Metal/Metal Free Mediated Heterocycle Synthesis Through C−N, C−S& C−C Bond Forming Reactions

BY

ANNARAM THIRUPATHI
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Jatni, Khurda, Odisha - 752050

A thesis submitted to the
Board of Studies in Chemical Sciences
In partial fulfilment of requirements
For the degree of

DOCTOR OF PHILOSOPHY
of
HOMI BHABHA NATIONAL INSTITUTE

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Recommendations of the Viva Voce Committee

As members of the Viva Voce Committee, we certify that we have read the dissertation prepared by **Annaram Thirupathi** entitled **"Metal/Metal Free Mediated Heterocycle Synthesis Through C−N, C−S & C−C Bond Forming Reactions"** and recommend that it may be accepted as fulfilling the thesis requirement for the award of Degree of Doctor of Philosophy.

Chairman	Prof. A. Srinivasan	Date: 21.06.2019
Guide / Convener	Dr. S. Peruncheralathan	Date: 21.06.2019
Examiner	Dr. R. Vijaya Anand (IISERM)	Date: 21.06.2019
Member 1	Dr. Venkatasubbaiah Krishnan	Date: 21.06.2019
Member 2	Dr. Sharanappa Nembenna	Date: 21.06.2019
Member 3	Dr. Tirumala Kumar Chowdary	Date: 21.06.2019

Final approval and acceptance of this thesis is contingent upon the candidate's submission of the final copies of the thesis to HBNI.

I hereby certify that I have read this thesis prepared under my direction and recommend that it may be accepted as fulfilling the thesis requirement.

Date: 21.06.2019

Place: NISER Bhubaneswar

Dr. S. Peruncheralathan

Guide

STATEMENT BY AUTHOR

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A. Thirupathi

ANNARAM THIRUPATHI

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.

A. Thirupathi

ANNARAM THIRUPATHI

List of Publications

Papers Published:

[# Indicates Manuscripts Pertaining to Thesis]

1) Chemoselective Ullman Coupling at Room Temperature: a facile access to 2-aminobenzo[b]thiophenes

Manojkumar Janni, ***Annaram Thirupathi****, Sahil Arora and S. Peruncheralathan, Chem. Commun.,* ***2017****, 53, 8439.*

#2) Copper Catalyzed Intramolecular N-Arylation of Ketene Aminals at Room Temperature: Synthesis of 2-Amino-3-cyanoindoles.

Annaram Thirupathi, *Manojkumar Janni and S. Peruncheralathan, J. Org. Chem.,* ***2018****, 83, 8668.*

#3) Nickel Catalysed Site Selective C−H Functionalization of α-Arylthioamides

Debashrurhi Bandyopadhyay[ǂ]*,* ***Annaram Thirupathi***[ǂ]*, Nagsen M Dhage, Nirmala Mohanta and S. Peruncheralathan, Org. Biomol. Chem.,(Accepted manuscript) [ǂ Represents equal contribution]*

Manuscripts Submitted:

#4) Transition Metal free Intramolecular Aromatic C-H thiolation of Thioanilides.

Annaram Thirupathi*, Manojkumar Janni, Shubhashree Pani and S. Peruncheralathan (Manuscript under Review).*

Manuscript Under Preparation:

#5) Bronsted Acid Mediated Synthesis of 4-Amino Quinolines

#6) New Approach for the Synthesis of Indolo Fused Quinolines and Quinolones

7). Palladium and Copper Catalyzed Multi-component Reaction for Synthesis of New Classes of Benzo[*b*]thieno Fused Quinolones

8) Synthesis and Biological Studies of 2-Amino Benzo[*b*]thiophenes

A Thirupathi

Conferences Attended

1. Poster (*Copper-Mediated 2-Amino Indole Synthesis: Easy Access to Synthesis of Neocryptolepine Derivatives*) presented in **XI-JNOST** Conference for Research Scholars (**J-NOST**) held on (14-17)th December 2015, NISER-Bhubaneswar, India.

2. Oral presentation (*New Approach for the Synthesis Indolo fused Quinolines via C—H Amination)* given in **IICM-2017** held on (20 – 22)ndJanuary**, 2017, IISER Bhopal,** India.

3. Participated in **Indo-French Symposium on Metal Organic Frameworks** held on (24-26)th February 2014, NISER-Bhubaneswar, India.

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

5. Participated in **IINCM-2018** (Inter IISER and NISER Chemistry Meet) held on (22 – 24)th December, **2017,** NISER-Bhubaneswar, India.

6. Participated in **ACS on Campus** held on 23rd July, 2018, NISER-Bhubaneswar, India.

A Thirupathi

ANNARAM THIRUPATHI

Dedicated to

My Parents

&

My Sisters

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Vijender Reddy, Prabhakar, Venkatesh, Vijender, Ranjith.P, Ranjith. T. for their pleasant company in my B.sc and M.Sc. Special thanks to Vijender Reddy (BVR) for his care and teaching the basic chemistry during undergraduation.

I am in paucity of words to express my inner feeling for my parents, whose constant encouragement and moral support always helped me to smile at the difficult times to achieve the goals of success. They have always sacrificed their own wishes and happiness just for the upliftment of my career. Without their care, love, sacrifice, support, prayers, wishes and motivation, it would have been difficult to imagine my present position in life. I struggle for words to thank my sister Swapna for her care and motivation in every moment of my life. She has always been there to help. Her advice has had a deep impression on many of decisions and so owe her a lot for my success in my personal and professional life. I also would like to thank my brothers Srinivas, Srikanth, Venkatesh and Sister Manasa for camaraderie and their sense of humor, which helped me to take things in lighter side. During difficult times they have spurred me to work hard and mitigated my frustration. It is difficult to describe in words the hardship that my Uncles and Aunts, have gone through emotionally during my research tenure for my better and prosperous future.

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

Annaram Thirupathi

CONTENTS

Chapter 4: New Approach for the Synthesis of Indolo Fused Quinolines and Quinolones: Synthesis of Isocryptolepine Derivatives

Homi Bhabha National Institute

SYNOPSIS OF Ph. D. THESIS

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1. **Name of the Student:** ANNARAM THIRUPATHI
2. **Name of the Constituent Institution**: National Institute of Science Education and Research (NISER), Jatni, Bhubaneswar
3. **Enrolment No. :** CHEM11201204002
3. **Title of the Thesis:** Metal/Metal Free Mediated Heterocycle Synthesis Through C─N, C─S and C─C bond Forming Reactions
5. **Board of Studies:** School of chemical sciences

SYNOPSIS

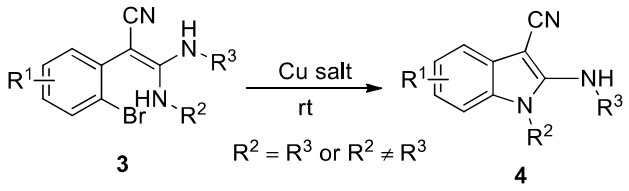
(Limited to 10 pages in double spacing)

The thesis has been divided into four chapters

The **first chapter** of the thesis will describe about a brief literature methods for synthesis of indolo fused quinolines and cryptolepine derivatives.

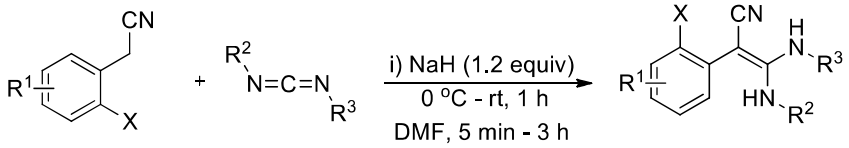
The **second chapter** of my thesis will deal with the synthesis of 2-aminoindoles via copper-mediated *N*-arylation of ketene aminals at room temperature. The 2-aminoindole

derivatives were known to be selective estrogen ligand receptors, *ß*-kinase inhibitor and metabolic kinase inhibitor and these derivatives were the key intermediate for the synthesis of various biologically active molecules. Synthesis of 2-aminoindole derivatives are well known, however the reported methods suffer with multistep syntheses, usage of expensive metals, high temperature, indole as a precursor, low yields and longer reaction times. To overcome these problems, I have developed simple and milder protocol to synthesize 2-aminoindoles via copper-mediated *N*-arylation of ketene aminals at room temperature (Scheme 1).



Scheme-1

The required ketene aminals **3** were prepared by treating the anion of commercially available and easily synthesizable 2-bromobenzyl cyanides **1** with various carbodiimides **2** (Scheme 2).



X = Br, H

R^1 = H, OMe, -OCH_2O-, C_4H_4

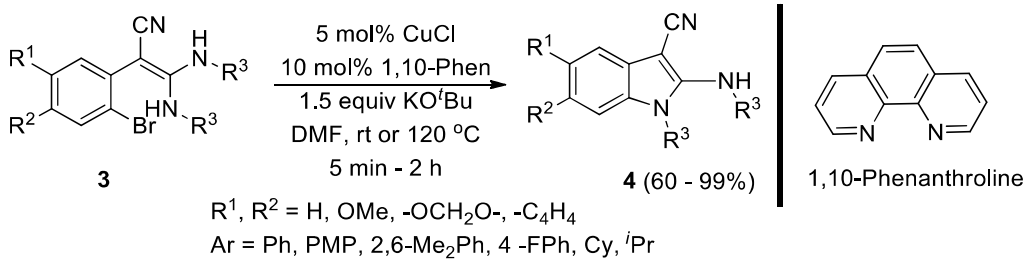
R^2, R^3 = Ph, PMP,4-FPh, 4-$NO_2C_2H_4$, 2,6-Me_2Ph, Cy, ^{i}Pr, ^{t}Bu

Scheme-2

After synthesis of various ketene aminals **3**, I studied various reaction conditions for Ullmann coupling at ambient temperature. I have chosen ketene aminal **3a** [R^1 = H, R^2, R^3 = 4-MeOPh] as a model substrate and the reaction was carried out with 5 mol% CuI, 10 mol% 1, 10- phenanthroline, Et_3N (1.5 equiv) in DMF at room temperature. However, only 5% of the

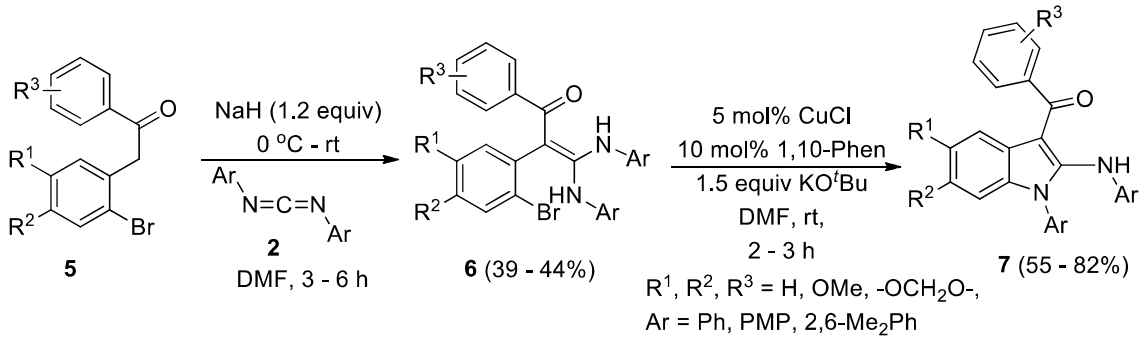
corresponding 2-amino indole **4a** was observed. To optimize this process, I screened several bases, solvents, ligands, and metal salts, I found that KO^{t}Bu as base, 1, 10- phenanthroline and DMF as solvent were appropriate for this *N*-arylation of ketene aminals and afforded 99% of yield in the presence of CuCl. In the absence of CuCl and ligand, the aminal **3a** failed to give the corresponding 2-amino indole derivative **4a**.

With the optimized conditions in our hand, I investigated the intramolecular *N*-arylation of several ketene aminals **3**. Thus, I studied electron donating, withdrawing and sterically crowded aminals and I observed 2-amino indoles **4** in good to excellent yields within a short time period. However, alkyl substituted ketene aminals **3** (R^3 = Alkyl) did not give the corresponding cyclized products at room temperature. However, the reaction was performed at 120 ^oC, *N*-alkyl substituted 2-aminoindoles **4** were obtained in good to high yields (Scheme 3).



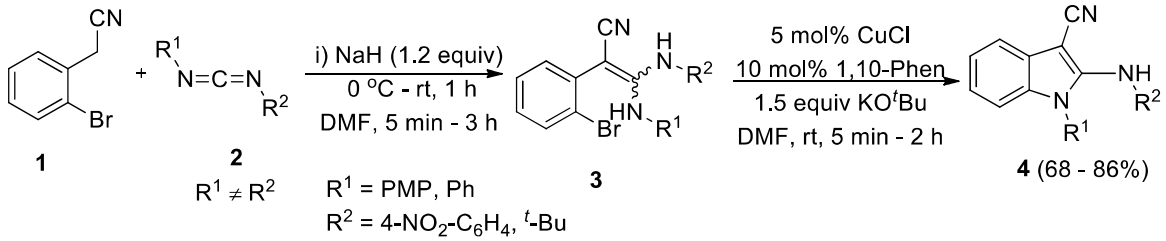
Scheme-3

I also studied the effect of electron withdrawing group on the *N*-arylation process. Thus, I synthesized ketene *N, N*-acetals **6** by treating the anion of deoxybenzoins **5** with carbodiimide **2**. These ketene aminals **6** were also converted to 2-amino indoles **7** with good to very good yields (55 – 82%) at room temperature (Scheme 4).



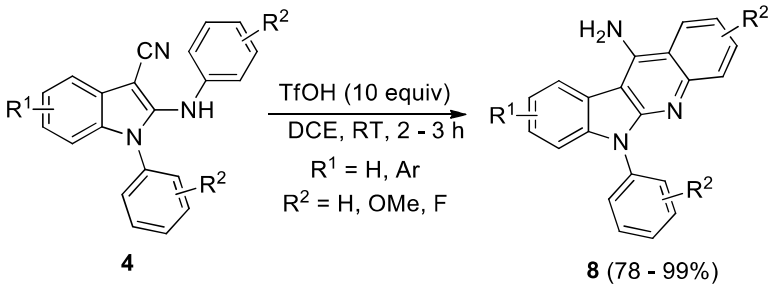
Scheme-4

Next, I examined the regioselective *N*-arylation of unsymmetrical ketene aminals by using the optimized reaction conditions. The required ketene aminals **3** were prepared by using 2-bromobenzyl cyanide (**1**) and unsymmetrical carbodiimides **2**. These ketene aminlas **3** were obtained as regioisomers. Further, when I subjected these ketene aminals **3** to optimized reaction conditions, I observed exclusively one regioselective product **4** with good to very good yields. The electron rich part of *N*-aryl ketene aminals was *N*-arylated over the electron deficient part. The same trend was observed in *N*-phenyl and *N*-alkyl ketene aminals (Scheme 5).



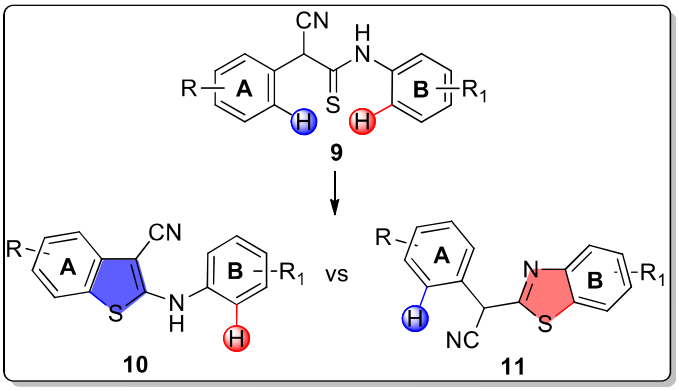
Scheme-5

Finally, I envisioned an activation of nitrile group by bronsted acid, followed by trapping with adjacent nucleophilic centre. This approach will result in the formation of indoloquinoline derivatives. Thus, I synthesized several indolo quinolines **8** at room temperature *via* TfOH mediated Gattermann type of cyclisation of 2-amino-3-cyano indoles **4**. (Scheme 6)



Scheme-6

The **third chapter** of thesis will describe the regioselective thiolation of the thioamides. This chapter is divided into two parts.



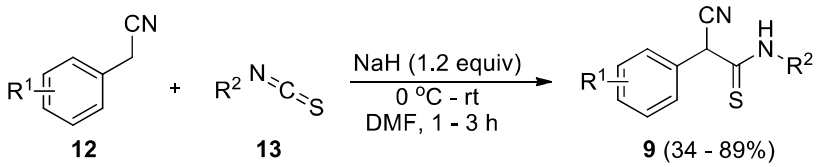
Scheme 7

The thioamide **9** has two different type of phenyl rings (ring A & B). The thiolation on thioamides **9** will give two separate products benzo[*b*]thiophene **10** & benzo[*d*]thiazole **11** respectively (Scheme 7). Our literature survey reveals that thioanilides are readily converted to benzo[*d*]thiazoles under various conditions via C─H functionalization strategy. On the other hand, synthesis of benzo[*b*]thiophene from thioamides is less explored. Recently, palladium catalyzed C─S bond forming reaction were reported at 90 ºC.

I was interested in studying a simple and practical method for regioselective benzo[*b*]thiophene synthesis via C─H thiolation. Recently, non-precious metals mediated carbon-heteroatom bond formation reactions are received much attention. Among these metals,

nickel is attractive because it's more abundance, less expensive and mild in nature. Although, Ni mediated C─S bond forming reactions were known, there was no report for Ni mediated S-heterocycles synthesis via C─H thiolation. Therefore, I initiated a systematic investigation of nickel and iodine mediated regioselective benzo[*b*]thiophene syntheses via C─H functionalization strategy.

The **part-A** of this chapter deals with the eco-friendly and inexpensive nickel mediated regioselective synthesis of 2-amino benzo[*b*]thiophenes **10** from thioamides **9**. The required thioamides **9** were synthesized by treating the anion of benzyl cyanides **12** with isothiocyanates **13** (Scheme 8).



12 **13** **9** (34 - 89%)

R^1= H, OMe,-OCH_2O, CF_3, Me,*t*Bu Cl, F, Br

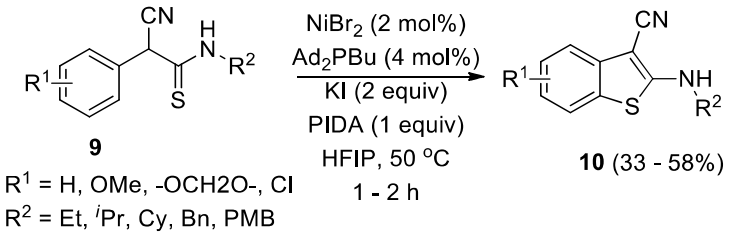
R^2= Ph, PMP, FC_6H_4, MeC_6H_4, $iPrC_6H_4$, Cy, iPr, Bn, PMB

Scheme-8

Thioamide **9a** [R^1 = OMe, R^2 = H] was taken as the model substrate for optimization studies. First, I performed the reaction in the presence of 2 mol% $NiBr_2$ and $PhI(OAc)_2$ (1 equiv) in dioxane solvent at room temperature. The reaction gave only 12% of 2-aminobenzo[*b*]thiophene **10a**, which was confirmed by all spectral analyses. Further, I screened various conditions and found that 2 mol% of $NiBr_2$, 1 equiv of $PhI(OAc)_2$ in the presence of additive KI (2 equiv) in HFIP solvent at 50 °C were appropriate condition where, the maximum yield of 62% was obtained.

During our literature survey, I found that nickel will functionalize both sp^2 and sp^3 C─H. Next, I turned our attention to regioselctive C─H bond functionalization of sp^2 C─H bond vs sp^3 C─H bond. I synthesized *N*-alkyl substituted thioamides by treating the anion of

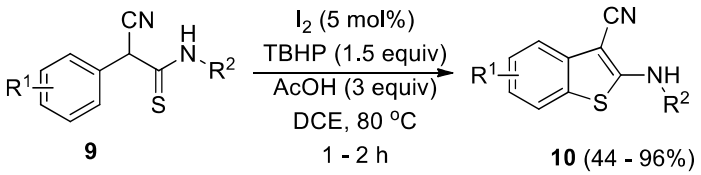
benzyl cyanides with alkyl isothiocyanates. These thioamides having two different types of C─H, one is sp^2 C─H and another is sp^3 C─H. Interestingly, when I carried out the reaction in the presence of optimized reaction conditions, I observed exclusively sp^2 C─H thiolated product over sp^3 C─H. In other words I observed exclusively benzo[*b*]thiophene **10** over benzo[*d*]thiazole **11**. However, when I used cataCXium®A ligand along with optimized conditions, I found that the yields of the corresponding benzo[*b*]thiophene **10** was increased. Thus, I used these optimized conditions and I synthesized several 2-aminobenzo[*b*]thiophenes **10** in moderate to good yields. (Scheme 9)



Scheme-9

The **part-B** of chapter three will deal with iodine mediated regioselective thiolation of thioamides **9**. 2-cyano-*N*-2-diphenylethanethioamide (**9b**) [R^1 = H, R^2 = Ph] was taken as a model substrate and initial reaction was carried out with 5 mol% iodine, 1.5 equiv TBHP in dioxane solvent at 80 ºC by using AcOH as an additive. Gratifyingly, the reaction was completed within 2 hours and delivered 73% of the corresponding 2-aminobenzo[*b*]thiophene **10b**, which was confirmed by NMR, Mass and X-ray analyses. Further, I screened several oxidants, solvents and I found that 5 mol% iodine, TBHP (1.5 equiv), in the presence of AcOH in DCE solvent at 80 ºC were appropriate for this thiolation.

With these optimized reaction conditions, I examined intramolecular thiolation of several thioamides **9**. The electron donating, withdrawing, alkyl substituted and halo substituted thioamides were smoothly converted into the corresponding benzo[*b*]thiophene derivatives **10** with good to excellent yields within shorter reaction time (Scheme 10).



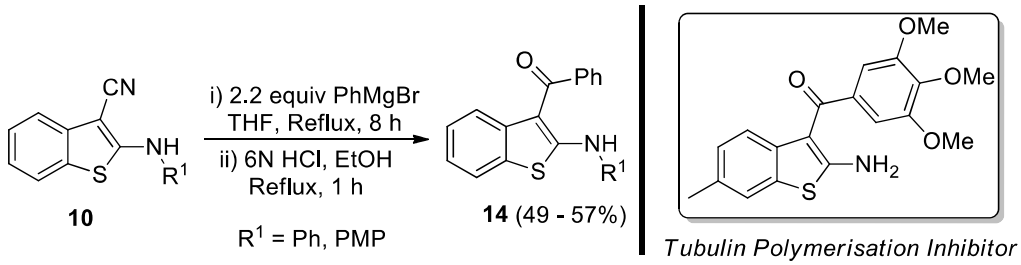
R^1 = H, OMe, -OCH2O-, Me, CF_3, Cl, Br, F

R^2 = Ph, PMP, MeC_6H_4, FC_6H_4, ^{i}Pr, Cy, Bn, PMB

Scheme-10

Next, I turned our attention to understand the mechanism of regioselective C─H thiolation process. Thus, I carried out the control experiments with different thioamides and found that acidic hydrogen adjacent to the nitrile group is the crucial for this thiolation process. Further, the experiment in the presence of radical scavenger TEMPO, did not give the desired product. Hence, I concluded that this reaction was proceeded through a radical pathway.

Finally, I synthesized the analogues of tubulin polymerization inhibitors by treating the 2-amino-3-cyanobenzo[*b*]thiophenes **10** with Grignard reagent (Scheme 11).

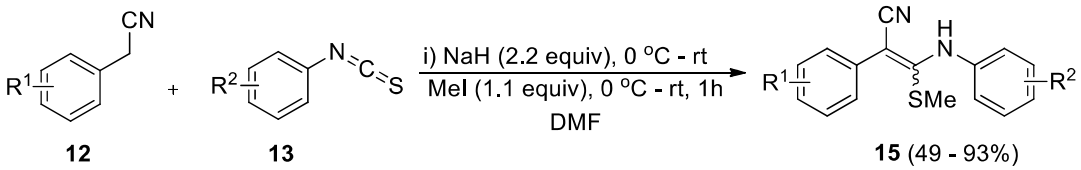


Scheme-11

The final fourth Chapter of the thesis will deal with the synthesis of indolo fused quinoline and quinolones via double hetroannulation strategy. Generally, these indolo fused quinolines can be synthesized from either indole or quinoline precursors. Only few reports were known where, indole and quinoline core consecutively constructed from the same precursors. Despite good yields, the reported methods are having limitations. To overcome those drawbacks, I designed a simple acyclic precursor, which can be derived from easily accessible starting materials. Our approach involves two steps 1) synthesis of synthetically and

biologically important 4-aminoquinolines 2) Syntheis of indoloquinolines *via* transition metal free intramolecular C─H amination of 4-aminoquinolines.

The part-A of this chapter will describe the bronsted acid mediated 4-amino quinoline synthesis from 3-aminoacrylonitrile. The required 3-aminoacrylonitrile derivatives **15** were synthesized by reacting the anion of benzyl cyanides **12** with aryl isothiocyanates **13** followed by methylation. (Scheme 12).

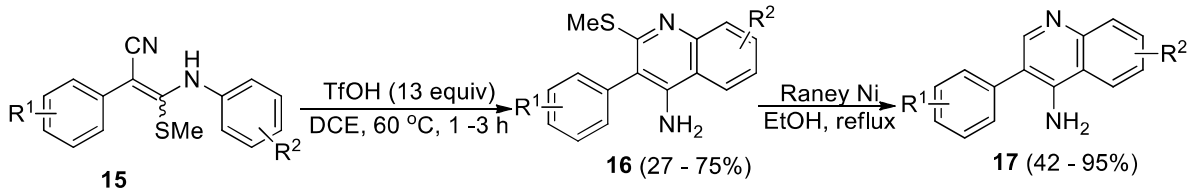


12 **13** **15** (49 - 93%)

R^1 = H, OMe, Me, ^{t}Bu, Cl, Br, NO_2, -C_4H_4-
R^2 = H, Me

Scheme-12

Next, I turned my attention to study optimization of reaction conditions for bronsted acid mediated Gattermann type of cyclisation of 3-aminoacrylonitriles. I screened several reaction conditions and found that TfOH in DCE solvent at 60 °C was the appropriate condition for this intramolecular cyclisation. With these optimized reaction conditions, I converted several 3-aminoacrylonitriles **15** into the corresponding 4-aminoquinoline derivatives **16** with moderate to good yield (27 -75%) in 2 -3 hrs reaction time. Later these 4-amino quinolines were desulfurized by using Raney Nickel (Scheme13).

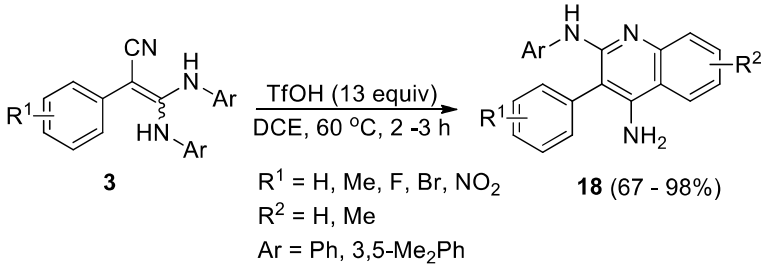


15 **16** (27 - 75%) **17** (42 - 95%)

R^1 = H, OMe, Me, ^{t}Bu, Cl, Br, NO_2, -C_4H_4-
R^2 = H, Me

Scheme-13

Further, I extended this methodology to ketene aminals to synthesize 2, 4-diamino substituted quinolines. (Scheme 13). These ketene aminals **3** afforded the corresponding amino quinoline 18 derivative with good to excellent yields (67-98%) (Scheme 14).

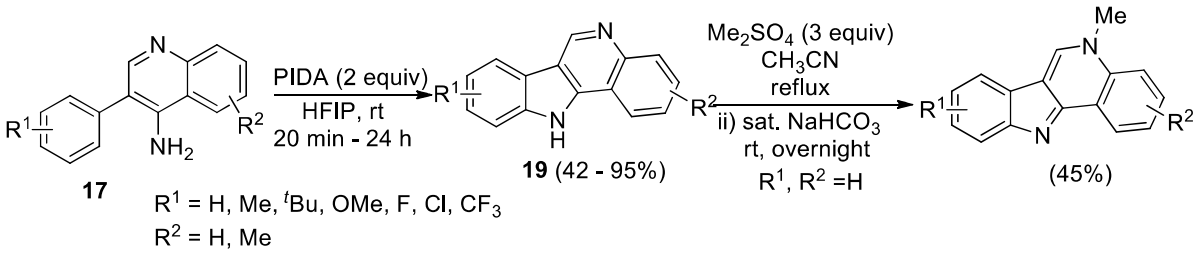


Scheme-14

The part-B of the chapter four deals with intramolecu**l**ar amination of 4-amino quinolines **17**, which leads to the formation of indolo quinoline derivatives. In literature, synthesis of carbazoles *via* intramolecular amination of 2-aryl anilines were well established. On the other hand, intramolecular amination of heteroaromatic compounds were less studied. Thus, I envisioned a simple methodology to synthesize indolo fused quinolines from 3-aryl-4-amino quinolines. Thus, I have taken 3-phenyl-4 aminoquinoline (**17a**) as a model substrate for the optimization studies. The first reaction was carried with 2 equivalents of $PhI(OAc)_2$ and 2 equivalents of K_3PO_4 in DMF at room temperature. To our delight, the desired indoloquinoline **19a** was observed in 77% yield in 1 hour. To improve the yield of the reaction I performed the reaction at high temperature (60 & 110 °C) and also in the presence of additives. Further, several solvents like DMSO, Dioxane, TFE and HFIP were screened. Interestingly, when I carried out the reaction in the presence of HFIP as solvent, the reaction yielded 95% of the indoloquinoline **19a** within 20 min. Surprisingly, I also observed the same yield in the absence of the base, suggested that base is not playing any role in this amination reaction.

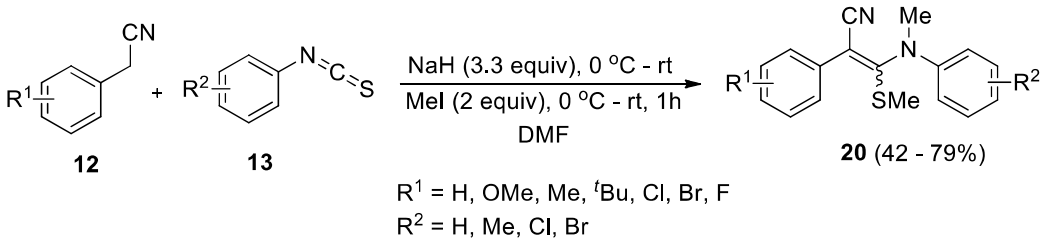
With these optimized reaction conditions, various indoloquinolines were synthesized with good to very good yield under optimized reaction conditions at room temperature. The electron deficient 4-amino quinolines **19** were also converted to the corresponding indolo fused

quinolines at 60 °C (Scheme 15). Further, one of the indolo quinoline was converted to isocryptolepine via known literature methods.



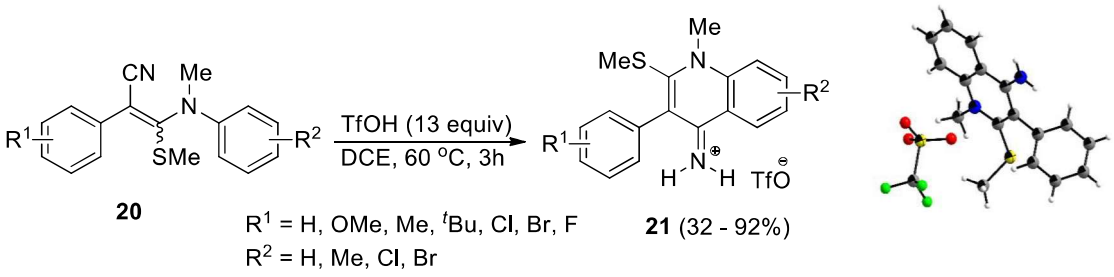
Scheme-15

The part-C of this Chapter will describe about the synthesis of indolo fused quinolones *via* intramolecular C─H imidation of 4-imino quinolines. The required imino quinolines were synthesized from 3-[methyl(aryl)amino]acrylo nitriles **20**. These 3-aminoacrylo nitriles **20** were obtained by treating anion of benzyl cyanides **12** with aryl isothiocyanates **13** followed by methylation (Scheme 16).



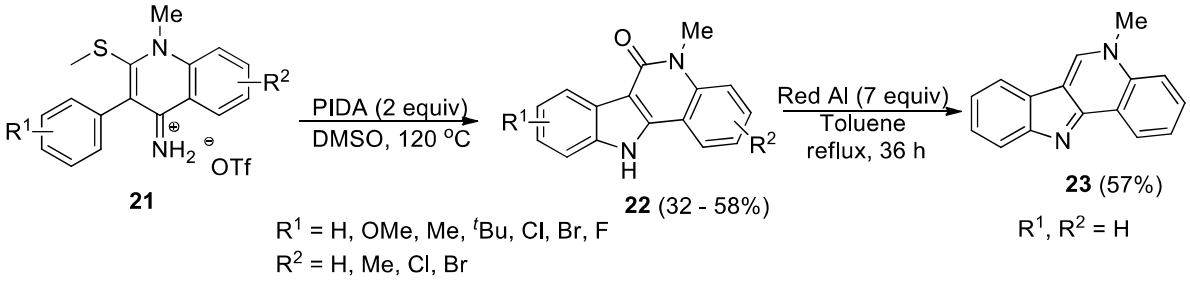
Scheme-16

Further, these 3-[methyl(aryl)amino]acrylo nitriles **20** were subjected to Gattermann type of nitrile cyclisation by using previously optimized conditions. The resulted 4-imino quinoline **21** products were obtained in the salt form with moderate to excellent yields (Scheme17).



Scheme-17

After synthesis of various 4-imino quinolines **21**, I moved to establish the optimization reaction conditions for intramolecular imidation. When I performed the reaction by using previously optimized conditions for intramolecular C─H amination, I did not observe even trace amount of the product. Interestingly, the reaction in DMSO solvent at 60 ºC afforded 36% C─H iminated product, which was characterized as an indolo fused quinolone derivative **22** by using spectral analyses. Further, I screened several oxidants, bases and solvents and found that the reaction with 2 equivalents of PIDA, 2 equiv K_3PO_4 in the presence of DMSO solvent at 120 ºC was delivered the maximum yield of the indolo quinolone derivative **22**. With these optimized reaction conditions, I investigated the intramolecular imidation of several 4-imino quinolines afforded the corresponding indolo quinolones in moderate to good yields (32 -58%)**.** Finally, one of the indolo fused quinolone (**22**) was converted in to isocryptolepine (**23**) by known literature method (Scheme 18).



Scheme-18

List of Figures

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
PIDA	(Diacetoxyiodo)benzene
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 the Indoloquinolines and Cryptolepine Derivatives

1.1 Introduction:

In the broad spectrum of heterocycles, indoloquinolines represent one of the important classes of heterocycles and found in various natural products.[1] These are unique structural moiety and exhibit strong antiplasmodial activity against chloroquine resistant P. *falciparum* species, which cause malaria in human beings.[2] Further, these types of molecules intercalate with DNA double helix and are responsible for changes in DNA conformation leading to inhibition of replication and transcription.[3] These moieties also exhibit various medicinal and pharmaceutical properties such as antimuscarinic, antibacterial, antiviral, antimicotic and antihyperglycemic properties.[4]

Since ancient times, West African people had been using roots of the *cryptolepine sanguinolenta* as a folk medicine for treatment of fever, amoebiasis, and malaria. This fact motivated the chemists to examine the chemical composition of this shrub, which revealed that this plant is rich of several indoloquinoline derivatives. In 1951, Gellert and co-workers isolated one of the indoloquinoline derivatives and named it as cryptolepine **1**.[5] They performed various structural elucidation studies and the proposed the structure of the newly isolated compound as 5-methyl-5*H*-indolo[3,2-*b*]quinoline **1** which is a linearly fused alkaloid. Interestingly, the synthesis of this molecule was reported in 1906, which is 45 years before its isolation from nature.[6]

In 1995, two independent research groups of Pousset and Sharaf reported the other isomer of indoloquinoline derivative and named it as isocryptolepine. The structure of this

compound was established as 5-methyl-5*H*-indolo[3,2-*c*]quinoline **2** by performing various structural elucidation studies.

Subsequently, in 1996, Pieter's and Shiff's groups independently reported the isolation of another isomer of indoloquinoline derivative. However, Pieter's group termed this newly isolated alkaloid as neocryptolepine.[7,8] Whereas, Shiff's group named it as cryptotackieine. They performed repeated column chromatographic experiments using

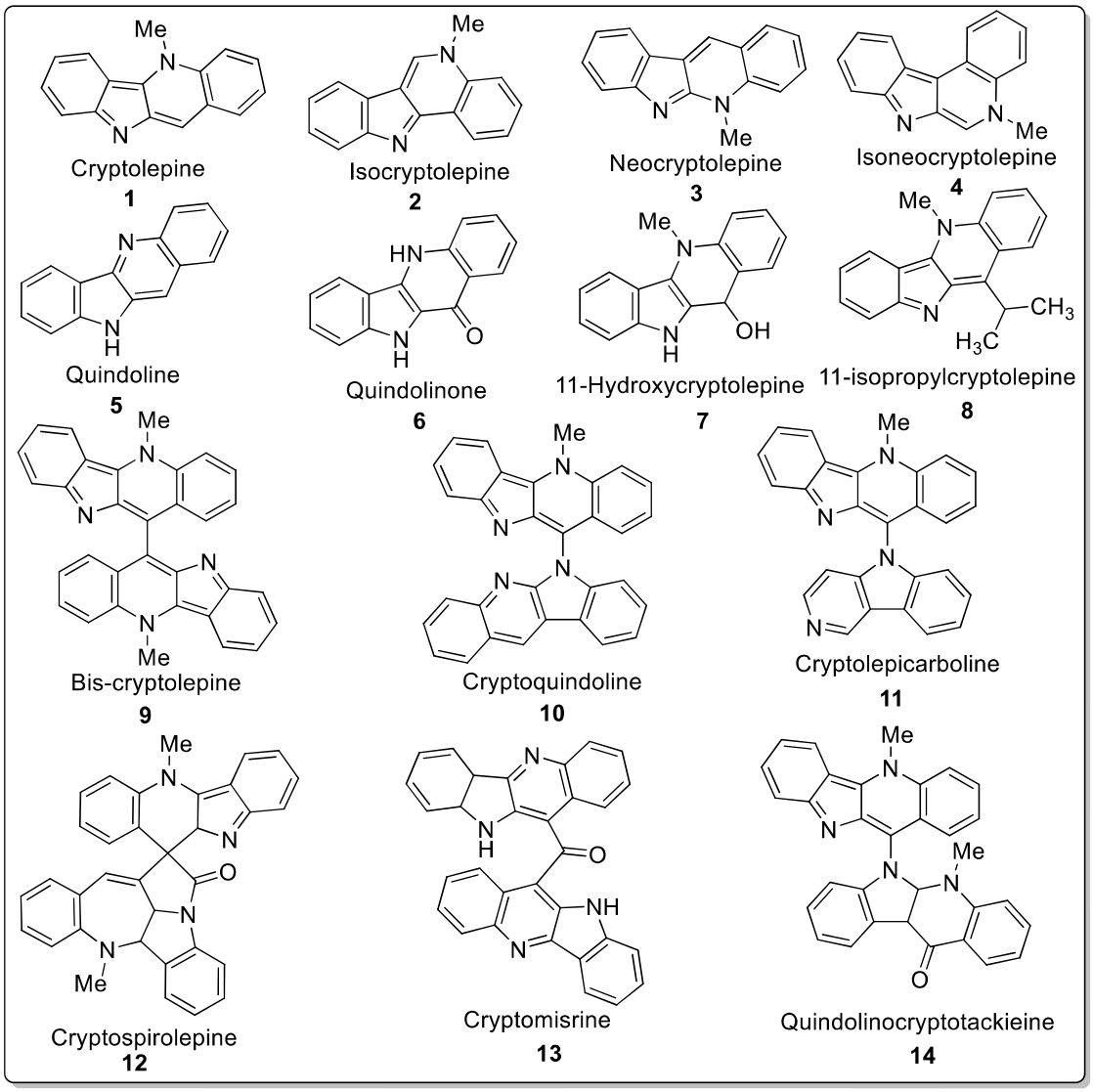


Figure 1.1: *Various Indoloquinoline Derivatives Isolated from Cryptolepine Sanguinolenta Along with one Unnatural Isoneocryptolepine* ***4***

silica/alumina and preparative RP-HPLC separations to obtain pure compound. They elucidated the structure of isolated compound as 5-methyl-5*H*-indolo[2,3-*b*]quinoline **3** with the aid of 1D- and 2D-NMR spectroscopic techniques. Same as cryptolepine, the synthetic approach for the synthesis of neocryptolpine was known in 1948 by Holt and co-workers.[9]

Other than these three isomers **1-3**, 10 more indoloquinoline alkaloids **5-14** were isolated from the same plant, which are shown in Figure 1.1.[10]

Interestingly, B. U. W. Maes and co-workers synthesized another isomer of indoloquinolines, which is an unnatural indoloquinoline derivative and termed it as isoneocryptolepine, where indole and quinoline moieties were fused resulting in the formation of 5-methyl-5*H*-indolo[2,3-*c*]quinoline **4**.[11] Further, the same group investigated the antiplasmodial activity of this newly synthesized compound.[12]

1.2 Previous Reports for the Synthesis of Various Indolo Fused Quinolines

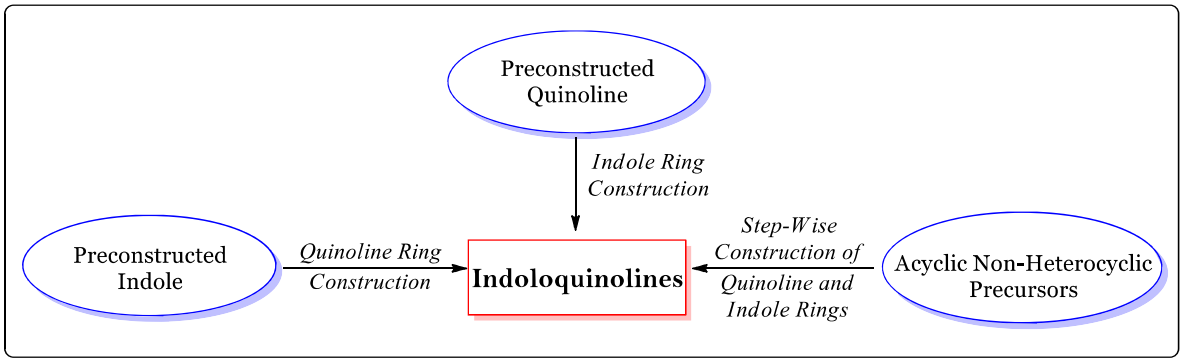


Figure 1.2: *Schematic Representation of Known Synthetic Approaches of Indoloquinolines*

Generally, three approaches are known in literature for synthesis of indoloquinolines. Those are

A) Construction of indole ring over prefunctionalised quinoline core.

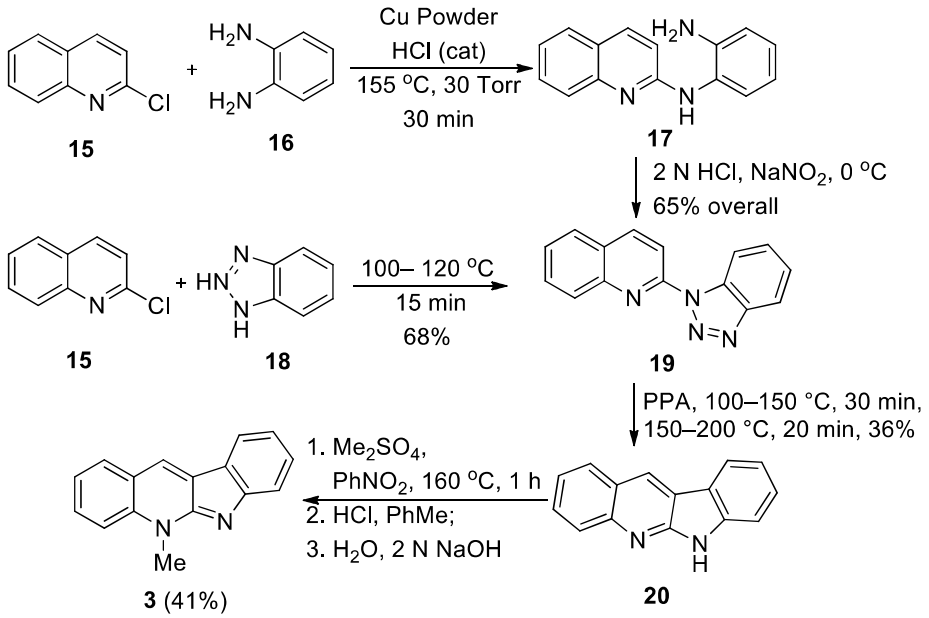
B) Construction of indole ring over prefunctionalised quinoline core.

C) Step-wise construction of indole and quinoline rings from non-heterocyclic acyclic precursors

All these three approaches were discussed individually in chronological order.

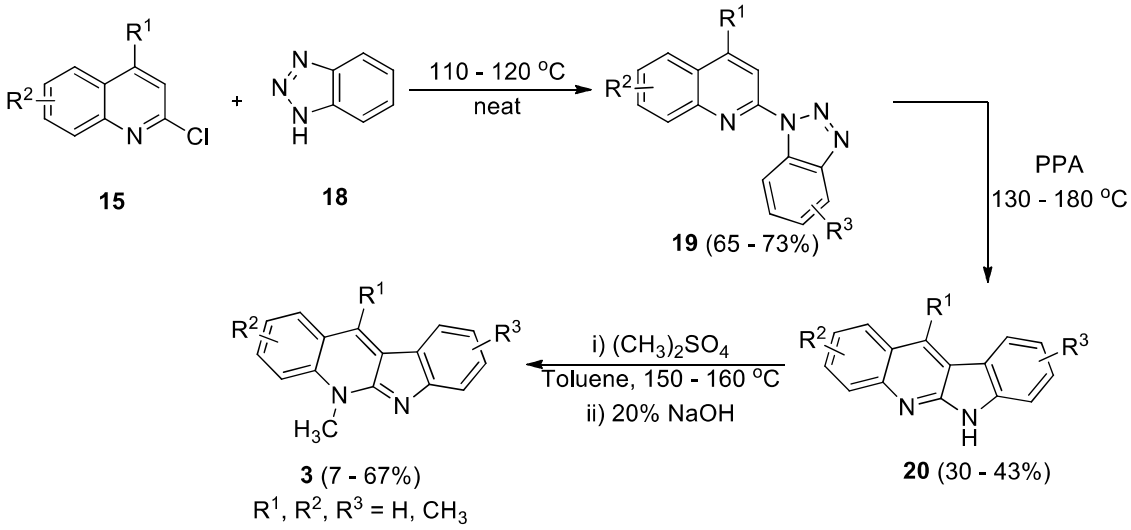
A) Construction of Indole Ring Over Prefunctionalised Quinoline Core.

As discussed earlier, the first synthesis of neocryptolepine **3** was reported way back in 1948 by Holt and co-workers, 40 years before its isolation and identification as a natural product.[9] Their strategy involves coupling between 2-chloroquinoline (**15**) and *o*-phenylene diamine (**16**) resulting in the formation of 2-anilinoquinoline **17**. Further, this aminoquinoline **17** was transformed into indoloquinoline **20** under Graebe–Ullmann conditions, where *in situ* generation of triazole **19** was followed by thermal decomposition of the traizole 1**9** in the presence of PPA. Finally, the resulted indolo[2,3-*b*]quinoline **20** was selectively *N*-methylated at quinoline ring over indole in the presence of dimethyl sulphate and nitrobenzene to furnish neocryptolepine **3** in 41% yield (Scheme 1.1).



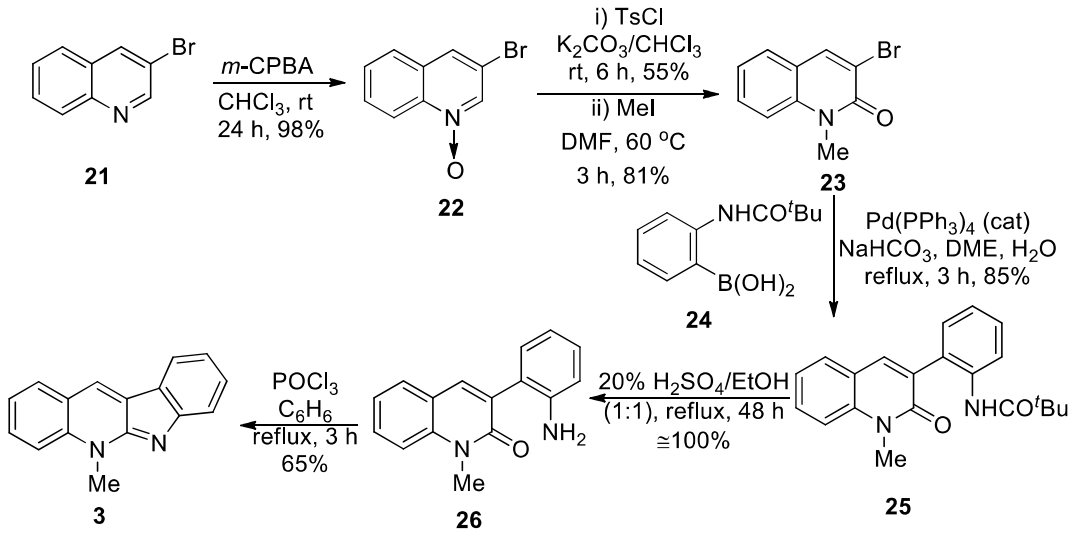
Scheme 1.1*: First Report for the Synthesis of Neocryptolepine*

In 1994, Peczyriska-Czoch and co-workers followed the similar strategy in a simplified manner to synthesize neocryptolepine derivatives **3**.[13] In this protocol, 2- choloquinolines **15** and benzotriazoles **18** underwent coupling reaction under neat reaction conditions resulted in the formation of C─N coupled product **19**, which on thermal decomposition followed by methylation gave neocryptolepine derivatives **3** (Scheme 1.2).



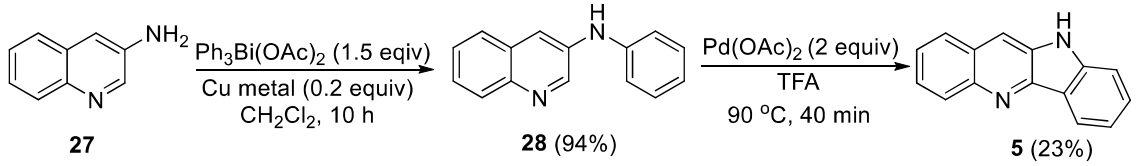
Scheme 1.2: *Synthesis of Neocryptolepines **3** via Thermal Decomposition of Benzotriazoles*

The first synthesis after the isolation of neocryptolepine **3** was reported in 1997 by G. Timari and co-workers.[14] They synthesized the desired indolo[3,2-*c*]quinoline derivative from 3-bromoquinoline (**21**) (Scheme 1.3). Initially, 3-bromoquinoline (**21**) was oxidized to the respective *N*-oxide derivative **22** in the presence of *m*-CPBA, followed by treatment with tosyl chloride afforded 2-quinolone derivative **25**. The *N*-oxide **22** was treated with tosyl chloride and followed by methylation affords quinolone **23**. The quinolone **23** underwent Suzuki coupling with 2-amidophenyl boronicacid **24** resulted in the formation of arylated product **25**. Further, deprotection of pivaloyl group under acidic conditions afforded amine **26**, which on treatment with $POCl_3$ gave desired neocryptolepine **3** in 65%.



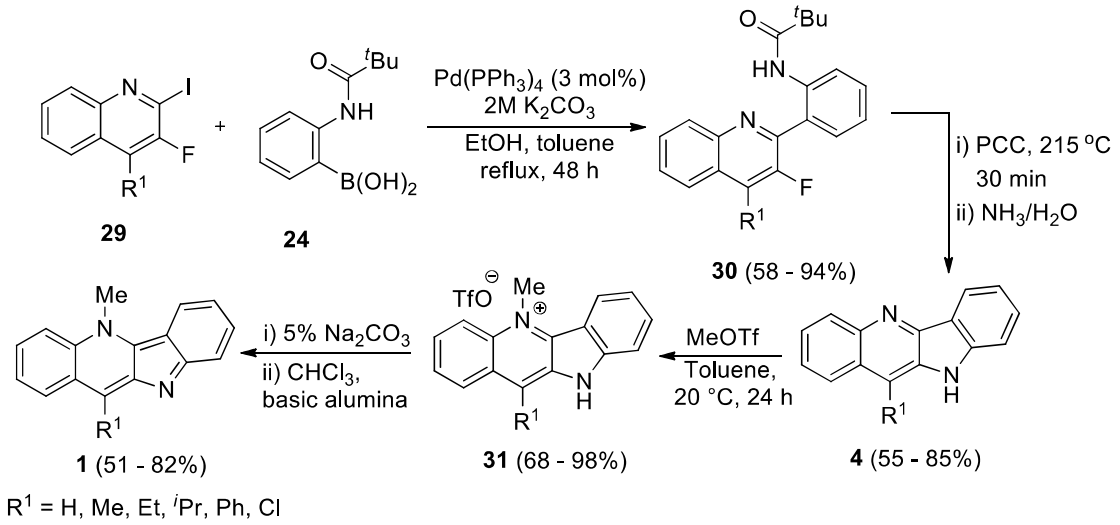
Scheme 1.3: *Suzuki Coupling Assisted Neocryptolepine Synthesis*

Subsequently, Y. Ablordeppy and co-workers reported the synthesis of quindoline **5** from 3-amino quinoline (**27**) (Scheme 1.4).[15] The first step of this protocol involves the *N*-arylation of amino quinoline **27** with triphenylbismuth diacetate followed by oxidative cyclisation resulted in the formation of quindoline **5** (Scheme 1.4).



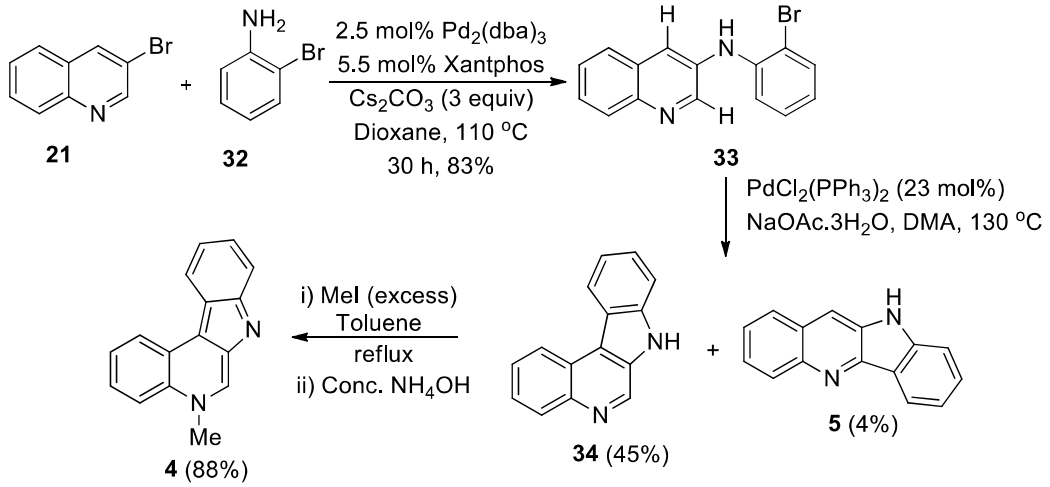
Scheme 1.4: *Palladium Mediated Intramolecular C-C bond formation of Anilinoquinolines*

P. Rocca and co-workers constructed quindolines **4** from 2-iodo-3-fluoro quinolines **29** *via* palladium mediated Suzuki coupling with *N*-protected 2-amino phenyl boronicacid **24** (Scheme 1.5).[16] The resultant coupled product **30** was converted to indolofused quinoline **4** by treating with pyridinium chloro chromate followed by MeOTf and Na_2CO_3 afforded cryptolepines **1** in moderate to very good yields.



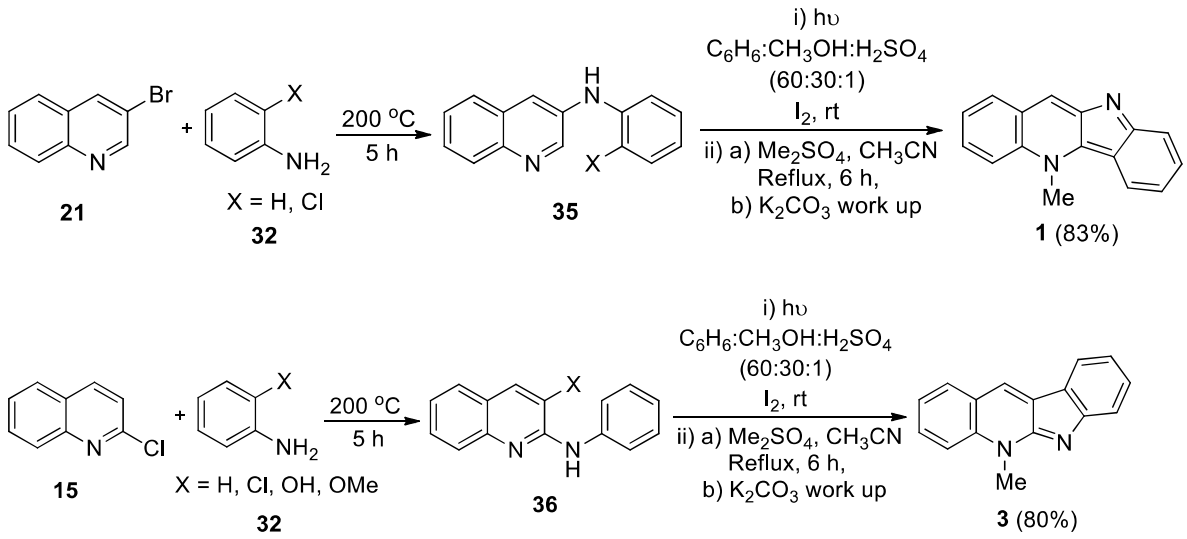
Scheme 1.5: *Hetero Ring Cross Coupling Mediated Cryptolepine Synthesis*

In 2005, Bert U. W. Maes and co-workers synthesized the other isomer of indoloquinoline alkaloid series.[11] This methodology involves the selective Buchwald-Hartwig amination between 3-bromo quinoline (**21**) and 2-bromo aniline (**32**) to afford bromo containing anilinoquinoline (**33**) in 83% yield. The resultant anilinoquinoline **33** was subjected to palladium mediated C−C bond formation reaction affording the indolo[2,3-*c*]quinoline (**34**) along with minor amount of indolo[3,2,-*c*]quinoline (**5**). Finally, indolo[2,3-*c*]quinoline was methylated to obtain the corresponding isoneocryptolepine derivative **4** (Scheme 1.6).

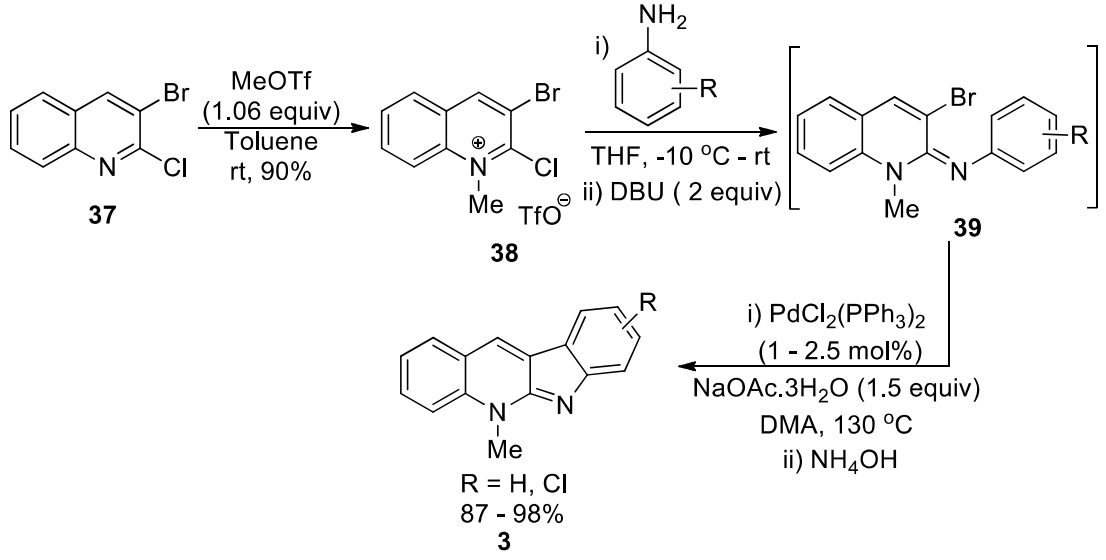


Scheme 1.6: *First report for the Synthesis of Isoneocryptolepine*

Next year, P. S. Mohan and his group investigated the photoannulation of anilino quinolines **75** & **77** to synthesize cryptolepine **1** and neocryptolepines **3** (Scheme 1.7).[17] The nucleophilic substitution reaction between halosubstituted quinolines **21** & **15** and anilines **32** afforded the corresponding anilinoquinolines **35** & **36** which upon photocyclization yielded the indoloquinolines. These indoloquinolines were selectively methylated by using known literature procedures to produce cryptolepine **1** and neocryptolepine **3** in very good yields.



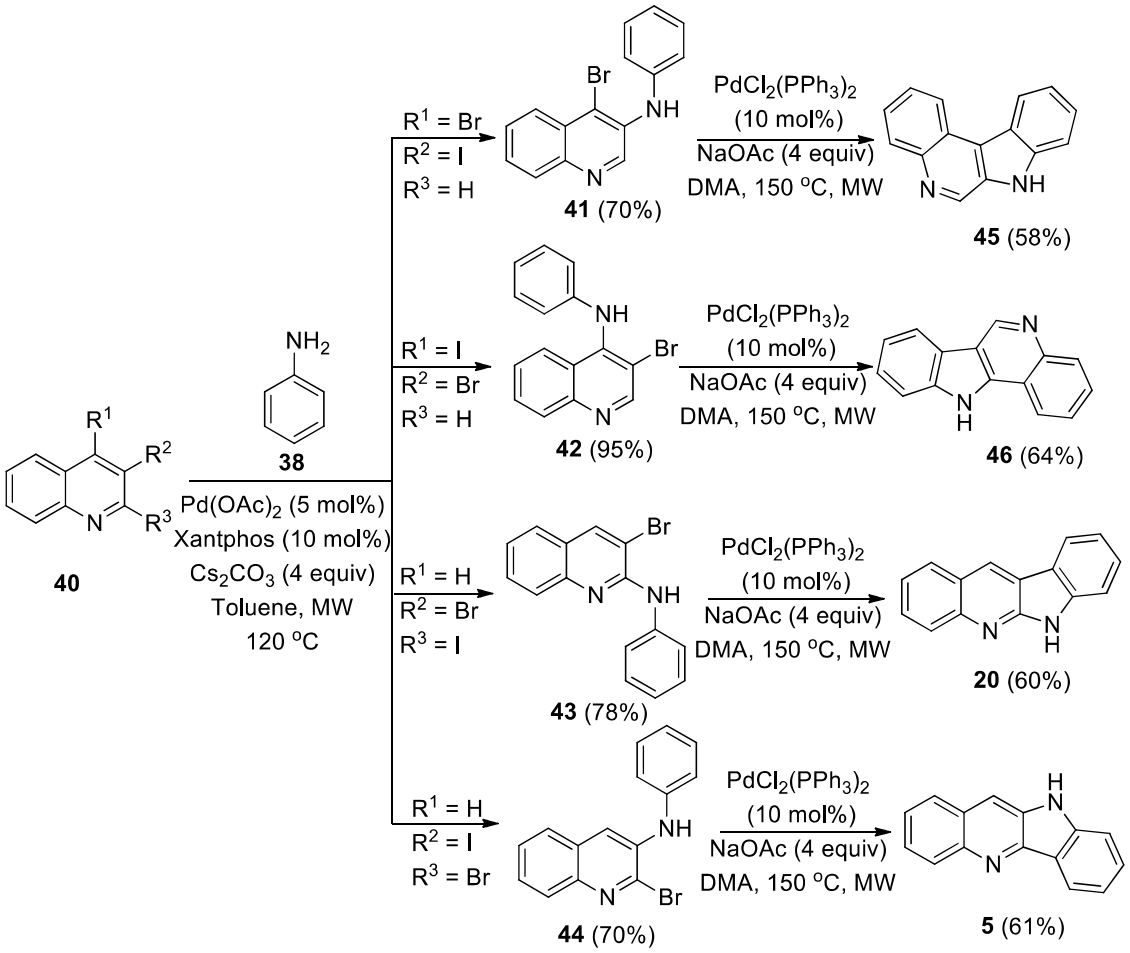
Scheme 1.7: *Synthesis of Cryptolepine Derivatives via Photocyclisation of Anilinoquinolines*



Scheme 1.8: *Pd Catalysed Intramolecular Direct Arylation of Bromo Anilinoquinolines*

Bert U. W. Maes and co-workers developed the palladium mediated synthesis of neocryptolpine derivatives from 3-bromo-2-chloro quinoline derivatives **37**.[18] Initially, dihaloquinoline **37** was methylated by reacting with MeOTf resulting in the formation quinolonium triflate **38**, which on reaction with aniline followed by palladium mediated Buchwald-Hartwig coupling reaction and intramolecular C─C bond formation to afford neocryptolepine derivatives **3** (Scheme 1.8).

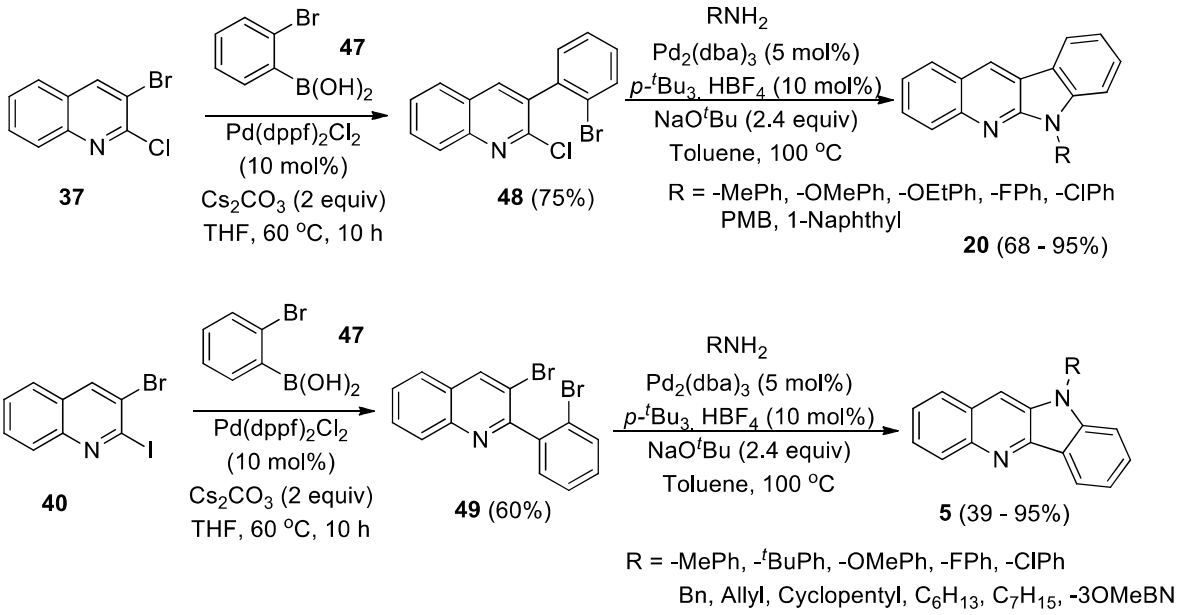
In 2013, Borgyani's group constructed the series of indoloquinolines **45-46**, **20** & **5** from haloquinolines **41-44** by consecutive C─N & C─C bond formation reactions.[19] Initially, the anilinoquinolines **41-44** were obtained by reaction of 1,2-dihalo quinoline **40** with anilines **38** under Buchwald-Hartwig reaction conditions. Further, these resulted anilinoquinolines **41-**



Scheme 1.9: *Palladium Catalysed Construction of Indoloquinolines from Haloquinolines*

44 were transformed into indolo fused quinolines **45**-**46**, **20** & **5** *via* palladium catalysed intramolecular C─C bond formation (Scheme 1.9).

Very recently, P. Langer's group examined the palladium mediated cascade Buchwald-Hartwig coupling of 3-(2-bromophenyl)-2-chloroquinoline (**48**) and 3-bromo-2-(2-bromophenyl)quinolines (**49**) (Scheme 1.10).[20] The required precursors were obtained by chemoselective Suzuki coupling of 2,3-dihalo quinolines **37** & **40** and 2-halo phenylboronic acid **47**. The resultant Suzuki coupled products were subjected to Buchwald-Hartwig reaction conditions to obtain the corresponding indoloquinolines **20** & **5**.

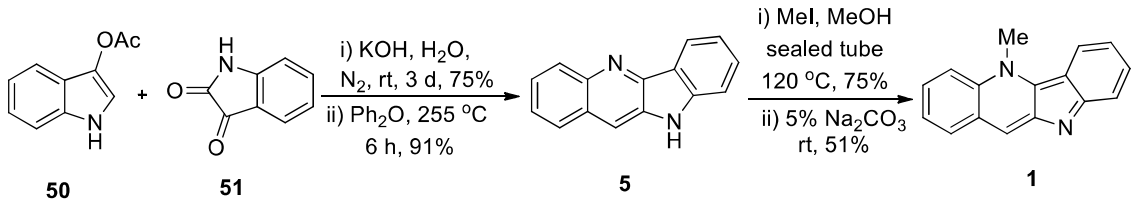


Scheme 1.10: *Sequential Suzuki & Buchwald-Hartwig Coupling to Indoloquinolines*

B) Construction of Quinoline Ring Over Prefunctionalised Indole core.

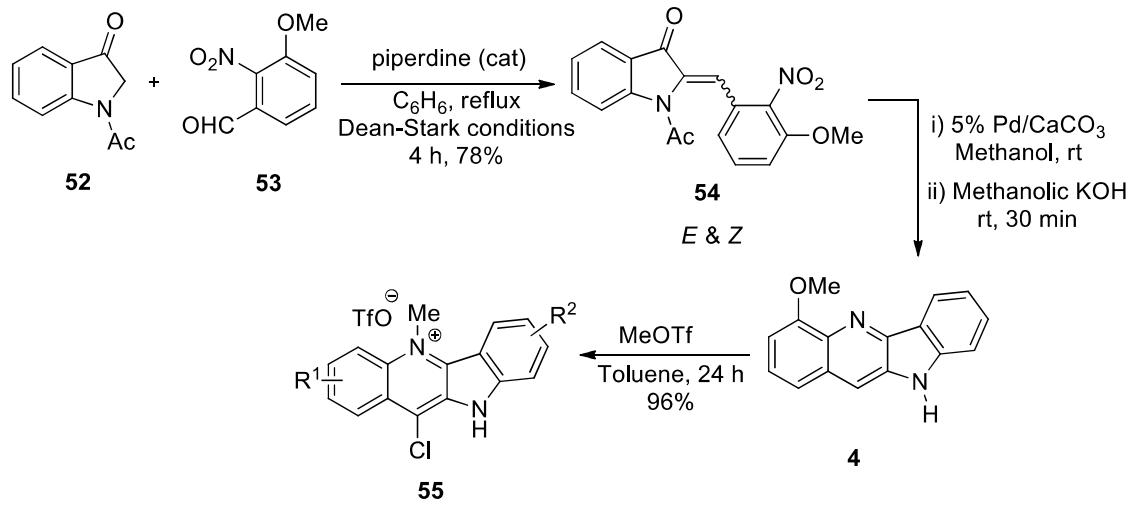
In 1998, D. E. Bierer and co-workers reported the synthesis of cryptolepine **1** from isatin (**51**) in three steps (Scheme 1.11).[21] In the first step, isatin (**51**) reacted with 3-indolyl acetate **50** in the presence of KOH afforded quindoline-11-carboxylic acid, which undergo decarboxylation upon heating produced indolo[3,2-*b*]quinoline (**5**) in 91%. The selective

methylation of this indoloquinoline **5** in the presence of MeI followed by treatment with Na_2CO_3 solution afforded desired cryptolepine **1**.



Scheme 1.11: *Synthesis of Cryptolepine from Isatin and 3-Indolyl Acetate*

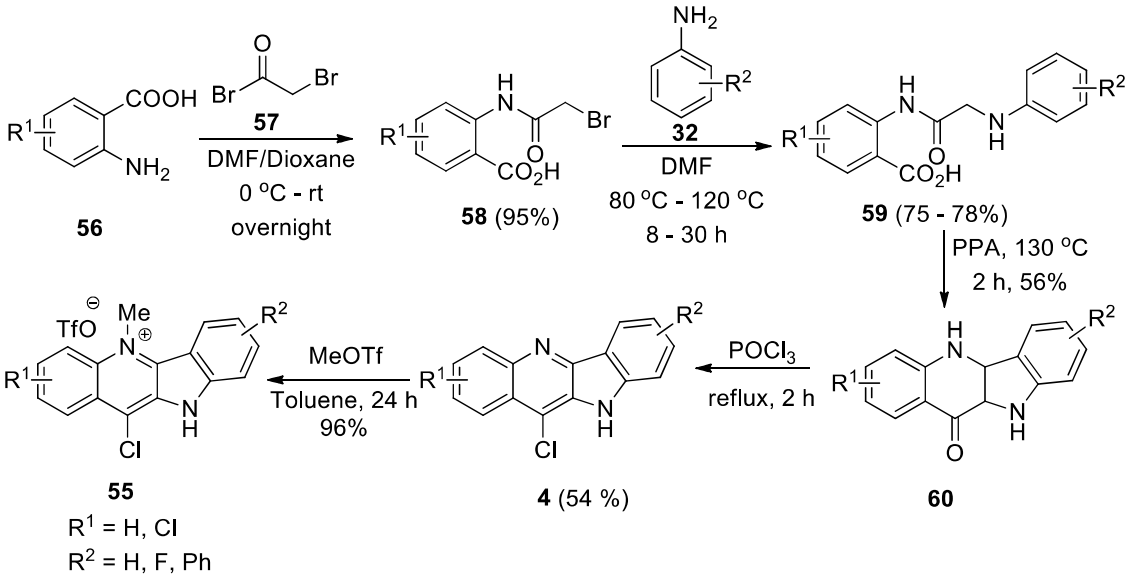
Subsequently, two different approaches were reported by the same group for the synthesis of these biologically active cryptolepine derivatives **1**.[22] In the first protocol, 1-acetyl-3-oxoindole **52** underwent Knoevenagel type of condensation with 2-nitrobenzaldehyde derivative **53** to afford the corresponding dehydrated product **54** in a mixture of *E* & *Z* isomers. Further, this Knoevenagel product **54** undergo reductive cyclisation in the presence of $Pd/CaCO_3$ and KOH to afford quindoline derivative **4**. Finally, this indoloquinoline **4** was converted into triflate salt of cryptolepine **55** in the presence of methyl triflate (Scheme 1.12).



Scheme 1.12: *Synthesis of Cryptolepines by Using Knoevenagel Approach*

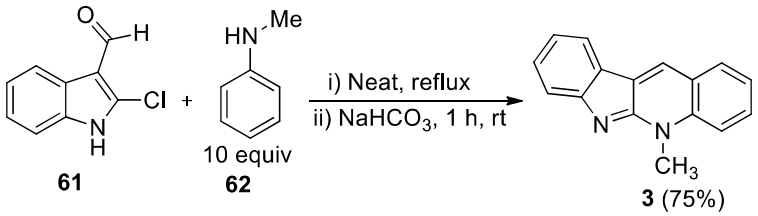
The second approach for synthesis of cryptolepine **1** was started with *N*-alkylation of anthranilic acid **56** with bromoacetyl bromide (**57**) in the presence of DMF, followed by

amination with anilines **32** provided the corresponding amide derivative **59**. In the presence of PPA under heating conditions this amide was transformed into quindolone derivative **60** within shorter reaction time. Next, indoloquinolone **60** was treated with $POCl_3$ followed by methyl triflate to obtain triflate salt of 11-chloro substituted cryptolepines **55** (Scheme 1.13).



Scheme 1.13: *PPA Assisted Cryptolepine Synthesis from Anthranilic Acid*

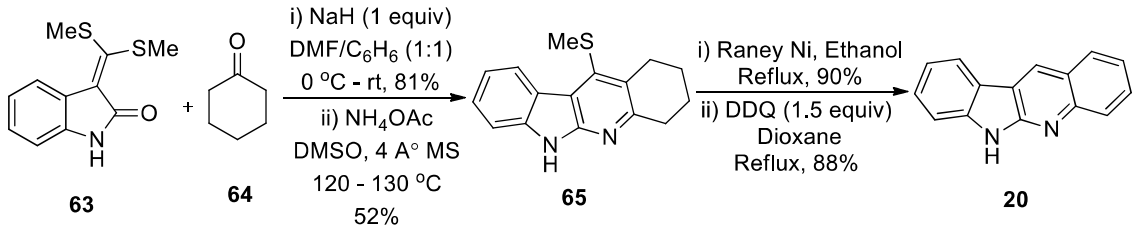
In 2004, J. Bergman's group demonstrated a simple one pot protocol for the synthesis of neocryptolepine **3**.[23] 2-Chloro-3-formyl indole **61** and *N*-methyl aniline (**62**) were refluxed under neat reaction conditions to afford hydrochloride salts of indoloquinoline, which on treatment with $NaHCO_3$ delivered neocryptolepine **3** in 75% yield (Scheme 1.14).



Scheme 1.14: *Single Step Protocol for the Synthesis of Neocryptolepine Derivatives*

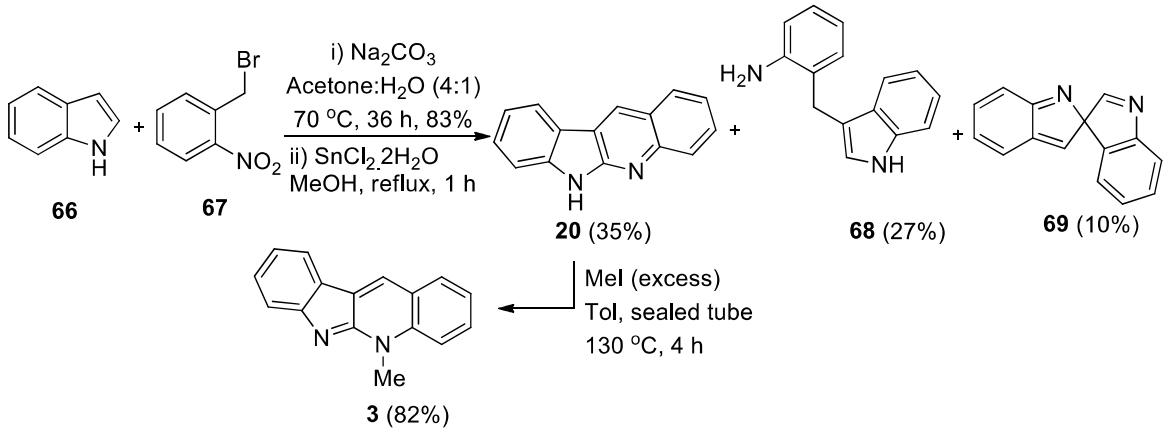
In the same year, Ila and co-workers developed a new protocol for the synthesis of indolo[3,2-*c*]quinoline **20** (Scheme 1.15).[24] The conjugate addition of enolate from

cyclohexanone (**64**) to bis[(methylthio)methylene]-2-oxindole **63** followed by heterocyclization by reacting with ammonium acetate yielded the tetracyclic compound **65** (Scheme 1.15). The resultant tetracyclic compound **65** was subjected to raney Ni, followed by aromatisation on treatment with DDQ yielding indolo fused quinoline **20** in 88% yield.



Scheme 1.15: *Synthesis of Indoloquinolines from Bis[(methylthio)methylene]-2-oxindoles*

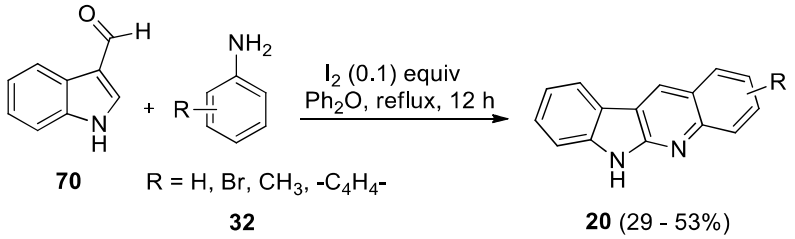
In 2008, B. Kundu's group reported the synthesis of neocryptolepine **3** *via* nucleophilic substitution of 2-nitrobenzylbromide (**67**) and indole (**66**) yielding the nitro intermediate which upon further reductive cyclization yielded a mixture of three compounds (Scheme 1.16).[25] Among them, indolo fused quinoline **20** was the major product along with uncyclized product **68** and the spiroindole **69**. Finally, this indolo[2,3-*b*]quinoline **20** was transformed into neocryptolepine **3** under established methylation conditions.



Scheme 1.16: *One-pot Protocol for Intramolecular Cyclization of 2-Substituted Nitroarenes*

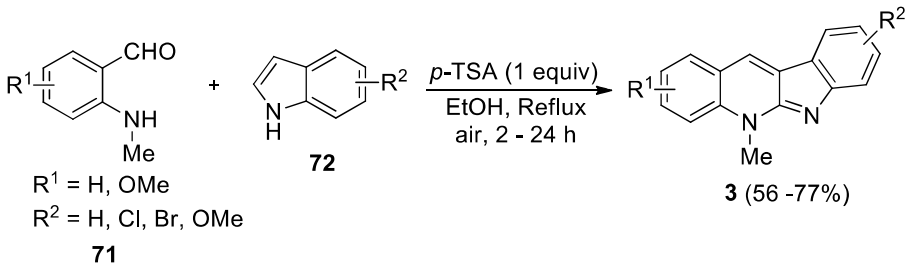
Consequently, S. G. Tilve's group came up with a simple strategy to synthesize these biologically important tetracyclic compounds under transition metal free conditions.[26] In this approach indolo-3-carboxaldehyde (**70**) was treated with various anilines **32** to afford the

corresponding imines, which upon nucleophilic attack by aniline, followed by iodine catalyzed intramolecular annulation yielded indoloquinolines **20** in poor to moderate yields (Scheme 1.17).



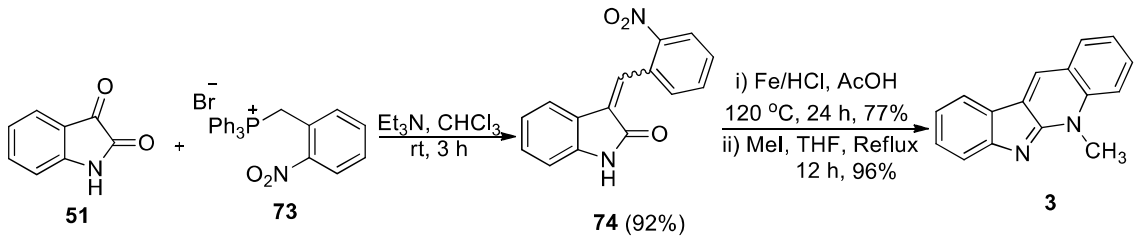
Scheme 1.17: *Iodine Mediated One Pot Protocol for Synthesis of Indoloquinolines*

In 2011, D. Seidel and co-workers developed a novel approach for the rapid construction of neocryptolepines **3** in one-pot condition.[27] In this methodology, the desired neocryptolepines **3** were obtained by treating *N*-methyl protected 2-amino benzaldehydes **71** with indoles **72** upon treatment with mild bronsted acid under heating conditions (Scheme 1.18).



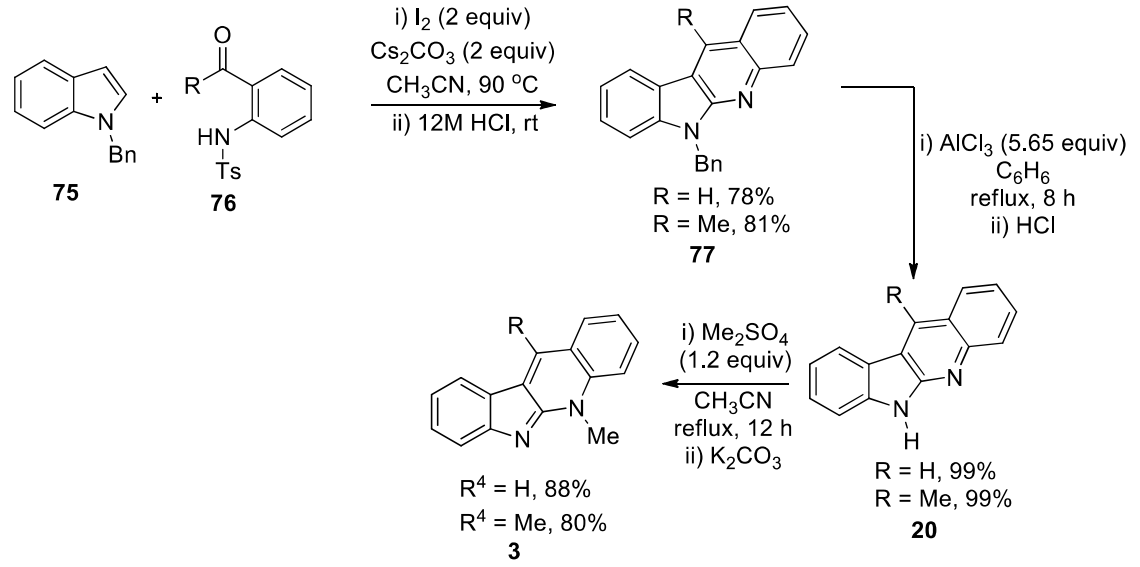
Scheme 1.18: *Protocol for Synthesis of Neocryptolepines from 2-Amino Benzaldehydes*

S. G. Tilve and co-workers described a simple protocol for the synthesis of neocryptolepine **3** in four steps from isatin **51** (Scheme 1.19).[28] In the current methodology, (2-nitrobenzyl)triphenylphosphonium bromide **73** undergoes Wittig reaction with isatin (**51**) upon treatment with Et_3N resulted in the formation of corresponding Wittig product **74**. This resultant product was subjected to reductive cyclisation followed by selective methylation delivering neocryptolepine **3**.



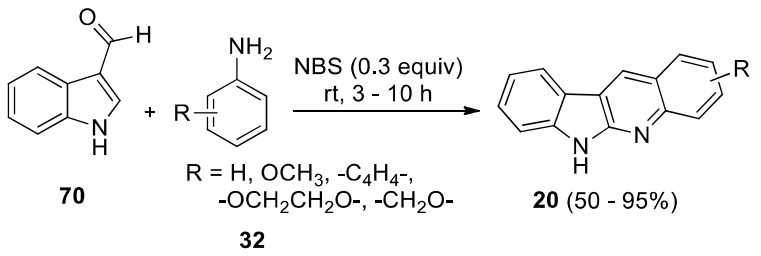
Scheme 1.19: *Synthesis of Neocryptolepines via Wittig reaction and reductive Cyclization*

Y. M. Liang and co-workers followed Seidel's approach to construct the indolo[2,3-*b*]quinolines 2**0** *via* iodine mediated hetero annulation of *N*-benzyl protected indoles **75**, 2-amino benzaldehydes and 2-amino acetophenone **76** (Scheme 1.20).[29] The resulted benzyl protected indoloquinoline **77** was deprotected under Lewis acid conditions leading to the formation of 11-substituted-6*H*-indolo[2,3-*b*]quinoline **20**, which was methylated by using known literature methods to afford neocryptolepine **3** with very good yields.



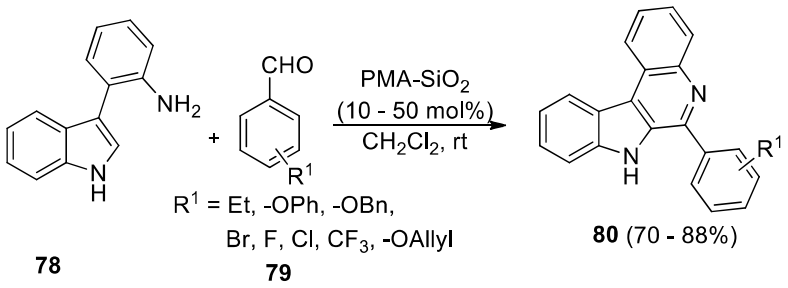
Scheme 1.20: *Transition Metal Free Annulation of Indoles to Indolo[2,3-b]quinolines*

R. G. Vaghei & co-workers followed the Tilve's approach for the synthesis of the indolo[2,3-*b*]quinolines from indole-3-carboxaldehyde **70** by using NBS as catalyst (Scheme 1.21).[30]



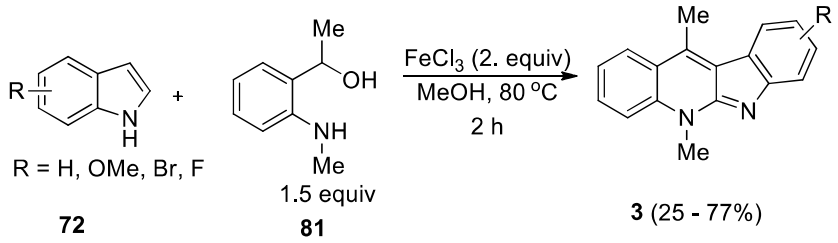
Scheme 1.21: *NBS Promoted Indoloquinoline Synthesis from Indole-3-Carboxaldehyde*

In 2015, P. Srihari and co-workers used a Pictet-Spengler approach to synthesize indolo[2,3-*c*]quinolines **80** from 2-(1*H*-indol-3-yl)aniline (**78**).[31] In contrast to the classical Pictet-Spengler reaction, they used PMA coated SiO_2 as a catalyst for this reaction (Scheme 1.22).



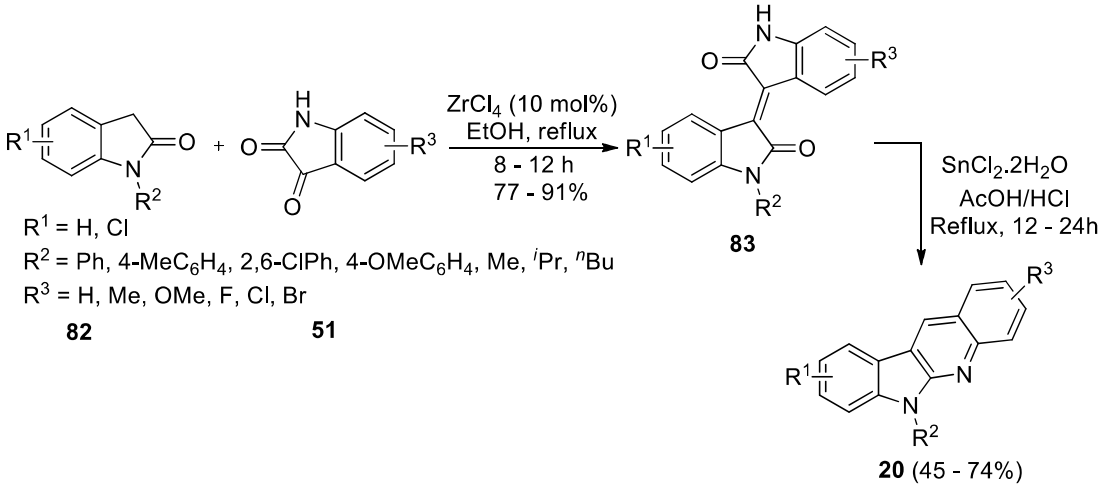
Scheme 1.22: *Pictet-Spengler Approach for the Synthesis of Indolo Fused Quinolines*

Consequently, Z. Wang and co-workers demonstrated the synthesis of neocryptolepines **3** under Lewis acid conditions.[32] The indole **72** reacted with aminophenyl alcohol **81** in the presence of $FeCl_3$ at 80 ºC to afford desired product **3** (Scheme 1.23).



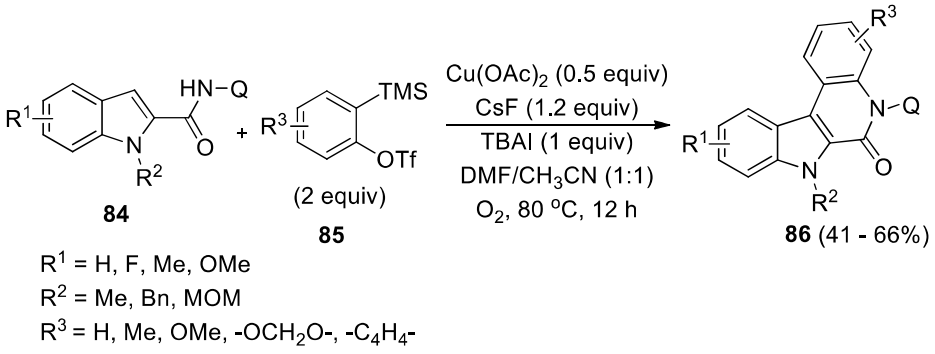
Scheme 1.23: *Neocryptolepine Synthesis from 2-Amino Benzyl alcohol & Indole*

In 2017, G. Yin and co-workers described a new protocol for the synthesis of indolo[2,3-*b*]quinolines **20** from isoindigos **83** *via* simultaneous construction of pyrrole and pyridine rings.[33] The required isoindigos **83** were obtained by treating the oxindole **82** with isatin **51** with catalytic amount of $ZrCl_4$. The resulted condensation products were treated with Lewis acid $SnCl_2$ to afford neocryptolepine derivatives **20** in 45- 74% yield (Scheme 1.24).



Scheme 1.24: *Synthesis of Indolo Fused Quinolines from Isoindigos*

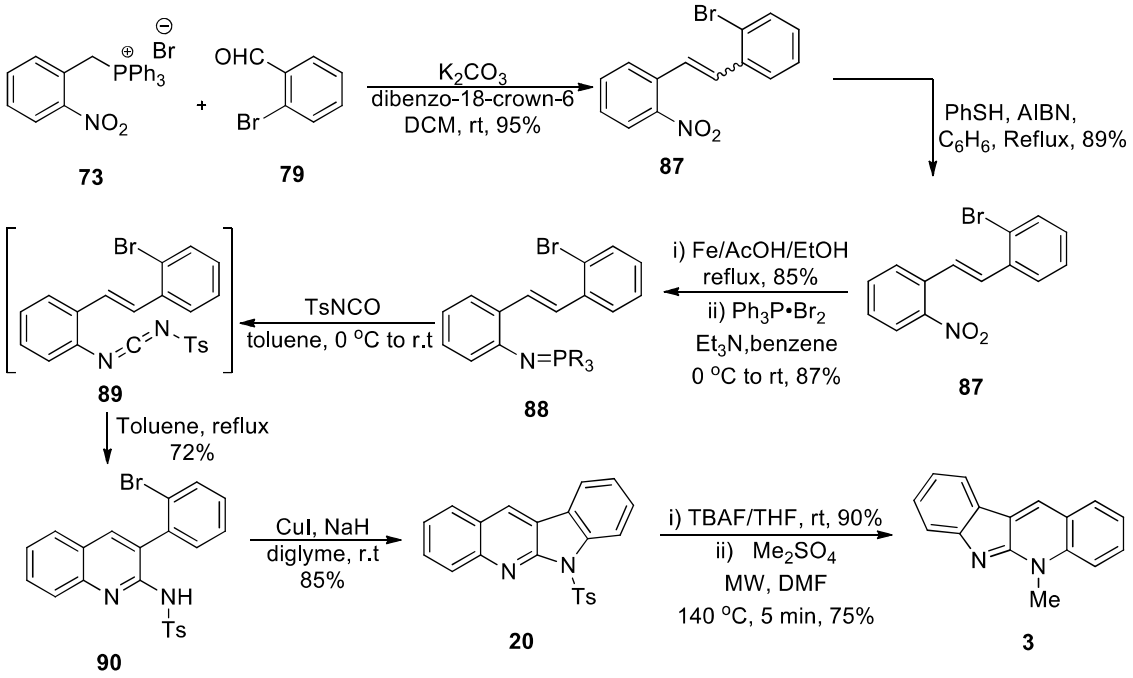
Recently, S. Y. Zhang and co-workers investigated directing group assisted copper mediated hetero annulation of indole-2-carboxamides **84** (Scheme 1.25).[34] This is an efficient protocol for the synthesis of isoneocryptolepine derivative **86** from the indole-2-carboxamides **84** and aryne **85** precursor *via* cascade C─H/N─H annulation pathway.



Scheme 1.25: *Copper Mediated C─H/N─H Annulation of Indole-2-carboxamides*

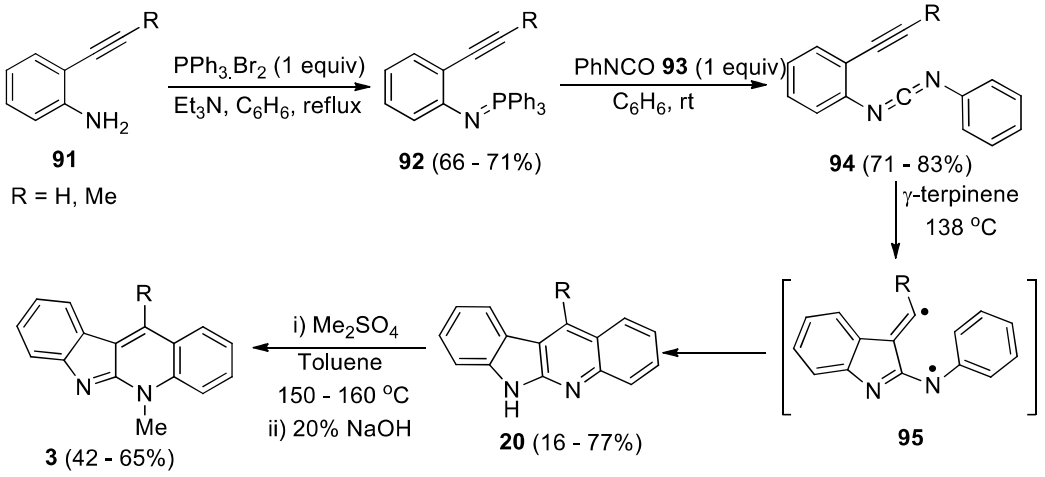
C) **Step-Wise Construction of Indole and Quinoline Rings From Non-Heterocyclic Acyclic Precursors**

In 1999, P. Molina and co-workers developed a first synthetic protocol for the synthesis of neocryptolepine **3** from two acyclic precursors *via* stepwise formation of the quinoline and indole ring in a consecutive manner (Scheme 1.26).[35] Initially, (2-nitrobenzyl) triphenylphosphonium bromide **73** underwent Wittig reaction with 2-bromo benzaldehyde (**79**) resulted in the formation of stilbene derivative **87** with a mixture of *E* & *Z* isomers. The *Z* isomer was isomerised exclusively into *E*-stilbene **87** on treatment with thiophenol and AIBN. The 2-nitrostilbene **87** was reduced by iron followed by treatment with triphenylphosphine dibromide yielded iminophosphorane **88** in 87% yield. The iminophosphorane **88** was treated with tosyl isocyanate affords carbodiimide derivative **89**, which underwent cyclization to deliver 2-amino-3-bromoaryl quinoline **90**. The desired indoloquinoline **20** was obtained from quinoline **90** *via* Cu mediated intramolecular cross-coupling. The resultant product **20** was detosylated and followed by methylation gave rise to neocryptolepine **3**.



Scheme 1.26: *Synthesis of Neocryptolepine via Imino Phosphorane Intermediate*

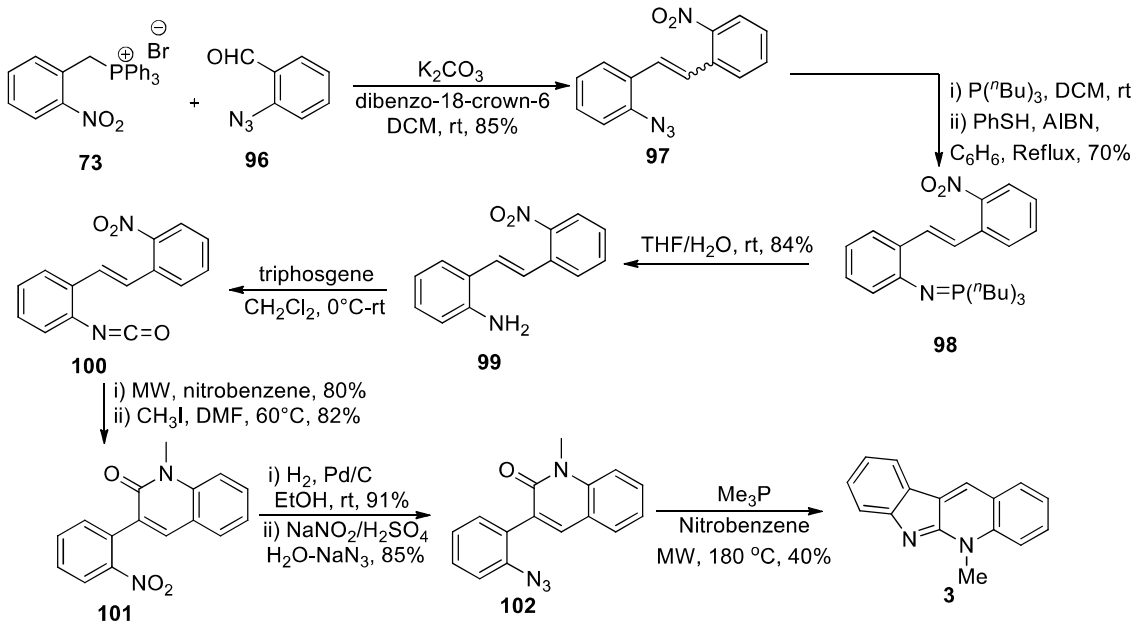
Subsequently, K. K. Wang and co-workers followed the similar strategy to synthesize neocryptolepine **3** from 2-(1-alkynyl)anilines **91**.[36] The alkyne **91** was treated with triphenylphosphonium bromide followed by addition of phenyl isocyanate yielding carbodiimide derivative **94**. The 2-alkynyl carbodiimide **94** underwent biradical cyclisation in the presence of γ-terpinene giving rise to indolo[2,3-*b*]quinoline **20**, which was selective *N*-methylation at quinoline affording the desired neocryptolepine **3** (Scheme 1.27).



Scheme 1.27: *Synthesis of Indoloquinolines via Biradical Cyclisation of 2-Alkynl Carbodiimide Derivatives*

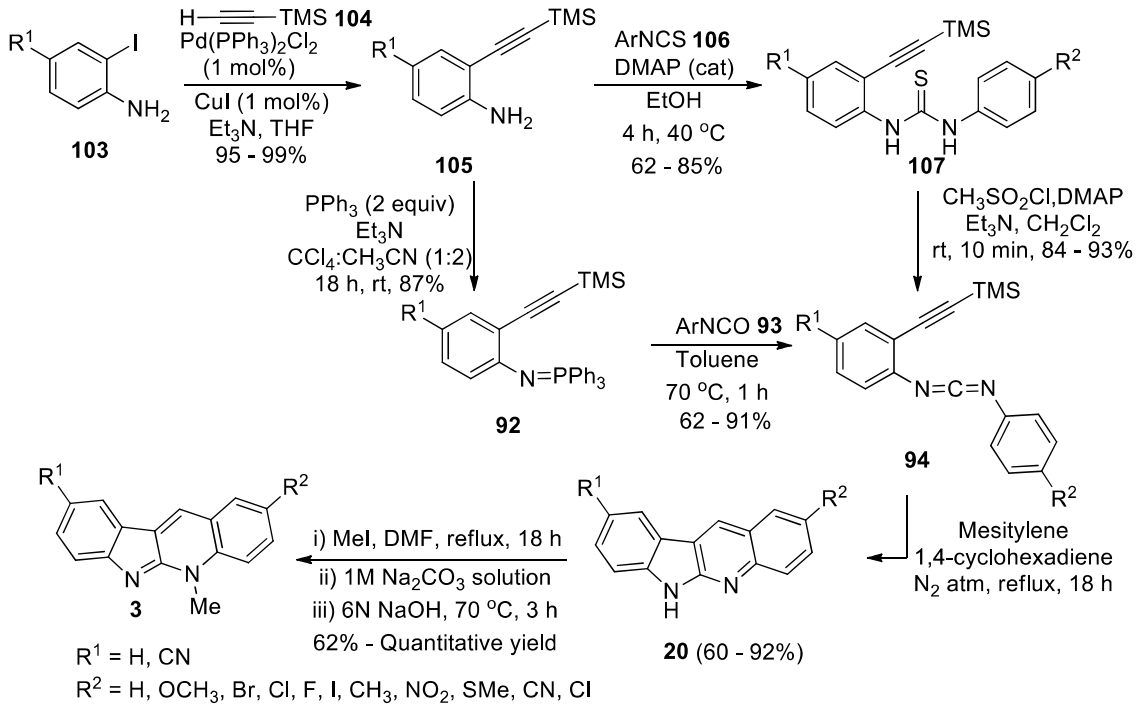
In the same year, P. Molina and co-workers again came up with an alternate strategy to synthesis of neocryptolepine **3** in eight steps (Scheme 1.28).[37] Firstly, Wittig reaction between (2-nitrobenzyl)triphenylphosphonium bromide **73** and *o*-azidobenzaldehyde (**96**) resulted in the formation of stilbene derivative **97** as *E*:*Z* isomeric mixture. The resultant derivative **97** was subjected to tributyl phosphine resulting in the formation of iminophosphorane **98** followed by isomerisation with PhSH/AIBN affording the transformed *E*-isomer of stilbene derivative **98** exclusively. The resultant stilbene derivative **99** was converted into quinolin-2-one derivative **101** by sequential treatment with triphosgene and microwave-promoted cyclization of the resulting isocyanate **100**. Later, this nitro quinolone was reduced, diazotised followed by

cyclisation *via in situ* generated iminophosphorane in the presence of trimethyl phosphine afforded the neocryptolepine **3** in 40% yield.



Scheme 1.28: *Eight Steps Protocol for the Synthesis of Neocryptolepine*

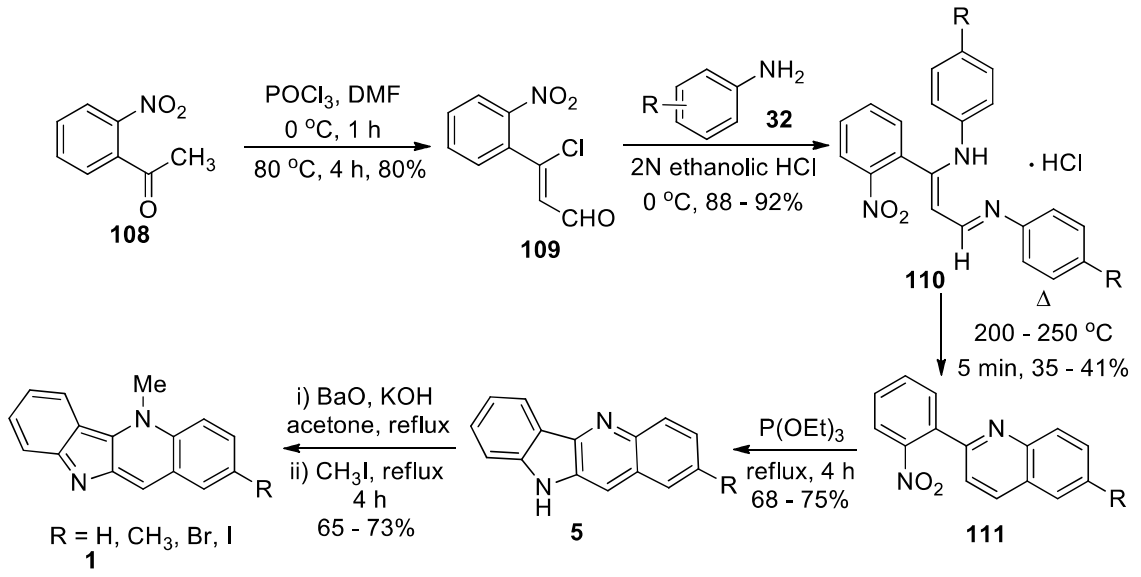
In 2002, Pieters and co-workers followed the Wang's approach for the synthesis of



Scheme 1.29: *Preparation of Neocryptolepines from o-Alkynyl Carbodiimide Derivatives*

series of neocryptolepine derivatives **3** *via in situ* generation of carbodiimides **94** from 2-alkynyl anilines **105** followed by biradical cyclization (Scheme 1.12).[38] The detailed synthetic steps were shown in Scheme 1.29.

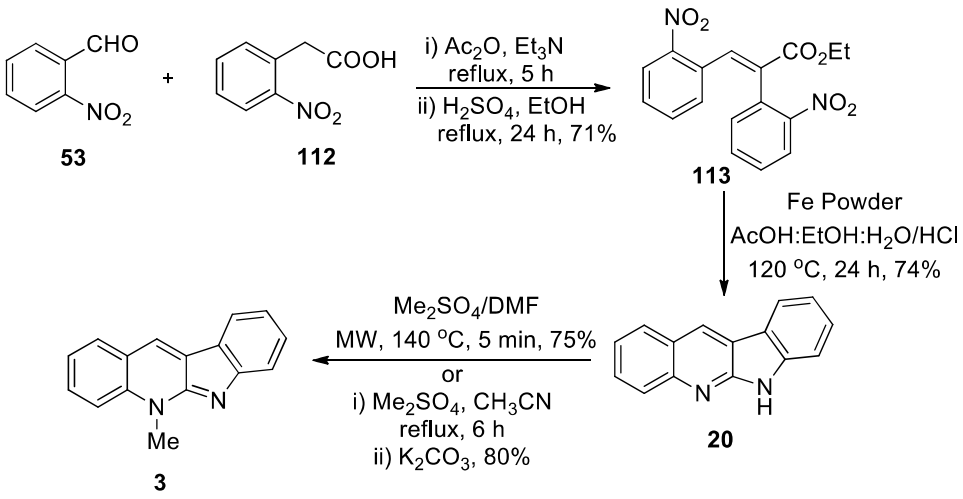
In 2006, J. K. Ray and co-workers reported the synthesis of cryptolepine **1** from 2-nitroacetophenone (**108**).[39] Firstly, 2-nitroacetophenone(**108**) undergo Vilsmeier–Haack reaction to yield the *β*-chlorocinnamaldehyde **109**, which on reaction with excess amount of anilines **32** delivered the corresponding enamines **110** in the form of hydrochloride salt, followed by thermal cyclisation of these enamines **110** affording the quinolines **111**, which on treatment with triethyl phosphite gave indolofused quinolines **5**. Finally, these indoloquinolines **5** were methylated selectively to afford cryptolepine derivatives **1** (Scheme 1.30).



Scheme 1.30: *Thermal Cyclization of 3-Arylamino-3-(2-nitrophenyl)-propenal Schiff Base*

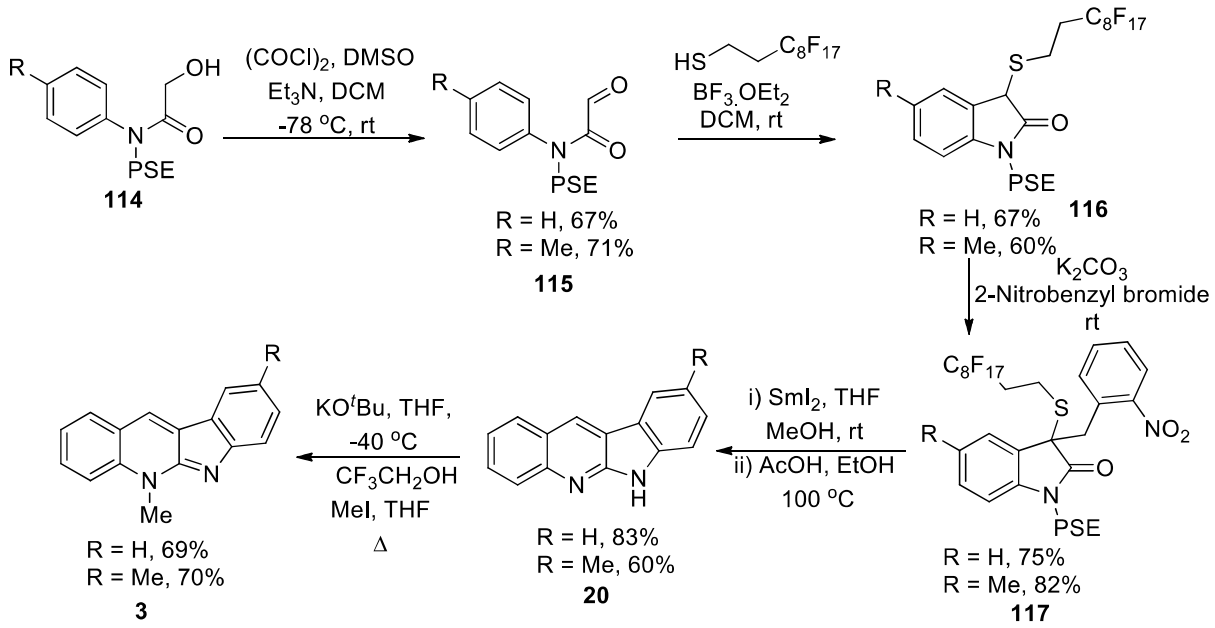
Consequently, S. G. Tilve and co-workers described a simple protocol for the synthesis of neocryptolepine **3** *via* tandem double reductive cyclisation.[40] Their strategy involved a Perkin reaction of 2-nitro benzaldehyde (**53**) and 2-nitrobenzoic acid (**112**) followed by esterification resulted in the formation of *α,β*-unsaturated ester **113**, which on treatment with

iron in acidic conditions at 120 °C underwent double reductive cyclisation to afford precursor of neocryptolepine **3** (Scheme 1.31).



Scheme 1.31: *Synthesis of Neocryptolepine via Double Reductive Cyclization*

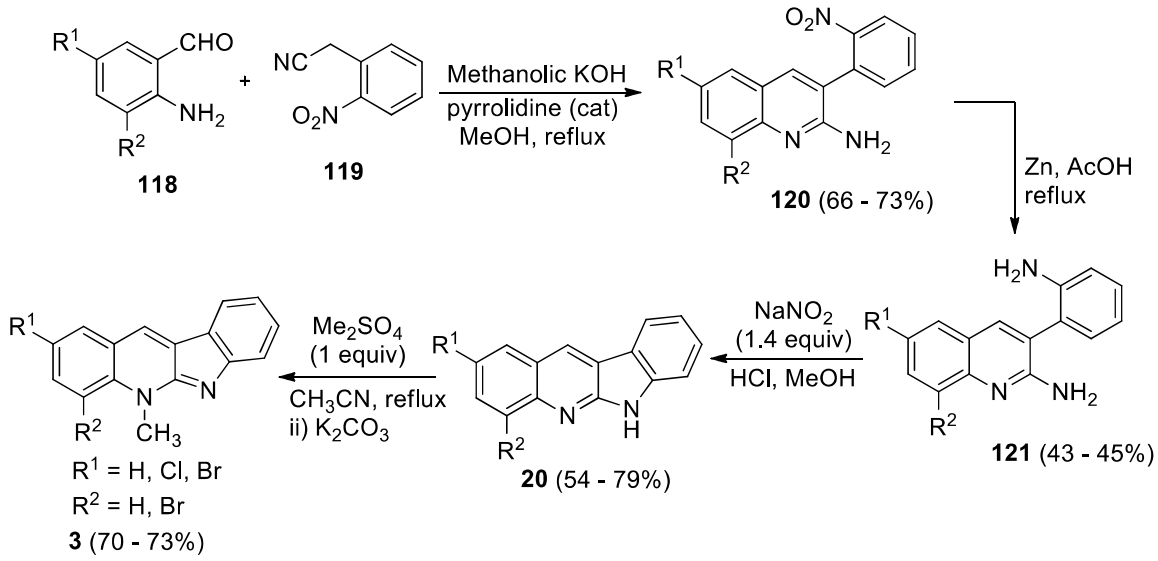
After two years, D. J. Proctor and co-workers utilised the connective Pummerer type of reaction between functionalized alkyl thiols and glyoxamides **115** derived from Swern oxidation of precursor **114**. The resultant cyclised moiety was subjected to SmI_2 yielding



Scheme 1.32: *Synthesis of Indoloquinolines via Pummerer Type Cyclization*

tetracyclic molecule **20** after reductive removal of sulfanyl groups, which was then treated with well-known methylation conditions affording neocryptolepines **3** in good yields (Scheme 1.32).[41]

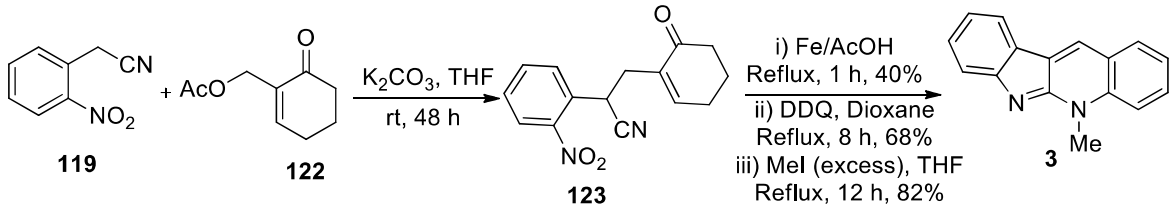
In 2010, J. C. Fettinger and co-workers synthesized neocryptolepine derivatives **3** from 2-amino benzaldehyde **118** and 2-nitro benzylcyanides (**119**) (Scheme 1.33).[42] The first step of this approach involves base mediated condensation reaction of 2-amino benzaldehyde (**118**) with 2-nitro benzylcyanide (**119)** yielding 3-(2-nitrophenyl)quinolin-2-amine **120**, which was reduced in the presence of Zn/AcOH to afford the corresponding amino compound **121**. Finally, this amino quinoline **121** was cyclised in the presence of acidic medium and sodium nitrite to afford indoloquinoline **20**, which on methylation gave neocryptolepine derivatives **3**.



Scheme 1.33: *Synthesis of Neocryptolepines from 2-Nitro Benzylcyanides and 2-Amino Benzaldehde*

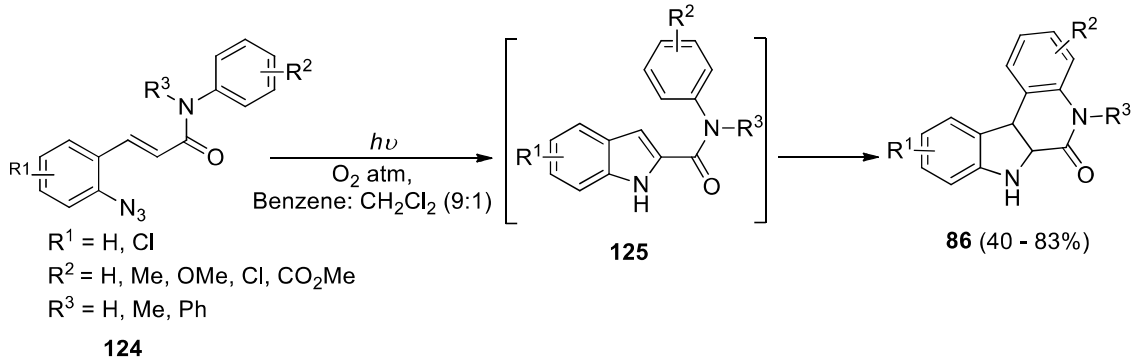
In 2012, D. Basavaiah and co-workers devised a simple procedure for synthesis of neocryptolepine **3** *via* Baylis-Hillman approach.[43] 2-nitrobenzyl cyanide (**119**) reacted with 4-acetoxy-3-methylene-4-phenylbutan-2-one (**122**) with K_2CO_3 as the base to yield the corresponding Baylis-Hillman adduct **123**, which underwent reductive cyclisation in the

presence of Fe/AcOH delivering the tetracyclic indoloquinoline. This indoloquinoline derivative was subjected to aromatization followed by selective methylation gave neocryptolepine **3** in 82% yield (Scheme 1.34).



Scheme 1.34: *Baylis-Hillman Approach Mediated Neocryptolepine Synthesis*

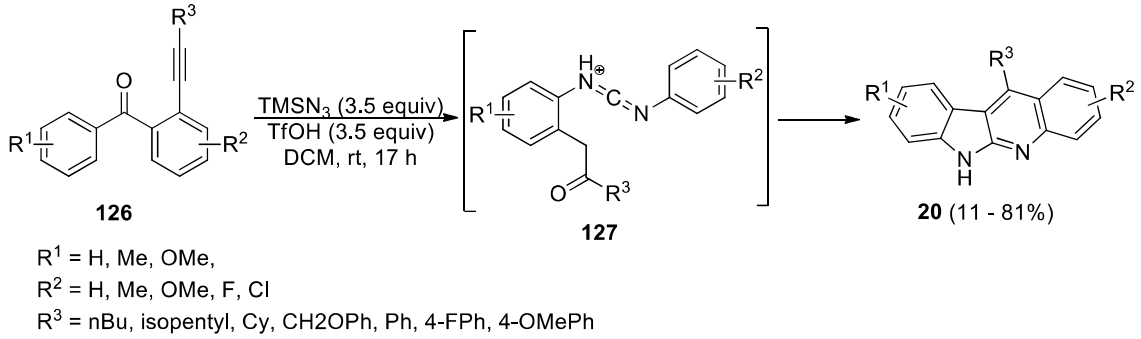
Next year, W. Zhang and co-workers reported a synthesis of indoloquinolones **86** under photochemical conditions.[44] The methodology involves photocyclization of 3-(2-azidophenyl)-N-phenylacrylamides **124** *via* insertion reaction resulted in the formation of indole-2-carboxamide derivative **125**, which upon subsequent electrocyclization in the presence of oxygen atmosphere gave isoneocryptolepine derivatives **86** (Scheme 1.35).



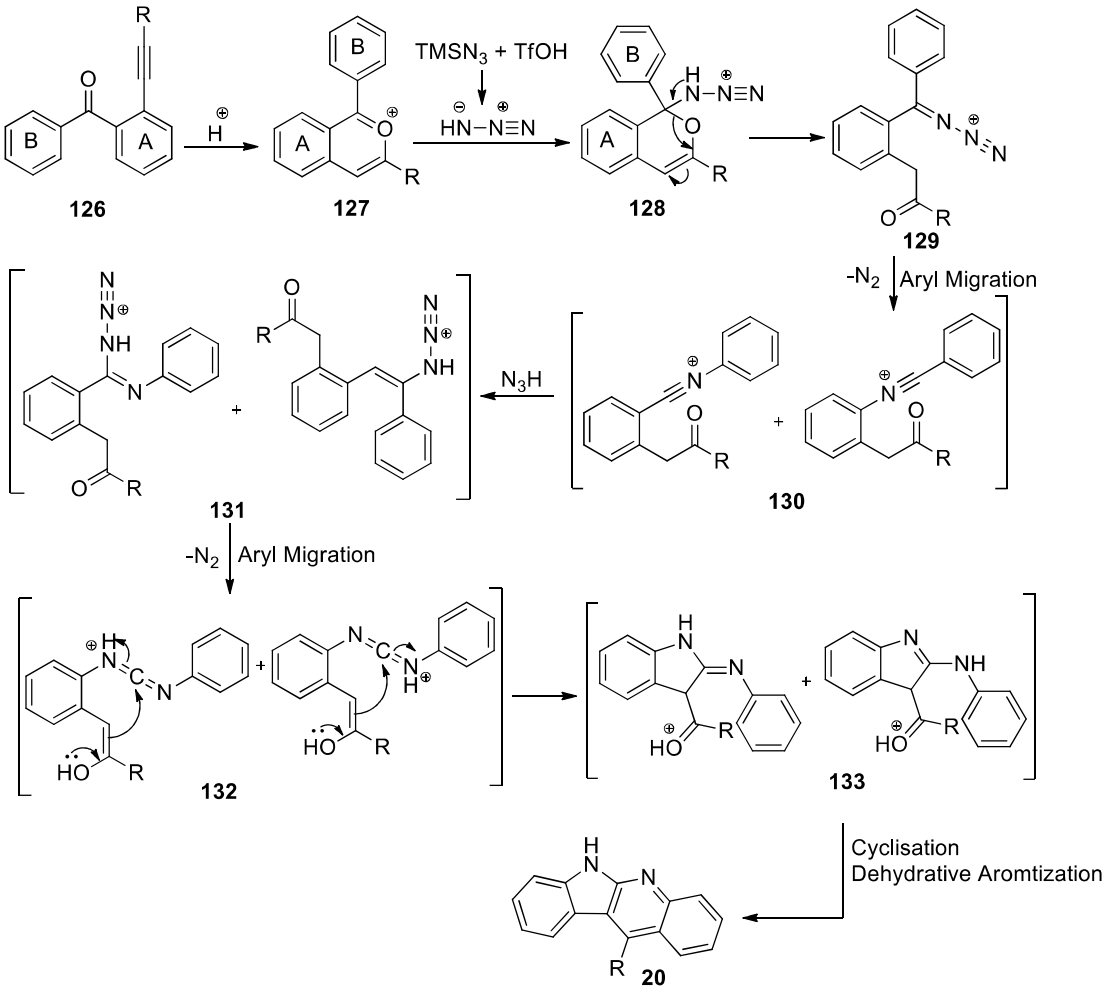
Scheme 1.35: *Synthesis of Indoloquinolones via Photo Catalysed Nitrene Insertion Reactions*

Recently, J. Tummatron and co-workers devised a new approach for the synthesis of neocryptolepine derivatives **3** from alkynylketones **126** under acidic conditions.[45] The key step of this protocol is the domino N_2 extrusion and aryl migration followed by *in situ* generation of carbodiimides **127**, which upon cyclisation gives rise to desired tetracyclic indoloquinoline

20 in low to good yields (Scheme 1.36). The detailed mechanism of the corresponding reaction is given below in Scheme 1.37.

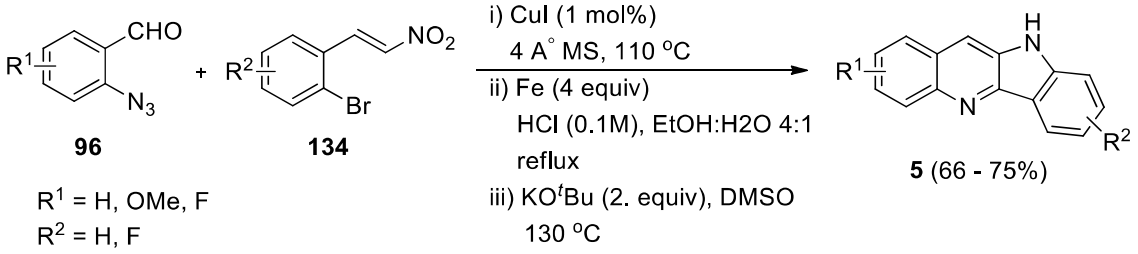


Scheme 1.36: *Synthesis of Indoloquinolines from 2-Alkynyl Benzophenone Derivatives*



Scheme 1.37: *Proposed Mechanism for the synthesis of Indoloquinolines from o-alkynylarylketones via domino N_2-extrusion and aryl migration*

Very recently, Z. Zhang and co-workers established the simple approach for the construction of cryptolepine derivative **1** from two acyclic precursors.[46] This method involves the reaction of 2-azido benzaldehydes **96** and *o*-bromo nitrostyrene **134** resulting in the formation of 3-nitroquinolines, which on reduction in the presence of iron afforded the corresponding amino compound. Lastly, 3-amino-2-bromoaryl quinolines underwent coupling reaction upon treatment with base at 130 °C to afford quindolines **5** in good yields (Scheme 1.38).



Scheme 1.38: *Copper Promoted Quindoline Preparation from 2-Azido benzaldehyde and Nitrostyrenes*

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Copper Catalysed 2-Amino Indole Synthesis: Easy Access to Synthesis of Neocryptolepine Derivatives

2.1 Introduction:

Transition metal catalysed carbon heteroatom bond forming reactions disclosed novel strategies for the construction of the wide range of heterocycles with functional group diversity.[1] Among those, C─N bond forming reactions received great attention to synthesize various nitrogen containing heterocycles.[2] In particular, devising new strategies to synthesize indole derivatives is highly demanding because it is the most abundant structural moiety present in the large number of natural products and biologically active molecules.[3]

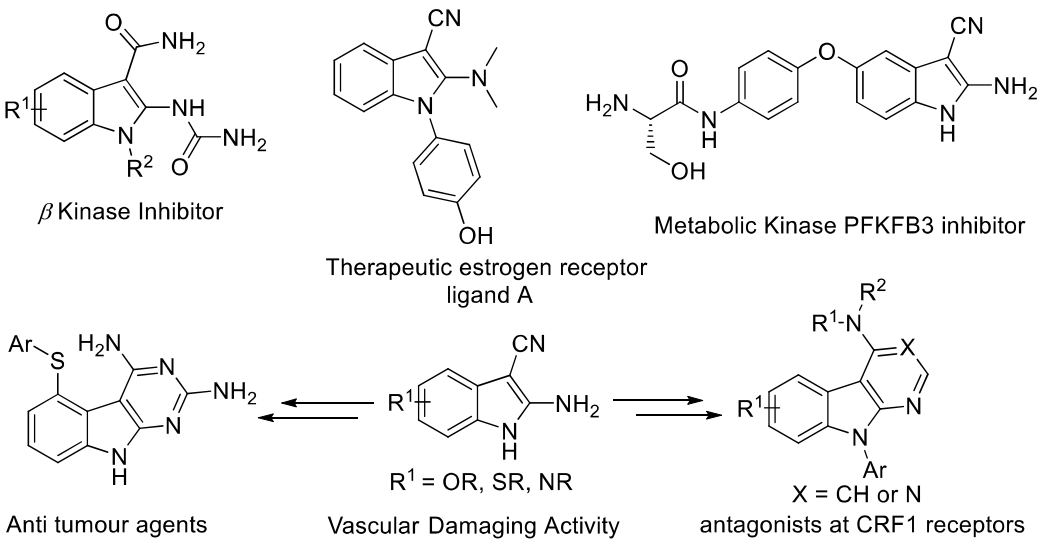


Figure 2.1: *Various Biologically Important 2-Aminoindole Derivatives*

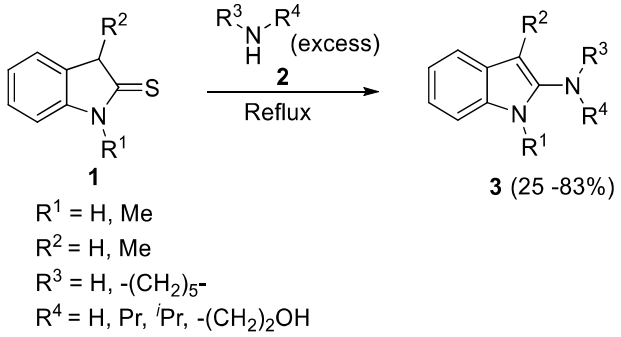
Particularly, 2-aminoindole is an interesting core and found in *β*-kinase inhibitor, metabolic kinase inhibitor and many other important biologically active compounds.[4] These are also the key intermediates for the synthesis of complex natural and unnatural bioactive molecules.[5] On the other hand, the recent studies revealed that nitrile moiety is a vital

pharmacophore, found in various pharmaceutically active molecules.[6] Among these molecules, 1,2-aminocyano substituted derivatives show interesting biological properties and some of these derivatives are in clinical trials.[7] Especially, 2-amino-3-cyanoindole derivatives exhibit potent vascular damaging activity and selective estrogen receptor ligand A (Figure 2.1).[8] Due to their versatile biological and pharmaceutical applications, several methods are reported to synthesize these 2-aminoindole derivatives.[9-24]

Despite these reported methods gave good to excellent yields of the desired 2-aminoindoles, each method has its own limitations such as harsh reaction conditions, high temperature, usage of expensive transition metals and multistep syntheses. In this chapter, we discussed previously reported methods for the synthesis of 2-aminoindole derivatives followed by our approach to synthesize 2-aminoindole derivatives under ambient reaction conditions.

2.2 Previous Reports for Synthesis of 2-Aminoindoles

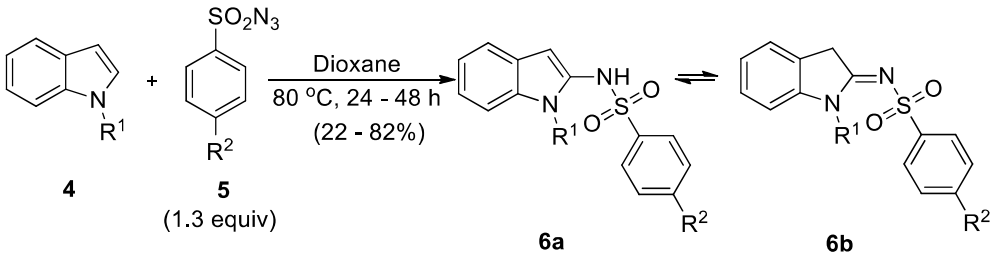
The first synthesis of 2-aminoindole was reported[9] in 1971 by S. Akaboshi *et. al.* from 2-indolinethieones **1** by refluxing with excess amount of various primary and secondary amines **2** in neat conditions (Scheme 2.1). In this method, *N*-substituted 2-indolinethione **1** gave less yield of the corresponding 2-aminoindoles **3** as compared to the *N*-unsubstituted



Scheme 2.1: *First Report for the Synthesis of 2-Aminoindole Derivatives* **3**

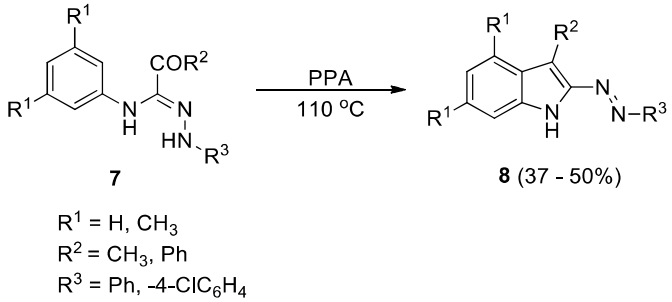
indolinethiones.

After two years, Harmon and co-workers came up with a new strategy to synthesize 2-amido indole derivatives.[10] Indoles **4** were treated with various sulfonyl azides **5** to afford 2-sulfanamido indoles **6** in 25 – 88% yield. In solution state, these 2-sulfonamide indole derivatives exist in tautomeric enamine **6a** and imine **6b** forms, whereas in crystalline state they exist mainly as imine tautomers (Scheme 2.2).



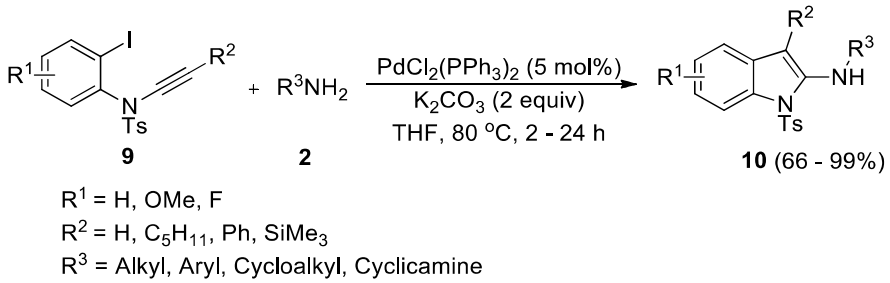
Scheme 2.2: *Synthesis of 2-Aminoindole Derivatives* **6** *from Indole* **4** *and Sulfonyl azides* **5**

In 1988, F. Sannicolo's group described a simple methodology to synthesize 2-amino indole derivatives **8** *via* intramolecular Gattermann-Koch type of cyclisation of various hydrazone derivatives **7** in the presence of polyphosphoric acid (Scheme 2.3).[11]



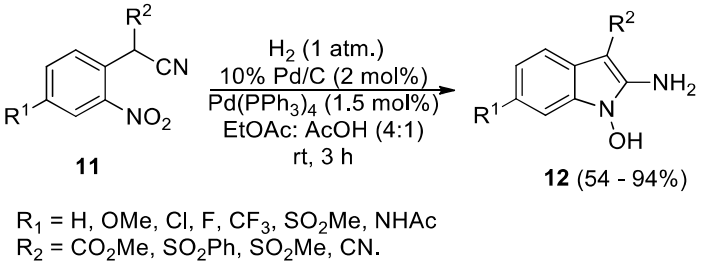
Scheme 2.3: *PPA Mediated Cyclisation of Hydrazone Derivatives* **7**

B. Witulski and co-workers developed novel palladium mediated heteroannulation reaction to synthesize 3-substituted-2-aminoindoles.[12] *N*-alkynyl-2-halogenanilides **9** were treated with various primary amines **2** in the presence of dichlorobis(triphenylphospine)palladium(II) resulted in the formation of 3-substituted 2-amino indoles **10** with excellent yields (Scheme 2.4). This reaction involves formation of the chelated palladium species between alkyne and aryl group followed by addition of amines to the carbon–carbon triple bond.



Scheme 2.4: *Palladium Catalysed Heteroannulation of Ynamides* **9**

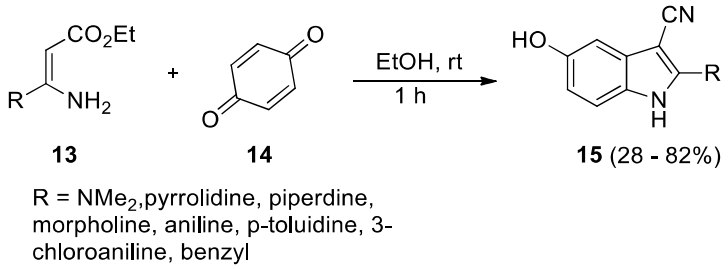
In 2006, M. Belly and co-workers reported the synthesis of 3-substituted *N*-hydroxy-2-aminoindoles **12** by reductive cyclisation method.[13] Thus, (2-nitrophenyl)acetonitriles **11** were catalytically hydrogenated to (2-aminophenyl)acetontriles followed by cyclisation of nitrile group in the presence of catalytic amount of $Pd(PPh_3)_4$ at room temperature. The



Scheme 2.5*: Reductive Cyclisation of (2-Nitrophenyl)acetonitriles* **11** *to Synthesis 2-Aminoindole Derivatives* **12**.

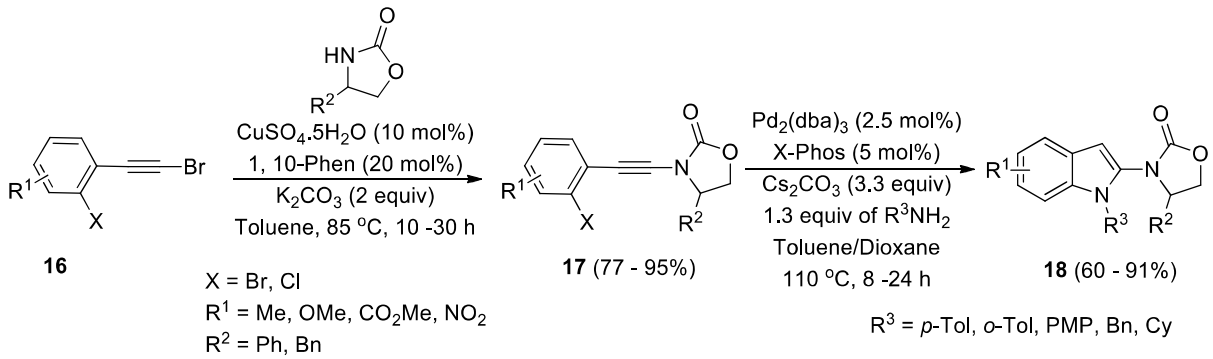
presence of hydrogen or methyl group at α-position of nitrile does not produce the desired *N*-hydroxy 2- amino indole derivative **12** (Scheme 2.5). The presence of electron withdrawing group facilitates this reductive cyclization.

In the same year, O. Werz and co-workers synthesized a series of 2-amino-5-hydroxy indoles **15** by using Nenitzescu indole synthesis.[14] Their strategy involves treating the ketene aminals **13** with 1,4-benzoquinone (**14**) at room temperature to obtain the desired 2-amino-5-hydroxy indoles **15** in moderate to good yields (Scheme 2.6). Further these 2-amino indoles were subjected to various biological studies and found that these are potential candidates for the pharmacological intervention with leukotriene's associated diseases.



Scheme 2.6: *Synthesis of 2-Amino-5-hydroxyindoles* **15** *via the Nenitzescu Reaction*

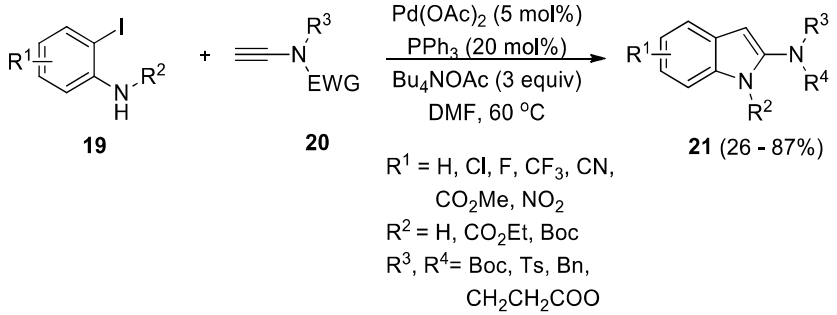
K. Zhao and co-workers studied a sequential metal-catalysed C─N bond forming reactions of *ortho*-haloaryl acetylenic bromides **16**.[15] The first step of this method involves



Scheme 2.7: *Synthesis of 2-Amidoindoles* **18** *via Sequential C─N bond Formation of ortho-Haloaryl Acetylenic Bromides* **16**

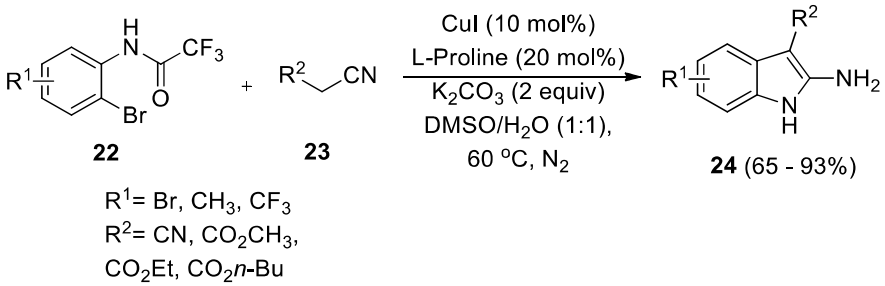
selective C_{sp}─N bond formation leading to the formation of ynamides **17**. Further, in the presence of $Pd_2(dba)_3$, these ynamide undergo Buchwald-Hartwig coupling with various amines followed by *5-endo-dig* cyclisation affording 2-amido indole derivatives **18** with good to excellent yields (Scheme 2.7).

In 2009, Skrydstrup and co-workers investigated the similar type of reaction by using 2-iodo aniline derivative **19** and ynamides **20**.[16] This approach involves the construction of C─C bond between 2-iodoanilines **19** and ynaimde **20** followed by *5-endo-dig* cyclisation delivering 2-amino indoles **21** in a tandem fashion (Scheme 2.8).



Scheme 2.8: *Synthesis of 2-Amidoindoles* **21** *from 2-Iodoanilines* **19** *& Terminal Ynamides*

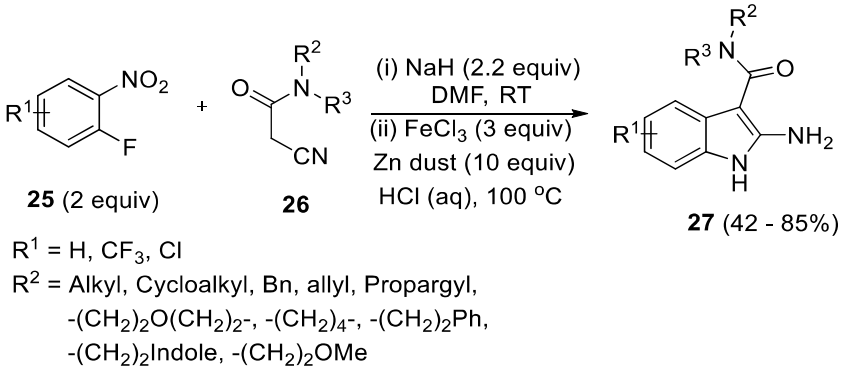
Fu and co-workers came up with a simple methodology to construct 2-amino-1*H*-indole-3-carboxylate derivatives **24** in tandem approach.[17] Their strategy involves Copper mediated C─C bond construction between derivatives of *N*-(2-halophenyl)-2,2,2-



Scheme 2.9: *Copper Catalysed Cascade Synthesis of 2-Aminoindole Derivatives* **24**

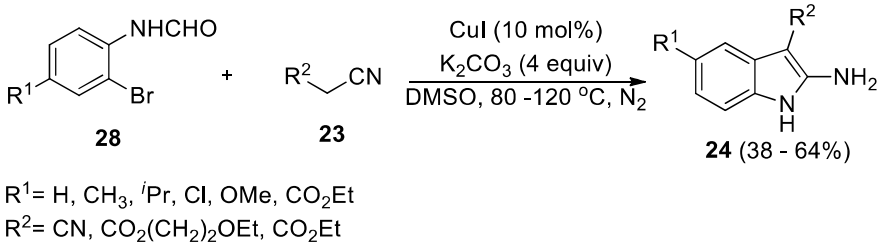
trifluoroacetamide **22** and 2-cyanoacetates or malononitrile **23**, followed by cyclisation of nitrile group yielding 2-amino indole derivatives **24** (Scheme 2.9).

Later, Domiling and co-workers developed a one pot approach for the synthesis of 3-substituted 2-amino indole derivatives **27** from cyano acetamides **26** and 2-fluoro nitrobenzene deirvatives **25**.[18] Initially 2-fluoro nitrobenzene **25** will undergo S_NAr reaction with anion of cyano acetamide under alkaline conditions followed by nitro group reduction and cyclisation delivers 2-amino-indole-3-carboxamides **27** in moderate to good yields (Scheme 2.10)



Scheme 2.10: *One-Pot Synthesis of 2-Amino-indole-3-carboxamide derivatives* **27**

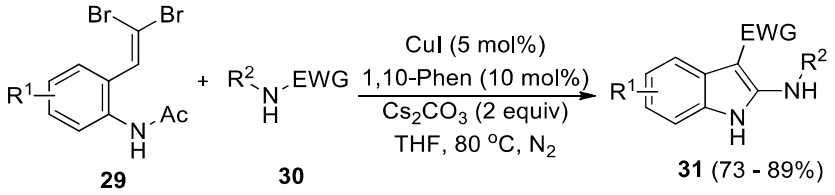
In the same year Kobayashi and co-workers studied the similar type of reaction in the presence of catalytic amount of copper salts by using *N*-(2-bromophenyl)formamides **28** and



Scheme 2.11: *Synthesis of 2-Aminoindoles* **24** *from N-(2-Bromophenyl)formamides* **28** *and Malononitrile or Cyanoacetates* **23**

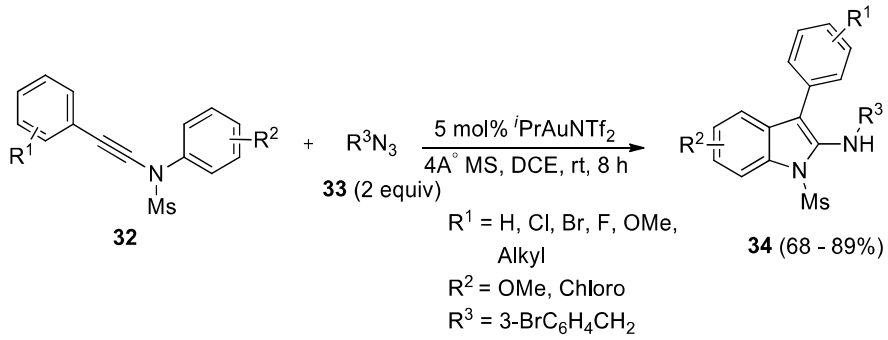
malononitrile or cyanoacetates **23** to synthesize 2-aminoindole-3-carbonitriles and 2-aminoindole-3-carboxylates **24** respectively under heating conditions (Scheme 2.11).[19]

In 2014, Perumal and co-workers established the Cu(I) catalysed intermolecular protocol for the synthesis of 2-amido indoles from *gem*-dibromovinylanilides **29** and sulfonamides **30**.[20] In the presence copper, sulfonamide **30** reacts with *gem*-dibromovinylanilide **29** generating ynamide *in situ*, which further undergoes 5-*endo-dig* cyclisation producing 2-amido indole derivatives **31** in shorter reaction time (Scheme 2.12).



Scheme 2.12: *Copper Mediated Coupling of gem-Dibromovinylanilides* **29** *and Sulfonamides*

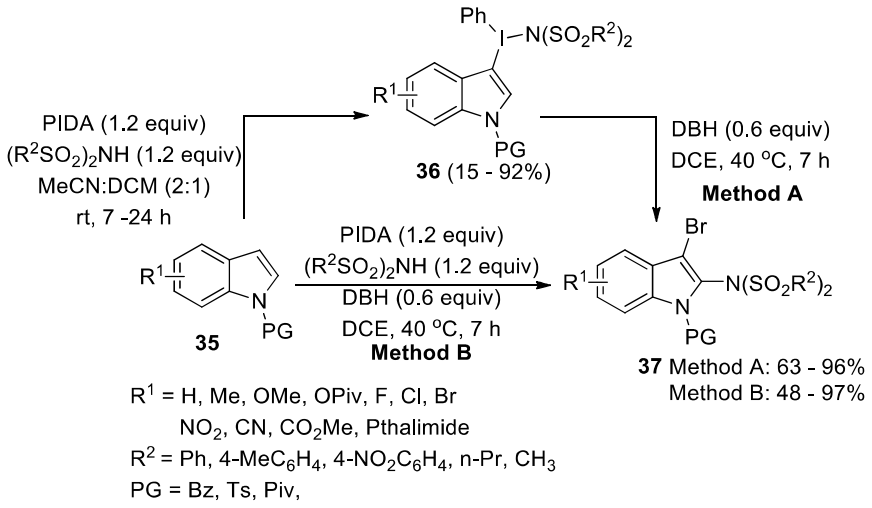
In 2015, Lu and co-workers disclosed a novel methodology to synthesize 2-amino indole derivatives **34** through α-imino gold carbenes.[21] The current method involves gold catalysed *in situ* generation of carbene derivative by intermolecular reaction of ynamide **32** with azides **33**, which on further cyclisation affords 2-amino indole derivatives **34** with good



Scheme 2.13: *Novel Approach for the Synthesis of 2-Aminoindoles* **33** *from α-Imino Gold Carbenes*

to very good yields at room temperature (Scheme 2.13). DFT calculations were also carried out in support of observed high regioselectivity.

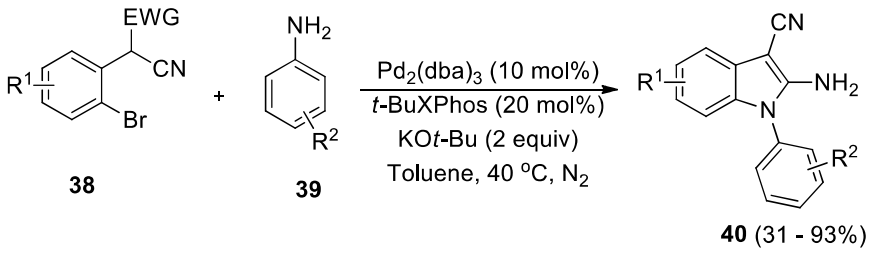
In the same year, Moriyama's group studied the transition metal free regioselective dual C─H functionalization of indoles to synthesize 2-bis(sulfonyl)amino-3-bromo-indoles **37**.[22] This process involves *in situ* generation of $PhI(OAc)(N(SO_2R)_2)$ from $PhI(OAc)_2$ and $(RSO_2)_2NH$, which was attacked by *N*-protected indole **35** produces indolyl (phenyl)iodonium(III) imides **36**. Further this intermediate will react with 1,3-dibromo-5,5-dimethylhydantoin (DBH) followed by 1,3-migration of imide group will affording 2-bis(sulfonyl)amino-3-bromo- indoles **37** in moderate to excellent yields (Scheme 2.14).



Scheme 2.14*: Transition Metal Free Synthesis of 2-Aminoindole Derivatives* **37** *from Indoles* **35**

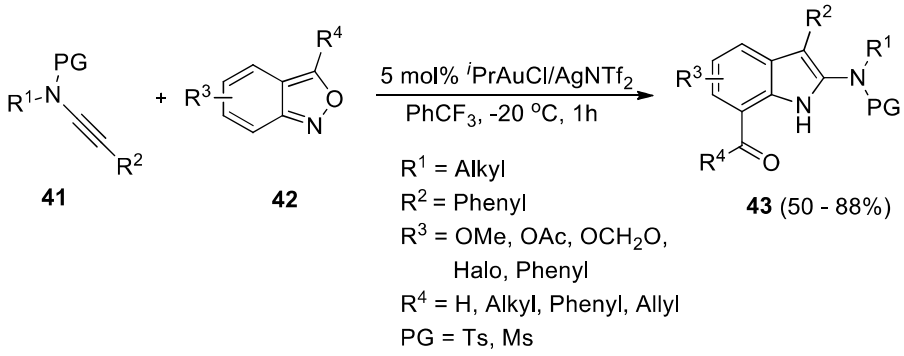
In 2015, Yang's group studied the palladium mediated Buchwald–Hartwig coupling of readily available 2-(2-bromophenyl)acetonitriles **38** and anilines **39** to obtain the corresponding aminated product, which on further intramolecular nucleophilic addition reaction with nitrile group giving rise to 3-substituted 2-amino indole derivative **40**.[23] On the

other hand, cheaper and eco-friendly copper salts were ineffective for this reaction (Scheme 2.15).



Scheme 2.15: *Pd Catalysed Domino Synthesis of 2-Aminoindoles* **40** *via Buchwald-Hartwig Coupling*

Recently, Hashmi and co-workers investigated the gold catalysed C─H annulation reaction of anthranil derivatives **42** with ynamides **41** to synthesize 2-amino-7-acyl indoles **43**.[24] The key step of this methodology involves *in situ* generation of α-imino gold carbene by intermolecular attack of anthranil **41** on ynamide **42**, which further undergoes intramolecular *ortho*-aryl C─H insertion affording desired 2-amino indole derivatives **43** (Scheme 2.16).



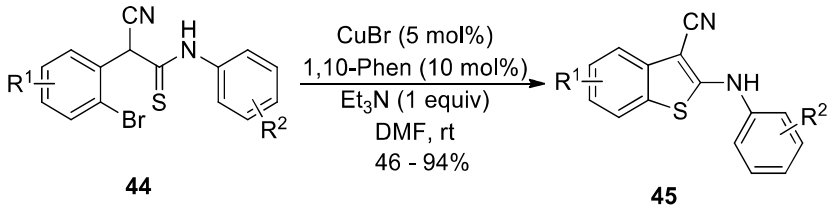
Scheme 2.16: *Synthesis of 2-Aminoindoles* **43** *from Anthranil Derivatives* **42** *and Ynamides*

Our literature survey clearly shows that every report has its own advantages and limitations. Some of these methods involve multistep syntheses, usage of expensive and non-eco-friendly metal salts like palladium and gold, high temperatures and longer reaction times.

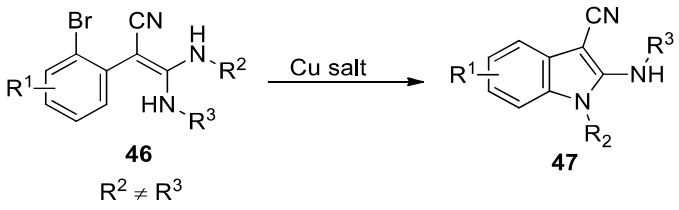
Further, indole is used as a precursor for the synthesis of 2-aminoindole derivatives, which hampers the wide substrate scope. In other words, the reported methods are less applicable in the area of industrial and process chemistry. Therefore, a general and practical method is needed for synthesis of 2-aminoindole derivatives that involves usage of cheaper and eco-friendly metals and milder reaction conditions.

2.3 Motivation:

Recently, our research group has investigated the copper mediated chemo and regioselective Ullmann coupling of easily synthesizable thioamides for the synthesis of 2-aminobenzo[*b*]thiophenes at room temperature (Scheme 2.17).[25] This protocol also provides the enantiospecific Ullmann reaction of enantiomeric pure thioamides without loss of optical purity. In continuation of our interest in chemoselective and regioselective construction of synthetically and biologically active heterocycles,[26] we envisioned to examine the intramolecular regioselective *N*-arylation of ketene aminals at ambient reaction conditions (Scheme 2.18).



Scheme 2.17: *Copper Mediated Chemoselective Thiolation of Thioamides*



Scheme 2.18: *Our Strategy for Synthesis of 2-Aminoindole Derivatives*

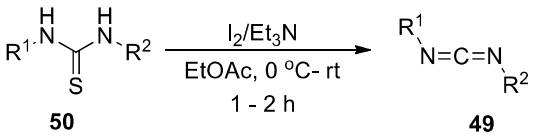
2.4. Results and Discussion

The required ketene aminals **46** can be synthesized from 2-haloaryl acetonitriles **48** and substituted carbodiimides **49**.

2.4.1. Synthesis of Carbodiimides

The required carbodiimides **49** were prepared from thioureas using known literature procedures.[27] The symmetrical thioureas were synthesized from anilines by the reaction of anilines and CS_2 in the presence of aqueous NaOH.[28] Whereas, the unsymmetrical thioureas were obtained by the reaction of isothiocyanates with anilines.[29] These thioureas were transformed into carbodiimides **49** with moderate yield in presence of iodine as desulfurizing agent (Table 2.1). The commercially available *N,N′*- dicyclohexylcarbodiimide, *N,N′*-diisopropylcarbodiimide were used directly without any purification.

Table 2.1: Synthesis of Carbodiimides 49



50 **49**

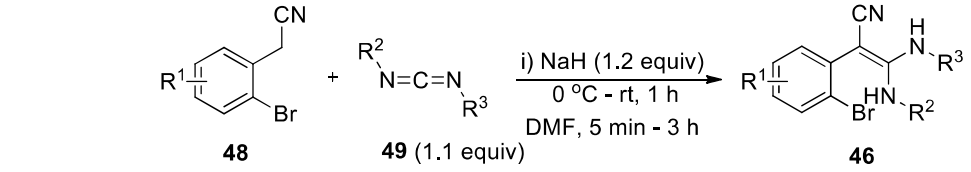
49a, $R^1 = R^2$ = Ph (52%)	**49e,** R^1 = 4-OMePh, R^2 = 4-NO_2Ph (39%)
49b, $R^1 = R^2$ = 4-OMePh (62%)	**49f,** R^1 = Ph, R^2 = 4-NO_2Ph (45%)
49c, $R^1 = R^2$ = 4-FPh (57%)	**49g,** R^1 = Ph, R^2 = ^{t}Bu (31%)
49d, $R^1 = R^2$ = 2,6-Me_2Ph (67%)	

2.4.2 Synthesis of Ketene Aminals 46

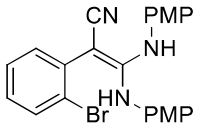
The required ketene aminals **46** were prepared by treating the anion of 2-bromo benzyl cyanides **48** with carbodiimides **49** forming *α*-(2-bromoaryl)-*ß*, *ß*-diamino

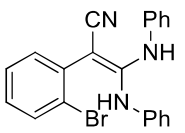
acrylonitriles **46** with moderate to good yields, which were confirmed by spectral and analytical data (Table 2.2).

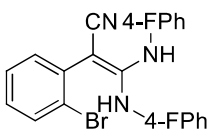
Table 2.2: Synthesis of Ketene Aminals 46 from Arylacetonitriles 48 & Carbodiimides 49

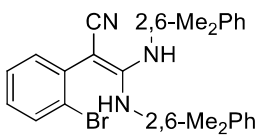


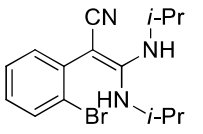
48 + **49** (1.1 equiv) → **46**

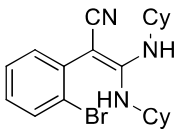

46a (51%)

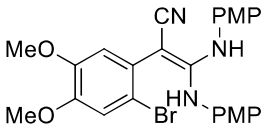

46b (66%)

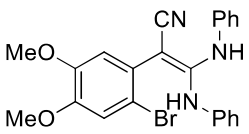

46c (73%)

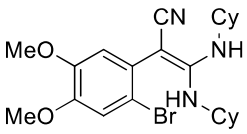

46d (68%)

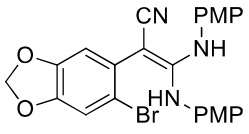

46e (50%)

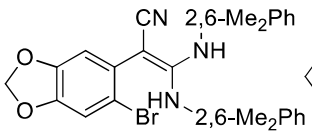

46f (42%)

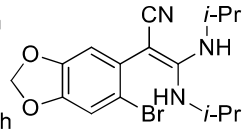

46g (54%)

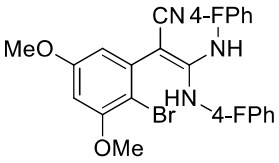

46h (59%)

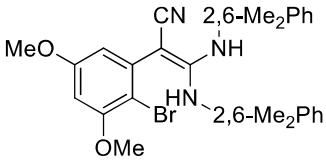

46i (29%)

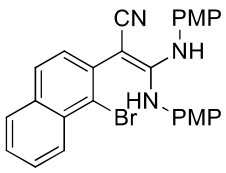

46j (58%)

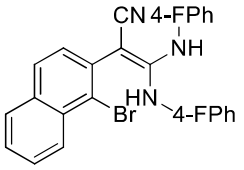

46k (62%)


46l (42%)


46m (59%)


46n (75%)


46o (40%)

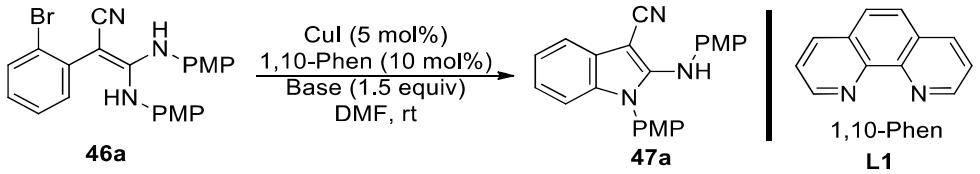

46p (56%)

2.4.3 Optimization of Intramolecular *N*-Arylation of Ketene Aminals

After synthesis of diverse range of ketene aminals **46a-p**, we moved to study the optimization of reaction conditions for the intramolecular *N*-arylation of ketene aminals **46**. Thus we have chosen ketene aminal **46a** as a model substrate and treated with 5 mol% CuI, 10 mol% 1,10-phenanthroline ligand, 1.5 equiv of Et_3N in the presence of DMF solvent at room

temperature. However, we observed only 5% of the desired 2-amino indole **47a** after 28 h. (Table 3, Entry 1). For further fine tuning of this process, we started screening several bases. The similar trend was observed in the presence of NaOAc (Table 2.3, Entry 2). Interestingly, when we carried out the reaction in the presence of K_2CO_3, the reaction was completed in 30 min and produced 91% of the intramolecular *N*-arylated product **47a** (Table 2.3, Entry 4). The similar trend was also observed with Cs_2CO_3. Similarly, K_3PO_4 was equally effective, however, the reaction took slightly longer time (Table 2.3, Entry 5). Gratifyingly, when we carried out the reaction with KO^{t}Bu, the reaction was completed in 5 min by delivering 96% of the corresponding 2-amino indole **47a** (Table 2.3, Entry 6). From base screening studies, we concluded that stronger base KO^{t}Bu is very effective for the *N*-arylation of ketene aminals.

Table 2.3: Base Screening of Intramolecular *N*-Arylation of *N,N*-Acetals

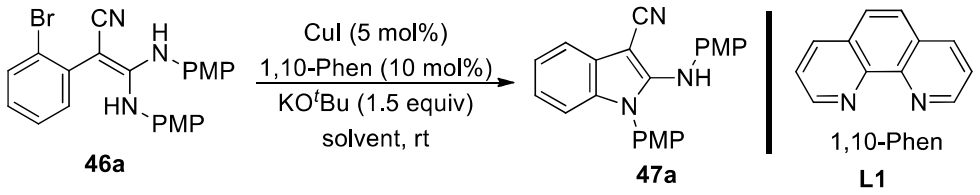


46a **47a** **L1**

S.No	Base	Time	Yield (%)
1.	Et_3N	28 h	5
2.	NaOAc	36 h	8
3.	K_2CO_3	30 min	91
4.	Cs_2CO_3	15 min	91
5.	K_3PO_4	3 h	90
6.	KO^{t}Bu	5 min	96

After the base screening, next we studied the effect of solvents on this intramolecular C─N bond coupling. Thus, we carried out the *N*-arylation in the presence of several solvents and the results were shown in Table 4. In the presence of THF, only 72% of the C─N bond coupled product **47a** was obtained (Table 2.4, Entry 1). However, the dioxane gave slightly better yield (85%, Table 2.4, Entry 2). On the other hand, the reaction was performed in the presence of non-polar solvent toluene, which afforded 79% of the *N*-arylated product **47a** and required slightly longer reaction time (Table 2.4, Entry 3). Whereas, polar solvents DMA and DMSO were comparable with DMF in terms of yield and giving rise to 90% and 94% of the 2-aminoindole **47a** respectively (Table 2.4, Entry 4-5).

Table 2.4: Solvent Screening of Intramolecular *N*-Arylation of Ketene Aminals

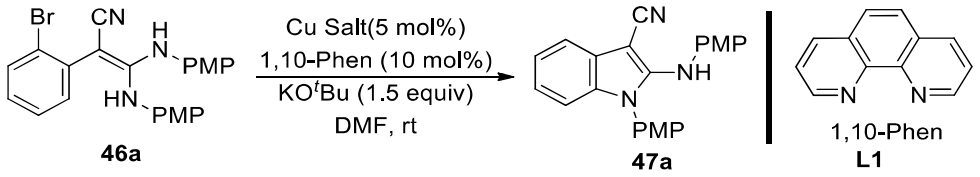


S.No	Solvent	Time	Yield (%)
1.	THF	1 h	72
2.	Dioxane	15 min	85
3.	Toluene	2 h	79
4.	DMA	15 min	90
5.	DMSO	15 min	94

We also studied the effect of copper salts on the *N*-arylation of ketene aminals (Table 2.5). Thus, we carried out the reactions with CuCl, CuBr and $Cu(OAc)_2$ and found that all the copper salts are comparable in terms of yield of 2-amino indole **47a** and reaction time (Table

2.5). Out of them, we have chosen CuCl for further studies because it is cheaper than other copper (Table 2.6, Entry 1).

Table 2.5: Investigation Copper Salts in Intramolecular *N*-Arylation of Ketene Aminals



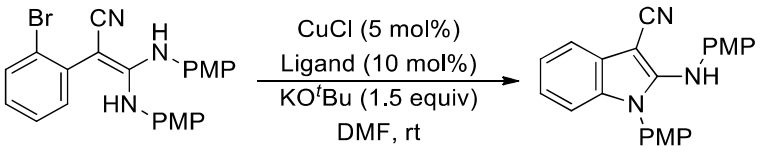
S.No	Cu Salt	Time	Yield (%)
1.	CuCl	5 min	99
2.	CuBr	5 min	97
3.	$Cu(OAc)_2$	10 min	98

Table 2.6: Price List of Copper Salts from Sigma-Aldrich[30]

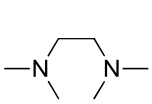
S.No	CAS NO	Product Code	Cu Salt & Purity	Price (INR)
1.	7758-89-6	212946-500G	CuCl, 97%	4,044.32
2.	7787-70-4	212865-250G	CuBr, 98%	3,215.41
3.	7681-65-4	205540-250G	CuI, 98%	3555.99
3.	142-71-2	326755-100G	$Cu(OAc)_2$, 98%	10,649.90

Next, we turned our attention towards investigation of the ligand on this C─N coupling reaction (Table 2.7). Thus, we investigated other nitrogen based ligands including *R*-BINAM and TMEDA, which were found to be less effective as compared to 1,10-phenanthroine in affording the indole **47a**. We also examined L-proline for this process and obtained only 47% of the desired product **47a**.

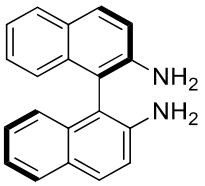
Table 2.7: Ligand Screening of Intramolecular *N*-Arylation of Ketene Aminals



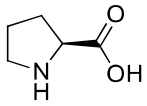
46a **47a**



L2, 45%, 16 h

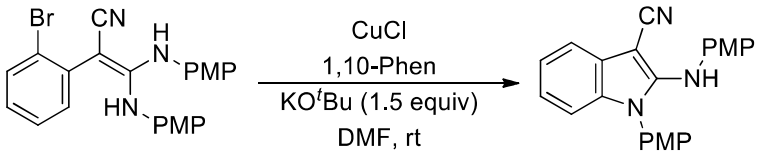


L3,48%, 14 h



L4,47%, 16 h

Table 2.8: Screening of Molar Ratio for Intramolecular *N*-Arylation of Ketene Aminals



46a **47a**

S.No	CuCl	1, 10-Phen	Time	Yield (%)
1.	3 mol%	6 mol%	45 min	82
2.	1 mol%	2 mol%	8 h	32
3.	5 mol%	-	32 h	56
4.	-	-	24 h	0

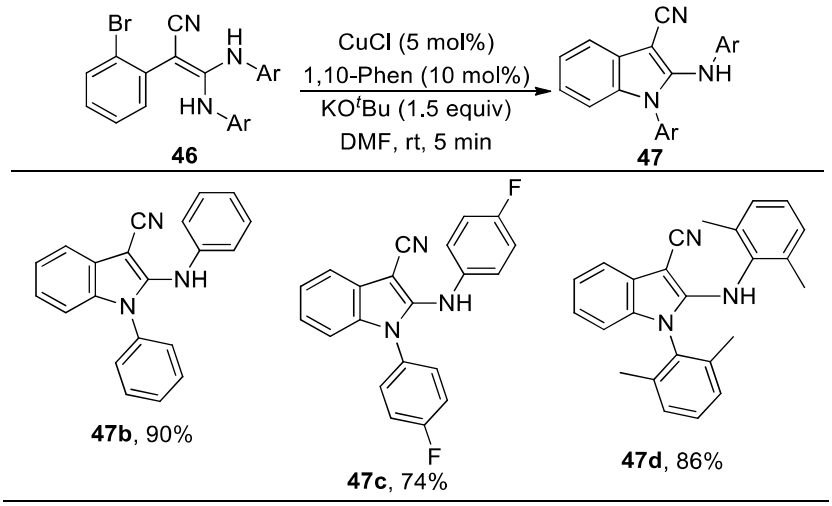
We also carried out the reaction by lesser amount of metal-ligand combinations, such as 3 mol% and 1 mol% CuCl and observed the diminishment of yield of the desired product **47a** (Table 2.8, Entry 1-2). Whereas, the reaction in the absence of ligand delivered only 56% of the corresponding product **47a** in 32 h (Table 2.8, Entry 3). Finally, when we carried out the reaction in the absence of copper salt and ligand, we did not observe even trace amount of coupled product (Table 2.7, Entry 4).

From the overall optimization studies, we concluded that 5 mol% CuCl, 10 mol% 1,10-phenanthroline, DMF, KO*t*Bu (1.5 equiv) at room temperature is found to be the most effective reaction conditions for the intramolecular *N*-arylation of ketene aminals.

2.4.4 Substrate Scope:

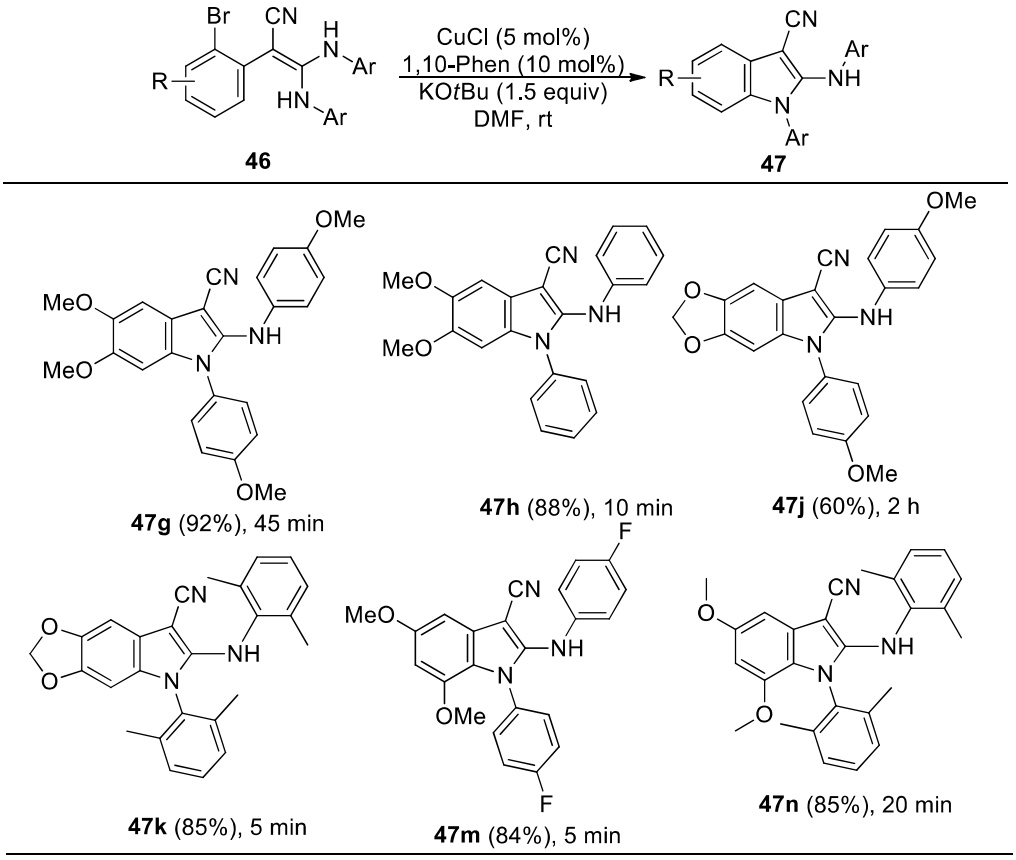
With the optimized conditions in our hands, we moved forward to studying the *N*-arylation of several ketene aminals **46b-p**. Initially, we wish to study the effect of substituted *N*-aryl groups on the intramolecular *N*-arylation (Table 2.9). Thus, we have carried out the reaction with *N,N*-diphenyl substituted *N,N*-acetal **46b** under optimized reactions and observed 90% of the corresponding *N*-arylated product **47b** within 5 min (Table 2.9). However, the electron withdrawing group containing ketene aminal **46c** delivered slightly lower yield of the desired product **47c** as compared to the standard *N,N*-acetal **46a** (Table 2.9). Interestingly, the sterically crowded 3,3-bis(arylamino)acrylonitrile derivative **46d** also afforded an excellent yield of the corresponding 2-amino indole **47d** within 5 min of reaction time (Table 2.9).

Table 2.9: Intramolecular *N*-Arylation of *N*-Aryl Substituted Ketene Aminals

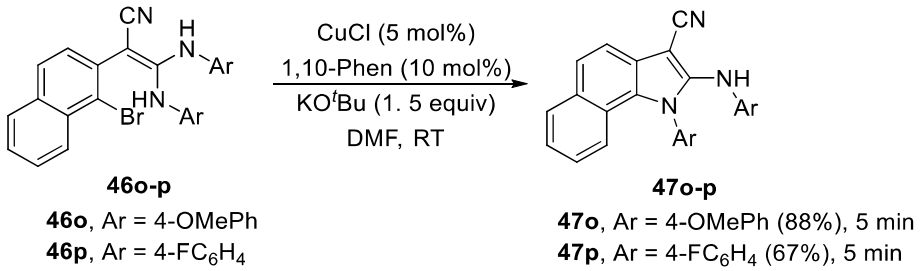


Next, we turned our attention towards the investigation of the effect of electron donating substituents at 2-bromoaryl group of *N,N*-acetals **46g-h**, **46j-k**, **46m-n** on the *N*-arylation reaction (Table 2.10). Thus, 2-(2-bromo-4,5-dimethoxyphenyl)-3,3-bis((4-methoxyphenyl)amino)cacrylonitrile (**46g**) was subjected to the optimization conditions and yielded 92% of the desired product **47g** (Table 2.10). The similar trend was observed in the case of 2-bromo-4,5-dimethoxy substituted ketene aminal **46h** (Table 2.10). However, the methylenedioxy substituted acrylonitrile derivative **46j** took slight longer reaction time by producing only 60% of the 2-aminoindole **47j** (Table 2.10). Whereas, the aminal **46k** which was derived from methylenedioxy substituted nitrile and 2,6-dimethyl substituted carbodiimide was also smoothly converted into the corresponding indole derivative **47k** with

Table 2.10: Synthesis of Electron Donating Group Containing 2-Aminoindoles



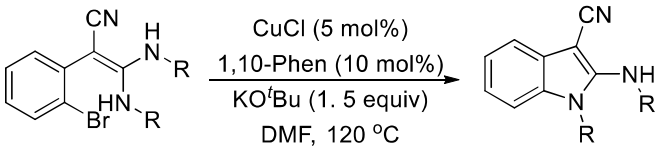
very good yield (Table 2.10). On the other hand, 2-(2-bromo-3,5-dimethoxyphenyl)-3,3-bis((4-fluorophenyl)amino)acrylonitrile (**46m**) was also *N*-arylated under the optimized conditions gave rise to 84% of the desired product **47m** (Table 2.10). Similarly, 3-cyano-1-(2,6-dimethylphenyl)-2-[(2,6-dimethylphenyl)amino]-5,7-dimethoxy-1*H*-indole (**47n**) was also observed from the corresponding aminal **46n** in 20 min of reaction time (Table 2.10).We also investigated the intramolecular *N*-arylation of naphtha substituted ketene aminals. Thus, the aminal **46o** was treated with the optimized reaction conditions and 2-amnioindole derivative **47o** was obtained in 88% yield (Scheme 2.19). On the other hand, electron withdrawing group containing ketene aminal **46p** was afforded only 67% of the aminated product **47p** (Scheme 2.19).



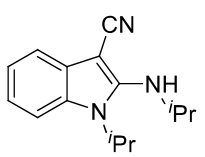
Scheme 2.19: *Synthesis of Naphtha Fused 2-Aminoindole Derivatives*

Next, we turned our attention to examine the alkyl substituted ketene aminals. The aminal **46e** was chosen as model substrate and was reacted under optimized reaction conditions at room temperature. To our surprise, the aminal did not transformed to the corresponding aminoindole **47e** and the starting material **46e** was completely recovered. However, when we performed the same reaction at 120 ºC, 80% of the 2-aminoindole **47e** was obtained as only sole product (Table 2.11). The modified reaction conditions was employed for C─N coupling of other alkyl substituted ketene aminals. It was found that the aminals **46f**, **46i** & **46l** were smoothly transformed to the corresponding 2-aminoindoles **47f**, **47i** & **47l** in 75 – 79% yields within 30 min (Table 2.11).

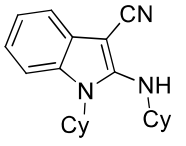
Table 2.11: Intramolecular *N*-Arylation of *N*-Alkyl Substituted Ketene Aminals 46



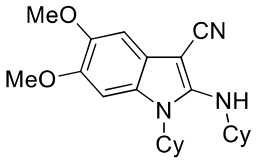
46 **47**



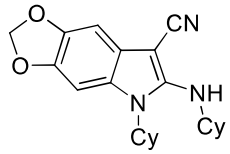
47e (80%), 90 min



47f (75%), 30 min



47i (75%), 30 min



47l (79%), 30 min

Further, we wish to investigate the regioselective *N*-arylation of unsymmetrical ketene aminals, which was derived from 2-bromo benzyl cyanide (**48**) and unsymmetrical carbodiimides **49e-g** (Table 2.12). Thus, we have chosen the aminal **46q** and subjected it to the optimized reaction conditions at room temperature. Interestingly, the reaction was completed within 5 min and afforded exclusively one regioisomer of *N*-arylated product in 81%. This was characterised as 3-cyano-1-(4-methoxyphenyl)-2-((4-nitrophenyl)amino)-1*H*-indole (**47q**) by using single crystal X-Ray analysis (Table 2.12, Figure 2.2). This indicates that, the electron rich part of aminal is undergoing coupling over the electron deficient. Similarly the 3-cyano-2-((4-nitrophenyl)amino)-1-phenyl-1*H*-indole (**47r**) was observed in 86% yield from the corresponding ketene aminal **46r** (Table 2.12). We also examined the *N*-alkyl, *N*-aryl substituted aminal **44s** under optimized reactions and found that aniline part was underwent the *N*-arylation over the alkyl amino part of *N,N*-acetal (Table 2.12, Figure 2.2). This can be accounted that probably CuCl will bind strongly to the tertiary butyl amine, which prevents the further process such as oxidative addition and reductive elimination. This trend was already observed in the case of *N*-arylation of *N*-alkyl substituted *N,N*-acetals, where the reactions carried out at 120 °C. Since this particular reaction was performed at room temperature, aniline core of *N,N*-acetal went C−N coupling over alkyl amine core.

Table 2.12: Regioselective *N*-Arylation of Unsymmetrical Ketene Aminals 46

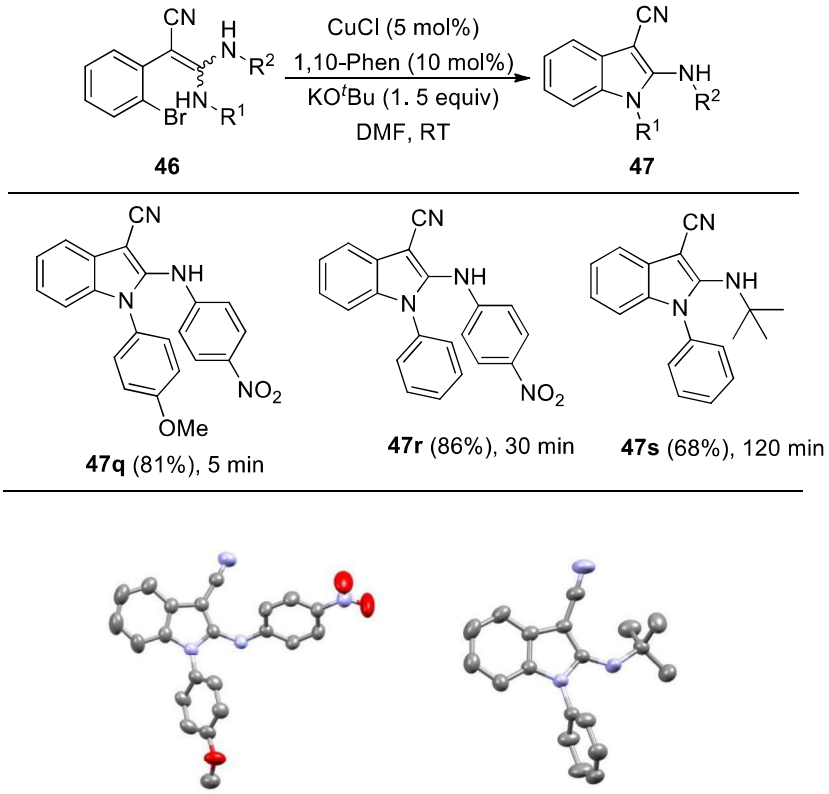
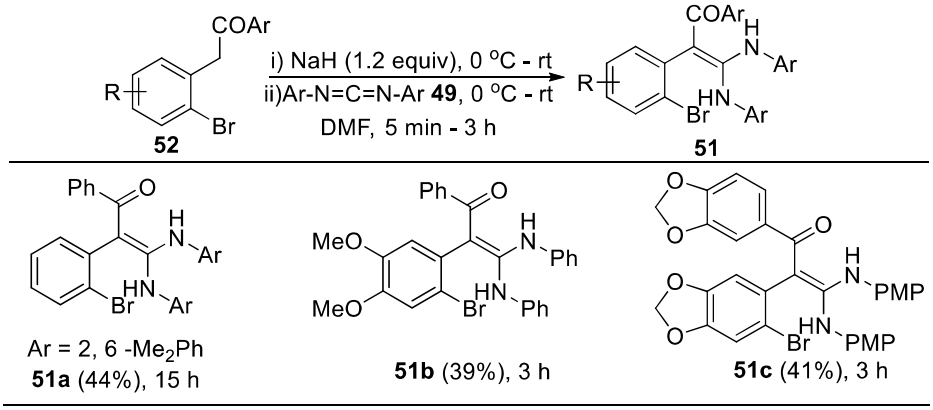


Figure 2.2: (A) *Single Crystal X-ray of **47q*** (B) *Single Crystal X-Ray of **47s***

Motivated by the aforesaid results, next we investigated the effect of the electron withdrawing group on this *N*-arylation process. Thus, we replaced cyano group with aroyl

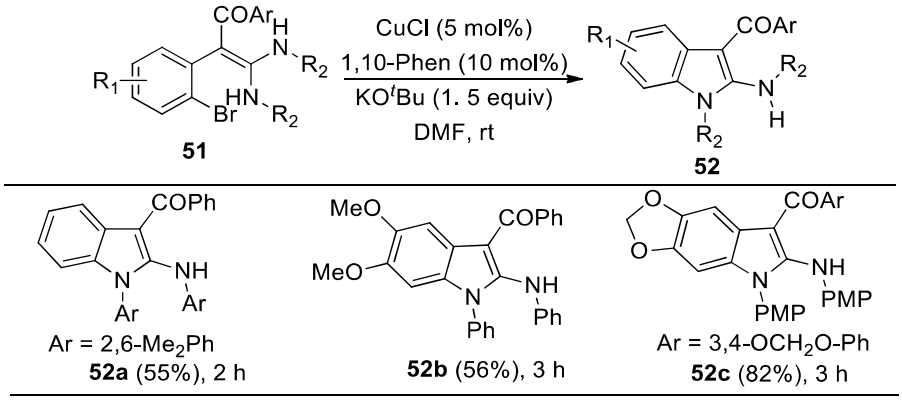
Table 2.13: Synthesis of α-Oxoketene Aminals 51 from Deoxybenzoins 50 and Carbodiimides 49



group. The required α-oxoketene aminals **51** were synthesized by treating the anion of deoxybenzoin **50** with carbodiimides **49** (Table 2.13).

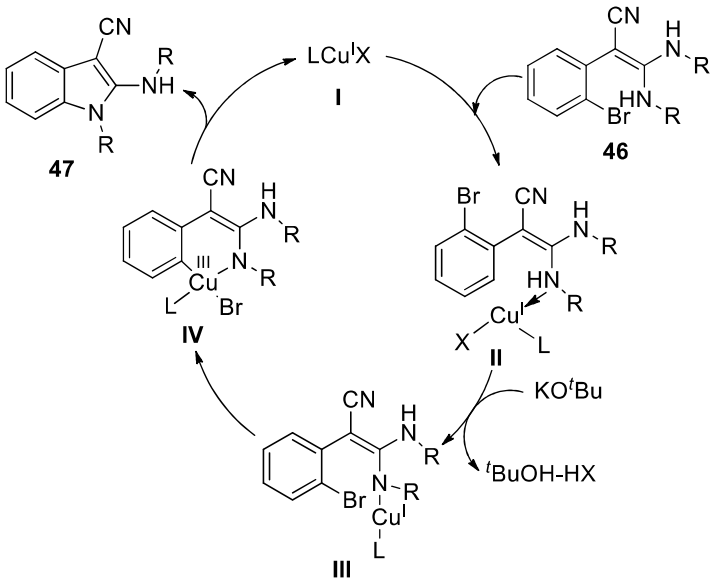
With these ketene aminals **51a-c** in our hands, we examined the intramolecular N-aryltion of newly synthesized ketene aminals **51**. In the presence of optimized conditions to ketene aminal **51a** was transformed to the corresponding 2-aminoindole **52a** in 55% yield. The reaction required 2h for complete conversion. Similarly, other α-oxoketene aminals **51b** & **51c** were also smoothly transformed to the corresponding 2-amino indoles **52b** & **52c** giving rise to 56-82% yields in 3 h (Table 2.14).

Table 2.14: Intramolecular *N*-Arylation of α-Oxoketene Aminals 51



2.4.5: Plausible Reaction Mechanism for the Copper-Mediated Intramolecular *N*-Arylation

Next, we turned our attention towards the proposing mechanism for this intramolecular C−N bond forming reactions. According to the known literature methods, in presence of ligand 1,10-phenanthrolione, copper salt will form the complex-**I**, where the Cu is in +1 oxidation state. Further, this complex-**I** binds to the amine of the ketene aminal *via* coordinate covalent bond delivers complex-**II**, which undergo deprotonation in the presence of KO^{t}Bu affords complex-III, where amine binds to the Cu in the form of anion. Then, this

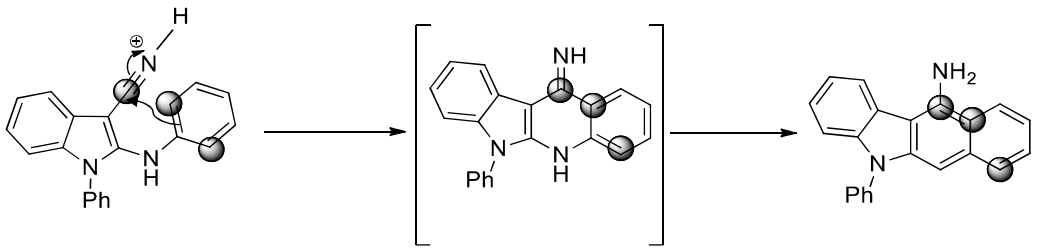


Scheme 2.20: *Proposed Mechanism for the Intramolecular N-Arylation of Ketene Aminals*

complex-**III** undergoes oxidative addition with adjacent bromoaryl group results in the formation of Cu(+3) complex-**IV**, which undergoes reductive elimination affords corresponding 2-aminoindole, with regeneration of Cu(+1) complex-**I** (Scheme 2.20).

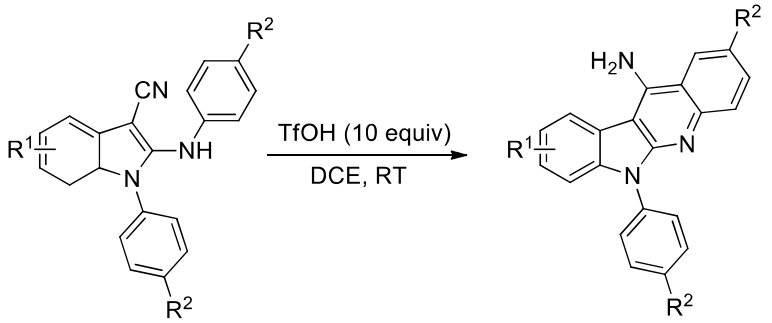
2.4.6 Synthetic Utility of 2-Aminoindole Derivatives

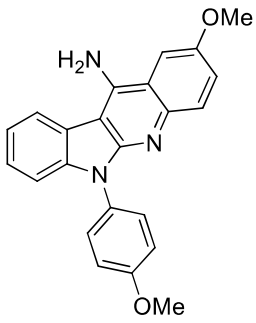
Finally, we envisioned intramolecular Gattermann type of reaction of newly synthesized 2-amino-3-cyano indoles **47**. This strategy involves activation of nitrile group by a bronsted acid, followed by trapping with adjacent nucleophilic centre. This approach will result in the formation of indoloquinoline derivatives (Scheme 2.21). By keeping this in mind, we treated the 2-amino-3-cyano indole **47a** with various bronsted acids and found that 10 equiv of triflic acid in the presence of DCE at room temperature obtained maximum yield of indoloquinoline **53a** (95%) in 3 h (Table 2.15).[25] Similarly, other 2-amino-3-cyanoindoles **47** which contain electron donating and withdrawing substitutions also smoothly transformed to the corresponding 11-aminoindolo-[2,3-*b*]quinolones **53** with good to excellent yields (Table



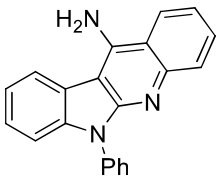
Scheme 2.21: *Schematic Representation of the Trapping the Activated Nitrile with Adjacent Nucleophilic Centre*

Table 2.15: Bronsted Acid Mediated Synthesis of Indolo Fused Quinolines 53

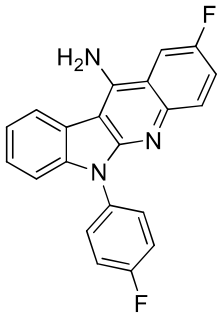




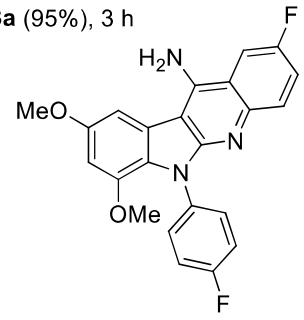
53a (95%), 3 h



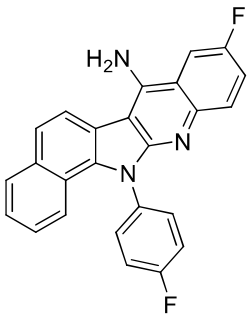
53b (75%), 3h



53c (80%), 2h



53m (82%), 3h



53p (72%), 2h

2.15). To the best of our knowledge, synthesis of 11-aminoindolo-[2,3-*b*]quinolones **53** *via* double heteroannulation at room temperature was not reported in literature.[31]

2.5 Conclusion:

In this chapter, we have discussed the simple and milder protocol for the CuCl mediated construction of 2-amino indoles *via* intramoleular *N*-arylation of *N*-aryl and *N*-alkyl substituted ketene aminals at ambient reaction conditions in shorter reaction times. We investigated the regioselecitve intramolecular *N*-arylation of unsymmetrical ketene aminals to afford a single regio isomer of 2-amino indole under optimized reaction conditions. We also extended this methodology to *N*-arylation of α-oxoketene aminals. Finally, we established the synthetic utility of these 2-amino-3-cyano indoles by transforming into tetracyclic 11-amino indolo[2,3-*b*]quinoline at room temperature. This is the useful approach for the rapid construction of neocryptolepine derivative from two easily synthesizable acyclic precursors *via* double heteroannulation strategy by using eco-friendly and cheaper metal copper under mild reaction conditions.

2.6 Experimental Section

2.6.1 General Information

All reactions were performed by using standard vial technique with rubber septum. All solids were weighed in air. Toluene, Dioxane, DMF, DMSO, DMA, Cs_2CO_3, K_3PO_4, NaOAc, DMAP, KO^{t}Bu, 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. Carbodiimides were synthesized from respective thioureas, which derived from aniline derivatives and few carbodiimides were purchased from Aldrich.

Tetramethylethylenediamine, (*R*)-(+)-1,1'-binaphthyl-2,2'-diamine, L-proline 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 F_{254} plates (Merck & co.) and were visualized by UV. NMR data were recorded on Bruker ARX 400 and 700 spectrometers. ^{13}C and ^{1}H NMR spectra were recorded in $CDCl_3$, MeOH-d_4 and DMSO-d_6 referenced according to signals of deutero solvents. ESI HR-MS measurements were performed on Bruker micrOTOF-Q-II mass-spectrometer.

2.6.2 General Procedure for the Synthesis of Symmetrical Thioures 50a-d

To a round-bottomed flask equipped with a magnetic stirrer and solution of NaOH (1.2 equiv) was added anilines (2 equiv) at 0 ºC, followed by CS_2 (1 equiv). Then the reaction mixture was allowed to stir at room temperature for 1 h. Then the reaction mixture was refluxed overnight, then cooled at r.t. A precipitate formed after the addition of 10 mL of water. The precipitate was filtered, washed with 20 mL water and dried to give thiourea.

2.6.3 General Procedure for the Synthesis of Unsymmetrical Thioureas 50e-g

Equimolar amounts of Arylisothiocyanates and Anilines/ Amines were taken in a mortar and reactant mixture was ground manually in a mortar for 15-20 minutes till completion of the starting materials (Monitored by TLC). The resulting solid thiourea product were directly used for further steps without any purification.

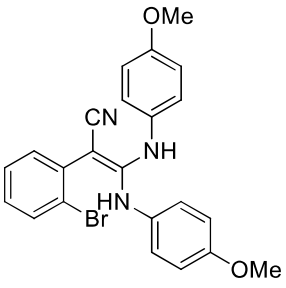
2.6.4 General Procedure for the Synthesis of Carbodiimides 49a-g

To a stirred and ice-cooled solution of thiourea derivatives 50 (1 equiv) in ethyl acetate, was added triethylamine (2 equiv). To this was added iodine (1.1 equiv) portion-wise over a period of 30 min. A light yellow colour precipitate of sulfur started separating out during this period. The precipitated sulfur was filtered, the organic layer evaporated and then extracted with hexane. The solution was concentrated under reduced pressure and purified by eluting through a short column of silica gel will affords corresponding carbodiimides.

2.6.5 Procedure for the Synthesis of Ketene Aminals 46 & 51

To a stirring suspension of NaH (60% suspension in mineral oil) (0.144 mg, 3.6 mmol, 1.2 equiv) in DMF at 0 ^{o}C was added drop wise the corresponding 2-haloaryl acetonitrile/deoxybenzoin (3 mmol) in DMF. After being further stirred for 1 h at room temperature, a solution of carbodiimide (3.6 mmol, 1.2 equiv) in DMF was added to the reaction mixture at 0 ^{o}C and followed by further stirring for 5 min - 15 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) and brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude products were purified by flash chromatography using hexane and EtOAc as eluent.

2-(2-Bromophenyl)-3,3-bis((4-methoxyphenyl)amino)acrylonitrile (46a)



Reaction Time: 5 min

Yield: 51% (695 mg), White Solid

R_f = 0.34 in 25% EtOAc in Hexanes;

Melting Point: 143 – 145 ºC;

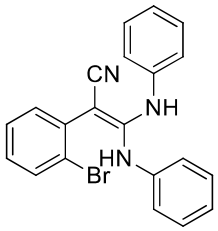
IR (KBr): ν (cm^{-1}) = 3292, 2933, 2171, 1601, 1579, 1510, 1371, 1240, 1031, 822

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 1H), 7.34 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 8.9 Hz, 2H), 7.02 – 6.94 (m, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.77 (d, *J* = 8.9 Hz, 2H), 6.59 (d, *J* = 8.9 Hz, 2H), 6.41 (s, 1H), 5.67 (s, 1H), 3.74 (s, 3H), 3.67 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 156.4, 153.9, 134.0, 133.3, 133.0, 131.9, 131.5, 128.5, 127.7, 125.9, 123.5, 123.2, 122.0, 114.6, 114.1, 67.1, 55.59, 55.54;

HRMS (ESI-TOF) m/z: Calcd. for $C_{23}H_{20}N_3O_2Br$ [M + H]: 450.0812 & 452.0792, found: 450.0814 & 452.0801.

2-(2-Bromophenyl)-3,3-bis(phenylamino)acrylonitrile (46b):



Reaction Time: 5 min

Yield: 66%, Pale yellow solid.

R_f = 0.31 in 25% EtOAc in Hexanes

Melting Point: 148 – 150 ºC

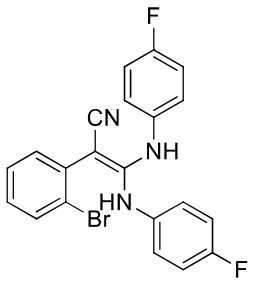
IR (KBr): ν (cm^{-1}) = 3368, 3237, 3050, 2924, 2193, 1573, 1344, 1028, 752

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.4 Hz, 1H), 7.38 – 7.34 (m, 1H), 7.21 (m, 3H), 7.12 –6.97 (m, 6H), 6.87 (m, 3H), 6.67 (s, 1H), 5.85 (s, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 139.2, 138.5, 133.6, 133.5, 132.8, 129.4, 128.9, 128.8, 127.8, 125.7, 123.9, 123.7, 121.4, 120.6, 120.5, 70.3

HRMS (ESI-TOF) m/z: Calcd. for $C_{21}H_{16}N_3Br$ [M + H]: 390.0600 & 392.0581, found: 390.0619 & 392.0601.

2-(2-Bromophenyl)-3,3-bis((4-fluorophenyl)amino)acrylonitrile (46c):



Yield: 73%, Pale yellow solid

R_f = 0.25 in 25% EtOAc in Hexanes

Melting Point: 217 – 219 ºC

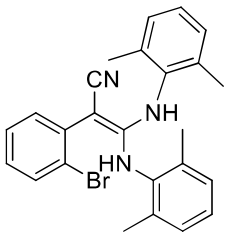
IR (KBr): ν (cm^{-1}) = 3376, 3246, 3055, 2192, 1579, 1508, 1215, 831

^{1}H NMR (400 MHz, DMSO-D_6) δ 9.06 (s, 1H), 8.69 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.30 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.24 (t, *J* = 7.1 Hz, 1H), 7.15 – 7.03 (m, 4H), 7.03 – 6.98 (m, 1H), 6.92 – 6.82 (m, 4H)

^{13}C NMR (100 MHz, DMSO-D_6) δ 157.4 (d, *J* = 238 Hz), 157.3 (d, *J* = 237 Hz), 152.0, 137.7, 136.4, 135.2, 132.9, 132.3, 127.8, 127.7, 124.2, 121.6, 121.2 (d, *J* = 7.2 Hz), 120.2 (d, *J* = 7.2 Hz), 115.4 (d, *J* = 22.3 Hz), 114.8 (d, *J* = 22.5 Hz), 69.6

HRMS (ESI-TOF) m/z: Calcd. for $C_{21}H_{14}F_2BrN_3$ [M + H]: 448.0231 & 450.0238, found: 448.0238 & 450.0220.

2-(2-Bromophenyl)-3,3-bis((2,6-dimethylphenyl)amino)acrylonitrile (46d):



Reaction Time: 10 min

Yield: 68%, White solid

R_f = 0.31 in 25% EtOAc in Hexanes

Melting Point: 176 – 177 ºC

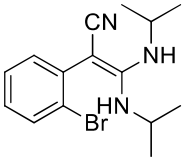
IR (KBr): ν (cm^{-1}) = 3374, 3254, 2924, 2174, 1600, 1585, 1470, 1222, 773

^{1}H NMR (400 MHz, $CDCl_3$, Major isomer only) δ 7.68 (d, *J* = 8 Hz, 1H), 7.51 (d, *J* = 6.8 Hz, 1H), 7.33 (t, *J* = 6.4 Hz, 1H), 7.19 – 7.16 (m, 3H), 7.11 – 7.07 (m, 2H), 7.04 – 7.03 (m, 2H), 5.57 (s, 1H), 5.22 (s, 1H), 2.46 (s, 6H), 2.35 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, Major isomer only) δ 154.6, 137.6, 134.6, 134.4, 134.3, 133.5, 133.4, 130.6, 129.4, 128.7, 128.3 (2C), 128.0, 123.6, 120.6, 60.0, 18.6, 18.5.

HRMS (ESI-TOF) m/z: Calcd. For $C_{25}H_{24}N_3Br$ [M + H]: 446.1226 & 448.1207, found: 446.1245 & 448.1228.

2-(2-Bromophenyl)-3,3-bis(isopropylamino)acrylonitrile (46e):



Reaction Time: 2 h

Yield: 50%, White solid

R_f = 0.38 in 30% EtOAc in Hexanes

Melting Point: 101 – 104 ºC

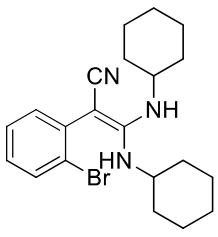
IR (KBr): ν (cm^{-1}) = 3328, 3089, 2967, 2158, 1604, 1561, 1479, 1304, 1144, 1023, 741

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 1H), 7.43 – 7.20 (m, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 4.25 - 3.23 (m, 4H), 1.16 (s, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 134.8, 133.4, 133.3, 128.7, 127.8, 126.8, 123.2, 64.3, 46.7(2C), 23.5(2C)

HRMS (ESI-TOF) m/z: Calcd. For $C_{15}H_{20}N_3Br$ [M + H]: 322.0913 & 324.0893, found: 322.0939 & 324.0923.

2-(2-Bromophenyl)-3,3-bis(cyclohexylamino)acrylonitrile (46f):



Reaction Time: 6 h

Yield: 42%, White solid

R_f = 0.3 in 15% EtOAc in Hexanes

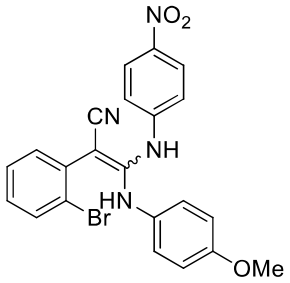
Melting Point: 100 – 102 ºC

IR (KBr): ν (cm^{-1}) = 3307, 2930, 2853, 2157, 1527, 1470, 1450, 1342

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.3 Hz, 1H), 7.34 - 7.24(m, 2H), 7.11 - 7.08 (m, 1H), 3.72 – 4.21 (m, 2H), 3.05 – 3.42 (m, 2H), 1.93 (s, 4H), 1.47 - 4.47 (m, 6H), 1.30 - 1.97 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 135.1, 133.1, 128.2, 127.6, 126.6, 123.6, 62.6, 53.4, 33.7, 25.2, 24.7

HRMS (ESI-TOF) m/z: Calcd. For $C_{21}H_{28}BrN_3$ [M + H]: 402.1539 & 404.1520 found: 402.1560 & 404.1545.

(*E*)&(Z)-2-(2-Bromophenyl)-3-((4-methoxyphenyl)amino)-3-((4-nitrophenyl)amino) acrylo nitrile (3ag):



Reaction Time: 5 min

Yield: 59%, Yellowish orange solid

R_f = 0.33 in 40% EtOAc in Hexanes

Melting Point: 109 – 111 ºC

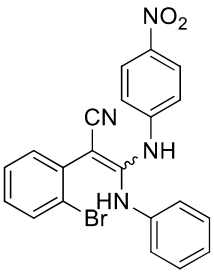
IR (KBr): ν (cm^{-1}) = 3371, 2928, 2370, 2184, 1595, 1510, 1333, 1305, 1248, 1179, 1111

^{1}H NMR (400 MHz, $CDCl_3$, Mixture of two isomers) δ 8.03 – 7.97 (m, 2H) [7.91 – 7.86 (m, 2H)], 7.58 – 7.55 (m, 1H) [7.49 – 7.46 (m, 1H)], 7.42 – 7.39 (m, 1H), 7.34 – 7.29 (m, 3H), [7.19 – 7.08 (m, 4H)], 7.02 -6.97 (m, 3H) [6.91 – 6.85 (m, 3H)], 6.77 – 6.71 (m, 2H), [6.65 – 6.59 (m, 2H)], 6.20 (s, 1H) [6.00 (s, 1H)], 3.71 (s, 3H), [3.66 (s, 3H)]

^{13}C NMR (100 MHz, $CDCl_3$, Mixture of two isomers) δ 156.9 (156.8), 151.0 (150.9), 146.2 (145.2), 142.8 (142.2),133.7 (133.6), 132.9 (132.8), 132.7 (132.4), 131.3 (130.8), 129.6 (129.2), 128.3 (128.0), 127.3 (125.7), 125.3 (124.9), 123.09 (123.02), 120.7 (118.2), 117.9 (114.7), 114.4 (114.2), 73.3 (72.7), 55.6 (55.4)

HRMS (ESI-TOF) m/z: Calcd. For $C_{22}H_{17}BrN_4O_3$ [M + Na]: 487.0376 & 489.0357, found: 487.0396 & 489.0374.

(*E*)&(Z)-2-(2-Bromophenyl)-3-((4-nitrophenyl)amino)-3-(phenylamino)acrylonitrile (3ah):



Reaction Time: 5 min

Yield: 65% (852 mg), Yellowish orange solid

R_f = 0.32 in 33% EtOAc in Hexanes

Melting Point: 129 – 131 ºC

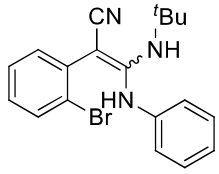
IR (KBr): ν (cm^{-1}) = 3385, 2924, 2366, 2186, 1596, 1499, 1330, 1258, 1181, 1112, 848, 751

^{1}H NMR (400 MHz, $CDCl_3$, Mixture of two isomers) δ 8.01 (d, *J* = 9.0 Hz, 2H) [7.90 (d, *J* = 9.0 Hz, 2H)], 7.58 (d, *J* = 8.0 Hz, 1H) [7.50 (d, *J* = 8.0 Hz, 1H)], 7.41 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.38 – 7.35 (m, 1H)], 7.34 – 7.31 (m, 1H) [7.31– 7.26 (m, 1H)], 7.23 - 7.18 (m, 3H), [7.15 -7.08 (m, 6H)], 7.06 – 6.98 (m, 3H), 6.94 - 6.89 (m, 2H) [6.94 - 6.89 (m, 2H)], 6.20 (s, 1H) [6.05 (s, 1H)].

^{13}C NMR (100 MHz, $CDCl_3$, Mixture of two isomers) δ 150.25 (150.22), 146.36 (146.32), 145.36 (145.32), 142.07 (142.05), 141.88 (141.85), 138.7 (138.0), 133.64 (132.8), 132.6 (132.4), 129.5 (129.45), 129.2 (129.1), 128.1 (127.9) 125.5 (125.2), 125.1 (124.8), 124.2 (124.1), 120.6 (120.3), 118.2 (117.8), 74.5 (74.1)

HRMS (ESI-TOF) m/z: Calcd. For $C_{21}H_{15}BrN_4O_2$ [M + Na]: 457.0271 & 459.0251, found: 457.0273 & 459.0252.

(*E*)&(Z)-2-(2-Bromophenyl)-3-(tert-butylamino)-3-(phenylamino)acrylonitrile (3ai):



Reaction Time: 15 min

Yield: 60%, Yellow solid

R_f = 0.29 in 25% EtOAc in Hexanes

Melting Point: 134 – 135 ºC

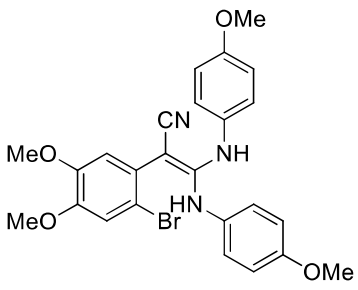
IR (KBr): ν (cm^{-1}) = 3393, 3295, 2964, 2369, 2172, 1570, 1421, 1394, 1286, 1229

^{1}H NMR (700 MHz, $CDCl_3$, Major isomer only) 7.29 (d, *J* = 7.7 Hz, 1H), 7.23 – 7.10 (m, 2H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.01 – 6.81 (m, 2H), 6.83 – 6.75 (m, 3H), 5.65 (s, 1H), 4.6 (s, 1H), 1.40 (s, 9H)

^{13}C NMR (175 MHz, $CDCl_3$, Major isomer only) δ 156.3, 139.2, 134.0, 133.1, 132.1, 128.6, 128.1, 127.3, 124.8, 122.9, 122.6, 119.7, 72.8, 55.0, 31.1

HRMS (ESI-TOF) m/z: Calcd. For $C_{19}H_{20}BrN_3$ [M + Na]: 392.0733 & 394.0713, found: 392.0704 & 394.0689.

2-(2-Bromo-4,5-dimethoxyphenyl)-3,3-bis((4-methoxyphenyl)amino)acrylonitrile(46g):



Reaction Time: 5 min

Yield: 54%, Yellow solid

R_f = 0.35 in 30% EtOAc in Hexanes

Melting Point: 148 – 150 ºC

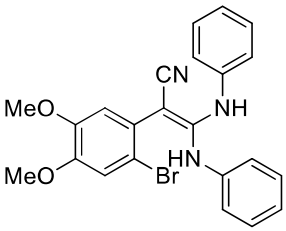
IR (KBr): ν (cm^{-1}) = 3339, 2931, 2835, 2169, 1608, 1504, 1245, 1172, 827

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 8.8 Hz, 2H), 6.95 (s, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.81 (s, 1H), 6.76 (d, *J* = 8.8 Hz, 2H), 6.61 (d, *J* = 8.8 Hz, 2H), 6.33 (s, 1H), 5.68 (s, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 3.68 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 156.4, 153.9, 148.7, 148.5, 132.1, 131.6, 125.7, 123.3, 123.2, 122.1, 116.4, 115.7, 115.0, 114.5, 114.1, 67.0, 56.2, 56.1, 55.5(2C);

HRMS (ESI-TOF) m/z: Calcd. For $C_{25}H_{24}N_3O_4Br$ [M + H]: 510.1023 & 512.1004, found: 510.1034 & 512.1021.

2-(2-Bromo-4,5-dimethoxyphenyl)-3,3-bis(phenylamino)acrylonitrile (46h):



Reaction Time: 5 min

Yield: 59%, Pale yellow solid

R_f = 0.32 in 30% EtOAc in Hexanes

Melting Point: 196 – 198 ºC

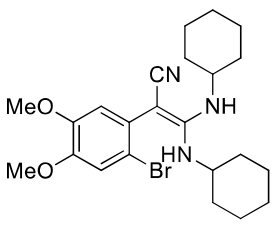
IR (KBr): ν (cm^{-1}) = 3374, 3332, 2928, 2169, 1600, 1497, 1432, 1245, 1172, 1014, 746

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.7 Hz, 2H), 7.12 – 7.02 (m, 4H), 7.03 – 6.94 (m, 2H), 6.93– 6.83 (m, 3H), 6.82 (s, 1H), 6.57 (s, 1H), 5.89 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 148.9, 148.6, 139.3, 138.8, 129.3, 129.0, 128.9, 125.3, 123.7, 121.5, 120.4, 120.3, 116.2, 115.7, 114.7, 70.2, 56.2, 56.1

HRMS (ESI-TOF) m/z: Calcd. For $C_{23}H_{20}N_3O_2Br$ [M + H]: 450.0812 & 452.0792, found: 450.0803 & 452.0790.

2-(2-Bromo-4,5-dimethoxyphenyl)-3,3-bis(cyclohexylamino)acrylonitrile (46i):



Reaction Time: 6 h

Yield: 29%, White solid

R_f = 0.28 in 25% EtOAc in Hexanes

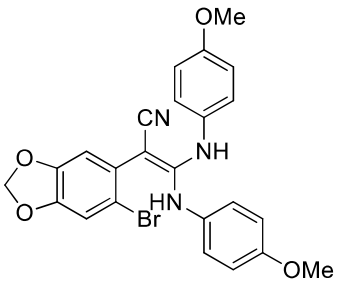
Melting Point: 137 – 138 ºC; IR (KBr): ν (cm^{-1}) = 3692, 3339, 2931, 2852, 2150, 1541, 1500, 1435, 1209.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.02 (s, 1H), 6.77 (s, 1H), 4.10 (brs, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.59 (brs, 1H), 3.36 – 3.23 (m, 1H), 3.05 – 2.91 (m, 1H), 2.07 – 1.95 (m, 2H), 1.86 – 1.73 (m, 4H), 1.64 – 1.51 (m, 4H), 1.28 – 0.95 (m, 10 H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 160.1, 148.9, 148.5, 126.4, 123.4, 117.4, 115.6, 115.4, 63.7, 56.1, 56.1, 54.4, 53.1, 48.8, 34.0, 33.9, 25.6, 25.3, 24.9.

HRMS (ESI-TOF) m/z: Calcd. For $C_{23}H_{32}BrN_3O_2$ [M + H]: 462.1751 & 464.1731, found: 462.1731 & 464.1712.

2-(6-Bromobenzo[d][1,3]dioxol-5-yl)-3,3-bis((4-methoxyphenyl)amino)acrylonitrile (46j):



Reaction Time: 5 min

Yield: 58%, Yellow solid

R_f = 0.32 in 30% EtOAc in Hexanes

Melting Point: 154 – 155 ºC

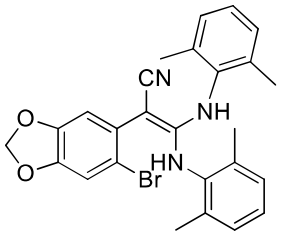
IR (KBr): ν (cm^{-1}) = 3261, 2913, 2161, 1510, 1470, 1242, 1028, 828

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.8 Hz, 2H), 6.94 (s, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.79 (s, 1H), 6.76 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 8.8 Hz, 2H), 6.33 (s, 1H), 5.91 (s, 2H), 5.62 (s, 1H), 3.74 (s, 3H), 3.69 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 156.5, 154.0, 147.8, 147.6, 131.9, 131.5, 126.6, 123.6, 123.5, 121.8, 117.3, 114.6, 114.2, 113.0, 112.2, 102.0, 67.1, 55.6, 55.5;

HRMS (ESI-TOF) m/z: Calcd. For $C_{24}H_{20}N_3O_4Br$ [M + H]: 494.0710 & 496.0691, found: 494.0691 & 496.0681.

2-(6-Bromobenzo[d][1,3]dioxol-5-yl)-3,3-bis((2,6-dimethylphenyl)amino)acrylonitrile (46k):



Reaction Time: 30 min

Yield: 62%, White solid

R_f = 0.3 in 20% EtOAc in Hexanes

Melting Point: 117 – 118 ºC

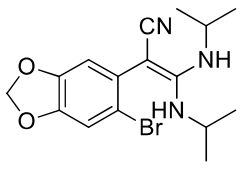
IR (KBr): ν (cm^{-1}) = 3377, 3261, 2920, 2176, 1585, 1474, 1223, 1035

^{1}H NMR (400 MHz, $CDCl_3$, Major isomer only) 7.13 – 7.09 (m, 2H), 7.07 – 7.02 (m, 4H), 7.00 (s, 1H), 6.86 (s, 1H), 5.94 (s, 2H), 5.47 (s, 1H), 5.19 (s, 1H), 2.37 (s, 6H), 2.29 (s, 6H)

^{13}C NMR (100 MHz, $CDCl_3$, Major isomer only) δ 154.7, 148.4, 147.7, 137.76, 137.70, 134, 128.7, 128.47, 128.42, 128.1, 127.3, 123.6, 119.5, 115.4, 113.4, 113.1, 102.0, 59.7, 18.7, 18.5

HRMS (ESI-TOF) m/z: Calcd. For $C_{26}H_{24}N_3O_2Br$ [M + H]; 490.1125 & 492.1106, found: 490.1136 & 492.1120.

2-(6-Bromobenzo[d][1,3]dioxol-5-yl)-3,3-bis(isopropylamino)acrylonitrile (46l):



Reaction Time: 1 h

Yield: 42%, Pale yellow solid

R_f = 0.3 in 25% EtOAc in Hexanes

Melting Point: 116-118 ºC

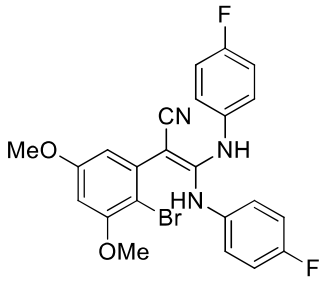
IR (KBr): ν (cm^{-1}) = 3394, 3307, 2972, 2930, 2152, 1572, 1552, 1477, 1034

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.77 (s, 1H), 5.98 (s, 2H), 4.0 – 3.89 (m, 1H), 3.76 – 3.63 (m, 1H), 3.43 (brs, 2H), 1.21 (s, 6H), 0.96 (s, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 147.9, 147.6, 127.2, 123.1, 117.9, 112.9, 112.4, 101.9, 64.4, 47.4, 46.1, 23.5(2C)

HRMS (ESI-TOF) m/z: Calcd. For $C_{16}H_{20}N_3O_2Br$ [M + H]: 366.0812 & 368.0792, found: 366.0816 & 368.0797.

2-(2-Bromo-3,5-dimethoxyphenyl)-3,3-bis((4-fluorophenyl)amino)acrylonitrile (46m):



Reaction Time: 5 min

Yield: 59%, Pale yellow solid

R_f = 0.25 in 30% EtOAc in Hexanes

Melting Point: 161 – 163 ºC

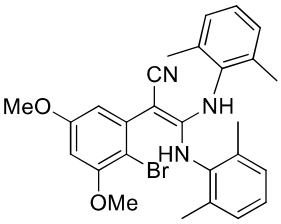
IR (KBr): ν (cm^{-1}) = 3406, 3319, 2930, 2173, 1585, 1509, 1336, 1215, 1156

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03-6.98 (m, 2H), 6.92 – 6.82 (m, 4H), 6.75 (t, *J* = 8.5 Hz, 2H), 6.60 (s, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 6.34 (d, *J* = 2.4 Hz, 1H), 5.76 (s, 1H), 3.83 (s, 3H), 3.75 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (d, *J* = 242 Hz)158.6 (d, *J* = 255 Hz) 152.9, 135.2 (d, *J* = 2.4 Hz), 134.9, 134.5 (d, *J* = 2.4 Hz), 122.9 (d, *J* = 8.2 Hz), 122.6 (d, *J* = 8.1 Hz), 121.4, 115.9 (d, *J* = 22.8 Hz), 115.5 (d, *J* = 22.8 Hz), 108.5, 106.4, 99.1, 69.8, 56.4, 55.7

HRMS (ESI-TOF) m/z: Calcd. For $C_{23}H_{18}F_2BrN_3O_2$ [M + Na]: 508.0443 & 510.0423, found: 508.0457 & 510.0442.

2-(2-Bromo-3,5-dimethoxyphenyl)-3,3-bis((2,6-dimethylphenyl)amino)acrylonitrile (46n):



Reaction Time: 15 min

Yield: 75%, White solid

R_f = 0.32 in 25% EtOAc in Hexanes

Melting Point: 166 – 167 ºC

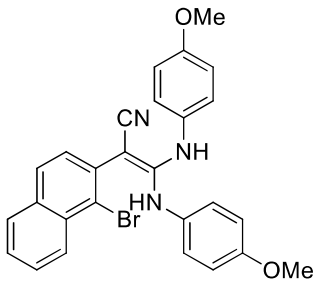
IR (KBr): ν (cm^{-1}) = 3365, 3250, 2926, 2176, 1581, 1451, 1340, 1025

^{1}H NMR (400 MHz, $CDCl_3$, Major isomer only) δ 7.10 – 7.07 (m, 2H), 7.06 – 6.94 (m, 4H), 6.64 (s, 1H), 6.42 (s, 1H), 5.43 (s, 1H), 5.25 (s, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 2.38 (s, 6H), 2.28 (s, 6H)

^{13}C NMR (100 MHz, $CDCl_3$, Major isomer only) δ 159.9, 157.5, 154.4, 137.6, 137.5, 136.7, 136.3, 134.4, 133.5, 128.6, 128.2, 128.1, 120.5, 110.0, 105.7, 99.4, 60.3, 56.4, 55.6, 18.6, 18.4

HRMS (ESI-TOF) m/z: Calcd. For $C_{27}H_{28}N_3O_2Br$ [M + H]: 506.1438 & 508.1419, found: 506.1436 & 508.1421.

2-(1-Bromonaphthalen-2-yl)-3,3-bis((4-methoxyphenyl)amino)acrylonitrile (46o):



Reaction Time: 5 min

Yield: 40%, Pale red solid

R_f = 0.38 in 30% EtOAc in Hexanes

Melting Point: 106 – 109 ºC

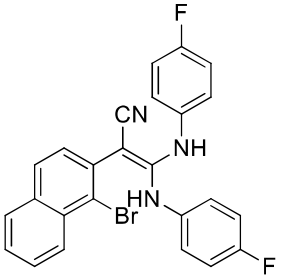
IR (KBr): ν (cm^{-1}) = 3361, 2931, 2834, 2170, 1604, 1582, 1510, 1242, 1179, 1035, 821.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.49 – 7.45 (m, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.10 – 7.05 (m, 2H), 6.85 – 6.80 (m, 2H), 6.80 – 6.75 (m, 2H), 6.54 – 6.50 (m, 2H), 6.48 (s, 1H), 5.72 (s, 1H), 3.74 (s, 3H), 3.57 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 156.3, 154.1, 133.3, 132.9, 132.1, 132.0, 131.4, 129.5, 128.0, 128.0, 127.6, 127.5, 126.6, 125.8, 123.4, 123.1, 121.9, 114.6, 114.0, 68.7, 55.5, 55.4;

HRMS (ESI-TOF) m/z: Calcd. For $C_{27}H_{22}N_3O_2Br$ [M + H]: 500.0968 & 502.0949, found: 500.0963 & 502.0944.

2-(1-Bromonaphthalen-2-yl)-3,3-bis((4-fluorophenyl)amino)acrylonitrile (46p):



Reaction Time: 15 min

Yield: 56%, Pale yellow solid

R_f = 0.30 in 25% EtOAc in Hexanes

Melting Point: 131 – 133 °C

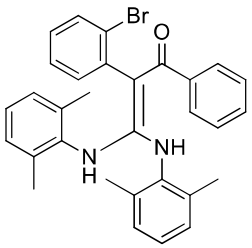
IR (KBr): ν (cm^{-1}) = 3265, 2925, 2184, 1587, 1508, 1320, 1217, 1156

^{1}H NMR (700 MHz, DMSO-D_6) δ 9.15 (s, 1H), 8.76 (s, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 7.87 - 7.80 (m, 2H), 7.67 – 7.56 (m, 1H), 7.56 – 7.48 (m, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.21 – 7.11 (m, 2H), 7.11 – 7.02 (m, 2H), 6.98 – 6.88 (m, 2H), 6.87 – 6.75 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9 (d, *J* = 236.9 Hz), 157.8 (d, *J* = 236.7 Hz), 152.9, 138.2, 137.0, 134.2, 133.1, 132.7, 129.9, 128.6, 128.34, 128.31, 127.1 (d, *J* = 2.45 Hz), 126.8 (d, *J* = 2.5 Hz), 124.1, 122.0, 121.7 (d, *J* = 4.3 Hz), 120.8 (d, *J* = 5.0 Hz), 116.6 (d, *J* = 22.2 Hz), 115.4 (d, *J* = 21.8 Hz), 71.7

HRMS (ESI-TOF) m/z: Calcd. For $C_{25}H_{16}BrF_2N_3$ [M + H]: 476.0568 & 478.0549, found: 476.0589 & 478.0577.

2-(2-Bromophenyl)-3,3-bis((2,6-dimethylphenyl)amino)-1-phenylprop-2-en-1-one (51a):



Reaction Time: 3 h

Yield: 44%, Yellow solid

R_f = 0.30 in 10% EtOAc in Hexanes

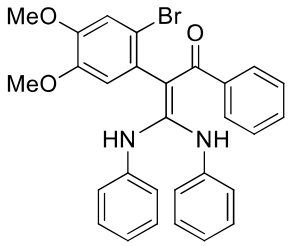
Melting Point: 158 – 160 ºC; IR (KBr): ν (cm^{-1}) = 3328, 3237, 2921, 1948, 1583, 1470, 1311, 1211, 1025, 766

^{1}H NMR (400 MHz, $CDCl_3$, Major isomer only) δ 8.17 – 8.94(m, 1H), 7.64 – 7.40(m, 2H), 7.40 – 7.23 (m, 3H), 7.20 – 6.94 (m, 5H), 6.94 – 6.70 (m, 3H), 5.6 (s, 1H), 2.6 – 1.9 (m, 12H)

^{13}C NMR (100 MHz, $CDCl_3$, Major isomer only) δ 195.4, 162.0, 142.8, 138.7, 136.2, 136.0, 135.8, 134.2, 133.0, 131.7, 130.3, 130.0, 129.4, 128.9, 128.6, 128.4, 128.2, 128.0, 127.8, 125.4, 97.9, 18.6, 18.4.

HRMS (ESI-TOF) m/z: Calcd. For $C_{31}H_{29}N_2OBr$ [M + H]: 525.1536 & 527.1517, found: 525.1508 & 527.1494.

2-(2-Bromo-4,5-dimethoxyphenyl)-1-phenyl-3,3-bis(phenylamino)prop-2-en-1-one (51b):



Reaction Time: 1 h

Yield: 39%, Yellow solid

R_f = 0.30 in 30% EtOAc in Hexanes

Melting Point: 156 – 158 ºC

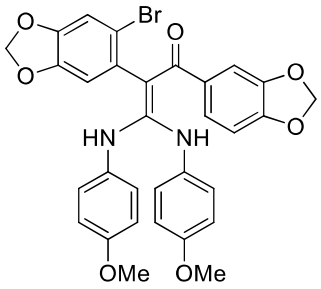
IR (KBr): ν (cm^{-1}) = 3316, 3054, 2931, 2839, 1599, 1500, 1323, 1234, 1027.

^{1}H NMR (700 MHz, $CDCl_3$, Major isomer only) δ 14.06 (s, 1H), 7.28 – 7.24 (m, 2H), 7.19 - 7. 11(m, 4H), 7.10 – 6.93 (m, 7H), 6.91 – 6.78 (m, 3H), 6.64 (s, 1H), 6.08 (s, 1H), 3.82 (s, 3H), 3.60 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$, Major isomer only) δ 190.0, 156.4, 149.0, 148.6, 142.8, 138.4, 129.9, 129.1, 128.6, 128.4, 128.1, 127.5, 127.1, 124.3, 123.0, 122.2, 121.9, 119.2, 118.0, 115.4, 100.2, 56.12, 56.15.

HRMS (ESI-TOF) m/z: Calcd. For $C_{29}H_{25}BrN_2O_3$ [M + H]: 529.1121 & 531.1102, found: 529.1120 & 531.1108.

1-(Benzo[d][1,3]dioxol-5-yl)-2-(6-bromobenzo[d][1,3]dioxol-5-yl)-3,3-bis((4-methoxy phenyl)amino)prop-2-en-1-one (51c):



Reaction Time: 52 h min

Yield: 41%, Yellow solid

R_f = 0.33 in 40% EtOAc in Hexanes

Melting Point: 159 – 161 ºC

IR (KBr): ν (cm^{-1}) = 3394, 2912, 1608, 1509, 1244, 1036, 933, 825

^{1}H NMR (400 MHz, $CDCl_3$, Major isomer only) δ 13.88 (s, 1H), 7.00 (s, 1H), 6.98 – 6.89 (m, 2H), 6.86 (s, 1H), 6.82 – 6.72 (m, 4H), 6.68 (s, 1H), 6.62 – 6.4 (m, 3H), 6.53 – 6.44 (m, 2H), 5.98 – 5.94 (m, 2H), 5.89 (s, 2H), 3.67 (s, 3H), 3.65 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$, Major isomer only) δ 187.6, 158.1, 156.7, 147.9, 147.8, 147.5, 146.8, 137.1, 131.3, 125.1, 124.8, 121.9, 120.0, 114.7, 114.4, 113.8 (2C), 112.9, 108.3, 108.1, 107.2, 102.2, 101.9, 100.9, 99.1, 55.5, 55.4.

HRMS (ESI-TOF) m/z: Calcd. For $C_{31}H_{25}N_2O_7Br$ [M + H]: 617.0918 & 619.0899, found: 617.0924 & 619.0908.

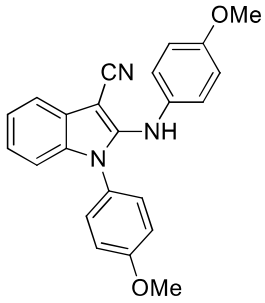
2.6.6 Procedure for Optimization of the *N*-Arylation of Ketene Aminal 46a

An oven-dried 8 mL reaction vial was charged with copper-salt (1-5 mol%), ligand (2-10 mol%) and base (0.75 mmol, 1.2 equiv), respective aminal **3aa** (0.5 mmol) in solvent (2.0 mL) was stirred at room temperature for 5 min – 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 using hexane and EtOAc as eluent.

2.6.7 General Procedure for Copper Catalyzed *N*-Arylation of Ketene Aminals 46 & 51

An oven-dried 8 mL reaction vial was charged with CuCl (5 mol%, 2.47 mg), 1,10-Phenanthroline (10 mol%, 9 mg) and KO*t*Bu (0.75 mmol, 1.2 equiv, 0.112 g), the respective ketene aminal **3** (0.5 mmol) in DMF (2.0 mL) was stirred at room temperature / 120 ºC for 5 min - 2 h. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was purified by flash chromatography using hexane and EtOAc as eluent.

3-Cyano-1-(4-methoxyphenyl)-2-((4-methoxyphenyl)amino)-1*H*-indole (47a):



Reaction Time: 5 min

Yield: 99%, Pale brick red colour solid

R_f = 0.36 in 25% EtOAc in Hexanes

Melting Point: 121 – 123 ºC

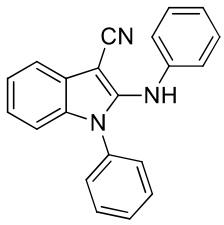
IR (KBr): ν (cm^{-1}) = 3337, 2931, 2195, 1561, 1514, 1253, 1029, 829

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.6 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.21 – 7.17 (m, 1H), 7.17 – 7.12 (m, 2H), 7.12 – 7.07 (m, 3H), 6.92 – 6.86 (m, 3H), 5.80 (br s, 1H), 3.89 (s, 3H), 3.80 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 157.6, 148.7, 134.6, 131.3, 129.5, 127.7, 126.4, 125.1, 122.2, 121.7, 117.6, 116.0, 115.7, 114.6, 109.6, 67.8, 55.7, 55.5

HRMS (ESI-TOF) m/z: Calcd. For $C_{23}H_{19}N_3O_2$ [M + H]: 370.1550, found: 370.1552.

3-Cyano-1-phenyl-2-(phenylamino)-1*H*-indole (47b):



Reaction Time: 5 min

Yield: 92%, Pale brick red colour solid

R_f = 0.34 in 25% EtOAc in Hexanes

Melting Point: 178 – 179 °C

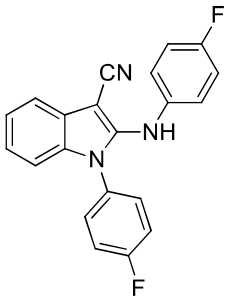
IR (KBr): ν (cm^{-1}) = 3444, 3265, 2919, 2212, 1559, 1220, 748

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 2H), 7.55 – 7.49 (m, 1H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.27 - 7.23 (m, 1H), 7.19 – 7.06 (m, 4H), 7.03 (d, *J* = 8.0 Hz, 1H), 5.94 (s, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 139.3, 134.4, 134.3, 130.5, 129.6, 129.4, 127.9, 127.4, 124.41, 122.7, 122.5, 120.6, 118.2, 115.7, 110.1, 71.9

HRMS (ESI-TOF) m/z: Calcd. For $C_{22}H_{14}N_3$ [M + H]: 310.1339, found: 310.1353.

3-Cyano-1-(4-fluorophenyl)-2-((4-fluorophenyl)amino)-1*H*-indole (47c):



Reaction Time: 5 min

Yield: 76%, White solid

R_f = 0.40 in 25% EtOAc in Hexanes

Melting Point: 188 – 189 ºC

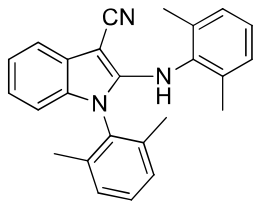
IR (KBr): ν (cm^{-1}) = 3277, 3056, 2210, 1563, 1510, 1212, 832

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.3 Hz, 1H), 7.44 (s, 2H), 7.23 - 7.26 (m, 3H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.11 (s, 2H), 7.03 (s, 2H), 6.98 (d, *J* = 7.8 Hz, 1H), 5.90 (s, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (d, *J* = 250.8 Hz), 159.9 (d, *J* = 244.3 Hz), 147.3, 135.1 (d, *J* = 2.5 Hz), 134.4, 130.2 (d, *J* = 2.9 Hz), 130.0 (d, *J* = 8.8 Hz), 127.2, 123.5 (d, *J* = 8.2 Hz), 122.7, 122.5, 118.0, 117.6 (d, *J* = 23.0 Hz), 116.2 (d, *J* = 22.9 Hz), 115.5, 109.8, 70.9

HRMS (ESI-TOF) m/z: Calcd. For $C_{21}H_{13}F_2N_3$ [M + H]: 346.1150, found: 346.1154.

3-Cyano-1-(2,6-dimethylphenyl)-2-((2,6-dimethylphenyl)amino)-1*H*-indole (47d):



Reaction Time: 5 min

Yield: 86%, Brick red colour solid.

R_f = 0.31 in 25% EtOAc in Hexanes

Melting Point: 225 – 228 ºC

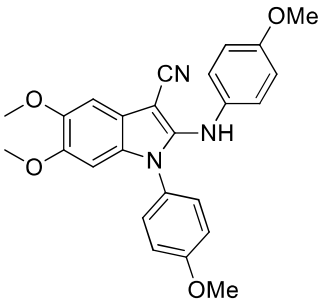
IR (KBr): ν (cm^{-1}) = 3266, 3026, 2921, 2192, 1596, 1560, 1519, 1469, 1202, 767

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.7 Hz, 1H), 7.45 – 7.39 (m, 1H), 7.36-7.31 (m, 2H), 7.21 (m, 1H), 7.16 7.12 (m, 3H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 5.41 (s, 1H), 2.29 (s, 6H), 2.12 (s, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 138.5, 137.3, 133.9, 132.8, 131.2, 130.4, 129.5, 128.7, 128.6, 128.2, 122.0, 121.4, 117.4, 115.1, 108.7, 64.4, 18.3, 17.7

HRMS (ESI-TOF) m/z: Calcd. For $C_{25}H_{23}N_3$ [M + H]: 366.1965, found: 366.1970.

3-Cyano-5,6-dimethoxy-1-(4-methoxyphenyl)-2-((4-methoxyphenyl)amino)-1*H*-indole (47g)



Reaction Time: 45 min

Yield: 92%, Brick red colour solid

R_f = 0.37 in 30% EtOAc in Hexanes

Melting Point: 195 – 197 ºC

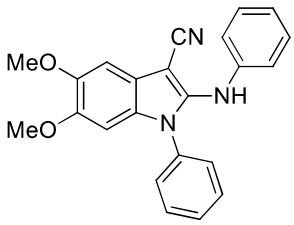
IR (KBr): ν (cm^{-1}) = 3322, 2932, 2194, 1567, 1519, 1490, 1252, 1186, 1026

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.15 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.99 (m, 3H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.51 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.70 (s, 3H), 3.65 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 157.0, 147.1, 146.7, 146.5, 132.4, 129.3, 128.3, 126.8, 123.7, 120.1, 116.3, 115.7, 114.6, 100.5, 94.6, 69.4, 56.6, 56.5, 55.7, 55.5

HRMS (ESI-TOF) m/z: Calcd. For $C_{25}H_{23}N_3O_4$ [M + H]: 430.1761, found: 430.1786.

3-Cyano-5,6-dimethoxy-1-phenyl-2-(phenylamino)-1*H*-indole (47h):



Reaction Time: 10 min

Yield: 88%, Brick red colour solid

R_f = 0.34 in 30% EtOAc in Hexanes

Melting Point: 179 – 180 ºC

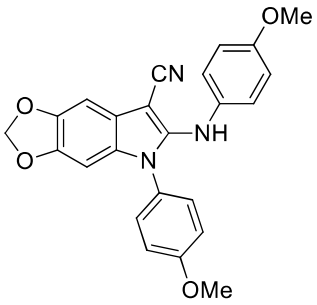
IR (KBr): ν (cm^{-1}) =3347, 2936, 2214, 1602, 1487, 1384, 1280, 1167

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 - 7.49 (m, 3H), 7.40 - 7.39 (m, 2H), 7.26 (s, 2H), 7.10 (s, 1H), 6.99 - 6.98 (m, 3H), 6.57 (s, 1H), 5.80 (s, 1H), 3.95 (s, 3H), 3.78 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 147.0, 144.1, 140.7, 134.7, 130.3, 129.3, 129.3, 128.0, 127.6, 123.0, 119.7, 118.7, 115.9, 100.6, 94.6, 74.4, 56.5, 56.5

HRMS (ESI-TOF) m/z: Calcd. For $C_{23}H_{19}N_3O_2$ [M + H]: 370.1550, found: 370.1554.

3-Cyano-5,6-methylenedioxy-1-(4-methoxyphenyl)-2-((4-methoxyphenyl)amino)-1*H*-indole (47j):



Reaction Time: 120 min

Yield: 60%, Reddish black colour solid

R_f = 0.33 in 30% EtOAc in Hexanes

Melting Point: 174 – 176 ºC

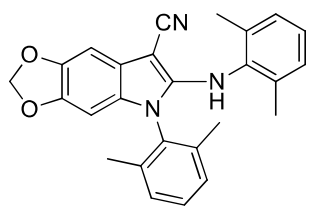
IR (KBr): ν (cm^{-1}) = 3353, 2912, 2202, 1514, 1338, 1254, 1164, 1034, 836.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.7 Hz, 2H), 7.07 – 7.03 (m, 4H), 6.98 (s, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.43 (s, 1H), 5.90 (s, 2H), 5.65 (s, 1H), 3.87 (s, 3H), 3.78 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 157.0, 147.0, 144.5, 144.4, 132.5, 129.3, 129.0, 126.7, 123.6, 121.1, 116.0, 115.7, 114.6, 100.9, 97.8, 92.0, 70.2, 55.8, 55.6

HRMS (ESI-TOF) m/z: Calcd. For $C_{24}H_{19}N_3O_4$ [M + H]: 414.1448, found: 414.1434.

3-Cyano-5,6-methylenedioxy-1-(2,6-dimethylphenyl)-2-((2,6-dimethylphenyl)amino)-1*H*-indole (47k):



Reaction Time: 5 min

Yield: 85% (174 mg), Reddish black colour solid

R_f = 0.3 in 20% EtOAc in Hexanes

Melting Point: More than 285 ºC

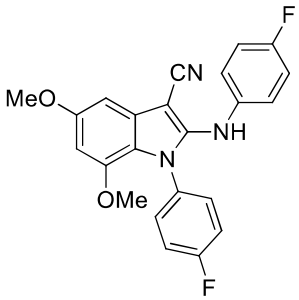
IR (KBr): ν (cm^{-1}) = 3353, 2922, 2855, 2202, 1562, 1472, 1280, 1166, 1036

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 1H), 7.33-7.31 (m, 2H), 7.22 – 7.16 (m, 1H), 7.13-7.11 (m, 2H), 6.95 (s, 1H), 6.16 (s, 1H), 5.88 (s, 2H), 5.24 (s, 1H), 2.27 (s, 6H), 2.12 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 144.0, 143.9, 138.4, 137.1, 134.2, 131.3, 130.4, 129.5, 128.6, 128.5, 127.0, 121.7, 115.2, 100.8, 98.0, 91.2, 65.1, 18.3, 17.6

HRMS (ESI-TOF) m/z: Calcd. For $C_{26}H_{23}N_3O_2$ [M + H]: 410.1863, found: 410.1856.

3-Cyano-1-(4-fluorophenyl)-2-((4-fluorophenyl)amino)-5,7-dimethoxy-1*H*-indole (47m):



Reaction Time: 5 min

Yield: 84%, White colour solid

R_f = 0.28 in 33% EtOAc in Hexanes

Melting Point: 242 - 244 ºC

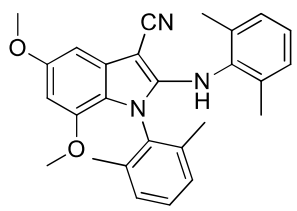
IR (KBr): ν (cm^{-1}) = 3293, 2205, 1560, 1542, 1510, 1308, 1213, 1015, 820

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.30 (s, 1H), 7.48-7.42 (m, 2H), 7.28 (t, *J* = 8.7 Hz, 2H), 7.08-7.04(m, 4H), 6.55 (d, *J* = 1.8 Hz, 1H), 6.36 (d, *J* = 1.8 Hz, 1H), 3.79 (s, 3H), 3.51 (s, 3H)

^{13}C NMR (100 MHz, DMSO-D_6) δ 161.7 (d, *J* = 244.9 Hz), 157.6 (d, *J* = 242.7 Hz), 156.4, 147.8, 147.0, 138.2, 132.9, 130.9 (d, *J* = 8.8 Hz), 128.7, 120.7 (d, *J* = 7.8 Hz), 117.6, 115.5 (d, *J* = 14.0 Hz), 115.3, 115.2 (d, *J* = 24.8 Hz), 95.5, 91.8, 73.1, 55.7, 55.5

HRMS (ESI-TOF) m/z: Calcd. For $C_{23}H_{17}F_2N_3O_2$ [M + H]: 406.1362, found: 406.1341.

3-Cyano-1-(2,6-dimethylphenyl)-2-((2,6-dimethylphenyl)amino)-5,7-dimethoxy-1*H*-indole (47n):



Reaction Time: 20 min

Yield: 93%, Brick red colour solid

R_f = 0.35 in 25% EtOAc in Hexanes

Melting Point: 236 - 238 ºC

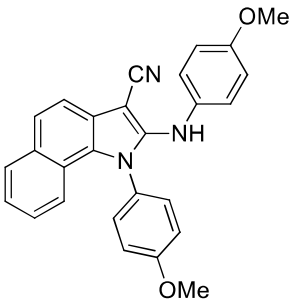
IR (KBr): ν (cm^{-1}) = 3353, 3003, 2923, 2199, 1620, 1595, 1558, 1151

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 1H), 7.25-7.22 (m, 1H), 7.20 – 7.16 (m, 1H), 7.12-7.10 (m, 1H), 6.60 (d, *J* = 1.9 Hz, 1H), 6.20 (d, *J* = 1.9 Hz, 1H), 5.26 (s, 1H), 3.82 (s, 3H), 3.49 (s, 3H), 2.26 (s, 6H), 2.13 (s, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 147.8, 146.9, 137.9, 137.3, 134.1, 134.1, 130.2, 129.5, 128.63, 128.60, 128.5, 116.0, 115.4, 94.3, 92.4, 65.5, 55.9, 55.9, 18.3, 17.9

HRMS (ESI-TOF) m/z: Calcd. For $C_{27}H_{27}N_3O_2$ [M + H]: 426.2176, found: 426.2181.

3-Cyano-1-(4-methoxyphenyl)-2-((4-methoxyphenyl)amino)-1*H*-benzo[*g*]indole (47o):



Reaction Time: 5 min

Yield: 95%, Pale red colour solid

R_f = 0.39 in 25% EtOAc in Hexanes

Melting Point: 206 - 208 ºC

IR (KBr): ν (cm^{-1}) = 3342, 2933, 2836, 2199, 1562, 1512, 1245, 1031, 813

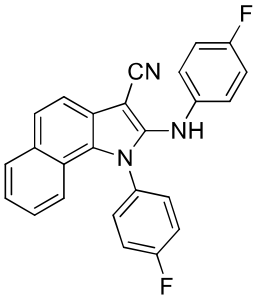
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.32 - 7.28 (m, 1H), 7.22 – 7.08 (m, 5H), 7.01 (d, *J* =

8.4 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.58 (s, 1H), 3.96 (s, 3H), 3.80 (s, 3H)

^{13}C NMR (175 MHz, $CDCl_3$) δ 161.0, 157.4, 147.8, 132.1, 131.0, 130.5, 129.4, 128.8, 126.7, 125.7, 124.6, 124.5, 123.4, 123.3, 121.6, 119.7, 117.6, 116.1, 115.8, 114.6, 70.4, 55.8, 55.5

HRMS (ESI-TOF) m/z: Calcd. For $C_{27}H_{21}N_3O_2$ [M + H]: 420.1707, found: 420.1699.

3-Cyano-1-(4-fluorophenyl)-2-((4-fluorophenyl)amino)-1*H*-benzo[*g*]indole (47p):



Reaction Time: 5 min

Yield: 67%, Brick red colour solid

R_f = 0.37 in 25% EtOAc in Hexanes

Melting Point: 254 - 256 ºC

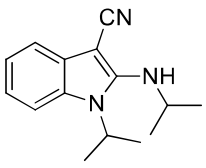
IR (KBr): ν (cm^{-1}) = 3395, 2211, 1542, 1510, 1227, 822

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 1H), 7.76-7.65 (m, 2H), 7.51-7.46 (m, 2H), 7.38-7.31 (m, 3H), 7.18 (t, *J* = 7.7 Hz, 1H), 7.06-76.9 (m, 4H), 6.95 (d, *J* = 8.6 Hz, 1H), 5.55 (s, 1H)

^{13}C NMR (100 MHz, DMSO-D_6) δ 162.7 (d, *J* = 247.5 Hz), 157.6 (d, *J* = 238.0 Hz), 147.1, 138.6, 133.1, 131.7 (d, *J* = 8.8 Hz), 130.8 , 129.3 , 126.6, 125.9 , 123.7(2C) , 123.4 , 121.2 , 120.6 (d, *J* = 8 Hz), 119.3, 117.3 , 117.0 (d, *J* = 4.0 Hz), 115.5 (d, *J* = 22.4 Hz), 115.1 , 75.6

HRMS (ESI-TOF) m/z: Calcd. For $C_{25}H_{15}F_2N_3$ [M + Na]: 418.1126, found: 418.1133.

3-Cyano-1-isopropyl-2-(isopropylamino)-1*H*-indole (47e):



Reaction Time: 90 min

Yield: 80%, White colour solid

R_f = 0.37 in 30% EtOAc in Hexanes

Melting Point: 158 - 159 ºC

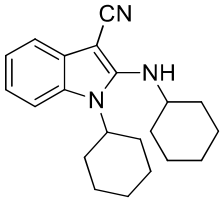
IR (KBr): ν (cm^{-1}) = 3327, 2972, 2188, 1566, 1470, 1321, 1166, 740

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.16-7.07 (m, 2H), 4.56-4.49 (m, 1H), 4.27-4.21 (m, 1H), 3.44 (brs, 1H) 1.60 (d, *J* = 7.0 Hz, 6H), 1.35 (d, *J* = 6.2 Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 131.9, 128.7, 121.1, 120.6, 118.5, 117.2, 110.5, 66.2, 46.8, 46.3, 23.7, 20.9

HRMS (ESI-TOF) m/z: Calcd. For $C_{15}H_{19}N_3$ [M + H]: 242.1652, found: 242.1667.

3-Cyano-1-cyclohexyl-2-(cyclohexylamino)-1*H*-indole (47f):



Reaction Time: 30 min

Yield: 78%, White colour solid

R_f = 0.4 in 15% EtOAc in Hexanes

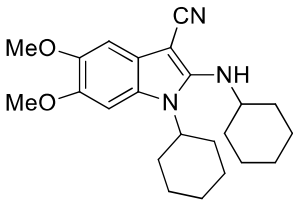
Melting Point: 175 - 176 ºC

IR (KBr): ν (cm^{-1}) = 3302, 3058, 2932, 2187, 1557, 1469, 1327, 1112, 733

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 6.0 Hz, 1H), 7.14 - 7.04 (m, 2H), 4.03 - 3.97 (m, 1H), 3.90 – 3.70 (m, 1H), 2.25 - 2.15 (m, 4H), 2.07 - 2.17 (m, 2H), 1.89 - 1.84(m, 2H), 1.83 -1.73 (m, 3H), 1.71 – 1.60 (m, 1H), 1.53 – 1.40 (m, 4H), 1.36 – 1.18 (m, 5H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 132.2, 128.6, 121.0, 120.4, 118.4, 117.1, 110.8, 66.3, 55.1, 53.8, 34.0, 30.8, 26.3, 25.5, 25.3, 24.5

HRMS (ESI-TOF) m/z: Calcd. For $C_{21}H_{27}N_3$ [M + Na]: 344.2097 found: 344.2107.

3-Cyano-1-cyclohexyl-2-(cyclohexylamino)-5,6-dimethoxy-1*H*-indole (47i):



Reaction Time: 30 min

Yield: 79%, White colour solid

R_f = 0.34 in 25% EtOAc in Hexanes

Melting Point: 131 - 133 ºC

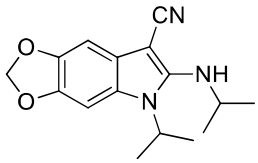
IR (KBr): ν (cm^{-1}) = 3761, 3348, 2934, 2856, 2191, 1560, 1491, 1405, 1259, 1057, 787

^{1}H NMR (700 MHz, DMSO-D_6) δ 7.00 (s, 1H), 6.76 (s, 1H), 6.27 (s, 1H), 4.23 (s, 1H), 3.76 (s, 6H), 3.68 (s, 1H), 2.18 - 2.015 (m, 4H), 1.92 – 1.54 (m, 8H), 1.45 - 1.17 (m, 8H)

^{13}C NMR (175 MHz, DMSO-D6) δ 149.7, 145.3, 144.2, 125.0, 121.7, 118.5, 99.7, 98.7, 62.5, 56.9, 55.9, 53.1, 53.0, 33.2, 29.7, 25.5, 25.2, 24.6, 24.5 (2C)

HRMS (ESI-TOF) m/z: Calcd. For $C_{23}H_{31}N_3O_2$[M + Na]: 404.2308, found: 404.2370.

3-Cyano-5,6-methylenedixy-1-isopropyl-2-(isopropylamino)-1*H*-indole (47l):



Reaction Time: 30 min

Yield: 81%, grey colour solid

R_f = 0.3 in 25% EtOAc in Hexanes

Melting Point: 164 - 166 ºC

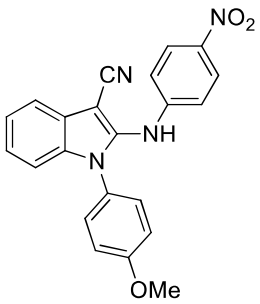
IR (KBr): ν (cm^{-1}) = 3319, 2973, 2195, 1564, 1473, 1316, 1255, 1161, 1038

^{1}H NMR (400 MHz, DMSO-D_6) δ 7.15 (s, 1H), 6.73 (s, 1H), 6.21 (d, *J* = 7.9 Hz, 1H), 5.92 (s, 2H), 4.7. 4.63 (m, 1H), 4.07 – 4.02 (m, 1H), 1.44 (d, *J* = 6.9 Hz, 6H), 1.25 (d, *J* = 6.3 Hz, 6H)

^{13}C NMR (100 MHz, DMSO-D_6) δ 149.5, 142.4, 142.3, 124.8, 122.2, 118.2, 100.3, 96.0, 94.0, 63.3, 45.7, 45.2, 21.3, 20.0

HRMS (ESI-TOF) m/z: Calcd. For $C_{16}H_{19}N_3O_2$ [M + H]: 286.1550, found: 286.1524.

3-Cyano-1-(4-methoxyphenyl)-2-((4-nitrophenyl)amino)-1*H*-indole (47q):



Reaction Time: 5 min

Yield: 81%, Yellow colour solid

R_f = 0.33 in 30% EtOAc in Hexanes

Melting Point: 196 - 198 ºC

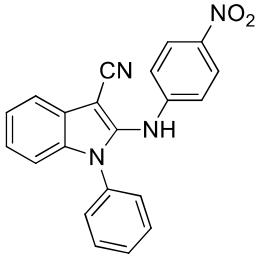
IR (KBr): ν (cm^{-1}) = 3423, 3246, 2217, 1601, 1552, 1330, 1307, 1250

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.7 Hz, 2H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.28 - 7.26 (m, 3H), 7.12 (d, *J* = 8.2 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.34 (s, 1H), 3.86 (s, 3H)

^{13}C NMR (100 MHz, DMSO-D_6) δ 159.4, 149.5, 143.5, 139.8, 134.6, 128.7, 126.7, 125.6(2C), 123.8, 122.8, 118.1, 115.0, 114.9, 114.8, 111.2, 78.2, 55.4

HRMS (ESI-TOF) m/z: Calcd. For $C_{22}H_{16}N_4O_3$ [M + Na]: 407.1115, found: 407.1094.

3-Cyano-2-((4-nitrophenyl)amino)-1-phenyl-1*H*-indole (47r):



Reaction Time: 30 min

Yield: 86%,Yellow colour solid

R_f = 0.32 in 30% EtOAc in Hexanes

Melting Point: 263 - 264 ºC

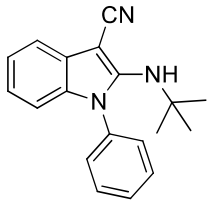
IR (KBr): ν (cm^{-1}) = 3256, 2363, 2219, 1601, 1552, 1499, 1308, 1223, 744

^{1}H NMR (400 MHz, DMSO-D_6) δ 9.75 (s, 1H), 8.04 (d, *J* = 9.1 Hz, 2H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 2H), 7.51 - 7.45 (m, 3H), 7.35 - 7.26 (m, 2H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 9.1 Hz, 2H)

^{13}C NMR (175 MHz, DMSO-D_6) δ 149.4, 143.2, 139.8, 134.3, 134.2, 129.8, 129.0, 127.4, 125.6, 125.6, 124.0, 122.9, 118.2, 115.0, 114.7, 111.2, 78.8;

HRMS (ESI-TOF) m/z: Calcd. For $C_{21}H_{14}N_4O_2$ [M + H]: 355.1190, found: 355.1203.

3-Cyano-2-(*tert*-butylamino)-1-phenyl-1*H*-indole (47s):



Reaction Time: 120 min

Yield: 68%, White colour solid

R_f = 0.34 in 25% EtOAc in Hexanes

Melting Point: 169 - 170 ºC

IR (KBr): ν (cm^{-1}) = 3403, 2930, 2370, 2195, 1563, 1370, 1211, 750

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.63 (t, *J* = 7.5 Hz, 2H), 7.59 - 7.54 (m, 2H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 4.12 (s, 1H), 1.41 (s, 9H)

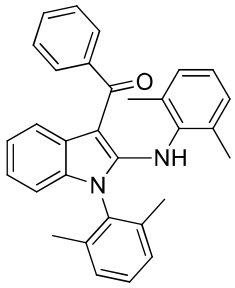
^{13}C NMR (175 MHz, $CDCl_3$) δ 148.7, 134.5, 134.2, 130.6, 129.7, 128.6, 128.5, 122.1, 121.6, 119.3, 117.4, 109.3, 68.0, 53.5, 30.5

HRMS (ESI-TOF) m/z: Calcd. For $C_{19}H_{19}N_3$ [M + Na]: 312.1471, found: 312.1442.

3-Benzoyl-1-(2,6-dimethylphenyl)-2-((2,6-dimethylphenyl)amino)-1*H*-indole (52a):

Reaction Time: 2 h

Yield: 55%, Red colour solid



R_f = 0.30 in 5% EtOAc in Hexanes

Melting Point: 216 - 218 ºC

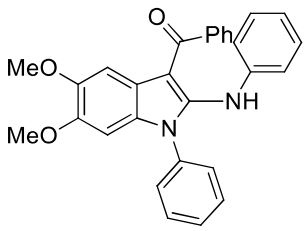
IR (KBr): ν (cm^{-1}) = 3041, 2923, 1697, 1573, 1534, 1475, 1203, 759

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 1H), 7.81 (d, *J* = 4.7 Hz, 2H), 7.63 -7.47 (m, 3H), 7.05 (d, *J* = 6.8 Hz, 1H), 6.98 – 6.83 (m, 6H), 6.78 (d, *J* = 6.3 Hz, 2H), 6.46 (d, *J* = 5.2 Hz, 1H), 2.10 (s, 6H), 1.83 (s, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 157.5, 142.1, 137.3, 137.2, 135.3, 134.1, 133.1, 130.3, 128.6, 128.4, 128.4, 128.1, 127.8, 126.9, 126.0, 122.0, 121.4, 119.1, 109.6, 99.6, 18.5, 17.8

HRMS (ESI-TOF) m/z: Calcd. For $C_{31}H_{28}N_2O$ [M + H]: 445.2274, found: 445.2284.

3-Benzoyl-(5,6-dimethoxy-1-phenyl-2-(phenylamino))-1*H*-indole (52b):



Reaction Time: 3 h

Yield: 56%, Pale red colour solid

R_f= 0.33 in 25% EtOAc in Hexanes

Melting Point: 169 - 171 ºC

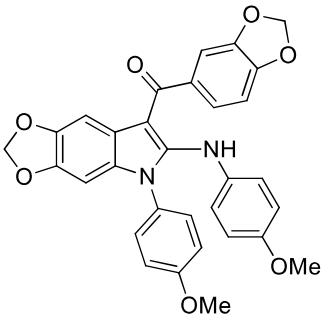
IR (KBr): ν (cm^{-1}) = 3057, 2943, 2826, 1584, 1339, 1193, 1154, 722

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (brs, 1H), 7.85 – 7.75 (m, 2H), 7.56-7.55 (m, 3H), 7.33 – 7.27 (m, 4H), 7.22-7.18 (m, 1H), 6.98 (t, *J* = 7.5 Hz, 2H), 6.87-6.82 (m, 3H), 6.62 (s, 1H), 6.40 (s, 1H), 3.77 (s, 3H), 3.60 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 150.2, 145.9, 145.9, 141.6, 139.0, 136.2, 130.4, 129.4, 129.3, 128.4, 128.3, 128.0, 127.9, 126.9, 123.7, 122.4, 118.6, 102.8, 101.0, 94.8, 56.5, 55.9

HRMS (ESI-TOF) m/z: Calcd. For $C_{29}H_{24}N_2O_3$ [M + H]: 449.1860, found: 449.1871.

3-(3,4-methylenedioxy-benzoyl)-5,6-methylenedioxy-1-(4-methoxyphenyl)-2-(4-methoxy phenylamino)-1*H*-indole (52c):



Reaction Time: 3 h

Yield: 82%, Black solid

R_f = 0.35 in 30% EtOAc in Hexanes

Melting Point: 192 - 194 ^oC

IR (KBr): ν (cm^{-1}) = 3415, 2904, 1580, 1513, 1465, 1337, 1248, 1169, 1034

^1H NMR (700 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.7 Hz, 1H), 7.28 - 7.25 (m, 1H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.54 - 6.51 (m, 3H), 6.42 (s, 1H), 6.08 (s, 2H), 5.85 (s, 2H), 3.76 (s, 3H), 3.69 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ :189.4, 159.0, 156.4, 151.8, 149.6, 147.7, 143.6, 143.5, 135.7, 132.3, 130.9, 128.8, 128.5, 125.1, 123.1, 119.4, 114.4, 113.7, 108.6, 108.1, 101.5, 100.6, 100.4, 99.6, 92.1, 55.5, 55.4

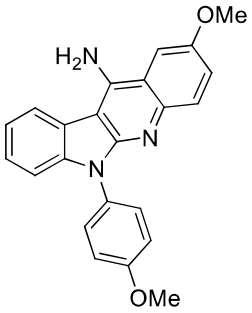
HRMS (ESI-TOF) m/z: Calcd. For $C_{31}H_{24}N_2O_7$ [M + H]: 537.1656, found: 537.1686.

2.6.8 General Procedure for the Synthesis of 11-Amino-indolo[2,3-*b*]quinolines 53

An oven-dried 8 mL reaction vial was charged with respective 2-aminoindole (0.5 mmol) in dry DCE (2.0 mL) was added triflic acid (5 mmol, 0.441ml, 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 (3x10 mL) & brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated

under reduced pressure. The crude products were purified by flash chromatography using EtOAc and hexane as eluent.

2-Methoxy-6-(4-methoxyphenyl)-6H-indolo[2,3-b]quinolin-11-amine (53a):



Yield: >99%, Grey colour solid

R_f = 0.3 in 40% EtOAc in Hexanes

Melting Point: 192 - 194 °C

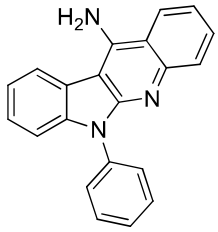
IR (KBr): ν (cm^{-1}) = 3313, 2924, 2052, 1621, 1598, 1454, 1248, 1232

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.51 (d, *J* = 7.5 Hz, 1H), 7.85 (s, 1H), 7.60 (d, *J* = 9.1 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.30 - 7.22 (m, 2H), 7.21 - 7.13 (m, 5H), 3.92 (s, 3H), 3.87 (s, 3H).

^{13}C NMR (175 MHz, DMSO-D_6) δ 158.2, 153.8, 152.6, 145.6, 142.8, 140.1, 129.2, 129.0, 128.8, 124.9, 121.6, 121.0, 120.5, 119.8, 115.1, 114.6, 108.4, 102.0, 97.8, 55.6, 55.3.

HRMS (ESI-TOF) m/z: Calcd. For $C_{23}H_{19}N_3O_2$ [M + H]: 370.1550, found: 370.1570.

6-Phenyl-6H-indolo[2,3-b]quinolin-11-amine (53b):



Reaction Time: 4 h

Yield: 80%, pale orange colour solid

R_f = 0.36 in 25% EtOAc in Hexanes

Melting Point: 103 - 105 °C

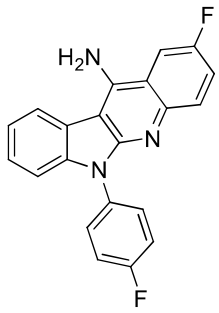
IR (KBr): ν (cm^{-1}) = 3373, 2924, 2853, 1626, 1402, 1214, 750, 702

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.54 (d, *J* = 7.6 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 7.73 – 7.61 (m, 5H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.54 - 7.48 (m, 1H), 7.42 – 7.22 (m, 6H)

^{13}C NMR (175 MHz, DMSO-D_6) δ 153.4, 147.2, 146.6, 139.5, 136.4, 129.4, 128.8, 127.8, 127.4, 127.3, 125.0, 122.8, 121.6, 121.3, 120.7, 120.3, 115.1, 108.6, 97.6.

HRMS (ESI-TOF) m/z: Calcd. For $C_{21}H_{15}N_3$ [M + H]: 310.1339, found: 310.1358.

2-Fluoro-6-(4-fluorophenyl)-6H-indolo[2,3-b]quinolin-11-amine (53c):



Reaction Time: 2 h

Yield: 80%, colourless solid

R_f = 0.37 in 20% EtOAc in Hexanes

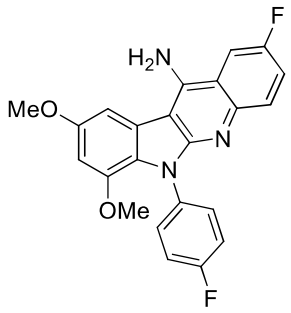
Melting Point: 202 - 203 ºC

IR (KBr): ν (cm^{-1}) = 3423, 1640, 1514, 1259, 1040

^{1}H NMR (700 MHz, DMSO-D_6) δ 8.54 (d, *J* = 7.5 Hz, 1H), 8.34 - 8.30 (m, 1H), 7.78 – 7.58 (m, 3H), 7.49 - 7.45 (m, 3H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.36 – 7.26 (m, 3H), 7.23 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (175 MHz, DMSO-D_6) δ 159.6 (d, *J* = 717.5 Hz), 158.2 (d, *J* = 710.5 Hz), 153.2, 146.1 (d, *J* = 3.5 Hz), 144.2, 139.8, 132.6 (d, *J* = 3.5 Hz), 130.0 (d, *J* = 8.92 Hz), 129.6 (d, *J* = 8.75 Hz), 125.4, 121.9, 120.9, 120.5, 118.3 (d, *J* = 24.5 Hz), 116.3 (d, *J* = 22.75 Hz), 115.1 (d, *J* = 8.75 Hz), 108.6, 106.6 (d, *J* = 22.75 Hz), 97.9;

HRMS (ESI-TOF) m/z: Calcd. For $C_{21}H_{13}N_3F_2$ [M + H]: 346.1150, found: 346.1149.

2-Fluoro-6-(4-fluorophenyl)-7,9-dimethoxy-6H-indolo[2,3-b]quinolin-11-amine (53d):



Reaction Time: 3 h

Yield: 82%, colourless solid

R_f = 0.34 in 30% EtOAc in Hexanes

Melting Point: 274 - 276 ºC

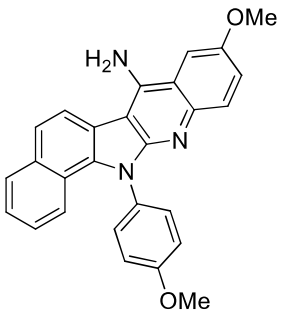
IR (KBr): ν (cm^{-1}) = 3410, 2839, 2037, 1631, 1513, 1303, 1206, 1031, 825

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.27 (dd, *J* = 11.3, 2.7 Hz, 1H), 7.73 – 7.58 (m, 2H), 7.49 – 7.37 (m, 3H), 7.29 (t, *J* = 8.8 Hz, 2H), 7.24 (brs, 2H), 6.68 (d, *J* = 1.8 Hz, 1H), 3.92 (s, 3H), 3.59 (s, 3H)

^{13}C NMR (100 MHz, DMSO-D_6) δ 160.6 (d, *J* = 242.7 Hz), 156.7 (d, *J* = 237.0 Hz), 155.2, 154.1, 146.2, 145.8, 144.2, 134.8, 130.5, 130.4, 129.5 (d, *J* = 8.0 Hz), 122.7 (d, *J* = 16.0 Hz), 118.2 (d, *J* = 24.9 Hz), 114.6, 114.4, 106.6 (d, *J* = 23.0 Hz), 98.6, 98.5, 98.5, 56.2, 55.8

HRMS (ESI-TOF) m/z: Calcd. For $C_{23}H_{17}N_3O_2F_2$ [M + H]: 406.1362, found: 406.1453.

9-Methoxy-13-(4-methoxyphenyl)-13H-benzo[6,7]indolo[2,3-b]quinolin-7-amine (53e):



Reaction Time: 2 h

Yield: 78%, Green colour solid

R_f = 0.34 in 30% EtOAc in Hexanes

Melting Point: 202 - 203 ºC

IR (KBr): ν (cm^{-1}) = 3433, 3329, 3241, 2995, 2834, 1722, 1643, 1614, 1512, 1439, 1713, 1234, 1035

^{1}H NMR (400 MHz, DMSO-D_6 + CF_3COOD) δ 8.73 (d, *J* = 6.8 Hz, 1H), 8.11 – 7.83 (m, 4H), 7.68 (d, *J* = 5.6 Hz, 2H), 7.50 - 7.35 (m, 2H), 7.38 – 7.18 (m, 3H), 7.16 – 7.01 (m, 1H), 3.95 (s, 3H), 3.89 (s, 3H)

^{13}C NMR (175 MHz, DMSO-D_6 + CF_3COOD) δ 161.8, 156.6, 151.7, 145.3, 133.3, 132.9, 131.8,

131.5, 129.6, 128.4, 126.6, 125.8, 124.1, 124.0, 121.4, 121.0 (2C), 120.1, 117.4, 116.7, 114.9, 104.4, 98.3, 56.4, 56.0;

HRMS (ESI-TOF) m/z: Calcd. For $C_{27}H_{21}N_3O_2$ [M + H]: 420.1707, found: 420.1719.

2.7 ^{1}H & ^{13}C Spectrum of Selected Compounds

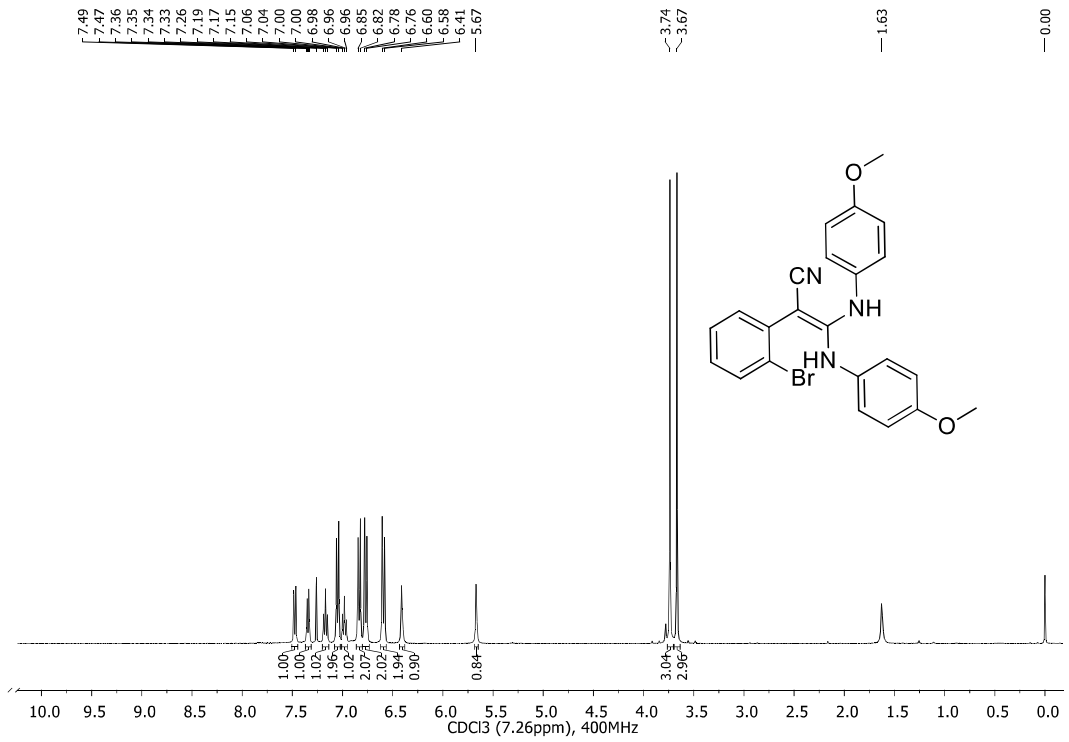


Figure 2.4a: ^{1}H NMR Spectrum of **46a**

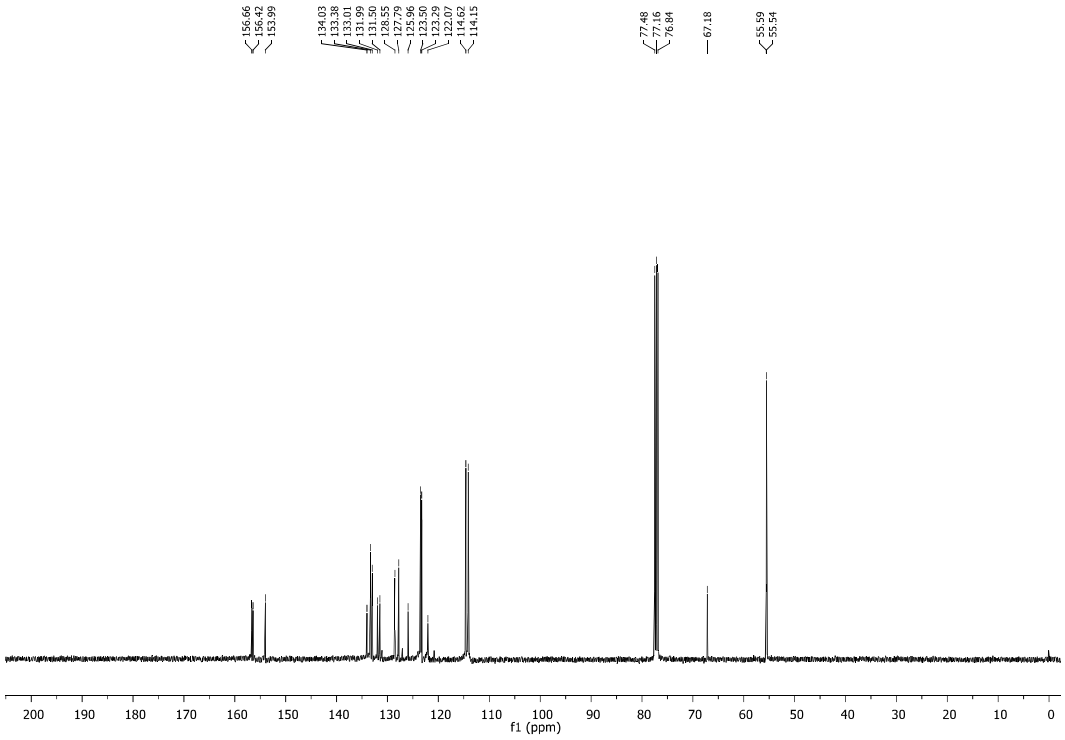


Figure 2.4b: ^{13}C NMR Spectrum of **46a**

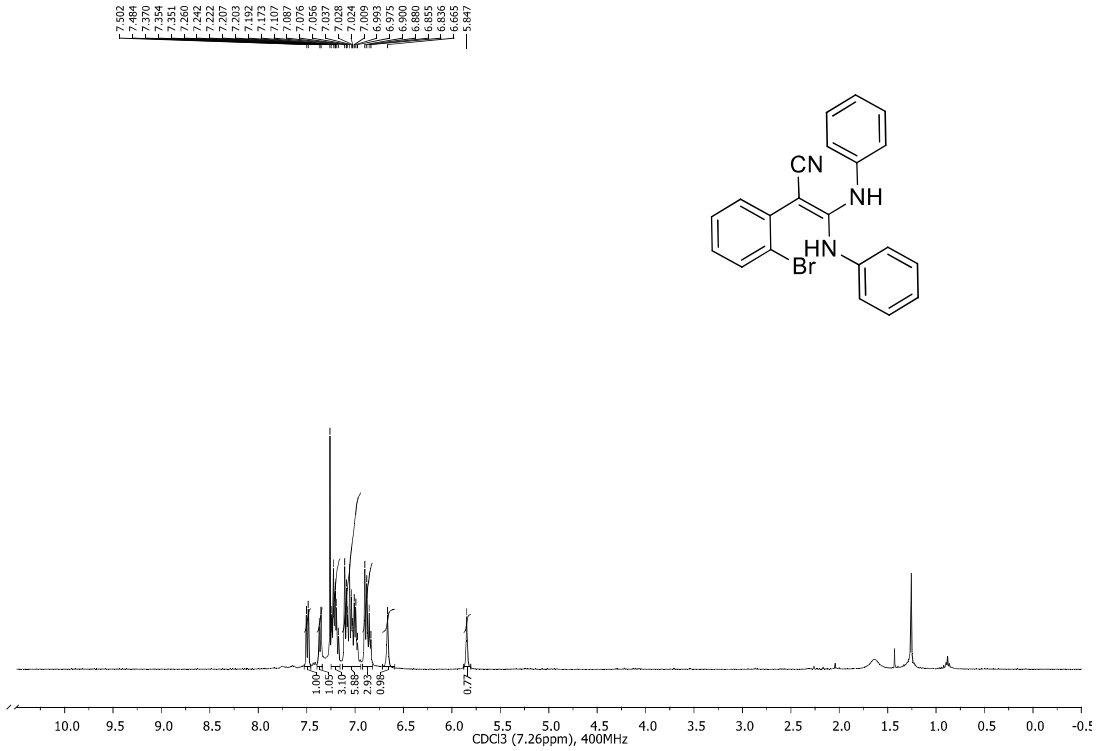


Figure 2.5a: ^{1}H NMR Spectrum of **46b**

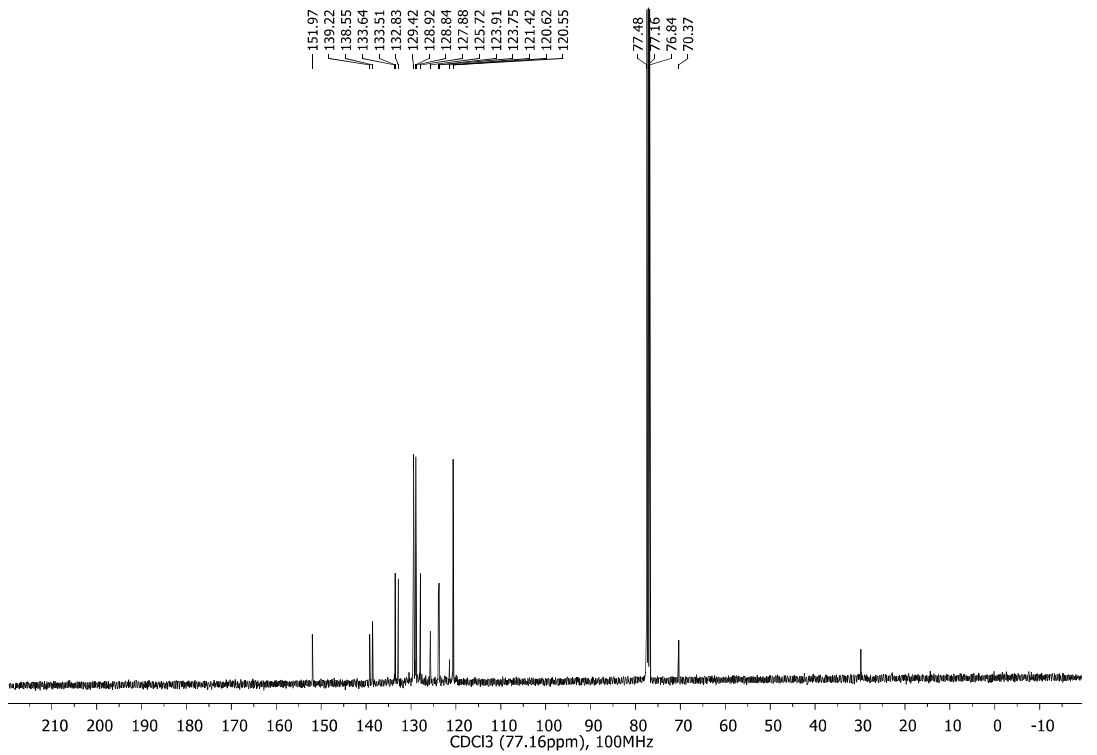


Figure 2.5b: ^{13}C NMR Spectrum of **46b**

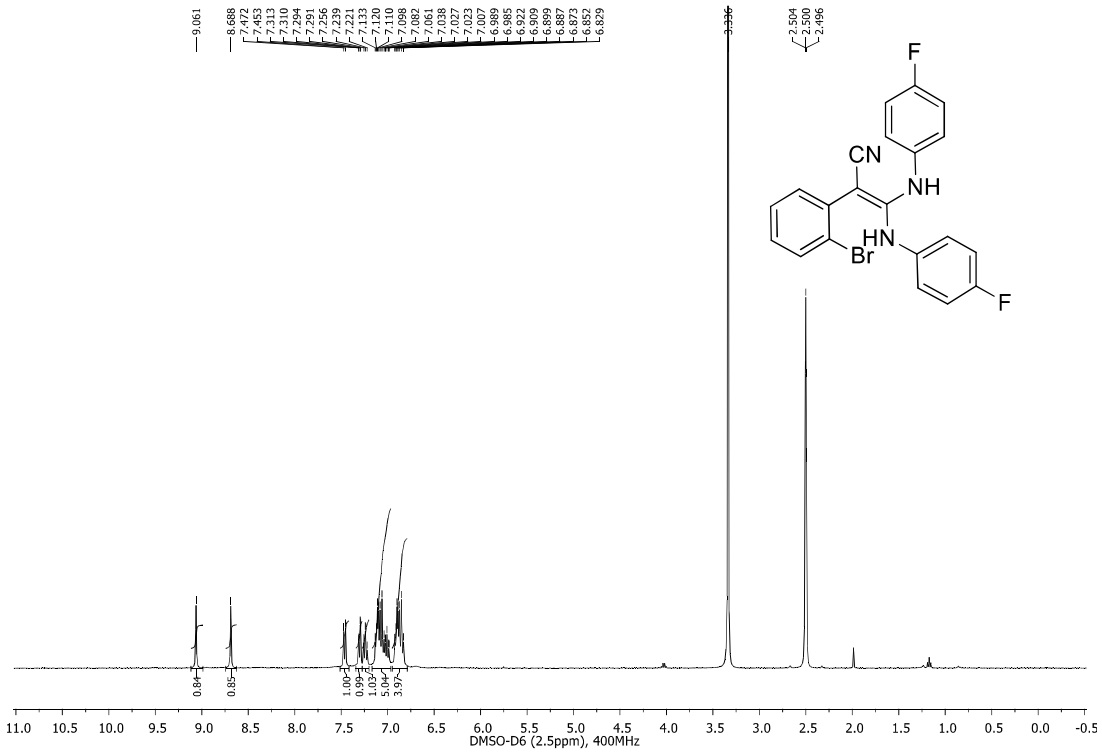


Figure 2.6a: ^{1}H NMR Spectrum of **46c**

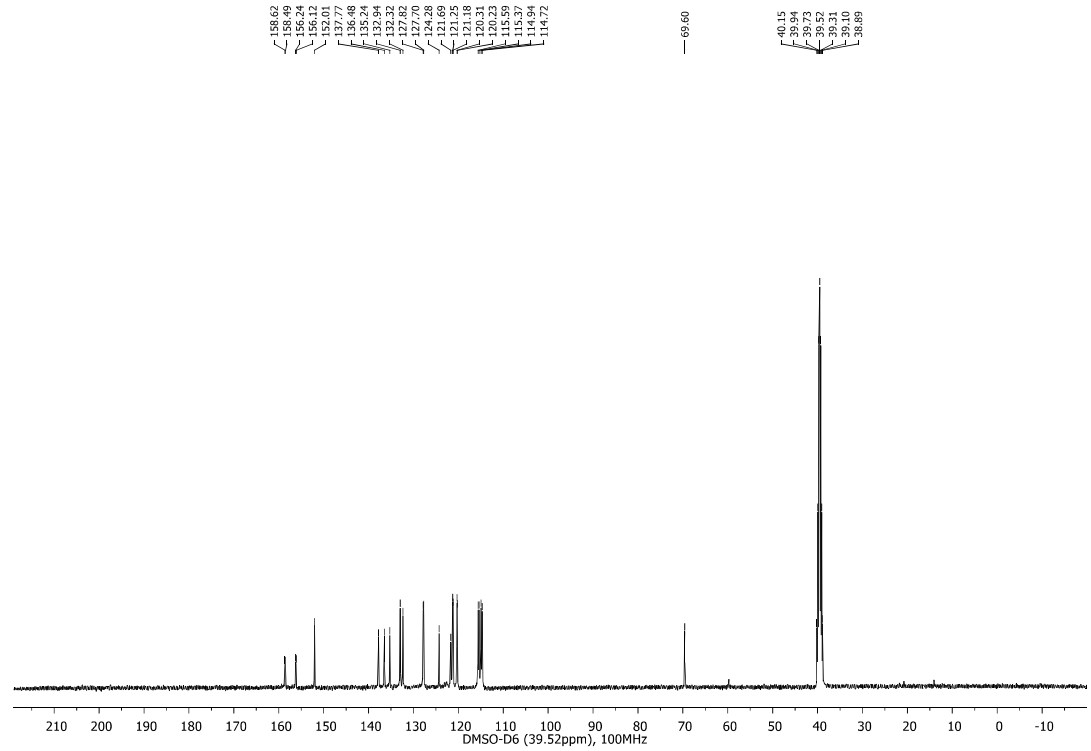


Figure 2.6b: ^{13}C NMR Spectrum of **46c**

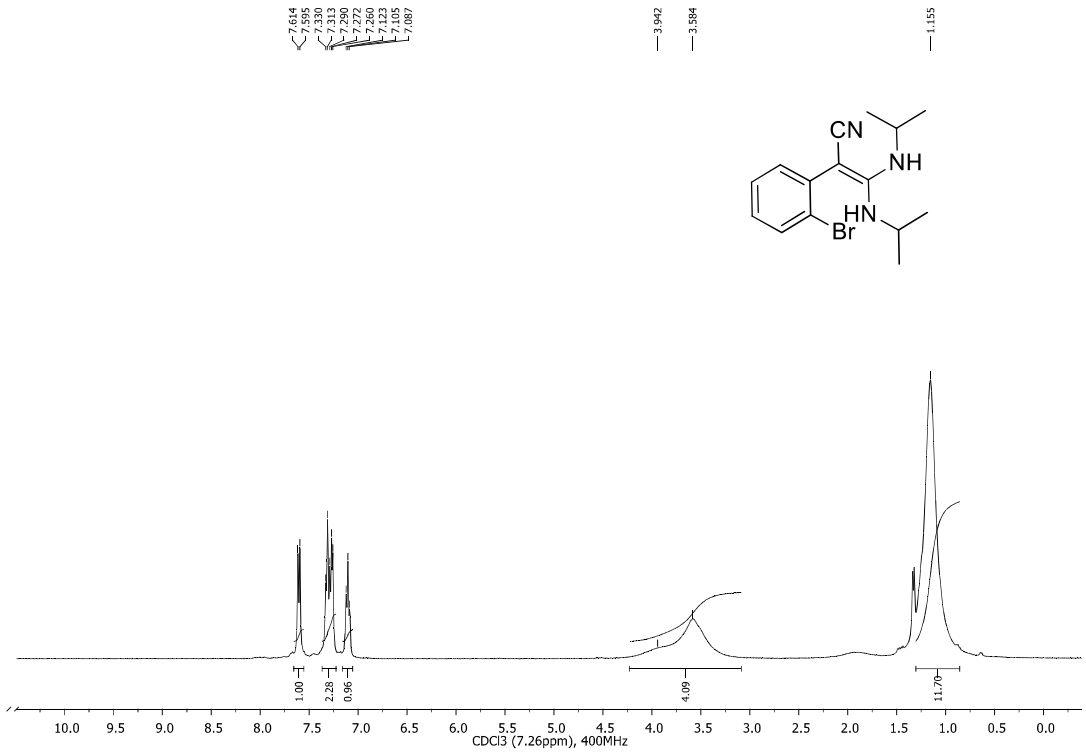


Figure 2.7a: ^{1}H NMR Spectrum of **46e**

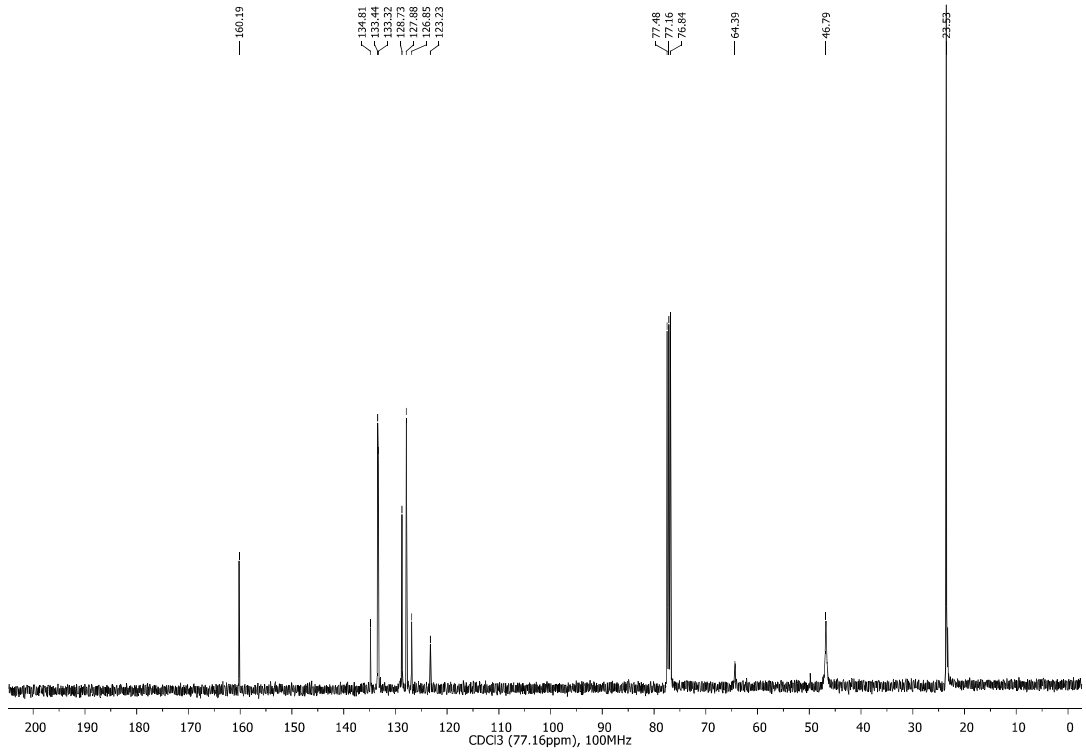


Figure 2.7b: ^{13}C NMR Spectrum of **46e**

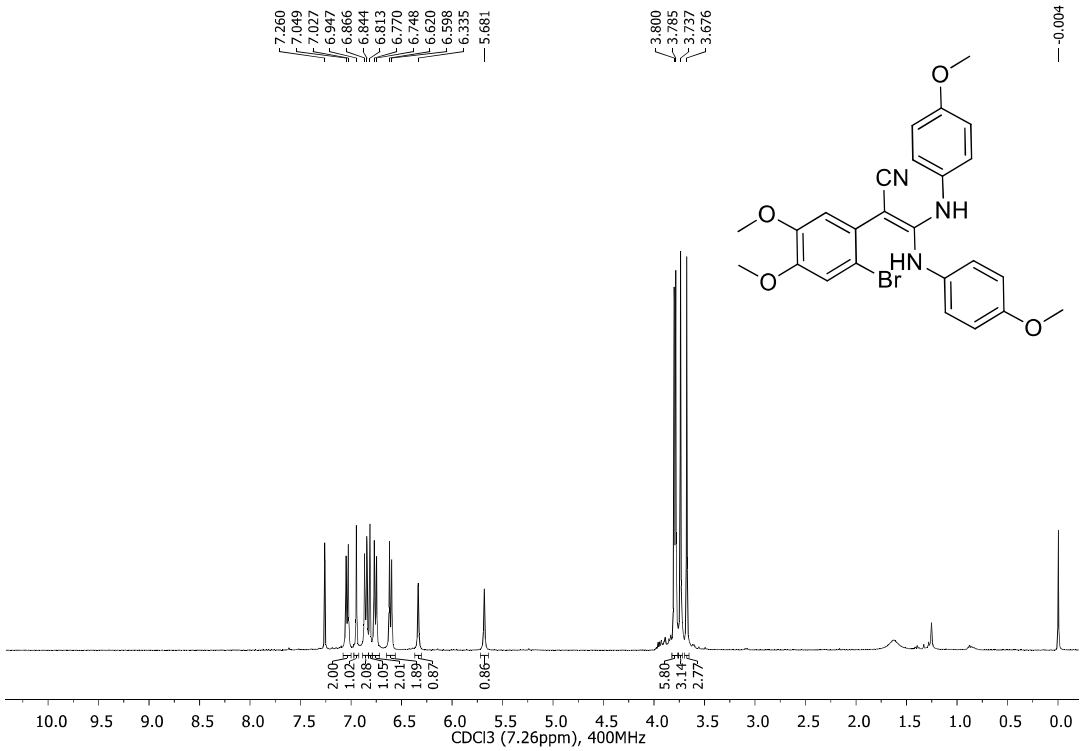


Figure 2.8a: ^{1}H NMR Spectrum of **46g**

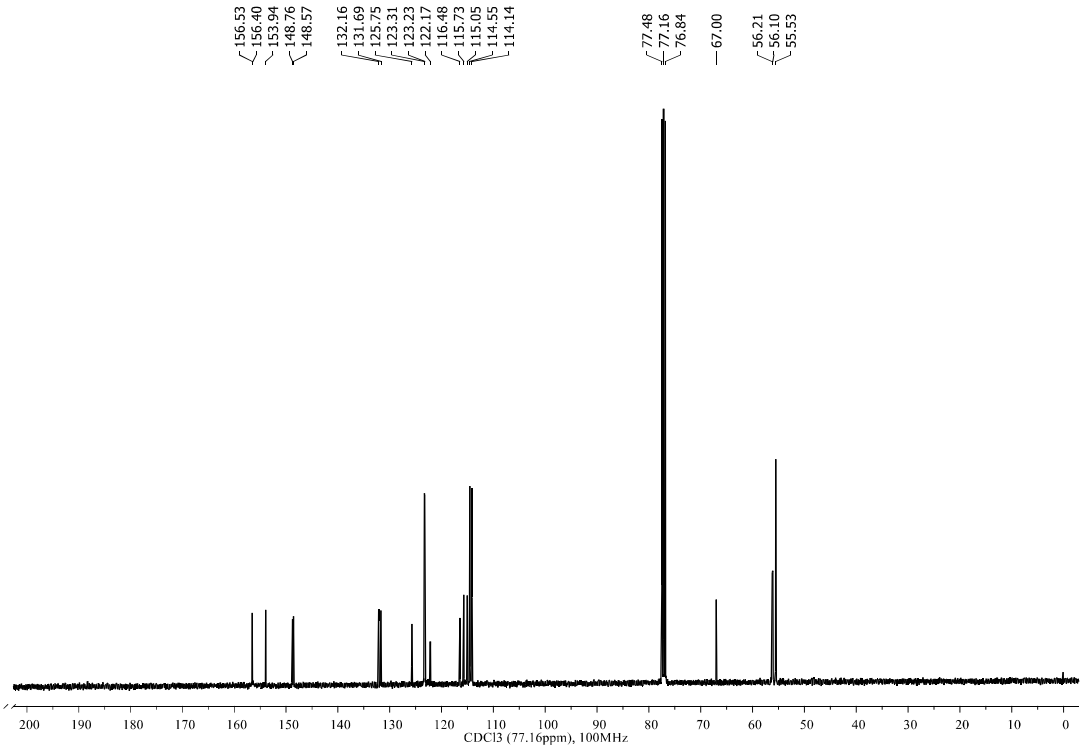


Figure 2.8b: ^{13}C NMR Spectrum of **46g**

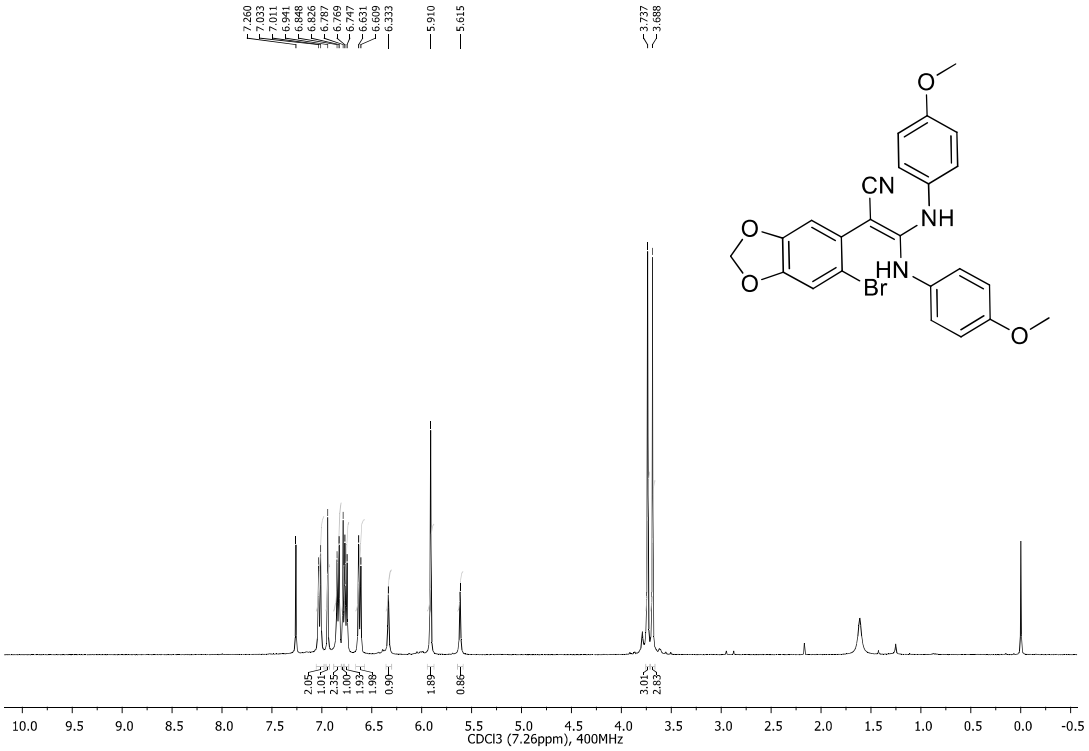


Figure 2.9a: ^{1}H NMR Spectrum of **46j**

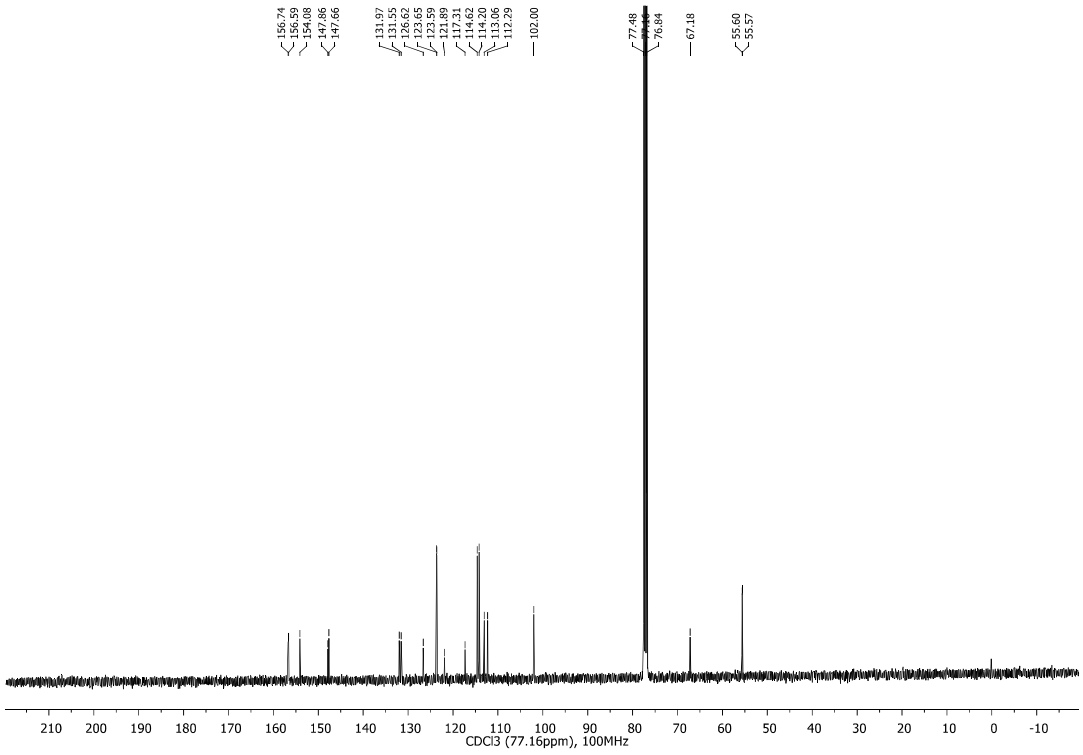


Figure 2.9b: ^{13}C NMR Spectrum of **46j**

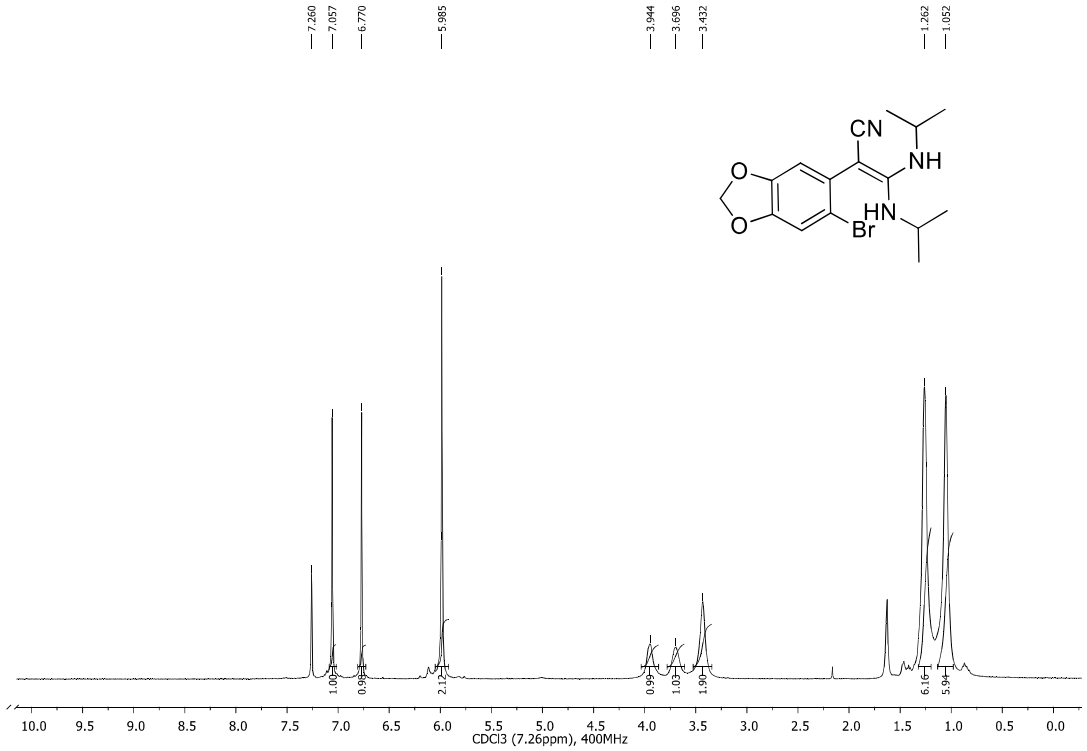


Figure 2.10a: ^{1}H NMR Spectrum of **46l**

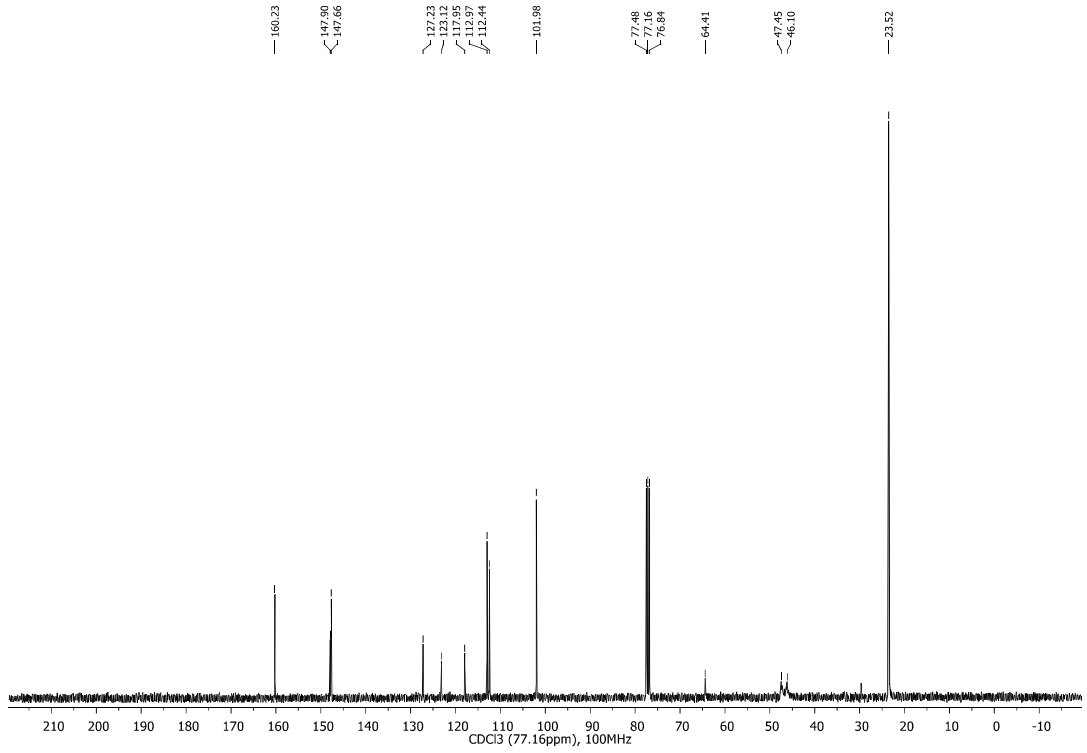


Figure 2.10b: ^{13}C NMR Spectrum of **46l**

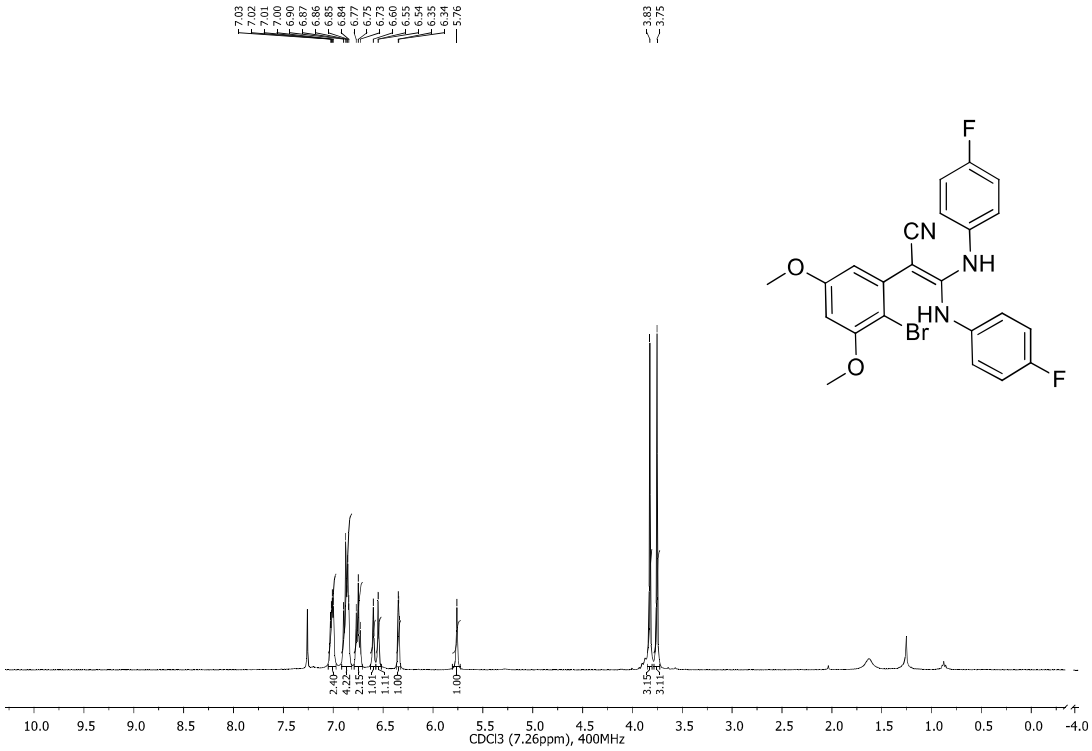


Figure 2.11a: ^{1}H NMR Spectrum of **46m**

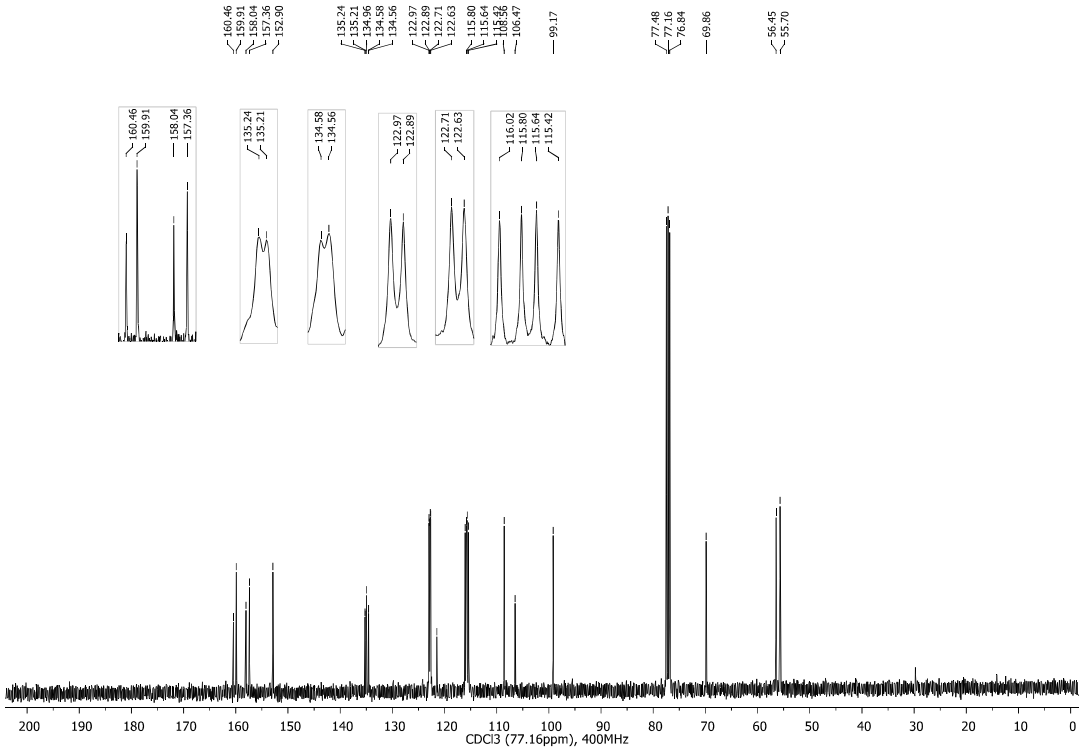


Figure 2.11b: ^{13}C NMR Spectrum of **46m**

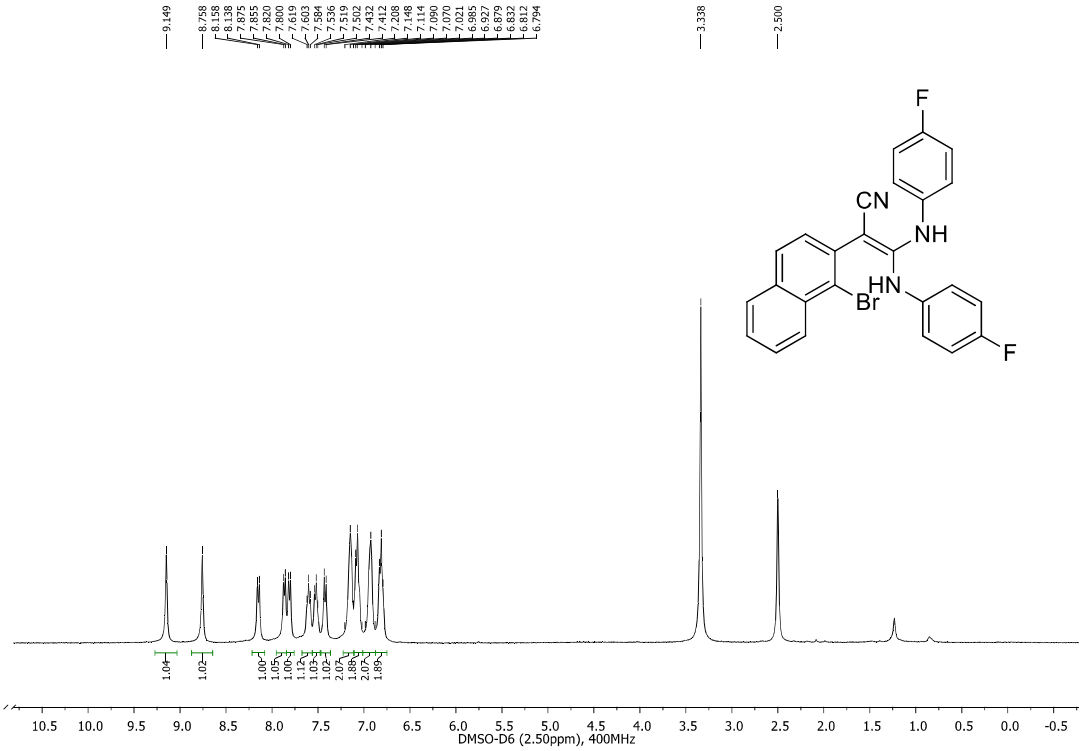


Figure 2.12a: ^{1}H NMR Spectrum of **46p**

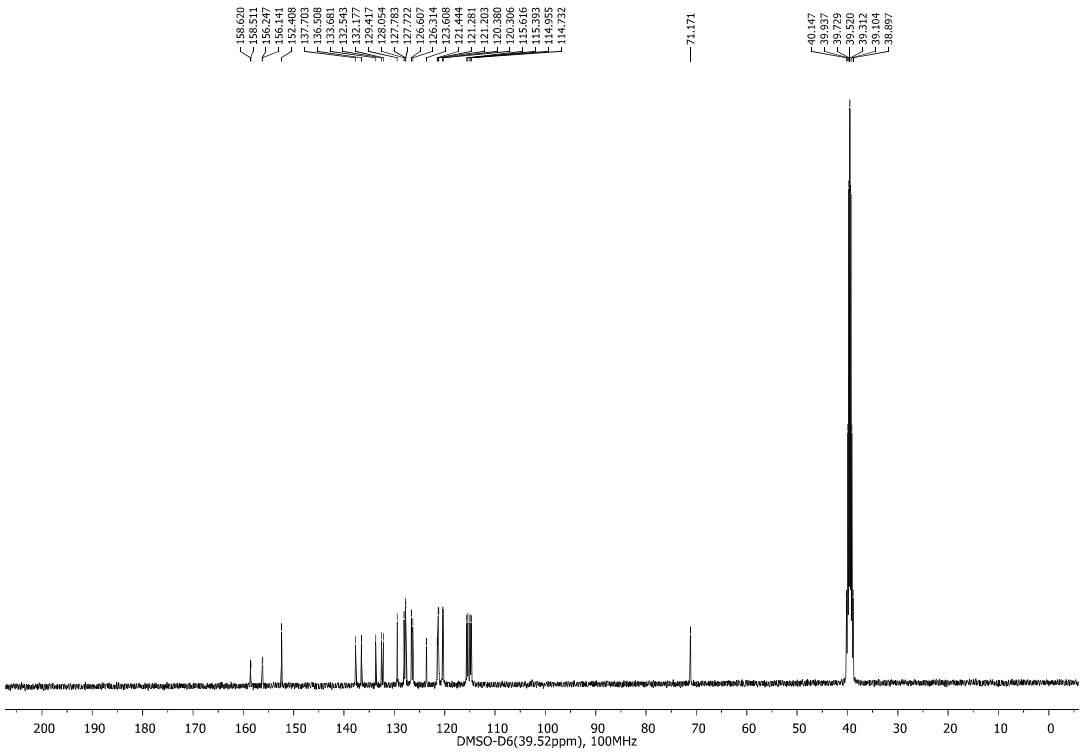


Figure 2.12b: ^{13}C NMR Spectrum of **46p**

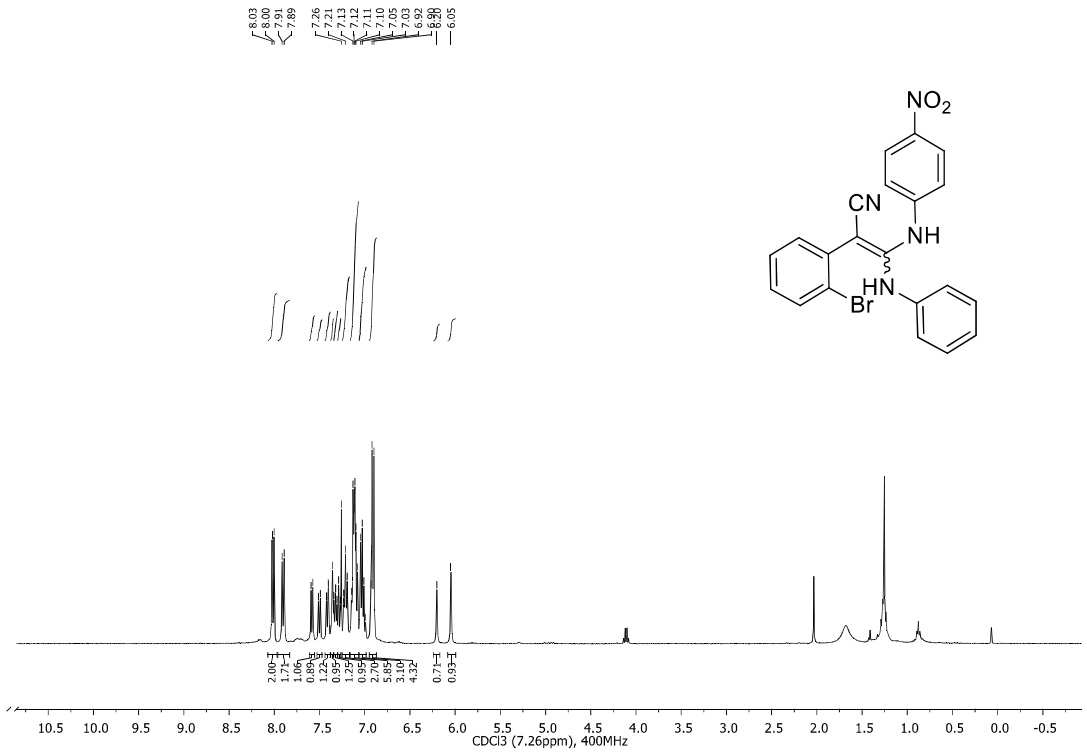


Figure 2.13a: ^{1}H NMR Spectrum of **46r**

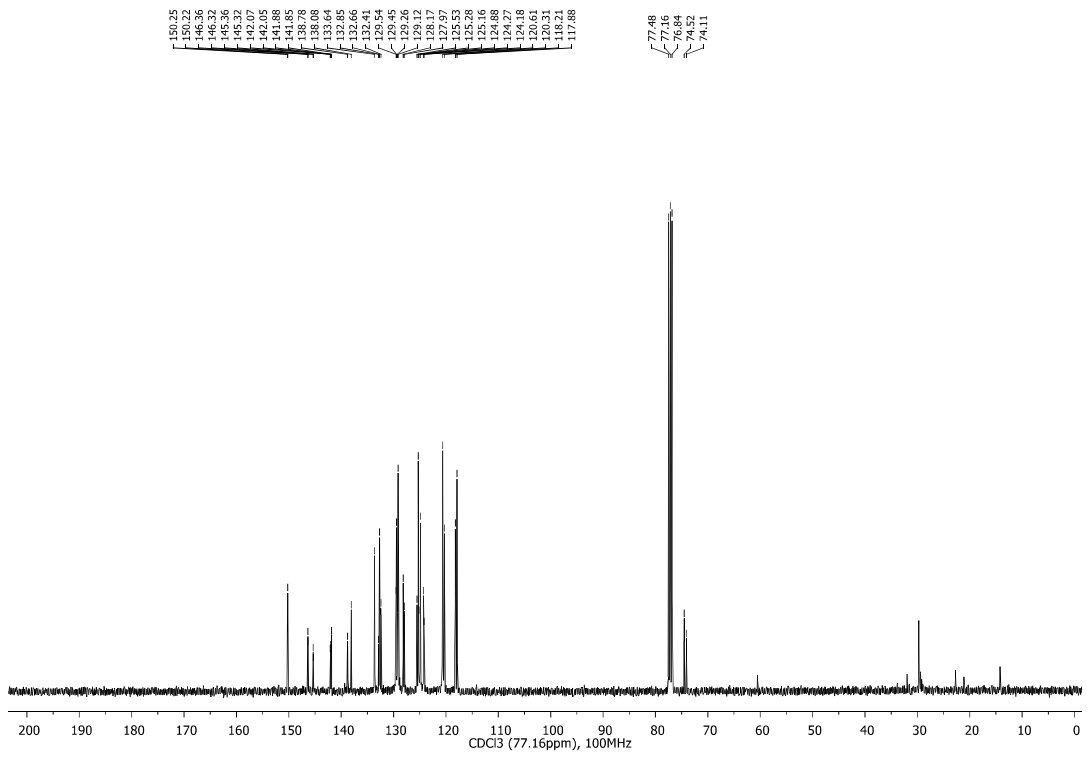


Figure 2.13b: ^{13}C NMR Spectrum of **46r**

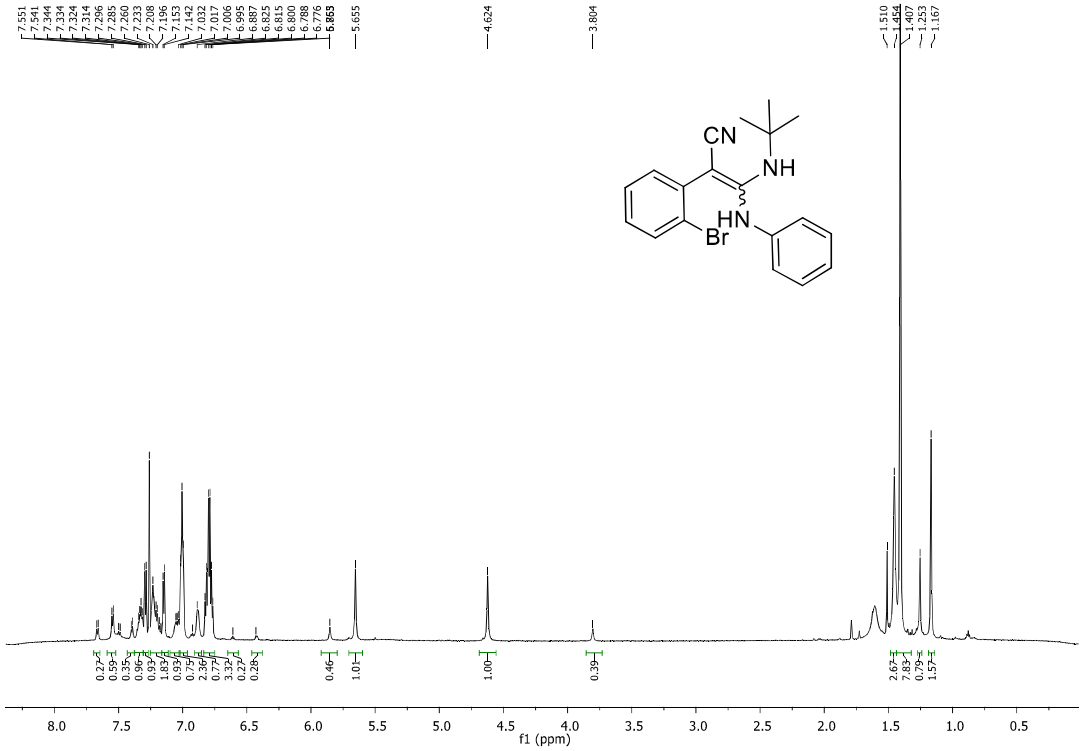


Figure 2.14a: ^{1}H NMR Spectrum of **46s**

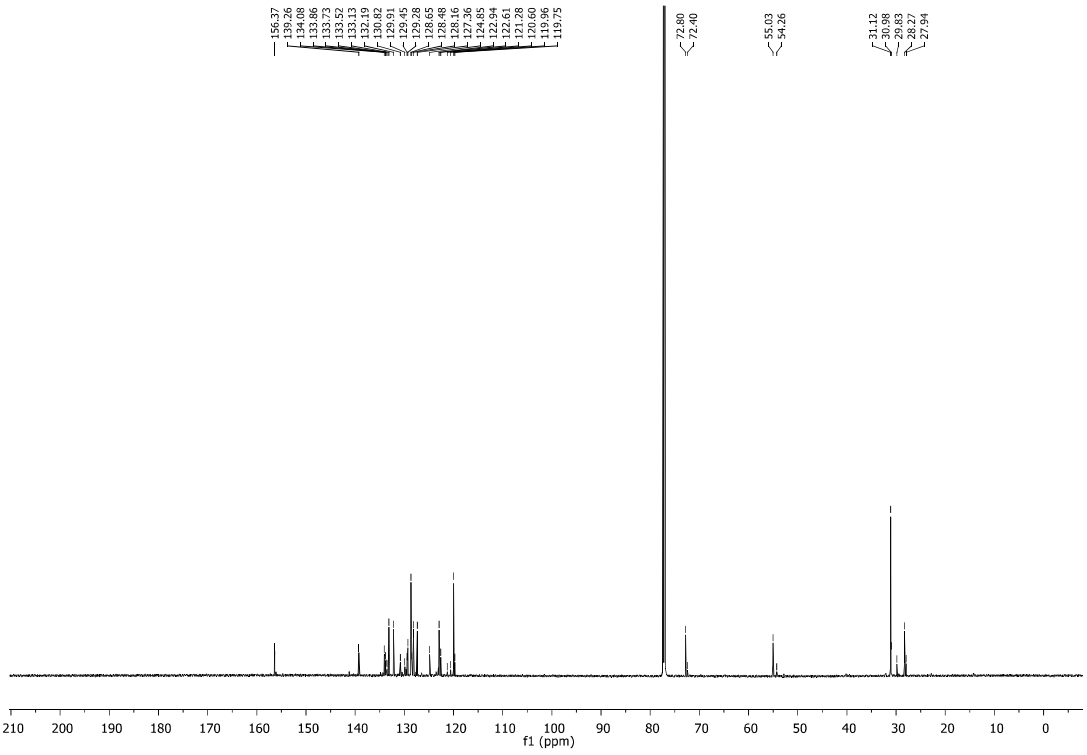


Figure 2.14b: ^{13}C NMR Spectrum of **46s**

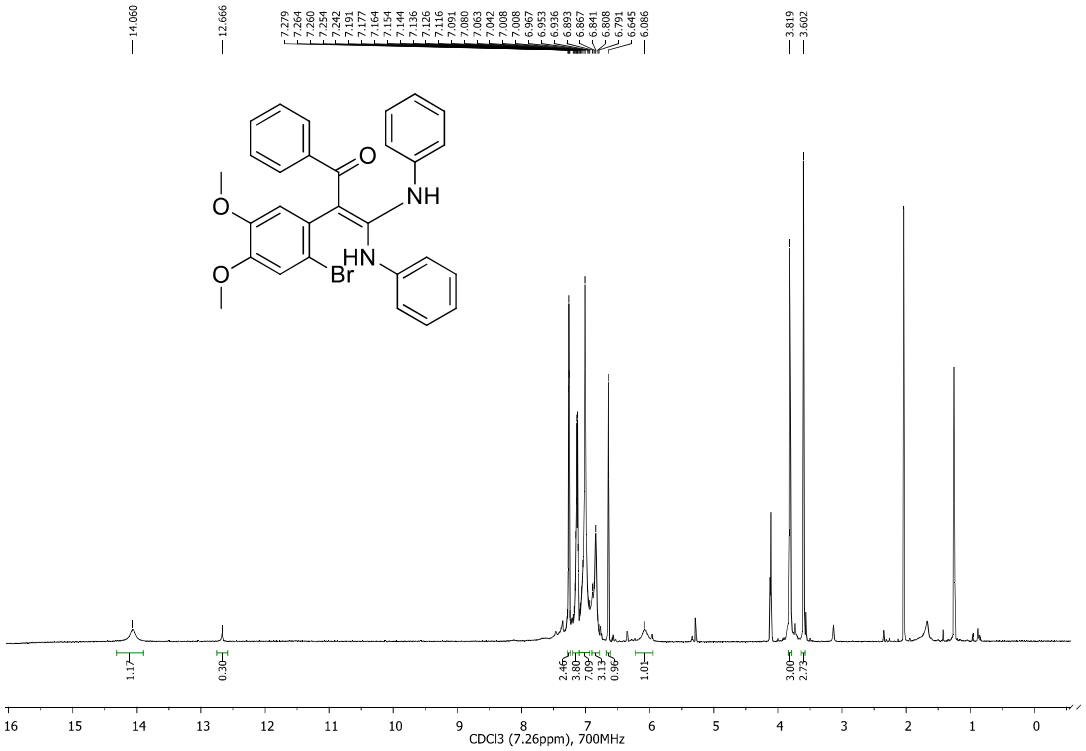


Figure 2.15a: ^{1}H NMR Spectrum of **51b**

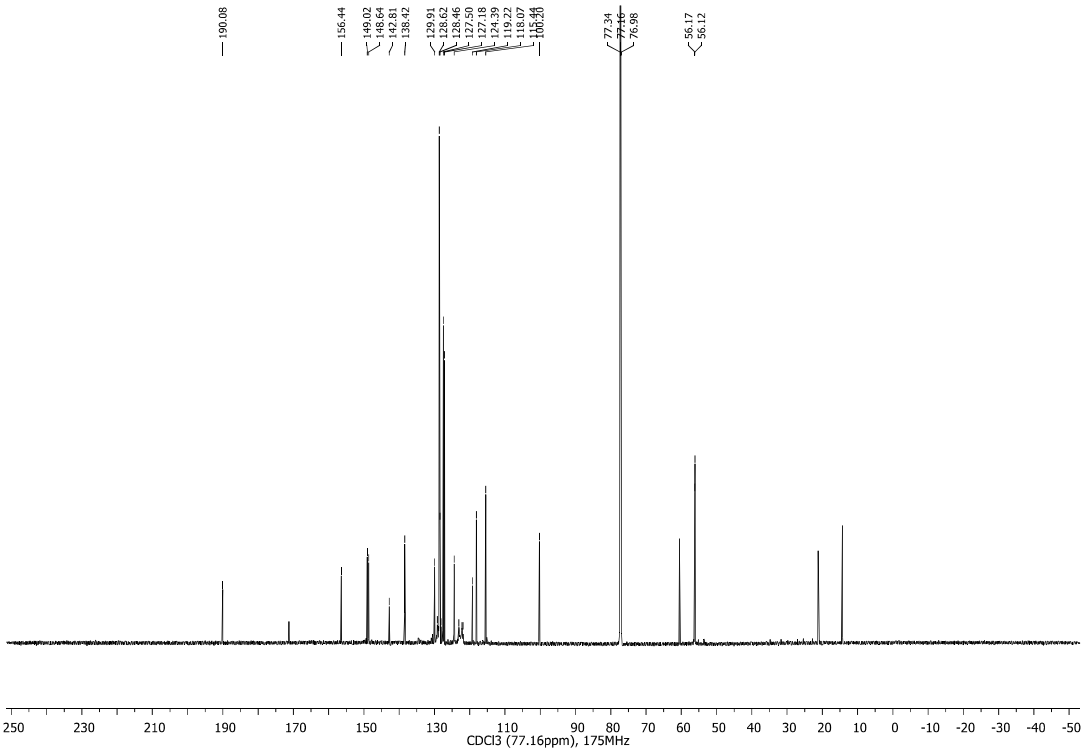


Figure 2.15b: ^{13}C NMR Spectrum of **51b**

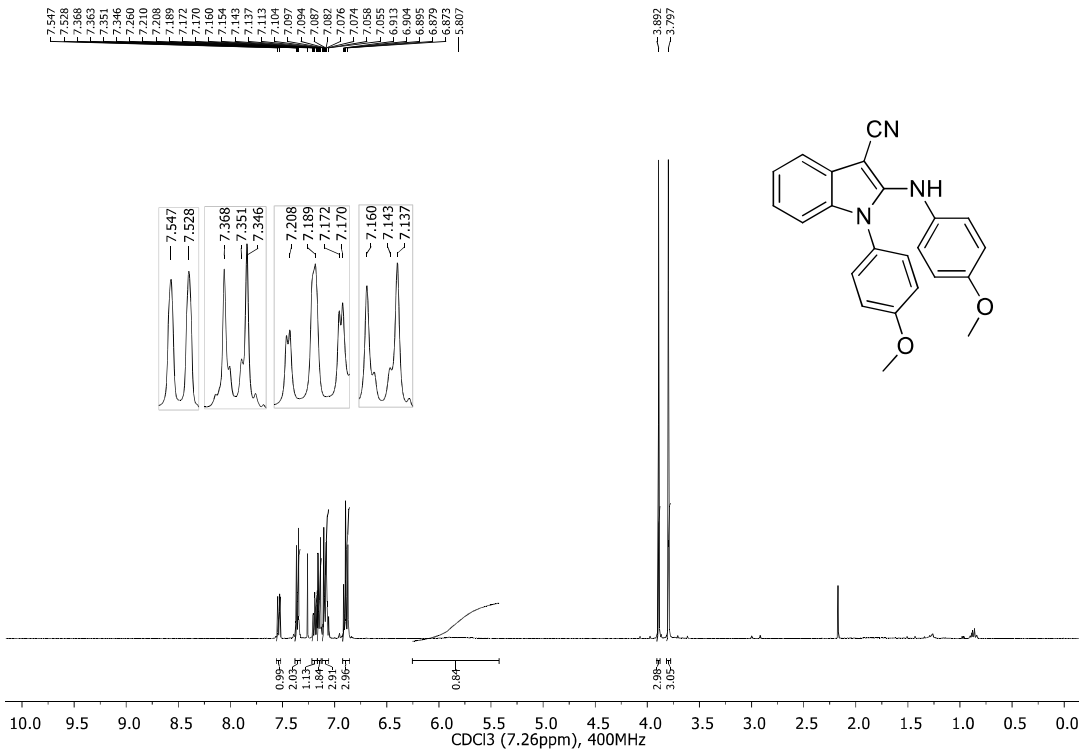


Figure 2.16a: ^{1}H NMR Spectrum of **47a**

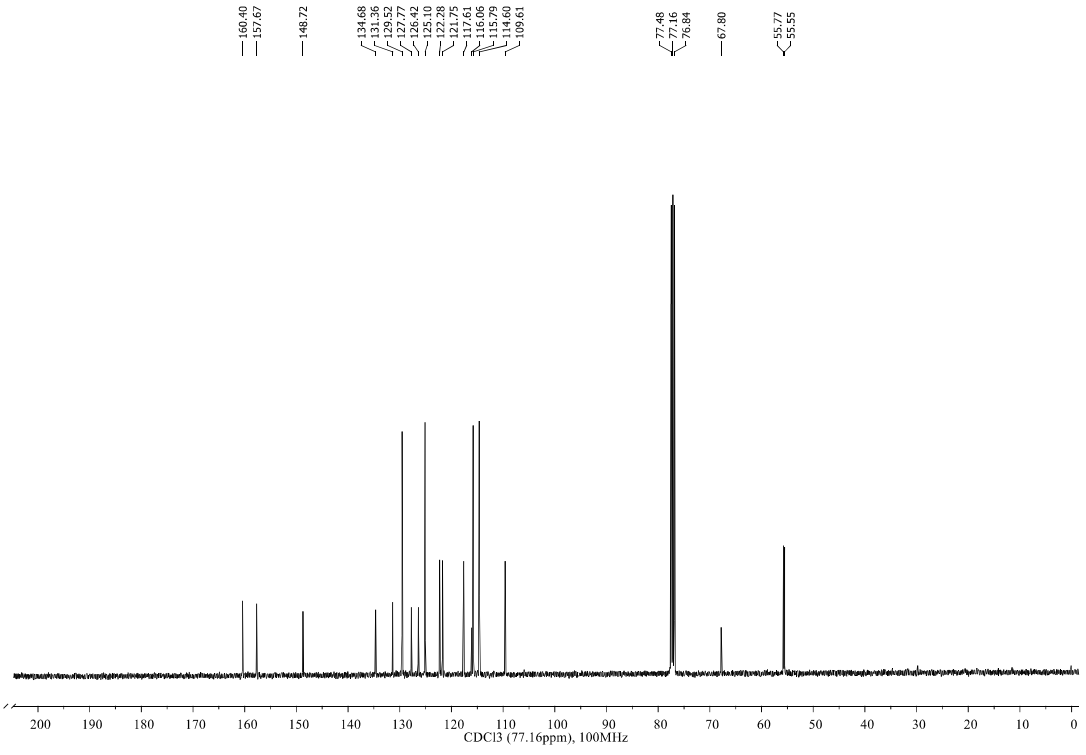


Figure 2.16b: ^{13}C NMR Spectrum of **47a**

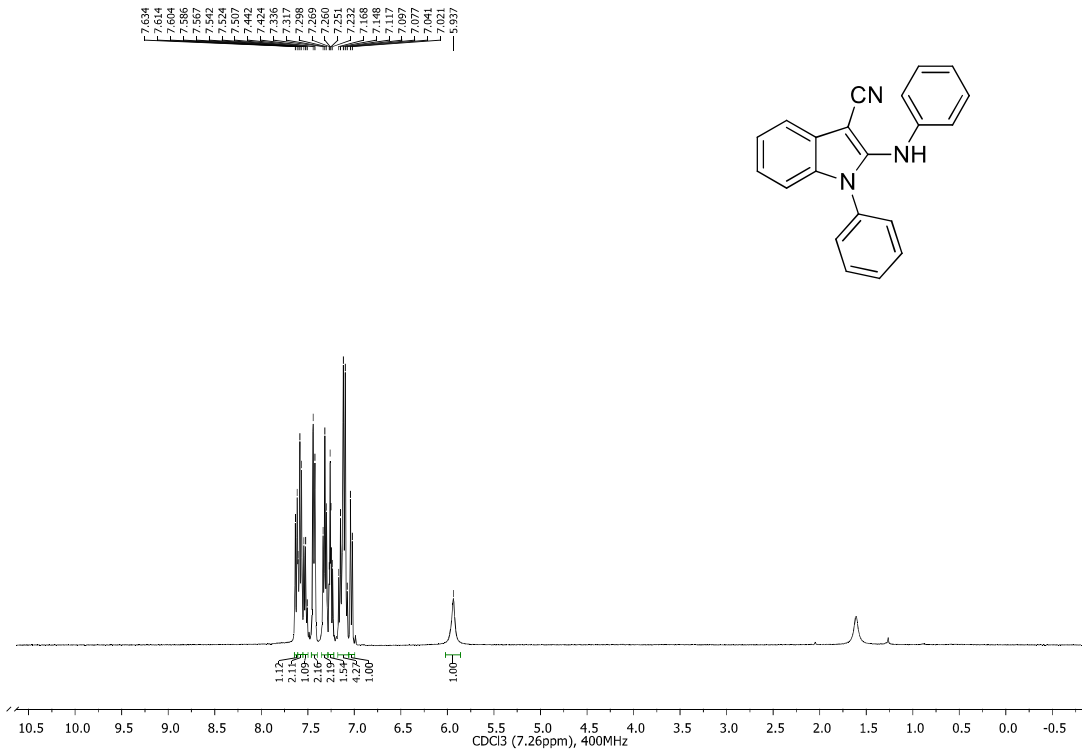


Figure 2.17a: ^{1}H NMR Spectrum of **47b**

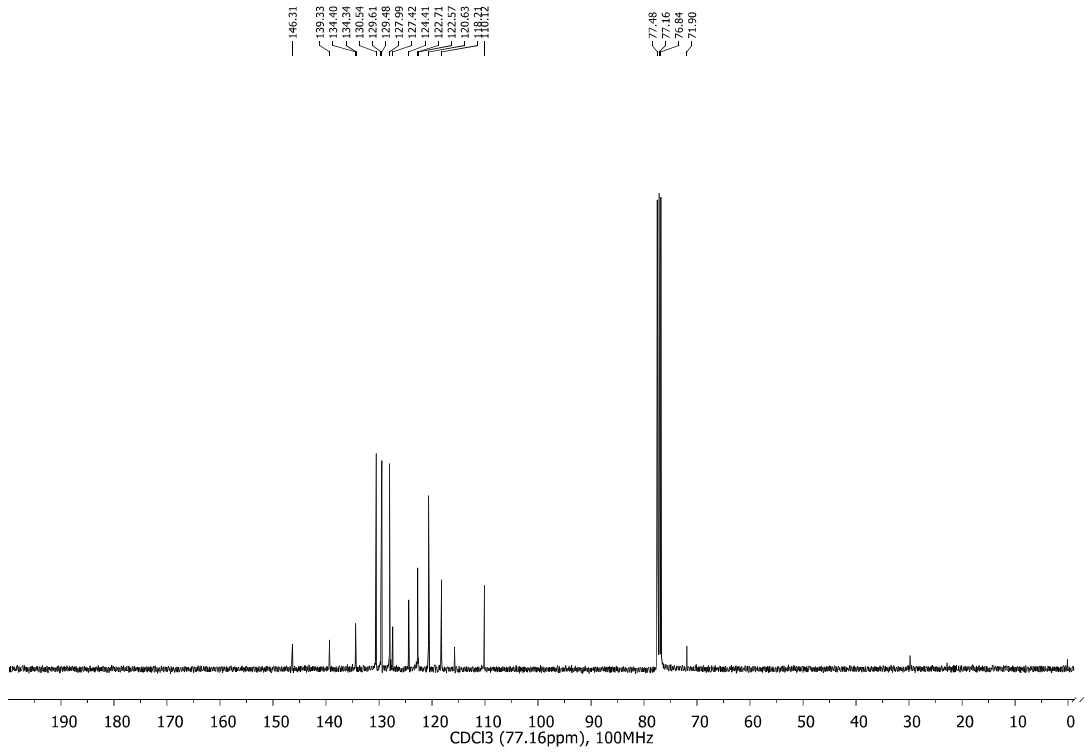


Figure 2.17b: ^{13}C NMR Spectrum of **47b**

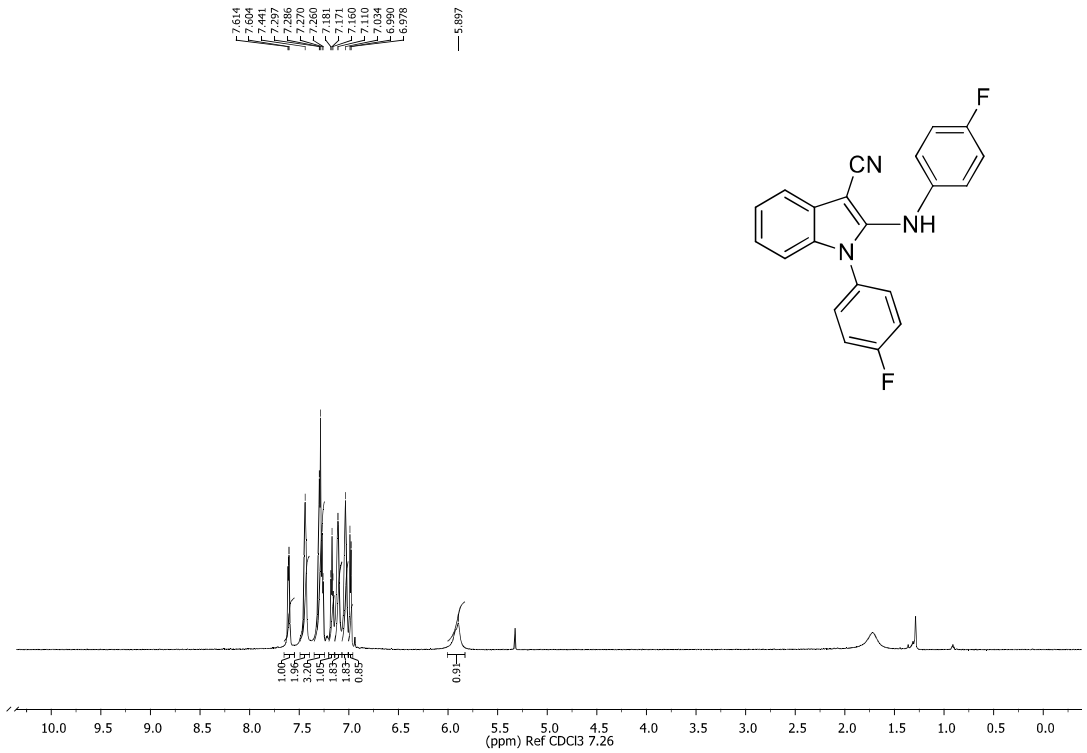


Figure 2.18a: ^{1}H NMR Spectrum of **47c**

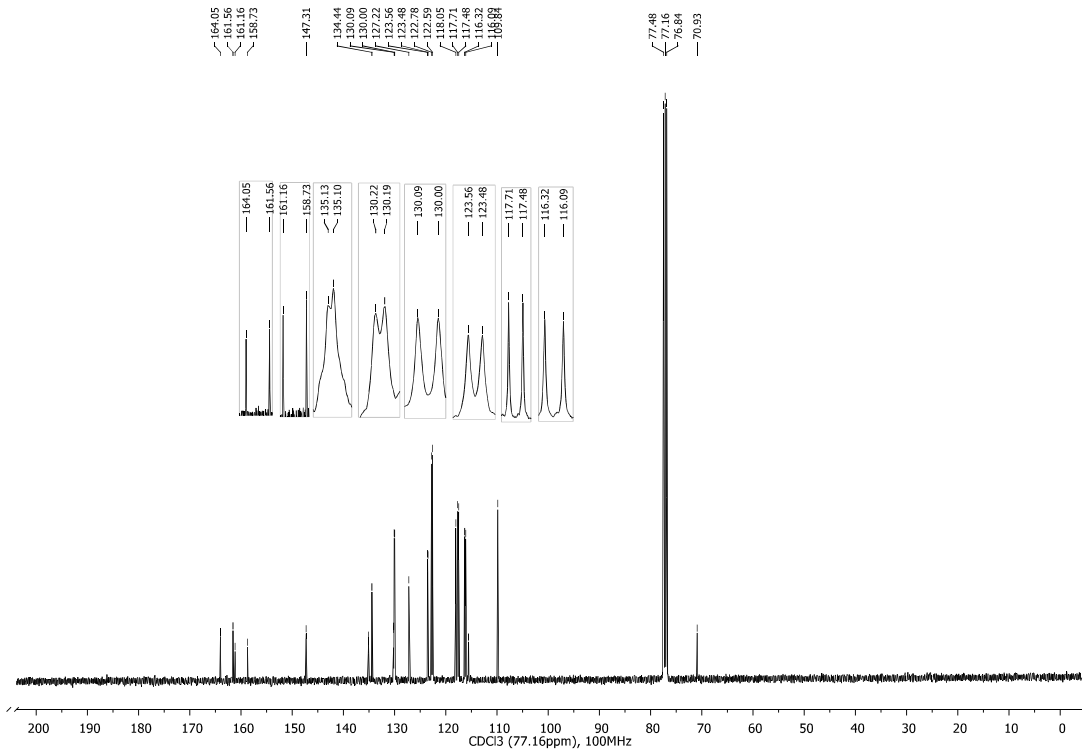


Figure 2.18b: ^{13}C NMR Spectrum of **47c**

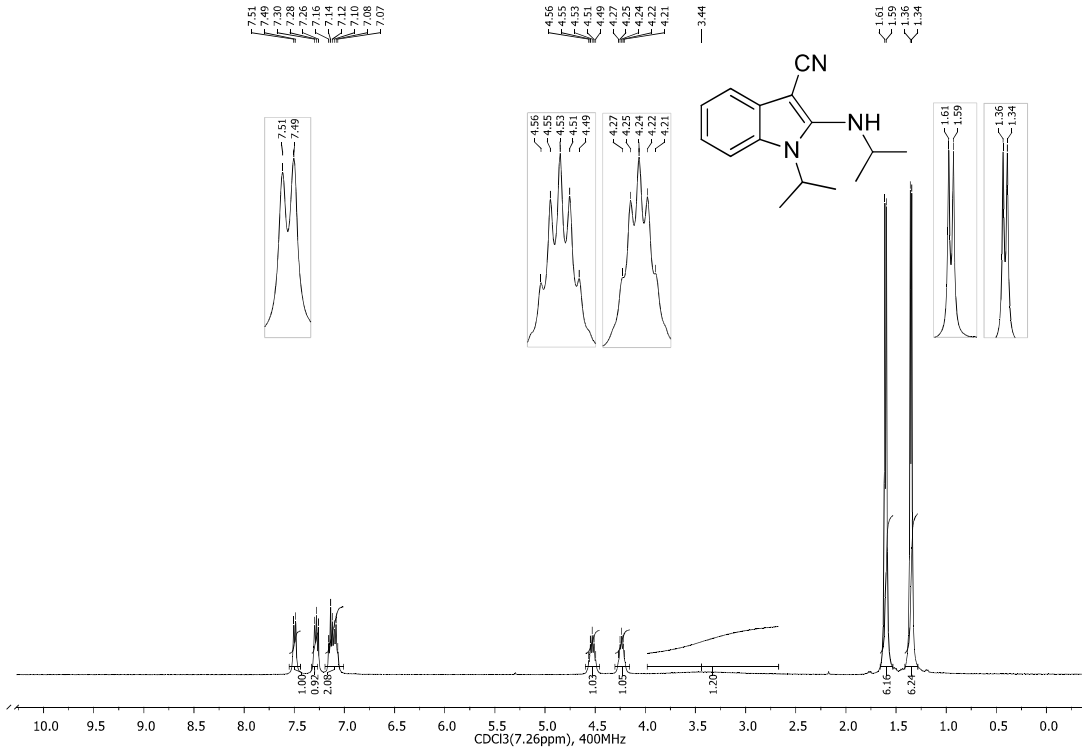


Figure 2.19a: ^{1}H NMR Spectrum of **47e**

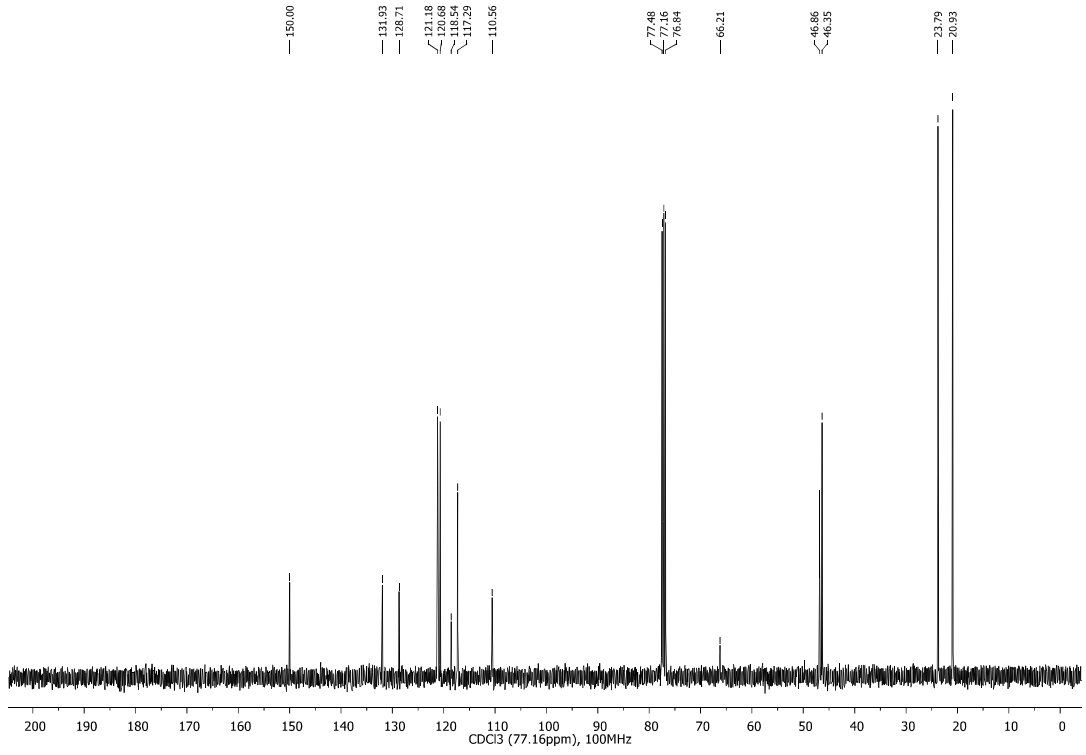


Figure 2.19b: ^{13}C NMR Spectrum of **47e**

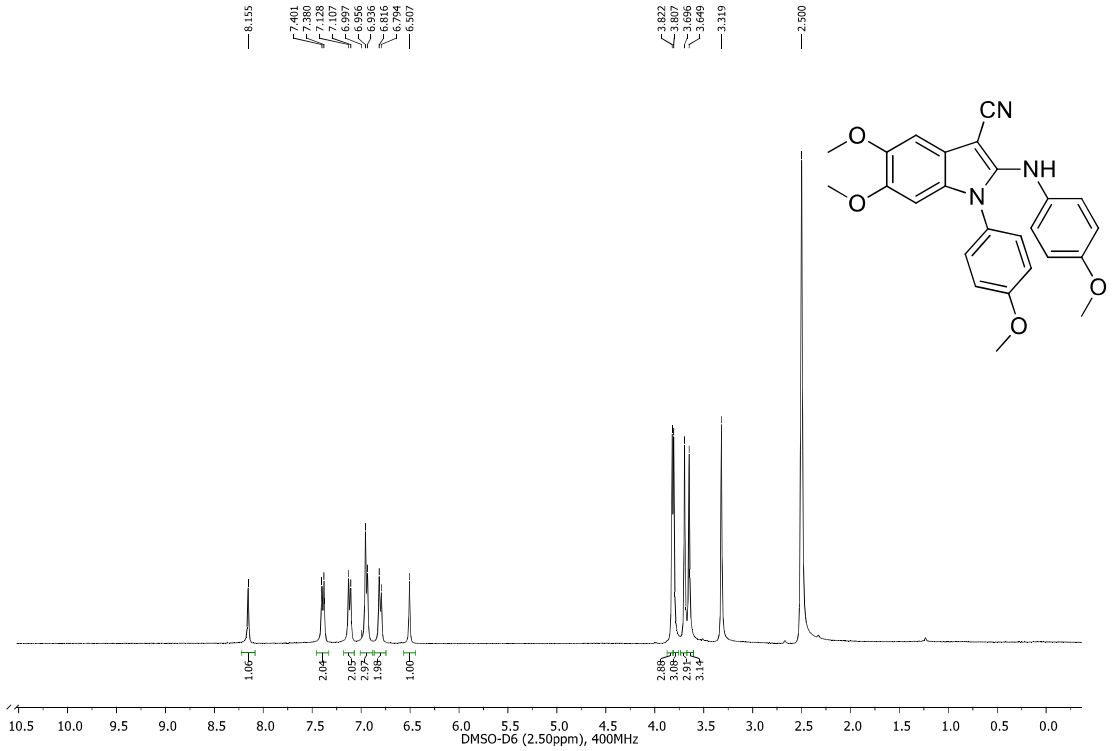


Figure 2.18a: ^{1}H NMR Spectrum of **47g**

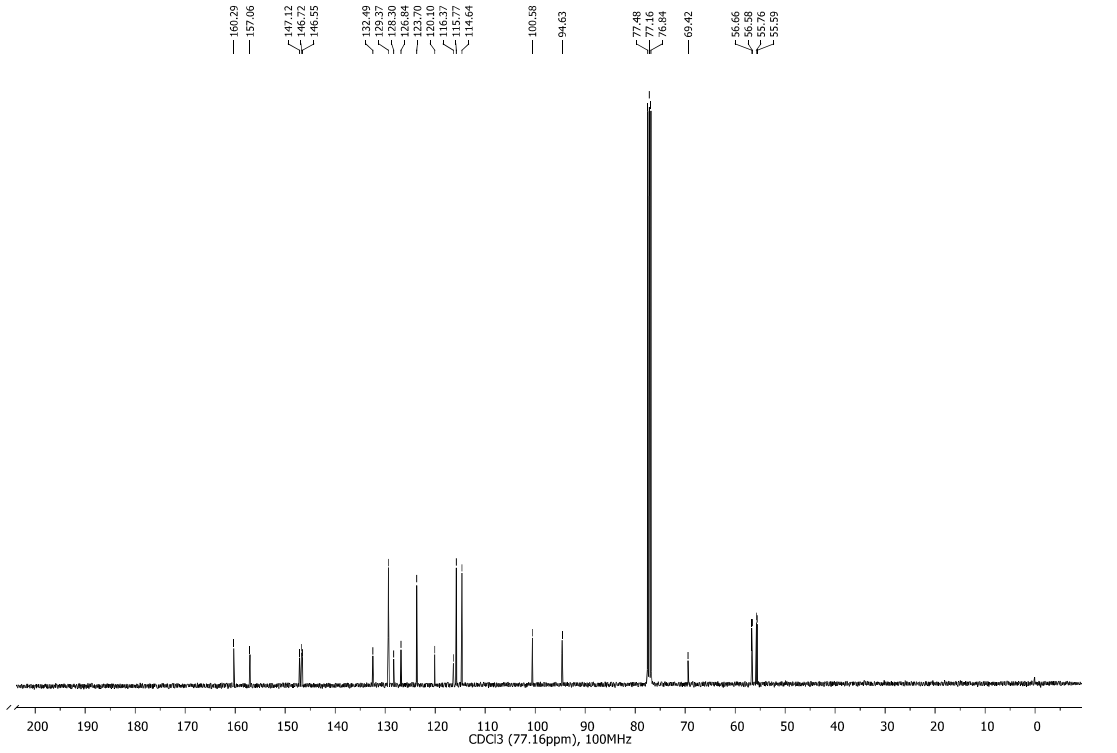


Figure 2.18b: ^{13}C NMR Spectrum of **47g**

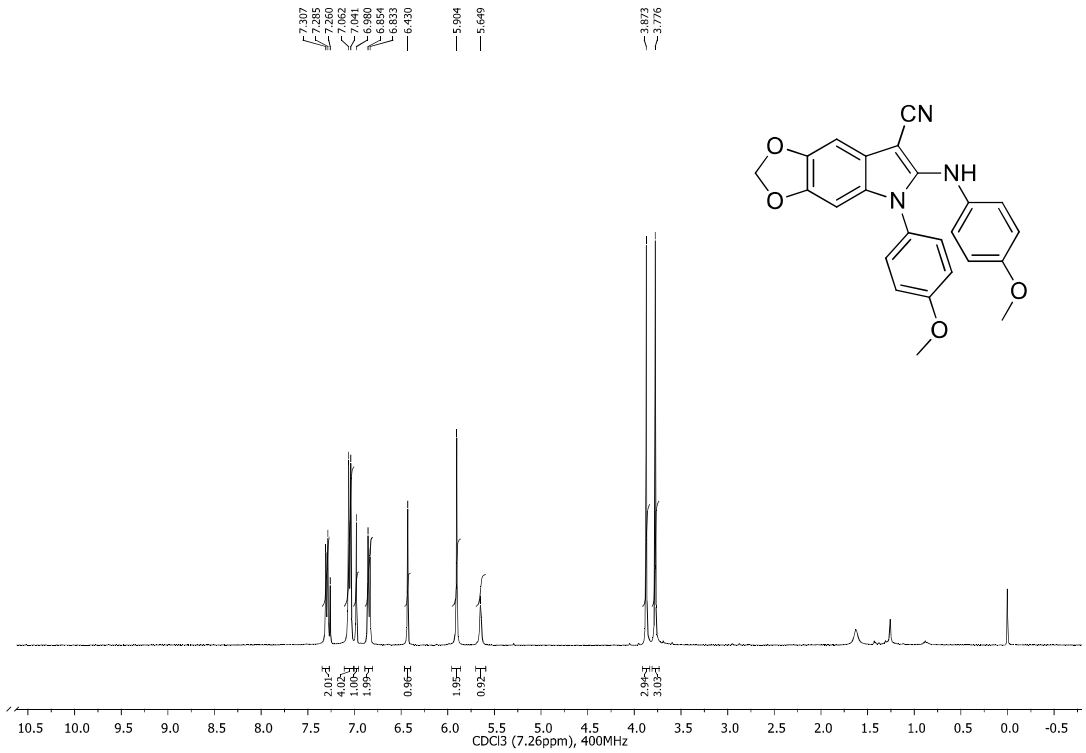


Figure 2.19a: ^{1}H NMR Spectrum of **47j**

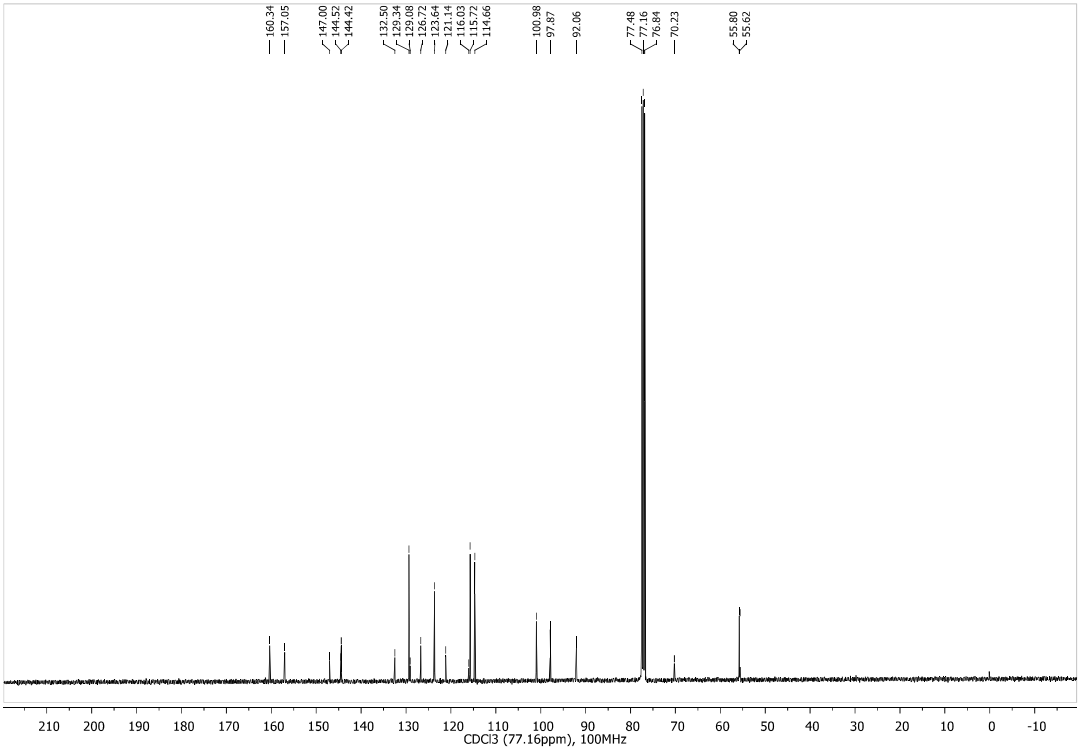


Figure 2.19b: ^{13}C NMR Spectrum of **47j**

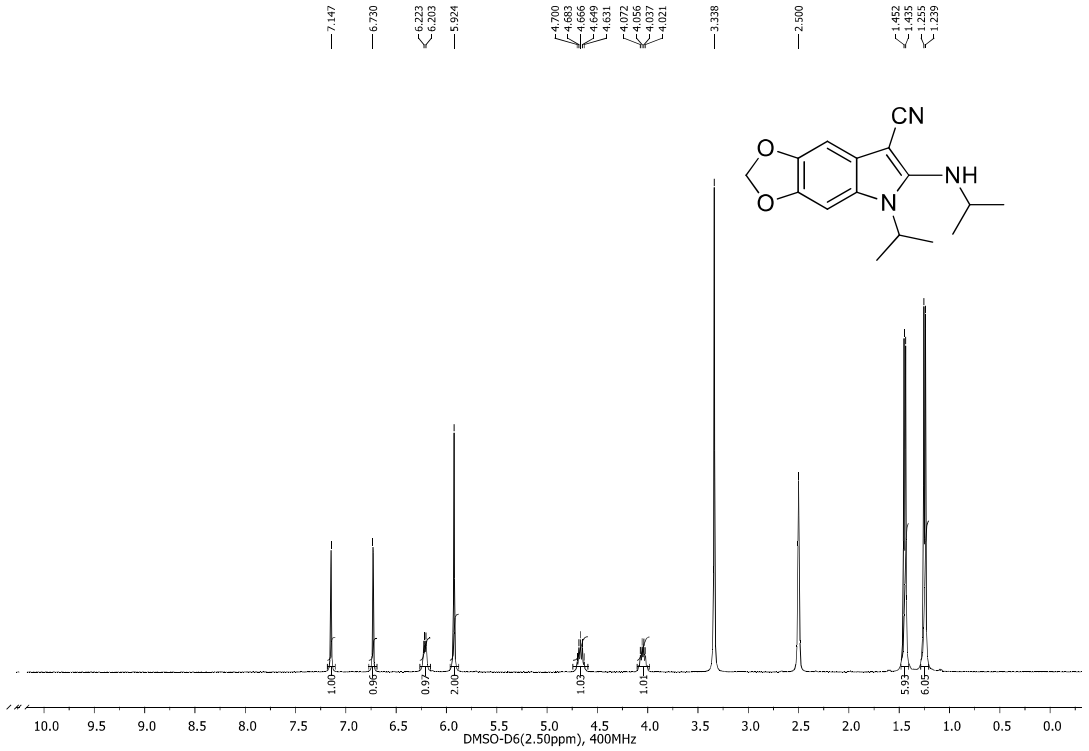


Figure 2.20a: ^{1}H NMR Spectrum of **47l**

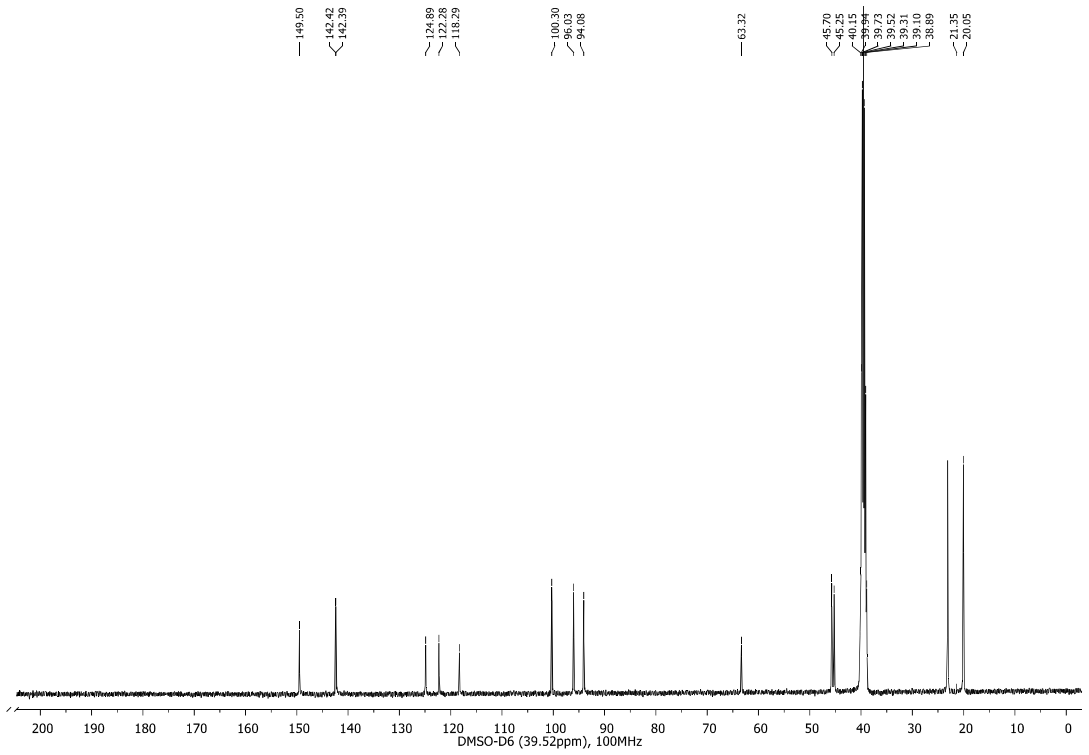


Figure 2.20b: ^{13}C NMR Spectrum of **47l**

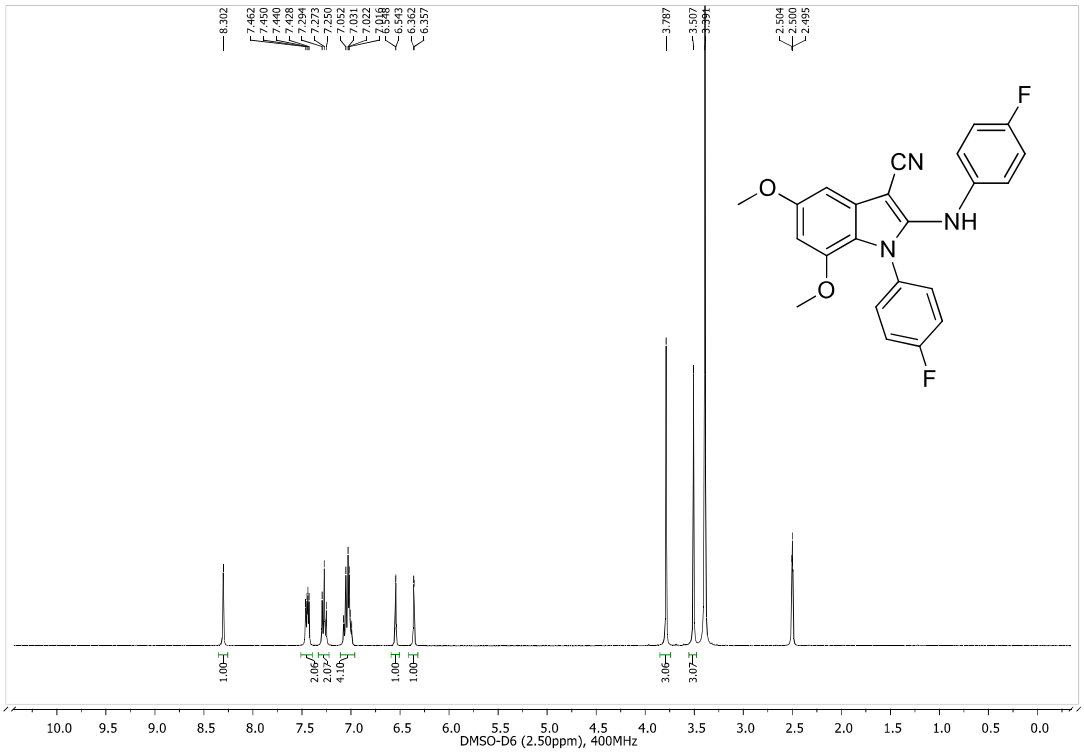


Figure 2.21a: ^{1}H NMR Spectrum of **47m**

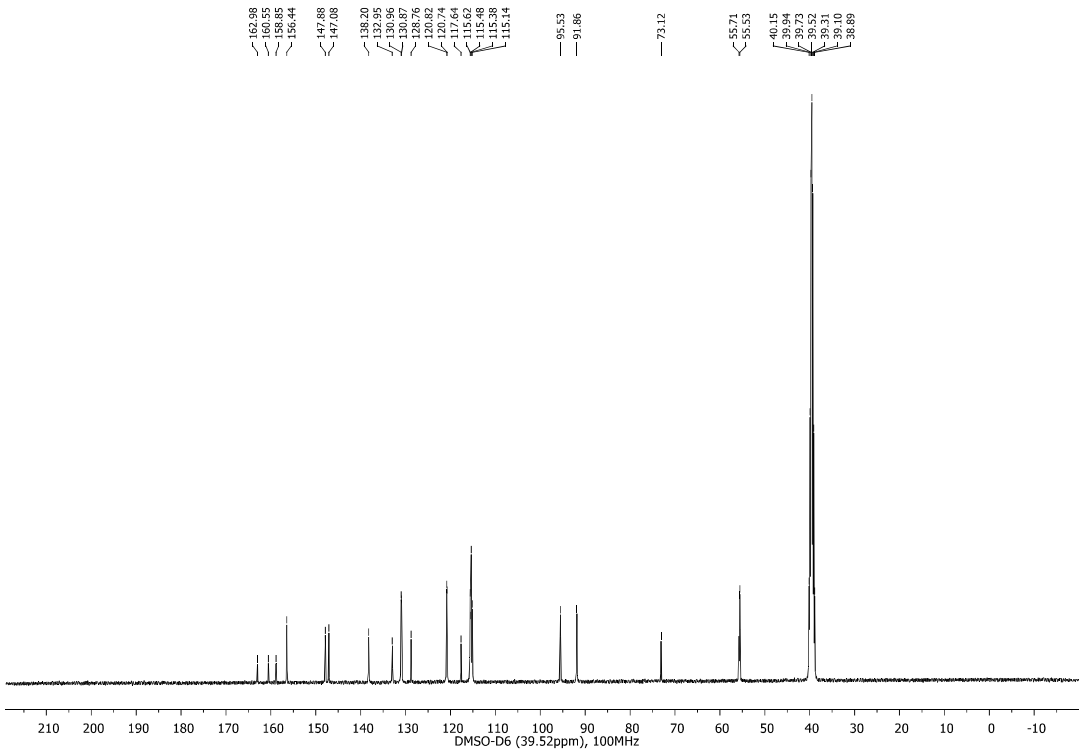


Figure 2.21b: ^{13}C NMR Spectrum of **47m**

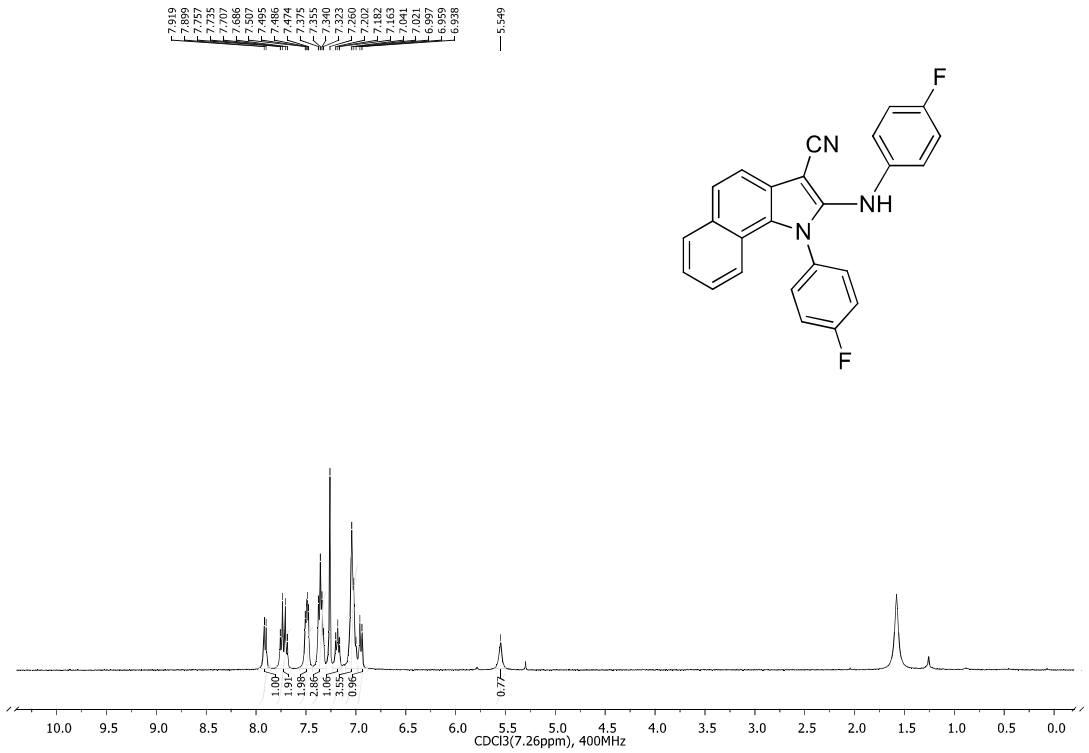


Figure 2.22a: ^{1}H NMR Spectrum of **47p**

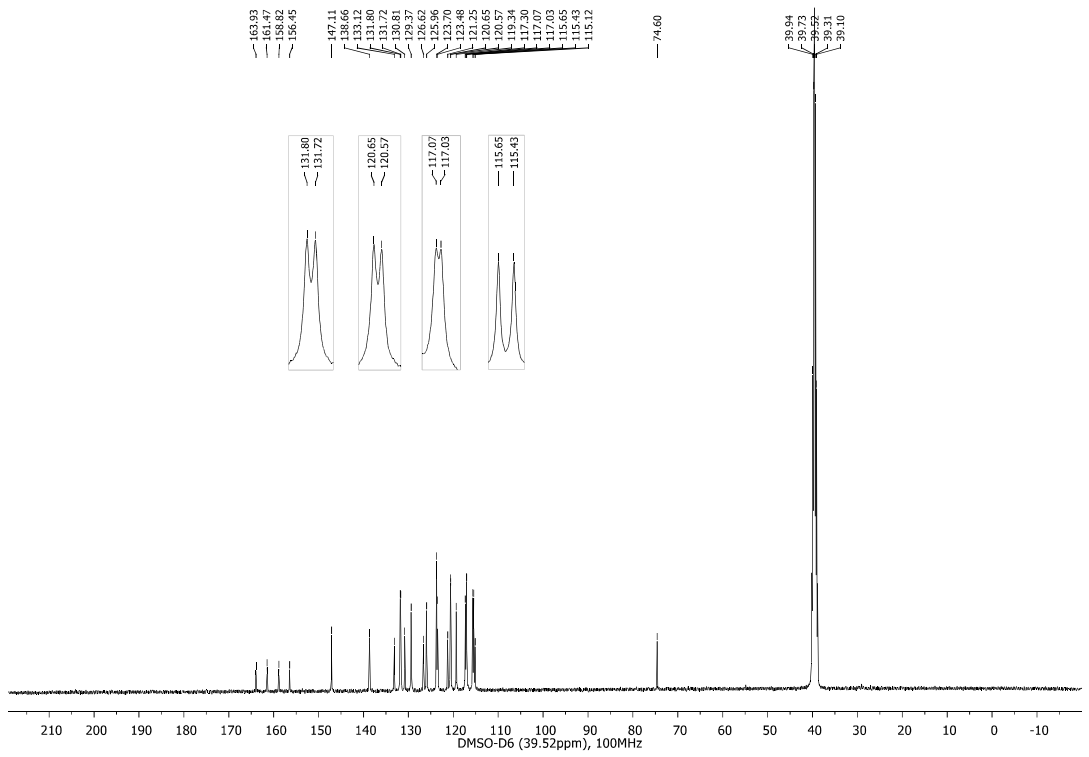


Figure 2.22b: ^{13}C NMR Spectrum of **47p**

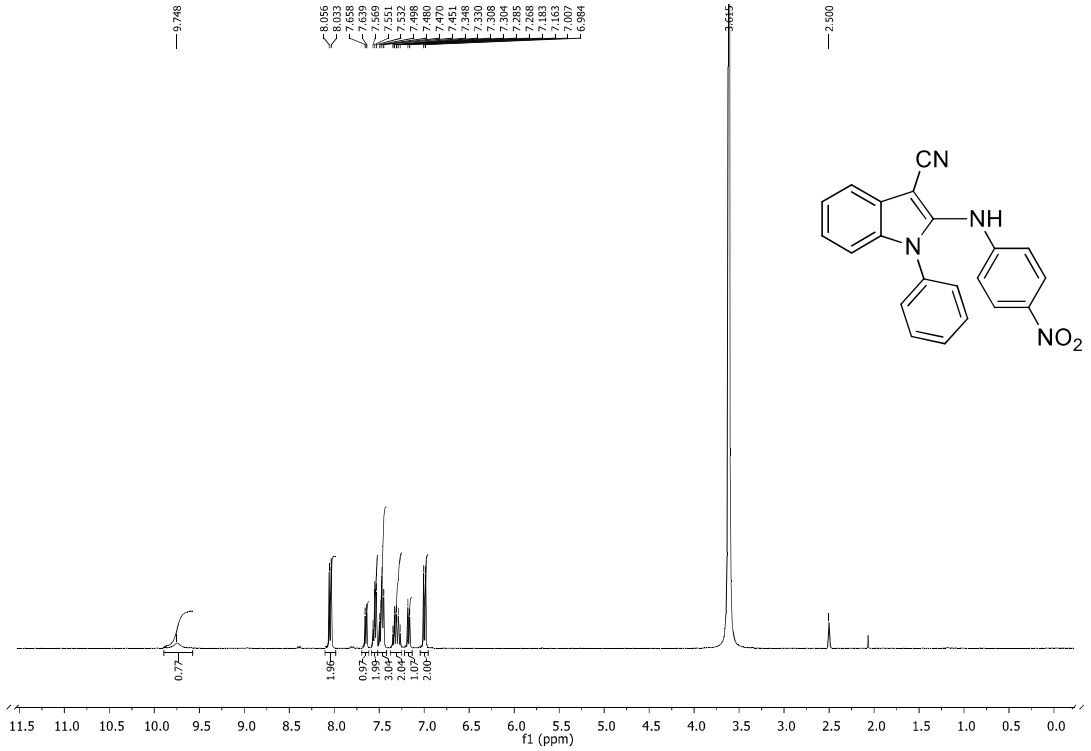


Figure 2.23a: ^{1}H NMR Spectrum of **47r**

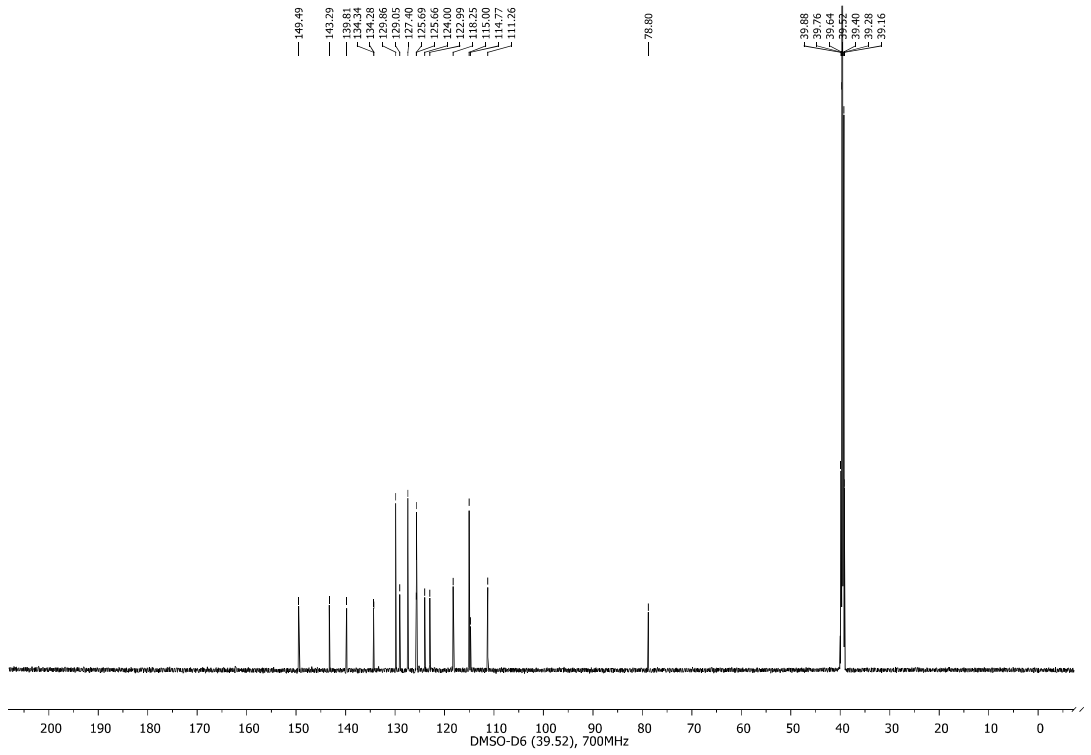


Figure 2.23b: ^{13}C NMR Spectrum of **47r**

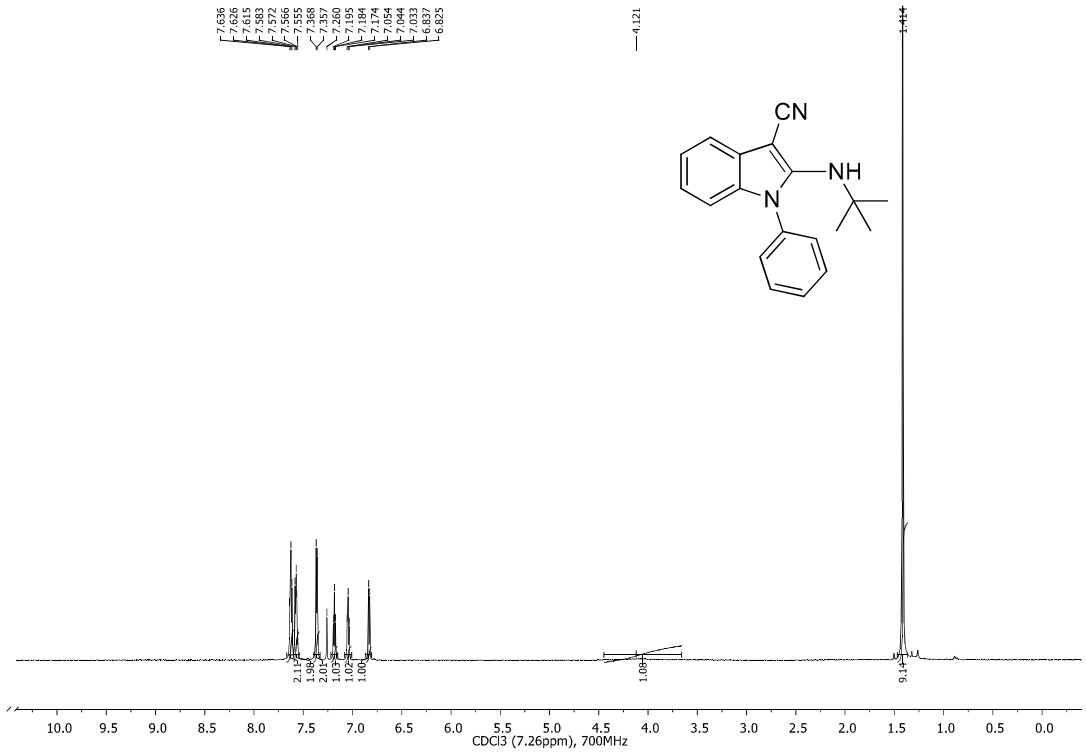


Figure 2.24a: ^{1}H NMR Spectrum of **47s**

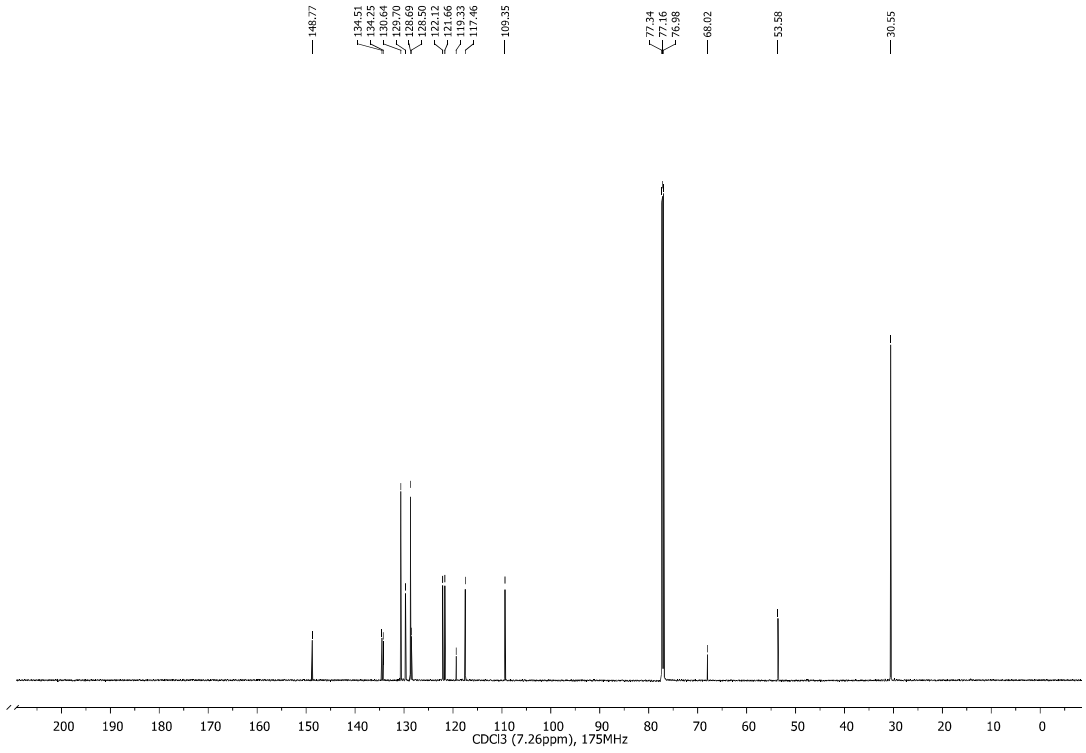


Figure 2.24b: ^{13}C NMR Spectrum of **47s**

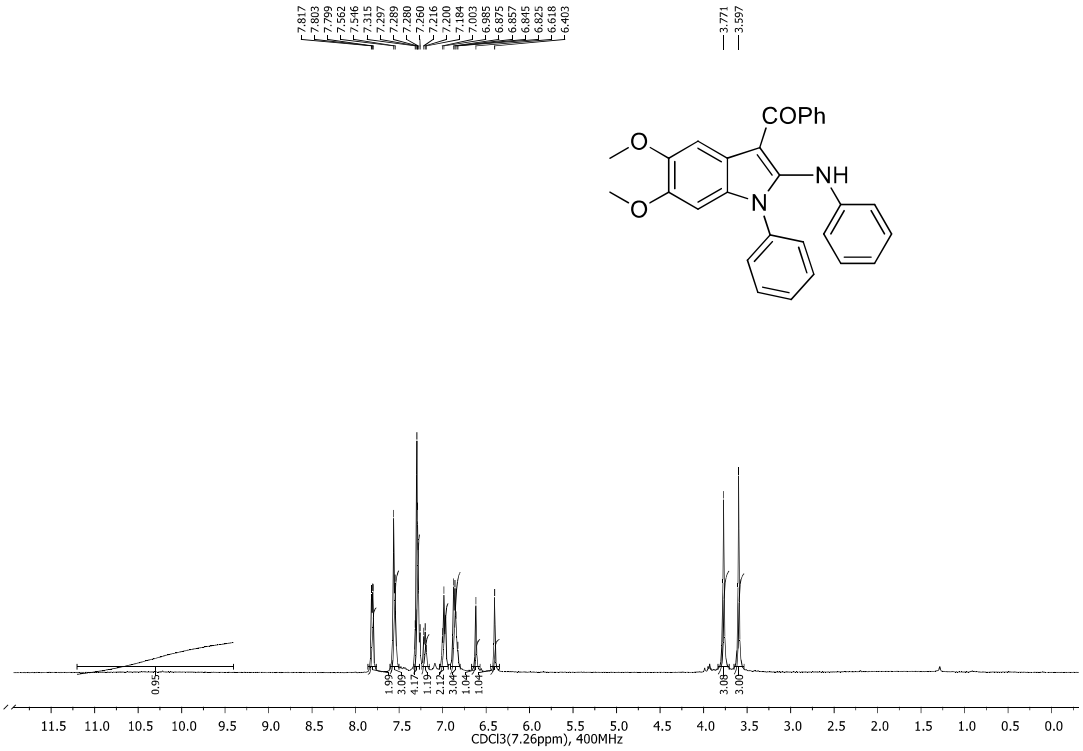


Figure 2.25a: ^{1}H NMR Spectrum of **52b**

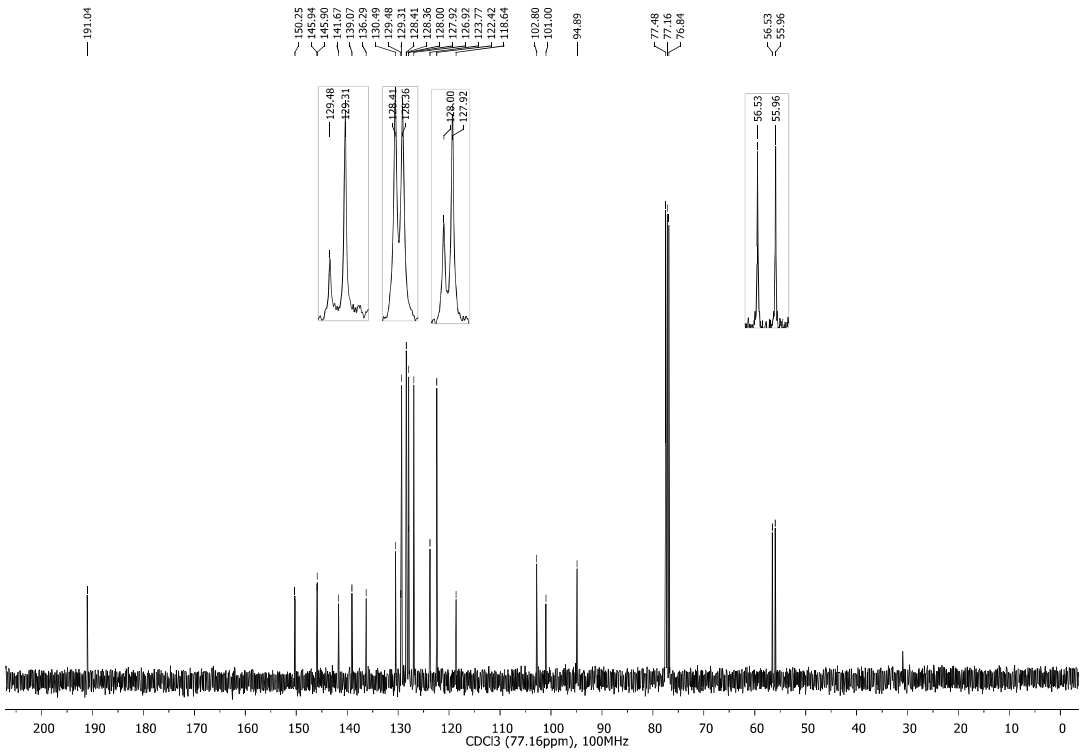


Figure 2.25b: ^{13}C NMR Spectrum of **52b**

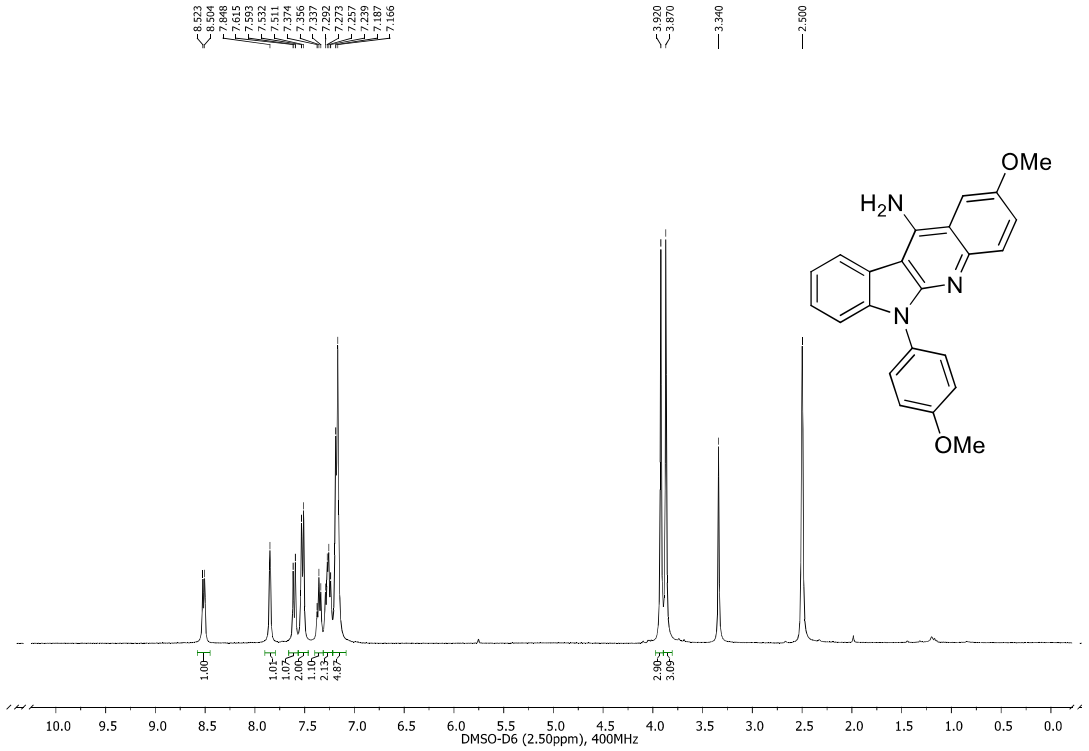


Figure 2.26a: ^{1}H NMR Spectrum of **53a**

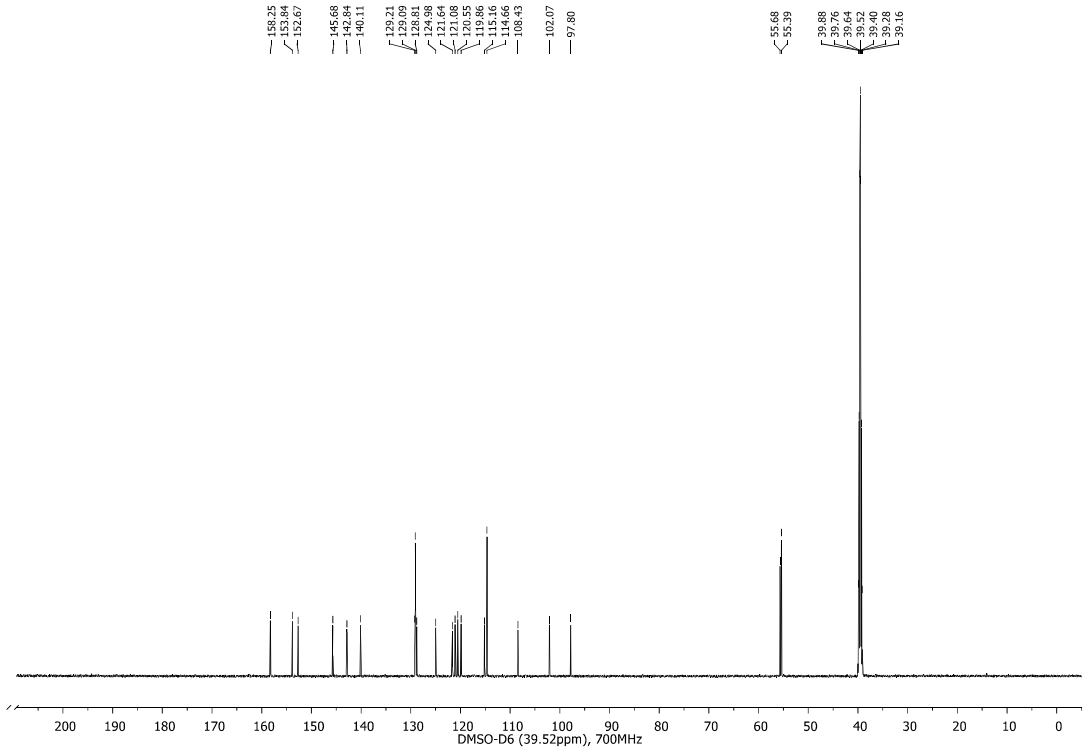


Figure 2.26b: ^{13}C NMR Spectrum of **53a**

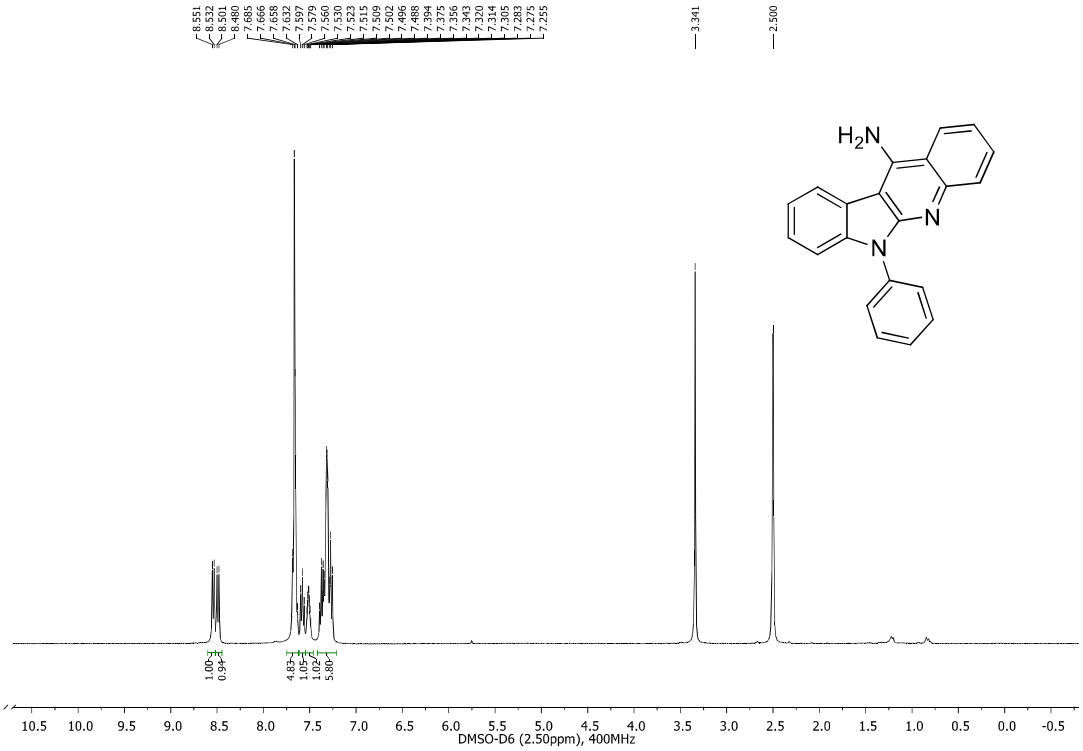


Figure 2.27a: ^{1}H NMR Spectrum of **53b**

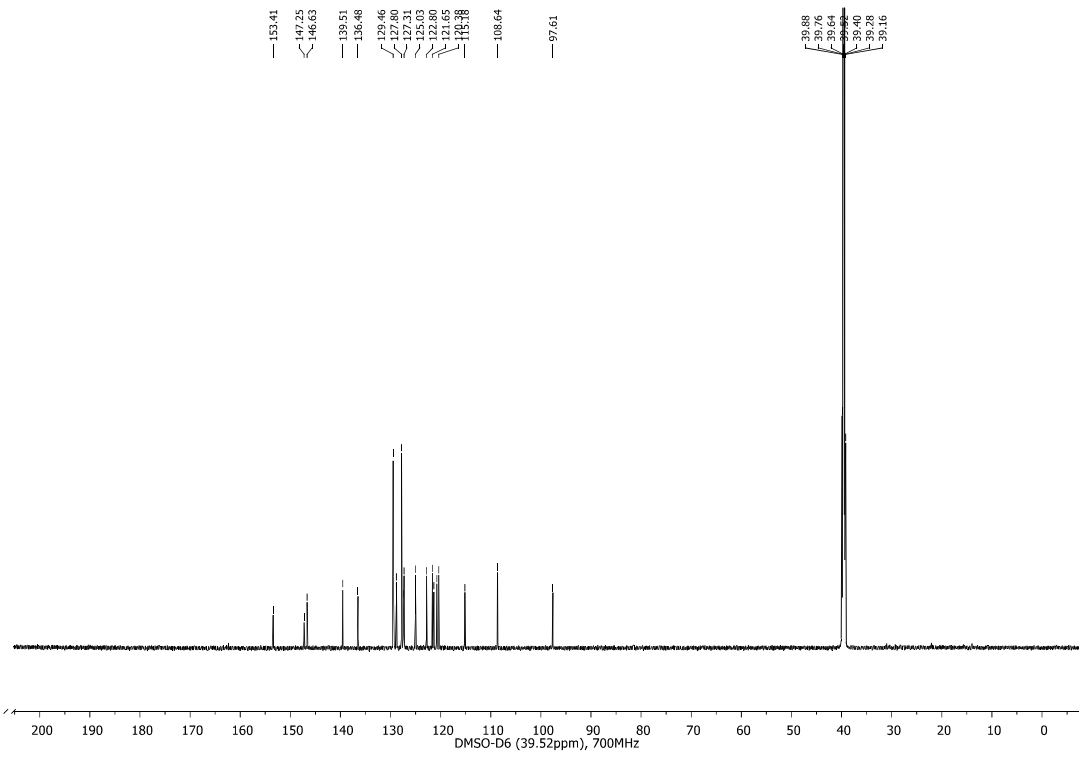


Figure 2.27b: ^{13}C NMR Spectrum of **53b**

2.8 Crystal Data

2.8.1 Crystallographic data of **47q** in CH_2Cl_2/n-hexane: $C_{22}H_{16}N_4O_3$, Mw = 384.39, monoclinic, space group P21/n, a = 8.4804(7) Å, b = 12.5579(11) Å, c = 18.2886(17) Å, α = 90 °, β = 102.799(6) °, γ = 90 °, V = 1899.3(3) Å^3, Z = 4, D_{calc} = 1.344 g/cm^3, T = 296(2) K, R_1 = 0.0623 {I>=2σ (I)}, wR_2 = 0.1844, GOF = 0.957.

2.8.2 Crystallographic data of **47s** in CH_2Cl_2/n-hexane: $C_{19}H_{19}N_3$, Mw = 289.37, monoclinic, space group P21/n, a = 9.4287(4) Å, b = 9.7444(5) Å, c = 18.0606(8) Å, α = 90 °, β = 103.808(2) °, γ = 90 °, V = 1611.40(13) Å^3, Z = 4, D_{calc} = 1.193 g/cm^3, T = 296(2) K, R_1 = 0.0575 {I>=2σ (I)}, wR_2 = 0.2386, GOF = 0.937.

2.9 References

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Nickel and Iodine Mediated Regioselective Thiolation of Thioamides: Synthesis of 2-Aminobenzo[*b*]thiophene Derivatives

3.1 Introduction:

In a wide range of sulphur heterocycles, benzo[*b*]thiophene is highly promising motif, which is associated with diverse range of medicinal and industrial applications.[1] Recent findings reveal that these benzo[*b*]thiophene derivatives were also useful in material science.[2] Further, these derivatives show interesting pharmaceutical applications such as antimalarial, antifungal, anti-angiogenic and anti-diabetic, and also well-known diagnostic agents for the treatment of Alzheimers disease.[3] Raloxifene is one of the benzo[*b*]thiophene based well known drug, which is a selective estrogen receptor modulator (SERM) and it is useful in the treatment of osteoporosis.[4] On the other hand, Zileuton, a derivative of benzo[*b*]thiophene is an orally active inhibitor of lipoxygenase.[5] Apart from the active drug molecules,

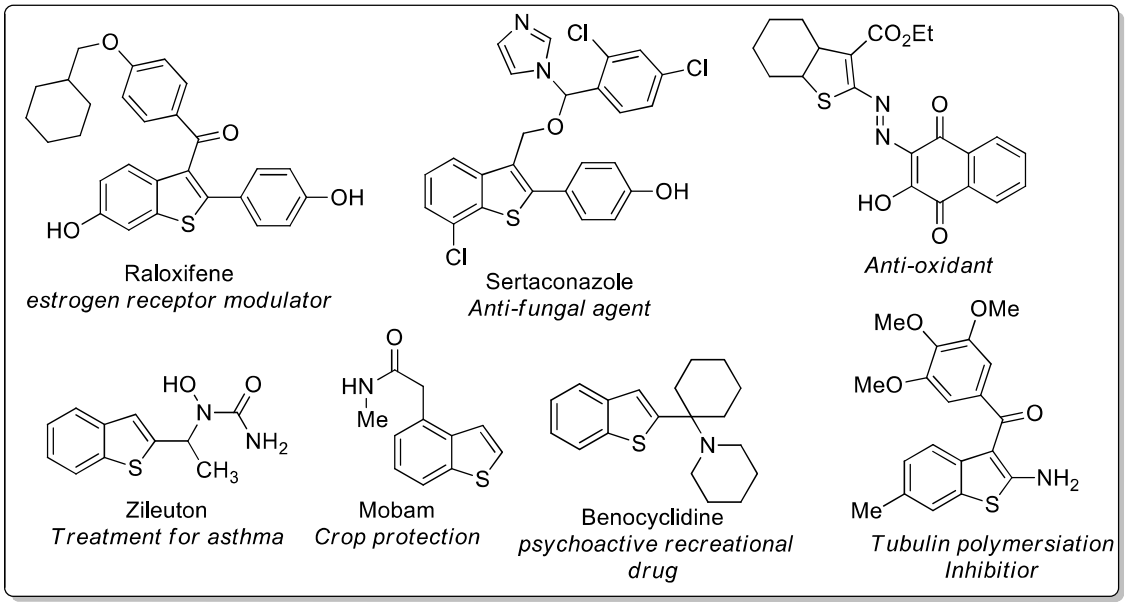


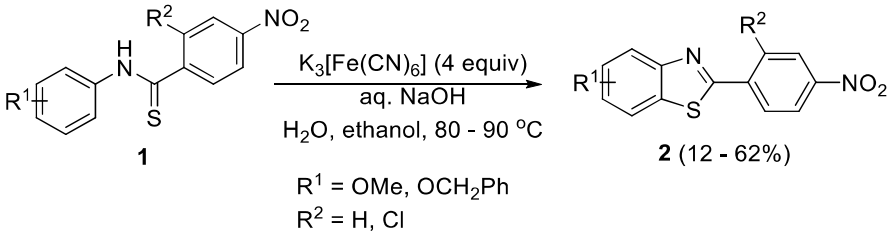
Figure 3.1*: Various Commercially Available Benzo[b]thiophene Based Drugs and Biologically Active Molecules.*

analogue of naphthalene, Mobam is a benzo[*b*]thiophene derivative, which is used in crop protection. Originally, the family of sulphur heterocycles involve stable aromatic compounds that showcase various physiochemical properties.[6] Despite of their wide range of applications, synthesis of these benzo[*b*]thiophene derivatives from an oxidative C─H functionalization method was less studied.

The transition metal mediated carbon–heteroatom bond formation is a powerful synthetic tool in the area of heterocyclic chemistry.[7] Among them, C−S bond formation reactions are less explored as compared with the other counterparts like C−N[8] and C−O[9] bond forming reactions. This is the powerful synthetic tool for the construction of various *S*-heterocycles by using mild reaction conditions. In this context, extensive efforts were devoted to cross-coupling reactions in which thiols were reacted with organic halides to afford the cross-coupled products along with stoichiometric amount of by-products.[10] On the other hand, direct C−H thiolation reactions are highly promising, because this strategy provides the desired coupled products without the requirement of prefunctionalised starting materials. This protocol is also very useful in applications of process and bulk chemistry.[11] The transition metals catalyzed C−H functionalization reactions were thoroughly investigated to synthesize various *N* and *O*-heterocycles,[12] but its utility for C−H thiolation reaction to synthesize *S*-hetrocycles was less explored. Thus, C−H thiolation methodology to construct various functional group rich *S*-heterocycles under milder reaction conditions is highly desirable.

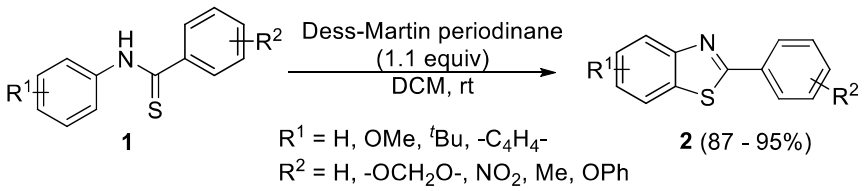
3.2 Previous Reports for *S*-Heterocycle Synthesis via C−H Thiolation

In 1996, M. F. G. Stevens and co-workers established the new synthetic route for the synthesis of benzothiazole derivatives **2** from thioanilides **1** by using potassium ferrricyanide as oxidant and NaOH as a base (Scheme 3.1).[13]



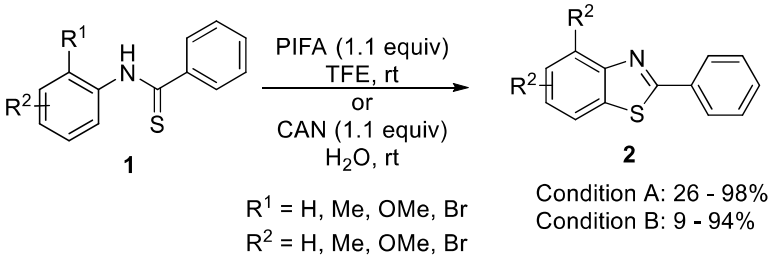
Scheme 3.1: *Metallic Oxidant Promoted Intramolecular Oxidative Cyclization of Thioanilides*

S. Bose and co-workers studied the intramolecular oxidant promoted C−H functionalization of thioanilides **1** to synthesize benzothiazole derivatives **2** (Scheme 3.2).[14] This method involved generation of thienyl radical by reacting with DMP followed by radical cyclization and aromatization yielded the desired products.



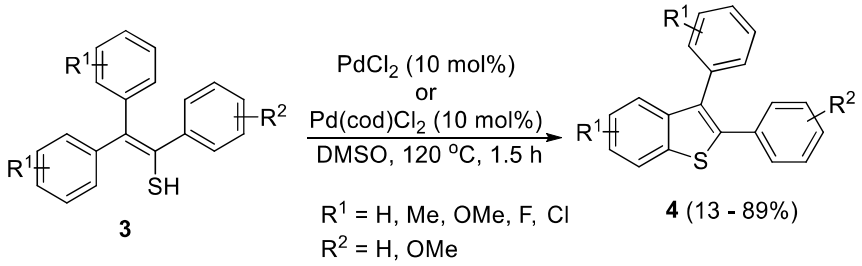
Scheme 3.2: *Organic Oxidant Mediated Oxidative Cyclization*

After two years, Y. A. Jackson's group studied the similar reaction by two alternative strategies, one using the hypervalent iodine reagent, PIFA and the other one involved ceric ammonium nitrate (Scheme 3.3).[15]



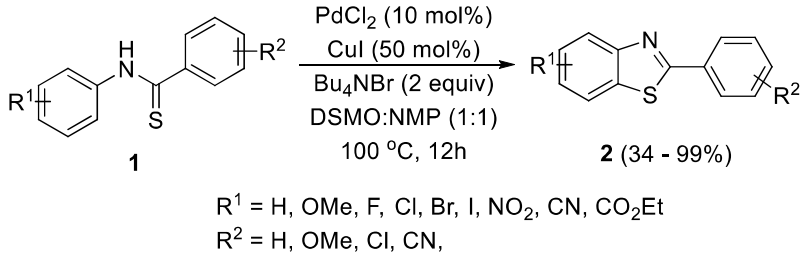
Scheme 3.3: *Hypervalent Iodine Reagent Mediated Intramolecular C─H Thiolation*

The inaugural report regarding the synthesis of benzo[*b*]thiophene **4** *via* C─H thiolation was reported by K. Inamoto and co-workers way back in 2008 (Scheme 3.4).[16] Their methodology involves palladium mediated intramolecular C─H thiolation of thioenols **3** (Scheme 1). In their approach, palladium has a dual role as in the formation of disulfides as well as in the oxidative C─H thiolation.



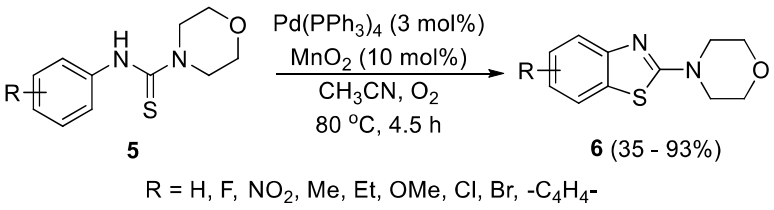
Scheme 3.4: *First Report for the Synthesis of Benzo[b]thiophenes via C─H Thiolation*

Later, the same group inventively utilized this similar approach to synthesize benzothiazole derivatives **2** from the corresponding thioanilides **1** (Scheme 3.5).[17]



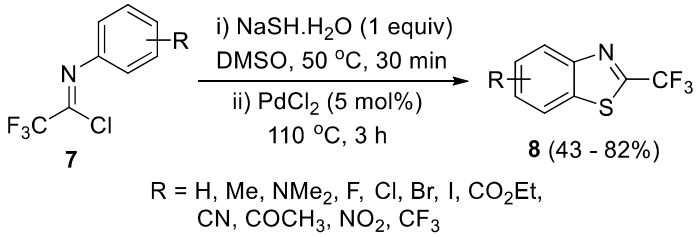
Scheme 3.5: *Palladium Mediated Intramolecular C─H Thiolation of Thioamides*

R. A. Batey and co-workers applied Inamoto's approach to thiourea derivatives **5** to synthesize 2-aminobenzothiazole **6** derivatives by using co-catalytic $Pd(PPh_3)_4/MnO_2$ system in the presence of oxygen (Scheme 3.6).[18]



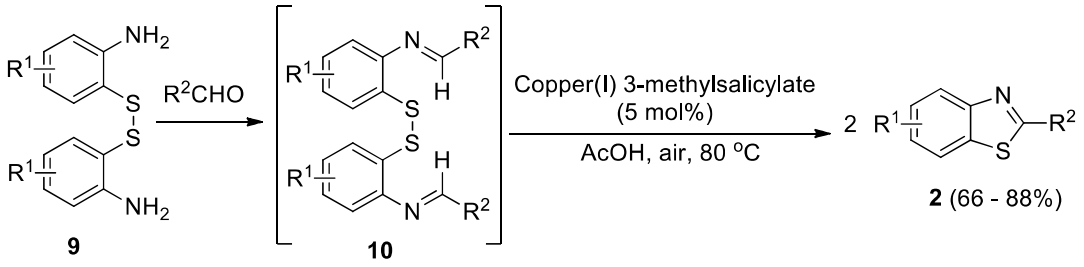
Scheme 3.6: *Palladium Promoted 2-Aminobenzothiazoles Synthesis from Thiourea Derivatives*

Y. Wu and co-workers demonstrated the palladium mediated one pot methodology for the synthesis of 2-trifluoromethylbenzothiazoles **8** from trifluoromethylimidoyl chlorides **7** and sodium hydrosulfide (Scheme 3.7).[19] This method involved nucleophilic displacement of chloride with sodium hydrosulfide producing the corresponding thiol, which undergo palladium mediated intramolecular C−H thiolation to afford 2-substituted benzothiazole derivatives **8** in the presence of DMSO as oxidant.



Scheme 3.7: *One-pot Protocol for the Synthesis of 2-Trifluoromethylbenzothiazoles via Double C─S Bond Formation*

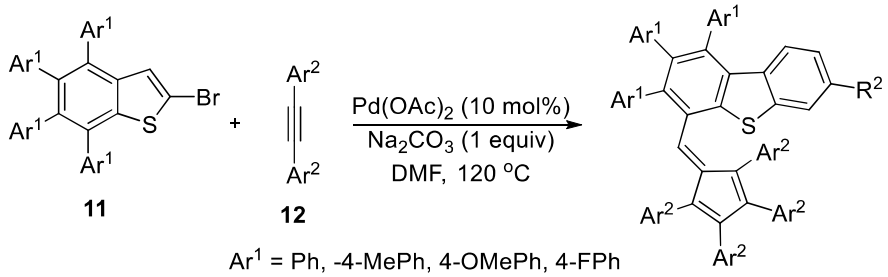
In 2010, J. Srogl and co-workers studied the synthesis of 2-substituted benzothiazole derivatives **2** from aminodisulfides **9** (Scheme 3.8).[20] This method involved the reaction of disulphide with aldehydes resulting in the formation of corresponding imine derivatives **10** *in situ*, which underwent disulphide cleavage followed by copper mediated vinylic C−H thiolation to afford benzothiazole derivatives **2**.



R^1 = H, Br, OMe, CN
R^2 = OMePh, BrPh, ClPh, IPh, Pyridyl, Tolyl, Benzoyl, COPh, ^{t}Bu, NO_2Ph

Scheme 3.8: *Copper Catalyzed C─H Thiolation of Disulfide*

In 2011, Z. Duan and co-workers developed palladium promoted sequential ring rearrangement and C─H thiolation to construct dibenzothiophene derivatives **13** (Scheme 3.9).[21] Primarily, palladium undergoes oxidative addition with 2-bromobenzo[*b*]thiophene **11** followed by carbopalladation with alkyne yields vinylic palladium intermediate which upon C─S bond cleavage and cycloaddition with one more equivalent of alkyne followed by C─H activation with the neighbouring phenyl group led to the formation of six-membered palladacycle, which upon reductive elimination resulted in the formation of dibenzothiophene derivative **13**.

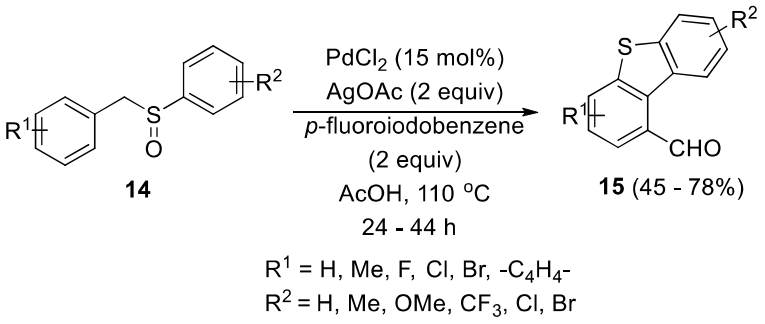


Ar^1 = Ph, -4-MePh, 4-OMePh, 4-FPh
Ar^2 = Ph, -4-MePh, 4-OMePh, 4-FPh
R^1 = H, Me, F, OMe

Scheme 3.9: *Palladium Mediated Dibenzothiophene Synthesis via Ring Rearrangement and C─H Functionalization*

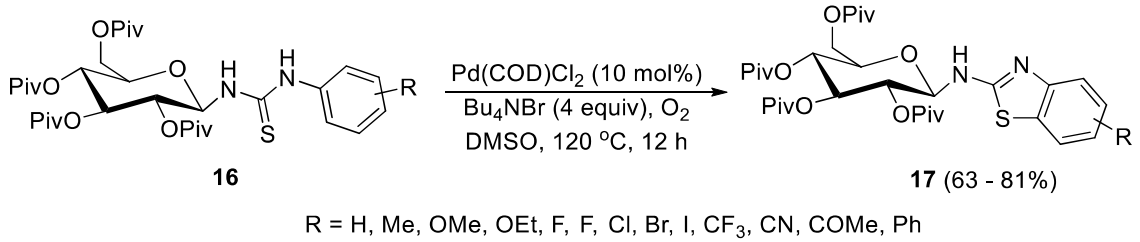
In 2011, A. Antonchick and co-workers demonstrated a novel palladium mediated sulfoxide group directed double C─H activation.[22] This methodology is equipped with good yields of dibenzothiophenes **15** from the sulfoxides **14** in the presence of AgOAc as an

oxidant. However, this reaction delivered satisfactory amount of yields involving *p*-fluoroiodobenzene, which facilitated the reductive elimination process in this reaction (Scheme 3.10).



Scheme 3.10: *Palladium Promoted Sulfoxide Group Directed Dibenzothiophene Synthesis*

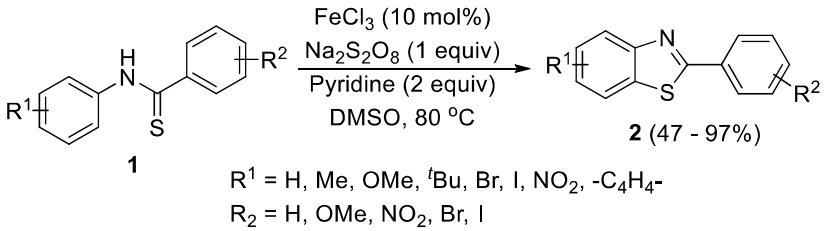
P. Zhang and co-workers extended this palladium mediated intramolecular C─H thiolation approach to glycosyl thioureas **16** to synthesize sugar based benzothiazole derivatives **17** (Scheme 3.11).[23] They carried out the theoretical calculations & mechanistic studies, which revealed that palladium-pivaloyl carbonyl coordination, which is assisted by the intramolecular hydrogen bonding is the sole reason for the efficiency and selectivity for this process.



Scheme 3.11: *Synthesis of Sugar Based Benzothiazoles From Glycosyl Thioureas*

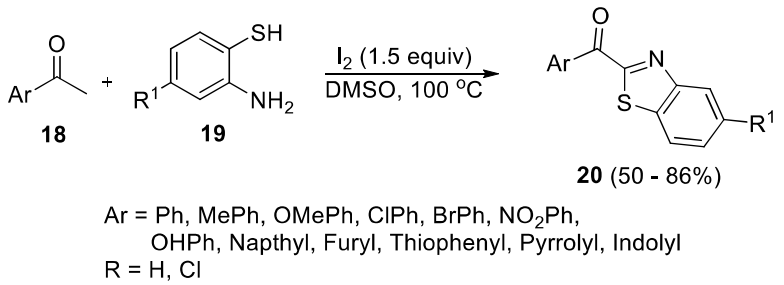
In 2012, A. Lei and co-workers investigated the intramolecular C─H thiolation of thioamides **1** in the presence of eco-friendly, abundant and cheaper iron metal (Scheme 3.12).[24] This method provided moderate to excellent yields of benzothiazole derivatives **2**

involving oxidant $Na_2S_2O_8$ and pyridine as an additive. They performed kinetic studies and demonstrated that pyridine has a vital role in the high selectivity.



Scheme 3.12: *Iron Mediated 2-Arylbenzothiazole Synthesis*

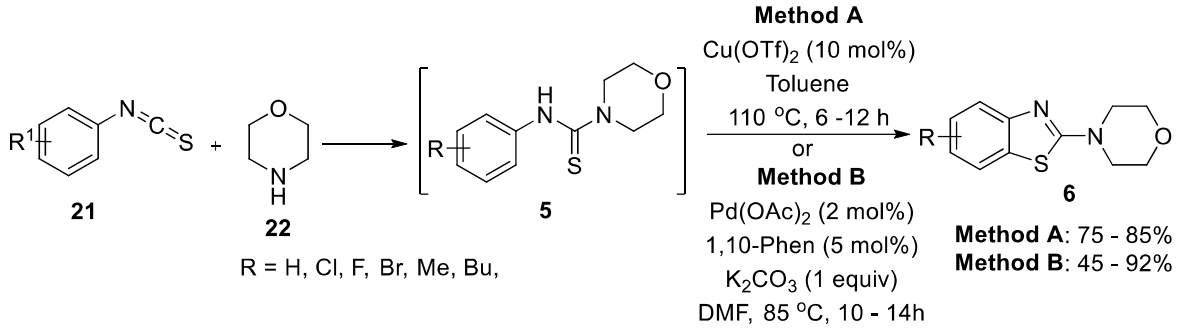
Subsequently, A. X. Wu and co-workers constructed benzothiazole derivatives **20** under transition metal free conditions.[25] This method involves iodine promoted domino oxidative cyclization of aromatic ketones/unsaturated methyl ketones **18** and *o*-aminobenzenethiols **19** to afford desired products in moderate to very good yields in the absence of peroxide oxidants (Scheme 3.13). They monitored the reaction with the aid of NMR and suggested that sequential iodination, Kornblum oxidation and heterocyclization were operative during the course of the reaction which facilitates this domino oxidative cyclization process.



Scheme 3.13: *Synthesis of Benzothiazole via I_2 Promoted Domino Oxidative Cyclization*

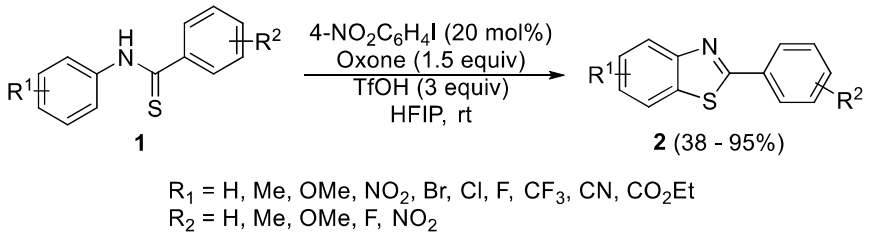
In 2012, B. K. Patel and co-workers studied two independent domino intramolecular aromatic C−H thiolation reactions in the presence of copper and palladium (Scheme 3.14).[26] In the first strategy, the desired benzothiazoles **6** were obtained by treatment with simple and

commercially available arylisothiocyantes **21** and amine **22** with $Cu(OTf)_2$ in the absence of ligand. On the other hand, palladium catalysed C─H thiolation was highly ligand dependent and it was successful only with electron rich thioureas **5**.



Scheme 3.14: *Investigation of Ligand Effect in Cu & Pd Mediated Intramolecular C─H Thiolation*

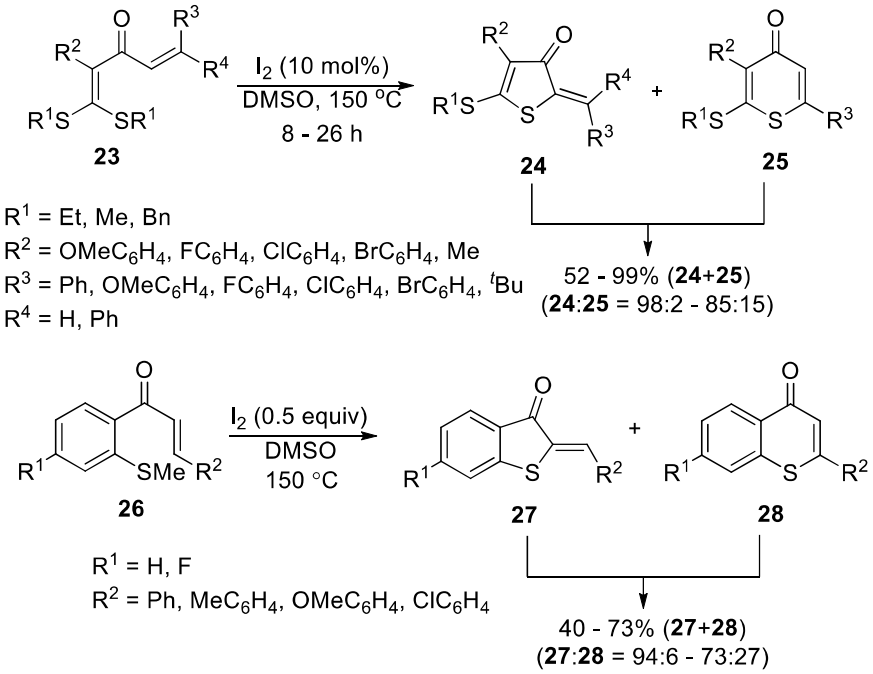
On the other hand, T. Punniyamurthy and co-workers established the organocatalytic approach for the synthesis of 2-substituted benzothiazoles **2** with moderate to excellent yields (Scheme 3.15).[27] In this method, 1-iodo-4-nitro benzene in the presence of oxone and triflic acid produces hypervalent iodine reagent *in situ*, which reacted with various alkyl/aryl substituted thioanilides **1** to afford benzothiazole derivatives **2** at room temperature.



Scheme 3.15: *Organocatalytic Benzothiazole Synthesis from Thioanilides*

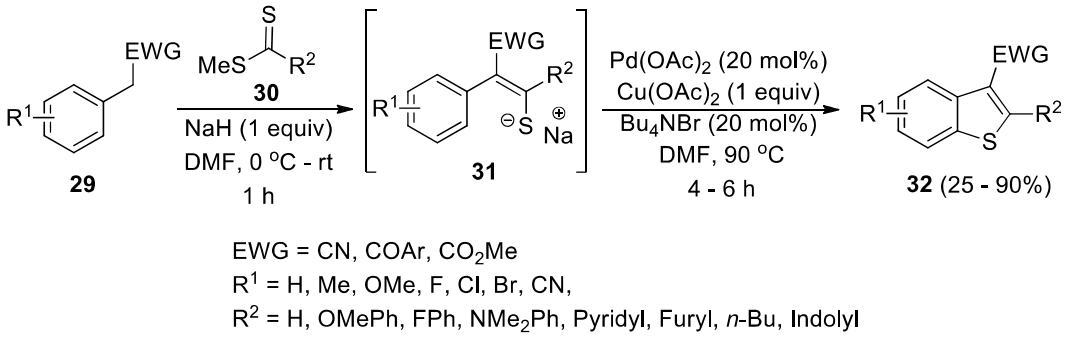
In 2012, M. Wang and co-workers described iodine promoted intramolecular vinylic C─H thiolation of ketene dithioacetals **23** to synthesize 2-methylene-3-thiophenone derivatives **24** (Scheme 3.16).[28] This reaction proceeds through tandem iodocyclization and

dehydroiodination to afford corresponding desired thiolated product **24** along with minor amounts of thiopyranone derivative **25**. They extended this methodology to *ortho*-methylthiophenyl vinyl ketones **26** which resulted in the formation of 2-methylene-3-benzothiophenone derivatives **27** under optimized reaction conditions.



Scheme 3.16: *Iodine Mediated Intramolecular Vinylic C─H Thiolation*

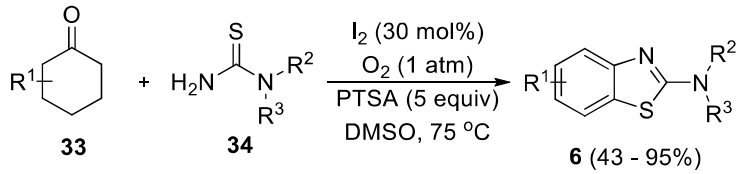
In 2015, H. Ila and co-workers demonstrated one-pot approach for synthesis of 2,3-disubstituted benzo[*b*]thiophenes **32** by palladium-catalyzed intramolecular oxidative C─H



Scheme 3.17: *Palladium & Copper Mediated C─H Thiolation of Thioenols*

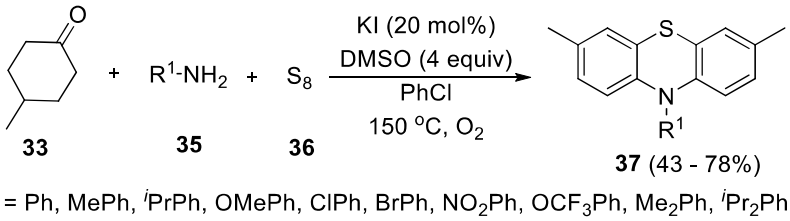
functionalization at 90 °C (Scheme 17).[29] They proposed a tentative mechanism where intramolecular electrophilic arylthiolation *via* either a Pd─S adduct or palladacycle intermediate are the key steps for the intramolecular thiolation.

In 2015, H. Jiang and co-workers came up with the simple strategy to construct 2-aminobenzothiazole derivatives **6** from cyclohexanones **33** and thiourea derivatives **34** in the presence of molecular iodine under oxygen atmosphere (Scheme 3.18).[30] This protocol involves formation of α-iodo cyclohexanone, which undergoes nucleophilic substitution with thiourea leading to the formation of corresponding imidothioate derivative which undergo cyclization followed by dehydration resulted in the formation of benzothiazole derivatives **6**.



Scheme 3.18: *Transition Metal Free synthesis of 2-Aminobenzothiazoles from Cyclohexanones and Thioureas*

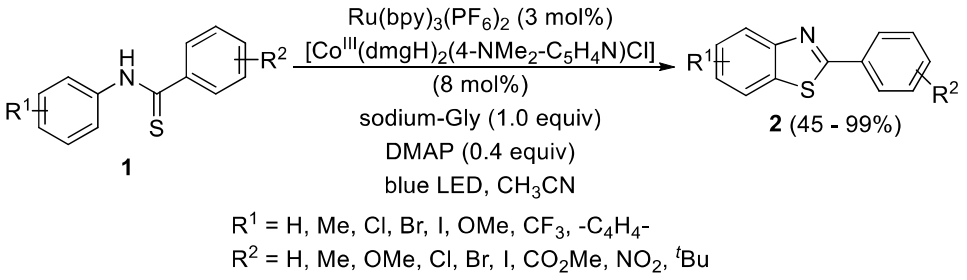
In 2015, G. J. Deng and co-workers established four component approach for the synthesis of phenothiazones **37** under transition metal free conditions by using amines **35**, cyclohexanone derivatives **33** and elemental sulphur (**36**) (Scheme 3.19).[31] This protocol



Scheme 3.19: *KI Promoted Four Component Approach for the Synthesis of phenothiazones*

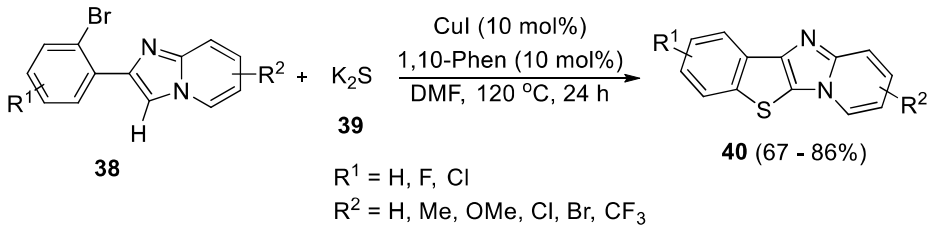
involved condensation reaction of amine with two equivalents of cyclohexanone **33** afforded enamine intermediate, which underwent double C─S bond formation upon treatment with KI/DMSO delivered phenothiazone derivatives **37** in one pot conditions.

A. Lei and co-workers devised novel protocol of cobalt mediated external oxidant free intramolecular oxidative C─H thiolation of thioamides **1** under photocatalytic conditions (Scheme 3.20).[32] This method exhibited excellent functional group tolerance and provided moderate to excellent yields of corresponding benzothiazole derivatives **2**.



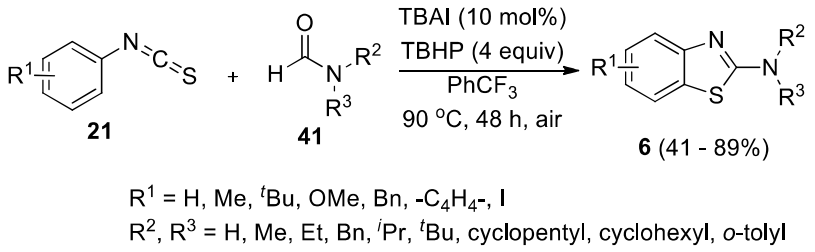
Scheme 3.20: *Cobalt Mediated Intramolecular C─H Thiolation of Thioanilides*

In 2016, H. Wang and co-workers investigated the copper mediated double C─S bond formation (Scheme 3.21).[33] The first step of this protocol involved generation of thiolate derivative by Ullmann coupling of bromoarenes **38** and potassium sulphide (**39**), which underwent intramolecular C─H thiolation delivering benzo[*b*]thiophene fused imidazo[1,2-*a*]pyridine derivatives **40** in good yields.



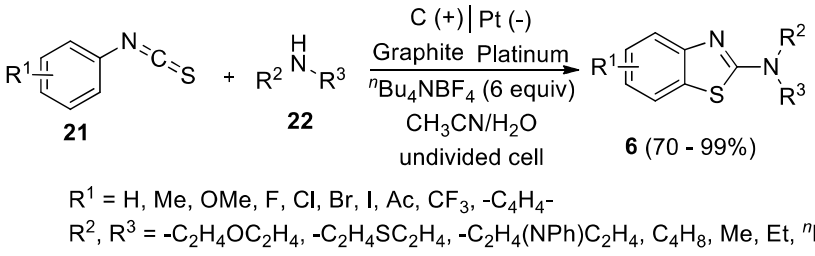
Scheme 3.21: *Copper Catalyzed Double C–S Bond Formation via Ullmann Coupling and C–H Thiolation*

In 2016, J. Huang and co-workers established the TBAI mediated tandem approach for the synthesis of 2-aminobenzothiazoles **6** from arylisothiocyanates **21** and formamides **41** (Scheme 3.22).[34] Formamides **41** produce aminyl radical upon treatment with TBAI/TBHP which underwent nucleophilic addition on isothiocyantes **21** resulting in the *in situ* generation of the thienyl radical, which underwent intramolecular oxidative cyclization yielding 2-aminobenzothiazole derivatives **6** with moderate to very good yields.



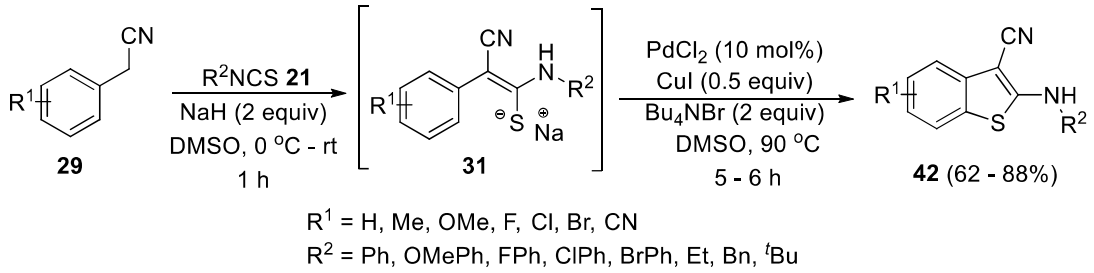
Scheme 3.22: *Metal Free 2-Aminobenzothiazoles Synthesis via Aminyl Radical*

Consequently, A. Lei and co-workers studied this reaction under environment friendly electrochemical conditions by using arylisothiocycantes **21** and amines **22** in the absence of an external oxidant (Scheme 3.23).[35`]



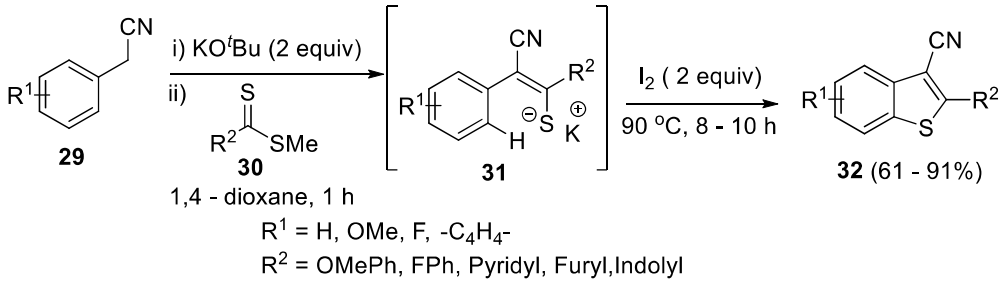
Scheme 3.23: *Electro catalysis Promoted 2-Aminobenzothiazole Synthesis*

H. Ila and co-workers extended their methodology to synthesize 2-amino-3-cyano-benzo[*b*]thiophenes **42**.[36] This report deals with the palladium mediated regioselective intramolecular C─H thiolation of *in situ* generated thioanilides **31** from aryl acetonitriles **29** and aryl/alkyl isothiocyanates **21** at 90 °C (Scheme 3.24).



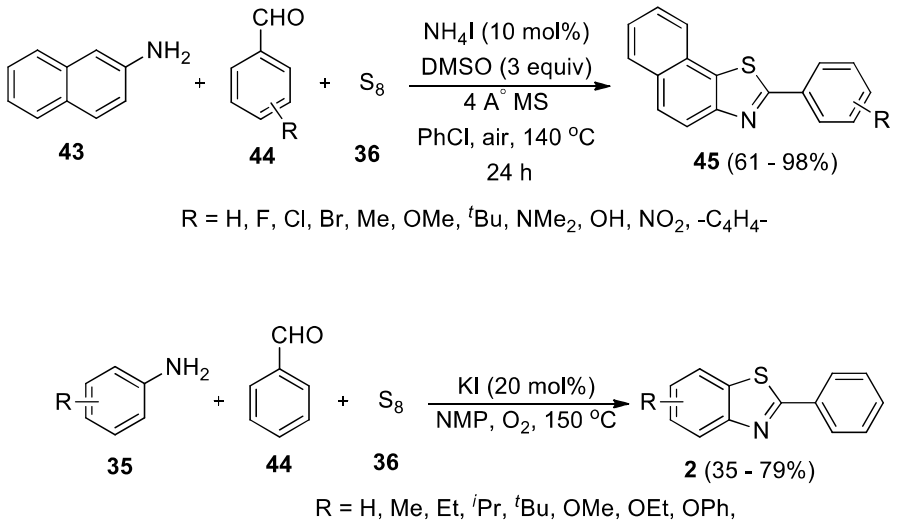
Scheme 3.24: *Regioselective Thiolation of Thioamides to Synthesis of 2-Aminobenzo[b]thiophenes*

Subsequently, they extended their approach to synthesize benzothiophenes **32** *via* molecular iodine mediated oxidative cyclization of enethiols **31** under transition metal free conditions (Scheme 3.25).[37]



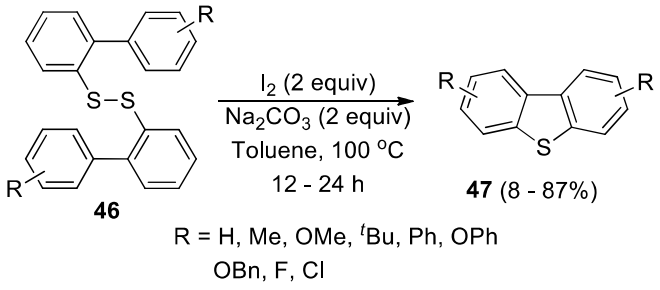
Scheme 3.25: *Iodine Mediated Intramolecular C─H Thiolation of Thioenols*

In 2017, H. Huang's group demonstrated the transition metal free three component one pot approach for the synthesis of benzothiazole derivatives **45** & **2** from readily available anilines **43** & **35**, benzaldehydes **44** and elemental sulphur (**36**) (Scheme 3.26).[38] The authors found that this novel oxidative cyclization approach was very effective with NH_4I and KI as the catalyst in combination with DMSO and oxygen as the oxidant to produce moderate to excellent yields of benzothiazole derivatives **45** & **2**.



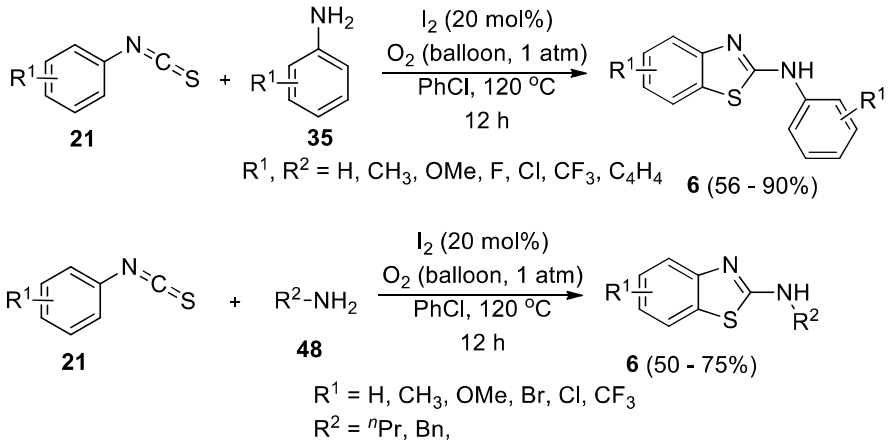
Scheme 3.26: *Transition Metal Free Three Component Oxidative Cyclization*

N. Sakai and co-workers reported the synthesis of dibenzothiophenes **47** *via* iodine mediated oxidative cyclization of 2-biarylyl disulfides **46** (Scheme 3.27).[39] The mechanism of this reaction involved oxidative S─S bond cleavage of disulphide **46** by treating with iodine followed by intramolecular S_EAr reaction afforded the desired dibenzothiophene derivative **47** in 12 – 24h.



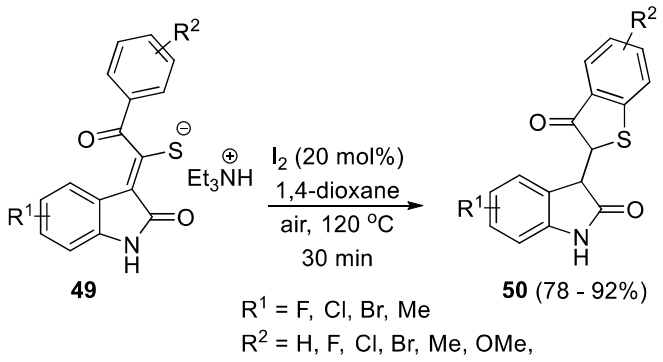
Scheme 3.27: *Synthesis of Dibenzothiophene Derivatives from 2-Biphenylyl Disulfides*

Recently, X. Zhang and co-workers followed the Huang's approach in simplified manner to construct 2-aminobenzothiazole derivatives **6**.[40] In the current method, they examined various alkyl and aryl amines **48** & **35** as nucleophiles during the course of the reaction with arylisothiocyantes **21** (Scheme 3.28). The resultant thiourea underwent oxidative cyclization in the presence of molecular iodine and oxygen as an oxidant.



Scheme 3.28: *Iodine Catalyzed Cascade Reaction of Arylisothiocyanates with Amines*

Very recently, G. Li and co-workers developed a new method to synthesize benzothiophenone derivatives **50** under transition metal free conditions (Scheme 3.29).[41] This reaction involved *in situ* generation of sulphur radical in the presence of catalytic amount of iodine followed by intramolecular C−H thiolation using atmospheric oxygen resulted in the formation of benzo[*b*]thiophene framework **50**.



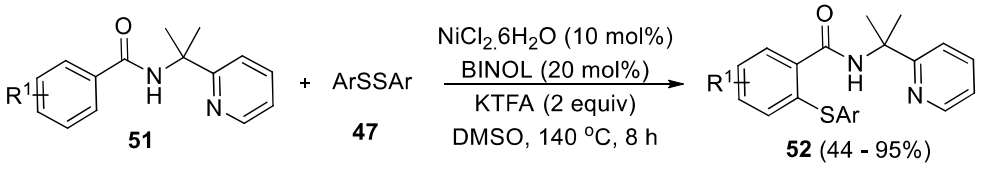
Scheme 3.29: *Molecular Iodine Promoted Benzo[b]thiophenone Synthesis*

From this detailed literature survey, we can conclude that palladium and copper were extensively used for C−S bond formation leading to the sulphur heterocycles and iodine mediated reports were also reported for the same. Synthetic chemists are bent towards the investigation of new catalytic systems which are cheaper, more abundant, easily available and environmentally benign. Thus, investigation of the first row transition metals such as Co,[42]

Fe,[43] Ni,[44] Mn,[45] and Cu[46] mediated C─H functionalization reactions have received much attention. In this regard, Ni catalysed C─H functionalization reactions have come into the limelight. Although, there were a few reports regarding the nickel mediated oxidative C─H functionalization reactions,[47] Chatani's pioneer reports of directing group assisted C─H functionalization disclosed a new approach for the nickel mediated oxidative carbon─carbon and carbon─heteroatom bond forming reactions.[48] The advantage of using Ni catalyst is eco-friendly, cheaper and provides unique selectivity at specific reaction sites, etc.[49] As compared to other metals of the same group, Ni undergoes a wide variety of oxidative addition between C─H, C─C[50], C─N[51] and C─O[52] bonds because of its high nucleophilicity character. Another interesting feature is the weak nickel─carbon bond as compared to the other metals of the same group which facilitates the catalytic transformation.[53]

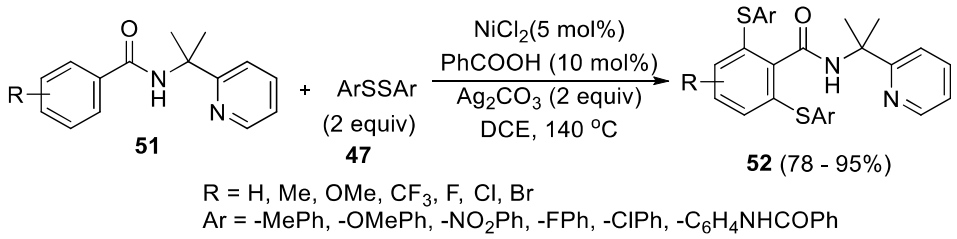
3.3 Previous Reports for Nickel Mediated C─H Thiolation

In 2015, B. F. Shi and co-workers studied the nickel mediated intermolecular aromatic C─H thiolation by using disulfides **47** as a sulphur source for the first time (Scheme 3.30).[54] This reaction was performed by using 2-(pyridine-2-yl)isopropylamine **51** as a directing group in the presence of $NiCl_2$ and BINOL as a ligand.



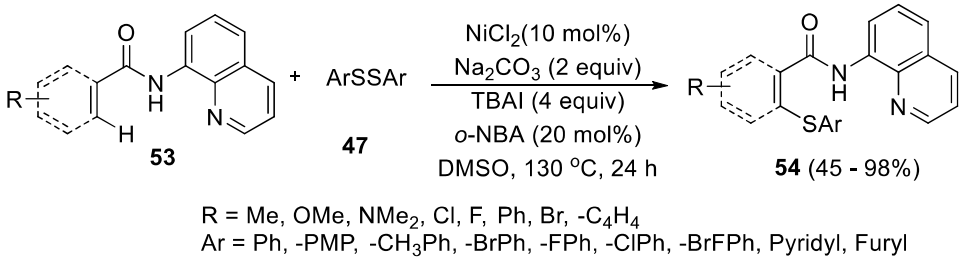
Scheme 3.30: *Nickel Catalyzed Aromatic C─H Thiolation by Using BINOL Ligand*

In 2015, by using same directing group H. Lu and co-workers demonstrated the nickel-catalyzed and benzoic acid-promoted double C─H thiolation reaction to afford disulfenylation products **52**.[55] (Scheme 3.31).



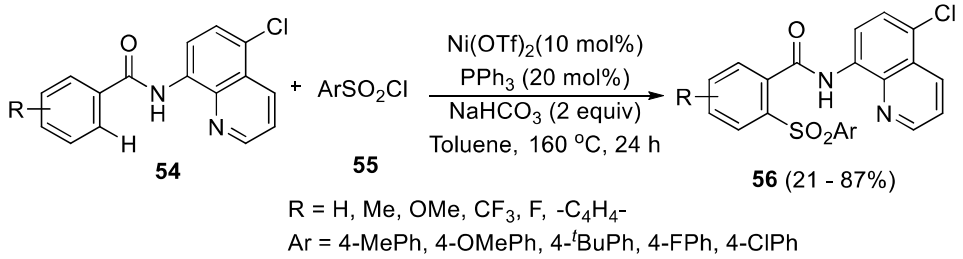
Scheme 3.31: *Nickel mediated Benzoic Acid Promoted Sulfenylation of Unactivated Arenes*

In 2015, Y. Zhang and co-workers demonstrated the nickel mediated highly efficient thiolation of aromatic and alkenyl C(sp^2)–H bonds with the assistance of an 8-aminoquinolyl auxiliary.[56] TBAI and *o*-nitro benzoic acid play a crucial role for this thiolation process (Scheme 3.32). They extended this methodology to heteroaromatic disulphides, which also afforded good to excellent yields of thiolated product **54**.



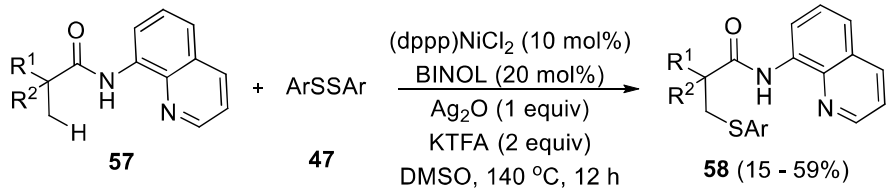
Scheme 3.32: *Bidentate Directing Group Assisted ortho Thiolation of Amides*

Subsequently, N. Chatani and co-workers examined the aromatic C–H thiolation by using $Ni(OTf)_2$ and PPh_3.[57] In contrast to the previous reports, here they used aryl sulfonyl chlorides **55** as thiolating reagent to afford *ortho* sulfenylated products **56** (Scheme 3.33).



Scheme 3.33*: Sulfonyl Chlorides as the Thiolating Agents for sp^2 C–H Sulfenylation*

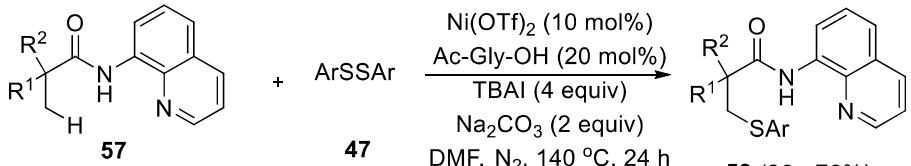
First report regarding the nickel catalysed sp^3 C─H thiolation was established by B. F. Shi and co-workers.[58] Their approach deals with the thiolation of β-methyl C(sp^3)─H bonds of aliphatic carboxamides **47**. They used aryl disulfides **47** as the thiolating reagent in the presence of (dppp)$NiCl_2$ as catalyst and BINOL as the ligand (Scheme 3.34). This current catalytic system is highly selective for the thiolation of *ß*-sp^3 C─H of methyl group over methylene groups of aliphatic carboxamides **57**.



R^1, R^2 = Ph, Et, ^{n}Bu, ^{i}pentyl, C_5H_{13}, C_6H_{13}, $C_{12}H_{15}$, allyl, C_2H_4, C_4H_8, C_5H_{10}
Ar = 4-OMePh, 4-MePh, 3-FPh, 4-ClPh, Furyl

Scheme 3.34: *First Nickel Catalyzed Thiolation of Unreactive C(sp^3)–H Bonds*

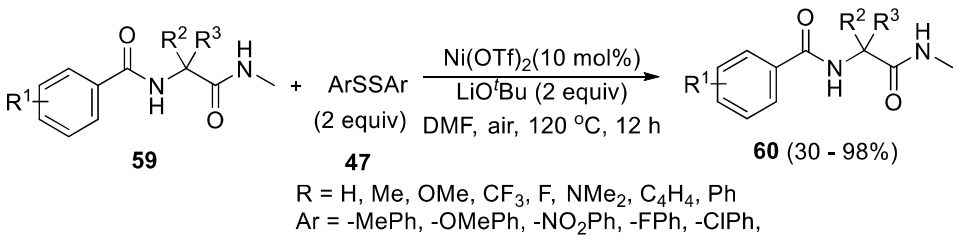
In 2015, Y. Zhang and co-workers also studied the nickel mediated β-thioetherification of sp^3 C─H bonds in a wide range of propionamides **57** with the aid of *N,N'*-bidentate auxillary (Scheme 3.35).[59] In this report, they studied several ligands and found that amino acid based ligand Ac-Gly-OH is the suitable one for this intermolecular sp^3 C─H thiolation.



R_1, R_2 = Me, Et, Pr, Ph, Bn, Bu, $-CH_2C_6H_4CH_3$, $-CH_2C_6H_4F$, $-CH_2$Naphth, CH_2CH_2Ph, C_5H_{10}, C_2H_4
Ar = OMePh, MePh, FPh, tBuPh, BrPh, ClPh, naphthyl

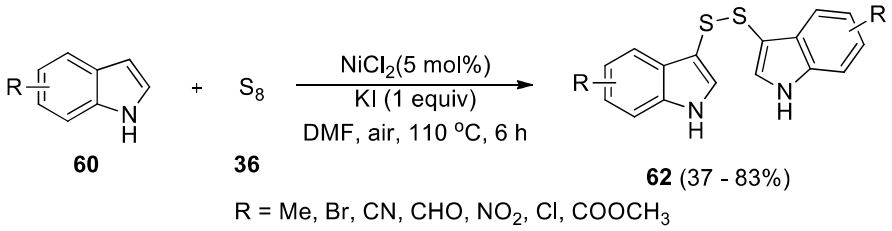
Scheme 3.35: *8-Aminoquinolinyl Directed Oxidative C─S Bond Formation of the sp^3 C−H Bonds*

Recently, H. Liu and co-workers extended this directing group assisted nickel mediated thiolation approach to *N*-Benzoyl-α-amino acid derivatives **59** for the first time.[60] This is one of the useful approaches for the construction of *ortho*-thiosubstituted *N*-benzoyl *α*-amino acid derivatives **60** with moderate to excellent yields (Scheme 3.36).



Scheme 3.36: *Nickel Mediated Thioetherification of N-Benzoyl-α-Amino Acid Derivatives*

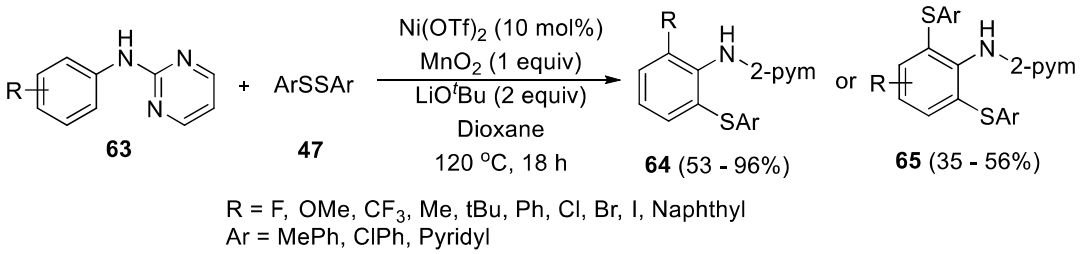
In 2016, W. Li and co-workers came up with a new strategy to synthesize 3,3-indolyl disulphide **62** from indole **60** through nickel mediated C─H functionalization (Scheme 3.37).[61] They presumed that I_2/O_2/metal salt combination will become an active catalytic system for this intermolecular C─S bond formation. Also, iodine is the main reason for regeneration of the metal catalyst.



Scheme 3.37*: C─H Functionalization of Indoles to Synthesize 3,3-Indolyl Disulphides*

Later, L. Ackermann and co-workers established new method for C─H thiolation of aniline derivatives with aid of $Ni(OTf)_2$ under ligand free conditions (Scheme 3.38).[62] In this report, C─H thiolation of anilines **63** with the assistance of easily removable directing pyrimidyl group resulted in the formation of 2-amino thiophenol derivatives **64** & **65**. They carried out mechanistic studies and found that C─H nickelation is the rate determining step in

this process, followed by oxidation to Ni(III) species by a sulfenyl radical that subsequently undergoes a reductive elimination.



Scheme 3.38: *Nickel Mediated C─H Thiolation of Anilines*

The above reports clearly indicate that, from the last few years nickel was extensively studied in C─H thiolation reactions for synthesis of various thioethers. During the course of this study, activation of sp^2 C─H bonds along with sp^3 C─H bonds were executed to afford excellent yields of thiolated products. Although, nickel has a great potential in C─S bond construction via C─H bond functionalization, there was no report regarding the nickel mediated synthesis of heterocycles via C─H thiolation.

3.4 Motivation:

Prior to this chapter, we investigated the regioselective *N*-arylation of ketene aminals. Those results motivated us to investigate regioselective thiolation. Thus, we have chosen the easily synthesizable thioamide as the requisite substrate for this regioselective thiolation process. These thioamides are interesting class of molecules which contain two types of functionalizable C─H bonds; sp^2 C─H bond and sp^3 C─H bond. Hence, there are two prominent probabilities, the first one being the thiolation at the aryl C─H bond affording 2-amino benzo[*b*]thiophene while the second one being the thiolation at the *N*-alkyl moiety yielding thiazole derivative.

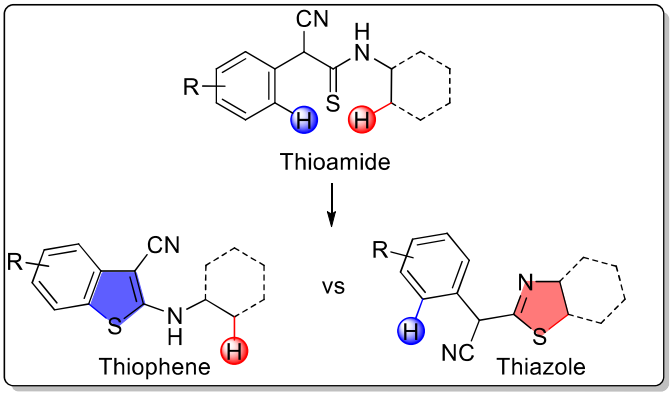
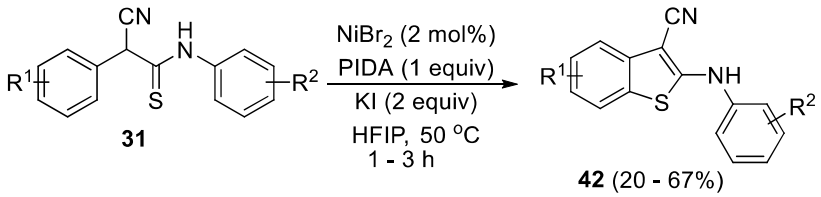


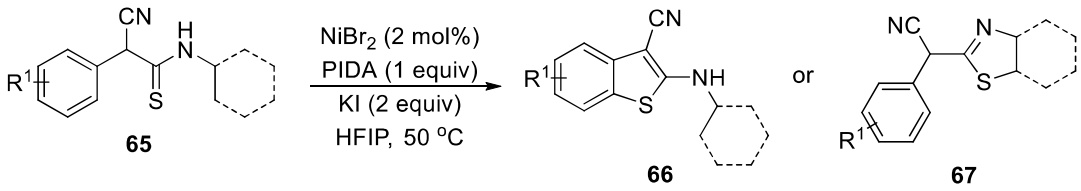
Figure 3.2: *Possible C—H Thiolated Products from Thioamides*

Our group has already established the nickel mediated regioselective synthesis of 2-amino benzo[*b*]thiophene derivatives **42** from *N*-aryl substituted thioanilides **31** (Scheme 3.39).



Scheme 3.39: *Our Previous Method for Nickel Mediated Site Selective C—H Thiolation of N-Aryl Thioamides*

Hence, by applying the aforementioned reaction conditions we wish to explore the probability of formation of the benzo[*b*]thiophene derivative **66** or the thiazole derivative **67** through the functionalization of the sp^2 or sp^3 C—H bonds respectively by using nickel catalyst (Scheme 3.40).



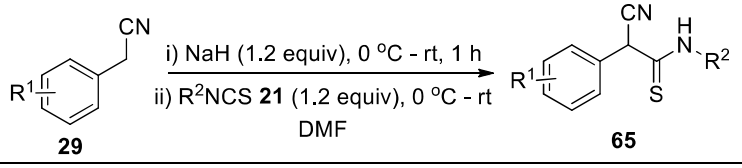
Scheme 3.40: *Investigation of sp^2 vs sp^3 C—H Thiolation of N-Alkyl Substituted Thioamides*

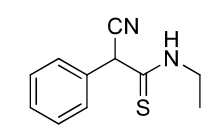
3.5. Result and Discussion

3.5.1 Synthesis of Thioamides 65

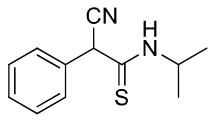
The required thioanilides **65** were prepared by treating the anion of arylacetonitriles **29** with alkyl isothiocyantes **21** in DMF at room temperature (Table 3.1). These resulted thioamides **65** were characterized by spectra and analytical data.

Table 3.1: Synthesis of Thioanilides 65 from Benzyl Cyanides 29 and Isothiocyanates 21

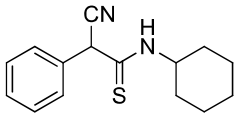




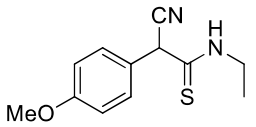
65a (72%)



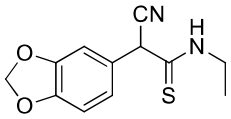
65b (98%)



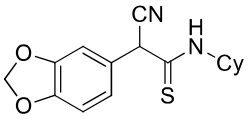
65c (64%)



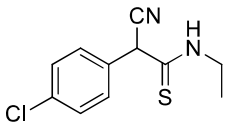
65d (78%)



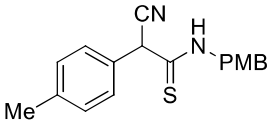
65e (89%)



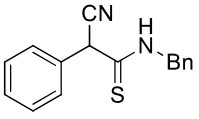
65f (98%)



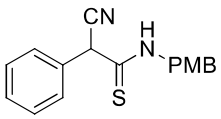
65g (78%)



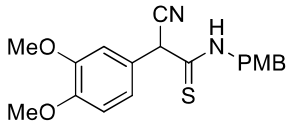
65h (66%)



65i (34%)



65j (82%)

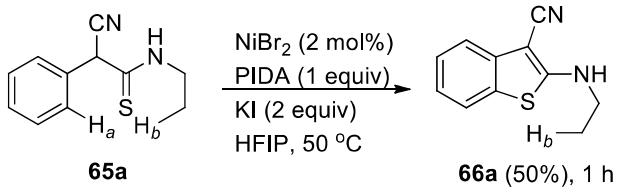


65k (63%)

3.5.2 Nickel Mediated Regioselective Thiolation of *N*-Alkyl Substituted Thioamides

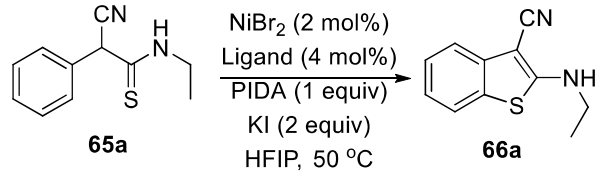
With the previously established reaction conditions in our hands, we interested in studying the intramolecular thiolation of *N*-alkyl substituted thioamides **65**. As we discussed earlier, nickel is prone to activate both sp^2 and sp^3 C─H bonds.[ref] Hence, site selective sp^2 C─H bond functionalization over sp^3 C─H bond functionalization is highly challenging. To examine this, we have chosen the *N*-ethyl thioanilide **65a** and subjected to our established

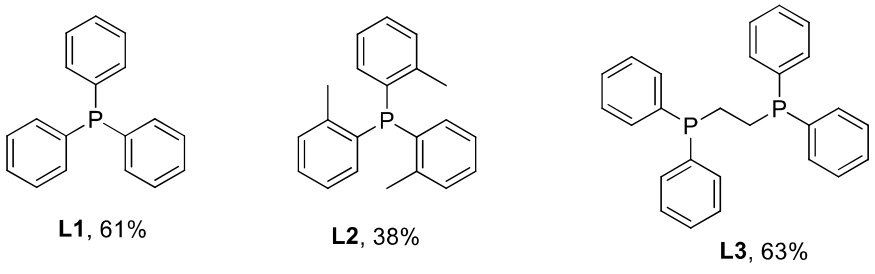
reaction conditions. Gratifyingly, this experiment yielded exclusively sp^2 C─H functionalised product **66a** over sp^3 C─H bond functionalised product **67a** in 50% (Scheme 3.41). The resulted thiolated product **66a** was characterised by using spectral and analytical experiments. Surprisingly, when we performed the same reaction in the presence of PPh_3 ligand we observed the enhancement of the yield (Table 3.2). So, we screened several phosphine based ligands and found that the reaction in the presence of cataCXium®A ligand **L5,** the best yield of 72% of the corresponding sp^2 C─H thiolated product **66a** was obtained in 1 h (Table 3.2).



Scheme 3.41: *Investigation of Intramolecular Thiolation of sp^2 C─H vs sp^3 C─H*

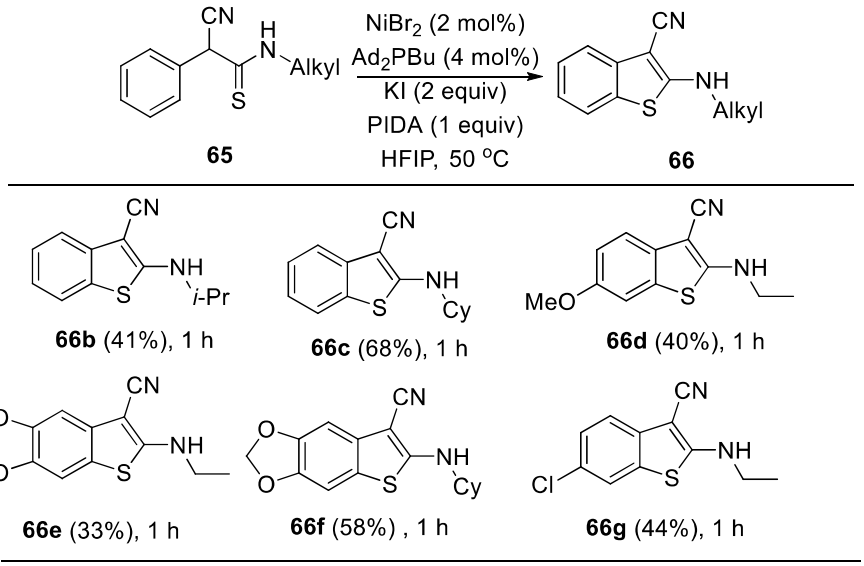
Table 3.2: Investigation of Ligand Effect on Selective sp^2 C─H Thiolation





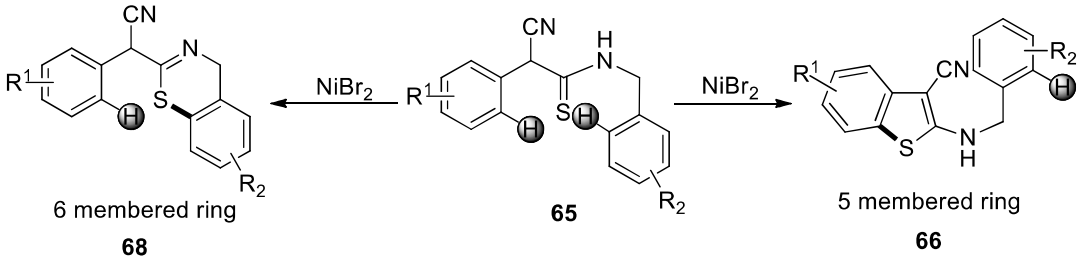
With this newly optimized reaction conditions, we investigated the thiolation of several *N*-alkyl substituted thioamides **65b-g**. Thus, *N*-isopropyl substituted thioamide **65b** was smoothly transformed to the desired product **66b** in 41% yield. Similarly, *N*-cyclohexyl substituted thioamide **65c** underwent regioselective intramolecular C─H thiolation to give corresponding thiolated product **66c** in 68% yield. Whereas, electron donating substituent containing thioamide **65d** afforded corresponding 2-amino benzo[*b*]thiophene derivative **66d** in moderate yield. The similar trend was observed in the case of methylenedioxy substituted thioamides **65e-f**, where 33-58% of the thiolated products **66e-f** were observed in the presence of ligand. However, halo substituted benzo[*b*]thiophene **66g** was obtained from the corresponding thioamide **65g** with 44% yield.

Table 3.3: Oxidative C─S bond Formation of *N*-Alkyl Substituted Thioamides



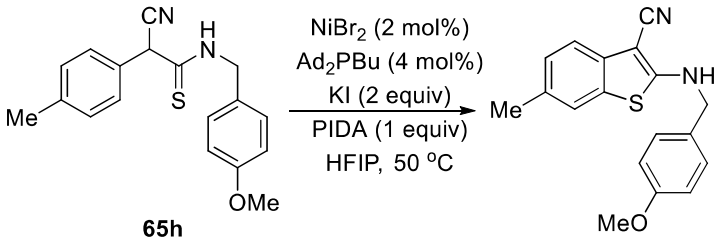
These results motivated us to investigate the C─H thiolation reaction of *N*-benzyl substituted thioamides **65h-k**, which have two different types of sp^2 C─H bonds. If, thiolation occurs on aryl ring, then it will give 5-membered benzo[*b*]thiophene derivative **66**. On the other hand, if thiolation occurs at the benzyl ring it will result in the formation of 6-membered ring **68** (Scheme 3.42). By keeping these things in mind, we treated the thioamide **65h** with the

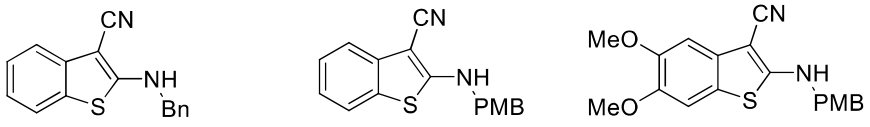
established reaction conditions and observed exclusively benzo[*b*]thiophene derivative **66h** over 6-membered ring formation **68h**, which was confirmed with the aid of spectral and analytical data (Table 3.4). Similarly, other benzyl and *p*-methoxy benzyl substituted thioanilides **65i-k** were also smoothly transformed to the corresponding benzo[*b*]thiophene **66i-k** derivative in shorter reaction time (Table 3.4).



Scheme 3.42: *Schematic Representation of Possible Intramolecular C─S Bond Formation of N-Benzyl Substituted Thioamides*

Table 3.4: Nickel Mediated Controlled C–H Thiolation of *N*-Benzyl Thioamides

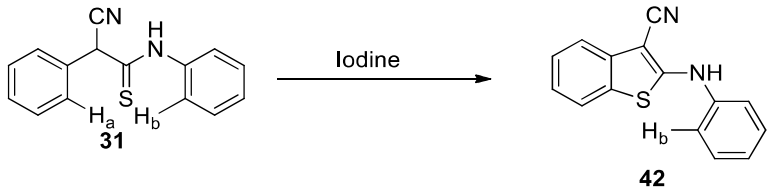




PART-B

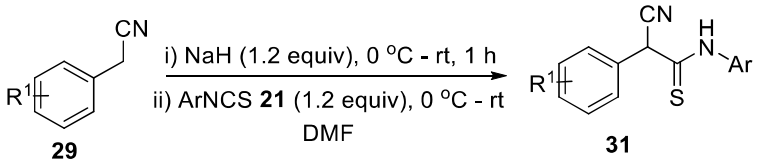
Earlier in this chapter, we devised a methodology to synthesize 2-amino benzo[*b*]thiophenes using Ni-mediated C−H bond functionalization by activating the sp^2 C−H over sp^3 C−H. This method was double-edged in terms of its application. The advantage of this method was the excellent regioselectivity attained, however the imperfection of the developed methodology was the poor yield. In the recent years, molecular iodine mediated oxidative carbon-heteroatom bond forming reactions are drawing great attention.[63] Iodine is one of the non-radioactive elements and the most polarizable one among the halogens. The convenience of using iodine is that it can exist in various oxidation states -1, 0, +1, +3, +5, +7. Because of its non-toxicity, ready availability, non-metallic lewis acid character and cost effectiveness, it was used extensively in the synthetic applications.[64] The preference for iodine comes because the reactive pattern of iodine compounds are similar to that of heavy transition metals involving oxidative addition, ligand exchange, reductive elimination and ligand coupling reactions. In comparison to the heavy transition metals, iodine is inexpensive and also an environmentally sustainable alternative to transition metals. In this regard, C−N,[65] C−S,[66] C−O[67] and C−C[68] bonds were constructed by using molecular iodine along with cheaper and easily available oxidizing agents such as peroxides[69] and molecular oxygen.[70] This is the powerful synthetic tool for the construction of heterocycles from acyclic precursors. In this regard, there were considerable amount of reports regarding the synthesis of *N*-heterocycles.[71] Although this strategy had great success in the construction of C−S bond formation by affording good to excellent yields, this approach is mostly limited to synthesis of benzothiazole derivatives.[72] On the other hand, our interest is regioselective thiolation of thioamide **31** which consists of two C−H bonds (C−H_a vs C−H_b). As mentioned earlier, both the C−H bonds are feasible to functionalise. We wish to understand

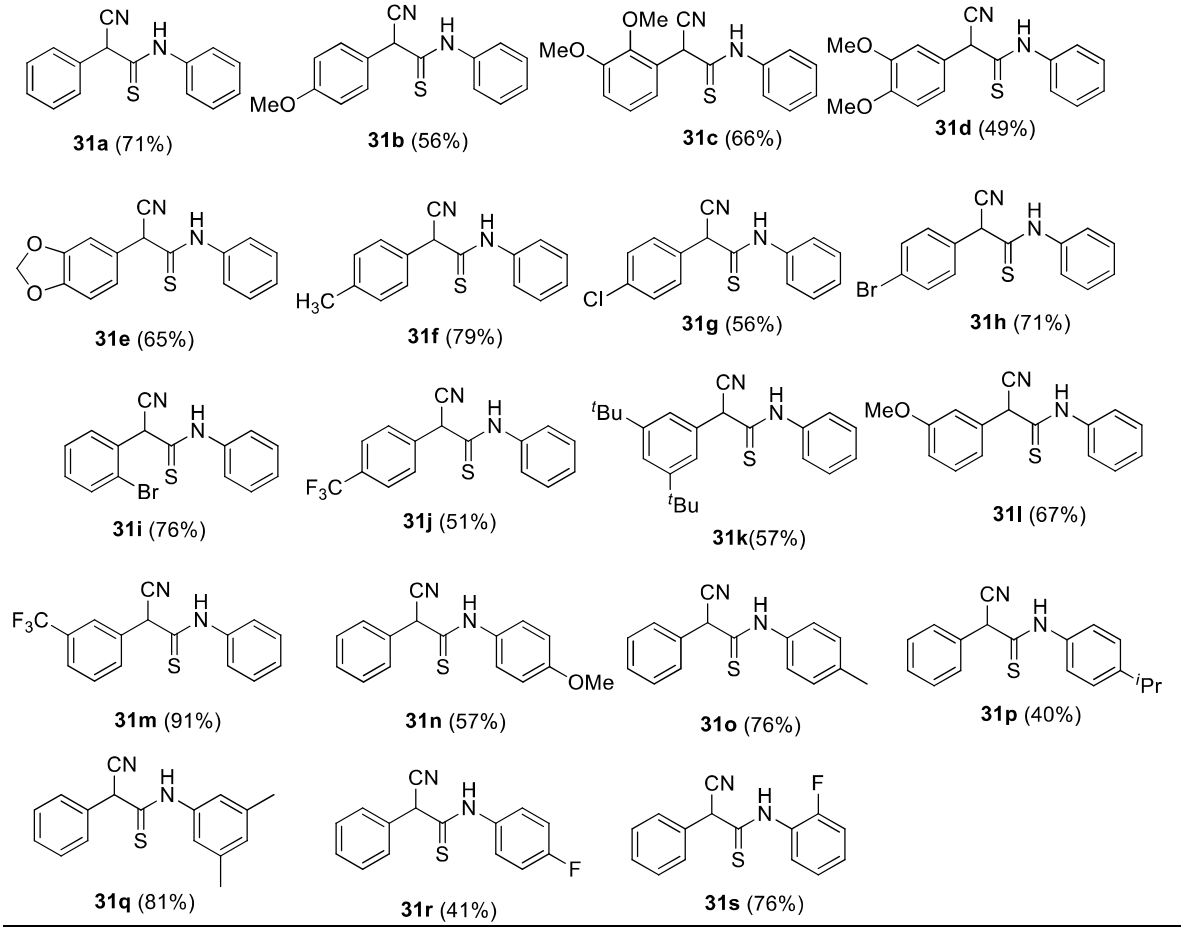
which C−H bond functionalise more selectively over the other one by using molecular iodine.



Scheme 3.43: *Iodine Mediated Regioselective Thiolation of N-Aryl Substituted Thioamides*

Table 3.5: Synthesis of *N*-Aryl Substituted Thioamides 31





3.5.3 Synthesis of *N*-Aryl Substituted Thioanilides 31

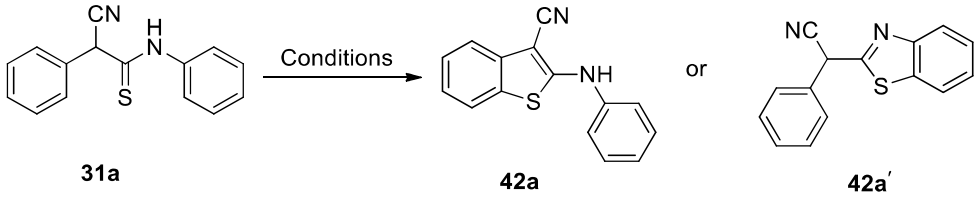
The required *N*-aryl thioanilides **31** were prepared by treating the anion of arylacetonitriles **29** with various arylisothiocyantes **21** in DMF at room temperature (Table 3.5). These resulted thioamides **31** were characterized by spectra and analytical data.

3.5.4 Optimization of Reaction Conditions for the Iodine Mediated Intramolecular Oxidative C─S Bond Formation

With the diverse range of thioamides in our hands **31a-s**, we moved to investigate optimization of regioselective C─S bond formation of thioanilides. Thus, we chosen thioamide **31a** as a model substrate and the initial reaction was carried out with 5 mol% iodine, 1.5 equiv TBHP (70% in water), 3 equiv of AcOH in the presence of dioxane at 80 ^{o}C. To our delight, the reaction delivered 73% yield of the 2-amino benzo[*b*]thiophene derivative **42a** in a highly regioselective manner, which was confirmed by spectral and analytical data (Table 3.6, Entry 1). In this reaction, we did not observe even trace amount of thiazole derivative **42a'**. These results encouraged us for further investigation of this thiolation reaction. Thus, we studied other oxidants like H_2O_2 and DTBP. But both of them are ineffective in this intramolecular C─H thiolation and huge amount of thioanilide **31a** was recovered from the reaction (Table 3.6, Entry 2 & 3). However, the experiment in the presence of oxone afforded only 43% yield of the corresponding 2-amino benzo[*b*]thiophene derivative **42a** (Table 3.6, Entry 4). Next, we investigated the effect of solvent on this C─S bond forming reaction. Thus, we carried out the reactions in the presence of CH_3CN and DCE and observed comparable yields, in which DCE afforded the maximum yield of 82% in 2 h (Table 3.6, Entry 5). Whereas, the reaction in the absence of solvent afforded only 43% of the thiolated product **42a** (Table 3.6, Entry 7). When we carried out the reaction in the absence of AcOH, diminishment of yield (70%) was observed (Table 3.6, Entry 8). On the

other hand, only 10% of the desired product **42a** was obtained in the absence of Iodine (Table 3.6, Entry 9). Finally, when we carried out the reaction at room temperature, gave only 27% of the 2-aminobenzo[*b*]thiophene derivative **42a** after 2 h (Table 3.6, Entry 10).

Table 3.6: Optimization of the Reaction Conditions for Iodine Mediated Site Selective C─H Thiolation of Thioanilides



31a **42a** **42a′**

Entry	Iodine	Oxidant	Additive	Solvent	Temp	Time	Yield of 42a (%)[a]
1.	5 mol%	TBHP	AcOH	Dioxane	80 ºC	2 h	73
2.	5 mol%	H_2O_2	AcOH	Dioxane	80 ºC	2 h	6 (86)
3.	5 mol%	DTBP	AcOH	Dioxane	80 ºC	2 h	17 (79)
4.	5 mol%	Oxone	AcOH	Dioxane	80 ºC	2 h	43
5.	5 mol%	TBHP	AcOH	DCE	80 ºC	2 h	82
6.	5 mol%	TBHP	AcOH	CH_3CN	80 ºC	2 h	78
7.	5 mol%	TBHP	AcOH	-	80 ºC	2 h	43
8.	5 mol%	TBHP	-	DCE	80 ºC	2 h	70
9.	-	TBHP	AcOH	DCE	80 ºC	2 h	10
10	5 mol%	TBHP	AcOH	DCE	rt	2 h	27

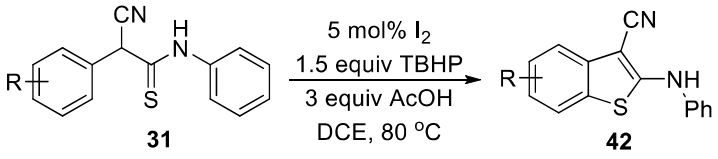
a = isolated yield, The values mentioned in parenthesis indicates recovered starting material

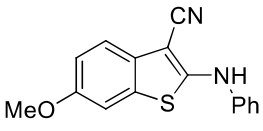
3.5.5 Substrate Scope of Iodine Mediated Regioselective Thiolation

With the optimization conditions in our hands, we started investigation of regioselective thiolation of various thioamides **31b-s**. Initially, we studied the effect of

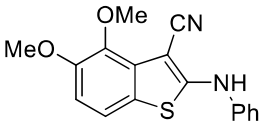
substituents at aryl group of thioamide on this intramolecular C─S bond formation reaction (Table 6). Thus, initially we studied the thioamides **41b-f** which was derived from the electron rich aryl acetonitriles **29** and phenyl isothiocyanate. 4-methoxy substituted thioanilide **31b** was smoothly transformed in to the corresponding benzo[*b*]thiophene derivative **42b** under optimized reaction conditions. Interestingly, 2, 3-dimethoxy substituted thioanilide **31c** afforded 96% thiolated product **42c**. However, 3-cyano-5,6-dimethoxy-2-(phenylamino)benzo[*b*]thiophene (**42d**) was observed in moderate yield. Similarly, methylenedioxy substituted thioamide **31e** also gave desired thiolated product **42e**. 4-Methyl substituted thioanilide **31f** also yielded the corresponding benzo[*b*]thiophene derivative **42f** under identical reaction conditions. On the other hand, halo substituted thioanilides **31g-h** were also smoothly transformed to the corresponding benzo[*b*]thiophene derivatives **42g-h**.

Table 3.7: **Investigation of Subtituted Thioanilides on Intramolecular Thiolation**

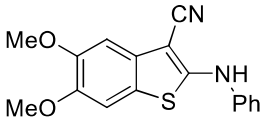




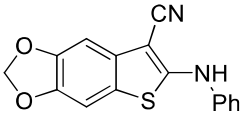
42b (68%), 90 min



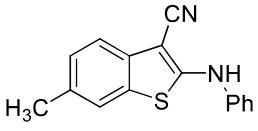
42c (96%), 1 h



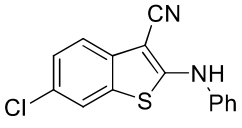
42d (44%), 2 h



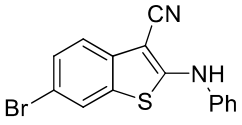
42e (52%), 2 h



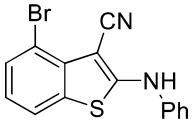
42f (71%), 1 h



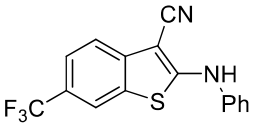
42g (86%), 2 h



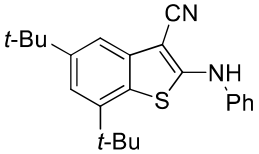
42h (81%), 2 h



42i (0%)



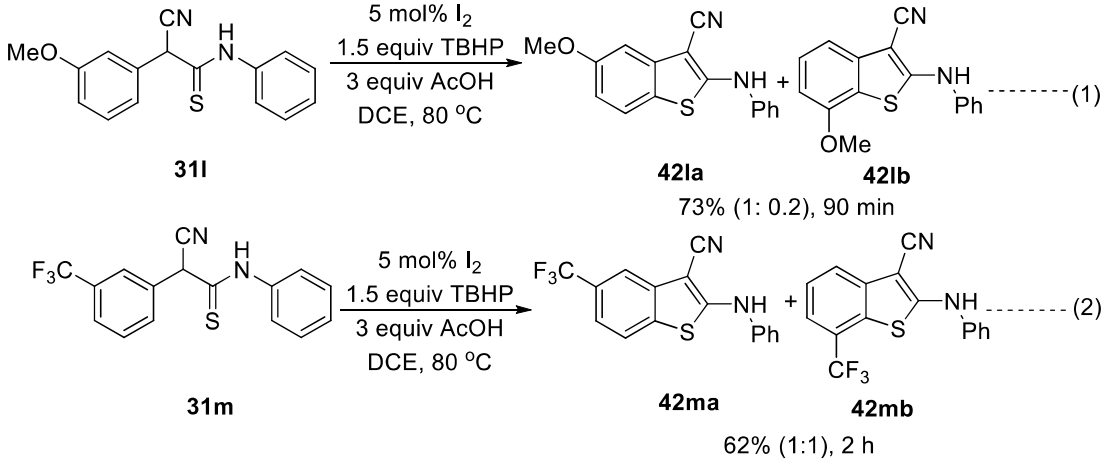
42j (57%), 2 h



42k (92%), 2 h

Whereas, 2-bromo substituted thioamides **31i** failed to give the corresponding benzo[*b*]thiophene derivative **42i** under optimized reaction conditions. However, electron withdrawing group substituted thioanilide **31j** delivered only 57% of the desired thiolated product **42j** (Table 3.7). Interestingly, when sterically crowded thioanilide **31k** was treated with optimized reaction conditions, we observed excellent yield of desired product **42k** in 2 h (Table 3.7).

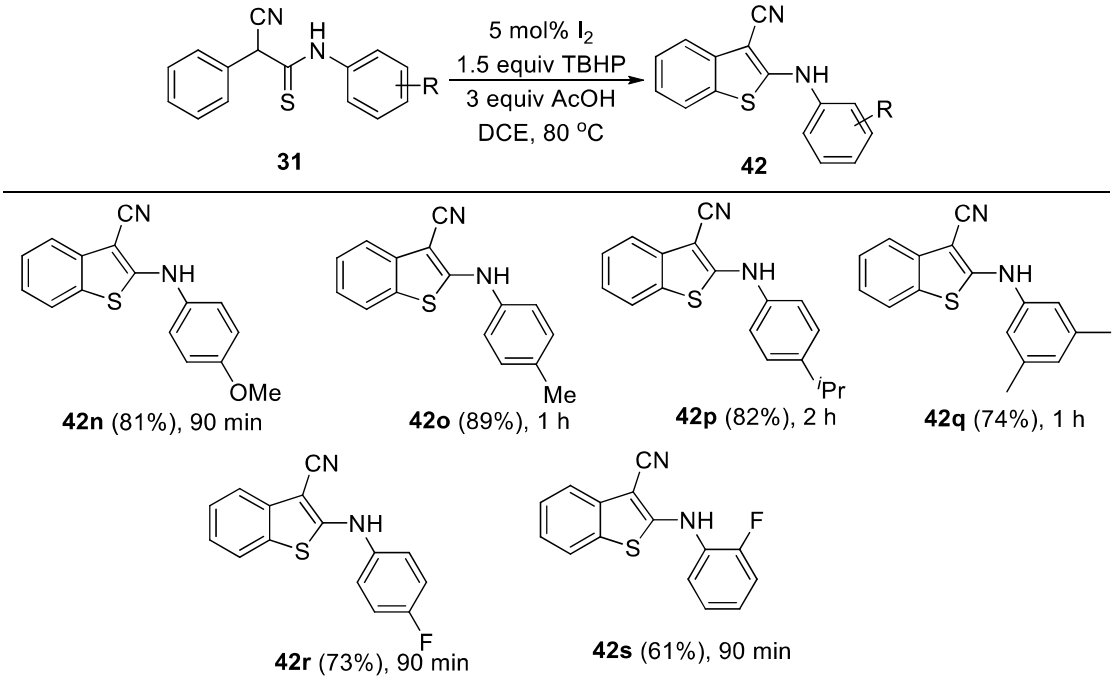
Next, we examined the thiolation of unsymmetrically substituted thioamides **31l-m**, which were derived from *meta* substituted benzylcyanides **29** and phenyl isothiocyanate **21** (Scheme 3.44). Thus, when we carried out the reaction with 2-cyano-2-(3-methoxyphenyl)-*N*-phenylethanethioamide **31l**, we observed 73% of inseparable regioisomers of 2-aminobenzo[*b*]thiophene derivatives **42la** & **42lb** in 1:0.2 ratio (Scheme 3.44). The *para*-thiolated product **42la** was observed as a major product in this reaction. On the other hand, 3-trifluoromethyl substituted thioamide **3lm** also afforded 62% of 2-anilino benzo[*b*]thiophenes **42ma** and **42mb** with an equal mixture of *para* and *ortho*-thiolated products (Scheme 3.44).



Scheme 3.44: *Regioselective Oxidative C─S bond Formation of meta-Substituted Thioamides*

Further, we turned our attention to study the effect of *N*-aryl substituted thioamides on this intramolecular thiolation reaction (Table 3.8). Thus, 4-methoxy substituted *N*-phenyl thioanilide derivative **31n** delivered the corresponding thiolated product **42n** in 81% within 90 min (Table 3.8). Similarly, 4-alkyl substituted *N*-phenylthioamides **31o-p** were also subjected to optimized reaction conditions and very good yields of benzo[*b*]thiophene derivatives **42o-p** were obtained in 1 - 2 h reaction time (Table 3.8). When we treated 3, 5-dimethyl substituted *N*-phenyl thioamide **31q** with optimized reaction conditions, we observed 74% of the C─S coupled product **42q** in 1 h. However, 3-cyano-2-[(4-fluorophenyl)amino]benzo[*b*]thiophene (**42r**) was obtained from respective thioamide **31r** in 73% yield. Whereas, 2-cyano-*N*-(2-fluorophenyl)-2-phenylethanethioamide (**31s**) gave only 61% of benzothiophene **42s** in 90 min (Table 3.8).

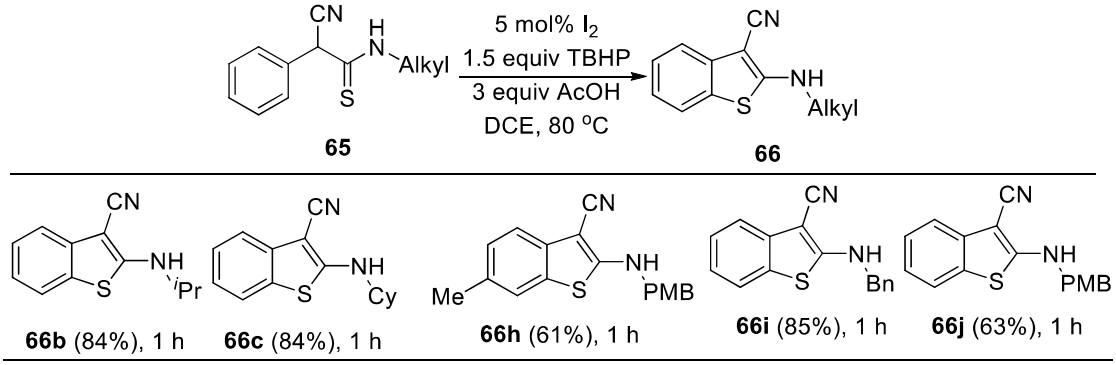
Table 3.8: Regioselective C─H Thiolation of *N*-Aryl Substituted Thioamides



Next, we extended this methodology to the *N*-alkyl substituted thioamides. Thus, when we treated the *N*-isopropyl substituted thioamide **65b** with optimized reaction

conditions we observed exclusive 84% of the corresponding 2-amino benzo[*b*]thiophene derivative **66b** in 1 hour. Similarly, 2-cyano-*N*-cyclohexyl-2-phenylethanethioamide **65c** also afforded the desired thiolated product **66c** in very good yield. *N*-4-Methoxybenzyl substituted thioamide **65h** which have two different types of sp^2 C─H also underwent a regioselective C─H thiolation and delivered exclusively 2-amino benzo[*b*]thiophene derivative **66h**. Similarly, 3-cyano-2-[(benzyl)amino]benzo[*b*]thiophene derivatives **66i-j** were obtained from the corresponding thioamides **65i-j** in 63 – 85% yield (Table 3.9) .

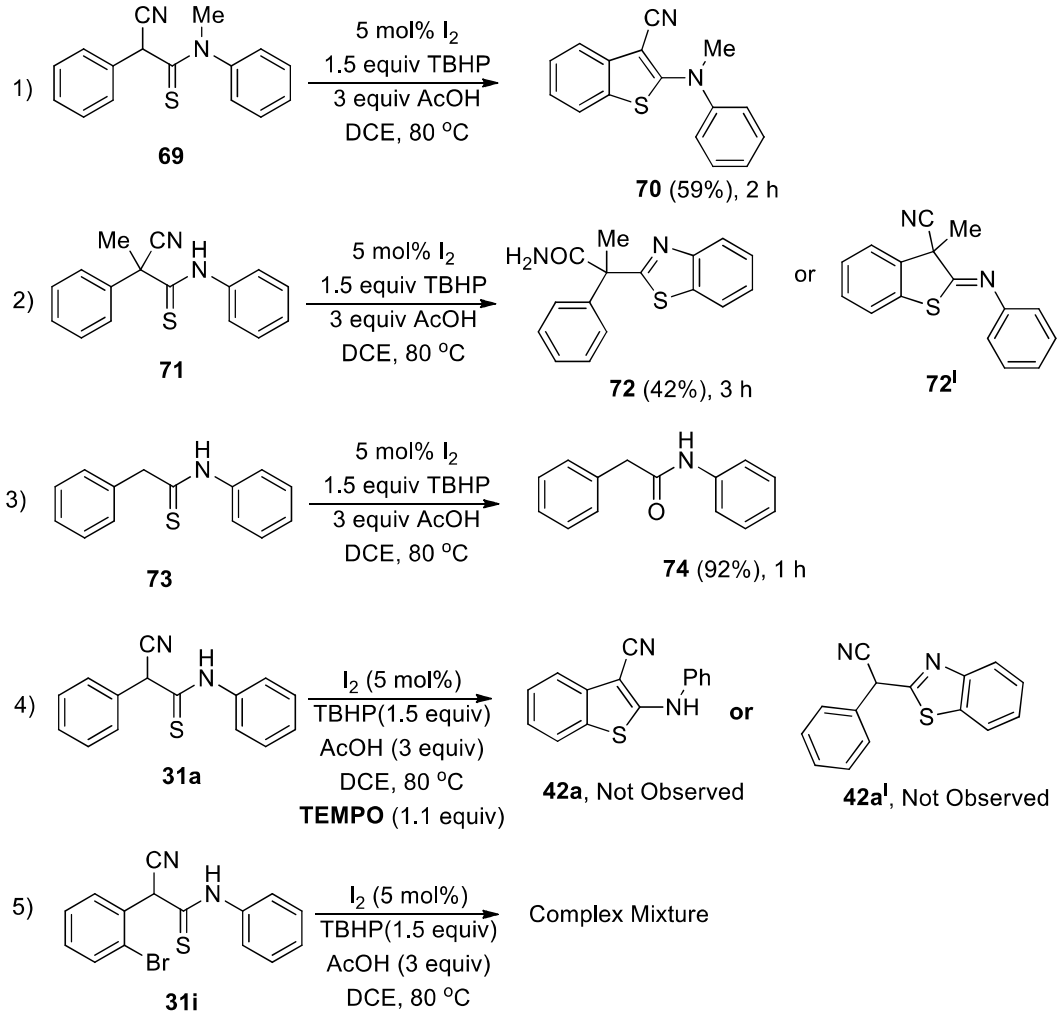
Table 3.9: A Controlled sp^2 C─H Thiolation to Synthesize *N*-Alkyl Substituted Benzo[*b*]thiophenes



Next, we turned our attention to understand the mechanism of intramolecular regioselective C─H thiolation of thioanilides. Thus, we designed few thioanilides and carried out the control experiments. Initially, we took the thioamide **69**, where N─H proton was protected with methyl group. The thioamide **69** was subjected to standard reaction conditions and gave rise to an exclusively 2-amino benzo[*b*]thiophene derivative **70** in 59% yield (Scheme 3.45). On the other hand, under optimized reaction conditions the thioanilide **71**, where the benzylic C─H was methylated, failed to give the benzo[*b*]thiophene derivative **72'**. Instead of that, we observed the benzothiazole derivative **72**, which was characterised by using spectral and analytical data (Scheme 3.45). Further, this product was also confirmed by

single crystal X-ray analysis. However, when we treated the thioanilide **73,** where nitrile group was removed, with the established reaction conditions, we observed only hydrolysed product **74** by exchanging sulphur atom with oxygen (Scheme 3.45). Further, when the experiment was carried out in the presence of radical scavenger TEMPO, we did not observe any thiolated products **42a** & **42a'** (Scheme 3.45). This is supported by the fact that, when we have carried out the reaction with *o*-bromothioanilide **31i**, we found complex reaction

3.5.6 Control Experiments:



Scheme 3.45: *Control Experiments for Intramolecular C─H Thiolation*

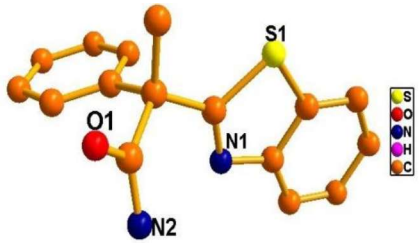
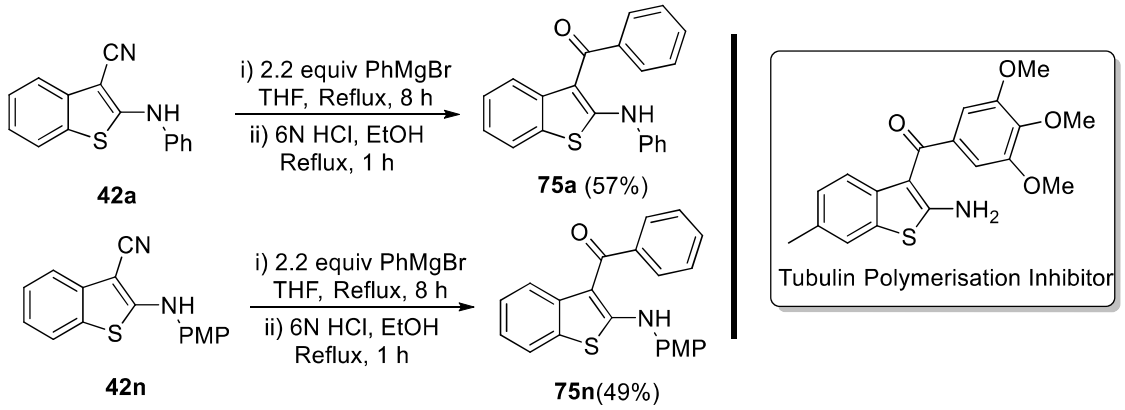


Figure 3.3: *Crystal Structure of* **72**

mixture. Hence, from this brief study, we concluded that acidic hydrogen adjacent to nitrile is crucial for this thiolation process and the reaction is going through radical pathway.

3.5.7 Synthesis of Analogues of Tubulin Polymerisation Inhibitor

Finally, we demonstrated the synthetic utility of 3-cyano-2-amino benzo[*b*]thiophene derivatives **42** by transforming the nitrile to keto group. Thus, 3-cyano-amino benzo[*b*]thiophenes **42** were treated with Grignard reagent followed by hydrolysis affording 3-aroyl-2-aminobenzo[*b*]thiophenes **75** in 49 – 57% yields which have structural similarity with tubulin polymerisation inhibitor.



Scheme 3.46: *Synthetic Utility of 2-Amino-3-Cyano Benzo[b]thiophenes*

3.6 Conclusion

In the first part of this chapter, we demonstrated a highly efficient protocol for the regioselective sp^2 C─H thiolation over sp^3 C─H thiolaion by using more abundant, cheaper and eco-friendly nickel catalyst. This is the first report for the nickel mediated *S*-heterocycle synthesis *via* C─H functionalization process. The current methodology is highly selective for the formation of 5-membered ring over 6-membered ring of the corresponding sulphur heterocycles.

We also developed iodine mediated 2-amino benzothiophenes synthesis in a highly regioselective manner under mild reaction conditions. We performed the control experiments and found that the benzylic hydrogen adjacent to nitrile is crucial for this regioselective thiolation. Further, TEMPO experiment suggested that the reaction proceeds through radical pathway. Finally, we synthesized the analogues of tubulin polymerisation inhibitor by treatment of the resulted 3-cyano-2-aminobenzothiophenes with Grignard reagent, which delivered moderate to good yields of the corresponding keto compounds.

When you compare the reactivities of both these catalytic systems, the nickel mediated thiolation process involved ionic mechanism, where both nickel and KI has a synergetic effect to afford required 2-amino benzo[*b*]thiophene derivatives. Although this method produced moderate yields, this is an excellent method for the synthesis of regioselective synthesis of benzo[*b*]thiophenes from thioamides. Whereas, iodine mediated thiolation involved radicle mechanism and where molecular iodine has a key role in the generation radicle and further thiolation. In contrast to the nickel catalysis, iodine catalytic system delivered good excellent yields of the corresponding thiolated products in regioselective fashion. However, the reaction times of the both the catalytic systems was relatively same.

3.7 Experimental Section:

3.7.1 Reagents

All reactions were performed by using standard vial technique with rubber septum. All solids were weighed in air. HFIP, Dioxane, DCE, CH_3CN, KI, PIDA, TBHP, DTBP, Oxone, H_2O_2 were purchased from Aldrich, Spectrochem or Alfa-Aesar and used as received. $NiBr_2$ and Ad_2PBu were purchased from Aldrich. The isothiocyanates were purchased from Aldrich and noncommercial isothiocyanates were 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 pre-coated silica gel $^{60}F_{254}$ plates (Merck & co.) and were visualized by UV lamp.

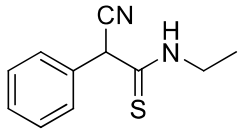
3.7.2 Analytical Methods

NMR data were recorded on Bruker ARX 400 & 700 & 300 spectrometers. ^{13}C and ^{1}H NMR Spectrum were recorded in $CDCl_3$ and DMSO-$_{d6}$ referenced according to signals of deutero solvents. ESI HR-MS measurements were performed on Bruker micrOTOF-Q-II mass spectrometer. The X-ray quality crystals for the compounds **4a** and **4b** were grown by slow diffusion of n-hexane over CH_2Cl_2 solution. Single-crystal X-ray diffraction data of **4a** and **4b** were collected on a Rigaku SuperNova fine-focused dual diffractometer, with Cu Kα radiation (λ = 1.54178 Å) equipped with a PILATUS200K detector. Using Olex2, the structures **4a** and **4b** were solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXL refinement package using Least Squares minimization. All non-hydrogen atoms were refined with anisotropic displacement coefficients. The H atoms were placed at calculated positions and were refined as riding atoms.

3.7.3 General Procedure for the Synthesis of Thioamides

To a stirring suspension of NaH (60% suspension in mineral oil) (1.2 equiv.) in DMF (10.0 mL) at 0 ºC was added drop wise the corresponding benzylcyanide (1 equiv.) in DMF (5.0 mL). After being further stirred for 1 h at room temperature, a solution of aryl/alkyl isothiocyanate (1.1 equiv.) in DMF (5.0 mL) was added to the reaction mixture at 0 ºC and followed by further stirring for 1 – 3h 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 (25 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-Cyano-*N*-ethyl-2-phenylethanethioamide (65a)



Reaction time: 1 h

Yield: 93%, as a yellow colour solid

Melting point: 101-102 °C

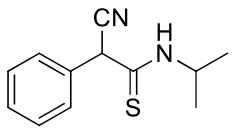
R_f: 0.34 in 30% ethyl acetate in hexanes

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 – 7.42 (m, 6H), 5.21 (s, 1H), 3.71 – 3.60 (m, 2H), 1.22 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.5, 131.9, 129.5, 129.4, 127.8, 117.6, 52.9, 41.8, 12.6.

HR-MS (ESI): Calcd. for $C_{11}H_{12}N_2S$ (M+H): 205.0794, found: 205.0780.

2-Cyano-*N*-isopropyl-2-phenylethanethioamide (65b)



Reaction Time: 2 h

Yield: 98%, yellow colour solid

Melting point: 104-105 °C

R_f: 0.33 in 30% ethyl acetate in hexanes

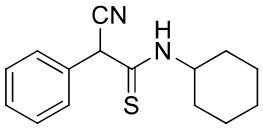
IR (KBr): ν (cm^{-1}) = 3256, 2253, 1549, 1101.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 - 7.42 (m, 5H), 7.23 (s, 1H), 5.17 (s, 1H), 4.78 – 4.37 (m, 1H), 1.25 (d, *J* = 6.5 Hz, 3H), 1.19 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 191.3, 132.0, 129.4, 129.3, 127.6, 117.6, 53.0, 48.5, 20.7.

HR-MS (ESI): Calcd. for $C_{12}H_{14}N_2S$ (M+H): 219.0950, found: 219.0975.

2-Cyano-*N*-cyclohexyl-2-phenylethanethioamide (65c)



Reaction Time: 3 h

Yield: 64%, yellow colour solid

Melting point: 93-94 °C

R_f: 0.38 in 25% ethyl acetate in hexanes

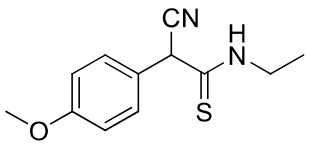
IR (KBr): ν (cm^{-1}) = 3282, 2936, 2249, 1537, 1437, 1070

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 - 7.40 (m, 5H), 7.26 (s, 1H), 5.17 (s, 1H), 4.32 – 4.23 (m, 1H), 2.04 - 1.93 (m, 2H), 1.69 - 1.60 (m, 3H), 1.45 – 1.29 (m, 2H), 1.29 – 1.09 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.1, 132.0, 129.4, 129.3, 127.6, 117.6, 55.1, 53.1, 30.7, 30.6, 25.1, 24.3.

HR-MS (ESI): Calcd. for $C_{15}H_{18}N_2S$ (M+H): 259.1263, found: 259.1235.

2-Cyano-*N*-ethyl-2-(4-methoxyphenyl)ethanethioamide (65d)



Reaction Time: 3 h

Yield: 91%, pale yellow colour liquid

R_f: 0.34 in 40% ethyl acetate in hexanes

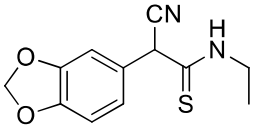
IR (KBr): 3445, 3006, 2360, 2270, 2341, 1559, 1275, 764.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 (s, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.08-7.00 (m, 2H), 6.94 – 6.89 (m, 1H), 5.18 (s, 1H), 3.79 (s, 3H), 3.66 – 3.56 (m, 2H), 1.18 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, DMSO-D_6) δ = 192.7, 159.4, 135.1, 130.0, 119.7, 118.1, 113.7, 113.6, 55.2, 50.8, 41.0, 12.4.

HR-MS (ESI) Calcd for $C_{12}H_{14}N_2OS$ [M+H]: 235.0900, Found: 235.0850

2-Cyano-*N*-ethyl-2-(3,4-methylenedioxyphenyl)ethanethioamide (65e)



Reaction Time: 3 h

Yield: 89%, pale yellow colour liquid

R_f: 0.30 in 10% ethyl acetate in hexanes

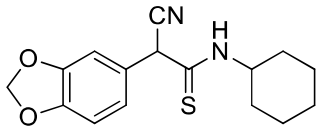
IR (KBr): 3445, 3012, 2915, 2362, 2236, 1652, 1539, 1488, 1275, 1032, 764.

^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.59 (s, 1H), 6.96 – 6.92 (m, 2H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.00 (s, 2H), 5.10 (s, 1H), 3.70 – 3.58 (m, 2H), 1.22 (t, *J* = 7.7 Hz, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ = 192.7, 148.6, 148.5, 125.3, 121.8, 117.7, 108.8, 108.0, 101.7, 52.5, 41.8, 12.6.

HR-MS (ESI) Calcd for $C_{12}H_{12}N_2O_2S$ [M+Na]: 271.0512, Found: 271.0481

2-Cyano-2-(3,4-methylenedioxyphenyl)-*N*-cyclohexylethanethioamide (65f)



Reaction Time: 3 h

Yield: 98%, yellow colour solid

Melting Point: 139-140 ºC.

R_f: 0.32 in 40% ethyl acetate in hexanes

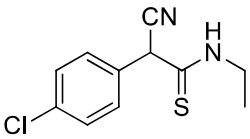
IR (KBr): 3279, 2853, 2929, 2199, 1560, 1108, 743.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.31 (s, 1H), 6.95 – 6.86 (m, 2H), 6.85 – 6.77 (m, 1H), 6.01 (s, 2H), 5.05 (s, 1H), 4.36 – 4.16 (m, 1H), 2.10 – 1.90 (m, 2H), 1.75 – 1.55 (m, 3H), 1.45 – 1.30 (m, 2H), 1.30 – 1.10 (m, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ = 191.2, 148.6, 125.4, 121.7, 117.5, 108.9, 108.0, 101.8, 55.1, 52.9, 30.9, 30.9, 25.3, 24.5.

HR-MS (ESI) Calcd for $C_{16}H_{18}N_2O_2S$ [M+H]: 303.1162, Found: 303.0963

2-(4-chlorophenyl)-2-cyano-*N*-ethylethanethioamide (65g)



Reaction Time: 2 h

Yield: 78%, brown colour solid

Melting point: 90-91°C

R_f: 0.38 % in 30% ethyl acetate in hexanes

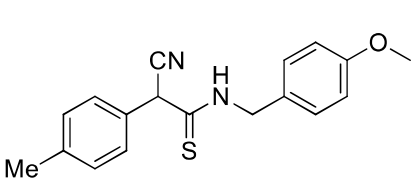
IR (KBr): ν (cm^{-1}) = 3325, 2255, 1538, 1015.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 (br s, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 5.18 (s, 1H), 3.69 – 3.59 (m, 2H), 1.23 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 191.9, 135.8, 130.6, 129.8, 129.2, 116.9, 52.4, 42.0, 12.8.

HR-MS (ESI): Calcd. for $C_{11}H_{11}ClN_2S$ (M+H): 239.0404, found: 239.0400.

2-Cyano-*N*-(4-methoxybenzyl)-2-(p-tolyl)ethanethioamide (65h)



Reaction Time: 3 h

Yield: 61%, Yellowish orange colour solid

Melting point: 104 – 106 ºC

R_f: 0.36 in 25% ethyl acetate in hexanes

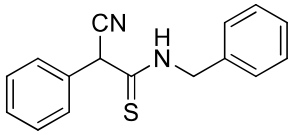
IR (KBr): ν (cm^{-1}) =3334, 2952, 2250, 2058, 1537, 1512, 1249, 1231, 1129, 1033, 815, 662.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.34 (d, *J* = 7.7 Hz, 2H), 7.22 (d, *J* = 7.7 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 7.0 Hz, 2H), 5.17 (s, 1H), 4.70 (d, *J* = 5.2 Hz, 2H), 3.79 (s, 3H), 2.36 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 192.8, 159.7, 139.7, 130.4, 129.5, 128.7, 127.7, 127.2, 117.2, 114.5, 55.4, 52.9, 50.4, 21.3.

HR-MS (ESI): Calcd. for $C_{18}H_{18}N_2OS$ (M+H): 311.1213, found: 311.1209.

2-Cyano-*N*-benzyl-2-phenylethanethioamide (65i)



Reaction Time: 3 h

Yield: 54% yellow colour solid

Melting point: 106-107 °C

R_f : 0.30 in 25% ethyl acetate in hexanes

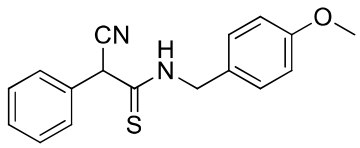
IR (KBr): ν (cm^{-1}) = 3303, 2800, 2318, 2257, 1537, 1410, 1136, 972.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (brs, 1H), 7.49 – 7.42 (m, 5H), 7.32 – 7.31 (m, 3H), 7.18 (m, 2H), 5.25 (s, 1H), 4.79 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.8, 135.2, 131.8, 129.77, 129.71, 129.1, 128.4, 128.0, 127.8, 117.1, 53.2, 50.8.

HR-MS (ESI): Calcd. for $C_{16}H_{14}N_2S$ (M+H): 267.0950, found: 267.0952.

2-Cyano-*N*-(4-methoxybenzyl)-2-phenylethanethioamide (65j)



Reaction Time: 2 h

Yield: 82%, brown colour solid

Melting point: 99-100 °C

R_f: 0.30 in 30% ethyl acetate in hexanes

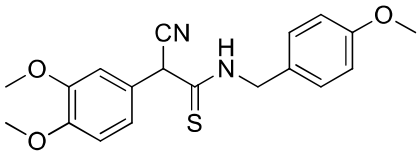
IR (KBr): ν (cm^{-1}) =3321, 2251, 1534, 1250, 1031.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.52 – 7.45 (m, 2H), 7.44 – 7.39 (m, 3H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.23 (s, 1H), 4.71 (d, *J* = 4.8 Hz, 2H), 3.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 159.6, 131.8, 129.6, 129.59, 129.50, 127.8, 127.2, 117.2, 114.4, 55.3, 53.1, 50.3.

HR-MS (ESI): $C_{17}H_{16}N_2SO$ [M+H]: 297.1056, Found: 297.1076.

2-Cyano-2-(3,4-dimethoxyphenyl)-*N*-(4-methoxybenzyl)ethanethioamide (65k)



Reaction Time: 3 h

Yield: 63%, yellow colour solid

Melting Point: 127-128 ºC.

R_f: 0.32 in 40% ethyl acetate in hexanes

IR (KBr): 3270, 2249, 1574, 1262, 1019

^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.75 (s, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.98 (dd, *J* = 6.3, 2.1 Hz, 1H), 6.93 (d, *J* = 2.1 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 2 H), 5.15 (s, 1H), 4.70 (d, *J* = 4.9 Hz, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ = 193.0, 159.4, 149.8, 149.5, 129.4, 127.3, 123.9, 120.5, 117.6, 114.2, 111.5, 110.5, 56.0, 55.9, 55.2, 52.5, 50.0.

HR-MS (ESI) Calcd for $C_{19}H_{20}N_2O_3S$ [M+H]: 357.1267, Found: 357.1276

3.7.4 General Procedure for Ligand Optimization of Nickel mediated Site Selective C–S Bond Formation

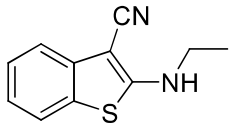
An oven-dried 8 mL reaction vial was charged with Nickel salt (2 mol%), ligand (4 mol%) PIDA (1 equiv) and KI (2 equiv), thioamide **65a** (0.5 mmol) in HFIP (2.0 mL), was stirred at 50 ºC. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was purified by flash chromatography.

3.7.5 General Procedure for Nickel Mediated Site Selective C–S Bond Formation of sp^2 C–H bond vs sp^3 C–H bond

An oven-dried 8 mL reaction vial was charged with $NiBr_2$ (2 mol%), Ad_2PBu (4 mol%) PIDA (0.5 mmol) and KI (1 mmol), respective thioamide **65** (0.5 mmol) in HFIP (2.0 mL), was stirred at 50 ºC for 1- 1.5 h. The reaction mixture was monitored by TLC. After the

starting material had been completely consumed, the reaction mixture was purified by flash chromatography.

2-(Ethylamino)benzo[*b*]thiophene-3-carbonitrile (66a)



Reaction Time: 1 h

Yield: 69%, white colour solid

Melting point: 161-162°C

R_f: 0.39 in 20% ethyl acetate in hexanes

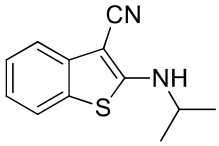
IR (KBr): ν (cm^{-1}) = 3292, 2195, 1566, 1083.

^1H NMR (400 MHz, $CDCl_3$) δ = 7.54 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.36 – 7.31 (m, 1H), 7.16 – 7.10 (m, 1H), 5.40 (br s, 1H), 3.39 (q, *J* = 7.2 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.4, 137.9, 128.6, 126.0, 122.47, 121.9, 119.3, 116.1, 78.0, 42.6, 14.8.

HR-MS (ESI): Calcd. for $C_{11}H_{10}N_2S$ (M+H): 257.1107, found: 257.1101.

3-Cyano-2-(isopropylamino)benzo[*b*]thiophene (66b)



Reaction Time: 1 h

Yield: 98%, white solid

Melting point: 106 – 109 ºC

R_f: 0.43 in 20% ethyl acetate in hexane

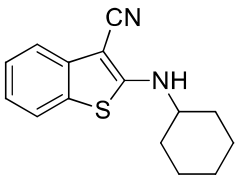
IR (KBr): ν (cm^{-1}) = 3446, 3323, 2973, 2372, 2346, 2194, 1560, 1451, 1169, 1075, 745.

^1H NMR (400 MHz, $CDCl_3$) δ = 7.53 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* =8.0 Hz, 1H), 7.35 – 7.31 (m, 1H), 7.15 – 7.11 (m, 1H), 5.24 (s, 1H), 3.70 – 3.67 (m, 1H), 1.36 (d, *J* = 6.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.3, 137.8, 128.7, 126.0, 122.5, 121.9, 119.3, 116.2, 78.2, 50.3, 23.1.

HR-MS (ESI): Calcd. for $C_{12}H_{12}N_2S$ [M+H]: 217.0794, Found: 217.0785.

3-Cyano-2-(cyclohexylamino)benzo[*b*]thiophene (66c)



Reaction Time: 1 h

Yield: 68%, white solid

Melting Point: 132 – 134 ºC

R_f: 0.38 in 15% ethyl acetate in hexanes

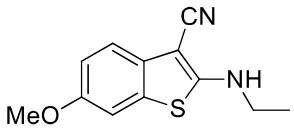
IR (KBr): ν (cm^{-1}) = 3267, 2989, 2930, 2854, 2199, 1563, 1467, 1364, 1109, 748.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.12 (t, *J* = 7.2 Hz, 1H), 5.23 (s, 1H), 3.46 – 3.13 (m, 1H), 2.19 – 2.10 (m, 2H), 1.88 – 1.78 (m, 2H), 1.73 – 1.63 (m, 1H), 1.49 – 1.17 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 137.8, 128.6, 126.0, 122.4, 121.8, 119.2, 116.1, 78.1, 57.3, 33.3, 25.3, 24.8.

HR-MS (ESI): Calcd. for $C_{15}H_{16}N_2S$ (M+H): 257.1107, found: 257.1101.

3-Cyano-2-(ethylamino)-6-methoxybenzo[*b*]thiophene (66d)



Reaction Time: 1h

Yield: 40%, yellow colour solid

Melting Point: 130-131 ºC.

R_f: 0.38 in 20% ethyl acetate in hexanes

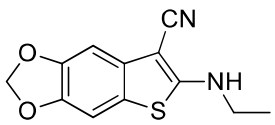
IR (KBr): 3284, 2203, 1574, 1095.

^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.39 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 2.8 Hz, 1H), 6.73-6.76 (m, 1H), 5.30 (s, 1H), 3.85 (s, 3H), 3.38 (q, *J* = 7.0 Hz, 2H), 1.36 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR (175 MHz, $CDCl_3$) δ = 166.5, 159.0, 139.1, 122.6, 120.2, 116.3, 111.5, 102.7, 78.1, 55.7, 42.5, 14.8.

HR-MS (ESI) Calcd for $C_{12}H_{12}N_2OS$ [M+H]: 233.0743, Found: 233.0724

3-Cyano-2-(ethylamino)-5,6-methylenedioxybenzo[*b*]thiophene (66e)



Reaction Time: 1 h

Yield: 33%, white colour solid

Melting Point: 195 ºC. Decomposed

R_f**:** 0.29 in 10% ethyl acetate in hexanes

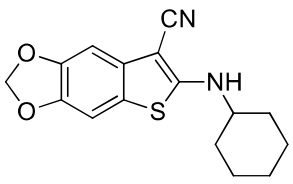
IR (KBr): 3218, 2197, 1573, 1103

^{1}H NMR (300 MHz, DMSO-D_6) δ = 8.03 (s, 1H), 7.33 (s, 1H), 6.82 (s, 1H), 6.01 (s, 2H), 3.41-3.20 (m, 2H), 1.40-1.05 (m, 3H)

^{13}C NMR (75 MHz, DMSO-D_6) δ = 164.0, 146.9, 143.7, 132.1, 119.3, 116.1, 102.6, 101.0, 98.1, 75.4, 41.5, 14.2.

HR-MS (ESI) Calcd for $C_{12}H_{10}N_2O_2S$ [M+H]: 247.0536, Found: 247.0531

3-Cyano-2-(cyclohexylamino)-5,6-methylenedioxybenzo[*b*]thiophene (66f)



Reaction Time: 1 h

Yield: 50%, White solid

Melting Point: 161-163 ºC.

R_f: 0.25 in 10 % ethyl acetate in hexanes

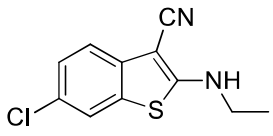
IR (KBr): 3555, 2846, 2243, 2065, 1635, 1556, 1472, 1260, 749

^{1}H NMR (300 MHz, DMSO-D_6) δ = 7.98 (d, *J* = 7.8 Hz, 1H), 7.32 (s, 1H), 6.80 (s, 1H), 6.01 (s, 2H), 2.05-1.90 (m, 2H), 1.81-1.68 (m, 2H), 1.67-1.52 (m, 1H), 1.40-1.09 (m, 6H).

^{13}C NMR (175 MHz, $CDCl_3$) δ = 163.4, 147.5, 144.5, 131.8, 120.3, 116.2, 102.0, 101.3, 99.6, 78.4, 57.2, 33.3, 25.3, 24.8.

HR-MS (ESI) Calcd for $C_{16}H_{16}N_2O_2S$ [M+H]: 301.1005, Found: 301.1001

3-Cyano-6-chloro-2-(ethylamino)benzo[*b*]thiophene (66g)



Reaction Time: 1 h

Yield: 44%, brown colour flakes

M.P: 135-136 ºC

R_f: 0.35 in 20% ethyl acetate in hexanes

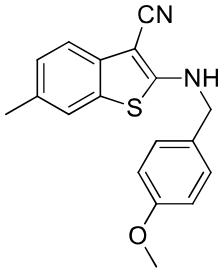
IR (KBr): ν (cm^{-1}) = 3325, 2937, 2255, 1902, 1538, 1284, 1015.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 (d, *J* = 1.8 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.30 (dd, *J* = 8.5, 1.8 Hz, 1H), 5.39 (br s, 1H), 3.40 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.3, 136.3, 129.5, 127.9, 126.7, 121.6, 120.0, 115.7, 77.8, 42.7, 14.8.

HR-MS (ESI): Calcd. for $C_{11}H_9ClN_2S$ (M+H): 237.0248 found: 237.0230.

3-Cyano-2-((4-methoxybenzyl)amino)-6-methylbenzo[*b*]thiophene (66h)



Reaction Time: 1 h

Yield: 51%, yellow solid

Melting Point: 108 – 110 ºC

R_f: 0.36 in 30% ethyl acetate in hexanes

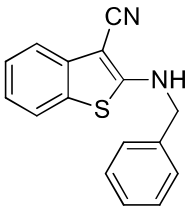
IR (KBr): ν (cm^{-1}) = 3430, 3271, 2363, 2198, 1598, 1567, 1262, 1167, 1027, 814.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.0 Hz, 1H), 7.34 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 5.47 (s, 1H), 4.45 (s, 2H), 3.82 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 159.6, 135.1, 132.5, 129.2, 129.0, 128.4, 127.4, 121.9, 119.1, 116.1, 114.4, 78.6, 55.4, 51.0, 21.4.

HR-MS (ESI): Calcd. for $C_{18}H_{16}ON_2S$ (M+Na): 331.0876, found: 331.0894.

3-Cyano-2-(benzylamino)benzo[*b*]thiophene (66i)



Reaction Time: 1 h

Yield: 37%, white solid

Melting point: 159-160°C

R_f: 0.32 in 20% ethyl acetate in hexanes

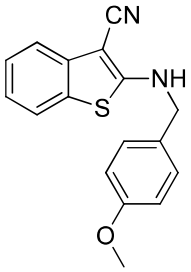
IR (KBr): ν (cm^{-1}) = 3376, 2291, 1570, 1136.

^1H NMR (400 MHz, $CDCl_3$) δ = 7.53 (dd, *J* = 9.0, 1.0 Hz, 2H), 7.40 – 7.33 (m, 6H), 7.18 – 7.13 (m, 1H), 5.66 (brs, 1H), 4.54 (s, 2H).

^{13}C NMR (100 MHz, CDCl3) δ = 165.1, 137.6, 136.3, 129.1, 128.8, 128.4, 127.8, 126.1, 122.7, 121.9, 119.4, 116.0, 79.0, 51.5.

HR-MS (ESI): Calculated for $C_{16}H_{12}N_2S$: $[M+H]^+$ 265.0794 found 265.0780

3-Cyano-2-(4-methoxybenzylamino)benzo[*b*]thiophene (66j)



Reaction Time: 1 h

Yield: 35%, colourless solid

Melting Point: 134 – 136 ºC

R_f: 0.35 in 20% ethyl acetate in hexanes

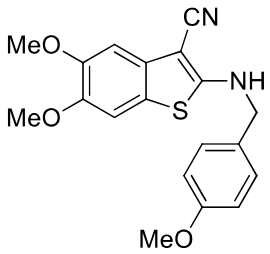
IR (KBr): ν (cm^{-1}) = 3436, 3301, 2929, 2196, 1586, 1569, 1512, 1450, 1351, 1248, 1036, 743.

^1H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.48 (m, 2H), 7.38 – 7.32 (m, 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.91 (dd, *J* = 9.0, 2.2 Hz, 2H), 5.68 (s, 1H), 4.47 (s, 2H), 3.82 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 159.7, 137.6, 129.2, 128.8, 128.2, 126.1, 122.7, 121.9, 119.4, 115.9, 114.5, 79.0, 55.4, 51.1.

HR-MS (ESI): Calcd. for $C_{17}H_{14}N_2OS$ (M+Na): 317.0719, found: 317.0705.

3-Cyano-5,6-dimethoxy-2-[(4-methoxybenzyl)amino]benzo[*b*]thiophene (66k)



Reaction Time: 1 h

Yield: 37%, white colour solid

Melting Point: 157-159 ºC.

R_f: 0.23 in 20% ethyl acetate in hexanes

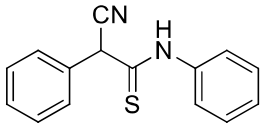
IR (KBr): 3249, 2206, 1491, 1250, 1027

^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.30 (d, *J* = 8.4 Hz, 2H), 7.01 (s, 1H), 6.98 (s, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.42 (s, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 3.81 (s, 3H)

^{13}C NMR (75 MHz, DMSO-D_6) δ = 164.2, 158.6, 148.8, 145.8, 130.7, 129.6, 128.8, 119.1, 116.3, 113.9, 106.0, 101.1, 76.0, 56.0, 55.6, 55.1, 49.3.

HR-MS (ESI) Calcd for $C_{19}H_{18}N_2O_3S$ [M+Na]: 377.0930, Found: 377.0918

2-Cyano-*N*-2-diphenylethanethioamide (31a)



Reaction time: 2 h

Yield: 62%, Yellow solid

Melting point: 105 – 106 ºC

R_f: 0.36 in 25% ethyl acetate in hexanes

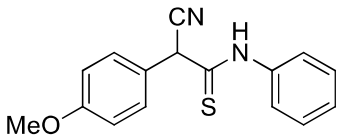
IR (KBr): ν (cm^{-1}) = 3450, 3274, 3141, 3095, 2252, 1598, 1558, 1492, 1403, 1279, 1118, 757

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.65 – 7.53 (m, 4H), 7.50 - 7.44 (m, 3H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.29 - 7.25 (m, 1H), 5.39 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 137.9, 131.8, 129.9, 129.8, 129.1, 127.9, 127.6, 123.6, 117.3, 54.8.

HR-MS (ESI): Calcd. for $C_{15}H_{12}N_2S$ (M+H): 253.0794, found: 253.0809.

2-Cyano-2-(4-methoxyphenyl)-*N*-phenylethanethioamide (31b)



Reaction Time: 2 h

Yield: 56%, pale yellow solid

Melting point: 84 -85 ºC

R_f: 0.3 in 20% ethyl acetate in hexanes

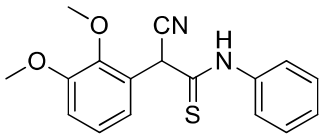
IR (KBr): ν (cm^{-1}) = 3604, 3271, 2955, 2836, 2252, 1607, 1509, 1405, 1254, 1180, 1110, 1031, 834, 744, 709.

^1H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.30 – 7.22 (m, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 5.32 (s, 1H), 3.82 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 160.4, 137.9, 129.2, 128.9, 127.4, 123.7, 123.5, 117.9, 115.0, 55.4, 53.7.

HR-MS (ESI): Calcd. for $C_{16}H_{14}N_2OS$ (M+Na): 305.0719, found: 305.0724.

2-Cyano-2-(2, 3-dimethoxyphenyl)-*N*-phenylethanethioamide (31c)



Reaction Time: 2 h

Yield: 89%, yellow solid

Melting point: 137 – 139 ºC

R_f: 0.35 in 25% ethyl acetate in hexanes

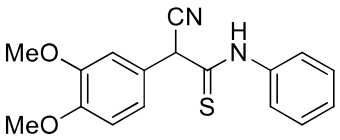
IR (KBr): ν (cm^{-1}) =3435, 3300, 3152, 3119, 2942, 2880, 2249, 1483, 1412, 1274, 1077, 996, 761, 742.

^1H NMR (300 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.18 (m, 1H), 7.16 - 7.11 (m, 2H), 7.00 - 6.98 (m, 1H), 5.47 (s, 1H), 4.12 (s, 3H), 3.91 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 191.3, 152.9, 145.4, 138.5, 129.0, 127.1, 126.1, 125.3, 123.0, 121.2, 117.4, 114.0, 61.6, 56.0, 51.0.

HR-MS (ESI): Calcd. for $C_{17}H_{16}N_2O_2S$ (M+H): 313.1005, found: 313.1007.

2-Cyano-2-(3, 4-dimethoxyphenyl)-*N*-phenylethanethioamide (31d)



Reaction Time: 2 h

Yield: 49%, Yellow solid

Melting point: 134 – 136 ºC

R_f: 0.31 in 20% ethyl acetate in hexanes

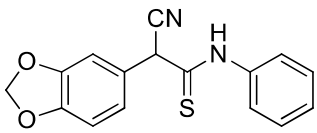
IR (KBr): ν (cm^{-1}) = 3450, 3251, 2960, 2367, 1596, 1517, 1396, 1263, 1235, 1141, 1015, 746, 694.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.08 (s, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 5.34 (s, 1H), 3.87 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 150.1, 149.8, 137.9, 129.0, 127.5, 123.9, 123.4, 120.6, 117.6, 111.7, 110.7, 56.1, 56.0, 54.3.

HR-MS (ESI): Calcd. for $C_{17}H_{16}N_2O_2S$ (M+Na): 335.0825, found: 335.0816.

2-Cyano-2-(3, 4-methylenedioxy)-*N*-phenylethanethioamide (31e)



Reaction Time: 2 h

Yield: 65%, yellow solid

Melting point: 120 – 122 ºC

R_f: 0.34 in 25% ethyl acetate in hexanes

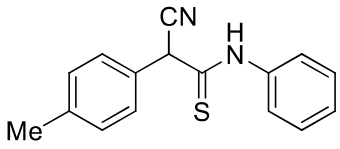
IR (KBr): ν (cm^{-1}) =3434, 3176, 3008, 2965, 2362, 2197, 1598, 1503, 1487, 1443, 1250, 1101, 1038, 936, 854.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.29 - 7.25 (m, 1H), 7.10 – 7.01 (m, 2H), 6.90 – 6.83 (m, 1H), 6.02 (s, 2H), 5.29 (s, 1H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 191.5, 148.9, 148.8, 137.9, 129.1, 127.6, 125.1, 123.6, 121.9, 117.5, 109.1, 108.1, 101.9, 54.3.

HR-MS (ESI): Calcd. for $C_{16}H_{12}N_2O_2S$ (M+Cl): 331.0303, found: 331.0331.

2-Cyano-*N*-phenyl-2-(p-tolyl)ethanethioamide (31f)



Reaction Time: 2 h

Yield: 79%, Brown solid

Melting point: 112 -114 ºC

R_f: 0.35 in 20% ethyl acetate in hexanes

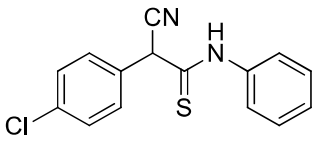
IR (KBr): ν (cm^{-1}) =3181, 3123, 3012, 2972, 2192, 1598, 1541, 1512, 1493, 1409, 1268, 1108.

^{1}H NMR (300 MHz, DMSO-D_6) δ 12.14 (s, 1H), 7.72 (d, *J* = 7.5 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.32 - 7.24 (m, 3H), 5.74 (s, 1H), 2.30 (s, 3H).

^{13}C NMR (75 MHz, DMSO-D_6) δ 192.8, 138.8, 138.2, 130.9, 129.5, 128.7, 127.3, 126.7, 123.2, 118.1, 51.9, 20.6.

HR-MS (ESI): Calcd. for $C_{16}H_{14}N_2S$ (M+Na): 289.0770, found: 289.0803.

2-Cyano-2-(4-chlorophenyl)-*N*-phenylethanethioamide (31g)



Reaction Time: 3 h

Yield: 56%, pale yellow solid

Melting point: 124 – 126 ºC

R_f: 0.33 in 20% ethyl acetate in hexanes

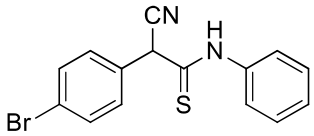
IR (KBr): ν (cm^{-1}) = 3445, 3006, 2387, 2347, 2260, 1635, 1275, 1260, 764, 749.

^{1}H NMR (700 MHz, DMSO-D_6) δ 12.20 (s, 1H), 7.72 (d, *J* = 7.7 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.42 (t, *J* = 8.4 Hz, 2H), 7.28 (t, *J* = 7.7 Hz, 1H), 5.82 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 137.8, 136.0, 130.6, 130.0, 129.2 (2C), 127.8, 123.7, 116.9, 53.9.

HR-MS (ESI): Calcd. for $C_{15}H_{11}ClN_2S$ (M+H): 287.0404, found: 287.0409.

2-Cyano-2-(4-bromophenyl)-*N*-phenylethanethioamide (31h)



Reaction Time: 3 h

Yield: 67%, Yellowish orange solid

Melting point: 120 – 122 ºC

R_f: 0.36 in 25% ethyl acetate in hexanes

IR (KBr): ν (cm^{-1}) = 3286, 3231, 2253, 195, 1519, 1412, 1398, 1105, 1073, 708.

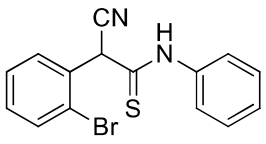
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.61 (d, *J* = 7.7 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.0 Hz, 1H), 5.34 (s, 1H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 190.7, 137.8, 132.9, 131.0, 129.5, 129.2, 127.8, 124.1, 123.7, 117.0, 53.9.

HR-MS (ESI): Calcd. for $C_{15}H_{11}BrN_2S$ (M+H): 330.9899, found: 330.9873.

332.9879, found: 332.9853.

2-(2-Bromophenyl)-2-cyano-N-phenylethanethioamide (31i)



Reaction time: 4 h

Yield: 70%, as a pale yellow colour viscous liquid. Rf: 0.32 in 25% ethyl acetate in hexane

IR (as film in CCl4): ν (cm^{-1}) = 3272, 3058, 2933, 2360, 2340, 2251, 2202, 1597,1409, 1275, 1204, 1089, 1027.

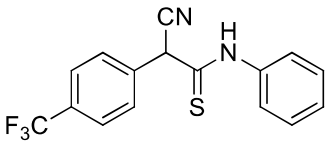
1H NMR (400 MHz, CDCl3) δ = 9.24 (s, 1H), 7.80 (dd, J = 8.0, 1.6 Hz, 1H), 7.66 – 7.61 (m, 3H), 7.47 – 7.43 (m, 1H), 7.38 (t, J = 7.6 Hz, 2H), 7.33 – 7.28 (m, 2H), 5.73 (s, 1H).

13C NMR (100 MHz, CDCl3) 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 C15H11BrN2S [M+H]: 330.9899, Found: 330.9896.

332.9879, Found: 332.9885.

2-Cyano-*N*-phenyl-2-(4-(trifluoromethyl)phenyl)ethanethioamide (31j)



Reaction Time: 2 h

Yield: 51%, Yellowish orange colour solid

Melting Point: 112 – 114 ºC

R_f: 0.34 in 25% ethyl acetate in hexanes

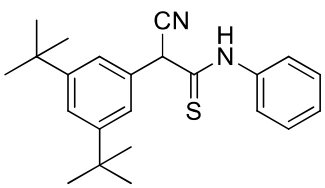
IR (KBr): ν (cm^{-1}) = 3266, 3086, 2770, 2389, 2355, 1609, 1498, 1409, 1330, 1164, 1127, 1070.

^{1}H NMR (700 MHz, DMSO-D_6) δ 12.28 (s, 1H), 7.89 - 7.83 (m, 4H), 7.72 (d, *J* = 7.7 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.29 (t, *J* = 7.7 Hz, 1H), 5.94 (s, 1H).

^{13}C NMR (175 MHz, DMSO-D_6) δ 191.5, 138.6, 138.2, 129.2 (q, *J* = 32.1 Hz), 128.5, 126.9, 126.0 (q, *J* = 3.6 Hz), 124.7, 123.2, 124.0 (q, *J* = 269.5 Hz), 117.6, 51.8.

HR-MS (ESI): Calcd. for $C_{16}H_{11}F_3N_2S$ (M+H): 321.0668, found: 321.0676.

2-Cyano-2-(3,5-di-tert-butylphenyl)-*N*-phenylethanethioamide (31k)



Reaction Time: 2.5 h

Yield: 57%, yellow solid

Melting point: 198 -199 ºC

R_f: 0.33 in 15% ethyl acetate in hexanes

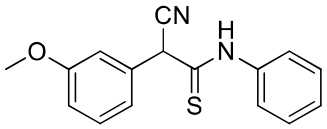
IR (KBr): ν (cm^{-1}) = 3261, 2995, 2379, 2281, 1600, 1410, 1276, 1125.

^{1}H NMR (300 MHz, DMSO-D_6) δ 12.13 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.54 (s, 2H), 7.45 – 7.40 (m, 3H), 7.29 (d, *J* = 6.3 Hz, 1H), 5.71 (s, 1H), 1.29 (s, 18H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 191.7, 152.9, 138.0, 130.7, 129.1, 127.6, 123.9, 123.5, 122.2, 117.6, 55.5, 35.2, 31.4.

HR-MS (ESI): Calcd. for $C_{23}H_{28}N_2S$ (M+Na): 387.1865, found: 387.1842.

2-cyano-2-(3-methoxyphenyl)-*N*-phenylethanethioamide (31l)



Reaction Time: 2 h

Yield: 67%, Yellow colour gelly compound

R_f: 0.34 in 25% ethyl acetate in hexanes

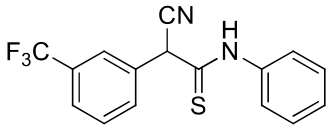
IR (thin film): ν (cm^{-1}) = 3648, 3269, 2777, 2426, 2250, 1700, 1653, 1599, 1490, 1405, 1269, 1047, 739.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.43 – 7.33 (m, 3H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 2 Hz, 1H), 6.98 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.34 (s, 1H), 3.83 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 160.6, 137.9, 132.9, 131.0, 129.1, 127.6, 123.6, 120.0, 117.2, 115.4, 113.6, 55.6, 54.8.

HR-MS (ESI): Calcd. for $C_{16}H_{14}N_2OS$ (M+Na): 305.0719, found: 305.0749.

2-Cyano-*N*-phenyl-2-(3-(trifluoromethyl)phenyl)ethanethioamide (31m)



Reaction Time: 2 h

Yield: 91%, Yellow colour gelly compound

R_f: 0.35 in 25% ethyl acetate in hexanes

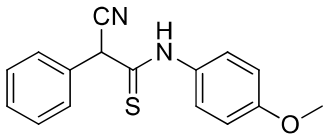
IR (thin film): ν (cm^{-1}) = 3675, 3446, 3008, 2367, 2283, 2193, 1699, 1652, 1540, 1456, 1269, 804.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.86 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H).5.41 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 137.9, 133.3, 131.9 (q, *J* = 32 Hz), 131.3 (q, *J* = 1 Hz), 130.2, 129.2, 127.8, 126.5 (q, *J* = 4 Hz), 124.7 (q, *J* = 3Hz), 123.7, 123.0 (q, *J* = 148 Hz), 117.0, 53.7.

HR-MS (ESI): Calcd. for $C_{16}H_{11}F_3N_2S$ (M+H): 321.0668, found: 321.0654.

2-Cyano-*N*-(4-methoxyphenyl)-2-phenylethanethioamide (31n)



Reaction Time: 2 h

Yield: 57%, pale yellow solid

Melting point: 119 – 121 ºC

R_f: 0.3 in 20% ethyl acetate in hexanes

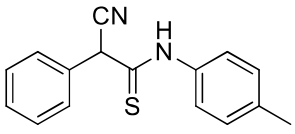
IR (KBr): ν (cm^{-1}) = 3281, 3211, 3137, 3099, 2253, 1607, 1569, 1509, 1427, 1404, 1253, 1184, 1031, 837, 756.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.62 – 7.54 (m, 2H), 7.51 – 7.40 (m, 5H), 6.92 – 6.84 (m, 2H), 5.36 (s, 1H), 3.79 (s, 3H).

^{13}C NMR (75 MHz, DMSO-D_6) δ 191.6, 157.5, 133.9, 131.7, 128.9, 128.6, 127.4, 124.7, 118.1, 113.8, 55.3, 52.0.

HR-MS (ESI): Calcd. for $C_{16}H_{14}N_2OS$ (M+H): 283.0900, found: 283.0916.

2-Cyano-*N*-(4-methylphenyl)-2-phenylethanethioamide (31o)



Reaction Time: 2 h

Yield: 76%, yellow solid

Melting point: 96 – 98 °C

R_f: 0.36 in 25% ethyl acetate in hexanes

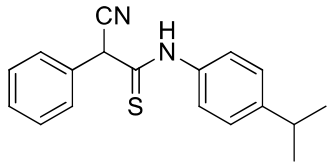
IR (KBr): ν (cm^{-1}) =3276, 3205, 3129, 3080, 2252, 1611, 1511, 1425, 1401, 1280, 1199, 1122, 819, 728.

^{1}H NMR (700 MHz, DMSO-D_6) δ 12.10 (s, 1H), 7.65 (d, *J* = 7.0 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.45 (t, *J* = 7.0 Hz, 2H), 7.40 (t, *J* = 7.0 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 5.77 (s, 1H), 2.29 (s, 3H).

^{13}C NMR (175 MHz, DMSO-D_6) δ 192.1, 136.3, 136.2, 133.9, 129.1, 128.9, 128.7, 127.5, 123.1, 118.1, 52.1, 20.6.

HR-MS (ESI): Calcd. for $C_{16}H_{14}N_2S$ (M+H): 267.0950, found: 267.0949.

2-Cyano-*N*-(4-isopropylphenyl)-2-phenylethanethioamide (31p)



Reaction Time: 3 h

Yield: 40%, yellow solid

Melting Point: 104 – 106 °C

R_f: 0.35 in 20% ethyl acetate in hexanes

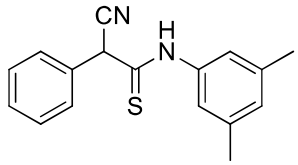
IR (KBr): ν (cm^{-1}) = 3447, 2961, 2898, 2344, 2268, 1635, 1558, 1506, 1269, 784.

^{1}H NMR (700 MHz, DMSO-D_6) δ 12.10 (s, 1H), 7.69 – 7.58 (m, 4H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 5.77 (s, 1H), 3.06 – 2.73 (m, 1H), 1.19 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 190.9, 148.4, 135.7, 132.1, 129.7, 129.6, 127.9, 127.0, 123.4, 117.4, 54.5, 33.8, 23.9.

HR-MS (ESI): Calcd. for $C_{18}H_{18}N_2S$ (M+H): 295.1263, found: 295.1280.

2-Cyano-*N*-(3,5-dimethylphenyl)-2-phenylethanethioamide (31q)



Reaction Time: 2 h

Yield: 81%, yellow solid

Melting point: 101 – 103 °C

R_f: 0.34 in 20% ethyl acetate in hexanes

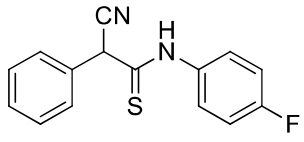
IR (KBr): ν (cm^{-1}) =3291, 3247, 2915, 2252, 1560, 1406, 1274, 1101, 1032, 847, 730, 696.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.03 (s, 1H), 7.60 – 7.58 (m, 2H), 7.49 – 7.43 (m, 3H), 7.16 (s, 2H), 6.92 (s, 1H), 5.75 (s, 1H), 2.29 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 138.9, 137.7, 131.8, 129.7, 129.6, 129.3, 127.8, 121.2, 117.3, 54.6, 21.2.

HR-MS (ESI): Calcd. for $C_{17}H_{16}N_2S$ (M+H): 281.1107, found: 281.1129.

2-Cyano-*N*-(4-flourophenyl)-2-phenylethanethioamide (31r)



Reaction Time: 1.5 h

Yield: 41%, pale yellow solid

Melting point: 136 – 138 °C

R_f: 0.34 in 20% ethyl acetate in hexanes

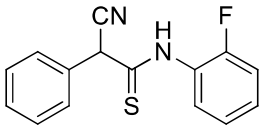
IR (KBr): ν (cm^{-1}) =3279, 3231, 3099, 2254, 1568, 1508, 1421, 1393, 1280, 1228, 839, 758, 739

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.61 - 7.56 (m, 2H), 7.53 – 7.46 (m, 5H), 7.07 (t, *J* = 8.4 Hz, 2H), 5.36 (s, 1H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 191.9, 161.2 (d, *J* = 248.4 Hz), 133.9, 131.7, 129.93, 129.91, 127.9, 125.9 (d, *J* = 8.4 Hz), 117.4, 116.0 (d, *J* = 22.9 Hz), 54.5.

HR-MS (ESI): $C_{15}H_{11}FN_2S$ [M-H]: 269.0543, Found: 269.0566.

2-Cyano-*N*-(2-flourophenyl)-2-phenylethanethioamide (31s)



Reaction Time: 2 h

Yield: 76%, yellowish orange gelly

R_f: 0.36 in 25% ethyl acetate in hexanes

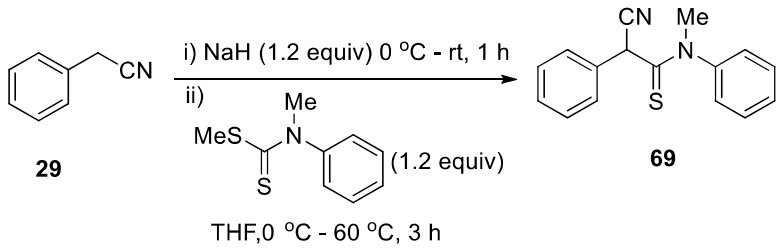
IR (KBr): ν (cm^{-1}) =3583, 3051, 2359, 2248, 1585, 1506, 1269, 1100, 760.

^{1}H NMR (700 MHz, DMSO-D_6) δ 12.01 (s, 1H), 7.66 (d, *J* = 7.7 Hz, 2H), 7.51 – 7.45 (m, 3H), 7.45 – 7.40 (m, 1H), 7.40 – 7.35 (m, 1H), 7.34 – 7.29 (m, 1H), 7.24 (td, *J* = 7.7, 1.1 Hz, 1H), 5.88 (s, 1H).

^{13}C NMR (175 MHz, DMSO-D_6) δ 195.7, 155.9 (d, *J* = 249.0 Hz), 133.7, 129.5 (d, *J* = 7.9 Hz), 129.0, 128.7, 128.0, 127.5, 126.3 (d, *J* = 12.1 Hz), 124.6 (d, *J* = 3.4 Hz), 118.0, 116.2 (d, *J* = 19.4 Hz), 51.2.

HR-MS (ESI): $C_{15}H_{11}FN_2S$ [M+Na]: 293.0519, Found: 293.0543.

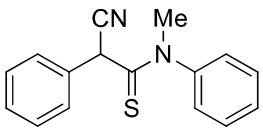
3.7.6 Procedure for the synthesis of 2-Cyano-*N*-methyl-*N*,2-diphenylethanethioamide (29)



To a stirring suspension of NaH (60% suspension in mineral oil) (1.2 equiv.) in THF (10.0 mL) at 0 ºC was added drop wise the benzylcyanide **29** (1 equiv.) in THFF (5.0 mL). After being further stirred for 1 h at room temperature, a solution of thiocarbamate (1.2 equiv.) in THF (5.0 mL) was added to the reaction mixture at 0 ºC and followed by further heat the reaction mixture at 60 ºC for 3h. 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 (25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography using EtOAc/Hexanes as eluent.

2-Cyano-*N*-methyl-*N*,2-diphenylethanethioamide (69)



Reaction Time: 3 h

Yield: 77%, white solid

Melting point: 100 – 102 ºC

R_f: 0.37 in 20% ethyl acetate in hexanes

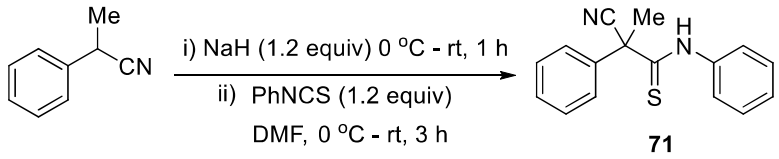
IR (KBr): 3056, 2889, 2831, 2557, 2251, 2190, 1495, 1385, 1150, 1114, 701.

^{1}H NMR (400 MHz, MeOD) δ 7.563 - 7.56(m, 1H), 7.46 - 7.41 (m, 2H), 7.36 – 7.18 (m, 4H), 7.11 -7.09 (m, 2H), 6.85 – 6.58 (m, 1H), 5.44 (s, 1H), 3.68 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 144.1, 132.7, 130.3, 129.3, 128.7, 127.8, 126.0, 125.4, 117.5, 49.6, 46.5.

HR-MS (ESI): Calcd. for $C_{16}H_{14}N_2S$ [M+H]: 267.0950, Found: 267.0938.

3.7.7 Procedure For the Synthesis of 2-cyano-*N*,2-diphenylpropanethioamide (31)

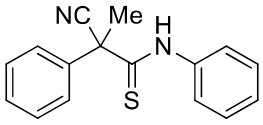


71

To a stirring suspension of NaH (60% suspension in mineral oil) (1.2 equiv.) in THF (10.0 mL) at 0 ºC was added drop wise the 2-phenylpropanenitrile (1 equiv.) in DMF (5.0 mL). After being further stirred for 1 h at room temperature, a solution of PhNCS (1.2 equiv.) in DMF (5.0 mL) was added to the reaction mixture at 0 ºC and followed by further stirring the reaction mixture at room temperature for 3 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 25

mL) & brine (25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography using EtOAc/Hexanes as eluent.

2-cyano-*N*,2-diphenylpropanethioamide (71)



Reaction Time: 3 h

Yield: 57%, Pale yellow solid

Melting point: 117 – 119 ºC

R_f: 0.32 in 15% ethyl acetate in hexanes

IR (KBr): 3271, 3057, 2833, 2388, 2244, 1598, 130, 1388, 1369, 1170, 1026.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.69 – 7.64 (m, 2H), 7.52 – 7.46 (m, 4H), 7.46 - 7.42 (m, 1H), 7.41 – 7.36 (m, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 2.21 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 138.1, 137.4, 129.6, 129.4, 129.1, 127.6, 126.2, 124.0, 121.2, 55.2, 28.5.

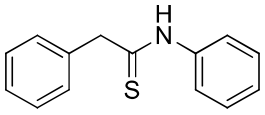
HR-MS (ESI): Calcd. for $C_{16}H_{14}N_2S$ [M+H]: 267.0950, Found: 267.0977.

3.7.8 Representative Procedure for the Synthesis of *N*,2-diphenylethanethioamide (73)

A Two necked necked round bottomed flask equipped with reflux condenser, is charged with magnesium turnings (2 equiv) and catalytic amount of iodine followed by dry THF was added. The mixture is heated at reflux until the purple iodine colour disappeared and to this solution was added benzylbromide in THF. The reaction mixture is allowed to stir at room temperature for 1 h. Then PhNCS diluted with THF was added to the reaction mixture at room temperature and allowed the reaction mixture at room temperature till completion of starting material. 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

(25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography using EtOAc/Hexanes as eluent.

***N*,2-diphenylethanethioamide (73)**



Reaction Time: 1 h

Yield: 92%, Pale yellow solid

Melting point: 86 – 88 ºC

R_f: 0.34 in 20% ethyl acetate in hexanes

IR (KBr): 3893, 3301, 3292, 2902, 2648, 2147, 120, 1338, 1121, 1072.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.47 – 7.40 (m, 2H), 7.38 - 7.33 (m, 5H), 7.24 (t, *J* = 7.6 Hz, 1H), 4.29 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 138.2, 135.1, 129.2, 129.0, 128.6, 127.7, 126.8, 123.6, 54.3.

HR-MS (ESI): Calcd. for $C_{14}H_{13}NS$ (M+H): 228.0841, found: 228.0834.

3.7.9. General Procedure for Optimization of Iodine mediated Site Selective C–S Bond Formation

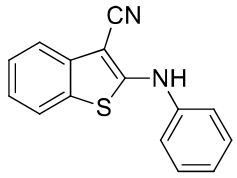
An oven-dried 8 mL reaction vial was charged with iodine (5 mol%), thioamide **7a**, AcOH (3 equiv), solvent (2.0 mL) followed by Oxidant (1.5 equiv) and was stirred at appropriate temperature. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was purified by flash chromatography.

3.7.10 General Procedure for Iodine Mediated Site Selective C–S Bond Formation

An oven-dried 8 mL reaction vial was charged with iodine (5 mol%), appropriate thioamide **7,** AcOH (3 equiv), DCE (2.0 mL) followed by Oxidant (1.5 equiv) and was stirred

at 80 ºC. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was purified by flash chromatography.

3-Cyano-2-(phenylamino)benzo[*b*]thiophene (42a)



Reaction Time: 2 h

Yield: 82%, Colourless solid

Melting point: 134 – 136 ºC

R_f: 0.36 in 15% ethyl acetate in hexane

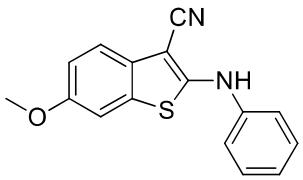
IR (KBr): ν (cm^{-1}) = 3436, 3263, 2211, 1602, 1561, 1426, 1081, 792, 744.

^{1}H 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.

3-Cyano-6-methoxy-2-(phenylamino)benzo[*b*]thiophene (42b)



Reaction Time: 1.5 h

Yield: 68%, Grey colour solid

Melting Point: 197 – 198 ºC

R_f: 0.29 in 15% ethyl acetate in hexanes

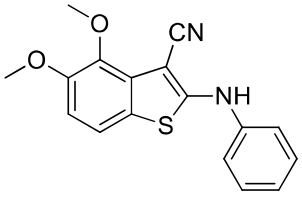
IR (KBr): ν (cm^{-1}) = 3435, 3260, 2929, 2202, 1566, 1513, 1247, 1028, 832, 751.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.32 – 7.24 (m, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.07 (s, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H).

^{13}C NMR (175 MHz, DMSO-D_6) δ 162.8, 156.9, 137.4, 133.8, 128.0, 126.0, 123.8, 122.9, 122.4, 118.2, 115.2, 114.6, 79.6, 55.3.

HR-MS (ESI): Calcd. for $C_{16}H_{12}ON_2S$ (M+H): 281.0743, found: 281.0712.

3-Cyano-4, 5-dimethoxy-2-(phenylamino)benzo[*b*]thiophene (42c)



Reaction Time: 1 h

Yield: 98%, yellow solid

Melting Point: 196 – 198 °C

R_f: 0.29 in 30% ethyl acetate in hexanes

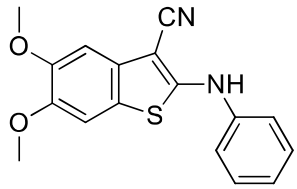
IR (KBr): 3436, 3243, 3138, 3088, 2209, 1597, 1556, 1464, 1440, 1417, 1265, 1039

^{1}H NMR (700 MHz, DMSO) δ = 10.05 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.40 - 7.39 (m, 4H), 7.17 – 7.14 (m, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ = 161.8, 150.9, 141.7, 139.9, 131.4, 129.8, 125.2, 122.2, 120.2, 117.5, 116.2, 110.5, 81.2, 61.8, 56.7.

HR-MS (ESI): Calcd. for $C_{17}H_{14}N_2O_2S$ (M+H): 311.0849, found: 311.0870.

3-Cyano-5, 6-dimethoxy-2-(phenylamino)benzo[*b*]thiophene (42d)



Reaction Time: 2 h

Yield: 44%, yellow solid

Melting point: 180 – 182 °C

R_f: 0.32 in 25% ethyl acetate in hexane

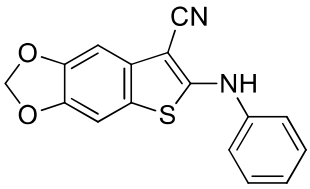
IR (KBr): ν (cm^{-1}) = 3272, 2993, 2963, 2199, 1601, 1491, 1474, 1402, 1298, 1246, 1083, 1033, 960, 836, 762.

^{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: 311.0824.

3-Cyano-5, 6-methylenedioxy-2-(phenylamino)benzo[*b*]thiophene (42e)



Reaction Time: 2 h

Yield: 52%, brown solid

Melting point: 222 – 225 ºC

R_f: 0.37 in 20% ethyl acetate in hexane

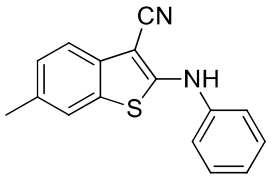
IR (KBr): ν (cm^{-1}) = 3441, 3255, 2371, 2345, 2204, 1561, 1474, 1295, 1052, 945, 823, 695.

^{1}H NMR (400 MHz, DMSO-D_6) δ = 9.97 (s, 1H), 7.41 (s, 1H), 7.39 – 7.34 (m, 4H), 7.10 (t, *J* = 5.9 Hz, 1H), 6.99 (s, 1H), 6.07 (s, 2H).

^{13}C NMR (100 MHz, DMSO-D_6) 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.

3-Cyano-6-methyl-2-(phenylamino)benzo[*b*]thiophene (42f)



Reaction Time: 1 h

Yield: 71%, Colourless solid

Melting Point: 155 – 157 ºC

R_f: 0.33 in 15% ethyl acetate in hexane

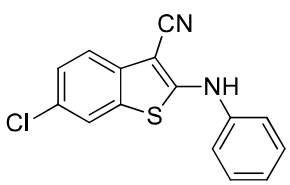
IR (KBr): ν (cm^{-1}) = 3455, 3248, 2368, 2213, 1597, 1567, 1475, 1323, 757, 696.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.38 – 7.30 (m, 3H), 7.25 - 7.17 (m, 3H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 140.3, 134.0, 133.7, 129.7, 129.4, 127.5, 124.8, 121.9, 119.9, 119.4, 115.6, 83.7, 21.5.

HR-MS (ESI): Calcd. for $C_{16}H_{12}N_2S$ (M+H): 265.0794, found: 265.0788.

3-Cyano-6-chloro-2-(phenylamino)benzo[*b*]thiophene (42g)



Reaction Time: 2 h

Yield: 86%, Colourless solid

Melting Point: 182 – 184 ºC

R_f: 0.33 in 15% ethyl acetate in hexanes

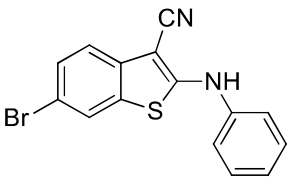
IR (KBr): ν (cm^{-1}) = 3678, 3253, 2920, 2211, 1604, 1567, 1464, 1397, 1247, 1062, 750, 694.

^{1}H NMR (700 MHz, DMSO-D_6) δ = 10.35 (s, 1H), 7.96 (s, 1H), 7.55 – 7.31 (m, 6H), 7.19 (t, *J* = 7.0 Hz, 1H)

^{13}C NMR (100 MHz, DMSO-D_6) δ = 161.5, 140.7, 135.9, 129.8, 129.5, 127.5, 126.4, 124.8, 122.2, 120.8, 119.8, 114.7, 81.5.

HR-MS (ESI): Calcd. for $C_{15}H_9ClN_2S$ (M+H): 285.0248, found: 285.0235.

3-Cyano-6-bromo-2-(phenylamino)benzo[*b*]thiophene (42h)



Reaction Time: 2 h

Yield: 81%, White solid

Melting Point: 200 – 202 ºC

R_f: 0.33 in 15% ethyl acetate in hexanes

IR (KBr): ν (cm^{-1}): 3211, 2328, 2209, 1601, 1556, 1461, 1391, 1249, 1058.

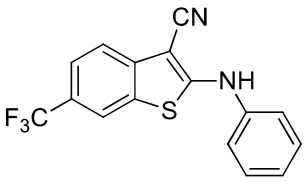
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.56 – 7.48 (m, 2H), 7.47 - 7.43 (m, 2H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.30 - 7.23 (m, 2H).

^{13}C NMR (175 MHz, DMSO-D_6) δ 161.4, 140.6, 136.2, 130.1, 129.5, 129.0, 124.9, 124.8, 120.8, 120.1, 115.2, 114.6, 81.5.

HR-MS (ESI): Calcd. for $C_{15}H_9BrN_2S$ (M+H): 328.9743 and 330.9722

Found: 328.9759 and 330.9743.

3-Cyano-2-(phenylamino)-6-(trifluoromethyl)benzo[*b*]thiophene (42j)



Reaction Time: 2 h

Yield: 65%, white solid

Melting Point: 187 – 189 ºC

R_f: 0.32 in 15% ethyl acetate in hexanes

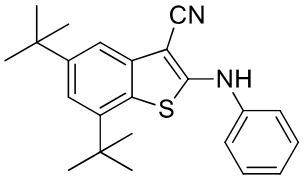
IR (KBr): ν (cm^{-1}) = 3255, 3148, 3106, 2210, 1599, 1569, 1474, 1317, 1123, 1085, 697.

^{1}H NMR (300 MHz, DMSO-D_6) δ 10.60 (s, 1H), 8.28 (s, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.49 – 7.38 (m, 4H), 7.30 – 7.16 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 139.7 (q, *J* = 1 Hz), 139.5, 130.1, 128.6, 126.1, 125.7 (q, *J* = 33 Hz), 124.3 (q, *J* = 270 Hz), 123.2 (q, *J* = 4 Hz), 121.05, 121.03, 119.6, 119.4 (q, *J* = 4 Hz), 82.7.

HR-MS (ESI): Calcd. for $C_{16}H_9F_3N_2S$ (M+H): 319.0511, found: 319.0532.

3-Cyano-5,7-di-*tert*-butyl-2-(phenylamino)benzo[*b*]thiophene (42k)



Reaction Time: 2 h

Yield: 92%, colourless solid

Melting Point: 235 – 237 ºC

R_f: 0.38 in 15% ethyl acetate in hexanes

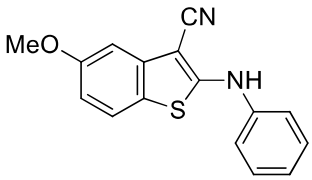
IR (KBr): ν (cm^{-1}) = 3122, 2961, 2321, 2231, 1596, 1561, 1415, 1309, 1252, 863.

^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.39 (s, 1H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.27 (d, *J* = 7.7 Hz, 2H), 7.19 (s, 1H), 7.15 (brs, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 1.38 (s, 9H), 1.29 (s, 9H).

^{13}C NMR (175 MHz, $CDCl_3$) δ = 159.3, 149.7, 144.3, 140.3, 137.6, 129.9, 124.7, 123.5, 119.8, 119.3, 115.9, 114.9, 84.8, 35.9, 35.1, 31.7, 29.8.

HR-MS (ESI): Calcd. for $C_{23}H_{26}N_2S$ (M+Na): 385.1709, found: 385.1692.

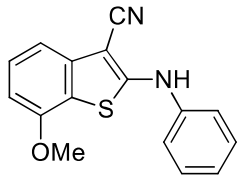
3-Cyano-5-methoxy-2-(phenylamino)benzo[*b*]thiophene (42la) & 3-Cyano-7-methoxy-2-(phenylamino)benzo[*b*]thiophene (42lb)



Reaction Time: 1.5 h

Yield: 73%, grey colour solid

Melting point: 150 – 157 ºC



R_f: 0.30 in 15% ethyl acetate in hexanes

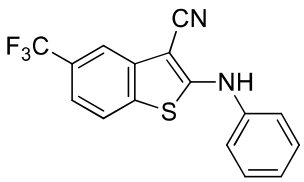
IR (KBr): ν (cm^{-1}) = 3261, 3003, 2830, 2387, 2202, 1593, 1553, 1460, 1414, 1295, 1034.

^{1}H NMR (700 MHz, $CDCl_3$) (Mixture of 2 isomers **8ja** : **8jb** = 1:0.2) δ 7.43 - 7.40 (m, 5H), 7.38 – 7.29 (m, 7H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.20 - 7.18 (m, 2H), 7.07 (d, *J* = 2.8 Hz, 1H), 6.84 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 3.94 (s, 3H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) (Mixture of 2 Isomers **8ja** & **8jb**) δ 161.7, 161.2, 158.9, 153.8, 140.2, 140.1, 138.1, 137.8, 129.7 (2C), 127.4, 124.9 (2C), 122.6, 120.7, 120.3, 120.1, 120.0, 116.8, 115.6, 112.8, 112.4, 104.1, 102.9, 83.8, 83.5, 55.7, 55.6. (One carbon less. It may merged with the 124.9 and 122.2).

HR-MS (ESI): Calcd. for $C_{16}H_{12}ON_2S$ (M+H): 281.0743, found: 281.0741.

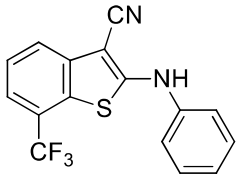
3-Cyano-2-(phenylamino)-5-(trifluoromethyl)benzo[*b*]thiophene (42ma) & 3-Cyano-2-(phenylamino)-7-(trifluoromethyl)benzo[*b*]thiophene (42mb)



Reaction Time: 2 h

Yield: 62%, pale brown colour solid

Melting point: 168 -173 ºC



R_f: 0.32 in 15% ethyl acetate in hexanes

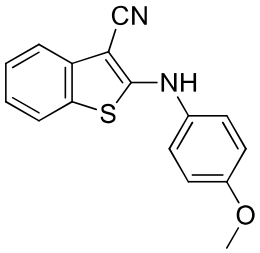
IR (thin film): ν (cm^{-1}) = 3446, 3209, 2986, 2362, 2216, 1652, 1558, 1365, 1269, 1116, 814.

^{1}H NMR (400 MHz, DMSO-D_6) (Mixture of 2 compounds **8ka** : **8kb** = 1:1 ratio) δ 10.57 (s, 2H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.75 -7.72 (m, 1H), 7.69 – 7.57 (m, 3H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.51 – 7.34 (m, 8H), 7.30 – 7.14 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$: so much complex

HR-MS (ESI): Calcd. for $C_{16}H_9F_3N_2S$ (M+H): 319.0511, found: 319.0531.

3-Cyano-2-((4-methoxyphenyl)amino)benzo[*b*]thiophene (42n)



Reaction Time: 1.5 h

Yield: 81%, colourless solid

Melting point: 193 – 195 ºC

R_f: 0.34 in 10% ethyl acetate in hexane

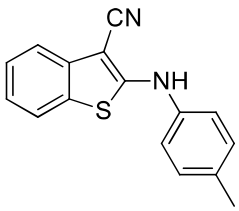
IR (KBr): ν (cm^{-1}) = 3440, 3261, 2210, 2202, 1598, 1566, 1513, 1466, 1438, 1247, 1027, 751.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 7.9 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: 281.0725.

3-Cyano-2-((4-methylphenyl)amino)benzo[*b*]thiophene (42o)



Reaction Time: 1 h

Yield: 89%, white solid

Melting Point: 190 – 192 ºC

R_f: 0.33 in 15% ethyl acetate in hexanes

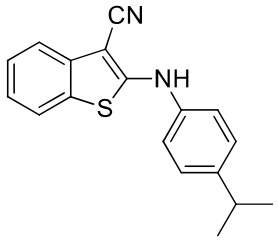
IR (KBr): ν (cm^{-1})3690, 3247, 2211, 1608, 1565, 1468, 1327, 1218, 812.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.43 – 7.34 (m, 1H), 7.30 (s, 1H), 7.27 – 7.17 (m, 5H), 2.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 137.3, 136.7, 135.3, 130.3, 128.9, 126.0, 123.4, 121.8, 120.8, 119.6, 115.4, 82.7, 20.9.

HR-MS (ESI): Calcd. for $C_{16}H_{12}N_2S$ (M+H): 265.0794, found: 265.0804.

3-Cyano-2-((4-isopropylphenyl)amino)benzo[*b*]thiophene (42p)



Reaction Time: 2 h

Yield: 82%, white solid

Melting Point: 174 -176 ºC

R_f: 0.31 in 15% ethyl acetate in hexanes

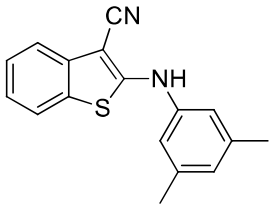
IR (KBr): ν (cm^{-1}) = 3252, 2954, 2211, 1554, 1439, 1324, 832.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.42 – 7.35 (m, 1H), 7.33 (s, 1H), 7.30 – 7.26 (m, 4H), 7.23 – 7.17 (m, 1H), 2.99 - 2.88 (m, 1H), 1.28 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 146.3, 137.7, 136.8, 129.0, 127.8, 126.1, 123.5, 121.9, 120.7, 119.6, 115.6, 82.7, 33.7, 24.1.

HR-MS (ESI): Calcd. for $C_{18}H_{16}N_2S$ (M+Na): 315.0926, found: 315.0928.

3-Cyano-2-((3,5-dimethylphenyl)amino)benzo[*b*]thiophene (42q)



Reaction Time: 1 h

Yield: 74%, white solid

Melting Point: 191- 193 ºC

R_f: 0.35 in 15% ethyl acetate in hexanes

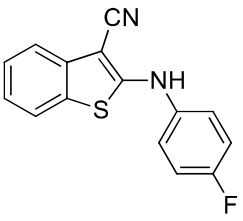
IR (KBr): ν (cm^{-1}) = 3449, 3263, 3111, 2919, 2365, 2206, 1598, 1569, 1466, 1333, 1165, 705

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (t, *J* = 8.1 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.15 (s, 1H), 6.97 (s, 2H), 6.84 (s, 1H), 2.35 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 139.9, 139.7, 136.6, 129.2, 127.0, 126.1, 123.5, 121.9, 119.7, 117.9, 115.5, 83.2, 21.5.

HR-MS (ESI): Calcd. for $C_{16}H_{14}N_2S$ (M+H): 279.0950, found: 279.0951.

3-Cyano-2-((4-fluorophenyl)amino)benzo[*b*]thiophene (42r)



Reaction Time: 1.5 h

Yield: 73%, colourless solid

Melting point: 186 – 188 °C

R_f:

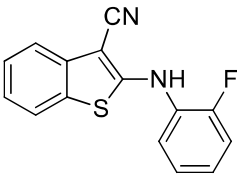
IR (KBr): ν (cm^{-1}) = 3435, 3248, 2365, 2214, 1576, 1513, 1234, 825, 740.

^{1}H NMR (300 MHz, DMSO-D_6) δ 10.23 (s, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.49 - 7.37 (m, 4H), 7.32 - 7.17 (m, 3H).

^{13}C NMR (100 MHz, DMSO-D_6) δ 161.4, 159.1 (d, *J* = 241.8 Hz), 137.2 (d, *J* = 18.4 Hz), 128.4, 126.1, 123.4, 123.3, 123.2, 122.5, 118.6, 116.2 (d, *J* = 22.8 Hz), 114.9, 81.6.

HR-MS (ESI): Calcd. for $C_{15}H_9FN_2S$ (M+H): 269.0543, found: 269.0540

3-Cyano-2-((2-fluorophenyl)amino)benzo[*b*]thiophene (42s)



Reaction Time: 1.5 h

Yield: 95%, colourless solid

Melting point: 121 – 123 °C

R_f: 0.32 in 15% ethyl acetate in hexanes

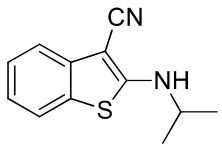
IR (KBr): ν (cm^{-1}) = 3251, 3090, 2957, 2370, 2203, 1901, 1554, 1498, 1420, 1364, 1259, 1234, 1197, 842

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 - 7.57 (m, 3H), 7.47 – 7.38 (m, 1H), 7.31 – 7.23 (m, 1H), 7.23 – 7.09 (m, 4H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 159.1, 153.9 (d, *J* = 246.1 Hz), 136.4, 129.6, 128.4 (d, *J* = 11.4 Hz), 126.3, 125.6 (d, *J* = 7.4 Hz), 124.9 (d, *J* = 3.9 Hz), 124.1, 122.0, 120.4, 120.2, 116.3 (d, *J* = 19.1 Hz), 114.7, 85.9.

HR-MS (ESI): $C_{15}H_9FN_2S$ [M+H]: 269.0543, Found: 269.0568.

3-Cyano-2-(isopropylamino)benzo[*b*]thiophene (66b)

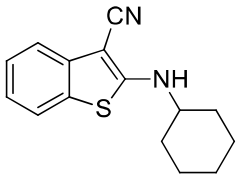


Reaction Time: 1 h

Yield: 98%, white solid

$R_{f,}$ Melting Point, IR, 1H NMR, 13C NMR and Mass values are reported in section: **3.6.7**

3-Cyano-2-(cyclohexylamino)benzo[*b*]thiophene (66c)

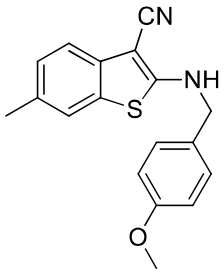


Reaction Time: 1 h

Yield: 64%, white solid

$R_{f,}$ Melting Point, IR, 1H NMR, 13C NMR and Mass values are reported in section: **3.6.7**

3-Cyano-2-((4-methoxybenzyl)amino)-6-methylbenzo[*b*]thiophene (66h)

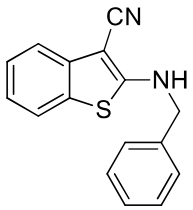


Reaction Time: 1 h

Yield: 65%, yellow solid

$R_{f,}$ Melting Point, IR, 1H NMR, 13C NMR and Mass values are reported in section: **3.6.7**

3-Cyano-2-(benzylamino)benzo[*b*]thiophene (66i)

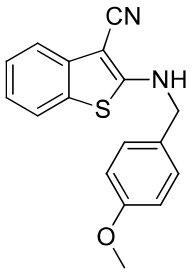


Reaction Time: 1 h

Yield: 85%, white solid

$R_{f,}$ Melting Point, IR, 1H NMR, 13C NMR and Mass values are reported in section: **3.6.7**

3-Cyano-2-(4-methoxybenzylamino)benzo[*b*]thiophene (66j)

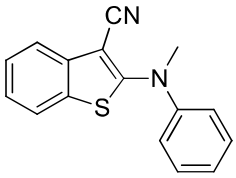


Reaction Time: 1 h

Yield: 63%, colourless solid

R_f, Melting Point, IR, 1H NMR, 13C NMR and Mass values are reported in section: **3.6.7**

3-Cyano-2-(methyl(phenyl)amino)benzo[*b*]thiophene (70)



Reaction Time: 2 h

Yield: 59%, yellowish orange colour gel

R_f: 0.38 in 15% ethyl acetate in hexanes

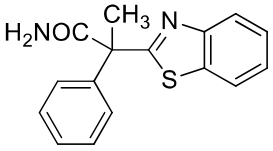
IR (thin film): ν (cm^{-1}) = 3685, 2991, 23322, 2265, 2197, 1700, 1526, 1490, 1269, 1080, 788.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.52 -7.47 (m, 3H), 7.40 - 7.36 (m, 4H), 7.24 – 7.17 (m, 1H), 3.75 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 146.7, 139.0, 130.0, 129.6, 127.6, 125.9, 125.5, 123.4, 121.4, 119.9, 115.9, 82.5, 43.6.

HR-MS (ESI): Calcd. for $C_{16}H_{12}N_2S$ [M+H]: 265.0794, Found: 265.0766.

2-(Benzo[*d*]thiazol-2-yl)-2-phenylacetamide(72)



Reaction Time: 3 h

Yield: 42%, Colourless solid

Melting Point: 134 – 136 ºC

R_f: 0.29 in 40% ethyl acetate in hexanes

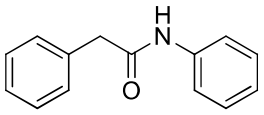
IR (KBr): ν (cm^{-1}): 3420, 3313, 2924, 2388, 2294, 1682, 1580, 1449, 1021, 761.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.99 (s, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.0 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.40 - 7.35 (m, 3H), 7.34 (t, *J* = 7.0 Hz, 1H), 5.90 (s, 2H), 2.21 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 174.2, 152.4, 143.3, 134.9, 128.8, 127.9, 127.2, 126.5, 125.6, 123.1, 121.6, 57.1, 27.2.

HR-MS (ESI): Calcd. for $C_{16}H_{14}N_2OS$ (M+H): 283.0900, found: 283.0899.

***N*,2-diphenylacetamide (74)**



Reaction Time: 1 h

Yield: 92%, pale yellow solid

Melting Point: 134 – 136 ºC

R_f: 0.32 in 25% ethyl acetate in hexanes

IR (KBr): ν (cm^{-1}): 3283, 3255, 2903, 2364, 1659, 1619, 1557, 1442, 1168, 1079.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 7 Hz, 2H), 7.35 - 7.32 (m, 3H), 7.28 (t, *J* = 7.7 Hz, 2H), 7.21 (s, 1H), 7.08 (t, *J* = 7.0 Hz, 1H), 3.73 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 137.7, 134.5, 129.5, 129.2, 128.9, 127.6, 124.5, 120.0, 44.7.

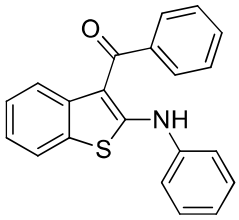
HR-MS (ESI): Calcd. for $C_{14}H_{13}NO$ (M+H): 212.1070, found: 212.1079.

3.7.11 Representative procedure for the reaction of Grignard Reagent with 2-Amino-3-cyanobenzo[*b*]thiophene Derivative.

Argon filled Two necked round bottomed flask equipped with reflux condenser, is charged with 2-Amino-3-cyanobenzo[*b*]thiophene derivatives (1 equiv) dry THF, followed by 2.2 equiv of PhMgBr in THF solution was added to the reaction mixture at 0 ºC. The mixture was heated at reflux until the completion of stating material (approximately 8h). 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 (25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. To the crude products, Ethanol and 6N

HCl was added followed by reflux at 120 ºC for 1-2 h. After complete consumption of the starting materials (monitored by TLC), the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with DCM. The combined organic layer washed with water (3 x 25 mL) & brine (25 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.

Phenyl(2-(phenylamino)benzo[*b*]thiophen-3-yl)methanone (75a)



Reaction Time: 8 + 1 h

Yield: 57%, Yellow colour solid

Melting point: 93 – 95 ºC

R_f: 0.32 in 5% ethyl acetate in hexane

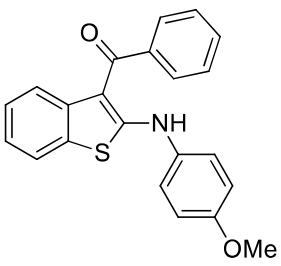
IR (KBr): ν (cm^{-1}) = 3057, 2354, 1586, 1538, 1455, 1351, 1255, 1232, 1197, 1174, 1054, 1022, 897, 849, 799, 752, 723, 696.7

^{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: 330.0933.

(2-((4-Methoxyphenyl)amino)benzo[*b*]thiophen-3-yl)(phenyl)methanone (75n)



Reaction Time: 8 + 1 h

Yield: 49%, Yellow solid

Melting Point: 134 – 136 ºC

R_f: 0.33 in 15% ethyl acetate in hexanes

IR (KBr): ν (cm^{-1}): 3202, 2994, 1713, 1616, 1508, 1269, 1025, 760.

^1H NMR (300 MHz, $CDCl_3$) δ 11.83 (s, 1H), 7.65 - 7.61 (m, 2H), 7.57 – 7.43 (m, 4H), 7.41 - 7.38 (m, 2H), 7.07 - 7.96 (m, 4H), 6.68 (d, *J* = 7.5 Hz, 1H), 3.85 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 166.4, 157.7, 141.5, 137.2, 133.0, 130.7, 128.9, 128.6, 127.7, 124.9, 123.9, 122.4, 121.7, 121.6, 114.9, 109.2, 55.6.

HR-MS (ESI): Calcd. for $C_{22}H_{17}NO_2S$ [M+H]: 360.1053, Found: 360.1081

3.8 ^{1}H and ^{13}C NMR Spectrum of Selected Compounds

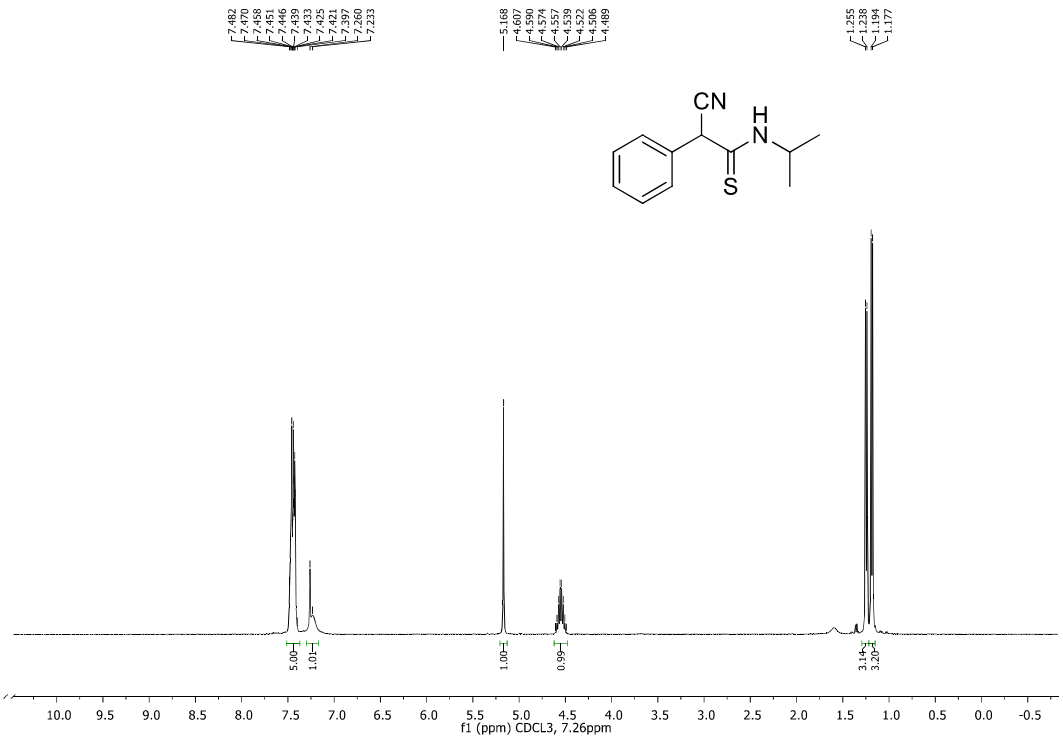


Figure 3.4a: ^{1}H NMR Spectrum of **65b**

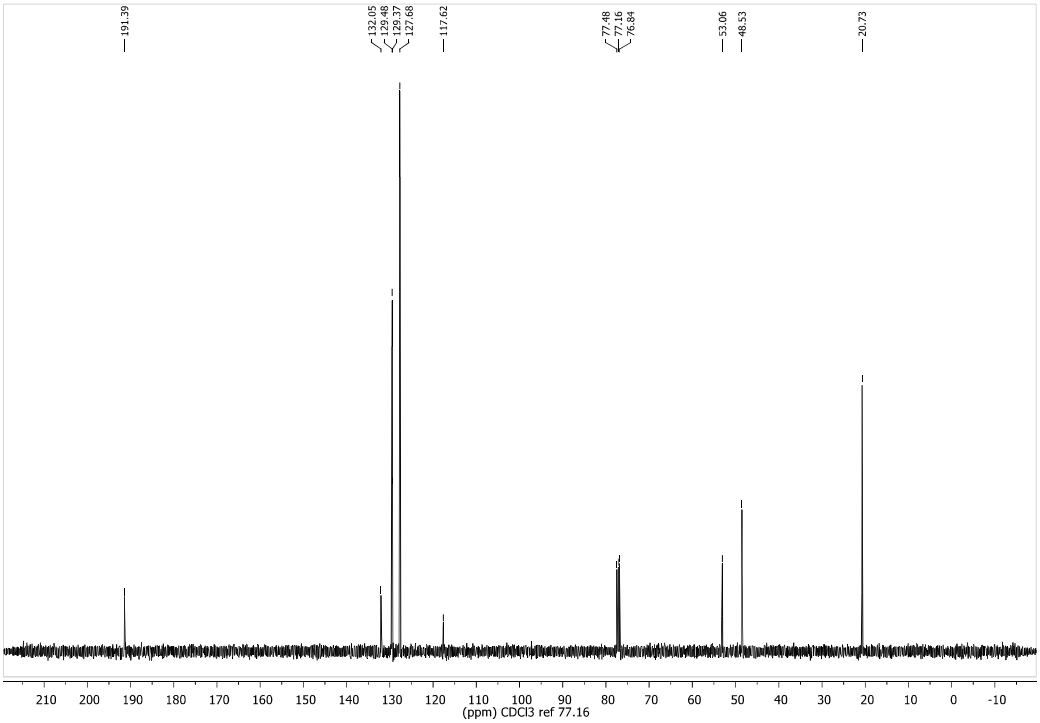


Figure 3.4b: ^{13}C NMR Spectrum of **65b**

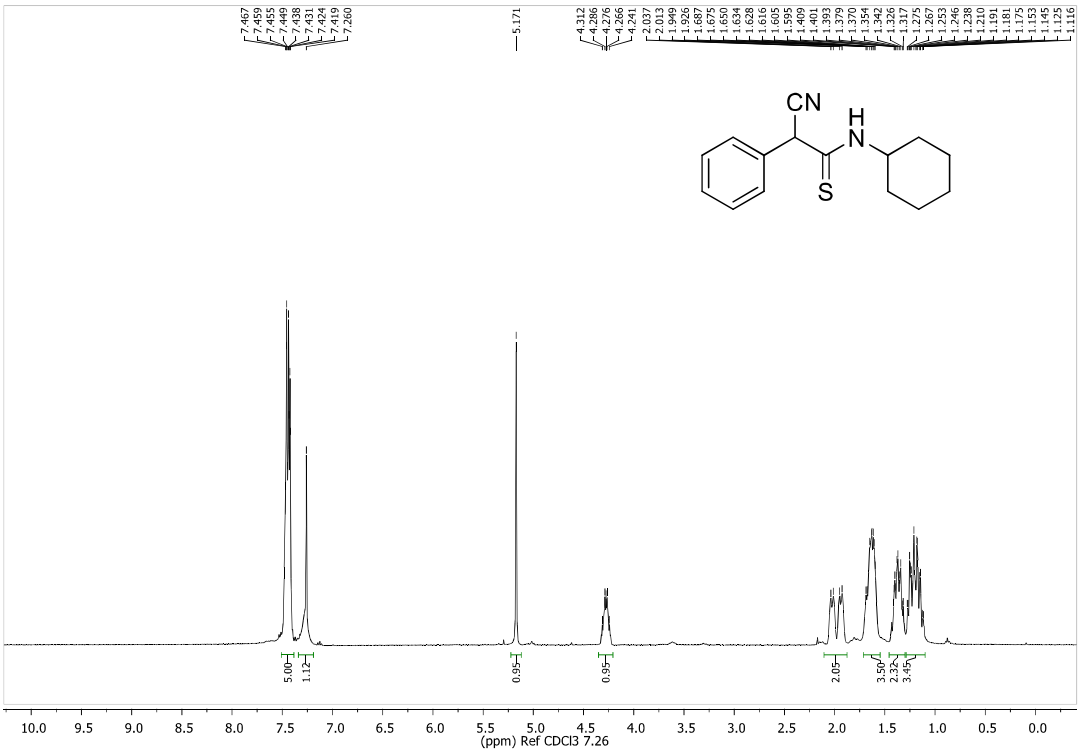


Figure 3.5a: ^{1}H NMR Spectrum of **65c**

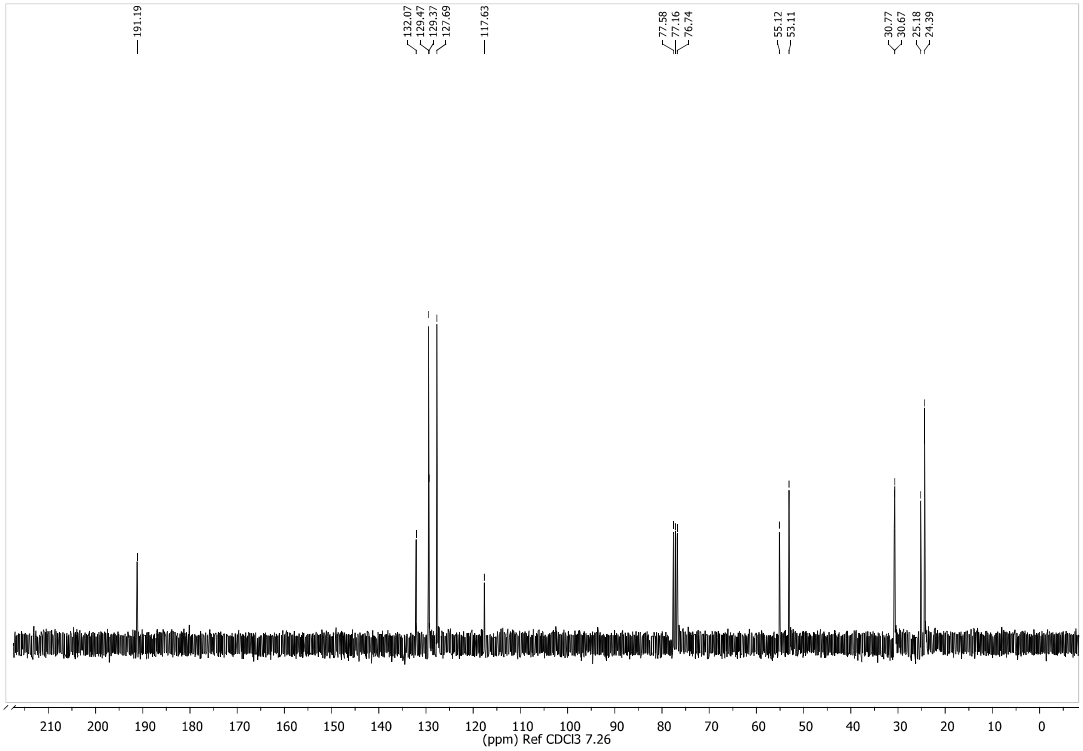


Figure 3.5b: ^{13}C NMR Spectrum of **65c**

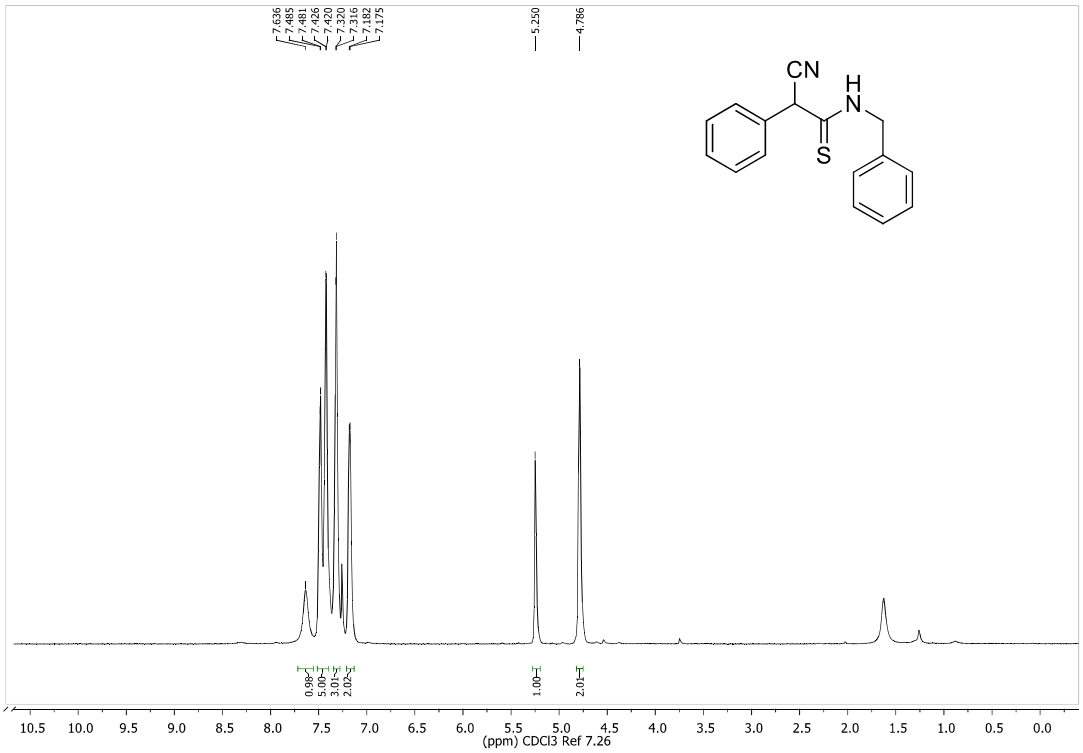


Figure 3.6a: ^{1}H NMR Spectrum of **65i**

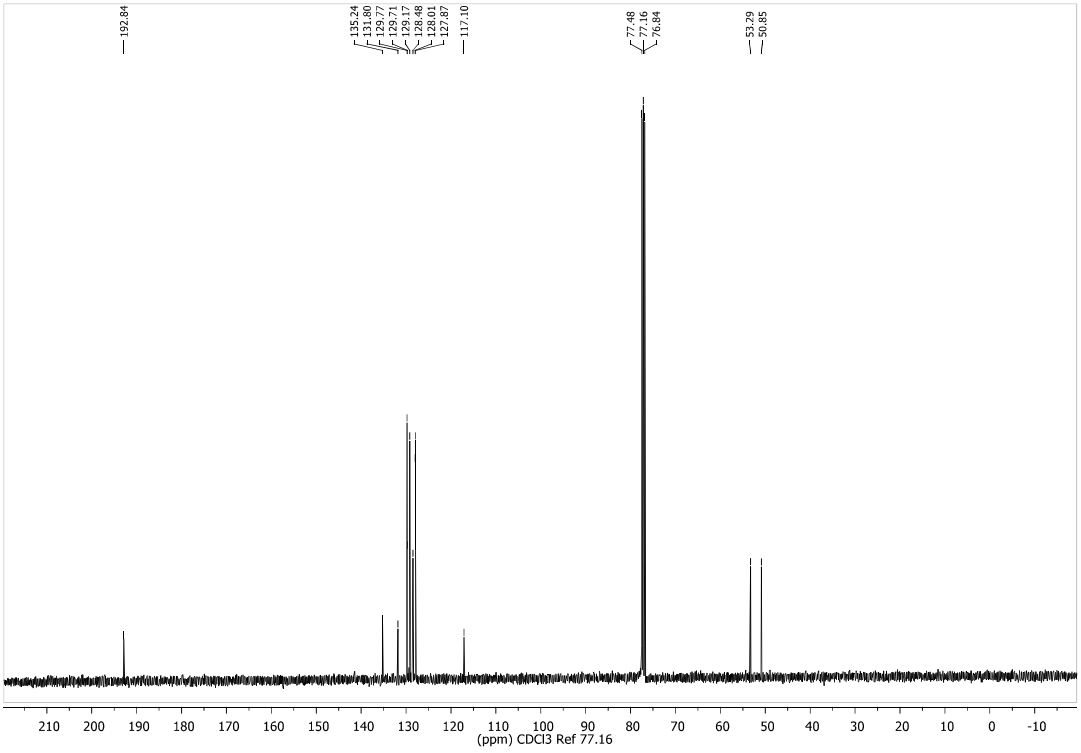


Figure 3.6b: ^{13}C NMR Spectrum of **65i**

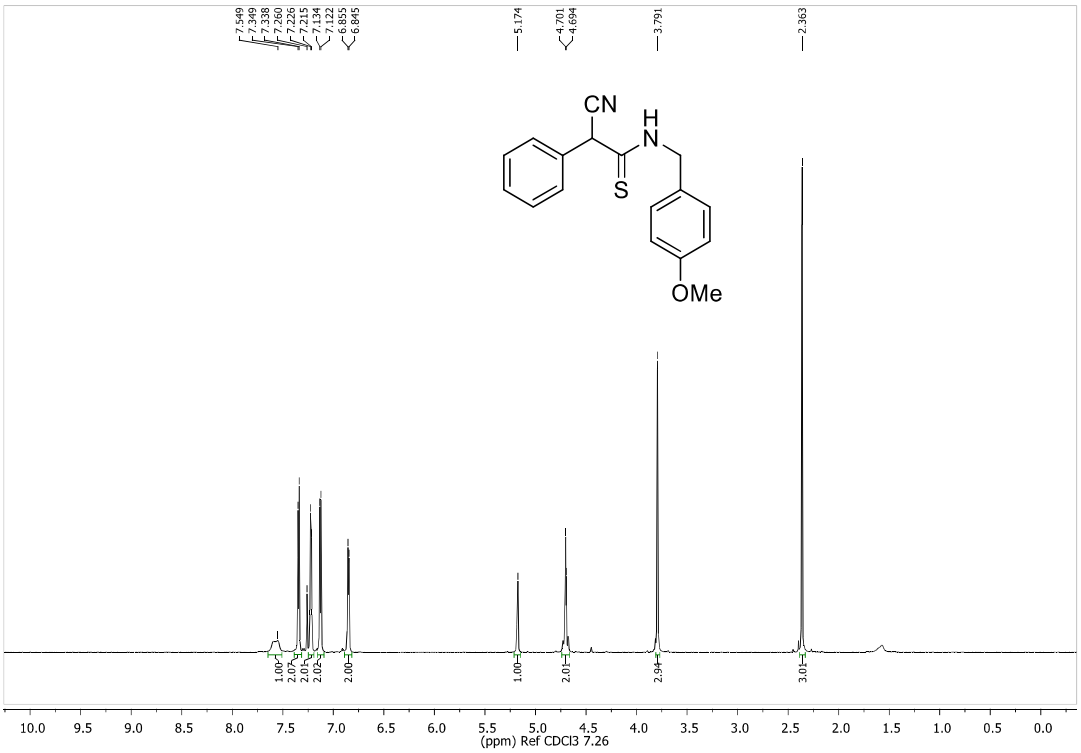


Figure 3.7a: ^{1}H NMR Spectrum of **65j**

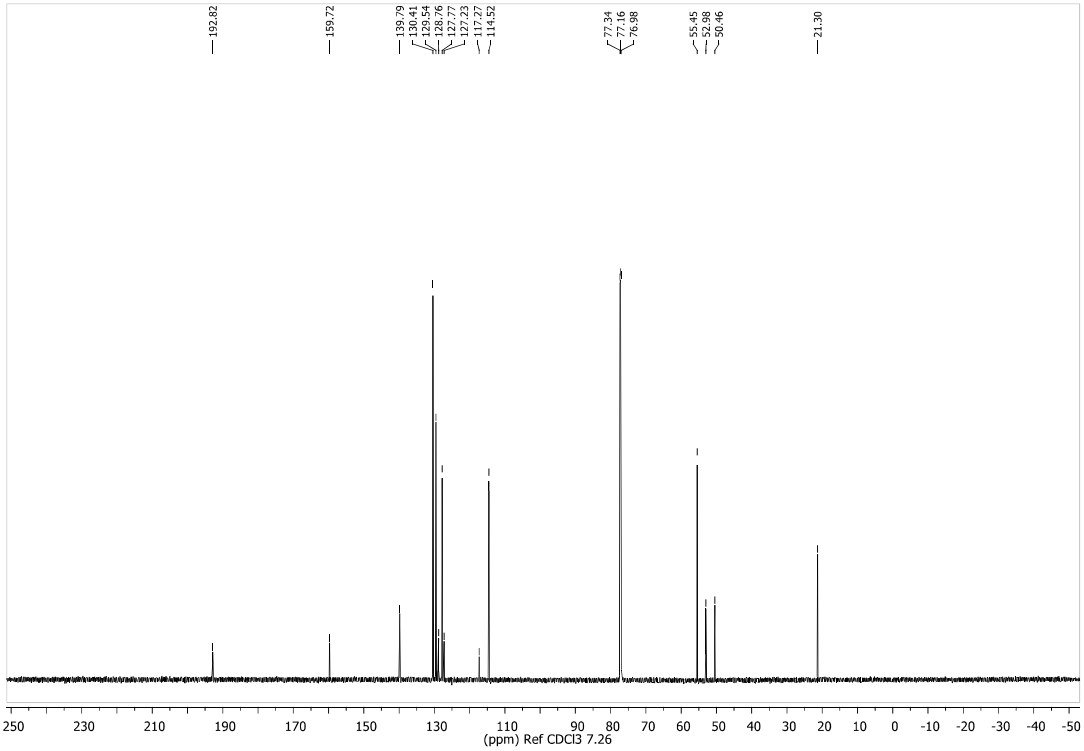


Figure 3.7b: ^{13}C NMR Spectrum of **65j**

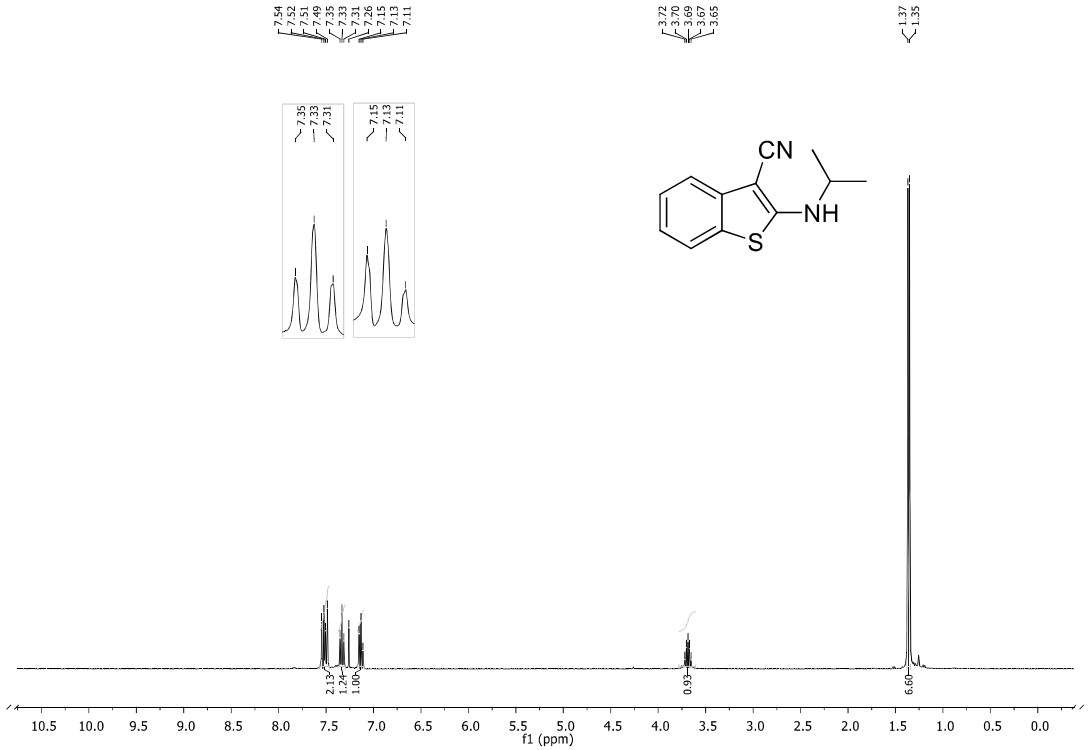


Figure 3.8a: ^{1}H NMR Spectrum of **66b**

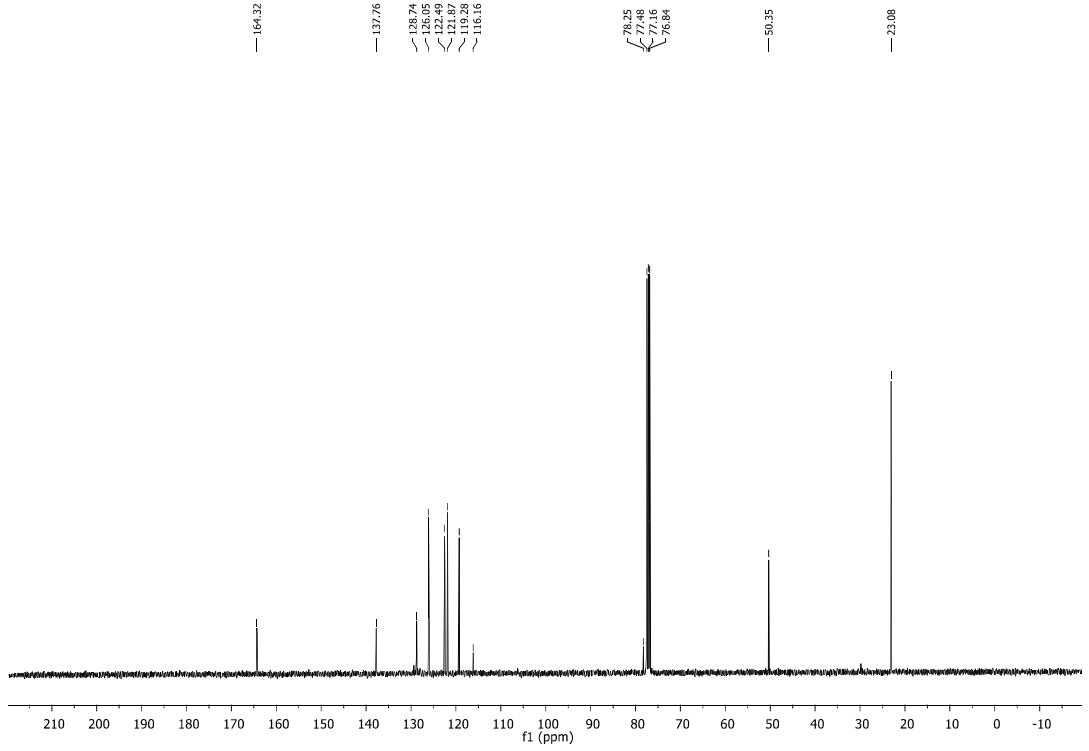


Figure 3.8b: ^{13}C NMR Spectrum of **66b**

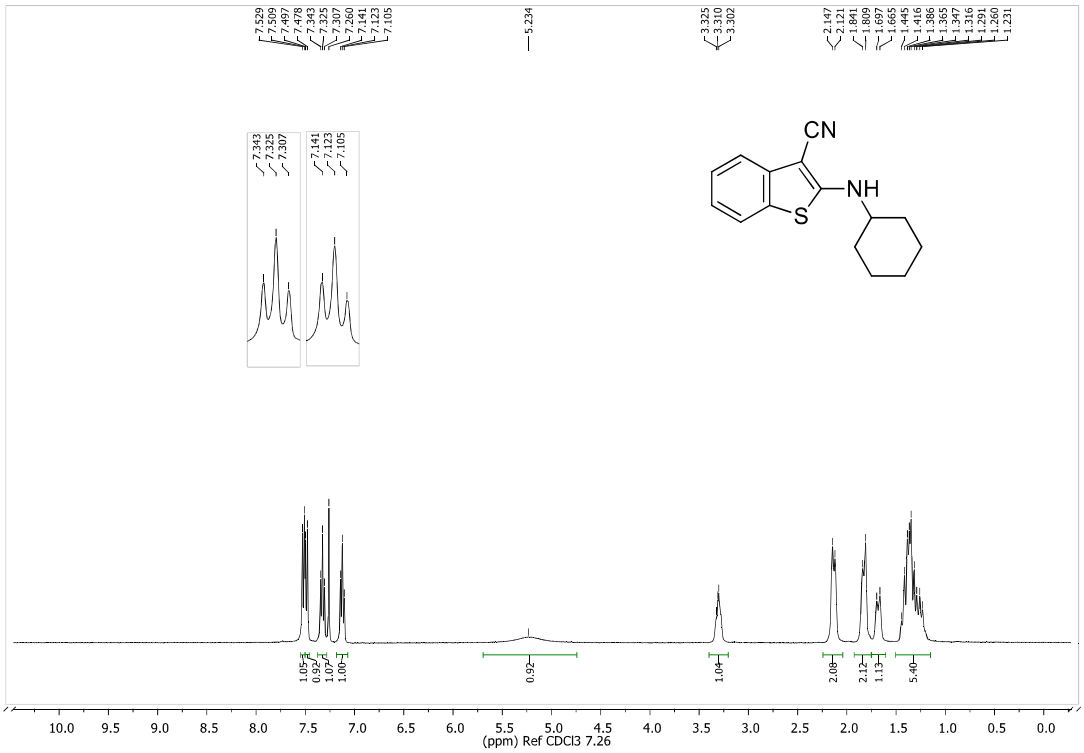


Figure 3.9a: ^{1}H NMR Spectrum of **66c**

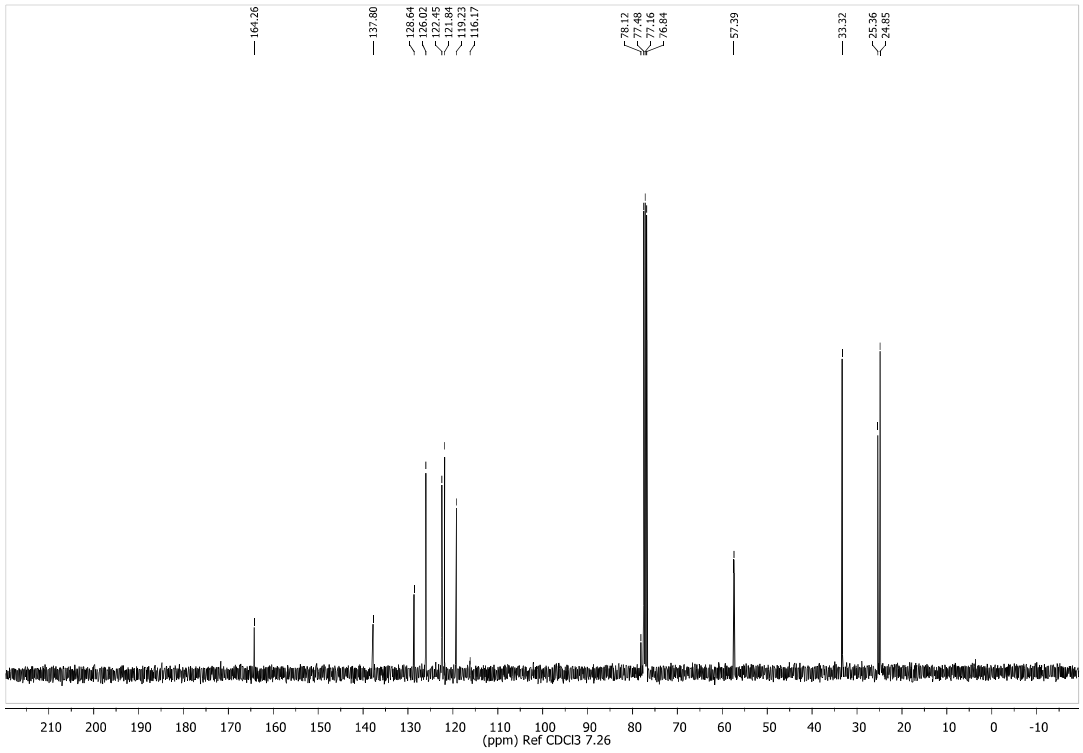


Figure 3.9b: ^{13}C NMR Spectrum of **66c**

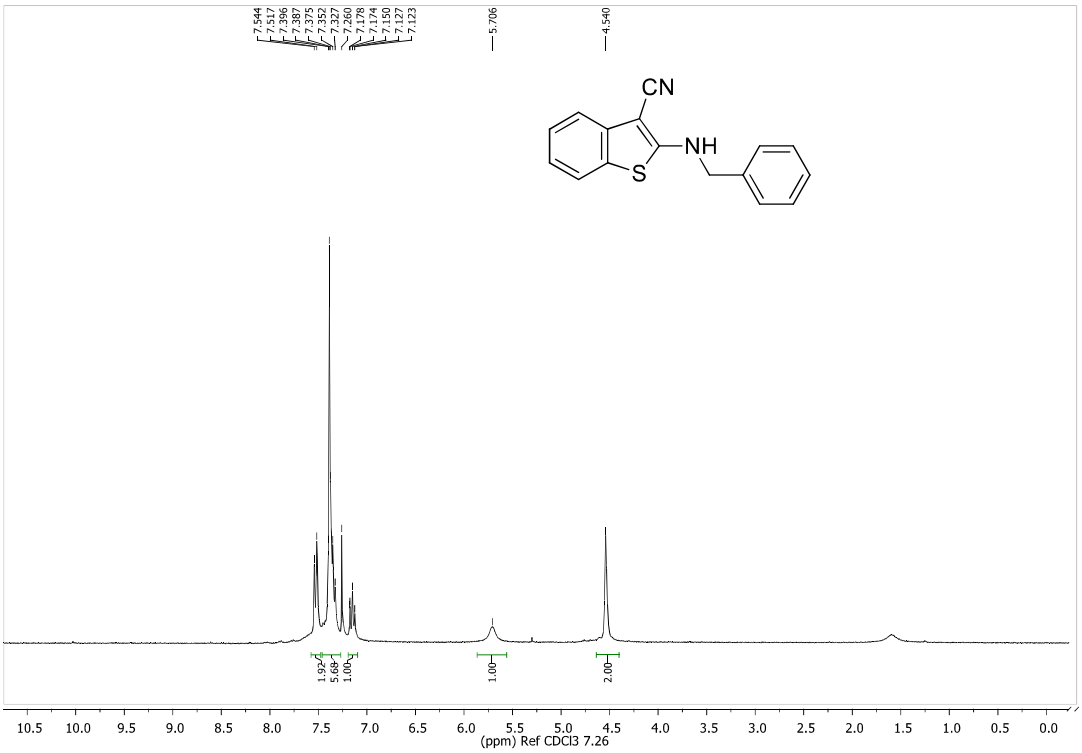


Figure 3.10a: ^{1}H NMR Spectrum of **66i**

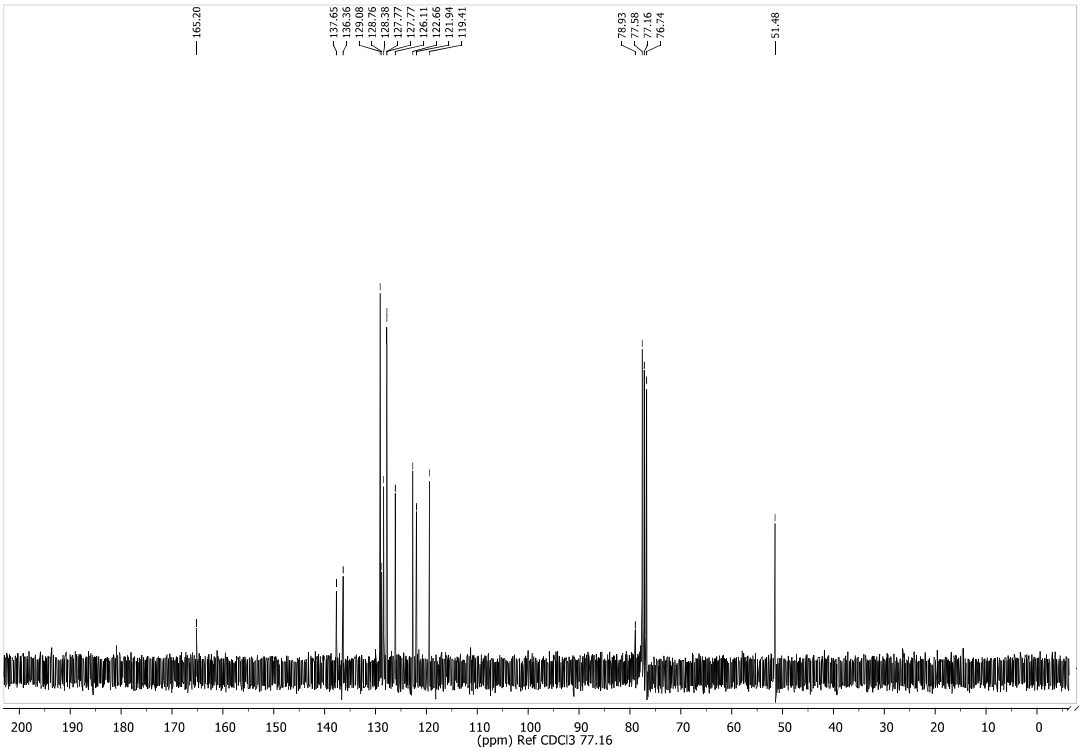


Figure 3.10b: ^{13}C NMR Spectrum of **66i**

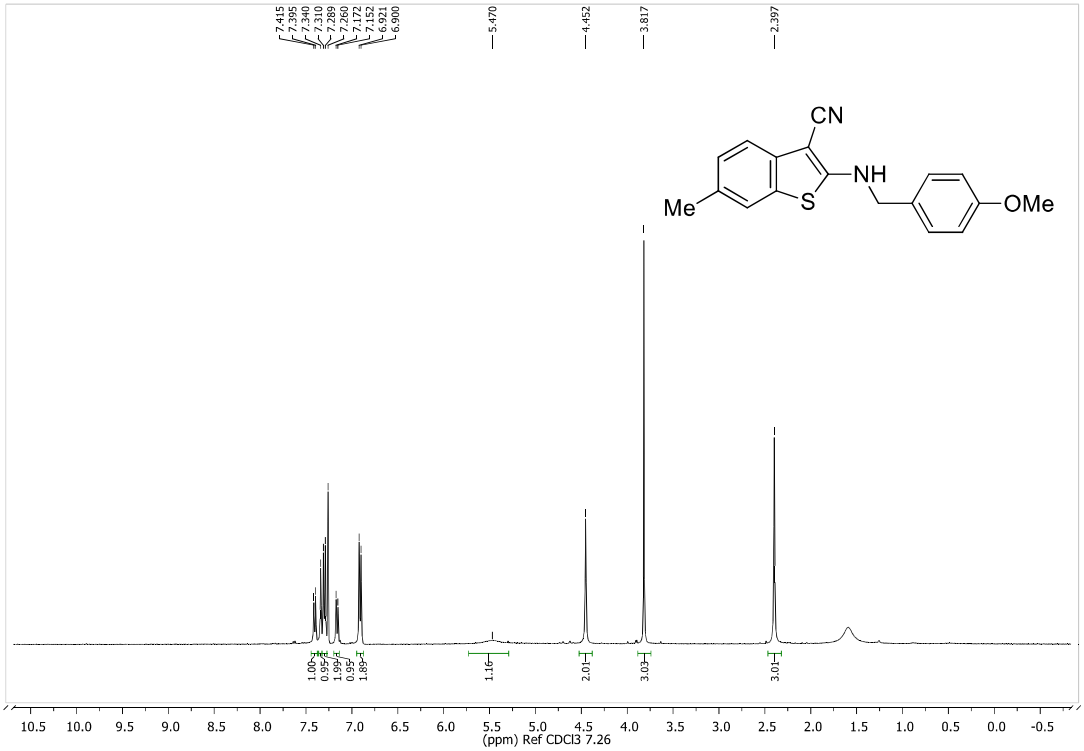


Figure 3.11a: ^{1}H NMR Spectrum of **66j**

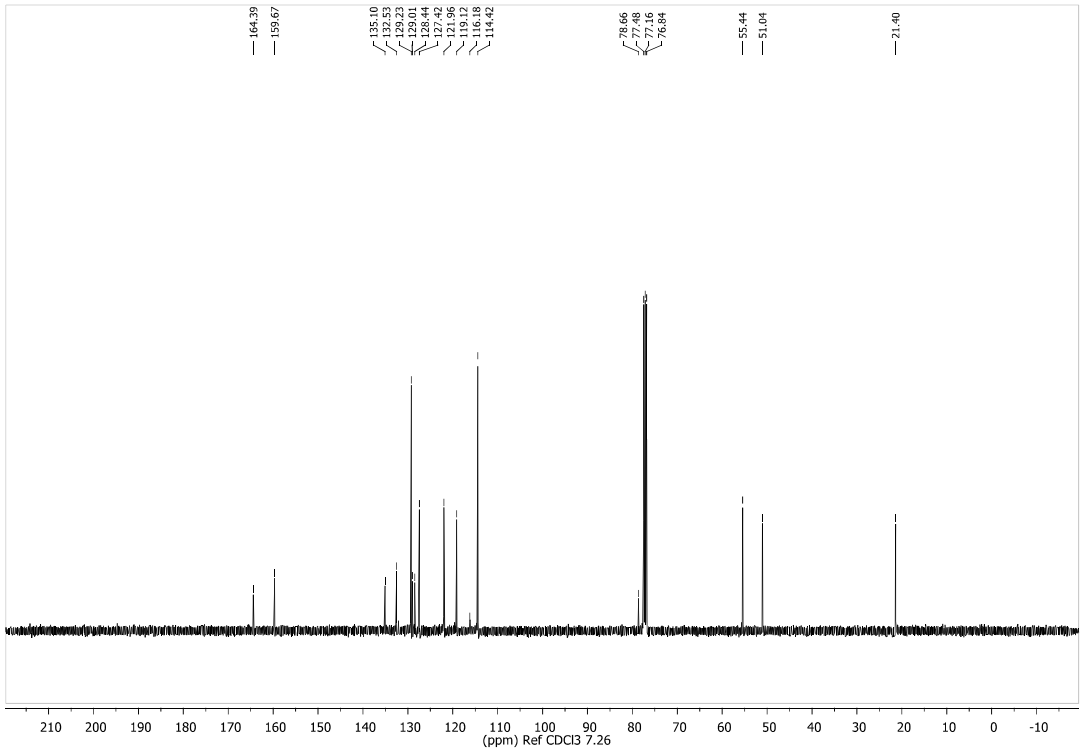


Figure 3.11b: ^{13}C NMR Spectrum of **66j**

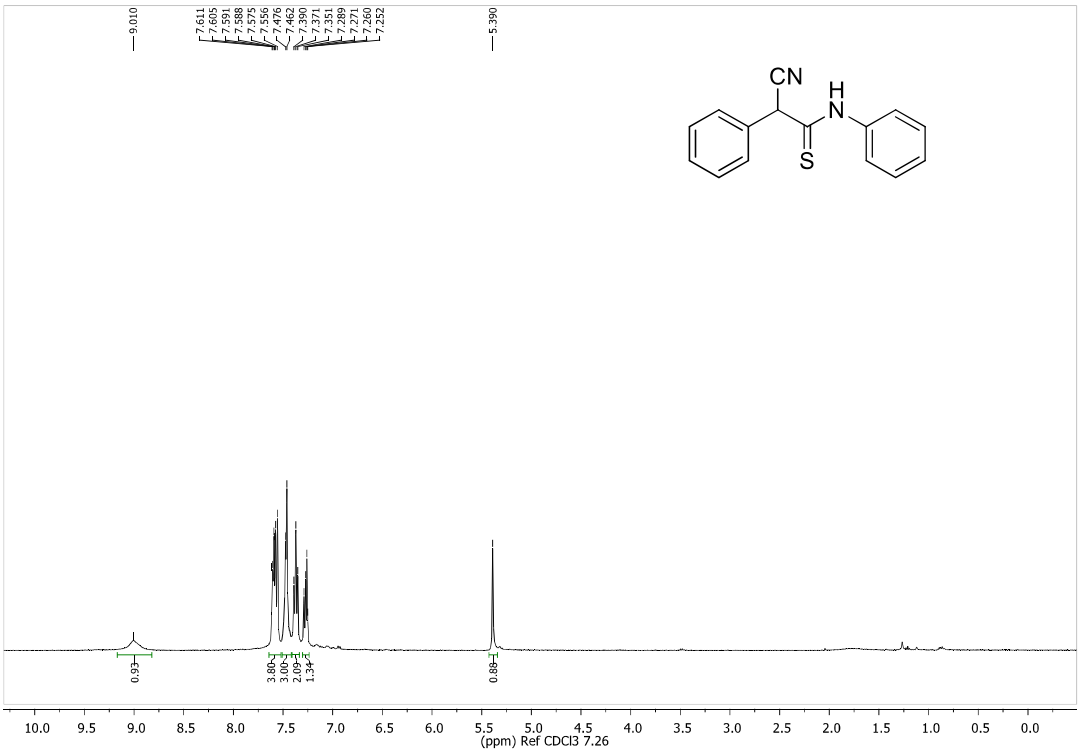


Figure 3.12a: ^{1}H NMR Spectrum of **31a**

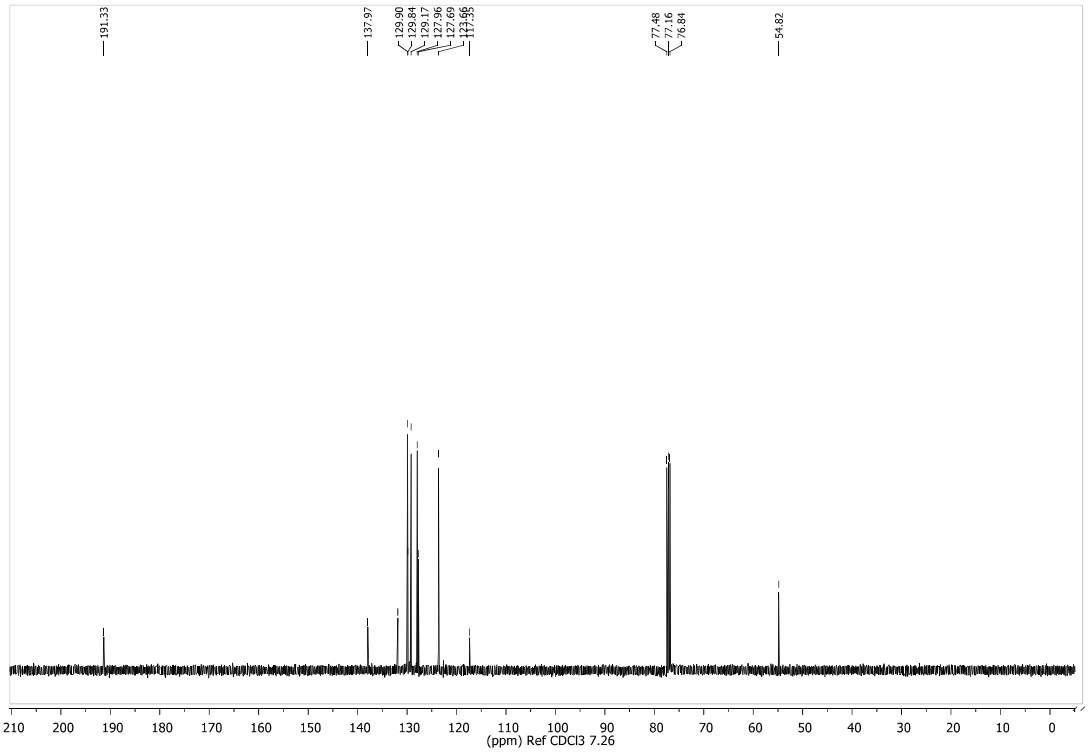


Figure 3.12b: ^{13}C NMR Spectrum of **31a**

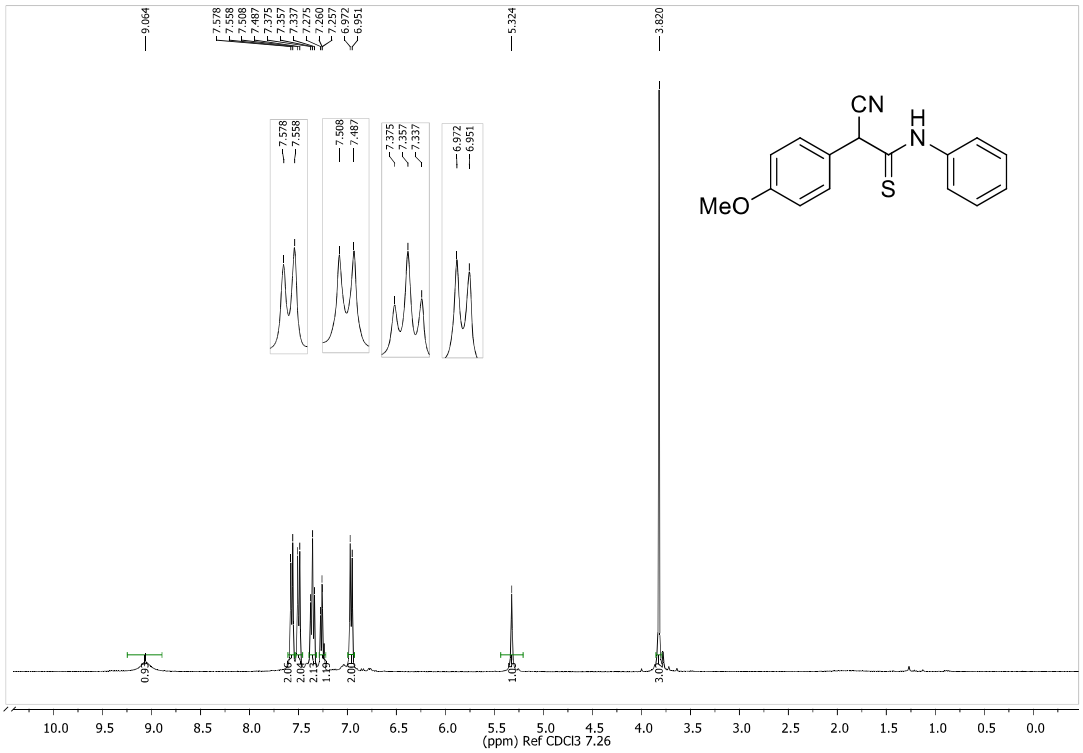


Figure 3.13a: ^{1}H NMR Spectrum of **31b**

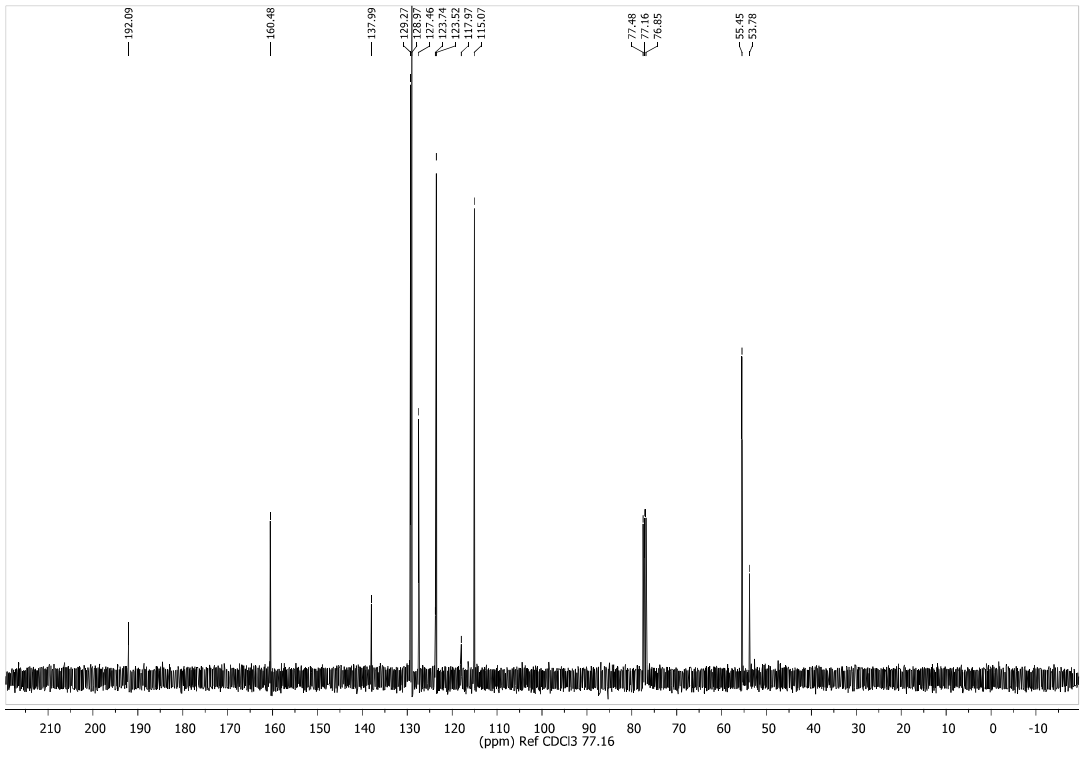


Figure 3.13b: ^{13}C NMR Spectrum of **31b**

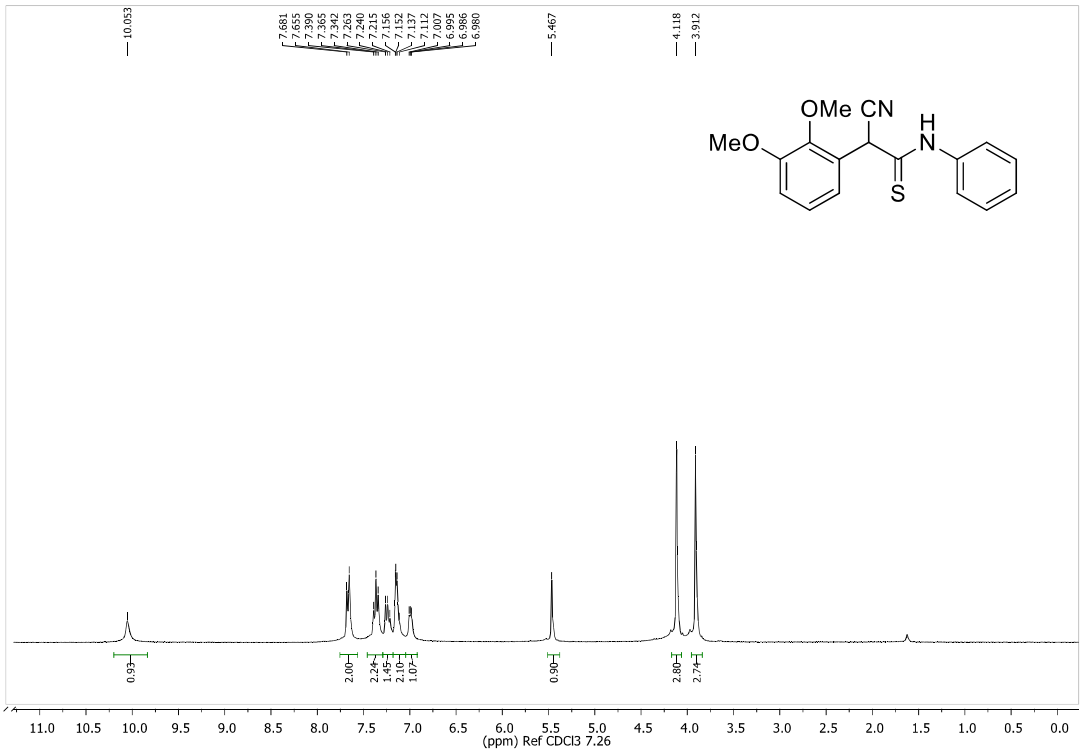


Figure 3.14a: ^{1}H NMR Spectrum of **31c**

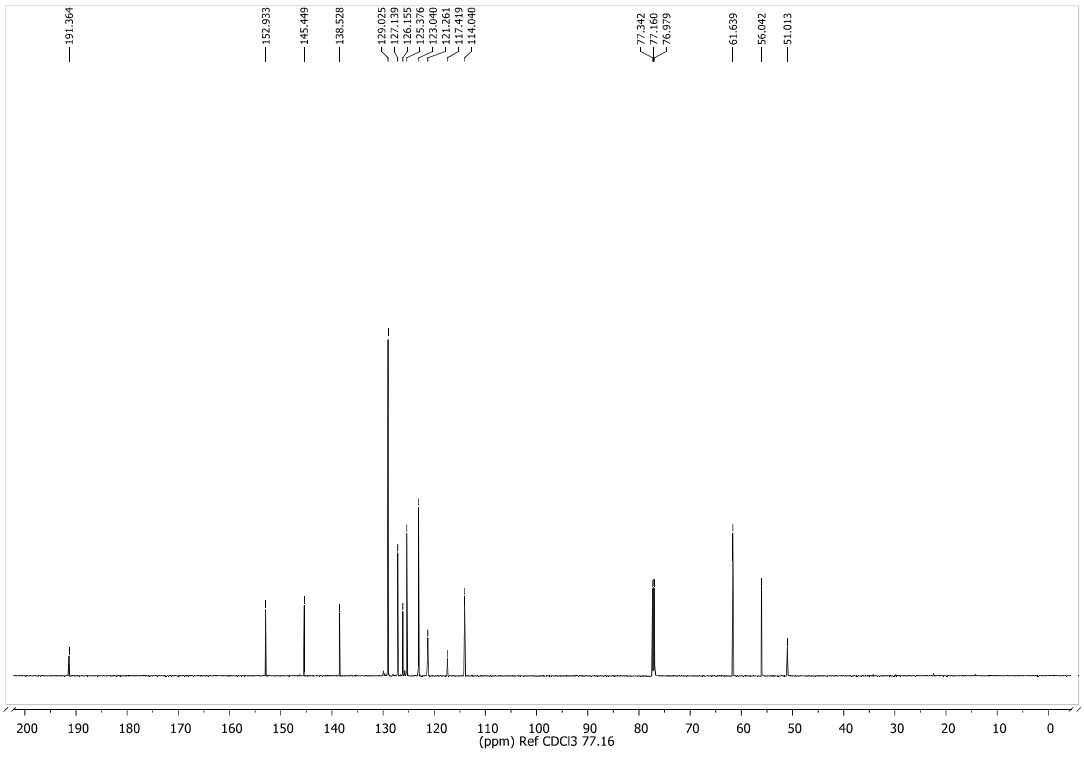


Figure 3.14b: ^{13}C NMR Spectrum of **31c**

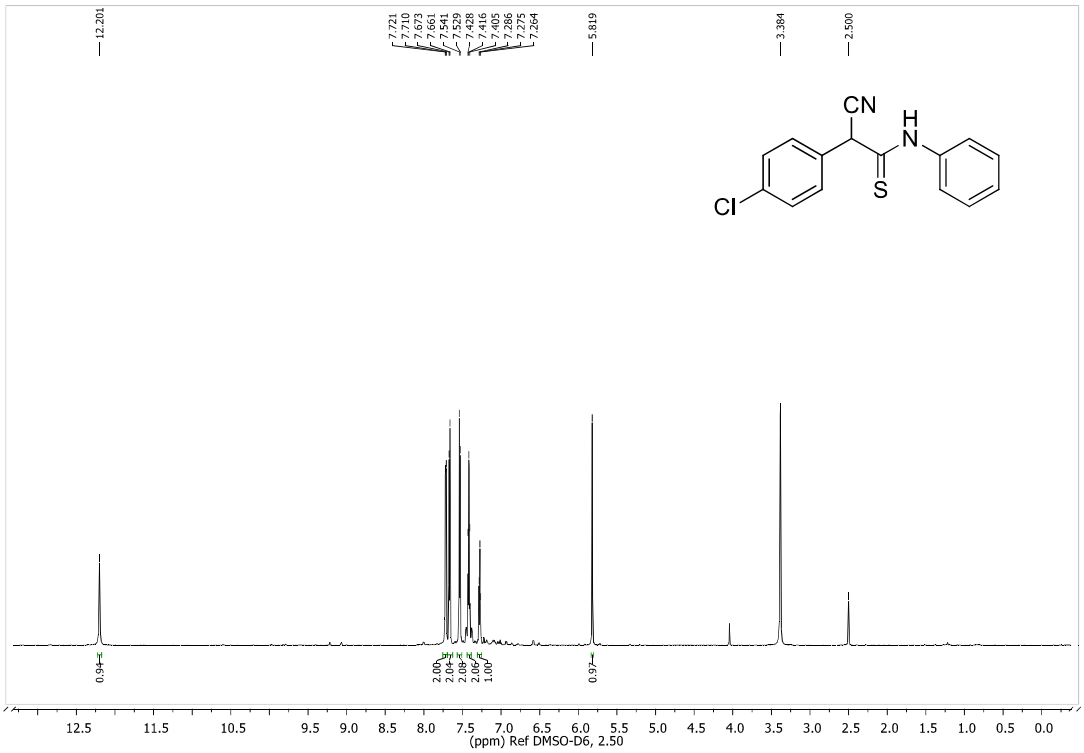


Figure 3.15a: ^{1}H NMR Spectrum of **31g**

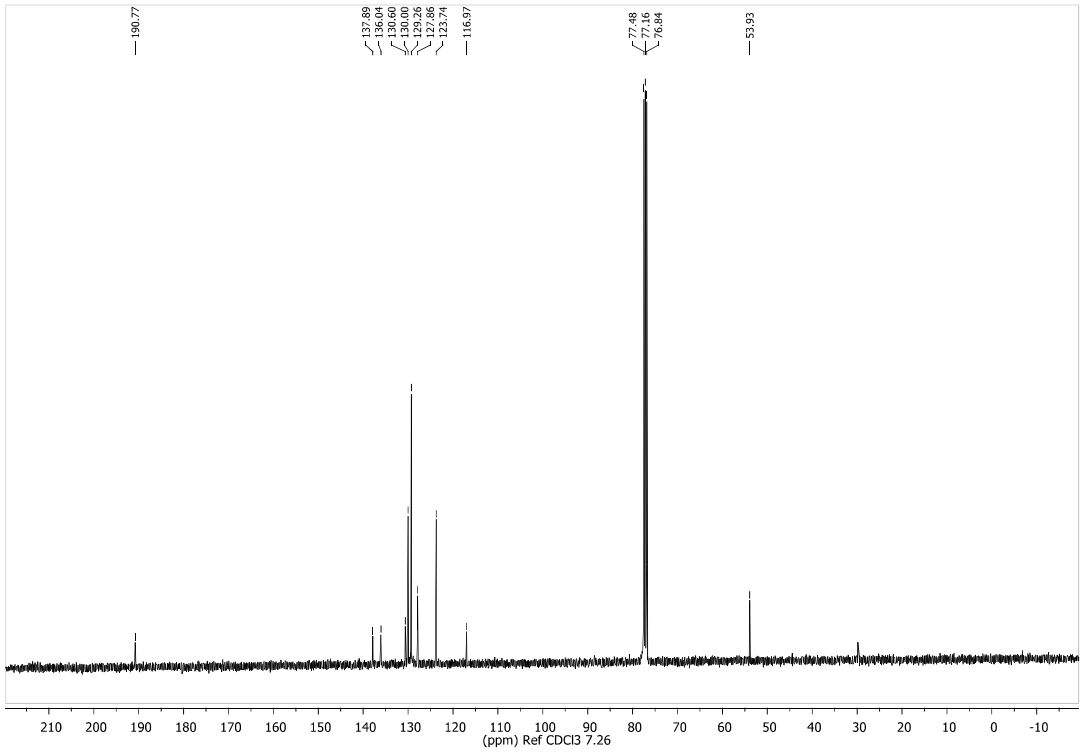


Figure 3.15b: ^{13}C NMR Spectrum of **31g**

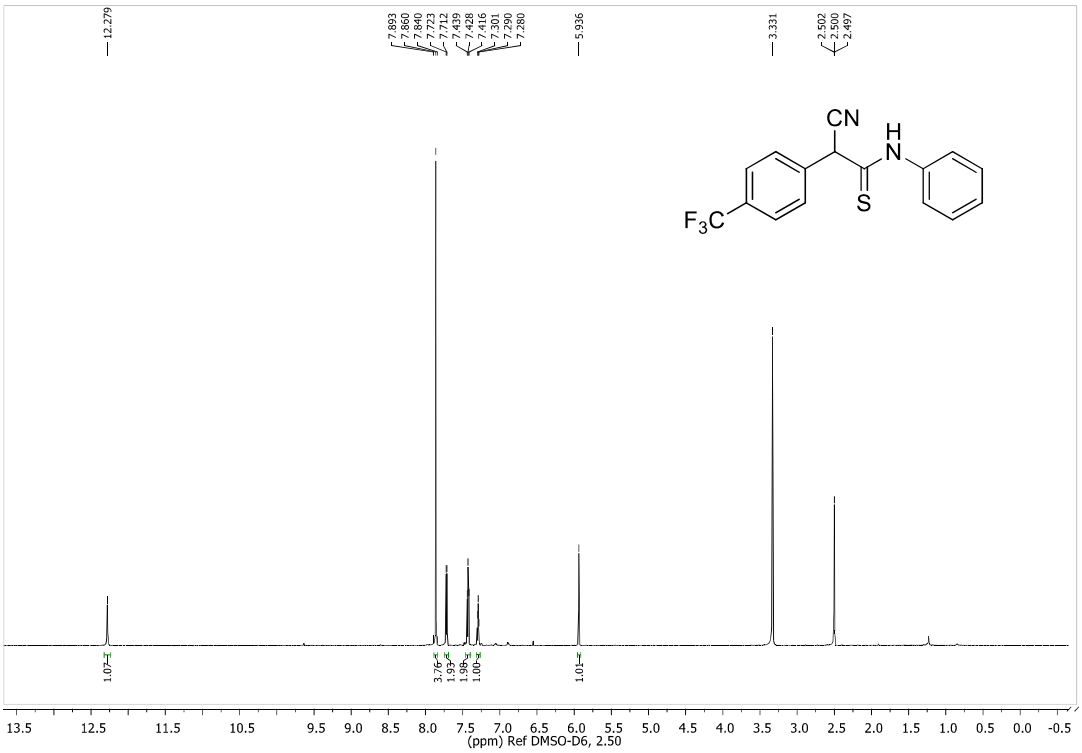


Figure 3.16a: ^{1}H NMR pectrum of **31j**

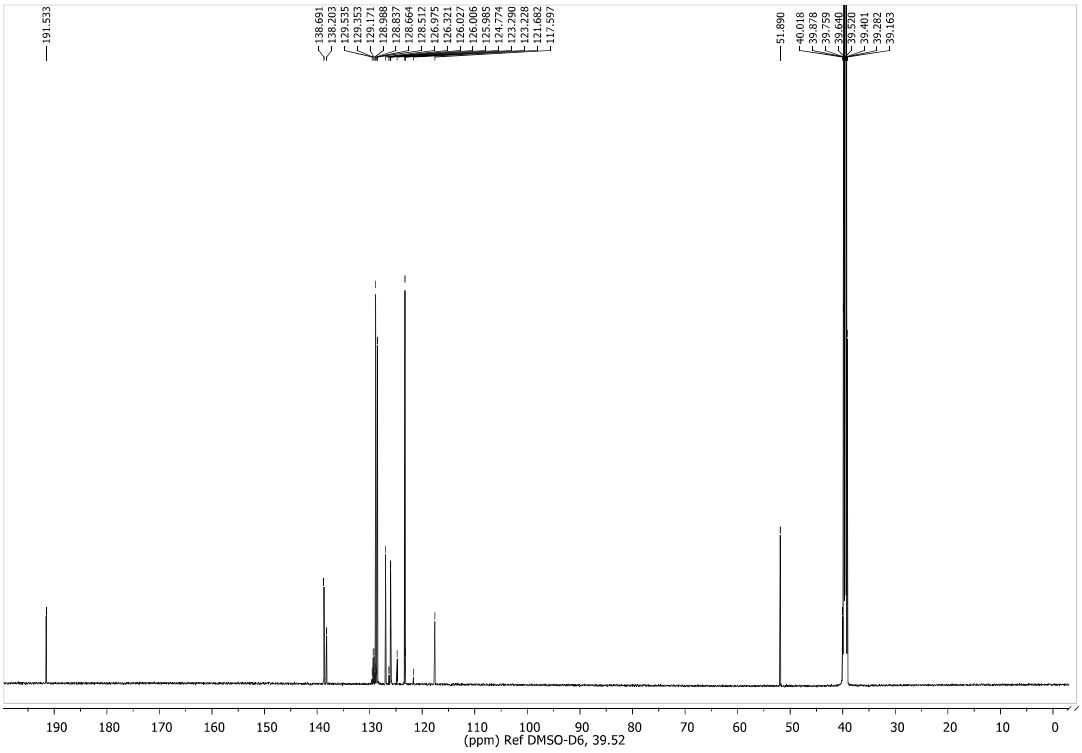


Figure 3.16b: ^{13}C NMR Spectrum of **31j**

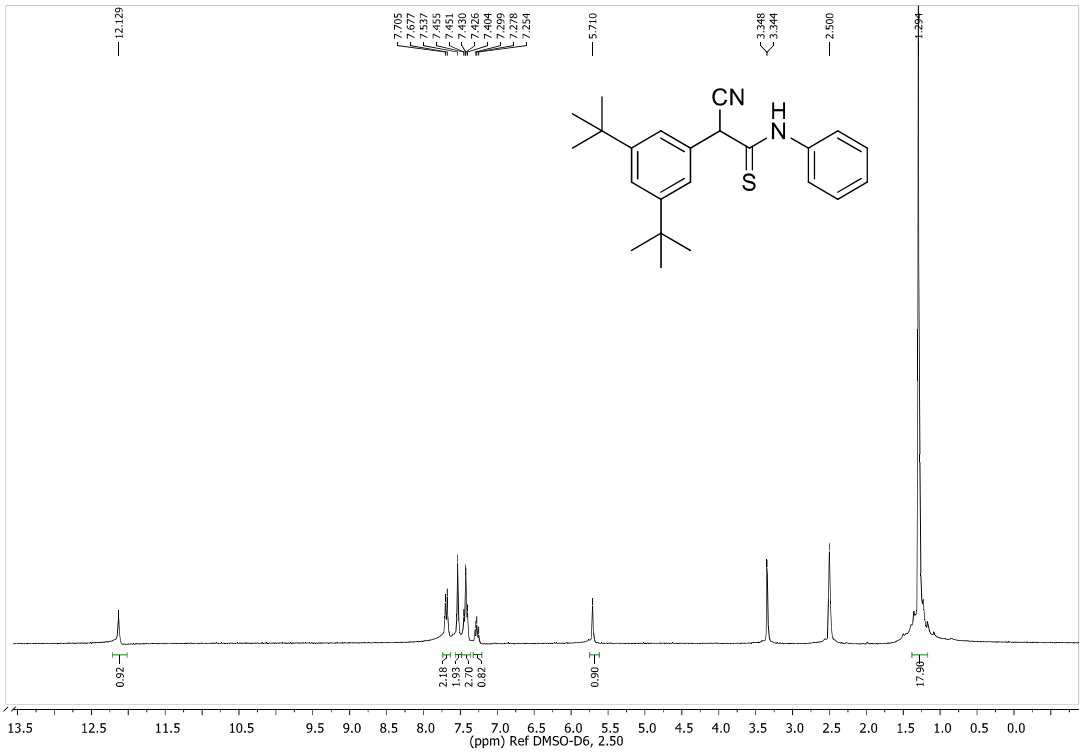


Figure 3.17a: ^{1}H NMR Spectrum of **31k**

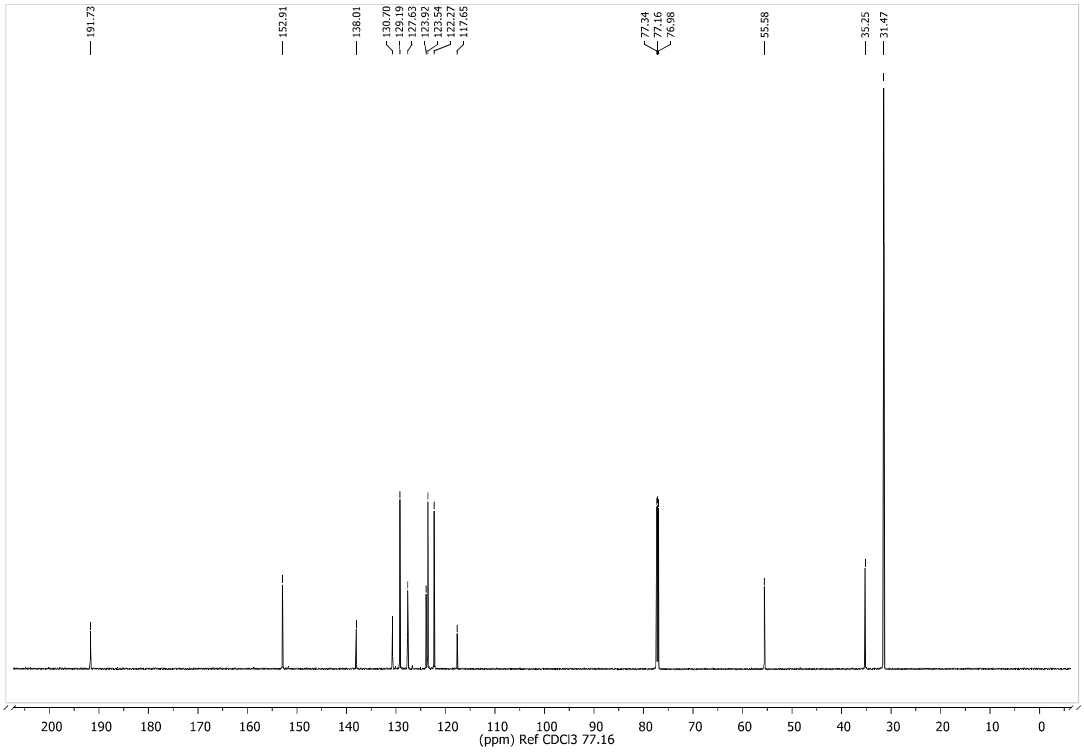


Figure 3.17b: ^{13}C NMR Spectrum of **31k**

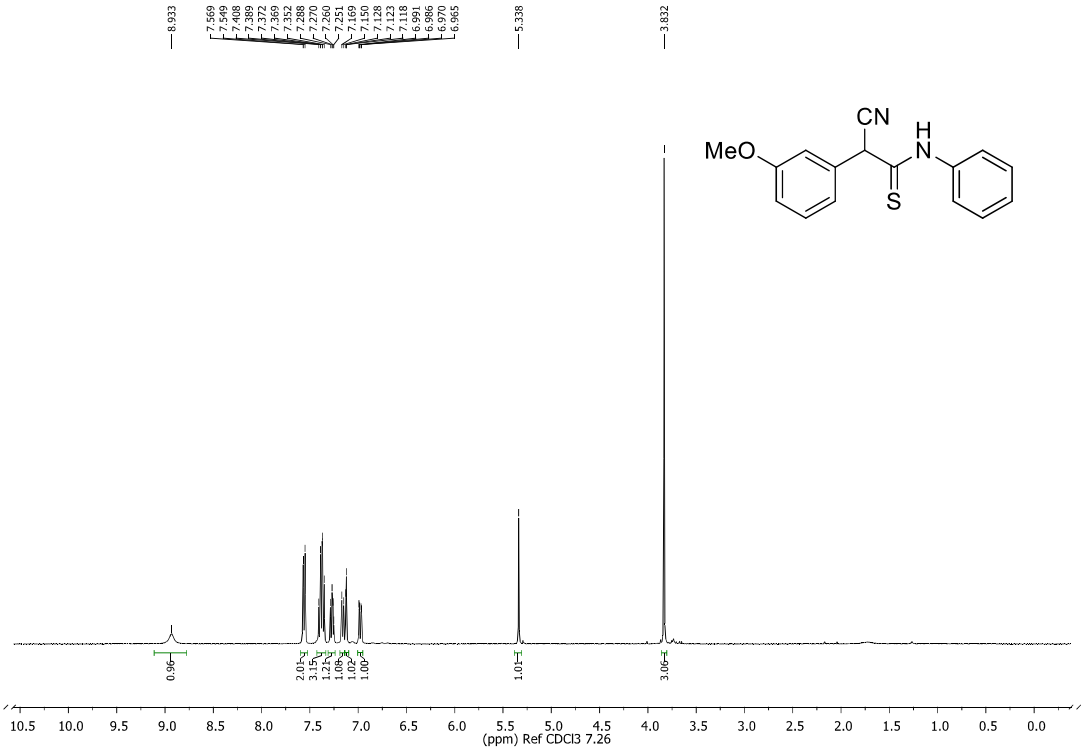


Figure 3.18a: ^{1}H NMR Spectrum of **31l**

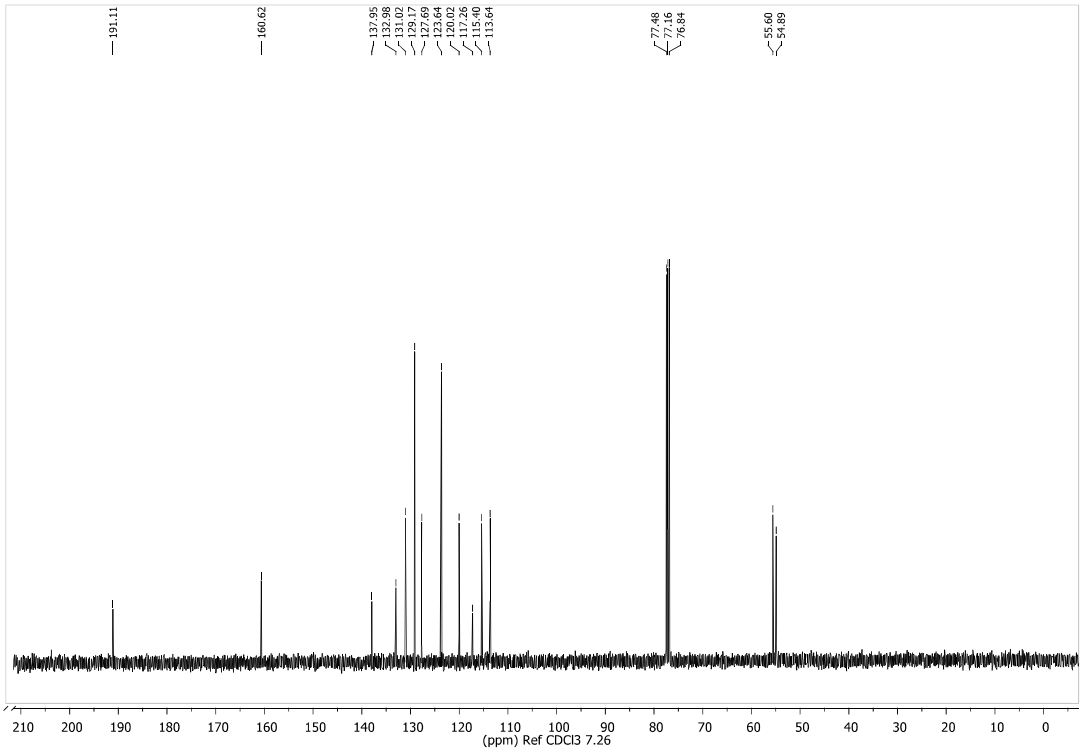


Figure 3.18b: ^{13}C NMR Spectrum of **31l**

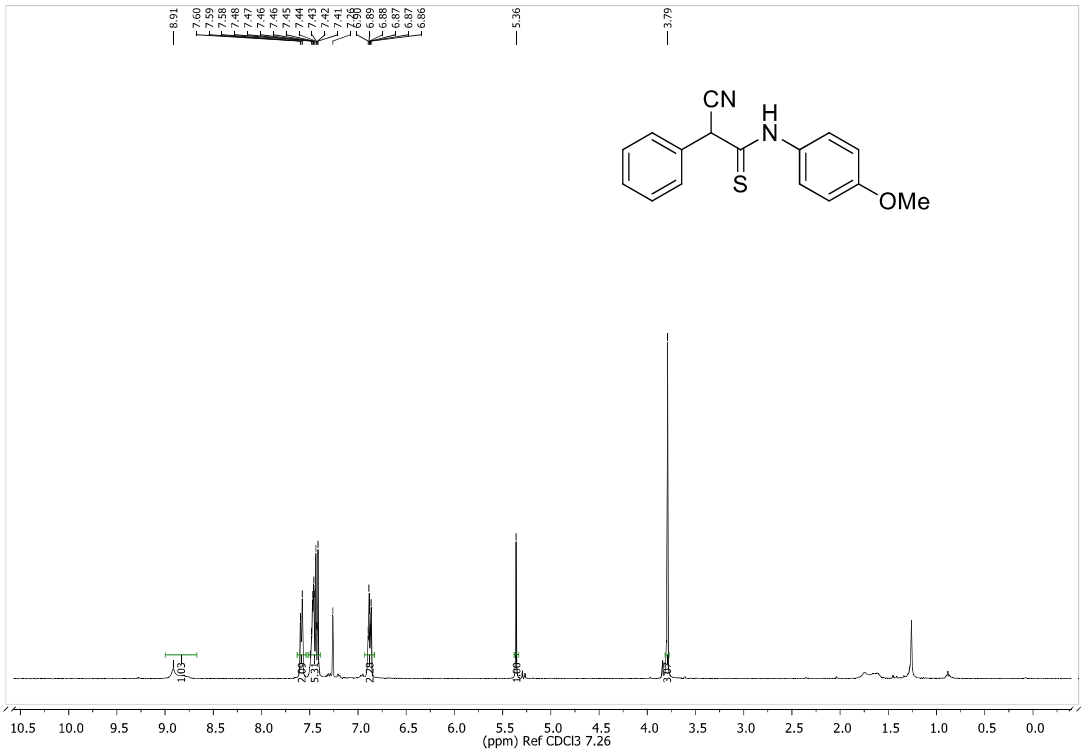


Figure 3.19a: ^{1}H NMR Spectrum of **31n**

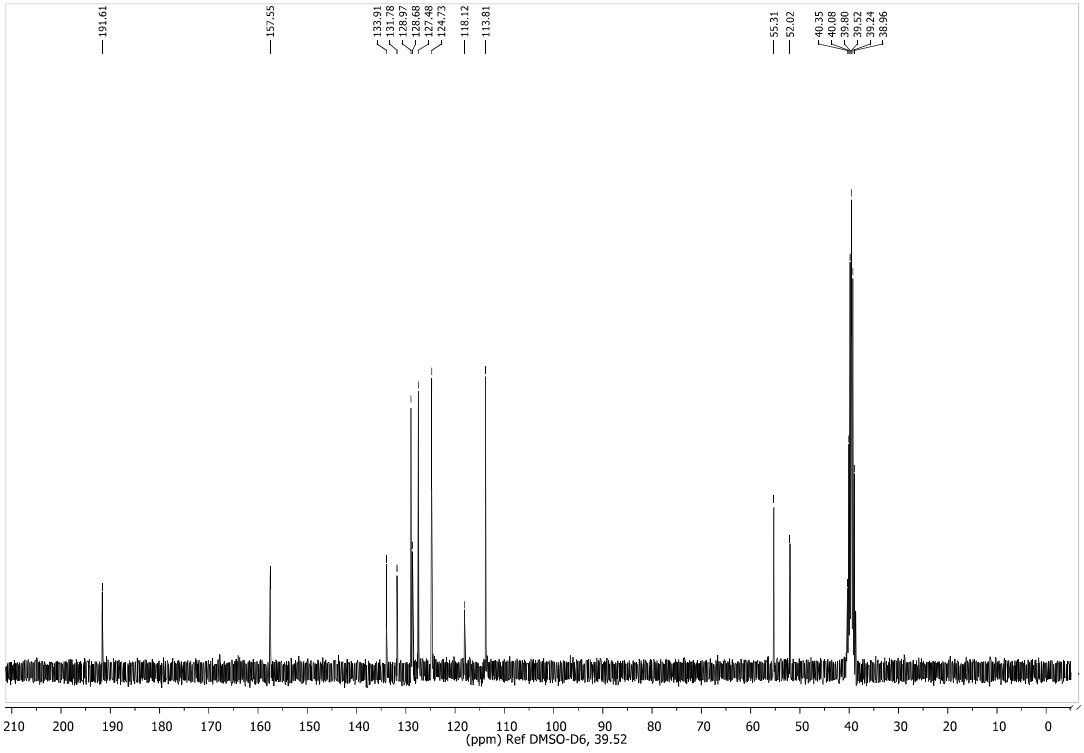


Figure 3.19b: ^{13}C NMR Spectrum of **31n**

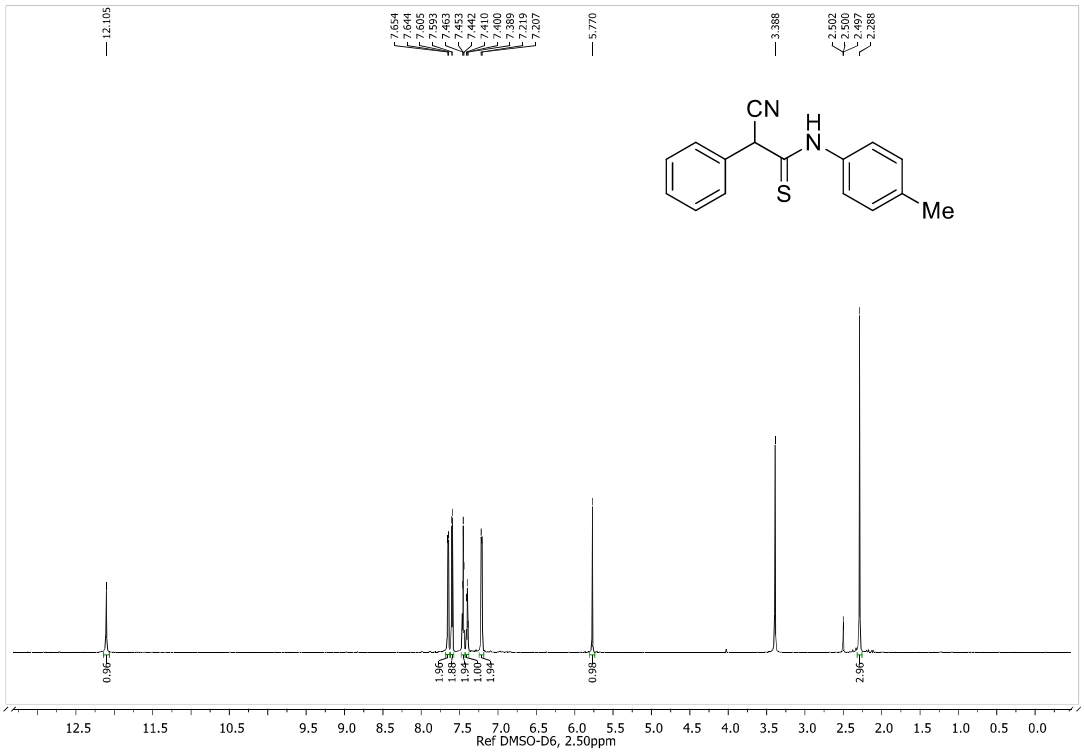


Figure 3.20a: ^{1}H NMR Spectrum of **31o**

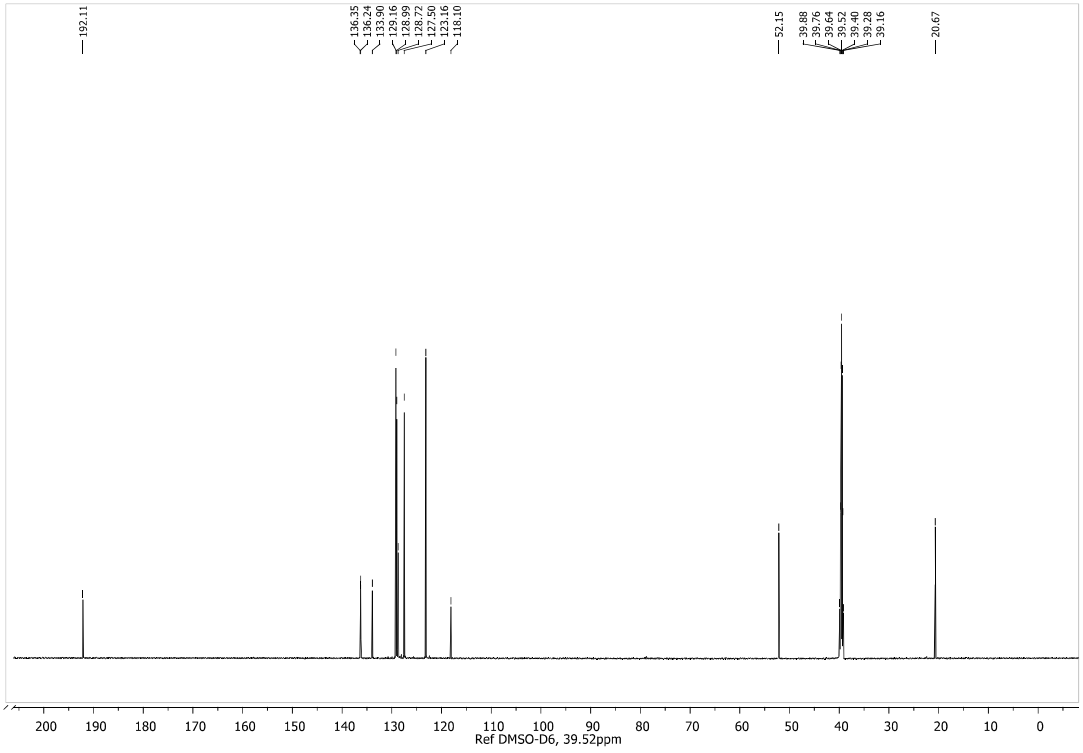


Figure 3.20b: ^{13}C NMR Spectrum of **31o**

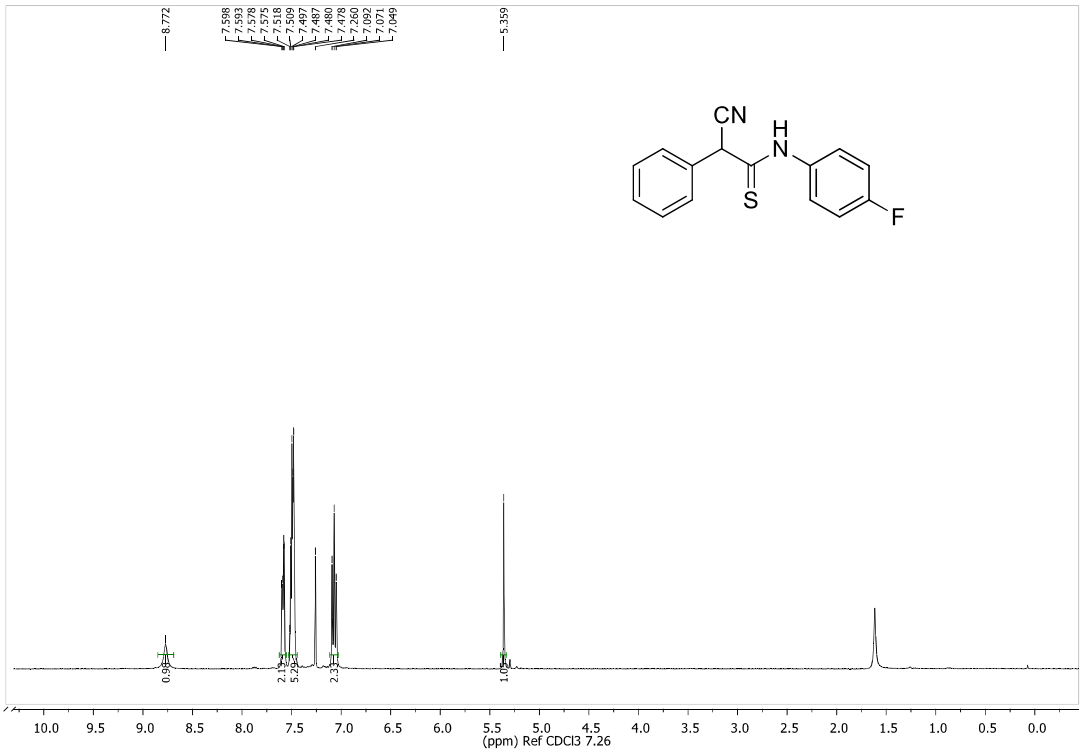


Figure 3.21a: ^{1}H NMR Spectrum of **31r**

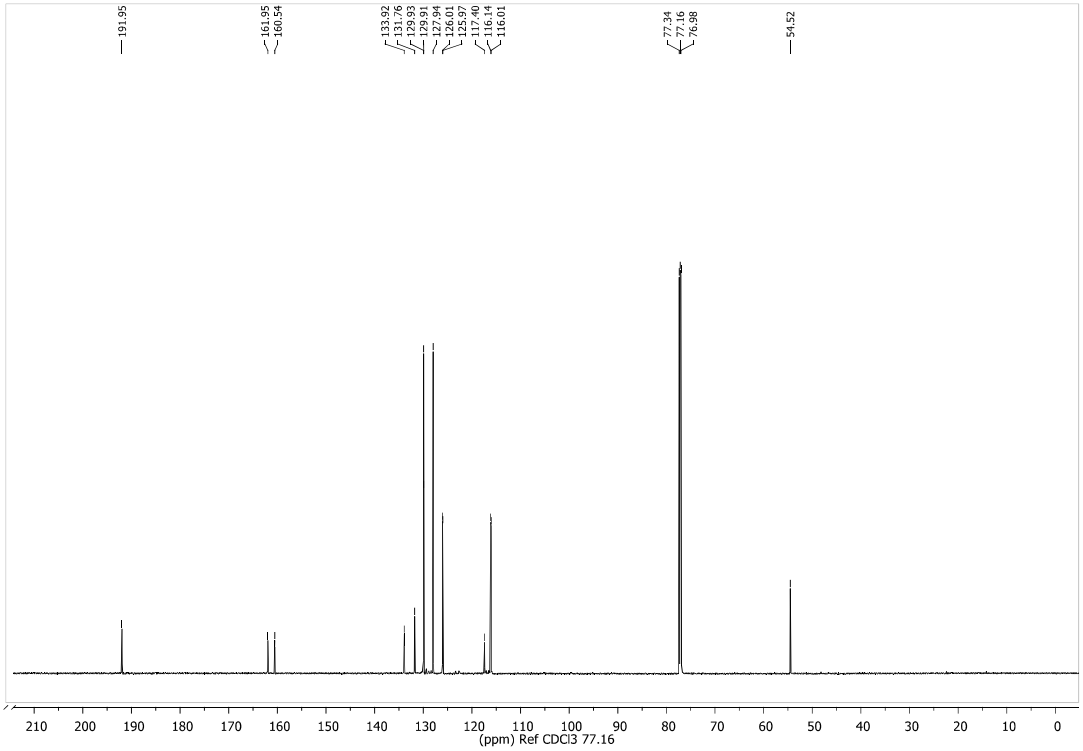


Figure 3.21b: ^{13}C NMR Spectrum of **31r**

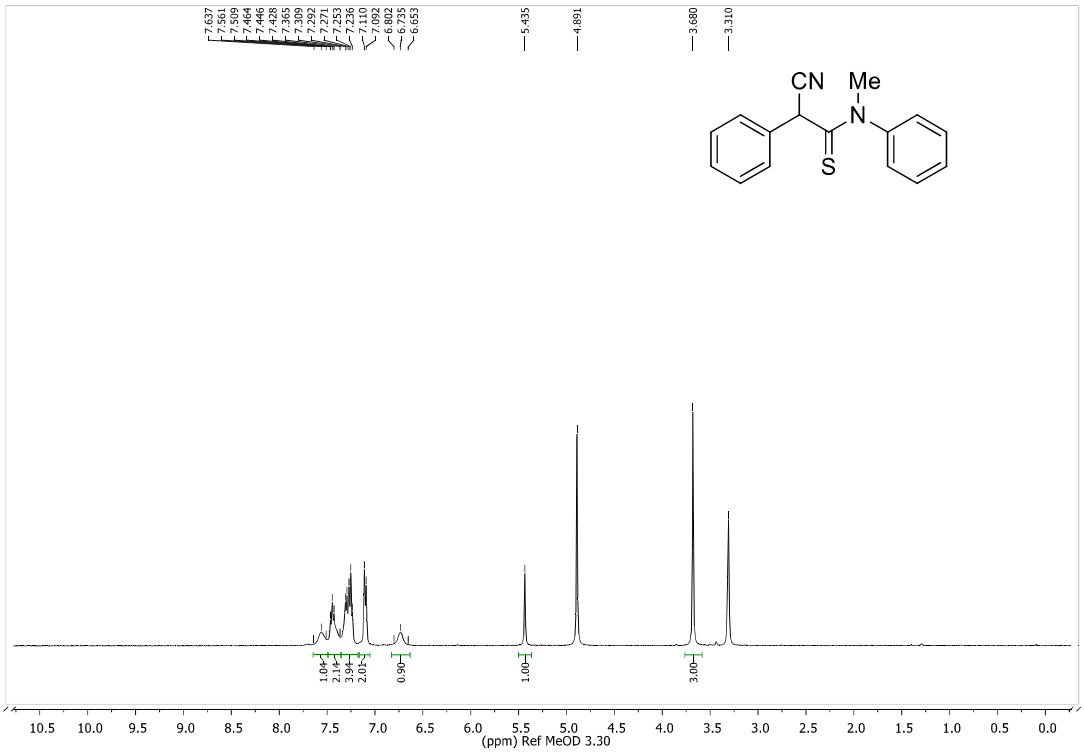


Figure 3.22a: ^{1}H NMR Spectrum of **69**

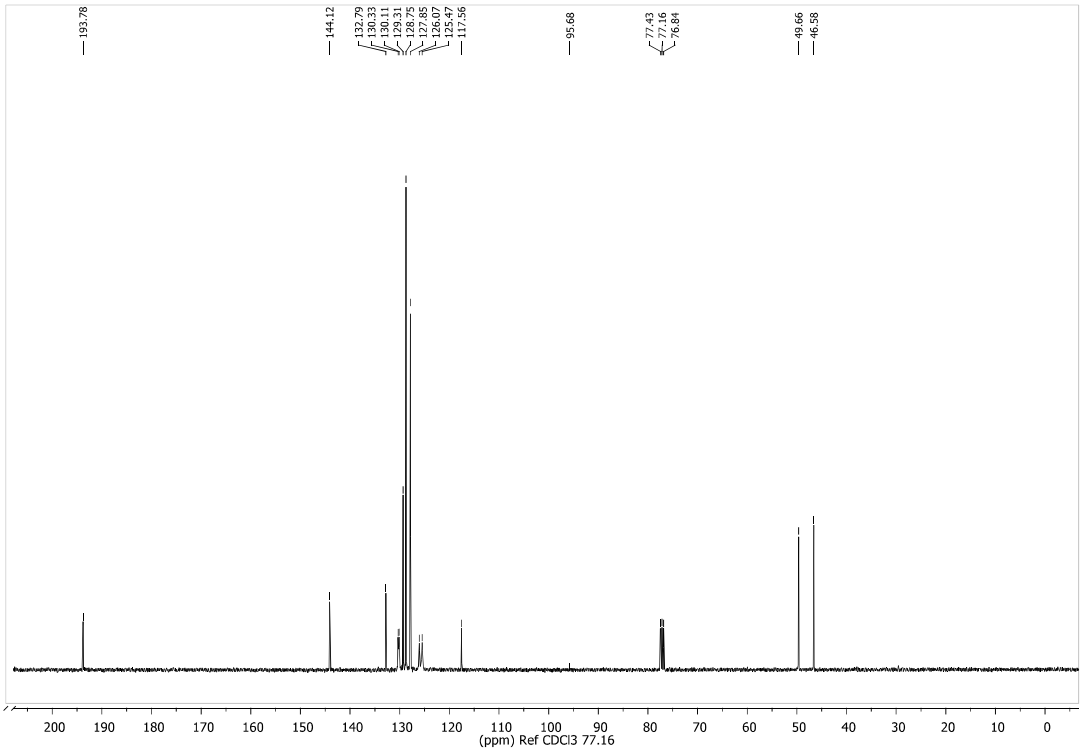


Figure 3.22b: ^{13}C NMR Spectrum of 6**9**

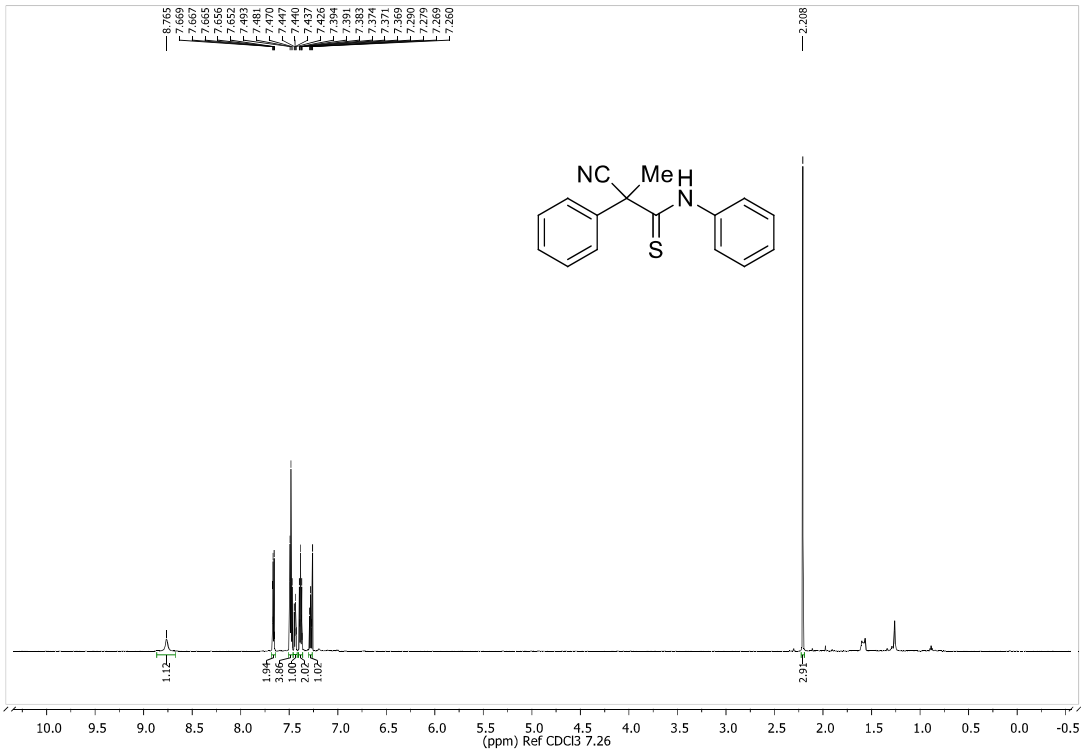


Figure 3.23a: ^{1}H NMR Spectrum of **71**

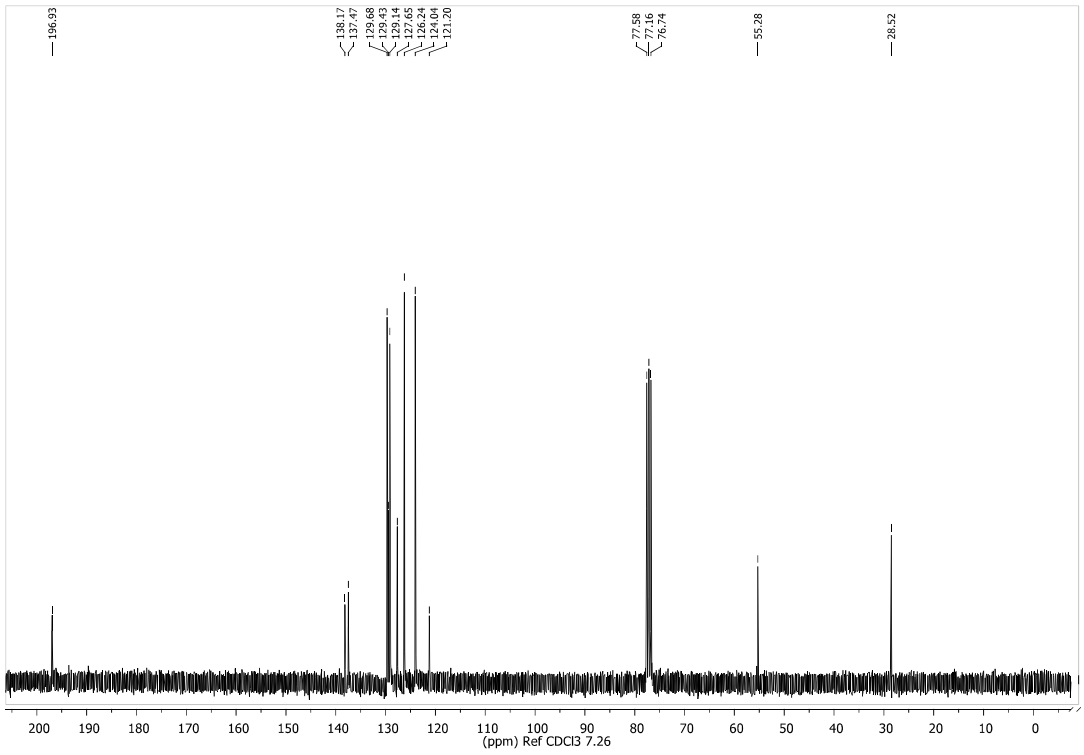


Figure 3.23b: ^{13}C NMR Spectrum of **71**

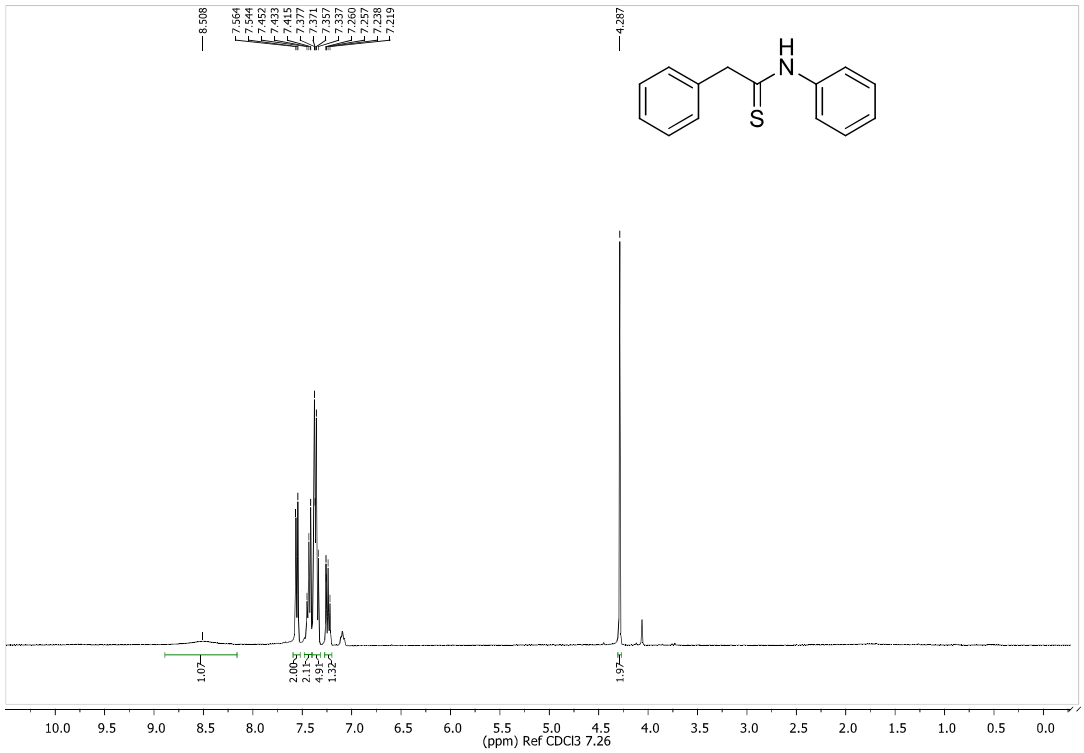


Figure 3.24a: ^{1}H NMR Spectrum of **73**

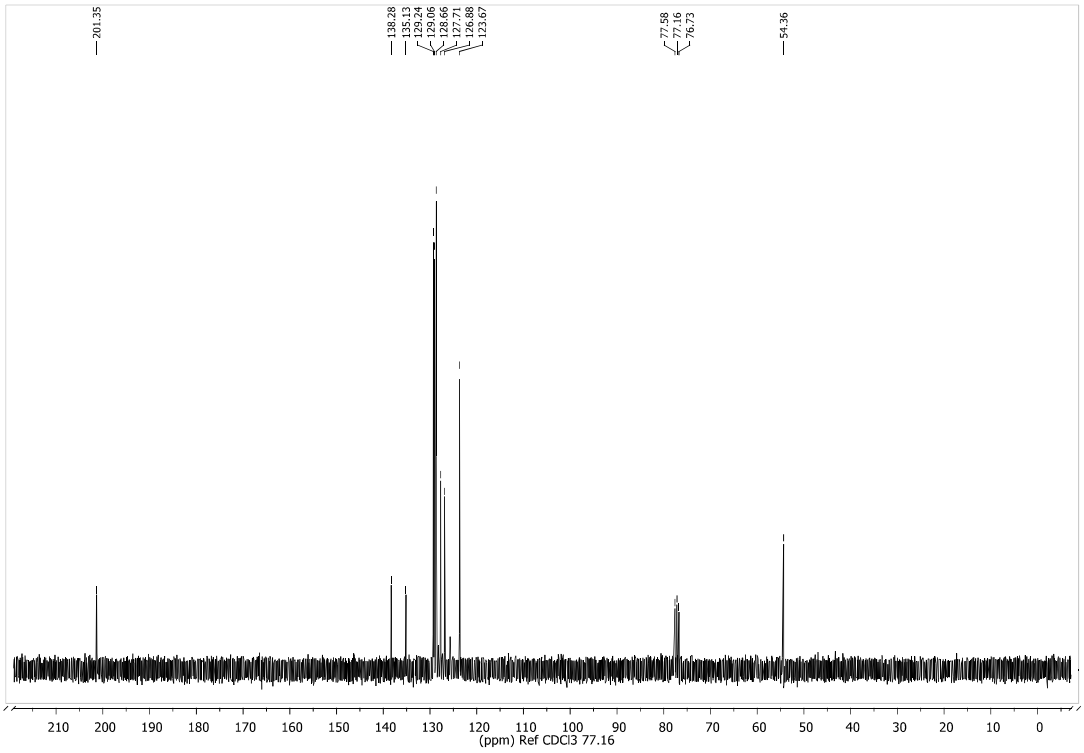


Figure 3.24b: ^{13}C NMR Spectrum of **73**

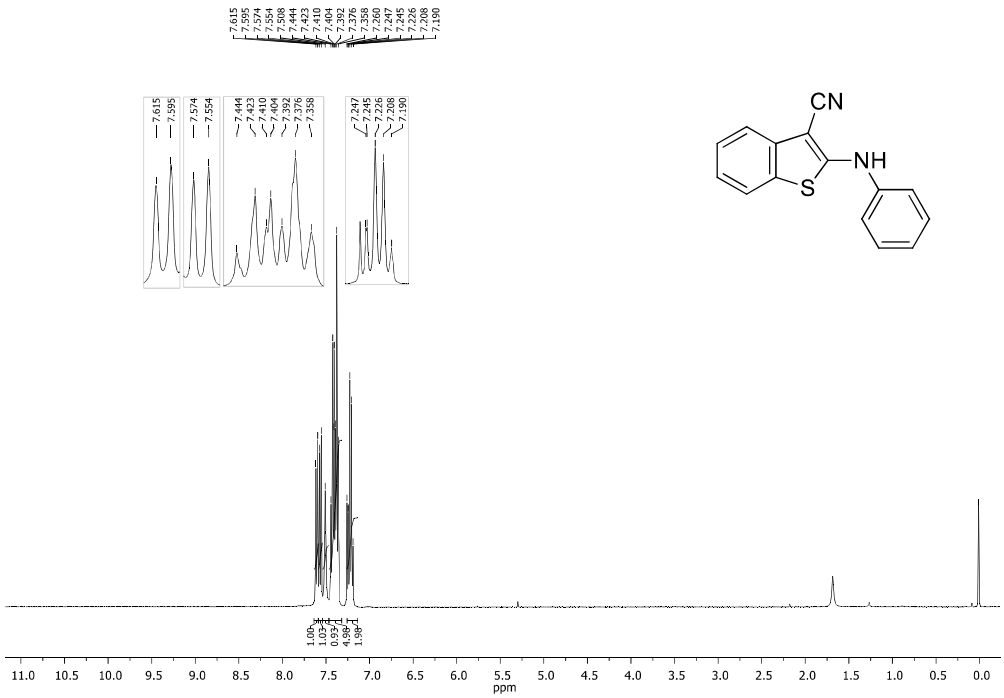


Figure 3.25a: ^{1}H NMR Spectra of **42a**

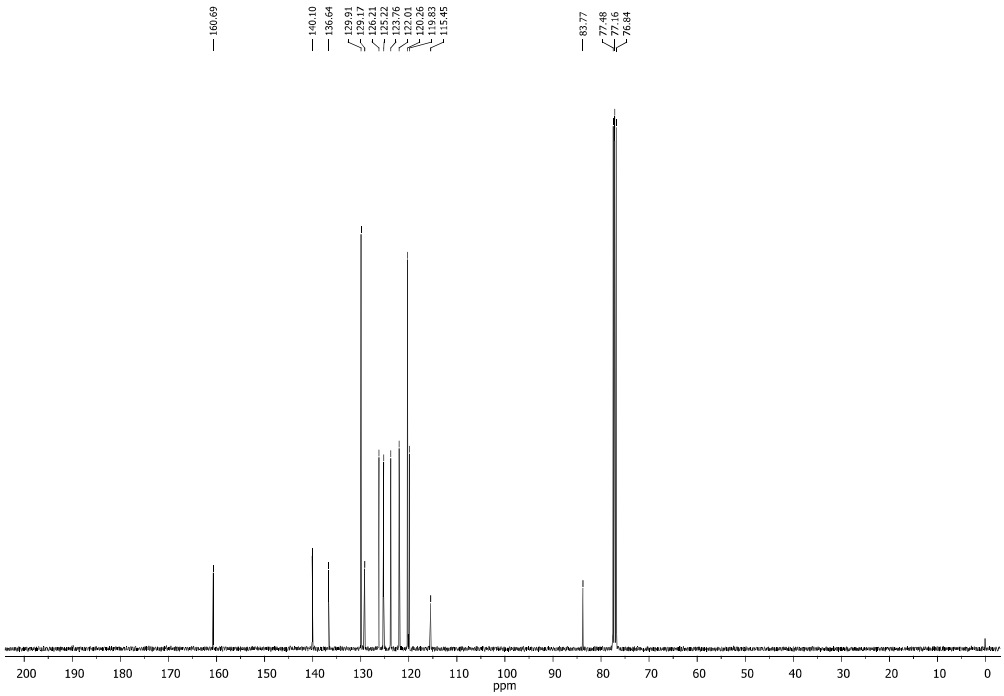


Figure 3.25b: ^{13}C NMR Spectra of **42a**

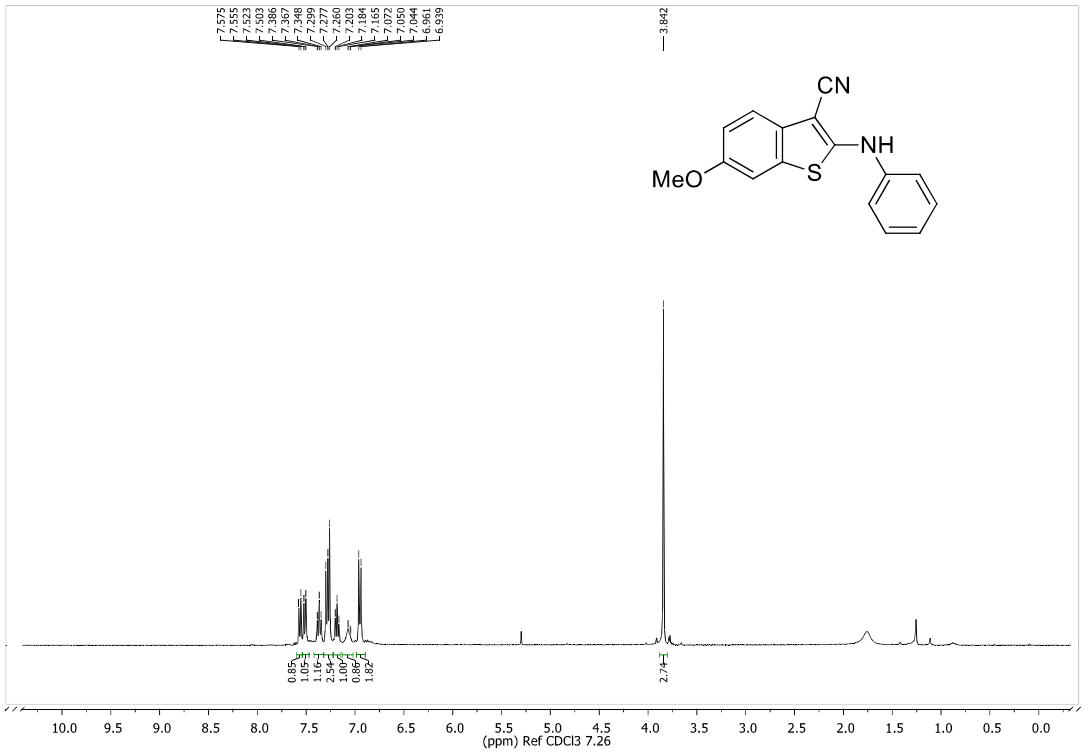


Figure 3.26a: ^{1}H NMR Spectrum of **42b**

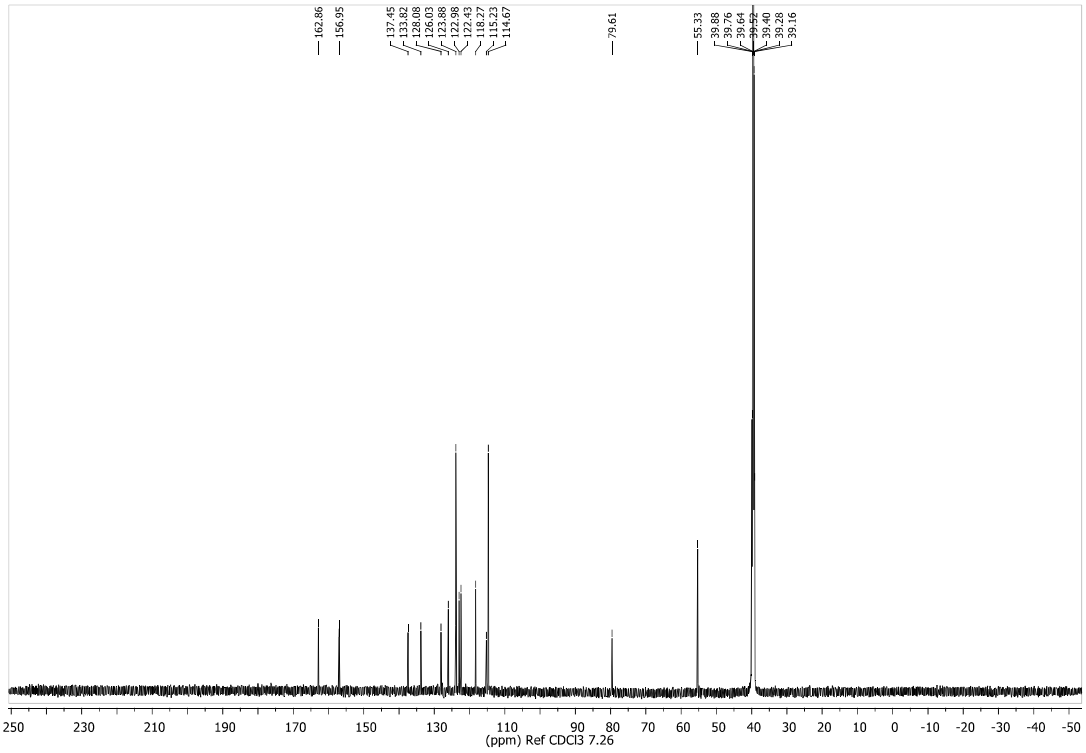


Figure 3.26b: ^{13}C NMR Spectrum of **42b**

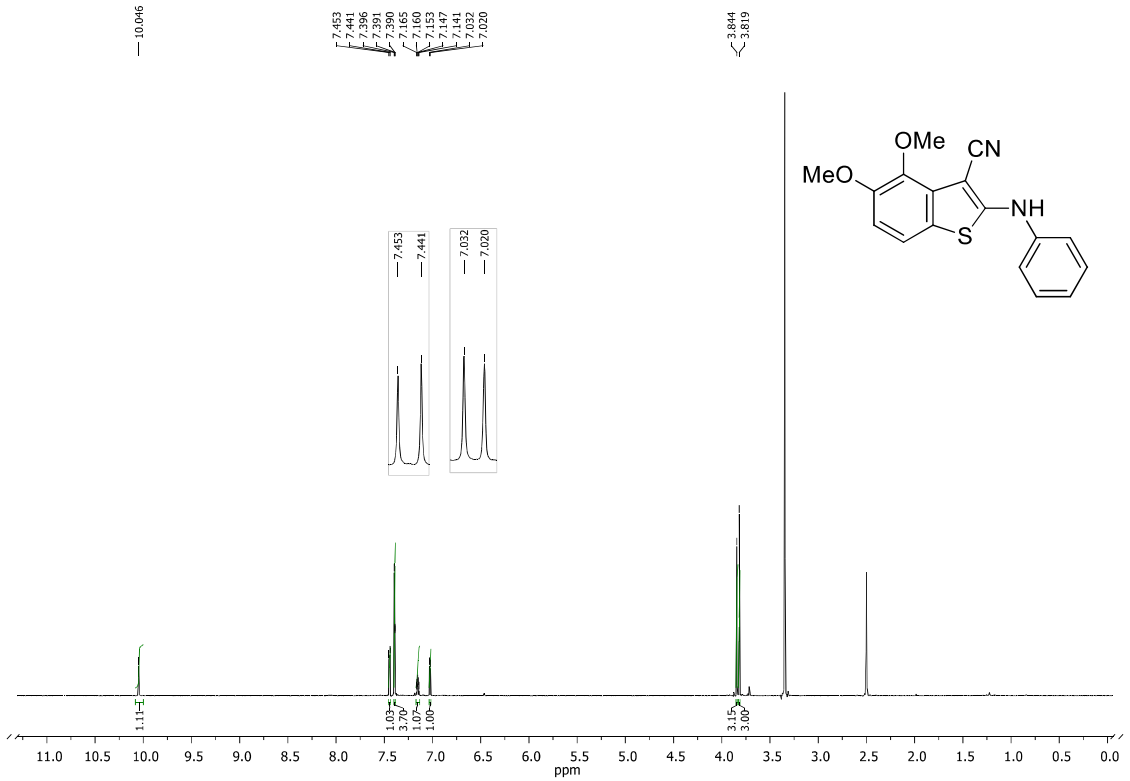


Figure 3.27a: ^{1}H NMR Spectrum of **42c**

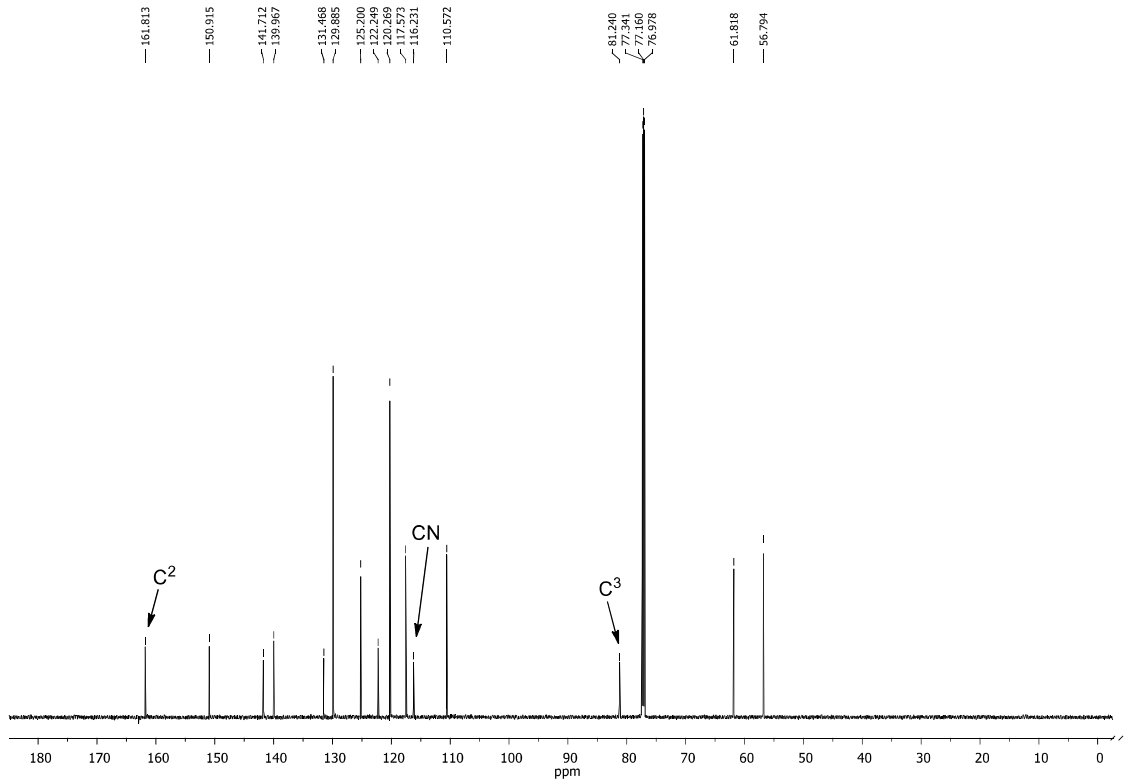


Figure 3.27b: ^{13}C NMR Spectrum of **42c**

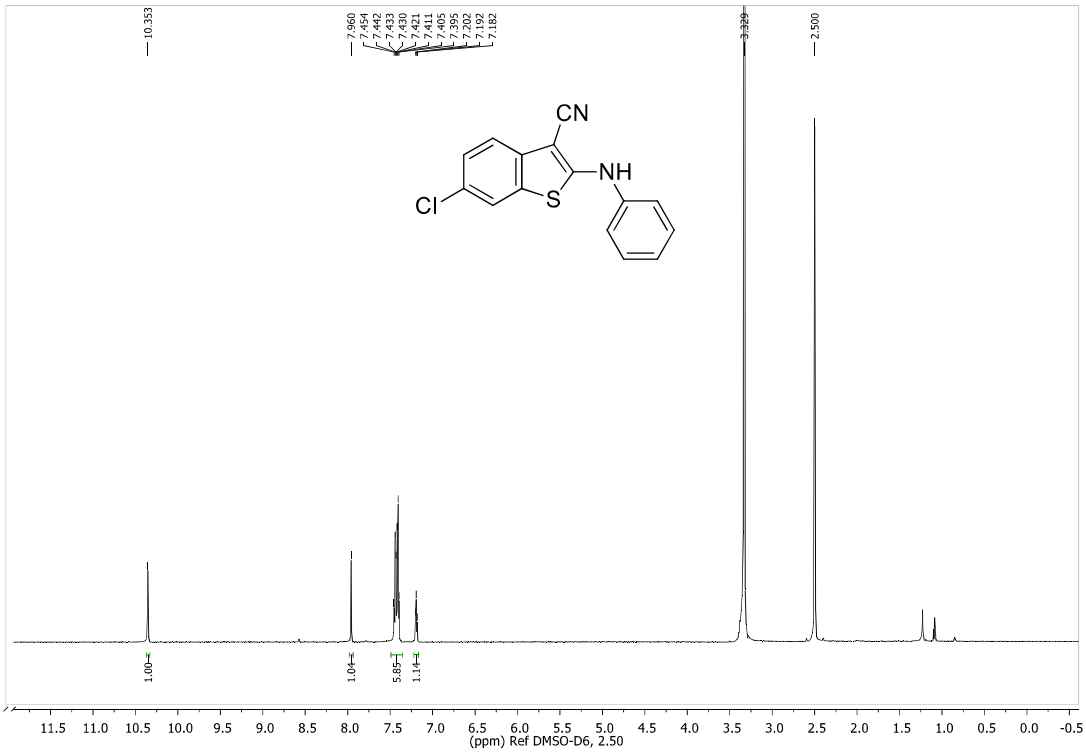


Figure 3.28a: ^{1}H NMR Spectrum of **42g**

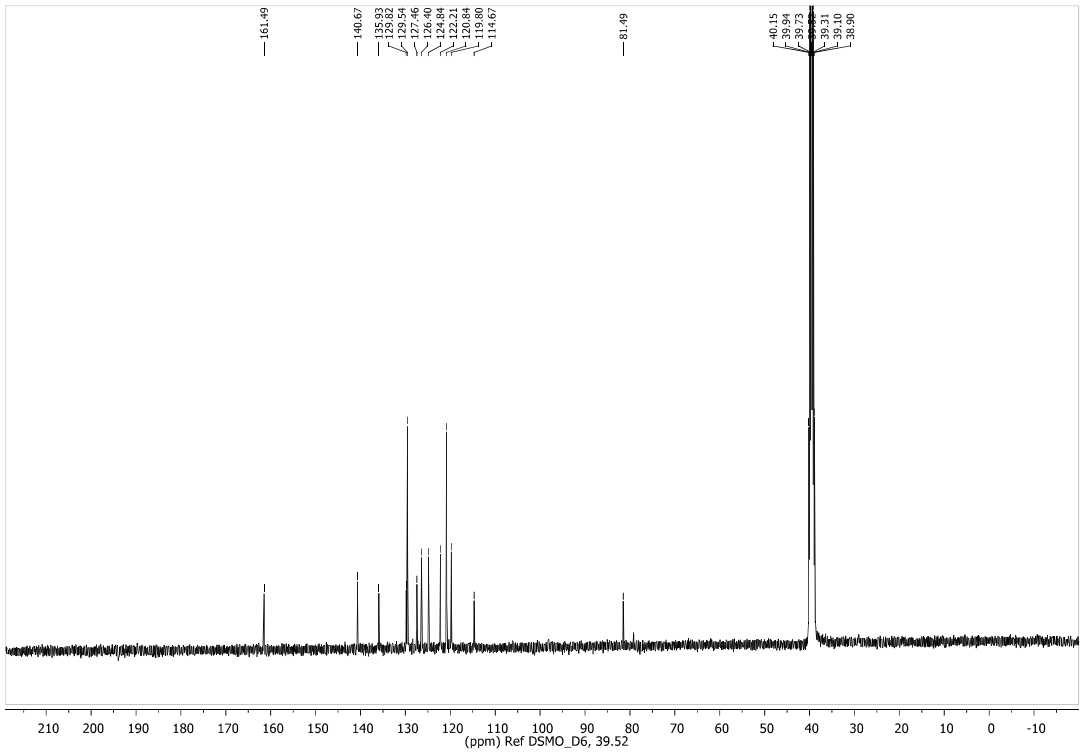


Figure 3.28b: ^{13}C NMR Spectrum of **42g**

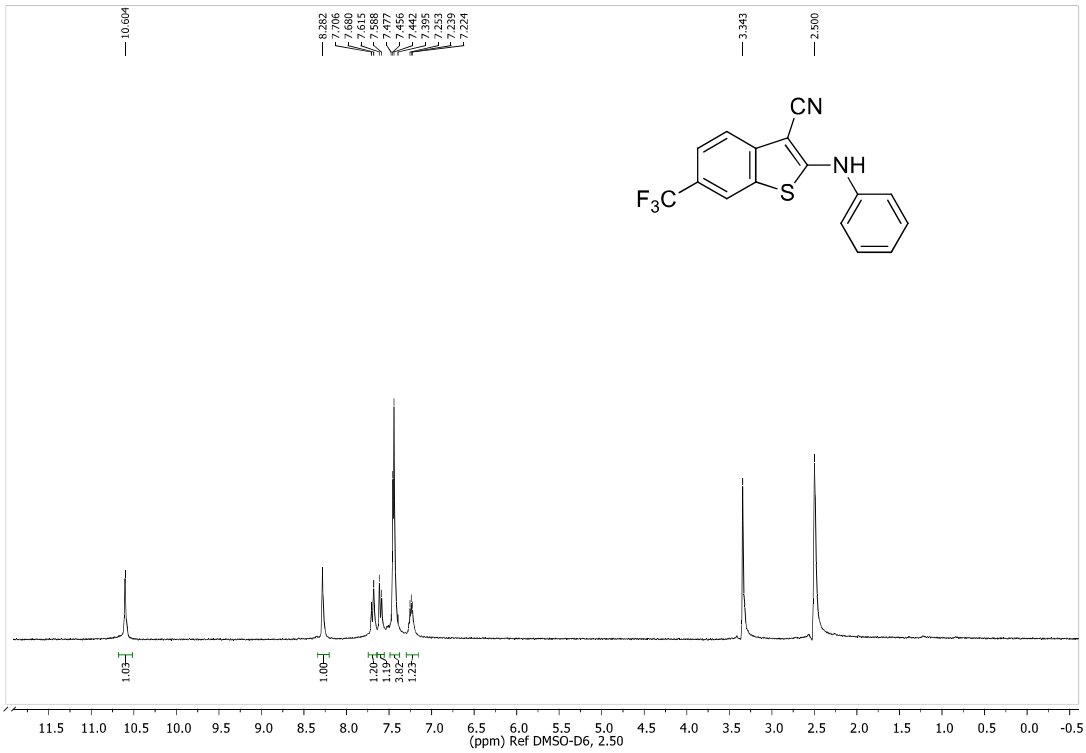


Figure 3.29a: ^{1}H NMR Spectrum of **42j**

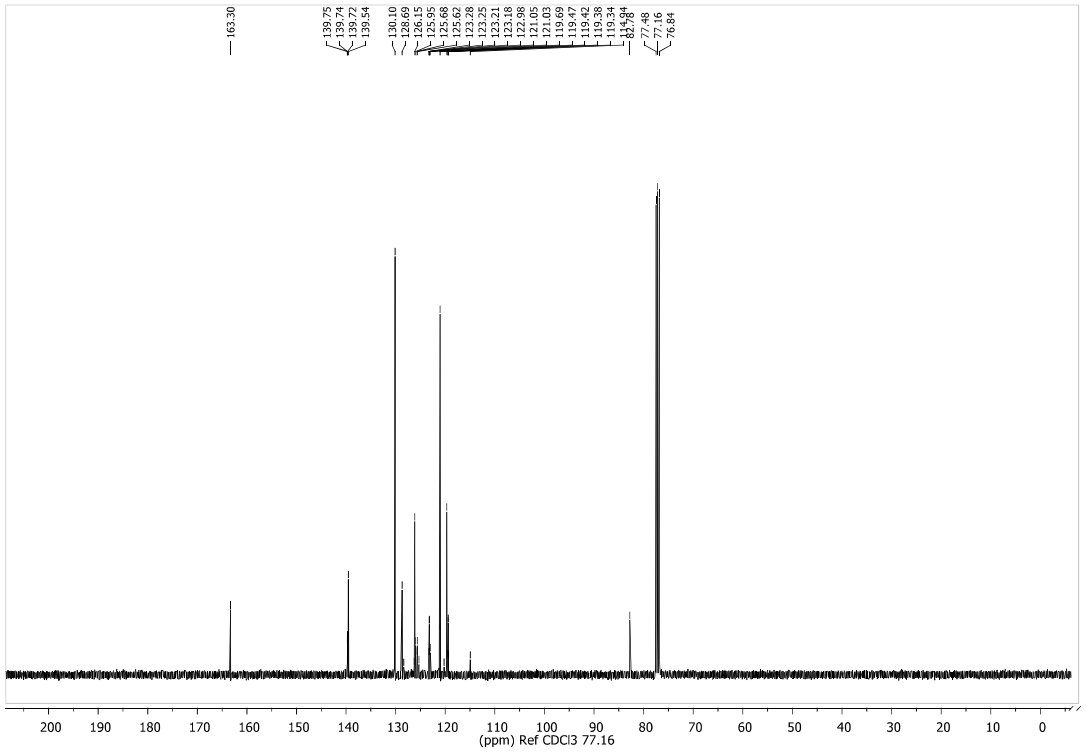


Figure 3.29b: ^{13}C NMR Spectrum of **42j**

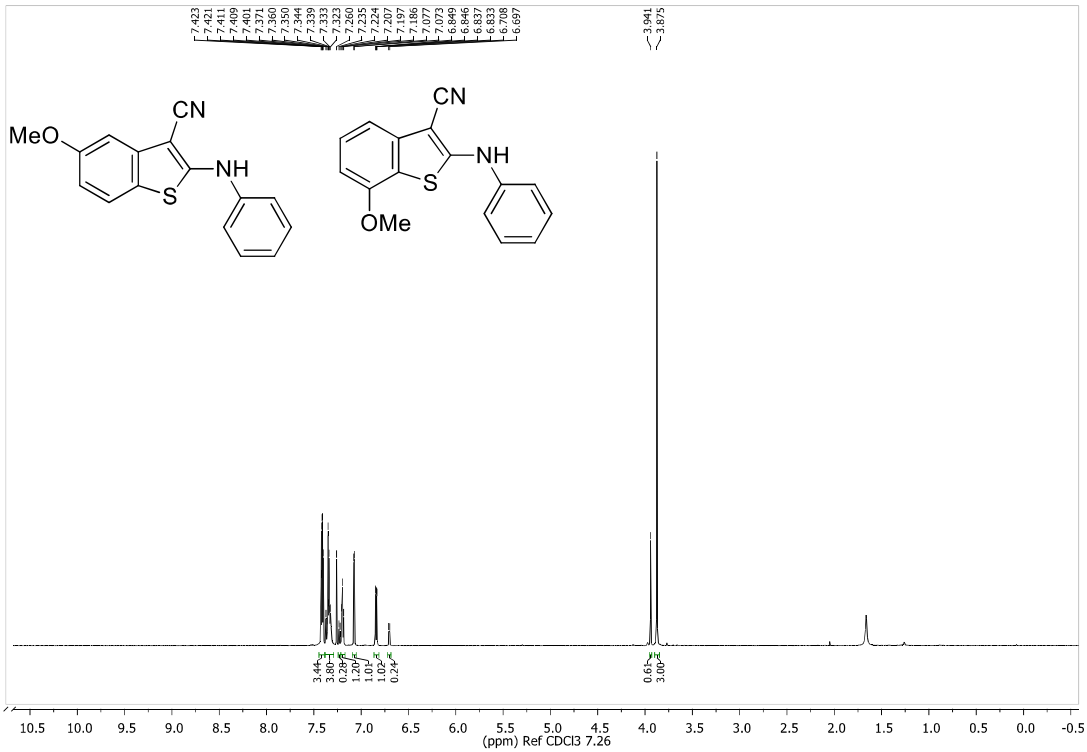


Figure 3.30a: ^{1}H NMR Spectrum of **42la & 42lb**

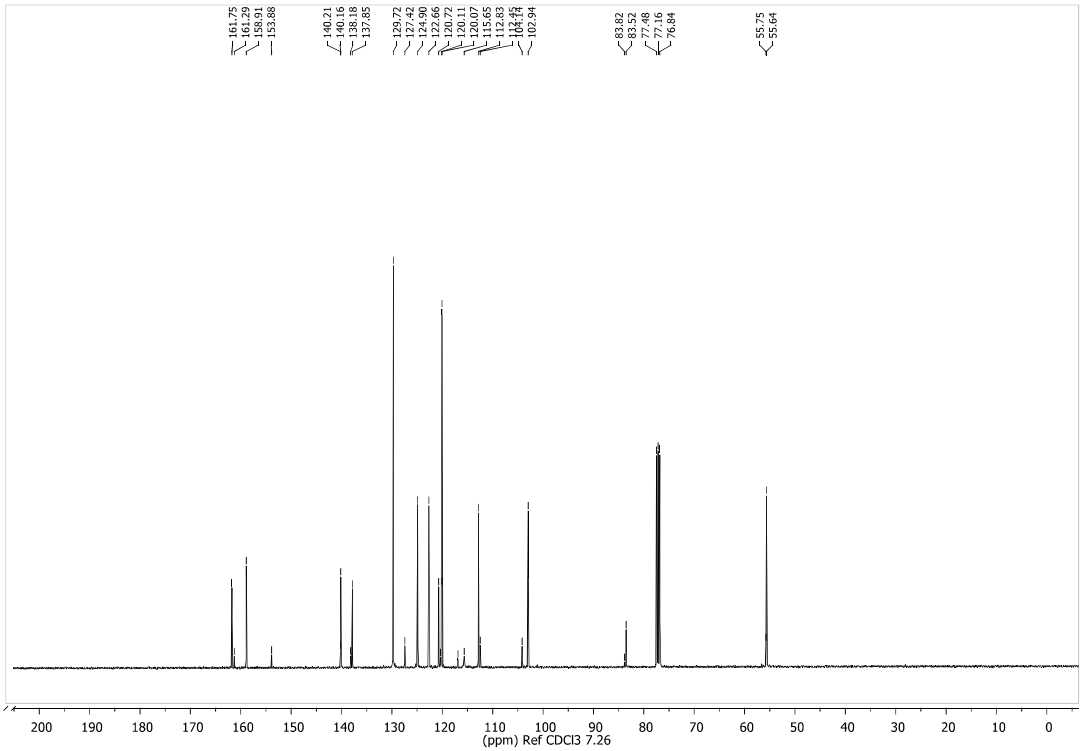


Figure 3.30b: ^{13}C NMR Spectrum of **42la & 42lb**

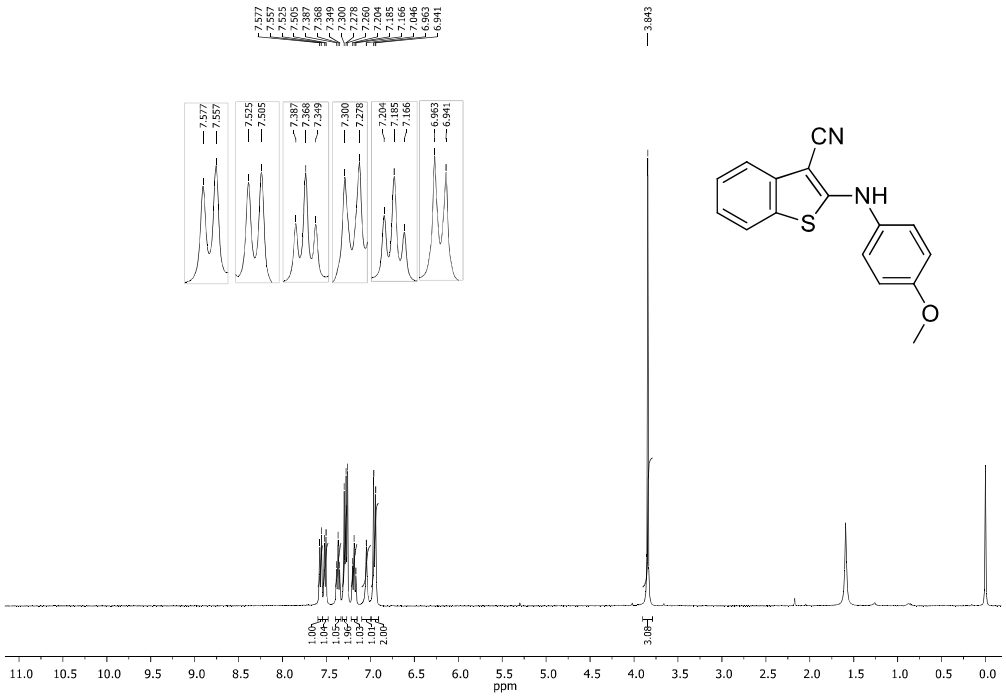


Figure 3.31a: ^{1}H NMR Spectrum of **42n**

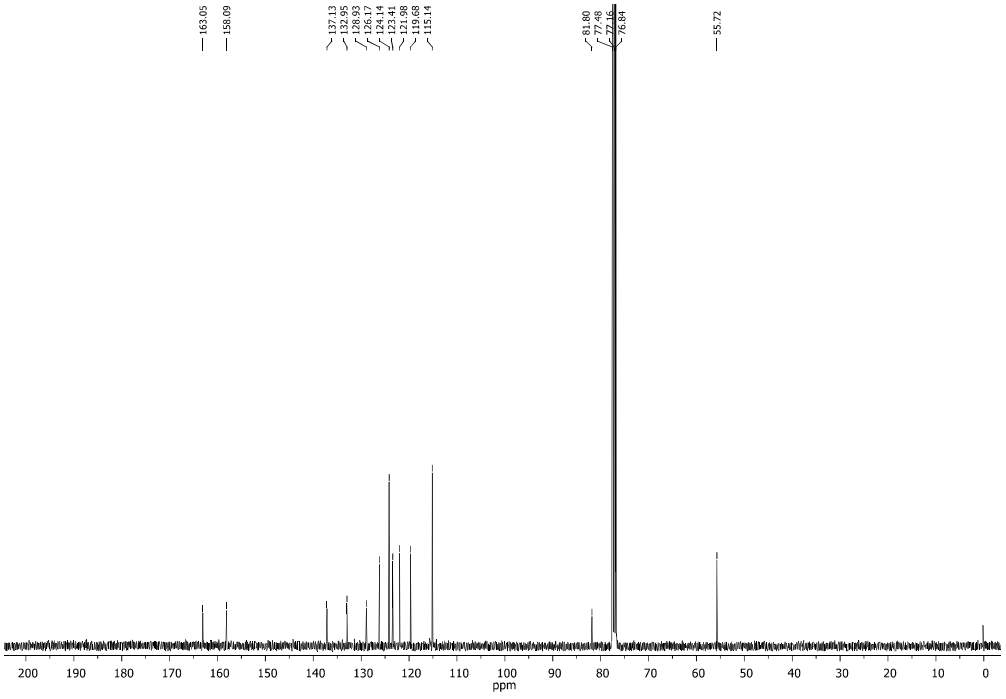


Figure 3.31b: ^{13}C NMR Spectrum of **42n**

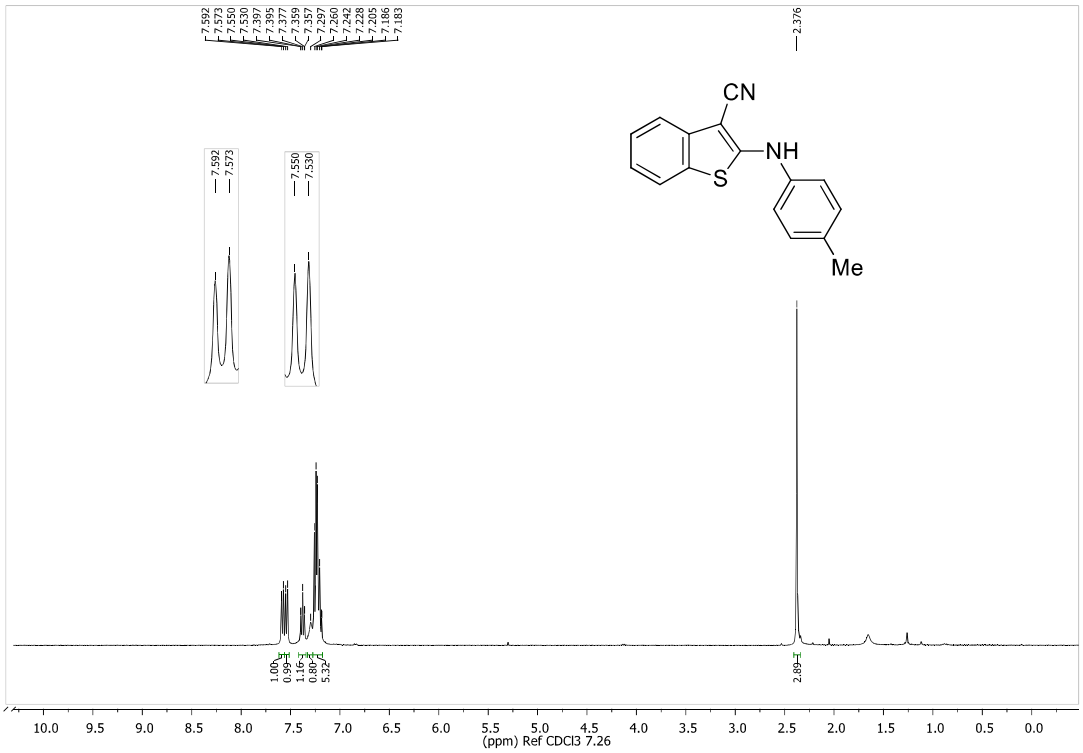


Figure 3.32a: ^{1}H NMR Spectrum of **42o**

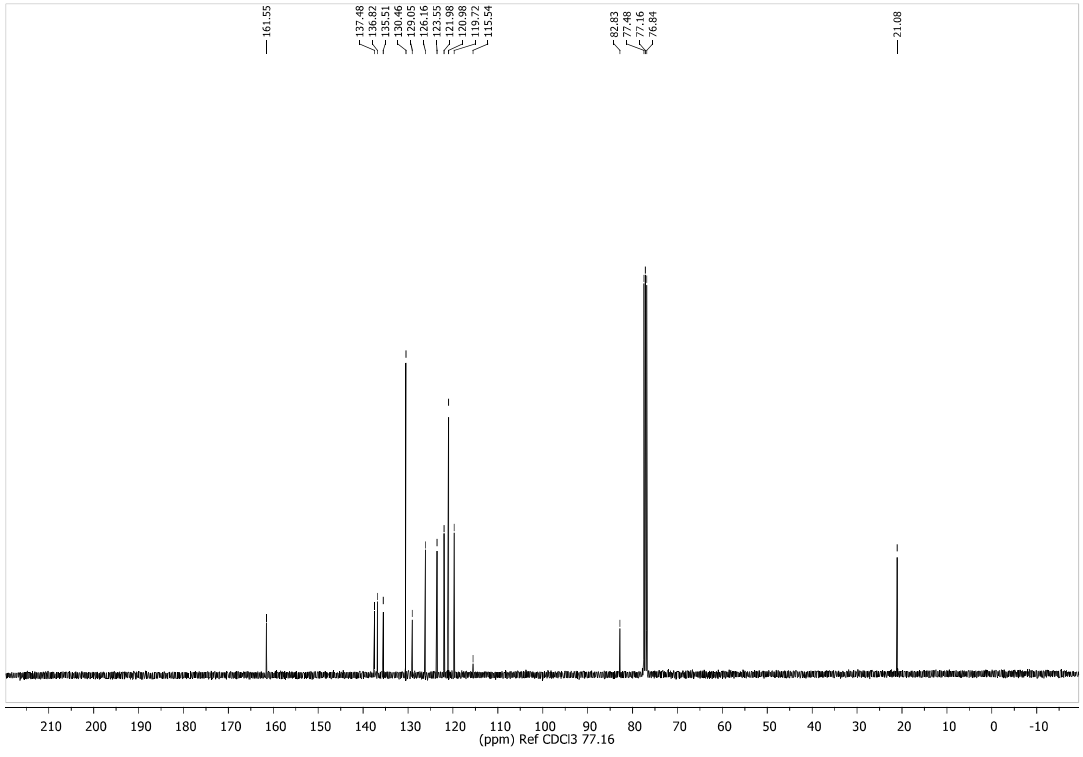


Figure 3.32b: ^{13}C NMR Spectrum of **42o**

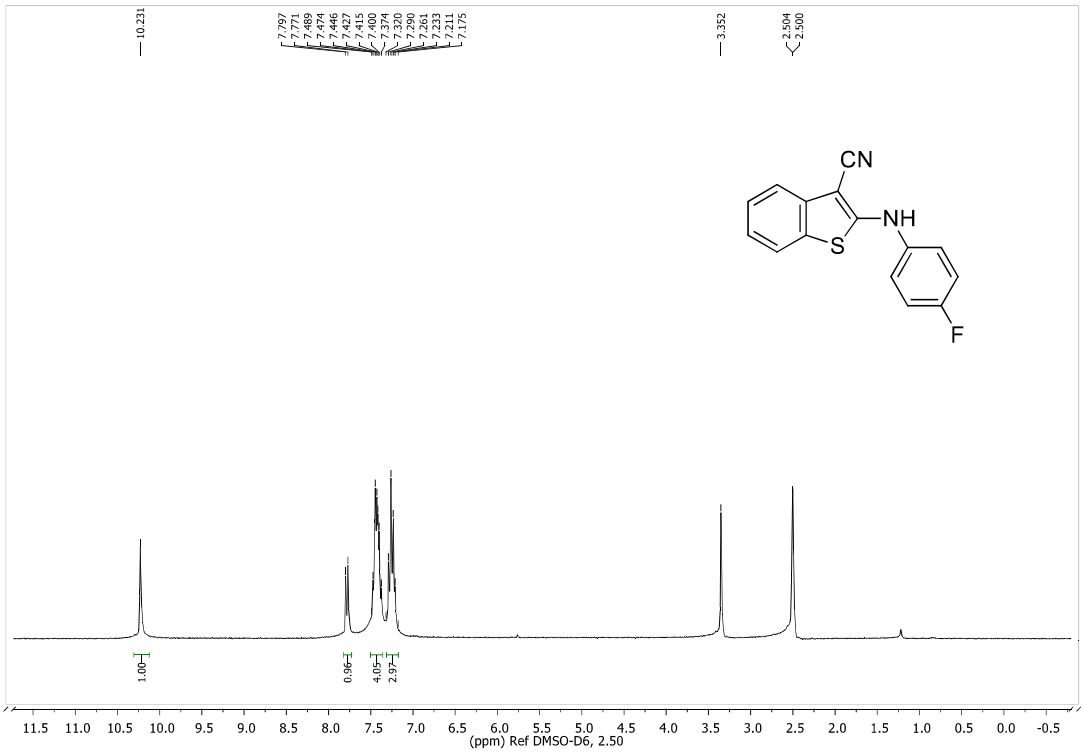


Figure 3.33a: ^{1}H NMR Spectrum of **42r**

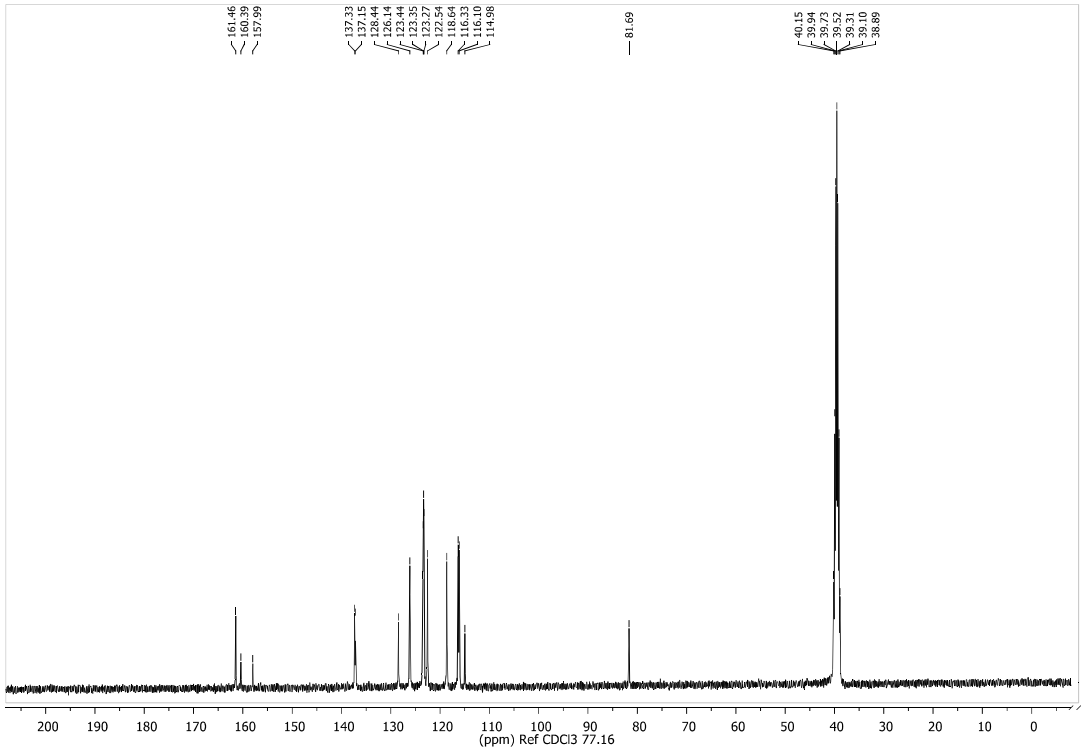


Figure 3.33b: ^{13}C NMR Spectrum of **42r**

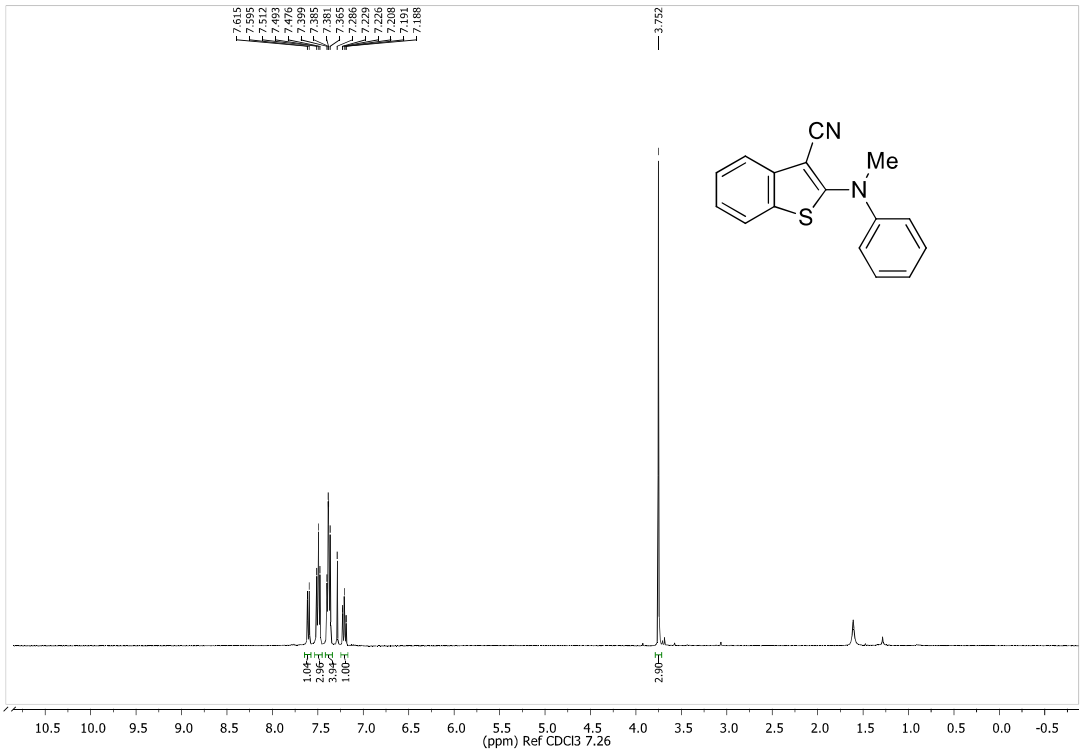


Figure 3.34a: ^{1}H NMR Spectrum of **70**

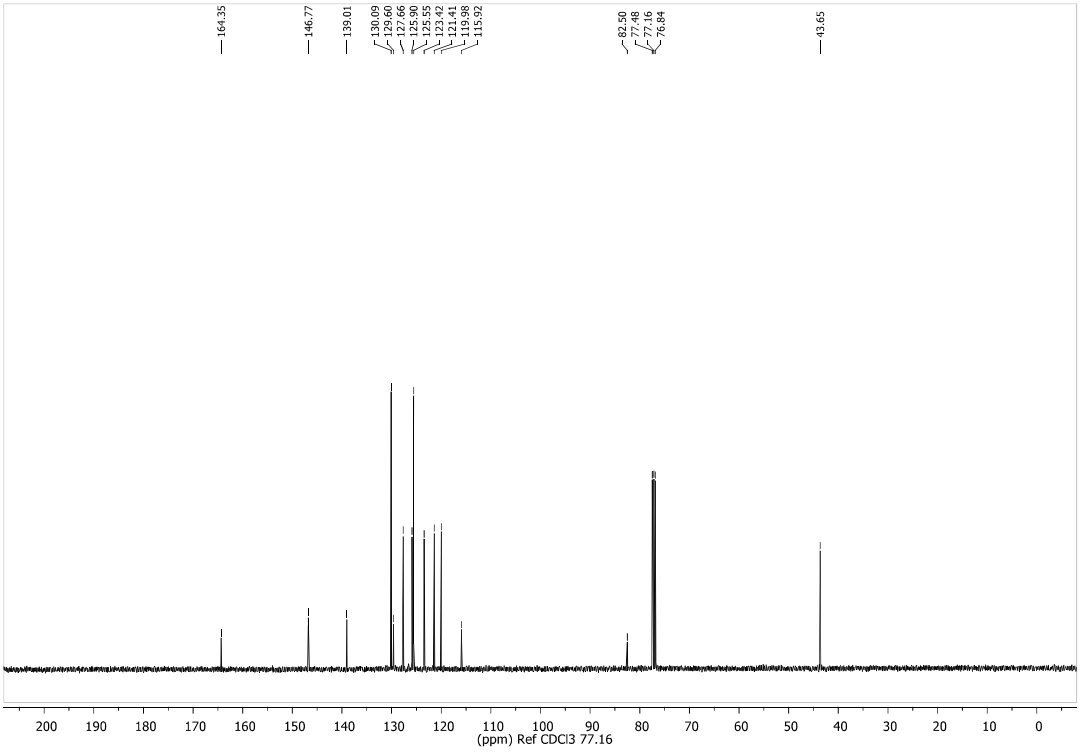


Figure 3.34b: ^{13}C NMR Spectrum of **70**

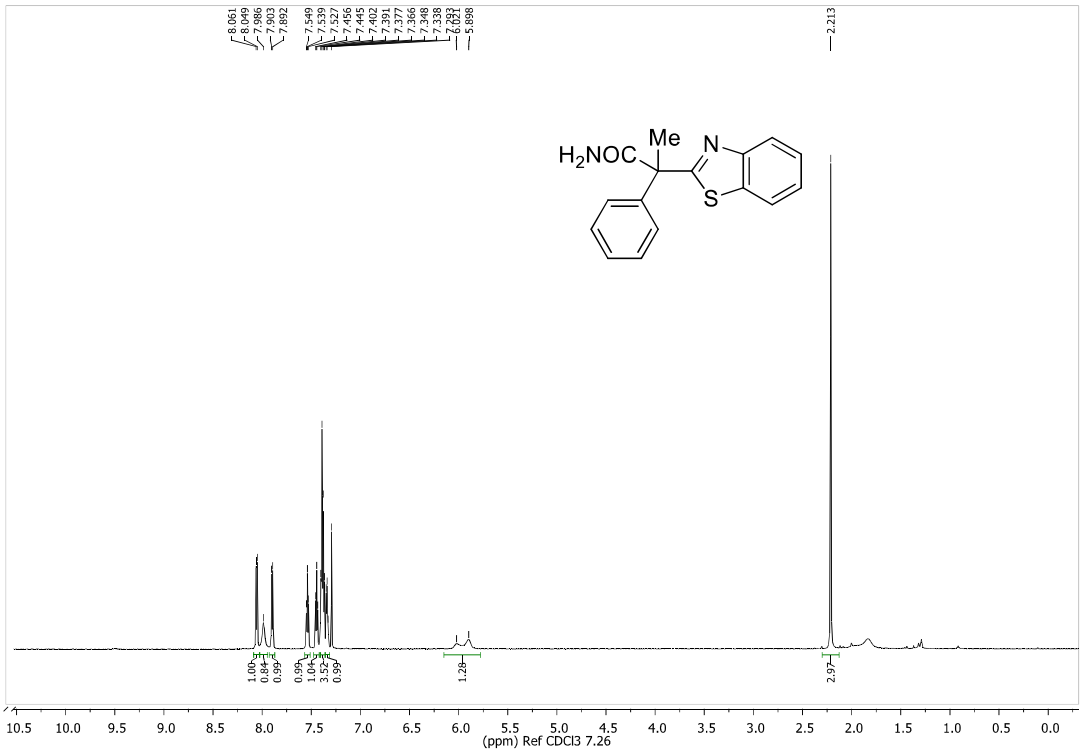


Figure 3.35a: ^{1}H NMR Spectrum of **72**

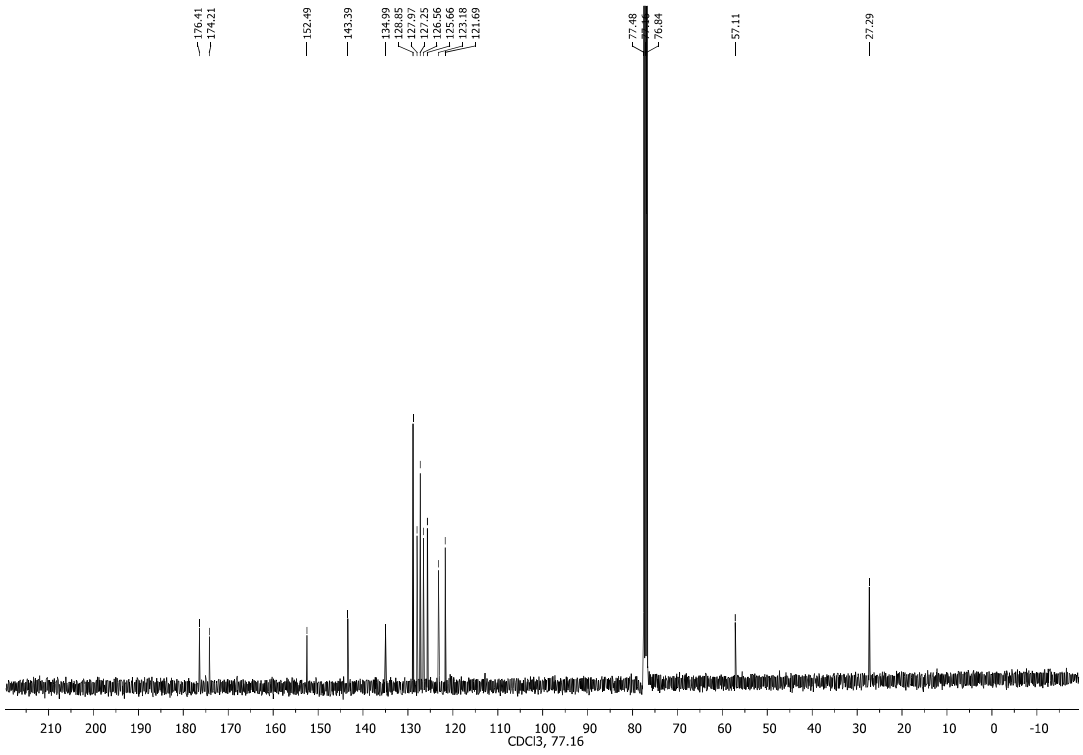


Figure 3.35b: ^{13}C NMR Spectrum of **72**

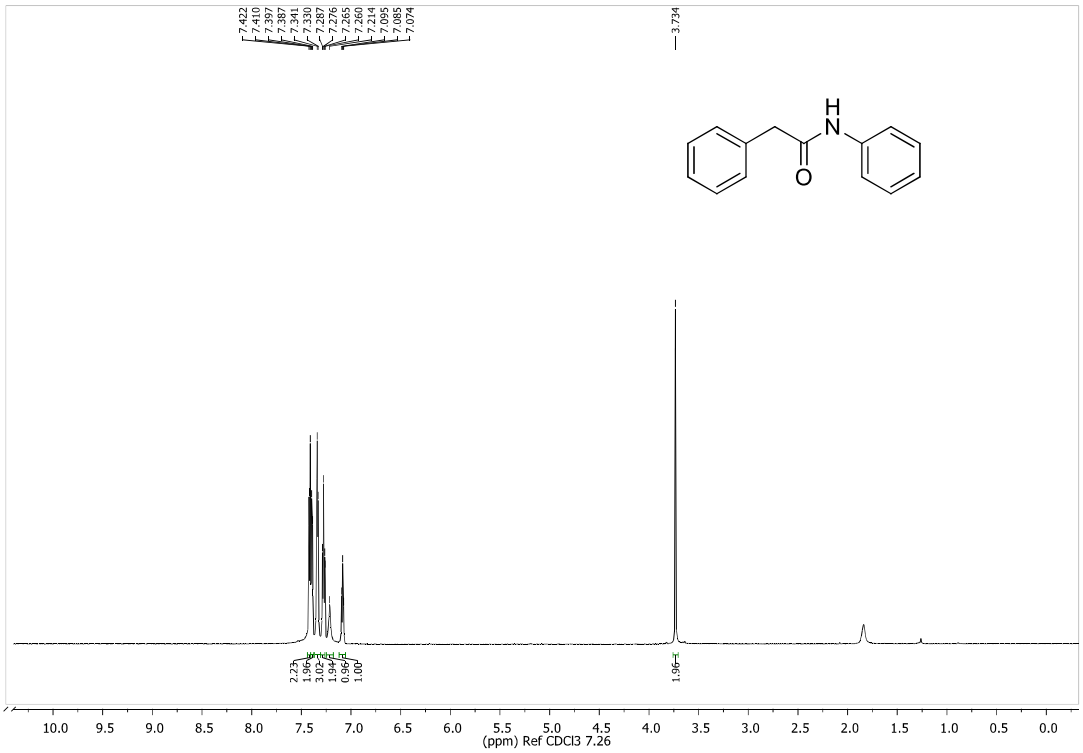


Figure 3.36a: ^{1}H NMR spectrum of **74**

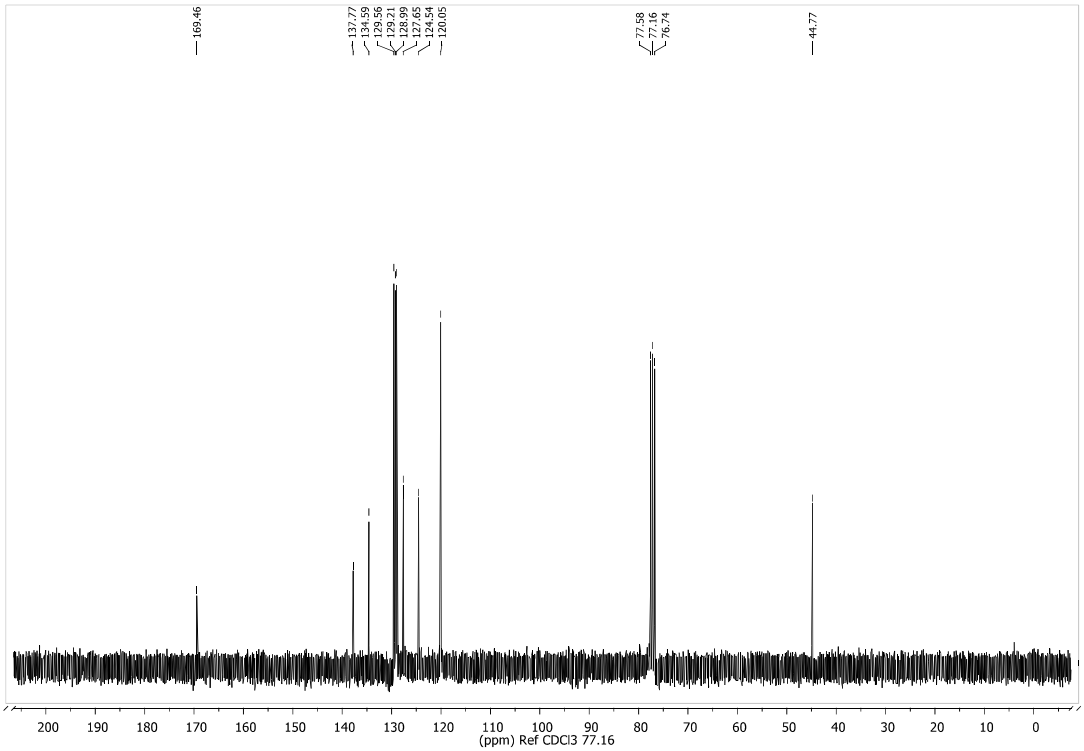


Figure 3.36b: ^{13}C NMR Spectrum of **74**

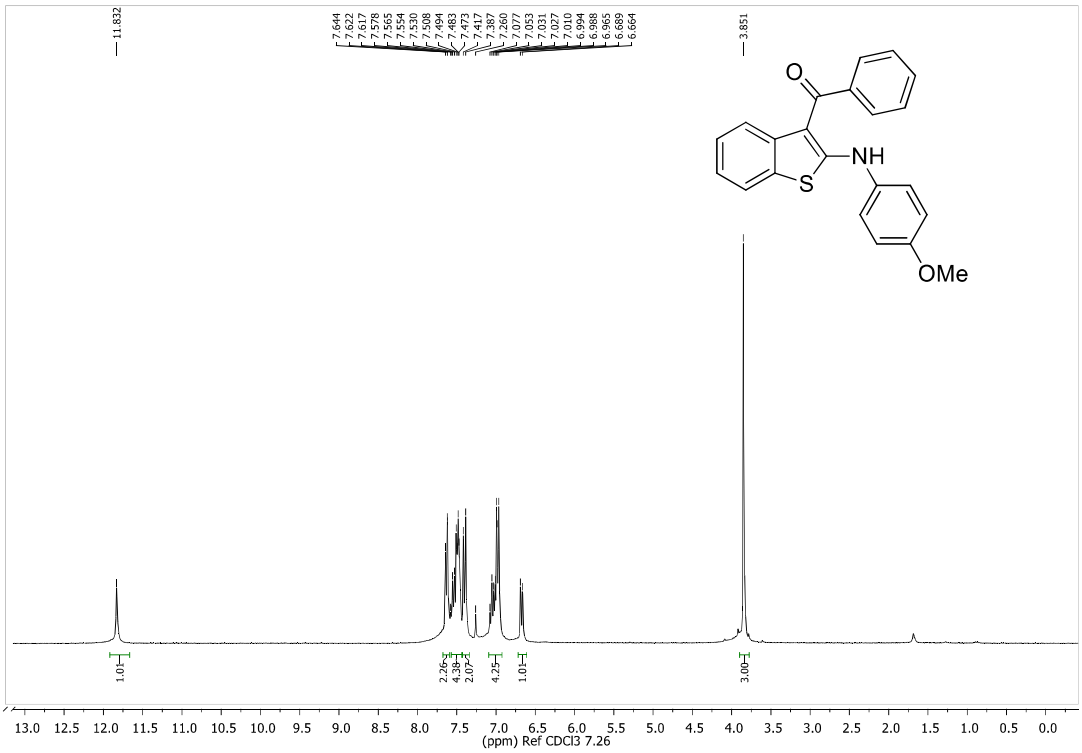


Figure 3.37a: ^{1}H NMR Spectrum of **75n**

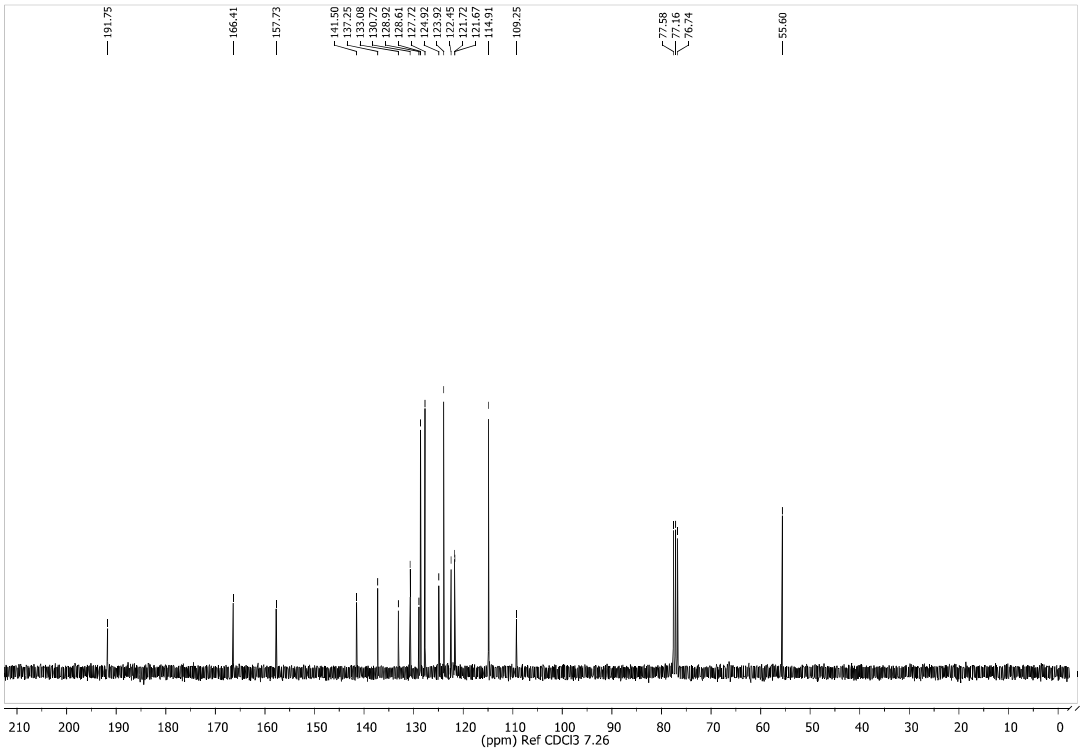


Figure 3.37b: ^{13}C NMR Spectrum of **75n**

3.9 Crystal Data

Crystallographic data of **72** in CH_2Cl_2/n-hexane: $C_{16}H_{14}N_2OS$, Mw = 282.35, monoclinic, space group P21, a = 9.9642(2) Å, b = 8.63850(10) Å, c = 16.1743(3) Å, α = 90 °, β = 94.7160(10) °, γ = 90 °, V = 1387.50(4) Å^3, Z = 4, D_{calc} = 1.352 g/cm^3, T = 296(2) K, R_1 = 0.0398 {I>=2σ (I)}, wR_2 = 0.1236, GOF = 1.027.

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New Approach for the Synthesis of Indolo Fused Quinolines and Quinolones: Synthesis of Iscocryptolepine Derivatives

4.1 Introduction

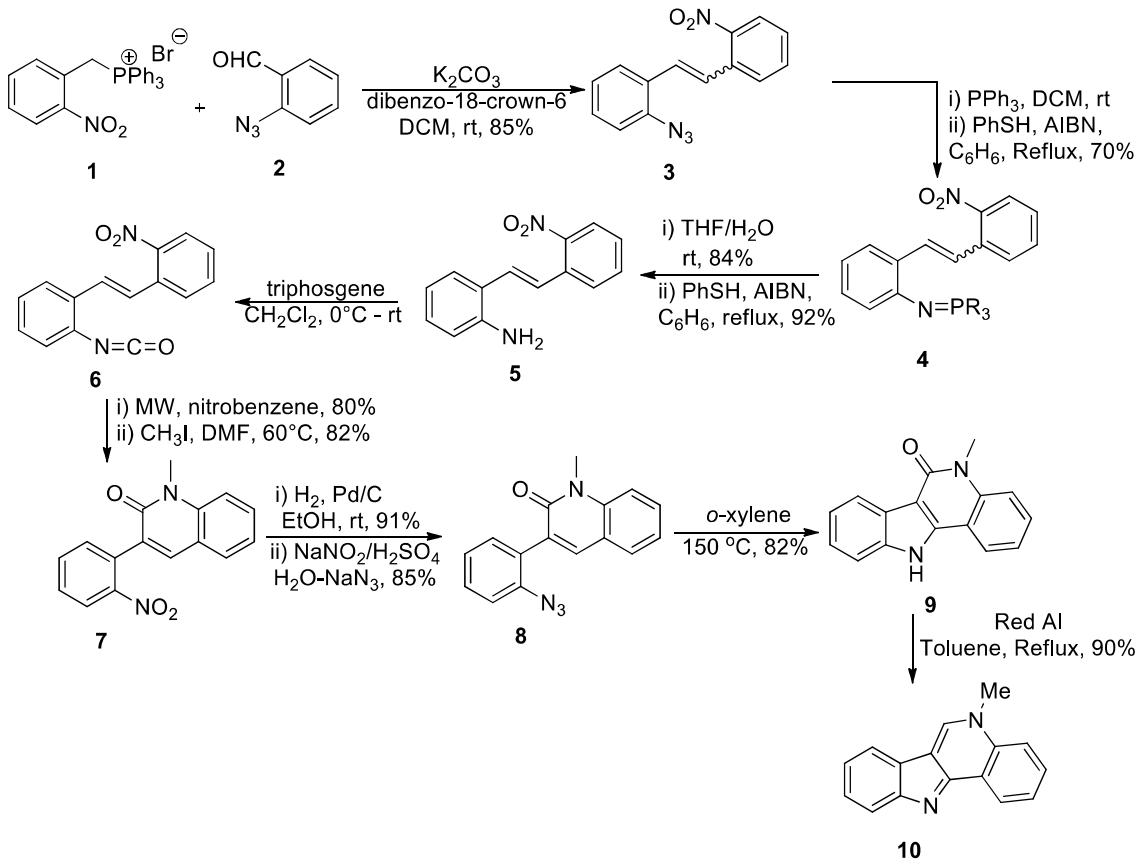
After the golden era of cross-coupling reactions, C−H bond functionalization reactions received great attention because the possibility of introduction of new functionality (or new C−C bond) without the requirement of pre-functionalized starting materials such as haloarenes, boronic acids, siloxanes, etc. is of great advantage.[1] Right from the beginning, synthetic chemists experimented C−H functionalization reactions by using Pd, Ru, and Rh.[2] The advantage of using these metals is that they are known to activate C−H bonds in a regio- and stereo-selective manner assisted with high functional group tolerance and very good yields. Although, these metals were capable of activating the C−H bonds, several drawbacks are associated with these metals such as toxic, expensive, and highly ligand dependant. Hence, to develop an alternative methodology for C−H bond activation; synthetic chemists explored cheaper, more abundant, and eco-friendly metals such as Cu, Fe, Co, Ni, Mn and other metals.[3] However, synthesis of pure compounds without any metal trace impurities is a necessity for biologically and pharmaceutically active molecules such as natural products and drugs. In this regard, using transition metals have a major drawback, because removal of trace amount of metal impurities from the resultant product is highly challenging. To overcome these drawbacks, in the recent days, synthetic chemists developed new methodologies, which are mild and cost effective under transition metal free conditions. In this context, hypervalent iodine reagent mediated C─H functionalization reactions are highly interesting.[4] Since the past few years, hypervalent iodine mediated oxidative C─N bond forming reactions have received much attention because this approach is a powerful synthetic tool for the construction of *N*-

heterocycles, which are found in many natural products and several biologically active molecules.

In the family of indoloquinolines, cryptolepines, isocryptolepine derivatives have unique properties i.e. they exhibit promising anticancer and antimalarial properties. Several methods were developed for synthesis of these molecules, but most of the reports involve either usage of indole or quinoline as the precursors. We envisioned a new method for the synthesis of isocryptolepines from two commercially available acyclic starting materials under transition metal free conditions. The results and previously known methods for synthesis of isocryptolepine have been discussed in this chapter.

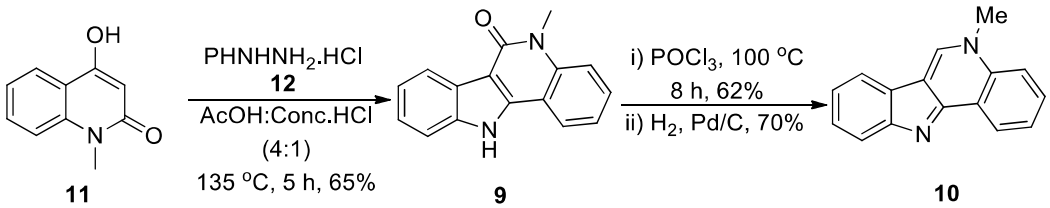
4.2 Previous Reports for the Synthesis of Isocryptolepines:

The first synthesis of isocryptolepine was reported back in 1999 by Fresneda and co-workers following a nine steps methodology from (2-nitrobenzyl)triphenylphosphonium bromide (**1**) and *o*-azidobenzaldehyde (**2)** as precursors. Initially, these two precursors undergo Wittig reaction to produce the corresponding stilbene derivative **3** in mixture of *E*:*Z* isomers. The resultant derivative **3** was subjected to triphenylphosphine resulting in generation of iminophosphorane **4** followed by isomerisation in the presence of thiophenol/AIBN afforded exclusively the *E*-isomer of stilbene derivative **5**. The resultant stilbene derivative **5** was converted to quinolin-2-one derivative **7** by sequential treatment with triphosgene and further microwave-promoted cyclization of the resulting isocyanate **6**. Later, the nitro groups of quinolone **7** was reduced, diazotised followed by indolization at 180 ºC gave the indoloquinolone derivative **9**. Finally, these indoloquinolone **9** was reduced in the presence of Red-Al to afford isocryptolepine (**10**)[5] in 90% yield (Scheme 4.1).



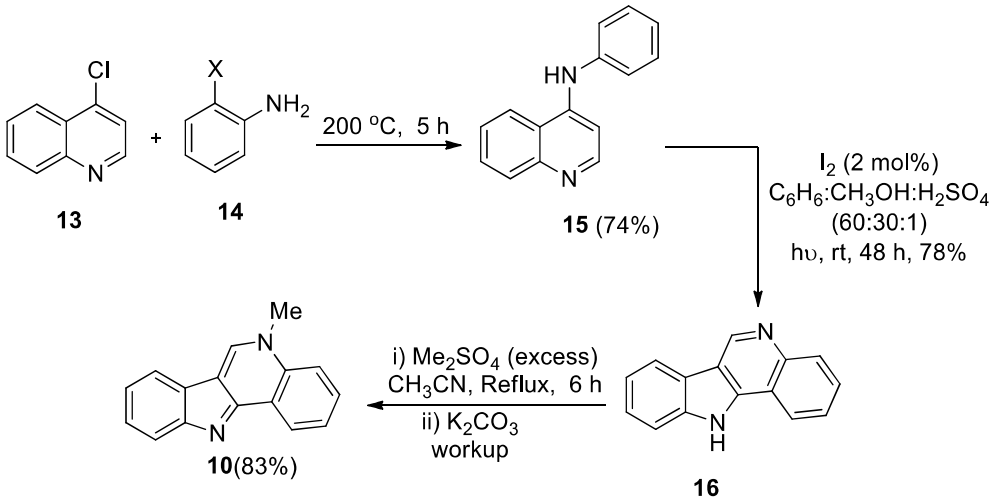
Scheme 4.1: *First Report for the Synthesis of Isocryptolepine*

In 2005, Mohan and co-workers used Fischer indole synthesis approach to synthesize isocryptolepine derivatives **10**.[6] Initially, 4-hydroxy-1-methyl-1*H*-quinolin-2-one (**11**) underwent Fischer indole reaction with phenylhydrazine hydrochloride (**12**) to yield the indoloquinolone **9** in 65%. Further, this indoloquinolone **9** reacted with $POCl_3$, followed by hydrogenolysis to afford isocryptolepine (**10**) (Scheme 4.2).



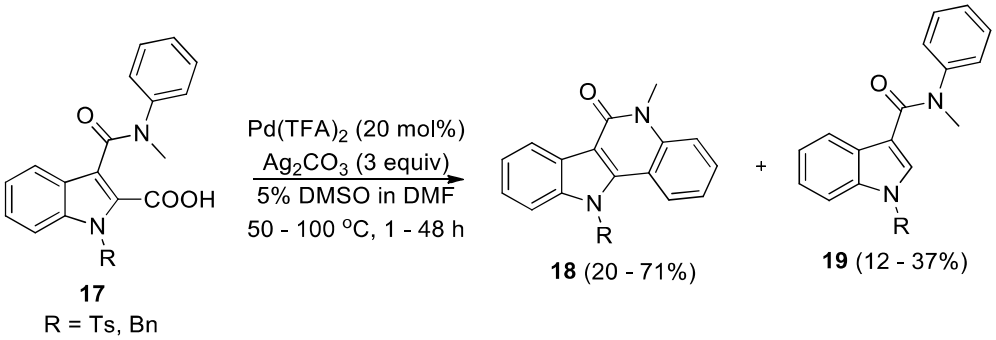
Scheme 4.2: *Synthesis of Isocryptolepines via Fischer Indole Approach*

In 2006, the same group developed an alternative three steps protocol for the synthesis of isocryptolepine derivatives **10**.[7] The first step of this protocol is the reaction of haloquinolines **13** with anilines **14** at 200 °C afforded the corresponding anilinoquinolines **15**, which upon photocyclization in the presence of molecular iodine delivers the indoloquinolines **16**. The resultant indolquinoline derivative **16** was methylated by using dimethyl sulphate followed by neutralisation to afford isocryptolepine **10** (Scheme 4.3).



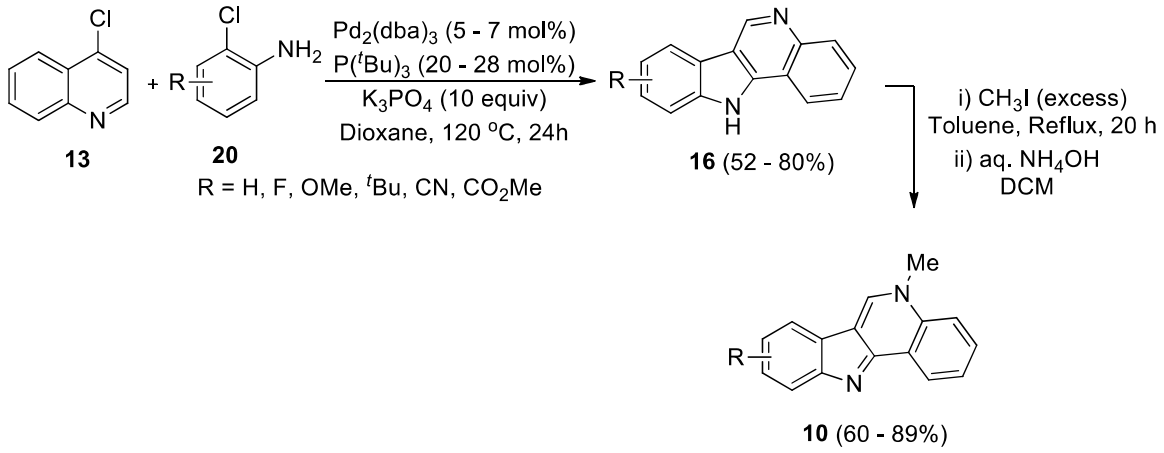
Scheme 4.3*: Synthesis of Iscocryptolepines via Photocyclisation of Anilinoquinolines*

Later, Miki and co-workers performed decarboxylative Heck type coupling of 1-benzenesulfonylindole-2-carboxylic acid **17** to synthesize indolo fused quinolones **18** in the presence of 20 mol% $Pd(TFA)_2$ by using silver carbonate. In this process, they also observed the decarboxylated product **19** along with the desired product **18** (Scheme 4.4).[8]



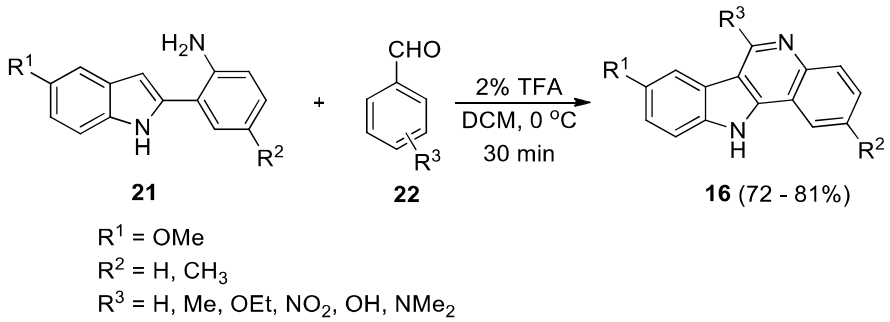
Scheme 4.4: *Decarboxylative Heck Approach for the Construction of Indoloquinolones*

In 2008, Maes's group constructed indoloquinolines in a tandem fashion from 4-chloroquinoline (**13**) and *N*-unsubstituted 2-chloroaniline **20**. The elementary step of the reaction involves palladium mediated intermolecular C─N bond formation under Buchwald-Hartwig approach followed by C─C bond formation resulting in the formation of desired double cross-coupled product **16**, which on methylation afforded isocryptolepine analogues **10** (Scheme 4.5).[9]



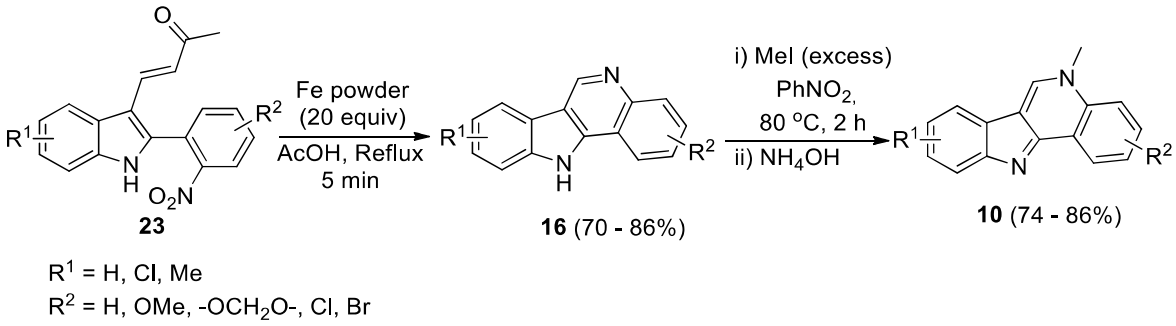
Scheme 4.5: *Palladium Mediated Cascade Double Heteroannualtion of 2-Chloroanilines*

In 2009, Kundu and co-workers devised a simple methodology to synthesize indoloquinoline derivatives **16** by using modified Pictet-Spengler approach. Initially, 2-(1*H*-indol-2-yl)anilines **21** reacted with benzaldehyde derivatives **22** resulted in the formation of imine, which on further nucleophilic attack by indole led to the formation of indoloquinoline derivatives **16** in good to very good yields (Scheme 4.6).[10]



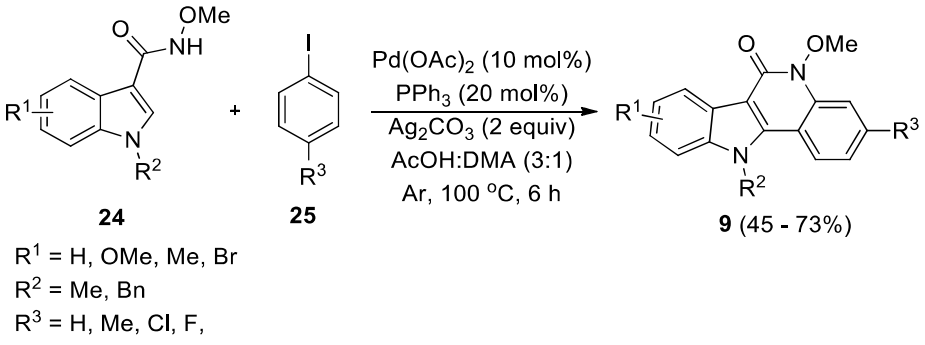
Scheme 4.6: *Synthesis of Indolo[3,2-c]quinolines via Modified Pictet-Spengler Approach*

Butin and co-workers reported the synthesis of indolo[3,2-*c*]quinoline derivatives **10** through reductive cyclisation of 3-(2-acylvinyl)-2-nitroaryl indoles **23** in the presence of Fe/HCl. Further, these indolo fused quinolines were transformed into isocryptolepines **10** in good to very good yields by treating with excess MeI in nitrobenzene solvent (Scheme 4.7).[11]



Scheme 4.7: *Reductive Cyclization Approach for the Synthesis of Indolo[3,2-c]quinolines*

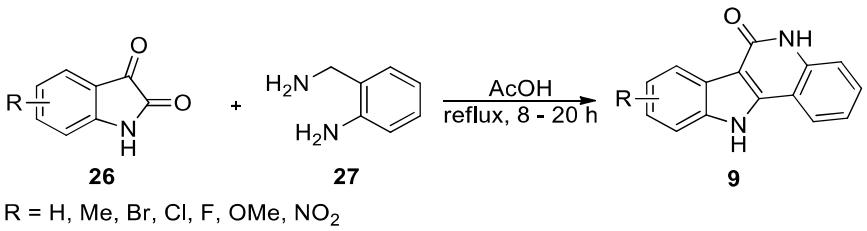
In 2014, Lin's group developed a new approach for the synthesis of indoloquinolones **9** via palladium catalysed tandem C─C/C─N bond formation of indole-3-carboxamides **24** and iodoarenes **25** (Scheme 4.8).[12]



Scheme 4.8: *Construction of Indoloquinolones via Pd(II)-Catalyzed Tandem C─C/C─N Bond Formation*

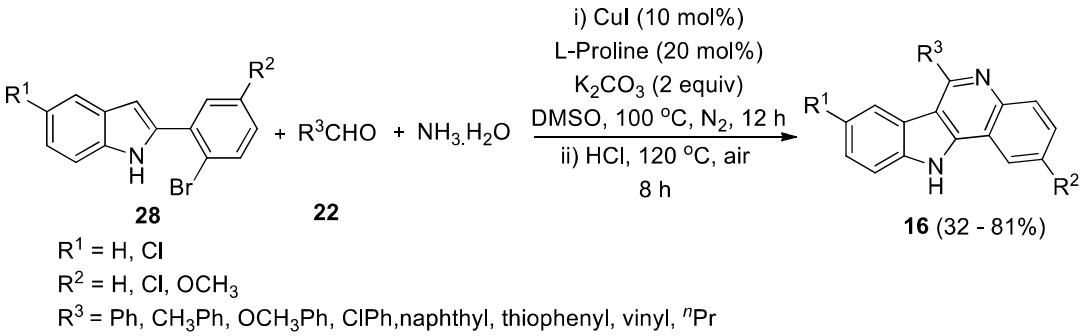
Inokuchi and co-workers developed a simple and mild method to achieve indoloquinolone derivatives **9** from isatin **26** and 2-aminobenzyl amine derivatives **27** upon

treatment with AcOH at reflux conditions. Further, these synthesized derivatives were studied for antimalarial, antiplasmodial, cytotoxic, *β*-haematin inhibition activities (Scheme 4.9).[13]



Scheme 4.9: *Synthesis of Indoloquinolones from Isatain and 2-Aminobenzyl Amine*

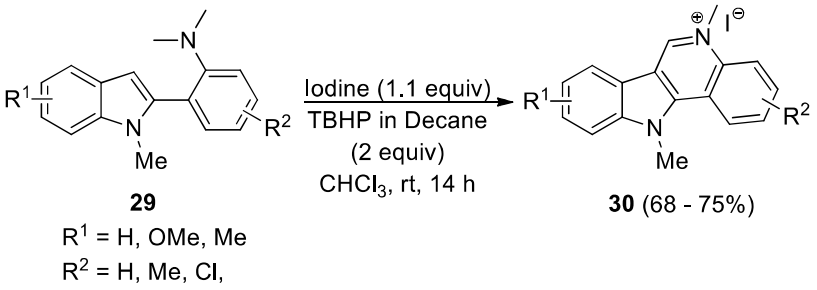
Guo and co-workers demonstrated highly selective and controlled method to synthesize 11*H*-indolo[3,2-*c*]quinolones **16** through copper-catalyzed one-pot cascade reactions of 2-(2-bromoaryl)-1*H*-indoles **28** with aldehydes **22** and aqueous ammonia. The first step of the reaction is the formation of 6-phenyl-5,6-dihydroindolo[1,2-*c*]quinazoline which undergoes rearrangement under acidic conditions to produce desired indolo fused quinoline derivatives **16** (Scheme 4.10).[14]



Scheme 4.10: *Copper-Catalyzed Cascade Reactions of 2-(2-Bromoaryl)-1H-indoles with Aldehydes and Aqueous Ammonia*

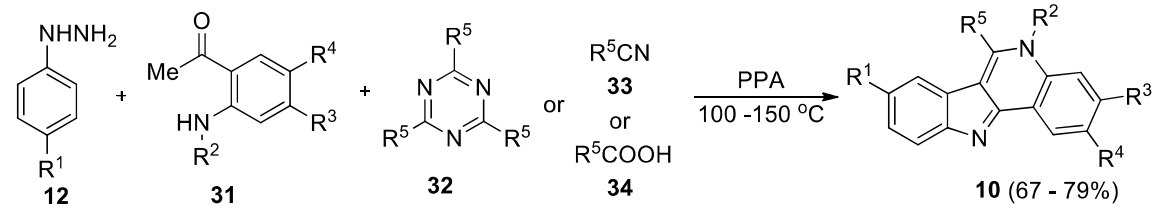
In 2016, Tilve and co-workers constructed the indoloquinoline derivatives **30** via transition metal free sp^3 C─H activation of *N,N*-dimethyl-2-(1-methyl-1*H*-indol-2-yl)aniline derivatives (**29**) through cross dehydrogenative coupling. They performed the control experiments and proposed the mechanism, involving generation of imminium ion in the

presence of I_2/TBHP, which undergo intramolecular nucleophilic attack by indole affording the isocryptolepine derivatives **30** (Scheme 4.11).[15]



Scheme 4.11: *Synthesis of Indoloquinolines via Iodine-Mediated Intramolecular Dehydrogenative Coupling*

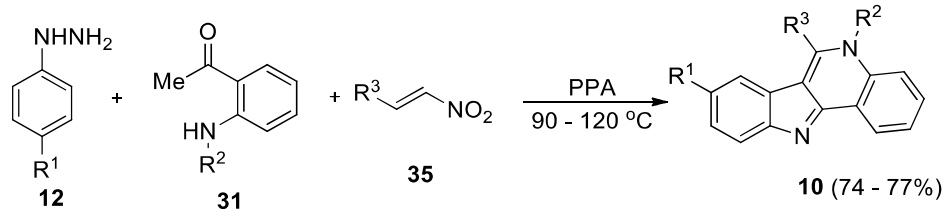
In 2017, Aksenov and coworkers developed a one pot approach to synthesize indoloquinoline derivatives **10** by Fischer indole synthesis. Their strategy involves PPA-assisted cascade 2-fold heteroannulation of arylhydrazines **12**, *o*-aminoacetophenones **31** and triazines **32** or nitriles **33** or carboxylic acids **34**. The first step of the method involves formation of hydrazone from acetophenone **31** and hydrazine **12** followed by Fisher indole cyclisation to afford indole. Further, acylation of the amine moiety of 2-aryl indole with carboxylic acid or nitrile or triazine which would spontaneously undergo an intramolecular Vilsmeier reaction to furnish indoloquinoline **10** (Scheme 4.12).[16]



Scheme 4.12: *Three Component One-Pot Synthesis of Isocryptolepines*

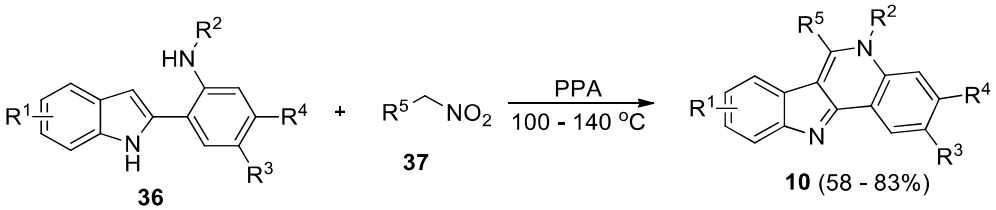
Later, the same group studied a three component one pot reaction by using nitrostyrene **35** and nitroalkanes **37** *via* Fischer indole reaction conditions (Scheme 4.13 & 4.14). Here,

nitrostyrene **35** and nitroalkanes **37** were electrophilically activated by PPA, which was attacked by indole followed by cyclisation resulted in the formation of indoloquinoline derivatives **10**.[17] They also carried out biological studies and found that the analogues of isocryptolepine derivatives exhibiting anti-proliferating activity against cancer cells.



R^1 = H, Me
R^2 = Me
R^3 = Ph

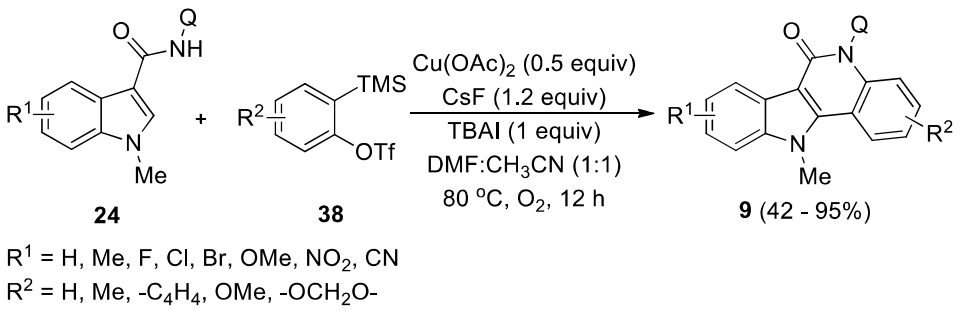
Scheme 4.13: *PPA Mediated Unexpected Cyclization of Fisher Indole Adduct 2-(2-Aminophenyl) Indole with Nitroalkene*



R^1 = H, Me
R^2 = Me
R^3, R^4 = H, OMe
R^5 = H, Me, Ph

Scheme 4.14: *Nitroalkane Based One –Pot Three Component Synthesis of Isocryptolepine*

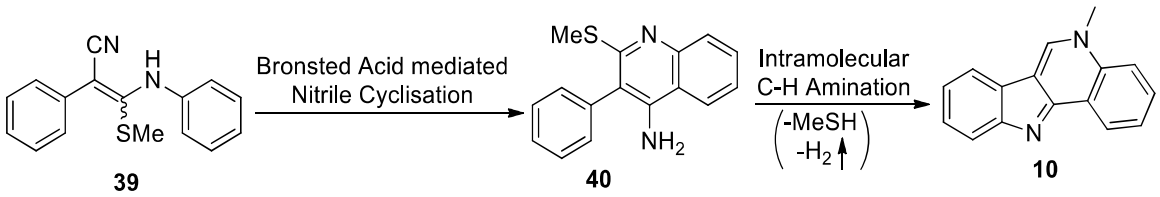
Very recently, Zhang and co-workers investigated the intermolecular annulation reaction to synthesize the isocryptolepine derivatives.[18] In the current method, the desired indoloquinolone derivatives **9** were obtained *via* directing group assisted intermolecular cascade C─H/N─H annulation of indole carboxamides **24** with arynes **38** by using environmentally benign copper metal (Scheme 4.15).



Scheme 4.15: *Copper-Mediated Cascade C−H/N−H Annulation of Indolocarboxamides with Arynes*

With this detailed literature survey, we concluded that each report has its own advantages and disadvantages. In most of the reports, they have used either indoles or quinolones as precursors to construct these indolo quinolines. The transition metals are mostly used for cross-coupling or C─H functionalization reactions. Despite good yields, some methods suffer from tedious reaction procedures, usage of specific starting materials, limited substrate scope and elevated temperatures.

Contrary to the aforesaid literature reports, we envisioned a methodology that utilizes acyclic precursors (*S,N*-acetals) which upon Bronsted acid mediated nitrile cyclisation yields 4-amino quinoline derivative; which upon intramolecular C─H amination affords indolo-quinoline derivative. The sole advantage of the envisioned method is the simple protocol with a wide substrate scope, single precursors and very minimum by-products such as MeSH & H_2 (Scheme 4.16).



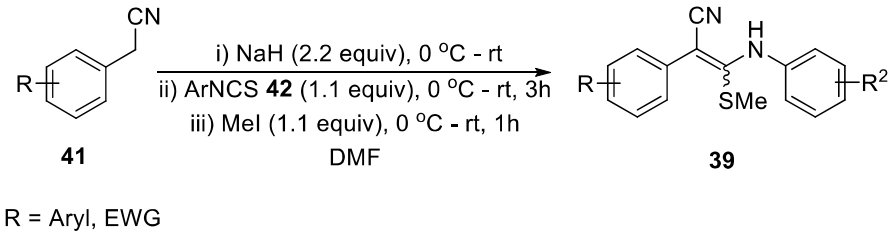
Scheme 4.16: *Our Approach for the Synthesis of Isocryptolepines*

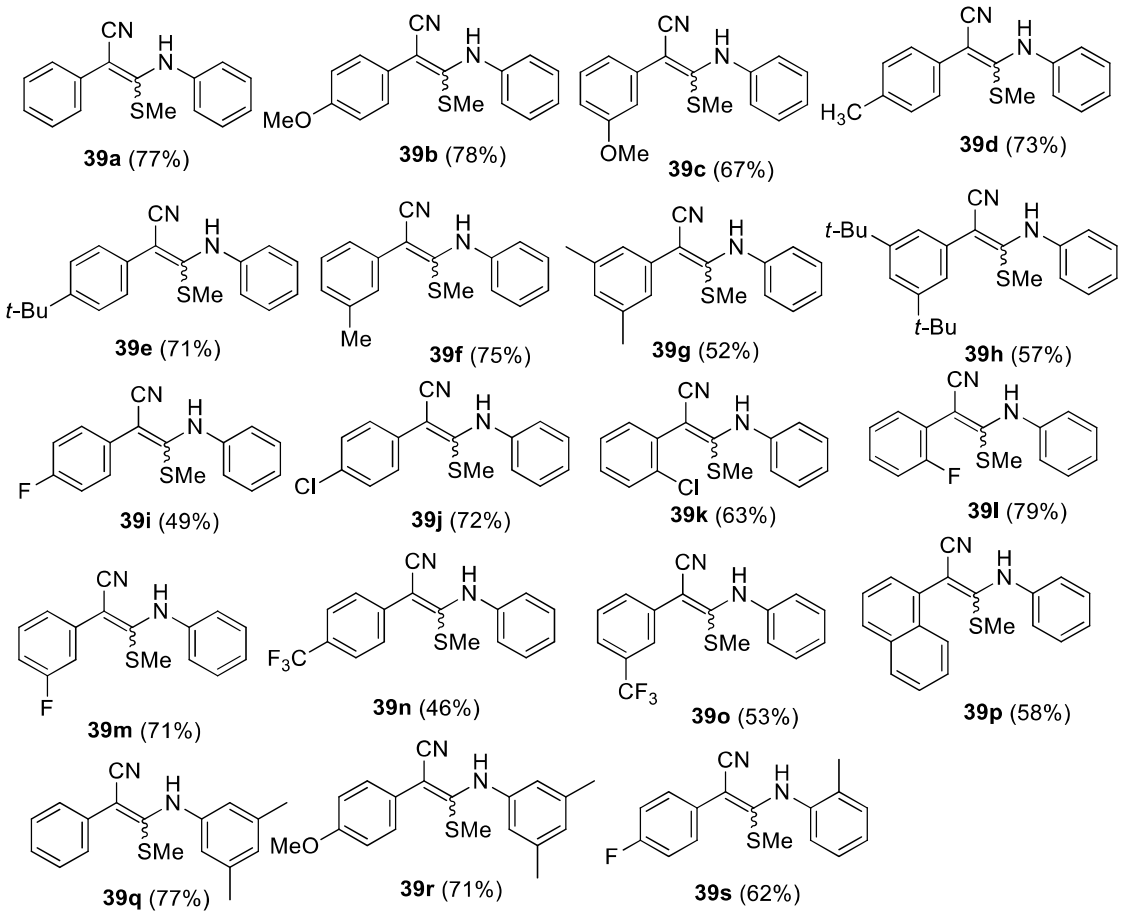
PART-A

The first part of isocryptolepine synthesis is the preparation of 3-aryl-4-amino quinolines. Hence, we envisioned a simple protocol to synthesize 3-aryl-4-amino-quinoline from substituted *β*-amino acrylonitriles under Gatterman type of cyclization conditions.

4.3 Results and Discussions:

Table 4.1: Synthesis of *β*-Aminoacrylonitriles





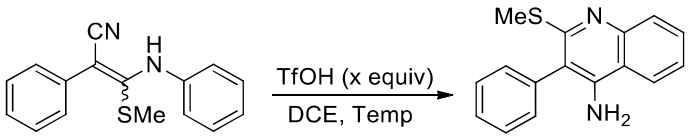
4.3.1 Synthesis of Ketene *S,N*-Acetals

Thus, the required ketene *S,N*-acetals were prepared by treating aryl acetonitriles with NaH in DMF to generate anion, which was further quenched with aryl isothiocyanates and 1 equiv methyl iodide to afford moderate to very good yields of the required ketene *S,N*-acetals **39a-s**. These resulted β-amino acrylonitrile derivatives **39** were characterised by using spectral and analytical data.

4.3.2 Optimization of Reaction Conditions for Intramolecular Gattermann Type Cyclization

After synthesis of various ketene *S*, *N*-acetals, we turned our attention to optimize the reaction conditions for intramolecular Gattermann type of cyclisation of nitrile. Thus, we have chosen the *β*-aminoacrylonitrile **39a** as model substrate and treated with 5 equiv of TfOH in the presence of DCE as a solvent. Unfortunately, this reaction produced complex mixture of products even at 60 ºC (Table 4.2, Entry 1). The similar trend was observed when we performed the reaction with 10 equiv of TfOH (Table 4.2, Entry 2). Interestingly, when we carried out the reaction in the presence of 13 equiv of TfOH (undistilled) at 60 ºC, we observed 50% of the corresponding 4-aminoquinoline derivative **40a** (Table 4.2, Entry 3). For further fine tuning of this process, we carried out the reaction with combination of 5 equiv TfOH and 5 equiv of triflic anhydride. But this reaction yielded only 40% of the cyclised product **40a** (Table 4.2, Entry 4). On the other hand, the reaction in the presence of molecular sieves was found to be ineffective (Table 4.2, Entry 5). The reaction with the combination of TfOH and TFA also a gave only 53% of the desired product **40a** (Table 4.2, Entry 6). Delightfully, when we carried out the reaction in the presence of 13 equiv of TfOH, which was distilled over P_2O_5 afforded excellent yield of the corresponding 4-aminoquinoline derivative **40a** (Table 4.2, Entry 7).

Table 4.2: Optimization of intramolecular Gattermann Reaction



39a **40a**

Entry	(X equiv) TfOH	Temp	Time	Product[a]
1	5	rt → 60˚C	3h	Multiple spots
2	10	rt → 60˚C	3h	Multiple spots
3	13 (Undistilled)	60 ˚C	3 h	50
4	5 + 5 (Triflic anhydride)	60 ˚C	3 h	42
5	13 + Molecular sieves	60 ˚C	3 h	49
6	13 + TFA	60 ˚C	3 h	53
7	13 (distilled over P_2O_5)	60 ˚C	3 h	90

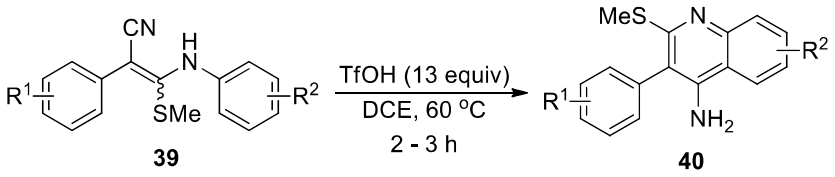
[a]*Along with uncharacterized product of 10-30%.*

With this brief optimization study, we concluded that 13 equiv of TfOH, which was distilled over P_2O_5 in the presence of 1,2-DCE at 60 ºC was the appropriate condition for this intramolecular Gattermann type of cyclisation.

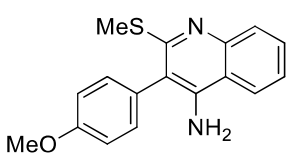
With the optimized conditions in our hands, we moved on to investigate the TfOH mediated Gattermann type of cyclisation of several ketene *S,N*-acetals **39b-s**. Initially, we studied the effect of substitutions at *α*-aryl group of acrylonitrile derivatives. Thus, 4-methoxy substituted acrylonitrile **39b** was treated with the optimized reaction conditions and 46% of the desired product **40b** was observed. Similarly, 3-methoxy substituted *S,N*-acetal **39c** was also smoothly converted into the corresponding 4-amino quinoline derivative **40c**. At the same time, alkyl substituted amino quinolines **40d-f** were synthesized from the corresponding precursors **39d-f** with 46 -51% yield. Interestingly, 3,5-dimethyl substituted 4-amino quinoline **40g** was obtained in 74% yield under the optimized reaction conditions. On the other hand, 3,5-ditertiary

butyl-phenyl substituted acrylonitrile derivative **39h** afforded only 47% of the Gattermann cyclised product **40h**. We also examined the halo substituted *S,N*-acetals **39i-m**, which also delivered moderate to good yields of the corresponding amino quinoline derivatives **40i-m** under established reaction conditions with high functional group

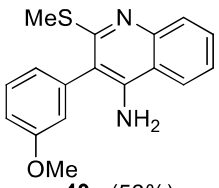
Table 4.3: Synthesis of 3-Aryl-4-Aminoquinolines 40



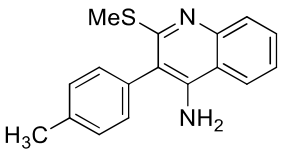
39 40



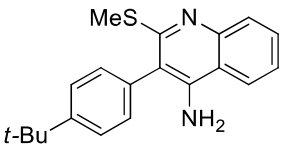
40b (46%)



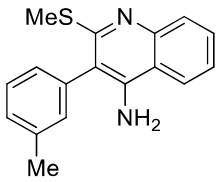
40c (53%)



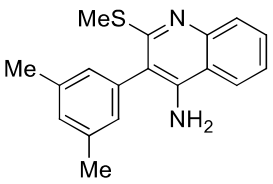
40d (47%)



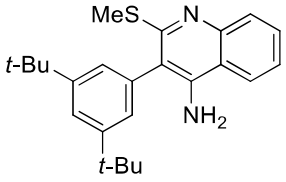
40e (46%)



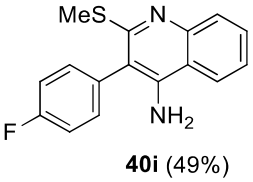
40f (51%)



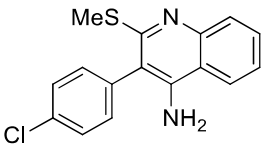
40g (74%)



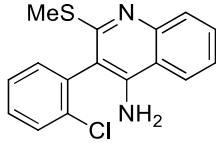
40h (47%)



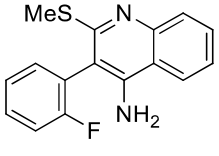
40i (49%)



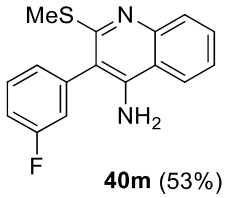
40j (44%)



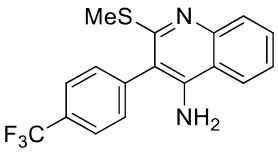
40k (73%)



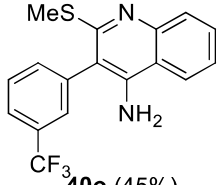
40l (44%)



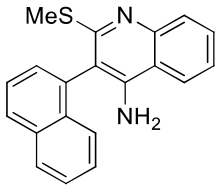
40m (53%)



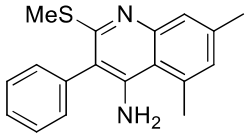
40n (49%)



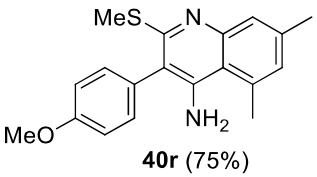
40o (45%)



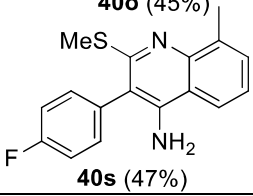
40p (37%)



40q (60%)



40r (75%)

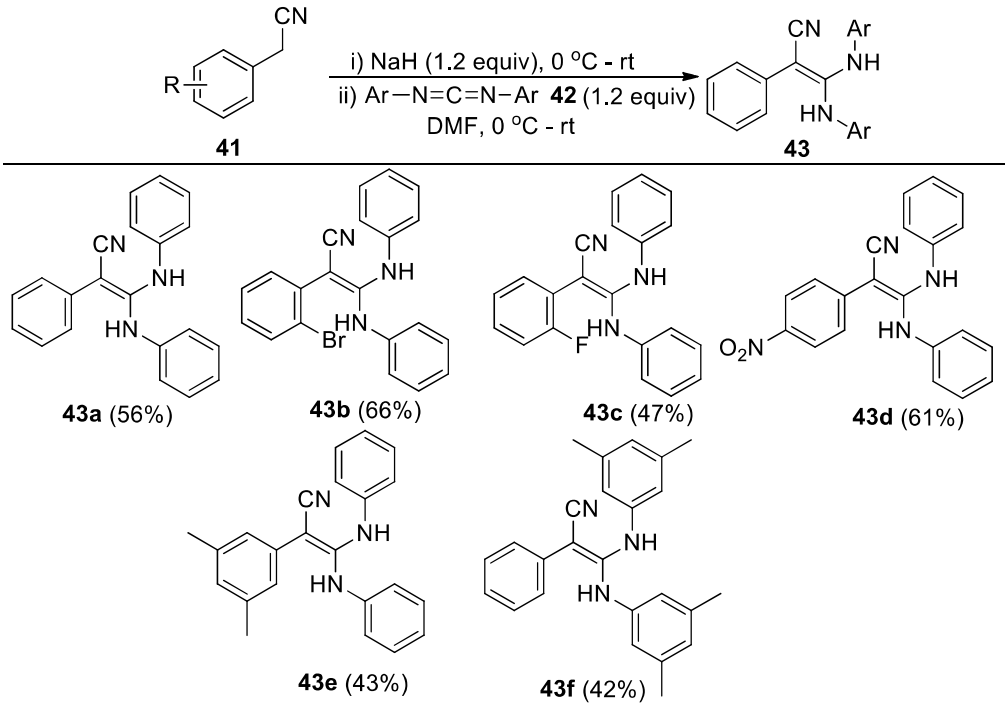


40s (47%)

tolerance. On the other hand, when we subjected the electron withdrawing group substituted acrylonitriles **39n-o** to identical reaction conditions, we observed 45 - 49% of the amino qinoline derivatives **40n-o**. Naphthyl substituted amino quinoline **40p** was obtained in 37% from the corresponding acrylonitrile derivative **39p**.

Next we moved to study the effect of substituted *N*-aryl ketene *S,N*-acetals **39q-s** on this intramolecular cyclisation process. Thus, *N*-(3,5-dimethyl-phenyl) substituted acrylonitrile derivative **39q** was treated with TfOH and 60% of the 4-amino quinoline derivative **40q** was observed. Similarly, (*E*) & (*Z*)-3-((3,5-dimethylphenyl)amino)-2-(4-methoxyphenyl)-3-(methylthio) acrylonitrile (**39r**) was also smoothly transformed into the corresponding cyclised product **40r** in 75% yield. 3-(4-Fluorophenyl)-8-methyl-2-(methylthio)quinolin-4-amine (**40s**) obtained from the respective *S,N*-acetal **39s** was obtained under optimized reaction conditions.

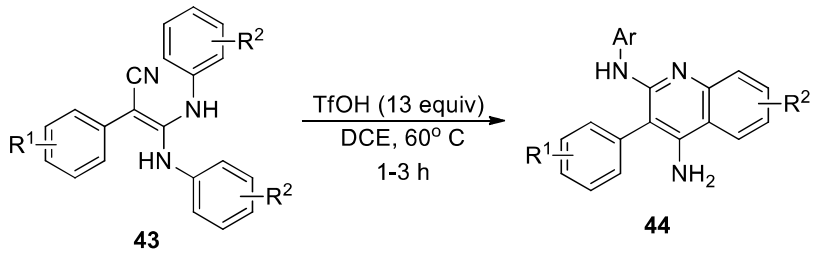
Table 4.4: Synthesis of Ketene Aminals 43



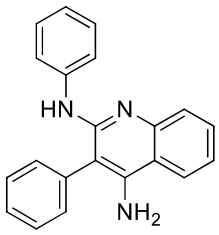
Next, we extended this methodology to ketene aminals for synthesizing 2,4-diamino quinoline derivatives. Therefore, the required ketene aminals were synthesized by reacting the anion of benzyl cyanides **41** with carbodiimides **42**. These ketene aminals **43** were obtained in moderate to good yields (Table 4.4).

With the ketene aminals in our hands, we moved on to investigate the intramoleular Gattermann type cyclisation. Thus, unsubstituted ketene aminal **43a** was treated with optimized reaction conditions and observed very good yield of the corresponding diamino quinoline derivative **44a**. Similarly, 2-halo substituted acrylonitrile derivatives **43b-c** were also smoothly transformed into desired products **44b-c** in very good to excellent yields. However, 4-nitro substituted ketene aminal **43d** yielded only 67% of the product **44d**. 2-(3,5-

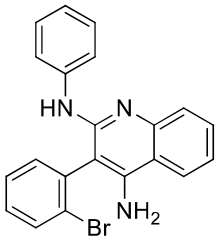
Table 4.5: Intramolecular Gattermann Type Cyclisation of Ketene Aminals 43



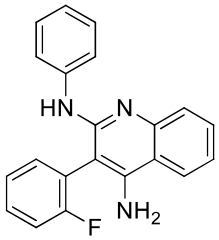
43 **44**



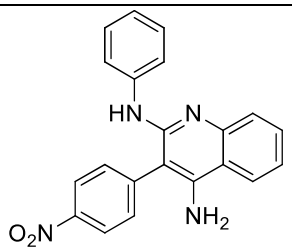
44a (84%)



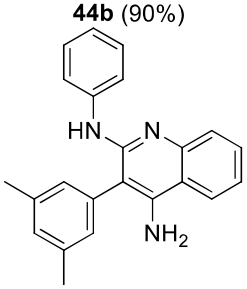
44b (90%)



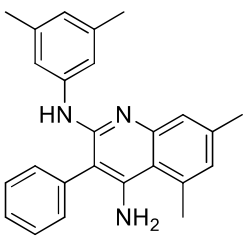
44c (80%)



44d (67%)



44e (84%)



44f (98%)

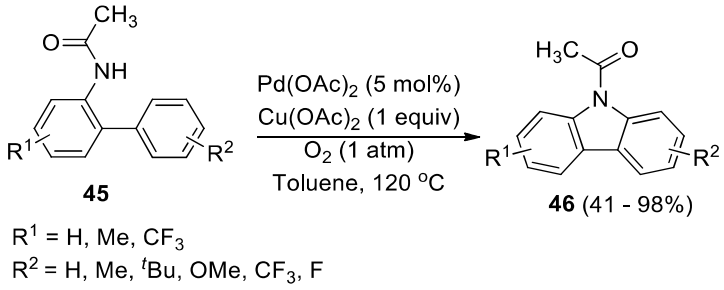
Dimethylphenyl)-3,3-bis(phenylamino)acrylonitrile (**43e**) underwent intramolecular nitrile cyclisation by affording very good yield of the amino quinoline derivative **44e**. Interestingly, *N*-(3,5-dimethylphenyl) substituted aminal **43f** afforded quantitative yield of the Gatttemann type cyclised product **44f** under optimized reaction conditions (Table 4.5).

PART-B

After successful synthesis of various 4-aminoquinolines with functional group diversity, we intended to demonstrate the synthetic utility these resulted products. The 4-amino-3-arylquinolines are important structural motifs for C─N bond formation because free amino group and aryl C─H bonds are in very close proximity which makes it easy for C─H functionalization. Focusing on the previous literature reports, the C─N bond formation became a highly useful approach for the synthesis of nitrogen based heterocycles. In this context, remarkable progress have been made by constructing a diverse range of Carbon–Nitrogen bonds under transition metal catalysis. According to the recent study, C─N bond formation reactions accounted a major portion in total synthesis of natural products and medicinally important molecules. In this context, cross-coupling reactions were widely investigated by using aryl/alkyl halides and amines/amides as the coupling partners. Consequently, these cross-coupling reactions were replaced by direct C─H functionalization reaction. As discussed earlier, a direct C─H functionalization strategy is a powerful synthetic tool for construction of heterocycles without prefunctionalized starting materials. In this context, various transition metals were extensively investigated to synthesize wide range of heterocycles including indoles, carbazoles, imidazoles, etc. In particular, carbazole is the privileged structural motif of several alkaloids and natural products. Due to its wide range of applications various attempts have been made to synthesize these carbazole derivatives via C─H functionalization strategy.

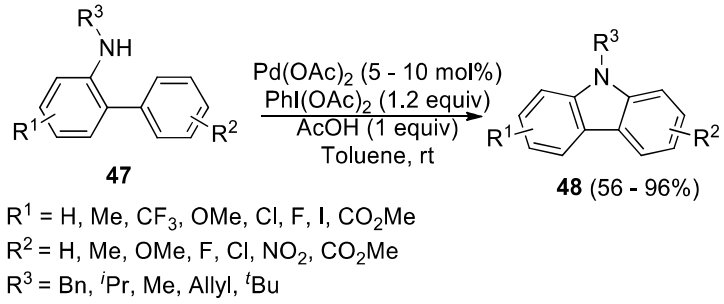
In this part, reported methods for synthesis of carbazoles via intramolecular C─H aminatiom/amidation have been discussed.

First report for the intramolecular C─N Formation *via* C─H functionalization was reported by Buchwald and co-workers. In this report, they studied palladium mediated tandem directed C─H functionalization and amide arylation to synthesize *N*-acetyl carbazole derivatives **46** from 2-acetaminobiphenyl derivatives **45** by using $Cu(OAc)_2$ as an oxidant at 120 ºC (Scheme 4.17).[19]



Scheme 4.17: *First Report for Synthesis of Carbazoles from 2-Acetamido Biphenyls*

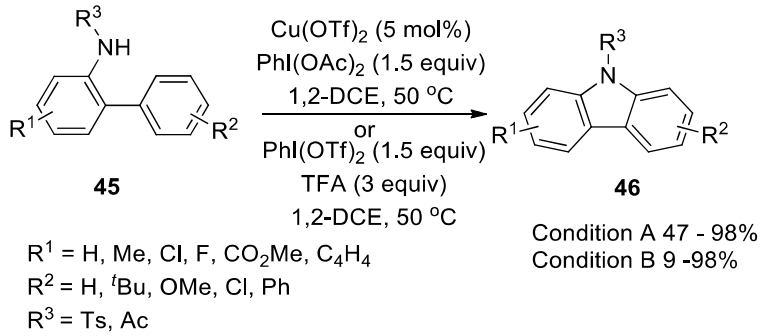
In 2008, Gaunt and co-workers investigated the palladium catalysed intramolecular C─H amination of 2-alkylminobiphenyl derivatives to afford *N*-alkyl protected carbazoles. They used a hypervalent iodine reagent $PhI(OAc)_2$ as an oxidant for this oxidative cyclization process. For proposing the mechanism, they isolated the trinuclear cyclopalladation complex



Scheme 4.18: *Palladium Mediated Oxidative C─N Bond Formation of N-Protected Amino Biphenyls*

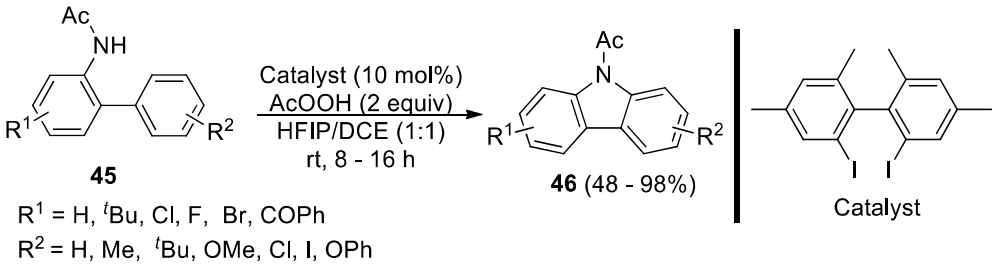
from the reaction mixture, where Palladium was existed in +4 oxidation state, which promotes rapid reductive elimination (Scheme 4.18).[20]

After 3 years, Chang and co-workers studied the intramolecular oxidative C─N bond formation reaction under either copper mediated or metal free conditions by using $PhI(OTf)_2$ as an oxidant. In this report, the combined use of $Cu(OTf)_2$ and $PhI(OAc)_2$ produced higher yields as compared to the oxidant based C─H amidation. Hence, they performed a series of mechanistic studies such as kinetic isotope effects, reaction rate profile, and radical inhibition and proposed that copper species involves in the activation of $PhI(OTf)_2$/ $PhI(OAc)_2$, which facilitates the C─N bond formation (Scheme 4.19).[21]



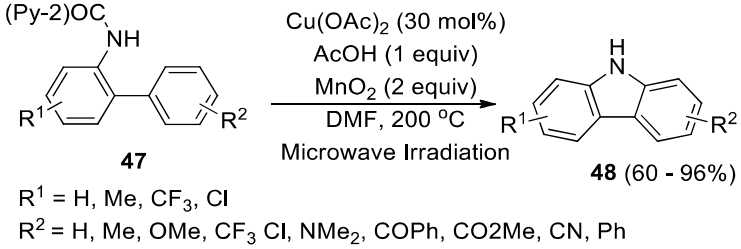
Scheme 4.19: *Synthesis of Carbzaoles via Copper and Transition Metal Free Intramolecular C─H Amidation*

In the same year, Antonchick and co-workers developed the first atom economic organocatalytic method for the synthesis of *N*-protected carbazole derivatives via intramolecular C─H amidation of 2-acetaminobiphenyl derivatives. They screened several iodoarenes and found that 10 mol% of 2,2'-diiodo-4,4',6,6'-tetramethyl-1,1'-biphenyl is the best iodo arene for this process and HFIP as cosolvent gave better results. At the same time unprotected 2-aminobiphenyls failed to give the carbazoles **46** in the current reaction conditions (Scheme 4.20).[22]



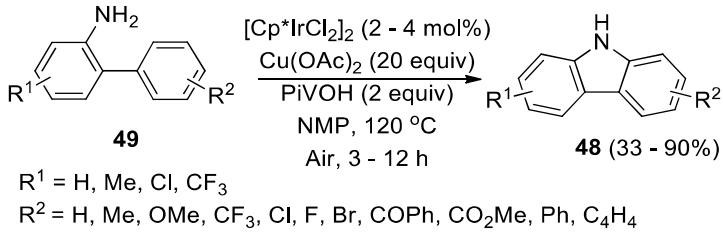
Scheme 4.20: *Organocatalytic Synthesis of N-Protected Carbazole Derivatives*

On the other hand, the first report for the synthesis of unprotected N-H carbazoles was published in 2014 by Miura and co-workers. This method involves copper mediated bidentate chelating group assisted intramolecular C─H/N─H coupling of *N*-picolinamide protected 2-amino biphenyl derivatives, which is spontaneously removed under the reaction conditions (Scheme 4.21).[23]



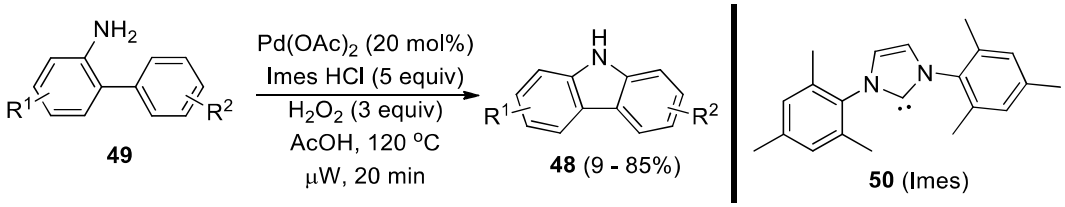
Scheme 4.21: *Directing Group Assisted Intramolecular C─H/N─H coupling*

In 2015, the same group came up with a simplified strategy, where the investigated intramolecular C─H amination of unprotected 2-aminobiphenyls for the first time. In this report they have demonstrated the iridium catalysed dehydrogenative cyclization of 2-aminobiphenyls to produce N−H carbazoles in the presence of copper as a co-catalyst under aerobic conditions (Scheme 4.22).[24]



Scheme 4.22: *First Report of the Intramolecular C-H Amination of Unprotected 2-Amino Biphenyls*

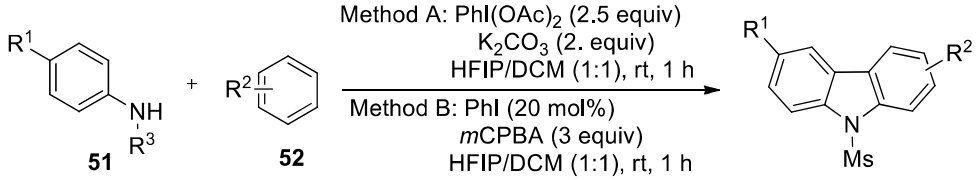
Another method for the construction N-H carbazoles *via* intramolecular C─H amination of 2-amino biphenyl scaffold was reported by Bjorsvik and co-workers[25] by using *N*-heterocyclic carbene under microwave conditions. They anticipated that the *N*-heterocyclic carbene ligand IMes in combination with $Pd(OAc)_2$ promoted well as the catalyst for the ring-closing reaction (Scheme 4.23)



R^1 = H, COOH, $COCH_3$, Me, Cl, CF_3
R^2 = H, Me, Et, OMe, Cl, OTBS

Scheme 4.23: *Microwave Assisted Intramolecular C─H Amination to Synthesize N-H Carbazoles*

Recently, Mal and co-workers[26] investigated the intermolecular tandem double hetero annulation of protected anilines with arenes under transition metal free conditions. They performed this oxidative dehdrogenative annulation in the presence of either oxidant mediated or organocatalytic approach where oxidant was generated *in situ* from iodobenzene and *m*CPBA (Scheme 4.24).

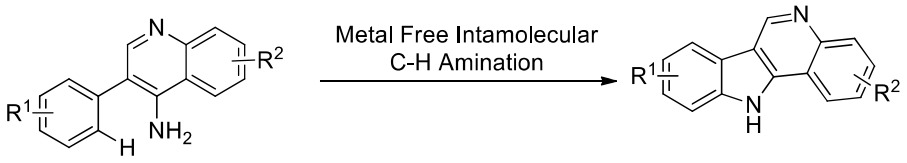


R^1 = Br, Cl, F, Me, ^{i}Pr, ^{t}Bu, Et, Ph
R^2 = H, OMe, Me, Et, Naphthyl
R^3 = Ms, Ts, Ns, SO_2Ph, COPh, Ac

Scheme 4.24: *Oxidant and Organocatalytic Double Hetero Annulation of Anilides*

As discussed, C─H functionalization strategy is an important synthetic approach for the C─N bond forming reactions. However, the reported methods require protected amino functionality. Rarely, unprotected amine was used for this strategy by using Pd and Ir metals.

Despite good yields, these methods involved drastic conditions. Hence, there is a need to develop a mild protocol for synthesis of carbolines from an unprotected amine. In this section, our results of transition metal free intramolecular C-H amination of 4-amino-3-aryl-quinolines and synthesis of natural product isocryptolepine will be discussed.

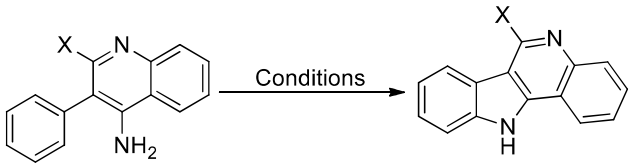


Scheme 4.25: *Our Approach to Construct Indolo[3,2-c]quinolines from 4-Aminoquinolines*

4.3.3 Optimization of Reaction Conditions for Intramolecular C—H Amination

With adequate amount of 4-amino quinolines in our hands, we turned our attention towards the optimization of reaction conditions for the intramolecular amination. Thus, we have chosen the amino quinoline **40a** as the model substrate and treated with 10 mol% of $Pd(OAc)_2$, 2 equiv of $PhI(OAc)_2$ as an oxidant in toluene solvent at room temperature. Unfortunately, this reaction failed to give the desired C—H aminated product even after 24 h. However, when we carried out the same reaction at 110 ^oC, we observed 20% of the corresponding indoloquinoline derivative **16a**, which was confirmed by spectral and analytical data (Table 4.6, Entry 2). Whereas, the reaction in the presence of metallic oxidant $Cu(OAc)_2$ afforded only trace amount of product (Table 4.6, Entry 3). Next, we performed the reaction in the presence of base K_3PO_4 and observed slight enhancement of the yield (Table 4.6, Entry 4). However, when we performed the reaction in DMF as solvent we observed 42% of the desired C—N coupled product **16a** (Table 4.6, Entry 5). Gratifyingly, when we performed the above reaction with desulfurized aminoquinoline **54a**, we observed 72% of the desired product **16a** (Table 4.6, Entry 6). These results encouraged us for further

Table 4.6: Optimization of Reaction Conditions for Oxidant Mediated Intramolecular C─H Amination



X = SMe, **40a**
H, **54a**

16a

Entry	$Pd(OAc)_2$	X	Oxidant[b]	Base[c]	Solvent	Temp	Time	Yield[a]
1	10 mol%	SMe	$PhI(OAc)_2$	-	Toluene	rt	24 h	-
2	10 mol%	SMe	$PhI(OAc)_2$	-	Toluene	110 ºC	1 h	20%
3.	10 mol%	SMe	$Cu(OAc)_2$	-	Toluene	110 ºC	1 h	Trace
4.	10 mol%	SMe	$PhI(OAc)_2$	K_3PO_4	Toluene	110 ºC	1 h	25%
5.	10 mol%	SMe	$PhI(OAc)_2$	K_3PO_4	DMF	110 ºC	1 h	42%
6.	10 mol%	H	$PhI(OAc)_2$	K_3PO_4	DMF	110 ºC	10 min	72%
7.	-	H	$PhI(OAc)_2$	K_3PO_4	DMF	110 ºC	10 min	70%
8.	-	H	$PhI(OAc)_2$	K_3PO_4	DMF	60 ºC	10 min	76%
9.	-	H	$PhI(OAc)_2$	K_3PO_4	DMF	rt	1 h	77%
10[d].	-	H	$PhI(OAc)_2$	K_3PO_4	DMF	rt	1 h	77%
11[e].	-	H	$PhI(OAc)_2$	K_3PO_4	DMF	rt	1 h	51%
12.	-	H	$PhI(OAc)_2$	K_3PO_4	DMSO	rt	1 h	71%
13.	-	H	$PhI(OAc)_2$	K_3PO_4	Dioxane	rt	1 h	51%
14.	-	H	$PhI(OAc)_2$	K_3PO_4	TFE	rt	20 min	68%
15.		H	$PhI(OAc)_2$	K_3PO_4	HFIP	rt	20 min	95%
16		H	$PhI(OAc)_2$	-	HFIP	rt	1 h	94%

a *= Isolated yield,* ***b*** *= 2 equiv of oxidant,* ***c*** *= 2 equiv of base,* ***d*** *= Reaction in the presence of AcOH as additive,* ***e*** *= Reaction in the presence of TFA as additive*

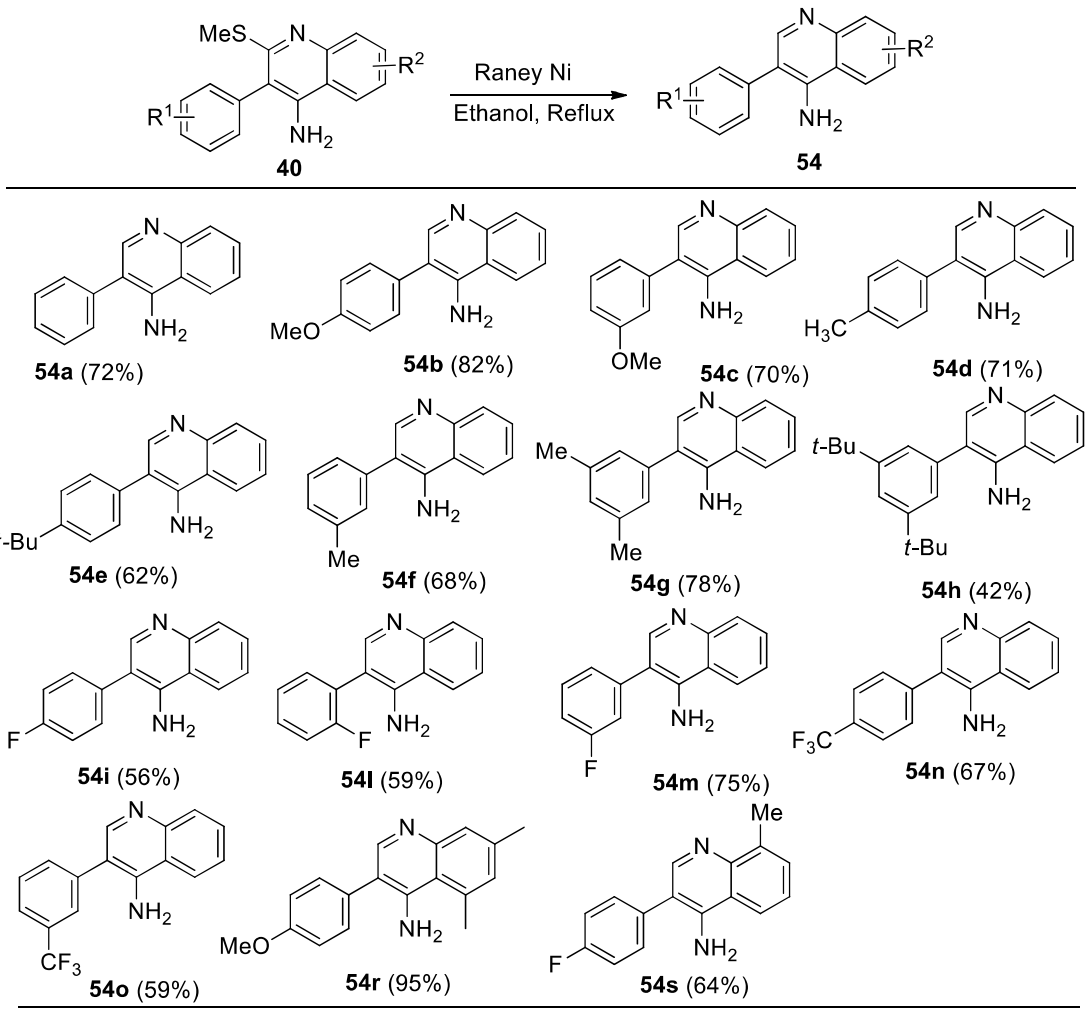
investigation of this intramolecular C─H amination reaction. Hence, we performed the reaction with various conditions. Surprisingly, in the absence of $Pd(OAc)_2$, this reaction also afforded the corresponding indoloquinoline **16a** in good yield (Table 4.6, Entry 7). Next, we carried out reactions at lower temperatures (Table 4.6, Entries 8-9). Interestingly, the reaction also worked at room temperature by delivering maximum yield of 77% of C─H aminated product (Table 4.6, Entry 9). We also examined the effect of additives on this C─H functionalization process. Thus, we performed the reactions in the presence of additives and found that these additives were ineffective in this reaction (Table 6, Entries 10 - 11). Next, we wish to investigate the effect of solvent in this oxidative C─N bond forming reaction.

Thus, we performed the reaction in DMSO, which afforded 71% of the indolquinoline **16a** (Table 4.6, Entry 12). Whereas, dioxane produced only 51% of the desired product **16a** in 1 h (Table 4.6, Entry 13). Further, we performed the reaction in the presence of highly polar alcoholic solvents. However, only 68% of the product **16a** was observed in the case of trifluoro ethanol (Table 4.6, Entry 14). Gratifyingly, when we carried out the reaction in the presence of hexafluoro isopropanol, we observed the 95% of the C─H aminated product **16a** in 20 min (Table 4.6, Entry 15). Interestingly, when we performed the reaction in the absence of base, we observed the similar amount of yield in 1 h (Table 4.6, Entry 16).

From the optimization study, we can conclude that 2 equiv of $PhI(OAc)_2$ in the presence of HFIP as a solvent at room temperature is appropriate for the intramolecular C─H amination of desulfurized 4-aminoquinoline **54a**.

Before studying the substrate scope of this intramoleular C─H amination, we desulfurized the 2-thiomethyl-3-aryl-4-aminoquinolines **40** by using raney nickel under reflux conditions. These desulfurized products **54** were obtained in good to very good yields, which were confirmed by spectral analytical data (Table 4.7).

Table 4.7: Raney Nickel Mediated Desulfurization of 4-Aminoquinolines

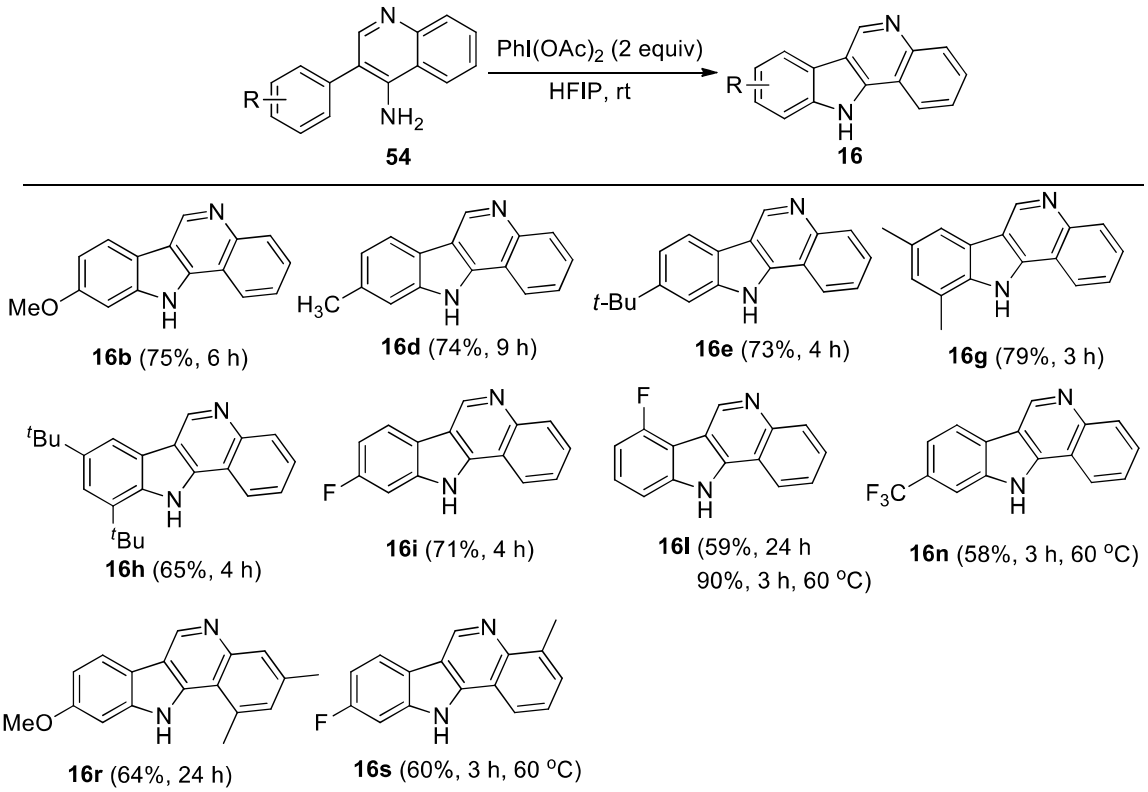


4.3.4 Substrate Scope:

With the optimized conditions in our hands, we moved to investigate the C─H amination of several 4-aminoquinolines **54**. Initially, we examined effect of substituted aryl groups on the amination. Thus, 3-(4-methoxyphenyl) aminoquinoline **54b** afforded 75% of the desired product **16b**. Whereas, 4-methyl and 4-tertiarybutyl substituted aminoquinolines **54d-e** were treated with optimized reaction conditions and observed 73-74% of the corresponding indoloquiunolnes **16d-e** in 4-9 h. Similarly, 3-(3,5-dimethylphenyl)quinolin-4-amine (**54g**) was underwent oxidative amination by giving 79% of the yield. Interestingly, sterically hindered amino quinoline **54h** also smoothly transformed to the corresponding indoloquinoline

derivative **16h** under optimized reaction conditions. 4-Flouro substituted indoloquinoline **16i** was obtained in 71% yield from the respective amino quinoline **54i**. On the other hand, 2-flouro substituted quinoline **54l** converted into indolquinoline derivative **16l** with 59% yield by taking longer reaction time. Interestingly, when we performed the same reaction at 60 °C, we observed 90% of the desired product **16l** in 3 h. Similarly, other electron withdrawing group substituted aminoquinoline **54n** was performed at 60 °C and giving rise to 58% of the corresponding C-H aminated product **16n** (Table 1.8).

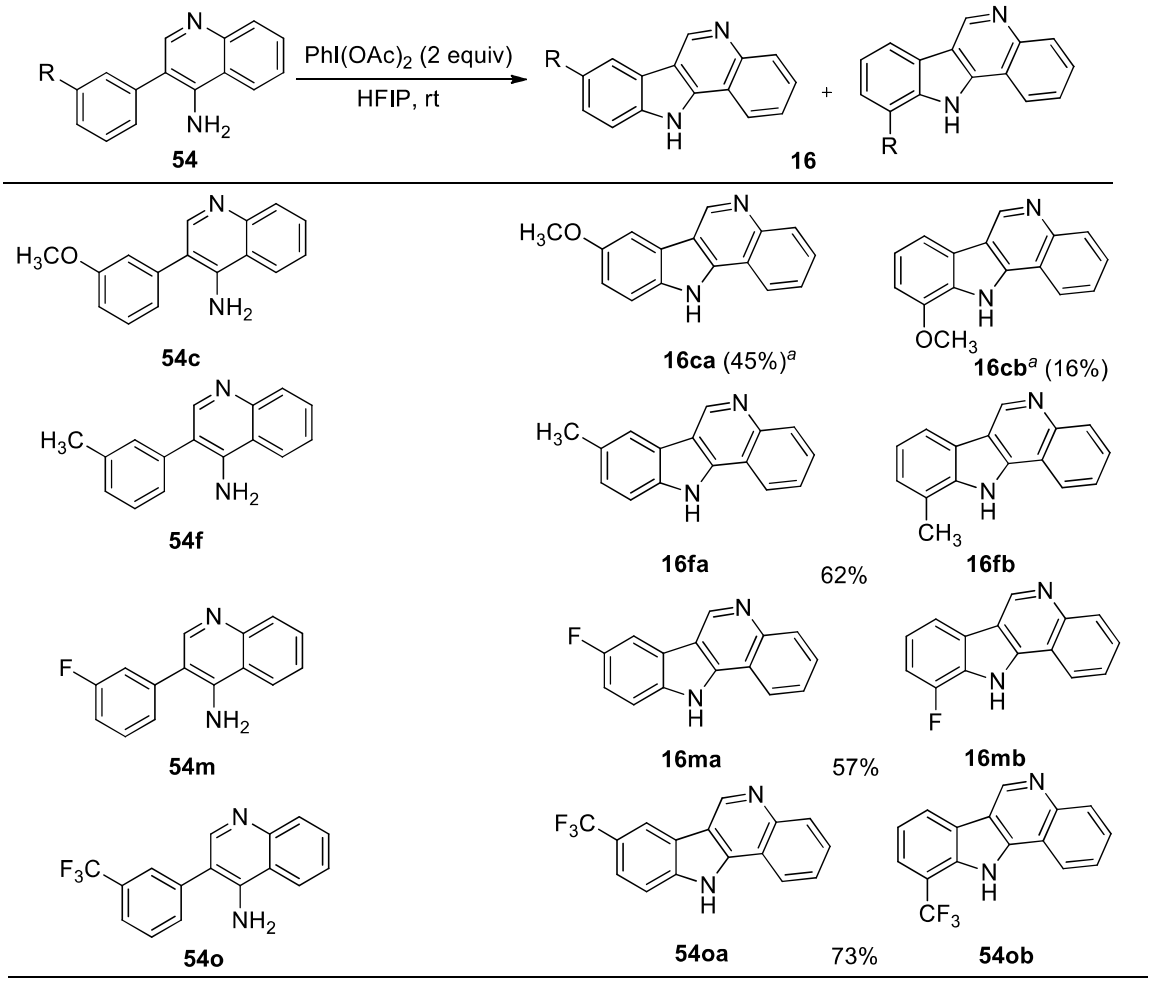
Table 4.8: Substrate Study of the Intramolecular C─H Amination of 4-Aminoquinolines



Next, we extended this methodology to the substituted quinolines to examine intramolecular C─H amination. Thus, 9-methoxy-1,3-dimethyl-11*H*-indolo[3,2-*c*]quinoline (**16r**) was obtained from the corresponding amino quinoline **54r** in 64% after 24 h. On the other hand, 3-(4-fluorophenyl)-8-methylquinolin-4-amine (**54s**) was converted into indoloquinoline derivative **16s** at 60 °C by affording 60% of the yield within shorter reaction time.

So far we investigated the symmetrically substituted amino quinolines. Further, we interested in examining the intramolecular C─H amination of unsymmetrically substituted aminoquinolines. Thus, 3-methoxy substituted aminoquinoline **54c** was treated with established reaction conditions and observed only trace amount of desired indoloquinoline **16c** in the presence of HFIP solvent. Interestingly, the same reaction when we performed in the presence of DMF solvent at room temperature we observed the mixture of products **16ca** & **16cb** in 61% yield. Surprisingly, these two isomers were separated by column chromatography. However, 3-methyl substituted aminoquinoline **54f** was produced 62% of inseparable mixture

Table 4.9: Intramolecular C─H Amination Unsymmetrically Substituted 4-Aminoquinolines

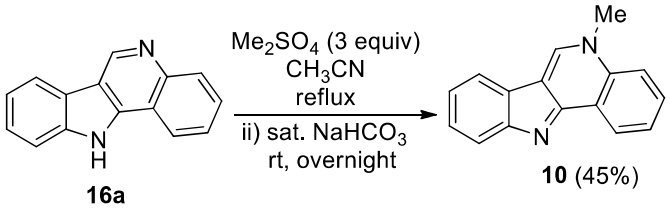


a = Reaction performed in DMF solvent

of two isomers of indolquinolines **16fa** & **16fb** in the presence of HFIP solvent. 3-(2-fluorophenyl)quinolin-4-amine (**54m**) was also smoothly transformed into corresponding isomeric indoloquinolines **16ma** & **16mb** by producing 57% yield under similar optimized reaction conditions. On the other hand, 3-CF_3 substituted aminoquinoline **54o** also produced mixture of two isomers **16oa** & **16ob** with the yield of 73% at 60 ºC.

4.3.5 Synthesis of Isocryptolepine:

Finally, indoloquinoline **16a** was converted into natural product isocryptolepine by using previously reported procedure.[27] Thus, the compound **16a** was treated with excess dimethyl sulphate in CH_3CN under reflux conditions at 90 ºC and followed by neutralisation with sat. $NaHCO_3$ affording isocryptolepine **10** in 45% yield (Scheme 4.26).

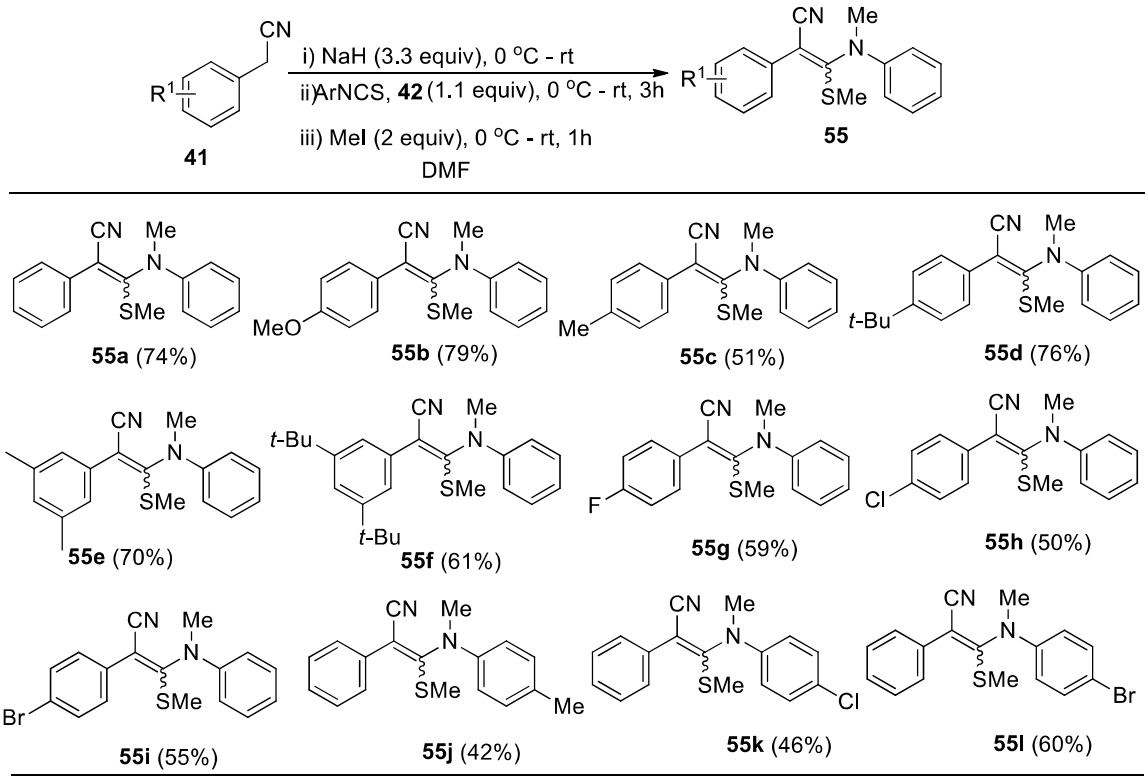


Scheme 4.26: *Synthesis of Natural Product Isocryptolepine **10***

PART –C

After successful C−H amination of 4-amino-3-arylquinolines **54**, we were interested in C−H imination of 4-amino-3-aryl-1-*N*-arylquinoline derivatives. These derivatives can be prepared from the corresponding *β*-*N*-methylanilino acrylonitriles. Thus, the anion of substituted benzyl cyanides **41** reacted with aryl isothiocyanates **42** in the presence of excess base at 0 ºC and followed by double methylation affording *S,N*-dimethyl amino acrylonitrile **55**.

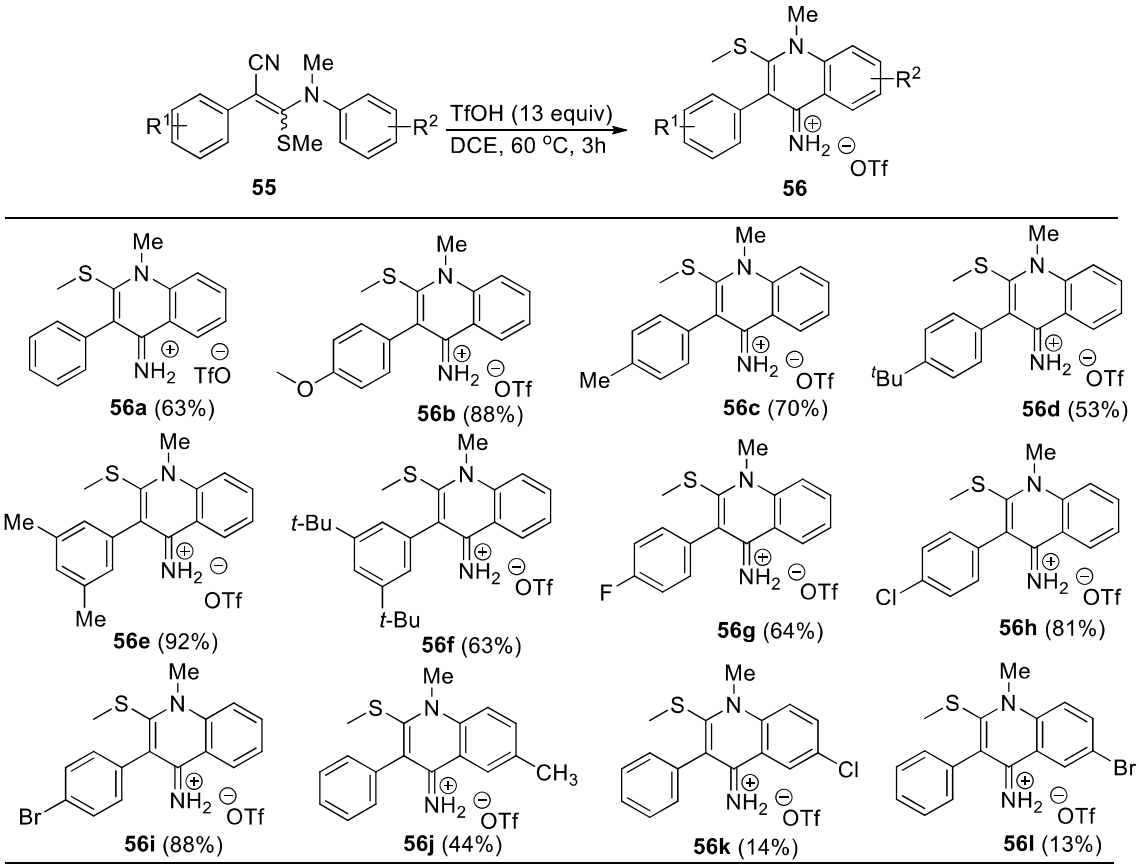
Table 4.10: Synthesis of *β*-Aminoacrylonitriles 55 from Aryl Acetonitriles 41 and Aryl Isothiocyantes 42



After synthesis of diverse range of *α*-aryl, *β*-(*N*-methyl anilino)acrylonitriles **55a-l**, we turned our attention towards the investigation of bronsted acid mediated Gattermann type of nitrile cyclization by using our previously optimized reaction conditions. Thus, we have chosen

ketene *S, N*-acetal **55a** as a model substrate and treated with TfOH in DCE as solvent at 60 °C. After 3 h, starting material was completely consumed and afforded the desired 4-

Table 4.11: Bronsted Acid Mediated Gattermann Type Cyclisation of Ketene *S,N*-Acetals 55



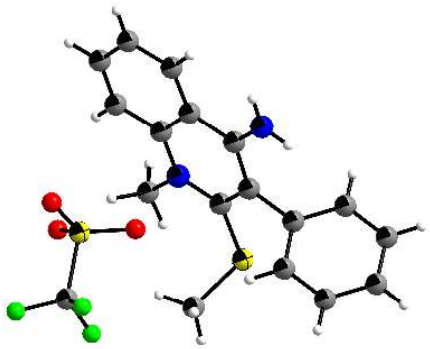


Figure 4.1: *Crystal structure of* ***56a***

imino quinoline **56a** in the form of triflate salt with 90% yield, which was confirmed by NMR (^{1}H and ^{13}C), HRMS and single crystal analysis (Figure). Similarly,4-methoxy substituted iminoquinoline **56b** was obtained in 88% yield from the corresponding ketene *S,N*-acetal. 4-Alkyl substituted acrylonitrile derivatives **55c-d** were also smoothly transformed into the corresponding iminoquinolines **56c-d** with moderate to good yields under optimized reaction conditions. 2-(3,5-Dialkylphenyl)-3-(methyl(phenyl)amino)-3-(methylthio)acrylonitriles **55e-f** were also treated with established reaction conditions and moderate to excellent yields of desired products **56e-f** was obtained. We also investigated the TfOH mediated intramolecular cyclisation of halo substituted ketene *S,N*-acetals **55g-i**, which also delivered the Gattermann type of cyclised products **56g-i** in 64 – 88% yield (Table 4.11).

Further, we examined the effect of *ß*-substituted anilines on this intramolecular cyclisation. Thus, 4-methyl substituted acrylonitrile derivative **55j** was treated with TfOH, which produced 44% of the quinoline derivative **56j**. However, 4-halo substituted *S,N*-acetals **55k-l** produced very poor yield of the corresponding desired products (Table 4.11).

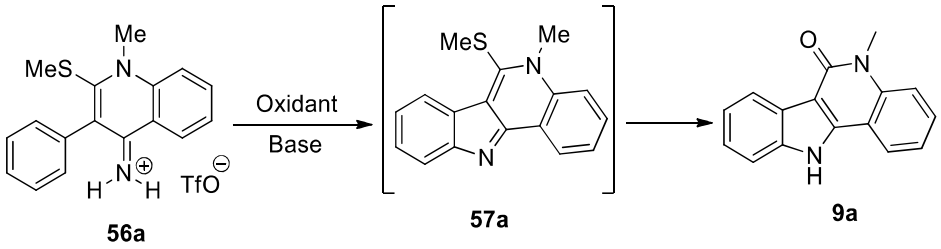
4.3.6 Optimization of Reaction Conditions for Intramolecular C─H imination of 4-Imino Quinolines

After successful synthesis of handful amount of iminoquinolines **56a-l**, we studied the intramolecular oxidative to C─N bond formation of iminoquinolines **16**. Thus, we have chosen the iminoquinoline **56a** as model substrate and first reaction was carried out with our previously optimized reaction conditions in the presence of base K_3PO_4 in HFIP solvent. Unfortunately, this reaction failed to give the indoloquinoline derivative **57a** and the starting material **56a** was retained as such (Table 4.12, Entry 1). Similar trend was observed in the case of trifluoro ethanol (Table 4.12, Entry 2). However, when we carried out the reaction in the presence of DMSO at 60 ºC, the starting material was completely consumed in 2 h and delivered a new

product **9a** with moderate yield (36%). The product **9a** was not expected **57a** and was confirmed as the indoloquinolone **9a** with the aid of spectral and analytical experiments. During the course of the reaction, SMe group was hydrolysed *in situ* to yield the observed indoloquinolone derivative **9a** (Table 4.12, Entry 3). For further fine tuning of the aforesaid reaction, we carried out the reaction at 120 ^{o}C, which afforded 49% of the corresponding indoloquinolone **9a** (Table 4.12, Entry 4). However, other hypervalent iodine based oxidant [bis(tifluoroacetoxy)iodo]benzene yielded only 32% of the desired product **9a** (Table 4.12, Entry 5). Next, we screened several solvents like dioxane, DMF and DCE (Table 4.12, Entry 6-8), among which only dioxane was comparable with the DMSO in terms of yield of the indoloquinolone derivative **9a** (Table 4.12, Entry 6). Further, we also studied the effect of base in this intramolecular oxidative *N*-arylation of iminoquinoline **56a** (Table 4.12, Entries 9-12). The reaction in the presence of stronger base LiO^{t}Bu afforded only 42% of the product **9a** (Table 4.12, Entry 9). However, only 34 – 38% of the corresponding indoloquinolne **9a** was observed in the presence of carbonate bases (Table 4.12, Entries 10-11). On the other hand, organic base triethylamine was ineffective in this reaction (Table 4.12, Entry 12). However, when we performed the reaction with decreased amount of K_3PO_4, we observed the diminishment of yield of desired indolo fused quinolone **9a** (Table 4.12, Entry 13).

From this brief optimization study, we can conclude that in the presence of 2 equiv of $PhI(OAc)_2$ and 2 equiv of K_3PO_4 in DMSO solvent at 120 ^{o}C, we observed the maximum yield of the indoloquinolone **9a**.

Table 4.12: Optimization of Reaction Conditions for Intramolecular C─H imination of 4-Imino Quinolines.



56a 57a 9a

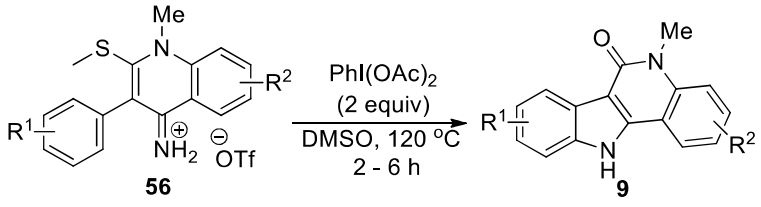
Entry	Oxidant (2 equiv)	Base (2 equiv)	Solvent	Temp	Time	Yield
1.	$PhI(OAc)_2$	K_3PO_4	HFIP	RT - 60 °C	24 h	-
2.	$PhI(OAc)_2$	K_3PO_4	TFE	RT - 60 °C	24 h	-
3.	$PhI(OAc)_2$	K_3PO_4	DMSO	RT - 60 °C	20 h	36%
4.	$PhI(OAc)_2$	K_3PO_4	DMSO	120 °C	2 h	49%
5.	$PhI(OCOCF_3)_2$	K_3PO_4	DMSO	120 °C	2 h	32%
6.	$PhI(OAc)_2$	K_3PO_4	Dioxane	120 °C	3 h	45%
7.	$PhI(OAc)_2$	K_3PO_4	DMF	120 °C	2 h	38%
8.	$PhI(OAc)_2$	K_3PO_4	DCE	120 °C	3 h	23%
9.	$PhI(OAc)_2$	LiO^tBu	DMSO	120 °C	2 h	42%
10.	$PhI(OAc)_2$	Cs_2CO_3	DMSO	120 °C	2 h	38%
11	$PhI(OAc)_2$	K_2CO_3	DMSO	120 °C	3 h	34%
12	$PhI(OAc)_2$	Et_3N	DMSO	120 °C	16 h	Trace
13[a]	$PhI(OAc)_2$	K_3PO_4	DMSO	120 °C	2 h	45%

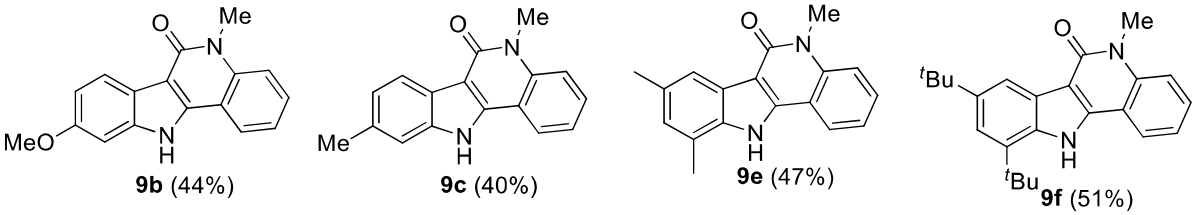
a = 1.2 equiv of K_3PO_4 was used

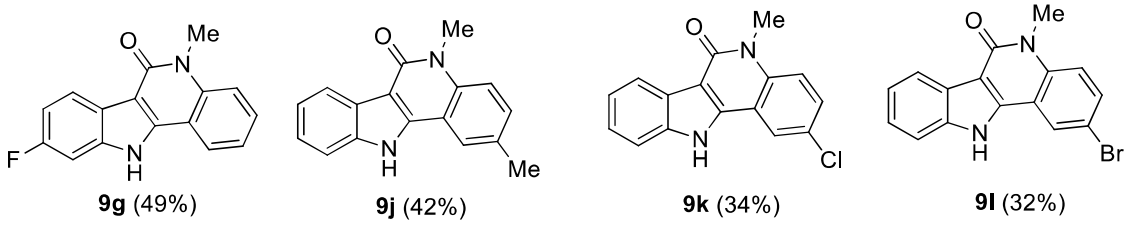
4.3.7 Substrate Scope:

With the optimized conditions in our hands, we moved to investigate the intramolecular oxidative *N*-arylation of several iminoquinolines **56**. Thus, initially we studied the effect of substituted aryl groups on this intramolecular C─H amination. Thus, 4-methoxy substituted iminoquinoline **56b** was treated with optimized reaction conditions and observed 44% of the desired product **9b** (Table 4.13). Similarly, 4-methyl substituted 4-iminoquinoline **56c** was also smoothly transformed into the corresponding indoloquinoline **9c** with 40% yield. 5,8,10-Trimethyl-5*H*-indolo[3,2-*c*]quinolin-6(11*H*)-one (**9e**) was obtained from the corresponding iminoquinoline **56e** in 47% yield. Surprisingly, sterically crowded imino qinoline **56f** was smoothly transformed to the corresponding C─H iminated product **9f** under optimized reaction conditions. The 4-fluoro substituted indoloquinolone **9g** was obtained from the corresponding precursor in 49% yield. We also studied the effect of substitutions at quinoline

Table 4.13: Substrate Study of the Intramolecular C─H Imination







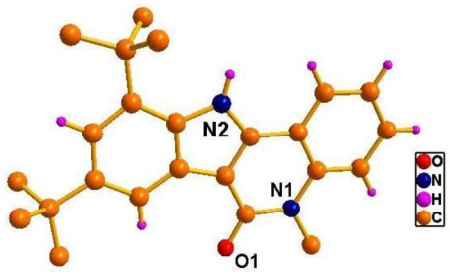
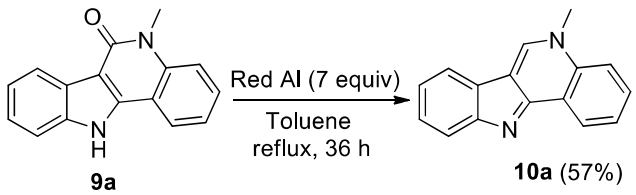


Figure 4.2: *Crystal structure of **9f***

ring on this intramolecular oxidative C─N bond formation. Thus, 4-alkyl substituted iminoquinoline **56j** underwent C─H functionalization reaction under optimized reaction condition by producing 42% of the corresponding indoloquinolone derivative **9j**. However, 4-halo substituted iminoquinolines **56k-l** produced only 32-34% of the desired isocryptolepine derivatives **9k-l**.

4.3.8 Synthesis of Iscocryptolpeine

Finally, we converted indoloquinolone **9a** to the isocryptolepine by using reported method.[28] Thus, **9a** was treated with Red Al in toluene at reflux conditions and 57% of the naturally occurring alkaloid isocryptolepine **10a** was observed.



Scheme 4.27: *Synthesis of Isocryptolepine from Indoloquinolone **9a***

4.4 Conclusion:

Overall, in this chapter we developed a simple protocol for synthesis of 4-amino and 4-iminoquinolines *via* Gatterman type cyclization with the aid of triflic acid at 60 ^{0}C. Various types of derivatives were synthesized with a broad structural diversity in moderate to good

yields. Further, the 4-amino and 4-iminoquinolines were transformed into the corresponding indoloquinoline and quinolone via unprotected C−H amination and imination reactions by using a hypervalent iodine reagent.

4.5 Experimental Section

4.5.1 Reagents

All reactions were performed by using standard vial technique with rubber septum. All solids were weighed in air. NaH, Isothiocyantaes, HFIP, TFE, $PhI(OAc)_2$, $PhI(OTf)_2$, 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. 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.

4.5.2 Analytical Methods

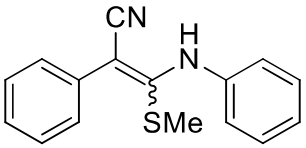
NMR data were recorded on Bruker ARX 400 and 700 spectrometers. ^{13}C and ^{1}H NMR spectra were recorded in $CDCl_3$, MeOH-d_4 and DMSO-d_6 referenced according to signals of deutero solvents. ESI HR-MS measurements were performed on Bruker micrOTOF-Q-II mass-spectrometer.

4.5.3 General Procedure for Preparation of Ketene *S,N*-Acetals

To a stirring suspension of NaH (2.2equiv, 60%) in dry DMF under N_2 atmosphere a solution of substituted Aryl acetonitriles (1 equiv) in dry DMF was added drop wise at 0 ˚C. The reaction mixture turns yellow and it was stirred for 1 h at room temperature. Then

arylisothiocyanates (1.1 equiv) in dry DMF was added slowly under N_2 atmosphere at 0 ˚C and then stirred for 3 hours, the TLC analysis showed that starting materials were consumed. Then the reaction mixture was cold to 0 ˚C and methyl iodide (1equiv) was added dropwise and was stirred for an hour. The reaction mixture was poured to ice cold saturated NH_4Cl solution and extracted with EtOAc (3 x 50 mL), washed with brine solution (100 mL) and dried over Na_2SO_4. The crude viscous oil liquid was purified through silica column chromatography using 10-20% EtOAc/hexane as eluent.

3-(Methylthio)-2-phenyl-3-(phenylamino)acrylonitrile (39a)



Reaction Time: 2 h + 0.5 h

Yield: 77%, Pale yellow solid

Melting Point: 118 – 119 ºC

R_f: 0.32 in 20% EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3818, 3254, 3027, 2925, 2301, 2187, 1597, 1536, 1519, 1496, 1440, 1303, 1251, 897, 751.

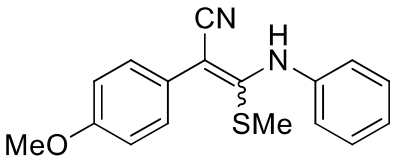
^{1}H NMR (400 MHz, $CDCl_3$) δ (Mixture of *E* & *Z* isomers 1 : 0.2) 7.54 (d, *J* = 7.2 Hz, 2H), 7.44 – 7.37 (m, 4H), 7.35 (d, *J* = 7.6 Hz, 2H), 7.33 – 7.25 (m, 5H), 7.23 - 7.18 (m, 3H), 7.15 – 7.04 (m, 4H), 6.73 (s, 1H), 6.43 (s, 1H), 2.23 (s, 3H), 2.00 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (Mixture of *E* & *Z* isomers) 156.1, 153.3, 140.5, 140.0, 133.4, 133.3, 129.3, 129.2, 129.0, 128.8, 128.3, 127.5, 127.5, 127.3, 123.5, 120.6, 120.0, 119.3, 92.6, 91.5, 15.8, 15.7.

HR-MS (ESI): Calcd. for $C_{16}H_{14}N_2S$ [M+H]: 267.0950, Found: 267.0938.

2-(4-Methoxyphenyl)-3-(methylthio)-3-(phenylamino)acrylonitrile (39b)

Reaction Time: 2 h + 0.5 h



Yield: 78%, Yellowish brown solid

Melting Point: 99 – 100 °C

R_f: 0.29 in 33% EtOAc in Hexanes

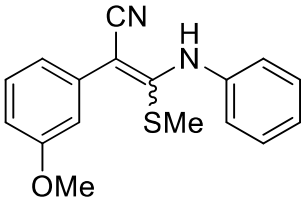
IR (KBr): ν (cm^{-1}) = 3423, 3021, 2922, 2348, 2190, 1657, 1630, 1529, 1368, 1069.

^1H NMR (400 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers 1: 0.3) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.36 – 7.28 (m, 4H), 7.28 - 7.24 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.11 - 7.03 (m, 3H), 7.01 -6.96 (m, 1H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.57 (s, 1H), 6.19 (s, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 2.20 (s, 3H), 1.99 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) Mixture of *E* & *Z* isomers) δ 159.1, 159.0, 154.9, 151.9, 140.8, 140.3, 130.9, 129.4, 129.3, 129.1, 125.7, 125.5, 123.7, 123.6, 120.6, 120.1, 119.7, 119.4, 114.5, 113.9, 93.8, 92.3, 55.4, 55.3, 15.9, 15.8.

HR-MS (ESI): Calcd. for $C_{17}H_{16}N_2OS$ [M+H]: 297.1056 Found: 297.1066.

2-(3-Methoxyphenyl)-3-(methylthio)-3-(phenylamino)acrylonitrile (39c)



Reaction Time: 2 h + 0.5 h

Yield: 67%, Yellow Solid

Melting Point: 101 – 102 °C

R_f: 0.29 in 25% EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3423, 3029, 2926, 2191, 1597, 1552, 1494, 1308, 1223, 1038, 838.

^1H NMR (400 MHz, $CDCl_3$) (Mixture of E & Z Isomers= 1: 0.3 ratio) δ7.35 - 7.29 (m, 2H), 7.28 - 7.23 (m, 3H), 7.22 (m, 3H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.10 - 7.03 (m, 5H), 6.97 (d, *J* =

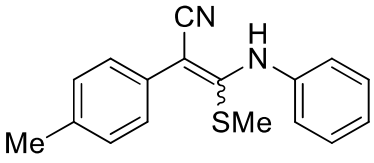
7.6 Hz, 1H), 6.94 - 6.90 (m, 1H), 6.88 – 6.82 (m, 1H), 6.73 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.70 (s, 1H), 6.44 (s, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 2.24 (s, 3H), 2.00 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 159.7, 153.6, 153.5, 140.2, 140.1, 134.9, 134.7, 130.1, 129.5, 129.4, 129.3, 124.0, 122.0, 120.5, 120.4, 120.4, 120.3, 120.1, 115.1, 113.7, 113.5, 113.26, 113.24, 93.5, 93.4, 55.4, 55.3, 16.1, 16.0.

HR-MS (ESI): Calcd. for $C_{17}H_{16}N_2OS$ [M+H]: 297.1056, Found: 249.1071.

3-(Methylthio)-3-(phenylamino)-2-(p-tolyl)acrylonitrile (39d)

Reaction Time: 2 h + 0.5 h



Yield: 73%, Yellow solid

Melting Point: 99 - 100 °C

R_f: 0.33 in 20% EtOAc in Hexanes

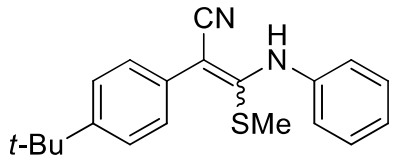
IR (KBr): ν (cm^{-1}) = 3720, 3254, 3023, 2917, 2393, 2194, 1598, 1520, 1441, 1325, 1305, 814, 693.

^{1}H NMR (400 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers 1 : 0.25) δ 7.41 (d, *J* = 8.0 Hz, 2H), 7.36 – 7.31 (m, 3H), 7.31 - 7.25 (m, 4H), 7.20 (d, *J* = 6.8 Hz, 1H), 7.12 - 7.07 (m, 5H), 7.07 - 7.03 (m, 3H), 6.65 (s, 1H), 6.30 (s, 1H), 2.37 (s, 3H), 2.30 (s, 3H), 2.19 (s, 3H), 1.99 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers) δ 155.4, 152.6, 140.7, 140.2, 137.5, 137.5, 130.5, 130.3, 129.6, 129.3, 129.2, 129.1, 127.5 (2C), 123.6, 123.5, 120.5, 120.1, 120.0, 119.3, 93.5, 92.2, 21.2, 21.1, 15.8, 15.7.

HR-MS (ESI): Calcd. for $C_{17}H_{16}N_2S$ [M+H]: 281.1107, Found: 281.1102.

2-(4-(*tert*-Butyl)phenyl)-3-(methylthio)-3-(phenylamino)acrylonitrile (39e)



Reaction Time: 2 h + 0.5 h

Yield: 71%, Yellow solid

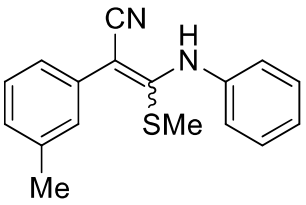
Melting Point: 97 – 98 ºC

R_f: 0.39 in 20% EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3249, 3026, 2963, 2390, 2351, 2197, 1598, 1524, 1441, 1309, 1249, 1309, 1121, 1026, 835, 759.

^{1}H NMR (400 MHz, $CDCl_3$) (Mixture of E & Z isomers 1 : 0.25) δ 7.47 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.38 - 7.25 (m, 7H), 7.20 (d, *J* = 7.6 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 7.2 Hz, 3H), 6.67 (s, 1H), 6.37 (s, 1H), 2.18 (s, 3H), 2.00 (s, 3H), 1.34 (s, 9H), 1.28 (s, 9H). (ATP_1_108)

3-(Methylthio)-3-(phenylamino)-2-(m-tolyl)acrylonitrile (39f)



Reaction Time: 3 h + 0.5 h

Yield: 75%, Yellow solid

Melting Point: 95 – 96 ºC

R_f: 0.33 in 20% EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3423, 3025, 2922, 2348, 2197, 1594, 1495, 1327, 1074, 844.

^{1}H NMR (400 MHz, DMSO-D_6) (Mixture of *E* & *Z* Isomers = 1:0.2) δ 9.13 (s, 1H), 9.11 (s, 1H), 7.35 - 7.28 (m, 1H), 7.27 (s, 1H), 7.19 – 7.06 (m, 6H), 7.06 - 6.98 (m, 5H), 6.97 - 6.89 (m, 3H), 6.88 - 6.80 (m, 2H), 2.32 (s, 6H), 2.13 (s, 3H), 2.07 (s, 3H).

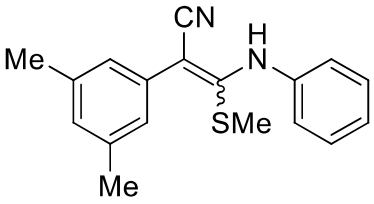
^{13}C NMR (100 MHz, DMSO-D_6) (Mixture of *E* & *Z* Isomers) δ 156.1, 153.1, 142.1, 140.8, 137.8, 137.2, 134.0, 133.9, 129.5, 129.0, 128.4, 128.1, 128.0, 127.6, 127.1, 126.3, 126.2, 124.0, 122.1, 121.8, 120.9, 118.98, 118.93, 118.3, 91.5, 89.8, 20.96. 20.91, 15.3, 15.1.

HR-MS (ESI): Calcd. for $C_{17}H_{16}N_2S$ [M+H]: 281.1107 Found: 281.1118

^{13}C NMR (100 MHz, $CDCl_3$) δ (Mixture of E & Z isomers) 155.2, 152.8, 150.9, 150.7, 140.8, 140.3, 130.5, 130.3, 129.3, 129.2, 129.1, 127.4, 126.0, 125.4, 125.3, 123.8, 123.7, 120.5, 120.4, 120.1, 93.8, 92.5, 34.6, 34.6, 31.3, 31.2, 16.0, 15.8.

HR-MS (ESI): Calcd. for $C_{20}H_{22}N_2S$ [M+H]: 323.1576, Found: 323.1573.

2-(3,5-Dimethylphenyl)-3-(methylthio)-3-(phenylamino)acrylonitrile (39g)



Reaction Time: 2 h + 0.5 h

Yield: 52%, Yellowish orange Solid

Melting Point: 111 – 112 °C

R_f: 0.35 in 10% EtOAc in Hexanes

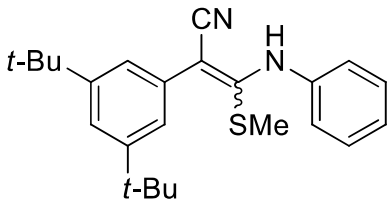
IR (KBr): ν (cm^{-1}) = 3262, 3026, 2923, 2391, 2295, 2192, 1603, 1548, 1519, 1440, 1332, 976, 844, 696.

^{1}H NMR (400 MHz, $CDCl_3$) (Mixture of *E* & *Z* isomers 1 : 0.25) δ 7.41 – 7.30 (m, 2H), 7.31 – 7.23 (m, 3H), 7.20 (d, *J* = 7.6 Hz, 2H), 7.15 - 7.03 (m, 5H), 6.99 (s, 2H), 6.95 (s, 1H), 6.84 (s, 1H), 6.61 (s, 1H), 6.33 (s, 1H), 2.34 (s, 3H), 2.22 (s, 9H), 2.20 (s, 3H), 1.99 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) (Mixture of *E* & *Z* isomers) δ 155.5, 152.9, 140.8, 140.2, 138.7, 138.1, 133.2, 133.0, 129.5, 129.4, 129.4, 129.2, 127.3, 125.5 (2C), 123.9, 123.7, 120.7, 120.5, 120.1, 93.5, 92.7, 21.37, 21.31, 16.04 (2C).

HR-MS (ESI): Calcd. for $C_{18}H_{18}N_2S$ [M+H]: 295.1263 Found: 295.1260.

2-(3,5-Di-*tert*-butylphenyl)-3-(methylthio)-3-(phenylamino)acrylonitrile (39h)



Reaction Time: 3 h + 1 h

Yield: 57%, Pale yellow solid

Melting Point: 92 – 93 °C

R_f: 0.40 in 20% EtOAc in Hexanes

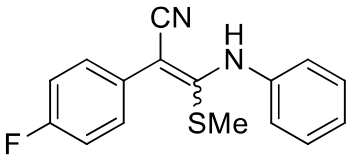
IR (KBr): ν (cm^{-1}) = 3453, 3051, 2902, 2232, 1602, 1105, 938, 765.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.33 (m, 2H), 7.31 – 7.19 (m, 10H), 7.06 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 7.2 Hz, 2H), 6.63 (s, 1H), 6.26 (s, 1H), 2.30 (s, 3H), 2.00 (s, 3H), 1.38 (s, 18H), 1.23 (s, 18H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 152.7, 151.7, 150.8, 140.9, 140.5, 132.8, 132.2, 129.4, 129.3, 124.0, 123.7, 123.6, 122.2, 122.1, 121.8, 120.6, 120.2, 119.7, 119.6, 95.3, 94.0, 35.0, 34.9, 31.5, 31.3, 16.0, 15.9.

HR-MS (ESI): Calcd. for $C_{24}H_{30}N_2S$ [M+H]: 379.2202 Found: 379.2172.

2-(4-Fluorophenyl)-3-(methylthio)-3-(phenylamino)acrylonitrile (39i)



Reaction Time: 2 + 0.5 h

Yield: 49%, Pale yellow solid

Melting Point: 97 – 98 ºC

R_f: 0.35 in 20% EtOAc in Hexanes

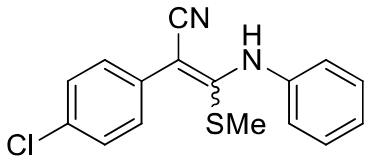
IR (KBr): ν (cm^{-1}) = 3780, 3290, 3063, 2396, 2191, 1594, 1535, 1508, 1441, 1306, 1223, 839.

^{1}H NMR (400 MHz, $CDCl_3$) (Mixture of *E* & *Z* isomers 1:0.25) δ 7.50 - 7.45 (m, 2H), 7.37 - 7.30 (m, 4H), 7.28 – 7.16 (m, 4H), 7.15 - 7.07 (m, 3H), 7.04 (d, *J* = 7.8 Hz, 3H), 6.94 (t, *J* = 8.4 Hz, 2H), 6.70 (s, 1H), 6.28 (s, 1H), 2.24 (s, 3H), 1.99 (s, 3H).)

^{13}C NMR (100 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers) δ 162.0 (d, *J* = 238 Hz), 161.7 (d, *J* = 246 Hz), 156.4, 153.4, 140.4, 139.9, 131.4 (d, *J* = 8.1 Hz), 129.609 (d, J = 8.1 Hz), 129.605, 129.4, 129.2, 123.9, 123.8, 120.5, 120.4, 120.1, 119.2, 116.0, 115.5 (d, *J* = 21.7 Hz), 91.7, 90.5, 15.9, 15.8.

HR-MS (ESI): Calcd. for $C_{16}H_{13}FN_2S$ [M+H]: 285.0856, Found: 285.0848.

2-(4-Chlorophenyl)-3-(methylthio)-3-(phenylamino)acrylonitrile (39j)



Reaction Time: 3 h + 0.5 h

Yield: 72%, Yellow solid

Melting Point: 144 – 145 °C

R_f: 0.29 in 25% EtOAc in Hexanes

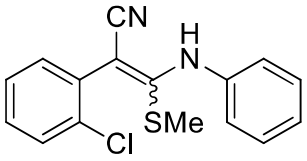
IR (KBr): ν (cm^{-1}) = 3292, 3036, 2390, 2293, 2189, 1593, 1529, 1505, 1495, 1441, 1312, 1245, 1095, 827.

^{1}H NMR (400 MHz, $CDCl_3$) δ (Mixture of *E* & *Z* isomers 1 : 0.2) 7.46 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.32 – 7.26 (m, 4H), 7.25 - 7.23 (m, 1H), 7.23 - 7.18 (m, 4H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.07 - 7.01 (m, 5H), 6.77 (s, 1H), 6.41 (s, 1H), 2.25 (s, 3H), 2.00 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) (Mixture of *E* & *Z* isomers) δ 156.6, 154.0, 140.3, 139.8, 133.5, 133.3, 132.1, 132.0, 130.9, 129.5, 129.4, 129.2, 129.0, 128.8, 124.3, 124.2, 120.8, 120.3, 120.2, 119.1, 92.2, 90.3, 16.1 (2C).

HR-MS (ESI): Calcd. for $C_{16}H_{13}ClN_2S$ [M+H]: 301.0561 Found: 301.0558.

2-(2-Chlorophenyl)-3-(methylthio)-3-(phenylamino)acrylonitrile (39k)



Reaction Time: 2 + 0.5 h

Yield: 63%, Yellow Solid

Melting Point: 124 – 125 °C

R_f: 0.29 in 20% EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3780, 3252, 3011, 2320, 2180, 1597, 1522, 1441, 1326, 1307, 1042, 875.

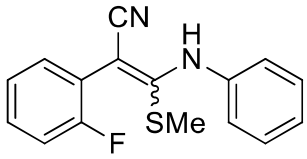
^{1}H NMR (400 MHz, $CDCl_3$) (Mixture of *E* & *Z* isomers 1 : 0.2) δ 7.50 – 7.44 (m, 1H), 7.44 – 7.39 (m, 1H), 7.38 – 7.28 (m, 4H), 7.28 – 7.23 (m, 2H), 7.21 - 7.17 (m, 1H), 7.16 - 7.13 (m,

3H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 2H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.86 (s, 1H), 6.24 (s, 1H), 2.29 (s, 3H), 1.97 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) (Mixture of *E* & *Z* isomers) δ 158.9, 156.2, 140.2, 139.4, 134.9, 134.0, 132.8, 132.2, 131.9, 131.7, 130.1, 129.8, 129.7, 129.4, 129.2, 128.7, 127.3, 127.0, 124.1, 124.0, 121.3, 120.8, 120.0, 118.1, 87.5, 87.2, 16.3, 15.5.

HR-MS (ESI): Calcd. for $C_{16}H_{13}ClN_2S$ [M+H]: 301.0561 Found: 301.0566.

2-(2-Fluorophenyl)-3-(methylthio)-3-(phenylamino)acrylonitrile (39l)



Reaction Time: 2 h + 0.5 h

Yield: 79%, Pale yellow solid

Melting Point: 134 – 135 °C

R_f: 0.30 in 20% EtOAc in Hexanes

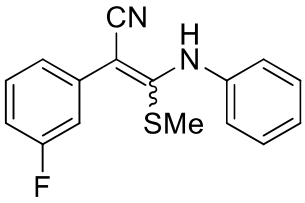
IR (KBr): ν (cm^{-1}) = 3774, 3237, 3143, 3007, 2929, 2507, 2207, 1596, 1562, 1494, 1476, 1340, 1310, 1215,756.

^{1}H NMR (400 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers 1 : 0.25) δ 7.40 (t, *J* = 7.6 Hz, 1H), 7.37 – 7.30 (m, 4H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.21 – 7.14 (m, 3H),7.14 – 7.09 (m, 3H)., 7.09 – 6.97 (m, 4H), 6.95 (s, 1H), 6.94 – 6.83 (m, 1H), 2.27 (s, 3H), 1.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers) δ 159.9 (d, *J* = 246.9Hz), 159.1 (d, *J* = 247 Hz), 158.8, 155.9, 140.1, 139.4, 132.3 (d, *J* = 2.0 Hz), 130.7 (d, *J* = 2.7 Hz), 130.1 (d, *J* = 8.2 Hz), 129.7 (d, *J* = 8.3 Hz), 129.3, 128.9, 124.6 (d, *J* = 3.5 Hz), 124.2 (d, *J* = 3.8 Hz), 124.2, 124.1, 121.4, 121.3, 121.1, 120.9, 120.2, 118.5, 116.1 (d, *J* = 21.8 Hz), 115.9 (d, *J* = 20.3 Hz), 84.5, 83.6, 16.3, 15.6.

HR-MS (ESI): Calcd. for $C_{16}H_{13}FN_2S$ [M+H]: 285.0856, Found: 285.0848.

2-(3-Fluorophenyl)-3-(methylthio)-3-(phenylamino)acrylonitrile (39m)



Reaction Time: 2 h + 0.5 h

Yield: 71%, Yellow solid

Melting Point: 132 – 133 °C

R_f: 0.30 in 20% EtOAc in Hexanes

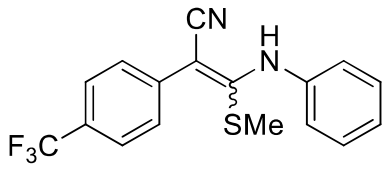
IR (KBr): ν (cm^{-1}) = 3423, 3029, 2924, 2853, 2190, 1583, 1548, 1494, 1467.

^{1}H NMR (400 MHz, DMSO-D_6) (Mixture of E & Z Isomers 1:0.15) δ 9.33 (s, 1H), 9.31 (s, 1H), 7.45 - 7.34 (m, 3H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.26 – 7.15 (m, 4H), 7.15 – 7.04 (m, 3H), 7.01 - 6.92 (m, 4H), 6.90 - 6.80 (m, 2H), 2.36 (s, 3H), 2.11 (s, 3H).

^{13}C NMR (100 MHz, DMSO-D_6) (Mixture of *E* & *Z* isomers) δ 162.0 (d, *J* = 242 Hz), 161.9 (d, J = 241 Hz), 157.6, 154.9, 141.6, 140.6, 136.8 (d, J = 8 Hz), 136.6 (d, J = 8 Hz), 130.4 (d, J = 9 Hz), 130.0 (d, J = 8 Hz), 128.9, 128.6, 125.1 (d, J = 2 Hz), 123.0 (d, J = 2 Hz), 122.6, 122.4, 120.7, 119.3, 119.2, 119.0, 115.7 (d, J = 22 Hz), 113.8 (d, J = 21 Hz), 113.5 (d, J = 22 Hz), 113.5 (d, J = 21 Hz), 88.6, 87.9, 15.4, 15.3.

HR-MS (ESI): Calcd. for $C_{16}H_{13}FN_2S$ [M+H]: 285.0856 Found: 285.0850.

3-(Methylthio)-3-(phenylamino)-2-(4-(trifluoromethyl)phenyl)acrylonitrile (39n)



Reaction Time: 3 h + 0.5 h

Yield: 46%, Pale yellow solid

Melting Point: 142 – 143 °C

R_f: 0.34 in 25% EtOAc in Hexanes

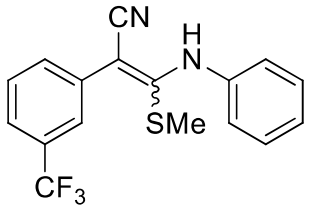
IR (KBr): ν (cm^{-1}) =3247, 3186, 3035, 2390, 2351, 2196, 1608, 1519, 1412, 1344, 1329, 1128, 1111, 1066, 842.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 - 7.60 (m, 4H), 7.55 – 7.41 (m, 4H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.29 – 7.20 (m, 4H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.08 - 7.01 (m, 3H), 6.83 (s, 1H), 6.42 (s, 1H), 2.30 (s, 3H), 2.01 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 155.5, 140.0, 139.6, 137.5, 137.4, 129.8, 129.58, 129.51, 129.2, 129.1, 127.9, 125.9 (q, *J* = 4 Hz), 125.52 (q, *J* = 4 Hz), 124.7, 124.5, 124.2 (q, *J* = 273 Hz), 123.9 (q, *J* = 270 Hz), 120.0, 119.0, 91.3, 89.6, 16.38, 16.33

HR-MS (ESI): Calcd. for $C_{17}H_{13}F_3N_2S$ [M+H]: 335.0824, Found: 335.0820.

3-(Methylthio)-3-(phenylamino)-2-(3-(trifluoromethyl)phenyl)acrylonitrile (39o)



Reaction Time: 3 + 0.5 h

Yield: 53%, Yellow solid

Melting Point: 118 – 119 ºC

R_f: 0.30 in 20% EtOAc in Hexanes

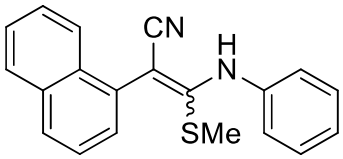
IR (KBr): ν (cm^{-1}) = 3441, 3034, 2924, 2854, 2194, 1631, 1548, 1335, 1165, 1124, 1073

^{1}H NMR (400 MHz, MeOD) (Mixture of *E* & *Z* Isomers 1:0.1)δ 7.82 - 7.77 (m, 2H), 7.59 - 7.3 (m, 3H), 7.48 - 7.43 (m, 1H), 7.42 - 7.38 (m, 1H), 7.34 – 7.20 (m, 6H), 7.05 (t, *J* = 7.6 Hz, 2H), 6.91 - 6.80 (m, 3H), 2.46 (s, 3H), 2.10 (s, 3H).

^{13}C NMR (100 MHz, MeOD) δ (Major isomer only) 157.5, 141.6, 136.8, 131.7, 131.4 (q, J = 32 Hz), 130.0, 129.8, 125.5 (q, J = 221 Hz), 124.9 (q, J = 1.2 Hz), 124.2, 123.8 (q, J = 1.2 Hz), 122.0, 120.8, 88.0, 16.2

HR-MS (ESI): Calcd. for $C_{17}H_{13}F_3N_2S$ [M+H]: 335.0824 Found: 335.0816.

3-(Methylthio)-2-(naphthalen-1-yl)-3-(phenylamino)acrylonitrile (39p)



Reaction Time: 2 h + 1 h

Yield: 70%, Orange colour solid

Melting Point: 120 – 121 ºC

R_f: 0.31 in 25% EtOAc in Hexanes

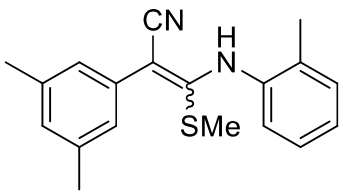
IR (KBr): ν (cm^{-1}) =3793, 3217, 3056, 2507, 2198, 1594, 1557, 1496, 1483, 1393, 1326, 1309, 899, 776.

^{1}H NMR (400 MHz, $CDCl_3$) (Mixture of *E* & *Z* isomers 1 : 0.3) δ 8.03 (d, *J* = 7.6 Hz, 2H), 7.93 - 7.88 (m, 2H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.64 – 7.47 (m, 5H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.21 – 7.11 (m, 3H), 7.04 - 6.98 (m, 5H), 6.95 (s, 1H), 6.05 (s, 1H), 2.25 (s, 3H), 1.86 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) (Mixture of *E* & *Z* isomers) δ 158.5, 155.2, 140.5, 139.5, 134.0, 133.8, 131.9, 130.9, 130.4, 130.1, 129.5, 129.4, 129.3, 129.3, 129.3, 128.9, 128.8, 128.4, 127.0, 126.8, 126.4, 126.2, 125.8, 125.4, 124.9, 124.9, 124.6, 124.3, 124.01, 124.00, 121.7, 120.6, 89.4, 88.5, 16.3, 15.7.

HR-MS (ESI): Calcd. for $C_{20}H_{16}N_2S$ [M+H]: 339.0926, Found: 339.0938.

2-(3,5-Dimethylphenyl)-3-(methylthio)-3-(o-tolylamino)acrylonitrile (39q)



Reaction Time: 2 h + 0.5 h

Yield: 45%, Colourless solid

Melting Point: 140 – 141 ºC

R_f: 0.40 in 20% EtOAc in Hexanes

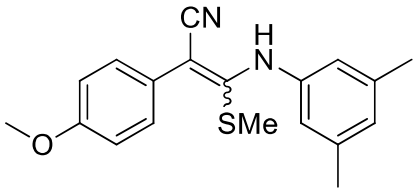
IR (KBr): ν (cm^{-1}) = 3256, 3013, 2392, 2352, 2191, 1601, 1548, 1513, 1326, 1260, 1040, 851, 631.

^{1}H NMR (400 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers 1 : 0.4) δ 7.31 (d, *J* = 6.8 Hz, 1H), 7.28 – 7.18 (m, 3H), 7.18 - 7.11 (m, 4H), 7.08 (d, *J* = 8 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 7.02 - 6.97 (m, 2H), 6.95 (s, 1H), 6.84 (s, 1H), 6.26 (s, 1H), 6.06 (s, 1H), 2.35 (s, 6H), 2.28 (s, 1H), 2.23 (s, 6H), 2.19 (s, 3H), 2.16 (s, 3H), 1.92 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers) δ 156.8, 154.1, 139.0, 138.6, 138.4, 138.0, 133.2, 133.1, 130.8, 130.6, 129.9, 129.8, 129.3, 127.2, 126.8, 126.7, 125.6, 125.5, 124.8, 124.7, 122.3, 121.7, 120.7, 119.5, 92.3, 91.3, 21.3, 21.2, 17.8 (2C), 15.8, 15.6.

HR-MS (ESI): Calcd. for $C_{19}H_{20}N_2S$ [M+H]: 309.1420, Found: 309.1433.

3-((3,5-Dimethylphenyl)amino)-2-(4-methoxyphenyl)-3-(methylthio)acrylonitrile (39r)



Reaction Time: 2 h + 0.5 h

Yield: 62%, Colourless solid

Melting Point: 90 – 93 °C

R_f: 0.30 in 20% EtOAc in Hexanes

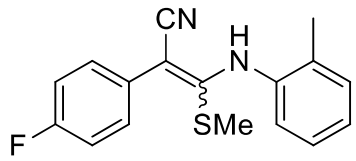
IR (KBr): ν (cm^{-1}) = 3656, 3316, 2833, 2201, 1553, 1283, 1247, 1029, 828.

^{1}H NMR (400 MHz, $CDCl_3$) δ (Mixture of *E* & *Z* isomers 1 : 0.2) 7.44 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.85 - 6.77 (m, 4H), 6.65 - 6.75 (m, 4H), 6.51 (s, 1H), 6.15 (s, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 2.30 (s, 6H), 2.26 (s, 6H), 2.20 (s, 3H), 2.00 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) (Mixture of *E* & *Z* isomers) δ 158.9, 158.8, 155.0, 152.0, 140.6, 140.1, 138.9, 138.8, 130.8, 129.0, 128.9, 125.9, 125.6, 125.3, 120.7, 119.4, 117.7, 117.6, 114.3, 113.8, 93.0, 91.8, 55.2 (2C), 21.3, 21.2, 15.8, 15.7.

HR-MS (ESI): Calcd. for $C_{19}H_{20}N_2OS$ [M+H]: 325.1369, Found: 325.1372.

2-(4-Fluorophenyl)-3-(methylthio)-3-(o-tolylamino)acrylonitrile (39s)



Reaction Time: 3 h + 0.5 h

Yield: 71%, Orange colour solid

Melting Point: 99 – 100 ºC

R_f: 0.28 in 20% EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3339, 2928, 2199, 1553, 1278, 1259, 1220, 979, 838, 757,

^{1}H NMR (400 MHz, $CDCl_3$) (Mixture of E & Z Isomers 1 : 3)δ 7.56 – 7.43 (m, 2H), 7.39 - 7.29 (m, 2H), 7.27 (d, *J* = 6.0 Hz, 1H), 7.25 - 7.17 (m, 2H), 7.16 - 7.09 (m, 3H), 7.08 - 6.99 (m, 3H), 6.99 - 6.91 (m, 3H), 2.35 (s, 3H), 2.18 (s, 6H), 1.92 (s, 3H).

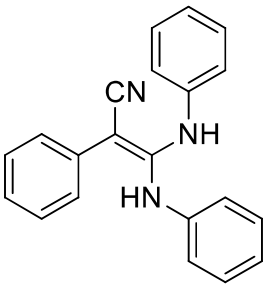
^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (d, J = 246 Hz), 161.6 (d, J = 246 Hz), 157.6, 154.7, 138.7, 138.2, 131.3 (d, *J* = 7.9 Hz), 130.9, 130.7, 130.1, 19.56, 129.5 (d, *J* = 8.2 Hz), 126.8, 126.7, 125.0, 124.8, 124.6, 122.2, 121.8, 120.5, 119.2, 115.9 (d, *J* = 21.8 Hz), 115.4 (d, *J* = 21.4 Hz), 90.9, 89.0, 17.9, 17.8, 15.6, 15.6.

HR-MS (ESI): Calcd. for $C_{17}H_{15}FN_2S$ [M+H]: 299.1013, Found: 299.1016.

4.5.4 General Procedure for the Synthesis of Ketene Aminals

Procedure is same as section 2.6.2

2-Phenyl-3,3-bis(phenylamino)acrylonitrile (43a**)**



Reaction Time: 10 min

Yield: 56%, Yellow solid

Melting Point: 220 – 221 ºC

R_f: 0.3 in 30% EtOAc in Hexanes

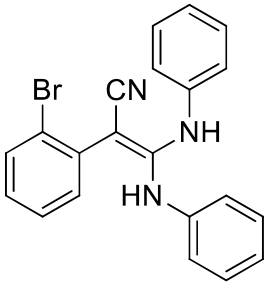
IR (KBr): ν (cm^{-1}) = 3390, 2179, 1601, 1578, 1537, 1495, 1247, 752.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.7 Hz, 2H), 7.24 (t, *J* = 7.7 Hz, 2H), 7.18 (t, *J* = 7.7 Hz, 2H), 7.13-7.08 (m, 3H), 7.02 (d, *J* = 7.7 Hz, 2H), 6.96 (t, *J* = 7.0 Hz, 1H), 6.91 - 6.86 (m, 3H), 6.63 (s, 1H), 6.12 (s, 1H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 149.9, 139.3, 139.2, 133.7, 129.3, 129.2, 128.9, 127.5, 126.0, 123.6, 123.4, 122.0, 120.0, 119.4, 73.1.

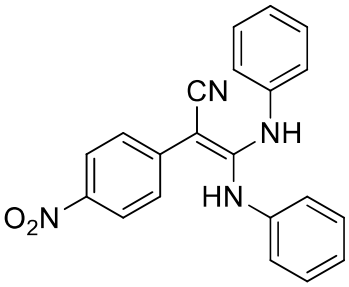
HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. For $C_{21}H_{17}N_3$: 334.1315, found: 334.1303.

2-(2-Bromophenyl)-3,3-bis(phenylamino)acrylonitrile (43b)



This compound data was reported in section 2.6.2

2-(4-Nitrophenyl)-3,3-bis(phenylamino)acrylonitrile (43c)



Reaction Time: 10 min

Yield: 61%, Brick red solid

Melting Point: 237 – 238 °C

R_f: 0.29 in 30% EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3367, 2923, 2850, 2183, 1652, 1592, 1558, 1539, 1506, 1328, 1111

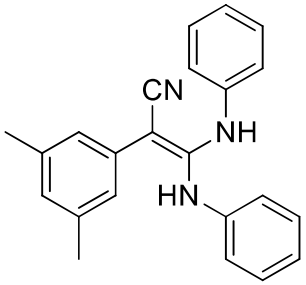
^{1}H NMR (400 MHz, DMSO) δ 9.65 (s, 2H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 4H), 7.07 (d, *J* = 8.0 Hz, 4H), 6.91 (t, *J* = 7.2 Hz, 2H).

^{13}C NMR (100 MHz, DMSO) δ 152.3, 144.4, 142.2, 140.1, 129.0, 124.9, 123.8, 122.7, 121.3, 119.1, 70.0.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{21}H_{16}N_4O_2$: 357.1346, found: 357.1333.

2-(3,5-Dimethylphenyl)-3,3-bis(phenylamino)acrylonitrile (43d)

Reaction Time: 10 min



Yield: 43%, Yellow solid

Melting Point: 146 – 147 °C

R_f: 0.38 in 30% EtOAc in Hexanes

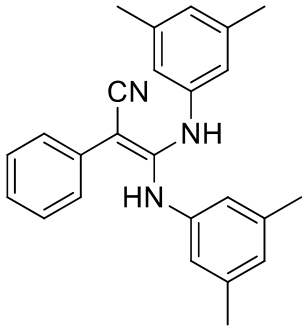
IR (KBr): ν (cm^{-1}) = 3396, 3052, 2359, 2181, 1709, 1657, 1600, 1579, 1497, 1265, 738.

^1H NMR (700 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.7 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 2H), 7.06 – 6.98 (m, 4H), 6.95 (t, *J* = 7.0 Hz, 1H), 6.90 (t, *J* = 8.4 Hz, 3H), 6.76 (s, 1H), 6.53 (s, 1H), 6.13 (s, 1H), 2.22 (s, 6H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 149.8, 139.4, 139.4, 138.5, 133.2, 129.3, 129.1, 127.9, 125.3, 123.5, 123.3, 122.1, 119.9, 119.4, 73.4, 21.4.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{23}H_{21}N_3$: 340.1808, found: 340.1844.

3,3-Bis((3,5-dimethylphenyl)amino)-2-phenylacrylonitrile (43e)



Reaction Time: 10 min

Yield: 42%, Yellow solid

Melting Point: 210 – 211 °C

R_f: 0.3 in 30% EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3440, 2920, 2171, 1692, 1635, 1013, 912.

^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.0 Hz, 3H), 7.22 (t, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.66 - 6.58 (m, 3H), 6.54 - 6.42 (m, 3H), 6.04 (s, 1H), 2.19 (s, 6H), 2.13 (s, 6H).

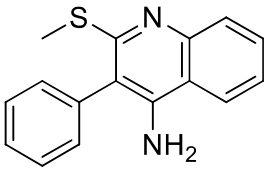
^{13}C NMR (100 MHz, DMSO) δ 149.2, 141.3, 140.7, 137.6, 137.3, 135.6, 128.2, 125.8, 124.3, 123.1, 122.3, 115.8, 72.6, 21.1, 20.9.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{25}H_{25}N_3$: 368.2121, found: 368.2111.

4.5.5 General Procedure for Preparation of functionalized 4-Aminoquinolines:

To a solution of ketene *S,N*-acetals or *N, N*-acetals in DCE, 13 equivalents of trifluoromethanesulphonic acid was added slowly under ice condition. Then it was heated to 60 ˚C for three hours. The reaction mixture turns dark green in colour. It was monitored by TLC. After completion, the reaction was quenched with ice cold sodium bicarbonate solution. extracted with DCM/water system. The crude mixture was passed through silica gel with EtOAc/Hexane as eluent to get pure product.

2-(Methylthio)-3-phenylquinolin-4-amine (40a)



Reaction Time: 3 h

Yield: 62%, White solid

Melting Point: 115 – 116 ºC

R_f: 0.32 in 15% EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3462, 3341, 3239, 3031, 2394, 2353, 1645, 1561, 1393, 1268, 1245, 1188, 1030, 961, 762.

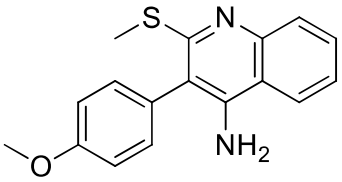
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.3 Hz, 2H), 7.51 – 7.44 (m, 1H), 7.43 - 7.36 (m, 3H), 4.52 (s, 2H), 2.61 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 147.6, 145.3, 134.6, 130.9, 129.5, 129.3, 128.7, 128.4, 123.9, 120.7, 117.2, 115.1, 13.6.

HR-MS (ESI): Calcd. for $C_{16}H_{14}N_2S$ [M+H]: 267.0950, Found: 267.0966.

3-(4-Methoxyphenyl)-2-(methylthio)quinolin-4-amine (40b)

Reaction Time: 3 h



Yield: 46%, White solid

Melting Point: 150 – 157 °C

R_f: 0.30 in 10% EtOAc in Hexanes

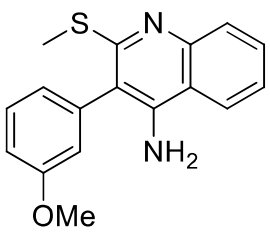
IR (KBr): ν (cm^{-1}) = 3439, 3326, 3200, 2492, 1637, 1575, 1559, 1432, 1369, 1287, 1247, 1022, 948.

^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.2 Hz, 1H), 7.74 – 7.65 (m, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.6 Hz, 2H), 4.48 (s, 2H), 3.88 (s, 3H), 2.59 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.92, 147.65, 145.70, 132.23, 129.37, 128.55, 128.53, 126.57, 123.98, 120.73, 117.36, 115.09, 114.87, 55.42, 13.76.

HR-MS (ESI): Calcd. for $C_{17}H_{16}N_2OS$ [M+H]: 297.1056, Found: 297.1057.

3-(3-Methoxyphenyl)-2-(methylthio)quinolin-4-amine (40c)



Reaction Time: 3 h

Yield: 53%, Pale yellow solid

Melting Point: 122 – 123 °C

R_f: 0.35 in 15% EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3401, 3034, 2926, 2366, 2077, 1615, 1576, 1493, 1360, 1287, 1206, 1038.

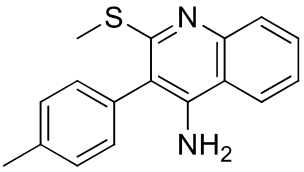
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (t, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.66 - 7.59 (m, 1H), 7.49 - 7.43 (m, 1H), 7.40 - 7.34 (m, 1H), 7.08 – 6.91 (m, 3H), 4.54 (s, 2H), 3.84 (s, 3H), 2.61 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 159.1, 147.1, 145.7, 135.8, 130.7, 129.6, 128.1, 124.1, 123.0, 120.8, 117.2, 116.2, 114.9, 114.4, 55.42, 13.85.

HR-MS (ESI): Calcd. for $C_{17}H_{16}N_2OS$ [M+H]: 297.1056 Found: 297.0941.

2-(Methylthio)-3-(p-tolyl)quinolin-4-amine (40d)

Reaction Time: 3 h



Yield: 47%, White solid

Melting Point: 170 – 171 °C

R_f: 0.35 in 10% EtOAc in Hexanes

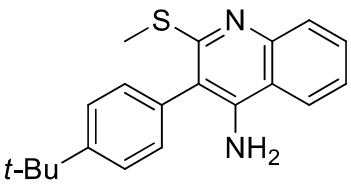
IR (KBr): ν (cm^{-1}) = 3452, 3321, 3218, 3195, 2922, 2851, 1630, 1574, 1495, 1431, 1368, 1289, 1114, 949.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.3 Hz, 1H), 7.76 – 7.65 (m, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.45 – 7.31 (m, 3H), 7.28 - 7.26 (m, 2H), 4.50 (s, 2H), 2.61 (s, 3H), 2.46 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 147.5, 145.4, 138.5, 131.5, 130.7, 130.3, 129.3, 128.4, 123.9, 120.7, 117.3, 115.1, 21.5, 13.6.

HR-MS (ESI): Calcd. for $C_{17}H_{16}N_2S$ [M+H]: 281.1107, Found: 281.1091.

3-(4-(*tert*-Butyl)phenyl)-2-(methylthio)quinolin-4-amine (40e)



Reaction Time: 3 h

Yield: 46%, White solid

Melting Point: 209 – 210 °C

R_f: 0.40 in 20% EtOAc in Hexanes

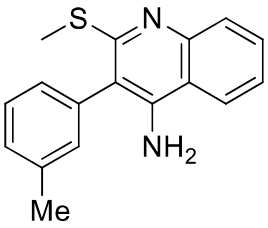
IR (KBr): ν (cm^{-1}) = 3448, 3331, 3233, 2963, 1643, 1568, 1394, 1272, 1245, 1029, 758, 638.

^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 7.4 Hz, 1H), 7.61 -7.59 (m, 1H), 7.55 (d, *J* = 6.9 Hz, 2H), 7.36 (d, *J* = 7.1 Hz, 1H), 7.31 (d, *J* = 6.9 Hz, 2H), 4.47 (s, 2H), 2.60 (s, 3H), 1.40 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 151.6, 147.6, 145.5, 131.5, 130.5, 129.3, 128.5, 126.5, 123.9, 120.6, 117.3, 115.2, 34.8, 31.4, 13.7.

HR-MS (ESI): Calcd. for $C_{20}H_{22}N_2S$ [M+H]: 323.1576 Found: 323.1590.

2-(Methylthio)-3-(m-tolyl)quinolin-4-amine (40f)



Reaction Time: 3 h

Yield: 51%, Pale yellow solid

Melting Point: 121 – 122 °C

R_f: 0.35 in 10% EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3395, 3029, 2922, 1614, 1573, 1493, 1350, 1287, 1051, 957.

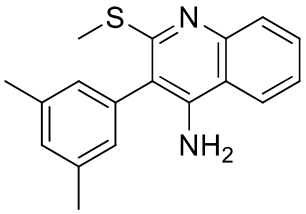
^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 1H), 7.75 - 7.65 (m, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 4.54 (s, 2H), 2.69 (s, 3H), 2.50 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 147.5, 145.3, 139.1, 134.4, 131.3, 129.3(2C), 129.2, 128.3, 127.8, 123.82, 120.6, 117.2, 115.1, 21.4, 13.6.

HR-MS (ESI): Calcd. for $C_{17}H_{16}N_2S$ [M+H]: 281.1107 Found: 281.1074.

3-(3,5-Dimethylphenyl)-2-(methylthio)quinolin-4-amine (40g)

Reaction Time: 3 h



Yield: 74%, white solid

Melting Point: 206 – 207 °C

R_f: 0.40 in 20% EtOAc in Hexanes

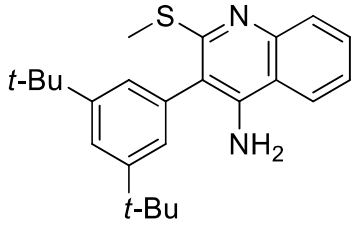
IR (KBr): ν (cm^{-1}) = 3433, 3299, 3169, 2174, 1638, 1498, 1431, 1367, 1291, 958, 767.

^1H NMR (700 MHz, $CDCl_3$) δ 7.95 (d, *J* = 5.3 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.62 - 7.59 (m, 1H), 7.38 - 7.5 (m, 1H), 7.10 (s, 1H), 6.98 (s, 2H), 4.49 (s, 2H), 2.61 (s, 3H), 2.39 (s, 6H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 159.3, 147.4, 145.5, 139.2, 134.3, 130.4, 129.3, 128.4, 127.7, 124.0, 120.7, 117.3, 115.5, 21.5, 13.8.

HR-MS (ESI): Calcd. for $C_{18}H_{18}N_2S$ [M+H]: 295.1263, Found: 295.1284.

3-(3,5-Di-*tert*-butylphenyl)-2-(methylthio)quinolin-4-amine (40h)



Reaction Time: 3 h

Yield: 47%, White solid

Melting Point: 220 – 221 °C

IR (KBr): ν (cm^{-1}) = 3549, 3136, 2954, 2389, 1575, 1369, 1158, 995, 962.

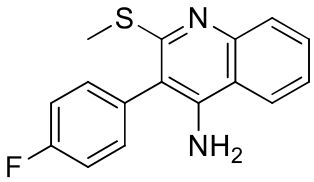
R_f: 0.35 in 10% EtOAc in Hexanes

^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 6.8 Hz, 1H), 7.73 (d, *J* = 6.4 Hz, 1H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.50 (s, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.25 - 7.20 (m, 2H), 4.61 (s, 2H), 2.61 (s, 3H), 1.38 (s, 18H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 151.8, 147.5, 145.3, 133.6, 129.2, 128.4, 125.0, 123.8, 122.2, 120.7, 117.3, 116.3, 35.0, 31.5, 13.8.

HR-MS (ESI): Calcd. for $C_{24}H_{30}N_2S$ [M+H]: 379.2202 Found: 379.2208.

3-(4-Fluorophenyl)-2-(methylthio)quinolin-4-amine (40i)



Reaction Time: 3 h

Yield: 49%, pale yellow solid

Melting Point: 121 – 122 °C

R_f: 0.35 in 10% EtOAc in Hexanes

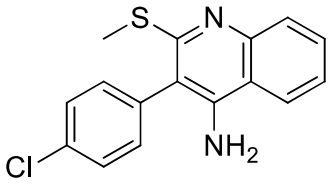
IR (KBr): ν (cm^{-1}) = 3454, 3371, 3065, 1620, 1578, 1504, 1492, 1378, 1212, 1050, 945, 763.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 6.5 Hz, 1H), 7.79 (d, *J* = 6.5 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.48 – 7.34 (m, 3H), 7.29 (d, *J* = 9.0 Hz, 2H), 4.66 (s, 2H), 2.67 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (d, *J* = 247.9 Hz), 159.4, 147.6, 145.5, 132.9 (d, *J* = 8.1 Hz), 130.4 (d, *J* = 2.8 Hz), 129.5, 128.5, 124.0, 120.6, 117.1, 116.6 (d, *J* = 21.4 Hz), 113.9, 13.6.

HR-MS (ESI): Calcd. for $C_{16}H_{13}FN_2S$ [M+H]: 285.0856 Found: 285.0842.

3-(4-Chlorophenyl)-2-(methylthio)quinolin-4-amine (40j)



Reaction Time: 3 h

Yield: 44%, Pale yellow solid

Melting Point: 123 – 124 °C

R_f: 0.35 in 10% EtOAc in Hexanes

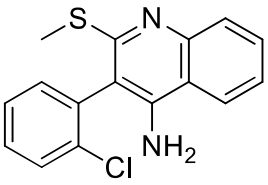
IR (KBr): ν (cm^{-1}) = 3464, 3342, 3231, 2925, 2394, 2351, 2291, 1633, 1576, 1496, 1435, 1372, 1287, 1090, 950.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 2H), 4.41 (s, 2H), 2.59 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.26, 147.92, 145.34, 134.87, 133.24, 132.60, 129.98, 129.60, 128.77, 124.15, 120.59, 117.25, 113.94, 13.64.

HR-MS (ESI): Calcd. for $C_{16}H_{13}ClN_2S$ [M+H]: 301.0561 Found: 301.0571.

3-(2-Chlorophenyl)-2-(methylthio)quinolin-4-amine (40k)



Reaction Time: 3 h

Yield: 73%

Melting Point: 150 – 151 °C

R_f: 0.32 in 15% EtOAc in Hexanes

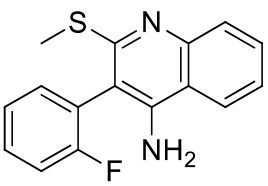
IR (KBr): ν (cm^{-1}) = 3472, 3349, 3195, 1625, 1618, 1576, 1496, 1431, 1374, 1352, 1289, 1038, 950, 759.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.67 – 7.56 (m, 2H), 7.48 – 7.41 (m, 2H), 7.41 – 7.33 (m, 2H), 4.39 (s, 2H), 2.62 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 148.0, 145.5, 135.5, 133.3, 133.2, 130.5 (2C), 129.6, 128.6, 127.9, 124.0, 120.7, 117.1, 112.5, 13.4.

HR-MS (ESI): Calcd. for $C_{16}H_{13}ClN_2S$ [M+H]: 301.0561 Found: 301.0577.

3-(2-Fluorophenyl)-2-(methylthio)quinolin-4-amine (40l)



Reaction Time: 3 h

Yield: 44%, White solid

Melting Point: 136 – 138 °C

R_f: 0.37 in 20% EtOAc in Hexanes

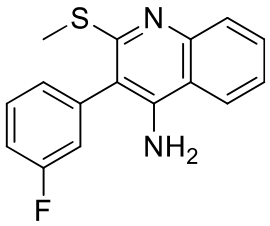
IR (KBr): ν (cm^{-1}) = 3483, 3462, 2414, 1648, 1566, 1393, 1270, 1229, 1184, 1032, 763, 640.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.54 – 7.43 (m, 1H), 7.43 – 7.29 (m, 3H), 7.26 (t, *J* = 8.8 Hz, 1H), 4.52 (s, 2H), 2.62 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ160.6 (d, *J* = 246.6 Hz), 159.5, 147.9, 146.1, 133.3 (d, *J* = 2.7 Hz), 131.1 (d, *J* = 8.0 Hz), 129.7, 128.5, 125.2 (d, *J* = 3.7 Hz), 124.1, 121.7 (d, *J* = 17.1 Hz), 120.7, 117.0, 116.7 (d, *J* = 21.8 Hz), 108.6, 13.5.

HR-MS (ESI): Calcd. for $C_{16}H_{13}FN_2S$ [M+H]: 285.0856 Found: 285.0852.

3-(3-Fluorophenyl)-2-(methylthio)quinolin-4-amine (40m)



Reaction Time: 3 h

Yield: 53%, Pale Yellow solid

Melting Point: 109 – 110 °C

R_f: 0.30 in 10% EtOAc in Hexanes

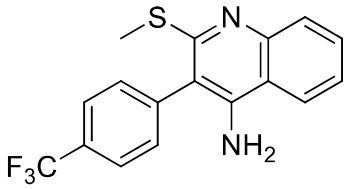
IR (KBr): ν (cm^{-1}) = 3404, 3030, 2923, 2359, 1620, 1581, 1493, 1377, 1349, 962.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.53 - 7.47 (m, 1H), 7.38 - 7.34 (m, 1H), 7.23 – 7.08 (m, 3H), 4.52 (s, 2H), 2.62 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (d, *J* = 247.9 Hz), 158.8, 147.5, 145.4, 136.8 (d, *J* = 7.7 Hz), 131.1 (d, *J* = 8.4 Hz), 129.6, 128.3, 126.7 (d, *J* = 2.9 Hz), 124.0, 120.7, 118.0 (d, *J* = 20.9 Hz), 117.1, 115.6 (d, *J* = 20.9 Hz), 113.7 (d, *J* = 1.8 Hz), 13.6.

HR-MS (ESI): Calcd. for $C_{16}H_{13}FN_2S$ [M+H]: 285.0856 Found: 285.0822.

2-(Methylthio)-3-(4-(trifluoromethyl)phenyl)quinolin-4-amine (40n)



Reaction Time: 3 h

Yield: 49%, White solid

Melting Point: 179 – 180 °C

R_f: 0.31 in 10% EtOAc in Hexanes

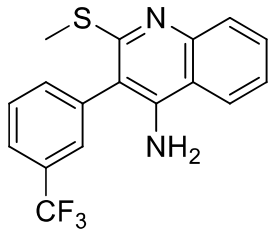
IR (KBr): ν (cm^{-1}) = 3481, 3343, 3238, 2398, 2326, 1638, 1497, 1432, 1325, 1165, 1122, 1070, 763.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 2H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 1H), 4.49 (s, 2H), 2.62 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 147.6, 145.5, 138.7, 131.7, 130.9 (q, *J* = 32.5 Hz), 129.8, 128.5, 126.6 (q, *J* = 3.6 Hz), 124.3, 124.1 (q, *J* = 270 Hz), 120.7, 117.1, 113.6, 13.6.

HR-MS (ESI): Calcd. for $C_{17}H_{13}F_3N_2S$ [M+H]: 335.0824 Found: 335.0847.

2-(Methylthio)-3-(3-(trifluoromethyl)phenyl)quinolin-4-amine (40o)



Reaction Time: 3 h

Yield: 45%, Pale Yellow solid

Melting Point: 124 – 125 °C

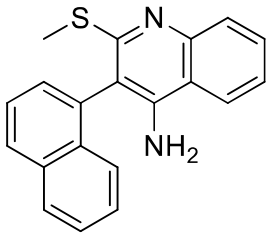
IR (KBr): ν (cm^{-1}) = 3396, 3021, 2922, 1617, 1575, 1494, 1331, 1301, 1124.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 1H), 7.73 (t, *J* = 8.8 Hz, 2H), 7.70 – 7.60 (m, 3H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 4.53 (s, 2H), 2.62 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 147.5, 145.7, 135.5, 134.8, 132.0 (q, *J* = 32.5 Hz), 130.1, 129.8, 128.3, 128.1 (q, *J* = 3 Hz), 125.6 (q, *J* = 3 Hz), 124.3, 124.0 (q, *J* = 271 Hz), 120.7, 117.1, 113.4, 13.7.

HR-MS (ESI): Calcd. for $C_{17}H_{13}F_3N_2S$ [M+H]: 335.0824 Found: 335.0816.

2-(Methylthio)-3-(naphthalen-1-yl)quinolin-4-amine (40p)



Reaction Time: 3 h

Yield: 37%, White solid

Melting Point: 230 – 231 °C

R_f: 0.30 in 10% EtOAc in Hexanes

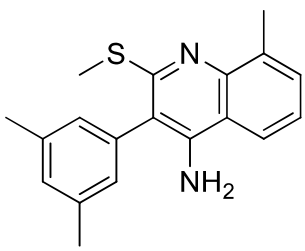
IR (KBr): ν (cm^{-1}) = 3443, 3306, 3186, 3050, 2921, 2851, 2391, 2291, 1593, 1496, 1439, 1369, 1285, 1003, 768.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (t, *J* = 9.0 Hz, 2H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.70 – 7.60 (m, 2H), 7.56 - 7.0 (m, 3H), 7.41 (q, *J* = 6.9 Hz, 2H), 4.35 (s, 2H), 2.56 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 147.9, 146.1, 134.3, 131.8, 129.8, 129.6, 129.4, 128.7, 128.6, 128.6, 126.9, 126.5, 126.2, 125.0, 124.0, 120.7, 117.2, 112.7, 13.6.

HR-MS (ESI): Calcd. for $C_{20}H_{16}N_2S$ [M+H]: 317.1107 Found: 317.1132.

3-(3,5-Dimethylphenyl)-8-methyl-2-(methylthio)quinolin-4-amine (40q)



Reaction Time: 3 h

Yield: 48%, White solid

Melting Point: 152 – 153 °C

R_f: 0.35 in 15% EtOAc in Hexanes

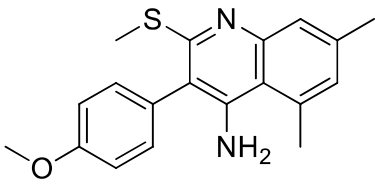
IR (KBr): ν (cm^{-1}) = 3463, 3385, 2922, 2351, 1608, 1479, 1375, 1297, 960, 754.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 6.8 Hz, 1H), 7.49 (d, *J* = 6.8 Hz, 1H), 7.34 – 7.21 (m, 1H), 7.10 (s, 1H), 6.99 (s, 2H), 4.40 (s, 2H), 2.78 (s, 3H), 2.60 (s, 3H), 2.39 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 146.4, 145.5, 139.0, 136.6, 134.6, 130.2, 129.4, 128.4, 123.4, 118.3, 116.9, 115.3, 21.4, 18.2, 13.6.

HR-MS (ESI): Calcd. for $C_{19}H_{20}N_2S$ [M+H]: 309.1420 Found: 309.1427.

3-(4-Methoxyphenyl)-5,7-dimethyl-2-(methylthio)quinolin-4-amine (40r)



Reaction Time: 3 h

Yield: 75%, White solid

Melting Point: 155 – 156 ºC

R_f: 0.35 in 15% EtOAc in Hexanes

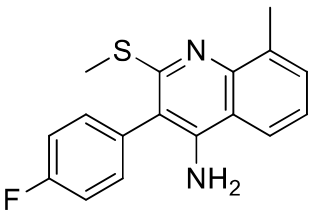
IR (KBr): ν (cm^{-1}) = 3472, 3377, 2956, 2922, 2394, 2352, 2303, 1616, 1568, 1557, 1467, 1355, 1240, 1031, 926.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.30 – 7.17 (m, 2H), 7.06 (d, *J* = 8.7 Hz, 2H), 6.92 (s, 1H), 4.71 (s, 2H), 3.87 (s, 3H), 2.87 (s, 3H), 2.57 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 158.6, 149.8, 148.3, 138.5, 133.0, 132.4, 129.4, 126.7, 126.6, 115.3, 115.0, 114.9, 55.2, 24.5, 21.2, 13.5.

HR-MS (ESI): Calcd. for $C_{19}H_{20}N_2OS$ [M+H]: 325.1369 Found: 325.1376.

3-(4-Fluorophenyl)-8-methyl-2-(methylthio)quinolin-4-amine (40s)



Reaction Time: 3 h

Yield: 47%, Pale yellow solid

Melting Point: 148 – 149 °C

R_f: 0.35 in 10% EtOAc in Hexanes

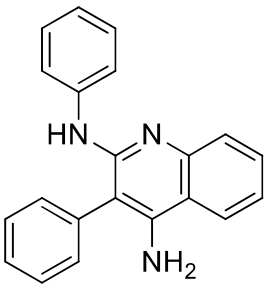
IR (KBr): ν (cm^{-1}) = 3455, 3371, 2481, 1901, 1619, 1578, 1484, 1383, 1330, 1212, 352, 759.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, *J* = 7.7 Hz, 2H), 7.36 (d, *J* = 5.7 Hz, 1H), 7.34 (d, *J* = 5.7 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.23 (t, *J* = 8.7 Hz, 2H), 4.36 (s, 2H), 2.77 (s, 3H), 2.59 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (d, *J* = 248.0 Hz), 158.0, 146.6, 145.7, 136.8, 132.9 (d, *J* = 8.2 Hz), 130.7 (d, *J* = 3.3 Hz), 129.7, 123.7, 118.3, 116.9, 116.7 (d, *J* = 21.4 Hz), 113.9, 18.2, 13.6.

HR-MS (ESI): Calcd. for $C_{17}H_{15}FN_2S$ [M+H]: 299.1013 Found: 299.0984.

***N*^{2},3-diphenylquinoline-2,4-diamine (44a)**



Reaction Time: 3 h

Yield: 84%, Pale yellow solid

Melting Point: 148 – 149 °C

R_f: 0.30 in 40% EtOAc in Hexanes

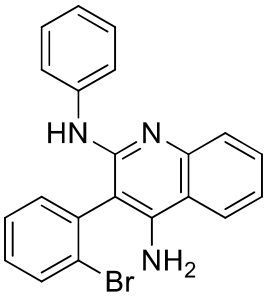
IR (KBr): ν (cm^{-1}) = 3420, 1619, 1524, 1493, 1440, 1404, 1349, 1238, 752.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.95 – 7.76 (m, 1H), 7.69 - 7.55 (m, 6H), 7.50 (s, 1H), 7.42 (s, 2H), 7.31 - 7.21 (m, 3H), 7.05 – 6.86 (m, 1H), 6.31 (s, 1H), 4.46 (d, 2H).

^{13}C NMR (175 MHz, DMSO) δ 152.1, 147.9, 146.6, 141.3, 133.8, 131.1, 130.1, 129.0, 128.3, 128.3, 126.7, 122.3, 121.2, 120.8, 118.9, 116.1, 103.9.

HRMS (ESI-TOF) m/z: Calcd. For $C_{21}H_{17}N_3$[M + H]: 312.1495, found: 312.1439

3-(2-Bromophenyl)-*N*^{2}-phenylquinoline-2,4-diamine (44b)



Reaction Time: 3 h

Yield: 90%, Pale yellow solid

Melting Point: 139 – 140 °C

R_f: 0.29 in 40% EtOAc in Hexanes

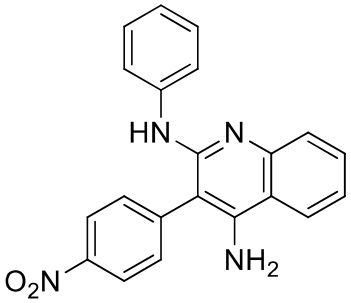
IR (KBr): ν (cm^{-1}) = 3442, 2816, 2360, 1734, 1683, 1521, 667.

^{1}H NMR (400 MHz, DMSO) δ 8.20 - 8.16 (m, 1H), 7.94 - 7.83 (m, 1H), 7.78 – 7.52 (m, 5H), 7.49 - 7.40 (m, 2H), 7.33 – 7.11 (m, 3H), 7.02 – 6.83 (m, 1H), 6.77 – 6.50 (m, 1H), 5.88 (s, 2H)

^{13}C NMR (100 MHz, DMSO) δ 151.8, 148.4, 146.4, 141.3, 134.3, 133.8, 133.7, 130.6, 129.4, 129.3, 128.2, 126.2, 126.1, 122.5, 121.3, 121.2, 119.9, 116.0, 103.2.

HRMS (ESI-TOF) m/z: Calcd. For $C_{21}H_{16}BrN_3$ [M + H]: 390.0600, found: 390.0610.

3-(4-Nitrophenyl)-*N*^{2}-phenylquinoline-2,4-diamine (44c)



Reaction Time: 3 h

Yield: 67%, Orange solid

Melting Point: 175 – 176 °C

R_f: 0.25 in 40% EtOAc in Hexanes

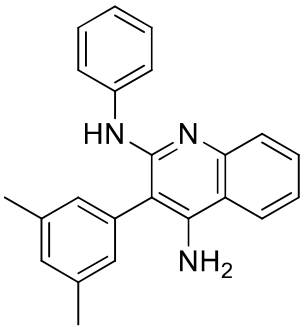
IR (KBr): ν (cm^{-1}) = 3437, 2885, 2829, 2360, 1630.

^{1}H NMR (700 MHz, DMSO) δ 8.42 (d, *J* = 8.4 Hz, 2H), 8.12 (d, *J* = 7.7 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.55 - 7.49 (m, 2H), 7.21 (t, *J* = 7.7 Hz, 3H), 6.91 (s, 1H), 6.88 (t, *J* = 7.7 Hz, 1H), 5.96 (s, 2H).

^{13}C NMR (175 MHz, DMSO) δ 151.8, 148.3, 147.2, 147.0, 142.2, 141.5, 133.1, 129.4, 128.0, 126.7, 125.0, 122.4, 121.3, 120.8, 119.8, 116.0, 102.2.

HRMS (ESI-TOF) m/z: Calcd. For $C_{21}H_{16}N_4O_2$ [M + H]: 357.1346, found: 357.1333.

3-(3,5-Dimethylphenyl)-*N*^{2}-phenylquinoline-2,4-diamine (44d)



Reaction Time: 3 h

Yield: 84%, Pale yellow solid

Melting Point: 126 – 127 °C

R_f: 0.32 in 40% EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3415, 2270, 1527, 1601, 1493, 1440, 1402, 1263, 752.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 1H), 7.71 – 7.61 (m, 3H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.30 - 7.25 (m, 3H), 7.12 (s, 1H), 7.04 - 7.00 (m, 2H), 6.97 (t, *J* = 7.7 Hz, 1H), 6.51 (s, 1H), 4.57 (s, 2H), 2.40 (s, 6H).

^{13}C NMR (100 MHz, DMSO) δ 152.3, 148.0, 146.5, 141.4, 139.5, 133.7, 130.1, 129.3, 128.5, 128.5, 126.7, 122.4, 121.5, 121.0, 119.1, 116.3, 104.2, 21.2.

HRMS (ESI-TOF) m/z: Calcd. For $C_{23}H_{21}N_3$ [M + H]: 340.1808, found: 340.1820.

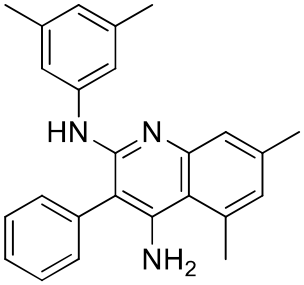
***N*^{2}-(3,5-Dimethylphenyl)-5,7-dimethyl-3-phenylquinoline-2,4-diamine (44e)**

Reaction Time: 3 h

Yield: 98%, Pale yellow solid

Melting Point: 184 – 185 °C

R_f: 0.3 in 40% EtOAc in Hexanes



IR (KBr): ν (cm^{-1}) = 3428, 3016, 2910, 2359, 1604, 1571, 1534, 1452, 1376, 1189.

^{1}H NMR (400 MHz, DMSO) δ 7.65 (t, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.38 (d, *J* = 6.8 Hz, 2H), 7.32 - 7.24 (m, 3H), 6.80 (s, 1H), 6.51 (s, 1H), 6.25 (s, 1H), 4.96 (s, 2H), 2.80 (s, 3H), 2.36 (s, 3H), 2.20 (s, 6H).

^{13}C NMR (100 MHz, DMSO) δ 151.4, 149.6, 148.6, 141.1, 137.8, 137.2, 133.8, 133.7, 131.3, 130.4, 128.6, 127.2, 125.0, 122.5, 116.5, 114.1, 105.3, 23.9, 21.2, 20.8.

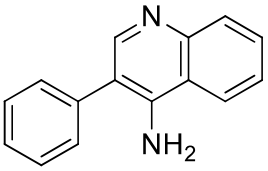
HRMS (ESI-TOF) m/z: Calcd. For $C_{25}H_{25}N_3$ [M + H]: 368.2121, found: 368.2120.

4.5.6 General Procedure for the Desulfurization of 4-Aminoquinolines 40

To a dried and argon filled round bottom flak equipped with reflux condenser was added 4-aminoquinoline, which dissolved in EtOH, followed by Raney Nickel very carefully. The reaction mixture was heated to refux till completion of the starting material. It was monitored by TLC. After completion, the reaction was filtered through celite to remove Raney nickel, which was quenched with water. The resultant filterate was evaporated, crude mixture was passed through silica gel with EtOAc/Hexane as eluent to get pure product

3-Phenylquinolin-4-amine (54a)

Reaction Time: 24 h



Yield: 72%, White solid

Melting Point: 186 – 188 °C

R_f: 0.3 in 3:1 EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3446, 3306, 3160, 2388, 2301, 164, 1564, 1500, 1433, 1366, 1285, 1115, 764.

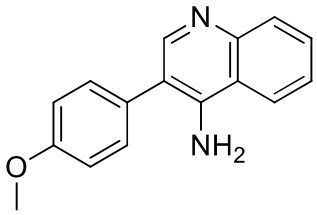
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.71 – 7.61 (m, 1H), 7.55 – 7.45 (m, 5H), 7.46 – 7.39 (m, 1H), 5.25 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.02, 147.69, 146.78, 136.35, 129.60 (2C), 129.43 (2C), 127.96, 125.37, 120.99, 118.31, 116.67.

HR-MS (ESI): Calcd. for $C_{15}H_{12}N_2$ [M+H]: 221.1073 Found: 221.1102 .

3-(4-Methoxyphenyl)quinolin-4-amine (54b)

Reaction Time: 24 h



Yield: 82%, White solid

Melting Point: 119 – 120 °C

R_f: 0.3 in 3:1 EtOAc in Hexanes

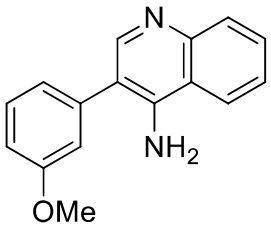
IR (KBr): ν (cm^{-1}) = 3416, 3323, 3193, 2919, 2396, 2352, 1651, 1567, 1511, 1440, 1245, 1178, 829, 762.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.74 – 7.59 (m, 1H), 7.52 – 7.43 (m, 1H), 7.44 – 7.34 (m, 2H), 7.11 – 6.99 (m, 2H), 5.13 (s, 2H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.31, 151.14, 147.56, 146.83, 130.71, 129.37, 129.21, 128.38, 125.24, 120.93, 118.31, 116.40, 114.81, 55.42.

HR-MS (ESI): Calcd. for $C_{16}H_{14}N_2O$ [M+H]: 251.1179 Found: 251.1169.

3-(3-Methoxyphenyl)quinolin-4-amine (54c)



Reaction Time: 24 h

Yield: 70%, White solid

Melting Point: 118 – 119 °C

R_f: 0.27 in 4:1 EtOAc in Hexanes

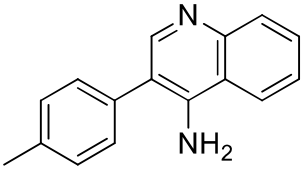
IR (KBr): ν (cm^{-1}) = 3437, 3026, 2923, 2853, 2348, 2077, 1631, 1535, 1502, 1367, 1214, 1029.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.70 – 7.55 (m, 1H), 7.50 – 7.33 (m, 2H), 7.05 (d, *J* = 7.6 Hz, 1H), 7.01 (s, 1H), 6.97 – 6.89 (m, 1H), 5.24 (s, 2H), 3.82 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 160.3, 150.9, 147.7, 146.7, 137.7, 130.4, 129.4, 125.3, 121.8, 121.0, 120.9, 118.2, 116.5, 115.1, 113.3, 55.4.

HR-MS (ESI): Calcd. for $C_{16}H_{14}N_2O$ [M+H]: 251.1179 Found: 251.1189.

3-(*p*-Tolyl)quinolin-4-amine (54d)



Reaction Time: 24 h

Yield: 71%, Colourless solid

Melting Point: 190 – 191 °C

R_f: 0.3 in 3:1 EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3457, 3433, 3302, 3185, 2699, 1635, 1583, 1505, 1428, 1354, 1292, 1027, 769.

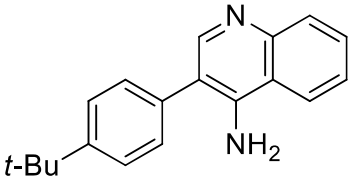
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.9 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 5.08 (s, 2H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 147.5, 146.7, 137.7, 133.2, 130.0, 129.4, 129.3, 129.3, 125.2, 120.9, 118.3, 116.6, 21.2.

HR-MS (ESI): Calcd. for $C_{16}H_{14}N_2$ [M+H]: 235.1230 Found: 235.1252 .

3-(4-(*tert*-Butyl)phenyl)quinolin-4-amine (54e)

Reaction Time: 24 h



Yield: 62%, White solid

Melting Point: 215 – 217 °C

R_f: 0.3 in 3:1 EtOAc in Hexanes

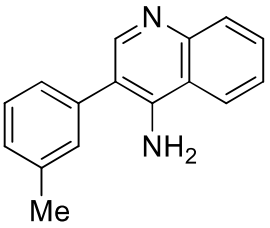
IR (KBr): ν (cm^{-1}) =3462, 3305, 3186, 2959, 2315, 1636, 1569, 1500, 1438, 1364, 1270, 1114, 764.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.48 - 7. 41 (m, 3H), 5.18 (s, 2H), 1.38 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.03, 150.97, 147.45, 146.91, 133.24, 129.41, 129.36, 129.26, 126.39, 125.38, 120.95, 118.32, 116.67, 34.80, 31.45.

HR-MS (ESI): Calcd. for $C_{19}H_{20}N_2$ [M+H]: 277.1699 Found: 269.1708.

3-(*m*-Tolyl)quinolin-4-amine (54f)



Reaction Time: 24 h

Yield: 68%, White solid

Melting Point: 159 – 160 °C

R_f: 0.3 in 3:1 EtOAc in Hexanes

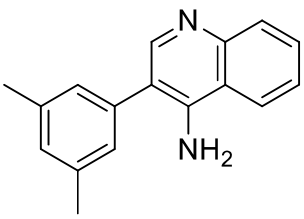
IR (KBr): ν (cm^{-1}) = 3346, 3021, 2921, 1640, 1584, 1567, 1502, 1439, 1366.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.33 – 7.25 (m, 2H), 7.22 (d, *J* = 7.6 Hz, 1H), 5.17 (s, 2H), 2.42 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 150.9, 147.5, 146.7, 139.2, 136.2, 130.2, 129.42, 129.41, 129.3, 128.7, 126.6, 125.3, 120.9, 118.3, 116.8, 21.6.

HR-MS (ESI): Calcd. for $C_{16}H_{14}N_2$ [M+H]: 235.1230 Found: 235.1242.

3-(3,5-Dimethylphenyl)quinolin-4-amine (54g)



Reaction Time: 24 h

Yield: 78%, White solid

Melting Point: 216 - 217 ºC

R_f: 0.34 in 3:1 EtOAc in Hexanes

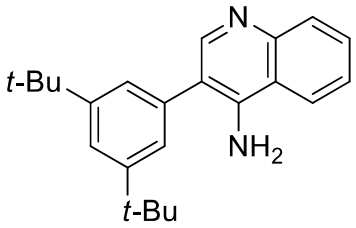
IR (KBr): ν (cm^{-1}) = 3463, 3301, 3124, 2266, 1645, 1596, 1502, 1443, 1366, 1290, 1119, 854, 769.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.10 (s, 2H), 7.06 (s, 1H), 5.18 (s, 2H), 2.39 (s, 6H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 150.5, 147.1, 147.0, 139.1, 136.0, 129.7, 129.5, 129.1, 127.3, 125.4, 120.9, 118.2, 117.0, 21.5.

HR-MS (ESI): Calcd. for $C_{17}H_{16}N_2$ [M+H]: 249.1386 Found: 249.1390.

3-(3,5-Di-*tert*-butylphenyl)quinolin-4-amine (54h)



Reaction Time: 24 h

Yield: 42%, White solid

Melting Point: 228 - 230 ºC

R_f: 0.38 in 2:1 EtOAc in Hexanes

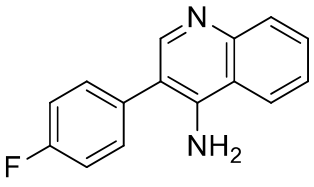
IR (KBr): ν (cm^{-1}) = 3452, 3304, 3180, 2923, 2391, 2352, 1639, 1583, 1510, 1500, 1431, 1218, 897, 771.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.97 - 7.91 (m, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.56 – 7.44 (m, 2H), 7.39 – 7.30 (m, 2H), 5.23 (s, 2H), 1.37 (s, 18H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 151.4, 147.8, 146.6, 135.5, 129.5, 129.0, 125.1, 123.7, 121.8, 120.9, 118.4, 117.7, 35.0, 31.5.

HR-MS (ESI): Calcd. for $C_{23}H_{28}N_2$ [M+H]: 333.2325 Found: 333.2337.

3-(4-Fluorophenyl)quinolin-4-amine (54i)



Reaction Time: 24 h

Yield: 56%, White solid

Melting Point: 145 – 146 ºC

R_f: 0.3 in 3:1 EtOAc in Hexanes

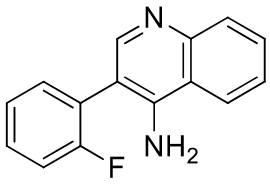
IR (KBr): ν (cm^{-1}) = 3461, 3300, 3140, 2060, 1645, 1567, 1508, 1443, 1365, 1219, 838, 768

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.72 – 7.62 (m, 1H), 7.54 – 7.48 (m, 1H), 7.47 – 7.41 (m, 2H), 7.25 – 7.15 (m, 2H), 5.22 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (d, *J* = 248.0 Hz), 150.0, 147.2, 146.9, 131.8 (d, *J* = 3.4 Hz), 131.3 (d, *J* = 8.1 Hz), 129.7, 128.8, 125.60, 120.9, 118.0, 116.4 (d, *J* = 21.5 Hz), 115.62.

HR-MS (ESI): Calcd. for $C_{15}H_{11}FN_2$ [M+H]: 239.0979 Found: 239.1001.

3-(2-Fluorophenyl)quinolin-4-amine (54l)



Reaction Time: 24 h

Yield: 59%, White solid

Melting Point: 154 – 155 ºC

R_f: 0.3 in 3:1 EtOAc in Hexanes

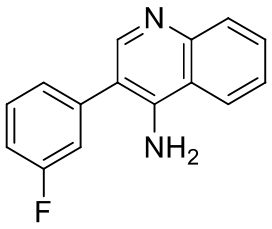
IR (KBr): ν (cm^{-1}) = 3437, 3025, 2922, 2077, 1631, 1501, 1364, 1038, 821.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.77 – 7.62 (m, 1H), 7.58 – 7.36 (m, 3H), 7.36 – 7.16 (m, 2H), 5.12 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (d, *J* = 246 Hz), 151.4, 148.0, 147.47, 147.41, 132.1 (d, *J* = 3 Hz), 130.0 (d, *J* = 8 Hz), 129.4, 125.1, 124.8 (d, *J* = 3 Hz), 123.4 (d, *J* = 17 Hz), 121.0, 118.2, 116.3 (d, *J* = 22 Hz), 110.3

HR-MS (ESI): Calcd. for $C_{15}H_{11}FN_2$ [M+H]: 239.0979 Found: 239.0956.

3-(3-Fluorophenyl)quinolin-4-amine (54m)



Reaction Time: 24 h

Yield: 75%, White solid

Melting Point: 134 – 135 ºC

R_f: 0.34 in 3:1 EtOAc in Hexanes

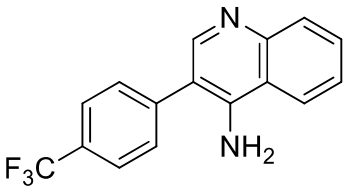
IR (KBr): ν (cm^{-1}) = 3360, 3021, 2922, 2253, 1612, 1583, 1503, 1368.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.50 - 7.43 (m, 2H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 9.2 Hz, 1H), 7.10 (td, *J* = 8.4, 1.6 Hz, 1H), 5.26 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (d, *J* = 247.8 Hz), 150.7, 147.8, 146.7, 138.6 (d, *J* = 7.8 Hz), 131.0 (d, *J* = 8.6 Hz), 129.6, 129.50, 125.4, 125.2 (d, *J* = 2.9 Hz), 120.9, 118.2, 116.5 (d, *J* = 21.3 Hz), 115.3, 114.8 (d, *J* = 21.0 Hz).

HR-MS (ESI): Calcd. for $C_{15}H_{11}FN_2$ [M+H]: 239.0979 Found: 239.0962

3-(4-(Trifluoromethyl)phenyl)quinolin-4-amine (54n)



Reaction Time: 24 h

Yield: 67%, White solid

Melting Point: 148 – 150 ºC

R_f: 0.3 in 3:1 EtOAc in Hexanes

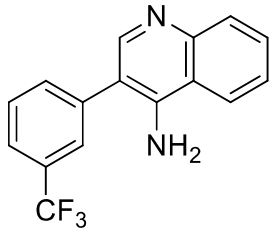
IR (KBr): ν (cm^{-1}) = 3436, 3327, 3201, 2646, 1648, 1615, 11503, 1409, 1367, 1332, 1157, 1113, 1073, 765.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.76 (d, *J* = 7.7 Hz, 2H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 5.18 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.28, 147.67, 147.37, 140.22, 129.75, 129.67, 129.45, 128.89, 126.04 (q, J = 3.47 Hz), 125.33, 124 (q, J = 270 Hz), 121.47, 118.17, 114.73.

HR-MS (ESI): Calcd. for $C_{16}H_{11}F_3N_2$ [M+H]: 289.0947 Found: 289.0963.

3-(3-(Trifluoromethyl)phenyl)quinolin-4-amine (54o)



Reaction Time: 24 h

Yield: 59%, White solid

Melting Point: 120 – 121 °C

R_f: 0.33 in 3:1 EtOAc in Hexanes

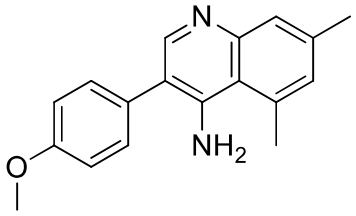
IR (KBr): ν (cm^{-1}) = 3441, 3030, 1638, 1807, 2926, 1340, 1124.

^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.76 (s, 1H), 7.73 – 7.57 (m, 4H), 7.48 (t, *J* = 7.6 Hz, 1H), 5.18 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 147.9, 146.8, 137.3, 133.1, 131.8 (q, *J* = 32.5 Hz), 130.0, 129.8, 129.6, 126.3 (q, *J* = 3.7 Hz), 125.6, 124.7 (q, *J* = 3.6 Hz), 124.0 (q, *J* = 271 Hz), 120.9, 118.2, 115.1.

HR-MS (ESI): Calcd. for $C_{16}H_{11}F_3N_2$ [M+H]: 289.0947 Found: 289.0947

3-(4-Methoxyphenyl)-5,7-dimethylquinolin-4-amine (54r)

Reaction Time: 24 h



Yield: 95%, Yellow solid

Melting Point: 104 – 105 °C

R_f: 0.27 in 4:1 EtOAc in Hexanes

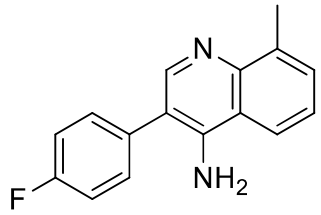
IR (KBr): ν (cm^{-1}) = 3491, 3393, 2948, 2829, 2394, 2292, 1617, 1581, 1512, 1450, 1349, 1248, 1041, 1022, 832.

^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.63 (s, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.07 - 6.99 (m, 3H), 5.13 (s, 2H), 3.86 (s, 3H), 2.94 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 159.3, 150.1, 149.8, 149.4, 138.8, 133.2, 131.1, 130.7, 128.4, 127.1, 117.2, 116.6, 114.8, 55.4, 24.9, 21.3.

HR-MS (ESI): Calcd. for $C_{18}H_{18}N_2O$ [M+H]: 279.1492 Found: 279.1504.

3-(4-Fluorophenyl)-8-methylquinolin-4-amine (54s)



Reaction Time: 24 h

Yield: 64%, White solid

Melting Point: 172 – 173 °C

R_f: 0.3 in 2:1 EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3425, 3053, 2986, 2304, 1275, 1361, 763, 749.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 6.8 Hz, 1H), 7.46 - 7.42 m, 2H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 8.5 Hz, 2H), 4.96 (s, 2H), 2.80 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (d, *J* = 247.5 Hz), 149.9, 146.9, 146.7, 137.3, 132.4 (d, *J* = 3.3 Hz), 131.3 (d, *J* = 8.0 Hz), 129.7, 125.0, 118.6, 118.0, 116.3 (d, *J* = 21.4 Hz), 115.6, 18.8.

HR-MS (ESI): Calcd. for $C_{16}H_{13}FN_2$ [M+H]: 253.1136 Found: 253.1107.

4.5.7 General Procedure for the Optimization of Reaction Conditions for Intramolecular C−H Amination

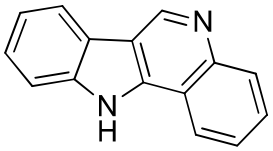
To an oven-dried 8 mL reaction vial was charged with $Pd(OAc)_2$, Oxidant and Base (1 mmol), respective aminoquinoline in solvent, was stirred at rt or heating till completion of the reaction. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was purified by flash chromatography.

4.5.8 General procedure for the Synthesis of Indoloquinolines

To an oven-dried 8 mL reaction vial was charged with PIFDA, respective aminoquinoline in HFIP, was stirred at rt or 60 ºC till completion of the reaction. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, solvent was evaporated and the reaction mixture was purified by flash chromatography.

11*H*-Indolo[3,2-*c*]quinoline (16a)

Reaction Time: 1 h



Yield: 94%, Grey solid

Melting Point: >295 ºC

R_f: 0.25 in 2:1 EtOAc in Hexanes

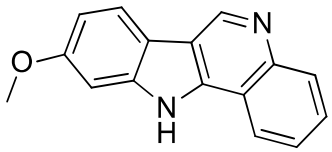
IR (KBr): ν (cm^{-1}) = 3429, 3056, 2980, 2946, 2892, 2849, 1589, 1509, 1364, 1339, 1237, 1216, 734.

^{1}H NMR (400 MHz, DMSO-D_6) δ 12.79 (s, 1H), 9.62 (s, 1H), 8.56 (d, *J* = 7.8 Hz, 1H), 8.32 (d, *J* = 7.8 Hz, 1H), 8.16 (d, *J* = 8.1 Hz, 1H), 7.81 – 7.63 (m, 3H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-D_6) δ 145.4, 144.8, 139.8, 138.8, 129.6, 128.0, 125.7, 125.5, 122.1, 121.9, 120.6, 120.1, 117.1, 114.3, 111.9.

HR-MS (ESI): Calcd. for $C_{15}H_{10}N_2$ [M+H]: 219.0917 Found: 219.0921.

9-Methoxy-11*H*-indolo[3,2-*c*]quinoline (16b)



Reaction Time: 6 h

Yield: 75%, White Solid

Melting Point: >295 ºC

R_f: 0.34 in 50% EtOAc in Hexanes

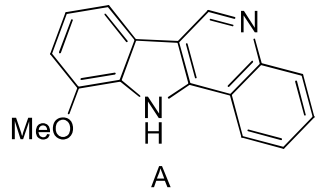
IR (KBr): ν (cm^{-1}) = 3676, 3024, 2766, 2263, 1559, 1495, 1342, 1197, 1150, 945.

^{1}H NMR (400 MHz, DMSO-D_6) δ 12.66 (s, 1H), 9.53 (s, 1H), 8.48 (d, *J* = 7.6 Hz, 1H), 8.19 (d, *J* = 8.6 Hz, 1H), 8.11 (d, *J* = 7.9 Hz, 1H), 7.73 - 7.65 (m, 2H), 7.17 (s, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 3.90 (s, 3H).

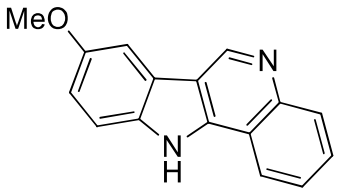
^{13}C NMR (100 MHz, DMSO-D_6) δ 158.4, 144.3, 143.8, 140.2, 139.6, 129.0, 127.6, 125.6, 121.8, 120.9, 116.9, 115.5, 114.4, 110.0, 95.3, 55.3.

HR-MS (ESI): Calcd. for $C_{16}H_{12}N_2O$ [M+H]: 249.1022 Found: 249.1045.

10-Methoxy-11*H*-indolo[3,2-*c*]quinoline (16ca) & 8-methoxy-11*H*-indolo[3,2-*c*]quinoline (16cb)



A



B

Reaction Time: 4 h

Yield: A = 16%, B = 45%

Melting Point: >295 ºC (16ca)

Melting Point: 292 – 293 ºC (16cb)

R_f: 0.2 in 2:1 EtOAc in Hexanes (16ca)

R_f: 0.2 in 3:1 EtOAc in Hexanes (16cb)

IR (KBr): ν (cm^{-1}) = 3548, 3478, 2985, 2165, 1648, 1574, 1301, 1015.

IR (KBr): ν (cm^{-1}) = 3437, 3030, 2923, 2853, 2077, 1631, 1547, 1467, 1377, 1056, 812. (16cb)

^{1}H NMR (400 MHz, DMSO) δ 12.88 (s, 1H), 9.60 (s, 1H), 8.82 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.75 (t, *J* = 7.2 Hz, 1H), 7.68 (t, *J* = 7.2 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 4.07 (s, 3H). (16ca)

^{13}C NMR (100 MHz, DMSO) δ 146.7, 145.0, 144.9, 140.1, 129.2, 129.1, 128.6, 126.3, 123.6, 123.2, 122.0, 117.8, 115.1, 112.8, 106.8, 55.9. (16ca)

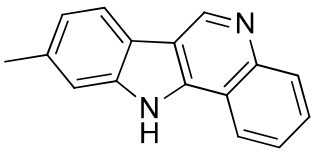
^{1}H NMR (400 MHz, DMSO) δ 12.61 (s, 1H), 9.58 (s, 1H), 8.50 (d, *J* = 7.6 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 2.0 Hz, 1H), 7.73 (t, *J* = 7.2 Hz, 1H), 7.67 (t, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.12 (dd, *J* = 8.8, 2.0 Hz, 1H), 3.90 (s, 3H). (16cb)

^{13}C NMR (100 MHz, DMSO) δ 154.48, 145.18, 144.92, 140.13, 133.52, 129.39, 127.93, 125.62, 122.48, 122.05, 117.24, 115.10, 114.41, 112.60, 102.52, 55.61. (16cb)

HR-MS (ESI): Calcd. for $C_{16}H_{12}N_2O$ [M+H]: 249.1022 Found: 249.1031 (16ca)

HR-MS (ESI): Calcd. for $C_{16}H_{12}N_2O$ [M+H]: 249.1022 Found: 249.1025 (16cb)

9-Methyl-11*H*-indolo[3,2-*c*]quinoline (16d)



Reaction Time: 9 h

Yield: 74%, Grey solid

Melting Point: 142 – 143 ºC

R_f: 0.33 in 1:1 EtOAc in Hexanes

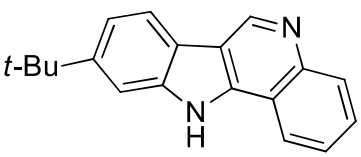
IR (KBr): ν (cm^{-1}) = 3439, 3144, 2923, 2851, 2229, 1628, 1506, 1333, 1272, 1240, 1225, 920, 747.

^{1}H NMR (400 MHz, DMSO-D_6) δ 12.66 (s, 1H), 9.60 (s, 1H), 8.37 (d, *J* = 7.8 Hz, 1H), 8.31 (d, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.67 – 7.53 (m, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 1H), 2.81 (s, 3H).

^{13}C NMR (175 MHz, DMSO-D_6) δ 144.2, 143.67, 140.3, 138.9, 137.0, 128.5, 125.6, 125.4, 121.9, 120.6, 120.1, 120.0, 116.9, 114.3, 111.9, 39.8, 39.7, 39.6, 39.5, 39.4, 39.2, 39.1, 18.8.

HR-MS (ESI): Calcd. for $C_{16}H_{12}N_2$ [M+H]: 233.1073 Found: 233.1054.

9-(*tert*-Butyl)-11*H*-indolo[3,2-*c*]quinoline (16e)



Reaction Time: 4 h

Yield: 73%, Colourless solid

Melting Point: >295 ºC

R_f: 0.34 in 40% EtOAc in Hexanes

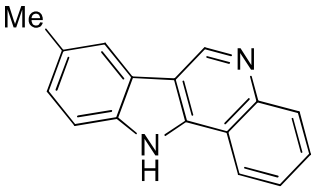
IR (KBr): ν (cm^{-1}) = 3444, 3055, 2957, 2923, 2853, 1621, 1459, 1365, 1277, 1245, 942, 869, 757.

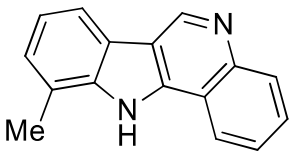
^{1}H NMR (400 MHz, DMSO-D_6) δ 12.63 (s, 1H), 9.55 (s, 1H), 8.50 (d, *J* = 7.6 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.78 – 7.61 (m, 3H), 7.40 (dd, *J* = 8.4, 1.2 Hz, 1H), 1.40 (s, 9H).

^{13}C NMR (100 MHz, DMSO-D_6) δ 148.6, 145.2, 144.6, 139.8, 139.0, 129.5, 127.7, 125.6, 122.0, 119.6, 119.5, 118.7, 117.1, 114.2, 107.8, 34.8, 31.5.

HR-MS (ESI): Calcd. for $C_{19}H_{18}N_2$ [M+H]: 275.1543 Found: 275.1543.

8-Methyl-11H-indolo[3,2-c]quinoline & 10-methyl-11H-indolo[3,2-c]quinoline (16fa & 16fb)





Reaction Time: 3 h

Yield: 62%, Grey solid

Melting Point: 268 – 270 ºC

R_f: 0.22 in 2:1 EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3406, 2885, 2361, 2271, 1584, 1364, 1069.

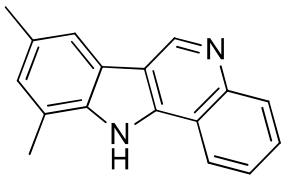
^{1}H NMR (400 MHz, DMSO-D_6) (Mixture of Isomers 1 : 1) δ 12.61 (s, 1H), 12.32 (s, 1H), 9.58 (s, 1H), 9.55 (s, 1H), 8.76 (dd, *J* = 7.6 1.2 Hz, 1H), 8.59 – 8.46 (m, 1H), 8.16 - 8.08 (m, 4H),

7.79 – 7.64 (m, 4H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 2.70 (s, 3H), 2.51 (s, 3H).

^{13}C NMR (100 MHz, DMSO-D_6) δ 145.5, 145.4, 144.9, 144.7, 139.9, 139.7, 138.2, 137.0, 129.5 (2C), 129.4 (2C), 127.9 (2C), 126.9, 126.1, 125.6, 125.5, 122.6, 122.1, 121.6, 121.4, 120.7, 119.7, 117.4, 117.6, 117.2, 114.8, 114.1, 111.5, 21.2, 17.3.

HR-MS (ESI): Calcd. for $C_{16}H_{12}N_2$ [M+H]: 233.1073 Found: 233.1069.

8,10-Dimethyl-11*H*-indolo[3,2-*c*]quinoline (16g)



Reaction Time: 3 h

Yield: 79%, White solid

Melting Point: >295 ºC

R_f: 0.34 in 30% EtOAc in Hexanes

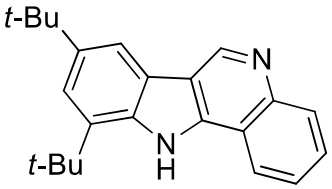
IR (KBr): ν (cm^{-1}) = 3436, 3138, 2920, 2852, 1585, 1457, 1343, 1287, 1224, 1034, 845, 756, 693.

^{1}H NMR (400 MHz, DMSO-D_6) δ 12.21 (s, 1H), 9.52 (s, 1H), 8.72 (d, *J* = 7.6 Hz, 1H), 8.12 (d, *J* = 7.9 Hz, 1H), 7.91 (s, 1H), 7.80 – 7.53 (m, 2H), 7.11 (s, 1H), 2.66 (s, 3H), 2.47 (s, 3H).

^{13}C NMR (100 MHz, DMSO-D_6) δ 145.3, 144.8, 139.7, 136.4, 129.5, 129.4, 127.7, 127.6, 125.4, 122.5, 121.7, 120.9, 117.3, 117.0, 114.5, 21.1, 17.1.

HR-MS (ESI): Calcd. for $C_{17}H_{14}N_2$ [M+H]: 247.1230 Found: 247.1249.

8,10-Di-*tert*-butyl-11*H*-indolo[3,2-*c*]quinoline (16h)



Reaction time: 4 h

Yield: 65%, White solid

Melting Point: 240 – 241 ºC

R_f: 0.32 in 1:1 EtOAc in Hexanes

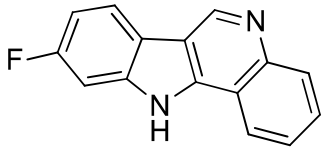
IR (KBr): ν (cm^{-1}) = 3423, 3025, 2908, 2095, 1657, 1630, 1547, 1368, 1056. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 9.15 (s, 1H), 8.26 (t, *J* = 9.2 Hz, 2H), 8.09 (s, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 1.2 Hz, 1H), 1.66 (s, 9H), 1.49 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 144.7, 144.4, 139.7, 134.4, 133.3, 130.0, 128.2, 125.9, 123.5, 121.2, 120.6, 116.9, 115.4, 114.1, 35.1(2C), 32.0, 30.8.

HR-MS (ESI): Calcd. for $C_{23}H_{26}N_2$ [M+H]: 331.2169 Found: 331.2180.

9-Fluoro-11*H*-indolo[3,2-*c*]quinoline (16i)

Reaction Time: 4 h



Yield: 71%, Grey Solid

Melting Point: >295 ºC

R_f: 0.3 in 2:1 EtOAc in Hexanes

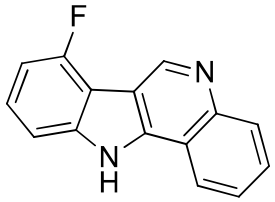
IR (KBr): ν (cm^{-1}) = 3402, 3054, 2875, 2775, 1858, 1612, 1339, 1233, 1141, 962, 758.

^{1}H NMR (400 MHz, DMSO-D_6) δ 12.86 (s, 1H), 9.59 (s, 1H), 8.51 (d, *J* = 7.9 Hz, 1H), 8.43 – 8.26 (m, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 7.77 - 7.67 (m, 2H), 7.50 (d, *J* = 9.0 Hz, 1H), 7.20 (t, *J* = 9.0 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-D$_6$) δ 160.9 (d, *J* = 239.3 Hz), 145.2, 144.5, 140.4 (d, *J* = 1.9 Hz), 139.2 (d, *J* = 12.8 Hz), 129.5, 127.9, 125.8, 121.9, 121.4 (d, *J* = 10.5 Hz), 118.6, 116.9, 114.0, 108.7 (d, *J* = 24.3 Hz), 98.3 (d, *J* = 26.1 Hz).

HR-MS (ESI): Calcd. for $C_{15}H_9FN_2$ [M+H]: 237.0823 Found: 237.0802.

7-Fluoro-11*H*-indolo[3,2-*c*]quinoline (16l)



Reaction Time: 24 h at RT, 3 h at 60 °C

Yield: 59%, Grey Solid

Melting Point: >295 °C

R_f: 0.30 in 2:1 EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3437, 3029, 2922, 2077, 1657, 1631, 1547, 1368, 1069.

^{1}H NMR (400 MHz, DMSO-D$_6$) δ 13.45 (s, 1H), 9.45 (s, 1H), 8.65 (d, *J* = 7.6 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.81 – 7.75 (m, 1H), 7.74 – 7.68 (m, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.52 - 7.45 (m, 1H), 7.18 - 7.13 (m, 1H).

^{13}C NMR (175 MHz, DMSO-D$_6$) δ 157.0 (d, *J* = 246.2 Hz), 145.12, 145.11 (d, *J* = 1.3 Hz), 141.2 (d, *J* = 10.4 Hz), 139.9, 129.4, 128.4, 126.4 (d, *J* = 7.9 Hz), 126.0, 122.5, 116.9, 111.7, 110.1 (d, *J* = 21.4 Hz), 108.4 (d, *J* = 3.1 Hz), 105.9 (d, *J* = 18.3 Hz).

HR-MS (ESI): Calcd. for $C_{15}H_9FN_2$ [M+H]: 237.0823 Found: 237.0830.

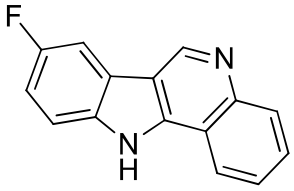
8-Fluoro-11H-indolo[3,2-c]quinoline & 10-fluoro-11H-indolo[3,2-c]quinoline (16ma & 16mb)

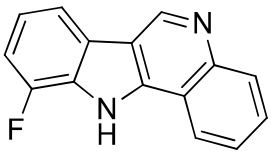
Reaction Time: 3 h

Yield: 57%, Grey solid

Melting Point: >295 °C

R_f: 0.22 in 1:1 EtOAc in Hexanes





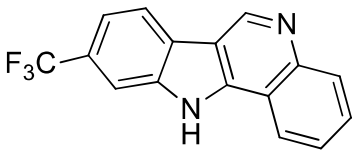
IR (KBr): ν (cm^{-1}) = 3437, 3029, 2922, 2082, 1657, 1547, 1368, 1069, 812.

^{1}H NMR (400 MHz, DMSO-D_6) (Mixture of Isomers 1:0.6) δ 13.08 (s, 1H), 12.80 (s, 1H), 9.62 (s, 1H), 9.59 (s, 1H), 8.70 (d, *J* = 8.0 Hz, 1H), 8.51 (d, *J* = 8.0 Hz, 1H), 8.23 – 8.01 (m, 4H), 7.88 – 7.64 (m, 5H), 7.41 – 7.21 (m, 3H).

^{13}C NMR (101 MHz, DMSO-D_6) (Mixture of 2 isomers)δ 157.6 (d, *J* = 234.2 Hz), 149.1 (d, *J* = 243.8 Hz), 145.7, 145.5, 145.2, 145.1, 141.0, 140.4, 135.3, 129.6, 128.5, 128.4, 126.5 (d, *J* = 15.0 Hz), 126.0, 125.9, 125.7 (d, *J* = 5.2 Hz), 122.5 (d, *J* = 5.5 Hz), 122.5, 122.1, 121.2 (d, *J* = 5.8 Hz), 117.2, 117.1, 116.3 (d, *J* = 3.1 Hz), 114.5 (d, *J* = 2.0 Hz), 114.3 (d, *J* = 4.3 Hz), 113.61, 113.3, 113.0 (d, *J* = 9.5 Hz), 110.7 (d, *J* = 16.1 Hz), 105.8 (d, *J* = 24.3 Hz).

HR-MS (ESI): Calcd. for $C_{15}H_9FN_2$ [M+H]: 237.0823 Found: 237.0827

9-(Trifluoromethyl)-11*H*-indolo[3,2-*c*]quinoline (16n)



Reaction Time: 3 h

Yield: 58%, Grey solid

Melting Point: >295 ºC

R_f: 0.25 in 1:1 EtOAc in Hexanes

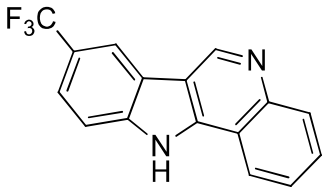
IR (KBr): ν (cm^{-1}) = 3456, 3211, 2923, 2853, 2691, 1600, 1460, 1323, 1283, 1175, 1124, 1102.

^{1}H NMR (400 MHz, DMSO-D_6) δ 13.12 (s, 1H), 9.69 (s, 1H), 8.63 – 8.40 (m, 2H), 8.31 – 8.09 (m, 1H), 8.06 – 7.94 (m, 1H), 7.89 – 7.70 (m, 2H), 7.65 (d, *J* = 7.2 Hz, 1H). (ATP_1_166)

^{13}C NMR (100 MHz, DMSO-D_6) δ 145.7, 145.2, 141.4, 137.8, 129.5, 128.8, 126.1, 125.5 (q, *J* = 31.4 Hz), 124.8 (q, *J* = 270 Hz), 124.7, 122.3, 121.1, 116.9 (q, *J* = 2.7 Hz), 116.8, 113.5, 108.9 (q, *J* = 3.2 Hz).

HR-MS (ESI): Calcd. for $C_{16}H_9F_3N_2$ [M+H]: 287.0791 Found: 287.0772.

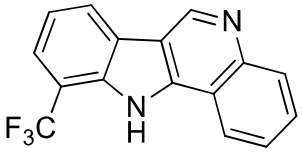
8-(Trifluoromethyl)-11*H*-indolo[3,2-c]quinoline & 10-(trifluoromethyl)-11*H*-indolo[3,2-c]quinoline (16oa & 16ob)



Reaction Time: 3 h

Yield: 73%, Grey solid

Melting Point: > 295 °C



R_f: 0.3 in 2:1 EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3441, 3029, 2922, 2348, 2090, 1635, 1318, 1106, 799.

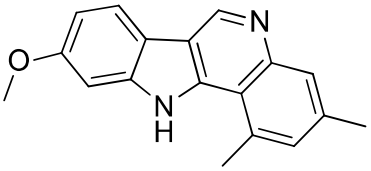
^{1}H NMR (400 MHz, DMSO-D_6) (Mixture of 2 isomers 1 : 0.3)δ 13.17 (s, 1H), 12.61 (s, 1H), 9.75 (s, 1H), 9.69 (s, 1H), 9.02 (d, *J* = 8.0 Hz, 1H), 8.81 (s, 1H), 8.65 (d, *J* = 7.6 Hz, 1H), 8.55 (d, *J* = 7.6 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 2H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.84 - 7.75 (m, 4H), 7.75 – 7.68 (m, 2H), 7.50 (t, *J* = 7.6Hz, 1H).

^{13}C NMR (100 MHz, DMSO-D_6) 146.0, 145.7, 145.2, 144.7, 141.0, 140.8, 140.5, 133.9, 129.6, 129.5, 129.4, 128.5, 126.7, 126.0, 124.5, 124.6 (q, J = 254 Hz), 124.3 (q, J = 269 Hz), 124.0 (q, J = 1.4 Hz), 122.4 (q, J = 4.8 Hz), 122.2, 121.9 (q, J = 3.4 Hz), 121.6, 121.3, 121.2 (q, J = 31.3 Hz), 120.2, 118.6 (q, J = 4.2 Hz), 117.09, 117.0, 114.1, 113.9, 112.7 (q, *J* = 32.5 Hz), 112.5.

HR-MS (ESI): Calcd. for $C_{16}H_9F_3N_2$ [M+H]: 287.0791 Found: 287.0766

9-Methoxy-1,3-dimethyl-11*H*-indolo[3,2-*c*]quinoline (16r)

Reaction Time: 24 h



Yield: 64%, White Solid

Melting Point: >295 ºC

R_f: 0.25 in 2:1 EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3311, 2947, 2837, 1618, 1457, 1341, 1255, 1225, 1196, 1161, 1025, 947, 833

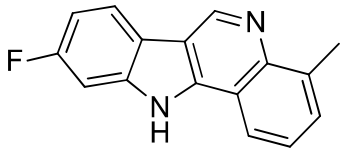
^{1}H NMR (400 MHz, DMSO-D_6) δ 11.52 (s, 1H), 9.46 (s, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.76 (s, 1H), 7.36 (s, 1H), 7.26 (s, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 3.88 (s, 3H), 3.03 (s, 3H), 2.48 (s, 3H).

^{13}C NMR (100 MHz, DMSO-D_6) δ 158.0, 146.3, 143.6, 140.4, 138.9, 136.1, 132.2, 128.7, 126.7, 120.1, 115.0, 114.8, 114.8, 110.1, 95.8, 55.2, 22.8, 21.0.

HR-MS (ESI): Calcd. for $C_{18}H_{16}N_2O$ [M+H]: 277.1335, Found: 277.1346.

9-Fluoro-4-methyl-11*H*-indolo[3,2-*c*]quinoline(16s)

Reaction Time: 3 h



Yield: 60%, Colourless solid

Melting Point: >295 ºC

R_f: 0.37 in 1:1 EtOAc in Hexanes

IR (KBr): ν (cm^{-1}) = 3905, 3158, 2882, 1940, 1602, 1522, 1469, 1334, 1238, 1125, 801.

^{1}H NMR (400 MHz, DMSO-D_6) δ 12.78 (s, 1H), 9.58 (s, 1H), 8.47 – 8.19 (m, 2H), 7.62 – 7.53 (m, 2H), 7.47 (d, *J* = 9.1Hz, 1H), 7.18 (t, *J* = 8.9 Hz, 1H).

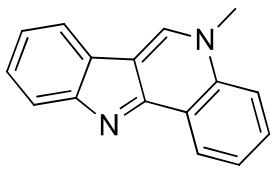
^{13}C NMR (100 MHz, DMSO-D_6) δ 160.9 (d, *J* = 239.4 Hz), 144.0, 143.2, 140.8 (d, *J* = 1.4 Hz), 139.3 (d, *J* = 12.8 Hz), 137.0, 128.3, 125.3, 121.4 (d, *J* = 10.4 Hz), 119.8, 118.6, 116.6, 113.9, 108.6 (d, *J* = 24.3 Hz), 98.2 (d, *J* = 26.1 Hz), 18.6.

HR-MS (ESI): Calcd. for $C_{16}H_{11}FN_2$ [M+H]: 251.0979 Found: 251.0998.

4.5.9 General Procedure for the Synthesis of Isocryptolepine (10)

To a solution of **16a** in acetonitrile, Me_2SO_4 (3 equiv) was added and the reaction mixture was stirred at reflux foe 5 h and was cooled to room temperature. The reaction mixture was then quenched with saturated $NaHCO_3$ and allowed to stir overnight. To the resulting mixture water was added and extracted with EtOAc. The combined extracts were washed with brine, dried over anhydrous sodium sulphate, filtered and filtrate was concentrated, the residue was puridied b using 20% MeOH in DCM as eluent to get pure compound.

5-Methyl-5H-indolo[3,2-*c*]quinoline



Reaction Time: 3 h + 6 h

Yield: 45%, Green solid

Melting Point: 114 – 116 ºC

R_f: 0.25 in 20% MeOH in DCM

IR (KBr): ν (cm^{-1}) = 3440, 2890, 283, 2250, 1628, 1120, 932.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 7.6 Hz, 1H), 7.97 – 7.84 (m, 2H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.56 – 7.40 (m, 3H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 3.77 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 153.2, 152.2, 135.3, 134.6, 128.9, 126.0, 124.7, 124.6, 124.0, 120.2, 119.9, 119.0, 118.1, 116.0, 115.9, 42.0.

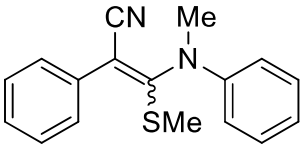
HR-MS (ESI): Calcd. for $C_{16}H_{12}N_2$ [M+H]: 233.1073 Found: 233.1062

4.5.10 General Procedure for Preparation of *S,N*-dimethyl amino acrylonitriles 55

To a stirring suspension of NaH (3.5 equiv, 60%) in dry DMF under N_2 atmosphere a solution of substituted Aryl acetonitriles (1 equiv) in dry DMF was added drop wise at 0 ˚C. The reaction mixture turns yellow and it was stirred for 1 h at room temperature. Then arylisothiocyanates (2.2 equiv) in dry DMF was added slowly under N_2 atmosphere at 0 ˚C and then stirred for 3 hours, the TLC analysis showed that starting materials were consumed. Then the reaction mixture was cold to 0 ˚C and methyl iodide (1equiv) was added dropwise and was stirred for an hour. The reaction mixture was poured to ice cold saturated NH_4Cl solution and extracted with EtOAc (3 x 50 mL), washed with brine solution (100 mL) and dried over Na_2SO_4. The crude viscous oil liquid was purified through silica column chromatography using 10-20% EtOAc/hexane as eluent.

3-(Methyl(phenyl)amino)-3-(methylthio)-2-phenylacrylonitrile (55a)

Reaction Time: 2 +1 h



Yield: 74%, Yellow Solid

Melting Point: 128 - 129 ºC

R_f: 0.34 in 15% Ethyl acetate in hexanes

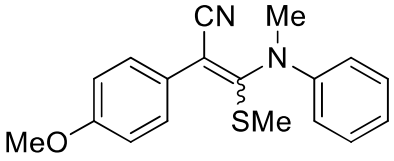
IR (KBr): ν (cm^{-1}) = 3444, 2359, 2340, 2196, 1635, 1539, 1491, 1340, 1266, 1108, 754

^1H NMR (400 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers 1 : 0.18) δ 7.61 (d, *J* = 7.2 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.38 – 7.30 (m, 4H), 7.28 (d, *J* = 4.8 Hz, 2H), 7.27 - 7.23 (m, 3H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.14 - 7.08 (m, 4H), 7.04 (t, *J* = 7.2 Hz, 2H), 3.57 (s, 3H), 3.09 (s, 3H), 2.13 (s, 3H), 2.01 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers) δ 162.7, 159.6, 145.9, 145.1, 134.1, 133.4, 129.2, 129.0, 129.0, 128.7, 128.5, 128.1, 127.8, 127.0, 122.7, 121.8, 120.4, 119.3, 118.6, 117.7, 102.0, 100.5, 41.1, 40.9, 15.2, 15.1.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{17}H_{16}N_2S$: 281.1107, found: 281.1107.

2-(4-Methoxyphenyl)-3-(methyl(phenyl)amino)-3-(methylthio)acrylonitrile (55b)



Reaction Time: 2 +1 h

Yield: 79%, Yellow solid

Melting Point: 100 – 101 ºC

R_f: 0.29 in 15% Ethyl acetate in hexanes

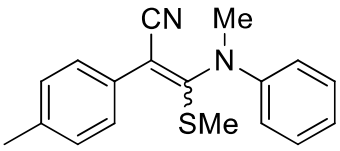
IR (KBr): ν (cm^{-1}) = 3779, 3551, 2388, 2293, 2202, 1605, 1548, 1505, 1247, 1181, 1020, 838.

^{1}H NMR (700 MHz, $CDCl_3$) (Mixture of *E* & *Z* isomers+ 1 : 0.2) δ 7.53 (d, *J* = 8.7 Hz, 2H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.30 (t, *J* = 7.9 Hz, 2H), 7.28 – 7.24 (m, 2H), 7.09 (dd, *J* = 8.6, 0.9 Hz, 2H), 7.07 – 7.04 (m, 2H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.3 Hz, 1H), 6.97 – 6.93 (m, 2H), 6.78 (d, *J* = 8.9 Hz, 2H), 3.84 (s, 3H), 3.76 (s, 3H), 3.52 (s, 3H), 3.08 (s, 3H), 2.10 (d, *J* = 1.0 Hz, 3H), 2.00 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers) δ 161.25, 159.51, 159.25, 157.67, 146.05, 145.14, 130.46, 129.29, 129.06, 128.45, 126.36, 125.49, 122.37, 121.36, 120.45, 118.84, 118.67, 116.92, 114.20, 114.01, 103.23, 101.39, 55.39, 55.30, 40.80, 40.62, 15.10, 15.03.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{18}H_{18}N_2OS$: 311.1213, found: 311.1193.

3-(Methyl(phenyl)amino)-3-(methylthio)-2-(p-tolyl)acrylonitrile (55c)



Reaction Time: 2 +1 h

Yield: 51%, Yellow solid

Melting Point: 113 – 114 ºC

R_f: 0.37 in 15% Ethyl acetate in hexanes

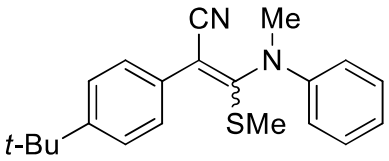
IR (KBr): ν (cm^{-1}) = 3656, 3184, 2390, 2197, 1531, 1345, 1111, 823.

^{1}H NMR (400 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers = 1 : 0.2) δ 7.48 (d, *J* = 8.1 Hz, 2H), 7.3 - 7.28 (m, 4H), 7.22 (d, *J* = 8.2 Hz, 4H), 7.11 - 7.0 (m, 8H), 3.53 (s, 3H), 3.06 (s, 3H), 2.38 (s, 3H), 2.28 (s, 3H), 2.10 (s, 3H), 1.99 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers) δ 161.8, 158.6, 145.9, 145.0, 138.1, 137.8, 131.0, 130.3, 129.3, 129.1, 128.9, 128.8, 127.1, 126.8, 122.4, 121.4, 120.3, 119.0, 118.5, 117.1, 102.8, 101.0, 40.98, 40.6, 21.2, 21.1, 15.0, 14.9.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{18}H_{19}N_2S$: 295.1263, found: 295.1270.

2-(4-(*tert*-butyl)phenyl)-3-(methyl(phenyl)amino)-3-(methylthio)acrylonitrile (55d)



Reaction Time: 2 +1 h

Yield: 76%, Yellow Solid

Melting Point: 124 – 125 ºC

R_f: 0.38 in 15% Ethyl acetate in hexanes

IR (KBr): ν (cm^{-1}) = 3720, 2962, 2290, 2197, 1533, 1492, 1269, 1105, 1034, 823

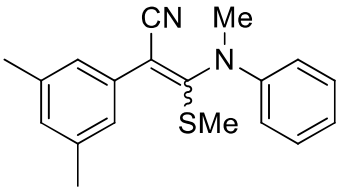
^{1}H NMR (700 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers= 1 : 0.2) δ 7.55 – 7.52 (m, 2H), 7.45 – 7.41 (m, 2H), 7.32 (dd, *J* = 8.6, 7.4 Hz, 2H), 7.31 – 7.27 (m, 2H), 7.26 – 7.24 (m, 4H), 7.08

(d, *J* = 7.7 Hz, 2H), 7.05 (d, *J* = 7.8 Hz, 1H), 7.03 – 6.97 (m, 2H), 3.52 (s, 3H), 3.07 (s, 3H), 2.10 (s, 3H), 2.00 (s, 3H), 1.34 (s, 9H), 1.26 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers) δ 161.7, 158.8, 151.3, 151.0, 146.0, 145.1, 131.0, 130.3, 129.2, 129.0, 128.7, 126.8, 125.6, 125.4, 122.5, 121.4, 120.4, 119.2, 118.6, 117.1, 103.1, 101.0, 41.1, 40.7, 34.7, 34.5, 31.2, 31.1, 15.18 15.1.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{21}H_{25}N_2S$: 337.1733, found: 337.1732.

2-(3,5-Dimethylphenyl)-3-(methyl(phenyl)amino)-3-(methylthio)acrylonitrile (55e)



Reaction Time: 2 +1 h

Yield: 70%, Yellow solid

Melting Point: 113 – 114 ºC

R_f: 0.34 in 10% Ethyl acetate in hexanes

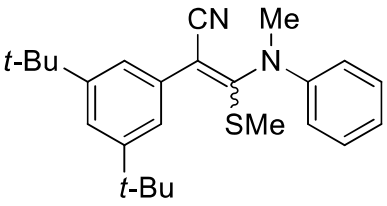
IR (KBr): ν (cm^{-1}) = 3428, 2389, 2288, 2203, 1595, 1541, 1492, 1326, 1112, 1036.

^{1}H NMR (700 MHz, $CDCl_3$) (Mixture of *E* & *Z* isomers 1:0.25) δ 7.33 (t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.7 Hz, 2H), 7.21 (s, 2H), 7.10 - 7.06 (m, 4H), 7.01 (t, *J* = 7.7 Hz, 3H), 6.98 (s, 1H), 6.92 (s, 2H), 6.82 (s, 1H), 3.53 (s, 3H), 3.09 (s, 3H), 2.36 (s, 6H), 2.21 (s, 6H), 2.13 (s, 3H), 1.99 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) (Mixture of *E* & *Z* isomers 1:0.25) δ 162.1, 159.0, 145.9, 145.2, 138.1, 138.0, 133.8, 133.0, 129.9, 129.5, 129.2, 128.9, 126.7, 124.8, 122.6, 121.4, 120.6, 119.4, 118.6, 117.0, 103.2, 100.6, 41.1, 40.6, 21.29, 21.28, 15.2, 15.1.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{19}H_{20}N_2S$: 309.1420, found: 309.1413.

2-(3,5-Di-*tert*-butylphenyl)-3-(methyl(phenyl)amino)-3-(methylthio)acrylonitrile (5f)



Reaction Time: 2 +1 h

Yield: 61%, Yellow Solid

Melting Point: 122 - 123 ºC

R_f: 0.35 in 10% Ethyl acetate in hexanes

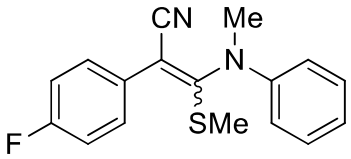
IR (KBr): ν (cm^{-1}) = 3443, 2885, 2824, 2361, 1638, 1535, 1492, 997.

^{1}H NMR (700 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers 1 : 0.16)δ 7.43 (s, 2H), 7.40 (s, 1H), 7.33 (t, *J* = 7.0 Hz, 2H), 7.26 – 7.18 (m, 3H), 7.10 (s, 2H), 7.06 (d, *J* = 7.8 Hz, 2H), 7.02 (d, *J* = 7.7 Hz, 2H), 7.00 – 6.97 (m, 1H), 6.94 (t, *J* = 7.0 Hz, 1H), 3.54 (s, 3H), 3.07 (s, 3H), 2.17 (s, 3H), 1.99 (s, 3H), 1.36 (s, 18H), 1.19 (s, 18H).

^{13}C NMR (175 MHz, $CDCl_3$) (Mixture of *E* & *Z* isomers)δ 161.7, 159.0, 151.1, 151.0, 146.0, 145.4, 133.2, 132.2, 129.3, 129.0, 123.5, 122.4, 122.2, 122.1, 121.5, 121.3, 120.5, 118.8, 118.6, 116.8, 104.9, 102.8, 40.8 (2C), 35.0, 34.8, 31.5, 31.3, 15.2, 15.1.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{25}H_{32}N_2S$: 393.2359, found: 393.2340.

2-(4-Fluorophenyl)-3-(methyl(phenyl)amino)-3-(methylthio)acrylonitrile (55g)



Reaction Time: 2 +1 h

Yield: 59%, Yellow Solid

Melting Point: 111 – 112 ºC

R_f: 0.27 in 15% Ethyl acetate in hexanes

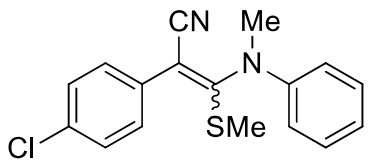
IR (KBr): ν (cm^{-1}) = 3441, 2953, 2248, 1631, 1275, 1205, 789.

^{1}H NMR (400 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers = 1 : 0.2) δ 7.61 – 7.51 (m, 2H), 7.35 - 7.31 (m, 2H), 7.31 – 7.22 (m, 4H), 7.13 – 7.03 (m, 6H), 7.02 - 7.0 (m, 2H), 6.96 – 6.88 (m, 2H), 3.54 (s, 3H), 3.09 (s, 3H), 2.13 (s, 3H), 1.99 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers) δ 162.9, 162.2 (d, *J* = 247.3 Hz), 161.9 (d, *J* = 247 Hz), 159.7, 145.9, 145.0, 131.0 (d, *J* = 8 Hz), 130.2 (d, *J* = 3 Hz), 129.5, 129.3, 129.1 (d, *J* = 3 Hz), 129.0 (d, *J* = 8 Hz), 122.8, 122.1, 120.2, 119.2, 118.5, 117.9, 115.7(d, *J* = 21 Hz), 115.6 (d, *J* = 21 Hz), 100.7, 99.6, 41.0, 40.9, 15.2, 15.1

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{17}H_{16}FN_2S$: 299.1013, found: 299.0985.

2-(4-Chlorophenyl)-3-(methyl(phenyl)amino)-3-(methylthio)acrylonitrile (55h)



Reaction Time: 2 +1 h

Yield: 50%, Yellow Solid

Melting Point: 116 – 117 ºC

R_f: 0.27 in 15% Ethyl acetate in hexanes

IR (KBr): ν (cm^{-1}) = 3874, 346, 2903, 2388, 2199, 1537, 1500, 1230, 1110, 1094, 825.

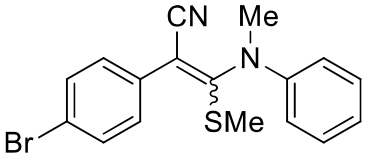
^{1}H NMR (700 MHz, $CDCl_3$) (Mixture of *E* & *Z* isomers = 1 : 0.2) δ 7.53 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.31 (m, 4H), 7.29 (t, *J* = 7.7 Hz, 2H), 7.23 - 7.18 (m, 4H), 7.1 - 7.06 (m, 4H), 7.05 - 7.01 (m, 2H), 3.56 (s, 3H), 3.10 (s, 3H), 2.13 (s, 3H), 2.00 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers) δ 163.5, 160.5, 146.0, 145.1, 133.9, 133.5, 132.7, 132.3, 130.5, 129.4, 129.2, 129.0, 128.9, 128.4, 123.1, 122.6, 120.2, 119.5, 118.8, 118.6, 99.7, 99.3, 41.5, 41.3, 15.6, 15.4.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{17}H_{16}ClN_2S$: 315.0717, found: 315.0712.

2-(4-Bromophenyl)-3-(methyl(phenyl)amino)-3-(methylthio)acrylonitrile (55i)

Reaction Time: 2 +1 h



Yield: 55%, Yellow Solid

Melting Point: 135 – 136 ºC

R_f: 0.34 in 10% Ethyl acetate in hexanes

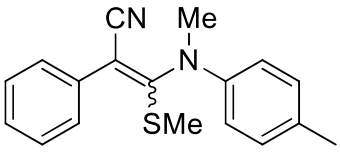
IR (KBr): ν (cm^{-1}) = 3770, 3426, 3062, 2388, 2200, 198, 1234, 1319, 1110, 824.

^1H NMR (700 MHz, $CDCl_3$) (Mixture of *E* & *Z* isomers 1:0.18) δ 7.53 – 7.50 (m, 2H), 7.49 – 7.45 (m, 2H), 7.37 – 7.34 (m, 2H), 7.34 – 7.32 (m, H), 7.31 – 7.27 (m, 2H), 7.19 – 7.14 (m, 2H), 7.10 -7.06 (m, 4H), 7.05 (d, *J* = 7.0 Hz, 1H), 7.03 (t, *J* = 7.7 Hz, 1H), 3.56 (s, 3H), 3.10 (s, 3H), 2.13 (s, 3H), 2.00 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers) δ 163.6, 160.5, 146.0, 145.0, 133.2, 132.8, 131.9, 131.8, 130.7, 129.4, 129.2, 128.7, 123.1, 122.7, 122.0, 121.6, 120.1, 119.5, 118.8, 118.5, 99.4, 99.1, 41.5, 41.3, 15.6, 15.3.

HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. For $C_{17}H_{16}BrN_2SNa$: 381.0032 & 383.0011, found: 381.0009 & 382.9988.

3-(Methyl(p-tolyl)amino)-3-(methylthio)-2-phenylacrylonitrile (55j)



Reaction Time: 2 +1 h

Yield: 42%, Yellow Solid

Melting Point: 119 – 120 ºC

R_f: 0.37 in 15% Ethyl acetate in hexanes

IR (KBr): ν (cm^{-1}) = 3855, 3537, 2926, 2388, 2296, 2204, 1544, 1510, 1331, 1315, 1229, 1111, 1026.

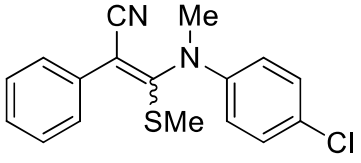
^{1}H NMR (400 MHz, $CDCl_3$) (Mixture of *E* & *Z* isomers in the ratio of 1 : 0.15) δ 7.59 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.35 - 7.30 (m, 3H), 7.29 - 7.23 (m, 2H), 7.21 - 7.15 (m, 2H), 7.15 - 7.10 (m, 3H), 7.06 – 6.99 (m, 4H), 3.57 (s, 3H), 3.04 (s, 3H), 2.32 (s, 6H), 2.11 (s, 3H), 1.98 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) (Mixture of *E* & *Z* isomers) δ 163.34, 159.88, 143.84, 142.85, 134.40, 134.04, 132.87, 132.26, 129.87, 129.69, 129.14, 128.79, 128.58, 127.85, 127.74, 127.16, 120.81, 120.07, 119.27, 119.14, 99.45, 99.31, 41.88, 41.77, 20.78, 20.76, 15.74, 15.48.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{18}H_{19}N_2S$: 295.1263, found: 295.1294.

3-((4-Chlorophenyl)(methyl)amino)-3-(methylthio)-2-phenylacrylonitrile (55k)

Reaction Time: 2 +1 h



Yield: 46%, Yellow Solid

Melting Point: 145 – 147 ºC

R_f: 0.29in 15% Ethyl acetate in hexanes

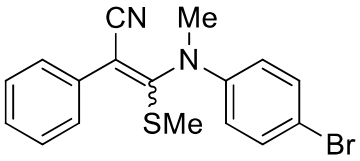
IR (KBr): ν (cm^{-1}) = 3443, 3029, 2388, 2203, 1546, 1491, 1334, 1225, 1111, 822

^{1}H NMR (700 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers = 1:0.2) δ 7.62 – 7.58 (m, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.39 – 7.34 (m, 2H), 7.32 - 7.28 (m, 4H), 7.28 – 7.24 (m, 3H), 7.23 - 7.20 (m, 1H), 7.04 - 7.00 (m, 4H), 3.53 (s, 3H), 3.07 (s, 3H), 2.15 (s, 3H), 2.02 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers)δ 162.1, 159.1, 144.6, 143.7, 133.8, 133.0, 129.5, 129.3, 129.1, 128.9, 128.7, 128.4, 128.2, 127.7, 127.1, 126.7, 120.0, 120.0, 118.3, 118.3, 103.6, 102.0, 41.1, 40.8, 15.2, 15.1.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{17}H_{15}ClN_2S$: 315.0717, found: 315.0702.

3-((4-Bromophenyl)(methyl)amino)-3-(methylthio)-2-phenylacrylonitrile (55l)



Reaction Time: 2 +1 h

Yield: 60%, Yellow solid

Melting Point: 157 – 158 ºC

R_f: 0.38 in 15% Ethyl acetate in hexanes

IR (KBr): ν (cm^{-1}) = 3062, 2388, 2202, 1545, 1488, 1330, 1223, 1109, 825.

^{1}H NMR (700 MHz, $CDCl_3$) (Mixture of *E* & *Z* Isomers 1 : 0.23) δ 7.61 – 7.58 (m, 2H), 7.46 – 7.42 (m, 1H), 7.42 – 7.38 (m, 2H), 7.38 – 7.34 (m, 1H), 7.31 – 7.25 (m, 7H), 7.24 – 7.20 (m, 1H), 6.98 – 6.92 (m, 4H), 3.52 (s, 3H), 3.06 (s, 3H), 2.15 (s, 3H), 2.02 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 162.0, 159.0, 145.1, 144.3, 133.8, 133.0, 132.3, 132.1, 129.1, 129.0, 128.7, 128.6, 128.3, 127.2, 120.3, 120.0, 118.6, 118.3, 115.2, 114.2, 104.1, 102.5, 41.0, 40.7, 15.2, 15.1.

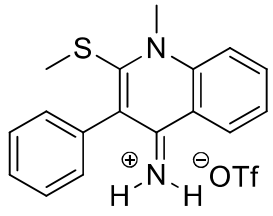
HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{17}H_{15}BrN_2S$: 359.0212 & 361.0192, found: 359.0187 & 361.0166.

4.5.11 General Procedure for the Synthesis of Iminoquinoline

Procedure is same as 4.5.5

1-Methyl-2-(methylthio)-3-phenylquinolin-4(1*H*)-iminium trillate (56a)

Reaction Time: 3 h



Yield: 63%, Brick red Solid

Melting Point:

R_f: 0.3 in 5% MeOH in DCM

IR (KBr): ν (cm^{-1}) = 3526, 3010, 2899, 2987, 1768, 1447, 1327, 1147, 965.

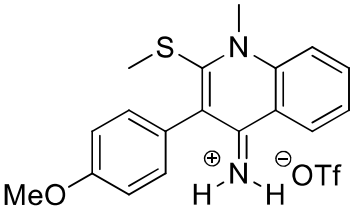
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.53 (d, *J* = 8.4 Hz, 1H), 8.06 – 7.85 (m, 2H), 7.66 – 7.60 (m, 1H), 7.59 – 7.50 (m, 3H), 7.27 (d, *J* = 6.8 Hz, 2H), 5.69 (s, 1H), 4.48 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 155.5, 141.0, 135.4, 132.8, 130.3, 130.2, 129.9, 127.7, 125.7, 121.6, 121.0 (q, J = 318 Hz), 118.6, 116.8, 40.5, 19.6.

HRMS (ESI-TOF) m/z: $[M]^+$ Calcd. For $C_{17}H_{16}N_2S$: 281.1107, found: 281.1109.

3-(4-Methoxyphenyl)-1-methyl-2-(methylthio)quinolin-4(1*H*)-iminium triflate (56b)

Reaction Time: 3 h



Yield: 88%, Brick red solid

Melting Point: 146 – 147 °C

R_f: 0.3 in 5% MeOH in DCM

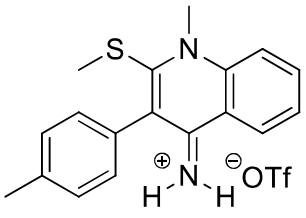
IR (KBr): ν (cm^{-1}) = 3376, 3331, 3227, 2387, 2265, 1650, 1515, 1277, 1255, 1157, 1031.

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.48 (d, *J* = 7.0 Hz, 1H), 7.99 (d, *J* = 7.0 Hz, 1H), 7.93 (s, 1H), 7.61 (s, 1H), 7.18 (d, *J* = 6.3 Hz, 2H), 7.06 (d, *J* = 6.3 Hz, 2H), 5.77 (s, 1H), 4.47 (s, 3H), 3.87 (s, 3H), 2.28 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 160.5, 156.0, 155.8, 140.9, 135.3, 131.5, 127.5, 125.5, 124.5, 121.1, 120. 6 (q, *J* = 318.15 Hz), 118.6, 116.6, 115.6, 55.5, 40.5, 19.5.

HRMS (ESI-TOF) m/z: $[M]^+$ Calcd. For $C_{18}H_{20}N_2OS$: 311.1213, found: 311.1210.

1-Methyl-2-(methylthio)-3-(p-tolyl)quinolin-4(1*H*)-iminium triflate (56c)



Reaction Time: 3 h

Yield: 70%, Pale Brick Red Solid

Melting Point: 144 – 145 °C

R_f: 0.29 in 5% MeOH in DCM

IR (KBr): ν (cm^{-1}) = 3885, 3328, 3217, 2387, 2041, 1652, 1516, 1274, 1253, 1165, 1153, 1027.

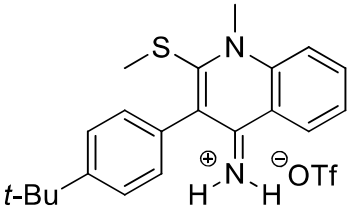
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.50 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.94 (t, *J* = 7.1 Hz, 1H), 7.62 (t, *J* = 7.3 Hz, 1H), 7.37 (d, *J* = 7.4 Hz, 2H), 7.15 (d, *J* = 7.6 Hz, 2H), 5.72 (s, 1H), 4.49 (s, 3H), 2.45 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 155.73, 155.60, 140.93, 140.08, 135.37, 131.00, 130.00, 129.74, 127.61, 125.60, 121.52, 120.61 (q, *J* = 316.75 Hz) 118.68, 116.70, 77.34, 77.16, 76.98, 40.63, 21.48, 19.68.

HRMS (ESI-TOF) m/z: $[M]^+$ Calcd. For $C_{18}H_{19}N_2S$: 295.1263, found: 295.1276.

3-(4-(*tert*-Butyl)phenyl)-1-methyl-2-(methylthio)quinolin-4(1H)-iminium triflate (56d)

Reaction Time: 3 h



Yield: 53%, Pale brick red Solid

Melting Point: 217 – 218 ºC

R_f: 0.29 in 5% MeOH in DCM

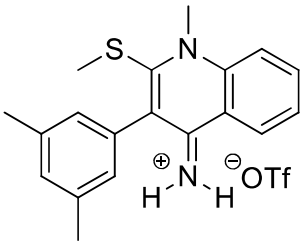
IR (KBr): ν (cm^{-1}) = 3441, 2359, 2060, 1633, 1015, 915

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.56 (d, *J* = 8.3 Hz, 1H), 8.03 – 7.87 (m, 2H), 7.64 (t, *J* = 6.8 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 5.80 (s, 1H), 4.49 (s, 3H), 2.29 (s, 3H), 1.40 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.74, 155.65, 153.03, 140.89, 135.28, 129.76, 129.64, 127.50, 127.17, 125.47, 121.36, 120.62 (q, *J* = 318 Hz), 118.67, 116.63, 40.50, 34.92, 31.28, 19.55.

HRMS (ESI-TOF) m/z: $[M]^+$ Calcd. For $C_{21}H_{25}N_2S$: 337.1733, found: 337.1733.

3-(3,5-Dimethylphenyl)-1-methyl-2-(methylthio)quinolin-4(1*H*)-iminium Triflate (56e)



Reaction Time: 3 h

Yield: 92%, Brick red solid

Melting Point: 209 – 210 °C

R_f: 0.29in 5% MeOH in DCM

IR (KBr): ν (cm^{-1}) = 3454, 3333, 3218, 2390, 2351, 2284, 1643, 1512, 1278, 1252, 1161, 1149, 1029.

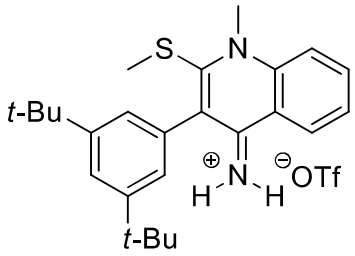
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.50 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 9.1 Hz, 1H), 7.94 (t, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.14 (s, 1H), 6.84 (s, 2H), 5.73 (s, 1H), 4.47 (s, 3H), 2.36 (s, 6H), 2.31 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 155.5, 155.3, 140.8, 140.0, 135.2, 132.5, 131.4, 127.4(2C), 125.4, 121.7, 120.5 (q, *J* = 318.5 Hz) 118.6, 116.5, 40.4, 21.3, 19.6.

HRMS (ESI-TOF) m/z: [M]$^+$ Calcd. For $C_{19}H_{21}N_2S$: 309.1420, found: 309.1423.

3-(3,5-di-*tert*-butylphenyl)-1-methyl-2-(methylthio)quinolin-4(1*H*)-iminium triflate (56f)

Reaction Time: 4 h



Yield: 63%, Colourless Solid

Melting Point: 224 – 225 °C

R_f: 0.28 in 5% MeOH in DCM

IR (KBr): ν (cm^{-1}) = 3453, 3332, 3223, 2962, 2388, 2266, 1650, 1513, 1287, 1251, 1147, 1033.

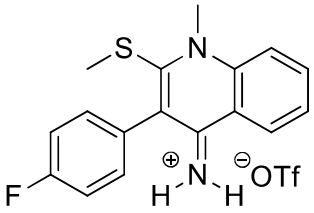
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.57 (d, *J* = 8.2 Hz, 1H), 8.00 (d, *J* = 8.7 Hz, 1H), 7.96 (t, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 1.7 Hz, 1H), 7.09 (d, *J* = 1.7 Hz, 2H), 5.84 (s, 1H), 4.49 (s, 3H), 2.25 (s, 3H), 1.34 (s, 18H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 155.7, 155.5, 153.1, 140.9, 135.3, 132.0, 127.6, 125.8, 124.1, 123.6, 122.5, 120.6 (q, J = 318 Hz), 118.4, 116.7, 40.3, 35.1, 31.4, 19.5.

HRMS (ESI-TOF) m/z: [M] Calcd. For $C_{25}H_{33}N_2S$: 393.2359, found: 393.2340.

3-(4-Fluorophenyl)-1-methyl-2-(methylthio)quinolin-4(1*H*)-iminium triflate (56g)

Reaction Time: 3 h



Yield: 64%, Colourless Solid

Melting Point: 181 – 183 ºC

R_f: 0.3 in 5% MeOH in DCM

IR (KBr): ν (cm^{-1}) = 3894, 3810, 3586, 3238, 2427, 1656, 1588, 1282, 129, 1032, 756.

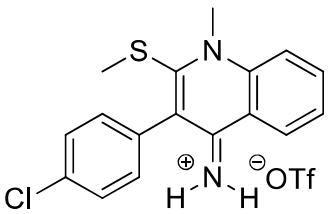
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.48 (d, *J* = 8.2 Hz, 1H), 7.97 (q, *J* = 8.8 Hz, 2H), 7.63 (t, *J* = 7.1 Hz, 1H), 7.35 – 7.22 (m, 4H), 5.68 (s, 1H), 4.49 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 163.42 (d, *J* = 251.2 Hz), 155.84, 155.83, 141.05, 135.56, 132.45 (d, *J* = 8.3 Hz), 128.87 (d, *J* = 3.6 Hz), 127.85, 125.75, 123.35, 121.53, 120.66, 120.19 (q, *J* = 316.75 Hz) 118.65, 117.90, 117.59 (d, *J* = 21.9 Hz), 116.87, 77.34, 77.16, 76.98, 40.66, 19.63.

HRMS (ESI-TOF) m/z: [M] Calcd. For $C_{17}H_{16}FN_2S$: 299.1013, found: 299.1045.

3-(4-Chlorophenyl)-1-methyl-2-(methylthio)quinolin-4(1*H*)-iminium triflate (6h)

Reaction Time: 3 h



Yield: 81%, Pale Brick Red Solid

Melting Point: 198 – 199 ºC

R_f: 0.3 in 5% MeOH in DCM

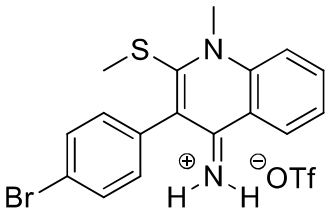
IR (KBr): ν (cm^{-1}) = 3873, 3384, 3334, 3225, 2388, 2282, 1655, 1515, 1275, 1258, 1154, 1031.

^{1}H NMR (700 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.63 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 9.1 Hz, 1H), 8.09 (t, *J* = 7.7 Hz, 1H), 7.79 (t, *J* = 7.7 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.49 (s, 1H), 7.39 (d, *J* = 8.4 Hz), 4.41 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (175 MHz, DMSO-D_6) δ 155.2, 155.1, 140.7, 134.6, 133.8, 133.2, 132.4, 129.6, 126.7, 124.5, 120.6 (q, J = 320 Hz), 120.1, 119.6, 116.6, 40.5, 18.8.

HRMS (ESI-TOF) m/z: $[M]^+$ Calcd. For $C_{17}H_{16}ClN_2S$: 315.0717, found: 315.0713.

3-(4-Bromophenyl)-1-methyl-2-(methylthio)quinolin-4(1*H*)-iminium triflate (56i)



Reaction Time: 3 h

Yield: 88%, Brick red solid

Melting Point: 193 – 194 °C

R_f: 0.3 in 5% MeOH in DCM

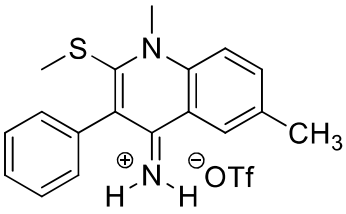
IR (KBr): ν (cm^{-1}) = 3384, 3333, 3224, 2390, 2284, 1656, 187, 1275, 1256, 1031, 763.

^{1}H NMR (700 MHz, DMSO-D_6) δ 9.13 (s, 1H), 8.63 (d, *J* = 7.7 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 8.12 - 8.06(m, 1H), 7.85 - 7.75 (m, 3H), 7.50 (s, 1H), 7.33 (d, *J* = 7.0 Hz, 2H), 4.41 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (175 MHz, DMSO-D_6) δ 155.1, 155.1, 140.7, 134.6, 133.6, 132.7, 132.5, 126.7, 124.5, 122.6, 120.6 (q, J = 320 Hz), 0120.1, 119.6, 116.6, 40.50, 39.1.

HRMS (ESI-TOF) m/z: $[M]^+$ Calcd. For $C_{17}H_{16}BrN_2S$: 359.0212 & 361.0192, found: 359.0197 & 361.0178.

1,6-Dimethyl-2-(methylthio)-3-phenylquinolin-4(1*H*)-iminium triflate (56j)



Reaction Time: 2 h

Yield: 73%, Yellow Solid

Melting Point: 120 – 121 °C

R_f: 0.3 in 5% MeOH in DCM

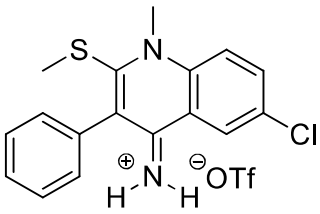
IR (KBr): ν (cm^{-1}) = 3438, 2960, 2360, 1639, 1518, 1257, 1031.

^1H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.44 – 8.30 (m, 1H), 7.93 – 7.72 (m, 2H), 7.66 – 7.49 (m, 3H), 7.36 – 7.18 (m, 2H), 5.69 (s, 1H), 4.48 (s, 3H), 2.54 (s, 3H), 2.28 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.17, 154.40, 139.23, 138.78, 137.32, 133.01, 130.25, 130.23, 129.83, 124.59, 121.42, 120.6 (q, J = 360 Hz), 118.51, 116.81, 40.59, 20.98, 19.72.

HRMS (ESI-TOF) m/z: $[M]^+$ Calcd. For $C_{18}H_{19}N_2S$: 295.1263, found: 295.1267.

6-Chloro-1-methyl-2-(methylthio)-3-phenylquinolin-4(1*H*)-iminium triflate (56k)



Reaction Time: 2 h

Yield: 14%. White solid

Melting Point: 210 – 212 °C

R_f: 0.3 in 5% MeOH in DCM

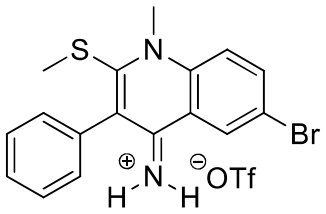
IR (KBr): ν (cm^{-1}) = 3564, 3490, 3304, 2046, 1638, 1514, 1329, 1260, 1178, 1115, 1034, 696.

^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.21 (d, *J* = 1.2 Hz, 1H), 8.05 (d, *J* = 9.2 Hz, 1H), 7.75 (d, *J* = 9.2 Hz, 1H), 7.68 – 7.50 (m, 3H), 7.30 (d, *J* = 6.8 Hz, 2H), 5.77 (s, 1H), 4.52 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 154.2, 139.4, 135.2, 133.3, 132.5, 130.2, 129.9, 129.9, 123.7, 121.8, 121.1, 120.3 (q, J = 318 Hz) 117.5, 40.8, 19.4.

HRMS (ESI-TOF) m/z: $[M]^+$ Calcd. For $C_{17}H_{16}ClN_2S$: 315.0717, found: 315.0698.

6-Bromo-1-methyl-2-(methylthio)-3-phenylquinolin-4(1*H*)-iminium triflate (6l)



Reaction Time: 3 h

Yield: 13%, White Solid

Melting Point: 190 – 191 ºC

R_f: 0.3 in 5% MeOH in DCM

IR (KBr): ν (cm^{-1}) = 3404, 2923, 2852, 2512, 1653, 1510, 1327, 1258, 1158, 1031, 698.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.54 (s, 1H), 8.02 - 7.78 (m, 2H), 7.65 - 7.45 (m, 3H), 7.40 – 7.07 (m, 2H), 5.71 (s, 1H), 4.47 (s, 3H), 2.27 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$) δ 156.2, 154.4, 139.9, 137.9, 132.6, 130.4, 130.1, 130.0, 127.5, 122.0, 121.1, 120. (q, *J* = 318.5 Hz), 118.0 (2C), 40.9, 19.5.

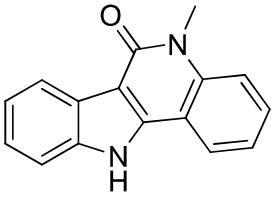
HRMS (ESI-TOF) m/z: $[M]^+$ Calcd. For $C_{17}H_{16}BrN_2S$: 359.0212 & 361.0192, found: 359.0234 & 361.0216.

4.5.12 General procedure for the Synthesis of Indoloquinolones

To an oven-dried 8 mL reaction vial was charged with $PhI(OAc)_2$, K_3PO_4, respective iminoquinoline in DMSO, was stirred at 120 ºC till completion of the reaction. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, solvent was evaporated and the reaction mixture was purified by flash chromatography.

5-methyl-5*H*-indolo[3,2-*c*]quinolin-6(11*H*)-one (9a)

Reaction Time: 2 h



Yield: 49%, Colourless Solid

Melting Point: >295 ºC

R_f: 0.35 in 40% EtOAc in hexanes

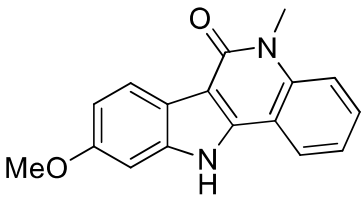
IR (KBr): ν (cm^{-1}) = 3437, 2937, 2360, 1720, 1632, 930

^{1}H NMR (400 MHz, DMSO-D_6) δ 12.61 (s, 1H), 8.55 – 8.14 (m, 2H), 7.87 – 7.50 (m, 3H), 7.44 - 7.34 (m, 2H), 7.33 – 7.16 (m, 1H), 3.74 (s, 3H).

^{13}C NMR (100 MHz, DMSO-D_6) δ 159.03, 139.63, 138.66, 137.77, 129.59, 124.60, 124.11, 122.62, 121.65, 121.06, 120.81, 115.66, 112.92, 111.67, 105.86, 28.48.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{16}H_{12}N_2O$: 249.1022, found: 249.1016.

9-Methoxy-5-methyl-5*H*-indolo[3,2-*c*]quinolin-6(11*H*)-one (9b)



Reaction Time: 2 h

Yield: 44%, Pale Yellow

Melting Point: >295 ºC

R_f: 0.35 in 50% EtOAc in hexanes

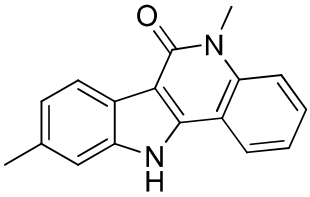
IR (KBr): ν (cm^{-1}) = 3539, 2878, 2808, 2361, 2340, 1839, 1753, 1667, 12475, 1260, 764.

^{1}H NMR (700 MHz, DMSO-D_6) δ 12.48 (s, 1H), 8.22 (d, *J* = 7.7 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.64 -7.58 (m, 2H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.09 (s, 1H), 6.91 (d, *J* = 9.0 Hz, 1H), 3.85 (s, 3H), 3.73 (s, 3H).

^{13}C NMR (175 MHz, DMSO-D_6) δ 159.1, 157.6, 139.1, 139.1, 138.2, 129.2, 122.3, 121.8, 121.6, 118.5, 115.8, 113.1, 110.7, 106.1, 95.2, 55.4, 28.6.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{17}H_{14}N_2O_2$: 279.1128, found: 279.1131.

5,9-Dimethyl-5*H*-indolo[3,2-*c*]quinolin-6(11*H*)-one (9c)



Reaction Time: 2 h

Yield: 40%, Colourless Solid

Melting Point: >295 ºC

R_f: 0.35 in 40% EtOAc in hexanes

IR (KBr): ν (cm^{-1}) = 3440, 2850, 2460, 2060, 1632, 1357, 1078.

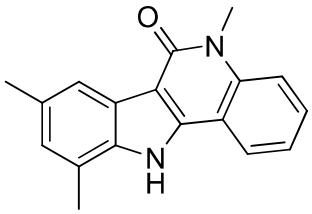
^1H NMR (400 MHz, DMSO-D_6) δ 12.45 (s, 1H), 8.28 (d, *J* = 7.2 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.73 – 7.53 (m, 2H), 7.50 – 7.29 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 1H), 3.74 (s, 3H), 2.50 (s, 3H).

^{13}C NMR (100 MHz, DMSO-D_6) δ 159.0, 139.2, 138.5, 138.2, 133.6, 129.3, 122.7, 122.4, 122.3, 121.6, 120.5, 115.6, 113.0, 111.5, 105.9, 28.5, 21.5.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{17}H_{16}N_2O$: 265.1355, found: 265.1345.

5,8,10-Trimethyl-5*H*-indolo[3,2-*c*]quinolin-6(11*H*)-one (9e)

Reaction Time: 3 h



Yield: 47%, Pale Yellow solid

Melting Point: >295 ºC

R_f: 0.35 in 40% EtOAc in hexanes

IR (KBr): ν (cm^{-1}) = 3450, 2921, 2359, 2340, 1658, 1640, 1612, 1640, 1551, 1316.

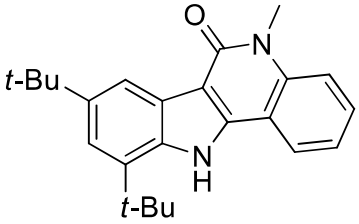
^1H NMR (400 MHz, DMSO-D_6) δ 12.00 (s, 1H), 8.49 (d, *J* = 7.6 Hz, 1H), 7.88 (s, 1H), 7.66 – 7.57 (m, 2H), 7.43 – 7.34 (m, 1H), 6.99 (s, 1H), 3.73 (s, 3H), 2.59 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (100 MHz, DMSO-D$_6$) δ 159.2, 139.5, 138.5, 135.5, 130.1, 129.4, 126.5, 124.6, 123.0, 121.5, 120.8, 118.1, 115.6, 113.2, 106.0, 28.5, 21.2, 17.1.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{18}H_{16}N_2O$: 277.1335, found: 277.1319.

8,10-Di-*tert*-butyl-5-methyl-5*H*-indolo[3,2-*c*]quinolin-6(11*H*)-one (9f)

Reaction Time: 5 h



Yield: 51%, Colourless Solid

Melting Point: >295 ºC

R_f: 0.35 in 33% EtOAc in hexanes

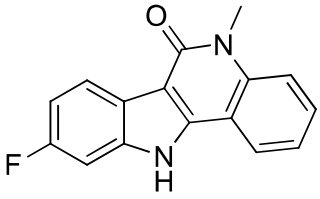
IR (KBr): ν (cm^{-1}) = 3438, 2951, 2103, 1709, 1657, 1614, 1571, 1476, 1243, 748.

^{1}H NMR (400 MHz, DMSO-D$_6$) δ 11.16 (s, 1H), 8.94 (d, *J* = 7.6 Hz, 1H), 8.27 (s, 1H), 7.61 (s, 2H), 7.38 - 7.33 (m, 2H), 3.75 (s, 3H), 1.57 (s, 9H), 1.39 (s, 9H).

^{13}C NMR (100 MHz, DMSO-D$_6$) δ 159.5, 143.7, 139.8, 138.8, 134.0, 133.5, 129.7, 126.1, 124.3, 121.6, 119.1, 115.8, 115.4, 113.5, 106.7, 34.9 (2C), 32.2, 30.4, 28.9.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{24}H_{29}N_2O$: 361.2274, found: 361.2281.

9-Fluoro-5-methyl-5*H*-indolo[3,2-*c*]quinolin-6(11*H*)-one (9g)



Reaction Time: 3 h

Yield: 49%, Colourless Solid

Melting Point: >295 ºC

R_f: 0.36 in 40% EtOAc in hexanes

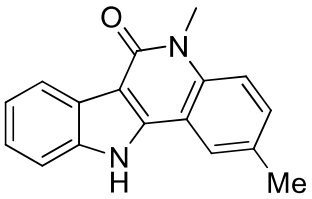
IR (KBr): ν (cm^{-1}) = 3853, 3444, 2360, 1733, 1648, 1558, 1506, 715

^{1}H NMR (400 MHz, DMSO-D$_6$) δ 12.68 (s, 1H), 8.26 (d, *J* = 7.5 Hz, 1H), 8.24 – 8.14 (m, 1H), 7.64 (s, 2H), 7.39 (d, *J* = 8.9 Hz, 2H), 7.13 (t, *J* = 9.1 Hz, 1H), 3.74 (s, 3H).

^{13}C NMR (100 MHz, DMSO-D$_6$) δ 160.1 (d, *J* = 238.2 Hz), 158.8, 140.3 (d, *J* = 2.3 Hz), 138.5, 138.0 (d, *J* = 12.8 Hz), 129.6, 122.5, 121.8 (d, *J* = 10.2 Hz), 121.7, 121.2, 115.7, 112.7, 109.3 (d, *J* = 24.1 Hz), 105.76, 98.1 (d, *J* = 26.1 Hz), 28.5

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{16}H_{11}N_2OF$: 267.0928, found: 267.0908.

2,5-dimethyl-5*H*-indolo[3,2-*c*]quinolin-6(11*H*)-one (9j)



Reaction Time: 4 h

Yield: 40%, Pale Yellow solid

Melting Point: >295 ºC

R_f: 0.35 in 40% EtOAc in hexanes

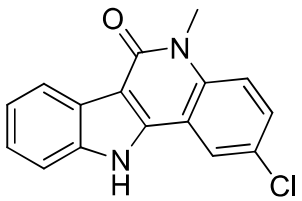
IR (KBr): ν (cm^{-1}) = 3451, 2885, 2103, 1706, 1675, 1613, 1630, 1545, 748

^{1}H NMR (400 MHz, DMSO-D$_6$) δ 12.50 (s, 1H), 8.23 (d, *J* = 7.6 Hz, 1H), 8.10 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.26 (t, *J* = 7.2 Hz, 1H), 3.72 (s, 3H), 2.46 (s, 3H).

^{13}C NMR (101 MHz, DMSO-D$_6$) δ 158.94, 139.51, 137.75, 136.77, 130.67, 130.65, 124.63, 124.03, 122.36, 121.00, 120.77, 115.62, 112.78, 111.63, 105.90, 28.45, 20.41.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{17}H_{14}N_2O$: 263.1179, found: 263.1167.

2-Chloro-5-methyl-5*H*-indolo[3,2-*c*]quinolin-6(11*H*)-one (9k)



Reaction Time: 4 h

Yield: 34%, Pale Yellow Solid

Melting Point: >295 ºC

R_f: 0.35 in 40% EtOAc in hexanes

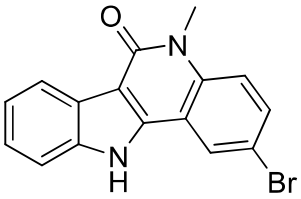
IR (KBr): ν (cm^{-1}) = 3428, 2853, 1657, 1631, 1551, 1275, 749

^{1}H NMR (400 MHz, DMSO-D_6) δ 12.73 (s, 1H), 8.25 (d, *J* = 7.6 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.70 – 7.59 (m, 3H), 7.42 - 7.37 (m, 1H), 7.29 (dd, *J* = 8.4, 1.8 Hz, 1H), 3.73 (s, 3H).

^{13}C NMR (100 MHz, DMSO-D_6) δ 158.7, 140.4, 138.7, 138.3, 129.9, 128.5, 123.3, 122.6, 121.9, 121.8, 121.4, 115.8, 112.6, 111.3, 105.7, 28.5.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{16}H_{11}ClN_2O$: 283.0633, found: 283.0624.

2-Bromo-5-methyl-5*H*-indolo[3,2-*c*]quinolin-6(11*H*)-one (9l)



Reaction Time: 3 h

Yield: 32%, Yellow Solid

Melting Point: >295 ºC

R_f: 0.35 in 40% EtOAc in hexanes

IR (KBr): ν (cm^{-1}) = 3439, 2931, 2356, 1631, 1031, 749.

^{1}H NMR (400 MHz, DMSO-D_6) δ 12.65 (s, 1H), 8.54 (s, 1H), 8.23 (d, *J* = 7.2 Hz, 1H), 7.76 (d, *J* = 8.0 Hz 1H), 7.67 – 7.54 (m, 2H), 7.46 – 7.35 (m, 1H), 7.32 – 7.25 (m, 1H), 3.73 (s, 3H).

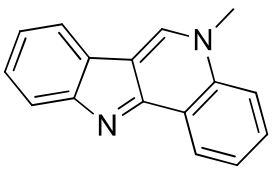
^{13}C NMR (100 MHz, DMSO-D_6) δ 158.79, 138.24, 137.80, 137.71, 131.79, 124.81, 124.55, 124.34, 121.31, 120.91, 118.06, 114.71, 113.77, 111.84, 106.50, 28.67.

HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd. For $C_{16}H_{11}BrN_2O$: 327.0128 & 329.0108, found: 327.0110 & 329.0183.

4.5.13 General Procedure for the Synthesis of Isocryptolepine (10)

To an oven dried and argon filled two neck RB, **9a** was added which was dissolved in toluene. To this reaction mixture Red al in Toluene solution was added at 0 ºC. Then the reaction was refluxed for 36 h. after completion of the reaction, the reaction mixture was then quenched with saturated NH_4Cl. To the resulting mixture water was added and extracted with EtOAc. The combined extracts were washed with brine, dried over anhydrous sodium sulphate, filtered and filtrate was concentrated, the residue was puridied b using 20% MeOH in DCM as eluent to get pure compound.

5-Methyl-5H-indolo[3,2-*c*]quinoline



Reaction Time: 36 h

Yield: 57%, Green solid

IR, M.P, HRMS, 1H and 13C were reported in earlier part of this chapter

4.6 Copies of ^{1}H and ^{13}C Spectrum of Selected Compounds

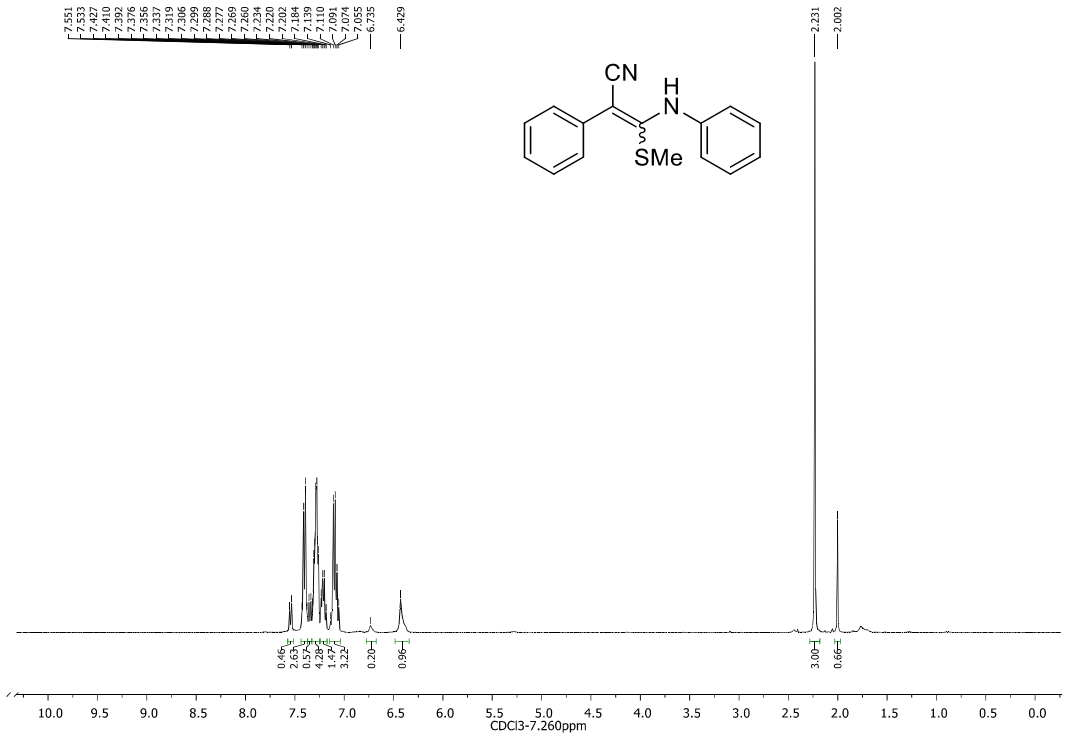


Figure 4.3a: ^{1}H NMR spectrum of **39a**

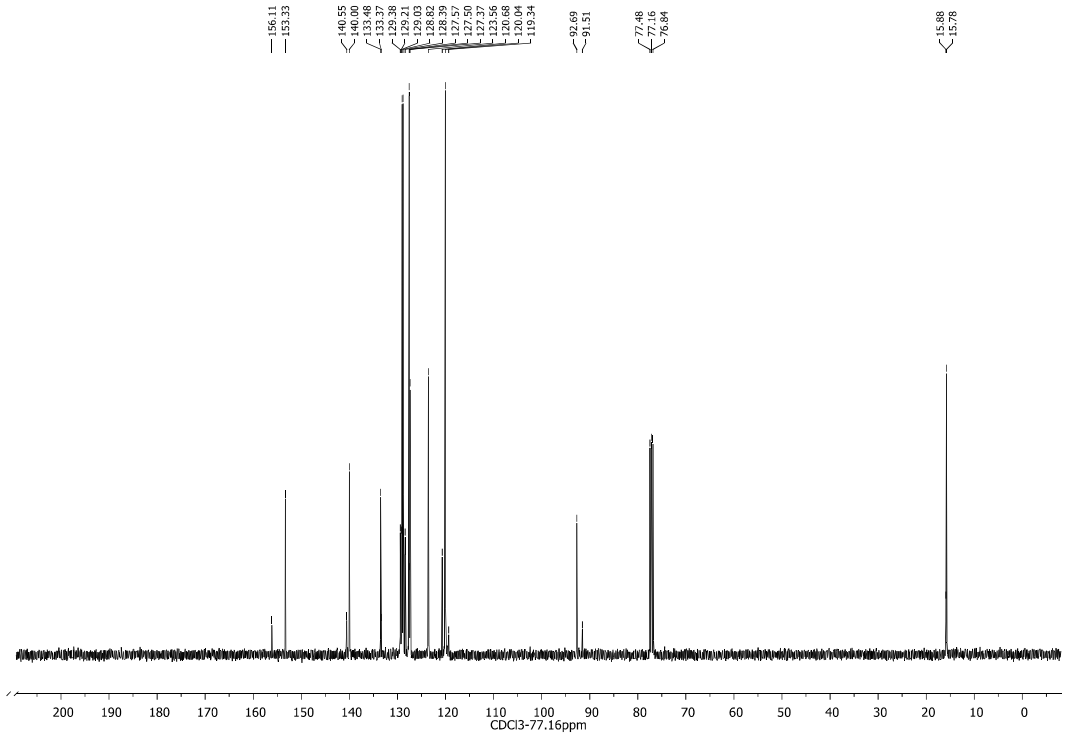


Figure 4.3b: ^{13}C NMR spectrum of **39a**

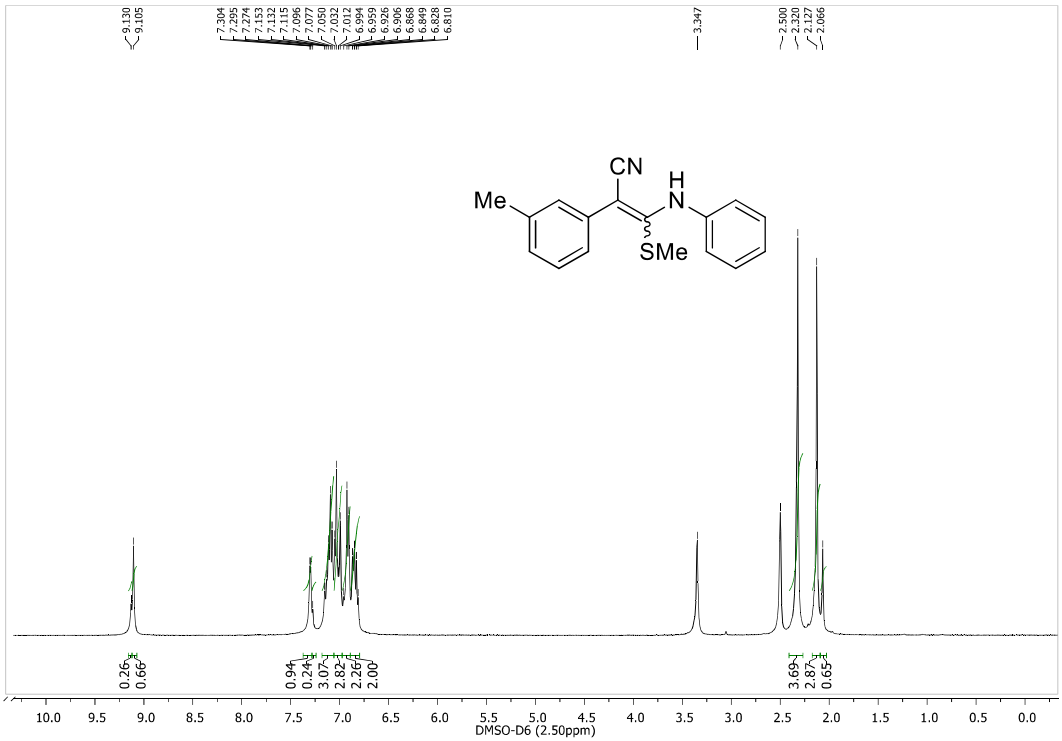


Figure 4.4a: ^{1}H NMR spectrum of **39f**

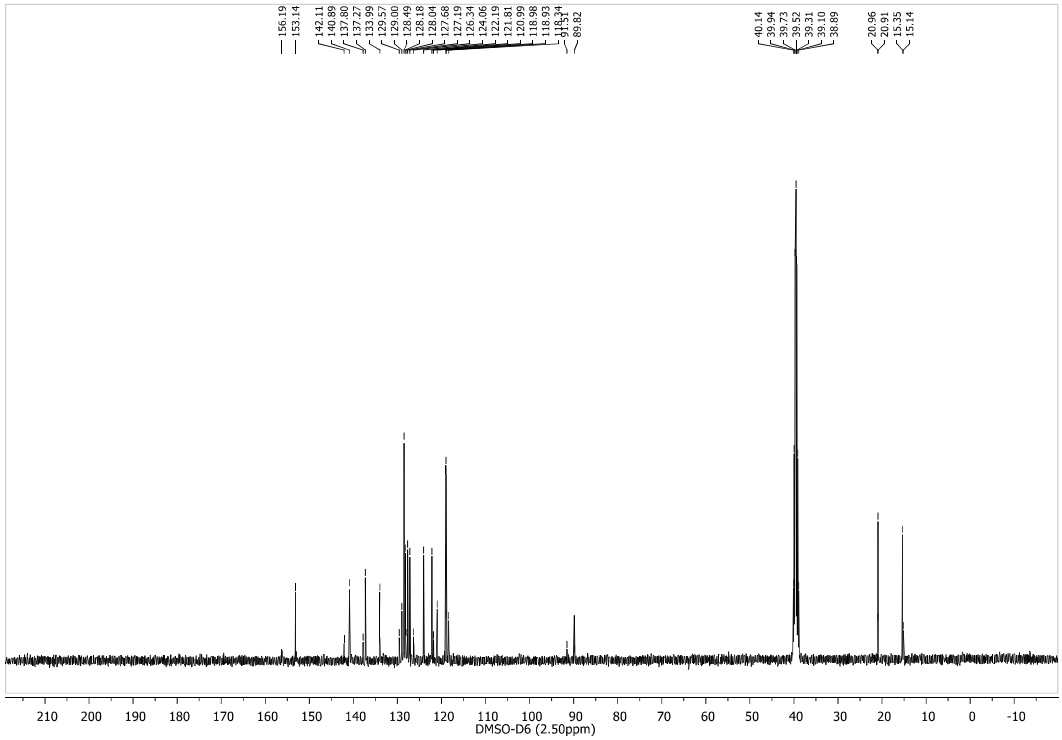


Figure 4.4b: ^{13}C NMR spectrum of **39f**

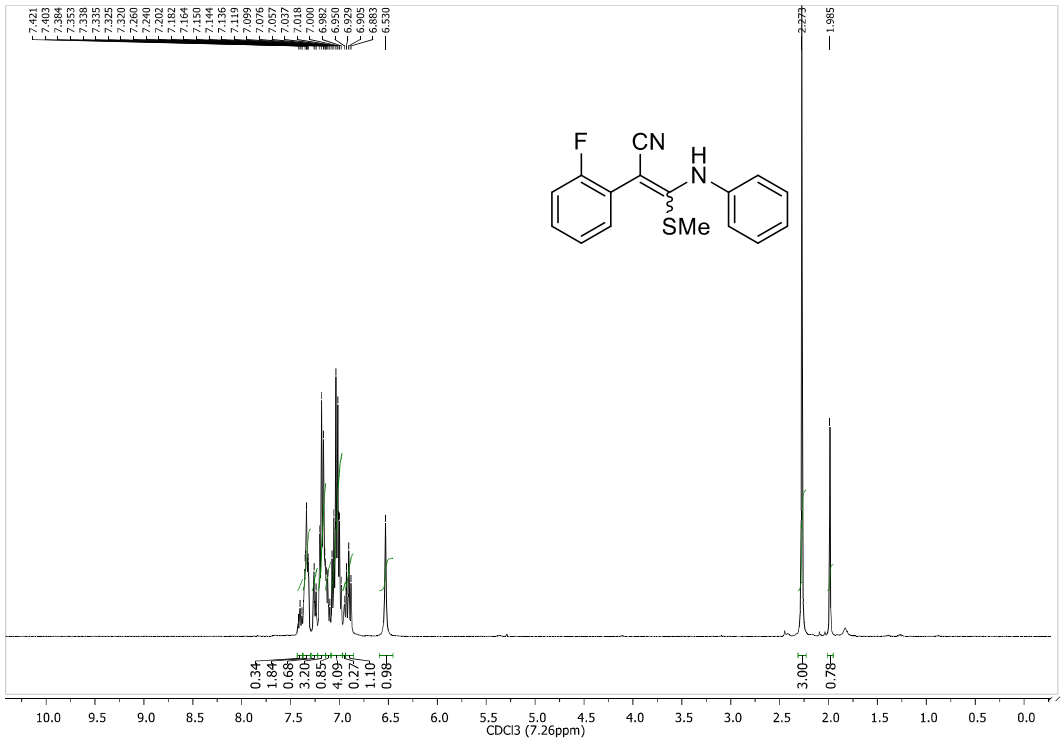


Figure 4.5a: ^{1}H NMR spectrum of **39l**

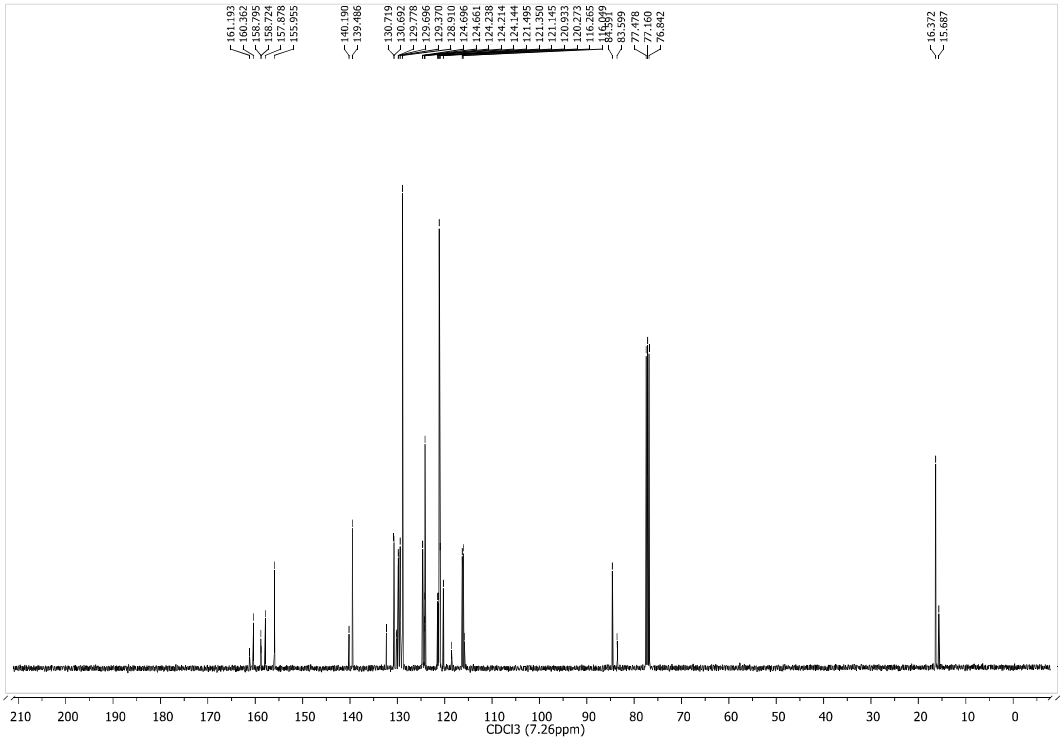


Figure 4.5b: ^{13}CNMR spectrum of **39l**

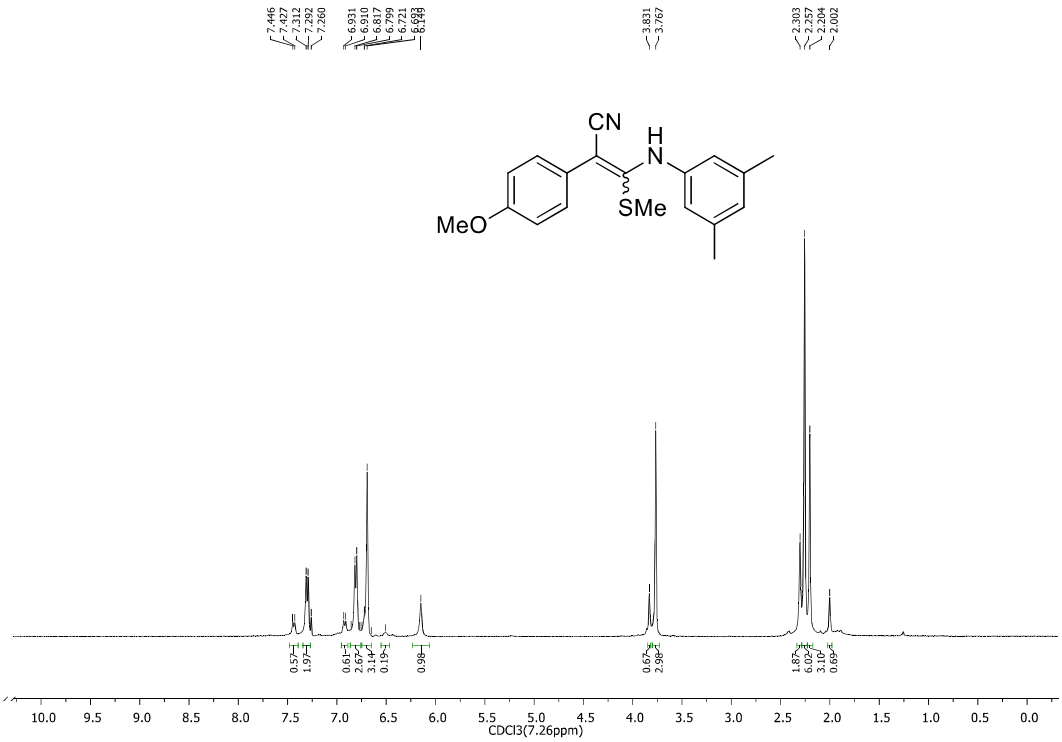


Figure 4.6a: ^{1}H NMR spectrum of **39r**

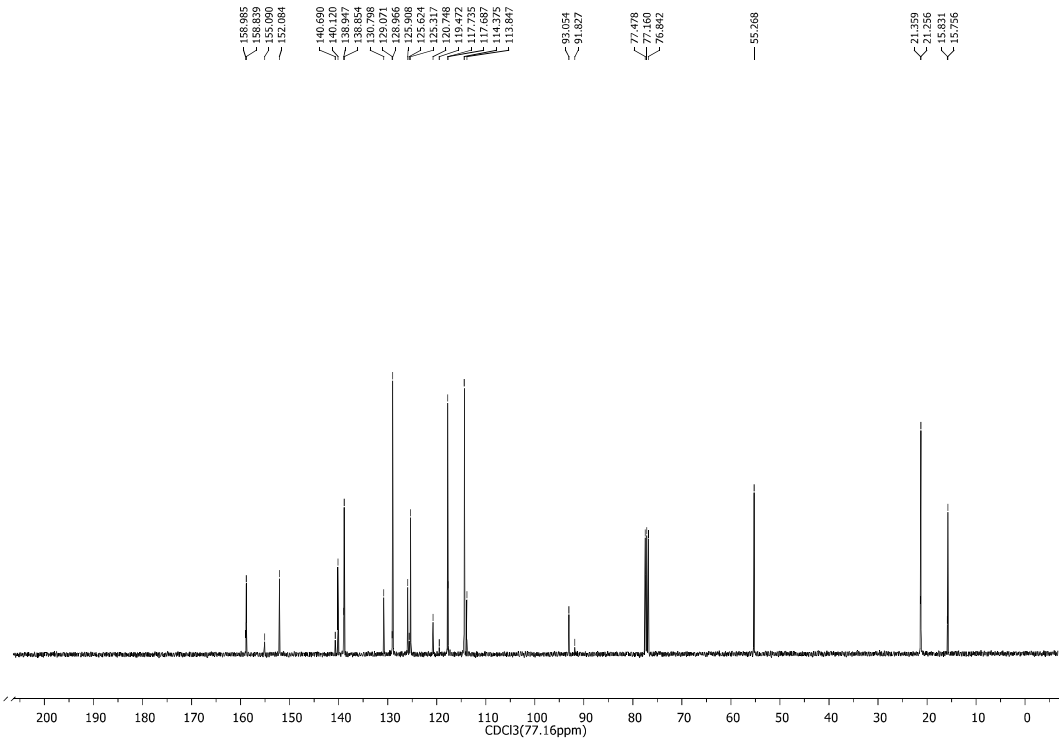


Figure 4.6b: ^{13}C NMR spectrum of **39r**

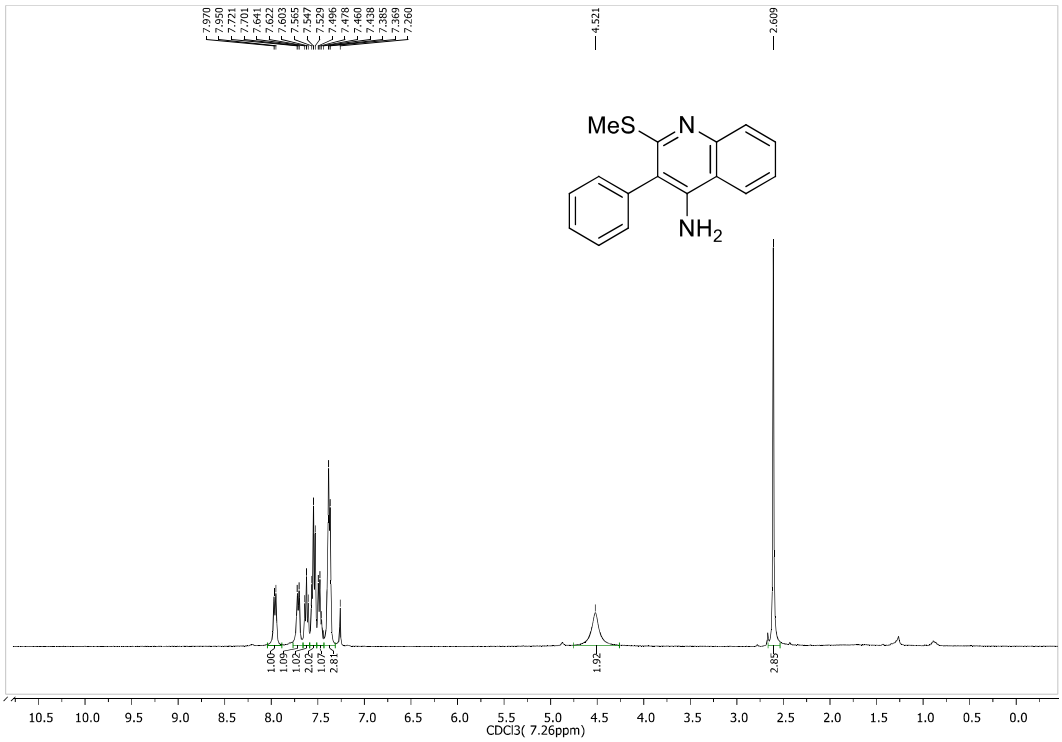


Figure 4.7a: ^{1}H NMR spectrum of **40a**

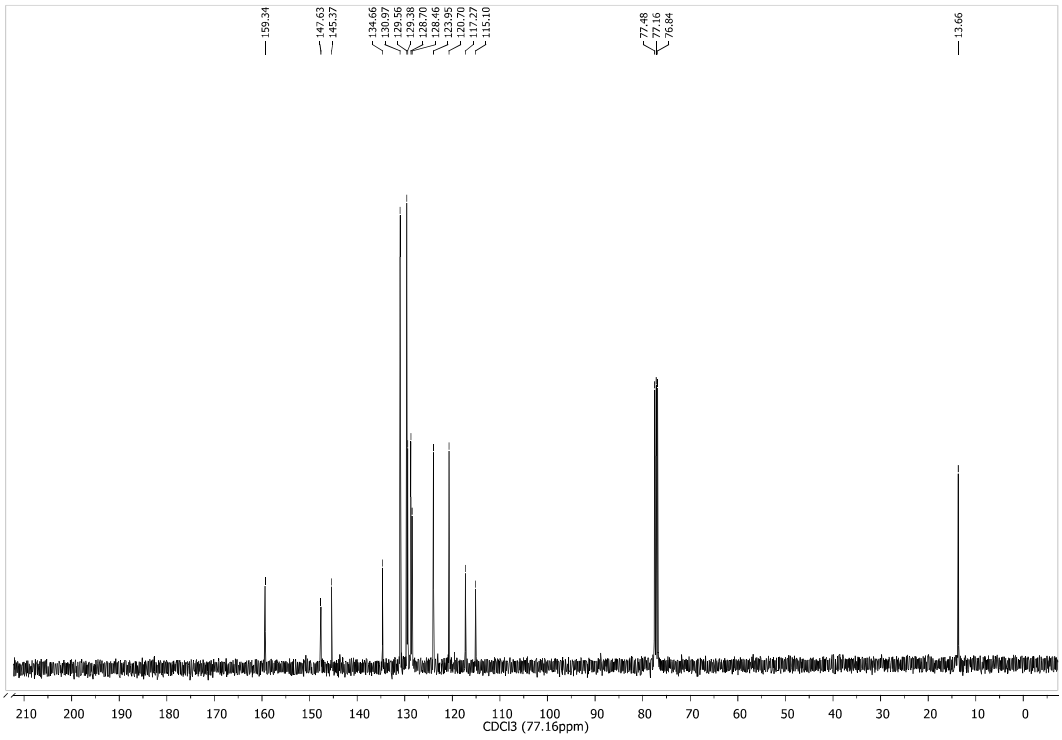


Figure 4.7b: ^{13}C NMR spectrum of **40a**

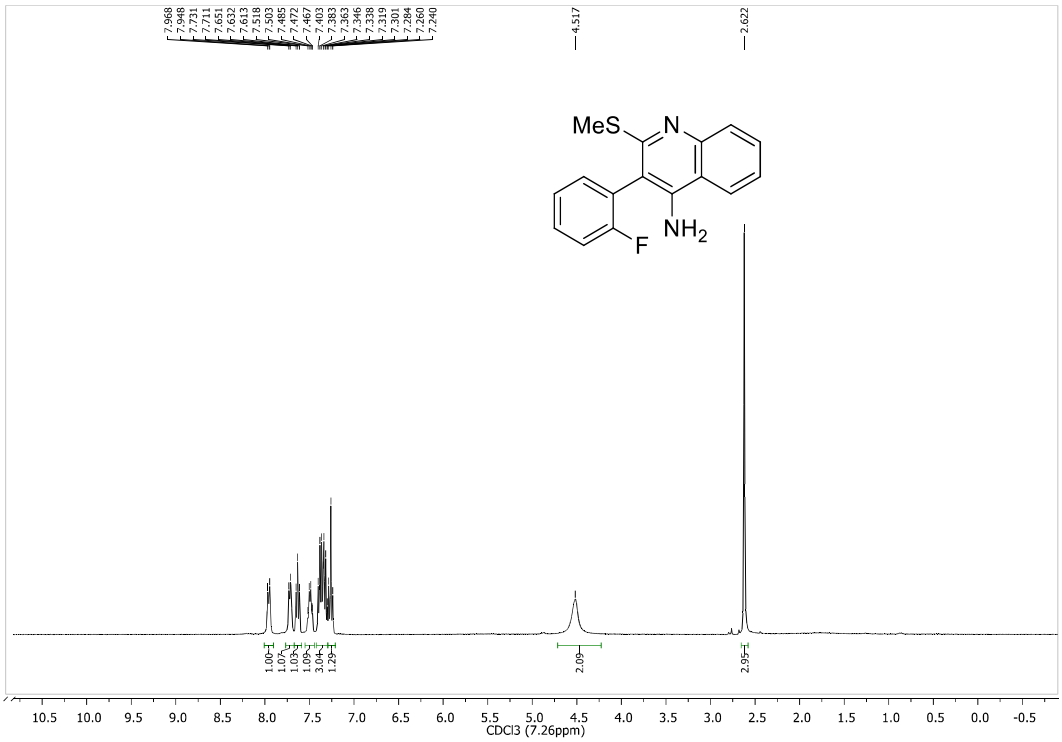


Figure 4.8a: ^{1}H NMR spectrum of **40l**

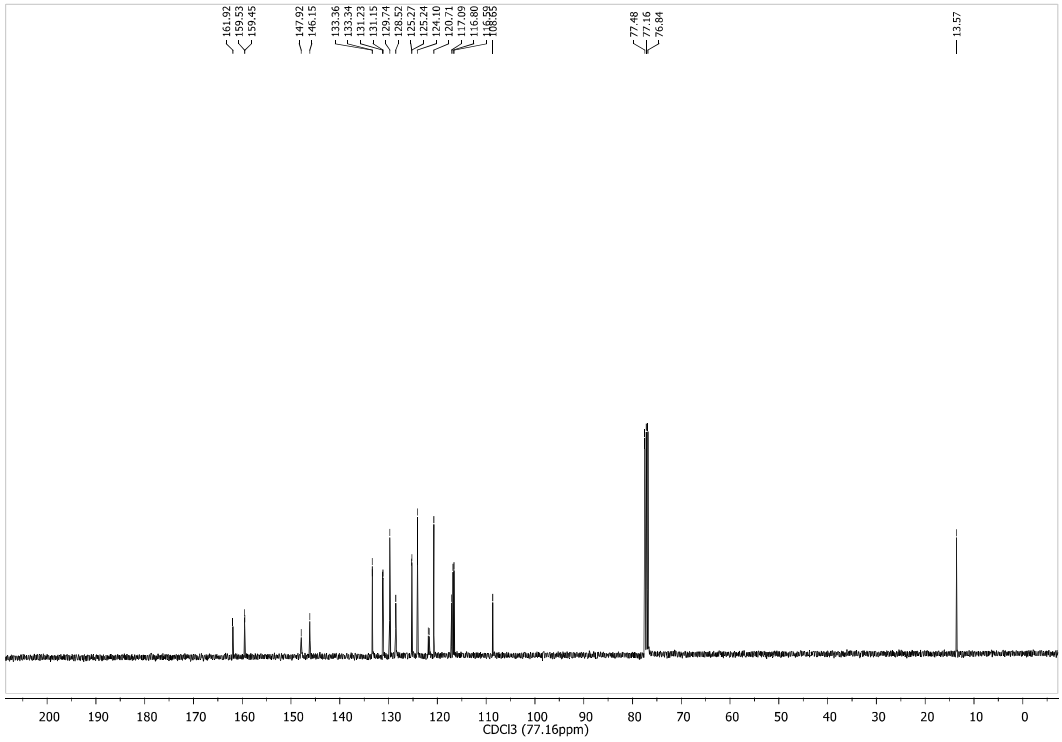


Figure 4.8b: ^{13}C NMR spectrum of **40l**

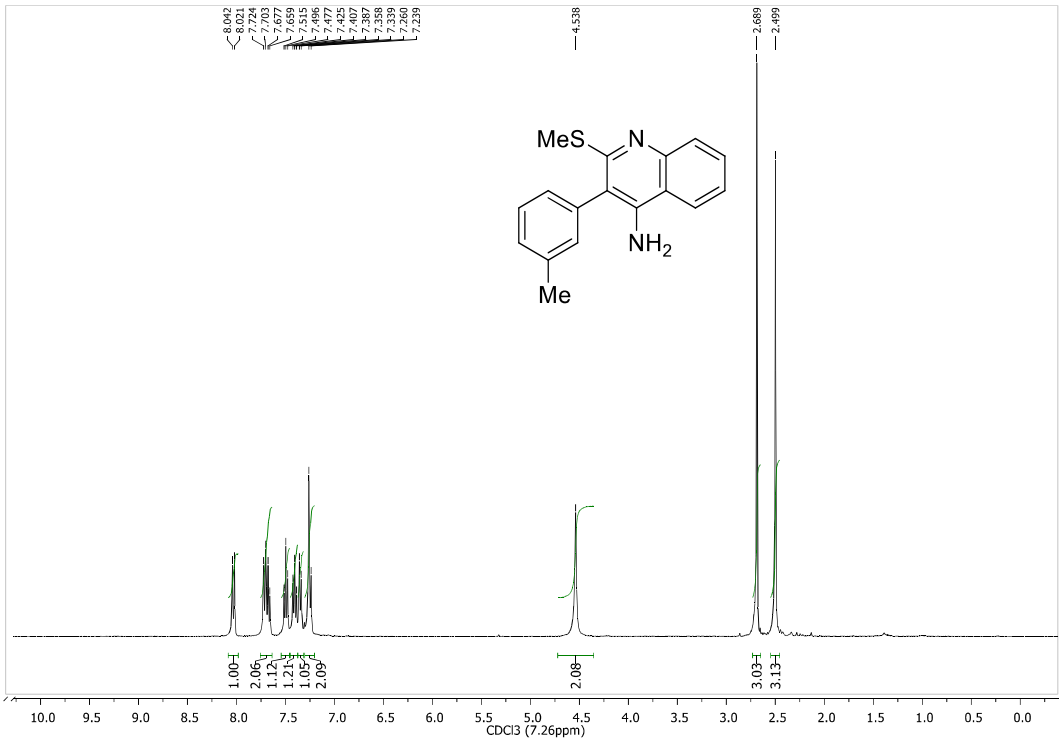


Figure 4.9a: ^{1}H NMR spectrum of **40f**

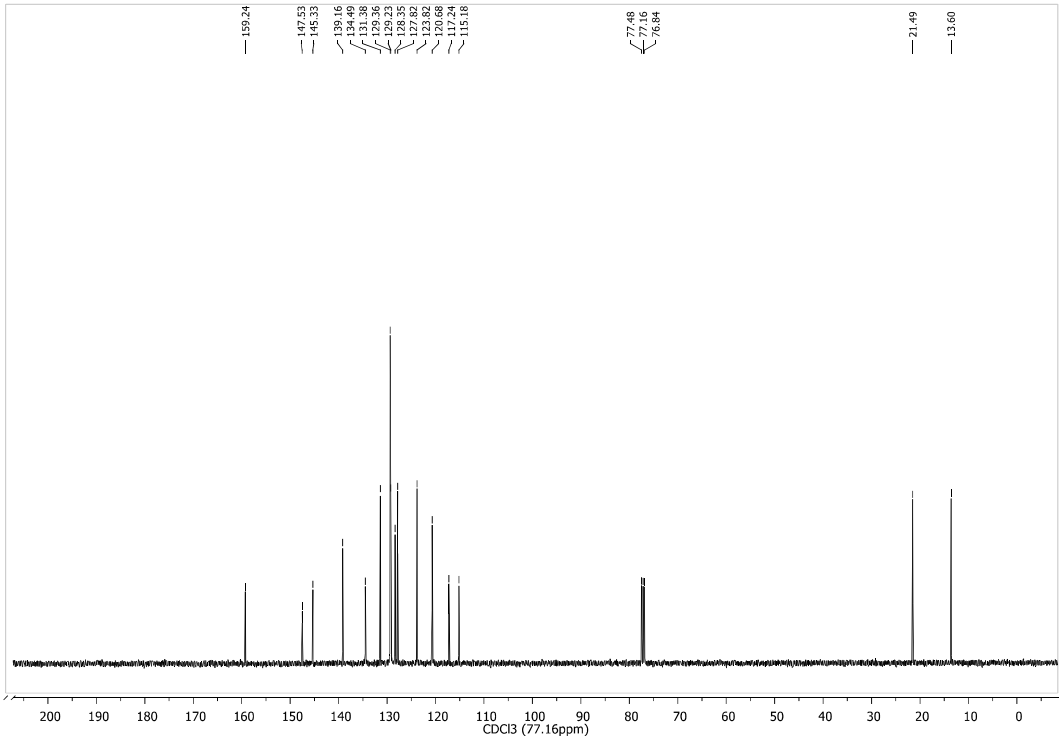


Figure 4.9b: ^{13}C NMR spectrum of **40f**

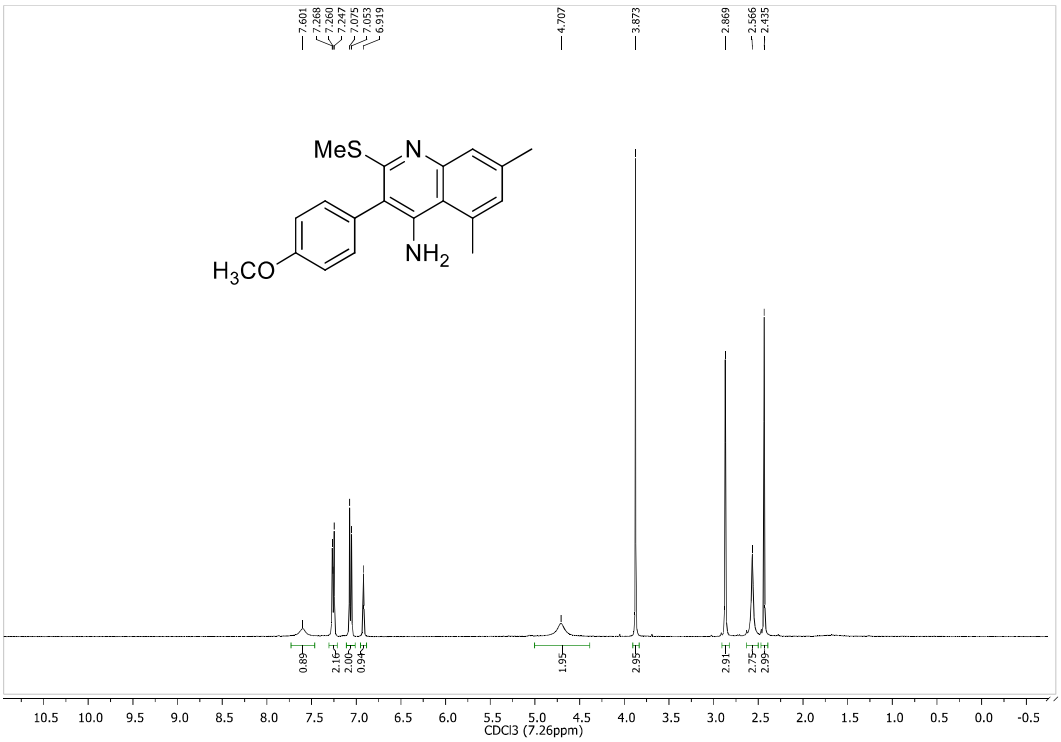


Figure 4.10a: ^{1}H NMR spectrum of **40r**

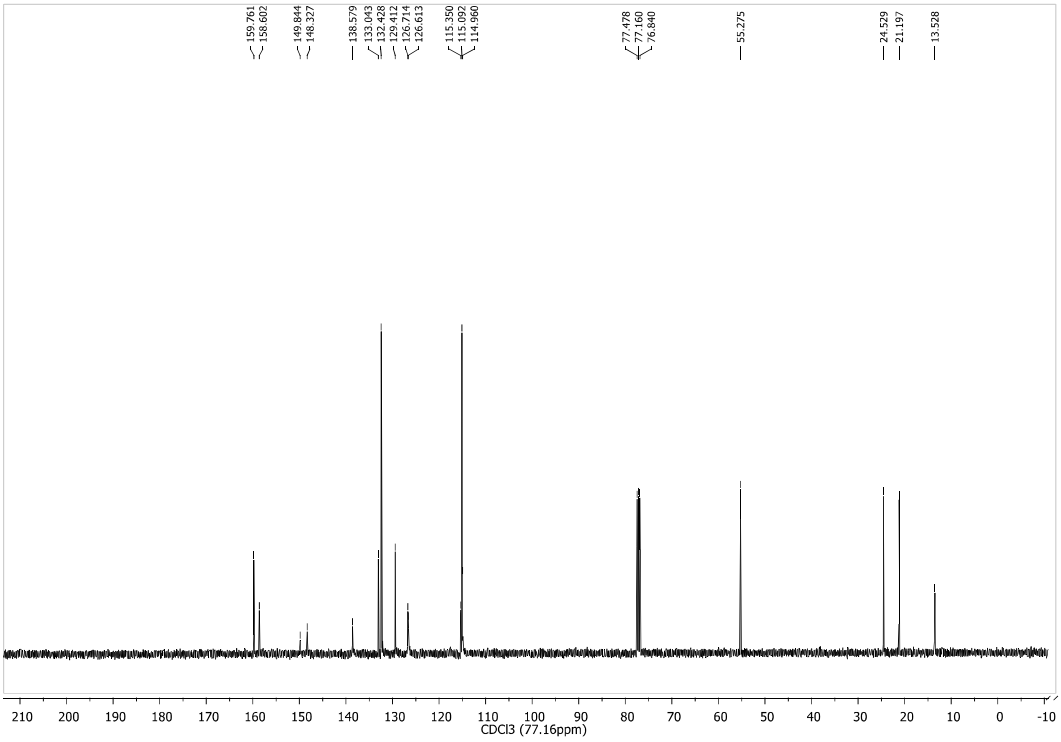


Figure 4.10b: ^{13}C NMR spectrum of **40r**

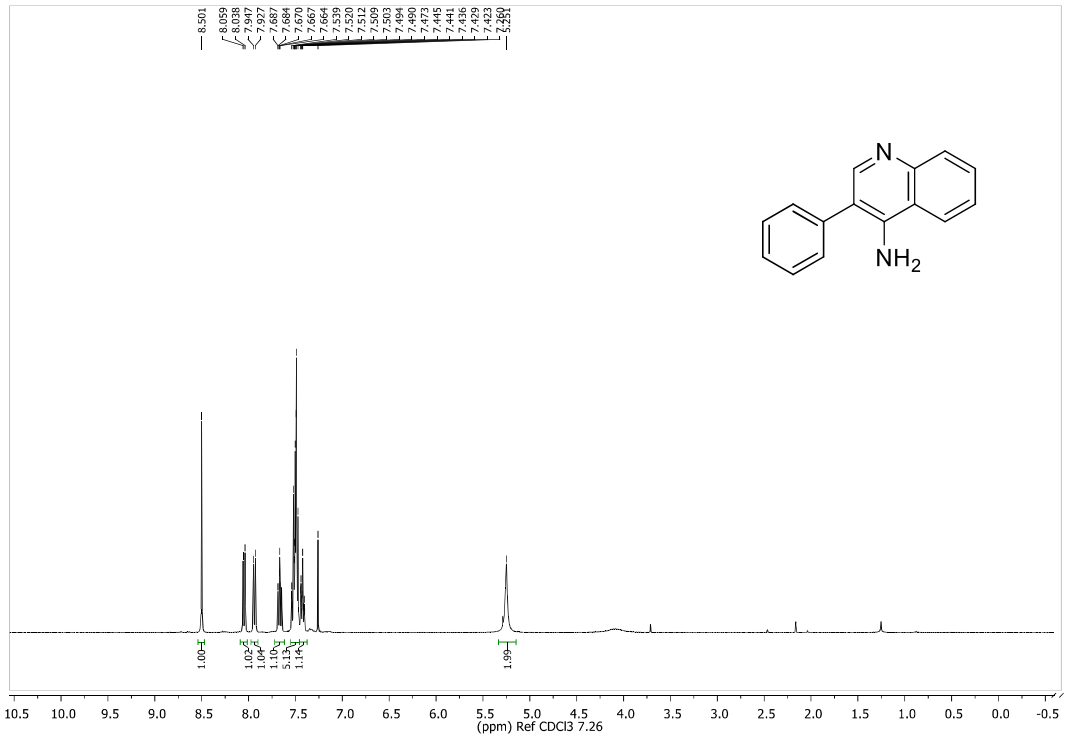


Figure 4.11a: ^{1}H NMR spectrum of **54a**

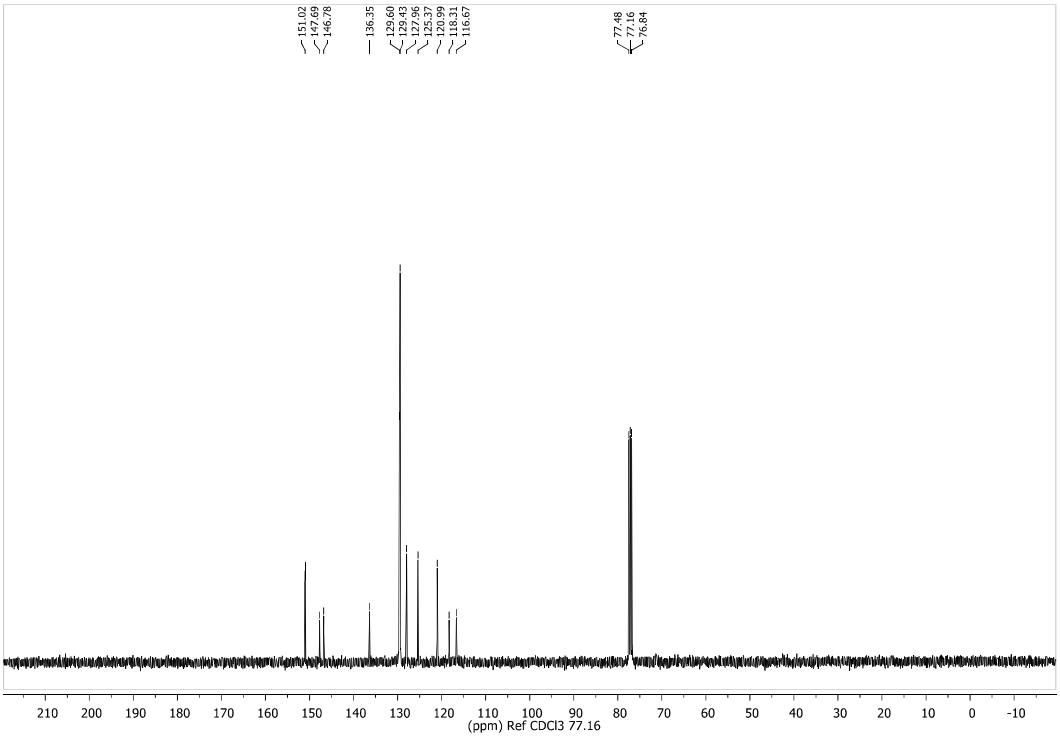


Figure 4.11b: ^{13}C NMR spectrum of **54a**

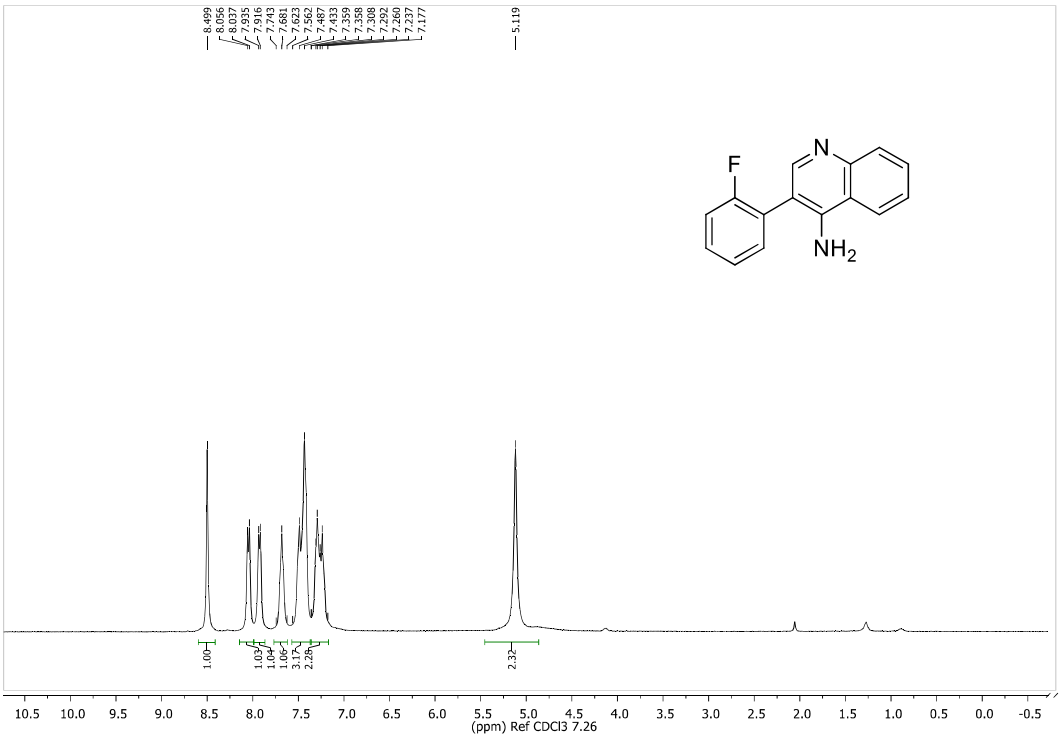


Figure 4.12a: ^{1}H NMR spectrum of **54l**

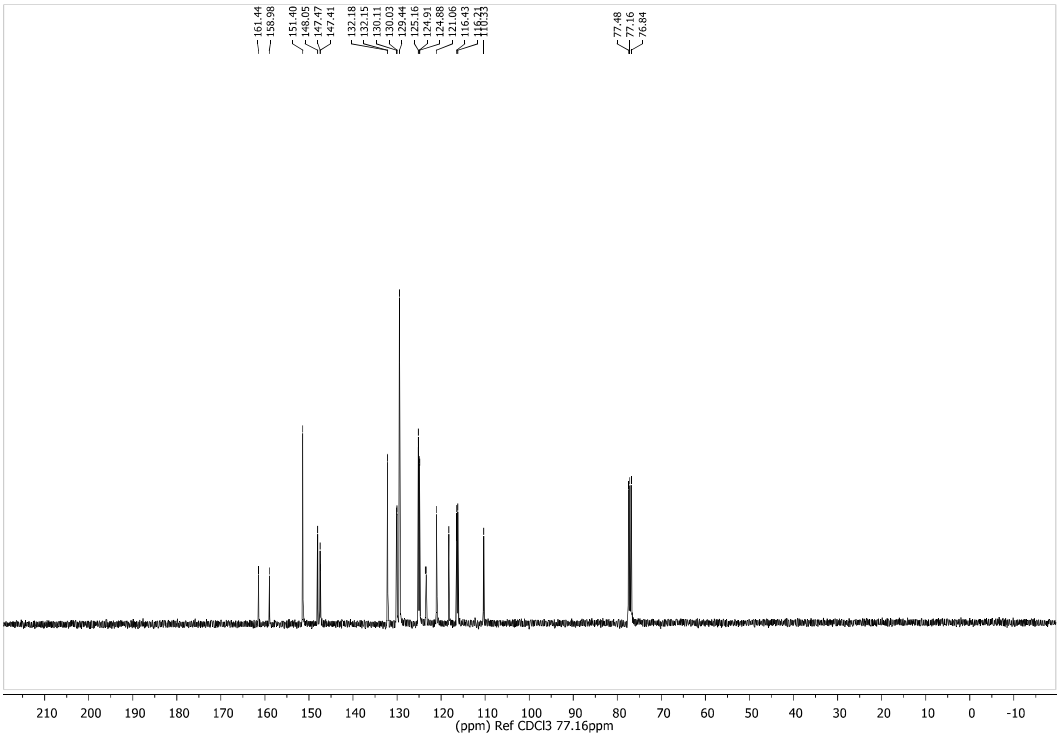


Figure 4.12b: ^{1}H NMR spectrum of **54l**

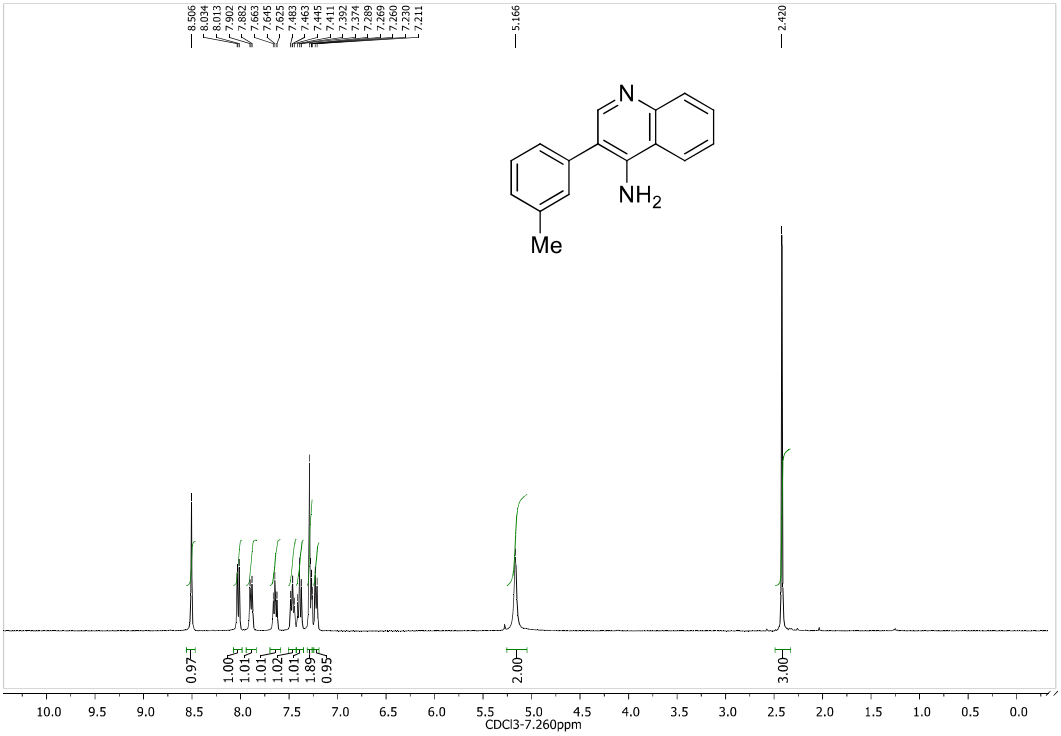


Figure 4.13a: ^{1}H NMR spectrum of **54f**

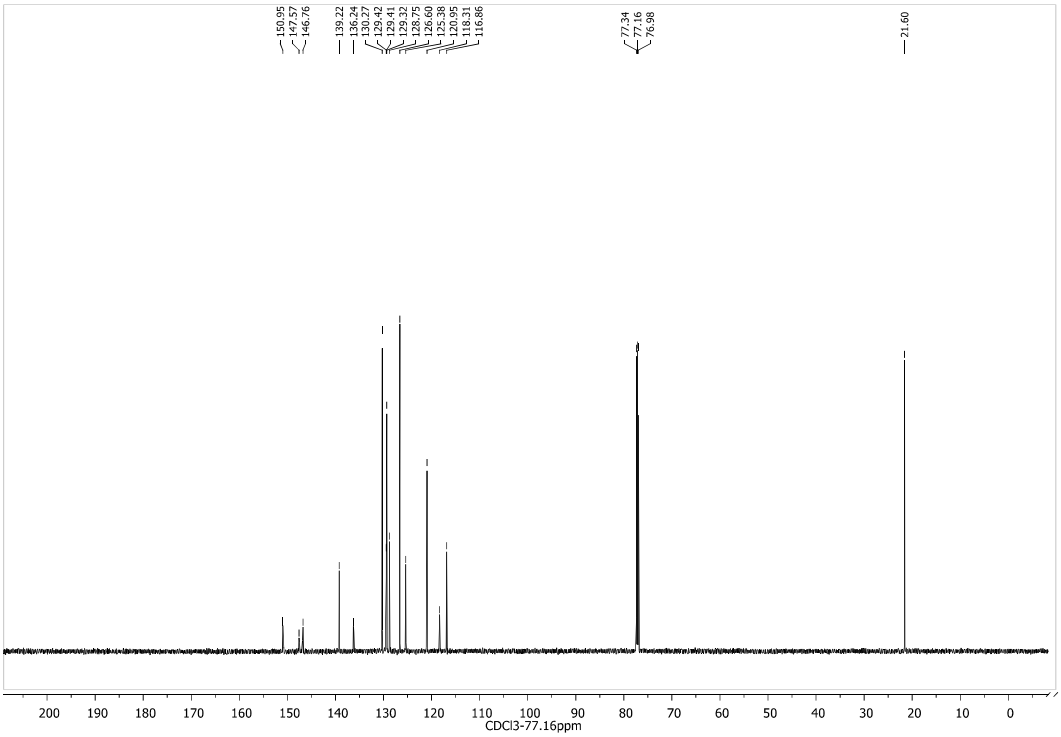


Figure 4.13b: ^{13}C NMR spectrum of **54f**

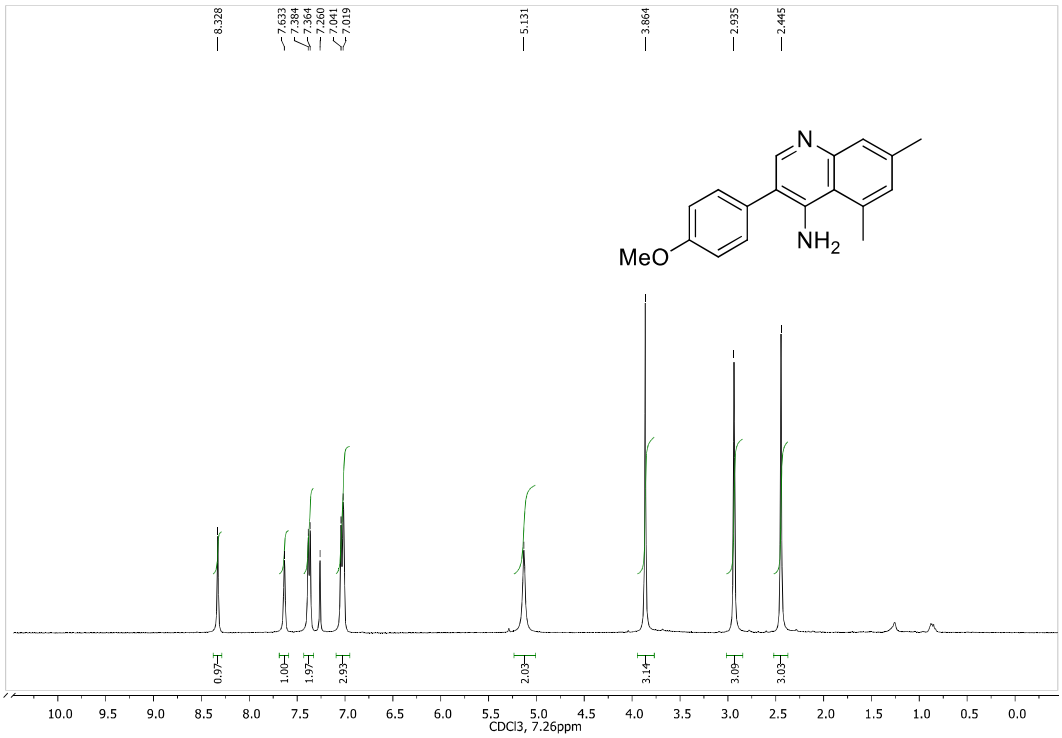


Figure 4.14a: ^{1}H NMR spectrum of **54r**

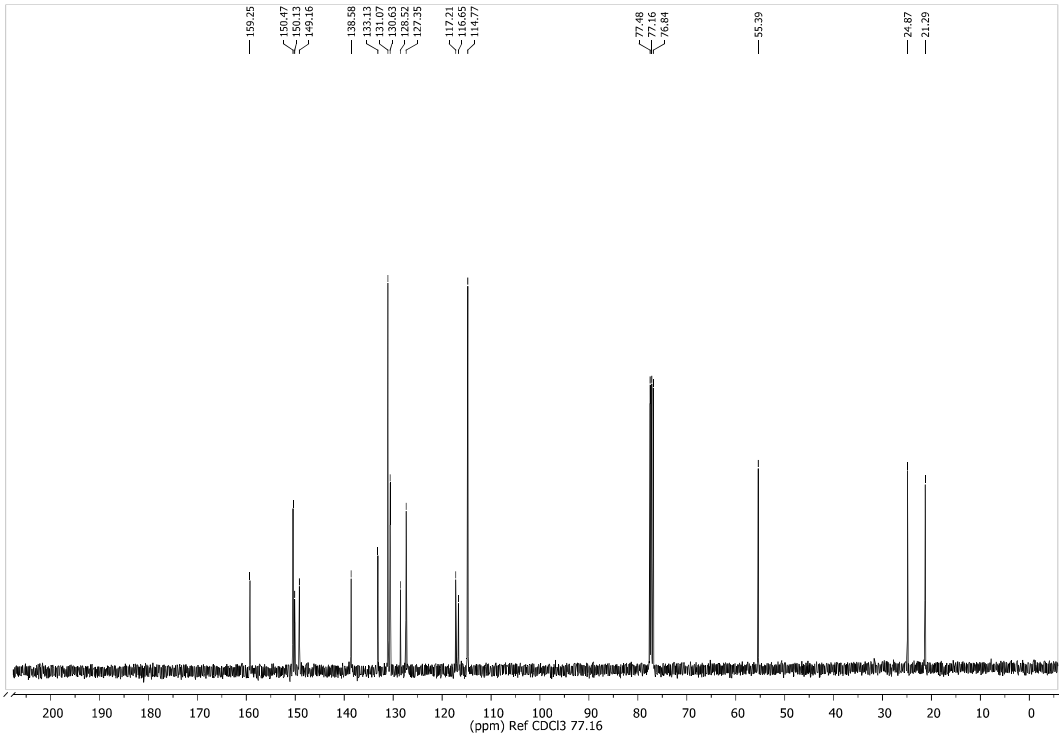


Figure 4.14b: ^{13}C NMR spectrum of **54r**

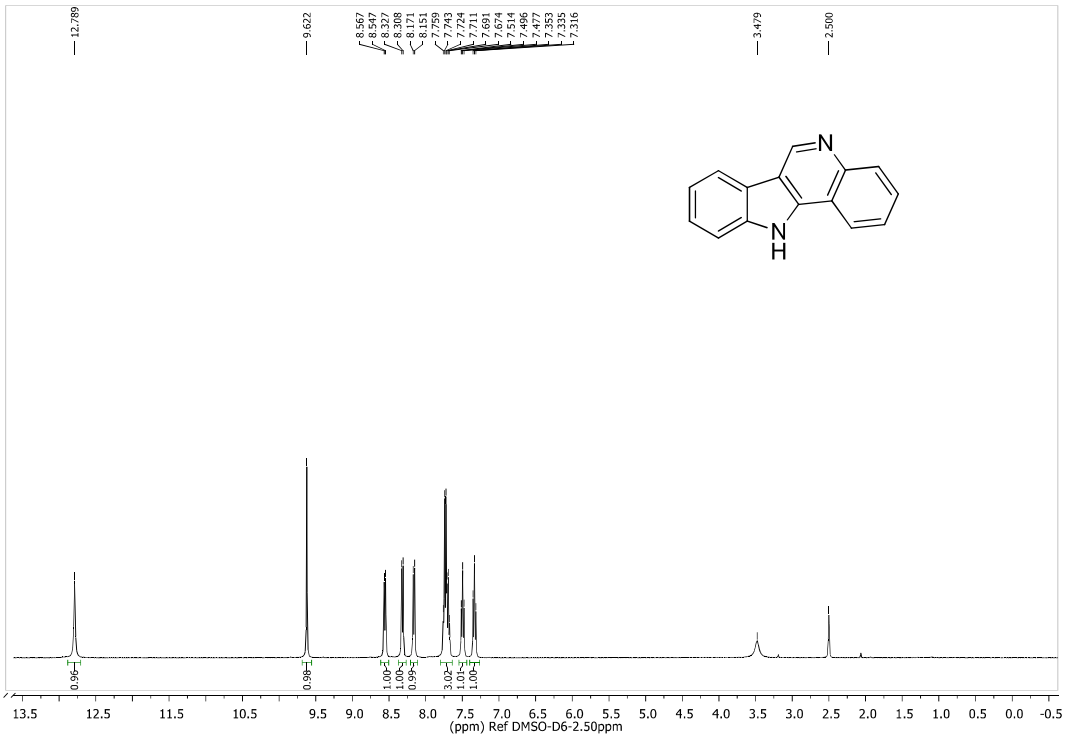


Figure 4.15a: ^{1}H NMR spectrum of **16a**

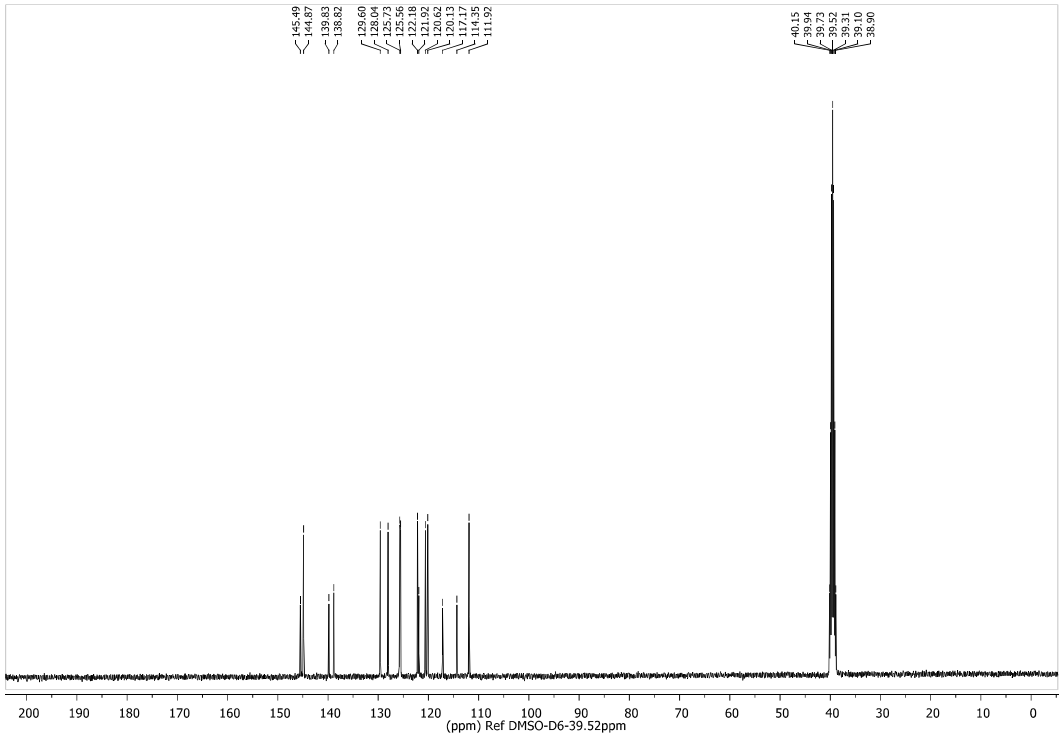


Figure 4.15b: ^{13}C NMR spectrum of **16a**

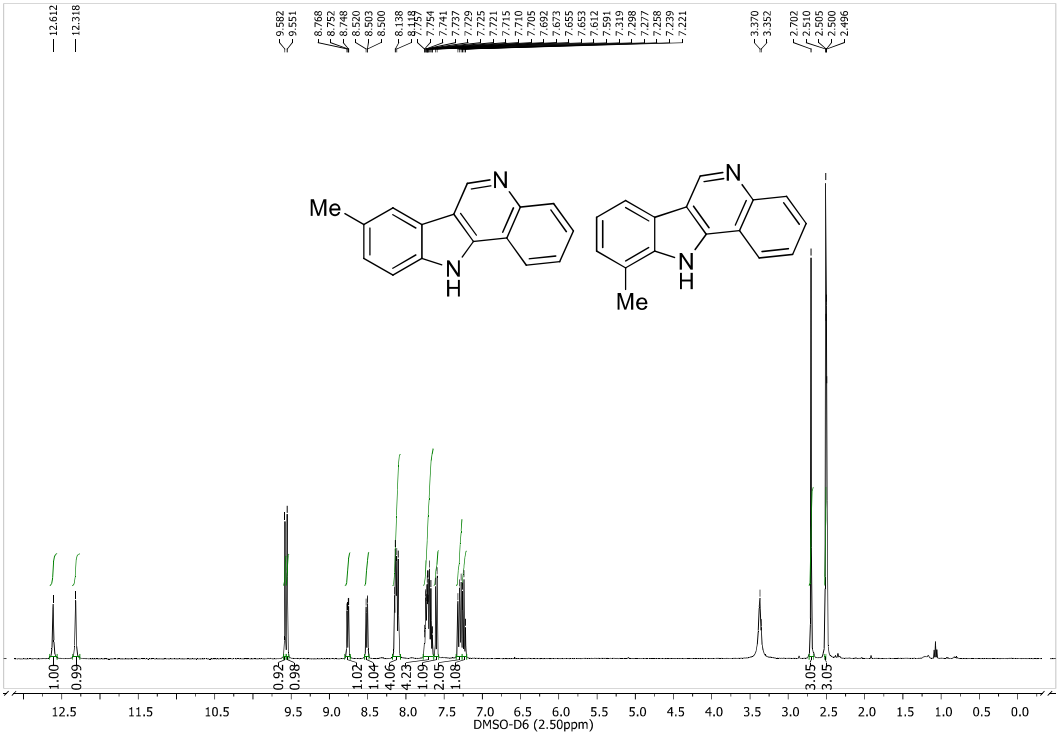


Figure 4.16a: ^{1}H NMR spectrum of **16fa & 16fb**

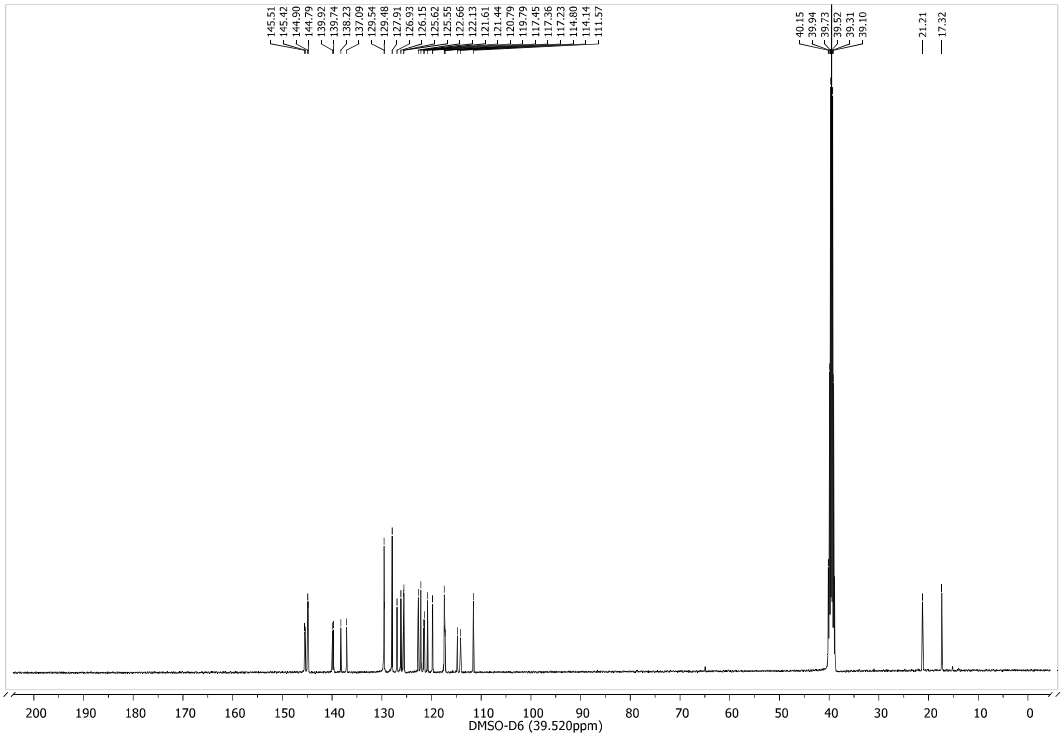


Figure 4.16b: ^{13}C NMR spectrum of **16a & 16b**

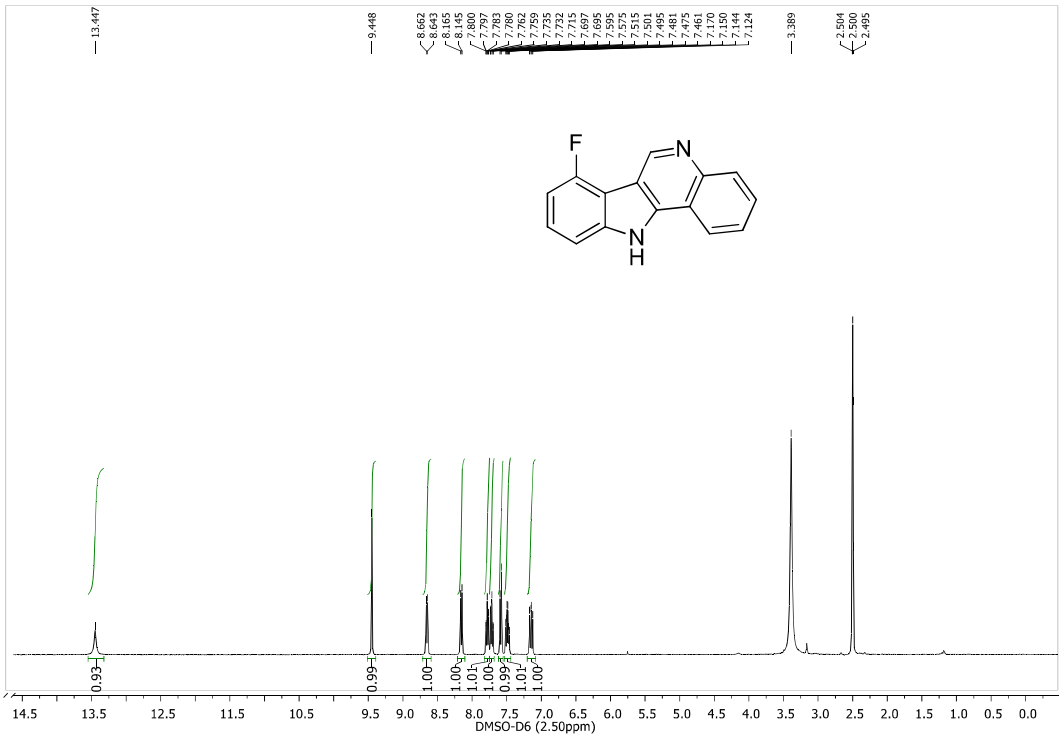


Figure 4.17a: ^{1}H NMR spectrum of **16l**

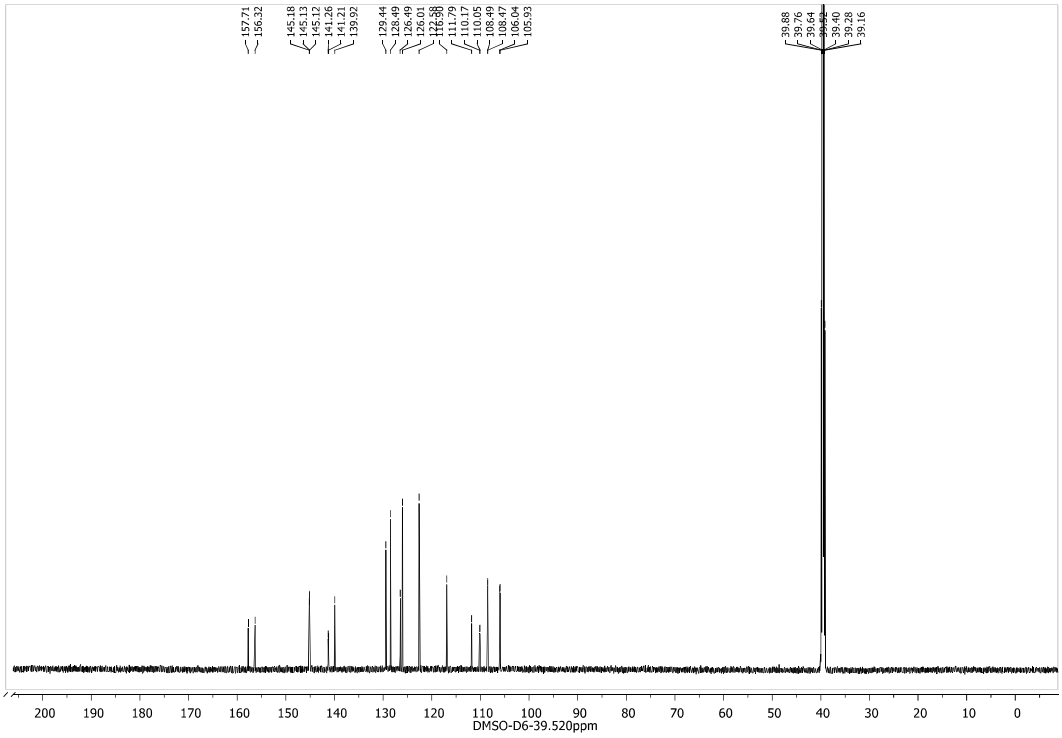


Figure 4.17b: ^{13}C NMR spectrum of **16l**

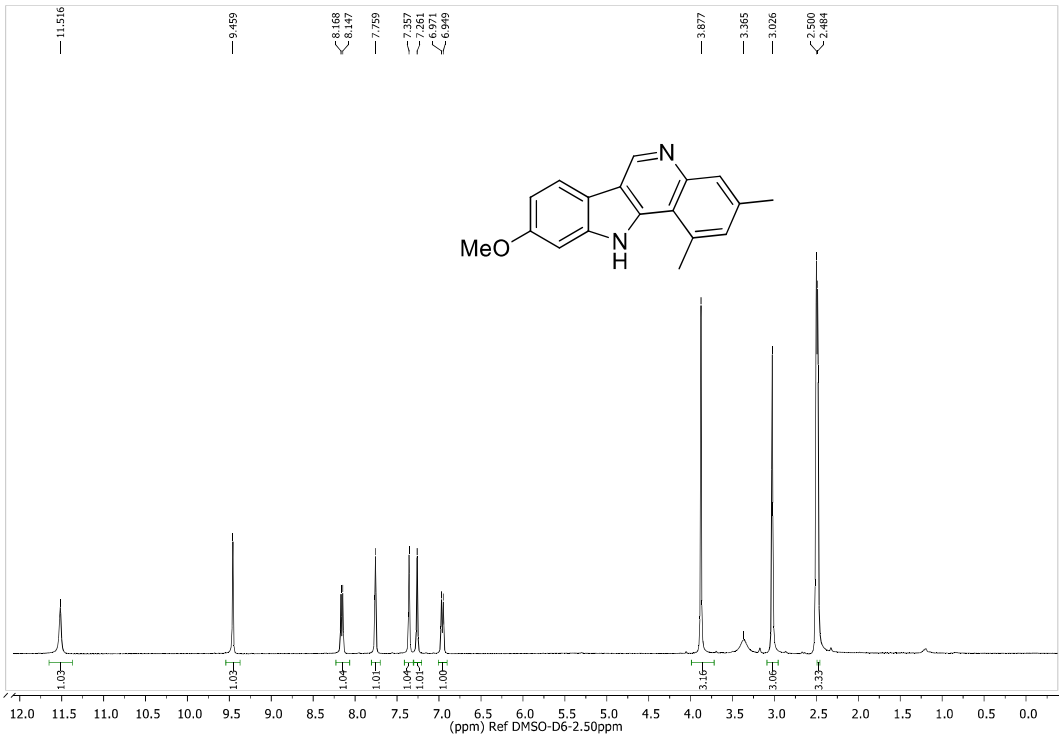


Figure 4.18a: ^{1}H NMR spectrum of **16r**

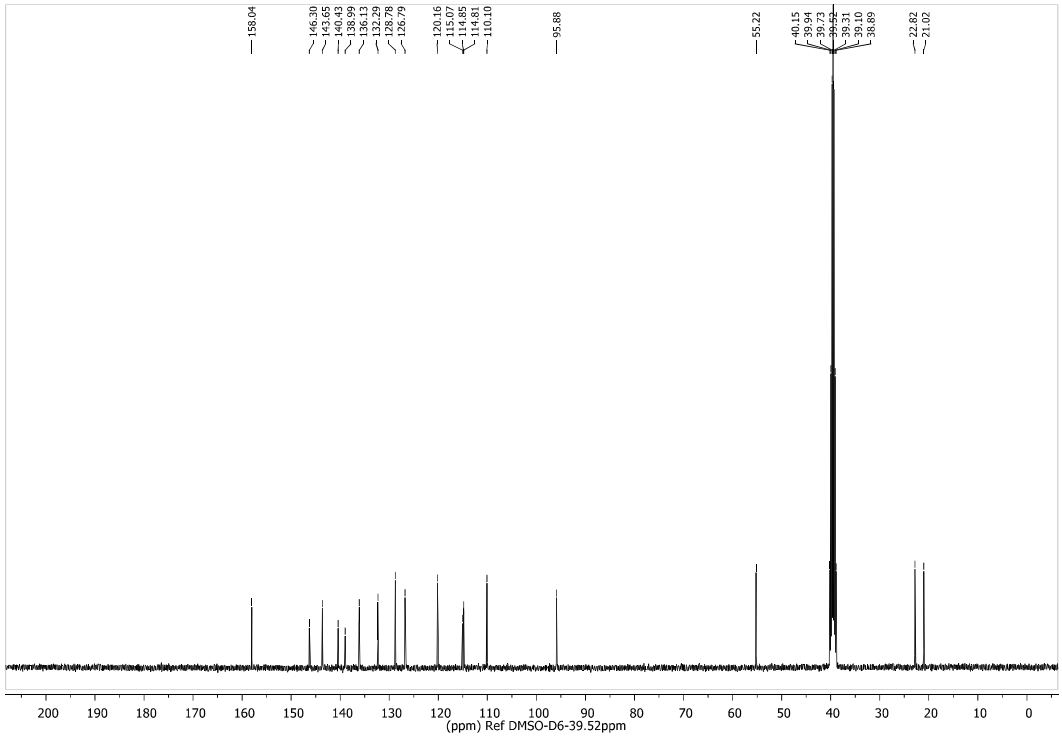


Figure 4.18b: ^{13}C NMR spectrum of **16r**

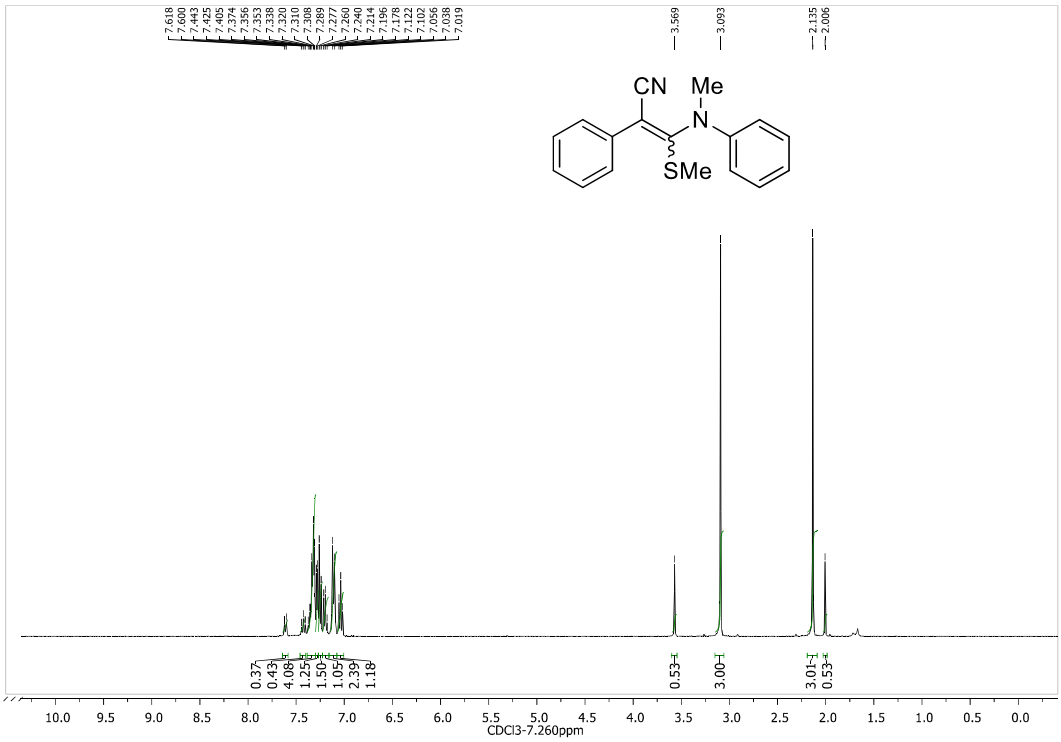


Figure 4.19a: ^{1}H NMR spectrum of **55a**

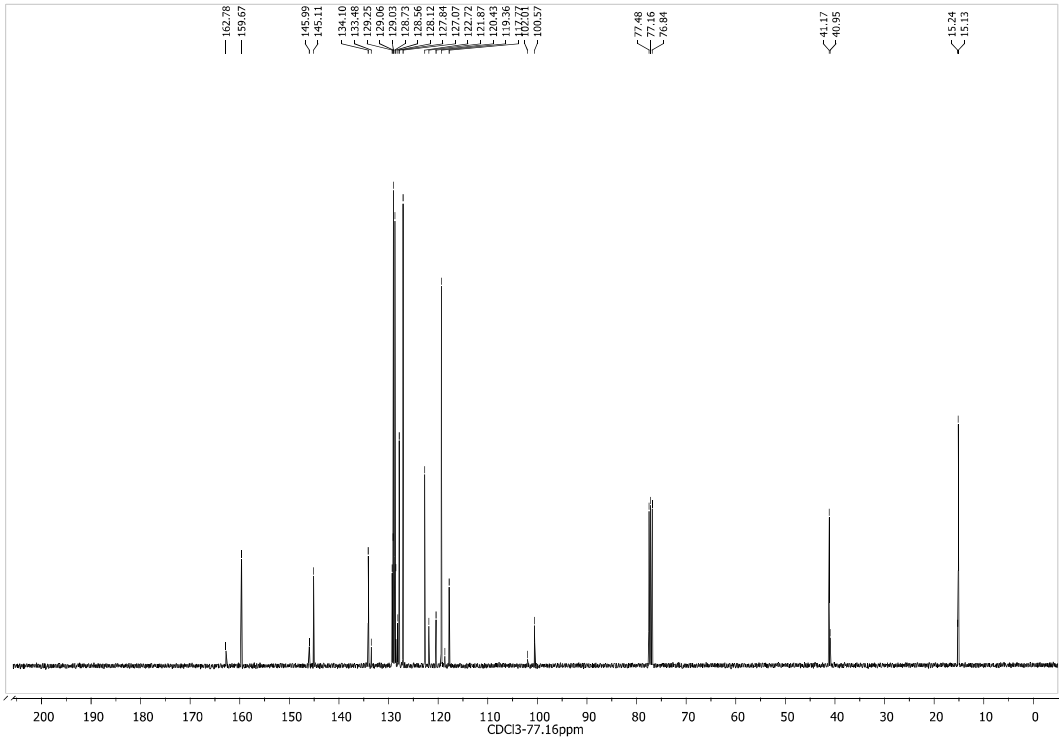


Figure 4.19b: ^{13}C NMR spectrum of **55a**

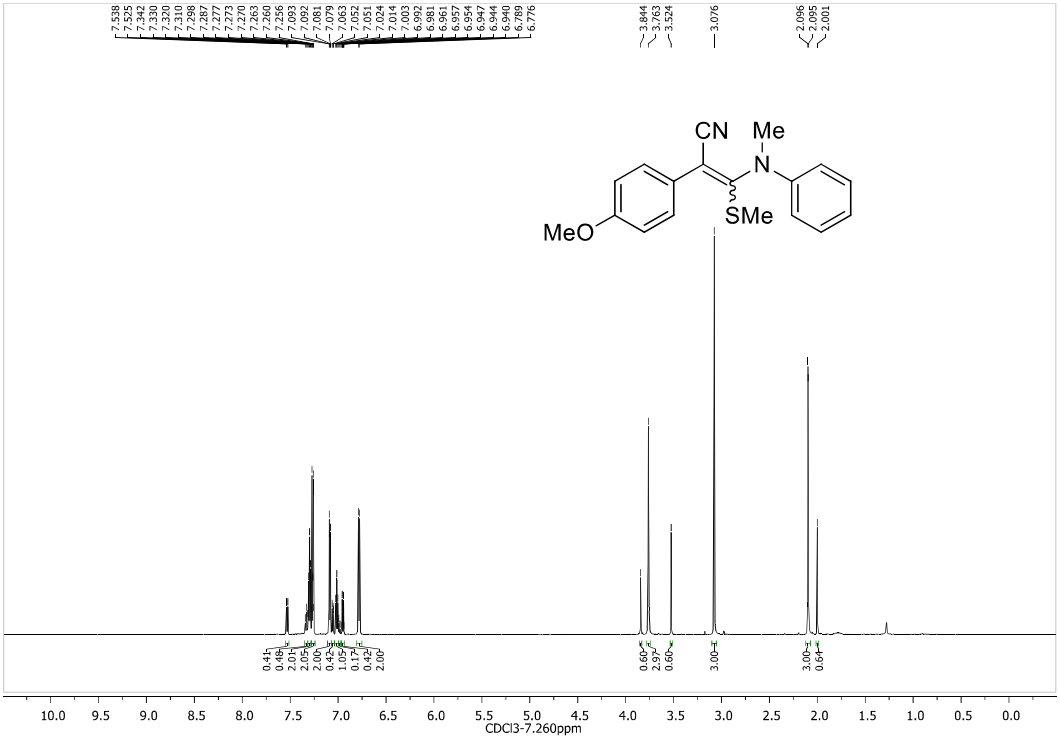


Figure 4.20a: ^{1}H NMR spectrum of **55b**

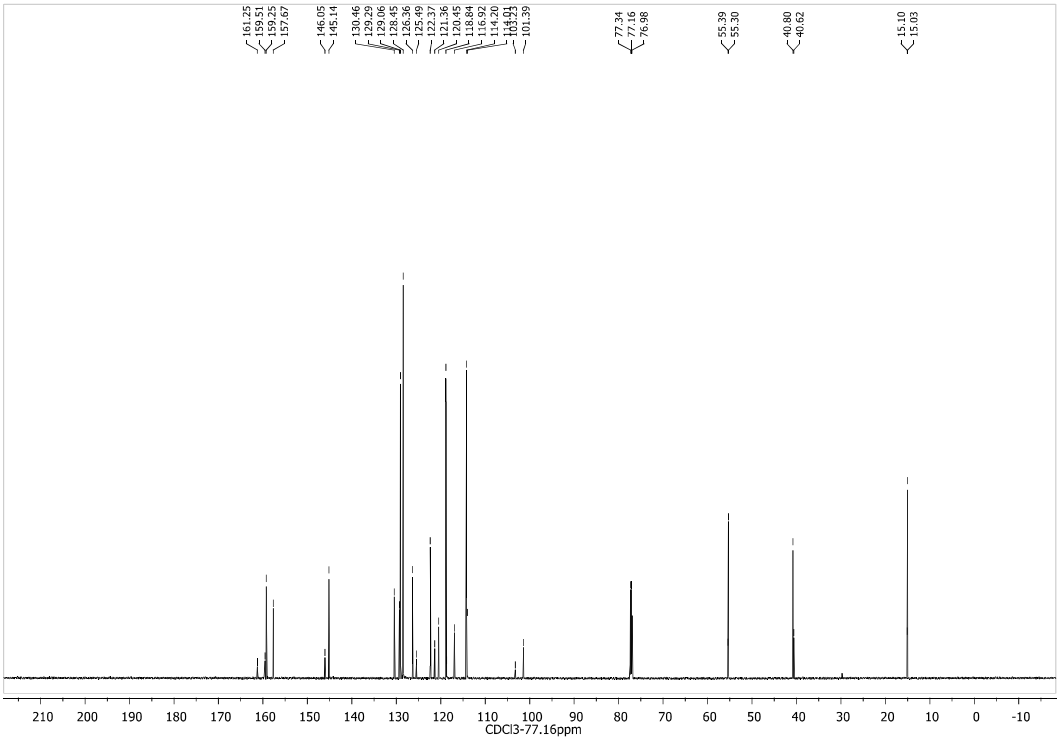


Figure 4.20b: ^{13}C NMR spectrum of **55b**

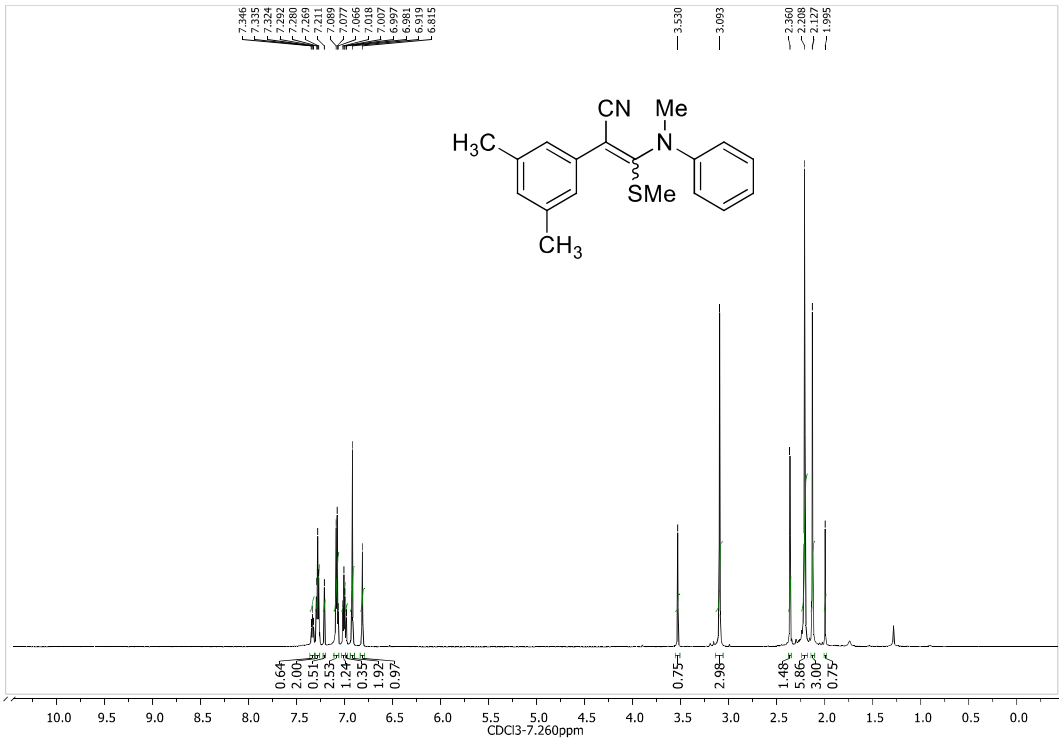


Figure 4.21a: ^{1}H NMR spectrum of **55e**

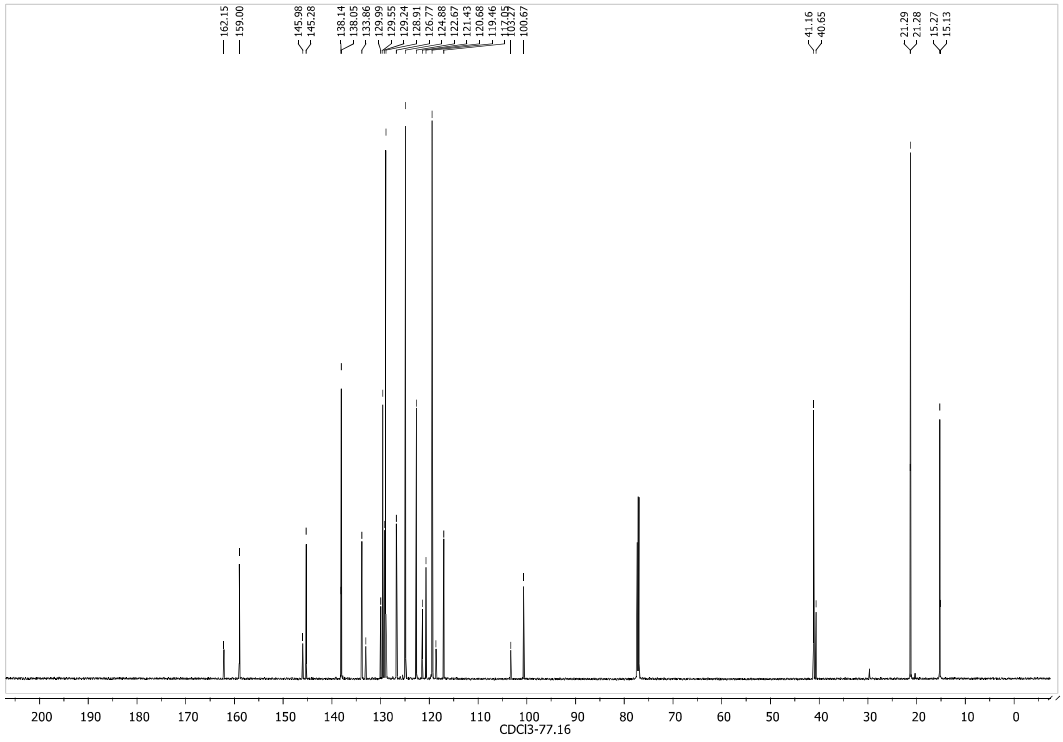


Figure 4.21b: ^{13}C NMR spectrum of **55e**

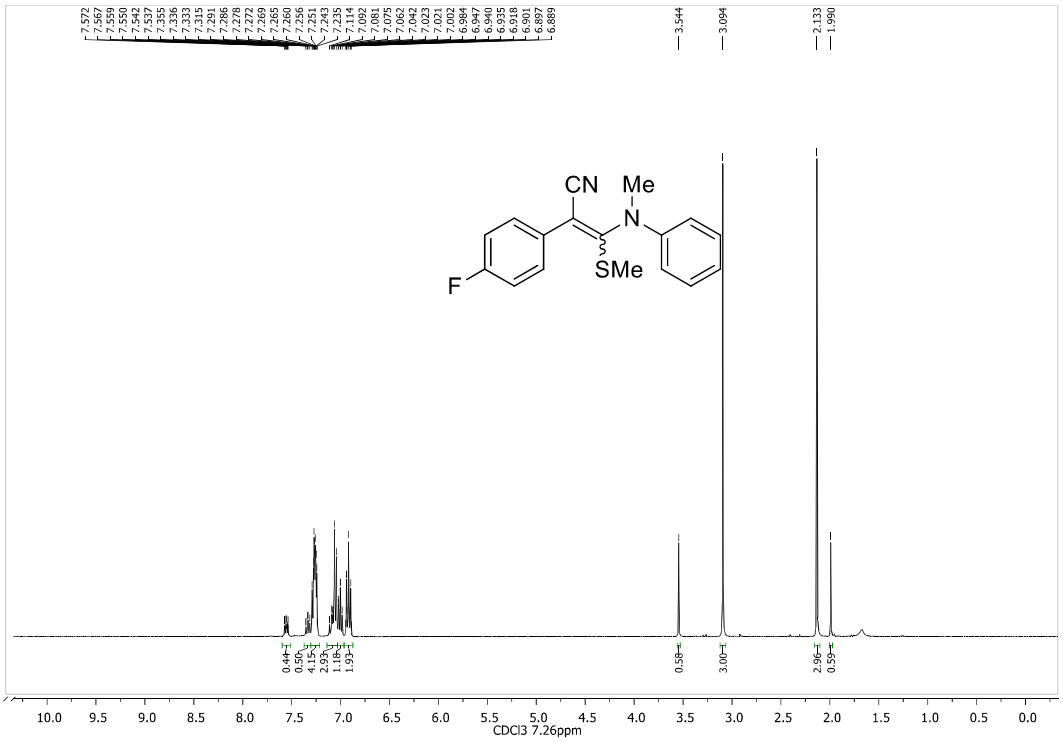


Figure 4.22a: ^{1}H NMR spectrum of **55g**

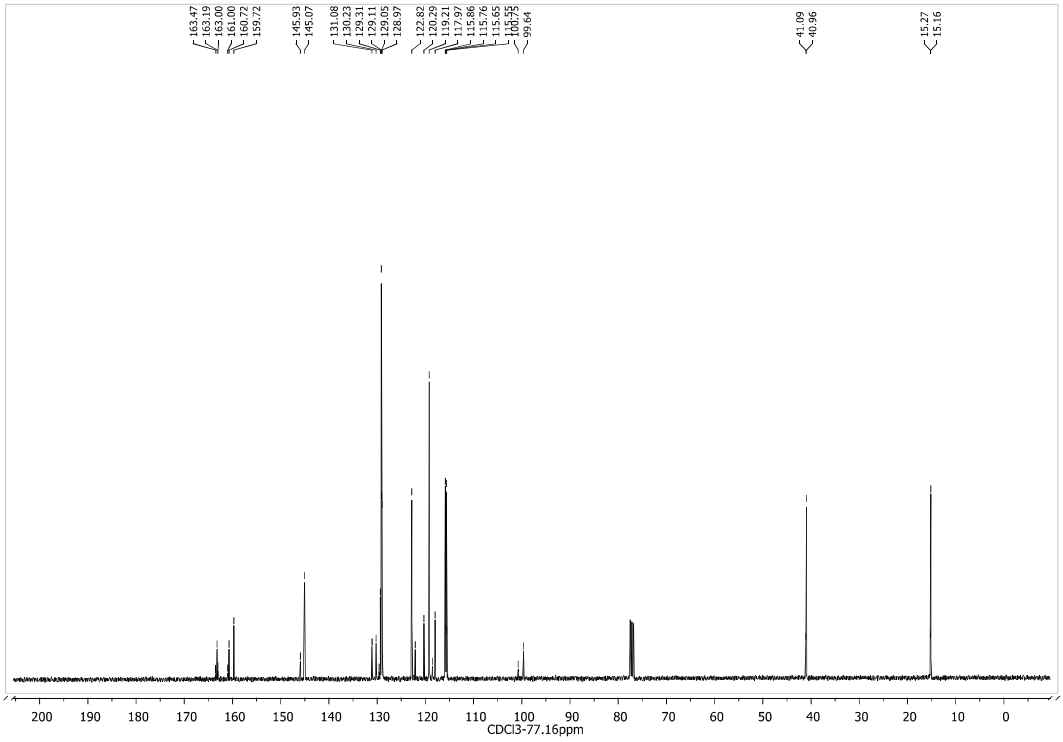


Figure 4.22b: ^{13}C NMR spectrum of **55g**

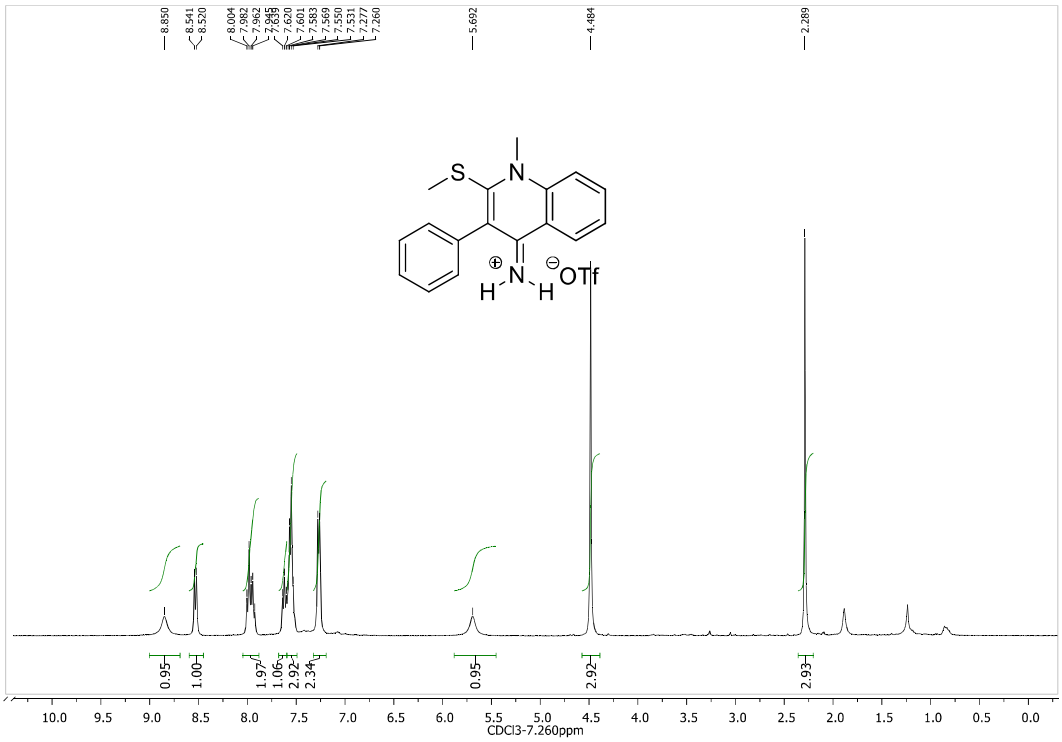


Figure 4.23a: ^{1}H NMR spectrum of **56a**

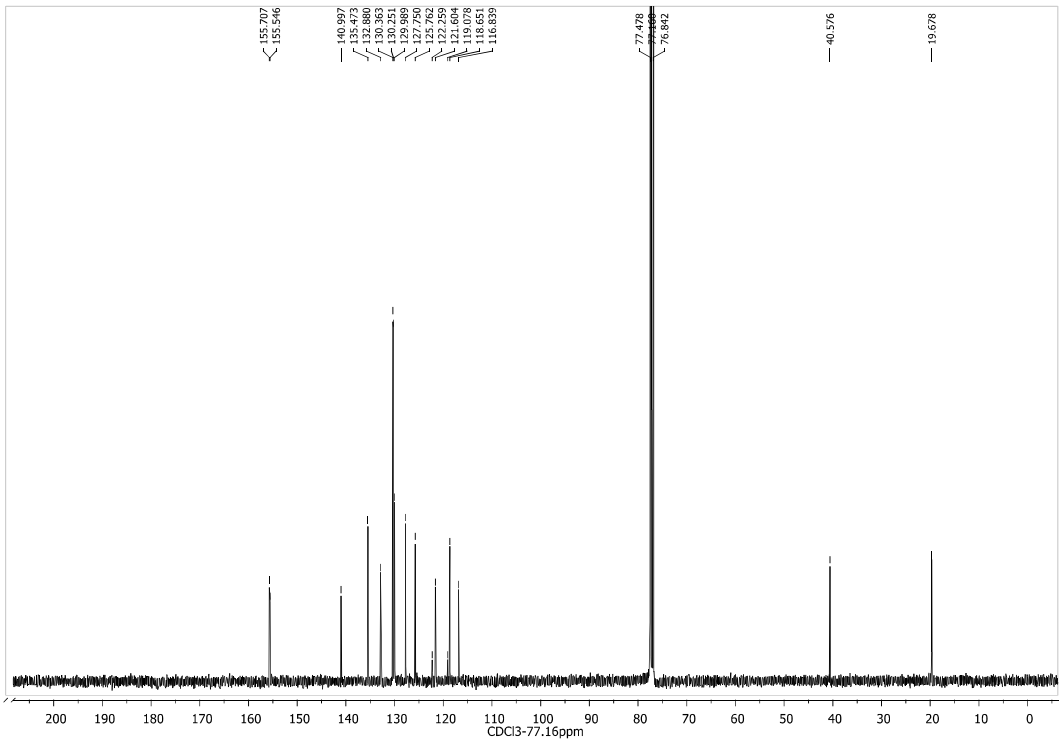


Figure 4.23b: ^{13}C NMR spectrum of **56a**

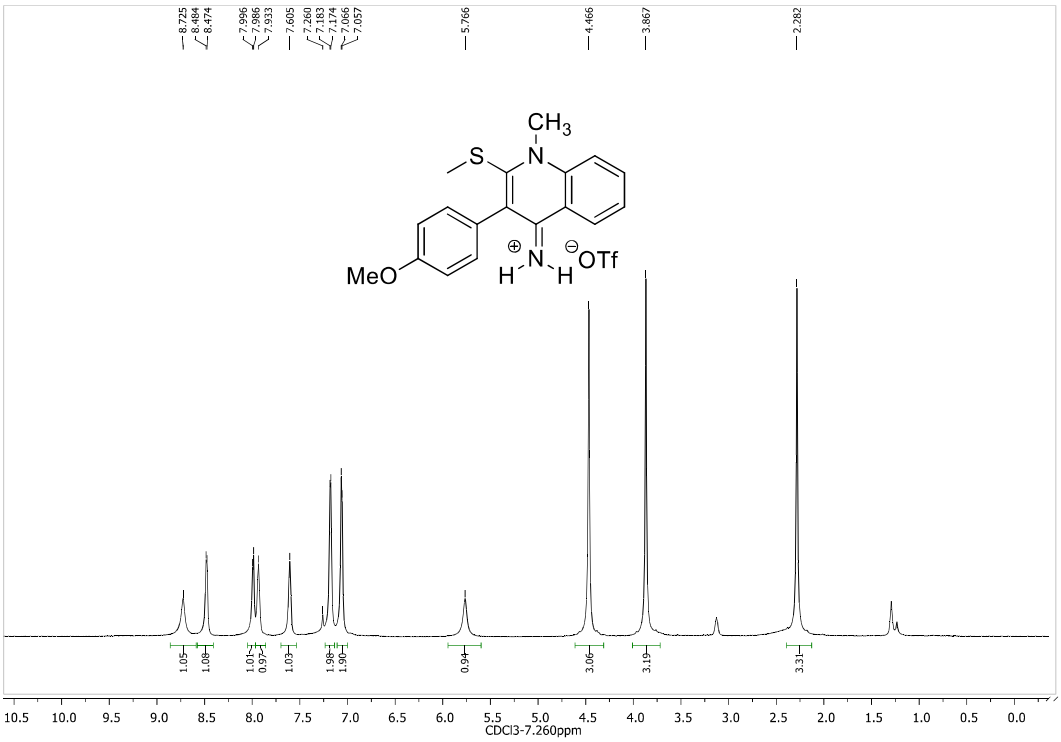


Figure 4.24a: ^{1}H NMR spectrum of **56b**

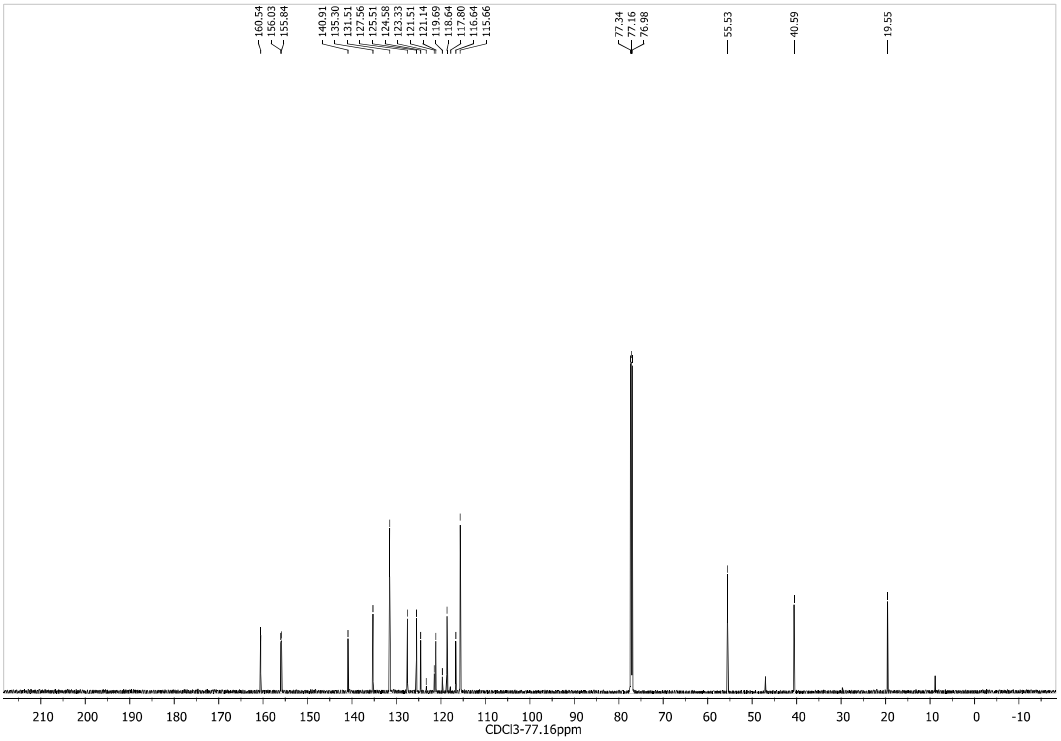


Figure 4.24b: ^{13}C NMR spectrum of **56b**

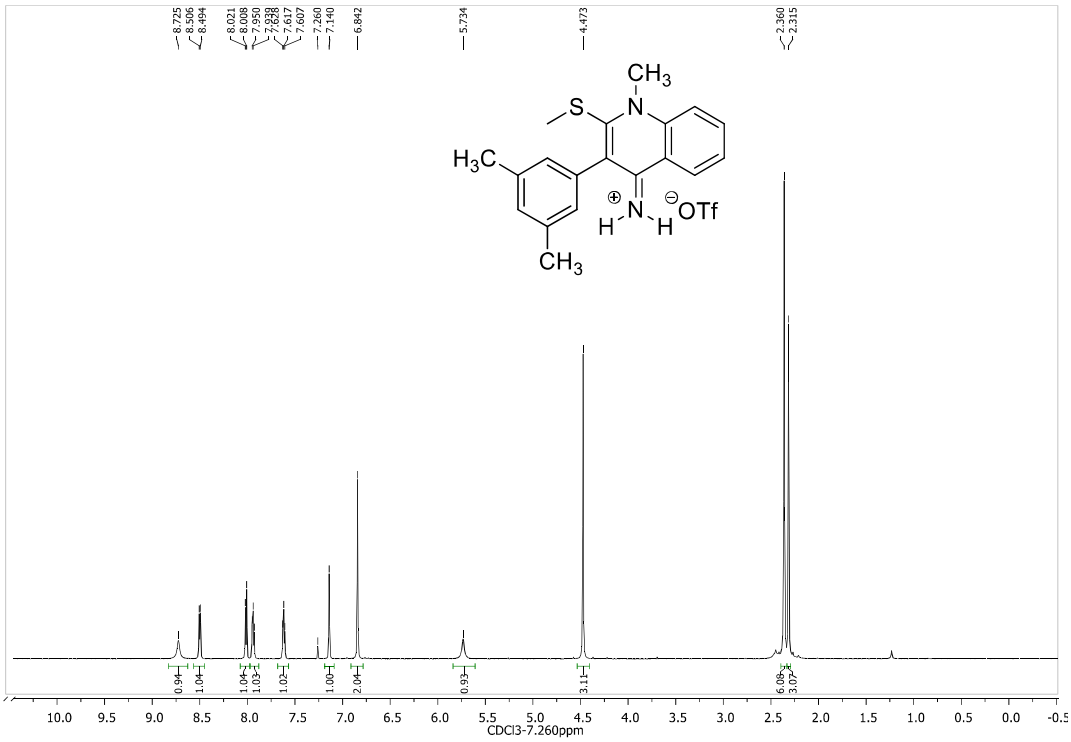


Figure 4.25a: ^{1}H NMR spectrum of **56e**

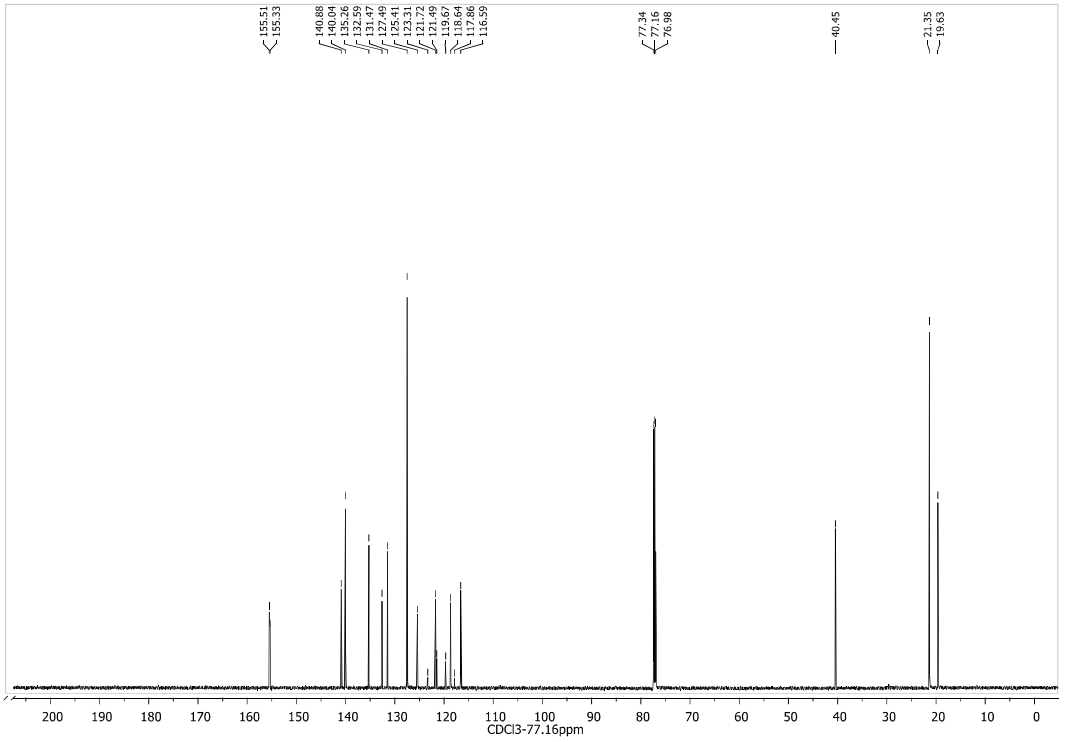


Figure 4.25b: ^{13}C NMR spectrum of **56e**

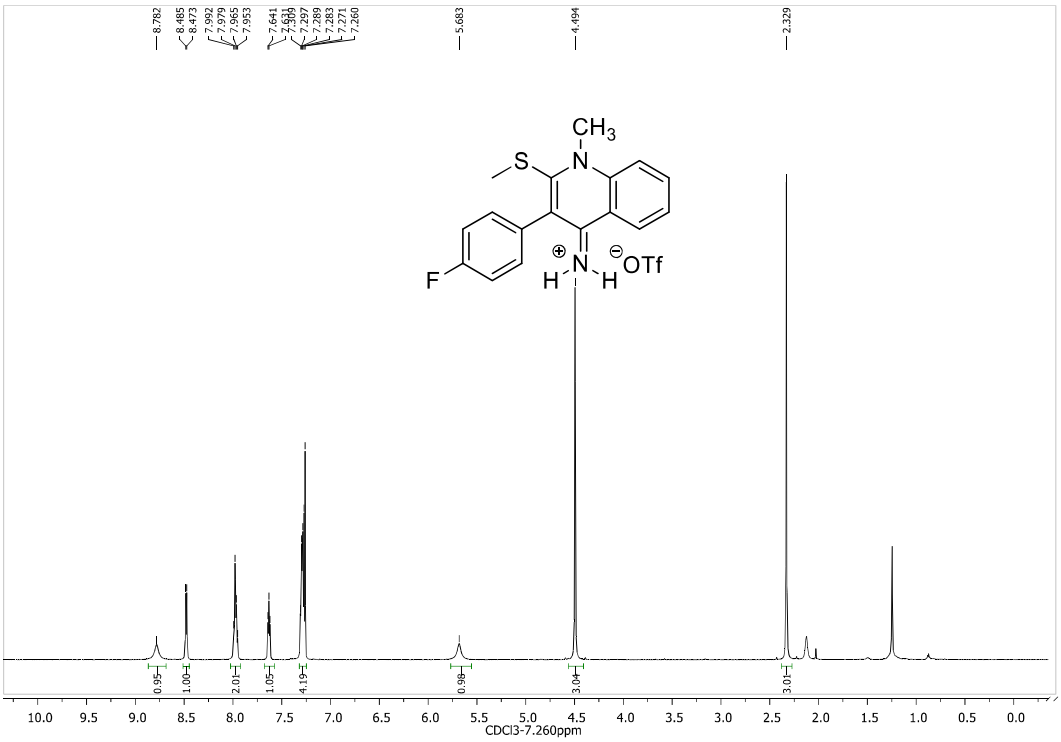


Figure 4.26a: ^{1}H NMR spectrum of **56g**

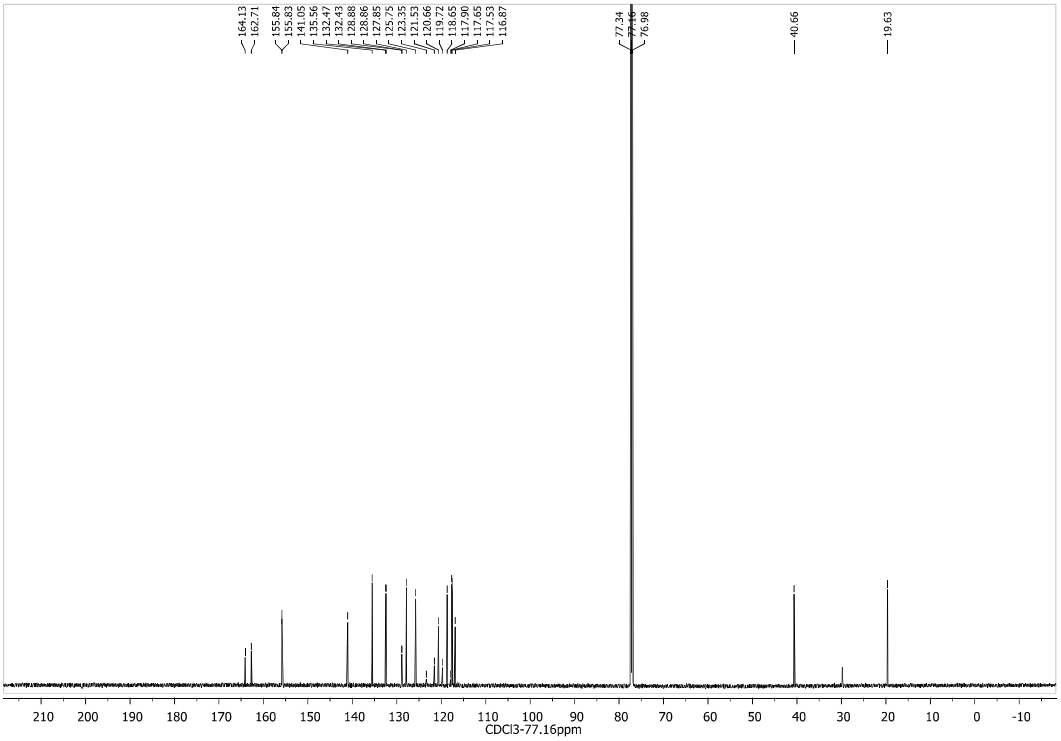


Figure 4.26b: ^{13}C NMR spectrum of **56g**

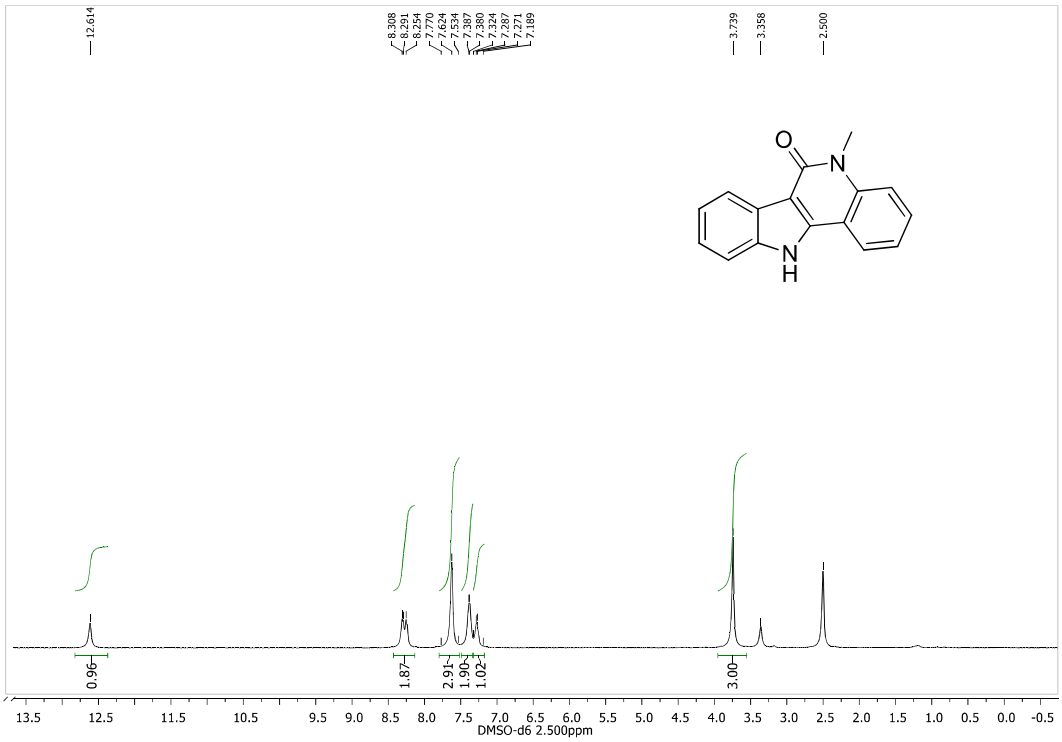


Figure 4.27a: ^{1}H NMR spectrum of **9a**

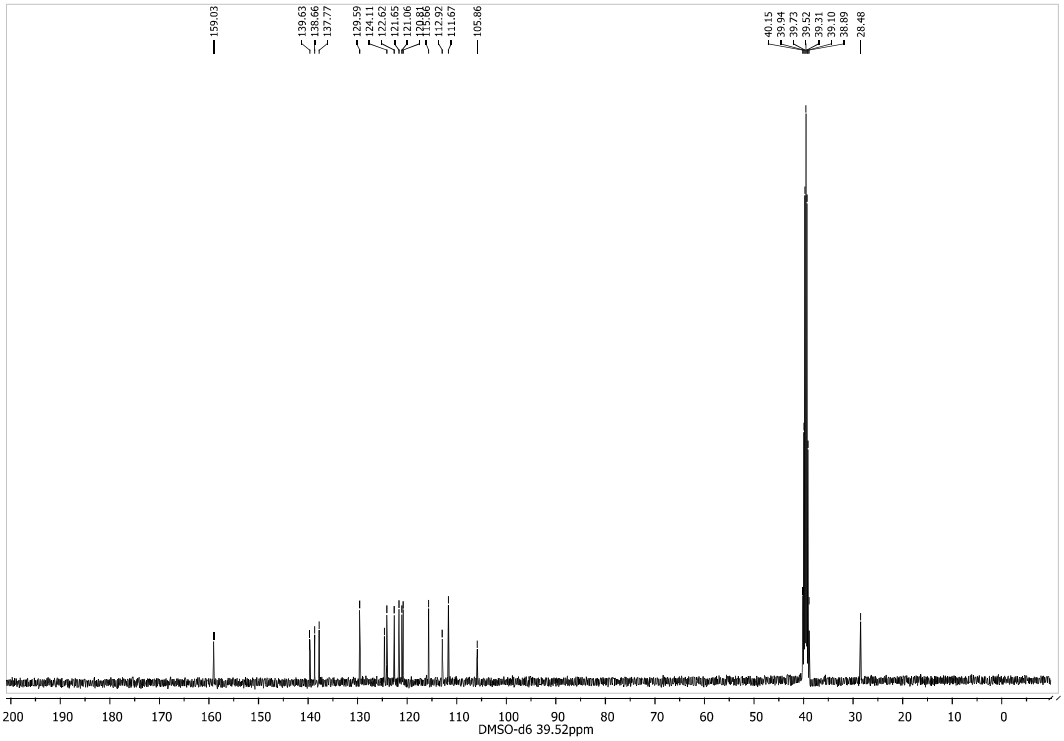


Figure 4.27b: ^{13}C NMR spectrum of **9a**

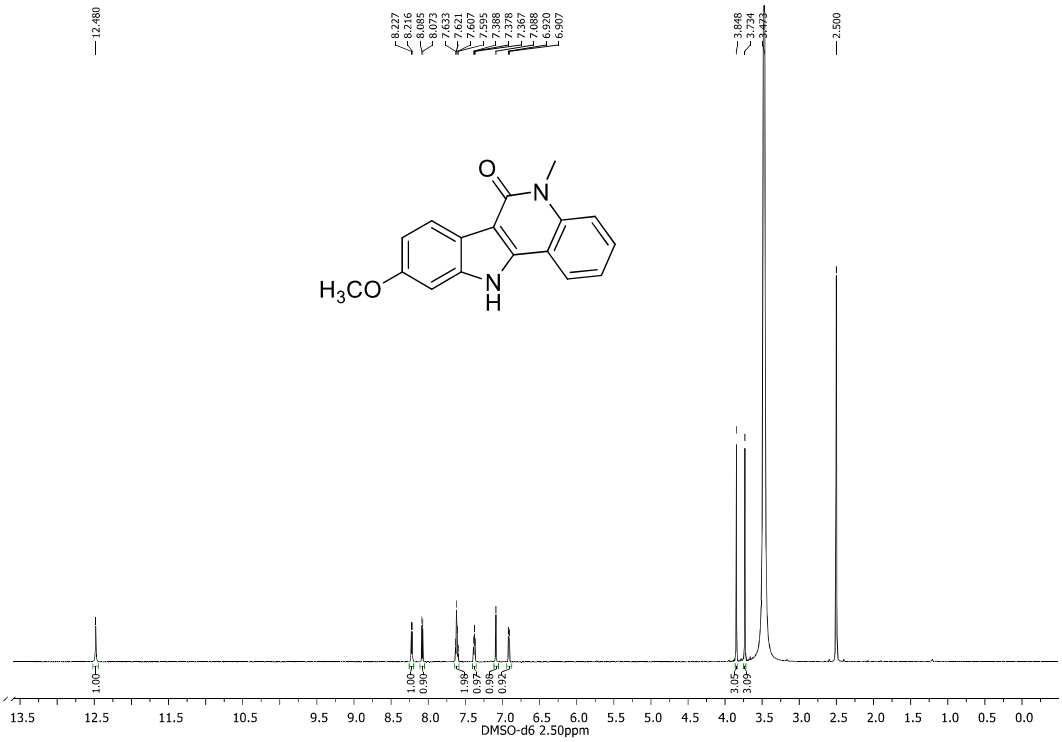


Figure 4.28a: ^{1}H NMR spectrum of **9b**

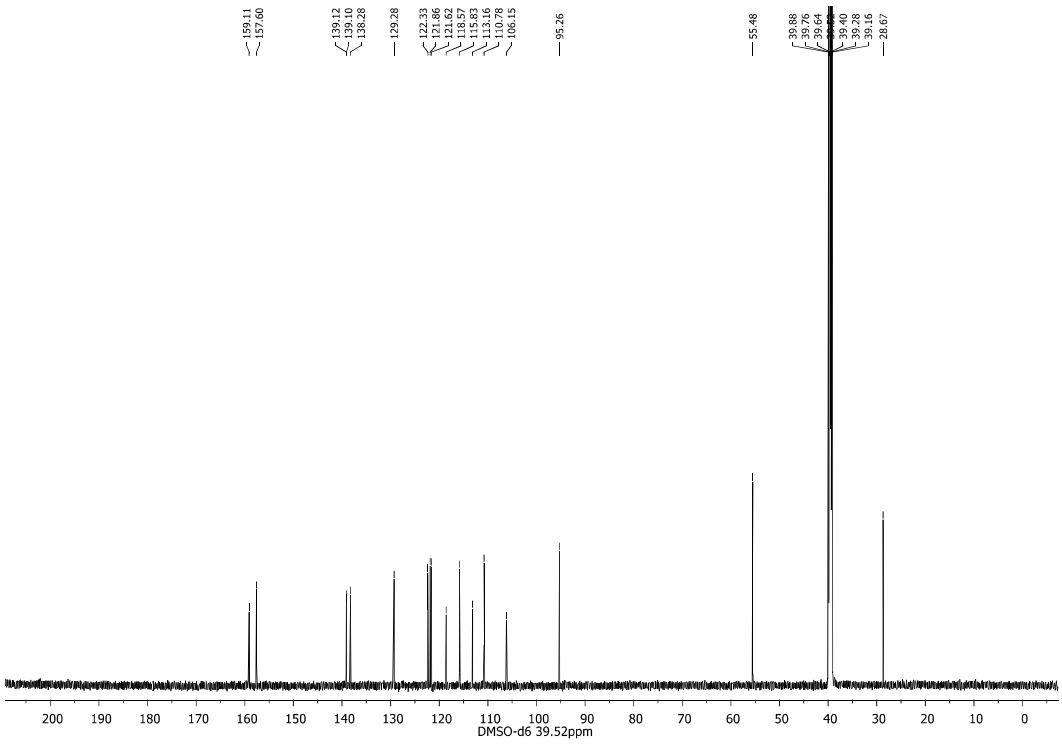


Figure 4.28b: ^{13}C NMR spectrum of **9b**

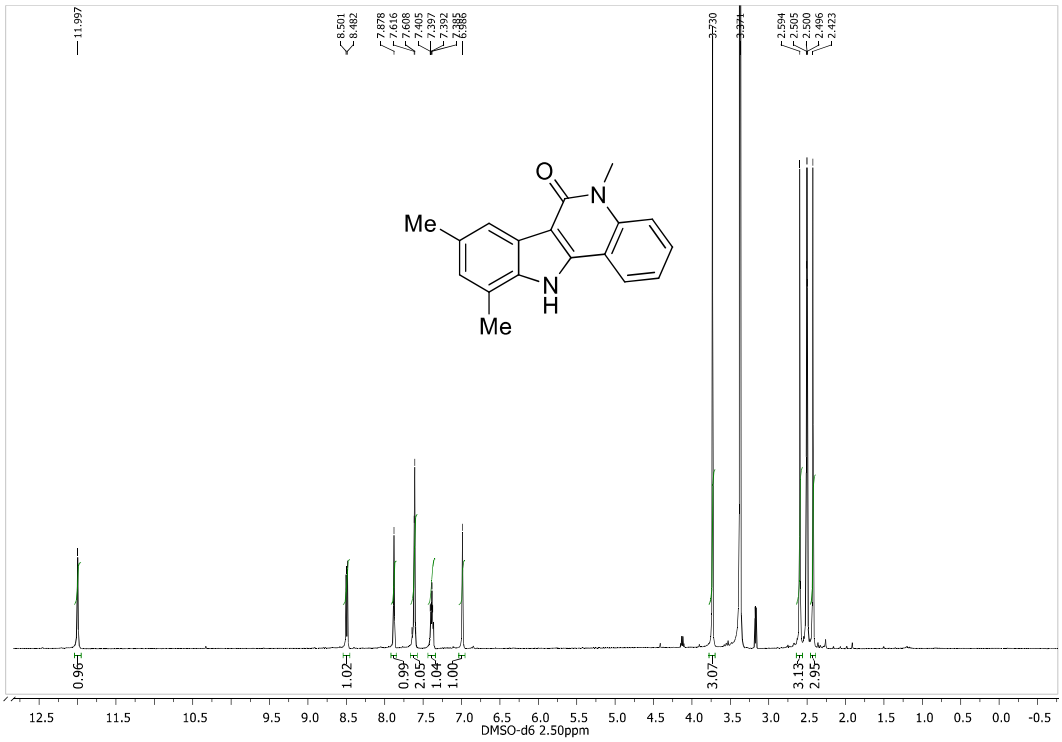


Figure 4.29a: ^{1}H NMR spectrum of **9e**

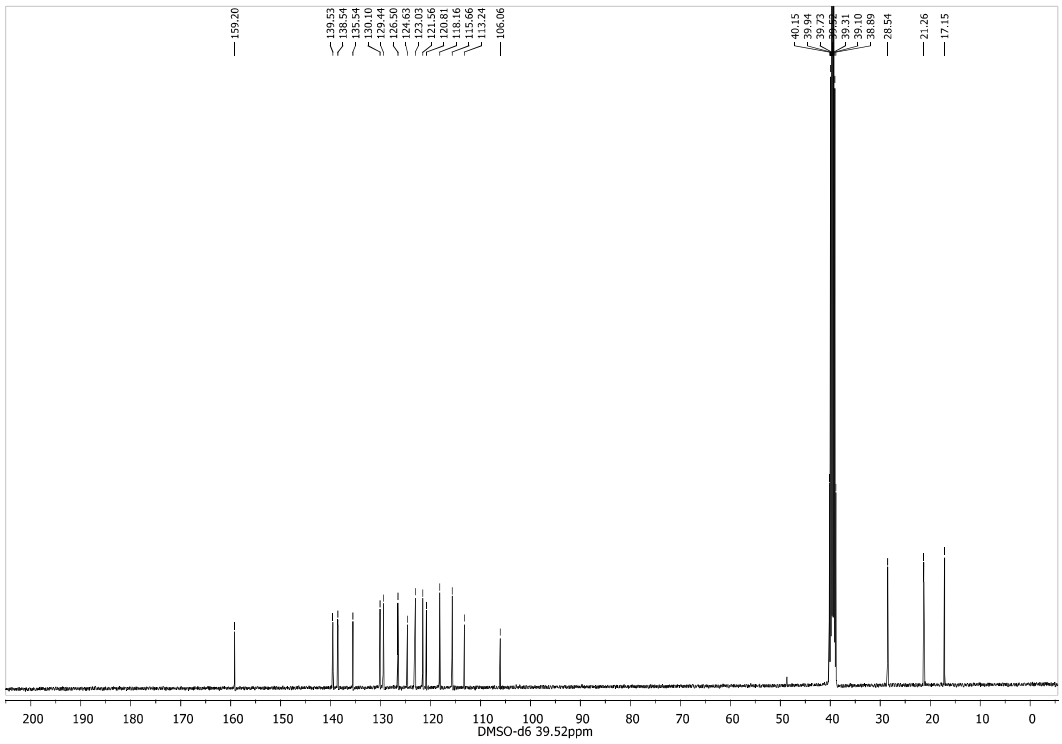


Figure 4.29b: ^{13}C NMR spectrum of **9e**

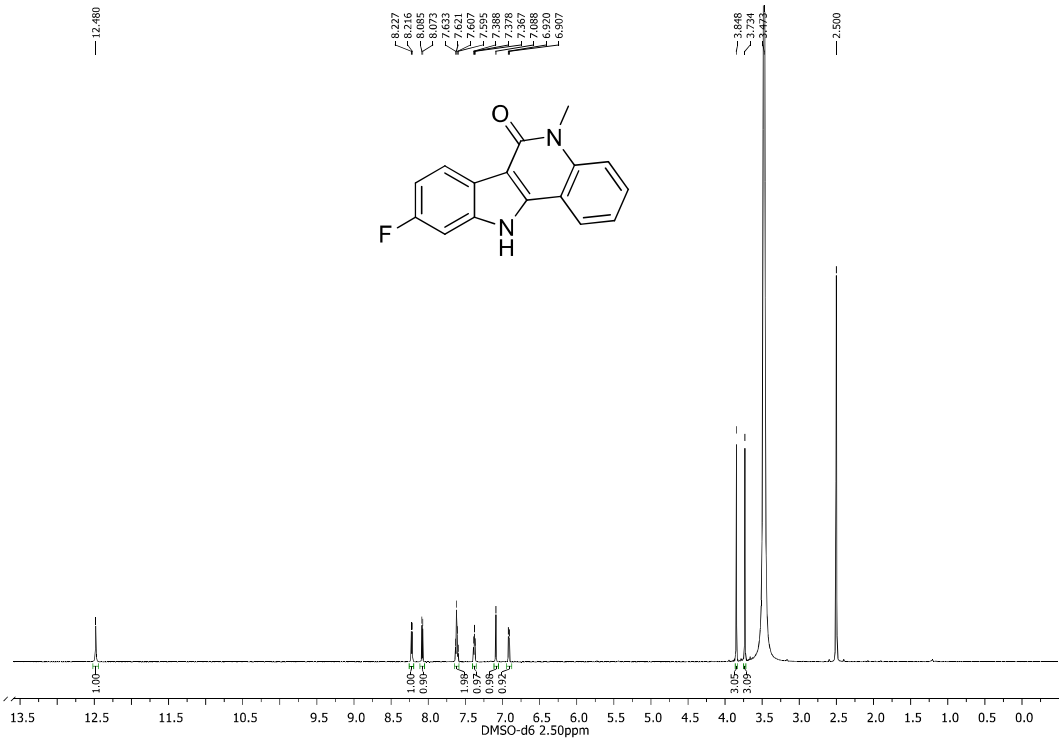


Figure 4.30a: ^{1}H NMR spectrum of **9g**

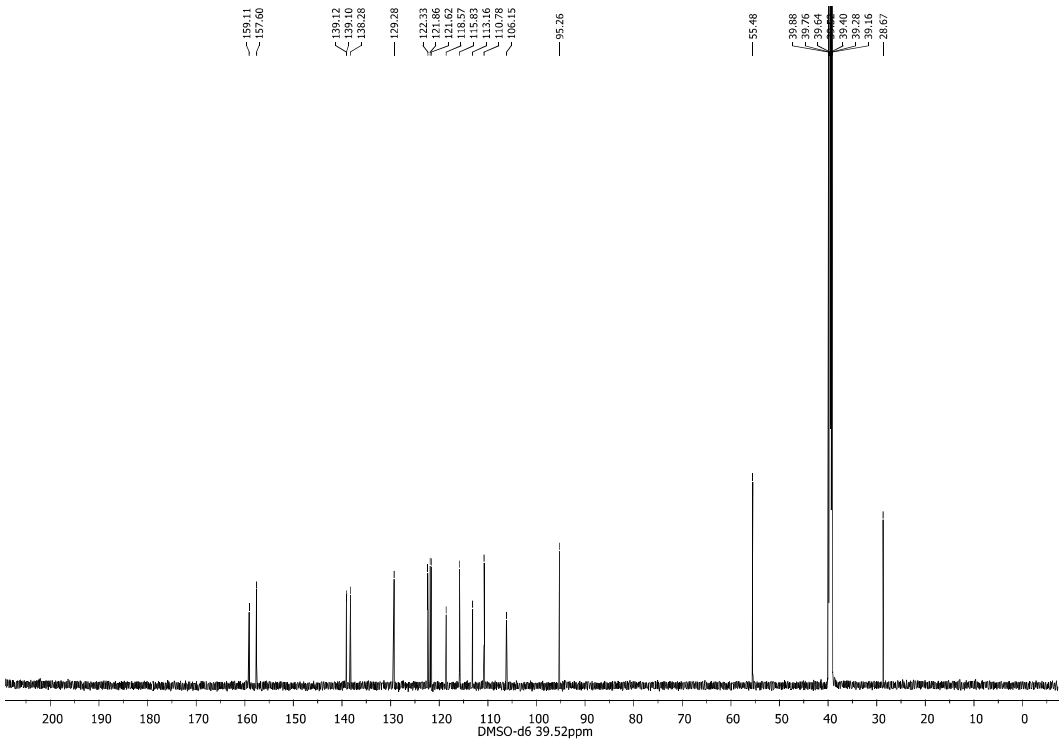


Figure 4.30b: ^{13}C NMR spectrum of **9g**

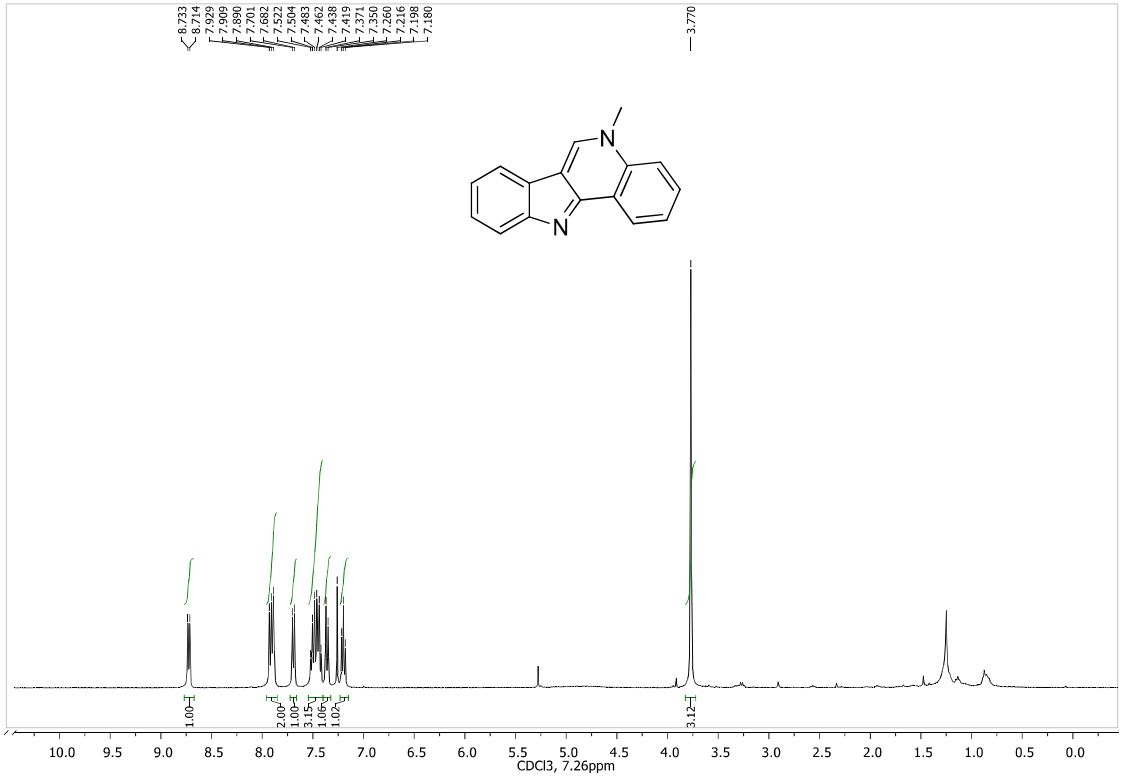


Figure 4.32a: ^{1}H NMR spectrum of **10**

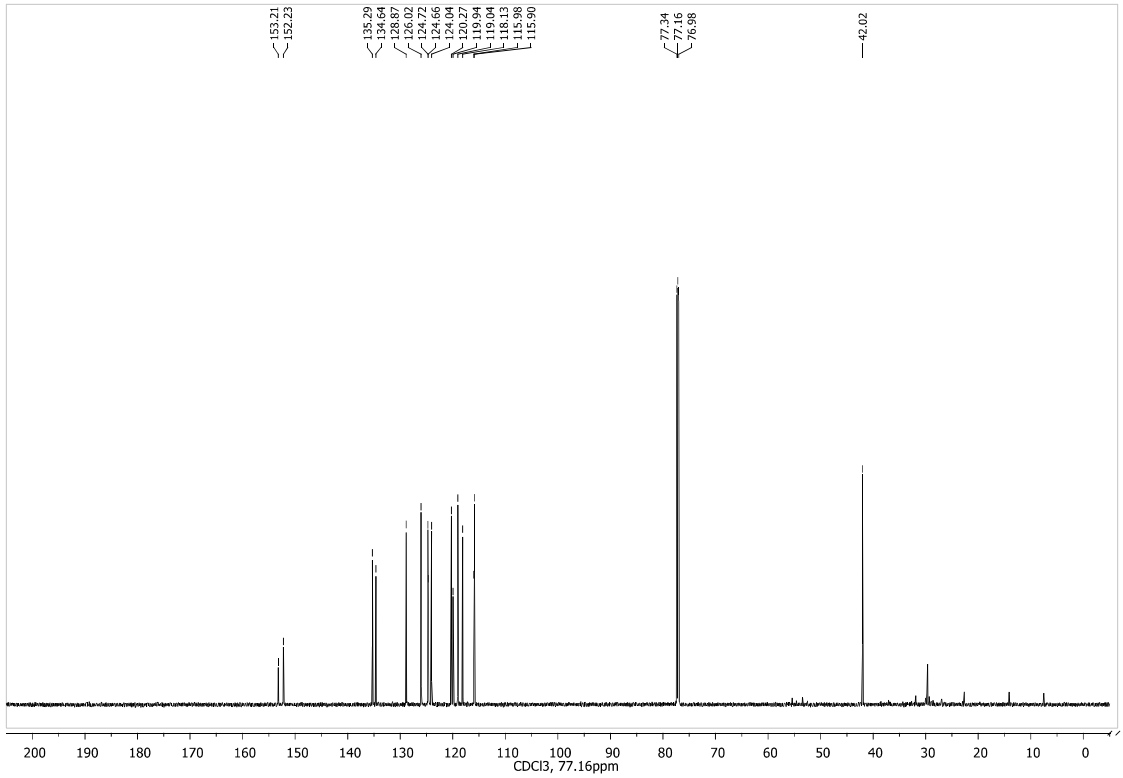


Figure 4.32b: ^{13}C NMR spectrum of **10**

4.7 Crystal Data:

4.7.1 Crystallographic data of **56a** in CH_2Cl_2/n-hexane: $C_{18}H_{17}N_2O_3F_3S_2$, Mw = 430.46, monoclinic, space group P21/c, a = 13.4672(6) Å, b = 10.8955(4) Å, c = 13.1879(6) Å, α = 90 °, β = 98.344(3) °, γ = 90 °, V = 1914.60(14) Å^3, Z = 4, D_{calc} = 1.493 g/cm^3, T = 296(2) K, R_1 = 0.0515 {I>=2σ (I)}, wR_2 = 0.1050, GOF = 0.952.

4.7.2 Crystallographic data of **9f** in CH_2Cl_2/n-hexane: $C_{24}H_{28}N_2OCl_{0.33}$, Mw = 372.30, monoclinic, space group P21/m, a = 12.5945(7) Å, b = 7.2401(3) Å, c = 14.7652(10) Å, α = 90 °, β = 115.160(7) °, γ = 90 °, V = 1218.63(14) Å^3, Z = 3, D_{calc} = 1.522 g/cm^3, T = 297.8(5) K, R_1 = 0.0756 {I>=2σ (I)}, wR_2 = 0.2384, GOF = 1.094.

4.8 References

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