum of **55s**

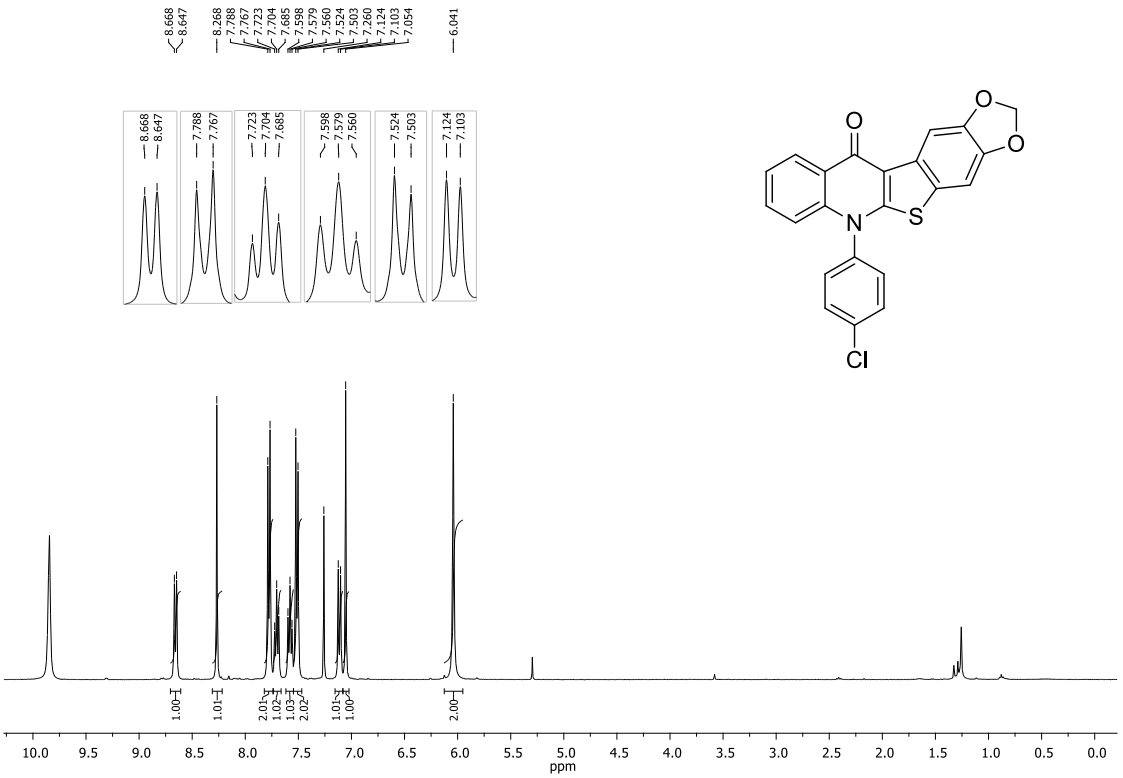



**Figure 4.6a**: $^{1}$H NMR Spectrum of **55x**

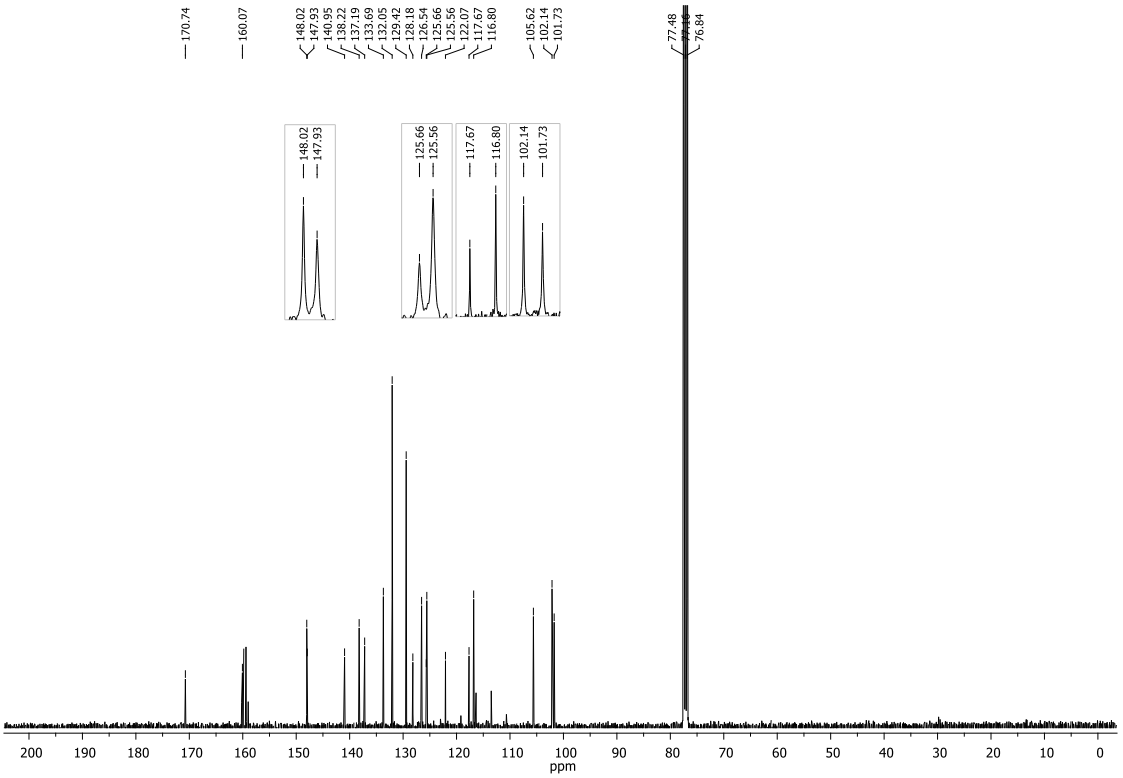



**Figure 4.6b**: $^{13}$C NMR Spectrum of **55x**

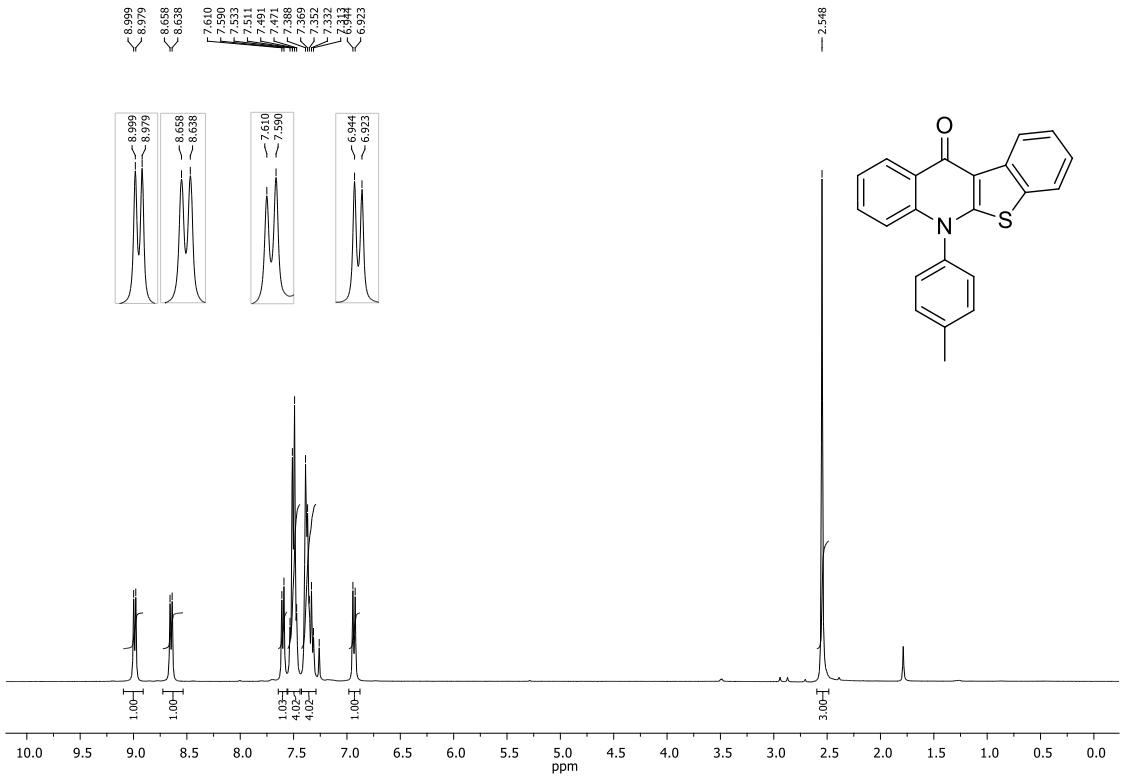



**Figure 4.7a**: $^{1}$H NMR Spectrum of **55e**

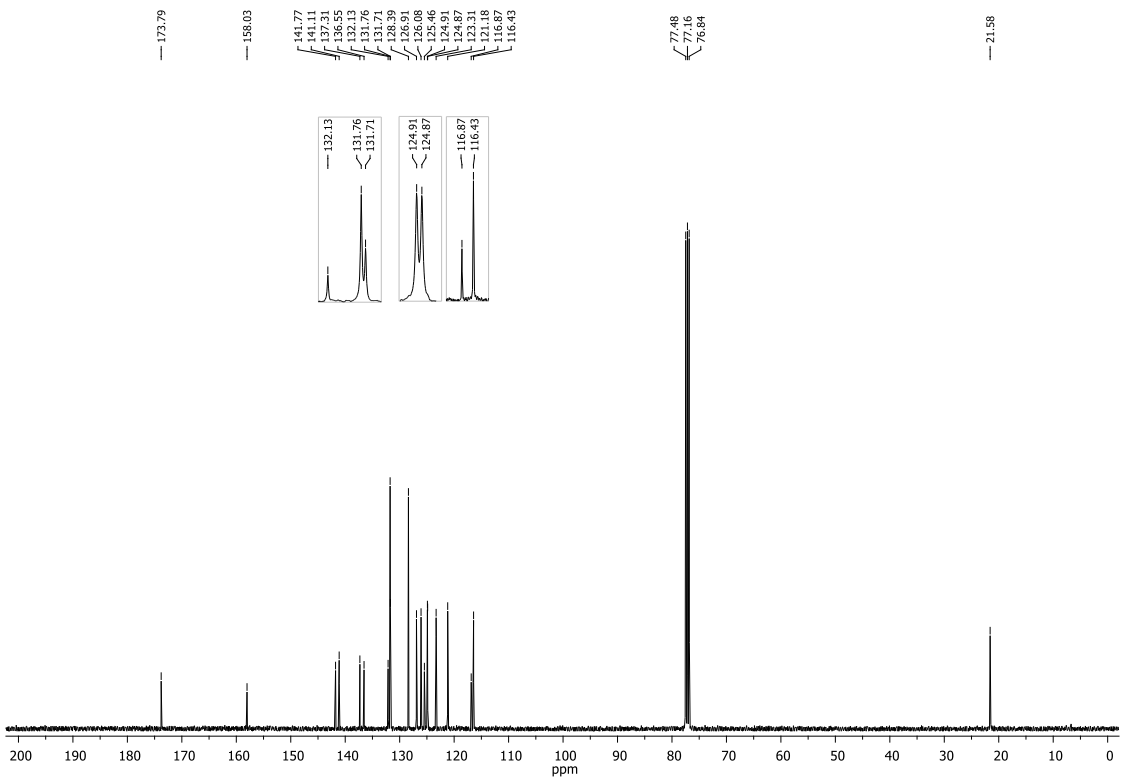



**Figure 4.7b**: $^{13}$C NMR Spectrum of **55e**

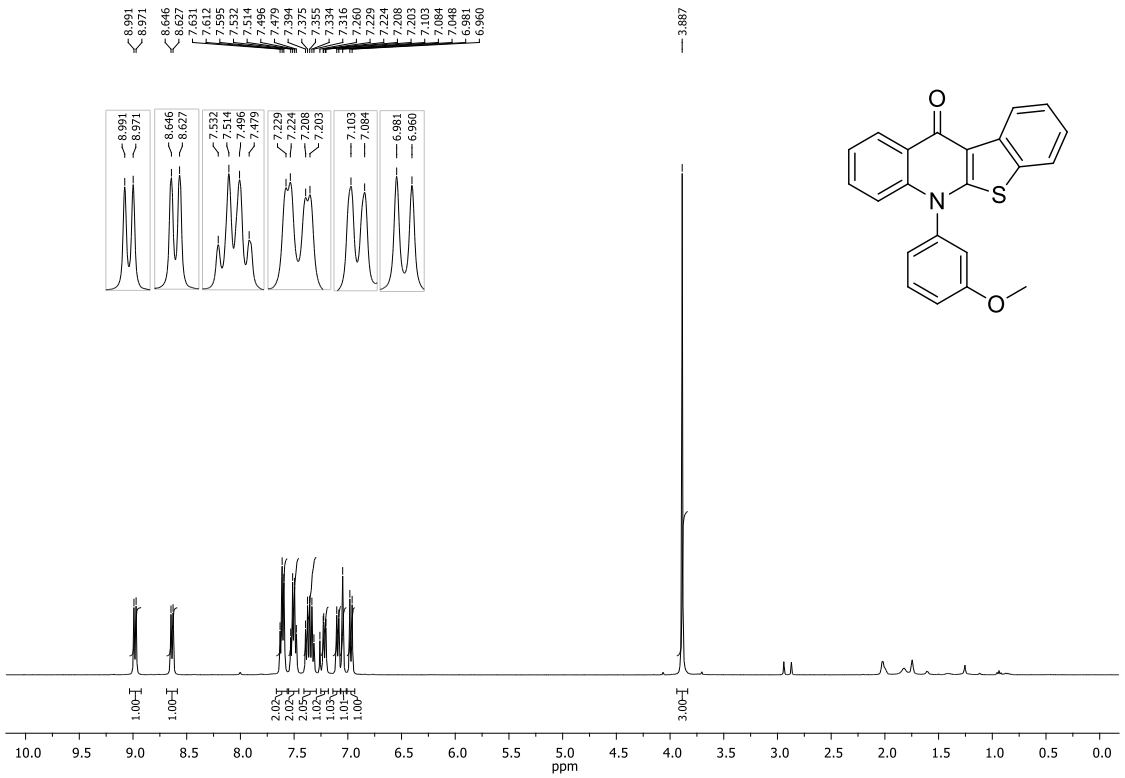



**Figure 4.8a**: $^{1}$H NMR Spectrum of **55j**

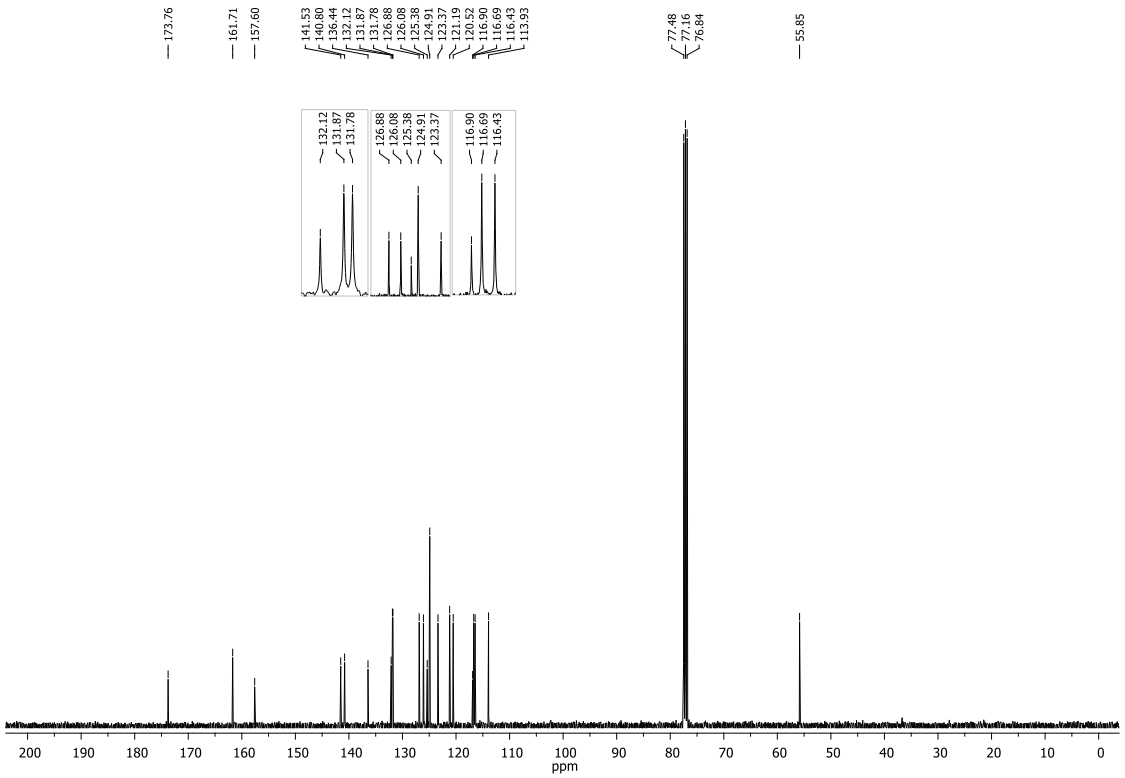



**Figure 4.8b**: $^{13}$C NMR Spectrum of **55j**

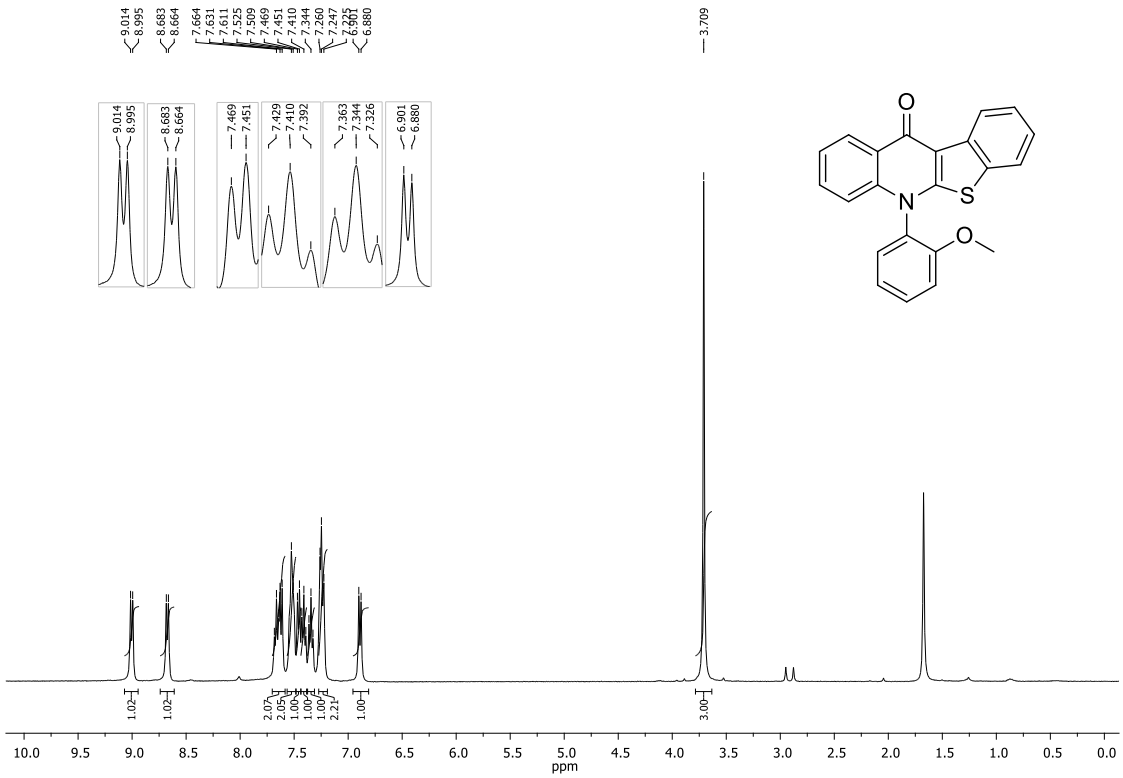



**Figure 4.9a**: $^{1}$H NMR Spectrum of **55h**

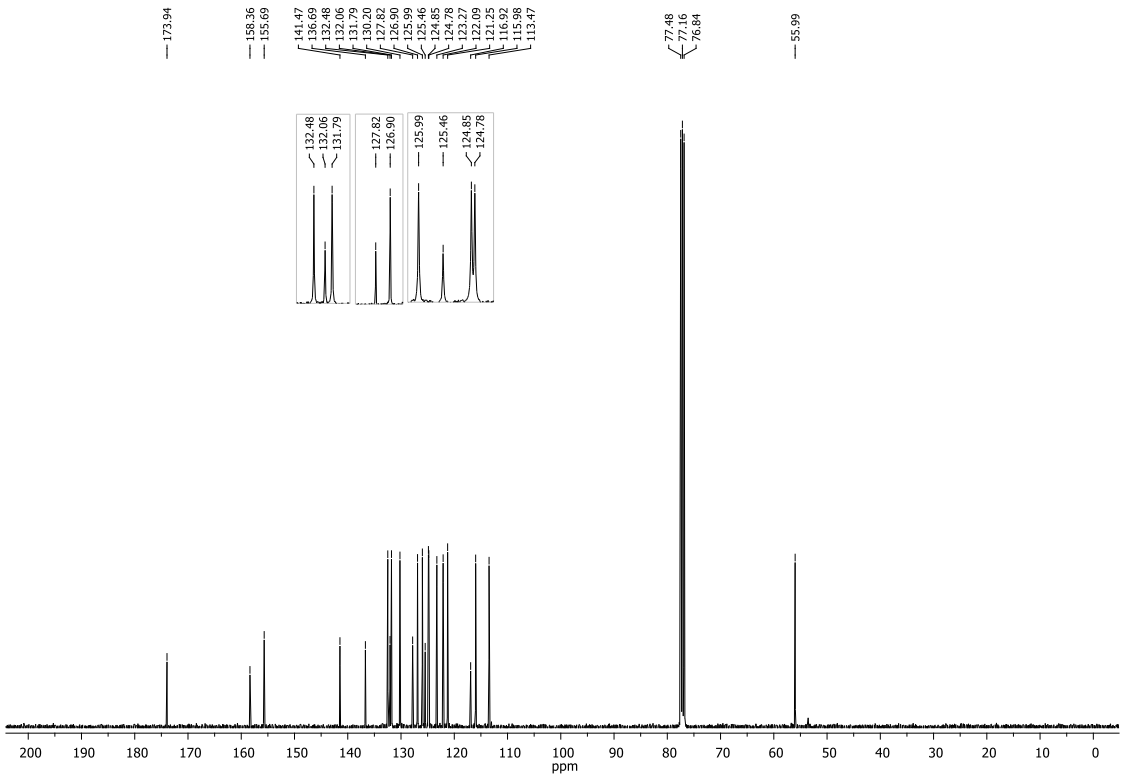



**Figure 4.9b**: $^{13}$C NMR Spectrum of **55h**

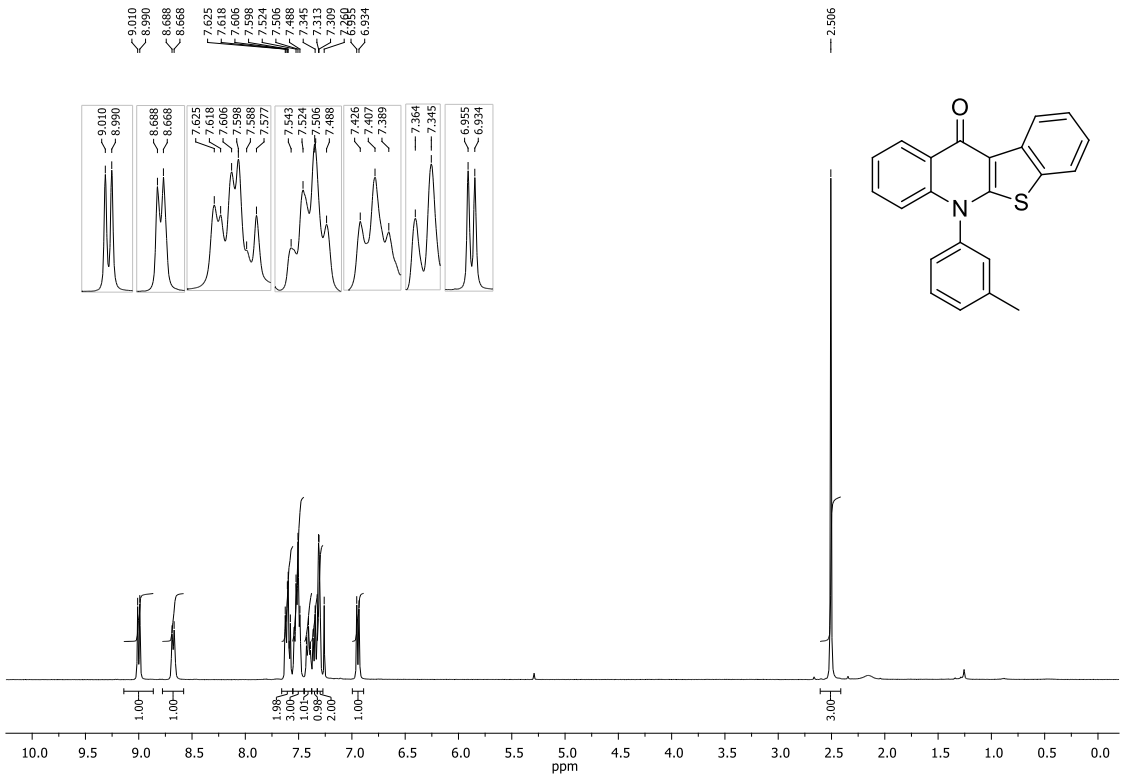



**Figure 4.10a**: $^{1}$H NMR Spectrum of **55ab**

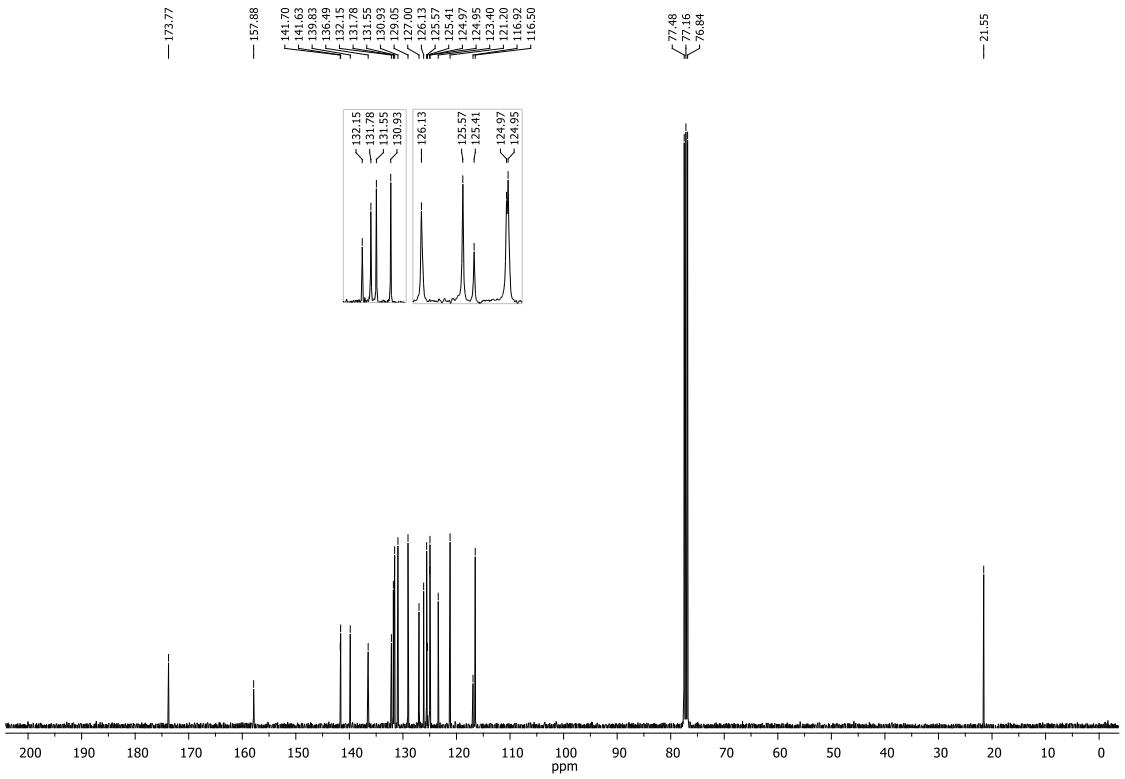



**Figure 4.10b**: $^{13}$CNMR Spectrum of **55ab**

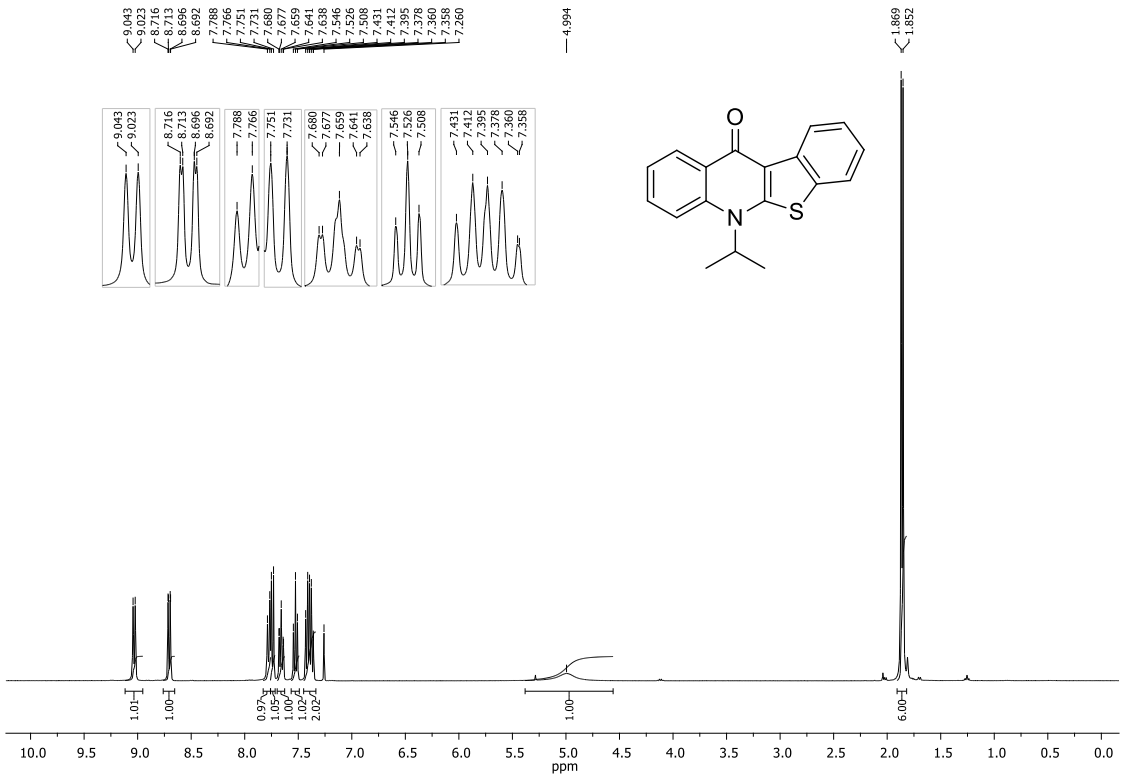



**Figure 4.11a**: $^{1}$H NMR Spectrum of **55o**

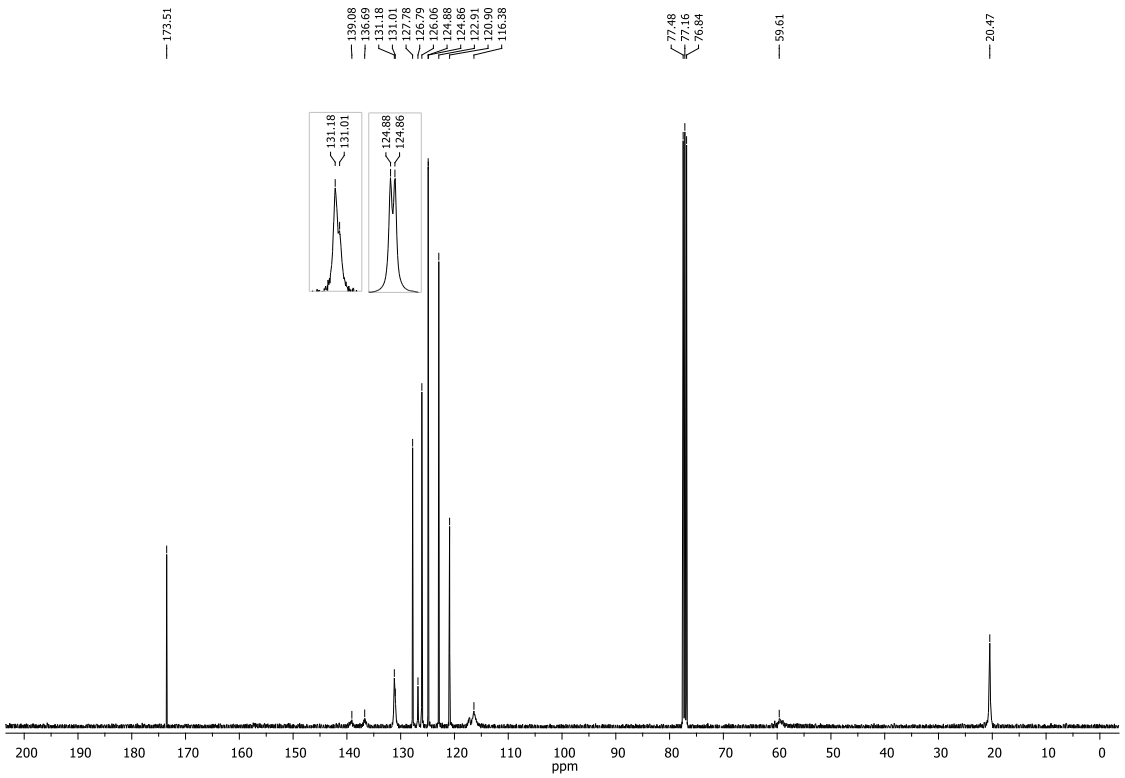



**Figure 4.11b**: $^{13}$C NMR Spectrum of **55o**

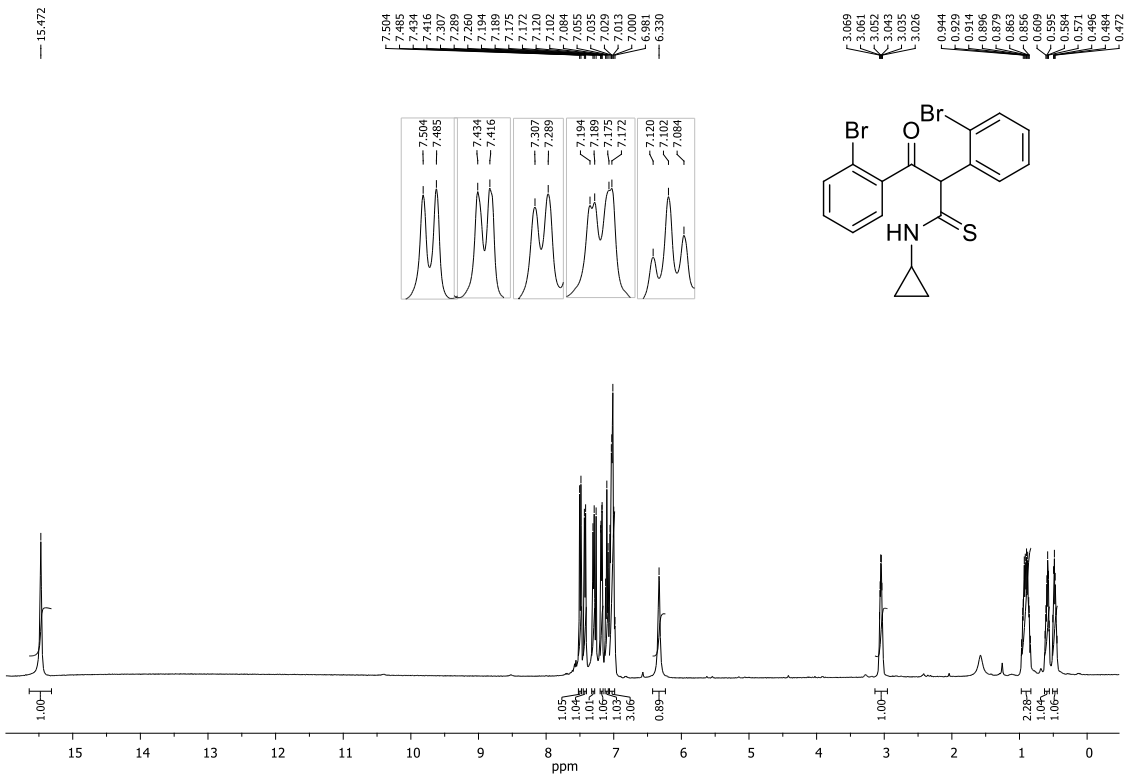



**Figure 4.12a**: $^{1}$H NMR Spectrum of **44p**

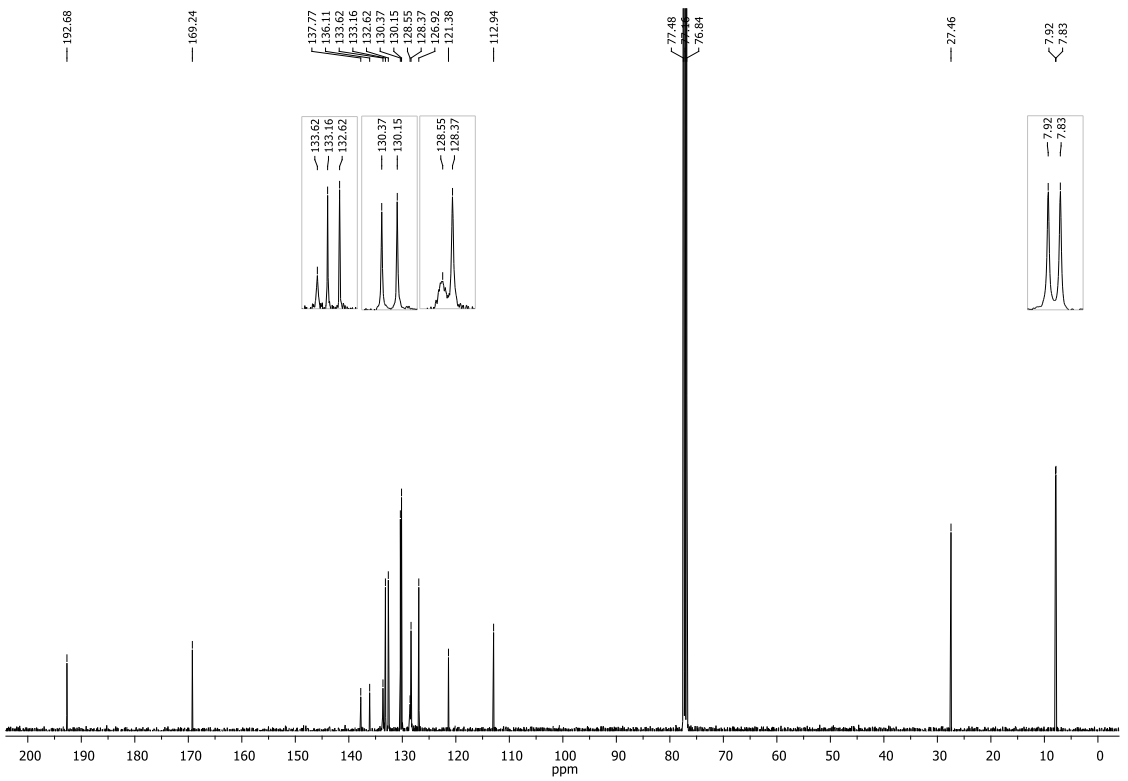



**Figure 4.12b**: $^{13}$C NMR Spectrum of **44p**

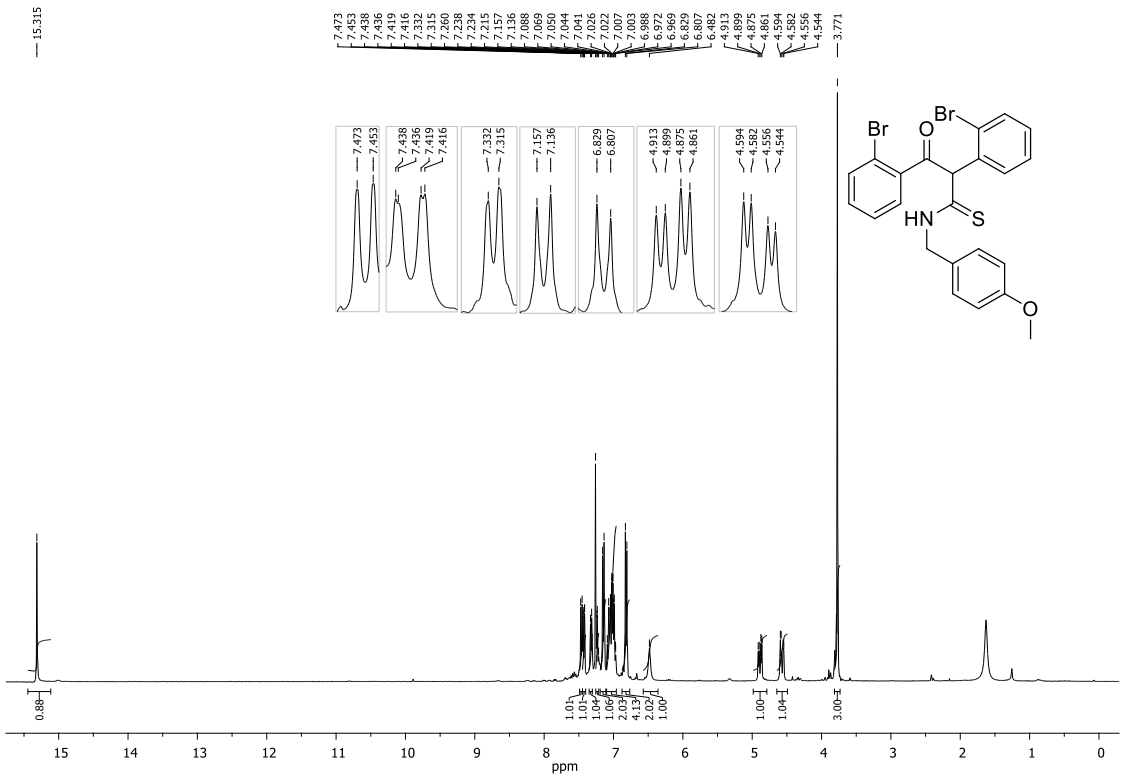



**Figure 4.13a**: $^{1}$H NMR Spectrum of **44n**

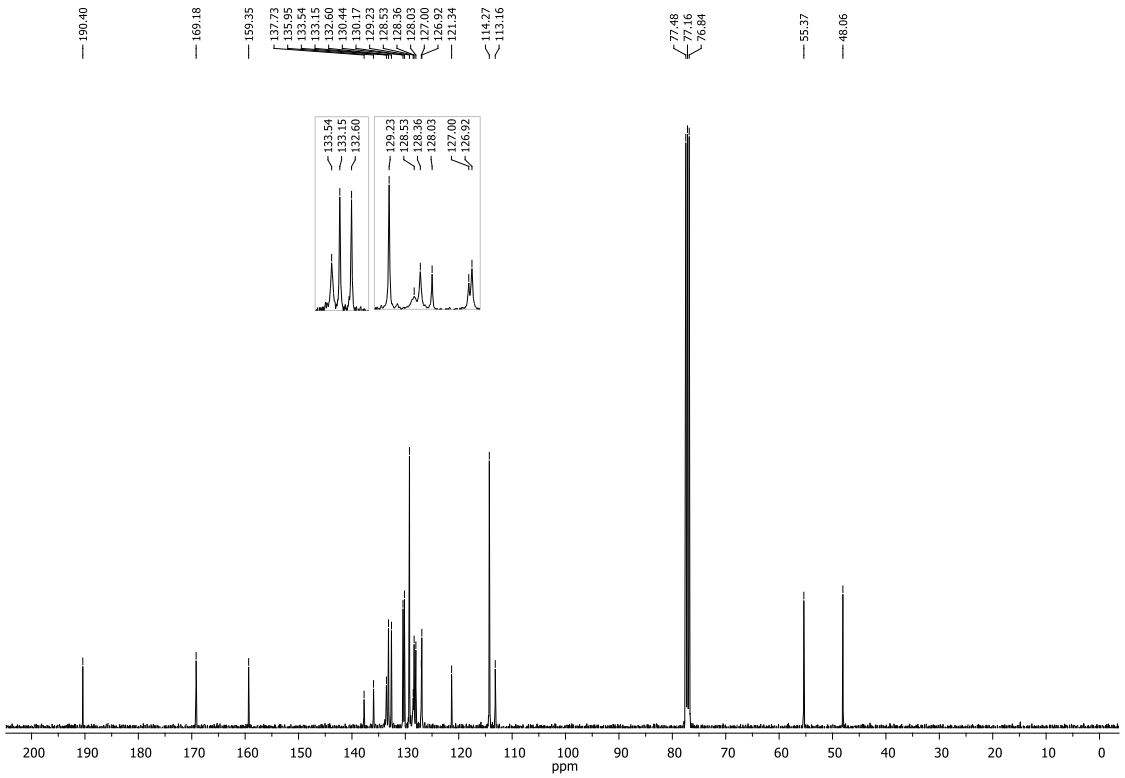



**Figure 4.13b**: $^{13}$C NMR Spectrum of **44n**

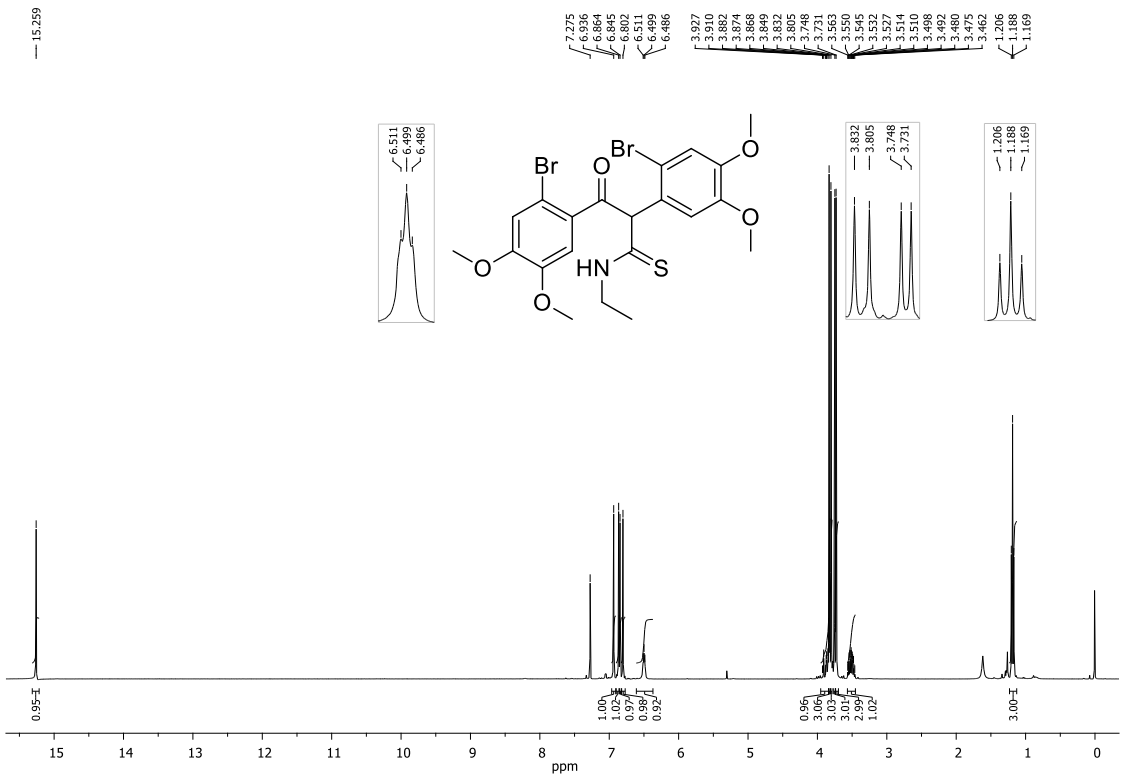



**Figure 4.14a**: $^{1}$H NMR Spectrum of **44s**

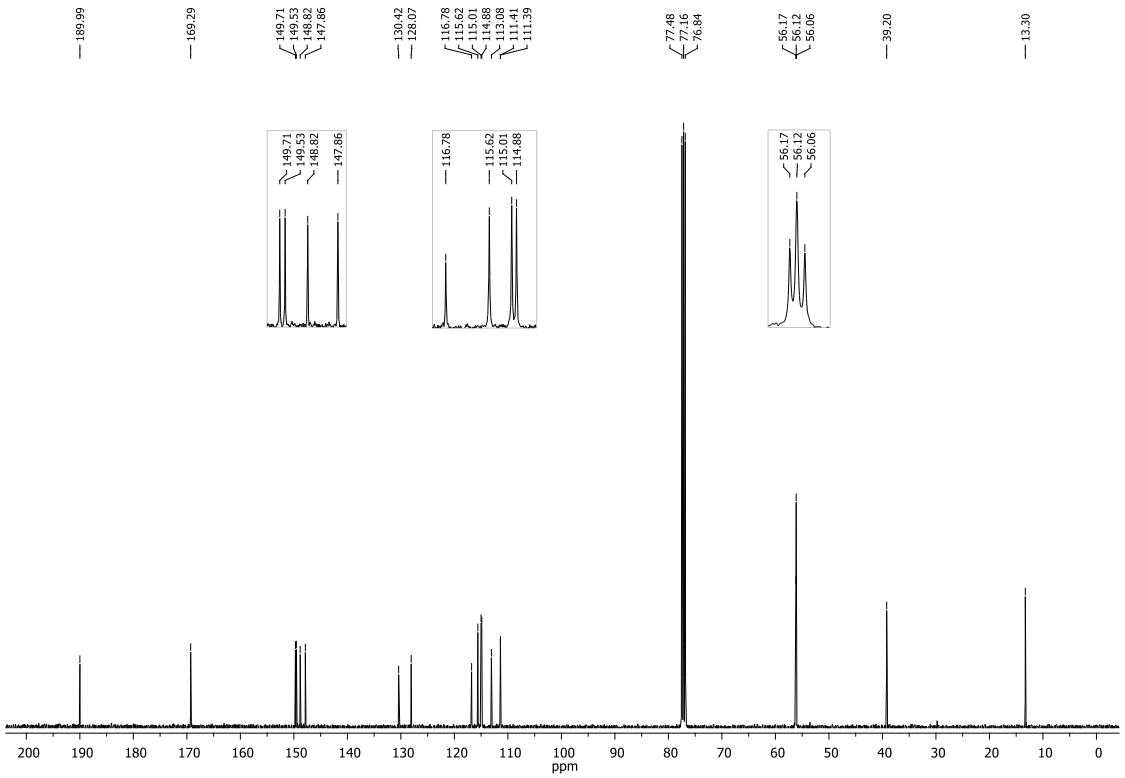



**Figure 4.14b**: $^{13}$C NMR Spectrum of **44s**

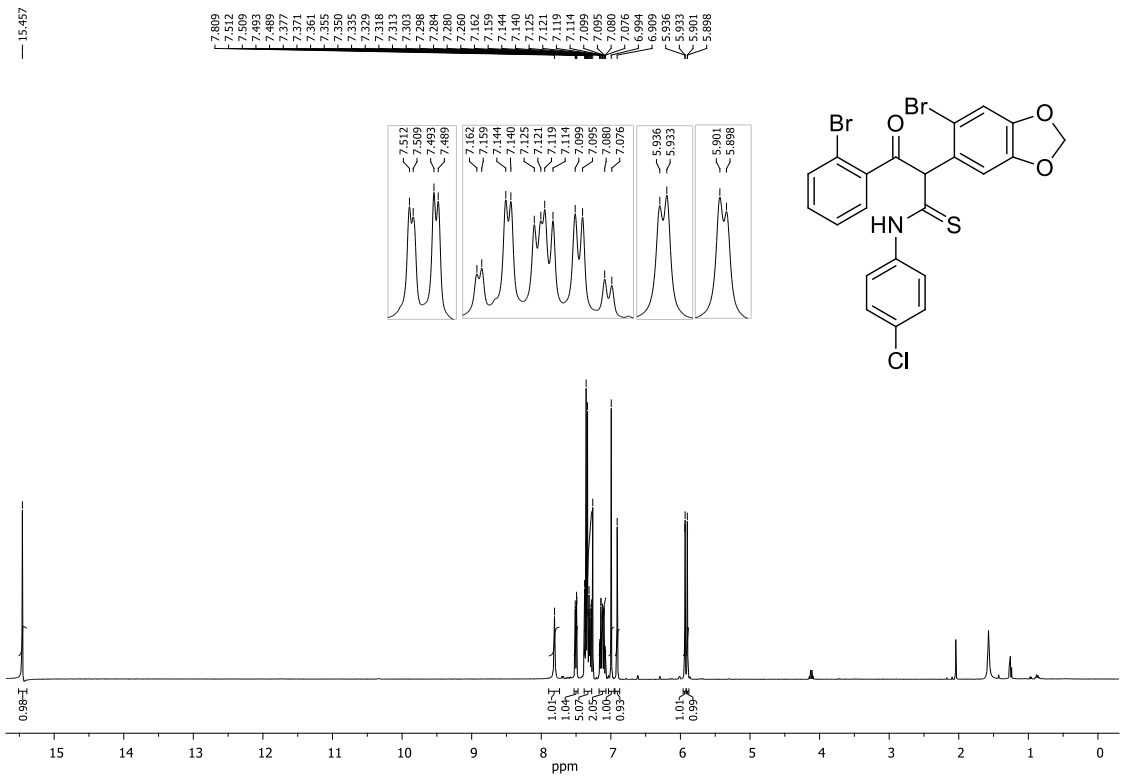



**Figure 4.15a**: $^{1}$H NMR Spectrum of **44x**

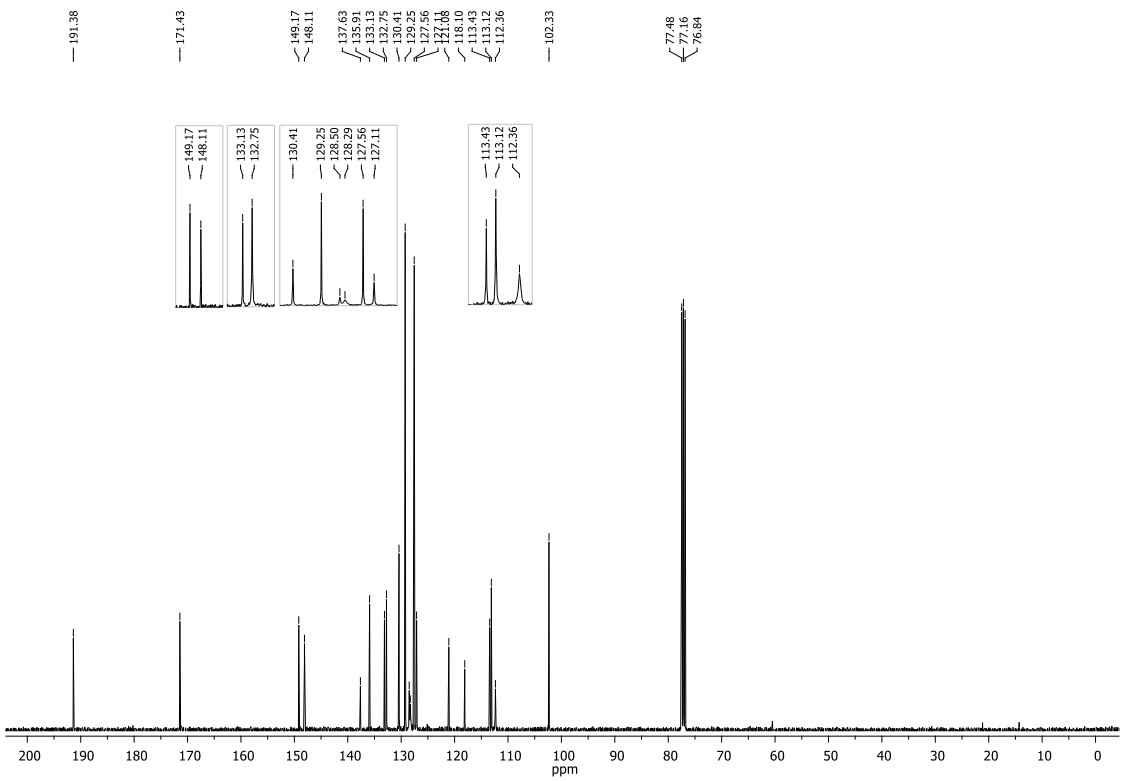



**Figure 4.15b**: $^{13}$C NMR Spectrum of **44x**

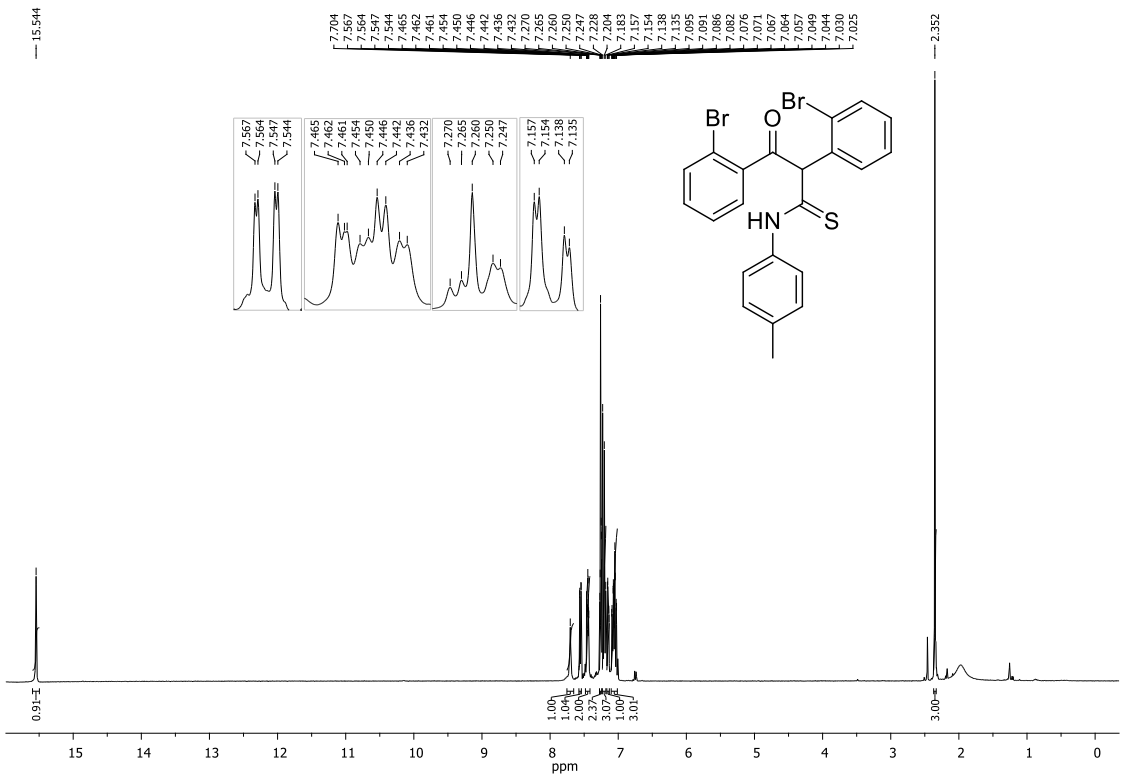



**Figure 4.16a**: $^{1}$H NMR Spectrum of **44e**

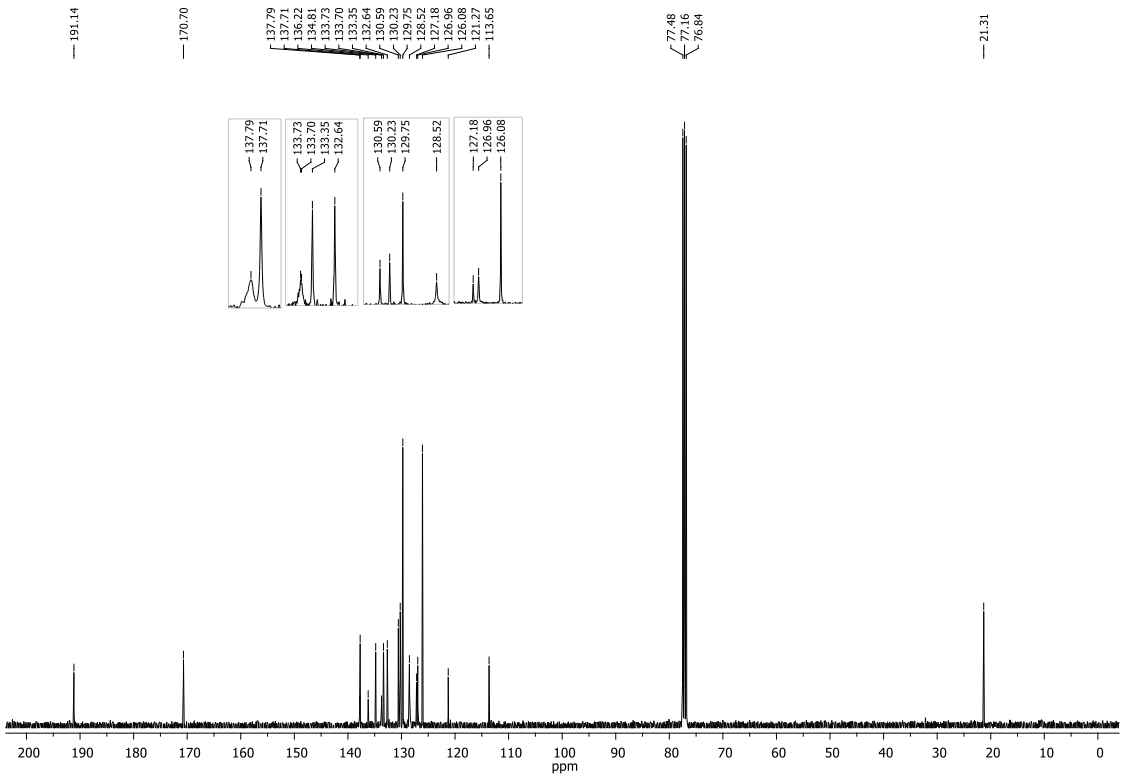



**Figure 4.16b**: $^{13}$C NMR Spectrum of **44e**

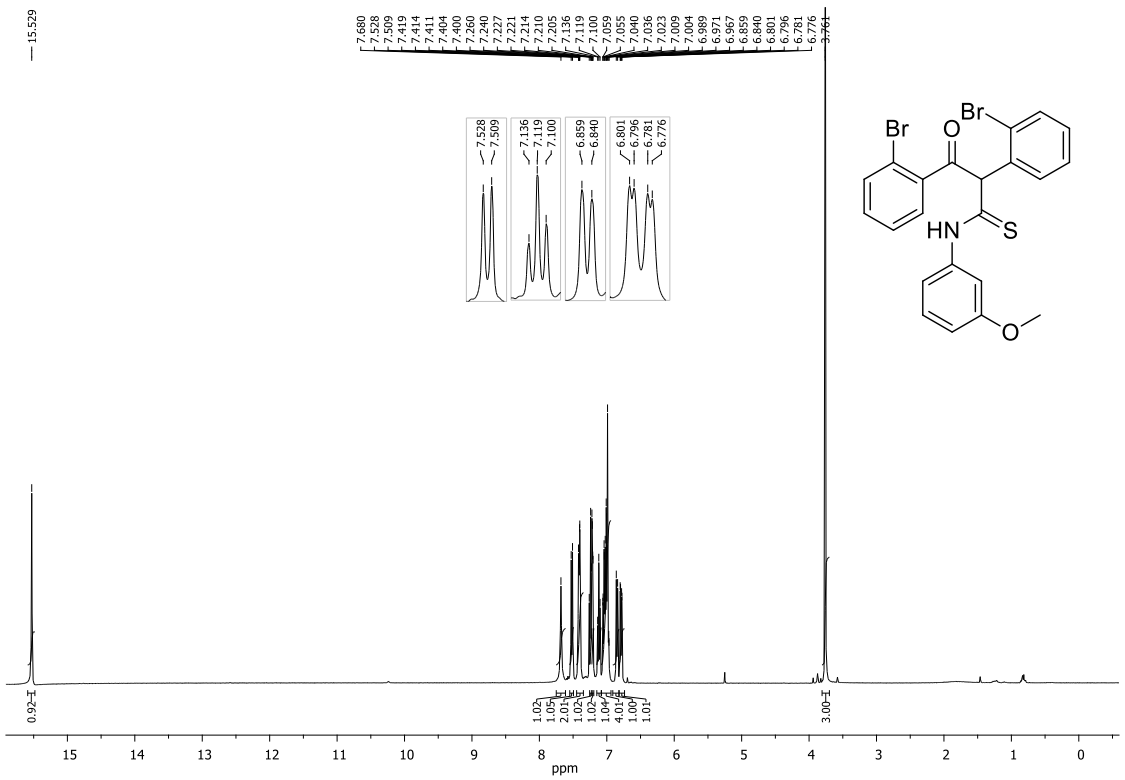



**Figure 4.17a**: $^{1}$H NMR Spectrum of **44j**

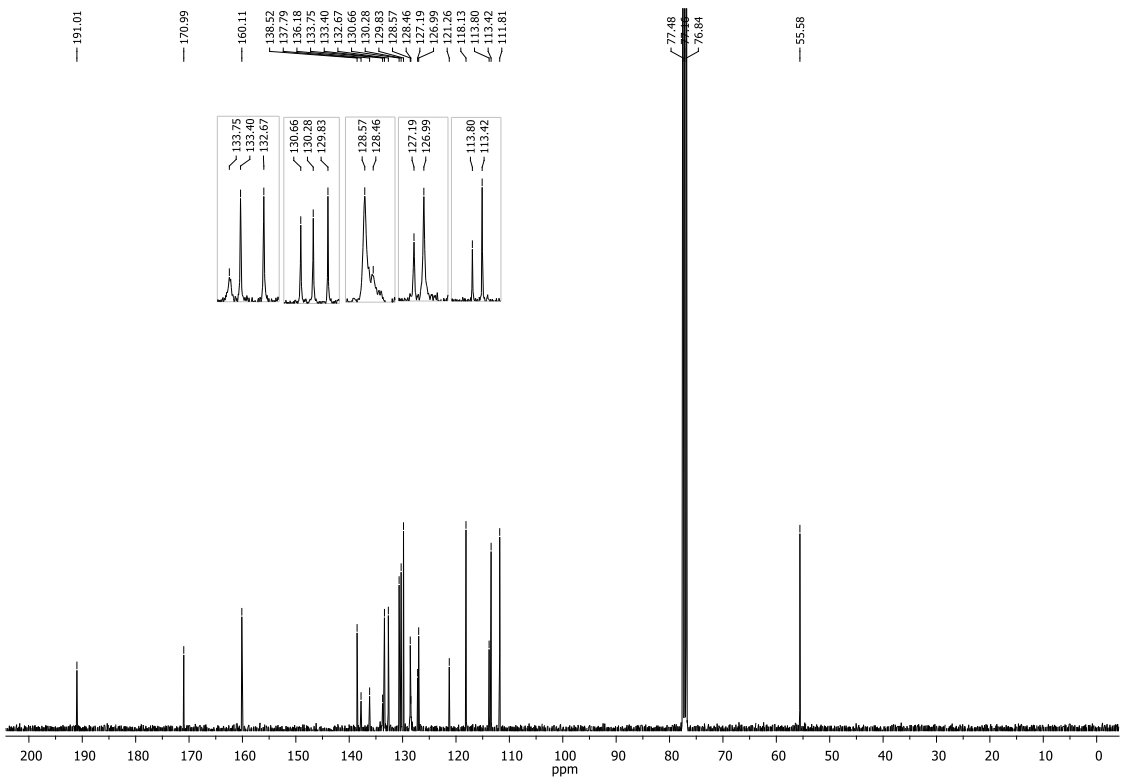



**Figure 4.17b**: $^{13}$C NMR Spectrum of **44j**

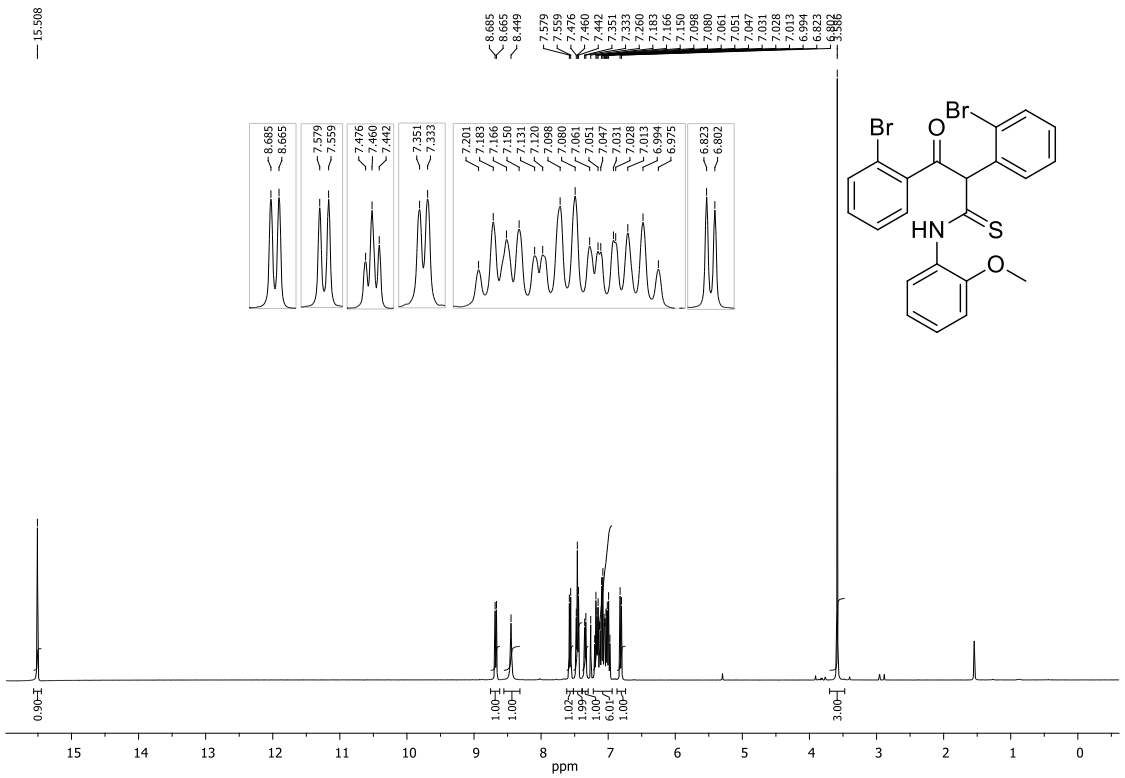



**Figure 4.18a**: $^{1}$H NMR Spectrum of **44h**

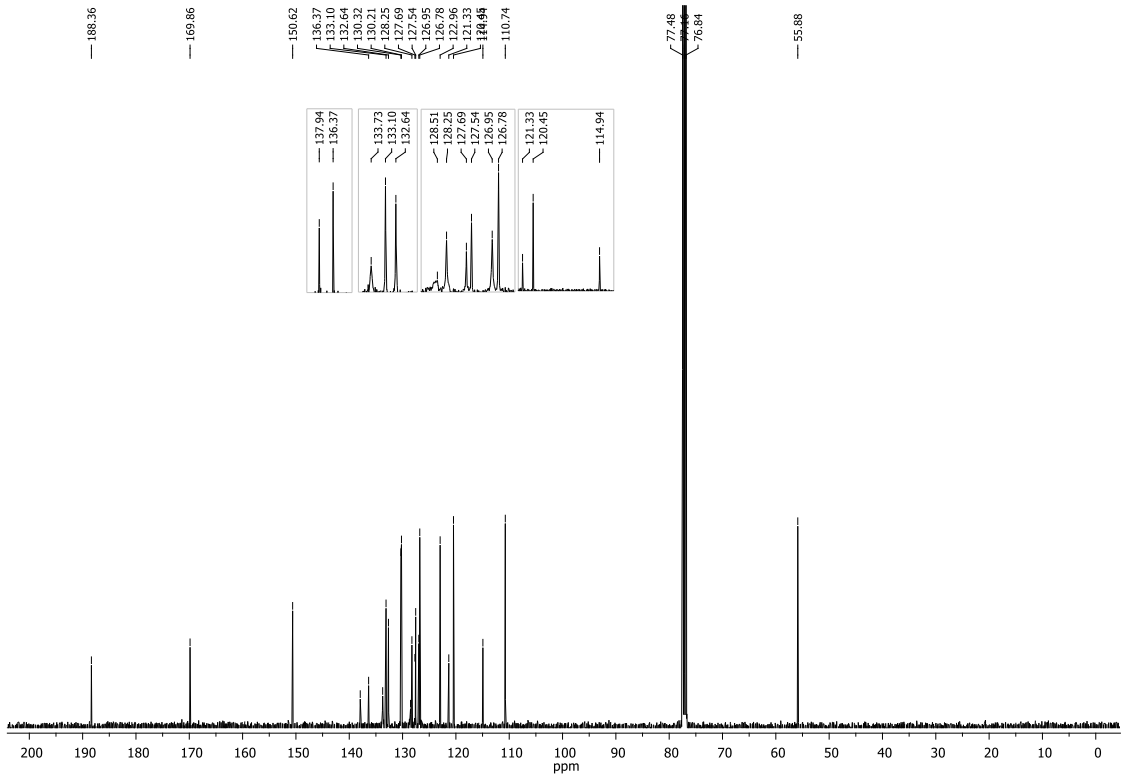



**Figure 4.18b**: $^{13}$C NMR Spectrum of **44h**

### 4.8 Crystallographic data of 55a

Crystallographic data of **55a** in $CH_2Cl_2$/*n*-hexane**:** $C_{21}H_{13}NOS$**,** Mw = 327.38, monoclinic, space group $P2_1$, a = 9.416 (5) Å, b = 11.06 (5) Å, c = 15.647 (5) Å, $\alpha$ = 90.00 º, β = 101.06 º, γ = 90.00º, *V* = 1599.4 (12) Å3, *Z* = 4, *D*calc = 1.360 mg/m3, *T* = 293 (2) K, R1 = 0.0435 {I > 2σ (I)}, R2w = 0.1082, GOF = 1.037.

## 4.9 References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# Chemoselective Amination of New Class of *S,N*-Acetals: Synthesis of Quinolones and their Fused Heterocycles

## 5.1 Introduction

Quinolone is considered as one of the privileged pharmacophores since the accidental discovery of nalidixic acid.[1] This core has been effectively utilized to study antibacterial activities, quorum sensing signalling and other therapeutic applications such as genitourinary infections, systemic and respiratory tract infections, due to excellent bioavailability, oral and intravenous formulations, high serum levels etc.[2] Therefore, several quinolone drugs are developed and marketed. Especially fluoroquinolone has captured the interest of pharmaceutical industries last two decades.[3] Quinolone core is also found in various natural products.[4] Recently isolated quinolone alkaloids waltheriones A and C showed significant activities in an *in vitro* anti-HIV cytoprotection assay.[5] They are orally and parenterally active, have a broad antimicrobial spectrum that includes many frequently encountered pathogens, are bactericidal in clinically achievable doses, generate comparatively tolerable resistance levels, possess a fascinating molecular mode of action, are comparatively easily synthesized and with a few notable exceptions are safe. Hence, quinolone moiety has a great potential to generate more valuable compounds with high therapeutic values.[6]

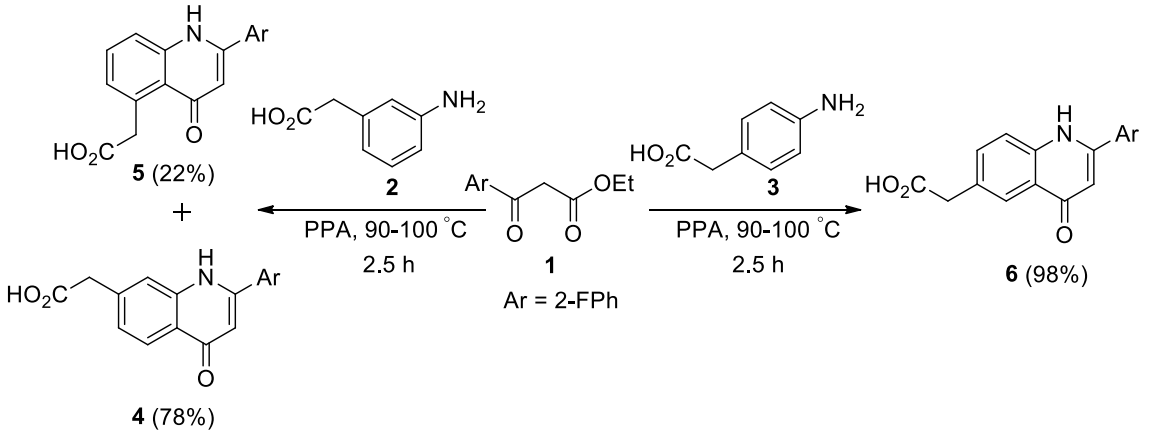
Transition metal catalyzed reactions have dominated in carbon—hetero bond formation and used as a power tool for synthesis of *N*-heterocycles *via* intramolecular C—N coupling reactions.[7] The trace metal contamination is a major problem in the coupling reaction.[8] To overcome this problem, new protocols have been developed.[9] However, an alternative solution is to develop a transition metal free cross-coupling reactions especially carbon—hetero bond

forming reaction for synthesis of *N*-heterocycles with biological importance[10]. Therefore, much efforts have been paid for synthesis of substituted quinolones by without use of transition metals and a few successful methods have been recently developed.[11] Despite excellent yields, each of these methods has its own limitations owing to multi-step synthesis of starting materials, use of large excess of base, highly substrate specific reactions & high temperature. The quinolones and fused analogues are in increasingly high demand in pharmaceutical and recently in the electronic world.[12] Therefore, developing a simple and mild method for quinolones derivatives is always needed.

## 5.2 Previous Reports on Quinolones

Synthesis of quinolones has been well reviewed.[13] In this chapter, we described here some of the selected set of reports among them.

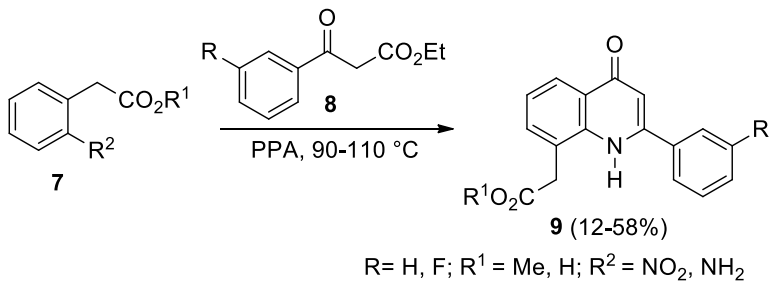
Among the early reports of synthesis of quinolones, Xia *et al.* prepared 2-phenyl-4-quinolone 5-, 6-, and 7-acetic acids **4-6** prepared by condensation of commercially available different aminophenylacetic acids **2**, **3** and ethyl 2-fluorobenzoylacetate **1** when heated (90–100 °C) in polyphosphoric acid (PPA) for 2.5 h. When *meta* substituted aminophenylacetic




**Scheme 5.1**: *Condensation Reaction of Amino Acetic Acids **2-3** and Benzoylacetates **1***

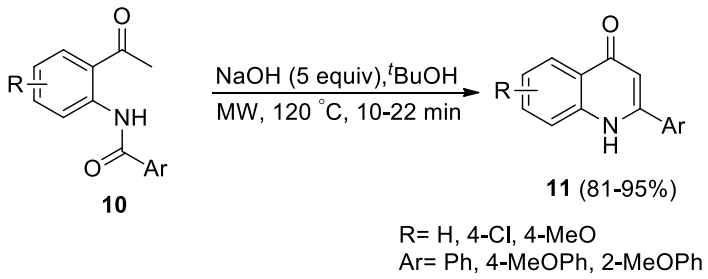
acid **2** was used, a mixture of two isomers **4** and **5** were obtained. These phenyl quinolone acetic acid derivatives **4-6** are used to check cytotoxicity against human tumor cell lines (Scheme 5.1).[14]

Two years later, in 2005, 2-phenyl-4-quinolone derivatives **9** were synthesized and screened as potential antitumor promoters. It was prepared by nitro/amino phenyl ester/acid **7** and *β*-keto ester **8** in the presence of polyphosphoric acid (Scheme 5.2).[15]



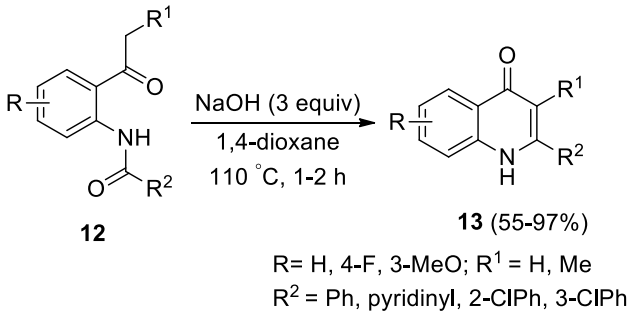

**Scheme 5.2**: *Synthesis of 2-Phenyl-4-quinolones **9** from β-Keto Ester **8***

A rapid and straightforward method to synthesize diverse set of 2-aryl-4-quinolone derivatives **11** was shown in Scheme 5.3. It was achieved by exposing corresponding acylated aminoacetophenones **10** to microwave irradiation in the presence of NaOH. The microwave accelerated cyclizations were complete within 10-22 min. at 120 ºC giving 81-95% isolated yields of **11** (Scheme 5.3).[16]



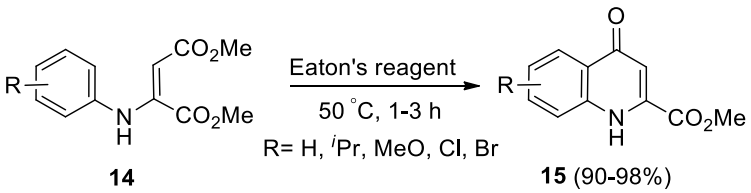

**Scheme 5.3**: *Synthesis of 2-Aryl-4-quinolones **11** from Acylated Aminoacetophenones **10***

Buchwald and co-workers devised a method for the preparation of 2-aryl- and 2-vinyl-4-quinolones **13** that undergoes base-promoted Camps cyclization of the *N*-(2-ketoaryl)amides **12** (Scheme 5.4).[17]



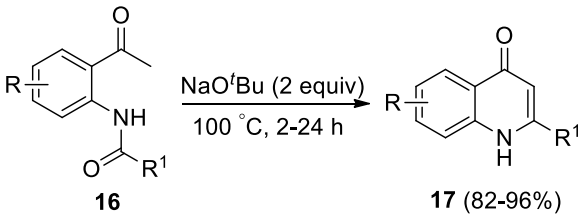

**Scheme 5.4**: *Base-Promoted Cyclization to 2-Aryl-4-quinolones **13***

The cycloacylation of aniline derivatives **14** to 4-quinolones **15** in the presence of Eaton's reagent (7.7 wt% phosphorus pentoxide solution in methanesulfonic acid) was reported (Scheme 5.5).[18] This high yielding methodology is applicable to a wide variety of functionalized anilines and requires milder conditions than those traditionally employed.



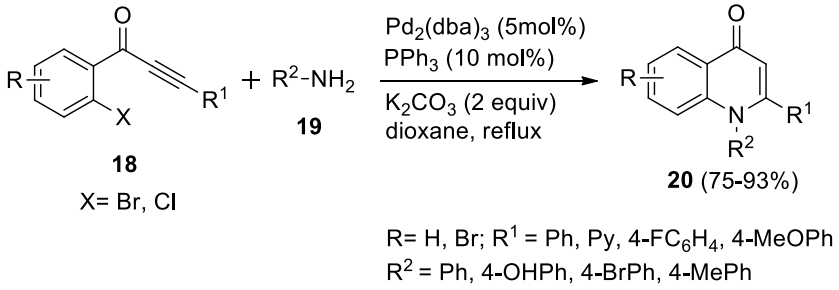

**Scheme 5.5**: *Cycloacylation of Aniline **14** by Eaton's Reagent*

Huang *et al.* reported a mild synthesis of 4-quinolones **17**. Under the optimal conditions, base-promoted intramolecular cyclization of freshly prepared aryl amides **16** (Scheme 5.6).[19]



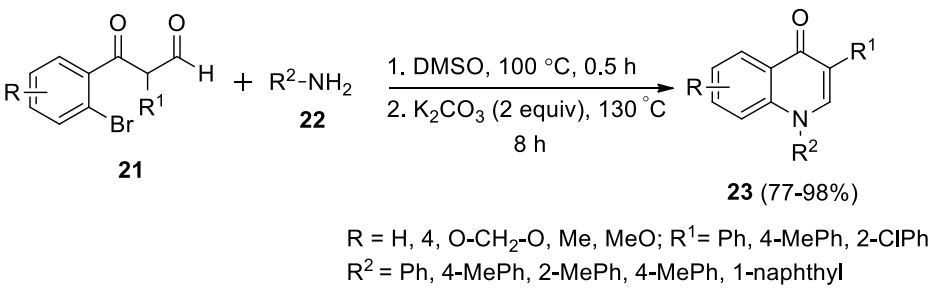

**Scheme 5.6**: *Base Mediated Intramolecular Cyclization of Aryl Amides **16***

In 2010, an efficient palladium catalyzed tandem amination approach was developed in one step to afford functionalized 4-quinolones **20** in good to excellent yields from easily accessible *ortho*-haloaryl acetylenic ketones **18** and primary amines **19** (Scheme 5.7).[20]



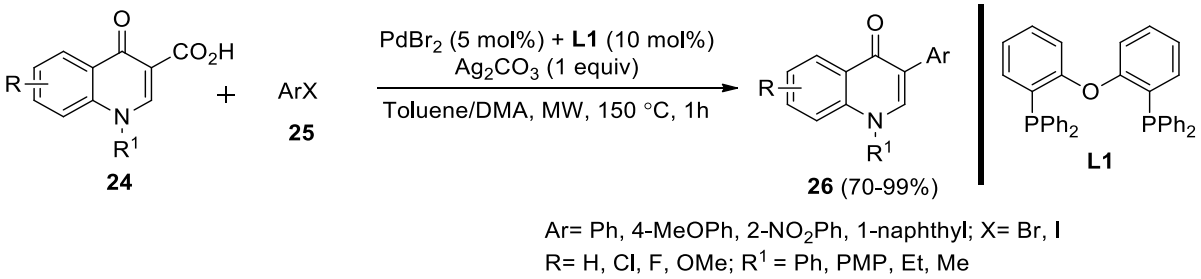

**Scheme 5.7**: *Palladium Catalyzed Tandem Amination Reaction*

A report from Liu *et al.* described the synthesis of 3-substituted 4-quinolones **23** using a one-pot metal-free strategy. It was carried out in dimethylsulfoxide (DMSO) *via* a sequential addition of materials. The methodology is tolerant of a wide range of functional groups and applicable to library synthesis (Scheme 5.8).[21]



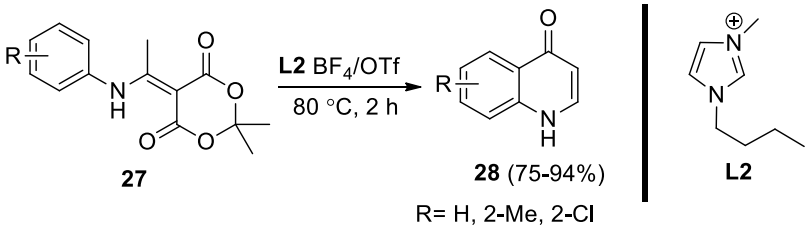

**Scheme 5.8**: *One-Pot Metal Free Synthesis of 3-Substituted 4-Quinolones **23***

Later in 2012 another report came whereby an efficient and practical decarboxylative cross-coupling reaction of quinolin-4(1*H*)-one 3-carboxylic acids **24** with (hetero)aryl halides has been established. Under a bimetallic system of $PdBr_2$ and $Ag_2CO_3$, the protocol proved to be general, and a variety of 3-(hetero)aryl 4-quinolinones, such as 3-arylquinolin-2(1*H*)-ones **26** were prepared (Scheme 5.9).[22]



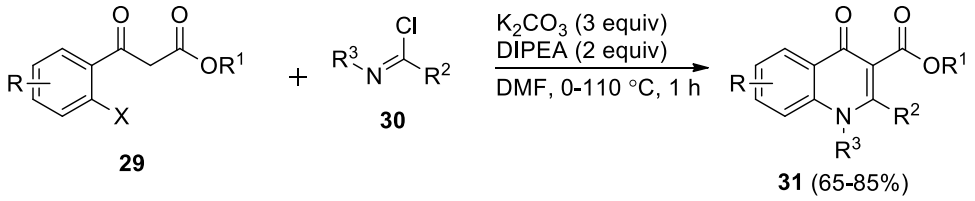

**Scheme 5.9**: *Decarboxylative Cross-Coupling of Quinolinocarboxylic Acids **24***

A new metal free approach to prepare quinolones was reported by Yadav *et al.* A pre-prepared enaminone **27** from condensation of meldrum's acid with acetyl aniline undergoes cyclization in 1-butyl-3-methyl imidazolium tetrafluoroborate/triflate at a moderate temperature gave 4(1*H*)-quinolones **28** in good to excellent yields (Scheme 5.10).[23]




**Scheme 5.10**: *Ionic Liquid Mediated Synthesis of 4-Quinolones*

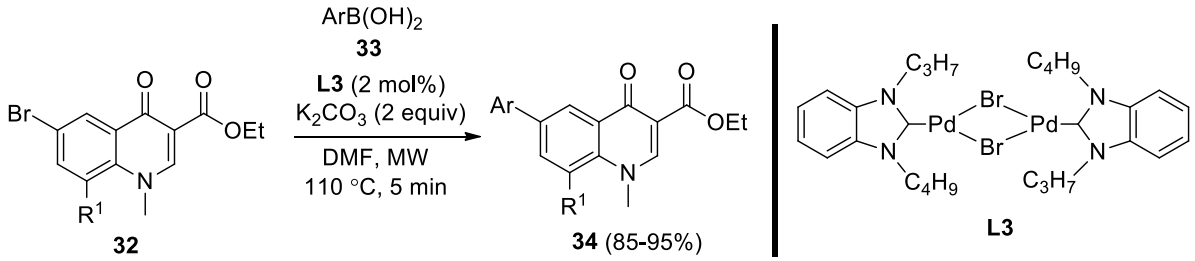
Another transition metal free approach was applied to report a novel one-pot synthesis of the 2-substituted 3-carboxy-4-quinolone derivatives **31** from readily available 3-oxo-3-arylpropanoates **29** and *N*-alkyl arylimidoyl chlorides **30** (prepared from amides) (Scheme 5.11).[24]




X= F, Cl, Br, I; R= F, I, F, $CF_3$, $NO_2$, MeO; $R^1$ = Me, Et; $R^2$ = Ph, 4-FPh 4-ClPh, 2-furanyl; $R^3$ = Me, allyl, cyclopropyl, Cy, $^i$Pr

**Scheme 5.11**: *Transition Metal Free One-Pot Synthesis of Carboxyquinolones **31***

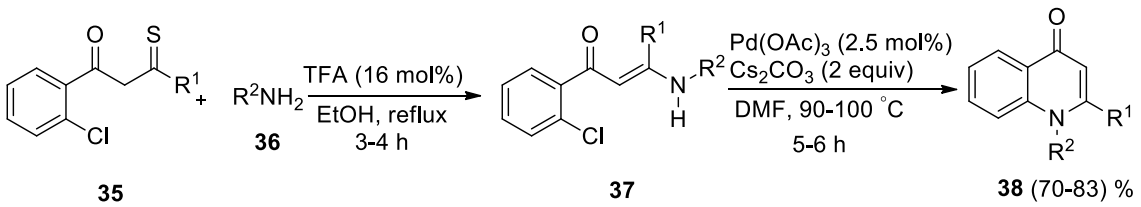
Gupta *et al.* illustrated arylation of ethyl 4-quinolone 3-carboxylates **32** by Suzuki cross coupling reaction under microwave irradiation that gave aryl functionalized 4-quinolone derivative **34** in 5 minutes (Scheme 5.12).[25]




Ar= Ph, 4-FPh, 4-PhMe; $R^1$= H, Me, F, MeO

**Scheme 5.12**: *Suzuki Cross Coupling Reaction of Quinolone Carboxylates **32***

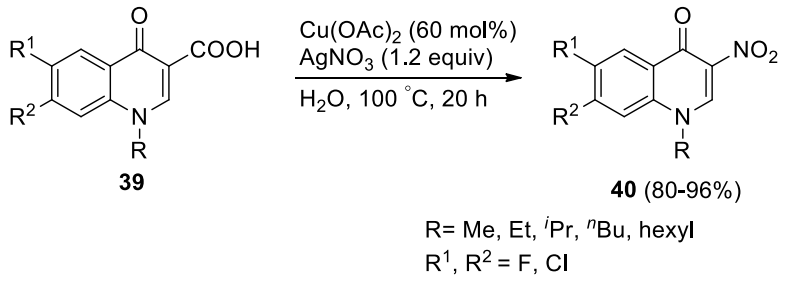
In 2014, another report was published explaining a new strategy to synthesize 1,2-disubstituted 4-quinolones **38** in good yield starting from 1,3-bisaryl-monothio-1,3-diketone substrates **35** (Scheme 5.13).[26] The synthesized compounds were evaluated for antimalarial activity which gave positive result for almost all the compounds.




$R^1$ = Ph, 4-MePh, 4-MeOPh
$R^2$ = Ph, 4-MeOPh, 4-FPh, 1-naphthyl

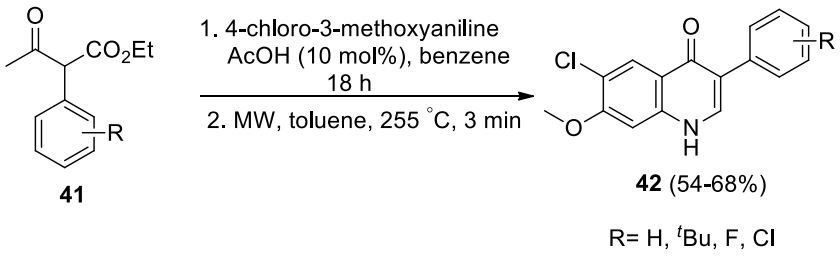
**Scheme 5.13**: *Synthesis of 1,2-Disubstituted 4-Quinolones **38***

Saxena and co-workers developed an efficient, cost effective and green methodology for ipso nitration in the synthesis of the 3-nitro derivative of 3-carboxy 4-quinolones **40** by the quantitative use of copper acetate and silver nitrate in water (Scheme 5.14).[27]



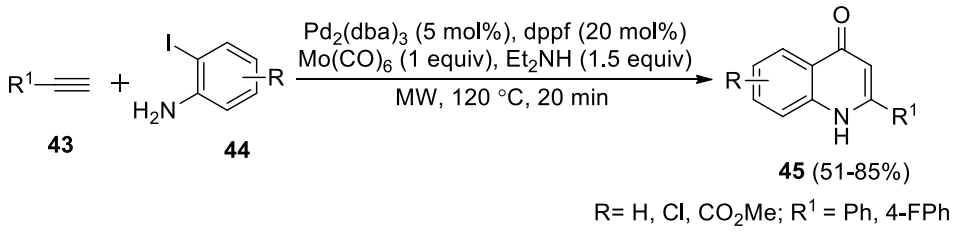

**Scheme 5.14**: *Ipso Nitration in the Synthesis of the 3-Nitro Derivative of 3-Carboxy-4-quinolones **40***

Later, condensation of *β*-keto esters **41** and aniline was carried out *via* Conrad–Limpach method to form 3-aryl 4(1*H*) quinolones **42**, an important class of antimalarial compounds undergoing preclinical development (Scheme 5.15).[28]



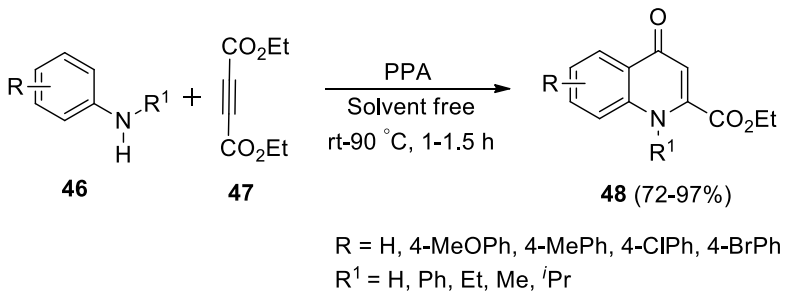

**Scheme 5.15**: *Conrad–Limpach Synthesis of 4-Quinolone*

Another addition in the quinolone synthesis was done by Akerbladh *et al.* in the same year whereby palladium catalyzed CO gas-free carbonylative Sonogashira/cyclization sequence for the preparation of functionalized 4-quinolones **45** from 2-iodoanilines **44** and alkynes **43** (Scheme 5.16).[29]



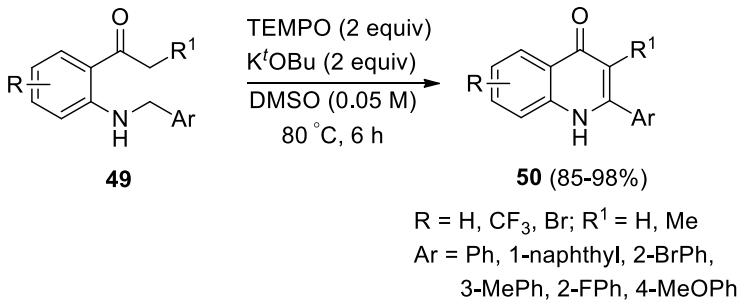

**Scheme 5.16**: *Synthesis of 4-Quinolones **45** via Sonogashira Cyclization*

Using commercially available diethyl acetylenedicarboxylate **47** and aromatic amines **46** as starting materials, the synthetic protocol has been achieved and afforded the product **48** *via* hydroamination at room temperature followed by PPA-catalyzed intramolecular ring closure. This metal free and mild reaction condition containing efficient strategy was developed by Yang and co-workers (Scheme 5.17).[30]




**Scheme 5.17**: *PPA Catalyzed Intramolecular Ring Closure*

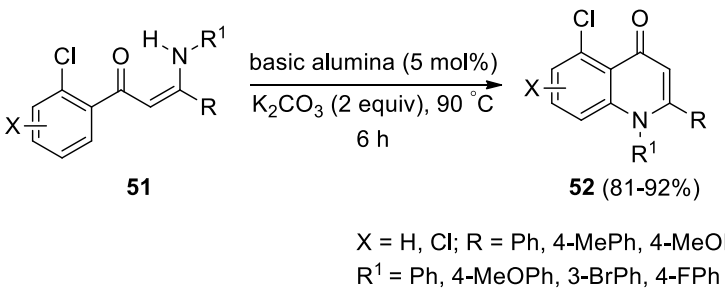
A novel, metal-free oxidative intramolecular Mannich reaction was developed by Hu *et al.* between secondary amines and unmodified ketones, affording a simple and direct access




**Scheme 5.18**: *Metal-free Oxidative Intramolecular Mannich Reaction*

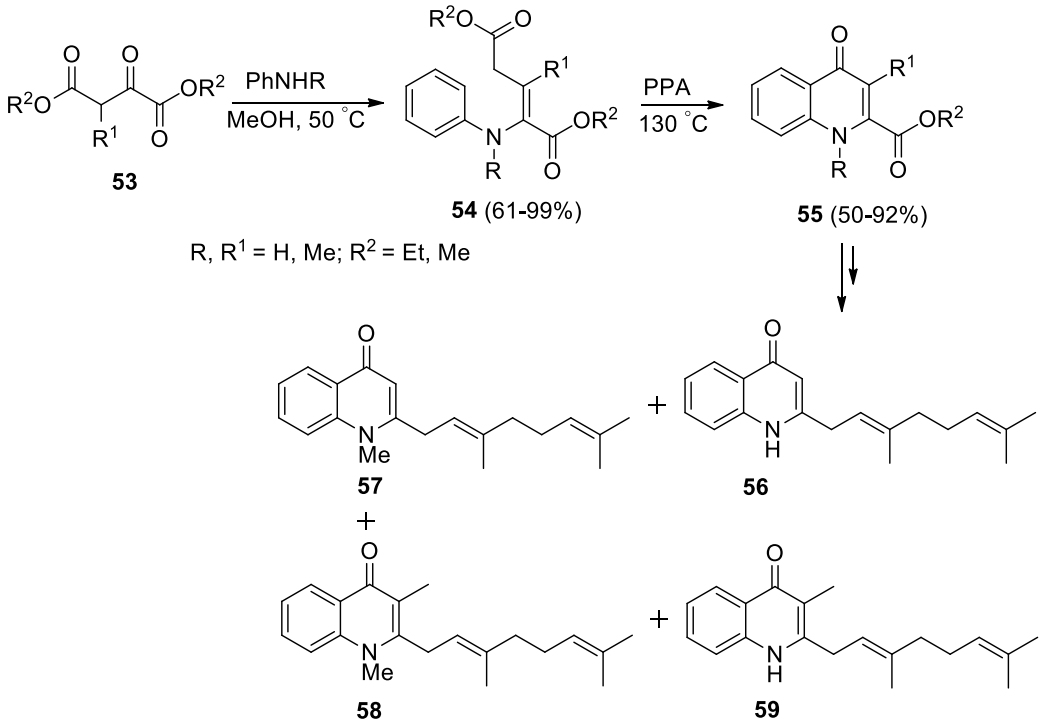
to a broad range of 2-arylquinolin-4(1*H*)-ones **50** through C($sp^3$)−H activation/C($sp^3$)−C($sp^3$) bond formation from readily available *N*-arylmethyl-2-aminophenylketones **49**, using TEMPO as the oxidant and KO$^t$Bu as the base (Scheme 5.18).[31]

Still discovery of novel methods in synthesizing various quinolones is continuing to be the most recent trend, which is evident from reports published in this year. One such report being the transition-metal-free economical solid phase synthesis of 1,2-disubstituted 4-quinolones **52** *via* the novel regiospecific synthesis of enaminones. The transformation of enaminones **51** to **52** was achieved in high yield *via* an alumina-supported solid phase reaction (Scheme 5.19).[32]



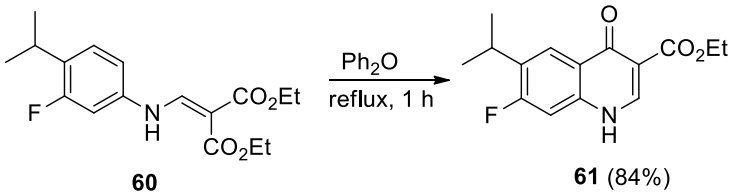

**Scheme 5.19**: *Transition Metal Free Solid Phase Synthesis of 4-Quinolones **52***

In addition to above another latest report came from Spring and co-workers wherein they developed an efficient and direct synthetic route to quinolone natural products **56-59** produced by the *actinomycete pseudonocardia sp.* (Scheme 20).[33]




**Scheme 5.20**: *Direct Synthetic Route to Quinolone Natural Product **57-59***

Moreover, in a yet another report 4-Quinolones-3-carboxylate **61** was synthesized to study their high affinity for cannabinoid receptor 2 (CB2R) ligands with higher aqueous solubility (Scheme 5.21).[34]

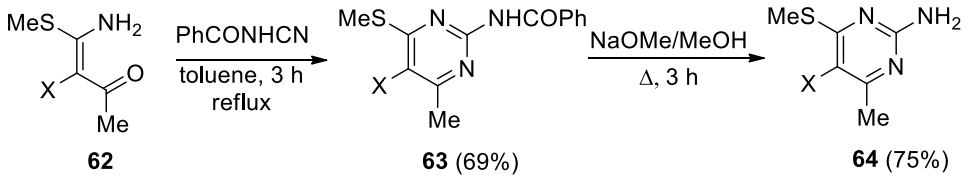



**Scheme 5.21**: *Synthesis of 4-Quinolones-3-carboxylates **61***

## 5.3 Previous Reports on *S,N*-acetals

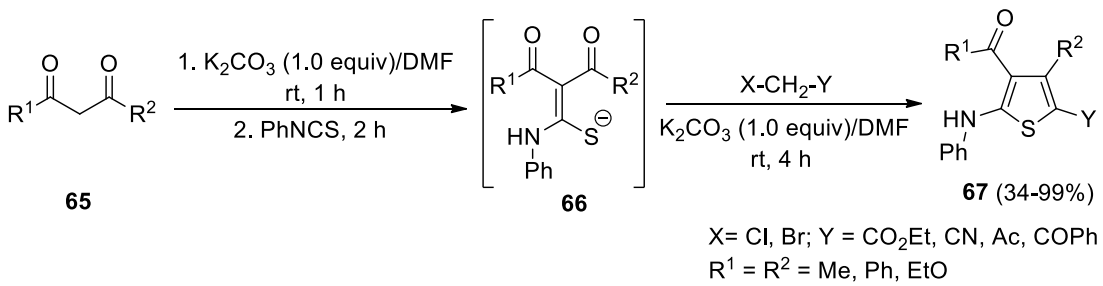
*α*-Oxoketene *S,N*-acetals is a versatile synthon and employed in synthesis of various heterocyclic compounds in the last few decades.[35]

Initially, the group of Dorokhov used acetyl ketene *S,N*-acetals **62** with benzoyl cyanamide for the synthesis of heterocycles such as 2-amino-4-methylthiopyrimidine derivatives **64** (Scheme 5.22).[36]



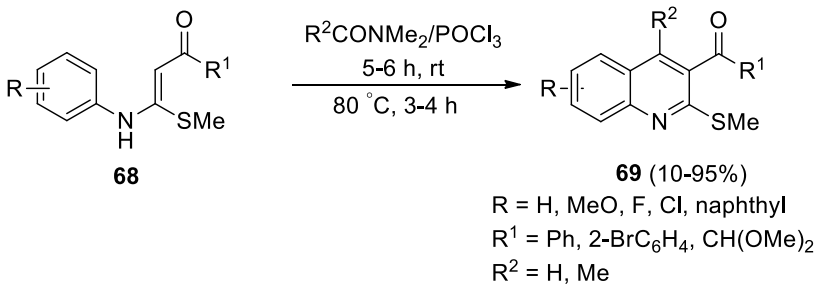

**Scheme 5.22**: *Use of S,N-acetals in Synthesis of Heterocycles **64***

Kirsch group demonstrated a process for the preparation of 2-aminothiophene derivatives **67** through the Dieckmann cyclization of aminothioacetals (Scheme 5.23).[37]



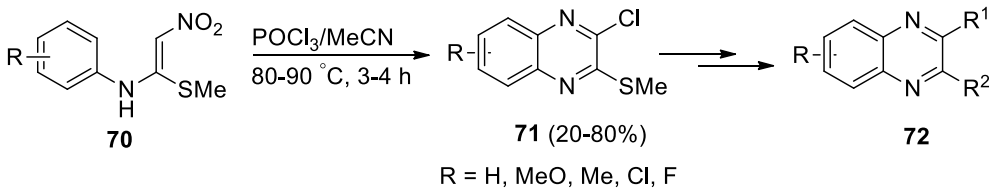

**Scheme 5.23**: *Dieckmann Cyclization of Aminothioacetals **65***

Next, the Ila research group found a simple, highly efficient and regioselective route to make highly functionalized quinolones **69** by the reaction of *α*-oxoketene-*N*,*S*-aminoacetals **68** with Vilsmeier reagents (Scheme 5.24).[38]



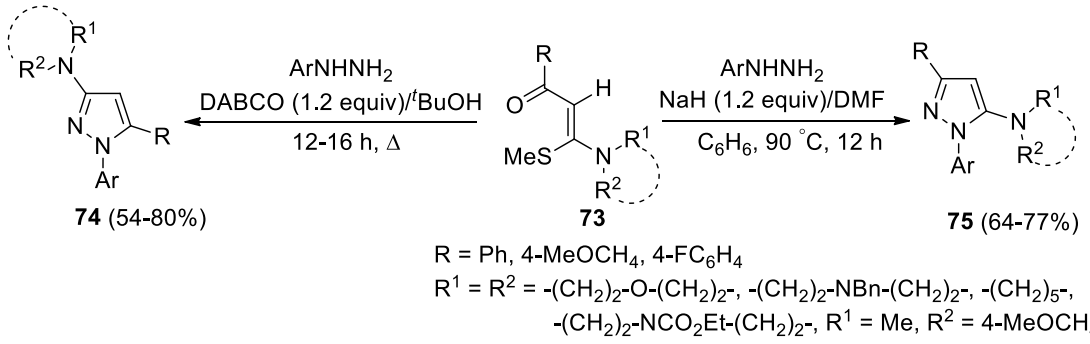

**Scheme 5.24**: *Reaction of α-Oxoketene-N,S-aminoacetals **68** with Vilsmeier Reagents*

They have also utilized the same strategy to the regioselective synthesis of substituted and fused 3-chloro-2-(methylthio)quinoxalines **71** in presence of $POCl_3$-mediated heteroannulation of *α*-nitroketene-*N,S*-anilinoacetals **70**. Later, these quinoxalines were further derivatized to afford **72** by metal mediated cross coupling reactions (Scheme 5.25).[39]



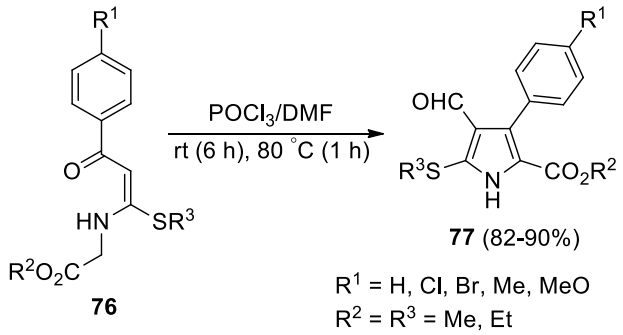

**Scheme 5.25**: *Regioselective Synthesis of Substituted and Fused Quinoxalines*

After intensive research on the *S,N*-acetals, the same group developed an efficient highly regioselective method for the synthesis of isomeric compounds of pyrazoles **74-75**. They isolated two different kind of pyrazole derivatives by cyclocondensation of *α*-oxoketene *N,S*-acetal precursors **73** with arylhydrazines by changing the reaction conditions (Scheme 5.26).[40]




**Scheme 5.26**: *Regioselective Synthesis of Pyrazoles **74, 75** from S,N-Acetals **73***

At an early stage in 2006, Mathew and Asokan successfully utilized *α*-oxoketene-*N,S*-acetals **76**, which was prepared by the reaction of alkyl glycinate hydrochlorides with *β*-oxodithiocarboxylates followed by alkylation to obtain pyrrole derivatives **77**. In this method *α*-oxoketene-*N,S*-acetals **76** underwent cyclization in presence of Vilsmeier reagents (Scheme 5.27).[41]




**Scheme 5.27**: *Cyclization of α-Oxoketene-N,S-acetals **76** using Vilsmeier Reagent*

## 5.4 Results and Discussions

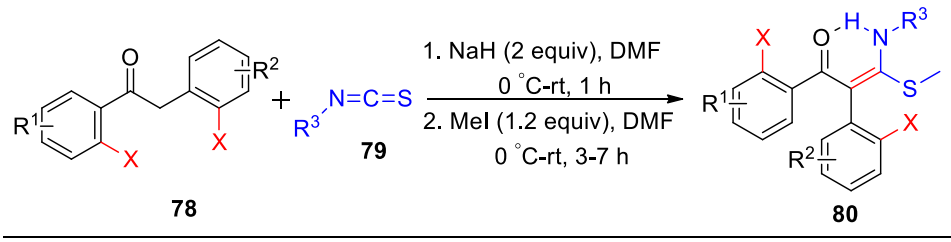
Developing a new class of *α*-oxo ketene *S,N*-acetals with multiple functionalities is always interesting because further functionalization can be smoothly achieved. Thus, we envisioned a new kind of *α*-(2-haloaroyl)-*α*-(2-bromo-aryl)-ketene *S,N*-acetals **80** which can be easily prepared from dihalo substituted deoxybenzoin **78** whose reactive halo groups can be tuned according to different reaction conditions. To our surprise, there are only two reports on intramolecular amination of doubly activated ketene *S,N*-acetals with limited substrates,[42] however, chemoselective amination of *α*-(2-haloaroyl)-*α*-(2-haloaryl)-ketene *S,N*-acetals is not explored.[43] In continuation of our ongoing interest in synthesis of highly substituted *N*-heterocycles with novel physical properties, herein, we report a highly chemoselective and base mediated amination of *α*-(2-haloaroyl)-*α*-(2-haloaryl)-ketene *S,N*-acetals **80** affording quinolones **81** with good to excellent yields. These quinolones **81** are transformed into fused heterocycles by using the reactive halo functional group.

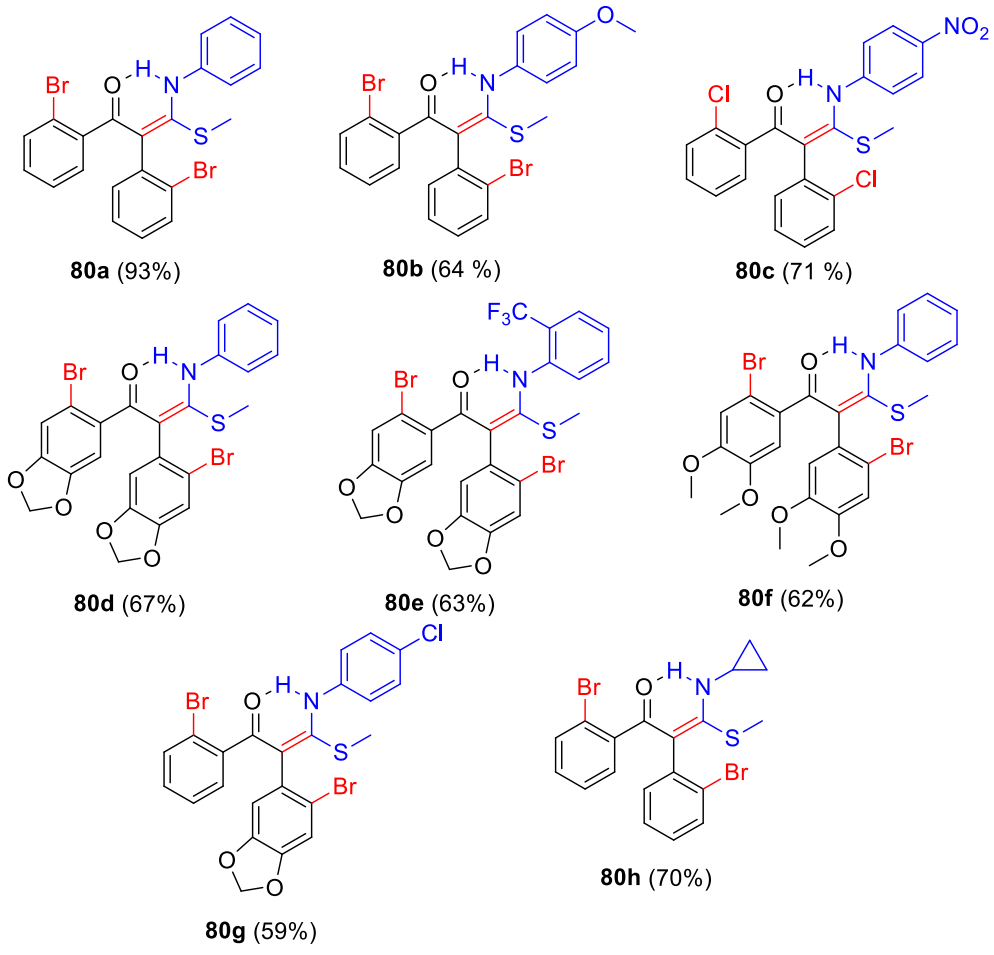
On the basis of all the available literature reports on the synthesis of the pharmaceutically important yet less accessed 4-quinolones as well as the use of *S,N*-acetals in the preparations of various hetrocycles, we decided to make use of *S,N*-acetals in synthesizing 4-quinolones.

### 5.4.1 Synthesis of *S,N*-Acetal Derivatives

The required *S,N*-acetals were synthesized from 2,2'-dihalo deoxybezoin in one pot by generation of nucleophilic centre in dihalodeoxybenzoin **78** by NaH followed by addition of isothiocyantes **79** and then methylation using MeI (Table 5.1).[44] The resulting *S,N*-acetals, **80**, obtained in moderate to good yields. They found a single regioisomer because of intramolecular hydrogen bonding which was established by NMR spectroscopy.

**Table 5.1**: **Synthesis of *S,N*-Acetals 80**



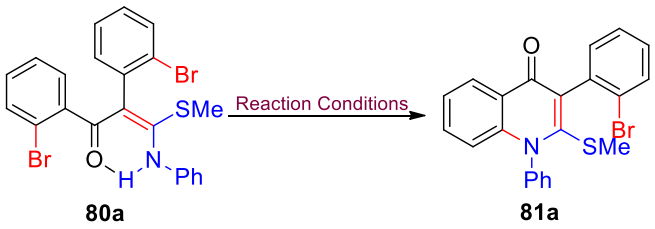



The synthesis of *S,N*-acetals **80**, was then further tuned using various substituents under reported reaction condition. The electronic effect was more or less similar with the presence of electron withdrawing group with nitrogen atom, **80c**, giving higher yield (Table 5.1, 71%) than the nitrogen atom attached to an electron donating group, **80b**, (Table 5.1, 64%). The steric factor also influenced the course of reaction. The presence of steric hindrance on the attached aromatic ring decreased the yield of the reaction considerably, **80e-g** (Table 5.1, 59-63%). However, the less stearically demanding group, cyclopropyl when attached to the nitrogen atom, **80h**, gave moderate yield of 70%.

### 5.4.2 Optimization reaction for the Synthesis of 4-Quinolones *via* Amination of *S,N*-Acetals

Next, we focused on the synthesis 4-quinolone *via* an intramolecular amination of the *S,N*- acetals. Thus, the amination reaction of *α*-(2-bromobenoyl)-*α*-(2-bromophenyl)-ketene *S,N*-acetals **80a**, as a model reaction, was treated with $K_2CO_3$ in dioxane at 90 °C for 6 h affording only 13% of 4-quinolone **81a** and the *S,N*-acetals **80a** was recovered in 85% (Table 5.2, Entry 1). Whereas KOH gave much better yield of the quinolone **81a** (77%). However, unreacted *S,N*-acetals **80a** was isolated in 20% (Table 5.2, Entry 2). Gratifyingly, other bases, $Cs_2CO_3$, NaO$^t$Bu and KO$^t$Bu, were very effective for the intramolecular amination of **80a** yielding the quinolone **81a** in 89-90% yields (Table 5.2, Entries 3-5).

**Table 5.2**: **Optimization of Amination of Ketene *S,N*-Acetals 80**




**80a** **81a**

| Entry | Solvent | Base | **81a**(% Yield)[a] | **80a** (%Yield)[b] |
|---|---|---|---|---|
| 1 | Dioxane | $K_2CO_3$ | 13 | 85 |
| 2 | Dioxane | KOH | 77 | 20 |
| 3 | Dioxane | $Cs_2CO_3$ | 90 | — |
| 4 | Dioxane | NaO$^t$Bu | 89 | — |
| 5 | Dioxane | KO$^t$Bu | 90 | — |
| 6 | Dioxane | TMG | 36 | 44 |
| 7 | $^t$BuOH | KO$^t$Bu | 60 | — |
| 8 | DMF | KO$^t$Bu | 64 | — |
| 9 | Toluene | KO$^t$Bu | 84 | — |
| 10 | DMSO | KO$^t$Bu | 69 | — |
| 11 | Dioxane | KO$^t$Bu | 99[c] | — |

[a] *Reaction conditions: (0.5 mmol), base (1.5 equiv), solvent (2.0 mL), 90 °C,* [b] *Isolated yields.*
[c] *Reaction performed under sealed tube condition. TMG- 1,1,3,3-Tetramethylguanidine.*

On the other hand, TMG (1,1,3,3-*tetramethylguanidine*), an organic base, gave only 36% of the product **81a** along with **80a** (44%) (Table 5.2, Entry 6). For further fine tuning of this process, other solvents such as $^t$BuOH, DMF, DMSO and toluene, were screened and Found to be less beneficial when compared with dioxane (Entries 7-10). Interestingly, an experiment performed under sealed tube conditions provided quantitative yield of quinolone **81a** (Table 5.2, Entry 11). This amination process is highly chemoselective and the 4-quinolone **81a** was obtained exclusively.

### 5.4.3 Substrate Scope for the Synthesis of 4-Quinolones

The optimized conditions in our hand, we examined a series of *S,N*-acetals **80** for the amination process. Electron donating and withdrawing substituents effect on aniline nitrogen were studied. Both groups gave the desired quinolones **81b** & **81c** in 70% & 71% yields respectively. Interestingly, we Found that *α*-2-chlorobenzoyl-ketene *S,N*-acetals **80c** is also equally effective for this process when compared with 2-bromo substituent (Table 5.3, **81c**). However, aliphatic amino *S,N*-acetals **80h** gave only 46% yield of the quinolone **81h** (Table 5.3). Whereas *para*-chloroanilino *S,N*-acetals **80g** was smoothly converted to the

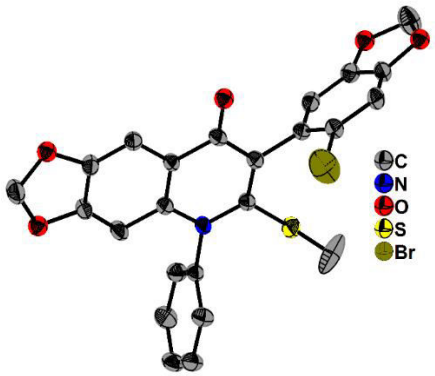
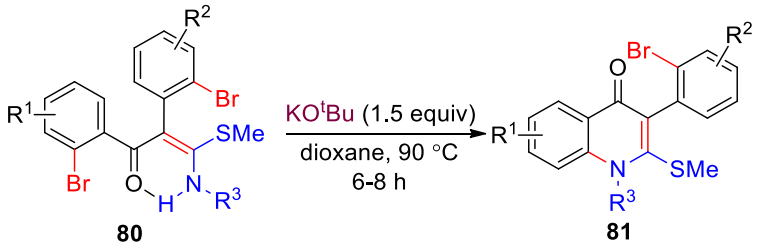



**Figure 5.1:** X-ray Crystal Structure of **81d**

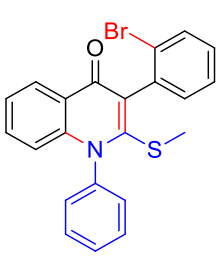
corresponding quinolone derivative **81g** in 71% yield (Table 5.3, **81g**). We also studied electron donating effect on the amination process. Thus, dimethoxy substituted bromo benzoyl ketene *S,N*-acetals **80f** gave the corresponding quinolone **81f** in 63% yield. On the other hand, methylene dioxy substituted bromo benzoyl *S,N*-acetals **80d** smoothly converted to the quinolone **81d** in excellent yield (85%) (Table 5.3, **81d**). The X-ray crystal structure of **81d** was also analysed (Figure 5.1). However, electron withdrawing

group at *ortho* position of aniline derivative **80e** gave only 43% of the desired quinolone compound **81e** (Table 5.3). Thus the steric hindrance affects the amination process.

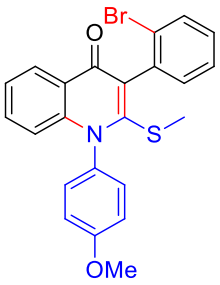
**Table 5.3**: **Base Assisted Amination of Ketene *S,N*-Acetals 80**



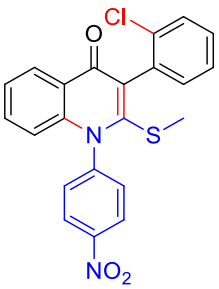

**80** **81**



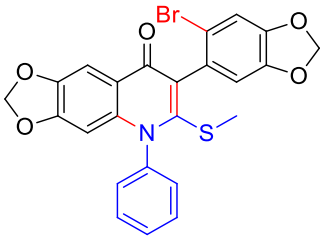

**81a** (99%)



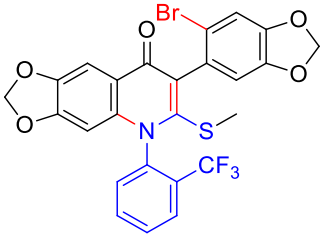

**81b** (70%)



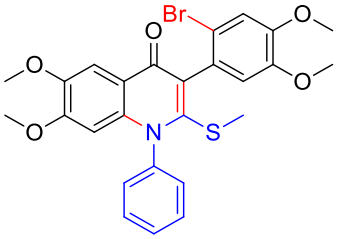

**81c** (71%)



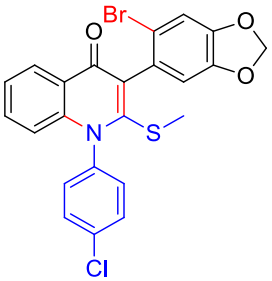

**81d** (85%)



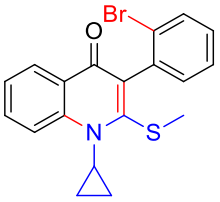

**81e** (43%)




**81f** (63%)




**81g** (71%)



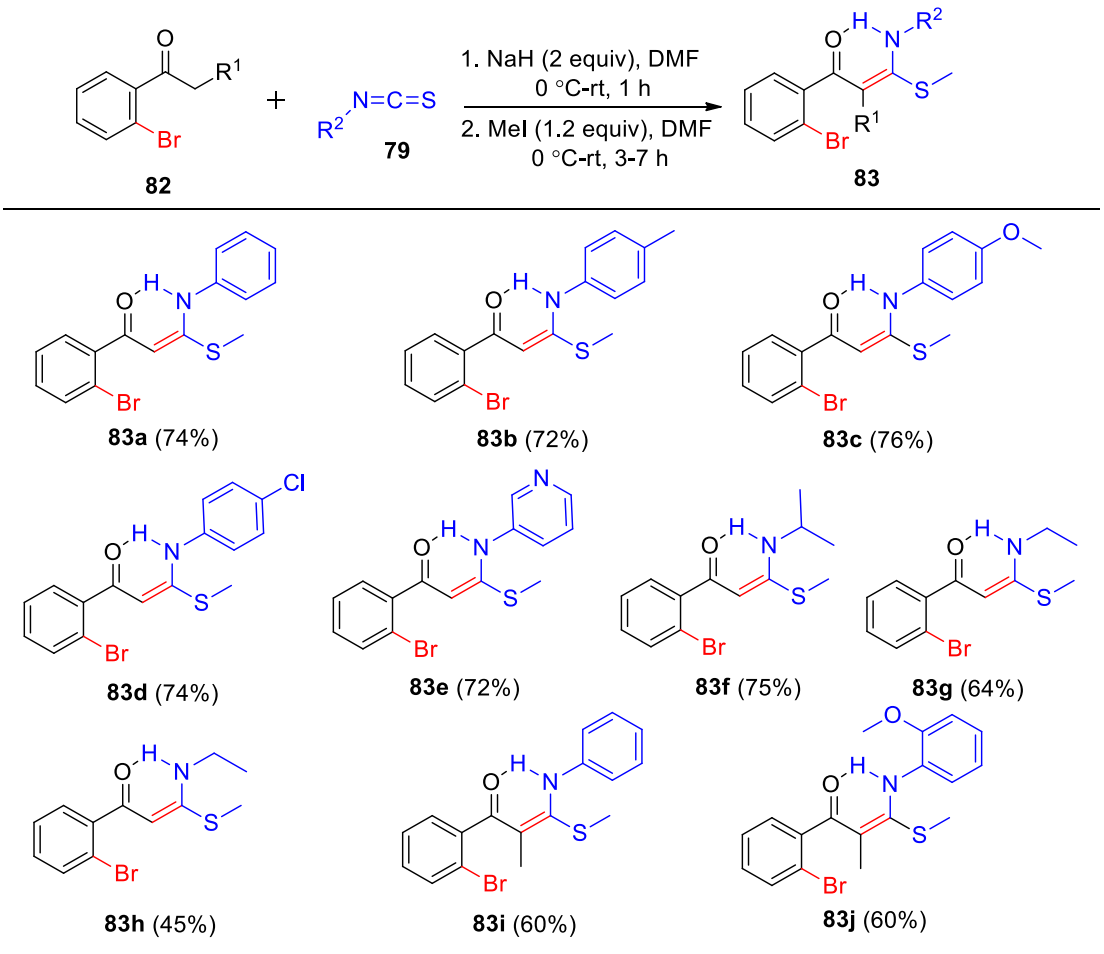

**81h** (46%)

### 5.4.4 Synthesis of *S,N*-acetals Derived from Bromoacetophenone and Bromopropiophenone

We next turned our attention towards to study ketene *S,N*-acetals **83** derived from 2'-bromoacetophenone & 2'-bromopropiophenone **82**. The required ketene *S,N*-acetals **83** were

synthesized by reaction of 2-bromobenzoyl derivatives with isothiocyanide and methylation of respective thioamides. On changing the various substituents attached with nitrogen atom and reacting it with 2'-bromoacetophenone and 2'-bromopropiophenone, we prepared various products. When 2-bromoacetophenone was treated with isothiocyanates having electron donating *para*-methoxyphenyl it gave the corresponding *S,N*-acetal, (Table 5.4, **83c**), with highest yield of 76%. Similarly the same ketone was reacted with electron withdrawing group

**Table 5.4**: **Synthesis of Ketene *S,N*-Acetals 83**




(4-chlorophenyl) as well as phenyl and *p*-tolyl substituted isothiocyanates, it gave the corresponding products **83d, 83a** and **83b** with good yields 72-76% (Table 5.4). Further we replaced the substituent on the nitrogen atom with an aliphatic groups such as isopropyl, ethyl & benzyl, and the corresponding S,N-acetals **83f-h** were isolated (Table 5.4). Furthermore, 2-

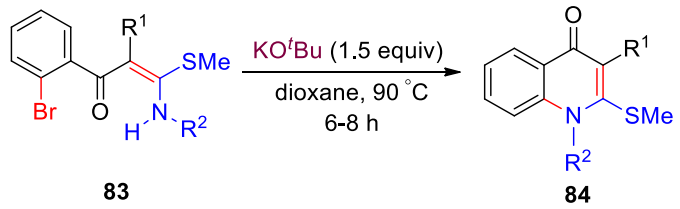
pyridyl substituted nitrogen atom containing *S,N*-acetal (Table 5.4, **83e**) was also prepared with 72% yield. However, when 2-bromopropiophenone is reacted with phenyl and o-methoxyphenyl, it produced the resulting ketene *S,N*-acetals, (Table 5.4, **83i-j**), with relatively lower yield 60%.

### 5.4.5 Synthesis of 4-Quinolone *via* Amination of the *S,N*-Acetals

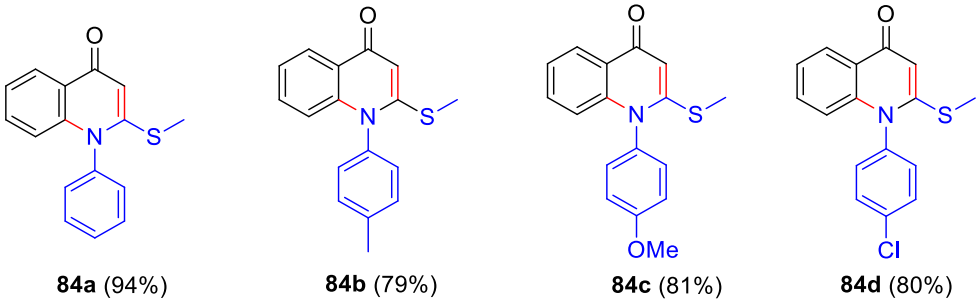
After synthesizing of *S,N*-acetals, the **83a** was treated under our established conditions yielding 1-phenyl-2-methylthio-4-quinolone (**84a**) in 94%. The highest yield was obtained as compared with reported methods.[45]

Similarly, other 1-aryl substituted quinolones **84b-d** were synthesized from the respective *S,N*-acetals **83b-d** in 79-80% yields (Table 5.5). Thus, the electronic effect of N-aryl

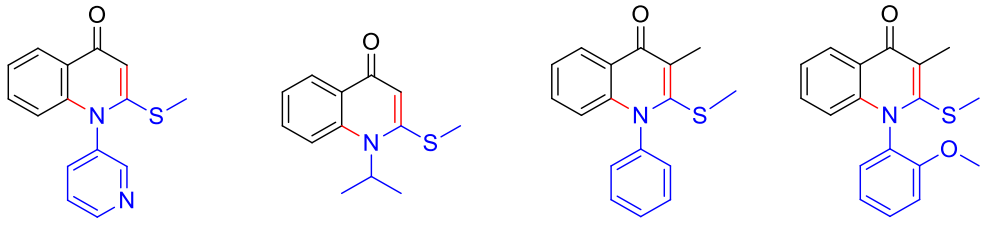
**Table 5.5**: **Synthesis of 1-Aryl-2-methylthio-4-quinolone 84 *via* Amination Process**




**83** **84**




**84a** (94%) **84b** (79%) **84c** (81%) **84d** (80%)



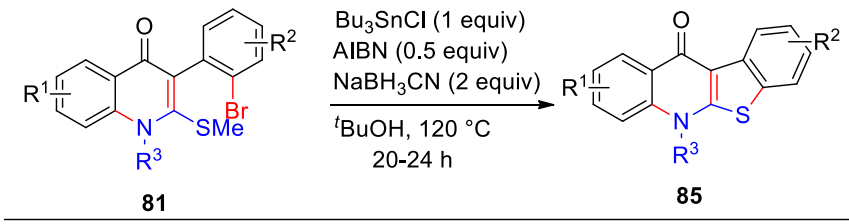

**84e** (63%) **84f** (0%) **84i** (61%) **84j** (39%)

groups were not influenced in the amination process. Interestingly, 1-(3-pyridyl)-2-thiomethyl-4-quinolone (**84e**) was also obtained in 61% under similar conditions (Table 5.5, **84e**). However, the present amination process was failed to give 1-(2-propyl)-4-quinolone **84f** (Table 5.5, **84f**). 1-Phenyl-3-methyl-2-thiomethyl-4-quinolone (**84i**) was synthesized from *S,N*-acetals **83i** in 61% (Table 5.5, **84i**). Whereas, electron donating group at ortho position of aniline derivative gave only 39% of the desired quinolone **84j** (Table 5.5, **84j**). We found that the steric hindrance plays a crucial role in the cyclization process.

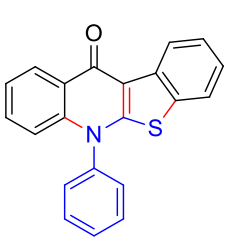
### 5.4.6 Synthesis of Benzothipheno Fused Quinolones *via* C—S Coupling

Quinolone fused heterocycles are found in natural products and pharmaceutically active molecules.[46] The newly synthesized halo fuctionalized quinolone derivatives **81** are easily transformed to the fused heterocycles through radical process or cross-coupling reactions. Thus, the quinolone **81a** was subjected under radical cyclization conditions, using free radical generator AIBN/$Bu_3SnCl$, we obtained a novel class of benzothieno[2,3-*b*]quinolone **85a** in 65% yield (Table 5.6). The structure was established with Spectruml and analytical data. These

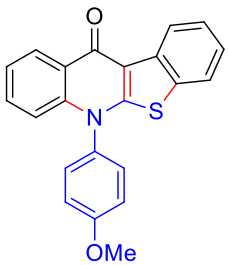
**Table 5.6: Synthesis of Benzothieno[2,3-*b*]quinolones 65 *via* Radical C—S Coupling Reaction**



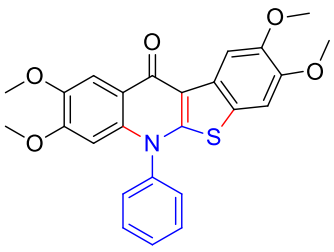

**81** **85**



**85a** (65%)



**85b** (72%)

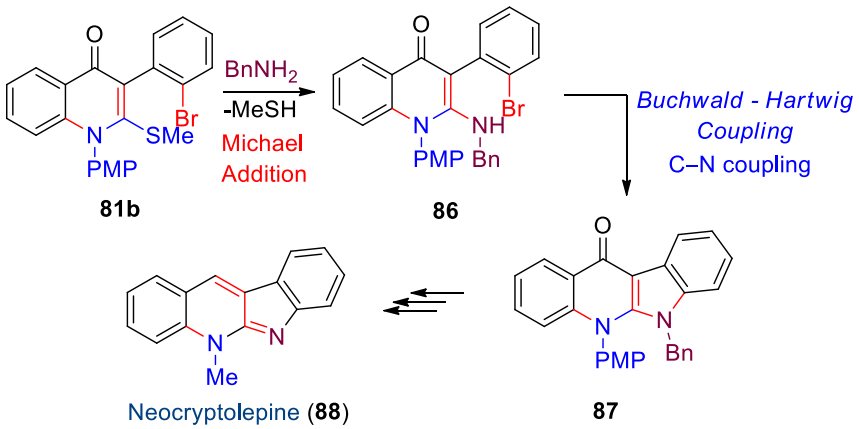


**85f** (62%)

conditions were suitable for converting other quinolones derivatives **81b** & **81f** to the corresponding benzothieno[2,3-*b*]quinolones **85b** & **85f** in 62-72% yields. To best of our knowledge, this class of thieno fused quinolones is not reported in literature.

### 5.4.7 Proposed Scheme for the Synthesis of Analogues of Neocryptolepine from 4-Quinolones

After successful synthesis of benzothieno[2,3-*b*] quinolones **85**, we were interested in synthesizing analogous of neocryptolepine (**88**) from quinolones **81**. The neocryptolepine is natural product and showed anti-malarial and other biological activities.[47] The proposed synthetic strategy is shown in Scheme 5.28.




**Scheme 5.28**: *Proposed Scheme for Synthesis of Neocryptolepine (88)*

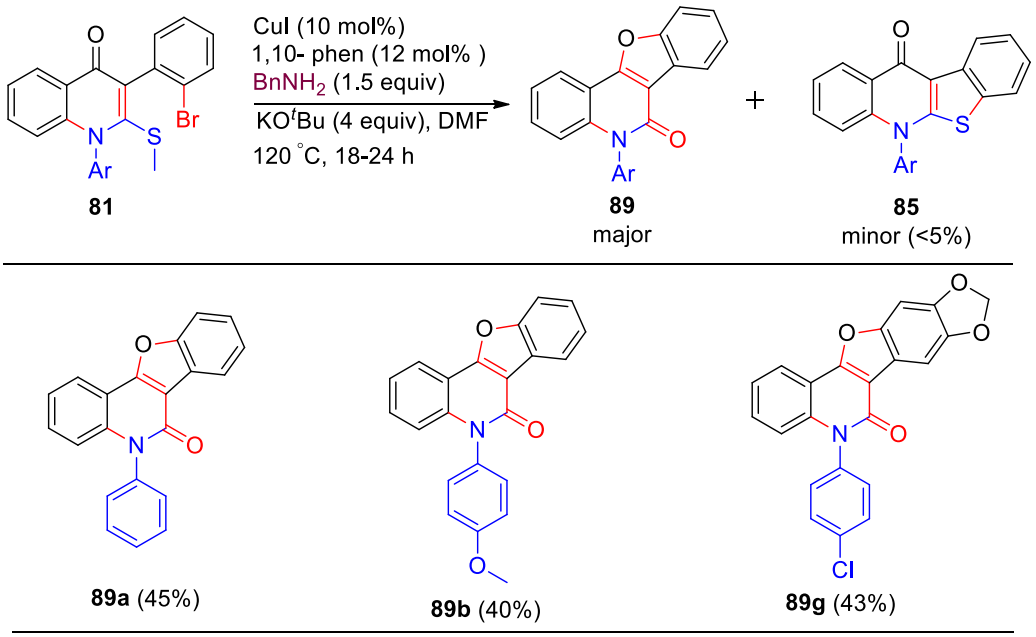
The key reactions are Michael addition and Buchwald – Hartwig cross-coupling reaction which could be performed in a single synthetic operation without isolating Michael adduct (Scheme 5.28).

### 5.4.8 Synthesis of Benzofurano Fused Quinolone *via* C—O Coupling Reaction

The quinolone **81a**, as a model substrate, was treated with benzyl amine in the presence of CuI, 1,10-phenanthroline with KO$^t$Bu as the desired base gave major and minor products. The minor product was characterized as benzothieno[2,3-*b*]quinolone

derivative **85a**. The Spectral data of **85a** is matched with aforementioned one. Whereas major product is not expected neocryptolepine derivative **88**. The product was identified as benzofuro[3,2-*c*]quinolone derivative **89a**. The structure of **89a** was confirmed by Spectruml and analytical data.

**Table 5.7**: **Synthesis of Benzofuro[3,2-*c*]quinolone 11 *via* Copper Mediated C—O Coupling Reaction**



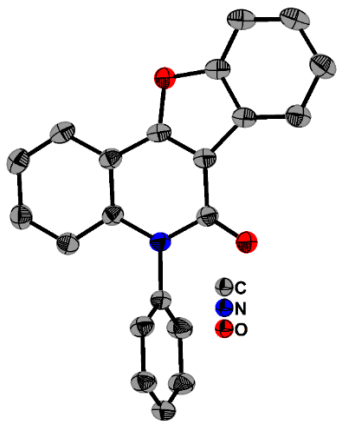
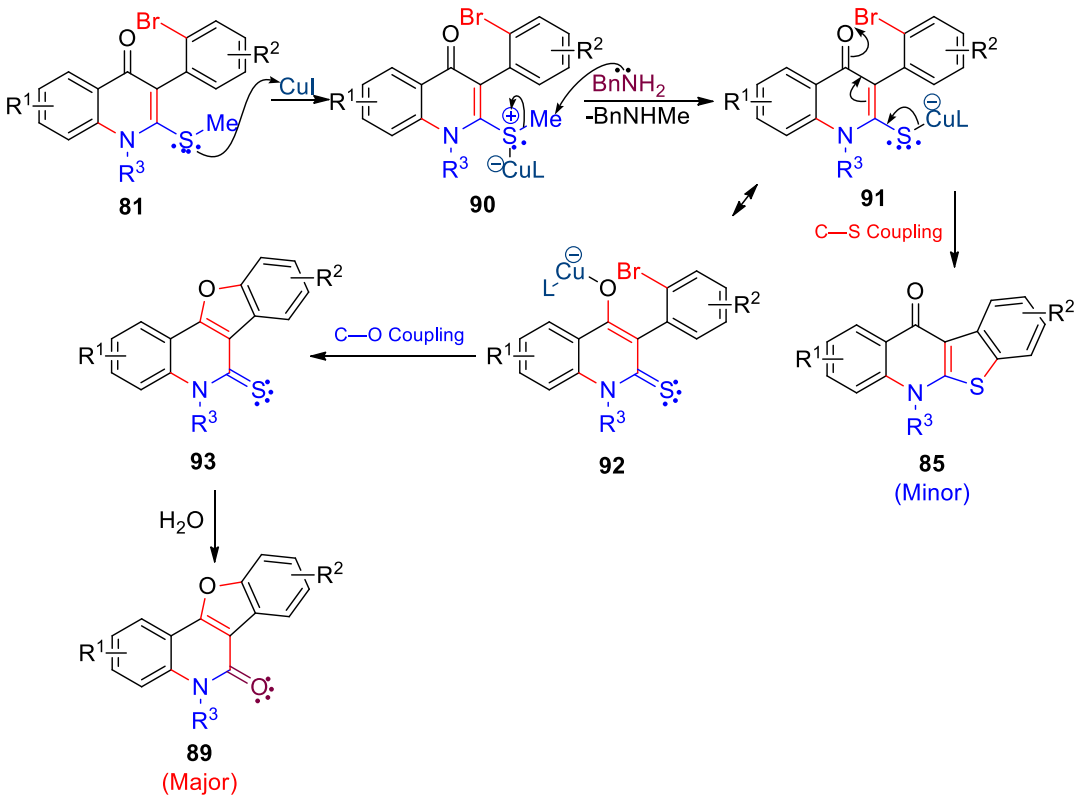




**Figure 5.2**: X-ray Crystal Structure of **89a**

Further, it was also confirmed by single crystal X-ray analysis (Figure 5.2). Other quinolones **81b** & **81g** were transformed into the predicted products **89b** & **89g** under similar reaction conditions along with minor products (**85b** & **85g**). However, our attempts to improve the yields of the benzofuro[3,2-*c*]quinolones **89** were not successful. There is only one report on the synthesis of this class of furo fused quinolones *via* acid-catalyzed annulation with a long synthetic route.[48]

### 5.4.9 Proposed Reaction Mechanism for the Formation of Benzofurano Fused Quinolones

Based on the controlled experiments, the probable mechanism is proposed in Scheme 5.29. The first step is CuI/$BnNH_2$ assisted thiomethyl ether deprotection of quinolone **81** giving



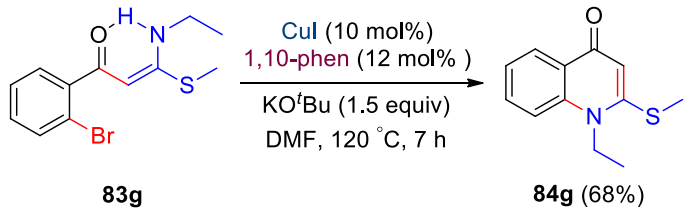

**Scheme 5.29**: *Proposed Mechanism for the Formation of **89** and **85***

thiolate derivative **90**. This is a crucial step which requires benzyl amine. The thiolate derivative **91** can undergo C—S cross coupling under the experimental conditions affording

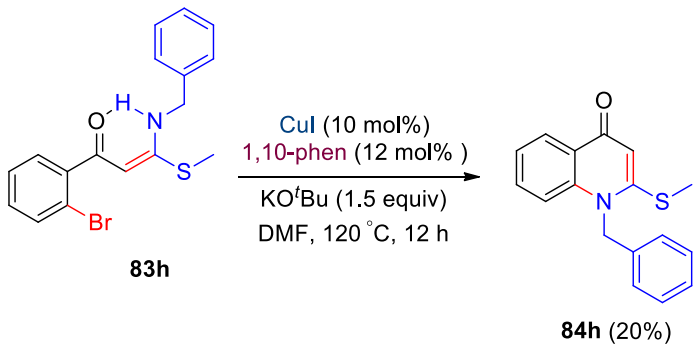
minor product **85**. Whereas thiolate **91** can also exist another resonance hydride enolate **92** which goes an intramolecular C—O coupling reaction leading benzofuro[3,2-*c*]quinolone. The thioamide **91** is converted into ketone derivative **89** during the purification.

### 5.4.10 Copper Catalyzed Synthesis of Aliphatic Substituted 4-Quinolones

Since, the synthesis of isopropyl substituted 4-quinolone was unsuccessful, we developed a new synthetic strategy to prepare such aliphatic substituted 4-quinolones **84g** & **84h** from the corresponding *S,N*-acetals **83g** & **83h**. The new synthetic strategy involves CuI in the presence of 1,10-phenanthroline (Scheme 5.30 & Scheme 5.31).




**Scheme 5.30**: *Metal catalyzed Synthesis of Ethyl Substituted 4-Quinolone* ***95***




**Scheme 5.31**: *Metal Mediated Synthesis of Benzyl Substituted 4-Quinolone* ***97***

## 5.5 Conclusion

We have developed a new class of ketene *S,N*-acetals **80** from 2,2'-halo substituted deoxy benzoin derivatives. These derivatives **80** were used for synthesis of 4-quinlones **81** in moderate to excellent yields *via* base assisted intramolecular amination reactions. Further other

quinolones were synthesized from ketene *S,N*-acetals **83**. The quinolones **81** were converted into a novel class of heterocyclic systems. The biological screening of new class of heterocyclic systems such as benzothieno[1,2-*b*]quinolones **85** and benzofuro[3,2-*c*]quinolone **89** through radical & C—O cross-coupling reactions.

## 5.6 Experimental Section

### 5.6.1 Reagents

All reactions were performed by using standard *via*l technique with rubber septum. All solids were weighed in air. Toluene, dioxane, $^{t}$BuOH, DMF, DMSO, $Cs_2CO_3$, KOH, $K_2CO_3$, KO$^{t}$Bu, NaO$^{t}$Bu and *N,N,N′,N′* -tetra methyl guanidine were purchased from Aldrich, Acros, Merck, Spectrochem or Alfa-Aesar and used as received. All isothiocyanates were purchased from Aldrich and few isothiocyanates synthesized from the corresponding amines. All other reagents were purchased from common suppliers and used without further purification. Flash chromatography was performed using Merck Silica gel (230-400 mesh). Fractions were monitored by thin-layer chromatography on precoated silica gel 60 F254 plates (Merck & co.) and were visualized by UV.

### 5.6.2 Analytical Methods

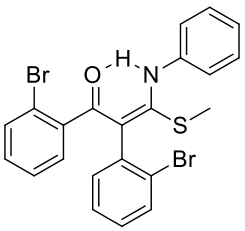
As described in Section **2.6.2** (Chapter-2).

The X-ray quality crystals for the compounds **81d** & **89a** were grown by slow diffusion of *n*-hexane over $CH_2Cl_2$ solution. Single-crystal X-ray diffraction data of **81d** & **89a** were collected in a Bruker KAPPA APEX-II, four angle rotation system, Mo-Kα radiation (0.71073 Å).

### 5.6.3 General Procedure for the Synthesis of *α*-(Bromoaroyl)ketene *N,S*-acetals:

To a stirring suspension of NaH (60% suspension in mineral oil) in (4.0 mL) of DMF at 0 ºC was added drop wise the corresponding deoxybenzoin (3.0 mmol) in (3.0 mL) of DMF. After being further stirred for 1 h at room temperature, a solution of isothiocyanate (3.0 mmol) in (2.0 mL) of DMF was added to the reaction mixture at 0 ºC and followed by further stirring for 1 h at room temperature. To this reaction mixture MeI (3.6 mmol) was added at 0 ºC and further stirred for 2-6 h. After complete consumption of the starting materials (monitored by TLC), the reaction mixture was quenched with saturated $NH_4Cl$ solution and extracted with EtOAc. The combined organic layer washed with water (3 x 20 mL) & brine (3 x 20 mL), dried over anhyd. $Na_2SO_4$ and concentrated under reduced pressure. The crude products were purified by flash chromatography using EtOAc/hexanes as eluent.

**1,2-Bis(2-bromophenyl)-3-(methylthio)-3-(phenylamino)prop-2-en-1-one (80a)**




Reaction time: 8 h

Yield: 93%, as a yellow colour solid.

Melting point: 116 – 118 ºC

$R_f$: 0.37 in 10% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3448, 3050, 3002, 2924, 2852, 1578, 1545, 1425, 1370, 1316, 1247, 1195, 1089, 1051, 1024, 976, 905, 850, 749, 734.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 13.54 (s, 1H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.47 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.42 – 7.37 (m, 4H), 7.24 – 7.22 (m, 1H), 7.19 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.08 (td, *J* = 7.6, 1.2 Hz, 1H), 7.05 – 6.94 (m, 3H), 1.91 (s, 3H).

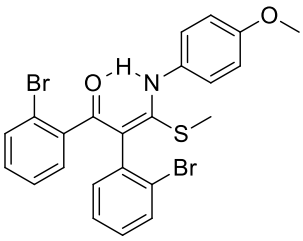
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 190.0, 165.5, 142.8, 139.8, 138.9, 134.0, 132.4, 132.2, 129.5, 129.4, 129.1, 128.7, 127.2, 126.9, 126.5, 125.8, 124.1, 119.2, 114.7, 17.2.

HR-MS (ESI): Calcd. for $C_{22}H_{17}Br_2NOS$ [M+H]: 501.9470, Found: 501.9491.

[M+H]: 503.9451, Found: 503.9474.

[M+H]: 505.9430, Found: 505.9450.

**1,2-Bis(2-bromophenyl)-3-((4-methoxyphenyl)amino)-3-(methylthio)prop-2-en-1-one (80b)**



Reaction time: 4 h

Yield: 64%, as a pale yellow colour solid.

Melting point: 128 – 130 °C

$R_f$: 0.43 in 10% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3428, 3072, 2989, 2958, 2927, 2830, 1550, 1509, 1375, 1314, 1245, 1179, 1025, 871, 829, 763, 746.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 13.60 (s, 1H), 7.46 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.44 – 7.37 (m, 4H), 7.18 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.06 (td, *J* = 7.4, 1.2 Hz, 1H), 7.02 (td, *J* = 7.2, 1.2 Hz, 1H), 6.99 – 6.90 (m, 4H), 3.83 (s, 3H), 1.89 (s, 3H).

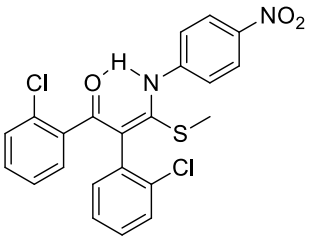
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 189.6, 166.2, 157.8, 142.9, 139.1, 134.1, 132.6, 132.4, 132.2, 129.3, 129.0, 128.9, 127.2, 126.9, 126.5, 125.8, 119.3, 114.6, 113.9, 55.6, 17.1.

HR-MS (ESI): Calcd. for $C_{23}H_{19}Br_2NO_2S$ [M+H]: 531.9576, Found: 531.9538.

[M+H]: 533.9557, Found: 533.9526.

[M+H]: 535.9536, Found: 535.9512.

**1,2-Bis(2-chlorophenyl)-3-(methylthio)-3-((4-nitrophenyl)amino)prop-2-en-1-one (80c)**



Reaction time: 4 h

Yield: 71%, as a yellow colour solid.

Melting point: 122 – 124 °C

$R_f$: 0.40 in 10% ethyl acetate in hexane

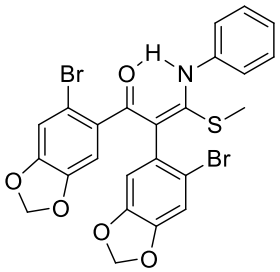
IR (KBr): ν ($cm^{-1}$) = 3447, 3050, 2925, 2843, 1587, 1560, 1514, 1423, 1364, 1338, 1312, 1266, 1250, 1112, 1091, 1062, 1032, 869, 854, 751.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 13.17 (s, 1H), 8.27 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 9.2 Hz, 2H), 7.33 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.29 – 7.27 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.15 – 7.06 (m, 4H), 7.02 – 6.98 (m, 1H), 2.02 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 191.6, 162.1, 146.2, 144.1, 140.1, 136.2, 136.0, 133.6, 130.1, 129.9, 129.6, 129.5, 129.2, 127.0, 126.7, 126.0, 125.4, 122.0, 116.4, 17.1.

HR-MS (ESI): Calcd. for $C_{22}H_{16}Cl_2N_2O_3S$ [M+H]: 459.0331, Found: 459.0356.

**1,2-Bis(6-bromobenzo[*d*][1,3]dioxol-5-yl)-3-(methylthio)-3-(phenylamino)prop-2-en-1-one (80d)**




Reaction time: 6.5 h

Yield: 67%, as a yellow colour solid.

Melting point: 197 – 199 $^oC$

$R_f$: 0.40 in 10% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3428, 3081, 2923, 2848, 1563, 1540, 1497, 1476, 1410, 1391, 1360, 1340, 1311, 1241, 1117, 1069, 1033, 928, 881, 866, 765.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 13.43 (s, 1H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 6.96 (s, 1H), 6.92 (s, 1H), 6.86 (s, 1H), 6.76 (s, 1H), 5.94 (d, *J* = 6.8 Hz, 2H), 5.90 (d, *J* = 11.2 Hz, 2H), 1.90 (s, 3H).

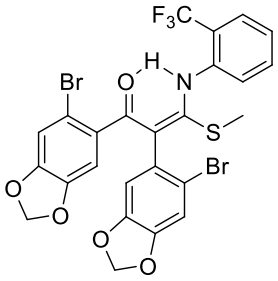
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 189.5, 166.1, 148.1, 148.0, 147.1, 146.6, 139.9, 136.5, 131.8, 129.5, 125.7, 124.0, 119.5, 114.4, 112.9, 112.7, 112.2, 110.3, 107.0, 101.9, 101.8, 17.1.

HR-MS (ESI): Calcd. for $C_{24}H_{17}Br_2NO_5S$ [M+H]: 589.9267, Found: 589.9247.

[M+H]: 591.9248, Found: 591.9226.

[M+H]: 593.9227, Found: 593.9202.

**1,2-Bis(6-bromobenzo[*d*][1,3]dioxol-5-yl)-3-(methylthio)-3-((2-trifluoromethyl)phenyl) amino)prop-2-en-1-one (80e)**



Reaction time: 4.5 h

Yield: 63%, as a yellow colour solid.

Melting point: 106 – 108 ºC

$R_f$: 0.33 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3448, 3010, 2917, 2848, 1555, 1543, 1506, 1478, 1412, 1391, 1361, 1340, 1315, 1281, 1243, 1167, 1124, 1057, 1035, 931, 874, 841, 786, 765.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 13.28 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 6.97 (s, 1H), 6.95 (s, 1H), 6.85 (s, 1H), 6.76 (s, 1H), 5.95 (dd, *J* = 7.4 Hz, 1.2 Hz, 2H), 5.91 (dd, *J* = 8.4 Hz, 1.2 Hz, 2H), 1.85 (s, 3H).

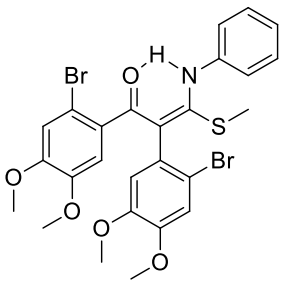
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 190.1, 165.1, 148.23, 148.18, 147.2, 146.7, 138.7 (d, *J* = 2 Hz), 136.0, 132.9, 131.3, 126.7 (q, *J* = 5.2 Hz), 125.8, 125.3, 123.8 (q, *J* = 271 Hz), 123.5 (q, *J* = 30 Hz), 119.1, 116.5, 112.7, 112.6, 112.3, 110.2, 107.0, 102.0, 101.9, 16.4.

HR-MS (ESI): Calcd. for $C_{25}H_{16}Br_2F_3NO_5S$ [M+H]: 657.9141, Found: 657.9176.

[M+H]: 659.9122, Found: 659.9151.

[M+H]: 661.9101, Found: 661.9135.

**1,2-Bis(2-bromo-4,5-dimethoxyphenyl)-3-(methylthio)-3-(phenylamino)prop-2-en-1-one (80f)**



Reaction time: 8 h

Yield: 62%, as a yellow colour solid.

Melting point: 79 – 81 ºC

$R_f$: 0.38 in ethyl acetate/hexane (1:2)

IR (KBr): ν ($cm^{-1}$) = 3448, 2997, 2929, 2838, 1594, 1542, 1507, 1459, 1381, 1356, 1327, 1256, 1206, 1168, 1098, 1026, 863, 831, 778.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 13.46 (s, 1H), 7.50 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 6.92 (s, 1H), 6.88 (s, 1H), 6.82 (s, 1H), 6.77 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.74 (s, 3H), 1.92 (s, 3H).

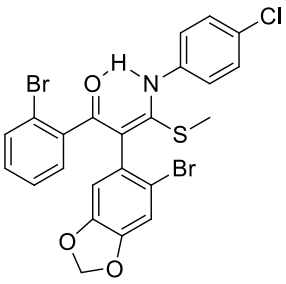
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 190.1, 165.9, 149.1, 148.9, 148.0, 147.5, 139.9, 135.4, 131.2, 129.5, 125.7, 123.9, 118.7, 116.0, 115.0, 114.6, 114.3, 110.1, 109.5, 56.10, 56.07, 56.065, 55.98, 17.1.

HR-MS (ESI): Calcd. for $C_{26}H_{25}Br_2NO_5S$ [M+H]: 621.9916, Found: 621.9893.

[M+H]: 623.9874, Found: 623.9900.

[M+H]: 625.9853, Found: 625.9877.

**2-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)-1-(2-bromophenyl)-3-((4-chlorophenyl)amino)-3-(methylthio)prop-2-en-1-one (80g)**




Reaction time: 6 h

Yield: 59%, as a yellow colour solid.

Melting point: 155 – 157 ºC

$R_f$: 0.28 in 5% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3448, 3090, 3054, 2918, 2887, 1557, 1551, 1481, 1419, 1368, 1314, 1233, 1198, 1130, 1080, 1036, 935, 859, 819, 751, 732.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 13.37 (s, 1H), 7.44 – 7.41 (m, 3H), 7.37 – 7.34 (m, 2H), 7.22 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.09 (td, *J* = 7.6, 1.2 Hz, 1H), 7.03 (td, *J* = 7.6, 1.2 Hz, 1H), 6.92 (s, 1H), 6.88 (s, 1H), 5.89 (d, *J* = 7.6 Hz, 2H), 1.94 (s, 3H).

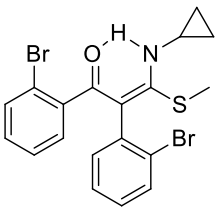
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 190.6, 165.5, 148.0, 147.1, 142.6, 138.5, 132.5, 131.6, 131.1, 129.6 (2C), 126.8, 126.7, 125.1, 119.4, 119.1, 115.1, 112.8, 112.2, 101.9, 17.1.

HR-MS (ESI): Calcd. for $C_{23}H_{16}Br_2ClNO_3S$ [M+H]: 579.8979, Found: 579.8955.

[M+H]: 581.8958, Found: 581.8941.

[M+H]: 583.8938, Found: 583.8919.

**1,2-Bis(2-bromophenyl)-3-(cyclopropylamino)-3-(methylthio)prop-2-en-1-one (80h)**



Reaction time: 4 h

Yield: 70%, as a brown colour solid.

Melting point: 146 – 148 ºC

$R_f$: 0.28 in 5% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3431, 3063, 3046, 2993, 2925, 2848, 1542, 1559, 1423, 1390, 1280, 1251, 1155, 1050, 1024, 930, 805,764, 751, 733.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 12.63 (s, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.29 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 7.02 – 6.90 (m, 4H), 3.14 – 3.09 (m, 1H), 2.32 (s, 3H), 0.99 – 0.95 (m, 4H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 188.8, 169.7, 143.1, 139.6, 134.4, 132.3, 132.1, 129.1, 129.0, 128.6, 127.0, 126.9, 126.4, 119.4, 111.4, 28.6, 17.5, 9.2, 8.6.

HR-MS (ESI): Calcd. for $C_{19}H_{17}Br_2NOS$ [M+H]: 465.9470, Found: 465.9486.

[M+H]: 467.9450, Found: 467.9490.

[M+H]: 469.9430, Found: 469.9450.

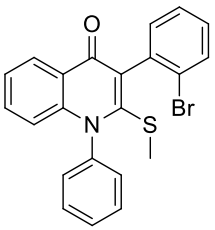
### 5.6.4 Procedure for the Optimization of Metal-free Regioselective Intramolecular Amination

An oven-dried 8 mL reaction vial was charged with respective *α*-(bromoaroyl)ketene *N,S*-acetal (0.5 mmol) and base (0.75 mmol) in solvent (2.0 mL) was stirred at 90 ºC for 6 h. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was then cooled to room temperature and was purified by flash chromatography.

### 5.6.5 General Procedure for the Synthesis of 4-Quinolones

An oven-dried 8 mL reaction vial was charged with respective *α*-(bromoaroyl)ketene *N,S*-acetal (0.5 mmol) and KO$^t$Bu (0.75 mmol) in dioxane (2.0 mL) was stirred at 90 $^o$C for 6-9 h. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was then cooled to room temperature and was purified by flash chromatography.

**3-(2-Bromophenyl)-2-(methylthio)-1-phenylquinolin-4(1*H*)-one (81a)**




Reaction time: 6 h

Yield: 99%, as a white colour solid.

Melting point: 192 – 194 $^o$C

$R_f$: 0.35 in ethyl acetate/hexane (1:2)

IR (KBr): ν ($cm^{-1}$) = 3059, 2953, 2924, 2848, 1620, 1597, 1528, 1473, 1376, 1313, 1245, 1082, 1022, 967, 882, 758, 702.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.50 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.63 – 7.58 (m, 3H), 7.48 – 7.44 (m, 1H), 7.40 – 7.34 (m, 5H), 7.25 – 7.21 (m, 1H), 6.76 (d, *J* = 8.6 Hz, 1H), 1.91 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 175.3, 150.5, 143.1, 140.2, 137.7, 132.75, 132.66, 132.1, 130.1, 130.0, 129.9, 129.7, 129.6, 129.1, 128.6, 127.4, 127.0, 126.1, 125.6, 124.0, 118.4, 18.9.

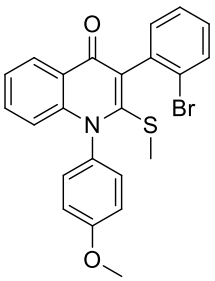
HR-MS (ESI): Calcd. for $C_{22}H_{16}BrNOS$ [M+H]: 422.0209, Found: 422.0207.

[M+H]: 424.0189, Found: 424.0275.

**3-(2-Bromophenyl)-1-(4-methoxyphenyl)-2-(methylthio)quinolin-4-(1*H*)-one (81b)**

Reaction time: 6 h

Yield: 70%, as a pale yellow colour solid.



Melting point: 200 – 202 ºC

$R_f$: 0.42 in ethyl acetate/hexane (1:1)

IR (KBr): ν ($cm^{-1}$) = 3059, 2993, 2958, 2927, 2830, 1618, 1594, 1529, 1509, 1467, 1375, 1313, 1296, 1242, 1082, 1028, 886, 844, 772, 749.

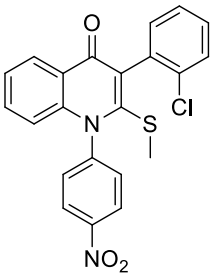
$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.47 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.47 – 7.43 (m, 1H), 7.39 – 7.37 (m, 2H), 7.36 – 7.27 (m, 3H), 7.25 – 7.21 (m, 1H), 7.12 – 7.08 (m, 2H), 6.81 (d, *J* = 8.8 Hz, 1H), 3.93 (s, 3H), 1.91 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 175.2, 160.2, 151.3, 143.5, 137.9, 132.81, 132.77, 132.7, 132.1, 130.9, 130.5, 129.1, 128.4, 127.4, 127.0, 126.1, 125.6, 123.9, 118.4, 115.2, 115.0, 55.7, 18.9.

HR-MS (ESI): Calcd. for $C_{23}H_{18}BrNO_2S$ [M+H]: 452.0314, Found: 452.0327.

[M+H]: 454.0295, Found: 454.0310.

**3-(2-Chlorophenyl)-2-(methylthio)-1-(4-nitrophenyl)quinolin-4(1*H*)-one (81c)**



Reaction time: 9 h

Yield: 71%, as a pale yellow colour solid.

Melting point: 224 – 226 ºC

$R_f$: 0.44 in ethyl acetate/hexane (1:1)

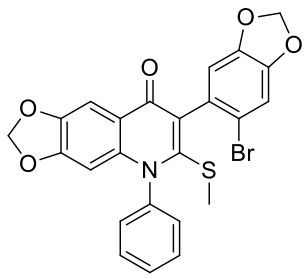
IR (KBr): ν ($cm^{-1}$) = 3107, 3075, 2926, 2857, 1617, 1587, 1524, 1492, 1470, 1375, 1348, 1314, 1244, 1087, 1030, 890, 855, 757, 701.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.51 – 8.48 (m, 3H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.52 – 7.46 (m, 2H), 7.40 – 7.31 (m, 4H), 6.65 (d, *J* = 8.4 Hz, 1H), 1.91 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 175.3, 149.4, 148.3, 145.7, 142.5, 135.2, 135.0, 132.63, 132.60, 131.2, 129.6, 129.3, 127.8, 127.4, 126.9, 125.5 (2C), 124.5, 117.7, 19.0.

HR-MS (ESI): Calcd. for $C_{22}H_{15}ClN_2O_3S$ [M+H]: 423.0565, Found: 423.0557.

**7-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)-6-(methylthio)-5-phenyl-[1,3]dioxolo[4,5-*g*]quinolin-8(5*H*)-one (81d)**



Reaction time: 8 h

Yield: 85%, as a white colour solid.

Melting point: 236 – 238 ºC

$R_f$: 0.36 in ethyl acetate/hexane (2:1)

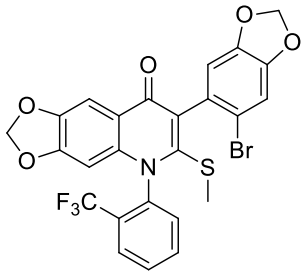
$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.83 (s, 1H), 7.61 – 7.59 (m, 3H), 7.36 – 7.33 (m, 2H), 7.13 (s, 1H), 6.83 (s, 1H), 6.13 (s, 1H), 6.02 – 5.99 (m, 4H), 1.96 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 174.1, 152.0, 148.9, 148.0, 147.4, 145.8, 140.6, 140.5, 130.8, 130.2, 130.1, 129.8, 129.6, 129.4, 128.2, 121.6, 116.7, 112.8, 112.2, 103.9, 102.2, 101.9, 97.9, 19.1.

HR-MS (ESI): Calcd. for $C_{24}H_{16}BrNO_5S$ [M+H]: 510.0005, Found: 510.0027.

[M+H]: 511.9986, Found: 512.0011.

**7-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)-6-(methylthio)-5-(2-(trifluoromethyl)phenyl)-[1,3]dioxolo[4,5-*g*]quinolin-8(5*H*)-one (81e)**



Reaction time: 8 h

Yield: 43%, as a pale yellow colour solid.

Melting point: 229 – 231 ºC

$R_f$: 0.43 in ethyl acetate/hexane (2:1)

IR (KBr): ν ($cm^{-1}$) = 3072, 3002, 2924, 2852, 1623, 1606, 1584, 1546, 1501, 1467, 1420, 1320, 1267, 1237, 1182, 1126, 1033, 931, 831, 803, 770.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 7.6 Hz, 1H), 7.84 – 7.82 (m, 1H), 7.79 (s, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.12 (s, 1H), 6.82 (s, 1H), 6.02 – 5.99 (m, 4H), 5.93 (s, 1H), 1.98 (s, 3H).

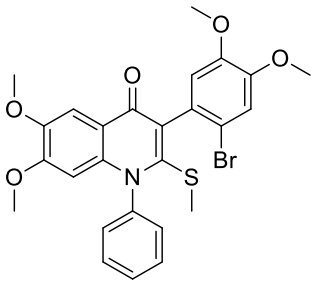
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 174.3, 152.1, 149.3, 148.1, 147.5, 145.8, 140.3, 138.3 (d, J = 2 Hz), 133.8, 131.5, 130.5, 130.3, 129.1 (q, *J* = 31 Hz), 128.7, 128.4 (q, *J* = 5 Hz), 122.8 (q, *J*

= 271 Hz), 121.4, 116.3, 113.0, 112.7, 104.0, 102.2, 102.0, 97.6, 18.5.

HR-MS (ESI): Calcd. for $C_{25}H_{15}BrF_3NO_5S$ [M+H]: 577.9879, Found: 577.9802.

[M+H]: 579.9860, Found: 579.9784.

**3-(2-Bromo-4,5-dimethoxyphenyl)-6,7-dimethoxy-2-(methylthio)-1-phenylquinolin-4(1*H*)-one (81f)**



Reaction time: 9 h

Yield: 71%, as a pale yellow colour solid.

Melting point: 201 – 203 ºC

$R_f$: 0.42 in 4% methanol in dichloromethane

IR (KBr): ν ($cm^{-1}$) = 3063, 3002, 2928, 2838, 1588, 1508, 1475, 1436, 1381, 1310, 1274, 1254, 1230, 1211, 1165, 1128, 1091, 1024, 1001, 879, 824, 787, 727.

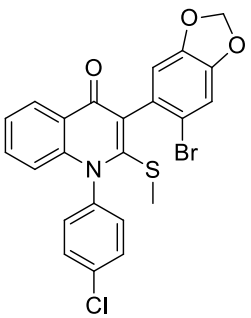
$^1$H NMR (400 MHz, $CDCl_3$) δ = 7.85 (s, 1H), 7.59 – 7.56 (m, 3H), 7.39 – 7.38 (m, 2H), 7.13 (s, 1H), 6.87 (s, 1H), 6.07 (s, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 3.83 (s, 3H), 3.59 (s, 3H), 1.92 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 174.1, 153.3, 149.0, 148.9, 148.4, 147.3, 140.5, 138.9, 130.1, 129.92, 129.86, 129.7, 129.6, 129.4, 127.9, 119.9, 116.3, 115.3, 115.2, 106.0, 99.9, 56.3, 56.1 (2C), 55.8, 18.9.

HR-MS (ESI): Calcd. for $C_{26}H_{24}BrNO_5S$ [M+H]: 542.0631, Found: 542.0666.

[M+H]: 544.0612, Found: 544.0642.

**3-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)-1-(4-chlorophenyl)-2-(methylthio)quinolin-4(1*H*)-one (81g)**



Reaction time: 8 h

Yield: 77%, as a white colour solid.

Melting point: 148 – 150 ºC

$R_f$: 0.32 in ethyl acetate/hexane (1:2)

IR (KBr): ν ($cm^{-1}$) = 3081, 2958, 2926, 2870, 1615, 1597, 1534, 1473, 1396, 1366, 1330, 1295, 1230, 1127, 1089, 1032, 930, 866, 830, 767.

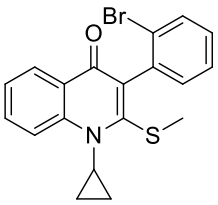
$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.46 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.48 – 7.44 (m, 1H), 7.37 – 7.33 (m, 3H), 7.13 (s, 1H), 6.83 (s, 1H), 6.74 (d, *J* = 8.6 Hz, 1H), 6.01 (dd, *J* = 13.2 Hz, 1.2 Hz, 2H), 1.98 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 175.4, 150.5, 148.1, 147.5, 143.0, 138.6, 135.7, 132.4, 131.3, 131.0, 130.4, 128.8, 127.2, 125.5, 124.2, 118.1, 116.8, 112.8, 112.1, 102.0, 19.0.

HR-MS (ESI): Calcd. for $C_{23}H_{15}BrClNO_3S$ [M+H]: 499.9717, Found: 499.9715.

[M+H]: 501.9697, Found: 501.9701.

**3-(2-Bromophenyl)-1-cyclopropyl-2-(methylthio)quinolin-4(1*H*)-one (81h)**




Reaction time: 7 h

Yield: 46%, as a brown colour solid.

Melting point: 194 – 196 $^o$C

$R_f$: 0.38 in ethyl acetate/hexane (1:1)

IR (KBr): ν ($cm^{-1}$) = 3049, 3006, 2923, 2848, 1613, 1597, 1522, 1471, 1420, 1383, 1352, 1309, 1250, 1166, 1088, 1040, 845, 761.

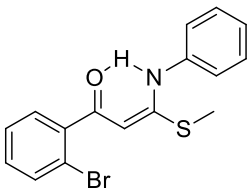
$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.38 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.68 – 7.64 (m, 2H), 7.39 – 7.29 (m, 3H), 7.22 (td, *J* = 7.6, 1.2 Hz, 1H), 3.45 – 3.39 (m, 1H), 2.20 (s, 3H), 1.50 – 1.41 (m, 2H), 1.13 – 0.99 (m, 2H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 175.1, 154.4, 143.4, 137.9, 133.0, 132.6, 131.6, 129.0, 128.1, 127.4, 126.9, 126.2, 126.0, 123.5, 117.7, 32.2, 18.8, 13.74, 13.66.

HR-MS (ESI): Calcd. for $C_{19}H_{16}BrNOS$ [M+H]: 386.0209, Found: 386.0244.

[M+H]: 388.0189, Found: 388.0221.

**1-(2-Bromophenyl)-3-(methylthio)-3-(phenylamino)prop-2-en-1-one (83a)**



Reaction time: 6.5 h

Yield: 74%, as a yellow colour solid.

Melting point: 118 – 120 ºC

$R_f$: 0.30 in 10% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3437, 3054, 3005, 2923, 1594, 1565, 1476, 1429, 1301, 1246, 1157, 1023, 835, 748.

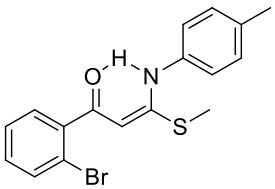
$^1$H NMR (400 MHz, $CDCl_3$) δ = 13.16 (s, 1H), 7.61 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.51 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.41 – 7.33 (m, 5H), 7.29 – 7.21 (m, 2H), 5.53 (s, 1H), 2.38 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 187.8, 168.1, 143.3, 138.0, 133.5, 130.4, 129.3, 129.2, 127.4, 126.8, 125.6, 119.6, 92.5, 14.9.

HR-MS (ESI): Calcd. for $C_{16}H_{14}BrNOS$ [M+H]: 348.0052, Found: 348.0080.

[M+H]: 350.0032, Found: 350.0059.

**1-(2-Bromophenyl)-3-(methylthio)-3-(*p*-tolylamino)prop-2-en-1-one (83b)**



Reaction time: 4 h

Yield: 72%, as a yellow colour solid.

Melting point: 88 – 90 ºC

$R_f$: 0.35 in 10% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3449, 3032, 2998, 2905, 2848, 1591, 1551, 1476, 1456, 1432, 1289, 1222, 1152, 1095, 1023, 986, 817, 773, 752.

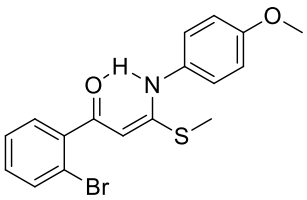
$^1$H NMR (400 MHz, $CDCl_3$) δ = 13.10 (s, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.21 – 7.15 (m, 5H), 5.49 (s, 1H), 2.34 (s, 3H), 2.31 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 187.3, 168.2, 143.1, 136.5, 135.0, 133.2, 130.1, 129.5, 129.1, 127.1, 125.2, 119.3, 91.9, 20.9, 14.5.

HR-MS (ESI): Calcd. for $C_{17}H_{16}BrNOS$ [M+H]: 362.0209, Found: 362.0220.

[M+H]: 364.0189, Found: 364.0205.

**1-(2-Bromophenyl)-3-((4-methoxyphenyl)amino)-3-(methylthio)prop-2-en-1-one (83c)**



Reaction time: 4 h

Yield: 76%, as a brown colour solid.

Melting point: 80 – 82 ºC

$R_f$: 0.33 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3448, 3032, 3003, 2956, 2930, 2837, 1598, 1570, 1512, 1478, 1456, 1296, 1246, 1180, 1091, 1035, 1026, 843, 787, 746, 723.

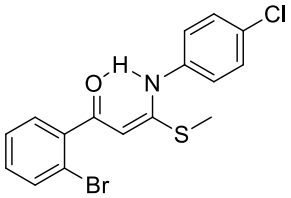
$^1$H NMR (400 MHz, $CDCl_3$) δ = 12.91 (s, 1H), 7.60 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.50 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.35 (td, *J* = 7.6, 0.8 Hz, 1H), 7.27 – 7.26 (m, 1H), 7.24 – 7.20 (m, 2H), 6.93 – 6.89 (m, 2H), 5.47 (s, 1H), 3.83 (s, 3H), 2.35 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 187.7, 169.2, 158.7, 143.5, 133.5, 130.7, 130.3, 129.3, 127.6, 127.4, 119.6, 114.4, 91.9, 55.6, 14.8.

HR-MS (ESI): Calcd. for $C_{17}H_{16}BrNO_2S$ [M+H]: 378.0158, Found: 378.0177.

[M+H]: 380.0138, Found: 380.0160.

**1-(2-Bromophenyl)-3-((4-chlorophenyl)amino)-3-(methylthio)prop-2-en-1-one (83d)**



Reaction time: 4.5 h

Yield: 74%, as a yellow colour solid.

Melting point: 130 – 132 ºC

$R_f$: 0.35 in 10% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3432, 3050, 2996, 2923, 1573, 1556, 1491, 1474, 1455, 1434, 1296, 1253, 1218, 1156, 1105, 1090, 1023, 1012, 984, 933, 845, 745.

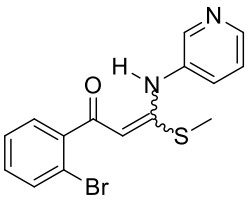
$^1$H NMR (400 MHz, $CDCl_3$) δ = 13.13 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.49 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.37 – 7.34 (m, 3H), 7.28 (d, *J* = 8.8 Hz, 2H), 7.26 – 7.22 (m, 1H), 5.54 (s, 1H), 2.39 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 188.1, 167.9, 143.1, 136.6, 133.6, 132.4, 130.5, 129.38, 129.36, 127.4, 126.8, 119.6, 93.0, 14.9.

HR-MS (ESI): Calcd. for $C_{16}H_{13}BrClNOS$ [M+H]: 381.9663, Found: 381.9614.

[M+H]: 383.9641, Found: 383.9592.

**1-(2-Bromophenyl)-3-(methylthio)-3-(pyridin-3-ylamino)prop-2-en-1-one (83e)**




Reaction time: 5 h

Yield: 72%, as a yellow colour solid.

$R_f$: 0.33 in 50% ethyl acetate in hexane

Melting point: 98 – 100 ºC

IR (KBr): ν ($cm^{-1}$) = 3420, 2921, 1580, 1555, 1482, 1451, 1422, 1293, 1253, 1158, 1020, 746.

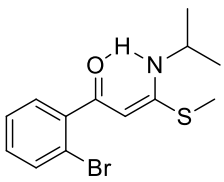
$^1$H NMR (400 MHz, $CDCl_3$) [obtained as a (7.7:1) inseparable mixture of E/Z isomers] δ = 13.17 (s, 1H) [4.66 (s, 1H)], 8.66 (d, *J* = 2.4 Hz, 1H) [8.38 – 8.37 (m, 1H)], 8.51 – 8.50 (m, 1H) [8.34 – 8.32 (m, 1H)], 7.72 – 7.70 (m, 1H) [7.76 – 7.74 (m, 1H)], 7.61 (d, *J* = 7.6 Hz, 1H), 7.49 (dd, *J* = 7.4, 1.6 Hz, 1H) [7.56 – 7.54 (m, 2H)], 7.36 – 7.32 (m, 2H) [7.38 (br s, 2H)], 7.24 – 7.21 (m, 1H) [7.264 (br s, 1H)], 5.60 (s, 1H) [6.82 (s, 1H)], 2.41 (s, 3H) [2.38 (s, 3H)].

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 188.4 [199.6], 167.8 [170.0], 147.4 [145.1], 146.6 [144.5], 142.8 [140.5], 134.9 [134.2], 133.5 [132.1], 132.7 [131.8], 130.6 [131.5], 129.3 [130.0], 127.4 [127.5], 123.6 [123.83], 119.4 [123.79], 93.6 [118.6], 14.8 [16.6].

HR-MS (ESI): Calcd. for $C_{15}H_{13}BrN_2OS$ [M+H]: 349.0005, Found: 349.0000.

[M+H]: 350.9984, Found: 350.9985.

**1-(2-Bromophenyl)-3-(isopropylamino)-3-(methylthio)prop-2-en-1-one (83f)**



Reaction time: 4 h

Yield: 75%, as a pale yellow colour solid.

$R_f$: 0.36 in 20% ethyl acetate in hexane

Melting point: 104 – 106°C

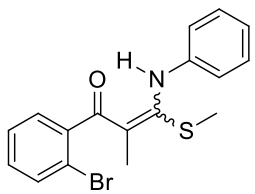
$^1$H NMR (400 MHz, $CDCl_3$) δ = 11.65 (s, 1H), 7.57 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.49 – 7.47 (m, 1H), 7.31 (td, *J* = 7.4, 0.8 Hz, 1H), 7.19 (td, *J* = 7.4, 1.6 Hz, 1H), 3.98 – 3.89 (m, 1H), 2.41 (s, 3H), 1.35 (d, *J* = 6.4 Hz, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 186.5, 168.4, 143.7, 133.3, 129.9, 129.3, 127.2, 119.5, 89.7, 46.4, 23.2, 14.4.

HR-MS (ESI): Calcd. for $C_{13}H_{16}BrNOS$ [M+H]: 314.0209, Found: 314.0234.

[M+H]: 316.0188, Found: 316.0214.

**1-(2-Bromophenyl)-2-methyl-3-(methylthio)-3-(phenylamino)prop-2-en-1-one (83i)**



Reaction time: 4 h

Yield: 60%, as a yellow colour viscous liquid.

$R_f$: 0.38 in 5% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3463, 3054, 2983, 2926, 1709, 1555, 1428, 1385, 1314, 1265, 1243, 1164, 1051, 1025, 993, 961, 902, 857, 761, 744.

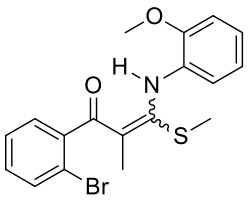
$^1$H NMR (400 MHz, $CDCl_3$) [obtained as a (2:1) inseparable mixture of E/Z isomers] δ = 12.95 (s, 1H) [4.69 (s, 1H)], 7.57 (d, *J* = 8.0 Hz, 1H) [7.519 – 7.511 (m, 1H)], 7.37 – 7.34 (m, 4H) [7.39 – 7.38 (m, 1H), 7.323 – 7.321 (m, 1H), 7. 31 – 7.29 (m, 2H)], 7.23 – 7.21 (m, 2H) [7.20 (br s, 1H), 7.18 – 7.16 (m, 1H)], 7.15 – 7.13 (m, 1H) [7.06 (t, *J* = 7.3 Hz, 1H)], 6.36 (m, 1H) [6.63 (br s, 1H)], 2.05 (s, 3H) [2.38 (s, 3H)], 1.90 (s, 3H) [1.48 (s, 3H)].

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 192.4 [200.3], 162.7 [167.6], 143.5 [150.0], 133.5 [128.7], 132.8 [140.7], 129.3 (2C) [129.7 (2C)], 127.60 [131.6], 127.56 [129.2], 124.9 [127.3], 123.3 [118.9], 119.7 [123.7], 106.9 [119.1], 16.8 [14.9], 16.5 [13.1].

HR-MS (ESI): Calcd. for $C_{17}H_{16}BrNOS$ [M+H]: 362.0209, Found: 362.0235.

[M+H]: 364.0189, Found: 364.0213.

**1-(2-Bromophenyl)-3-((2-methoxyphenyl)amino)-2-methyl-3-(methylthio)prop-2-en-1-one (83j)**




Reaction time: 4.5 h

Yield: 60%, as a yellow colour solid.

Melting point: 88 – 90 ºC

$R_f$: 0.40 in 20% ethyl acetate in hexane

IR (KBr): ν ($cm^{-1}$) = 3447, 3002, 2962, 2933, 1592, 1582, 1553, 1495, 1458, 1383, 1312, 1254, 1177, 1112, 1026, 989, 862, 751.

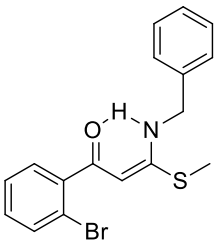
$^1$H NMR (400 MHz, $CDCl_3$) [obtained as a (2.7:1) inseparable mixture of E/Z isomers] δ = 12.34 (s, 1H) [4.54 (br s, 1H)], 7.59 (d, *J* = 7.6 Hz, 1H) [7.48 – 7.46 (m, 1H)], 7.54 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H) [7.29 – 7.28 (m, 2H)], 7.24 – 7.21 (m, 1H) [7.16 – 7.15 (m, 1H)], 7.19 – 7.17 (m, 1H) [7.03 (t, *J* = 7.8 Hz, 1H)], 7.11 – 7.07 (m, 1H) [6.85 (d, *J* = 8.1, 1H)], 6.94 – 6.88 (m, 2H) [6.79 – 6.77 (m, 1H), 6.13 (br s, 1H)], 3.89 (s, 3H) [3.67 (s, 3H)], 2.09 (s, 3H) [2.41 (s, 3H)], 1.93 (s, 3H) [1.47 (s, 3H)].

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 192.3 [200.7], 151.6 [161.4], 143.8 [148.7], 133.3 [140.9], 132.7 [128.9], 131.4 [138.6], 129.8, 129.6 [127.2 (2C)], 127.7 [124.7], 127.5 [122.4], 125.1 [121.4], 122.4 [121.6], 120.7 [121.1], 118.9 [111.5], 111.0 [108.0], 55.9 [55.5], 16.57 [14.3], 16.47 [13.2].

HR-MS (ESI): Calcd. for $C_{18}H_{18}BrNO_2S$ [M+H]: 392.0314, Found: 392.0319.

[M+H]: 394.0294, Found: 394.0298.

**3-(Benzylamino)-1-(2-bromophenyl)-3-(methylthio)prop-2-en-1-one (83h)**



Reaction time: 5 h

Yield: 20%, as a white colour solid.

$R_f$: 0.38 in 20% ethyl acetate in hexane

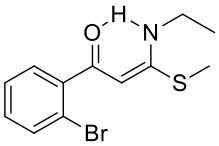
$^1$H NMR (400 MHz, $CDCl_3$) δ = 11.93 (s, 1H), 7.58 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.37 – 7.35 (m, 4H), 7.34 – 7.29 (m, 2H), 7.20 (td, *J* = 7.8, 1.8 Hz, 1H), 4.62 (d, *J* = 5.8 Hz, 2H), 2.40 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 187.0, 169.8, 143.4, 136.8, 133.2, 130.0, 129.1, 128.8, 127.7, 127.3, 127.2, 119.5, 90.7, 47.9, 14.3.

HR-MS (ESI): Calcd. for $C_{17}H_{16}BrNOS$ [M+H]: 362.0209, Found: 362.0212.

[M+H]: 364.0189, Found: 364.0194.

**1-(2-Bromophenyl)-3-(ethylamino)-3-(methylthio)prop-2-en-1-one (83g)**



Reaction time: 4 h

Yield: 64%, as a brown colour solid.

$R_f$: 0.35 in 20% ethyl acetate in hexane

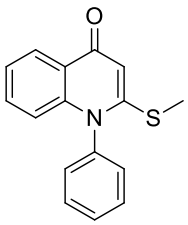
$^1$H NMR (400 MHz, $CDCl_3$) δ = 11.60 (s, 1H), 7.56 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.46 – 7.44 (m, 1H), 7.31 (td, *J* = 7.2, 1.2 Hz, 1H), 7.19 (td, *J* = 7.6, 1.6 Hz, 1H), 3.47 – 3.40 (m, 2H), 2.41 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 186.6, 169.7, 143.6, 133.2, 129.9, 129.1, 127.2, 119.5, 89.8, 38.9, 14.7, 14.2.

HR-MS (ESI): Calcd. for $C_{12}H_{14}BrNOS$ [M+H]: 300.0052, Found: 300.0029.

[M+H]: 302.0032, Found: 302.0008.

**2-(Methylthio)-1-phenylquinolin-4(1*H*)-one (84a)**



Reaction time: 8 h

Yield: 94%, as a white colour solid.

Melting point: 224 – 226 ºC

$R_f$: 0.29 in ethyl acetate/hexane (3:1)

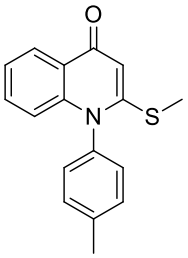
IR (KBr): ν ($cm^{-1}$) = 3041, 2958, 2921, 2848, 1618, 1597, 1521, 1490, 1394, 1306, 1146, 1026, 961, 819, 768, 707.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.42 (d, *J* = 7.2 Hz, 1H), 7.63 – 7.61 (m, 3H), 7.42 – 7.38 (m, 1H), 7.35 – 7.29 (m, 3H), 6.63 (d, *J* = 8.8 Hz, 1H), 6.28 (s, 1H), 2.41 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 176.3, 157.4, 143.2, 138.0, 131.9, 130.5, 130.4, 130.1, 126.4, 125.2, 123.7, 117.0, 105.7, 16.2.

HR-MS (ESI): Calcd. for $C_{16}H_{13}NOS$ [M+H]: 268.0791, Found: 268.0811.

**2-(Methylthio)-1-(*p*-tolyl)quinolin-4(1*H*)-one (84b)**



Reaction time: 6 h

Yield: 79%, as a pale yellow colour solid.

Melting point: 216 – 218 ºC

$R_f$: 0.31 in ethyl acetate/hexane (3:1)

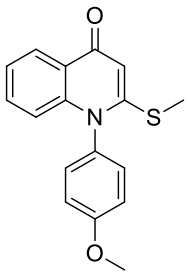
IR (KBr): ν ($cm^{-1}$) = 3034, 2993, 2922, 2857, 1617, 1595, 1571, 1519, 1476, 1460, 1391, 1306, 1213, 1145, 1111, 1026, 965, 858, 823, 769, 756.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.41 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.42 – 7.38 (m, 3H), 7.32 – 7.30 (m, 1H), 7.22 – 7.19 (m, 2H), 6.66 (d, *J* = 8.4 Hz, 1H), 6.25 (s, 1H), 2.50 (s, 3H), 2.40 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 176.1, 157.7, 143.3, 140.9, 135.3, 131.8, 131.0, 129.6, 126.2, 125.1, 123.6, 117.1, 105.5, 21.5, 16.1.

HR-MS (ESI): Calcd. for $C_{17}H_{15}NOS$ [M+H]: 282.0947, Found: 282.0970.

**1-(4-Methoxyphenyl)-2-(methylthio)quinolin-4(1*H*)-one (84c)**



Reaction time: 7 h

Yield: 87%, as a pale yellow colour solid.

Melting point: 196 – 198 ºC

$R_f$: 0.26 in ethyl acetate/hexane (3:1)

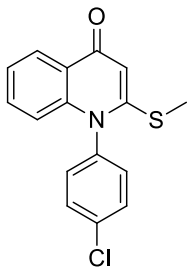
IR (KBr): ν ($cm^{-1}$) = 3048, 3003, 2922, 2830, 1621, 1597, 1570, 1510, 1478, 1462, 1394, 1297, 1252, 1175, 1143, 1030, 834, 806, 769.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.40 (d, *J* = 8.0 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 1H), 6.23 (s, 1H), 3.91 (s, 3H), 2.39 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 176.0, 160.9, 158.3, 143.5, 131.8, 131.0, 130.4, 126.2, 125.1, 123.6, 117.1, 115.4, 105.4, 55.7, 16.1.

HR-MS (ESI): Calcd. for $C_{17}H_{15}NO_2S$ [M+H]: 298.0896, Found: 298.0919.

**1-(4-Chlorophenyl)-2-(methylthio)quinolin-4(1*H*)-one (84d)**



Reaction time: 6 h

Yield: 80%, as a white colour solid.

Melting point: 196 – 198 ºC

$R_f$: 0.47 in 5% methanol in dichloromethane

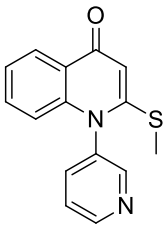
IR (KBr): ν ($cm^{-1}$) = 3083, 3043, 3026, 2971, 2927, 2857, 1616, 1598, 1572, 1521, 1491, 1475, 1462, 1390, 1302, 1143, 1084, 1019, 960, 856, 823, 768, 756.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.39 (d, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.43 – 7.39 (m, 1H), 7.33 – 7.28 (m, 3H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.23 (s, 1H), 2.41 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 176.1, 157.0, 143.0, 136.7, 136.4, 132.0, 131.5, 130.7, 126.5, 125.2, 123.8, 116.7, 105.9, 16.1.

HR-MS (ESI): Calcd. for $C_{16}H_{12}ClNOS$ [M+H]: 302.0401, Found: 302.0425.

**2-(Methylthio)-1-(pyridin-3-yl)quinolin-4(1H)-one (84e)**



Reaction time: 6 h

Yield: 63%, as a pale yellow colour solid.

Melting point: 270 – 272 ºC

$R_f$: 0.42 in 5% methanol in dichloromethane

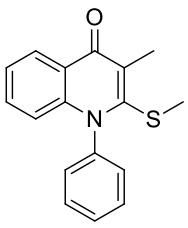
IR (KBr): ν ($cm^{-1}$) = 3038, 2918, 2852, 1618, 1599, 1525, 1474, 1424, 1395, 1311, 1189, 1146, 1027, 956, 820, 771, 752, 724.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.86 (d, *J* = 4.0 Hz, 1H), 8.62 (s, 1H), 8.40 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.60 – 7.57 (m, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 6.27 (s, 1H), 2.42 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 176.0, 157.2, 151.5, 151.1, 143.1, 137.9, 134.8, 132.2, 126.6, 125.2, 124.7, 124.1, 116.4, 106.1, 16.2.

HR-MS (ESI): Calcd. for $C_{15}H_{12}N_2OS$ [M+H]: 269.0743, Found: 269.0761.

**3-Methyl-2-(methylthio)-1-phenylquinolin-4(1*H*)-one (84i)**



Reaction time: 6 h

Yield: 61%, as a white colour solid.

Melting point: 233 – 235 ºC

$R_f$: 0.35 in ethyl acetate/hexane (1:2)

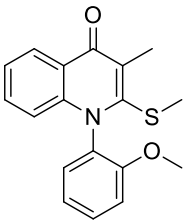
IR (KBr): ν ($cm^{-1}$) = 3043, 2921, 2843, 1612, 1592, 1570, 1528, 1488, 1386, 1367, 1349, 1302, 1246, 1194, 1146, 1040, 770, 757, 705.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.44 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.62 – 7.56 (m, 3H), 7.39 – 7.36 (m, 1H), 7.30 – 7.26 (m, 3H), 6.66 (d, *J* = 8.4 Hz, 1H), 2.50 (s, 3H), 2.21 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 177.5, 148.3, 142.8, 141.2, 131.7, 130.0, 129.5, 129.4, 126.5, 125.3, 124.1, 123.5, 118.4, 19.3, 14.7.

HR-MS (ESI): Calcd. for $C_{17}H_{15}NOS$ [M+H]: 282.0947, Found: 282.0977.

**1-(2-Methoxyphenyl)-3-methyl-2-(methylthio)quinolin-4(1*H*)-one (84j)**



Reaction time: 6 h

Yield: 39%, as a white colour solid.

Melting point: 166 – 168 °C

$R_f$: 0.30 in ethyl acetate/hexane (1:2)

IR (KBr): ν ($cm^{-1}$) = 3024, 2984, 2921, 2830, 1616, 1594, 1529, 1503, 1467, 1385, 1366, 1306, 1283, 1255, 1193, 1119, 1013, 805, 765.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.44 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 6.8 Hz, 1H), 7.15 – 7.10 (m, 2H), 6.69 (d, *J* = 8.4 Hz, 1H), 3.72 (s, 3H), 2.50 (s, 3H), 2.21 (s, 3H).

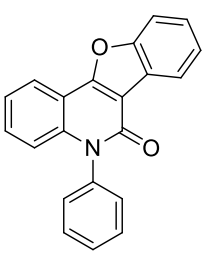
$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 177.7, 156.1, 149.0, 142.5, 131.7, 130.9, 130.3, 129.7, 126.5, 125.1, 124.4, 123.3, 121.2, 117.8, 112.2, 55.8, 18.7, 14.7.

HR-MS (ESI): Calcd. for $C_{18}H_{17}NO_2S$ [M+H]: 312.1053, Found: 312.1072.

### 5.6.6 General Procedure for the Synthesis of Benzofuro[3,2-*c*]quinolin-6-one Derivatives

An oven-dried 8 mL reaction vial was charged with CuI (10 mol%), 1,10-phenanthroline (12 mol%), benzyl amine (0.75 mmol), and KO$^t$Bu (2.0 mmol), respective 4-quinolone (0.5 mmol) in DMF (2.0 mL) was stirred at 120 °C for 18-24 h. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was then cooled to room temperature and was purified by flash chromatography.

**5-Phenylbenzofuro[3,2-*c*]quinolin-6(5*H*)-one (89a)**



Reaction time: 18 h

Yield: 45%, as a white colour solid.

$R_f$: 0.32 in 20% ethyl acetate in hexane

Melting point: 240 – 242 ºC

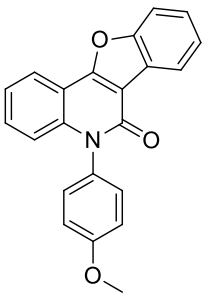
IR (KBr): ν ($cm^{-1}$) = 3055, 2923, 2852, 1661, 1633, 1450, 1323, 1284, 1199, 1137, 1088, 912, 833, 762, 742, 703.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.26 – 8.24 (m, 1H), 8.21 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.50 – 7.32 (m, 6H), 6.82 (d, *J* = 8.4 Hz, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 159.9, 158.0, 155.7, 140.7, 137.8, 130.4, 130.3, 129.4, 129.2, 126.4, 124.71, 124.67, 122.7, 122.4, 122.0, 117.1, 112.7, 111.5, 110.6.

HR-MS (ESI): Calcd. for $C_{21}H_{13}NO_2$ [M+H]: 312.1019, Found: 312.1025.

**5-(4-Methoxyphenyl)benzofuro[3,2-*c*]quinolin-6(5*H*)-one (89b)**



Raction time: 24 h

Yield: 40%, as a white colour solid.

$R_f$: 0.30 in 20% ethyl acetate in hexane

Melting point: 253 – 255 ºC

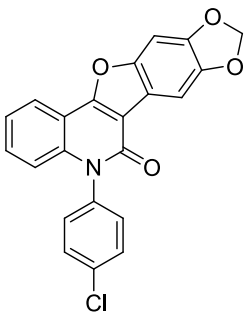
IR (KBr): ν ($cm^{-1}$) = 3050, 2953, 2927, 2835, 1665, 1594, 1515, 1479, 1406, 1285, 1252, 1024, 839, 750, 730.

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.25 (d, *J* = 7.6 Hz, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.49 – 7.40 (m, 3H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 9.2 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 1H), 3.92 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 160.1, 159.9, 158.0, 155.7, 141.0, 130.4 (2C), 130.2, 126.3, 124.73, 124.68, 122.7, 122.5, 122.0, 117.2, 115.6, 112.7, 111.5, 110.7, 55.7.

HR-MS (ESI): Calcd. for $C_{22}H_{15}NO_3$ [M+H]: 342.1125, Found: 342.1157.

**5-(4-Chlorophenyl)-[1,3]dioxolo[4′,5′:5,6]benzofuro[3,2-*c*]quinolin-6(5*H*)-one (89g)**



Reaction time: 24 h

Yield: 43%, as a white colour solid.

$R_f$: 0.37 in 20% ethyl acetate in hexane

Melting point: >340°C

IR (KBr): ν ($cm^{-1}$) = 3107, 3054, 2962, 2917, 1675, 1491, 1461, 1359, 1303, 1285, 1264, 1148, 1091, 1037, 944, 890, 851, 755.

$^1$H NMR (400 MHz, $CDCl_3$ + TFA-d) δ = 8.25 – 8.23 (m, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.54 (s, 1H), 7.52 – 7.46 (m, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.21 (s, 1H), 6.88 – 6.85 (m, 1H), 6.09 (s, 2H).

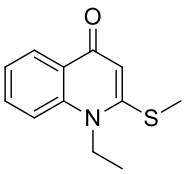
$^{13}$C NMR (100 MHz, $CDCl_3$ + TFA-d) δ = 158.6, 151.5, 148.2, 146.2, 138.9, 136.3, 135.1, 131.0, 130.61, 130.57, 124.4, 121.8, 118.9, 117.6, 117.0, 116.1, 113.3, 102.2, 100.7, 94.1.

HR-MS (ESI): Calcd. for $C_{22}H_{12}ClNO_4$ (M): 389.0449, Found: 389.0482.

### 5.6.7 General Procedure for the Synthesis of Aliphatic Substituted 4-Quinolone Derivatives

An oven-dried 8 mL reaction vial was charged with CuI (10 mol%), 1,10-phenanthroline (12 mol%), corresponding *S,N*-acetals (0.5 mmol), and KO$^t$Bu (0.75 mmol) in DMF (2.0 mL) was stirred at 120 °C for 7-12 h. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was then cooled to room temperature and was purified by flash chromatography.

**1-Ethyl-2-(methylthio)quinolin-4-(1*H*)-one (84g)**



Reaction time: 7 h

Yield: 68%, as a white colour solid.

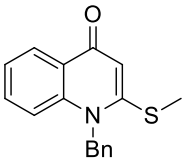
$R_f$: 0.30 in 50% ethyl acetate in hexane

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.42 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 6.19 (s, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 2.54 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 175.6, 155.9, 141.1, 132.3, 127.1, 126.1, 123.5, 114.9, 106.0, 42.7, 16.0, 13.5.

HR-MS (ESI): Calcd. for $C_{12}H_{13}NOS$ [M+H]: 220.0791, Found: 220.0809.

**1-Benzyl-2-(methylthio)quinolin-4-(1*H*)-one (84h)**



Reaction time: 12 h

Yield: 20%, as a white colour solid.

$R_f$: 0.28 in 50% ethyl acetate in hexane

$^1$H NMR (400 MHz, $CDCl_3$) δ = 8.43 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.54 – 7.50 (m, 1H), 7.36 – 7.28 (m, 5H), 7.12 – 7.11 (m, 2H), 6.37 (s, 1H), 5.59 (s, 2H), 2.56 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ = 175.7, 157.2, 142.0, 135.0, 132.5, 129.3, 128.0, 126.9, 125.9, 125.8, 123.9, 115.9, 106.4, 51.4, 16.3.

HR-MS (ESI): Calcd. for $C_{17}H_{15}NOS$ [M+H]: 282.0947, Found: 282.0949.

## 5.7 Copies of Selected $^{1}H$ & $^{13}C$ Spectra

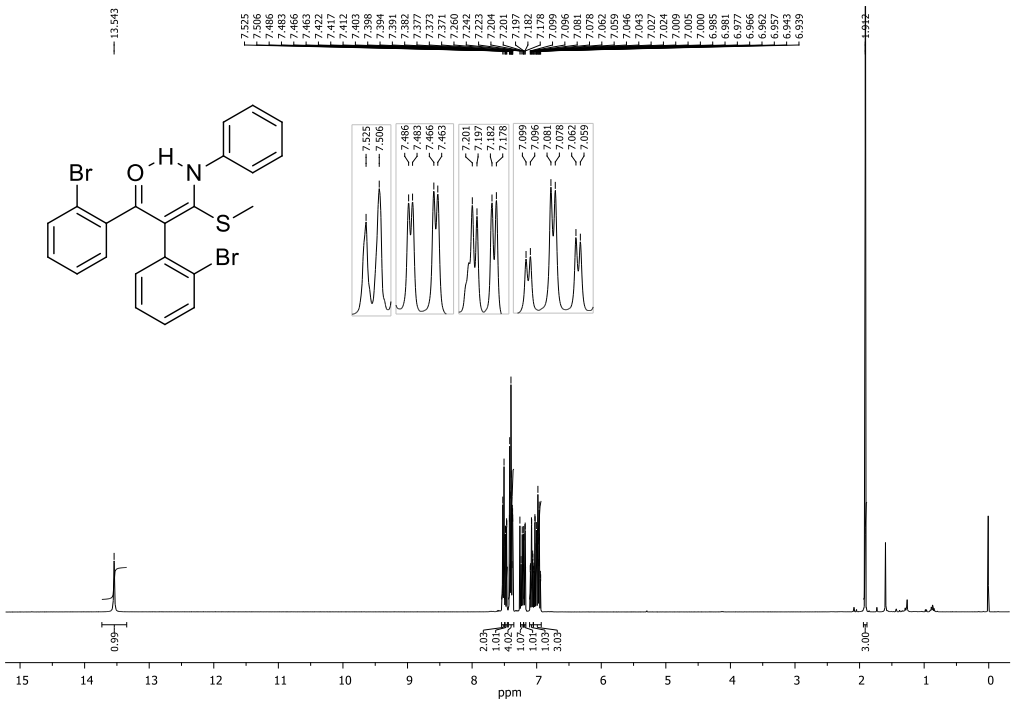



**Figure 5.3a**: $^{1}H$ NMR Spectrum of **80a**

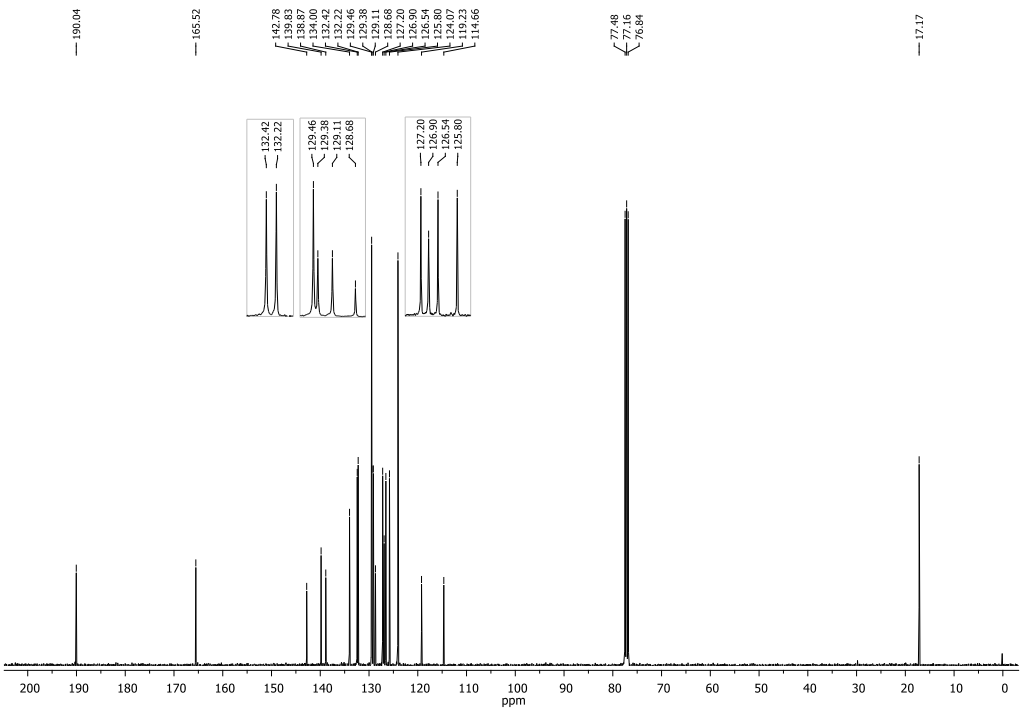



**Figure 5.3a**: $^{13}C$ NMR Spectrum of **80a**

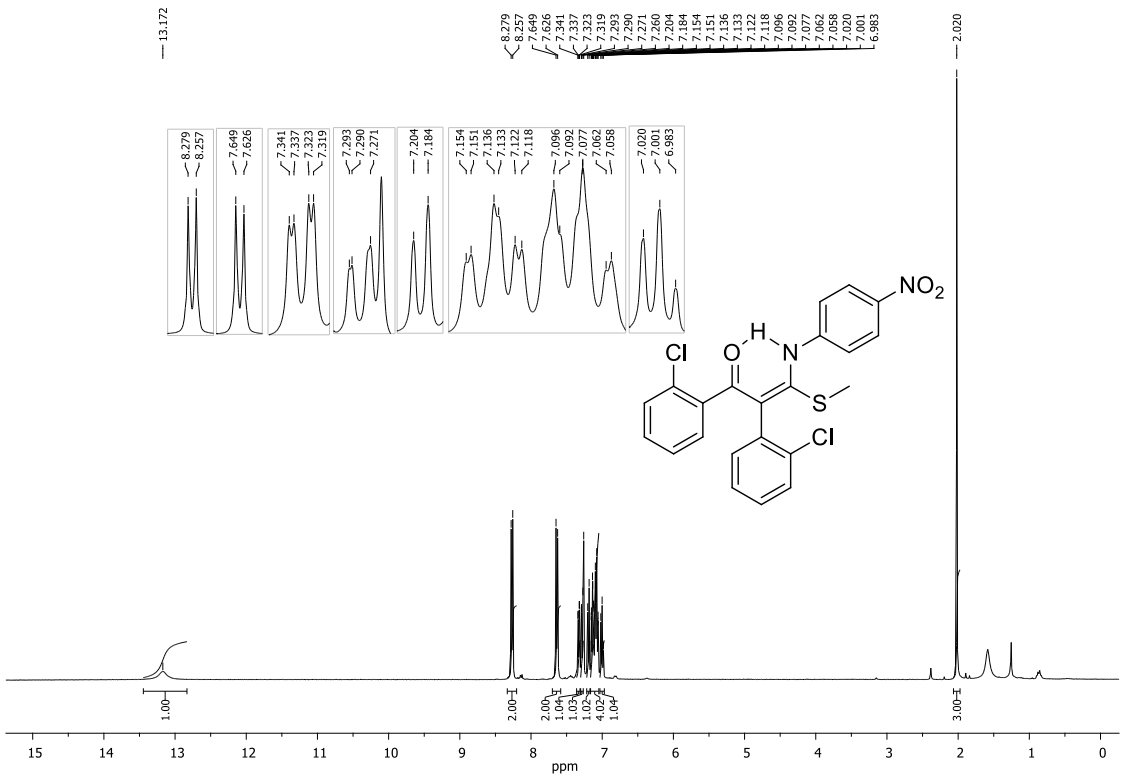



**Figure 5.4a**: $^{1}$H NMR Spectrum of **80c**

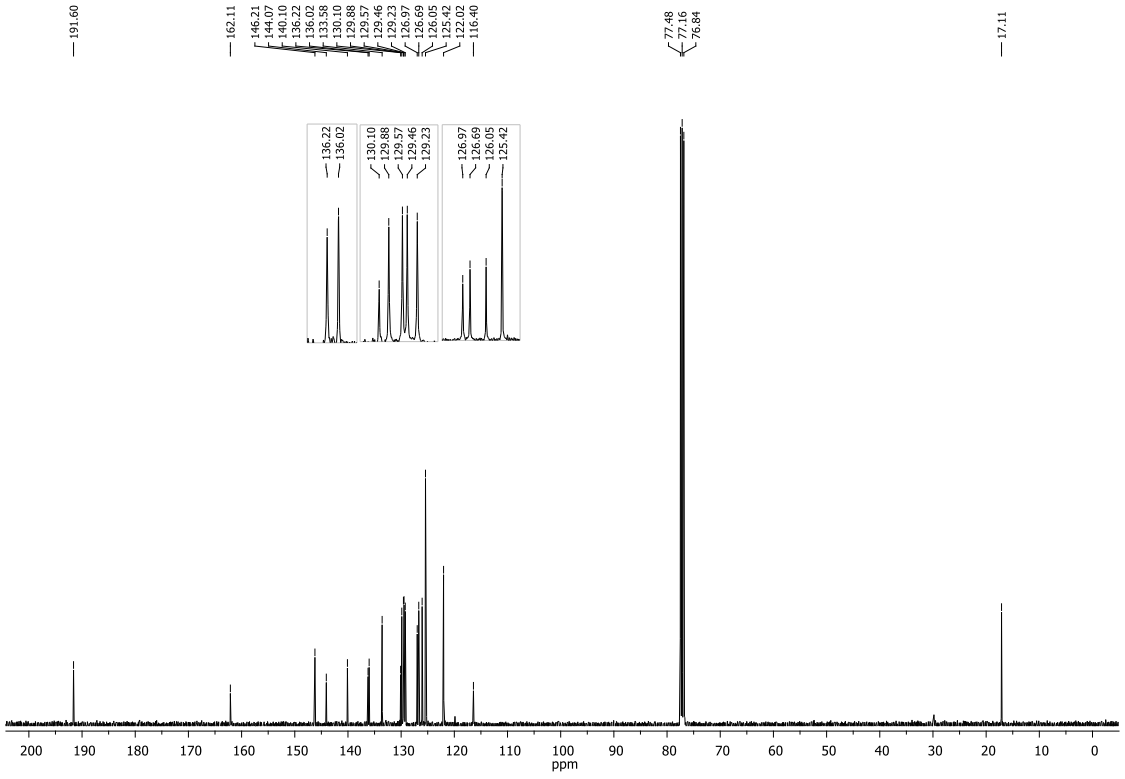



**Figure 5.4b**: $^{13}$C NMR Spectrum of **80c**

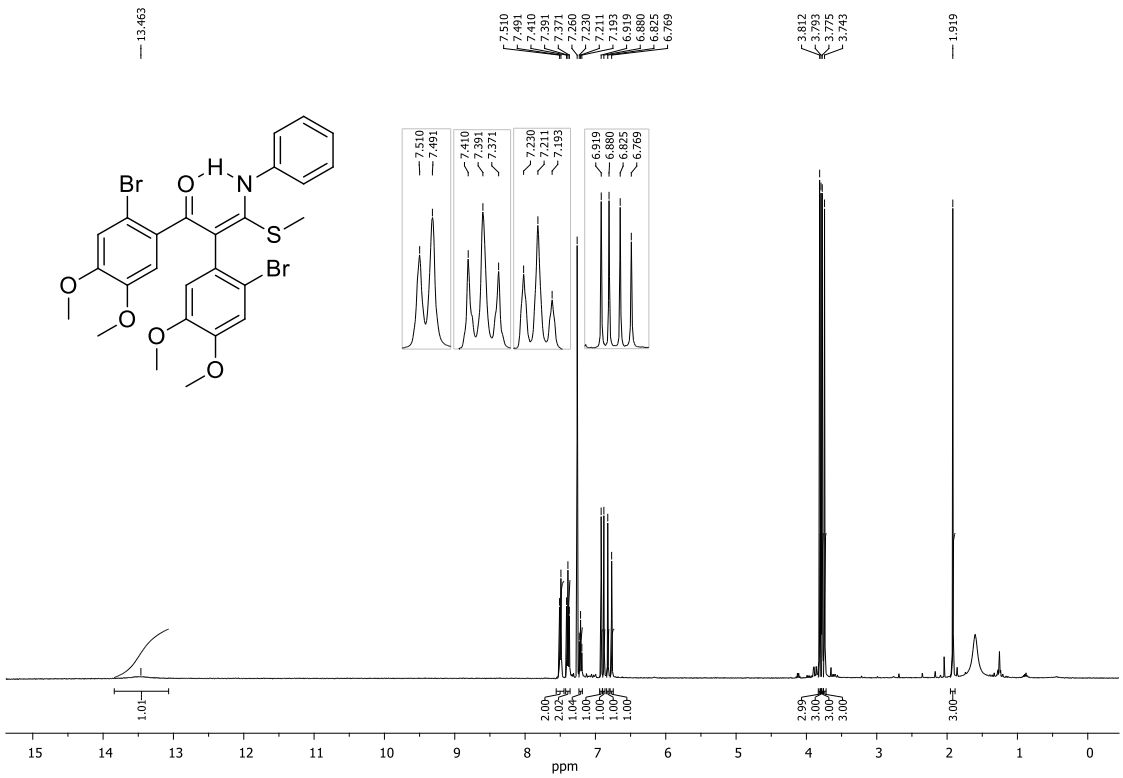



**Figure 5.5a**: $^{1}$H NMR Spectrum of **80f**

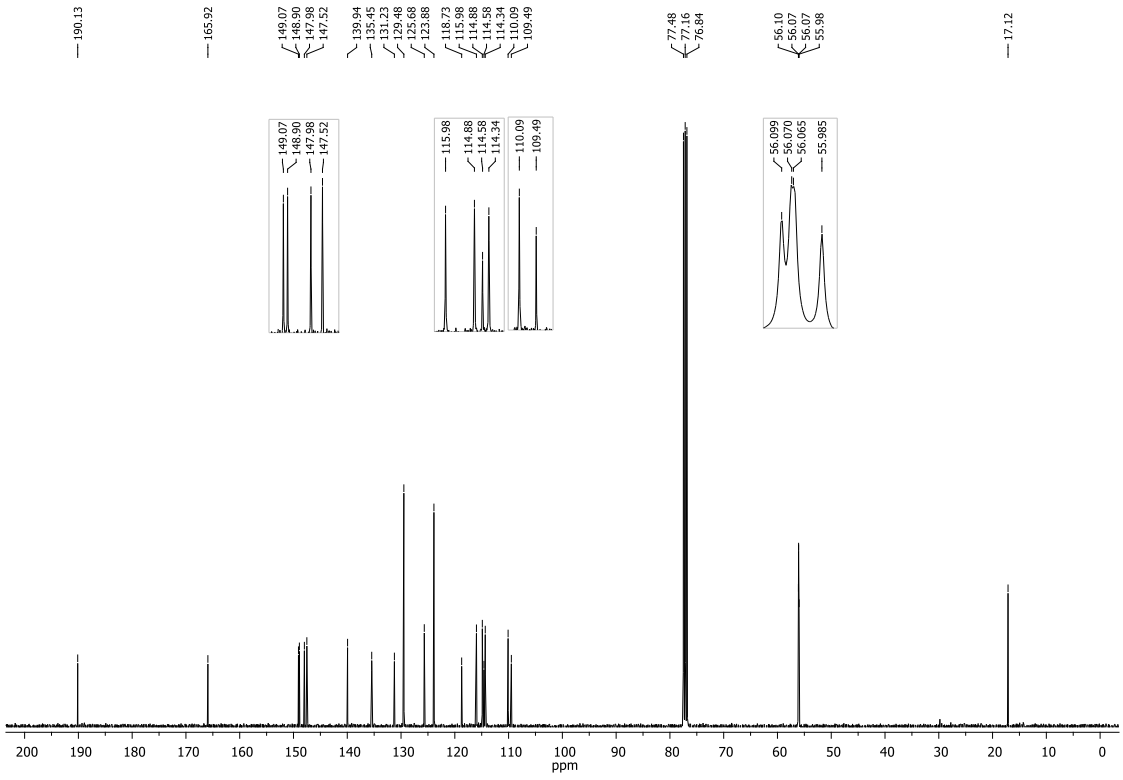



**Figure 5.5b**: $^{13}$C NMR Spectrum of **80f**

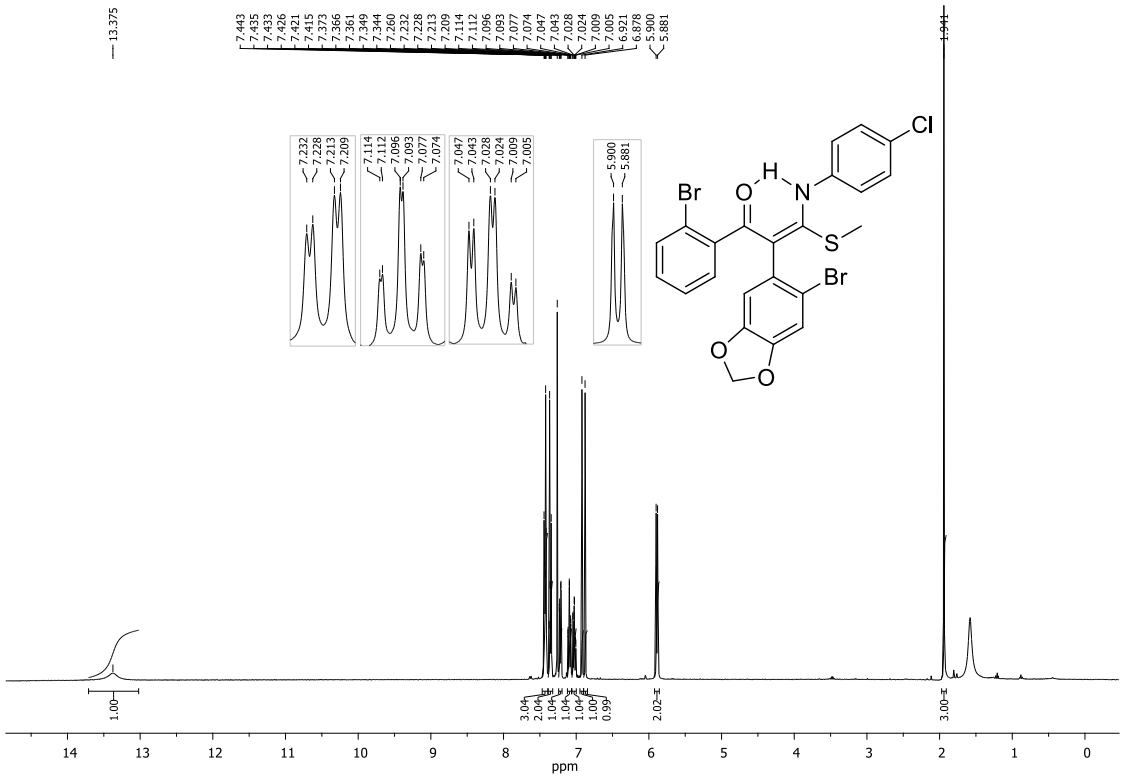



**Figure 5.6a**: $^{1}H$ NMR Spectrum of **80g**

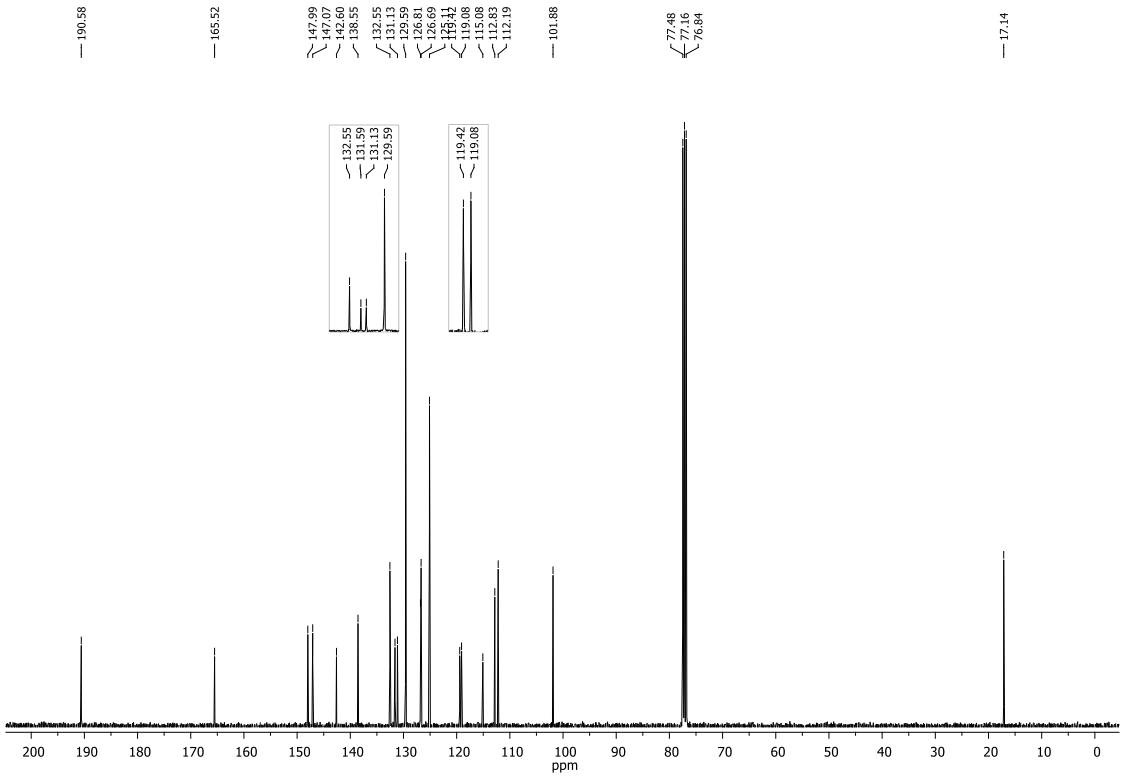



**Figure 5.6b**: $^{13}C$ NMR Spectrum of **80g**

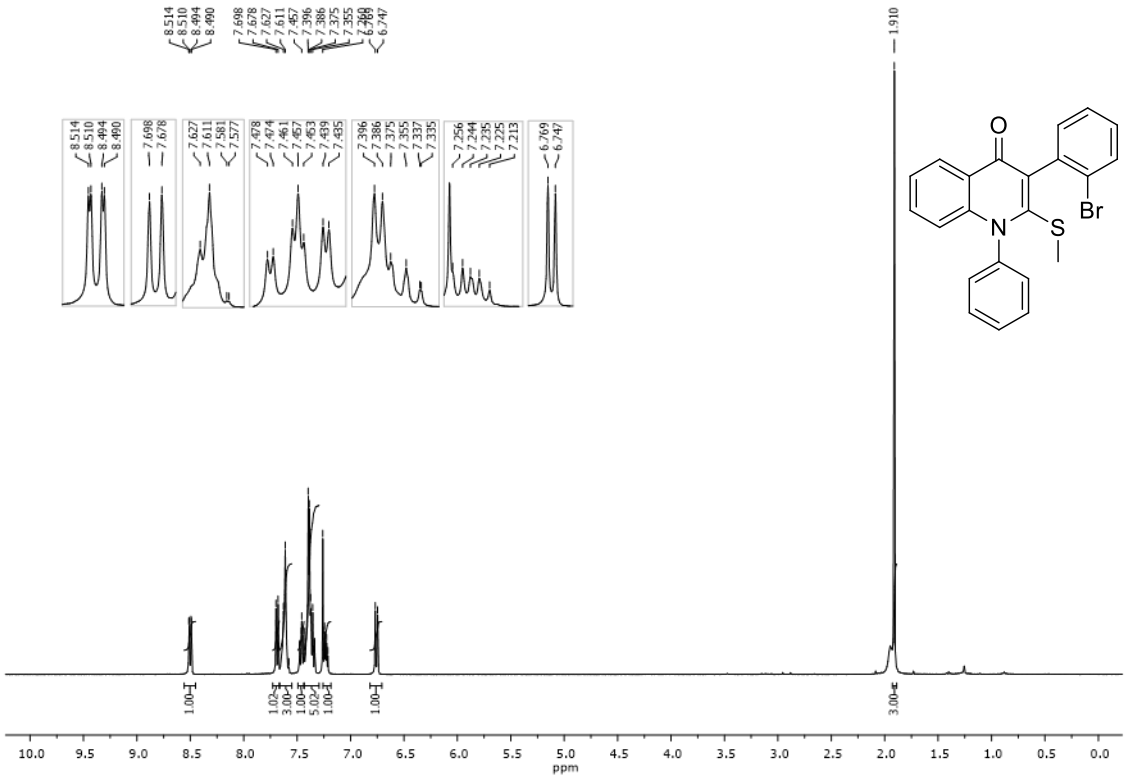



**Figure 5.7a**: $^{1}$H NMR Spectrum of **81a**

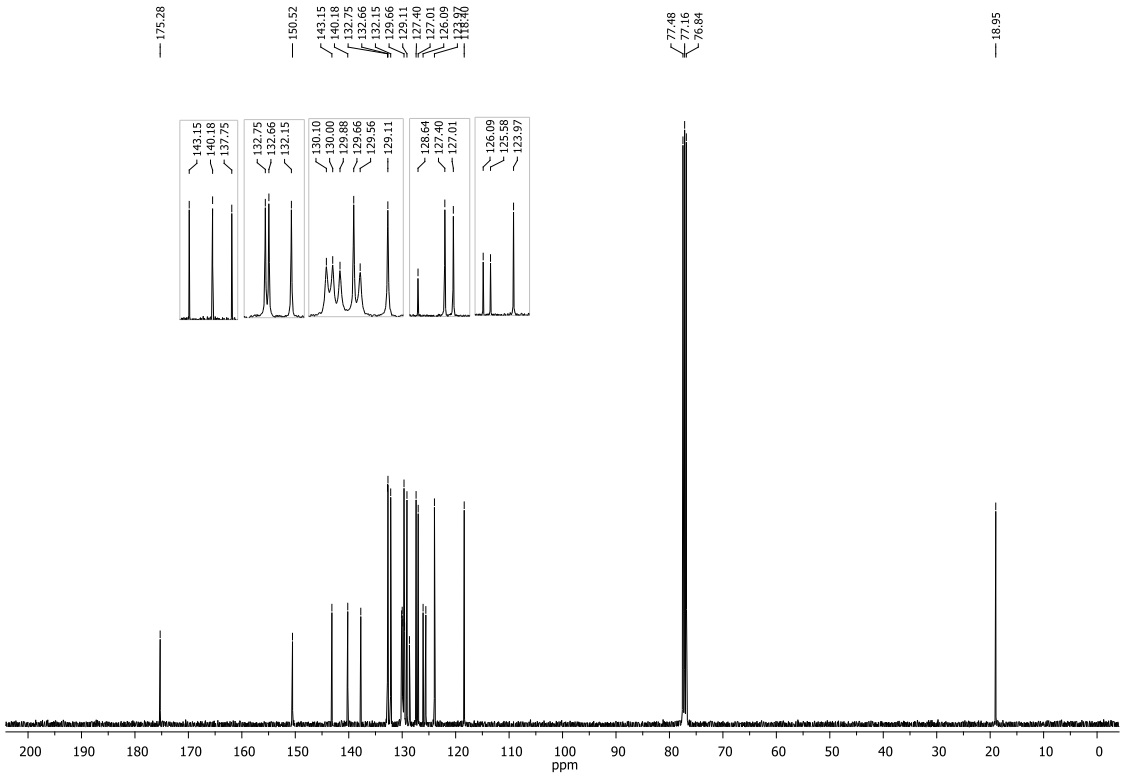



**Figure 5.7b**: $^{13}$C NMR Spectrum of **81a**

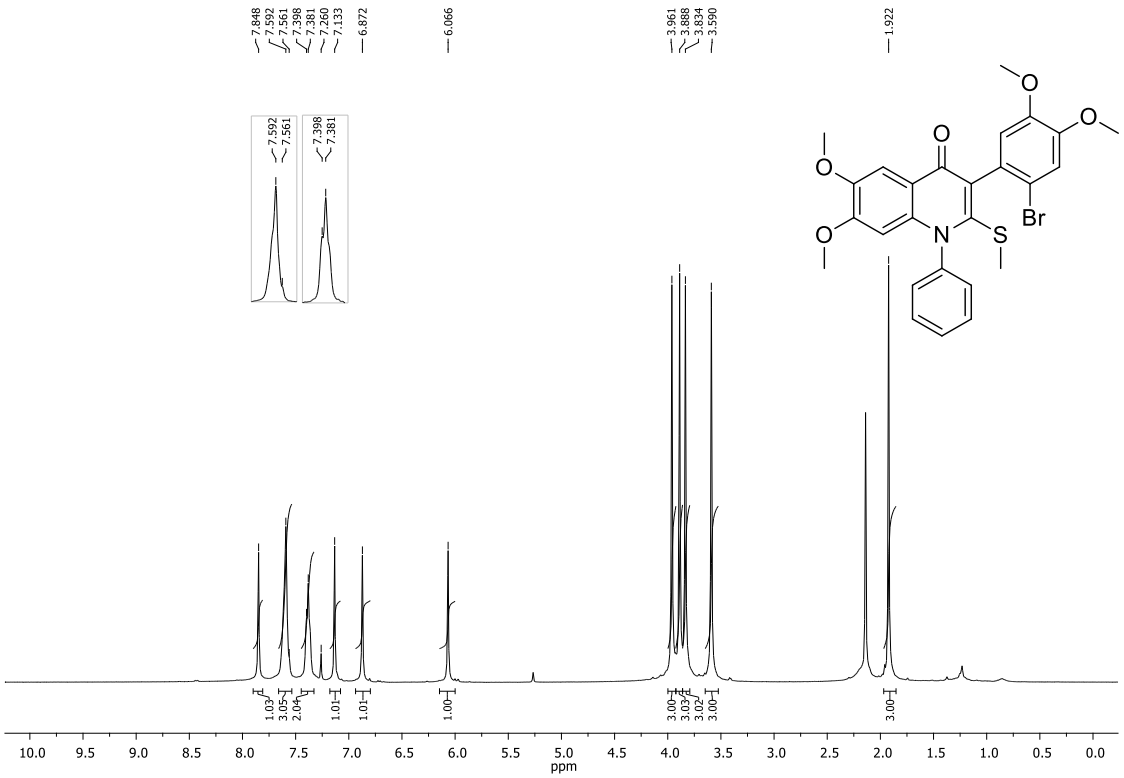



**Figure 5.8a**: $^{1}H$ NMR Spectrum of **81f**

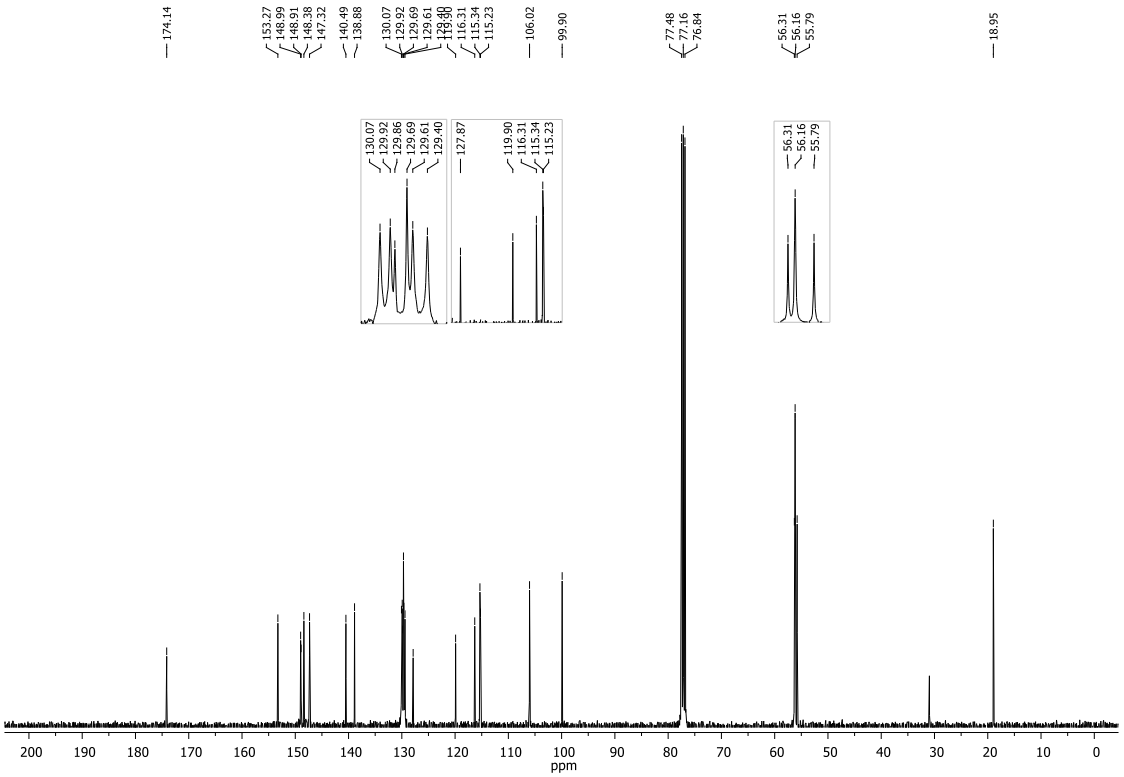



**Figure 5.8b**: $^{13}C$ NMR Spectrum of **81f**

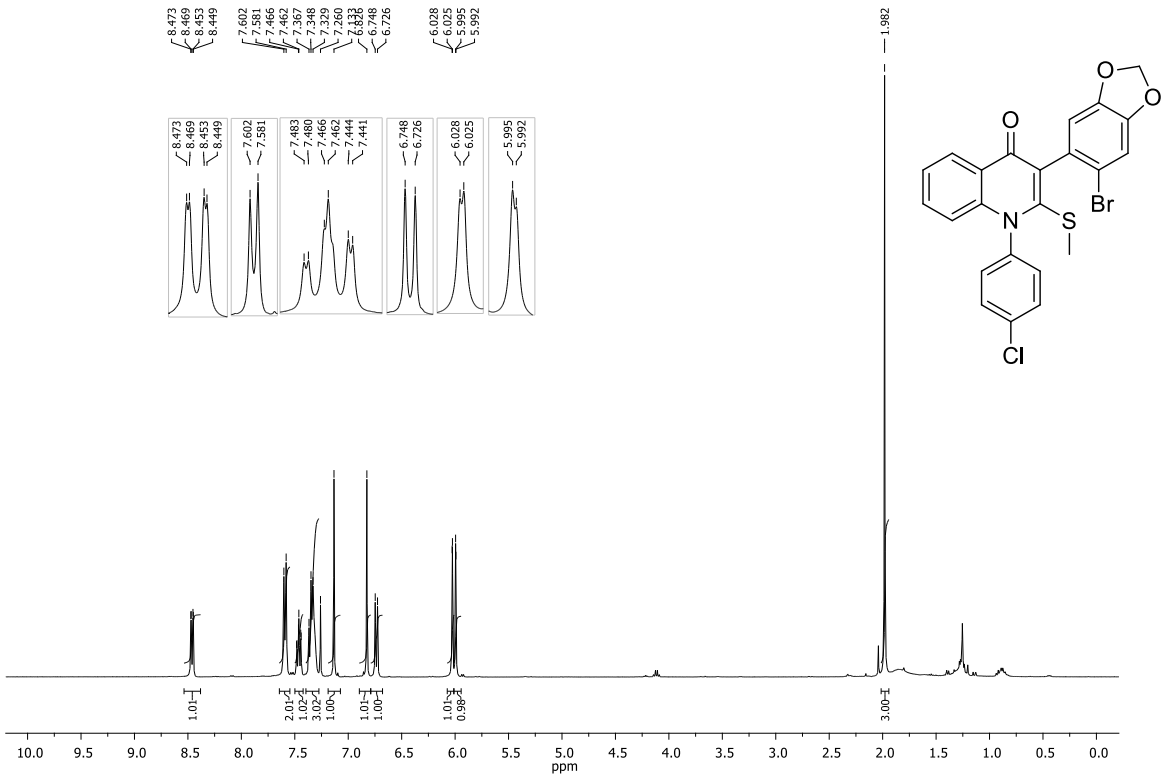



**Figure 5.9a**: $^{1}H$ NMR Spectrum of **81g**

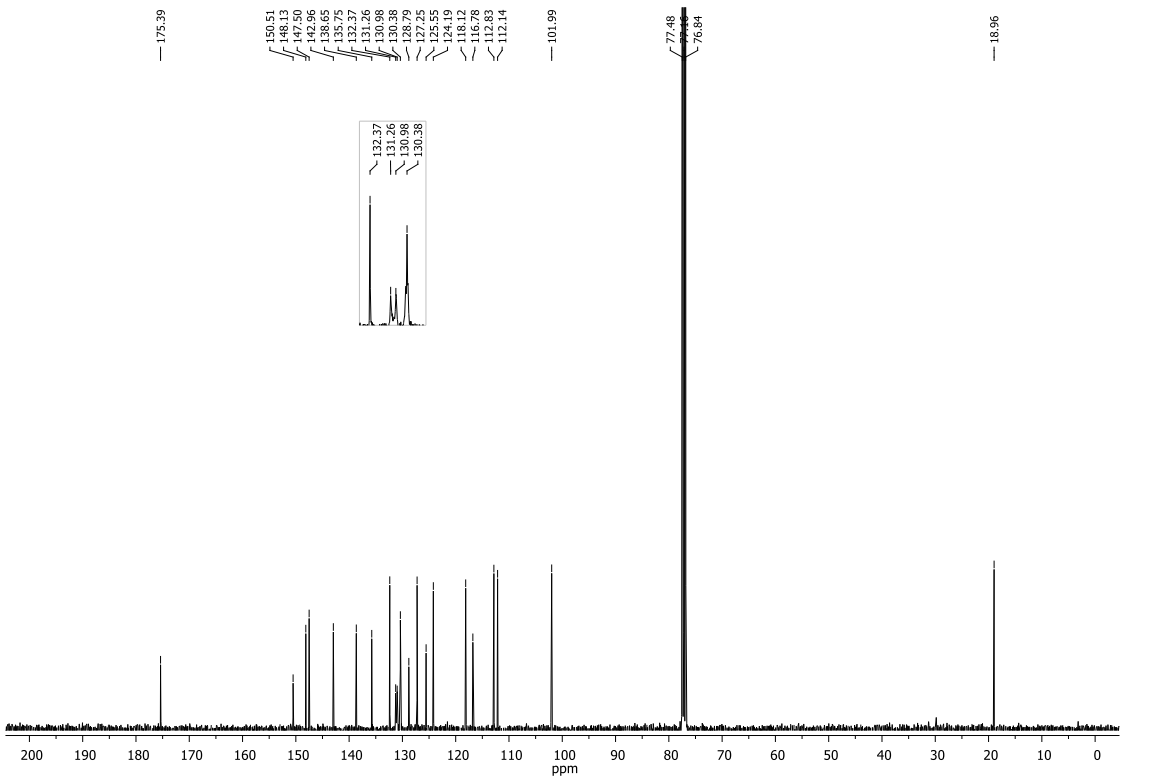



**Figure 5.9b**: $^{13}C$ NMR Spectrum of **81g**

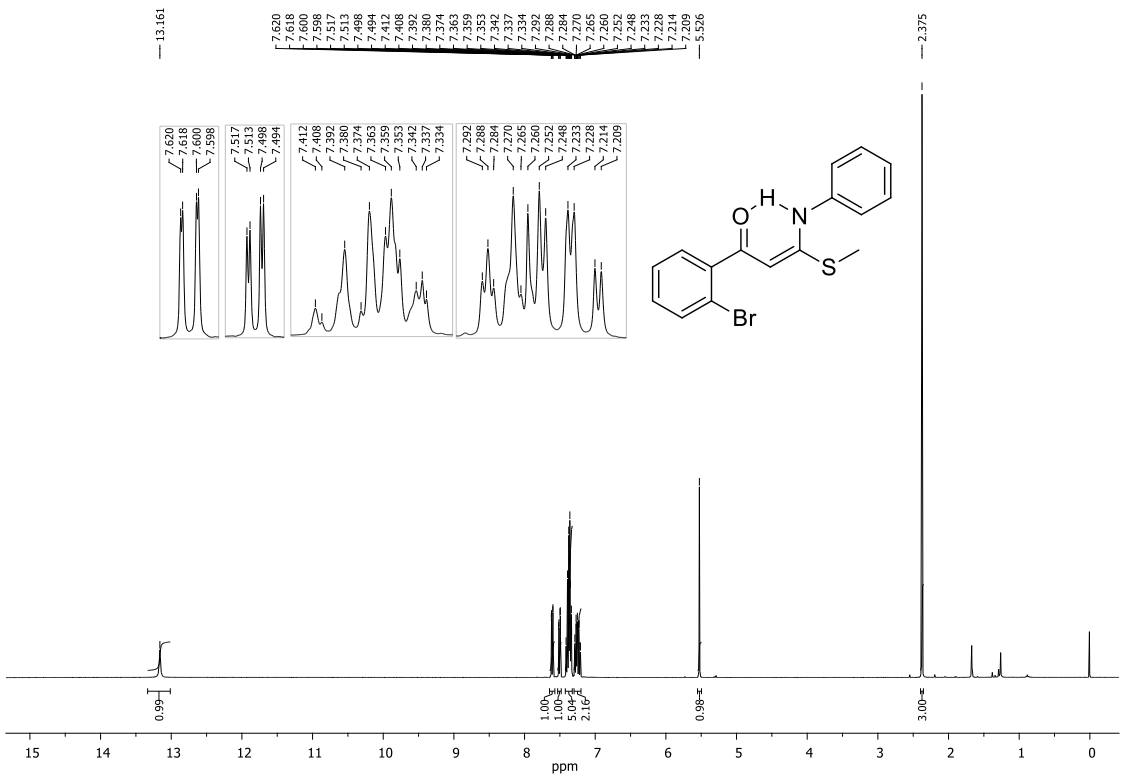



**Figure 5.10a**: $^{1}$H NMR Spectrum of **83a**

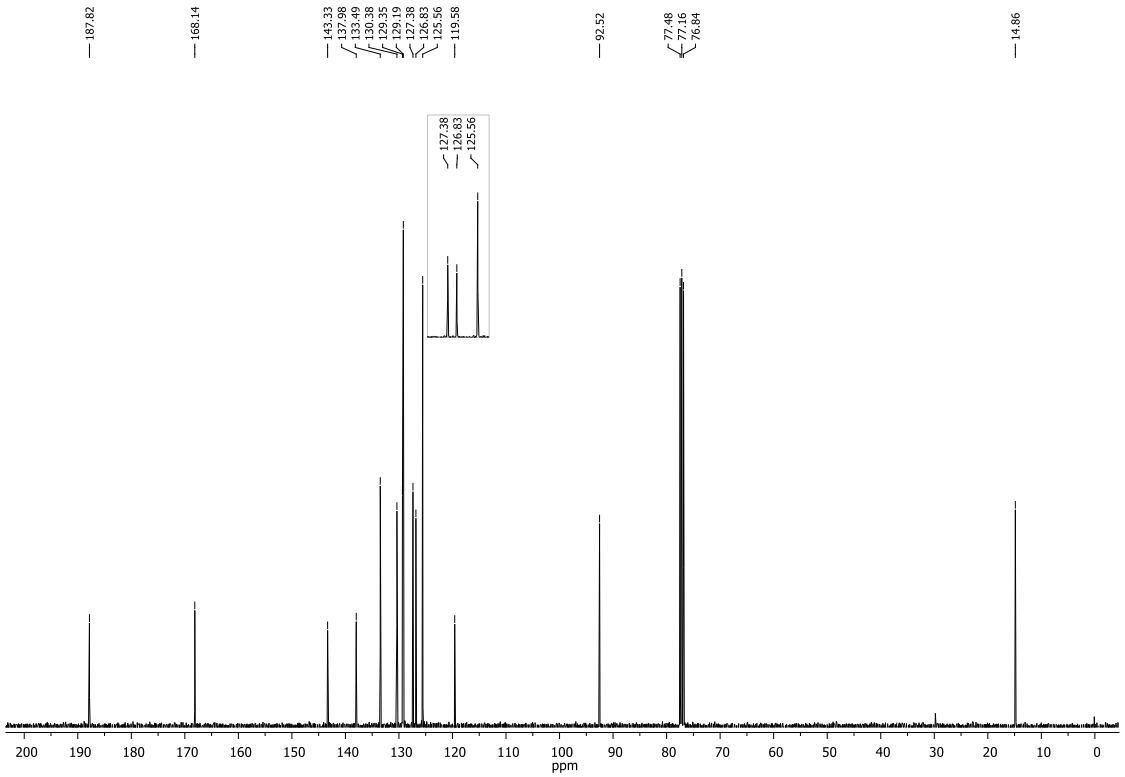



**Figure 5.10b**: $^{13}$C NMR Spectrum of **83a**

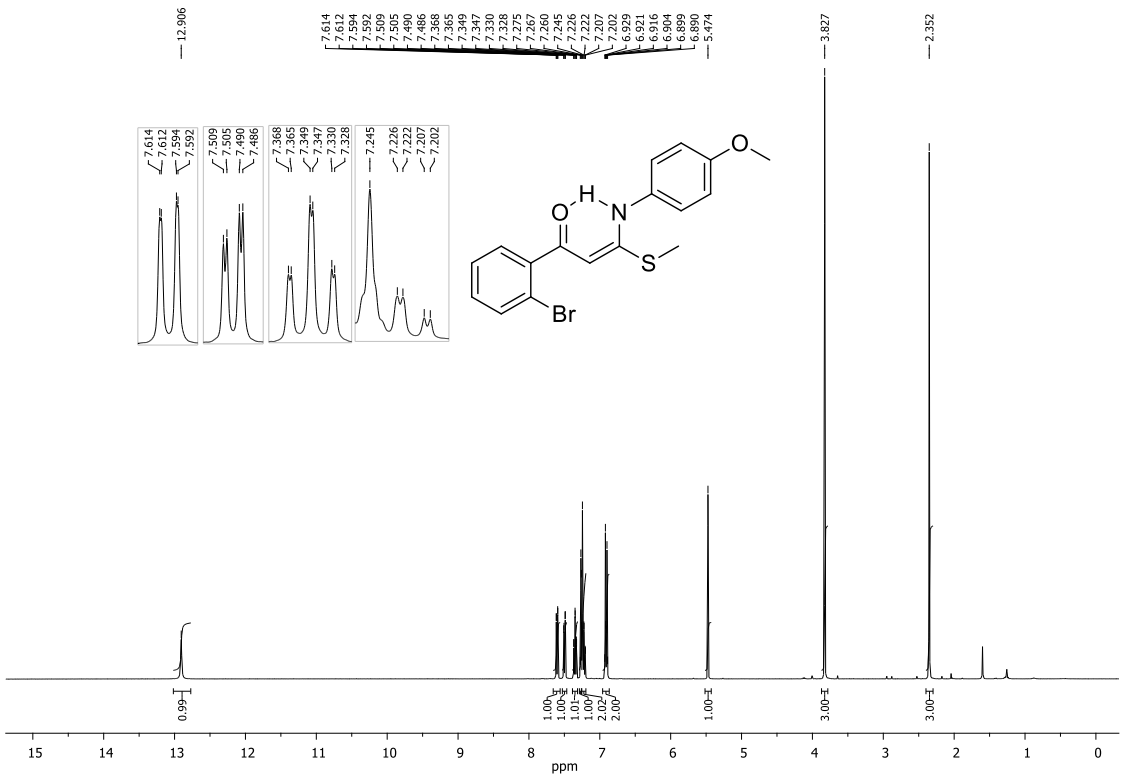



**Figure 5.11a**: $^{1}$H NMR Spectrum of **83c**

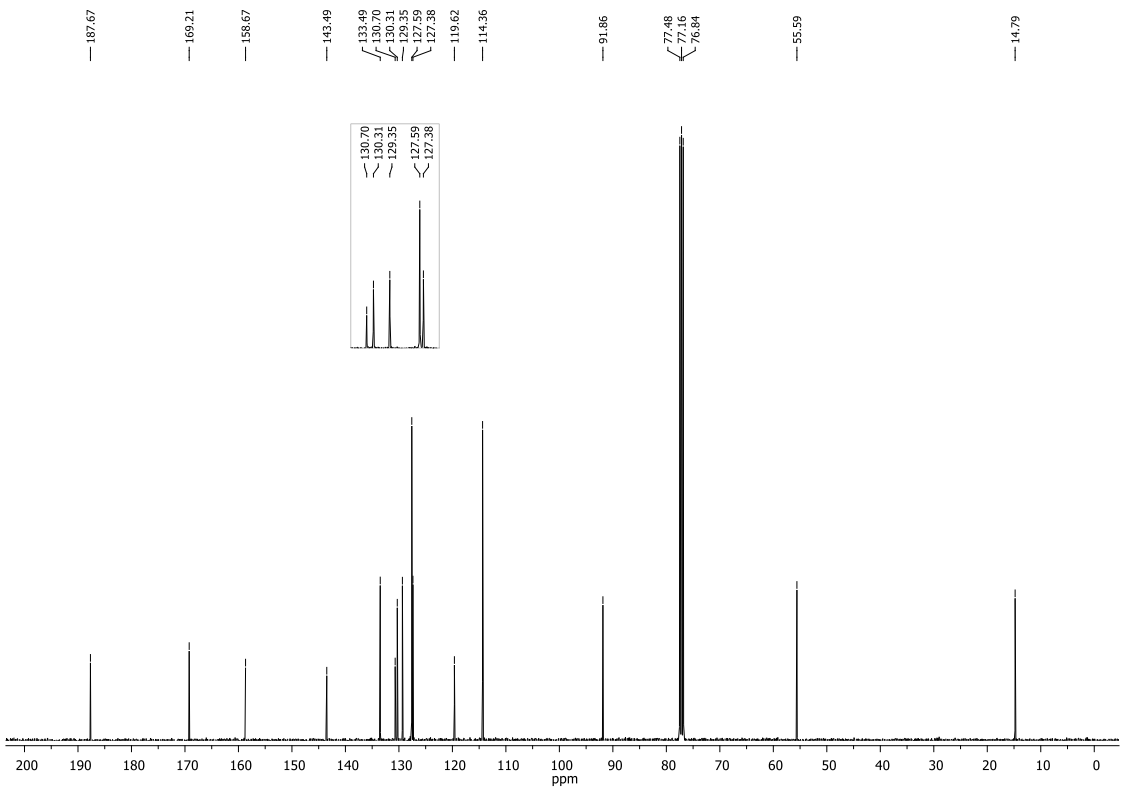



**Figure 5.11b**: $^{13}$C NMR Spectrum of **83c**

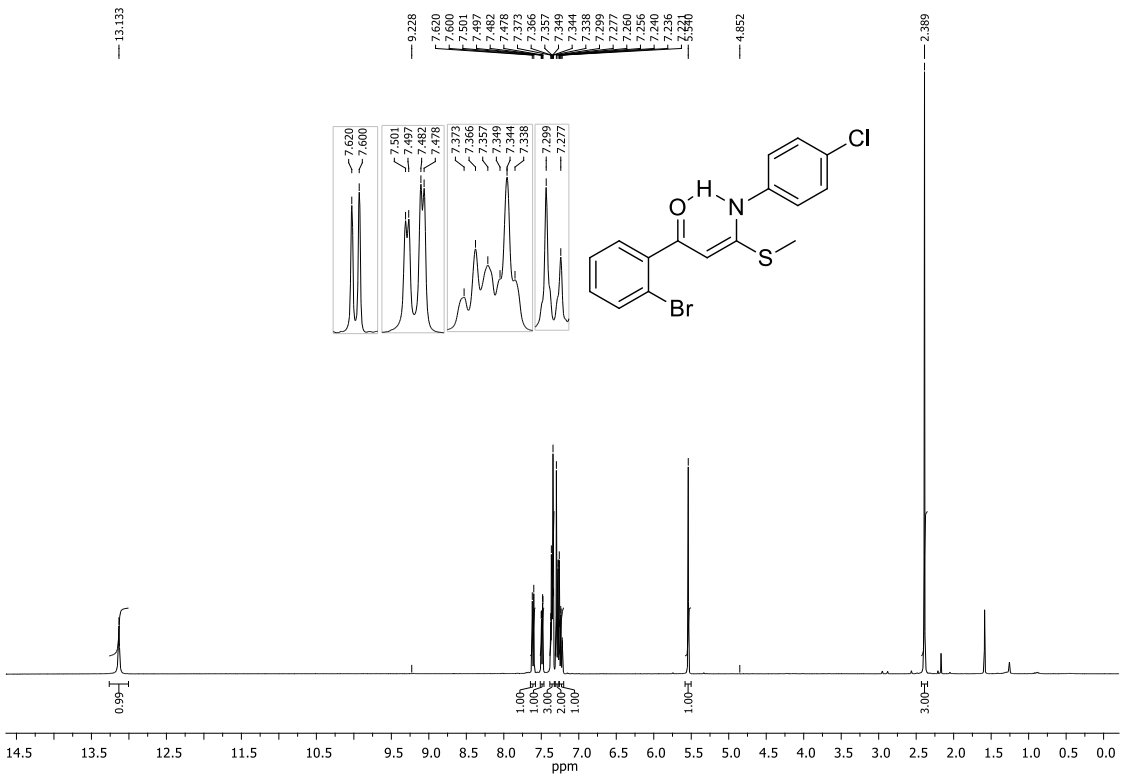



**Figure 5.12a**: $^{1}$H NMR Spectrum of **83d**

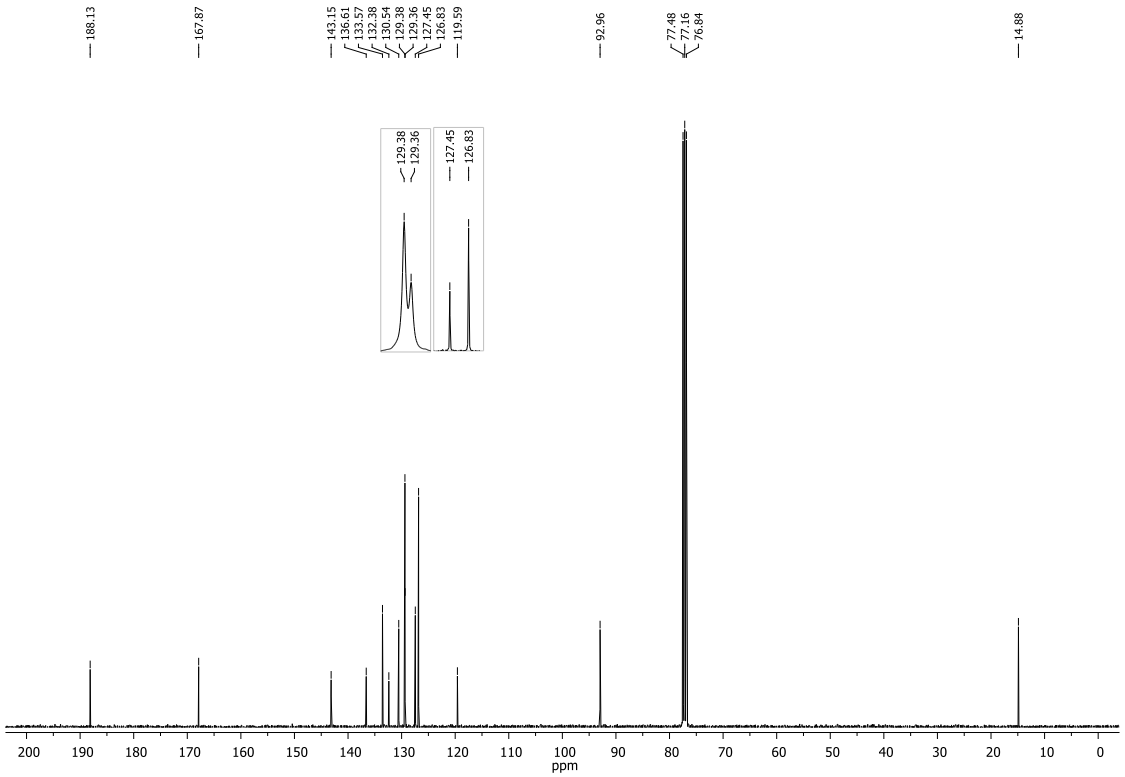



**Figure 5.12b**: $^{13}$C NMR Spectrum of **83d**

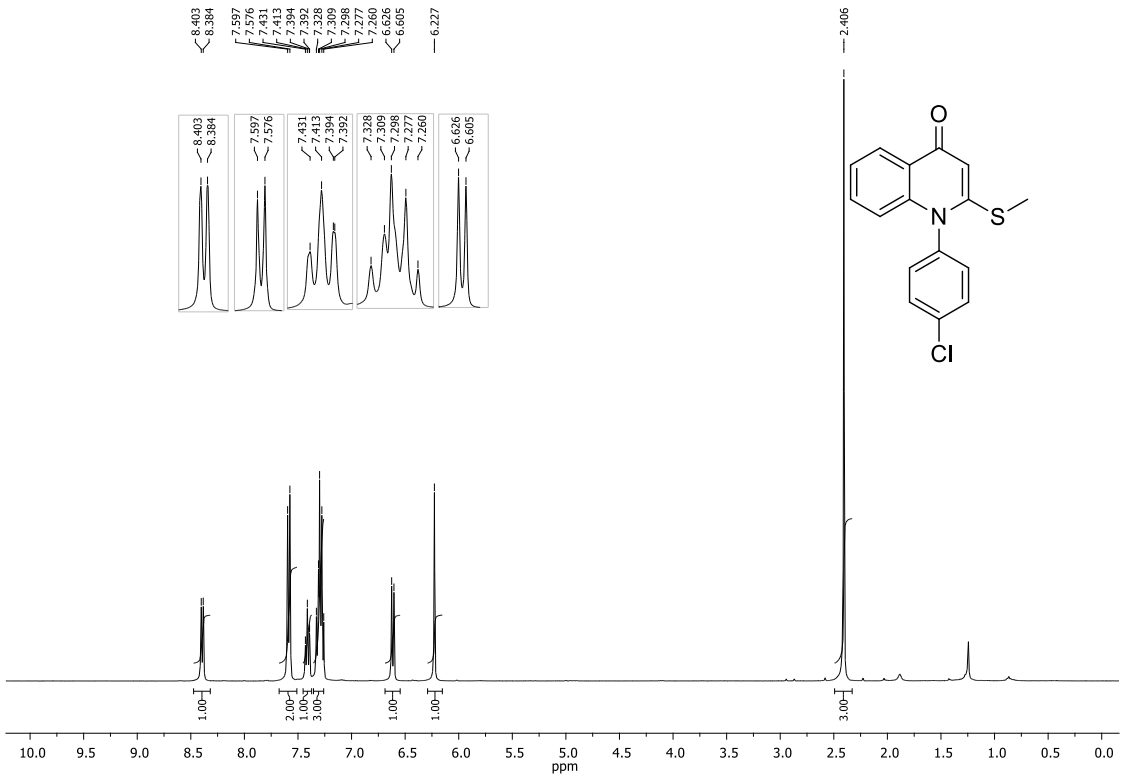



**Figure 5.13a**: $^{1}$H NMR Spectrum of **84d**

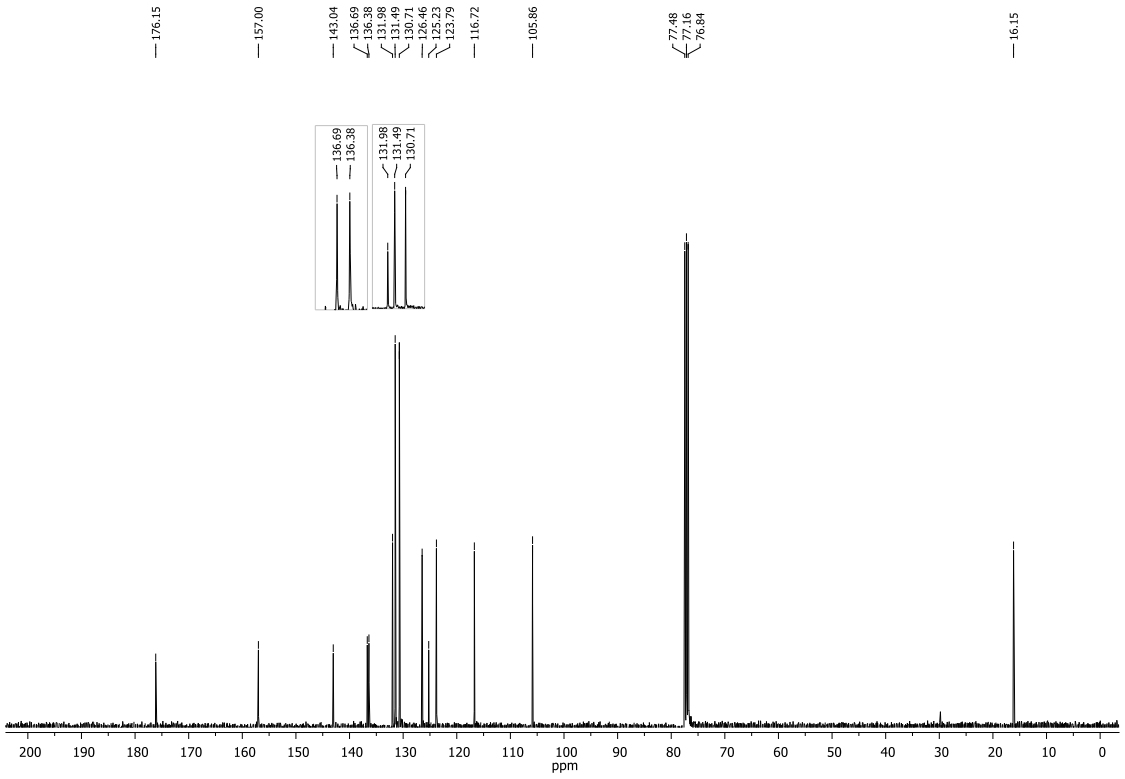



**Figure 5.13b**: $^{13}$C NMR Spectrum of **84d**

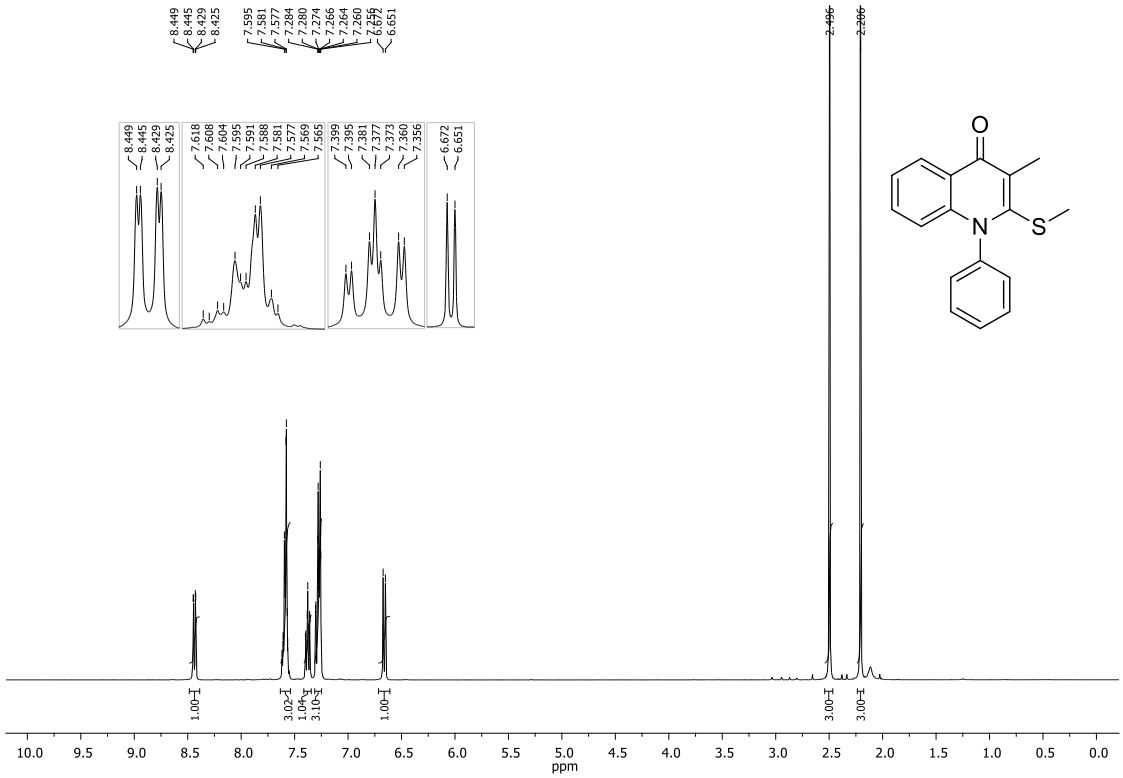



**Figure 5.14a**: $^{1}$H NMR Spectrum of **84i**

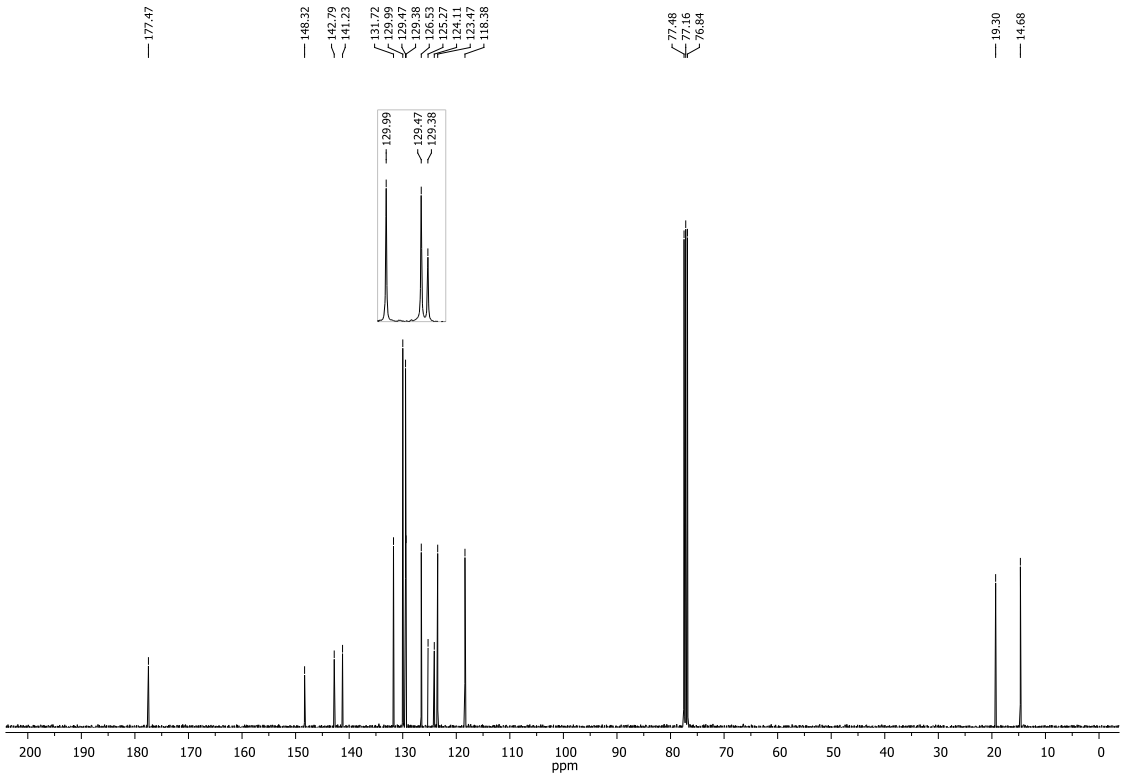



**Figure 5.14b**: $^{13}$C NMR Spectrum of **84i**

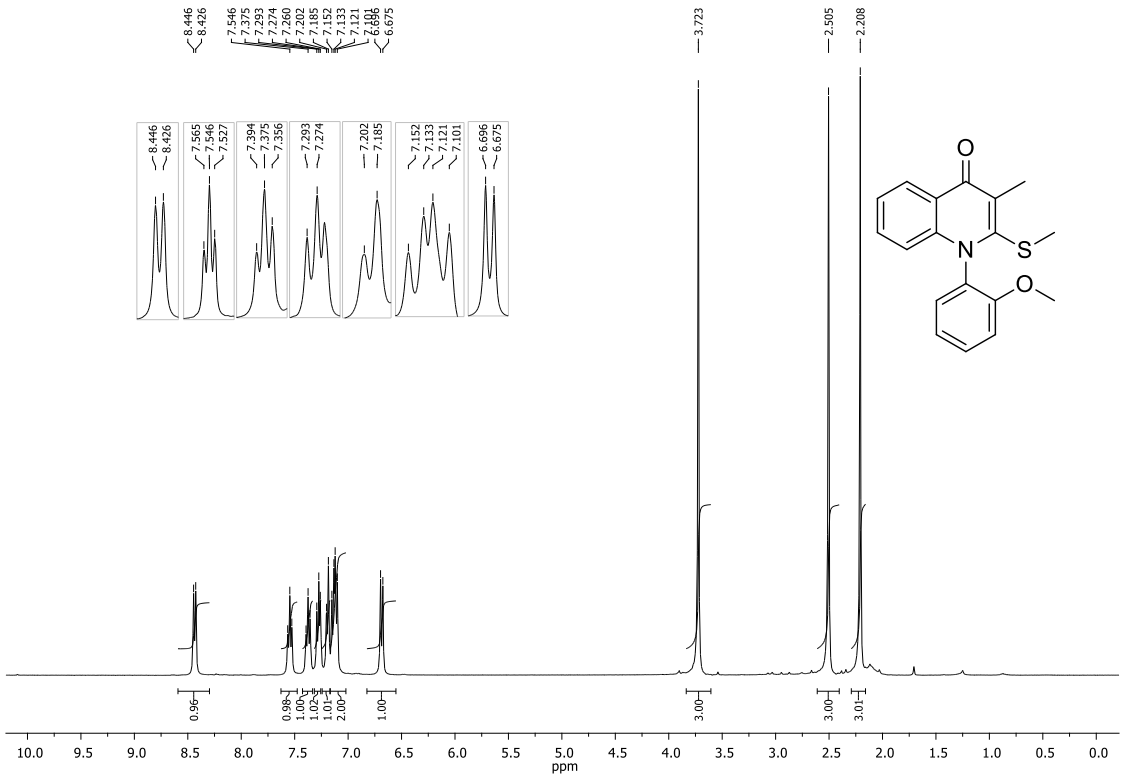



**Figure 5.15a**: $^{1}$H NMR Spectrum of **84j**

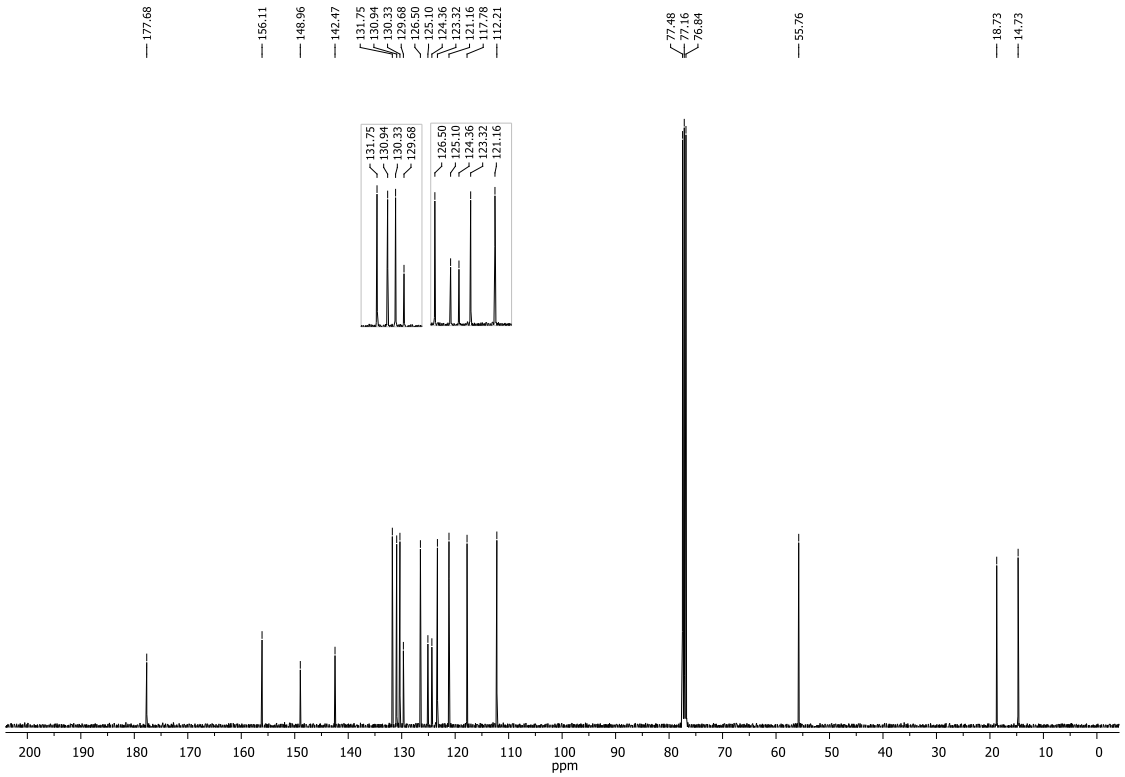



**Figure 5.15b**: $^{13}$C NMR Spectrum of **84j**

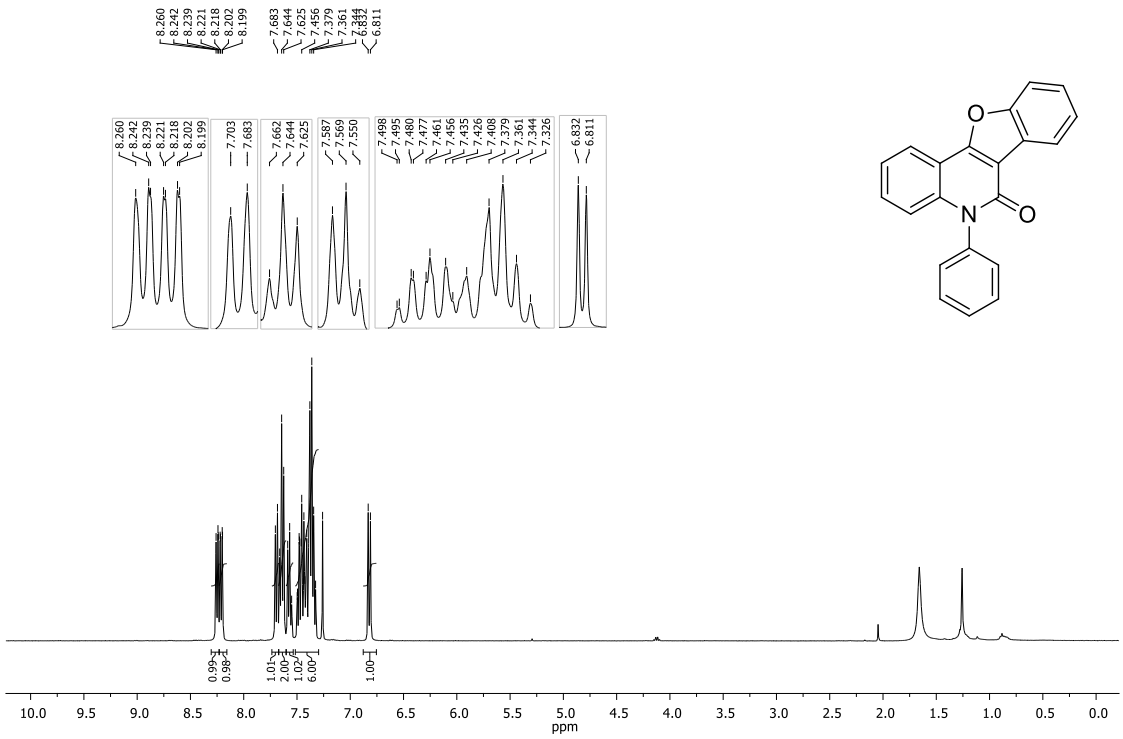



**Figure 5.16a**: $^{1}$H NMR Spectrum of **89a**

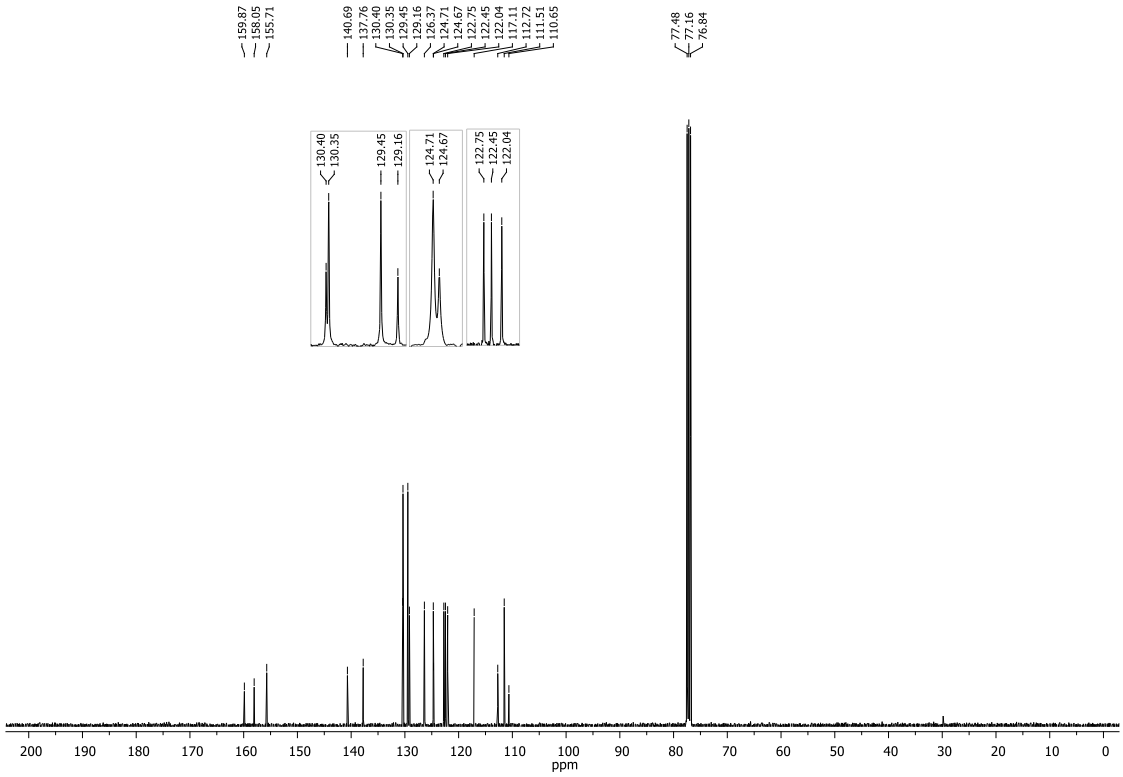



**Figure 5.16b**: $^{13}$C NMR Spectrum of **89a**

## 5.8 X-ray Crystal Data`

Crystallographic data of **81d** in $CH_2Cl_2$/*n*-hexane: $C_{24}H_{16}BrNO_5S$, Mw = 510.34, monoclinic, spacegroup P21, a = 10.4343 (4) Å, b = 4.6016 (5) Å, c = 13.8826 (4) Å, α = 90°, β = 92.748 (2)°, γ = 90°, V = 2112.69 (12) Å, Z = 4, Dcalc = 1.605 mg/$m^{3\cdot}$, T = 296 K, R1 = 0.0527 (2721), wR2 = 0.1559 (5467).

Crystallographic data of **89a** in $CH_2Cl_2$/*n*-hexane: $C_{21}H_{13}NO_2$, Mw = 311.32, monoclinic, spacegroup P21, a = 5.2728 (2) Å, b = 25.3300 (7) Å, c = 11.4784 (4) Å, α = 90°, β = 99.154 (2)°, γ = 90°, V = 1513.53 (9) Å, Z = 4, Dcalc = 1.366 mg/$m^{3\cdot}$, T = 296 K, R1 = 0.434 (2275), wR2 = 0.1494 (3346).

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