Design and Development of Benzo Fused Heterocycles via C–H/C–Br Bond Functionalization

BY

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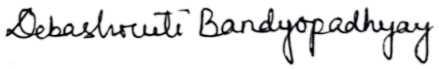
DECLARATION

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.



DEBASHRUTI BANDYOPADHYAY

List of Publications

a. <u>Published</u>

[#]1. Nickel catalyzed site selective C─H functionalization of α-aryl-thioanilides. **Debashruti Bandyopadhyay**[$], Annaram Thirupathi[$], Nagsen M Dhage, Nirmala Mohanta, S. Peruncheralathan*, *Org. Biomol. Chem.*, **2018**, *16*, 6405 – 6409. ($ Represents equal contribution)

[#]2. Triflic acid-mediated *N*-heteroannulation of *β*-anilino-*β*-(methylthio)acrylonitriles: A facile synthesis of 4-amino-2-(methylthio)quinolines. **Debashruti Bandyopadhyay**, Annaram Thirupathi, Divya Radhakrishnan, Adyasha Panigrahi, and S. Peruncheralathan* ***Org. Biomol. Chem.***, 2021, **19**, 8544 – 8553.

b. <u>Communicated:</u>

3. Metal-free ring-opening of 5-amino-1,4-diaryl-1*H*-pyrazoles: A facile access to 2-aryl-3-arylazo acrylonitriles. Arpita Chatterjee, Divya Radhakrishnan, **Debashruti Bandyopadhyay**, Selvaraj Kanchithalaivan and S. Peruncheralathan* (Submitted)

c. <u>Manuscript under preparation:</u>

[#]4. Copper mediated *N*-arylation of 5-aminotriazoles: Synthesis of triazolo fused indoles. **Debashruti Bandyopadhyay**, Syed Ramizul Kabir, Divya Radhakrishnan, Arpita Chatterjee, A. C. Murali, V. Krishnan and S. Peruncheralathan* (Manuscript under preparation)

5. Nitrile controlled *S*-arylation of Thioanilides: Benzothiophene vs benzothiazole. Annaram Thirupathi, Manojkumar Janni, Divya Radhakrishnan, **Debashruti Bandyopadhyay**, Shubhashree Pani, Nishant Sharma, U. Lourderaj, S. Peruncheralathan* (Manuscript under preparation)

[#]6. C─H Bond functionalization of 2-amino-3-aryl quinoline and its derivatives: A facile route

to natural product analogues. **Debashruti Bandyopadhyay**, Annaram Thirupathi, Anwesha Bhattacharya, Parvathy Anupkumar and S. Peruncheralathan* (Manuscript under preparation)

Conferences Attended

1. Poster (*Iodine Mediated Chemoselective C─H Functionalisation: Benzo fused Thiophene vs Thiazole*) presented in **IINCM-2017** (Inter IISER and NISER Chemistry Meet) held on (22 – 24)th December 2017, **NISER Bhubaneswar**, Odisha, India.
2. Poster (*Nickel Catalyzed Site Selective C─H Functionalization of α-Aryl-thioacetanilides: Synthesis of 2-Aminobenzo[b]thiophenes*) presented in **ACS on Campus** held on 23rd July 2018, **NISER Bhubaneswar**, Odisha, India.
3. Poster (*C─H bond functionalization 2-amino-3-aryl-pyridine and its derivative: A facile route to natural product analogues*) presented in International Conference on "Chemical and Biological Science in Drug Discovery-2019" (**IC-CBSDD-2019**) held on (08 – 10)th March 2019, PG Department of Chemistry, **Berhampur University**, Odisha, India.
4. Oral presentation (*N-Arylation of 5-Amino-4-aryl/(2-bromoaryl)triazoles: Synthesis of Triazolo[5,4-b]indoles and α-Oxo-amidines*) given in **56th Annual Convention of Chemists 2019 and International Conference on Recent Trends in Chemical Sciences** held on (14 – 16)th November 2019, School of Studies in Chemistry, **Pt. Ravishankar Shukla University**, Raipur, India.
5. Participated in **National Bioorganic Chemistry Conference (NBCC)** held on (22 – 24)th December 2018, **NISER Bhubaneswar**, Odisha, India.
6. Participated in **Royal Society of Chemistry Publishing Workshop** held on 23rd September 2016, **NISER Bhubaneswar**, Odisha, India.

7. Participated in **XI-JNOST** Conference for Research Scholars (**J-NOST**) held on (14 – 17)th December 2015, **NISER Bhubaneswar**, Odisha, India.

Debashruti Bandyopadhyay

DEBASHRUTI BANDYOPADHYAY

Dedicated

To

My Parents & My Husband

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Debashruti Bandyopadhyay

DEBASHRUTI BANDYOPADHYAY

CONTENTS

Chapter 3: New Strategy to Synthesize Indolo fused Heterocycles: A Facile Route to Natural Product Analogues

Homi Bhabha National Institute

SYNOPSIS OF Ph. D. THESIS

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2.	**Name of the Constituent Institution:**	National Institute of Science Education and Research (NISER) Bhubaneswar
3.	**Enrolment No. :**	CHEM11201504012
4.	**Title of the Thesis:**	Design and Development of Benzo Fused Heterocycles via C─H/C─Br Bond Functionalization
5.	**Board of Studies:**	School of Chemical Sciences

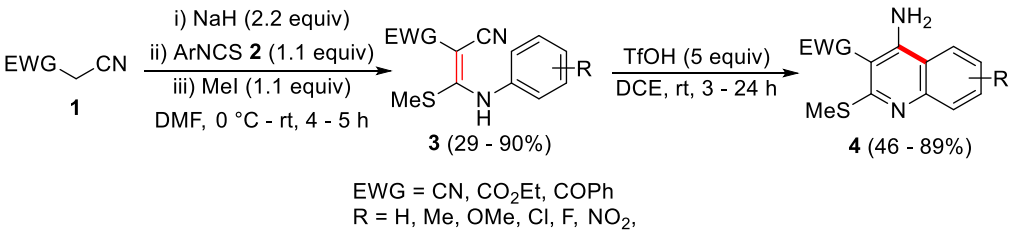
SYNOPSIS

The thesis has been divided into four chapters.

The **first chapter** deals with the general introduction of benzo fused heterocycles and their applications. A brief literature survey of the synthetic methods is described.

The **second chapter** of the thesis discusses the synthesis of functionalized 4-aminoquinolines via the *N*-heteroannulation process. The 4-aminoquinoline core is a privileged class of heterocyclic compounds used in various therapeutic applications such as treating Alzheimer's disease, human immunodeficiency virus, malaria, and others. Owing importance of heterocyclic compounds, several methods have been developed. Despite good yields, these methods suffer from harsh reaction conditions, the use of expensive metal catalysts, quinolines as precursors, and long reaction times. Hence, we designed a simple method to overcome the existing limitations.

Thus, we have demonstrated that triflic acid can effectively activate the nitrile group of *β*-anilino acrylonitrile followed by intramolecular trapping of anilino moiety yielding 4-aminoquinolines in good to excellent yields. The synthetic precursor *α*-substituted-*β*-anilino acrylonitriles were employed for the *N*-heteroannulation process. The compound **3** was prepared in two steps by reacting the anion of *α*-substituted acetonitriles **1** with aryl isothiocyanates **2**, followed by methylation (Scheme 1). Initial experiments were performed with various protic acids for the activation of the nitrile group. We found that TfOH (5 equiv) effectively activates the nitrile group, and protonated species is smoothly trapped by anilino moiety yielding the desired 4-aminoquinoline **4** in 55% yields. This *N*-heteroannulation process is further optimized with different reaction conditions. We found that in $C_2H_4Cl_2$, the yield of 4-aminoquinoline **4** is increased to 89%. We also observed that thiomethyl group is essential for the *N*-heteroannulation process. We screened a series of *β*-substituted anilino derivatives of acrylonitriles **3**. Generally, methyl and chloro derivatives **3** are effective in the *N*-heteroannulation process affording 4-aminoquinolines **4** in very good to excellent yields. Further, keto and ester groups are tolerant under the optimized conditions yielding 3-keto, and 3-ester substituted 4-aminoquinolines **4** in moderate yields. The present method does not apply to deactivated anilino derivatives **3**. Besides, the 4-methoxy derivative **3** gave a demethylated product of *β*-anilino acrylonitrile **3** (Scheme 1).



Scheme 1. *Synthesis of 4-aminoquinolines from α-substituted-β-anilino acrylonitriles*

The meta substituted substrates **3** were observed to give mixtures of regioisomers. The 3-OMe and 3-Me *β*-anilino acrylonitriles **3** afforded the 4-amino-3-arylquinolines **4** in very good yield with a mixture of C5 : C7 regioisomers. However, in case of 3-Cl substituted substrate **3**, we observed only one isomer of 4-aminoquinoline **4** (Scheme 1). This trend can further be explained by H-

bonding interaction (Figure 1).

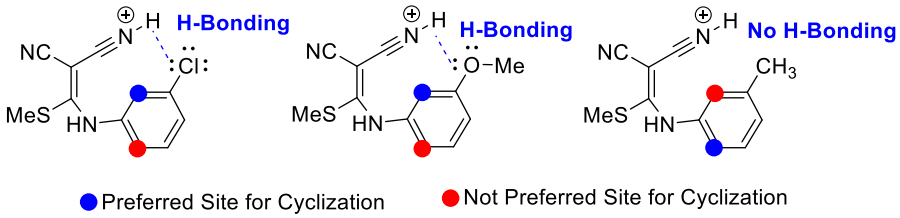
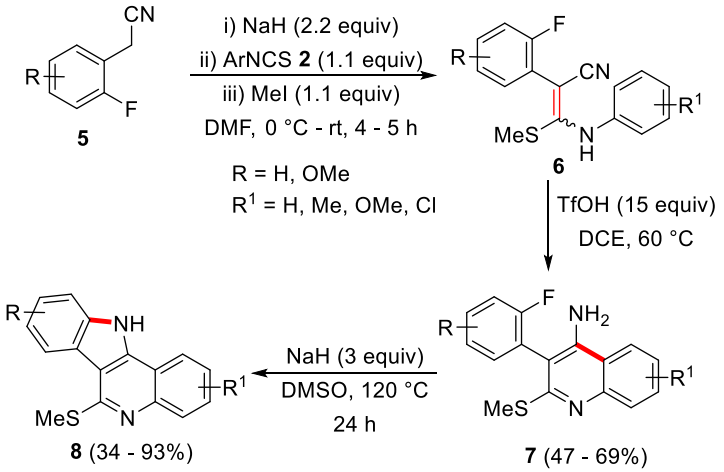


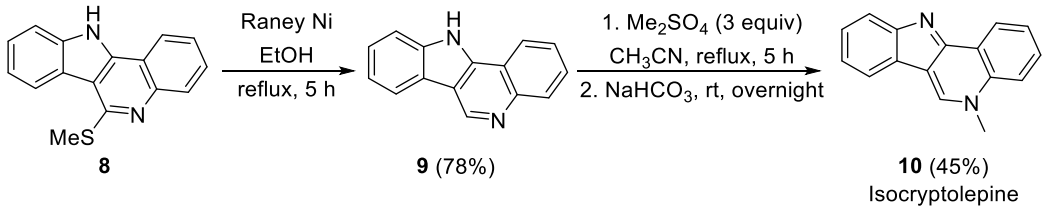
Figure 1. *H-Bonding interaction of protonated species of β-anilinoacrylonitriles*

The **third chapter** deals with the intramolecular *N*-arylation of aminoheterocycles, leading to the synthesis of indolo fused heterocycles. Indolo fused heterocycles are prominent cores because of their extensive pharmaceutical importance and are found in various natural products. Till now, several methods have been reported for the synthesis of indolo fused heterocycles. These methods involve either heterocycles or indole as a precursor. Acyclic precursors are rarely employed for these heterocyclic syntheses. Hence, we designed a general method for the synthesis of indolo fused heterocycles from a simple and easily accessible acyclic precursor. We adopted *N*-arylation and *N*-heteroannulation of substituted benzyl cyanides, aryl isothiocyanates, 2-amino benzaldehydes, and azides via metal and metal-free reaction conditions for the synthesis of indolo fused heterocycles. This chapter is further sub-divided into three chapters. C**hapter 3A** deals with the synthesis of indolo[3,2-*c*]quinoline through base mediated *N*-arylation of 4-amino-3-arylquinolines. The 4-amino-3-arylquinolines **7** were prepared by TfOH mediated *N*-heteroannulation of *α*-aryl-*β*-anilinoacrylonitriles **6** in two steps (Scheme 2). The *N*-heteroannulation of *β*-anilinoacrylonitrile **6**



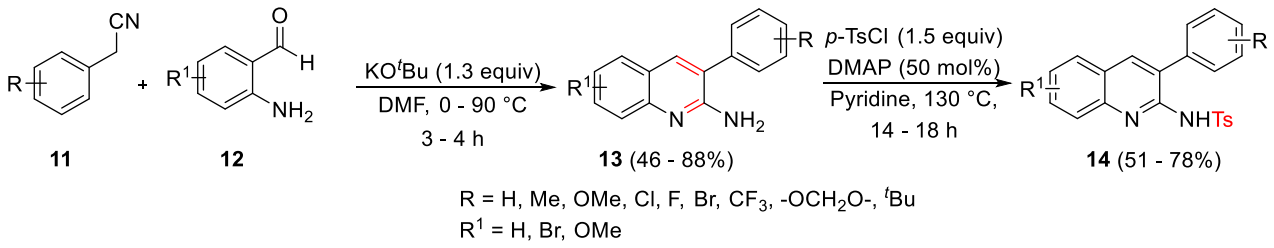
Scheme 2. *Synthesis of indolo[3,2-c]quinolines via S_NAr reaction*

required higher temperature, 60 °C. Various bases were examined for *N*-arylation of 4-amino-3-arylquinolines **7**. We found that NaH is an effective base for this transformation. Several 4-amino-3-arylquinolines **7** were transformed to indolo[3,2-*c*]quinolines **8** (Scheme 2). One of the indolo[3,2-*c*]quinolines **8** was converted into natural product isocryptolepine **10** by desulphurization and methylation (Scheme 3).



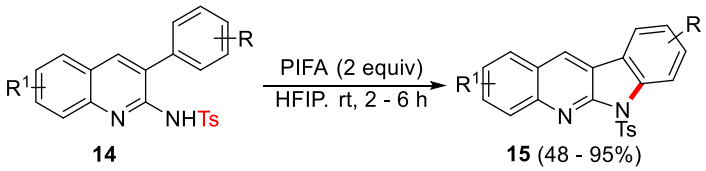
Scheme 3. *Synthesis of isocryptolepine*

C**hapter 3B** discusses the synthesis of indolo[2,3-*b*]quinoline through hypervalent iodine mediated *N*-arylation of 2-amino-3-arylquinolines. The 2-amino-3-arylquinolines **13** were synthesized by cyclocondensation of 2-amino benzaldehyde **12** and aryl acetonitriles **11**. This reaction proceeds via aldol condensation followed by intramolecular amine addition to the nitrile group (Scheme 4). The initial experiments were performed with 2-amino-3-phenylquinoline **13** with various oxidants. Our attempts were failed to give the expected indolo[2,3-*b*]quinoline. Next, amino moiety **13** was protected with the tosyl group (Scheme 4).



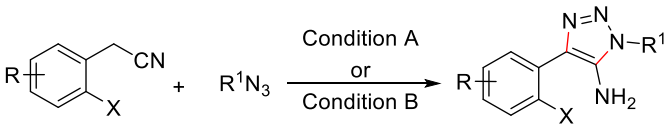
Scheme 4. *Synthesis of N-Ts 2-amino-3-arylquinolines*

The *N*-tosyl protected 2-amino-3-phenylquinoline **14** were exposed to various reaction conditions, and we found that PIFA (2 equiv) in HFIP at room temperature is the best condition affording indolo[2,3-*b*]quinoline **15** in 91% yield. Series of *N*-tosyl protected 2-amino-3-arylquinolines **14** were transformed into indolo[2,3-*b*]quinoline **15** in good to excellent yields (Scheme 5).



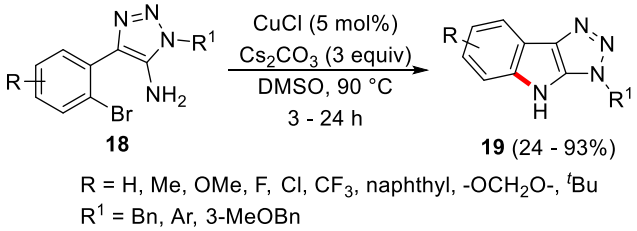
Scheme 5. *Synthesis of indolo[2,3-b]quinolines via PIFA mediated C─H bond functionalization*

C**hapter 3C** deals with the synthesis of triazolo fused indoles via copper-mediated *N*-arylation of 5-amino-4-aryltriazoles. The required 5-amino-4-aryltriazoles **18** were synthesized from cyclocondensation of substituted azides **17** with aryl acetonitriles **16**. We adopted two reaction conditions to synthesize 1*N*-substituted 5-aminotriazoles **18** (Scheme 6).



Scheme 6. *Synthesis of N-substituted 5-aminotriazoles*

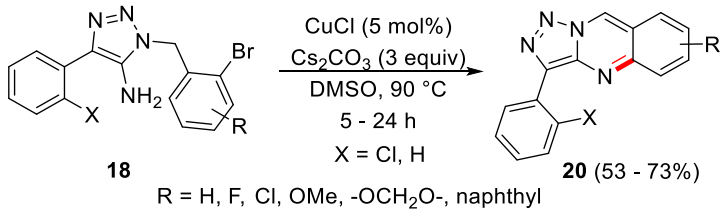
We examined different reactions conditions for the *N*-arylation process by changing bases, salts, and halo precursors. We found that *N*-arylation occurs with 5 mol% of CuCl, yielding 93% of triazolo fused indoles **19**. This condition was applied to other 5-aminotriazoles **18**, affording triazolo fused indoles **19** in moderate to excellent yields (Scheme 7).



Scheme 7. *Synthesis of triazolo fused indoles via copper-mediated N-arylation process*

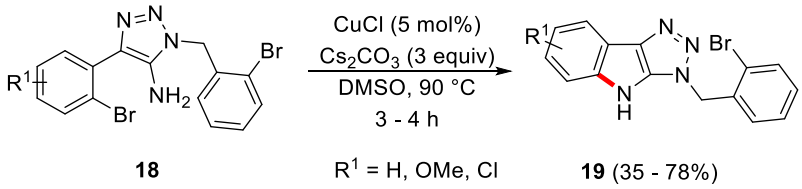
A similar strategy was used to synthesize other classes of heterocyclic compounds. The scope of this method was extended to other 5-aminotriazole derivatives **18** affording triazolo fused quinazolines **20** in good to excellent yields (Scheme 8). We performed photophysical studies with

the newly synthesized compounds.



Scheme 8. *Synthesis of triazolo fused quinazolines via copper-mediated N-arylation process*

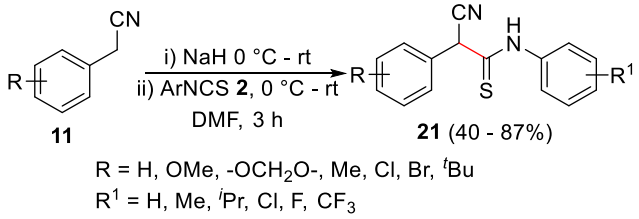
An interesting observation was noticed when diaryl bromo derivatives **18** were examined. The dibromo derivatives **18** gave only triazolo fused indoles **19**. No trace amount of triazolo fused quinazolines **20** were observed, because the *N*-arylation prefers to go through a 6-membered transition state (Scheme 9).



Scheme 9. *Regioselective N-arylation of dibromo substituted 5-aminotriazoles*

The final and **fourth chapter** of the thesis discusses with regioselective C─H bond functionalization of *α*-aryl thioanilides. The *α*-aryl thioanilides has three potential C─H bonds, which can be functionalized through ortho C─H bond functionalization strategies. Further, each type of C─H bond functionalization leads to three different heterocycles: benzothiophenes, benzothiazoles, and indoles. Further, the synthesis of these compounds involves intramolecular cross-coupling reactions, which requires a pre-functionalized starting material. Nickel salts are used to construct carbon-hetero bonds but are rarely employed in the synthesis of heterocyclic compounds. In particular, *S*-heterocycles are not reported with nickel mediated cyclization conditions. In this chapter, we studied a systematic investigation of nickel catalyzed C─H bond functionalization of α-aryl thioanilides.

Various *α*-aryl thioanilides **21** were prepared by reaction of aryl acetonitriles **11** with aryl isothiocyanates **2** (Scheme 10).

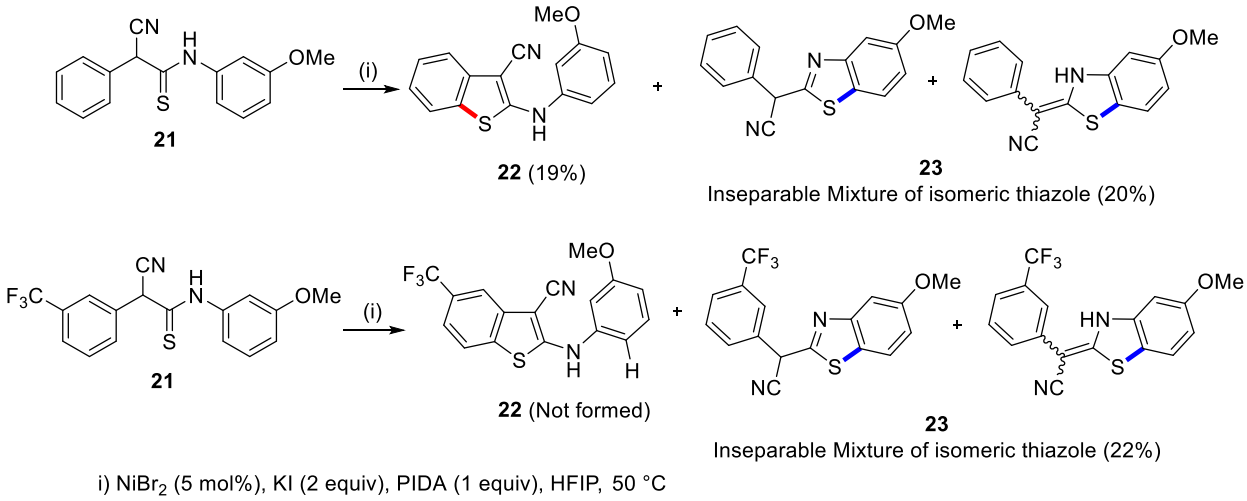


Scheme 10. *Synthesis of α-aryl thioanilides*

The electron-rich *α*-phenyl thioanilide **21** was chosen as the model substrate and was exposed to a wide range of reaction conditions. After screening several reaction conditions, we found that 2 mol% of $NiBr_2$, 2 equiv of KI, 1 equiv of PIDA in HFIP at 50 °C is the best condition for the selective C─H bond functionalization of *α*-phenyl thioanilides **21**, affording 2-aminobenzo[*b*]thiophene **22** in 62% yield, as the sole product. The various substituted *α*-aryl thioanilides **21** were smoothly transformed into 2-aminobenzo[*b*]thiophene **22** in moderate to good yields under the optimized reaction conditions (Scheme 11).

Scheme 11. *Synthesis of benzo[b]thiophenes via C─H bond functionalization*

Further to understand the regioselective C─H bond functionalization, we have chosen a set of experimental conditions and found that radical is not involved in this reaction. In addition, electronic factor influences this reaction (Scheme 12).



Scheme 12. *Role of electronic factor in C─H bond functionalization*

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List of Schemes

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List of Abbreviations

Ac	Acetyl
AcOH	Acetic acid
Ad_2PBu	Di-(1-adamantyl)-*n*-butyl phosphine
Anhyd	Anhydrous
Ar	Aryl
BINOL	1,1′- Binaphthyl-2,2′-diol
Bn	Benzyl
Bz	Benzoyl
cPr	Cyclopropyl
Cp	Cyclopentyl
CAN	Cerium ammonium nitrate
DCM	Dichloromethane
DCE	Dichloroethane
DMAP	4-(Dimethylamino)pyridine
DMA	N,N'-Dimethylacetamide
dppp	1,3-Bis(diphenylphosphino)propane
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DpePhos	Bis[(2-diphenylphosphino)phenyl] ether
Equiv	Equivalence
Et	Ethyl
EWG	Electron withdrawing group

h	hours
Het	Heterocycle
(Het)Ar	Heteroaryl
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
^{i}Bu	Iso butyl
^{i}Pr	Iso propyl
KI	Potassium iodide
*m*CPBA	Meta-Chloroperoxybenzoic acid
Me	Methyl
MW	Microwave
NHC	*N*-Heterocyclic carbene
OMe	Methoxy
1,10-Phen	1,10-Phenanthroline
PIDA	(Diacetoxyiodo)benzene
PIFA	(Bis(trifluoroacetoxy)iodo)benzene
PTSA	Para Toluenesulphonic acid
Ph	Phenyl
Py	Pyridine
rt	Room temperature
S_NAr	Aromatic Substitution reaction
SET	Single electron transfer
Ts	Tosyl
Tert.	Tertiary
^{t}Bu	Tertiary butyl
TBAI	Tetra butyl ammonium iodide

TfOH	Triflic acid
TFA	Trifluoro acetic acid
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
TBHP	Tertiary butyl hydroperoxide
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TLC	Thin layer chromatography
W	Watt
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

General Introduction for the Synthesis of Various Benzo Fused Heterocycles

1.1. Introduction

Heterocyclic compounds are an integral part of organic compounds because of its biological properties, and its application in material science, agrochemicals and biomedical sciences.[1] Among these, the benzo fused heterocycles are of utmost interest because of their involvement in the synthesis of drugs, dyes and agrochemicals.[2] For instance, indoles are considered as a vital core of the benzo fused heterocycles due to its extensive biological and medicinal activities, presence in natural products and in optoelectronic materials (Fig. 1.1).[3] Various studies have shown that the indole derivatives are anti-HIV agent, anti-cancer, anti-bacterial, anti-inflammatory agents and are used in chemotherapy and in the treatment of

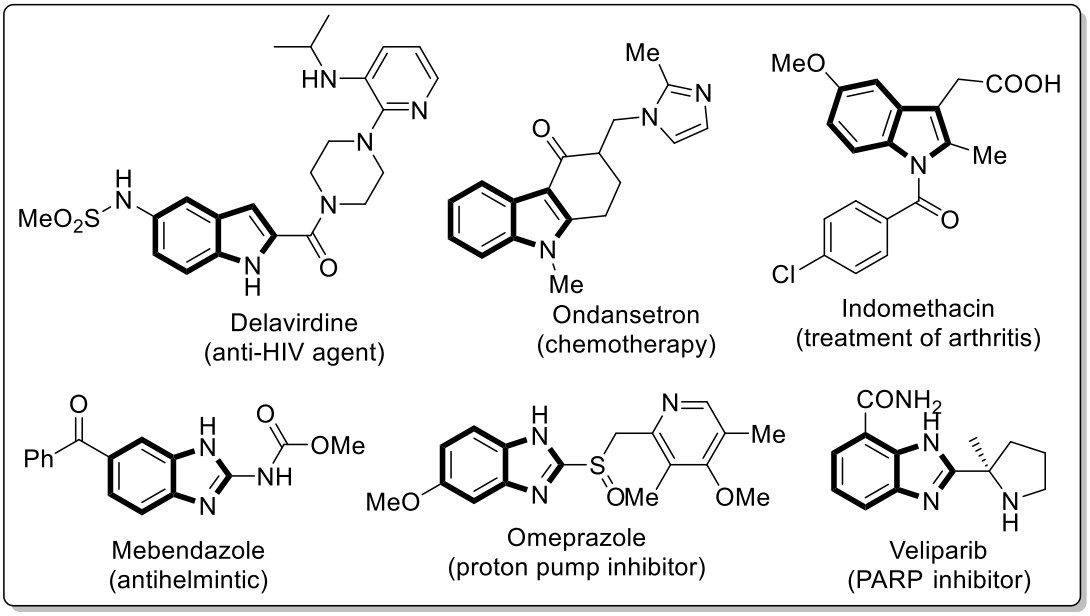


Figure 1.1. *Representation of Biological Applications of N-Heterocycles*

arthritis (Fig. 1.1).[4] Similarly, benzimidazole is also a crucial structural unit in medicinal chemistry and also exhibit some photophysical properties.[5] Mebendazole, having

benzimidazole core, acts as an antihelmintic and thus is used for the treatment of worm infection (Figure 1.1).[5a] Likewise, veliparib, a well-known drug for the treatment of cancer, contains benzimidazole core (Figure 1.1).[5e] Other heterocyclic compounds are also reported having biological activities (Fig. 1.2).[6] Among them, indazole in another nitrogen containing heterocyclic compounds which possess broad applications in pharmaceutical industry.[7] For illustration, these molecules are anti-viral[7c], anti-inflammatory[7d], anti-tubercular agents[7e]. Similarly, benzothiazole, a sulphur and nitrogen containing heterocycle, have engaged the attention of organic chemists because of their enormous functions in the field of pharmaceuticals, and existence in natural products.[8] Heterocyclic compounds like, benzofurans and benzotriazoles are also important units in the field of medicinal chemistry because of their profound chemotherapeutic and physiological properties.[9] Drugs like, Ramelteon[9b], Darifenacin[9c], and Vilazodone[9d], containing benzofuran derivatives, are used for the treatment of insomnia, urinary inconvenience and depression respectively. Similarly, benzotriazoles are also potent antibacterial, antiplasmodial and anti-fungal agents (Figure 1.2).[9e-g]

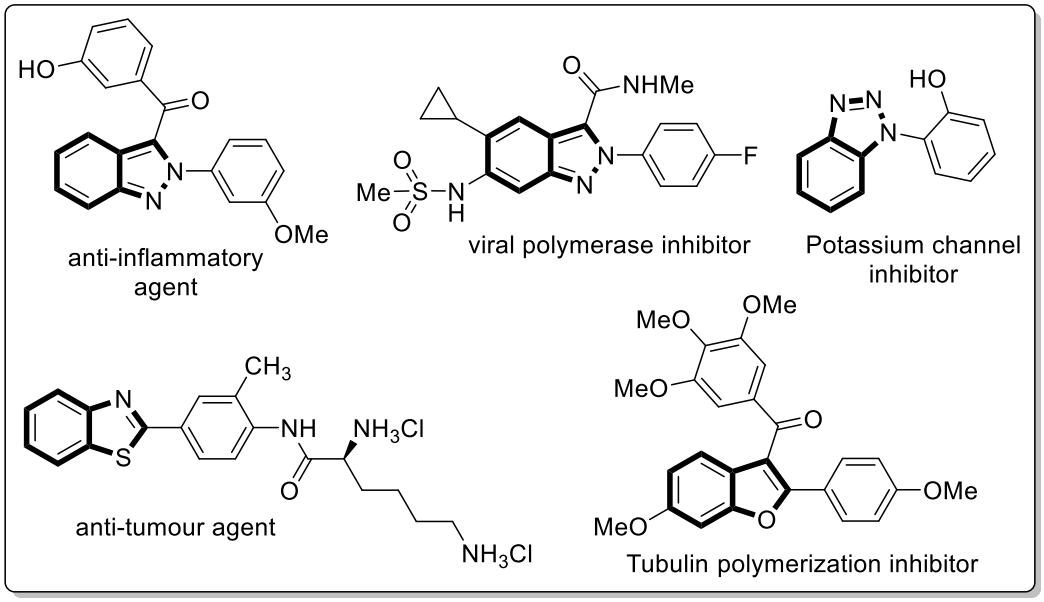


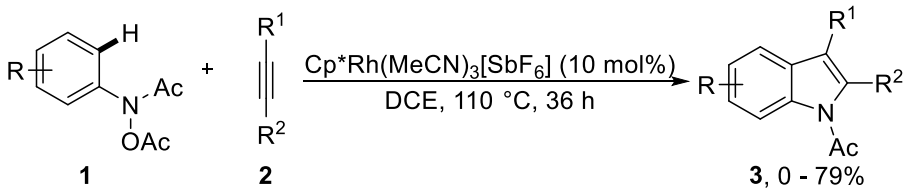
Figure 1.2. *Representation of Biologically Active Heterocycles*

1.2. Previous Reports

As they are crucial scaffolds, their synthesis is also of great importance. In literature, there are several methodologies reported to synthesize various benzo fused heterocycles.[10] They have either been synthesized via C─C, C─N or C─heteroatom bond formation reaction, as these are attractive and powerful tool to synthesize various benzo fused heterocycles.[11] In this section, we have discussed about the selected methodologies to synthesize benzo fused heterocycles.

1.2.1. Synthesis of Indoles

Anbarasan and co-workers established a new methodology for the synthesis of indoles **3**.[12] This methodology involved Rh-catalyzed cyclization of *N*-acetoxyacetanilides **1** along with symmetrical or unsymmetrical alkynes **2**. Various substituted indoles **3** were obtained in moderate to very good yield. They have observed that unsymmetrical alkynes **2** yield regioisomers of indole derivatives **3**. They have further extended their methodology to synthesize pyrrolo[3,2-*f*]indoles and dibenzo[*a*,*c*]carbazoles (Scheme 1.1).

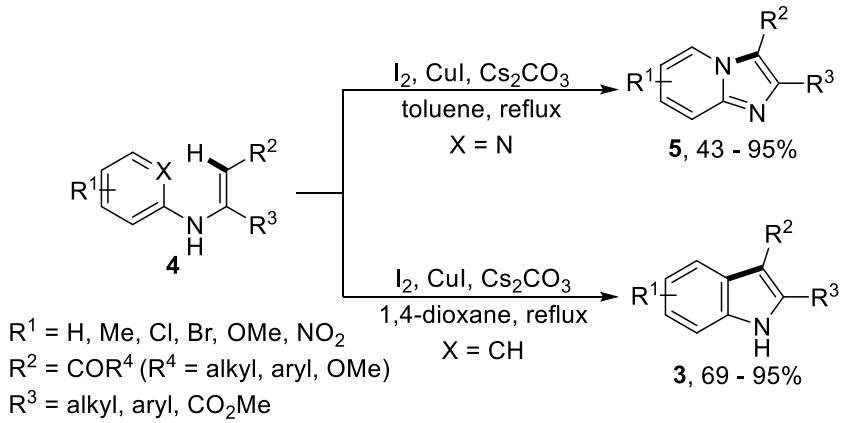


R = H, Me, F, OMe, NMe_2, CH_2OMe, CHO, NHCOMe, CO_2Me, OCOMe
R^1 = Me, Et, Bu, Ph, Ar, Bn,thiophene
R^2 = Me, Et, Bu, Ph, Ar, Bn, thiophene

Scheme 1.1. *Rh-Catalyzed Synthesis of Indoles*

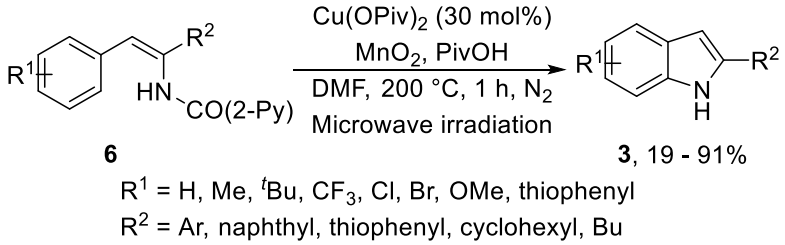
Chang and co-workers have devised a new methodology for the synthesis of indole **3** and imidazo[1,2-*a*]pyridine **5**.[13] This protocol involved I_2/Cu mediated cyclization of enamines **4**. With toluene, they have observed imidazo[1,2-*a*]pyridine and with 1,4-dioxane they

observed indole as the product. Both the products were observed in moderate to excellent yields (Scheme 1.1).



Scheme 1.2. *I_2/Cu-mediated Cyclization of Enamines*

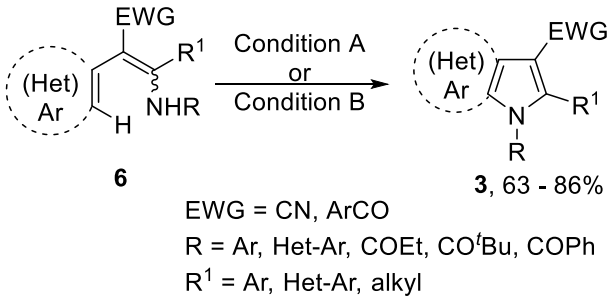
Miura and co-workers studied the synthesis of indoles **3** from enamides **6**.[14] This method proceeds by a divergent way involving $Cu(OPiv)_2$ as the catalyst and MnO_2 as the oxidant. The mechanistic approach indicates that this protocol involved an organometallic pathway followed by an amidyl radical pathway. The series of substituted indoles **3** were isolated in low to excellent yield. They have further synthesized oxazoles (Scheme 1.3).



Scheme 1.3. *Cu-catalyzed Divergent Way for Synthesis of Indoles*

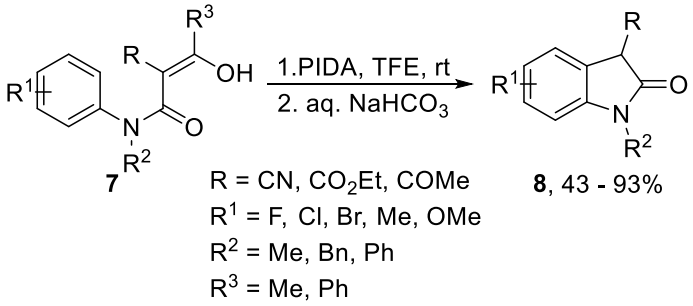
Ila and co-workers have synthesized indoles **3** via intramolecular Pd-catalyzed C─H amination reaction.[15] They have used enaminonitriles **6** as the precursor and employed Pd/Cu catalytic cycle. They have also used another catalytic cyclic involving $Pd(OAc)_2$ and Ag_2CO_3 as the catalysts and PivOH as the additive. They have shown the activation of the aromatic C─H bond by amino group of anilino moiety, acting as a directing group. With both the

conditions they have isolated moderate to excellent yield of the substituted indoles **3**. The enaminonitriles **6** can be synthesized from *β*-(thiomethyl)acrylonitriles via nucleophilic displacement reaction (Scheme 1.4).



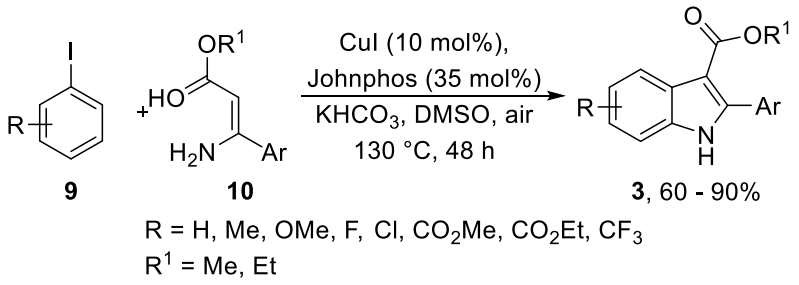
Scheme 1.4. *Synthesis of Substituted Indoles via C─H Amination Reaction*

Zhao and co-workers studied the synthesis of substituted 2-oxindoles **8** under metal free condition.[16] They have employed PIDA for the oxidative cyclization of anilides **7**. They have further shown that the addition of aq. $NaHCO_3$ facilitates the deacylation step and affords the substituted 2-oxindoles **8** in moderate to excellent yield (Scheme 1.5).



Scheme 1.5. *Hypervalent Iodine-mediated sp^2 C─C Bond Formation*

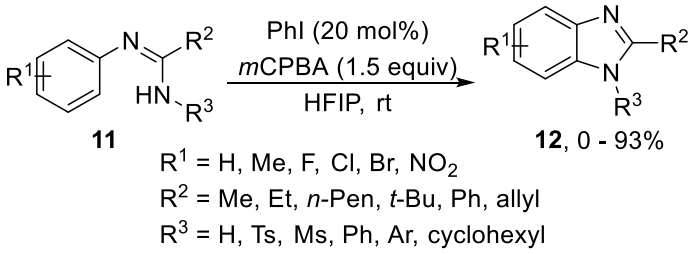
Chen and co-workers devised a one-pot tandem reaction for the synthesis of indoles **3**.[17] This methodology involved two step arylation process. At first, the reaction proceeded through Ullmann type C─N bond formation and then cross-dehydrogenative coupling reaction for the C─C bond formation. The isolated yields of the substituted indoles **3** were ranging from 60 – 90% (Scheme 1.6).



Scheme 1.6. *Synthesis of Indoles via Ullmann and Cross-Dehydrogenative Coupling Reaction*

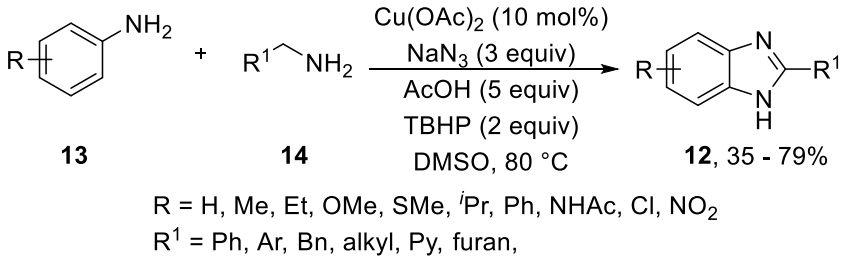
1.2.2. Synthesis of Benzimidazole

The synthesis of benzimidazole **12** via hypervalent iodine mediated cyclization was reported by Punniyamurthy and co-workers.[18] They have employed phenyl iodide as the catalyst and *m*CPBA as the oxidant. This reaction proceeds under ambient temperature. The benzimidazoles **12** were isolated in excellent yields (Scheme 1.7).



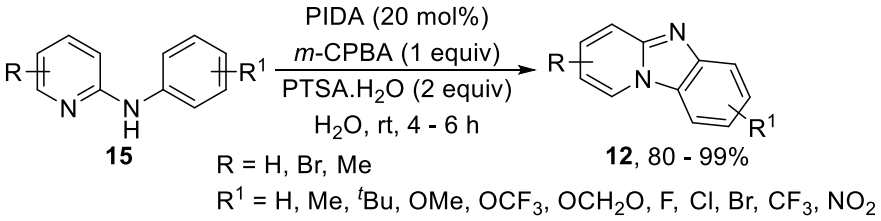
Scheme 1.7. *Synthesis of Substituted Benzimidazoles*

Punniyamurthy and co-workers have further investigated the synthesis of benzimidazole **12** via an oxidative Cu-catalyzed cross-coupling reactions.[19] They employed anilines **13**, primary amines **14** as the precursors and subjected it to oxidative conditions, which involved $Cu(OAc)_2$ as the catalyst, AcOH and TBHP as the additive and oxidant respectively. This method basically followed four main steps – (i) sp^2 and sp^3 C─H bond functionalization, which led to (ii) transamination, followed by (iii) amination by azide, and finally (iv) oxidative cyclization. They have also extended the protocol by using benzyl alcohols and aldehydes instead of primary amines (Scheme 1.8).



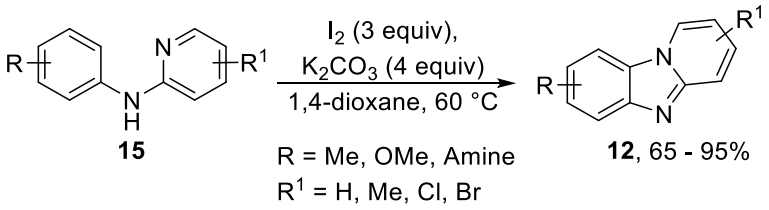
Scheme 1.8. *Oxidative Cu-Catalyzed Cross Coupling Reaction*

Das and co-workers have developed a methodology to synthesize fused benzimidazole derivatives **12** under hypervalent iodine mediated conditions.[20] This methodology involved 2-aminopyridines **15** as the precursors. The hypervalent iodine reagent, PIDA, facilitates the oxidative sp^2 C─H amination reaction and afforded the fused benzimidazoles **12** in excellent yields. The usage of water as the solvent makes this method more greener and environment friendly. The methodology was further expanded for the synthesis of benzimidazo[1,2-*a*]quinolines and benzimidazo[2,1-*a*]isoquinolines (Scheme 1.9).



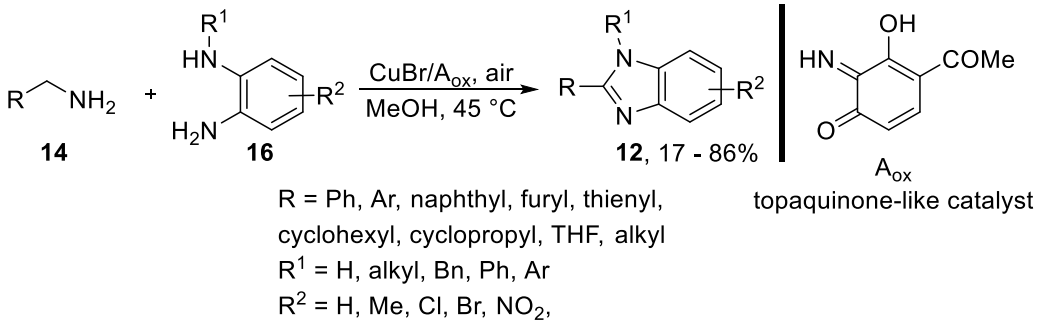
Scheme 1.9. *Hypervalent Iodine-mediated C─H Amination Reaction*

Chang and co-workers have demonstrated the synthesis of benzimidazole **12** and pyrido[1,2-*a*]benzimidazole via molecular iodine mediated amination reaction.[21] Iodine being the oxidant and under the influence of K_2CO_3, they reported 65 – 95% of the pyrido[1,2-*a*]benzimidazoles. They have applied this strategy on substituted *N*-aryl amidines that afforded benzimidazole in moderate yield (Scheme 1.10).



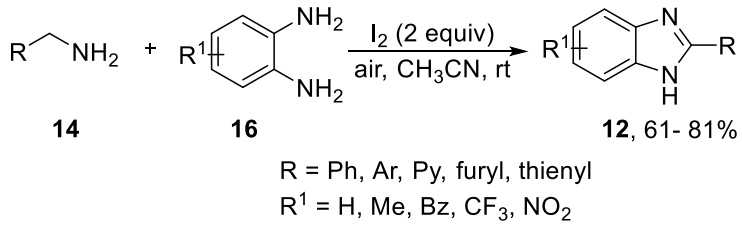
Scheme 1.10. *Molecular Iodine-mediated sp^2 C─H Amination*

Largeron and co-workers have devised a new synthetic procedure to produce substituted benzimidazole derivatives **12** under aerobic conditions.[22] They have used Cu(II)/topaquinone-like molecule as the catalytic couples. The involvement of milder reagents transforms this methodology into a greener approach. The various substituted benzimidazoles **12** were observed in moderate to excellent yields (Scheme 1.11).



Scheme 1.11. *Aerobic Oxidative Cyclization Reaction*

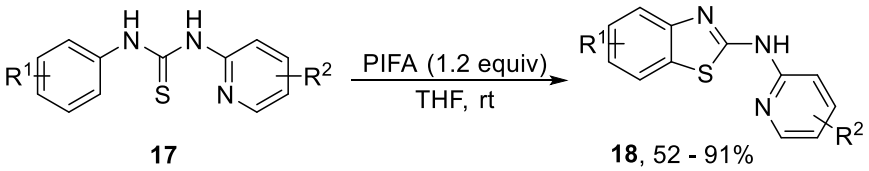
Narender and co-workers have synthesized benzimidazole **12** from primary amines **14** and 1,2-diamines **16** via iodine-mediated aerobic oxidative cyclization.[23] The yields of the isolated benzimidazoles **12** were ranging between 61 – 81% (Scheme 1.12).



Scheme 1.12. *Iodine-mediated C─N Bond Formation Reaction*

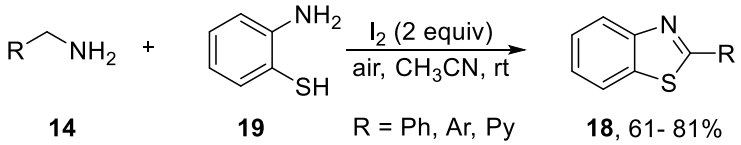
1.2.3. Synthesis of Benzothiazole

Muthusubramanian and co-workers established a new approach to synthesize benzothiazole **18** from *N*-pyridyl thiourea **17** via hypervalent iodine mediated intramolecular C─H thiolation.[24] This approach involved acyclic precursors and can also tolerate with various functional groups. The benzothiazoles **18** were isolated in 52 – 91% (Scheme 1.13).



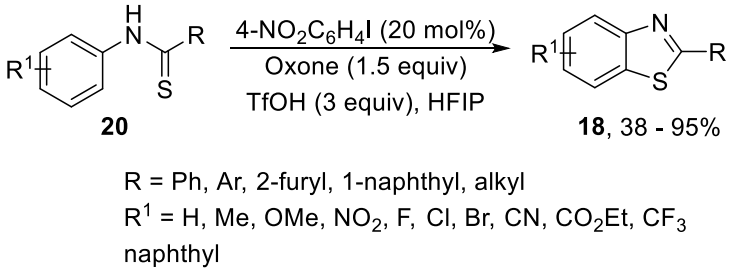
Scheme 1.13. *Synthesis of Benzothiazole via C─H Bond Functionalization*

Narender and co-workers developed the synthesis of thiazole **18** via iodine mediated C─S bond formation. Various primary amines **14** and 2-mercaptoanilines **19** were assigned as the starting materials.[23] They have further synthesized an uncommon product, benzo[*e*][1,2,4]thiadiazines, by switching the solvent to ethyl acetate. The products **18** were observed in moderate to excellent yield (Scheme 1.14).



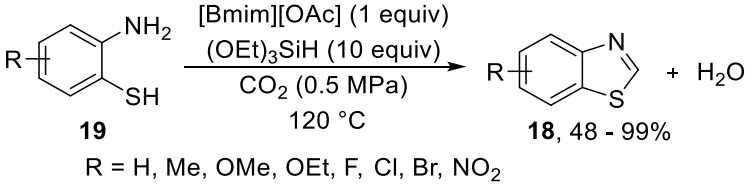
Scheme 1.14. *Iodine-mediated C─H Thiolation Process*

Punniyamurthy and co-workers devised an efficient protocol to synthesize benzothiazole **18** from thioanilides **20**.[25] This protocol involved 1-iodo-4-nitrobenzene as the organocatalyst and oxone as the oxidant in fluorinated solvent HFIP. The involvement of TfOH in the reaction facilitates the generation of hypervalent iodine intermediate. The benzothiazoles **18** were observed in moderate to excellent yields. They have further synthesized benzoxazoles from anilides, following the same approach (Scheme 1.15).



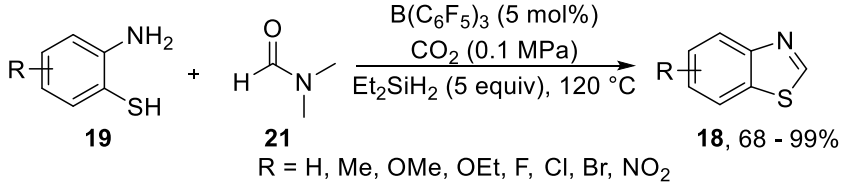
Scheme 1.15. *Synthesis of Benzothiazole by Organocatalytic Process*

Liu and co-workers synthesized benzothiazoles **18** from 2-mercaptoanilines **19**, triethoxysilanes and atmospheric CO_2.[26] They have employed ionic liquid, [Bmim][OAc] as the catalyst. This catalyst facilitates the cyclization by activating triethoxysilanes, CO_2 and 2-mercaptoanilines **19**. This methodology is environmentally benign approach and give water molecule as the by-product (Scheme 1.16).



Scheme 1.16. *Synthesis of Benzothiazole Promoted by Ionic Liquid and Atmospheric CO_2*

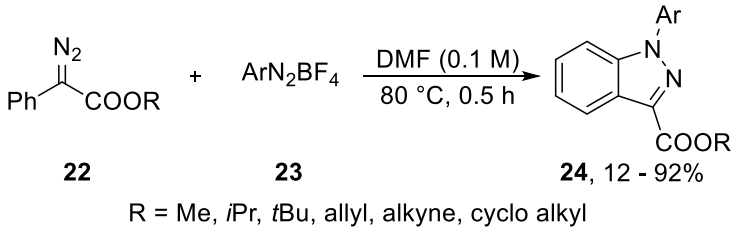
The same group have also demonstrated a strategy for the synthesis of benzothiazole **18** via C─S and C─N bond formation reaction.[27] This strategy involved $B(C_6F_5)_3$ as the catalyst along with atmospheric CO_2. The substituted 2-mercaptoanilines **19** and DMF were smoothly transformed to the corresponding benzothiazoles **18** in moderate to excellent yield. They have expanded their strategy for synthesizing other *N*-heterocycles, following the same reaction condition (Scheme 1.17).



Scheme 1.17. *Synthesis of Benzothiazole Promoted by Atmospheric CO_2*

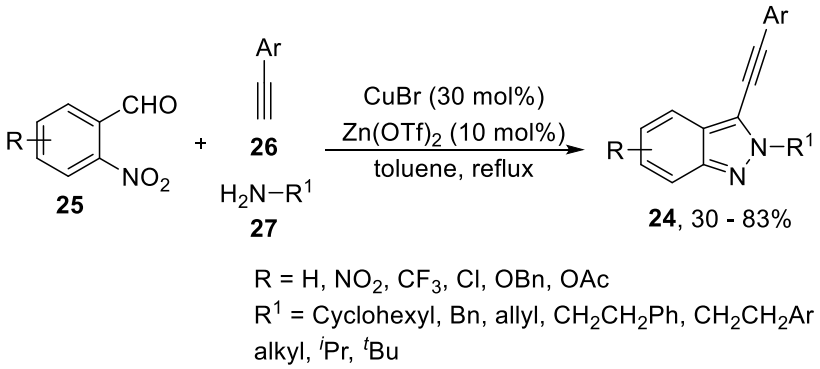
1.2.4. Synthesis of Indazole

Shi and co-workers have developed a donor/acceptor approach for the synthesis of indazole **24** and its derivatives.[28] This approach included the activation of diazo compound **22** by the diazonium salts **23** in the absence of any catalysts. It has been established that the reaction proceeds via a diazenium intermediate, which promoted the cyclization to afford indazoles **24** in low to excellent yields. When nitriles were used along with the optimized condition, they observed 1,2,4-triazoles as the product (Scheme 1.18).



Scheme 1.18. *C─H Amination Reaction*

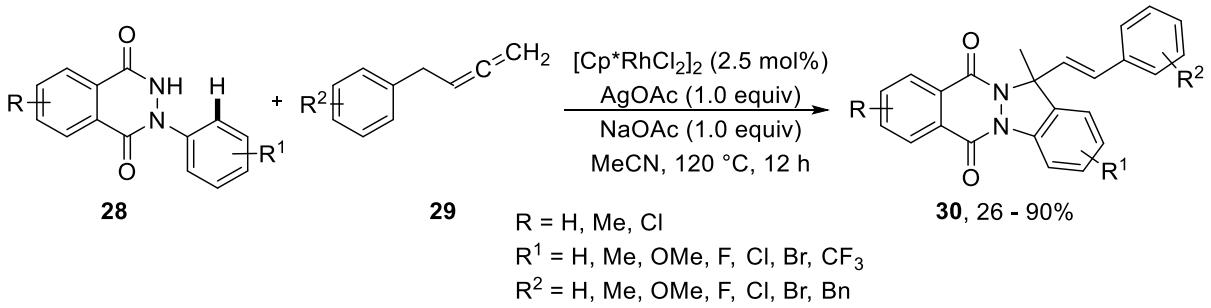
Saikia and co-workers proposed a new methodology for the synthesis of substituted indazoles **24**.[29] They have employed CuBr/$Zn(OTf)_2$ as the catalytic system. This is a multi-component reaction involving 2-nitrobenzaldehyde **25**, alkynes **26**, and primary amines **27** as the precursors. The yield of the indazoles **24** was in the range of 30 -83% (Scheme 1.19).



Scheme 1.19. *Synthesis of Indazole via Cu/Zn Catalytic System*

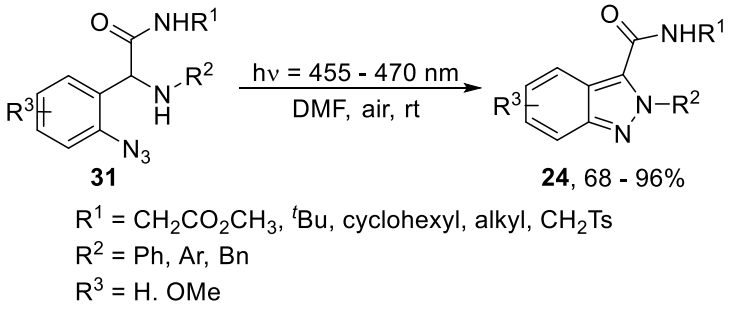
Yu and co-workers demonstrated a metal mediated strategy for the synthesis of indazole derivatives **30**.[30] They have subjected *N*-aryl phthalazinones **28** and substituted allenes **29** to

the C─H activation reaction involving $[Cp^*RhCl_2]_2$ as the catalyst. The indazole derivatives **30** were observed to bear quaternary center and were isolated in low to excellent yields. This approach involves four steps, C─H activation, then insertion of olefins, which is led by *β*-hydride elimination, and finally intramolecular cyclization (Scheme 1.20).



Scheme 1.20. *Metal-catalyzed C─H Activation Reaction*

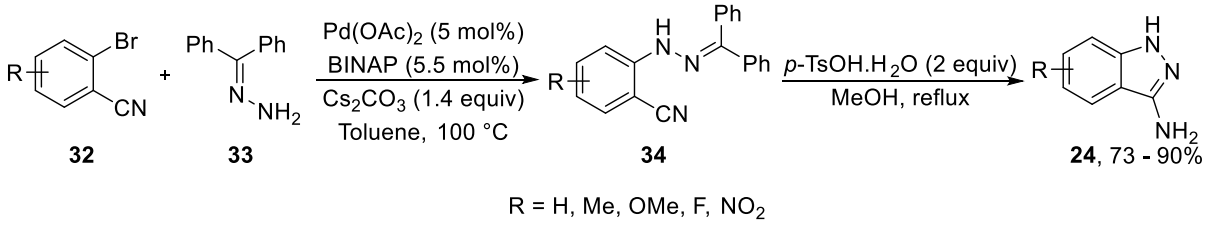
Wang and co-workers have added a new dimension in the synthesis of indazoles **24** via photocyclization using visible light irradiation.[31] They have considered aryl azides **31** as the precursors. This methodology does not engage any external additive and photocatalyst. They have employed sunlight for irradiation to transform aryl azides **31** into indazoles **24** (Scheme 1.21).



Scheme 1.21. *Visible Light Irradiated Photocyclization of Aryl azides*

Fabis and co-workers have synthesized 3-aminoindazoles **24** following a two-step protocol.[32] The 3-aminoindazoles **24** were smoothly obtained from substituted 2-bromobenzonitriles **32** and benzophenone hydrazone **33**. This methodology followed a two-

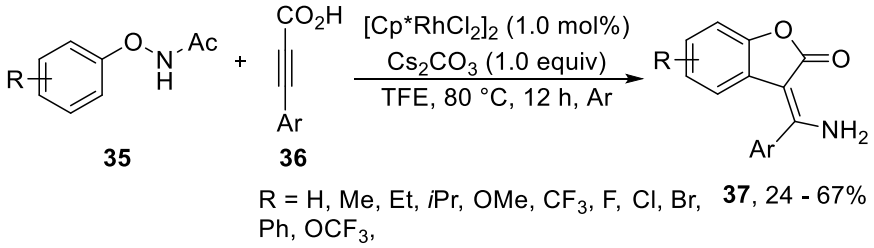
step route, first the synthesis of intermediate via palladium catalyzed C─N bond formation, then cyclization under acidic medium, to afford 3-aminoindazoles **24** (Scheme 1.22).



Scheme 1.22. *Synthesis of 3-Aminoindazoles*

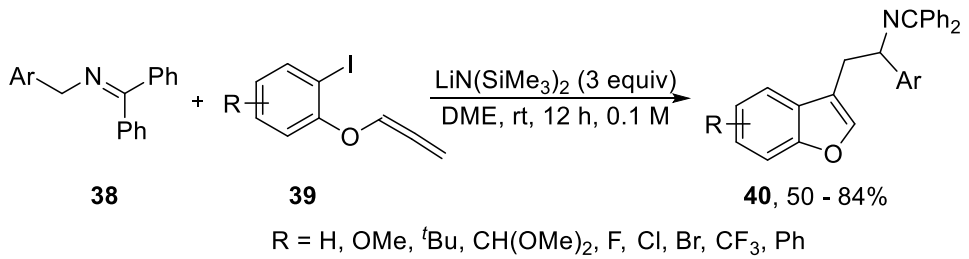
1.2.5. Synthesis of Benzofuran

Zhu and co-workers have explained [3+2] annulation reaction for the synthesis of benzofuran-2(3*H*)-ones **37** from 3-(hetero)arylpropiolic acids **36** and *N*-aryloxyacetamides **35**.[33] They have used $[Cp^*RhCl_2]_2$ as the catalyst for C─H bond functionalization. These benzofuran derivatives **37** can be used in sensing metal cations as s fluorescent probe (Scheme 1.23).



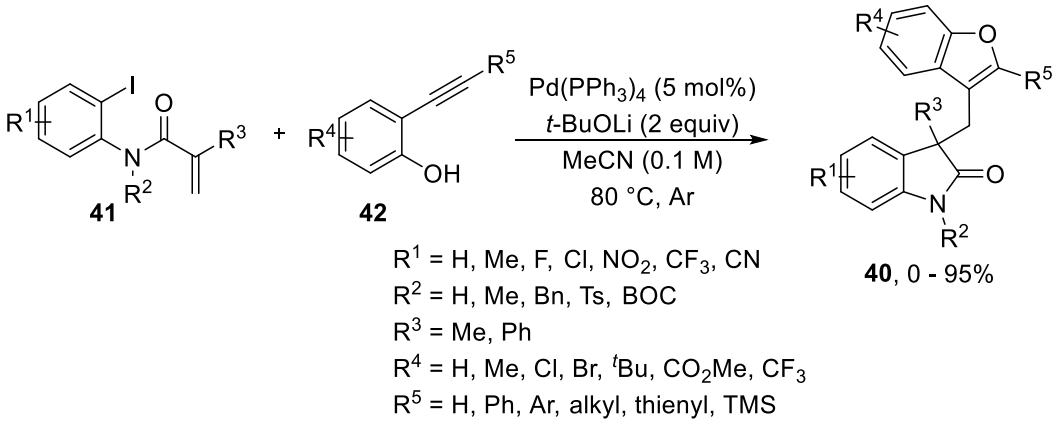
Scheme 1.23. *Rh-catalyzed Synthesis of Benzofurans*

Walsh and co-workers have developed a rare approach for the synthesis of benzofurans **40**.[34] In their methodology, they have adopted radical cyclization via single electron transfer approach to synthesize benzofurylethylamine derivatives **40** from 2-aza allyls **38** and 2-iodo aryl allenyl ethers **39** (Scheme 1.24).



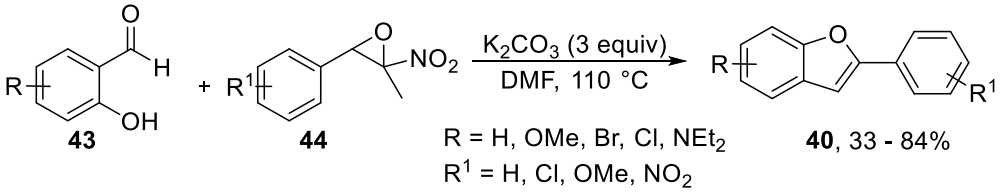
Scheme 1.24. *Synthesis of Benzofuran by Radical Cyclization Coupling Reaction*

Chen and co-workers have developed aryl furanylation via palladium catalyzed cascade reaction.[35] This methodology involved intramolecularly Heck coupling, followed by phenol-palladation leading to an intermediate, which further forms C─O bond and two C─N bonds affording 2-oxindole and furan ring in a single step. The 3-oxindole substituted benzofurans **40** were observed in low to excellent yields (Scheme 1.25).



Scheme 1.25. *Synthesis of Benzofuran containing Oxindoles*

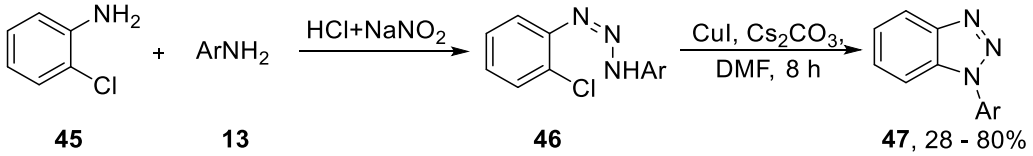
Tavakol and co-workers established a new base mediated strategy for the synthesis of 2-substituted benzofurans **40.**[36] They have employed salicylaldehydes **43** and nitroepoxides **44** under the influence of potassium carbonate to afford substituted benzofurans in 33 – 84% yields (Scheme 1.26).



Scheme 1.26. *Base-mediated Synthesis of Benzofuran*

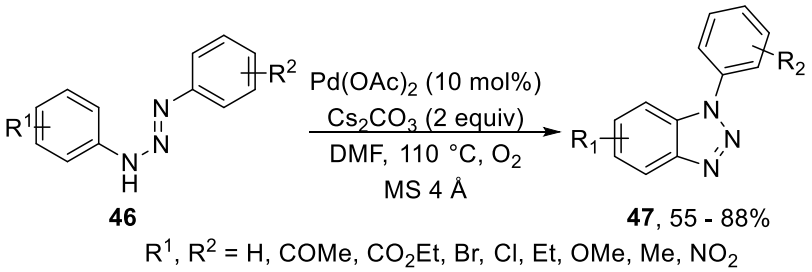
1.2.6. Synthesis of fused Triazoles

Tiwari and co-workers established the synthesis of benzotriazole **47** via copper catalyzed *N*-arylation reaction.[37] They have used 2-chloro anilines **45** and aryl amines **13** as the precursors, which on treatment with HCl and $NaNO_2$ forms triazene. This triazene **46** on treatment with copper iodide underwent intramolecular *N*-arylation reaction affording *N*-aryl benzotriazoles **47** in 28 – 80% yield (Scheme 1.27).



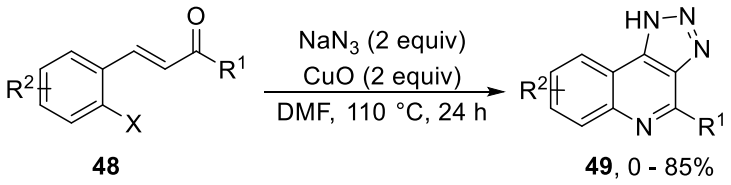
Scheme 1.27. *CuI Catalyzed C─H Amination Reaction for the Synthesis of Benzotriazoles*

Punniyamurthy and co-workers have established a strategy for the synthesis of benzotriazoles **47** from aryl triazenes **46**.[38] They have employed $Pd(OAc)_2$ as the catalyst to furnish the C─N bond formation reaction. The substituted benzotriazoles **47** were obtained in 55 – 88% yield (Scheme 1.28).



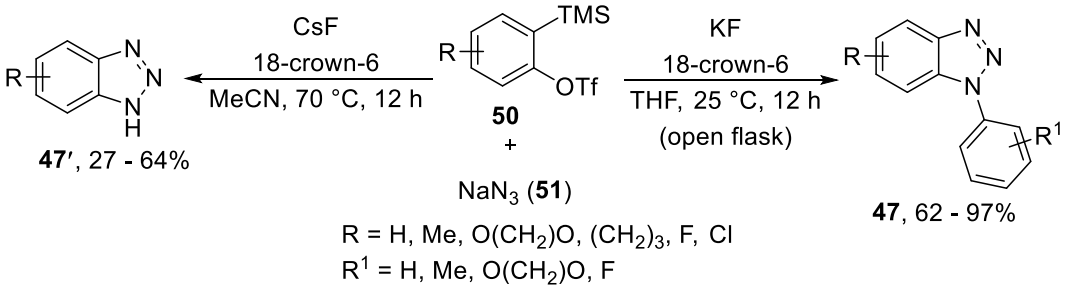
Scheme 1.28. *Pd-catalyzed C─H Amination Reaction*

Chen and co-workers have synthesized triazolo quinolines **49** via copper mediated tandem cyclization.[39] They have subjected (*E*)-3-(2-bromoaryl)-1-arylprop-2-en-1-ones **48** and sodium azide to copper-catalyzed conditions and reported up to 85% of 1H-[1,2,3]triazolo[4,5-*c*]quinolines **49**. They have shown two rings were form in one-pot reaction (Scheme 1.29).



Scheme 1.29. *Cu-mediated Cyclization Reaction*

Biju and co-workers have demonstrated a new methodology for the synthesis of benzotriazoles **47** via [3+2] annulation reaction.[40] The in situ generation of arynes from 2-(trimethylsilyl)aryltriflates **50** underwent [3+2] annulation reaction with sodium azides in the presence of crown ethers. When they have used KF in THF under open flask condition, then they observed *N*-aryl benzotriazoles **47** as the sole product in 62 – 97% yield. On using CsF in MeCN, they reported *N*-H benzotriazoles **47′** in moderate yields (Scheme 1.30).



Scheme 1.30. *[3+2] Annulation Reaction for Synthesis of Benzotriazoles*

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Triflic Acid-mediated Cyclization of *β*-Anilino-*β*-(thiomethyl)acrylonitriles: Synthesis of 4-Amino-2-(methylthio)quinolines

2.1. Introduction:

Heterocycles are an important class of organic compounds because of their utilization in various fields such as material, agro and biomedical sciences.[1] Among the heterocycles, the nitrogen-containing heterocycles attract the attention of synthetic chemists, as a wide range of natural products comprises *N*-containing heterocycles, and are used in the synthesis of dyes, drugs, and agrochemicals.[2] Especially, quinolines are considered as the vital core of the *N*-heterocyclic compounds because of their extensive medicinal and biological properties and are found in drugs.[3] Precisely, 4-aminoquinolines have been extensively studied for their therapeutic applications.[4] For example, Tacrine (acetylcholine esterase inhibitor) is used for the treatment of Alzheimer's disease, specifically against the cognitive dysfunction arising

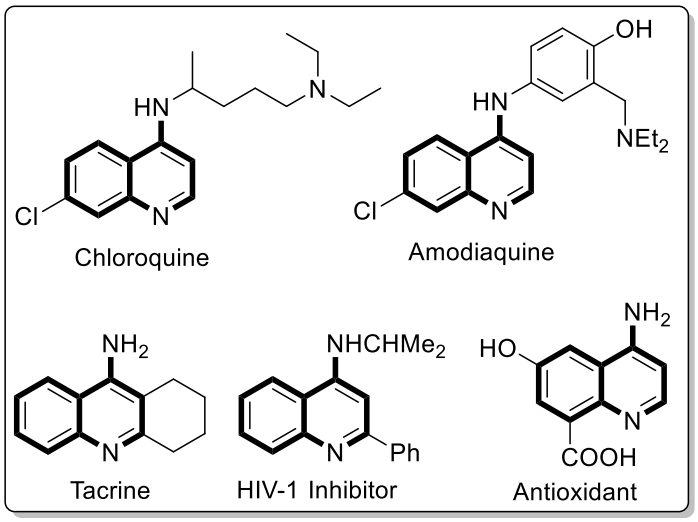


Figure 2.1. Representation of Biologically Active Molecules Containing 4-Aminoquinoline Core

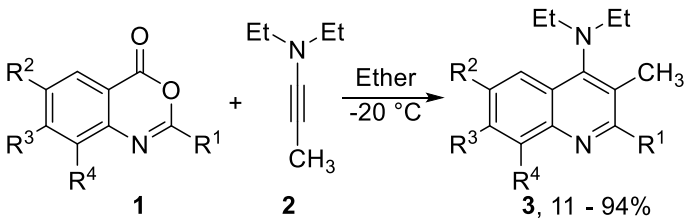
from this disease,[5] contains 4-aminoquinoline core. Antimalarial drugs, chloroquine, amodiaquine, also contain 4-aminoquinoline core.[6] 4-Aminoquinoline and its derivatives are also known to be potent antivirals[7a], antifilarials[7b], tuberculosis ATP synthase inhibitors[7c], nociceptin receptor antagonists[7d], and translocator protein biomarker ligands.[7e]

2.2. Previous Reports for the Synthesis of 4-Aminoquinolines

In literature, various methodologies have been developed to synthesize 4-aminoquinoline and its derivatives.[8] Classically, 4-aminoquinolines were synthesized from 4-haloquinolines and primary amines via S_NAr reaction.[9] Recently, the transition metal catalyzed Buchwald-Hartwig amination was the favourable choice for the synthesis of 4-aminoquinolines.[10] Further, various other methodologies have also been developed in the recent years. In the following section, selected synthesis of 4-amino quinoline is discussed.

2.2.1. Selected Reports for the Synthesis of 4-Aminoquinoline from Heterocyclic Precursors

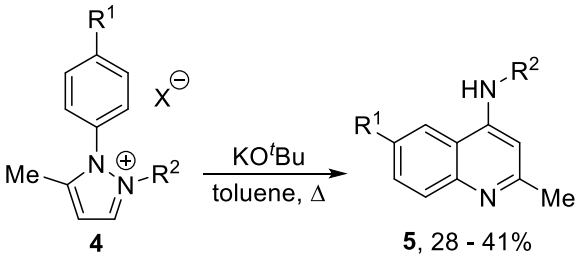
Steglich and co-workers demonstrated a new protocol for the synthesis of 4-aminoquinolines **3**.[11] Benzoxazinones **1** and *N*,*N*-diethyl-1-propynylamine **2** were condensed at -20 °C, affording 4-aminoquinolines **3** with the evolution of CO_2 (Scheme 2.1).



R^1 = H, CF_3, CH_3, C_6H_5
R^2 = H, Cl, Br
R^3 = H, Cl
R^4 = H, Cl, Br

Scheme 2.1. *Synthesis of 4-Aminoquinolines*

The substituted 4-aminoquinolines **5** can also be synsthesized by rearrangements of *N*-heterocyclic carbene of pyrazole **4**, as explained by Schmidt and co-workers.[12] This methodology involved ring-opening, ring-closure and tautomerization to finally afford 4-aminoquinolines **5**. The mechanistic studies revealed that it involved the inversion of imine nitrogen (Scheme 2.2).

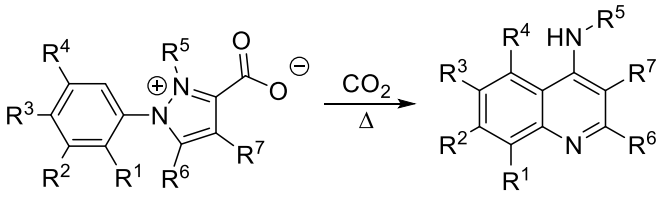


4 **5**, 28 - 41%

R^1 = H, Br, Cl
R^2 = -CH_2Ph, -$(CH_2)_7$Me, -$(CH_2)_9$Me, -$(CH_2)_{15}$Me
X = Br, I

Scheme 2.2. *Rearrangement of NHC of Pyrazole*

Schmidt and co-workers again synthesized 4-aminoquinoline **3** following rearrangement of pyrazole **6** NHC.[13] The transformation to 4-aminoquinolines **3** involved the rearrangement of pyrazol-3-ylidenes, which is generated in situ by decarboxylation of betaines (Scheme 2.3).



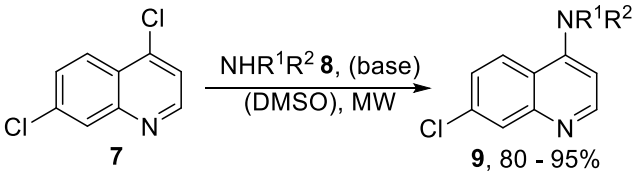
6 **3**, 0 - 99%

R^1 = H, F, Me, OMe, COOH
R^2 = H, OMe, Cl
R^3 = H, Me, OMe, Cl, Br
R^4 = H, Me, OMe, Cl
R^5 = Me, Et
R^6 = Me, Ph, 2-thienyl
R^7 = H, Et

Scheme 2.3. *Synthesis of 4-Aminoquinolines via Rearrangement of Pyrazole NHC*

2.2.2. Selected Reports for the Synthesis of 4-Aminoquinoline from Halo Precursors

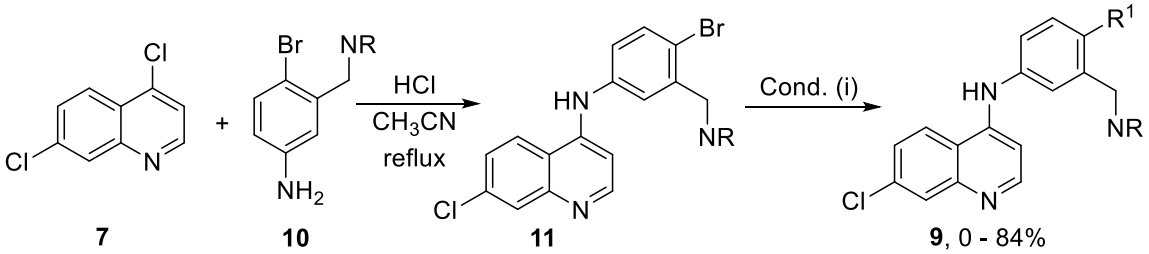
Monti and co-workers have established a new protocol for the synthesis of 4-aminoquinolines **9** via microwave mediated S_NAr reactions of 4,7-dichloroquinolines **7**.[14] This protocol does not involve any harsh reaction condition and led to the formation of 4-aminoquinolines **9** without any toxic by-products (Scheme 2.4).



R^1 = H, R^2 = aliphatic
R^1, R^2 = *N*′-substituted piperazine
R^1 = H, R^2 = aromatic

Scheme 2.4. *Microwave Mediated S_NAr Reaction*

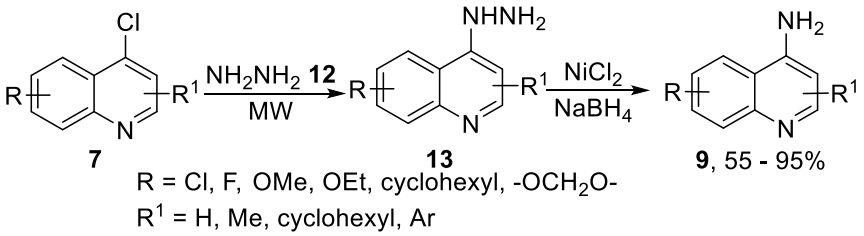
Melnyk and co-workers synthesized derivatives of 4-aminoquinolines **9** having antimalarial activities.[15] This methodology involved the regioselective S_NAr of the 4-chloro substitutent of quinoline derivative **7** by the aniline derivative **10**. They have reported various derivatives of amodiaquine and amopyroquine, which are known for exhibiting antimalarial activities (Scheme 2.5).



Condition (i): R^1–$B(OH)_2$, $Pd(OAc)_2$, P(*o*-tol)$_3$,
TBAB, Na_2CO_3, Toluene, EtOH, 60 °C
R = Et, pyrrolidine
R^1 = Ph, Ar, 2-thienyl, 2-furyl, Me, Et

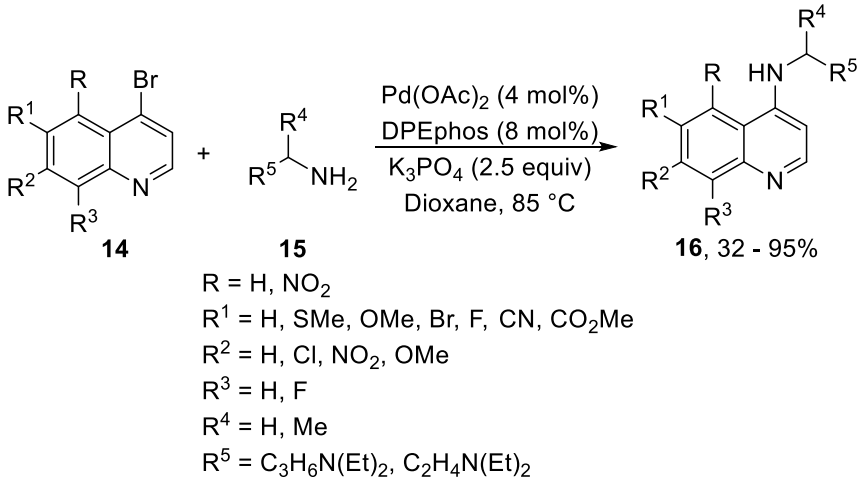
Scheme 2.5. *Suzuki-Miyaura Coupling Reaction*

Campiani and co-workers devised a new protocol to synthesize 4-aminoquinolines **9** from 4-quinolylhydrazines **13** by reduction in the presence of $NiCl_2/NaBH_4$ combination.[16] These 4-quinolylhydrazines **13** were synthesized from 4-chloroquinolines **7** via microwave assisted reaction (Scheme 2.6).



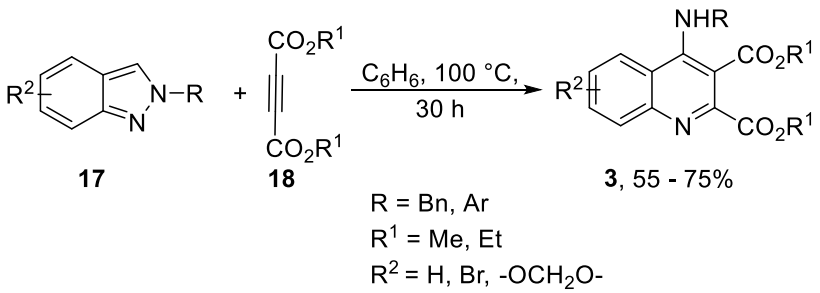
Scheme 2.6. *Synthesis of 4-Aminoquinolines via Nickel Mediated Reduction*

Margolis and co-workers investigated the synthesis of a series of 4-aminoquinolines **16** via a mild and efficient C─N bond formation reaction.[17] This methodology involved palladium acetate as the catalyst along with DPEphos as ligand and K_3PO_4 as base (Scheme 2.7).



Scheme 2.7. *Palladium Catalyzed C─H Amination Reaction*

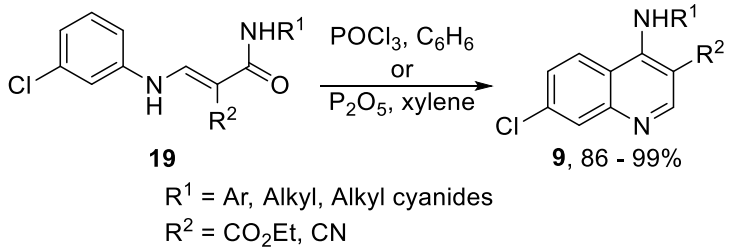
Sharada and co-workers established a new protocol for the synthesis of substituted 4-aminoquinolines **3** following aza hetero-Diels-Alder reaction.[18] This is the first report where 2*H*-indazole **17** has been used as a diene partner in the Diels-Alder reaction (Scheme 2.8).



Scheme 2.8. *Aza Hetero Diels-Alder Reaction*

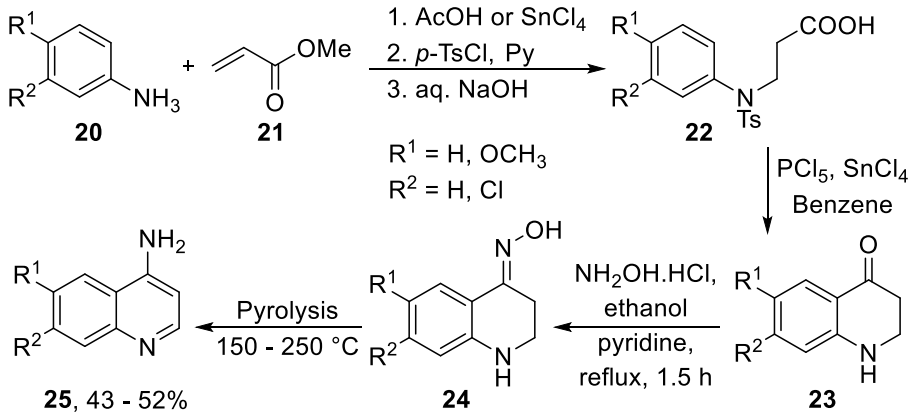
2.2.3. Selected Reports for the Synthesis of 4-Aminoquinoline from Aniline Derivatives

Price and co-worker reported the synthesis of 4-aminoquinolines **9** via cyclodehydration of various *β*-anilinoacrylamides **19**.[19] The cyclization was carried out by treating the respective *β*-anilinoacrylamides **19** either with phosphorus oxychloride or phosphorus pentoxide in boiling benzene or xylene, respectively (Scheme 2.9).



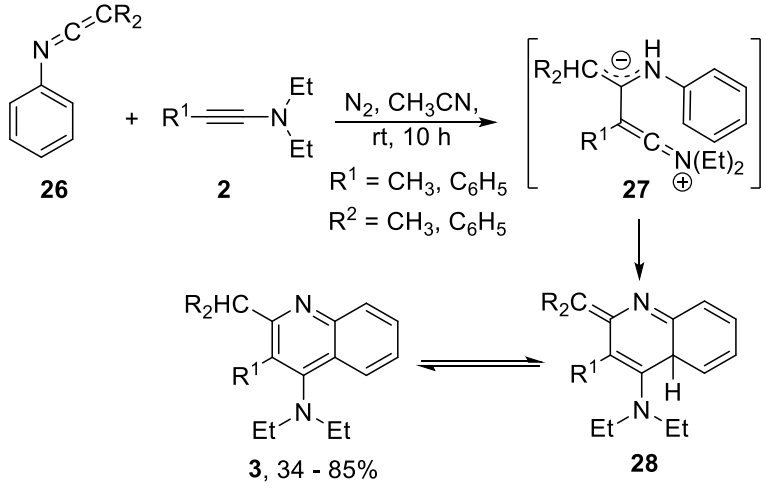
Scheme 2.9. *Synthesis of 4-Aminoquinolines via Cyclodehydration of β-Anilinoacrylamides*

Buell and co-workers synthesized 4-aminoquinoline **24** from aromatic amines **20** via a seven-step methodology.[20] This method involved the reaction of aromatic amines **20** with methyl acrylate **21** in the presence of stannic chloride or acetic acid to give the michael adducts. These michael adducts were further tosylated and hydrolysed to give the corresponding acids **22**, further cyclized to cyclic ketones **23**. These cyclic ketones **23** were then detosylated to afford 4-quinolones and finally converted to oximes **24**. Pyrolysis of these oximes led to 4-aminoquinolines 2**5** in moderate yields (Scheme 2.10).



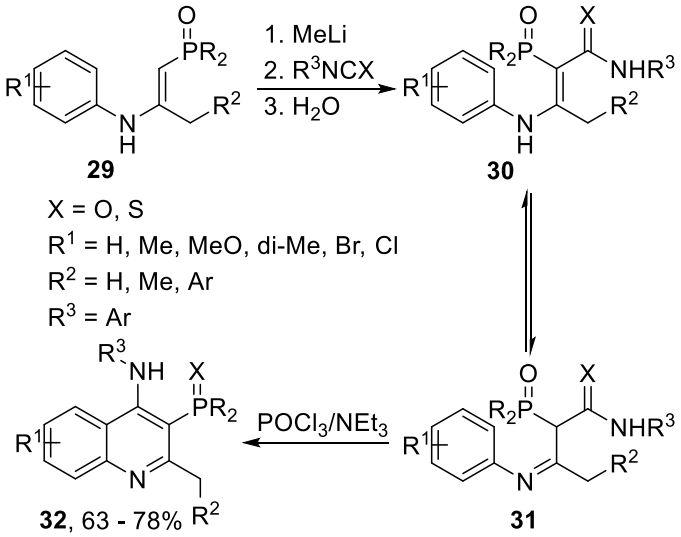
Scheme 2.10. *Palladium Catalyzed Dehydration of Oximes*

Ghosez and co-worker synthesized 4-aminoquinolines **3** via polar cycloaddition of substituted keteneimines **26** and aminoacetylenes **2**.[21] The 4-aminoquinolines **3** were obtained in upto 85% yield (Scheme 2.11).



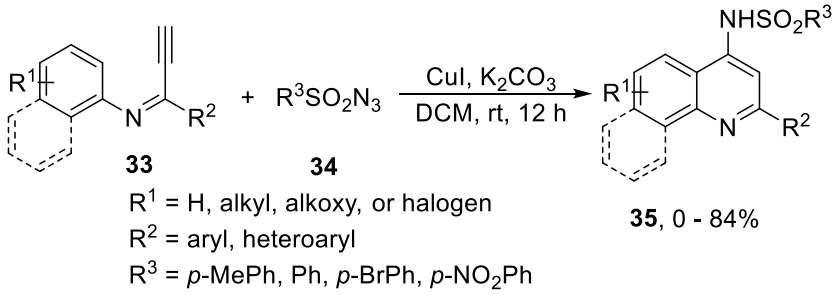
Scheme 2.11. *Synthesis of 4-Aminoquinolines via Polar Cycloaddition of Keteneimines*

Palacios and co-workers devised a strategy for the synthesis of substituted 4-aminoquinolines **32**.[22] This strategy involved anilines, isocyanates or isothiocyanates, phosphine oxides and phosphonates as the precursors. The regioselective addition of phosphonates and phosphine oxides to isothiocyanates and isocyanates is the key step of this methodology. Phosphorus oxychloride in triethyl amine facilitated the cyclization and afforded the 3-substituted 4-aminoquinolines **32** (Scheme 2.12).



Scheme 2.12. *Synthesis of 3-Substituted 4-Aminoquinolines*

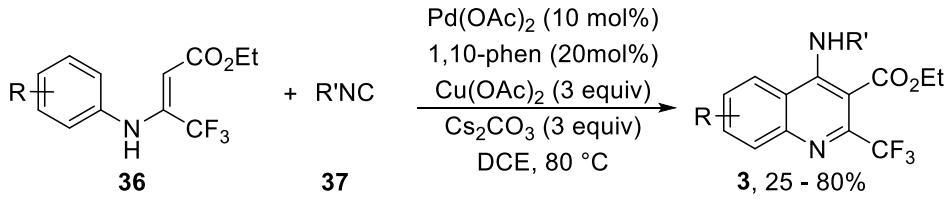
Cui and co-workers established a methodology for the synthesis of *N*-substituted 4-aminoquinolines **35** via copper catalyzed cyclization of alkynyl imines **33** and sulfonyl azides **34**.[23] The mechanistic studies revealed that the methodology involved a 1,3-dipole cycloaddition, followed by ketenimine formation, which led to 6π-electrocyclization and then [1,3]-H shift, thus affording the *N*-substituted 4-aminoquinolines **35** (Scheme 2.13).



Scheme 2.13. *Copper Catalyzed Cyclization of Alkynyl Imines and Sulfonyl Azides*

Ding and co-workers devised a new methodology for the synthesis of 4-aminoquinolines **3** via oxidative cyclization.[24] This protocol follows palladium catalyzed intermolecular cyclization of isocyanides **37** and *N*-aryl enamines **36** involving cleavage of two

sp^2 C─H bonds leading to the formation of substituted 4-aminoquinolines **3** in moderate to very good yields. This methodology is tolerant to various functionalities (Scheme 2.14).

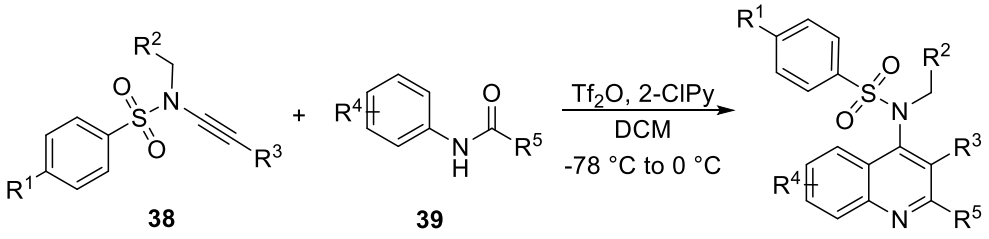


R = ^{i}Pr, Me, OMe, NMe_2, OPh, F, Cl, Br, OCF_3, CN, CO_2Et CF_3, Et

R' = ^{t}Bu, Ad, cyclohexyl, Ph

Scheme 2.14. *Pd-Catalyzed Oxidative Intermolecular Cyclization*

The functionalized 4-aminoquinolines **40** can also be synthesized from ynamides **38** and *N*-substituted aniline derivatives **39** under the influence of triflic anhydride.[25] This strategy was first proposed by Bräse and co-workers. This methodology involved 2-chloropyridine, *N*-substituted aniline **39,** triflic anhydride and ynamides **38** as the key precursors (Scheme 2.15).



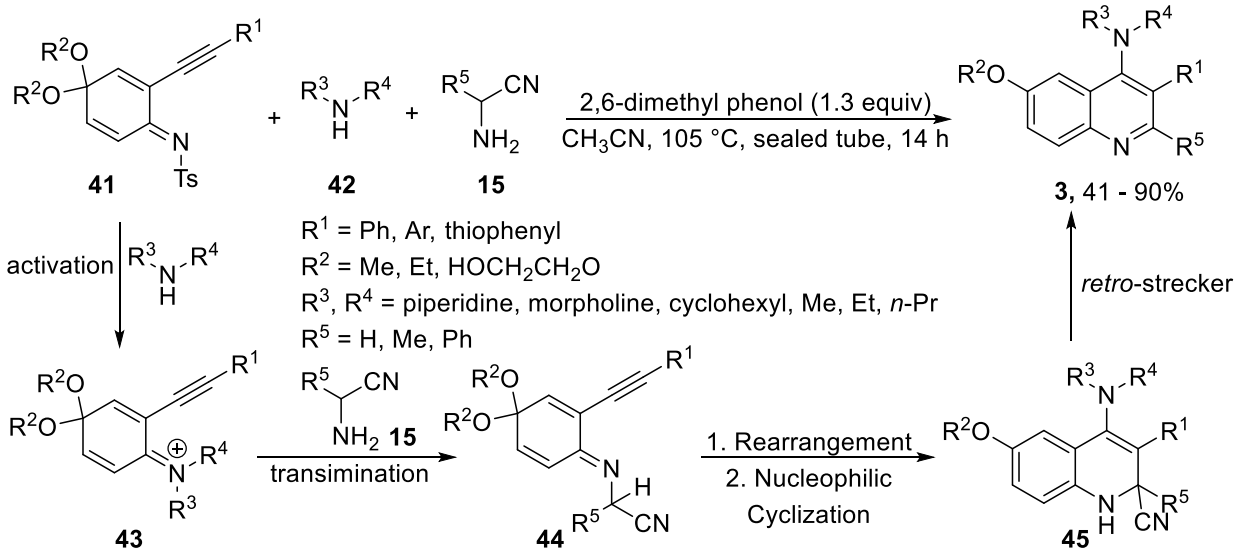
R^1 = Me, CO_2Me R^4 = H, Cl, CF_3, CO_2Et

R^2 = Ar, Het R^5 = CH_3, cyclohexyl, *c*Pr

R^3 = H, Me, Ph, *c*Pr, Het

Scheme 2.15. *Triflic Anhydride-mediated Synthesis of Functionalized 4-Aminoquinolines*

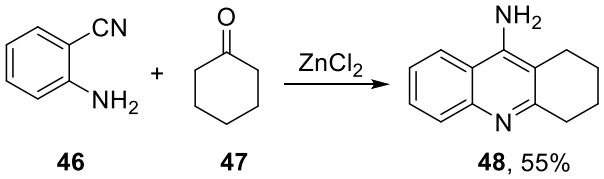
Fan and co-workers established an efficient protocol to synthesize polyfunctionalized 4-aminoquinolines **3**.[26] The various 4-aminoquinolines **3** can be obtained from acyclic precurssors following multi-component reaction. This protocol involves four steps, the transimination of secondary amines **42** with α-amino nitriles **15**, followed by rearrangement that facilitates the nucleophilic cyclization and further retro-strecker. The aromatization is believed to be the driving force for the rearrangement step (Scheme 2.16).



Scheme 2.16. *Multi-component Reaction for the Synthesis of Polysubstituted 4-Aminoquinolines*

2.2.4. Selected Reports for the Synthesis of 4-Aminoquinoline from *o*-Substituted Aniline Derivatives

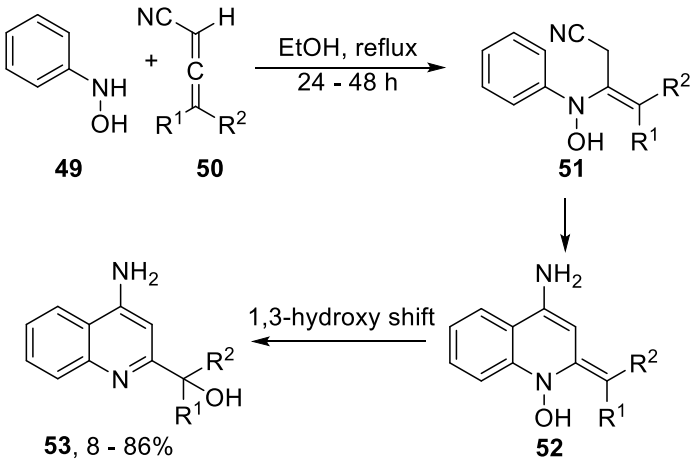
Moore and co-workers have performed cyclocondensation of cyclohexanone **47** with anthranilonitrile **46** for the synthesis of 4-aminoquinoline **48**.[27] This method needed an acidic medium for the transformation to 4-aminoquinoline **48**, hence zinc chloride was used. It has been found that zinc chloride had enhanced the yield drastically (Scheme 2.17).



Scheme 2.17. *Synthesis of 4-Aminoquinoline via Cyclocondensation Reaction*

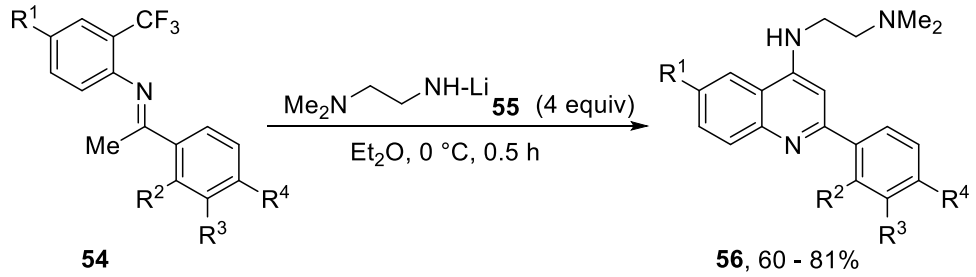
Landor and co-workers synthesized 4-aminoquinolines **53** from phenylhydroxylamines **49** and allenic nitriles **50**. Phenylhydroxylamines **49** and allenic nitriles **50**, on refluxing in ethanol gives the intermediate **51** which further cyclizes to form 1,2-

dihydro-1-hydroxyquinolines **52**.[28] These quinolines **52** spontaneously rearrange via 1,3-hydroxyl shift to afford 2-substituted 4-aminoquinolines **53** (Scheme 2.18).



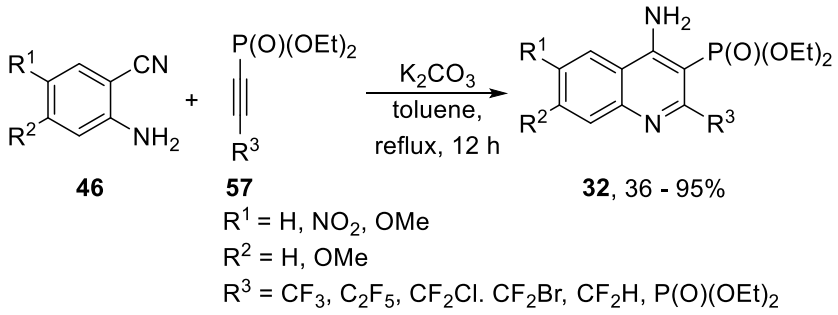
Scheme 2.18. *Synthesis of 2-Substituted 4-Aminoquinolines via 1,3-Hydroxy Shift*

Strekowski and co-workers established a new methodology to synthesize 4-aminoquinolines **56**.[29] In this methodology the ketimines **54** were transformed to 4-aminoquinolines **56** under the influence of a lithium regeant **55** (Scheme 2.19).



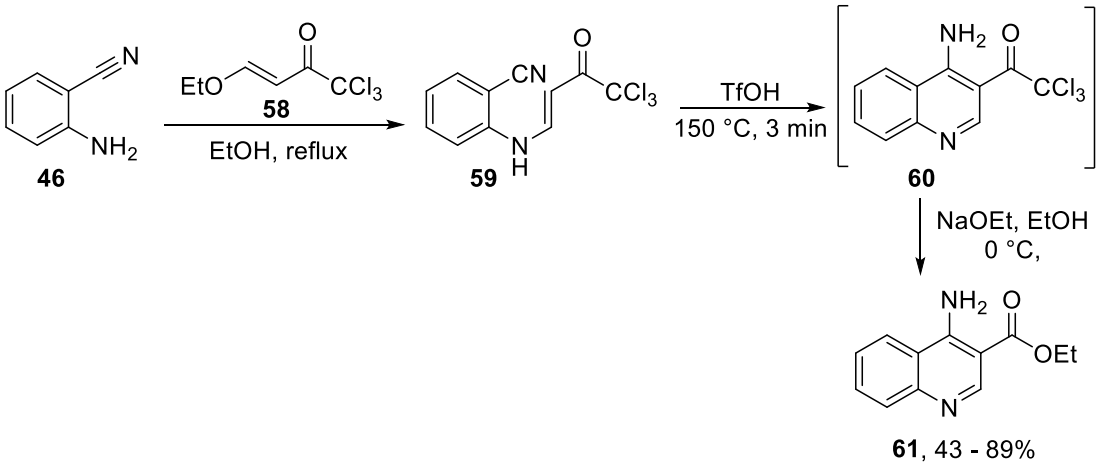
Scheme 2.19. *Synthesis of Substituted 4-Aminoquinolines*

Tverdomed and co-workers have delveloped a new approach for the synthesis of 2,3-disubstituted 4-aminoquinolines **32**.[30] This strategy involved base-mediated heterocyclization of alkynyl phosphonates **57** and anthranilonitriles **46** under refluxing condition (Scheme 2.20).



Scheme 2.20. *Synthesis of 2,3-Disubstituted 4-Aminoquinolines via Base-mediated Heterocylization Reaction*

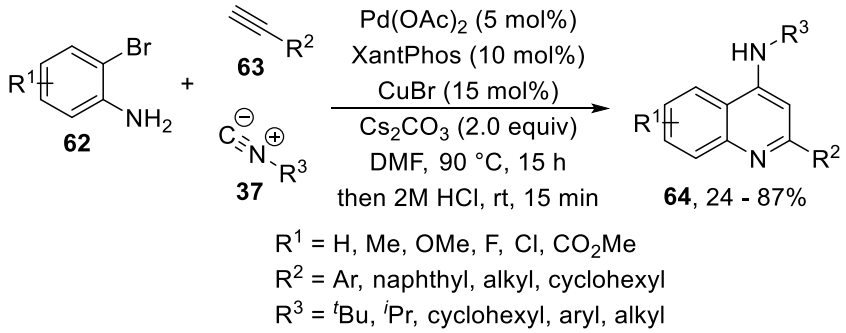
Popowycz and co-workers developed a methodology for the synthesis of various functionalized 4-aminoquinolines **61** via a three-step synthesis.[31] This methodology involved triflic acid mediated cyclization of enamine **59**, this enamine **59** can further be prepared by condensation of substituted anthranilonitriles **46** and 1,1,1-tricholoro-4-ethoxybut-3-en-2-one **58**. The triflic acid mediated cyclization led to an unstable intermediate **60** which on further treatment with NaOEt in ethanol afforded the 3-ester substituted 4-aminoquinolines **61** (Scheme 2.21).



Scheme 2.21. *Synthesis of Substituted 4-Aminoquinoline via Super-acid Mediated Cyclization of 2-Aminobenzonitriles*

Ruijter and co-workers developed a new strategy for the synthesis of 4-aminoquinolines **64** following a two-step one-pot reaction.[32] This methodology involved a three component palladium catalyzed Sonogashira coupling reaction. This methodology is tolerant to various

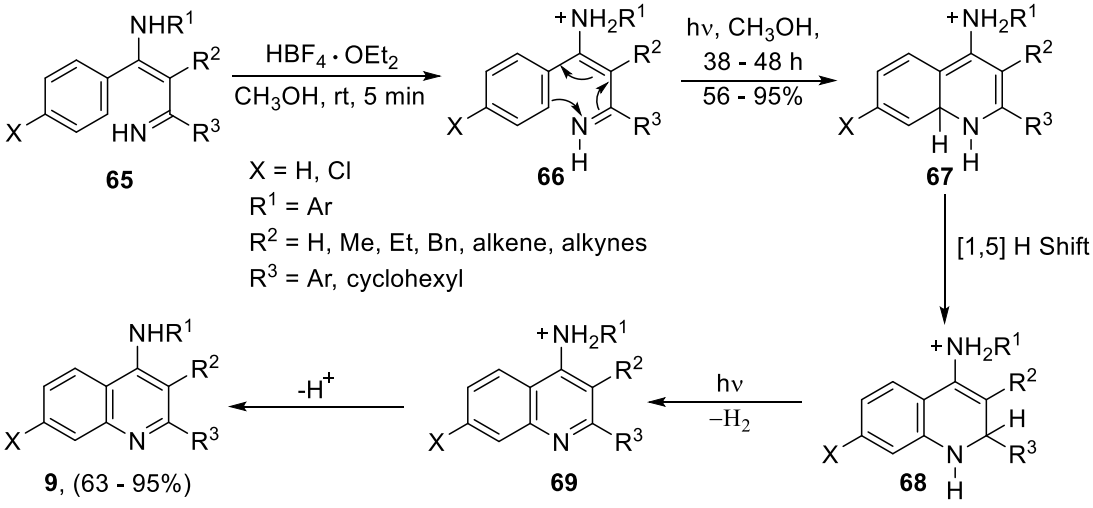
functionalities, including various functionalized isocyanides **37** which led to the synthesis of chloroquine analogues **64** (Scheme 2.22).



Scheme 2.22. *Multi-component Sonogashira Coupling*

2.2.5. Selected Reports for the Synthesis of 4-Aminoquinoline from Acyclic Precursors

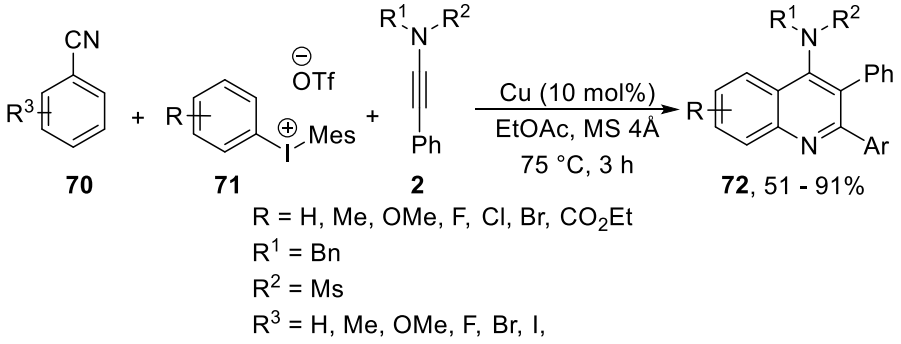
Campos and co-workers synthesized substituted 4-aminoquinolines **9** via irradiation of alkene imines **65**.[33] The irradiation was done in presence of tetrafluoroboric acid that leads to the formation of the required 4-aminoquinolines **9** via [1,5]-H shift, in excellent yield (Scheme 2.23).



Scheme 2.23. *Tetrafluoroboric Acid-mediated Irradiation of Imines*

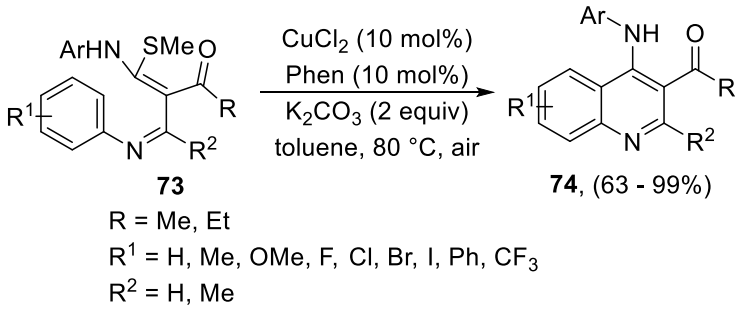
Park and co-workers have designed a new protocol for the synthesis of 4-aminoquinolines **72** via a three component reactions involving ynamindes **2**, diaryliodonium

salts **71**, and nitriles **70**.[34] They observed C7-substituted 4-aminoquinolines **72** as the sole regioselective product in case of *meta*-substituted phenyliodonium salts **71** (Scheme 2.24).



Scheme 2.24. *Synthesis of 2,3-Disubstituted 4-Aminoquinolines via Copper Catalyzed Multi-Component Reaction*

Liu and co-workers have synthesized a series of 4-aminoquinolines **74** via copper catalyzed 6π-electrocyclization.[35] This methodology passes through an oxidative desulfitative pathway to afford the various substituted 4-aminoquinolines **74**. It witnessed disulfide as a by-product, hence proceeded without any thiolate scanvengers (Scheme 2.25).

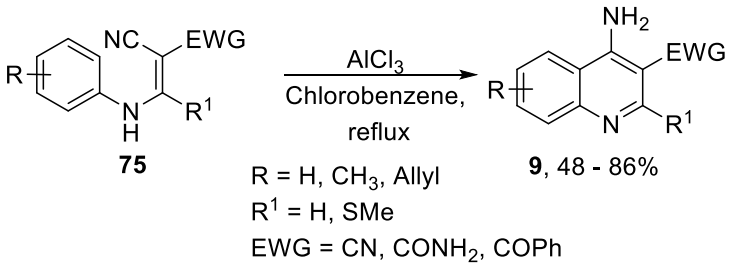


Scheme 2.25. *Copper Catalyzed Oxidative Electrocyclization*

2.3. Motivation

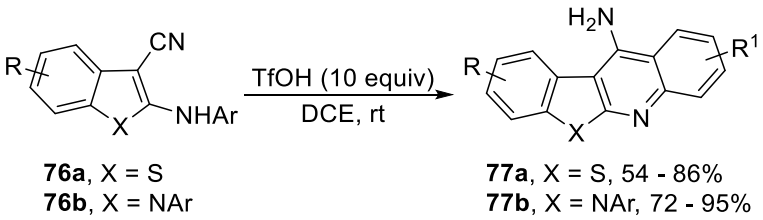
Due to the importance of 4-aminoquinoline, its synthesis is still an intense area of research that needs a continuous effort for the development of new and facile protocols. Gewald and co-workers have synthesized 4-aminoquinolines **9** via intramolecular Friedel-Crafts reaction.[36] They have transformed *β*-anilinoacrylonitriles **75** into 4-aminoquinolines **9** under

the influence of Lewis acid, $AlCl_3$, in refluxing chlorobenzene (Shceme 2.26). This methodology has its own advantages but suffers from various disadvantages like harsh reaction conditions and not tolerant to various functional groups.



Scheme 2.26. *Synthesis of 4-Aminoquinoline via Lewis Acid Mediated Cyclization*

We have reported heterocyclic fused 4-aminoquinolines **77** via triflic acid mediated cyclization of 2-anilino-benzothiophenes **76a** and 2-anilino-indoles **76b** at room temperature (Scheme 2.27).[37] Keeping this in mind, we have designed a milder approach towards the synthesis of 4-aminoquinoline, involving *β*-anilino-*β*-(thiomethyl)acrylonitriles. Our approach involves acid mediated intramolecular cyclization at ambient temperature. The acid is expected to protonate the nitrogen end of the nitrile of *β*-anilinoacrylonitrile thereby enhances the electrophilicity of the nitrile carbon and facilitates the cyclization, leading to the formation of 4-aminoquinoline and its derivatives in good to excellent yields.



Scheme 2.27. *Triflic Acid-mediated Cyclization of Benzothiophenes and Indoles*

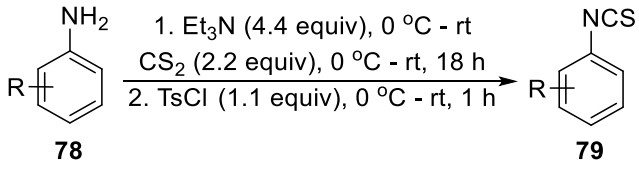
2.4. Results and Discussion

The *β*-anilino-*β*-(thiomethyl)acrylonitriles can be synthesized from acyclic precursors. The isolated *β*-anilino-*β*-(thiomethyl)acrylonitriles were characterized by spectral and analytical data.

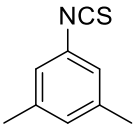
2.4.1. Synthesis of Isothiocyanate

The commercially available isothiocyanates **79** were used without any purification. The required isothiocyanates **79** were synthesized from anilines **78** by reacting with triethylamine and carbon disulfide. After formation of the salt, the reaction was quenched with *p*-toluenesulfonyl chloride. The isothiocyanates **79** were obtained in good to excellent yield (Table 2.1).

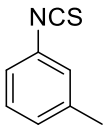
Table 2.1: Synthesis of Isothiocyanate



78 **79**



79f (78%)



79k (63%)

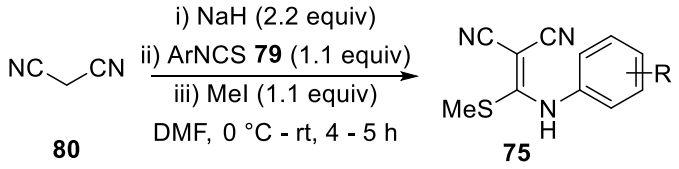
2.4.2. Synthesis of *β*-Anilino-*β*-(thiomethyl)acrylonitriles

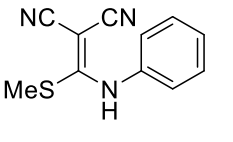
The required *β*-anilino-*β*-(thiomethyl)acrylonitriles **75, 82, and 84** can be prepared by condensation reaction of malononitrile **80** or ethyl cyanoacetate **81** or *β*-ketonitrile **83** with aryl isothiocyanate **79** under basic condition. The malononitrile **80** was stirred with sodium hydride at 0 ℃ in DMF and after the formation of salt it was treated with aryl isothiocyanates **78**.

Further, the corresponding salts were methylated with methyl iodide at 0°C, affording the product **75** (Table 2.2).

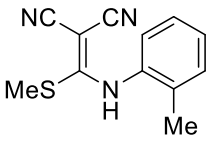
The diverse range of *β*-anilino-*β*-(thiomethyl)acrylonitriles **75** having electron rich, alkyl, electron deficient, halo substituent on the phenyl ring of isothiocyante **79**, derived from malononitrile **80**, were isolated in moderate to excellent yields (Table 2.2).

Table 2.2: Synthesis of *β*-Anilino-*β*-(thiomethyl)acrylonitriles from Malononitrile

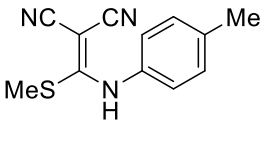




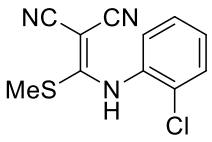
75a, 57%



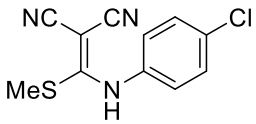
75b, 64%



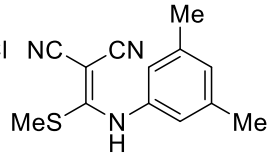
75c, 64%



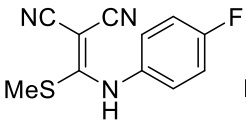
75d, 89%



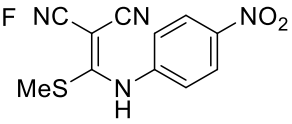
75e, 54%



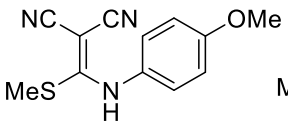
75f, 50%



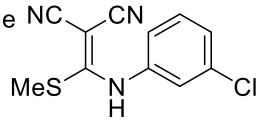
75g, 58%



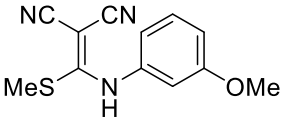
75h, 69%



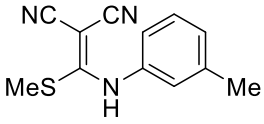
75i, 90%



75j, 88%



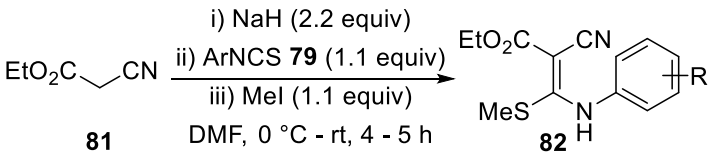
75k, 71%

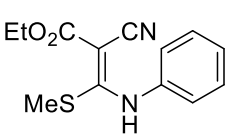
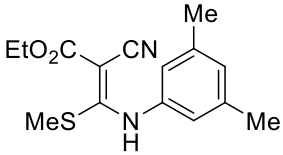
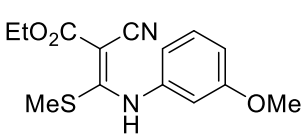


75l, 78%

Another series of *β*-anilino-*β*-(thiomethyl)acrylonitriles **82** were synthesized from ethyl cyanoacetate **81** and aryl isothiocyanates **79** with alkyl and electron rich substitutents. All the *β*-anilino-*β*-(thiomethyl)acrylonitriles **82** were observed in 29 – 63% (Table 2.3).

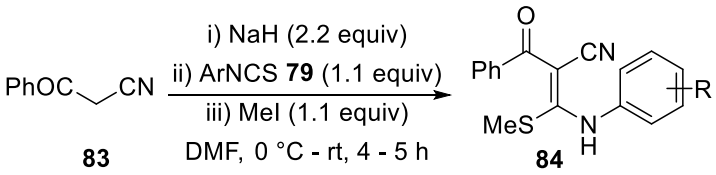
Table 2.3: Synthesis of *β*-Anilino-*α*-carbmethoxy-*β*-(thiomethyl)acrylonitriles from Ethyl Cyanoacetate

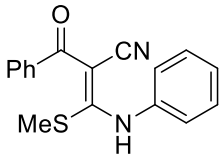
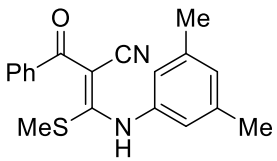


		
82a, 63%	**82f**, 40%	**82k**, 56%

Further, we synthesized *β*-anilino-*β*-(thiomethyl)acrylonitriles **84** with *α*-benzoyl substitution from *β*-ketonitrile **83** and aryl isothiocyanates **79**. The *β*-anilino-*α*-benzoyl-*β*-thiomethylacrylonitriles **84** were obtained in low yield (Table 2.4).

Table 2.4: Synthesis of *β*-Anilino-*α*-benzoyl-*β*-(thiomethyl)acrylonitriles from *β*-Ketonitrile



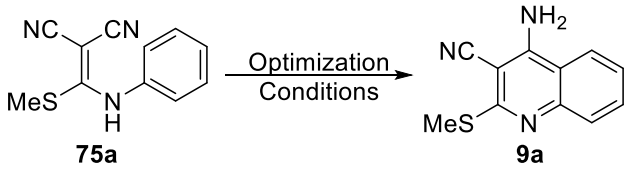
	
84a, 30%	**84f**, 29%

2.4.3. Optimization of *N*-Heteroannulation Reaction

The crucial step of our methodology is the acid-mediated intramolecular cyclization of *β*-anilino-*β*-(thiomethyl)acrylonitriles **75**. The *β*-anilino-*β*-(thiomethyl)acrylonitrile **75a** was subjected to various reaction conditions (Table 2.5). The acid-mediated intramolecular cyclization was conducted on *β*-anilino-*β*-(thiomethyl)acrylonitrile **75a** using 2 equivalence of trifluoroacetic acid in CH_2Cl_2 at room temperature (entry 1, Table 2.5). After 24 h, we did not

observe the product **9a** and recovered 78% of the starting material **75a** (entry 1, Table 2.5). We screened other acids, like acetic acid and triflic acid, and either observed incomplete conversion of the starting material **75a** or complex reaction mixture (entries 2 – 3, Table 2.5)**.** Interestingly**,** when we increased

Table 2.5. **Optimization for the Acid Mediated Intramolecular C–H Arylation of *β*-Anilino-*β*-(thiomethyl)acrylonitrile**



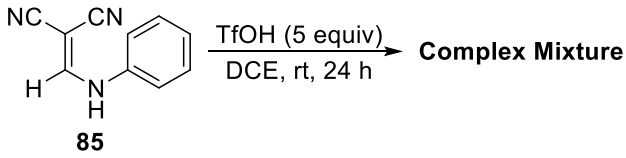
75a **9a**

Entry	Acid	Solvent	Temp	Time	% Yield[a]	
					9a	**75a**
1.	TFA (2equiv)	CH_2Cl_2	rt	24 h	-	78%
2.	AcOH (2 equiv)	CH_2Cl_2	rt	24 h	-	68%
3.	TfOH (2equiv)	CH_2Cl_2	rt	24 h	-	-[b]
4.	TfOH (5 equiv)	CH_2Cl_2	rt	24 h	55%	21%
5.	TfOH (5 equiv)	$CHCl_3$	rt	9 h	65%	-
6.	TfOH (5 equiv)	CCl_4	rt	24 h	-	-[b]
7.	TfOH (5 equiv)	Toulene	rt	24 h	-	-[b]
8.	**TfOH (5 equiv)**	**$C_2H_4Cl_2$**	**rt**	**6 h**	**89%**	**-**
9.	TfOH (10 equiv)	$C_2H_4Cl_2$	rt	5 h	80%	-
10.	TfOH (15 equiv)	$C_2H_4Cl_2$	rt	5 h	83%	-
11.	TfOH (5 equiv)	$C_2H_4Cl_2$	60 ℃	5 h	87%	-

Reaction Conditions: Substrate (0.5 mmol), acid, Solvent (2 mL). [a]Isolated yields; [b]Complex mixture was observed. TFA = Trifluoroacetic acid, AcOH = Acetic acid, TfOH = Triflic acid

the equivalence of triflic acid we observed 55% of the cyclized product **9a** and isolated 21% of the unreacted *β*-anilino-*β*-(thiomethyl)acrylonitriles **75a** (entry 4, Table 2.5). This product was characterized as 4-amino-3-cyano-2-(methylthio)quinoline **9a** by spectral and analytical analyses. However, on using $CHCl_3$ as the solvent we observed complete conversion of the

starting material **75a** along with 65% of the 4-aminoquinoline **9a** (entry 5, Table 2.5). On screening other solvents, like CCl_4 and toluene, we observed complex reaction mixture (entries 6-7, Table 2.5). With $C_2H_4Cl_2$ as the solvent we marked a drastic change in the yield of the reaction and isolated 89% of the cyclized product **9a** (entry 8, Table 2.5). On increasing the equivalence of TfOH, we observed 80 – 83% of the 4-aminoquinoline **9a** in 5 h (entries 9 – 10, Table 2.5). Next, we heated the reaction at 60 ℃ and observed comparable yield of the reaction (entry 11, Table 2.5).



85

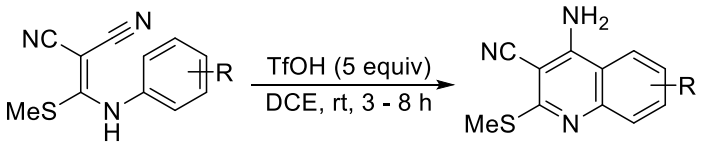
Scheme 2.28. *Role of thiomethyl group*

Further, we shifted our focus towards the role of thiomethyl group in the reaction. So, we synthesized *β*-anilinoacrylonitrile **85** without the thiomethyl group and subjected it to our optimized condition (Scheme 2.28). Unfortunately, we observed a complex reaction mixture with no sign of 4-aminoquinoline **9** (Scheme 2.28). This implies that the thiomethyl group is important for the *N*-heteroannulation process as it stabilises the *β*-anilinoacrylonitriles.

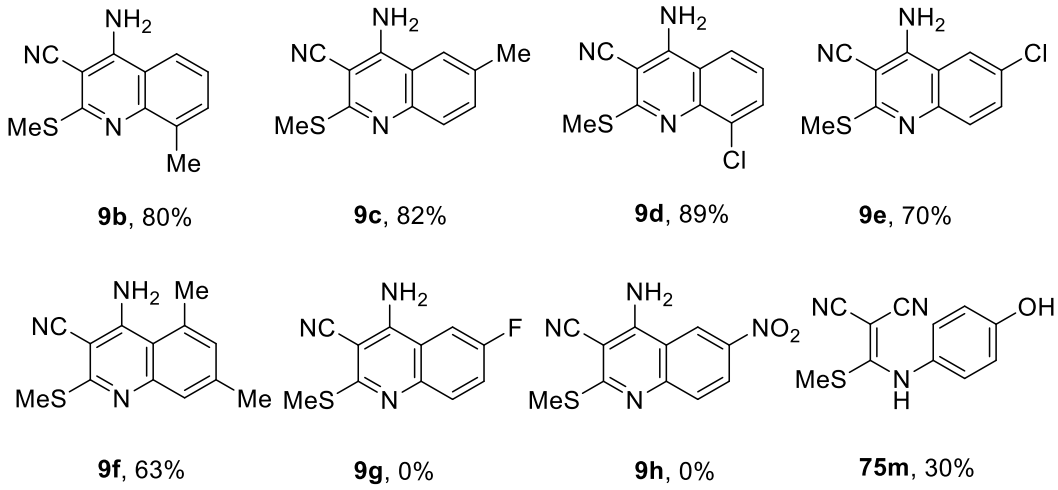
2.4.4. Substrate Scope

We then investigated a series of *β*-anilino-*β*-(thiomethyl)acrylonitriles **75** for the acid-mediated intramolecular cyclization reactions with the optimized conditions (Table 2.6). The steric and electronic effects on the cyclization of *β*-anilino-*β*-(thiomethyl)acrylonitriles **75** were

Table 2.6. Triflic Acid-mediated *N*-Heteroannulation of *β*-Anilino-*β*-(thiomethyl)acrylonitriles



75 **9**



9b, 80% **9c**, 82% **9d**, 89% **9e**, 70%

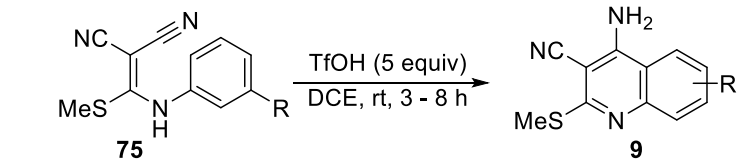
9f, 63% **9g**, 0% **9h**, 0% **75m**, 30%

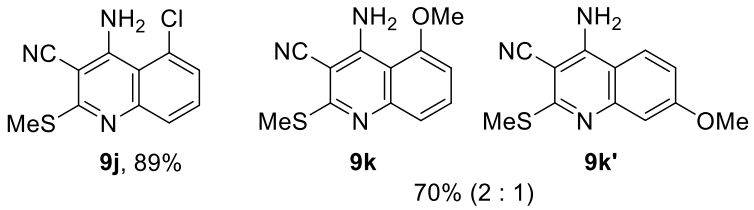
studied. 2-methyl and 4-methyl *β*-anilino-*β*-(thiomethyl)acrylonitriles **75b** & **75c** were subjected to the optimized reaction conditions, affording the respective 4-aminoquinolines **9b** & **9c** in 80 – 82% (Table 2.6). Chloro groups at the *ortho* and *para* position of the aniline ring of the *β*-anilino-*β*-(thiomethyl)acrylonitriles **75d** and **75e** were also examined (Table 2.6). 2-chloro *β*-anilino-*β*-(thiomethyl)acrylonitriles **75d** gave 70% of 4-aminoquinoline **9d** and 4-chloro *β*-anilino-*β*-(thiomethyl)acrylonitrile **75e**, afforded 89% of the corresponding 4-aminoquinoline **9e** (Table 2.6). The dimethyl substituted 4-aminoquinolines **9f** were isolated in 63% of yield (Table 2.6). However, in the case of 4-fluoro *β*-anilino-*β*-(thiomethyl)acrylonitrile **75g**, we did not observe the expected product **9g** (Table 2.6). Similarly, electron-withdrawing group, like nitro, at the para position of aniline ring **75h** did not furnish the corresponding 4-aminoquinoline **9h** (Table 2.6)**.** When the methoxy group was introduced at the *para* position of the *β*-anilino-*β*-(thiomethyl)acrylonitrile **75i**, the desired 4-

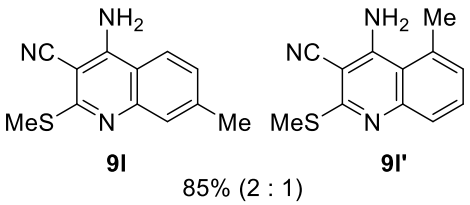
aminoquinoline **9i** was not detected, instead we observed 30% of 4-hydroxy-*β*-anilino-*β*-(thiomethyl)acrylonitrile **75m** as the sole product (Table 2.6).

Next, we studied *meta* substituted *β*-anilino-*β*-(thiomethyl)acrylonitriles **75j-k** (Table 2.7). We noticed a mixture of regioisomers was isolated in case of *meta* substituted substrates **75j-k** (Table 2.7). In case of 3-chloro *β*-anilino-*β*-(thiomethyl)acrylonitrile **75j**, we observed only a single regioisomer, i.e. C5 isomer **9j**, in 89% of yield (Table 2.7). Whereas, in the case of 3-methoxy and 3-methyl *β*-anilino-*β*-(thiomethyl)acrylonitriles **75k-l** we observed the mixture of regioisomers. The 3-methoxy *β*-anilino-*β*-(thiomethyl)acrylonitrile **75k** afforded the corresponding 4-aminoquinoline **9k** & **9k′** in 70% of yield with a 2:1 mixture of C5:C7 regioisomers (**9k**:**9k′**), C5 isomer **9k** being the major one (Table 2.7). Similar trend was observed in case of 3-methyl-*β*-anilino-*β*-(thiomethyl)acrylonitrile **75l**, yielding 85% of the 4-aminoquinoline **9l** & **9l′** with a 2:1 mixture of C7:C5 (**9l**:**9l′**) regioisomers, C7 isomer **9l** being the major one (Table 2.7).

Table 2.7. Triflic Acid-mediated *N*-Heteroannulation of *meta* Substituted *β*-Anilino-*β*-(thiomethyl)acrylonitriles 75

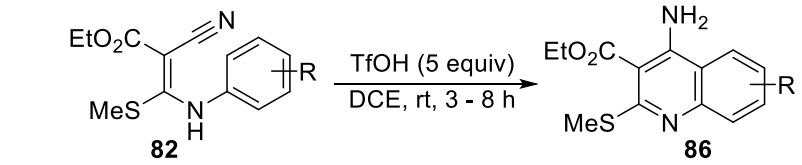




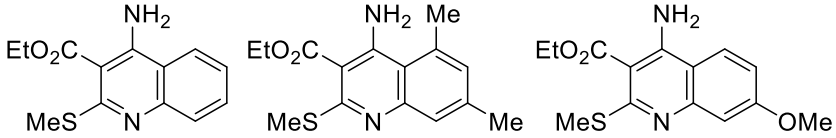


We also studied a handful of carbmethoxy substituted *β*-anilino-*β*-(thiomethyl)acrylonitriles **82** (Table 2.8). With *α*-carbmethoxy-*β*-anilino-*β*-(thiomethyl)acrylonitrile **82a**, we observed 69% of the corresponding 4-aminoquinoline **86a** (Table 2.8). The dimethyl substituted *α*-carbmethoxy-*β*-anilino-*β*-(thiomethyl)acrylonitrile **82f**, afforded the corresponding cyclized product **86f** in 72% yield (Table 2.8). We observed 55% of 4-aminoquinoline **86k** in the case of 3-methoxy-*α*-carbmethoxy-*β*-anilino-*β*-(thiomethyl)acrylonitrile **82k** (Table 2.8).

Table 2.8. Triflic Acid-mediated *N*-Heteroannulation of *β*-Anilino-α-carbmethoxy-*β*-(thiomethyl)acrylonitriles 82



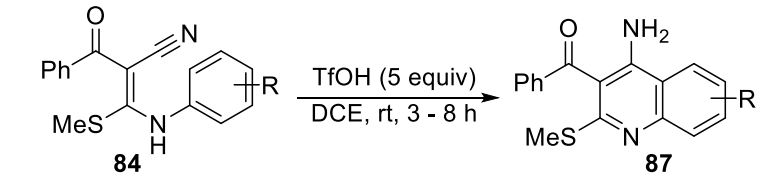
82 **86**



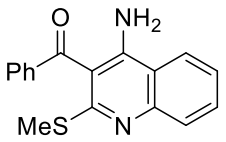
86a, 69% **86f**, 72% **86k**, 55%

Further, we studied a group of *α*-benzoyl substituted *β*-anilino-*β*-(thiomethyl)acrylonitriles **84**. The *β*-anilino-*α*-benzoyl-*β*-(thiomethyl)acrylonitrile **84a** gave 4-aminoquinoline **87a** as the cyclized product with 46% yield (Table 2.9). The dimethyl substituted *α*-benzoyl-*β*-anilino-*β*-(thiomethyl)acrylonitrile **84f** gave only 53% of the desired 4-aminoquinoline **87f** (Table 2.9)**.**

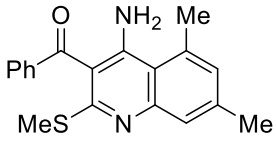
Table 2.9. Triflic Acid-mediated *N*-Heteroannulation of *β*-Anilino-*α*-benzoyl-*β*-(thiomethyl)acrylonitriles 84



84 87



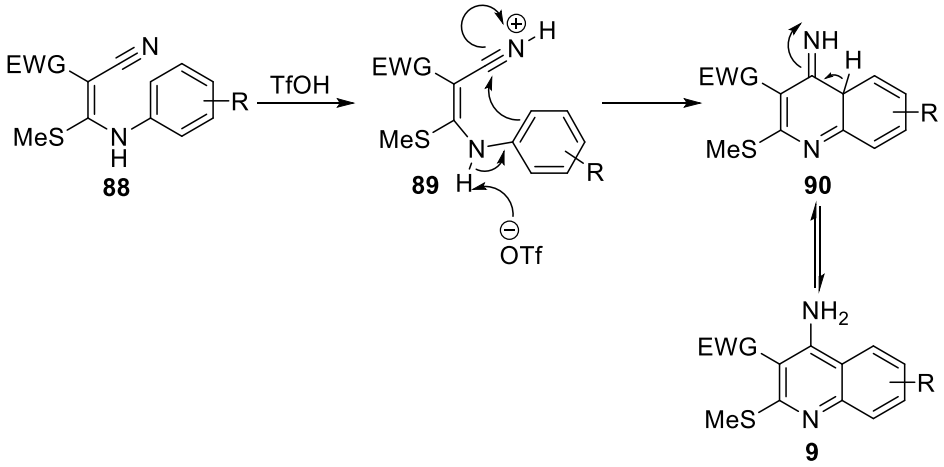
87a, 46%



87f, 53%

2.4.5. Mechanism for the Formation of 4-Aminoquinoline

The plausible mechanism can be explained for this methodology follows an ionic pathway (Scheme 2.29). Triflic acid protonates the nitrile group of *β*-anilino-*β*-(thiomethyl)acrylonitriles **88** and thereby facilitates the electrophilic attack by the aryl ring of the anilino group, leading to the formation of imine derivative **90** (Scheme 2.29). This imine derivative **90** further aromatizes to afford the 4-aminoquinoline **9** (Scheme 2.29).



88 89 90 9

Scheme 2.29. *Plausible Mechanism for Triflic Acid-mediated N-Heteroannulation reaction*

2.4.6. Plausible Explanation for the Regioselectivity

This trend of regioselectivity can be explained by *H*-bonding interaction (Figure 2.2). In case of 3-chloro and 3-methoxy *β*-anilino-*β*-(thiomethyl)acrylonitriles **75j** and **75k**, we detected C5-isomer **9j** & **9k** either being the sole product or the major isomer (Figure 2.2). This

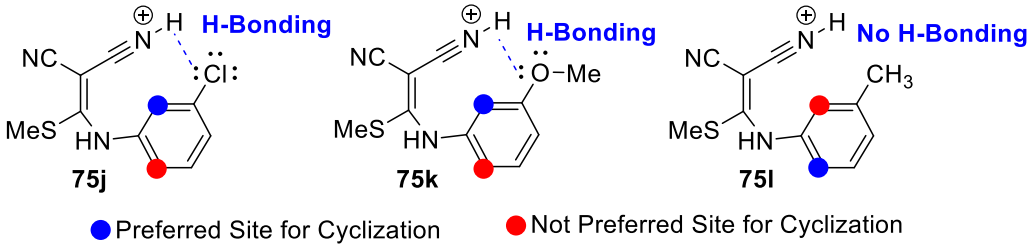


Figure 2.2. Plausible *H*-bonding interaction

can be explained by the intramolecular *H*-bond interaction between the hydrogen of protonated nitrile and the 3-chloro and 3-methoxy substituents, thereby the preferred site for cyclization is ortho to the substituents leading to the C5-subsituted 4-aminoquinolines **9j** and **9k** as the sole product or major isomer (Figure 2.2). However, 3-methyl *β*-anilino-*β*-(thiomethyl)acrylonitrile **75l** does not experience such kind of *H*-bond interaction, hence the preferred site for cyclization is *para* to the substituent (Figure 2.2). Thus, affording the C7-substituted 4-aminoquinoline **9l** as the major product (Figure 2.2).

2.5. Conclusion

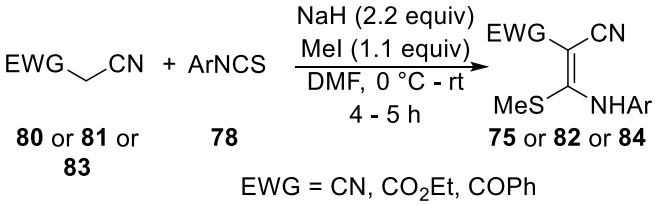
In this chapter we have discussed about the synthesis of various substituted 4-aminoquinolines via triflic acid mediated cyclization of *β*-anilino-*β*-(thiomethyl)acrylonitriles at room temperature. This method is highly chemoselective and tolerates various functional groups. We have also investigated about the role of thiomethyl group and discovered that the thiomethyl group stabilises the *β*-anilino-*β*-(thiomethyl)acrylonitriles and thereby facilitates the reaction. We isolated all the 4-aminquinolines in moderate to excellent yields. Further, we have proposed the plausible mechanism for this reaction.

2.6. Experimental Section

2.6.1. General Information

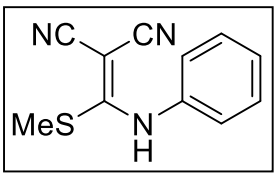
All reactions were performed by using standard vial technique with rubber septum. All solids were weighed in air. Triflic acid, TFA, AcOH, sodium hydride, Aldrich, Merck, TCI, Spectrochem or Alfa-Aesar, and used as received. Dried DMF, DMSO, Toluene and DCM were used. Isothiocyanates were synthesized from respective substituted anilines, and few isothiocyanates 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 $CDCl_3$ and DMSO-d_6 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 compound **86f** were grown by slow diffusion of n-hexane over CH_2Cl_2 solution. Single-crystal X-ray diffraction data of **86f** was 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 structure **86f** was solved with 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.

2.6.2. General Procedure for the Synthesis of *β*-Anilino-*β*-(thiomethyl)acrylonitriles 75, 82, and 84



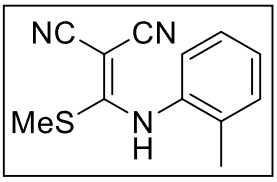
To a stirring suspension of sodium hydride (13.2 mmol, 2.2 equiv) in DMF, a solution of substituted acetonitriles (6 mmol, 1 equiv) in DMF was added dropwise at 0 °C. After being further stirred for 1 h at room temperature, a solution of isothiocyanates (6.6 mmol, 1.1 equiv) in DMF was added to the reaction mixture at 0 ^{o}C and followed by further stirring for 2 – 3 h at room temperature. Then a solution of methyl iodide (6.6 mmol, 1.1 equiv) in DMF was added and left for 30 min stirring 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.

3-Anilino-2-cyano-3-(methylthio)acrylonitrile (75a):



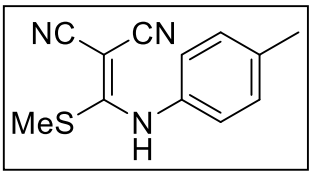
Yield: 57% (0.736 g), pale yellow solid; R_f: 0.15 in 20% ethyl acetate in hexanes; mp: 164 – 166 °C; IR (KBr, ν cm^{-1}) = 3678, 3289, 2999, 2367, 2201, 1594, 1450, 1297, 1079, 762, 494; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (s, 1H), 7.42 (m, 2H), 7.28 (m, 3H), 2.52 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 171.6, 138.4, 129.3 (2C), 126.7, 123.9 (2C), 52.9, 15.8. HR-MS (ESI-TOF) m/z: Cal. for $C_{11}H_9N_3S$ $[M+H]^+$: 216.0590, found: 216.0589.

2-Cyano-3-(2-methyl)anilino-3-(methylthio)acrylonitrile (75b):



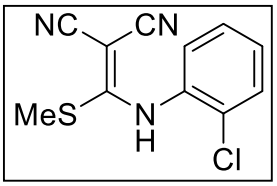
Yield: 64% (0.880 g), pale yellow solid; R_f: 0.37 in 30% ethyl acetate in hexanes; mp: 129 – 131 °C; IR (KBr, ν cm^{-1}) = 3735, 3569, 3237, 2362, 2330, 2209, 1512, 1267, 1116, 757, 449.^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 7.34 – 7.21 (m, 4H), 2.62 (s, 3H), 2.22 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 135.8, 134.4, 131.4, 128.8, 127.2, 126.7, 115.3, 114.1, 55.0, 18.0, 16.5. HR-MS (ESI-TOF) m/z cal for $C_{12}H_{11}N_3S$ $[M+H]^+$: 230.0746, found: 230.0752.

2-Cyano-3-(4-methyl)anilino-3-(methylthio)acrylonitrile (75c):



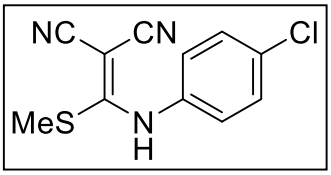
Yield: 64% (0.880 g), pale yellow solid; R_f: 0.13 in 20% ethyl acetate in hexanes; mp: 165 – 167 °C; IR (KBr, ν cm^{-1}) = 3658, 3242, 3036, 2350, 2253, 1594, 1423, 1297, 965, 759, 489; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 7.02 (m, 4H), 2.32 (s, 3H), 2.12 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 137.9, 134.7, 130.4, 124.3, 115.1, 114.6, 56.6, 21.2, 16.9. HR-MS (ESI-TOF) m/z cal. for $C_{12}H_{11}N_3S$ [M+H]+: 230.0746, found: 230.0732

3-(2-Chloro)anilino-2-cyano-3-(methylthio)acrylonitrile (75d):



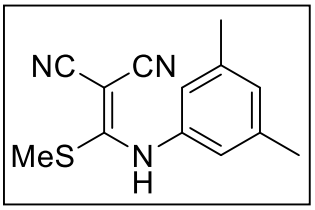
Yield: 89% (1.330 g), white solid; R_f: 0.17 in 20% ethyl acetate in hexanes; mp: 158 – 160 °C; IR (KBr, ν cm^{-1}) = 3737, 3217, 3011, 2357, 2214, 1654, 1480, 1294, 1061, 762, 447.^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 7.65 - 7.54 (m, 1H), 7.53 – 7.46 (m, 1H), 7.45 – 7.35 (m, 2H), 2.66 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 134.4, 130.6, 129.62, 129.18, 128.1, 126.6, 114.2, 113.5, 59.7, 16.9. HR-MS (ESI-TOF) cal. for $C_{11}H_8ClN_3S$ $[M+H]^+$: 250.0200, found: 250.0181.

3-(4-Chloro)anilino-2-cyano-3-(methylthio)acrylonitrile (75e):



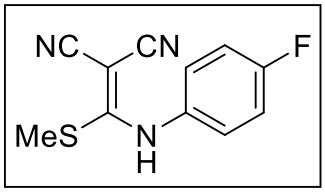
Yield: 54% (0.809 g), white solid; R_f: 0.12 in 20% ethyl acetate in hexanes; mp: 162 – 164 °C; IR (KBr, ν cm^{-1}) = 3849, 3651, 3210, 3001, 2357, 2211, 1488, 1277, 1091, 769, 501. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 2.55 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 135.9, 133.4, 130.0, 125.5, 114.51, 114.34, 58.3, 17.0. HR-MS (ESI-TOF) m/z cal. for $C_{11}H_8ClN_3S$ $[M+H]^+$: 250.0200, found: 250.0218.

2-Cyano-3-(3,5-dimethyl)anilino-3-(methylthio)acrylonitrile (75f):



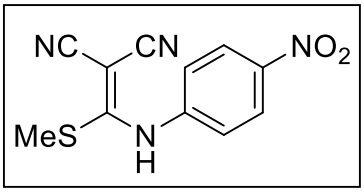
Yield: 50% (0.730 g), white solid; R_f: 0.12 in 20% ethyl acetate in hexanes; mp: 164 – 166 °C; IR (KBr, ν cm^{-1}) = 3658, 3269, 3011, 2350, 2221, 1567, 1279, 764, 489; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.43 (s, 1H), 6.90 (s, 3H), 2.52 (s, 3H), 2.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.6, 139.8, 137.0, 129.5, 122.0, 114.92, 114.45, 57.2, 21.4, 17.0. HR-MS (ESI-TOF) m/z cal. for $C_{13}H_{13}N_3S$ $[M+Na]^+$: 266.0722, found: 266.0736.

2-(((4-Fluorophenyl)amino)(methylthio)methylene)malononitrile (75g):



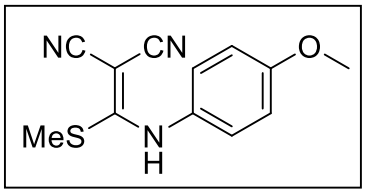
Yield: 81% (1.130 g), pale yellow solid; R_f: 0.10 in 20% ethyl acetate in hexanes; mp: 156 – 158 °C; IR (KBr): ν (cm^{-1}) = 3737, 3626, 3234, 3006, 2335, 2211, 1743, 1607, 1433, 1215, 670, 422; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.47 (s, 1H), 7.40 - 7.33 (m, 2H), 7.30 – 7.22 (m, 2H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.9, 160.5 (d, *J* = 242.7 Hz), 134.6 (d, *J* = 2.8 Hz), 126.6 (d, *J* = 8.7 Hz) (2C), 116.0 (d, *J* = 22.8 Hz) (2C), 52.4, 15.7. HR-MS (ESI) Calcd for $C_{11}H_8FN_3S$ [M+H]: 234.0496, found: 234.0504.

2-Cyano-3-methylthio-3-(4-nitro)anilinoacrylonitrile (75h):



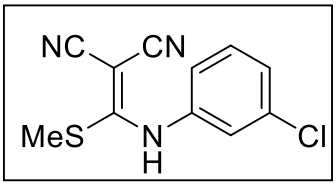
Yield: 69% (1.080 g), orange solid; R_f: 0.17 in 50% ethyl acetate in hexanes; mp: 149 – 151 °C; IR (KBr, ν cm^{-1}) = 3745, 3252, 3009, 2925, 2367, 2216, 1597, 1260, 767, 439; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.95 (s, 1H), 8.27 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 2.55 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.3, 145.0, 143.9, 125.0 (2C), 122.7 (2C), 57.4, 16.1. HR-MS (ESI-TOF) m/z cal. for $C_{11}H_8N_4O_2S$ $[M+Na]^+$: 283.0260, found: 283.0265.

2-(((4-Methoxyphenyl)amino)(methylthio)methylene)malononitrile (75i):



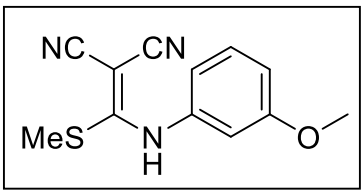
Yield: 90% (1.320 g), pale yellow solid; R_f: 0.30 in 30% ethyl acetate in hexanes; mp: 153 – 155 °C; IR (KBr, ν cm^{-1}) = 3849, 3628, 3239, 2843, 2357, 2209, 1609, 1438, 1252, 829, 516.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.17 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 2.28 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 159.1, 129.8, 126.3, 115.1, 114.9, 114.7, 56.0, 55.7, 16.9. HR-MS (ESI) Calcd for $C_{12}H_{11}N_3OS$ $[M+H]^+$: 246.0696, found: 246.0704

3-(3-Chloro)anilino-2-cyano-3-(methylthio)acrylonitrile (75j):



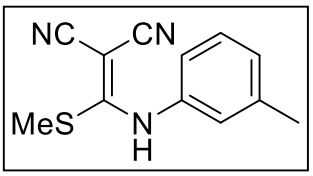
Yield: 88% (1.320 g), white solid; R_f: 0.20 in 20% ethyl acetate in hexanes; mp: 150 -152 °C; IR (KBr, ν cm^{-1}) = 3784, 3668, 3224, 2360, 2243, 1557, 1497, 1297, 1061, 762, 529; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 7.48 – 7.37 (m, 2H), 7.35 – 7.24 (m, 2H), 2.55 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 171.9, 139.9, 133.4, 130.7 (2C), 126.3, 123.5 (2C), 122.4, 54.2, 15.9. HR-MS (ESI-TOF) m/z cal. for $C_{11}H_8ClN_3S$ $[M+H]^+$: 250.0200, found: 250.0181

2-Cyano-3-methylthio-3-(3-methoxy)anilinoacrylonitrile (75k):



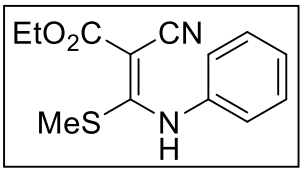
Yield: 78% (1.150 g), white solid; R_f: 0.25 in 30% ethyl acetate in hexanes; mp: 142 – 144 °C; IR (KBr, ν cm^{-1}) = 3851, 3651, 3232, 2939, 2360, 2332, 2215, 1609, 1490, 1151, 1039, 670; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.54 (s, 1H), 7.31 (t, *J* = 8.4 Hz, 1H), 6.91 – 6.78 (m, 3H), 3.76 (s, 3H), 2.52 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.6, 160.6, 138.4, 130.5, 116.2, 114.9, 114.5, 113.0, 109.9, 57.4, 55.6, 16.8. HR-MS (ESI-TOF) m/z cal for $C_{12}H_{11}N_3OS$ $[M+Na]^+$: 268.0515, found: 268.0518.

2-Cyano-3-(3-methyl)anilino-3-(methylthio)acrylonitrile (75l):



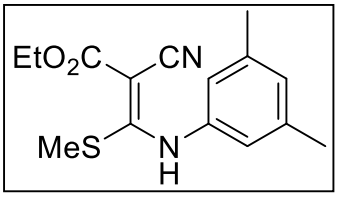
Yield: 71% (0.977 g), white solid; R_f: 0.15 in 20% ethyl acetate in hexanes; mp: 109 – 111 °C; IR (KBr, ν cm^{-1}) = 3737, 3237, 3006, 2367, 2206, 1510, 1279, 767, 432.^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.16 – 7.02 (m, 3H), 2.52 (s, 3H), 2.32 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 139.9, 137.2, 129.4, 128.3, 124.6, 121.1, 115.2, 114.5, 56.4, 21.4, 16.7. HR-MS (ESI-TOF) m/z cal. for $C_{12}H_{11}N_3S$ $[M+H]^+$: 230.0746, found: 230.0740.

Ethyl 3-anilino-3-(methylthio)acrylonitrile-2-carboxylate (82a):



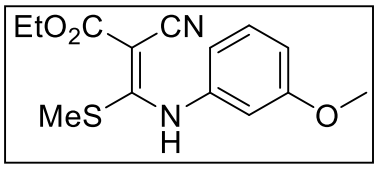
Yield: 63% (0.991 g), white solid; R_f: 0.30 in 20% ethyl acetate in hexanes; mp: 82 – 84 °C; IR (KBr, ν cm^{-1}) = 3490, 3167, 2982, 2362, 2204, 1661, 1594, 1260, 1029, 767, 519; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.51 (s, 1H), 7.44 – 7.37 (m, 2H), 7.31 - 7.27 (m, 3H), 4.27 (q, *J* = 7.2 Hz, 2H), 2.24 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 167.9, 137.7, 129.5, 127.3, 124.9, 117.7, 77.6, 61.3, 17.3, 14.4. HR-MS (ESI-TOF) m/z cal. for $C_{13}H_{14}N_2O_2S$ $[M+H]^+$: 263.0849, found: 263.0848

Ethyl 3-(3,5-dimethyl)anilino-3-(methylthio)acrylonitrile-2-carboxylate (82f):



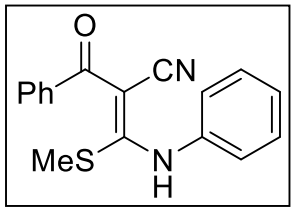
Yield: 40% (0.700 g), white solid; R_f: 0.40 in 20% ethyl acetate in hexanes; mp: 135 – 137 °C; IR (KBr, ν cm^{-1}) = 3735, 3063, 2996, 2362, 2209, 1649, 1379, 1257, 1039, 858, 516; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 6.97 (s, 2H), 6.92 (s, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 2.27 (s, 6H), 2.24 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 169.8, 165.8, 138.6, 138.2, 128.0, 121.5, 117.7, 76.2, 60.5, 20.8, 16.6, 14.2. HR-MS (ESI-TOF) m/z cal. for $C_{15}H_{18}N_2O_2S$ $[M+Na]^+$: 313.0981, found: 313.1013

Ethyl 3-methylthio-3-(3-methoxy)anilinoacrylonitrile-2-carboxylate (82k):



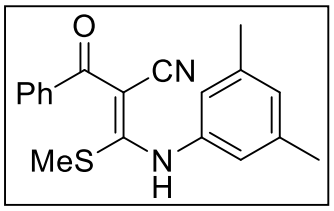
Yield: 56% (0.982 g), white solid; R_f: 0.17 in 20% ethyl acetate in hexanes; mp: 117 – 119 °C; IR (KBr, ν cm^{-1}) = 3690, 3009, 2984, 2318, 2204, 1552, 1374, 1262, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.45 (s, 1H), 7.28 (t, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.85 – 6.78 (m, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 2.25 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 167.9, 160.4, 138.8, 130.3, 117.7, 117.0, 112.8, 110.5, 77.7, 61.3, 55.6, 17.4, 14.4. HR-MS (ESI-TOF) m/z cal. for $C_{14}H_{16}N_2O_3S$ $[M+Na]^+$: 315.0774, found: 315.0762.

3-Anilino-2-benzoyl-3-(methylthio)acrylonitrile (84a):



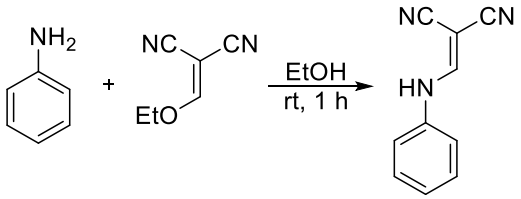
Yield: 30% (0.530 g), yellow jelly; R_f: 0.30 in 20% ethyl acetate in hexanes; IR (KBr, ν cm^{-1}) = 3849, 3730, 3009, 2280, 2199, 1733, 1589, 1450, 1374, 1277, 757, 420; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 7.74 – 7.68 (m, 2H), 7.59 - 7.51 (m, 1H), 7.51 – 7.45 (m, 3H), 7.44 - 7.39 (m, 3H), 7.35 – 7.29 (m, 1H), 2.34 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 190.2, 172.4, 138.5, 137.9, 131.7, 129.5, 128.17, 128.04, 127.1, 124.4, 119.9, 85.1, 16.9. HR-MS (ESI-TOF) m/z cal. for $C_{17}H_{14}N_2OS$ $[M+H]^+$: 295.0900, found: 295.0892

2-Benzoyl-3-(3,5-dimethyl)anilino-3-(methylthio)acrylonitrile (84f):



Yield: 29% (0.560 g), yellow solid; R_f: 0.37 in 20% ethyl acetate in hexanes; mp: 139 – 141 °C; IR (KBr, ν cm^{-1}) = 3680, 2999, 2974, 2315, 1760, 1572, 1460, 1374, 1272, 769, 412; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 (s, 1H), 7.80 - 7.63 (m, 2H), 7.60 - 7.40 (m, 3H), 7.01 (s, 2H), 6.96 (s, 1H), 2.38 (s, 3H), 2.28 (s, 6H).^{13}C NMR (100 MHz, DMSO-d_6) δ 190.7, 172.8, 139.3, 139.0, 138.1, 132.0, 129.1, 128.6, 128.4, 122.3, 120.3, 85.3, 21.2, 17.5. HR-MS (ESI-TOF) m/z cal. for $C_{19}H_{18}N_2OS$ $[M+H]^+$: 323.1213, found: 323.1220

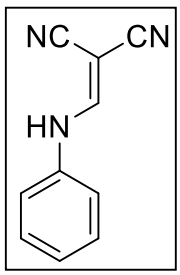
2.6.3. Synthesis of 2-(Phenylamino)methylene Malononitrile



78 **91** **85**, 78%

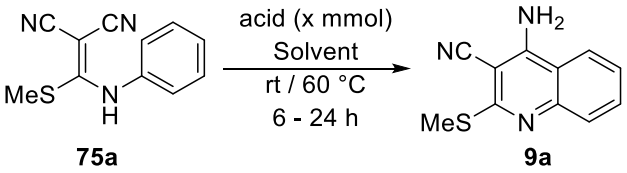
To a saturated solution of 2-(ethoxymethylene)malononitrile **91** (6 mmol, 1 equiv) in ethanol (20 ml), aniline **78** (7.2 mmol, 1.2 equiv) was added under stirring. After 1 h, the resulting precipitate was filtered and washed with ethanol and diethyl ether. The product **85** was not purified further and used as such for the next step.

3-Anilino-2-(cyano)acrylonitrile 85



Yield: 78% ; ^{1}H NMR (700 MHz, DMSO-d_6) δ 11.11 (s, 1H), 8.49 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.37 (t, *J* = 8.4 Hz, 2H), 7.17 (t, *J* = 7.7 Hz, 1H). ^{13}C NMR (175 MHz, DMSO-d_6) δ 155.8, 139.2, 129.4, 125.2, 118.0, 116.5, 114.2, 51.8. HR-MS (ESI-TOF) m/z: cal. for $C_{10}H_7N_3$ $[M+H]^+$: 170.0713, found: 170.0708.

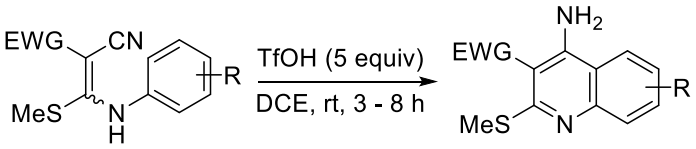
2.6.4. General Procedure for Optimization of *β*-Anilino-*β*-(thiomethyl)acrylonitrile 75a



75a **9a**

An oven-dried sealed tube was charged with the respective *β*-anilino acrylonitrile (0.5 mmol) **3a**, acid (mmol), in solvent (2.0 mL). The mixture was stirred at room temperature or 60 ℃ for 6 – 24 h. The reaction mixture was monitored by TLC. After the starting material was completely consumed, the reaction mixture was quenched with saturated $NaHCO_3$ 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 product was purified by flash chromatography using hexane and EtOAc as eluent.

2.6.5. General Procedure for the Synthesis of 4-Aminoquinolines 9 and 82

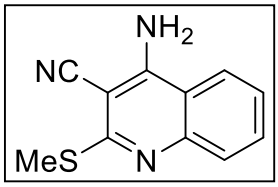


75, 82, 84 **9, 86, 87**

EWG = CN, CO_2Et, COPh, 2-FAr

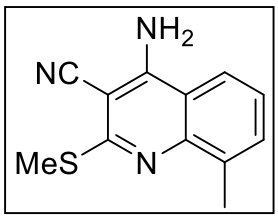
An oven-dried sealed tube was charged with the respective *β*-anilino acrylonitriles (1 mmol), triflic acid (5 mmol or 15 mmol) in DCE (4.0 mL). The mixture was stirred at room temperature or 60 ℃ for 3 – 6 h. The reaction mixture was monitored by TLC. After the starting material was completely consumed, the reaction mixture was quenched with saturated $NaHCO_3$ 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 product was purified by flash chromatography using hexane and EtOAc as eluent.

4-Amino-3-cyano-2-(methylthio)quinoline (9a):



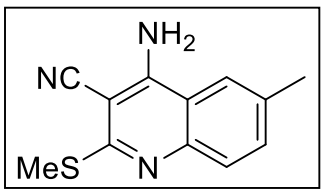
Reaction Time: 6 h; Yield: 87% (0.187 g), white solid; R_f: 0.32 in 20% ethyl acetate in hexanes; mp: 249 – 251 °C; IR (KBr, ν cm^{-1}) = 3701, 3353, 2945, 2834, 2228, 2040, 1667, 1457, 1284, 1027, 746; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, *J* = 8.4 Hz, 1H), 7.87 (brs, 2H), 7.75 – 7.65 (m, 2H), 7.46 - 7.37 (m, 1H), 2.59 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 159.2, 155.4, 147.6, 132.3, 128.0, 124.6, 123.0, 116.0, 115.5, 82.4, 12.3. HR-MS (ESI-TOF) m/z cal. for $C_{11}H_9N_3S$ $[M+H]^+$: 216.0589, found: 216.0618

4-Amino-3-cyano-8-methyl-2-(methylthio)quinoline (9b):



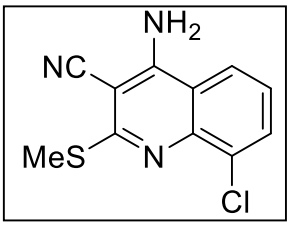
Reaction Time: 4 h; Yield: 80% (0.183 g), pale yellow solid; R_f: 0.17 in 20% ethyl acetate in hexanes; mp: 209 – 211 °C; IR (KBr, ν cm^{-1}) = 3706, 3355, 3063, 2947, 2307, 2048, 1658, 1450, 1270, 1030, 766; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.0 Hz, 1H), 7.77 (brs, 2H), 7.58 (d, *J* = 6.8 Hz, 1H), 7.33 - 7.27 (m, 1H), 2.61 (s, 3H), 2.58 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 155.8, 146.1, 135.5, 132.6, 124.1, 120.7, 116.2, 115.1, 82.3, 17.8, 12.4. HR-MS (ESI-TOF) m/z cal. for $C_{12}H_{11}N_3S$ $[M+H]^+$: 230.0746, found: 230.0750.

4-Amino-3-cyano-6-methyl -2-(methylthio)quinoline (9c):



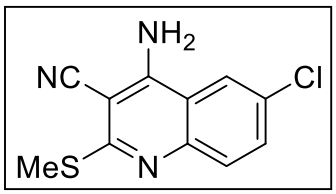
Reaction Time: 3 h; Yield: 43% (0.099 g), white solid; R_f: 0.27 in 20% ethyl acetate in hexanes; mp: 193 – 195 °C; IR (KBr, ν cm^{-1}) = 3765, 3696, 3014, 2888, 2312, 2058, 1759, 1472, 1257, 1032, 753; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 1H), 7.75 (brs, 2H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 2.58 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.1, 155.1, 146.0, 134.1, 133.9, 127.8, 122.2, 116.1, 115.3, 82.4, 21.1, 12.3. HR-MS (ESI-TOF) m/z cal. for $C_{12}H_{11}N_3S$ $[M+H]^+$: 230.0746, found: 230.0751

4-Amino-8-chloro-3-cyano-2-(methylthio)quinoline (9d):



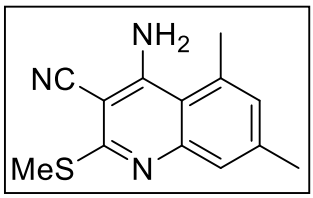
Reaction Time: 4 h; Yield: 89% (0.222 g), pale yellow solid; R_f: 0.35 in 20% ethyl acetate in hexanes; mp: 263 – 265 °C; IR (KBr, ν cm^{-1}) = 3701, 3649, 3350, 2843, 2359, 2068, 1784, 1509, 1270, 1032, 761, 664; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, *J* = 8.4 Hz, 1H), 8.03 (brs, 2H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 155.6, 143.5, 132.4, 131.4, 124.5, 122.3, 117.0, 115.6, 83.1, 12.4; HR-MS (ESI-TOF) m/z cal. for $C_{11}H_8ClN_3S$ $[M+H]^+$: 250.0200, found: 250.0201.

4-Amino-6-chloro-3-cyano-2-(methylthio)quinoline (4e):



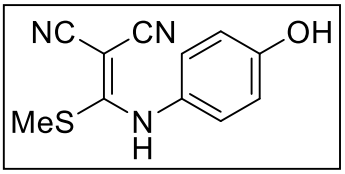
Reaction Time: 3 h; Yield: 70% (0.175 g), pale yellow solid; R_f: 0.28 in 20% ethyl acetate in hexanes; mp: 223 – 225 °C; IR (KBr, ν cm^{-1}) = 3711, 3367, 2949, 2512, 2362, 2043, 1662, 1452, 1267, 1030, 758; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 7.93 (s, 2H), 7.73 – 7.67 (m, 2H), 2.59 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 160.0, 154.6, 146.2, 132.4, 130.0, 129.0, 122.4, 116.5, 115.6, 83.1, 12.3. HR-MS (ESI-TOF) m/z cal for $C_{11}H_8ClN_3S$ $[M+H]^+$: 250.0200, found: 250.0255.

4-Amino-3-cyano-5,7-dimethyl-2-(methylthio)quinoline (9f):



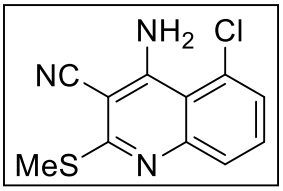
Reaction Time: 3 h; Yield: 63% (0.153 g), white solid; R_f: 0.25 in 20% ethyl acetate in hexanes; mp: 229 – 231 °C; IR (KBr, ν cm^{-1}) = 3745, 3686, 3007, 2881, 2307, 2065, 1507, 1275, 1257, 1045, 761; ^{1}H NMR (400 MHz, TFA-d) δ 8.92 (s, 1H), 8.75 (s, 1H), 4.32 (s, 3H), 4.27 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, TFA-d) δ 156.73, 156.62, 146.9, 137.4, 134.3, 131.4, 114.7, 108.69, 108.46, 81.8, 19.1, 17.1, 9.7; HR-MS (ESI-TOF) m/z cal. for $C_{13}H_{13}N_3S$ $[M+H]^+$: 244.0903, found: 244.0921.

2-Cyano-3-(4-hydroxy)anilino-3-(methylthio)acrylonitrile (75m):



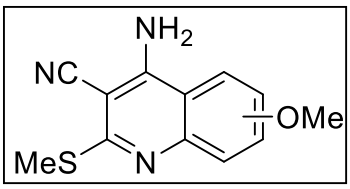
Reaction Time: 3 h, Yield: 30% (0.069 g), pale yellow solid; R_f: 0.22 in 30% ethyl acetate in hexanes; IR (KBr, ν cm^{-1}) = 3673, 3265, 3115, 2889, 2374, 2230, 1590, 1450, 1235, 847, 523; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 9.66 (s, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 2.53 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 171.3, 156.5, 129.4, 126.3 (2C), 115.7 (2C), 50.8, 15.6. HR-MS (ESI-TOF) m/z calcd for $C_{11}H_9N_3OS$ [M + H]+: 232.0539, found: 232.0535.

4-Amino-5-chloro-3-cyano-2-(methylthio)quinoline (9j):



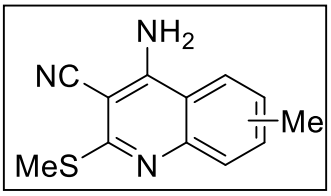
Reaction Time: 4 h; Yield: 80% (0.200 g), pale yellow solid; R_f: 0.25 in 20% in ethyl acetate in hexanes; mp: 200 – 202 °C; IR (KBr, ν cm^{-1}) = 3750, 3686, 3335, 2836, 2332, 2040, 1704, 1452, 1129, 1030, 652; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 – 7.58 (m, 4H), 7.47 (d, *J* = 6.4 Hz, 1H), 2.59 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.0, 154.8, 149.8, 132.0, 128.9, 128.3, 127.6, 115.4, 112.3, 84.8, 12.2. HR-MS (ESI-TOF) m/z cal. for $C_{11}H_8ClN_3S$ $[M+H]^+$: 250.0200, found: 250.0200.

4-Amino-3-cyano-5/7-methoxy-2-(methylthio)quinoline (9k & 9k′): (Major Isomer)



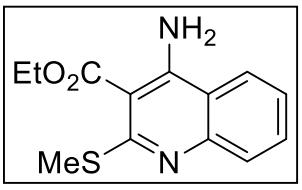
Reaction Time: 3 h; Yield: 70% (0.172 g), pale yellow solid; R_f: 0.32 in 30% ethyl acetate in hexanes; mp: 194 – 196 °C; IR (KBr, ν cm^{-1}) = 3681, 3360, 2975, 2942, 2364, 2073, 1684, 1452, 1267, 1032, 756; Diastereomeric ratio, (C5:C7): 2:1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (brs, 2H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 3.98 (s, 3H), 2.56 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 159.5, 157.7, 155.9, 149.6, 132.5, 120.5, 115.9, 105.4, 82.7, 56.4, 12.1. HR-MS (ESI-TOF) m/z cal. for $C_{12}H_{11}N_3OS$ $[M+H]^+$: 246.0696, found: 246.0702.

4-Amino-3-cyano-5/7-methyl -2-(methylthio)quinoline (9l & 9l′): (Major Isomer)



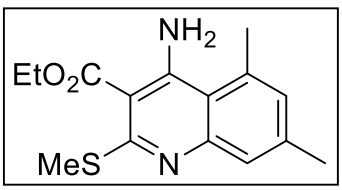
Reaction Time: 3 h; Yield: 73% (0.167 g), white solid; R_f: 0.20 in 20% ethyl acetate in hexanes; mp: 200 – 202 °C; IR (KBr, ν cm^{-1}) = 3701, 3345, 2949, 2510, 2362, 2048, 1448, 1275, 1025, 758, 659; Diastereomeric ratio, (C7:C5): 2:1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, *J* = 8.4 Hz, 1H), 7.74 (brs, 2H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.02 (s, 1H), 2.58 (s, 3H), 2.43 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 159.1, 155.3, 147.7, 135.4, 131.5, 127.3, 122.8, 116.1, 113.3, 82.0, 21.1, 12.3. HR-MS (ESI-TOF) m/z cal. for $C_{12}H_{11}N_3S$ $[M+H]^+$: 230.0746, found: 230.0757.

Ethyl 4-amino-2-(methylthio)quinoline-3-carboxylate (86a):



Reaction Time: 3 h; Yield: 69% (0.181 g), pale yellow jelly; R_f: 0.27 in 20% ethyl acetate in hexanes; IR (KBr, ν cm^{-1}) = 3678, 3362, 2945, 2532, 2055, 1677, 1448, 1277, 1025, 758, 672; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, *J* = 8.4 Hz, 1H), 8.05 (s, 2H), 7.71 – 7.60 (m, 2H), 7.43 – 7.35 (m, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 2.46 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 167.3, 160.1, 153.8, 146.8, 131.6, 127.8, 124.1, 123.1, 116.4, 99.9, 60.7, 14.2 (2C). HR-MS (ESI-TOF) m/z cal. for $C_{13}H_{14}N_2O_2S$ $[M+H]^+$: 263.0849, found: 263.0841

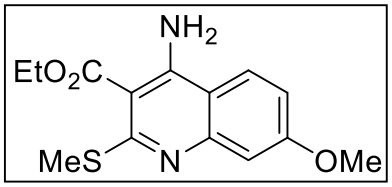
Ethyl 4-amino-5,7-dimethyl-2-(methylthio)quinoline-3-carboxylate (86f):



Reaction Time: 4 h; Yield: 72% (0.209 g), white solid; R_f: 0.32 in 20% ethyl acetate in hexanes; mp: 99 – 101 °C; IR (KBr, ν cm^{-1}) = 3701, 3348, 2945, 2834, 2532, 2055, 1677, 1448, 1277, 1025, 763, 659; ^{1}H NMR (700 MHz, DMSO-d_6) δ 7.95 (s, 2H), 7.89 (s, 1H), 7.37 (s, 1H), 4.41 – 4.30 (m, 2H), 2.54 (s, 3H), 2.44 (s, 3H), 2.40 (s, 3H), 1.37 (t, *J* = 7.0 Hz, 3H).^{13}C NMR (175 MHz, DMSO-d_6) δ 167.6, 158.1, 154.1, 143.8, 135.2, 133.6, 132.8, 119.8, 115.8, 99.4, 60.6, 21.2,

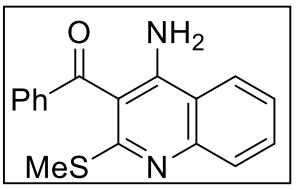
17.6, 14.3, 14.2.HR-MS (ESI-TOF) m/z cal. for $C_{15}H_{18}N_2O_2S$ $[M+H]^+$: 291.1162, found: 291.1164

4-Amino-7-methoxy-2-(methylthio)quinoline-3-carboxylate (86k):



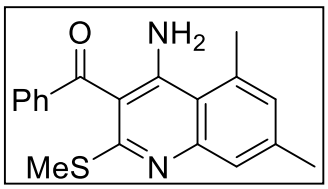
Reaction Time: 4 h; Yield: 55% (0.161 g), white solid; R_f: 0.30 in 20% ethyl acetate in hexanes; mp: 91 – 93 °C; IR (KBr, ν cm^{-1}) = 3703, 3348, 3081, 2947, 2537, 2080, 1682, 1453, 1262, 1035, 761, 662; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, *J* = 8.8 Hz, 1H), 7.92 (s, 2H), 7.06 (d, *J* = 2.4 Hz, 1H), 7.01 (dd, *J* = 9.2, 2.4 Hz, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 2.46 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (175 MHz, DMSO-d_6) δ 167.3, 161.9, 160.8, 153.7, 148.8, 124.5, 115.2, 110.4, 107.3, 98.8, 60.4, 55.3, 14.09, 14.05. HR-MS (ESI-TOF) m/z cal. for $C_{14}H_{16}N_2O_3S$ $[M+H]^+$: 293.0954, found: 293.0961

4-Amino-3-benzoyl-2-(methylthio)quinoline (87a):



Reaction Time: 8 h; Yield: 46% (0.135 g), orange jelly; R_f: 0.28 in 20% ethyl acetate in hexanes; IR (KBr, ν cm^{-1}) = 3752, 3368, 2962, 2545, 2047, 1710, 1655, 1485, 1265, 1045, 763; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 8.43 (s, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.47 – 7.38 (m, 3H), 7.21 (t, *J* = 7.2 Hz, 2H), 6.99 (d, *J* = 7.2 Hz, 2H), 6.32 (d, *J* = 7.6 Hz, 1H), 2.47 (s, 3H).^{13}C NMR (175 MHz, DMSO-d_6) δ 186.5, 167.8, 163.2, 150.5, 139.8, 134.9, 131.42, 131.38, 129.3, 124.6, 123.8, 121.4, 120.0, 100.4, 11.7. HR-MS (ESI-TOF) cal. for $C_{17}H_{14}N_2OS$ $[M+H]^+$: 295.0900, found: 295.0900

4-Amino-3-benzoyl-5,7-dimethyl-2-(methylthio)quinoline (87f):



Reaction Time: 8 h; Yield: 53% (0.171 g), orange jelly; R_f: 0.24 in 20% ethyl acetate in hexanes; IR (KBr, ν cm^{-1}) = 3730, 3365, 2831, 2041, 1715, 1645, 1465, 1262, 1035, 758, 662; ^{1}H NMR (400

MHz, DMSO-d_6) δ 10.47 (s, 1H), 8.05 (d, *J* = 7.2 Hz, 2H), 7.67 - 7.61 (m, 1H), 7.61 - 7.55 (m, 3H), 7.34 (s, 1H), 7.12 (s, 1H), 2.70 (s, 3H), 2.63 (s, 3H), 2.43 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 165.9, 158.5, 150.6, 142.7, 139.2, 133.92, 133.87, 132.1, 130.7, 128.7, 127.7, 126.0, 120.7, 118.6, 22.7, 20.9, 12.3. HR-MS (ESI-TOF) m/z cal. for $C_{19}H_{18}N_2OS$ $[M+H]^+$: 323.1213, found: 323.1281.

2.7. Crystal Data

Crystal Data for **86f** in CH_2Cl_2/n-hexane: $C_{15}H_{18}N_2O_2S$, Mw = 290.37, monoclinic, space group P 1 21/c 1, a = 9.3141(1) Å, b = 7. 60332(10) Å, c = 20.7811(2) Å, α = 90 °, β = 93.9407(9) °, γ = 90 °, V = 1468.20(3) Å^3, Z = 4, D_{calc} = 1.314 g/cm^3, T = 297 K, R1 = 0.0414(2769), wR2 = 0.1186(2960), GOF = 1.038

2.8. 1H & 13C Spectrum of Selected Compounds

Figure 2.4a. ^{1}H Spectrum of **75a** in DMSO-d_6 (400 MHz)

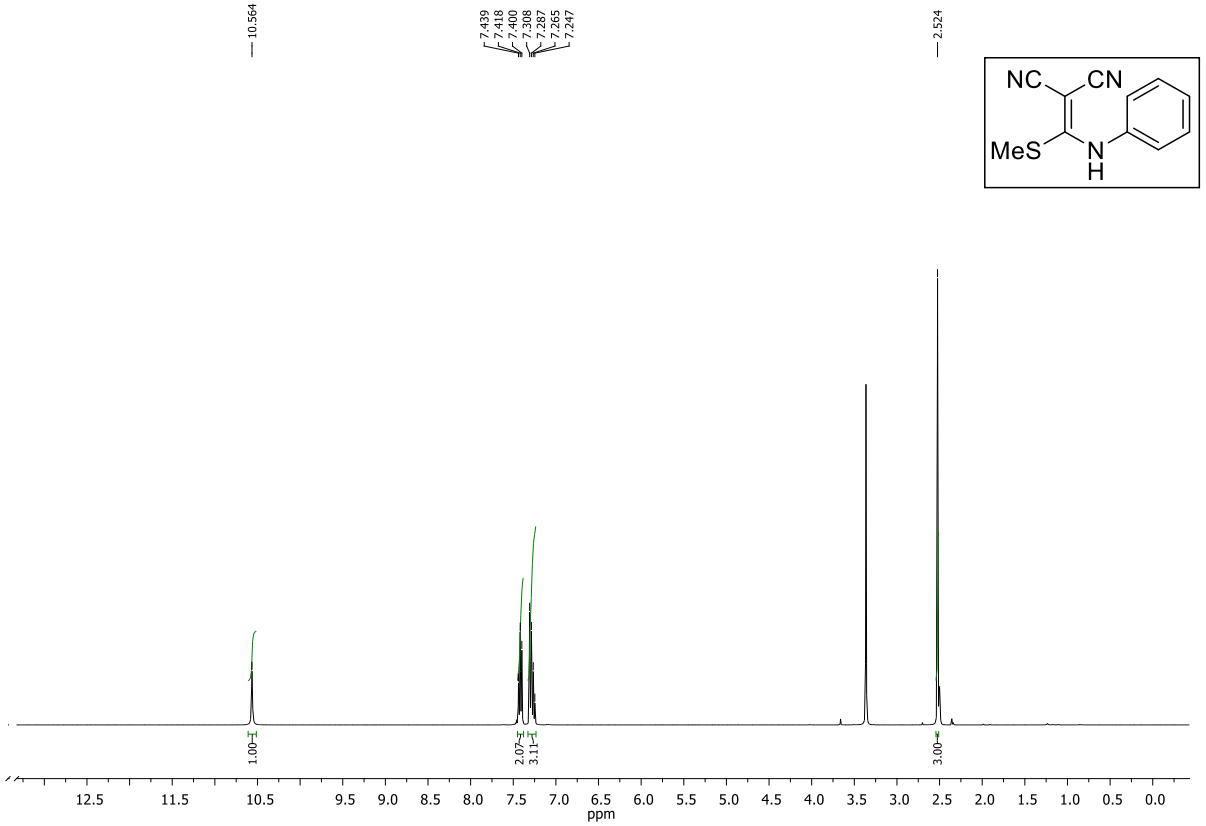


Figure 2.4b. ^{13}C Spectrum of **75a** in DMSO-d_6 (100 MHz)

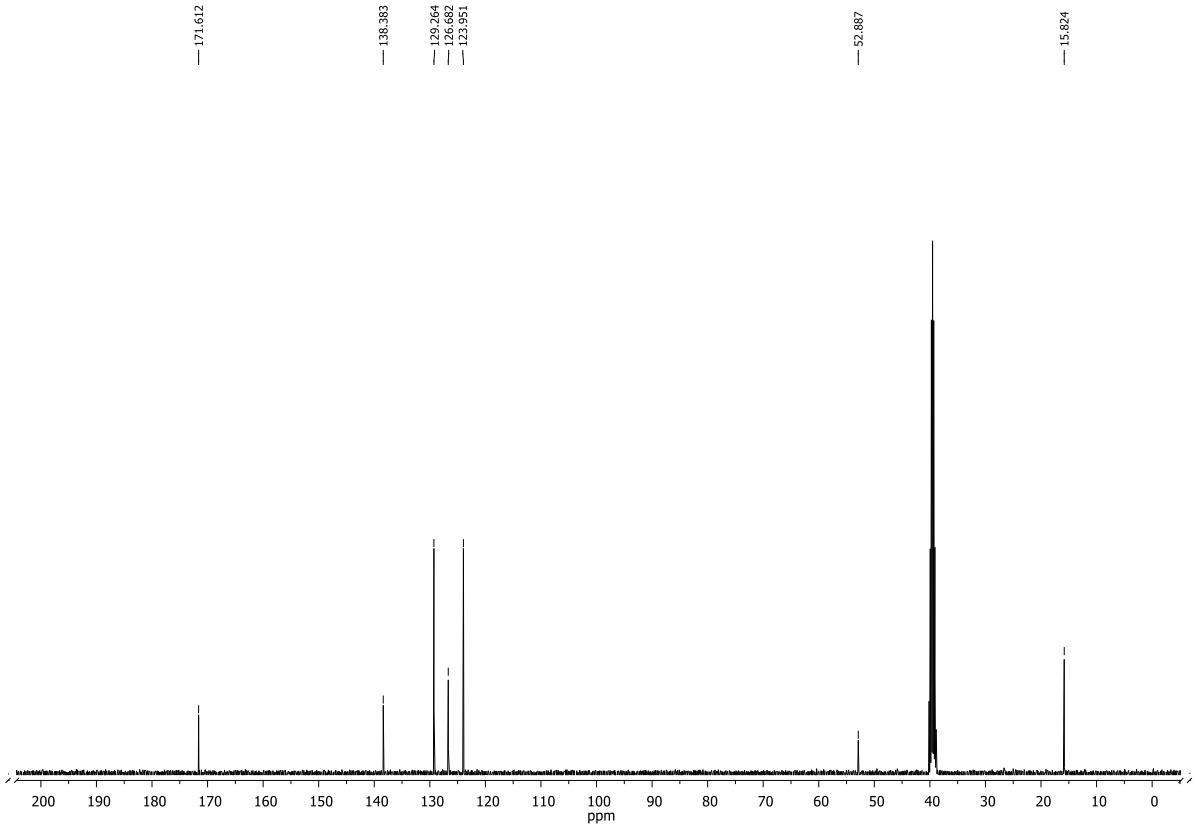


Figure 2.5a. ^{1}H Spectrum of **75b** in DMSO-d_6 (400 MHz)

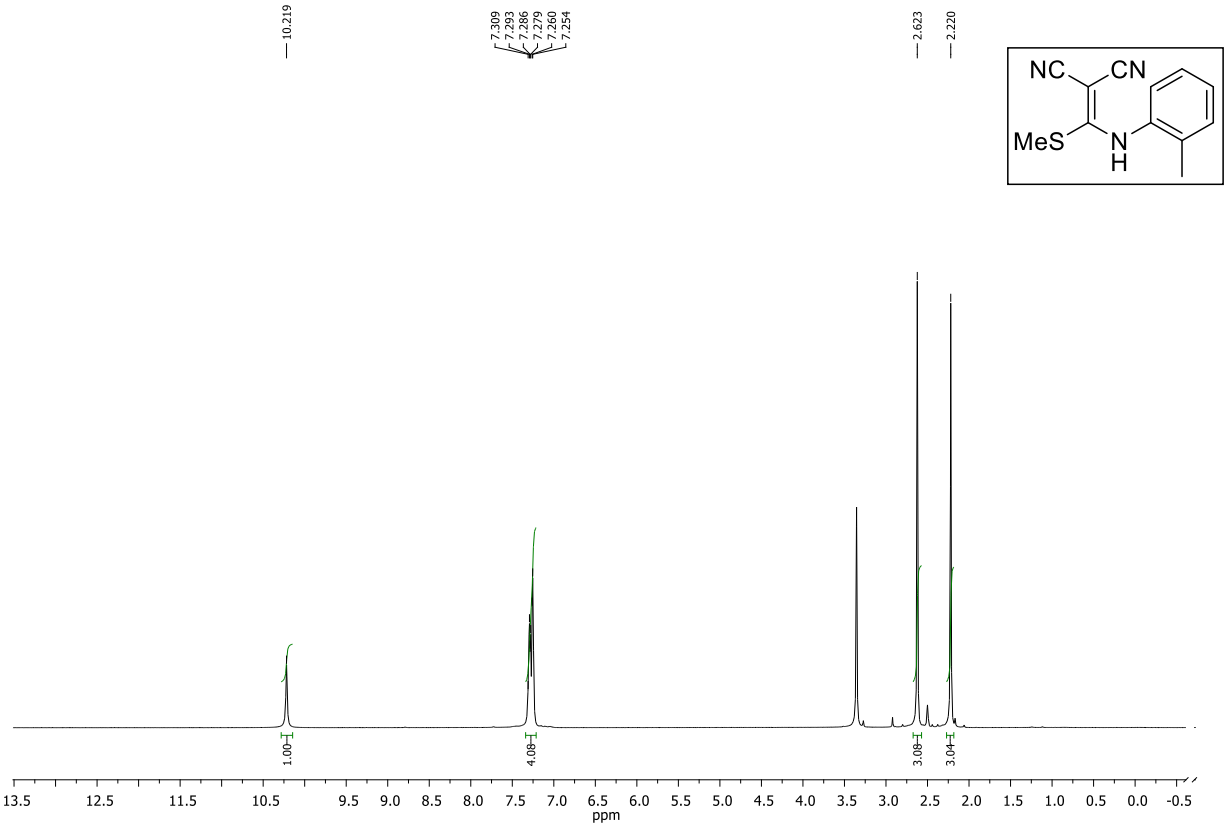


Figure 2.5b. ^{13}C Spectrum of **75b** in $CDCl_3$ (100 MHz)

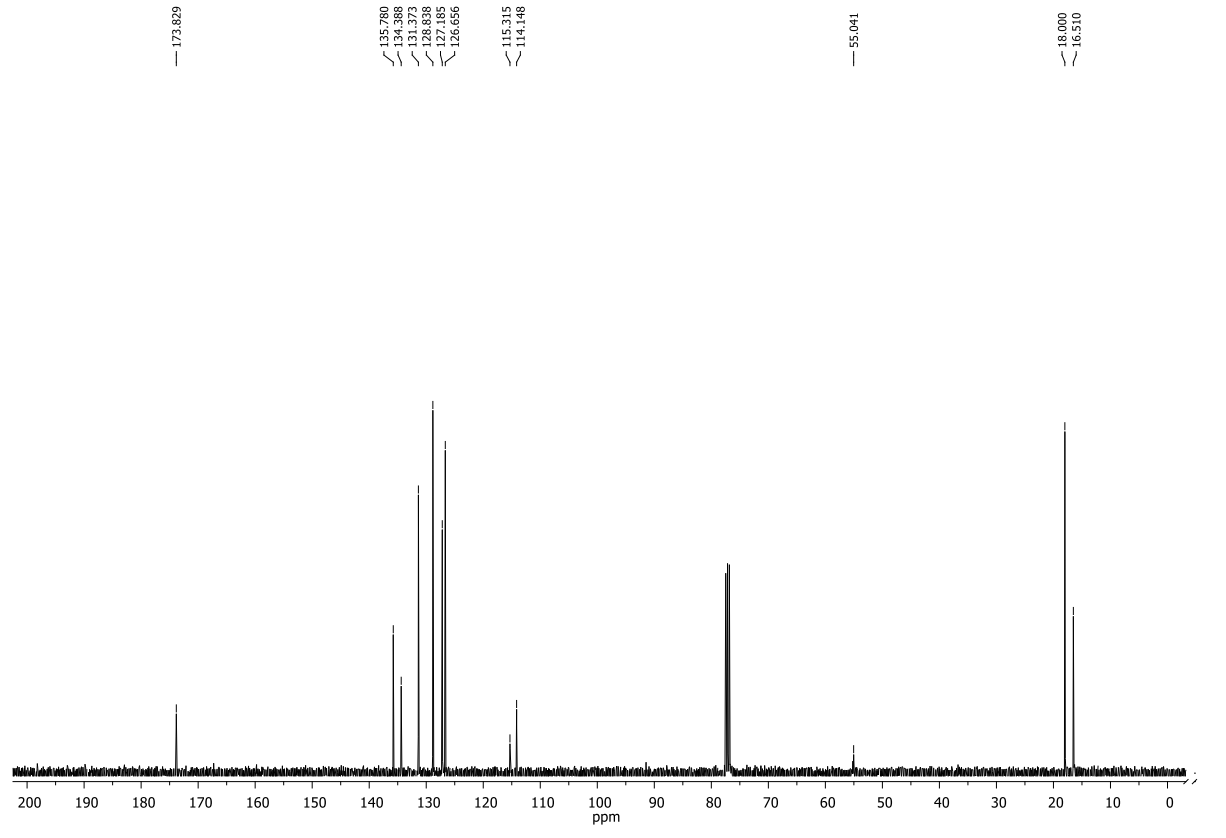


Figure 2.6a. ^{1}H Spectrum of **75c** in DMSO-d_6 (400 MHz)

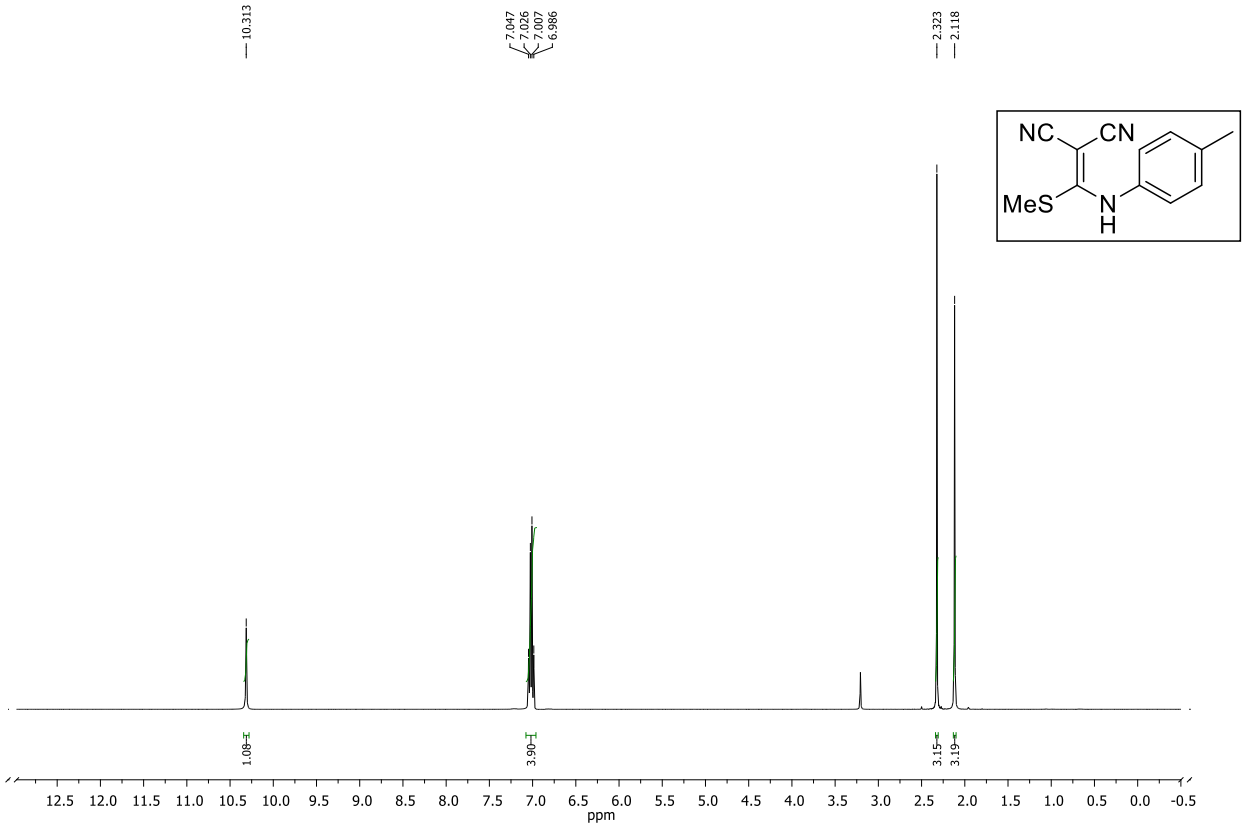


Figure 2.6b. ^{13}C Spectrum of **75c** in $CDCl_3$ (100 MHz)

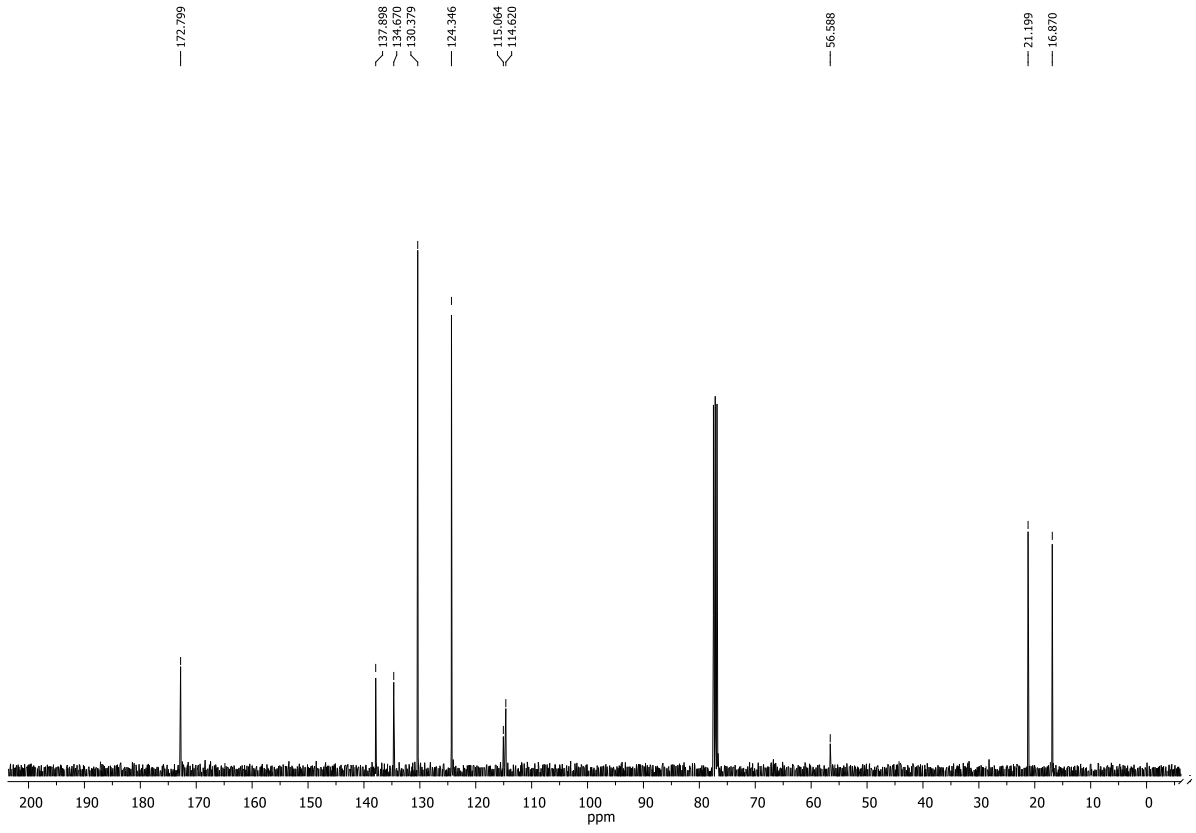


Figure 2.7a. ^{1}H Spectrum of **75h** in DMSO-d_6 (400 MHz)

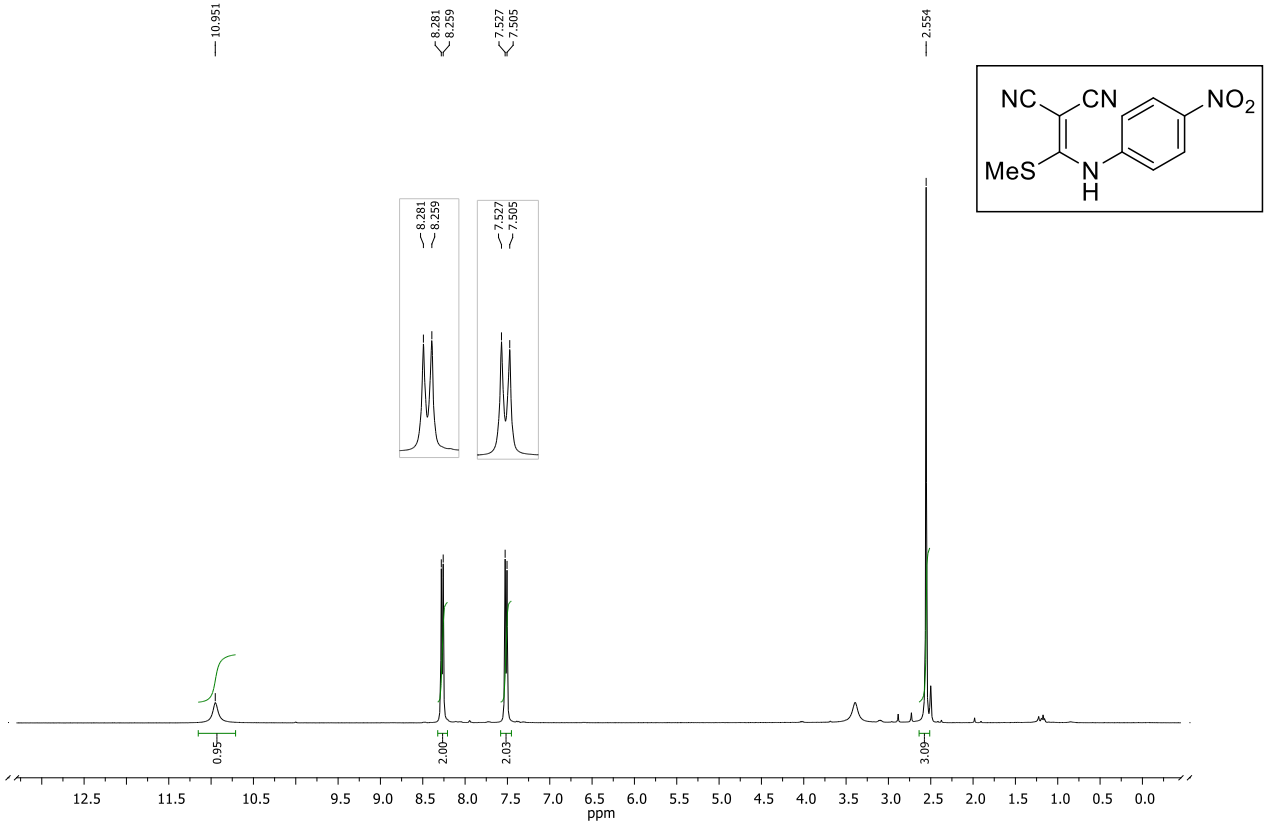


Figure 2.7b. ^{13}C Spectrum of **75h** in DMSO-d_6 (100 MHz)

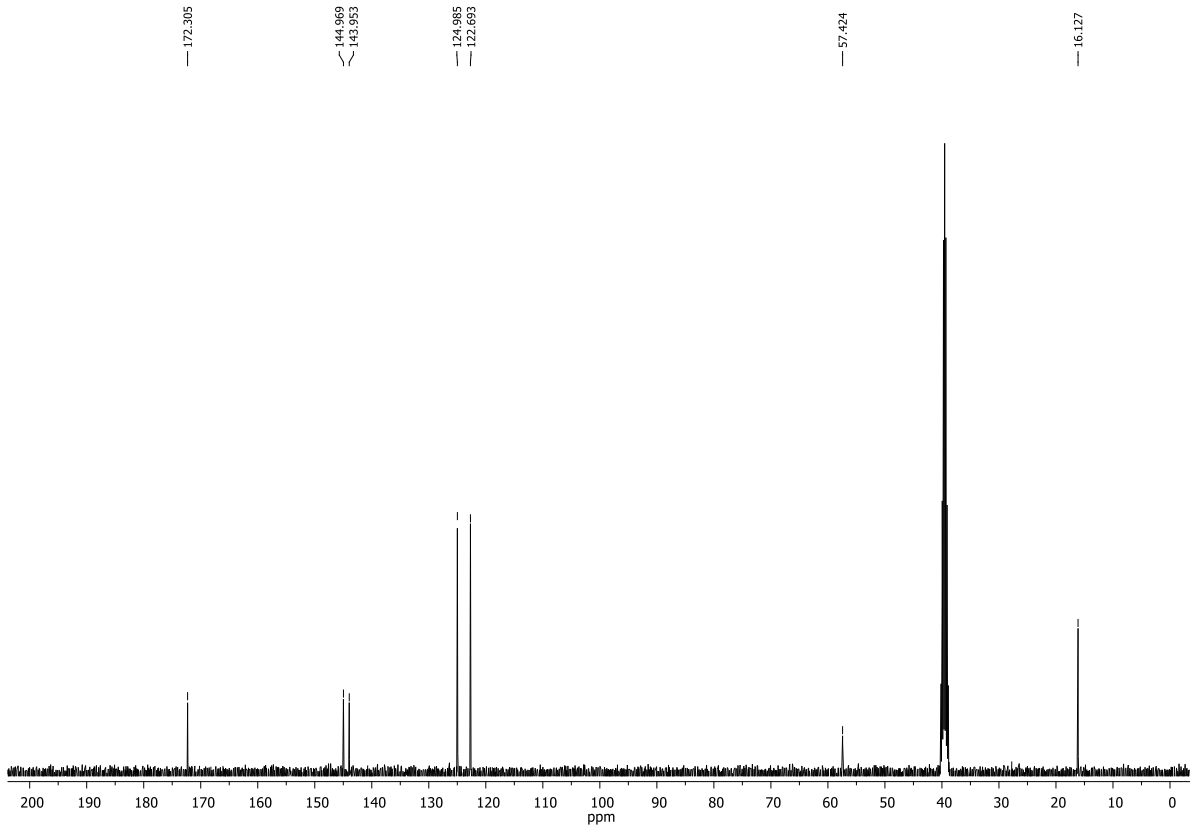


Figure 2.8a. ^{1}H Spectrum of **75i** in $CDCl_3$ (400 MHz)

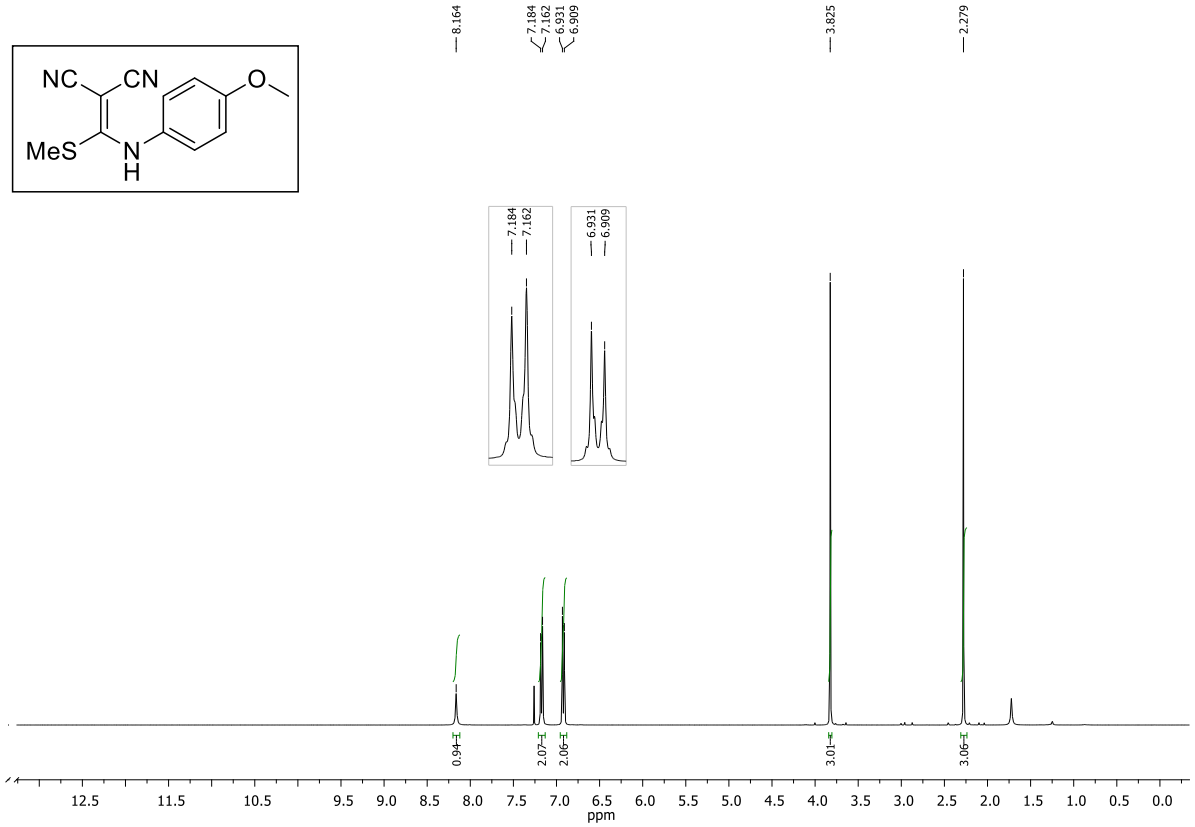


Figure 2.8b. ^{13}C Spectrum of **75i** in $CDCl_3$ (400 MHz)

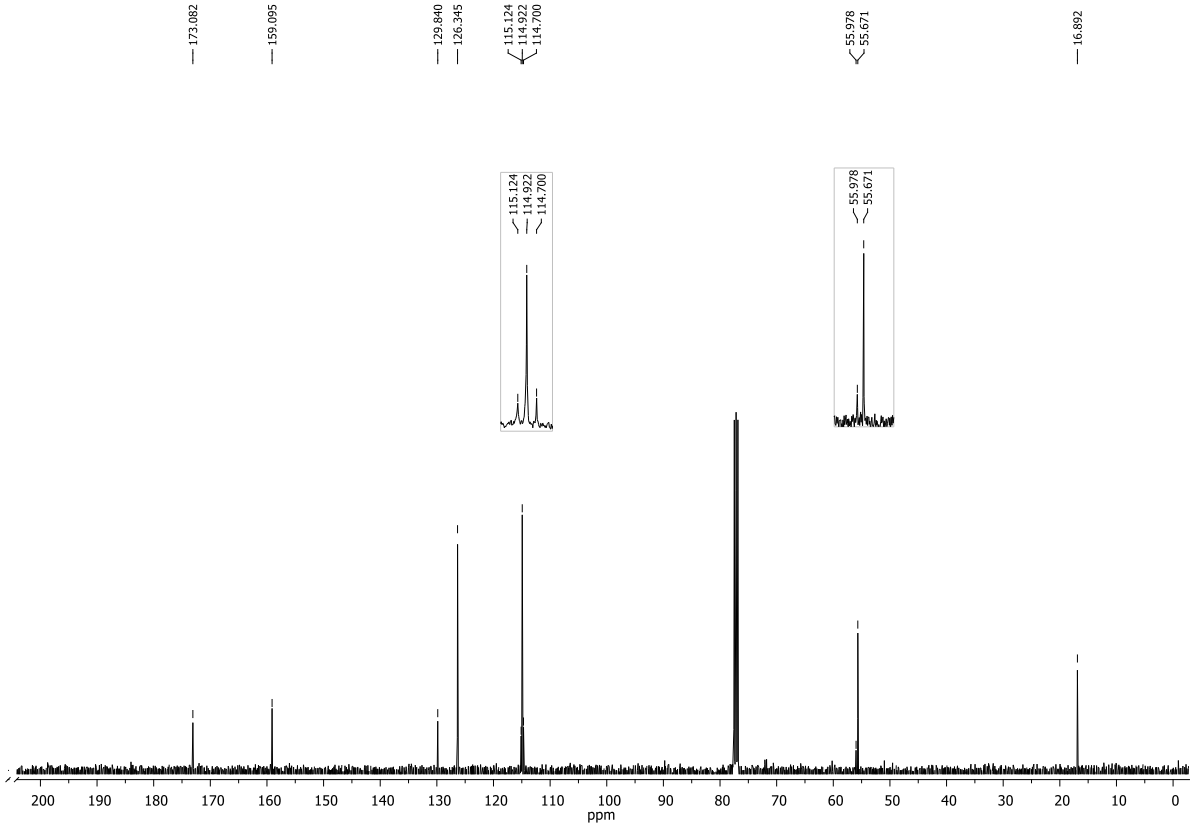


Figure 2.9a. ^{1}H Spectrum of **75j** in DMSO-d_6 (400 MHz)

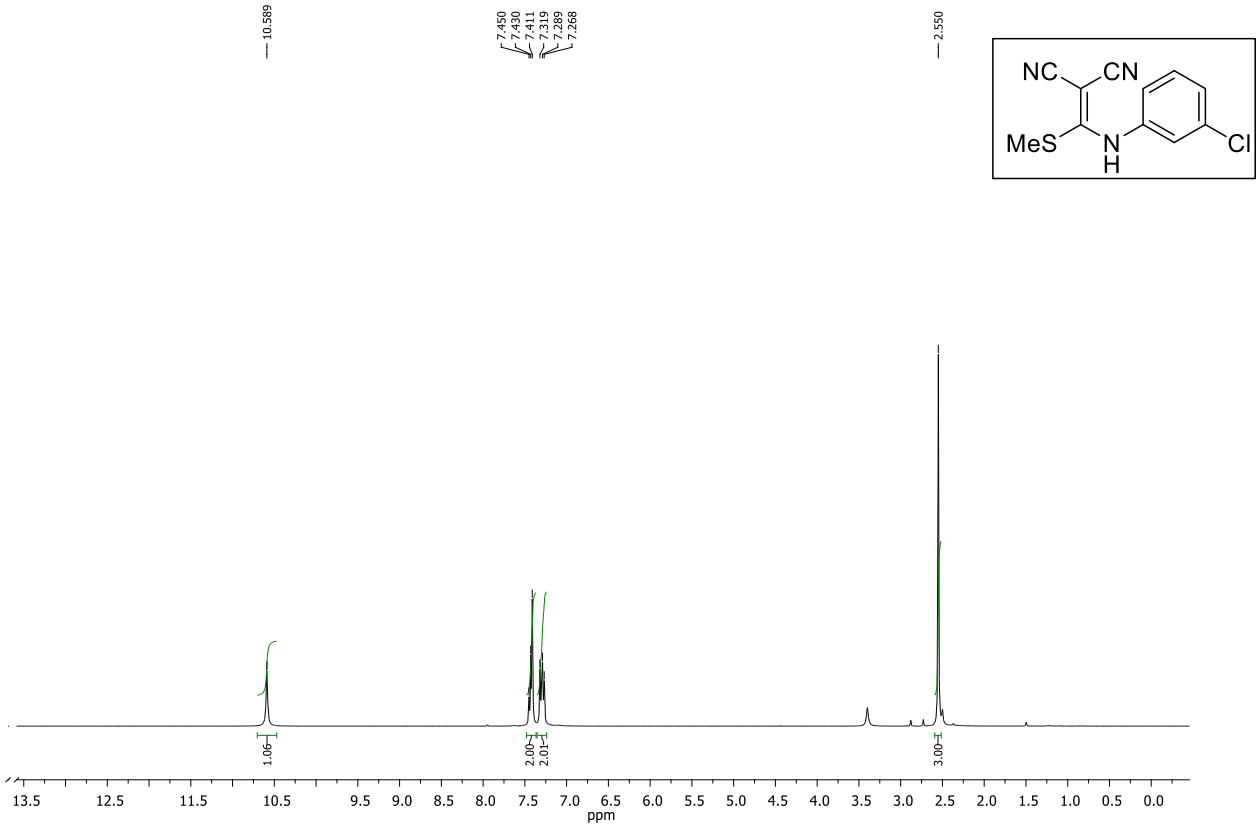


Figure 2.9b. ^{13}C Spectrum of **75j** in DMSO-d_6 (100 MHz)

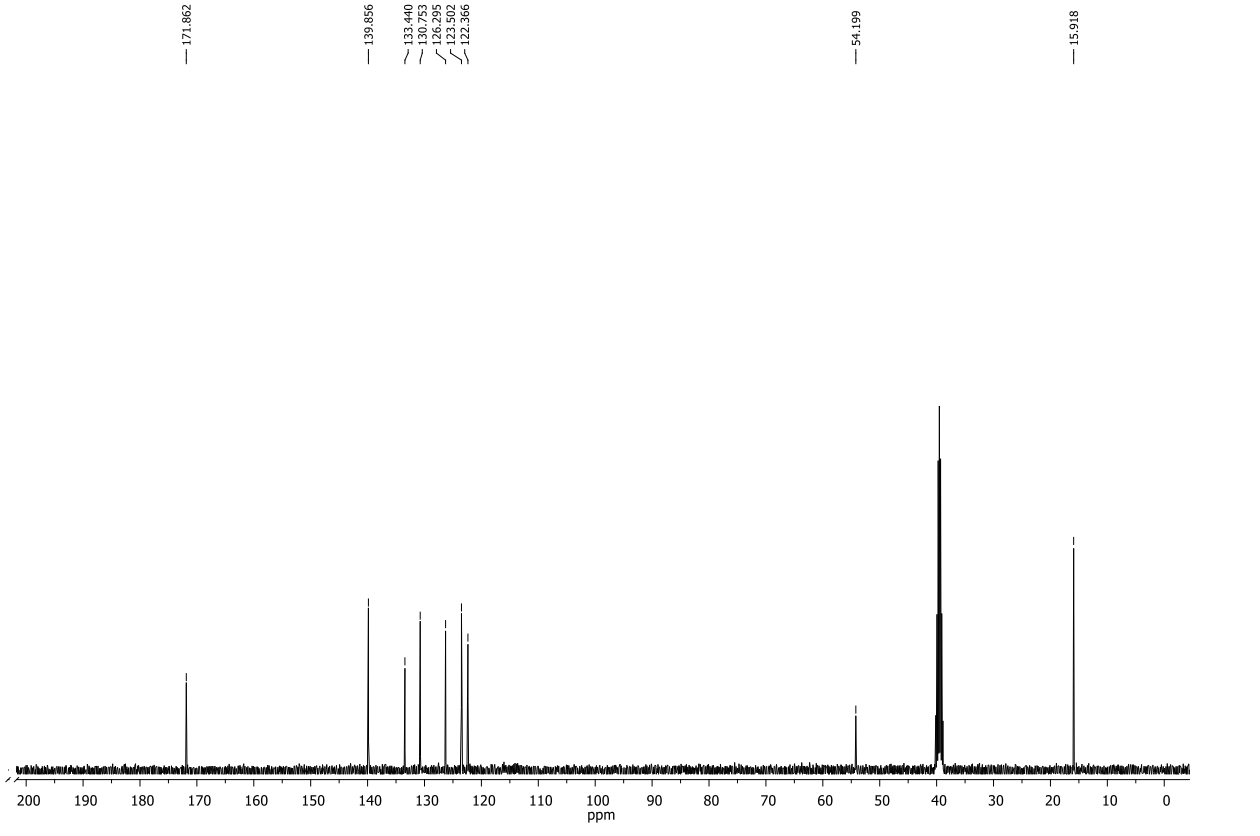


Figure 2.10a. ^{1}H Spectrum of **75k** in DMSO-d_6 (400 MHz)

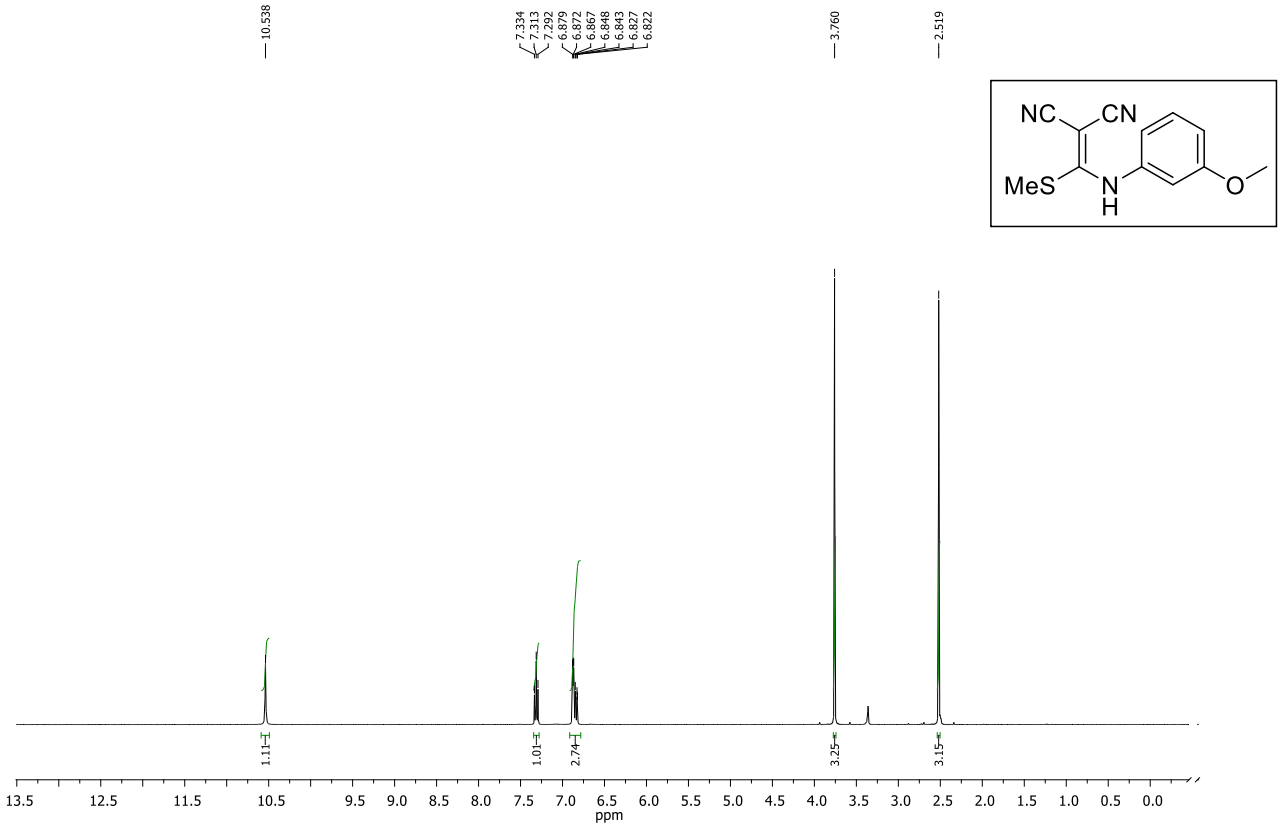


Figure 2.10b. ^{13}C Spectrum of **75k** in $CDCl_3$ (100 MHz)

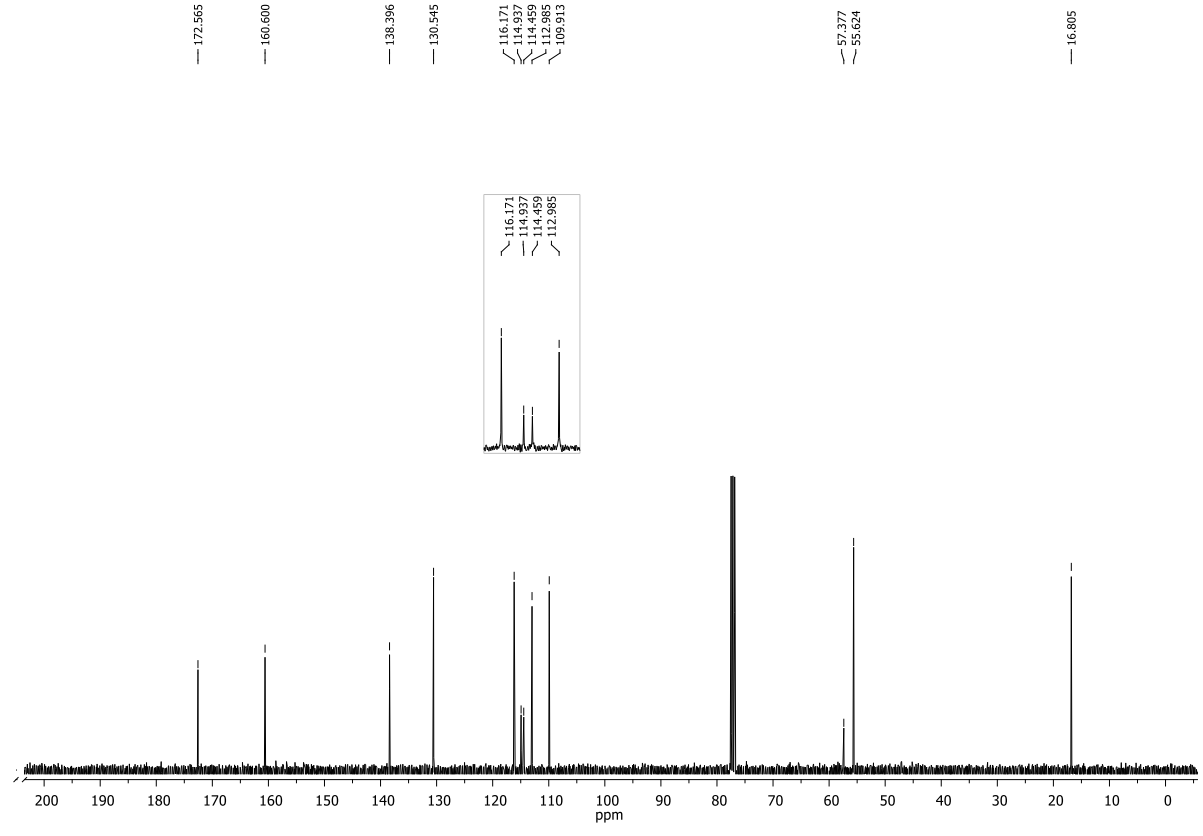


Figure 2.11a. ^{1}H Spectrum of **75l** in DMSO-d_6 (400 MHz)

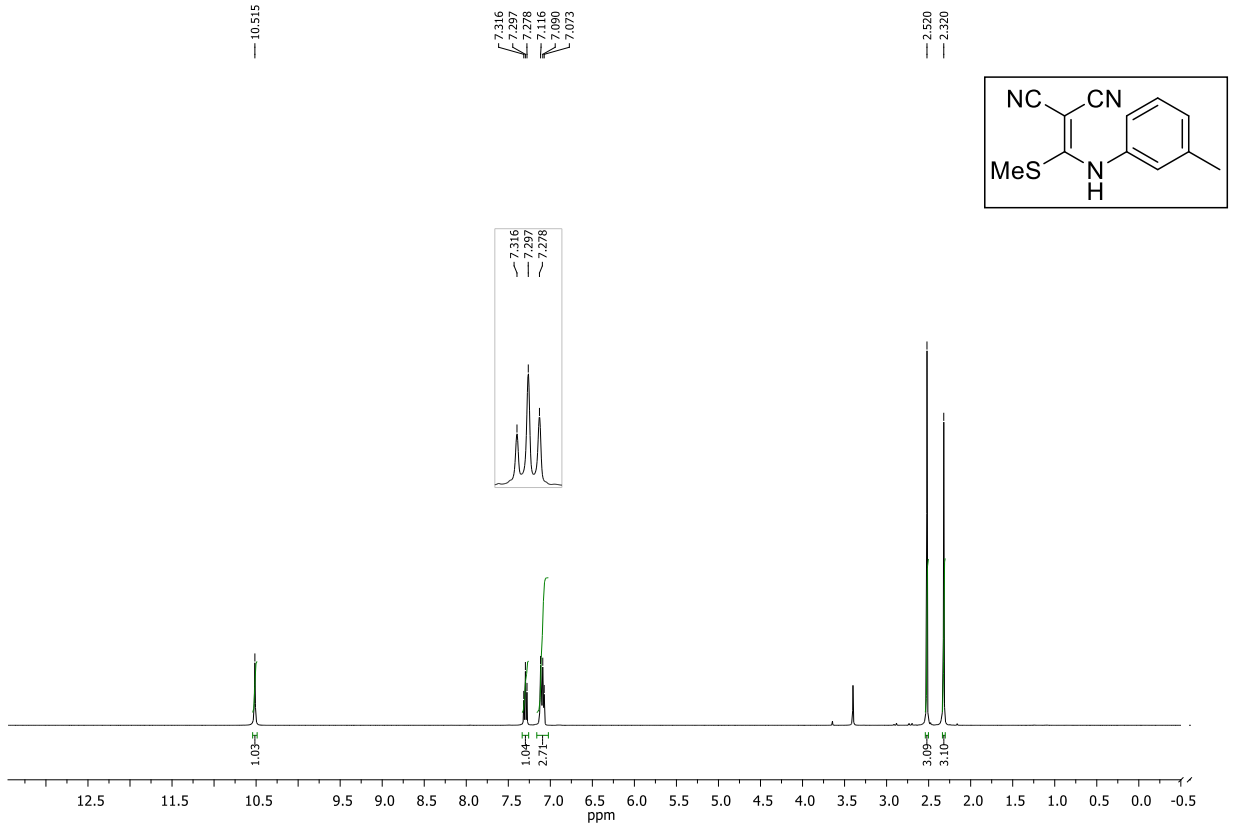


Figure 2.11b. ^{13}C Spectrum of **75l** in $CDCl_3$ (100 MHz)

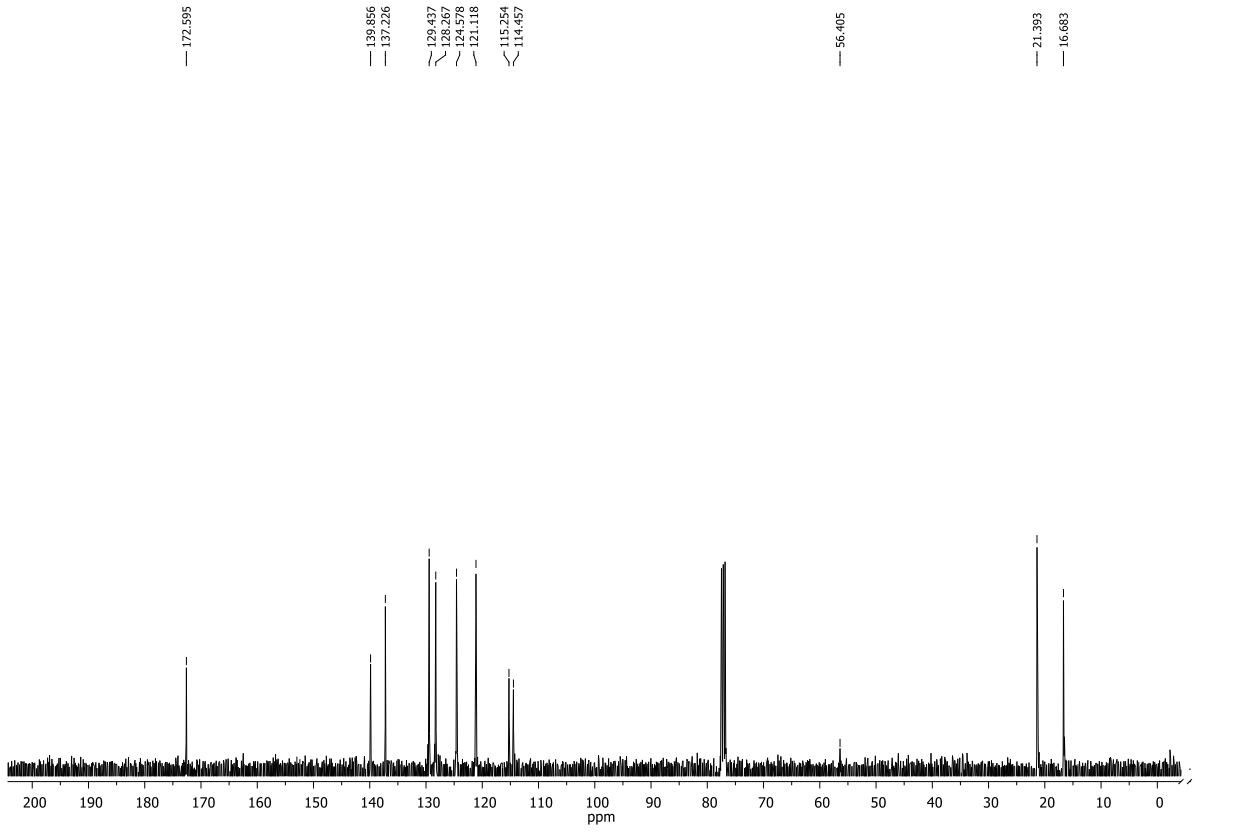


Figure 2.12a. ^{1}H Spectrum of **82a** in $CDCl_3$ (400 MHz)

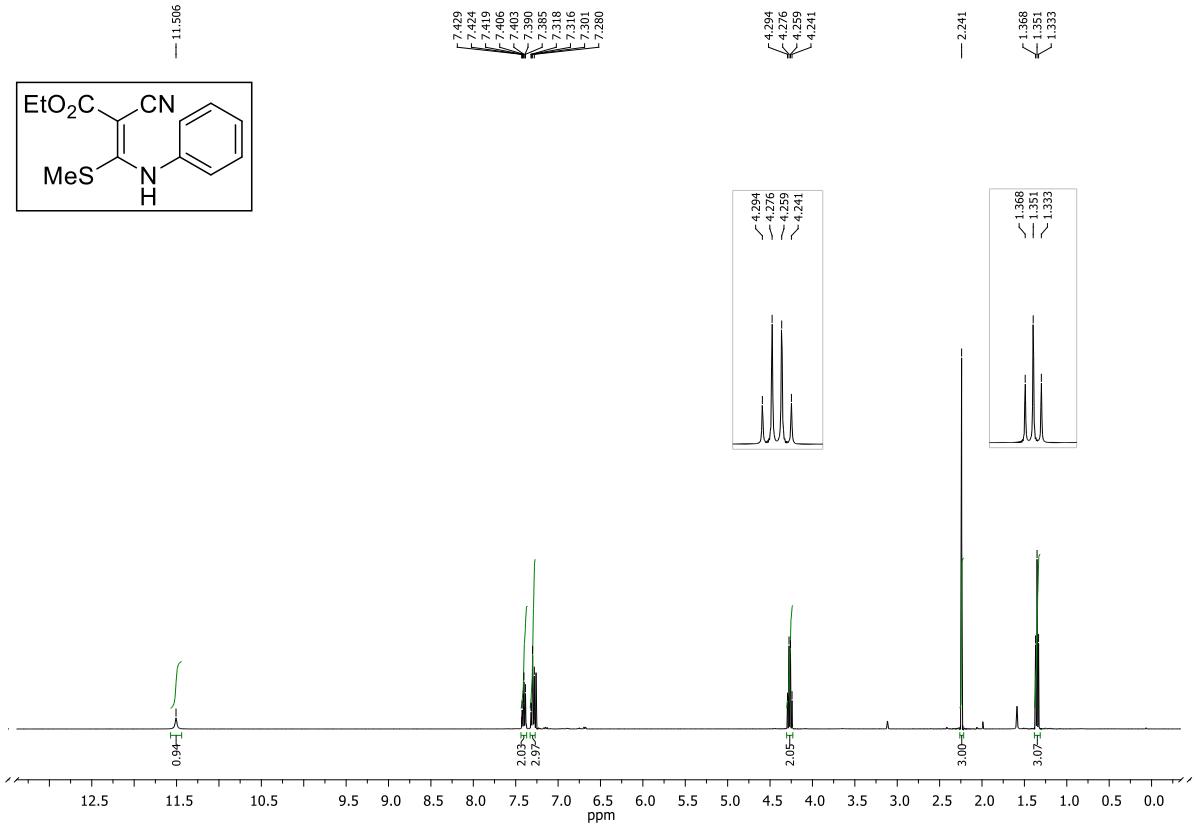


Figure 2.12b. ^{13}C Spectrum of **82a** in $CDCl_3$ (100 MHz)

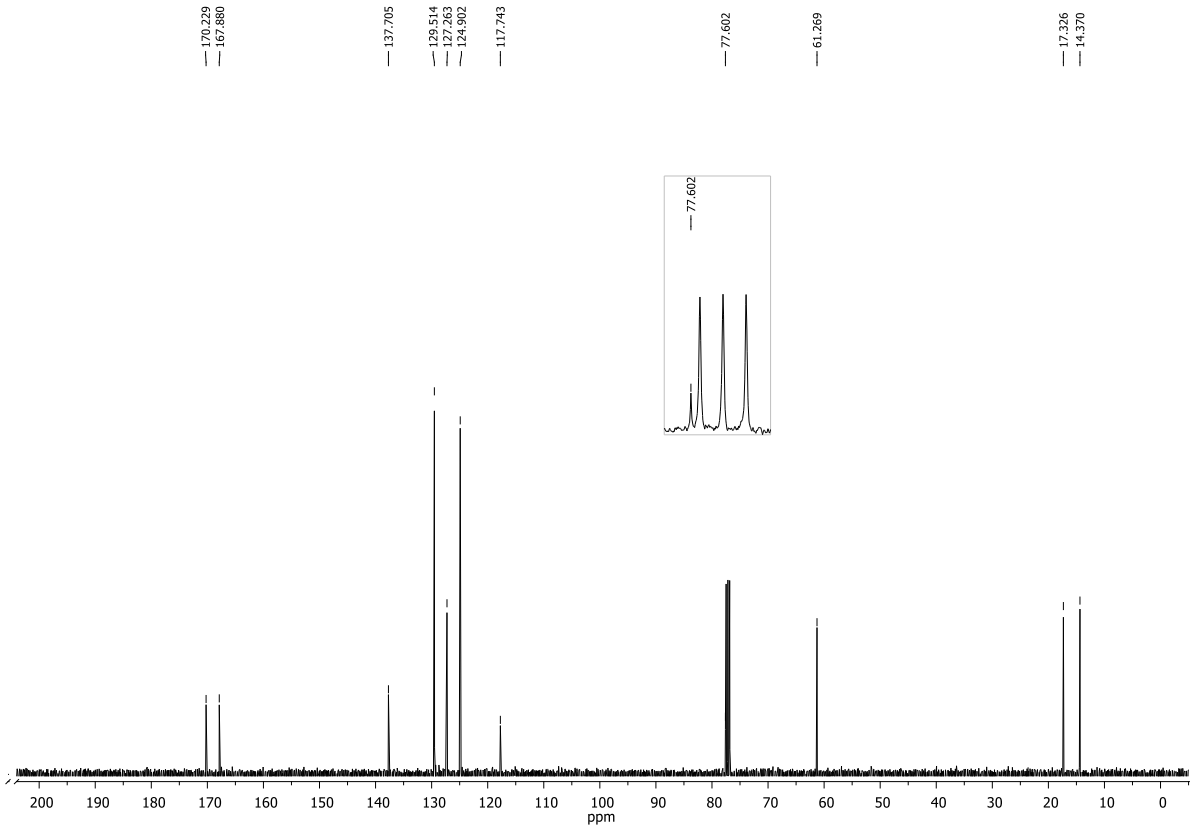


Figure 2.13a. ^{1}H Spectrum of **82f** in DMSO-d_6 (400 MHz)

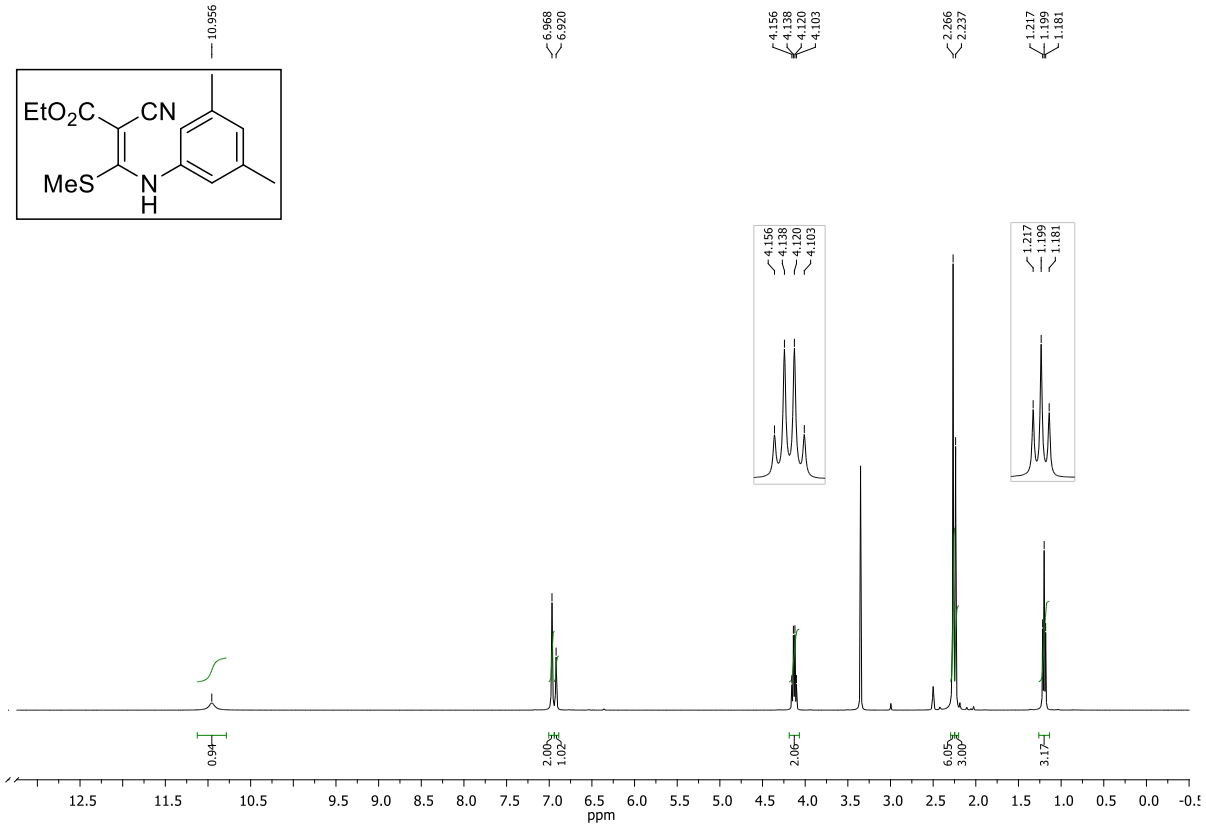


Figure 2.13b. ^{13}C Spectrum of **82f** in DMSO-d_6 (100 MHz)

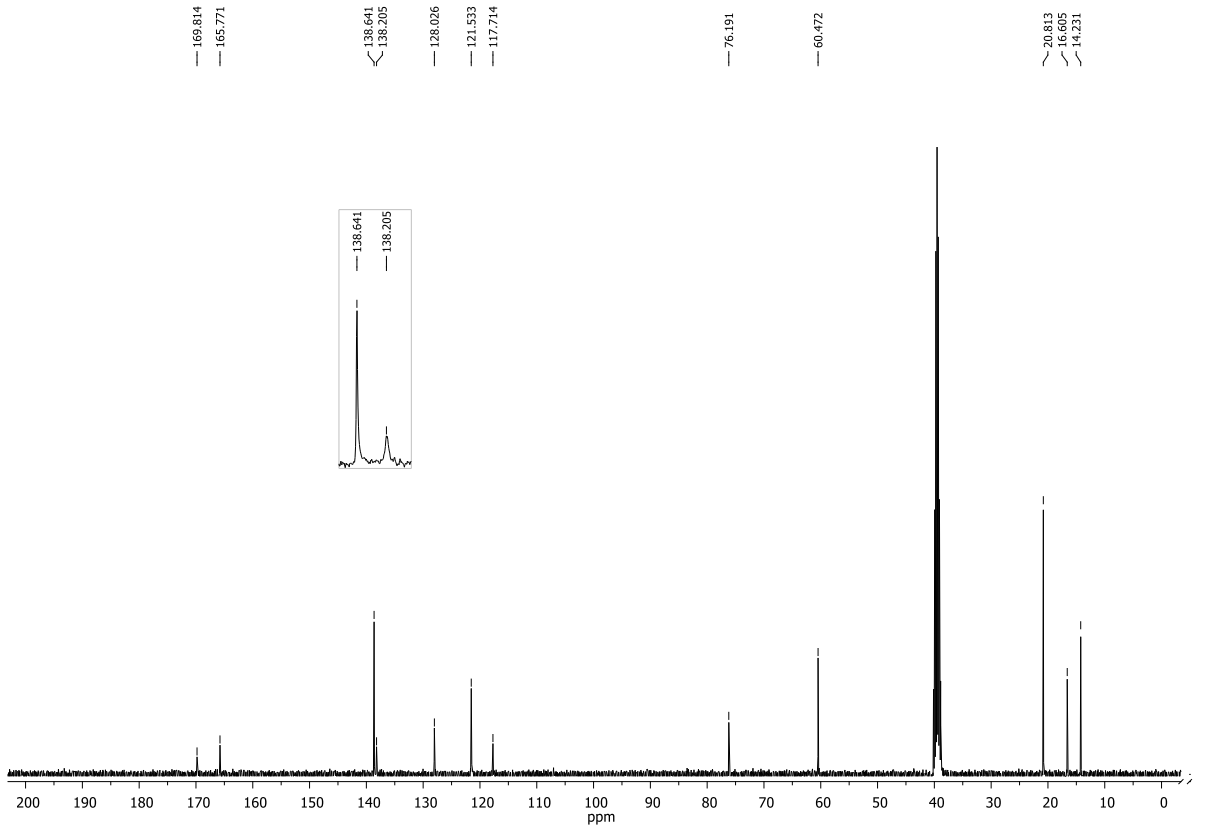


Figure 2.14a. ^{1}H Spectrum of **82k** in $CDCl_3$ (400 MHz)

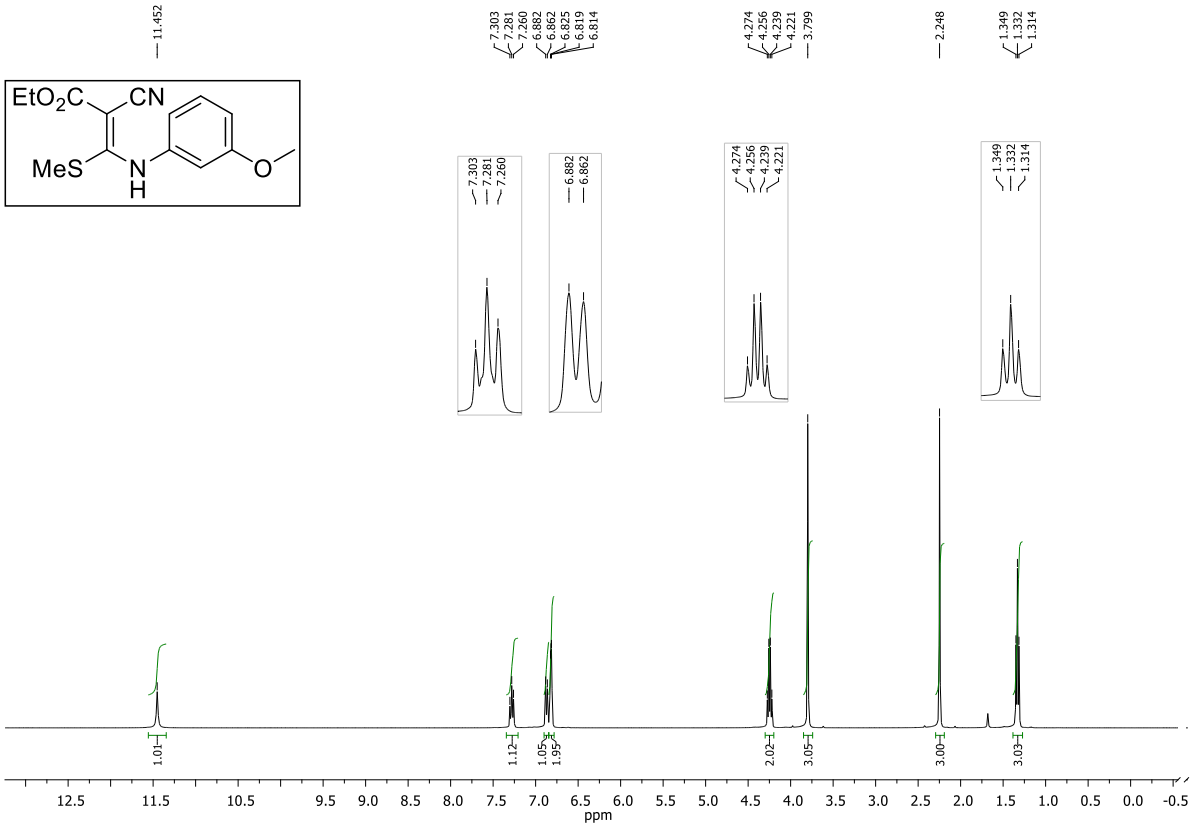


Figure 2.14b. ^{13}C Spectrum of **82k** in $CDCl_3$ (100 MHz)

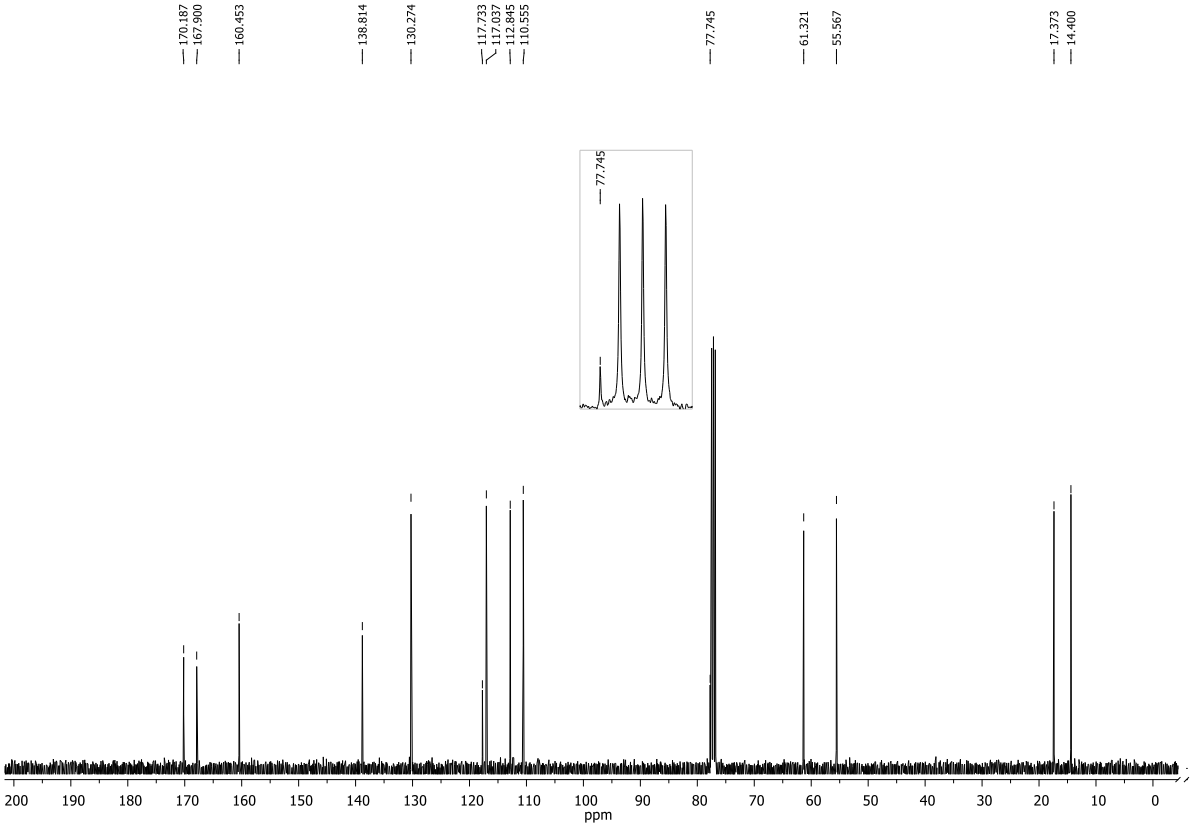


Figure 2.15a. ^{1}H Spectrum of **84a** in DMSO-d_6 (400 MHz)

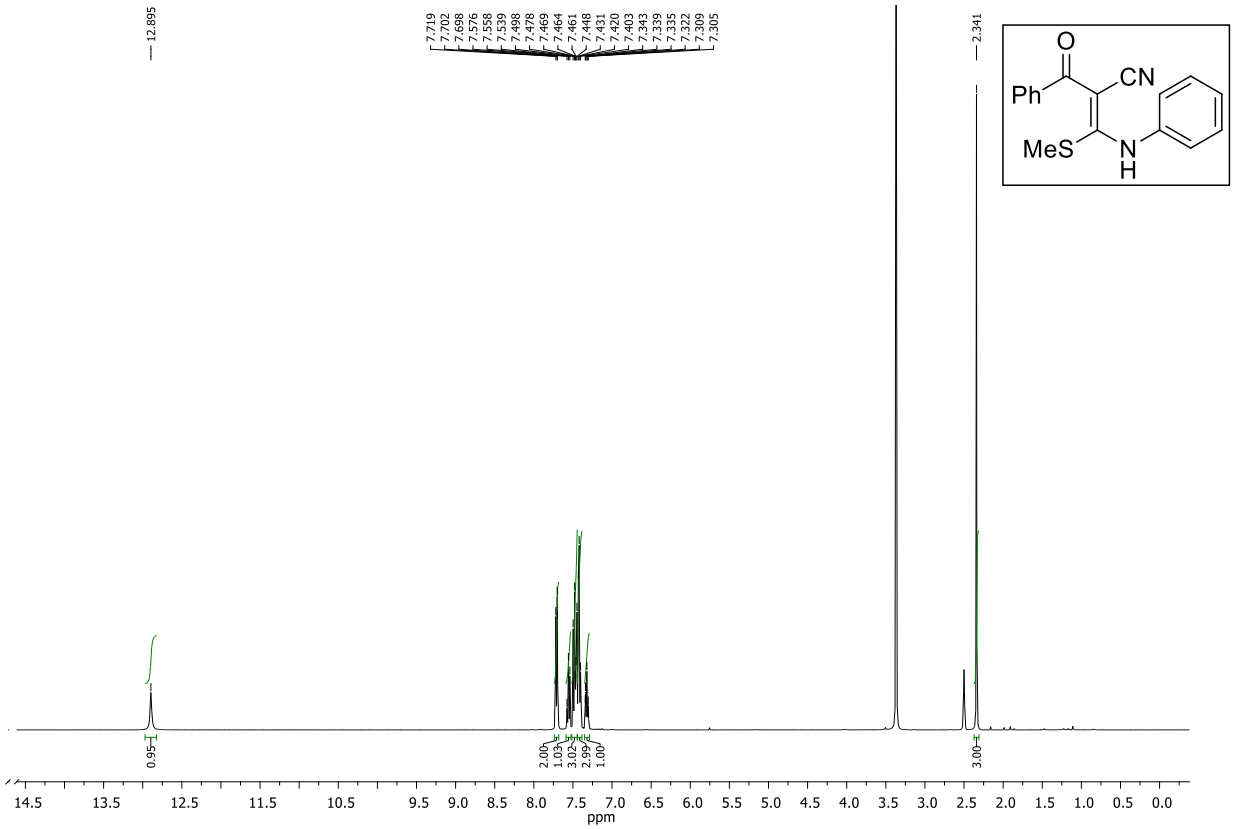


Figure 2.15b. ^{13}C Spectrum of **84a** in DMSO-d_6 (100 MHz)

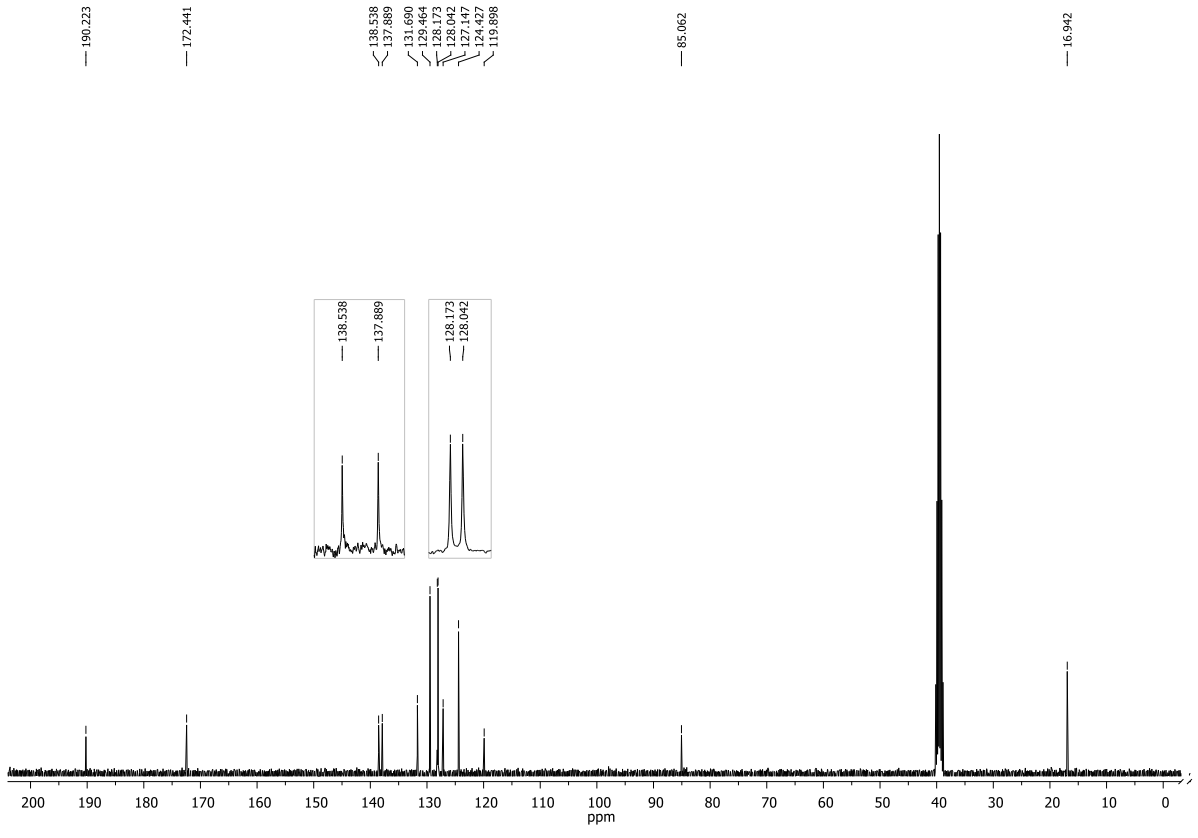


Figure 2.16a. ^{1}H Spectrum of **84f** in DMSO-d_6 (400 MHz)

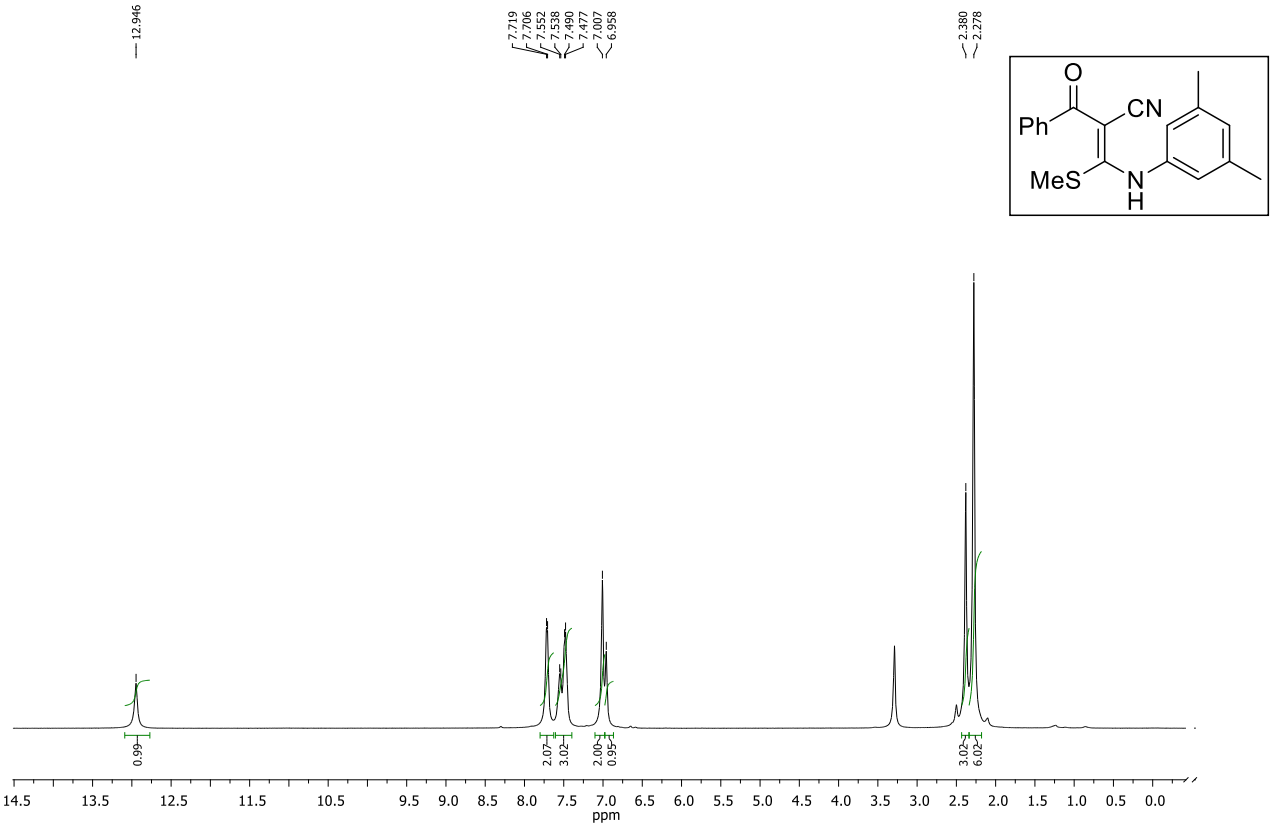


Figure 2.16b. ^{13}C Spectrum of **84f** in DMSO-d_6 (100 MHz)

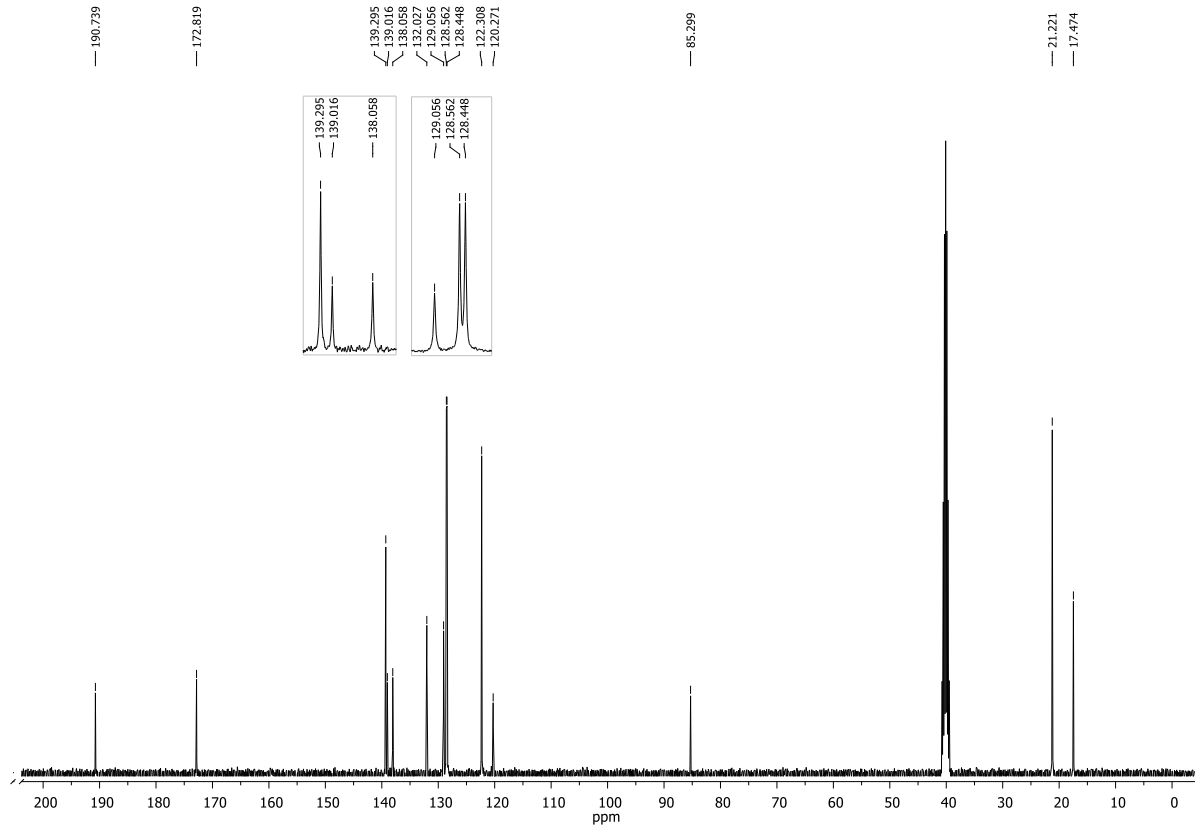


Figure 2.17a. ^{1}H Spectrum of **85** in DMSO-d_6 (700 MHz)

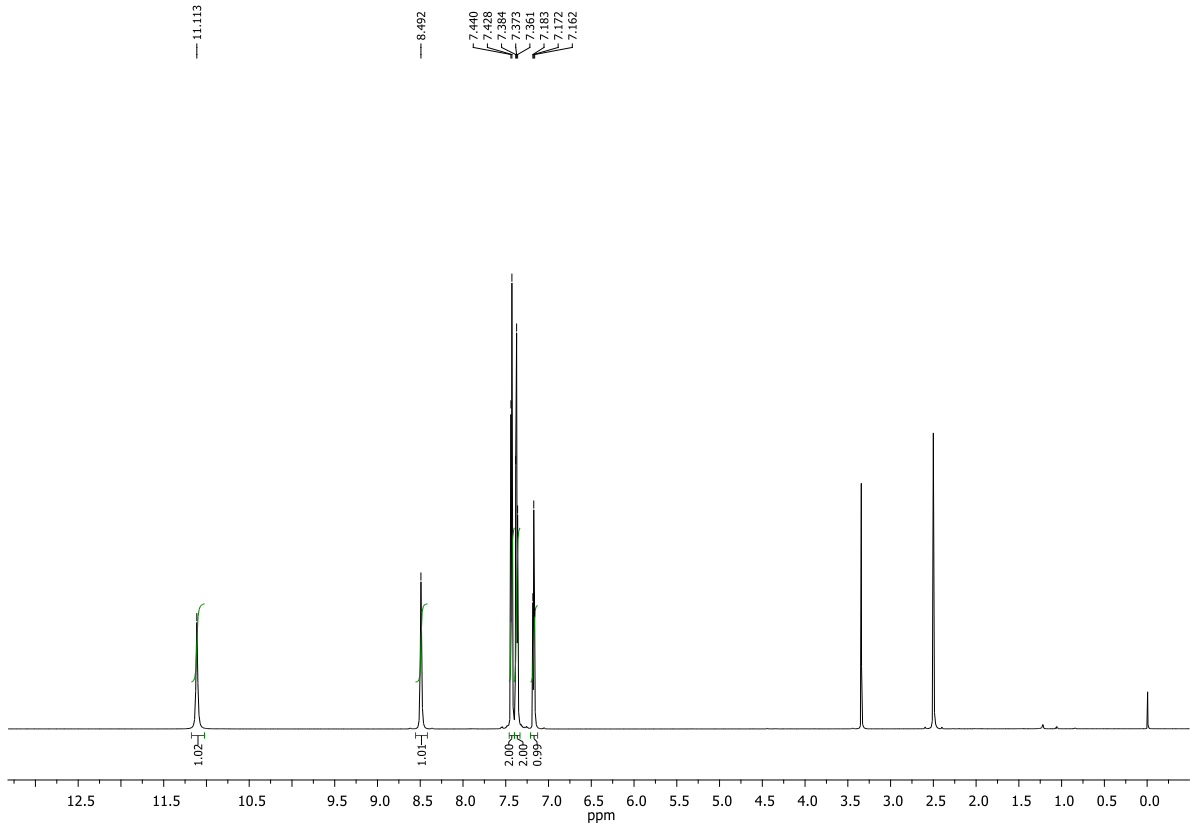


Figure 2.17b. ^{13}C Spectrum of **85** in DMSO-d_6 (175 MHz)

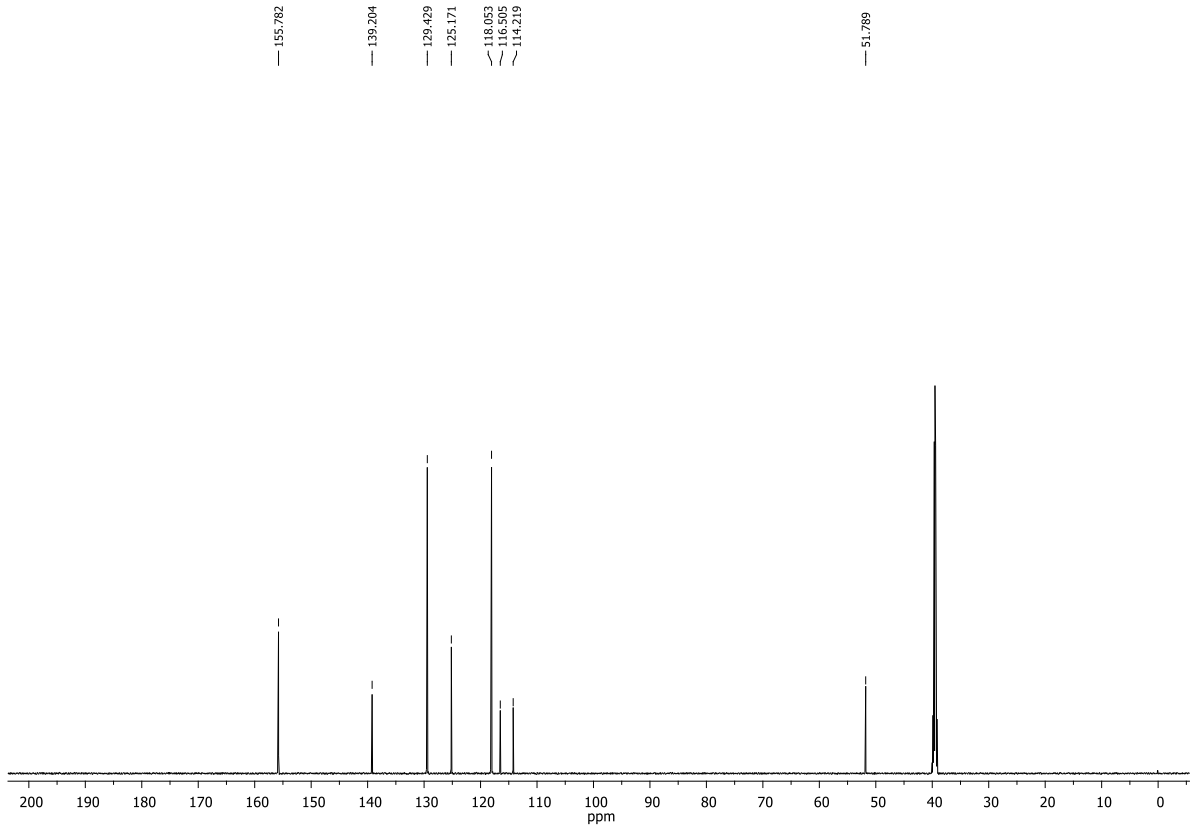


Figure 2.18a. ^{1}H Spectrum of **9a** in DMSO-d_6 (400 MHz)

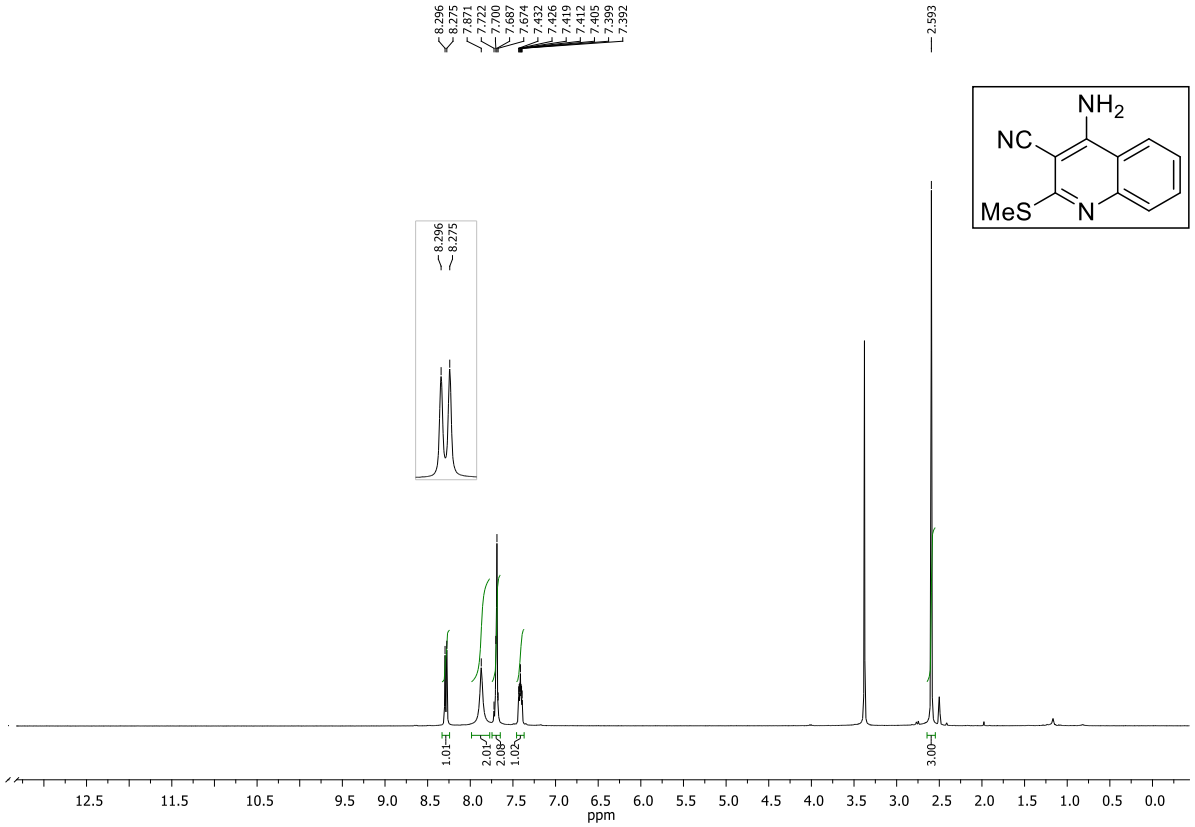


Figure 2.18b. ^{13}C Spectrum of **9a** in DMSO-d_6 (100 MHz)

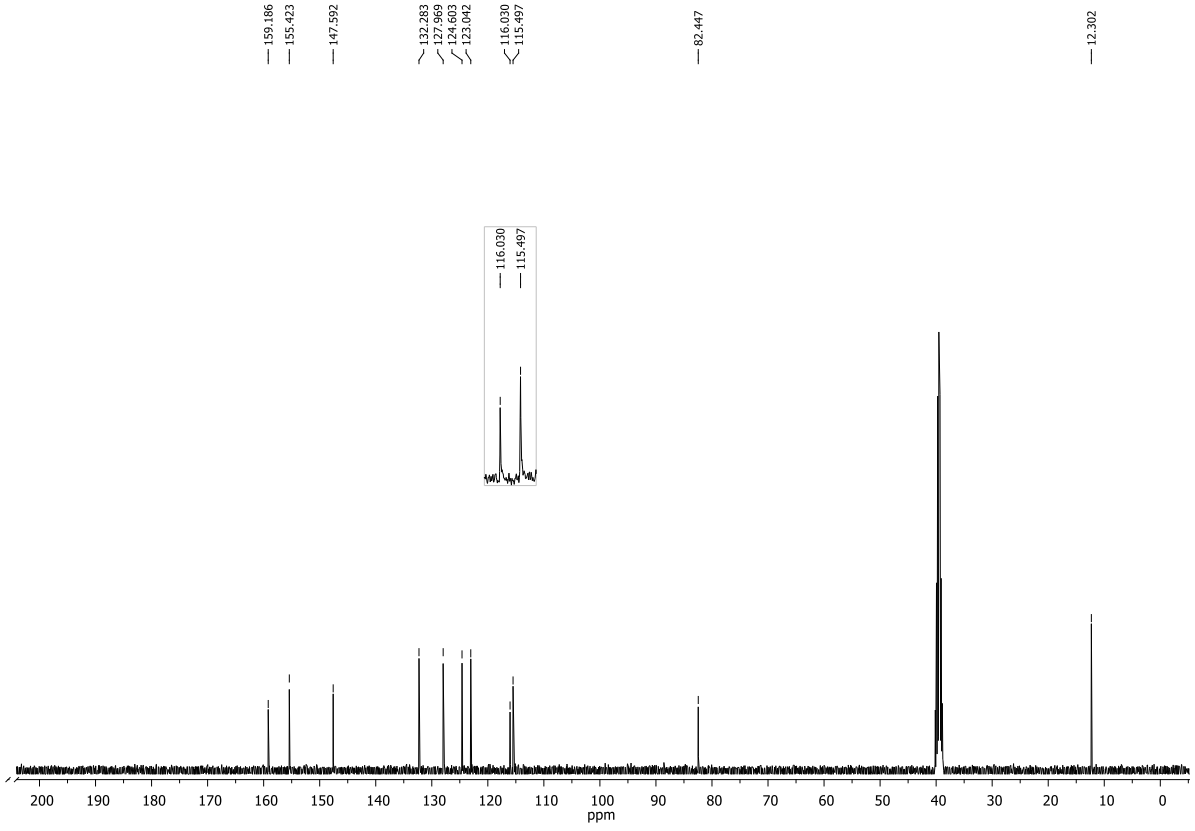


Figure 2.19a. ^{1}H Spectrum of **9b** in DMSO-d_6 (400 MHz)

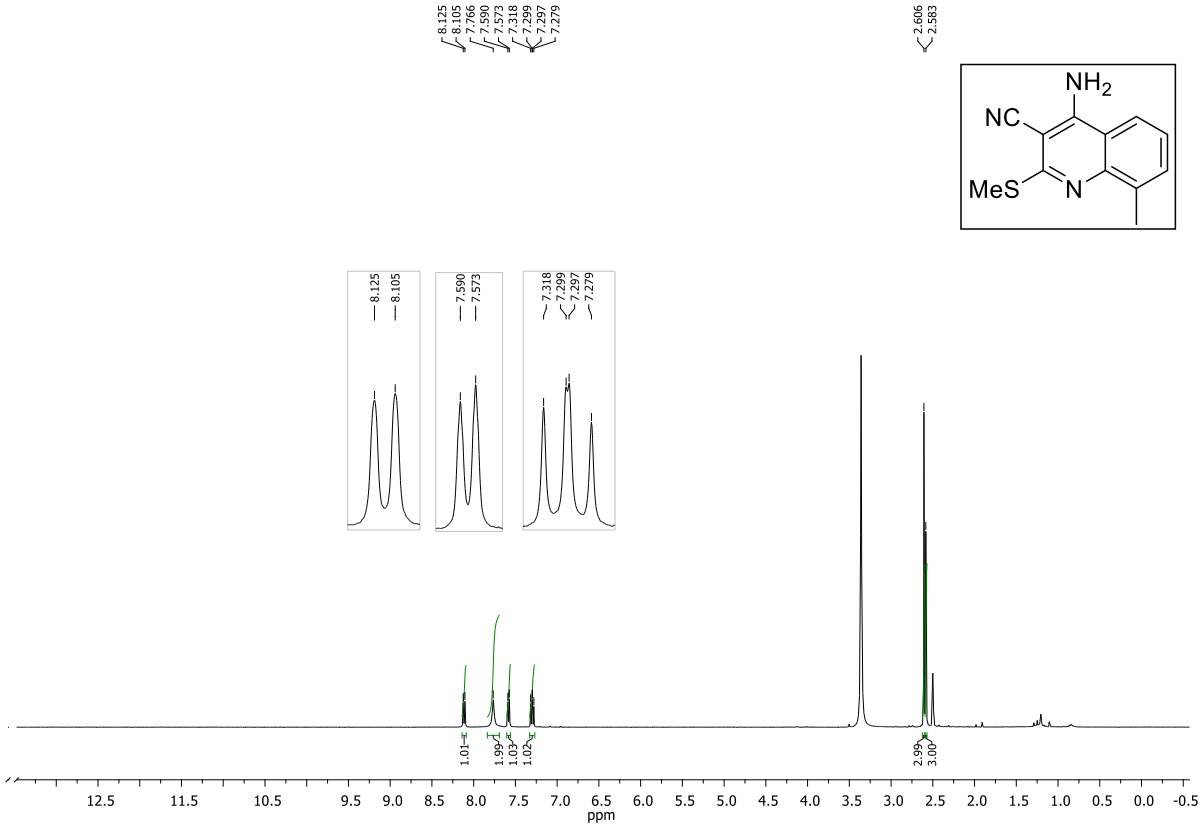


Figure 2.19b. ^{13}C Spectrum of **9b** in DMSO-d_6 (100 MHz)

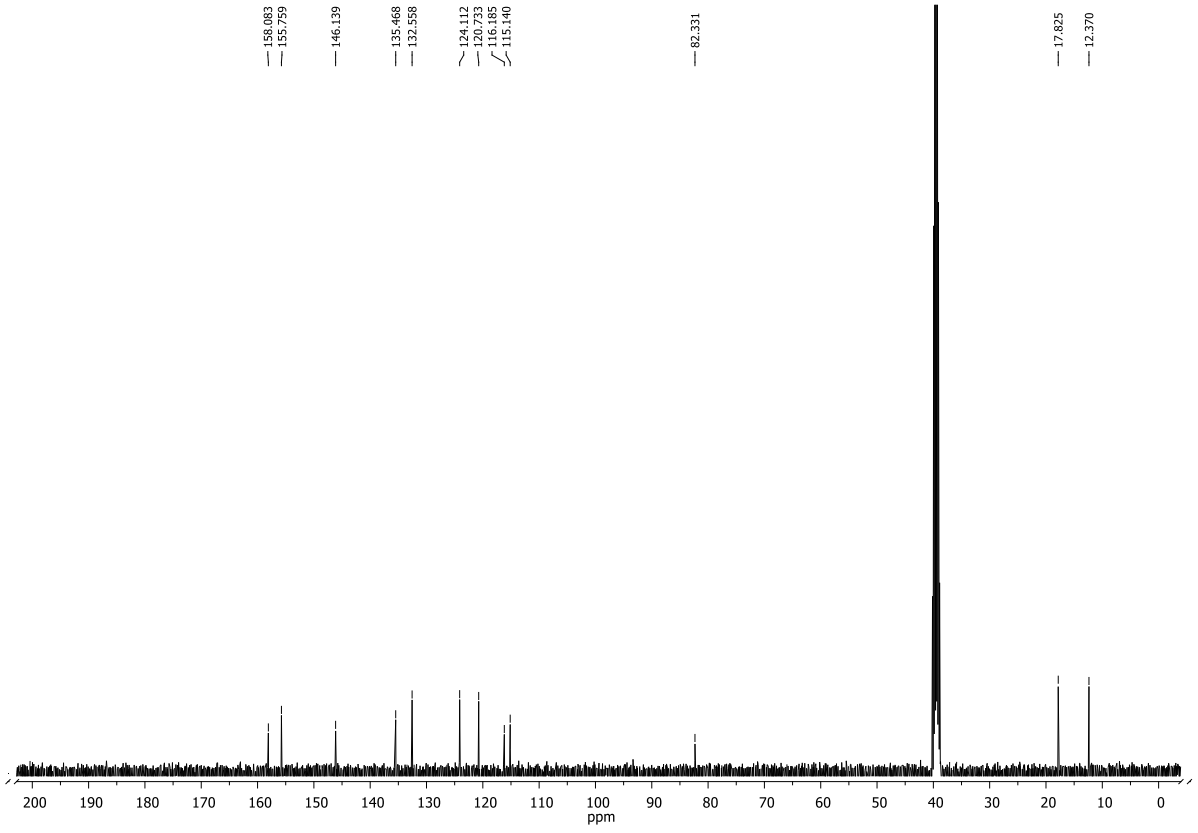


Figure 2.20a. ^{1}H Spectrum of **9c** in DMSO-d_6 (400 MHz)

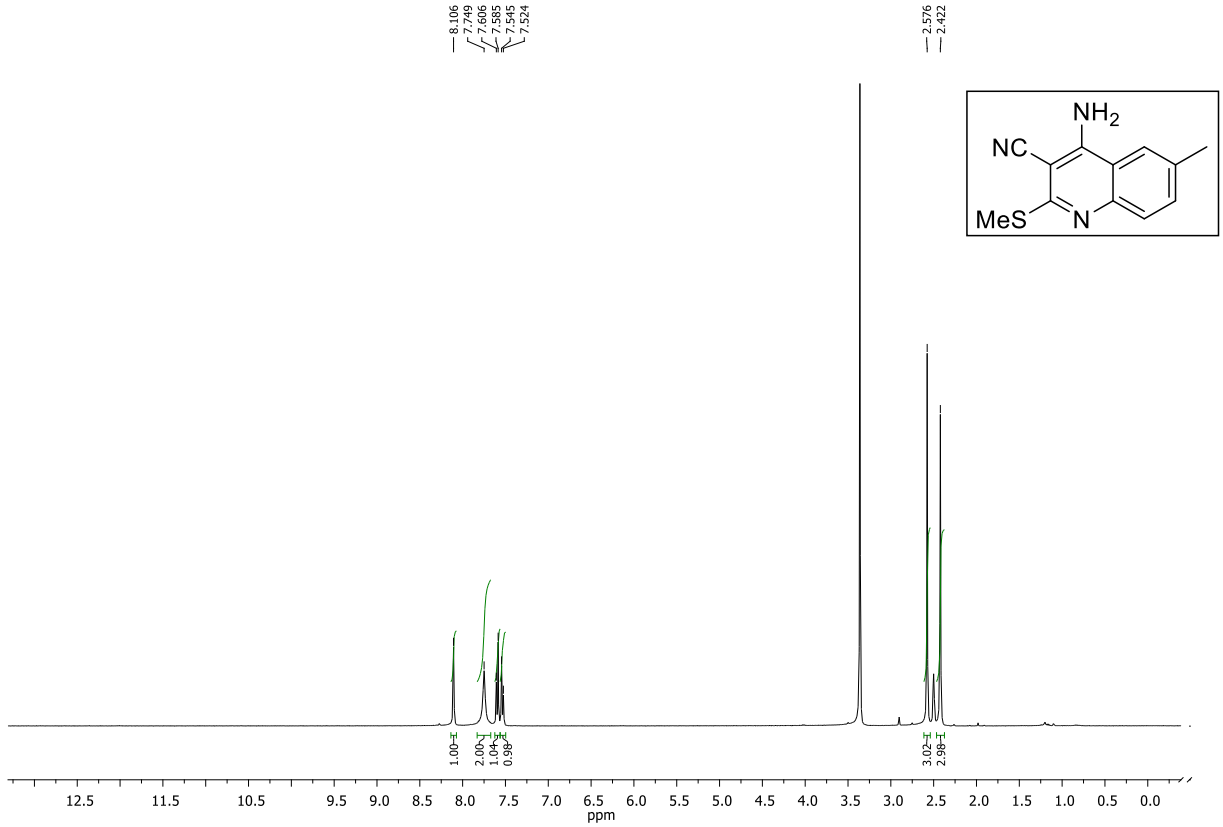


Figure 2.20b. ^{13}C Spectrum of **9c** in DMSO-d_6 (400 MHz)

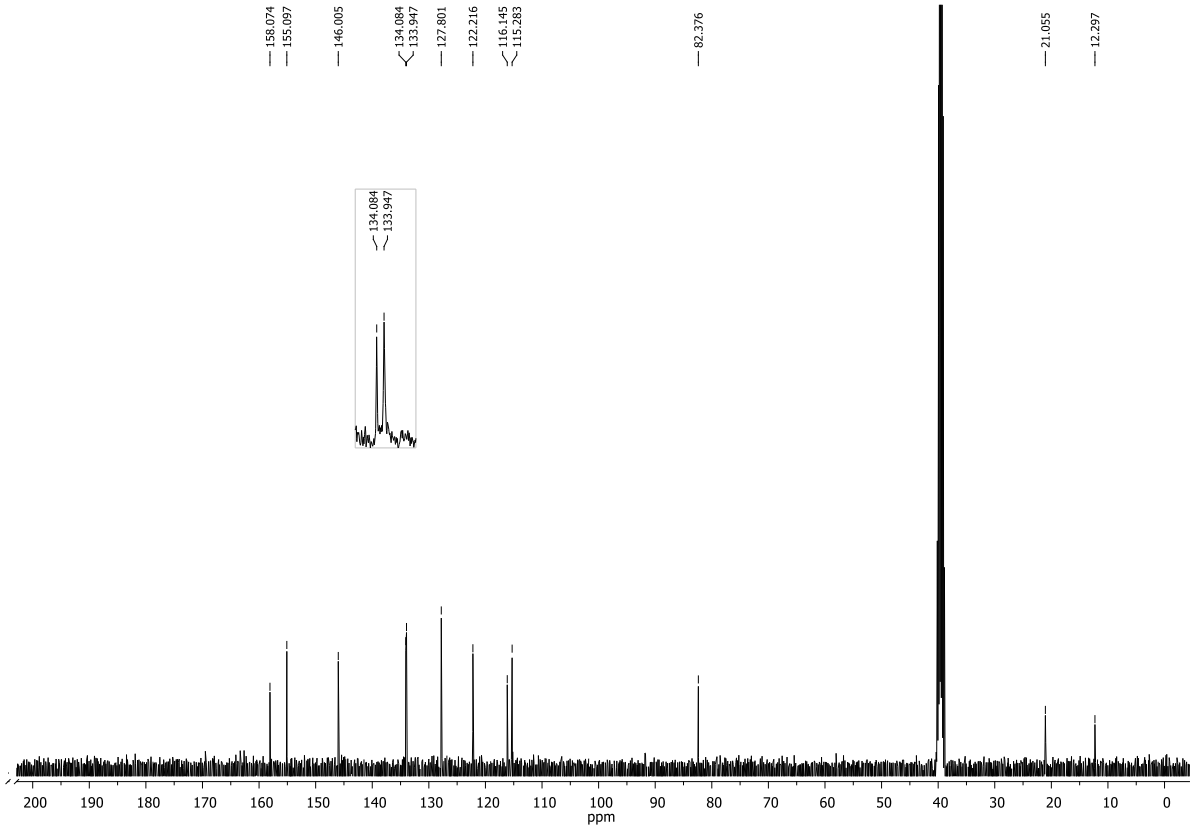


Figure 2.21a. ^{1}H Spectrum of **75m** in DMSO-d_6 (400 MHz)

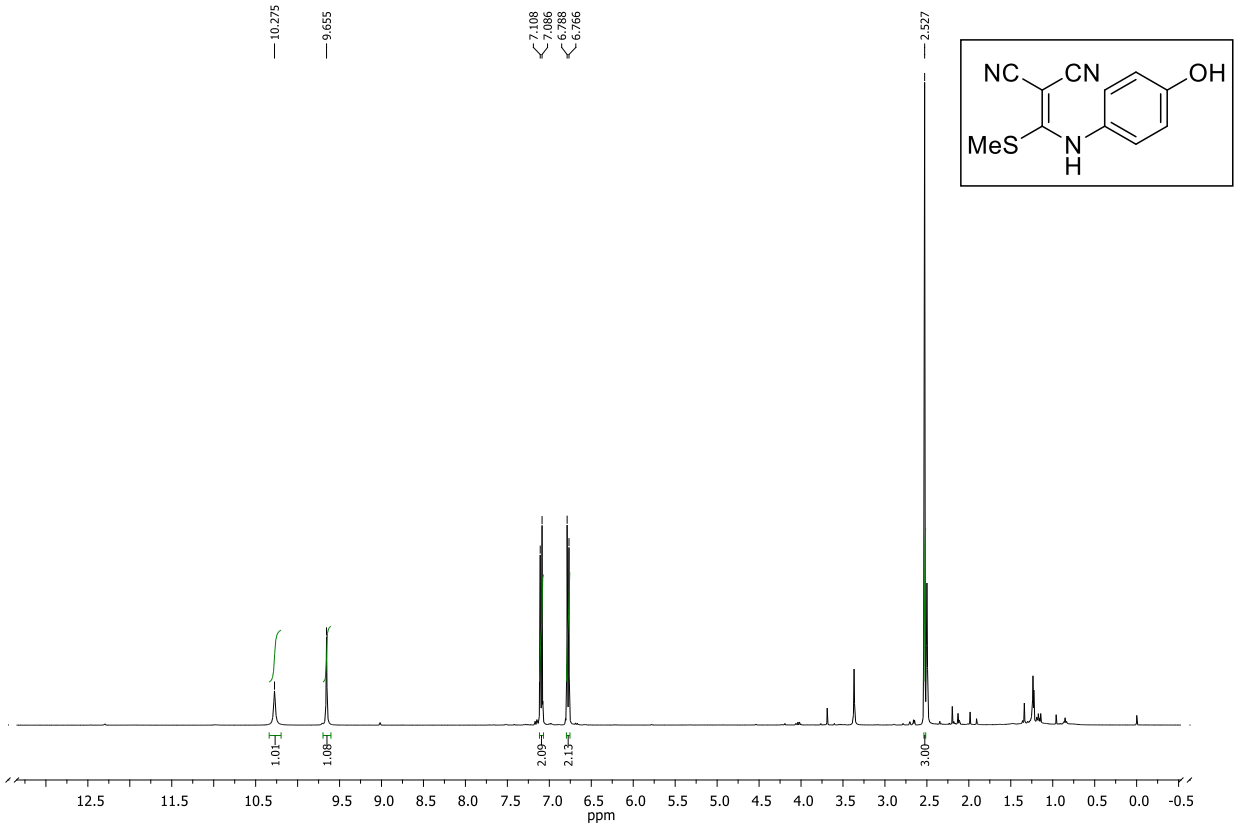


Figure 2.21b. ^{13}C Spectrum of **75m** in DMSO-d_6 (100 MHz)

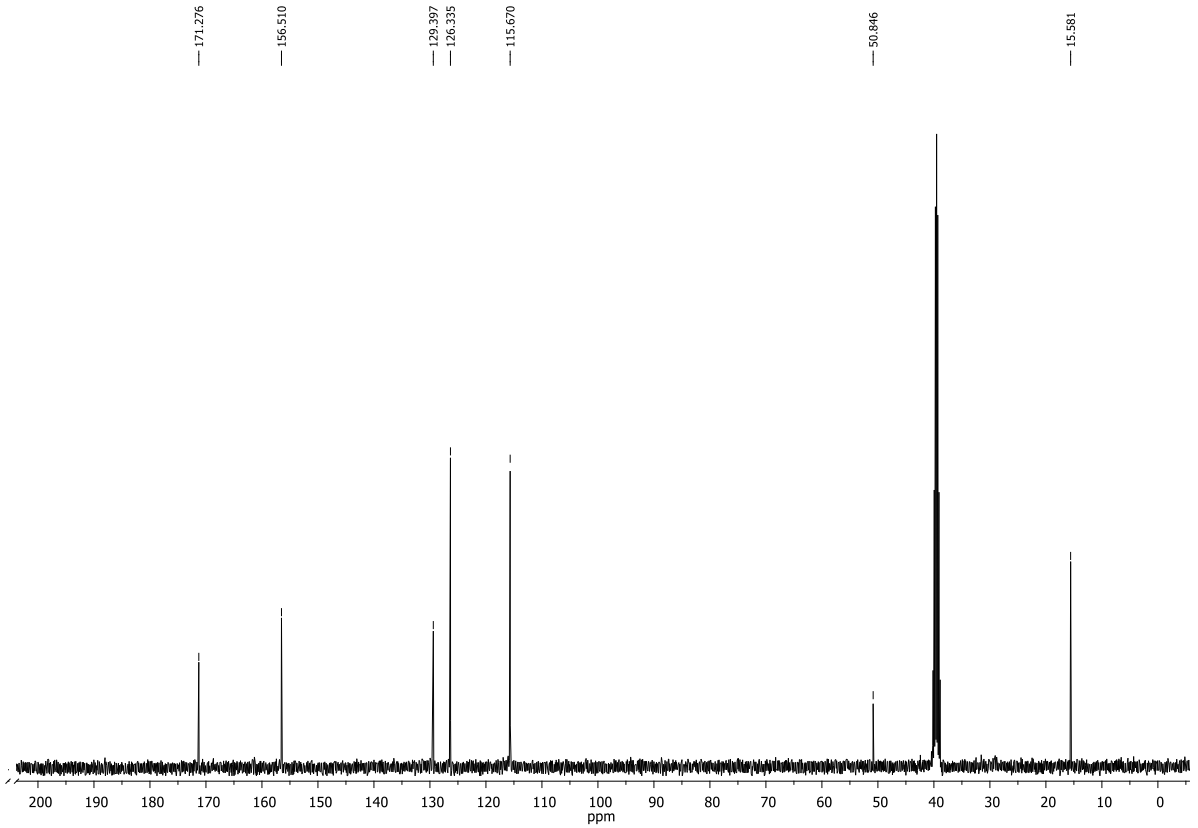


Figure 2.22a. ^{1}H Spectrum of **9j** in DMSO-d_6 (400 MHz)

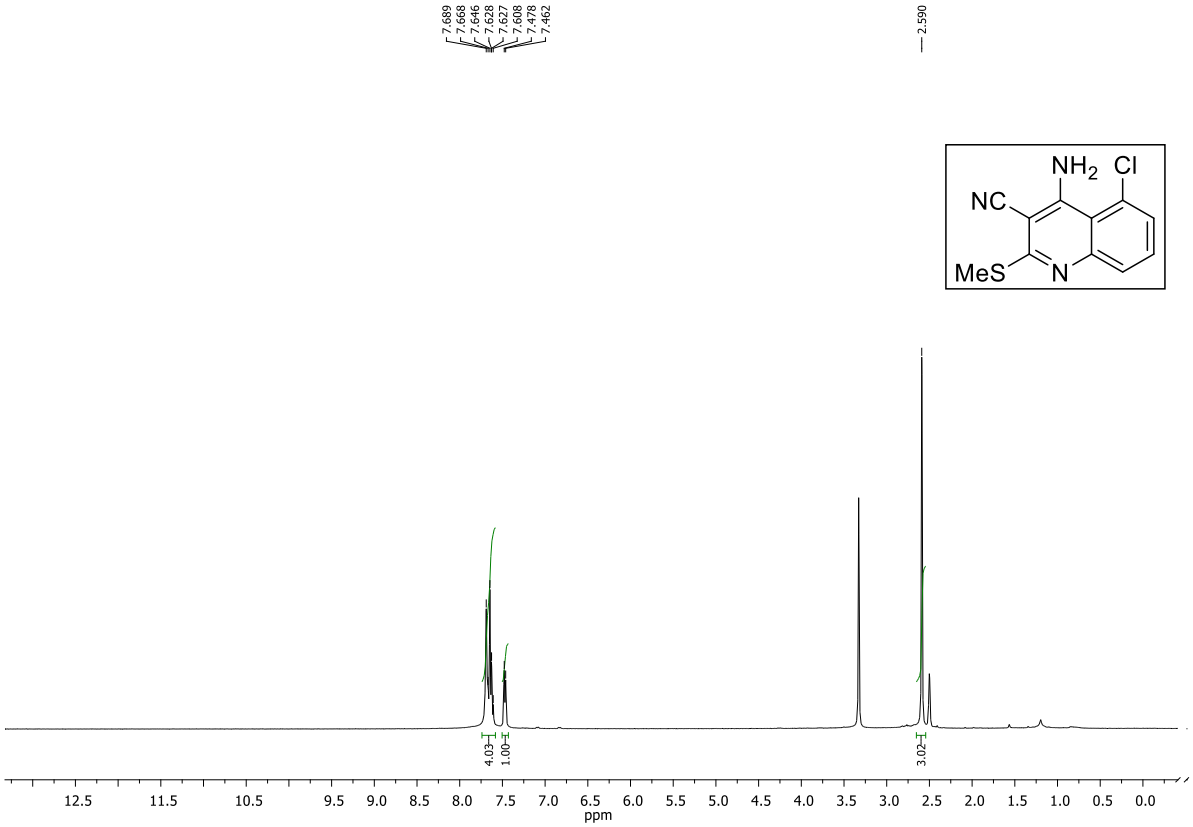


Figure 2.22b. ^{13}C Spectrum of **9j** in DMSO-d_6 (100 MHz)

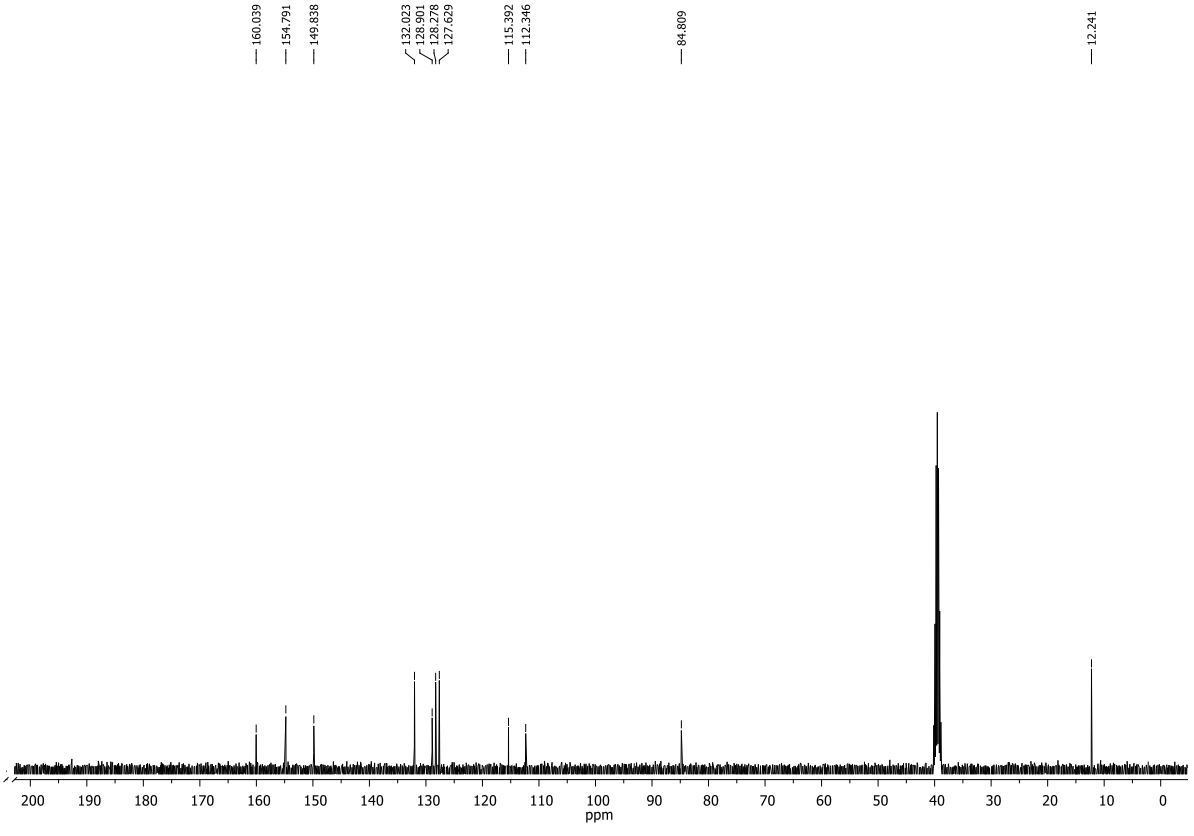


Figure 2.23a. ^{1}H Spectrum of **9k** & **9k′** in DMSO-d_6 (400 MHz)

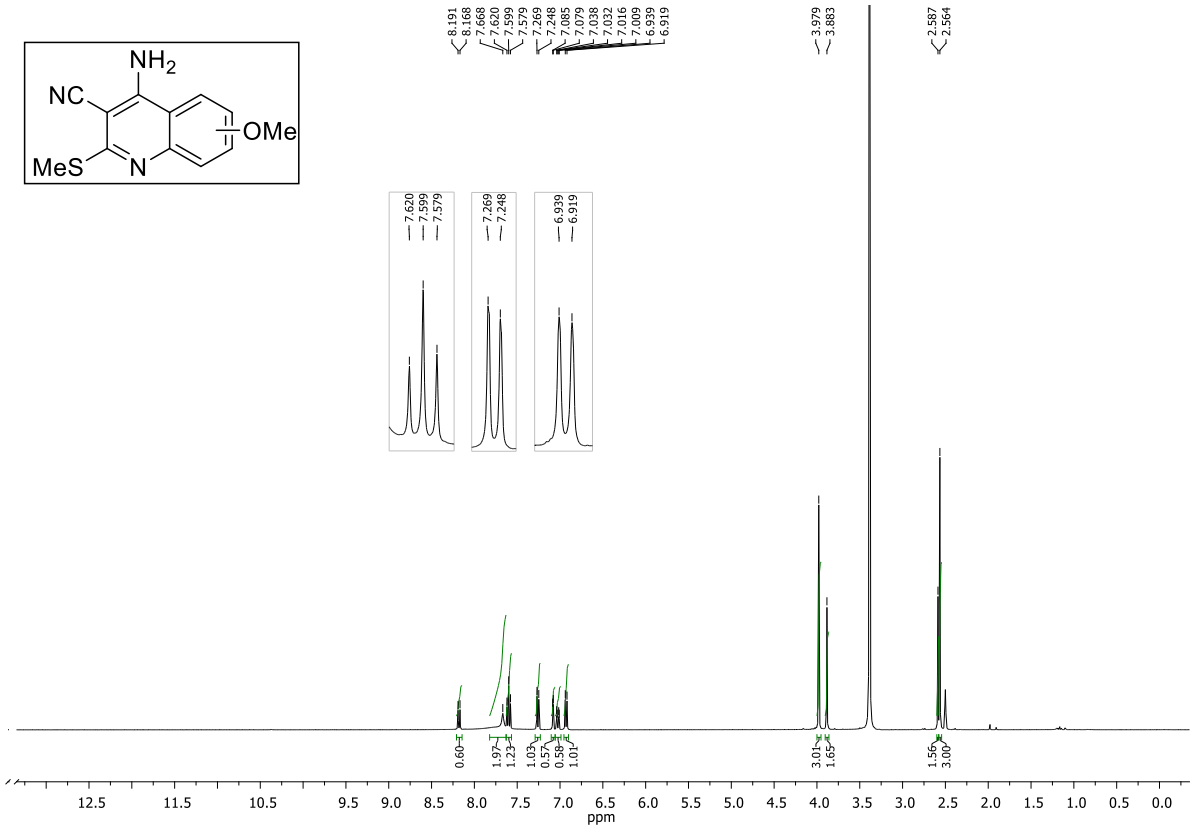


Figure 2.23b. ^{13}C Spectrum of **9k** & **9k′** in DMSO-d_6 (100 MHz)

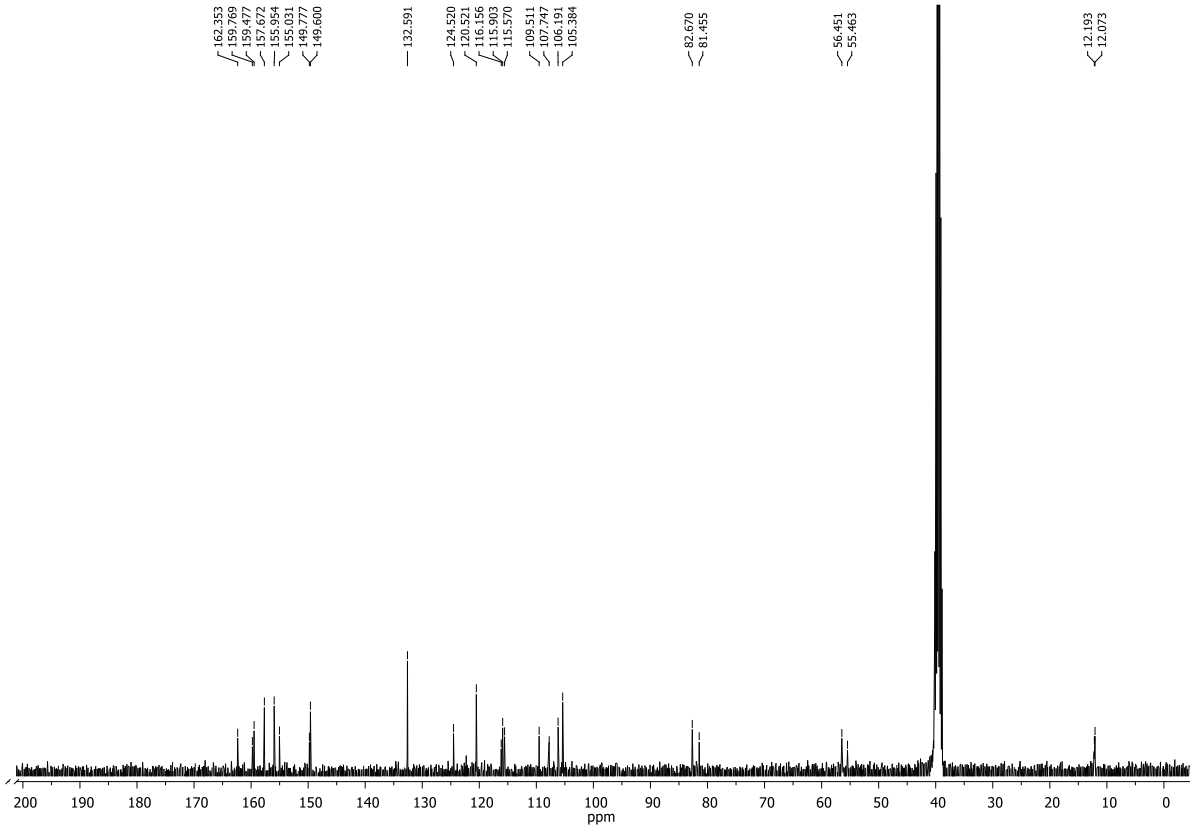


Figure 2.24a. ^{1}H Spectrum of **9l** & **9l′** in DMSO-d_6 (400 MHz)

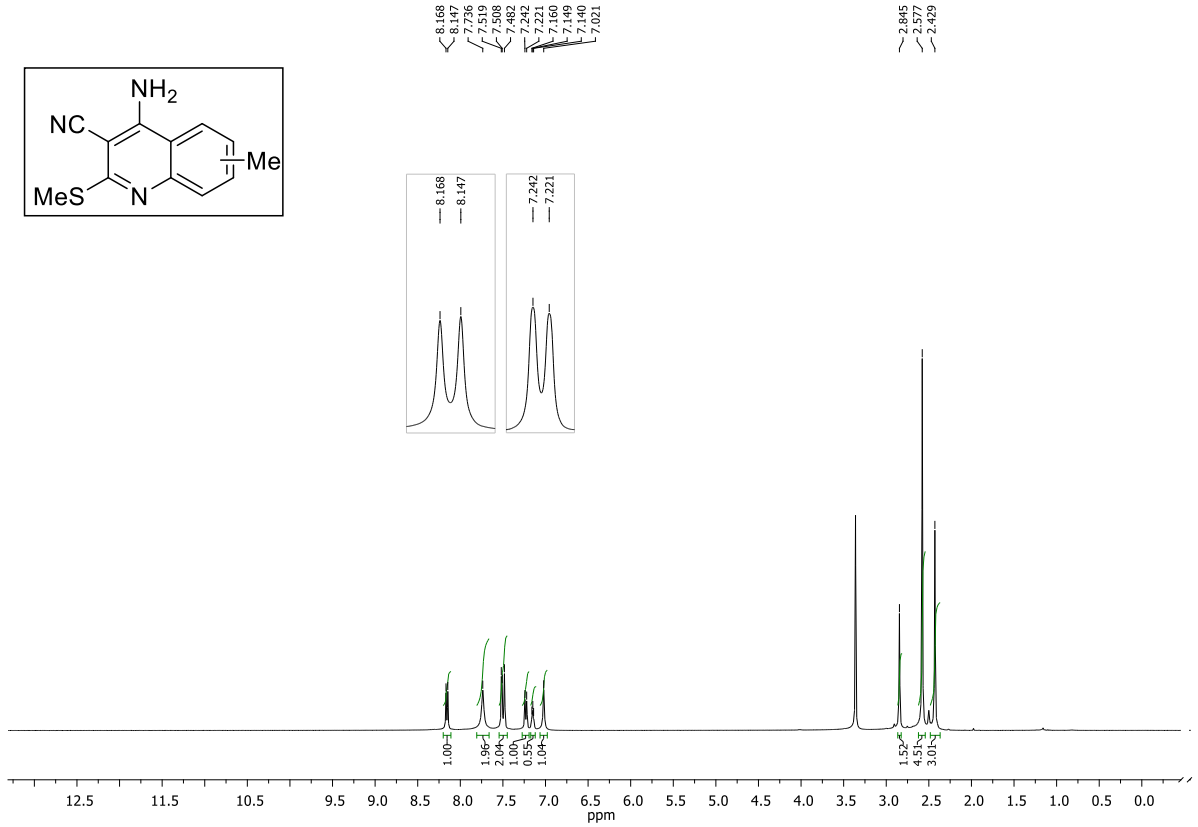


Figure 2.24b. ^{13}C Spectrum of **9l** & **9l′** in DMSO-d_6 (100 MHz)

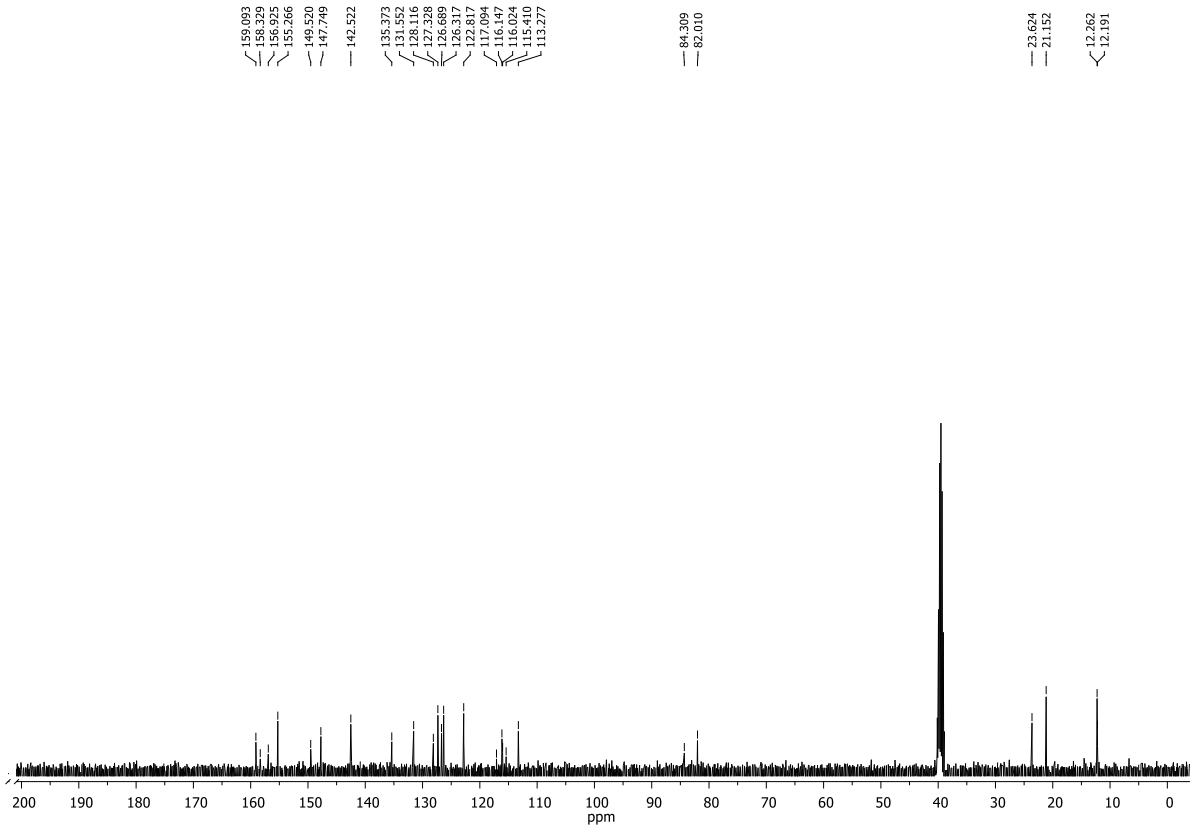


Figure 2.25a. ^{1}H Spectrum of **86a** in DMSO-d_6 (400 MHz)

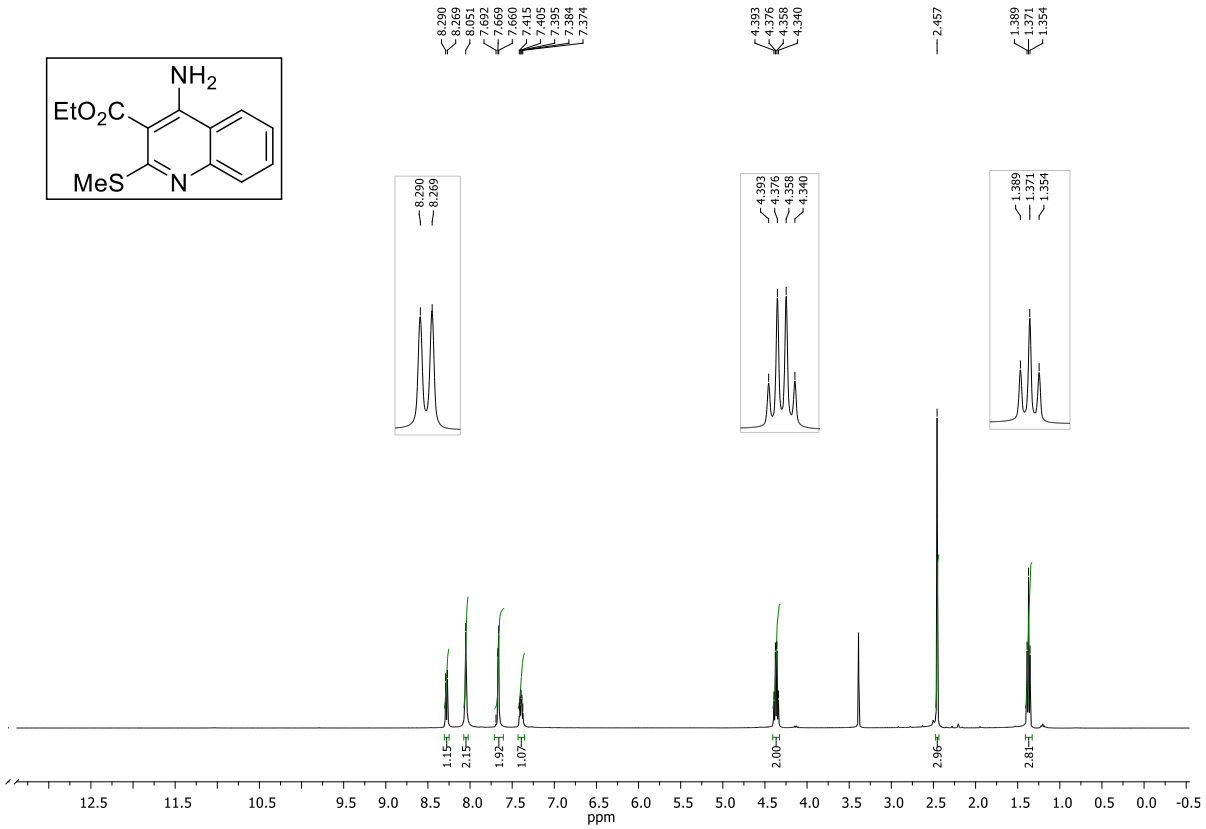


Figure 2.25b. ^{13}H Spectrum of **86a** in DMSO-d_6 (100 MHz)

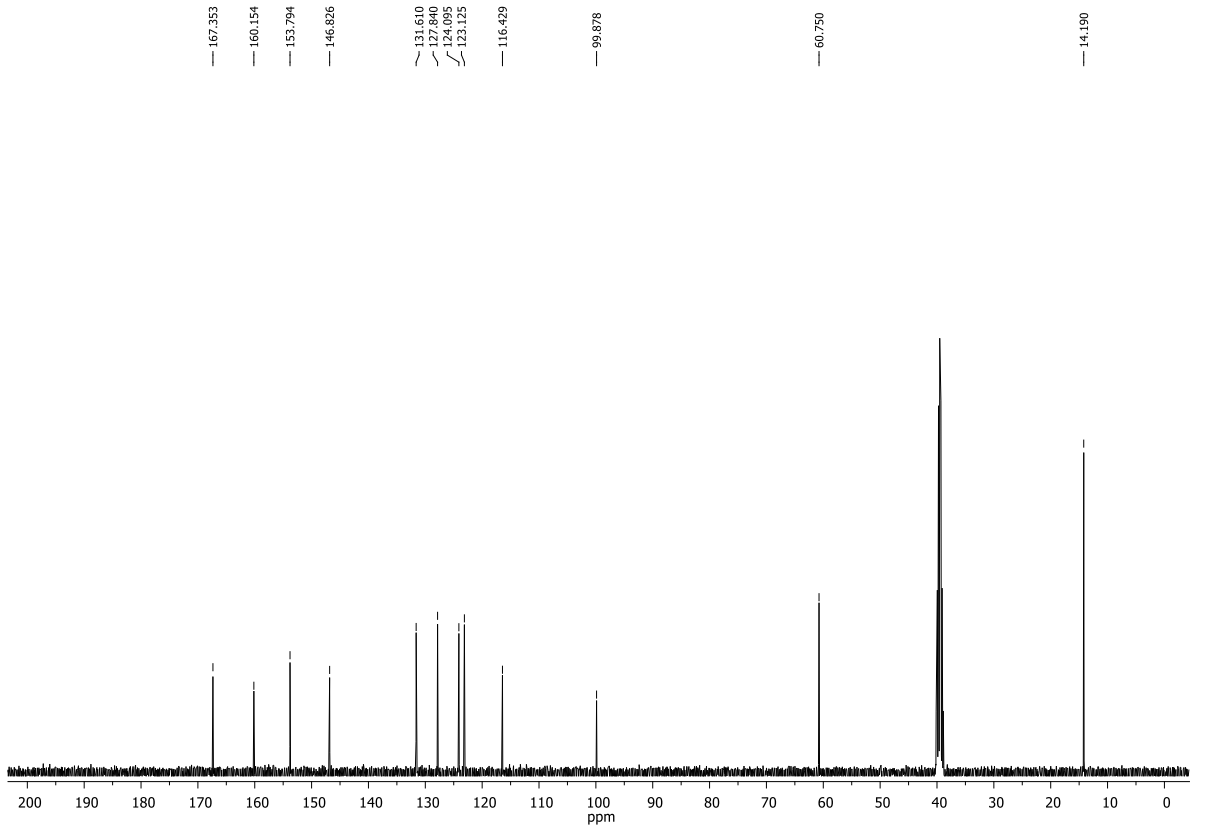


Figure 2.26a. ^{1}H Spectrum of **86f** in DMSO-d_6 (400 MHz)

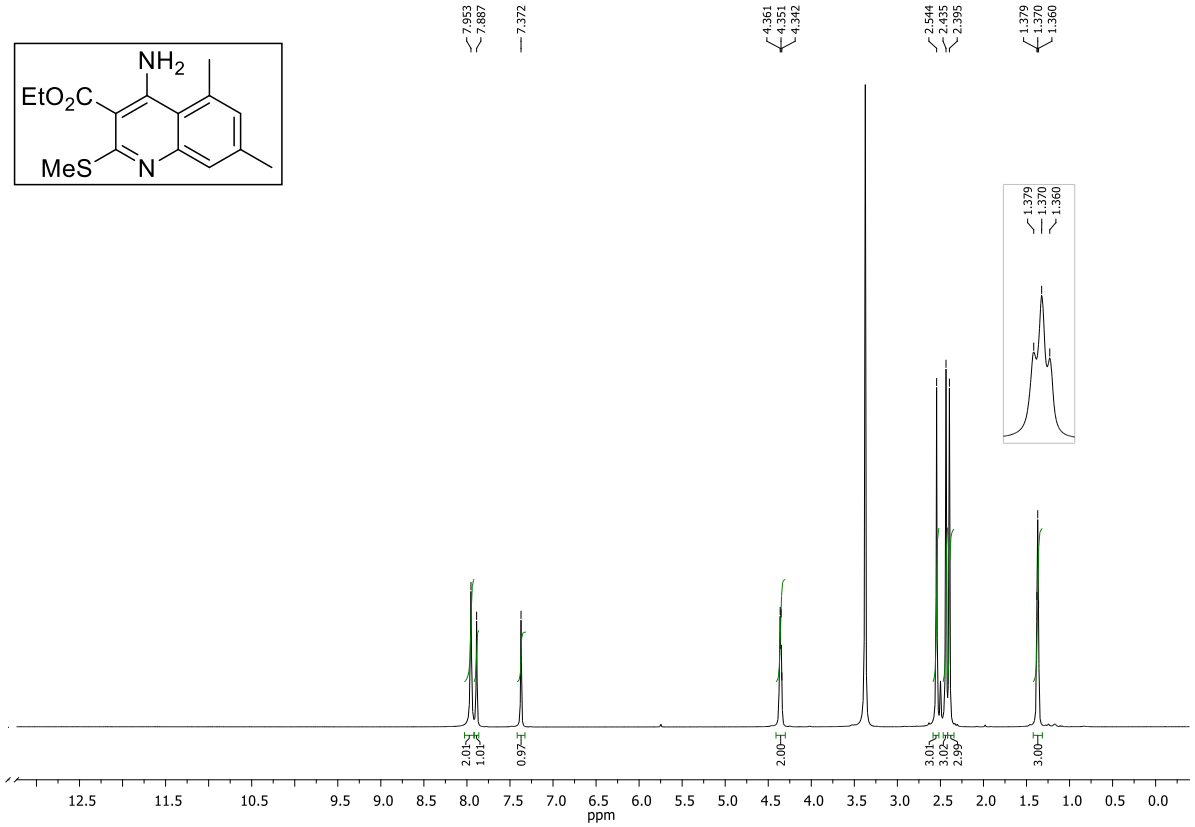


Figure 2.26b. ^{13}C Spectrum of **86f** in DMSO-d_6 (100 MHz)

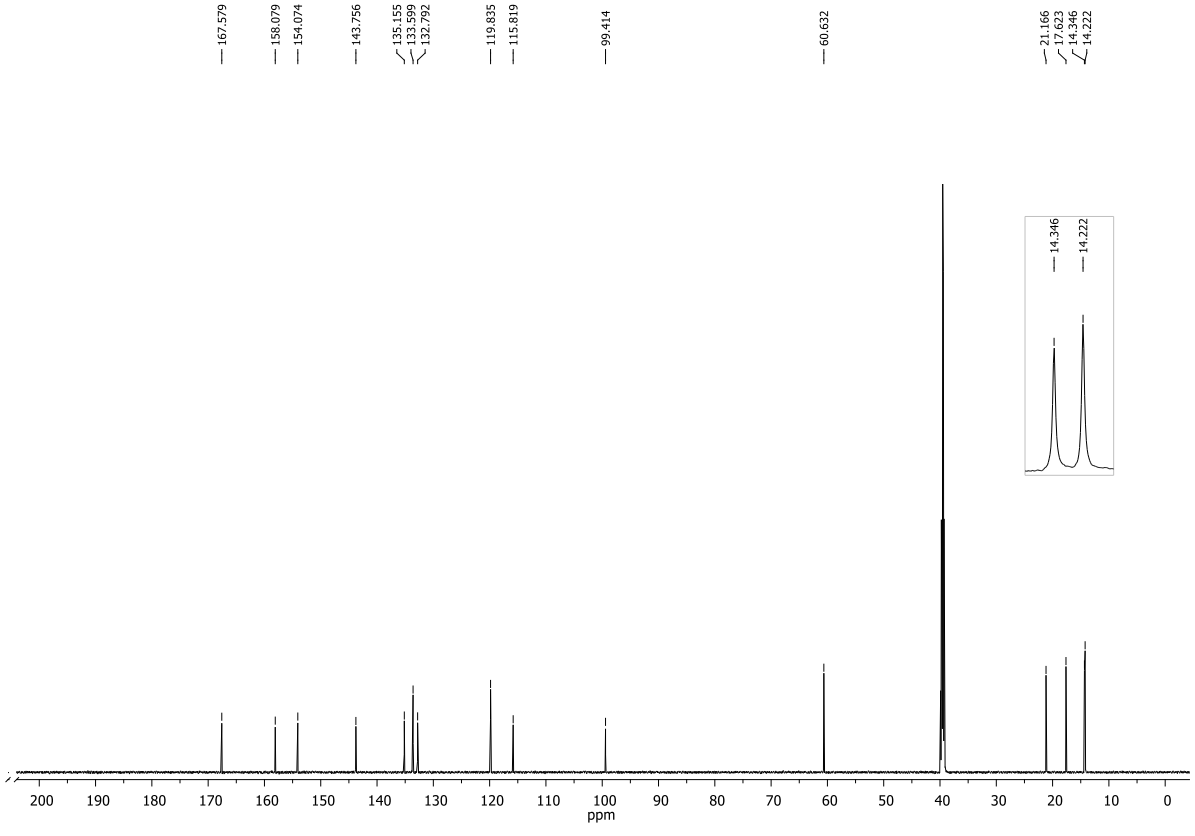


Figure 2.27a. ^{1}H Spectrum of **86k** in DMSO-d_6 (400 MHz)

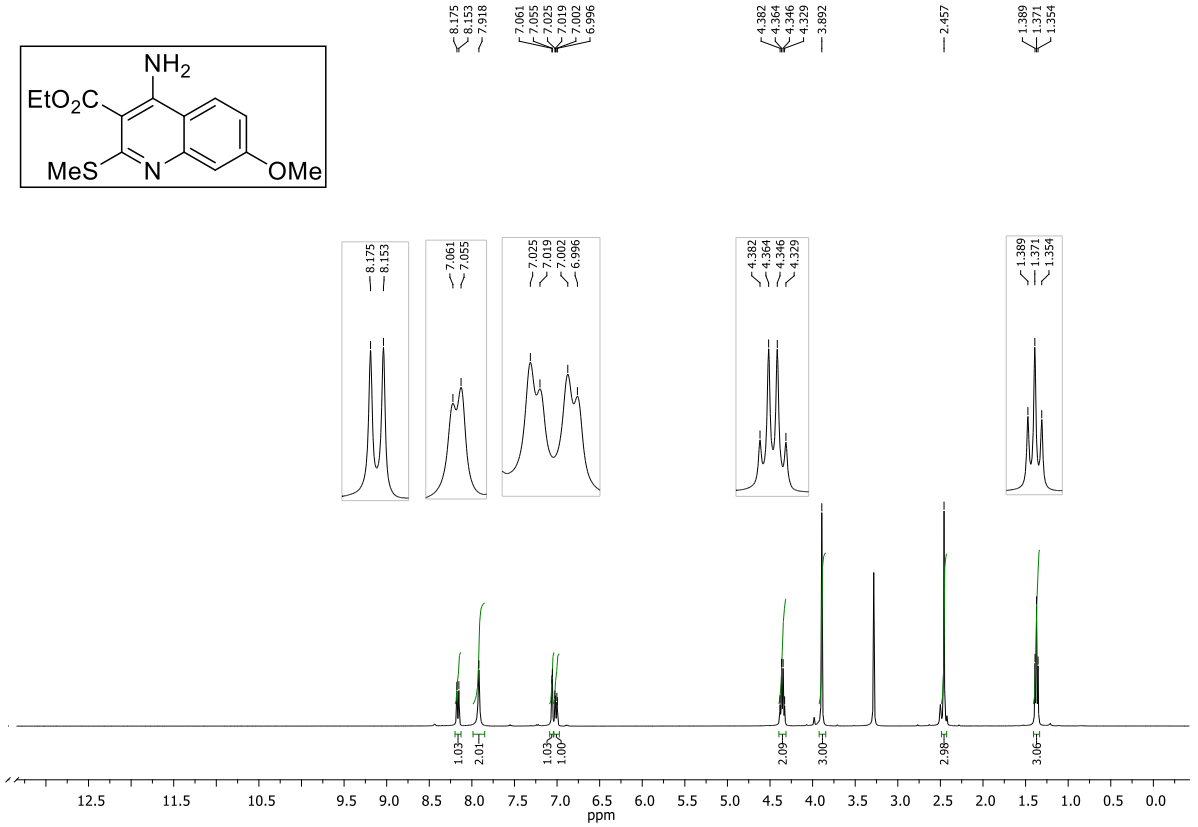


Figure 2.27b. ^{13}C Spectrum of **86k** in DMSO-d_6 (100 MHz)

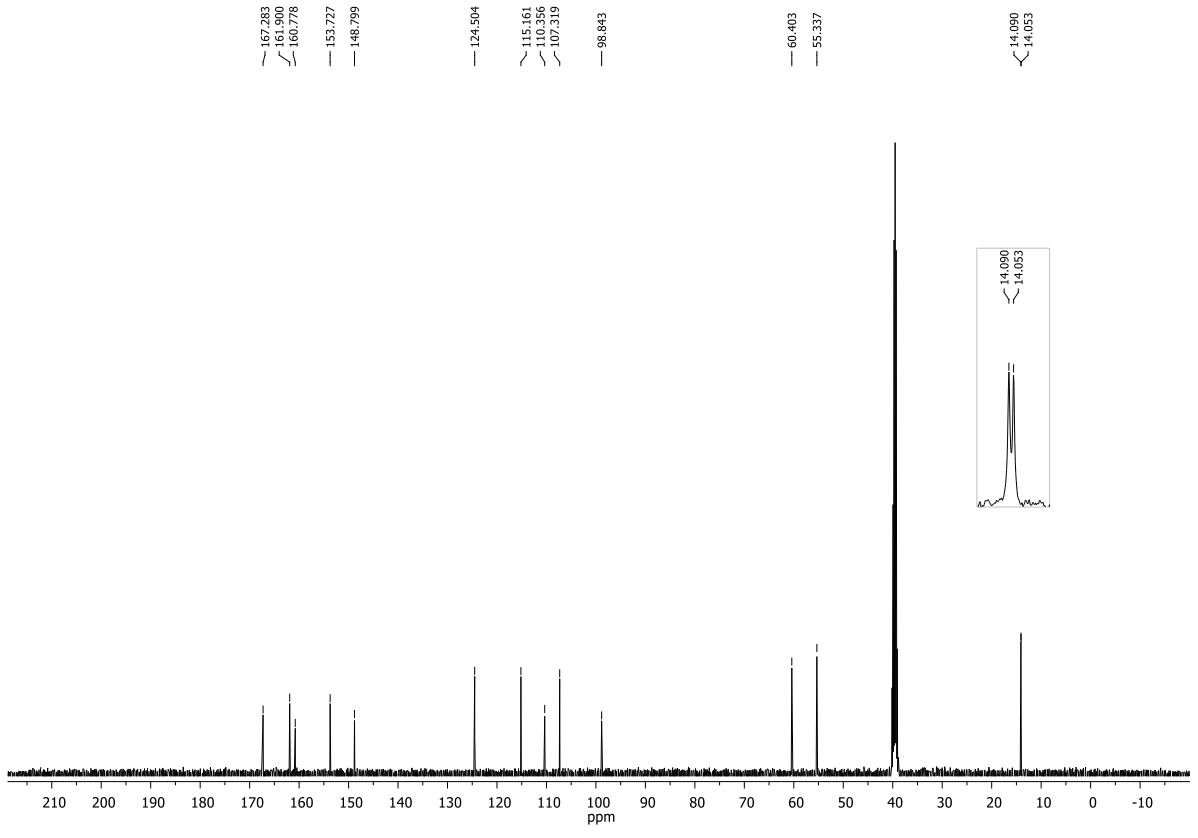


Figure 2.28a. ^{1}H Spectrum of **87a** in DMSO-d_6 (400 MHz)

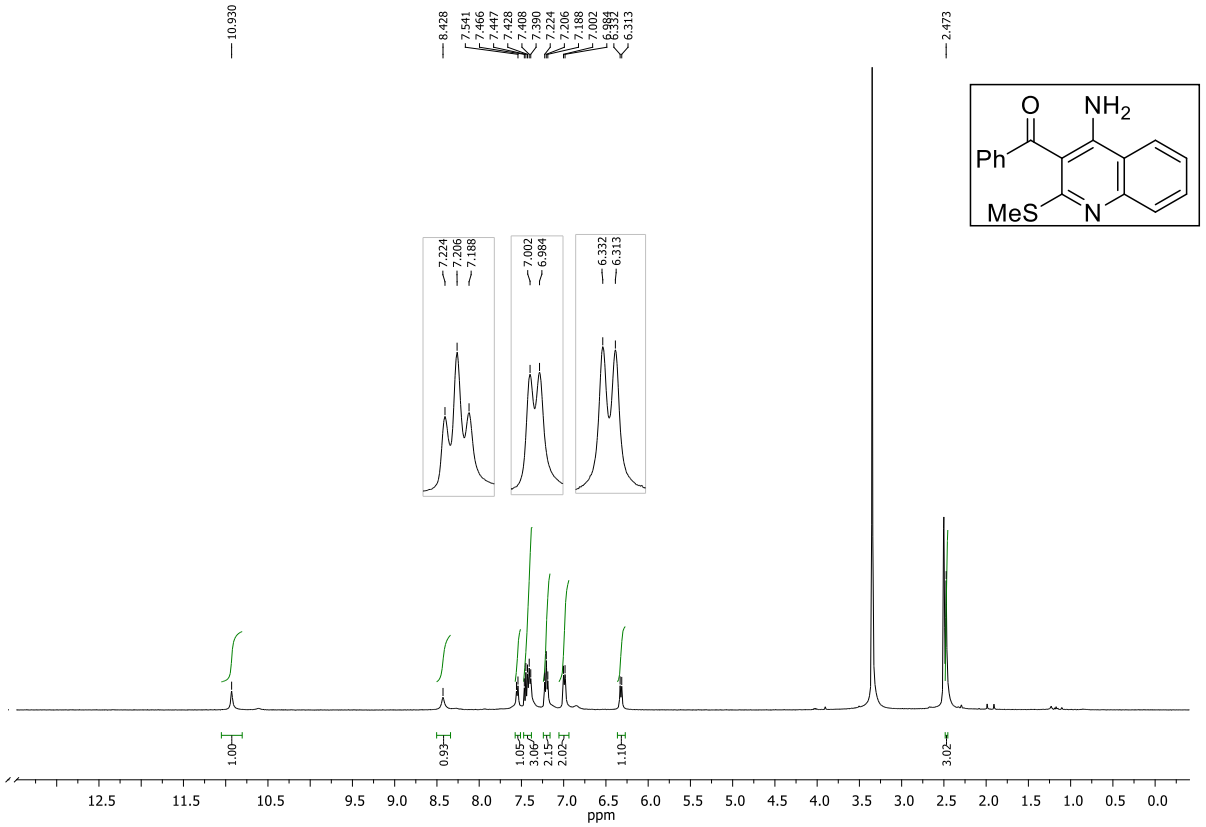


Figure 2.28b. ^{13}C Spectrum of **87a** in DMSO-d_6 (175 MHz)

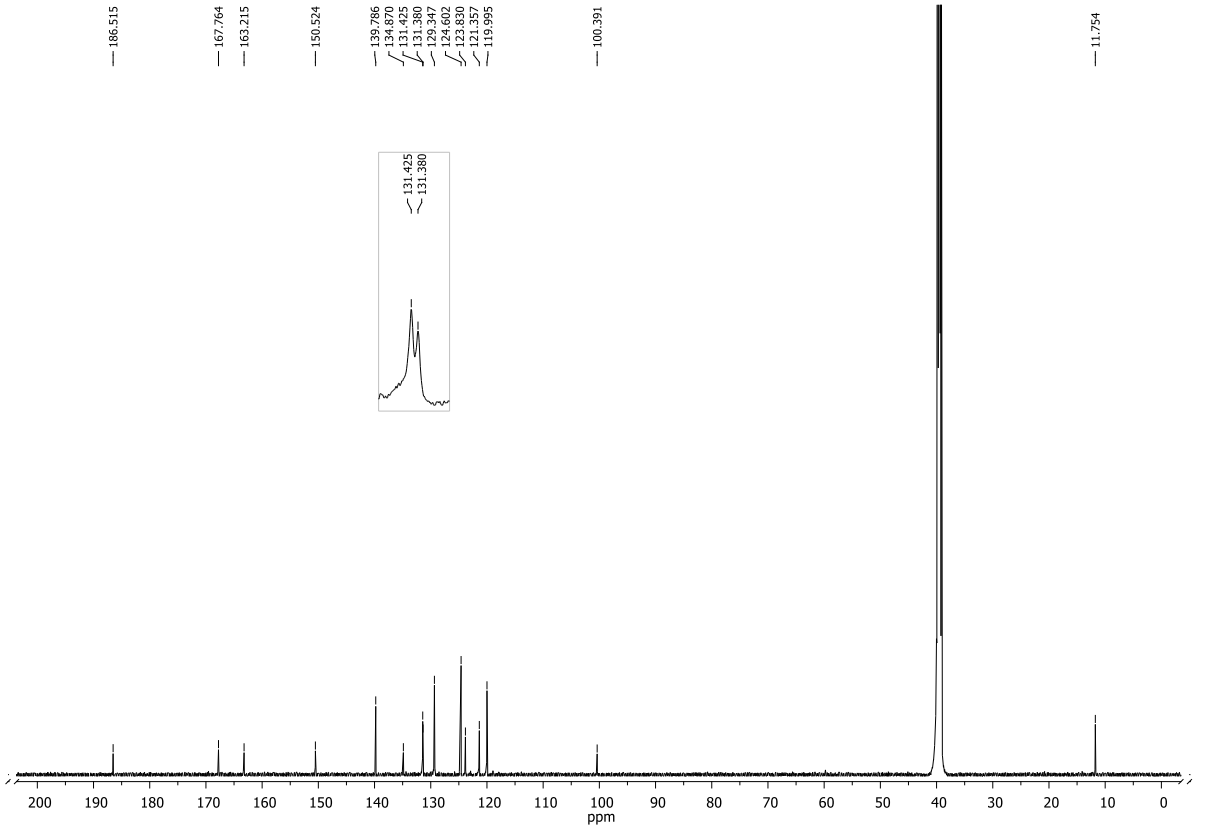


Figure 2.29a. ^{1}H Spectrum of **87f** in DMSO-d_6 (400 MHz)

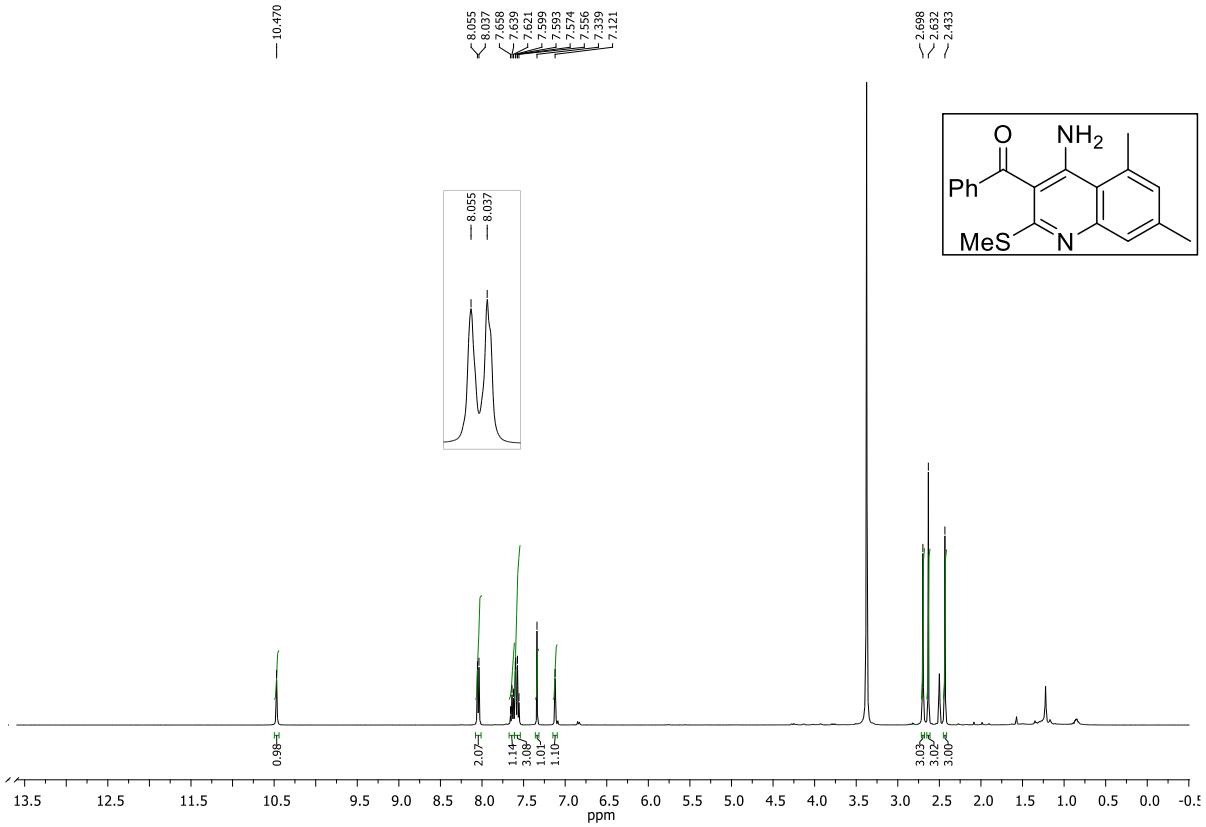
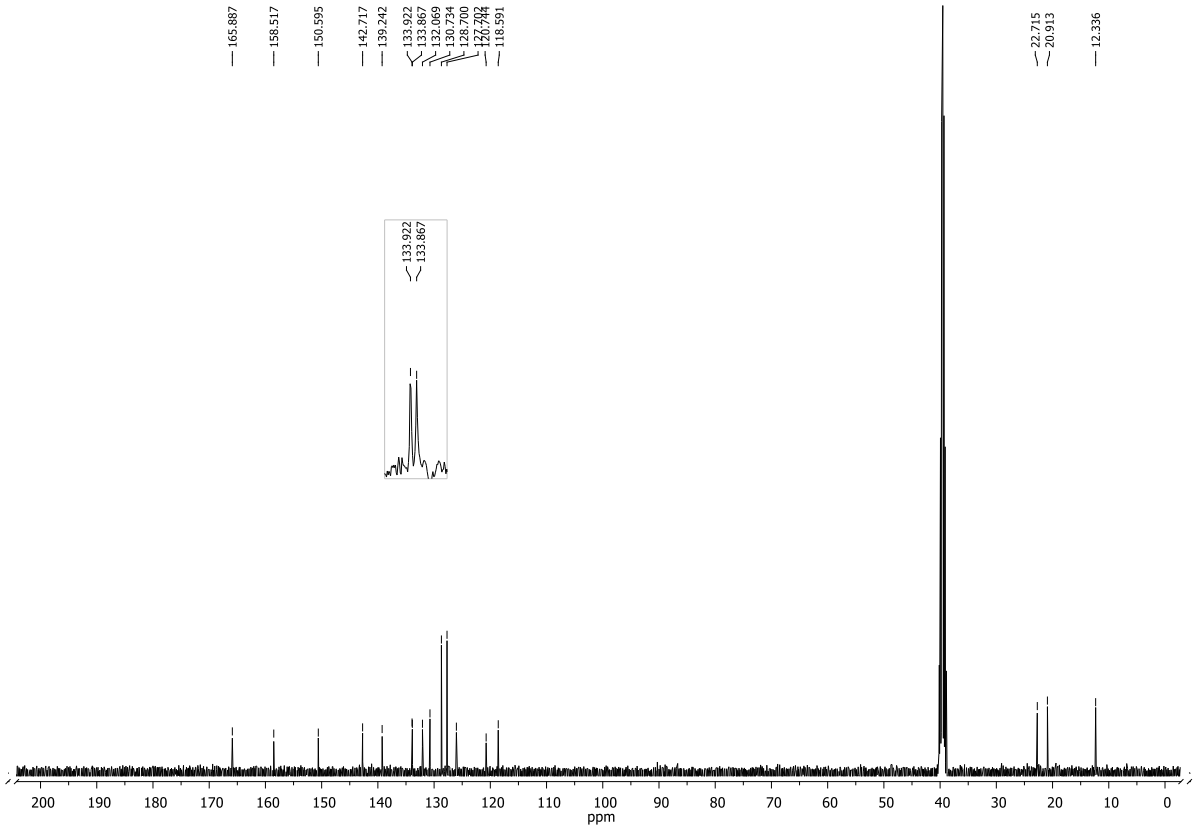


Figure 2.29b. ^{13}C Spectrum of **87f** in DMSO-d_6 (100 MHz)



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New Strategy to Synthesize Indolo fused Heterocycles: A Facile Route to Natural Product Analogues

3.1. Introduction

Nitrogen containing heterocycles are an important class of molecules because of their importance in the field of pharmaceuticals and material chemistry.[1] Among these *N*-heterocycles, indoles hold a crucial place because of its biological activities and its role in agrochemicals, essential oils and dyes.[2] Likewise, indolo fused heterocycles are also an important class of heterocyclic compounds.[3] For instance, indoloquinolines have attracted the attention of organic chemist because of its medicinal properties and are present in various natural products (Fig. 3.1).[4] Cryptolepine is the subclass of indoloquinoline, isolated and found in the roots of *Cryptolepis sanguinolenta*, West Africa (Fig. 3.1). This cryptolepine was first isolated by Gellert and co-workers in 1951.[5] After four decades, the other isomer was synthesized by Fresneda and was named as isocryptolepine (Fig. 3.1).[6] Subsequently, the third

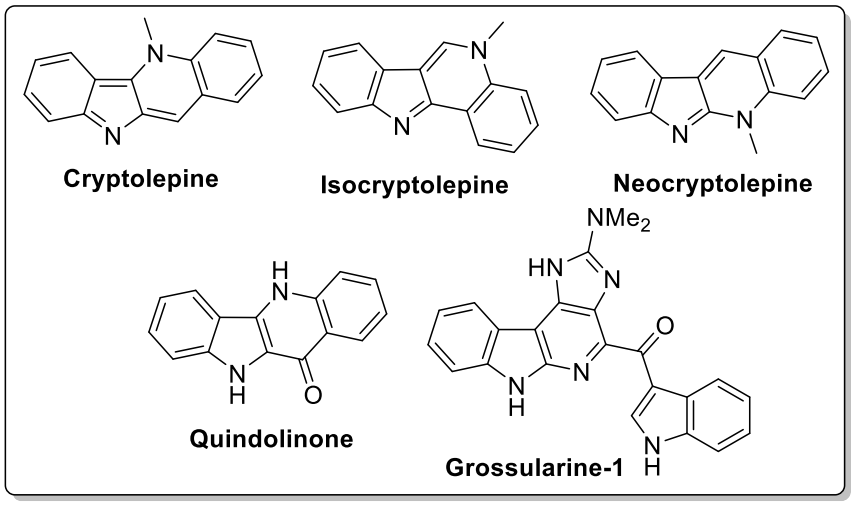


Figure 3.1. *Selective Biologically Active Molecules Containing Indolo Fused Heterocycles*

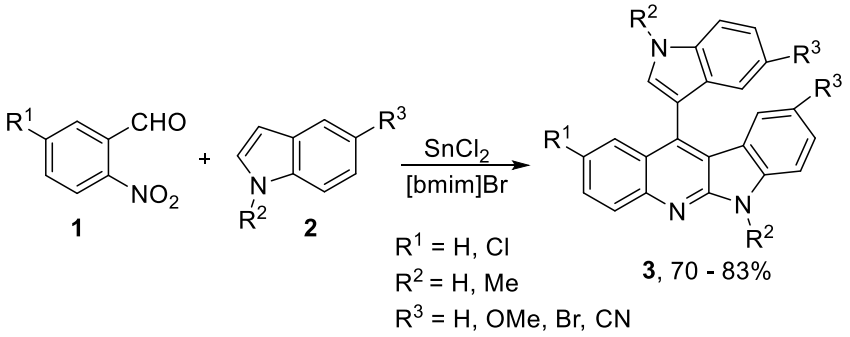
isomer was isolated independently by Pieter's and Schiff's group and was recognized as neocryptolepine (Fig. 3.1).[7] All these alkaloids were found to exhibit some biological

applications, like antimalarial, antiplasmodial, DNA intercalating agents etc.[8]So far, there are several methodologies that have been developed for the synthesis of indolo fused heterocycles.[9] But these methodologies are known to involve prefunctionalized starting materials or involve indoles or quinolines as the precursors.[10] In the following section, some selected methodologies for the synthesis of indolo fused heterocycles has been discussed.

3.2. Previous Reports

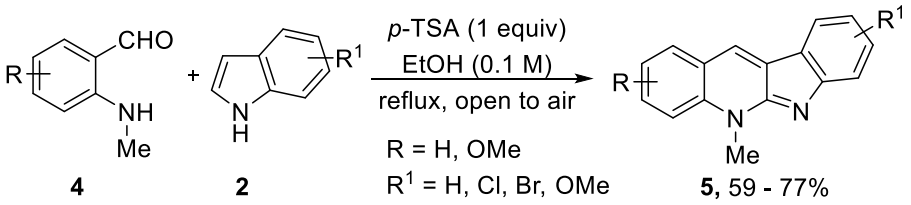
3.2.1 Synthesis of Indolo Fused Heterocycles from Indole Precursor

Wang and co-workers have developed a new methodology for the synthesis of substituted indoloquinolines **3**.[11] They have employed substituted indoles **2** and 2-nitrobenzaldehyde **1** as the precursors and carried out the reaction under the influence of $SnCl_2$ in the ionic liquid [bmim]Br. The substituted indoloquinolines were obtained in moderate to very good yield (Scheme 3.1).



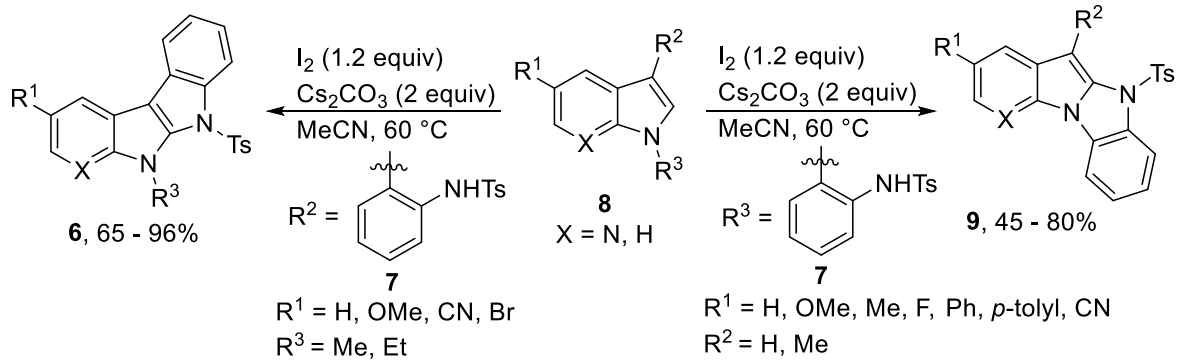
Scheme 3.1. *Synthesis of Substituted Indoloquinolines*

Seidel and co-workers have synthesized a natural product, neocryptolepine **5**, from 2-aminobenzaldehyde **4**.[12] Their methodology involved the acid-mediated annulation of indoles **2**, followed by aerial oxidation of the intermediate that leads to the formation of neocryptolepine (Scheme 3.2).



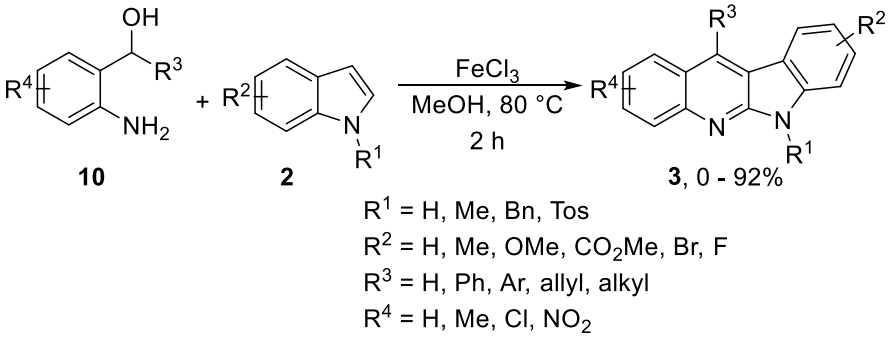
Scheme 3.2. *Synthesis of Neocryptolepine*

Sekar and co-workers devised a new methodology for the synthesis of indolo fused heterocycles **9** & **6**.[13] This methodology involved the iodine mediated intramolecular amidation of C2 of indoles or azaindoles **8**. This amidation reaction affords indolo fused heterocycles **9** & **6** which are tertacycles. They have shown that the less reactive C2 centre takes part in the amidation reaction. The indolo fused heterocycles **6** & **9** were obtained in moderate to excellent yields (Scheme 3.3).



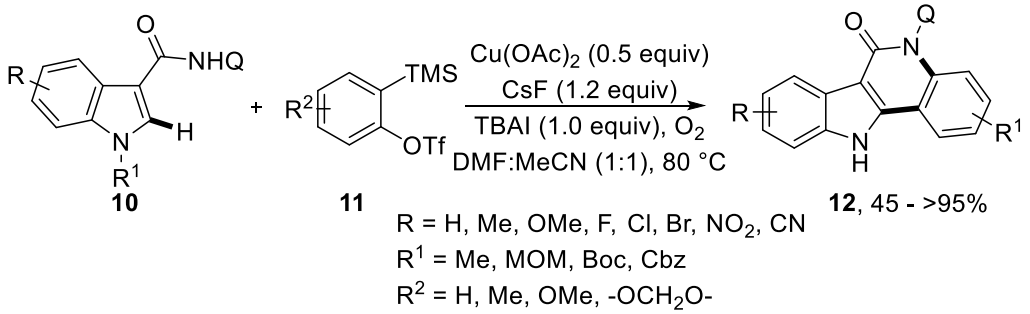
Scheme 3.3. *Synthesis of Indolo Fused Heterocycles via C2-Amidation Reaction*

Wang and co-workers have reported a new method to synthesize indoloquinolines **3**. They have used 2-aminobenzylalcohols **10** and indoles **2** as the starting materials.[14] They have successfully converted the starting materials to indoloquinolines **3** in moderate to excellent yields, using $FeCl_3$. Further, they have demonstrated the synthesis of neocryptolepine (Scheme 3.4).



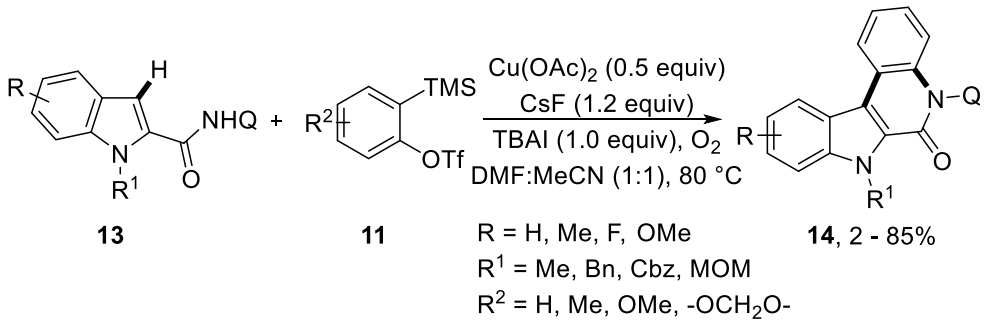
Scheme 3.4. *Iron Catalyzed Synthesis of Indolo Fused Quinolines*

Zhang and co-workers envisioned a new protocol to synthesize indolo fused quinolone **12** via copper mediated *N*-heteroannulation reaction.[15] Indole **10** and *in situ* generation of aryne derivatives are used as the precursors. The use of copper salt and O_2 makes this protocol environmentally benign. The indolo fused quinolone **12** were isolated in moderate to excellent yields (Scheme 3.5).



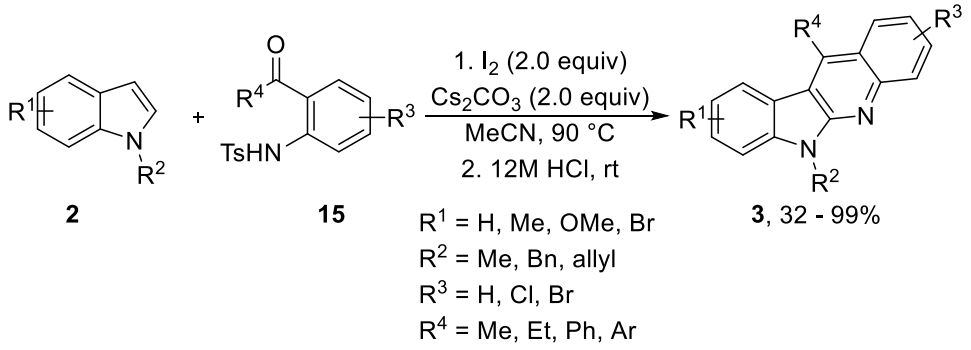
Scheme 3.5. *Copper Mediated N-Heteroannulation Reaction*

They have further extended this methodology to synthesize the other regioisomer of indoloquinolines **14**, by employing indole-2-carboxamides **13** as the precursors.[15] The indolo fused quinolones **14** were obtained in low to very good yields (Scheme 3.6).



Scheme 3.6. *Copper Mediated N-Heteroannulation Reaction*

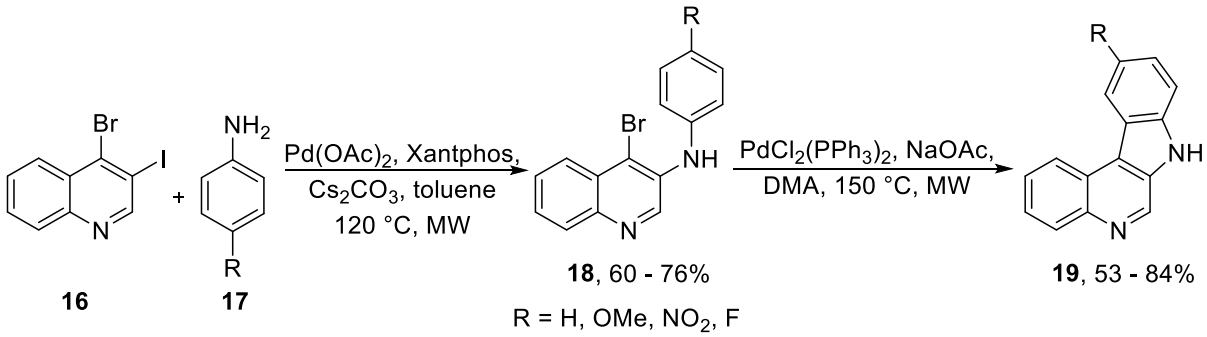
The polysubstituted indoloquinolines **3** can also be synthesized via iodine mediated Friedel-Crafts alkylation reaction of indoles **2**. Y.-M. Liang and co-workers have successfully developed this methodology to synthesize neocryptolepine and its derivatives.[16] They have used o-substituted *N*-Ts anilines **15** as the annulation partner of *N*-protected indoles **2**. The neocryptolepine analogues **3** were obtained in moderate to excellent yields (Scheme 3.7).



Scheme 3.7. *Iodine Mediated Friedel-Crafts Alkylation Reaction*

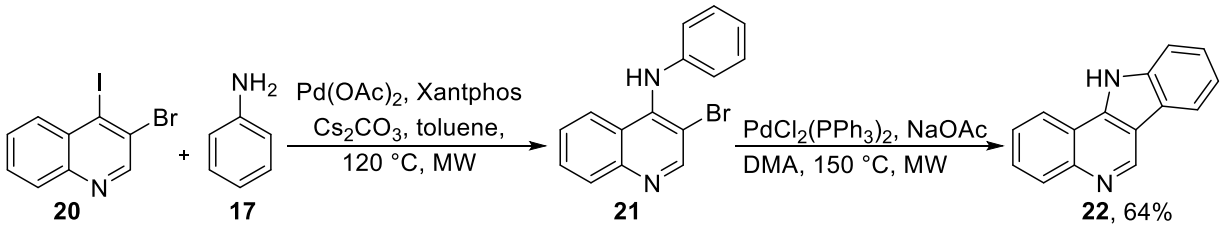
3.2.2. Synthesis of Indolo Fused Heterocycles from Quinoline Precursor

Boganyi and co-worker have devised a methodology for the synthesis of indoloquinolines **19** from dihalo substituted quinolines **16**.[17] This methodology involved two sequential Pd-catalyzed cross-coupling reactions, namely, Buchwald-Hartwig amination and intramolecular Heck coupling. They have utilized microwave irradiation to obtain the products **19** in good yields (Scheme 3.8).



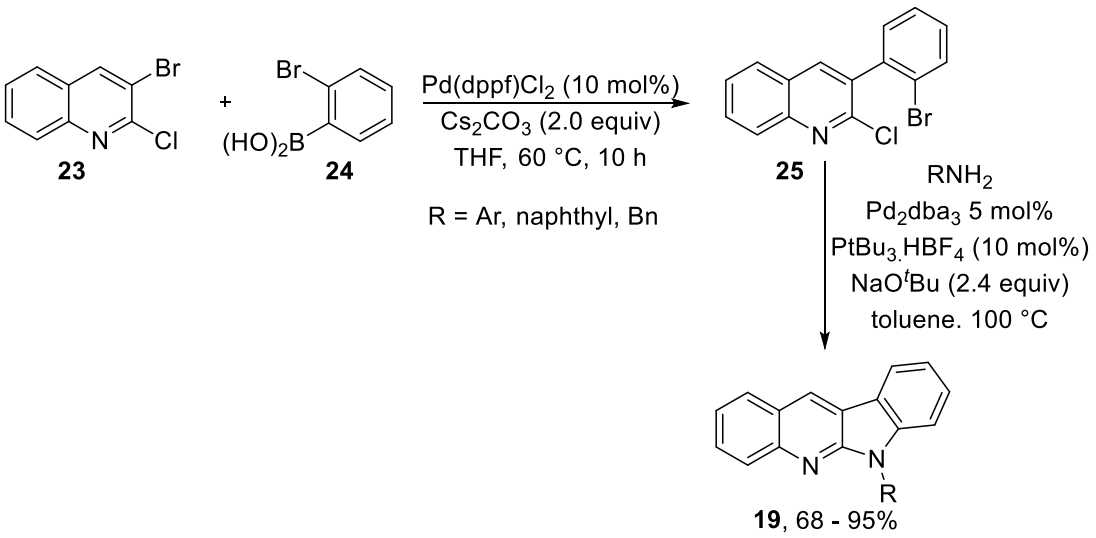
Scheme 3.8. *Synthesis of Indolo Fused Quinoline via Pd-catalyzed Double Cross-coupling Reaction*

They have also synthesized the other regioisomer of indoloquinoline **22** via Pd-catalyzed inter and intramolecular cross-coupling reactions (Scheme 3.9).[17]



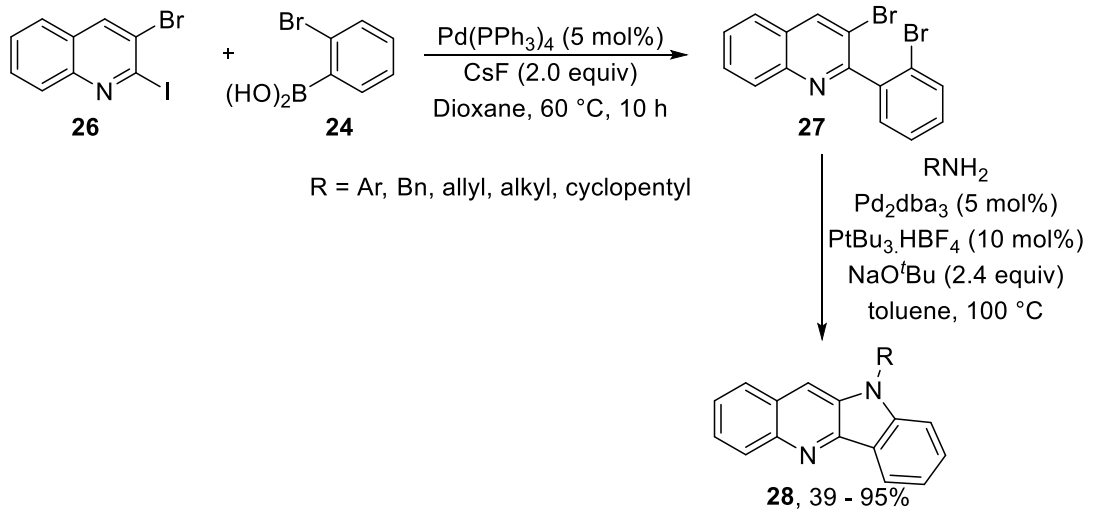
Scheme 3.9. *Synthesis of Indolo Fused Quinoline via Pd-Catalyzed Double Cross-Coupling Reaction*

Langer and co-workers have designed a protocol for the synthesis of indoloquinolines **19** following a double C─N bond formation reactions.[18] This methodology involved Suzuki coupling, and then a double Buchwald-Hartwig coupling reaction (Scheme 3.10).



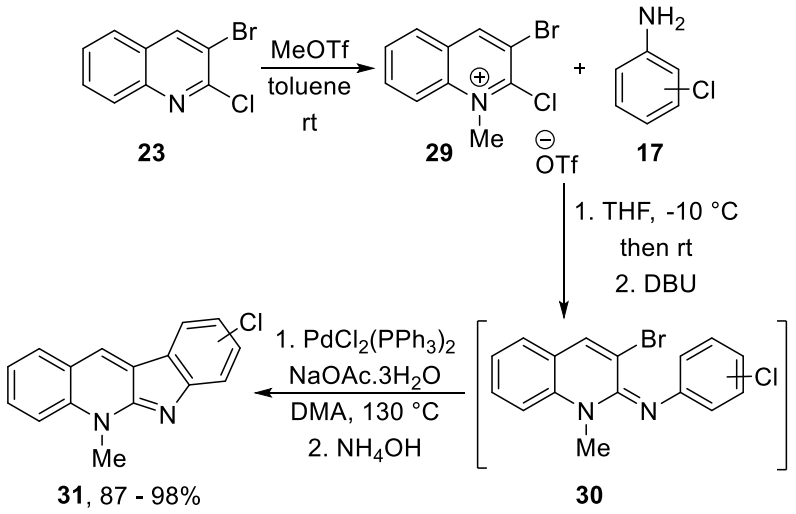
Scheme 3.10. *Synthesis of Indoloquinoline via Cross-Coupling Reaction*

They have further synthesized another isomer of indoloquinoline **28** following the same methodology of cross coupling reaction.[18] The indoloquinolines **28** were obtained in moderate to excellent yields (Scheme 3.11).



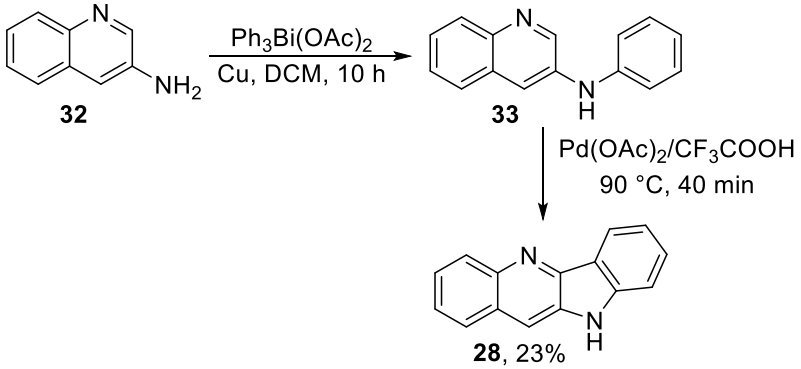
Scheme 3.11. *Synthesis of Indoloquinoline via Cross-Coupling Reaction*

Maes and co-workers have synthesized neocryptolepine **31** from quinoline precursor.[19] This protocol involved one-pot synthesis of neocryptolepine **31** via Pd-catalyzed C─C bond formation reactions. The neocryptolepine **31** and its derivatives were obtained in excellent yields (Scheme 3.12).



Scheme 3.12. *Synthesis of Neocryptolepine via Pd-Catalyzed Cyclization*

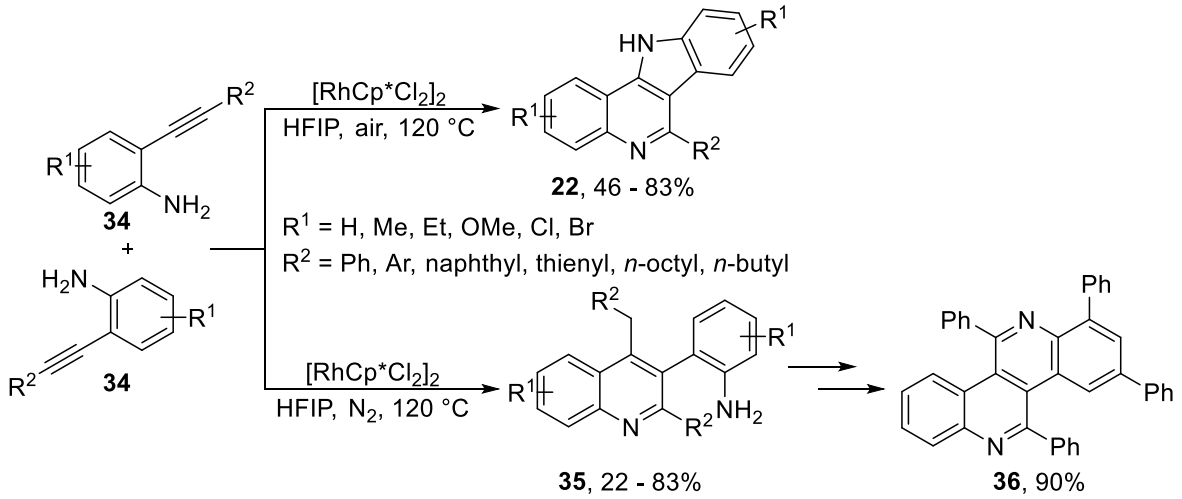
Ablordeppey and co-workers devised a new methodology for the synthesis of indoloquinoline **28**.[20] They have employed 3-aminoquinoline **32** as the precursor. The 3-aminoquinoline **32** was *N*-arylated using $Ph_3Bi(OAc)_2$. The *N*-arylated aminoquinoline **33** underwent palladium catalyzed oxidative cyclization affording the indoloquinoline **28** in 23% yield (Scheme 3.13).



Scheme 3.13. *Synthesis of Cryptolepine Pd-Catalyzed Oxidative Cyclization*

3.2.3. Synthesis of Indolo Fused Heterocycles from Acyclic Precursors

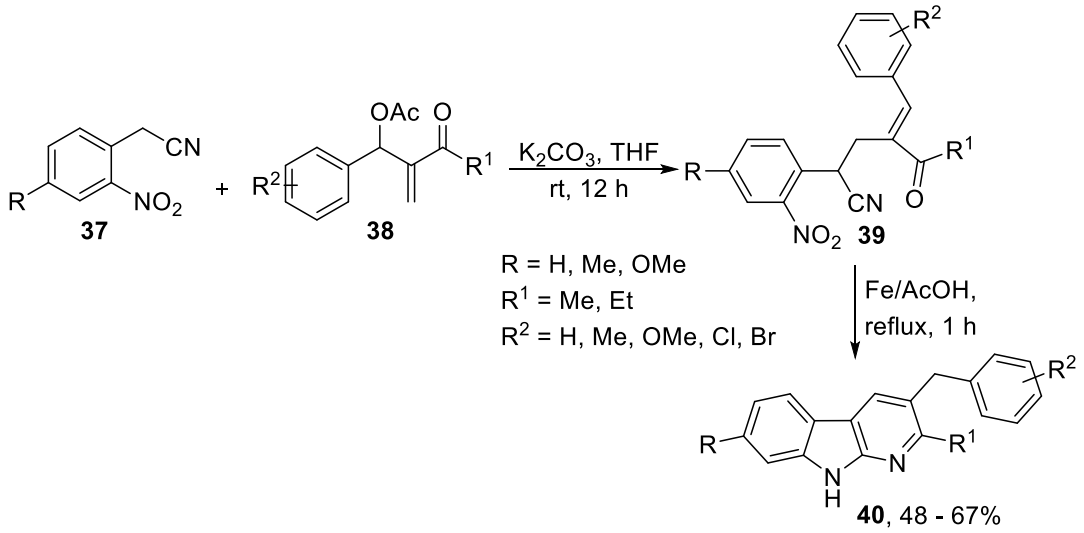
Fan and co-workers devised a new methodology for the synthesis of indoloquinoline **22** and quinoline derivatives **35** for the first time by tuning the atmosphere of the reaction.[21]



Scheme 3.14. *Synthesis of Quinoline Derivatives by Tuning the Atmosphere of Reaction*

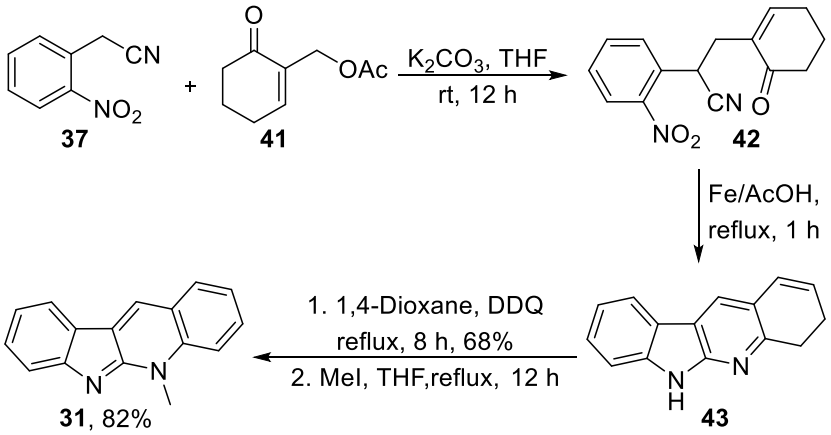
When the aerobic condition was imposed, they observed indoloquinoline **22** as the sole product and under inert condition they obtained substituted quinoline **35** as the product which was further transformed to quinolino fused quinoline **36**. HFIP plays a dual role of solvent as well as promoter in this transformation (Scheme 3.14).

Basavaiah and co-workers have synthesized α-carboline core **40** via one-pot protocol.[22] This methodology involved the base-mediated allylation of aryl acetonitriles **37** with Baylis-Hillman adduct **38** leading to the generation of intermediate **39**, followed by iron catalyzed reduction under acidic condition that afforded the α-carboline derivative **40** in 61% yield (Scheme 3.15).



Scheme 3.15. *Synthesis of α-Carboline Core from Baylis-Hillman Adduct*

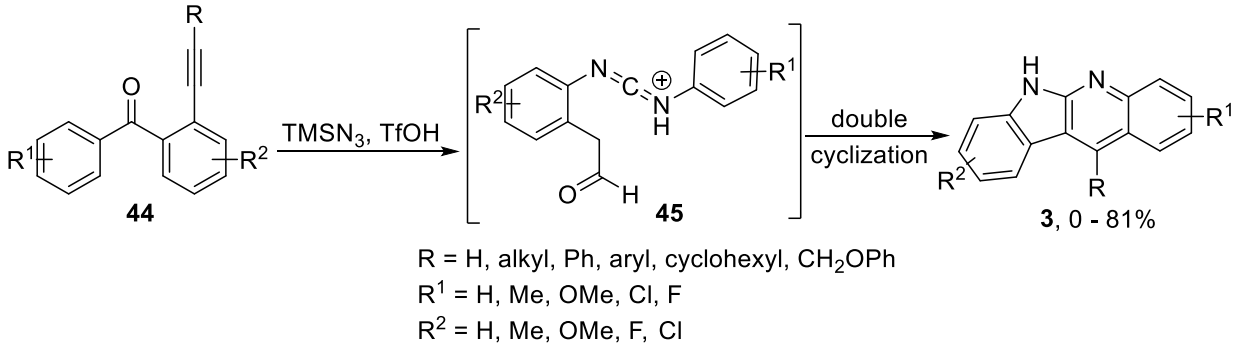
They have further extended this methodology to synthesize neocryptolepine **31**.[22] The hexenone derived Baylis-Hillman adduct **41** was employed. After the formation of the α-carboline core **43**, they have performed oxidation followed by methylation to obtain the neocryptolepine **31** in 82% (Scheme 3.16).



Scheme 3.16. *Synthesis of Neocryptolepine from Baylis-Hillman Adduct*

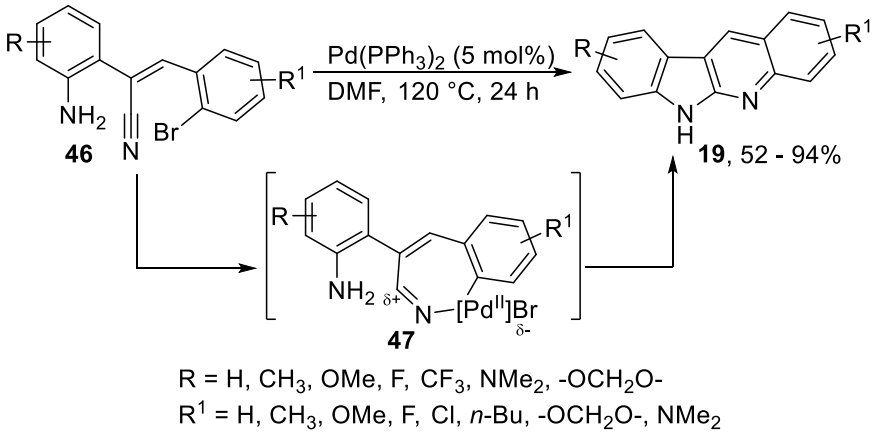
Tummaton and co-workers have developed a methodology for the synthesis of indoloquinoline **3**.[23] The alkynylketones **44** were smoothly converted to indoloquinolines **3** via double N_2-extrusion or double aryl migration via the formation of carbodiimide **45** as the

intermediate. The intramolecular double cyclization finally led to the indoloquinolines **3** in moderate yields (Scheme 3.17).



Scheme 3.17. *Synthesis of Indoloquinoline from Alkynylketones*

Hsieh and co-workers have envisioned the synthesis of norneocryptolepine **19** from (*Z*)-2-(2-aminophenyl)-3-(2-bromophenyl)acrylonitrile **46** via Pd-catalyzed reaction.[24] The palladium underwent an oxidative addition leading to the generation of a seven membered intermediate **47**, facilitating the first cyclization. This intermediate **47** behaves as a Lewis acid, facilitating the attack of the amino group to the nitrile group, thereby promoted the second cyclization. The generation of Pd(0) by reductive elimination led to the formation of indoloquinolines or norneocryptolepine **19** in moderate to excellent yields (Scheme 3.18).



Scheme 3.18. *Pd Catalyzed N-Heteroannulation Reaction*

PART-A:

Triflic Acid Promoted Cyclization of *α*-Aryl-*β*-anilino-*β*-(thiomethyl)acrylonitriles: Synthesis of Isocryptolepine analogues

The part-A of this chapter discusses about the synthesis of indolo fused quinolines. We envisaged an efficient protocol for the synthesis of indolo fused quinolines from 4-aminoquinolines under metal free conditions.

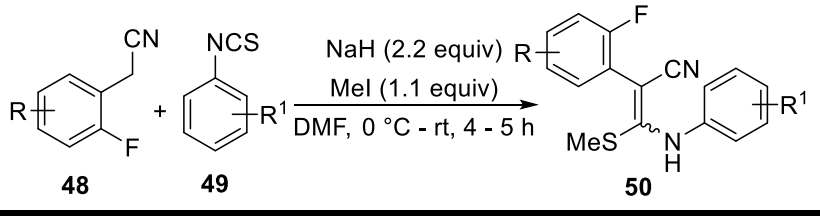
3.3. Results and Discussions:

The required 4-aminoquinolines can be synthesized from *β*-anilinoacrylonitriles **50** from acyclic precursors under basic condition.

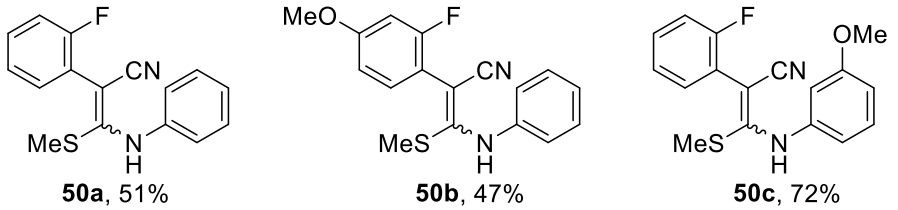
3.3.1. Synthesis of *β*-Anilinoacrylonitriles

The required *β*-anilinoacrylonitriles **50** can be obtained by treating aryl acetonitriles **48** with NaH in DMSO at 0 ℃. After the generation of anion, the reaction mixture was treated

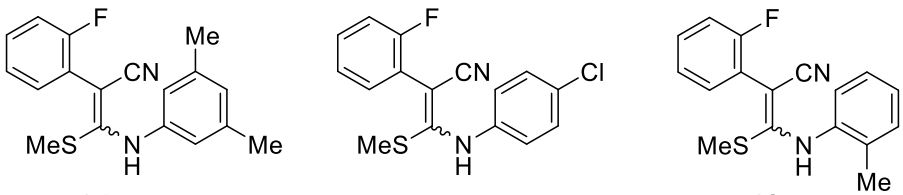
Table 3.1. Synthesis of *β*-Anilinoacrylonitriles



48 **49** **50**



50a, 51% **50b**, 47% **50c**, 72%



50d, 58% **50e**, 88% **50f**, 79%

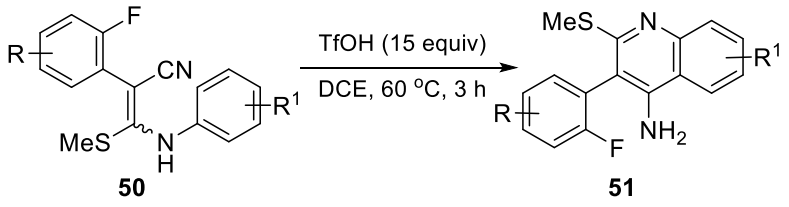
with aryl isothiocyanates **49**. Further, methyl iodide in DMF was added to the reaction mixture and was stirred for 1 h. A handful of *β*-anilinoacrylonitriles **50** having electron rich and halo substituents were isolated in moderate to excellent yields (Table 3.1).

3.3.2. Synthesis of 4-Amino-3-arylquinolines

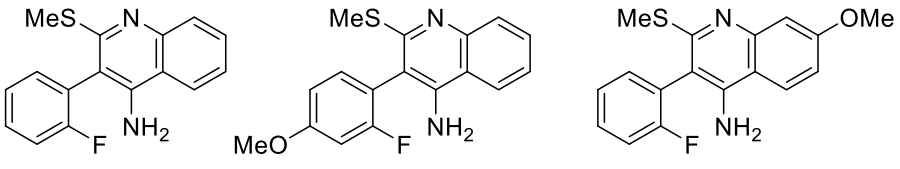
The various 4-amino-3-arylquinolines **51** were synthesized from *β*-anilinoacrylonitriles **50** under acidic conditions. The *β*-anilinoacrylonitrile **50a** was at first subjected to 5 equiv. of TfOH in DCE at room temperature, unfortunately due to incomplete conversion of starting material and poor yield we increased the equivalence of TfOH, and heated the reaction mixture at 60 ℃, we observed complete conversion of the starting material **50**. A modification is required for an effective *N*-heteroannulation of *α*-Aryl-*β*-anilino-*β*-(thiomethyl)acrylonitriles **50** (Table 3.2).

α-(2-Fluorophenyl)-*β*-anilinoacrylonitrile **50a** was successfully converted to 4-amino-3-(2-fluorophenyl)-2-(methylthio)quinoline **51a** with 69% yield (Table 3.2). The *α*-(2-flouro-4-methoxyphenyl)-*β*-anilinoacrylonitrile **50b** gave the corresponding 4-aminoquinoline **51b** in 34% yield (Table 3.2). We observed only one regioisomer of the 4-aminoquinoline **51c** in 66% yield in the case of *meta*-methoxy *α*-(2-flourophenyl)-*β*-anilinoacrylonitriles **50c** (Table 3.2). The dimethyl substitution at the *N*-aryl ring of the *α*-aryl-*β*-anilinoacrylonitriles **50d** afforded 90% of two regioisomers of the cyclized 4-aminoquinoline **51d** (Table 3.2). However, *para*-chloro *α*-(2-flourophenyl)-*β*-anilinoacrylonitrile **50e** gave only 33% of the 4-aminoquinoline **51e** (Table 3.2). 4-amino-3-(2-fluorophenyl)-8-methyl-2-(methylthio)quinoline **51f** was obtained in 56% yield from the respective *ortho*-methyl *α*-(2-flourophenyl)-*β*-anilinoacrylonitrile **50f** (Table 3.2).

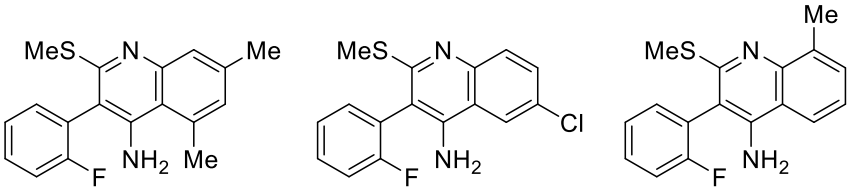
Table 3.2. Triflic Acid mediated *N*-Heteroannulation Reaction



50 **51**



51a, 69% **51b**, 34% **51c**, 66%



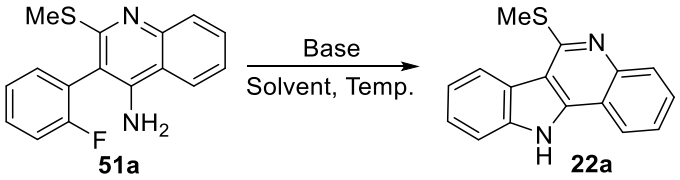
51d, 90% **51e**, 33% **51f**, 56%

3.3.3 Optimisation of Base-Mediated C─H Amination Reaction

After synthesizing a handful of 4-amino-3-arylquinolines **51** we studied various reaction conditions to optimize the C─H amination process (Table 3.3). We have considered 4-amino-3-(2-fluorophenyl)-2-(methylthio)quinoline **51a** as the model substrate and treated with 3 equiv of NaH in DMSO at room temperature (entry 1, Table 3.3). After 24 h, we observed no conversion of the starting material **51a** and isolated the starting material **51a** in quantitative yield (entry 1, Table 3.3). On increasing the temperature to 60 °C, we observed partial conversion of the starting material **51a** leading to the formation of product in 66% and recovery of 30% starting material **51a** (entry 2, Table 3.3). The product was further characterized by spectral and analytical data and was identified as indolo fused quinoline **22a**. To increase the yield of the reaction we further increased the temperature and observed a slight increase in the yield of the reaction (entry 3, Table 3.3). On heating the reaction at 120 °C, we noticed a drastic change in the yield of the reaction with complete conversion of the starting

material **51a** (entry 4, Table 3.3). On changing the solvent, we again observed incomplete conversion of the starting material **51a** with 70% of the final product **22a** (entry 5, Table 3.3). The bases like KO^{t}Bu and Cs_2CO_3 could not enhance the yield of the reaction (entries 6 – 7, Table 3.3).

Table 3.3. **Optimization Conditions for Base Mediated C─H Amination Reaction**



51a **22a**

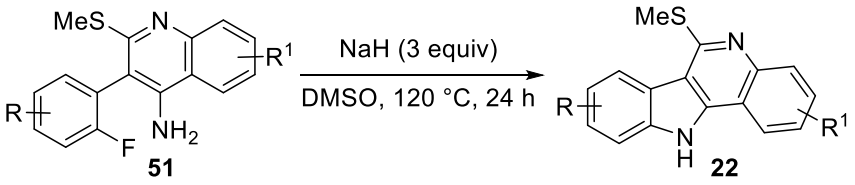
Entry	Base (3 equiv)	Solvent	Time	Temp.	Yield	
					22a	**51a**
1.	NaH	DMSO	24 h	rt	-	>99%
2.	NaH	DMSO	24 h	60 ℃	66%	30%
3.	NaH	DMSO	24 h	90 ℃	71%	20%
4.	**NaH**	**DMSO**	**24 h**	**120 ℃**	**84%**	**-**
5.	NaH	DMF	24 h	120 ℃	70%	25%
6.	KO^{t}Bu	DMSO	24 h	120 ℃	27%	67%
7.	Cs_2CO_3	DMSO	24 h	120 ℃	trace	97%

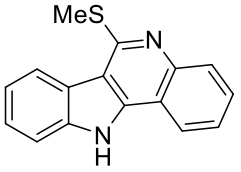
3.3.4. Substrate Scope for Base Mediated C─H Amination Reaction

With the optimized condition in our hands, we then shifted our focus to study C─H amination reaction of the various 4-amino-3-arylquinolines **51** (Table 3.4). 4-amino-3-(2-fluoro-3-methoxyphenyl)-2-(methylthio)quinoline **51b** was smoothly converted to the corresponding indolo fused quinoline **22b** in excellent yield (Table 3.4). The electron rich substrate **51c** afforded 72% of the corresponding product **22c** (Table 3.4). 4-amino-3-(2-fluoro-

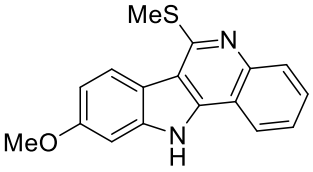
3-methylphenyl)-5,7-dimethyl-2-(methylthio)quinoline **51d** was successfully converted into the cyclized product **22d** in 64% of yield (Table 3.4). Further halo substituted 4-aminoquinoline **51e** yielded 93% of the indoloquinoline **22e** (Table 3.4). 8-Methyl substituted 4-aminoquinoline **51f** also afforded the corresponding indolo fused quinoline **22f** in excellent yield (Table 3.4).

Table 3.4. Base-Mediated C─H Amination Reaction

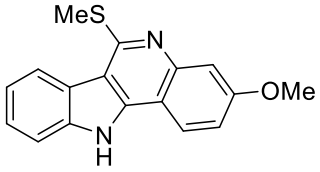




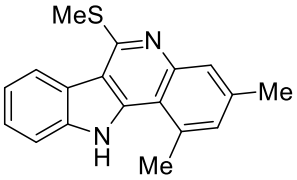
22a, 84%



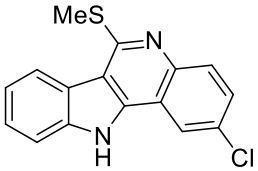
22b, 92%



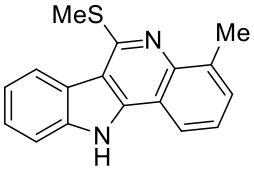
22c, 72%



22d, 64%

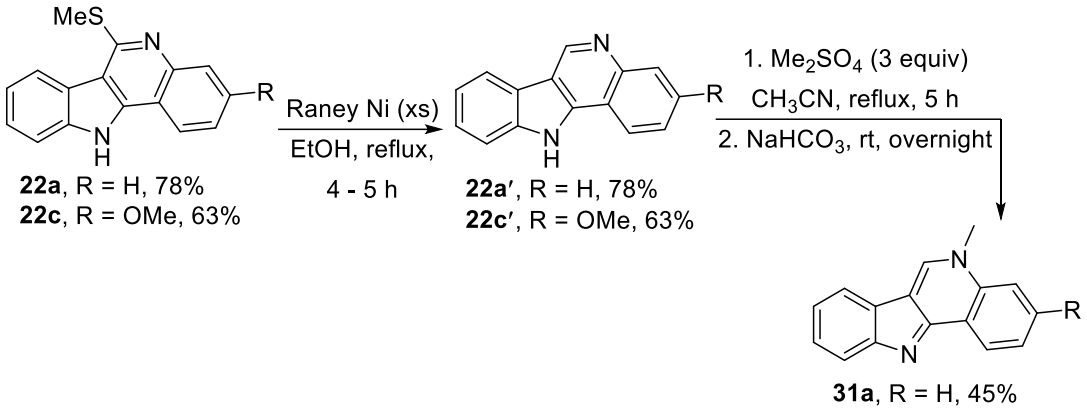


22e, 93%



22f, 89%

Further, we synthesized isocryptolepine **31a** from the previously synthesized indolo fused quinoline **22a** (Scheme 3.19). 6-(Methylthio)-11*H*-indolo[3,2-*c*]quinoline **22a** was converted to the desulfurized product **22a′** in 78% of yield in presence of Raney nickel in ethanol under refluxing conditions (Scheme 3.19). Similarly, 3-methoxy-6-(methylthio)-11*H*-indolo[3,2-*c*]quinoline **22c** was also desulfurized, affording 63% of the corresponding product **22c′** (Scheme 3.19). The natural product, isocryptolepine **31a**, was achieved by methylation of the desulfurized product **22a′** under the assistance of dimethyl sulphate in 45% yield (Scheme 3.19).



Scheme 3.19. Synthesis of Isocryptolepine

3.4. Conclusion

We can conclude that we have designed an acid mediated intramolecular cyclization of *β*-anilino acrylonitriles for the synthesis of biologically important 4-amino3-arylquinoline and its derivatives. Our approach is mild, that proceeds in ambient temperature and does not involve the use of any expensive metals. The potential application of the protocol was further extended to the synthesis of natural product, isocryptolepine, following already reported methodologies.

PART-B:

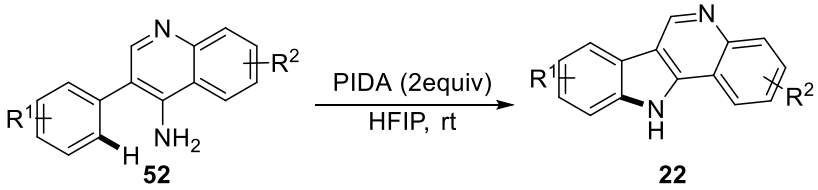
C─H Bond Functionalisation of 2-Amino-3-arylquinolines: A Facile Route to Synthesize Indoloquinolines

The part-B of this chapter deals with the C─H bond functionalization of 2-aminoquinolines leading to the synthesis of indolo fused quinolines.

3.5. Motivation

As we have discussed the importance of indoloquinolines, its synthesis is of utmost importance. The aforementioned syntheses of indoloquinolines have their own advantages and limitations. Our aim is to design a simple and competent protocol for the synthesis of indoloquinolines that can overcome the underlying disadvantages associated with the previous methodologies. In our laboratory we have established a mild protocol for the synthesis of indolo

fused quinolines from 4-amino-3-arylquinolines via metal free hypervalent iodine-mediated C─H bond functionalization.[25]



Scheme 3.20. *Hypervalent Iodine mediated C─H amination reaction*

Keeping this result in mind, we were focused to study the synthesis of indolo[2,3-*b*]quinolines via iodine-mediated C─H bond functionalization of 2-amino-3-arylquinolines.

3.6. Results and Discussions

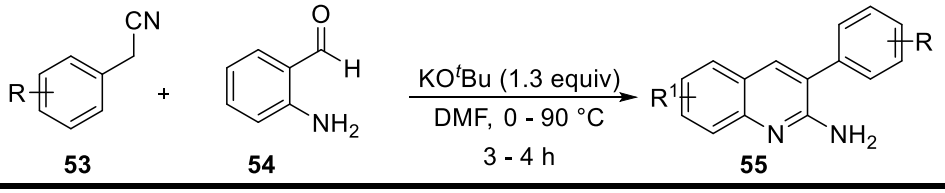
The required 2-amino-3-aryl quinolines were synthesized from acyclic precursors via base mediated condensation reaction.

3.6.1. Synthesis of 2-Amino-3-arylquinolines

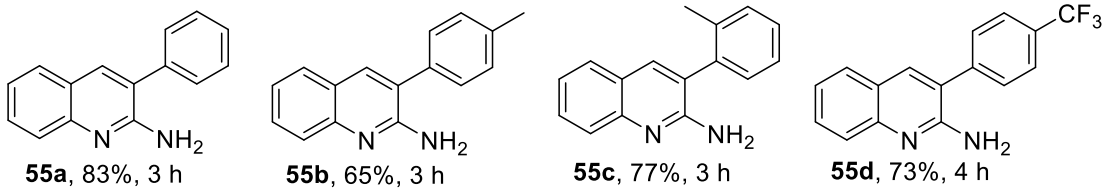
The required 2-amino-3-arylquinolines **55** can be obtained from aryl acetonitriles **53** and substituted 2-aminobenzaldehyde **54** via base-mediated condensation reaction. The aryl acetonitriles **53** were stirred with KO^{t}Bu in 0 ℃ for 15 min, then the reaction mixture was treated with 2-aminobenzaldehyde **54** at 0 ℃ and the reaction was heated at 90 ℃ (Table 3.5).

Various 2-amino-3-arylquinolines **55** with electron rich, electron deficient, alkyl and halo substituents were synthesized and isolated in moderate to excellent yields (Table 3.5).

Table 3.5. Synthesis of 2-Amino-3-arylquinolines



53 **54** **55**

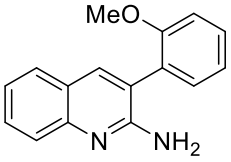


55a, 83%, 3 h

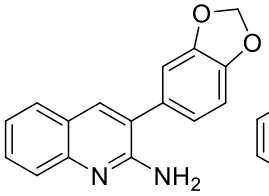
55b, 65%, 3 h

55c, 77%, 3 h

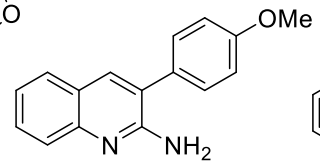
55d, 73%, 4 h



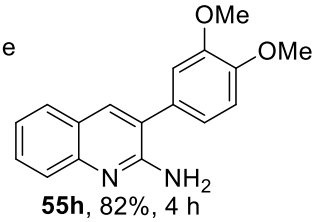
55e, 86%, 4 h



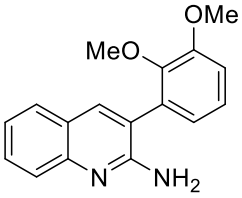
55f, 70%, 4 h



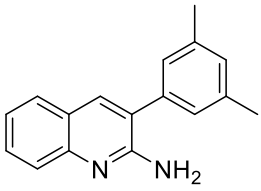
55g, 79%, 4 h



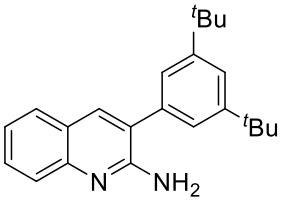
55h, 82%, 4 h



55i, 46%, 3 h



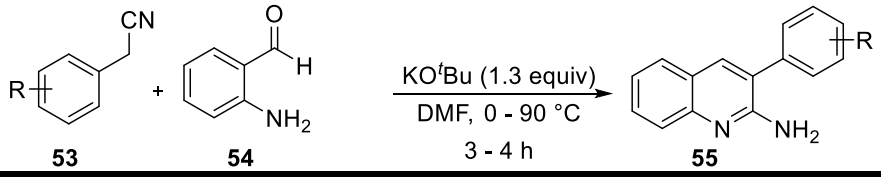
55j, 68%, 4 h



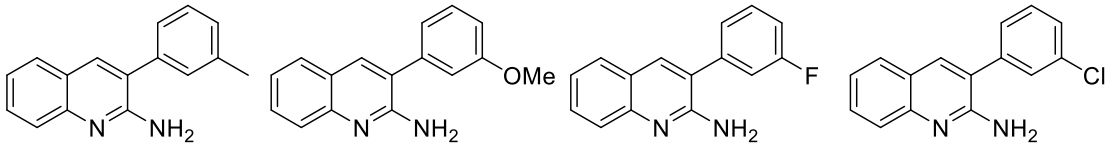
55k, 68%, 4 h

Further, we have synthesized another series of 2-amino-3-arylquinolines **55** and were obtained in moderate to excellent yields (Table 3.6).

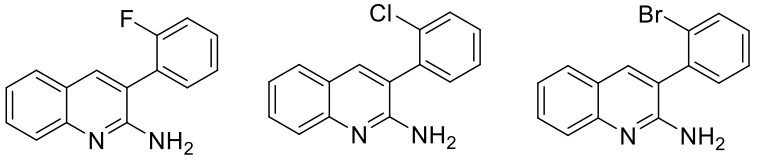
Table 3.6. Synthesis of Substituted 2-Amino-3-arylquinolines



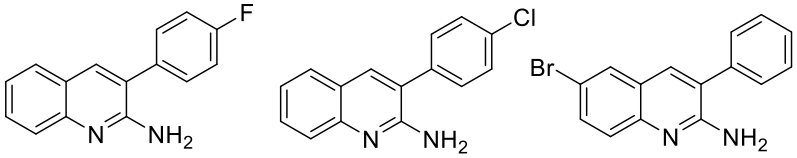
53 54 55



55l, 88%, 3 h **55m**, 68%, 3 h **55n**, 78%, 4 h **55o**, 79%, 3 h



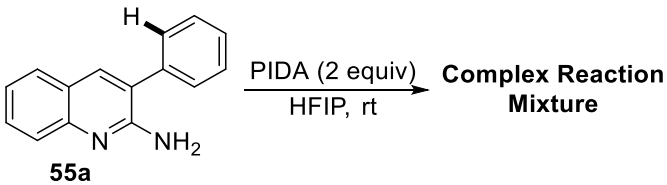
55p, 41%, 3 h **55q**, 57%, 3 h **55r**, 58%, 4 h



55s, 68%, 3 h **55t**, 71%, 3 h **55u**, 62%, 4 h

3.6.2. Optimization Conditions for the C─H Bond Functionalization Reaction

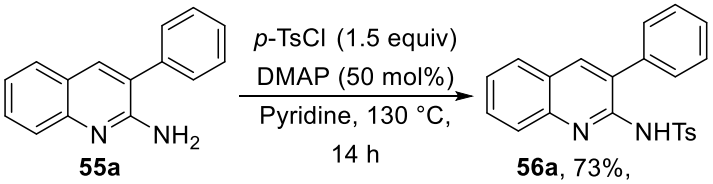
After synthesizing an array of 2-amino-3-arylqinolines **55**, we performed iodine-mediated C─H bond functionalization reaction employing previously optimized condition. Our initial attempts to study intramolecular *N*-arylation of 2-amino-3-phenylquinoline **55a** were unsuccessful (Scheme 3.21).



55a

Scheme 3.21. *C─N Bond Formation of Free Amine*

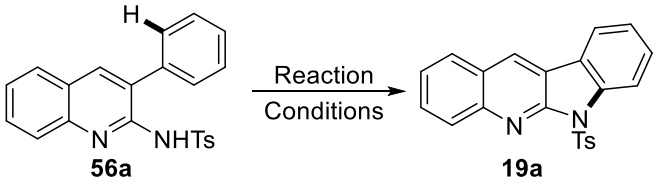
Thus, we decided to protect the free amino group of 2-amino-3-arylquinoline **55a** with tosyl group. The tosylation was done under basic condition involving *p*-TsCl (Scheme 3.22).



Scheme 3.22. *Protection of Free Amine Group*

The *N*-Ts 2-amino-3-phenylquinoline **56a** was subjected to the previously optimized condition, i.e 2 equiv of PIDA in HFIP at room temperature, and we observed 72% of a product with complete conversion of the starting material (entry 1, Table 3.7). This product was further confirmed with spectral and analytical data as indoloquinoline **19a**. With this result we turned to investigate the C–N bond functionalization using hypervalent iodine reagents with *N*-Ts 2-amino-3-phenylquinoline **56a** as the model substrate. We then performed the reaction with TFE, but we observed incomplete conversion of the starting material and recovered 50% of the starting material **56a** along with 35% of the cyclized product **19a** (entry 2, Table 3.7). We screened several solvents like CH_3CN, $C_2H_4Cl_2$, CH_2Cl_2, DMF, DMSO, and THF, but in all the cases we did not observe the required indolo fused quinoline **19a** and recovered the starting material in quantitative yield (entries 3 – 8, Table 3.7). Instead of PIDA, when we used PIFA as the oxidant and we observed a drastic change in the yield of the reaction, affording 91% of the indolo fused quinoline **19a** (entry 9, Table 3.7). On using TFE we observed comparable yield of the product 84% (entry 10, Table 3.7). Further, we decreased the equivalence of PIFA, and noticed a decrease in the yield of the reaction as well (entries 11-12, Table 3.7).

Table 3.7. Optimization Conditions of Hypervalent Iodine Mediated C─H Bond Functionalization



56a 19a

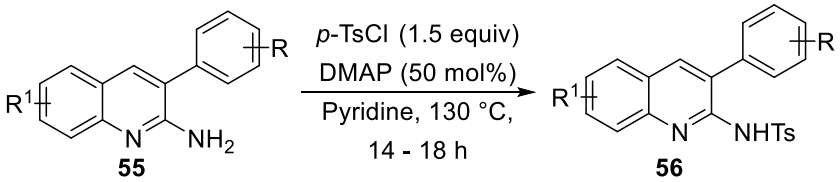
Entry	Oxidant	Solvent	Temp.	Time	Yield[a]
1.	PIDA (2 equiv)	HFIP	rt	8 h	72%
2.	PIDA (2 equiv)	TFE	rt	24 h	35% (50%)[b]
3.	PIDA (2 equiv)	CH_3CN	rt	24 h	-[c]
4.	PIDA (2 equiv)	$C_2H_4Cl_2$	rt	24 h	-[c]
5.	PIDA (2 equiv)	CH_2Cl_2	rt	24 h	-[c]
6.	PIDA (2 equiv)	DMF	rt	24 h	-[c]
7.	PIDA (2 equiv)	DMSO	rt	24 h	-[c]
8.	PIDA (2 equiv)	THF	rt	24 h	-[c]
9.	PIFA (2 equiv)	HFIP	rt	2 h	91%
10.	PIFA (2 equiv)	TFE	rt	3 h	84%
11.	PIFA (1.5 equiv)	HFIP	rt	2 h	80%
12.	PIFA (1 equiv)	HFIP	rt	2 h	73%

[a]Isolated yields, [b]yields in the parenthesis represents recovered starting material, [c]Recovered starting materials in quantitative yield

3.6.3. Synthesis of *N*-Ts 2-amino-3-arylquinolines

The free amine of 2-amino-3-arylquinolines **55** were then protected with tosyl group. The quinolines **55** were stirred in pyridine and then *p*-TsCl and DMAP were added. The reaction mixture was then refluxed for overnight. The *N*-Ts 2-amino-3-aryl quinolines **56** were isolated in moderate yields (Table 3.8).

Table 3.8. Synthesis of *N*-Ts 2-Amino-3-arylquinoline



55 **56**

56b, 78%, 14 h

56c, 75%, 14 h

56d, 61%, 14 h

56e, 64%, 14 h

56f, 77%, 14 h

56g, 56%, 15 h

56h, 72%, 14 h

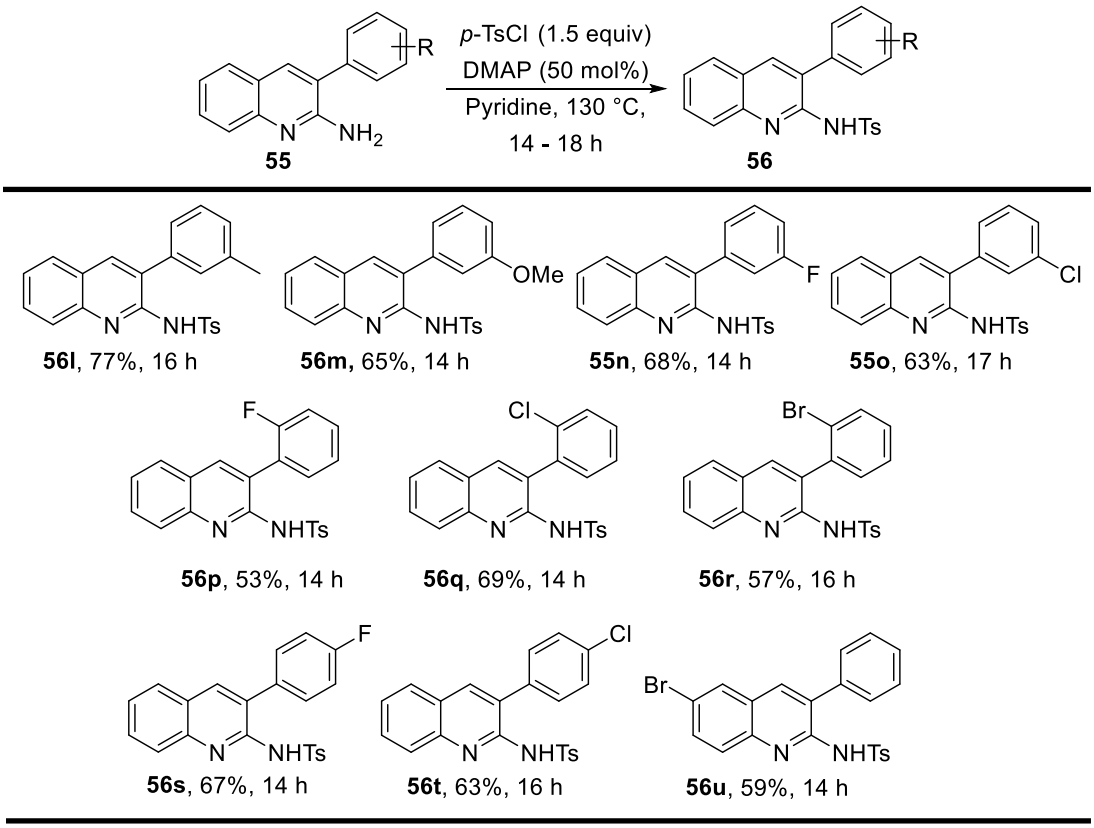
56i, 68%, 15 h

56j, 69%, 18 h

56k, 61%, 18 h

Further, we protected another series 2-amino-3-arylquinolines **55** and various *N*-Ts 2-amino-3-arylquinolines **56** were obtained in moderate yields (Table 3.9).

Table 3.9. Synthesis of Substituted *N*-Ts 2-Amino-3-arylquinolines

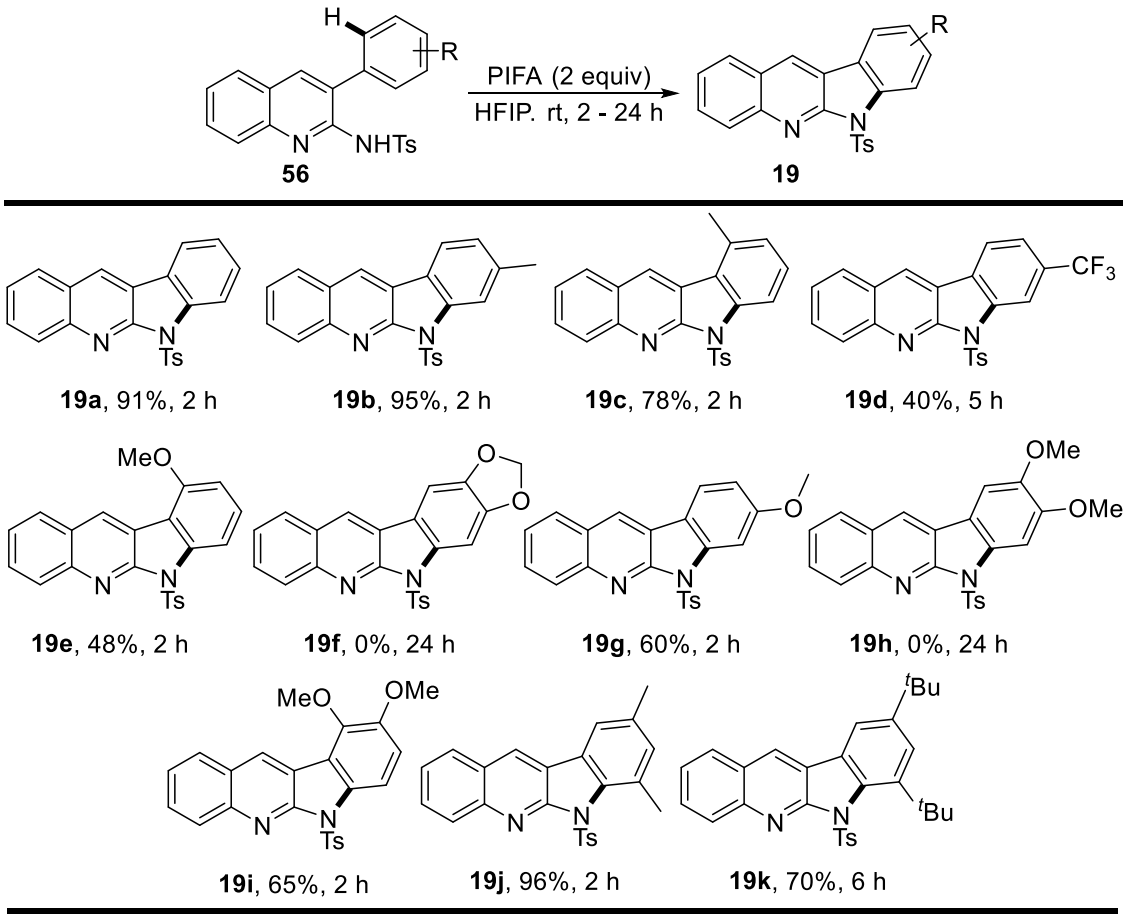


3.6.4. Substrate Scope for Hypervalent Iodine Mediated C─H Bond Functionalization

With the optimised condition in our hands, we studied the scope of the reaction with various *N*-Ts 2-amino-3-aryl quinolines **19**. We investigated the 2-amino-3-(4-methyl)quinoline **56b** and observed the indolo fused quinoline **19b** in 95% of yield (Table 3.10). Whereas, the *o*-methyl substitution at the 3-aryl ring of 2-amino-3-arylquinoline **56c** afforded only 78% of the corresponding cyclized product **19c** (Table 3.10). However, in case of electron deficient substrate **56d** the moderate yield of the product **19d** was observed (Table 3.10). We shifted our focus towards electron rich substrates with substitution at the aryl ring. The *o*-methoxy substitution at the 3-aryl ring of 2-aminoquinoline **56e** gave only 48% of the corresponding indoloquinoline **19e** (Table 3.10). Unfortunately, methylene dioxo substituted 2-aminoquinolines **56f** did not transform into the corresponding cyclized product **19f** (Table 3.10). Similarly, 2-amino-3-(4-methoxyphenyl)quinoline **56g** also gave comparable yield of

the indoloquinoline **19g** (Table 3.10). In case of di-substituted substrates **56h** and **56i,** the indolo fused quinolines **19h** and **19i** were obtained in moderate yield (Table 3.11). 8,9-dimethoxy-6-tosyl-6*H*-indolo[2,3-*b*]quinoline **19h** was not observed even after 24 h. 9,10-dimethoxy-6-tosyl-6*H*-indolo[2,3-*b*]quinoline **19i** in 65% (Table 3.10). We then examined sterically hindered substrates **56j-k** and observed moderate to excellent yields of the products **19j-k** (Table 3.11). The dimethyl substituted substrate **56j** was smoothly transformed into the product **19j** with 96% yield. However, di-tert-butyl substituted 2-aminoquinoline **56k** gave only 78% of the indoloquinoline **19k** (Table 3.10).

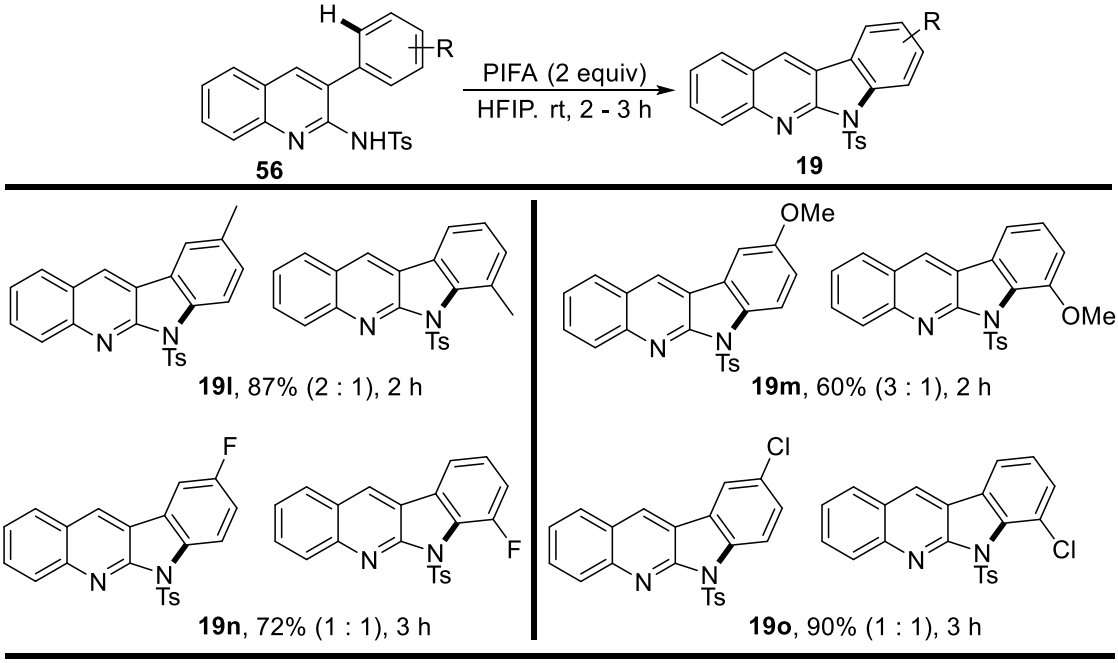
Table 3.10. Substrate Scope of C─H Bond Functionalization Reaction



On the other hand, the *N*-tosyl quinolines having meta substituents on the 3-aryl ring **56l-o** contains two active sites for the cyclization, thus mixtures of two regio-isomers were observed (Table 3.11). The yields of the final products **19l-o** were dependent on the electronic

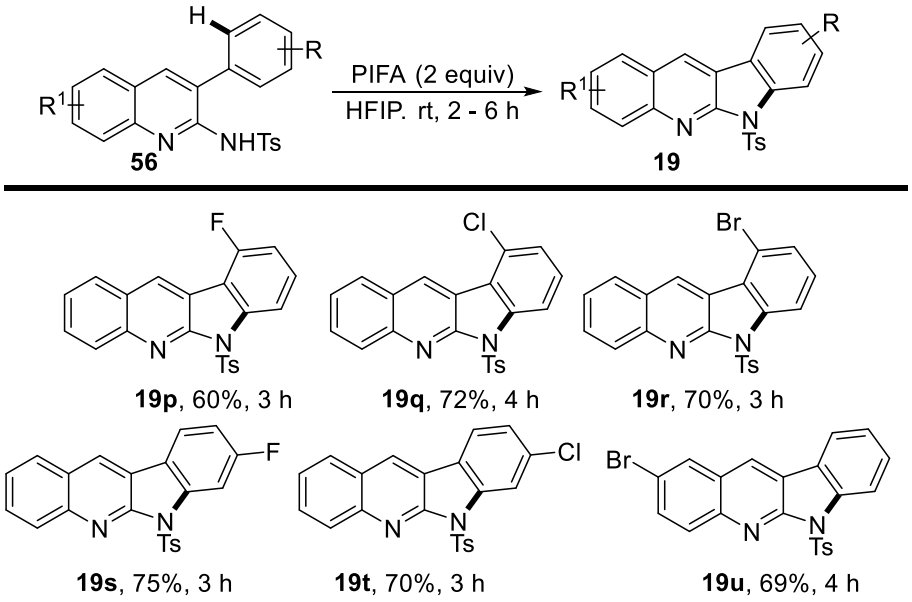
effect of the substrates, the electron rich substrate **56m**, gave only 60% of the final product **19m** in 3:1 ratio of C9:C7 regioisomers, C9 being the major isomer (Table 3.11). Whereas, alkyl substituents **56l** afforded 87% the indolo fused quinoline **19l** in 2:1 ratio of C9:C7 regioisomers (Table 3.11). The meta substituted halo substrates **56n-o** also yielded moderate to excellent yield of the final product **19n-o** (Table 3.11). The *m*-F substituted *N*-Ts 2-aminoquinoline **56n** afforded 72% of indolo fused quinoline **19n** in 1:1 ratio of C9:C7 regioisomers (Table 3.12). Similarly, *m*-Cl substituted substrate **56o** also gave 1:1 ratio of C9:C7 regioisomers of indolo fused quinoline **19o** with excellent yield (Table 3.11).

Table 3.11. C─H bond Functionalization of meta Substituted *N*-Ts 2-Aminoquinolines

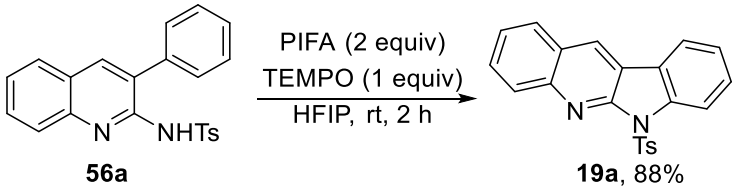


Then, we shifted our focus to investigate the substrates to having halo substitutents (Table 3.12). In case of *o*-halo substituted *N*-Ts 2-amino-3-arylquinolines **56p-r** moderate yields of the indolo fused quinolines **19p-r** was observed (Table 3.12). The *p*-F and *p*-Cl substituted 2-amino-3-arylquinoline **56s-t** afforded 70 – 75% of respective indolo fused quinolines **19s-t** (Table 3.12). With bromo substitution at the quinoline ring **56u** we observed 69% of the indoloquinoline **19u** (Table 3.12).

Table 3.12. Substrate Scope for C─H Bond Functionalization of 2-Amino-3-arylquinolines



To have an insight on the mechanistic pathway, whether the reaction involves any radical intermediate or ionic intermediate, we performed a controlled experiment (Scheme 3.23). This involves a radical scavenger, TEMPO, used along with the optimized reaction condition, and we observed 88% of the desired product **19a**. Thus, the reaction involves ionic intermediate (Scheme 3.23).



Scheme 3.23: *Controlled Experiment*

3.7. Conclusion:

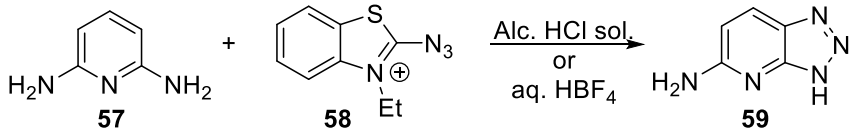
In this part we have discussed about the synthesis of various indolo fused quinolines via hypervalent iodine mediated C─H bond functionalization. This method is mild and efficient. This methodology tolerates various functional groups. This indoloquinolines can further be converted to the natural product neocryptolepine, following literature methods.

PART-C: Copper Mediated N-Arylation of 5-Aminotriazoles: Synthesis of Triazolo fused Heterocycles

It is well evident that triazoles play pivotal roles in various fields such as drug design, agriculture, fluorescent labelling, material science, and supramolecular chemistry.[26] Among that, 1,2,3-triazole fused heterocycles are vital core which show various biological activities and are pharmaceutical targets, such as benzodiazepine receptor and G-protein-coupled receptor agonists and are also chemotherapeutic and cardiovascular agents.[27] Because of its biological and pharmaceutical significance, development of synthetic protocols for the synthesis of triazolo fused heterocycles are extremely desirable.[28] Even though most of the triazolo fused heterocycles have drawn a lot of attention, 1,2,3-triazolo fused indoles are hardly studied and synthesized, owing its limited synthetic methods. So far, only two methodologies have been reported for its synthesis.[29]

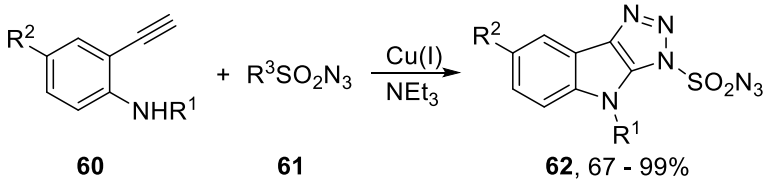
3.8. Previous Reports on the Synthesis of Triazoloindole

The first report for the synthesis of triazoloindole **59** was published in 1978 by Felder and co-worker.[29a] This methodology involved the diazonium group transfer with azidinium salt **58** in presence of alcoholic ethanol or aqueous fluoroboric acid, which further led to the formation of triazoloindole **59** (Scheme 3.24).



Scheme 3.24. *Synthesis of Triazoloindole via Diazonium Group Transfer*

In 2014, Wang and co-workers demonstrated a new protocol for the synthesis of triazoloindole **62** via copper mediated tandem reaction of alkynes **60** with azides **61**.[29b] In this methodology, triethylamine is required in excess amount to facilitate the intramolecular C─N bond formation. Azide **61** also played the role of an oxidant (Scheme 3.25).



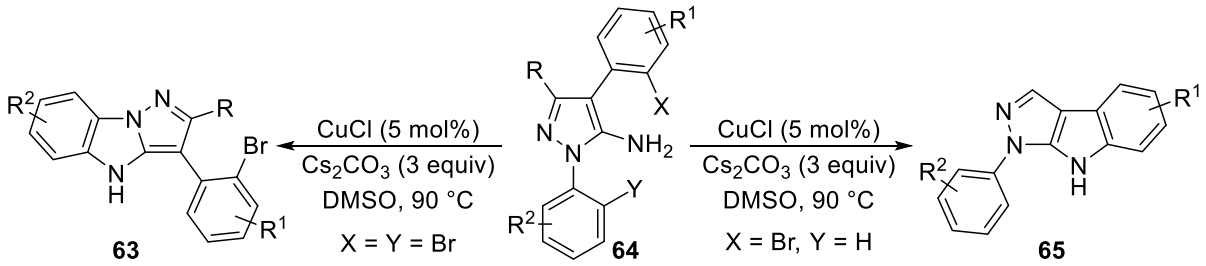
60 **61** **62**, 67 - 99%

R^1 = Me, Et, ^{i}Pr, ^{t}Bu, cyclohexane, allyl, Ph, furan, pyridine, Bn
R^2 = H, OMe, Me, Cl, CN, NO_2
R^3 = *p*-$MeOC_6H_4$, Ph, *p*-ClC_6H_4, *p*-$NO_2C_6H_4$

Scheme 3.25. *Copper Mediated Tandem Reaction of Alkynes with Azides*

3.9. Motivation

The presence of two biologically important cores in 1,2,3-triazolo fused indole have made the evolution of its synthetic procedures more interesting. Recently we have synthesized various *N*-containing fused heterocycles **63** & **65** via copper catalyzed Ullmann coupling reaction (Scheme 3.26).[30] With these results, we focussed to design a methodology to synthesize 1,2,3-triazoloindoles involving 5-aminotriazoles. Our methodology involves *N*-arylation of 5-aminotriazoles via copper catalyzed Ullmann coupling reaction.



Scheme 3.26. *Copper-mediated N-Arylation of 5-Aminopyrazoles*

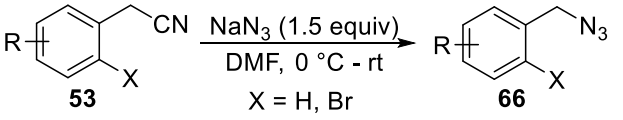
3.10. Results and discussions

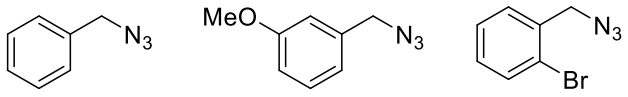
The substituted 5-amino-1-aryl-4-(bromoaryl)triazoles can be prepared from the base mediated click reaction involving aryl acetonitriles and benzyl/aryl azides as the acyclic precursors. Various 2-halo substituted aryl acetonitriles were condensed with substituted benzyl/aryl azides under basic condition. The triazoles were characterized by analytical and spectral data.

3.10.1. Synthesis of benzyl azides

The required benzyl azides **66** were obtained from aryl acetonitriles **53** by reacting with sodium azide. The benzyl azides **66** were isolated in moderate to excellent yields (Table 3.13).

Table 3.13. **Synthesis of benzyl azides**



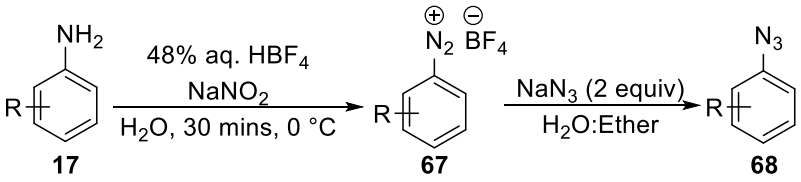


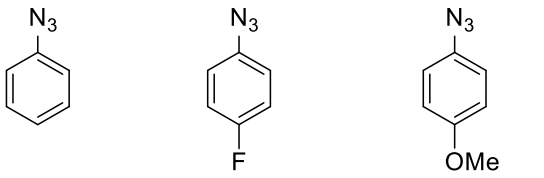
66a, 98% **66b**, 75% **66c**, 63%

3.10.2. Synthesis of Aryl azides

The required phenyl azides **68** were synthesized from anilines **17** in two steps (Table 3.14). The anilines **17** were first converted to diazonium salts **67** by treating the anilines **17**

Table 3.14. **Synthesis of Aryl azides**





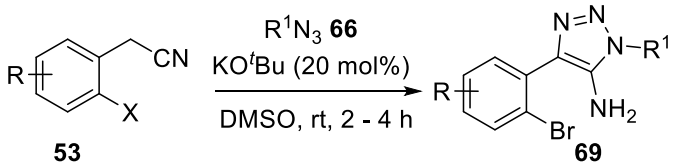
68a, 67% **68b**, 58% **68c**, 65%

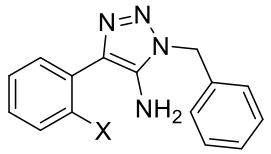
with aq. tetrafluoroboric acid and sodium nitrite in water. These diazonium salts **67** were then converted to azides **68** by the treatment of sodium azide in water:ether (Table 3.14). The phenyl azides **68** were isolated in 58 – 67% (Table 3.14).

3.10.3. Synthesis of 5-Aminotriazoles

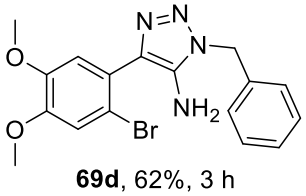
The required 5-aminotriazoles **69** can be synthesized from 2-halo substituted aryl acetonitriles **53** and aryl azides **66** under basic condition. The 2-halo substituted aryl acetonitriles **53** were stirred with potassium tert. butoxide at 0 ℃ in DMSO and then the reaction mixture was treated with substituted benzyl azides **66** in DMSO at 0 ℃ (Table 3.15). Various triazoles **69** having electron rich and deficient, alkyl, sterically hindered groups were isolated in moderate to excellent yields (Table 3.15).

Table 3.15: Synthesis of *N*-Benzyl 5-Aminotriazoles

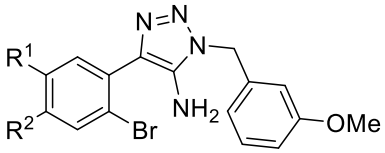




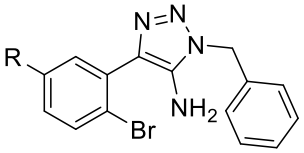
69a, X = Br, 55%, 2 h
69b, X = Cl, 83%, 3 h
69c, X = I, 82%, 3 h



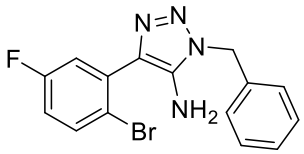
69d, 62%, 3 h



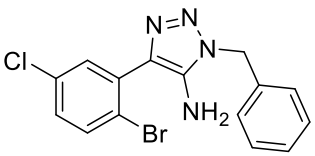
69e, $R^1 = R^2$ = H, 40%, 2 h
69f, $R^1 = R^2$ = OMe, 30%, 3 h



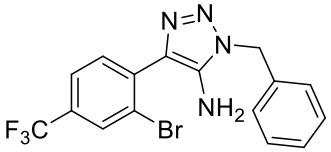
69g, R = OMe, 60%, 2 h
69h, R = Me, 78%, 2 h



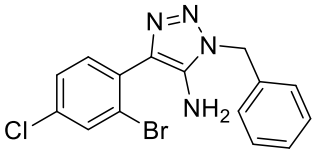
69i, 88%, 2 h



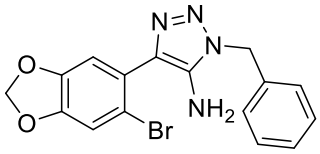
69j, 90%, 2 h



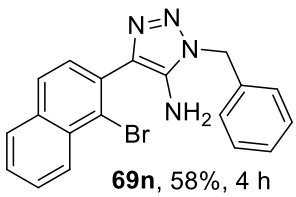
69k, 51%, 2 h



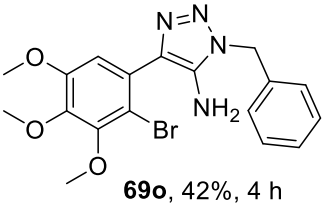
69l, 85%, 1.5 h



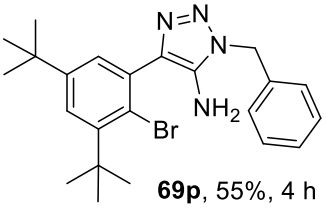
69m, 31%, 3 h



69n, 58%, 4 h



69o, 42%, 4 h

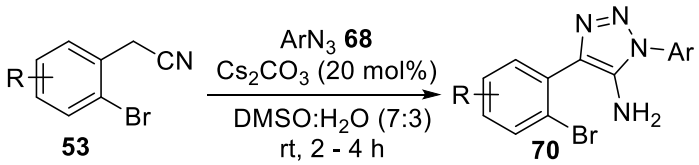


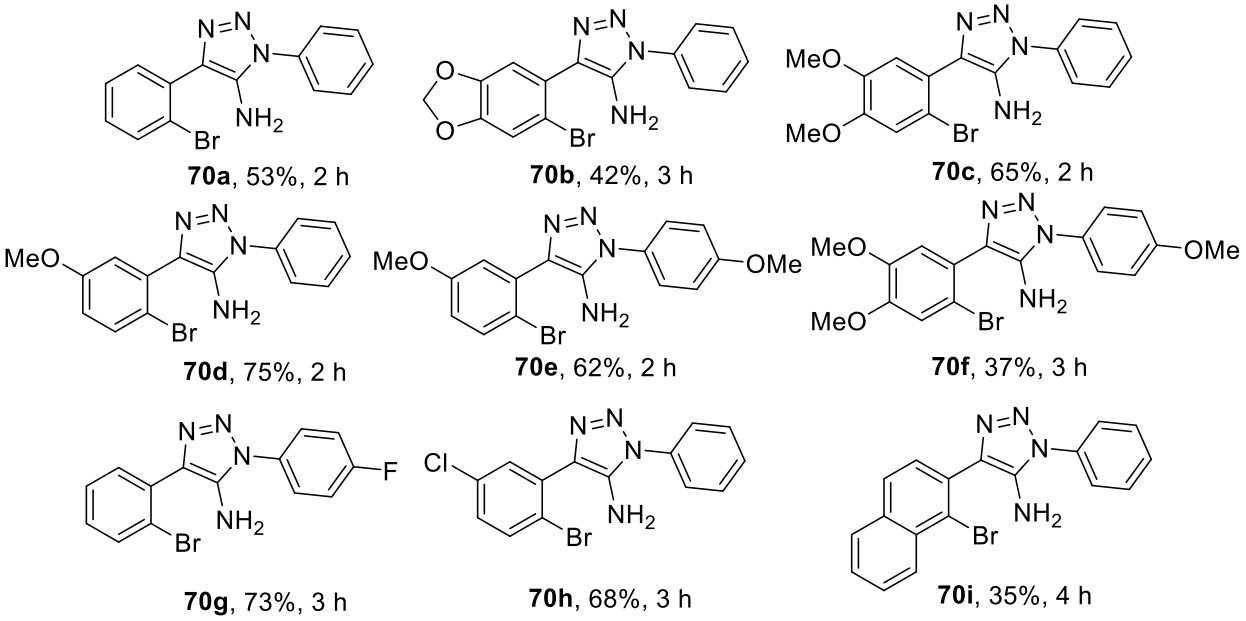
69p, 55%, 4 h

We had synthesised a handful of *N*-phenyl 5-aminotriazoles **70** using the aforementioned base mediated click reaction (Table 3.16). The 2-bromo aryl acetonitriles **53** were stirred with cesium carbonate in DMSO:H_2O (7:3) at 0℃. This was further treated with aryl azides **68** in DMSO at 0 ℃ (Table 3.16).

A library of substituted *N*-phenyl 5-aminotriazoles **70** with various functional groups were obtained in 35 – 75% (Table 3.16).

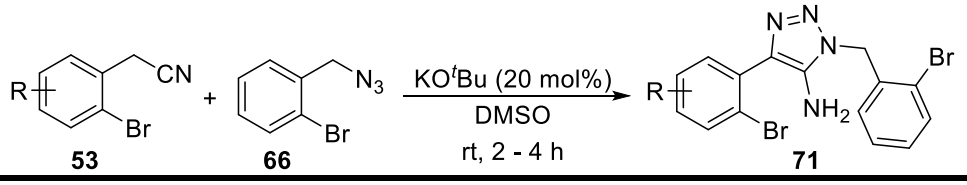
Table 3.16: Synthesis of *N*-Phenyl 5-Aminotriazoles

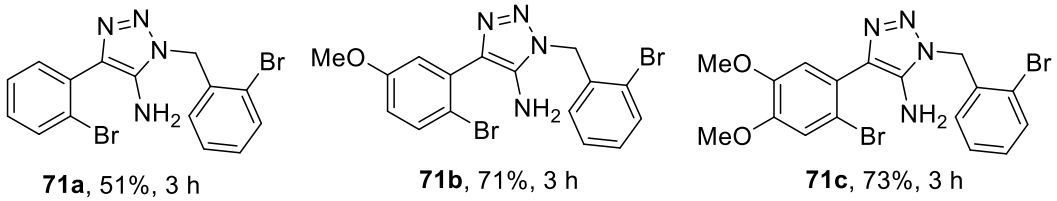




Another series of 5-aminotriazoles **71** had been synthesized which contains bromo substitution in both the aryl rings (Table 3.17). At first, the 2-bromo aryl acetonitriles **53** were stirred with potassium tert. butoxide in DMSO at 0 ℃ and then the reaction mixture was treated with substituted 2-bromo benzyl azides **66** in DMSO at 0 ℃. The di-bromo substituted 5-aminotriazoles **71** having electron rich and halo substitution were isolated in moderate yield (Table 3.17).

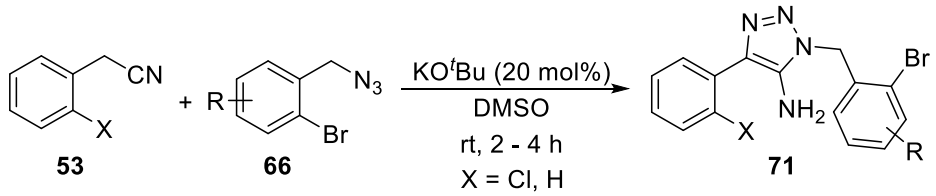
Table 3.17. Synthesis of Di-bromo 5-Aminotriazoles

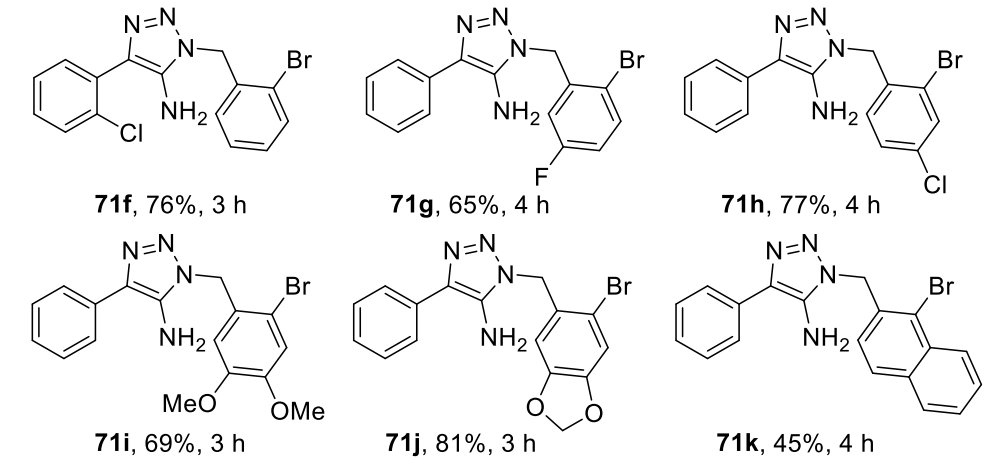




Further, we have synthesized a handful of 5-aminotriazoles **71** with 2-bromo benzyl azides. The aryl acetonitriles **53** were stirred with potassium tert. butoxide in DMSO at 0℃

Table 3.18. Synthesis of *N*-2-Bromobenzyl 5-Aminotriazoles



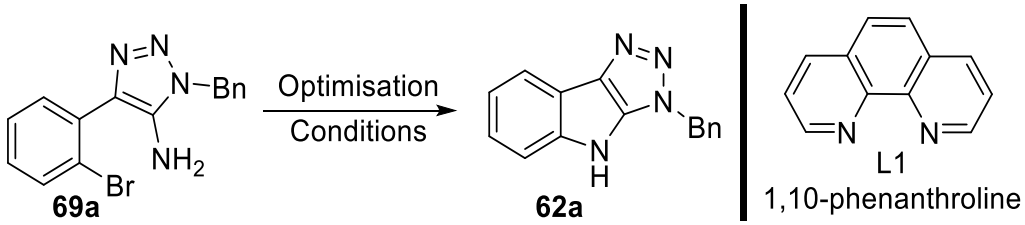


and then the reaction mixture was treated with substituted 2-bromo benzyl azides **66** in DMSO at 0 ℃. All the 5-aminotriazoles **71** were observed in 45 – 81% (Scheme 3.18).

3.10.4. Optimisation of C─N Bond Formation

After synthesizing a series of substituted 5-aminotriazoles **69**, we then investigated the optimization condition for the C─N bond formation reaction (Table 3.19). Considering 1-benzyl-4-(2-bromophenyl)-1*H*-1,2,3-trriazol-5-amine **69a** as the model substrate, we subjected it to various conditions for C–N bond formation reaction (Table 3.19). At first, we used 5 mol% of copper iodide, 10 mol% of 1,10-phenanthroline and 3 equiv of cesium carbonate in DMF at room temperature to furnish the cyclization (entry 1, Table 3.19). Even after 24 hrs we did not observe trace amount of triazolo fused indole **62a** and recovered 86% of the starting material **69a** (entry 1, Table 3.19). Further we heated the reaction at 90 ℃ and we observed 88% of the triazoloindole **62a** (entry 2, Table 3.19). We performed the reaction in DMSO and observed a decrease in the yield of the reaction (entry 3, Table 3.19). With potassium phosphate we observed a comparable yield of the reaction (entry 4, Table 3.19). So, further optimisation was carried at 90 ºC. To study the role of the reaction, we performed a reaction in the absence of ligand L1, and surprisingly we observed comparable yield of the indolo fused triazole **62a** after 9 hrs (entry 5, Table 3.19). So, we can conclude that ligand is not playing any role in this reaction. However, a drastic change in the yield of the reaction was observed when DMSO was used as the solvent (entry 6, Table 3.19). After 3 hrs we observed 91% of indolo fused triazole

Table 3.19: Optimisation of *N*-Arylation of 5-Aminotriazoles



Entry	X	Cu Salt	Ligand	Base	Solvent	Temp.	Time	Yield[a]
1.	Br	CuI	L1	Cs_2CO_3	DMF	rt	24 h	Trace (86%)
2.	Br	CuI	L1	Cs_2CO_3	DMF	90 °C	6 h	88%
3.	Br	CuI	L1	Cs_2CO_3	DMSO	90 °C	4 h	77%
4.	Br	CuI	L1	K_3PO_4	DMSO	90 °C	4 h	71%
5.	Br	CuI	-	Cs_2CO_3	DMF	90 °C	9 h	74%
6.	Br	CuI	-	Cs_2CO_3	DMSO	90 °C	3 h	91%
7.	Br	CuBr	-	Cs_2CO_3	DMSO	90 °C	4 h	88%
8.	**Br**	**CuCl**	**-**	**Cs_2CO_3**	**DMSO**	**90 °C**	**4 h**	**93%**
9.	Br	CuCl	-	Cs_2CO_3 (2 equiv)	DMSO	90 °C	4 h	92%
10.	Br	CuCl	-	Cs_2CO_3	Dioxane	90 °C	12 h	Trace (88%)
11.	Br	$Cu(OAc)_2.H_2O$	-	Cs_2CO_3	DMSO	90 °C	5 h	82%
12.	Cl	CuCl	-	Cs_2CO_3	DMSO	90 °C	5 h	- (95%)
13.	I	CuCl	-	Cs_2CO_3	DMSO	90 °C	4 h	89%

Reaction Conditions: Substrate (0.5 mmole), copper salt (5 mol%), solvent (2 mL). Yields in parentheses represent recovered starting material. L1 used in 10 mol% in entries 1 – 4. [a]Isolated yields.

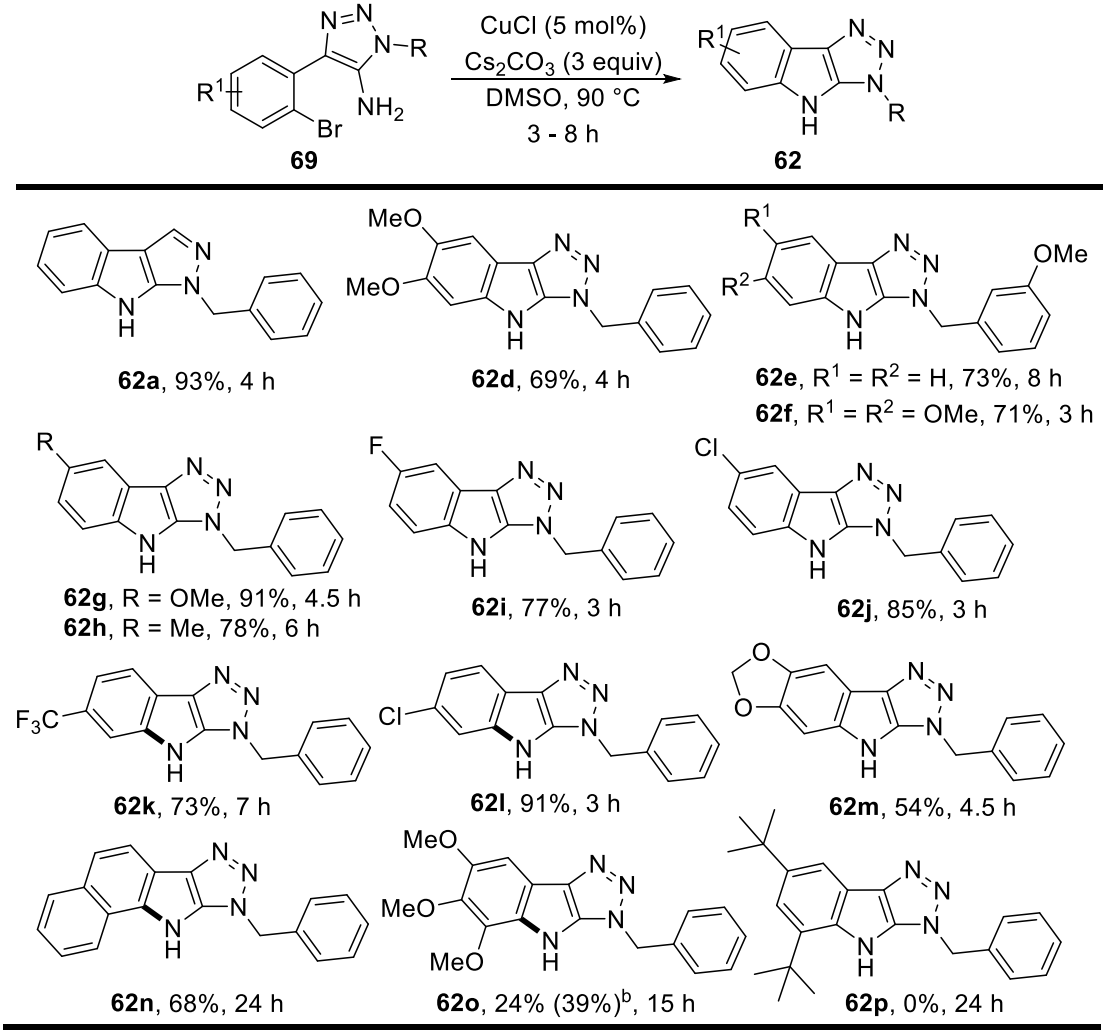
62a (entry 6, Table 3.19). Then we screened the copper salts, copper bromide, afforded 88% of the triazoloindoles **62a** (entry 7, Table 3.19). In case of copper chloride, we observed 93% of the desired product **62a** after 3 hrs (entry 8, table 3.19). Then we used 2 equiv of caesium carbonate and did not observe any remarkable change in the yield of the reaction (entry 9, Table 3.19). On changing the solvent to dioxane we observed trace amount of product **62a** and isolated 88% of the starting material **69a** (entry 10, Table 3.19). With copper acetate monohydrate we isolated 82% of the triazoloindole **62a** after 5 h (entry 11, Table 3.19). Further we replaced bromo group with other halogens like chloro and iodo groups. We found that the chloro substituted substrate **69b** did not afford the triazoloindole **62a** and we recovered 95% of the starting material **69b** (entry12, Table 3.19). Whereas, in case of iodo substituted 5-aminotriazole **69c** we observed 89% of the final product **62a** (entry 13, Table 3.19).

3.10.5. Substrate Scope for C─N Bond Formation via Copper Mediated Ullmann Coupling Reaction

With the optimized condition in our hands, we then examined the applicability of our methodology. The various 5-aminotriazoles **69** were subjected to our optimized condition (Table 3.20). The 3,4-dimethoxy substituted triazole **69d** afforded 69% of the triazolo fused indole **62d** (Table 3.20). The electron donating substituents on both the phenyl rings **69e-f** were smoothly transformed to triazoloindoles **62e-f** in 71 – 73% yield (Table 3.20). The 5-methoxy substituted 5-aminotriazole **69g-h** afforded the corresponding cyclized product **62g-h** in excellent yield (Table 3.20). When 5-methyl substituent **69h** was used, we observed a decrease in the yield with increase in the reaction time and isolated 78% of the respective triazolo fused indole **62h** (Table 3.20). We investigated the effect of halo substituents on the 5-aminotriazoles **69i-j** (Table 3.20). The 5-flouro substituted 5-aminotriazole **69i** gave 77% of the respective cyclized product **62i** (Table 3.20). Similarly, 5-chloro substituted 5-aminotriazole **69j** also gave comparable yield of the corresponding triazoloindole **62j** (Table 3.20). The 5-aminotriazole

69k with electron donating group, i.e. CF_3 group, was smoothly converted to the cyclized product **62k** (Table 3.20). The 4-chloro substituted substrate **69l** afforded excellent yield of the triazolo fused indole **62l** (Table 3.20). In case of 4,5-methylenedioxy triazoles **69m** we observed moderate yield of the final product **62m** (Table 3.20). When we studied naphthyl substituent **69n**, we observed the reaction to yield 68% of the cyclized product **62n** after 24 h

Table 3.20. Substrate Scope for Copper Catalyzed Ullman Coupling Reaction

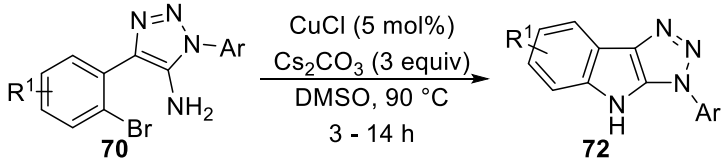


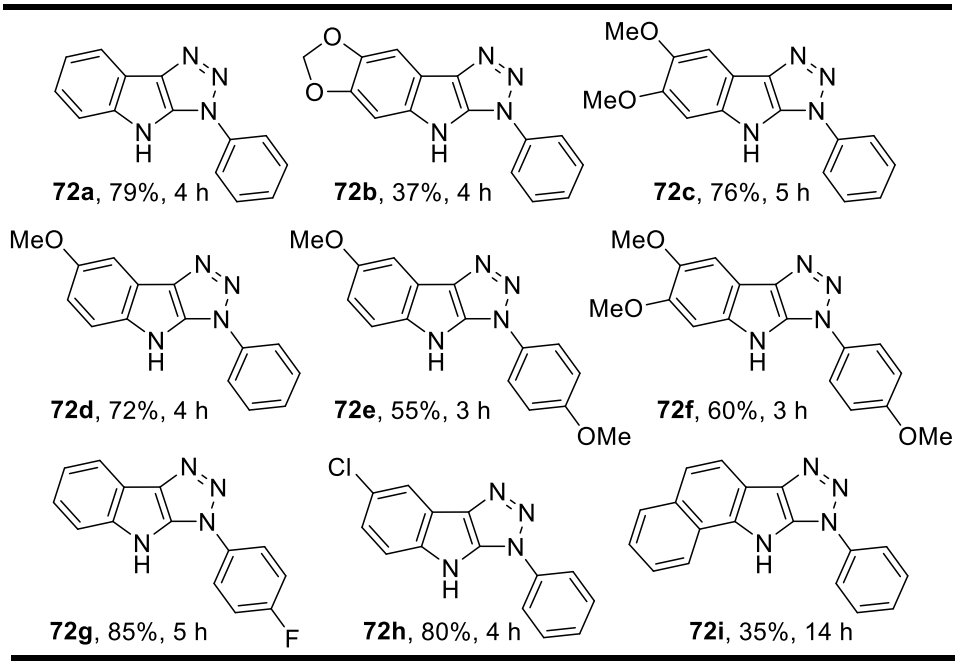
(Table 3.20). Next, we studied the effect of multi substituent on the phenyl ring. In case of trimethoxy **69o**, with our optimized condition we observed only 24% of the triazolo fused indole **62o** after 15 h, to increase the yield of the reaction we used 10 mol% of copper iodide, but unfortunately there was not much change in the yield of reaction (Table 3.20). However,

substrate with sterically hindered substituents **69p** did not afford the product **62p** even after 24 h (Table 3.20).

Further, we shifted our focus to study the various *N*-aryl 5-aminotriazoles **70**. All the *N*-phenyl 5-aminotriazole **70** were subjected to our optimized condition (Table 3.21). The *N*-phenyl 5-aminotriazole **70a** yielded 79% of the triazolo fused indole **72a** (Table 3.21). 4,5-methylenedioxy substituted substrate **70b** afforded low yield of the final product **72b** (Table 3.21). The electron rich substrates **70c-f** gave 55 – 76% of the triazoloindole **72c-f** (Table 3.21). The 4,5-dimethoxy substrate **70c** and the 5-methoxy substrate **70d** yielded 76% and 72% of the respective triazolo fused indole **72c** & **72d** (Table 3.21). The electron donating substituents

Table 3.21. C─N Bond Forming Reaction of *N*-Phenyl 5-Aminotriazole



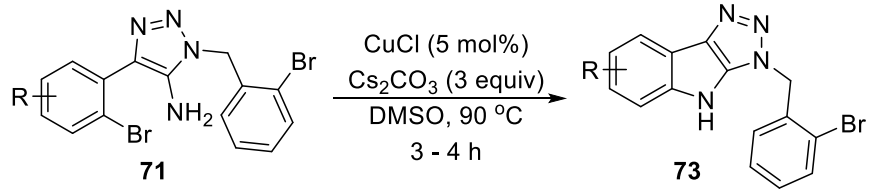


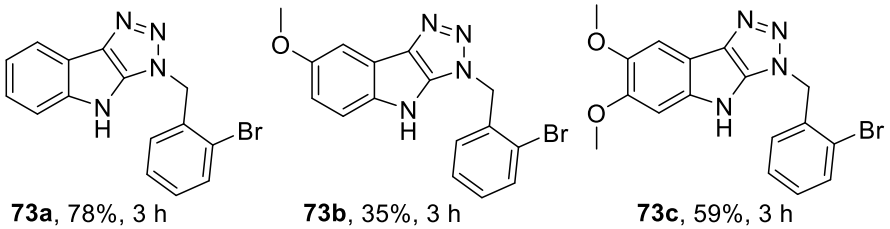
on both the *N*-phenyl and aryl ring **70e-f** were also converted to the respective cyclized product **72e-f** in moderate yields (Table 3.21). The *N*-4-fluoro phenyl 5-aminotriazoles **70g** afforded 85% of the triazoloindole **72g** (Table 3.21). The chloro substituted triazoles **70h** gave

comparable yield of the cyclized product **72h** (Table 3.21). The naphthyl derivative **70i** gave lower yield of the product **72i** with increased reaction time (Table 3.21).

To examine the regioselectivity of our methodology, we subjected the previously synthesized 5-aminotriazoles **71**, containing 2-halo substituents at both the phenyl rings, to our optimized condition (Table 3.22). Surprisingly, we marked the formation of triazolo indole **73a** as the sole product and did not observe a trace amount of the other side cyclized product, i.e. triazolo fused quinazolines **74** (Table 3.22). The unsubstituted dibromo 5-amino triazole **71a** yielded 78% of the triazolo fused indole **73a** (Table 3.22). However, the electron rich substrates **71b-c** afforded 35 – 59% of the respective cyclized product **73b-c** (Table 3.22). Whereas, the chloro substituted substrates **71d-e** were smoothly transformed into the products **73d-e**, affording 60 – 61% of the triazoloindoles (Table 3.22).

Table 3.22. Regioselective Copper Catalyzed C─N Bond Formation of 5-Aminotriazoles

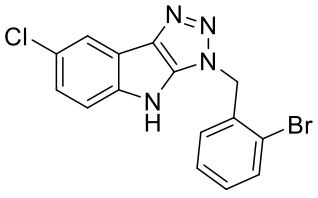




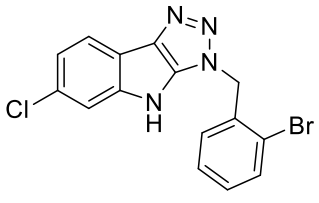
73a, 78%, 3 h

73b, 35%, 3 h

73c, 59%, 3 h



73d, 60%, 4 h

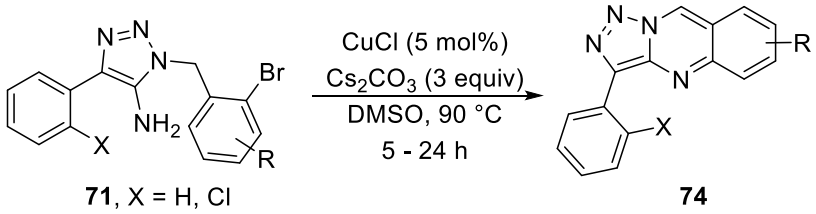


73e, 61%, 4 h

Further we investigated the other side cyclization leading to the synthesis of triazoloquinazolines **74** (Table 3.23). With 2-chloro 5-aminotriazole **71f** we observed the

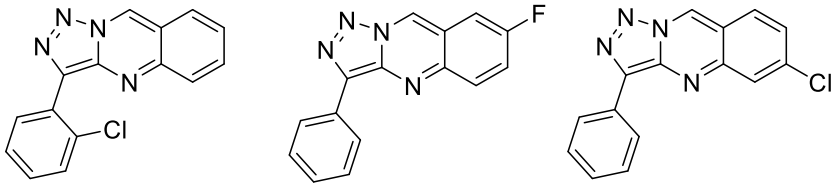
triazoloquinazoline **74f** in 73% as the sole product and was characterized by spectral and analytical data (Table 3.23). The desired triazolo fused indole **72** was not observed even in trace amount. *N*-halo substituted substrates **71g-h** afforded the corresponding triazolo fused quinazoline **74g-h** in moderate yield as the sole product (Table 3.23). The electron rich substrates **71i-j** were also observed to yield the triazoloquinazolines **74i-j** in 61 – 64% (Table 3.23). The naphthyl derivative **71k** was also smoothly converted to the triazolo fused quinazoline **74k** in 76% (Table 3.23).

Table 3.23. Synthesis of Triazolo Fused Quinazolines via Copper Mediated Ullmann Coupling Reaction



71, X = H, Cl

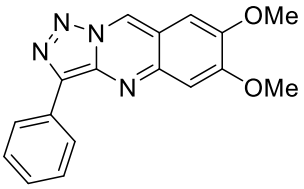
74



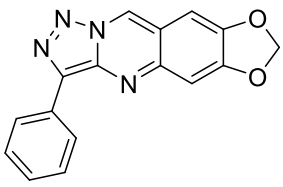
74f, 73%, 5 h

74g, 67%, 5 h

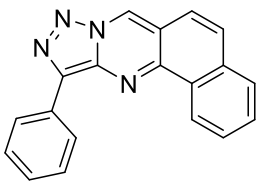
74h, 53%, 24 h



74i, 61%, 6 h



74j, 64%, 24 h



74k, 76%, 5 h

Table 3.24. Compounds for Photophysical Properties

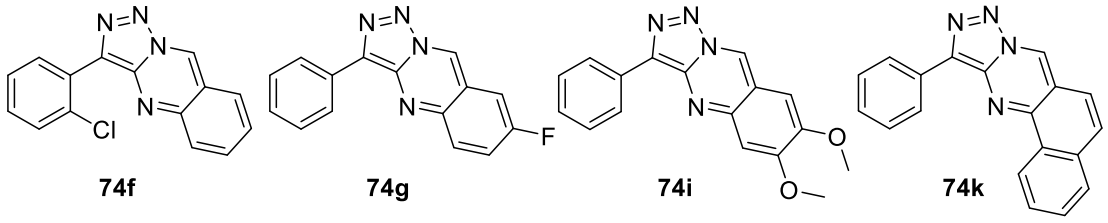


Table 3.25. Photophysical data of compounds 74f, 74g, 74i, 74k at 298K in CH_2Cl_2.

COMPOUNDS	λmax[a](nm)	λem[b](nm)	Δ (cm^{-1})	ϕ_F[c]
74f	251, 343	478	8234	35
74g	263, 376	520	7365	11.9
74i	264, 368	482	6427	52.7
74k	263, 369	511	7531	8.7

[a]absorption maximum ($1.5*10^{-5}$ M). [b]excited at the higher wavelength of absorption maximum. [c]relative quantum yields were measured using quinine sulphate as a reference with a UV absorption value less than 0.1 OD.

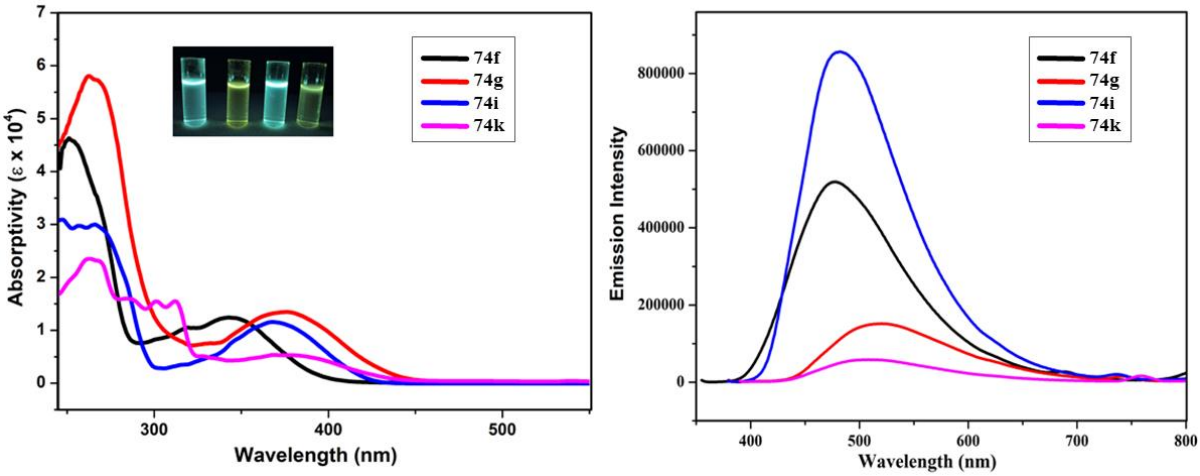


Figure 3.2 Absorption spectra (Left) and Emission spectra (right) of compounds **74f, 74g, 74i, 74k** in CH_2Cl_2 (1.5×10^{-5}M). Inset (Left): photograph of compounds **74f , 74g, 74i, 74k** in CH_2Cl_2 under a hand-held UV lamp at 365 nm.

These triazolo fused quinazolines **74** were synthesized for the first time, so we studied the photophysical property of these fused quinazoline moieties. Among these, four substrates **74** were found to show photophysical properties (Table 3.24).

As the triazole fused quinazolines are coplanar, we expected that they will show interesting photophysical properties. We selectively chose and analysed the photophysical property compounds **74f, 74g, 74i, 74k** in CH_2Cl_2 at 1.5 x 10^{-5}M. The photophysical data of the compounds are presented in figure 3.2 and table 13. All four compounds **74f, 74g, 74i,** and **74k** showed two absorption bands ranging from 250-380 nm and emission bands ranging from 470-520 nm (Fig. 3.2). Among the compounds studied, compound **74i** showed 53% fluorescence quantum yield which is the highest compared to other derivatives which may be due to the presence of –OMe groups in the fused phenyl ring. We expect that our approach will aid in the production of a wide range of substituted triazole fused quinolines which will have applications in various fields (Table 3.25).

3.11. Conclusion

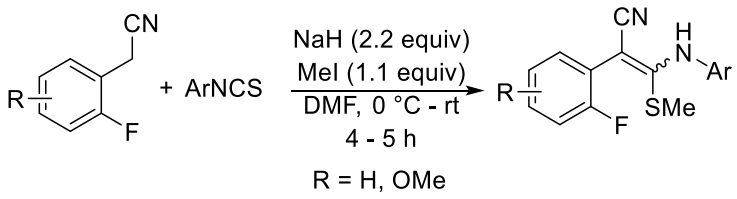
In this chapter, we have discussed the synthesis of rarely explored 1,2,3-triazoloindoles from easily available acyclic precursors. We have employed mild catalyst for the C─N arylation reaction. Further, we have studied the regioselectivity of the methodology and we observed the formation of 1,2,3-triazoloindole as the sole product. Then, we have synthesized triazoloquinazoline via copper catalyzed Ullmann coupling reaction, for the first time. The photophysical properties of the newly synthesized triazoloindoles were also studied.

3.12. Experimental Section

3.12.1. General Information

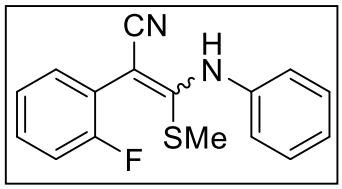
All reactions were performed by using standard vial technique with rubber septum. All solids were weighed in air. Triflic acid, TFA, AcOH, sodium hydride, PIDA, PIFA, Cs_2CO_3, HFIP, etc., were from Aldrich, Merck, TCI, Spectrochem or Alfa-Aesar, and used as received. Dried DMF, DMSO, Toluene and DCM were used. Isothiocyanates were synthesized from respective substituted anilines, and few isothiocyanates 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 $CDCl_3$ and DMSO-d_6 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 compound **86f** were grown by slow diffusion of n-hexane over CH_2Cl_2 solution. Single-crystal X-ray diffraction data of **86f** was 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 structure **86f** was solved with 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.

3.12.2. General Procedure for the Synthesis of *β*-anilinoacrylonitriles 50



To a stirring suspension of sodium hydride (13.2 mmol, 2.2 equiv) in DMF, a solution of aryl acetonitriles (6 mmol, 1 equiv) in DMF was added dropwise at 0 °C. After being further stirred for 1 h at room temperature, a solution of aryl isothiocyanates (6.6 mmol, 1.1 equiv) in DMF was added to the reaction mixture at 0 ^{o}C and followed by further stirring for 2 – 3 h at room temperature. Then a solution of methyl iodide (6.6 mmol, 1.1 equiv) in DMF was added and left for 30 min stirring 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.

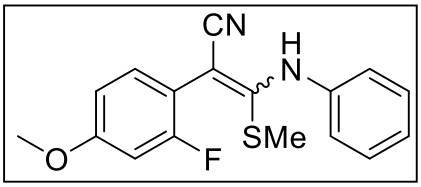
3-Anilino-2-(2-fluorophenyl)-3-(methylthio)acrylonitriles (50a) (Major Isomer)



Yield: 51% (0.870 g), pale yellow solid; R_f: 0.25 in 20% ethyl acetate in hexanes; mp: 129 – 131 °C; IR (KBr, ν cm^{-1}) = 3851, 3650, 3262, 3009, 2362, 1557, 1440, 1265, 754, 417; Diastereomeric ratio: 4:1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 1H), 7.28 – 7.16 (m, 2H), 7.15 – 7.09 (m, 1H), 7.09 – 6.98 (m, 3H), 6.91 - 6.85 (m, 2H), 6.81 (t, *J* = 7.2 Hz, 1H), 2.36 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 158.4 (d, *J* = 246.3 Hz), 155.9, 140.2, 130.2 (d, *J* = 2.6 Hz) 129.2 (d, *J* = 8.3 Hz), 129.0, 128.2, 124.4 (d, *J* = 3.1 Hz), 122.6, 119.9, 119.1, 115.6 (d, *J*

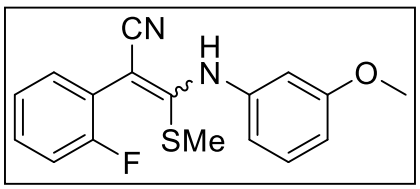
= 21.6 Hz), 81.3, 15.5. HR-MS (ESI-TOF) m/z cal. for $C_{16}H_{13}FN_2S$ $[M+H]^+$: 285.0856, found: 285.0858.

3-Anilino-2-(2-fluoro-4-methoxyphenyl)-3-(methylyhio)acrylonitrile (50b) (Major Isomer)



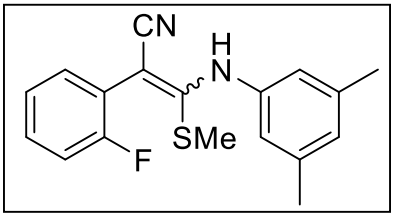
Yield: 47% (0.886 g), yellow jelly; R_f: 0.32 in 20% ethyl acetate in hexanes; IR (KBr, ν cm^{-1}) = 3742, 3646, 3269, 2954, 2355, 2210, 1733, 1554, 1292, 754, 476; Diastereomeric ratio: 3:1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (s, 1H), 7.14 – 7.03 (m, 3H), 6.90 (d, *J* = 7.2 Hz, 2H), 6.87 - 6.80 (m, 1H), 6.68 - 6.56 (m, 2H), 3.66 (s, 3H), 2.30 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 160.0 (d, *J* = 11.1 Hz), 159.2 (d, *J* = 246.0 Hz), 154.6, 140.4, 130.8 (d, *J* = 4.7 Hz), 128.3, 122.4, 119.7, 118.7, 114.2 (d, *J* = 14.5 Hz), 110.7, 101.6 (d, *J* = 25.5 Hz), 82.1, 55.6, 15.4. HR-MS (ESI-TOF) m/z cal. for $C_{17}H_{15}FN_2OS$ $[M+Na]^+$: 337.0781, found: 337.0787.

2-(2-Fluorophenyl)-3-(3-methoxy)anilino-3-(methylthio)acrylonitrile (50c) (Major Isomer)



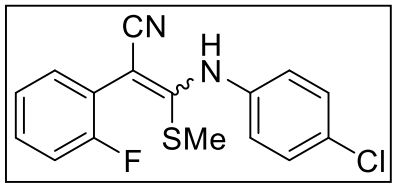
Yield: 72% (1.360 g), pale yellow solid; R_f: 0.30 in 20% ethyl acetate in hexanes; mp: 109 - 111°C; IR (KBr, ν cm^{-1}) = 3735, 3264, 2932, 2365, 2199, 1604, 1552, 1448, 1260, 1158, 1054, 757, 469; Diastereomeric ratio: 4:1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H), 7.36 – 7.08 (m, 3H), 7.07 – 6.88 (m, 3H), 6.46 – 6.31 (m, 2H), 3.62 (s, 3H), 2.37 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 158.4 (d, *J* = 246.5 Hz), 159.2, 155.7, 141.5, 130.2 (d, *J* = 2.0 Hz), 129.2 (d, *J* = 8.1 Hz), 129.1, 124.4 (d, *J* = 2.9 Hz), 120.4, 118.2, 115.6 (d, *J* = 21.5 Hz), 112.2, 108.5, 105.3, 81.7, 54.8, 15.5. HR-MS (ESI-TOF) m/z cal. for $C_{17}H_{15}FN_2OS$ $[M+H]^+$: 315.0962, found: 315.0947.

3-(3,5-Dimethyl)anilino-2-(2-fluorophenyl)-3-(methylthio)acrylonitriles (50d) (Major Isomer)



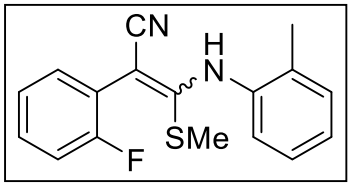
Yield: 58% (1.090 g), white solid; R_f: 0.25 in 20% ethyl acetate in hexanes; mp: 103 – 105 °C; IR (KBr, ν cm^{-1}) = 3735, 3271, 3009, 2362, 2226, 1601, 1554, 1279, 760, 472; Diastereomeric ratio: 6:1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 7.21 - 7.14 (m, 1H), 7.13 - 7.07 (m, 1H), 7.03 - 6.97 (m, 1H), 6.97 – 6.90 (m, 1H), 6.45 (s, 2H), 6.41 (s, 1H), 2.39 (s, 3H), 2.05 (s, 6H).^{13}C NMR (100 MHz, DMSO-d_6) δ 158.4 (d, *J* = 246.0 Hz), 155.6, 139.8, 137.1, 130.0 (d, *J* = 2.8 Hz), 129.1 (d, *J* = 8.2 Hz), 124.3 (d, *J* = 3.1 Hz), 124.1, 122.6 (d, *J* = 14.1), 120.7, 117.5, 115.4 (d, *J* = 21.5 Hz), 80.7, 20.8, 15.6. HR-MS (ESI-TOF) m/z cal. for $C_{18}H_{17}FN_2S$ $[M+Na]^+$: 335.0989, found: 335.1025.

3-(4-Chloro)anilino-2-(2-fluorophenyl)-3-(methylthio)acrylonitrile (50e) (Major Isomer)



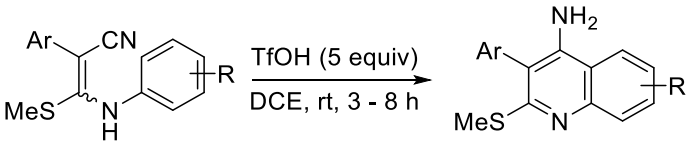
Yield: 88% (1.680 g), orange solid; R_f: 0.25 in 20% ethyl acetate in hexanes; mp: 105 – 107 °C; IR (KBr, ν cm^{-1}) = 3725, 3267, 2357, 2191, 1552, 1493, 1329, 1272,1086, 762, 504; Diastereomeric ratio: 4:1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 7.31 – 7.18 (m, 2H), 7.13 - 7.01 (m, 3H), 7.00 – 6.92 (m, 1H), 6.92 - 6.82 (m, 2H), 2.38 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 159.3 (d, *J* = 248.3 Hz), 155.6, 139.3 (d, *J* = 2.6 Hz), 130.2, 129.4 (d, *J* = 8.1 Hz), 128.1, 126.2, 124.5, 122.1 (d, *J* = 13.9 Hz), 121.2, 120.4 (d, *J* = 25.9 Hz), 115.8, 82.1, 15.5. HR-MS (ESI-TOF) m/z cal. for $C_{16}H_{12}ClFN_2S$ $[M+Na]^+$: 341.0286, found: 341.0284

2-(2-Fluorophenyl)-3-(2-methyl)anilino-3-(methylthio)acrylonitriles (50f) (Major Isomer)



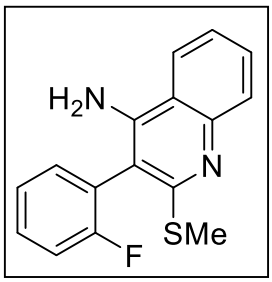
Yield: 79% (1.410 g), orange jelly; R_f: 0.25 in 20% ethyl acetate in hexanes; IR (KBr, ν cm^{-1}) = 3732, 3626, 3061, 2360, 2191, 1557, 1495, 1265, 754, 467; Diastereomeric ratio: 3:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 - 7.13 (m, 1H), 7.01 – 6.92 (m, 3H), 6.91 - 6.85 (m, 3H), 6.77 – 6.69 (m, 2H), 6.13 (s, 1H), 2.08 (s, 3H), 2.02 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (d, *J* = 247.5 Hz), 156.9, 137.7, 130.5 (d, *J* = 2.6 Hz), 130.4, 130.3, 129.5 (d, *J* = 8.2 Hz), 126.2, 125.0, 124.4 (d, *J* = 3.5 Hz), 123.0, 121.3 (d, *J* = 14.5 Hz), 120.3, 115.8 (d, *J* = 21.7 Hz), 83.0, 17.7, 16.1. HR-MS (ESI-TOF) m/z cal. for $C_{17}H_{15}FN_2S$ $[M+H]^+$: 299.1013, found: 299.1019

3.12.3. General Procedure for the synthesis of 4-aminoquinolines 51



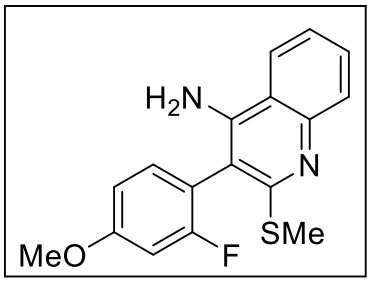
An oven-dried sealed tube was charged with the respective *β*-anilinoacrylonitriles (1 mmol), triflic acid (15 mmol) in DCE (4.0 mL). The mixture was stirred at room temperature or 60 ℃ for 3 – 6 h. The reaction mixture was monitored by TLC. After the starting material was completely consumed, the reaction mixture was quenched with saturated $NaHCO_3$ 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 product was purified by flash chromatography using hexane and EtOAc as eluent.

4-Amino-3-(2-fluorophenyl)-2-(methylthio)quinoline (51a):



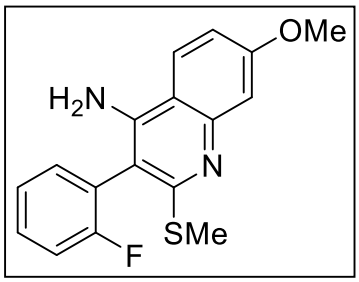
Reaction Time: 3 h; Yield: 69% (0.196 g), yellow solid; R_f: 0.33 in 20% ethyl acetate in hexanes; mp: 123 – 125 °C; IR (KBr, ν cm^{-1}) = 3703, 3357, 3049, 2831, 2527, 2033, 1667, 1452, 1267, 1032, 756; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.56 – 7.49 (m, 1H), 7.38 – 7.29 (m, 4H), 6.10 (s, 2H), 2.45 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 160.4 (d, *J* = 243.1 Hz), 158.4, 147.8, 147.5, 133.65, 133.62, 130.9 (d, *J* = 8.1 Hz), 129.5, 127.6, 125.2 (d, *J* = 3.4 Hz), 123.0 (d, *J* = 38.3 Hz), 121.9 (d, *J* = 17.3 Hz), 117.1, 116.2 (d, *J* = 21.8 Hz), 106.4, 12.7. HR-MS (ESI-TOF) m/z cal. for $C_{16}H_{13}FN_2S$ $[M+H]^+$: 285.0856, found: 285.0881

4-Amino-3-(2-fluoro-4-methoxyphenyl)-2-(methylthio)quinoline (51b):



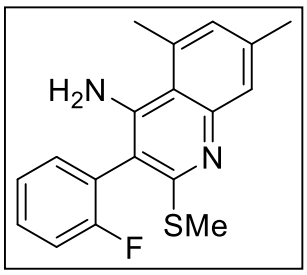
Reaction Time: 3 h; Yield: 34% (0.107 g), yellow jelly; R_f: 0.21 in 20% ethyl acetate in hexanes; IR (KBr, ν cm^{-1}) = 3694, 3363, 2970, 2845, 2535, 2048, 1683, 1459, 1271, 1043, 765, 672; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.69 – 7.63 (m, 1H), 7.44 – 7.39 (m, 1H), 7.32 – 7.27 (m, 1H), 6.91 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.88 – 6.82 (m, 1H), 4.48 (s, 2H), 3.91 (s, 3H), 2.63 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4 (d, *J* = 245.7 Hz), 161.9 (d, *J* = 10.8 Hz), 160.2, 148.1, 146.3, 133.6 (d, *J* = 4.9 Hz), 129.6, 128.8, 124.0, 120.6, 117.2, 113.5 (d, *J* = 17.5 Hz), 111.2 (d, *J* = 3.0 Hz), 108.6, 102.7 (d, *J* = 25.4 Hz), 55.8, 13.5. HR-MS (ESI-TOF) m/z cal. for $C_{17}H_{15}FN_2OS$ $[M+H]^+$: 315.0962, found: 315.0979.

4-Amino-3-(2-fluorophenyl)-7-methoxy-2-(methylthio)quinoline (51c):



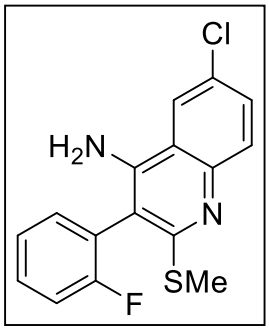
Reaction Time: 3 h; Yield: 66% (0.207 g), yellow solid; R_f: 0.28 in 20% ethyl acetate in hexanes; mp: 166 – 168 °C; IR (KBr, ν cm^{-1}) = 3685, 3357, 2950, 2839, 2527, 2055, 1672, 1457, 1032, 756, 672; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, *J* = 8.8 Hz, 1H), 7.55 – 7.46 (m, 1H), 7.38 – 7.25 (m, 3H), 7.10 (d, *J* = 2.4 Hz, 1H), 6.97 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.00 (s, 2H), 3.88 (s, 3H), 2.43 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 160.5 (d, *J* = 243.1 Hz), 160.3, 158.5, 149.4, 147.8, 133.8 (d, *J* = 2.8 Hz), 130.7 (d, *J* = 8.3 Hz), 125.1 (d, *J* = 3.0 Hz), 124.2, 122.1 (d, *J* = 17.3 Hz), 116.2 (d, *J* = 21.9 Hz), 114.7, 111.4, 106.9, 105.2, 55.3, 12.6. HR-MS (ESI-TOF) m/z cal. for $C_{17}H_{15}FN_2OS$ $[M+H]^+$: 315.0962, found: 315.0956

4-Amino-3-(2-fluorophenyl)-5,7-dimethyl-2-(methylthio)quinoline (51d):



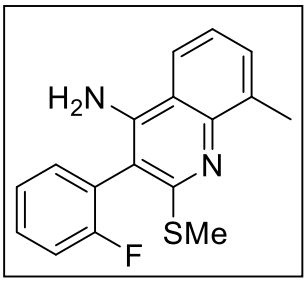
Reaction Time: 3 h; Yield: 90% (0.281 g), white solid; R_f: 0.38 in 30% ethyl acetate in hexanes; mp: 172 – 174 °C; IR (KBr, ν cm^{-1}) = 3696, 3355, 2950, 2063, 1662, 1457, 1272, 1027, 758, 672; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41 – 7.27 (m, 5H), 6.96 (s, 1H), 5.28 (s, 2H), 2.83 (s, 3H), 2.41 (s, 3H), 2.38 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 160.4 (d, *J* = 243.7 Hz), 157.3, 149.7, 149.2, 138.4, 134.2, 133.7 (d, *J* = 2.8 Hz), 131.2 (d, *J* = 8.1 Hz), 128.9, 125.9, 125.5 (d, *J* = 3.4 Hz), 121.8 (d, *J* = 17.1 Hz), 116.4 (d, *J* = 21.8 Hz), 115.1, 107.9, 23.9, 20.8, 12.5. HR-MS (ESI-TOF) m/z cal. for $C_{18}H_{17}FN_2S$ $[M+H]^+$: 313.1169, found: 313.1187.

4-Amino-6-chloro-3-(2-fluorophenyl)-2-(methylthio)quinoline (51e):



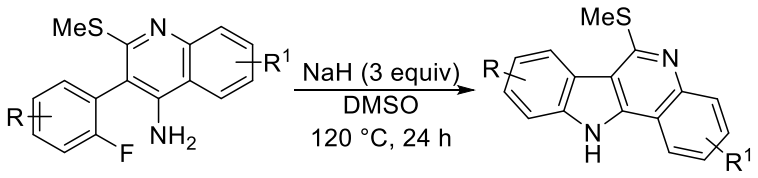
Reaction Time: 3 h; Yield: 33% (0.105 g), yellow jelly; R_f: 0.35 in 30% ethyl acetate in hexanes; IR (KBr, ν cm^{-1}) = 3705, 3365, 3050, 2945, 2831, 2520, 2030, 1670, 1453, 1270, 1033, 755; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.75 – 7.48 (m, 3H), 7.40 – 7.25 (m, 3H), 6.19 (s, 2H), 2.43 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 160.3 (d, *J* = 243.4Hz), 159.3, 147.2, 146.1, 133.50, 133.48, 131.1 (d, *J* = 7.9 Hz), 129.8 (d, *J* = 14.5 Hz), 127.6, 125.3 (d, *J* = 2.8 Hz), 122.1, 121.6 (d, *J* = 17.2 Hz), 118.0, 116.3 (d, *J* = 22.2 Hz), 107.1, 12.7. HR-MS (ESI-TOF) m/z cal. for $C_{16}H_{12}ClFN_2S$ $[M+H]^+$: 319.0467, found: 319.0486.

4-Amino-3-(2-fluorophenyl)-8-methyl-2-(methylthio)quinoline (51f):



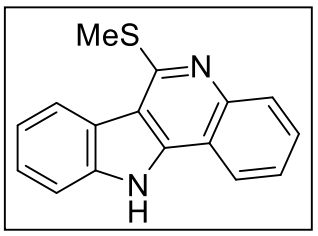
Reaction Time: 3 h; Yield: 56% (0.167 g, white solid); Melting Point: 172 – 174 °C; R_f: 0.42 in 30% ethyl acetate in hexanes; IR (KBr, ν cm^{-1}) = 3698, 3355, 2942, 2836, 2033, 1452, 1272, 1040, 758. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, *J* = 7.6 Hz, 1H), 7.55 - 7.46 (m, 2H), 7.38 – 7.29 (m, 3H), 7.27 - 7.21 (m, 1H), 6.02 (s, 2H), 2.64 (s, 3H), 2.46 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 161.4 (d, *J* = 243.2 Hz), 157.2, 148.1, 146.1, 134.9, 133.6 (d, *J* = 2.8 Hz), 130.7 (d, *J* = 8.1 Hz), 129.5, 125.2 (d, *J* = 3.2 Hz) 122.7, 122.1 (d, *J* = 17.2 Hz), 120.6, 116.7, 116.2 (d, *J* = 22.0 Hz), 106.4, 17.9, 12.7. HR-MS (ESI) Calcd for $C_{17}H_{15}FN_2S$ $[M+H]^+$: 299.1077, found: 299.1013

3.12.4. General Procedure for Synthesis of Indoloquinolines 22



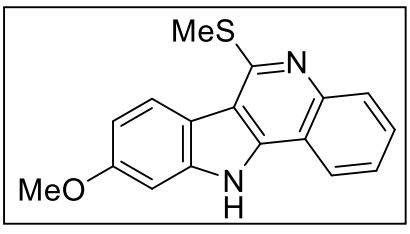
An oven-dried 8ml reaction vial was charged with sodium hydride (1.5 mmol), the respective 4-aminoquinolines (0.5 mmol) **22** in DMSO (2.0 mL). The mixture was stirred at 120 °C for 24 h. The reaction mixture was monitored by TLC. After the starting material was completely consumed, the reaction mixture was purified by flash chromatography using hexane and EtOAc as eluent.

6-(Methylthio)-11*H*-indolo[3,2-*c*]quinoline (22a):



Reaction Time: 24 h; Yield: 84% (0.111 g), pale yellow solid; R_f: 0.22 in 20% ethyl acetate in hexanes; mp: 146 – 148 °C; IR (KBr, ν cm^{-1}) = 3691, 3352, 2947, 2839, 2055, 1452, 1275, 1032, 756; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (s, 1H), 8.48 (d, *J* = 7.6 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.79 - 7.67 (m, 2H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 2.85 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 154.5, 144.9, 139.3, 138.5, 128.5, 128.0, 125.1, 124.6, 122.0, 121.7, 121.3, 120.8, 115.7, 111.9, 111.7, 11.6. HR-MS (ESI-TOF) m/z cal. for $C_{16}H_{12}N_2S$ $[M+H]^+$: 265.0794, found: 265.0801

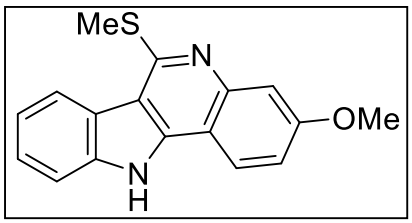
9-Methoxy-6-(methylthio)-11*H*-indolo[3,2-*c*]quinoline (22b):



Reaction Time: 24 h; Yield: 92% (0.135 g), pale yellow solid; R_f: 0.20 in 20% ethyl acetate in hexanes; mp: 174 – 176 °C; IR (KBr, ν cm^{-1}) = 3753, 3610, 3028, 2891, 2068, 1541, 1440, 1281, 1045, 746; ^{1}H NMR (400 MHz, DMSO-

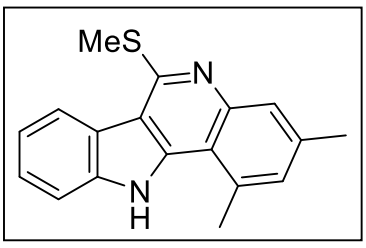
d_6) δ 12.69 (s, 1H), 8.41 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 2.0 Hz, 1H), 7.01 (dd, *J* = 8.8, 2.0 Hz, 1H), 3.89 (s, 3H), 2.83 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 158.1, 153.6, 144.5, 139.9, 139.0, 128.0 (2C), 124.5, 122.5, 121.8, 115.7, 115.2, 111.9, 110.1, 95.3, 55.4, 11.6. HR-MS (ESI-TOF) m/z cal. for $C_{17}H_{14}N_2OS$ $[M+H]^+$: 295.0900, found: 295.0891

3-Methoxy-6-(methylthio)-11*H*-indolo[3,2-*c*]quinoline (22c):



Reaction Time: 24 h; Yield: 72% (0.106 g), white solid; R_f: 0.17 in 20% ethyl actate in hexanes; mp: 206 – 208 °C; IR (KBr,ν cm^{-1}) = 3750, 3350, 2947, 2829, 2522, 2045, 1650, 1453, 1272, 1025, 753; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.66 (s, 1H), 8.36 (d, *J* = 8.8 Hz, 1H), 8.25 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.51 – 7.44 (m, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.25 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.94 (s, 3H), 2.84 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 159.8, 154.7, 146.8, 139.9, 138.4, 124.8, 123.3, 121.52, 121.48, 120.7, 116.0, 111.7, 110.6, 109.8, 107.9, 55.4, 11.6. HR-MS (ESI-TOF) m/z cal. for $C_{17}H_{14}N_2OS$ $[M+H]^+$: 295.0900, found: 295.0922.

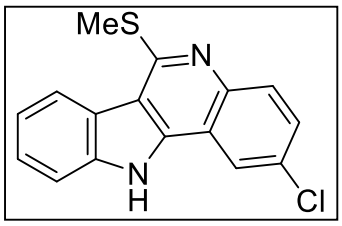
1,3-Dimethyl-6-(methylthio)-11*H*-indolo[3,2-*c*]quinoline (22d):



Reaction Time: 24 h; Yield: 64% (0.093 g), white solid; R_f: 0.28 in 20% ethyl acetate in hexanes; mp: 126 – 128 °C; IR (KBr, ν cm^{-1}) = 3713, 3370, 2942, 2834, 2043, 1680, 1448, 1116, 1035, 758. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.63 (s, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.67 (s, 1H), 7.52 - 7.44 (m, 1H), 7.41 - 7.33 (m, 1H), 7.17 (s, 1H), 3.34 (s, 3H), 2.82 (s, 3H), 2.46 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 153.9, 146.4, 139.0, 138.8, 137.3, 132.6, 128.0, 125.8, 124.6, 121.3, 120.77, 120.51, 113.3, 112.6,

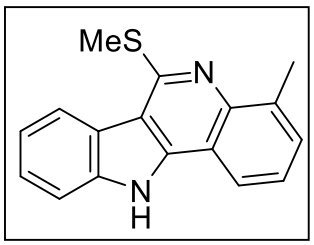
111.9, 23.0, 21.0, 11.6. HR-MS (ESI-TOF) m/z cal. for $C_{18}H_{16}N_2S$ $[M+H]^+$: 293.1107, found: 293.1099

2-Chloro-6-(methylthio)-11*H*-indolo[3,2-*c*]quinoline (22e):



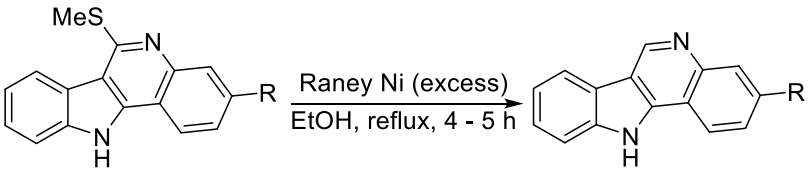
Reaction Time: 24 h; Yield: 93% (0.070g), white solid; R_f: 0.46 in 40% ethyl acetate in hexanes; mp: 162 – 168 ℃; IR (KBr, ν cm^{-1}) = 3745, 3345, 2940, 2826, 2050, 1455, 1265, 1037, 758; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (s, 1H), 8.55 (s, 1H), 8.28 (d, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 2.82 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 155.3, 143.3, 138.5, 138.3, 130.0, 128.6 (2C), 125.5, 121.9, 121.25, 121.07 (2C), 116.5, 112.19, 112.04, 11.7. HR-MS (ESI-TOF) m/z cal. for $C_{16}H_{11}ClN_2S$ $[M+H]^+$: 299.0404, found: 299.0390.

4-Methyl-6-(methylthio)-11*H*-indolo[3,2-*c*]quinoline (22f):



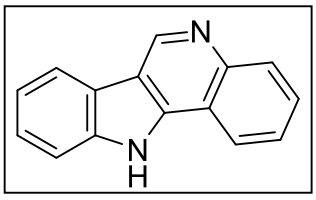
Reaction Time: 24 h; Yield: 79% (0.139 g), pale yellow solid; R_f: 0.25 in 20% ethyl acetate in hexanes; mp: 153 – 155 °C; IR (KBr, ν cm^{-1}) = 3711, 3355, 2942, 2836, 2041, 1665, 1452, 1267, 1030, 760; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.68 (s, 1H), 8.30 (t, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.61 - 7.54 (m, 1H), 7.53 - 7.44 (m, 2H), 7.38 (t, *J* = 7.2 Hz, 1H), 2.86 (s, 3H), 2.80 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 153.0, 143.5, 139.8, 138.6, 135.5, 128.8, 125.1, 124.2, 121.6, 121.3, 120.7, 119.8, 115.2, 111.80, 111.63, 18.3, 11.6. HR-MS (ESI-TOF) m/z cal. for $C_{17}H_{14}N_2S$ $[M+H]^+$: 279.0950, found: 279.0974.

3.12.5. General Procedure for desulfurization of Indoloquinolines 22a′ and 22c′



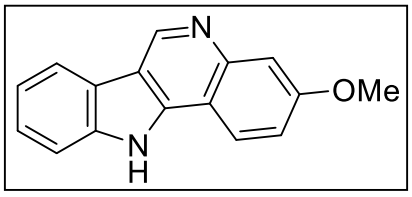
An oven-dried RB flask was charged with the indoloquinolines **22a** & **22c** (1 mmol) and ethanol (30 mL). Then excess of raney nickel was added in the stirring reaction mixture and was refluxed for 5 h. The reaction mixture was monitered by TLC. After the starting material was completely consumed, the reaction mixture was filtered through celite funnel and the raney nickel was quenched with water. The filtrate was collected and concentrated under reduced pressure. The crude product was purified by flash chromatography using hexane and EtOAc as eluent.

11*H*-Indolo[3,2-*c*]quinoline (22a′):



Reaction Time: 5 h; Yield: 83% (0.054 g), white solid; R_f: 0.22 in 50% ethyl acetate in hexanes; mp: >295 °C; IR (KBr, ν cm^{-1}) = 3429, 3056, 2980, 2849, 1589, 1364, 1339, 1216, 734; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.81 (s, 1H), 9.60 (s, 1H), 8.55 (d, *J* = 7.6 Hz, 1H), 8.32 (d, *J* = 7.6 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.78 – 7.66 (m, 3H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H).^{13}C NMR (100 MHz, DMSO-d_6) δ 145.9, 145.3, 140.2, 139.2, 130.0, 128.5, 126.2, 126.0, 122.6, 122.3, 121.0, 120.6, 117.6, 114.8, 112.4. HR-MS (ESI-TOF) m/z cal. for $C_{15}H_{10}N_2$ $[M+H]^+$: 219.0917, found: 219.0921.

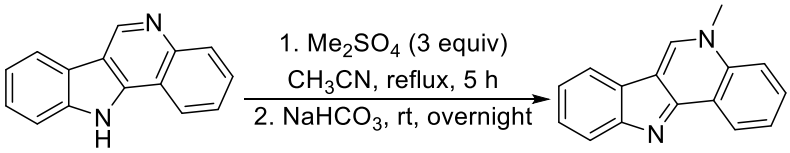
3-Methoxy-11*H*-Indolo[3,2-*c*]quinoline (22c′):



Reaction Time: 5 h; Yield: 76% (0.057 g), white solid; R_f: 0.18 in 50% ethyl acetate in hexanes; mp: >295 °C; IR (KBr, ν cm^{-1}) = 3760, 3590, 2999, 2150, 1550, 1435, 1190, 1060,

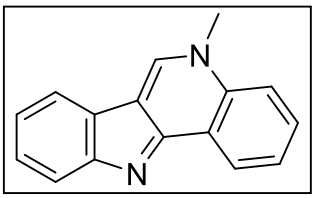
750; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.81 (s, 1H), 9.51 (s, 1H), 8.48 (d, *J* = 8.8 Hz, 1H), 8.26 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 2.4 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.36 – 7.26 (m, 2H), 3.94 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 159.3, 147.3, 145.0, 140.3, 138.7, 125.1, 123.5, 122.0, 120.4, 119.8, 117.4, 113.4, 111.7, 111.5, 109.0, 55.4. HR-MS (ESI-TOF) m/z cal. for $C_{16}H_{12}N_2O$ $[M+H]^+$: 271.0842, found: 271.0806.

3.12.6. General Procedure for the Synthesis of Isocryptolepine 31a



To a stirring solution of **22a′** in acetonitrile, Me_2SO_4 (excess) was added and the reaction mixture was stirred at reflux for 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 purified by using 20% MeOH in DCM as eluent to get pure compound.

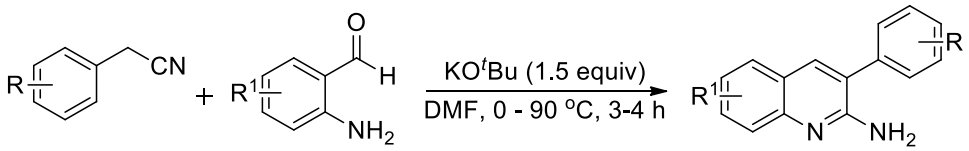
5-Methyl-5*H*-indolo[3,2-*c*]quinoline (31a):



Reaction Time: 12 h; Yield: 45% (0.021 g), green solid; R_f: 0.28 in 20% MeOH in DCM; mp: 112 – 114 °C; IR (KBr, ν cm^{-1}) = 3443, 2890, 2838, 1790, 1633, 1520, 1480, 1135, 862; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 7.6 Hz, 1H), 7.98 – 7.86 (m, 2H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.54 – 7.41 (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 (100 MHz, $CDCl_3$) δ 153.2, 152.2, 135.3, 134.6, 128.9, 126.0, 124.72, 124.66, 124.0, 120.3, 119.9,

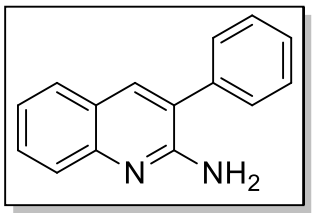
119.0, 118.1, 115.98, 115.90, 42.0. HR-MS (ESI-TOF) m/z cal. for $C_{16}H_{12}N_2$ $[M+H]^+$: 233.1073, found: 233.1062.

3.12.7. General Procedure for the Synthesis of 2-Amino-3-aryl quinolines 55



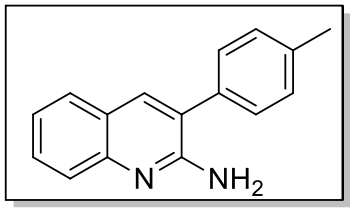
To a stirring suspension of KO^{t}Bu (1.5 equiv.) in DMF (15.0 mL) at 0 °C was added dropwise the corresponding benzylnitrile (1.3 equiv.) in DMF (5.0 mL). After being further stirred for 1 h at room temperature, a solution of 2-amino benzaldehyde (1.0 equiv.) in DMF (5.0 mL) was added to the reaction mixture at 0 °C and followed by further stirring for 3 – 4 h at 90 °C. After complete consumption of the starting materials (monitored by TLC), the reaction mixture was quenched with water and if solid comes, then it was filtered off and the solid was dried in vacuum, otherwise 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.

3-Phenylquinolin-2-amine (55a)



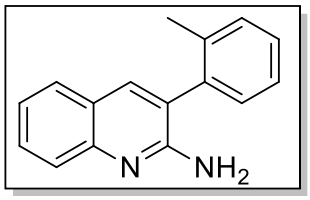
Reaction Time: 3 h; Yield: 83%, Melting Point: ;R_f: 0.27 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3742, 3480, 3014, 2365, 2332, 1743, 1633, 1431, 1277, 675; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.55-7.46 (m, 4H), 7.45-7.39 (m, 1H), 7.25 (t, *J* = 7.2 Hz, 1H), 5.30 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.4, 147.2, 137.6, 137.3, 129.7, 129.2, 129.0, 128.3, 127.6, 125.5, 125.1, 124.2, 122.7; HR-MS (ESI) Calcd for $C_{15}H_{12}N_2$ [M+H]: 221.1073, Found: 221.1088

3-(*p*-Tolyl)quinolin-2-amine (55b)



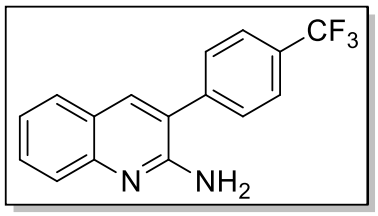
Reaction Time: 3 h; Yield: 65%; Melting Point: 155 – 157 °C; R_f: 0.22 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3628, 3455, 3103, 1639, 1267, 759, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.58-7.51 (m, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.33-7.22 (m, 3H), 5.15 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ = 155.61, 147.23, 138.12, 137.10, 134.73, 129.89, 129.54, 128.84, 127.54, 125.61, 125.15, 124.32, 122.70, 21.32; HR-MS (ESI) Calcd for $C_{16}H_{14}N_2$ [M+H]: 235.1230, Found: 235.1241.

3-(*o*-Tolyl)quinolin-2-amine (55c)



Reaction Time: 3 h; Yield: 77%; Melting Point: 97 – 99 °C; R_f: 0.25 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3480, 3066, 2925, 2375, 1634, 1423, 1265, 757, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 - 7.69 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.39 – 7.23 (m, 5H), 4.77 (s, 2H), 2.21 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ = 155.6, 147.5, 137.2, 137.1, 136.6, 130.7, 130.1, 129.6, 128.7, 127.6, 126.6, 125.8, 124.8, 124.0, 122.7, 19.8; HR-MS (ESI) Calcd for $C_{16}H_{14}N_2$ [M+H]: 235.1230, Found: 235.1247.

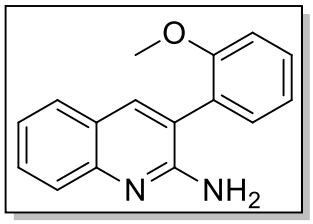
3-(4-(Trifluoromethylphenyl)quinolin-2-amine (55d)



Reaction Time: 4 h; Yield: 73%; Melting Point: 205 – 207 °C; R_f: 0.33 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3619, 3002, 2952, 2367, 1643, 1490, 1267, 763; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.72 – 7.62 (m, 4H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 5.05 (s, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 154.7, 147.6, 141.5, 137.8, 130.6 (q, *J* = 32.5 Hz,), 130.3, 129.5, 127.8, 126.3

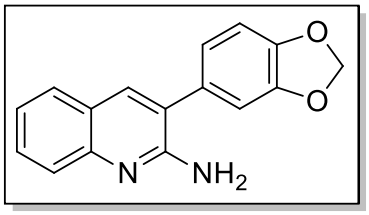
(q, *J* = 3.7 Hz), 125.9, 124.2, 124.1 (q, *J* = 270.5 Hz), 123.7, 123.2; HR-MS (ESI) Calcd for $C_{16}H_{11}F_3N_2$ [M+H]: 289.0947, Found: 289.0903.

6-Bromo-3-(4-fluorophenyl)quinolin-2-amine (55e)



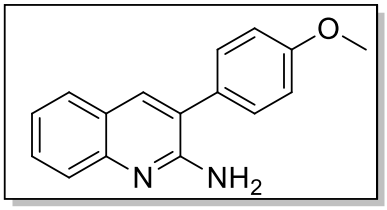
Reaction Time: 4 h; Yield: 86%; Melting Point: decomposed; R_f: 0.27 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3745, 3056, 2838, 2364, 1771, 1655, 1438, 1270, 1248, 763, 669; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.80 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 6.8 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 4.93 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.0, 156.0, 147.4, 138.1, 131.7, 130.1, 129.6, 127.6, 126.4, 125.8, 124.2, 122.7, 122.5, 121.4, 111.5, 55.8; HR-MS (ESI) Calcd for $C_{16}H_{14}N_2O$ [M+H]: 251.1179, Found: 251.1188.

3-(Benzo[*d*][1,3]dioxol-5-yl)quinolin-2-amine (55f)



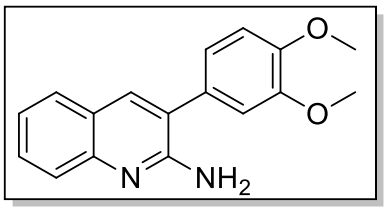
Reaction Time: 4 h; Yield: 70%; Melting Point: decomposed; R_f: 0.27 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3631, 3053, 2996, 2360, 2340, 1698, 1651, 1540, 1272, 767. 670; ^1H NMR (700 MHz, $CDCl_3$) δ = 7.72 (s, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.4Hz, 1H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.24 (t, *J* = 7.3 Hz, 1H), 6.98 (s, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.01 (s, 2H), 5.21 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.5, 148.3, 147.7, 147.1, 137.1, 131.3, 129.6, 127.5, 125.6, 124.8, 124.2, 122.8, 122.5, 109.4, 109.0, 101.4; HR-MS (ESI) Calcd for $C_{16}H_{12}N_2O_2$ [M+H]: 265.0972, Found: 265.0981.

3-(4-Methoxyphenyl)quinolin-2-amine (55g)



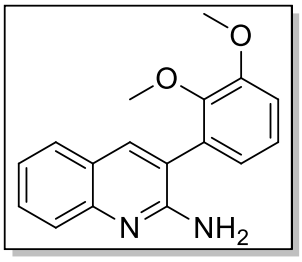
Reaction Time: 4 h; Yield: 79%; Melting Point: 142 – 144 °C; R_f: 0.15 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3452, 3155, 2365, 2318, 1651, 1609, 1436, 1247, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.57-7.50 (m, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.28-7.21 (m, 1H), 7.00 (d, *J* = 7.2 Hz, 2H), 5.24 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.6, 155.7, 146.9, 137.1, 130.1, 129.7, 129.5, 127.5, 125.4, 124.8, 124.3, 122.7, 114.6, 55.4; HR-MS (ESI) Calcd for $C_{16}H_{14}N_2O$ [M+H]: 251.1179, Found: 251.1195.

3-(3,4-Dimethoxyphenyl)quinolin-2-amine (55 h)



Reaction Time: 4 h; Yield: 82%; Melting Point: 105 – 107 °C; R_f: 0.15 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3624, 3429, 3000, 2372, 1645, 1514, 1270, 1139, 763; ^{1}H NMR (400 MHz, DMSO) δ = 7.82 (s, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.56-7.44 (m, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.11-7.00 (m, 3H), 6.07 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ = 155.5, 149.5, 149.2, 147.2, 137.1, 130.2, 129.6, 127.5, 125.8, 125.0, 124.4, 122.9, 121.4, 112.2, 111.8, 56.2, 56.1; HR-MS (ESI) Calcd for $C_{17}H_{16}N_2O_2$ [M+H]: 281.1285, Found: 281.1300.

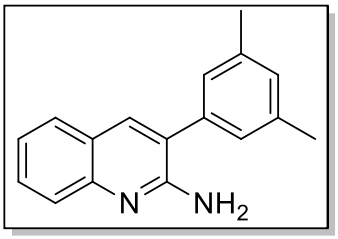
3-(2,3-Dimethoxyphenyl)quinolin-2-amine (55i)



Reaction Time: 3 h; Yield: 46%; Melting Point: 155 – 157 °C; R_f: 0.22 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3585, 3051, 3000, 2493, 1625, 1431, 1269, 1096, 763; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.31 – 7.24 (m, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.01 (d, *J*

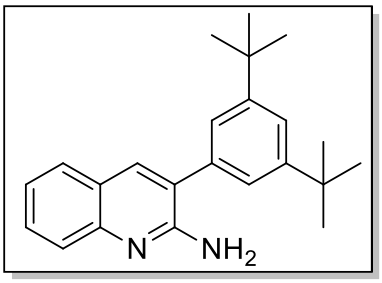
= 8.0 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 4.96 (s, 2H), 3.93 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ = 155.89, 153.28, 147.51, 146.88, 138.00, 131.87, 129.70, 127.62, 125.82, 124.92, 124.01, 123.18, 122.73, 122.04, 112.67, 61.23, 56.02; HR-MS (ESI) Calcd for $C_{17}H_{16}N_2O_2$ [M+H]: 281.1285, Found: 281.1298.

3-(3,5-Dimethylphenyl)quinolin-2-amine (55j)



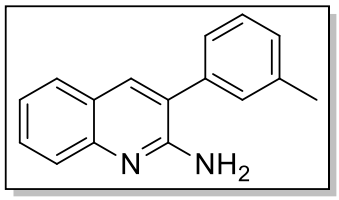
Reaction Time: 4 h; Yield: 68%; Melting Point: 196 – 198 °C; R_f: 0.35 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3745, 3464, 3145, 2335, 1734, 1638, 1277, 766, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (s, 1H), 7.84 – 7.59 (m, 3H), 7.37 (s, 1H), 7.30 - 7.08 (m, 3H), 5.43 (s, 2H), 2.51 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.6, 147.2, 138.8, 137.6, 137.0, 129.9, 129.5, 127.5, 126.6, 125.5, 125.4, 124.2, 122.6, 21.4; HR-MS (ESI) Calcd for $C_{17}H_{16}N_2$ [M+H]: 249.1386, Found: 249.1359.

3-(3,5-Di-tert-butylphenyl)quinolin-2-amine (55k)



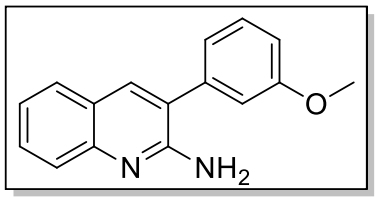
Reaction Time: 4 h; Yield: 68%; Melting Point: decomposed; R_f: 0.37 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3747, 3004, 2974, 2340, 1557, 1272, 767, 672; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.51 (s, 1H), 7.38 (s, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 5.09 (s, 2H), 1.40 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.5, 151.7, 147.1, 137.0, 136.8, 129.5, 127.5, 126.1, 125.6, 124.3, 123.1, 122.7, 122.2, 35.0, 31.5 (2C); HR-MS (ESI) Calcd for $C_{23}H_{28}N_2$ [M+H]: 333.2325, Found: 333.2330.

3-(*m*-Tolyl)quinoline-2-amine (55l)



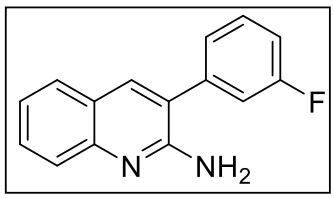
Reaction Time: 3 h; Yield: 88%; Melting Point: 118 – 120 °C; R_f: 0.22 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3480, 3296, 3046, 3000, 2365, 2332, 1631, 1436, 1267, 1208, 762, 670; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.57-7.51 (m, 1H), 7.41-7.34 (m, 1H), 7.33-7.27 (m, 2H), 7.26-7.20 (m, 2H), 5.18 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.4, 147.1, 139.0, 137.6, 137.2, 129.7, 129.1, 129.1, 127.6, 126.0, 125.5, 125.3, 124.2, 122.8, 21.6; HR-MS (ESI) Calcd for $C_{16}H_{14}N_2$ [M+H]: 235.1230, Found: 235.1235.

3-(3-Methoxyphenyl)quinolin-2-amine (55m)



Reaction Time: 3 h; Yield: 68%; Melting Point: 166 – 168 °C R_f: 0.29 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3627, 3103, 3000, 2359, 1633, 1433, 1270, 761; ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.79 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.06 (s, 1H), 6.99 – 6.97 (m, 1H), 5.11 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ = 160.2, 155.3, 147.3, 139.1, 137.2, 130.3, 129.7, 127.6, 125.7, 125.0, 124.2, 122.8, 121.2, 114.6, 113.8, 55.4; HR-MS (ESI) Calcd for $C_{16}H_{14}N_2O$ [M+H]: 251.1179, Found: 251.1188.

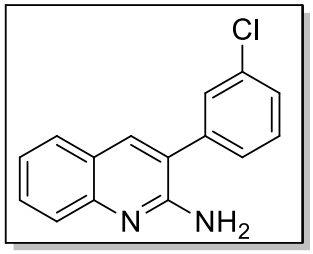
3-(3-Fluorophenyl)quinolin-2-amine (55n)



Reaction Time: 4 h; Yield: 78%; Melting Point: decomposed; R_f: 0.21 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3653, 3001, 2377, 1624, 1438, 1269, 1242, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.50 - 7.40 (m, 1H), 7.36 – 7.20 (m, 3H), 7.12 (t, *J* = 8.2 Hz, 1H), 5.29 (s, 2H); ^{13}C NMR

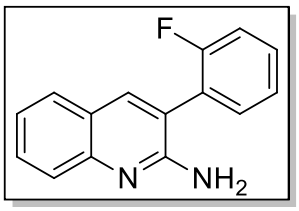
(100 MHz, $CDCl_3$) δ = 163.1 (d, *J* = 246.1 Hz), 155.1, 147.3, 139.8 (d, *J* = 7.6 Hz), 137.5, 130.8 (d, *J* = 8.4 Hz), 130.0, 127.6, 125.6, 124.7 (d, *J* = 2.8 Hz), 124.0, 123.8, 122.9, 116.1 (d, *J* = 21.6 Hz), 115.2 (d, *J* = 20.8 Hz); HR-MS (ESI) Calcd for $C_{15}H_{11}FN_2$ [M+H]: 239.0979, Found: 239.1004.

3-(3-Chlorophenyl)quinolin-2-amine (55o)



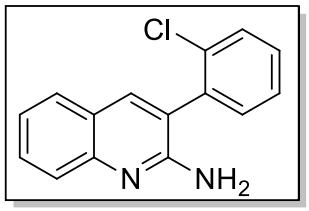
Reaction Time: 3 h; Yield: 79%; Melting Point: 113 – 115 °C; R_f: 0.22 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3623, 3009, 2984, 2335, 1748, 1448, 1262, 751, 670; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.49 (s, 1H), 7.42 – 7.34 (m, 3H), 7.25 – 7.21 (m, 1H), 5.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.0, 147.5, 139.6, 137.6, 135.2, 130.5, 130.1, 129.2, 128.5, 127.7, 127.2, 125.8, 124.1, 123.7, 123.0; HR-MS (ESI) Calcd for $C_{15}H_{11}ClN_2$ [M+H]: 255.0684, Found: 255.0691.

3-(2-Flourophenyl)quinolin-2-amine (55p)



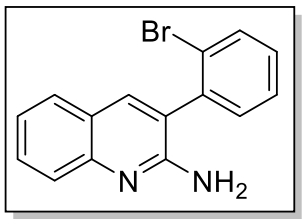
Reaction Time: 3 h; Yield: 41%; Melting Point: 159 – 161 °C; R_f: 0.23 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3581, 2989, 2367, 1651, 1490, 1272, 1007, 759, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.45 – 7.34 (m, 2H), 7.25 – 7.15 (m, 3H), 5.07 (s, 2H); ^{13}C NMR (176 MHz, $CDCl_3$) δ = 160.8 (d, *J* = 247.8 Hz), 155.3, 147.7, 138.7, 131.8 (d, *J* = 3.0 Hz), 130.5 (d, *J* = 7.9 Hz), 130.1, 127.7, 125.9, 124.9 (d, *J* = 3.9 Hz), 124.8, 123.9, 123.0, 118.9, 116.5 (d, *J* = 21.8 Hz); HR-MS (ESI) Calcd for $C_{15}H_{11}FN_2$ [M+H]: 239.0979, Found: 239.0991.

3-(2-Chlorophenyl)quinolin-2-amine (55q)



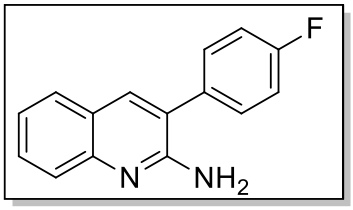
Reaction Time: 3 h; Yield: 57%; Melting Point: decomposed; R_f: 0.25 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3621, 3133, 2944, 2337, 1661, 1218, 764, 667; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.72 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.44 - 7.36 (m, 3H), 7.34 - 7.27 (m, 1H), 4.73 (s, 2H); ^{13}C NMR (176 MHz, $CDCl_3$) δ = 155.0, 147.7, 138.2, 136.1, 134.1, 131.9, 130.4, 130.11, 130.10, 127.8, 127.6, 126.0, 123.9, 123.0, 122.6; HR-MS (ESI) Calcd for $C_{15}H_{11}ClN_2$ [M+H]: 255.0684, Found: 255.0696.

3-(2-Bromophenyl)quinolin-2-amine (55r)



Reaction Time: 4 h; Yield: 58%; Melting Point: 195 – 197 °C; R_f: 0.27 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3636, 3006, 2979, 2360, 1490, 1279, 1265, 769, 747; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.85-7.67 (m, 3H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.47-7.35 (m, 2H), 7.35-7.20 (m, 2H), 4.85 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.0, 147.7, 138.1, 137.9, 133.5, 131.8, 130.2, 130.0, 128.2, 127.7, 125.9, 124.4, 124.1, 123.7, 122.9; HR-MS (ESI) Calcd for $C_{15}H_{11}BrN_2$ [M+H]: 299.0178, Found: 299.0199; 301.0158, Found: 301.0175.

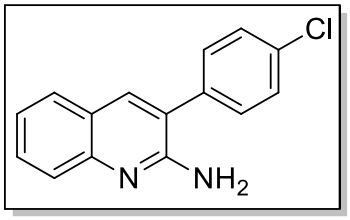
3-(4-Fluorophenyl)quinolin-2-amine (55s)



Reaction Time: 3 h; Yield: 68%; Melting Point: 201 – 203 °C; R_f: 0.25 in 20% in ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3431, 3125, 2999, 2367, 1644, 1440, 1270, 759, 648; ^1H NMR (700 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.72 - 7.60 (m, 2H), 7.59 - 7.42 (m, 3H), 7.29 – 7.13 (m, 3H), 4.99 (s, 2H); ^{13}C NMR (176 MHz, $CDCl_3$) δ = 162.8 (d, *J* = 247.6 Hz), 155.3, 147.4,

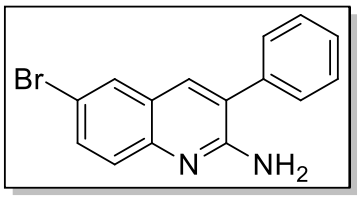
137.5, 133.7, 130.9 (d, *J* = 8.1 Hz), 129.9, 127.6, 125.8, 124.2 (d, *J* = 32.9 Hz), 123.04, 116.3 (d, *J* = 21.5 Hz); HR-MS (ESI) Calcd for $C_{15}H_{11}FN_2$ [M+H]: 239.0979, Found: 239.0991.

3-(4-Chlorophenyl)quinolin-2-amine (55t)



Reaction Time: 3 h; Yield: 71%; Melting Point: 201 – 203 °C; R_f: 0.20 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3622, 3439, 3120, 3000, 1645, 1435, 1270, 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.61-7.54 (m, 1H), 7.50-7.43 (m, 4H), 7.31-7.27 (m, 1H), 5.09 (s, 2H); ^{13}C NMR (176 MHz, $CDCl_3$) δ = 154.9, 146.2, 138.0, 135.6, 134.7, 130.4, 130.4, 129.6, 125.1, 123.99, 123.98, 123.4; HR-MS (ESI) Calcd for $C_{15}H_{11}ClN_2$ [M+H]: 255.0684, Found: 255.0650.

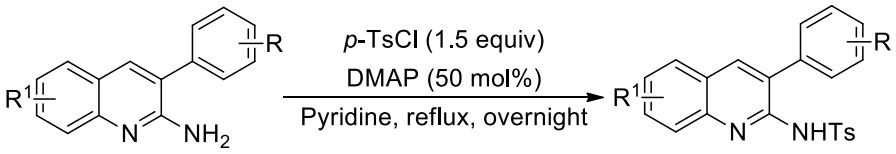
6-Bromo-3-phenylquinolin-2-amine (55u)



Reaction Time: 4 h; Yield: 62%; Melting Point: 130 – 132 °C

R_f: 0.23 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3745, 3629, 3009, 2989, 2342, 1736, 1564, 1283, 766, 748, 669; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (s, 1H), 7.66 (s, 1H), 7.62 – 7.57 (m, 1H), 7.56 – 7.47 (m, 5H), 7.46-7.41 (m, 1H), 5.13 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.6, 146.0, 137.2, 136.2, 132.9, 129.6, 129.4, 128.9, 128.6, 127.4, 126.0, 125.5, 115.7; HR-MS (ESI) Calcd for $C_{15}H_{11}BrN_2$ [M+H]: 300.1521, found: 300.1538.

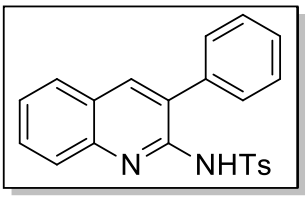
3.12.8. General Procedure for the Synthesis of tosylated derivastives of 2-amino-3-aryl quinolines 56



To the stirring suspension of corrresponding 2-amino-3-aryl quinoline **55** (1.0 equiv) in pyridine (10 mL), 4-dimethylaminopyridine (DMAP, 50 mol%) and *p*-toluenesulphonyl

chloride (1.5 equiv) was added and the reaction mixture was refluxed for overnight. . After complete consumption of the starting materials (monitored by TLC), pyridine was evaporated under reduced pressure and the crude products were purified by flash chromatography using EtOAc/hexanes as eluent.

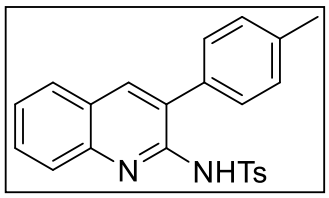
4-Methyl-*N*-(3-phenylquinolin-2-yl)benzenesulfonamide (56a)



Reaction Time: overnight; Yield: 78%; Melting Point: 168 – 170 °C

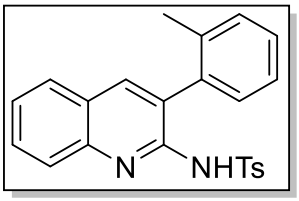
R_f: 0.29 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3637, 3000, 2362, 1630, 1541, 1361, 1270, 1074, 879, 761, 679; ^{1}H NMR (700 MHz, DMSO) δ = 12.13 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.74 – 7.64 (m, 1H), 7.49 (d, *J* = 7.7 Hz, 2H), 7.45 – 7.41 (m, 1H), 7.41 – 7.35 (m, 3H), 7.33 (d, *J* = 7.7 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ = 151.5, 142.1, 140.4, 135.9, 135.6, 131.9, 131.4, 129.3, 128.7, 128.6, 128.3, 128.0, 127.8, 125.6, 124.7, 121.1, 117.4, 20.9; HR-MS (ESI) Calcd for $C_{22}H_{18}N_2O_2S$ [M+H]: 375.1162, Found: 375.1158.

4-Methyl-*N*-(3-(*p*-tolyl)quinoline-2-yl)benzenesulfonamide (56b)



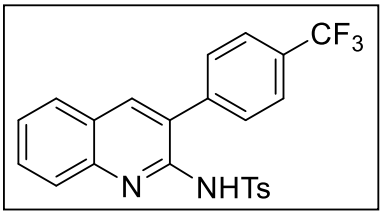
Reaction Time: overnight; Yield: 78%; Melting Point: 219 – 221 °C; R_f: 0.27 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3606, 3215, 2863, 2323, 1631, 1547, 1260, 1089, 767, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.09 (s, 1H), 8.15 (s, 1H), 7.90 (d, *J* = 7.4 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.77 (d, *J* = 7.1 Hz, 2H), 7.65 (t, *J* = 7.1 Hz, 1H), 7.45 – 7.26 (m, 5H), 7.17 - 7.15 (m, 2H), 2.32 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.9, 147.3, 138.7, 134.67, 134.65, 133.1, 132.9, 131.7, 130.5, 129.3, 128.8, 128.0, 127.1, 123.5, 122.9, 120.4, 21.1(2C); HR-MS (ESI) Calcd for $C_{23}H_{20}N_2O_2S$ [M+H]: 389.1318, Found: 389.1323.

4-Methyl-*N*-(3-(*o*-tolyl)quinolin-2-yl)benzenesulfonamide (56c)



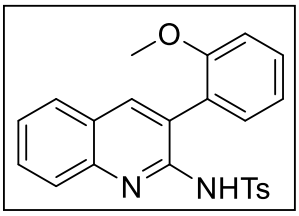
Reaction Time: overnight; Yield: 75%; Melting Point: 192 – 194 °C; R_f: 0.28 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3656, 3061, 3002, 2952, 2367, 1645, 1490, 1267, 763; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84 - 7.73 (m, 3H), 7.66 - 7.58 (m, 2H), 7.49 (s, 1H), 7.41 – 7.34 (m, 1H), 7.33 – 7.27 (m, 1H), 7.25 - 7.17 (m, 4H), 7.15 – 7.08 (m, 1H), 2.37 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 142.7, 140.1, 139.9, 137.1, 135.7, 131.3, 130.0, 129.9 (2C), 129.2 (3C), 128.54, 128.10 (2C), 126.4, 125.8, 124.8, 121.5, 21.6, 19.9; HR-MS (ESI) Calcd for $C_{23}H_{20}N_2O_2S$ [M+H]: 389.1318, Found: 389.1309.

4-Methyl-*N*-(3-(4-(trifluoromethyl)phenyl)quinolin-2-yl)benzenesulfonamide (56d)



Reaction Time: overnight; Yield: 73%; Melting Point: decomposed; R_f: 0.15 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3637, 3061, 2998, 2386, 1601, 1273, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.27 (s, 1H), 7.91 (s, 1H), 7.82 (d, *J* = 7.6 Hz, 2H), 7.72 – 7.59 (m, 6H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.27 (d, *J* = 7.2 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = Data was difficult to interpret due to the presence of two isomers; HR-MS (ESI) Calcd for $C_{23}H_{17}F_3N_2O_2S$ [M+H]: 443.1036, Found: 443.1001.

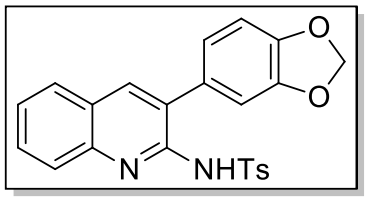
***N*-(3-(2-Methoxyphenyl)quinolin-2-yl)-4-methyl-benzenesulfonamide (56e)**



Reaction Time: overnight; Yield: 64%; Melting Point: decomposed; R_f: 0.25 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3674, 3004, 2693, 1630, 1280, 1079, 877, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.29 (s, 1H), 7.83 (s, 1H), 7.79 (d, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.25 – 7.16 (m, 3H), 6.97 (t, *J* = 7.2 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 3.48 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 157.3, 153.4, 142.3,

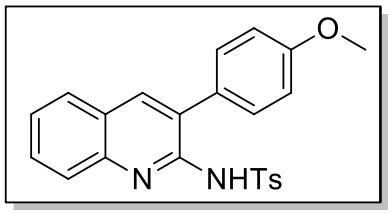
140.7, 140.5, 135.8, 131.7, 131.2, 131.1, 129.9, 129.2, 128.2, 126.2, 125.2, 124.6, 121.3, 120.5, 116.6, 110.8, 55.3, 21.6; HR-MS (ESI) Calcd for $C_{23}H_{20}N_2O_3S$ [M+H]: 405.1267, Found: 405.1283.

***N*-(3-(3,4-Methylenedioxyphenyl)quinolin-2-yl)-4-methylbenzenesulfonamide (56f)**



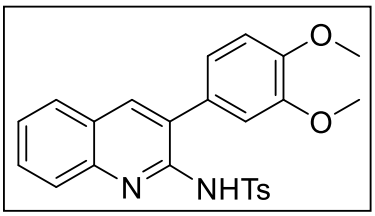
Reaction Time: overnight; Yield: 77%; Melting Point: 105 – 107 °C; R_f: 0.19 in 20% ethyl acetate in hexanes ; IR (KBr): ν (cm^{-1}) = 3484, 3009, 2982, 2345, 1609, 1277, 762, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.12 (s, 1H), 8.21 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 2H), 7.73 – 7.59 (m, 1H), 7.49 – 7.37 (m, 1H), 7.34 (d, *J* = 7.2 Hz, 2H), 7.08 – 6.89 (m, 3H), 6.05 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.4, 149.6, 147.7, 144.1, 140.5, 138.5, 136.1, 134.3, 133.9, 132.6, 131.7, 131.3, 130.7, 130.3, 129.1, 127.4, 125.8, 124.6, 113.4, 107.8, 104.1, 20.1; HR-MS (ESI) Calcd for $C_{23}H_{18}N_2O_4S$ [M+H]: 419.1060, Found: 419.1061.

***N*-(3-(4-Methoxyphenyl)quinolin-2-yl)-4-methylbenzenesulfonamide (56g)**



Reaction Time: overnight; Yield: 56%; Melting Point: decomposed; R_f: 0.25 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3623, 3058, 2994, 2362, 1631, 1371, 1269, 1076, 761, 675; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.26 (s, 1H), 7.85 (m, 3H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.44-7.37 (m, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 3.84 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.2, 151.7, 142.2, 140.4, 139.6, 135.4, 131.5, 131.2, 130.7, 129.4, 128.1, 128.0, 125.7, 124.7, 121.2, 117.4, 113.3, 55.2, 20.9; HR-MS (ESI) Calcd for $C_{23}H_{20}N_2O_3S$ [M+H]: 405.1267, Found: 405.1282.

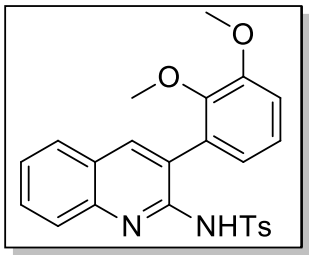
***N*-(3-(3-Dimethoxyphenyl)quinolin-2-yl)-4-methyl-benzenesulfonamide (56h)**



Reaction Time: overnight; Yield: 72%; Melting Point: decomposed; R_f: 0.32 in 20% ethyl acetate in hexanes

IR (KBr): ν (cm^{-1}) = 3684, 2999, 2352, 1628, 1267, 1072, 761, 677; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.59 (s, 1H), 8.14 (d, *J* = 8.1 Hz, 1H), 7.91 – 7.86 (m, 2H), 7.62 (d, *J* = 8.2 Hz, 3H), 7.32 (d, *J* = 8.2 Hz, 3H), 7.27 (s, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 3.86 (s, 3H), 3.63 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.6, 150.2, 148.8, 147.5, 138.8, 136.3, 133.2, 131.6, 129.3, 128.9, 128.7, 128.1, 127.0, 124.4, 123.5, 122.1, 120.4, 115.5, 112.7, 56.6, 21.2; HR-MS (ESI) Calcd for $C_{24}H_{22}N_2O_4S$ [M+H]: 435.1373, Found: 435.1399.

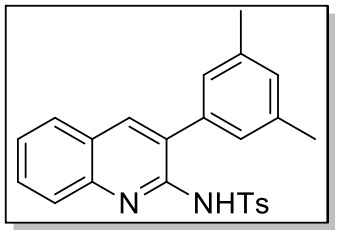
***N*-(3-(2,3-Dimethoxyphenyl)quinolin-2-yl)-4-methylbenzenesulfonamide (56i)**



Reaction Time: 4 h; Yield: 68%; Melting Point: 190 – 192 °C

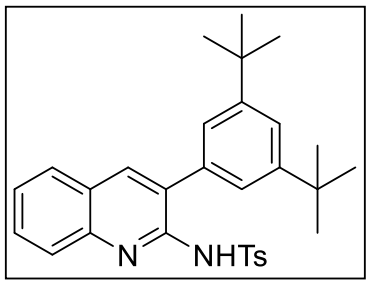
R_f: 0.23 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3671, 3009, 2982, 2362, 1628, 1556, 1277, 1260, 761; ^{1}H NMR (400 MHz, DMSO) δ = 12.09 (s, 1H), 8.10 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.76-7.65 (m, 4H), 7.47-7.40 (m, 1H), 7.28 (d, *J* =8.0 Hz, 2H), 7.11-7.04 (m, 2H), 6.78-6.72 (m, 1H), 3.83 (s, 3H), 3.49 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.5, 152.2, 146.4, 142.1, 140.8, 140.3, 135.8, 131.4, 130.5, 130.3, 129.2, 128.1, 125.8, 124.7, 123.5, 122.5, 120.8, 117.5, 113.2, 60.0, 55.7, 20.9; HR-MS (ESI) Calcd for $C_{24}H_{22}N_2O_4S$ [M+H]: 435.1373, Found: 435.1369.

***N*-(3-(3,5-Dimethylphenyl)quinolin-2-yl)-4-methylbenzenesulfonamide (56j)**



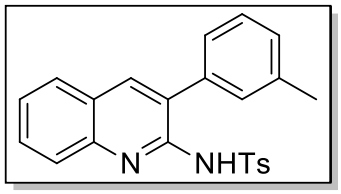
Reaction Time: overnight; Yield: 68%; Melting Point: decomposed; R_f: 0.35 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3606, 3254, 3011, 2986, 2362, 2345, 1636, 1274, 1081, 759, 670; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.12 (s, 1H), 8.18 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.70 – 7.62 (m, 1H), 7.46 – 7.37 (m, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.02 (s, 2H), 6.97 (s, 1H), 2.35 (s, 3H), 2.22 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.3, 142.0, 140.7, 140.0, 136.6, 135.7, 135.6, 132.2, 131.3, 129.4, 129.3, 128.2, 127.1, 125.6, 124.6, 121.1, 117.4, 20.9, 20.8; HR-MS (ESI) Calcd for $C_{24}H_{22}N_2O_2S$ [M+H]: 403.1475, Found: 403.1467.

***N*-(3-(3,5-Di-tert-butylphenyl)quinolin-2-yl)-4-methylbenzenesulfonamide (56k)**



Reaction Time: overnight; Yield: 61%; Melting Point: 154 – 156 °C; R_f: 0.25 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3641, 3016, 2360, 1748, 1629, 1364,1277, 1081, 751, 685; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.29 (s, 1H), 7.89 (s, 3H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.31 – 7.22 (m, 5H), 2.40 (s, 3H), 1.3 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.6, 150.3, 142.7, 140.2, 139.5, 134.9, 131.1, 129.4 (2C), 128.1, 126.5, 124.7, 123.8 (2C), 122.6, 121.7 (2C), 34.9, 31.5, 21.6.; HR-MS (ESI) Calcd for $C_{30}H_{34}N_2O_2S$ [M+H]:487.2414, Found: 487.2419.

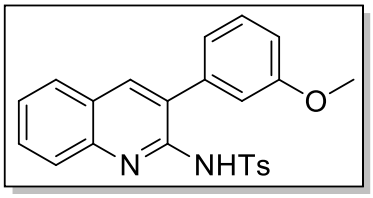
4-Methyl-*N*-(3-(*m*-tolyl)quinolin-2-yl)benzenesulfonamide (56l)



Reaction Time: overnight; Yield: 88%; Melting Point: 162 – 164 °C; R_f: 0.15 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3628, 3061, 2382, 1634, 1542, 1364, 1081, 955, 838, 677; ^{1}H

NMR (400 MHz, $CDCl_3$) δ = 12.13 (s, 1H), 8.22 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.73 – 7.64 (m, 1H), 7.47 – 7.37 (m, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.29 – 7.25 (m, 2H), 7.23 (s, 1H), 7.20 – 7.14 (m, 1H), 2.35 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.9, 156.2, 153.1, 148.4, 147.6, 141.2, 140.5, 139.4, 135.2, 133.1 131.9, 131.3, 130.5, 129.9(2C), 128.1, 126.5, 125.50, 124.1, 120.8, 119.5, 21.2, 20.0; HR-MS (ESI) Calcd for $C_{23}H_{20}N_2O_2S$ [M+H]: 389.1318, Found: 389.1313.

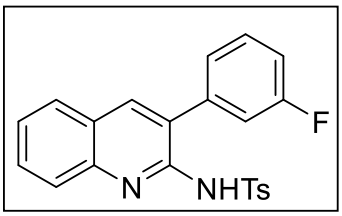
***N*-(3-(3-Methoxyphenyl)quinolin-2-yl)-4-methylbenzenesulfonamide (56m)**



Reaction Time: 4 h; Yield: 65%; Melting Point: decomposed

R_f: 0.31 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3595, 2994, 2354, 1633, 1551, 1270, 1074, 761; ^1H NMR (400 MHz, $CDCl_3$) δ = 12.14 (s, 1H), 8.27 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.49 – 7.40 (m, 1H), 7.33 (d, *J* = 8.4, 2H), 7.31 – 7.25 (m, 1H), 7.08 – 7.01 (m, 2H), 6.93 (d, *J* = 8.0 Hz, 1H), 3.64 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.6, 151.5, 142.2, 140.5, 140.5, 137.2, 135.7, 131.7, 131.5, 129.4, 128.9, 128.3, 125.7, 124.7, 121.6, 121.1, 117.4, 114.8, 114.1, 54.9, 20.9; HR-MS (ESI) Calcd for $C_{23}H_{20}N_2O_3S$ [M+H]: 405.1267, Found: 405.1272.

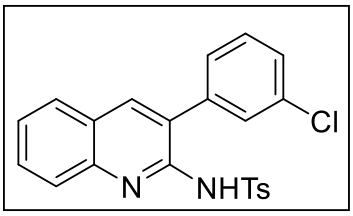
***N*-(3-(3-Fluorophenyl)quinolin-2-yl)-4-methyl-benzenesulfonamide (56n)**



Reaction Time: overnight; Yield: 68%; Melting Point: 185 – 187 °C; R_f: 0.20 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3634, 3012, 2987, 2335, 1756, 1653, 1277, 763; ^1H NMR (400 MHz, $CDCl_3$) δ = 12.27 (s, 1H), 7.90 (s, 1H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.69 - 7.60 (m, 2H), 7.47 – 7.32 (m, 3H), 7.31 - 7.21 (m, 4H), 7.06 (t, *J* = 7.8 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.6 (d, *J* = 243.6 Hz), 152.4, 142.8, 140.2, 140.0, 137.7 (d, *J* = 8.3 Hz), 135.7, 131.8, 129.6 (d, *J* = 9.3 Hz), 129.4 (3C), 128.4, 126.1, 125.2 (d, *J* = 2.9 Hz), 124.9,

121.2, 116.8 (d, *J* = 22.7 Hz), 115.4 (d, *J* = 20.9 Hz), 21.6; HR-MS (ESI) Calcd for $C_{22}H_{17}FN_2O_2S$ [M+H]: 393.1068, Found: 393.1072.

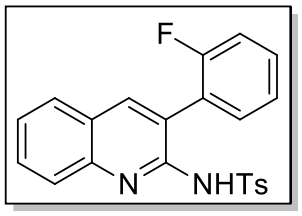
***N*-(3-(3-Chlorophenyl)quinolin-2-yl)-4-methyl-benzenesulfonamide (56o)**



Reaction Time: overnight; Yield: 63%

Melting Point: decomposed; R_f: 0.23 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3743, 3007, 2989, 2332, 1789, 1593, 1270, 1077, 753, 667; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.23 (s, 1H), 7.88 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.67 - 7.58 (m, 2H), 7.48 (s, 1H), 7.44 - 7.35 (m, 3H), 7.32 (t, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ = 151.1, 142.2, 141.0, 140.4, 137.9, 135.9, 132.4, 131.7, 130.3, 129.7, 129.4, 129.3, 128.5, 128.06, 127.96, 125.6, 124.8, 121.0, 117.6, 20.9; HR-MS (ESI) Calcd for $C_{22}H_{17}ClN_2O_2S$ [M+H]: 409.0772, Found: 409.0767.

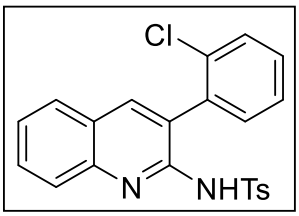
***N*-(3-(2-Fluorophenyl)quinolin-2-yl)-4-methylbenzenesulfonamide (56p)**



Reaction Time: overnight; Yield: 53%; Melting Point: decomposed

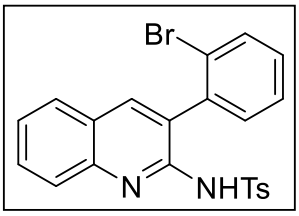
R_f: 0.21 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3631, 3247, 3061, 2920, 2357, 1639, 1599, 1366, 1270, 1084, 829, 685; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.10 (s, 1H), 8.25 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.49 – 7.32 (m, 5H), 7.30 (d, *J* = 7.6 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ = 160.0 (d, *J* = 245 Hz), 152.1, 142.6, 142.2, 140.7, 136.5, 132.2 (d, *J* = 13 Hz), 130.9 (d, *J* = 8 Hz), 129.7, 128.8, 128.0, 126.1, 125.3, 124.6, 124.4 (d, *J* = 15 Hz), 121.1, 118.1, 115.8 (d, *J* = 22 Hz), 21.4; HR-MS (ESI) Calcd for $C_{22}H_{17}FN_2O_2S$ [M+H]: 393.1068, Found: 393.0814.

***N*-(3-(2-Chlorophenyl)quinolin-2-yl)-4-methyl-benzenesulfonamide (56q)**



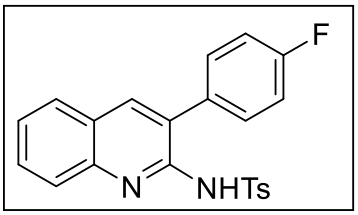
Reaction Time: overnight; Yield: 69%; Melting Point: decomposed; R_f: 0.23 in 20%in ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3748, 3012, 2989, 2335, 1739, 1277, 768, 667.; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.25 (s, 1H), 7.82 (s, 1H), 7.79 (d, *J* = 7.6 Hz, 2H), 7.67 – 7.59 (m, 2H), 7.49 – 7.35 (m, 3H), 7.34 - 7.25 (m, 3H), 7.21 (d, *J* = 8.0 Hz, 2H), 2.37 (s, 3H).; ^{13}C NMR (100 MHz, DMSO) δ = 152.2, 142.6, 141.8, 140.6, 136.6, 135.8, 133.4, 132.26, 132.13, 131.3, 130.4, 129.62, 129.51, 128.8, 127.5, 126.2, 125.3, 121.2, 118.2, 21.4; HR-MS (ESI) Calcd for $C_{22}H_{17}ClN_2O_2S$ [M+H]: 409.0772, Found: 409.0777

***N*-(3-(2-Bromophenyl)quinolin-2-yl)-4-methyl-benzenesulfonamide (56r)**



Reaction Time: overnight; Yield: 59%; Melting Point: 198 – 200 °C; R_f: 0.21 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3147, 3009, 2987, 2369, 1479, 1277, 768; ^{1}H NMR (400 MHz, DMSO) δ = 12.13 (s, 1H), 8.15 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.77 – 7.63 (m, 4H), 7.48 – 7.39 (m, 2H), 7.35 (d, *J* = 7.2 Hz, 2H), 7.28 (d, *J* = 6.8 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.7, 142.1, 141.1, 140.2, 137.3, 136.1, 132.4, 132.1, 131.8, 131.6, 130.0, 129.1, 128.3, 127.5, 125.8, 124.8, 123.4, 120.7, 117.7, 20.9; HR-MS (ESI) Calcd for $C_{22}H_{17}BrN_2O_2S$ [M+H]: 453.0267, Found: 453.0284; Calcd: 455.0247, Found: 455.0266.

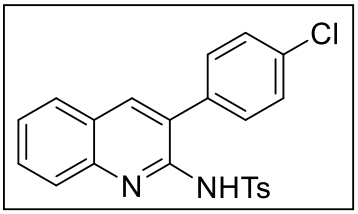
***N*-(3-(4-Fluorophenyl)quinolin-2-yl)-4-methylbenzenesulfonamide (56s)**



Reaction Time: overnight; Yield: 67%; Melting Point: 219 – 221 °C; R_f: 0.22 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3745, 3004, 2364, 1630, 1277, 1262, 753, 674; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.13 (s, 1H), 7.79 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.48 - 7.60 (m, 2H), 7.46 - 7.37 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H),

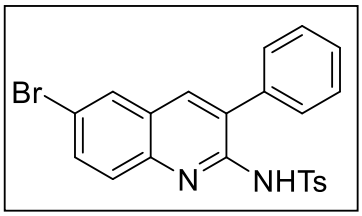
7.02 - 6.92 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.9 (d, *J* = 246.5 Hz), 152.6, 142.7, 140.2, 139.6, 135.6, 132.2, 131.7 (d, *J* = 3.4 Hz) 131.5, 131.4 (d, *J* = 8.2 Hz), 129.4, 128.3, 126.1, 124.9, 121.3, 116.6, 115.0 (d, *J* = 21.5 Hz), 21.6; HR-MS (ESI) Calcd for $C_{22}H_{17}FN_2O_2S$ [M+H]: 393.1068, Found: 393.1051.

***N*-(3-(4-Chlorophenyl)quinolin-2-yl)-4-methylbenzenesulfonamide (56t)**



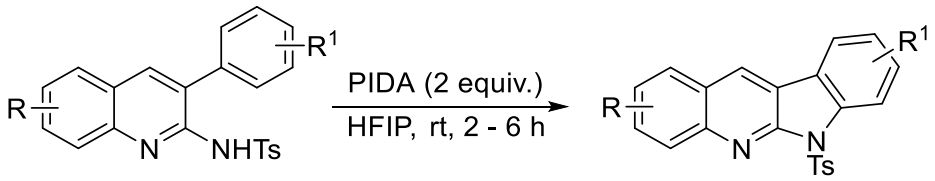
Reaction Time: overnight; Yield: 63%; Melting Point: 227 – 229 °C; R_f: 0.19 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3581, 3068, 2991, 2360, 1629, 1062, 1309, 1081, 764, 675; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.13 (s, 1H), 7.75 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.55 – 7.45 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.25 – 7.18 (m, 3H), 7.13 (d, *J* = 7.6 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ =151.8, 142.7, 141.1, 140.8, 136.3, 135.2, 133.4, 132.1, 131.7, 131.1, 129.9, 128.8, 128.3, 126.1, 125.2, 121.5, 118.0, 21.4; HR-MS (ESI) Calcd for $C_{22}H_{17}ClN_2O_2S$ [M+H]: 409.0772, Found: 409.0756.

***N*-(6-Bromo-3-phenylquinolin-2-yl)-4-methyl-benzenesulfonamide (56u)**



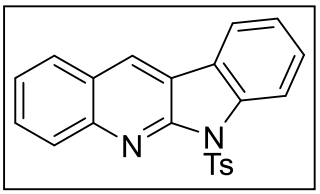
Reaction Time: overnight; Yield: 59%; Melting Point: decomposed; R_f: 0.22 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3664, 3059, 2997, 2332, 1789, 1593, 1270, 1077, 753, 667; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.25 (s, 1H), 7.81 (d, *J* = 4.0 Hz, 2H), 7.77 (s, 2H), 7.67 (d, *J* = 4.8 Hz, 1H), 7.53 - 7.35 (m, 5H), 7.32 – 7.21 (m, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.6, 142.8, 140.0, 138.1, 135.3, 134.6, 134.5, 134.3, 130.4, 129.6, 129.4, 128.8, 128.2, 126.2, 122.8, 118.1, 117.5, 21.6; HR-MS (ESI) Calcd for $C_{22}H_{17}BrN_2O_2S$ [M+H]: 453.0267, Found: 453.0285; Calcd: 455.0247, Found: 455.0266.

3.12.9. General Procedure for the C—H Functionalization of *N*-Ts-2-amino-3-arylquinoline for the Synthesis of Indolo fused quinoline 19a



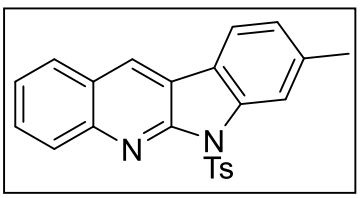
An oven-dried 8 mL reaction vial was charged with PIDA (2 equiv) and respective *N*-Ts quinolines (1 equiv) in HFIP (2.0 mL) and was stirred at room temperature for 2 - 6 h. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was purified by flash chromatography, using EtOAc/Hexanes as eluent.

6-Tosyl-6*H*-indolo[2,3-*b*]quinoline (19a)



Reaction Time: 2 h; Yield: 91%; Melting Point: 225 – 227 °C; R_f: 0.33 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3648, 3009, 2984, 2360, 2335, 1748, 1448, 1277, 752, 670; ^{1}H NMR (700 MHz, $CDCl_3$) δ = 8.55 (s, 1H), 8.50 (d, *J* = 8.4 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 7.7 Hz, 2H), 8.00 (d, *J* = 7.7 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.74 (t, *J* = 7.7 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (175 MHz, DMSO) δ = 150.8, 146.1, 146.0, 139.1, 135.2, 130.5, 130.3, 130.0, 129.2, 129.0, 128.7, 128.0, 126.0, 125.8, 124.9, 122.9, 122.6, 119.0, 114.9, 21.5; HR-MS (ESI) Calcd for $C_{22}H_{16}N_2O_2S$ [M+H]: 373.1005, Found: 373.1010.

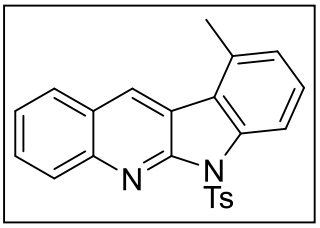
8-Methyl-6-tosyl-6*H*-indolo[2,3-*b*]quinoline (19b)



Reaction Time: 2 h; Yield: 95%; Melting Point: decomposed; R_f: 0.35 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3651, 3086, 3001, 2855, 1659, 1393, 1374, 1178, 811, 749; ^{1}H NMR (400 MHz, CD_2Cl_2) δ = 8.55 (s, 1H), 8.31 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* =

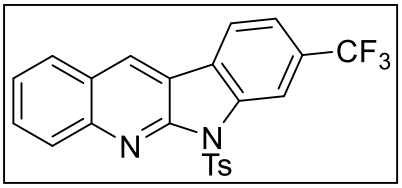
8.4 Hz, 2H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.79 - 7.72 (m, 1H), 7.57 – 7.51 (m, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 2.60 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ = 151.7, 146.5, 145.9, 140.6, 140.3, 136.2, 129.9, 129.8, 129.1, 128.6, 128.5, 127.3, 126.2, 125.7, 125.6, 121.4, 120.8, 119.9, 115.8, 22.8, 21.8; HR-MS (ESI) Calcd for $C_{23}H_{20}N_2O_2S$ [M+H]: 387.1162, Found: 387.1158.

10-Methyl-6-tosyl-6*H*-indolo[2,3-*b*]quinoline (19c)



Reaction Time: 2 h; Yield: 78%; Melting Point: decomposed; R_f: 0.37 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3519, 3115, 2721, 2362, 1651, 1557, 1279, 764, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.63 (s, 1H), 8.41 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 8.8 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.78 - 7.71 (m, 1H), 7.57 – 7.46 (m, 2H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 2.84 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.8, 145.0, 139.7, 135.9, 134.6, 129.8, 129.4 (2C), 129.0, 128.9 (2C), 128.34, 128.28, 125.7 (2C), 125.3, 121.3, 119.9, 112.7, 21.7, 21.0; HR-MS (ESI) Calcd for $C_{23}H_{18}N_2O_2S$ [M+H]: 387.1162, Found: 387.1171.

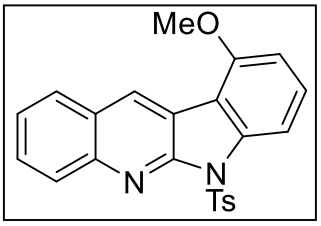
6-Tosyl-8-(trifluoromethyl)-6*H*-indolo[2,3-*b*]quinoline (19d)



Reaction Time: 5 h; Yield: 40%; Melting Point: decomposed above 200 °C; R_f: 0.33 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3675, 3009, 2979, 2335, 1753, 1272, 918, 762; ^{1}H NMR (700 MHz, $CDCl_3$) δ = 8.81 (s, 1H), 8.68 (s, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 7.7 Hz, 2H), 8.13 (d, *J* = 7.7 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.80 (t, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 151.2, 147.2, 145.6, 139.2, 135.5, 131.03 (q, *J* = 32.2 Hz), 130.3, 129.6 (2C), 129.3, 128.8, 128.51, 128.43, 125.76, 125.64, 124.2 (q, *J* = 270.9 Hz), 121.5, 120.8

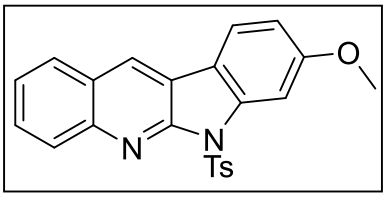
(q, *J* = 4.02 Hz), 117.9, 112.6 (q, *J* = 4.5 Hz), 21.8; HR-MS (ESI) Calcd for $C_{23}H_{15}F_3N_2O_2S$ [M+H]: 441.0879, Found: 441.0879.

10-Methoxy-6-tosyl-6*H*-indolo[2,3-*b*]quinoline (19e)



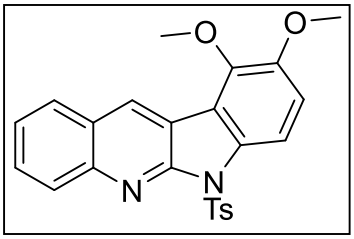
Reaction Time: 2 h; Yield: 48%; Melting Point: 243 – 245 °C; R_f: 0.31 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3628, 3013, 2360, 1743, 1379, 1275, 1099, 752, 667; ^{1}H NMR (700 MHz, $CDCl_3$) δ = 8.79 (s, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 7.7 Hz, 2H), 8.10 (d, *J* = 7.7 Hz, 1H), 7.94 (d, *J* = 7.7 Hz, 1H), 7.76 - 7.69 (m, 1H), 7.56 – 7.47 (m, 2H), 7.17 (d, *J* = 7.7 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 1H), 4.10 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 156.6, 150.6, 145.70, 145.07, 140.6, 135.9, 130.29, 130.08, 129.48, 129.13, 129.1, 128.3, 126.1, 125.2, 118.5, 114.0, 111.9, 107.7, 105.5, 55.9, 21.7; HR-MS (ESI) Calcd for $C_{23}H_{18}N_2O_3S$ [M+H]: 403.1111, Found: 403.1121.

9-Methoxy-6-tosyl-6*H*-indolo[2,3-*b*]quinoline (19g)



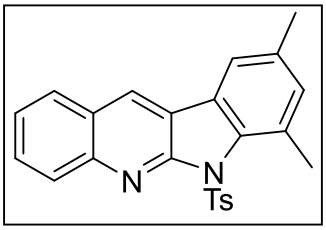
Reaction Time: 2 h; Yield: 60%; Melting Point: 211 – 213 °C; R_f: 0.39 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3566, 3006, 2969, 2394, 1740, 1443, 1373, 1274, 757, 672; ^{1}H NMR (700 MHz, DMSO-d_6) δ = 8.89 (s, 1H), 8.15 (d, *J* = 7.7 Hz, 1H), 8.13 – 8.07 (m, 3H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.91 (s, 1H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 1H), 3.95 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 160.7, 150.6, 145.5, 144.7, 140.0, 134.7, 129.8, 129.3, 128.22, 128.17, 127.6, 126.8, 125.50, 125.47, 123.0, 118.6, 115.3, 111.5, 99.8, 55.7, 21.0; HR-MS (ESI) Calcd for $C_{23}H_{18}N_2O_3S$ [M+H]: 403.1111, Found: 403.1129.

9,10-Dimethoxy-6-tosyl-6*H*-indolo[2,3-*b*]quinoline (19i)



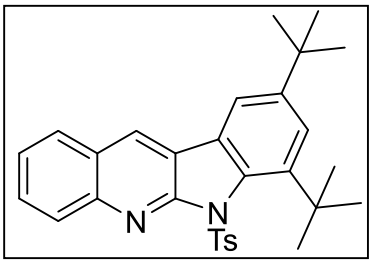
Reaction Time: 2 h; Yield: 65%; Melting Point: decomposed above 200 °C; R_f: 0.35 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3435, 3046, 2251, 1657, 1275, 1037, 824, 762, 628; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.98 (s, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 8.04 - 8.01 (m, 3H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 4.06 (s, 3H), 3.92 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.4, 147.4, 147.1, 146.7, 142.9, 138.5, 131.8, 131.7, 129.5, 128.4, 128.1, 127.74, 127.72, 127.6, 124.2, 119.8, 118.5, 117.1, 107.9, 60.6, 56.8, 21.1; HR-MS (ESI) Calcd for $C_{24}H_{20}N_2O_4S$ [M+H]: 433.1217, Found: 433.1240.

7,9-Dimethyl-6-tosyl-6*H*-indolo[2,3-*b*]quinoline (19j)



Reaction Time: 2 h ; Yield: 96%; Melting Point: decomposed; R_f: 0.39 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3571, 3053, 2982, 2365, 1691, 1386, 1272, 1084, 767, 675; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.80 (s, 1H), 8.01 - 7.7 (m, 2H), 7.84 – 7.73 (m, 2H), 7.60 (d, *J* = 7.6 Hz, 3H), 7.26 (s, 1H), 7.16 (d, *J* = 7.6 Hz, 2H), 2.65 (s, 3H), 2.42 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 154.2, 145.4, 144.7, 137.5, 135.3, 134.6, 133.3, 129.9, 129.28, 129.13, 128.45, 128.26, 128.0, 127.6, 126.7, 126.0, 121.1, 119.4, 21.5, 20.94, 20.69; HR-MS (ESI) Calcd for $C_{24}H_{20}N_2O_2S$ [M+H]: 401.1318, Found: 401.1321.

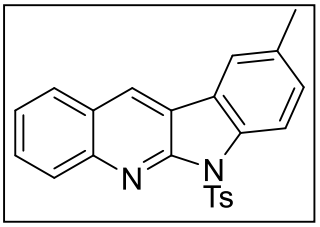
7,9-Di-tert-butyl-6-tosyl-6*H*-indolo[2,3-*b*]quinoline (19k)



Reaction Time: 6 h; Yield: 70% ; Melting Point: decomposed; R_f: 0.50 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3599, 3053, 2999, 2362, 1656, 1267, 762, 695; ^{1}H NMR (700 MHz, DMSO-d_6) δ = 8.68 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 1H),

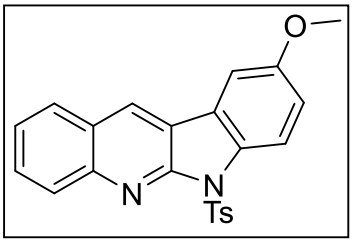
7.93 - 7.87 (m, 2H), 7.80 - 7.72 (m, 2H), 7.56 (s, 1H), 6.87 - 6.76 (m, 4H), 2.02 (s, 3H), 1.63 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (175 MHz, DMSO-d_6) δ = 156.1, 149.4, 145.4, 144.3, 143.8, 136.0, 131.9, 129.7, 129.3, 128.52, 128.33, 128.16, 127.9, 127.7, 127.3 (2C), 126.3, 123.1, 115.7, 37.3, 34.7, 32.3, 31.2, 20.7; HR-MS (ESI) Calcd for $C_{31}H_{34}N_2O_2S$ [M+H]: 485.2383, Found: 485.2390.

9-Methyl-6-tosyl-6*H*-indolo[2,3-*b*]quinoline (19l)



Reaction Time: 2 h; Yield: 87%; Melting Point: 171 – 173 °C; R_f: 0.35 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3646, 3123, 2925, 2347, 1661, 1178, 672.; Diastereomeric ratio: 2:1 (C9:C7); ^{1}H NMR (400 MHz, Acetone-d_6) δ = 8.90 (s, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 8.04 – 7.97 (m, 3H), 7.84 – 7.75 (m, 3H), 7.31 (d, *J* = 8.4 Hz, 2H), 2.50 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (175 MHz, DMSO-d_6) δ = 153.8, 150.5, 145.4, 144.7, 139.5, 134.7, 132.4, 129.9, 129.7, 129.3, 128.4, 128.2, 128.2, 127.6, 126.6, 126.0, 121.0, 119.2, 114.2, 21.7, 20.9.; HR-MS (ESI) Calcd for $C_{23}H_{18}N_2O_2S$ [M+H]: 387.1162, Found: 387.1155.

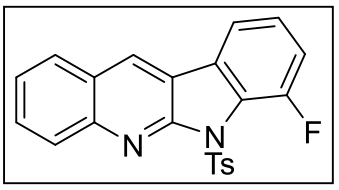
9-Methoxy-6-tosyl-6*H*-indolo[2,3-*b*]quinoline (19m)



Reaction Time: 2 h ; Yield: 60%; Melting Point: decomposed above 200 °C; R_f: 0.25 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3633, 3013, 2989, 2360, 2340, 1743, 1277, 767, 670; Diastereomeric ratio: 3:1 (C9:C7); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.51 (s, 1H), 8.38 (d, *J* = 9.1 Hz, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 8.1 Hz, 2H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.77 - 7.69 (m, 1H), 7.54 - 7.43 (m, 2H), 7.20 – 7.11 (m, 3H), 3.92 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.76, 152.1, 142.9, 138.4, 133.4, 131.3, 130.1, 129.35, 129.23, 129.1, 128.9, 128.6, 128.5, 128.4, 124.38, 124.23, 118.3,

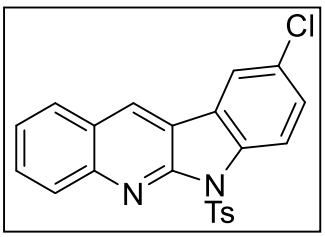
, 115.9, 110.6, 55.0, 20.1; HR-MS (ESI) Calcd for $C_{23}H_{18}N_2O_3S$ [M+H]: 403.1111, Found: 403.1123.

7-Fluoro-6-tosyl-6*H*-indolo[2,3-*b*]quinoline (19n)



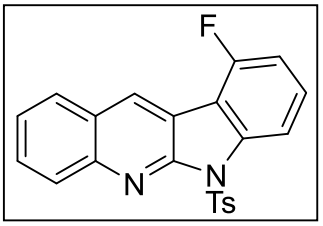
Reaction Time: 3 h; Yield: 72%; Melting Point: decomposed above 200 °C; R_f: 0.48 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3745, 3627, 2933, 1734, 1658, 1561, 1462, 1178, 672; Diastereomeric ratio: 1:1 (C9:C7); ^{1}H NMR (400 MHz, CD_2Cl_2) δ = 8.60 (s, 1H), 8.45 (dd, *J* = 9.2, 4.4 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.83 - 7.76 (m, 1H), 7.72 (dd, *J* = 8.0, 2.8 Hz, 1H), 7.60 – 7.53 (m, 1H), 7.38 - 7.29 (m, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ = 160.2 (d, *J* = 240.5 Hz) 151.8, 147.2, 146.1, 136.1 (d, *J* = 1.4 Hz) 135.9, 130.5, 130.0, 129.2, 128.9, 128.7, 128.5, 126.0, 124.7 (d, *J* = 9.4 Hz), 119.1 (d, *J* = 3.1 Hz), 116.9 (d, *J* = 4.5 Hz), 116.8, 116.7, 108.0 (d, *J* = 24.3 Hz), 21.8; HR-MS (ESI) Calcd for $C_{23}H_{17}FN_2O_2S$ [M+H]: 391.1037, Found: 391.0925.

9-Chloro-6-tosyl-6*H*-indolo[2,3-*b*]quinoline (19o)



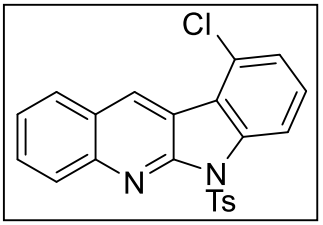
Reaction Time: 3 h; Yield: 70%; Melting Point: decomposed above 200 °C; R_f: 0.44 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3660, 3539, 2999, 2352, 1872, 1718, 1277, 769; Diastereomeric ratio: 1:1 (C9:C7); ^{1}H NMR (700 MHz, $CDCl_3$) δ = 8.53 (s, 1H), 8.43 (d, *J* = 9.1 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 2H), 7.96 (s, 1H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.76 (t, *J* = 7.7 Hz, 1H), 7.56 - 7.51 (m, 2H), 7.19 (d, *J* = 7.7 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 151.0, 146.8, 145.4 (2C), 137.9, 135.6, 130.0, 129.8, 129.6, 129.22, 129.20, 128.32, 128.28, 128.10, 125.6, 124.3, 121.1, 118.2, 116.4, 21.7; HR-MS (ESI) Calcd for $C_{22}H_{15}ClN_2O_2S$ [M+H]: 407.0616, Found: 407.0623.

10-Fluoro-6-tosyl-6*H*-indolo[2,3-*b*]quinoline (19p)



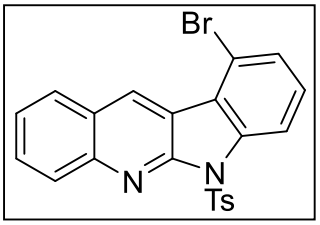
Reaction Time: 3 h; Yield: 60%; Melting Point: 217 – 219 °C; R_f: 0.47 in 20% ethyl acetate; IR (KBr): ν (cm^{-1}) = 3685, 3004, 2350, 2169, 1807, 1557, 1279, 769; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.71 (s, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 2H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.81 – 7.72 (m, 1H), 7.57 - 7.51 (m, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.11 (t, *J* = 8.8 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.0 (d, *J* = 246.7 Hz), 152.6, 142.6, 141.3, 140.1, 136.3, 131.9 (d, *J* = 2.8 Hz), 131.8, 130.4 (d, *J* = 8.2 Hz), 129.6, 128.3, 126.2, 124.8, 123.9 (d, *J* = 4.5 Hz), 123.5 (d, *J* = 14.6 Hz), 121.1, 117.0, 115.7 (d, *J* = 21.9 Hz), 21.6; HR-MS (ESI) Calcd for $C_{22}H_{15}FN_2O_2S$ [M+H]: 391.0911, Found: 391.0907.

10-Chloro-6-tosyl-6*H*-indolo[2,3-*b*]quinoline (19q)



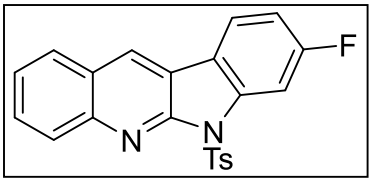
Reaction Time: 4 h; Yield: 72%; Melting Point: decomposed above 230 °C; R_f: 0.46 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3653, 2994, 2347, 1740, 1559, 1274, 980, 670; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.14 (s, 1H), 8.48 (d, *J* = 8.0 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.78 (t, *J* = 8.0 Hz, 1H), 7.58 - 7.49 (m, 2H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.5, 146.3, 145.4, 140.5, 135.6, 131.1, 130.0, 129.86, 129.56, 129.4, 129.0, 128.7, 128.4, 125.63, 125.49, 124.9, 120.5, 118.0, 113.4, 21.7; HR-MS (ESI) Calcd for $C_{24}H_{20}N_2O_2S$ [M+H]: 407.1289, Found: 407.1312.

10-Bromo-6-tosyl-6*H*-indolo[2,3-*b*]quinoline (19r)



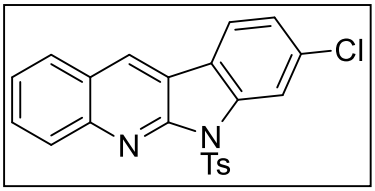
Reaction Time: 3 h; Yield: 70%; Melting Point: 250 – 252 °C; R_f: 0.39 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3663, 3415, 3004, 2704, 2268, 1698, 1279, 747; ^{1}H NMR (400 MHz, CD_2Cl_2) δ = 9.36 (s, 1H), 8.53 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 2H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.65 - 7.53 (m, 2H), 7.48 (t, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ = 150.98, 146.73, 146.21, 141.15, 135.90, 131.14, 130.66, 130.05, 129.96, 129.34, 128.95, 128.66, 128.60, 125.93, 125.81, 122.32, 119.11, 118.06, 114.27, 21.88; HR-MS (ESI) Calcd for $C_{22}H_{15}BrN_2O_2S$ [M+H]: 451.0110, Found: 451.0093; Calcd: 453.0091, Found: 453.0070.

8-Fluoro-6-tosyl-6*H*-indolo[2,3-*b*]quinoline (19s)



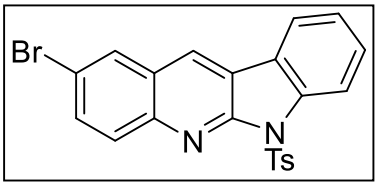
Reaction Time: 3 h; Yield: 75%; Melting Point: 233 – 235 °C; R_f: 0.45 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3623, 3058, 2982, 2365, 2332, 1604, 1485, 1265, 1106, 749, 670; ^{1}H NMR (400 MHz, CD_2Cl_2) δ = 8.58 (s, 1H), 8.25 – 8.18 (m, 2H), 8.15 (d, *J* = 8.4 Hz, 2H), 8.04 – 7.94 (m, 2H), 7.81 – 7.74 (m, 1H), 7.60 - 7.52 (m, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.20 - 7.12 (m, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ = 163.9 (d, *J* = 244.4 Hz) 151.8, 146.52, 146.24, 140.9 (d, *J* = 13.0 Hz), 136.0, 130.13, 130.04, 129.2, 128.7 (2C), 127.6, 126.26, 126.01, 122.9 (d, *J* = 10.1 Hz), 119.6, 119.1, 112.1 (d, *J* = 23.9 Hz), 103.5 (d, *J* = 29.8 Hz), 21.9; HR-MS (ESI) Calcd for $C_{22}H_{15}FN_2O_2S$ [M+H]: 391.0911, Found: 391.0901.

8-Chloro-6-tosyl-6*H*-indolo[2,3-*b*]quinoline (19t)



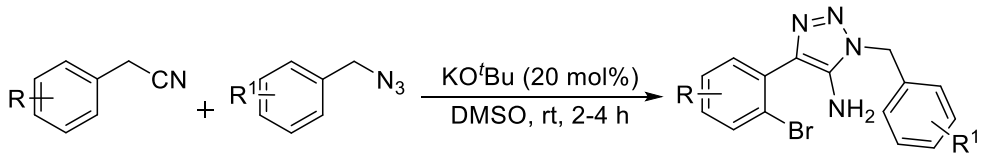
Reaction Time: 3 h; Yield: 70%; Melting Point: 251 – 253 °C; R_f: 0.48 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3559, 3120, 2972, 2169, 1594, 1272, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.54 (s, 1H), 8.53 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 2H), 7.95 - 7.89 (m, 2H), 7.79 – 7.72 (m, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.39 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.0, 146.6, 145.5, 140.0, 135.6, 135.1, 129.8, 129.6, 129.2, 128.4, 128.2, 127.6, 125.69, 125.60, 124.5, 121.9, 121.3, 118.4, 115.6, 21.8; HR-MS (ESI) Calcd for $C_{22}H_{15}ClN_2O_2S$ [M+H]: 407.0616, Found: 407.0608.

2-Bromo-6-tosyl-6*H*-indolo[2,3-*b*]quinoline (19u)

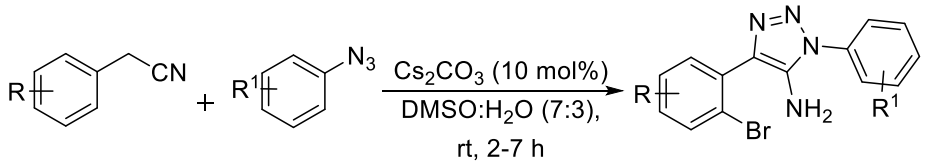


Reaction Time: 4 h; Yield: 69%; Melting Point: 284 – 286 °C; R_f: 0.39 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3012, 2989, 2362, 2340, 1734, 1655, 1507, 1364, 1275, 1171, 758, 669; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.50 (d, *J* = 8.4 Hz, 1H), 8.46 (s, 1H), 8.16 - 8.08 (m, 3H), 8.07 (d, *J* = 2.0 Hz, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.79 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.65 – 7.57 (m, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ = 151.2, 145.30, 145.08, 139.9, 135.8, 132.8, 130.8, 130.0, 129.81, 129.56, 128.2, 126.8, 126.3, 124.2, 122.4, 121.4, 120.0, 118.9, 115.3, 21.7; HR-MS (ESI) Calcd for $C_{23}H_{17}BrN_2O_2S$ [M+H]: 451.0236, Found: 451.0110, Calcd: 453.0216, Found: 453.0091.

3.12.10. General Procedure for the Synthesis of 5-amino-4-aryl triazoles 69 & 70

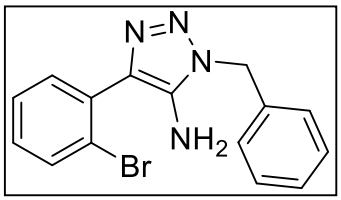


To a stirring suspension of KO^{t}Bu (20 mol%) in DMSO (2.0 mL) at 0 ^{o}C was added dropwise the corresponding benzyl azide (1.1 equiv.) in DMSO (2 .0 mL). After being further stirred, a solution of corresponding aryl acetonitrile (1.0 equiv.) in DMSO (2.0 mL) was added to the reaction mixture at 0 ^{o}C and followed by further stirring for 2 – 4 h at rt. After complete consumption of the starting materials (monitored by TLC), the reaction mixture was quenched with water 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.



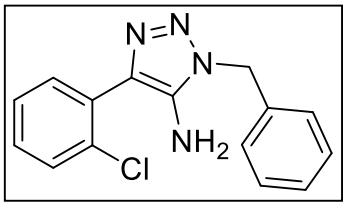
To a stirring suspension of Cs_2CO_3 (10 mol%) in DMSO:H_2O (2.0 mL) at 0 ^{o}C was added dropwise the corresponding benzylazide (1.1 equiv.) in DMSO:H_2O (2 .0 mL). After being further stirred, a solution of corresponding benzylnitrile (1.0 equiv.) in DMSO (2.0 mL) was added to the reaction mixture at 0 ^{o}C and followed by further stirring for 2 – 7 h at rt. After complete consumption of the starting materials (monitored by TLC), the reaction mixture was quenched with water 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.

1-Benzyl-4-(2-bromophenyl)-1*H*-1,2,3-triazol-5-amine (69a)



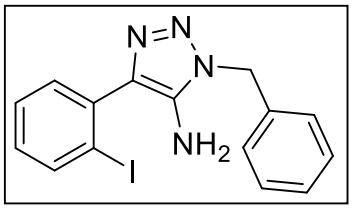
Reaction Time: 2 h; Yield: 55%; Melting Point: 92 – 95 ºC; R_f: 0.25 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3455, 2942, 1922, 1723, 1627, 1356, 1215, 893, 539; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 8.0 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.40 - 7.34 (m, 2H), 7.33 – 7.23 (m, 4H), 5.55 (s, 2H), 5.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.8, 136.3, 132.8, 132.7, 132.1, 129.3, 128.4, 127.6, 127.45, 127.44, 127.3, 123.2, 48.5; HR-MS (ESI) Calcd for $C_{15}H_{13}BrN_4$ [M+H]: 329.0396, found: 329.0356.

1-Benzyl-4-(2-chlorophenyl)-1*H*-1,2,3-triazol-5-amine (69b)



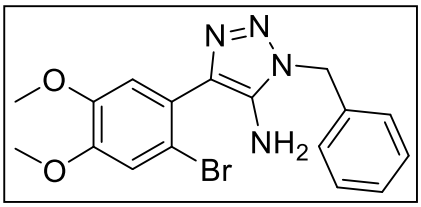
Reaction Time: 3 h; Yield: 83%, white solid; Melting Point: 84 - 86 ºC; R_f: 0.18 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3854, 3742, 3626, 2999, 2360, 1718, 1683, 1269, 759.; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.56 – 7.51 (m, 1H), 7.49 – 7.44 (m, 1H), 7.42 – 7.34 (m, 4H), 7.33 – 7.24 (m, 3H), 5.67 (s, 2H), 5.45 (s, 2H).; ^{13}C NMR (100 MHz, DMSO-d_6) δ = 140.3, 136.4, 132.5, 131.8, 130.9, 129.7, 129.0, 128.6, 127.6, 127.4, 127.1, 126.0, 48.6.; HR-MS (ESI) Calcd for $C_{15}H_{13}ClN_4$ [M+H]: 285.0902, found: 285.0906.

1-Benzyl-4-(2-iodophenyl)-1*H*-1,2,3-triazol-5-amine (69c)



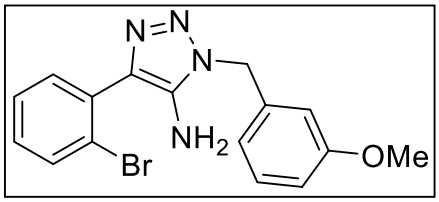
Reaction Time: 3 h; Yield: 82%; Melting Point: 120 – 122 °C; R_f: 0.23 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3720, 3608, 2998, 2343, 1760, 1655, 1365, 1265, 759.; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 8.0 Hz, 1H), 7.48 - 7.41 (m, 1H), 7.39 - 7.28 (m, 4H), 7.25 (d, *J* = 6.8 Hz, 2H), 7.15 - 7.08 (m, 1H), 5.60 (s, 2H), 5.44 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 139.6, 139.2, 136.8, 136.5, 131.5, 130.3, 129.5, 128.6, 128.2, 127.5, 127.3, 100.4, 48.5.; HR-MS (ESI) Calcd for $C_{15}H_{13}IN_4$ [M+H]: 377.0258, found: 377.0268.

1-Benzyl-4-(2-bromophenyl-4,5-dimethoxy)-1*H*-1,2,3-triazol-5-amine (69d)



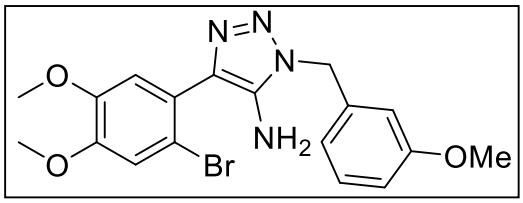
Reaction Time: 3 h; Yield: 62%; Melting Point: 137 – 138 ºC; R_f: 0.22 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3490, 2978, 1917, 1733, 1376, 1208, 1027, 885, 523; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.29 (m, 3H), 7.27 – 7.22 (m, 2H), 7.04 (s, 1H), 7.03 (s, 1H), 5.45 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.62 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.7, 148.6, 137.8, 134.4, 132.1, 129.3, 128.6, 127.3, 124.4, 115.3, 114.7, 112.7, 56.3, 56.2, 50.8; HR-MS (ESI) Calcd for $C_{17}H_{17}BrN_4O_2$ [M+H]: 389.0608, found: 389.0599; [M+2]: 391.0588, found: 391.0578.

4-(2-Bromophenyl)-1-(3-methoxybenzyl)-1*H*-1,2,3-triazol-5-amine (69e)



Reaction Time: 2 h; Yield: 40%; Melting Point: 137 - 140 ºC; R_f: 0.18 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3459, 2978, 1729, 1452, 1271, 1152, 826, 519.; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 (d, *J* = 7.2 Hz, 1H), 7.55 - 7.49 (m, 1H), 7.40 - 7.33 (m, 1H), 7.30 – 7.18 (m, 2H), 6.89 - 6.80 (m, 2H), 6.76 (s, 1H), 5.42 (s, 2H), 3.75 (s, 3H), 3.64 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.4, 138.1, 135.9, 133.0, 132.6, 132.3, 131.9, 130.4, 129.9, 127.8, 122.7, 119.4, 114.3, 112.6, 55.4, 50.7; HR-MS (ESI) Calcd for $C_{16}H_{15}BrN_4O$ [M+H]: 359.0502, found: 359.0498; [M+2]: 361.0482, found: 361.0477.

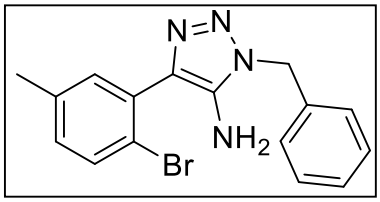
4-(2-Bromo-4,5-dimethoxyphenyl)-1-(3-methoxybenzyl)-1*H*-1,2,3-triazol-5-amine (69f)



Reaction Time: 3 h; Yield: 30%; Melting Point: 162 – 163 ºC; R_f: 0.05 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3629, 3023, 2977, 2359, 1741, 1696, 1368, 1221, 1033, 668; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (t, *J* = 8.0 Hz, 1H), 7.05 (s, 2H), 6.90 - 6.81 (m, 2H), 6.78 (s, 1H), 5.44 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H),

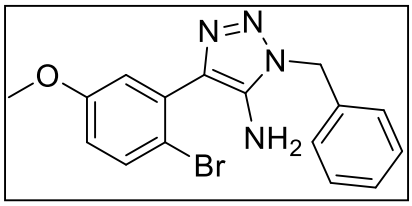
3.77 (s, 3H), 3.56 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.4, 149.8, 148.6, 137.8, 135.9, 132.2, 130.4, 124.4, 119.4, 115.3, 114.7, 114.3, 112.72, 112.68, 56.3, 56.2, 55.4, 50.9; HR-MS (ESI) Calcd for $C_{18}H_{19}BrN_4O_3$ [M+H]: 419.0713, found: 419.0715, Calcd: 421.0694, found: 421.0693

1-Benzyl-4-(2-bromo-5-methylphenyl)-1*H*-1,2,3-triazol-5-amine (69g)



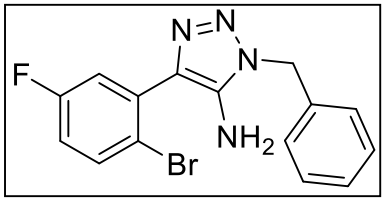
Reaction Time: 2 h; Yield: 60%; Melting Point: 108 - 111 ºC; R_f: 0.21 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3456, 3014, 2972, 2947, 2149, 1741, 1438, 1371, 1220, 899, 531; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43 (d, *J* = 8.4 Hz, 1H), 7.35 - 7.25 (m, 4H), 7.20 (d, *J* = 6.8 Hz, 2H), 7.04 - 6.95 (m, 1H), 5.41 (s, 2H), 3.57 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 137.9, 137.8, 134.4, 133.3, 132.8, 132.4, 131.9, 130.8, 129.4, 128.6, 127.3, 119.2, 50.9, 20.9; HR-MS (ESI) Calcd for $C_{16}H_{15}BrN_4$ [M+H]: 343.0553, found: 343.0568, [M+2]: 345.0533, found: 345.0550.

1-Benzyl-4-(2-bromo-5-methoxyphenyl)-1*H*-1,2,3-triazol-5-amine (69h)



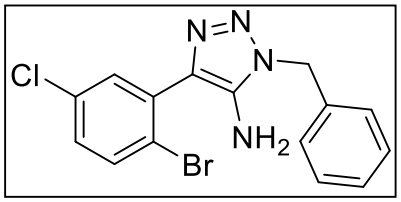
Reaction Time: 2 h; Yield: 78%; Melting Point: 124 – 126 ºC; R_f: 0.24 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3477, 3142, 2978, 1916, 1730, 1628, 1351, 1221, 1029, 829, 541; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 (d, *J* = 8.8 Hz, 1H), 7.42 – 7.30 (m, 3H), 7.29 – 7.24 (m , 2H), 7.09 (d, *J* = 3.2 Hz, 1H), 6.80 (dd, *J* = 9.0, 3.2 Hz, 1H), 5.47 (s, 2H), 3.80 (s, 3H), 3.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.0, 138.1, 134.4, 133.6, 133.0, 131.8, 129.2, 128.5, 127.3, 116.9, 116.7, 112.9, 55.6, 50.7; HR-MS (ESI) Calcd for $C_{16}H_{15}BrN_4O$ [M+H]: 359.0502, found: 359.0503; [M+2]: 361.0482, found: 361.0482.

1-Benzyl-4-(2-bromo-5-fluorophenyl)-1*H*-1,2,3-triazol-5-amine (69i)



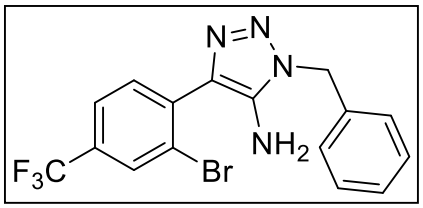
Reaction Time: 2 h; Yield: 88%; jelly; R_f: 0.29 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3859, 3742, 3631, 3317, 2999, 2359, 1733, 1635, 1506, 1265, 668; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 (dd, *J* = 8.8, 5.6 Hz, 1H), 7.40 – 7.29 (m, 3H), 7.28 - 7.19 (m, 3H), 6.99 - 6.89 (m, 1H), 5.44 (s, 2H), 3.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.9 (d, *J* = 246.4 Hz), 138.2, 134.3 (d, *J* = 8.2 Hz) 134.24, 134.17, 130.9 (d, *J* = 1.7 Hz), 129.3, 128.7, 127.3, 119.3 (d, *J* = 23 Hz), 117.1 (d, *J* = 22.3 Hz), 116.6 (d, *J* = 3.2 Hz) 50.8;HR-MS (ESI) Calcd for $C_{15}H_{12}BrFN_4$ [M+H]: 347.0302, found: 347.0306, Calcd: 349.0282, found: 349.0281

1-Benzyl-4-(2-bromo-5-chlorophenyl)-1*H*-1,2,3-triazol-5-amine (69j)



Reaction Time: 2 h; Yield: 90%; jelly; R_f: 0.27in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3480, 3202, 2962, 1917, 1720, 1634, 1354, 1221, 1028, 814, 541; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51 (d, *J* = 8.8 Hz, 2H), 7.39 – 7.28 (m, 3H), 7.22 (d, *J* = 7.2 Hz, 2H), 7.17 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.43 (s, 2H), 3.79 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 138.4, 134.1, 134.1, 133.8, 133.6, 132.2, 130.3, 129.7, 129.2, 128.5, 127.2, 120.4, 50.6; HR-MS (ESI) Calcd for $C_{15}H_{12}BrClN_4$ [M+H]: 363.0007, found: 363.0001; Calcd: 364.9986, found: 364.9983

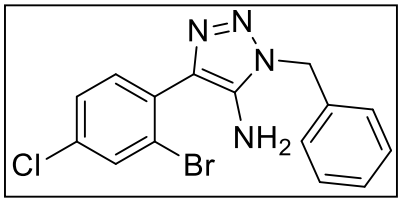
1-Benzyl-4-(2-bromo-4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-5-amine (69k)



Reaction Time: 3 h; Yield: 51%; Melting Point: 80 – 83 ºC; R_f: 0.15 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3853, 3779, 3626, 3006, 2986, 2692, 2343, 1767, 1648, 1316, 1277, 749; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.89 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.44 - 7.33 (m, 3H), 7.27 (d, *J* = 7.2 Hz, 2H), 5.48 (s, 2H), 3.64

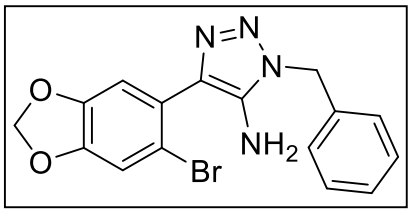
(s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 140.6, 137.3, 136.3, 132.7, 129.6 (q, *J* = 3.7 Hz), 129.5 (q, *J* = 32.2 Hz), 128.6, 127.6, 127.4, 126.2, 123.4 (q, *J* = 270.8 Hz), 124.4 (q, *J* = 3.6 Hz), 123.4, 48.6; HR-MS (ESI) Calcd for $C_{16}H_{12}BrF_3N_4$ [M+H]: 397.0270, found: 397.0268; Calcd: 399.0250, found: 399.0249

1-Benzyl-4-(2-bromo-4-chlorophenyl)-1*H*-1,2,3-triazol-5-amine (69l)



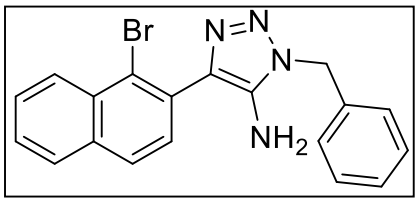
Reaction Time: 2 h; Yield: 85%; jelly; R_f: 0.28 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3467, 3141, 3026, 2978, 1917, 1743, 1634, 1371, 1218, 1029, 831, 511; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.41 - 7.33 (m, 4H), 7.27 - 7.22 (m, 2H), 5.46 (s, 2H), 3.60 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 138.1, 134.9, 134.2, 133.3, 132.7, 131.00, 130.97, 129.4, 128.7, 128.1, 127.3, 122.9, 50.9; HR-MS (ESI) Calcd for $C_{15}H_{12}BrClN_4$ [M+H]: 363.0007, found: 363.0005; [M+2]: 364.9986, found: 364.9982.

1-Benzyl-4-(6-bromobenzo[*d*][1,3]dioxol-5-yl)-1*H*-1,2,3-triazol-5-amine (69m)



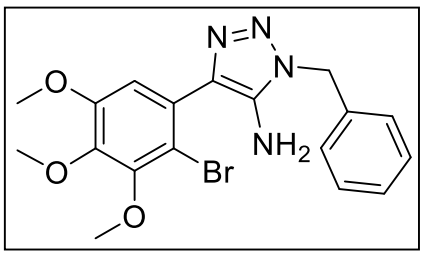
Reaction Time: 3 h; Yield: 31%; Melting Point: 105 – 107 ºC; R_f: 0.23 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3466, 3189, 2978, 1918, 1744, 1628, 1364, 1220, 1029, 901, 834, 528; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 – 7.30 (m, 3H), 7.27 – 7.21 (m, 2H), 7.06 (s, 1H), 6.99 (s, 1H), 6.00 (s, 2H), 5.46 (s, 2H), 3.50 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 147.9, 147.0, 139.9, 136.4, 128.62, 128.57, 127.6, 127.4, 125.9, 114.4, 112.5, 111.5, 102.0, 48.5; HR-MS (ESI) Calcd for $C_{16}H_{13}BrN_4O_2$ [M+H]: 373.0295, found: 373.0291; [M+2]: 375.0275, found: 375.0270.

1-Benzyl-4-(1-bromonaphthalen-2-yl)-1*H*-1,2,3-triazol-5-amine (69n)



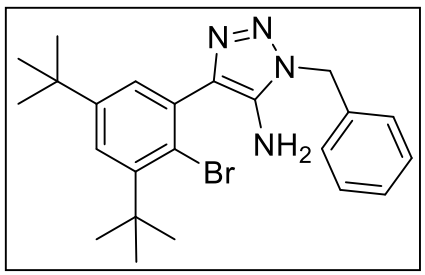
Reaction Time: 4 h; Yield: 58%; Melting Point: 127 – 129 ºC; R_f: 0.28 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3413, 3160, 2969, 1917, 1743, 1635, 1404, 1221, 1027, 826, 576; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (d, *J* = 8.4 Hz, 1H), 8.01 (t, *J* = 8.6 Hz, 2H), 7.71 (t, *J* = 7.4 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.43 - 7.36 (m, 2H), 7.35 - 7.27 (m, 3H), 5.64 (s, 2H), 5.49 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.1, 136.3, 133.4, 131.9, 131.3, 129.1, 128.50, 128.46, 128.2, 127.8, 127.49, 127.46, 127.3, 127.0, 126.7, 122.8, 48.5; HR-MS (ESI) Calcd for $C_{19}H_{15}BrN_4$ [M+H]: 379.0553, found: 379.0576; Cald: 381.0533, found: 381.0557.

1-Benzyl-4-(2-bromophenyl-3,4,5-dimethoxy)-1*H*-1,2,3-triazol-5-amine (69o)



Reaction Time: 4 h; Yield: 42%; Melting Point: 164 – 166 ºC; R_f: 0.20 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3655, 3566, 2977, 1394, 1221, 581; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43 – 7.29 (m, 3H), 7.28 – 7.24 (m, 2H), 6.92 (s, 1H), 5.46 (s, 2H), 3.90 (s, 6H), 3.86 (s, 3H), 3.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.1, 151.1, 143.3, 137.8, 134.3, 132.3, 129.4, 128.7, 127.8, 127.3, 111.1, 109.2, 61.2, 61.2, 56.3, 50.9; HR-MS (ESI) Calcd for $C_{18}H_{19}BrN_4O_3$ [M+H]: 419.0713, found: 419.0715, [M+2]: 421.0694, found: 421.0694.

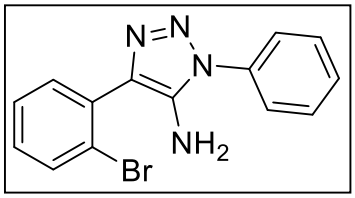
1-Benzyl-4-(2-bromophenyl-3,5-di-*tert*-butylphenyl)-1*H*-1,2,3-triazol-5-amine (69p)



Reaction Time: 4 h; Yield: 55%; Melting Point: decomposed; R_f: 0.41 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3510, 3033, 2968, 2950, 2130, 1810, 1450, 1398, 1267, 933, 630, 525; ^{1}H NMR (400 MHz,

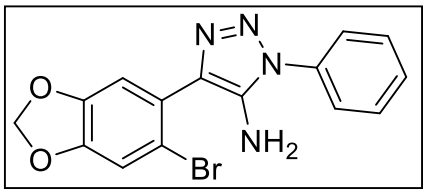
$CDCl_3$) δ = 7.53 (m, 1H), 7.38 (m, 3H), 7.34 (m, 1H), 7.29 (d, *J* = 6.8 Hz, 2H), 5.49 (s, 2H), 3.41 (s, 2H), 1.55 (s, 9H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.1, 146.3, 145.9, 137.5, 134.2, 130.2, 129.4, 128.1, 126.3, 124.8, 122.6, 107.5, 51.2, 38.3, 37.1, 34.8, 33.2; HR-MS (ESI) Calcd for $C_{18}H_{19}BrN_4O_3$ [M+H]: 442.2457, found: 442.2478.

4-(2-Bromophenyl)-1-phenyl-1*H*-1,2,3-triazol-5-amine (70a)



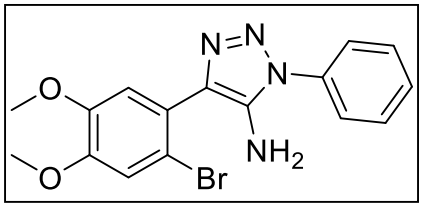
Reaction Time: 2 h; Yield: 53%; Melting Point: 85 – 87 ºC; R_f: 0.25 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3853, 3308, 2972, 2343, 1958, 1736, 1652, 1368, 1276, 896, 764, 678; ^{1}H NMR (400 MHz, DMSO) δ = 7.75 (d, *J* = 8.0 Hz, 1H), 7.71 – 7.65 (m, 2H), 7.62 (t, *J* = 7.2 Hz, 2H), 7.57 – 7.43 (m, 3H), 7.38 – 7.30 (m, 1H), 5.60 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.9, 135.7, 133.0, 132.4 (2C), 129.7 (2C), 128.7, 128.1, 127.7, 124.0, 123.5. (Two carbon missing); HR-MS (ESI) Calcd for $C_{14}H_{11}BrN_4$ [M+H]: 315.0240, found: 315.0454; Calcd: 317.0220, found: 317.0436.

4-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)-1-phenyl-1*H*-1,2,3-triazol-5-amine (70b)



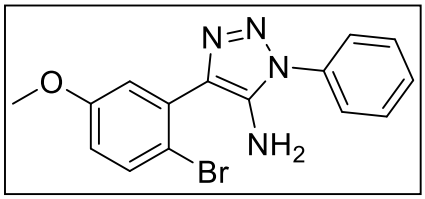
Reaction Time: 3 h; Yield: 42%; Melting Point: 146 – 148 ºC; R_f: 0.22 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3527, 3159, 2978, 1917, 1720, 1452, 1358, 1272, 1205, 1030, 827, 523; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 – 7.43 (m, 5H), 7.09 (s, 1H), 7.04 (s, 1H), 6.03 (s, 2H), 4.00 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.9, 147.8, 137.9, 135.4, 130.3, 130.0, 129.5, 125.3, 124.4, 113.8, 112.9, 112.0, 102.2; HR-MS (ESI) Calcd for $C_{15}H_{11}BrN_4O_2$ [M+H]: 359.0138, found: 359.0104; [M+2] Calcd: 361.0118, found: 361.0084.

4-(2-Bromo-4,5-dimethoxyphenyl)-1-phenyl-1*H*-1,2,3-triazol-5-amine (70c)



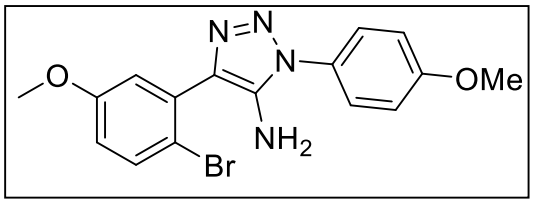
Reaction Time: 2 h; Yield: 65%; Melting Point: 152 – 155 ºC; R_f: 0.22 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3456, 3197, 2978, 2960, 1917, 1717, 1634, 1367, 1211, 830, 528; ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 7.7 Hz, 2H), 7.58 (t, *J* = 7.7 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.12 (s, 1H), 7.10 (s, 1H), 4.03 (s, 2H), 3.91 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ = 149.9, 148.8, 137.9, 135.5, 130.5, 130.1, 129.5, 124.5, 124.4, 115.5, 114.9, 112.7, 56.4, 56.3; HR-MS (ESI) Calcd for $C_{16}H_{15}BrN_4O_2$ [M+H]: 375.0451, found: 375.0476; [M+2] Calcd: 377.0431, found: 377.0457.

4-(2-Bromo-5-methoxyphenyl)-1-phenyl-1*H*-1,2,3-triazol-5-amine (70d)



Reaction Time: 2 h; Yield: 75%; Melting Point: 104 – 106 ºC; R_f: 0.24 in 30% in ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3470, 3160, 2978, 1922, 1733, 1404, 1221, 1022,826, 536; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 – 7.62 (m, 2H), 7.58 (t, *J* = 7.6 Hz, 2H), 7.55 – 7.47 (m, 2H), 7.16 (d, *J* = 3.2 Hz, 1H), 6.84 (dd, J = 8.8, 3.2 Hz, 1H), 4.07 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.2, 138.2, 137.8, 135.3, 133.8, 132.8, 130.0, 129.6, 124.5, 117.1, 117.0, 112.9, 55.7; HR-MS (ESI) Calcd for $C_{15}H_{13}BrN_4O$ [M+H]: 345.0346, found: 345.0357, [M+2]: 347.0326, found: 347.0340.

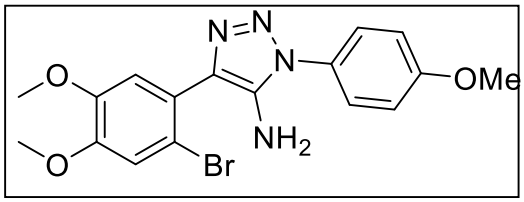
4-(2-Bromo-5-methoxyphenyl)-1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-5-amine (70e)



Reaction Time: 2 h; Yield: 62%; Melting Point: 135 – 138 ºC; R_f: 0.11 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3526, 3197, 2967, 1739, 1371, 1218, 1035, 833, 532; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 – 7.49 (m, 3H), 7.15 (d, *J* = 3.2 Hz, 4H), 7.09 – 7.04 (m, 2H), 6.82 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.02 (s, 2H), 3.88 (s,

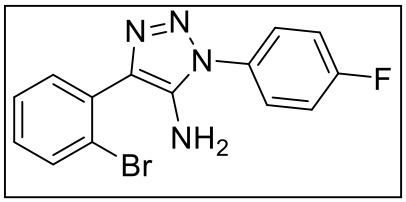
3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ = 159.3, 158.5, 140.0, 133.7, 133.2, 128.4, 127.6, 125.9, 117.0, 115.8, 114.7, 113.5, 55.6, 55.4; HR-MS (ESI) Calcd for $C_{16}H_{15}BrN_4O_2$ [M+H]: 375.0451, found: 375.0469; Calcd: 377.0431, found: 377.0452.

4-(2-Bromo-4,5-dimethoxyphenyl)-1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-5-amine (70f)



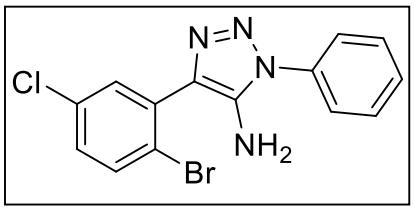
Reaction Time: 7 h; Yield: 37%; Melting Point: 170 – 173 ºC; R_f: 0.05 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3515, 3339, 2978, 2961, 2040, 1721, 1627, 1367, 1217, 835, 532; ^{1}H NMR (400 MHz, DMSO) δ = 7.54 (d, *J* = 8.8 Hz, 2H), 7.24 (s, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.99 (s, 1H), 5.39 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H) 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO δ = 159.31, 149.15, 148.08, 139.83, 128.59, 127.99, 125.86, 124.36, 115.79, 114.87, 114.78, 113.53, 56.03, 55.68, 55.60; HR-MS (ESI) Calcd for $C_{17}H_{17}BrN_4O_3$ [M+H]: 405.0557, found: 405.0607, Calcd: 407.0537, found: 407.0587.

4-(2-Bromophenyl)-1-(4-fluorophenyl)-1*H*-1,2,3-triazol-5-amine (70g)



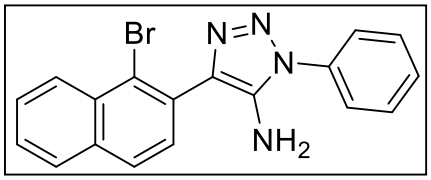
Reaction Time: 3 h; Yield: 73%; Melting Point: 134 – 136 ºC; R_f: 0.23 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3469, 3021, 2970, 2942, 1742, 1443, 1368, 1220, 904, 533; ^{1}H NMR (400 MHz, DMSO) δ = 7.78 – 7.65 (m, 3H), 7.54 - 7.40 (m, 4H), 7.38 – 7.29 (m, 1H), 5.66 (s, 2H); ^{13}C NMR (100 MHz, DMSO) δ = 161.7 (d, *J* = 244.1 Hz), 140.1, 133.0, 132.3 (2C), 132.0 (d, *J* = 2.8 Hz), 129.7, 127.9, 127.7, 126.6 (d, *J* = 8.9 Hz), 123.5, 116.5 (d, *J* = 23.0 Hz). (One carbon less); HR-MS (ESI) Calcd for $C_{15}H_{12}N_2$ [M+H]: 354.9965, found: 354.9975; [M+2]: 356.9945, found: 356.9952.

4-(2-Bromo-5-chlorophenyl)-1-phenyl-1*H*-1,2,3-triazol-5-amine (70h)



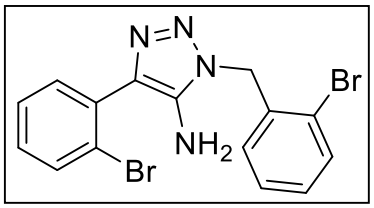
Reaction Time: 3 h; Yield: 68%; Melting Point: 128 – 130 ºC; R_f: 0.28 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3314, 2989, 2343, 1622, 1505, 1455, 1393, 1275, 764, 693; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.76 (d, *J* = 8.8 Hz, 1H), 7.69 – 7.58 (m, 4H), 7.57 – 7.52 (m, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.40 (dd, *J* = 8.4, 2.6 Hz, 1H), 5.80 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 140.3, 135.5, 134.5, 134.2, 132.2, 131.6, 129.7, 129.3, 128.7, 126.7, 124.0, 121.9; HR-MS (ESI) Calcd for $C_{14}H_{10}BrClN_4$ [M+H]: 348.9850, found: 348.9851; Calcd: 350.9829, found: 350.9833

1-Benzyl-4-(2-bromonaphthalen-2-yl)-1*H*-1,2,3-triazol-5-amine (70i)



Reaction Time: 4 h; Yield: 35%; Melting Point: 154 – 156 ºC; R_f: 0.23 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3504, 3203, 2942, 1922, 1753, 1628, 1361, 1222, 1027, 826, 549; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.37 (d, *J* = 8.4 Hz, 1H), 7.91 – 7.83 (m, 2H), 7.73 – 7.60 (m, 4H), 7.56 (t, *J* = 7.6 Hz, 3H), 7.49 (t, *J* = 7.2 Hz, 1H), 4.13 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 138.3, 135.4, 134.2, 132.5, 131.1, 130.5, 130.0, 129.5, 129.3, 128.3, 128.2, 127.9, 127.8, 127.1, 124.5, 122.7; HR-MS (ESI) Calcd for $C_{18}H_{13}BrN_4$ [M+H]: 365.0396, found: 365.0366; [M+2]: 367.0377, found: 367.0345.

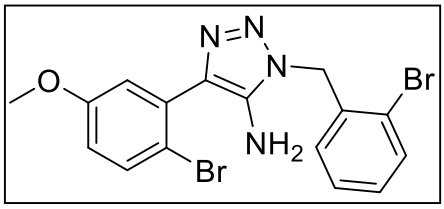
1-(2-Bromobenzyl-4-(2-bromophenyl)-1*H*-1,2,3-triazol-5-amine (71a)



Reaction Time: 3 h; Yield: 51%; Melting Point: 104 – 106 ºC; R_f: 0.26 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3854, 3802, 3740, 2994, 2365, 2345, 1733, 1652, 1265, 1027, 764; ^{1}H NMR (400 MHz, DMSO) δ = 7.76 – 7.66 (m, 2H), 7.49 – 7.42 (m, 2H), 7.40 – 7.25 (m, 3H), 6.70 (d, *J* = 7.2 Hz, 1H), 5.70 (s, 2H), 5.47 (s, 2H); ^{13}C NMR (100 MHz, DMSO) δ =

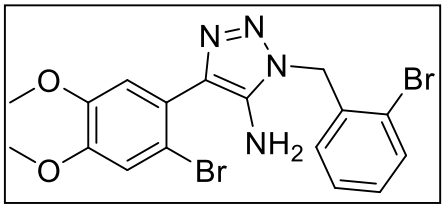
140.5, 135.3, 132.73, 132.71, 132.5, 132.2, 129.4 (2C), 128.1, 127.9, 127.7, 127.5, 123.3, 121.8, 49.0; HR-MS (ESI) Calcd for $C_{15}H_{12}Br_2N_4$ [M+H]: 406.9501, found: 406.9500; Calcd: 408.9482, found: 408.9482; Calcd: 410.9461, found: 410.9460.

4-(2-Bromo-5-methoxyphenyl)-1-(2-bromobenzyl)-1*H*-1,2,3-triazol-5-amine (71b)



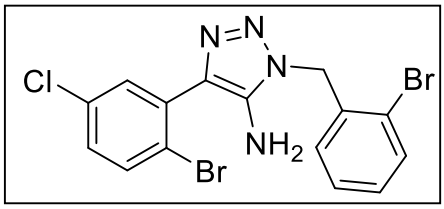
Reaction Time: 3 h; Yield: 73%; Melting Point: 101 – 104 ºC; R_f: 0.18 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3897, 3791, 3003, 2343, 1889, 1766, 1665, 1279, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.19 - 7.11 (m, 1H), 7.05 (d, *J* = 3.2 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.76 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.48 (s, 2H), 3.80 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.1, 138.2, 133.8, 133.7, 133.1, 133.0, 131.7, 130.0, 128.6, 128.4, 122.4, 117.0, 116.9, 112.9, 55.7, 50.2; HR-MS (ESI) Calcd for $C_{16}H_{14}Br_2N_4O$ [M+H]: 458.9427, found: 458.9417; Calcd: 460.9407, found: 460.9403; Calcd: 462.9386, found: 462.9380

4-(2-Bromo-4,5-dimethoxyphenyl)-1-(2-bromobenzyl)-1*H*-1,2,3-triazol-5-amine (71c)



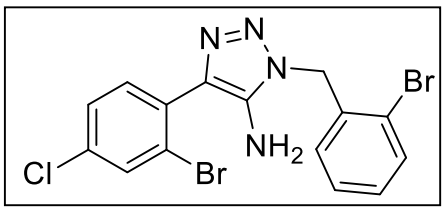
Reaction Time: 3 h; Yield: 73%; Melting Point: 135 – 137 ºC; R_f: 0.15 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3852, 3646, 2996, 2358, 2343, 1733, 1652, 1273, 786; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.69 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.32 - 7.19 (m, 2H), 6.97 (s, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 5.59 (s, 2H), 5.45 (s, 2H), 3.82 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 149.1, 148.0, 140.5, 135.5, 132.6, 129.6, 128.14, 128.06, 127.8, 124.7, 121.8, 115.7, 114.9, 113.7, 56.0, 55.7, 49.1; HR-MS (ESI) Calcd for $C_{17}H_{16}Br_2N_4O_2$ [M+H]: 468.2305, found: 468.2338, Calcd: 470.0481, found: 479.0511.

4-(2-Bromo-5-chlorophenyl)-1-(2-bromobenzyl)-1*H*-1,2,3-triazol-5-amine (71d)



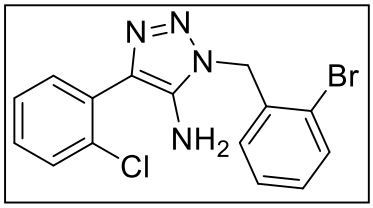
Reaction Time: 3 h; Yield: 67%; jelly; R_f: 0.18 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3851, 3648, 3312, 3059, 2974, 2852, 2357, 2332, 1891, 1634, 1046; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (d, *J* = 8.0 Hz, 1H), 7.58 – 7.48 (m, 2H), 7.32 - 7.25 (m, 1H), 7.24 - 7.15 (m, 2H), 6.94 (d, *J* = 7.6 Hz, 1H), 5.52 (s, 2H), 3.87 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 138.4, 134.1, 133.9, 133.8, 133.7, 133.2, 132.4, 130.4, 130.1, 129.9, 128.7, 128.4, 122.5, 120.4, 50.3; HR-MS (ESI) Calcd for $C_{15}H_{11}Br_2ClN_4$ [M+H]: 440.9112, found: 440.9059; Calcd: 442.9091, found: 442.9040; Calcd: 444.9070, found: 444.9021.

4-(2-Bromo-4-chlorophenyl)-1-(2-bromobenzyl)-1*H*-1,2,3-triazol-5-amine (71e)



Reaction Time: 3 h; Yield: 55%; jelly; R_f: 0.18 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3854, 3744, 3628, 3319, 2926, 2367, 1772, 1634, 1516, 1265, 1100, 784; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 2.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.36 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.32 - 7.27 (m, 1H), 7.24 - 7.16 (m, 1H), 6.94 (d, *J* = 7.6 H z, 1H), 5.52 (s, 2H), 3.82 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 138.3, 135.0, 133.7, 133.3, 133.2, 132.7, 130.9, 130.5, 130.1, 128.7, 128.4, 128.2, 122.9, 122.5, 50.3; HR-MS (ESI) Calcd for $C_{15}H_{11}Br_2ClN_4$ [M+H]: 440.9112, found: 440.9106; Cald: 442.9091, found: 442.9081; Calcd: 444.9070, found: 444.9059.

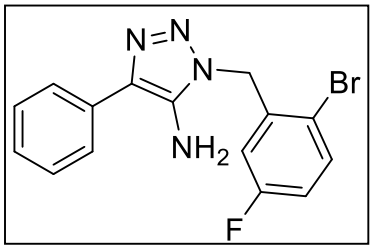
1-(2-Bromobenzyl)4-(2-chlorophenyl)-1*H*-1,2,3-triazol-5-amine (71f)



Reaction Time: 3 h; Yield: 76%; Melting Point: 110 – 112 ºC R_f: 0.19 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3852, 3674, 2986, 2350, 1733, 1652, 1277, 751, 407; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.70 (d, *J* = 8.0 Hz, 1H), 7.60 – 7.48 (m, 2H), 7.46 – 7.33 (m, 3H),

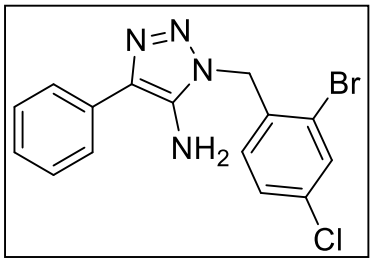
7.28 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 7.2 Hz, 1H), 5.75 (s, 2H), 5.48 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 140.9, 135.4, 132.7 (2C), 131.9, 130.8, 129.7, 129.6, 129.2, 128.1, 128.0, 127.1, 126.1, 121.9, 49.1; HR-MS (ESI) Calcd for $C_{15}H_{12}BrClN_4$ [M+H]: 363.0007, found: 362.9999, Calcd.: 364.9986, found: 364.9983.

1-(2-Bromo-5-fluorobenzyl)-4-phenyl-1*H*-1,2,3-triazol-5-amine (71g)



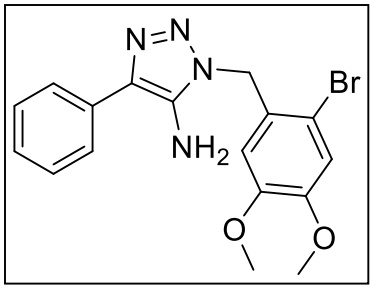
Reaction Time: 4h; Yield: 65%; Melting Point: 120 – 122 °C; R_f: 0.21 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3451, 3027, 2988, 2941, 1750, 1442, 1373, 1225, 910, 535.; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.85 – 7.71 (m, 3H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.29 – 7.14 (m, 2H), 6.45 (dd, *J* = 9.2, 2.4 Hz, 1H), 5.98 (s, 2H), 5.48 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 161.5 (d, *J* = 243.3 Hz), 139.8, 137.9 (d, *J* = 7.3 Hz), 134.5 (d, *J* = 8.1 Hz), 132.1, 128.6, 127.3, 125.9, 124.6, 116.6 (d, J = 22.4 Hz), 116.5 (d, *J* = 3.1 Hz), 115.2 (d, *J* = 24.3 Hz), 48.9; HR-MS (ESI) Calcd for $C_{15}H_{12}BrFN_4$ [M+H]: 347.0302, found: 347.0282, calcd.: 349.0282, found: 349.0262.

1-(2-Bromo-4-chlorobenzyl)-4-phenyl-1*H*-1,2,3-triazol-5-amine (71h)



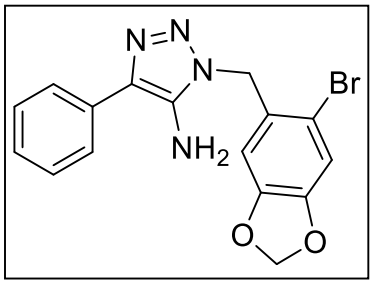
Reaction Time: 4 h; Yield: 77%; Melting Point: 151 – 153 °C; R_f: 0.23 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3421, 3058, 2954, 2324, 2028, 1978, 1731, 1635, 1524, 1267, 770, 471; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.87 (d, *J* = 2.0 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.48 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 7.6 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.00 (s, 2H), 5.49 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 139.9, 134.6, 133.1, 132.2, 131.9, 129.4, 128.6, 128.2, 127.2, 125.9, 124.6, 122.6, 48.6; HR-MS (ESI) Calcd for $C_{15}H_{12}BrClN_4$ [M+H]: 363.0007, found: 362.9987, Calcd: 364.9986, found: 364.9966.

1-(2-Bromo-4,5-dimethoxybenzyl)-4-phenyl-1*H*-1,2,3-triazol-5-amine (71i)



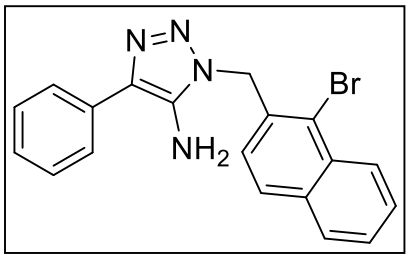
Reaction Time: 3 h; Yield: 69%; Melting Point: decomposed; R_f: 0.15 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3689, 3370, 2972, 2166, 1973, 1504, 1262, 1030, 746; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 7.6 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.30 – 7.21 (m, 2H), 6.67 (s, 1H), 5.92 (s, 2H), 5.41 (s, 2H), 3.81 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 149.2, 148.3, 139.6, 132.3, 128.6, 127.4, 126.9, 125.9, 124.7, 115.8, 113.0, 112.8, 56.1, 55.7, 48.9; HR-MS (ESI) Calcd for $C_{17}H_{17}BrN_4O_2$ [M+H]: 389.0608, found: 389.0586, Calcd: 391.0588, found: 391.0566.

1-((6-Bromobenzo[*d*][1,3]dioxol-5-yl)methyl)-4-phenyl-1*H*-1,2,3-triazol-5-amine (71j)



Reaction Time: 3 h; Yield: 81%; Melting Point: decomposed; R_f: 0.22 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3441, 3357, 2925, 2354, 2179, 1968, 1632, 1504, 1245, 763, 419; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 8.0 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.31 (s, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 6.36 (s, 1H), 6.08 (s, 2H), 5.92 (s, 2H), 5.39 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 147.82, 147.4, 139.6, 132.2, 128.6, 128.3, 127.4, 125.8, 124.6, 112.7, 112.6, 108.4, 102.2, 48.9; HR-MS (ESI) Calcd for $C_{16}H_{13}BrN_4O_2$ [M+H]: 373.0295, found: 373.0288, Calcd: 375.0275, found: 375.0268.

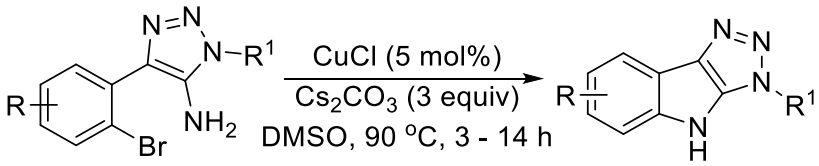
1-((1-Bromonaphthalen-2-yl)methyl)-4-phenyl-1*H*-1,2,3-triazol-5-amine (71k)



Reaction Time: 4 h; Yield: 45%; Melting Point: 130 – 132 °C; R_f: 0.17 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3219, 2364, 2164, 1969, 1894, 1702, 765, 437, 422; ^1H NMR (400 MHz, DMSO-d_6) δ = 8.28 (d, *J* = 8.4 Hz, 1H), 7.96 (t, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 7.6 Hz, 2H), 7.73 (t, *J* = 7.2 Hz, 1H), 7.63 (t, *J* =

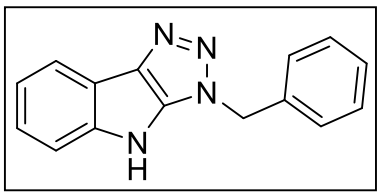
7.2 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.25 (t, *J* = 7.2 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 1H), 5.99 (s, 2H), 5.75 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 139.9, 133.7, 133.5, 132.3, 131.5, 128.57, 128.41, 128.32, 128.27, 127.3, 127.0, 126.2, 125.8, 125.0, 124.6, 121.7, 49.9; HR-MS (ESI) Calcd for $C_{19}H_{15}BrN_4$ [M+H]: 379.0553, found: 379.0541; Calcd: 381.0553, found: 381.0523.

3.12.11. General Procedure for Copper Catalyzed C—N Bond Formation for the Synthesis of Triazolo Fused Indoles 62



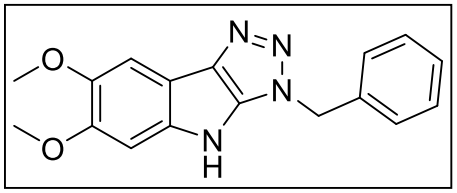
An oven-dried 8 mL reaction vial was charged with CuCl (5 mol%), Cs_2CO_3 (3 equiv) and respective 5-amino-4-aryl triazoles (0.5 mmol) in DMSO (2.0 mL) and was stirred at 90 ºC for 3 - 14 h. The reaction mixture was monitored by TLC. After the starting material had been completely consumed, the reaction mixture was purified by flash chromatography using EtOAc/hexanes as eluent.

3-Benzyl-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (62a)



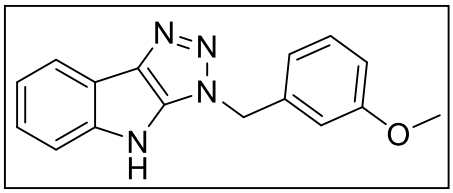
Reaction Time: 4 h; Yield: 93%; Melting Point: 164 – 165 ºC; R_f: 0.30 in 50% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3804, 3329, 2996, 2700, 2343, 1779, 1732, 1652, 1269, 757; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.58 (s, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.41 – 7.31 (m, 5H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 5.74 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 143.0, 140.0, 136.9, 135.9, 128.8, 128.1, 127.6, 123.8, 120.3, 118.6, 116.0, 113.0, 51.0; HR-MS (ESI) Calcd for $C_{15}H_{12}N_4$ [M+H]: 249.1135, found: 249.1142.

3-Benzyl-6,7-dimethoxy-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (62d)



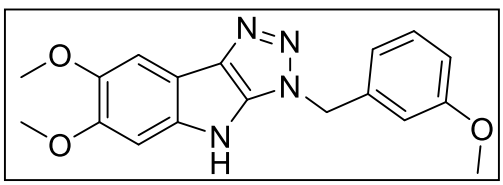
Reaction Time: 4 h; Yield: 69%; Melting Point: 185 – 186 ºC; R_f: 0.09 in 40% ethyl acetatein hexanes; IR (KBr): ν (cm^{-1}) = 3487, 3146, 2978, 1917, 1728, 1635, 1354, 1221, 827, 531; ^{1}H NMR (400 MHz, DMSO) δ = 11.21 (s, 1H), 7.40 (s, 1H), 7.39 – 7.29 (m, 5H), 7.04 (s, 1H), 5.71 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (175 MHz, DMSO) δ = 147.2, 144.5, 139.4, 137.4, 137.3, 135.9, 128.8, 128.0, 127.6, 108.4, 102.2, 97.4, 56.1, 55.8, 50.9; HR-MS (ESI) Calcd for $C_{17}H_{16}N_4O_2$ [M+H]: 309.1346, found: 309.1351.

3-(3-Methoxybenzyl)-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (62e)



Reaction Time: 8 h; Yield: 73%; Melting Point: 147 - 150 ºC; R_f: 0.17 in 60% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3469, 3024, 2970, 2940, 1742, 1440, 1371, 1215, 894, 523; ^{1}H NMR (400 MHz, DMSO) δ = 11.58 (s, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.94 (s, 1H), 6.91 - 6.84 (m, 2H), 5.70 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ = 159.5, 143.0, 140.0, 137.3, 136.9, 130.1, 123.9, 120.4, 119.7, 118.7, 116.0, 113.6, 113.3, 113.1, 55.2, 50.9; HR-MS (ESI) Calcd for $C_{16}H_{14}N_4O$ [M+H]: 279.1240, found: 279.1242.

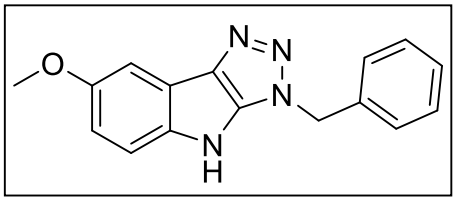
6,7-Dimethoxy-3-(3-methoxybenzyl)-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (62f)



Reaction Time: 3 h; Yield: 71%; Melting Point: 149 – 151 ºC; R_f: 0.15 in 60% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3748, 3648, 2998, 2359, 1733, 1634, 1265, 814; ^{1}H NMR (700 MHz, DMSO-d_6) δ = 11.17 (s, 1H), 7.38 (s, 1H), 7.28 (t, *J* = 8.4 Hz, 1H), 7.02 (s, 1H), 6.91 (d, *J* = 1.4 Hz, 1H), 6.89 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 5.65 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-

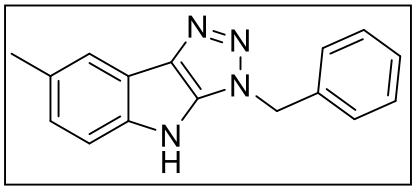
d_6) δ = 159.5, 147.2, 144.5, 139.3, 137.4, 137.33, 137.26, 130.0, 119.7, 113.5, 113.2, 108.4, 102.2, 97.4, 56.1, 55.8, 55.1, 50.8; HR-MS (ESI) Calcd for $C_{18}H_{18}N_4O_3$ [M+H]: 339.1452, found: 339.1457.

3-Benzyl-7-methoxy-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (62g)



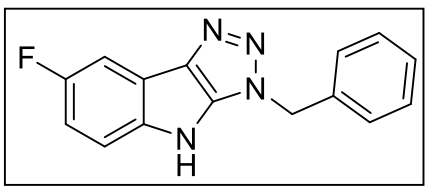
Reaction Time: 4.5 h; Yield: 91%; Melting Point: jelly R_f: 0.08 in 40% ethyl acetate with 1% triethyl amine; IR (KBr): ν (cm^{-1}) = 3484, 3144, 2978, 1917, 1713, 1634, 1404, 1221, 1030, 821, 546; ^{1}H NMR (700 MHz, DMSO) δ = 11.29 (s, 1H), 7.41 - 7.35 (m, 4H), 7.35 - 7.29 (m, 3H), 6.92 - 6.87 (m, 1H), 5.71 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (175 MHz, DMSO) δ = 154.0, 140.6, 137.5, 137.0, 135.8, 128.8, 128.0, 127.6, 116.5, 113.6, 112.2, 102.1, 55.5, 50.9; HR-MS (ESI) Calcd for $C_{16}H_{14}N_4O$ [M+H]: 279.1240, found: 279.1246.

3-Benzyl-7-methyl-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (62h)



Reaction Time: 3 h; Yield: 81%; Melting Point: 156 - 159 ºC; R_f: 0.10 in 40% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3515, 3237, 2961, 1917, 1720, 1404, 1367, 1211, 668, 522; ^{1}H NMR (400 MHz, DMSO) δ = 11.38 (s, 1H), 7.63 (s, 1H), 7.41 – 7.27 (m, 6H), 7.09 (d, *J* = 8.0 Hz, 1H), 5.71 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ = 141.2, 140.2, 136.7, 135.9, 129.1, 128.8, 128.0, 127.6, 125.0, 118.6, 116.2, 112.7, 50.9, 21.0; HR-MS (ESI) Calcd for $C_{16}H_{14}N_4$ [M+H]: 263.1291, found: 263.1292.

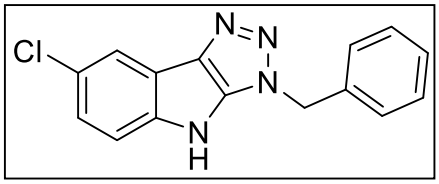
3-Benzyl-7-fluoro-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (62i)



Reaction Time: 3 h; Yield: 73%, white solid; Melting Point: decomposed above 100 ºC; R_f: 0.35 in 50% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3852, 3743, 3325, 2923, 2853, 2359, 1750, 1652, 1506, 1265, 829, 668; ^{1}H NMR (400 MHz, DMSO) δ = 11.62

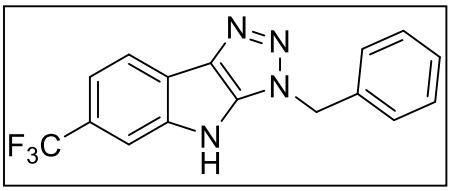
(s, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.53 - 7.44 (m, 1H), 7.43 – 7.22 (m, 5H), 7.12 (t, *J* = 8.2 Hz, 1H), 5.74 (s, 2H); ^{13}C NMR (100 MHz, DMSO) δ = 157.1 (d, *J* = 232.6 Hz), 141.1, 139.4, 136.6 (d, *J* = 3.5 Hz), 135.7, 128.8, 128.1, 127.6, 116.2 (d, *J* = 10.5 Hz), 113.9 (d, *J* = 9.5 Hz), 111.2 (d, *J* = 25.1 Hz), 104.6 (d, *J* = 24.9 Hz), 51.0; HR-MS (ESI) Calcd for $C_{15}H_{11}FN_4$ [M+H]: 267.1031, found: 267.1041

3-Benzyl-7-chloro-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (62j)



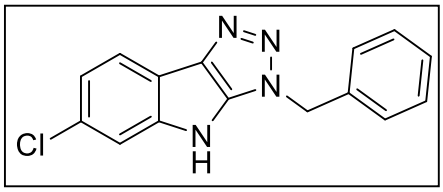
Reaction Time: 3 h; Yield: 85%, pale yellow solid; Melting Point: 176 – 178 ºC; R_f: 0.12 in 40% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3485, 3145, 2978, 2883, 1925, 1728, 1630, 1361, 1221, 1029, 930, 509; ^{1}H NMR (400 MHz, DMSO) δ = 11.76 (s, 1H), 7.88 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.41 – 7.27 (m, 6H), 5.74 (s, 2H); ^{13}C NMR (100 MHz, DMSO) δ = 141.9, 141.2, 136.5, 136.1, 129.3, 128.6, 128.1, 125.1, 124.1, 118.6, 117.4, 115.0, 51.5; HR-MS (ESI) Calcd for $C_{15}H_{12}N_2$ [M+H]: 283.0745, found: 283.0739.

3-Benzyl-6-(trifluoromethyl)-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (62k)



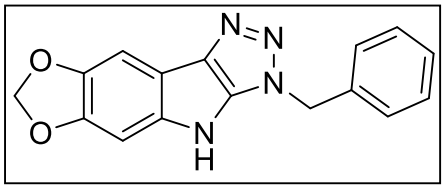
Reaction Time: 7 h; Yield: 73%; Melting Point: 166 – 167 ºC; R_f: 0.12 in 40% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3851, 3745, 3628, 2999, 2365, 2342, 1738, 1652, 1265, 1112, 739; ^{1}H NMR (400 MHz, DMSO) δ = 11.99 (s, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.83 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.43 – 7.28 (m, 5H), 5.80 (s, 2H); ^{13}C NMR (100 MHz, DMSO) δ = 142.4, 141.8, 136.6, 136.1, 129.3, 128.6, 128.1, 125.3 (q, *J* = 269.8 Hz), 124.4 (q, *J* = 31.3 Hz), 119.7, 119.0, 117.3 (q, *J* = 3.7 Hz), 110.7 (q, *J* = 4.2 Hz), 51.5; HR-MS (ESI) Calcd for $C_{16}H_{11}F_3N_4$ [M+H]: 317.1009, found: 317.1006

3-Benzyl-6-chloro-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (62l)



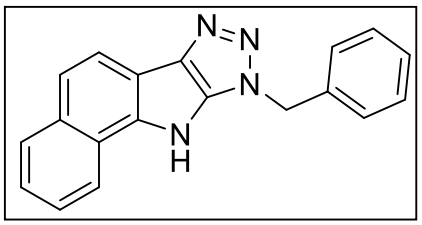
Reaction Time: 3 h; Yield: 91%; Melting Point: 167 – 169 ºC; R_f: 0.22 in 50% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3428, 3141, 2942, 1925, 1745, 1630, 1376, 1232, 1028, 832, 536; ^{1}H NMR (400 MHz, DMSO) δ = 7.85 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.39 – 7.30 (m, 5H), 7.20 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.75 (s, 2H); ^{13}C NMR (100 MHz, DMSO) δ = 143.7, 140.6, 136.5, 135.8, 129.2, 128.5, 128.3, 127.9, 120.8, 120.2, 114.9, 113.1, 51.3; HR-MS (ESI) Calcd for $C_{15}H_{12}N_2$ [M+H]: 283.0745, found: 283.0724.

3-Benzyl-3,4-dihydro-[1,3]dioxolo[4,5-*f*][1,2,3]triazolo[4,5-*b*]indole (62m)



Reaction Time: 4.5 h; Yield: 54%; Melting Point: 199 – 201 °C; R_f: 0.10 in 40% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3674, 3585, 2996, 2358, 1616, 1506, 1472, 1269, 795; ^{1}H NMR (400 MHz, DMSO) δ = 11.28 (s, 1H), 7.45 - 7.22 (m, 6H), 7.05 (s, 1H), 6.01 (s, 2H), 5.68 (s, 2H); ^{13}C NMR (100 MHz, DMSO) δ = 144.8, 142.2, 139.2, 137.7, 137.1, 135.8, 128.7, 127.9, 127.5, 109.1, 100.7, 98.3, 94.6, 50.8; HR-MS (ESI) Calcd for $C_{16}H_{12}N_4O_2$ [M+H]: 293.1033, found: 293.1046.

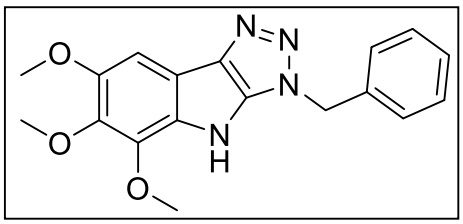
9-Benzyl-9,10-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*b*]indole (62n)



Reaction Time: 11 h; Yield: 58%; Melting Point: decomposed above 100 °C; R_f: 0.23 in 60% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3428, 3157, 2978, 1917, 1730, 1634, 1356, 1221, 1023, 826, 501; ^{1}H NMR (400 MHz, DMSO) δ = 12.44 (s, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 8.08 - 7.98 (m, 2H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.42 – 7.28 (m, 5H), 5.82 (s, 2H); ^{13}C NMR (100 MHz, DMSO) δ = 139.0, 138.1, 137.3, 136.1, 130.7, 128.82, 128.69, 128.0,

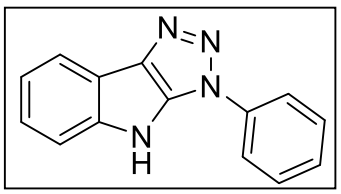
127.4, 126.0, 124.78, 122.3, 120.88, 120.77, 118.3, 111.1, 51.1; HR-MS (ESI) Calcd for $C_{19}H_{14}N_4$ [M+H]: 299.1291, found: 299.1298.

5,6,7-Trimethoxy-3-phenyl-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (62o)



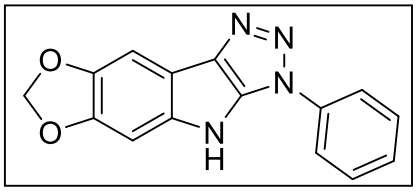
Reaction Time: 14 h (5 mol%), 12 h (10 mol%); Yield: 24% (5 mol%), 39% (10 mol%); jelly; R_f: 0.15 in 60% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3455, 3159, 2980, 1921, 1735, 1404, 1221, 1027, 821, 551; ^{1}H NMR (400 MHz, DMSO) δ = 11.44 (s, 1H), 7.41 – 7.26 (m, 5H), 7.22 (s, 1H), 5.69 (s, 2H), 3.97 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ = 148.8, 140.2, 139.5, 139.0, 137.5, 136.2, 130.4, 128.7, 127.9, 127.6, 111.6, 97.4, 61.05, 60.96, 56.3, 50.7; HR-MS (ESI) Calcd for $C_{18}H_{18}N_4O_3$ [M+H]: 339.1452, found: 339.1359

3-Phenyl-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (72a)



Reaction Time: 4 h ; Yield: 79%, off-white solid; Melting Point: 178 – 180 ºC; R_f: 0.30 in 40% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3856, 3801, 3744, 3631, 2994, 2365, 1735, 1686, 1651, 1267, 757; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.27 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.68 (t, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 143.2, 137.9, 137.4, 136.1, 130.0, 127.7, 124.3, 120.9, 119.2, 118.8, 115.6, 113.3; HR-MS (ESI) Calcd for $C_{14}H_{10}N_4$ [M+H]: 235.0978, found: 235.0980.

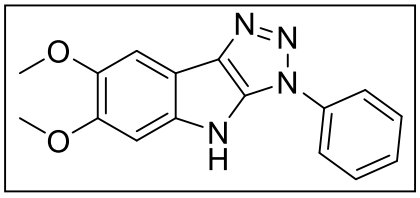
3-Phenyl-3,4-dihydro-[1,3]dioxolo[4,5-*f*][1,2,3]triazolo[4,5-*b*]indole (72b)



Reaction Time: 4 h; Yield: 37%; jelly; R_f: 0.09 in 40% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3854, 3745, 2999, 2699, 2344, 1730, 1649, 1269, 762, 663; ^{1}H NMR

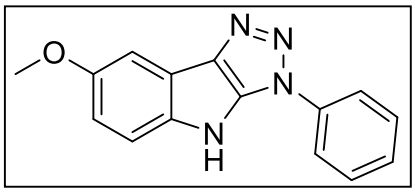
(700 MHz, DMSO) δ = 11.96 (s, 1H), 7.93 (d, *J* = 7.7 Hz, 2H), 7.61 (d, *J* = 7.0 Hz, 2H), 7.45 - 7.39 (m, 1H), 7.36 (s, 1H), 7.03 (s, 1H), 6.02 (s, 2H); ^{13}C NMR (175 MHz, DMSO) δ = 145.1, 142.7, 137.8, 137.6, 136.9, 136.1, 129.7, 127.2, 118.7, 108.8, 100.7, 98.3, 94.5; HR-MS (ESI) Calcd for $C_{15}H_{10}N_4O_2$ [M+H]: 279.0877, found: 279.0877.

6,7-Dimethoxy-3-phenyl-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (72c)



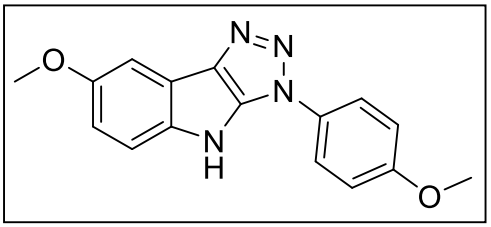
Reaction Time: 5 h; Yield: 76%; Melting Point: 192 – 193 ºC; R_f: 0.09 in 40% ethyl acetate with 1% triethyl amine; IR (KBr): ν (cm^{-1}) = 3425, 3048, 2978, 1753, 1366, 1210, 1029, 955, 835, 539; ^{1}H NMR (700 MHz, DMSO) δ = 11.94 (s, 1H), 7.97 (d, J = 7.7 Hz, 2H), 7.67 (t, J = 7.4 Hz, 2H), 7.51 - 7.44 (m, 2H), 7.05 (s, 1H), 3.85 (s, 6H); ^{13}C NMR (175 MHz, DMSO) δ = 147.6, 145.0, 137.8, 137.4, 137.1, 136.2, 130.0, 127.5, 118.9, 108.0, 102.1, 97.3, 56.1, 55.8; HR-MS (ESI) Calcd for $C_{16}H_{14}N_4O_2$ [M+H]: 295.1190, found: 295.1191.

7-Methoxy-3-phenyl-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (72d)



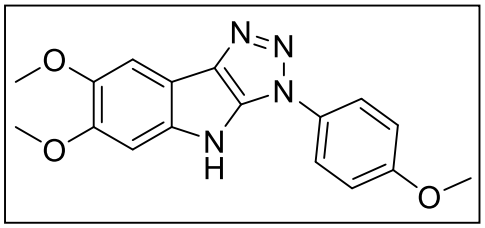
Reaction Time: 4 h; Yield: 72%; jelly; R_f: 0.08 in 40% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3856, 3747, 3678, 3631, 2957, 2360, 1698, 1557, 1232, 759, 670; ^{1}H NMR (400 MHz, DMSO) δ = 12.01 (s, 1H), 7.97 (d, *J* = 7.6 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 2H), 7.54 - 7.38 (m, 3H), 6.96 (d, *J* = 7.6 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (175 MHz, DMSO) δ = 154.4, 138.3, 137.7, 137.4, 136.1, 130.0, 127.6, 119.0, 116.1, 113.9, 112.8, 102.1, 55.5; HR-MS (ESI) Calcd for $C_{15}H_{12}N_4O$ [M+H]: 265.1084, found: 265.1073.

7-Dimethoxy-3-(4-methoxyphenyl)-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (72e)



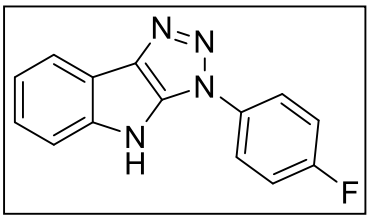
Reaction Time: 3 h; Yield: 55%; jelly; R_f: 0.07 in 40% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3488, 3202, 2978, 1958, 1732, 1364, 1220, 1029, 901, 834, 528; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.91 (s, 1H), 7.86 (d, *J* = 8.8 Hz, 2H), 7.45 (s, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.98 – 6.92 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 158.5, 154.3, 138.5, 137.7, 137.3, 129.4, 121.0, 116.2, 115.0, 113.8, 112.7, 102.1, 55.6, 55.5; HR-MS (ESI) Calcd for $C_{16}H_{14}N_4O_2$ [M+H]: 295.1190, found: 295.1183.

6,7-Dimethoxy-3-(4-methoxyphenyl)3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (72f)



Reaction Time: 3 h; Yield: 55%; Melting Point: 192 – 194 ºC; R_f: 0.17 in 40% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3876, 3672, 3565, 1751, 1662, 1464, 1226, 814; ^{1}H NMR (700 MHz, DMSO-d_6) δ = 11.84 (s, 1H), 7.85 (d, *J* = 9.1 Hz, 2H), 7.46 (s, 1H), 7.21 (d, *J* = 9.1 Hz, 2H), 7.03 (s, 1H), 3.86 (s, 3H), 3.843 (s, 3H), 3.841 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 158.5, 147.5, 144.9, 137.7, 137.4, 137.3, 129.5, 120.9, 115.0, 108.1, 102.2, 97.3, 56.1, 55.8, 55.6; HR-MS (ESI) Calcd for $C_{17}H_{16}N_4O_3$ [M+H]: 325.1295, found: 325.1286.

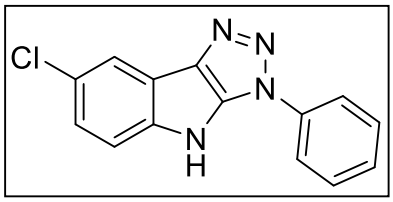
3-(4-Fuorophenyl)-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (72g)



Reaction Time: 4 h; Yield: 85%; Melting Point: 204 – 207 ºC; R_f: 0.13 in 40% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3768, 3565, 2981, 2343, 1761, 1652, 1532, 1275, 764; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.25 (s, 1H), 8.05 - 8.97 (m, 2H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.59 - 7.49 (m, 3H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-

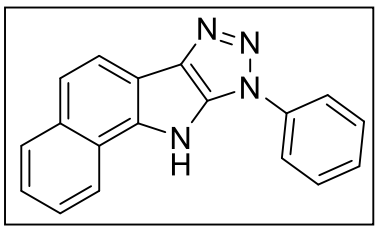
d_6) δ = 161.03 (d, J = 243.2 Hz), 143.17, 137. 64 (d, *J* = 63.5 Hz), 132.6 (d, *J* = 2.7 Hz), 124.34, 121.6 (d, *J* = 8.7 Hz), 120.89, 118.78, 116.9 (d, *J* = 23 Hz), 115.66, 113.27; HR-MS (ESI) Calcd for $C_{14}H_9FN_4$ [M+H]: 253.0884, found: 253.0885.

7-Chloro-3-phenyl-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (72h)



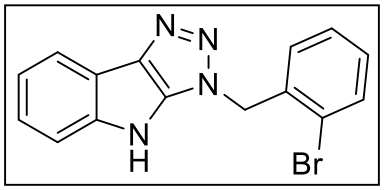
Reaction Time: 4 h; Yield: 80%; Melting Point: 208 – 209 ºC; R_f: 0.27 in 40% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3852, 3628, 2998, 2358, 1652, 1456, 1275, 762; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.46 (s, 1H), 8.03 – 8.92 (m, 3H), 7.68 (t, *J* = 7.6 Hz, 2H), 7.60 – 7.46 (m, 2H), 7.37 (dd, *J* = 8.4, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 141.6, 138.7, 136.4, 135.9, 130.1, 127.9, 125.2, 124.1, 119.3, 118.3, 116.6, 114.7; HR-MS (ESI) Calcd for $C_{14}H_9ClN_4$ [M+H]: 269.0589, found: 269.0595.

3-Phenyl-9,10-dihydrobenzo[*g*][1,2,3]triazolo[4,5-*b*]indole (72i)



Reaction Time: 14 h; Yield: 35%; Melting Point: decomposed above 100 ºC; R_f: 0.33 in 60% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3458, 3210, 2988, 1950, 1777, 1450, 1260, 1050, 870, 560; ^{1}H NMR (400 MHz, DMSO) δ = 8.61 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 2H), 8.06 (d, *J* = 8.8 Hz, 2H), 7.78 – 7.63 (m, 4H), 7.58 – 7.50 (m, 2H); ^{13}C NMR (100 MHz, DMSO) δ = 138.7, 136.2, 131.0, 130.0, 128.8, 128.7, 127.9, 126.0, 125.0, 122.74, 122.68, 121.45, 121.37, 119.8, 118.2, 111.0; HR-MS (ESI) Calcd for $C_{18}H_{12}N_4$ [M+H]: 285.1135, found: 285.1126.

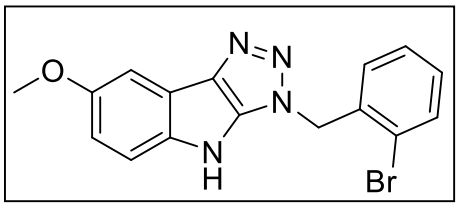
3-(2-Bromobenzyl)-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (73a)



Reaction Time: 3 h; Yield: 78%, brown solid; Melting Point: 146 – 149 ºC; R_f: 3852, 3743, 3003, 2356, 2343, 1733, 1652, 1506, 1268, 760; IR (KBr): ν (cm^{-1}) = 3852, 3743, 3003,

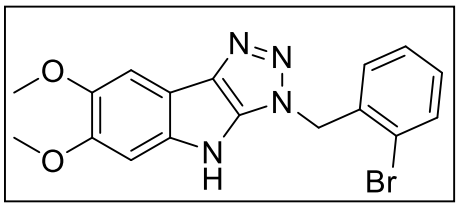
2356, 2343, 1733, 1652, 1506, 1268, 760; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.51 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.40 – 7.34 (m, 1H), 7.34 – 7.25 (m, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.00 (dd, *J* = 7.6, 1.6 Hz, 1H), 5.80 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 143.0, 140.4, 136.7, 134.9, 132.9, 130.2, 129.4, 128.3, 123.9, 122.3, 120.4, 118.7, 116.0, 113.1, 51.1; HR-MS (ESI) Calcd for $C_{15}H_{11}BrN_4$ [M+H]: 327.0240, found: 327.0246; Calcd: 329.0220, found: 329.0224

3-(2-Bromobenzyl)-7-methoxy-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (73b)



Reaction Time: 3 h; Yield: 35%, pale yellow solid; Melting Point: 160 – 162 ºC; R_f: 0.23 in 40% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3851, 3733, 3647, 2359, 2343, 1734, 1698, 1506, 1275, 764; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.25 (s, 1H), 7.70 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.33 - 7.27 (m, 1H), 6.99 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.90 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.78 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 154.1, 141.0, 137.6, 136.8, 134.8, 132.9, 130.2, 129.5, 128.3, 122.3, 116.5, 113.7, 112.3, 102.2, 55.6, 51.1; HR-MS (ESI) Calcd for $C_{16}H_{13}BrN_4O$ [M+H]: 357.0346, found: 357.0334; Calcd: 359.0326, found: 359.0318

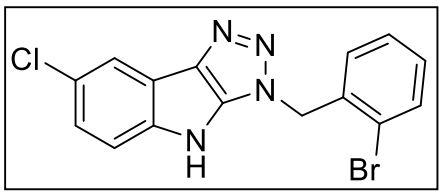
3-(2-Bromobenzyl)-6,7-methoxy-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (73c)



Reaction Time: 3 h; Yield: 59%, Off white solid; Melting Point: 163 – 166 ºC; R_f: 0.20 in 40% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3879, 3744, 3619, 3007, 2985, 2361, 2343, 1774, 1680, 1463, 1275, 764; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.11 (s, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.40 (s, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.04 (s, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 5.77 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 147.2, 144.6, 139.7, 137.25, 137.24, 134.9, 132.9, 130.2,

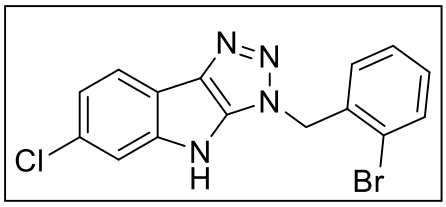
129.4, 128.3, 122.3, 108.3, 102.2, 97.5, 56.1, 55.8, 51.1; HR-MS (ESI) Calcd for $C_{17}H_{15}BrN_4O_2$ [M+H]: 387.0451, found: 387.0468; Calcd: 389.0431, found: 389.0437.

3-(2-Bromobenzyl)-7-chloro-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (73d)



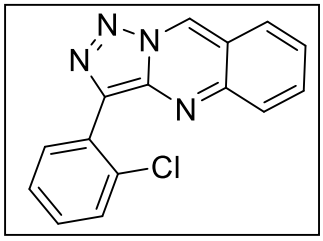
Reaction Time: 60%; Yield: 4 h; Melting Point: 165 – 167 °C; R_f: 0.32 in 40% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3800, 3674, 3618, 2996, 2358, 2343, 1733, 1652, 506, 668; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.75 (s, 1H), 7.91 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.38 (t , *J* = 7.6 Hz, 1H), 7.34 - 7.28 (m, 2H), 7.03 (d, *J* = 7.6 Hz, 1H), 5.81 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 141.4, 141.1, 135.8, 134.7, 132.9, 130.3, 129.6, 128.3, 124.7, 123.7, 122.4, 118.2, 116.9, 114.6, 51.2; HR-MS (ESI) Calcd for $C_{15}H_{10}BrClN_4$ [M+H]: 382.9670, found: 382.9671; Calcd: 384.9649, found: 384.9662

3-(2-Bromobenzyl)-6-chloro-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (73e)



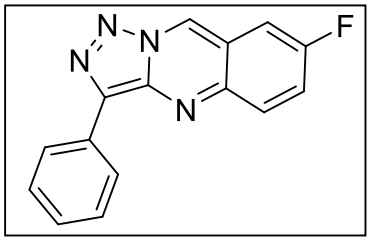
Reaction Time: 4 h; Yield: 61%; Melting Point: 181 – 183 °C; R_f: 0.19 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3852, 3743, 3674, 2359, 2330, 1699, 1506, 782; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.74 (s, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.71 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.56 (d, *J* = 1.6 Hz, 1H), 7.42 - 7.34 (m, 1H), 7.34 - 7.27 (m, 1H), 7.22 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.99 (dd, *J* = 7.6, 1.2 Hz, 1H), 5.82 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 143.4, 140.8, 136.1, 134.7, 132.9, 130.2, 129.5, 128.3, 128.0, 122.3, 120.6, 119.9, 114.7, 112.9, 51.2; HR-MS (ESI) Calcd for $C_{15}H_{10}BrClN_4$ [M+H]: 360.9850, found: 360.9851, [M+2] Calcd: 362.9829, found: 362.9786.

3-(2-Bromobenzyl)-3,4-dihydro-[1,2,3]triazolo[4,5-*b*]indole (74f)



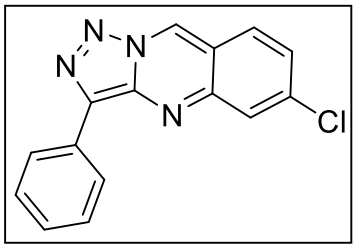
Reaction Time: 5 h; Yield: 73%; Melting Point: decomposed; R_f: 0.21 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3852, 3743, 3003, 2356, 2343, 1733, 1652, 1506, 1268, 760; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.32 (s, 1H), 8.66 (d, *J* = 8.0 Hz, 1H), 8.37 (d, *J* = 7.6 Hz, 1H), 8.22 - 8.14 (m, 1H), 7.89 (t, *J* = 7.6 Hz, 1H), 7.83 - 7.75 (m, 1H), 7.71 - 7.64 (m, 1H), 7.58 – 7.49 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 155.7, 137.9, 136.1, 135.7, 132.79, 132.53, 132.45, 130.5, 130.1, 129.7, 128.8, 128.5, 127.3, 118.8, 114.7; HR-MS (ESI) Calcd for $C_{15}H_{11}ClN_4$ [M+H]: 281.0589, found: 281.0584.

7-Fluoro-3-phenyl-[1,2,3]triazolo[5,1-*b*]quinazoline (74g)



Reaction Time: 5 h; Yield: 67%; Melting Point: decomposed; R_f: 0.19 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3693, 2970, 2359, 2320, 2171, 2031, 1742, 1403, 1270, 1225, 753, 422; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.20 (s, 1H), 8.58 (d, *J* = 4.0 Hz, 1H), 8.30 (d, *J* = 6.8 Hz, 2H), 8.15 (d, *J* = 6.8 Hz, 1H), 7.97 (t, *J* = 6.8 Hz, 1H), 7.58 - 7.34 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 160.3 (d, *J* = 245.1 Hz), 154.3, 136.5, 130.2, 129.6, 128.8, 128.1, 125.7 (2C), 123.9 (d, *J* = 25.9 Hz), 120.1 (d, *J* = 9.1 Hz), 117.6 (d, *J* = 7.9 Hz), 114.4 (d, *J* = 24.8 Hz); HR-MS (ESI) Calcd for $C_{15}H_9FN_4$ [M+H]: 265.3214, found: 265.3224.

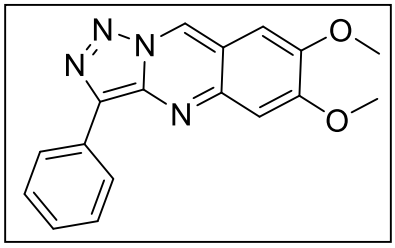
6-Chloro-3-phenyl-[1,2,3]triazolo[5,1-*b*]quinazoline (74h)



Reaction Time: 24 h; Yield: 53%; jelly; R_f: 0.25 in 30% in ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3694, 2992, 2359, 2189, 2016, 1806, 1512, 1406, 1314, 1163, 750, 479; ^{1}H NMR (700 MHz, DMSO-d_6) δ = 9.35 (s, 1H), 8.65 (s, 1H), 8.42 - 8.37 (m,

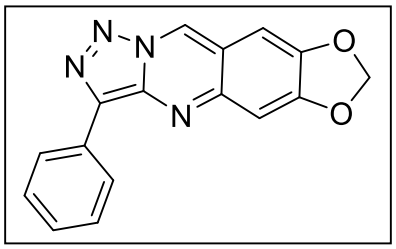
3H), 7.97 - 7.92 (m, 1H), 7.56 (t, *J* = 7.7 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (175 MHz, DMSO-d_6) δ = 155.3, 140.4, 137.4, 137.0, 133.9, 132.1, 130.7, 129.41, 129.29, 128.7, 126.3, 118.1, 115.0; HR-MS (ESI) Calcd for $C_{15}H_9ClN_4$ [M+H]: 281.0589, found: 281.0594.

6,7-Dimethoxy-3-phenyl-[1,2,3]triazolo[5,1-*b*]quinazoline (74i)



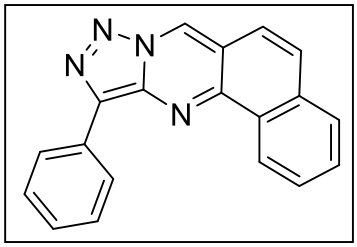
Reaction Time: 6 h; Yield: 61%; jelly; R_f: 0.23 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3696, 2967, 2364, 2161, 1739, 1623, 1551, 1294, 696, 469; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.15 (s, 1H), 8.39 (d, *J* = 6.0 Hz, 2H), 7.98 (s, 1H), 7.83 (s, 1H), 7.60 - 7.48 (m, 2H), 7.45 – 7.33 (m, 1H), 4.10 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 156.2, 153.7, 149.8, 137.1, 136.0, 131.2, 129.30, 129.20, 128.3, 126.1, 113.6, 109.2, 96.6, 57.2, 56.6; HR-MS (ESI) Calcd for $C_{17}H_{14}N_4O_2$ [M+H]: 307.1190, found: 307.1191.

3-Phenyl-[1,3]dioxolo[4,5-*g*][1,2,3]triazolo[5,1-*b*]quinazoline (74j)



Reaction Time: 24 h; Yield: 64%; Melting Point: decomposed above 200 °C; R_f: 0.17 in 30% in ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3634, 2972, 2357, 1737, 1650, 1579, 1480, 1277, 756, 420; ^{1}H NMR (700 MHz, DMSO-d_6) δ = 9.06 (s, 1H), 8.35 (d, *J* = 7.0 Hz, 2H), 8.01 (s, 1H), 7.74 (s, 1H), 7.52 (d, *J* = 7.0 Hz, 2H), 7.42 – 7.34 (m, 1H), 6.34 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 154.0, 153.4, 148.0, 136.7, 135.4, 130.6, 130.3, 128.8, 127.8, 125.5, 114.6, 105.7, 103.5, 94.4; HR-MS (ESI) Calcd for $C_{16}H_{10}N_4O_2$ [M+H]: 291.0877, found: 291.0883.

11-phenylbenzo[*h*][1,2,3]triazolo[5,1-*b*]quinazoline (74k)



Reaction Time: 5 h; Yield: 76%; Melting Point: decomposed above 100 °C; R_f: 0.18 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3687, 3039, 2970, 2579, 2361, 2038, 1976, 1410, 1223, 760; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.24 (d, *J* = 8.4 Hz, 1H), 9.50 (s, 1H), 8.49 (d, *J* = 8.4 Hz, 2H), 8.39 - 8.29 (m, 3H), 8.09 - 7.96 (m, 2H), 7.59 (t, *J* = 7.6 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (175 MHz, DMSO-d_6) δ = 154.8, 138.8, 135.9, 134.9, 130.8, 130.4, 130.2, 129.4, 129.1, 128.93, 128.89, 128.17, 127.95, 126.0, 124.3, 121.6, 117.3; HR-MS (ESI) Calcd for $C_{19}H_{12}N_4$ [M+H]: 297.1135, found: 297.1108.

3.12.12. 1H & 13C Spectrum of Selected Compounds

Figure 3.3a. ^{1}H Spectrum of 50a in DMSO-d$_6$ (400 MHz)

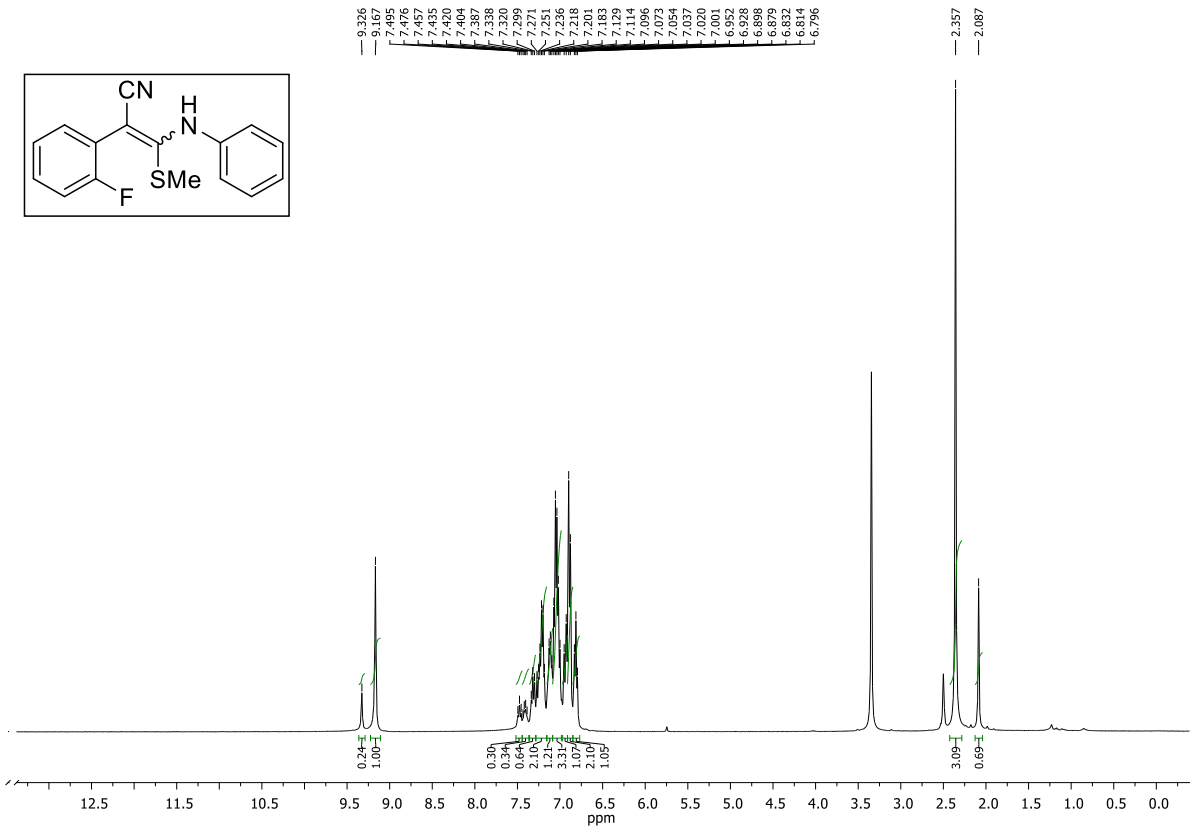


Figure 3.3b. ^{13}C Spectrum of 50a in DMSO-d$_6$ (100 MHz)

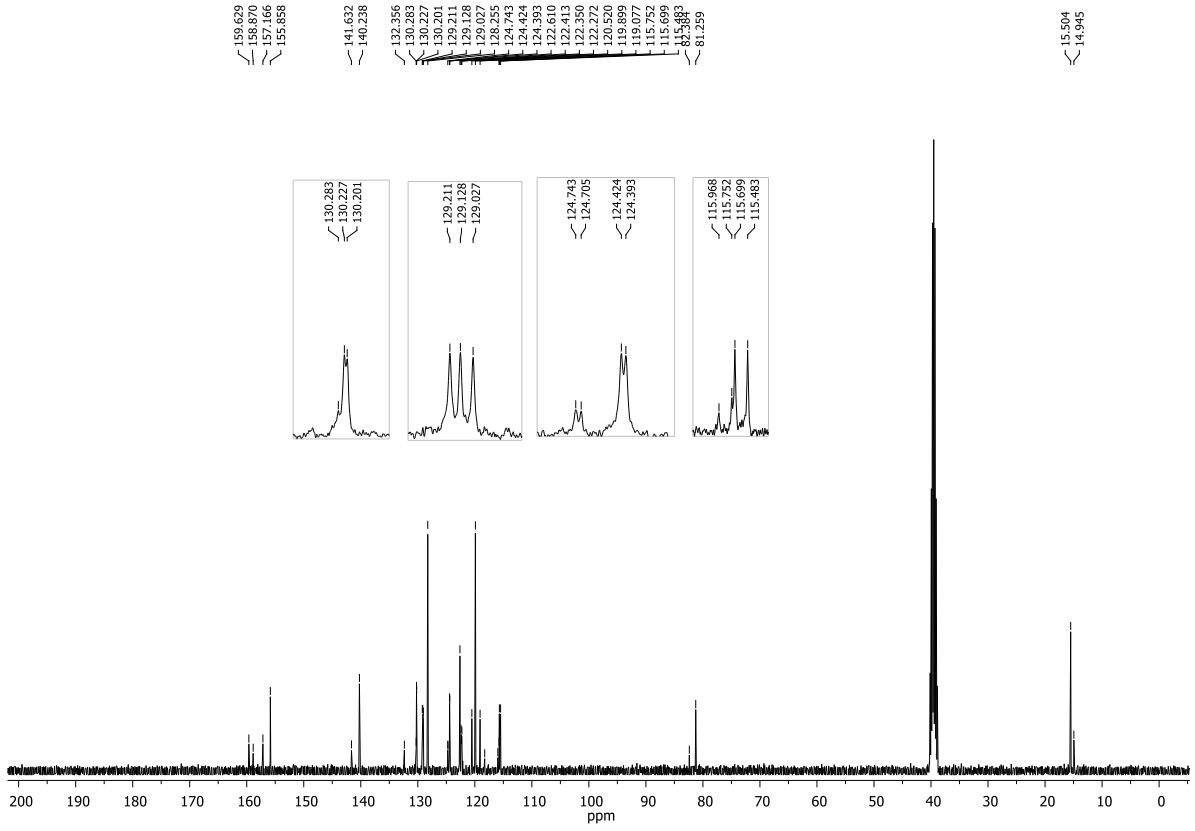


Figure 3.4a. ^{1}H Spectrum of 50b in DMSO-d$_6$ (400 MHz)

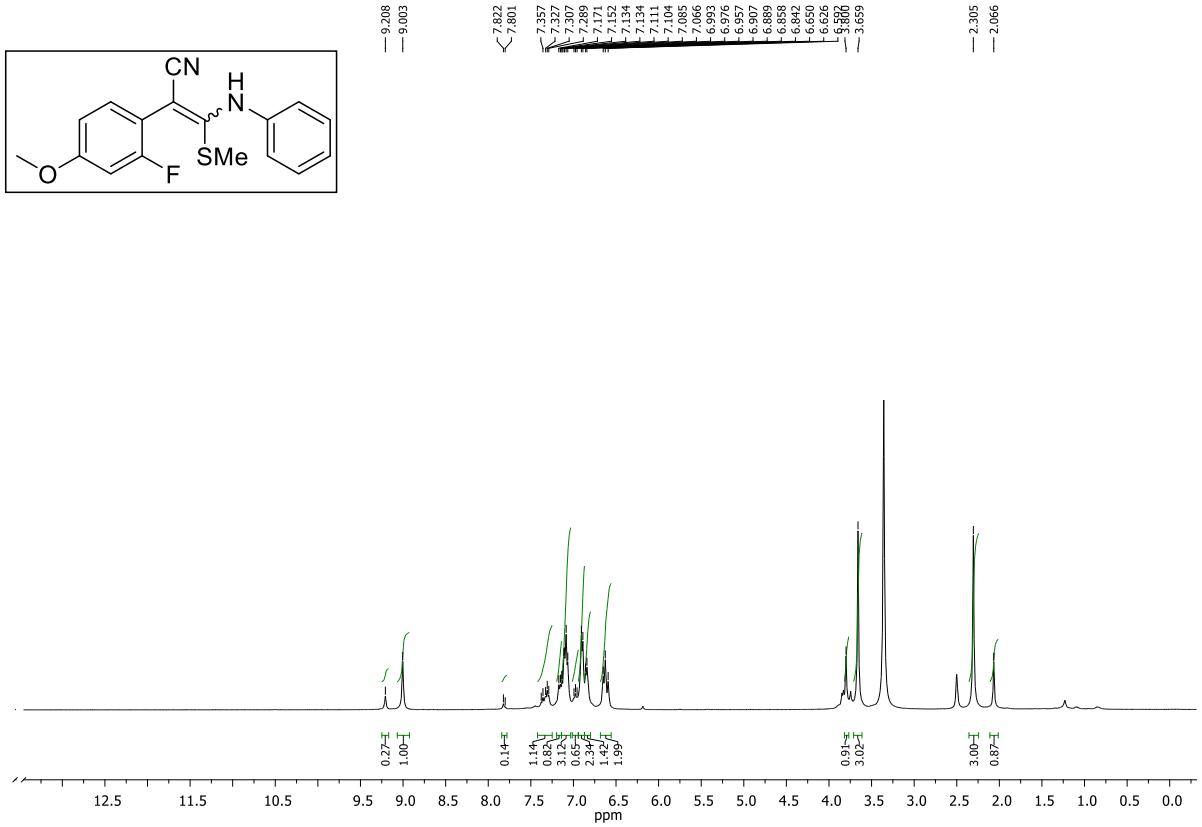


Figure 3.4b. ^{13}C Spectrum of 50b in DMSO-d$_6$ (100 MHz)

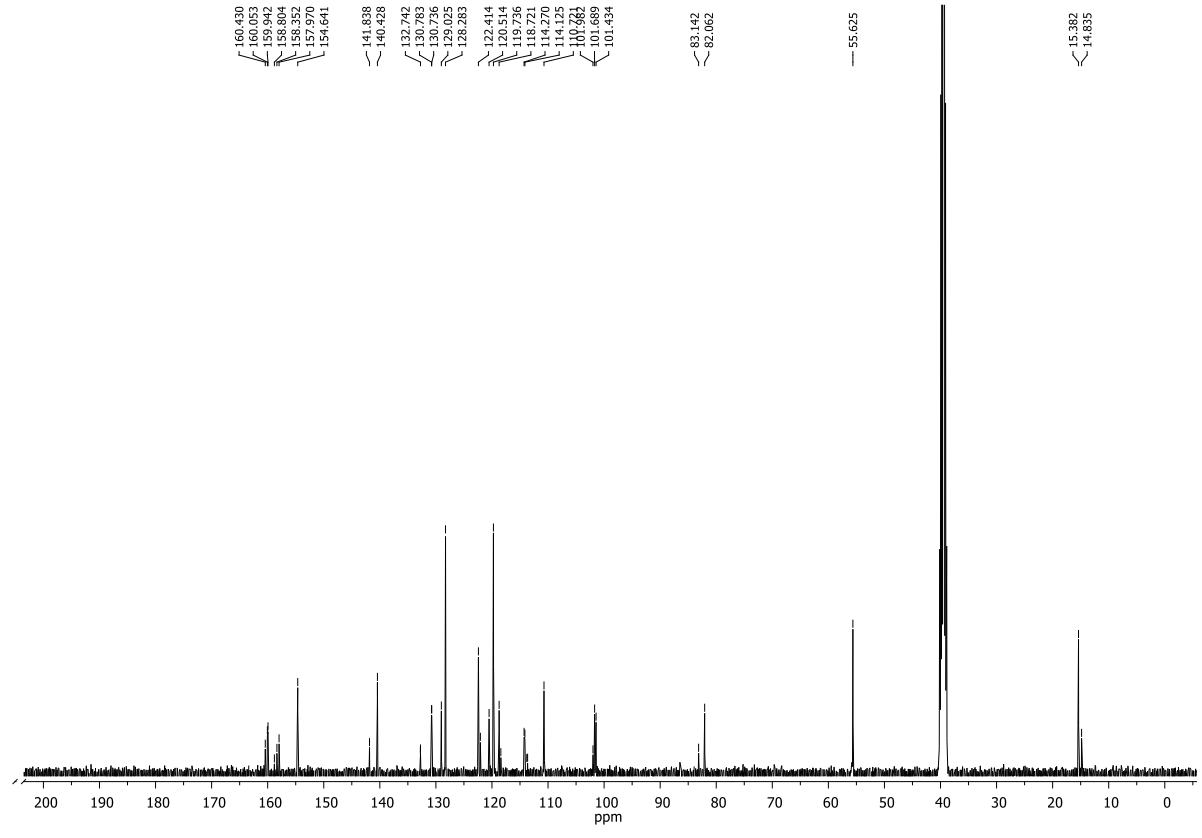


Figure 3.5a. ^{1}H Spectrum of 50c in DMSO-d$_6$ (400 MHz)

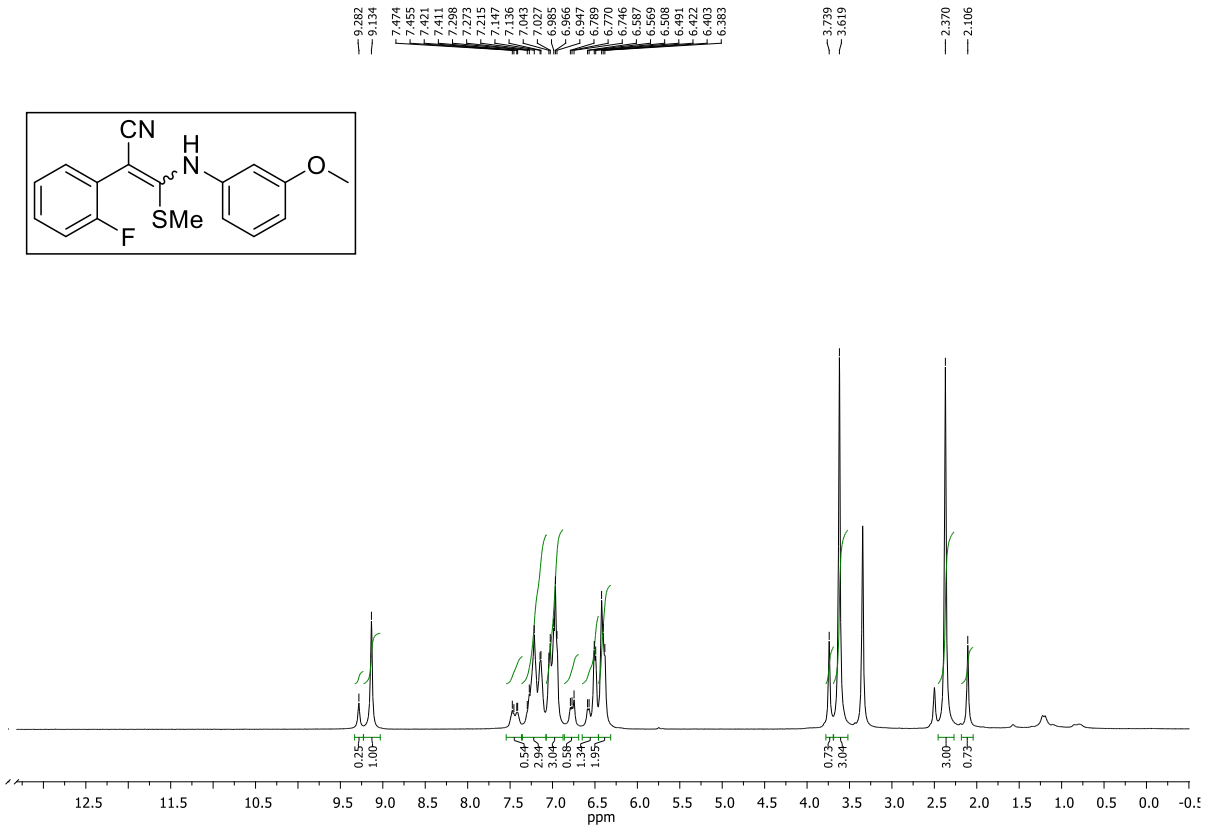


Figure 3.5b. ^{13}C Spectrum of 50c in DMSO-d$_6$ (400 MHz)

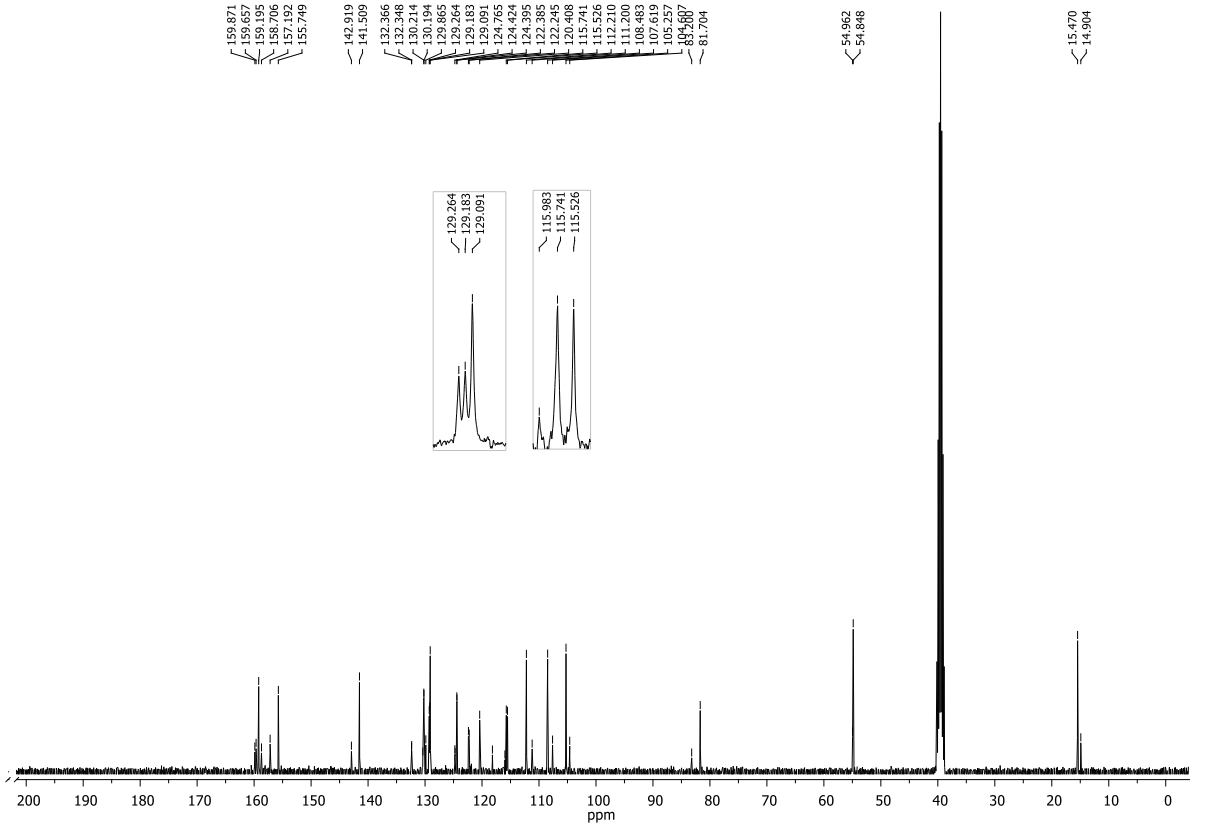


Figure 3.6a. ^{1}H Spectrum of 51a in DMSO-d_6 (400 MHz)

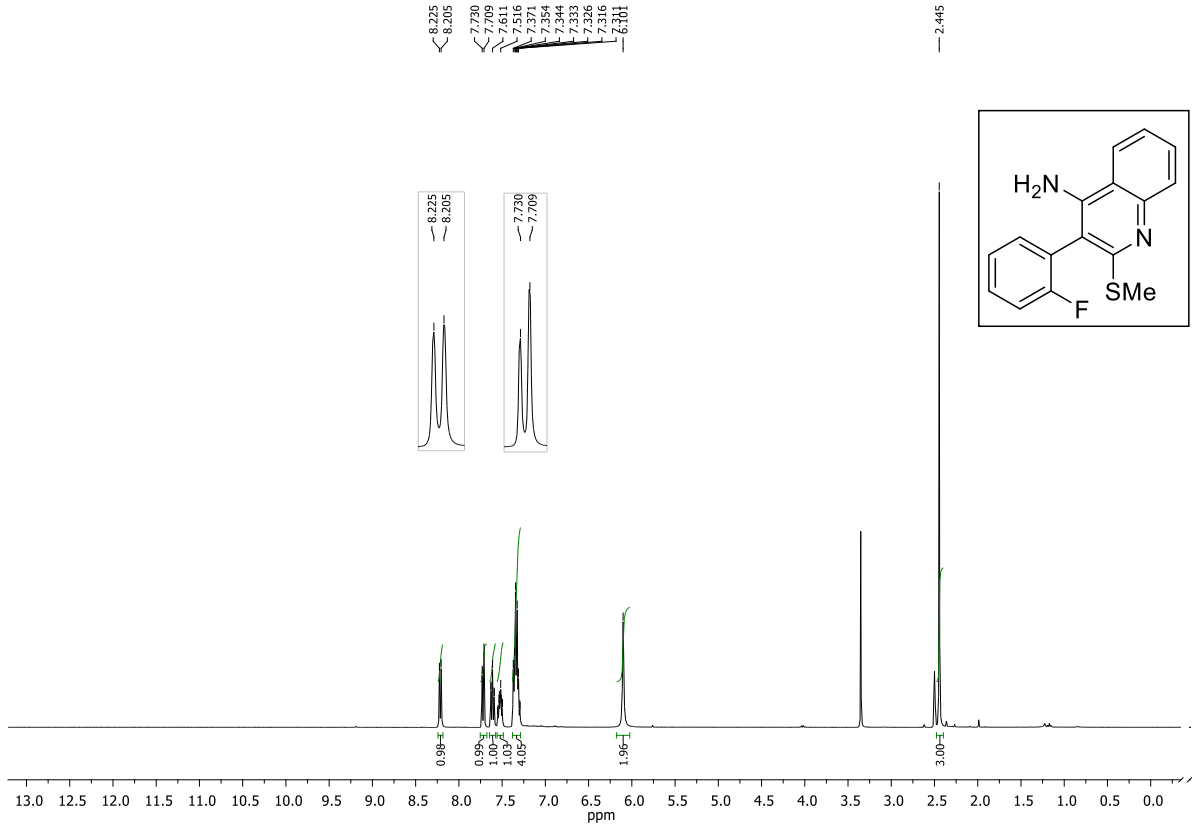


Figure 3.6b. ^{13}C Spectrum of 51a in DMSO-d_6 (100 MHz)

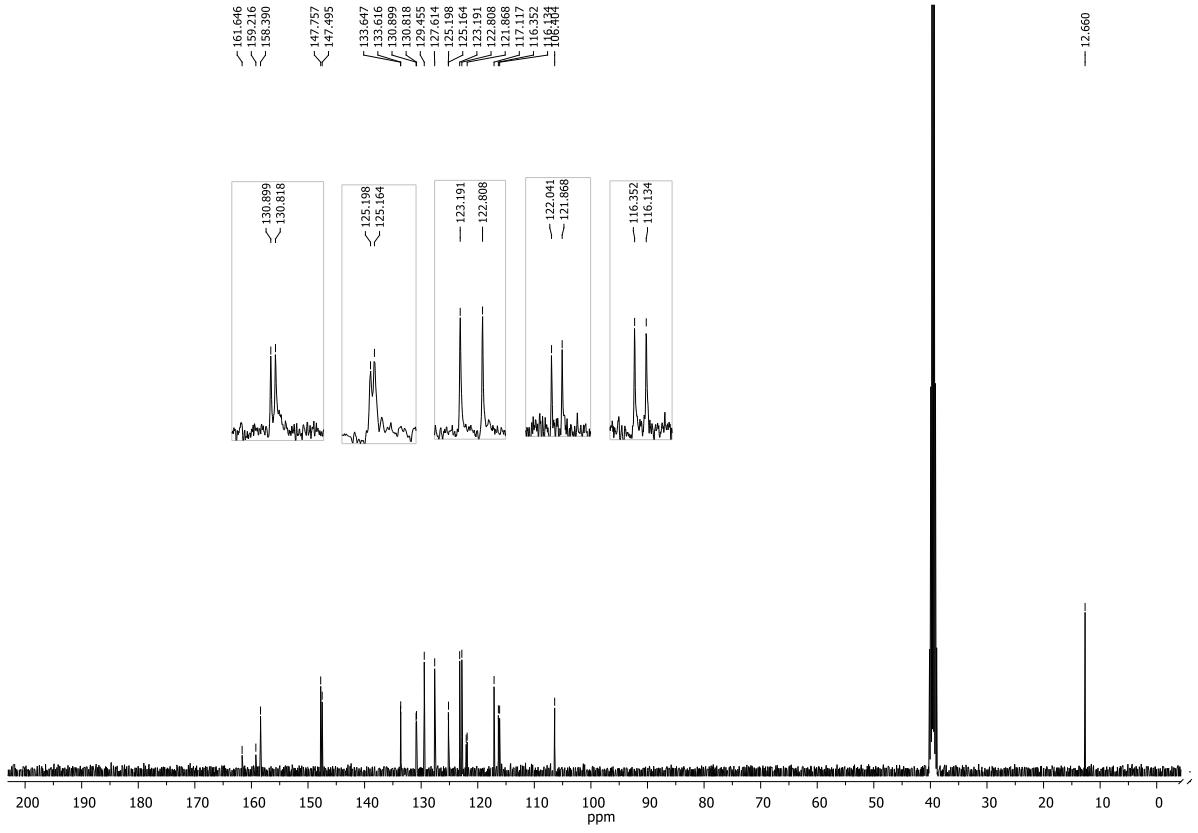


Figure 3.7a. ^{1}H Spectrum of 51b in $CDCl_3$ (400 MHz)

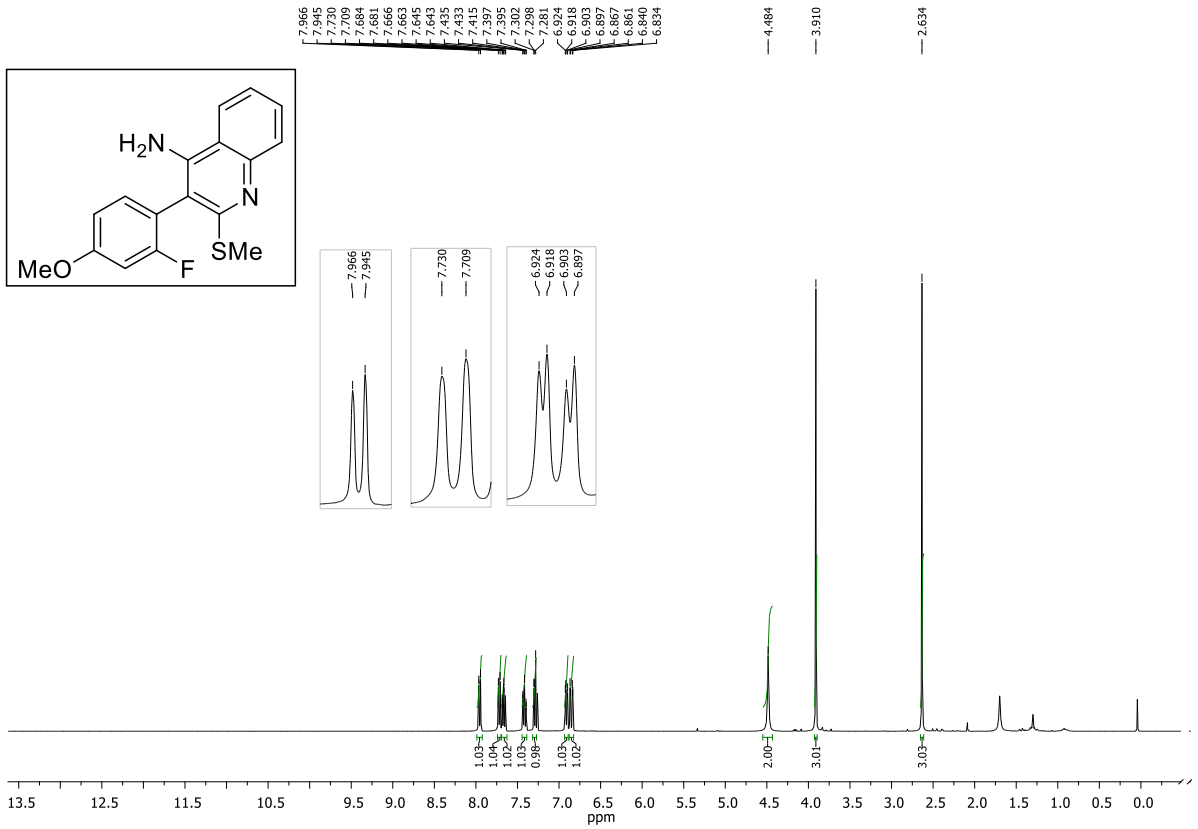


Figure 3.7b. ^{13}C Spectrum of 51b in $CDCl_3$ (100 MHz)

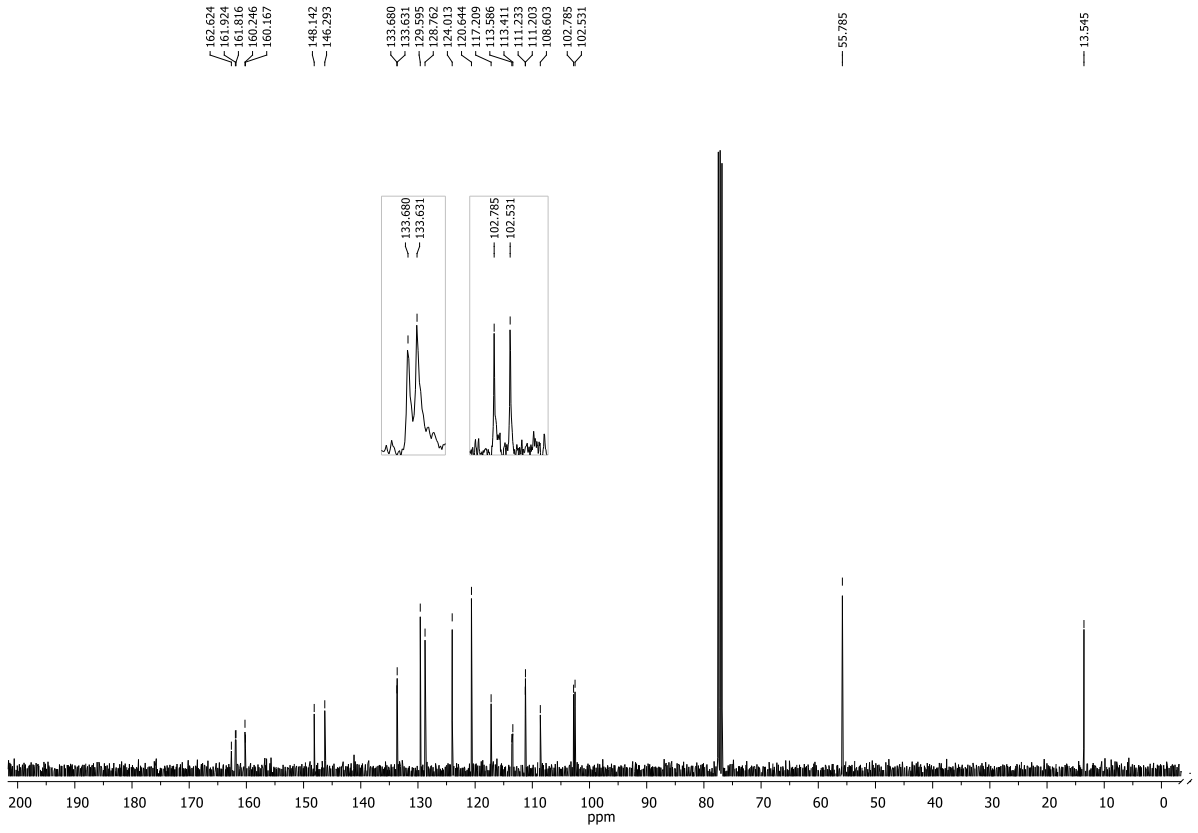


Figure 3.8a. ^{1}H Spectrum of 51c in DMSO-d$_6$ (400 MHz)

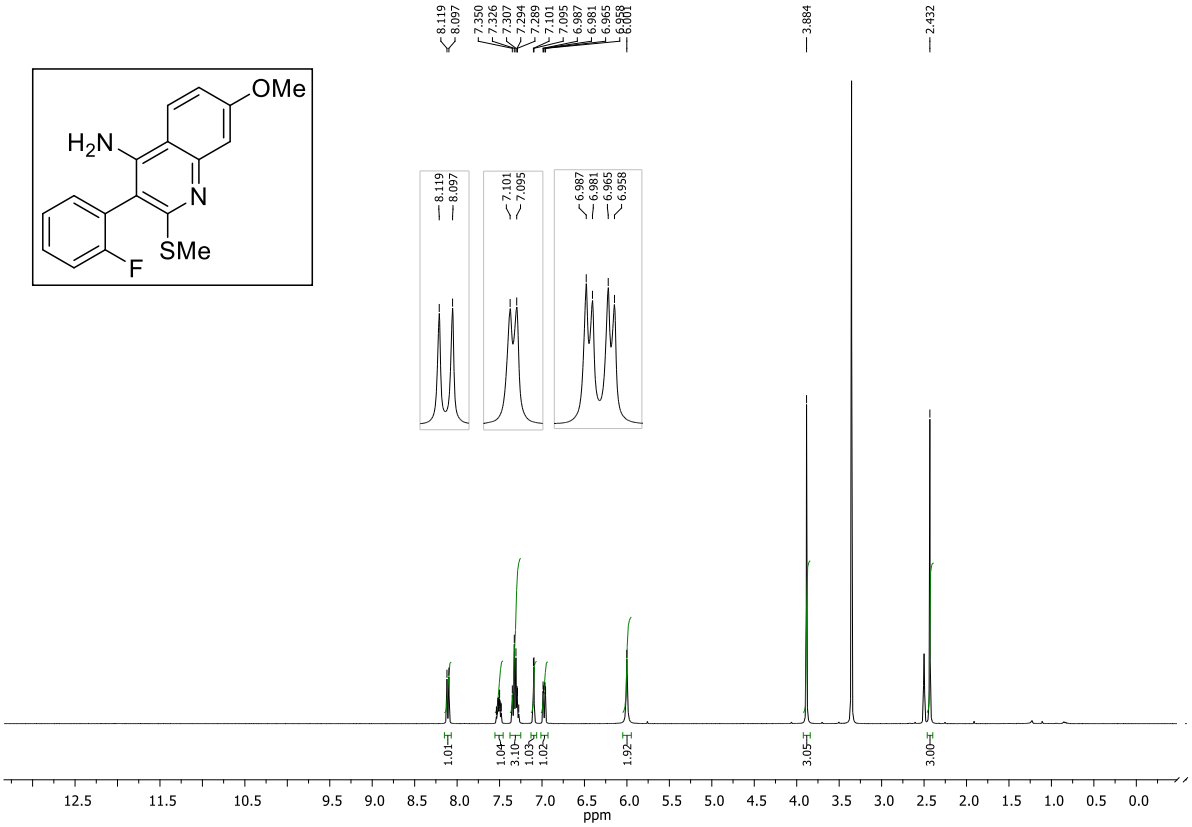


Figure 3.8b. ^{13}C Spectrum of 51c in DMSO-d$_6$ (100 MHz)

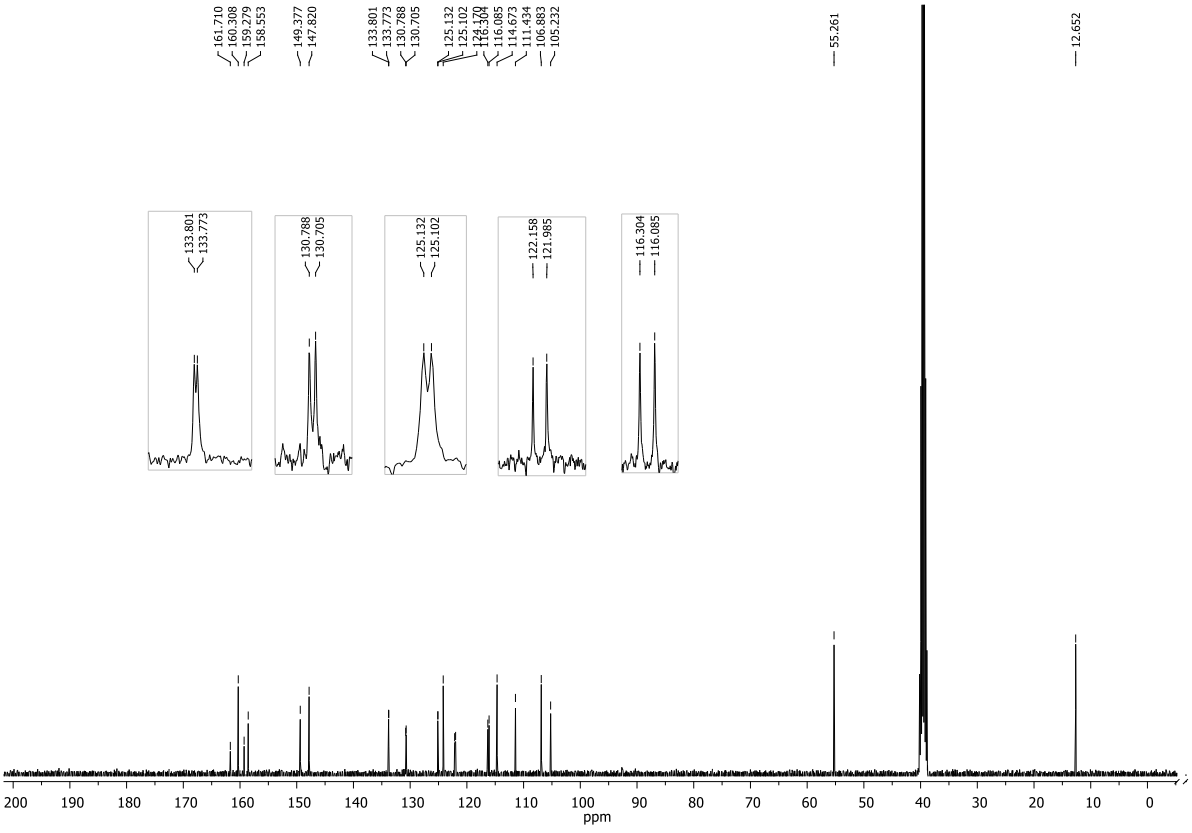


Figure 3.9a. ^{1}H Spectrum of 22a in DMSO-d_6 (400 MHz)

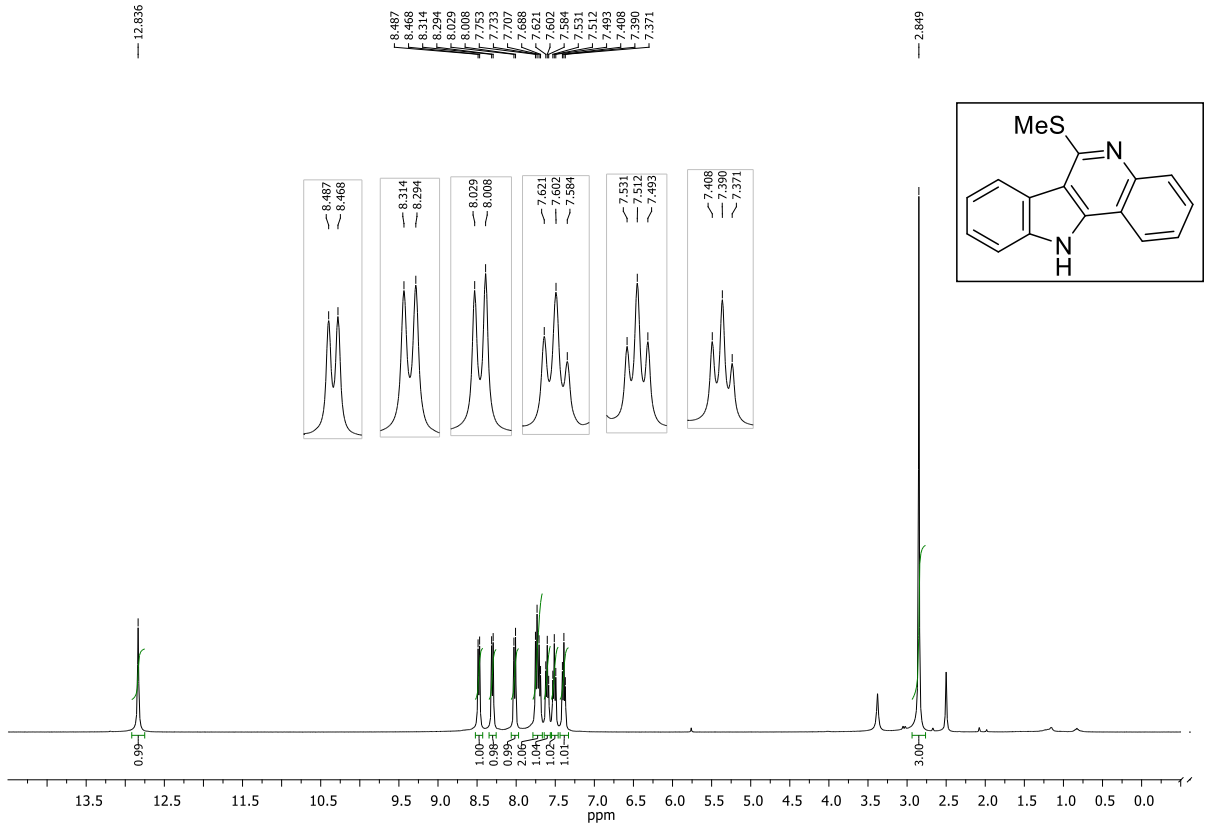


Figure 3.9b. ^{13}C Spectrum of 22a in DMSO-d_6 (100 MHz)

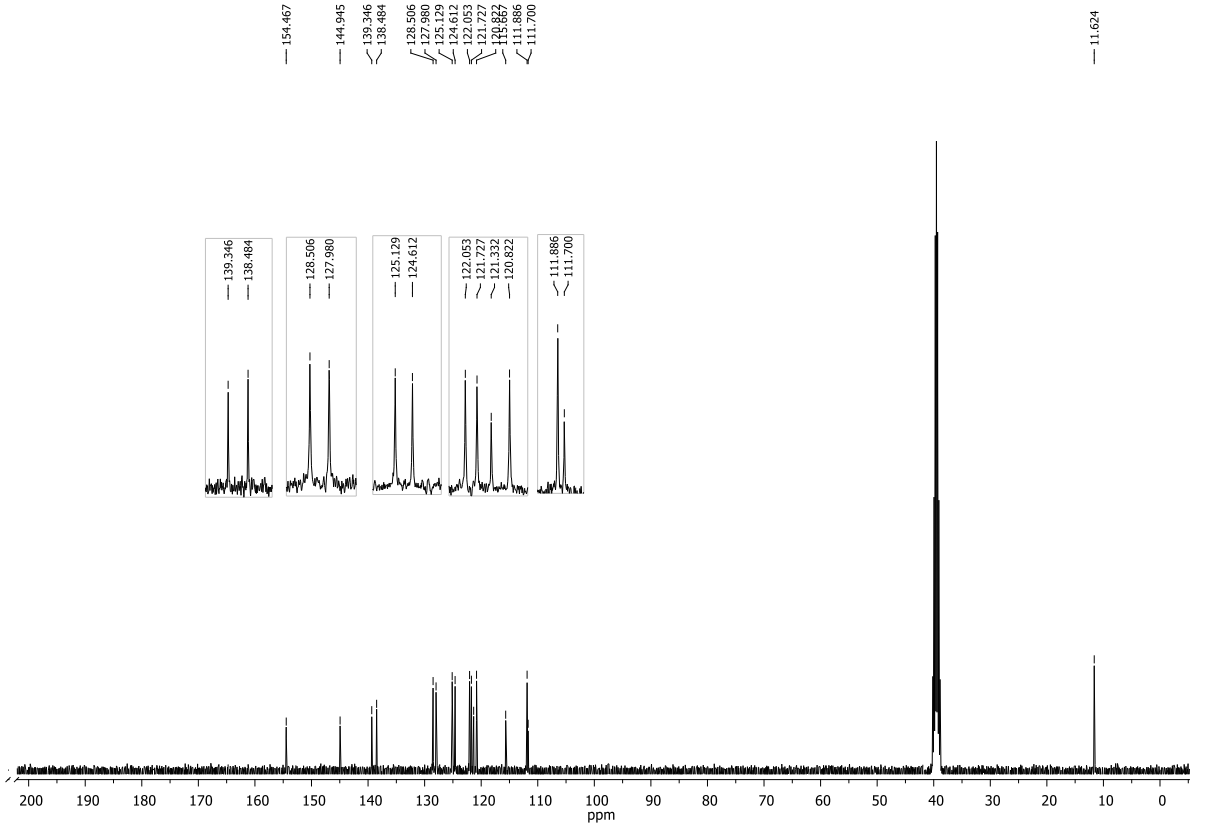


Figure 3.10a. ^{1}H Spectrum of 22b in DMSO-d$_6$ (400 MHz)

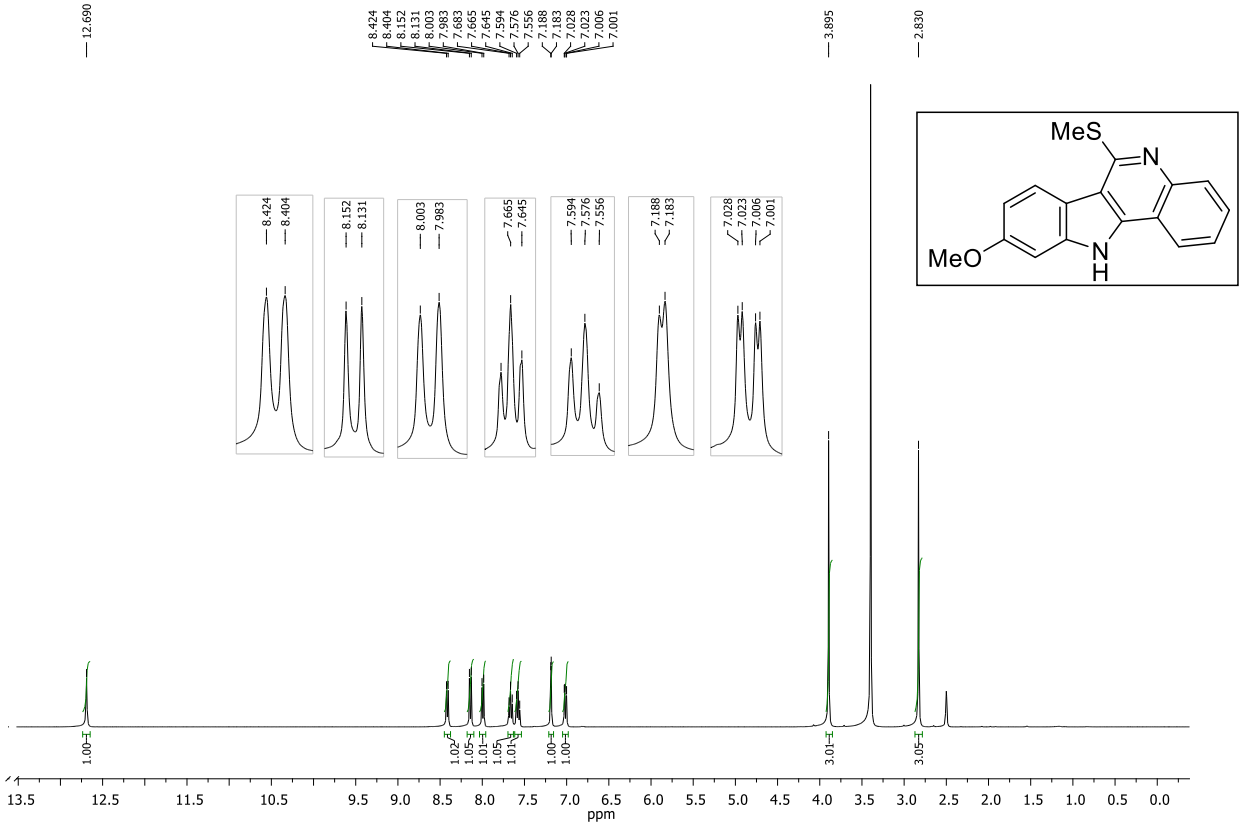


Figure 3.10b. ^{13}C Spectrum of 22b in DMSO-d$_6$ (100 MHz)

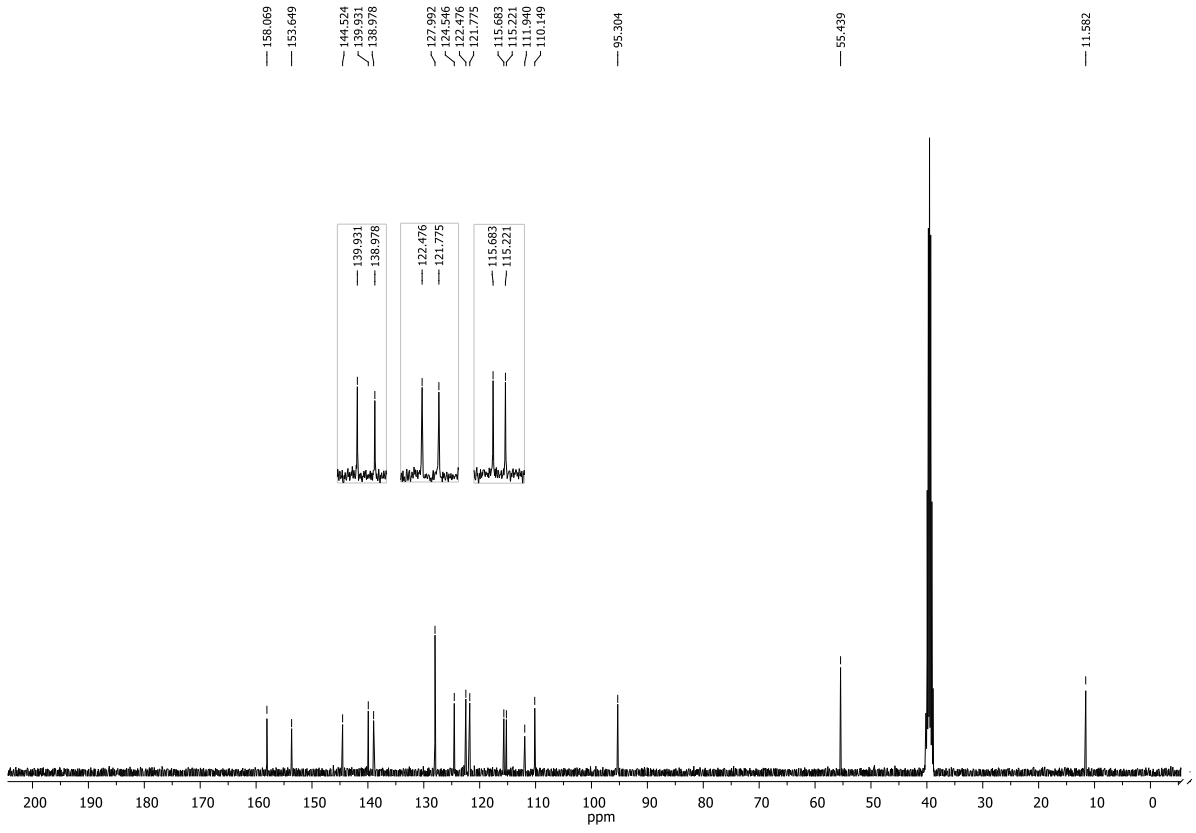


Figure 3.11a. ^{1}H Spectrum of 22c in DMSO-d$_6$ (400 MHz)

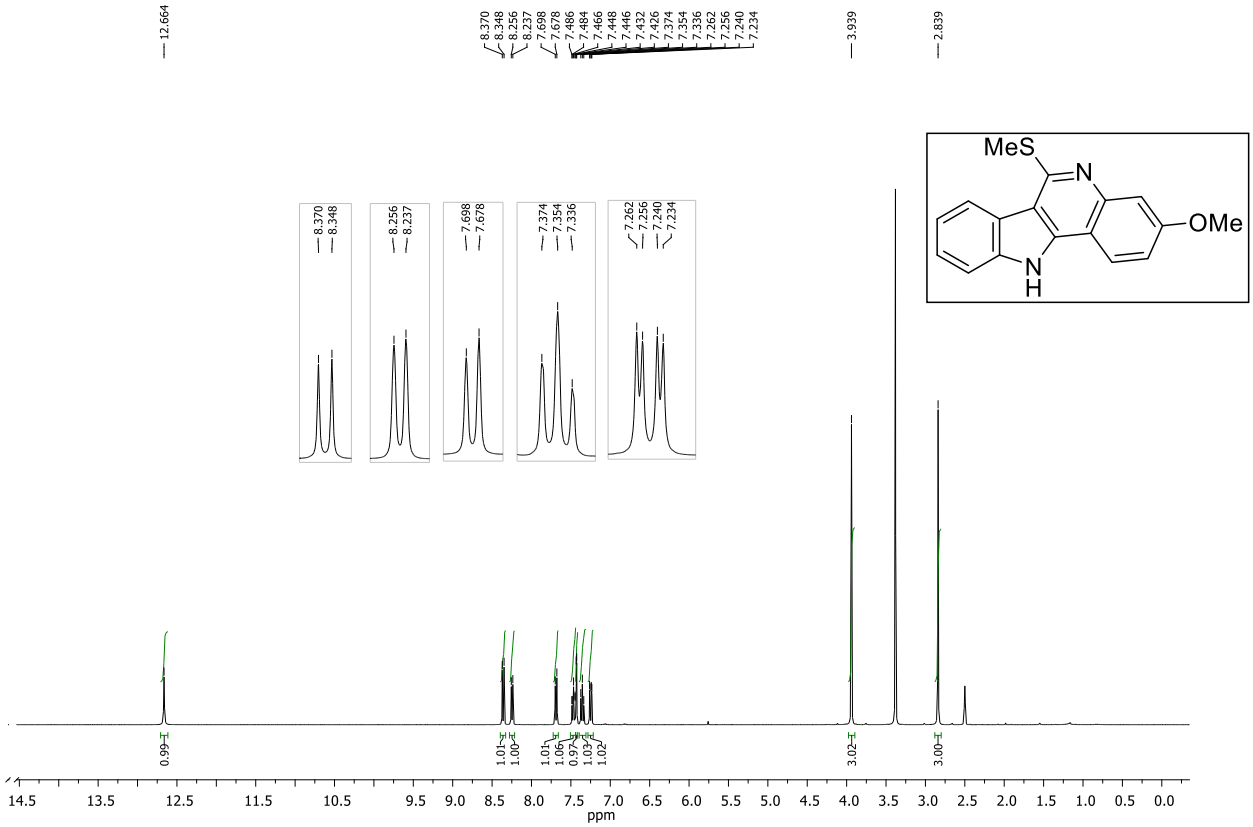


Figure 3.11b. ^{13}C Spectrum of 22c in DMSO-d$_6$ (100 MHz)

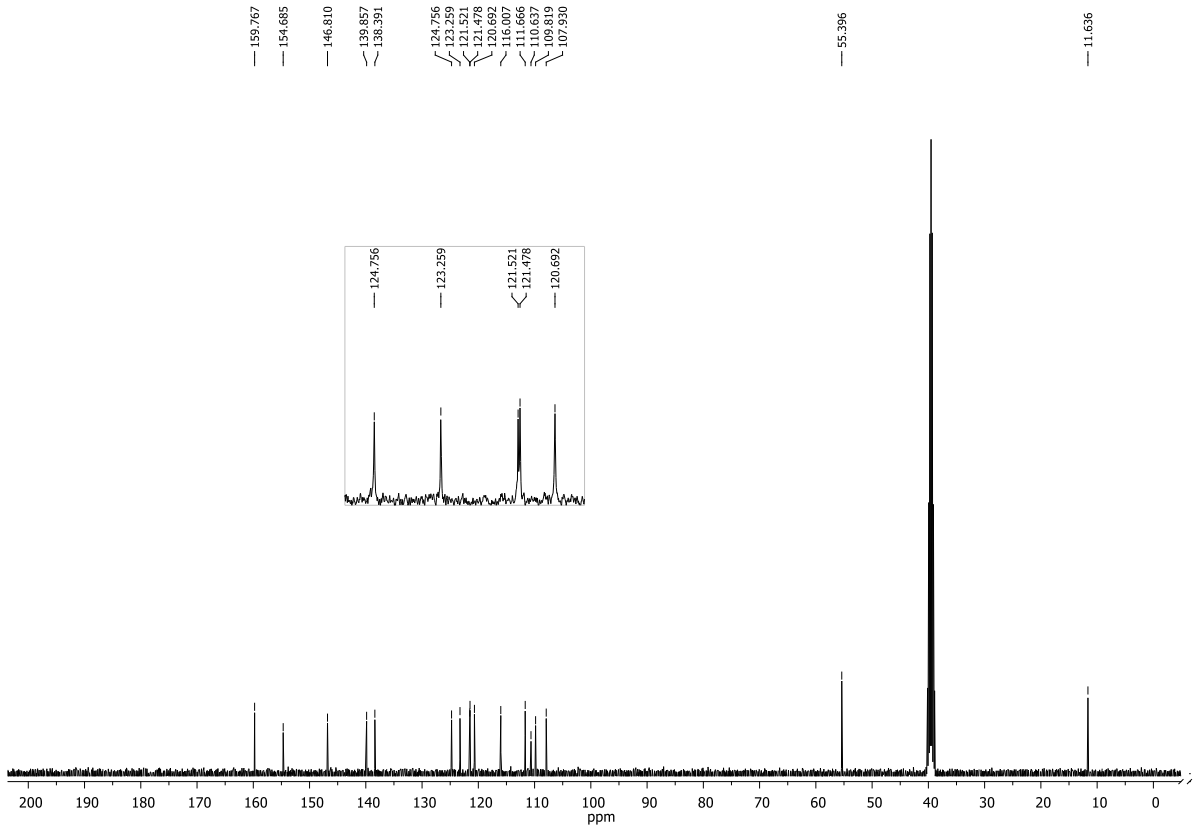


Figure 3.12a. ^{1}H Spectrum of 22a′ in DMSO-d$_6$ (400 MHz)

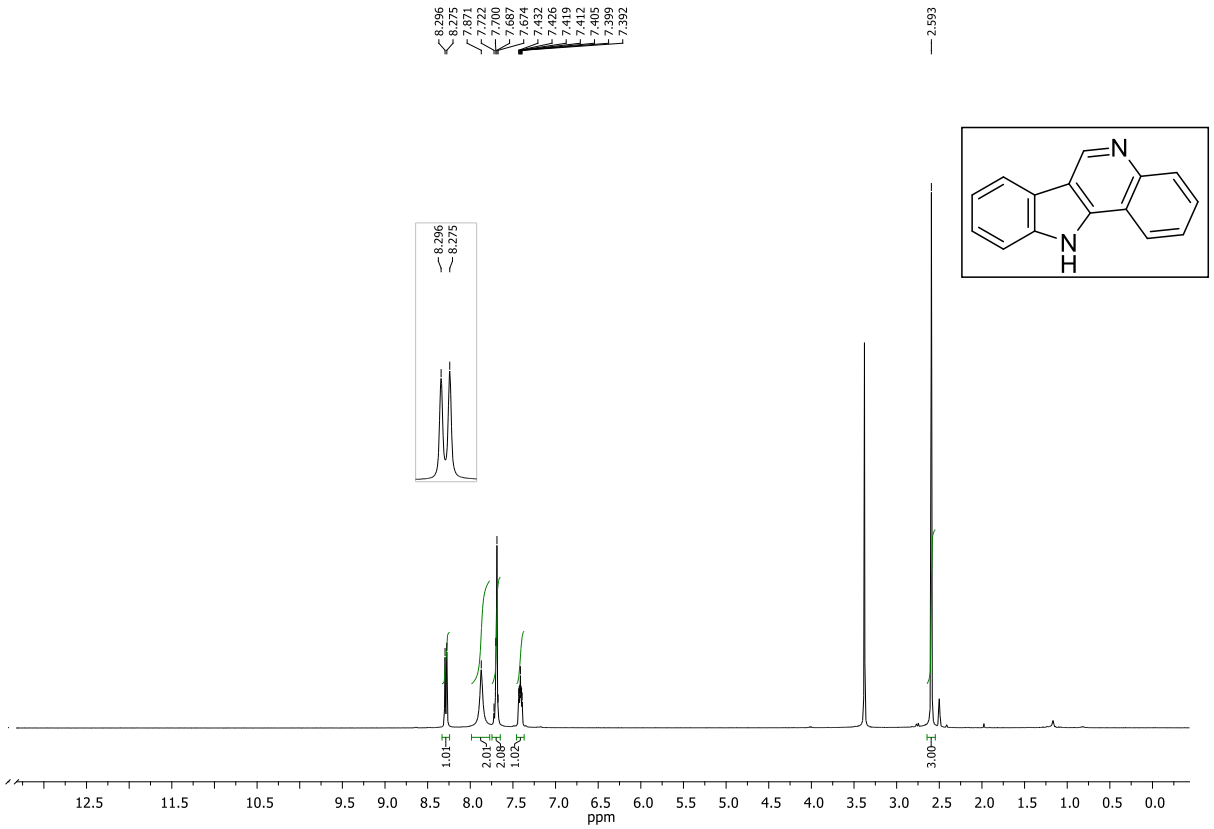


Figure 3.12b. ^{13}C Spectrum of 22a′ in DMSO-d$_6$ (100 MHz)

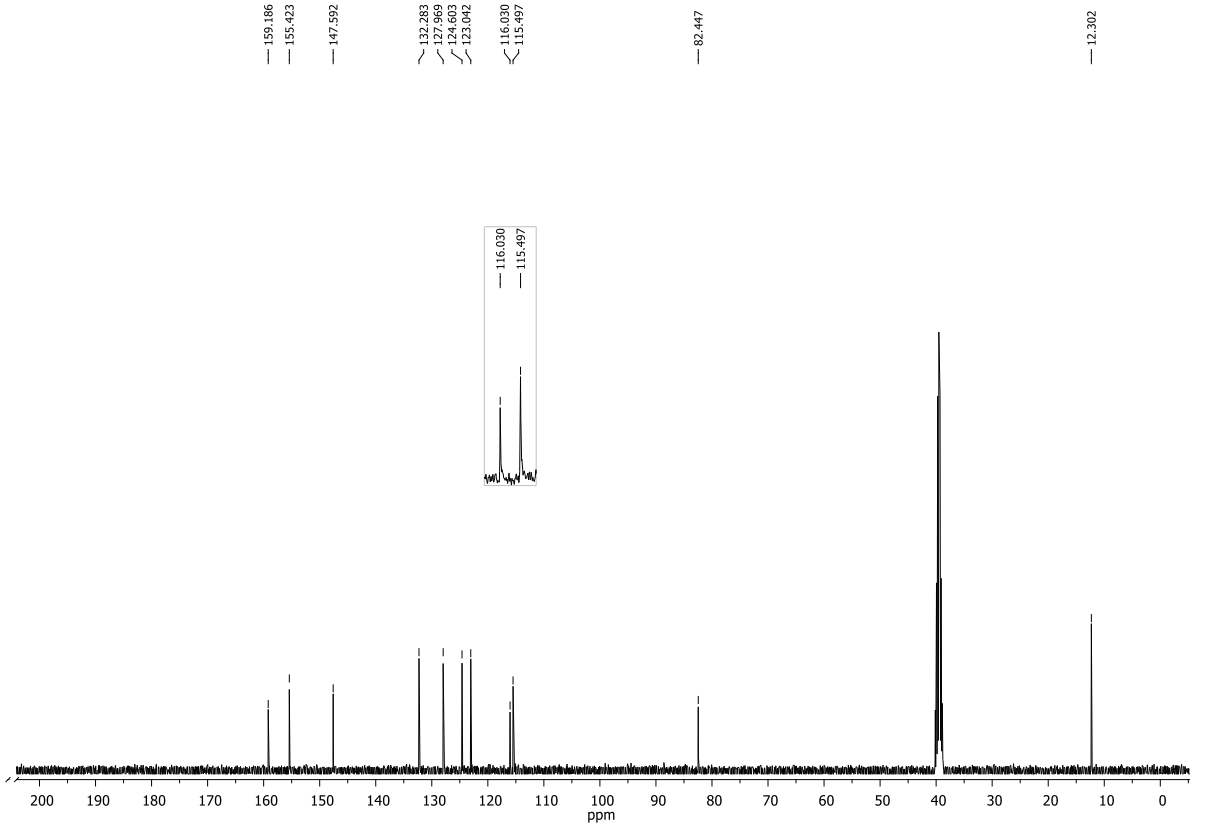


Figure 3.13a. ^{1}H Spectrum of 31a in DMSO-d$_6$ (400 MHz)

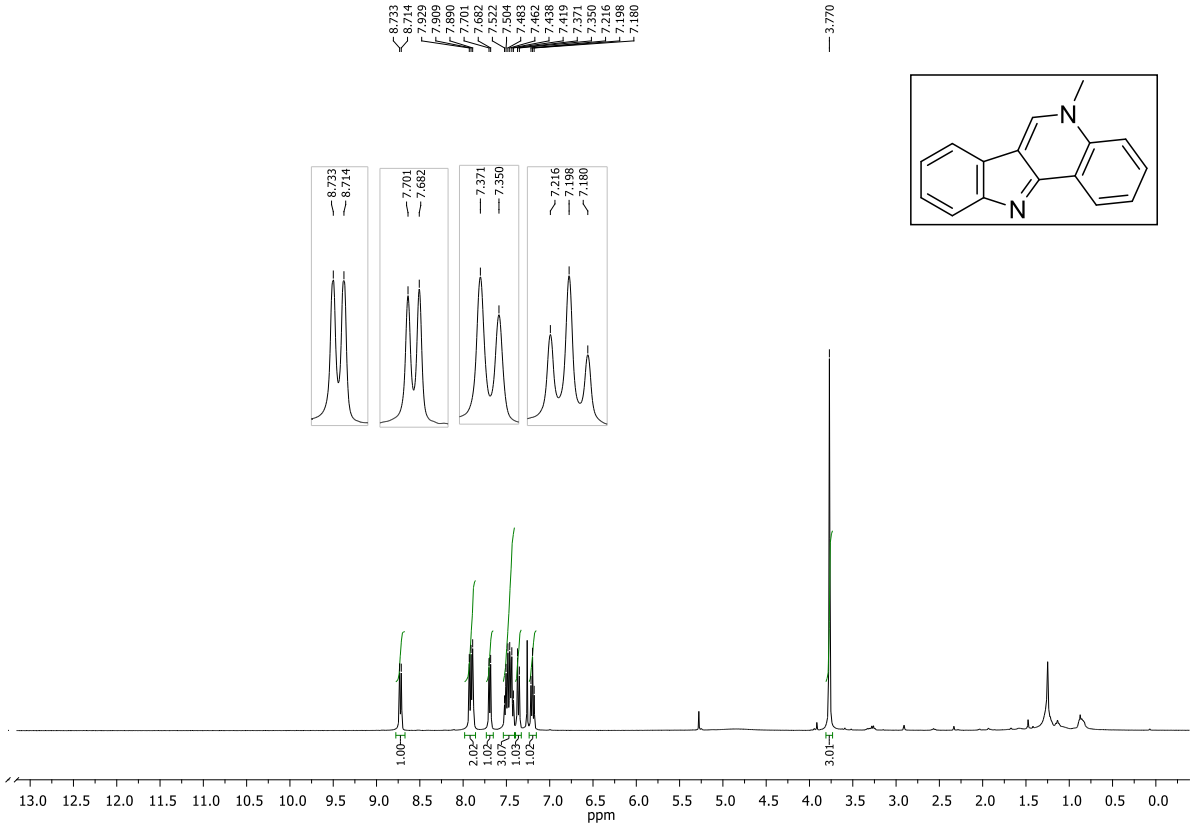


Figure 3.13b.^{13}C Spectrum of 31a in DMSO-d$_6$ (100 MHz)

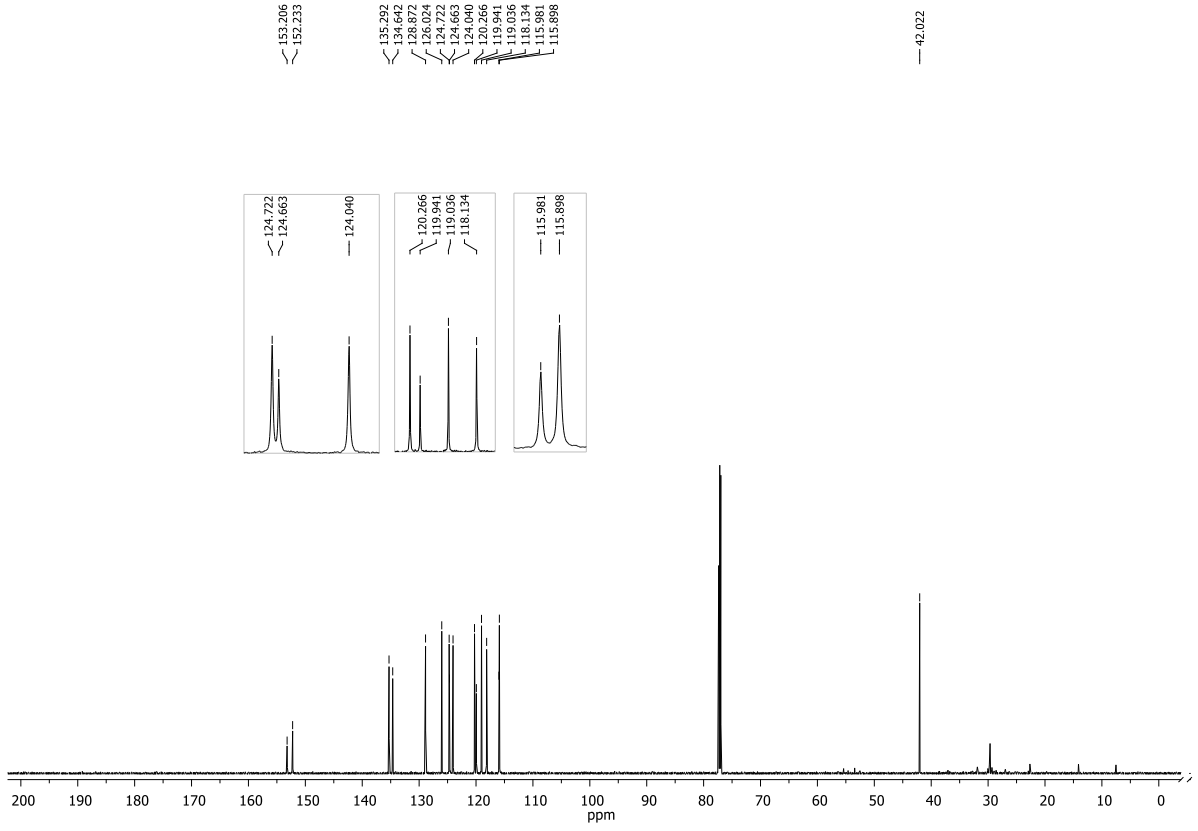


Figure 3.14a. ^{1}H NMR Spectrum of 55a in $CDCl_3$ at 400 MHz

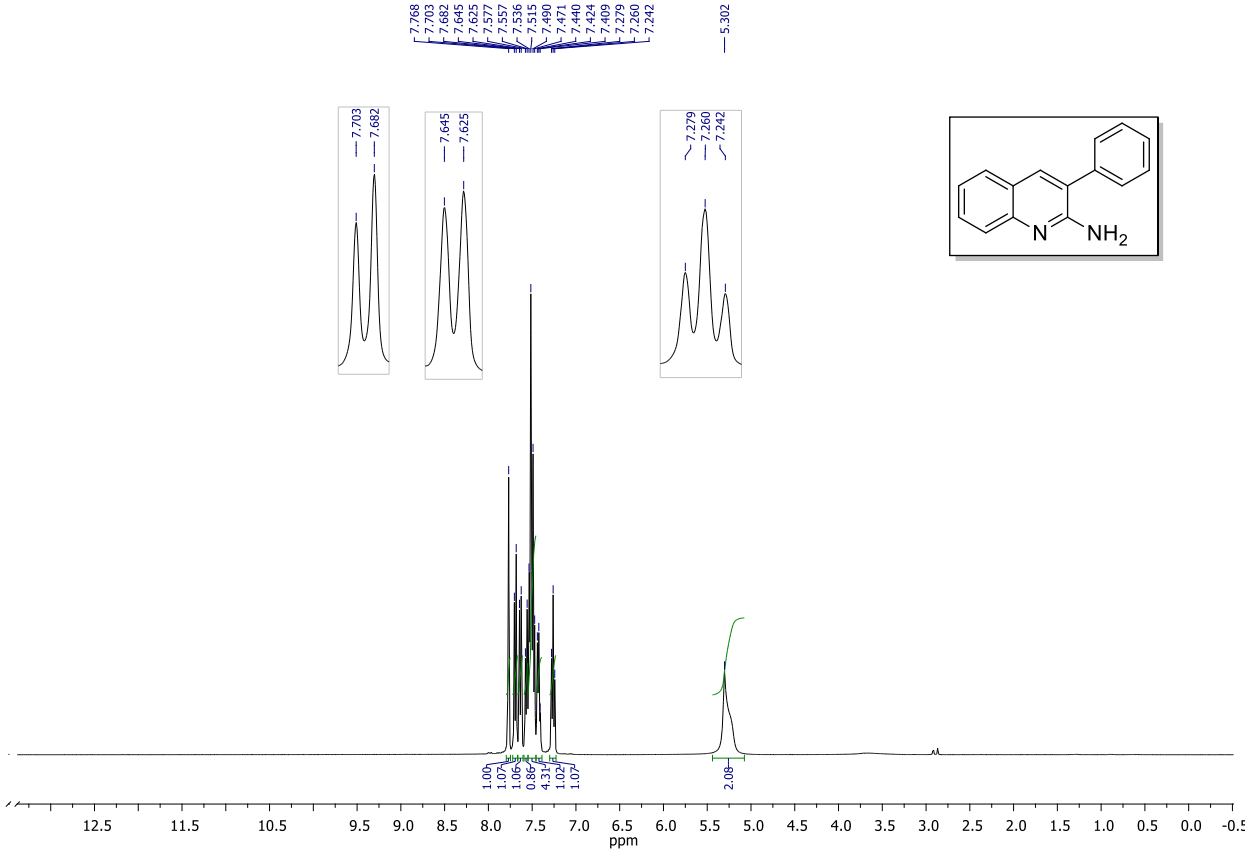


Figure 3.14b. ^{13}C NMR of Spectrum of 55a in $CDCl_3$ at 100 MHz

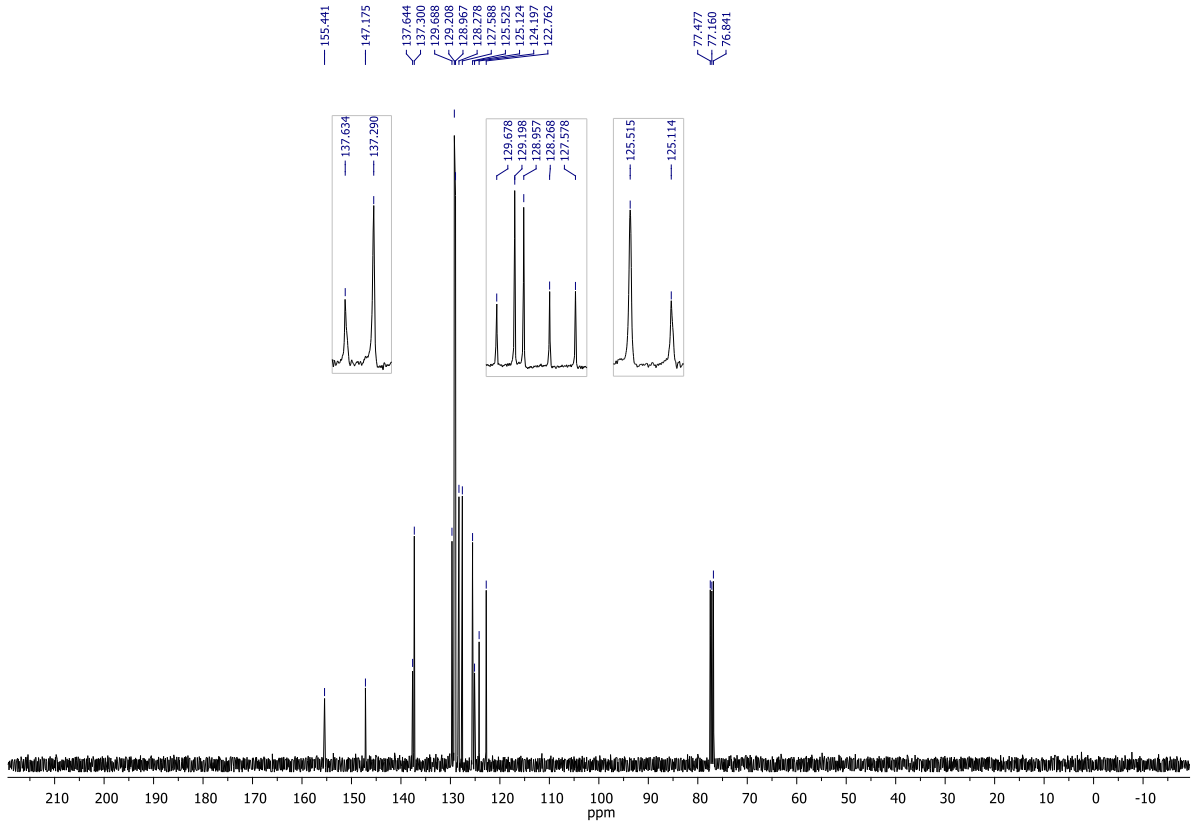


Figure 3.15a. ^{1}H NMR Spectrum of 55b in $CDCl_3$ at 400 MHz

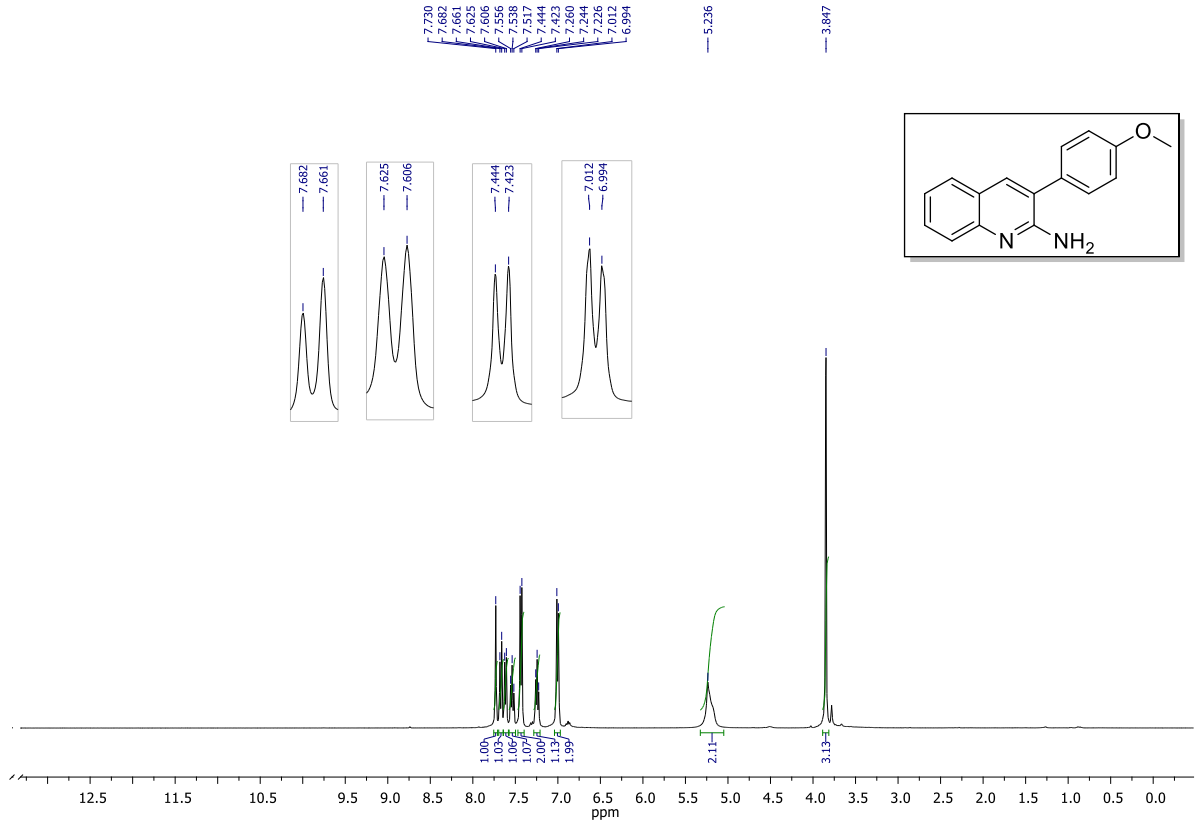


Figure 3.15b. ^{13}C NMR of Spectrum of 55b in $CDCl_3$ at 100 MHz

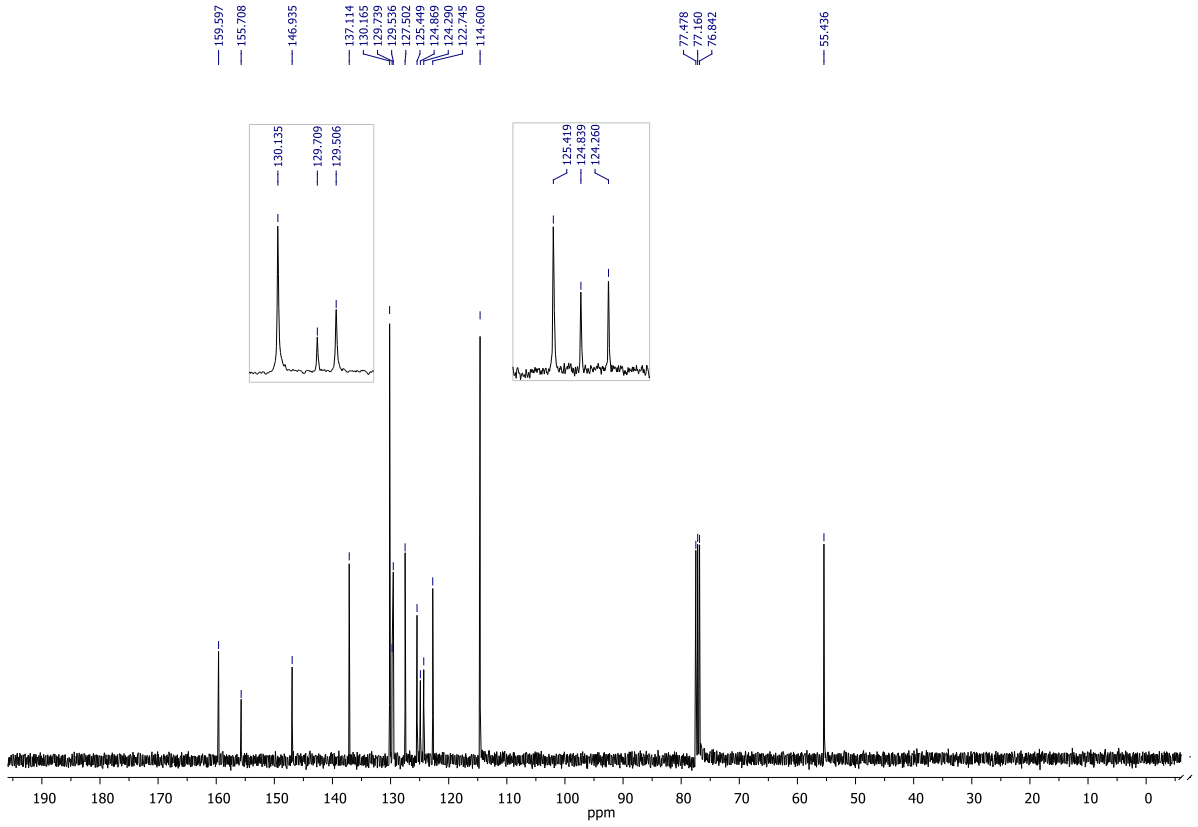


Figure 3.16a. ^{1}H NMR Spectrum of 55p in $CDCl_3$ at 400 MHz

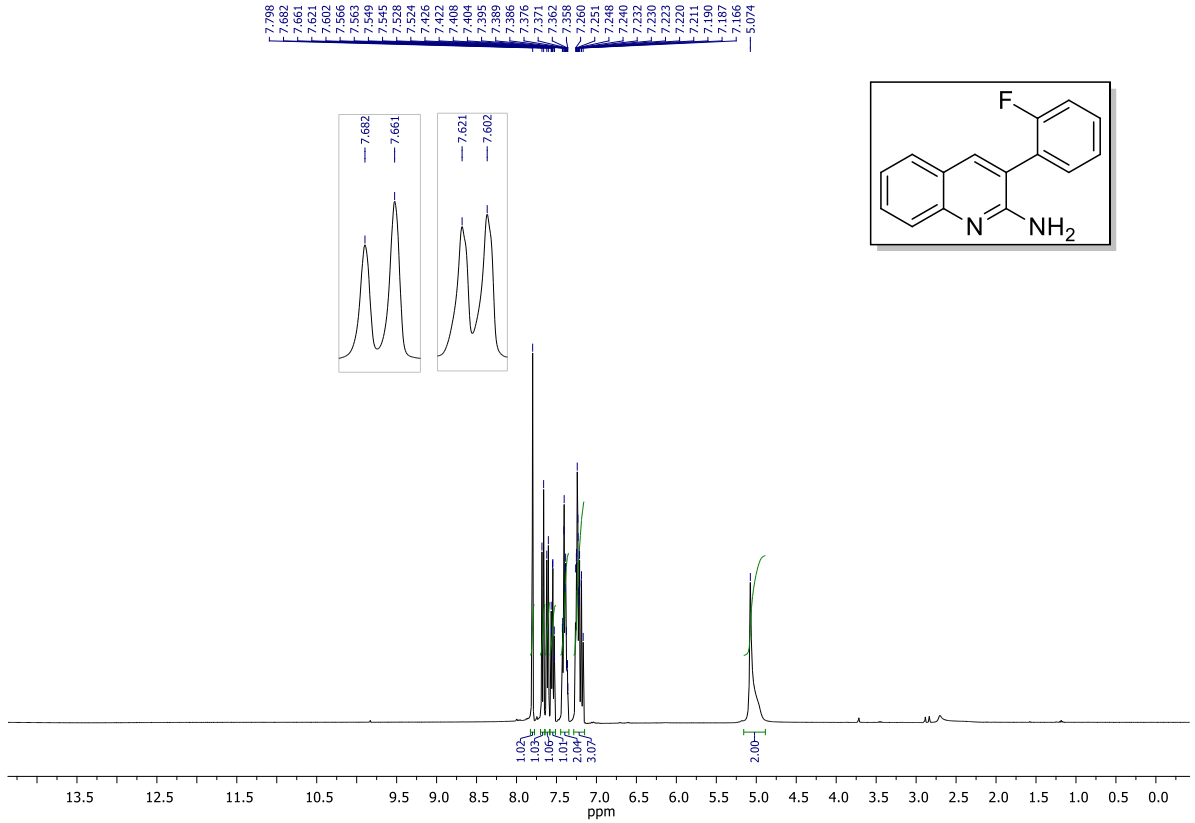


Figure 3.16b. ^{13}C NMR Spectrum of 55p in $CDCl_3$ at 176 MHz

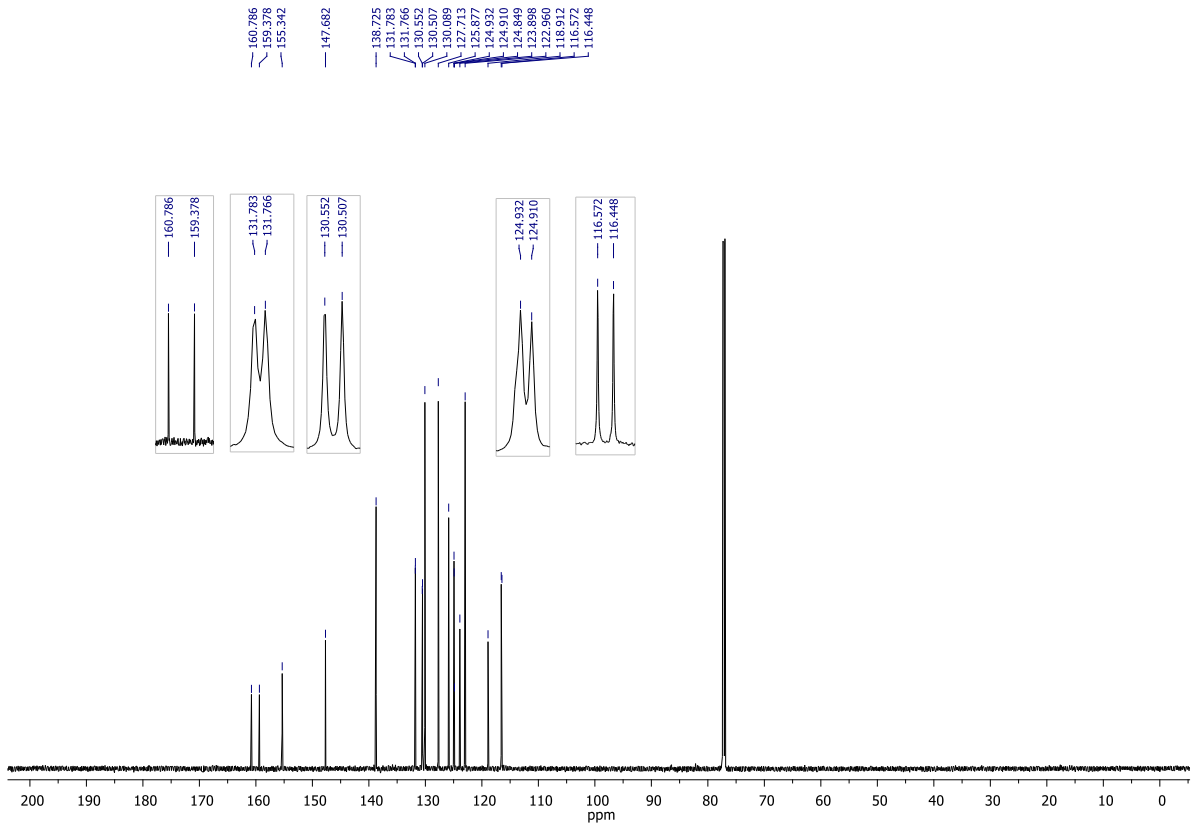


Figure 3.17a. ^{1}H NMR Spectrum of 55t in $CDCl_3$ at 400 MHz

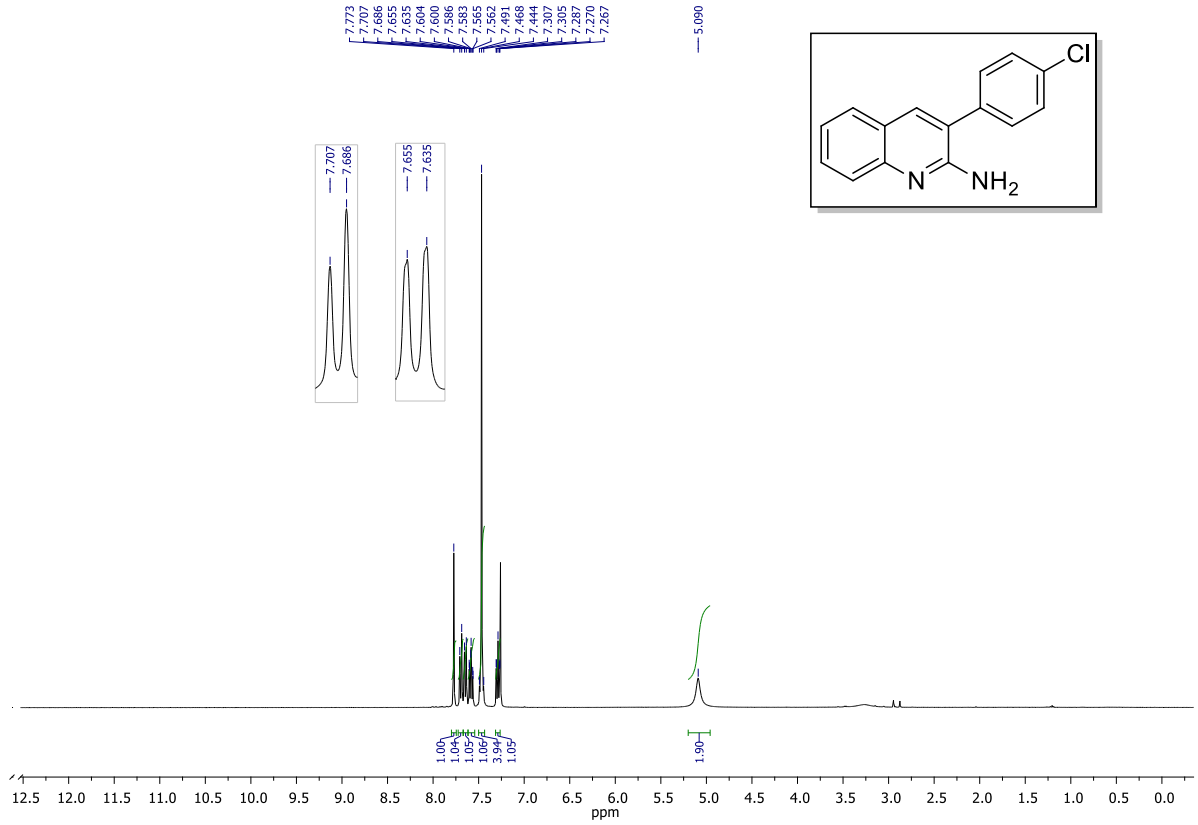


Figure 3.17b. ^{13}C NMR Spectrum of 55t in $CDCl_3$ at 176 MHz

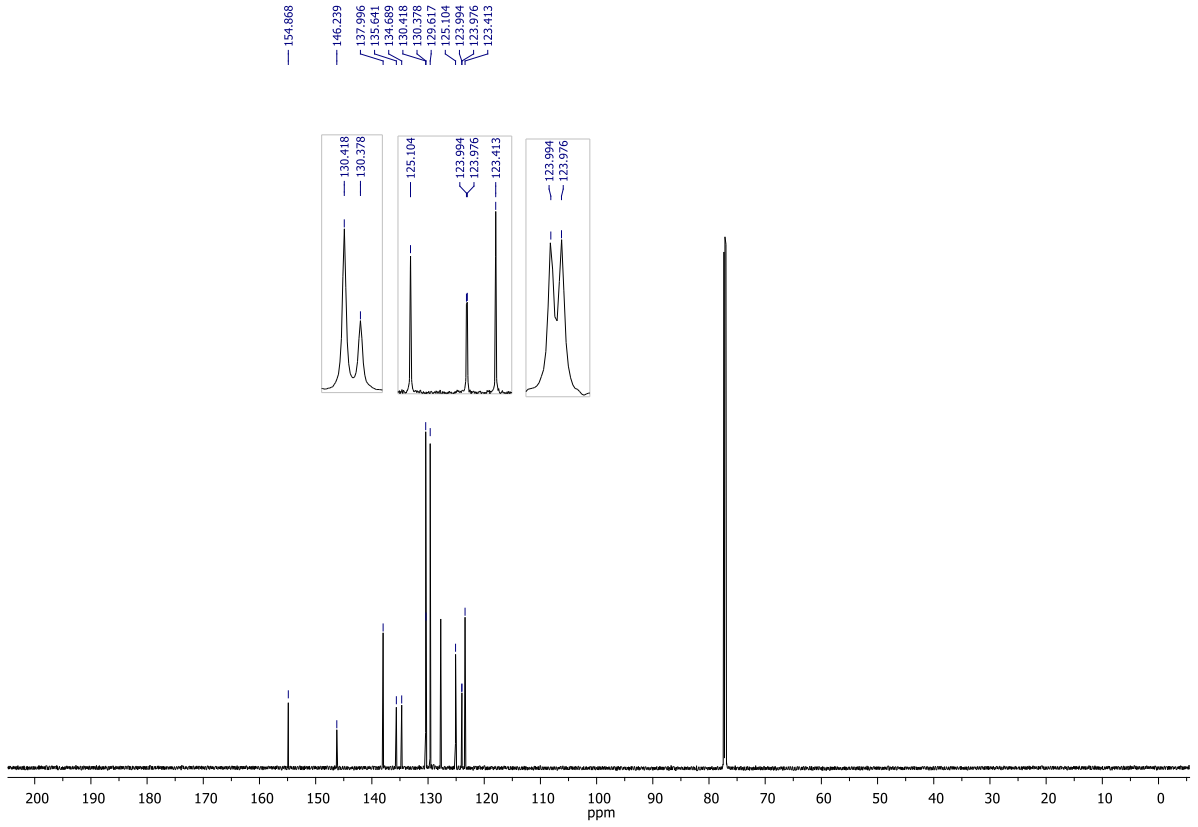


Figure 3.18a. ^{1}H NMR Spectrum of 55u in $CDCl_3$ at 400 MHz

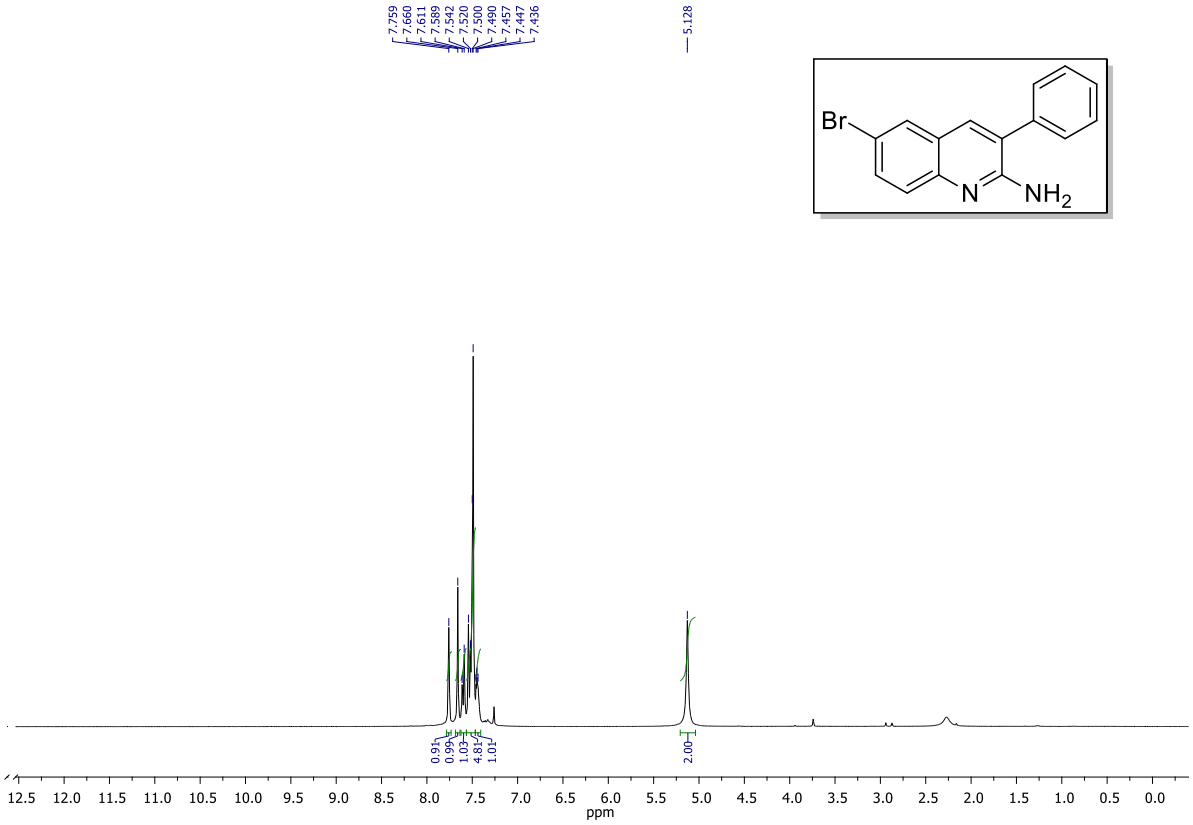


Figure 3.18b. ^{13}C NMR Spectrum of 55u in $CDCl_3$ at 100 MHz

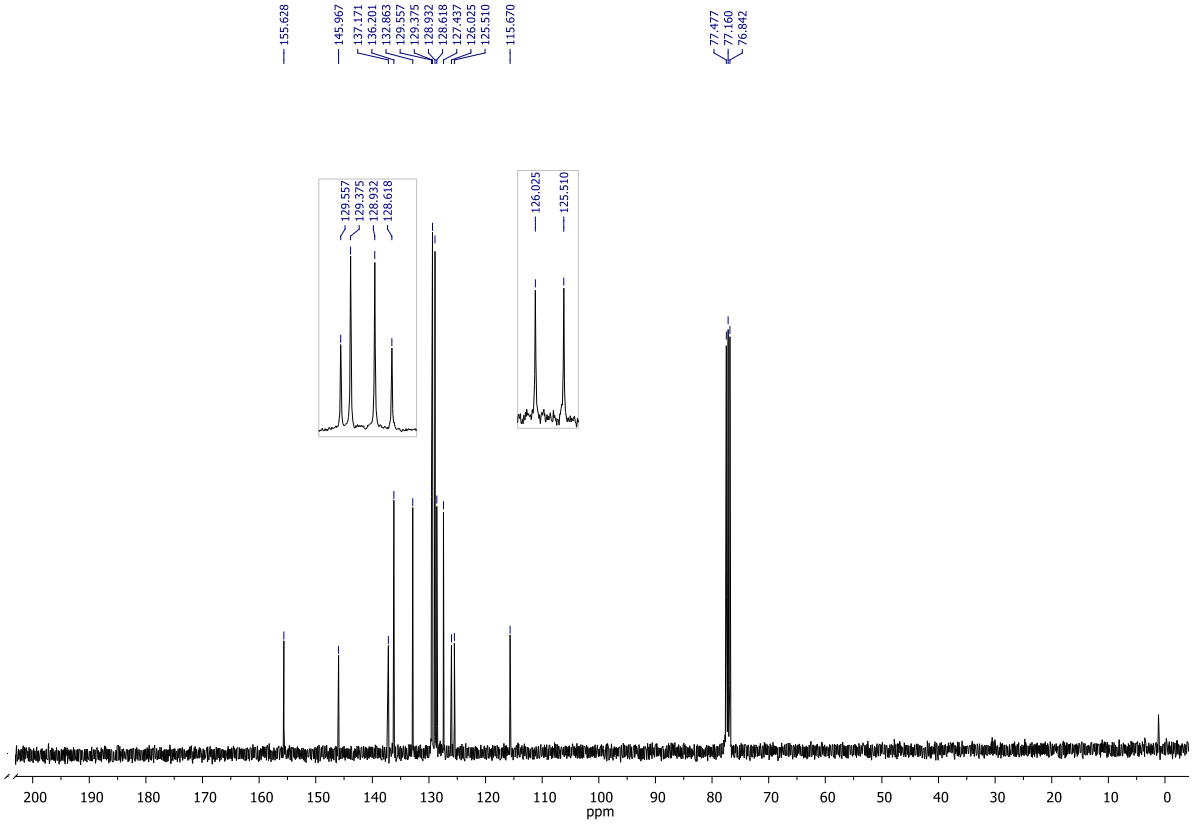


Figure 3.19a. ^{1}H NMR Spectrum of 56a in DMSO at 700 MHz

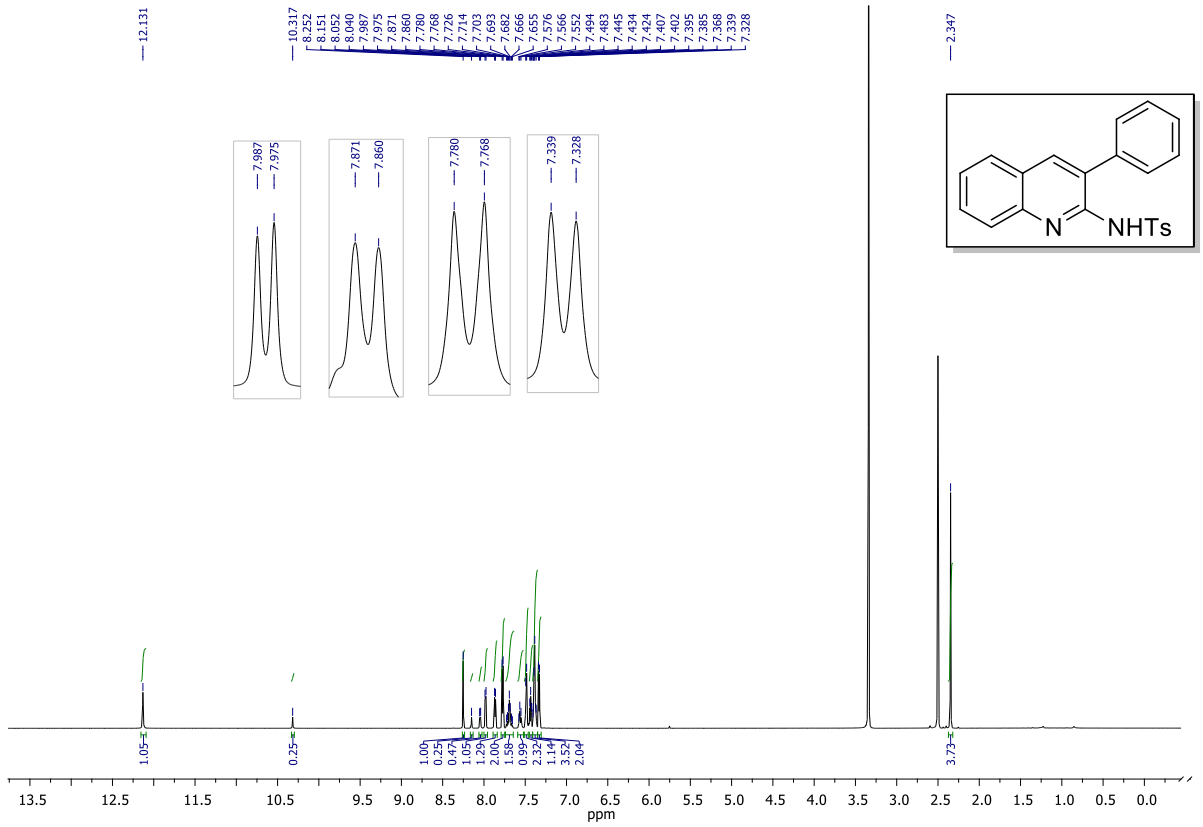


Figure 3.19b. ^{13}C NMR Spectrum of 56a in DMSO at 100 MHz

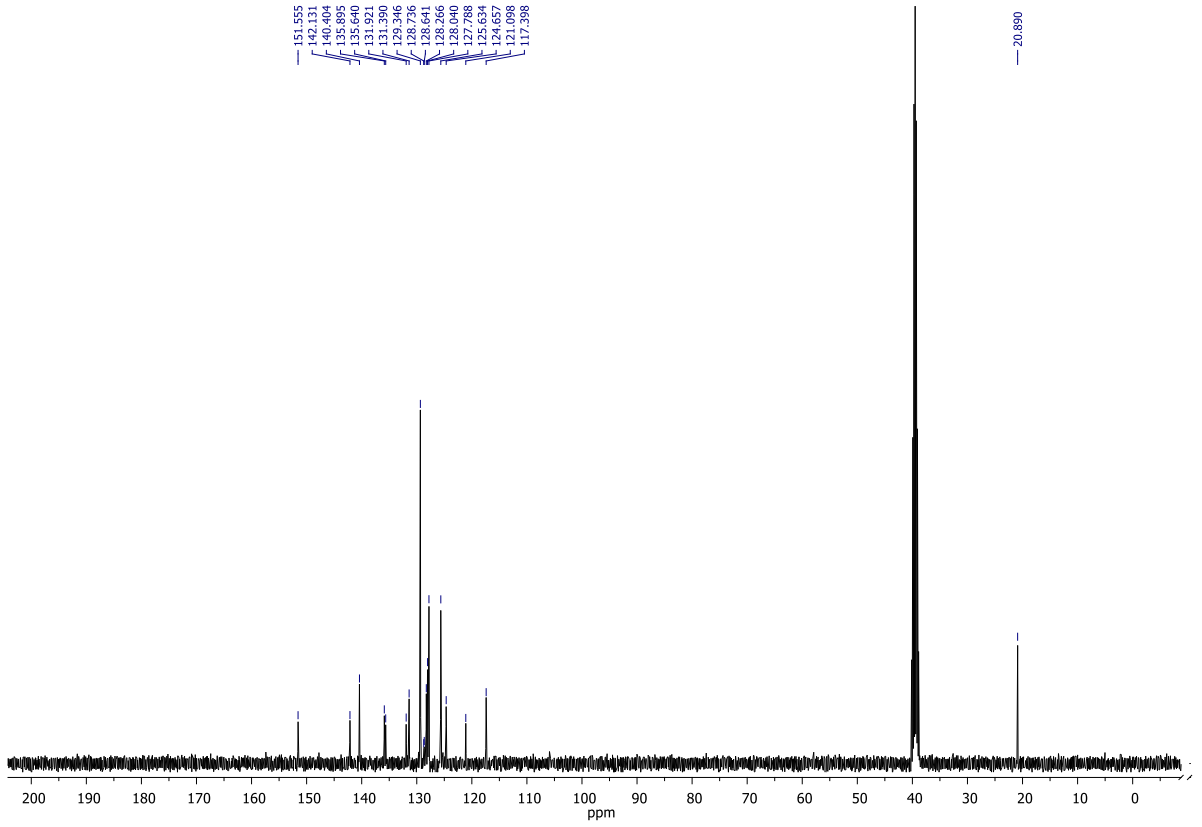


Figure 3.20a. ^{1}H NMR Spectrum of 56g in $CDCl_3$ at 400 MHz

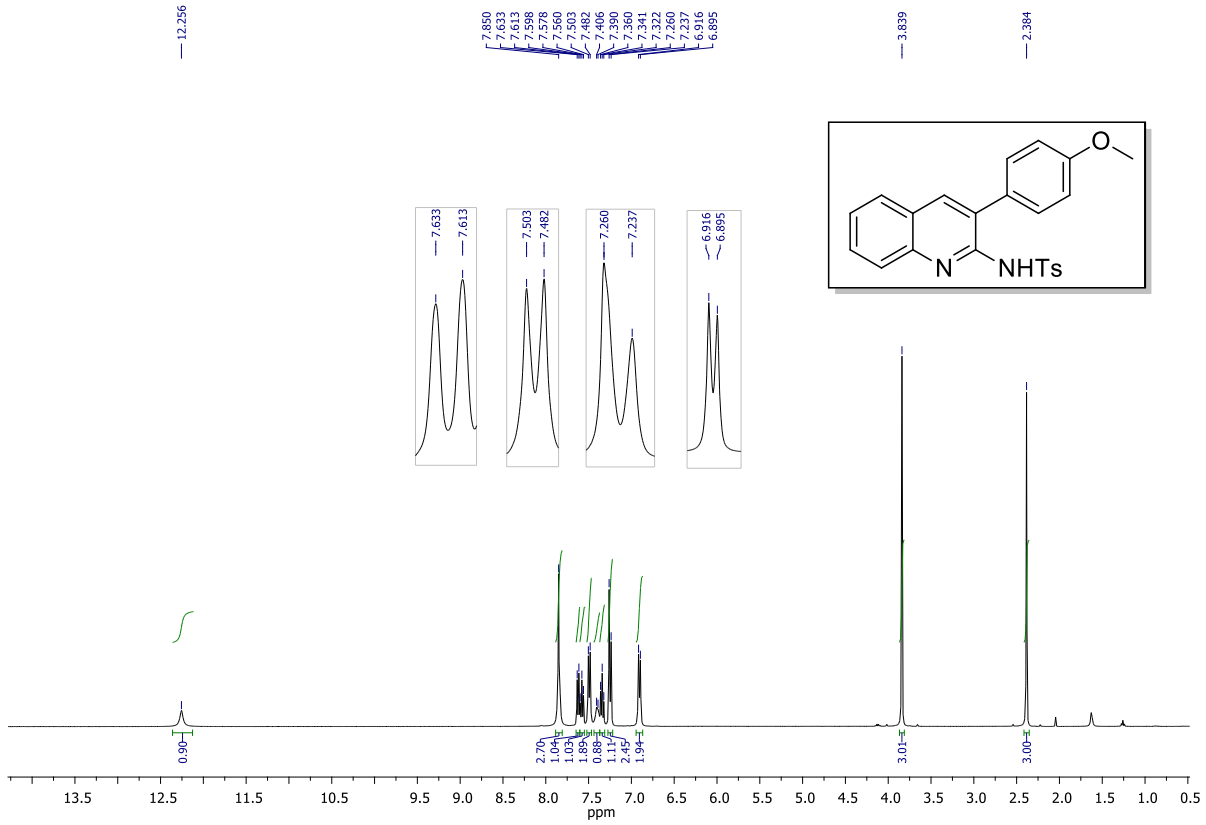


Figure 3.20b. ^{13}C NMR Spectrum of 56g in $CDCl_3$ at 100 MHz

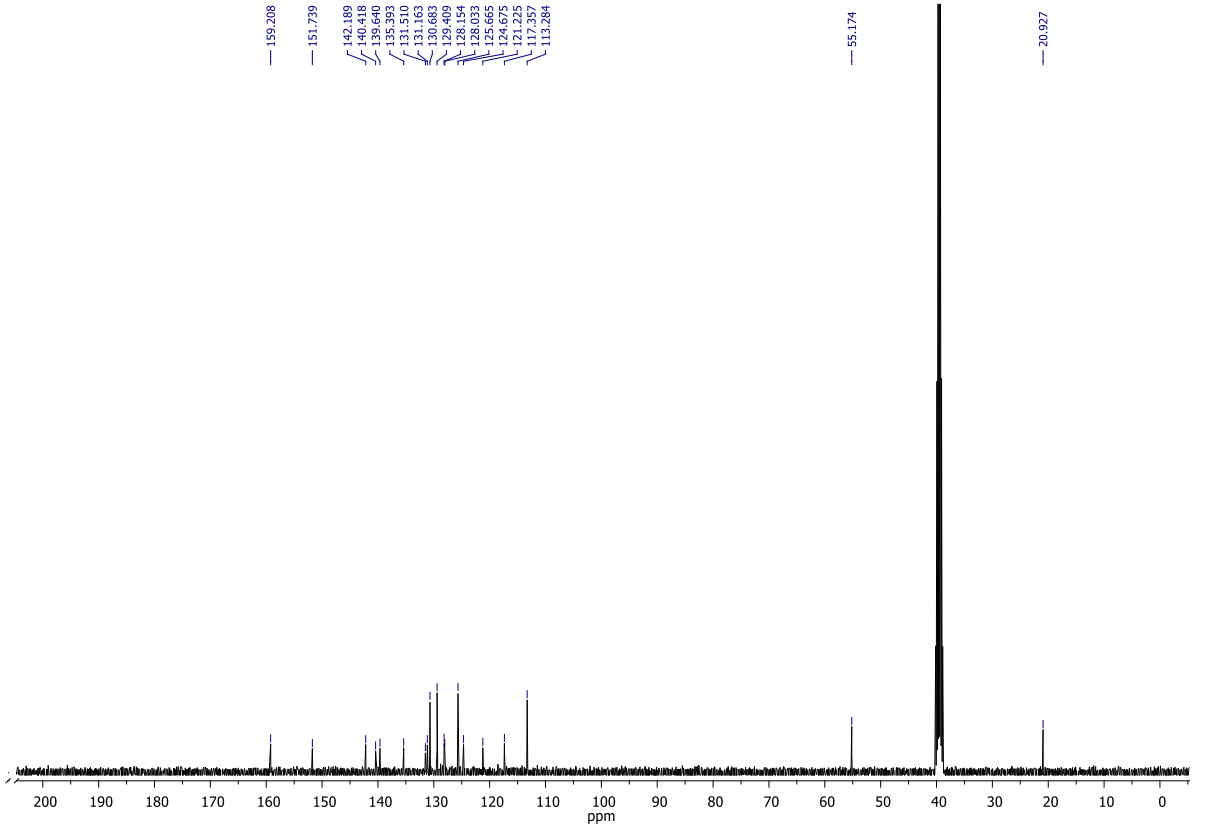


Figure 3.21a. ^{1}H NMR Spectrum of 56p in DMSO at 400 MHz

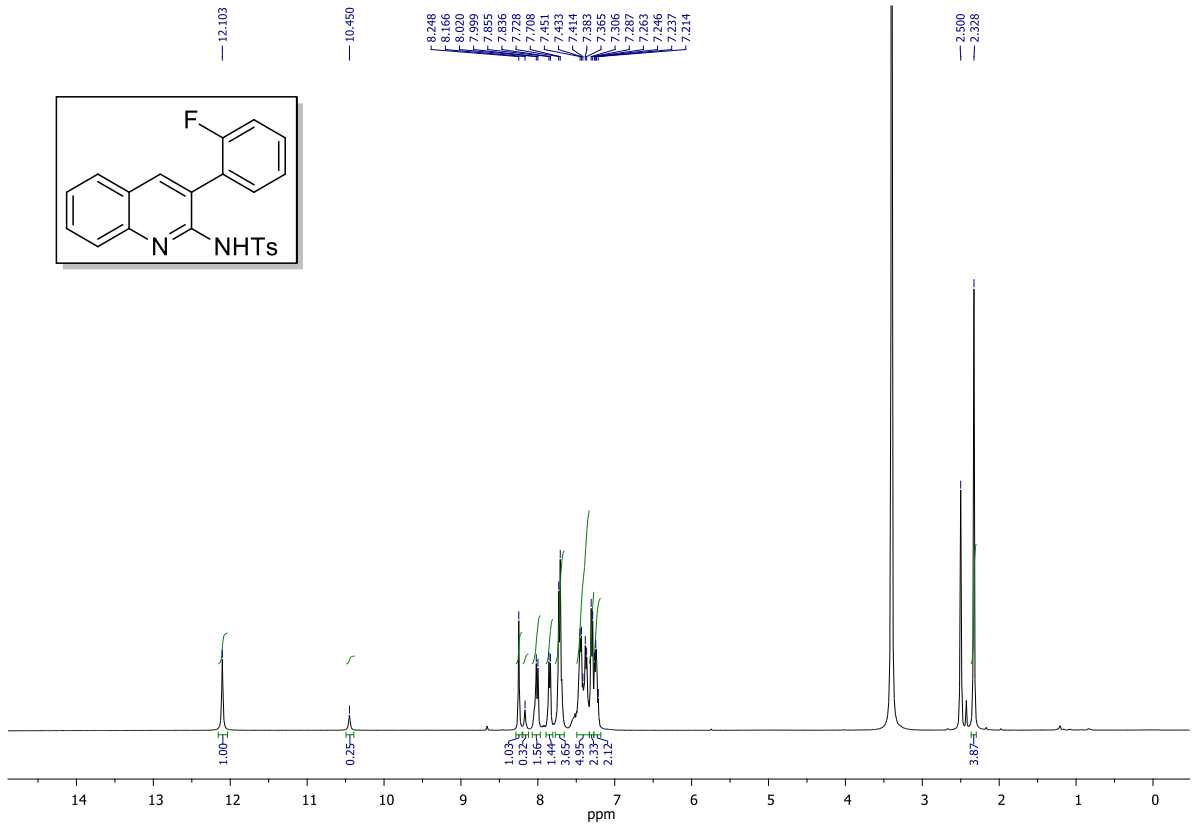


Figure 3.21b. ^{13}C NMR Spectrum of 56p in DMSO at 100 MHz

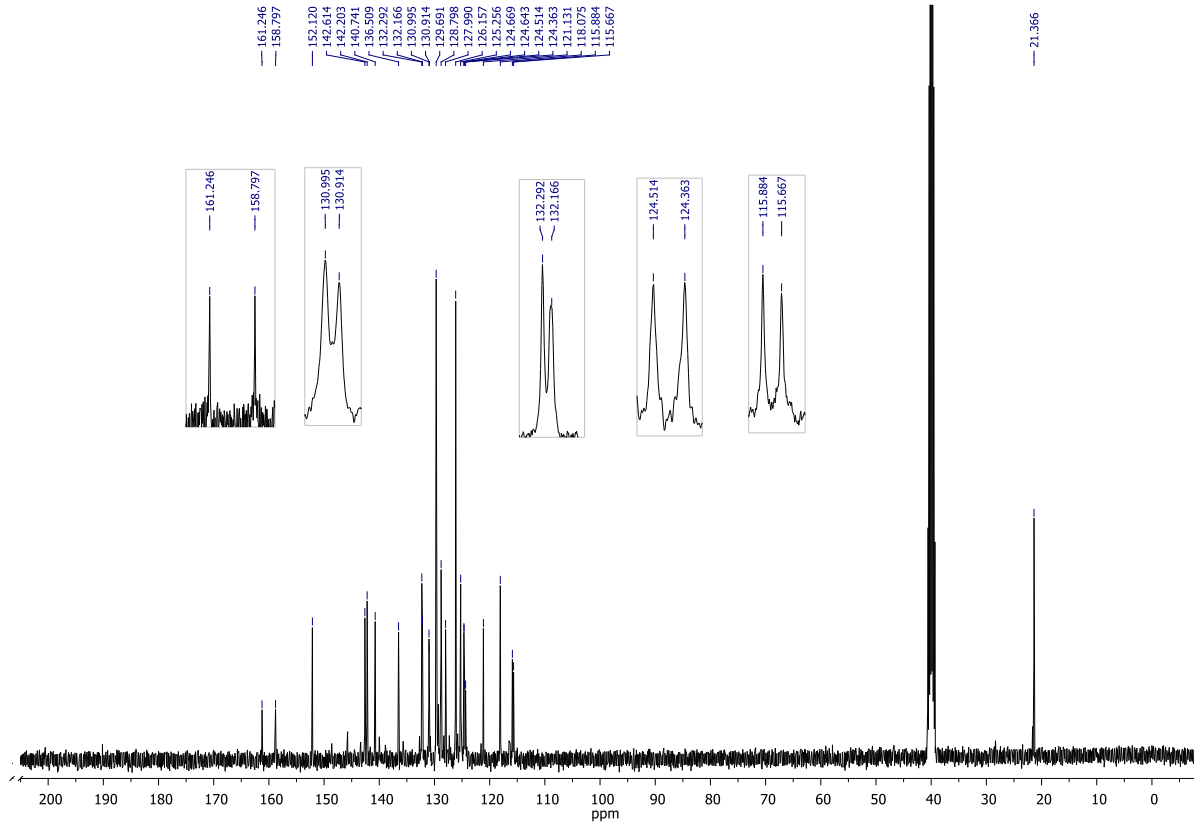


Figure 3.22a. ^{1}H NMR Spectrum of 55t in $CDCl_3$ at 400 MHz

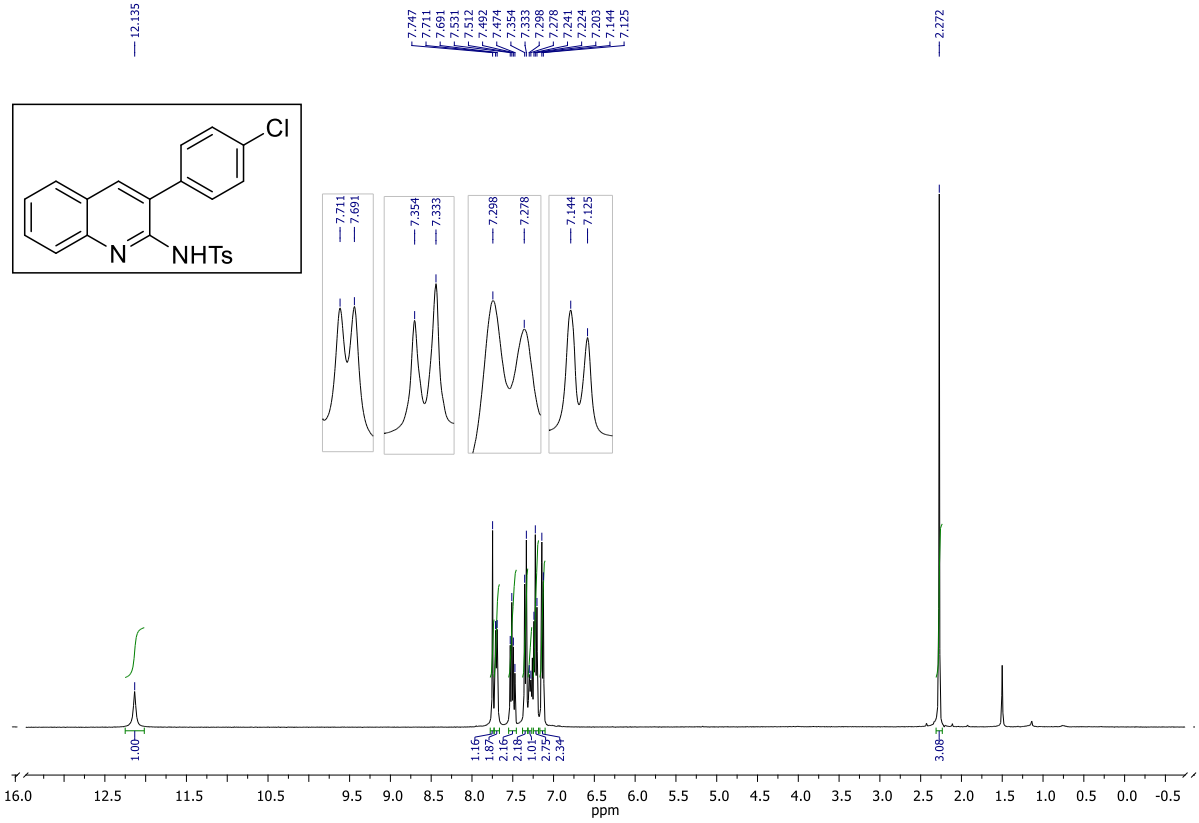


Figure 3.22b. ^{13}C NMR Spectrum of 55t in DMSO at 100 MHz

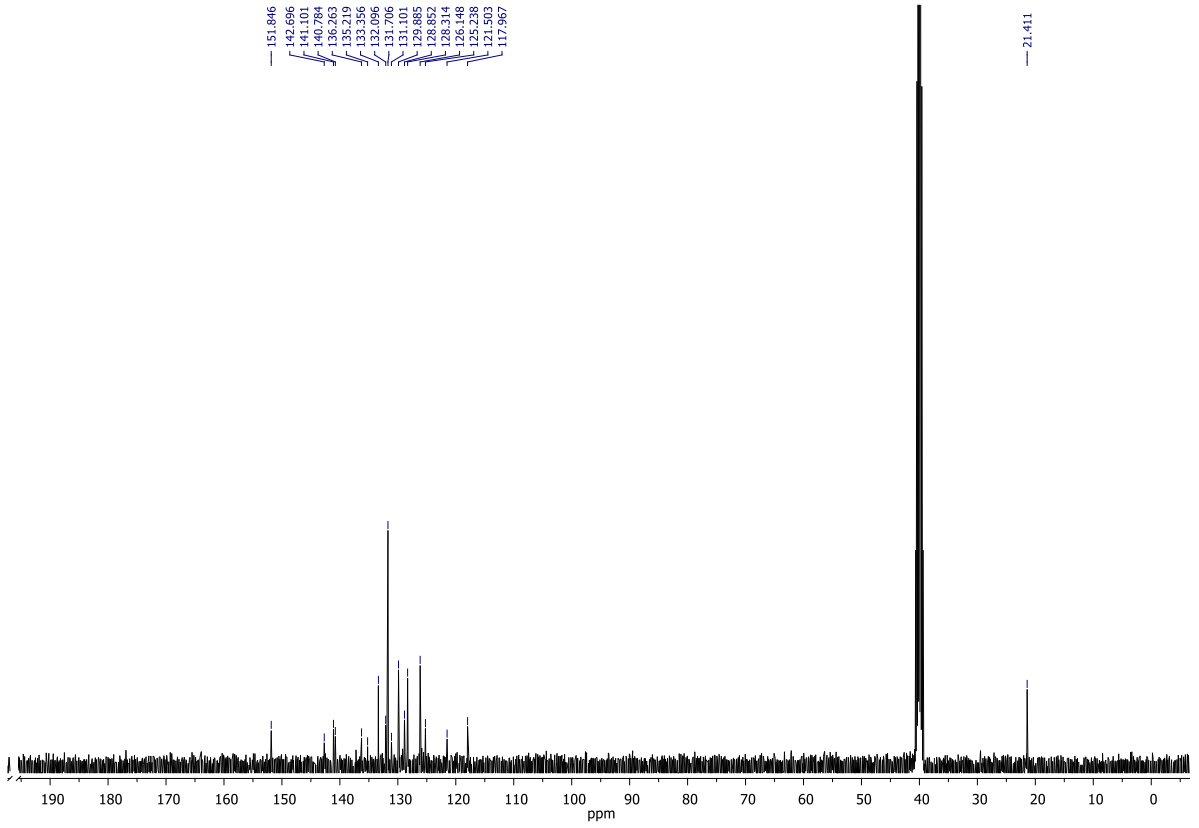


Figure 3.23a. ^{1}H NMR Spectrum of 56u in $CDCl_3$ at 400 MHz

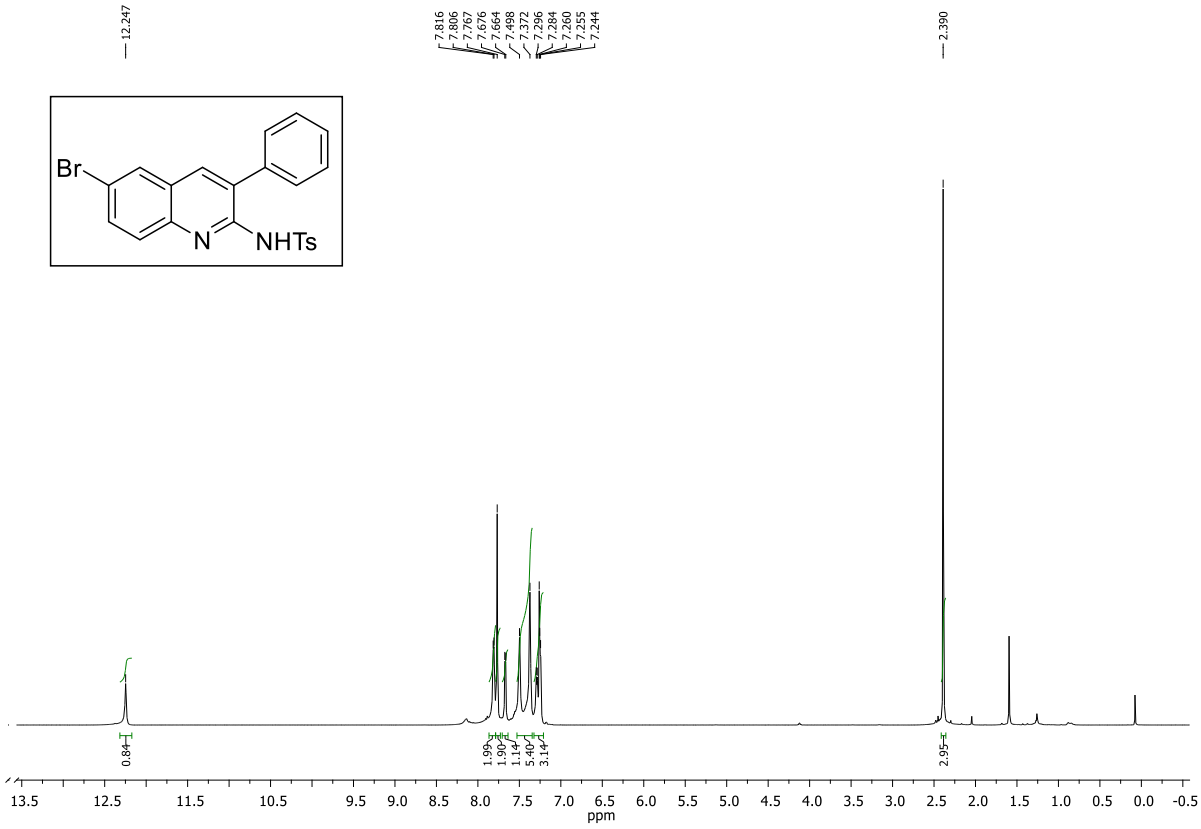


Figure 3.23b. ^{13}C NMR Spectrum of 56u in $CDCl_3$ at 100 MHz

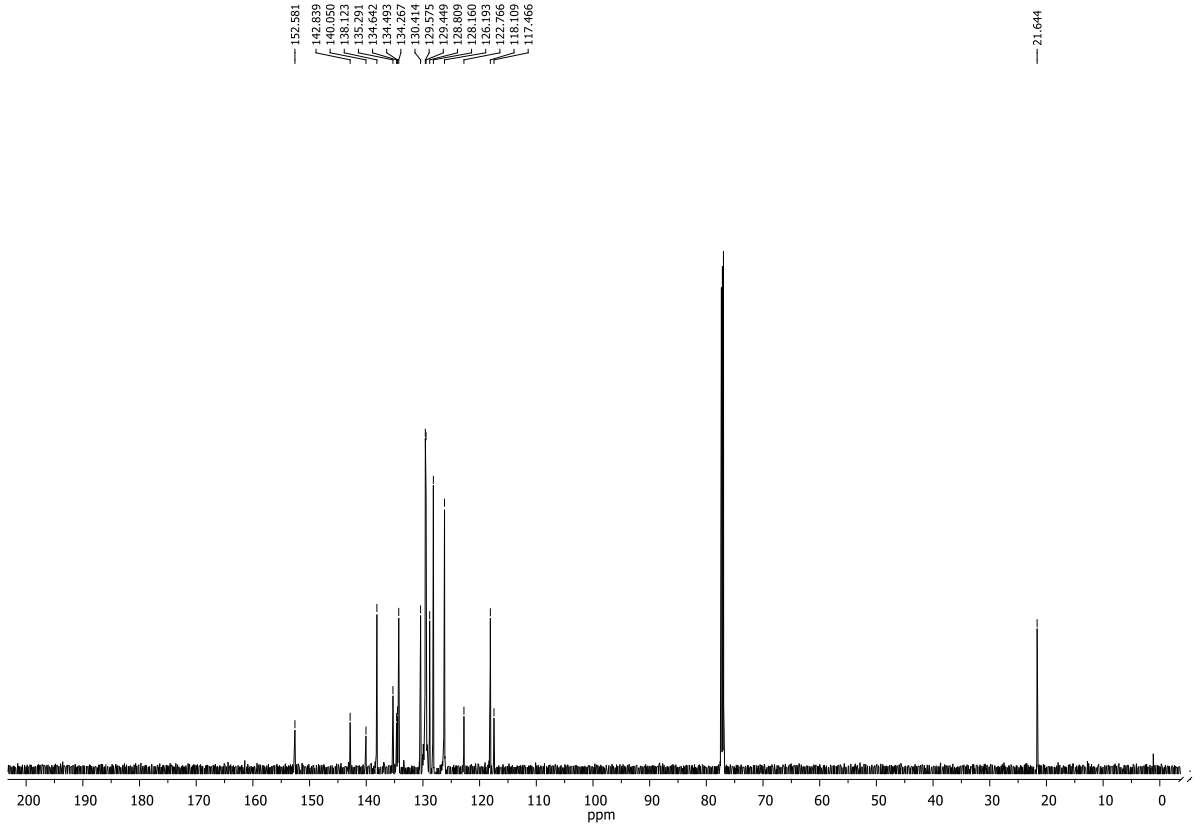


Figure 3.24a. ^{1}H NMR Spectrum of 19a in $CDCl_3$ at 400 MHz

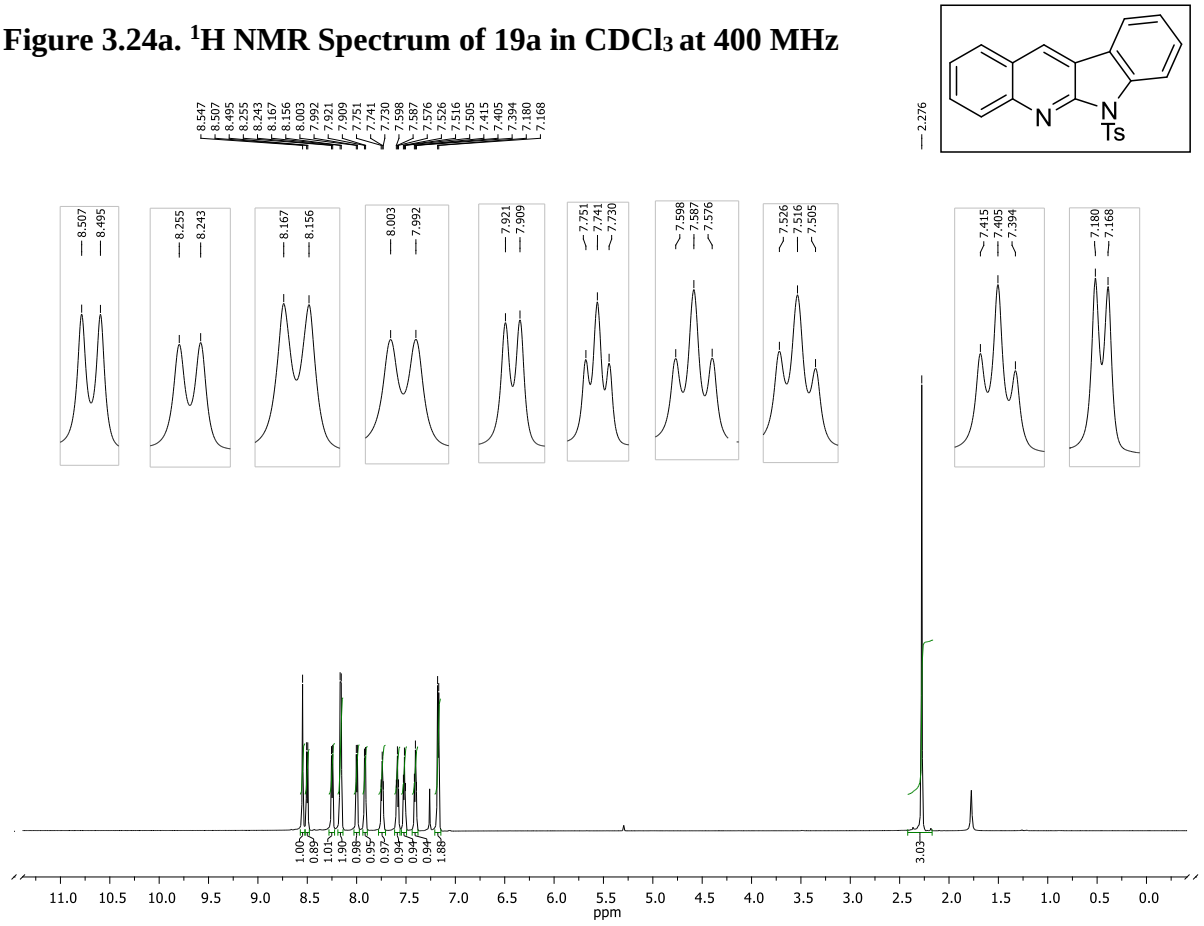


Figure 3.24b. ^{13}C NMR Spectrum of 19a in $CDCl_3$ at 100 MHz

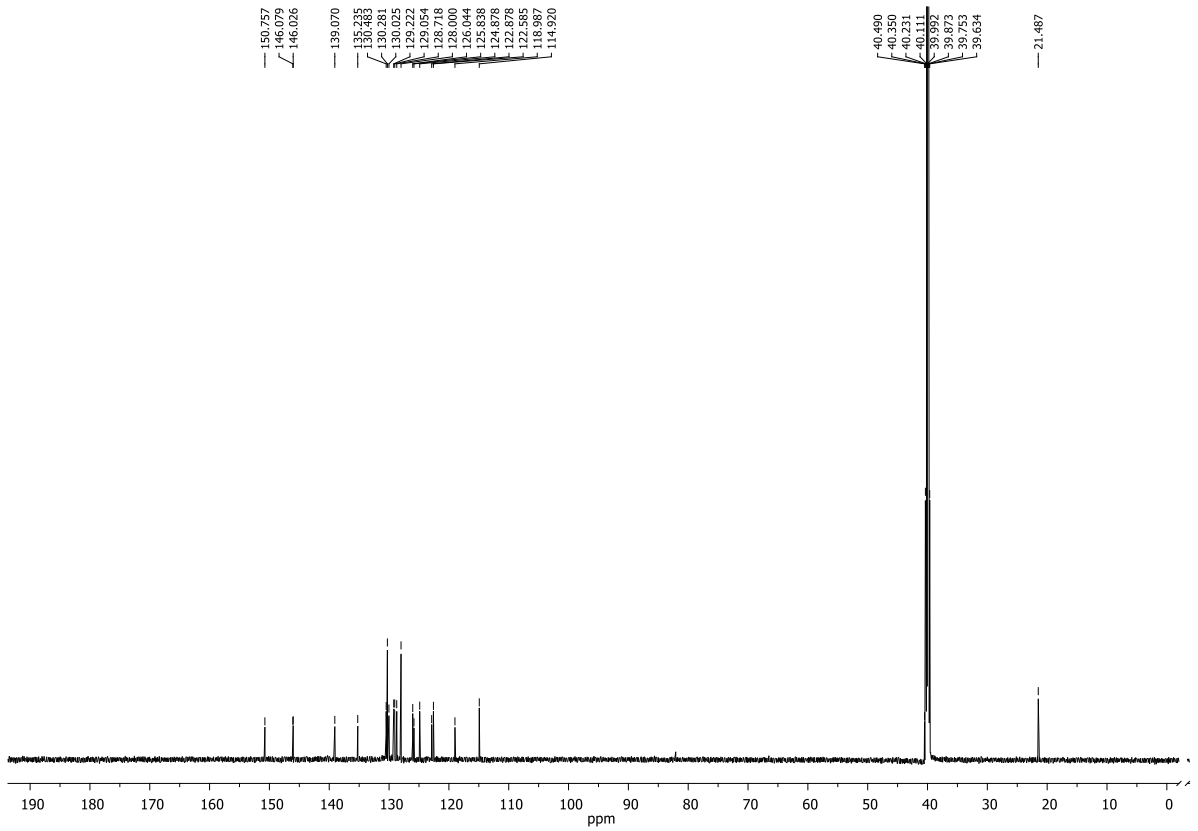


Figure 3.25a. ^{1}H NMR Spectrum of 19b in $CDCl_3$ at 400 MHz

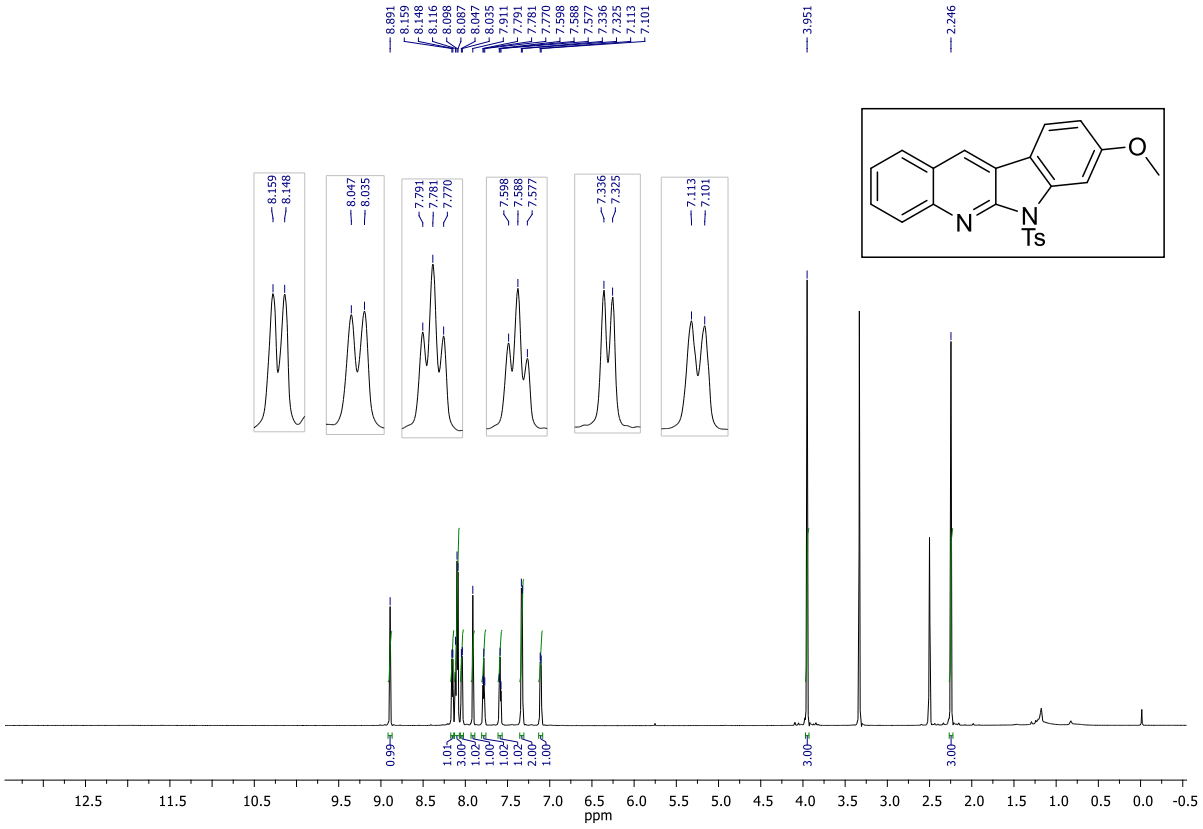


Figure 3.25b. ^{13}C NMR Spectrum of 19b in $CDCl_3$ at 100 MHz

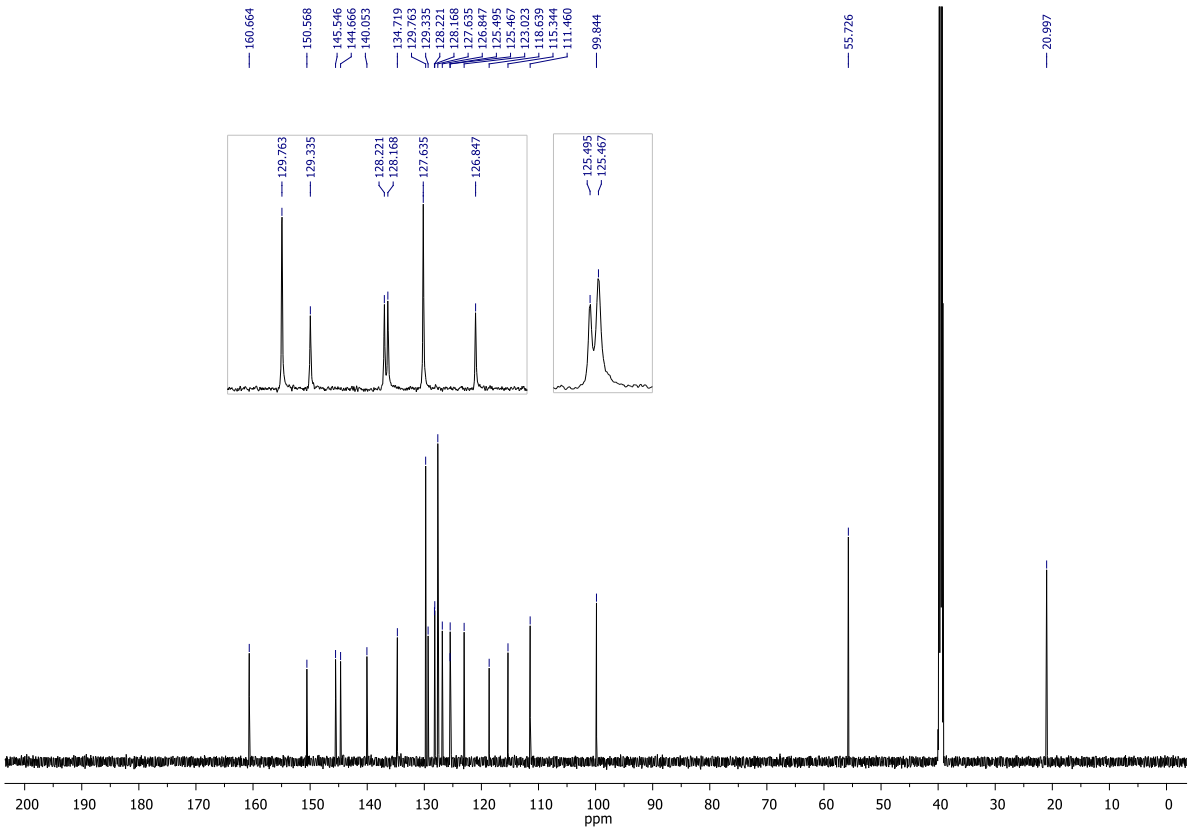


Figure 3.26a. ^{1}H NMR Spectrum of 19p in $CDCl_3$ at 400 MHz

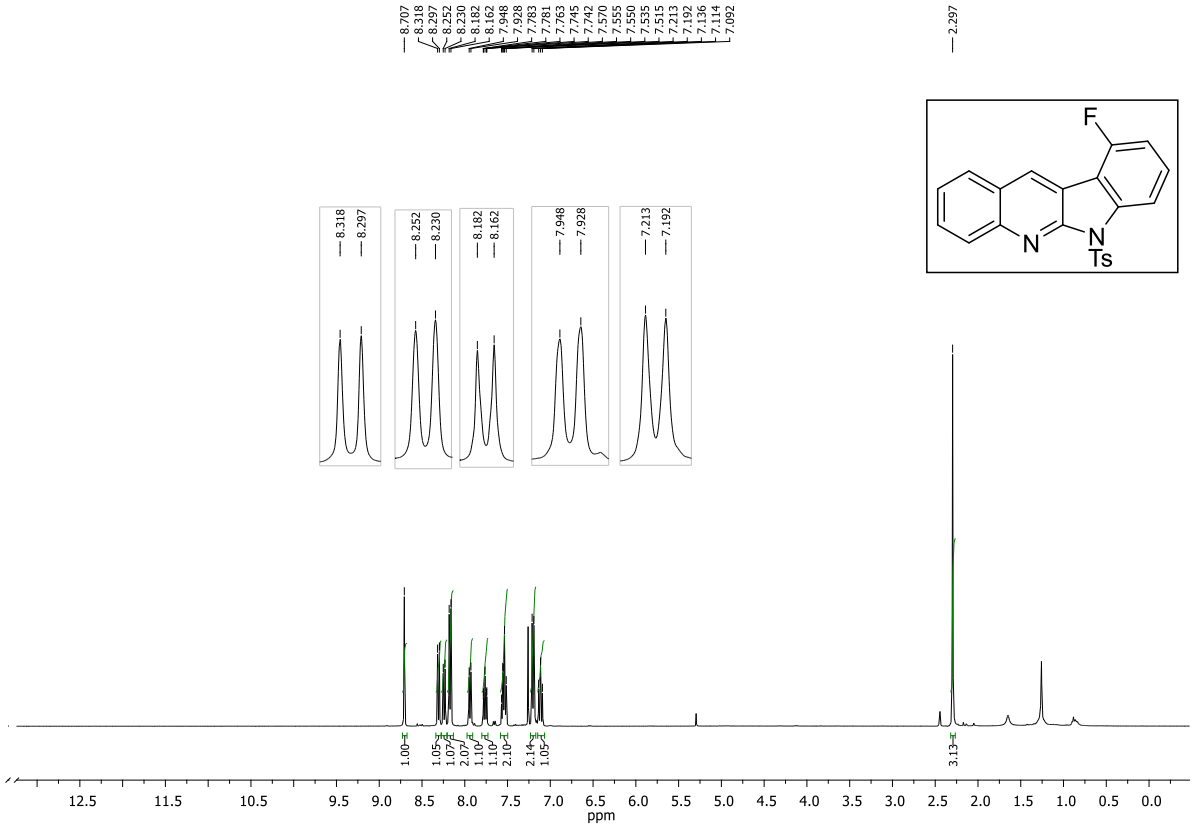


Figure 3.26b. ^{13}C NMR Spectrum of 19p in $CDCl_3$ at 100 MHz

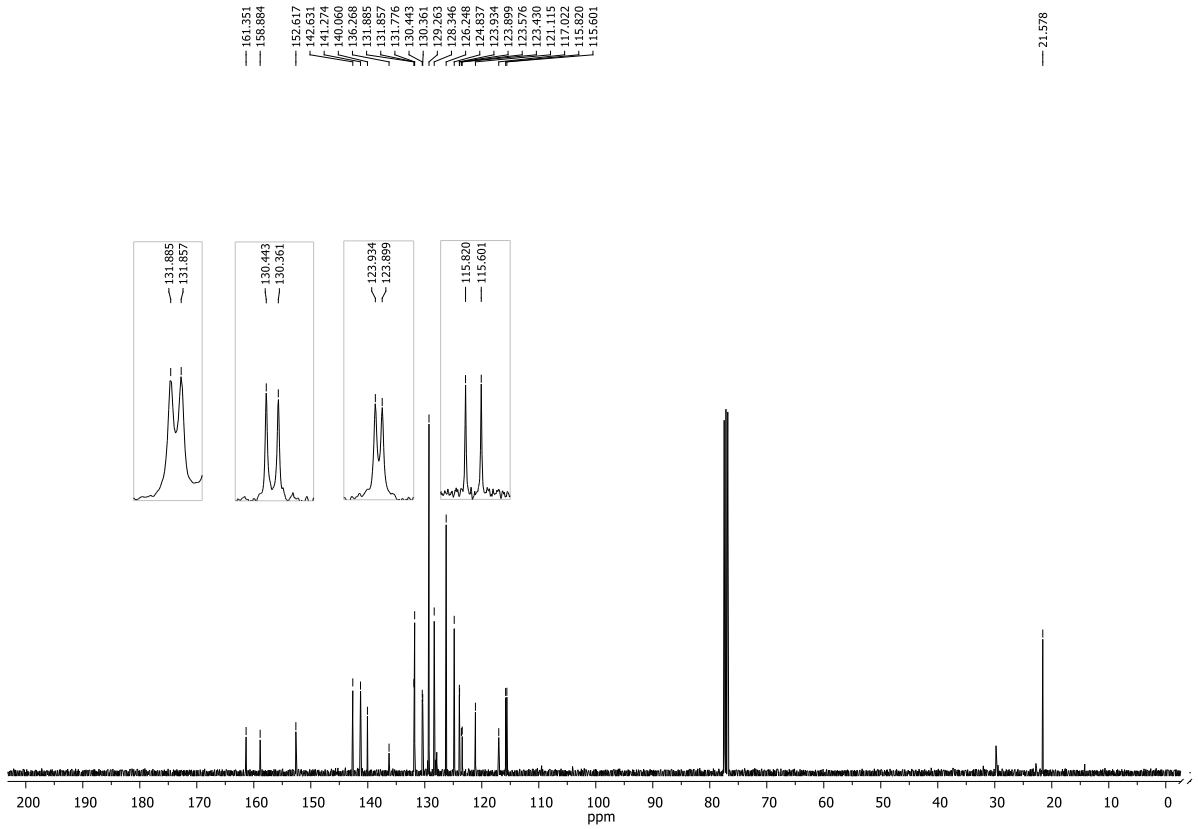


Figure 3.27a. ^{1}H NMR Spectrum of 19t in $CDCl_3$ at 400 MHz

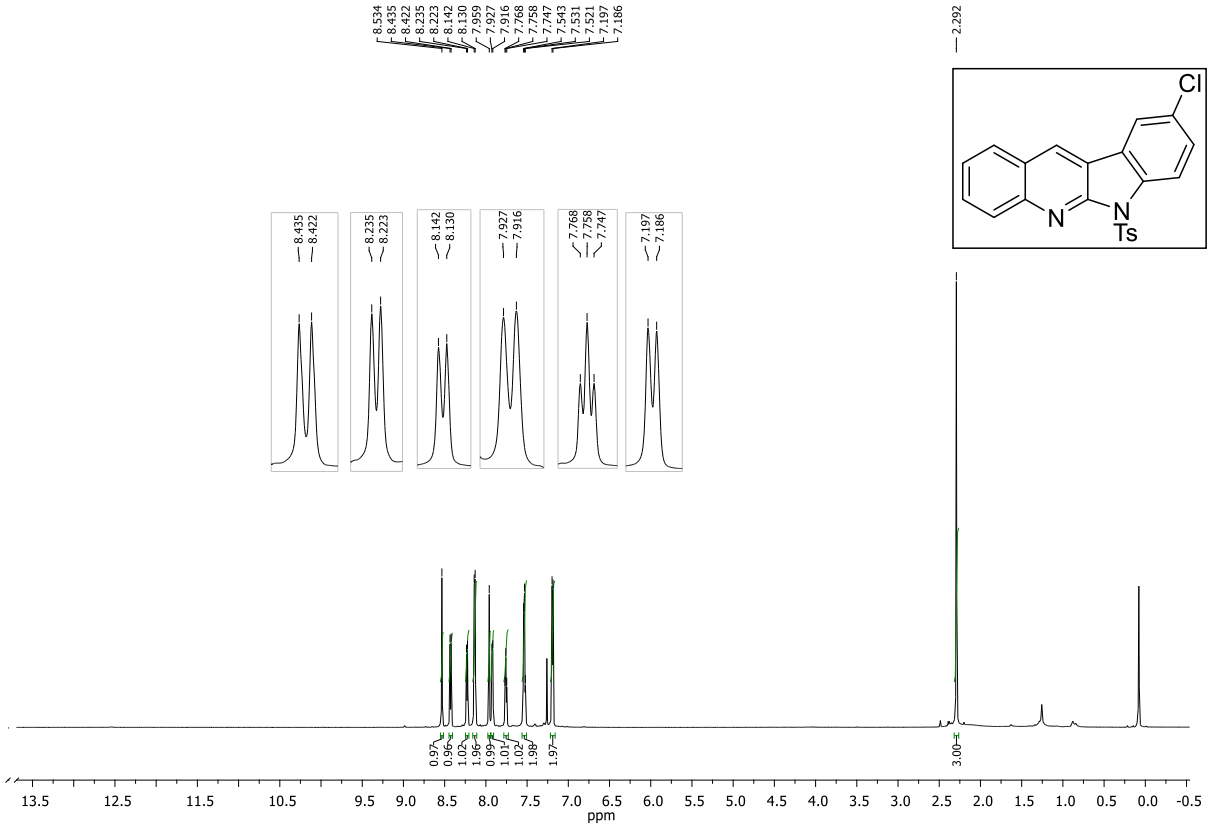


Figure 3.27b. ^{13}C NMR Spectrum of 19t in $CDCl_3$ at 100 MHz

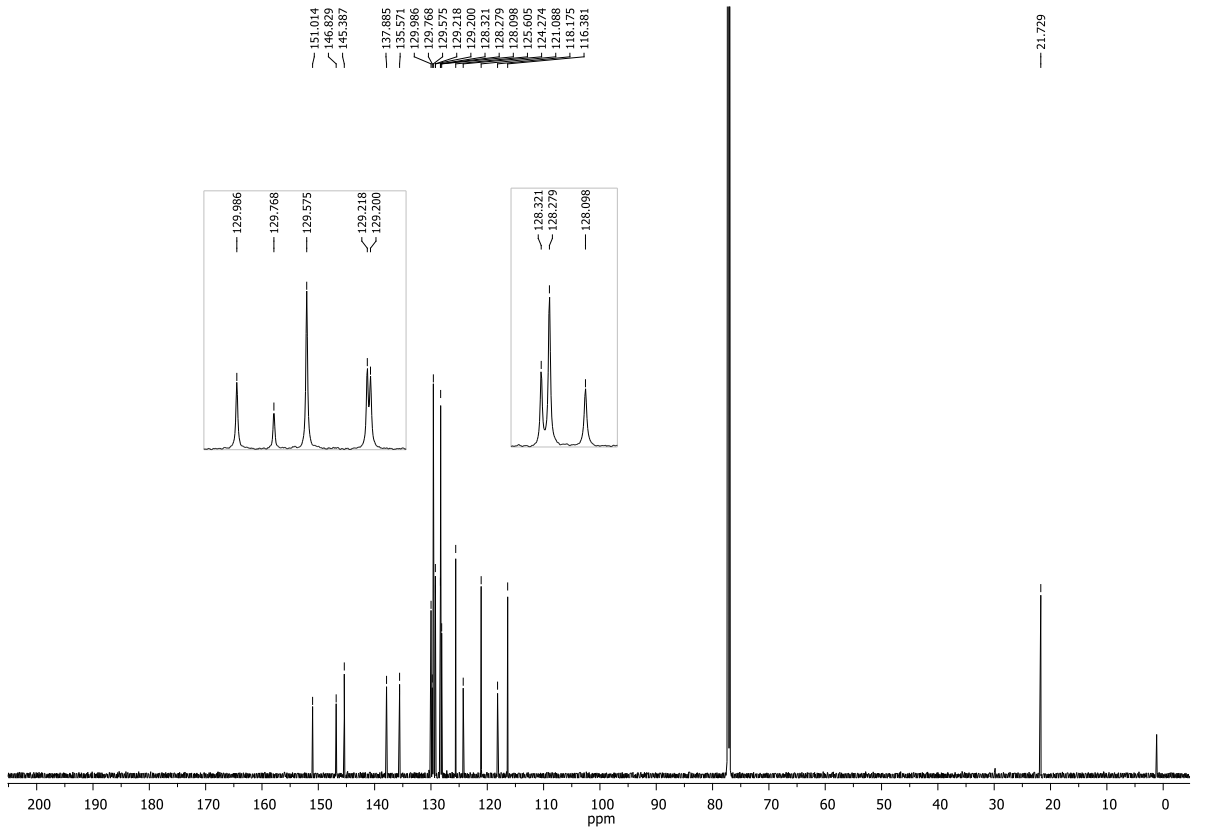


Figure 3.28a. ^{1}H NMR Spectrum of 19u in $CDCl_3$ at 400 MHz

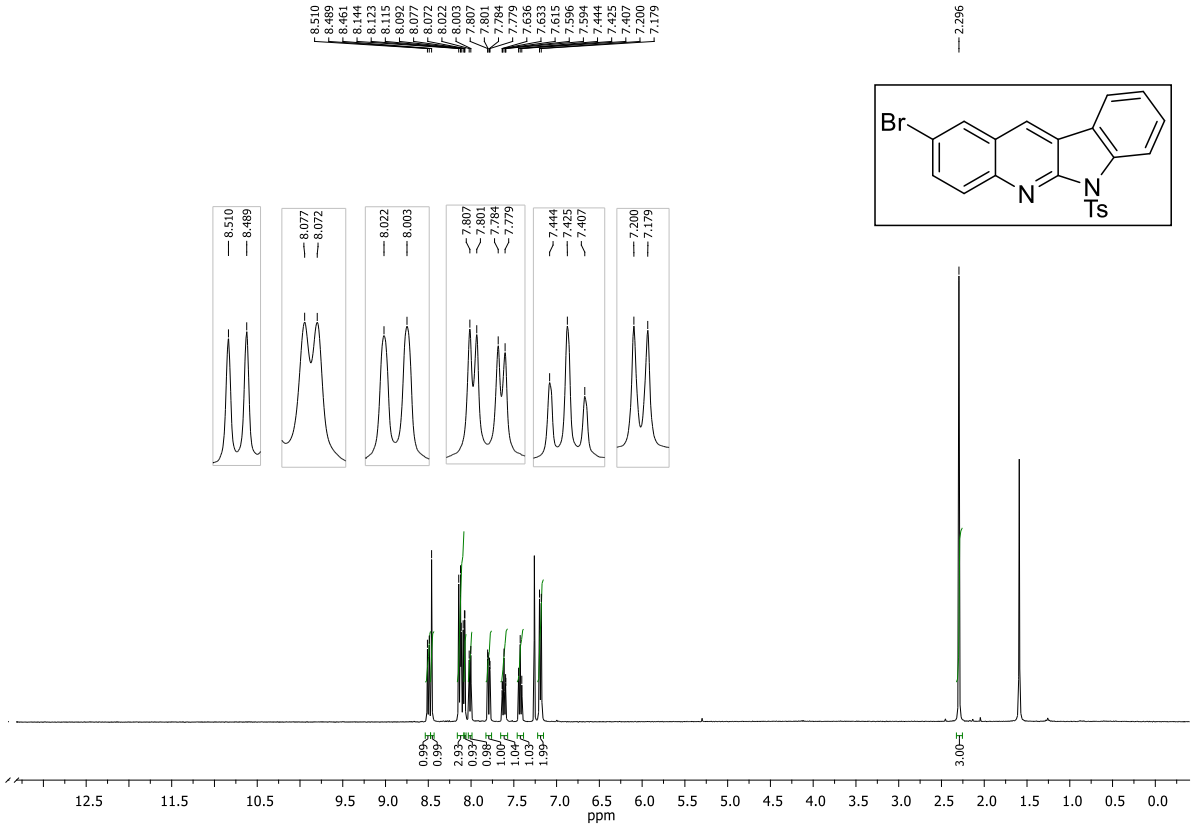


Figure 3.28b. ^{13}C NMR Spectrum of 19u in $CDCl_3$ at 176 MHz

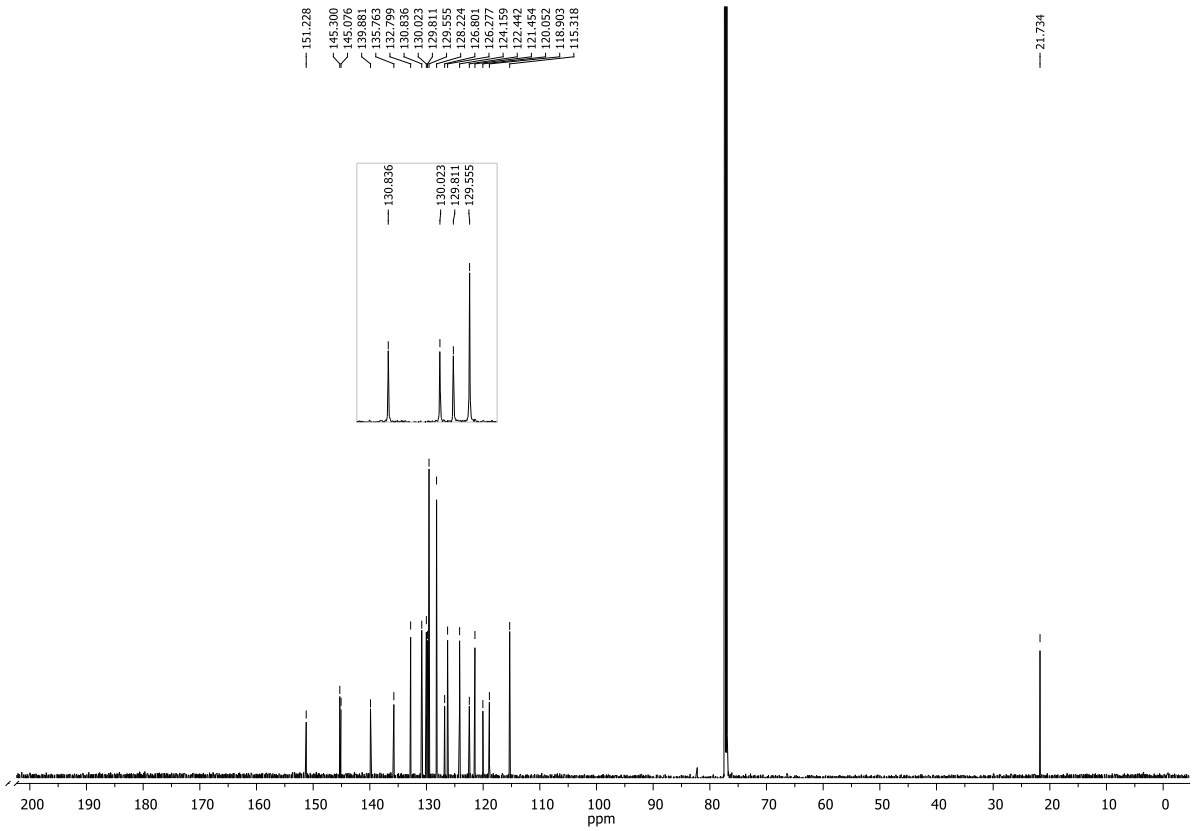


Figure 3.29a. ^{1}H NMR Spectrum of 69a in DMSO at 400 MHz

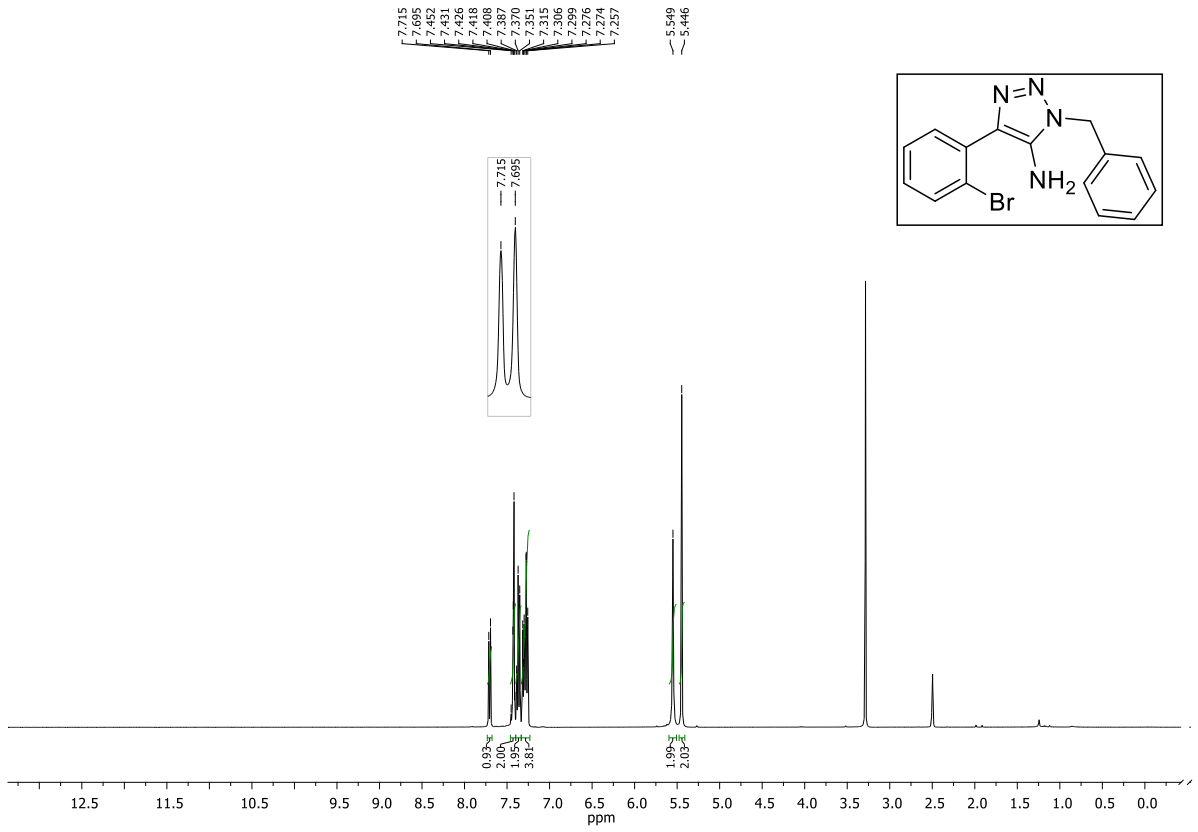


Figure 3.29b. ^{1}H NMR Spectrum of 69a in DMSO at 100 MHz

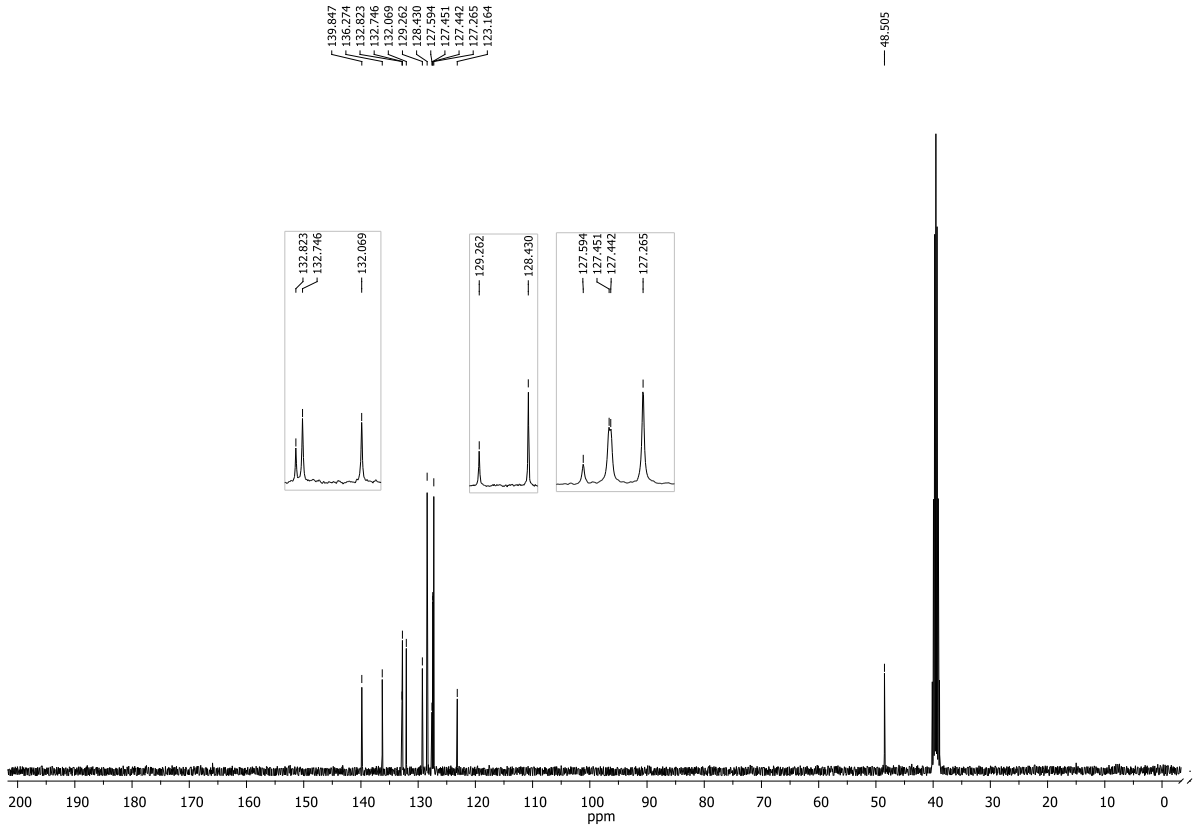


Figure 3.30a. ^{1}H NMR Spectrum of 69f in $CDCl_3$ at 400 MHz

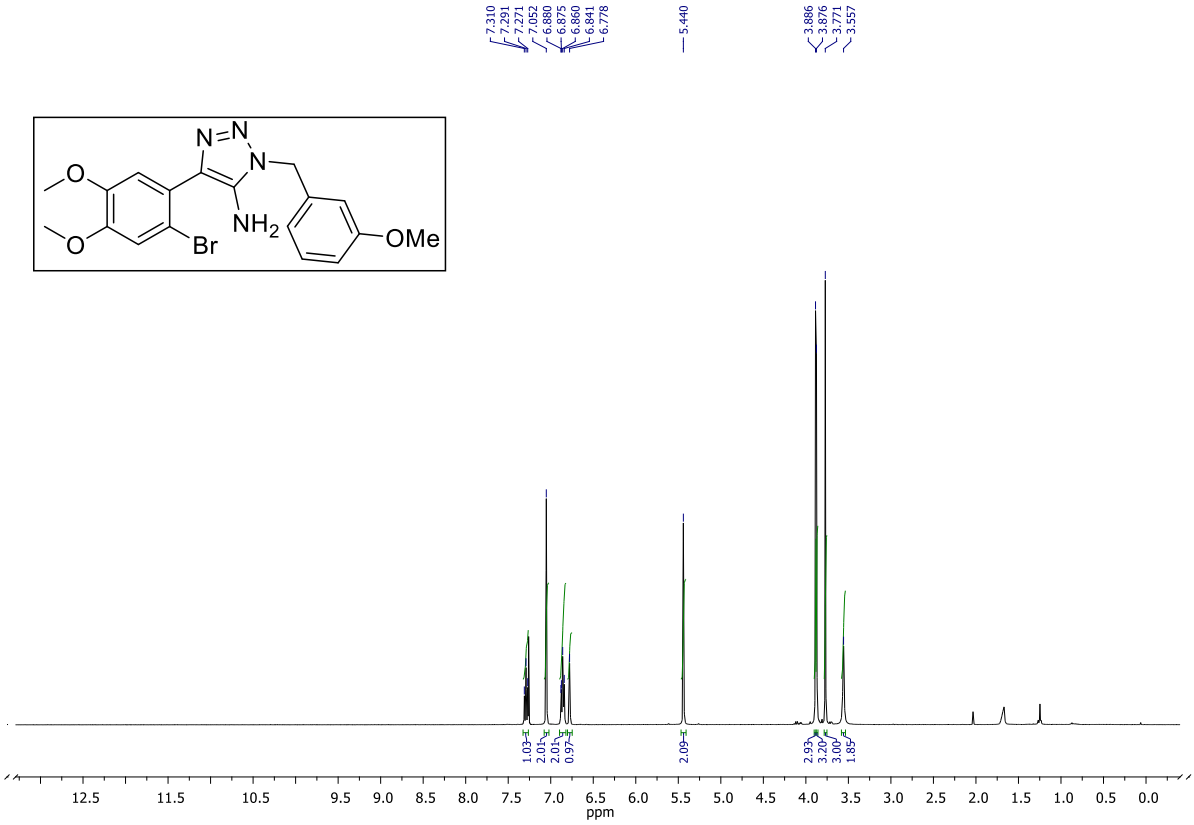


Figure 3.30b. ^{13}C NMR Spectrum of 69f in $CDCl_3$ at 100 MHz

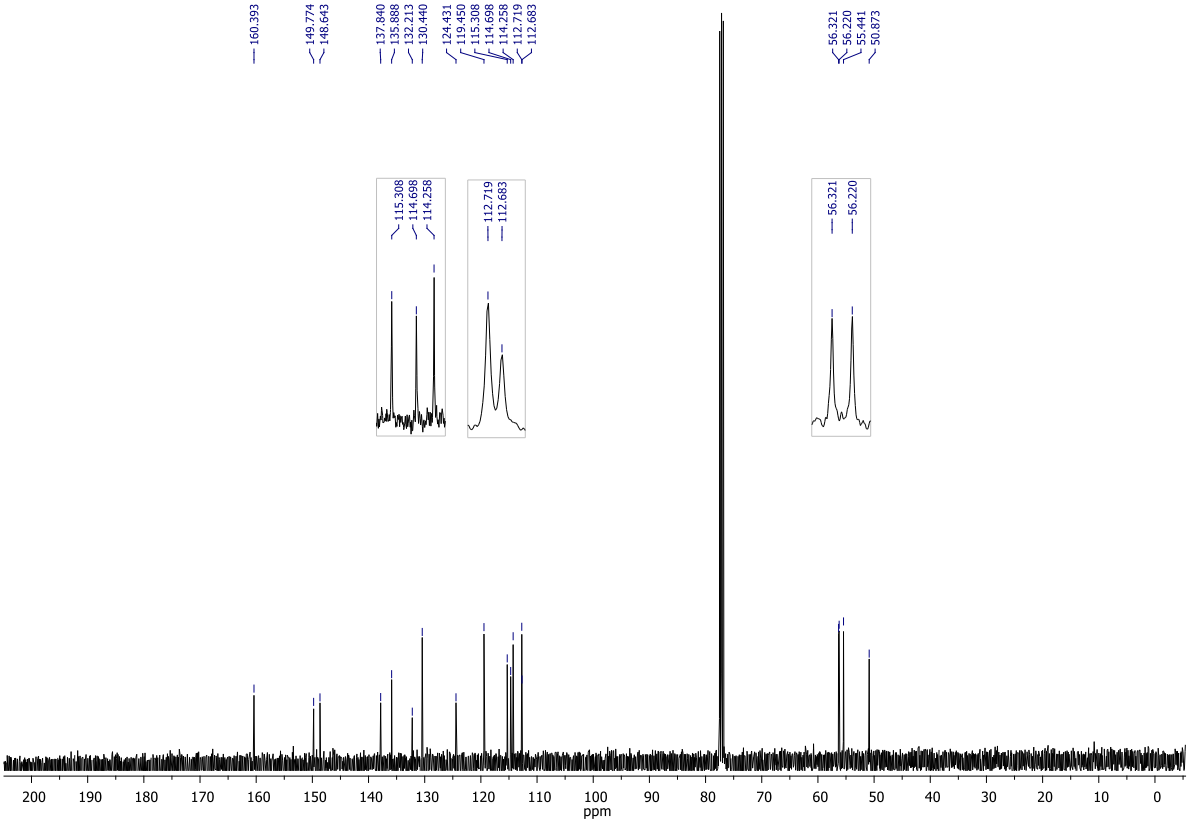


Figure 3.31a. ^{1}H NMR Spectrum of 69g in $CDCl_3$ at 400 MHz

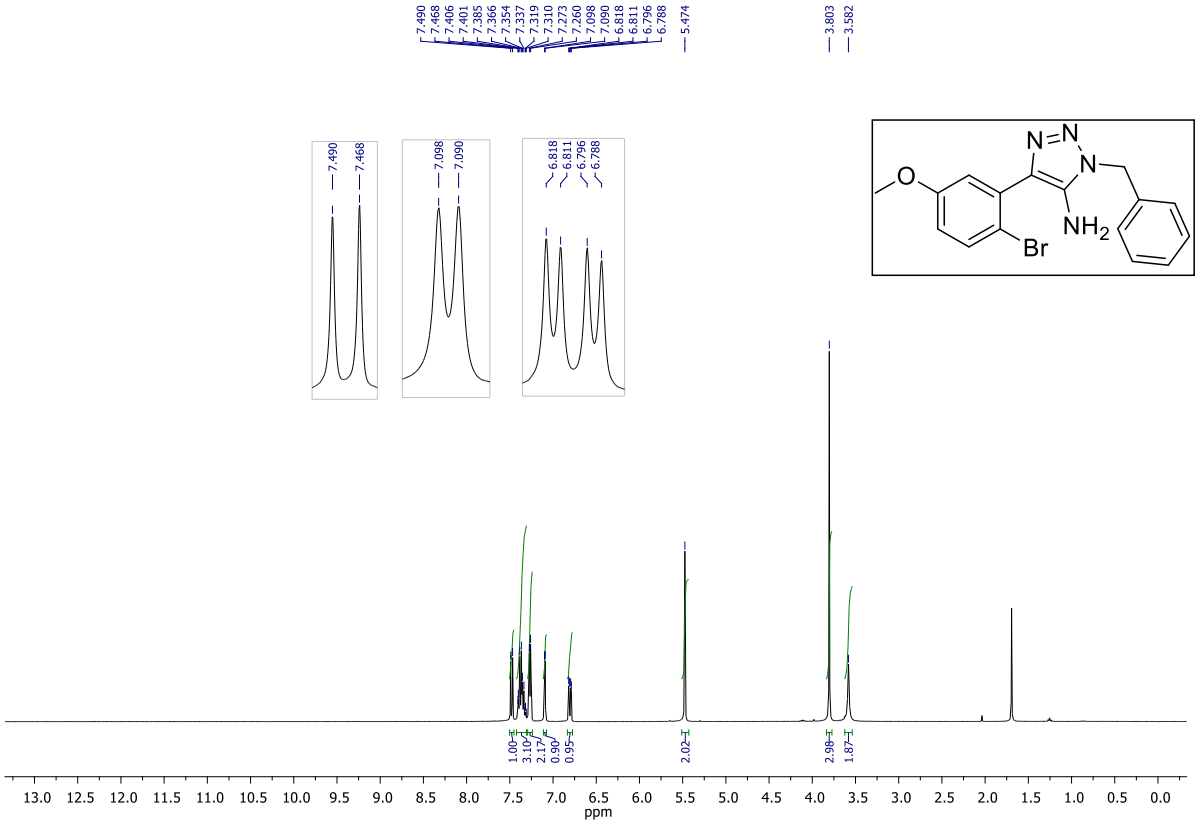


Figure 3.31b. ^{13}C NMR Spectrum of 69g in $CDCl_3$ at 100 MHz

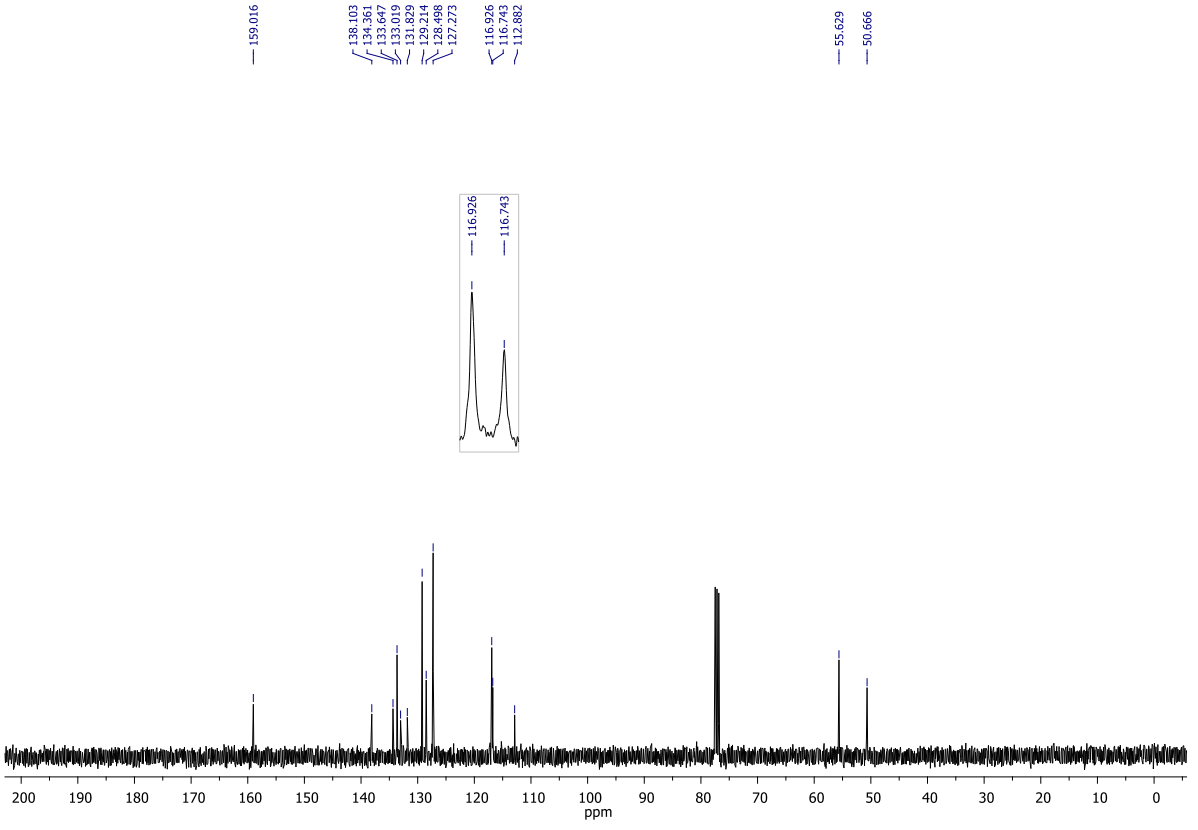


Figure 3.32a. ^{1}H NMR Spectrum of 69k in $CDCl_3$ at 400 MHz

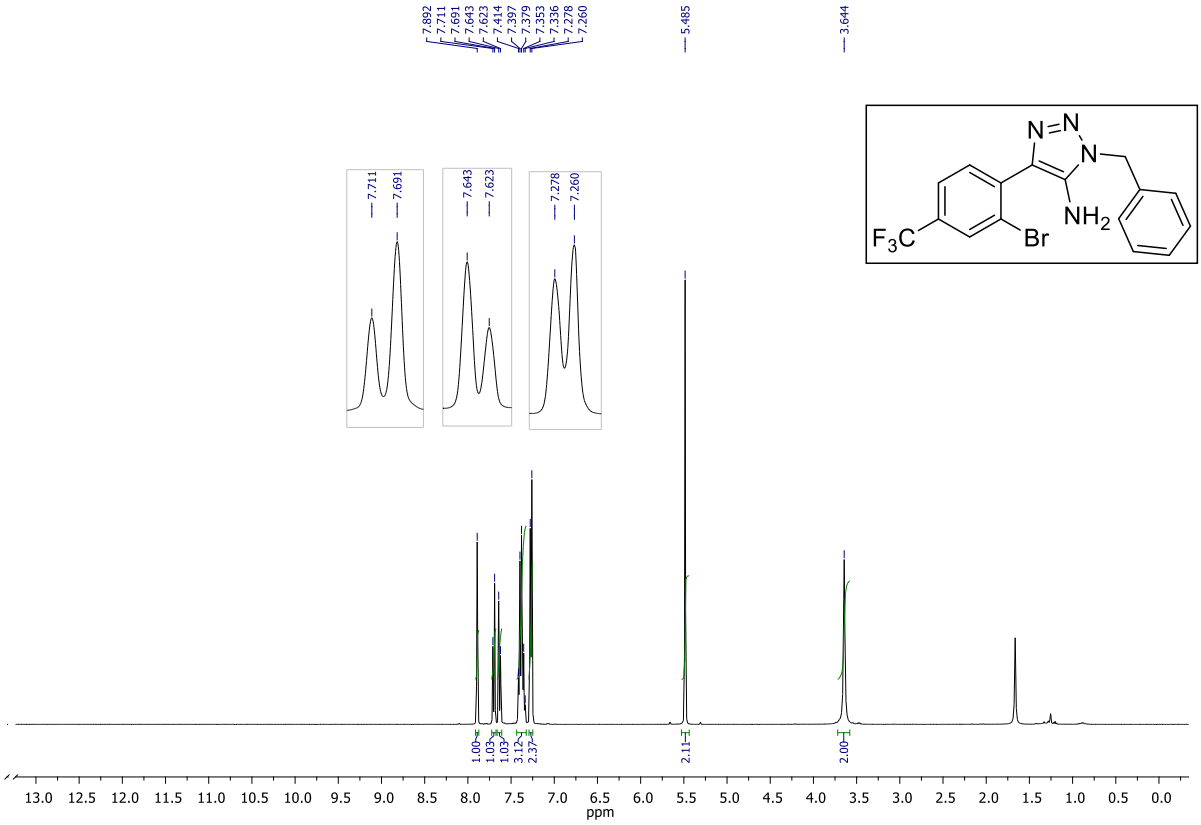


Figure 3.32b. ^{13}C NMR Spectrum of 69k in $CDCl_3$ at 100 MHz

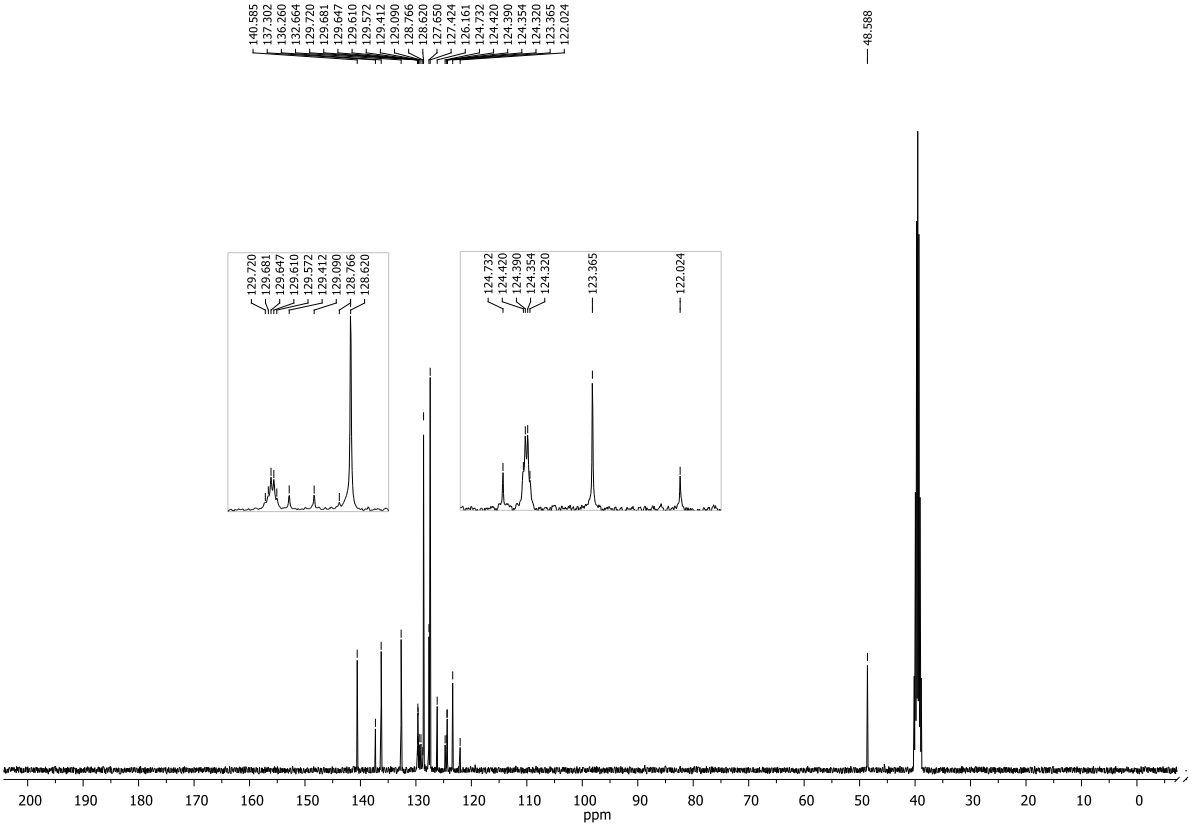


Figure 3.33a. ^{1}H NMR Spectrum of 69m in $CDCl_3$ at 400 MHz

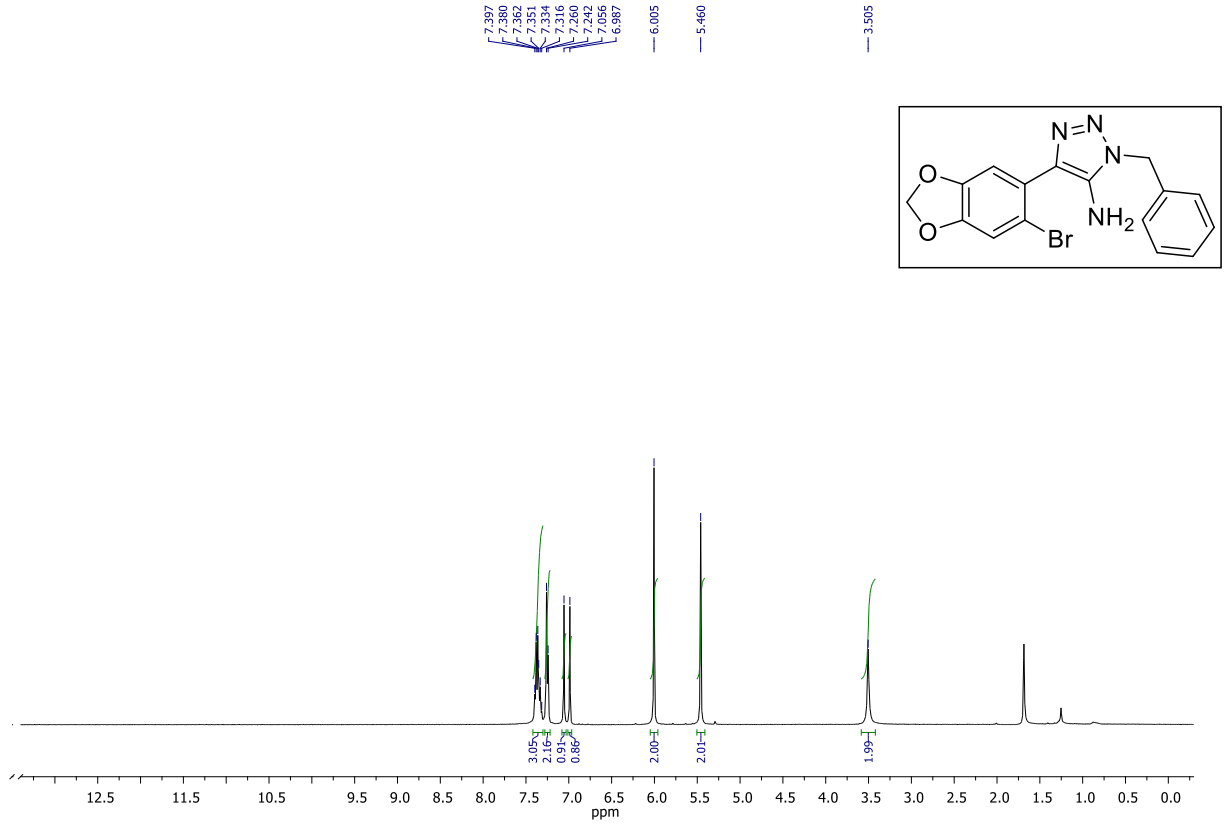


Figure 3.33b. ^{13}C NMR Spectrum of 69m in $CDCl_3$ at 100 MHz

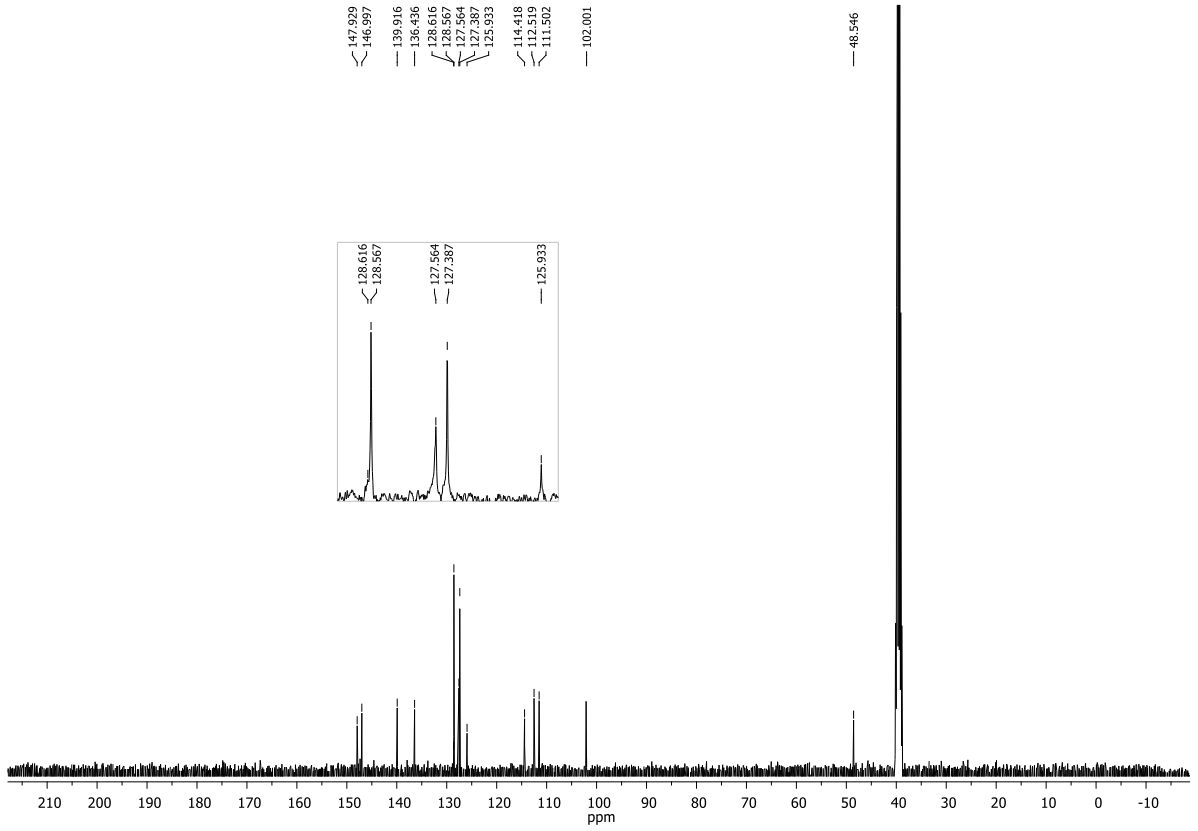


Figure 3.34a. ^{1}H NMR Spectrum of 70b in $CDCl_3$ at 400 MHz

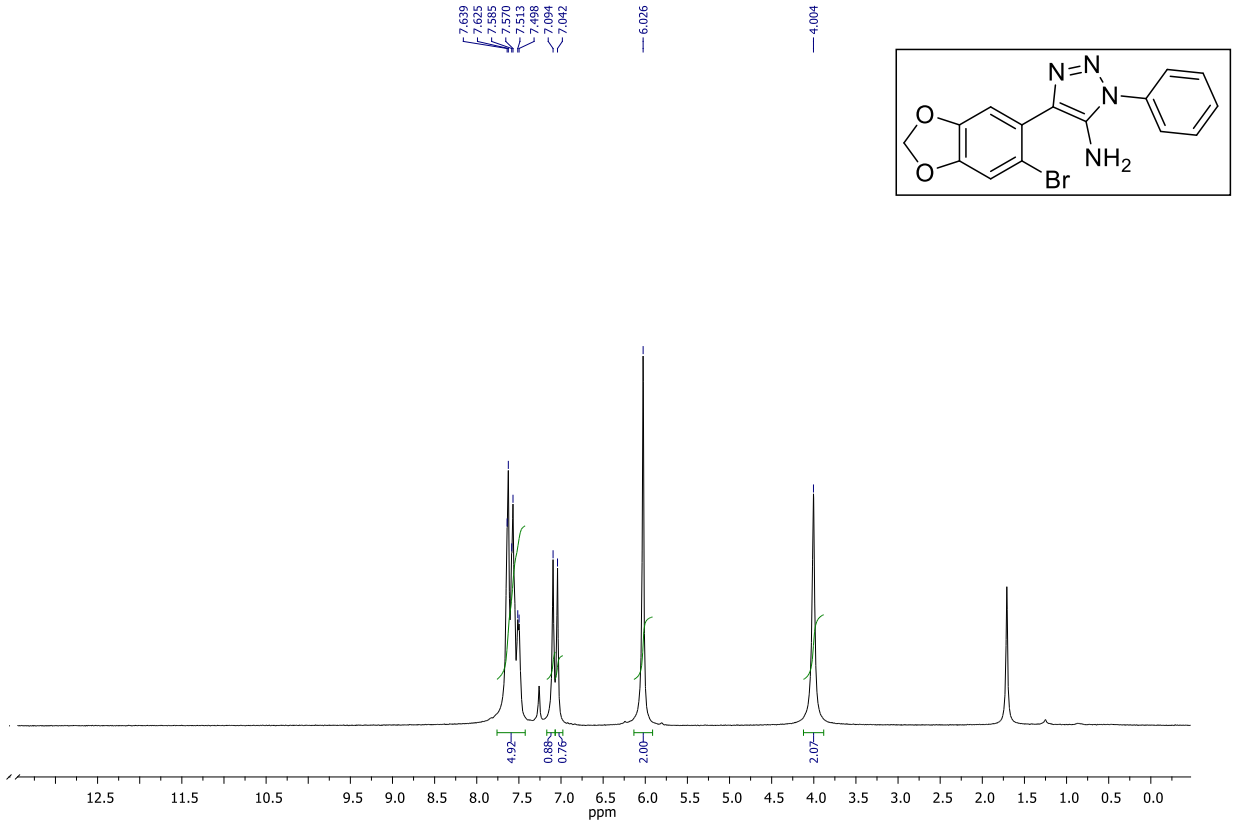


Figure 3.34b. ^{13}C NMR Spectrum of 70b in $CDCl_3$ at 100 MHz

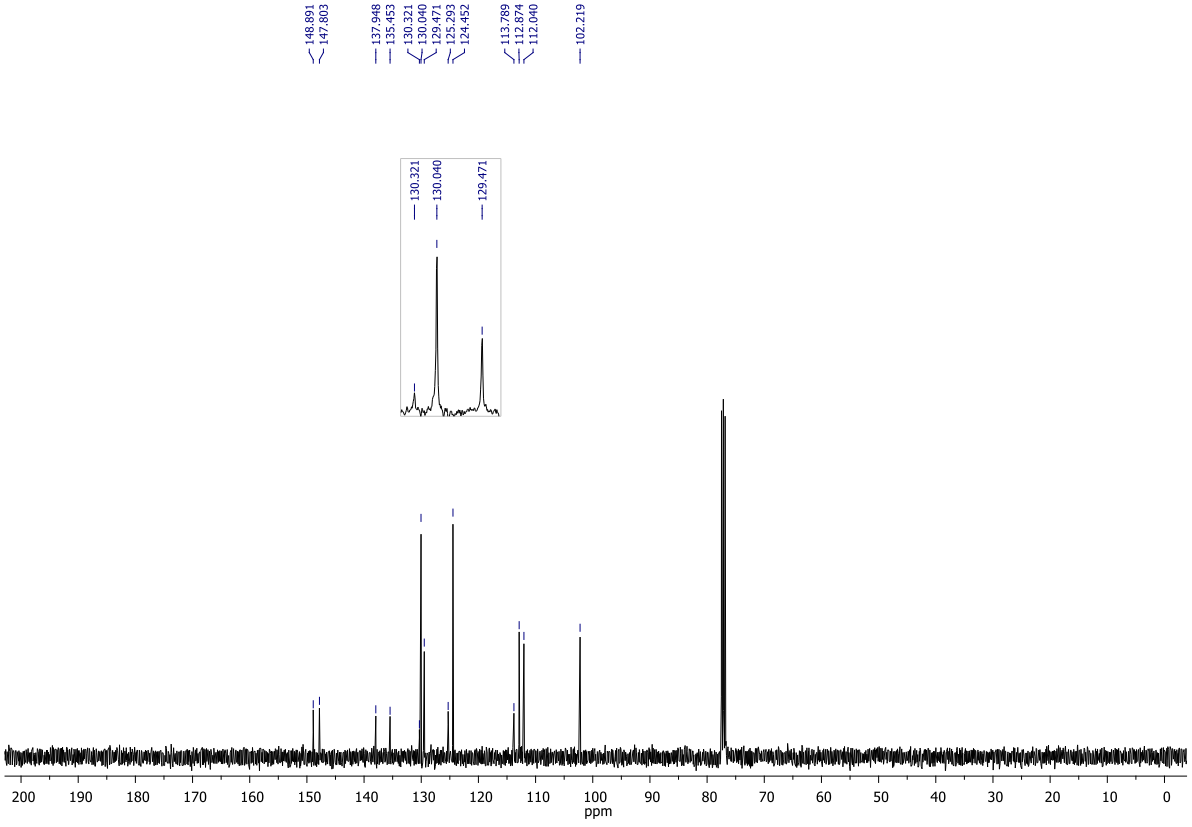


Figure 3.35a. ^{1}H NMR Spectrum of 70c in $CDCl_3$ at 400 MHz

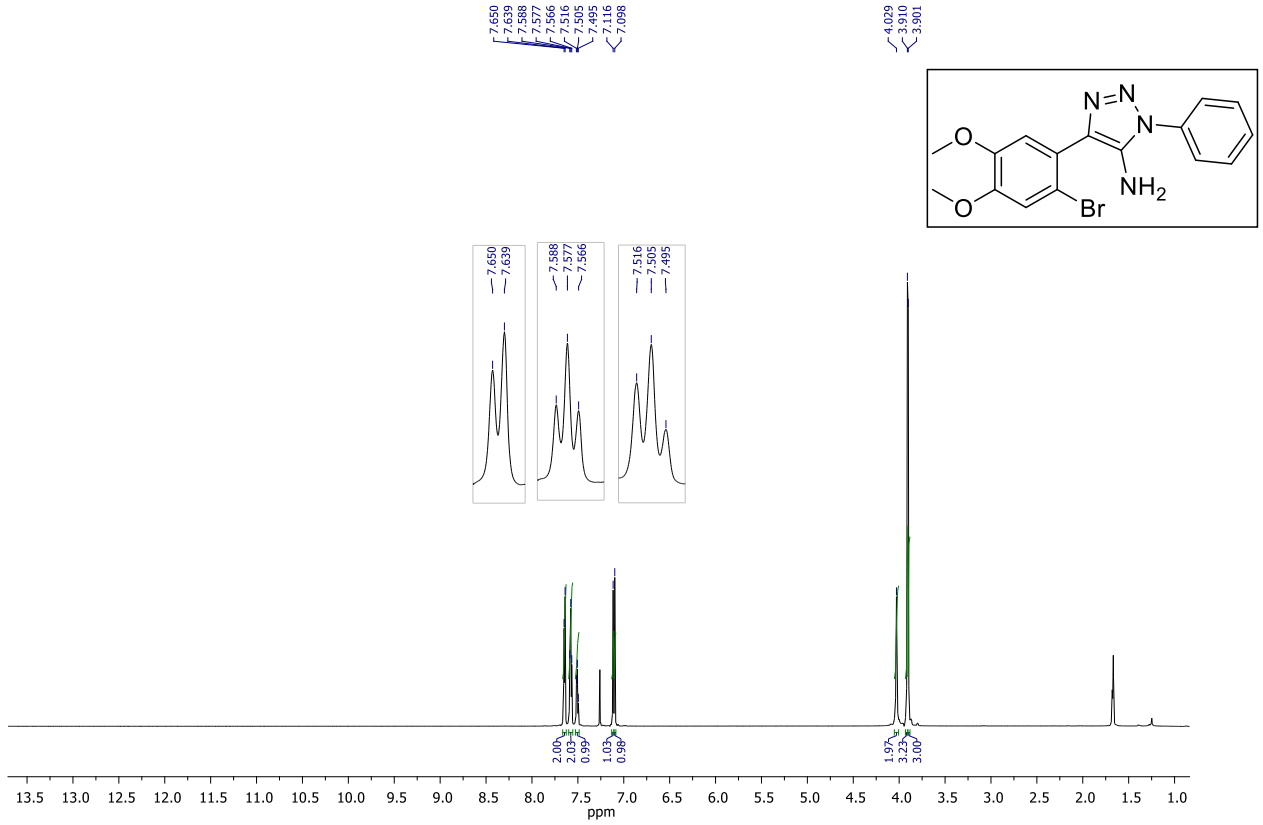


Figure 3.35b. ^{13}C NMR Spectrum of 70c in $CDCl_3$ at 100 MHz

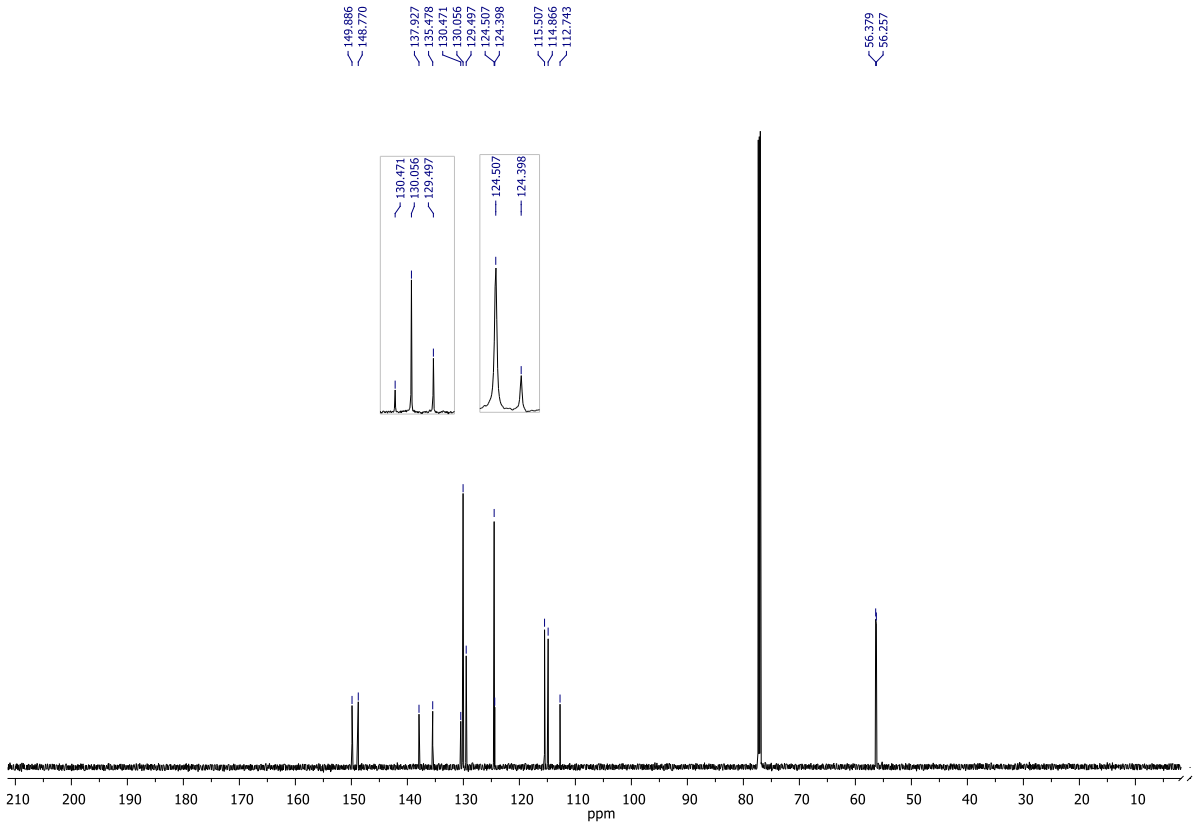


Figure 3.36a. ^{1}H NMR Spectrum of 70d in $CDCl_3$ at 400 MHz

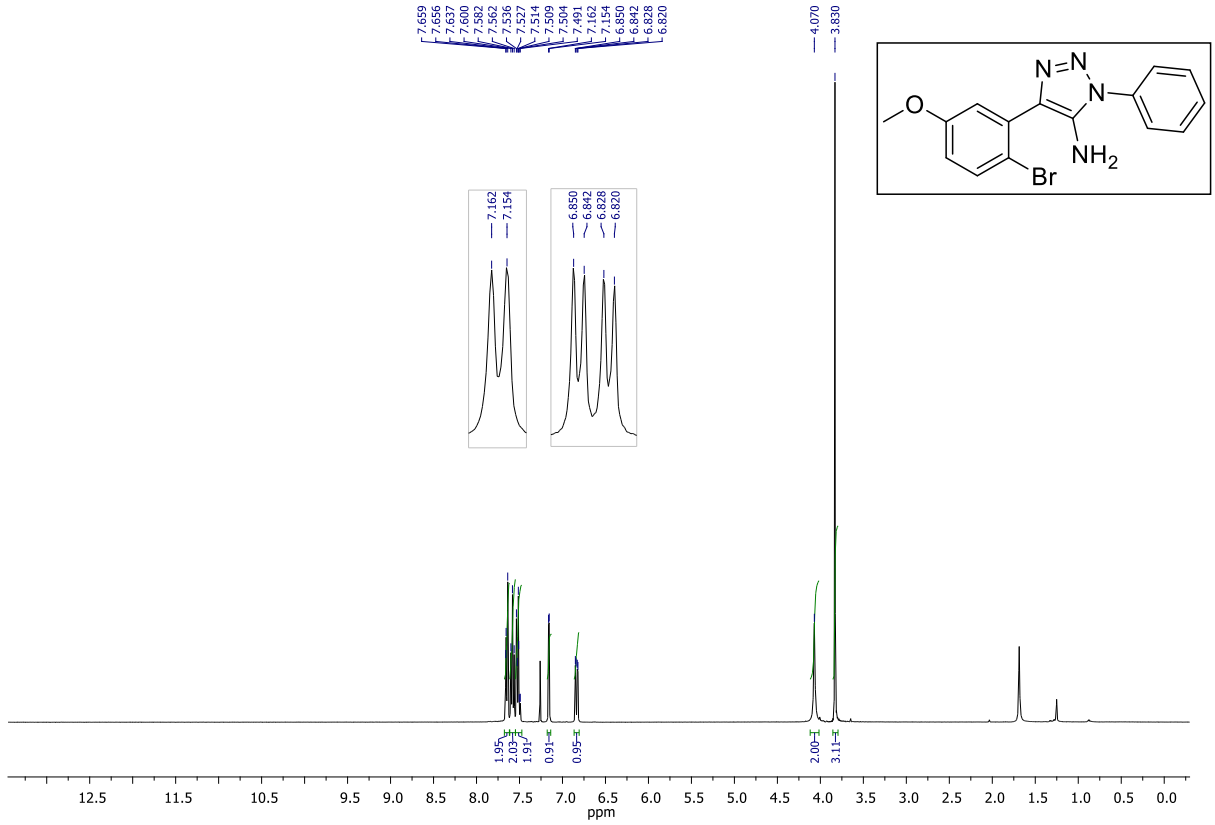


Figure 3.36b. ^{13}C NMR Spectrum of 70d in $CDCl_3$ at 100 MHz

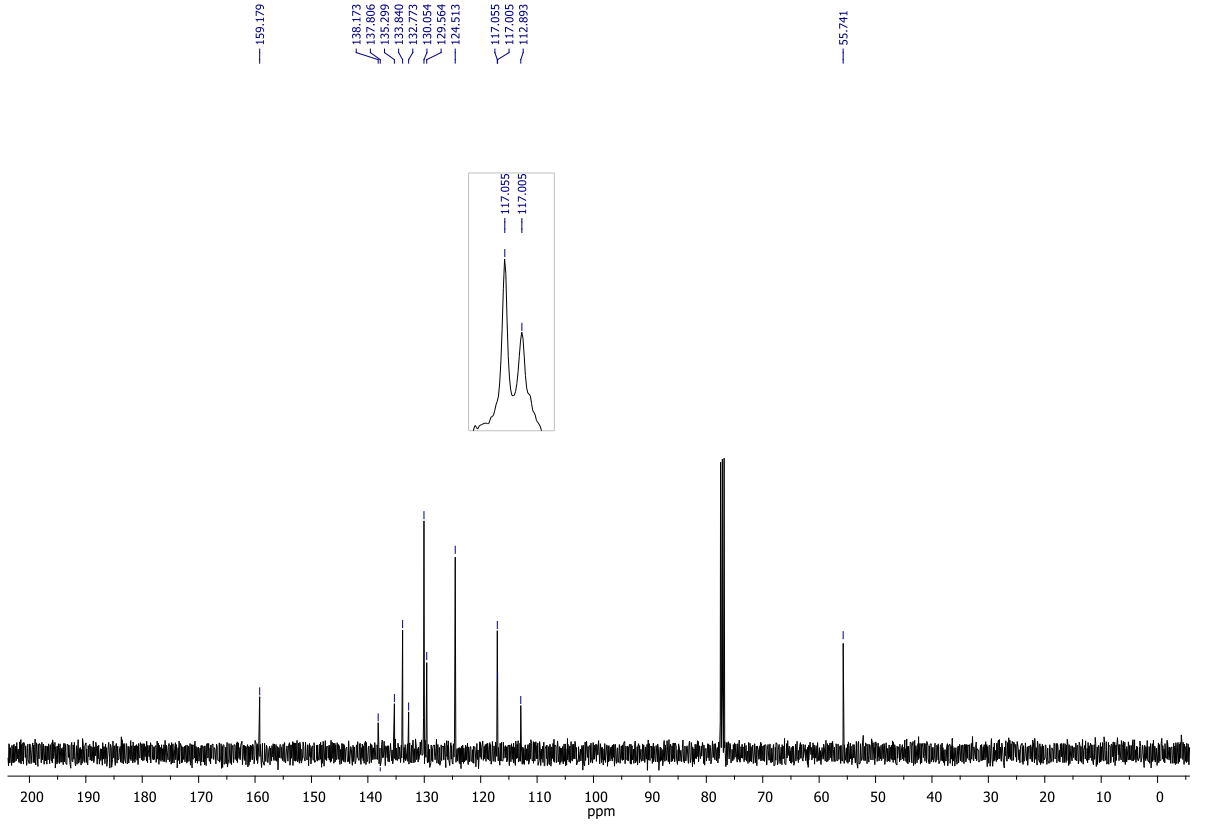


Figure 3.37a. ^{1}H NMR Spectrum of 70e in $CDCl_3$ at 400 MHz

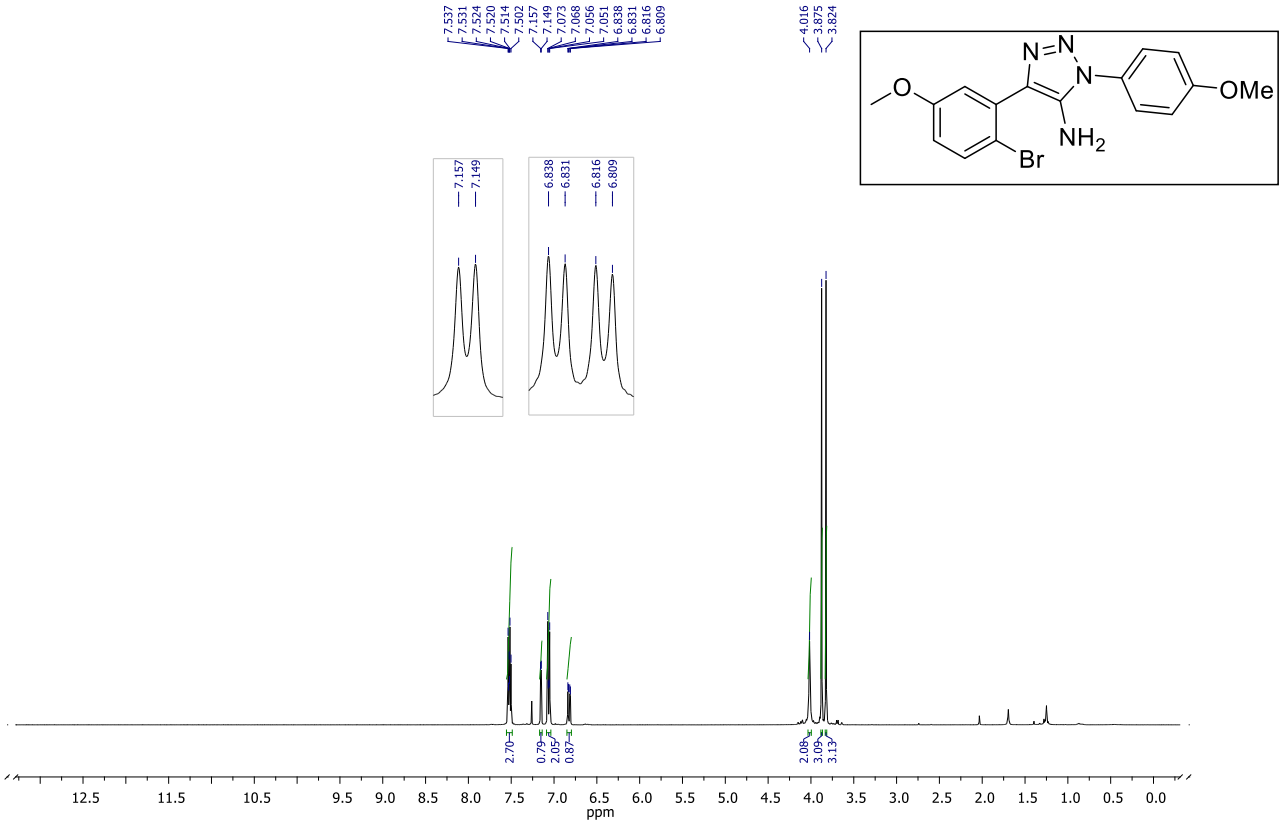


Figure 3.37b. ^{13}C NMR Spectrum of 70e in $CDCl_3$ at 100 MHz

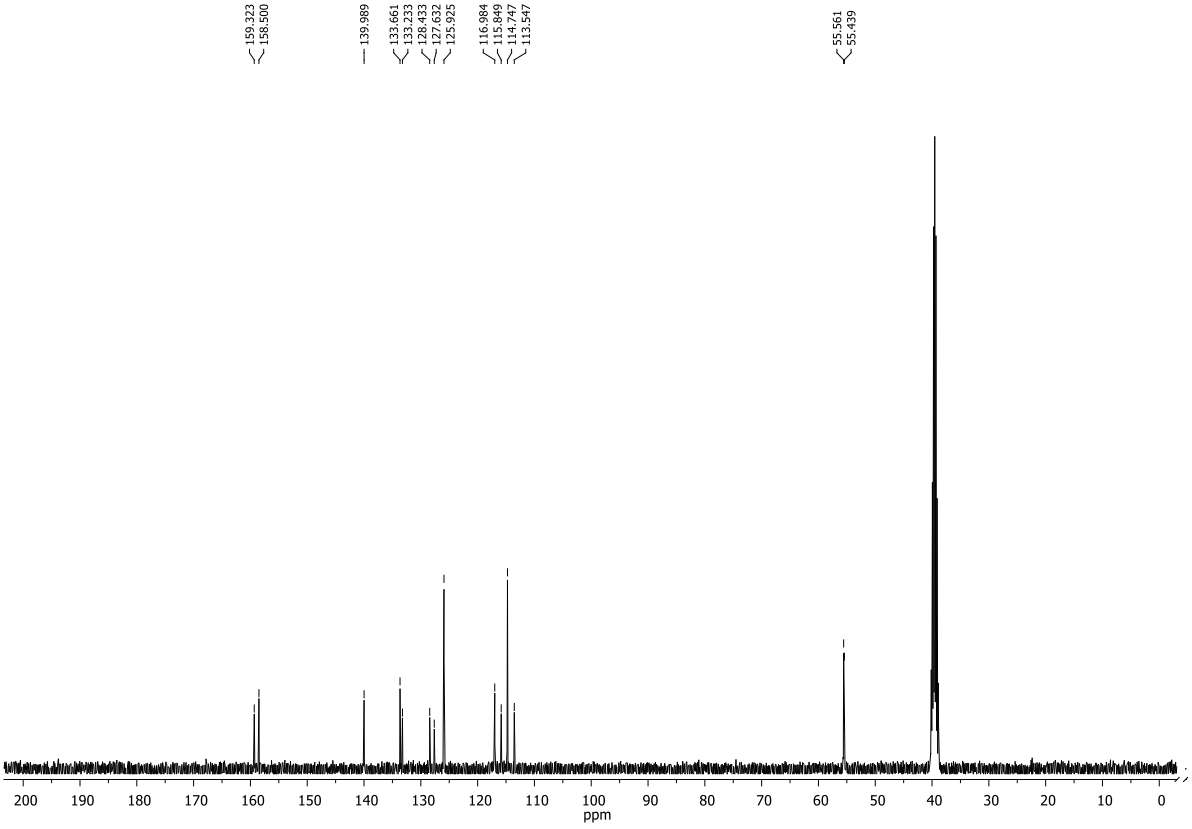


Figure 3.38a. ^{1}H NMR Spectrum of 70i in $CDCl_3$ at 400 MHz

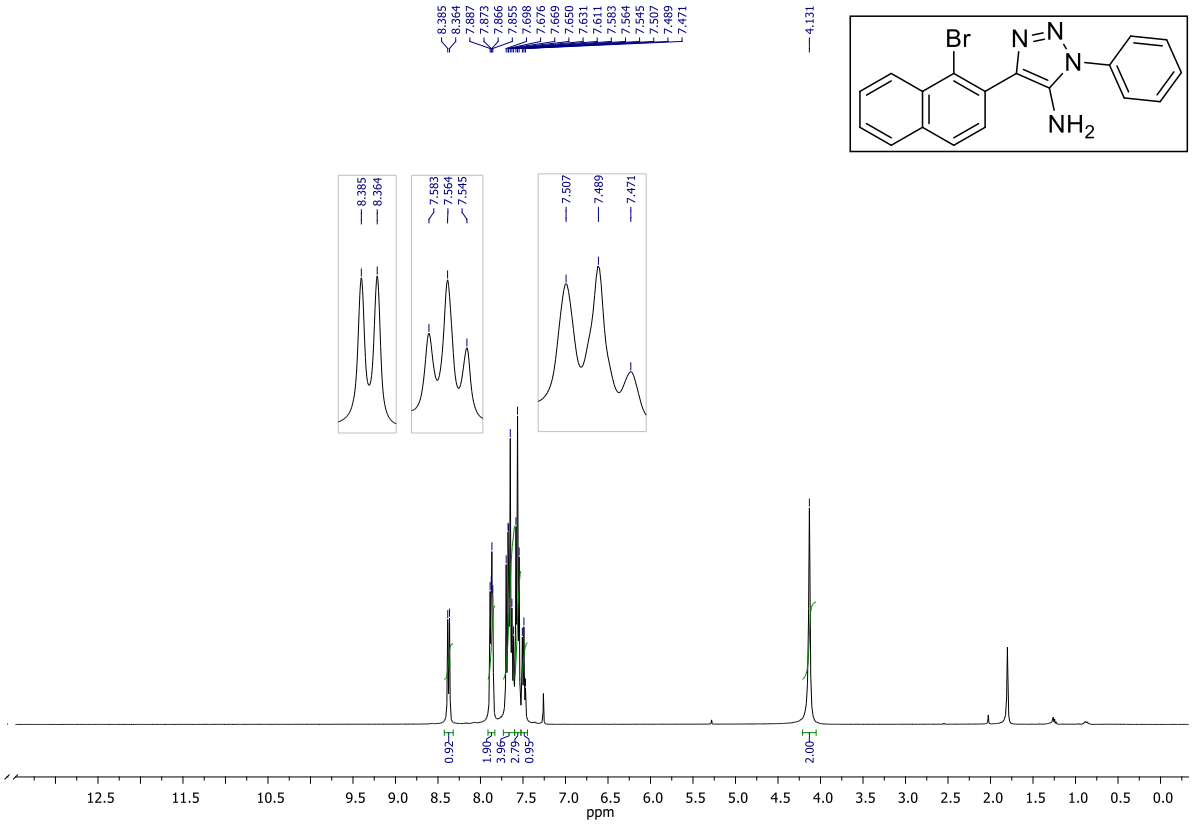


Figure 3.38b. ^{13}C NMR Spectrum of 70i in $CDCl_3$ at 100 MHz

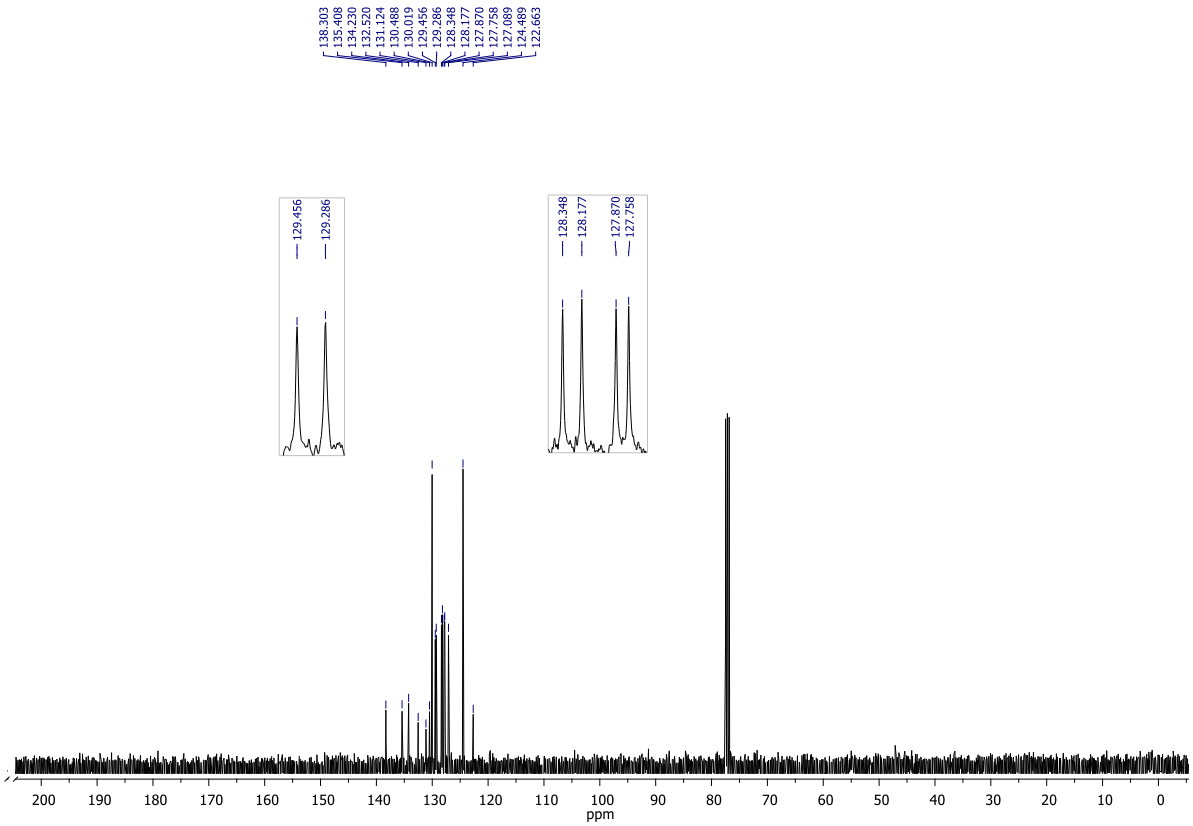


Figure 3.39a. ^{1}H NMR Spectrum of 71a in DMSO at 400 MHz

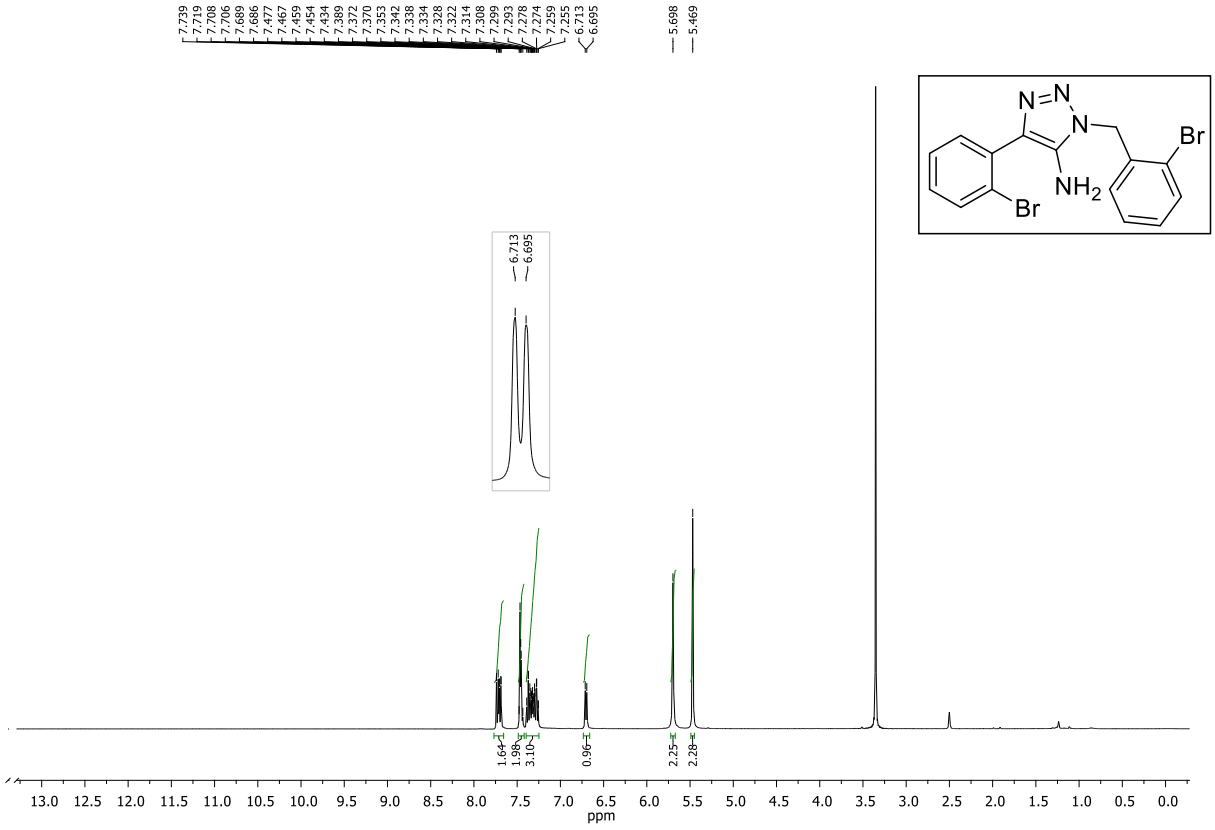


Figure 3.39b. ^{13}C NMR Spectrum of 71a in DMSO at 100 MHz

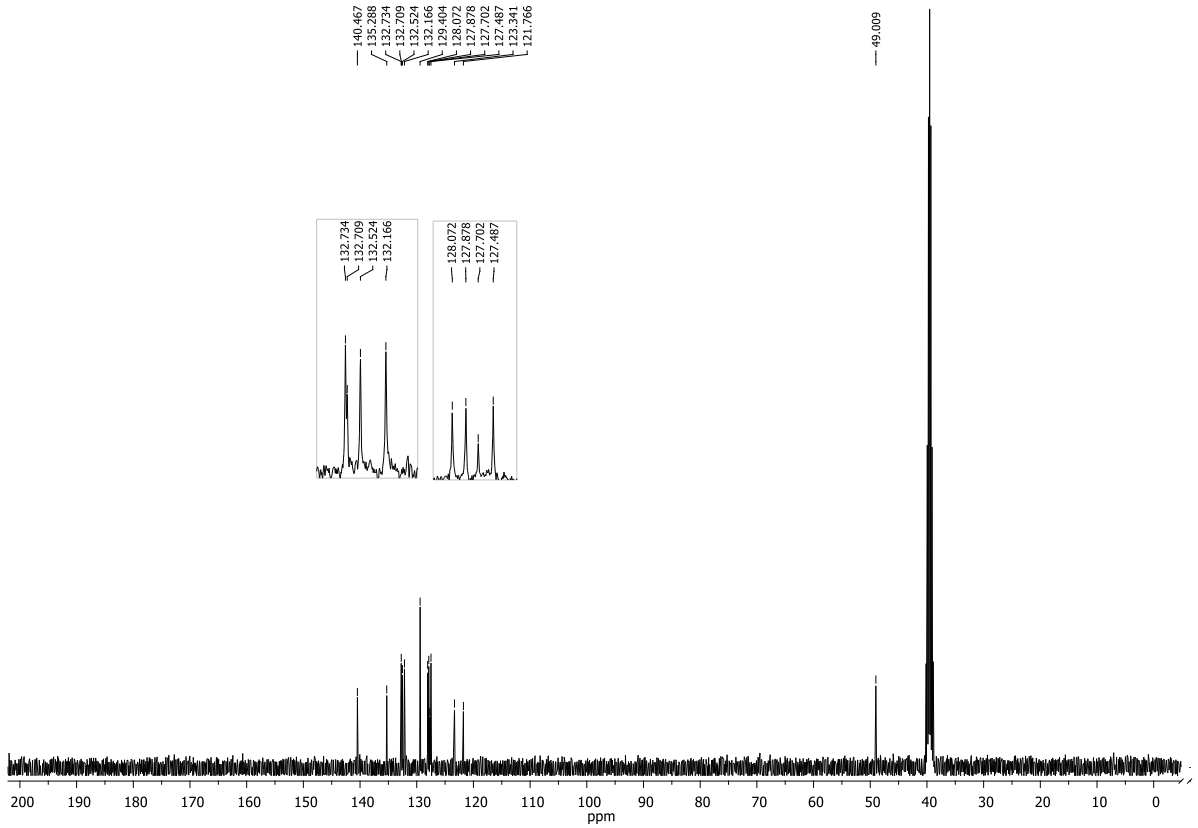


Figure 3.40a. ^{1}H NMR Spectrum of 71b in $CDCl_3$ at 400 MHz

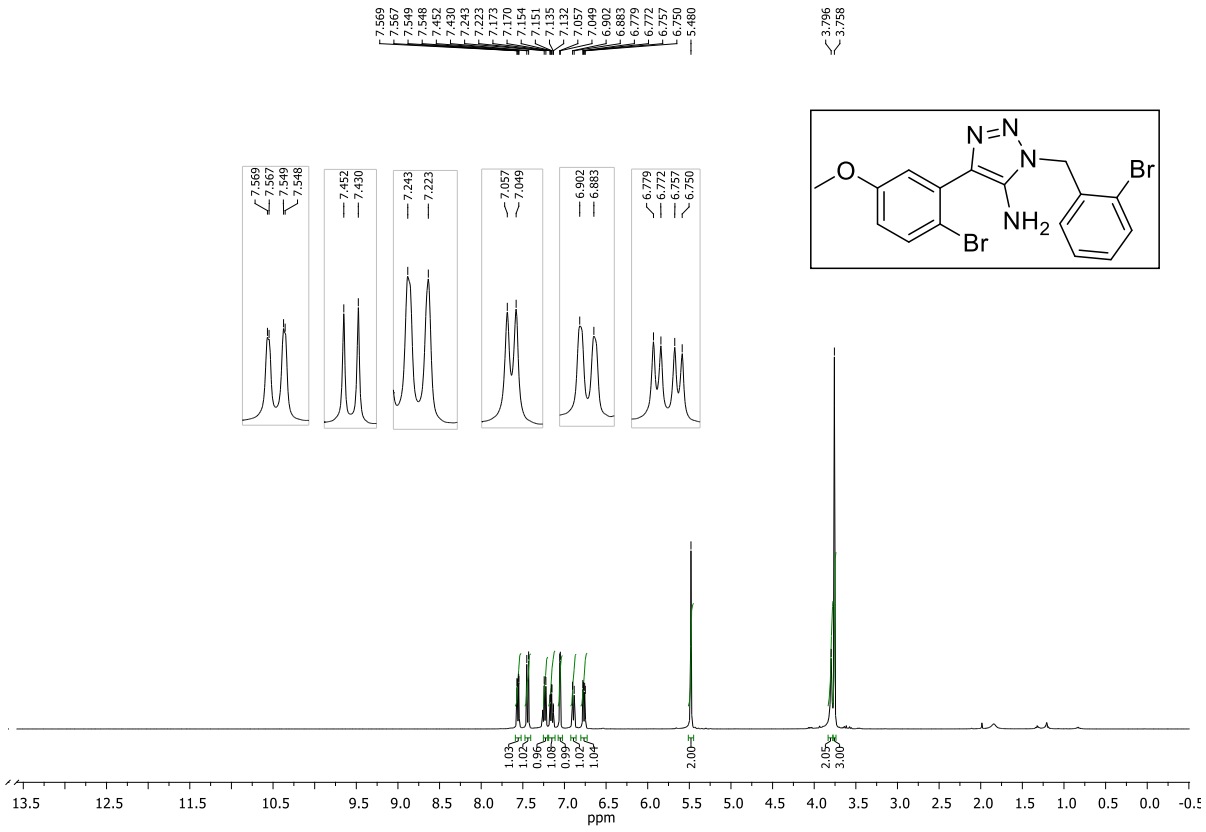


Figure 3.40b. ^{13}C NMR Spectrum of 71b in $CDCl_3$ at 100 MHz

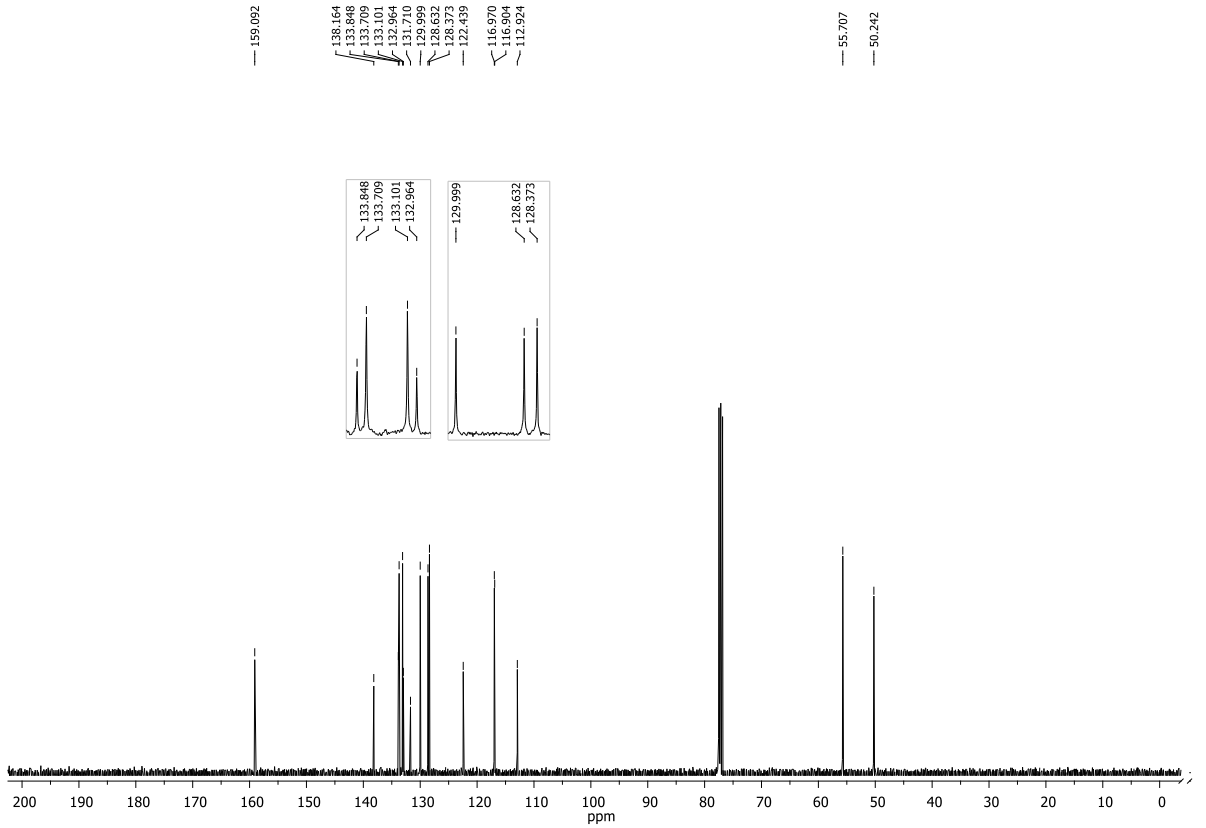


Figure 3.41a. ^{1}H NMR Spectrum of 71c in $CDCl_3$ at 400 MHz

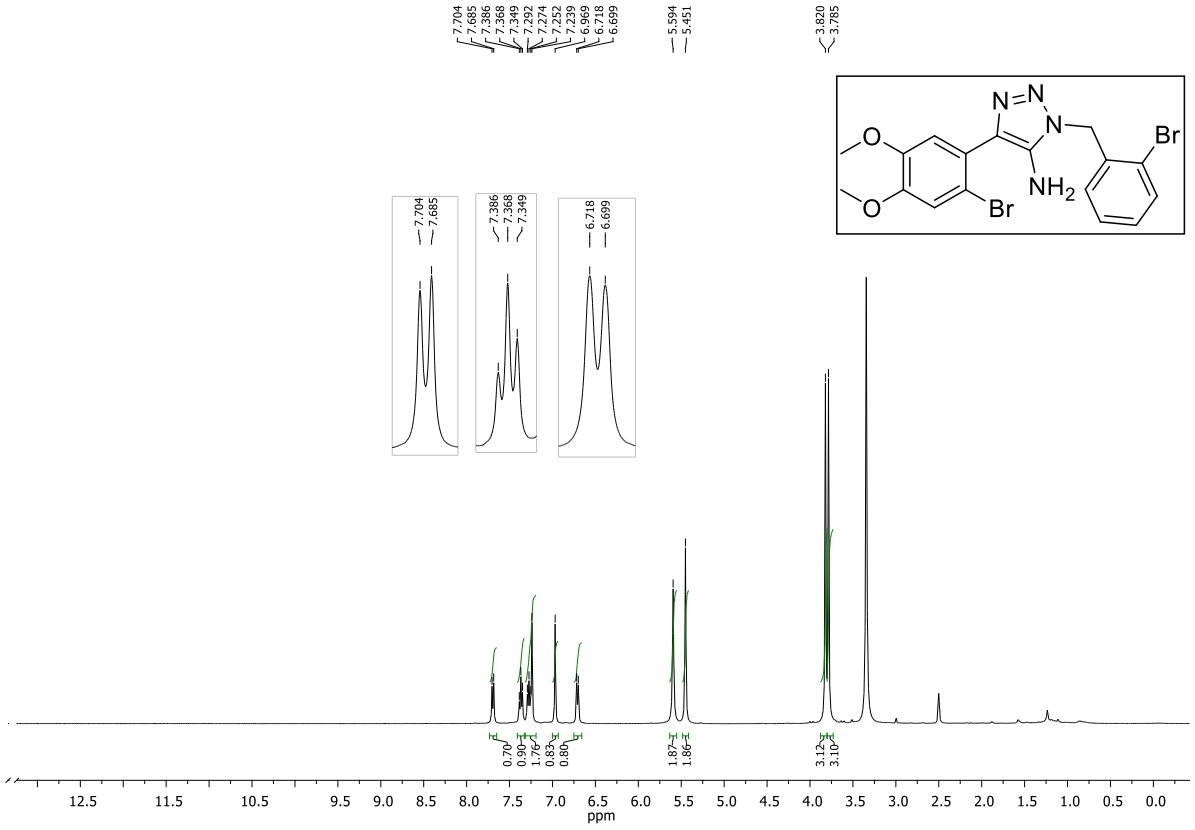


Figure 3.41b. ^{13}C NMR Spectrum of 71c in $CDCl_3$ at 100 MHz

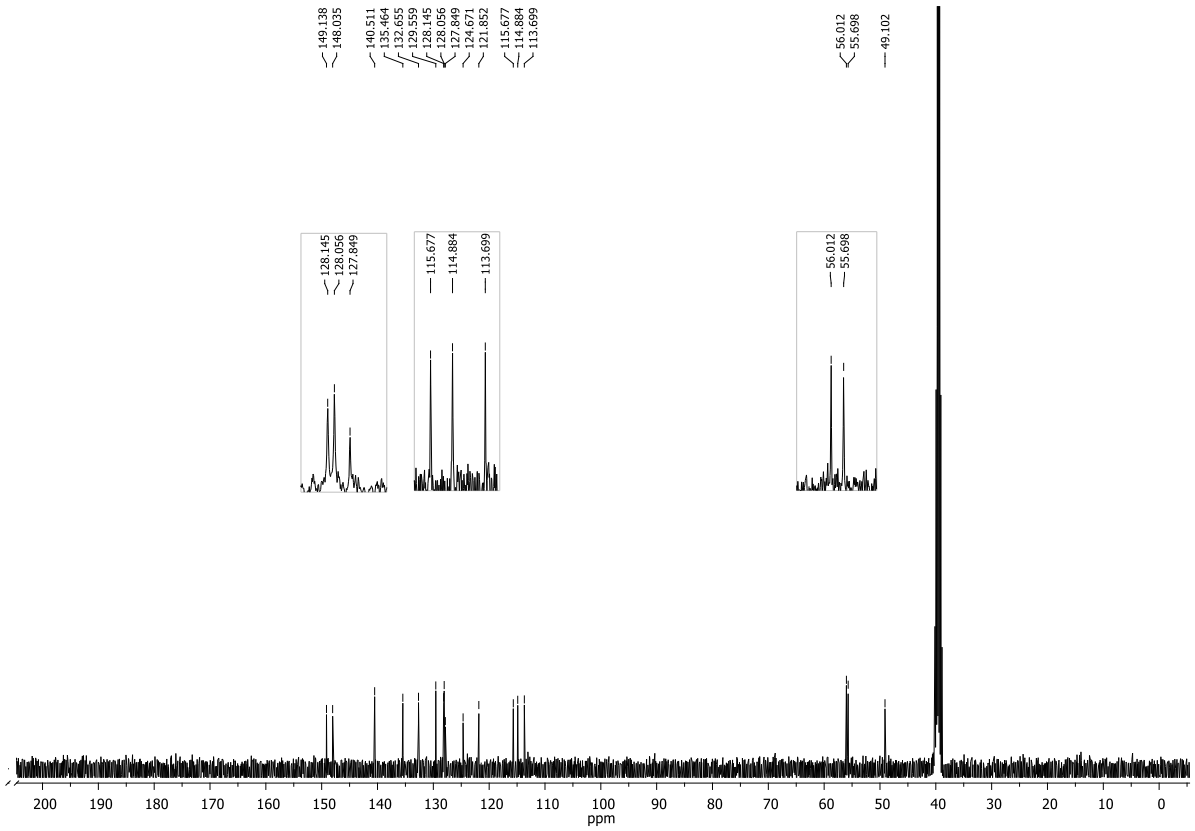


Figure 3.42a. ^{1}H NMR Spectrum of 71f in $CDCl_3$ at 400 MHz

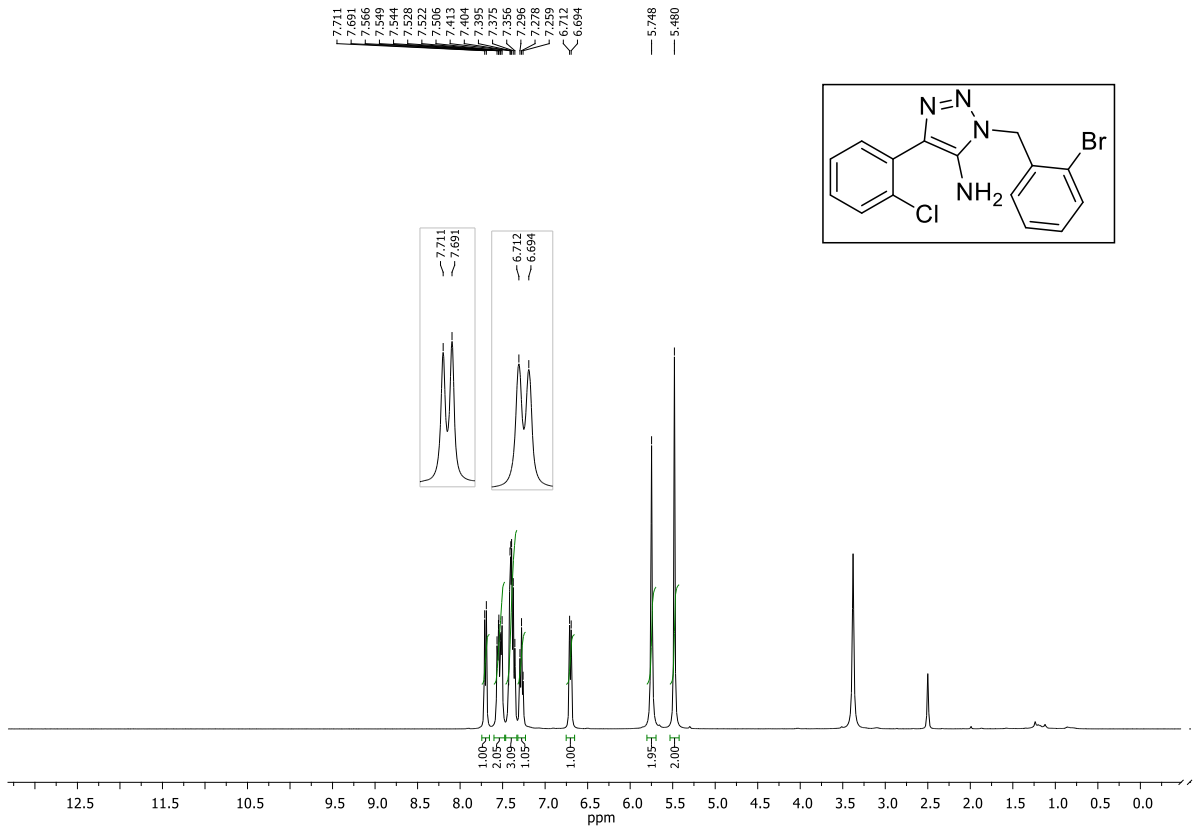


Figure 3.42b. ^{13}C NMR Spectrum of 71f in $CDCl_3$ at 100 MHz

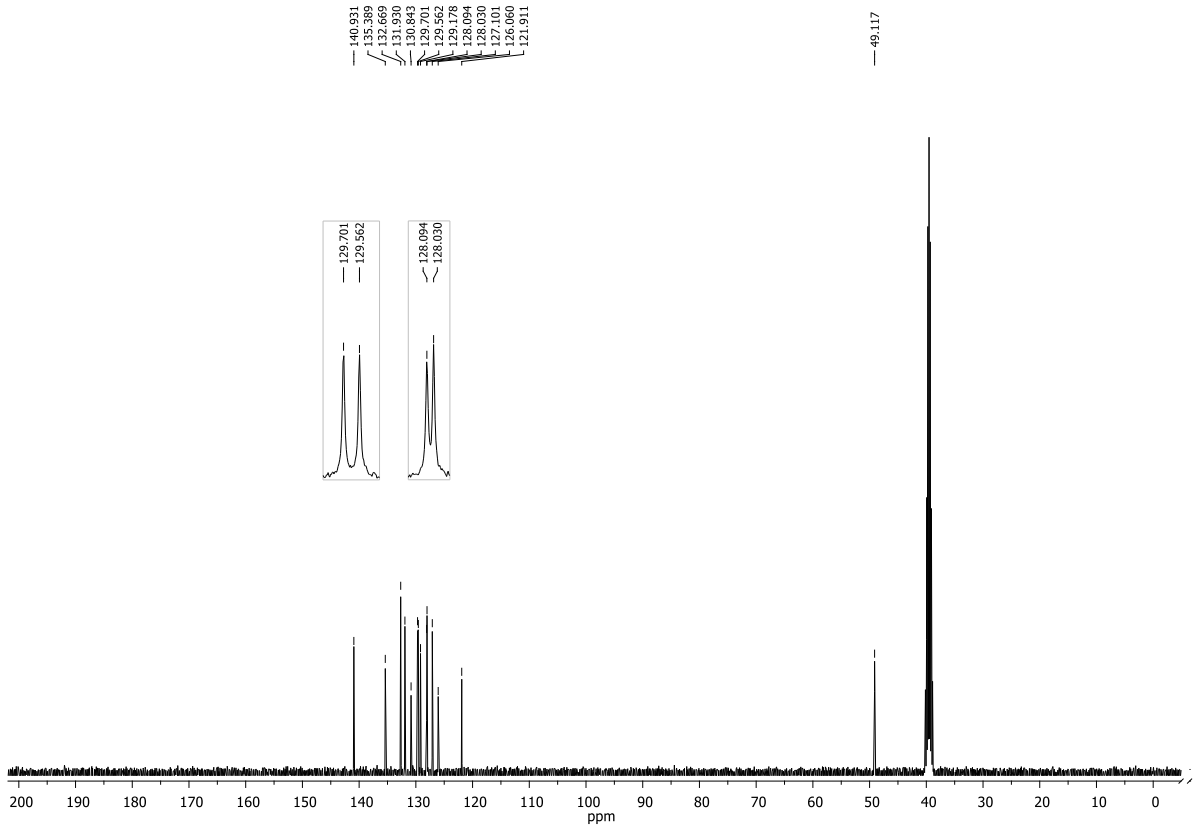


Figure 3.43a. ^{1}H NMR Spectrum of 71h in $CDCl_3$ at 400 MHz

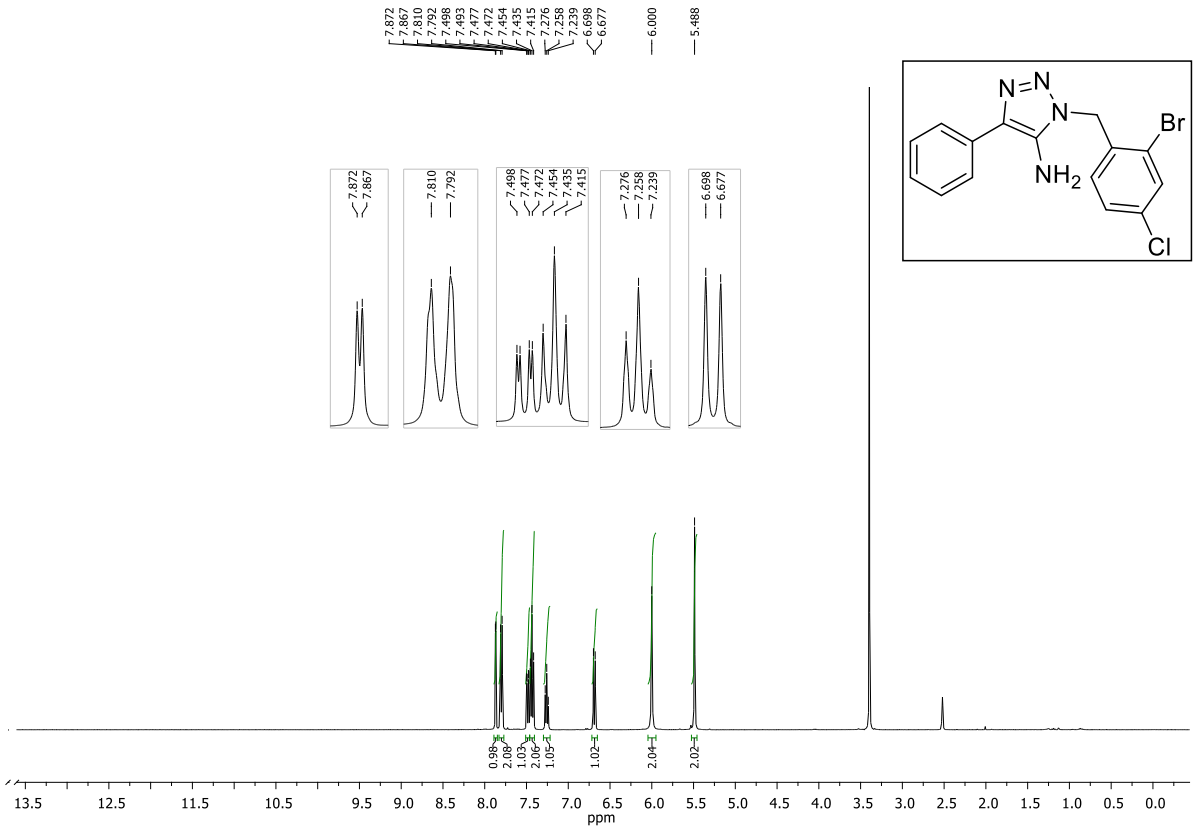


Figure 3.43b. ^{13}C NMR Spectrum of 71h in $CDCl_3$ at 100 MHz

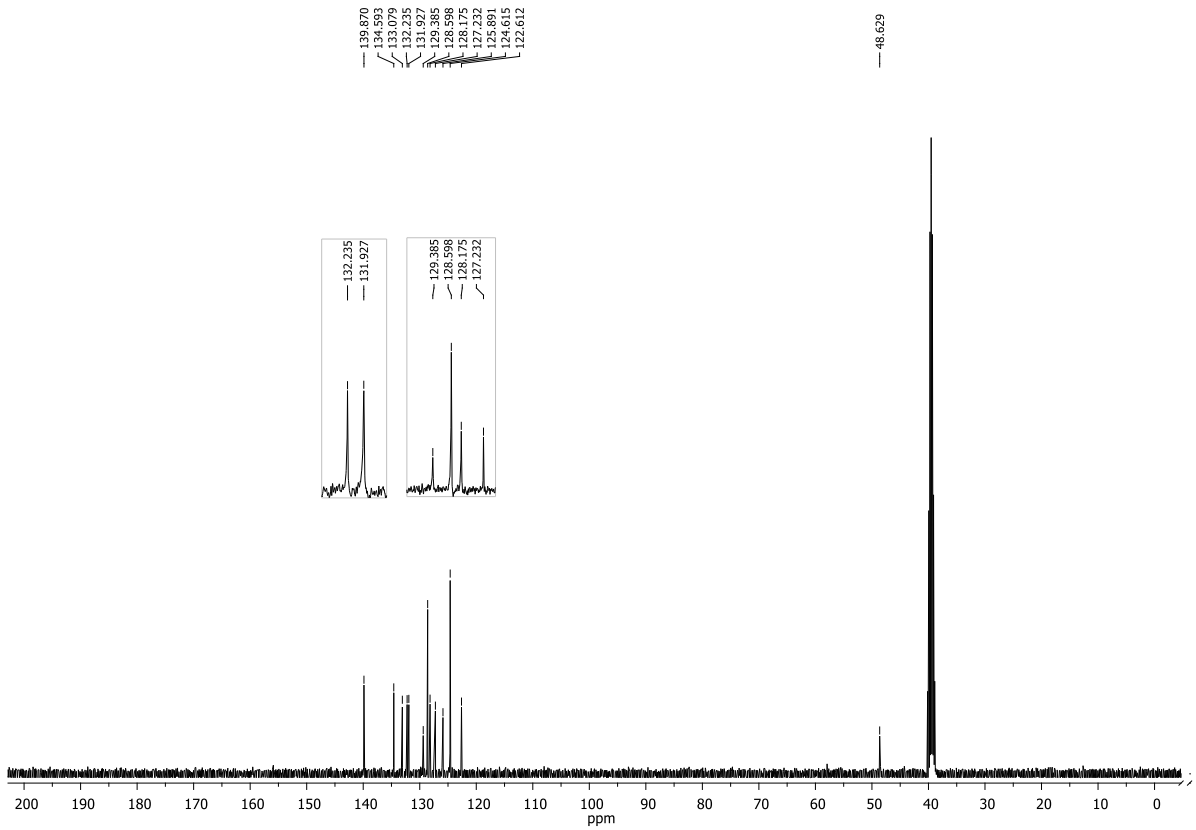


Figure 3.44a. ^{1}H NMR Spectrum of 71j in $CDCl_3$ at 400 MHz

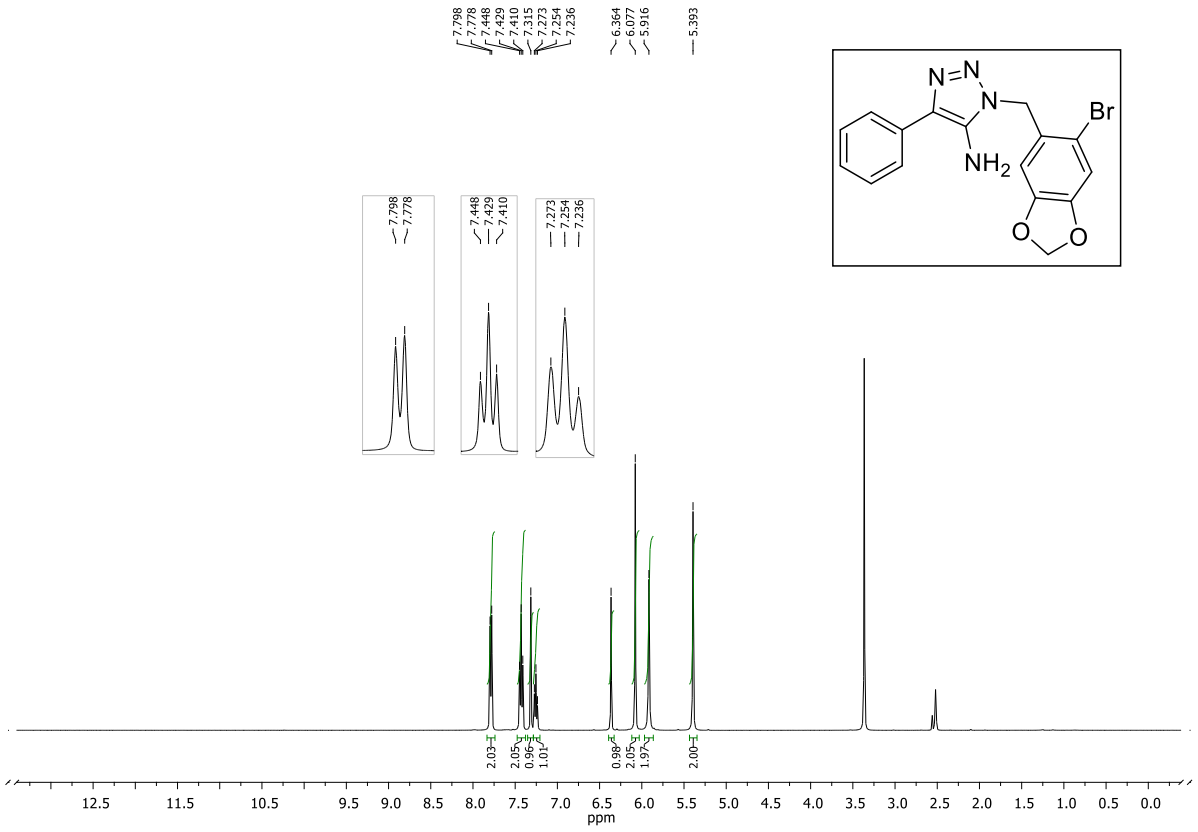


Figure 3.44b. ^{13}C NMR Spectrum of 71j in $CDCl_3$ at 400 MHz

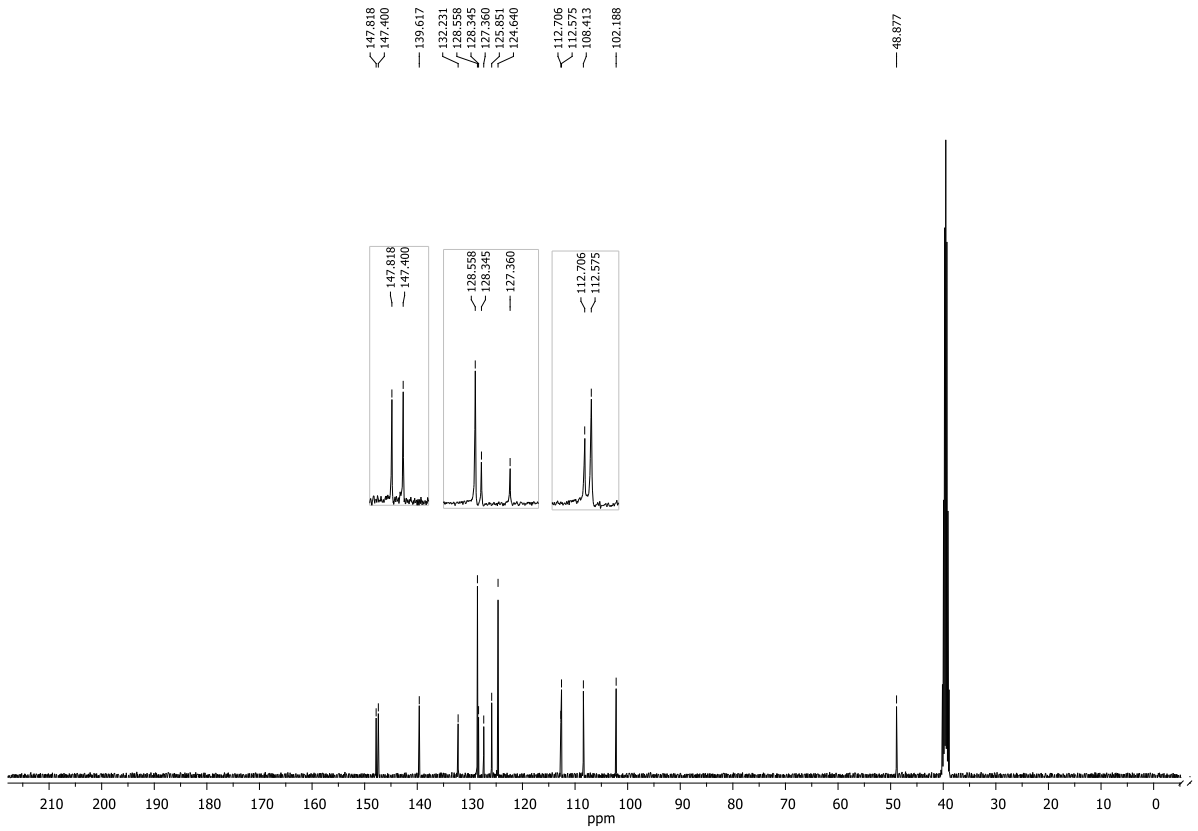


Figure 3.45a. ^{1}H NMR Spectrum of 62a in DMSO at 400 MHz

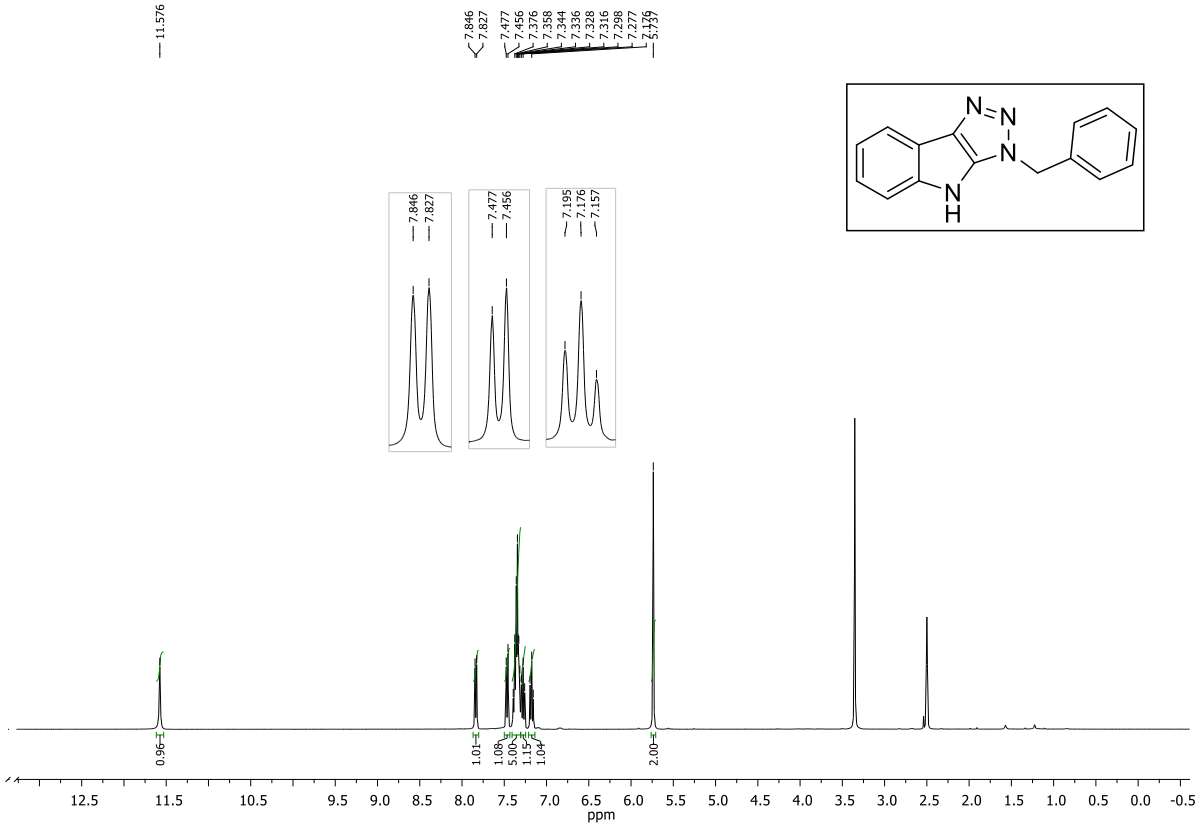


Figure 3.45b. ^{13}C NMR Spectrum of 62a in DMSO at 400 MHz

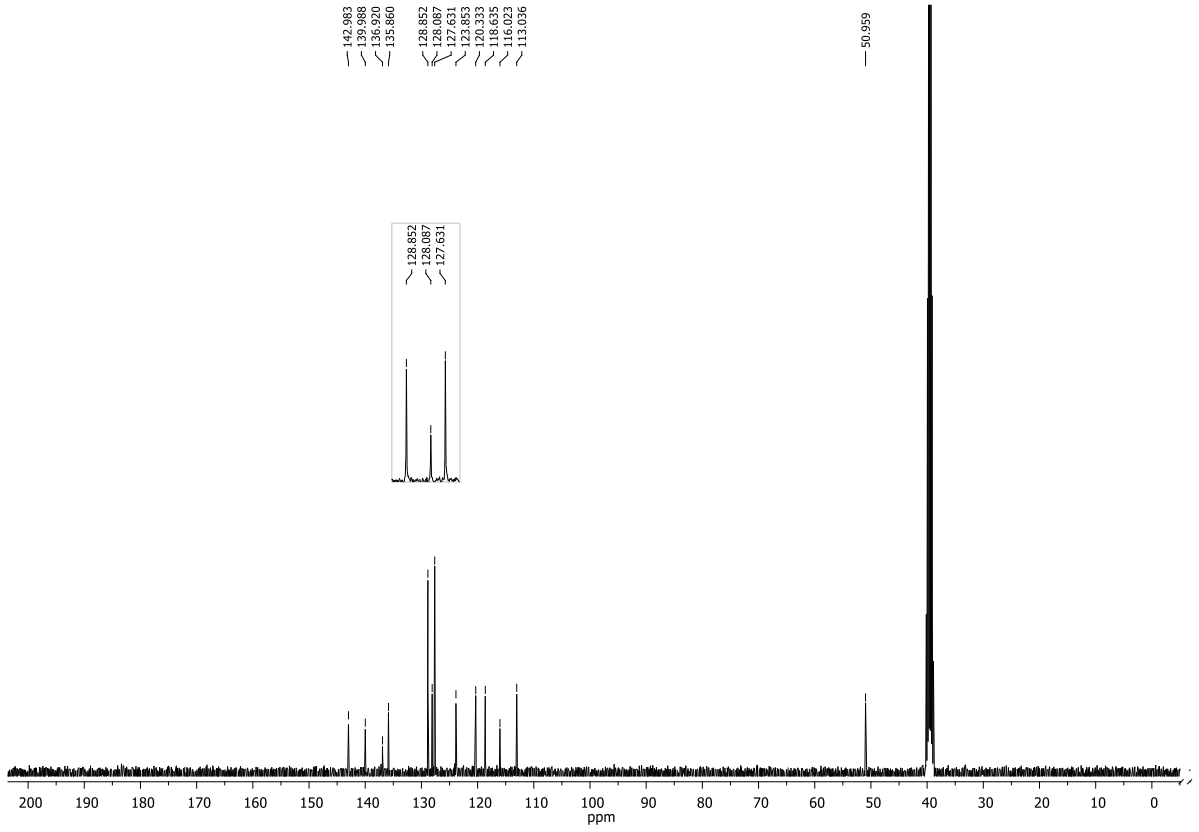


Figure 3.46a. ^{1}H NMR Spectrum of 62f in DMSO at 400 MHz

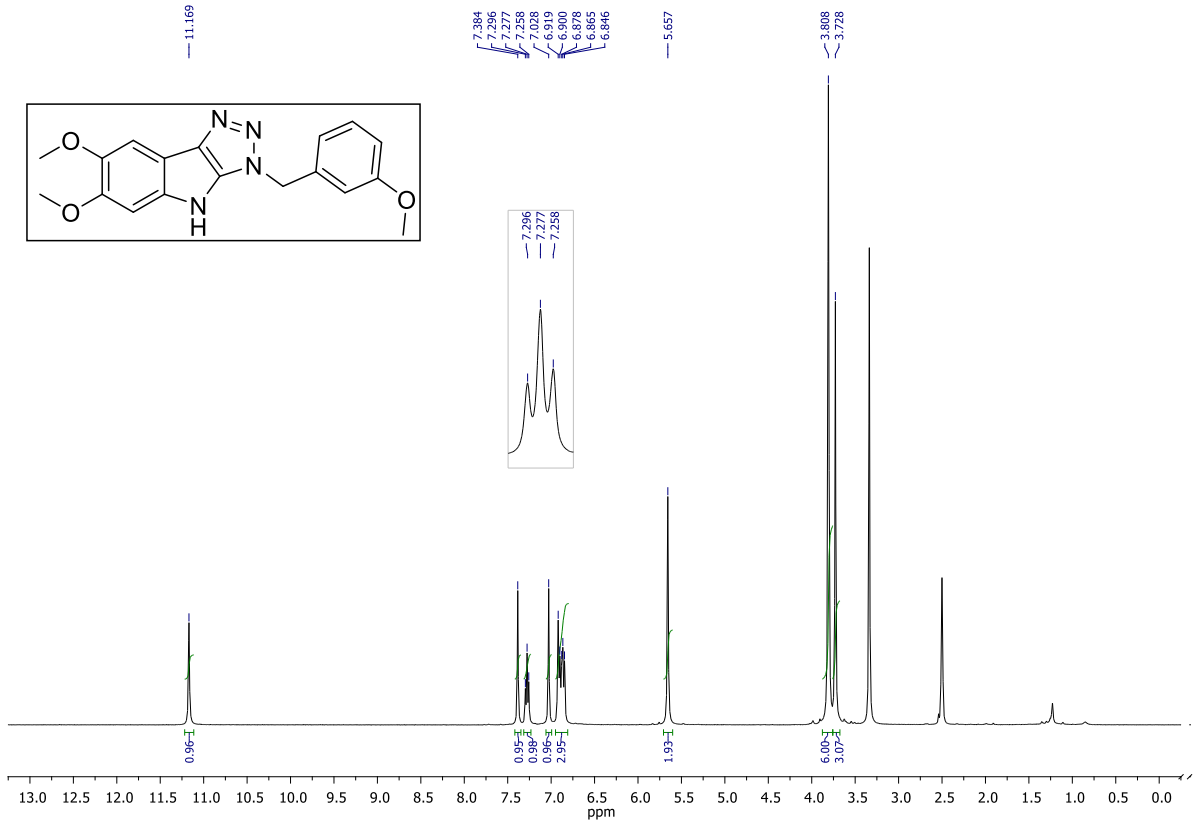


Figure 3.46b. ^{13}C NMR Spectrum of 62f in DMSO at 100 MHz

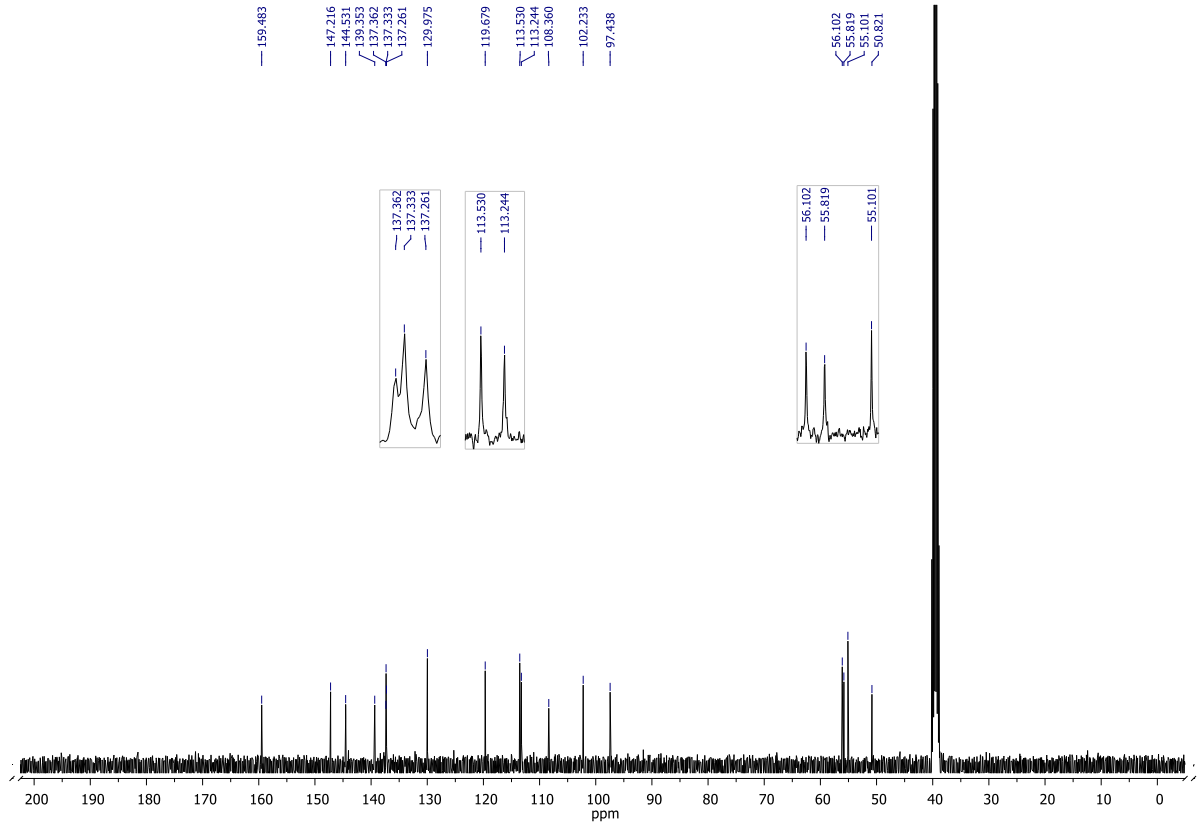


Figure 3.47a. ^{1}H NMR Spectrum of 62g in DMSO at 700 MHz

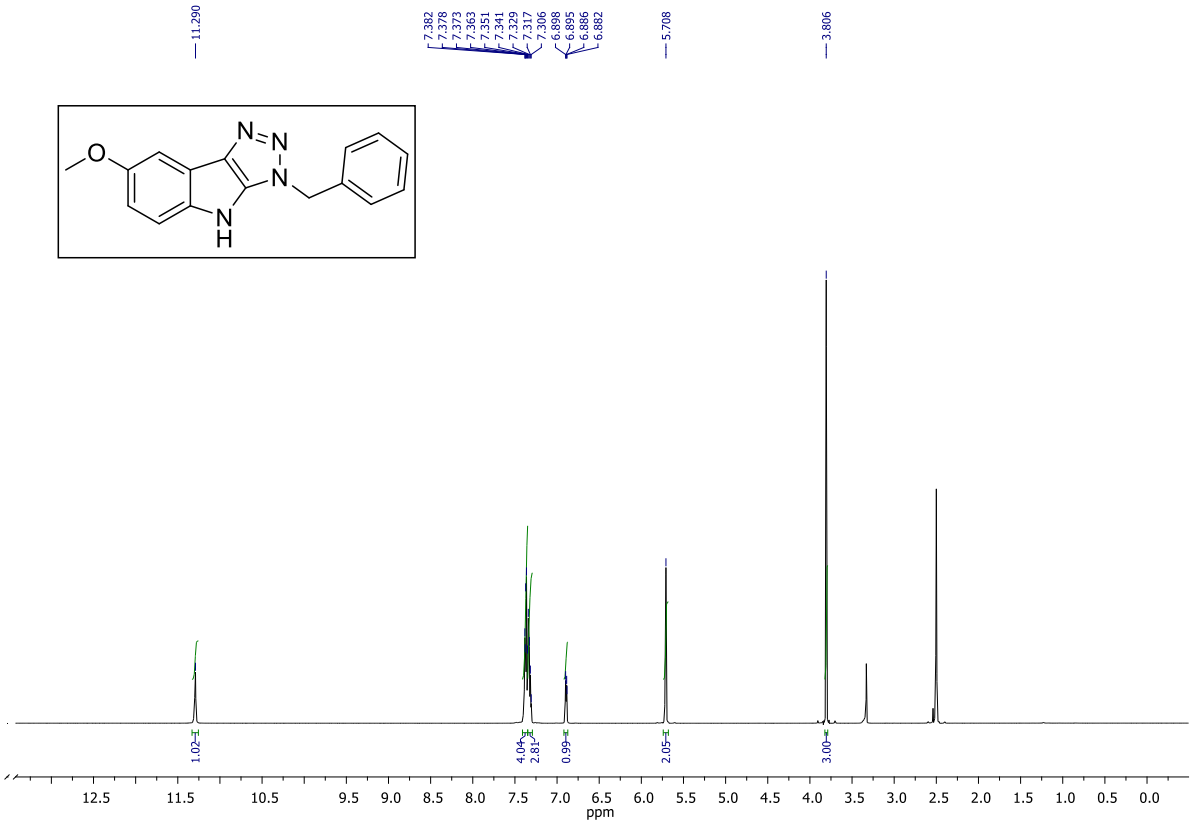


Figure 3.47b. ^{13}C NMR Spectrum of 62g in DMSO at 175 MHz

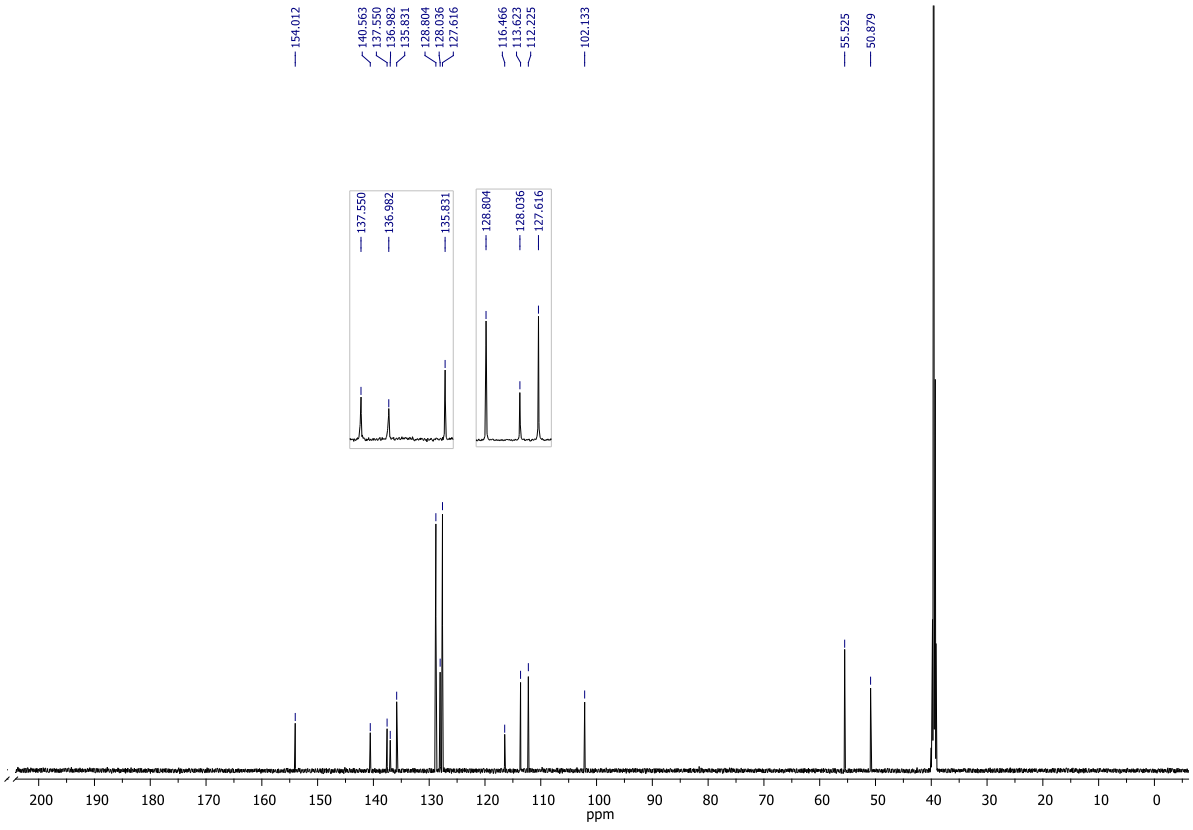


Figure 3.48a. ^{1}H NMR Spectrum of 62k in DMSO at 400 MHz

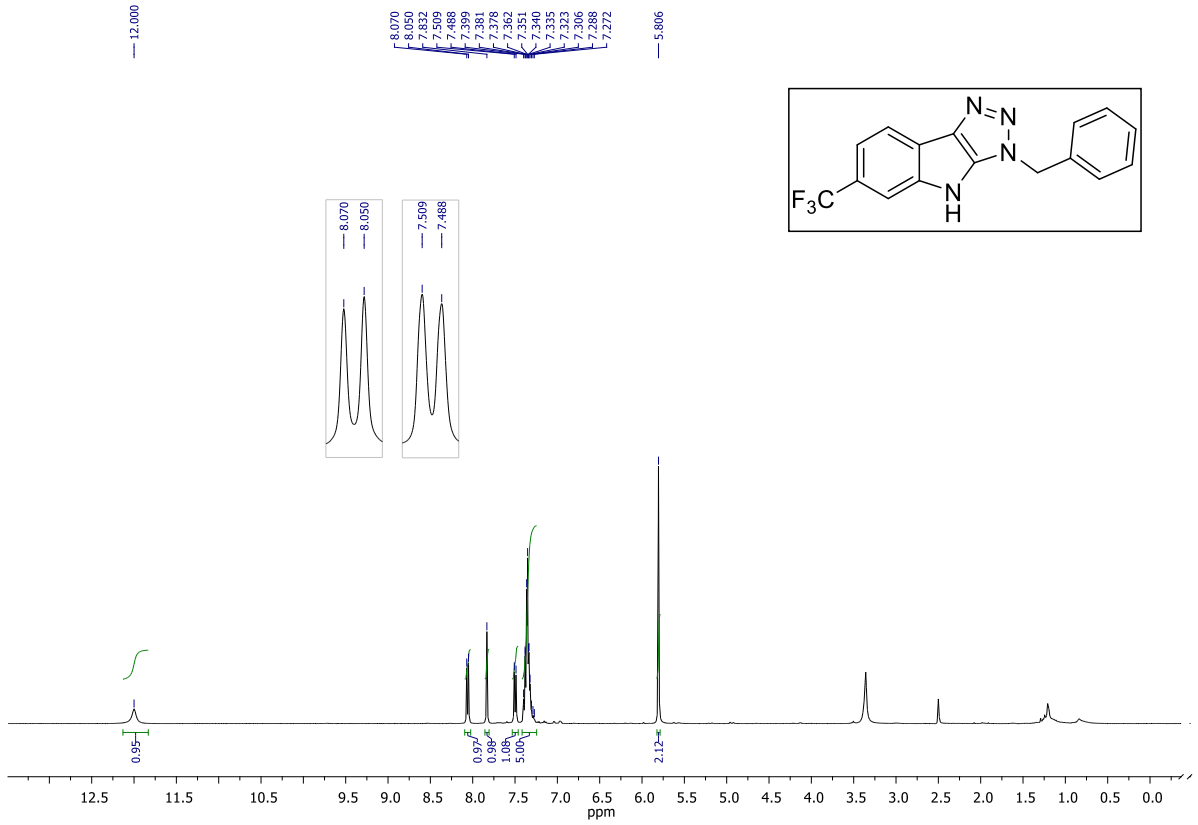


Figure 3.48b. ^{13}C NMR Spectrum of 62k in DMSO at 100 MHz

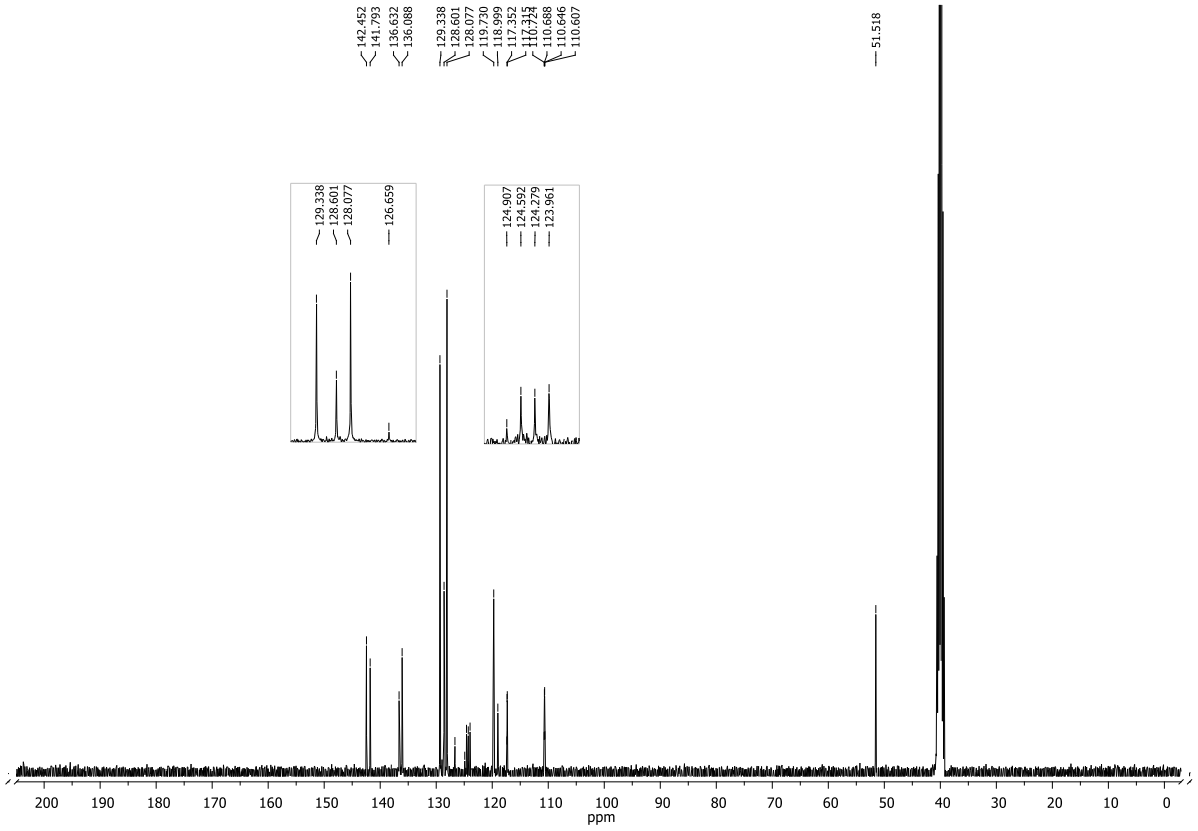


Figure 3.49a. ^{1}H NMR Spectrum of 62m in DMSO at 400 MHz

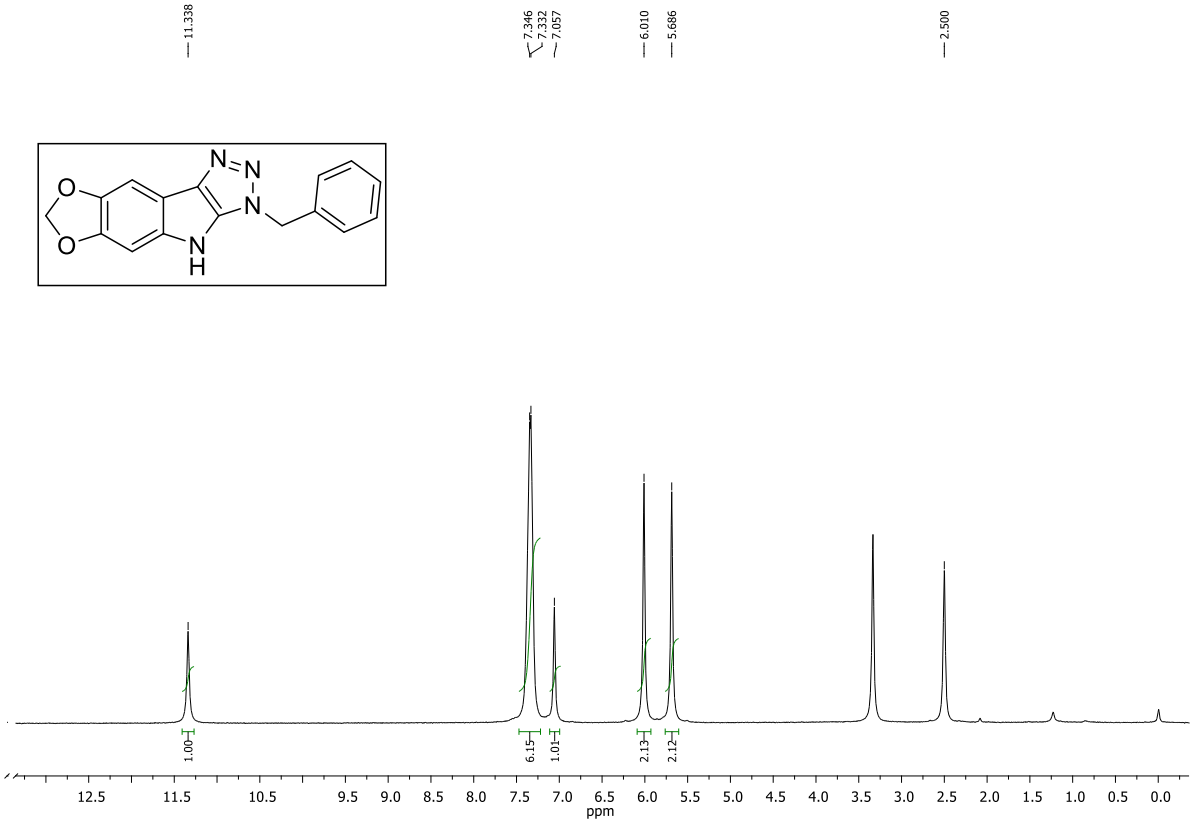


Figure 3.49b. ^{13}C NMR Spectrum of 62m in DMSO at 100 MHz

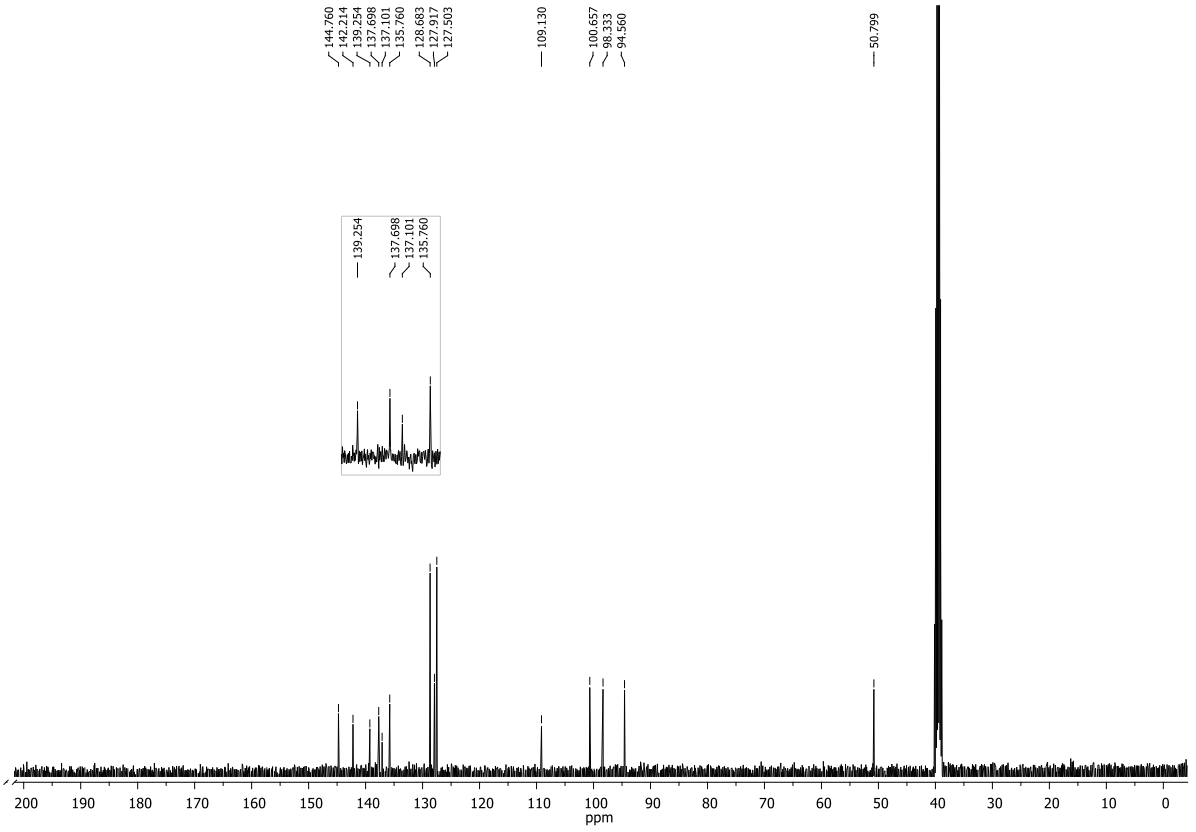


Figure 3.50a. ^{1}H NMR Spectrum of 72b in DMSO at 700 MHz

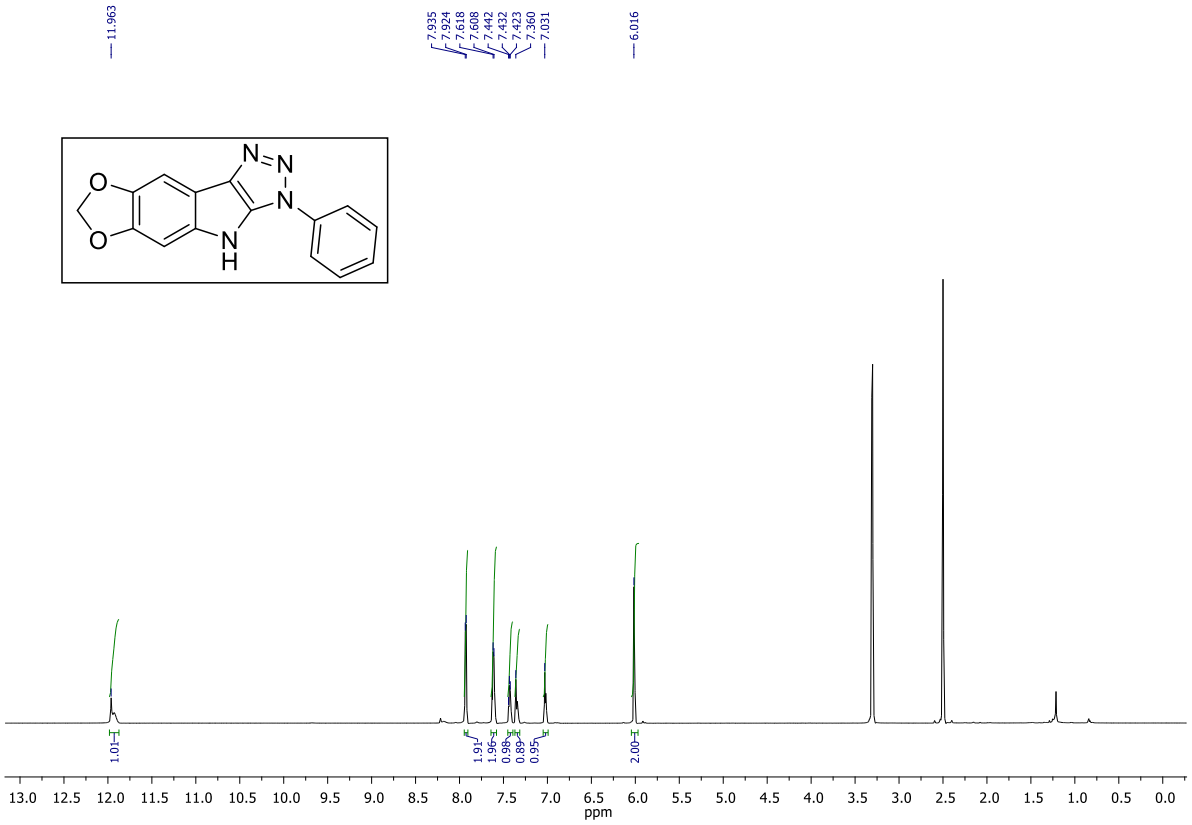


Figure 3.50a. ^{13}C NMR Spectrum of 72b in DMSO at 175 MHz

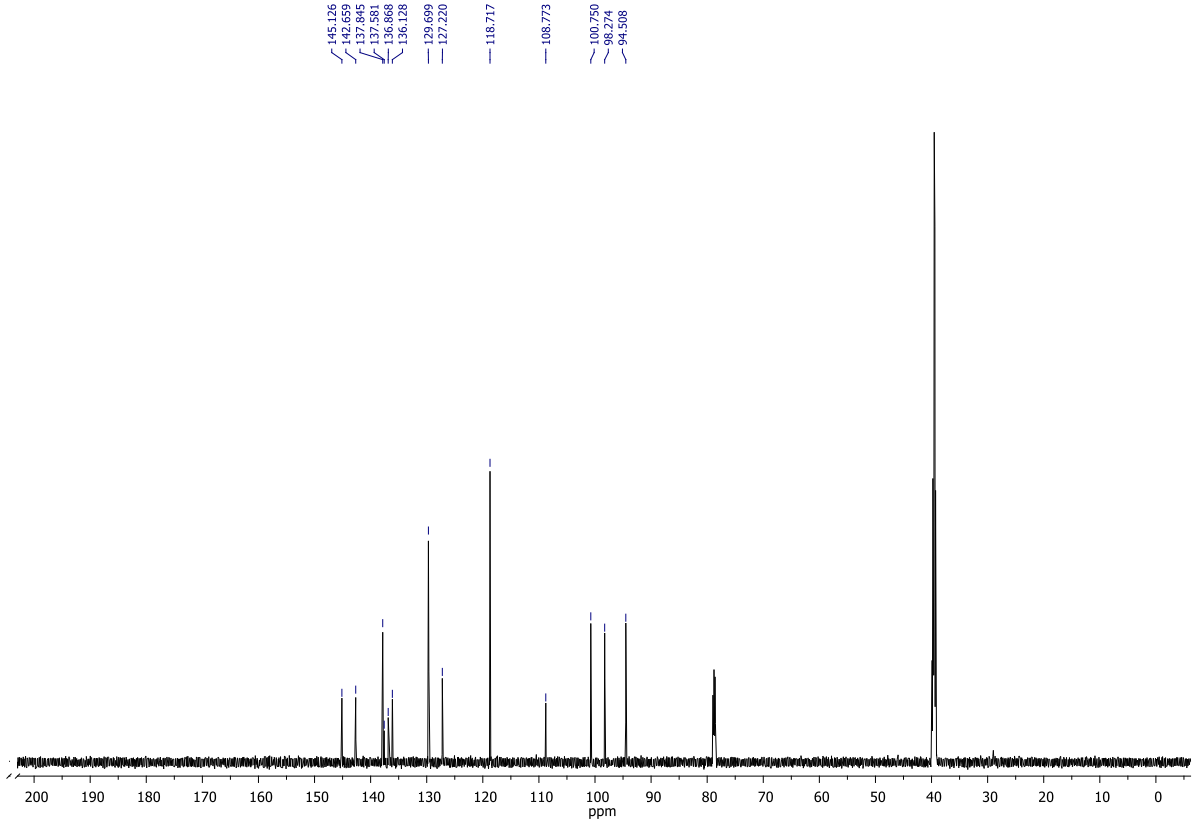


Figure 3.51a. ^{1}H NMR Spectrum of 72c in DMSO at 700 MHz

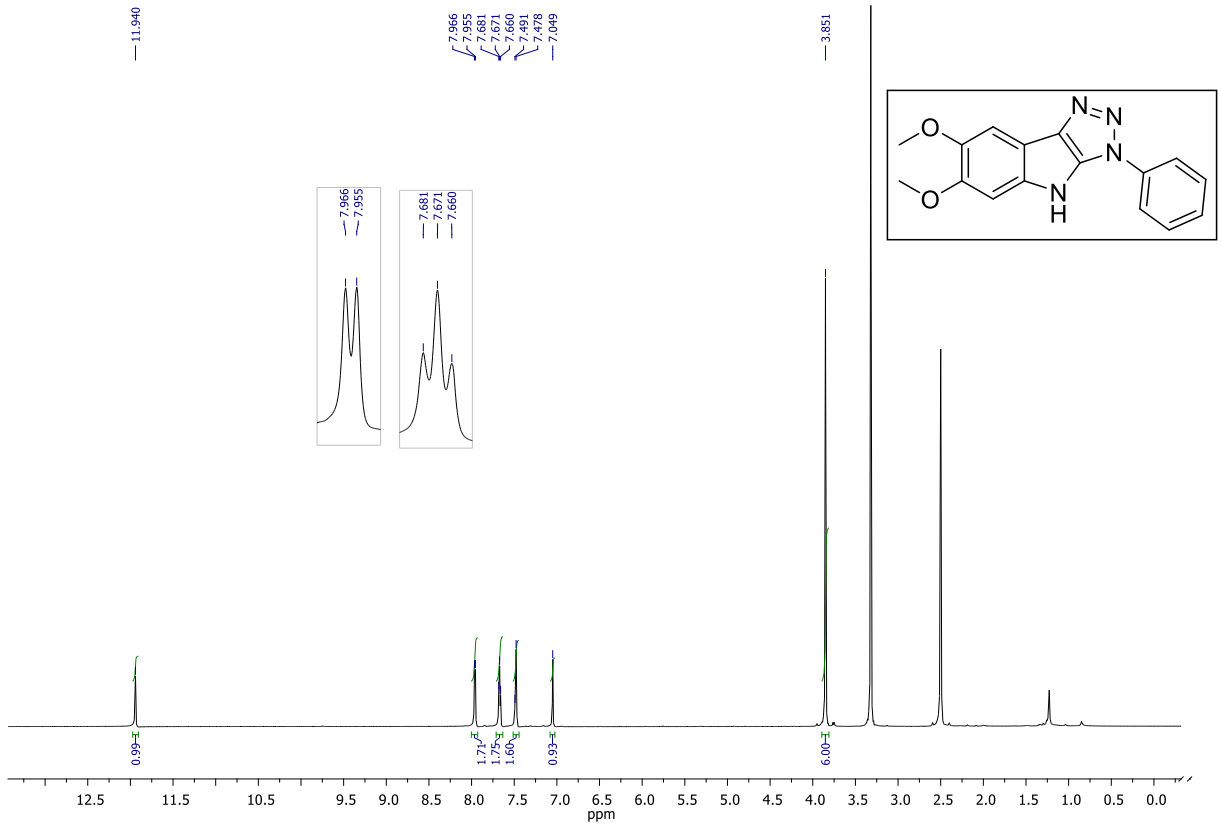


Figure 3.51b. ^{13}C NMR Spectrum of 72c in DMSO at 175 MHz

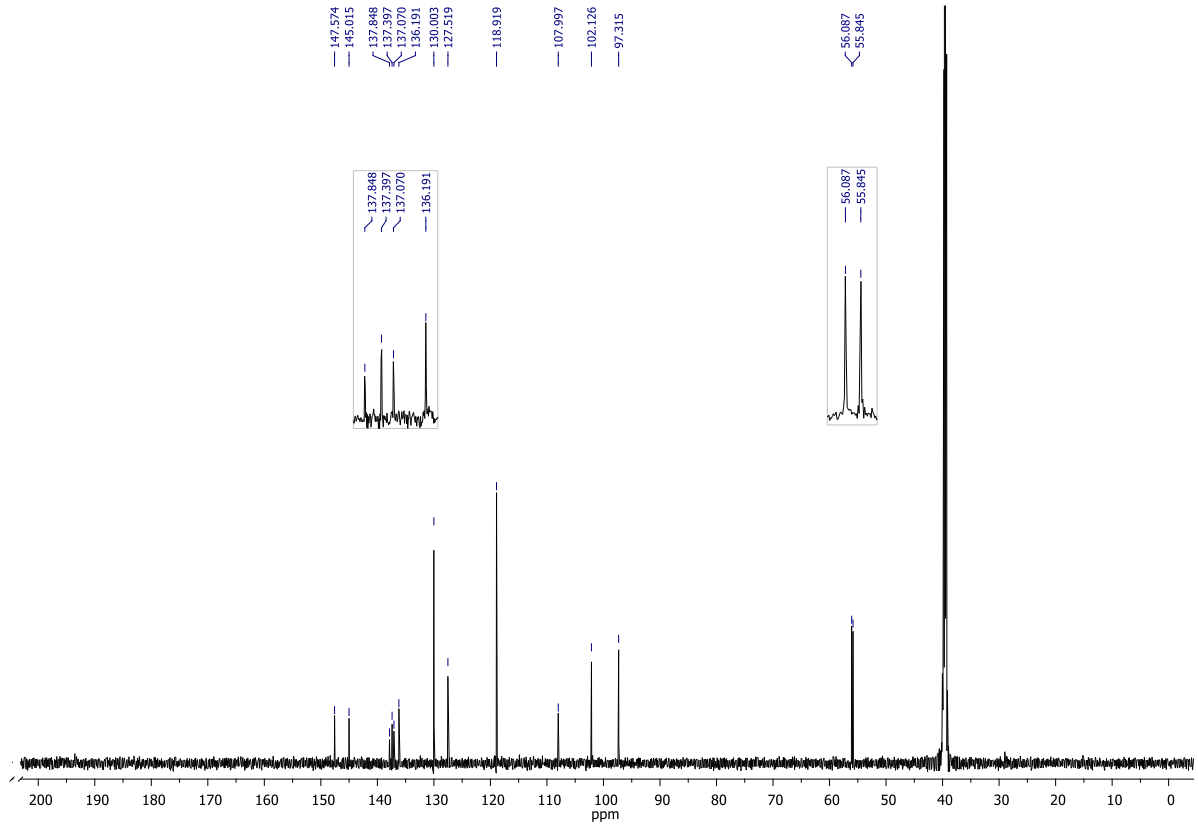


Figure 3.52a. ^{1}H NMR Spectrum of 72d in DMSO at 400 MHz

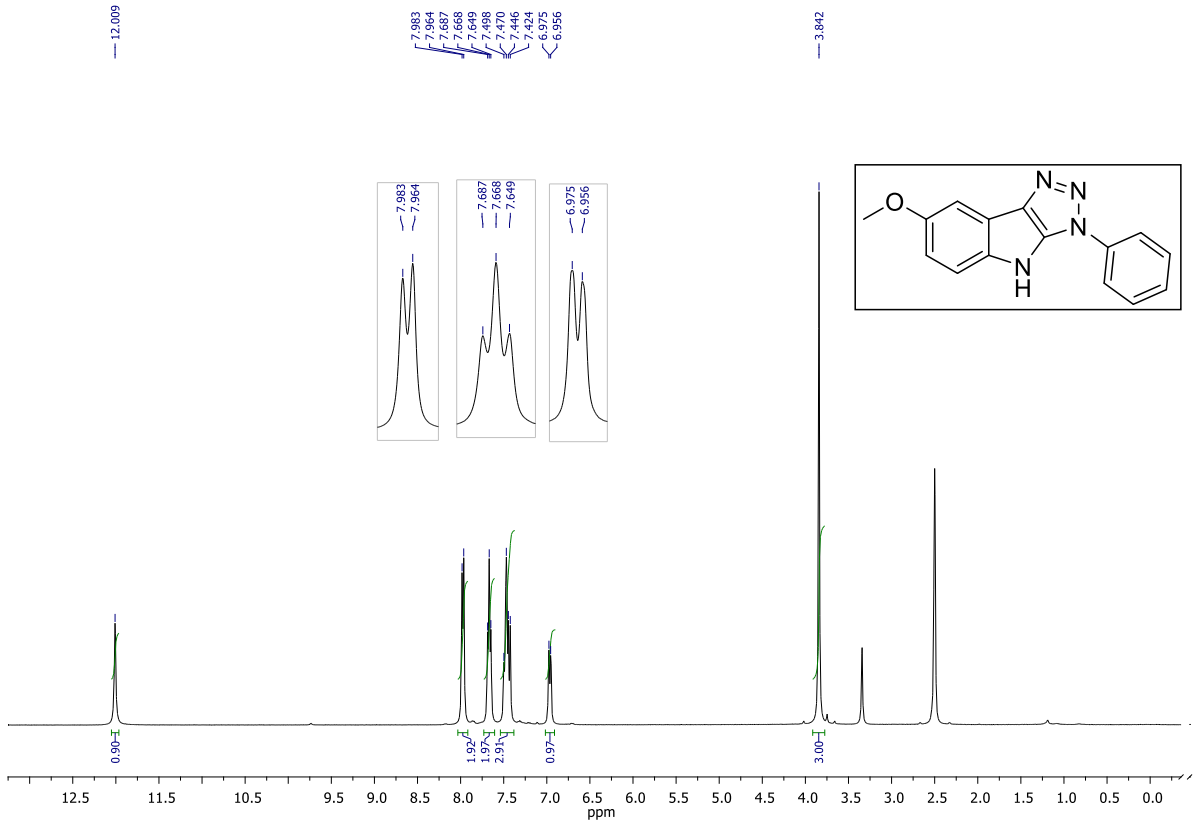


Figure 3.52b. ^{13}C NMR Spectrum of 72d in DMSO at 175 MHz

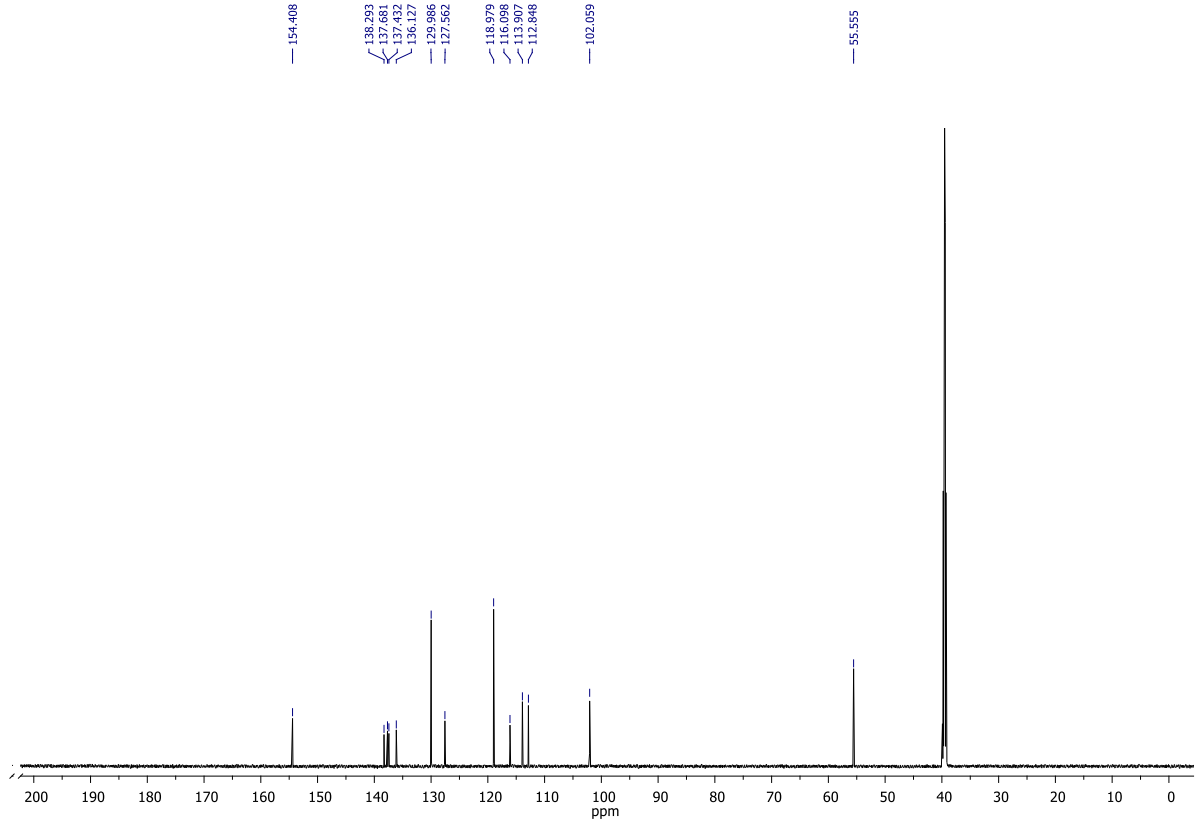


Figure 3.53a. ^{1}H NMR Spectrum of 72e in DMSO at 400 MHz

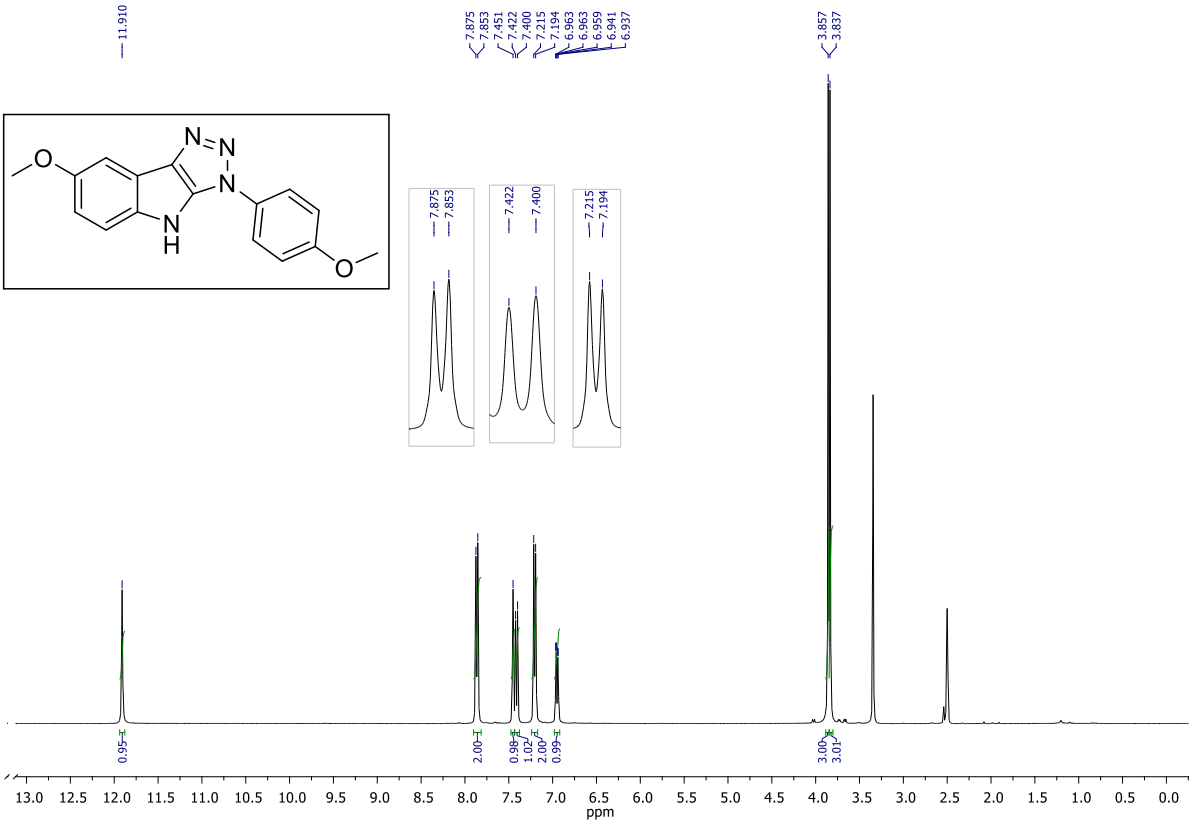


Figure 3.53b. ^{13}C NMR Spectrum of 72e in DMSO at 100 MHz

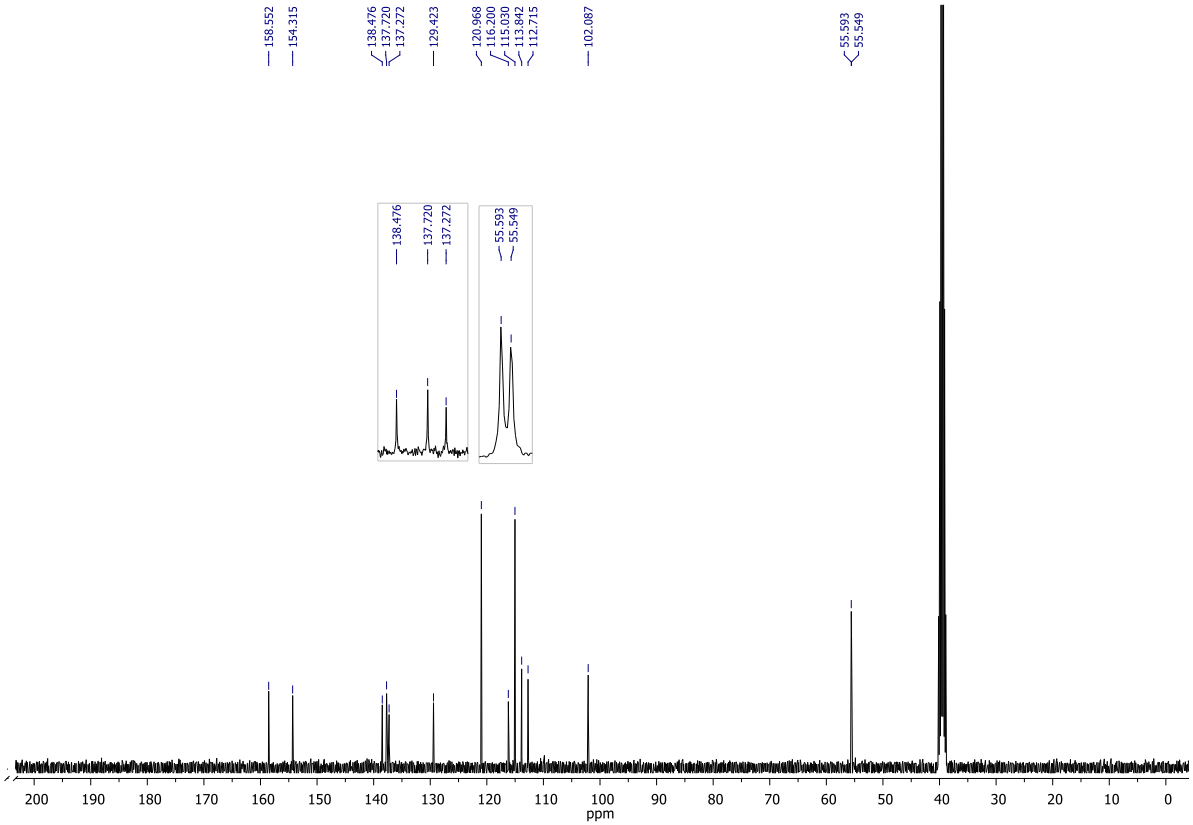


Figure 3.54a. ^{1}H NMR Spectrum of 72i in DMSO at 400 MHz

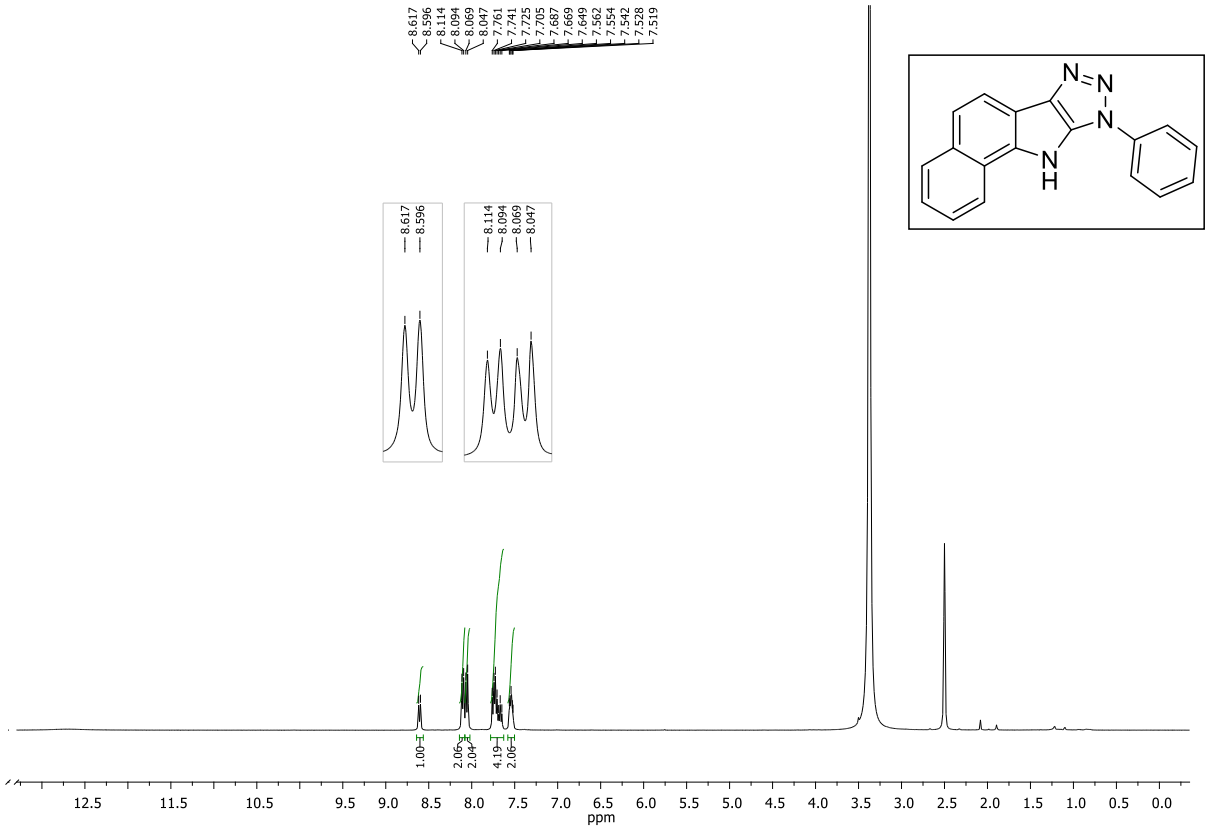


Figure 3.54b. ^{13}C NMR Spectrum of 72i in DMSO at 100 MHz

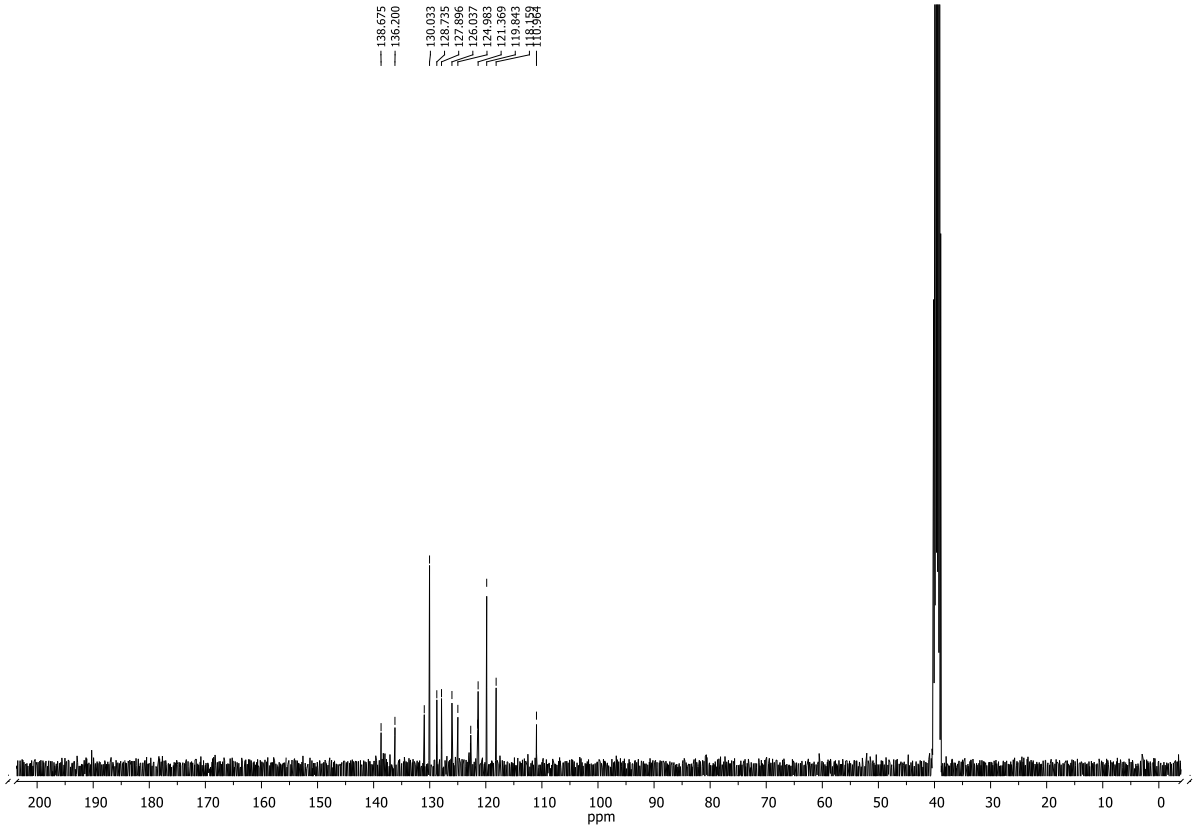


Figure 3.55a. ^{1}H NMR Spectrum of 73a in DMSO at 400 MHz

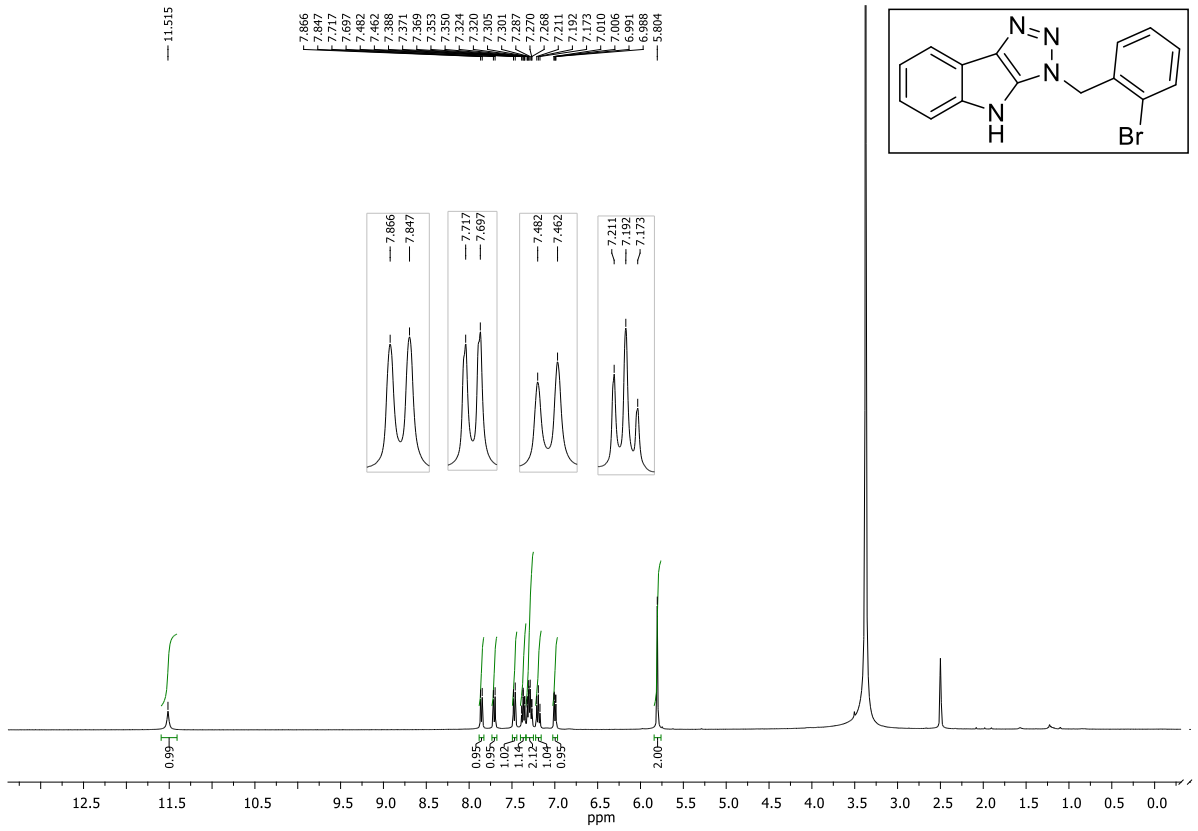


Figure 3.55b. ^{13}C NMR Spectrum of 73a in DMSO at 100 MHz

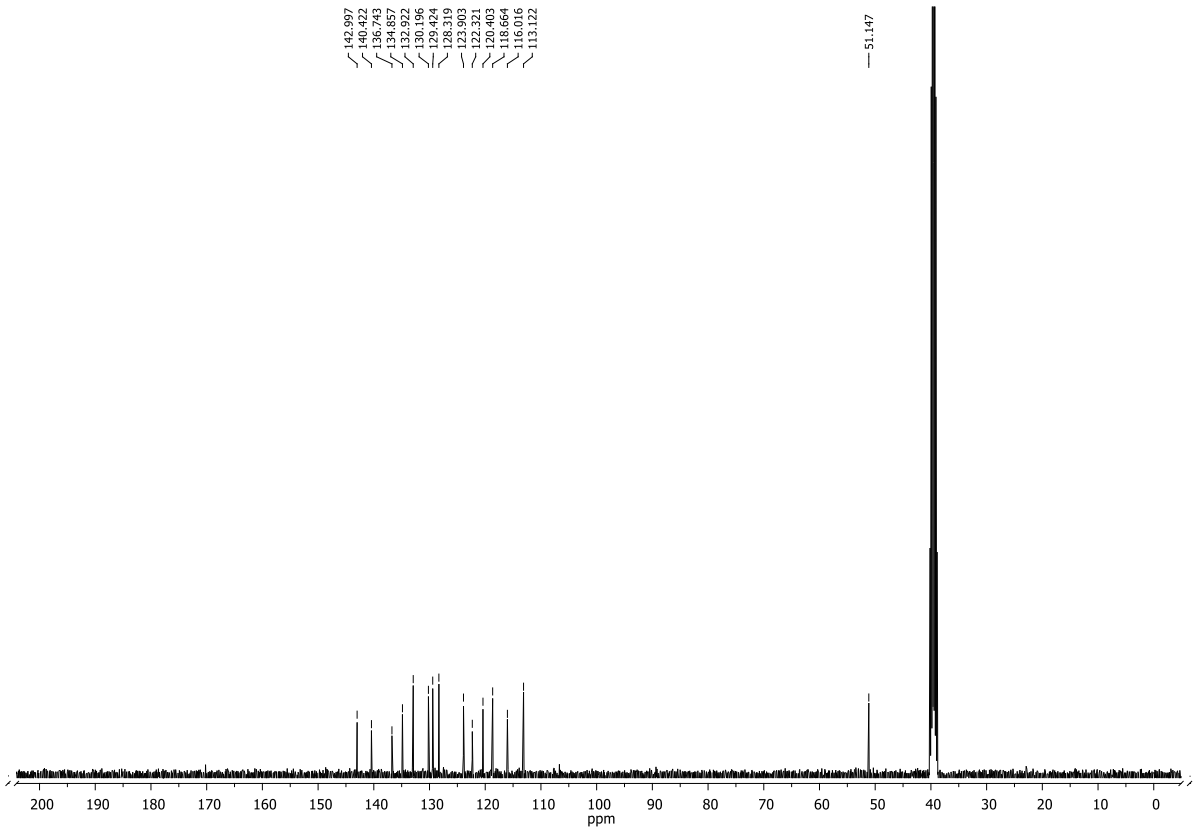


Figure 3.56a. ^{1}H NMR Spectrum of 73b in DMSO at 400 MHz

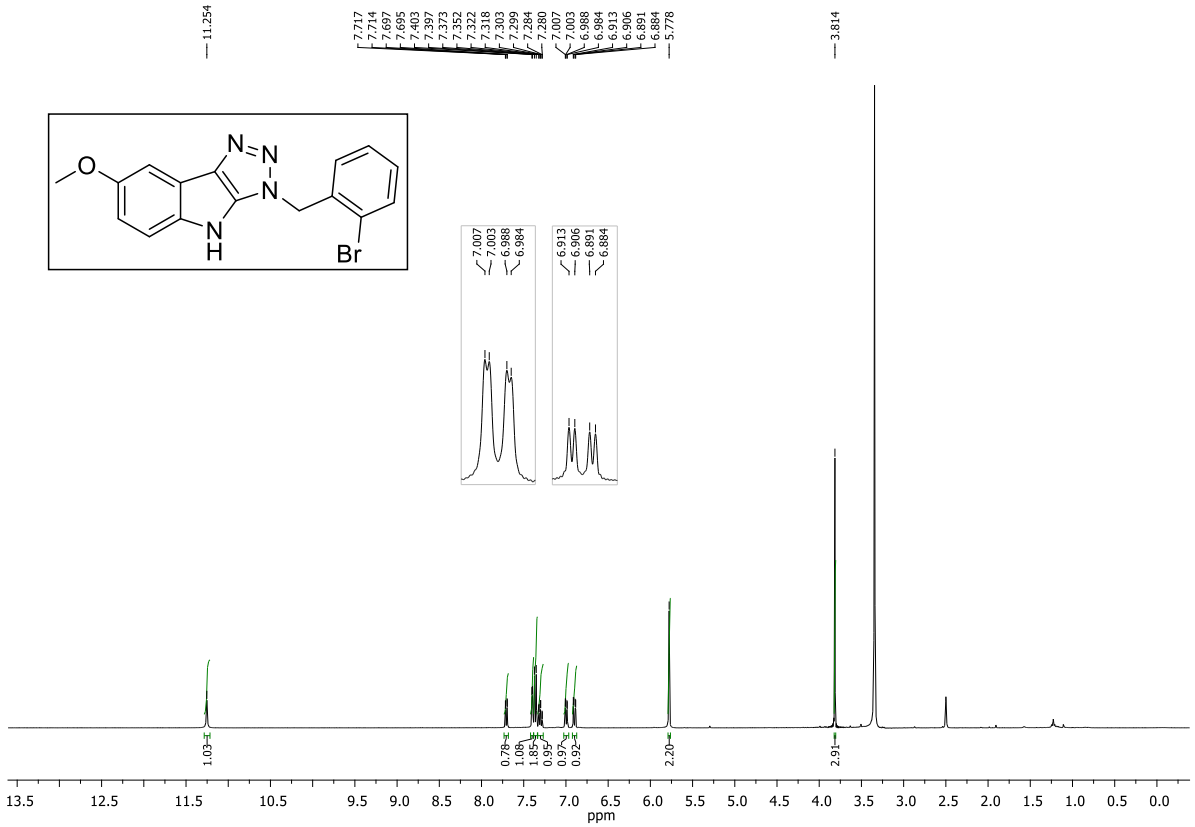


Figure 3.56b. ^{13}C NMR Spectrum of 73b in DMSO at 100 MHz

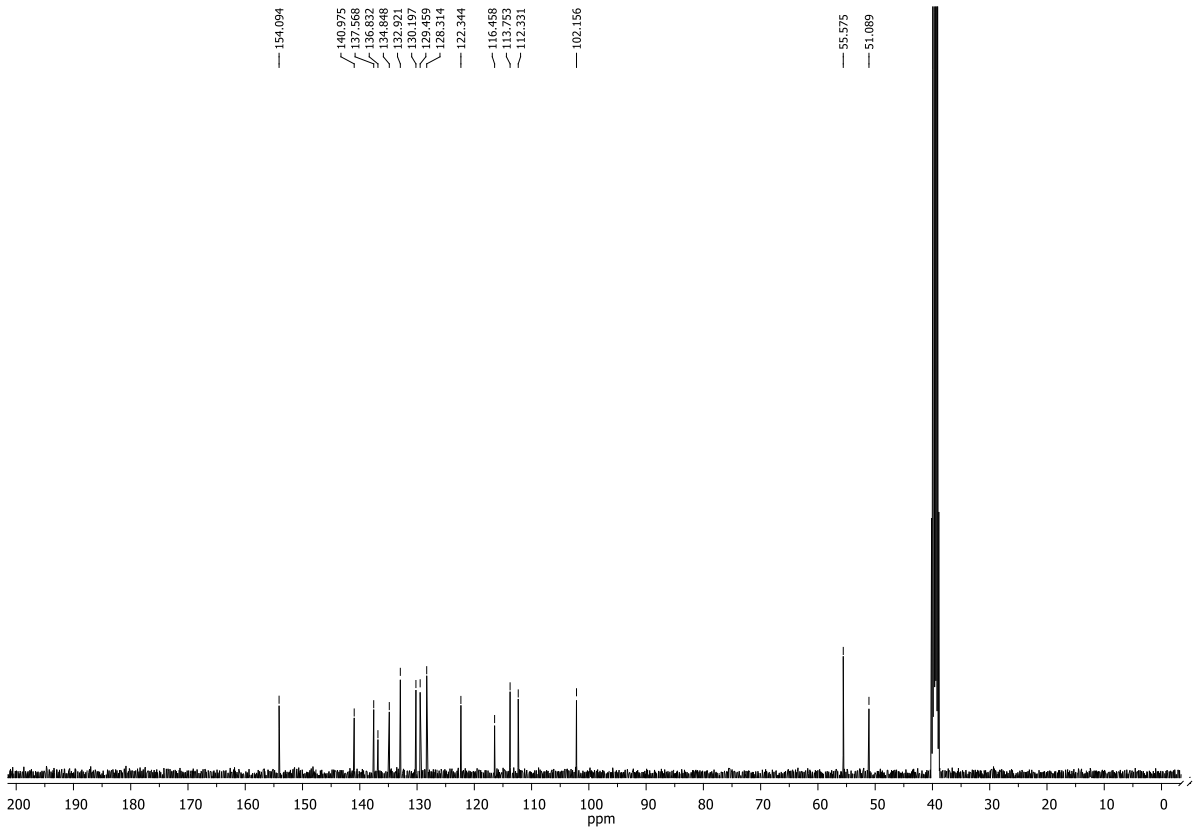


Figure 3.57a. ^{1}H NMR Spectrum of 73c in DMSO at 400 MHz

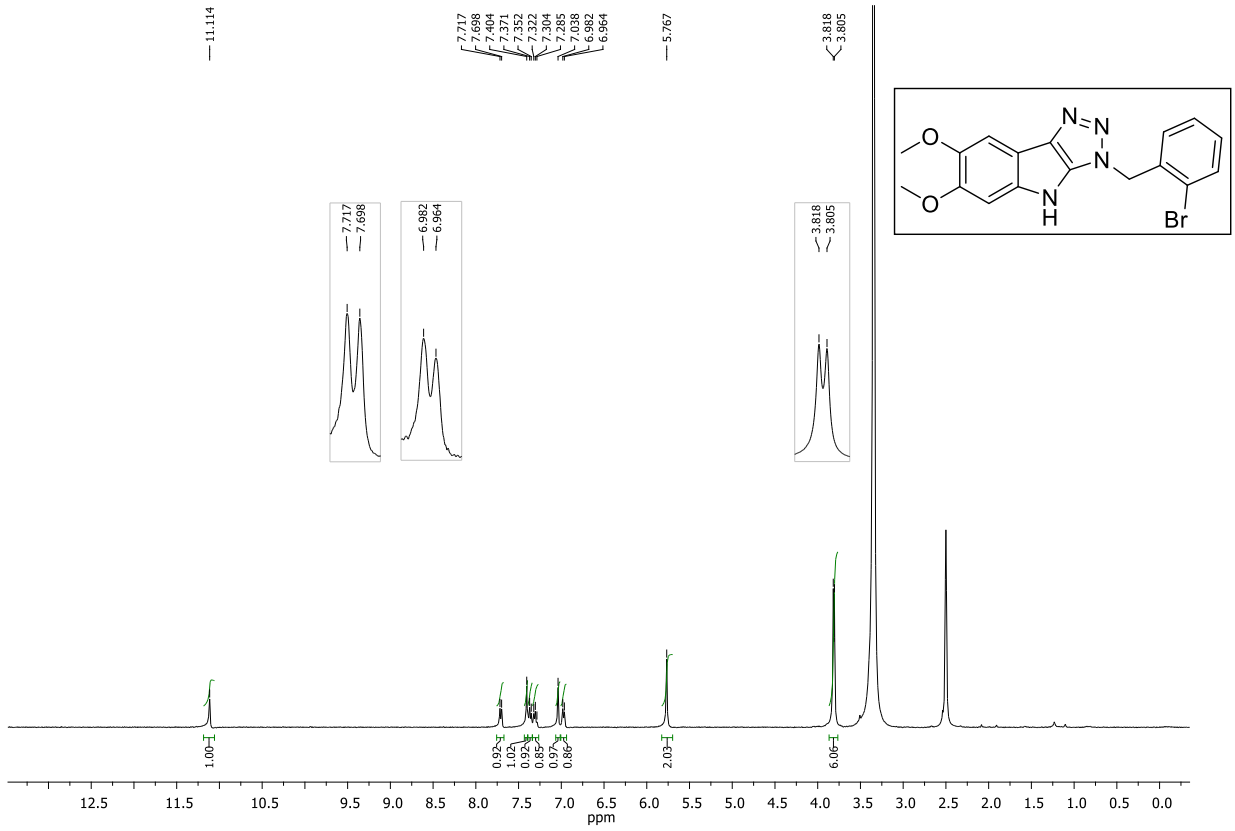


Figure 3.57b. ^{13}C NMR Spectrum of 73c in DMSO at 100 MHz

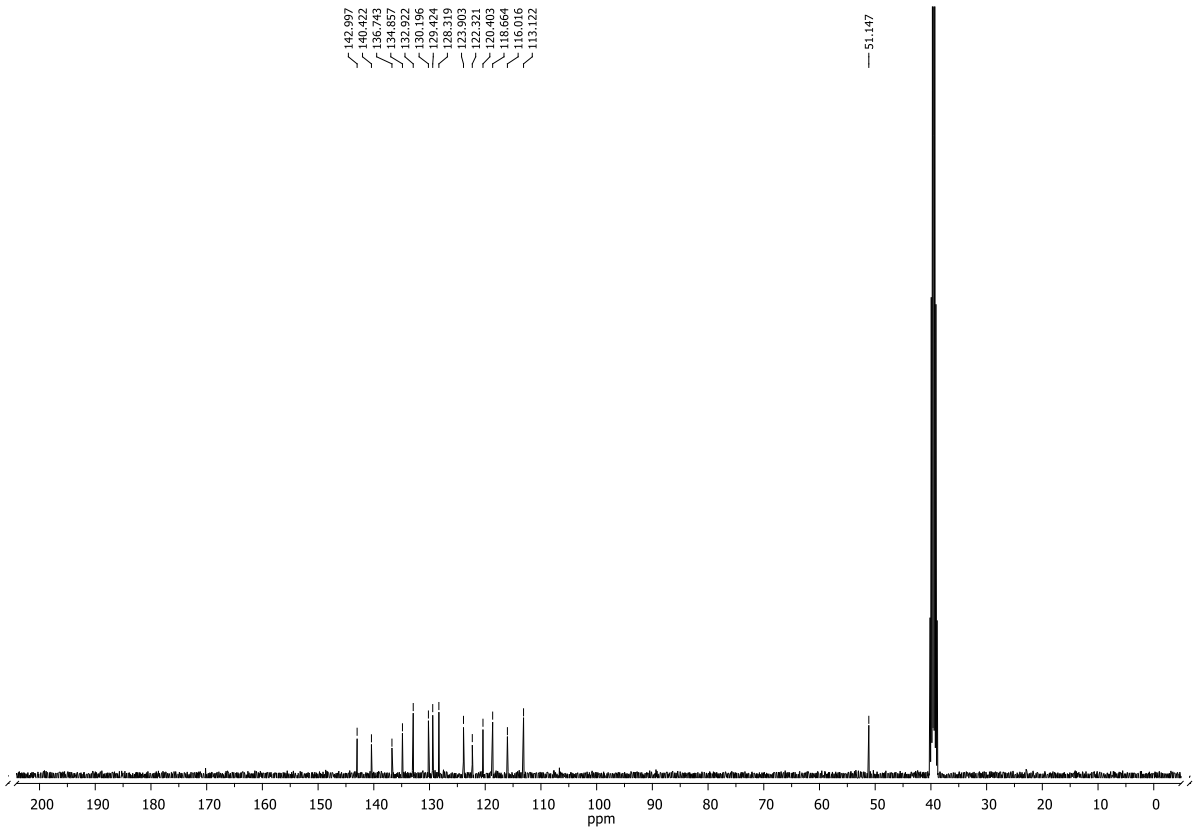


Figure 3.58a. ^{1}H NMR Spectrum of 74f in DMSO at 400 MHz

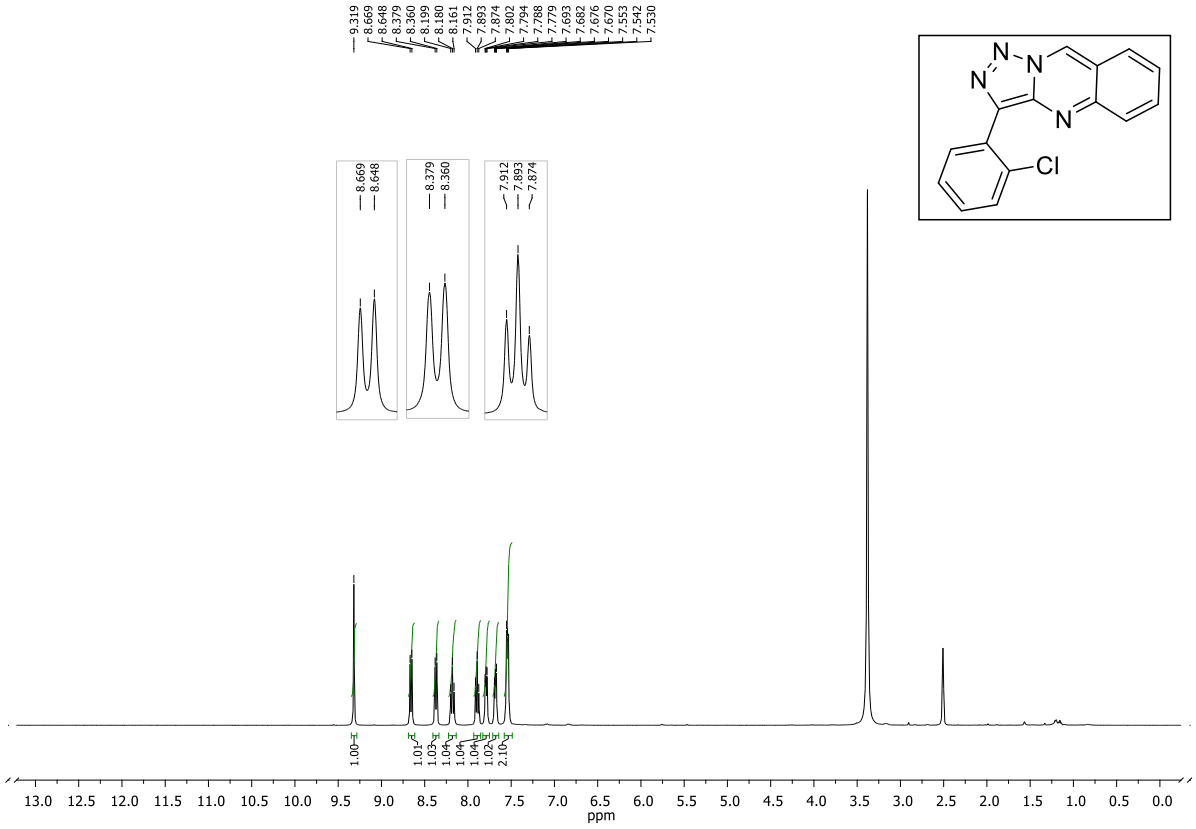


Figure 3.58b. ^{13}C NMR Spectrum of 74f in DMSO at 100 MHz

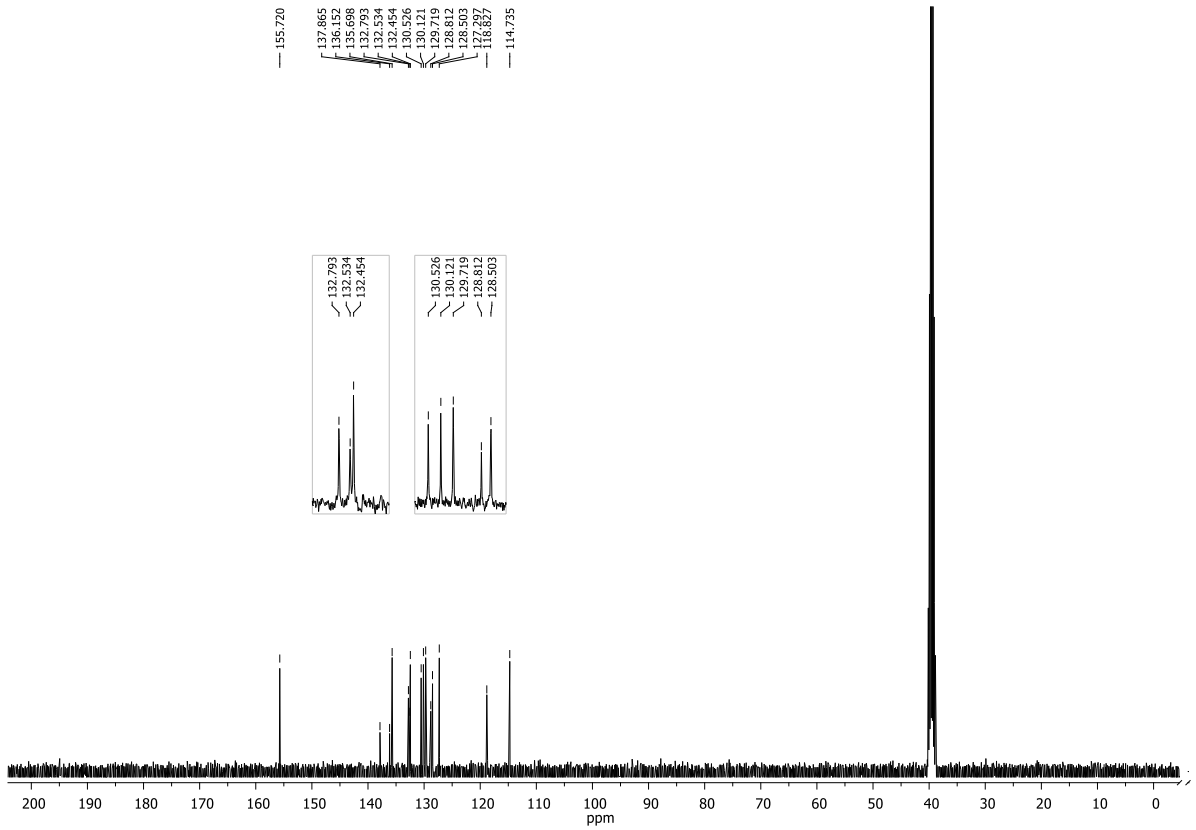


Figure 3.59a. ^{1}H NMR Spectrum of 74h in DMSO at 400 MHz

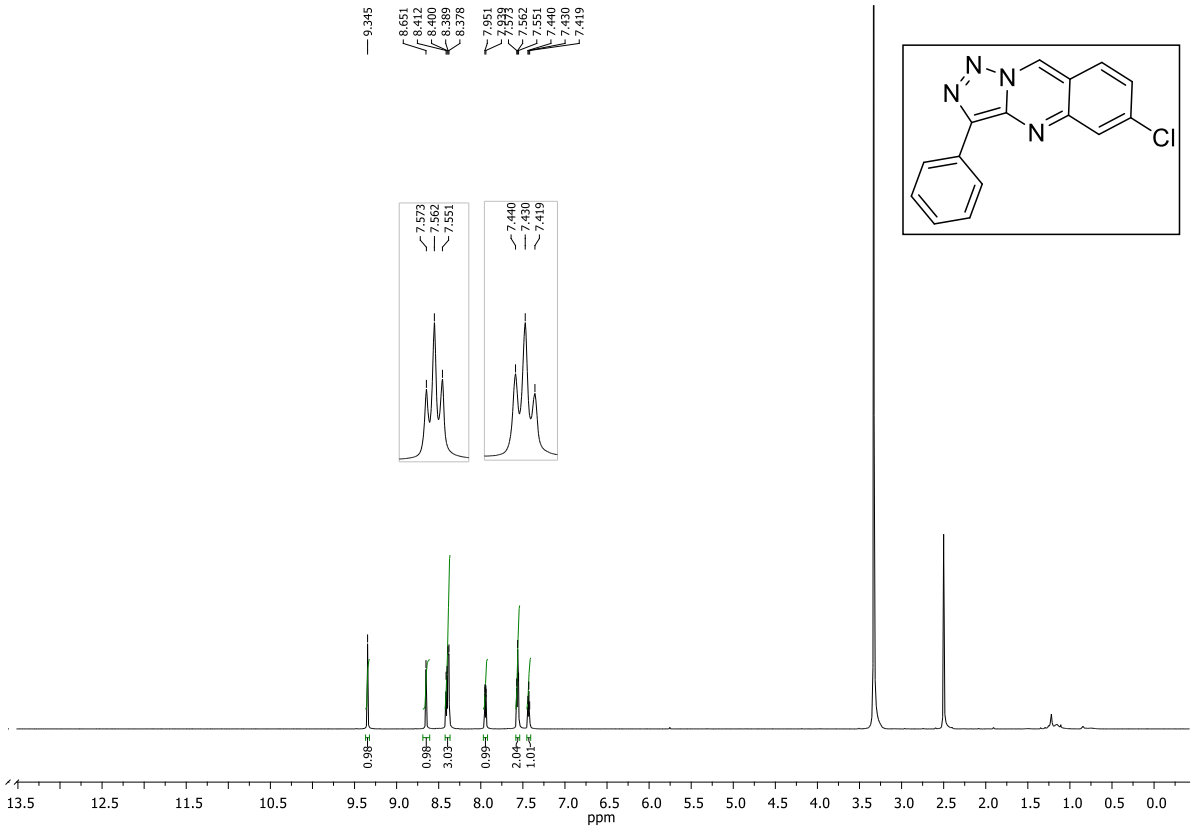


Figure 3.59b. ^{13}C NMR Spectrum of 74h in DMSO at 100 MHz

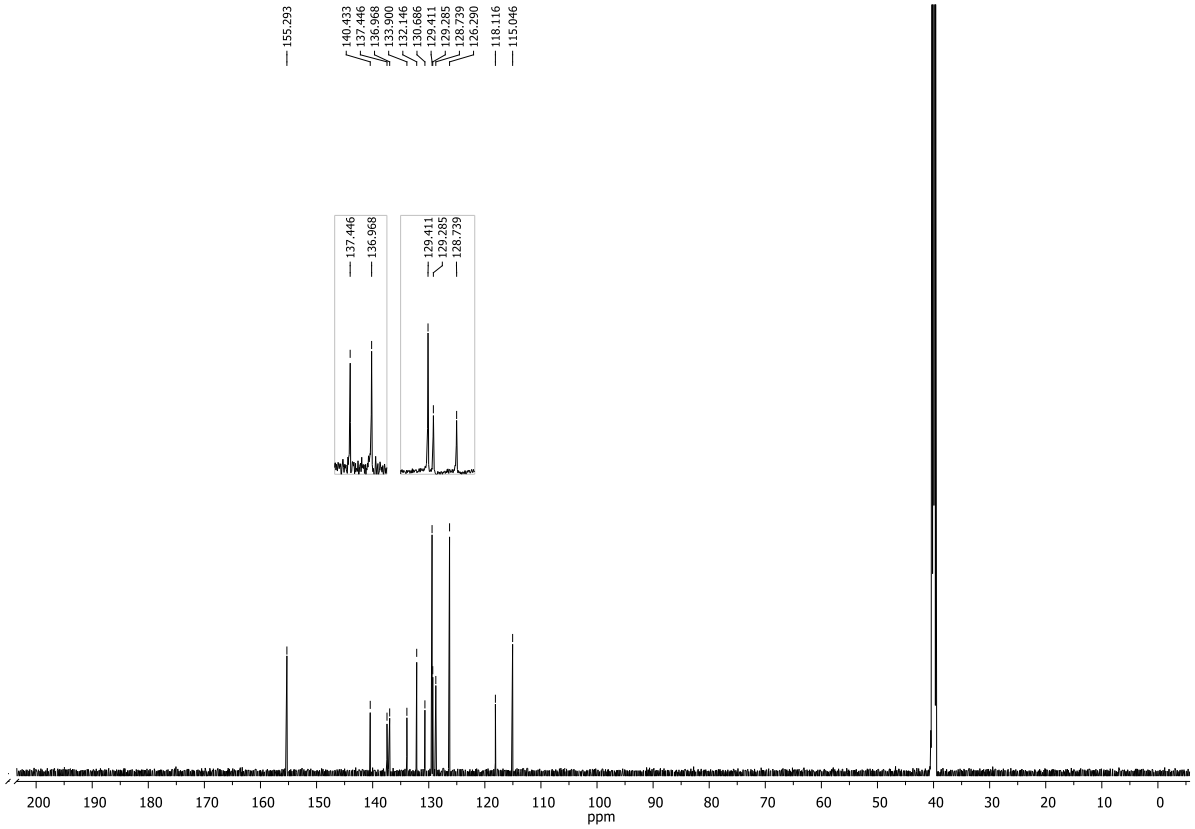


Figure 3.60a. ^{1}H NMR Spectrum of 74j in DMSO at 400 MHz

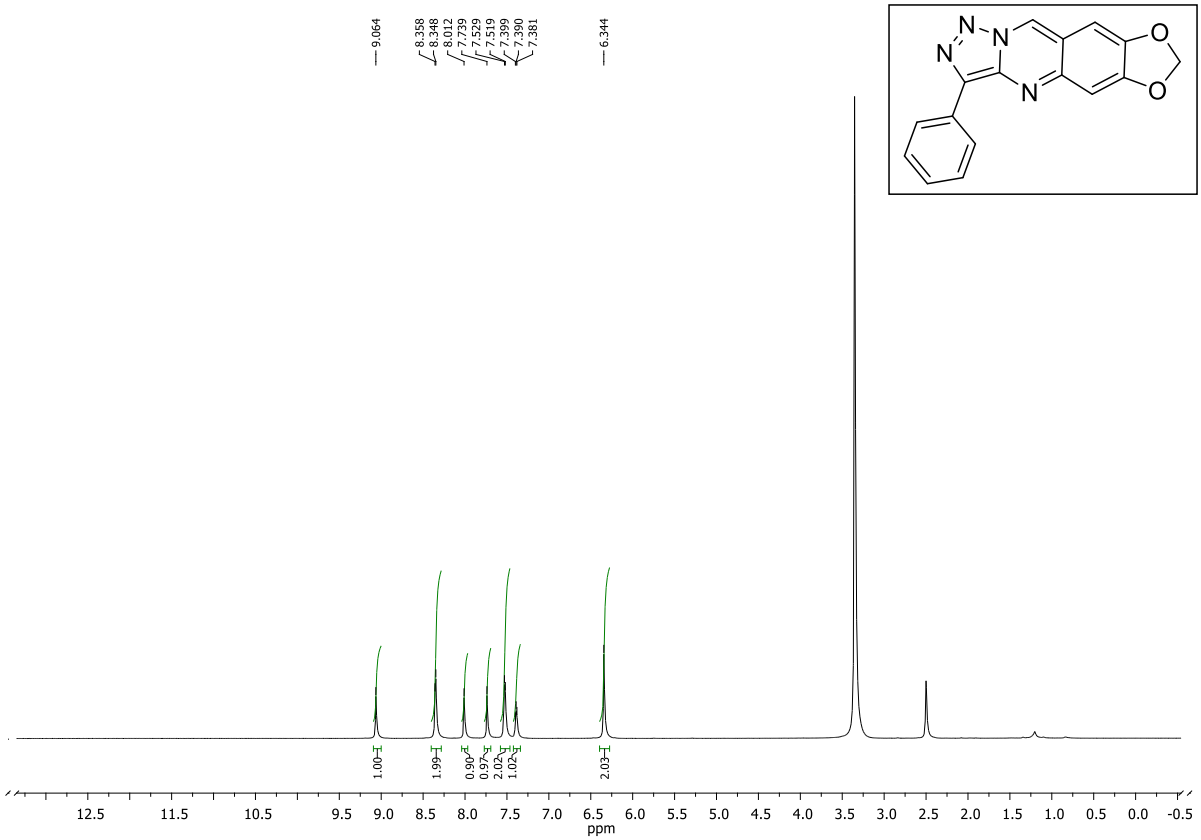
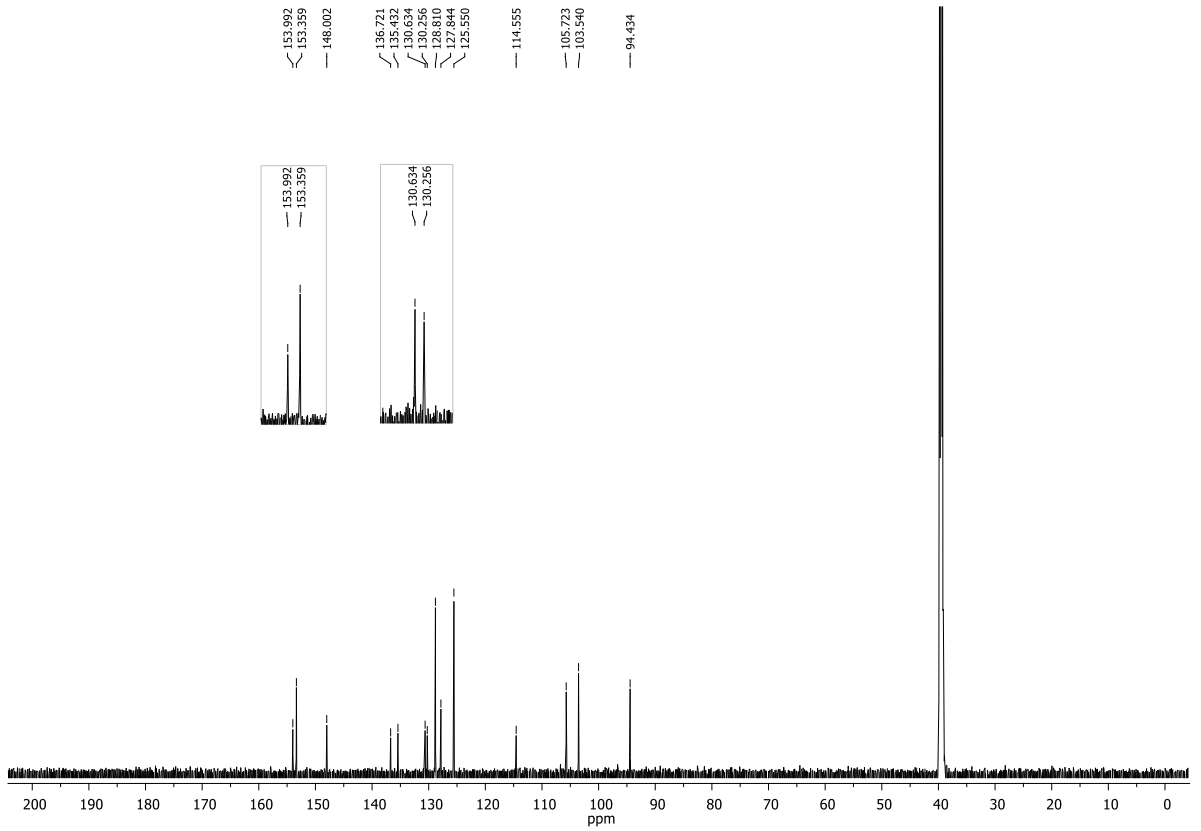


Figure 3.60b. ^{13}C NMR Spectrum of 74j in DMSO at 100 MHz



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Nickel Promoted C–H thiolation Reaction: A Facile Route to synthesize 2-Aminobenzo[*b*]thiophenes

4.1. Introduction:

Heterocycles, especially sulphur containing heterocycles, are an important class of organic compounds that attract the attention of medicinal and synthetic chemists.[1] Among these, benzo[*b*]thiophenes are the most vital cores that are associate with distinct range of biological and industrial applications.[2] In the past few years, it has been shown that benzo[*b*]thiophenes are also useful in material science.[3] Further, these derivatives are the privileged structures in pharmaceutical industry as they display some interesting biological activities, such as antimalarial, anti-inflammatory, antifungal, anti-diabetic and anti-angiogenic.[4] Recent studies show that benzothiophenes are also well-known diagnostic agents for the treatment of Alzheimer's disease.[5]

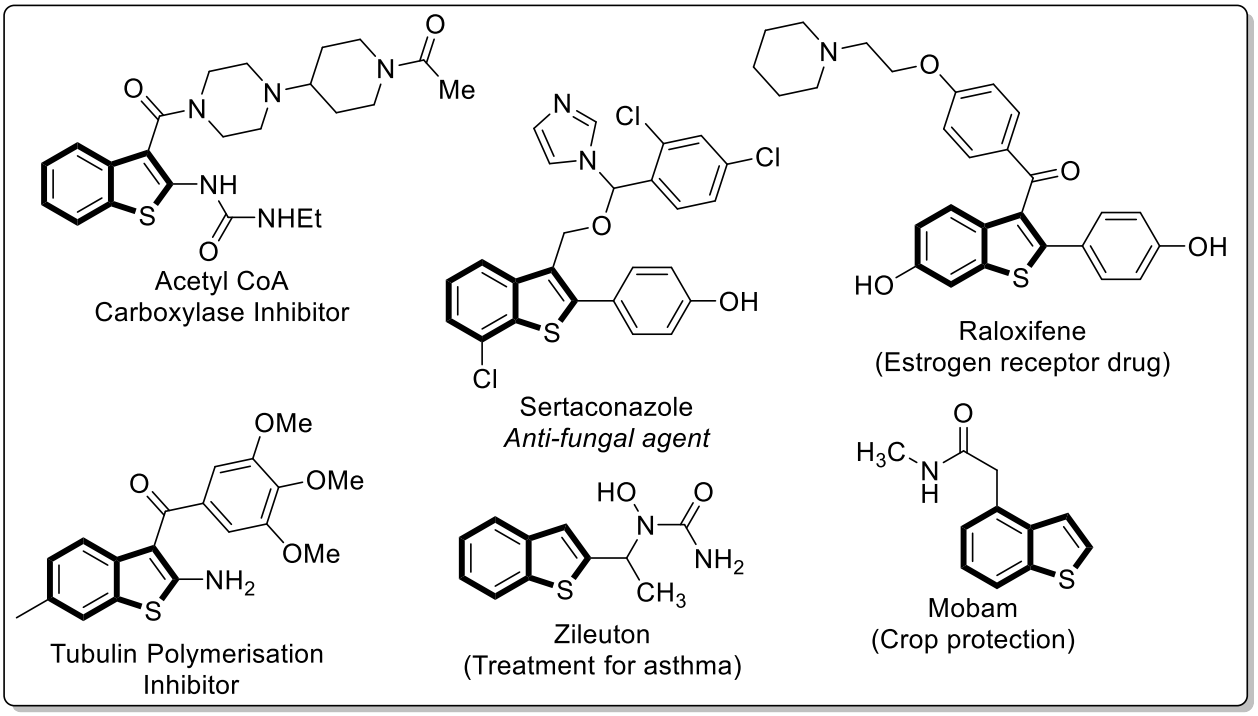


Figure 4.1: *Selected Bioactive Benzo[b]thiophene*

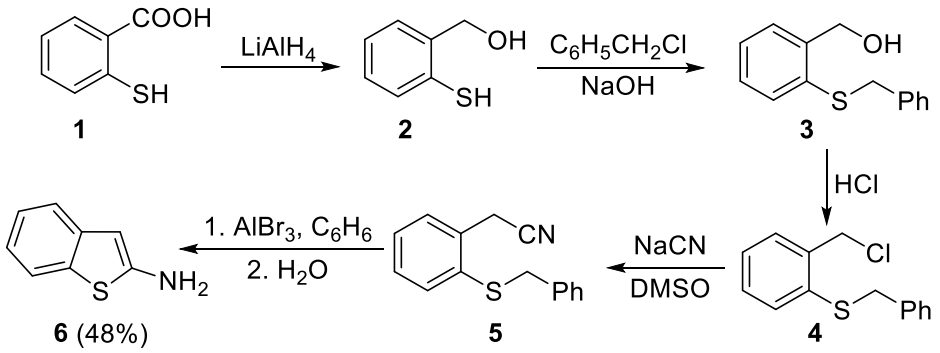
They act as inhibitor in tubulin polymerisation and acetyl CoA carboxylase.[6] The benzothiophene core is an imperative structural unit present in some well-known drugs. Raloxifene, that is a selective estrogen receptor modulator (SERM) contains the benzo[*b*]thiophene core.[7] Also, Zileuton that is used for the treatment of asthma, constitutes the benzothiophene core.[8] Along with the pharmaceutical applications, benzothiophene is also present as an integral part in Mobam, which acts as a crop protector.[9] Sertaconazole is a benzothiophene based anti-fungal agent.[10] Because of their wide range of applications, their synthesis has become a prime interest for the synthetic chemist.

In the past few years, several protocols for the synthesis of benzo[*b*]thiophene have been established.[11] Most of the classical methods depend upon the electrophilic cyclization or cross coupling of organic halides.[12] Despite good yields of the products these methods suffer from limitations, like they either need harsh reaction condition or involve multi step synthesis, require prefunctionalized starting material, produces stoichiometric amount of by-products.[13] Transition metal mediated C─H bond functionalization involves milder reaction conditions, and afford the desired products without any prefunctionalized starting material.[14] The C─S bond formation reactions, via C─H bond functionalization, are less explored as compared to C─N and C─O bond formation reactions.[15] This route has been extensively used for the synthesis of nitrogen and oxygen containing heterocycles[16], but in the case of *S*-heterocycles this methodology is unexplored. Hence, developing metal mediated C─H bond thiolation for the synthesis of benzo[*b*]thiophene under miler reaction condition is highly desirable.

4.2. Previous Reports on the Synthesis of Benzo[*b*]thiophene via C–H thiolation

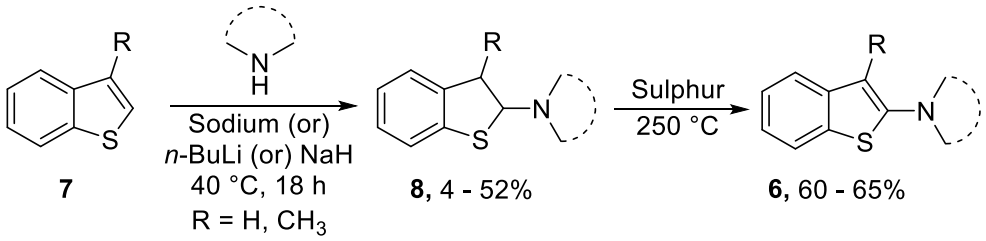
The first report for the synthesis of benzo[*b*]thiophenes **6** was reported in 1965 by Wollner and co-workers (Scheme 4.1).[17] The approach involved a five-step reaction, using thiosalicylic acid **1** as the starting material, affording benzo[*b*]thiophene **6** in 48% overall yield. The method included

complexation of the intermediate with $AlBr_3$, then disproportionation and finally hydrolysis which led to ring closure to yield the product.



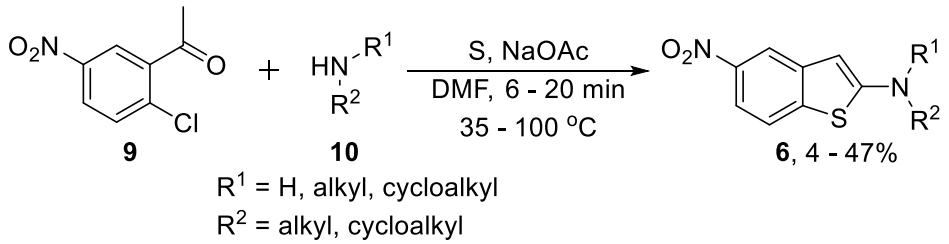
Scheme 4.1: *Synthesis of 2-Aminobenzo[b]thiophene*

The second report was devised by Combier and coworkers in 1978.[18] Their protocol involves metal catalyzed addition of primary and secondary amines to benzothiophenes **7** in the presence of base that leads to the formation of amino substituted 2,3-dihydrobenzo[*b*]thiophene **8**, which aromatized further to afford 2-aminobenzo[*b*]thiophene **6** at 250 ℃ in the presence of elemental sulphur (Scheme 4.2). The 2-aminobenzo[*b*]thiophenes **6** were obtained in moderate yields.



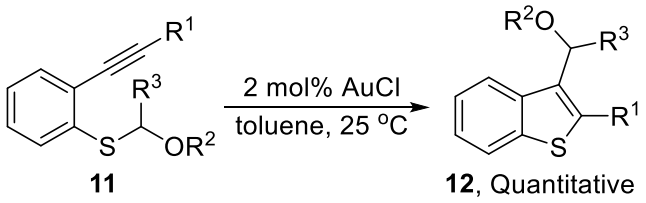
Scheme 4.2: *Synthesis of 2-Aminobenzo[b]thiophene by Addition/Rearomatization protocol*

Neckers and co-workers proposed a synthetic route for the synthesis of 2-aminobenzo[*b*]thiophenes **6** (Scheme 4.3).[19] This route involved a three component one pot synthesis, via Willgerodt- Kindler route, starting with substituted acetophenones **9** and primary and secondary amines **10** under basic condition at variable temperature (Scheme 4.3).



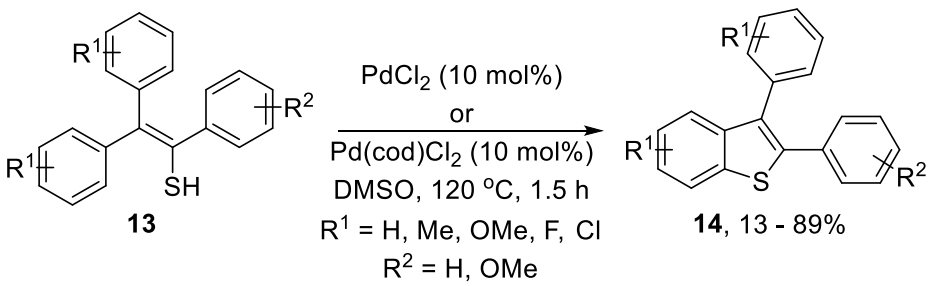
Scheme 4.3: *Base Promoted One-Pot Synthesis of 2-Aminobenzo[b]thiophenes*

Nakamura and co-workers elucidated the synthesis of 2,3-disubstituted benzothiophenes **12** via gold catalyzed C–H thiolation of (α-alkoxy alkyl) (*ortho*-alkynyl phenyl) sulfides **11** (Scheme 4.4).[20] These sulfides **11** can be obtained from *ortho*-bromobenzenethiol on acetalization and then by Sonogashira coupling.



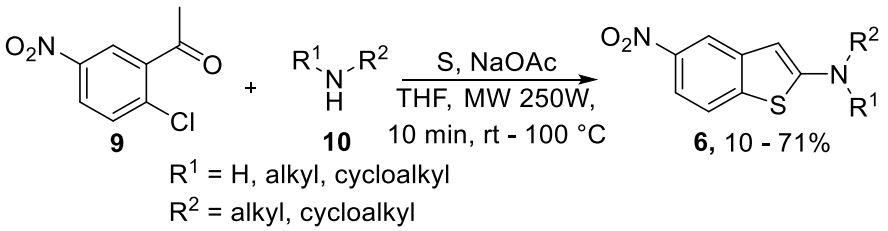
Scheme 4.4: *Synthesis of 2,3-Disubstituted Benzothiophenes via Gold Catalyzed C─H Thiolation*

Inamoto and co-workers proposed a methodology for the synthesis of benzo[*b*]thiophenes **14** via palladium mediated C-H thiolation (Scheme 4.5).[21] They had introduced a one-pot transformation of thioenols **13** to benzothiophenes **14,** using $PdCl_2$ or $Pd(cod)Cl_2$ as the palladium catalyst.



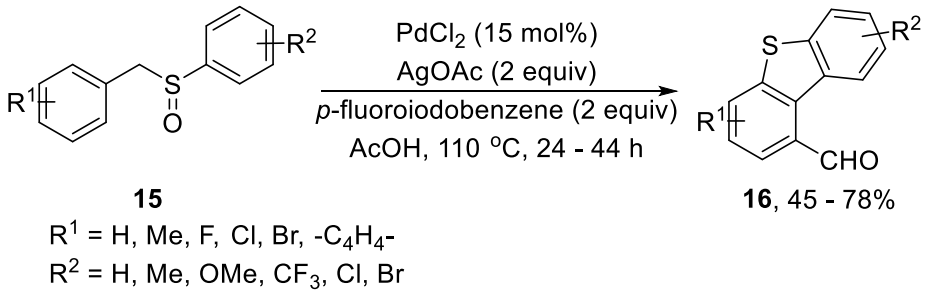
Scheme 4.5: *Palladium Catalyzed Intramolecular C─H thiolation*

Biehl and co-workers demonstrated the Necker's protocol (Scheme 4.3) under microwave irradiation (Scheme 4.6).[22] This protocol afforded substituted benzo[*b*]thiophenes **6** in slightly better yields than conventional heating methodology.



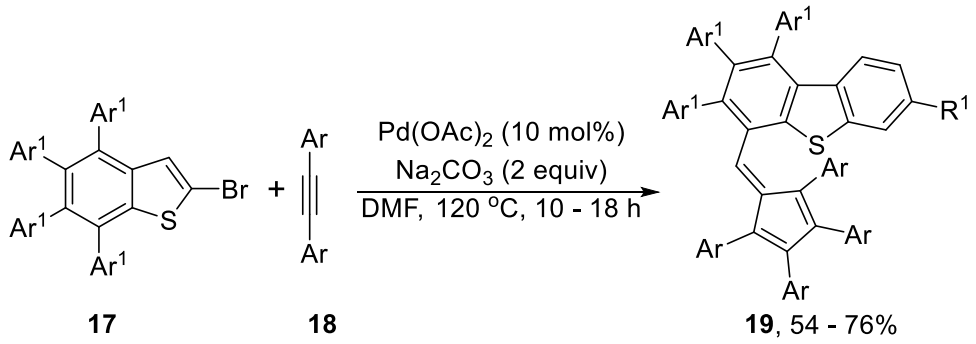
Scheme 4.6: *Microwave Assisted One-pot Synthesis of Substituted 2-Aminobenzo[b]thiophenes*

Antonchick and co-workers described the synthesis of dibenzothiophenes **16** starting from sulfoxides **15** (Scheme 4.7).[23] This method involved palladium mediated double C-H bond activation of sulfoxides **15**. In this methodology AgOAc was used as an oxidant, which facilitated the reaction with good yields of dibenzothiophenes **16**. To further enhance the yield of the product, *p*-fluoroiodobenzene was used as an additive, which increased the yield satisfactorily (Scheme 4.7).



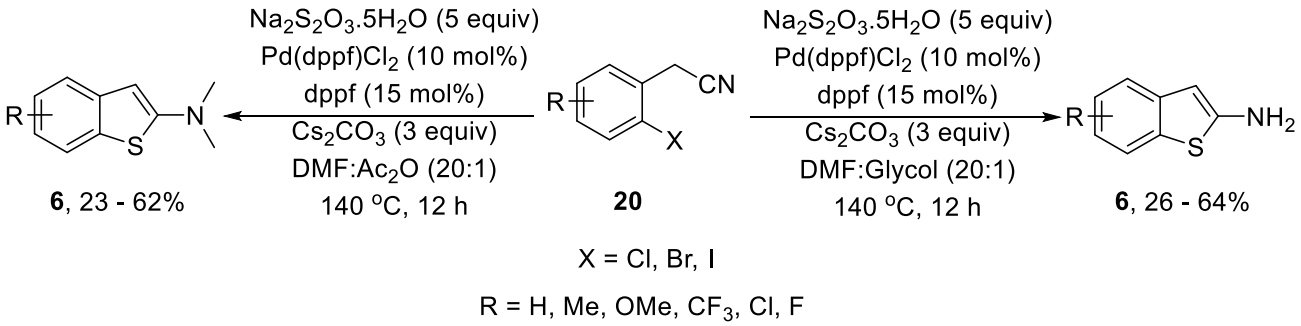
Scheme 4.7: *Palladium Promoted Double C─H bond Activation*

The synthesis of dibenzothiophenes **19** was further carried out by Duan and co-workers (Scheme 4.8).[24] This methodology follows a sequential ring rearrangement through C-S bond activation in presence of palladium catalyst. It had been reported as the first palladium catalyzed ring opening reaction of *S*-heterocyclic compounds **17**. It follows oxidative addition, carbopalladation, cycloaddition, followed by reductive elimination to yield the dibenzothiophenes **19** (Scheme 4.8).



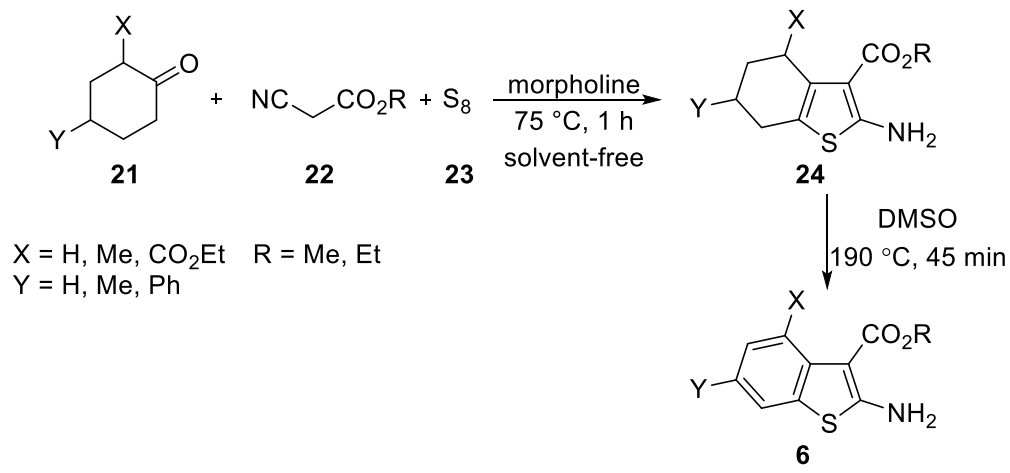
Scheme 4.8: *Palladium Catalyzed Sequential Ring Rearrangement*

For the first time the synthesis of 2-aminobenzo[*b*]thiophene **6** from convenient sulfur source was reported by Yang and co-workers (Scheme 4.9).[25] They have implemented a combination of palladium catalyst, $Pd(dppf)Cl_2$ and a phosphorus-based ligand, 1,1'-bis(diphenylphosphino)ferrocene (DPPF) along with the sulfur source, $Na_2S_2O_3$ for the C─H bond thiolation. They have further protected the free amino group with acetic anhydride to afford 2-(dimethylamino)benzo[*b*]thiophene **6**, an intermediate for the synthesis of well-known drug raloxifene (Scheme 4.9).



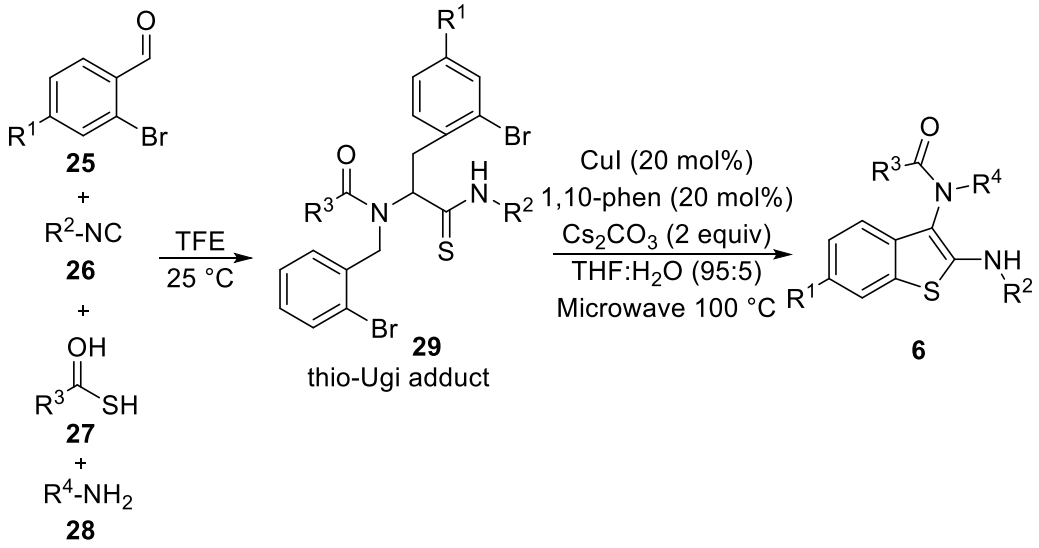
Scheme 4.9: *Synthesis of 2-Aminobenzo[b]thiophenes from Convenient Sulfur Source*

Adib and coworkers synthesized substituted benzothiophene **6** by a three-components condensation reaction (Scheme 4.10).[26] This methodology involves simple starting materials and does not require metal catalysts. The benzothiophenes **6** were obtained in high yields (Scheme 4.10).



Scheme 4.10: *Three-component Condensation Reaction*

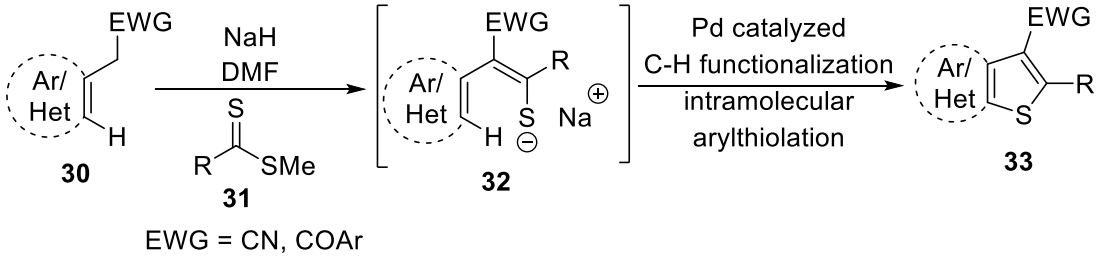
The thio-Ugi adduct **29** was utilized by Gong and co-workers for the synthesis of benzo[*b*]thiophene **6** via copper catalyzed intramolecular C─H bond thiolation.[27] Other fused heterocycles were also obtained from these thio-Ugi adducts in moderate yields (Scheme 4.11).



Scheme 4.11: *Synthesis of Benzothiophene from Thio-Ugi Adduct via Intramolecular C─H Bond Thiolation*

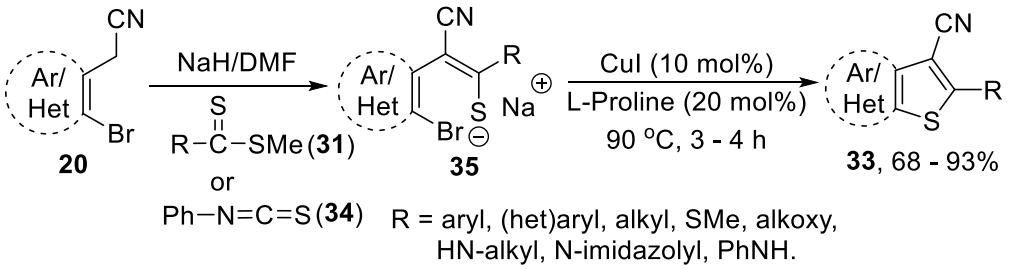
Ila and co-workers came up with a new and coherent strategy that involves palladium catalyzed intramolecular C–H bond functionalization of enethiolate salts **32** (Scheme 4.12).[28] This protocol follows a two-step one-pot strategy, where the enethiolate salts **32** undergo C–H thiolation

or functionalization in the presence of palladium salts. The benzothiophenes **33** were isolated in high yields with a variety of substitutions.



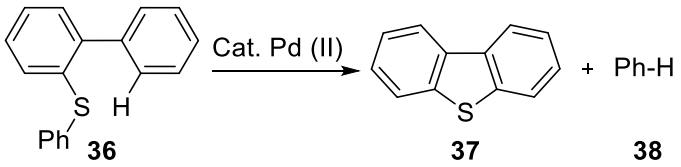
Scheme 4.12: *One-pot Two Step Synthesis of Substituted Benzothiophenes*

Further, a new and efficient one-pot protocol for the synthesis of 2-substituted benzo[*b*]thiophenes **33** was also reported by Ila's group (Scheme 4.13).[29] The 2-bromo-(het)arylacetonitriles **20** have been condensed with (het)aryl/alkyldithioesters **31** or isothiocyanate **34** by a base mediated tandem reaction. Without isolating the thioenolate intermediates **35**, it was further been subjected to intramolecular C–H thiolation in presence of copper catalyst to achieve the benzothiophenes **33** in high yields.



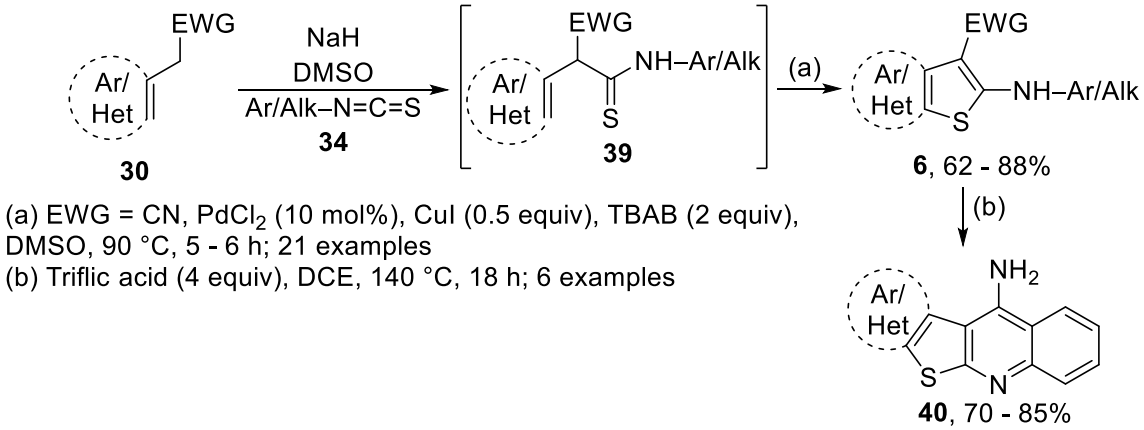
Scheme 4.13: *Copper Catalysed One-pot Synthesis of Substituted Benzo[b]thiophenes*

N. Chatani and coworkers synthesized dibenzothiophene **37** via palladium(II) catalyzed C─H/C─S coupling.[30] Unlike the other established methodologies, this protocol does not require any oxidant or reactive functionalities (Scheme 4.14).



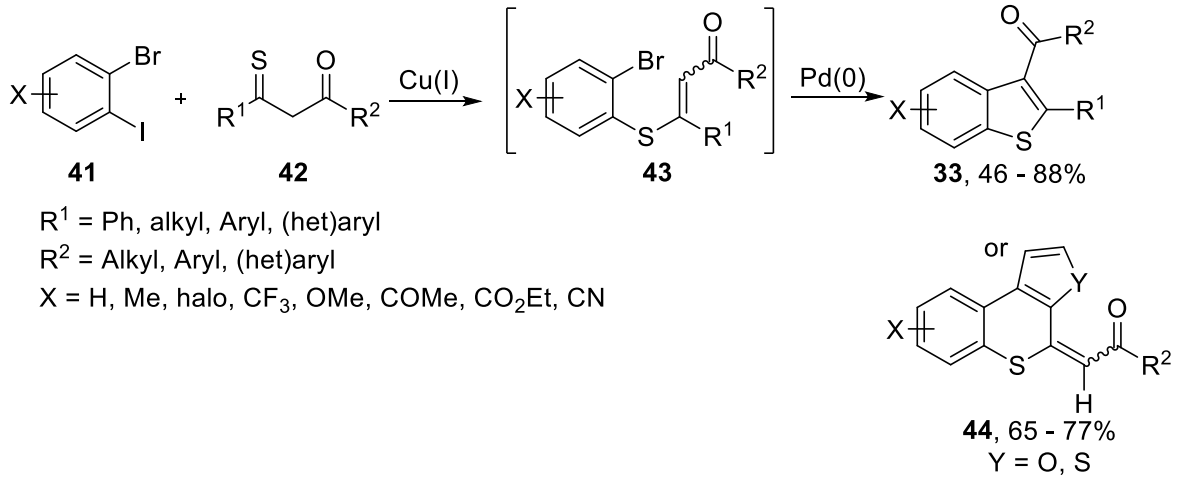
Scheme 4.14: *Synthesis of Dibenzothiophene via Palladium Catalyzed C─H/C─S Coupling*

H. Ila and co-workers devised a palladium catalyzed one-pot strategy for the synthesis of substituted benzothiophenes **6**.[31] Later, they have also synthesized thieno fused 4-aminoquinolines **40** via triflic acid mediated cyclocondensation reaction (Scheme 4.15).



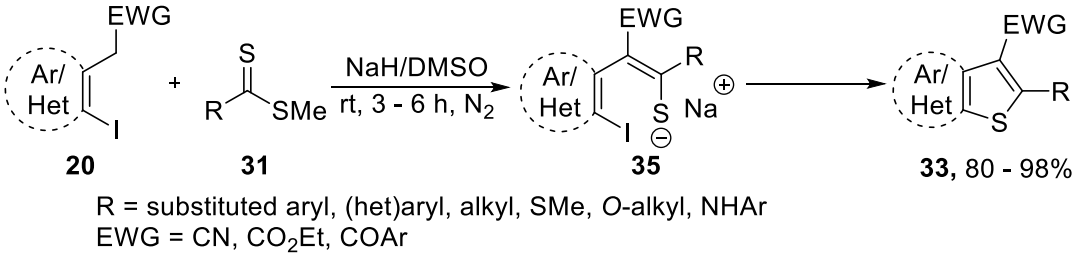
Scheme 4.15: *Palladium Catalyzed One-pot Synthesis of Benzothiophene*

Ila and co-workers designed a sequential one-pot synthesis of substituted benzo[*b*]thiophenes **33** (Scheme 4.16).[32] This protocol involves a sequential copper catalysed intermolecular sp^3 C–H bond thiolation followed by palladium catalysed intramolecular arene-alkene coupling. They have also depicted the synthesis of thieno or furano fused chromenes **44** via different palladium catalysed intramolecular sp^2 C–H bond arylation (Scheme 4.16).



Scheme 4.16: *Sequential One-pot Synthesis of Benzo[b]thiophene via Cu and Pd Catalyzed Reactions.*

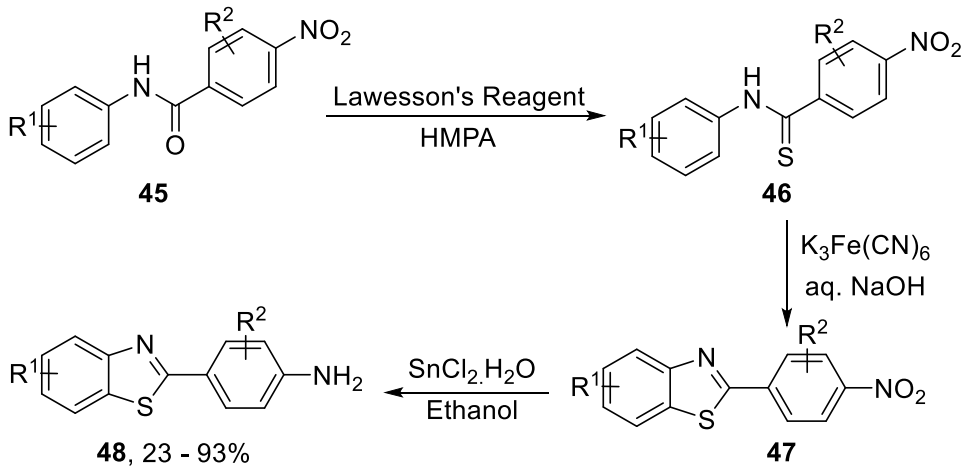
Very recently H. Ila and co-workers reported a new methodology for the synthesis of 2,3-substituted benzo[*b*]thiophenes **33**.[33] This protocol involves a tandem base-mediated condensation of substituted aryl acetonitriles **20** or ketones **20** or acetates **20** with (hetero)aryldithioesters **31**, followed by C–H thiolation to afford the (hetero)aryl fused thiophenes in excellent yields. They further have shown that the reaction proceeds through a radical pathway via SET process (Scheme 4.17).



Scheme 4.17. *Synthesis of (Hetero)aryl Fused Thiophenes via Tandem Base-mediated Condensation Reaction*

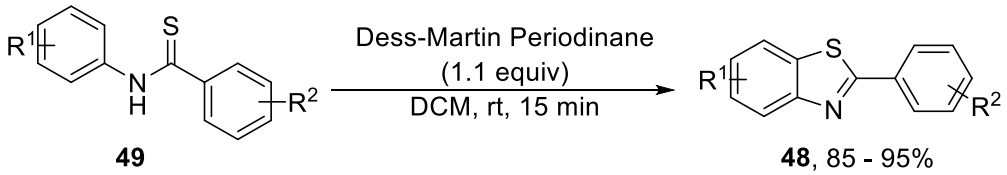
4.3. Previous Reports on the Synthesis of Benzothiazole via C–H Thiolation

Stevens *et* al. synthesized benzothiazole **48**, another *S*-heterocycle, from benzanilides **45** by converting it to benzthioanilides **46** with Lawesson's reagent in HMPA (Hexamethylphosphoramide), and then cyclization by Jacobson's synthesis in presence of alkaline potassium ferricyanide [34] The nitro group attached at the aryl moiety **47** was then reduced to amino group by the action of stannous chloride monohydrate ($SnCl_2.H_2O$) in ethanol, yielding 2-aminobenzothiazole **48** (Scheme 4.18).



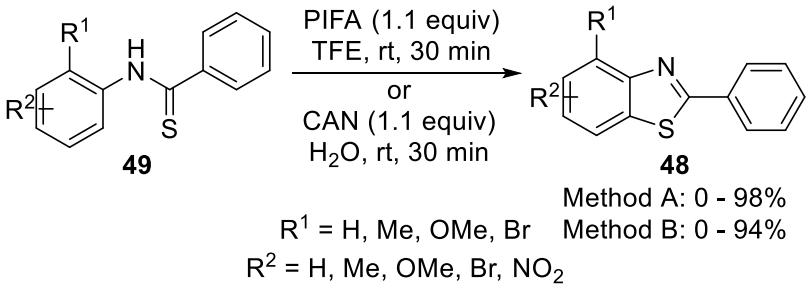
Scheme 4.18: *Intramolecular Oxidative Cyclization of Thioanilides*

The synthesis of 2-substituted benzothiazoles **48** was further designed by Bose and co-workers.[35] They have established a protocol following C–H bond functionalization of thioanilides **49** in presence of hypervalent iodine reagent. This hypervalent iodine reagent, DMP, generated a thiyl radical on reacting with thioanilides **49**, this radical underwent cyclization followed by aromatisation, and afforded the desired product **48** (Scheme 4.19).



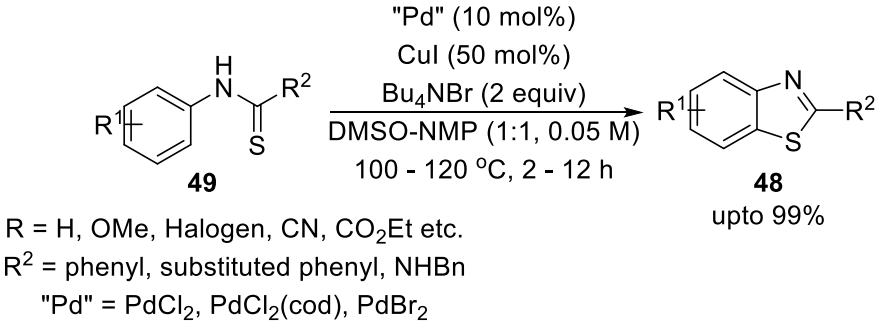
Scheme 4.19: *Hypervalent Iodine Mediated Intramolecular C–H functionalization*

Jackson and co-workers proposed two different strategies for the synthesis of benzothiazoles **48**, adopting the concept of using hypervalent iodine reagent, PIFA, [phenyliodine(III)bis(trifluoroacetate)], in one of the strategies and CAN (cerium ammonium nitrate) in the other strategy.[36] Both the strategies proceeded through aryl radical cations as intermediates (Scheme 4.20).



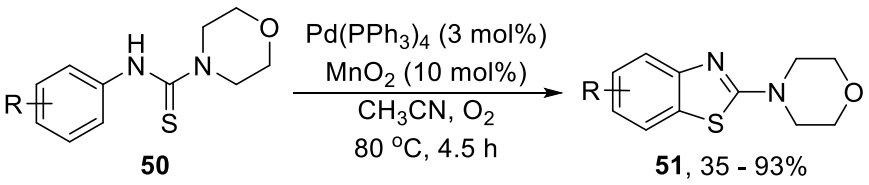
Scheme 4.20: *Hypervalent Iodine Promoted C–H Thiolation of Thiobenzamides*

Inamoto and co-workers published a report on the synthesis of 2-substituted benzothiazoles **48** by using a novel catalytic system.[37] In this method they have used a combination of Pd(II) and Cu(I) catalysts in 10 mol% and 50 mol%, along with TBAB to furnish the cyclization and afforded high yields of benzothiazoles **48** (Scheme 4.21).



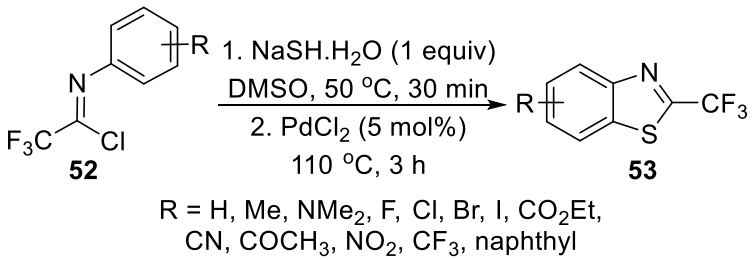
Scheme 4.21: *Synthesis of Benzothiazoles via Intramolecular C─H Functionalization*

Batey and co-workers synthesized 2-aminobenzothiazoles **51** from thiourea derivatives **50** by using a co-catalytic system of $Pd(PPh_3)_2/MnO_2$ in presence of oxygen at 80 °C (Scheme 4.22).[38]



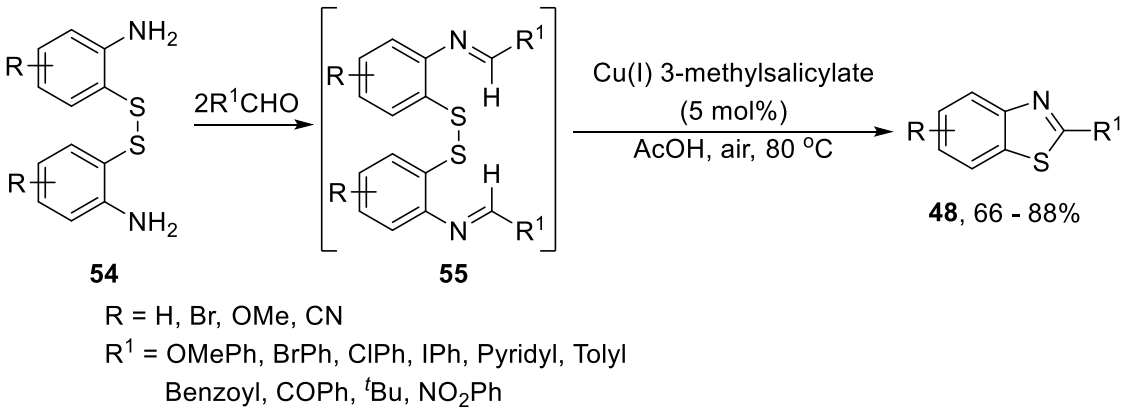
Scheme 4.22: *C–H Thiolation in Presence of co-Catalytic system*

Wu and co-workers illustrated the synthesis of 2-trifluoromethylbenzothiazoles **53** from trifluoromethylimidoyl chlorides **52** and sodium hydrosulfide hydrate.[39] The reaction progressed via C-H thiolation, exclusively in presence of palladium catalyst (Scheme 4.23). This protocol is believed to involve nucleophilic displacement of the chloride with sodium hydrosulfide producing the corresponding thiol, which undergoes C-H thiolation to afford the corresponding benzothiazoles **53** (Scheme 4.23).



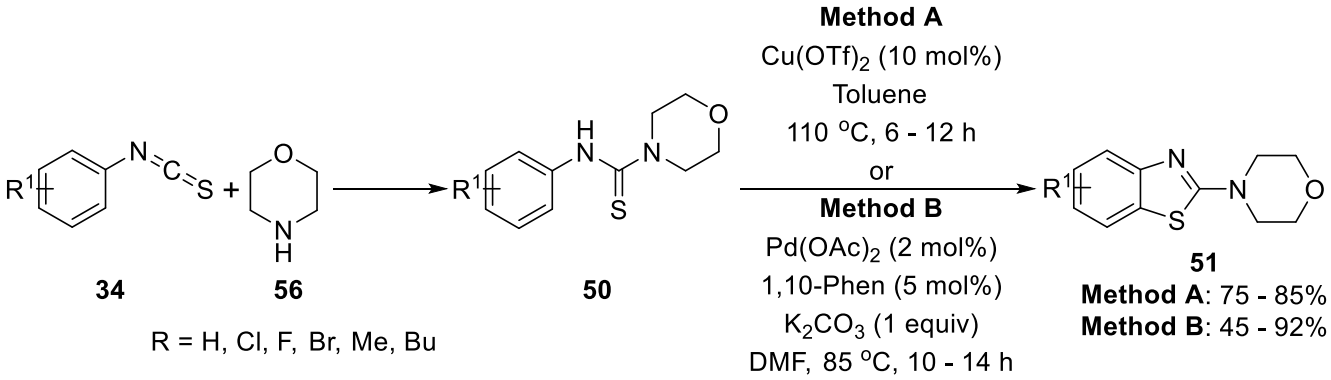
Scheme 4.23: *Synthesis of 2-Trifluoromethylbenzothiazoles via Palladium Mediated C─H thiolation*

Srogl and co-workers illuminated the protocol for the synthesis of 2-substituted benzothiazoles **48** from amino disulfides **54** (Scheme 4.24).[40] This method involved the reaction of disulfide **54** with the aldehyde to form an imine disulfide intermediate **55** which on treatment with copper underwent disulphide bond cleavage, leading to the synthesis of 2-substituted benzothiazoles **48** via C─H bond activation. In this transformation, they were observing a by-product, dihydrobenzothiazoles, along with benzothiazoles **48**. The former was converted to 2-substituted benzothiazoles **48** under aerobic conditions. Based on their experimental studies, they have proposed the C-H activation step as the key step (Scheme 4.24).



Scheme 4.24: *Copper Catalyzed C─H Activation of Disulfide under Aerobic Condition*

B. K. Patel and co-workers studied two independent domino intramolecular aromatic C–H thiolation reactions in the presence of copper and palladium salts (Scheme 4.25).[41] In the first strategy, the desired benzothiazoles **51** were obtained by treatment with simple and commercially available arylisothiocyanates **34** and amine **56** with $Cu(OTf)_2$ in the absence of ligand. On the other hand, palladium catalyzed C–H thiolation was highly ligand dependent and it was successful only with electron rich thioureas **50** (Scheme 4.25).



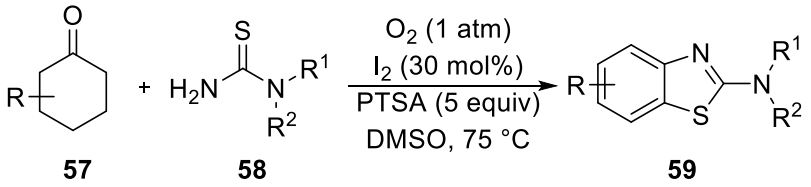
Scheme 4.25: *Investigation of Ligand Effect in Cu & Pd Mediated Intramolecular C–H Thiolation*

Lei and co-workers used an eco-friendly, abundant and cheaper metal, iron, as the catalyst, to furnish C–H bond thiolation of *N*-phenylbenzothioamide **49** via C–H bond activation under oxidative condition (Scheme 4.26).[42] To gain an insight in the mechanistic pathway they performed several experiments. Isotopic effect experiments revealed that the rate determining step is not the C–H bond cleavage. Pyridine was an imperative additive for high selectivity. When the reaction was carried out

in presence of a radical scavenger, TEMPO, only a trace amount of product was observed. This indicates that the reaction follows a radical pathway through thioyl radical intermediate. It had been shown that for the C-H thiolation and C-H activation step to occur, the co-existence of iron catalyst, oxidant, pyridine and substrates are essential (Scheme 4.26).

Scheme 4.26: *Iron Promoted Synthesis of 2-Substituted Benzothiazoles*

Jiang and co-workers further synthesized various substituted benzothiazoles **59** from cyclohexanones **57** and thioureas **58** via aerobic oxidative cyclization in the presence of iodine and molecular oxygen.[43] A diverse range of substituted benzothiazoles **59** were synthesized in moderate yields (Scheme 4.27).

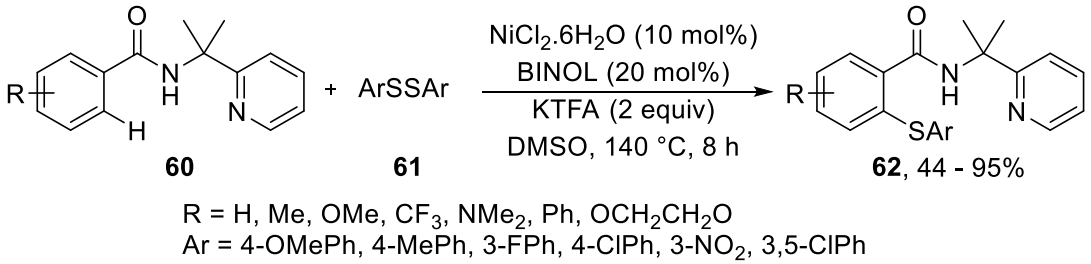


Scheme 4.27: *Aerobic Oxidative Cyclization for the Synthesis of Benzothiazoles*

4.4. Previous Reports on Nickel Catalyzed C–H Thiolation

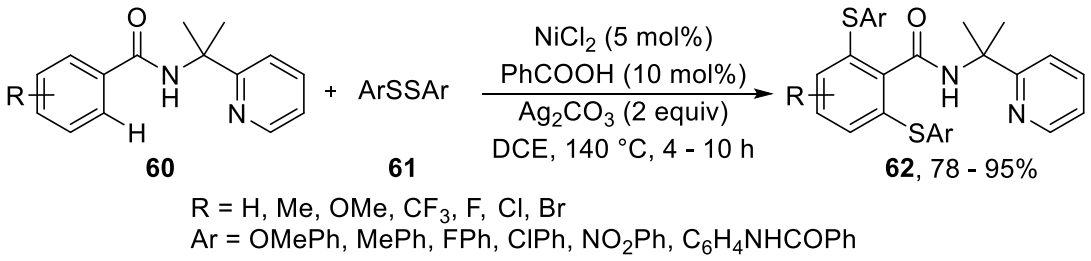
Shi and co-workers, in 2015, demonstrated for the first time the C─H bond thiolation of inactivated aromatic C(sp^2)─H bond **60** in the presence of disulfides **61** as the sulfur source (Scheme 4.28).[44] This protocol involved the usage of 2-(pyridine-2-yl)isopropylamine (PIP) as the directing group. It did not require any metallic oxidants and co-catalysts for affording the product **62**. The

intermolecular C─H bond thiolation, involving various functionalities and heteroarenes, was observed in moderate yields (Scheme 4.28).



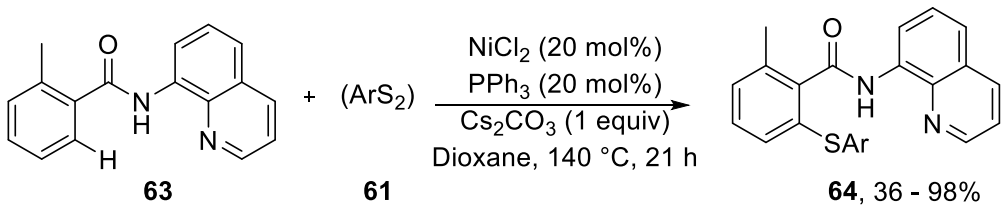
Scheme 4.28: *Nickel Catalyzed C─H Bond Thiolation*

Lu and co-workers also illustrated the nickel catalyzed and acid promoted C─H bond thiolation under the assistance of 2-(pyridine-2-yl)isopropylamine as the directing group (Scheme 4.29).[45]



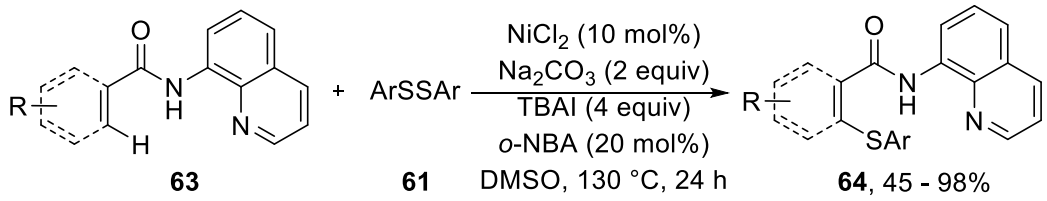
Scheme 4.29: *Nickel Mediated Benzoic Acid Promoted C─H Thiolation*

Kambe and co-workers also devised a new protocol for C─H thiolation through nickel catalysis (Scheme 4.30).[46] They have described a direct sulfenylation of aromatic C─H bond using nickel as catalyst and under the assistance of 8-aminoquinoline, which is acting as a bidentate directing group. They have also demonstrated the direct sulfonylation of aromatic C─H bond using the same methodology (Scheme 4.30).



Scheme 4.30: *Bidentate Directing Group Assisted Nickel Catalyzed C─H thiolation*

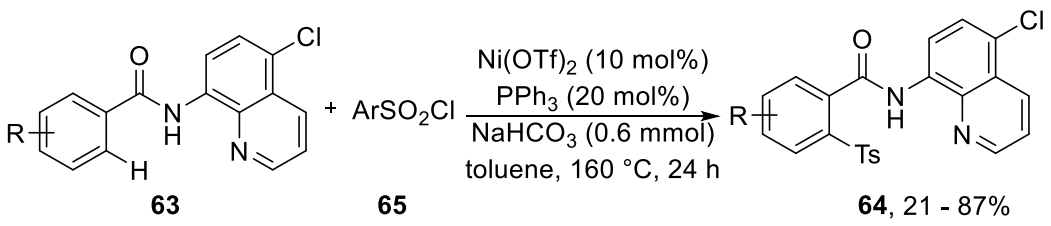
Zhang and co-workers established an efficient protocol through nickel mediated C─H thiolation involving aromatic and alkenyl C(sp^2)─H bonds with the assistance of 8-aminoquinolyl auxiliary (Scheme 4.31).[47] TBAI and *o*-nitro benzoic acid play an important role in this conversion. This methodology was tolerant to various functionalities, affording the diaryl sulfides **64** in excellent yields (Scheme 4.31).



R = Me, OMe, NMe_2, Cl, F, Ph, Br, $-C_4H_4$
Ar = Ph, -PMP, $-CH_3Ph$, -BrPh, -FPh, -ClPh, -BrFPh, -Pyridyl, -Furyl

Scheme 4.31: *Nickel Catalyzed Sulfenylation of Aromatic C─H bond*

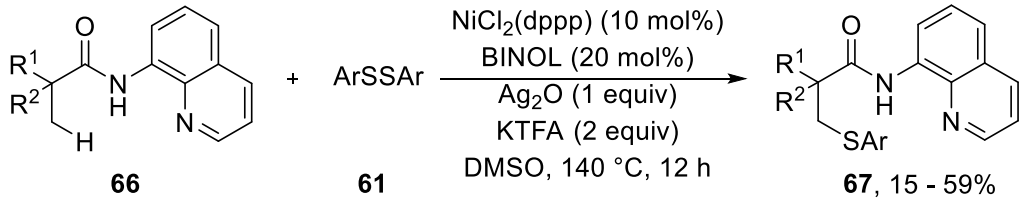
Chatani and co-workers introduced sulfonyl groups in the aromatic C─H bond through nickel catalyzed chelation-assisted C─H bond functionalization, for the first time (Scheme 4.32).[48] They have used substituted tosyl chlorides **65** as the sulfone reagent and employed 5-chloro-8-aminoquinoline as the directing group. Various functionalized substrates **64** were obtained in good yields (Scheme 4.32).



63 **65** **64**, 21 - 87%

Scheme 4.32: *Sulfonylation of Aromatic C─H bond Through Nickel Catalyzed Bidentate Ligand Assisted Reaction*

Shi and co-workers demonstrated for the first time the C─H bond thiolation of unactivated sp^3 C─H bonds of β-methyl aliphatic carboxamides **66** using Ni salt as the catalyst and BINOL as the ligand.[49] For the sulphur source, they have used various substituted disulfides **61**. This methodology is highly selective and leads to a variety of thioethers **67** (Scheme 4.33).

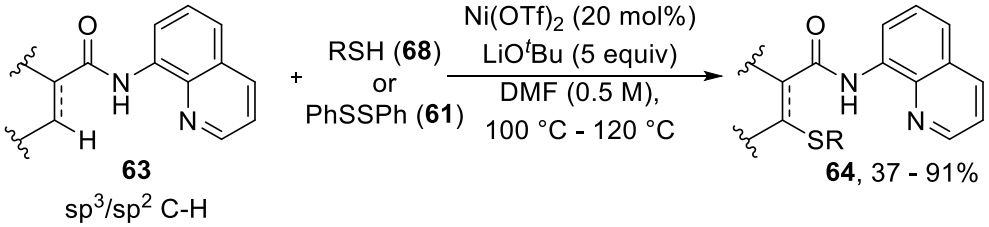


66 **61** **67**, 15 - 59%

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 4.33: *First Nickel Catalyzed Thiolation of sp3 C─H Bonds*

Shi and co-workers then investigated sulfenylation of both sp^2 and sp^3 C─H bonds (Scheme 4.34).[50] Their approach deals with the thiolation of β-methyl amides **63** and aromatic amides **63** with the assistance of nickel catalyst and 8-aminoquinoline. They have used thiols **68** as the thiolating agent, instead of disulfides **61**. The electron deficient thiols **68** afforded good yields of the product **64**, whereas electron rich thiols **68** gave relatively poorer yields of the product **64** (Scheme 4.34).

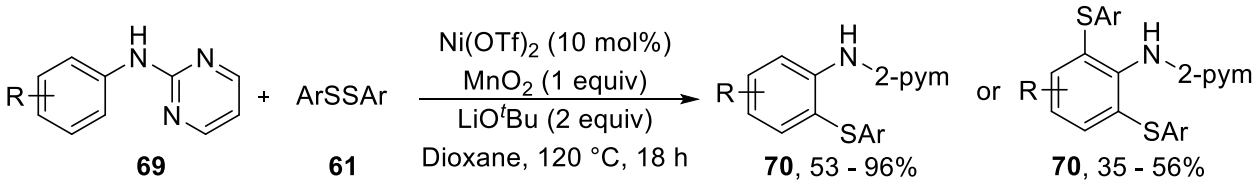


63
sp^3/sp^2 C-H

64, 37 - 91%

Scheme 4.34: *Sulfenylation of sp^3 and sp^2 C─H Bonds*

A new methodology involving C─H bond thiolation had been coined by Ackermann and co-workers (Scheme 4.35).[51] They performed C─H bond thiolation of aniline derivatives **69** with the assistance of $Ni(OTf)_2$ as the catalyst under ligand free conditions. In this report pyrimidyl group has been used as the directing group. The easy removal of the directing group made this C─H thiolation process feasible towards the formation of 2-amino thiophenol derivatives **70** & **71**. In the mechanistic studies they have proposed that the reaction involves single electron transfer and C─H nickelation is the rate determining step (Scheme 4.35).



R = F, OMe, CF_3, Me, ^{t}Bu, Ph, Cl, Br, I, Naphthyl
Ar = MePh, ClPh, Pyridyl

Scheme 4.35: *Nickel Catalyzed C─H Thiolation of Anilines*

4.5. Motivation

Owing to the aforementioned methodologies and the importance of benzo[*b*]thiophene derivatives we have focussed towards the synthesis of 2-aminobenzo[*b*]thiophene. Thus, we have chosen easily accessible thioamides **A** as the model substrate for the site selective C─H bond functionalization. We have designed these thioamides **A** in such a way that they contain two functionalizable sp^2 C─H bonds. Hence there are two notable possibilities of products, the first being the benzo[*b*]thiophene **B**, obtained by the C─H bond functionalisation at the aryl C─H bond and the second being benzothiazole **C**, resulted from the C─H thiolation at the *N*-aryl C─H bond (Fig. 4.2).

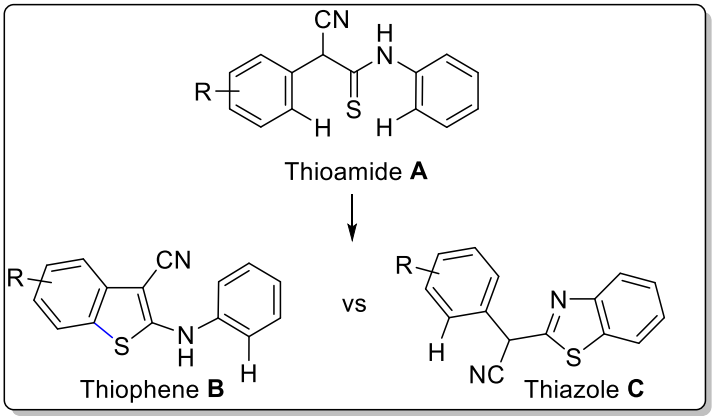
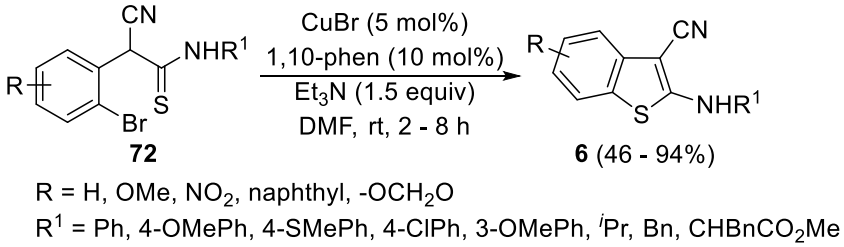


Figure 4.2: *Possible Products for Site-Selective C─H functionalization*

Our group has already established the synthesis of 2-aminobenzo[*b*]thiophene **6** from thioanilides **72** via copper mediated Ullmann coupling reactions (Scheme 4.36).[52]



Scheme 4.36: *Our Previous Methodology for the Synthesis of 2-Aminobenzo[b]thiophene*

Hence, we have envisioned a new methodology via nickel catalyzed regioselective C─H bond thiolation of substituted thioamides or thioanilides. As already mentioned, in this methodology we wish to explore the synthesis of 2-aminobenzo[*b*]thiophenes through the cyclization of one of the two functionalizable sp^2 C─H bond.

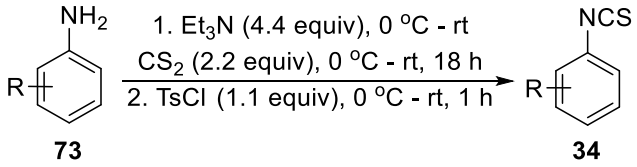
4.6. Results and discussion

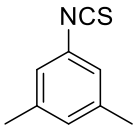
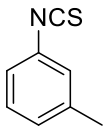
The thioamides **39** for the synthesis of benzo[*b*]thiophenes **6** can be derived from two acyclic precursors, aryl acetonitriles **30** and aryl isothiocyanates **34**, under basic condition at room temperature. The thioamides **39** were characterized by spectral and analytical data.

4.6.1. Synthesis of Isothiocyanates

The required isothiocyanates **34** were synthesised from anilines **73**, on reacting it with triethylamine and carbon disulfide. Once the conversion of the salt was completed the reaction was quenched with p-toluenesulfonyl chloride. The isothiocyanates **34** were synthesised in good to excellent yield (Table 4.1). The commercially available isothiocyanates **34** were used without any purification.

Table 4.1: Synthesis of Isothiocyanate



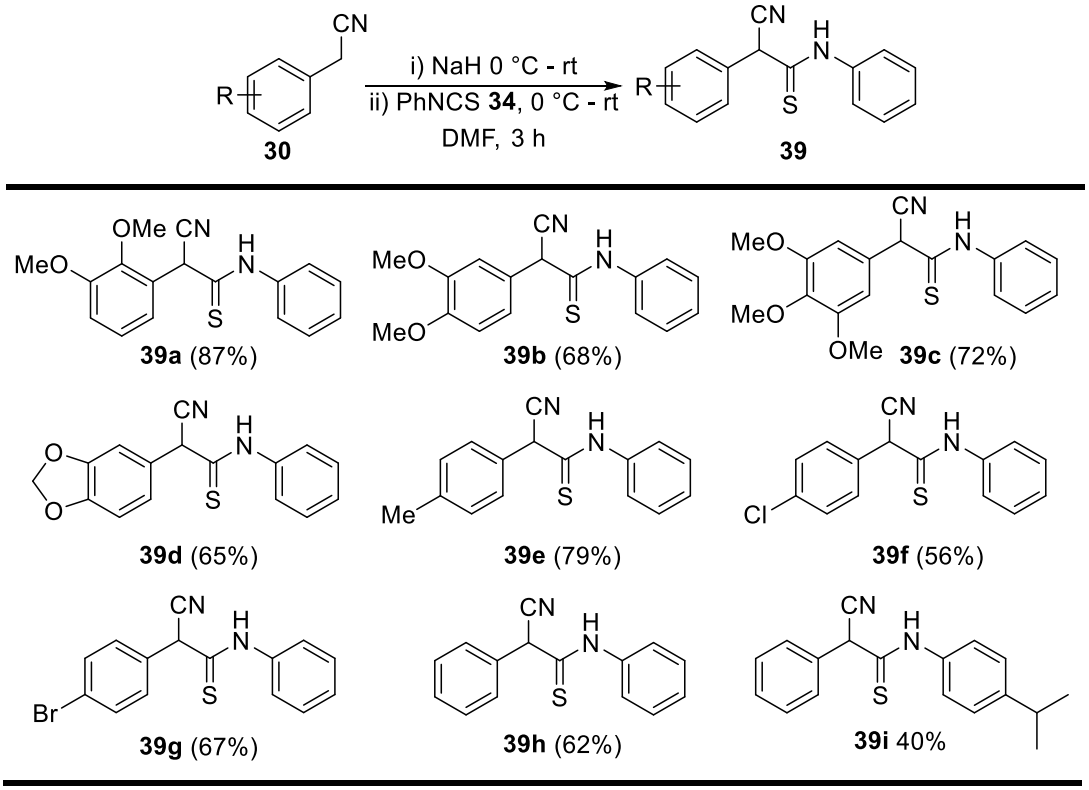
 **34a**, 78%	 **34b**, 63%

4.6.2. Synthesis of Thioamides

The required thioamides **39** can be synthesised from corresponding aryl acetonitriles **30** and aryl isothiocyanates **34** under basic condition. The aryl acetonitriles **30** were stirred with sodium hydride at 0 °C in DMF and then treated with aryl isothiocyanates **34** (Table 4.2 & Table 4.3).

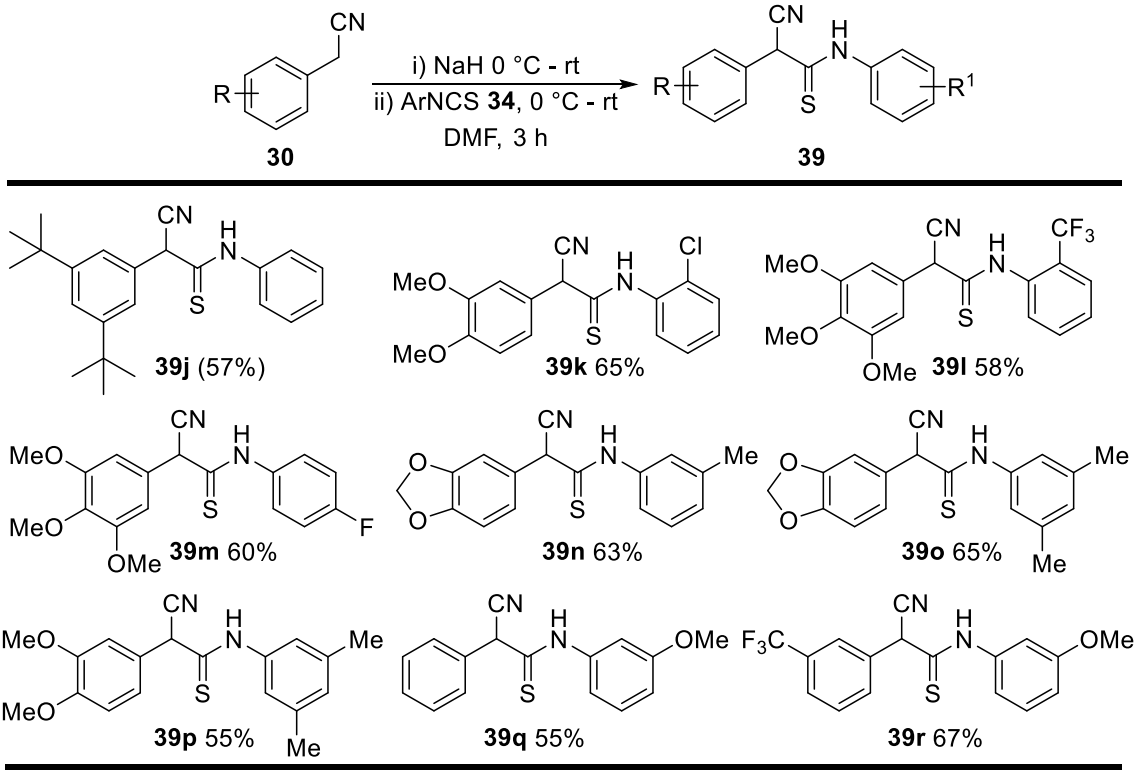
Various thioamides **39** with electron rich, alkyl, halo and sterically hindered substituents at the aryl ring of acetonitrile part **30** were observed in 56 – 87% of yield (Table 4.2).

Table 4.2: Synthesis of Thioamides



A series of thioamides **39** with substitutions on both the aryl rings were also synthesized. Aryl cyanides **30** having electron donating substituents formed the respective thioamides **39**, via base mediated condensation reaction with substituted isothiocyanates **34**, in moderate yields (Table 4.3).

Table 4.3: Synthesis of Thioamides



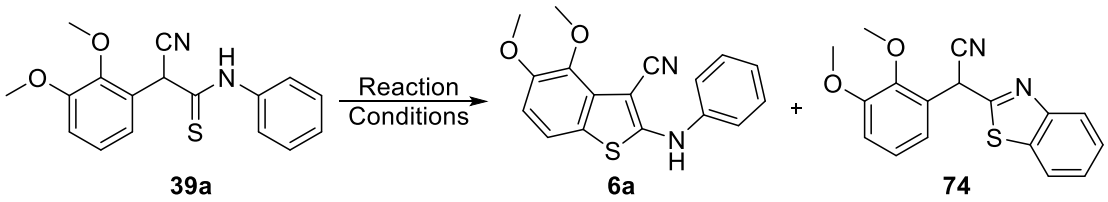
mediated condensation reaction with substituted isothiocyanates **34**, in moderate yields (Table 4.3).

4.6.3. Optimisation of C–H bond Functionalization

After synthesizing the required thioamides **39**, we performed the optimization for the C–S bond formation via nickel mediated C–H bond functionalization (Table 4.4). The 2,3-dimethoxy substituted thioamide **39a** has been selected as the model substrate and subjected to various reaction conditions (Table 4.4). Initially, the model thioamide **39a** was treated with 2 mol% of $NiBr_2$, 1 equiv of PIDA (oxidant) in dioxane at room temperature, we observed only 12% of benzo[*b*]thiophene **6a** with high regioselectivity, which was further characterized by spectral analysis (entry 1, Table 4.4). In this reaction we did not observe a trace amount of benzothiazole **74a**. Thus, this result encouraged us to modulate the reaction conditions further. To enhance the yield and conversion of the reaction, we heated the reaction at 60 ºC and observed an increase in the yield to 22% (entry 2, Table 4.4). Further we increased the temperature to 120 ºC and isolated the desired product **6a** in 32% of yield (entry 3, Table 4.4). We were curious to see the effect of the solvent, so we used 1,1,1,3,3,3-

hexafluoroisopropanol (HFIP) instead of dioxane. We spotted a slight increase in the yield (35%) associated with decrease in the reaction temperature (entry 4, Table 4.4). Thus, we decided to

Table 4.4: Optimisation for C–S Bond Formation via Nickel Mediated C–H Bond Functionalization



39a **6a** **74**
Not Observed

Sl. No.	$NiBr_2$	Additive (2 equiv)	Oxidant (2 equiv)	Solvent (2 mL)	Temp. (°C)	Yield[b] 6a
1.	2 mol%	–	PIDA	Dioxane	rt	12
2.	2 mol%	–	PIDA	Dioxane	60	22
3.	2 mol%	–	PIDA	Dioxane	120	32
4.	2 mol%	–	PIDA	HFIP	50	35
5.	2 mol%	KI	PIDA	HFIP	50	62
6.	2 mol%	KI	PIDA	HFIP	50	52[c]
7.	2 mol%	–	PIDA	HFIP	50	18[c]
8.	5 mol%	KI	PIDA	HFIP	50	60
9.	10 mol%	KI	PIDA	HFIP	50	54
10.	–	KI	PIDA	HFIP	50	30
11.	–	–	PIDA	HFIP	50	10
12.	2 mol%	KI	PIDA	HFIP	50	60[d]

[b]isolated yield, [c]Ad_2PBu (4 mol%), [d]TEMPO (1 equiv) was used.

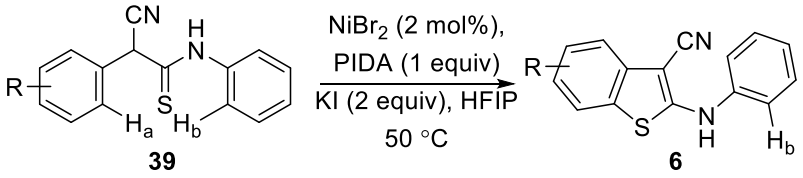
proceed with HFIP as the solvent. We then examined the effects of additive. So, we used 2 equiv of potassium iodide as the additive. Surprisingly, the yield of the reaction increased drastically, giving 62% of benzo[*b*]thiophene **6a** (entry 5, Table 4.4). Whereas, the usage of ligand Ad_2PBu afforded the desired product **6a** in 52% of yield (entry 6, Table 4.4). In absence of KI, the yield of the reaction dropped to 18% (entry 7, Table 4.4). We did not observe any impact on increasing the catalyst loading to 5 mol% and 10 mol% (entries 8 & 9, Table 4.4). On the other hand, only 30% of the product **6a** was formed in the absence of $NiBr_2$ (entry 10, Table 4.4). Oxidant alone afforded only

10% of the product **6a** (entry 11, Table 4.4). To explore the reaction pathway we performed the reaction with radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine-1-yl)oxy (entry 12, Table 4.4). The reaction was found to be effectively producing the product **6a**. So, we can predict that the reaction does not involve any radical pathway.

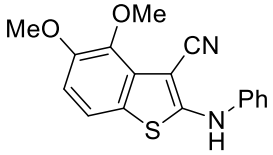
4.6.4. Substrate Scope for C–S Bond Formation via Nickel Mediated C–H Bond Functionalization

With the optimized condition in our hands, we explored the applicability of our methodology. The functionalized thioamides **39** were subjected to our optimized reaction condition. Initially, we projected our study towards the effect of substituents at the aryl ring of the aryl acetonitriles **30**. The electron donating thioamides **39** derived from electron rich aryl acetonitriles **30** and phenyl isothiocyanates **34** gave moderate to good yields. At first, 2,3-dimethoxy substituted thioamide **39a**

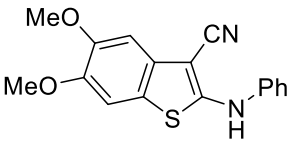
Table 4.5: C–H Thiolation via Nickel Mediated C–H Bond Functionalization of Electron Rich Substrates



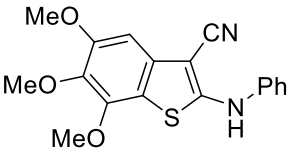
39 **6**



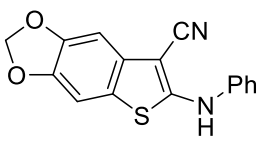
6a (62%, 1 h)



6b (59%, 2 h)



6c (67%, 1.5 h)

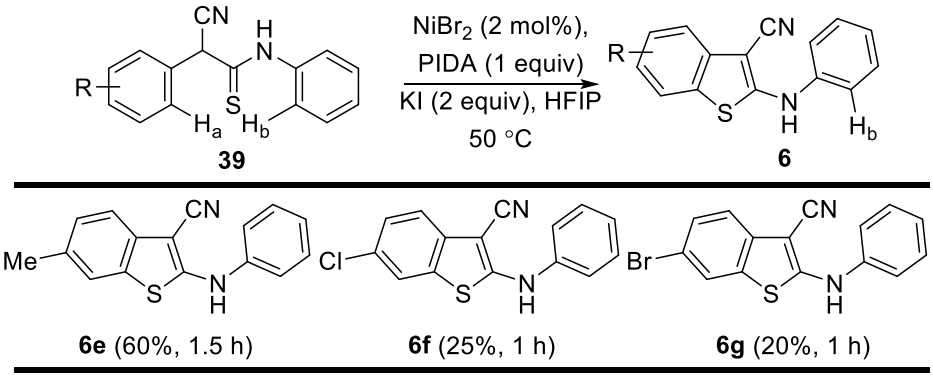


6d (61%, 1 h)

was subjected to the optimized condition and afforded the desired benzothiophene **6a** in 62% (Table 4.5). Similarly, 3,4-dimethoxy substituted thioamide **39b** gave comparable yield of corresponding benzothiophene **6b** (Table 4.5). Then 3,4,5-trimethoxyphenyl ethanethioamide **39c** was studied and the product **6c** was observed in 67% of yield (Table 4.5). 3,4-methylenedioxy thioamide **39d** was smoothly converted into the cyclized product **6d** in 1 h with comparable yield (Table 4.5).

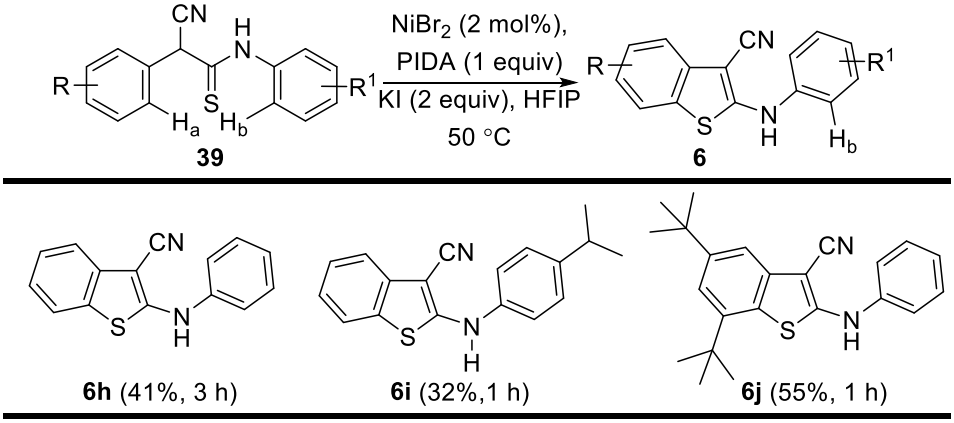
Next, the electron donating substituents were replaced with methyl at the aryl ring of aryl acetonitrile part **39e**, and the corresponding product **6e** was detected in 60% of yield in 1.5 h (Table

Table 4.6: Oxidative C–S Bond Formation of Substituted Thioamides



4.6). However, in the case of halo substituted thioanilides **39f-g** the corresponding benzo[*b*]thiophene **6f-g** was observed in low yield (Table 4.6). 4-Chloro substituted thioamide **39f** afforded only 25% of the cyclized product **6f** (Table 4.6). Similarly, 4-bromo substituted thioamide **39g** also gave comparable yield of the corresponding benzothiophene **6g** (Table 4.6).

Table 4.7: Nickel Mediated Controlled C─H Thiolation

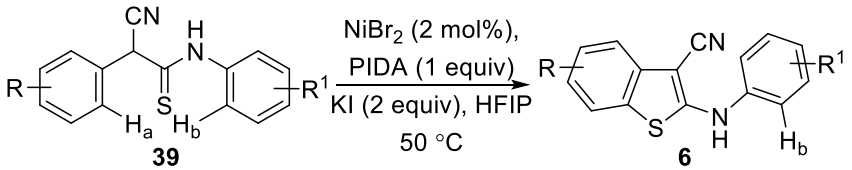


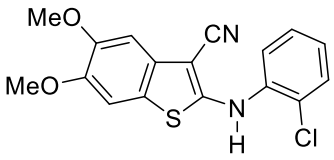
Unsubstituted thioanilide **39h** afforded 41% of the desired product **6h** in slightly longer time (Table 4.7). However, when isopropyl group was imported to the *N*-phenyl ring of isothiocyanate part of the thioamide **39i**, we observed relatively lower yield of the benzo[*b*]thiophene **6i** (Table 4.7). Then we introduced sterically hindered substituent at the aryl ring of the acetonitrile part of the thioamide **39j**

and we observed a smooth conversion of the thioanilide **39j** into the product **6j** with moderate yield in 1 h (Table 4.7).

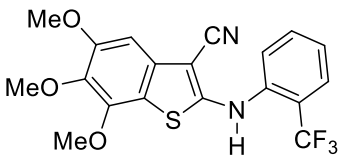
Subsequently, a group of thioamides **39** were derived from electron rich phenyl acetonitriles **30** and substituted phenyl isothiocyanates **34**. These substituted thioamides **39** were then subjected to the optimized reaction condition (Table 4.8). Favorably, we did not find a trace amount of the other regioisomer, i.e., thiazole (Table 4.8). *N*-2-chlorophenyl substituted thioamide **39k** was smoothly transformed into benzo[*b*]thiophene **6k**, giving a moderate yield in 1 h (Table 4.8). On introducing electron deficient group on the *N*-phenyl ring **39l**, we detected 61% of the corresponding cyclized product **6l** (Table 4.8). Similarly, *N*-4-fluorophenyl substituted thioamide **39m** also afforded the desired product **6m** in comparable yield (Table 4.8).

Table 4.8: Regioselective Nickel Catalyzed C─H Bond Thiolation of Thioamides

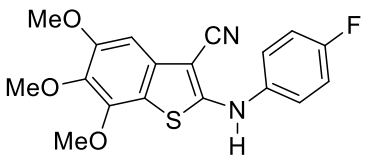




6k (55%, 1 h)



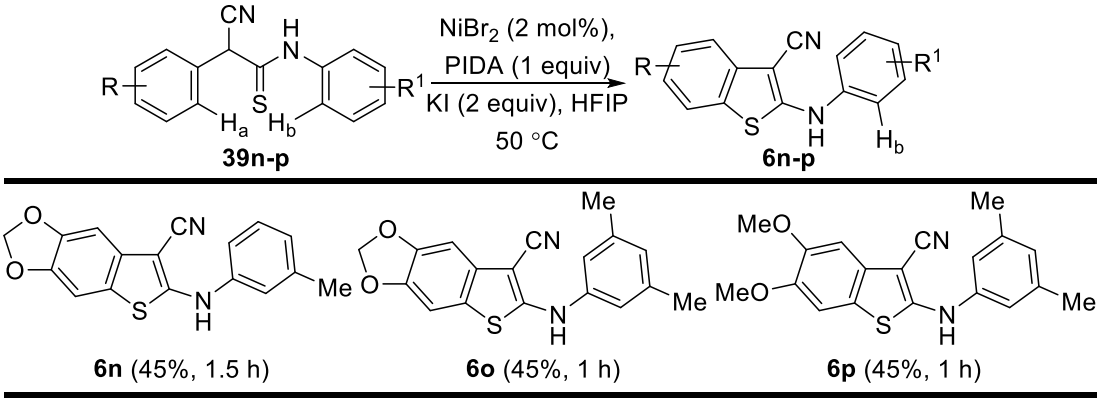
6l (61%, 1 h)



6m (58%, 1.5 h)

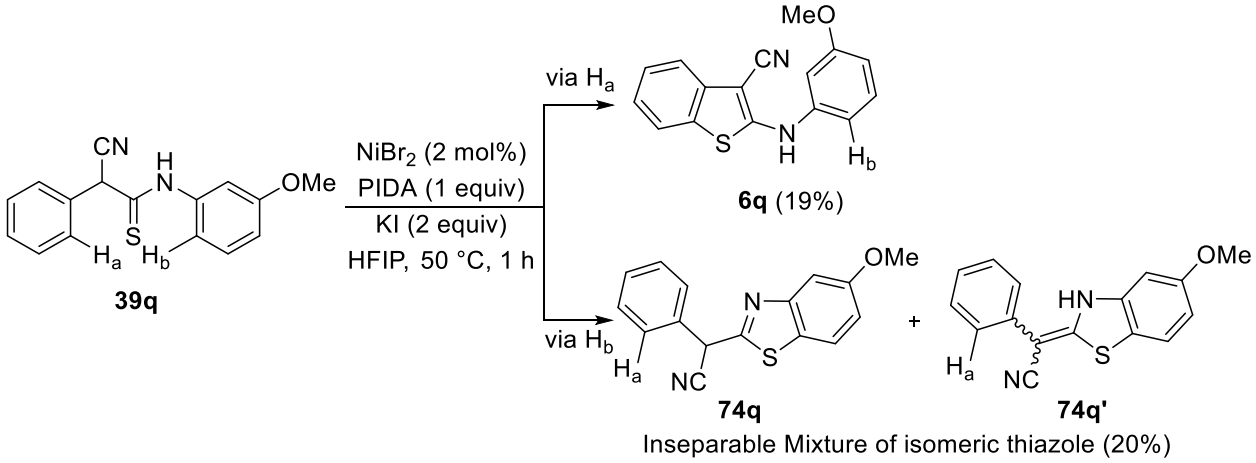
When alkyl groups were introduced in the *N*-phenyl ring of thioanilides **39**, moderate yield of the benzo[*b*]thiophene **6** was detected (Table 4.9). *N*-3-methylphenyl substituted thioanilide **39n** afforded 45% of the product **6n** in 1.5 h (Table 4.9). The *N*-3,5-dimethylphenyl substituted thioamide **39o** with 3,4-methylenedioxy substituent on the aryl ring of acetonitrile part afforded only 45% of the corresponding benzothiophene **6o** (Table 4.9). Similarly, with 3,4-dimethoxy substituent on the aryl acetonitrile part of the thioamide **39p** formed the cyclized product **6p** of comparable yield (Table 4.9).

Table 4.9: Intramolecular Regioselective Thiolation of Substituted *N*-Aryl Thioanilides



4.6.5. Controlled Experiments:

Further, we have performed some controlled experiments to have some insight into the reaction pathway (Scheme 4.37 & 4.38). *N*-3-methoxyphenyl thioamide **39q** was subjected to the

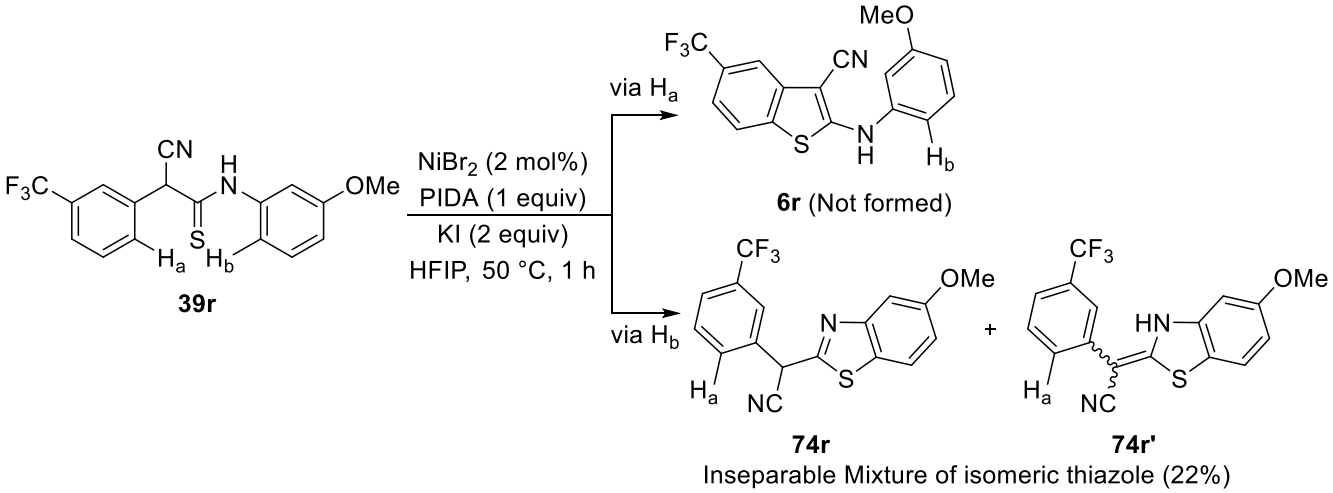


Scheme 4.37: *Control Experiment for Intramolecular C─H Functionalization of Electron Rich Substrate*

optimized condition and surprisingly we isolated 19% of benzo[*b*]thiophene **6q** and 20% of inseparable mixture of isomeric thiazole **74q** and **74q′** (Scheme 4.37).

To check the electronic effect on the regioselectivity of the methodology, we synthesized electron deficient thioamide **39r** (Scheme 4.38). 3-Trifluoromethylphenyl thioamide **39r** was then subjected to our optimized condition and we observed mixture of isomeric thiazole **74r** & **74r′** in

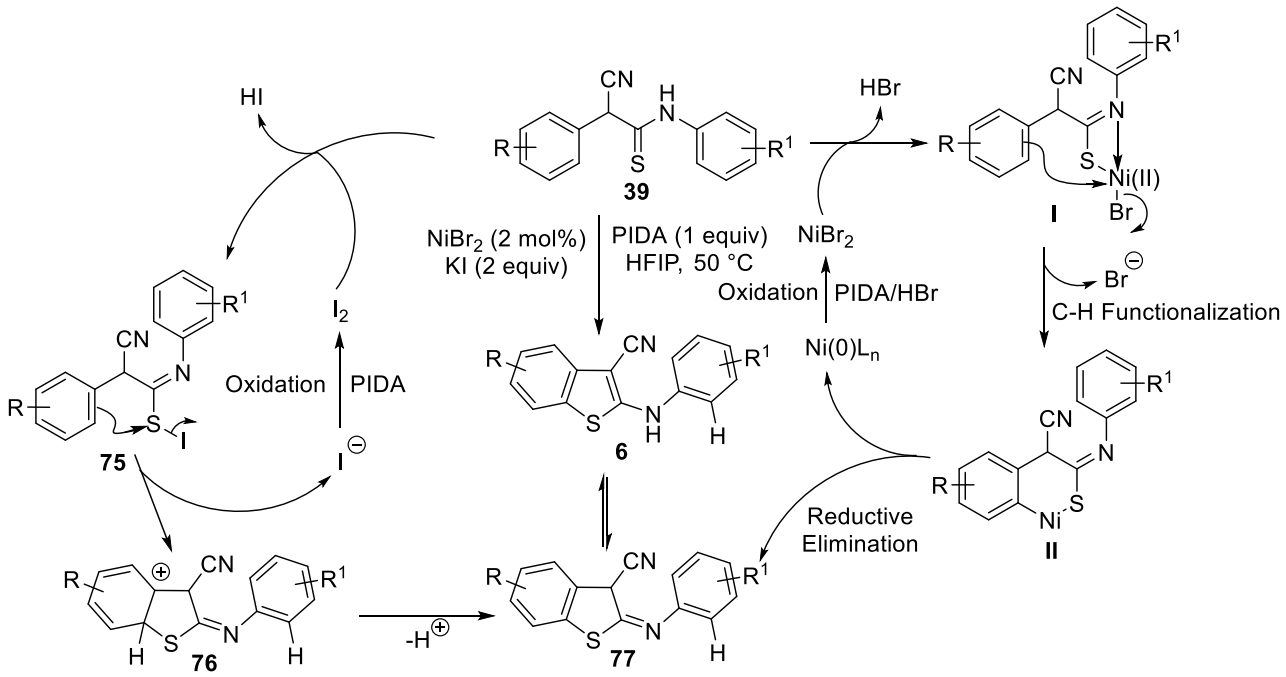
22% and did not isolate a trace amount of the desired benzo[*b*]thiophene **6r** (Scheme 4.38). These experiments show that electronic effect play a partly role in the site-selective C─H thiolation.



Scheme 4.38: *Control Experiment for Intramolecular C─H Functionalization of Electron Deficient Substrate*

4.6.6. A Possible Mechanism for the Formation of Benzothiophene

As we have already accounted that the reaction did not involve any radical pathway. So, we have proposed the mechanistic approach for the reaction pathway (Scheme 4.39). There are two approaches that can be explained. According to the literature methods, the nickel salt undergoes oxidative addition with sulfur center of the thioamide **39** and attains +2 oxidation state. The amine group of the thioamide **39** then binds with the nickel salt via coordinate covalent bond and forms complex **II**. This complex **II,** then forms a six membered intermediate complex **III** via C─H bond



Scheme 4.39: *Plausible Mechanism for Nickel Catalyzed Site-Selective C─H Thiolation*

functionalization with the elimination of bromide ion. The complex **III** then undergoes reductive elimination and forms 2-imino-3-hydrobenzothiophene **77**, that further aromatizes to afford the cyclized benzo[*b*]thiophene **6**. The nickel salt is regenerated by the oxidation of nickel(0) under the influence of PIDA.

In the alternate approach, molecular iodine, generated by the oxidation of PIDA, attacks the sulfur center of thioamide **39** forming the imino complex **75**. The C─H bond functionalization further leads to the formation of dearomatized complex **76**, which forms 2-imino-3-hydrobenzothiophene **77** by the elimination of proton. On aromatization, the complex **77** affords 2-aminobenzo[*b*]thiophene **6**.

4.7. Conclusion:

In this chapter we have discussed the C-H bond functionalization of various thioanilides via nickel catalyzed regioselective reactions for the synthesis of 2-aminobenzo[*b*]thiophenes, for the first time. This approach involves short reaction time, low catalyst loading, and milder reaction conditions and is tolerant to diverse substitutents, including electron rich and electron deficient substrates. The

corresponding 2-aminobenzo[*b*]thiophenes were obtained in good to moderate yields. We have performed some controlled experiments to propose the plausible mechanism.

4.8. Experimental Section

4.8.1. Reagents

All reactions were performed by using standard vial technique with rubber septum. All solids were weighed in air. HFIP, Dioxane, KI, PIDA, 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.

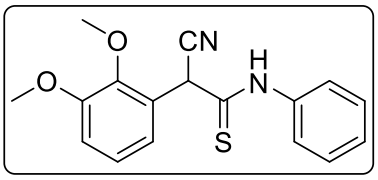
4.8.2. Analytical Methods

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 **6a** and **6b** were grown by slow diffusion of n-hexane over CH_2Cl_2 solution. Single-crystal X-ray diffraction data of **6a** and **6b** 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 **6a** and **6b** 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.

4.8.3. General Procedure for the Synthesis of Thioanilides 39

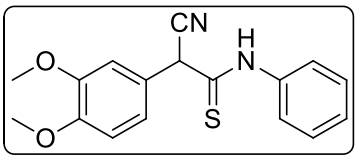
To a stirring suspension of NaH (60% suspension in mineral oil) (1.2 equiv.) in DMF (10.0 mL) at 0 ^{o}C was added dropwise the corresponding aryl acetonitriles **30** (1 equiv.) in DMF (5.0 mL). After being further stirred for 1 h at room temperature, a solution of aryl isothiocyanate **34** (1.1 equiv.) in DMF (5.0 mL) was added to the reaction mixture at 0 ^{o}C and followed by further stirring for 0.5 – 1 h at room temperature. After complete consumption of the starting materials (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined organic layer washed with water (3 x 25 mL) & brine (25 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude products **39** were purified by flash chromatography using EtOAc/hexanes as eluent.

2-Cyano-2-(2,3-dimethoxyphenyl)-*N*-phenylethanethioamide (39a)



Reaction Time: 2 h; yield: 87%; mp: 137 – 139 ^{o}C; R_f: 0.27 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3435, 3300, 3152, 3119, 2942, 2880, 2249, 1483, 1412, 1274, 1077, 996, 761, 742; ^{1}H NMR (300 MHz, $CDCl_3$) δ = δ 10.05 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 7.1 Hz, 2H), 7.26 – 7.21 (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 = 191.4, 152.9, 145.4, 138.5, 129.0, 127.1, 126.2, 125.4, 123.0, 121.3, 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.

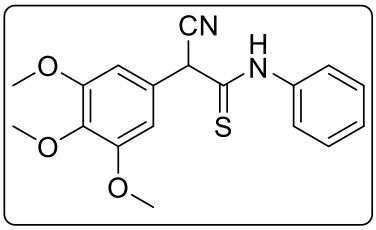
2-Cyano-2-(3,4-dimethoxyphenyl)-*N*-phenylethanethioamide (39b)



Reaction Time: 2 h; yield: 68%; mp: 134 - 136 ^{o}C; R_f: 0.31 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3450, 3251, 2960, 2367, 2237, 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* = 7.6

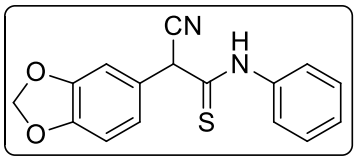
Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.08 (s, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 5.34 (s, 1H), 3.87 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 191.7, 150.1, 149.8, 138.0, 129.0, 127.5, 123.9, 123.4, 120.7, 117.7, 111.7, 110.7, 56.2, 56.1, 54.3; HR-MS (ESI) Calcd for $C_{17}H_{16}N_2O_2S$ [M+Na]: 335.0825, found: 335.0816.

2-Cyano-*N*-phenyl-2-(3,4,5-trimethoxyphenyl)ethanethioamide (39c)



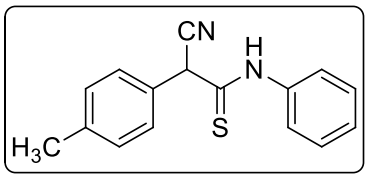
Reaction Time: 2 h; yield: 72%; mp: 144-146 ºC; R_f: 0.20 in 40% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3234, 2943, 2265, 1597, 1508, 1464, 1424, 1331, 1251, 1129; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.77 (s, 1H), 7.35-7.20 (m, 2H), 7.14-7.01 (m, 2H), 7.00-6.91 (m, 1H), 6.48 (s, 2H), 5.02 (s, 1H), 3.55 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.5, 153.7, 138.3, 138.0, 128.9, 127.6, 127.4, 123.4, 117.7, 105.0, 60.9, 56.2, 54.2; HR-MS (ESI) Calcd for $C_{18}H_{18}N_2O_3S$ [M+H]: 343.1111, Found: 343.1118.

2-Cyano-2-(3,4-methylenedioxyphenyl)-*N*-phenylethanethioamide (39d)



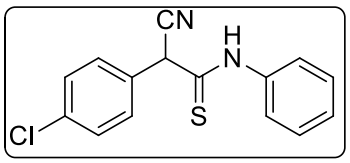
Reaction Time: 2 h; yield: 65%; mp: 120 - 122 ºC; R_f: 0.34 in 25% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) =3434, 3176, 3008, 2965, 2362, 2197, 1598, 1503, 1487, 1443, 1250, 1101, 1038, 936, 854; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.04 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.7 Hz, 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 (100 MHz, $CDCl_3$) δ =191.6, 149.0, 148.9, 137.9, 129.1, 127.6, 125.2, 123.6, 122.0, 117.5, 109.1, 108.1, 101.9, 54.3; HR-MS (ESI) Calcd for $C_{16}H_{12}N_2O_2S$ [M-H]: 295.0536, Found: 295.0584.

2-Cyano-*N*-phenyl-2-(p-tolyl)ethanethioamide (39e)



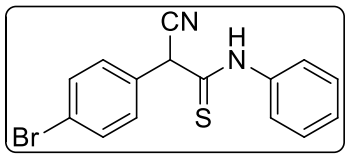
Reaction Time: 2 h; yield: 79%; mp: 112 – 114 ºC; R_f: 0.35 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) =3181, 3123, 3012, 2972, 2192, 1598, 1541, 1512, 1493, 1409, 1268, 1108; ^{1}H NMR (300 MHz, DMSO) δ = 12.14 (s, 1H), 7.72 (d, *J* = 7.5 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.48 – 7.34 (m, 2H), 7.32 - 7.24 (m, 3H), 5.74 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, DMSO) 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-(4-Chlorophenyl)-2-cyano-*N*-phenylethanethioamide (39f)



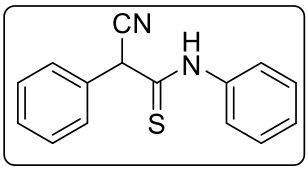
Reaction Time: 3 h; yield: 56%; mp: 124 – 126 ºC; R_f: 0.33 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3445, 3006, 2387, 2347, 2260, 1635, 1275, 1260, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.02 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.36-7.25 (m, 4H), 7.18 (t, *J* = 7.2 Hz, 1H), 5.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.8, 137.9, 136.0, 130.6, 130.0, 129.3 (2C), 127.9, 123.7, 117.0, 53.9; HR-MS (ESI) Calcd for $C_{15}H_{11}ClN_2S$ [M+H]: 287.0404, found: 287.0409.

2-(4-Bromophenyl)-2-cyano-*N*-phenylethanethioamide (39g)



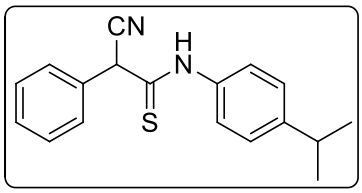
Reaction Time: 3 h; yield: 67%; mp: 120 – 122 ºC; R_f: 0.36 in 25% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3286, 3231, 2253, 195, 1519, 1412, 1398, 1105, 1073, 708; ^{1}H NMR (700 MHz, $CDCl_3$) δ = 8.96 (s, 1H), 7.61 (d, *J* = 7.7 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 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 = 190.72, 137.82, 132.94, 131.03, 129.52, 129.23, 127.86, 124.18, 123.73, 117.08, 53.94; HR-MS (ESI): Calcd. for $C_{15}H_{11}BrN_2S$ (M+H): 330.9899, found: 330.9873, Calcd: 332.9879, found: 332.9853.

2-Cyano-*N*-2-diphenylethanethioamide (39h)



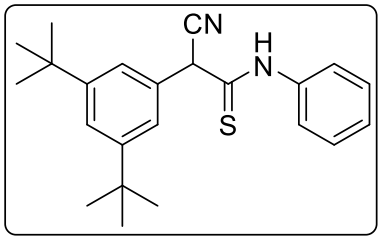
Reaction Time: 2 h; yield: 62%; mp: 105 – 106 ºC; R_f: 0.36 in 25% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3450, 3274, 3141, 3095, 2252, 1598, 1558, 1492, 1403, 1279, 1118, 757; ^{1}H NMR (400 MHZ, $CDCl_3$) δ = 9.01 (s, 1H), 7.61 – 7.55 (m, 4H), 7.48 - 7.46 (m, 3H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.29 - 7.25 (m, 1H), 5.39 (s, 1H); ^{13}C NMR (175 MHZ, $CDCl_3$) δ = 191.3, 138.0, 131.9, 129.9, 129.8, 129.2, 128.0, 127.7, 123.7, 117.3, 54.8; HR-MS (ESI) Calcd for $C_{15}H_{12}N_2S$ [M+H]: 253.0794, found: 253.0809.

2-Cyano-*N*-(4-isopropylphenyl)-2-phenylethanethioamide (39i)



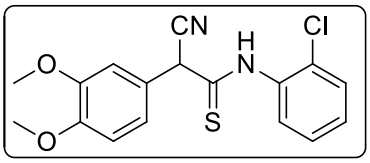
Reaction Time: 3 h; yield: 40%; mp: 104 – 106 ºC; R_f: 0.35 in 20% ethyl acetate in hexanes; IR (KBr): 3447, 2961, 2898, 2344, 2268, 1635, 1558, 1506, 1269, 784; ^{1}H NMR (700 MHz, DMSO) δ = 12.10 (s, 1H), 7.67 – 7.61 (m, 4H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 5.77 (s, 1H), 2.92 – 2.85 (m, 1H), 1.19 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 191.0, 148.5, 135.8, 132.1, 129.8, 129.7, 128.0, 127.0, 123.5, 117.4, 54.6, 33.9, 23.9; HR-MS (ESI) Calcd for $C_{18}H_{18}N_2S$ [M+H]: 295.1263, Found: 295.1280.

2-Cyano-2-(3,5-di-tert-butylphenyl)-*N*-phenylethanethioamide (39j)



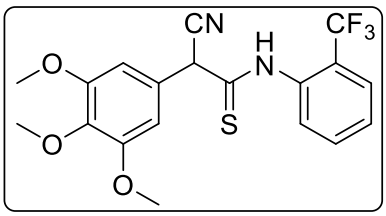
Reaction Time: 2.5 h; yield: 57%; mp: 198 – 199 ºC; R_f: 0.30 in 30% ethyl acetate in hexanes; IR (KBr): 3261, 299, 2379, 2281, 1600, 1410, 1276, 1125; ^{1}H NMR (300 MHz, DMSO) δ = 12.13 (s, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.54 (s, 2H), 7.45-7.40 (m, 3H), 7.29 (d, *J* = 6.5 Hz, 1H), 5.71 (s, 1H), 1.29 (s, 18H); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 191.7, 152.9, 138.0, 130.7, 129.2, 127.6, 123.9, 123.5, 122.3, 117.6, 55.6, 35.2, 31.5; HR-MS (ESI) Calcd for $C_{23}H_{28}N_2S$ [M+Na]: 387.1865, Found: 387.1842.

***N*-(2-chlorophenyl)-2-cyano-2-(3,4-dimethoxyphenyl)ethanethioamide (39k)**



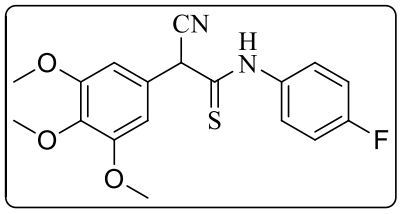
Reaction Time: 2 h; yield: 65%; mp: 141-142 ºC; R_f: 0.28 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3280, 2920, 2841, 2039, 1596, 1509, 1401, 1257, 1024; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.06 (s, 1H), 8.46 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.04 (s, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 5.31 (s, 1H), 3.90 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.8, 150.3, 149.9, 134.5, 129.6, 128.2, 127.2, 127.1, 124.9, 123.1, 121.0, 117.3, 111.7, 110.7, 56.1, 56.0, 54.8; HR-MS (ESI) Calcd for $C_{17}H_{15}ClN_2O_2S$ [M+H]: 347.0616, Found: 347.0603.

2-Cyano-*N*-(2-(trifluoromethyl)phenyl)-2-(3,4,5-trimethoxyphenyl)ethanethioamide (39l)



Reaction Time: 2 h; yield: 58%; mp: 117-119 ºC; R_f: 0.23 in 30% in ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3752, 3322, 3272, 2973, 2941, 2843, 2260, 1596, 1506, 1462, 1320, 1126, 1060, 1006; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.78 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 6.76 (s, 2H), 5.32 (s, 1H), 3.88 (s, 6H), 3.86 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 193.6, 154.4, 139.3, 135.5, 132.7, 128.9, 128.2, 126.7 (q, *J* = 5.3 Hz), 125.9, 124.6 (q, *J* = 29.8 Hz), 123.2 (q, *J* = 271.9 Hz), 116.9, 105.3, 61.0, 56.4, 54.8; HR-MS (ESI) Calcd for $C_{19}H_{17}F_3N_2O_3S$ [M+H]: 411.0985, Found: 411.0968.

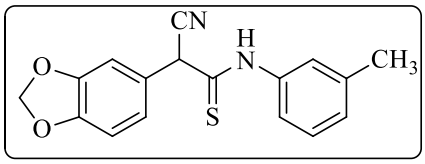
2-Cyano-*N*-(4-fluorophenyl)-2-(3,4,5-trimethoxyphenyl)ethanethioamide (39m)



Reaction Time: 2 h; yield: 60%; mp: 64-66 ºC; R_f: 0.10 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3536, 3272, 2940, 2838, 2249, 1595, 1422, 1127, 837; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.11 (s, 1H), 7.53 (s, 2H), 7.06 (t, *J* = 7.8 Hz, 2H), 6.79 (s, 2H), 5.36 (s, 1H), 3.87 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.9, 161.1 (d, *J* = 246.1 Hz), 153.9, 138.7, 134.1 (d, *J* = 2.6 Hz),

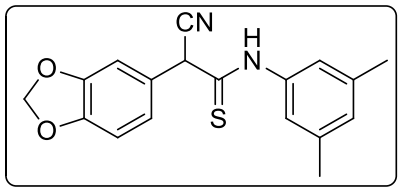
127.3, 125.8 (d, *J* = 8.2 Hz), 117.5, 115.9 (d, *J* = 22.8 Hz), 105.1, 61.0, 56.4, 54.2; HR-MS (ESI) Calcd for $C_{18}H_{17}N_2O_3F$ [M+H]: 361.1017, Found: 361.0999.

2-Cyano-2-(3,4-methylenedioxyphenyl)-*N*-(m-tolyl)ethanethioamide (39n)



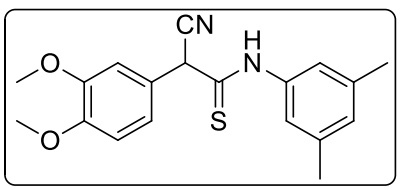
Reaction Time: 2 h; yield: 63%; mp: 137-139 ºC; R_f: 0.19 in 30% in ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3123, 2943, 2231, 1842, 1606, 1486, 1246, 1217, 1040; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.10 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.39 (s, 1H), 7.29 (t, *J* = 4.4 Hz, 1H), 7.14-7.05 (m, 3H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.04 (s, 2H), 5.30 (s, 1H), 2.36 (s, 3H); 13C NMR (175 MHz, $CDCl_3$) δ = 191.5, 148.9, 148.8, 139.2, 137.9, 128.9, 128.4, 125.4, 124.01, 121.9, 120.7, 117.6, 109.1, 108.1, 101.9, 54.1, 21.4; HR-MS (ESI) Calcd for $C_{17}H_{14}N_2O_2S$ [M+H]: 311.0849, Found: 311.0832.

2-Cyano-*N*-(3,5-dimethylphenyl)-2-(3,4-methylenedioxyphenyl)ethanethioamide (39o)



Reaction Time: 2 h; **y**ield: 65%; mp: 168-170 ºC; R_f: 0.20 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3327, 2326, 2247, 1504, 1415, 1293, 1254, 1098, 1040; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.88 (s, 1H), 7.17 (s, 2H), 7.09 – 6.97 (m, 2H), 6.95 – 6.80 (m, 2H), 6.02 (s, 2H), 5.23 (s, 1H), 2.30 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.3, 148.9, 148.8, 138.9, 137.8, 129.4, 125.3, 121.9, 121.2, 117.6, 109.1, 108.1, 101.9, 54.2, 21.3; HR-MS (ESI) Calcd for $C_{18}H_{16}N_2O_2S$ [M+H]: 325.1005, Found: 325.1002.

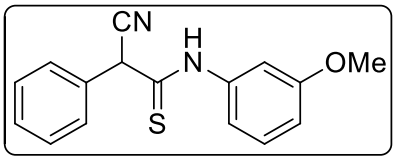
2-Cyano-2-(3,4-dimethoxyphenyl)-*N*-(3,5-dimethylphenyl)ethanethioamide (39p)



Reaction Time: 3 h; yield: 55%; mp: 167-169 ºC; R_f: 0.30 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3666, 3250, 2910, 2250, 2064, 1565, 1480, 1260, 1090; ^{1}H NMR (700 MHz, DMSO) δ = 11.92 (s, 1H), 7.29 (s, 2H), 7.24 (s, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.90

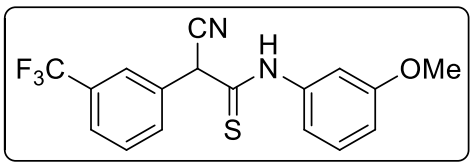
(s, 1H), 5.64 (s, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 2.25 (s, 6H); ^{13}C NMR (175 MHz, DMSO) δ = 192.8, 149.2, 148.7, 138.8, 138.0, 128.2, 126.0, 120.9, 120.0, 118.3, 112.0, 111.3, 55.6, 55.6, 51.9, 20.9; HR-MS (ESI) Calcd for $C_{19}H_{20}N_2O_2S$ [M+H]: 341.1318, Found: 341.1317.

2-Cyano-*N*-(3-methoxyphenyl)-2-phenylethanethioamide (39q)



Reaction Time: 3 h; yield: 60%; R_f: 0.25 in 20% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.57 (s, 1H), 7.66 – 7.58 (m, 2H), 7.47 – 7.37 (m, 4H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.84 – 6.76 (m, 1H), 5.43 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 191.5, 159.7, 139.1, 132.1, 129.7, 129.5, 129.5, 127.8, 117.8, 115.5, 113.1, 109.0, 55.4, 54.2; HR-MS (ESI) Calcd. for $C_{16}H_{14}N_2OS$ [M+H]: 283.0900, Found: 283.1093.

2-Cyano-*N*-(3-methoxyphenyl)-2-(3-trifluoromethylphenyl)ethanethioamide (39r)

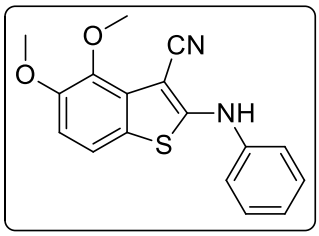


Reation Time: 3 h; yield: 55%; mp: 99 – 103 ºC; R_f: 0.32 in 30% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.39 (s, 1H), 7.90 – 7.79 (m, 2H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.39 (s, 1H), 7.31 – 7.22 (m, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 5.48 (s, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.1, 160.1, 139.0, 133.3, 132.0 (q, *J* = 32.0 Hz), 131.3, 130.2, 130.0, 126.6 (q, *J* = 4.0 Hz), 124.8 (q, *J* = 3.6 Hz), 123.6 (q, *J* = 270.8 Hz), 116.9, 115.7, 113.6, 109.2, 55.6, 54.0; HR-MS (ESI) Calcd for $C_{17}H_{13}F_3N_2OS$ [M+H]: 351.0773, Found: 351.0932.

4.8.4. General Procedure for Nickel Catalyzed Site Selective C—H Functionalization of α-Aryl-thioacetanilide 45 for the Synthesis of 2-Aminobenzo[*b*]thiophenes 6

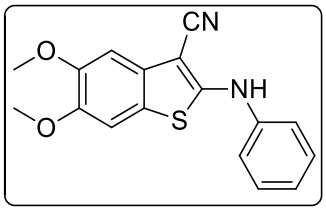
An oven-dried 8 mL reaction vial was charged with $NiBr_2$ (2 mol%), PIDA (0.5 mmol) and KI (1 mmol), respective thioamides **39** (0.5 mmol) in HFIP (2.0 mL) and was stirred at 50 ºC for 1-3 h. The reaction mixture was monitored by TLC. After the starting material **39** had been completely consumed, the reaction mixture was purified by flash chromatography.

3-Cyano-4,5-dimethoxy-2-(phenylamino)benzo[*b*]thiophene (6a)



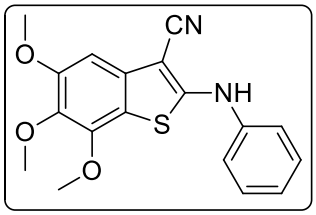
Reaction Time: 1 h; yield: 62%; mp: 196-198 ºC; R_f = 0.34 in 20% ethyl acetate in hexanes; IR (KBr): 3436, 3243, 3138, 3088, 2209, 1597, 1556, 1464, 1440, 1417, 1265, 1039; ^{1}H NMR (700 MHz, DMSO) δ = 10.05 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.40 - 7.39 (m, 4H), 7.17 – 7.14 (m, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 161.81, 150.91, 141.71, 139.97, 131.47, 129.88, 125.20, 122.25, 120.27, 117.57, 116.23, 110.57, 81.24, 61.82, 56.79; HR-MS (ESI) Calcd for $C_{17}H_{14}N_2O_2S$ [M+H]: 311.0849, found: 311.0871.

3-Cyano-5,6-dimethoxy-2-(phenylamino)benzo[*b*]thiophene (6b)



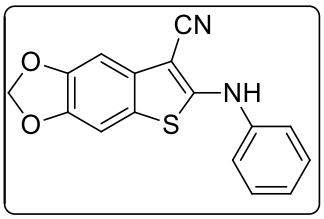
Reaction Time: 2 h; yield: 59%; mp: 180 – 182 ºC; R_f: 0.32 in 25% ethyl acetate in hexane; IR (KBr): 3272, 2993, 2963, 2199, 1601, 1562, 1491, 1474, 1461, 1435, 1402, 1298, 1246, 1208, 1173, 1083, 1033, 960, 836, 762, 700, 621; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 – 7.37 (m, 2H), 7.31 – 7.29 (m, 2H), 7.18 – 7.14 (m, 1H), 7.09 (s, 1H), 7.06 (s, 1H), 7.04 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.6, 149.5, 147.6, 140.4, 129.9, 129.8, 124.6, 121.1, 119.4, 115.5, 104.6, 102.4, 85.1, 56.5, 56.3; HR-MS (ESI) Calcd for $C_{17}H_{14}N_2O_2S$ [M+H]: 311.0849, Found: 311.0890.

3-Cyano-2-(phenylamino)-5,6,7-trimethoxybenzo[*b*]thiophene (6c)



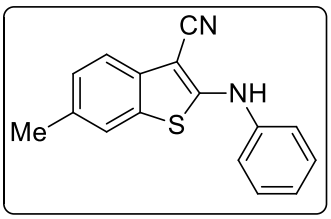
Reaction Time: 1.5 h; yield: 67%; mp: 167-170 ºC; R_f = 0.33 in 20% ethyl acetate in hexanes; IR (KBr): 3441, 3056, 2984, 2307, 2240, 1635, 1558, 1507, 1110, 895; ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.48 (s, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.35 (d, *J* = 7.7 Hz, 2H), 7.17 (t, *J* = 7.7 Hz, 1H), 6.83 (s, 1H), 4.02 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 160.7, 154.2, 147.3, 140.2, 138.2, 132.4, 129.8, 124.9, 120.0, 115.6, 114.1, 97.8, 84.3, 61.5, 61.0, 56.4; HR-MS (ESI) Calcd for $C_{18}H_{16}N_2O_3S$ [M+Na]: 363.0774, Found: 363.0799.

3-Cyano-5,6-methylenedioxy-2-(phenylamino)benzo[*b*]thiophene (6d)



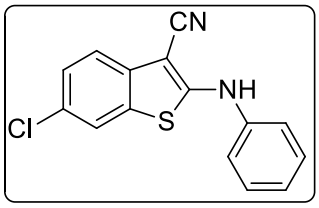
Reaction Time: 1 h; yield: 61%; mp: 222 – 225 ºC; R_f = 0.37 in 20% ethyl acetate in hexane; IR (KBr): 3441, 3255, 2371, 2345, 2204, 1561, 1474, 1295, 1052, 945, 823, 695; ^{1}H NMR (400 MHz, DMSO) δ = 9.97 (s, 1H), 7.41 (s, 1H), 7.39 – 7.34 (m, 4H), 7.10 (t, *J* = 5.9 Hz, 1H), 6.99 (s, 1H), 6.07 (s, 2H); ^{13}C NMR (100 MHz, DMSO) δ = 158.9, 147.3, 145.2, 141.4, 130.7, 129.4, 123.6, 121.2, 119.4, 114.9, 102.7, 101.4, 98.9, 84.3; HR-MS (ESI) Calcd for $C_{16}H_{10}N_2O_2S$ [M+Na]: 317.0355, Found: 317.0362.

3-Cyano-6-methyl-2-(phenylamino)benzo[*b*]thiophene (6e)



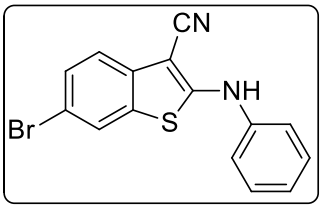
Reaction Time: 1 h; yield: 60%; mp: 155-157 ºC; R_f = 0.25 in 10% ethyl acetate in hexanes; IR (KBr): , 3248, 2368, 2213, 1597, 1567, 1475, 1323, 757, 696; ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.45 (d, *J* = 8.4 Hz, 1H), 7.43 (brs, 1H), 7.42-7.39 (m, 2H), 7.37-7.33 (m, 3H), 7.21 - 7.17 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.8, 140.3, 134.0, 133.7, 129.8, 129.4, 127.5, 124.8, 121.9, 119.9, 119.5, 115.6, 83.7, 21.5; HR-MS (ESI) Calcd for $C_{16}H_{12}N_2S$ [M+H]: 265.0794, Found: 265.0790.

6-Chloro-3-cyano-2-(phenylamino)benzo[*b*]thiophene (6f)



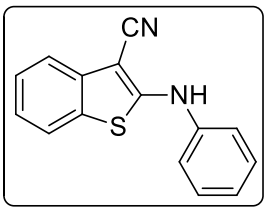
Reaction Time: 1 h; yield: 25%; mp: 182 – 184 ºC; R_f = 0.30 in 10% ethyl acetate in hexanes; IR (KBr): 3678, 3253, 2920, 2211, 1604, 1567, 1464, 1397, 1247, 1062, 750, 694; ^{1}H NMR (700 MHz, DMSO) δ = 10.35 (s, 1H), 7.96 (s, 1H), 7.55 – 7.31 (m, 6H), 7.19 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) 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: 285.0238.

3-Cyano-6-bromo-2-(phenylamino)benzo[*b*]thiophene (6g)



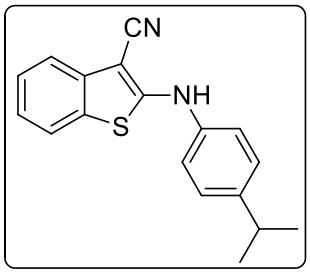
Reaction Time: 2 h; yield: 20%; mp: 200 – 202 ºC; R_f: 0.33 in 15% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}): 3211, 2328, 2209, 1601, 1556, 1461, 1391, 1249, 1058; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 (s, 1H), 7.56 – 7.48 (m, 2H), 7.47 - 7.43 (m, 2H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.30 - 7.23 (m, 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 calcd: 330.9722, found: 328.9759 and 330.9743.

3-Cyano-2-(Phenylamino)benzo[*b*]thiophene (6h)



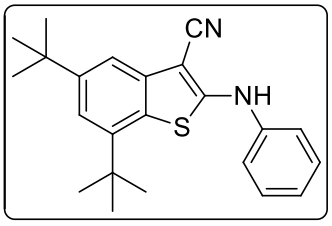
Reaction Time: 3 h; yield: 41%; mp: 134-136 ºC; R_f = 0.23 in 10% ethyl acetate in hexanes; IR (KBr): 3376, 2291, 1570, 1136; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.51 (s, 1H), 7.44 – 7.36 (m, 5H), 7.25 – 7.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 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]: 265.0794, Found: 265.0780.

3-Cyano-2-[(4-isopropylphenyl)amino]benzo[*b*]thiophene (6i)



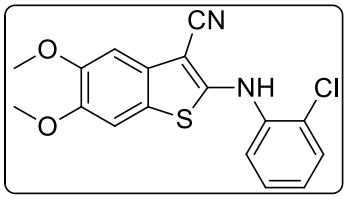
Reaction Time: 1 h; yield: 32%; mp: 174 -176 ºC; R_f: 0.32 in 15% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3773, 3252, 2957, 2394, 2280, 1605, 1552, 1514, 1439, 1324; ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 8.4 Hz, 1H), 7.28 – 7.26 (m, 5H), 7.10 (t, *J* = 7.7 Hz, 1H), 2.85 - 2.81 (m, 1H), 1.17 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz. $CDCl_3$) δ = 161.5, 146.3, 137.8, 136.8, 129.0, 127.8, 126.1, 123.5, 121.9, 120.8, 119.7, 115.6, 82.7, 33.8, 24.1; HR-MS (ESI) Calcd for $C_{18}H_{16}N_2S$ [M+Na]: 315.0926, found: 315.0928, [M+H]: 293.1107, Found: 293.1113.

3-Cyano-5,7-di-tert-butyl-2-(phenylamino)benzo[*b*]thiophene (6j)



Reaction Time: 1h; yield: 55%; mp: 235-237 ºC; R_f = 0.28 in 10% ethyl acetate in hexanes; IR (KBr): 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: 385.1712.

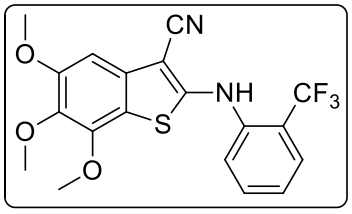
2-[(2-Chlorophenyl)amino]-3-cyano-5,6-dimethoxybenzo[*b*]thiophene (6k)



Reaction Time: 1h.; yield: 55%; mp: 186-189 ºC; R_f = 0.36 in 30% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3791, 3313, 2924, 2854, 2214, 1594, 1498, 1274, 1256, 1212, 1032; ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.54 (d, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 7.17 (s, 1H), 7.11 (s, 1H), 7.08 (s, 1H), 7.04 (t, *J* = 7.7 Hz, 1H), 3.96 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 155.7, 149.5, 148.1, 137.4, 130.1, 129.4, 128.0, 124.1, 123.5, 122.3, 117.7, 114.7, 104.3,

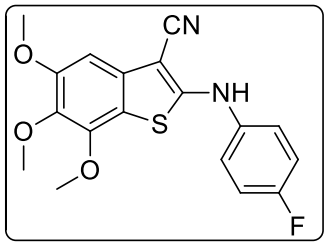
102.5, 89.1, 56.4, 56.3; HR-MS (ESI) Calcd. for $C_{17}H_{13}ClN_2O_2S$ [M+H]: 345.0459, Found: 345.0452; [M+Na]: 367.0278, Found: 367.0274.

3-Cyano--2-[{2-(trifluoromethyl)phenyl}amino]-5,6,7-trimethoxybenzo[*b*]thiophene (6l)



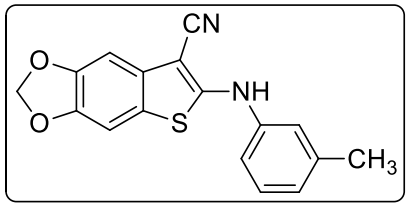
Reaction Time: 1h; yield: 61%; mp: 134-137 ºC; R_f = 0.30 in 20% ethyl acetate in hexanes; IR (KBr): 3430, 3054, 2982, 2262, 1635, 1457, 1265, 889; ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 7.7 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 7.02 (s, 1H), 6.89 (s, 1H), 4.02 (s, 3H), 3.94 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 159.2, 154.4, 147.2, 138.8, 138.5, 133.4, 132.3, 127.2 (q, *J* = 5.2 Hz), 125.1, 123.9 (q, *J* = 271.3 Hz), 122.5, 121.9 (q, *J* = 29.8 Hz), 115.2, 114.3, 98.2, 88.0, 61.5, 60.9, 56.4; HR-MS (ESI) Calcd. for $C_{19}H_{15}F_3N_2O_3S$ [M+Na]: 431.0648, Found: 431.0650.

3-Cyano-2-[(4-fluorophenyl)amino]-5,6,7-trimethoxybenzo[*b*]thiophene (6m)



Reaction Time: 1h; yield: 58%; mp: 174-177 ºC; R_f = 0.23 in 15% in ethyl acetate in hexanes; IR (KBr): 3454, 3258, 2920, 2211, 1511, 1115, 825; ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.33-7.31 (m, 3H), 7.10 (t, *J* = 8.4 Hz, 2H), 6.81 (s, 1H), 4.01 (s, 3H), 3.93 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 161.7, 160.3 (d, *J* = 243.25 Hz), 154.3, 147.3, 138.3, 136.3 (d, *J* = 3.5 Hz), 132.6, 123.1 (d, *J* = 8.8 Hz), 116.7 (d, *J* = 22.8 Hz), 115.6, 113.9, 97.8, 83.8, 61.5, 61.0, 56.5; HR-MS (ESI) Calcd for $C_{18}H_{15}FN_2O_3S$ [M+Na]: 381.0680, Found: 381.0665.

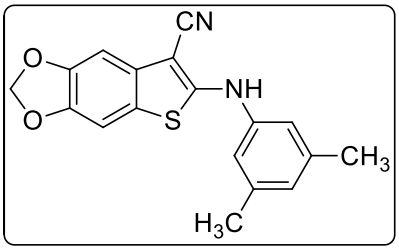
3-Cyano-5,6-methylenedioxy-2-[(3-methylphenyl)amino]benzo[*b*]thiophene (6n)



Reaction Time: 1.5 h; yield: 45%; mp: 201-203 ºC; R_f = 0.36 in 10% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3242, 2921, 2205, 1563, 1473, 1294, 1221, 1039; ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.25-7.21 (m, 1H), 7.13 (brs, 1H), 7.09 (s, 1H), 7.07 (s, 1H), 7.00 (s, 1H), 6.97-6.92 (m, 2H),

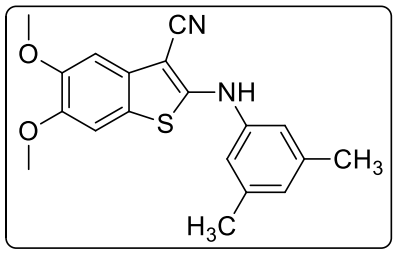
5.97 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 159.0, 147.8, 145.7, 140.3, 140.0, 130.7, 129.7, 125.5, 121.6, 120.2, 116.5, 115.4, 101.9, 101.6, 100.0, 84.7, 21.6; HR-MS (ESI) Calcd. For $C_{17}H_{12}N_2O_2S$ [M+H]: 309.0692, Found: 309.0682.

3-Cyano-2-[(3,5-dimethylphenyl)amino]-5,6-methylenedioxybenzo[*b*]thiophene (6o)



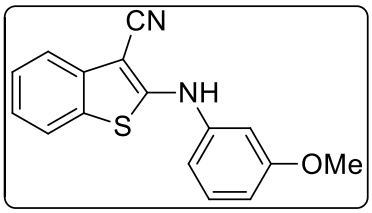
Reaction Time: 1 h; yield: 45%; mp: 197-200 ºC; R_f = 0.22 in 10% ethyl acetate in hexanes; IR (KBr): 3649, 3503, 3447, 2373, 2249, 1830, 1772, 1560, 939, 828, 760; ^{1}H NMR (300 MHz, DMSO) δ = 9.87 (s, 1H), 7.41 (s, 1H), 6.98 (s, 1H), 6.95 (s, 2H) 6.73 (s, 1H), 6.06 (s, 2H), 2.25 (s, 6H); ^{13}C NMR (75 MHz, DMSO) δ = 158.9, 147.1, 145.0, 141.2, 138.5, 130.7, 125.2, 121.2, 117.0, 114.8, 102.6, 101.3, 98.7, 84.1, 20.9; HR-MS (ESI) Calcd for $C_{18}H_{14}N_2O_2S$ [M+H]: 323.0849, Found: 323.0858.

3-Cyano-2-((3,5-dimethylphenyl)amino)-5,6-dimethoxybenzo[*b*]thiophene (6p)



Reaction Time: 1 h; yield: 45%; mp: 168-170 ºC; R_f = 0.30 in 20% ethyl acetate in hexanes; IR (KBr): ν (cm^{-1}) = 3658, 3294, 2938, 2197, 2063, 1561, 1491, 1288, 1035; ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.05 (s, 1H), 7.04 (s, 1H), 6.96 (brs, 1H), 6.92 (s, 2H), 6.80 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 2.33 (s, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ = 158.9, 149.4, 147.5, 140.2, 139.8, 129.8, 126.5, 121.0, 117.2, 115.6, 104.6, 102.3, 84.5, 56.5, 56.3, 21.5; HR-MS (ESI) Calcd for $C_{19}H_{18}N_2O_2S$ [M+H]: 339.1162, Found: 339.1153.

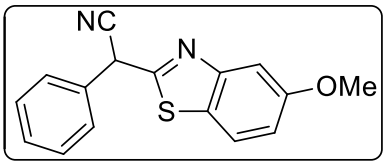
3-Cyano-2-(3-methoxyphenylamino)benzo[*b*]thiophene (6q)



Reaction Time: 2 h; yield: 19%; R_f: 0.38 in 15% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.36 - 7.24 (m, 3H), 6.99 – 6.90 (m, 2H), 6.77 (d, *J* = 8.4 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.0,

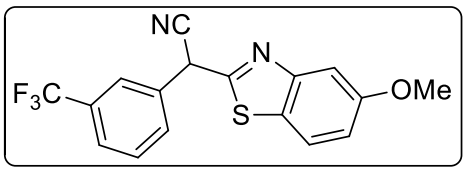
160.1, 141.2, 136.5, 130.7, 129.5, 126.2, 123.9, 122.0, 120.0, 115.22, 112.3, 110.7, 105.9, 84.4, 55.6; HR-MS (ESI) Calcd for $C_{16}H_{12}N_2OS$ [M+H]: 281.0743, Found: 281.0834.

2-(5-Methoxybenzo[*d*]thiazol-2-yl)-2-phenylacetonitrile (74q & 74q′)



Reaction Time: 2 h; yield: 20%; R_f: 0.35 in 15% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ = (Mixture of 3-isomers 1: 0.1 : 0.1)7.67 (d, *J* = 8.8 Hz, 1H), 7.60 - 7.52 (m, 3H), 7.48 - 7.38 (m, 3H), 7.06 (dd, *J* = 8.8, 2.0 Hz, 1H), 5.63 (s, 1H), 3.88 (s, 3H). (Major Isomer only); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.7, 159.4, 153.8, 132.9, 129.6, 129.3, 129.1, 127.9, 121.9, 116., 110.6, 105.8, 55.6, 41.9. (Major Isomer only); HR-MS (ESI) Calcd for $C_{16}H_{12}N_2OS$ [M+H]: 281.0743, Found: 281.0920.

2-(5-Methoxybenzo[d]thiazol-2-yl)-2-(3-(trifluoromethyl)phenyl)acetonitrile (74r & 74r′)



Reaction Time: 2 h; yield: 22%; R_f: 0.40 in 20% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 - 7.76 (m, 2H), 7.74 – 7.66 (m, 2H), 7.62 - 7.53 (m, 1H), 7.57 - 7.53(m, 1H), 7.11 - 7.06 (m, 1H), 5.69 (s, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ was very complicated. However, the characteristic peak of benzo[*b*]thiophene was not found in the spectrum (80 ppm); HR-MS (ESI) Calcd for $C_{17}H_{11}F_3N_2OS$ [M+H]: 349.0617, Found: 349.0792.

4.9. Crystal Data

Crystallographic data of **6a** in CH_2Cl_2/*n*-hexane: $C_{17}H_{14}N_2O_2S$, Mw = 310.38, monoclinic, space group $P2_1/c$, a = 11.7047 (2) Å, b = 10.3186 (2) Å , c = 13.6857 (2) Å , $\alpha = 90^o$, $\beta = 113.046\ (2)^o$, $\gamma = 90^o$, V = 1520.99 (6) Å, Z = 4, Dcalc = 1.355 mg/m^3, T = 293 K, R1 = 0.0443 {I > 2σ (I)}, wR2 = 0.1241, GOF = 1.056.

Crystallographic data of **6b** in CH_2Cl_2/*n*-hexane: $C_{17}H_{14}N_2O_2S$, Mw = 310.36, orthorhombic, space group Pbca, a = 14.4456 (3) Å, b = 9.07642 (17) Å , c = 22.7259 (5) Å , $\alpha = 90^o$, $\beta = 90^o$, $\gamma = 90^o$, V = 12979.69 (11) Å, Z = 8, Dcalc = 1.384 mg/m^3, T = 293 K, R1 = 0.0930{I > 2σ (I)}, wR2 = 0.2464, GOF = 1.165.

4.10. 1H & 13C Spectrum of Selected Compounds

Figure 4.4a. ^{1}H NMR Spectrum of 39a in $CDCl_3$ at 300 MHz

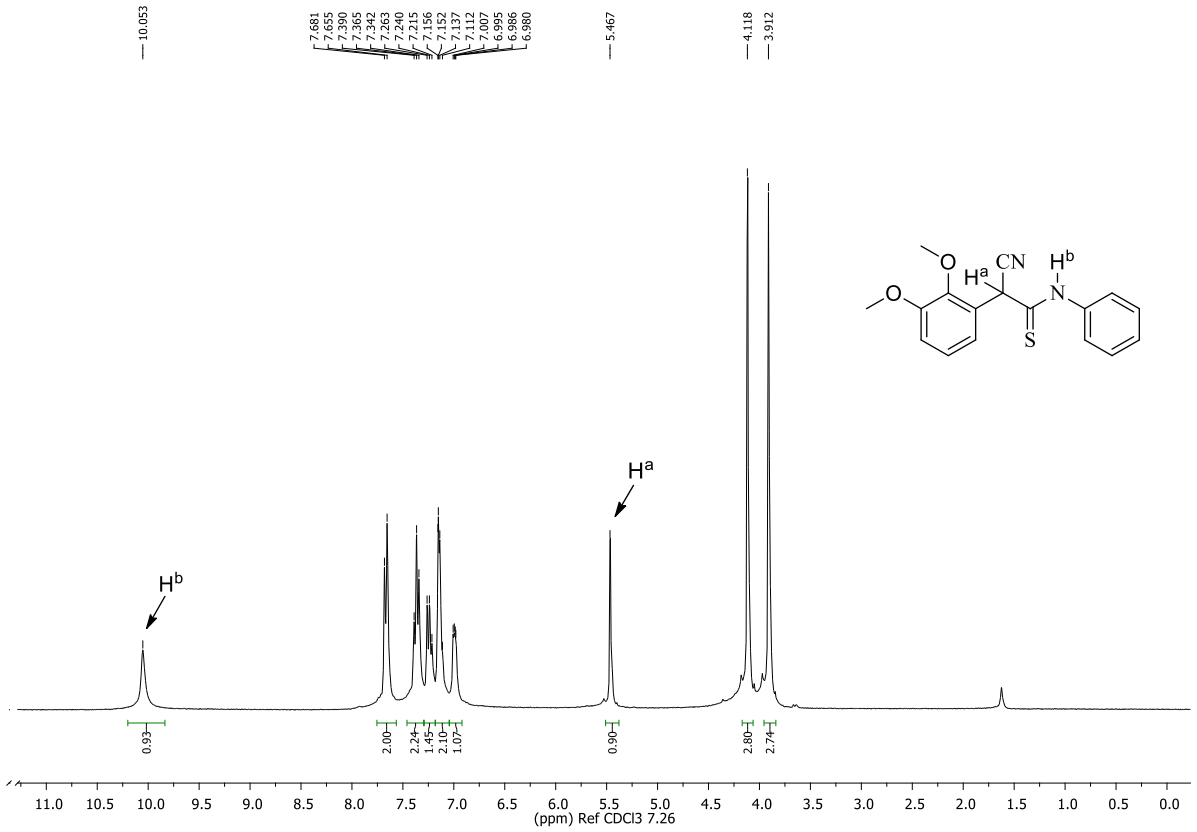


Figure 4.4b. ^{13}C NMR of Spectrum of 39a in $CDCl_3$ at 175 MHz

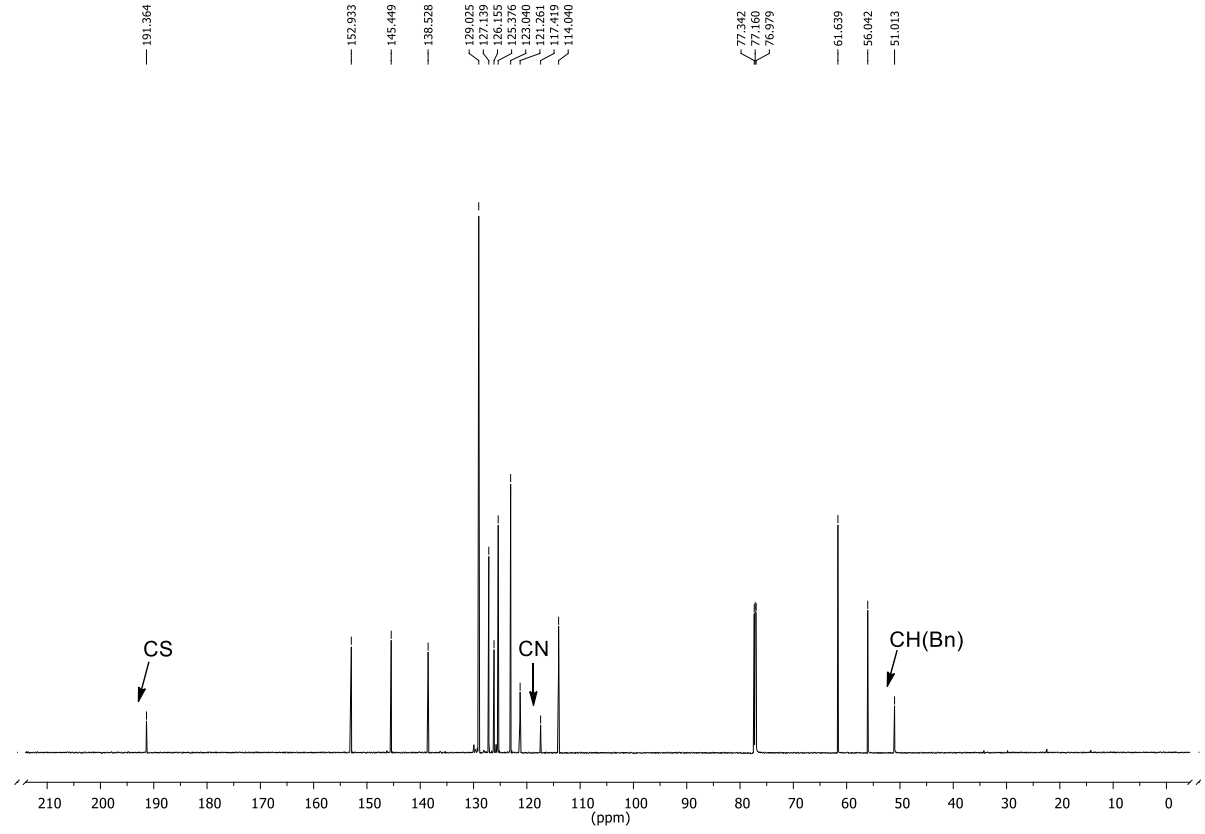


Figure 4.5a. ^{1}H NMR Spectrum of 39e in DMSO at 300 MHz

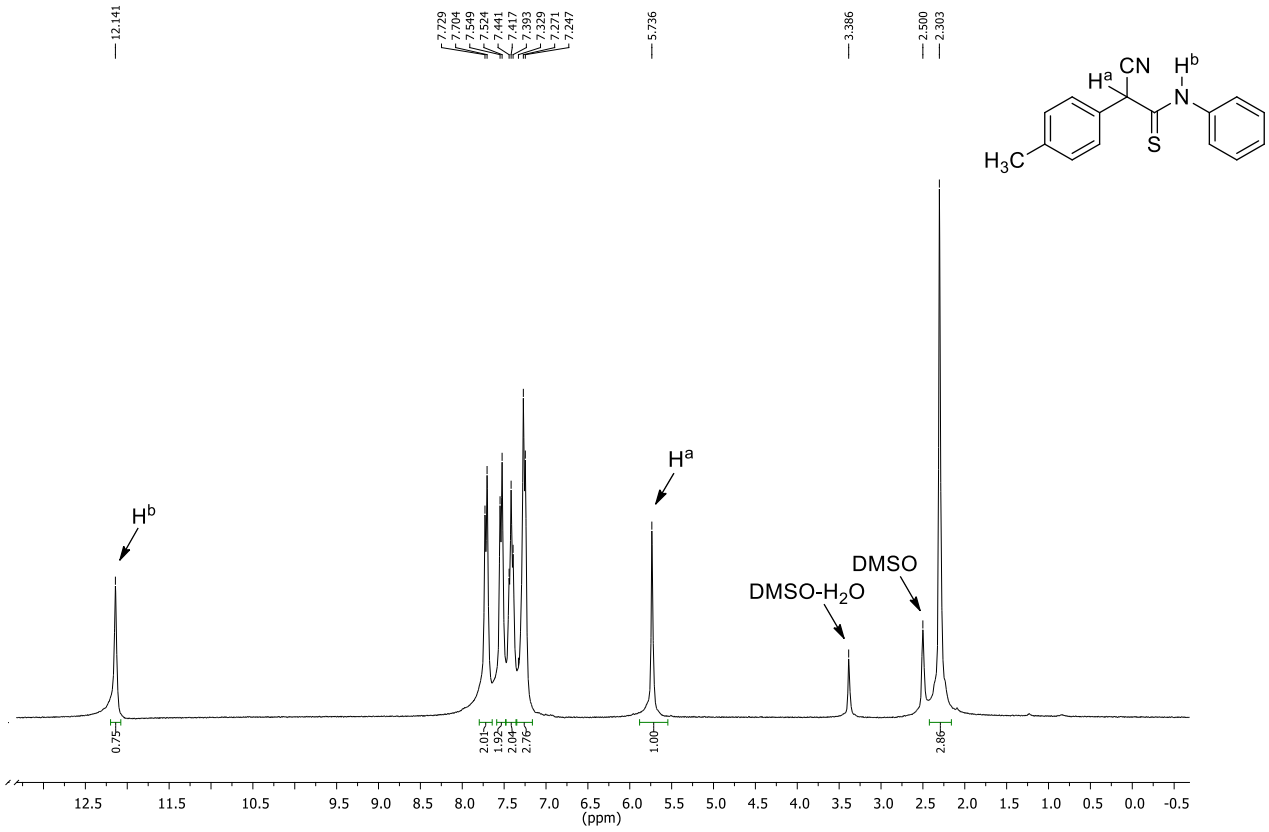


Figure 4.5b. ^{13}C NMR Spectrum of 39e in DMSO at 75 MHz

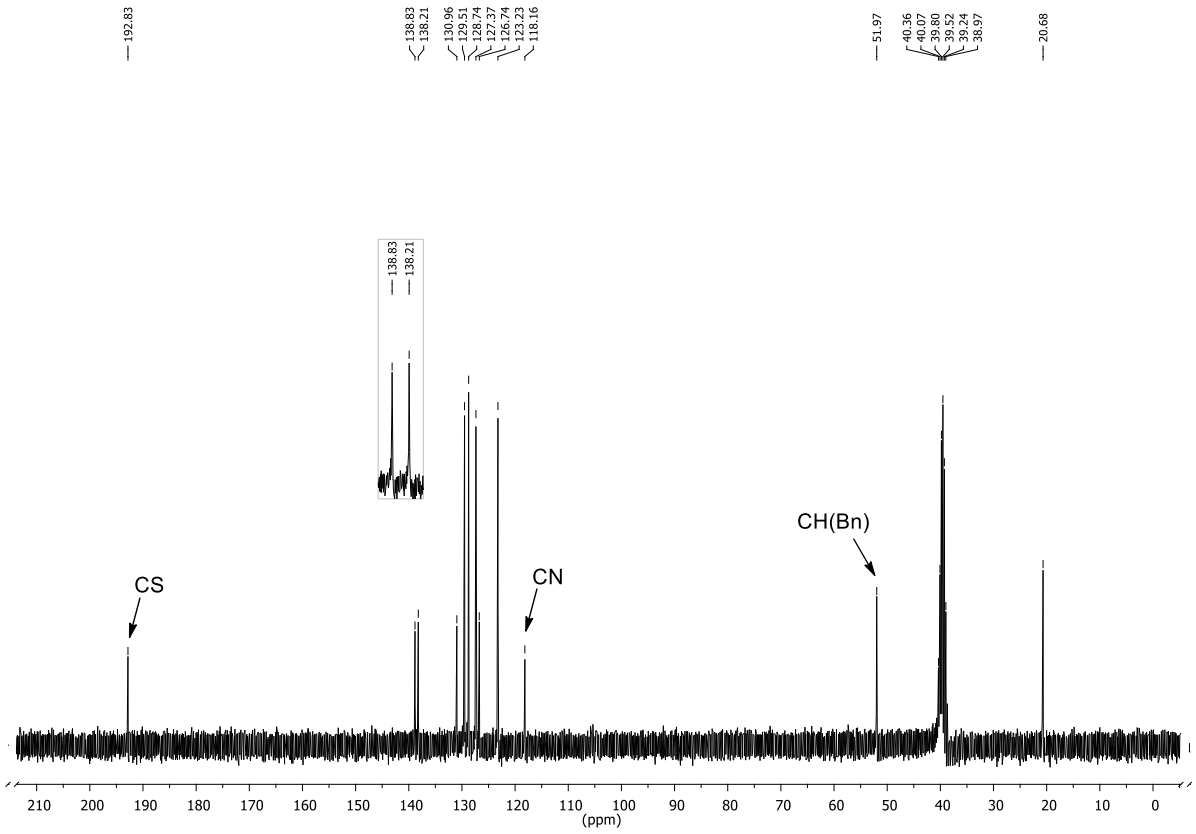


Figure 4.6a. ^{1}H NMR Spectrum of 39h^{1} in $CDCl_3$ at 400 MHz

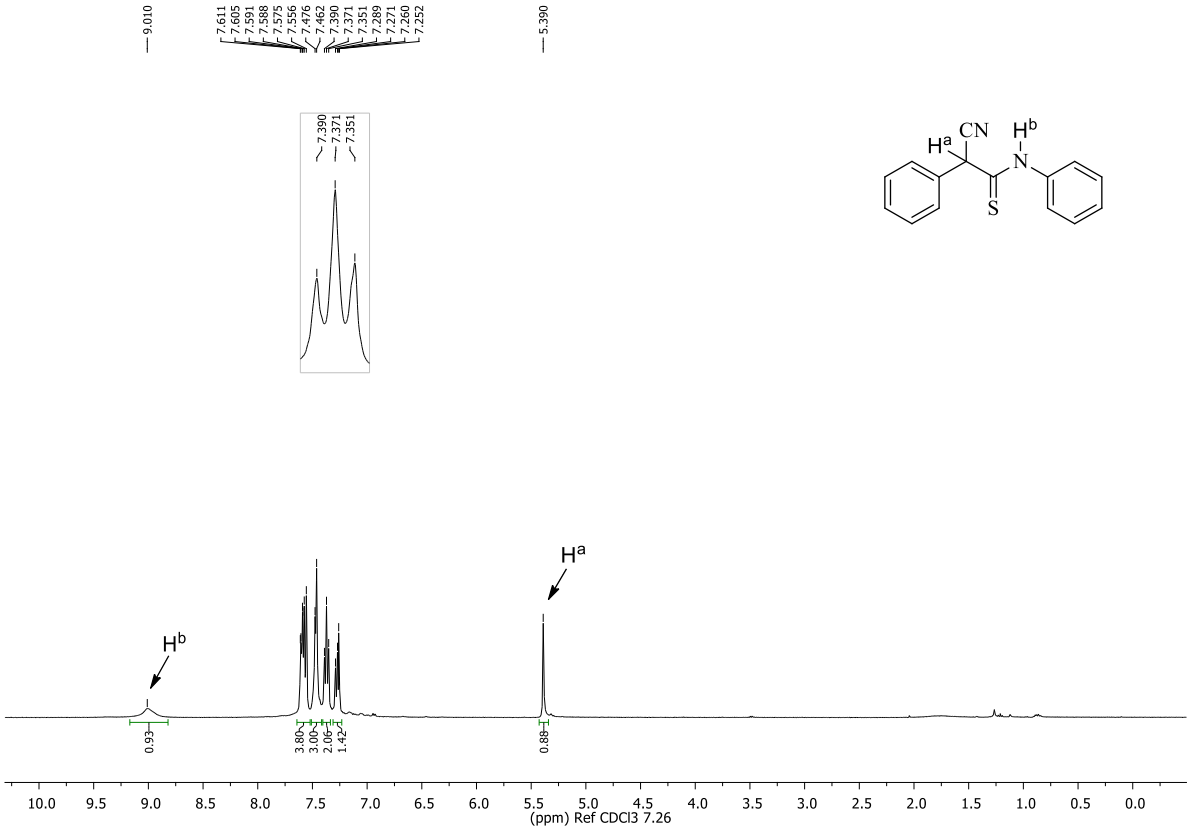


Figure 4.6b. ^{13}C NMR Spectrum of 39h^{1} in $CDCl_3$ at 175 MHz

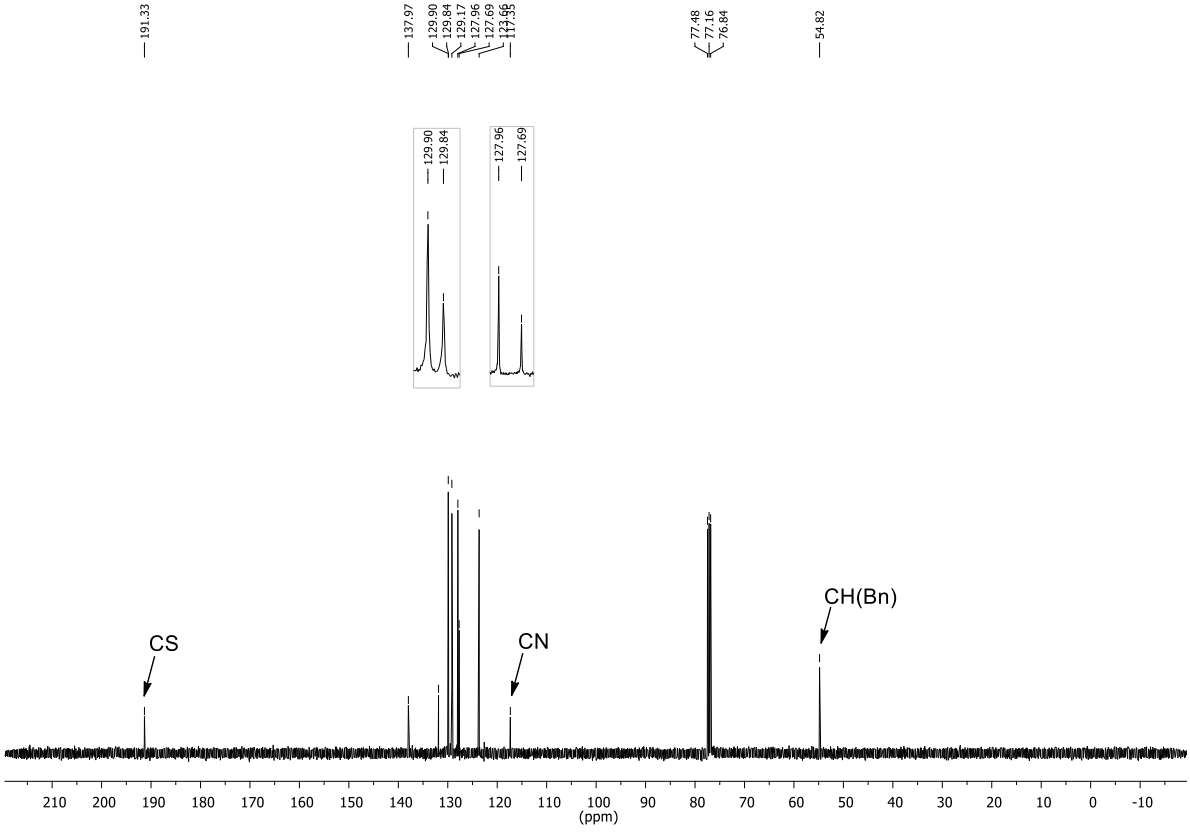


Figure 4.7a.^{1}H NMR Spectrum of 39i in DMSO at 700 MHz

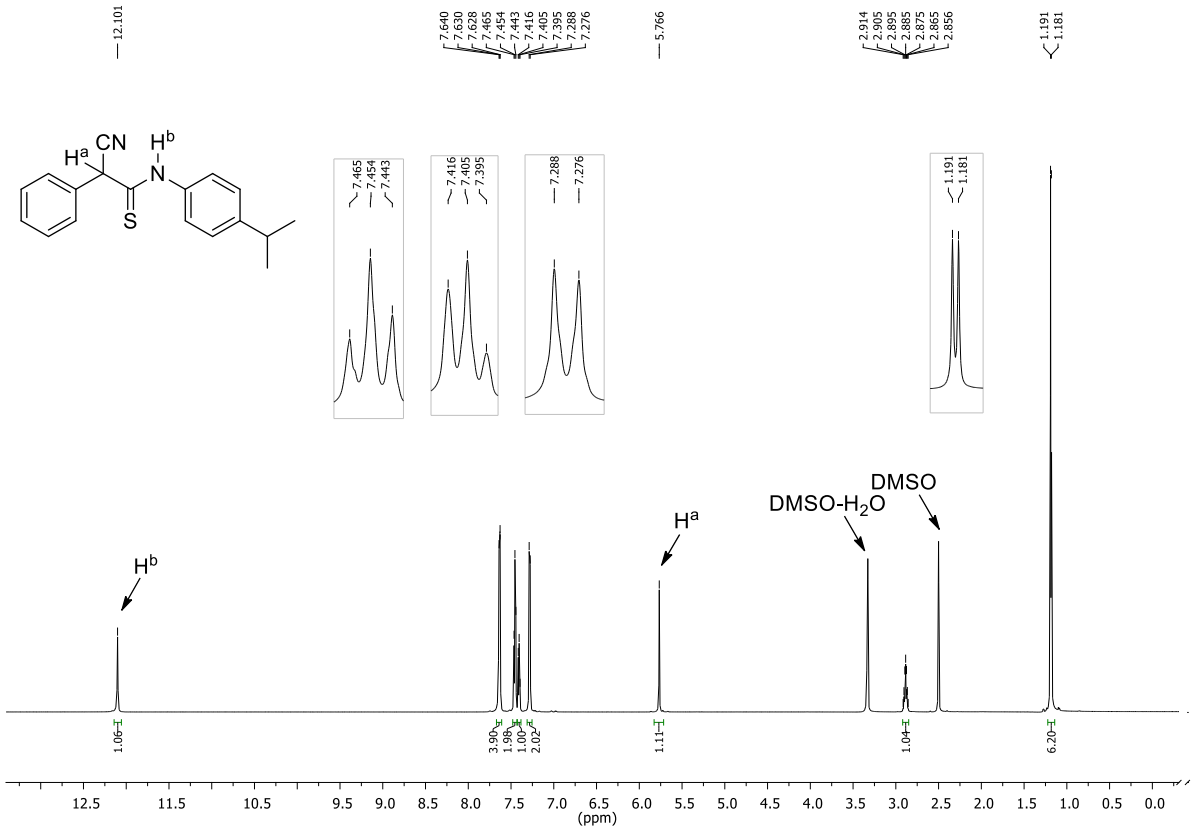


Figure 4.7b. ^{13}C NMR Spectrum of 39i in $CDCl_3$ at 175 MHz

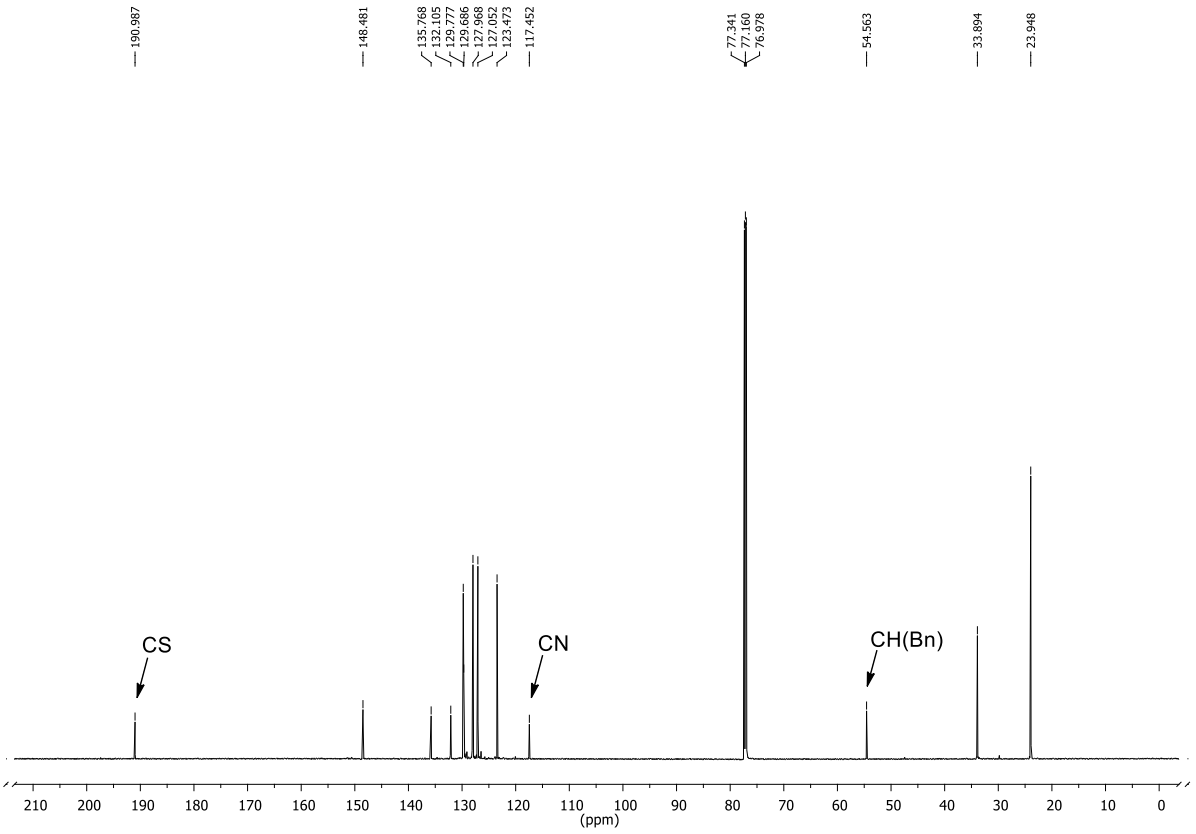


Figure 4.8a. ^{1}H NMR Spectrum of 39j in DMSO at 300 MHz

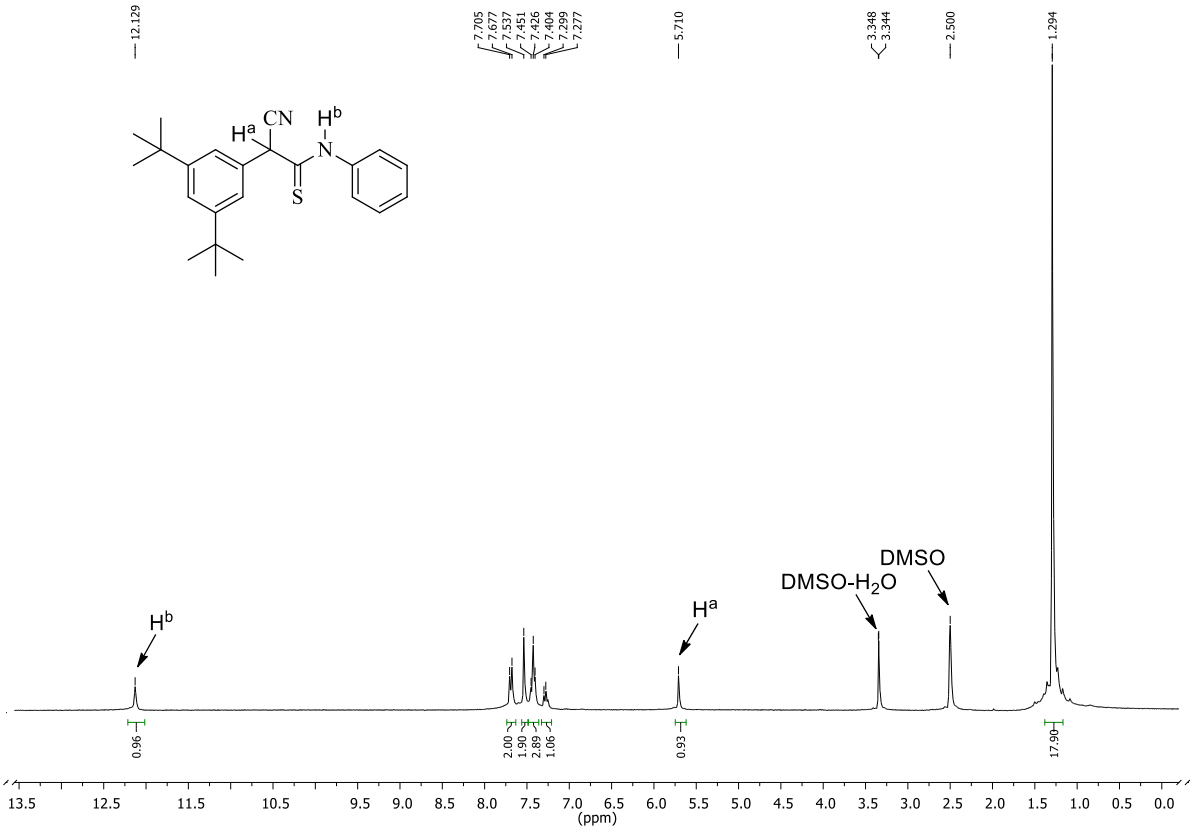


Figure 4.8b. ^{13}C NMR Spectrum of 39j in $CDCl_3$ at 175 MHz

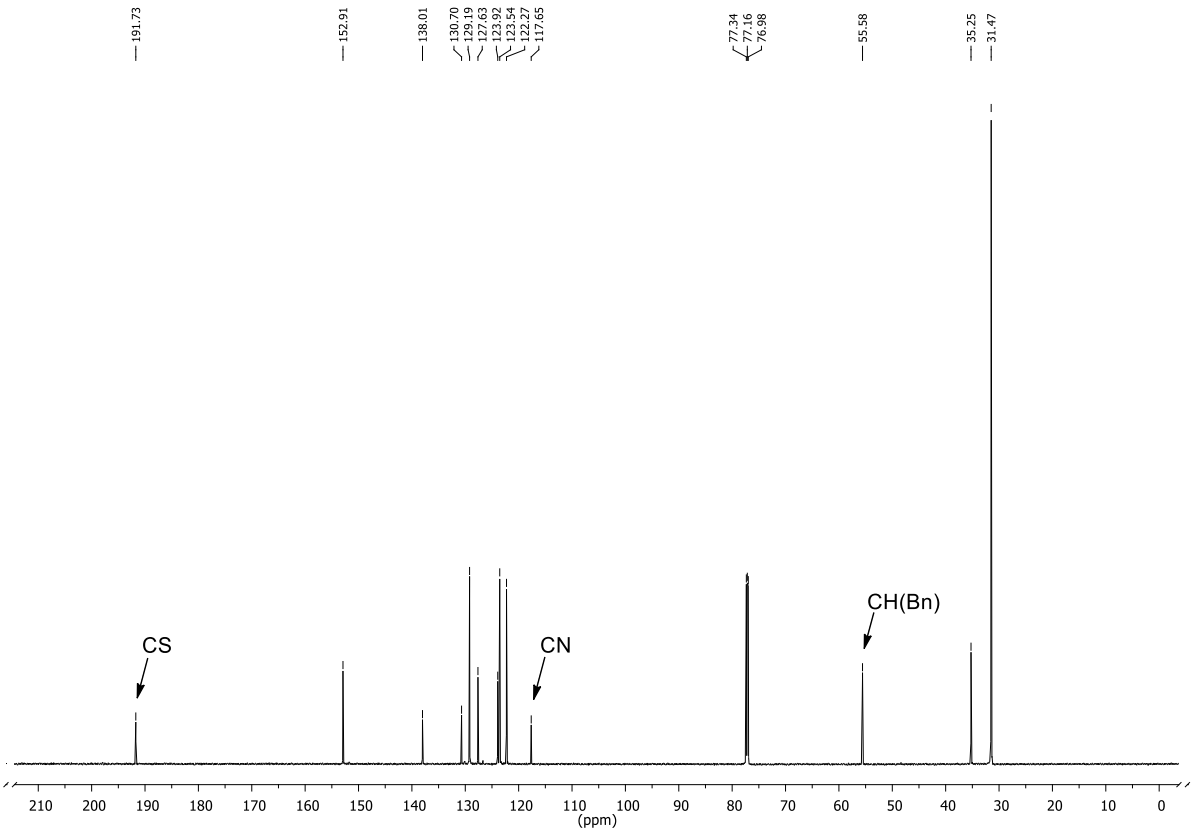


Figure 4.9a. ^{1}H NMR Spectrum of 39l in $CDCl_3$ at 400 MHz

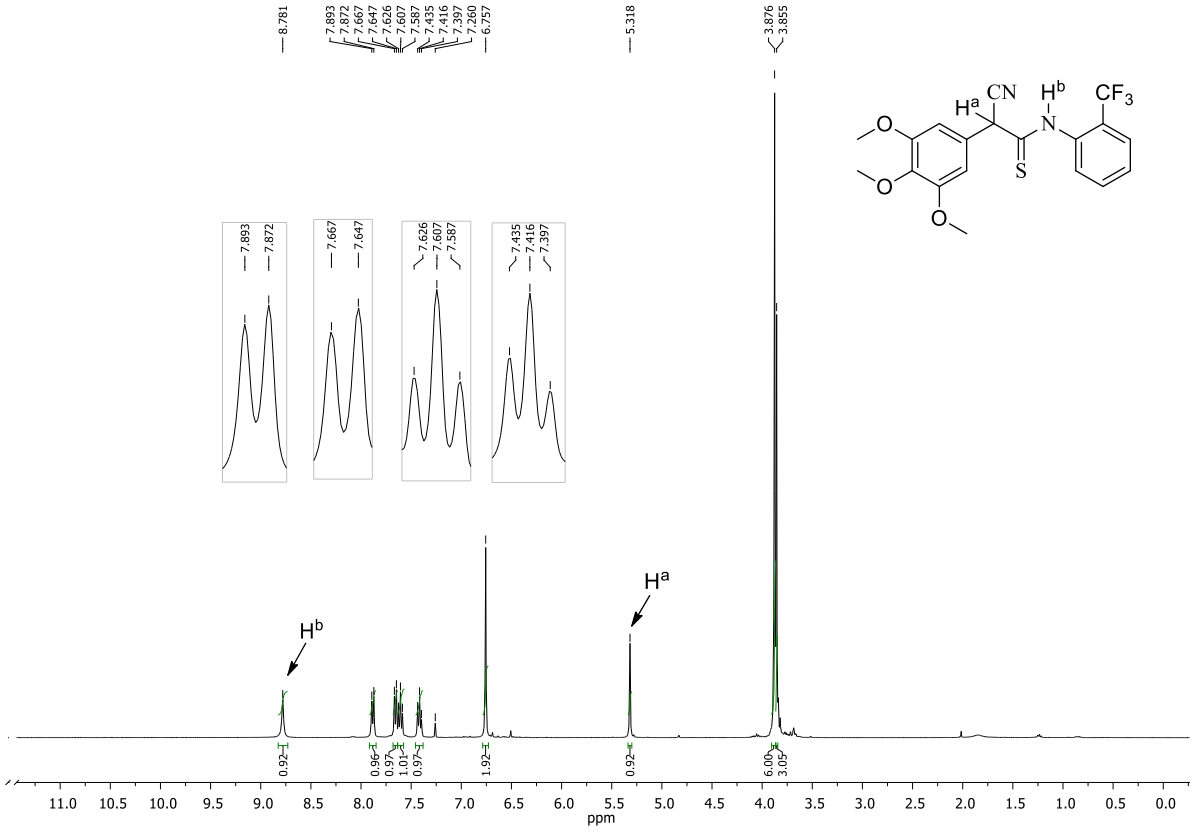


Figure 4.9b. ^{13}C NMR Spectrum of 39l in $CDCl_3$ at 175 MHz

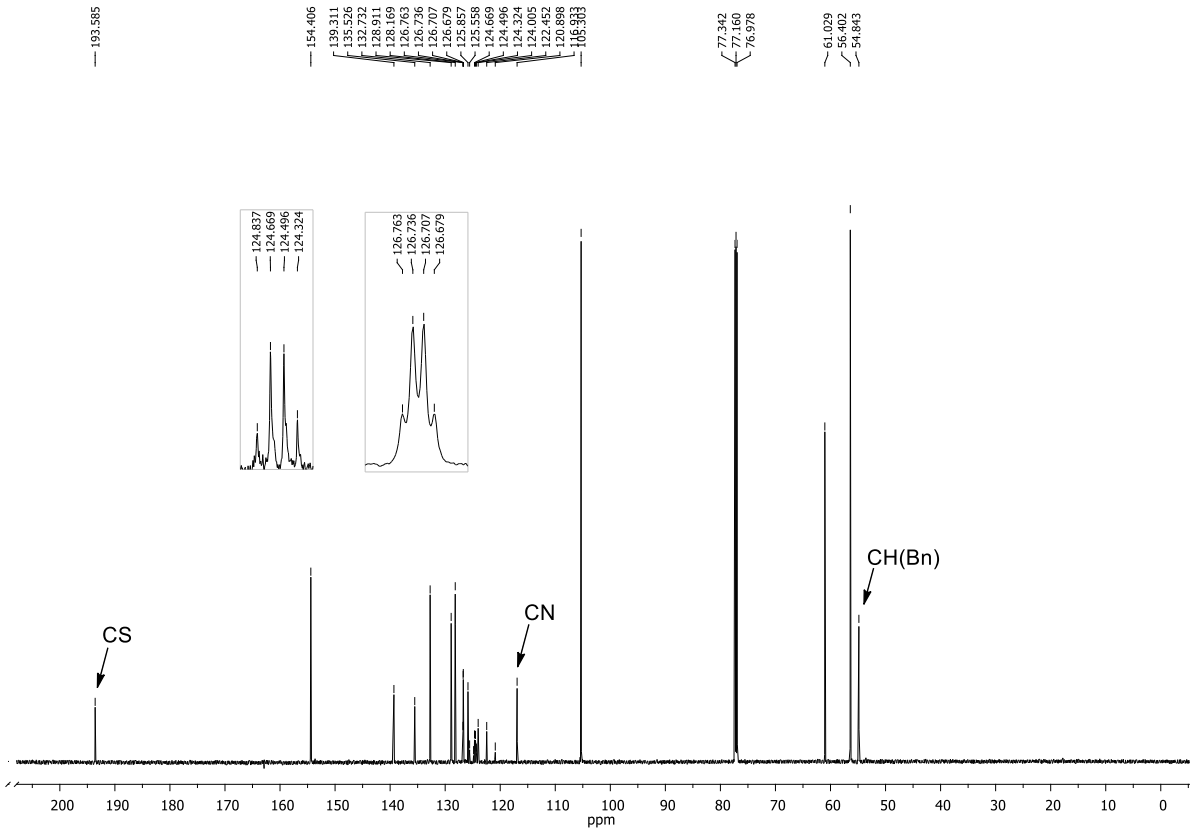


Figure 4.10a. ^{1}H NMR Spectrum of 39p in DMSO at 700 MHz

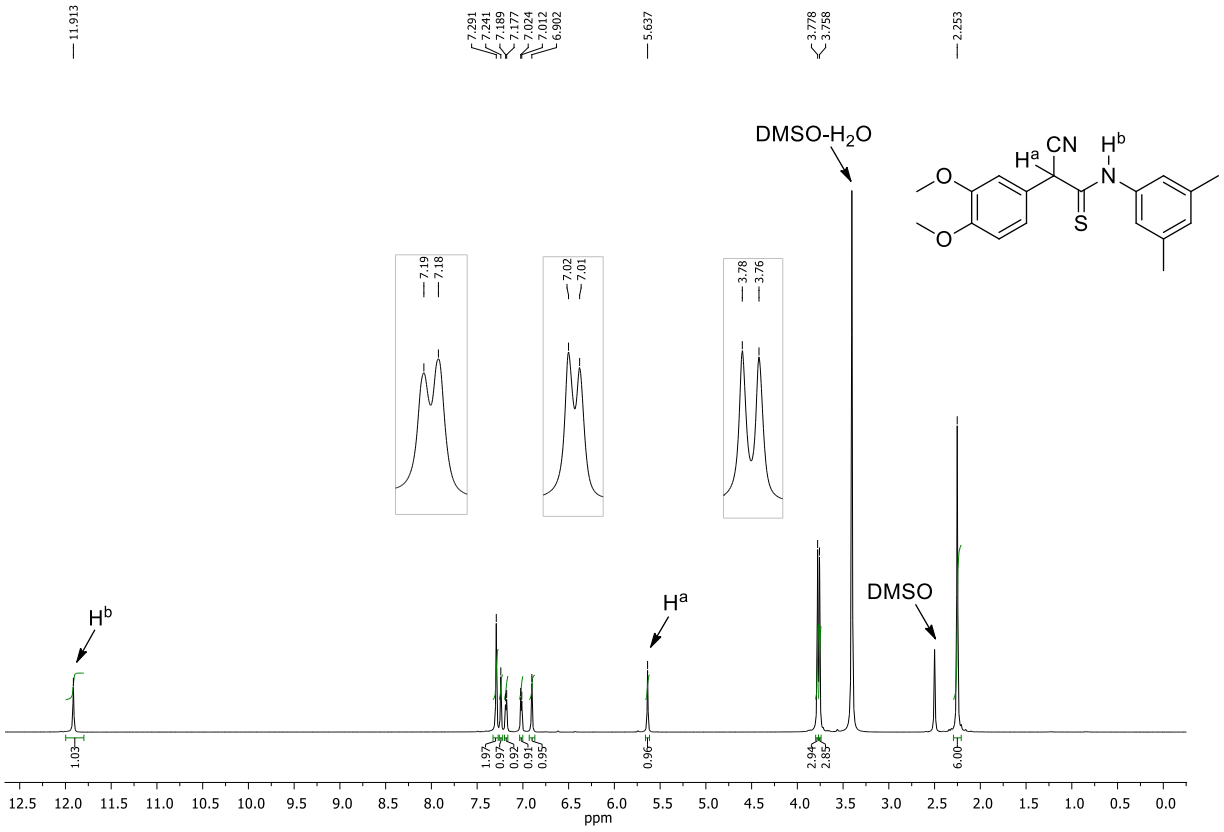


Figure 4.10b. ^{13}C NMR Spectrum of 39p in DMSO at 175 MHz

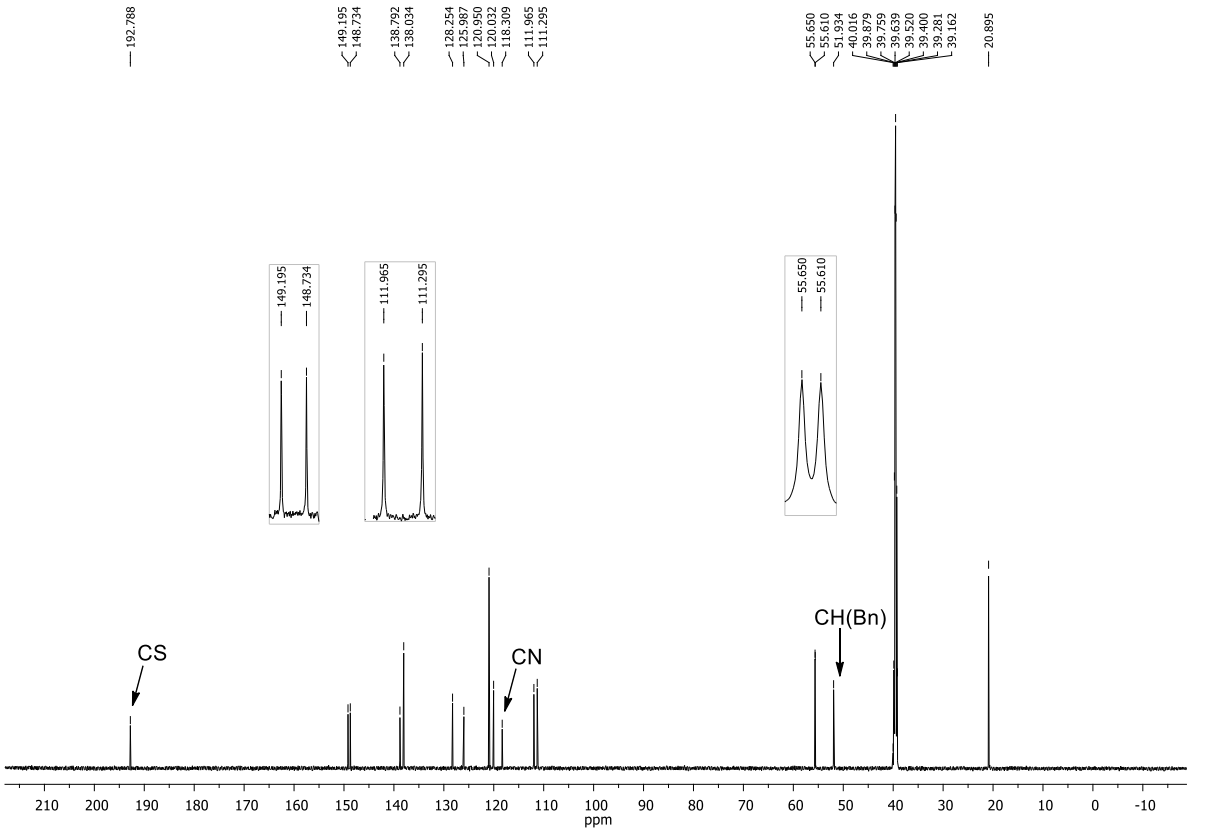


Figure 4.11a. ^{1}H NMR Spectrum of 39q in $CDCl_3$ at 400 MHz

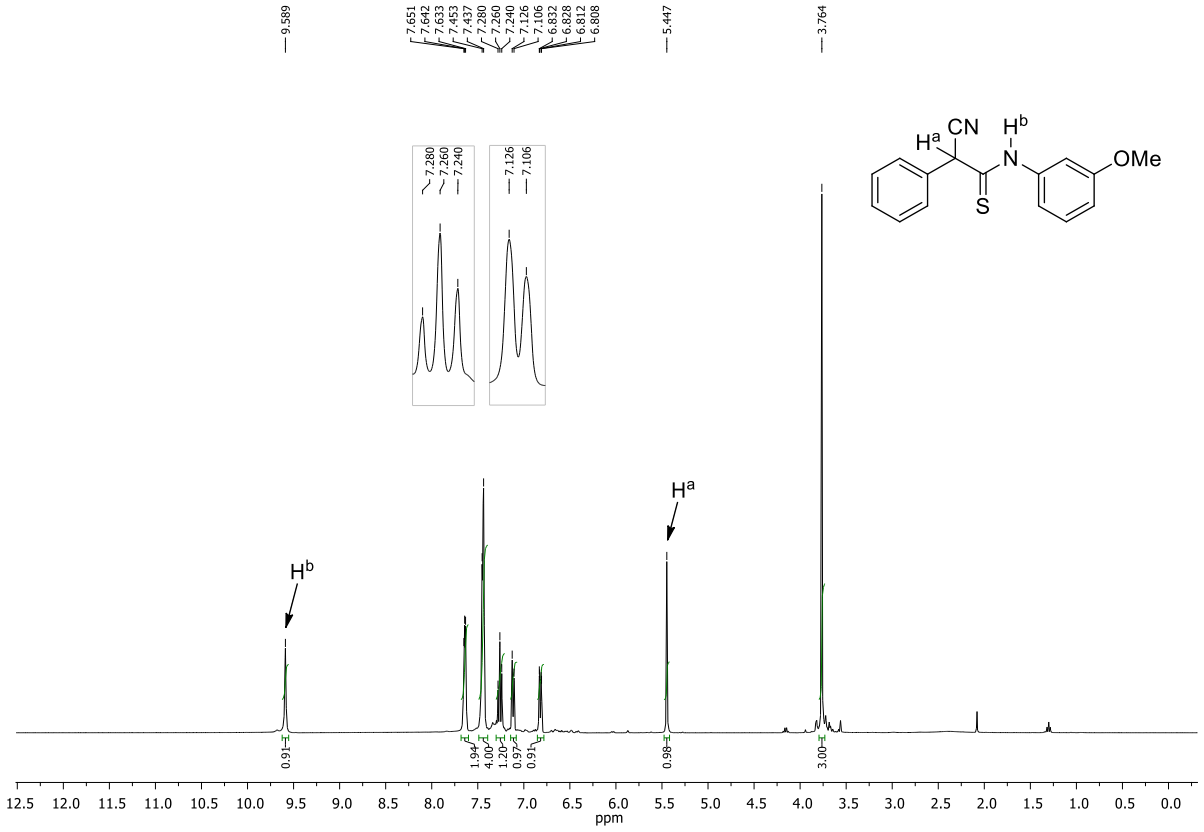


Figure 4.11b. ^{13}C NMR Spectrum of 39q in $CDCl_3$ at 100 MHz

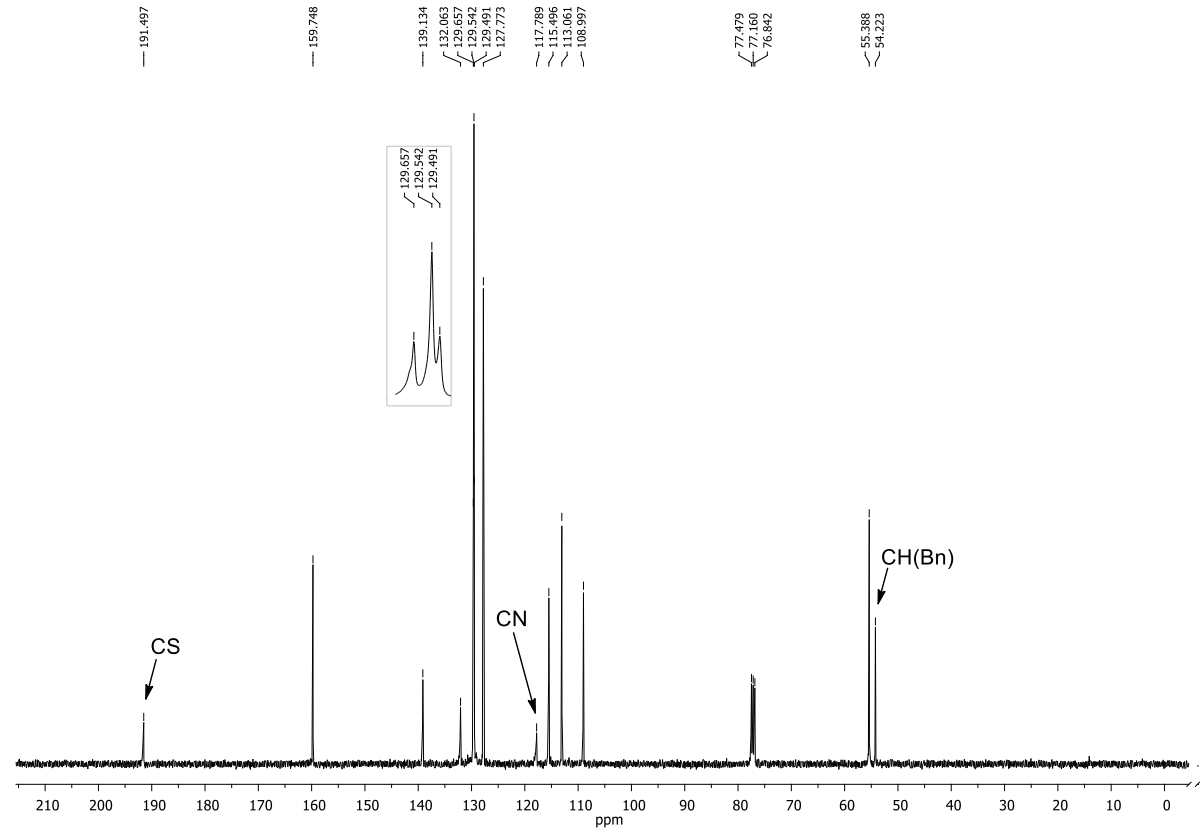


Figure 4.12a. ^{1}H NMR Spectrum of 39r in $CDCl_3$ at 400 MHz

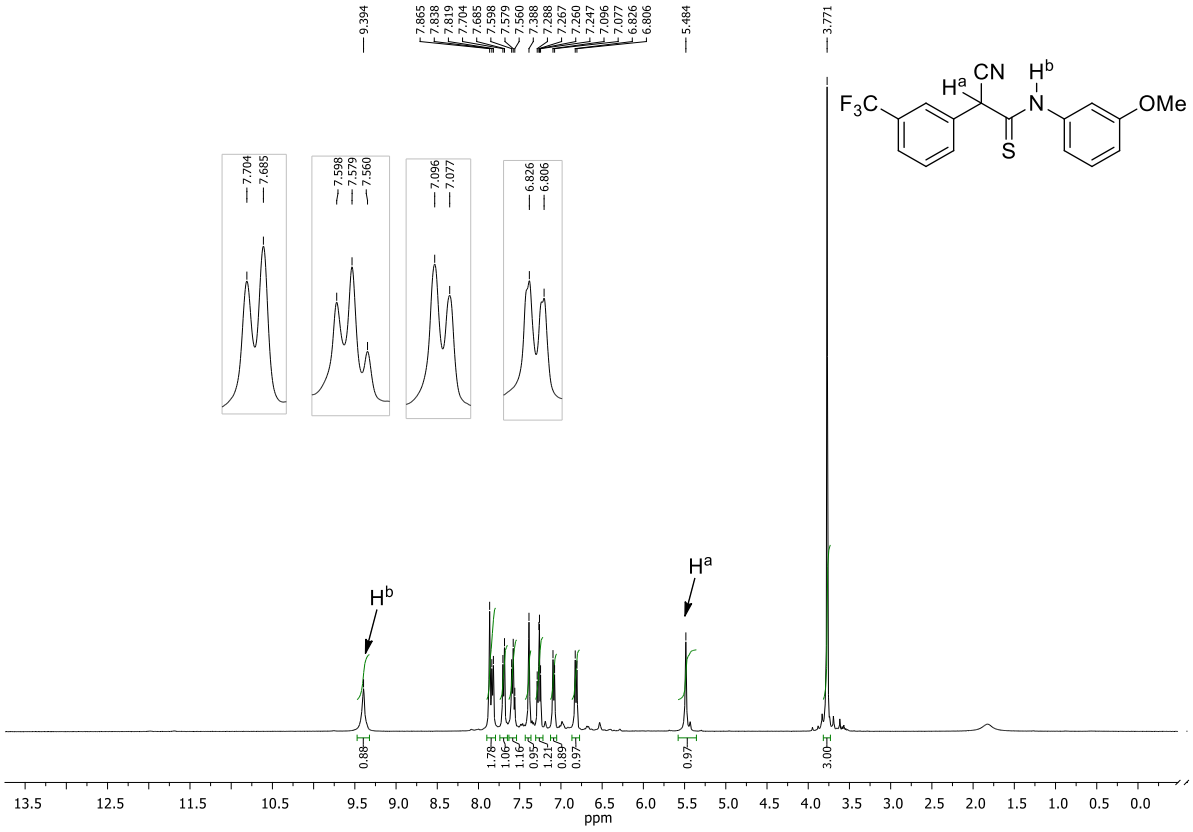


Figure 4.12b. ^{13}C NMR Spectrum of 39r in $CDCl_3$ at 100 MHz

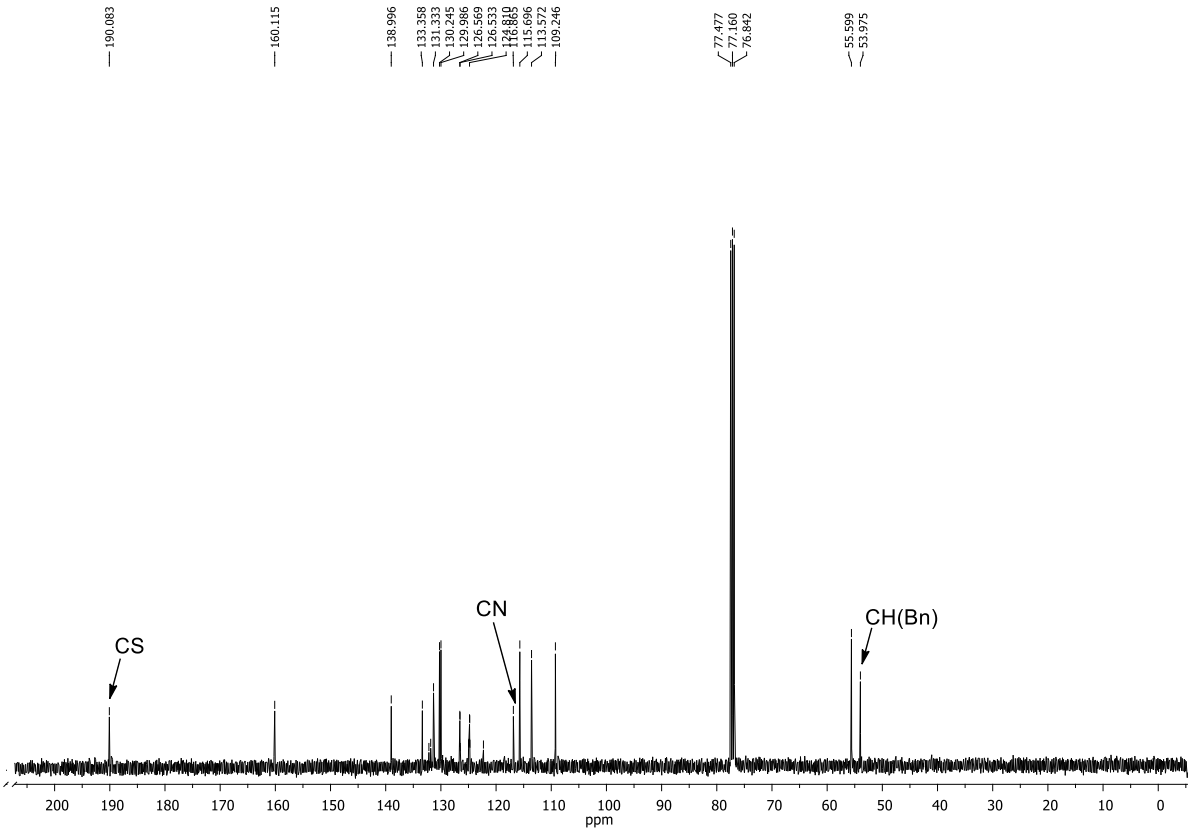


Figure 4.13a. ^{1}H NMR spectrum of 6a in DMSO at 700 MHz

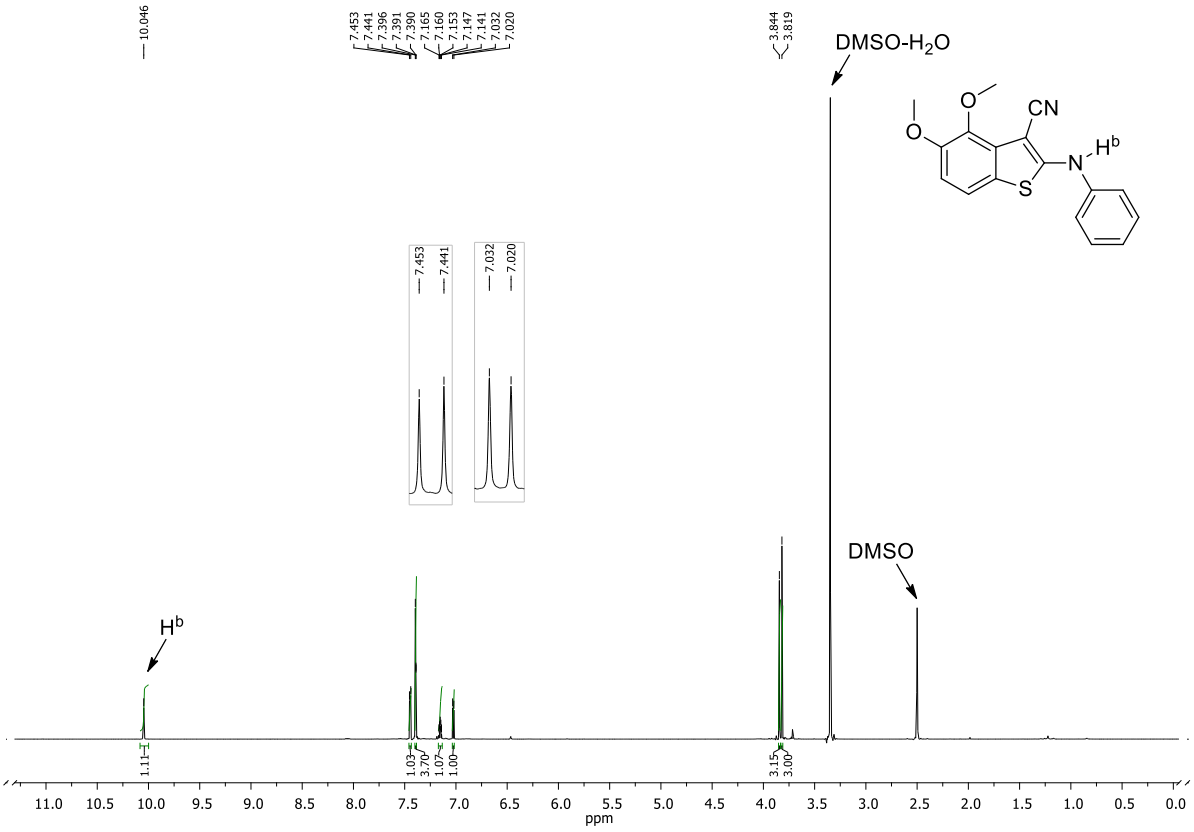


Figure 4.13b. ^{13}C NMR Spectrum of 6a in $CDCl_3$ at 175 MHz

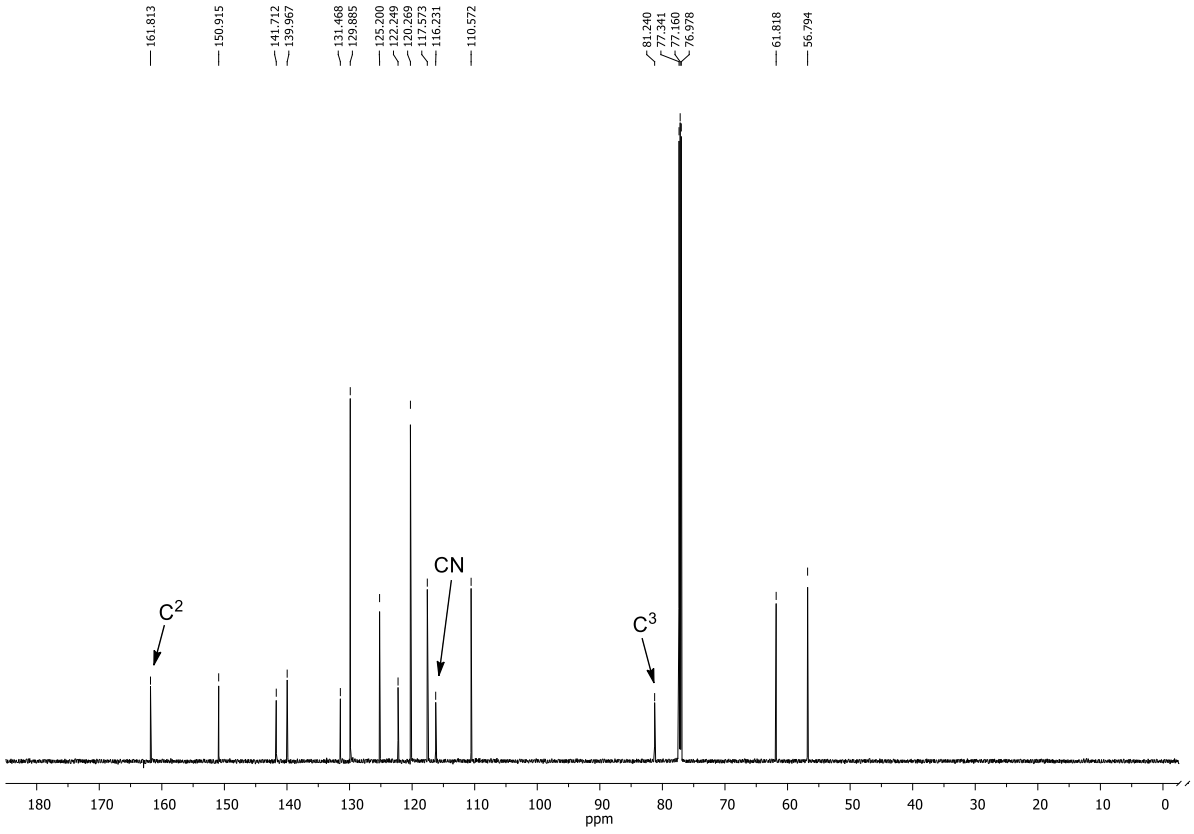
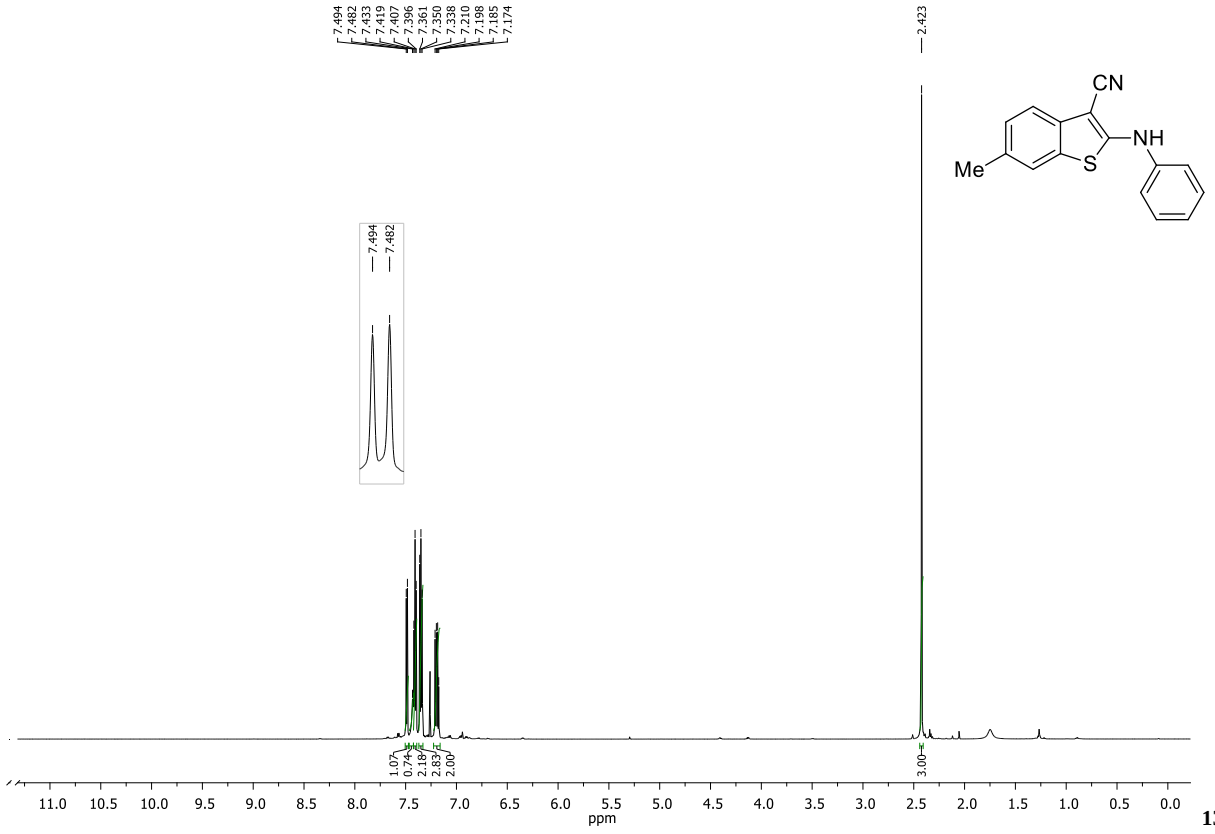


Figure 4.14a. ^{1}H NMR Spectrum of 6e in $CDCl_3$ at 700 MHz



^{13}C

Figure 4.14b. ^{13}C NMR Spectrum of 6e in $CDCl_3$ at 100 MHz

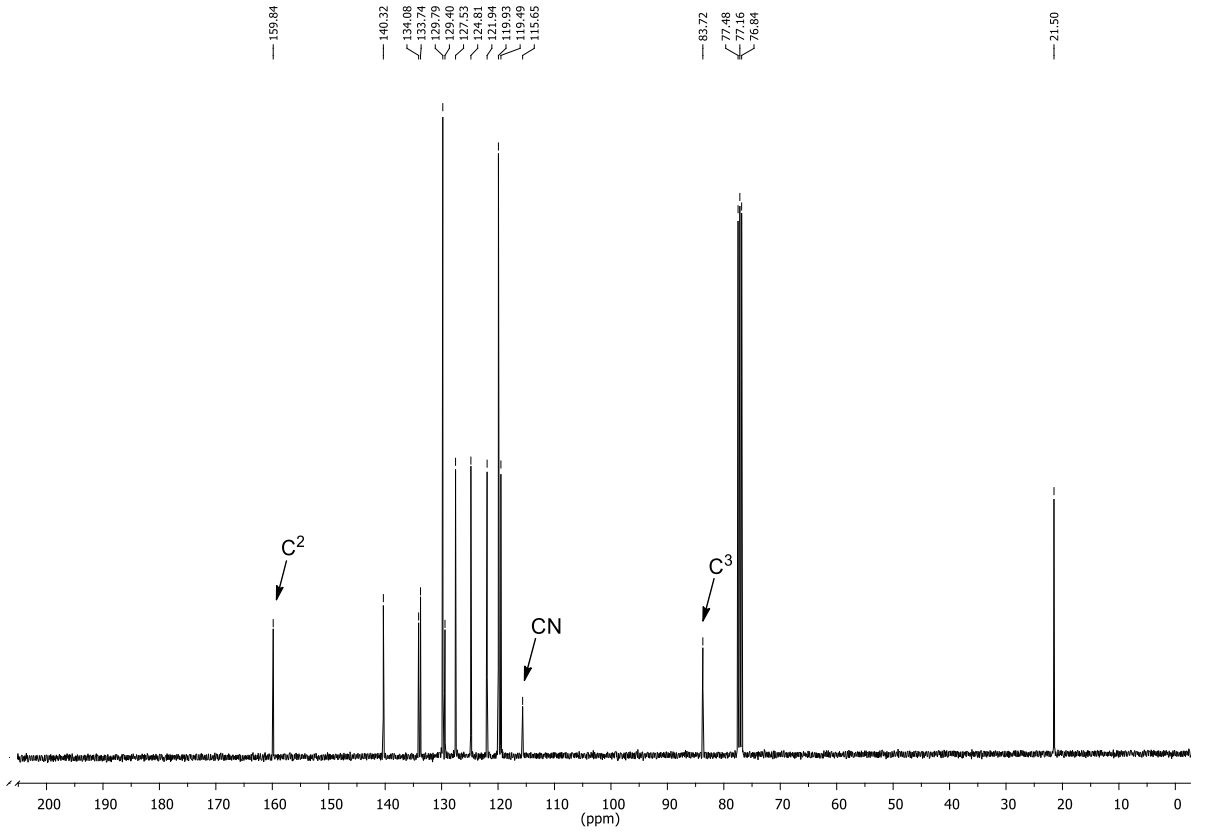


Figure 4.15a. ^{1}H NMR Spectrum of 6h^{2} in $CDCl_3$ at 400 MHz

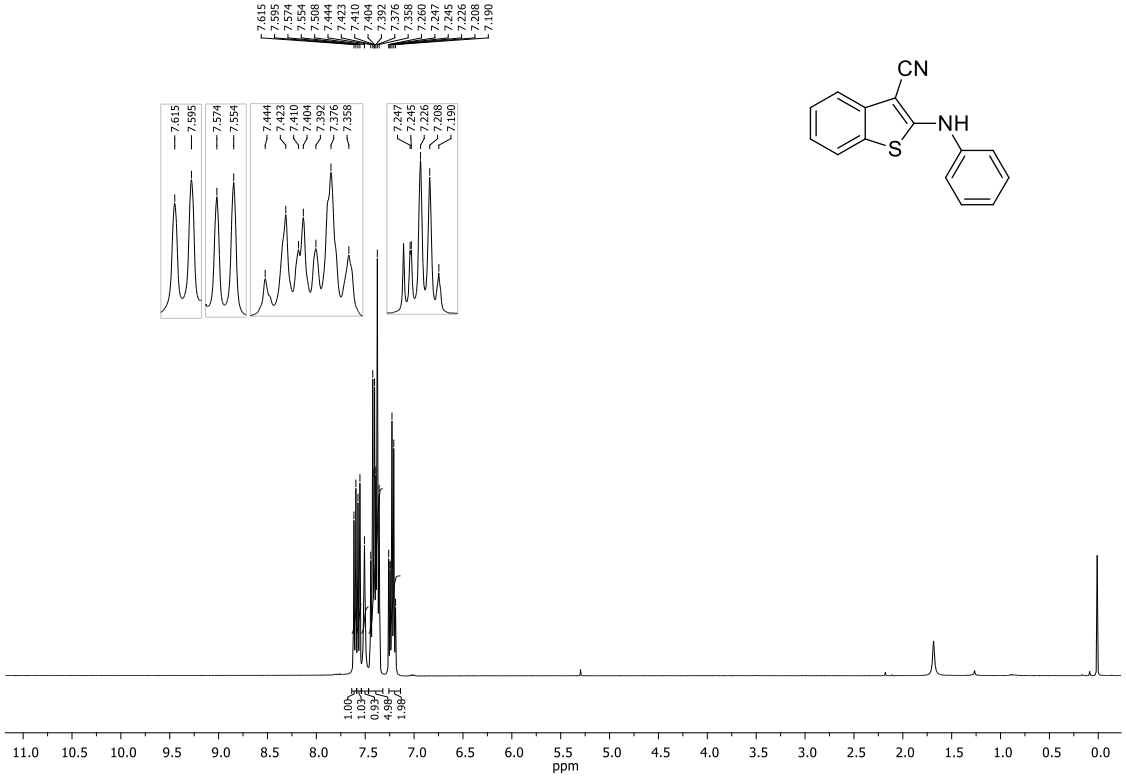


Figure 4.15b. ^{13}C NMR Spectrum of 6h^{2} in $CDCl_3$ at 100 MHz

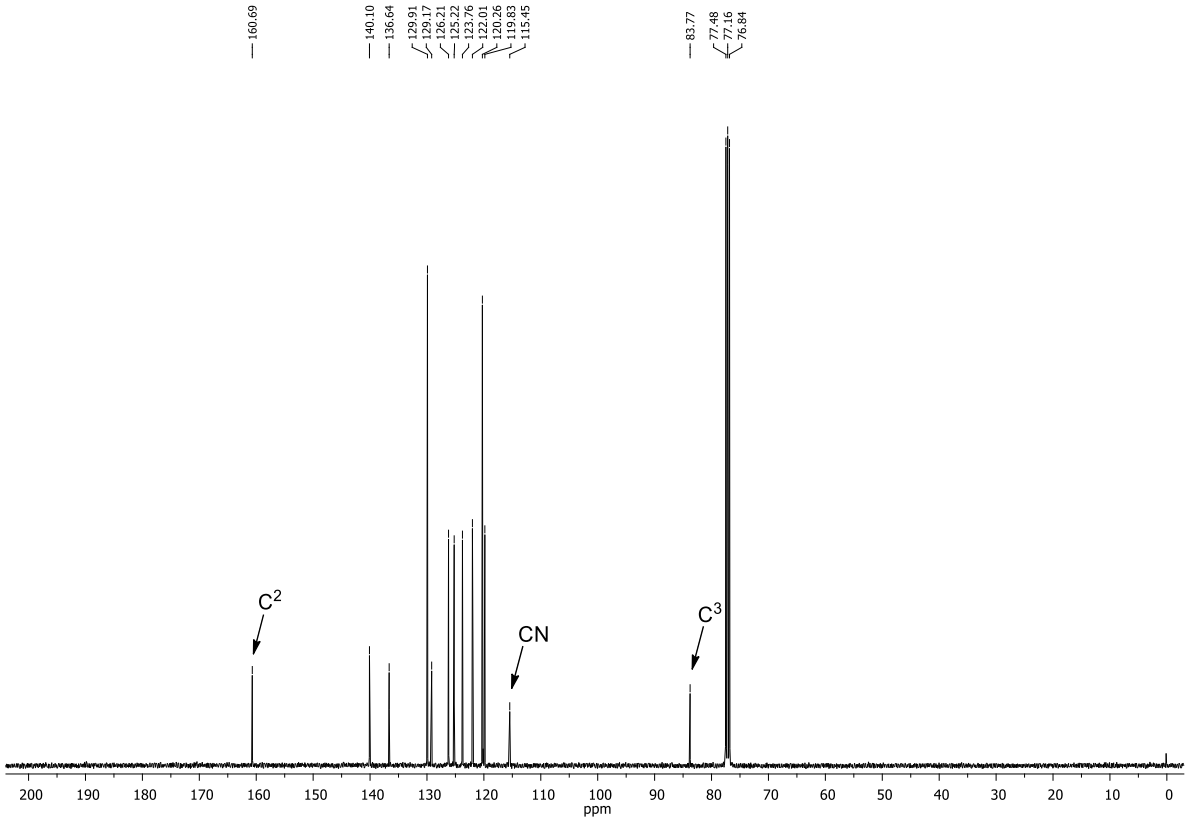


Figure 4.16a. ^{1}H NMR Spectrum of 6i in $CDCl_3$ at 700 MHz

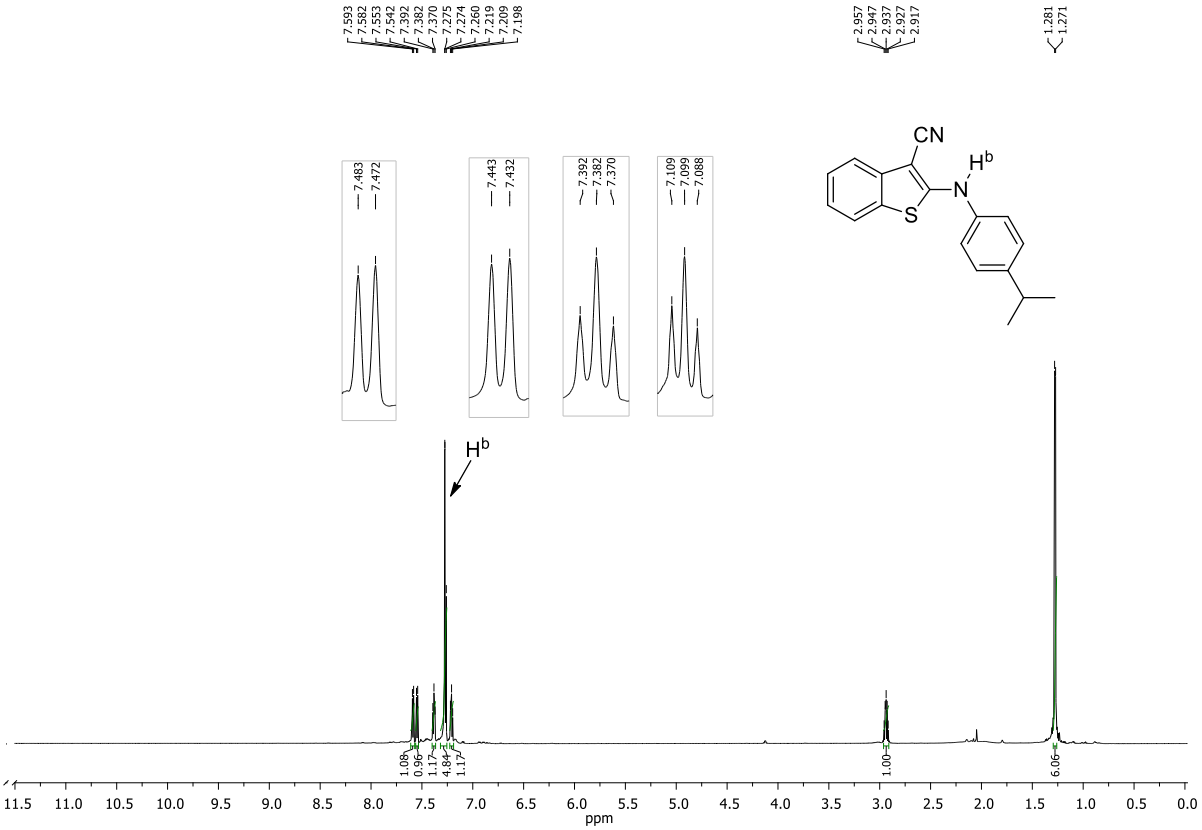


Figure 4.16b. ^{13}C NMR Spectrum of 6i in $CDCl_3$ at 100 MHz

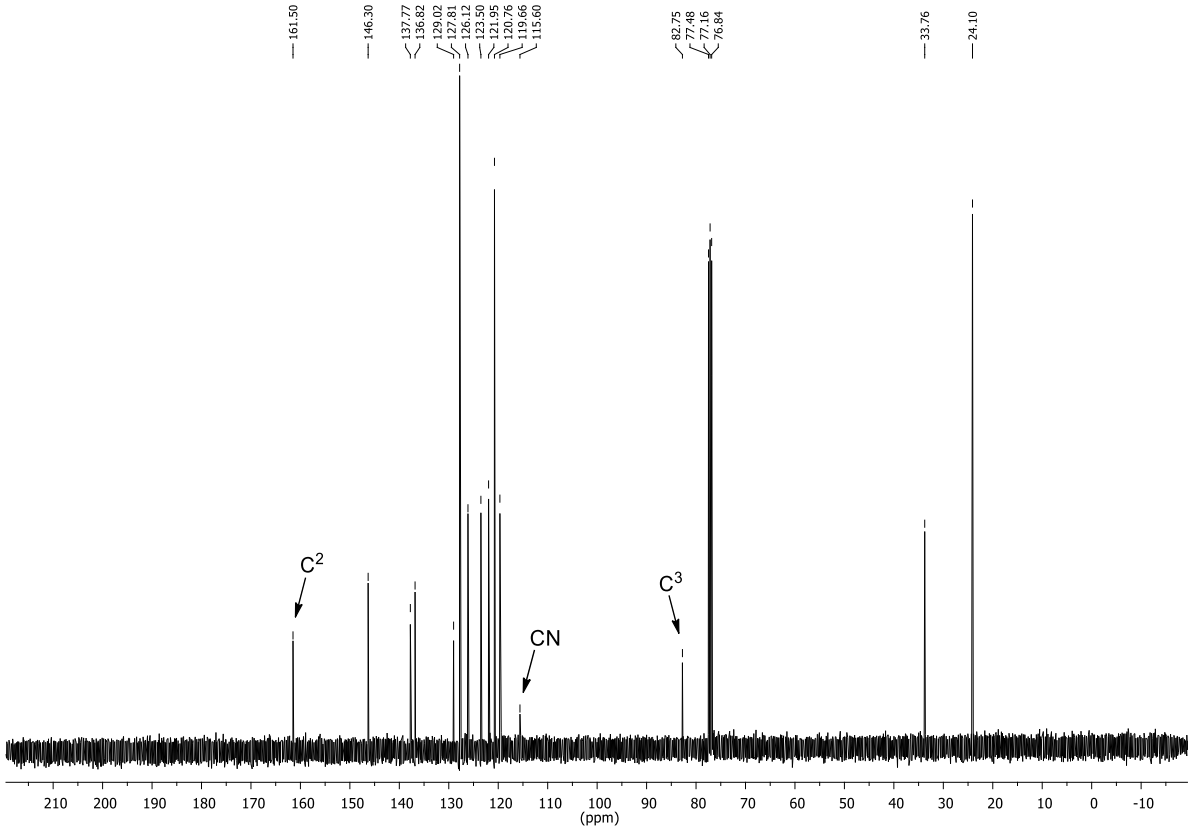


Figure 4.17a. ^{1}H NMR Spectrum of 6j in $CDCl_3$ at 700 MHz

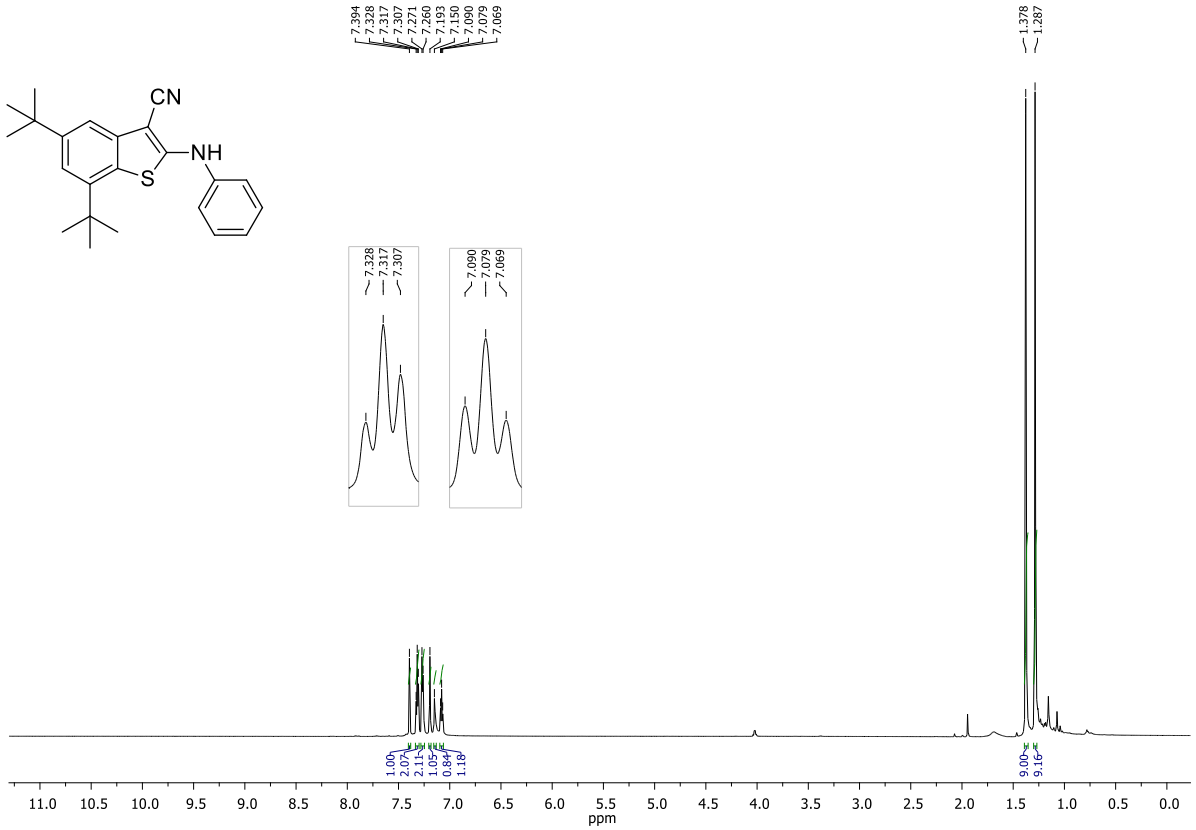


Figure 4.17b. ^{13}C NMR Spectrum of 6j in $CDCl_3$ at 175 MHz

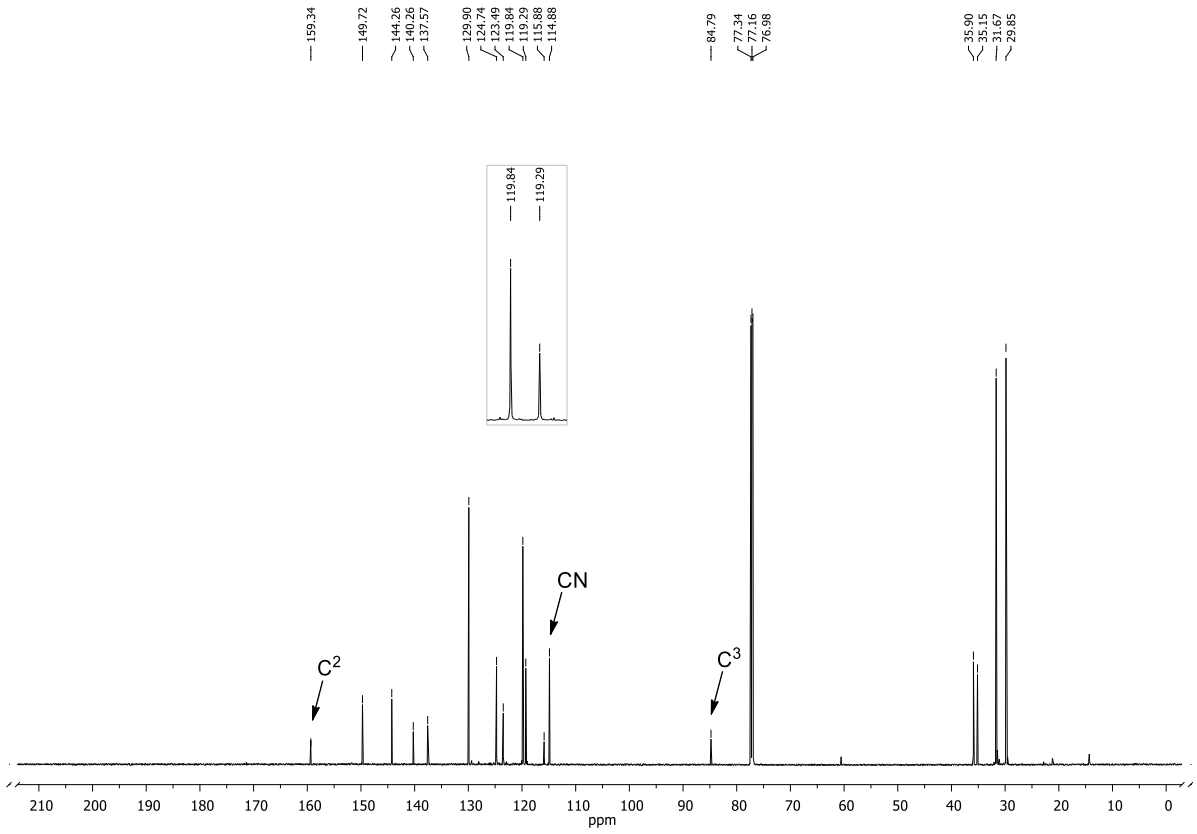


Figure 4.18a. ^{1}H NMR Spectrum of 6l in $CDCl_3$ at 700 MHz

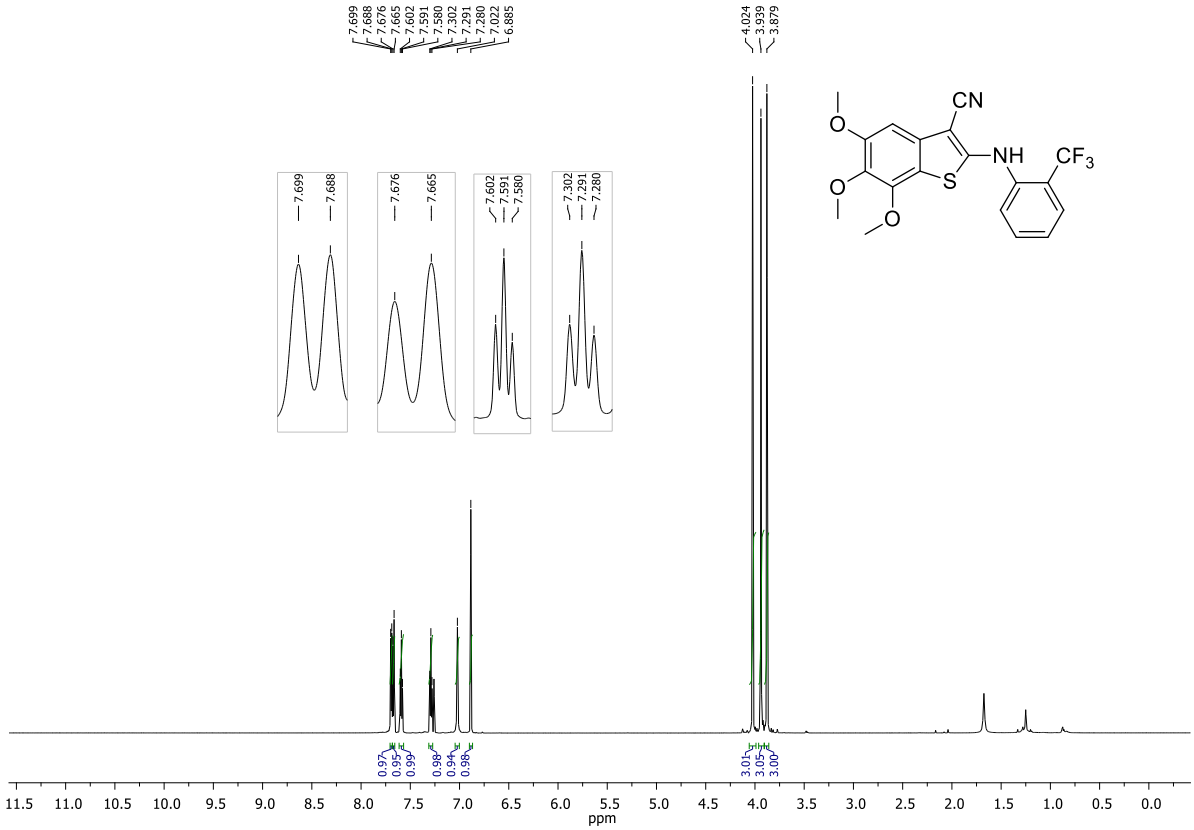


Figure 4.18b. ^{13}C NMR Spectrum of 6l in $CDCl_3$ at 175 MHz

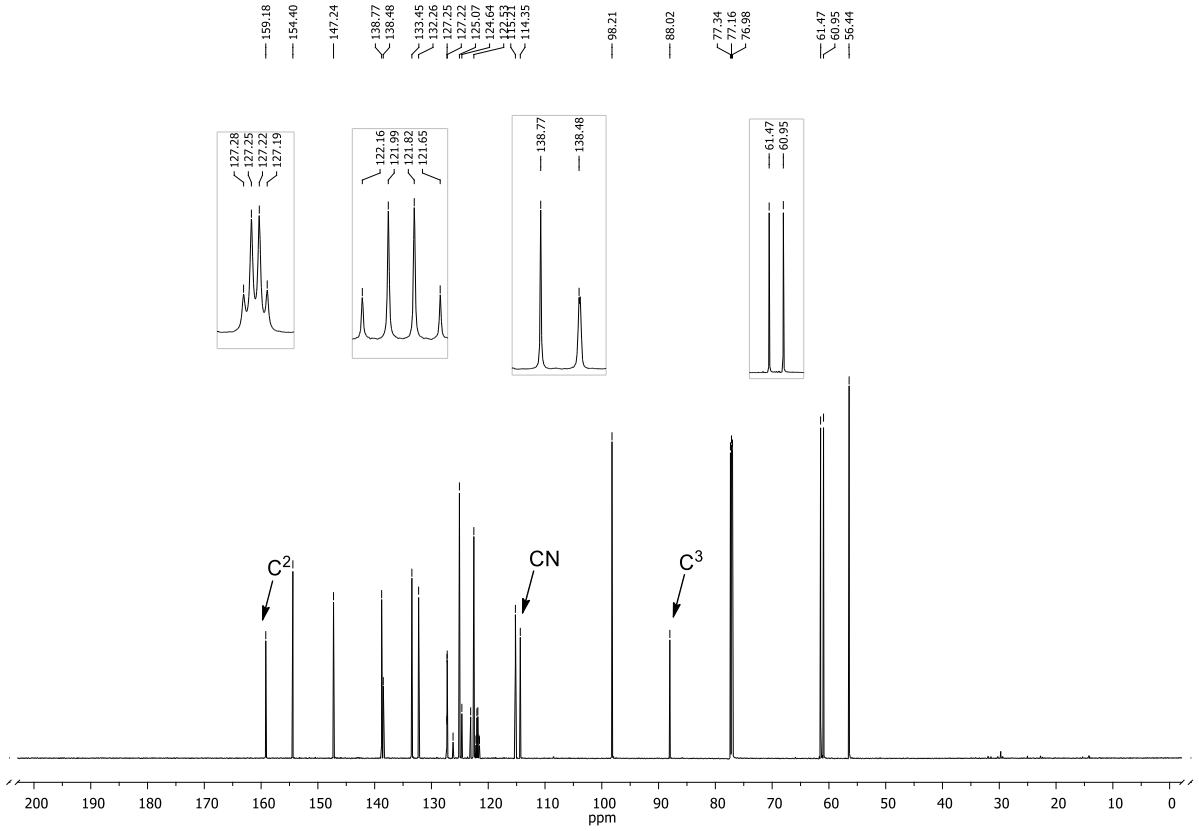


Figure 4.19a. ^{1}H NMR Spectrum of 6p in $CDCl_3$ at 700 MHz

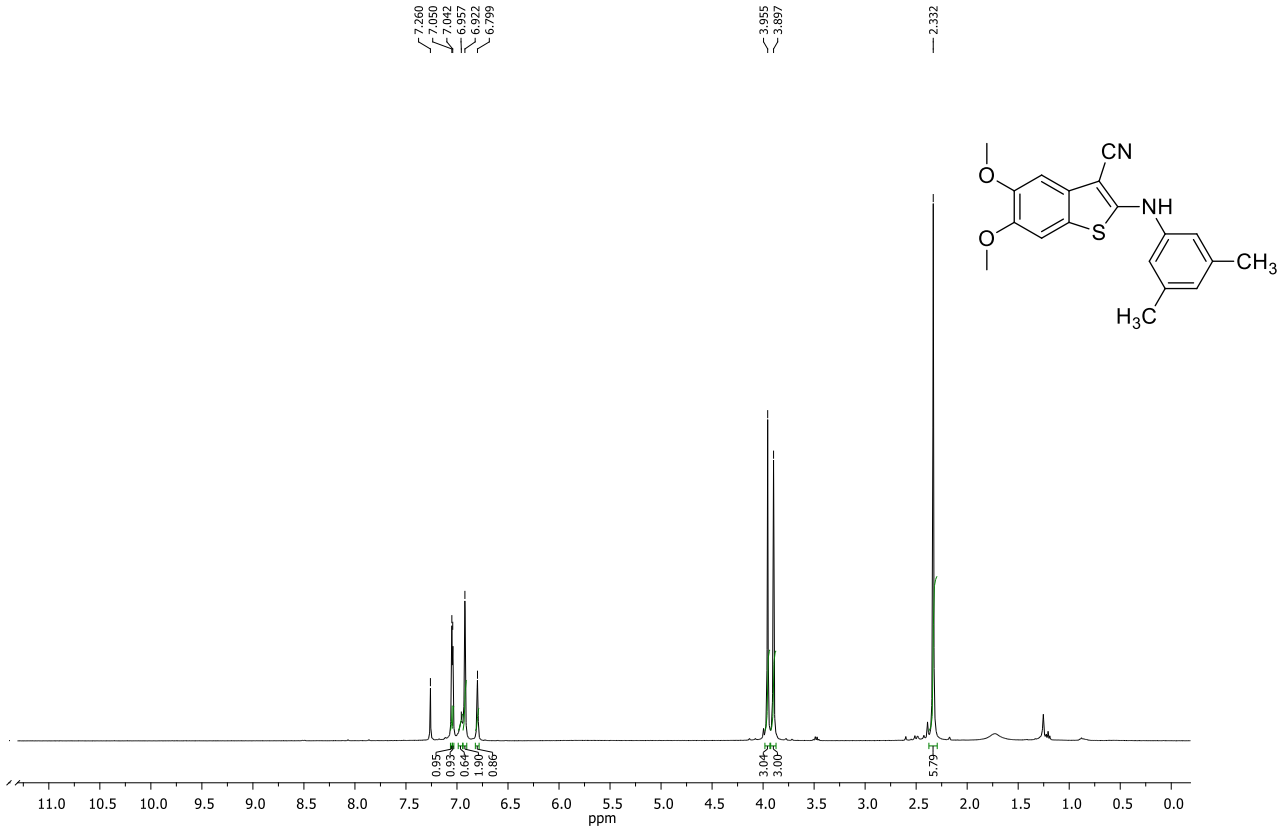


Figure 4.19b. ^{13}C NMR Spectrum of 6p in $CDCl_3$ at 175 MHz

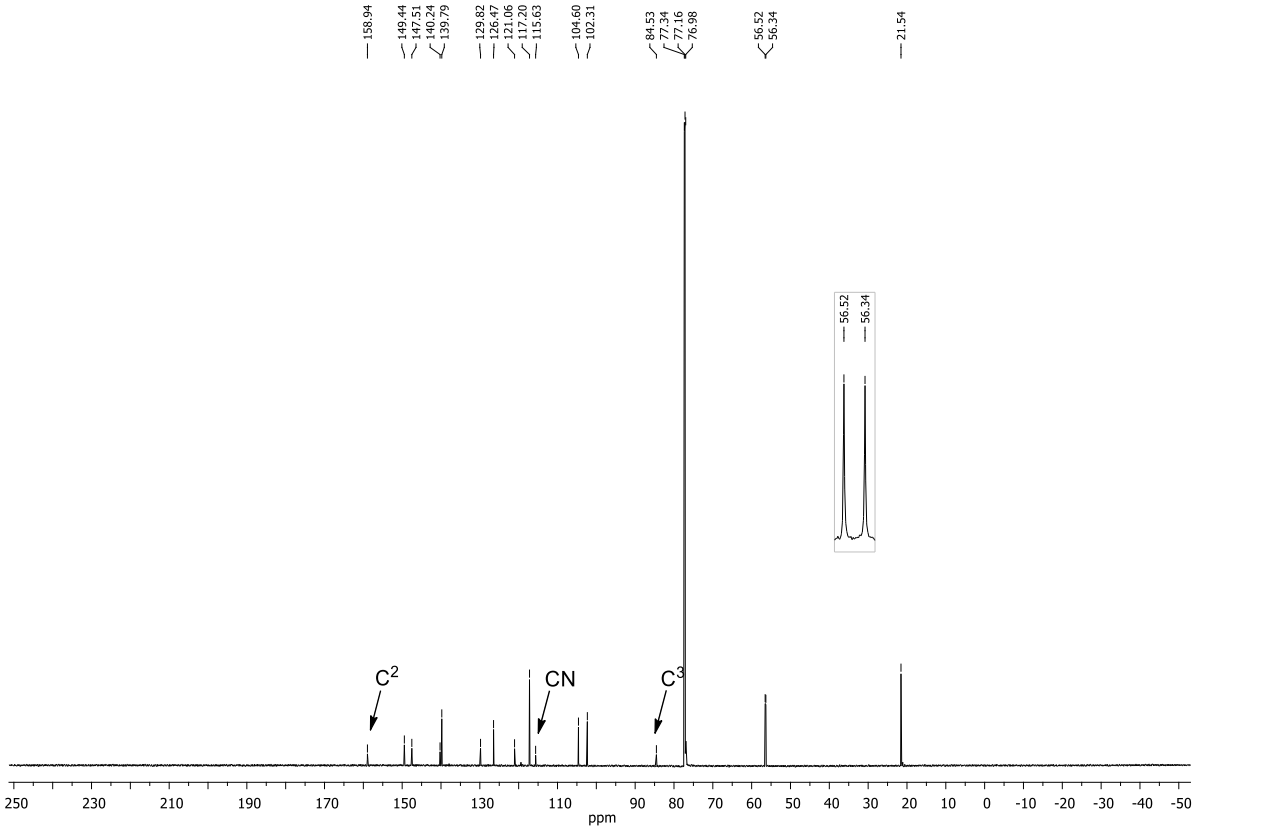


Figure 4.20a. ^{1}H NMR Spectrum of 6q in $CDCl_3$ at 400 MHz

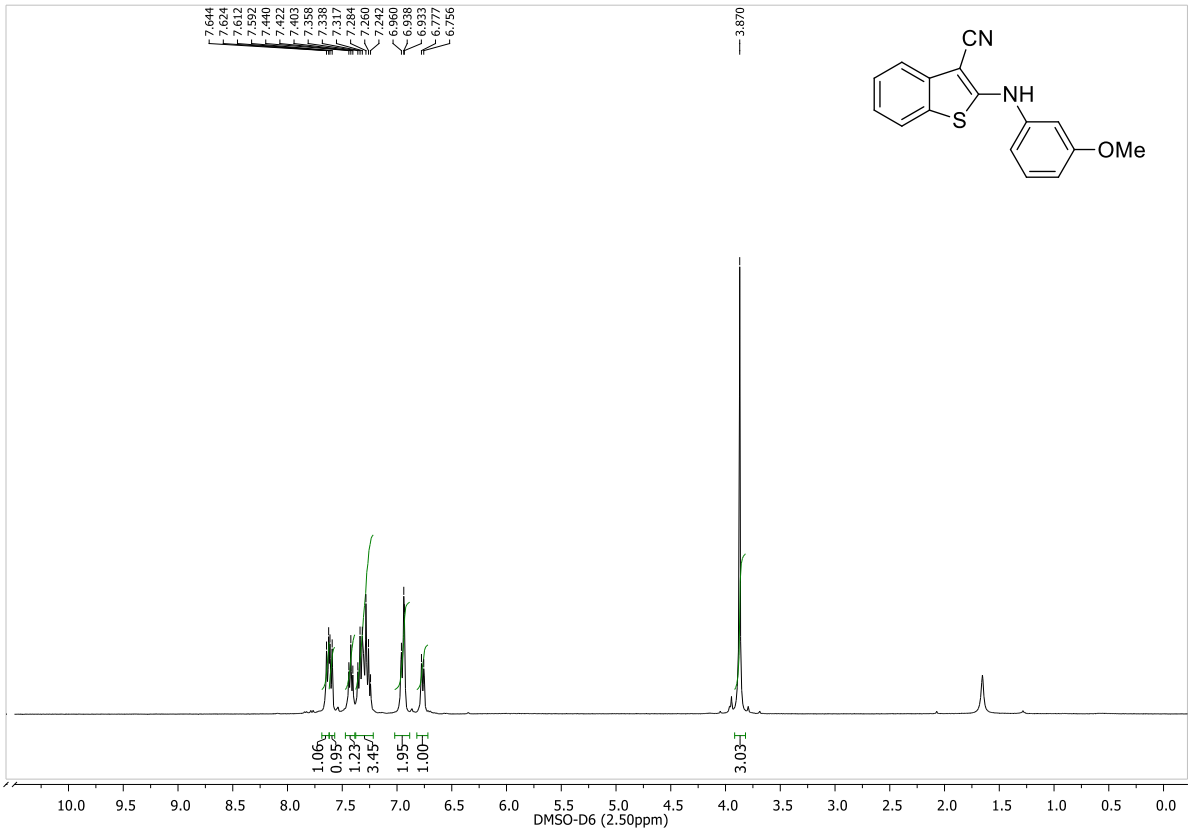


Figure 4.20b. ^{13}C NMR Spectrum of 6q in $CDCl_3$ at 100 MHz

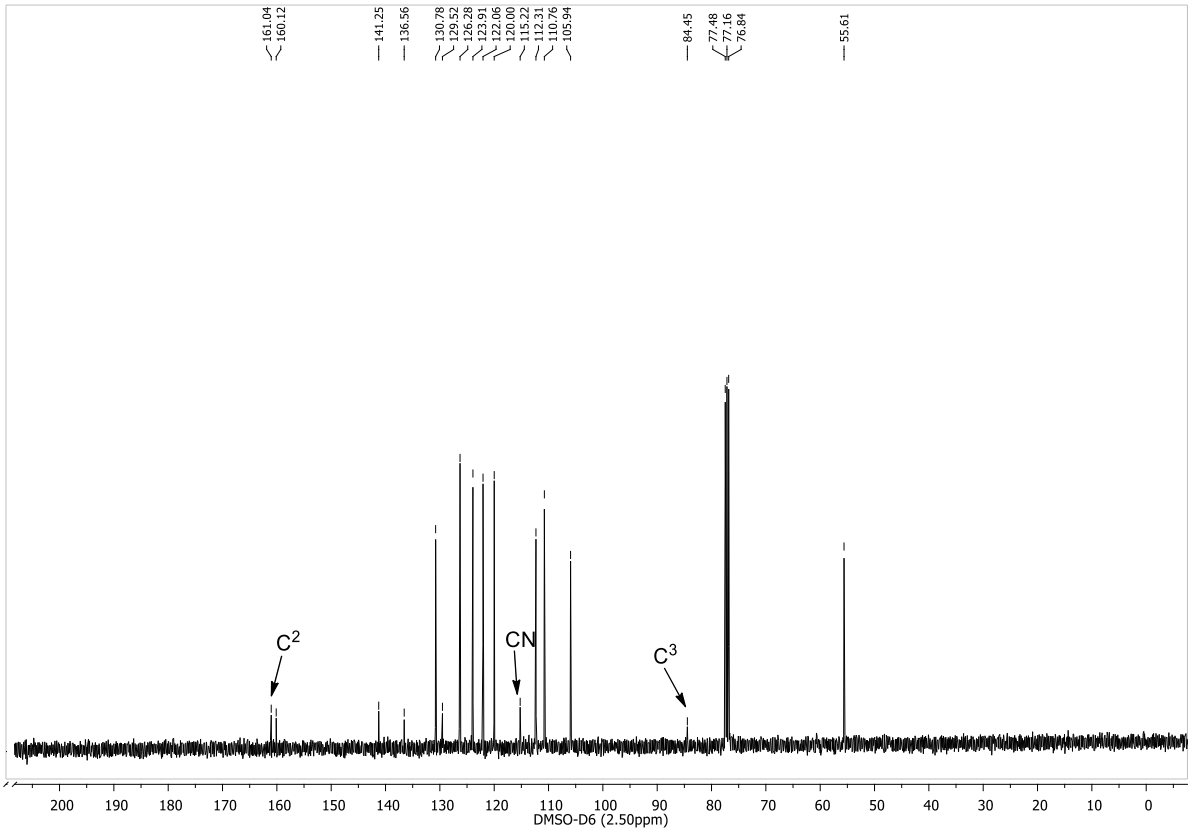


Figure 4.21a. ^{1}H NMR Spectrum of 74q and 74q′ in $CDCl_3$ at 400 MHz

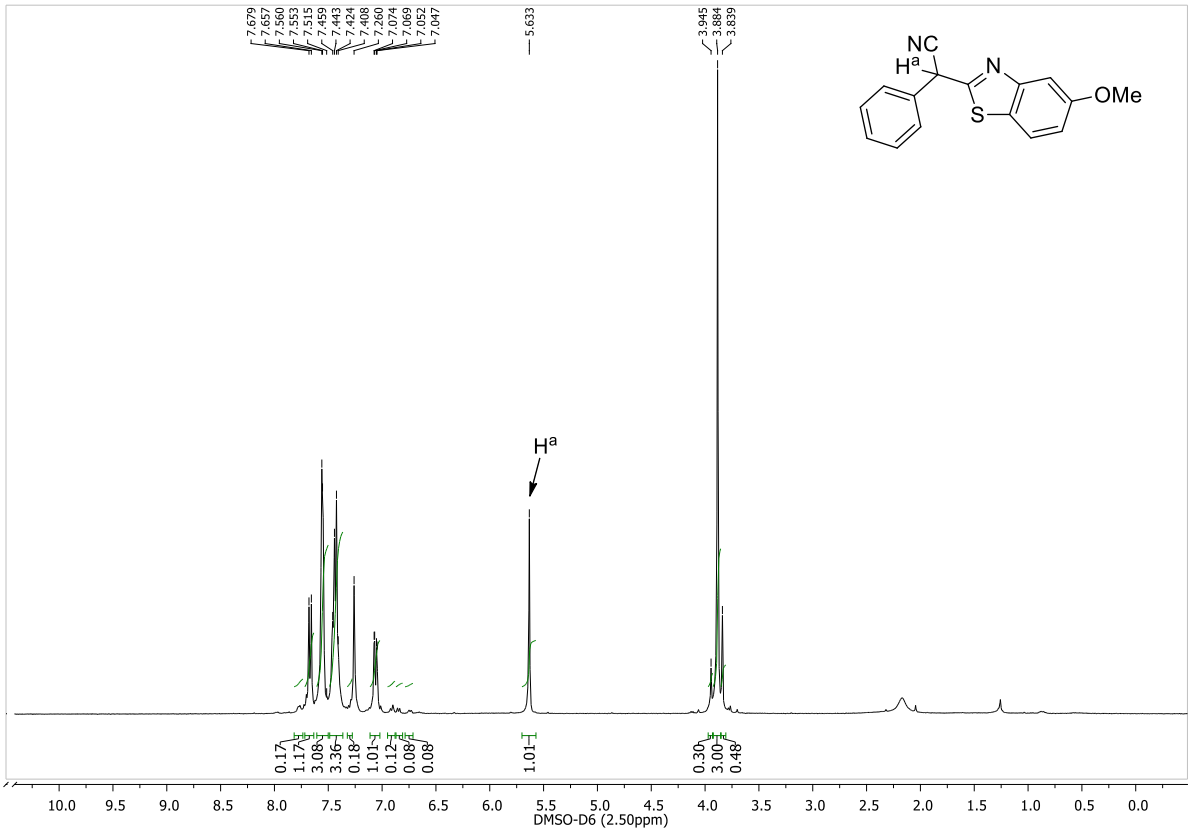
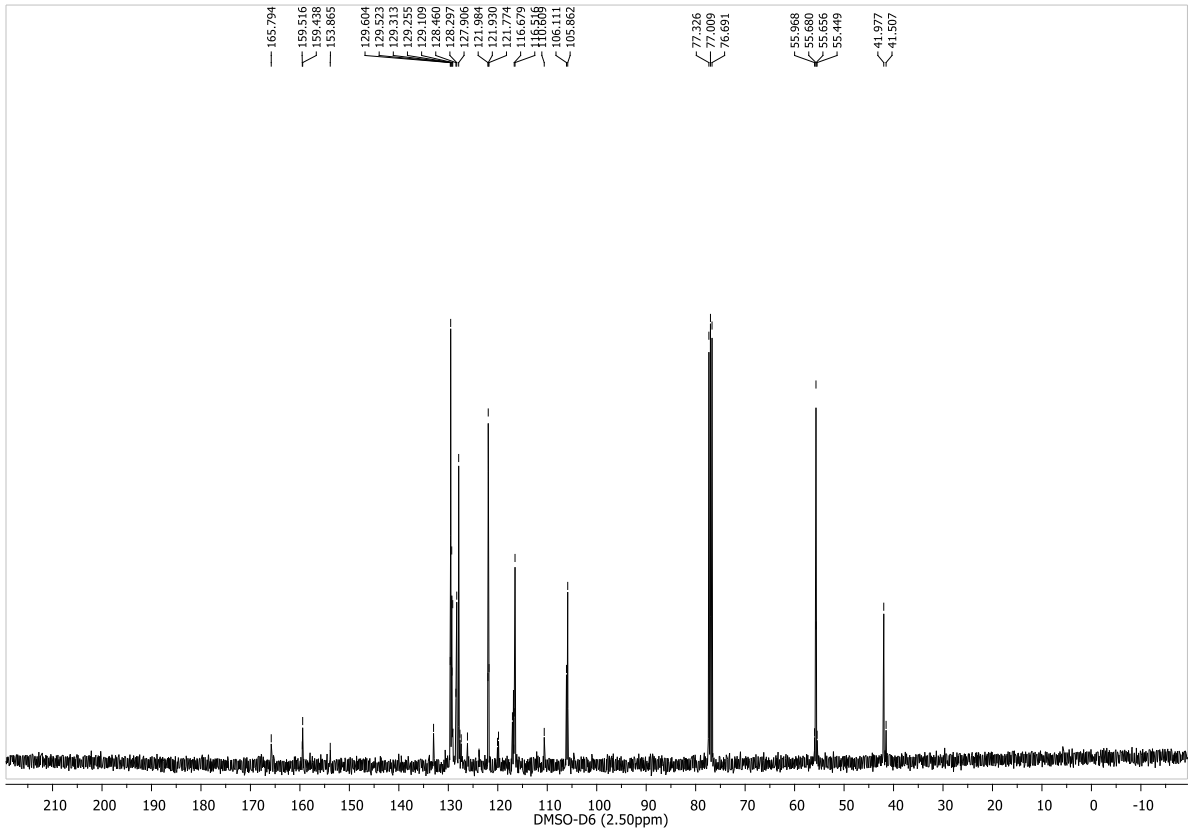


Figure 4.21b. ^{13}C NMR Spectrum of 74q and 74q′ in $CDCl_3$ at 100 MHz



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