Sequential One-Pot Synthesis of 3,5-Disubstituted-1*H*-pyrazoles from Oxime Acetates and Cyclic Sulfamidate Imines

M.Sc. Thesis

By

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DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY INDORE

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A THESIS

Submitted in partial fulfillment of the
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By

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CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled " **Sequential One-Pot Synthesis of 3,5-Disubstituted-1*H*-pyrazoles from Oxime Acetates and Cyclic Sulfamidate Imines** " in the partial fulfillment of the requirements for the award of the degree of **MASTER OF SCIENCE** and submitted in the **DEPARTMENT OF CHEMISTRY, Indian Institute of Technology Indore** is an authentic record of my own work carried out during the time period from July 2021 to May 2022 under the supervision of **Prof. Sampak Samanta**, IIT Indore.

The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other institute.

Sajal Halder 25.05.2022

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This is to certify that the above statement made by the candidate is correct to the best of my/our knowledge.

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SAJAL HALDER has successfully given his/her M.Sc. Oral Examination held on **25.05.2022**.

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Dedicated to My Family…

Abstract

Efficient CuCl catalyzed domino reaction of various oxime esters with cyclic sulfamidiate imines provides a new pathway to a diverse set of pyrazoles in good yields. This one-pot two-step sequential reaction proceeds between cyclic sulfamidate imines and oxime esters to afford intermediate **3aa** (2-phenyl-1,10b-dihydrobenzo[*e*]pyrazolo[1,5-*c*] [1,2,] oxathiazine 5,5-dioxide), followed by the addition of strong base 1,5-diazabicyclo[4.3.0]non-5-ene.

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ACRONYMS

ACN	Acetonitrile
$CDCl_3$	Chloroform-D
^{13}C NMR	Carbon-13 NMR spectroscopy
DMSO	Dimethyl sulphoxide
DCM	Dichloromethane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DMF	N, N-dimethyl formamide
EtOAc	Ethyl acetate
HRMS	High resolution mass spectrometry
2-MeTHF	2-Methyltetrahydrofuran
M	Molar
NMR	Nuclear magnetic resonance spectroscopy
ppm	Parts per million
UV	Ultraviolet spectroscopy

NOMENCLATURE

δ	Chemical shift
cm	Centimeter
^{O}C	Degree Celsius
mmol	Millimole
mL	Milliliter
rt	Room temperature
λ	Wavelength

CHAPTER 1

1.1 Introduction

In recent years, the structural diversity and biological significance of nitrogen-containing heterocyclic molecules have risen. These nitrogen-containing heterocyclic compounds are essential in natural products, biological chemistry, synthetic organic chemistry, and material sciences. Their importance as the precursors to many biologically active natural molecules has created focused attention on developing various efficient methods for the synthesis of these systems. Pyrazole is the most studied five-membered compound among the azole family. The presence of pyrazole moieties in several biologically active molecules and natural products holds all types of pharmacological activities and has diversified applications in medicine, agriculture, and technology. Pyrazoles inhibit protein glycation and are also known as anti-microbial *[1-6]*, anti-inflammatory *[7-10]*, antiviral agents *[11,12]*, antidiabetic *[13]*, antiparasitic properties *[14]*, analgesic *[15]*, antioxidant, antibacterial, antifungal, antidepressant *[16,17]*, and inhibitory activities toward nNOS/iNOS *[18]*. Pyrazole has anticancer properties that are promising *[18-24]*. Over the years, numerous pyrazole derivatives have been produced and investigated in the research for a superior anticancer treatment *[25-28]*. Pyrazole systems have recently become popular as biomolecules due to their remarkable pharmacological activities. This heterocycle can be found in several well-known medications from various therapeutic categories: celecoxib, CDPPB, meprizole, betazole, fezolamine, rimonabant, lonazolac, difenamizole, etc. (**Figure** 1) *[29-36]*.

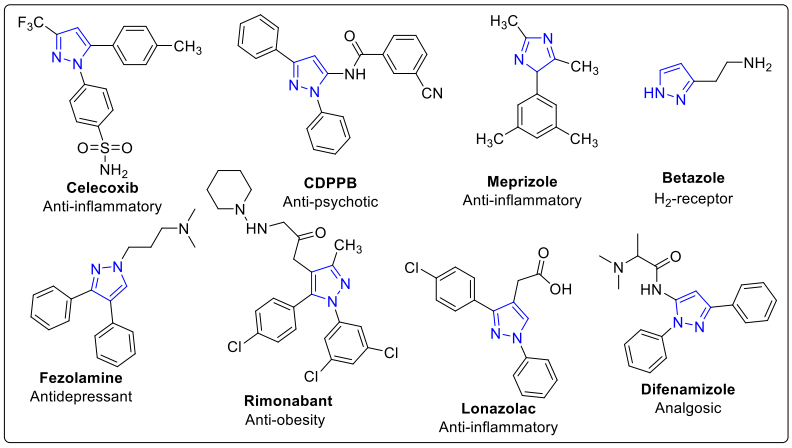


Figure 1. Pyrazole unit containing drugs.

Also, many pyrazole-containing medicines are available to treat diseases like cancer and neurologic disorders, which drugs are shown in **Figure 2** *[37-39]*. As apixaban is an anticoagulant medicine, it prevents blood clotting and stroke; also, doctors prescribe this medicine to patients who have an abnormal heartbeat (atrial fibrillation). It is also used in the case of hip/knee joint replacement surgery. In 2018, apixaban became the second most popular drug *[40]*. Also, biomolecules that contain pyrazole moiety treat neurodegenerative diseases, mainly those target pathologies which originated in Alzheimer's disease or Parkinson's disease. Apart from their therapeutic properties, polysubstituted pyrazoles have been used as ligands for cross-coupling reactions *[41]* and dyes *[42]*. Pyrazoles are essential ligand building blocks for transition metals, supermolecules, and liquid crystals.

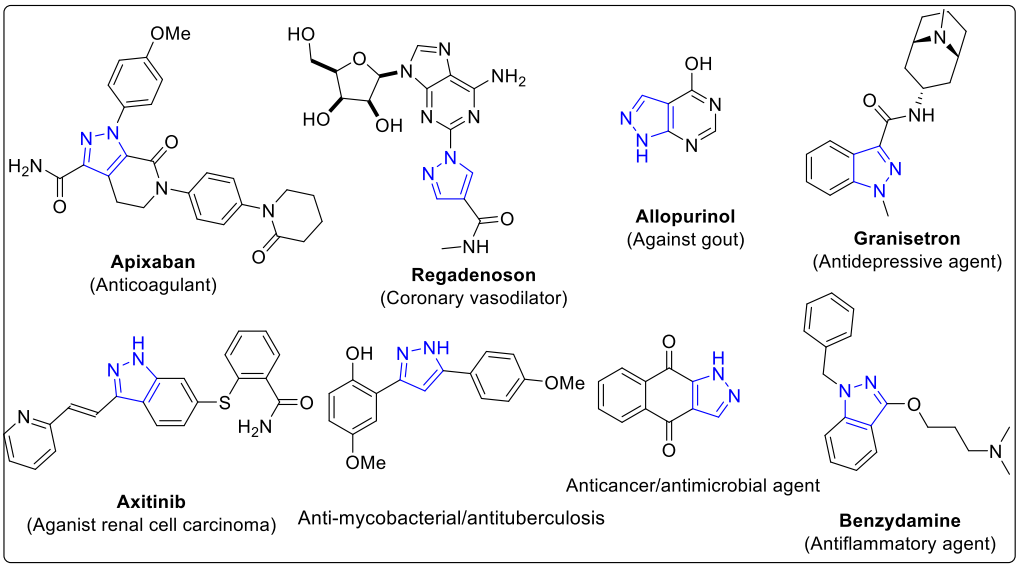
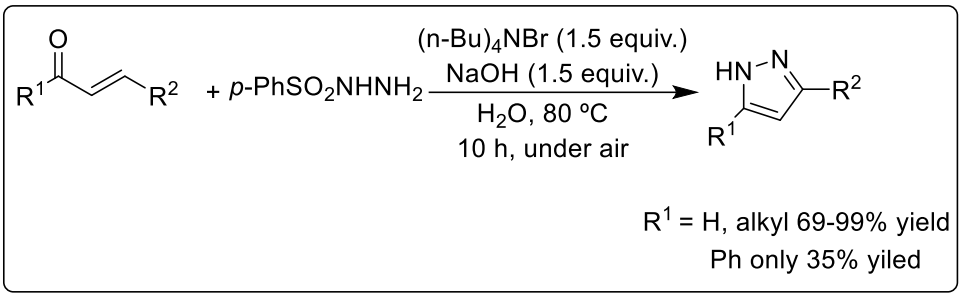


Figure 2. Structure of pyrazole containing drugs

There are several reports from the past century on efficiently synthesizing pyrazole derivatives for their importance. The 1,3-dipolar cycloaddition reaction of diazo compounds with alkynes and the condensation reaction of 1,3-dicarbonyls with hydrazines are two basic methods for synthesizing pyrazoles *[43]*. Although these procedures give acceptable yields of pyrazoles, they have their own set of drawbacks, including the use of toxic transition metals and carcinogenic hydrazines, a limited substrate scope, and poor regioselectivity. A few recent reports on the synthesis of pyrazole derivatives have been discussed in the review work.

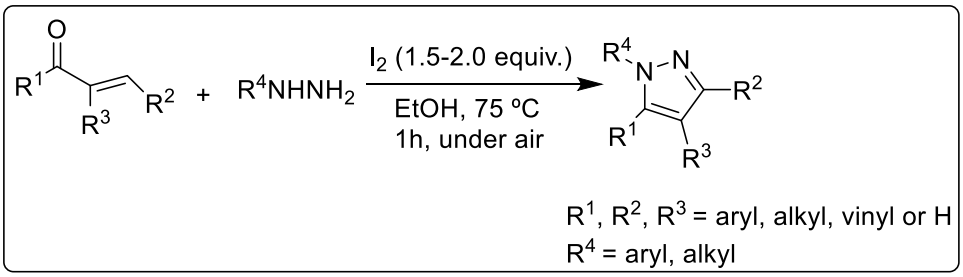
1.2 Review work

In 2011, Yu and colleagues established a very efficient and ecologically friendly method for synthesizing substituted 1*H*-pyrazoles using a one-pot condensation reaction of α,β-unsaturated carbonyl compounds with tosyl hydrazide in water, facilitated by stoichiometric tetrabutylammonium bromide. (**Scheme 1**) *[44]*.



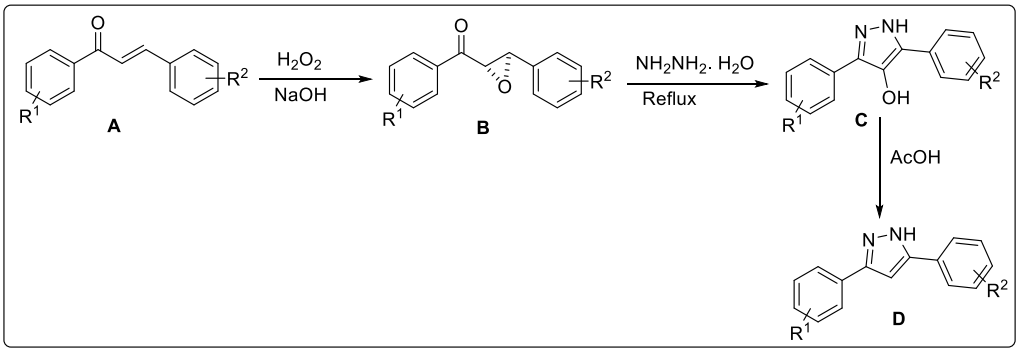
Scheme 1. Synthesis of substituted pyrazoles from α,ß-unsaturated carbonyl compounds, and sulfonyl hydrazides.

In 2014, Chang et al. discovered one synthetic method for the access to regioselective pyrazoles. They have formed the reaction through I_2-promoted oxidative intramolecular C–N bond formation from α,β-unsaturated aldehydes/ketones and hydrazines. (**Scheme** 2) *[45]*.



Scheme 2. Synthesis of substituted pyrazole from α,β-unsaturated carbonyl compounds, and hydrazide using I_2 source.

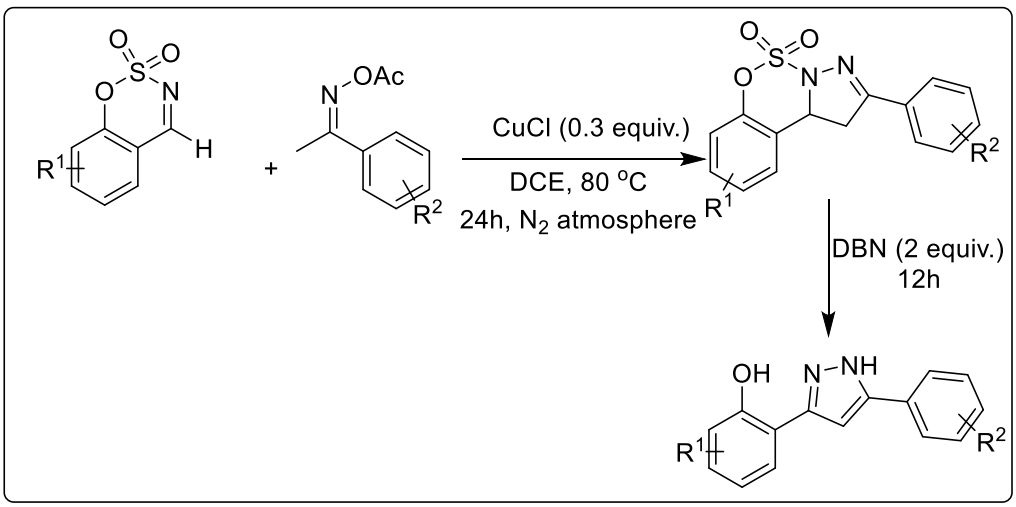
Bhat et al. proposed a technique for synthesizing 3,5-diaryl-1*H*-pyrazoles from epoxides **B** produced by the reaction of β-arylchalcones **A** with hydrogen peroxide. The addition of hydrazine hydrate produced pyrazoline intermediates **C**, which were dehydrated to provide the required 3,5-diaryl-1*H*-pyrazoles **D** (**Scheme 3**) *[46]*.



Scheme 3. Synthesis of 3,5-diaryl-1*H*-pyrazoles from the reaction of β-arylchalcone.

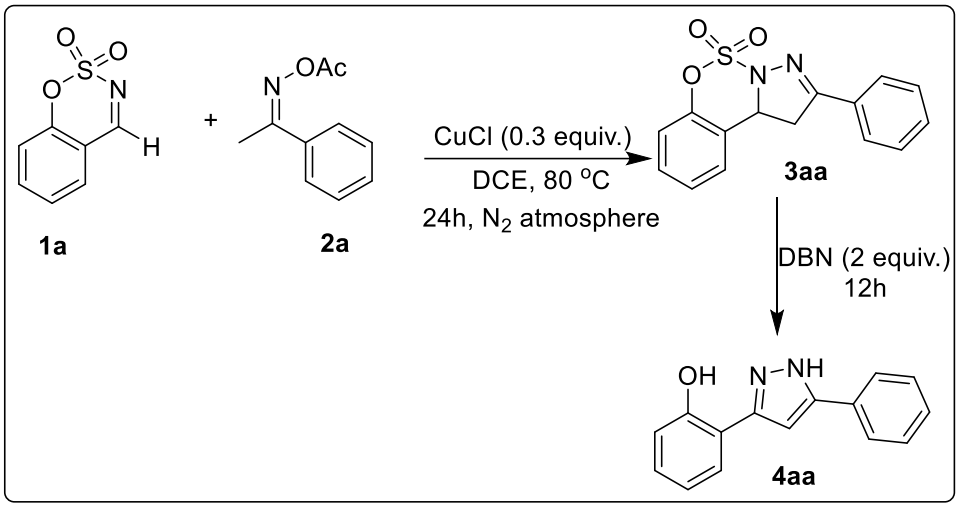
1.3 Objective of the present work

The synthesis of 3,5-disubstituted-1*H*-pyrazole derivatives has been successfully established using several methodologies, as we have seen in the review of previous research. The majority of the procedures described have significant limitations, including the usage of an expensive metal salt, carcinogenic hydrazines, and low yields of products due to the formation of large amounts of by-products. Because of those intrinsic defects, the development of a simple, efficient methodology with broad substrate scope under mild conditions is significant. As a result, we're looking for a new catalytic strategy to synthesize C2 and C3 functionalized substituted pyrazole from simpler starting materials. We hereby disclose a CuCl catalyzed technique for the modular synthesis of 3,5-disubstituted-1*H*-pyrazoles from cyclic sulfamidate imines and oxime acetates as part of our research on the development of new one-pot methods for synthesizing biologically relevant N-containing heterocycles (**Scheme 4**).



Scheme 4. One-pot sequential synthesis of 3,5-disubstituted-1*H*-pyrazole compounds using cyclic sulfamidate imines and oxime esters.

To verify this synthetic plan, we put the model reaction involving cyclic sulfamidate imine (**1a**) and acetophenone oxime acetate (**2a**) in DCE solvent at 80 °C in an N_2-atmosphere using 30 mol% CuCl acts as a catalyst and intermediate **3aa** generated in situ from cyclic sulfamidate imines and oxime esters. The intermediate **3aa** was characterized by HRMS, ^{1}H and ^{13}C NMR data. The desired product 3,5-disubstituted-1*H*-pyrazole **4aa** is formed by the sequential addition of DBN to the reaction mixture. Then after 12h, 3,5-disubstituted pyrazole compound was isolated in 90% yield (**Scheme 5**).



Scheme 5. Synthesis of **4aa** (2-(5-phenyl-1*H*-pyrazol-3-yl)phenol).

CHAPTER 2

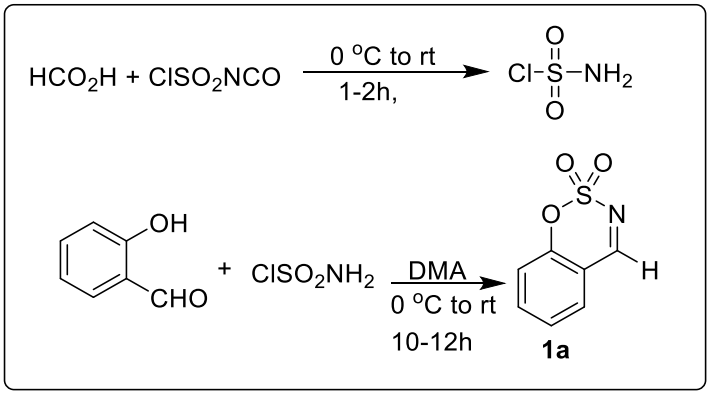
2. Experimental Section

2.1 Materials and Instrumentation

Chemicals were used as received unless otherwise indicated. All reactions were carried out under N_2-atmosphere and monitored by TLC using Merck 60 F254 pre-coated silica gel plate (0.25 mm thickness), and the product was visualized by UV detection. All the oxygen or moisture-sensitive reactions were carried out under an argon atmosphere. Silica gel (60 - 120 mesh) was used for column chromatography. NMR spectra were obtained on a Bruker 500 spectrometer in $CDCl_3$ or DMSO-d_6 operating at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR. Data for ^{1}H NMR Chemical shifts are reported in delta (δ) units, expressed in parts per million (ppm) downfield from tetramethylsilane (TMS) using residual protonated solvent as an internal standard {$CDCl_3$, 7.26 ppm}. Data for ^{13}C NMR Chemical shifts are reported in delta (δ) units, expressed in parts per million (ppm) downfield from tetramethylsilane (TMS) using the solvent as internal standard {$CDCl_3$, 77.16 ppm}. The ^{1}H NMR splitting patterns have been described as "s, singlet; d, doublet; t, triplet and m, multiplet.". Compounds were named by using Chem draw Ultra 12.0 and NMR data processed by MestReNova.

2.2 General procedure for the synthesis of precursor:

2.2.1 Synthesis of cyclic sulfamidate imines:

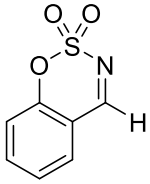


Scheme 6. Synthesis of cyclic sulfamidate imine **1a.**

Firstly, in a two-neck 250 mL round bottom flask, anhydrous formic acid (1.5 mL, 40 mmol) was taken, and a balloon was put on one of the two necks. The

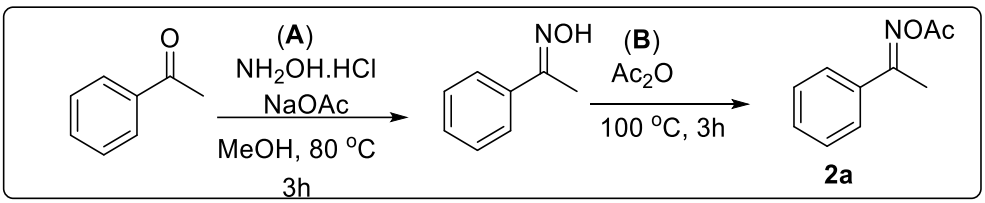
flask was then poured with neat chlorosulfonyl isocyanate (3.5 mL, 40 mmol.) and rapidly stirred at 0 °C. After removing the ice bath, the reaction mixture was left to stir for 1-2 hours. Once sulfamoyl chloride was obtained, salicylaldehyde (2.08 mL, 20 mmol.) and DMA (30 mL) were poured into it at 0 °C. Removed the reaction mixture from the ice bath and stirred it for 10-12 hours. After that reaction was quenched by adding ice to the reaction mixture, and workup was done with EtOAc. Under reduced pressure, the mixed organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (1:20; EtOAc/hexane) was used to purify the crude products. By comparing ^{1}H and ^{13}C NMR data to published data, the product was confirmed.[*47*]

Benzo[*e*][1,2,3]oxathiazine 2,2-dioxide (1a); Grey Solid; yield 88%; $\mathbf{R}_f$ = 0.55 (EtOAc:hexane = 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.68 (s, 1H), 7.79 – 7.74 (m, 1H), 7.70 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.44 (td, *J* = 7.6, 0.6 Hz, 1H), 7.31 – 7.26 (m, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.6, 154.2, 137.6, 130.8, 126.2,118.6, 115.3 ppm.



1a

2.2.2 Synthesis of acetophenone oxime acetate



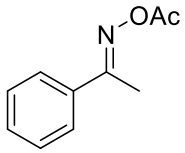
Scheme 7. Synthesis of phenyl oxime acetate **2a.**

(**A**): At 100 mL single-necked round-bottomed flask, hydroxylamine hydrochloride (2.08g, 30.0 mmol.) and sodium acetate anhydrous (3.94 g, 48.0 mmol.) were added. By syringe, acetophenone (2.4 mL, 20 mmol.) and anhydrous methanol (40 mL) were added. The flask was fitted with a water-cooled reflux condenser and brought to reflux by placement onto a pre-heated oil bath (80 °C, oil bath temperature) for three hours. Water (60 mL) was added upon cooling to room temperature; ethyl acetate was used to extract the mixture (3 x 30 mL). The organic layers were mixed together, then dried over anhydrous

Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure with a rotary evaporator to yield crude acetophenone oximes pale yellow liquid, as it was used in the next step without purification.

(**B**): By syringe, crude oxime and acetic anhydride (3.80 mL, 40 mmol.) were added to a 100 mL single-necked round-bottomed flask. The flask was fitted with a water-cooled reflux condenser, and the resulting yellow solution was heated for 3 hours under air by placing it on a pre-heated oil bath (oil bath temperature of 100 °C). The reaction mixture was separated into 50 mL of water and 50 mL of ethyl acetate in a 250 mL separatory funnel after cooling to room temperature. After separating the layers, the aqueous layer was extracted with ethyl acetate (2 × 40 mL). The organic layers were mixed and dried over anhydrous Na_2SO_4 before being filtered. A rotary evaporator was used to concentrate the filtrate. The crude residue was purified by recrystallization or/and column chromatography on silica gel to obtain acetophenone O-acetyl oxime. By comparing ^{1}H and ^{13}C NMR data to published data, the product was confirmed. [*48*]

(*E*)-1-Phenylethan-1-one O-acetyl oxime (2a); White Solid; yield 80%; $\mathbf{R_f}$ = 0.81 (EtOAc:hexane = 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.76 – 7.72 (m, 2H), 7.46 – 7.38 (m, 3H), 2.39 (s, 3H), 2.27 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 169.0, 162.4, 134.8, 130.5, 128.5, 127.0, 19.8, 14.4 ppm.

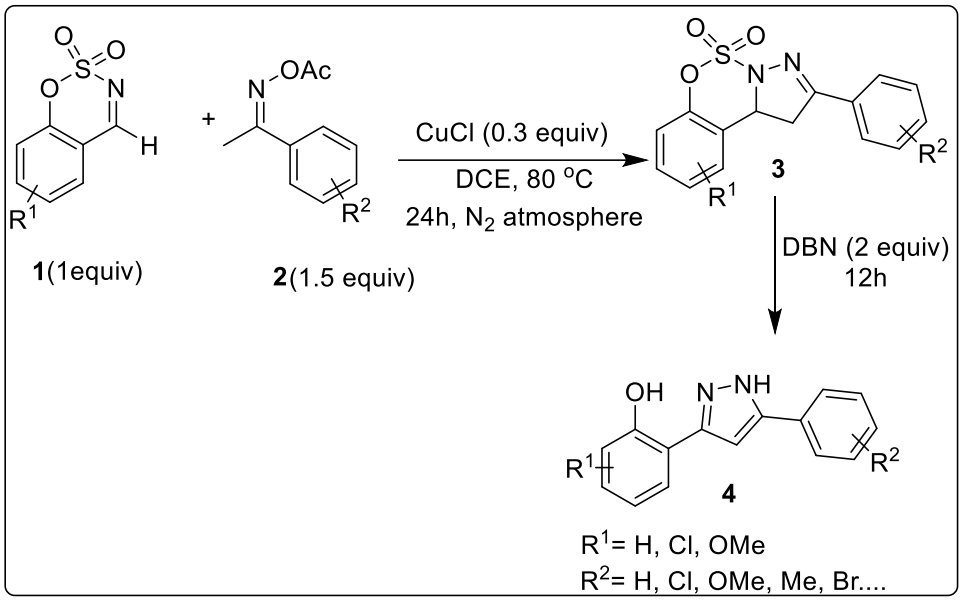


2a

2.2.3 Sequential one-pot procedure for the synthesis of 3,5-disubstituted-1*H*-pyrazole derivatives:

To a stirred solution of compound **1** (100 mg, 0.55 mmol, 1 equiv.) and **2** (146 mg, 0.82 mmol, 1.5 equiv.) in DCE (1.5 mL) was added anhydrous CuCl (17 mg, 0.16 mmol, 0.3 equiv.) in inert atm. Then the reaction mixture was heated at 80 °C for 24h. After completion of the reaction as indicated by TLC, DBN (136.6 mg, 1.10 mmol, 2 equiv.) was added to the resulting mixture. Then the reaction mixture was heated at 80 °C for 12 h. After the reaction was finished, as indicated by TLC, the reaction mixture was extracted with ethyl acetate (3 ×10 mL), washed with water and brine, and dried over Na_2SO_4. The mixed organic phases were evaporated under reduced pressure to obtain the crude

product. Finally, the product was purified using column chromatography over silica gel with an eluent mixture of EtOAc/hexane (1:4, v/v). (**Scheme 8**). HRMS, ^{1}H, and ^{13}C NMR spectroscopic data were used to characterize the product comprehensively.

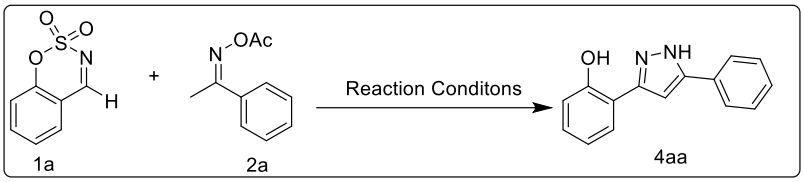


Scheme 8. Synthesis of 3,5-disubstituted-1*H*-pyrazole derivatives.

CHAPTER 3

3. Results and Discussions

3.1 Table 1. Optimization of reaction condition[a]



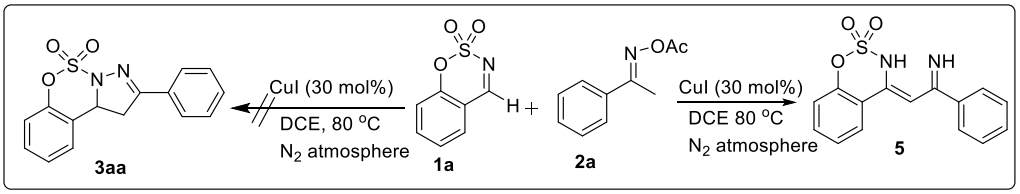
Entry	Catalyst (30 mol%)	Base	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1.	CuCl	DBN	DCE	rt	36	NR
2.	CuCl	DBN	DCE	40	36	20
3.	CuCl	DBN	DCE	60	36	50
2.	**CuCl**	**DBN**	**DCE**	**80**	**36**	**92**
3.	CuCl	DBU	DCE	80	36	50
4.	CuCl	DABCO	DCE	80	36	10
5.	CuCl	DBN	toluene	80	36	55
6.	CuCl	DBN	DMSO	80	36	20
7.	CuCl	DBN	1,4-dioxane	80	36	70
8.	CuCl	DBN	DMF	80	36	75
9.	CuCl	DBN	ACN	80	36	35
10.	CuCl	DBN	2-MeTHF	80	36	25
11.	CuCl	DBN	EtOH	80	36	70
12.	$CuCl_2$	DBN	DEC	80	36	65
13.	CuBr	DBN	DCE	80	36	30
14.	CuI	DBN	DCE	80	36	ND
15.	$Cu(OAc)_2.H_2O$	DBN	DCE	80	36	35
16.	$Cu(OTf)_2$	DBN	DCE	80	36	10
17.	$CuBr_2$	DBN	DCE	80	36	30

[a]All the reactions were carried out with cyclic sulfamidate imines (0.10 mmol), oxime ester (0.16 mmol), and catalyst (30 mol%) in a specified dry solvent (1.5 mL) under argon atmosphere and temperature. [b] Isolated yield after column chromatography.

First, we put the reaction between cyclic sulfamidate imines and oxime acetate in DCE using 30 mol% of anhydrous CuCl as a catalyst at 80 °C in a Schlenk tube for 24 hours. Then the base is added sequentially to the reaction mixture. After 12h, the reaction was completed (monitored by TLC), and a novel class 3,5-disubstituted-1*H*-pyrazole derivative **4aa** was isolated in moderate yield. To improve the yield further, several common solvents such as toluene, 2-MeTHF, dioxane, DMF, DMSO, ACN, and EtOH were tested for this reaction. We found that anhydrous CuCl gave the best yield of the desired product in DCE at 80 °C. Next, we screened other catalysts such as CuBr, $CuCl_2$, CuI, and $Cu(OAc)_2$. H_2O, $CuBr_2$, $Cu(OTf)_2$.

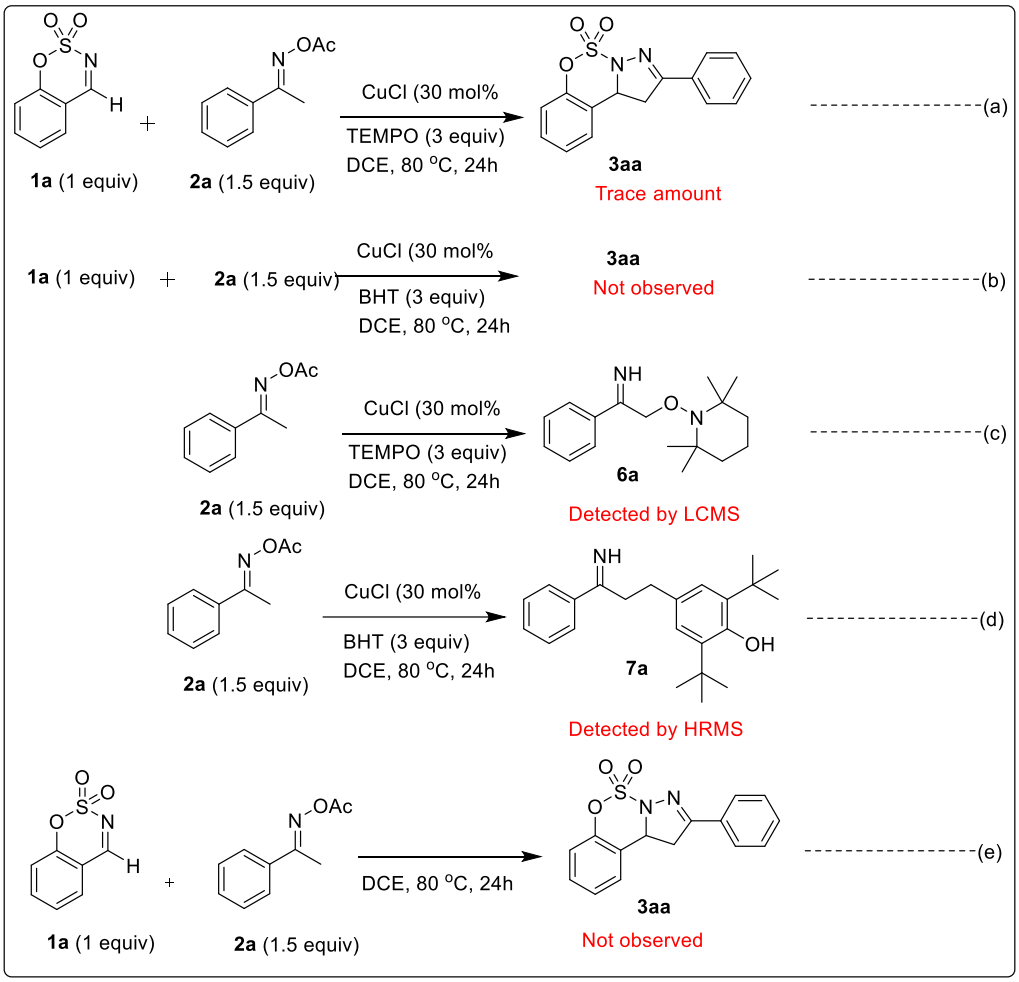
Furthermore, 30% and 35% yields were obtained by using $CuBr_2$ and $Cu(OAc)_2$. H_2O as catalysts, respectively. Next, we added bases like DBN, DBU, and DABCO. We found that DBN gave the best result. Therefore, considering the yield, CuCl was the best catalyst compared to other Cu-salts, with the solvent DCE and DBN being the best base and an optimized reaction time of 36h.

So, in the presence of catalyst CuCl, the reaction of cyclic sulfamidate imines and oxime esters underwent free radical reaction to form intermediate **3aa**, and sequential addition of DBN in the same reaction pot gave 3,5-disubstituted-1*H*-pyrazole **4aa**. But when CuI was added instead of CuCl with the same reaction condition, different product **5** ((*Z*)-4-(2-imino-2-phenylethylidene)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide) was formed. This imino compound **5** is not our targeted product. Our target is the synthesis of 3,5-disubstituted-1*H*-pyrazole compounds.



Scheme 9. Synthesis of **5** ((*Z*)-4-(2-imino-2-phenylethylidene)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide) by using CuI.

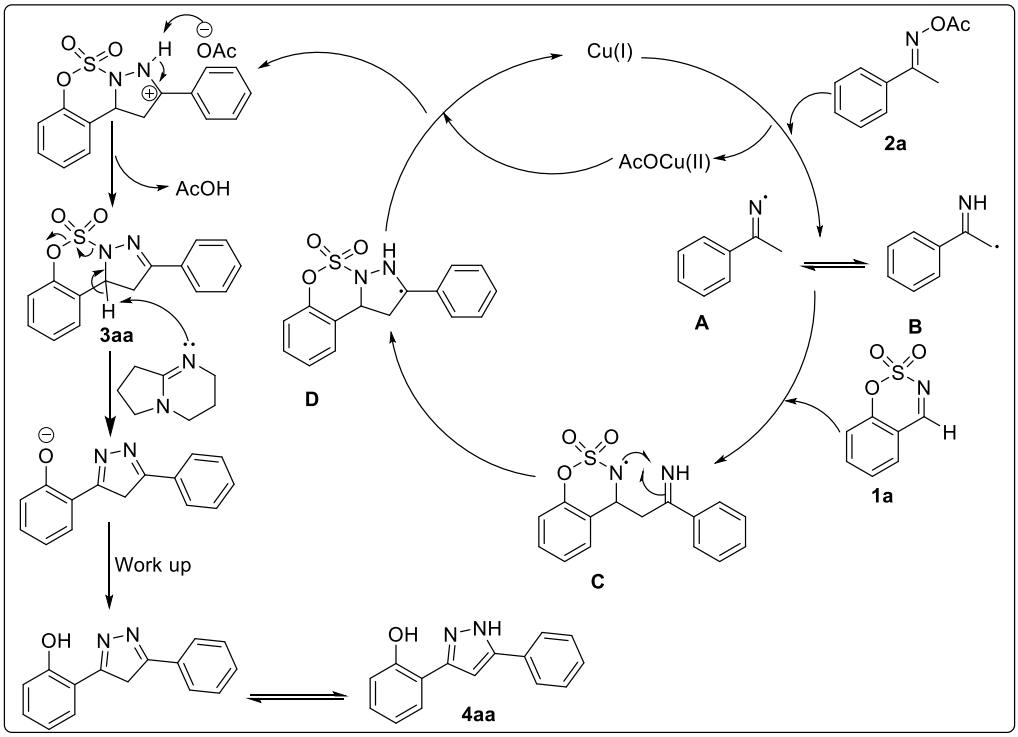
Control experiments were carried out to gain insight into the reaction pathway (**Scheme 10**). It should be noted that while a trace amount of **3aa** was formed in the presence of the radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) (**Scheme 10a**), no **3aa** was formed in the presence of butylated hydroxytoluene **(**BHT) (**Scheme 10b**). This observation confirmed that the cyclization reaction followed a radical pathway and that combining TEMPO and BHT with radical species produced during the catalytic cycle would inhibit the transformation. The radical produced by **2a** was trapped using TEMPO and butylated hydroxytoluene in the following two experiments, and the radical coupling products were detected using LCMS and HRMS (**Scheme 10c** and **d**). In another experiment, the reaction was carried out in the absence of CuCl, and it was observed that **3aa** was not formed (**Scheme 10e**). These results indicate that the radical process of the reaction may begin with the reaction of **2a** and copper catalyst.



Scheme 10. Control experiments

3.2 Plausible Reaction Mechanism

Based on the above control experiments and literature report [*49*] a plausible reaction mechanism is outlined in **Scheme 11**. Initially, iminium radical **A** was generated by oxidation of Cu (I) to AcOCu(II), and this radical was rapidly tautomerized to **B**. Then **B** underwent radical addition to **1a** and formed **C**. Then nitrogen radical adds to the intramolecular imine group to form radical species **D**. Then compound **3aa** was formed via a single-electron-transfer (SET) process between AcOCu(II) and, releasing AcOH and regenerating the Cu (I) species back to the catalytic cycle. Then DBN was added, which eliminates SO_2 from **3aa** to give the desired product **4aa** (2-(5-phenyl-1*H*-pyrazol-3-yl)phenol).

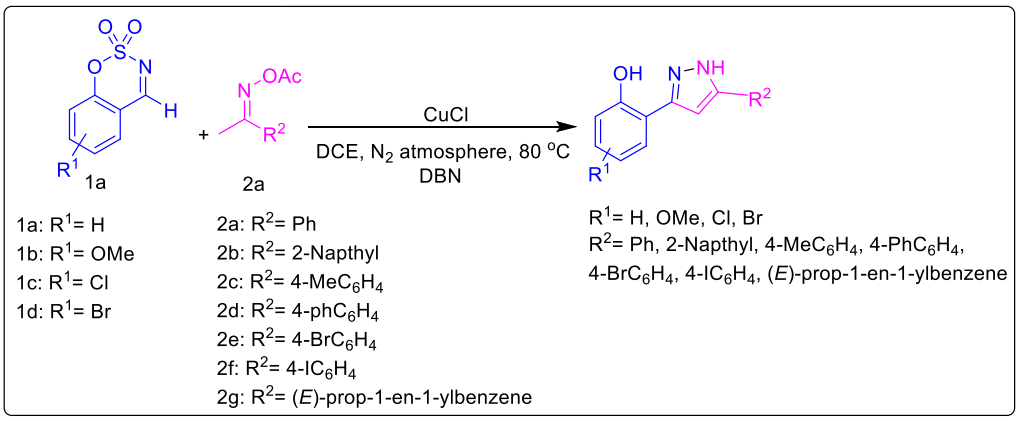


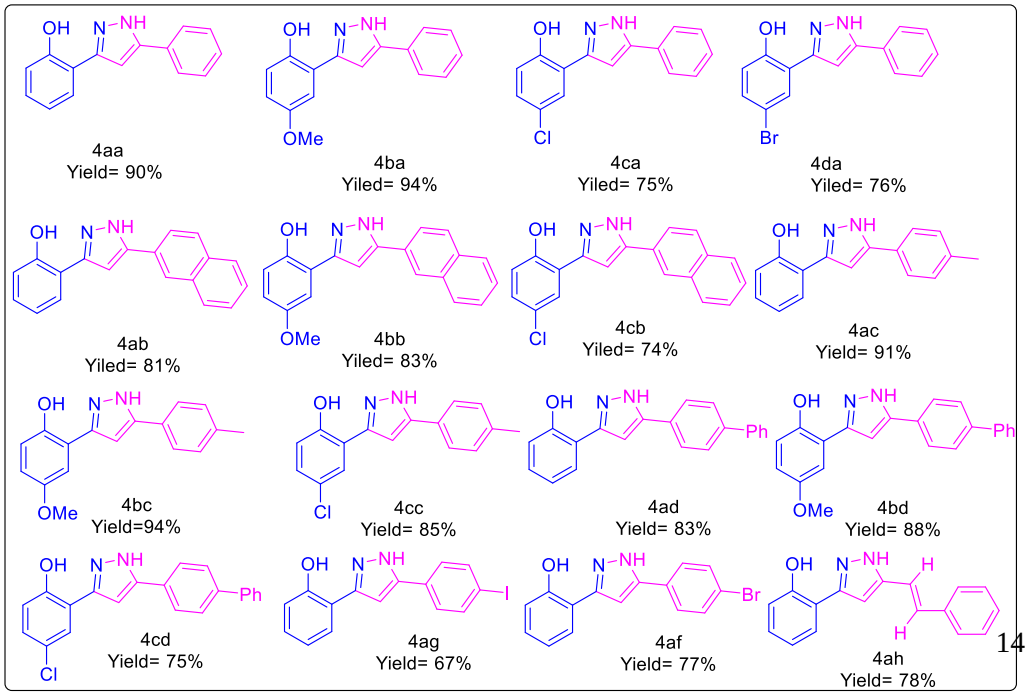
Scheme 11. Reaction mechanism for synthesis of 3,5-disubstituted-1*H*-pyrazole derivatives.

CHAPTER 4

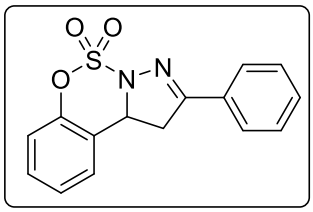
4.1 Substrate Scope and Generality of the Reaction

We demonstrated the substrate scope of the CuCl catalyzed reaction by taking various cyclic sulfamidate imines and a wide range of oxime esters under established conditions after successfully developing a simple sequential one-pot synthesis of 3,5-disubstituted-1*H*-pyrazole derivatives. **Scheme 12** includes the obtained results. It was observed that electron-donating substituents in oxime esters and cyclic sulfamidate imines, such as MeO in **4ba**, and Me substituent in **4ac**, responded very well to provide the corresponding C2, C3-substituted pyrazoles (**4ba** and **4ac**) with higher yields (94% and 91% respectively) than electron-withdrawing substituents (Cl, Br, I; **4ca, 4da**, **4ag** and **4af** for 75%, 76%, 67% and 77% yield respectively). Remarkably, oxime esters generated from the bulky naphthyl group were well tolerated, resulting in good yields of the desired heterocycles **4ab**.

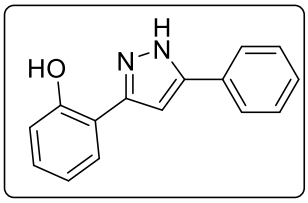




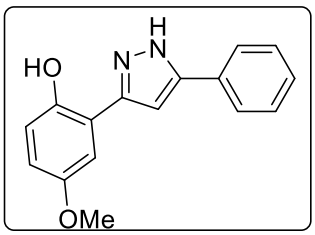
4.2 Data of all synthesized compounds

2-Phenyl-1,10b-dihydrobenzo[*e*]pyrazolo[1,5-*c*][1,2,3]oxathiazine 5,5-dioxide (3a): 

Brown solid; yield 92% (151.6 mg); $\mathbf{R_f}$ = 0.60 (EtOAc:hexane = 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.1 Hz, 2H), 7.37 – 7.29 (m, 3H), 7.24 – 7.13 (m, 3H), 6.91 (d, *J* = 7.8 Hz, 1H), 5.74 (d, *J* = 9.0 Hz, 1H), 3.74 (dd, *J* = 16.2, 9.4 Hz, 1H), 3.46 (d, *J* = 16.3 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.6, 150.2, 131.4, 129.8, 129.7, 128.7, 127.4, 127.1, 126.4, 121.7, 119.1, 64.4, 42.9 ppm; **HRMS** (ESI) m/z calculated for $C_{15}H_{12}N_2O_3S[M+H]^+$: 301.0641, found 301.0620.

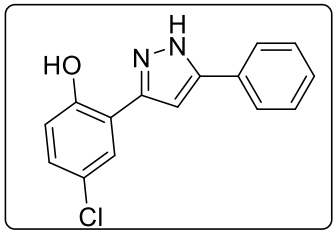
2-(5-phenyl-1*H*-pyrazol-3-yl)phenol (4aa): 

white solid; yield 90% (116.7 mg); **mp**: 120-122 °C; $\mathbf{R_f}$ = 0.69 (EtOAc:hexane = 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.75 (s, 1H), 10.32 (s, 1H), 7.57 – 7.52 (m, 3H), 7.40 – 7.32 (m, 3H), 7.19 – 7.15 (m, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.83 (s, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 155.9, 153.0, 144.0, 129.4, 129.2, 129.1, 128.7, 126.6, 125.6, 119.4, 117.1, 116.5, 99.5 ppm; **HRMS** (ESI) m/z calculated for $C_{15}H_{12}N_2O[M+H]^+$: 237.1022, found 237.1022.

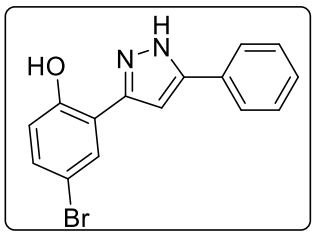
4-Methoxy-2-(5-phenyl-1*H*-pyrazol-3-yl)phenol (4ba): 

white solid; yield 94% (117.4 mg); **mp**: 118-120 °C; $\mathbf{R_f}$ = 0.55 (EtOAc:hexane = 1:4)**; ^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.43 (s, 2H), 7.52 (d, *J* = 6.9 Hz, 2H), 7.40 – 7.30 (m, 3H), 7.09 (s, 1H), 6.90 (d, *J* = 8.7 Hz, 1H), 6.82 – 6.73 (m, 2H), 3.75 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 152.6, 152.6, 150.0, 144.1, 129.2, 129.1, 128.7, 125.6, 117.6, 116.7, 115.3, 111.6, 99.5, 56.0 ppm; **HRMS** (ESI) m/z calculated for $C_{16}H_{14}N_2O_2[M+H]^+$: 267.1128, found 267.1116.

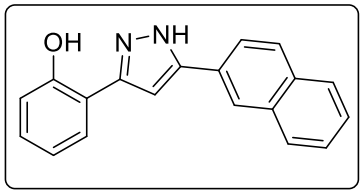
4-Chloro-2-(5-phenyl-1*H*-pyrazol-3-yl)phenol (4ca): white solid; yield 75% (93.3 mg); **mp**: 154-156 °C; $\mathbf{R_f}$ = 0.64 (EtOAc:hexane = 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.77 (s, 1H), 10.16 (s, 1H), 7.60 (dd, *J* = 8.7, 5.0 Hz, 3H), 7.52 – 7.43 (m, 3H), 7.18 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 6.89 (s, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 155.1, 152.0, 144.1, 132.0, 129.4, 129.3, 129.0, 128.3, 125.6, 119.0, 118.3, 111.1, 99.6 ppm; **HRMS** (ESI) m/z calculated for $C_{15}H_{11}ClN_2O[M+H]^+$: 271.0633, found 271.0620.



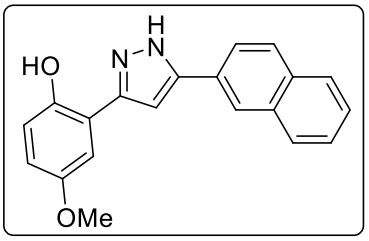
4-Bromo-2-(5-phenyl-1*H*-pyrazol-3-yl)phenol (4da): white solid; yield 76% (91.4 mg); **mp**: 178-180 °C; $\mathbf{R_f}$ = 0.65 (EtOAc:hexane = 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.81 (s, 1H), 10.20 (s, 1H), 7.73 (d, *J* = 2.3 Hz, 1H), 7.61 (d, *J* = 7.3 Hz, 2H), 7.51 – 7.43 (m, 3H), 7.32 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 1H), 6.89 (s, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 155.1, 152.0, 144.1, 132.0, 129.4, 129.3, 129.0, 128.3, 125.6, 119.0, 118.3, 111.1, 99.6 ppm; **HRMS** (ESI) m/z calculated for $C_{15}H_{11}{}^{79}BrN_2O[M+H]+$: 315.0128, found 315.0117; HRMS (ESI) m/z calculated for $C_{15}H_{11}{}^{81}BrN_2O[M+H]+$: 317.0107, found 317.0090.



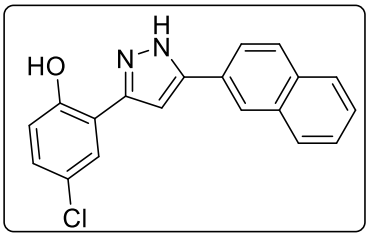
2-(5-(naphthalen-1-yl)-1*H*-pyrazol-3-yl)phenol (4ab): white solid; yield 81% (127.3 mg); **mp:** 156-158 °C; $\mathbf{R_f}$ = 0.64 (EtOAc:hexane = 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.79 (s, 1H), 10.34 (s, 1H), 8.11 (s, 1H), 8.00– 7.92 (m, 3H), 7.75 – 7.70 (m, 2H), 7.58 (s, 2H), 7.28 (s, 3H), 7.10 – 7.06 (m, 2H), 7.01 (s, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 156.0, 144.0, 133.4, 133.3, 129.5, 129.2, 128.2 (2C), 127.9 (2C), 127.0, 126.9, 126.6, 124.6, 123.3, 119.4, 117.1, 116.4, 99.9 ppm; **DEPT-135** (125 MHz, $CDCl_3$): δ 128.8, 128.6, 128.1, 127.6 (2C), 126.6, 126.4, 124.5, 123.6, 119.2, 116.7, 99.0 ppm; **HRMS** (ESI) m/z calculated for $C_{19}H_{14}N_2O[M+H]^+$: 287.1179, found 287.1179.



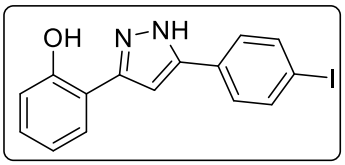
4-Methoxy-2-(5-(naphthalen-1-yl)-1*H*-pyrazol-3-yl)phenol (4bb): white solid; yield 83% (123.2 mg); **mp**: 156-158 °C; $\mathbf{R_f}$ = 0.60 (EtOAc:hexane = 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 13.13 (s, 1H), 10.65 (s, 1H), 8.14 (s, 1H), 7.81 – 7.72 (m, 4H), 7.42 – 7.36 (m, 2H), 7.29 – 7.28 (m, 1H), 7.08 (d, *J* = 2.7 Hz, 1H), 6.90 (s, 1H), 6.81 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.70 – 6.66 (m, 1H), 3.72 (t, *J* = 3.1 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 152.5, 152.5, 149.8, 133.3, 133.3, 133.0, 128.6, 128.6, 128.1, 127.7, 126.6, 126.4, 124.5, 123.6, 117.3, 116.9, 115.0, 111.2, 99.2, 55.8 ppm. **DEPT-135** (125 MHz, $CDCl_3$): δ 128.6, 128.1, 127.7, 127.0, 126.6, 126.5, 124.6, 123.6, 117.3, 115.0, 111.2, 55.8 ppm; **HRMS** (ESI) m/z calculated for $C_{20}H_{16}N_2O_2[M+H]^+$: 317.1285, found 317.1279.



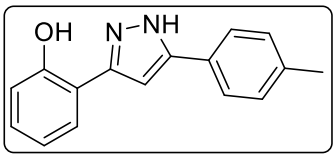
4-Chloro-2-(5-(naphthalen-1-yl)-1*H*-pyrazol-3-yl)phenol (4cb): white solid; yield 74% (109.1 mg); **mp:** 206-208 °C; $\mathbf{R_f}$ = 0.66 (EtOAc:hexane = 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.77 (s, 1H), 10.31 (s, 1H), 8.09 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.91 (s, 2H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 2.2 Hz, 1H), 7.59 – 7.55 (m, 2H), 7.22 – 7.17 (m, 1H), 7.02 (s, 1H), 6.99 (d, *J* = 8.7 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 154.4, 145.0, 142.0, 134.4, 133.2, 133.0, 128.6, 128.4, 128.1, 127.6, 126.6, 126.5, 125.8, 124.6, 123.7, 123.6, 118.2, 118.1, 99.2 ppm; **DEPT-135** (125 MHz, $CDCl_3$): δ 128.6, 128.4, 128.1, 127.6, 126.6, 126.4, 125.8, 124.6, 123.5, 118.1, 99.2 ppm; **HRMS** (ESI) m/z calculated for $C_{19}H_{13}ClN_2O[M+H]^+$: 321.0789, found 321.0793.



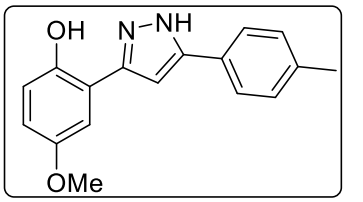
2-(5-(4-Iodophenyl)-1*H*-pyrazol-3-yl)phenol (4ag): pale yellowish solid; yield 67% (133.2 mg); **mp**: 168-170 °C; $\mathbf{R_f}$ = 0.63 (EtOAc:hexane = 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 13.07 (s, 1H), 10.93 (s, 1H), 7.62 (s, 2H), 7.47 (s, 1H), 7.41 – 7.27 (m, 2H), 7.04 (s, 1H), 6.87 – 6.74 (m, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.3, 155.8, 153.9, 141.6, 138.0, 129.0, 127.4, 126.4, 119.3, 116.8, 116.6, 98.9, 93.9 ppm; **DEPT-135** (125 MHz, $CDCl_3$): δ 137.8, 128.9, 127.3, 126.9, 119.2, 116.7, 98.8 ppm; **HRMS** (ESI) m/z calculated for $C_{15}H_{11}IN_2O[M+H]^+$: 362.9989, found 362.9984.



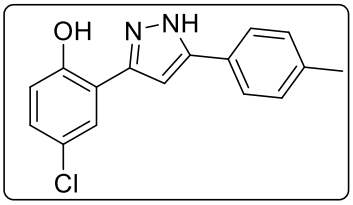
2-(5-(p-tolyl)-1*H*-pyrazol-3-yl)phenol (4ac): white solid; yield 91% (125.0 mg); **mp:** 150-152 °C; $\mathbf{R_f}$ = 0.68 (EtOAc:hexane = 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.74 (s, 1H), 10.09 (s, 1H), 7.17 – 7.15 (m, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.19 (s, 1H), 7.18 – 7.15 (m, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.87 (t, *J* = 7.5 Hz, 1H), 6.80 (s, 1H), 2.34 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 156.0, 153.2, 143.9, 139.3, 129.9, 129.4, 126.5, 125.8, 125.5, 119.3, 117.1, 116.5, 99.1, 21.3 ppm; **HRMS** (ESI) m/z calculated for $C_{16}H_{14}N_2O[M+H]^+$: 251.1179, found 251.1165.



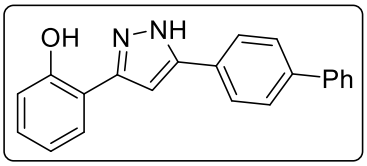
4-Methoxy-2-(5-(p-tolyl)-1*H*-pyrazol-3-yl)phenol (4bc): white solid; yield 94% (123.6 mg); **mp:** 136-138 °C; $\mathbf{R_f}$ = 0.64 (EtOAc:hexane = 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.36 (s, 2H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.29 – 7.25 (m, 2H), 7.16 (d, *J* = 2.8 Hz, 1H), 6.97 (d, *J* = 8.9 Hz, 1H), 6.83 (dd, *J* = 7.5, 4.1 Hz, 2H), 3.83 (s, 3H), 2.41 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 152.8, 152.6 150.1, 144.0, 139.3, 129.9, 125.8, 125.5, 117.6, 116.7, 115.3, 111.5, 99.2, 56.0, 21.3 ppm; **HRMS** (ESI) m/z calculated for $C_{17}H_{16}N_2O_2$ $[M+H]^+$: 281.1285, found 281.1287.



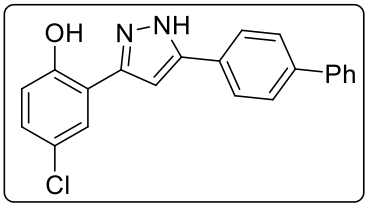
4-Chloro-2-(5-(p-tolyl)-1*H*-pyrazol-3-yl)phenol (4cc): white solid; yield 85% (111.2 mg); **mp**: 184-186 °C; $\mathbf{R_f}$ = 0.66 (EtOAc:hexane = 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.79 (s, 1H), 10.13 (s, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.18 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 6.85 (s, 1H), 2.42 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 154.6, 152.1, 144.1, 139.6, 130.0, 129.0, 126.0, 125.5, 125.5, 124.0, 118.4, 117.7, 99.3, 21.3 ppm; **HRMS** (ESI) m/z calculated for $C_{15}H_{11}BrN_2O$ $[M+H]^+$: 285.0789, found 285.0775.



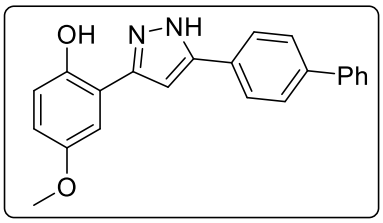
2-(5-([1,1'-Biphenyl]-4-yl)-1*H*-pyrazol-3-yl)phenol (4ad): white solid; yield 83% (142.3 mg); **mp**: 128-130 °C; $\mathbf{R_f}$ = 0.70 (EtOAc:hexane = 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 12.77 (s, 1H), 11.12 (s, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.68 – 7.59 (m, 5H), 7.44 (t, *J* = 7.1 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.29 – 7.27 (m, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.95 – 6.89 (m, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 155.8, 154.3, 152.3, 133.3, 133.0, 128.9, 128.7, 128.1, 127.6, 126.8, 126.5, 124.5, 123.6, 119.2, 116.8, 116.7, 99.0 ppm; **HRMS** (ESI) m/z calculated for $C_{21}H_{16}N_2O[M+H]^+$: 313.1335, found 313.1336.



2-(5-([1,1'-Biphenyl]-4-yl)-1*H*-pyrazol-3-yl)-4-chlorophenol (4cb): white solid; yield 75% (119.6 mg); **mp**: 160-162 °C; $\mathbf{R_f}$ = 0.69 (EtOAc:hexane = 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 13.13 (s, 1H), 11.19 (s, 1H), 7.83 (d, *J* = 7.7 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.65 – 7.61 (m, 2H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 6.9 Hz, 1H), 7.35 (d, *J* = 2.9 Hz, 1H), 7.19 – 7.13 (m, 1H), 6.98 – 6.91 (m, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 154.5, 151.1, 144.7, 141.3, 140.1, 128.8, 128.8, 128.5, 127.6, 127.5, 126.9, 126.1, 125.9, 123.8, 118.2, 118.1, 98.91 ppm; **DEPT-135** (125 MHz, DMSO): δ 129.4, 128.8, 128.2, 127.7, 127.3, 127.0, 126.4, 118.7, 101.3 ppm; **HRMS** (ESI) m/z calculated for $C_{21}H_{15}ClN_2O[M+H]^+$: 347.0946, found 347.0947.

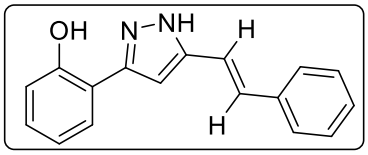


2-(5-([1,1'-Biphenyl]-4-yl)-1*H*-pyrazol-3-yl)-4-methoxyphenol (4bd): pale yellowish solid; yield 88% (141.3 mg); **mp:** 150-152 °C; $\mathbf{R_f}$ = 0.65 (EtOAc:hexane = 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.29 (s, 2H), 7.70 (q, *J* = 8.5 Hz, 4H), 7.65 – 7.62 (m, 2H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 3.0 Hz, 1H), 6.98 (d, *J* = 8.9 Hz, 1H), 6.92 (s, 1H), 6.85 (dd, *J* = 8.9, 3.0 Hz, 1H), 3.84 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 152.9, 152.6, 150.1, 143.7, 142.0, 140.0, 128.9, 127.9, 127.8, 127.4, 127.0, 126.0, 117.7, 116.5, 115.4, 111.5, 99.6, 56.0 ppm; **DEPT-135** (125 MHz, $CDCl_3$): δ 128.9,

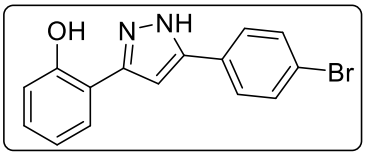


127.9, 127.0, 126.0, 117.7, 115.4, 111.5, 99.6, 56.0 ppm; **HRMS** (ESI) m/z calculated for $C_{22}H_{18}N_2O_2[M+H]^+$: 343.1441, found 343.1434.

(*E*)-2-(5-Styryl-1*H*-pyrazol-3-yl)phenol (4ah) : white solid; yield 78% (112.3 mg); **mp:** 98-100 °C; $\mathbf{R_f}$ = 0.68 (EtOAc:hexane = 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.62 (s, 2H), 7.61 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.25 – 7.22 (m, 1H), 7.12 – 7.04 (m, 2H), 6.99 – 6.93 (m, 2H), 6.80 (s, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 156.0, 152.9, 142.0, 135.8, 132.2, 129.4, 128.9, 128.7, 126.6, 126.5, 119.3, 117.1, 116.4, 114.3, 99.7 ppm; **HRMS** (ESI) m/z calculated for $C_{17}H_{14}N_2O$ $[M+H]^+$: 263.1179, found 363.1182.



2-(5-(4-Bromophenyl)-1*H*-pyrazol-3-yl)phenol (4af) : white solid; yield 77% (133.0 mg); **mp:** 184-186 °C; $\mathbf{R_f}$ = 0.72 (EtOAc:hexane = 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.56 (s, 1H), 10.21 (s, 1H), 7.62 (d, *J* = 6.8 Hz, 2H), 7.51 (t, *J* = 11.6 Hz, 3H), 7.26 – 7.24 (m, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 6.95 (t, *J* = 7.0 Hz, 1H), 6.91 (s, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 157.8, 156.8, 155.9, 143.0, 132.5, 129.6, 127.1, 126.5, 123.3, 119.4, 117.1, 116.2, 99.8 ppm; **HRMS** (ESI) m/z calculated for $C_{15}H_{11}{}^{79}BrN_2O[M+H]+$: 315.0128, found 315.0129; HRMS (ESI) m/z calculated for $C_{15}H_{11}{}^{81}BrN_2O[M+H]+$: 317.0107, found 317.0105.



CHAPTER 5

5.1 Conclusion

Finally, we have developed a simple one-pot sequential method for synthesizing biologically attractive 3,5-disubstituted-1*H*-pyrazole derivatives in satisfactory yields by involving cyclic sulfamidate imines and oxime acetates using 30 mol% CuCl. Several vital points are associated with this method, such as broad substrate scope, good yields, cheap catalyst, etc. Therefore, we firmly believe that this method will be suitable for synthetic organic chemistry.

Appendix A

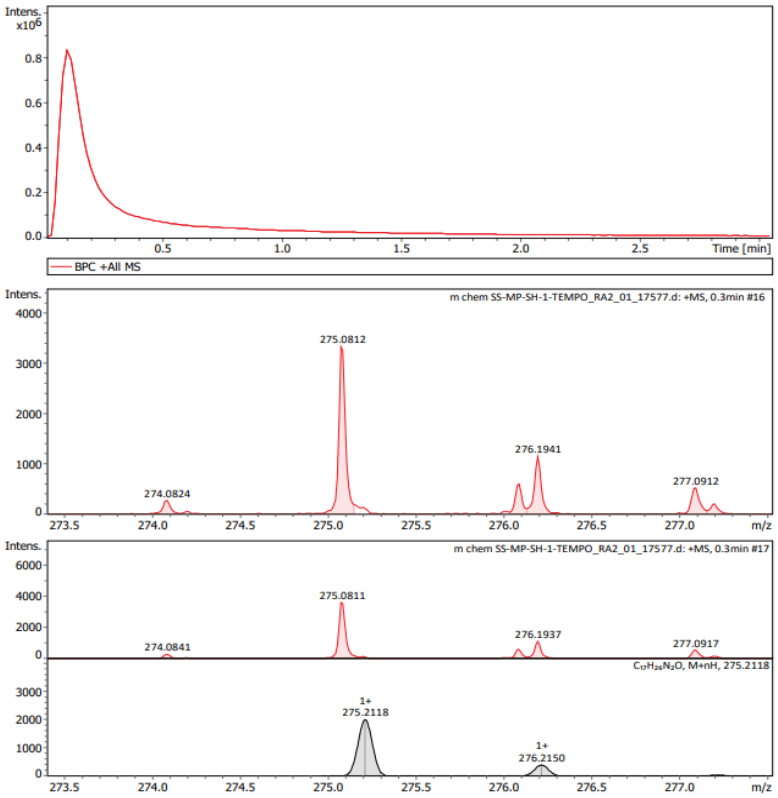


Figure 3. Mass spectrum of **6a** in MeOH

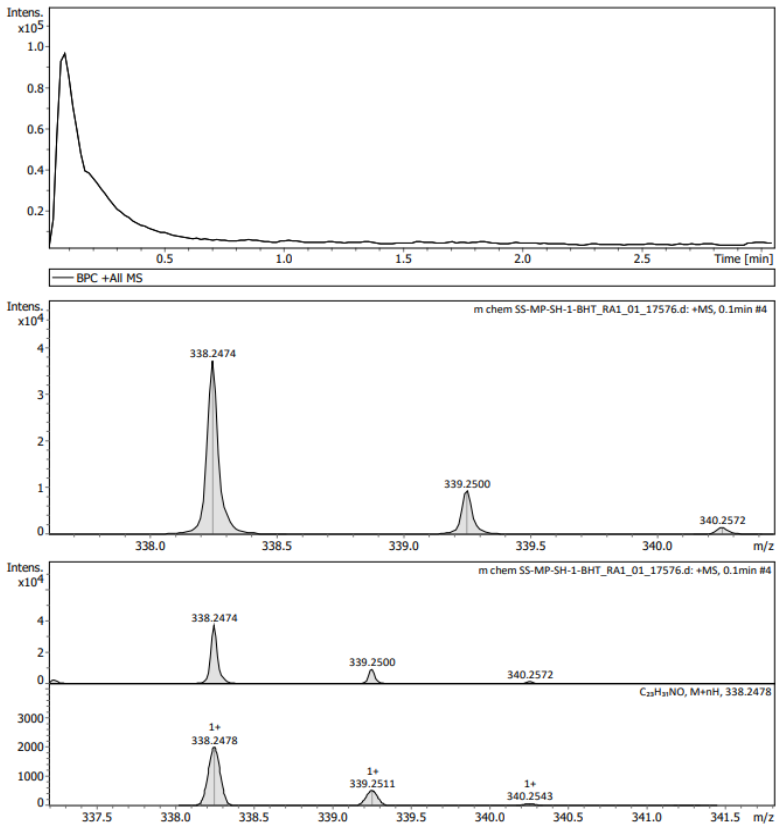


Figure 4. HRMS of **7a** in MeOH

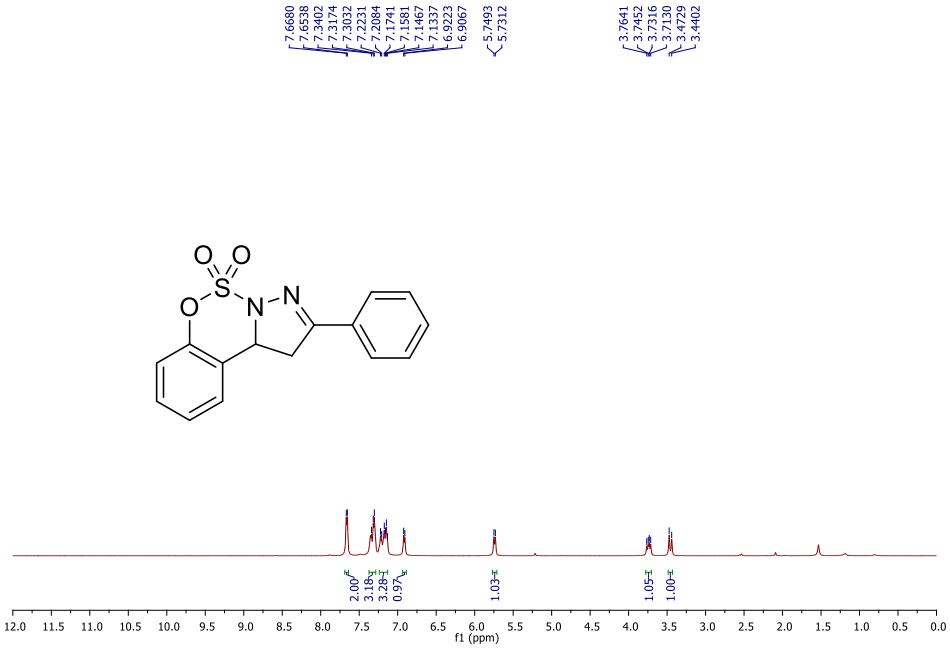


Figure 5. ^{1}H NMR spectrum (500 MHz) of **3aa** in $CDCl_3$

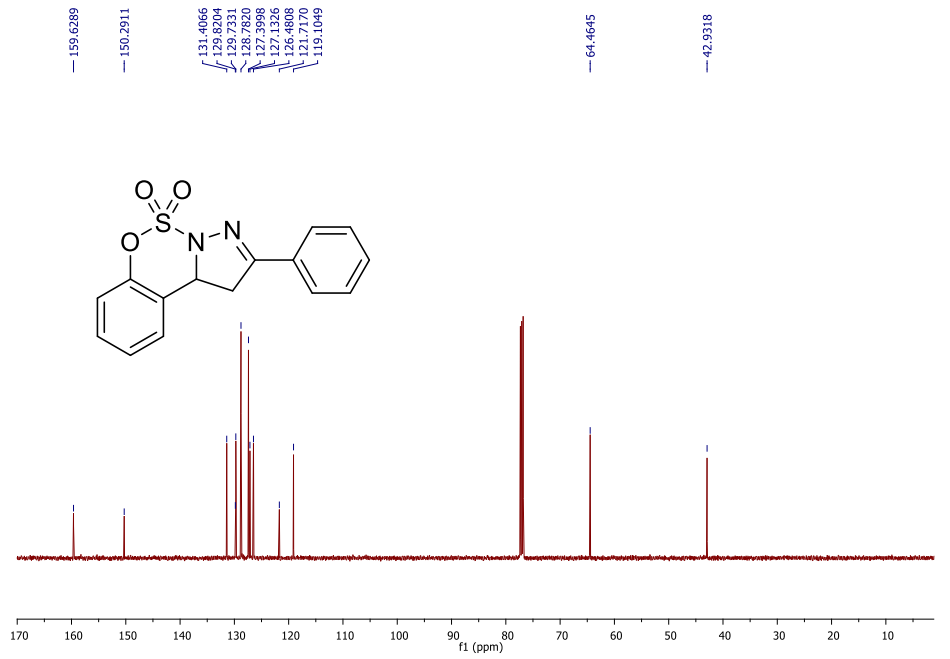


Figure 6. ^{13}C NMR spectrum (125 MHz) of **3aa** in $CDCl_3$

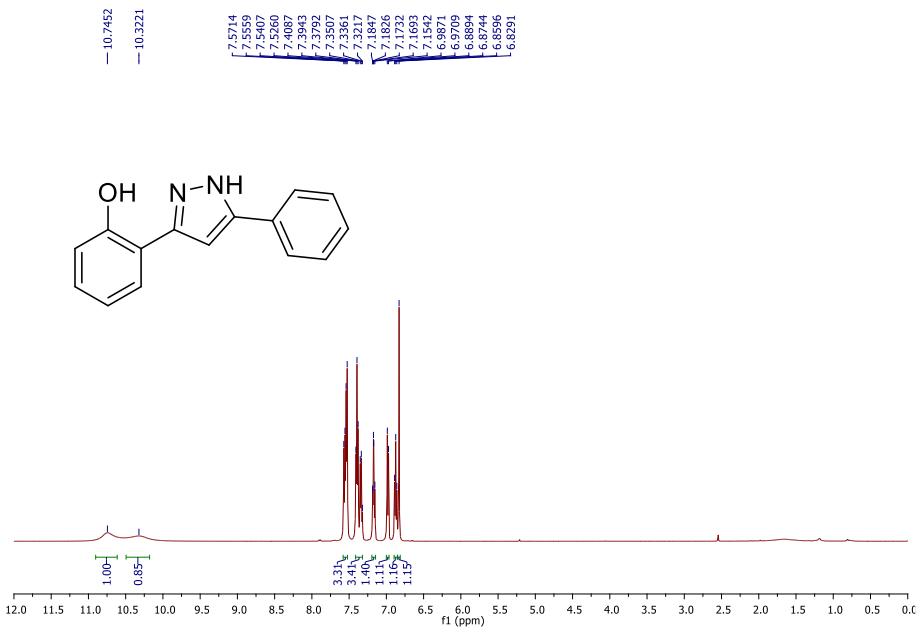


Figure 7. ^{1}H NMR spectrum (500MHz) of **4aa** in $CDCl_3$

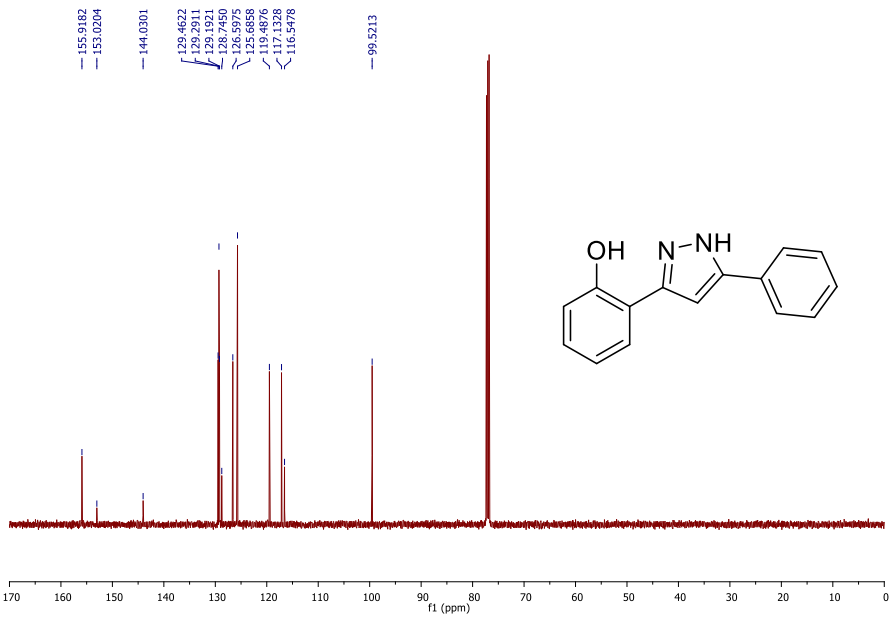


Figure 8. ^{13}C NMR spectrum (125MHz) of **4aa** in $CDCl_3$

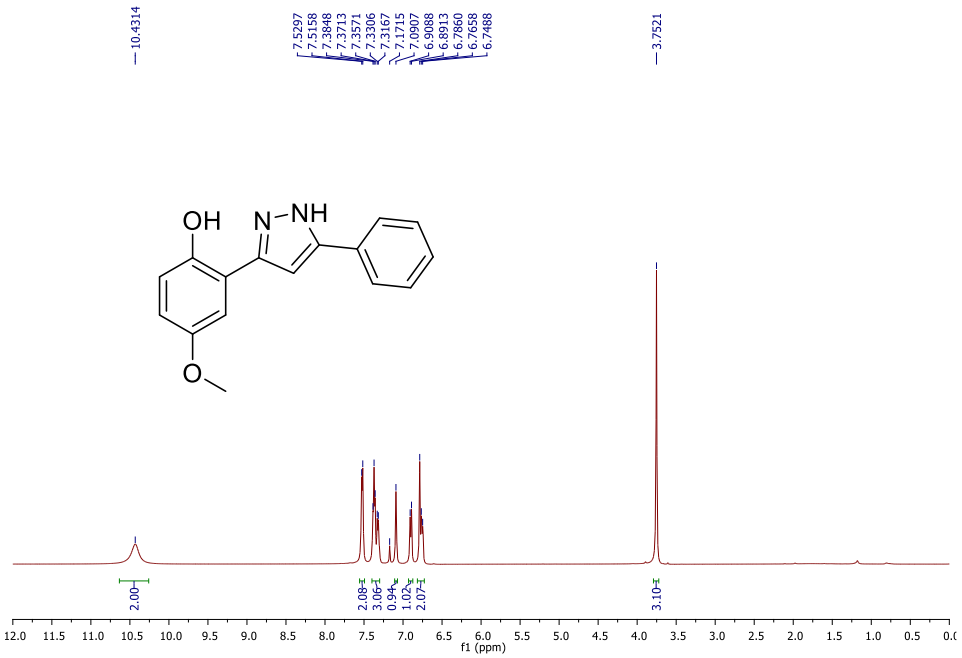


Figure 9. ^{1}H NMR spectrum (500MHz) of **4ba** in $CDCl_3$

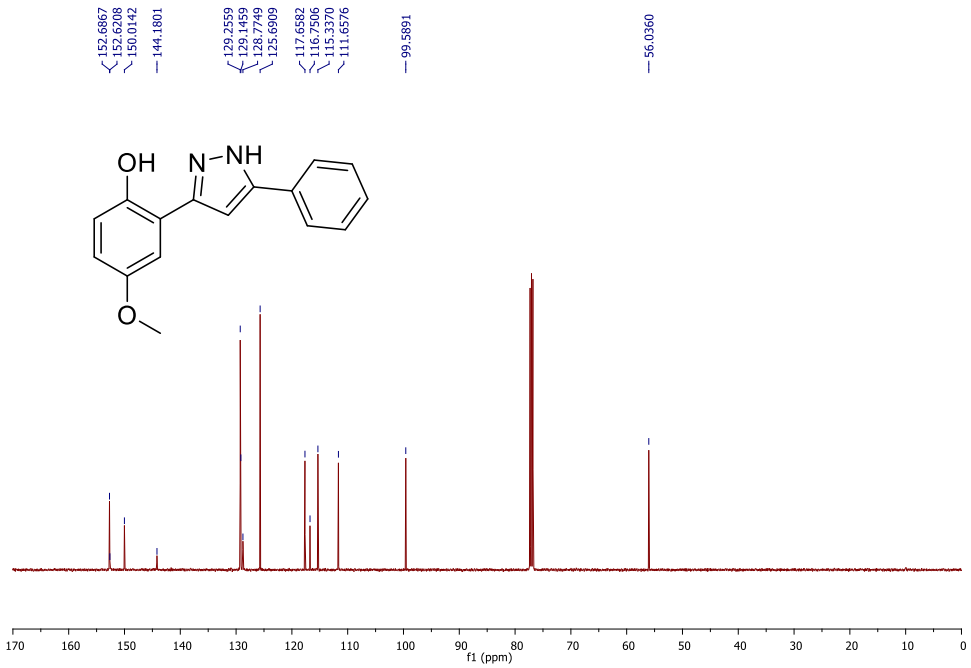


Figure 10. ^{13}C NMR spectrum (125 MHz) of **4ba** in $CDCl_3$

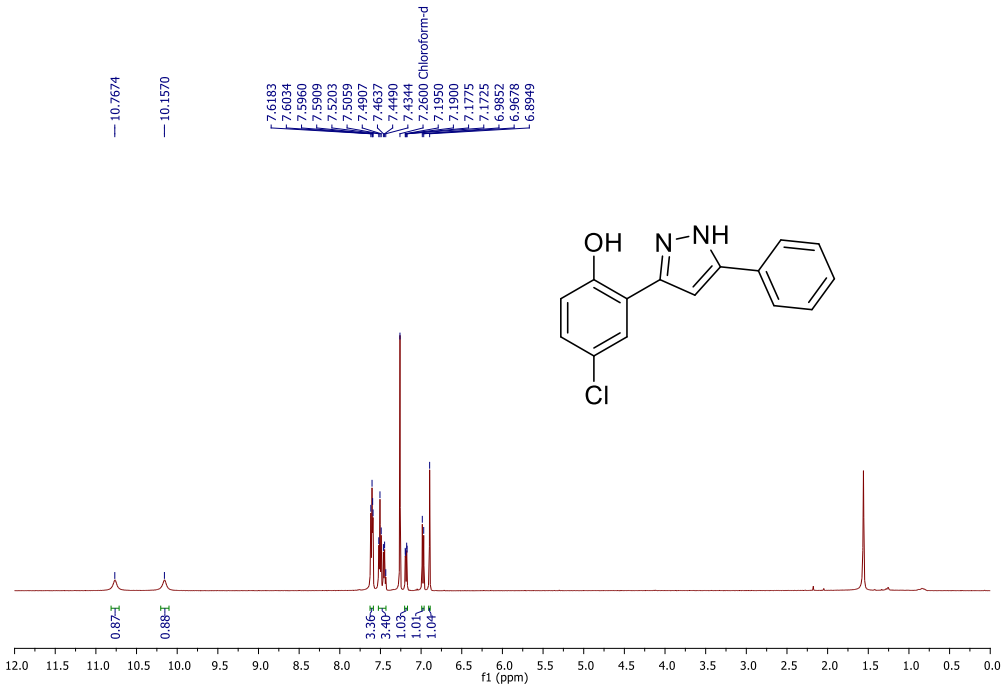


Figure 11. ^{1}H NMR spectrum (500 MHz) of **4ca** in $CDCl_3$

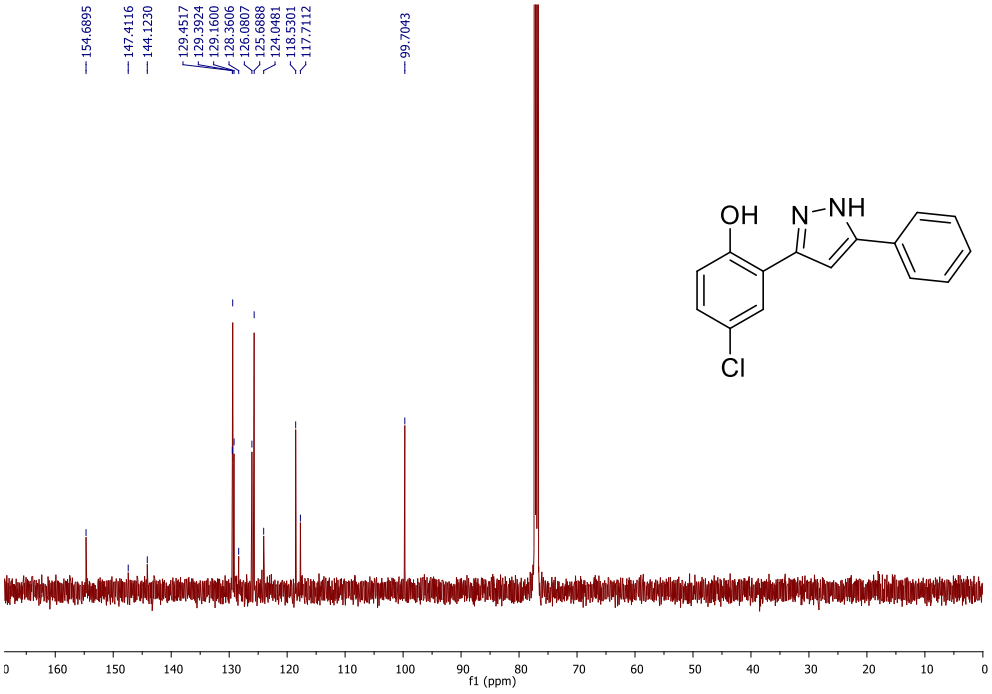


Figure 12. ^{13}C NMR spectrum (125 MHz) of **4ca** in $CDCl_3$

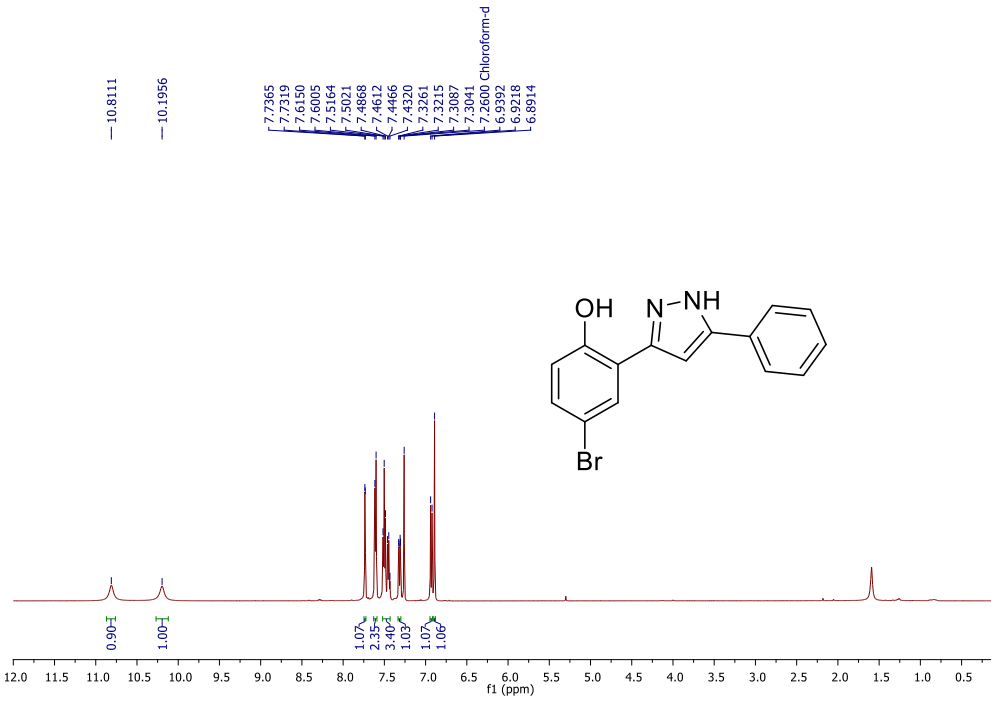


Figure 13. ^{1}H NMR spectrum (500 MHz) of **4da** in $CDCl_3$

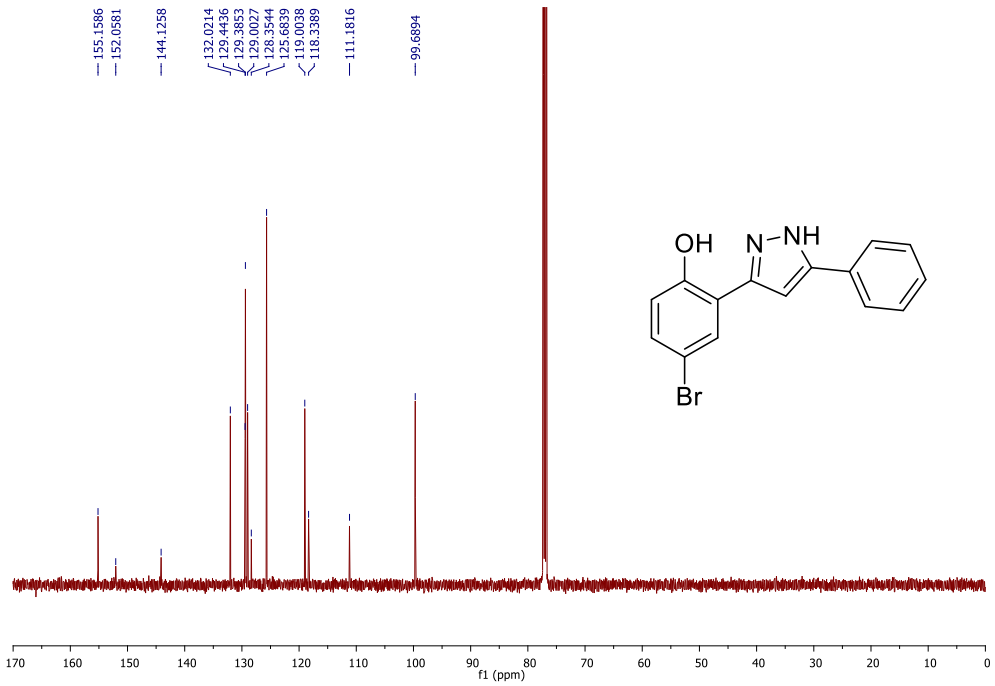


Figure 14. ^{13}C NMR spectrum (125MHz) of **4da** in $CDCl_3$

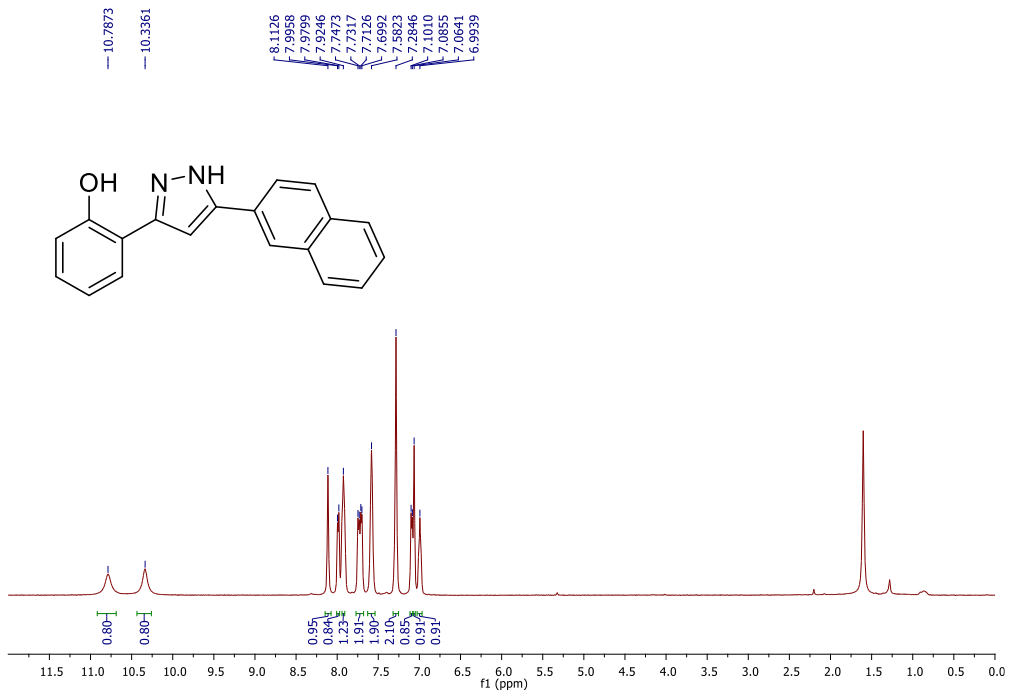


Figure 15. ^{1}H NMR spectrum (500 MHz) of **4ab** in $CDCl_3$

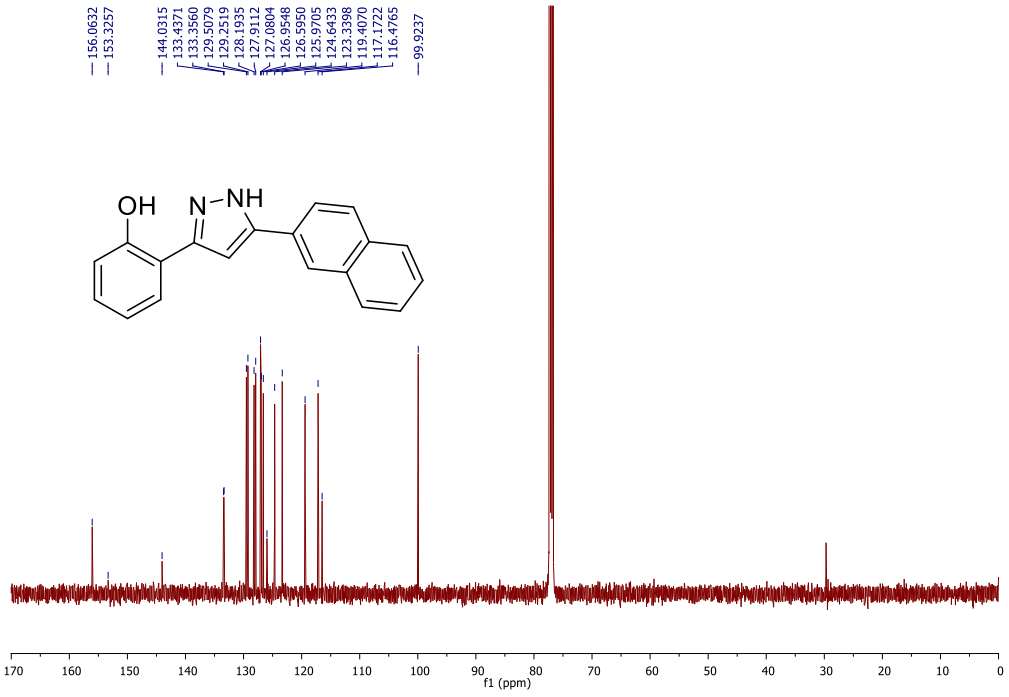


Figure 16. ^{13}C NMR spectrum (125 MHz) of **4ab** in $CDCl_3$

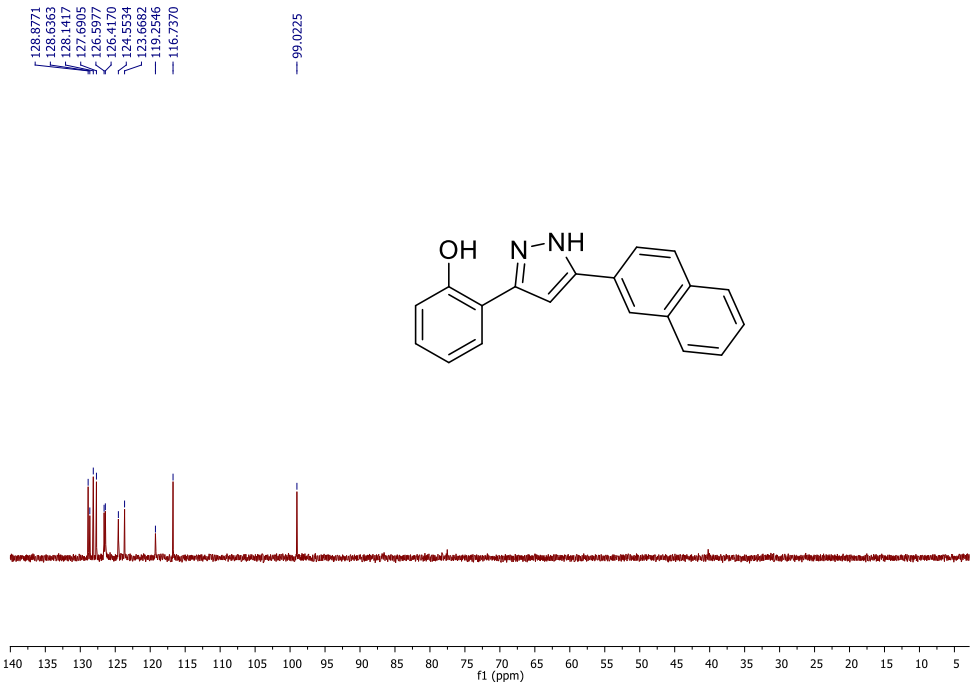


Figure 17. DEPT-135 spectrum (125 MHz) of **4ab** in $CDCl_3$

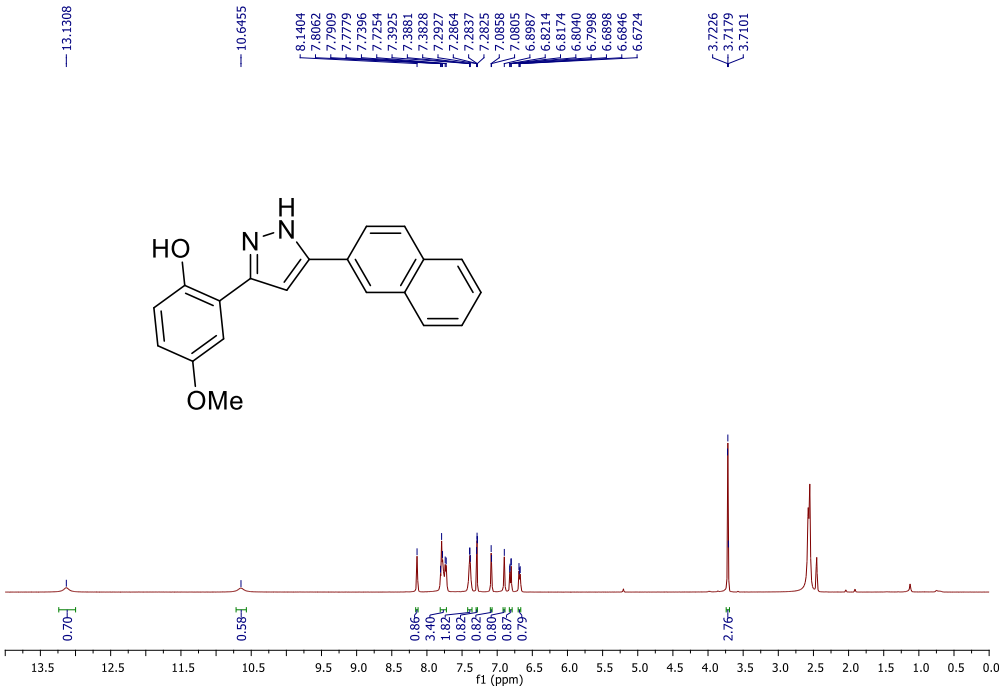


Figure 18. ^1H NMR spectrum (500 MHz) of **4bb** in $CDCl_3$

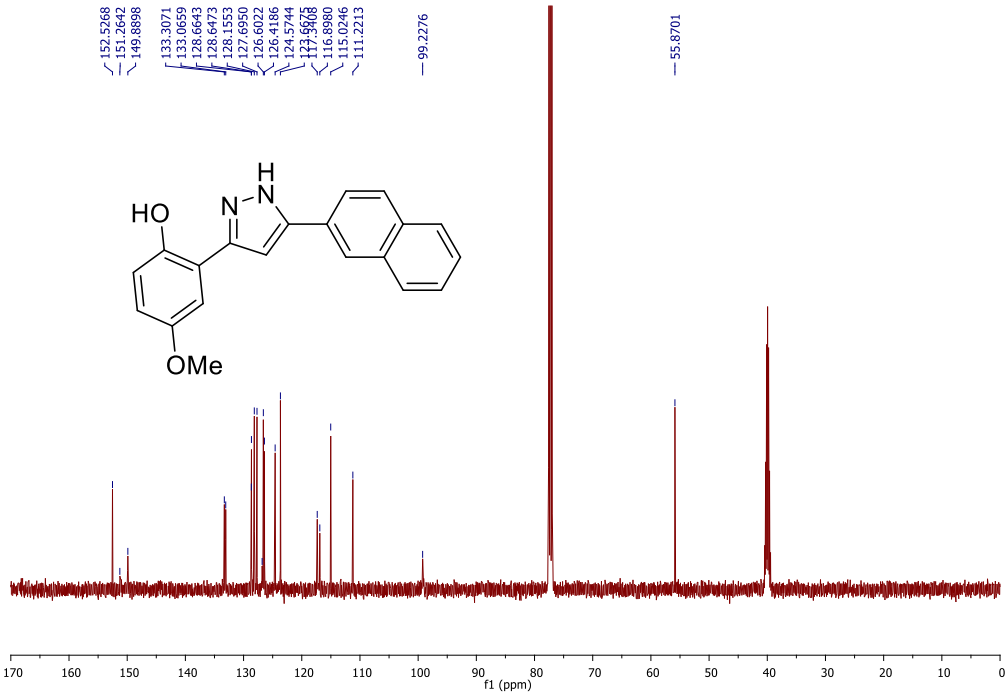


Figure 19. ^{13}C NMR spectrum (125 MHz) of **4bb** in $CDCl_3$

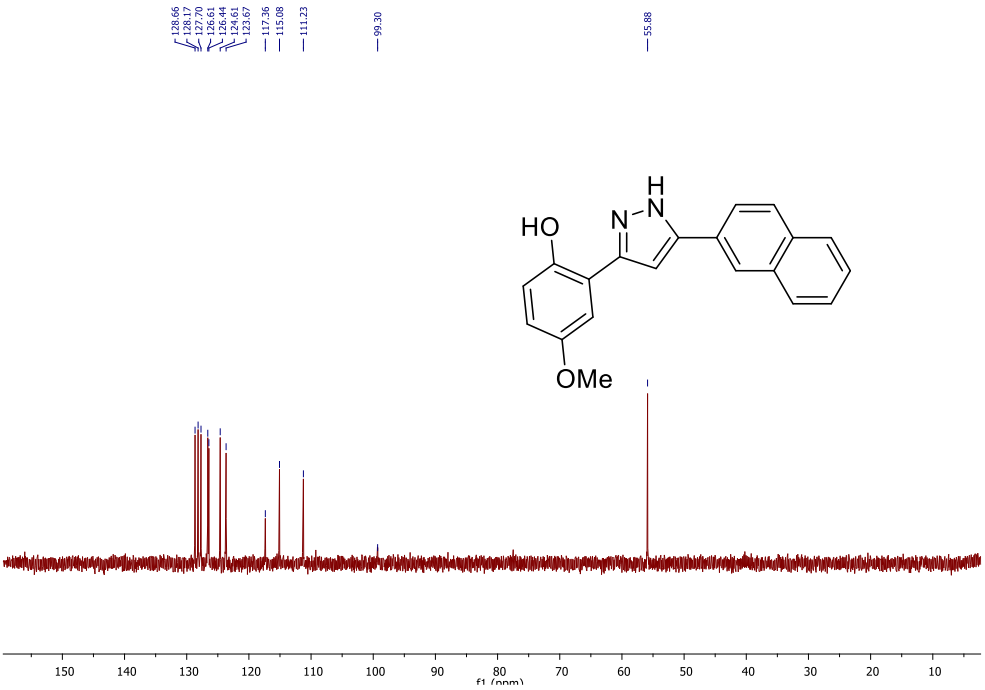


Figure 20. DEPT-135 spectrum (125 MHz) of **4bb** in $CDCl_3$

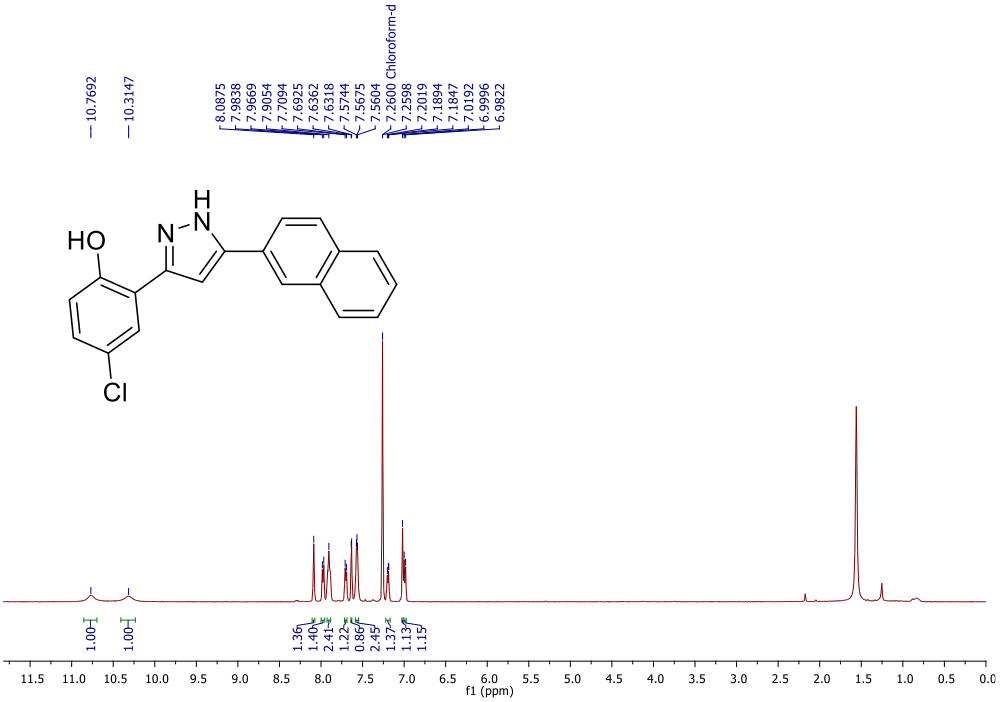


Figure 21. ^{1}H NMR spectrum (500 MHz) of **4cb** in $CDCl_3$

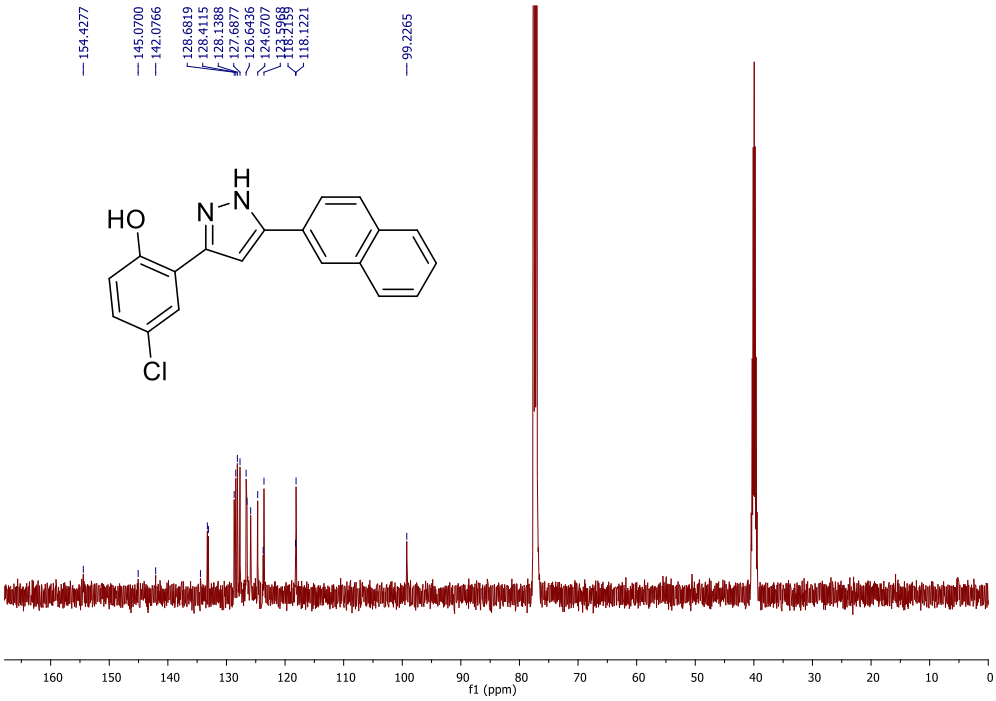


Figure 22. ^{13}C NMR spectrum (125 MHz) of **4cb** in $CDCl_3$

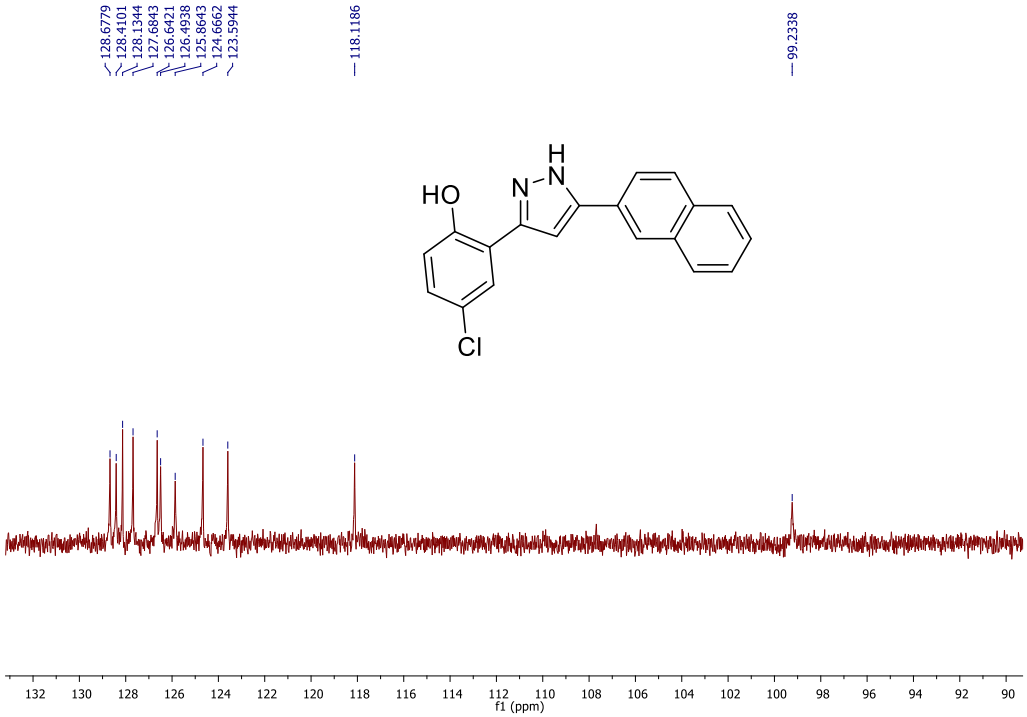


Figure 23. DEPT-135 spectrum (125 MHz) of **4cb** in $CDCl_3$

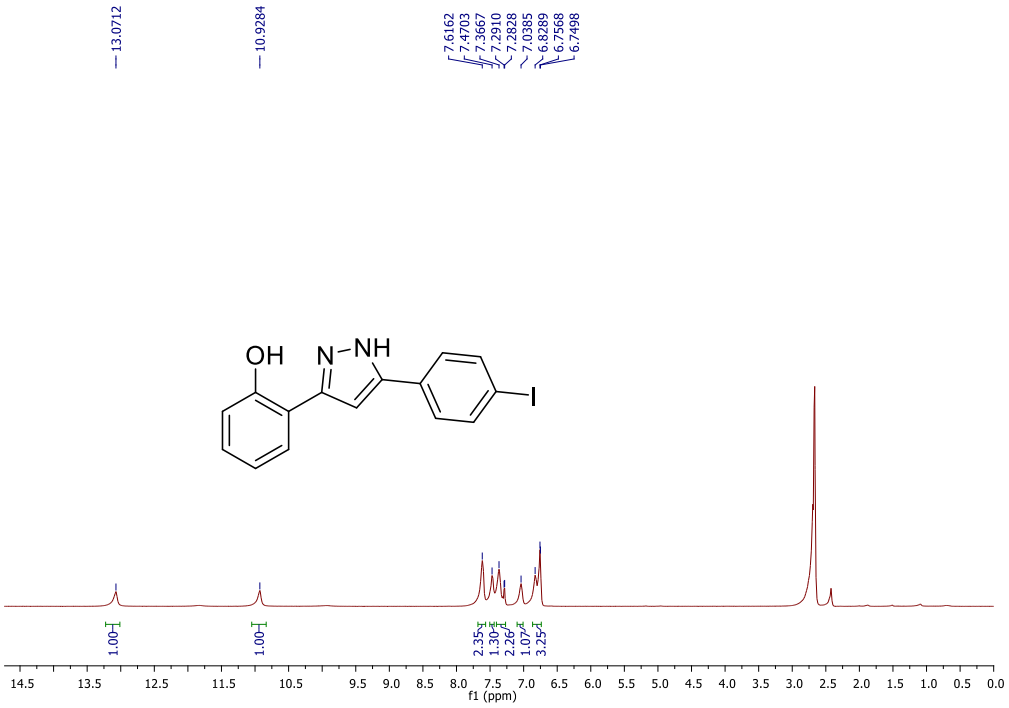


Figure 24. ^1H NMR spectrum (500 MHz) of **4ag** in $CDCl_3$

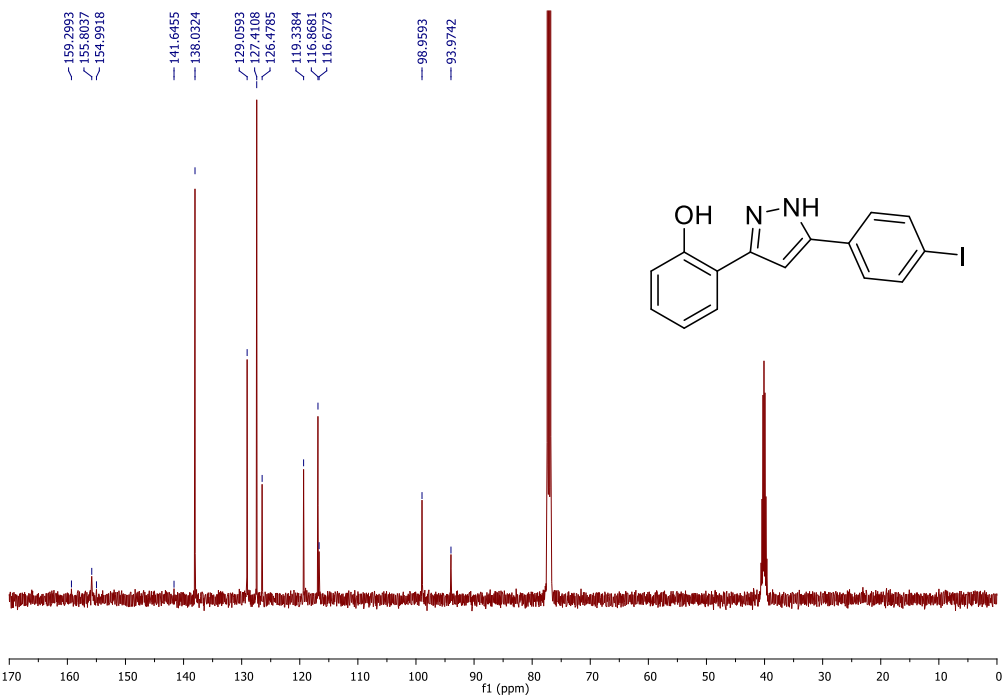


Figure 25. ^{13}C NMR spectrum (125 MHz) of **4ag** in $CDCl_3$

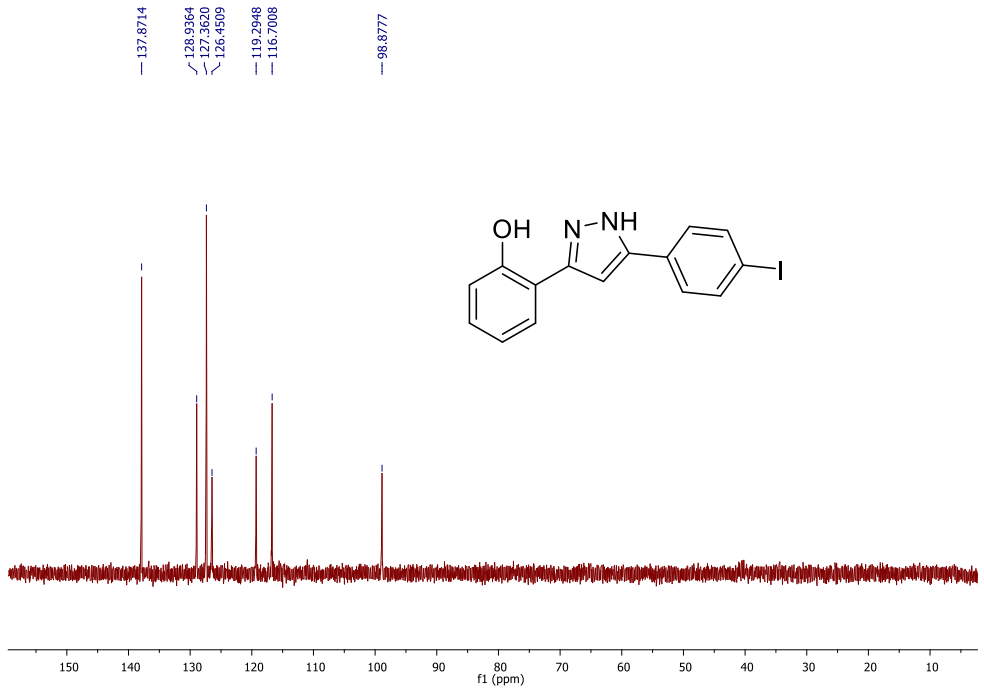


Figure 26. DEPT-135 spectrum (125 MHz) of **4ag** in $CDCl_3$

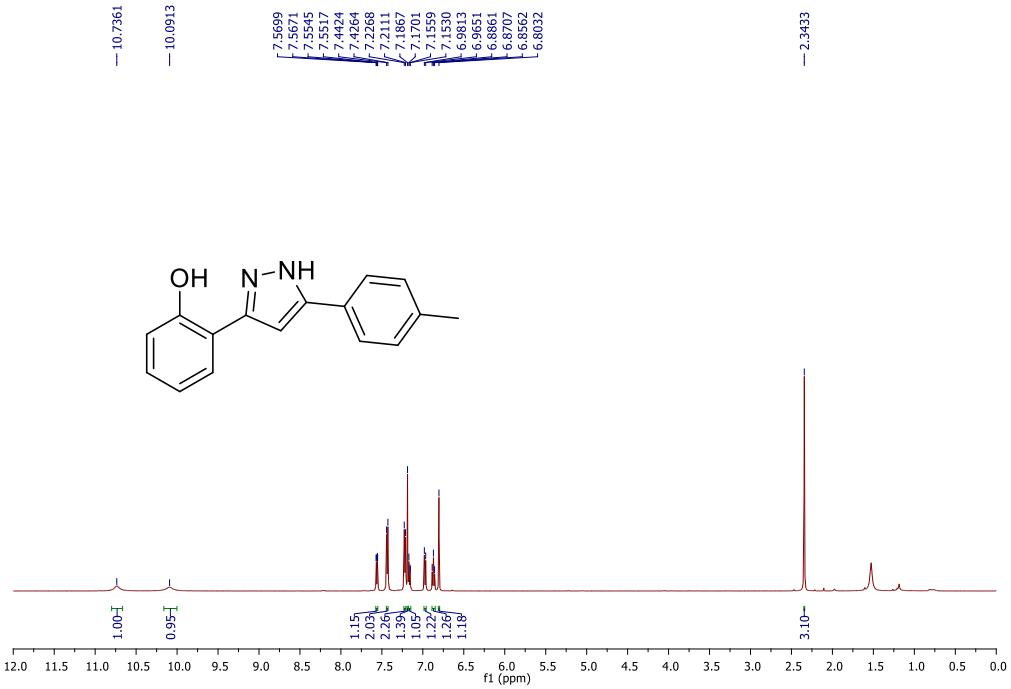


Figure 27. ^{1}H NMR spectrum (500 MHz) of **4ac** in $CDCl_3$

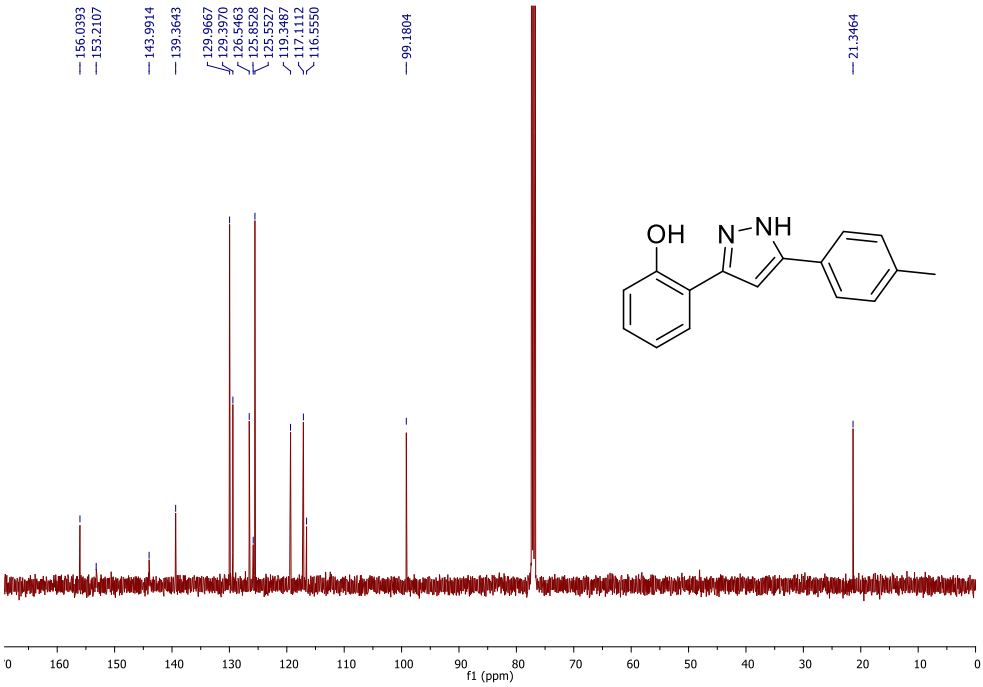


Figure 28. ^{13}C NMR spectrum (125 MHz) of **4ac** in $CDCl_3$

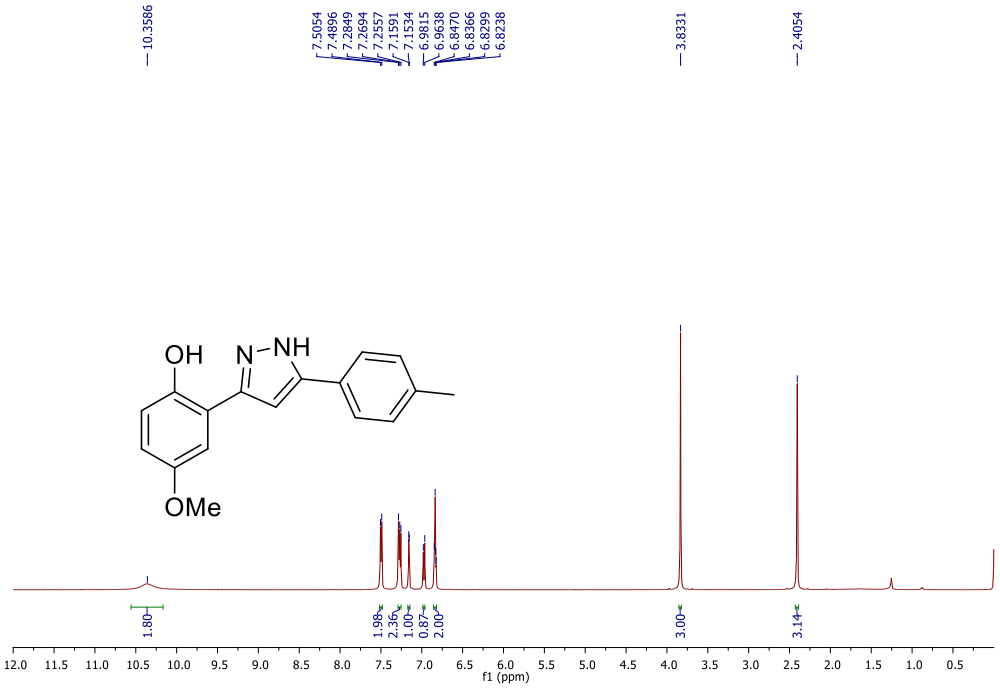


Figure 29. ^{1}H NMR spectrum (500 MHz) of **4bc** in $CDCl_3$

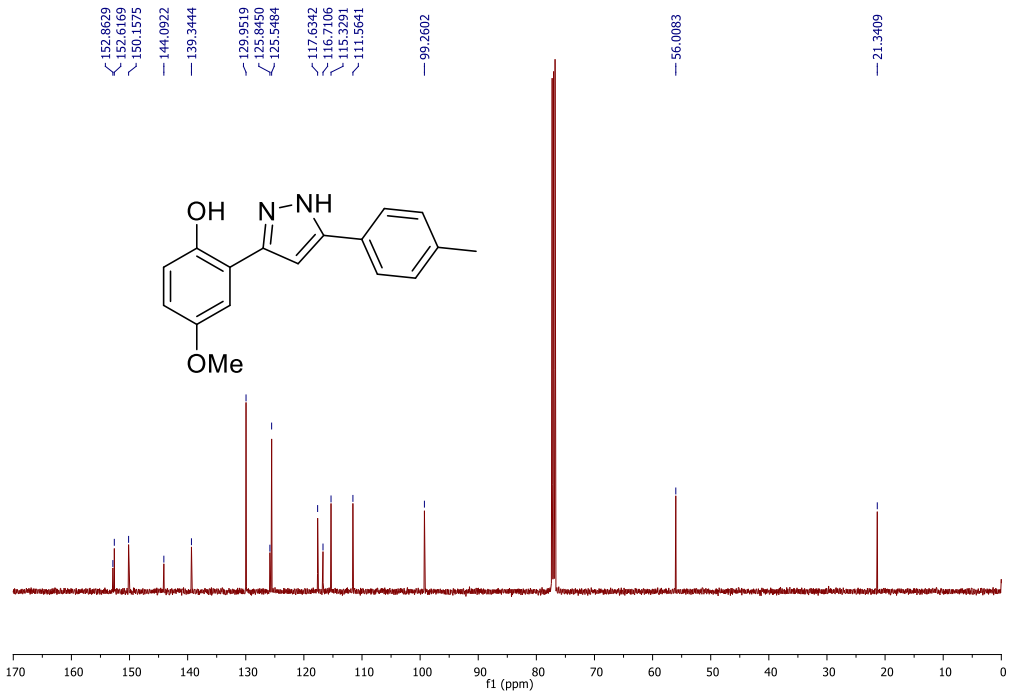


Figure 30. ^{13}C NMR spectrum (125 MHz) of **4bc** in $CDCl_3$

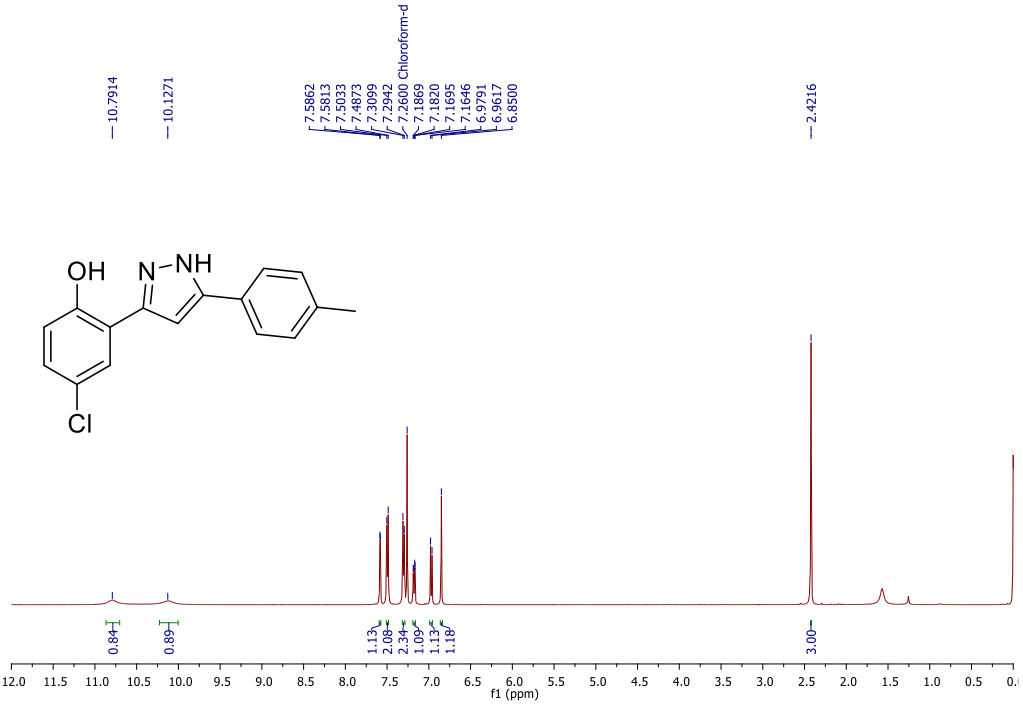


Figure 31. ^{1}H NMR spectrum (500 MHz) of **4cc** in $CDCl_3$

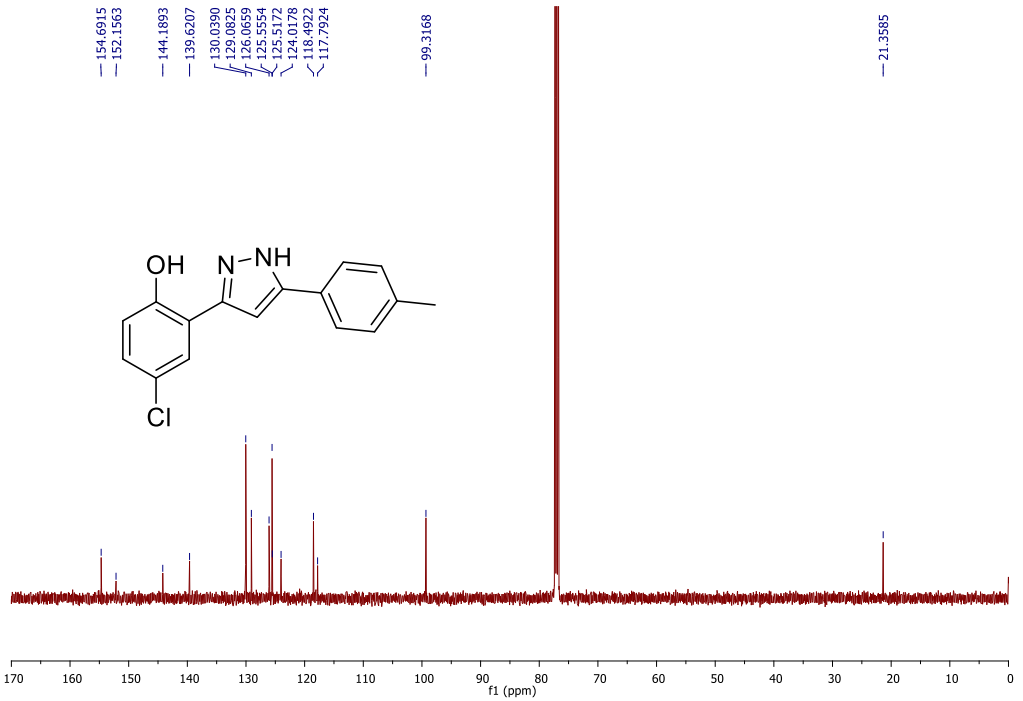


Figure 32. ^{13}C NMR spectrum (125 MHz) of **4cc** in $CDCl_3$

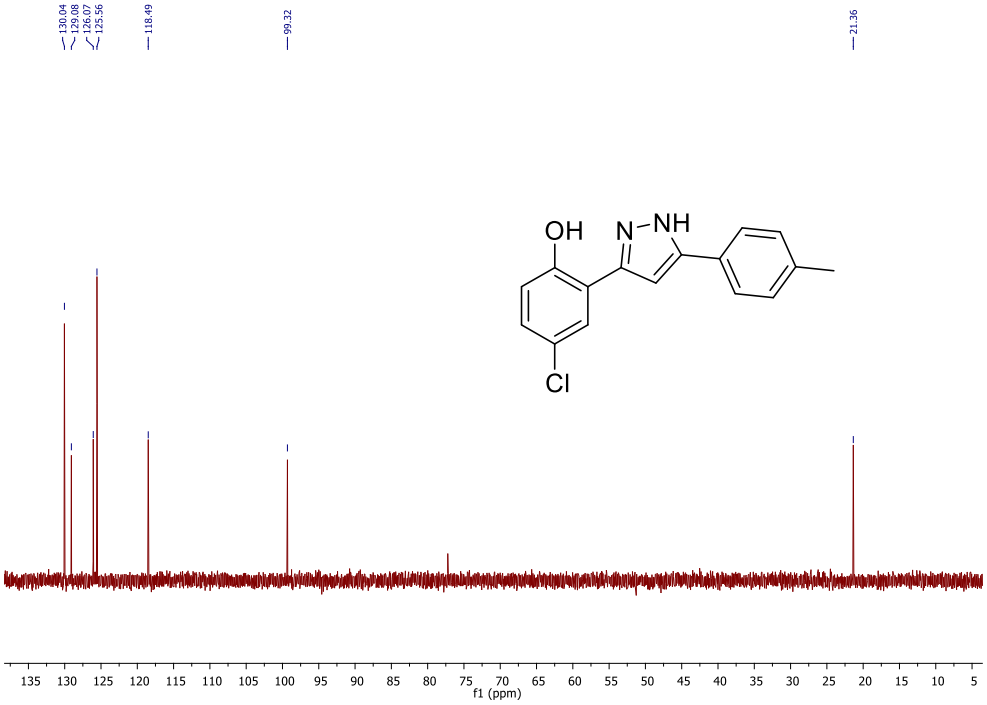


Figure 33. DEPT-135 spectrum (125MHz) of **4cc** in $CDCl_3$

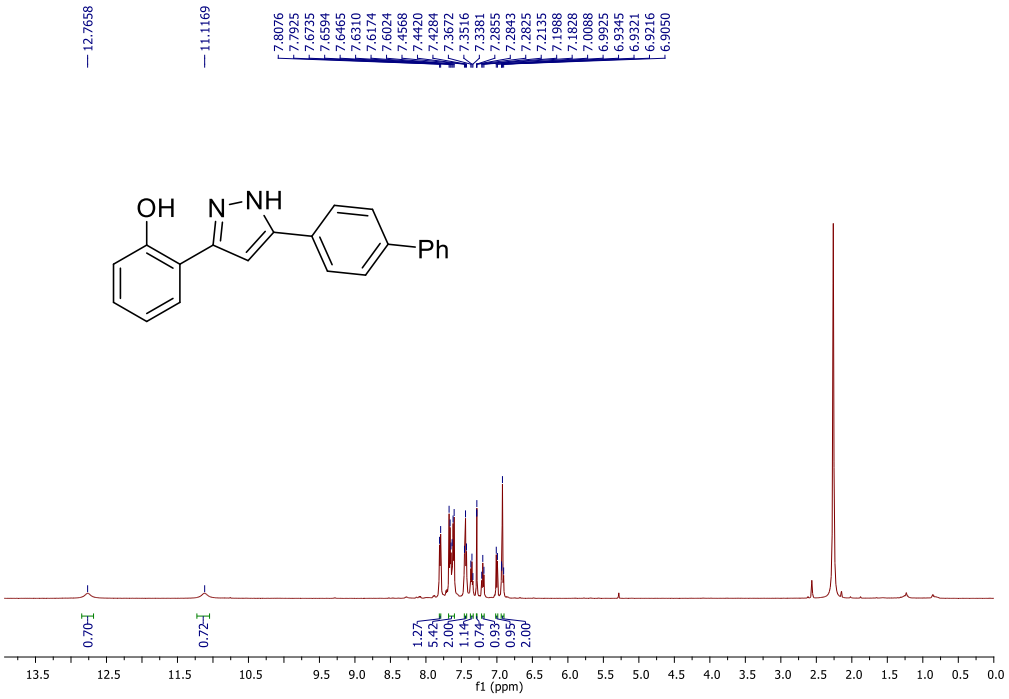


Figure 34. 500 MHz ^{1}H NMR spectrum of **4ad** in $CDCl_3$

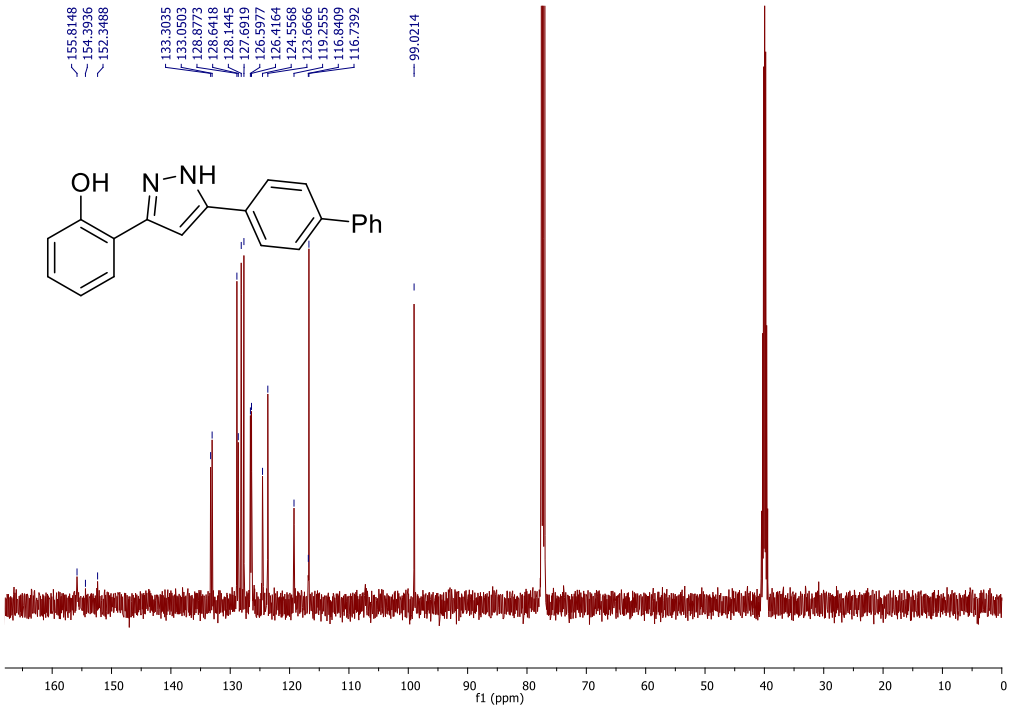


Figure 35. ^{13}C NMR spectrum (125MHz) of **4ad** in $CDCl_3$

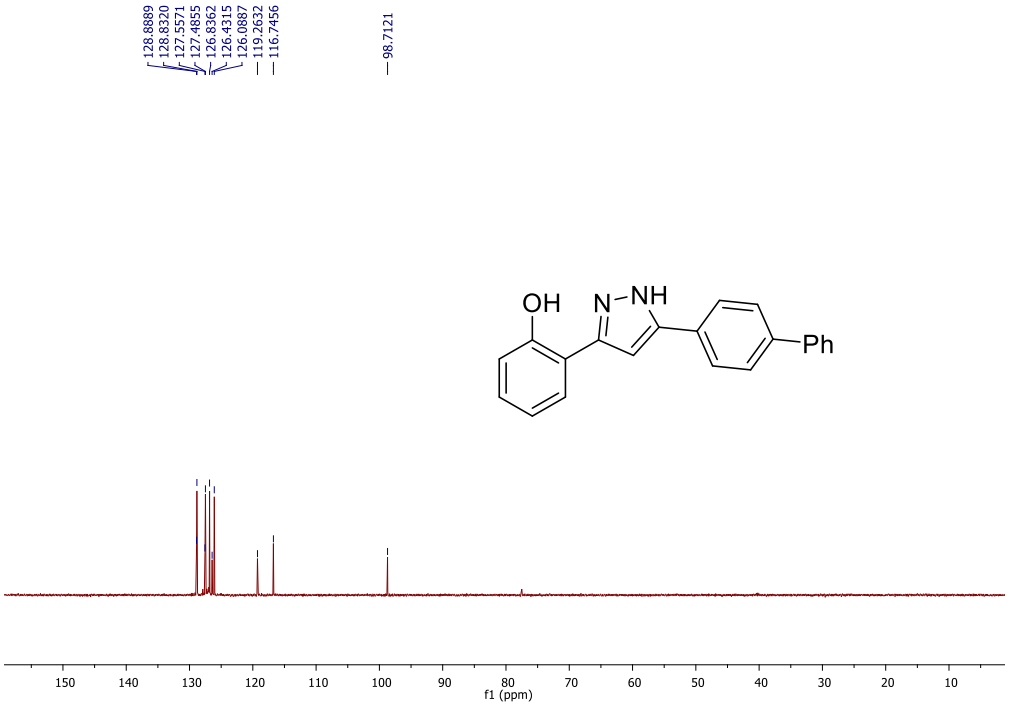


Figure 36. DEPT-135 spectrum (125 MHz) of **4ad** in $CDCl_3$

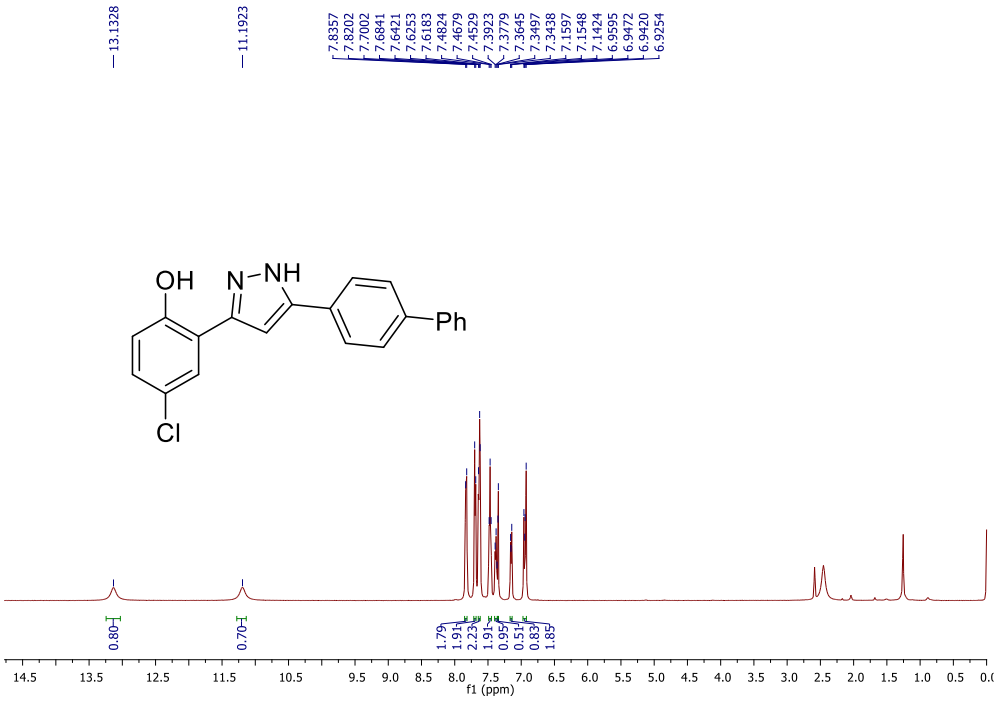


Figure 37. ^{1}H NMR spectrum (500 MHz) of **4cd** in $CDCl_3$

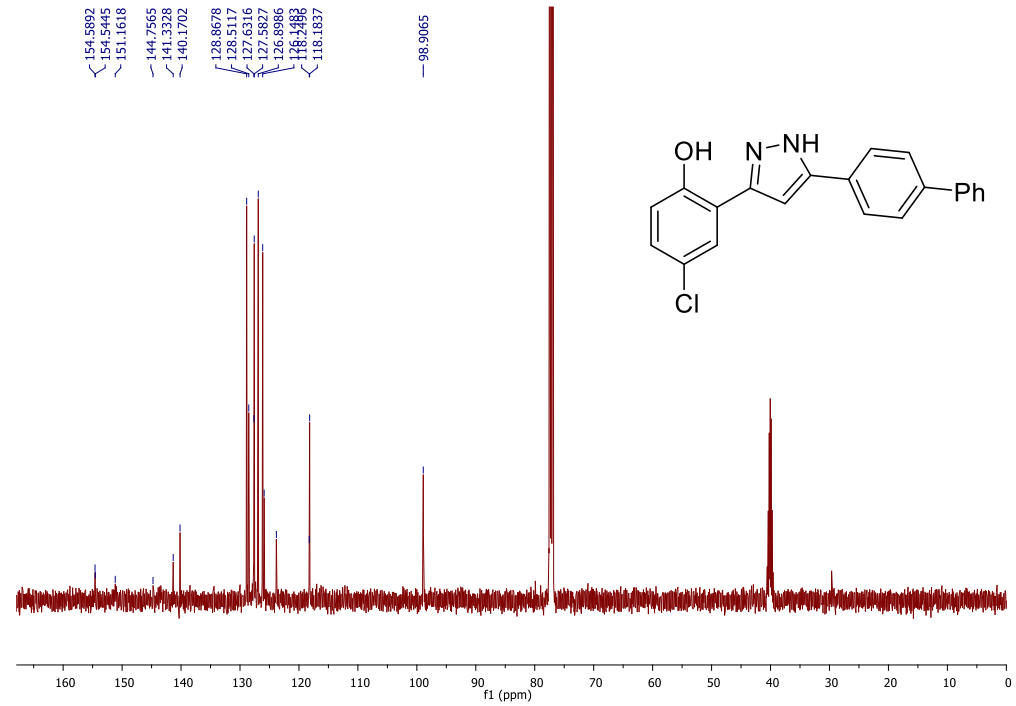


Figure 38. ^{13}C NMR spectrum (125MHz) of **4cd** in $CDCl_3$

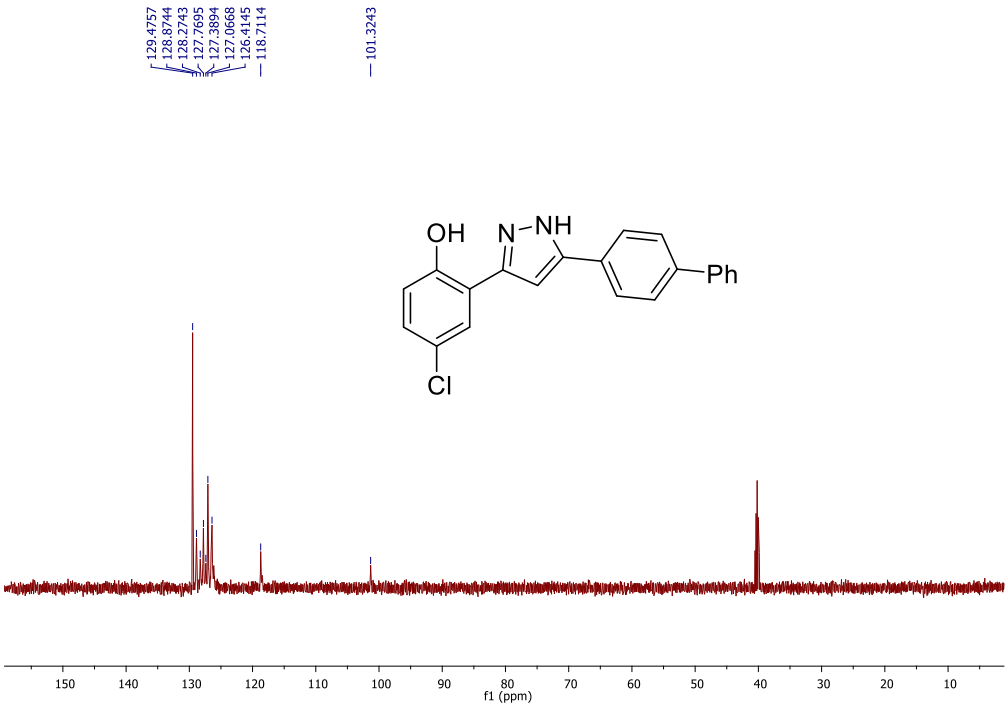


Figure 39. DEPT-135 spectrum (125MHz) of **4cd** in DMSO-d_6

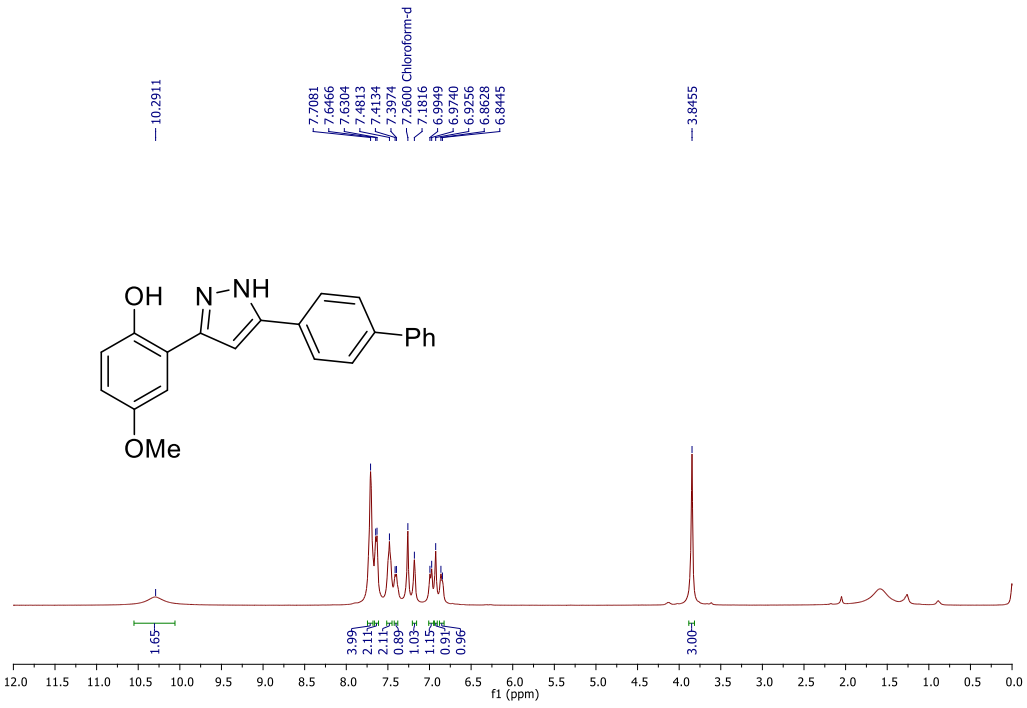


Figure 40. ^{1}H NMR spectrum (500 MHz) of **4bd** in $CDCl_3$

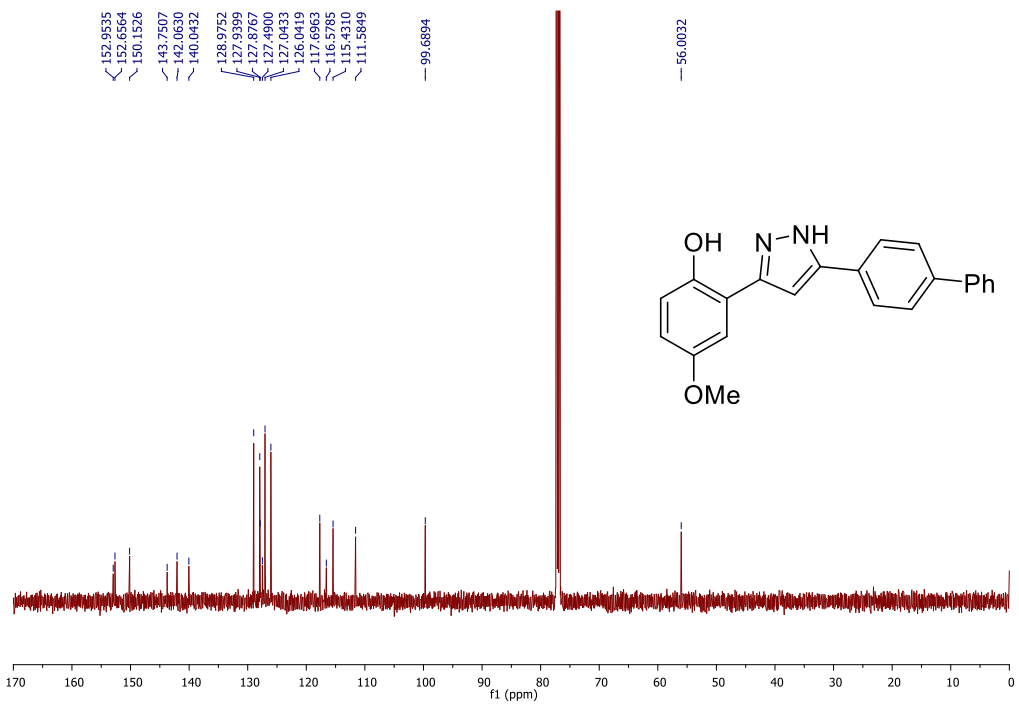


Figure 41. ^{13}C NMR spectrum (125MHz) of **4bd** in $CDCl_3$

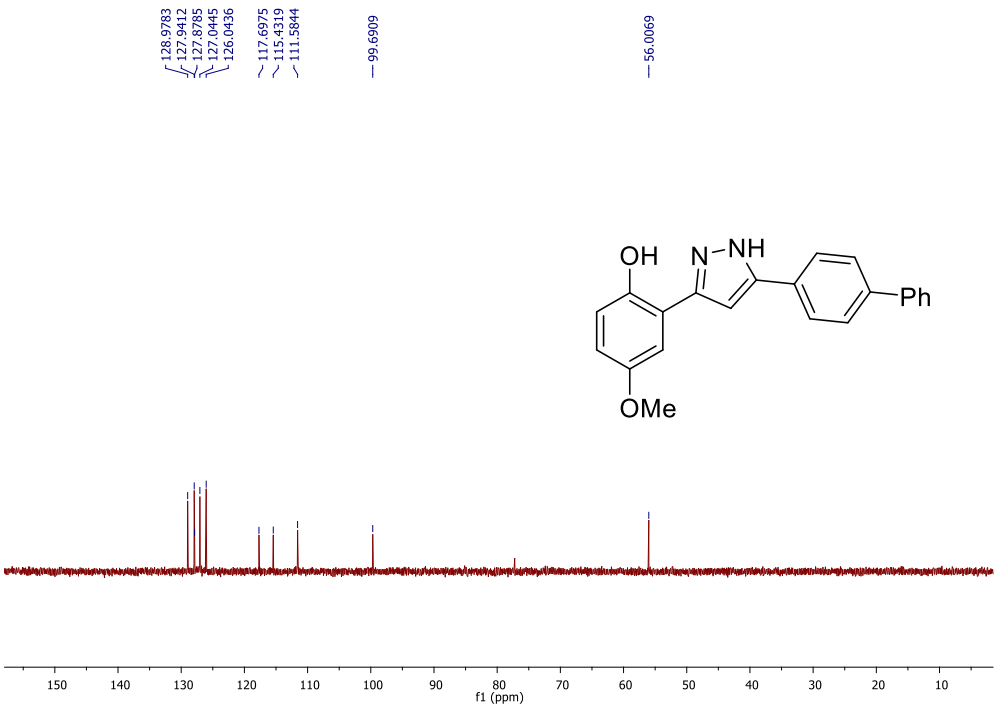


Figure 42. DEPT-135 spectrum (125MHz) of **4bd** in $CDCl_3$

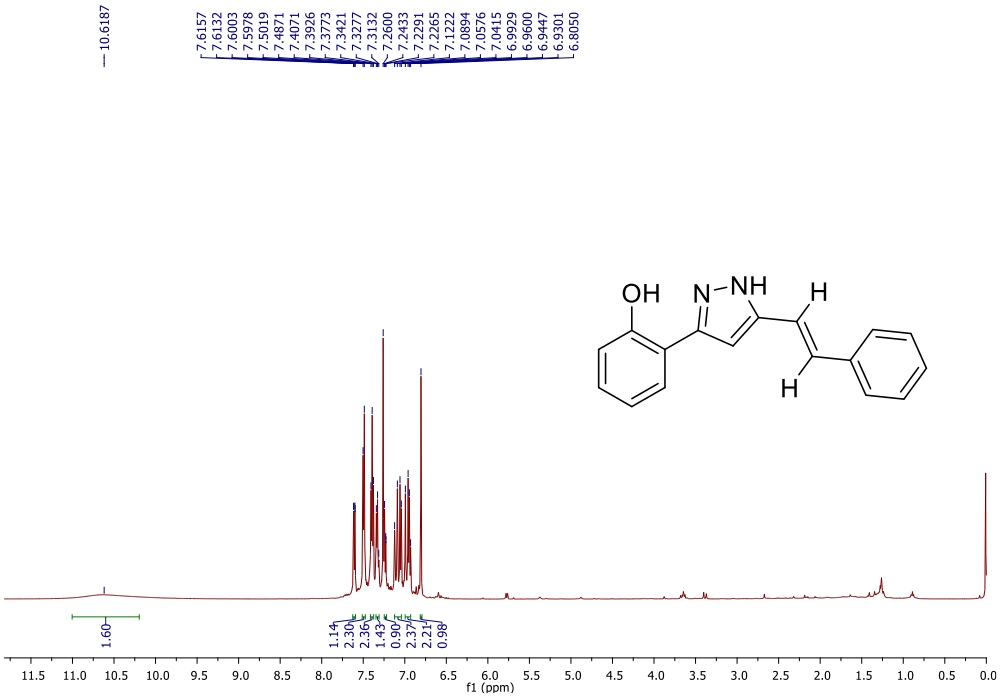


Figure 43. ^{1}H NMR spectrum (500 MHz) of **4ah** in $CDCl_3$

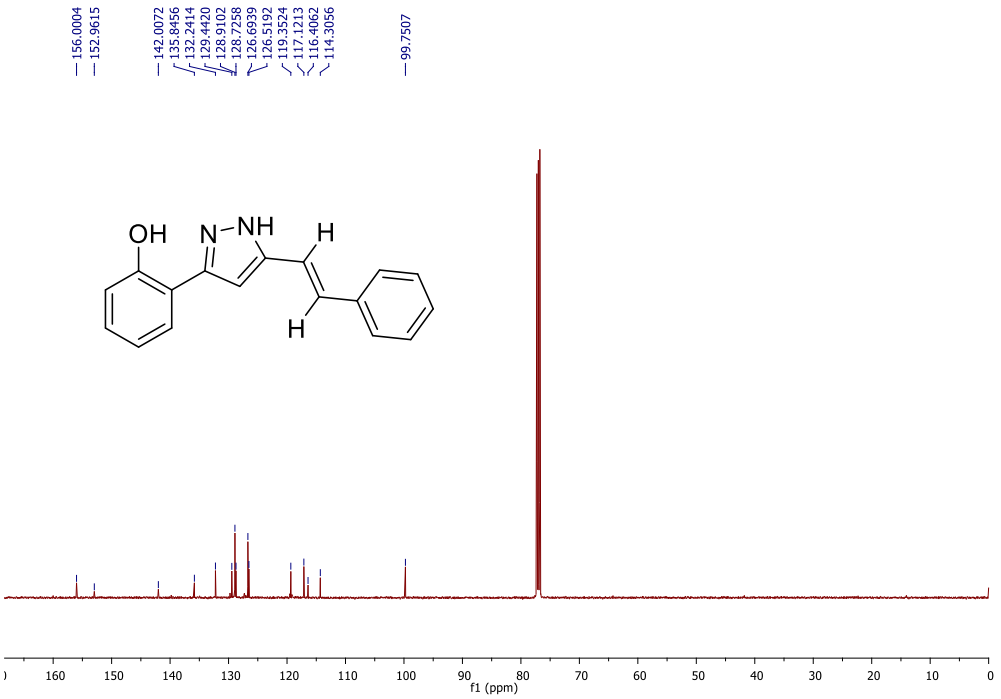


Figure 44. ^{13}C NMR spectrum (125MHz) of **4ah** in $CDCl_3$

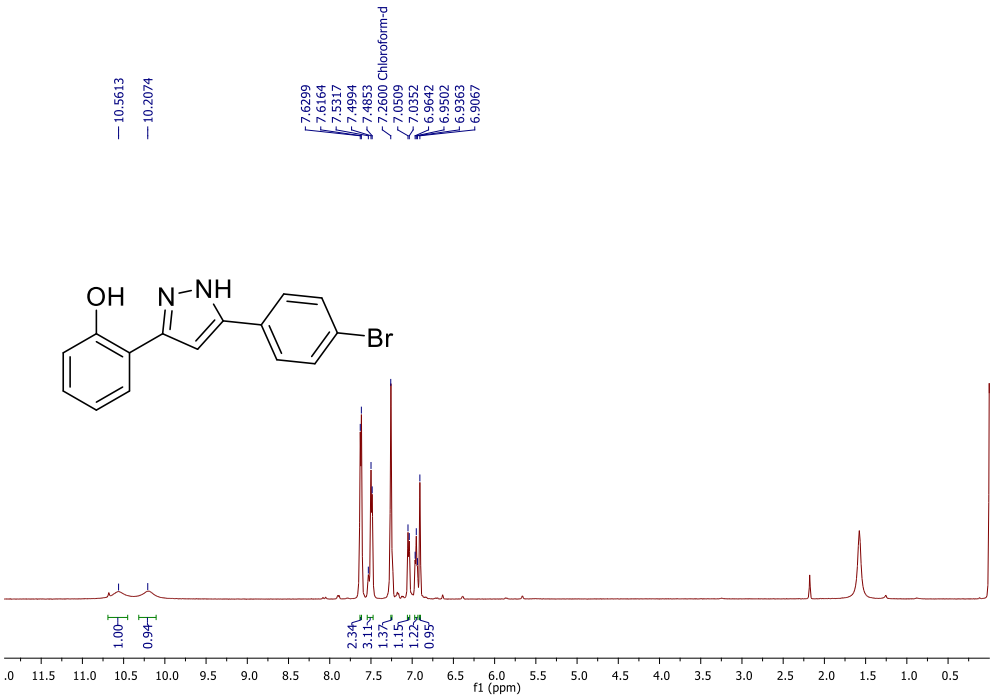


Figure 45. ^{1}H NMR spectrum (500 MHz) of **4af** in $CDCl_3$

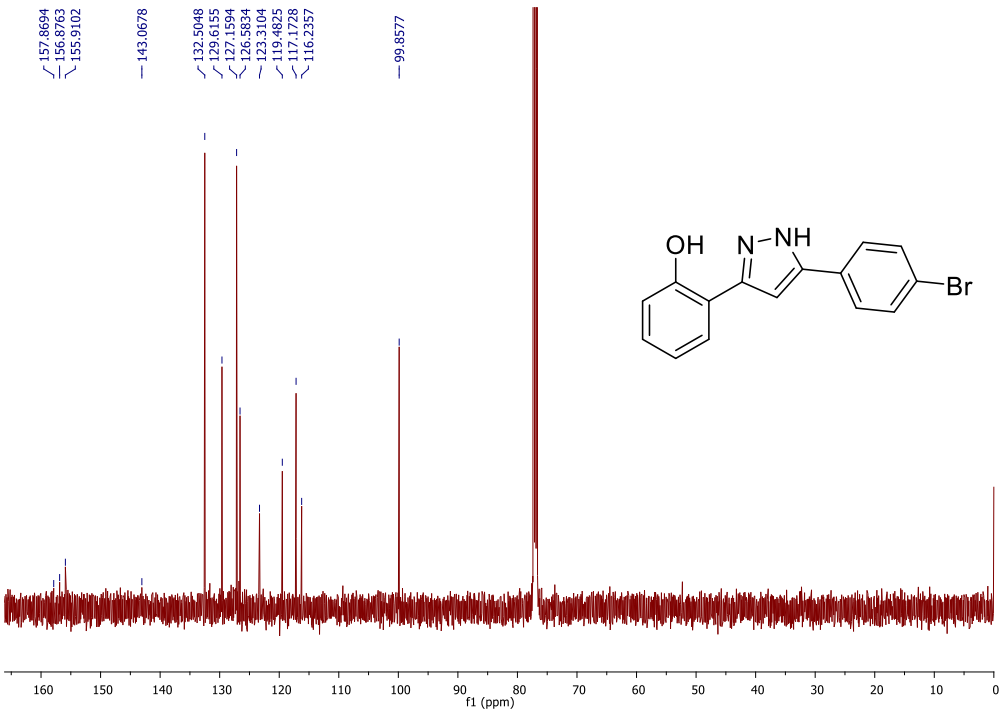


Figure 46. ^{13}C NMR spectrum (125MHz) of **4af** in $CDCl_3$

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