$CuCl_2$-Catalyzed One-Pot synthesis of Imidazohetrocycles and Furo[3,2-*c*]chromenyl Fused Imidazoles

M.Sc. Thesis

By

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DISCIPLINE OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY INDORE

JUNE 2020

$CuCl_2$-Catalyzed One Pot synthesis of Imidazoheterocycles and Furo[3,2-*c*]chromenyl Fused Imidazoles

A THESIS

Submitted in partial fulfillment of the
requirements for the award of the degree
of
Master of Science

by

Amanpreet Kaur

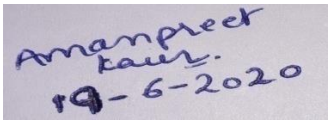
DISCIPLINE OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY INDORE
JUNE 2020

INDIAN INSTITUTE OF TECHNOLOGY INDORE

CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled **$CuCl_2$-Catalysed One Pot Synthesis of Imidazoheterocycles and Furo[3,2-*c*]chromenyl Fused Imidazoles** in the partial fulfillment of the requirements for the award of the degree of **MASTER OF SCIENCE** and submitted in the **DISCIPLINE OF CHEMISTRY, Indian Institute of Technology Indore**, is an authentic record of my own work carried out during the time period from July 2019 to June 2020 under the supervision of Dr. Sampak Samanta, Associate Professor, 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.



Signature of the student with date

(Amanpreet kaur)

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

Signature of the Supervisor of M.Sc. thesis

(Dr. Sampak Samanta)

Amanpreet Kaur has successfully given his/her M.Sc. Oral Examination held on**24/06/2020**.

Signature of Supervisor of MSc thesis
Date:

Convener, DPGC
Date:

Signature of PSPC Member
Dr. Shaikh M.Mobin
Date:

Signature of PSPC Member
Dr. Chelvam Venkatesh
Date:

ACKNOWLEDGEMENTS

I wish to express my feelings to those, whose support and motivation made possible to present my research work in the form of dissertation.

At this moment of acknowledgement, first of all, I would like to say special thanks to my thesis supervisor **Dr.Sampak Samanta** (Associate Professor, Discipline of Chemistry, IIT Indore) for the valuable guidance, suggestions, and supervision throughout my research work. Further I would like to thank my PSPC members Dr. Shaikh M. Mobin and Dr. Chelvam Venkatesh for their valuable suggestions and support.

I would like to thank to all faculty members, seniors (research scholars), SIC, staff and lab mates of IIT Indore for their help and cooperation during this dissertation work.

I wish to express my special thanks to the lab mates Dr. Santosh, Dr. Debasis Majee, Anubha Yadav, Meher Prakash Rajpoot, Hemont, Rajni, Ashwini, Bhanu, Sikha and Monika Ahuja at Dr. S. S. Lab, and IIT Indore for their valuable co-operation in the completion of the project.

I personally want to extend my thanks to my batch mates who were always there and never let me down during these M.Sc. days. Last but not least I would like to pay sincere gratitude to my loving parents for their continuous help and moral support throughout my project work.

Dedicated to My LOVELY Family…..

Abstract

A new route to diverse set of imidazoheterocycles is developed via anhydrous $CuCl_2$ catalyzed aza-annulation reaction of several oxime esters with 2-amino-azaarenes. Gratifyingly, implementation of this chemistry is further stretched for the synthesis of furo[3,2-*c*]chromenyl fused imidazoles via squential C-N bond formation, follwed by 5-endo-dig-oxacyclization of in situ produced fused imidazoles with cyclic enynones in the presence of $CuCl_2$ as the naturally available lewis acid catalyst.

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ACRONYMS

UV	Ultraviolet spectroscopy
DMSO	Dimethyl sulphoxide
DCM	Dichloromethane
$CDCl_3$	Chloroform-D
DMF	N,N-dimethyl formamide
THF	Tetrahydrofuran
CH_3CN	Acetonitrile
CH_3OH	Methanol
EtOAc	Ethyl acetate
HRMS	High Resolution Mass Spectrometry
NMR	Nuclear magnetic resonance spectroscopy
^{1}H NMR	Proton NMR spectroscopy
^{13}C NMR	Carbon-13 NMR spectroscopy
IR	Infrared spectroscopy
M	Molar
Ppm	Parts per million

NOMENCLATURE

π	pi
β	Beta
λ	Wavelength
δ	Chemical shift
cm	Centimeter
nm	Nanometer
^{o}C	Degree Celsius
mmol	Millimole
mL	Milliliter
RT	Room temperature

CHAPTER 1

Introduction

1.1 General Introduction

In the last many years, the structural diversity and the biological importance of the nitrogen containing heterocyclic compounds have increased. These nitrogen containing heterocyclic compounds occupy an important role in the realm of 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 *[1,2]*.

Imidazo[1,2-*a*]pyridines are one of the most interesting classes of fused nitrogen containing heterocyclic scaffolds of versatile concern. The chemistry of imidazopyridine have drawn attention in the last few years due to their involvement in the various medical applications viz., antiviral, anticancer, antibacterial, anti-inflammatory, antiprotozoal, antipyretic *[3-5]* etc. Most importantly, the imidazopyridine substituted drugs constitute a number of best marketable drugs such as alpidem and saripdem (anxiolytic drugs), zolimidine (antiulcer drug), olprinone (for treatment of acute heart failure), zolpidem (for treatment of insomnia), minodronic acid (for treatment of osteoporosis) and some drugs are under development, such as GSK812397 (for treatment of HIV), ND-09759 and Q203 (for treatment of tuberculosis) *[6-9]*.

As a result, rapid development has been achieved in this research field and chemists have developed a variety of methods for the efficient synthesis of imidazo[1,2-*a*]pyridines and their derivatives.

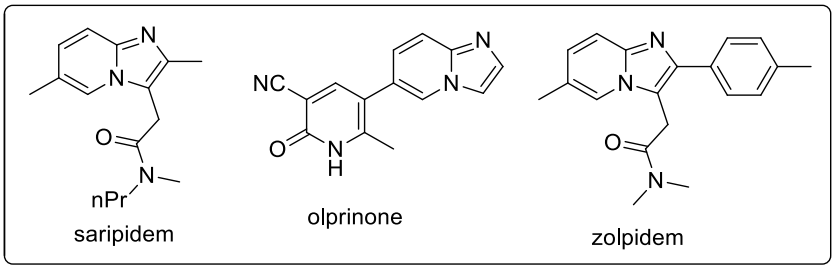


Figure 1: Structure of imidazo[1,2-*a*]pyridine containing drugs.

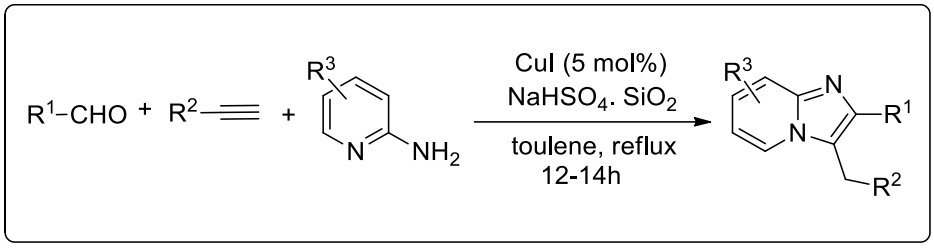
Therefore, many powerful and elegant synthetic strategies have been developed by several research groups for their efficient synthesis. These includes oxidative cyclizations *[10]*, oxidative coupling reactions *[11]*, Vilsmeier cyclizations *[12]*, aminooxygenation/C-H amination reactions *[13-14]*, Groebke-Blackburn-bienayme reactions *[15-16]* etc. In most of the methods listed above one of the starting materials was 2-aminopyridine due to its binucleophilic nature *[17-18]*.

From literature survey, most innovative routes to the synthesis of substituted imidazoheterocycles have been developed by using transition metal catalysts such as $Pd(OAc)_2$ *[19]*, CuI *[20]*, ZnO *[21]*, $Cu(OTf)_2$ *[23]*, ZnI_2 *[22]*, $RuCl_3$ *[24]*, Ag_2CO_3, AgOAc etc. However, most of these methods involve expensive metal catalyst, long reaction time, unsatisfactory yields etc. Therefore, it is a great idea to use commercially available cheap catalysts for the synthesis of substitiuted imidazo[1,2-*a*]pyridines.

Some of the recent reports for the synthesis of imidazoheterocycles have been described in the next section.

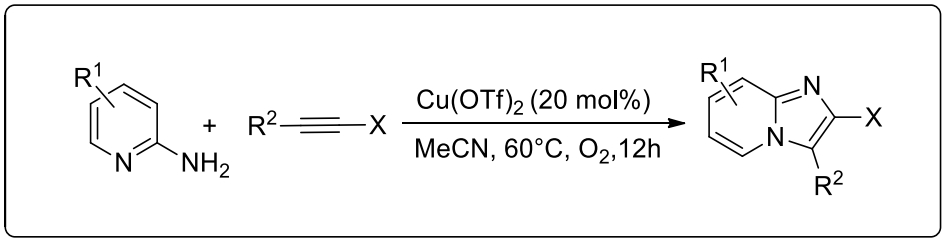
1.2 Review work

In 2011, Ghosh and Mishra developed the domino reactions for the synthesis of imidazoheterocycles involving aldehydes, terminal alkynes and 2-aminopyridine as the starting materials. The reaction was catalyzed by CuI and co-catalyzed by $NaHSO_4.SiO_2$ system.



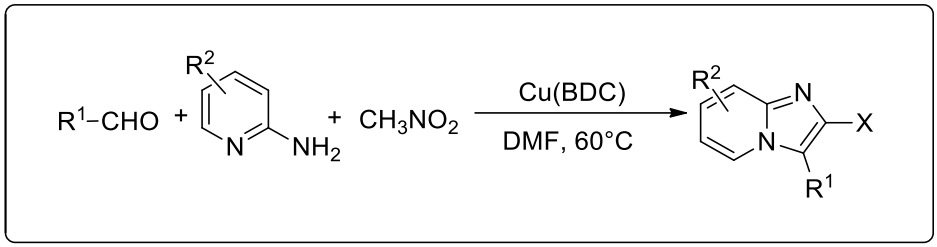
Scheme 1. One-pot synthetic reaction for synthesis of imidazo[1,2-a]pyridines.

In 2013, Gao *et al.* developed the two component nucleophilic addition reaction for the synthesis of 2-haloimidazo[1,2-*a*]pyridines involving 2-aminopyridine and haloalkynes as the starting materials. The reaction was catalyzed by $Cu(OTf)_2$.



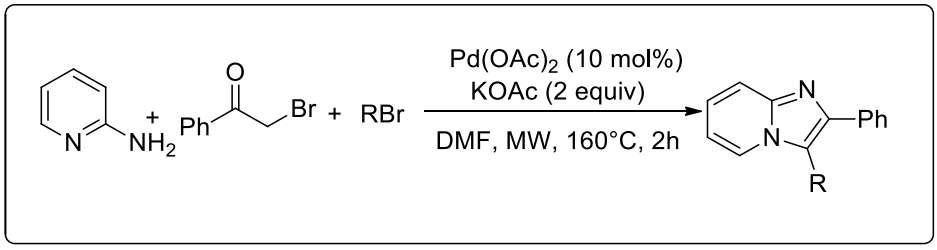
Scheme 2. Two component synthesis of 2-haloimidazo[1,2-*a*]pyridine.

In 2014, Puthiaraj *et al.* reported the hetrocyclic synthesis of imidazoheterocycles involving aldehyde, 2-aminopyridines and nitromethane as the starting materials in the presence of coppertetrapthalate metal organic framework.



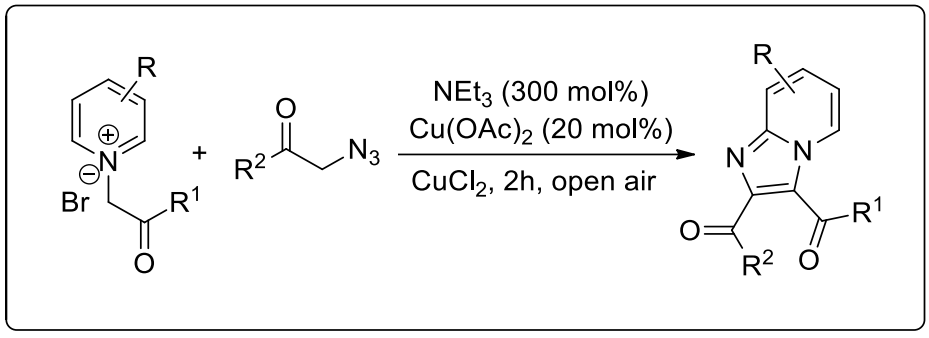
Scheme 3. Cu(BDC) catalyzed synthesis of imidazo[1,2-*a*]pyridine derivatives.

In 2014, Li *et al.* developed the three component synthesis of substituted imidazo[1,2-*a*]pyridines involving 2-aminopyridines, phencylbromides and alkylbromides as the starting materials. The reaction was catalyzed by $Pd(OAc)_2$. All the desired products were obtained in good to high yields.



Scheme 4. Three component synthesis of 2,3-diarylimidazo[1,2-*a*]pyridines.

In 2019, Kamal and Reddy reported the coupling reaction for the synthesis of substituted imidazo[1,2-*a*]pyridines involving. alpha azido ketones and pyridinium ylides as the starting materials. The reaction was catalyzed by $Cu(OAc)_2$.



Scheme 5. Synthesis of substituted imidazo[1,2-*a*]pyridine under $Cu(OAc)_2$ catalyzed system.

1.3 Objective of the Present Work

As we have seen in review and past works, different strategies have been successfully established for the synthesis of substituted imidazo[1,2-*a*]pyridines derivatives. Most of the reported methods are linked with several drawbacks such as use of a co-catalyst, additive or ligand, high temperature and long reaction time. Therefore, we are interested to devise an alternative catalytic approach towards the synthesis of C2 and C3 functionalized substituted imidazo[1,2-*a*]pyridines from simpler substances.

As part of our research works is related to the development of new domino methods for making biologically important N-containing heterocycles including alpidem derivatives, herein, we further disclose a $CuCl_2$ catalyzed aza-annulation method for modular synthesis of substituted imidazoheterocycles from 2-aminopyridines and oxime acetates without using any co-catalyst and additive.

CHAPTER 2

Experimental Section

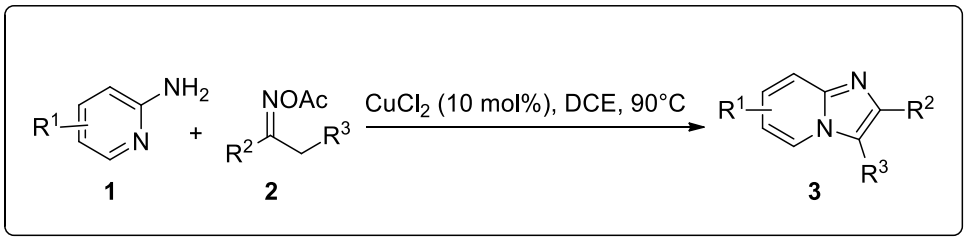
2.1 Materials and Instrumentation

Chemicals were used as received unless otherwise indicated. All the reactions were carried out under air and monitored by TLC using Merck 60F254 pre coated silica gel plate and the products were visualized by UV detection. All the oxygen or moisture sensitive reactions were carried out under argon atmosphere. Column chromatography was carried out with silica gel (200-300 mesh). ^{1}H NMR spectra were recorded using a Bruker AV 400 MHz spectrometer. 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}. ^{13}C NMR spectra were recorded using a 400 MHz spectrometer. 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 synthesis of imidazo[1,2-*a*]pyridines

A mixture of 2-aminopyridines **1 (**0.2 mmol), oxime esters **2** (0.24 mmol) and anhydrous $CuCl_2$ **(**0.02mmol) in dry DCE (1.5 mL) under nitrogen atmosphere was heated in oil bath at 90 °C. The reaction was monitored by TLC. After reaction was finished, it was quenched with water, extracted with ethyl acetate (3 ×10 mL) and dried over Na_2SO_4. The combined filtrate was concentrated under reduced pressure to leave the crude mass which was purified by silica-gel column chromatography

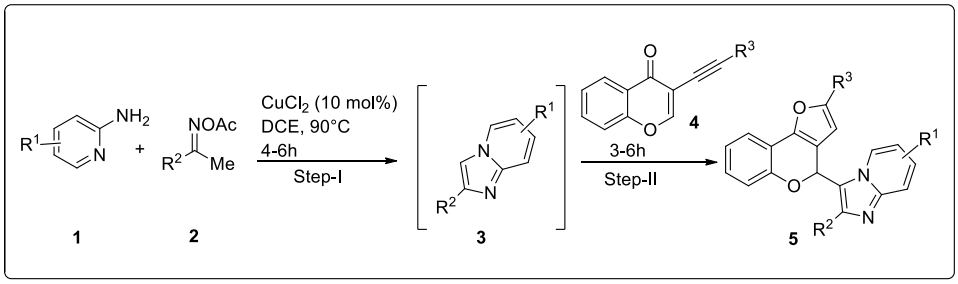
technique (hexane/ethyl acetate = 70:30**)** to afford the desired imidazoheterocycles **3.**



Scheme 6: Synthesis of substituted imidazo[1,2-*a*]pyridines.

2.3 General Experimental Procedure for the Synthesis of 4*H*-Furo[3,2-*c*]chromen-4-yl)imidazo[1,2-*a*]pyridines

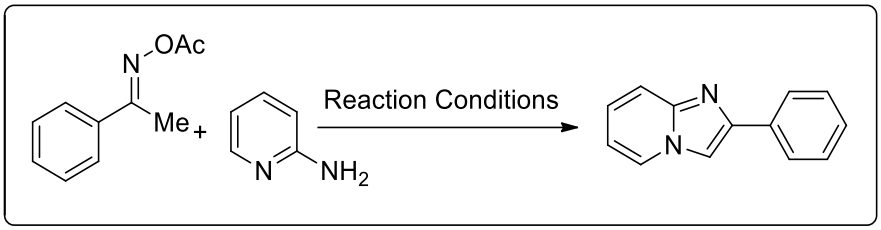
To a stirred solution of 2-aminopyridines **1 (**0.2 mmol), oxime esters **2** (0.24 mmol) and anhydrous $CuCl_2$ **(**0.02mmol) in dry DCE (1.5 mL) under nitrogen atmosphere was heated at 90 °C for 4-6h (monitored by TLC). After wards, cyclic enynones **4** (0.24 mmol) in DCE (0.5 mL) was added to the above reaction mixture at same temperature for another 3-6h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 ×10 mL), washed with water and dried over Na_2SO_4. The combined organic solvents were concentrated under reduced pressure to give the crude product which was purified by silica-gel column chromatography technique (hexane/ethyl acetate = 70:30**)** to afford the desired product **5.** All the products were characterized by ^{1}H NMR, ^{13}C NMR and HRMS data.



Scheme 7: Synthesis of furo[3,2-*c*]chromenyl fused imidazoles.

CHAPTER 3

Results and discussions



Scheme 8: New route for synthesis of imidazo[1,2-*a*]pyridines.

Entry	Catalyst	Solvent	T C	Time(h)	Yield(%)
1	$CuCl_2$	Toulene	90	6	66
2	$CuCl_2$	DMF	90	6	25
3	$CuCl_2$	THF	80	8	25
4	**$CuCl_2$**	**DCE**	**90**	**6**	**81**
5	$CuCl_2$	Dioxane	80	6	50
6	$CuCl_2$	Dioxane	90	6	62
7	$CuCl_2$	Dioxane	100	8	60
12	$Cu(OTf)_2$	DCE	90	12	45
9	$FeCl_3$	DCE	90	12	Nd
10	$CuBr_2$	DCE	90	12	60
11	AgOAc	DCE	90	12	Nd
12	$CuCl_2$	DCE	90	12	60

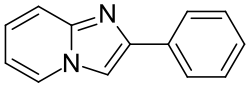
Table 1. Optimization of reactions conditions.

[a]All the reactions were carried out with 2-aminopyridine (0.2 mmol), oxime ester (0.24 mmol) and catalyst (10 mol%) in specified dry solvent (1.5 mL) under N_2 atmosphere and temperature. [b]Isolated yield after column chromatograpy. [c]nd= not detected

First we put the reaction between 2-aminopyridine and oxime acetate in toluene using 10 mol% of anhydrous $CuCl_2$ as a naturally accessible catalyst at 90°C in a closed reaction tube. To our delight after 6h, reaction was completed (monitored by TLC) and a novel class of imidazo[1,2-*a*]pyridine was isolated in moderate yield. Taking this result in hand to improve the yield further, several common solvents such as DCE, THF, dioxane and DMF were tested for this reaction. We found that anhydrous $CuCl_2$ gave the best yield of the desired product in DCE at 90°C. Next, we screened other catalysts such as $FeCl_3$, $CuBr_2$ and

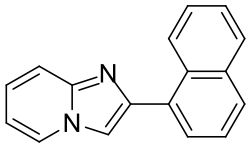
AgOAc. Futhermore 60% and 45% yields were obtained by using $CuBr_2$ and $Cu(OTf)_2$ as catalysts respectively. Therefore, taking into the consideration of the yield, $CuCl_2$ was found to be superior catalyst as compared to other Cu-salts with the solvent DCE and optimized reaction time of 6h.

2-Phenylimidazo[1,2-*a*]pyridine (3aa):



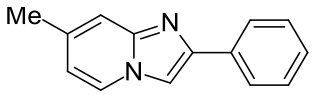
Colourless solid; mp 133-135 ^oC; Yield 81% (31.4 mg); R_f= 0.60 (ethyl acetate/hexane = 3:7); ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 6.4 Hz, 1H), 7.96 (d, *J* = 7.4 Hz, 2H), 7.86 (s, 1H), 7.66 (d, *J* = 9.0 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.1 Hz, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 6.78 (t, *J* = 6.4 Hz, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 145.6, 145.5, 133.5, 128.7, 128.0, 126.1, 125.6, 124.8, 117.5, 112.6, 108.1 ppm; HRMS-ESI: *m/z* calcd for $C_{13}H_{11}N_2[M+H]^+$: 195.0917; found: 195.0914.

2-(Naphthalen-1-yl)imidazo[1,2-*a*]pyridine (3ab):



Yellow solid; mp 132-134 ^oC; Yield 73% (35.6 mg); R_f= 0.56 (ethyl acetate/hexane = 3:7); ^1H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, *J* = 7.8 Hz, 1H), 8.06 (d, *J* = 6.6 Hz, 1H), 7.92 – 7.80 (m, 2H), 7.80 – 7.71 (m, 2H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.56 – 7.42 (m, 3H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.72 (t, *J* = 6.6 Hz, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 145.1, 145.0, 134.0, 131.6, 131.5, 128.5, 128.4, 127.8, 126.5, 125.9, 125.8, 125.7, 125.4, 124.8, 117.5, 112.5, 111.3 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}N_2$: 245.1073; found: 245.1088.

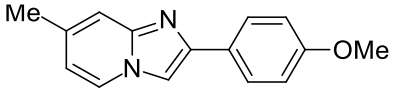
7-Methyl-2-phenylimidazo[1,2-*a*]pyridine(3ac):



Colourless solid; mp 166-168 ^oC; Yield 80% (33.2 mg); R_f= 0.58 (ethyl acetate/hexane = 3:7); ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 6.8 Hz, 1H), 7.98 – 7.92 (m, 2H), 7.78 (s, 1H), 7.43 (t, *J* = 7.5 Hz, 3H), 7.32 (t, *J* = 7.3 Hz, 1H), 6.63 (d, *J* = 6.8 Hz, 1H), 2.40 (s, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 145.8, 145.0, 136.0, 133.5, 128.7, 127.9, 125.9, 124.8, 115.6, 115.2,

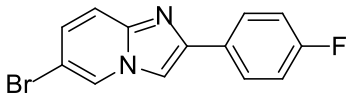
107.6, 21.3 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{13}N_2$: 209.1073; found: 209.1085.

2-(4-Methoxyphenyl)-7-methylimidazo[1,2-*a*]pyridine (3ad):



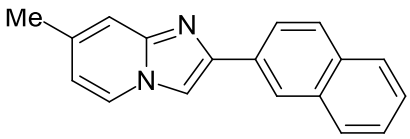
Pale yellow solid; mp 167-169ºC; Yield 76% (36.2 mg); R_f= 0.56 (ethyl acetate/hexane = 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 6.9 Hz, 1H), 7.86 (d, *J* = 8.7 Hz, 2H), 7.69 (s, 1H), 7.43 (s, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.62 (dd, *J* = 6.8, 1.0 Hz, 1H), 3.85 (s, 3H), 2.40 (s, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 159.6, 145.7, 144.8, 136.0, 127.3, 126.0, 124.7, 115.4, 115.2, 114.1, 106.6, 55.3, 21.3 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{15}N_2O$: 239.1179; found: 239.1169.

6-bromo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine (3ae):



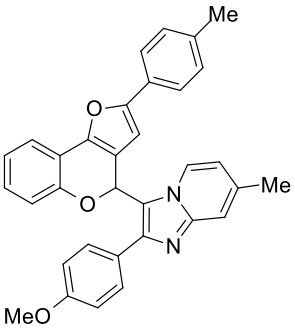
Yellow solid; Yield 63% (36.7 mg); R_f= 0.55 (ethyl acetate/hexane = 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.91 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.78 (s, 1H), 7.59 (d, *J* = 9.5 Hz, 1H), 7.29 (d, *J* = 1.4 Hz, 1H), 7.15 (dd, *J* = 14.6, 5.9 Hz, 2H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 162.9 (d, *J* = 247.6 Hz), 145.7, 144.0, 129.3 (d, *J* = 3.1 Hz), 128.3, 127.8 (d, *J* = 8.2 Hz), 125.5, 118.0, 115.8 (d, *J* = 21.7 Hz), 107.9, 107; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_9BrFN_2$: 290.9928; found: 290.9897.

7-Methyl-2-(naphthalen-2-yl)imidazo[1,2-*a*]pyridine (3af):



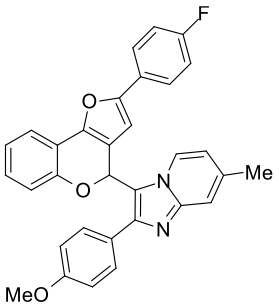
Brown liquid; Yield 69% (35.6 mg); R_f= 0.56 (ethyl acetate/hexane = 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 – 8.51 (m, 1H), 8.06 (d, *J* = 6.9 Hz, 1H), 7.94 – 7.84 (m, 2H), 7.82 (d, *J* = 7.1 Hz, 1H), 7.76 (s, 1H), 7.60 – 7.46 (m, 4H), 6.67 (d, *J* = 6.9 Hz, 1H), 2.43 (s, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 145.6, 144.8, 135.7, 133.9, 131.7, 131.5, 128.4, 128.3, 127.6, 126.3, 125.9, 125.7, 125.4, 124.7, 115.9, 115.2, 110.6, 21.4 ppm; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{14}N_2Na$: 281.1049; found: 281.1041.

2-(4-methoxyphenyl)-7-methyl-3-(2-(4-methylphenyl)-4*H*-furo[3,2-*c*]chromen-4-yl)imidazo[1,2-*a*]pyridine (3ba):



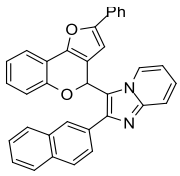
Light yellow solid; mp 204-206ºC; Yield 61% (60.8 mg); R_f= 0.67 (ethyl acetate/hexane = 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.0 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 2H), 7.44 (s, 1H), 7.22 – 7.11 (m, 4H), 7.08 – 7.03 (m, 1H), 7.01 (d, *J* = 8.2 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 6.9 Hz, 1H), 6.15 (s, 1H), 3.84 (s, 3H), 2.37 (s, 3H), 2.35 (s, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 159.8, 155.4, 153.2, 146.5, 146.2, 145.9, 137.9, 136.6, 130.2, 129.4, 128.8, 127.3, 126.3, 125.4, 123.7, 122.0, 119.7, 116.6, 116.2, 116.1, 115.8, 115.4, 114.9, 114.1, 102.6, 71.0, 55.3, 21.3, 21.3 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{33}H_{27}N_2O_3$: 499.2016; found: 499.2017.

3-(2-(4-Fluorophenyl)-4*H*-furo[3,2-*c*]chromen-4-yl)-2-(4-methoxyphenyl)-7-methylimidazo[1,2-*a*]pyridine (3bb):



Yellow solid; mp 190-192ºC; Yield 64% (64.3 mg); R_f= 0.68 (ethyl acetate/hexane = 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.0 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.59 (t, *J* = 8.7 Hz, 3H), 7.45 (s, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 7.14 (s, 1H), 7.06 (t, *J* = 8.1 Hz, 3H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.50 (d, *J* = 7.0 Hz, 1H), 6.14 (s, 1H), 3.84 (s, 3H), 2.37 (s, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 162.45 (d, *J* = 248.3 Hz), 159.9, 154.3, 153.3, 146.5, 146.3, 146.3, 136.7, 130.2, 129.1, 126.4 (d, *J* = 3.3 Hz), 126.3, 125.6 (d, *J* = 8.1 Hz), 125.3, 122.1, 119.7, 116.7, 116.1 (d, *J* = 13.2 Hz), 115.9, 115.8, 115.3, 115.0, 114.2, 103.0, 70.9, 55.3, 21.3 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{24}FN_2O_3$: 503.1765; found: 503.1795.

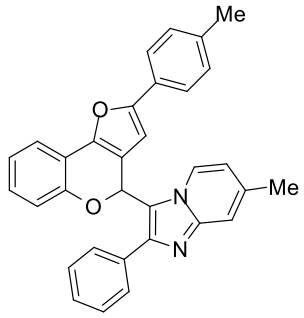
2-(Naphthalen-2-yl)-3-(2-phenyl-4*H*-furo[3,2-*c*]chromen-4-yl)imidazo[1,2-*a*]pyridine (3bc):



Yellow solid; mp 208-210ºC; Yield 62% (60.8 mg); R_f= 0.68 (ethyl acetate/hexane = 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 6.8 z, 1H), 8.25 (d, *J* = 8.2 Hz,

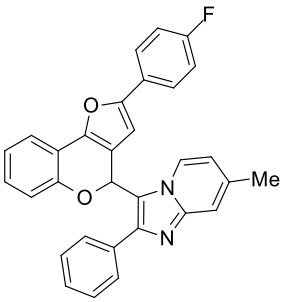
1H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.62 (d, *J* = 6.8 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 4H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.31 – 7.22 (m, 2H), 7.15 (t, *J* = 7.7 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 12.3 Hz, 2H), 6.77 (t, *J* = 6.7 Hz, 1H), 6.18 (s, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 155.0, 153.1, 146.3, 146.2, 145.8, 133.8, 132.6, 131.0, 130.0, 129.1, 129.0, 128.8, 128.6, 128.2, 127.9, 126.5, 126.3, 126.1, 126.0, 125.6, 125.1, 123.8, 122.1, 119.8, 118.6, 117.9, 116.7, 116.1, 115.8, 112.6, 103.3, 70.6 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{23}N_2O_3$: 491.1754; found: 491.1768.

7-Methyl-2-phenyl-3-(2-(4-methylphenyl)-4*H*-furo[3,2-*c*]chromen-4-yl)imidazo[1,2-*a*]pyridine (3bd):



Pale yellow solid; mp 180-182ºC; Yield 69% (64.6 mg); R_f= 0.70 (ethyl acetate/hexane = 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.0 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.59 (d, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 2H), 7.51 – 7.44 (m, 3H), 7.44 – 7.34 (m, 1H), 7.17 (d, *J* = 5.1 Hz, 4H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.50 (d, *J* = 6.9 Hz, 1H), 6.16 (s, 1H), 2.38 (s, 3H), 2.35 (s, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 155.5, 153.2, 146.7, 146.5, 145.9, 138.0, 136.7, 133.9, 129.5, 129.0, 128.9, 128.7, 128.3, 127.3, 125.5, 123.7, 122.1, 119.7, 116.7, 116.2, 116.1, 116.1, 116.0, 115.1, 102.6, 70.9, 21.4, 21.3 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{35}H_{25}N_2O_2$: 469.1911; found: 469.1940.

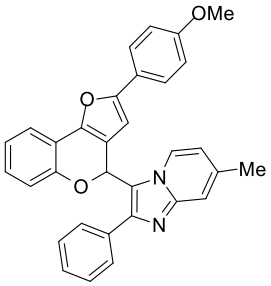
3-(2-(4-Fluorophenyl)-4*H*-furo[3,2-*c*]chromen-4-yl)-7-methyl-2-phenylimidazo[1,2-*a*]pyridine (5be):



Pale yellow solid; mp 172-174ºC; Yield 68% (64.2 mg); R_f= 0.70 (ethyl acetate/hexane = 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 6.9 Hz, 1H), 7.77 (d, *J* = 7.3 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 3H), 7.48 (d, *J* = 8.5 Hz, 3H), 7.43 – 7.35 (m, 1H), 7.19 (d, *J* = 12.4 Hz, 2H), 7.06 (t, *J* = 8.0 Hz, 3H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.51 (d, *J* = 6.9 Hz, 1H), 6.15 (s, 1H), 2.38

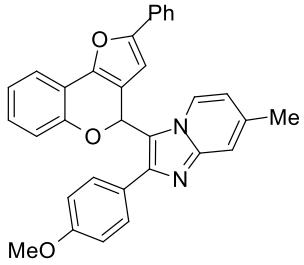
(s, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 162.4 (d, *J* = 248.4 Hz), 154.3, 153.2, 146.7, 146.5, 146.3, 136.7, 133.9, 129.1, 129.0, 128.7, 128.3, 126.4 (d, *J* = 3.3 Hz), 125.6 (d, *J* = 8.1 Hz), 125.4, 122.1, 119.7, 116.7, 116.0 (d, *J* = 10.4 Hz), 115.8, 115.8, 115.1, 103.0, 70.9, 21.4 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{31}H_{22}FN_2O_2$: 473.1660; found: 473.1673.

3-(2-(4-Methoxyphenyl)-4*H*-furo[3,2-*c*]chromen-4-yl)-7-methyl-2-phenylimidazo[1,2-*a*]pyridine (3bf):



Pale yellow solid; mp 220-222ºC; Yield 70% (68.7 mg); R_f= 0.68 (ethyl acetate/hexane = 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 7.0 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 3H), 7.53 – 7.43 (m, 3H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.21 – 7.11 (m, 2H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.92 (dd, *J* = 14.4, 8.4 Hz, 3H), 6.51 (d, *J* = 7.0 Hz, 1H), 6.08 (s, 1H), 3.82 (s, 3H), 2.38 (s, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 159.5, 155.3, 153.1, 146.7, 146.5, 145.6, 136.7, 133.9, 129.0, 128.8, 128.7, 128.3, 125.5, 125.3, 123.0, 122.0, 119.6, 116.6, 116.3, 116.1, 116.1, 116.0, 115.1, 114.3, 101.7, 71.0, 55.4, 21.4 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{25}N_2O_3$: 485.1860; found: 485.1821.

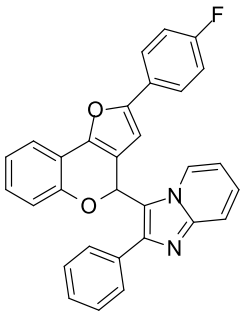
(4-Methoxyphenyl)-7-methyl-3-(2-phenyl-4*H*-furo[3,2-*c*]chromen-4-yl)imidazo[1,2-*a*]pyridine (3bg):



Colorless solid; mp 60-62ºC; Yield 63% (61.0 mg); R_f= 0.69 (ethyl acetate/hexane = 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.0 Hz, 1H), 7.71 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 7.5 Hz, 2H), 7.60 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.46 (s, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.31 – 7.23 (m, 1H), 7.18 (td, *J* = 8.0, 1.4 Hz, 1H), 7.15 (s, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.50 (dd, *J* = 7.0, 1.1 Hz, 1H), 6.21 (s, 1H), 3.84 (s, 3H), 2.37 (s, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 159.8, 155.1, 153.3, 146.5, 146.3, 136.6, 130.2, 129.9, 129.0, 128.7, 127.9, 126.2, 125.3, 123.7,

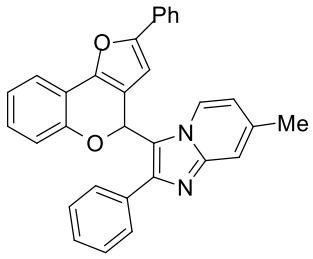
122.0, 119.7, 116.7, 116.1, 116.0, 115.8, 115.3, 114.9, 114.1, 103.3, 70.9, 55.3, 21.3 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{32}H_{25}N_2O_3$: 485.1860; found: 485.1879.

3-(2-(4-fluorophenyl)-4*H*-furo[3,2-*c*]chromen-4-yl)-2-phenylimidazo[1,2-*a*]pyridine (3bh):



Colourless solid; mp 242-244ºC; Yield 70% (64.2 mg); R_f= 0.70 (ethyl acetate/hexane = 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 6.8 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 2H), 7.72 (d, *J* = 9.1 Hz, 1H), 7.66 – 7.56 (m, 3H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.32 – 7.15 (m, 3H), 7.06 (t, *J* = 8.7 Hz, 3H), 6.95 (d, *J* = 8.1 Hz, 1H), 6.69 (t, *J* = 6.8 Hz, 1H), 6.16 (s, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 162.5 (d, *J* = 248.5 Hz), 154.4, 153.2, 146.63 (d, *J* = 39.6 Hz), 146.3, 133.8, 129.2, 129.18 (d, *J* = 8.7 Hz), 129.1, 128.8, 128.5, 126.4 (d, *J* = 3.3 Hz), 126.3, 125.6 (d, *J* = 1.7 Hz), 125.6, 122.2, 119.8, 117.8, 116.8, 116.4, 116.0 (d, *J* = 1.7 Hz), 116.0, 115.8, 112.5, 103.0, 70.8 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{20}FN_2O$: 459.1503; found: 459.1524.

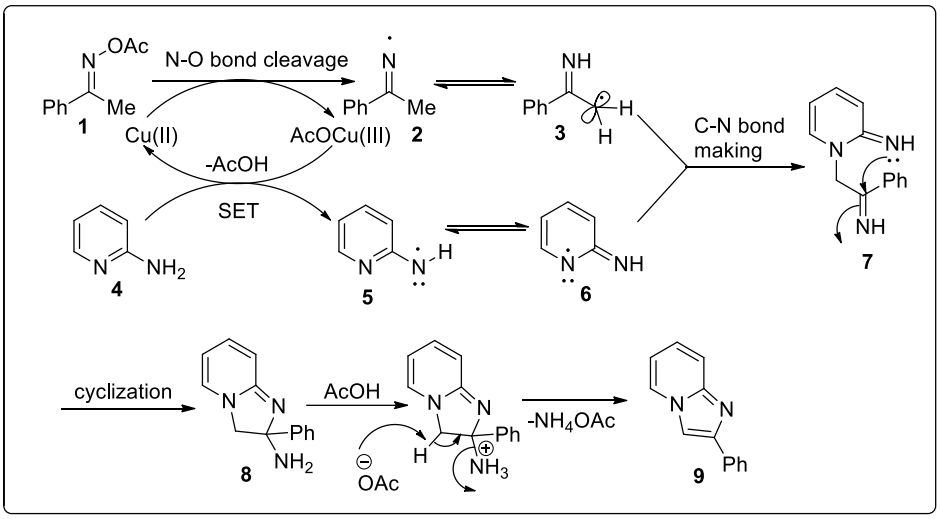
Methyl-2-phenyl-3-(2-phenyl-4*H*-furo[3,2-*c*]chromen-4-yl)imidazo[1,2-*a*]pyridine (3bi):



White solid; mp 164-166ºC; Yield 66% (60 mg); R_f= 0.70 (ethyl acetate/hexane = 3:7); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.1 Hz, 1H), 7.77 (d, *J* = 7.2 Hz, 2H), 7.63 (d, *J* = 7.5 Hz, 2H), 7.60 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.53 – 7.44 (m, 3H), 7.44 – 7.33 (m, 3H), 7.31 – 7.23 (m, 1H), 7.22 – 7.15 (m, 2H), 7.07 (t, *J* = 7.3 Hz, 1H), 6.95 (d, *J*= 7.9 Hz, 1H), 6.52 (dd, *J* = 7.0, 1.1 Hz, 1H), 6.22 (s, 1H), 2.38 (s, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ 174.6, 155.2, 153.2, 146.5, 146.3, 146.1, 137.0, 133.4, 129.9, 129.0, 128.7, 128.7, 128.4, 127.9, 125.4, 125.0, 123.7, 122.1, 119.7, 116.7, 116.0, 116.0, 115.9, 115.2, 103.2, 70.8, 21.3 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{31}H_{23}N_2O_2$: 455.1754, found: 455.1766.

3.1 Plausible Reaction Mechanism

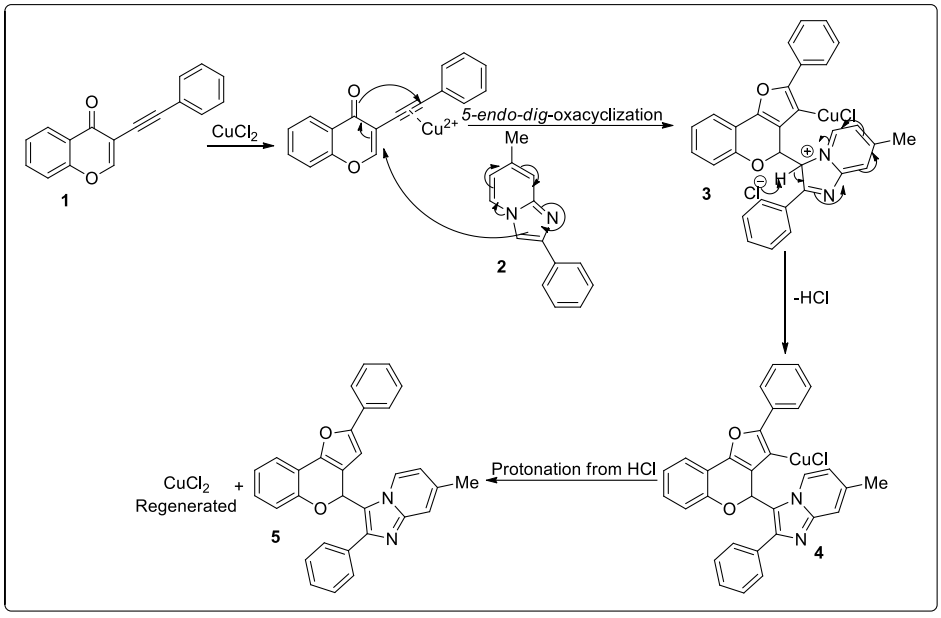
A possible tentative reaction mechanism for the synthesis of imidazoheterocycles is depicted in **Scheme 9**. Firstly, the oxidative addition of Cu (II) to oxime ester **1** generates iminium radical **2** along with AcOCu(III) via homolytic cleavage of N- O bond. This iminium radical undergoes tautomerization to **3**. On the other hand, a single electron transfer process takes place between **4** and AcOCu(III) to form aminyl radical **5** which undergoes tautomerization to give more stable pyridinium radical **6**. It should be noted that the AcOH generated during this single electron transfer process is required for next catalytic cycle. Next, the radical coupling between **3** and **6** leads to C-N bond formation, resulting in formation of intermediate **7** which in turn cyclizes to give intermediate **8.** The elimination of NH_4OAc from intermediate **8** triggered by AcOH, leads to the formation of desired imidazoheterocycle **9**.



Scheme 9: Mechanistic pathway for the synthesis of Imidazo[1,2-*a*]pyridine.

A possible tentative reaction mechanism for the synthesis of furo[3,2-c]chromenyl fused imidazoheterocycles is depicted in the **Scheme 10**. Firstly, π-electrophilic Lewis acid catalyst $CuCl_2$ coordinates with the alkyne bond of 3-(phenylethynyl)-4H-chromen-4-one, making it more electrophlic then, it reacts with the imidazoheterocycle **2** to form the

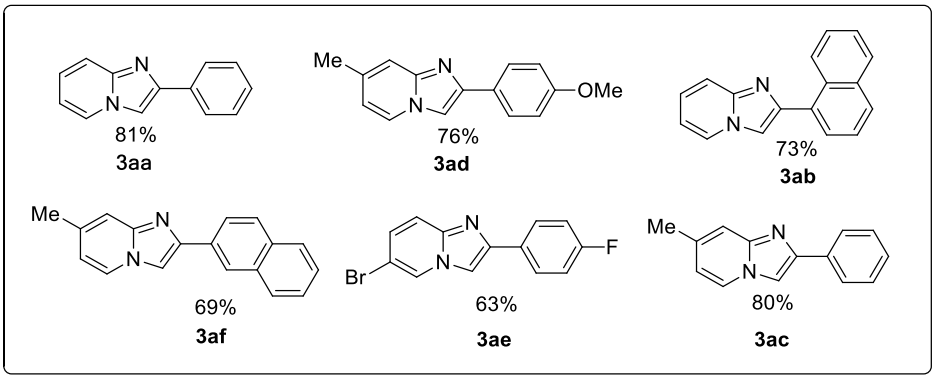
intermediate **3** by 5-endo-dig-oxacyclization. The intermediate **3** undergoes deprotonation to give intermediate **4**. The protonation of intermediate **4** by HCl gives the final desired product **5** along with the $CuCl_2$ catalyst regenerated.



Scheme 10: Mechanistc pathway for the synthesis of furo[3,2-*c*]chromenyl imidazoheterocycles

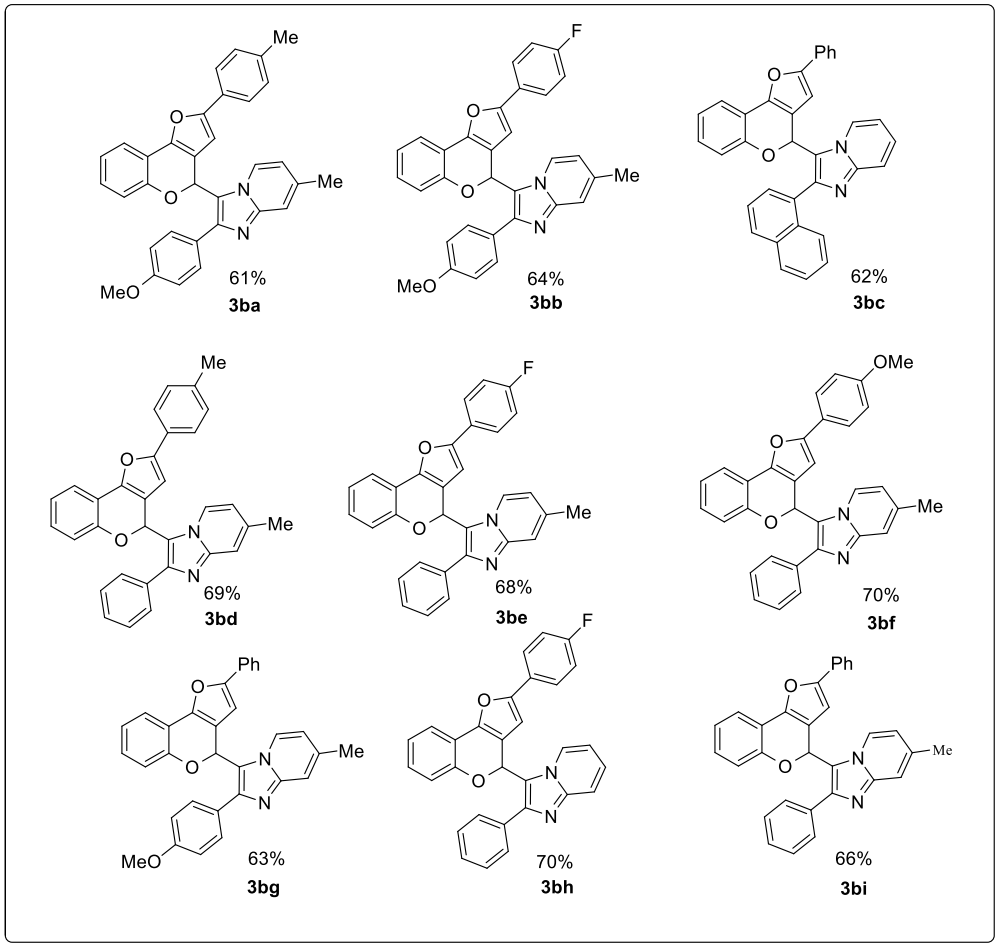
3.2 Substrate Scope and Generality of Reaction Conditions

With optimal catalytic conditions in hand, we demonstrated the substrate scope of the [3+2] annulation reaction taking several 2-aminopyridines and a wide range of oxime esters under established conditions. The obtained results are included in **Scheme 11**. It was found that the oxime esters and the 2-aminopyridines having electron-donating substituents such as MeO and Me substituent in **3ad** and Me substituent in **3ac**, responded very well to provide the corresponding C2-substituted imidazopyridines (**3ac** and **3ad**) with better yields (80% and 76%) than electron-withdrawing ones (B and F,; **3ae** for 63% yield). Interestingly, oxime esters derived from bulky naphthyl group were well tolerated to give the targeted heterocycles **3ab** and **3af** in promising yields in 73% and 69% yields respectively. Notably, the presence of electron withdrawing functionalities on either 2-aminopyridines or oxime esters had reduced the rate of the reactions and resulted in slight lower yields and required extra time to complete the cyclization process.



Scheme 11: List of derivatives of substituted imidazo[1,2-*a*]pyridines.

For the synthesis of various derivatives of furo[3,2-*c*]chromenyl fused imidazoheterocycles several aryl and naphthyl substituted imidazopyridines (in situ formed) were efficiently trapped by a family of 3-(1-alkynyl)- 4*H*-chromen-4-ones, possessing Me, MeO and F substituent on the acetylenic part, via 5-endo-dig- oxacyclization process catalyzed by $CuCl_2$. Consequently, all produced were obtained in promising yields (61-70%).



Scheme 12: List of various derivatives of furo[3,2-*c*]chromenyl fused imidazoheterocycles.

CONCLUSION

In conclusion, we have successfully synthesized biological important imidazoheterocycles in good yields through aza-annulation reaction of 2-aminopyridines with several oxime acetates in the presence of $CuCl_2$ as the catalyst. Moreover, several furo[3,2-*c*]chromenyl fused imidazoles are also prepared using the same catalyst. Broad substrate scope, easy tolerance to many functional groups and low catalyst loading makes this method good alternative to the known procedures. Therefore, we strongly believe that our developed method will find a suitable place in synthetic organic chemistry.

APPENDIX A

^{1}H NMR, ^{13}C NMR Spectra

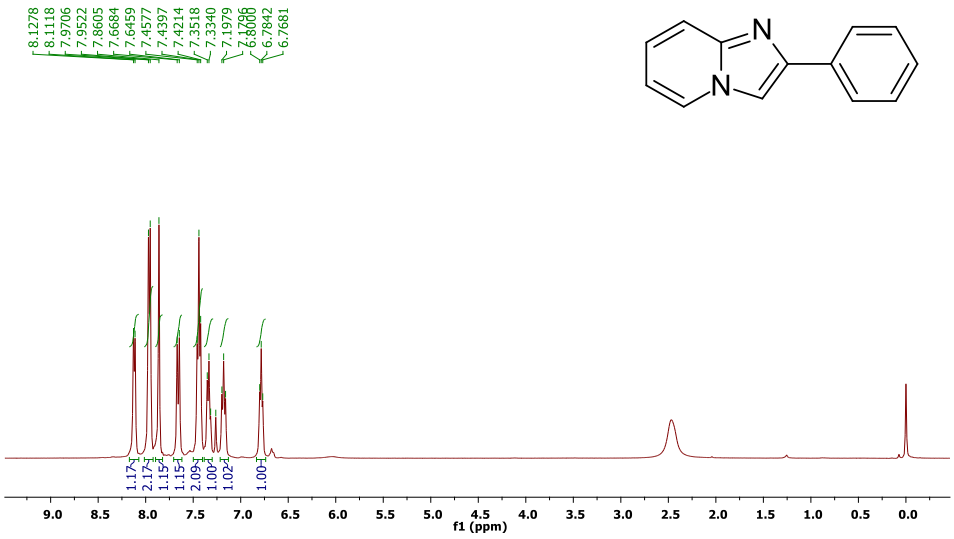


Figure 2: 400 MHz ^{1}H NMR spectrum of **3aa** in $CDCl_3$.

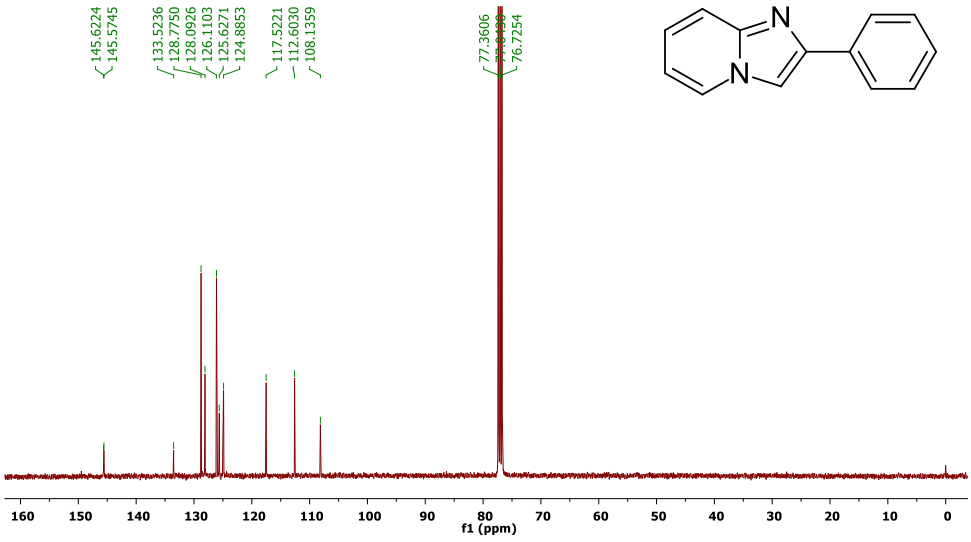


Figure 3: 400 MHz ^{13}C NMR spectrum of **3aa** in $CDCl_3$.

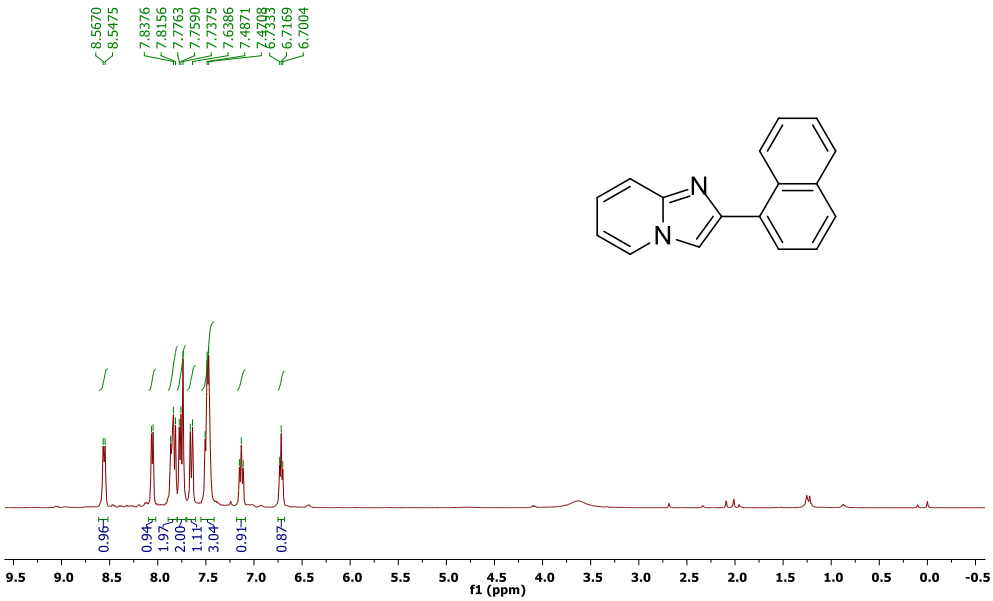


Figure 4: 400 MHz ^{1}H NMR spectrum of **3ab** in $CDCl_3$.

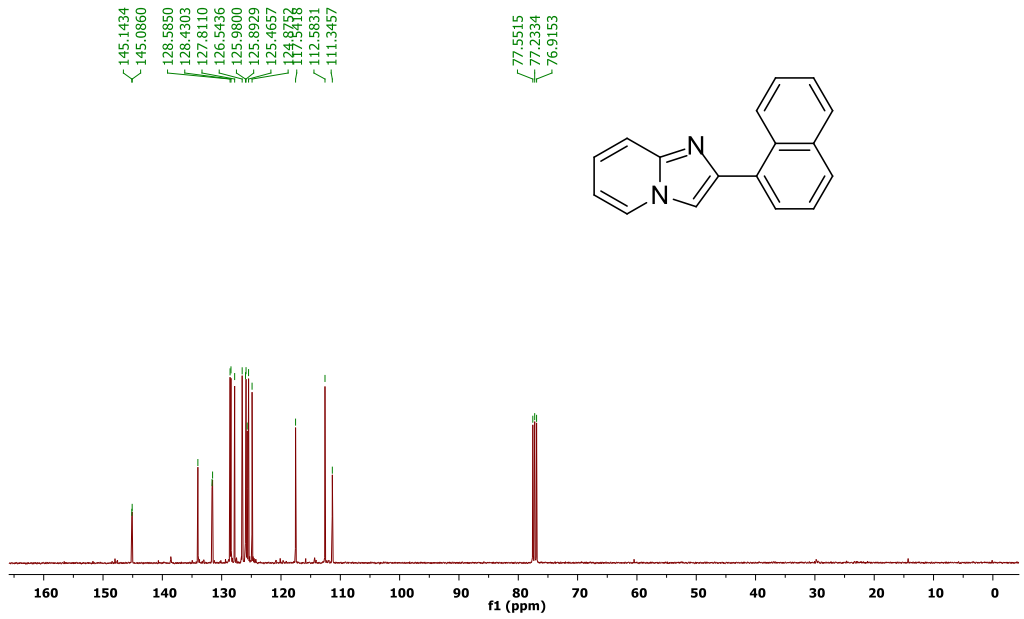


Figure 5: 400 MHz ^{13} C NMR spectrum of **3ab** in $CDCl_3$.

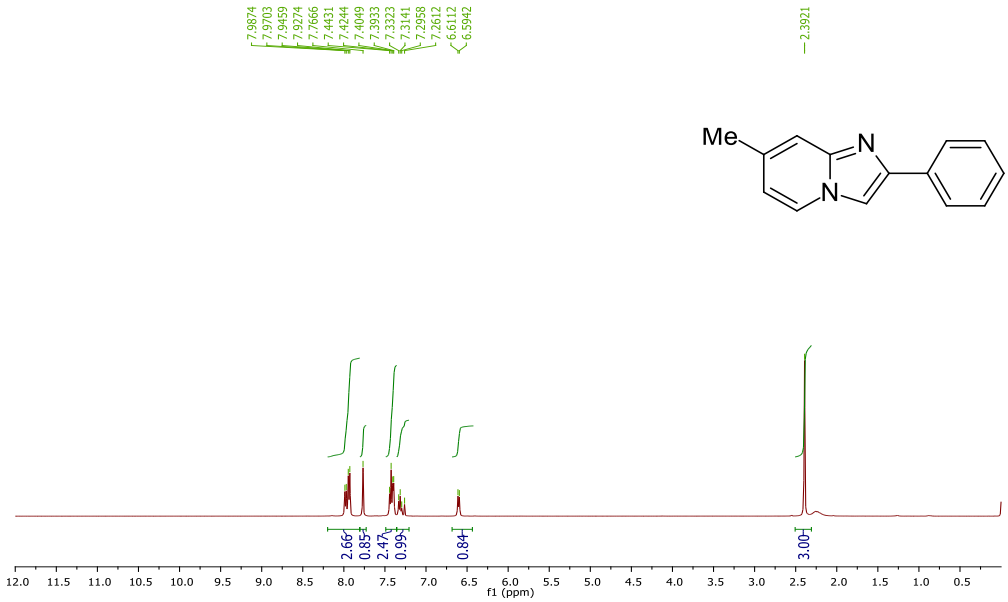


Figure 6: 400 MHz ^{1} H NMR spectrum of **3ac** in $CDCl_3$.

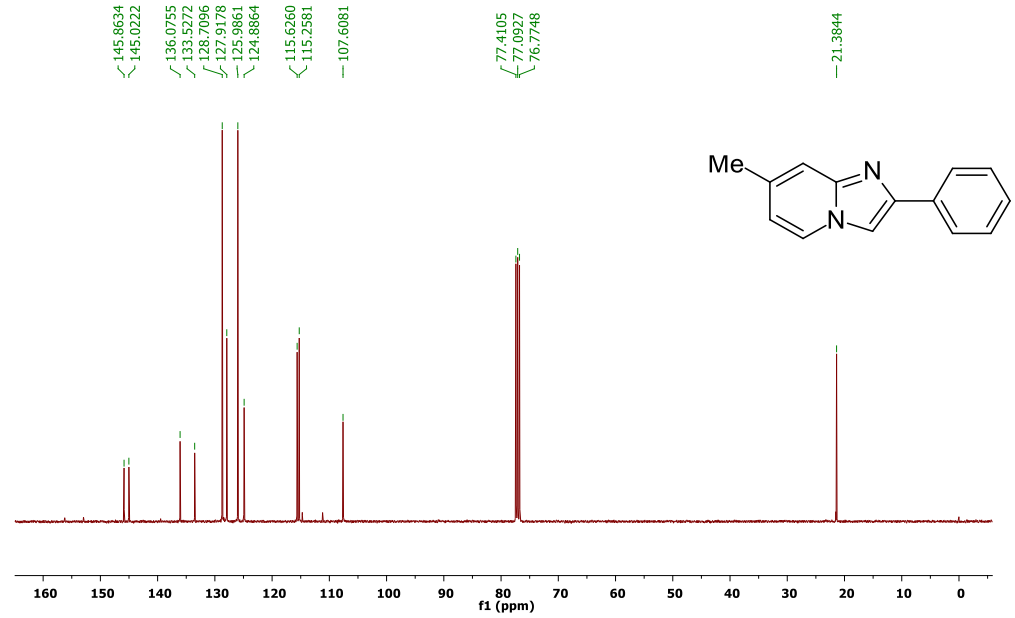


Figure 7: 400 MHz ^{13} C NMR spectrum of **3ac** in $CDCl_3$.

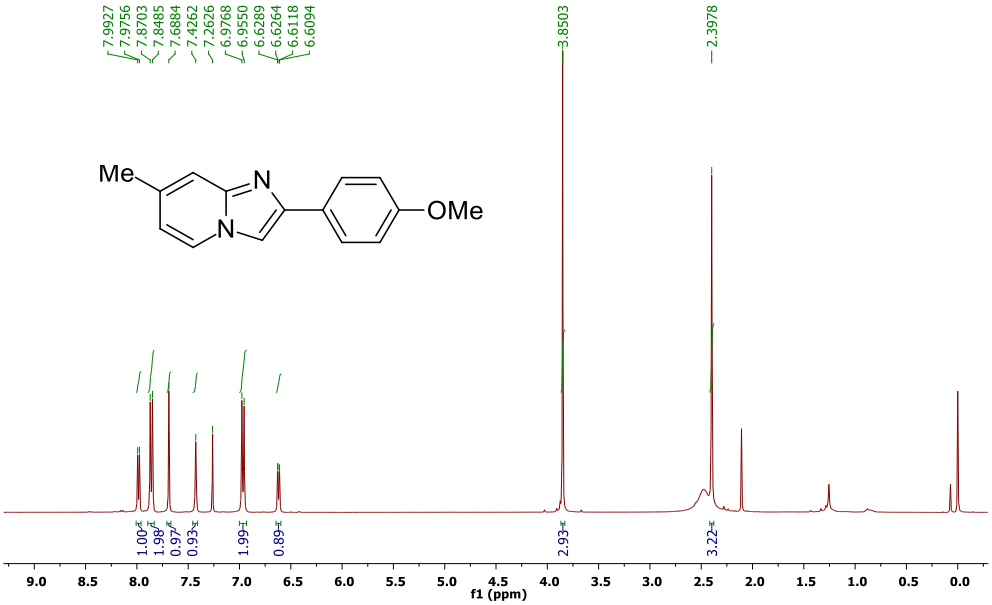


Figure 8: 400 MHz ^{1}H NMR spectrum of **3ad** in $CDCl_3$.

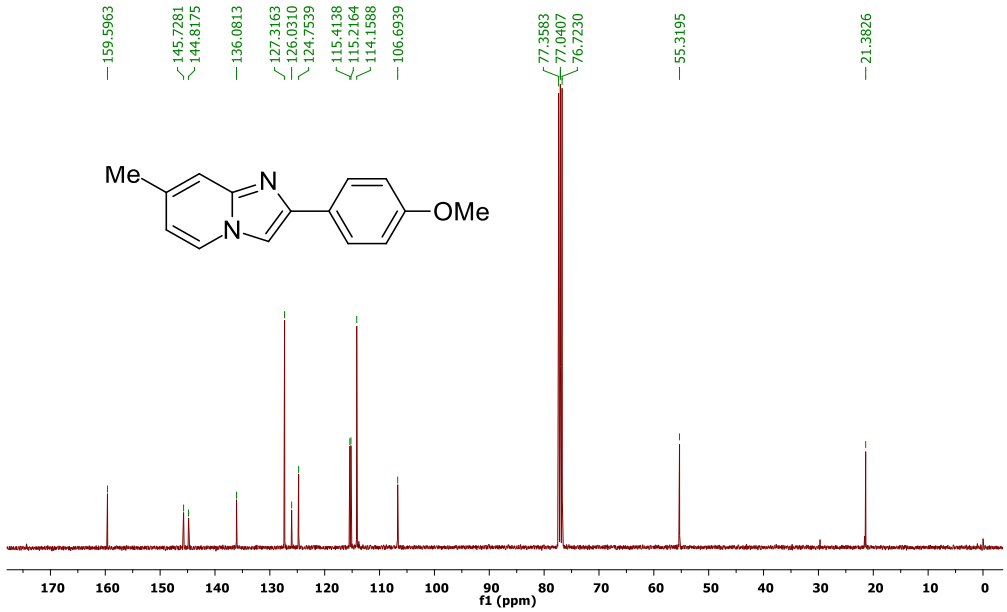


Figure 9: 400 MHz ^{13} C NMR spectrum of **3ad** in $CDCl_3$.

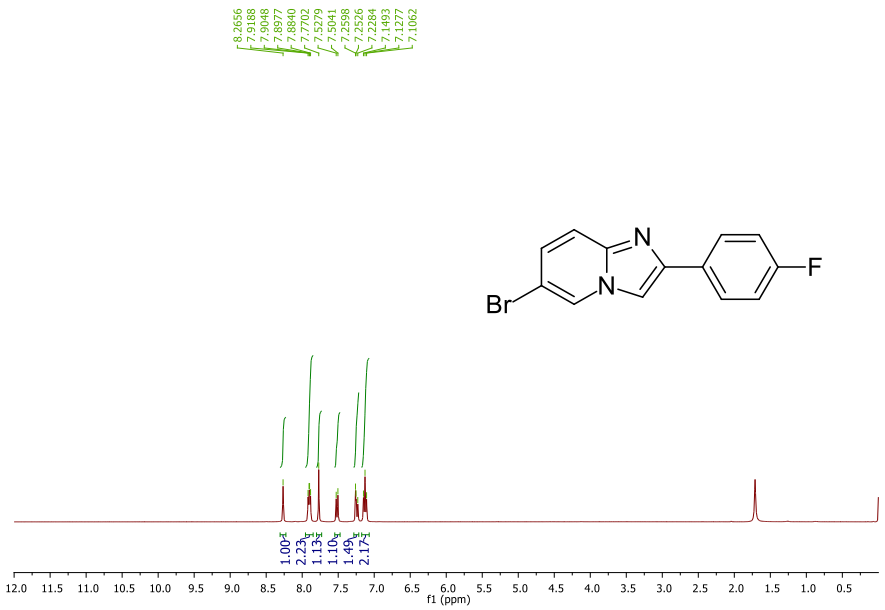


Figure 10: 400 MHz ^{1}H NMR spectrum of **3ae** in $CDCl_3$.

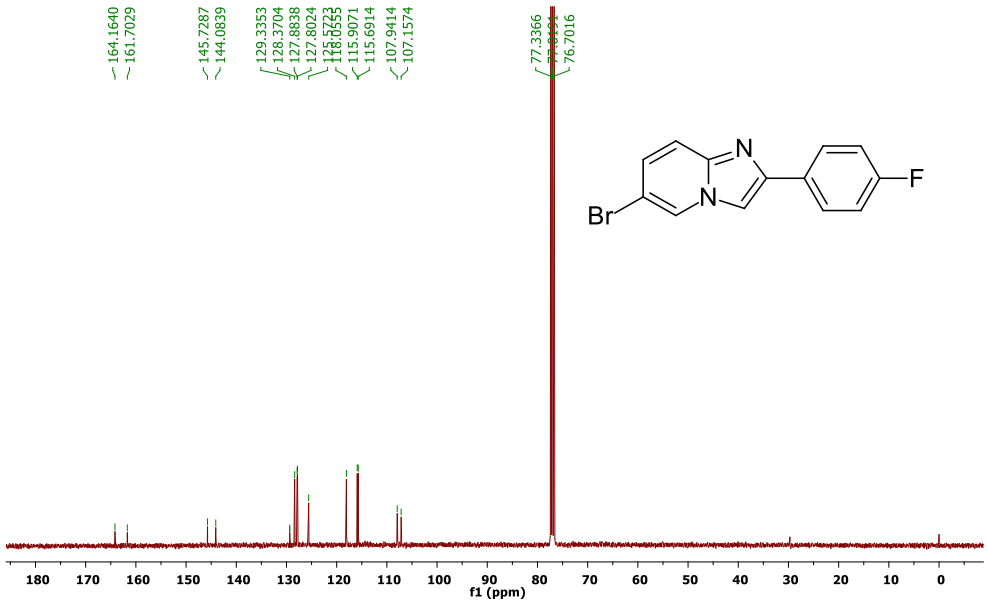


Figure 11: 400 MHz ^{13}C NMR spectrum of **3ae** in $CDCl_3$.

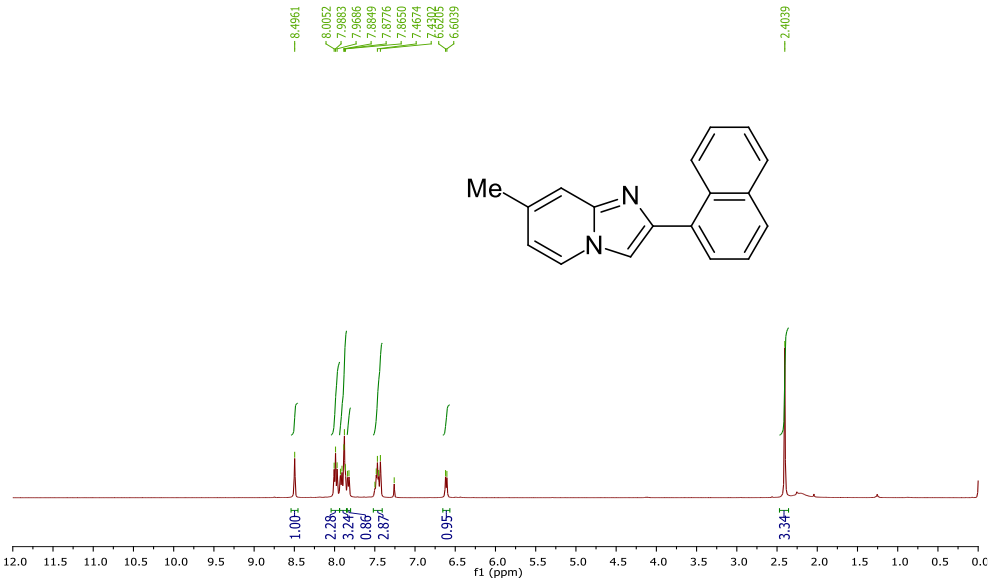


Figure 12: 400 MHz ^{1}H NMR spectrum of **3af** in $CDCl_3$.

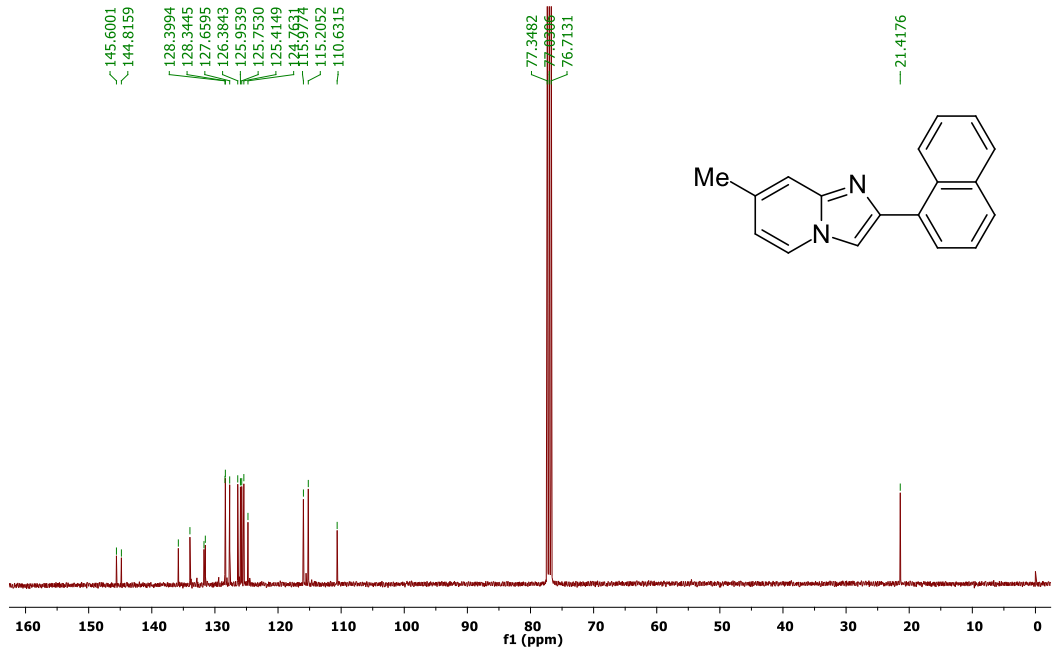


Figure 13: 400 MHz ^{13} C NMR spectrum of **3af** in $CDCl_3$.

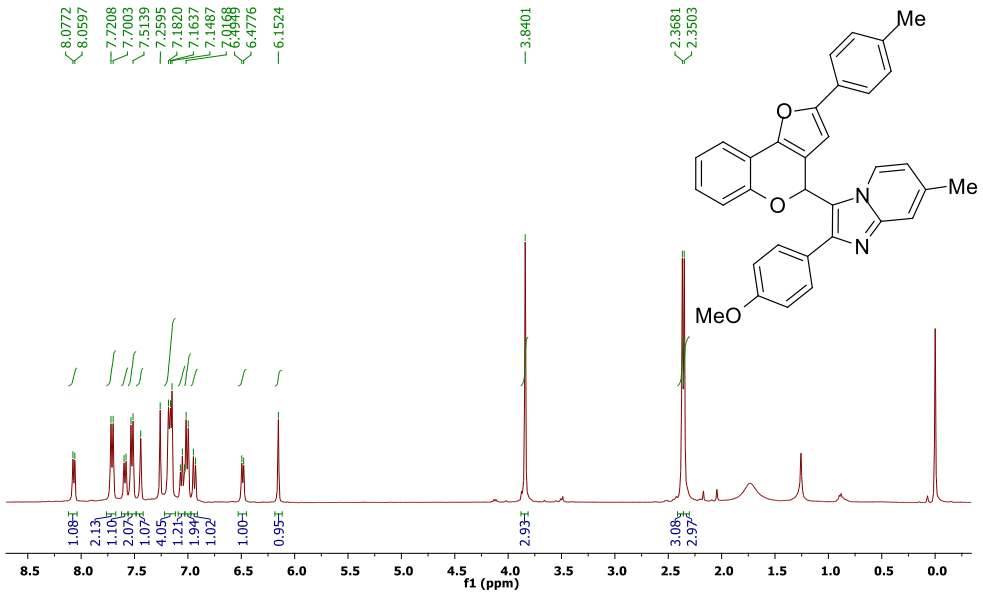


Figure 14: 400 MHz ^{1}H NMR spectrum of **3ba** in $CDCl_3$.

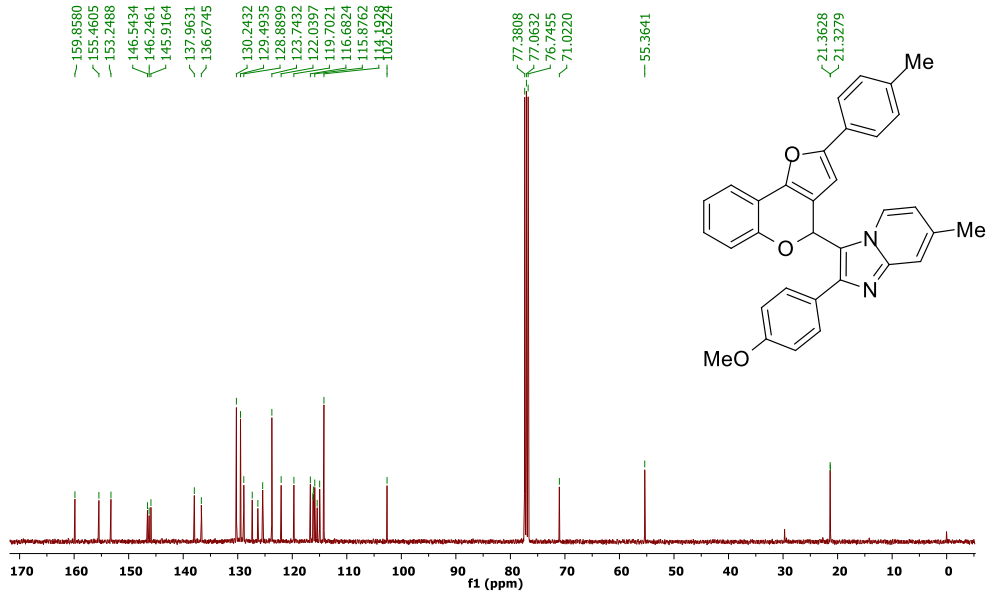


Figure 15: 400 MHz ^{13} C NMR spectrum of **3bb** in $CDCl_3$.

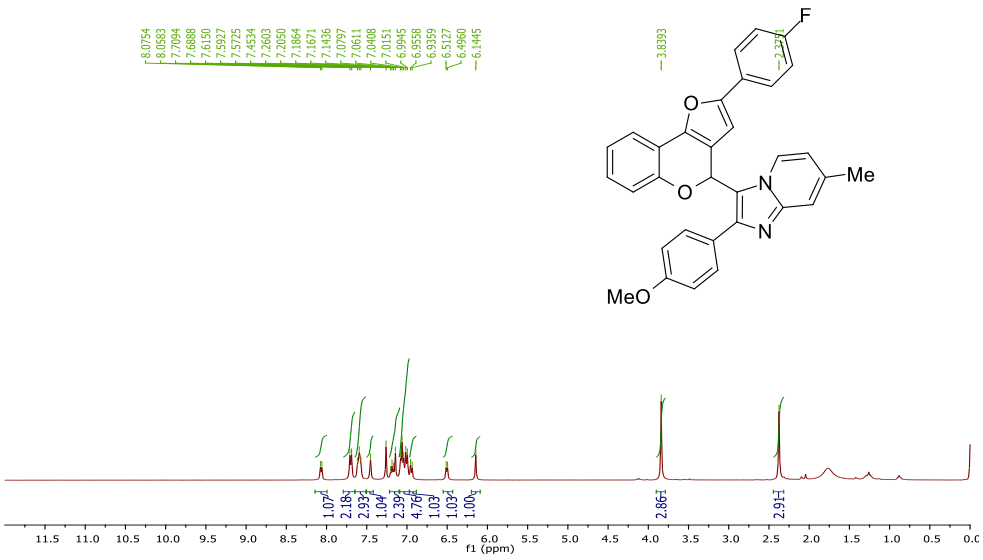


Figure 16: 400 MHz ^{1}H NMR spectrum of **3bb** in $CDCl_3$.

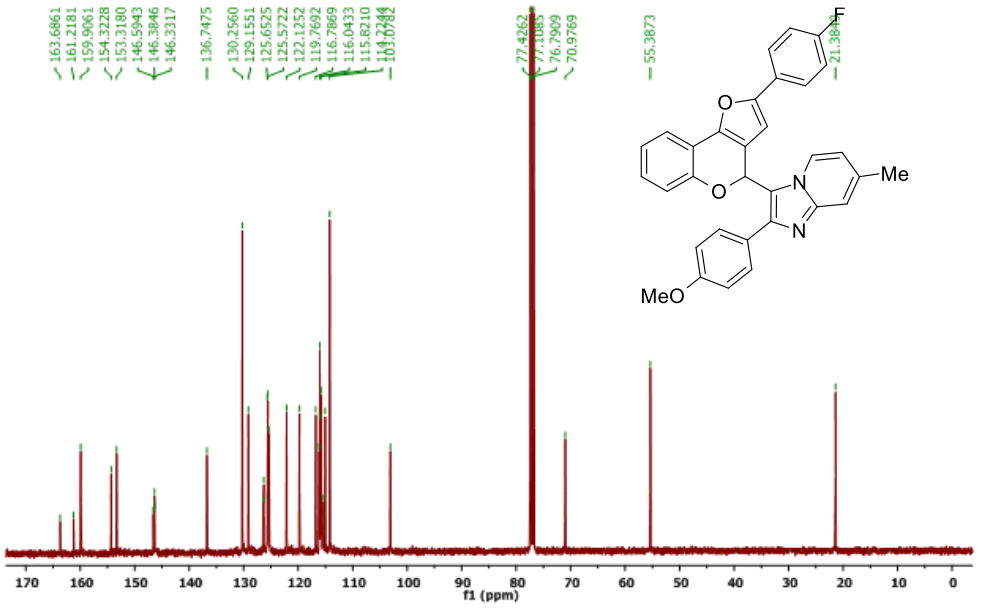


Figure 17: 400 MHz ^{13} C NMR spectrum of **3bb** in $CDCl_3$.

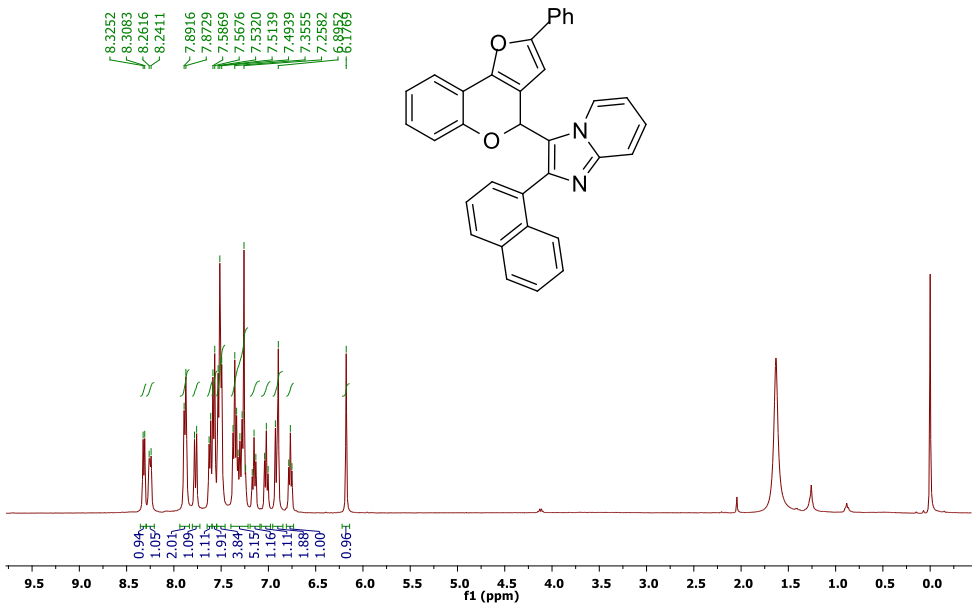


Figure 18: 400 MHz ^{1}H NMR spectrum of **3bc** in $CDCl_3$.

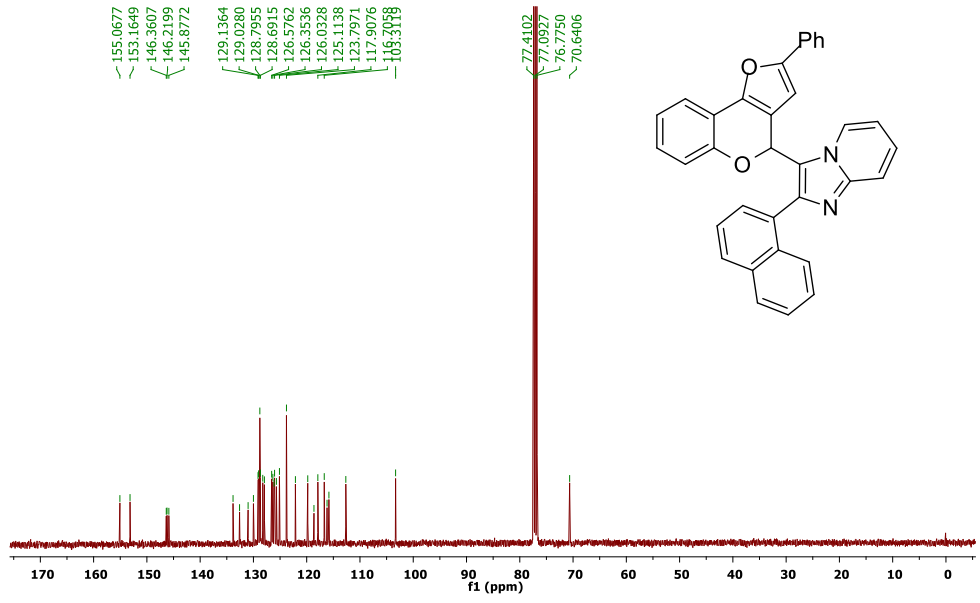


Figure 19: 400 MHz ^{13} C NMR spectrum of **3bc** in $CDCl_3$.

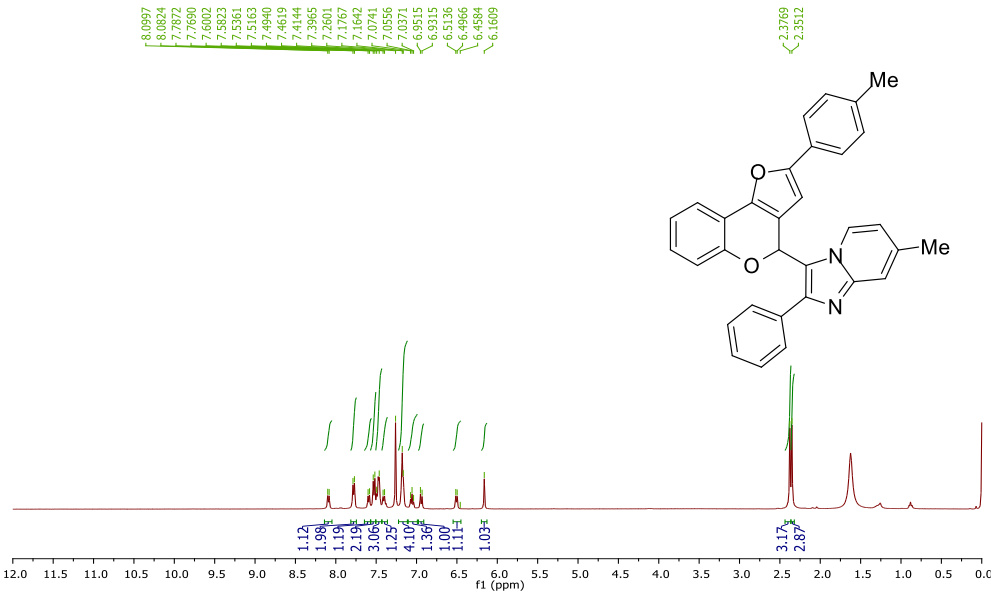


Figure 20: 400 MHz ^{1}H NMR spectrum of **3bd** in $CDCl_3$.

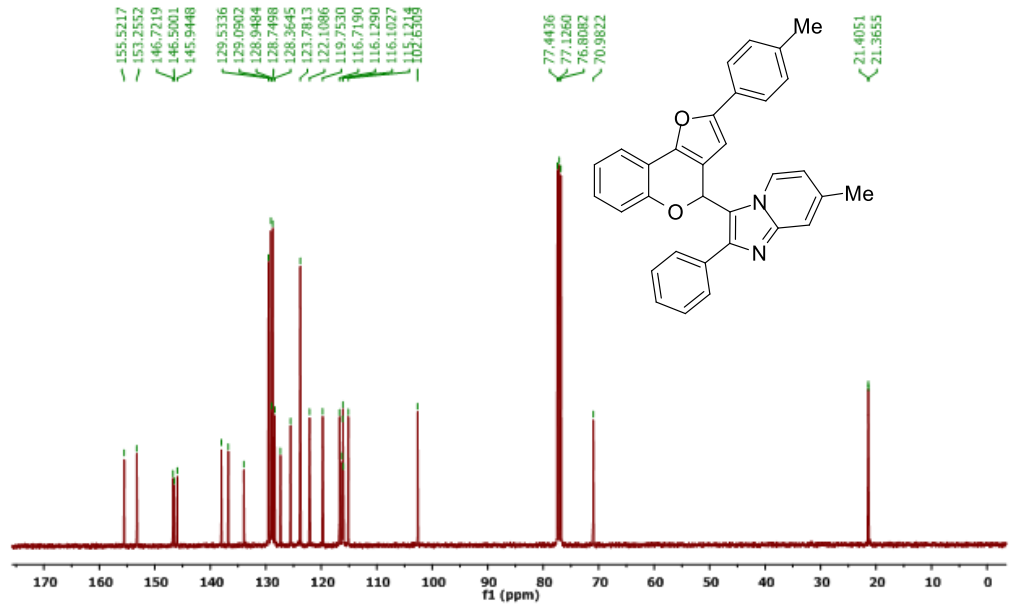


Figure 21: 400 MHz ^{13} C NMR spectrum of **3bd** in $CDCl_3$.

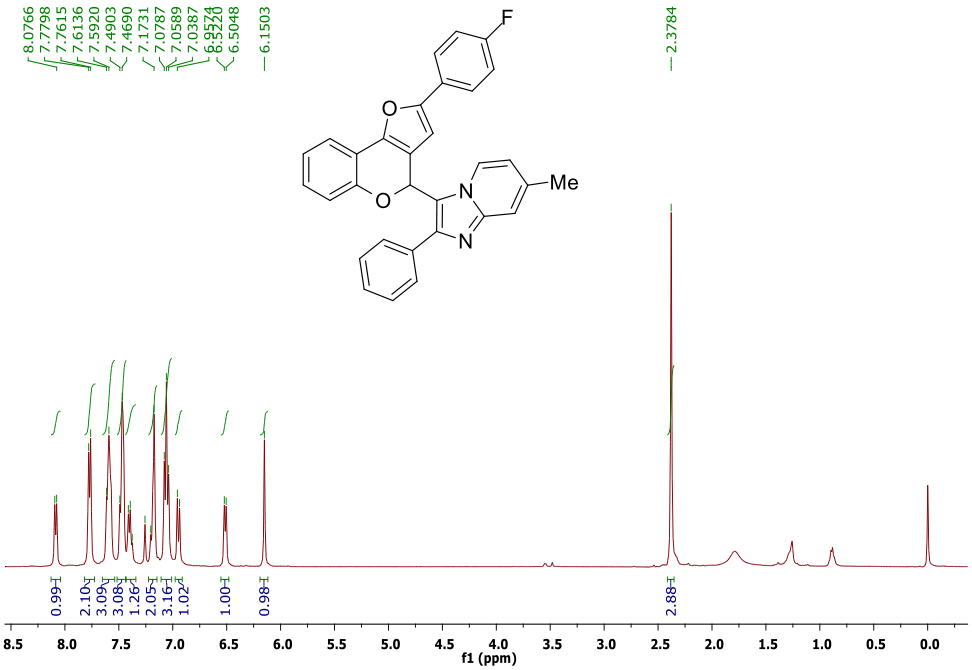


Figure 22: 400 MHz ^{1}H NMR spectrum of **3be** in $CDCl_3$.

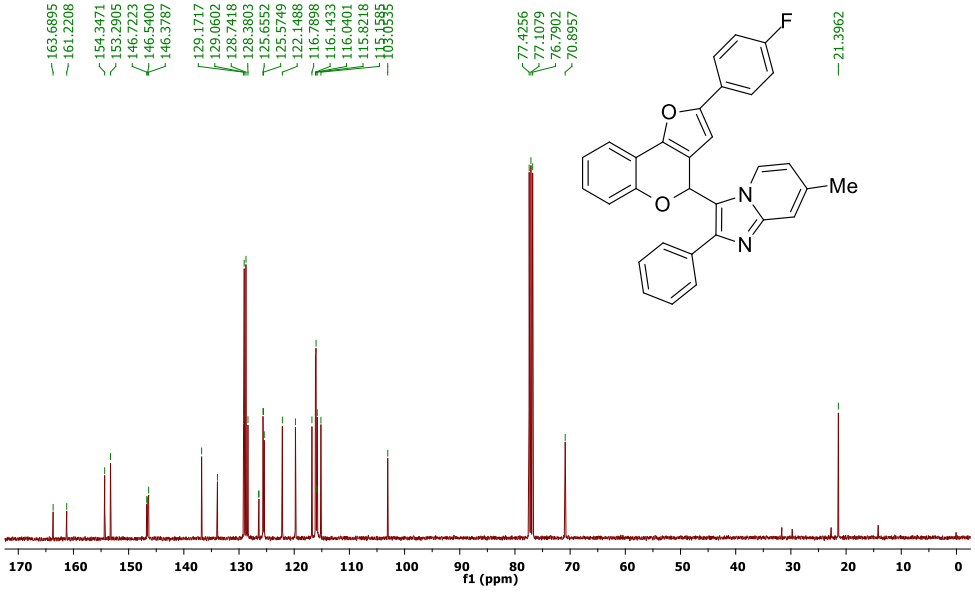


Figure 23: 400 MHz ^{13} C NMR spectrum of **3be** in $CDCl_3$.

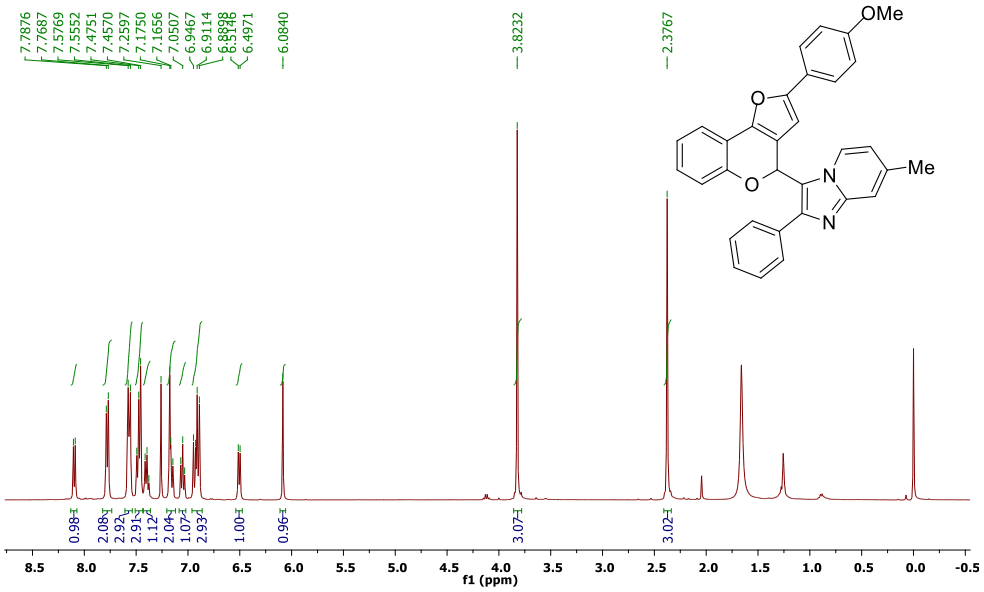


Figure 24: 400 MHz ^{1}H NMR spectrum of **3bf** in $CDCl_3$.

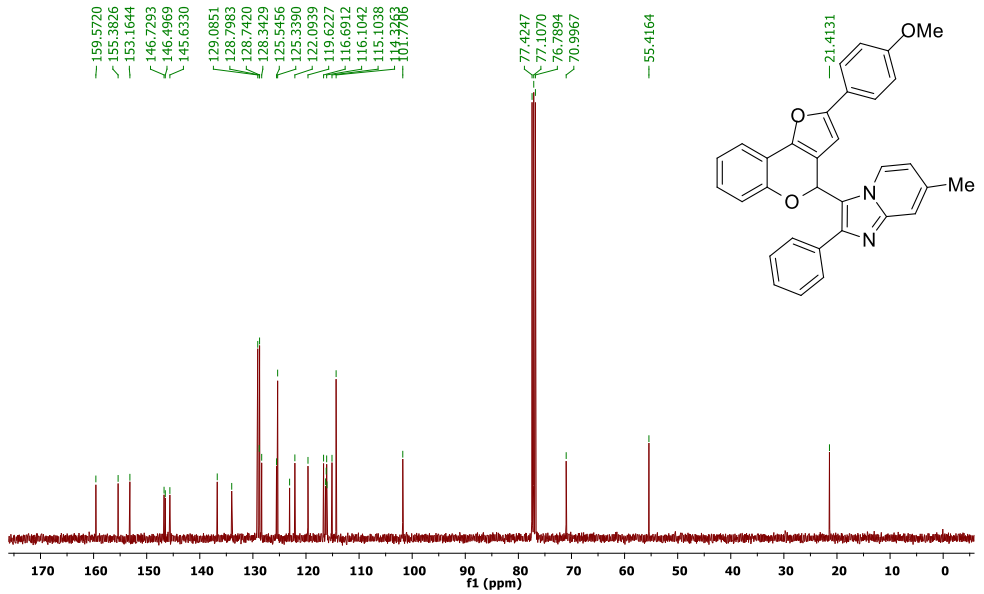


Figure 25: 400 MHz ^{13} C NMR spectrum of **3bf** in $CDCl_3$.

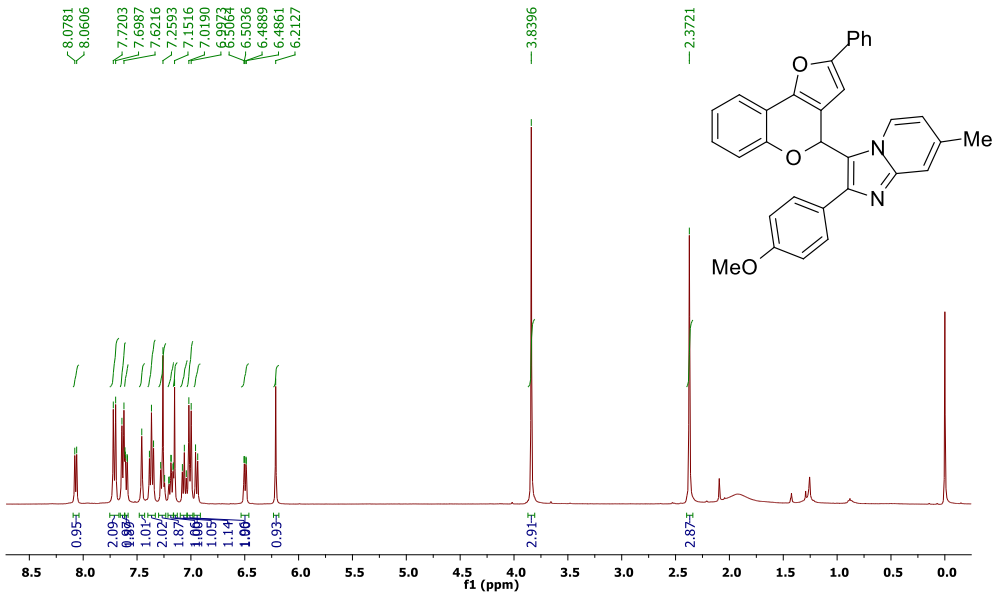


Figure 26: 400 MHz ^{1}H NMR spectrum of **3bg** in $CDCl_3$.

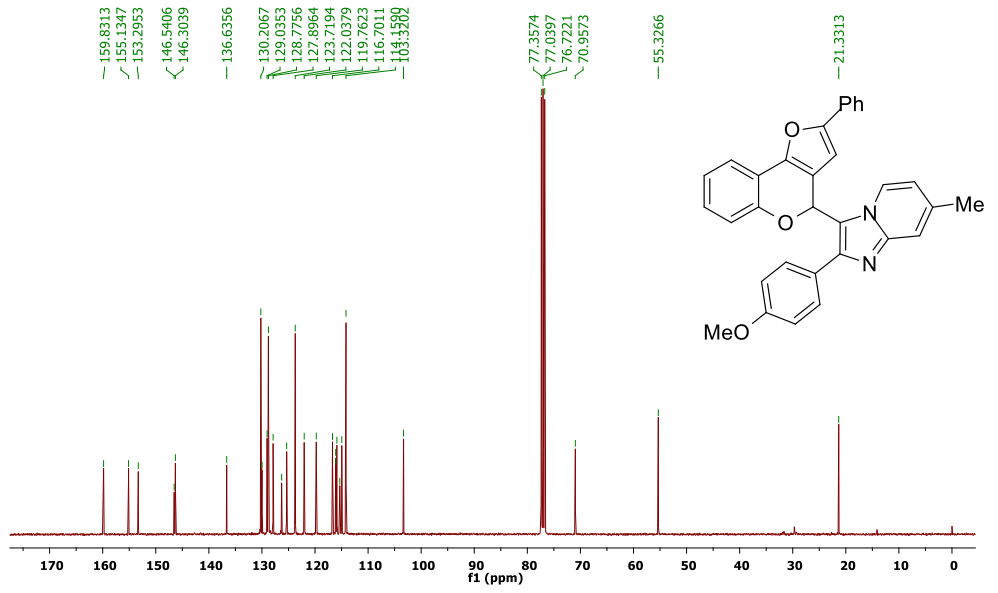


Figure 27: 400 MHz ^{13} C NMR spectrum of **3bg** in $CDCl_3$.

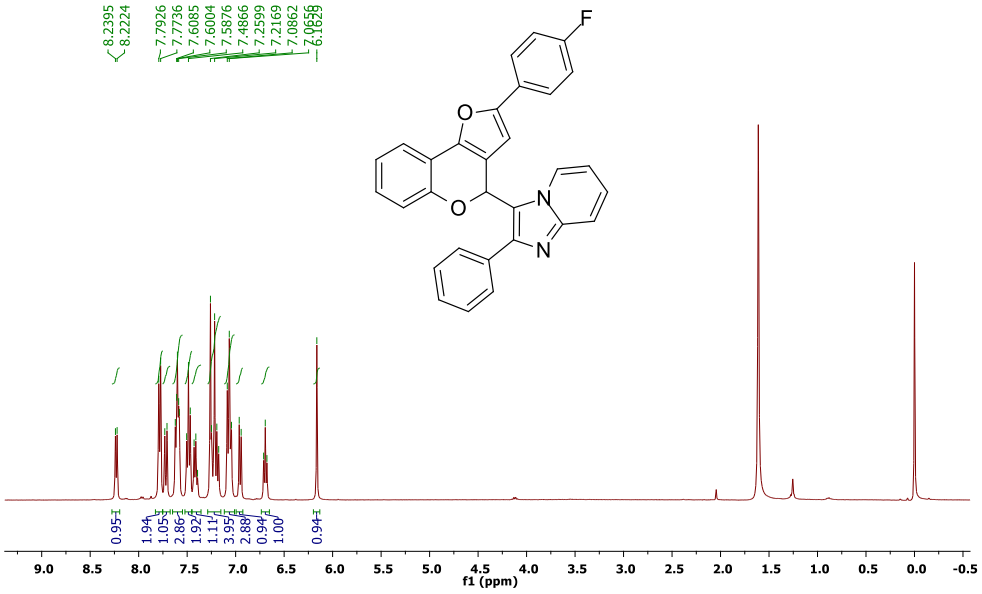


Figure 28: 400 MHz ^{1}H NMR spectrum of **3bh** in $CDCl_3$.

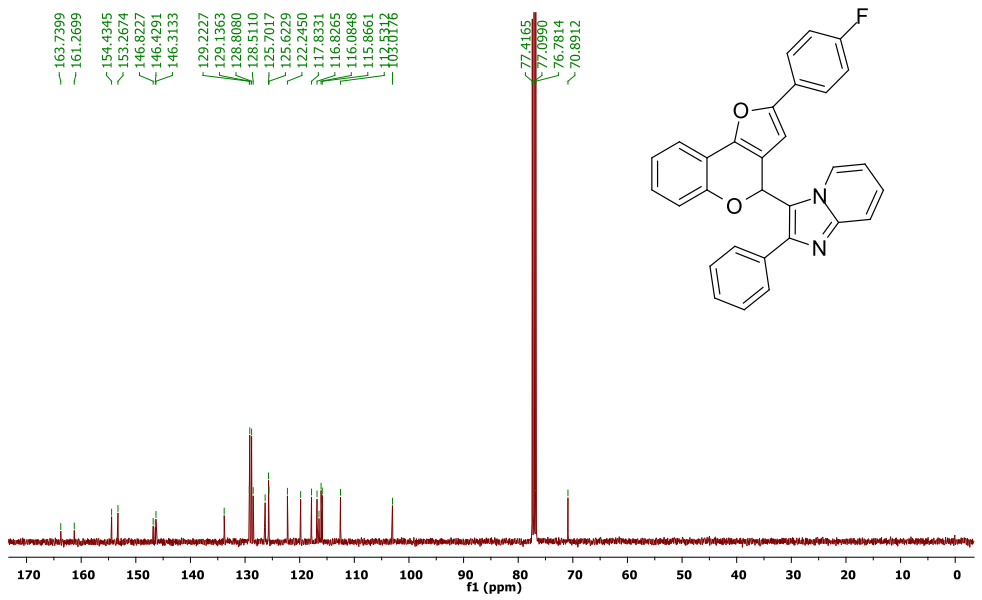


Figure 29: 400 MHz ^{13} C NMR spectrum of **3bg** in $CDCl_3$.

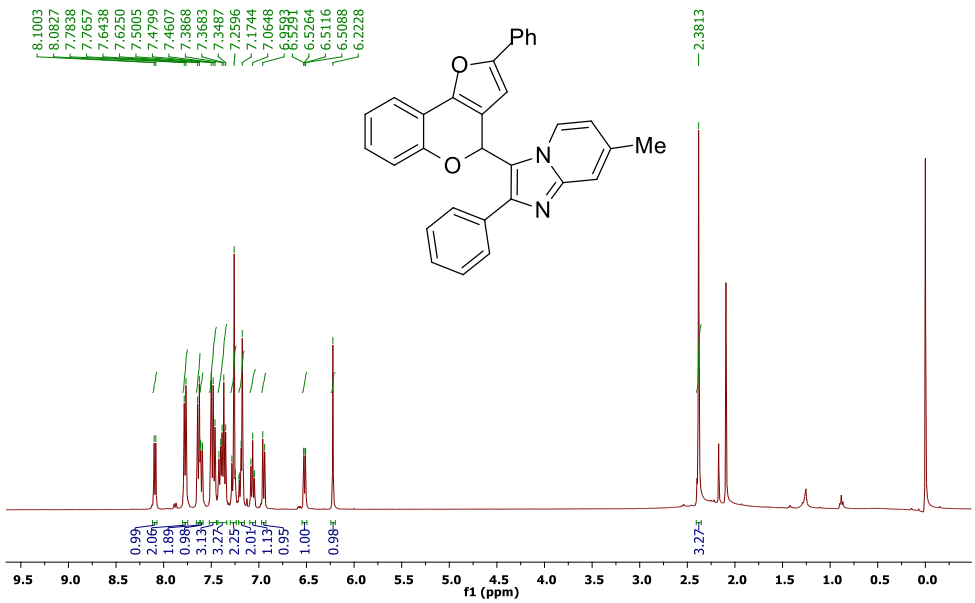


Figure 30: 400 MHz ^{1}H NMR spectrum of **3bi** in $CDCl_3$.

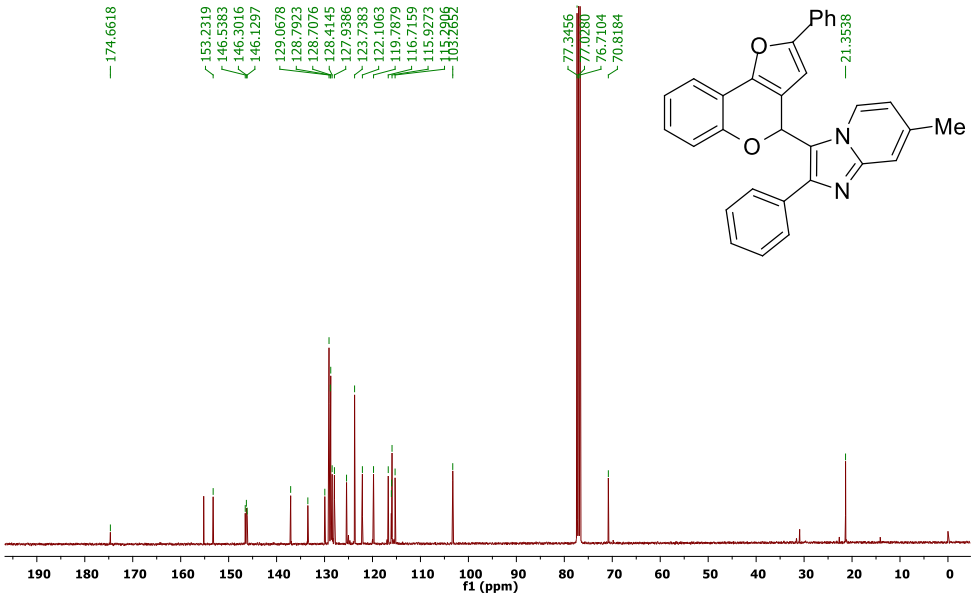


Figure 31: 400 MHz ^{13} C NMR spectrum of **3bi** in $CDCl_3$.

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